# Facilitating End-to-End Development of Individualized Therapeutics
# Public Workshop
# U.S. Food and Drug Administration
# Center for Biologics Evaluation and Research (CBER)

**FDA White Oak Campus**
**10903 New Hampshire Ave.**
**Bldg. 31 Conference Center Great Room**
**Silver Spring, MD 20993**

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***This transcript appears as received from the commercial transcribing service after inclusion of minor corrections to typographical and factual errors recommended by the DFO***

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| Neil Thakur | ALS Association |
| Rich Horgan | Cure Rare Disease |
| Anita Nosratieh | FasterCures |
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## INTRODUCTION: DR. GOPA RAYCHAUDHURI

**DR. RAYCHAUDHURI:** Good morning, everyone, and welcome to the CBER workshop on facilitation and development of individualized therapeutics. My name is Gopa Raychaudhuri. I'm a senior scientist in the Office of the Director at CBER, and I coordinate and oversee CBER's individualized therapeutics program.

It is my distinct pleasure to welcome all the stakeholders who are here today, including patients, family members, patient advocacy organizations, healthcare professionals, and individuals from nonprofit organizations, academia, industry, and government. In addition, I would like to thank everyone who's participating in today's proceedings via webcast. We appreciate you taking the time to join and contribute online.

Before we begin today's proceedings, I have a few general announcements. First, please silence your cell phones and any mobile devices. If you haven't done so already, we ask that all attendees sign in at

the registration tables just outside this meeting room.

If you would like to preorder lunch, you can do so at the food kiosk that's just outside the conference room. Lunch must be preordered by 9:30. If you decide not to preorder, you may purchase snacks, sandwiches, and other food items a la carte at the kiosk. And that's open until 5:00 today.

This meeting is being transcribed, and a live webcast is being recorded. There also is an official photographer, as you can see, who will be taking photos during the course of the workshop. For any urgent issues, please speak to the registration staff that are just outside or any FDA staff member with a tag, and we will be able to assist.

I'd like to open today's workshop by defining what we mean by individualized therapeutics and why we need to think differently about development, licensure, and access to these products. Out of thousands of rare, hereditary, and acquired diseases, there are hundreds of disorders affecting one or a small group of people each year that could be addressed with

individualized or bespoke therapies. These therapies are based on engineering a product aimed at the specific mechanism underlying a patent's, or a small group of patients', illness. That is the therapeutic product is engineered specifically for a given patient or small group of patients.

Examples include gene therapy or gene editing for monogenic diseases, antisense oligonucleotides, or genetically-engineered phages for multidrug-resistant infection. Today's workshop will focus on individualized therapeutic products regulated by CBER, specifically, gene therapies and phage therapies. But we work in close collaboration with our colleagues in CDER, who are very active in this space to facilitate development of antisense oligonucleotide products for patients with rare diseases.

This slide shows the traditional regulatory pathway, from discovery to licensure and post-licensure monitoring, for biologics and other medical products regulated by FDA. Individualized therapeutic products present unique challenges because they do not fit the

traditional paradigm for manufacturing and clinical development. This requires that we think outside the box, to establish an evidence-based, clear, and practical pathway for development, regulation, and access for patients to these products, while assuring that the standards for quality, safety, and efficacy are maintained.

During the course of this workshop, you will hear about existing challenges and potential solutions to adapt the current process to meet the need and opportunities for stakeholder collaboration to move this field of work forward. This slide shows the large number and wide range of stakeholders that play a critical role in this field of work. As a community working towards a common goal, each stakeholder brings valuable perspective, knowledge, skills, and resources to the effort. We are pleased that so many stakeholder groups are participating in this workshop. And we look forward to your contribution during today's discussions.

The workshop is divided into four sessions.

The first is on manufacturing. The second session focuses on nonclinical development and tools for safety testing. The third is on clinical development. And I should note that there is one change in the program in the clinical section. Unfortunately, Dr. Kohn is not able to be here in person because of flight delays yesterday. But he has kindly agreed to join us remotely and will be giving his presentation remotely. And the fourth session will focus on what is the ultimate objective, which is getting products to patients in an efficient and sustainable way and the critical role of partnerships and collaborations to make this a reality.

Each session will start with a short introduction by one of my FDA colleagues, who will serve as the moderator for the session. That will be followed by two or three 20-minute presentations by external experts. And we are very happy to have each of them here today.

Following the presentations, there will be a panel discussion, where we will open the floor for

comments and questions for the speakers and panelists. Online participants will have an opportunity to write in their questions. This is an important part of today's workshop because one of our main objectives is to hear from you, the stakeholders, on what we can do as individual organizations and collectively as a community to facilitate end to end development and timely and sustainable access to these important products for the patients who need them.

And with that, I would like -- it's my pleasure to introduce Dr. Peter Marks. Dr. Marks is the Director for the Center for Biologics Evaluation and Research at FDA. And he will give a few introductory remarks on the current state, and he will set the stage for today's discussion. Dr. Marks.

**SPEAKER: DR. PETER MARKS**

**DR. MARKS:** Thanks very much. Good morning. And thanks everyone in the room for coming today. And thank you all online for listening in.

I just want to spend a couple minutes setting

the stage for what leads us to be here today. And one of those things is just to back up and say where we've come over the past few decades. At the end of the last millennium, we were in this era of personalized medicine, where, increasingly, we were beginning to understand characteristics of people's disease that led us to choose medicines off the shelf that uniquely address their diseases, whether that be for cancers, infectious diseases, rheumatologic diseases.

And so this concept of personalized medicines, where you find the right drug on the shelf to treat the patient, became prevalent. But we're now moving into a different era. And that's an era where we understand the molecular defects at the level of the genome, and we actually are needing to create the right drug to treat the patient. We don't have things right off the shelf. And so what we're really moving into is an era of individualized medicine.

And yes, one could say that this is a semantic difference, but there is a difference here in how we as regulators, and I think how we as a field in general,

deal with this. And I just want to say that, as you start to cogitate over this some, you realize that individualized medicine actually breaks down further into products that are essentially customized products and products that are created. The customized products are one where you could imagine they have the same indication and the same mode of action, but there's something different about each one that's unique for an individual.

One can imagine that if one is making dendritic cells against some cancer that a patient has, some particular cancer -- it could be a lung cancer or some other cancer. But if you have different product, because it's got different peptides on it, you could have a lot of different ones with some unique attribute on some basic product. And those are customized.

On the other hand, there are products which are going to be for different indications, different lysosomal storage disorders, which may be very similar in that they have the same backbone vector, if they're a gene therapy, but they'll have different inserts.

And so I think this concept of customized and created products is something that we'll hear more about today, but it is something that we'll think about going forward. And there probably are some regulatory distinctions between these two classes.

Just to make this point a little further, personalized medicine is a little bit like ready-to-wear. You find stuff on the shelf that kind of fits you, and it just is -- it's there. It's like medicines off the shelf that you find that fit.

On the other hand, this concept of customized products probably has the analogy of something that's made to measure. Made to measure, for those of you who are not familiar with tailoring -- and I'm not one to talk because I'm not one for sartorial splendor -- made to measure is actually not a custom-made suit, a made to measure suit is one in which the fabric's been all cut. It's just the seams are left open so that they can be stitched closed once they adjust it to your fit. And that's kind of the analogy to customized products.

On the other hand, there are these created

products, which is more like a bespoke suit. A bespoke suit is somebody -- you choose the yards of cloth and someone cuts them and puts them together. And so this is kind of the analogy here I'd like to use. It's not perfect, but it does give us the idea of what we're dealing with.

Now, there are some challenges that go with these individualized therapies. And that's what we're here to talk about today. And we have sessions to talk about manufacturing, nonclinical development, clinical development, and product access. And we certainly don't have the answers for these. But I think I'd like to go through and kind of pose some of the questions.

Just to show you on the manufacturing side, manufacturing in this area is really a challenge. In the field of gene therapy, we have moved so fast in the science we're now on to second and third generation of genome editing constructs. We've moved on past the initial generation of CRISPR to new novel genome editors. That being said, we're still making vectors much the same way that we made them at the turn of the

millennium. And we really need to figure out how to move that forward.

The reason for that is that, right now, we have one sweet spot, which is the grande-size cup in the middle, where commercial viability relies on products that are going to treat between a hundred and maybe a thousand or a few thousand people. If one wanted to treat very large numbers of patients -- that's something for another day's talk and another day's meeting -- the technology is simply not there. One would need essentially to fill Lake Erie as a bioreactor to make enough vector to treat thousands of people. That's just not where we are. We're going to have to find more efficient ways to do that.

On the other hand, what we are here to talk about today is how do we deal with making these products for small numbers of individuals. And that's a challenge because the setup costs currently to make a gene therapy for 20 people are very similar to the setup costs to make a gene therapy for 200 people, in terms of a commercial process. So that's something we

have to really think about because it's limiting the ability to get access to these products.

Nonclinical development is also a challenge because animal models may be much less than ideal here. And that's particularly true when we start to think of genome editing because you might want to do toxicity studies of a genome editor. You might want to understand off-target effects on a genome editor.

But last I looked, although some people think I look a little like a mouse, my genome does not look exactly like a mouse. And it's a real problem. Despite the fact that there's a fair amount of identity, there's enough difference that you wouldn't want to trust a mouse model for a genome editor with the guide. So we may need to think about new model systems, such as how can human organoid systems, humanized mice, other models, help in this area for safety testing.

For clinical development, I think we really are going to have to think very novel-ly about how we deal with very small populations. We're going to have

to think about how we document disease, the natural history of disease, or collect baseline data so that, when we actually have small numbers of patients treated, we can see that there's some difference from that baseline.

And once we start to treat patients, can we find some way of using some type of continuous reassessment model or some other statistical method, a Bayesian or other design, to see if there's some point at which one crosses where one declares victory that you actually have an effective product, rather than developing a sample size and running a traditional clinical trial. And very importantly, we have to deal with product access. How do we deal with the fact that, for some of these product, once you've even gotten them through development, how do you make sure you have continued access to them given the complexity and the cost of providing that access?

We already know what can happen. One of the gene therapies that was approved in Europe is now no longer on the market. Now, obviously, it can be made

available in other ways. But it shows you what can happen here if we don't think about access and we don't think about the costs and the complexity of these products.

And so one of the things we've been thinking about here is whether public-private partnerships could at least help access in the United States and perhaps even globally through the streamlined production of products. Because when you think about it, if we're making products for very small numbers of patients with rare diseases, we shouldn't reinvent the wheel globally. There shouldn't be initiative here in the United States, initiative in Europe, initiative in Asia. It probably would be better to have everyone contributing to the effort.

So the idea here of a gene therapy public-private partnership would be to try to drive down the time it takes to get these products to patients by using reproduceable processes or leveraging data to make things happen. Because, typically, when investigators, individual investigators develop a gene

therapy, they go through all the normal stages of drug development, including submitting an IND, doing the necessary tox studies, doing the manufacturing, which oftentimes they have to learn to do from scratch. And that whole process takes four to eight years often on average.

One could imagine that if one was able to leverage manufacturing processes, use templated INDs, templated protocols -- obviously, it would have to be customized somewhat -- you could potentially shorten this a fair amount. And those -- that shortening of years means a lot. For patients, when you talk to parents of children with rare diseases, years matter, a few years matter.

So our goal of this workshop is really to think about where the opportunities are to adapt processes from beginning to end. You see the traditional process here. No one is suggesting that, for these products, we're going to have traditional phase one, two, three development.

The question is, where can we go with these to

end up at the end of the day with products that are both safe and effective? Because I think, in the process of trying to develop this paradigm, we want to maintain the ability to know that, at the end of the day, what we're providing to patients is something that is similar in nature to the gold standard that we provide patients with now with approved products. And with that, I will turn it back over to Gopa.

But before I do, I just want to -- I just nearly forgot one thing. I mean to have a slide here. But I want to just take the moment to thank both Dr. Raychaudhuri, as well as Leslie Haynes, for tremendous work putting together this workshop.

There is a -- there are others as well from our office who spent a lot of time taking care of logistics of travel, making sure that things run well. So thank you so much. And with that, I will wish everyone a wonderful day. We look forward to the discussions. Thank you.

**DR. RAYCHAUDHURI:** Thank you, Dr. Marks, for that overview and vision of approaches and

opportunities that we can think about to advance development and access to individualized therapeutic products.

So we will begin the program now with Session 1. I would like to introduce Dr. Zenobia Taraporewala. Dr. Taraporewala is a CMC reviewer, and Acting Team Lead for the Gene Therapy Branch in the Division of Cellular and Gene Therapies in the Office of Tissues and Advanced Therapies at CBER. Dr. Taraporewala will be the moderator for Session 1, which is on manufacturing challenges and opportunities for gene therapy and phage therapy products. Dr. Taraporewala?

## SESSION 1: MANUFACTURING

### SESSION 1 MODERATOR INTRODUCTION: DR. ZENOBIA TARAPOREWALA

**DR. TARAPOREWALA:** Good morning. All right. So let's get started. As Gopa said, I am Zenobia Taraperwala, and I am from the Office of Tissues and Advanced Therapies, commonly referred to as OTAT in CBER. And I will be the moderator for the session.

We have two very distinguished speakers in the

session, Dr. Guangping Gao from University of Massachusetts Medical School and Dr. Jason Gill from Texas A&M University. Following the two presentations, we will have a panel discussion. And the panel will include speakers from this session and CBER representatives from the Office of OVRR -- from OVRR the Office of Vaccine Research Review, Dr. Roger Plaut, and from the Office of OCBQ, which is Ms. Anita Richardson. And during the panel, we will field questions from the audience and from those attending online.

So this is advancing but that is not. Okay. Thank you. All right. So this slide illustrates the manufacturing development, where manufacturing feasibility is assessed, and analytical tests are -- so this basically gives you a manufacturing development paradigm that is currently followed for biologics and drugs in general.

It starts with the discovery and the preclinical stage where manufacturing feasibility is assessed and analytical tests that are suitable for

release of research and developmental lots and IND-enabling lots are developed. That manufacturing experience is then leveraged for the manufacturing of clinical lots under GMP suitable for early phase studies. And with the release of multiple clinical lots, there is greater understanding of the variables in the starting and the raw materials and for the process on analytical assays used in release testing, all that are critical to ensure lot-to-lot consistency.

In late phase studies, the analyticals needed for thorough product characterization and in-process testing to meet the future demands of commercial process are put in place. Finally, for licensure, the expectation is that full GMPs are in place for manufacturing of PPQ lots to demonstrate that the process is capable of consistently manufacturing safe and efficacious product at commercial scale. The quality controls are in place at that time, and all the assays are validated. The product stability during storage and shipping has been demonstrated for expiration labeling.

So considering this paradigm then, where are the opportunities for flexibility in manufacturing for individualized therapeutics? Next slide. When discussing the challenge -- thank you. When discussing the challenges to the development of individualized therapeutics, one must consider the complexity of manufacturing biologics for a large patient population and whether the challenges apply or are similar for individualized therapeutics, where one would expect limited manufacturing experience with an N of one lot, or patient-specific lots, or small lots.

What then are the challenges towards achieving lot-to-lot consistency and quality for the licensure of individualized therapeutics? So what do we recommend sponsors do to ensure manufacturing consistency during standard development of a biologic? It starts with ensuring quality, safety, and consistency of the starting material, minimize the risk of adventitious agents, and ensure reliable supply chain.

The manufacturing process should be optimized with robust process controls and a good understanding

of the variables, which comes with manufacturing experience with the release of safe, potent, and quality lots that are qualified or validated early in development and generating well-characterized reference standards that can be used throughout clinical development. Consistency in product stability can be achieved by developing a platform suite of assays for quality control and release testing and by using assays that are qualified and validated early in development and generating well-characterized reference standards that can be used throughout clinical development. Product stability can be achieved by adopting standard or previously tested formulations, standard container closures, and storage conditions.

What are the considerations then to facilitate the development of individualized therapeutics? Go to the next. In this session, as we discuss and think about the manufacturing of individualized therapeutics and the related regulatory challenges, it is important to note that regulatory flexibility is currently afforded to patient-specific biologics and biologics

that are developed for rare and orphan diseases. And such flexibility is afforded based on the risk/benefit analysis on a case-by-case basis. For example, in early-phase studies, assays that measure product potency or processed impurities and release testing plan for clinical lots may not be sufficiently developed or qualified.

There is limited product characterization, and we allow products that may have limited shelf life to be released, based on rapid sterility testing and sampling flexibility of small lots. In early-phase studies, stability testing may be limited. Product stability assessments are made on data collected in real time from clinical lots that are placed on stability.

This slide lists the examples of the regulatory flexibility afforded in late-phase studies, which includes release of clinical lots with potency assay that measures the biological activity of product that may not be completely -- an assay that is not completely developed or qualified. We may allow for

release of lots with wide acceptance criteria for release testing of some critical quality attributes of the product. When limited lots are made during clinical development, we have allowed comparability to be established with limited data, for example, by a side-by-side analysis of critical quality attributes and without robust statistical analysis.

Process validation in support of licensure for products that have limited demand, such as orphan drugs, we have allowed PPQ protocols, which is process performance qualification protocols that are developed for process validation, and to release for process a PPQ batch for the distribution before complete execution of the process validation. So we call that concurrent release. And that is consistent with the FDA's guidance on process validation. It is key to note that, even in such cases, any lot release concurrently must comply with all CGMPs, regulatory approval requirements, and PPQ protocol lot release criteria.

So with that introduction to the session and

the manufacturing issues in general, we hope that the speakers and the discussion following the presentation will address the challenges of small-scale batch manufacturing that may be needed for individualized therapeutics, ways in which we can ensure manufacturing consistency for such patient-specific therapies, the regulatory challenges in manufacturing and how these can be addressed, and whether there is a need for additional guidance, standards, or other regulatory tools. So with that introduction to the session, it is my pleasure to invite Dr. Guangping Gao, who is the co-director of the Li Weibo Institute for Rare Disease Research. He's also the director of the Horae Gene Therapy Center and Viral Vector Core.

He holds multiple appointments at the University of Massachusetts Medical School and is an elected fellow for the U.S. National Academy of Inventors and the American Academy of Microbiology. He's also the president of the American Society of Gene and Cell Therapy. He's an internationally recognized gene therapy researcher. He's been instrumental in the

discovery and characterization of many AAV serotypes that have revitalized the gene therapy field. And he has made several impactful contributions in this field of AAV vector gene therapy.

With that introduction, I welcome you to give the first talk.

**CHALLENGES AND OPPORTUNITIES IN DEVELOPMENT AND MANUFACTURING OF INDIVIDUALIZED THERAPEUTICS WITH AAV VECTOR-BASED GENE THERAPIES - DR. GUANGPING GAO**

**DR. GAO:** Thank you to FDA and our colleagues here inviting me to talk about AAV gene therapy for individualized therapeutics. So what I would like to use this time to tell you about some basic concepts and challenges in AAV gene therapy for individualized medicine. This is my disclosure.

And so gene therapy strategy, I would like first to take a broad view with you what are the gene therapy approach strategies. The first one is traditional or conventional medicine developments, that is you use gene therapy such as AAV based vector as a

drug directly given to human patients and accomplished therapeutic efficacy. And here, we have three drugs approved by EMA and by FDA.

The second strategy is, basically, genetically modify the cell therapy. In this case, you take out human cells and genetically modify in vitro, expand it and give back as a live medicine, a living medicine, and give back to patients. Okay. And there are three drugs approved by EMA and FDA.

So to accomplish gene therapy, I personally believe there are four critical components: therapeutic gene and the pathomechanisms, vector delivery methods, and animal model to perform preclinical product developments. And among those, the delivery vehicle vector is most important. So if you look at the field of the gene therapy in the past two-and-a-half decades, you can see that, basically, gene therapy has been going through different vector platform, includes adenovirus and lentivirus.

So we, as the gene therapists, our wish list is the following. We want the vector to have a high

efficiency, long-term stability, low immunogenicity and toxicity, and no genotoxicity. So among those features, adeno-associated virus has it all. So this virus is really a teamwork inside-out, with the capsid determining where the vector should go and how to get there, where to drop the gene payload in the right zip code.

And the vector genome itself, it actually carries gene payload for gene therapy. One of the major limitations that we have here is adeno-associated virus is very small. It only can carry the transgene cassette, no more than 4.6, 4.7 kb.

And however, this genome is critical in terms of formed, stable episome vector structures to be persistent in terminally-differentiated tissues. So how we transform this almost a virus -- because without helper, this virus is doing nothing -- into amazing vector. So basically, what we do is we take out wild-type genome section of regulatory protein and a capsid protein. And then we put back our expression cassette, therapeutic gene. And then we provide helper function

in trans. We provide the packaging plasmid, the regulatory sequence, and capsid sequence in trans.

If we put those three things together, either by transient transfection, stable transfection, or infection, we can create -- get into the producer cells and then generate AAV vectors. The beauty of this virus is that what AAV dressed doesn't matter. So what you can do simply is change the dress, change the capsid and become a new vector. For example, this we change to AAV8. 9 capsid become AAV9 vector. And then if you change to AAV8, it becomes AAV8 vector.

So exactly how AAV works, I just want to use a simple cartoon to demonstrate how AAV works as a gene therapy drug. Basically, like any other viruses, AAV's getting to the cells by receptorology process, and then going through endosome trafficking. There you have two pathways. One, you probably can get into a proteasome, get degraded. And another, you can enter the nucleus. And efficiency or the ratio of those two proportions of the viruses depends on serotypes.

Some serotypes have more efficient escape from

endosome, and some it's more efficient to get into the cells, into the nucleus. Once you get into the nucleus, the first step AAV need to uncoating and then that release, let single strand AAV genome are both negative strand and positive strand. Then you can form double-strand genome through host machinery or self-annealing. And then, you generate a vector genome that is a ready to expression.

However, there's a mechanism because of a terminal repeat of AAV8. It can form a circular version and then can be stabilized in a terminally-differentiated tissue. Very small portion of AAV could be potentially integrated.

And then once you have a stabilized genome that you have a gene expression, you can generate gene therapy products in this case. So if you look at the AAV gene therapy -- and currently, AAV gene therapy has entered an exponential growth period. And there are nine different therapeutic areas using AAV gene therapy vector.

Ophthalmology or ocular gene therapy and CNS

gene therapy takes the lead but followed by many other different applications. So now we know -- we talk about this strategy. We talk about the vector delivery. And exactly how can you accomplish gene-based therapy, I summarize here in four different formats.

The first one is a classic gene therapy, that when you have a gene not functional, you can provide a healthier gene to replace these malfunctioning genes. This is a very classic version of the gene therapy. The second part is that you may have nothing wrong with your gene, but you need certain gene products to fight diseases such as cancer or infectious diseases. You can add genes to fight those diseases.

The third one is, when you have a genetic mutation, when you get a gain of toxicity, gain of function outcome, you can silence this gene and accomplish therapeutic treatment. And the final one could be gene editing. And this is now entering a rapid growth using gene editing as a tool for gene therapy.

So now, I would like to use one of my personal-professional journey about a disease called the Canavan disease demonstrating how gene therapy works. This disease was discovered in 1931 by Dr. Canavan. And this is a very tragic disease, devastating disease.

Basically, you have a quite high prevalence in Ashkenazi Jewish population, but also, in general population, you have 1 in 300 mutations. The genes could've been mutated. And then this patient dies usually before five. There's no medicine to treat this patient -- those patients. And this is a spongy degeneration, the disease is.

And this is a picture I took in 2013, when I went to a Canavan disease meeting and I took this with a dozen of the patients. And 2016, I went back to the same meeting, only a few kids still running around. And this really picture remind me, we as gene therapy researchers, we have to work as hard as we can to have the race with time to develop a therapy to save the lives of those children.

And as you can see, because of this leukodystrophy is a spongy degeneration, the brain, whole brain is just like Swiss cheese. And this is my mentor, PhD mentor, Dr. Rueben Matalon, who discovered biochemical defect of this disease in 1988. Basically, what happened, there's a product called NAA made in neurons, in mitochondria. And they transport into oligodendrocytes where it should be degraded by aspartoacylase.

However, if we have this gene mutation, then all the tragic starts here. You have NAA accumulating in inter-tissue space in the brain, and then you generate spongy degeneration. I entered this Canavan research in 1989 as a graduate student and published my thesis research in 1993. And this allows the gene therapy possible. But the issue is, as everybody knows that -- the key issue, as I said from the beginning, it's the vector.

So I decide to start my post-training with Dr. Jim Wilson at the University of Pennsylvania. And then, Jim and I started this joint venture that is

looking for more efficient AAV. And we basically designed primers across the variable regions of the AAV genome, amplifying the capsid. Using this method, we generated a library of AAV capsids.

And I want to give you an example. This is one of the most expensive but most popular virus, that's AAV9 -- everybody knows that, AAV9, so widely used for different applications in gene therapy. So we isolated this from human tissue, human liver. And that's the original lab record showing what isolates clone 28.4 as a gene AAV9 vector. And the beauty of this vector is it can cross blood/brain barrier and transduce the brain quite efficient.

So with this available, then we, at the University of Massachusetts, start to develop gene therapy for the disease. This is my MD PhD fellow, Dr. Dominic Gessler. So basically, we developed it using AAV9. And through extensive optimization, we developed the vector treat an animal model exactly recalculate human disease.

As you can see, the gene therapy here,

basically, this is Canavan disease. The neurotrack, it's very short. This is normal. But after gene therapy, you basically, through this tractography, you see we restore neurotrack in the patient mice.

And very importantly, this gene therapy can reverse pathology. As shown in here after one week of gene therapy and this Canavan disease still there. And this is wild-type, and this is Canavan treated there, so not yet. But if you look at week four, then the situation will be very different. And this is the Canavan disease that we have treatment, this is normal, this is treated. As you can see, we basically restored myelination and reversed pathology.

So with this available -- and I collaborated with Dr. Barry Byrne of the University of Florida -- we started as a Phase 1 -- not Phase 1, sorry -- expanded access trial with two-year-old patients. And basically, we -- in this process, we also applied immunosuppression to leave a potential window of treatment for future dosing if this treatment didn't work. And as you can see, treatment is safe.

Transaminitis, we do not have transaminitis elevation. And also, this patient growth curve, as showing here, is quite encouraging.

And so if you summarize the data from this expanded access, is we know the immune modulation worked perfectly because up to today, we still cannot detect any anti-AAV9 antibody in the patient's bloodstream.

And also, AAV gene therapy improved the myelination and also the motor development and restored the vision. The patient could not see before. Now, when you walk in the room, the patient can follow you around with his eyes.

And also, using DTI, the MRI, we demonstrate that we show the development findings as we saw the patients start moving with their hands. And this is a patient before the treatment, and this is the patient about, I would say, 15 months after treatment. You can see, really, we improved their mobility and also quality of life.

And whenever I saw these pictures, I feel very

much rewarding as a scientist who spends your life and your professional research on this disease. The family will be able to see the patient can save his life and improve the quality of his life. So this is a powerful -- a powerful outcome of the gene therapy. However, I want to remind you, with gene therapy, we still have a long way to go.

And in this journey of gene therapy express reach to hospital usage and clinical application, we have several hurdles we're going to face. The first one, number one, I can see is the manufacturing. And we -- I don't think we have enough vector to treat patients as a commercial drug. And particularly, the potency of the vector, we also need to improve.

The second part is this pre-existing and also adaptive capsid transgene responses. And this can -- immunotoxicity could generate safety concerns. The third part is, even though we want to say we should have cell-specific, tissue-specific gene therapy -- but I have to tell you, at this stage, my personal belief is we only have efficient vector and nonefficient

vector. I don't think we really can control tissue tropism and cell specificity.

And the final hurdle is, so far, we thought the gene therapy, the more the better. Actually, soon, I personally believe we will see that we need to have a regulated gene therapy, long-time, overexpressed, super physiological level may not be good. So once we have those hurdles overcome, we'll have regulated gene therapy arrow, have as a drug for clinical usage.

So how to address those questions? I want to give you one example. That is we continue looking for better vectors and for -- basically, this is an effort we have done -- and generate about -- so through the PCR and the high-throughput sequencing, we generate about 70,000 more AAV capsid. Through complicated bioinformatics pipeline, we eventually identify about 1,000 vectors. And some of those vectors can overcome the production hurdle. AAV2 is one of the poorest producers, as you guys doing gene therapy should know.

But we found in those variants, AAV2, 25 percent of them produce much better than AAV2. Some of

them produce 20-fold higher than AA2. And I want to show you one example of such efforts. And that is we isolated AAV2 variants, only have 13 amino acid difference from AAV2.

However, this translates to -- into 13-fold more efficient than gene delivery, seeing as you can see here, you have AAV2 injected in one side of hippocampus. And then if you look at other side injected with new vectors, you can see 13-fold of enhancement. It tells you we still have the room to improve our vector.

And we also continue this kind of search. The first one, we screened about 38 vector, and then here, we screened about 50 vector or so. We identified 21 vector that's as efficient as AAV9. Seven of them, I actually can see either equal or pass AAV9 performance. So it tells you we have further room to improve identify more efficient vectors for CNS gene therapy.

So -- but now, for gene therapy manufacturing, that's one of the topics of today's meeting. And so far, the current platform technology, there are two

categories.

One is transfection-based. This is developed by Drs. Xiao Xiao and Jude Samulski in 1998. This is a very popular process for AAV manufacturing. And then if you look at the other category that's infection based, either HeLa -- producer cell line HeLa, rep/cap cell line, herpes virus, or Sf9 Baculovirus. Those are infection-based process.

But if you look at the current -- I give a snapshot of where we are in terms of manufacturing -- you can see here 293 transfections still dominate the manufacturing process. And second is a Baclovirus quickly catch up. And third on is a HeLa-based -- the herpes virus or adenovirus-based and herpes virus-based. So this is kind of current trend in manufacturing platform technology. However, if you look at the whole field, you will see CDMO's play a major role, only about 30 percent of the company, doing AAV themselves, and CDMO becomes a rapid-growth industry here.

So now, for AAV manufacturing, what are the

major challenges we are facing? So I would say it depends on many different factors, such as targeted tissues, eyes, versus muscle, and route of administration, subretinal injection versus systemic injection and patient population size or patient size, such as pediatric versus adult patients, and the serotype and transgene cassette also contributed to manufacturing. But the gap between the current producibility and the clinical needs is either a one-log, two-log, or three-logs, depends how big the patient population size is.

So the second issue is how are we going to close this gap? I personally believe we need -- really cannot just do by increasing the bioreactor size, and we need to enhance yield per cell. This will definitely require collaborations between vector biologists and bioengineers.

So one thing we should consider is AAV replication and packaging biology, understand there's a timing sequencing and a level of different gene expression. The second part is cellular factor. We

have to figure out the cellular factor that can further boost replication of packaging. And third is, ideally, we should have a producer cell line, real producer cell line, just adding the compounds that trigger entire AAV manufacturing.

And this we have a lot of work to do ahead. Of course, like any other FDA-approved product, quality control and the bioanalytics is very important. One of the major issues with AAV is empty-to-full ratios. And right now, because it's manufacturing we've still not optimized yet, it's 90 percent empty to 10 percent full, and if you do not have a special process to purify it -- but our goal is to reverse it, 10 percent empty and 90 percent full.

The second part is a biopotency assay, infectivity assay. This is very hard because, ideally, you should develop a kind of across different product pipeline, infective assay. And we also need a biopotency assay. This is product dependent.

And finally, it's about the vector genome itself. And currently, for many different reasons, we

really do not understand what we have in AAV package. I'm going to show you an example here. So if you put guide RNA into this construct, if there's a simple guide RNA structure, you can see you get a uniform band, single band. However, what's exactly in this band, we do not know.

My colleague, Phil Tai start looking to this black box of AAV. He developed this sequencing for ITR to ITR, every single molecule of AAV prep and to understand exactly what's there. You can see the majority of the vector here is full-length.

And however, if you put two guide RNA into the vector, and then in these head-to-tail -- head-to-head configurations, you can see you have many truncated genomes. And if you use the sequencing we call the AAV-Gp Seq we consider as a next-generation QC pipeline, you can see you virtually have no full-length molecule. You have many different truncated forms of the molecule. If without this technology, you do not know exactly what you have.

And however, interestingly, if you change that

configuration to head-to-tail of the two guide RNA, then you come predominantly a single band. And this is confirmed by sequencing itself. So this tells us we still have a way -- a lot of work to do to figure out quality control and give the best medicine, safest medicine to our patients.

And so finally, I want to summarize what's the difference between this individualized therapy-based traditional gene therapy. And so we have one problem. We have realized that, pre-clinical development, we need better understanding the genetic causes and the pathomechanism.

Depends on -- it’s loss of function, gain of function, autosomal recessive versus dominant, X-link or haploid insufficiency, this -- you will have a different strategy for gene therapy. And also, many ultra-rare diseases, there's no animal model for it. So this in vitro versus in vivo model versus normal versus disease model, expressing versus the function and versus the phenotype correction, those are the things we have to figure out at least, those ultra-rare

diseases with the patient of 1 to 10 to 100.

And also, the timing and the cost remain the same. If you do a gene therapy drug to preclinically develop this drug, it's the same cost, the same time. It doesn't matter it's 10 patients or 10,000 patients. And I don't think from NIH funding point of view, when you -- disease from a small -- I don't know how much funding opportunities we could get.

And the regulatory and supportive flexibility, again, to generate this data to support in vivo data for efficacy to help prepare IND and prepare the pivotal toxicology studies, I think the time and regulatory support required is same. Finally, GMP manufacturing and the QC bioanalytics, so most of the challenge remains the same. It doesn’t matter this drug for 1 patient, 10 patients, or 10,000 patients. And additional unique challenges include technology transfer and the process development lot cost remain the same. It doesn't matter it's 1 lot, 1,000 patients, or 10 patients.

And cost for the smaller batches may not be

even linearly scaled down. You probably cost more for small-pack batches. And 1 dose versus 100 doses, if we have existing patient treated with 10 patients treated, what about a future patient? Where we should store and maintain the stability and distribution of those gene therapy vectors? I think as that's some of those topics we should discuss after this meeting. Thank you very much.

**DR. TARAPERWALA:** All right. Thank you, Dr. Gao. Our next speaker is going to be Dr. Jason Gill from Texas A&M. He was born and raised in Canada and received his BSc and MSc degrees from Brock University and his PhD in Food Microbiology from the University of Guelph in Canada.

He holds a faculty position at the Department of Animal Sciences at Texas A&M University, where the major research focus in his lab is the biology and application of bacteriophages. These are often also referred to as phages. And you're going to hear more about it. These are viruses that can infect bacteria.

Specifically, the research in his lab includes

phage genomics, basic phage biology, and application of phages in real-world settings against many bacterial pathogens. Dr. Gill holds many joint appointments in the faculty of genetics in the Department of Microbial Pathogenesis and Immunology in the College of Medicine. And he serves as the associate director for the Center for Phage Technology and Interdisciplinary Research and Teaching Initiative, supported by Texas A&M AgriLife Research. So welcome, Dr. Jason Gill.

**DEVELOPMENT OF PHAGE THERAPY: PERSONALIZED MEDICINE AND INDIVIDUALIZED THERAPEUTICS - DR. JASON J. GILL**

**DR. GILL:** So good morning. I'd like to thank the organizers for inviting me here to give this talk. So what I'm going to talk about -- what I was asked to talk about development of phages, as a therapeutic and really, more on the manufacturing side. And so to understand the manufacturing part, we're going to have to understand more about the biology of that as well. This is my COI statement. So I did some consulting for Merck last year.

So to understand about the development of

phages as a therapeutic, we have to understand that phages are very diverse. And so Dr. Gao talked about adenoviral vectors. And they're quite variable. And so phages are probably the most diverse set of organisms on earth. They're very ancient, and they've been coevolving with bacteria for many billions of years.

