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Center for Biologics Evaluation and Research (CBER)
Office of Tissues and Advanced Therapies (OTAT)
71st Cellular, Tissue and Gene Therapies Advisory Committee (CTGTAC) Meeting

OPEN SESSION

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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.

ATTENDEES

COMMITTEE MEMBERS	
Lisa Butterfield, Ph.D.	Parker Institute for Cancer Immunotherapy
Kenneth Berns, M.D., M.P.H.	University of Florida
Bernard Fox, Jr., Ph.D.	Providence Portland Medical Center
Randy Hawkins, M.D.	Private Practice
Christopher K. Breuer, M.D.	Nationwide Children's Hospital
Jeannette Yen Lee, Ph.D.	University of Arkansas for Medical Sciences
Joseph Wu, M.D., Ph.D.	Stanford University
John A. Zaia, M.D.	Beckman Research Institute of City of Hope
Geoffrey Nichol, M.D.	BioMarin Pharmaceutical
Shah, Nirali N., M.D., MHSc	National Institutes of Health
Gil Wolfe, M.D.	University at Buffalo/SUNY
FDA PARTICIPANTS/SPEAKERS	
Peter W. Marks, M.D., Ph.D.	Food and Drug Administration
Wilson Bryan, M.D.	Food and Drug Administration
Karen Elkins, Ph.D.	Food and Drug Administration
Rachael Anatol, Ph.D.	Food and Drug Administration
Chava Kimchi-Sarfaty, Ph.D.	Food and Drug Administration
Steven Oh, Ph.D.	Food and Drug Administration
Andrew Byrnes, Ph.D.	Food and Drug Administration

FDA ADMINISTRATIVE STAFF	
Prabhakara Atreya, Ph.D.	Food and Drug Administration
Tonica Burke, B.S.	Food and Drug Administration
Joanne Lipkind, M.S.	Food and Drug Administration
Christina Vert, M.S.	Food and Drug Administration
Michael Kawczynski	Food and Drug Administration

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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning. I'm Mike Kawczynski. I'm project manager at FDA. And I'd like to welcome you to our 71st meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee. This is a live virtual meeting with participants from around the country, sometimes even around the world, so once in a while we do expect some technical difficulties. But let's cross our fingers today and hope everything goes well.

We will have a scheduled break. If you do need the agenda, everything is posted. But at this time let's get this meeting started. I'm going to kick it off to our chair, Dr. Lisa Butterfield. Lisa, are you there?

DR. LISA BUTTERFIELD: All right. Good morning, everyone. Welcome to today's meeting. I'd like to welcome the committee members, our colleagues at FDA, all of the online participants who will be joining us today. A quick housekeeping reminder, please use that raised hand icon if you'd like to

contribute to our discussion today and turn your camera on so that I, as chair of today's meeting, can recognize you and have you joined the conversation. So, thank you for that.

And I'd like to now hand the meeting to Christina Vert for our administrative announcements and roll call. Thank you.

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, AND CONFLICT OF INTEREST STATEMENT

MS. CHRISTINA VERT: Thank you, Dr. Butterfield. Good morning, everyone, this is Christina Vert. And it is my great honor to serve as the designated federal officer for today's 71st Cellular, Tissue, and Gene Therapies Advisory Committee meeting. On behalf of the FDA, the Center for Biological Research, and the Committee, I would like to welcome everyone to today's virtual meeting.

The meeting for today will be to hear an overview of the research program of the Gene Transfer and Immunogenicity Branch. Today's meeting topic was

described in the federal register notice that was published on February 16th, 2022. I would now like to introduce and acknowledge the excellent contributions of the staff in the Division of Scientific Advisors and Consultants including our director, Dr. Prabhakara Atreya, who is my backup and co-DFO for this meeting.

Other staff are Ms. Joanne Lipkind, Ms. Karen Thomas, and Ms. Tonica Burke, who have provided excellent administrative support in preparing for this meeting. And I would also like to express CBER's sincere appreciation to Mr. Mike Kawczynski in facilitating the meeting today. Please direct any press media question for today's meeting to FDA's Office of Media Affairs at fdaoma@fda.hhs.gov. The transcriptionist for today's meeting is Ms. Linda Giles.

We will begin today's meeting by taking a roll call of the Committee members. When it is your turn, please turn on your video camera and unmute your phone, then state your first and last name, your organization, and your expertise. When finished, please turn your camera off and we will proceed to the next person.