They tend to be very adaptive to their hosts at the strain and species level. So they're very specific. They have very diverse genome content. So you'd have two phages that infect the same host which have really zero detectable DNA sequence similarity at all. So there's a large diversity there in terms of -- that drive how you do your developments. And there's also a lot we don’t understand about how phages work on a more fundamental level.

So a lot of phages carry like hypothetical genes, genes of unknown function, which as far as we can tell have no phenotype. But again, for regulatory purposes, that may become more important. So the development of phages, this is actually not a new idea.

So phages were actually used as a relatively mainstream therapeutic up until the 1940s when antibiotics were developed. And then they were kind of abandoned in the west and revived really with the rise in antimicrobial resistance, starting really intensely about 20 years ago.

So this is from an older paper. But this lays out two theoretical development pipelines for using phages. So the top one, you have this -- what's called “pret a porter” system. And this is what was talked about in the opening talk with this idea that you kind of have a mass-produced predefined product. So you'd isolate a phage or a set of phages against a particular pathogen. You would understand them as well as you could. You would have a GMP manufacturing process.

You take them through a regular phase one, two, three approval pipeline. And then, you would mass produce that product and then market it. You'd have like a CGMP-produced, very well-defined product.

And the alternate approach on the lower panel, in blue, is this kind of “sur mesure” idea, which is

this made to order idea. And so this is that you would have a collection of phages, maybe 100 phages, maybe 200 phages, 500 phages, in a library. You would get bacteriology back from a patient.

You would then identify phages that worked against that particular -- that patient's particular strain because remember phages are very specific for their hosts. And you would then work that up into some kind of product then administer that to the patient.

So the idea there is that when you have this kind of product, you have tying to the bacteriology. But you have a lot of issues on the regulatory side. So the product identity is not as clear in that kind of situation. The manufacturing is likely to be less controlled. And this really thought of -- this is about a 10-year-old paper. And this was thought of as really kind of a -- not necessarily with the idea of developing a large commercial product in mind. This is really a way to treat patients.

And so this kind of approach works well if you want to just kind of keep doing like expanded access or

eIND administrations, which have been happening. But it's hard to see how that would be commercializable. So I think what we're talking about here today is this personalized medicine approach, where you would want to take part of that sur mesure idea, where you have this library of phages, and try to then take that through some kind of regulatory process. So that could actually be a widely available, possibly even mass-produced product.

So product identity is pretty important for any kind of therapeutic. And so on the -- if you have a fixed product, that's a lot easier to define. So you'll have a phage isolate or a set of phage isolates. They'll be grown on a host or a set of hosts. There will be some kind of production and purification process that will be defined. And then you end up with a product at the end. So that's a lot more straight-forward, even for a biological.

And personalized approaches becomes -- the idea of product identity becomes a little fuzzier. So if you have, say, a collection of phage isolates, they

may or may not be grown on the same host. So you're going to have that variance. You're going to have not just new phages but phage host pairs in the manufacturing process. There's going to be possibly different manufacturing processes for different phages. They may not all work in exactly the same manufacturing process.

And then you're going to end up with, hopefully, some CGMP manufactured individual phage isolates, which you then blend together and then give to a patient. And then so when you're talking about product identity -- so is the product identity each of the individual phages? Is it the final mixture of phages? And right now, I don't know how -- if that aspect is very clear.

So the size of the library you're going to need is also going to be pretty variable between things you want to treat. So different pathogens have different levels of diversity, and that will affect the size of the library that you're going to need to have. So if you have very diverse targets, like for example,

Acinetobacter baumannii or Burkholderia cenocepacia, which are organisms that we deal with, the host range of those phages is really narrow.

So on the right, there's some data from our lab on some collections of phages against Acinetobacter baumannii. And this isn't the full table; this is just the table that shows where the hits are. There's another panel about this size, where the phages also don't infect any of those strains. So the host strains with these phages are very narrow. But if you look at organisms like, for example, staph aureus or listeria monocytogenes or shigella, those organisms are much more clonal. And in that case, you can have a smaller phage collection, which will cover most or more of those strains.

So the target really affects the diversity of the library. So if you're talking about a personalized approach, if you're talking about this for staph aureus, you may need a library of only 20 phages or 10 phages. But if you want to do this for Acinetobacter baumannii, you're probably going to need a few hundred

on hand if you want to actually be able to cover most strains of the pathogen.

So phages can be developed in a few different ways. So they can be completely natural. They can contain engineered components. This is -- some of this also is still really evolving in the field. So you can have the engineering be present in the phage chromosomes. Actually, when the phage replicates, that is a transmissible change, or they could also be expressed in trans. So really, just the phages you produced have the engineered or modified component, but they don't pass that on to their offspring. Or they may not produce any offspring at all, depending on how you've engineered them.

There's a few companies that are looking at synthetic phages right now. But you have to keep in mind, even when they're talking about a synthetic phage, it's still based on natural DNA sequence from other phages. It's just been pieced together. So there's a few different ways then that these are being developed. There's a replicative phage therapy, which

I call this the classic approach.

So this is you're taking natural phages from the environment, selecting them, working them up into some kind of treatment, and then they are going to infect cells. And they're going to replicate and lyse those cells and release progeny. And that can happen with naturally occurring phages or with engineered phages.

And another route which is being explored is using highly engineered phages, which don't necessarily replicate. And they will -- they might just adsorb to a cell and then deliver some kind of cytolethal agent, like a CRISPR protein or something else that would cause the cell to die. Or it's possible to have a phage deliver a genetic payload to a cell to alter its phenotype, for example, to just remove resistance plasmid. Or it's even been proposed to say allow the cell to now start synthesizing new metabolites and that -- this is like a microbiome engineering type of thing.

But these are various ways that you can -- they are neat phage tricks that you can do. So they're

quite versatile in how you can engineer them. And this isn't exhaustive either. I'm sure people are thinking of all kinds of wild new ways you can use phages.

So one of the limitations here is the knowledge base of phage biology as it exists today. So phages are relatively complex viruses. This is a map of the genome of phage lambda. And you can argue that phage lambda is the best understood organism in biology because of its long history of study. It has about a 49-and-a-half kb genome, as you can see here. But even though this phage has been studied for, like, thousands of person years of work likely, there are still some genes we actually -- the functions are not known.

So if you can delete those genes, they don't appear to have a phenotype. And those are highlighted there in green. The rest of it is all pretty well understood.

But then we move that focus from lambda. This is what we call an inch wide and a mile deep. So we know a lot about lambda. If you move that focus over just a little bit, this is a group of phages that are

morphologically similar to lambda.

They infect salmonella. They're called 9NA-like. 9NA is the first of this type to be isolated, so that's what they're all called. So they have a relationship to lambda. They're roughly the same size, a little over 50kb. But if we look at this group of phages, there's 176 genes in this group of phages.

Only 32 of those genes actually have a predicted function. And 143 don't have a known function, at least not what we can tell bioinformatically. And 68 don't even have a counterpart in the database. So they're completely novel genes.

And this is not that unusual when you're finding new phages against new bacterial targets that you'll have a section of protein-coating genes. Actually, they're the first example of those genes that have been found in biology. So we've done this for Caulobacter. And in that case, I think something like two-thirds of the genes were actually novel in those organisms.

So phage production is going to be based around -- it's a biological manufacturing process. So they're generally going to have to be propagated in a live host. It's not very hard to get titers of 10 to the 9 or 10 to the 10 pfu per ml in a culture. That's just in the lab. If you optimize that, you can probably drive that up to 10 to the 11 or maybe 10 to the 12 even.

There's a few different ways you can get from your crude production lysate down to the final product, which are up here. So you're starting with a lysate to somehow -- and you can use a few different methods to take you from that, which is going to be the crude liquor, basically, of the culture, down to somewhat of a clarified lysate. And then there's a few technologies that exist to take you from that to kind of a relatively pure concentrate, which you can then put through additional polishing steps, too, so we can help remove endotoxin or further purify it.

So the clarified lysate is really just going to be spent cultured media with phage in it. It's

going to have a lot of cell debris and media components in it. A clean concentrate might be relatively pure. It's mostly phage. And it will be more concentrated.

Most of the media components have been removed and the cell debris. The endotoxin level will be reduced. It may not be as low as you need, so you may need to do additional steps to remove endotoxin or to remove additional contaminants until you get to a purified phage, which you would then blend and package.

So the methods are still very much in development. And the different companies have their own internal processes for that. But they're not completely alien, I don't think, to the world of manufacturing. This is a -- they're not that different, say, from production of common proteins from bacteria or certain viral vectors or vaccines. You're having a biological production process. The technologies aren't -- they're comparable; they're not completely different.

But also, it's important to remember that the production process here is likely to be a major part of

a company's IP around that product because the phages you can't necessarily patent themselves if they're natural. So one of the things you can have you can patent, and also even protect the trade secret, is the manufacturing process. And so you have to keep that in mind when it's going through the regulatory process.

So the purification method that you use will probably then determine that product identity. And also, you have to remember that, because phages are very diverse, not all phages are going to necessarily respond the same way to the same manufacturing process. So you may have to have, basically, a -- you might have a set process that you're going to have to have variances built in for or maybe even several different parallel processes, depending on the phage you want to produce. And they can vary in terms of their pH stability and their surface charge, their stability in various buffers, and formulation agents. And so you're probably going to need to be able to have room for adjustment depending on different phages from that -- from a library.

So just a note about phage production though. So the technology really to maximize that yield would really be a big help in this field. So this is a picture from the Patterson case that we were involved with, with the groups from UCSD -- and Dr. Schooley's here -- and the group from the Navy.

And so when phages were actually administered to Dr. Patterson, they were administered as doses of 10 to the 9 pfu and diluted into 100 ml Ringers and infused. So 10 to 9 pfu is actually not that much. We can actually grow cultures of 10 to the 9 to 10 to the 10 pfu per ml in the lab. And you can grow up a couple liters of that even just in the lab scale.

And so in theory, one liter of culture could produce like a thousand doses of this phage for a patient. But in practice, by the time we actually went through our purification process, our recovery was something like 0.1 percent. So we had to produce multiple batches. So any technology that you can use to -- if you can recover even half of the initial particles that are in the -- that initial culture, that

makes it much more efficient than at least what we've been able to do in the lab so far in a rush. So having an optimized production process certainly helps.

So if we're looking at then producing phages possibly of different strains, so the variation of the host is also going to be a contributing factor to your product identity. And it's going to determine partly the contaminant profile. So if you had a very diverse phage collection, you're likely going to have more than one host you're going to have to grow all these guys on. And so different strains of the same species, they can vary in their toxin production, their LPS structure and how pyrogenic it is. Mobile element content will change. And also, many bacterial strains carry multiple prophages.

And this is just a map from a relatively old review. But this shows maps of -- these are actually active prophages in bacterial genomes. And so it's not that unusual for the average bacterial genome to carry one to three functional prophages. And when you propagate the phage, your phage, your virulent phage,

on that strain, some of that prophage will be induced and will end up in that culture as well.

It likely is a very minority component. For example, if you have 10 to the 10 of the phage you want, you might have a 10 to the 4 or 10 to the 5 per ml of this other phage. But it's going to be there, and it's going to vary depending on the strains that you want to use.

And these are an issue because they could possibly, in theory, transduce DNA from your propagation host into another host in the patient or possibly between strains in the same -- in the patient once they're administered. Maybe, right? These are all just theoretical possibilities.

It is possible to take bacterial strains and engineer them to reduce their contaminant profile. So this is an example of the bacillus strains, the root of strain 168 that as it's called MG1M, which is developed by, I believe, a Japanese group. And really, they just took the bacillus strain 168, which is kind of the go-to model strain for bacillus subtilis, and they removed

all the prophages and the polyketide synthesis and a whole bunch of other stuff they thought the cell didn't really need. And they ended up removing about 23 percent of the genome.

And this was for a -- for using the cell as a biofactory. They wanted to be able to put your own metabolites in here. It will grow more efficiently and make more of the enzyme or whatever it is that you wanted. But you could theoretically do the similar thing here for phage hosts as well and remove all the components that you don't want from that genome. It's not a -- it's a nontrivial undertaking to do this.

So if you had to do this, say, with 50 strains to propagate your phage, that will be -- that would be an undertaking but certainly doable. It also maybe is possible to generate like a universal host or at least a much broader host range host that you have. So instead of having to take your hundred phages and propagate them on 50 different hosts, you would propagate them on five different hosts, which would certainly simplify your manufacturing process. It's

also maybe possible that you could express phages from a completely orthologous host. For example, in yeast, they could be recombinantly produced in a yeast cell or some other method. Again, I'm not aware of anybody actually doing that, but maybe it's possible.

So product identity, also the -- in terms of active ingredient concentrations, are important. So in a phage product, the actual concentration of active ingredients is likely to be very low, in the order of a microgram per ml or less. So the kind of standard HPLC peak or something you're looking at for a drug is likely not going to work here. And so the way people normally evaluate the potency of the product then is turn to an active titer. You're looking for plaque-forming units on a lawn of bacteria.

And so that's the way we have done it. As far as I know, that’s the way other groups are doing it as well. And so you actually are measuring infected particles, which is nice. They have to be viable to form a plaque. But you also have to be aware that the number of plaques you'll get can vary a lot depending

on the host that you put the strain on and the plating conditions.

So this is an example from our group of some staph aureus phages. And you can see the plating efficiencies can vary by half a log, depending on the host you put them on. So you can get -- if you have your phage product, if you titer on one host, they'll tell you you have 10 to the 9. A different host might tell you you have 5 times 10 to the 9.

And so you have to think about these plaque-forming unit assays. It's kind of that's kind of the minimum number of viable phages that are in there. If you could find a better host that gives you more plaques, then that would kind of -- that raises that floor up.

Another issue then is product impurities, as well. So crude lysate contains media components and bacterial cell debris, and it's going to have endotoxin in it if it's a gram-negative phage. And these range from relatively harmless, right? You're going to have some sugars in there. And also, it could be very

dangerous like endotoxin. And there has to be something -- a decision arrived at really on what impurities you can tolerate in the final product.

And this is probably going to vary depending on how you're administering it. So if it's going to be a phage product for oral or topical use, you could probably tolerate more impurities than you would for something which is going to be introduced parenterally. And again, this is -- in, at least where I am in the field, nobody really knows what the rules are right now. So that's something that has to be developed, I think in conjunction with the regulators and the people who are actually manufacturing this to decide what are the acceptable impurity profiles that are going to be tolerable because that will then also drive the manufacturing process as well.

The other issues around phages, which are not really necessarily manufacturing-related, but they're intellectual property related. So patent protection for phages are difficult to determine. They are products of nature. So engineered phages are certainly

more patentable than the natural ones.

There's a lot of prior art dating back to the 1920s. For example, there are patents that exist that they have patented the idea of using phages to treat bacterial infections, an idea which was invented in, I believe 1917 or 1918. So it's more difficult, then, to get intellectual property protection.

And if your product is actually a viable phage, it's going to replicate in the host, you can't necessarily rely on trade secrecy either because anybody can just take your products and just culture the phage out of it. And then, they've got the phage. So trade secrets aren't going to work there either, so some kind of intellectual property protection is still -- that's still evolving.

They're very narrow spectrum. So I think it's harder to get companies to get involved in this field because you're developing very narrow-spectrum treatments, which are -- you're not going to be able to cross-market them very broadly, so that makes, I think, a lot of companies reluctant to invest.

And really, the idea around this is the traditional business model of a single mass-produced antibiotic aren't going to work, of course, for personalized medicine. But something we've been hearing a lot lately in the last few years is about just how the model of antibiotic development in general -- a lot of companies have just gotten away from developing antibiotics because they're not profitable, because they're -- you're not going to have a large market. They're expensive to develop.

And if that's true for small molecules, it's also true for this. And so if there's a fundamental issue with the economics of this developing anti-infectives, that's less of a scientific issue. I think it's more of an economic or a policy issue. But it also -- that's going to drive the availability of these products.

So just to wrap up, so some solutions that -- to address some of these things, we need better understanding of some of the non-paradigm phages that are infecting different hosts. Like we know a lot

about a few phages that infect e coli and salmonella but relatively little about most other phages -- and also, really to be able to work in these ESKAPE pathogens and more tools to be able to do molecular biology in wild clinical strains, rather than just model strains. There needs to be some more guidance, I think -- and this is the purpose of this workshop, to address issues around what are the production standards, contamination profiles, how you define product identity in this case, and how you develop IP protection and that IP protection may actually help get more investment in the field and, finally, just to address that policy and economic landscape, really to make actually any infective development just attractive in general or to have it -- make it happen some way.

All right. So I would like to thank the organizers and thank the audience. And I'll wrap up.

## PANEL SESSION WITH Q&A

**DR. TARAPOREWALA:** All right. So we will -- I

now invite the speakers and the panelists to come join us here in the front. We'll take a few questions from the audience. And we may take a few questions online if there are any. And please feel free to state your name and affiliation. And also, keep your questions to the point so that we stay focused on the topic of the session, which is manufacturing.

Okay. So we have the speakers, and then we have Dr. Roger Plaut from the Office of Vaccine Research and Review and Ms. Anita Richardson from the Office of Compliance and Biologic Quality, all in CBER. And I don't see any questions and none online as yet. So I will take the first stab.

So I was wondering if -- we talked about the challenges. And I was wondering if maybe we could discuss what are the advantages of -- what have we learned from the rare and orphan disease drug product development that can be directly applicable to individualized therapeutics?

**DR. GAO:** So I believe the experience from the ultra-rare disease or rare disease gene therapy can be

very helpful or informative to developing the individualized therapy because I think, if you think about the process of discovery or develop gene therapy product -- it doesn't matter for ultra-rare, or rare, or moderate-rare disease, or prevalent diseases -- I think should be the same. And actually, the good thing is, unlike large applications such as Duchenne's muscular dystrophy, each patient may need several, 10 to 15 or even up to 10 to 16 dose, vector dose, per patient. But for those rare diseases, the population is much bigger -- much smaller, and particularly ultra-rare.

So the manufacturing burden is less. I think current technology should be able to apply for manufacturing. So that's advantage.

**DR. TARAPOREWALA:** Anybody else who would like to take a stab?

**DR. GILL:** I have a question for Dr. Gao actually. So for these ultra-rare diseases, is the manufacturing mostly just lab scale at that point, or are you still finding a CRO to try to make this stuff?

**DR. GAO:** Yes, this is a very interesting question. Based on our experience as a gene therapy center at UMASS and Rare Diseases Institute, so far, I think for those kind of few patients, single patients, or a couple patients, even academic viral vector core should be able to address the needs. And we have been very much enjoying this kind of collaboration with academic GMP manufacturing core. I will say it's quite -- much easier than bigger trials and bigger disease population.

**DR. TARAPOREWALA:** We'll take one from the audience.

**GUY:** So my name is Guy (phonetic). And I don't know if you can hear me. Is the microphone working?

**UNIDENTIFIED MALE:** This one's working. You can come back here if you want.

**GUY:** Oh, okay.

**UNIDENTIFIED MALE:** Just come back here. Use this one.

**GUY:** Okay. It's an individualized microphone

here. All right. So this is a question direct to Professor Gao. You mentioned that manufacturing capacity is clearly the challenge to produce AAV. Obviously -- and if we can actually create a cell line that can produce high titers of the AAV, you don't have to do the transfection. So what exactly the challenges are they and to produce such a cell line, if we actually can do that and the manufacturing capacity should be easily overcome? So I'd like to hear your opinion on that.

**DR. GAO:** Thank you. I think you refer to AAV production. So the major issue is that it's we need regulatory protein and a capsid protein for manufacturing process, particularly REP, regulatory protein. That protein is very cytotoxic. And the capability to generate stable integrated and producer cell line, introduce the REP express under controllable levels, particularly inducible levels, it has been a major challenge. So that could be one issue.

The second issue is that other than replication biology and packaging biology, AAV very

much depends on cellular factors to -- actually, cellular factors contribute to all this replication and packaging process. Our understanding of the cellular factors that can enhance or improve gene therapy vector production, we do not understand. I think if we can understand the REP, where you establish your stable REP cell line, as well as understand the cellular factors and, importantly, if we can come up much tighter inducible system that you can pharmacologically or some other ways induce regulatory protein expression, that will significantly give us opportunities to generate so-called real producer cell line.

**DR. TARAPOREWALA:** Thanks. We can take the next question from the audience.

**MR. ALDRICH:** Hello. Good morning. My name is Steve or Stephen Aldrich. I'm 64 years old. I'm the founder of a company called MyCancerDB. I am a stage-4 adenocarcinoma of the esophagus patient.

I was diagnosed in March, late March of 2017. For those of you who aren't familiar with that, most people die for sure within two years. It's a very,

very deadly cancer.

Here I am three years later. Part of the reason is that I was able, being a Harvard-trained biologist, to recognize that if there was an answer to my problem , because the prognosis is -- or the prescriptive care is strictly palliative, that it was going to be found in my data. And so I had -- was very fortunate to be able to have all of my fundamental sequencing data, my cancer genome, my healthy genome, my microbiome, et cetera, and the related datasets, done. And with that information, I was able to leverage it to, first, identify a clinical trial that kept me alive for a while.

And while that was going on, I had designed, tested, and manufactured a fully personalized neoantigen peptide cancer vaccine. And as a consequence of going through that, I realized that the current system was broken and that we needed to be able to accelerate access to this kind of fully personalized N of 1 therapy to the 1,700,000 patients who were diagnosed with cancer in the U.S. last year and

especially the 610,000 that died.

So a couple of points I want to make about the panel. The first is that, in order to enable the kind of gene therapy that was presented, we have to completely reengineer the entire system. And that reengineering starts with the fundamental genetic data of the patient, the sequencing data.

Clearly, to all your presentations, it's the sequencing data that's fundamental. Whether it's for phages or for people, it's the sequencing data that we must have. But who controls that data?

If that data is the most important personalized information about an individual, shouldn't we create an infrastructure that keeps control and ownership of that data with the individual? I just thought I'd bring that to the panel and ask them for comment. I think what we're doing at MyCancerDB is putting in place that infrastructure.

And the idea is to be able to leverage that information to virtualize the supply chain in a way that shrinks the cost, speeds up the development

process, and maybe does something about the 610,000 people who died of cancer. So I -- last year, which is 12 times the number that died in the Vietnam War. I'd be interested in your comment.

**DR. TARAPOREWALA:** So I guess that was a comment, maybe not a question. And if nobody in the panel has a comment towards that, we might move on to the next question, if there's one from the audience.

**MR. CAMPBELL:** Hi. This is Joe Campbell from NIAD. I have a question for Dr. Gao. I was wondering -- you mentioned the advantage of flipping the ratio from 90 to 10 to 10 to 90. And that obviously would be a great advantage. And I'm just wondering if you have any thoughts on whether -- what's likely to be important, the vector, the payload, or the strain in which you grow it in? And I guess one further question. Have you ever, thought about making the unfilled vector have something like an endonuclease, a very rare endonuclease cut site that the filled one wouldn't have, so that you could select against it?

**DR. GAO:** Very interesting questions. So this

flip from 90 to 10 to 10 to 90, it's quite challenging. Actually, if you ask me the answer, I don't have the answer. But I know where to go.

That is what I just talked to the first person who asked the question from [inaudible]. It's the same issue. It's we have to understand how AAV replicates and packages.

And we have to understand how cellular factors can help us. Because AAV itself, it's almost a virus. It needs a lot of things from host and from the helper virus. So that is definitely one thing to consider.

Second thing is the purification methods. If we are defective -- I mean virus is defective to packaging for particles. But if we have a scalable GMP-compatible process to separate empty from full, then we should be able to enhance the potency of our drug, reduce immunogenicity of those useless empty particles.

**DR. TARAPOREWALA:** Okay. Thank you. We'll take the next question from the audience.

**MR. KELLY:** Good morning. My name is Matt

Kelly from Sarepta Therapeutics. I just had a follow-up question on the empty/full ratio.

**DR. TARAPOREWALA:** Could you speak up a little bit because we cannot hear you.

**MR. KELLY:** I just have a follow-up question on the empty/full ratio. As Dr. Gao highlighted, a 90 percent full count would be acceptable. From an FDA perspective, a commercial scale, is this also an acceptable reality for an approval?

**DR. TARAPOREWALA:** So I think at this point, we are taking questions to see what the researchers think in how to develop individualized therapeutics. And I think Dr. Gao just mentioned that the empty ratios does affect the potency and does affect the purity and the immunogenic load. So I think that applies rather product is in clinical trial or being developed for licensure. So I think his answer is pretty broad and comprehensive in that respect.

**MR. KELLY:** Okay. Thank you.

**DR. TARAPOREWALA:** We'll take the next question from the audience.

**MS. HESTERLEE:** Hi. This is Sharon Hesterlee from the Muscular Dystrophy Association. So I appreciate very much all the improvements in process development that have helped increase the yield in manufacturing. But I'm wondering if we're going to hit a limit at some point where we really can't further increase the yield in a practical way. And should we be looking at things more like targeting? You mentioned early on that that was one of the issues.

For example, AAV9, if you're trying to target the brain, the vast majority, if you go systemic, is still going to liver. So I could see that you might get an order of magnitude improvement if you could just better-target vectors rather than increase manufacturing. Is that something to consider?

**DR. GAO:** Yeah. That is a great question. Actually, that's the whole field of gene therapies and particularly AAV gene therapies. We have been struggling for 50 years. That's what we're trying to do.

But what I have to tell you is I think recent

research demonstrated what is achievable. I refer to Dr. Ban Deverman's publication in *Nature Biotech* a couple years ago. I think he demonstrated that you can accomplish that more efficient cell type, tissue type, targeting. But the only issue we're running into now, soon afterwards, we realized what you select against will be what you get out of the selection system.

So previously, the selection was done in mouse. And we generated the super mouse CNS vectors. So the next stage, I think as was discussed by Dr. Marks, that we look into potential humaned mice, as well as probably primates, animal models, to do that selection. I think that people know how to do it, just have to switch the system.

**MS. HESTERLEE:** Thank you.

**DR. TARAPOREWALA:** We'll take the next question from the audience again.

**MR. MCFARLANE:** Thanks. Richard McFarland for the Advanced Regenerative Manufacturing Institute. So as Dr. Gao said for the hyper-rare diseases, you think maybe laboratory scale manufacturing would be

sufficient. It seems that raises -- we've done a lot of talking about traditional CMC, but it seems that also raises questions about distributed inspection and regulatory compliance for those centers. And I wonder if you can share any thinking about what you've had about how you're going to inspect those facilities if they do exist across multiple hospitals.

**DR. TARAPOREWALA:** You can go ahead, and then Anita can weigh upon it. Go ahead, Dr. Plaut.

**MS. RICHARDSON:** Richard, thank you for that question. And I'm not sure I have a simple answer. I think that we are looking at those types of facilities on a case by case basis, taking all the facts and circumstances and the product into consideration and, also, the flexibility needed in this field.

**MR. MCFARLANE:** Well, Anita, I'm glad you don't have a simple answer because I don't think it's a simple solution. But I think it's something that I know we're thinking about and I think others may be thinking about. So maybe it's a place for focus workshops or guidance, something in the future to help

think through those issues as you go from an IND to a true manufacturing facility.

**DR. TARAPOREWALA:** Okay. We'll take the next question from the audience again.

**MS. GALEMBO:** Marian Galembo from BiomX (phonetic). And I will talk about phage therapy. So Dr. Gill has really put forward a whole lot of the dilemmas and the problems that we may be facing with individualized therapy and manufacturing in hosts that could be derived from individual patients and each one with different characteristics. I would like to hear a bit about the Agency's approach on how to handle those differences and variations in terms of impurity characterization, if there is any thoughts about that.

**DR. PLAUT:** So the goals of this workshop are to get feedback from the community, from stakeholders. So we are not really prepared to make any public statements about our -- how we're regulating these products or how we intend to regulate these products. I can tell you that every decision we make is based on science, based on evidence. And we ask sponsors or

potential sponsors to come to us and provide all their data and to propose to us what they think their specifications should be, what they think the limits should be.

And then we have a discussion with the sponsor. This is one reason why we think it's very important that sponsors interact with us as early in the process as they can. We're happy to have these sorts of discussions in -- early on in development. But again, I think it's important for you to understand that we have an open mind, and we make our decisions based on science and evidence.

**MS. GALEMBO:** Thank you.

**DR. TARAPOREWALA:** Thank you. We'll take the next question from the audience again.

**MS. WALKER:** Hi. My name is Karen Walker. I'm from Genentech. I want to thank you both for such good talks.

I actually have a question for both of you. In each of your cases, you talked about manufacturing challenges from an intellectual property perspective

and a capacity perspective. And Dr. Gao, you talked about the large role that CGMOs are playing in the field.

And given that these are individualized therapies and given that manufacturing platforms and establishment of these platforms would drive down cost, what are your ideas about how we could open up access to those platforms so that we could really drive targeted individualized therapy treatments to patients with predictable outcomes?

**DR. GAO:** So I have to say, not myself, but two weeks ago, NCATS and P.J. Brooks, and other colleagues from NIH, they held a meeting on AAV gene therapy manufacturing. And that meeting, their whole purpose was really understand the landscape, understand the challenging, understand to kind of brainstorm this, all the scientists, and regulator and administrator to figure a way to ask -- to address that question. So I think I don't know whether P.J. is still here or not. He was here in the morning.

They do have actually, in after reading

communications, I think they gradually -- is in the process of formulating some kind of solutions for ultra-rare, rare, giving these individualized therapies.

**DR. TARAPOREWALA:** Dr. Brooks, would you like to comment on that?

**DR. BROOKS:** Yes. Thank you for that. Thank you, Guangping. At NCATS, we are certainly interested in these kind of broad issues and making these platforms more widely available for these types of treatments. And, specifically, our -- the Cures Acceleration Network, which is part of the NCATS Council, is very much focused on addressing this issue.

And part of the goal of the meeting that we had a couple weeks ago was to identify the opportunities that might be available to make certain investments in research approaches to really bring this forward. So it is something that is under active investigation, by NCATS as well as with other -- our other partners within the NIH and industry, and of course the FDA as well.

**MS. WALKER:** Thank you. And just maybe a comment. I think this also speaks to the fourth bullet point on the slide, which is it would be interesting for FDA to think about additional guidance on how we could have regulatory flexibility around establishing production platforms for these individualized therapies, which then would change the focus of the review more to the therapy itself and the safety and efficacy of those, where we could maybe control some of the variability around the platforms.

**DR. BROOKS:** That issue might come up later on in the afternoon as well.

**MR. ALDRICH:** Can I just follow up that excellent question and the point? There was actually a question in my earlier comment. And it has to do with -- for the reengineering that we're going to have to do around manufacturing, there are methodologies that are well-known to the FDA that are used in the regulation of, for example, the food industry, where you use hazard and critical control-point methodologies to regulate, in a scientific way, the safety of a

particular supply chain.

And I -- that is something like that, where we substitute the regulation of the end product as a standard product, with the regulation of the process that we use to get to that end product, is inevitably the endpoint, in my opinion, of enabling N of 1 therapies to come to fruition. And this isn't a hypothetical issue for me. This is a very concrete, real issue for cancer patients everywhere, when it comes to something like access to fully personalized neoantigen peptide cancer vaccines.

So I'd just like you to comment on -- perhaps our two representatives from CBER -- could comment on, is there an awareness within the FDA of this idea of using well-known GMP and HASIP-related methodologies to -- as a basis for approving an “N of one” manufacturing process, and if not, why not?

**DR. PLAUT:** So again, I will say that we are openminded about these different approaches to these kinds of therapies. And we see that the IND process, as it stands now, is appropriate for the process for

getting products into the clinic. For as far as how a product or a process could be -- could lead to licensure, that is something that will remain to be seen. We don't really have any sort of policy statement to make at this point. But again, we have an open mind about these issues.

**DR. GILL:** I'd just like to make a point. So on the phage side, that's sort of -- I think what we're looking at, is that you have to have kind of the process approved rather than individual phages. Because at least the way the field is moving right now, if you're looking at, say, a personalized therapeutic, say, for Acinetobacter baumannii, there's going to be a collection of 200 phages or 500 phages. You're not going to have detailed preclinical and clinical data on all of those phages. You're going to have maybe on the subset of those.

And then the rest of them are going to be kind of carried along, based on some criteria that are set -- that they look like the phages that work and so on. Because I think if you require that every phage goes

through a full clinical evaluation, then it's really never -- I don't think it's ever going to happen because you can't run clinical trials on 200 individual products.

**DR. TARAPOREWALA:** In the interest of time, because we have a very good number of sessions, I urge you to -- the two attendees that have gotten up to ask questions, I'd urge you to get hold of the speakers offline -- they will be around here for the whole day -- and perhaps ask the question. So in the interest of time, let's thank the speakers and the panelists for a very nice session. Thank you.

**DR. RAYCHAUDHURI:** So I'd like to thank all the speakers, the panelists, and the audience, for a stimulating discussion. And I'm really sorry we had to cut it short. But please do take advantage of the speakers being here to speak with them one on one.

We'd like to now take a short, maybe 10-minute break, just to stretch your legs, and we will reconvene with session 2. Thank you.

**[BREAK]**

**SESSION 2: TOOLS FOR SAFETY TESTING AND DEVELOPMENT**

**DR. RAYCHAUDHURI:** Okay. Could everybody please take your seats because we'd like to get Session 2 started? So that was a short break. And I hope you had a chance to stretch your legs. We are ready to start Session 2.

I'd like to introduce Dr. Sandhya Sanduja, who will moderate the session. Dr. Sanduja is acting team lead for Pharmacology Toxicology Branch I in the Division of Clinical Evaluation, Pharmacology, and Toxicology in Office of Tissues and Advanced Therapies. Dr. Sanduja will moderate this session, which is on nonclinical evaluation and tools for safety testing for individualized therapeutics.

**SESSION 2 MODERATOR INTRODUCTION: DR. SANDHYA SANDUJA (CBER)**

**DR. SANDUJA:** Thank you, Gopa, and thank you, everybody who's present here as part of our workshop to facilitate end-to-end development of these individualized therapies. So after a very interesting and engaging Session 1 on manufacturing of these individualized therapies, it is my pleasure to take you to our Session 2, which will focus on tools for preclinical testing of these individualized therapy products that are regulated by CBER. The session will begin with presentations by our distinguished speakers, Dr. Albert Seymour from Homology Medicines, Dr. Malachi Griffith from Washington University School of Medicine, and Dr. Keith Joung from Harvard Medical School. These presentations will be followed by a panel discussion, which will be led by our speakers and our CBER subject matter expert, Dr. Zuben Sauna, and our audience.

All right. So to give you a high-level overview for this session, let me begin with this schematic, which shows the traditional drug development pathway. The preclinical testing paradigm for individual therapeutic products looks very similar to

these other therapeutic modalities, where efforts are spent during the discovery phase. They focus on identification and optimization of the lead candidate, followed by IND-enabling preclinical studies that evaluate and establish proof of concept and safety of these products.

However, when we talk about individualized therapeutic products, the key distinction -- obvious distinction that these products have are that they are patient-specific. They are patient-tailored products, and testing a healthy individual is either not feasible or not ethical. So this is where the standard paradigm of drug development won't apply.

During our session, we will hear from each of our speakers some of the key challenges that are encountered during preclinical safety testing and development of these individualized therapeutic products. We'll also hear from them what are some of the opportunities we have to address these challenges, including some of the regulatory -- the existing regulatory framework to address these challenges, and

these challenges and opportunities, how they are perceived by the developers as well as regulators. So as we know, these products are patient-specific. These are tailored for either one or a small number of patients, instead of being tested in healthy individuals.

So this brings in an inherent challenge associated with these therapeutic products. And what we expect from a preclinical testing program for these individualized therapy is, that since these are going into one or a small set of patients, to strike a balance or to strike that favorable benefit-risk profile, preclinical evidence to support the rationale for safety of administration of these products and patients. Such support must come from one or more preclinical studies that are conducted in a relevant animal model of disease using the intended route of administration, since for these individualized products, many times, these can be rare or ultra-rare diseases, where the only patient population is pediatric and in those cases, preclinical studies need

to establish prospect of direct benefit, as is required by Code of Federal Regulation.

So fulfillment of all these parameters can get extremely challenging in the absence of a relevant animal model of disease. When there is actually a relevant animal model of disease, there may be other challenges associated with preclinical development of these products.

And these challenges may vary. They may arise on a case by case basis and may include appropriate dose-level extrapolation, delivery with respect to the intended clinical route of administration, the procedure and device, as well as informing the appropriate clinical monitoring for the clinical trial. For in silico or computational tools that are used for preclinical testing, there are challenges that lie in validation of these algorithms to test -- and other test methods for robustness, whether they can confidently and reproducibly perform to the desired standards of safety and activity of these personalized therapeutic products.

Some additional challenges, which can arise later in development, may include additional -- conduct a requirement of additional nonclinical studies that may be needed, depending on if there are significant manufacturing changes that happen during later part of development, also for the potential for development and reproductive toxicities that may be present. So these challenges, which may actually seem as hurdles to begin with, may not necessarily be roadblocks to development of these individualized therapeutic products. Instead, they may be taken as opportunities which can drive innovation, so particularly, with these products, where we know there is so much science-based evidence in development.

So they can drive innovation, particularly advancement, in science and technology for better models and approaches to preclinical testing. For example, in silico methods that are used to inform safety and activity of products can have adaptive design to them. And as our experience -- clinical experience grows with these products, that adaptive

design can be -- is incorporated in the tools that are used to inform safety and activity.

Similarly, innovation happens when novel in vitro methods are being developed. There can be -- we have seen examples where patient-derived IPSCs or patient-derived organoids can be used, particularly when a relevant animal disease model is not available. And there, such in vitro models can actually allow for reduction, refinement, and replacement of animal testing. Innovation can also play a role in developing relevant and more robust in vivo models for testing safety and activity of these products.

Next is collaboration. These hurdles can actually be instrumental in driving collaborative efforts, knowledge sharing in the community. So instead of reinventing the wheel, as Dr. Marks alluded to earlier, every single time, especially when using a similar vector or similar platform technologies, stakeholders may have the opportunity to leverage existing preclinical and clinical data. That way, we are harmonizing our efforts and leveraging data that's

already available to facilitate a faster translation to the bedside.

And finally, these hurdles are instrumental again in driving engagement with regulators, in basically interactions with regulators to discuss the preclinical program and how we can all agree and come to terms for a feasible path forward for a specific product. So with our session -- as we start the session, after hearing from our speakers, I think we all will be engaging in a discussion where the key points to discuss would be what are some of the challenges that are associated with preclinical testing and development of these products including: platform-based versus any product-specific concerns, use of computational tools in safety testing of these products, how leveraging existing nonclinical data across similar products can be done, and regulatory approaches and flexibility to preclinical testing of these products.

So without any further delay, I would like to welcome our first speaker, Dr. Albert Seymour. He's a

chief scientific officer of Homology Medicine, a company that's developing gene therapy and gene editing technology to treat patients for rare diseases. He has a Biology from University of Delaware, an MS in Molecular Biology from Johns Hopkins University.

And he received his PhD in post-doc training in human genetics at the University of Pittsburg. He has more than 20 years of experience in taking human genetics to pharmaceutical RND, resulting in delivery of multiple therapeutic programs into development. So we welcome you and looking forward to your presentation.

**PRECLINICAL APPROACHES/CHALLENGES IN DEVELOPMENT OF INDIVIDUALIZED THERAPEUTICS - DR. ALBERT B. SEYMOUR**

**DR. SEYMOUR:** Thank you. Thanks, everybody, and first, thank the FDA for giving me this opportunity to come and talk a little bit about some of the preclinical approaches and challenges to developing these individualized therapeutics. I have to admit,

when I got the invitation, I really sat and gave it a lot of thought, working with my colleagues as well, for what are some of these challenges? Because we've been focusing a lot on bringing therapies to rare, ultra-rare disorders. And so I think a lot of those unique opportunities and challenges fall also within very individualized therapies.

And so I sort of pulled a collection of these together. So one of the things I looked at right away is some of the work that actually came out of Dr. Yu's lab out of Children. And this was -- really got a lot of press. But it really exemplified that, where there's a need, there is an opportunity to bring these forward. And this was when publishing in *New England Journal of Medicine* with this patient-customized oligonucleotide therapy for a young child with a form of Batten's disease.

And in ten months, going from sequencing, identifying the unique mutation within that patient to having an oligo that could actually correct that to them being able to treat that patient, was just

fascinating to actually read and see how they were able to go through that in leveraging some of the aspects around cell-based models from that individual patient because there wasn't an in vivo model. But then you could also pull some information that was also available on just the chemistries of the unique oligonucleotides.

So with that, there are a lot of platform data that can be leveraged to improve the efficiency. But as we were thinking about this, there are really three buckets that go into this, that the fundamentals of benefit and risk assessment must still apply. We are still bringing therapies forward to treat human patients.

The other aspect is -- you heard from some of the earlier speakers, so Dr. Gao, and then some of the work that we're doing at Homology, there's single administration versus chronic dosing. So something like AAV, it's a single administration. It brings, I think unique challenges to an individualized patient because of the ability you really can only dose once.

You really have to get it right that first time versus something that you can do with chronic dosing. Perhaps you can come in with a much lower dose and work your way up to look for activity.

And then finally, with that, there are very modality-specific requirements. And I'll walk through some of these and exemplify these as I go along. So as I think about these considerations, establishing the fundamentals of benefit and risk, I really broke it down into two categories, product-specific -- and what I mean by that is that the actual -- if you're going to replace the gene, the actual molecule that you're going to replace versus a platform. So this would be, say, if you're looking at a capsid AAV9, AAV15, AAV2 -- that could be, can you leverage some of that that's more platform-driven.

So from a product-specific perspective, you still have to establish some form of biological plausibility. This could be proof of concept in a model, if one exists. But a lot of times, the timeline that you need is not there to develop a new model. So

you may have to go to more in vitro models.

You also have to think about projecting the dose for the clinical testing. Can you establish a minimal efficacious dose? I think a really important aspect is to identify dose response relationship early and establish that pharmacology, particularly as you're moving into that patient because a lot of these patients may not have characterized natural history. So you're going to want to know, if your drug gets into that patient, are you actually engaging with the target and seeing a pharmacology that you would be expecting. And then finally, the safety margin would be very product specific.

From a platform perspective, establishing the delivery vehicle biodistribution. So there are a lot of studies out there that perhaps you could cross-reference if existing biodistribution are using AAV capsid, for example. If you have biodistribution of the capsid itself, say, in non-human primates or other relevant species, can you leverage that when you come in with another product but using the same AAV-based

capsid delivery?

And then there are also other aspects around class-specific effects. So with the oligonucleotides, the example that I just brought up from Dr. Yu at the Boston Children's with the Batten's patient, really looking at the underlying backbone of the chemistry. Can you leverage what was already out there to then bring that forward to help eliminate or reduce some of the risk that may be associated with moving that forward?

So upon establishing biological plausibility, it's really characterizing the impact on this. And this, I think, is really unique to the specific product on that biological plausibility. What I mean by that, if we're going after a monogenic disorder, we know what the mutation is. We may be able to characterize that. Are there cell lines that harbor that patient-specific mutation? And ideally, depending on the therapy, is there an animal model of that particular disease?

Because there's several things you'd want to test: will the therapy reverse the effect of the

mutation? Will we see an increase in a protein activity for something where that activity is missing? Or can you decrease that activity in something that has what's called a gain of function type of mutation?

So utilizing that to characterize the activity establishes the dose response, understand durability of that. And then I think one thing I really want to bring up is establishing these endpoints that perhaps you can test preclinically, that are the same aspects and the same endpoints that you would test clinically as you move into that, even into an individualized patient. I want to use here just one -- an example of that and establish a biological plausibility.

Here's the gene therapy for a disease called PKU. There fortunately is a mouse model for this disease. The mouse is missing or has a mutation in the same enzyme that causes a human disease, phenylalanine hydroxylase.

In this mouse, when you have two missing copies of that or two mutations on that, you -- that mouse cannot metabolize phenylalanine, very similar to

the human condition. So we can use that mouse to actually do a single administration, and then see not only do we reduce phenylalanine, but we can see that loss durably over the lifetime of the mouse. So this really helps establish the biological plausibility of that specific product. We're adding back in phenylalanine hydroxylase. We see it in vivo in an animal model.

Here's another example, trying to understand the dose relationship. So this is in a different disease. This is a disease called metachromatic leukodystrophy. It's a rare genetic disorder of lysosomal storage.

These patients are missing an enzyme called arylsulfatase. And unfortunately, when they're missing that enzyme, that enzyme typically works in a lysosome that is responsible for breaking down a product called sulfatides. What happens in these children is these sulfatides increase, and that increase in sulfatide is toxic to the cells.

We can reference human data from people that

are out there that have roughly 10 to 15 percent of normal human ARSA activity. There's a common polymorphism within the ARSA that results in that. These people generally are normal. And so we know that at least if we can hit a 10 to 15 percent of a normal activity, that should get us into something that would be therapeutically relevant. And what you see on the right is looking in a knockout model of that, showing that as we increase doses with those, we can start to see an increase in that activity in the brain trying to shoot for that target threshold of 10 to 15 percent, based on human data.

The other aspect is really trying to project a starting dose for the clinical administration. So again, this is unique to the specific product, but there might be some platform-specific challenges and opportunities to overcome that. So using AAV specifically, AAV really does require in vivo data to project a dose. You see differences in how AAV works from an in vitro to an in vivo setting.

So here, you can either use an animal model of

human disease, if one exists. That will allow you to assess the effect on the actual underlying mutation that's similar to the example that I just gave on introducing phenylalanine hydroxylase into ENU 2 mouse model of PKU. So you can assess either an increase in activity there or a decrease in vivo.

However, if you don't have an animal model, at least of the things you can do is look in referencing different data. So if you're using a specific delivery approach such as AAV, if we already have that data from other studies, can we reference that? Because that will give us a sense of different doses, how many vector genomes, at least we get from the capsid, delivery into the liver, into crossing the blood/brain barrier into the CNS. Can we leverage that to move those forward?

So along these lines, again, unique to the specific product, platforms that require repeat dosing, you can utilize these models either in vitro or in vivo to establish a dose response, to define that minimal efficacious dose, and perhaps to develop biomarkers

indicative of pharmacodynamic activity, meaning that your drug is engaging with the target and then having the effect pharmacologically that you were expecting coming in. For single administration platforms, meaning a single dose, you can do -- all the first three are the same. The only thing is for that fourth that's very unique for these is that establishing the starting dose that has a high likelihood of benefit.

Because particularly, with AAV or other types of these approaches, the ability to re-dose at this point is challenging. And so if you're coming into an individualized person, you really want to make sure that that first dose is going to have the activity that you want. So that sort of raises the bar a little bit form an AAV perspective. But the opportunities are there, I think, to utilize different models to begin to address that.

Just to exemplify that, again, I show a lot of PKU data because we have a program that just is in early clinical programs right now for that. Here's some of the data from a 28-day dose ranging finding

study in ENU 2 mice. And so what we're able to show is characterizing both males and female mice, looking across a variety of doses, looking at a reduction in phenylalanine. So that's a direct measure of increasing PAH activity. So we're putting back in something that was missing.

We can pick a dose that identifies that. And then we can also look at another marker, which is called tyrosine. So tyrosine is the direct product of phenylalanine metabolism via phenylalanine hydroxylase. And so we have two approaches that we can look at to help identify what are those doses, at least in the mouse model, that may deliver the effect that we're looking for.

And then taking that information, we could actually apply some PKPD modeling. And so we can utilize those models to try to get an assessment of, if we go into a patient population that, say, has a baseline serum phenylalanine levels of 1,200, 1,800, or even all the way up to 2,400, are there doses that, based on the preclinical data, would deliver that kind

of result. We can then take the modeling and identify and make some predictions around what percentage or proportion of subjects would we expect to have that.

So based on this modeling, it's based on mouse efficacy data. So what's unique about these mice, they are homozygous for a genotype phenotype. We know that if we go into the general population of humans, they're not usually homozygous for a specific genotype, so it's much more heterogenous.

But it really can allow us to select a dose range that we know would have activity. And then we can align that up with what we're seeing from our GLP toxicology studies to assess where is our safety margin, if you will, to make sure that these can fall into that. I think the translation to humans is required to fully characterize these, just given the inherent variability of what you would see in human populations compared to what you see in a very well-controlled mouse and animal model environment.

So then moving along is really establishing that safety margin. Here's where some of the, I think,

challenges come that would be unique to the specific product. I know that if you're using one particular AAV, the inside of that AAV is different as you go across different diseases. And we know that any kind of safety effect can be both based on the delivery vehicle but also based on the actual API, if you will, that's going to be delivered to that.

So you can use a model of human disease of what's the safety margin, aligned with the pharmacology. That's where, if you do have a model, it really gives you a lot of that information, seeing assessment or pharmacology, but then you can also see assessment of where that safety margin is to assess that. If you don't have a model, you can still use wild-type animals to get a sense of the safety margin, as well as the biodistribution of the therapy.

And then finally here, you can pull in some reference studies particularly around the delivery vehicle, so whether it's an AV capsid where you can utilize that or some of the known class effects. What I mean by here is -- again, I will use AAV as an

example. We know that AAV, there's immune responses to it, and a lot of those are cytotoxic t-cell mediated, against the liver. And so one of the main tox organs is the liver. So you can reference that from other studies to then guide you as to what to monitor, at least as you think about moving into the clinic.

As far as safety and biodistribution, again, from a product-specific, there could be mechanism-driven safety. So what are the expression levels of the specific product? What are the level of inhibition that you need? If you inhibit 50 percent, you might be safe. But perhaps, if you inhibit too much, you might have some safety consequences and vice-versa on the cell-specific challenges around maybe expressing too much.

I think Dr. Gao brought that up a little bit, as one of the last hurdles in getting into the clinic is trying to regulate this. Some cells, based on delivery, you may hit them very hard, and then you may have overexpression of your product in that particular cell. And so we need to be cognizant of those aspects

as well.

There are also chemical or structure-driven safety aspects, so off-target effects. I think we're going to hear a little bit about that in two speakers from now, with Dr. Joung, and then also, the interaction with the immune system. I mentioned briefly about AAV. We also know with other oligonucleotides, other antibodies, there are just unique class-specific effects that you need to take into consideration.

As far as the platform, once you move to the platform, again, you can look at the properties of the delivery vehicle. So I've spoken quite a bit about the specific AAV capsid and understanding how that capsid delivers. The capsid is really what's delivering it to the different cell types. And so whatever -- regardless of what you have inside that capsid, the capsid itself is usually what's going to deliver it to those particular cells. Or you could also think the same thing with a lipid nanoparticle or an antibody as you get a sense, if you're utilizing them as drug

delivery vehicles.

The other aspects from platforms are assays for measuring. So one of the unique things that, as you start to develop this, there are assays out there for measuring caspids and specific antibodies against the capsid. So how do you measure that?

If it's against a specific capsid, you should be able to leverage those across many different studies or even other things such as anti-antibodies. So if you're coming in with a biologic and you develop those antibodies, if it's the same antibody being utilized in a different thing, I think you can leverage some of that data going forward for those biodistribution.

So here's an example of biodistribution data that we generated in cynomolgus monkeys, with one of our capsids, AAV HSC15. So we did this in two different dose. And we were able to collect a variety of tissues. This data now, these data, we can then cross-reference for other studies that were using AAV HSC15. And it really helps accelerate some of those preclinical testing that we would be looking into for

utilizing AAV HSC15.

So finally, I just wanted to sort of wrap up with the last few slides. As we think about this, different targets require both product-specific nonclinical characterization, as well as platform. So just the example here, if we're using an AAV HSC15, and we have disease one, the AAV HSC, the capsid, is exactly the same, whether we're going after disease one or disease two, just to exemplify this. So we can cross-reference by distribution. We can utilize capsid assays. We can utilize a lot of these different aspects, just thinking about moving that forward to help accelerate that.

But the inside is very different. So we may have different promotors. We may have different trans genes. And that's the product-specific aspect that we do have to generate some testing for in -- preclinically, and so really looking at establishing biological plausibility. So this disease and that disease will have different cell-based models, perhaps different animal models that we still have to go

through and assess, dose selection, and then finally the underlying safety margin.

And then I talked a little bit about this before. But the class effects can be informative but perhaps not sufficient for a total safety assessment. But we can pull that information in to utilizing as we think about these. So one of the things just to highlight here is just, as that data is being collected and we're seeing more and more of these technologies generate more data, publishing these data, you can start to think about, from an individualized perspective, moving those forward and using that to help accelerate some of these individualized type approaches.

So finally, platform-specific considerations, in terms of selecting a dose, platforms that are amenable to repeat dosing, so basically small molecules and oligonucleotides, antibodies, protein replacement -- a lot of those you can start at a lower dose and increasing those doses with a safety margin. It really gives you that opportunity to move forward with that.

And I think that's similar to what that example in Batten's disease they were able to utilize that.

Ideally, align it with a PD biomarker because we heard about this already. A lot of these individualized diseases just don't have an established natural history. So ideally, you want to know what your drug is doing inside the patient and making sure it's engaging with the target and seeing that activity, so anything that can be done to spend time on understanding those pharmacodynamic markers.

And then there also is some guidance around microdosing. So maybe there's a unique opportunity around microdosing options to even accelerate these even further, as we think about taking these individualized therapies forward. Again, coming back, just to summarize on this. Platforms that are not amenable to repeat dosing, so AAV, a lot of the other genetic medicines, it is a single administration aspect.

So I think the bar is a little bit higher in terms that for particularly in individualized therapy -

- it’s an N of one -- getting that first dose right is going to be essential for that particular patient. And so really, that's where understanding the likelihood of clinical benefit, understanding your preclinical dose modeling data, going either from an in vitro, if that's what you have, or really, pulling whatever you can from in vivo to help drive that first dose. And maybe there's an opportunity here, based on taking into class effects. If you have the safety margin for an individualized therapy, is that something to consider that, instead of starting at the minimal efficacious dose for that one patient depending on the benefit, the likely benefit could be there? Do you start at a much higher dose but still within your safety margin?

And then one of the things I wanted to -- as I was thinking about this is putting in aspect around repurposing existing drugs. This could actually be the fastest because you'll probably have a host of information already available to you, with respect to safety profile, with respect to PD activity, to then move pretty rapidly into these individualized

therapies. I think this is more of a rare exception though because a lot of these individualized therapies are going to be based on DNA sequence mutation and very personalized. There just aren't a lot of existing drugs out there that can target that. But it is a possibility.

In terms of challenges and possibilities to streamline this, I think the product-specific characteristics, I think, have to be determined every time. I think that's sort of par for the course. But are there opportunities to streamline?

So one of the things I was thinking about is, is there a form to share precompetitive platform data? We heard a little bit earlier about IP. IP is always going to be a consideration. But are there precompetitive platform data? So whether it's AAV, biodistribution, if someone is working on someone else -- another AAV and we already -- and someone else already has that data, how can we get that to share particularly for a very severe disease that needs therapy very quickly?

Commercial assays, specific to the platform, so if we have neutralizing antibodies against certain AAVs, can we share those? Can we get these out there quickly? And then one of the other aspects that came up around common manufacturing assays to support a platform. So whether it's triple transfection and HEK293s or whether it's SF9, are there different aspects that we can take advantage of?

And then finally, I just want to end on really thinking about this microdosing. Are there guidance or white papers on the application that we can take advantage of existing guidelines or initiatives that are already there that the FDA has made available to us? So microdosing in support of dose escalation for individualized therapies, can we -- is there a possibility to expand that?

And then the last thing I just want to bring up is -- and it was brought up a little bit earlier -- the possibility and the openness of the FDA for what are called Interact meetings. We found these to be extremely helpful. And I think for something like

individualized therapy, this could be an avenue to really start engaging with the regulators very early because you can get quite a bit of feedback before you start all of your nonclinical studies.

And so I just wanted to end on that aspect of the different approaches. And again, thank the FDA, thank the audience for listening to me.

**DR. SANDUJA:** Thank you, Dr. Seymour, for a very interesting and exciting presentation. I would now like to welcome our next speaker, Dr. Malachi Griffith. Dr. Griffith is currently an assistant professor of medicine and the assistant director for the McDonnell Genome Institute at Washington University School of Medicine.

Dr. Griffith completed his Bachelor of Science with honors in biochemistry and biology in 2002 at University of Winnipeg, followed by additional formal training in computer science. He worked as a molecular biologist and then as a computational biologist during 2003 to 2004 before beginning a PhD in medical genetics and bioinformatics at the University of British

Columbia. After his PhD, he joined Washington University School of Medicine in 2011.

Dr. Griffith's research is focused on the development of personalized medicine strategies for cancer using genomics and informatics. His lab has made substantial contributions to open-access resources for cancer research. Recently, the development of bioinformatics for immunogenomics has become a major focus of his lab.

Dr. Griffith now has more than 14 years of experience in the field of genomics, bioinformatics, datamining, and cancer research. He has over 80 publications and has received numerous research awards and has held several large grants, including an NIH K99. So I would like to welcome Dr. Griffith.

**BIOINFORMATICS TOOLS FOR DEVELOPMENT, ANALYSIS & PRECLININCAL TESTING OF INDIVIDUALIZED THERAPEUTICS - DR. MALACHI GRIFFITH**

**DR. GRIFFITH:** Okay. Thank you for inviting me to speak today. It's been a really interesting

morning so far. I'm going to talk about something that's been mentioned in several of the previous presentations of bioinformatics but much more in passing. So we're going to dive a little bit deeper into the bioinformatics aspect of all this right now.

And I'd like to start by making an argument that neoantigen vaccines in particular are a really nice exemplar for individualized therapeutic. So we heard a really interesting comment and question from the audience this morning about neoantigen vaccines. And I think that they're a great exemplar for a couple of reasons.

One is that they're, in some ways, the most personalized or individualized example of therapy that we see today. So what's depicted here is a very high-level 10,000-foot view of a workflow for developing a neoantigen vaccine for an individual patient where you start with a piece of their tumor tissue, taken at biopsy or in some cases from a surgery. And then you sequence the whole genome or whole exome of that tumor DNA and compare it to the normal DNA from that

individual, from blood usually.

And you would usually also sequence the transcriptome of that individual and then do a very complicated bioinformatics analysis, which I'm going to dive into a little bit more deeply here, to identifying variation that leads to unique amino acid changes in the genome of the tumor. So these are peptide sequences that are specific to the tumor cells. And then you use knowledge of those peptides on how the immune system works to try to develop a vaccine made up of these peptides that will stimulate the person's immune system to respond to their tumor.

And so a typical example of this right now, in many of the clinical trials that are underway, is something like 5 to 20 peptides that are unique to the tumor cells that you manufacture in a variety of ways. And there are various manufacturing strategies being used that get delivered, in the hopes of stimulating the immune system to attack their tumor. And those peptides are totally unique to that individual. They'll never be used again. You're leveraging the

unique features of that tumor genome.

They're largely passenger mutations, so they don't need to be functional per se. They just need to be present in every tumor cell and cause an amino acid change. And because they're passenger mutations and they don't drive the biology of the cancer, every person has a somewhat random set of them.

So I've been involved in probably now 50 to 100 vaccine designs. We've never used the same peptide twice. It's always a different set for every single patient.

So it's sort of the pinnacle of individual or personalized therapy. And the other sort of large reason, I think, that it's a good exemplar is just the scale of the target patient population. Since somatic mutation is a fundamental feature of virtually all cancers, the potential application is potentially all cancer patients. Everyone has an adaptive immune system, and everyone's tumor has unique features of those cells that could be targeted by their adaptive immune system.

So the number of people that could potentially benefit from this strategy is huge. So you have a combination of a challenge, which is that it's completely personalized. There's never going to be an off-the-shelf drug that you can give to someone. But at the same time, the potential market is absolutely massive.

So just to dive in a little bit more detail in terms of what this pipeline looks like. So I don't expect you to read this. It's just to -- along with several slides, to give you kind of a sense of the complexity and detail that goes into this.

So it all starts with sequence data. So we've heard this morning how important access, robust access to that data is. And there's a series of complicated bioinformatic steps that are undergone to sort of convert that in raw genomic information into predictions of first variation.

So you align your sequences against a reference genome, and then you perform a variety of different kinds of genomic variant calling and HLA

typing to characterize the immune system of that patient. And then you run those variations through customized pipelines that attempt to prioritize and rank these variants according to their potential usefulness as an immunogenic target. So all of this is incredibly complicated. And there are a ton of tools out there. And it's becoming increasingly sort of automated and robust. But it's still also quite an art form.

So currently, the vaccine design process involves considering quite a large number of factors. And this is often done in an immunotherapy tumor board setting for the trials that are experimenting with this therapeutic modality. And this is a group of experts in immunology, genomics, bioinformatics, and the treatment of the type of cancer that's being targeted, who consider a variety of criteria for each of the candidates that you're thinking of making the individual personalized vaccine for.

And these are some of the things that are features of the patient, and some of them are of their

genome. And some of them are individual to the particular variants that you're thinking of targeting. And I've just listed some of the examples on the right side. And really, what we're doing in my group is trying to automate as much of this as possible, formalize the stuff that still involves human intervention, replace as much of the human interaction with machine learning as possible, and develop sort of best practices and SOPs to help make this process really reproduceable.

So we've heard a lot this morning about process. This is a great example of that. So the therapy is always different, but the process really, really matters. And it's an incredibly complicated process. So it's right for people thinking deeply about the details of it and how we can make it robust and reproduceable and make the process accessible to as many patients as possible.

So part of the reason why this is a moving target and we're still developing new approaches is that this is a very new treatment strategy. And we're

just still kind of learning the rules of what makes a good immunogenic neoantigen, so the peptides that are specific to a tumor that actually lend themselves to this approach. And one of the best ways that we're learning this is by doing it in early-stage trials in patients. And I've listed the trials that I'm involved in here, which are a relatively small set of the trials that are underway worldwide.

As you can see, they involve a variety of cancer types, and they're relatively small scale being mostly phase one trials. But they all follow the same process, which is that we start with a patient sample, a piece of their tumor. We sequence the genome of it, and we go through a pipeline that is both bioinformatic and manufacturing and a preclinical assessment to arrive at a vaccine that is actually safe and able to be delivered to the patient by injection either peptides or a dendritic cell vaccine or, in some cases, the vaccine is incorporated into vectors that are sort of similar to some of the vectors that have been described this morning for delivering genetic payloads.

There's a huge amount of variability in these trials. So they vary in their delivery approach. As I mentioned, there's several manufacturing and delivery strategies being used, the site of the tumors that are being considered. It's almost every cancer type now that has one of these trials underway somewhere. These are some of the examples of the ones that are happening locally at Wash U.

And then they vary in their combination with other therapies. So many of them are being combined with checkpoint blockade therapy, where the idea here is to sort of take the brakes off the immune system, while also simultaneously giving a kind of roadmap to the immune system, so telling the immune system, these are the unique features of the tumor in this patient that you should be targeting, and then simultaneously sort of stimulating the immune system to attack. So in many of the talks we heard this morning, there was concern about sort of immune toxicity or the effects of the immune system are almost a problem.

But here, it's the reverse. We're trying to

enrage the immune system against the tumor but also sort of provide some guidance in terms of what specifically it attacks. And the level of specificity here is quite exquisite because it's this very personalized genomic base therapy individualized to each patient.

So what I'm going to do now is just walk through a list of some of the bioinformatics concepts. So these are the things that keep me up at night, when we're thinking about how do we do this whole process from raw data to vaccine design and production in a reproduceable and robust way so that the process is constrained, and given the same set of input data, you would arrive at the same answer. And I'm not going to list those here because I'm going to go through them one by one.

So it all starts with the sequence data, which must ideally be of high quality. This part of the process has become quite robust and sort of production-ified, if you will, where there are many, many sequencing cores and facilities and services where you

can send nucleic acid for the tumor and for the reference blood and get DNA and RNA isolated, libraries constructed, sequences generated. And then you think of this sort of commodity sequencing, where everyone has sequencing from the same platform, and they kind of all look the same. The reads will be a certain length, and they'll be paired and so forth. Those are certain standards that have been widely adopted.

And I think that's largely true. But I would just caution at this stage that the apparent consolidation of many sequencing efforts to single sequencing platform can lead to a false sense of reliability in terms of sequence quality and the nature of each sequence dataset. So I think that assessing quality of your raw sequence data is still very, very important. But I won't go into much more detail on that.

The analysis of the data really starts with a reference genome. So people think of the human reference genome project as complete. It's not really complete. It's still ongoing. But there is this sort

of pervasive fallacy that there's one human reference genome, which for a bioinformatician is very much not true.

So while the raw human genome assembly is centrally maintained and you can sort of go and get the centrally maintained build or assembly, there are many, many, many derivatives of it. And these are in common, common use. So we all hopefully know that there are multiple assemblies or builds in common use. So we think of build 37, build 38, or HG19, HG20. But there are also many subversions, patches within those. And the actual raw files used in a referenced genome can matter.

And so usually, what's happening is people aren't getting the raw assembly files themselves. They're getting them through some second party, like Ensembl, UCSC, 1000 Genomes, the Genome Data Commons. And each of these vary in a variety of ways that can really matter for downstream analysis and interpretation. So for example, some of them used so-called decoy sequences. Some of them include

alternative haplotypes and some don't.

There are light versions that simplify the genome down to the chromosomes and throw away all of the unplaced contigs. Chromosome naming amazingly is not consistent to this day. Some viral genomes are included, and some referenced genome sequences repeat, masking may vary, et cetera.

So this still remains a large problem in terms of consistency. The Global Alliance is really working on trying to standardize some of this by developing SOPs and best practices for uniquely identifying what your reference genome really is. Variant discovery is another area of a lot of variability. So you start with alignment. And then with an alignment, you run a series of variant calling algorithms or transcriptome analysis.

And there is a huge diversity of how these algorithms work and how they're used in combination. And there are generally a series of tools used for each broad type of variation. So for example, you might have three variant callers, strelka, mutect, and

varscan, just to pick some examples, for calling single nucleotide variants in a different set of variant callers for SVs. And so you could have dozens of tools potentially involve, just in identifying the potential variation that's the grist for the mill, to identify your neoantigens for these personalized vaccines.

Because of the complexity of this process, again, manual review human intervention remains a common part of many of these pipelines, where humans actually look at raw sequence data. They manually review variant calls that they're going to invest a lot of effort or make something around. And so that part of the process can be variable. We've worked to develop standard operating procedures for the manual review aspect of this and, also, machine-learning tools to help automate it so to take humans out of the equation.

Once you have variance, so you have identified a genome variation that could be a source of a neoantigen, there's a big representation problem in the field. We can't agree on how to refer to variance.

And this creates a lot of confusion and inconsistency across the field.

So I'm showing at the top here six different depictions of the same variants, all being named in different ways, only one of which is actually unambiguous and computationally interpretable, and even then is not in a very efficient computationally interpretable form. So that's the bottom one. And the bullet point is an HGVS string. The others are just essentially colloquial ways of referring to a variant -- that many of us know what BRAF V600E means. But that's a sort of ambiguous way of representing it, to just name it like that.

So this creates a problem because it's difficult to know when two resources or two groups or two labs are talking about the same or different variation, which creates a sort of consistency challenge. Again, there are many efforts to harmonize variant identification. I'm involved in several of these consortia that are sort of having conversations around how we develop standards and ontologies to

really fix this part of the problem.

And the one that I really like to mention specifically is the ClinGen Allele Registry, which is depicted on the right here. And this is not the perfect solution, but it's available now. And it fixes a lot of the variant identification problems for many people.

Just like the reference genome has many versions, the reference transcriptome has many competing versions. And when you're trying to think of an amino acid change that arises from a change in the tumor genome, that relies on interpretation in the context of a specific transcript sequence. And we don't actually know what that is. It's an interpretation. And so it relies on predictions for what transcripts look like.

And there are many competing reference transcriptome efforts. Each of them handle prominence and versioning differently, which creates a problem for building robust reproduceable pipelines. For example, Ensembl versions each individual transcript and their

overall set. But they're currently on release 99, which creates another problem, which is that it's constantly shifting targets.

You always have this temptation to be on the latest set of reference transcripts, but at the same time, that creates an instability in your pipeline where it makes it harder to kind of lock down the pipeline, where you can run it multiple times and get the same answer. But Ensembl is popular among bioinformaticians because of their sort of formal handling of certain aspects of this problem. But it's really important.

So we've identified several examples in our own recent experience in these clinical trials where, for a given referenced transcriptome, how you interpret genomic events can really radically change based on how you prioritize transcripts and consequences. So there's this one variant, one consequence problem. We like to think of one variation in the genome leading to one amino acid change in one gene. But it's more complicated than that because of overlapping genes,

because of alternative isoforms of genes.

And so there's very complicated tools that attempt to solve this problem for you. And they have to make difficult choices about how to prioritize the referenced transcript that you're using for your inference. And this can create a variety of problems. So two examples of problems we had recently where cases where the variant effect predictor we were using changed the way they internally represented frame shifts. And this caused us to have the potential to create incorrect peptide sequences. And we can also miss high-priority targets when an inappropriate transcript gets selected as the highest priority.

Clinical variant and gene interpretation is another challenge that several consortia are now working to resolve. So the -- in the sort of rare human disease space, the ACMG guidelines have really helped to solidify how we do variant interpretation. In cancer, there's been -- we're sort of behind because we have the somatic variant problem that's been less addressed. But we're starting to make progress with

the AMP, ASCO, CAP guidelines and other efforts like CVC. And again, the Global Alliance has really been organizing efforts to improve the consistency of both gene and variant interpretation in a clinical context.

And then I really just want to end on the sort of most bioinformatics heavy aspect of this whole process, which is that you have this incredibly complicated analysis pipeline for individualized therapeutics. I'm depicting a small slice of our pipeline here as a graph, with nodes and edges, depicting steps, tools, data coming in, and interpretations coming out. That's actually a small piece of the overall neoantigen vaccine prediction pipeline that we use that goes from raw data to a new antigen vaccine. It involves dozens of tools, hundreds of parameter settings, hundreds of input and output files, and thousands of individual compute steps, which makes it very difficult to have an actual reproduceable pipeline.

So it gives us this question of how do we actually ensure reproduceable results for very complex

pipelines? And so this is an area that we've really been working on formalizing. And the short answer is you should adopt a formal way of describing your pipeline first of all. So there's been several recent advances in things like workflow definition languages.

You should containerize everything. So place all of tools inside of containers that isolate the environment from compute dependencies. And you should use a workflow execution system that runs the whole pipeline.

And then ideally, you should organize these layers into an analysis platform. And there are some great examples out there like TARA. And don't forget the importance of software engineering and bioinformatic support.

So it's harder than it seems to keep a computational pipeline locked down. There's an assumption among many that because a bioinformatics pipeline is computational, it must be inherently stable or reproduceable, and this is actually surprisingly not true.

It's potentially stable and reproduceable. But that's actually much harder to achieve than you imagine because of the complexity and the number of steps and the dependencies on environment and how much those environments and inputs and reference files -- everything can change. And it's harder than it sounds to keep things locked down. So I'd just sort of urge caution when thinking about the reproducibility of these pipelines.

And then I'll just end with a short list of -- so I've thrown a lot of terminology and resources and efforts out, but this is sort of the short list of things, that if you're just going to check out a few things or you want to become engaged in this kind of work, these are the four things that I would recommend starting with. I'd be curious to hear if anyone has any examples of bioinformatics issues for individualized therapeutics that I really missed. And then I'll just end by acknowledging the wonderful group that I'm privileged to codirect with my twin brother and partner in crime, Obi, and of course, my funding

from the NHGRI and NCI in incredibly grateful for. I look forward to talking to you later if you have questions.