Please see the member roster slides in which we will begin with the chair, Dr. Lisa Butterfield. Dr. Butterfield, please go ahead and introduce yourself.

DR. LISA BUTTERFIELD: Thank you very much. My name is Lisa Butterfield. I'm a vice president of R&D at the Parker Institute for Cancer Immunotherapy, also an adjunct professor of microbiology and immunology at the University of California San Francisco, and I'm a cancer immunotherapist focused on cell therapies and cancer vaccines.

MS. CHRISTINA VERT: Thank you. Dr. Ahsan was not able to attend today so we will move on to Dr. Berns.

DR. KENNETH BERNS: Good morning. I'm Ken Berns. I'm Distinguished Professor Emeritus of Molecular Genetics and Microbiology at the University of Florida College of Medicine, and my expertise is the molecular biology of AAV.

MS. CHRISTINA VERT: Thank you. Dr. Breuer.

DR. CHRISTOPHER BREUER: Hi, my name is Chris Breuer. I'm a professor of surgery at the Ohio State University and the director of the Regenerative

Medicine Center at Nationwide Children's Hospital. My expertise is in tissue engineered (audio skip).

MS. CHRISTINA VERT: Thank you. Dr. Fox.

DR. BERNARD FOX: Good morning. My name's Bernard Fox. I'm the Harder Family Chair for Cancer Research at the Early Child's Research Institute in Portland, Oregon. My expertise is in tumor immunology and cancer immunotherapy with a focus on cancer vaccines and adopted cellular therapy.

MS. CHRISTINA VERT: Thank you. Dr. Hawkins.

DR. RANDY HAWKINS: Good morning, Randy Hawkins. Private practice pulmonary and critical care medicine, Charles University.

MS. CHRISTINA VERT: Thank you. Dr. Lee.

DR. JEANNETTE LEE: Good morning. My name is Jeannette Lee. I am professor of biostatistics and a member of the Winthrop P. Rockefeller Cancer Institute at the University of Arkansas for Medical Sciences. Thank you.

MS. CHRISTINA VERT: Thank you. Dr. Nichol.

DR. GEOFFREY NICHOL: Good morning. I'm Geoff Nichol. I am the industry representative on the

Advisory Committee. I have recently been the chief medical officer and am currently a senior advisor at BioMarin Pharmaceutical.

MS. CHRISTINA VERT: Thank you. Dr. Shah.

DR. NIRALI SHAH: Hi. I'm Nirali Shah, head of the Hematologic Malignancies Section of the Pediatric Oncology Branch. I'm a clinical researcher and my work has involved the implementation of immunotherapy, but mostly CAR T-cell therapies in pediatric and young adults (inaudible) relapsed refractory leukemia. Thank you.

MS. CHRISTINA VERT: Thank you. Dr. Wolfe.

DR. GIL WOLFE: Hi, I'm Gil Wolfe. I'm a new member of the Advisory Committee. I apologize for my attire. I was taken out of Buffalo on an emergency basis earlier this week. I am a neuromuscular neurologist with an interest in both auto immune disorders and hereditary disorders in neuromuscular disease. I'm the chair at the University of Buffalo. That's part of the SUNY system. And I just head yesterday I'm actually going to be named a SUNY distinguished professor shortly as well.

MS. CHRISTINA VERT: Great. Thank you for taking the time today to join us and you're welcome. Dr. Wu.

DR. JOSEPH WU: I'm a professor of medicine and a professor of radiology at Stanford. I also direct the Stanford Cardiovascular Institute. I'm a cardiologist. My research is in clinical genomics, iPSC, stem cells, and also cardiovascular imaging.

MS. CHRISTINA VERT: Thank you. Dr. Zaia.

DR. JOHN ZAIA: Hi. My name's John Zaia. I am the director of the Center for Gene Therapy at City of Hope. I am an infectious disease physician as well. And I would say my level of expertise is as a clinical trialist for gene therapy trials.

MS. CHRISTINA VERT: Thank you. Thank you for your introductions. I would also like to acknowledge CBER leadership and management including Dr. Marks, Dr. Elkins, Dr. Bryan, Dr. Anatol, Dr. Kimchi-Sarfaty, Dr. Oh, and Dr. Byrnes, some of whom will be joining the meeting later today and others who will be providing overview presentations shortly.

MR. MICHAEL KAWCZYNSKI: Dr. Marks, are you

with us right now?

MS. CHRISTINA VERT: Okay.

DR. PETER MARKS: I am. Thank you.