**DR. SANDUJA:** Thank you, Dr. Griffith. So we'll now move on to our next speaker, Dr. Keith Joung. Dr. Joung is currently a Desmond and Ann Heathwood Research scholar and pathologist at Mass General Hospital and a professor of pathology at Harvard Medical School. Dr. Joung holds a PhD degree in genetics from Harvard University and an MD from Harvard Medical School. He's a leading innovator in the field of gene editing.

Dr. Joung has pioneered development of important technologies for targeted genome editing and epigenetic editing of human cells. He has received numerous awards, including an NIH Director's Pioneer Award, an NIH Director's Transformative Research Project R01 Award, the MGH Research Scholar Award, and an NIH R35 MIRA Award. So we would like to welcome Dr. Joung.

**DEFINING OFF-TARGET EFFECTS OF GENE EDITING TECHNOLOGIES - DR. J. KEITH JOUNG**

**DR. JOUNG:** Thank you. And thank you to Dr. Marks and the other FDA staff for the opportunity to come and speak. So I'm going to talk today about defining off-target mutations and effects of gene editing technologies broadly. I have a conflict of interest slide, which I'm required to show you by my institution.

And so what I hope to do today is three things. One is review the challenges and strategies that exist now for defining gene editing nuclease, as well as sort of next-generation CRISPR-based editor off-target effects, and then tell you about our latest assay, which we call ONE-Seq, which is a universal platform for identifying off-target effects of all gene editing nucleases and CRISPR-based editors that we think also has advantages of scalability as well as reproducibility, and then, at the end, just share some perspectives on kind of the state of the field and then

what I see as issues and challenges moving forward. So first, starting with a review of the strategies and challenges involved in defining off-target effects of gene editing nucleases.

So as Dr. Marks mentioned in his intro remarks this morning, there are now a variety of different platforms for doing gene editing. There are the four sort of classical, if you will, nuclease platforms, zinc finger nucleases, TALENs, mega-nucleases, and CRISPR CAS RNA-guided nucleases, and then more next-generation technologies, such as the CRISPR-based cytosine- and adenine-based editors developed by David Liu's group, which used the CRISPR system to direct specific nucleobase deaminase enzymes to specific locations in the genome.

So we've gotten very good now at being able to put mutations where we want in the genome. But one of the big challenges for the field for many years has been defining and quantifying where else in the genome we may be making alterations other than our intended on-target site. And part of the challenge is that the

alterations in use by nucleases and base editors are double-strand breaks and nicks. And so these are short-lived events that are then repaired by cellular DNA repair processes.

And so it's hard to actually directly identify these alterations. And instead, what we do is identify their outcome, so things like nonhomologous mediated -- nonhomologous end joining mediated indels or the base substitutions induced by base editors. This can be challenging to do, particularly in repetitive genomic regions. And because of limitations in our ability to do sequencing, it can be hard to distinguish these alterations relative to background mutations or just errors in the process of doing the analysis itself. And this is particularly true for base editors.

Another challenge is that there really is no gold standard for the field for off-target determination. Whole genome sequencing is neither practical nor particularly sensitive for finding these alterations. And then on top of that, because of tremendous interest in the field, it's a rapidly

evolving space with continuous improvements and discoveries coming at a very rapid pace.

So how does the field address this? Well, essentially right now, we use a consensus two-step approach for being able to identify gene editor off-target mutations. So the first step is what's called a nomination or discovery process. And here, what you're trying to do is identify potential sites of off-target cleavage or mutations in a surrogate setting.

And so that surrogate setting can either be cell-based assays, like the GUIDE-Seq assay developed from my group and bless/bliss methods developed by Feng Zhang's group. Or it can be in vitro methods, where you in a test tube have purified genomic DNA and purified nuclease or base editors, and you ask whether you can identify off-target effects. Now, you want this to be as sensitive a method as possible. And you want it obviously to be genome-wide in scope, so that you can define the superset, if you will, of all possible sites that the editor might be making alterations at.

It's also important to note that not all sites identified in this step may ultimately be -- ultimately show evidence of alterations in the context of the cells that you actually want to modify for a therapeutic because there are other factors that come into play that would be specific to your therapeutic setting, such as, for example, the epigenetic status of the gene. So the second step then is to take all of the sites that you get from the nomination process, and then ideally in the setting, therapeutic setting of the cells that you want to be able to the therapy in, actually look directly at those sites and ask whether or not you see evidence of alterations at those sites. And so this is why it's really important for that first step to be as sensitive as possible because, if you don't identify it in that first step, you won't even look at it in the second step.

And here, there are a number of challenges, which I'm not going to read through, but that also exist with identifying whether an alteration has occurred here. Typically, what people have been using

is targeted amplicon sequencing to be able to look for the presence of indels. But it is important to note that it is equally important to try to identify other types of alterations that can occur when you create more than one double-strand break in the cells, so things like large-scale inversions or deletions or translocations.

And then overall, I think it's important to try to quantify risk as the sum, if you will, of the on-target effect, but also all of the off-target effects and the overall double-strand break burden that you're actually inducing in the cell. Now, there's a number of critical parameters. I don't have time to go through all of them in a talk this short. But I do want to mention assay sensitivity as being one that's particularly important.

As I mentioned, for the nomination or discovery step, this is very important because, if you're not sensitive enough to pick up everything, again, you won't even bother to look at it in the second confirmation step. And in vitro assays, I

think, have the advantage over cell-based assays for the nomination step of being more sensitive. We can't quantify that sensitivity at this point, again, because of the low frequency sites having some challenges being able to confirm due to the error rate of next-gen sequencing, which also limits the second confirmation validation step as well.

Because if you amplify a section segment of the genome, the process of doing PCR and then doing next-generation sequencing, you can often see indels at those sites at rates anywhere from 0.1 to 0.01 percent. And so distinguishing a real alteration introduced by your base editor or nuclease of interest from just background error rates can be challenging. And then ultimately, too, risk assessment is important because you may make a break, but it may not have any -- ultimately any functional consequence. But here, we're limited to some degree, or to a large degree, by our understanding or knowledge of biology and genome function at a particular identified off-target site.

Assay quality control is also equally

important. So some of the parameters to think about here are positive and negative controls, particularly for a negative study that shows or reports no detectable off-target effects. It's also important to account for sequence variation relative to reference genome sequence.

And we've just heard about some of the challenges, even in what constitutes referenced genome sequencing in and of itself. But certainly, differences among different cell types are important to account for, so doing an untreated control is very, very important when you're looking for off-targets. And then there's a lot of other parameters, which again, I don't have time to get into, but that relate to the number of input genomes that are going into your assay, the number of assays that you do, and assay replicates that you do and biological replicates that you do, sequencing depth, and then all the informatic pipelines that you use to actually process the data.

So there are a lot of challenges. The NIST has formed a consortium on gene editing led by Samantha

Maragh that I think is trying to address some of these challenges. And it may be that, ultimately, commercial service providers may be able to help with providing a standardized trusted set of services that would address these requirements.

Okay. So next, I want to tell you about a new assay that has been recently developed by my lab. And again, this is unpublished work. And here, it's an assay we call ONE-Seq, which we think provides -- we believe provides a universal platform for being able to identify off-target mutations of gene editors both of the nuclease class and the base editor class and to do so with unsurpassed sensitivity.

So this is an in vitro assay, again, purified components, in a test tube. If you look at all the other assays that have been described previously in this field, so things like Digenome-seq, SITE-seq, and even CIRCLE-seq previously described by my lab, what those assays do is they purify genomic DNA out of cells or a particular tissue. And then they build some kind of library out of that, treat with the nuclease, and

then attempt to identify in the context of all these genomic sites, which are the sites that are actually being cleaved by the nuclease.

And so the representation in the middle is sort of the mess of genomic DNA, if you will, that you get. In the human genome, obviously, you're going to have at least three times 10 to the 9 of different sites. And only a very small number of these will actually end up being cleaved by the nuclease of interest.

And what we've learned from a variety of different studies performed to date is that these sites all have some degree of resemblance to the intended on-target site of the nuclease or the base editor. That is that they are the same, but they differ at a certain number of positions, as many as six or seven, within the target site that you're trying to hit. And so it's important then to emphasize that this is a very, very small number of sites relative to the total content, if you will, in a genome sequence.

So with ONE-Seq, what we do is we take whole

genome sequence for a particular cell type -- so for example, for a human genome, we may use human reference genome sequence -- and we go through and computationally identify all the sites that have a certain number of mismatches relative to the on-target site. So you can go through and computationally identify these. And you end up, for example, with Cas9, typically, you have a list of sites of anywhere from about 20,000 to 80,000 sites, depending on the degree of orthogonality relative to the human genome sequence.

And so you can then extract these sites out of the genome and then synthesize all of them using high throughput oligonucleotides synthesis, which now has the capability to be able to synthesize up to millions of these sequences precisely and give you exactly what you want. And so what we do is we embed these sequences in a fixed-length oligonucleotide. They're always at the same position in the middle. And all of these oligos are the same length.

And then after synthesis, they can be released

from the chip, converted to double-strand DNA. And then this becomes your library that you then treat with your nuclease of interest. And then I'll show in a second how we extract the off-target cleavage sites.

So this type of approach using, if you will, a more focused library that's been synthesized in vitro relative to just using genomic DNA, has a number of advantages. So one of them is that you can characterize the entire library when you build it, just by doing a simple MiSeq run because you're talking about, again, anywhere from 20,000 to 80,000 sites. And so you can sequence that library at high coverage and know exactly what's going into the reaction in the first place.

And so these are some examples of multiple libraries that we've built for different target sites. And you can see that the dropout of sites is actually very, very low. It's also very, very reproduceable, these libraries. So you do two independent syntheses, and then you do sequencing and compare them. The reproducibility of this is very, very high. And so

these are two different libraries here, which we've done in duplicate and then done high-coverage sequencing. And you can see that the reproducibility between the libraries is also very high.

So this is a description of how we then use this approach with Cas9 nuclease. So you take this library, where you have a bunch of these different target sites. You then treat with the Cas9 nuclease. And so all the sites that are cleaved will be broken into two. And then those free ends then serve as substrate for ligating a sequencing adapter. And then you can sequence the products that come out of this and know which sites are being cut.

We then process the data. And so you end up with these types of outputs, where you identify a whole bunch of different sites. And typically, the highest site, although not always, is the on-target site, shown here with an asterisk. And you can assign what we call a ONE-Seq score, which represents quantification of how frequently these sites are being cut in the in vitro reaction.

Now, another nice thing about this assay is the unique capability to be able to set false-positive thresholds for the assay. This is something that you can't really do with a genomic DNA library. And the way that you do this is for a given target site library, let's say against a target in the FANCF gene, instead of treating that library with a FANCF-targeted nuclease, you target it with a different nuclease target it to a different gene, so for example, to an EMX1 target site.

And so what that allows you to do then is see what the false positive rate is because nothing in that library should be cut by a nuclease that doesn't target that site. And so you can set precise cutoffs. And so you can see the scatter plot on the right here are two different library experiments. And again, you see high reproducibility in the ONE-Seq scores of the different sites. And the red lines represent the false positive cutoffs that can be set based on doing these types of mismatched nuclease experiments.

Okay. So to show you that ONE-Seq performs at

least as well, if not actually better than all the other previous existing methods, here are comparisons for four different sites of ONE-Seq against our GUIDE-Seq cell-based method. And this is for identifying bona fide, verified cleavage sites that actually are cut in human cells. And so you can see that GUIDE-Seq identifies -- sorry, ONE-Seq identifies all of the GUIDE-Seq sites but then also identifies additional sites as well.

This is a comparison of how well CIRCLE-Seq, another method we had previously described, an in vitro method we previously described, performs at finding these bona fide GUIDE-Seq sites. And you can see the CIRCLE-Seq sometimes can miss the different sites. The two different colors represent doing CIRCLE-Seq on two different cell type DNAs. And then finally, Digenome-Seq, which is another in vitro method previously described by Jin-Soo Kim's lab, you can see also misses sites, bona fide GUIDE-Seq sites. Although, this was a result that's sort of known from the previous literature.

We wanted to show that ONE-Seq was actually capable of identifying sites in an in vivo context as well. And so here, we used a liver-humanized mouse model. And so this is a mouse model, where essentially, a good portion of the mouse liver has been replaced by human hepatocytes.

And so the nice thing about this model is it allows you to examine off-targets in the context of human cells but in a mouse model. And so this addresses something that actually Dr. Marks was talking about this morning, that when you want to look at off-targets in a mouse model that's not really relevant to look at off-targets in a mouse genome if ultimately the goal is to use these nucleases for human therapeutic. So I'm not going to go into the details of how we build these types of mice. And I should say that this is work done with Karin Musunuru at UPenn in collaboration with his group.

So we wanted to do a particularly challenging site. So we -- Karin had identified this GUIDE RNA for Cas9 that targets early exon in the PCSK9 gene. And

the nice thing about this GUIDE is that it has very few closely matched sites in the genome. So it has no off by one, off by two, or off by three sites. So the most closely matched sites are off by four and then go up from there.

And so we like this site because we thought it would be particularly challenging to find off-targets for this type of site, and we wanted to see how ONE-Seq would do in identifying potential sites that ultimately would be modified in vivo. And so this is the ONE-Seq output. The top site here would be the on-target site. And then underneath are the off-target sites. Little colored squares indicate mismatches relative to the on-target site. And on the left column, there are the ONE-Seq scores.

And so these are the top 40 sites, off-target sites, identified by ONE-Seq. Karin then went and took genomic DNA from the livers of these mice that have been treated with this nuclease and asked whether you could identify indels at those sites. So you can see on the right that, the on-target site, you get very

high modification. And then within this set of 40 sites, there are at least four sites where we can see very reproduceable, in triplicate, evidence of indel mutations.

And these are sites that have either four mismatches, the two higher sites, or five mismatches relative to the on-target site. And you can see from the numbers of sites there that it would be very hard if you went through -- wanted to go through and actually look at every single one of these sites in these livers. But here, we're able to sort of rank-order the sites based on ONE-Seq and then focus on those sites and quickly identify off-target.

So this validates that ONE-Seq is capable of finding these sites in this in vivo context and in this more therapeutically relevant mouse model system as well. I don't have time to go through all the data, but we have a lot of data showing that ONE-Seq outperforms other methods for other types of nucleases. So Cas9 is a nuclease that leaves a blunt end. But there are other nucleases that leave overhangs, like

Cas12a (Cpf1) or engineered zinc finger nucleases, mega nucleases, or TALENs.

And here's some data showing you that ONE-Seq outperforms GUIDE-Seq for identifying Cas12a nucleases. So we find all the sites previously identified by GUIDE-Seq. But we also find additional bona fide sites using ONE-Seq. And we've also adapted ONE-Seq for the base editor technologies as well.

And so here, we show that for a variety of different sites -- that for the sizing-base editors, ONE-Seq outperforms the Digenome-Seq assay, which is the only assay that's been used to date to identify off-target sites for cytosine-based editors. And it also outperforms Digenome-Seq for adenine-based editors as well. So we believe that ONE-Seq is, as I say, at least as good, if not actually superior to all the other methods out there for identifying off-target sites for nucleases that leave blunt ends, overhang ends, as well as for the cytosine- and adenine-base editors.

Okay. So I have a few minutes left because,

actually, I think the intro was counted in my 20 minutes. So I think I have a couple more minutes to talk about briefly some perspectives on looking forward. So first of all, some viewpoints and perspectives on the current situation. So it is not possible to really ensure a complete lack of off-target effects at present.

And I don't think it's a reasonable goal to ensure that, given where our technologies lie right now. The goal really should be to minimize off-targets as much as possible. And this can be done through things like protein engineering and other technologies that have been described in the literature over the last few years -- but still understand that they may occur. And also, there needs to be an understanding that not all off-target mutations will necessarily be problematic.

We also need to recognize that there are sensitivity limitations of the existing assays and that there's also restrictions imposed by sampling for both ex vivo and in vivo therapeutics. You just can't look

at all of the cells that are actually being modified. Off-target profiling, it's also important to remember is only one aspect of safety analysis. So there are other tox studies that still need to be done. And in general, when you talk about risk assessment of off-targets, it's not possible to really make a general recommendation about specificity outside of the given intended use of a particular nuclease.

So looking forward, I do want to say that my own personal opinion is that it is very, very important that we continue to try to improve and extend both the experimental and the computational approaches for identifying off-target effects. There are a growing number of voices now in the gene editing space, particularly on the kind of academic research side but also to some degree from the industry side, that some folks will say, well, this is -- we've done enough. We've done enough to be able to look at this.

And so I would strongly disagree with those opinions. I think not continuing to do so, given the limitations and sensitivity that existing technologies

have, and does a disservice to patients because these -- especially as these technologies become more widely used beyond a small number of diseases. At the same time, I want to emphasize that I think it's important that we not get hung up on trying to get a situation where we have nothing that is -- we believe that no off-target effects are happening.

So it's important for the sake of patients to be able to define risk as well as we can at any given moment and then to balance that against benefit. And I continue to be very bullish and very, very enthusiastic about trying to move forward with these different gene editing therapeutics into the clinic. We do need to continue to improve sensitivity as well as to be able to have assays that predict functional consequences of off-target effects. And I do think, ultimately, a lot of the limitations in sensitivity we have come down to error rates of next-generation sequencing technology. So providing strong support for the development or advancement of next-gen sequencing technologies and improving their error rates will be very, very

important for the future as well.

There's other newer technologies. So David Liu's group recently described prime editors. And so we are working on trying to actually adapt ONE-Seq for prime editors as well. And then there are other types of, if you will, Cas9-independent or non-sequence recognition-based edits that can occur. So for example, we recently described RNA off-target edits that occur with the cytosine- and adenine-based editors that are due to the deaminase portion of those enzymes functioning on their own. And other groups have described off-targets on DNA that are not -- of base editors that are not necessarily guided again by the Cas9. And so these are important areas to continue to push forward on as well.

And then another very important area that I believe will be important to account for in the future is human genetic variation. So at the end of the day, these are sequence-specific reagents that are using to target sites. And so the profiles of off-targets are not going to be the same in everyone. You can define

them for a reference genome, but it's actually very important, ultimately, to be able to define them for specific individuals if not actually specific populations or subpopulations of individuals.

And although it's not possible to do this practically or feasibly for every single patient at present, I think advancing technologies that allow us to better understand the impact of human genetic variation on off-target profiles is a very, very important goal for the future. And ultimately, being able to define off-target profiles individually for patients is important as well. And then it's also important to continue to focus research efforts on better functional assays that allow us to identify what the functional consequences are and, in particular, for tumorigenic risks of off-target effects because, again, this is an area where we just don't have very good assays at present. And then in the longer-term, follow-up studies and considering how to -- how and how long to look at patients going forward are important areas of continued development and research as well.

So I will stop there. I'm only like a minute-and-a-half, I think actually overtime. I do want to acknowledge Vikram Pattanayak and Karl Petri in my group, who led the development of the ONE-Seq assay. And this was largely funded by DARPA, with some additional funding from NIH and the MGH Research scholars, and done in collaboration with the Lie Lab, so David Liu's group at Harvard and Greg Newby.

And then I also want to acknowledge the American Society of Gene & Cell Therapy, who had some input in some of the slides that I did early on for another presentation I gave about a year-and-a-half ago as well on this topic. So thank you for your attention. And I guess I'll be happy to take any questions about these issues in the Q&A. Thanks.

**DR. SANDUJA:** We'll start with our panel discussion now. I'd like to welcome our speakers and Dr. Zuben Sauna from OTAT to join us. Yes, please.

## PANEL DISCUSSION WITH Q&A

**MS. HOWARD:** Hello. I'm Marilyn Howard from the University of Pennsylvania. I have a question for Dr. Griffith. I was very intrigued by the multiple steps that you have in your bioinformatics process. And I'm wondering what the metrics are for feeding back to the machine learning in that process and whether or not any of the clinical trials have yet reached a stage where the clinical outcomes can feed back into the machine learning.

**DR. GRIFFITH:** That is a great question. The short answer is that it's pretty early days for the clinical trial, so none of those clinical trials have actually completed yet. And many of the trials involve vaccination in a setting where the tumor is not actually on board anymore, so they've been -- the tumor has been surgically removed. And the vaccine is being used in almost like a vaccine sense to prevent recurrence. So it will take some time for the survival information to accumulate. So we're probably at least two or three years away from that sort of real gold

standard of is this actually improving outcomes.

That being said, you mentioned the word metrics, which I love. There's a lot of other earlier-stage things we can look at. So many of the trials are building in a variety of innovative immunological monitoring steps to try to get an early sense of are we seeing t-cell responses, in terms of changes on the TCR repertoire or functional assays of t-cells, screening for particular candidates before and after vaccination. So that data should come sooner.

It's still going to be relatively sparse because the trials are so small. But we can probably learn quite a lot on a per peptide basis because many of the assays are giving us a specific readout and useful metrics for each of the peptides that we tested. In some of these patients, we have up to 20 candidate peptides. And we really don't know what the rules are for what makes a good peptide.

So we're potentially going to learn a lot in the next few years, subject to sufficient sharing of that data and all of the usual challenges that go into

these kinds of studies. But I think that there's reason to be very optimistic that we'll improve our understanding of how to actually design a vaccine significantly in the next few years and hopefully, more like four to five years for the gold standard survival analysis.

**MS. HOWARD:** Thank you.

**MS. ADOMAKO:** Hi. My name is Jessica Adomako, and I'm from Genentech. This question is for you. And it's --

**DR. SANDUJA:** Can you please speak up? It's hard to --

**MS. ADOMAKO:** Can you hear me?

**DR. SANDUJA:** Yes.

**MS. ADOMAKO:** Yeah. This question is a follow on to what the previous person asked. And there's a second part, which is to the FDA. You talked a lot about the bioinformatic challenges. And I completely agree with you. And my question is have you looked to the work that has already been done by the community at large in establishing standards for analytic validity,

everything from referenced genomes to databases to validity of bioinformatic pipeline software, et cetera, et cetera, in the related field of developing NGS-based tests?

Because there's a lot that can be learned. And it's the exact same question to the CBER folks on the panel. Your compatriots at CDRH have really done an amazing job of establishing widely accepted community standards.

And what we would like to know is are these learnings being shared? Are there things that you can develop based on what they've already established? And completely conceding that this field is, as you said, constantly evolving, we're always chasing a new goal. But can we ping off of what we've already done?

**DR. GRIFFITH:** Yeah. So that's a really great point. And I meant to mention this actually in my talk that I think that there are many, many common themes and similarities between what is going on, for example, in the new antigen vaccine design process that can benefit from the years and years of labs producing,

conducting genomic diagnostic tests and producing a clinical report with interpretations for a specific variance. They face many of the same challenges.

So we absolutely can learn a lot from those practices and standards. And we're definitely -- all of the consortium that I mentioned really evolved out of those groups and heavily involve experts that have years and years of experience in those areas. So yes, absolutely.

**MS. ADOMAKO:** I'm just waiting to hear from someone from CBER. Are you speaking here?

**DR. SAUNA:** I didn't quite get what do you want -- what is the question to CBER?

**MS. ADOMAKO:** The question to CBER is, has all of the work that's gone on at CDRH in establishing these protocols, processes -- they even have wonderful final guidance documents that are now being widely used by sponsors. Is any of that, do you think, translatable to CBER?

**DR. SAUNA:** I think Dr. Carolyn Wilson wants to address your question.

**DR. WILSON:** I'm going to just step in real quickly. Carolyn Wilson from Center for Biologics. I just wanted to say, yes, we actually have at the agency level a genomics working group, where we've actually been exchanging and learning from other centers, working in this space for about five years. And then we also have a CBER genomic working group. And we've actually brought the CDRH guidance documents to that group and looked at them very carefully, as well as ICH guidance documents and so on. So certainly, we're well-aware of those other efforts and are incorporating them into our own thinking.

**MS. ADOMAKO:** Thank you.

**MS. WITKOWSKY:** Hi. Lea Witkowsky from Innovative Genomics Institute at UC Berkley and UCSF. That was a really great session. Thank you, everybody. And I have a question for Keith Joung in particular. Very exciting data.

I'm wondering for ONE-Seq, if you're starting with a prediction algorithm, presumably, you're starting that -- you're running that prediction on some

sort of reference genome. And as we think about individualized therapies and kind of harkening back to the vaccines, developing these at an individual level, how do you expect, or do you expect, to be able to adapt that for individual patients?

And you mentioned a little bit about this human variability. And what is the capacity, or where do you see the future going to be able to run something like that to catch things that might be off-targets only for an individual that happens to have a mutation that makes it a new off-target that you wouldn't catch normally in a reference genome, for example?

**DR. JOUNG:** Yeah. That's a great question. Thanks, Lea, for that. So I think one of the strengths of ONE-Seq is the ability to be able to look in a detailed way at specific sequence changes for an individual, or potentially even a group of individuals.

It is dependent on having all genome sequence data for that person. When we set out to start developing ONE-Seq actually about two, two-and-a-half years ago, we assumed two things would start to come

down in cost. So one would be oligonucleotide synthesis, which I think has already begun to play out, and hopefully will continue to only get less and less expensive. And the other was the assumption in the continuing drop in the cost of being able to do whole genome sequencing.

So if you envision a world going forward where it's relatively inexpensive to do whole genome sequencing and to do oligosynthesis, then I think it becomes very reasonable to assume that you could combine those two, be able to practice ONE-Seq, and then be able to get information that's specific to a particular individual. I also think it's just generally easier to scale something like ONE-Seq to cover more people and variants in more people than it is to scale something like doing one-off in vitro assays, the way you do Digenome-Seq, CIRCLE-Seq, or SITE-Seq right now.

So I hope that makes sense. And that is our hope, is that we will be able to account for more individualized genetic variability because, as I said,

at the end of the day, these things are sequence-specific agents. And so they are -- you expect -- it's entirely reasonable to expect that their impact will be specific to a particular individual based on their genome sequence.

**MS. WITKOWSKY:** Thanks.

**MR. STEIN:** My name is Aron Stein with Sangamo Therapeutics. This is a question for Dr. Joung. This is in regard to your methodology for the validation of your targets using a humanized mouse. Why that model versus primary human hepatocytes?

**DR. JOUNG:** You could do it certainly in primary human hepatocytes as well. We validated ONE-Seq-predicted sites in cells in culture. So there's no reason why you couldn't do it that way. Although there are some challenges with getting the reagents efficiently into human hepatocytes. It's certainly not unreasonable to try that experiment.

The reason we did it in the context to the mouse was that we wanted to look at in vivo in an in vivo setting, where you would be delivering these

reagents in an in vivo setting, whether we would predict those off-targets there. Because if you look at the literature, to date, no one has actually been able to identify these off-target sites, especially those that have a large number of mismatches relative to the on-target site in the context of something like an in vivo animal model. In fact, our -- especially when you're using a nuclease that has been designed to be relatively orthogonal to the human genome. And so that's why we chose that particular guide because it would be easy to spot an off by one, off by two, off by three. That I don't think anybody would be surprised by.

But this is the first demonstration to our knowledge where you're able to find off by fours or off by five sites in an in vivo animal model where you've delivered the nucleases in that way. So there were a number of reasons for doing it. You certainly could do it in cells. I didn't mean to imply that you couldn't do it that way.

**DR. SEYMOUR:** Okay. Thank you.

**MR. ALDRICH:** Time for one more? Okay. I just wanted to follow up with Malachi on his answer to a previous question. Regarding -- I think a lot of folks don't quite appreciate that the biggest problem that comes out of the predictive algorithm is false positives for neoantigens that aren't really present or -- and that that's a problem which we can address by running spot tests against -- ELISpot spot tests against t-cells and eliminating false positives by identifying, of the predicted and synthesized top candidate antigens, synthesizing the peptides that correspond to the neoantigens and then testing them against the patient's t-cells for reactivity.

We kind of eliminate that problem of the false positives in the -- and in terms of issues that are really front and center for me as a patient, it's making sure that, of the 5 to 20 peptides that we're going to use in a final vaccine, that they're all validated in some sense as having a corresponding T-cell, which, hopefully, they'll amplify. I just wondered if you'd comment on that. Thanks.

**DR. GRIFFITH:** Yeah. I mean it's a really interesting question and topic that I think both the false positives and false negatives are interesting. I think that we think of the false positives as being more tractable because as you say, you're right. We can think about validating them further, and we can look for specific T-cell responses.

Although, I guess I would say that it's still falling short of -- ideally, we would know that they were not just T-cell immunogenic but therapeutically useful. And that's sort of like the next stage of --

**MR. ALDRICH:** Yeah.

**DR. GRIFFITH:** -- another layer of false positives that's yet to be learned about.

**MR. ALDRICH:** Right.

**DR. GRIFFITH:** But I think we also don't know what we don't know, in terms of false negatives. So we don't really have a great sense, of the candidates that we're nominating, how many great candidates did we leave on the table just for not knowing about them, not looking for the right kinds of variation or

prioritizing them incorrectly because of our lack of complete understanding of how the immune system works. So I think that's also an area for significant improvement. And we are starting to see a little bit more by unbiased assays looking at with the peptide mass spec elution dataset started to give you a bit of a sense of just sort of serving, like what are all the peptides that we're sticking to a particular MHC molecule and getting a more comprehensive readout of that. Although, it also has some pretty significant caveats to those datasets that we could probably talk about for an hour.

**MR. ALDRICH:** For -- we will. But just one last thing to have you comment on is one of the things that ties into the talk we heard earlier, about platform versus product and characteristics of the neoantigen platform, as opposed to the specific vaccine -- one of the things that I'm very impressed by is that, when you read across the literature, we have a great deal of familiarity with peptide vaccines. I mean, historically, it's something where there's a lot

of data, not necessarily neoantigen peptide vaccines, but peptide therapies have been around a long time.

And I think that one of the problems or one of the challenges is that we have to recognize when we have a platform where we know enough, so that we can declare the platform as relatively safe. And as a consequence, if you perform best practices, with respect to the neoantigen platform, you can be pretty well-assured that a patient isn't going to drop dead when they're -- in fact, one of the incredible things about the neoantigen trials that are going on is that, to my knowledge, there hasn't been a single severe adverse event reported from a safety point of view.

And yet, we are still waiting for the first approval of a neoantigen peptide vaccine for any indication of cancer. And so one of the things that occurs to me is that, gee, if we have a safe platform and we know enough about it and it proves efficacious in phase-one trials saving lives, what is -- where do we get comfortable enough to say, oh, well, if you're following this best practice in terms of the supply

chain, we really ought to make it available to lots of cancer patients? Just that's where I'm coming from.

**DR. GRIFFITH:** Yeah. I mean I guess my main comment would just be to completely agree with you. I think the pieces are in place to create such a platform or process that we can really carefully document and become confident that it is robust and reproduceable and safe. My impression is -- as I said, many of these have not published. Basically, none of them have. But the early impression does seem to be that the safety profile of this approach is outstanding.

And so that comes back to my initial comment that the potential patient population this could be applied to is just huge. I mean if it's safe and even just a little bit efficacious for some people and we could do it cheaply and broadly, you could imagine this being added into the course of treatment in so many current clinical cancer regimes, just to get a little boost, just to get a little boost from the immune system against that person's tumor in a way that seems to be very safe. But we need to establish efficacy, or

this is all moot. But yeah.

**DR. SANDUJA:** I would like to add another point of view to that. From a regulatory perspective, if you look at that, we have gained and we have gathered a lot of confidence in the platform approaches that these are able to really very confidently, and with a lot of robustness, can inform safety of these products. And that's what has enabled a much faster translation into clinical trials.

However, when it comes to approval or licensure, that's a different question there. So we are gathering confidence with respect to safety of these platform approaches to further facilitate. And that's being evaluated as we move forward with clinical development of these products.

**MS. WALKER:** Hi. Karen Walker from Genentech. Thanks for some really interesting conversations. I have a couple of questions, again, going back to the data and the bioinformatics. While I agree that safety is a very important aspect -- and so is efficacy, also so is supply and control -- once you have -- you're

treating lots of patients and the variability that you described increases exponentially, how do you continue to learn and identify what is important out of all of the data that you're gathering versus what is just a datapoint?

And I think that's a really important question to ask and to answer. So I would be interested in your thoughts.

**DR. GRIFFITH:** Yeah. I mean it's a hard question. Do you think the increased variability from doing the set scale on sort of a population scale, is the implication there because there are so many players in the space, and that's kind of a wild west of a hundred different people doing it a hundred different ways? Or do you just -- or do you mean more that we're just servicing the tip of the iceberg in terms of how patients respond and how different tumors behave?

**MS. WALKER:** I think it's more the latter.

**DR. GRIFFITH:** Okay.

**MS. WALKER:** But I also think it's what you mentioned about the standard reference genome changing,

and what are disease-causing elements or the disease-related elements versus just natural variability in our own genetic sequences. This is the kind of thing that I think we need to understand more.

**DR. GRIFFITH:** Yeah. I mean I think from a personalized genomics aspect of it, personalizing it to the reference genome of the individual, so that you're comparing that against their tumor, that is a tractable problem and one that has been tackled in other areas of cancer genomics and NGS testing for cancer with tumor genomes. In terms of just, yeah, how do we figure out how to do it better in the face of all this variability for different cancer types, I mean, I guess the high-level answer, I would say, is to share the data openly and let people have access to it and try to make the -- look inside the black box, that we really need to understand what's going on in these pipelines, what the process actually is, and what features are important.

All of the metrics, the readout, everything needs to be exposed, so that we can -- because it's so complicated it's going to be very difficult for one

group to understand. The pipeline is already so complex that it's actually pretty much impossible for a single person to really even understand the whole thing from end to end. So it's really going to be a sort of community team science or big team approach, even just for the bioinformatics part of it. And that's just one small piece of the complexity of this overall process.

**MS. WALKER:** Thank you.

**DR. SAUNA:** Could I follow with the question?

**DR. GRIFFITH:** Yeah.

**DR. SAUNA:** So to follow up on this question, would it help if -- so you're already at some level of precision by looking at an individual. As you get to a deeper level of precision, looking at particular cell types or single -- if you do single-cell sequencing, and particular subsets of that tumor, which would probably be more susceptible to the antigen and making a tumor antigen targeting -- say a metastatic cell, for example, rather than the tumor cells in general. Would that level of precision help making it more effective?

**DR. GRIFFITH:** I think it's definitely

relevant to interpreting the response to the therapy because the tumors are heterogenous.

And this is definitely a consideration of ours, when we think about designing the vaccine, do we specifically target only those antigens that are thought to be in the trunk or a clone of the tumor that will be in all of the tumor cells and not in a subclone? Or is it, in some cases, okay to target subclonal mutations? And then in terms of interpreting the immune response, then the single-cell analysis of the tumor microenvironment becomes very, very relevant and useful potentially. But it's also very much a developing area where there's so much to be learned.

**MS. MCLELLAN:** Hi. My name is Lorraine McLellan. I'm a cancer patient and actual cancer survivor. But I have something that's going to relapse here in the next year or two. And I have done my genome, and I am hopeful that I can do an neoantigen vaccine.

But here we are in the headquarters for the

FDA. And what I would like to ask, because each of you have done such an impressive job, is if I was able to grant you one wish each to give a message to the FDA today about what you would like them to do near-term, and near-term, let's say 12, 18 months, to advance your work individually, what would that be?

Would that be a question that I could each of you to answer, so that we have a real takeaway and some action items? Because we do have a bit of a need for speed. I can appreciate that it's going to take a couple years to get to gold standard. But what does the FDA need to do near-term for each of you to advance your work? Thank you.

**DR. GRIFFITH:** Do you want me to start? So in terms of my individual work, I guess I would rather answer more for the overall translation of this work to patients. I think there is a challenge. And I've heard this from quite a few representatives of -- in research and in industry, that it's difficult to think about developing a commercial version of a new antigen vaccine without any clarity around whether the process

can be approved as safe, something that we're comfortable with.

So I think that this meeting is very timely. And I assume it is accompanied by an interest on the part of the FDA, although I have no idea, to gather information about how one might think of ultimately giving some kind of regulatory oversight to these -- to the process that's come up so many times. So yeah, I would encourage the sort of continued serious thought of that idea.

Because right now, I think it's a little bit of an impediment for someone who's thinking about trying to do this as a company that there isn't really an obvious -- you know, you're not going to be able to patent a drug. So -- and there's sort of risk averse problem, where if they're -- if you don't have any sort of stamp of approval that the process has been evaluated in some kind of formal way as being safe, then it makes it seem riskier to pursue it.

**DR. SEYMOUR:** I'll go second. So I think it's a really good question and one of the things I've sort

of put a hat on in trying to determine those different aspects. So there is getting these therapies to patients in a timely matter. And I think it sounds like that is of critical need because a lot of these diseases do progress very rapidly. So you don't have a lot of time, particularly for the individualized therapies.

And I think some of the discussion topics that the FDA is having right now, I think are a path towards that. And so I look at what does it take to get something to a patient so that you can test it rapidly. I think a lot of the pathways are already in place for that in getting it to go into early-stage testing very, very rapidly, whether it's individualized therapies or not.

The second aspect is moving towards the commercialization and licensure. And I kind of divide those two separately when really thinking about individualized therapies versus, say, bringing therapies for a much larger population. I think they're two separate questions. And so I think my wish

to the FDA is to continue discussions like this, work with both industry as well as academic partners to come forward with creative ways of bringing and testing these products safely in patients and always keeping in mind -- and I think everyone does on that -- that benefit/risk and the severity of the indication that we're trying to move forward with.

**DR. JOUNG:** Yeah. I don't have any specific request for the FDA in terms of the work that we do. I think for the community, as a whole though for gene editing, I would encourage the community to have maybe broader and wider-ranging discussions about how to better standardize how to benchmark and how to develop consistency around some of the safety and in particular off-target testing because I think it's become very fragmented. And so some of the issues that I raised in my talk I think are things that we as a community need to address.

And if we can do that, I think it will make it easier for companies, academics, to be able to know what it is that they need to do. Also, that it is an

evolving and fast-moving field, so the standards will change over time. So to the extent that we can build a mechanism by which there is -- I don't know exactly what the form will be or what the body would be that would do this -- but some kind of ability to respond to changes as they occur, to be able to keep those standards current and up to date. I think that would be helpful for the field.

**DR. SANDUJA:** And to conclude that discussion, I would like to -- from the FDA side -- would like to reiterate that FDA acknowledges the challenges that are associated with development of these individualized drug products. And as we have seen, during all our presentations and also during the discussion, there are pathways and there are opportunities to discuss these challenges and come to an agreement how they can be resolved. Of course, we already agree that the standard paradigm of drug development may not apply to development of these individualized therapies. And as the science behind these products is continuously immerging and evolving, the Agency itself is open to

these discussions and further efforts, like the one we are having today, to continue development of these products. Thank you.

**DR. RAYCHAUDHURI:** I would like to thank all the speakers and panelists and the audience participants for what has been really an excellent discussion this morning. And I'd like to thank Dr. Sanduja for moderating this session. We are now at the lunch break. And we have a very exciting afternoon session ahead of us. So I ask that you please return back to this room at 1:15, and we will proceed with the afternoon sessions. Thank you.

**[BREAK]**

**SESSION 3: CLINICAL**

**DR. RAYCHAUDHURI:**

So I hope everybody had a nice break. So in the morning sessions, we heard about challenges and opportunities related to manufacturing of gene therapies and phage therapies and tools for safety testing and development of individualized therapeutics products. This afternoon we're going to focus on

clinical development. The challenges and opportunities to leverage what is known to facilitate development of related products. And in session four, we will come full circle on the focus and the reason for this workshop, which is to discuss how we collectively can increase access for patients to these critical products in a timely and sustainable way.

So we have a very exciting agenda set for this afternoon. I would like to introduce Dr. Rebecca Reindel. Dr. Reindel is a medical officer in the Division of Vaccines and Related Products Applications in the Office of Vaccines Research and Review at CBER. Dr. Reindel will be the moderator for session three, which is on challenges and opportunities for clinical development of gene therapy and phage therapy products. Dr. Reindel.

**SESSION 3 MODERATOR INTRODUCTION: DR. REBECCA REINDEL**

**DR. REINDEL:** Thank you. I'm really excited to be part of this third session. We have two

presenters. Dr. Schooley and Dr. Kohn will be presenting, and then we'll have a panel session to follow similar to the other sessions.

So by now you've seen several versions of this slide. And I wanted to bring it back around to clinical development and talk about the clinical development of individualized therapeutics within this paradigm. And as you can see, this figure describes clinical development all the way through discovery and pre-clinical, which we've covered quite a bit this morning, and into the clinical phase of things where I think this afternoon's sessions will sort of start to take over.

Within this paradigm, typically you see smaller Phase 1 studies that are designed to assess safety and dose selection and then move up through larger populations into Phase 2 and Phase 3 studies, which study safety in an ongoing manner, and also start to assess for effectiveness. However, individualized therapeutics may not lend themselves as well to this classic paradigm. And therefore, it's really important

that we look for opportunities for flexibility within this paradigm with regard to clinical development.

In this session, we hope to identify both the challenges that we face and anticipate in this space, as well as any opportunities we can identify for ongoing clinical development of individualized therapeutics. So I like to think that every challenge presents us with an equal opportunity to meet those challenges and rise above them. So this is no -- by no means an exhaustive list of all the challenges we face in this space but some key highlights that we hope to get to today as well as others include the following: clinical investigations in the context of potential manufacturing challenges, many of which were discussed this morning.

In these studies, we need to pay a lot of attention to study design when the product may be different for every recipient or may need to be tailored to a specific recipient or subject in real time, such as to accommodate individualized treatment of a patient with an infection that requires a specific

phage for that infection and then the impact of these differences on the study procedures in the trial and the interpretation of data that arises from these trials. How do we interpret data that comes from individual patients or subjects within the context of a clinical trial that may include only maybe one or several subjects? And also, how are we to interpret novel endpoints? For example, micrologic- -- microbiologic endpoints for bacteriophage treatment. This may pose some challenges in interpreting endpoints in the absence of precedent.

Again, so what are the opportunities? And I think a lot of the discussions today will focus on what some of these opportunities are. So how do we create infrastructure around a development program for an individualized therapy for which there may be no similar products developed or licensed in the past? An example of this is, again, individualized bacteriophage therapy where there's no existing model or structure for clinical development or a specific guidance for this type of product. And as experts in the field

emerge and collaborate, we can build systems that facilitate the development of multiple research programs. And we hope to address that today.

The roadmap of this infrastructure will necessarily include novel clinical development programs that may include innovative clinical trial designs and statistical approaches to small population-based clinical studies. Ideally, these early approaches to building infrastructure can create a foundational basis for future development. If we're able to leverage both prior and collective experiences to guide us forward, we can expedite and optimize the development of these products that can meet specific individual needs.

So in order to maximize these opportunities that we identify to meet the challenges that we see, we will require flexibility. And where are there opportunities for flexibility? Today, we hope to discuss some innovative approaches to the clinical portion of our product development program, including areas where regulatory flexibility may be applicable. Some examples of this include, as I mentioned, novel

clinical endpoints and statistical approaches that allow for the enrollment of small populations of subjects or subjects that may receive different products within the same clinical study.

So some of the major areas that we hope to cover today in our presentations and our panel discussion include: the approach to designing and interpreting efficacy assessments in studies that may occur for a single individual or in a small group of subjects. Again, the example of this is the development of infrastructure around approaches to demonstrate clinical benefits with phage therapy. Along similar lines, accumulating safety data across a range of disorders for treatments with genetically modified hematopoietic stem cells can be informative.

Our presenters will also be addressing the need for study designs that facilitate the interpretation of clinical data that may present unique challenges, such as the use of bacteriophages adjunctive therapy in the context of complex and varying antibiotic regimens across a variety of

anatomic locations and etiologic agents. Of course, another important consideration, and many people have already addressed this in the morning session, are the timelines for development of much needed individualized therapies. Today, we'll discuss the impact of these timelines on end-to-end development and approaches to optimizing this timeline in the context of advanced therapies.

As we move from our presentations into our panel discussion, we hope to touch on the some of the following points, and we're looking forward to a thoughtful and insightful discussion with our patient -- - with our panelists, speakers, and audience members. Some of these include the approaches that may facilitate the assessment of efficacy in individualized therapeutics, especially in the context of small groups of subjects. Are there ways to leverage accumulated safety data to enhance assessments of safety? How do we approach the interpretation of safety data in clinical development programs that may not progress according to the usual paradigm? And what

are some statistical and study design approaches that we can consider as we exercise flexibility?

So I'd like to introduce our first speaker. This is Dr. Schooley, who currently serves as Professor of Medicine and Senior Director of International Initiative at UCSD, one of my alma maters. He completed medical school and an internal medicine residency at Johns Hopkins and an ID fellowship at NIH and Mass General Hospital. He was at Harvard in 1981 with early research efforts directed at the pathogenesis and therapy of herpes group and retroviral infections. He was head of the Division of Infectious Diseases at University of Colorado in 1990, another one of my alma maters. And he led the NIH AIDS Clinical Trials Group from 1995 to 2002. And he's currently, as I said, now at UCSD, and he's serving as the head of UCSD's Infectious Disease Division. And his recent interests have focused on the use of bacteriophage to treat infections. And we are excited to hear his talk today.

**OPPORTUNITIES AND CHALLENGES IN THE CLINICAL DEVELOPMENT OF BACTERIOPHAGE THERAPEUTICS - DR. ROBERT T. SCHOOLEY**

**DR. SCHOOLEY:** Thanks very much. It's a pleasure to be -- to follow someone who's had such an illustrious pathway in terms of institutions she's been in and to try to talk to you today a bit about a juncture in phage therapeutics. I'm going to try to bridge some of the elegant discussion you heard this morning from Jason Gill about some of the aspects of phage production, phage biology, say a little bit about the -- where phage therapeutics are today and then to go on to reach forward to the final discussion this afternoon where we'll be talking about access to emerging therapeutics with a few comments about how those might be able to fit into some of the clinical trial development approaches as well.

So, the -- today, I'm going to try to briefly talk about some of the limitations of antibiot- -- anti-microbial therapy. Everyone here is quite aware

of most of that, say a little bit about how phage therapeutics might fit into some of these gaps. I'll say a small amount about what we know today, go on to talk about some of the key gaps, and then talk about moving from where we are today to orderly clinical development.

Obviously, these days as you read the increasing number of reports of multidrug resistant bacterial infections, it's clear that the microbial evolution on a global platform is outpacing our ability to keep up with them with small molecule traditional antibiotics. So one of the obvious places for phage therapeutics is to deal with this because they've been innovating in terms of any microbial activity for about 300 million years, and we only started about 80 years ago. The -- we also know that phages do some things that antibiotics don't do, for example, interfering with biofilms. We know that phages can go to some places that are difficult to penetrate with antibiotics and places where antibiotics don't work as well. So they're -- in addition to just spectrum, there's some

other aspects of phage therapeutics that are attractive in thinking about how we might take advantage of these activities in individualized applications.

So what are the opportunities here? There's a virtually unlimited number of and diversity of phages in nature. And we have tools now to genetically modify those phages. Whether we will need to do that and what we can do to make them better than they already are, I think, remains an area of intense interest and one that will have to be validated in the clinic in a series of iterative clinical studies.

We know that there's some opportunities with phages that are quite attractive, particularly the pharmacodynamics. With antibiotics, we give a dose of antibiotic, and we're already worried about whether the kidneys or the liver or both are leaching the antibiotic away from the site of infection before the next dose. With phages, in theory at least, once the site of infection is seeded, self-replication can continue to provide a phage to deal with the antimicrobial challenge.

We also know that phages can disrupt biofilms. There have been an increasing number of animal studies and clinical anecdotes in which this seems to be playing a role. Phages have a theoretical advantage of being less disruptive to the microbiome and contributing to further antibiotic resistance when they're used in -- as targeted therapeutics. And finally, there are some reports of how phages can re-sensitize organisms to antibiotics through both mechanism-based approaches and more generally.

Now, where would you think about using phages? Obviously, for patients that have organisms that are not susceptible or to antibiotics that patients can tolerate, places where we're not -- where antibiotic delivery or activity is limited by the anatomy, and in situations in which having something to deal with biofilms might be particularly attractive. And these are areas that are already under investigation and also targets of individual experiences in the clinic.

So what do we know today? Well, we know this morning that -- from Dr. Gill's comments, we can make

relatively large batches of phages quite safely and quite uniformly. And we can administer them to the patients with very little evidence of toxicity if the phages are produced in ways that are cognizant of contaminants and deal with issues related to genes you might not want to have in the phage and so forth. So the technology is there to produce phages in a very homogenous way. There are a fair number of nuances about phage stability in different conditions and host strains and so forth that are quite different from the antibiotic situation. But they're all solvable in this context of individualized therapy.

We know that there have been a lot of -- a large number of anecdotal cases in which phages seem to have shown benefit for individual patients. But these are all anecdotes. And we need to move from anecdotes to more organized data to be able to understand how to actually use phages in clinical practice. And we know that, as with antibiotics, resistance develops quickly. And we need to understand how to circumvent this with phage cocktails and other approaches that are also

under development.

So what are the gaps? Well, one of the major gaps is how do we know which phage or phage combination is best to use in a given patient? If one remembers back to the early antibiotic days, early antimicrobial testing involved agar plates, broth dilutions. And we spent a long time, 20 or 30 years optimizing predictive mod- -- approaches for clinical efficacy, and we're still not there. Phages are the same story.

We have very little knowledge about what the optimal dosing levels, routes of administration, and duration of therapy should be with phage therapeutics, the classical Phase 2 sorts of data that one would want to have of an antibiotic before proceeding to clinical endpoint trials. We don't know enough about the antimicrobial activity of phages in vivo in humans. We know that they can select for resistance, which is a very good measure of demonstrating they have any bacterial activity. But they -- how the antimicrobial activity compares, for example, to antibiotics head-to-head is something that is still up in the air.

We know that resistance develops quickly, but we don't understand the determinants and the kinetics of resistance and how that may be affected by things like phage host range and other aspects of phage biology. And we need to understand how to mitigate this. And finally, we need to move on to think about how to demonstrate phage efficacy in specific clinical situations.

Now, where is phage therapy these days? Well, there's been a lot of off-line use for over 100 years in many parts of the world. And I think the take home message for most of this is that, by and large when phages are given orally or topically, there's very little evidence of toxicity. But it's been very difficult to assess objectively whether there's any evidence of efficacy because many of the endpoints are chosen post-hoc.

Many of the patient populations tested were not homogenous, and very few of the phage preparations used were well-characterized. We know that there are increasing number of individual uses under eINDs. And

again, we're beginning to see that some of these are becoming more organized and more standardized, in some ways bridging the way to early clinical trials from the standpoint of a little more homo- -- homogeneity.

So how might this eIND experience bridge towards IND experiences? Well, one approach is that as people who are confronting patients along with the -- often with similar clinical indications confer with each other, we often will converge on the same approaches and based on what other people have done so that each patient isn't a brand new patient. I'll talk to you a little bit about how the iPATH center at UCSD, which has begun to both do clinical trials and assist with clinical cases, has been trying to do that.

We also know that with -- standardized clinical approaches do emerge when people do the same thing over and over again. There was a very nice case series in the *Nature Microbiology* that appeared in paper this month and online last month about a dozen or so patients with staph sepsis from Australia. And the M. abscessus experience with Graham Hatfull, since

Graham is about the only one who has M. abscessus, we've been collaborating with him. And most of the therapeutic interventions there have been pretty standardized because we really don't have many data points to start variation.

Now, how have we tried to do some of this at iPATH in terms of trying to, while the clinical trials are up and going, make phages available to people who need them? We have been engaged in this -- initially stumbling into it about four years ago with a faculty member at UCSD. And then one of our astute clinicians began to identify other patients who needed phage therapy. And since that time, another eight or nine patients have been treated at UCSD. And then, we began to get calls from other places about how to approach phage therapeutics. And the Chancellor of UCSD put together some seed money for us to put an infrastructure together to be able to respond to some of these requests as they came in.

The approach we currently take is, when we get a request from a patient or family or treating

physician, is to try to get back to the treating physician because we are not trying to be the patient's doctor. And many times in those settings, things get lost in translation, and we don't want to be giving medical advice to people who are not in front of us.

After we talk to the doctor, often the doctor will tell us what this patient needs is a dose of ampicillin, or what this patient needs is nothing. And we move on, or sometimes the physician will say, "You know, I don't really know what else to do but would phage therapy be reasonable?" If it seems reasonable we'll talk through some of the options. And if the physician wants to proceed, then we proceed to try to help them do that, with the first step being trying to help them find a phage product that can be used.

There aren't many sources for those these days in terms of phage production and discovery operations that provide phages of sufficient quality that we would feel comfortable giving to patients in any kind of an organized way. We have kind of -- there are a group of collaborating institutions and investigators who have

expertise with specific organisms. People at Texas A&M are particularly good at Burkholderia. Baylor works on E. coli and Klebsiella. Yale has been very interested in Pseudomonas and so forth.

And so what we'll often do is say to a physician, “We don't have any solution for you, but you might want to talk to Jason Gill or to someone at one of the other places.” They will then send an isolate to that location, and they will then -- at this location, if they have agreed to try to screen, will either come up with a phage or not. So one of the bottlenecks is whether or not the receiving laboratory can come up with a phage that -- or phage, preferably a cluster of phages that might be active against the patient's isolate.

If they find a suitable phage, there are a couple of -- the next bottleneck is moving from an academic laboratory discovery operation to being able to have a product that be given to a patient perennially. And many academic labs haven't done that before. They have been -- they have very high-quality

operations. But things -- thinking about pharmacologic stability, how to dispense the product over a period of days or weeks from an investigational pharmacy, dealing with things like bacterial contamination with a USP 71 testing and so forth, these are not things that many academic labs think about. And one of the things we've tried to do is help them at least become aware of those.

And increasingly, these labs have -- are now incorporating that so that when they talk to the FDA in conjunction with the referring physician -- because that's where the eIND has to come from -- many of these things have already been taken care of before the FDA reviewer has to say, “So what have you done about sterility?” If they ask us about dosing we say, “We don't know the answer to that, but this is what we've done in the past. And these are things you might consider.”

And what often happens is people will use doses that are similar, routes that are similar to what we've used before. And while clinical trials are

proceeding and being developed, we hope that some of this homogeneity will help, at least within the agency, begin to look at cases in more of a -- in the aggregate than as each case being a different approach with different doses given by different routes for different durations. And the phage therapy that is given to the patient is obviously given -- provided by the referring -- by the laboratory and given under eIND.

So another thing that is happening under this is, as time has gone on and more of these experiences have evolved, there are certain very frequent flyers that come up, including treatment of non-tuberculous mycobacterial infections. Graham Hatful has been collaborating with us for about two-and-a-half years now and has had about 90 requests for treatment, mainly of M. abscessus, mainly in trans- -- renal transplant, liver transplant patients, immunocompromised patients. And the bottleneck there has been mainly finding isolates that are -- phage that are active against any given isolate.

Having said that, because the patients are

similar, the requests are similar, we've developed a shell protocol that we're currently trying to refine and work with people at the NIAID to begin to think about how this might move on into a real clinical trial but, in the meantime, suggesting approach like this when patient -- when physicians want to take this to the FDA as eINDs before this emerges. Now, where do you go from there? Well, it's not rocket science about how to develop antibiotics, and these are antibiotics.

I think one of the things that has happened with phage therapy is that it has been treated as if it's something else. These are antibiotics; they just happen to be living. And we've had paradigms to develop antibiotics for 80 years. And if we don't use those paradigms, taking into account some of the biological variabilities, differences with phages, we won't know how to use them in clinical practice.

And we won't know how to benchmark them with antibiotics when choices are made. And we won't know how to use them together because phages will not be used instead of antibiotics except in some

circumstances. At least initially, they will be used with antibiotics. We need to use them in a context that we understand. And we developed -- we, collectively as a community, have developed approaches to evaluate antimicrobials.

Now, there are some nuances to phage therapeutics that are different, and you have to think about in terms of the typical Phase 1, Phase 2, Phase 3 design and issues related to CMC. We've -- some of which were talked about this morning by Jason Gill. So the clinical trials are -- have begun and one of the challenges has been trying to think about how they can be done in an orderly way.

You've seen most recently what amounted to a Phase 3 trial done in Europe on burn patients before Phase 2 data had been generated in terms of understanding dosing, understanding stability on the way to the patient, understanding phage interactions, and even understanding the microbiology of what was being treated. So we've had a lot of enthusiastic efforts to get ahead of the curve without going through

the steps between here and there to develop the kind of data to have studies be done in a more organized way that you would do if you had an antibiotic.

Now, Phase 1 trials, if you start going through the typical approach with phage therapeutics, I would argue are almost useless at this point. We know phages are basically safe if they are prepared well. It doesn't make a lot of sense to try to understand pharmacokinetics and pharmacodynamics of phages in patients that don't have an organism the phage will grow in. So the traditional, "But have you given that to a human yet," whenever a new phage comes along is a waste of time to talk about and really, I would argue, don't help much anymore.

Moving to Phase 2, the major caveat I would make about this is in -- with antibiotics we would demand Phase 2 data before going to Phase 3. And if any generalization can be made about drug development, going to Phase 3 before you understand Phase 2 has been a graveyard for drugs of all classes. And I think phage therapeutics is one that needs to be careful not

to fall into that trap.

So one of the Phase 2 trials that is being developed is one that is being supported by NIAID and being carried out by the Antibiotic Resistance Leadership Group. It's a very simple study trying to understand the activity of phages in humans outside the context of when antibiotics are given in conjunction. This is a study that would be done in patients with cystic fibrosis, who are clinically stable, and don't need antibiotics at the time but are shedding Pseudomonas aeruginosa chronically.

The inclusion criteria would be mainly -- we would be looking at people who repetitively shed pseudomonas in their sputum. There are quite a few people like this who are clinically stable. The goal here would be to do a standard single ascending dose study to understand when phages are given by an intravenous or by an aerosolized route, how long they reside in the lung, what they're antimicrobial activity is, what the evolution of the phage and the organism is under treatment when used together, and to use that to

build a database to move on to do multi-dose studies and studies along with antibiotics in Phase 3 trials. It's a very similar -- very simple design of multiple cohorts with a placebo in each cohort and, at the end of the day, expanding the cohort that looks optimal to get more precision around the measurement.

Now, Phase 3 trials are moving along. I've already made the point that we need to, I think, be careful about launching Phase 3 trials unless we understand what we're doing because the worst thing for this field would be several failed Phase 3 trials that are done in a way in which the data were uninterpretable. The -- it didn't work. See, they've been trying for 100 years, here's another failure is probably the biggest, I think, short term danger to this field because it may or may not have promise. But it would be a shame to have it put aside without understanding the science under the hood.

So in terms of Phase 3 trials, I've already made this point. These studies should be done as if these are antibiotics. That's what they are. And we

need to have microbial endpoints. We need to put them together with clinical endpoints. We need to think about them in the kinds of trial designs that one would use for treatment of multi-drug resistant organisms, if that's what you're after.

We can think about other clinical applications: implanted prosthetic devices in which you might be trying to show, in a placebo-controlled way, that you can salvage devices that would otherwise have to be removed. There are many clinical trial designs, but they should be thought about in ways that give crisp endpoints and that are -- give you information that will help you clinically.

In these Phase 3 trials, the unique aspects that are different from antibiotics are that they -- the organism that the antibiotic in question actually replicates after you give it at the site of infection. And I think mathematical modeling will be very important was we move ahead to understand relationships between population sizes and clinical scenarios. We're going to be in a situation where we will have to think

about aggregating patients with specific clinical conditions, like E. coli UTIs, in clinical trials in which each patient will be treated with a different agent. And by using endpoints that are well-defined and agents that are well-defined in terms of how they are made, we should be able to develop systematic information that will inform clinical use.

Finally, people have talked about phage therapeutics as being high risk, high gain. I would argue that's not really the case. They really are potentially high gain, but are they really high risk? Phage have been around for 300 million years, and they're still here killing antibiotics -- or killing antibiotics -- not yet. They're still here killing bacteria. And what we've had over the last 15 or 20 years is a lot of advancement in terms of how to prepare phage, how to work with them in laboratories, how to purify them, and get them to the bedside.

And what we need to do now is to develop rigorous clinical trials to figure out how best to use them and to have us understand that the reason we do

clinical trials isn't to get drugs approved; it's to learn how to use them in clinical practice. And so of course the optimal clinical trial is when you can do both at the same time, and I think phage therapeutics is ripe for that at this point. Thank you very much.

**DR. REINDEL**: So our next presentation is going to be conducted remotely due to travel issues. Dr. Kohn is a professor in the Departments of Microbiology, Immunology, and Molecular Genetics as well as Pediatric Hematology/Oncology at UCLA. He's board certified with more than 30 years of experience in treating children in the clinical bone marrow transplantation space.

His principle area of research is the development and application of methods for gene therapy of blood cell diseases using autologous hematopoietic stem cells. His lab has investigated methods for optimal gene delivery and expression and gene editing with human hematopoietic stem cells performed in clinical trials of gene therapy for genetic diseases and pediatric HIV and AIDS. He's won many awards and

been appointed to many prestigious positions, and we're excited to hear his talk today.

## CHALLENGES TO DEVELOPING INDIVIDUALIZED STEM CELL GENE THERAPIES - DR. DONALD B. KOHN

**DR. KOHN**: Well, thank you. Can you hear me? Okay. Thank you. Talking to a phone, it's hard to know. Sorry, my travel issue isn't a virus. It was multiple mechanical problems on United Airlines that couldn't get me there.

So I'm going to talk about work that we've done over the last couple of decades actually to develop gene therapy for a rare disease, ADA SCIDs that I'll talk about, kind of, to show that, maybe, if anything, this is the old school traditional route and, at the end, talk about ways that we can possibly bring these kinds of therapies about more quickly forward. So the next slide is my disclosure. And it's relevant. I'm on the board for a company called Orchard Therapeutics, and my university has licensed IP to

them. And I'll talk about that today. That's the ADA SCID gene therapy. Next slide.

So what I'm going to talk about is just give a little background on sort of this area of therapeutics targeting hematopoietic stem cells with gene therapy to treat blood cell diseases. Then I'll talk about it as a case example gene therapy for ADA SCID. And then I'll close with some not so deep insights on lessons that are learned that might be useful for development of individualized therapies. Next slide.

So this is required by our union to be shown at all presentations. This is a hematopoietic tree, making the point that it's the hematopoietic stem cell that lives normally in our bone marrow that both self-renews and gives rise to all the blood cells. Next slide.

And so hematopoietic stem cell transplants can cure a whole list of genetic diseases of blood cells, and this is now over 40, 50 years of work. We can take allogeneic stem cells from a well-matched donor, or even a haplo-identical donor now, and transplant them

to essentially replace the patient's own stem cells, burying the monogenic defect to treat classes of primary immune deficiencies. And I'll talk about SCID, hemoglobinopathies like sickle cell and thalassemia, a whole list of lysosomal storage and metabolic and leukodystrophies, and congenital cytopenias.

So they -- it won't -- you can't treat everything with hematopoietic stem cells, but there's at least several dozen blood cell related diseases that are macrophage, monocyte-related disorders that can be treated by replacing the defective stem cells. Next slide. And so, again, showing on this tree, so then the technical task is that the gene correction event needs to occur in the multi-potent long-term hematopoietic stem cells. Everything after that is sort of entrenched and amplifying effect cell, and the effect would be short-lived if we put the gene into, for example, a progenitor.

And so the two sort of major approaches that have developed now are adding a gene using an integrating virus, as I'll show you. Or the really

exciting emerging area that Keith touched on a little bit in the therapeutic approach is to edit the gene in the stem cell. And either of these if you make a permanent change in the genome of the stem cell that will then be propagated to all the blood cells that follow. Next slide.

And so this is cartoon, sort of, the process. And it starts with the patient. And their hematopoietic stem cells are isolated, which is one of the things that makes this therapy much easier than all the other in vivo approaches that we take the cells out of the body, then in the laboratory either add the gene with a integrating vector and several of the types of viruses that are listed there, or use the new -- all the gene correction methods to site-specifically correct the defect or knock out a gene or change a base or whatever you want to do in the stem cells ex vivo.

And then, typically before the cells are given back to the patient, the patient will receive some types of chemotherapy, or in the future hopefully, monoclonal antibodies to get rid of some of their own

hematopoietic stem cells to make space so that when you give back this modest amount of cells that you've take from the patient they can reconstitute a lot of their blood cell production. Next slide. And so the field has gone through sort of two major rounds of viral vectors. And so the first generation of vectors shown at the top were from -- typically from murine Moloney leukemia virus, where the virus' long terminal repeats were intact and had strong enhancer promotors that make a lot of the transgene messenger RNA and transgene protein then. But these were dangerous because they had strong enhancers in their LTRs that can transactivate an adjacent gene so that, when you add these cells to 10 to the 8th cells from the patient's bone marrow, they land relatively randomly. And if they happen to land next to a proto-oncogene, the enhancers could turn them on. And that in fact occurred in some of the clinical trials in the 2000s.

So the field has largely turned to sort of the types of vector shown at the bottom, these second-generation self-inactivating, or SIN vectors, where the

enhancers are deleted from the long terminal repeats. And then the gene can -- transgene can run off an internal promoter that can be selected, either that it's a reasonably strong promoter without a lot of enhancer activity or, in fact, can be lineage specific like beta globin to make beta globin for sickle- -- thalassemia or sickle cell. Next Slide.

And so using this approach -- and this lists a number of the disorders now that have been treated, not approved drugs yet but at least in preliminary Phase 1 and 2 trials, show evidence of clinical efficacy and good safety. So many of the diseases that were on that initial list have now been approached. And one of the challenges here that, you know, is even more extreme in individualized therapies is that each genotype requires a separate vector carrying the gene and a developmental project.

And so it sort of limits the development and the number of disorders that are approached. But in fact, the safety record from these vectors to the present time has been quite good. There have been no

vector related serious adverse events that I'm aware of. And one of the worries has always been, since you're using a vector based on HIV, the potential for elements of the vector and the packaging that come together to make replication confident lentiviral vectors that could spread. And to my knowledge again, this has never been reported in either products or in patients.

And using the lentiviral vectors, the integration sites don't show preferential integration near oncogenes. And there have not been any clinically significant clonal expansions, again, that I'm aware of. So they're looking relatively safe, although still it's probably maybe 500 people or maybe 1,000 worldwide that have received these kinds of vectors into hematopoietic stem cells. So it's still relatively early in the developing a safety base. Next slide.

And so then I want to talk about what's been my favorite disease to treat for many years now, Severe Combined Immune Deficiency or SCID. And SCID is the most severe of the human primary immune deficiencies,

of which there's several hundred. SCID has absent T and B cells, and NK function is variable depending on the genetic type. And in fact, SCID can be caused by more defects than any -- in any one of more than 20 genes. And in total, SCID is quite rare. About 1 in 58,000 is one of the best estimates from -- now that there's newborn screening we're getting a much better feel for the frequency. And SCID as a severe immune deficiency has been uniformly fatal in infancy before treatments were developed.

Typically, there'd be severe recurrent infections, chronic diarrhea, failure to thrive leading to death in infancy. And there was one famous child who was maintained in a germ-free bubble for more than a decade. And that's why it's sometimes called bubble baby disease.

And we know that bone marrow transplant can be curative. So we know that giving normal hematopoietic stem cells can essentially replace the immune deficiency. And in fact, if there is an HLA-matched sibling donor, which occurs in about 20 percent of

patients, there's more than a 95 percent success rate. And the small failures are typically patients who have severe infections at the time of transplant. But for the majority of patients that don't have a matched sibling, the results have been less good. Although, they continue to improve using either matched unrelated donors or haplo-identical typically parental donors. Next slide.

And so then, just the specific disorder that we focused on, ADA SCID, it's the cause of about 10 to 15 percent of human SCID. So it's the second or third most common gene that can cause SCID. And we estimate there's about 10 children born a year in the U.S. and Canada based on the referrals that we've had and the population incidences. And ADA SCID patients have profound pan-lymphopenia. So they have typically -- essentially no T, B, or NK cells at shortly after birth from accumulating the toxic adenine metabolites that ADA would normally be part of catabolizing.

So ADA SCID has been the focus because it was the first genetic form of these more than 20 of human

SCID with a biochemical. And then the genes were cloned sort of in the mid-'80s. And so it's the first where things began because the gene was in hand. And so as I referred to there, there are multiple therapeutic options for patients including all the allogeneic stem cell transplants from matched siblings, matched unrelated, or haplo-identical donors.

There's also an FDA approved, and in fact two serially, a purified one and now a recombinant, enzyme replacement of polyethylene glycol modified ADA that can be used to lower systemic ADA levels. And then there's also emerging autologous stem cell transplant gene therapy that I'll talk about. So the next slide shows the lentiviral vector that we've worked with now for the last seven, eight years.

So we've been doing trials sort of successively over 20 years using the earlier type of vectors that I showed you. And then about eight years ago, talking to colleagues at the University College London, Adrian Thrasher and Bobby Gaspar, we said we should move to a lentiviral vector, and this one was

developed. So it has the human ADA cDNA running off the elongation factor alpha core promoter, which is one of those promoters I mentioned. It's a pretty strong promoter but doesn't have much transactivating activity of trans enhanced nearby genes.

And this turned out to be a very well-behaved vector. So it's one of the SIN types of vector with an elongation factor promoter. The cDNA is codon optimized to get better expression. The WPRE elements stabilizes the method so you get more bang for the buck. You get more protein per transcript, and it's pseudotype VSV-G. And it has a very high titer. This is from our lab. We can get very high titers after we concentrate it, so it goes into stem cells very efficiently. Next slide.

And so we spent about two years once we had this vector chosen doing the pre-clinical work that comprised the IND pharmtox package. And so we looked at efficacy in term of the transfer and expression of the ADA gene in patient derived bone marrow cells, both in vitro, and then put into immune deficient mice in

vivo. And compared to a retroviral vector that we were using before, MND ADA, the EFS ADA lenti had higher gene transfer and higher ADA production per vector copy number. So we had good activity.

And then we did a series of safety studies. We put this vector into bone marrow of either ADA deficient mice or to human cells in immune deficient mice. And in fact, either the retro or the lenti, neither showed any leukemia or clonal expansion in these models, maybe suggesting these models are not very robust. Integration set analysis did show that the retroviral vector was more often near the transcriptional start sites in cancer related genes that the lentiviral vectors.

That's kind of a very well-known recurrent pattern of integration for these two classes of vectors. And in fact, in an in vitro assay, the murine gamma retroviral vector caused murine lineage negative bone marrow cells to clonally expand using an assay called in vitro mutagenesis assay and the lentiviral vector didn't. And so in fact, we had used the gamma

retroviral vector that we're comparing here for several trials beforehand and have had no adverse events from the vector. But these pre-clinical studies showed the lenti was at least as safe and possibly safer. And so that's sort of those studies which we published composed the toxicology and pharm package for the IND. Next slide.

And so I just wanted to take -- you know, what did it take to do? So this is the slow road to lenti, which is a pun. And so this shows you in the academics what it took us to get from, “Hey, we should make a lenti” to an open trial. And so the gree- -- highlighted in green are the funding applications where we got funding in various stages to do the -- pre-clinical work was done on a program project grant we had from heart, lung, and blood. Heart, lung, and blood also had a gene therapy resource program that paid for the GMP comparable vector for the pharm-tox study. And then the NIAID, we received an U01 award for the clinical trial, for the Phase 1 trial.