MR. MICHAEL KAWCZYNSKI: Go ahead, Dr. Marks.

MS. CHRISTINA VERT: Thank you, Dr. Marks. If you want to say anything you're welcome to.

DR. PETER MARKS: Just to say thank you. Big thanks to the Committee members for taking the time today. This is a really important thing for us to be doing, and we really appreciate you taking the time to do it. Thank you.

MS. CHRISTINA VERT: Yes, we do. Thank you. I will now proceed with the conflict-of-interest statement. Thank you. The Food and Drug Administration is convening virtually today, March 10th, 2022, for the 71st meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. Welcome to the March 10th, 2022 meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee.

CTGCAC Committee will meet in an open session

to hear an overview of the research programs in the Gene Transfer and Immunogenicity Branch which is in the Division of Cellular and Gene Therapies in the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research. Per agency guidance, these topics are determined to be non-particular matters which would have no impact on outside financial interests. Hence, no affected firms are identified, and members are not screened for this topic.

Today's meeting will have a closed session from approximately 12:40 p.m. to 1:30 p.m. to permit discussions where disclosure would constitute a clearly unwarranted invasion of personal privacy, 5 U.S.C. 552 (b)(6). Dr. Lisa Butterfield is serving as the chair for both the open and the closed sessions for this meeting. The following information on the status of this Advisory Committee's compliance with federal ethics and conflict of interest laws, including but not limited to 18 U.S. Code 208, is being provide to participants at this meeting and the public.

With the exception of the industry

representative, all participants of the Committee are either special government employees or regular federal government employees from other agencies and are subject to the federal conflict of interest laws and regulations. Given that the topic of this meeting is determined to be a non-particular matter, it has also been determined that the overview and updates of this meeting present no actual or appearance of financial conflict of interest.

Dr. Geoffrey Nichol is currently serving as the industry representative to this Committee. Dr. Nichol is employed by the BioMarin Pharmaceutical. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in the closed sessions.

Dr. Randy Hawkins is serving as the consumer representative for this Committee. Consumer representatives are appointed special government employees and are screened and cleared prior to their participation. They are voting members of the

Committee and hence do have voting privileges, and they do participate in the closed session.

FDA encourages all meeting participants, members, and consultants, including open public hearing speakers to advise the DFO and the Committee if they realize they have any financial, professional, or regulatory relationships with any of the topics or individuals being discussed today that were not previously disclosed, and recuse themselves from Committee discussions. And their absence will be noted for the record.

This concludes my meeting of the open session conflicts of interest statement for the public record. At this time, I would like to hand over the meeting to Dr. Butterfield. Thank you.

DR. LISA BUTTERFIELD: Terrific. Thank you, very much. It is now my privilege to introduce our first speaker from FDA today. And that is Dr. Karen Elkins, the Associate Director for Science, FDA. Dr. Elkins.

OVERVIEW OF CBER RESEARCH PROGRAMS

DR. KAREN ELKINS: Good morning, everyone. Thank you so much for joining us today. I'm going to give you a brief overview of CBER research programs in general to provide some context for your discussions today. And then my colleagues will give you more details about parts of the research program that are particularly pertinent to today's site visit review.

So CBER is responsible for regulation of biological products as the name obviously implies. Biological products are defined in a particular way in law, but as a practical matter the products that we are tasked with regulation include vaccines. And within the vaccines group, also live biotherapeutic products and allergenic products are dealt with. We also have a responsibility for a large range of blood and blood products and then the subject of today's discussions, which is cell tissue and gene therapies.

To do that we invoke large range of scientific expertise. When we ask our scientists to identify their areas of training and current areas of research

interests, that results in this word cloud. And so, you can see that cell biology and related areas are well represented among our areas of expertise. CBER has recently updated its strategic plan, which runs from 2021 to 2025, and conducting research to address the challenges in the development and evaluation of our products is an explicit goal of our strategic plan.

And to do our business we have a fairly unique arrangement within FDA. And that is our research investigators are also reviewers. As you'll see in today's report, research programs are investigator initiated. Our topics are in the context of the regulatory review work that people are assigned and in relationship to the products that we are tasked with regulation. And they are all intended to support product development.

Our active research programs range from topics that you might consider rather basic to more targeted studies that are very tightly related to regulated products. And they are all designed to ensure a state-of-the-art understanding of techniques that are the source of data and regulatory decisions to ensure that

our reviews are efficient, effective, and credible and to support decisions on regulatory activities that are based on sound science. I belabor this to emphasize that CBER's research and review are tightly integrated.