And we went through a regulatory gauntlet of

the RAC, the FDA pre-IND. This study was initially opened up for both UCLA and the NIH. So we had IRBs and IBCs at both places. And then, so we submitted the IND at the end of 2012, so about four years from sort of proof of concept to an IND. And I think probably that can be done more quickly. We were sort of learning as we were going. Next slide.

And so in fact, we opened up this Phase 1 trial in the U.S., and a parallel trial opened up in London where we treated patients with this vector in low dose relatively Busulfan conditioning. And we'd roll patients who had ADA SCID without a matched sibling donor. They had adequate organ function and could not have an ongoing active infection.

And our primary endpoint was safety, survival, event free survival, event being, sort of, failure and needing to have a rescue transplant, and scored adverse events. And then secondary endpoints were more for efficacy, measuring the production of gene marked blood cells from the stem cells we treated, looking at immune reconstitution, and clinical endpoints of infections,

and hospitalization. So the trial opened up in May 2013 under an IND. Next slide.

And we actually went through and treated patients relatively quickly. The initial plan was to treat 10 patients, but we kept getting referrals. So we wound up treating 20 patients. So over the course of about five years, we went from the first patient into the last patient visit treating 20 of the ADA SCID patients. Next slide.

And these are some early interim data. These aren't the official data, but these are data when about, I think, 15 of the patients had been -- were out at least a year, looking at various outcome parameters. And so, red blood cell ADA went from zero because of their ADA deficiency to, in fact, slightly above the normal range for red cells from healthy donors. Their bad metabolites, the deoxyadenosine metabolites dropped down. When these patients initially present untreated, these dAXPs are in the 50 percent or higher. And then you can see that they also had immune reconstitutions, so their T cell numbers and B cell numbers came up

after the gene therapy, after we stopped their enzyme therapy. Next slide.

And so the second part of the slow road to lenti -- so I sort of showed you the first half of this. And so at the bottom half, so I just talked about the Phase 1 and 2 trial. In fact, we decided we should move to producing the cells in a cryopreserved formulation and planned that as we then -- as this property was licensed from our university, UCLA, to this company, Orchard Therapeutics. So all this -- and I moved into a new world of commercialization. And they've then taken the ball from that point, and I will be submitting a BLA application for licensure. Next slide.

And so then, this slide just shows sort of for this disease kind of the timeline from discovery of the cause to treatments. And so ADA SCID was observed sort of serendipitously being present in a few babies with ADA SCID by Eloise Giblett back in 1972. Then we moved forward to identifying the gene, cloning it, making vectors and then a series of clinical trials. And in

fact, a gamma retroviral vector for this disease is approved in the European Union as a drug called Strimvelis which is available for therapy. And then there's the lentiviral vector. So next slide.

So I showed this list before. I'll skip this slide. Next one. So that's the work it took us to develop a treatment for one of the hundreds of PIDs. And in fact, I'm aware of currently that there are three genotypes of SCID in gene therapy trials: ADA SCID, X-linked SCID, and Artemis SCID. One form of chronic granulomatous disease, Wiskott-Aldrich Syndrome and Leukocyte Adhesion Deficiency, I believe those are all the immune deficiencies currently being treated by gene therapy, but in fact there's many others. So there's another at least 17 other genotypes of SCID, four other genotypes of CGD. And there's a whole list of other even rarer monogenic primary immune deficiencies that could be treated by this approach.

So the question is what would be needed to develop individualized therapies for these other even rarer primary immune deficiencies using an analogous

approach? Obviously, it's, you know, we can't spend 10 years, and companies are not going to invest in diseases that are going to be treating, you know, two, three patients a year. And then beyond the immune deficiencies, there's all the other blood cell diseases that would fall under this treatment: red blood cells, white cells, platelets, stem cells, and then, you know, even beyond that, other genetic diseases. Next slide.

So I guess the question is, you know, how do we do this in less than 45 years? I mean, that's obviously intolerable for patients who have diseases that need to be treated right away or very soon. And so over this period that I just showed you, the development of this treatment, the investigative capacity of biomedicine has vastly expanded as we've all witnessed.

So we have far greater resources now, reagents, materials, all the multiple -omics and informatics to really move things quicker. And in fact, we now have established a number of broad gene manipulation capabilities both virally, vector addition

of AAV or lentis, and all the editing approaches that Keith talked about briefly with growing positive experience for safety and efficacy.

I think, you know, when this started out when I -- at the beginning of the field, there was, you know, it was unknown what kind of problems might develop. And I think we are -- although there have been some problems certainly along the way, we are developing a growing experience of safety and efficacy. And so we now have this cumulative experience in gene and cell therapy product development, pre-clinical evaluation, manufacturing, and clinical trial performance. Next slide.

So how would newly identified genetic disorders be fast tracked for individualized therapies? Well, as someone said earlier this morning, the first step is to understand the pathogenesis so we can understand the therapeutic approach. One issue, you know, is it an absent gene product that we just need to add back the gene, or is there an abnormal dominant negative or dominant adverse gene product that needs to

be overridden or knocked out?

And then we need to understand, you know, what are the relevant cell targets? So if it affects the blood cells, then what I was talking about would be do allogeneic stem cell transplant or ex vivo gene therapy may be beneficial. Other disorders like CNS, the defective microglia, that are -- many of which are blood cell derived can benefit. But this won't help all the other organs most likely.

If it affects -- is an autosomal recessive disease affecting motor neurons, then IV or intrathecal routes might be needed. If it's an autosomal dominant disorder affecting neurons, we may need to deliver the cells or genes in situ. Deficiency of serum proteins made in the liver, then intravenous AAV looks like a very viable approach to treat those. And so there won't be one size fit approach for all these genetic diseases. It's really going to depend on which organs are involved and what's the nature of the defect.

So we have a number of models to sort of work this up in, and one of the most important always is

patient derived cells that have the defect that can be studied. And now, we have great capabilities to make induced pluripotent stem cells and make organoids that can recreate elements of the disease. But, of course, all the murine knockout and gene manipulation models provide a way to test the new therapeutics.

And then, you know, once we've developed it, we need to define the nature of it and, you know, is it something that we've experience with? So is it just AAV for a new genotype of a retinal disorder, for example? Is it a cell type we've used, or is it something new, and how much experience to do have also then with the cell type hematopoietic stem cells, T cells, liver cells, et cetera? Next slide.

So what are some of our opportunities to try and use this experience for other diseases? Well, one is that we can rapidly identify these responsible rare gene defects underlying the inherited and de novo diseases, whole exon, whole genome, CGH, et cetera. We can relatively rapidly develop vectors and CRISPR-based therapeutic targeting reagents. You know, within a few

weeks to months, we can have reagents targeted to a specific disorder.

And as I said, the record certainly for lenti and AAV vectors are mature with expanding safety records. So it raises the question of how much pre-clinical testing is needed if you just change a transgene or you just change a small guide RNA. There are clearly potential adverse events from a different transgene or a different guide, but the more we can leverage platforms and experience, the quicker it will be. And then we can use gene engineered murine human iPSC as I mentioned in patient derived cells to determine the disease modifying activity. Next slide.

So some of the challenges still though are quite significant. And one of them that has plagued gene therapy and cell therapy since the beginning is the challenge of in vivo delivery. So in vivo delivering cells, genes or editing reagents to specific cell types, and sites and tissues remains really suboptimal in many cases. And I think that's still limiting and, you know, I think is a very important

area. We're all hoping that there will nano techno- - - nanoparticle technologies that will do that, but that's still an early area I'd say.

And then beyond sort of the simple monogenic disorders that I've talked about is there are many other more complex genetic disorders that are chromosomal deletions or duplications. Those are going to be much more challenging to treat by either replacing the large deletions or selectively removing duplicate segments than are these single gene targets. And then many of our diseases obviously are multigenic, and these would be much more complex to approach by either gene addition or editing methods. And these cases, cell therapies that have the whole package might be better.

And so I think Dr. Marks in his opening remarks talked about a four to eight year typical timeline, and I think I would agree with that. And so the breadth of activity in toxicological testing for pre-clinical studies that are typically done to support IND are expensive and take a long time. And I was

probably low-balling at a $500,000 to $20 million and one to three years. And I will stop there and look forward to the discussion. Thank you.

## PANEL SESSION WITH Q&A

**DR. REINDEL**: I'd like to invite our panelists up to the front here, please. So in addition to Dr. Kohn, who will continue to participate in the panel discussion over the phone, we also have several FDA representatives, including Dr. Lapteva from the Division of Clinical Evaluation Pharmacology and Toxicology and the Office of Tissues and Advanced Therapies and Dr. Xu, who is a Senior Mathematical Statistician in the Office of Biostatistics and Epidemiology.

So I see no one has approached the microphones yet. I'd like to encourage the audience to do so. If you have questions, we'd really like to engage in discussions, but I'll be happy to start the discussion off with a question that I think is relevant to both

Dr. Kohn and Dr. Schooley. I was really impressed with the way that both of you sort of united resources across the country to enable collaboration in a space that -- where you may be able to only enroll one or two patients with a certain condition. Can either or both of you talk a little bit about strategies that have been effective to promote that kind of collaboration?

**DR. SCHOOLEY:** I think the main thing is really being open to collaboration and realizing we're all facing the same problems there. We gain by collaborating. And there has been a lot of publicity about MDR infections, so patients drive a lot of this as well. And I think listening to patients and physicians and their needs and trying to meet them is one of the things we should do as investigators. I'm sure that -- let's move to a genetic perspective on that as well.

**DR. KOHN:** Yeah. And if I can comment, so we've done a few trials for ADA SCID and CGD, for example, with two or three or four different academic sites. And besides having the colleagues to

collaborate with, which is enjoyable, spreading it out geographically is helpful for patients so they don't all have to go to one place in the country. And one of the things that we've learned that's very important, obviously, is having very careful monitoring of the sites so that everyone is doing things exactly the same.

And obviously, drug companies do this all the time when they're doing multi-centered trials. But coming from the academic perspective, it's a lesson we had to learn to have ongoing active monitoring of the clinical data, and also, in our trials at least, we've mainly been doing cell manufacturing at each academic's GMP site. And to harmonize that activity takes a lot of work because, in general, people think they all know how to do it. And -- but if you work with sites that are agreeable, you can sort of standardize even something as relatively complex as processing hematopoietic stem cells with viral vectors.

**MS. MCGRATH**: Yeah. Lynne McGrath. I was curious about your comment that you're hoping that it

doesn't take 45 years. And I'd like to turn the question on to the group to say that was a technology that has evolved over the last 45 years, and I've personally been involved with programs that took over 20 years. But the question is, when new technology emerges today, how do we not let that go 45 years?

Because certainly we have a lot of things that have happened. But just your thoughts on some of the new and emerging scientific discoveries that -- how do we get that baseline information to be able to use those as therapies? You know, the 45 years may still be -- hopefully not but may still be something that we would consider because of, you know, going forward with new discoveries. So that's kind of a question that I have is how do we shorten that? I don't know if anybody has any thoughts.

**DR. KOHN**: Well, I mean, one example are the use of CRISPR. So you know, that was only really identified, what, seven or eight years ago or something. And they're already -- it's already in clinical trials. And so clearly, we have accelerated

our process of -- from discovery to clinical applications.

It'll still need to go through now the process of Phase 1 and Phase 2 trials to some extent. But I think it's such a nimble platform for developing a therapeutic if you're targeting a gene that I, you know -- I think that will be one thing that will, for genetic diseases at least, really accelerate the timeline.

**DR. SCHOOLEY**: You could argue that phage therapeutics has been going on for 100 years, so that 45 years is nothing. And I think the real key is trying to understand what you're doing in as precise a way as you can so you learn from it and can generalize, and other people can either repeat or improve on the experience. Where we make mistakes is where we do things without characterizing them as carefully as we can to be able to learn when it doesn't work, to learn from things when they do work, and to build on what we know.

So I think that should be probably the most

critical aspect of trying to accelerate discovery across all fields. And I think it fits what was said earlier today by some of the other people talking about platforms that different companies might be developing for different applications and indications. Why not learn from each other? You're not competing for the same product, and the more you share the more you can focus on things that matter which is your particular application.

So I think that phage therapeutics are the same way. Companies aren't competing with each other. It's not like people are lining up to decide which company to invest in. People are trying to decide whether this is crazy or not, and so the more collaboration the better.

**MS. WITKOWSKY**: Hi, this is Lea Witkowsky from IGI at UCSF and UC Berkeley. Hello, Dr. Kohn online.

**DR. KOHN**: Pleasure.

**MS. WITKOWSKY**: I'm wondering, all this talk about the ability to separate product specific attributes and processes from platforms seems like a

really important distinction, if we can come up with ways to streamline creating evidence and being able to leverage that evidence from one application to the next. And since we're mentioning genome editing, I'm wondering, Dr. Kohn in particular, as you've worked in -- with hematopoietic stem cells across various different diseases, how much do you expect an organ system -- so for example, platforms of using lentivirus in one organ system or tissue system to be standardizable so that, if you're doing genome editing for example, you're simply changing one component, kind of leveraging the modularity aspect of things like genome editing? I wonder if you could speak to that as you've worked on multiple different diseases within the blood organ. Thank you.

**DR. KOHN**: Yeah. No. Thank -- that's a really good question. You know, I don't know fully the answer. So if we use the example of using CRISPR-Cas9 to modify specific sites, obviously every time you go to a new guide, it has a different on-target, off-target profile. But as to -- by what Keith talked

about, our development to really identify that, you know, that may be some -- you know, that kind of safety analysis may be enough to let you not have to do the full developmental package, just to target a different genomic site, for example.

And the same thing with lentiviral vectors. When you look at all the different papers now that have been published looking at integration sites for lentiviral vectors with a number of different diseases, it's getting very monotonous because you kind of see the exact same pattern. So we know that, and so it then just becomes what are the transgene specific issues that need to be studied. Obviously, you need to show disease activity modification.

But beyond that can we, based on the class of gene -- that it's a metabolic enzyme for example -- not have to do all the extensive testings I showed you that we did in mouse models, transplant models, et cetera. And so I think some of it -- I think some of that is a regulatory issue of what will be acceptable to allow existing data to be leveraged and not have to start at

square one every time you change a guide or a cDNA.

**DR. REINDEL**: We have some questions from the online audience.

**THE OPERATOR:** So we have two questions from online. They're both pretty short, so I'll give them to you at once. The first one is Dr. Schooley mentioned about how phages are similar to antibiotics. How do we ensure the environmental safety of phages? Do we have any knowledge of how they might affect the safety of the microbiome outside the patient? That's question number one. And question number two is how can the phage and gene therapy fields learn from each other?

**DR. SCHOOLEY**: Well, question number one is we're all loaded with phages, and we have -- we walk around with more phages than we give to patients. They've been around for 300 million years, and when there is not substrate for them to grow in, they no longer propagate. So phages are kind of self-renewing and self-extinguishing when their substrate is gone.

One of the things that make them, I think,

less dangerous environmentally than antibiotics is their spectrum is so narrow. So although I certainly understand the issue, unless we were to come up with some genetically engineered phage that had broad host range, would take out all but one particular bacterium, and that were, for example, Pasteurella pestis, I think competition among phages will take care of that. And the other question was related to --

**THE OPERATOR**: To field learning from --

**DR. SCHOOLEY**: Oh, I'm sorry. Learning from each other. So let's, Dr. Kohn, see if there's anything to learn and vice versa. Sorry.

**DR. KOHN**: Well, yes. I mean, I think, again, I tend to think that a lot of these types of novel therapies emerge from academic medical centers. And we all spent our time in medical school and not doing manufacturing. So I think some of the CMC issues that you touched on we've also needed to learn and develop. So I think, although we're making a different product, we're using similar processes. So I think this bit of crosstalk is useful. And maybe this is a Gordon

Conference topic or something to have adjacent meetings and some overlap and talk about developing these kinds of therapeutics.

**DR. SCHOOLEY**: Some of the same issues in terms of producing phage are ones that Dr. Kohn is talking about because different academic labs are producing phages of different types but are beginning to converge in terms of how they're purified. And those kinds of convergences, I think, are very helpful and make it easier to think about what's being done in different places as well.

**DR. KOHN**: Right. And standardization of potency testing and even titering is something that, at least for lentiviral vectors, is totally lab specific what a titer value is because there is not standardized method. So I think, again, we face a lot of the similar issues in these products even though they're different products.

**DR. REINDEL**: If there are no additional comments from the audience, I had another question that I think will be helpful to the audience to hear. Could

you, Dr. Schooley or Dr. Kohn, discuss any specific challenges you've faced in the design of these clinical trials in terms of the challenges that you discussed just now in terms of product and the approaches you've taken to overcome those challenges?

**DR. SCHOOLEY**: Well, I think the challenges that are common to both are -- have to do with the fact that we're -- that the interventions are quite individualized from patient to patient. And we have to think about how to, as one person put this morning, talk about the process by which they are made and what standards and what metrics are used to say that these products are similar enough that, when you use them in different patients directed at the same organism but with a different, for example, host range, that you're -- you can aggregate the data in a generalizable way.

So being able to characterize the products in a way that you can talk about their potency, talk about their host range, what receptors they use, things that let you, again, know what you're giving makes it easier to design a hypothesis generated trial. That looks at

both clinical endpoints and biology and to -- at the same time you're looking at the clinical endpoints, learn enough about whether you're delivering the -- just like you're delivering a gene to the cell you want to get to, we have to deliver the phages to the site of infection, know they stay there, know that they remain active, and measure those things at the same time the clinical trials are being designed.

So what the challenge is there is that many of the companies that are developing phages are, as therapeutic agents, are relatively thinly capitalized. And it's very difficult for them to support a lot of the translational research that needs to be done. So finding ways to get that done at the same time, I think, is critical to moving the field as a whole forward. But I'll stop there because there are obviously other things that have to do with oncology that are important, too.

**DR. KOHN**: Right. Well, so of course number one is always funding. So as I showed on the timeline, we had a -- every six months to a year or so we had to

apply for another set of funding to make it to the next step. So I think CERM in California has done a very nice job of sort of laying out their funding mechanisms to follow the developmental timeline. And I think some of the NIH institutes are also moving towards sort of more multi-stage funding, so you don't need to back to complete new R01 application for each stage of the product -- project. So that's one of the issues.

The timelines are long for developing these. And for academic careers it's not the best thing if it's going to take you, you know, 10 years from when you start to when you have your Phase 1 trial done. It's hard to become an associate professor if you start as an assistant with that. And so that's a challenge.

And then, you know, it's -- they're expensive. To manufacture these products at high quality costs a lot of money for the GMP, for the testing, the staff, and also then the clinical trials are expensive. So I guess that comes back to my first point of funding. And so, you know, I think those have been the challenges. We've obviously overcome them because

we're talking today, but those, I think, probably limit what's developed.

**DR. SCHOOLEY**: Stability of funding is really critical in phage therapeutics as well. The -- we've seen over the last -- this trial that we talked about briefly today has been in the works for two-and-a-half years and watched multiple companies come and go, each of which has gone down because of inability to maintain their development plan. So it's critical to have overarching mechanisms and support approaches that let you plan for something that be carried out from beginning to end. And having the government support some of the basic and translational work, really, I think move both fields forward in a way that get us products, which is what we're all trying to do. Because that, at the end of the day, is why we go to the lab.

**DR. KOHN**: Yeah. And just to comment -- and these challenges are probably even more intense for individualized therapies, to get back to the theme, that, you know, a one-off therapy that might be

lifesaving, if it costs a lot, if it takes a long time, won't be valued. And so we have to find ways to do these quicker and cheaper. Not sure what that answer is, but I think that's the challenge.

**DR. LAPTEVA**: Yeah. So I would like to make a comment and perhaps address some of the questions that were asked earlier about product specific versus platform and how we approach individualized therapeutics and how if we have only one patient that would need to be treated with a particular therapy, how can we make this clinical development program looking efficient and really deliver to the patient who needs the therapy? A number of people this morning and the afternoon spoke about the need to digress, to some extent, or maybe apply regulatory flexibility to the traditional medical product development model in order to make the development of individualized therapeutics more efficient. And although at this stage we don't know collectively how these development programs may look like and it's likely there would no one size that would fit all and some of them will be very different

from others, we could at least try to identify some the factors that would influence this digression from the traditional development.

So one potential factor that we've heard about today, and I could foresee, is the ability to make a reasonable prediction about the product effect at the time when the decision to treat for therapeutic purposes is made. Another is the general expectation that individualized therapeutics should work in patients for whom they've been designed. And one other important aspect, I think, is the determination of the dosing. This is one of the very challenging aspects in the development of individualized therapeutics.

But speaking about the decision to treat, if you look at the traditional model of product development, the decision to treat the disease for therapeutic purpose typically does not come into the picture until later because when people participate in clinical trials, and when it is a group setting where some people are treated with the investigational therapy -- and the drug is the same for everybody --

and some people may be treated with placebo, and some may be treated with active comparator --it depends on the clinical trial design -- there is a little more acceptance from the perspective of the patient as well as the investigator that the product may not work. It didn't work. It was investigational. This was a clinical trial which failed to demonstrate the product effectiveness.

If the product does work and there are appropriate statistical methodologies that support the positive therapeutic effect of the product, then we can make an inferential conclusion that the patient population with the disease will likely be benefitting from this product. So when the next patient with the disease comes to their physician in clinical practice and the decision to treat is being made, then both the patient and the physician have already some information that gives them the ability to reasonably predict the treatment effect because you would know that patients who had the same disease, maybe similar characteristics, were treated in clinical trials. And

you have some ability to predict the magnitude of the effect of the product, whether it would or would not work, and to understand some basic toxicities.

With the development of individualized therapeutics, the decision to treat comes much earlier. Even at the investigational stage, there is this expectation that the product should work because it was designed for this -- for the particular patient. Yet the step which is so common for all of the different products about taking the representative sample of patients, testing the hypothesis, observing the effects, and then translating it to the population with the disease is absent. So there has to be something that fills the gap with individualized therapeutics. It would serve the information -- as the information with the sufficient predictive capacity to enable this decision to treat.

And so speaking of the novel technologies, what we see although in very, very few examples of such individualized therapeutics developments -- and thank you to the person who spoke this morning who is the

patient with cancer. You didn't realize probably, but you were one of the examples of what we're actually seeing. We're seeing development of new methods and methodologies that are based specifically on that individual patient's genetic parameters, physiological parameters, understanding of the cellular metabolism, how cellular phenotype may be changing with the introduction of a transgene in that particular patient. So what we will likely see in the field with the development of individualized therapeutics is the growth and development of these methodologies that are predicting the individual patient's response to that particular individual therapy. So that's one.

The other is the expectation that with these types of treatments we will see positive treatment effects, if not to say large treatment effects. So if you take a gene therapy, for example, which is targeted to correct a functional gene or if you take a cell therapy that's intended to replace some lost functional cellular tissue, then you would expect that not one and not two, but many physiological processes, downstream

physiological processes will be affected. And likely also maybe some anatomical changes will occur which would result in previously unseen quantitative or qualitative effects of the therapy previously unseen in the disease progression.

And in that case, and my clinical colleagues will understand me, something that we call minimally clinically important difference will not be hinged anymore on the comparison between the two groups. But it would be very important to receive the input from the patients and their caregivers. And that's where the collaboration between the patient community and the investigators would be very critical in understanding as to what is the meaningful effect of that individual therapy or a number of individual therapies and not only that but also how these effects progress over time and how we can monitor and evaluate the effects of individual treatments in the long term.

And we have to create systems to do this. And I'm sure the next panel will be talking about it -- systems that are able to collect clinical data. But

not only that, but to go back and maybe -- somebody also mentioned it this morning. If you have a predictive statistical model which feeds and includes physiological variables and IT variables and other variables, why can't you fit -- feed the clinical data back into this model to make it a little more predictive? And so this is something that we will also likely see developing.

And lastly, for collection of safety data, particularly when it is a platform based product where, say, a vector treatment that's been optimized already with understanding how different elements of the vector may interact with one or more transgenes that would potentially be inserted for treating different diseases -- if you take this type of platform and we have a clinical data collection attached to it and you may call it a master protocol or a platform protocol -- but it would be important to incorporate common variables into that platform to enable perhaps a meta analytical activities to be done later down the road specifically with regard to safety because safety could potentially

be evaluated across different diseases for very related but slightly changed products.

**DR. REINDEL**: Okay. I think that concludes the panel discussion for today. Thank you for all of our -- to all of our participants.

**DR. KOHN**: Thank you.

**DR. RAYCHAUDHURI**: So, I'd like to thank all the speakers and panelists and the audience for sharing your perspectives. And I'd like to thank Dr. Reindel for moderating the session. And Dr. Kohn, I'm very sorry about your travel challenges but so very happy that you could give your presentation and join the discussion also. So we're going to --

**DR. KOHN**: Thanks for having me, Gopa.

**DR. RAYCHAUDHURI**: Thanks so much. So we will take a short 10-minute break. And we have three excellent speakers coming up in session four in what I know will be a very thoughtful and very thought-provoking session. So please take a quick break and join us in ten minutes. Thanks.

**[BREAK]**

## SESSION 4: PRODUCTS TO PATIENTS

**DR. RAYCHAUDHURI:** Okay. If everybody could take your seats, we'd like to get started with session four. So I just want to say, in addition to everybody in the room we've had -- we have over 400 people online who are following the workshop. So it's great to see this level of interest.

So it's my pleasure to introduce Dr. Celia Witten. Dr. Witten is the Deputy Director of CBER, and she will be moderating session four, which focuses on how to get products to patients in a timely manner and maintain access for patients in a sustainable way. Dr. Witten.

### SESSION 4 MODERATOR INTRODUCTION: DR. CELIA WITTEN

**DR. WITTEN:** Thank you. In the prior three sessions, we talked about the scientific and clinical

aspects of development and heard about the importance of regulatory flexibility leveraging knowledge across applications, the challenges in manufacturing and testing, and the need for collaborations. There will be three speakers in this session: Jill Wood from Phoenix Nest, Dr. Alison Bateman-House from New York University Langone Health, and Dr. Phillip Brooks from NIH. For the panel discussion, the speakers will be joined by Captain Julie Vaillancourt from the Rare Disease Program at CBER and Dr. Chip Schooley who participated in the prior session.

The focus of this session is on ethical issues, collaborations, and stakeholder roles in the end-to-end development of individualized therapeutics. In general, the role of individual stakeholders can be quite different in the development of products for rare diseases than in the development of products for common disease indications. This may be even more so in the development of individualized therapeutics intended for one or a small number of individuals.

As stakeholders take on certain roles in the

development of these products, including close collaboration with other stakeholders, certain ethical issues arise. Furthermore, the focus of collaborations may need to go beyond development to consider future sustainability issues, since not all products or approaches may be commercializable. In addition, new development paradigms may pose ethical conundrums that are not necessarily features of the standard drug development paradigm. Therefore, these three issues are somewhat related.

Some of the ethical issues that we see are noted on this slide. One question that needs to be addressed for any drug product and development is the determination of sufficient manufacturing and safety information for a trial to proceed and also, as we've heard, sufficient information to develop other aspects of the trial, such as determining the starting dose for a product that can only dosed once. So these kinds of questions about manufacturing safety information may be even more of an issue for products for a single individual or a small number of patients because

testing can be resource intensive.

Note that the determination of whether there's sufficient information for a trial to begin is not a simple risk-benefit question because there may be considerable uncertainty in the safety testing or, for that matter, an assessment of activity. Often the discussion regarding N of 1 development is focused on the acceptability of administering the product to the individual. But the boundary between research and clinical care may be very unclear. However, we need to make sure we learn from each clinical investigation, including single subjects.

Some of the development programs have been funded or championed by a patient, family member, or a small group of patient families. While this is commendable and there have been some striking successes, it involves a heroic effort on the part of these family members, many of whom describe the effort as being equal to more than a full-time job. Do we need to figure out what to do to ensure that this is not the expectation for families and caregivers? And

that is one of the issues regarding funding of development. Another potential ethical issue, particularly with regard to funding, is the question of how development decisions are made, for example, which patients get treated. Dr. Bateman-House will be providing her perspective on ethical issues that arise in this area.

Patients and patient groups have always been stakeholders in medical product development, but these groups are increasingly taking a lead role, particularly for products with rare diseases. We will hear about an outstanding example of these efforts from Jill Wood in this session. Academic developers play a larger role in the development of many of these therapies than traditional pharmaceutical companies, in many cases developing and performing early clinical testing and, in some cases, partnering with pharmaceutical companies or forming small companies to shepherd the product across the finish line. Philanthropic organizations are playing an increasingly significant role in development programs for some

pharmaceuticals and will be important in this area also.

We've already heard from a number of speakers that collaborations are needed. These collaborations are needed for many reasons, which have been discussed in previous sessions. Some of the products may have limited commercial viability. Academic developers may have limited resources. In addition, as previous speakers have noted, information sharing to eliminate duplication of expensive development work would help these products move forward.

There are many different models for collaborations, and some amazing individuals and organizations are currently leading collaborations to develop individualized therapeutics. And there are many models for information sharing. We can learn from these examples as we work together to find a way to develop and make available such products in a way that is ethical and as resource efficient as possible.

However, it's possible some new models of collaborations are needed because development work may

be duplicated, and these innovative areas benefit from information sharing. There may be something to be learned across patients for each product platform, as we've heard during the prior sessions. And this could include what we learn for a gene therapy vector for related applications that could be related by tissue target or by disease.

There could be a bio-distribution study done for a vector that there'll be something gained in our knowledge for applications with similar tissue targets and delivery. And we may learn more about test methods that will help in product development by gaining an understanding of how these test methods work in different applications. So it's important not just to think about how to develop the therapy for each individual or small group of patients but how we can -- you have to scroll down. Can you scroll down? -- how we can do that sustainably across a range of applications so valuable information is not lost or overlooked but can be added to. Thus, we need to think about development more holistically than one patient at

a time when we can. And we're going to hear a great example of an effort in that direction from the talk that P.J. Brooks will be giving during the session.

One last point I want to mention, we've been referring to sustainability in this workshop. Why is this important and why do we mention it when we discuss collaborations? The questions of how to sustainably provide products is important because, once a product or a platform for designing individualized products has been developed, how will patients be able to receive these products? The traditional model has been for pharmaceutical companies to take over production and delivery. But some of these products may be valuable to patients but not necessarily commercializeable. Next slide.

So you've seen versions of this slide in each of the previous talks illustrating the challenges and opportunities in this -- in the area of product development. This slide illustrates the fact that traditional roles of how products are developed from discovery through marketing are being upended, with

discovery being driven by patients and advocacy groups as well as by NIH and other research grants funding or by pharmaceutical companies. This upending of traditional roles is seen all the way through development. The question is where are the opportunities for stakeholder collaboration among these stakeholders and end-to-end development of individualized therapeutics so we can move the field forward?

Examples of areas for collaboration can include availability of GMP grade material for clinical studies. We have heard, both at this meeting and at other venues held, how this challenge is limiting development of AAV vector-based gene therapy. If this same GMP grade material were available across multiple researchers, for each product and development across researchers, shared safety testing information could help to reduce development costs for each product in development for each researcher.

In addition, shared clinical data for leveraging understanding would become possible.

Development of templates to facilitate IND submission for collaborative development program might involve multiple products but also could streamline development. So as I mentioned, Dr. Brooks in this session is going to describe NIH efforts of a collaboration that's aimed at addressing these issues.

There are challenges for collaborations, also. I've only listed a few examples on this slide, and I'm sure the audience can come up with many more. But including -- included among the examples would be funding and governance. And by governance, I mean how decisions are made regarding the collaboration goals and the process, including the kinds of development decisions I mentioned earlier when I discussed ethical issues. And then there's the question of how intellectual property is treated which also has come up in this meeting.

And the last item, sustainability, I've already mentioned, which is that we have to think about not just development but what happens after the development is completed because the goal of all of our

efforts should be to make sure our patients are able to benefit from these new development programs. And therefore, thoughts about how to do technology transfer for commercialization are important, and also how to ensure continuing availability.

I summarized at a high level the background for the three related issues in this session: ethical issues, collaborations, and stakeholder roles. And now I'd like to introduce the first speaker. Do you have the -- So our first speaker is Jill Wood. She's the co-founder of Phoenix Nest, Inc., and she also has funded a foundation to look at -- to try to develop natural history studies and to try to develop funding for Sanfilippo Syndrome. So please welcome Jill Wood.

## THE TRIALS AND TRIBULATIONS OF DRIVING A TREATMENT FOR AN UBER-RARE DISEASE TO THE CLINIC AND BEYOND-A PARENT'S PERSPECTIVE - MS. JILL A. WOOD

**MS. WOOD**: Hi. Thanks for having me here. I am Jill Wood. I am the mother of a child with an uber-

rare disease called Sanfilippo Syndrome Type C. And I'm gonna walk you through our journey of what it's been like trying to create a treatment and bring it to the clinic for this disease. I really want to thank the FDA for having me here today. It means a lot to me. I greatly appreciate the fact that the FDA is starting to look at the issues coming from the families that are driving the science here.

So my clicker -- so before we can get to our gene therapy utopia, we need a need. My need was born on July 30, 2008. Jonah was full term. He was absolutely perfect. We had no idea that he harbored this insidious disease.

It was at our first year well visit that our pediatrician noted that Jonah's head circumference was off the charts, and we should probably go and get it checked out. So we did. With due diligence, we went to get our MRI, which was done at NYU, very fortunate that we landed at NYU where the lab technicians there knew exactly what they were looking at, which is extremely rare in a disease like this. So they

suggested to our geneticist that we do a panel screen for the MPSs.

So real quick about the diseases, I don't want to bore everybody with any more science. Sanfilippo Syndrome is MPS III. There are several different MPSs. You've probably heard of many of them. The top portion of those MPSs all have treatments. Sanfilippo is the only version that does not have a treatment.

And I have four sub-types here: Type A, B, C, and D. My son has type C, and my company is focused on a treatment for type C and type D. And you can see that our diseases are 1 in 1.5 million, which estimate, maybe there's 100 kids in the United States by that number. But I only know of 20 for type C and four for type D.

Because our disease was so rare, we were told that nobody was picking us up, that nobody would touch us. One venture capitalist actually told me he wouldn't touch my disease with a 10-foot pole. Yeah. So you know, this was my first child. My husband and I had done everything right. We had bought our first

house, paid off our school loans, and here you're gonna tell me that my child has a terminal illness and there's nothing I can do about it.

We hit the ground running, and we called people that cared. We found these guys off of PubMed. We brought our physicians -- fortunately, again, I'm from Brooklyn, and I'm surrounded by wonderful hospitals with geneticists and neurologists that were ready to jump on our bandwagon and help us out. We had a meeting in 2011, and we sat down with a few patients that I had found, and our physicians and our scientists. And we hammered out what it was that we were going to do and that was to go for gene therapy.

So I'm going to go through -- the FDA asked me how hard it was, you know, what did I have to do and how we could do it better And so my first learning curve was working with academia and finding the scientists to help you start your program, getting the -- your mouse model made. There's Alexi Bedeski with our first mouse. I asked him to name him Juniper because I wanted to name my second child Juniper. But

I'm not gonna ever have any more children, so there's a Juniper.

But all of our science was funded outside of the United States. It began in Montreal, with Brian Bigger up there, and in Manchester. We funded these guys through grass roots fundraising. We nickeled and dimed it. That's a garage sale, a picture of a garage sale there. This is how we did it.

It was a learning curve for me. We had to write grants, hired lawyers, made sure that our scientists were held accountable, that we had milestones, and their payments were conditional on their milestones. But for the people on the phone, it's hard working with academia. These guys have a school schedule. They take a lot of time off. And sometimes they're post-docs, graduate, or they want to get married or something. And you have to hire someone else. It's not easy.

So during this process of nickel and diming and trying to find -- scraping every dollar that you possibly can, I met a gentleman who suggested that I

create my own company and go for NIH small business grants. And I was like, you know, that sounds like a great idea. Let's go for it. So we applied for an STTR, these small technology transfer grants. I hope many of you know who they are, what they are.

And unfortunately, there's small business technology grants, and they don't want to fund researchers that don't live in the United States. Makes sense. So my type C research has not yet been funded, but during this time I created a knockout mouse for MPS III D. I actually applied for a competition, Assay Depot, I want to give them some props for this Be HEARD contests. I applied and we won the main prize, a knockout mouse.

And that was 10 years ago about -- no, maybe eight years ago, and that was like winning a car. You know, it was before CRISPR, so that was pretty amazing. Then, I went back, and I licensed our gene therapy program from Manchester, brought it back into the United States, and we're now working with our dosage study with a CRO here. And I'm being helped with

additional funding from our friends at the Cure Sanfilippo Foundation. Sorry.

So where we did not do so well with type C grants, we have excelled with III D grants. And again, major props to the NIH, we are now well on our way to the clinic for MPS III D with an enzyme replacement therapy. That one -- that started off from winning that knockout mouse and snowballed into almost $7 million in SBIR grants. And like I said, there's four patients, and those come from two different families, a set of identical twins that you can see here, and a younger family as well.

So while I'm developing treatments for type C and D, I'm watching my sister diseases Sanfilippo type A and B, which are much more prevalent than type C and D. And it was really very exciting. They had several programs in the pipeline. then all of a sudden, look, Alexion/Synogeva, their ERT in MPS III B was shelved. It was shut down; the trial was shut down before it even got to the end. Same goes for ERT for -- with Shire. BioMarin, if you might've heard from the press

releases, they did divest and were found a partner, Levits. So that, thankfully, that trial will continue on. But here we're sitting in limbo with Sobi, who also wants to divest their ERT for MPS III A. You can imagine how devastating this is for our community.

This is Will. Will's parents were told the same thing that I was, that their child had an ultra-rare disease and there was no treatment. A few months later, lo and behold, here's a trial, and Will was accepted into it. It says Shire right there. I'm sorry to beat on Shire. That was actual Alexion's trial. So sorry, Shire. That was actually Alexion that dropped that trial, and they shelved it. They dropped Will cold turkey. Took him straight off of his ERT and is back to being told, “I'm sorry, your child is going to die.”

Why is this happening? There's a lot of speculations. I, for one, think that they have chosen wrong endpoints. They're looking for cognitive changes when our children have profound brain damage. And we're not gonna change the cognitive in our children,

and it's really not what we're looking for. Financial risks, a lot of these companies as you can see, have changed hands, and not everybody's on the same page as the previous CEO. BioMarin, bless them -- have nothing against BioMarin -- but they went in a different direction. They're not doing ultra-rare diseases anymore.

And then, I think people don't realize our diseases are slow to progress, but Will, Jonah, they could die in their sleep tonight. It just happens. Did I turn off my slide? Okay. Oh, but that -- okay.

This slide just kind of goes to shows you how much our patient community has done. I am very, very proud to be part of this Sanfilippo community. I don't know that I've ever seen another rare disease community work as hard as we have. Again, there's four different sub-types, and we have four different enzymes. And there's some things that are different about us.

So take for example these six programs that have gene therapy programs in the works right now. The first one nationwide was entirely -- pre-clinic was

entirely paid for by these foundations. And I think I forgot to write the Cure Sanfilippo Foundation up there, too. But all these foundations came in and funded the pre-clinical, and then Abeona came in and licensed it. Right now, they have A and B in the clinic, and hopefully, it'll stay. And we'll have our first treatment for Sanfilippo.

Lysogene was started by Karen Aiach. Unfortunately, her daughter Amelia passed away just before November and did not benefit from this treatment. The trial still goes on underneath Sarepta. I think I heard somebody from Sarepta here, so thank you Sarepta for picking this trial up.

And then we have Estevee out in Spain, lay low. Notable, Amicus has picked up MPS III A and B. No, John Crowley is not a Sanfilippo parent, but he is a Pompeii parent. Orchard was entirely funded pre-clinical from the U.K. MPS Society. And, I think it was the Ormond Street Hospital as well. And then there's Phoenix Nest, who's driving the science for type C and D.

The patient organizations, just, I mean, does this shock the people in the audience that this has been funded by us? And it shouldn't be this way. I mean, we have children at home that are dying, and we're here working our butts off trying to create treatments for the next generation.

Okay. Don't you love the emojis on Apple? So and this is also -- I had to throw this in there because this really annoys me. It keeps me up at night. Our SBIR grants, you know, you have a collaboration with academia, and they get subawards. They get a nice substantial subaward. They don't -- pays for all their overhead.

And, you know, they get to ask for some, a bioreactor, you know, a $300,000 bioreactor. They get some nice equipment. And then they get licensing rights because it happens on their -- in their hallways and on their property. And then they get all the fame and glory and get to write papers and publish and go around.

But then, I have to go back and license what

it is that my company won. I have to go and license this. And what I don't think people really realize is that I have to hire a lawyer. I have to hire patent lawyers. Do you guys have any idea how much lawyers cost? SBIR grants do not cover lawyer fees.

So to add insult to injury, here we are just trying to scrape by on a disease for four kids. I spent -- I actually spent over a year fighting this. No milestone payments, no upfront fees. I mean, it's just ridiculous to ask that from me. When you do, they don't realize that you're sucking any incentives that I had for commercial partners away. When you're treating four kids, how many patients -- how much money are you gonna make off of this?

So I'm throwing that out there. If there's something we can -- some template we could put on our SBIR grants that -- what do I want to say -- makes both sides happy but realizes that these are ultra-rare diseases and you can't treat me like a Parkinson's drug company. Oh, boy. Things that I think the FDA, or the NIH, could do for us that are no brainers, and I know

you know that they're no brainers because we've talked about them a lot, natural history studies. One good one, one we started -- we knew we needed to do a natural history study.

But my families did not want to fund a natural history study. They are extremely expensive. And when you have $1 million dollars, do you want to send it sending your kid to a clinic to be poked and prodded, or do you want to put the money in making a mouse model and making a gene therapy? I mean it's the mentality of it. The families want to fund the research. And now we're stuck.

We really, really have got to get our natural history study undergoing. Mouse models, I have them. But there are so many rare disease groups that don't even have mouse models. And they're extremely easy to make now and to house. I think if there was something that the FDA could do for us, it would be to go through and find out who doesn't have their mouse models.

Registries, registry's another major contention amongst our patient groups. It's something

that we absolutely have to have as well, but again, they extremely expensive to maintain. You have to be HIPAA approved, GDPR approved, and those things have to happen yearly. And who's going to do that? Who's going to keep up on that? We really need help managing and maintaining that. And that's, I think, another thing our federal government could do for us and could do it flawlessly.

And then one last topic I wanted to sneak in here because nobody really likes to talk to their patients about this -- patient groups. But biobanking -- oh, there is a major lack of donations out there. And if we could have this sensitive conversation with our families that it is imperative that we keep some of these tissues, brains, eyes, so you know -- it would be extremely helpful. I think we talked a lot about mutations as well and knowing the mutations of these families. And I like this company, and the NIH supports them as well. And I'm putting that up there so people can take notes at home.

Here comes our Orphan Drug Act. And we love

Abby Meyer and what she did for us. That was done almost 25 years ago, and I think it's about time that we update our Orphan Drug Act. We all know that there are 7,000 rare diseases, and here we consider that 1 in 20,000 with a patient population of 200,000. That's a rare disease. So if you're a drug company and you're gonna create a drug for a rare disease, who are you gonna pick? One with 100,000 patient population or a patient population of 20?

We're starting to talk about ultra-rare quite a bit, but what is that number? What does that look like? How do you go from 200,000 to 100? So if you're gonna -- I think we need to get ultra-rare on the map. We might as well get uber-rare on the map as well. And we really need to figure out ways that we can incentivize this.

I've been doing this for nine years. My drugs are ready to go to the clinic. We're handing everything over on a silver platter, and I still do not have anybody knocking on my door. Pediatric review vouchers are absolutely amazing, but it's still not

trickling down to us.

Just to let you know, we did do our pre-IND meetings for both type D and type C. They went very well. We went in really early because we were scared about the slowly progressive heterogeneity, the tiny patient population, and the lack of natural history. How were we going to pull this off?

And CDER and CBER both gave us the same advice was get creative and get more natural history, which we are trying. I'm trying so hard to get our natural history off the ground. And we will be looking at mosaic endpoints, kids being their own control. We're hoping to hang our hat on the guidance that was put out last June and using heparan sulfate as our surrogate marker.

Okay. You don't have to stare at this long. You can look over at me, but you know, you read what Sanfilippo looks like on paper. You read what these diseases look like on paper, but to see it for yourself is a huge difference. Yes, this is my bathroom at 8:00 in the morning. “Mom, I had an accident.” Okay, I'm

going to go and clean up his pants. You know, you're parents. Somebody has an accident in his pants you might throw them in the garbage. I look at my husband and I --"Can we just throw the toilet in the garbage? I can't deal with this." Imagine this at Starbucks. Picture that. Okay. You're never going back to that Starbucks again.

Some families, their children scream and cry nonstop for months on end, and nobody can figure out what it is. Is it neurological? Does my child have a bladder infection? Is it tooth decay? What is going on here? And it al- -- it seems to end up being neurological.

But these kids, I mean, it's terrifying for the families. They don't sleep for months on end, and these kids are mobile. So the families have to put in safe rooms and lock the doors and lock everything down, and their kids just walk around the room with the lights on, switching it on and off, turning the T.V. on and off. They're up all night long. It's horrible. Imagine that.

So anyhow, yeah. This goes back to the point that we don't care about cognitive endpoints. We need to take care of some of the serious issues that we live with day in and day out that will make our lives better. I threw this in there, and we talked a little bit about the workshop that happened last month for the expanding AAV manufacturing capacity.

And that happened here, as well. And if -- I encourage you guys to go back and watch this conference. And I bring this up as -- for the end-to-end gene therapy. And this company, I was very much impressed with this company, the Discovery Lab, which is doing exactly what we're -- we want to see happen.

I am now in the process of creating our vector, putting it all together. This is another huge hurdle for me and mind blowing. Three different plasmids made at three different CROs that all have to come together at one place and, if one isn't working, then it throws everything off and you have to go back. I mean, the level of expertise needed here is huge. It's very time sensitive and the error for margin is

huge. So I commend this group for making this happen. I would love to see it trickle down to the FDA for the ultra-rare diseases as well.

Again, this was from that last conference, the AAV conference. Last month alone I had three new families from diseases that I had never even heard of before calling me up that found me from random places and say, “Hey, I need help. This is what's happening to my child,” and it sounds very similar to what's happening to my child. Each one of those diseases breaks down into several other different subtypes. They're all conducive to gene therapy. Just pull out the gene and put in the next one.

And finding these gene therapy scientists, I hate to even put pictures of Steve Gray up there. I haven’t even talk about him because I don't want to share him. But we have got to have more Steve Grays out there and how it is that we're going to train these people and, if they are there, to come out of the closet somehow. You know, reach out to the FDA or the NIH or Global Genes or EveryLife Foundation and say,

"Hey, I want to help. I have a lab; I'm interested in gene therapy." And these families are ready to fundraise for you.

And yes, to my rescue, Jude Samulski, you might have heard of him. His company AskBio has spun out for Viralgene, and they have created a nonprofit company where they are holding suites for uber-rare diseases for people like myself. And we talked about the bottleneck, these guys are holding a suite for our gene therapy. So thank you very much.

Now, I always have to throw in my newborn screening because I think this is vitally important for all of our children, whether we have treatments or not. Ignorance is bliss. That's my baby, a few weeks old. But knowledge is power. Like I mentioned that Jonah was diagnosed very early, he is the youngest child known to ever be diagnosed asymptomatic without an older brother or sister.

Because of that, he had tubes put in his ears. He was a year-and-a-half. I didn't know he couldn't hear. Put the tubes in, it gushed out, and he was

pointing out airplanes the next day. I was like he couldn't hear that it was an airplane. It breaks your heart to know that your child -- he can say ball, and mom, and dad, but he couldn't hear. He also had bad sight, so we got glasses.

His behavior, you can imagine during the formative years how important it is to be able to hear. Not only does it help you read and sit still and participate in class, but it takes away that frustration and helps with the behavior. Sanfilippo is strife with behavioral issues. The kids are very -- can be very aggressive. So I actually feel guilty that my son is doing better than any other Sanfilippo child that I have ever met, and I attribute that single handedly to the fact that he had early intervention and we caught his hearing before he was deaf.

So that brings me to a close, and I have some people that I want to thank. And lots of people aren't on there. I can't thank everybody enough. There have been plenty of professionals that have helped me with pro bono services. But most importantly, I want to

thank my families.

We're very diverse. I have friends all around the world. We don't speak each other's languages, but we're family. And if it wasn't for them, I'd probably quit by now, but I know that they need me. And if it's not for our kids, it's for the next generation because no family should ever be told their child has a terminal illness and there's nothing you can do about it. Thank you.

**DR. WITTEN**: Thank you very much. Our next speaker is Alison Bateman-House. She's an Assistant Professor in the Division of Medical Ethics at NYU Grossman School of Medicine. She's co-chair of the Working Group on Compassionate Use and Pre-Approval Access, an academic group that studies ethical issues concerning access to investigational medical products. She has published and spoken extensively on how to best handle requests for non-trial access to investigational drugs and related ethical issues. And she's also written and spoken frequently on the history and ethics of using humans in research subjects and on clinical

trial accessibility. So welcome.

**ETHICAL ISSUES IN PRODUCT DEVELOPMENT AND SUSTAINABILITY FOR INDIVIDUALIZED THERAPIES-DR. ALISON BATEMAN-HOUSE**

**DR. BATEMAN-HOUSE**: Hi, everyone. I want to thank the FDA for the invitation to speak today and I want to thank Ms. Wood for that very illuminating presentation. So there's no way I can follow that, so I won't even try. The best I can probably do is entertain y'all with my lack of ability to manipulate mechanics. So we'll see how this works.

So we've heard numerous people say today, you know, maybe the time has come that we need to come up with a paradigm shift in this drug development traditional model that we've heard of. You know, this pre-clinical, Phase 1, Phase 2, Phase 3, it's too slow. Maybe there's situations in which we need to modify it somehow. And I think that's probably true, and we're here to talk about that. But before we talk about

that, I want to just remind us how we got to where that is. So let's see if I can move forward.

Okay. So in the 1940s, we basically said, you know, let's do medicine scientifically, and we're going to sort of disaggregate research and treatment. And they may look very similar, the same products may be involved, but they have different intentions. And as a result -- sorry, I'm getting distracted by -- see, I told you I'm bad at technology. I should just look up here.

They have different intentions. So they may involve, you know, similar procedures. They may involve similar, you know, products, but the intention is different. And here's the classic definition from the 80s. Research talks about a class of activities designed to develop or contribute to generalizable knowledge. Whereas, practice is referring to a class of activities designed solely to enhance the well-being of an individual patient or client.

So when people go into research, we often hope that there will be benefit to them, but it's not the

motivating factor behind research. And this has been sort of a core disaggregation that happened, like I said, in the '40s and has been systematized over time. With this Phase 1, this Phase 2, Phase 3 paradigm that we have now really came into place in the '60s, and it said, research, it is a formal thing. It has a method, and it has a procedure. And it's different from treatment.

And as a result of that we sort of came up with this traditional model of who is responsible for what. Patients, your responsibility is to be treated, be a good patient, do what your doctor tells you to do. Doctors, your responsibility is to treat patients. That is your patient in front of you. It is your job to advocate for them and do whatever you can do to help them. Researchers, your responsibility is to conduct research and to get that generalizable data that will move science and knowledge forward. Research subjects, you are passive. Your role and responsibility is to be researched upon. Funders, your role is to figure out what research is promising, to vet it, to fund it. And

then, as we mentioned earlier, typically the pharmaceutical companies are the ones who have come in and said, you know, “We'll take it from here. We'll take the most promising research and turn it into a marketable medical product.”

Now, this started collapsing around the '80s. We had activist patients, particularly in the context of HIV/AIDS who said, “I don't want to be a passive research subject. I want to have agency. This is not working for me anymore.” And there are many, many people today who say this is not working for me anymore. And we've heard examples all throughout today of patients or parents who have taken science into their own hands and said, “In the effort to treat my child, I need to get involved in the research world.”

So the traditional model is evolving. Just to give some examples, you know, as we've heard today, research may be intended primarily as therapy. If you have a research endeavor that is anticipated to help one patient, that's not research for the sake of research. That's research as therapy.

As a result, your research subjects, they may not me acting as passive research subjects. They're saying "I'm a patient. I'm here to be cured or helped. This is my therapeutic option." Patients and advocates, as we just heard a stunning demonstration of, they may be the ones now who are picking what science to fund, what science to push forward, what science to really try to get out of the realm of theory and actually into the lab.

This means that companies may be sidelined, and not necessarily because they're being pushed out by patients. I don't mean that. But as we mentioned earlier, if there's no market incentive, companies are basically leaving the space, and that's why these parents or advocacy groups are coming in. And they may not be sidelined, but they're playing a less prominent role. And in some cases, they're almost even like subcontractors.

And then there's the question that, you know, we bring to the FDA of, well, what and how are we going to approve something out of this? I mean, typically

speaking, if it's a N of 1, like really an N of 1 bespoke that no one other than person with the de novo mutation is gonna use, you don't need anything approved. But if there's something that we can extrapolate form this like a platform technology, then maybe there is something we can approve. What is it and how are we gonna approve it? And will something be brought to the market?

So these are all new questions that everyone in this room is currently, you know, grappling with and I just wanted to lay them out. And of course, anytime you shift between paradigms, it's difficult and there are complications. And so some of the questions that arise as we're making this shift right now is I showed you that traditional outlay of roles. And one of the questions is who should be playing what roles?

So for example, if you have a laboratory scientist, are those the people that we want making treatment decisions for individual patients? Maybe yes, maybe no, but it's not necessarily something that they've done before or been trained for. And this is a

new reality that we need to be grappling with.

Funding. Funding has always impacted decisions as to what's going to be developed, but is funding now going to be impacting treatment decisions? And I'll just give you an example from a patient advocacy group that I work with. They funded the clinical trial, and so the expectation was, you know, well, we get to pick what patients go first. Who's the first to get dosed? Who's the second to get dosed? Who's the third to get dosed? And are we okay saying, you know, this wouldn't be happening without you so okay, you get to make that decision? Or is that sort of a no go request?

So research and therapy traditionally have been distinct, and there has always been rampant confusion between where is this -- I think Dr. Witten says, you know, sometimes there's a fuzzy line. And there's a concept called therapeutic misconception. Which, I used to work in cancer, and you saw therapeutic misconception all the time with patients in Phase 1 clinical trials. It used to be, before our

modern era of molecularly targeted cancer, Phase 1 clinical trials were not intended to be therapeutic. They were intended to get dosage information and to move the development of a molecule along. But the patients enrolled in that Phase 1 trial were really not anticipated to benefit.

Yet, we saw time and time again that if you surveyed those patients and ask why they were participating in the clinical trial they would say, "You know, I'm hoping to get something out of it." So there's been this ongoing confusion about, am I participating in research? And if so is that therapy? Is it not therapy? And it's been even more complicated when the same health care provider has been the investigator and the clinician. And the patient or parent is like, "Well, am I being recommended to go into this trial because they think it'll help me or because they're the PI of this trial and they need people?"

So this has been an ongoing issue for decades. And of course, now we're getting to the situation where

research and treatment are getting even closer together and, in some cases, becoming completely inseparable. And that's what we're looking at in some cases with some of the individualized therapeutics.

Although I was struck today as we heard different stories from cancer vaccines to gene therapy to gene editing, that there are distinctions between them. You know, you can't make a one size fits all statement here. But regardless, in general, we're seeing the situation in these individualized therapeutics where there is this sort of merger of, you know, from the expectation of the participant, is this research or is this treatment?

And that has implications for those of us who are in the field. Those of -- implications for, you know, the companies, the clinicians, the researchers, the academic medical centers. So if something is experimental but it's intended as treatment, how do we handle that? Because traditionally we've had a model where those have been disaggregated. And it has legal implications. It has regulatory implications. It has

ethical implications.

And just to single out one, IRBs. So if you're doing research, you have to go through an IRB. You have to get ethical review of your research. That's very different from what happens in treatment.

In treatment, there's still the idea of you need to have informed consent, but you don't go through an IRB. Your paperwork that you fill out to enroll in a clinical trial is very different, normally speaking, from the paperwork you fill out to have, like, your gall bladder removed. So you -- we have these concepts that, yes, there must be informed consent. But how we actually formalize them, change has been different depending on which one of these realms you're in. And so we need to figure out really where we are.

So a number of people have pointed out today that some of these individualized therapies have been given under the rubric of expanded access, also known as compassionate use, in some cases called the eIND. And I spent a lot of time in this field, so I just wanted to make some comments about it. So we mentioned

IRBs a second ago. IRBs are involved in both research and EA.

But the level of oversight is very different. So if you have an IRB involved in our research, there's gonna be multiple rounds of review probably, looking at every line of the protocol and trying to decide how is this gonna be advertised, and who's gonna be recruited, and how do we make sure they understand what they're getting into, and what sort of data are we gonna return to them? The IRBs on expanded access basically say, does this seem reasonable and is there some piece of paper that we can hand somebody, either the patient or the family member, to have them sign off that they understand that this is experimental?

The levels of oversight are completely different. So there are just practical ramifications to trying to figure out -- we need to figure out which one of these paradigms we're working in. And, just as I'm saying right now, what does it matter?

So you know, pick a paradigm and just move forward. Say it's research, say it's expanded access,

say it's treatment, say whatever, it doesn't matter. It does matter because we need clarity about the procedures. We need clarity both within a particular institution or within a particular multi-center initiative or what have you. We need to make sure that patients understand what's being proposed, why and what the possible risk and benefits are.

And of course, the way we currently do that is through an informed consent discussion that is memorialized with informed consent form. But we need to know what that form looks like, and we need to try to choose which one of these to use to do that properly. And we need to make sure that the stakeholders involved understand their responsibilities.

So I just wanted to go briefly over this. And expanded access when you're talking about, you know, sort of, like, your classic idea of an unapproved drug, the request to do, you know, use this unapproved drug outside of a clinical trial has to be initiated by the physician. Of course, the patient may be the one who

initiates this conversation with the physician, but you have to have the physician on board. And the physician is the one who is in charge of reaching out to the company who is developing this new product and saying, "May we please use this outside of the clinical trial. Here is the patient, here's why I want to use it, and here's why I can't use it in a trial."

And if the company says no, that's basically the end of the story. This is where we see social media campaigns and whatnot trying to make companies change their minds. But generally speaking, if a company says no, that's the end of the story.

If a company says yes, this is where the FDA gets involved to look over the proposal, make sure that there's no obvious safety concerns, see if there are any amendments that they think need to be added to the proposal. And of course, this is where the IRB gets involved. So this is your sort of ladder that you have to go through to do expanded access for a single patient.

And I just want to note that really the

gatekeeper in this situation is the company. Again, if the company says no, that's basically the end of the story. The FDA cannot say to the company, “You must do this.” The IRB cannot say to the company, “You must do this.” It's the company that's the gatekeeper. And I want to point this out because, in the situations that we've been hearing today, the roles of companies have been changed, if not minimized or completely removed. And we're really talking about things that are happening in the academic center.

So is the role of gatekeeper now being taken over by this investigator, and, if so, does that investigator know that they are now the gatekeeper? Do they want to be the gatekeeper? Are they comfortable being the gatekeeper? You could say there is no gatekeeper; everyone gets what they want. But I don't think that's a sustainable model, and we probably shouldn't advocate it.

But if the investigator doesn't want to be the gatekeep do we say, “Okay, FDA, now you're the gatekeeper? Every time someone wants to use one of

these individualized products outside of a clinical trial, you really need to do the due diligence and decide yes or no." And it's up to the FDA to decide if they're comfortable with that role or not, but that's an additional burden over what they've currently been asked to assume.

Or we could say to the IRB, "Hey, before you've kind of done a rubber stamp. You know you've looked at this and said, 'Is it reasonable?' and okay make sure that there's a piece of paper for someone to sign. But now we're in a new paradigm, and you really need to be involved." I don't know. Any of these are possible, but there's a question. And we need to figure out what to do.

I just want to point out that I do have a concern about the idea of this investigator being the gatekeeper, although it might seem like the obvious choice, simply in that I'm concerned that having proximity to a patient might make that investigator make decisions that are a little bit too close for comfort. And the sort of paradigmatic example I'm

thinking of is if you have a patient who is deteriorating in front of you. Is there some point where the investigator would say, “Gosh, in an ideal world we would, you know, do some more work on this? I'm not 100 percent comfortable, but we can't wait anymore.” And maybe that's okay if it really is an N of 1 and this is the only patient that it's gonna impact.

But I don't think that's okay if there are other patients out there that we're gonna be trying this intervention on, and hopefully we'll be collecting data from this first experiment. And to the idea that someone might be -- jump the gun a little bit, that makes me concerned. And of course, there's also the point where if that patient or that patient's family or that patient's community is the one funding the investigator, is there even more of this potential conflict of interest?

And, you know, if you can think of these problems happening theoretically then they're probably gonna happen in real life. And so is there something

we can do to prevent foreseeable issues? Say, we're fine with the investigator being the one making these decisions, but let's come up with some rules of engagement.

So just to repeat, we need to decide is this research? And if it is research, we need to modify the way that we think about these. And we need to train IRBs so they understand what they're looking at. And we need to come up with some way of deciding what experimental procedures we really are happy with and whatnot. Or if we say this is clinical care, fine. That's fine. I'm okay with that, but we need to, again, come up with rules of engagement.

And one of the questions I have is, you know, do we say any licensed M.D. in the country should be able to do this or only certain M.D.s, only in certain settings, only with certain oversight? And if we are gonna say there are some sort of rules of engagement, who's gonna develop them and who's gonna enforce them? All right. So then to get into the bread and butter of ethics concerns I always have to talk about justice.

So one of the things that I'm concerned about here -- and this is not to say we should not do this. I absolutely think we should do this, but these are questions we need to ask. How do we justify extensive use of resources to benefit only one person or maybe very few people?

And I think everyone in the room today has been hitting upon the same theme of, you know, we collect data from those N of 1s, and we find some way to have that data push us forward in ways that will help more patients. So I think that's great that we're all on the idea of leveraging findings to help wider numbers of patients. But we need to figure out how to do that. We must plan for it, and it must be something that we say is non-negotiable, not something that, you know, after we do some cases, we'll figure out how to go back and do a reanalysis of the data. I don't think that's acceptable. I think we need to say right from the start, as we're building our plans, here's how we're gonna do this.

Enhancing access, decreasing obstacles, and

costs. I think just last week there was a meeting, maybe here at FDA -- I don't know -- for Rare Disease Week. And there was a panel on individualized therapeutics, and there was a patient who had received phage therapy. And she talked very movingly about how she was receiving care in Richmond, Virginia. And she had a very bad intractable infection and came up with the idea of phage therapy.

And her physician either was unable or unwilling to do it, and so she had to go to Yale to get access and how she literally thought she might die on the train because it was just too much to ask for her to do it. And she did it. And it worked, and that's a success story. But it's also a cautionary tale because I'm deeply concerned about the idea that we are, you know, not thinking about access from the get-go and trying to figure out how to minimize those barriers as much as possible.

We live in a country that has unjust access to health care, and so I understand when I'm saying we need to enshrine justice as a core principle in access

to research that seems a little bit odd because we don't have it in access to just normal clinical care. But I'm aspirational like that. What can I say?

You know, so as we're building a phage bank or as we're developing consortium, I just am encouraging people to invest the time, the money, and the planning up front to try to figure out how to minimize barriers to patients both in real time and downstream. And also, I have an international point here -- I'm not sure we've talked internationally yet today -- about is it possible to harmonize regulations now from the get-go so that once something is successful in the United States we can very easily translate it to, say, Canada or other countries where people will be wanting to try these?

More justice concerns. We've talked about this numerous times today in terms of how do we decide how much information we need to acquire before we use a product on a patient. And, you know, I don't have a magic bullet answer for this. This is an ongoing question anytime you have a novel intervention. We're

trying to balance earlier access and the possible benefit it offers with the risk that comes with getting something, you know, earlier before all the testing has been done.

So my only recommendation here is that we need to embed frequent evaluations of safety. It can't be something where we do, you know, we're gonna do 20 people, and then we're gonna do a, you know, a post hoc analysis. I think we should be looking at this in real time as we go along and manage risk cautiously.

And then, last but not least, I just wanted to say, the thing that really gives me heartburn about all of this is that, as we are doing this novel, like, amazing science for certain patients, there are other patients who are being told, “I'm sorry you can't get access because it hasn't gone through a mouse model yet, or it hasn't gone through a primate model yet.” Or “the Phase 1 was only enrolling 20 patients, and they've already enrolled those 20 patients. so you're gonna have to wait until a Phase 2 trial opens.” It is hard for me to understand how we are gonna justify to

other patients who are not in this, like, exclusive, individualized therapy category about why they still need to observe a status quo and rules that are, you know, being turned and modified in this particular context.

So that's the thing that keeps me up at night. And in the meantime, the thing that makes me really happy is the fact that we're having, like, amazing science that's gonna help patients. So I want the amazing science to help patients to go forward, but I want us to be aware of all the challenges that it presents for us and to be proactive about addressing them. Thank you.

**DR. WITTEN**: I'd like to next introduce Dr. P.J. Brooks. He's a program director at the NCATS Office of Rare Diseases and Research. He received his Ph.D. in neurobiology from the University of North Carolina at Chapel Hill and completed a postdoctoral fellowship at the Rockefeller University. Since joining NCATS and the Office of Rare Diseases, Dr. Brooks has been working on accelerating clinical trials

in rare diseases by moving beyond one disease at a time approaches. Examples include the development of therapeutics that target shared molecular mechanisms, underlying multiple rare diseases, platform technologies for delivery of nucleic acid therapeutics, and the implementation and recommendations from the NCATS Cures Acceleration Network regarding the acceleration of gene therapy clinical trials. Thank you.

**BEYOND 'ONE DISEASE AT A TIME:' ACCELERATING CLINICAL TRIALS OF GENETIC THERAPIES BY GROUPING RARE DISEASE PATIENTS ACCORDING TO UNDERLYING DISEASE MECHANISM - DR. PHILIP J. BROOKS**

**DR. BROOKS**: Thank you Celia and thank you to my FDA colleagues for the invitation to participate in this meeting. It's really exciting and it's something that we think about a lot. And I'm very happy to participate. And I'll be focusing on, more generally, the idea of trying to go beyond one disease at a time and how we can accelerate clinical trials of genetic

therapies by grouping rare disease patients according to underlying mechanism.

This is my standard federal government disclosure slide. And here you see the basic problem that I think we're all trying to address is the rapidly increasing number of disorders with a known molecular basis, due in large part to DNA sequencing. And this is likely to continue. And the big problem is that, at the present time, we've only about 600, 500 or 600 or so with therapy. And at the rate we're going, as my director, Chris Austin, said, it's gonna take about 2,000 years to get treatments for every one of these diseases, and that's just too darn long. And if we're gonna do something about this we don't need sort of minor tweaks to the process. We need some pretty fundamental changes in the way we think about these diseases and the way we design clinical trials.

And there's another aspect to this as well that sometimes doesn't get appreciated, but I think Jill Wood kind of hit on it. And that has to do with this issue of the different types of rare diseases. So

this is a slide taken from a recent publication by Orphanet, and we're looking at, within rare disease, there's different prevalence, you know, the highest and the lowest. And if you're thinking about the percentage of all rare disease patients, the majority of them are these high prevalence diseases, right? That makes sense, about 70 percent of the patients. But if you think about the number of diseases, it's a very small fraction. Way on the other side, the low prevalence diseases, the Sanfilippo, you know, III C, D, et cetera, you've got a very small number of patients but about 3,000 or so diseases.

And then, if we're gonna develop these treatments according to a standard model, the diseases of commercial interest are these ones for obvious reasons. But who's ever gonna do anything about these diseases here, these 3,000 diseases? If we're gonna do this one at a time I'm not sure we're gonna get to any of them. So we have to really reevaluate how we approach this problem, particularly because, as I'll get to later, when we're talking about some of these

diseases and monogenic diseases, we really do have therapies and treatments that have a pretty high prior probability of success. Oops. Wrong way. Okay.

So I think it comes down to the old lumpers and splitter distinction that we're all familiar with from different facets of life. This was taken from a paper written by Victor McKusick, the famous geneticist, many years ago. And he was talking about limpers and -- lumpers and splitters in the context of nosology. As you can tell by the way he drew these different pictures, he was a big fan of the splitters and not so much the lumpers. And maybe that made sense for the point he was trying to make; I honestly don't know. But with all due respect, I think in this day and age we've got to be lumpers wherever we can. And we've really got to focus on the commonalities across diseases rather than what makes them different.

And the really, I think, wonderful opportunity here is in the area of monogenic diseases. And you could say this is perhaps the biggest lump of all, at least within personalized or individual therapies.

Because, when you talk about monogenic diseases, these are diseases that relate from mutations in a single gene. And that means we know what the problem is, and we know at least what some solutions are, which is quite different than many other diseases.

So we have gene therapy which could deliver a normal version of that mutant gene into the relevant cell types of the patient and then, more increasingly now, genome editing where you can -- need to deliver genome editors or enzymes into these cell populations to correct that disease-causing mutation in the patient's cells. Particularly here we're talking about somatic cells. That's what we focus on in the United States. We're not -- we don't do germline editing in the United States.

And so the idea then -- so the real challenge for both of these is to deliver these treatments to enough target cells at the right time in development of disease progression to potentially treat, cure, or even prevent some of these diseases. And this is really fundamentally true for all monogenic diseases. And the

good news here is that we've actually made some progress in being able to do this. As Guangping Gao talked about adeno-associated virus or AAV, these really are effective vectors to deliver genes into cells.

They have an excellent safety record in humans to date, clinical success stories to approved products, and we see a lot of pre-clinical success stories. If you go to the American Society for Gene and Cell Therapy meetings, there's a lot of people curing a lot of mice of a lot of genetic diseases. It works quite well. But when you go to develop these into the clinic, we run into this one disease at a time approach.

And quite often you see the focus on the more common rare diseases. And this is slow, inefficient and results in duplications of efforts across different programs. It costs animals, time, and money and particularly the time and money in some cases of the parents who are trying to develop these therapies, of which there isn't very much. And there's this obvious

bias towards the more common rare diseases. So what makes sense would be to do -- to start these clinical trials for multiple diseases at a time using the same platform vector and that should increase the efficiency and reduce the time of clinical trial start up, would make sense.

So we're gonna try to test that specifically in a program we call the Platform Vector Gene Therapy or PaVe-GT project. And this is a collaborative effort between our office, Office of Rare Diseases Research at NCATS, and other collaborators at NCATS, in particular the Therapeutics Development Branch led by Don Lo and strategic alliances led by Lili Portilla, as well as colleagues from NHGRI and NINDS who will be working with us on the clinical trial. Do you have some water?

So to be clear, this is a pilot project where we're gonna be doing essentially a public platform vector gene therapy trial at the NIH Clinical Center involving all investigators from NIH. And the idea is to move forward with -- ultimately, towards clinical trials for gene therapy for four rare genetic diseases

together, each of which are of no commercial interest. So these are -- these -- the very far end of that graph I showed before. We use the same AAV vector, the same route of administration, the same serotype, use the same production purification methods because we've heard from our FDA colleagues many, many times that the process is the product. And the only thing that will be different are the therapeutic gene constructs for the different diseases. And the question is to what extent can we increase the speed and efficacy of clinical trials startup by really trying to maximize this explicit platform vector-based approach.