And that's illustrated more specifically in the job description for our researcher reviewers. Regulatory submissions, whether it be IND or the licensing level, are reviewed by a team that is comprised of a regulatory project manager that has overall responsibility for the management of the team, a pharm tox reviewer, a clinical reviewer who is obviously dedicated to reviewing the clinical data and to understanding and impacting the design of the clinical trials, and a statistical reviewer who verifies all of the data that are submitted by sponsors.

And our researchers are the next part of the team, so-called chemistry manufacturing and control reviewers or product reviewers. And they are responsible for looking at the scientific rationale underpinning the product and any data submitted in support of proof of concept. And they are specifically

responsible for the product itself, for how it is produced and how it is tested at the end of it and potentially for any clinical assays that are used in the clinical trial itself.

More junior reviewers start out with maybe 10 to 20 percent of their time devoted to regulatory review work. And that increases with increasing experience and seniority up to about 50 percent of job time for PIs. We believe that operating this way allows our science and our research activities particularly to impact the entire lifecycle of a product. The submission of a new product IND presents unique challenges.

Our scientific programs are designed to discover tools that are needed to understand the challenges inherent in any given product, to inform regulatory and policy decisions, to inform judgements of risk benefit, and to be useful to moving something toward a licensed product. Our research programs are in a facility on the White Oak Campus in Silver Spring, Maryland. We wish that we were able to welcome you there today, which is the usual thing for Advisory

Committee meetings. Obviously not an option yet in our continuing virtual environment.

Our facility is comprised of about 450,000 square feet that houses about 150 labs that range from BSL-1 to BSL-3 and offices with about 500 research staff. And we have the luxury of several useful core technology facilities on campus for flow cytometry, for imaging, for high performance computing, and for all aspects of biotechnology. And we have a state-of-the-art vivarium that can house up to seven different specifics of animals with imaging facilities and transgenic derivation options.

Our scientists are integrated well with the rest of the world. As you might expect, a lot of our collaborations are with academia, with other parts of the Agency, and with other parts of the federal government. But we do have interactions that are controlled and guided by conflict-of-interest policies for industry, international industries, and some nonprofit organizations.

And they result in a number of agreements that are reflected by formal mechanisms including contracts,

grants, and tech transfer agreements and some patent inventions and the like. So, we think that doing business this way has a number of benefits. Having an active engaged scientific research staff prepares our review staff for future products that we may see that are innovated and for public health challenges. I think we're living the example of that benefit for the last two years in our exhausted virologists and immunologists involved in the COVID-19 response.

In some cases, our research programs develop specific data and tools that support the development of classes of products. Our sponsors and manufacturers are responsible for the tools necessary for their individual products, but I think you'll see some examples today of data and tools that are pertinent to classes of products. And we seek to fill knowledge gaps that we see out there by virtue of our window on product development and also inform policy development in all of our regulatory decision-making. And perhaps underpinning all of that is the research program facilitates the recruitment and the retention of highly trained scientists with the necessary expertise to

quickly and efficiently review regulatory submissions.

So, our research programs are evaluated in a number of different ways. We have an annual reporting system, which all layers of supervisors and management review the progress on an annual basis. We have a formal horizon scanning process that seeks to identify future needs. That is conducted approximately every four years. We're actually in the process of bolstering that so it'll be a little more frequent and periodic.

New projects are reviewed in a particular way, usually at the office and the center level. And then today's activity focuses on the fourth component of our research evaluation, which is site visits, which are intended to be conducted every four years. That schedule has flipped a little bit in the pandemic, but we're trying to get back on track. And in this activity, we ask you all, as external subject matter experts, to look at the quality of the science over the last four-year period.

And the criteria for evaluation are what you might expect. We are interested in comments on mission

relevance. We understand that some of those are unique, and you may not be fully familiar with what we consider mission relevant. But we are sure that you can evaluate that in a general way.

We look at how well the results of our research efforts are being disseminated in terms of publications, presentations, whether they result in tech transfer activities. And probably the most important criteria for us is what the impact is of our research activities. How is the knowledge or the tools that we're developing taken up by the scientific community and by all of our stakeholders?