But the other thing I think that's gonna be different about this is that we intend to do this publicly and make all of the data, including the biodistribution data, the toxicology data, all of our communications with the FDA up to and including the IND submissions that will hopefully get approved -- we intend to make that public and publicly available so that all these documents and things can be used by others perhaps even in a cut and paste manner. And in

doing this and thinking about this approach, honestly, we had in mind people like Jill and all the parents that we meet who are trying to figure out how to do this by themselves. You know, it's got to be hard enough having a child with a rare genetic disease.

But then to expect them to become entrepreneurs and drug developers, and we think how can we provide help for some of these individuals? And I wish there was more we can do, but this is one approach that we think has potential benefit. And essentially, the idea here is that if we're going to do these one disease at a time for each vector we would make, for each gene, for each disease, we go through each of these steps in parallel, one right after the other. And that takes time and money, and time is an issue. But the question is, if you group them all together, can we utilize the fact that we're doing everything in the same pathway to avoid having to do, perhaps the biodistribution studies or some of the other steps, and reduce the amount of time to clinical trial startup?

And so here's sort of where we are on this.

We've got the collaborating investigator Carsten Bonnemann from NINDS, and Chuck Venditti from NHGRI. And we'll be working with two neuromuscular diseases and two rare organic acidemias using AAV9 for all four. And we're undergoing -- proof of concept studies and mouse models in human cells.

And I say we're gonna let you know about our communication with the FDA, and I can tell you that we had a communication with the FDA a few months ago and talked to them about this. And it went quite well, better than I kind of anticipated. They were quite good about the idea and I think were all supportive about being as transparent as possible. And we'll be anticipating our initial INTERACT meeting with the FDA later this year. And the key challenge we're facing, which I guess is one that everybody is facing and probably led to the meeting we had a few weeks ago, is how do we get AAV vector made for the clinical trials? Because we run into the same problem that everybody else does. So we are working on that as well.

And then earlier, Peter Marks, mentioned the

effort that we've been involved with working with them, as well as the FNIH, to develop a more broad public-private partnership for some of these individualized therapies and specifically focusing on AAV gene therapy. And it's a pleasure to be working with them and look forward to continue doing so. And I just wanted to point out that there are some actual parallels between our PaVe-GT effort and this other public-private partnership that is in progress that we hope can ultimately be leveraged.

In both cases, there has to be some decision about the serotype that's going to be used for the different diseases. We're choosing a single one. Perhaps there'll be multiples here. I put question marks on all these because there's still some questions about how our -- this public-private partnership is gonna work, but I think there's some clearly -- clear issues that'll need to be addressed. We're doing all of our work at the NIH Clinical Center.

I might point out, in part because we want to utilize that resource, but also because we're so

committed to making all of the data publicly available that we felt that the most efficient way to do it is by having everyone be a government employee. If we had a commercial company involved or even academic medical centers, we might have to deal with some of the intellectual property issues. So having it all done within the NIH kind of avoids that problem.

In -- oops. But ultimately in this effort we might be involving many clinical sites. As I said, we're gonna make all of our communications public. And what we had kind of hoped, actually, is that some of these documents and things might ultimately spill over and benefit this potential public-private partnership. The single manufacturer is, of course, key.

But one might consider a consortium here, and, you know, we chose four rare diseases for specific reasons and largely due to the availability of diseases and the investigators at the NIH. But here in this, whatever, effort, I think a big question is gonna be how do we choose and determine what diseases that would be under consideration? But I think both of these

things are kind of moving forward towards a day in which we can really make access to these treatments a lot more available for a lot -- much larger numbers of patients and families and hopefully take the burden off of people like Jill and other parents.

So then also the next phase, if you will, of the way to treat genetic diseases is genome editing. And I just want to briefly touch upon a program that we're involved within at NIH. This is a program funded by the NIH Common Fund, part of the Office of the Director. And it's on somatic cell genome editing. And it's coordinated by NCATS, Chris Austin, myself, and in association with many other program directors across the NIH.

And the goals of this program are to lower the barriers for new genome editing therapies by testing genome editing reagents and delivery systems and better animal models. These are not specific disease models but rather animal models created to allow us to detect genome editing in different cell types to maximize a broad utility, a big focus on testing unintended

biological effects. And I should say, unintended biological effects specifically in human cells and human cell systems for the reasons that Peter mentioned, that the human genome is special. We also have some interest in monitoring these cells in vivo.

We have some -- the biggest focus of the program is finding ways to deliver genome editors to different cell types. There's also a small part on increasing the genome editing repertoire, sending genome editing enzymes, and of course a coordinating center. And to give you a sense of the breadth of the program, this is the number of awards. The total budget of the program is around $180 million. And you can see that by far the majority of the awards -- almost half of them are focused on the delivery systems because that, as we see, is the biggest challenge. There are some cells and tissues we can deliver to pretty well but many that we can't at all, and that's really what the focus is on.

And if you want to learn more about it, here's the website. And the way we see this focused --

getting into the IND enabling process is kind of illustrated here, that this program will not specifically be funding any clinical studies, but rather what we think about is filling gaps. And there might -- one gap might be for a specific disease a need to be able to deliver genome editors to a particular cell type. But another gap actually that we focus on, and would really like to have some impact on, is the gaps in the regulatory process. That would allow our FDA colleagues to be able to regulate these products more effectively. And indeed, when we were developing this program and as we are going through it, we have close communication with people in FDA CBER to try to maximize that potential.

So finally, let me turn to addressing the question that FDA asked us to address which is what kind of opportunities and possibilities might work in the future to make some of these approaches scalable and sustainable. And I have some thoughts about that. So one would be to adapt the approach they use now in the development of vaccines, when one is producing a

new vaccine using a new strain. I should say that this is not an idea I came up by myself. This was originally brought to me by one of my colleagues, Mike Cirillo at NCATS, and I've heard Peter talk about it also.

But the basic idea is that, when someone's first gonna set up a vaccine production facility, the FDA would review -- would have to consider all of the aspects of setting up the process: the manufacturing facility, CMC potency assays, all kinds of things in addition to specific strains. But once a system is ongoing and producing, if from one year to the next you're just simply switching strains, then the FDA review can just focus on what's different, what's new, which in this case would be the new strain. And I'm a little imprecise about this because I've never regulated a vaccine, but I think you kind of get the idea.

And so we could take the same basic principle and apply it to gene therapy. When you're originally developing a gene therapy product, the FDA's gonna have

to consider all these things, the manufacturing and the whole, sort of, regulatory process. But the idea and the hope is that once we're making the same vector, and in the same manufacturing facility and holding all these things the same and simply changing the therapeutic transgene, the FDA review can focus on this. And that could streamline the process. And not surprisingly, that's basically the idea we're trying to test in PaVe-GT.

But I think the real exciting option has to do with genome editing. And late last year this publication came out from David Liu, who is funded by our consortium in part, a new genome editor that can carry out editing without creating double strand breaks. And the notable thing about this prime editing effort -- this prime editing enzyme is that this single enzyme could, in principle, correct almost 90 percent of known genetic disease-causing mutations. And that really seems like a potentially exciting platform.

And so if you imagine -- and again, obviously, I'm thinking about the future here. These are perhaps

forward-thinking statements. But if you think about the production utilization of such a biologic, you can end up with a single biologic that would be of potential therapeutic relevance to almost 90 percent of genetic diseases.

And once that would be approved, then, if you just want to add additional diseases to it, the only things that would be different are these guide RNAs that would direct the location of the editor within the genome. Guide RNAs of course are oligonucleotides, and oligonucleotides are regulated by the Center for Drugs. But the good news is, of course, a lot of excitement going on in this area with the oligonucleotide therapies for the rare genetic diseases.

And I'm sure you've all heard about the work by Tim Yu on the development of Milasen, and obviously the FDA, CBER, and CEDR are able to communicate on this. So it doesn't seem like an insurmountable problem. And so if you get back to this sort of optimized situation in the future, we'd be looking at perhaps a single biologic. And then the guide RNAs

would be assessed under really a streamlined process that takes into account the platform capacity of oligonucleotides to be able to see them as a class of molecules that would optimize the toxicology assessment of those as well. And, you know, thinking about the future of treating monogenic disease, this seems to me to be at least an aspirational idea of where we might want to go.

And so I think I'll just kind of stop there and summarize that, for monogenic diseases, gene therapy and gene editing have clear and obvious therapeutic potential for many monogenetic diseases. This one disease at a time approach that we're doing now is not going to address these low prevalence diseases of no commercial interest, despite the fact that the biological rationale of treating those diseases is just as good as the common diseases. And that does not seem acceptable. That's a major reason why we need to do something different. And so we need radically different types of clinical trials and regulatory platforms to bring gene therapy and gene

editing therapies to all the patients who might benefit from them.

Oh, and just one last thing. I think we've been always talking about individual therapies, and I understand why we're saying that. But I was telling you at the beginning, there's lumpers and there's splitters. And when you talk about individual diseases you're focused on splitting.

And I think -- I happened to come across this from a publication in *Stat News.* And I like the idea of industrializing personalization because I think that's sort of what we're talking about, how to take making individualized therapies into some sort of an industrial process. So I guess I'll leave you with that as well as our NCATS contact information. Thank you very much.

**PANEL DISCUSSION WITH Q&A**

**DR. WITTEN**: Okay. Thank you. I'm gonna ask the speakers and the -- to take their seats at the panel. And also, I'm going to ask Dr. Chip Schooley

and Dr. Julienne Vaillancourt. Dr. Schooley was introduced in the last session, but I just want to introduce Captain Julie Vaillancourt, whom many of you know. She's an officer in the U.S. Public Health Service, and she's the Rare Disease Liaison for the Center for Biologics Evaluation and Research and coordinates our rare disease program.

Thank you for joining. We'll take questions from the audience, but, in the meantime, I have a few questions to start off the discussion. I'd like to ask the two panel members who just joined us first. So I'll start with Julie. This session has been about collaborations, ethics, and stakeholder roles. And I wonder if you can comment on collaborations at FDA, CBER, and the rare disease area that supports product development?

**CAPT. VAILLANCOURT**: Absolutely. Actually, we have a really rich -- oh, thank you. At CBER, we have a very rich collaborative environment when it comes to our focus on advancing development of biological products for rare diseases. We have collaboration

internally in CBER. We actually, as part of our rare disease program, have a Rare Disease Coordinating Committee that meets on a monthly basis. It's comprised of representatives from each of the offices in CBER: our product offices, our Office of Epidemiology and Biostatistics, our -- and others.

And also, we collaborate extensively across the agency with the Office of Orphan Products Development, OOPD, and with CDER's rare diseases program. And I also want to say a newer entity in the last two or more years is the Patient Affairs staff in the Office of the Commissioner. And they are very instrumental in helping to facilitate making sure that the patient voice is heard and that there are ways and many mechanisms to engage patients with each of the centers. And we continue to work with these different groups across the agency, and we're developing new collaborations every day.

Since I've been the rare disease liaison in September of 2015, I've been participating in a Rare Disease Council that is headed by the Office of Orphan

Products. And again, it's an effort that brings representatives that work in -- on rare disease focused development from across the agency. We meet periodically. We share information, best practices. Sometimes we bring in outside speakers. There's also a new Rare Disease Round Table that was started by Theresa Mullen in the Office of Drugs that is engaging some outside stakeholders as well.

We have -- I'm going on and on, but you can see it's very rich. We also coordinate and have a rare disease cluster with our European colleagues. It's a rare disease cluster that is headed by CDER's Rare Diseases Program, but a number of us from CBER participate. And sometimes we are asked to have discussions with CBER regulated products and issues with our EMA colleagues. And Health Canada has more recently joined in those monthly discussions.

And we also coordinate with our outside stakeholders, our external stakeholders, such as the National Organization for Rare Disorders, NORD. We have been part of their planning committee for a number

of years. And we also have some newer cooperative agreements with them like our -- someone from our Office of Biostatistics and Epidemiology is working on a collaborative project with NORD and with a patient advocacy group on a natural history study and the use of a mobile app.

So there's lot of exciting work going on. And I'll have to say we're making room for the whole topic of today's meeting of individualized therapeutics. And it's, for example, we've mentioned -- a few people have mentioned today about the rare disease meeting that took place last Monday or -- yeah, it was last Monday. It's gone by so fast.

Anyway, that was headed by Dr. Janet Maynard from the Office or Orphan Products. However, it was a collaborative team effort, and there was representation from CBER and from CDER. And the afternoon was all focused on individualized therapeutics. And, you know, there are other examples, so I hope I've given you a sense of the breadth and depth of collaboration that CBER is involved in, as we really work toward the

development of biologics for patients with rare diseases.

**DR. WITTEN**: Okay. Thank you. I'm gonna take a question from the audience.

**MS. HESTERLEE**: Hi, so it's Sharon Hesterlee from the Muscular Dystrophy Association. So I'm very interested in this problem of the ultra-rare diseases. At MDA, you know, we hear a lot about Duchenne and SMA and ALS, but the majority of the over 45 diseases we cover are ultra-rare. So this is a problem that I think about a lot and that keeps me up at night. And I've also spent the last three-and-a-half years working in industry in gene therapy and heading gene therapy projects, in charge of budgets for gene therapy projects. So this is kind of comments for P.J.

I'm really interested in this effort to create a platform approach. But the caution I would give you is that this idea of using the same serotype, or the same capsid and vector, the same route of administration, you know, same manufacturing techniques, these are things that companies are already

doing. I mean, they're already doing that to try to get those economies of scale. And I'm gonna tell you, your savings in money are very, very small. Savings in time, also pretty small. So I don't know that this platform approach and this idea of this platform approach at the pre-clinical, early clinical phase is really gonna be that big of a time or cost savings.

I do think where you could see more savings are doing things like doing a platform trial approach. The problem is these transgenes matter, so there's only so much you can do to sort of combine your efforts at the pre-clinical stage. You can have tox related to different transgenes and expression of transgenes. I just wanted to make that point that I think companies are already doing this.

They're already standardizing those things. They're already standardizing their manufacturing assays. They're doing all of those things. It's not enough. Your budgets are still $20, $30 million, even for an ultra-rare disease. So I think it's just something to consider that that may not be as tractable

a target in trying to reduce costs.

**DR. WITTEN**: Thank you. Are there comments? Do you have comments on this?

**DR. BROOKS**: Yeah. I think -- I'm sure there are companies doing that, but I think that information isn't made available. So we would want to make it available to the whole community so it's not kept within a company. And I think that certainly there are many cost drivers in this, and we don't expect that this effort by itself will, you know, reduce that.

I think our focus of the AAV manufacturing meeting that we had was to try to find ways to reduce the cost. But improving not just even the pre-clinical stuff, but even as we think about the clinical trial design within PaVe-GT, I do think we'll also be looking for ways to increase the efficiency of the process. But to try to learn what we can do and also to make it public so everybody can benefit from it is a major aspect of this goal. But certainly there's -- there are -- there's more to do than that. I would agree.

**DR. WITTEN**: Thank you. I'd like to address a

question to Dr. Schooley. So Dr. Schooley, this is about developing products. So you described in your talk the collaboration of iPATH and of the phage referral network so that, if a patient came in need of a treatment, the group would collectively search their inventory to see if there was phage available that would benefit them. But that that only -- that was not true for the -- I think you said it was the minority of the patients who came that you were able to find something. So I'm wondering what type of collaboration or what type of effort do you think would be needed and by whom in order to be able to develop phages for -- so that no infectious disease is left behind, so to speak?

**DR. SCHOOLEY**: Over the short term, the problem is the biology. You actually physically have to have the organism in -- the bacterium in the same -- on the same plate or in the same liquid medium as the phage candidate you want to use, which requires you to have -- to disseminate that organism to whatever labs or groups have libraries of phages that target that organism. So right now, the limitation is how many

groups have large enough libraries that you can practically get a given patient's organism out in time to be able to help the patient.

Having more comprehensive libraries that could be screened more easily would be act- -- and methods by which you could screen them quickly would be great. Down the longer term, if you had -- if we could by AI learn to predict from AI what bacteria could be attacked by which phages, you could actually do it with whole genome sequencing. We're a long way from that because there are more variables than equations these days. But that would be the -- down the road, I think, a very important approach.

One could also envision situations in which phages were engineered to have a broader host range, in essence become more like antibiotics and less like phages. What you would be giving up there is the specificity of phages from the standpoint of the microbiome and the other advantages of the laser like approach. And you would also begin to see, if you had widespread use of phages with engineered phage with

broad host range, they would behave like antibiotics do in the hospital. You would begin to have phage resistant organisms that would then behave the same way antibiotic resistant organisms do.

So I think, over the short term, larger phage banks that could be searched more easily and production facilities that were able to take that burden off the hands of academic laboratories and produce phages in a more standardized way would increase the throughput. The sources of funding for those really haven't yet been identified.

**DR. WITTEN**: Thank you. Question from the audience?

**MR. THAKUR**: Yes, I'm Neil Thakur from the ALS Association. So I had a question for P.J. about the model that you're talking about and the ultimate vision of success. And so I think what you were saying is the idea is that you would get a manufacturing process approved by the FDA. And when it comes time to bring on a new disease or a new application of the technology, the FDA review would be expedited. And so

what I'm trying to understand then is does that mean that the clinical center or the facility that's doing all this manufacturing would then become the hub for AAV9 for these ultra-rare applications? Or would somehow -- could this model be expanded or exported to other facilities as well? So what's your -- what's the step after this project, in other words?

**DR. BROOKS**: So I guess I'm trying to be clear because I'm talking about two different things. The PaVe-GT is one and then the individualized therapies that we're working with FNIH and FDA CBER -- is that what you're referring to?

**MR. THAKUR**: No. You had a slide where you talked about on one side you had here's what the FDA is gonna review in great detail, and then ultimately, when you bring on a new thing, it'll happen faster. And I'm -- I think that was the PaVe-GT ultimate thinking. But I'm not clear on what the final status that you're trying to drive to, how you see the manufacturing, and the FDA, and the NIH all working together.

**DR. BROOKS**: Yeah. I think there's different

levels and different projects. But I think the idea in part was to make the regulatory process easier for the FDA. When we're adding on -- if they want to add on -- we want to add on a new disease, if the vector manufacturing is one they've seen before and the biodistribution has been seen before that we wouldn't have to repeat that. And that could increase our clinical trial startup and make the regulatory path easier.

I don't think I would imply that we're gonna get FDA to approve a manufacturing process. I don't see -- it's not obvious to me how that would work, but I think it would be something like having a -- you know, using the same process over and over again and having the focus just be on what's different.

**MR. THAKUR**: And that'll be the clinical center doing that going forward in long term?

**DR. BROOKS**: No. I don't think in long term. I think optimally in long term we'd want to expand this. And I think expanding beyond the PaVe-GT, our pilot project, would ultimately hope- -- potentially be

the FNIH public-private partnership, and that would not be limited to the NIH Clinical Center.

**MR. THAKUR**: Thank you.

**DR. WITTEN**: Before we take the next question, I just want to clarify. So I -- what P.J. said is correct. I mean, that is a shared, you know, his description of it. We don't license processes. But if we learn from the process or what happens and we learn from our review and we learn from the science, that'll facilitate continuing development, which is I think what the goal of the program is. So that's -- I think we're in agreement about what we think will happen, the benefit could be. Yes?

**MR. HORGAN**: Rich Horgan from Cure Rare Disease. One of the things tying together the ethical and the stakeholder issues I think we may have been overlooking a bit is the role of the payer in this. So in the last two months we've had conversations with chief medical officers of two of the biggest payers or insurance companies in the United States. They are aware of the development of customized therapeutics.

And the current mechanism for reimbursement is one that is not at all conducive to reimbursing customized therapies. More of a comment than a question, but an urge to consider the payer perspective as you're designing these, whether it's a platform trial or other thinking both at the NIH as well as the FDA, because I think, at the end of the day, if we can prove that we have efficacious and safe custom drugs for one or two patients, that's certainly great. But it's not sustainable if we don't have payers on our side and supportive of this approach.

So sort of urge thinking and more thought surrounding that area because these certainly aren't cheap, especially when we get to larger volume AAV deliveries like with a Duchenne or another neuromuscular disease. It's not an eye, and it's not as privileged as the CNS in being compartmentalized to some degree, but, you know, would urge some thinking around that area.

**DR. WITTEN**: Thank you. Are there comments from the panel on this topic?

**DR. BATEMAN-HOUSE:** I want to thank you for bringing that up. I've been thinking a lot about payers today. And I don't remember who said it, so I'm not calling out names. But someone today said something about, you know, well, if we had an add on therapy that was safe, and even it was only a little effective, why wouldn't we do it? And I immediately thought because payers won't pay for it. So I think you can't lose sight of that, especially when you're thinking about access downstream.

So it's one thing to say in this interim period, we don't need to worry about payers. But whenever I talk with a company, and in this case whenever I talk with an academic center or anybody doing novel development, I would say think downstream. Who you plan on using this product, and what evidence do you need to get? At what level of certainty do you need to convince payers to make that actually happen? Because it's one thing to get FDA approval; it's another thing to go through that other set of gatekeepers which are payers.

**DR. WITTEN**: Thank you. I think --

**DR. BROOKS**: Oh --

**DR. WITTEN**: Sorry.

**DR. BROOKS**: I just -- I'll just make one point. I think, I mean, I certainly agree about the payer point. I think one of the other efforts that we have in the Office of Rare Diseases Research is to try to understand the cost of all these rare diseases on our current health care system. Because when the payers are going to be thinking about this, it's the cost of paying for the therapy compared to the cost of not having the therapy. And understanding the current costs of all these rare diseases on our medical system is -- we don't really have good data on that for a variety of reasons, in part because of the difficulty of the lack of ICD codes for some of these diseases. So we have quite an effort going on at NCATS to come up with a good estimate of what we call the cost of rare because that will help the payer consideration.

**DR. WITTEN**: Do we have a question from the online viewers?

**THE OPERATOR**: Yes, we do. The topic is ethics.

**DR. WITTEN**: It's hard to hear you.

**THE OPERATOR**: The topic is ethics. And the question is, in what I'm hearing, clinical trials are very much being spoken of as treatment. How much concern is there about research subjects or patients clearly understanding and giving consent to early trials that have not yet established safety?

**DR. BATEMAN-HOUSE**: So I think that was the point that I was trying to make is that, traditionally, we have said that there is research that should not be thought of as therapy and that there is a high bar that is expected to be cleared in terms of the informed consent process that is asked of when a patient goes to participate versus we had a much lower informed consent process to participate in a therapeutic endeavor. And the example I gave was surgery. So you know, you sign a one page very small consent form to have your gall bladder removed versus a very complex consent form to participate in a clinical trial.

That's the model that we all grew up with. That's the model that has always been said is a best practice. But the question is are we at a point where that model need transforming? And, in some cases, it may be that it does need transforming.

If a truly bespoke therapy is being done on one person even though it is experimental, it's not necessarily research anymore. So we need to come up with some understanding of how to navigate that divide. And then the other point that I had hoped to make is that that doesn't mean that that distinction is gonna collapse across the board. So there is still going to be areas where there is a divide between research and therapy, and we still need to make sure that patients in those contexts understand that going into this clinical trial is not necessarily a therapeutic endeavor.

And so there's a possibility of having mixed messages about, you know, yay, all research is treatment when that's really not true. And how do you make those clarifications clear to potential research

subjects? I'm sorry. I'm looking at you because you're the one that asked the question. I should be looking -- I don't know who I'm supposed to be looking at. The camera. Hello, camera.

So I just -- I'm very concerned in terms of understanding, transparency, and expectations that we need to be very clear about what is status quo, what is different, and, if there are differences, why there are differences and, if people are being held to the status quo per se, why that is as opposed to it just being, like, we like this disease and we don't like this disease, or this disease has more engaged patients versus this disease doesn't? I think we need to be more clear as to why we're acting in certain ways in certain paradigms.

**DR. WITTEN**: Thank you. I'm going to take the two questions from the people who are already lined up and then take the chair's prerogative to ask the final question before closing the session.

**MS. NOSRATIEH**: Thank you. This is Anita Nosratieh from FasterCures. This is a question going

back to the payer considerations and thinking about this truly end-to-end access. Do you think, P.J., it would be possible to incorporate CMS into the pilot that you guys are spearheading between NIH, FDA? Just seems like a natural, kind of, inclusion.

**DR. BROOKS**: I'm looking over at Peter. Okay. Yeah. So Peter's going to address that later. Thank you.

**MS. BLACK**: Hello. Lauren Black with Charles River Laboratories and ex-CBER. I'm interested to see the analogies between the current personalized medicine and where we stand today in terms of monogenic diseases. Within the context of monogenic diseases, I think it's more like surgery, as Alison pointed out, where the patient comes in. You can do an analysis that's equivalent to saying, okay, the artery is bleeding. We know what's wrong with the patient.

We know that they need a specific enzyme to be replaced, or they need a certain gene replaced or knocked out. We know exactly what's wrong with those patients. So for that subset, this is very surgical.

It seems as if the payer would take a more surg- -- investigational surgery type approach to saying okay, we're gonna replace that gene. We can measure that. We can say if the initial drugs are working and have a pharmacodynamic response.

And then say that yes, there's a blurred line between treatment and research, but we can see that the gene that was missing is now producing that protein. And we can detect that protein in the blood and the CSF. That seems to be a lot more clear than trying to treat a disease that we didn't understand the cause or had multiplicities of causes.

Here we have a much more specific thing that we're looking to accomplish, so why shouldn't the lines be blurred? Because as soon as we can detect the replaced protein in the person, we know that we're much closer to actually remediating their condition. So I think this is actually a place where we can make a sea change because we can see what's wrong, and we can see how to fix it.

**DR. WITTEN**: Well, I think it's -- we're all

optimistic that this approach will work. So I think we'll have to see what happens with this.

**DR. BATEMAN-HOUSE:** Can I say something about it?

**DR. WITTEN:** Oh, sure.

**DR. BATEMAN-HOUSE:** So I'm not sure there was a question there, and, if there was, I didn't get it. So sorry if I don't answer correctly. But I just wanted to say -- one thing that I just want to make sure is clear, when I am saying that the intention may be therapeutic but something being done is still experimental and hence we need to figure out how to deal with the informed consent and other problems of that nature, is I want to share a conversation I had with Dr. Timothy Yu who has been mentioned several times.

So he had a terminally ill child who had a de novo mutation of Batten's disease and was able to say, I think I can come up with a customized therapy that will help this child based on a platform from Spinraza that I can make some alterations and use it to

potentially help this child. The thing that he was concerned about he told me going into this was no one had done this before, and there was a possibility that by infusing this experimental product into this child, who was blind, was not really able to communicate, and was obviously headed towards an early demise, he could, yes, actually, intervene in that trajectory, but he could have other potentially unintended side effects.

And the one that he was concerned about was awakening or reinvigorating some part of the brain that would allow her to experience pain and thought I really don't want to give this intervention to a child that may, yes, prolong her life but may also make her current state of being worse. So I think even though there's a very sort of cut and paste mentality, like, of course this is gonna work -- it's very logical and it could work -- it's still experimental. We don't know what's gonna happen.

And even though we could say it's more of an experimental therapy than research because the intent is to help this person, you can't lose fact of the --

sight of the fact that it is experimental. And you have to have that understanding going into it and make sure that there is the informed consent and make sure that everybody understands, you now, we don't know what's gonna happen here. Maybe after a couple iterations in a couple different settings, we'll have a better basis for being able to make predictions but not at first.

**DR. WITTEN**: Thank you. So my last question -- and I'm gonna ask everyone on the panel. And I'll start with Jill, if that's okay -- is -- of course you don't know the question, so I guess it's maybe not fair to ask if it's okay. Is, if there's one thing -- so we obviously at CBER are looking at these questions very carefully as to what we can do to facilitate the process or what we need to look at, what our next steps should be to try to benefit patients and benefit product development.

And so I just would like to know from each of you, if you have any thoughts, if you do have any thoughts on what would success look like for us just

for the next year? I don't mean 10 years, you know, 20 years success, but just, if we could accomplish something in the next year, what would it look like? If you have a comment on that.

**MS. WOOD**: Well, I think what P.J. is suggesting is profound, and it's absolutely amazing. And if you could pull it off, you'd be pulling off a decade of success right there. Something very easy I would say, a success is to identify those ultra-rare diseases and uber rare diseases that really need -- have a need for mouse models and registries and natural history studies and help facilitate those -- development of those things by either working with their patient organizations or trying to figure out an in-house way of doing that for all.

**DR. WITTEN**: Thank you. Next. Alison.

**DR. BATEMAN-HOUSE**: I think the fairest answer to say is I don't know.

**DR. WITTEN**: Okay.

**DR. BATEMAN-HOUSE**: But I guess I would just say I really think it's important to be transparent in

these ongoing conversations and also, in terms of -- to the extent that CBER is starting to lean certain ways, to divulge that as soon as possible because it sounds like there's a lot of people waiting for some sort of -- certainly as to whether they're on the right path or not. And the sooner that they can feel some sense of assurance that, you know, maybe we don't have a final guidance yet, but we see that there's a wind blowing this way, that would be helpful.

**DR. WITTEN**: Thank you.

**DR. BROOKS**: So I think one of the most exciting things that I see is the effort that involved with Peter and FNIH to develop this public-private partnership and really test a very different way to do gene therapy clinical trials for bespoke therapies. I don't know that we can pull it off and get it started within a year. But I think if we can do that, to have the FDA leadership involved in an effort like this seems like a very different approach for the FDA leadership. And I think it's really wonderful and exciting for all of us who are participating in it and

I think, you know, for the whole community. So…

**DR. WITTEN**: Thank you.

**DR. SCHOOLEY**: You know, we're working with often rare diseases. And we should try to learn how to generalize our knowledge base, so we don't have to discover the same thing over and over again in each specific clinical indication, so learning how to generalize with the skepticism you need about over generalization, at the same time -- and to focus our resources on moving the field forward rather than just repetitively doing the same thing over and over again, just say this is the way we develop this therapeutic. In other words, connecting the dots in a more -- among these efforts in a more cross-fertilizing way will help us move forward. And I think that, at the end of the day, if we can do that, we'll help in both these kinds of diseases and how we approach other diseases as well. The innovation that we've seen today in these approaches, I think, is really breathtaking, and that innovation needs to be balanced with the care that we approach human engagement in research.

But also, we need to make sure that what we learn on platform that has a lot of similarities to others is shared so we didn't have to discover the same thing over and over again. And parallel efforts, that holds everybody back because of proprietary needs that put these people at risk over and over again who studied the same thing and slows the field. So generalization early in the process helps everyone, particularly our patients, so early sharing of approaches, platforms, techniques. We're all here for the same thing, and there's plenty of room for innovation in any given field is what I would argue.

**DR. WITTEN**: Thank you. And as usual FDA gets the last word, so…

**CAPT. VAILLANCOURT**: Thank you. Well, I think today is an extremely important day. We're starting a public dialogue about this critically important area and in a way of -- to go forward without having all the burden on patients and parents, such as Jill and others out there. And I think it's so important that we keep the dialogue going, that we don't lose momentum.

And I'd like to agree with what P.J. said, and, being from FDA, I think this announcement of this public-private partnership is very, very exciting. So be great if we could convene again and see some -- hear about the status of what's happening with that public-private partnership, also to get an update on how the NIH program is going. I mean, these are all really exciting initiatives -- but also to hear more from our stakeholders.

We're just so thrilled that everybody is here. For those of you in the room and everybody on the phone, the whole intention was to get the stakeholders together today and to hear from everyone. So again, keep the dialogue going, keep the momentum going.

**DR. WITTEN**: Thank you. I'd like to thank the panel and the speakers. And next I'm going to turn it over to Dr. Peter Marks, our Center Director for -- to wrap it up.

**WRAP UP AND CLOSING REMARKS: DR. PETER MARKS**

**DR. MARKS**: So thank you everyone in the room and online who had stuck with us for the full day. I think rather than summarizing each of the sessions, I think what I just want to say is, I think what really came through pretty clearly is that I think we all see the compelling need to make headway here in these individualized or bespoke therapies. And I think we -- in each of the sessions we have these building blocks that we can build upon, whether it's on the manufacturing, the non-clinical aspects, the clinical aspects, or patient access to these things.

Just to back up to try to address some of this because the issue of how do you pay for these things has come up. So I think there are lots of different ways to think about this. But the way I would think about this for at least for the reason why we're very interested in a public-private partnership is I think we're in a time of transition here. We're in a time of transition where -- there was a model several years ago where every rare disease would be commercially viable somehow because you could charge enough for the gene

therapy.

I think it's -- I'm oversimplifying it, but I think what we've realized is -- and what companies have realized is that commercial viability lies beyond many of the diseases that we're talking about today, which means we have to find some other way to fill in that gap. I will tell you an opinion. This is not the opinion of the United States Government Health, and Human Services or the Food and Drug Administration of the United States of America.

This is my own opinion that, 10 to 15 years from now, this issue will be fixed because there will be commercial viability for very rare bespoke therapies inasmuch as I think much of this will be essentially dealt with by having machines that can -- this will be a device issue. Many of these gene therapies will be made potentially on non-viral platforms or by mechanisms that don't require the kind of setup that they currently do. And we will have had a lot more experience about what you can leverage.

But for this interval of the next 5 to 10

years, I think we have to find a way to get these therapies to individuals in need. I don't know that we're gonna find a way to get payers to pay for them, at least in the short term. But what I do think is there's a lot of good will going between companies, non-profit organizations, and, for that matter, government wanting to collaborate with them to find ways to try to make these therapies available to those in need.

There's gonna be a lot of ethical issues, a lot of prioritization issues that'll have to be worked through in this. But I think that's the goal of these public-private partnerships is to try to find a way forward. And ultimately, the reason why this is so important, at least to me, is that this is a case where, if we can get it right for these very small numbers of patients, ultimately the entire field of gene therapy is bound to benefit. So it's one of these things that start small and local and then go more globally.

And just so that I just mention that we didn't

concentrate here today on the discussion of the more global issues for gene therapy. But part of the reason for getting it right here is that, if we can take care of these products on a small scale here, hopefully, we can have a global framework so that patients around the globe will benefit from their development. It really would be a shame if we spent the time developing these here, and then they're not accessible -- you know, it would be really sad for a Sanfilippo type C or a type III C or D patient here not to get something and not to have a patient in Asia or in Africa benefit from that same advance that we've made.

So ultimately, I think we're gonna go back from this. We will do what FDA likes to do is we will cogitate for a while. I think we do understand that ultimately the way we try to put forth our thinking is in guidance. Hopefully that will be forthcoming at some point in the future and in the not too distant future.

And we'll also continue to work with our partners at FNIH and NCATS to try to move forward this

public-private partnership. Is success assured? No, it's not. But I think it's certainly worth a try because there's a lot of good will there. There are a lot of patients in need of these therapies, and I do think we have to try to do something differently that will try to get us there.

We have actually -- just to answer another question, we have actually spent some time with business folks and with companies talking about economies of scale. And there probably are some economies of scale to be had here in part by using excess capacity, in part by reusing certain aspects of files and et cetera. It's not gonna ever be cheap, but we do think this is something that could hopefully lead us to be able to more efficiently get there for patients.

So with that I just want to close by saying I really want to thank all of the speakers today, particularly Ms. Wood who I really think really shared a very compelling picture of what it's like to deal with this type of situation from a variety of aspects.

And to all of you for -- thank you for coming today and for really caring about this issue. And I'd also echo something that Julie Vaillancourt said which is that we look forward to continuing the dialogue with everyone.

And with that I have two last things to do. One of them is to once again to thank Leslie Haynes and Gopa Raychaudhuri for really planning an incredibly excellent workshop. So let's give them a round of applause. And then I told Gopa I'd give her the last word. So here she goes. You're good. Okay. With that, thank you very much. Okay. Thanks again, everyone.

**[MEETING ADJOURNED]**