So, your task, I think, is to focus on the scientific quality. And as I mentioned, we have a number of internal processes to look at other components that you may be a little bit less familiar with. The result of the site visit is a site visit report, and you have that today in front of you to act on. The draft report is now distributed to the full Advisory Committee, and that's the main subject of today's deliberations. And then the outcomes of today's meeting can be for you to accept the report as

you see it, to amend it, or to reject the report and send it back to the site visit team for further work.

Once it is finally approved by the full Advisory Committee, we use this report in many different ways. First, of course, it's used by the PIs themselves to receive constructive criticism and to improve their research program. Lab chiefs and supervisors of PIs, of course, use the material similarly for an internal review of the program's progress. And then all the layers up use the outcome of the report to further consider the future of the program itself and to allocate resources to it.

And so, the resources are already somewhat limited. I don't want to give you the impression that all of the site visit report leads directly to resource reallocation, but that's certainly a component in considering how the program is resourced in the future. Mostly I really want to thank you for your time and your energy and your attention in conducting this site visit and in commenting on its outcome.

Your input is really critical to ensuring that we have high quality science, that our programs are the

highest possible quality, and that we can fulfill our regulatory mission. And we very much value and appreciate your expertise and your hard work on this on our behalf. We are really most grateful. And I'm happy to answer questions.

DR. LISA BUTTERFIELD: Terrific. Thank you so much, Dr. Elkins. So, we do have a few moments for questions from the Committee. So, I'm going to look at my list for raised hands for any of the Committee members who would like to ask a question since we have Dr. Elkins with us.

DR. KAREN ELKINS: And I'll be with you all day, so it's not your last chance.

DR. LISA BUTTERFIELD: Great. Thank you. Dr. Breuer, please.

DR. CHRISTOPHER BREUER: In previous meetings we've heard about the volume of reviews, how it's been growing exponentially. And I was wondering if that continues and if you've been able to increase your manpower to provide people with adequate time to do their work?

DR. KAREN ELKINS: Going backwards on your

question, we will have some increase in congressionally appropriated resources. We got some this year by virtue of COVID-19 supplemental funding. And we are anticipating some improvements next year and in the following years by virtue of a new Prescription Drug User Fee Act negotiation. PDUFA VII is the colloquial name of that legislation. That will increase our resources. Of course, those increases always lag the needs.

And I think Dr. Oh is going to detail some of the specifics in the cell and gene therapy arena that will illustrate all too well the increase in interest. The good news is that many arenas of biomedical products, including cell and gene therapy, are coming to fruition and maturing as industries. And that's resulting in products that we hope will benefit people. But it certainly places demands on the review.

And so, the workload is substantial. I think there's no way of sugar coating that. Needless to say, the COVID-19 situation has exacerbated that.

DR. CHRISTOPHER BREUER: With a follow-up. From your perspective, with the added resources coming

do you think the problem is getting better or (audio skip) just treading water or making improvements?

DR. KAREN ELKINS: You know, I'm not sure I'm prepared to render a judgement exactly on that. You know, I think we have always had probably fewer resources than we would like for the workload. I think our supervisors and managers have become quite adept at prioritizing and juggling and trying to adjust. But that is not to say that it isn't a demanding position.

DR. CHRISTOPHER BREUER: Thank you.

DR. LISA BUTTERFIELD: All right. Thank you, very much, Dr. Breuer. So, with that -- and I'm not seeing any other questions at this time, so I'm going to thank you again, Dr. Elkins --

DR. KAREN ELKINS: Thank you, all.

DR. LISA BUTTERFIELD: -- for your presentation. And I'd like now to introduce Dr. Steven Oh who is the deputy director of the Division of Cellular and Gene Therapies at OTAT. Dr. Oh.

OVERVIEW OF OTAT AND DCGT RESEARCH PROGRAMS

DR. STEVEN OH: Yes. Can you hear me well?

MR. MICHAEL KAWCZYNSKI: Yes, we can, sir. Take it away.

DR. STEVEN OH: Thank you. So, good morning. My name is Steven Oh. I am the Deputy Director of the Division of Cellular and Gene Therapy, and I also serve as interim director of the division. I'd like to first thank Dr. Lisa Butterfield and the subcommittee co-chairs, Dr. Butterfield and Dr. Kenneth Berns, the site visit review team, and the Advisory Committee members. We appreciate your time and effort in reviewing the intermural research program in Gene Transfer Immunogenicity Branch in the division. I would like to also thank CBER's Division of Scientific Advisory and Consultants and the IT team that helped with today's meeting.

So, in my presentation today I'll discuss the current organizational structure of Office of Tissues and Advanced Therapies, which I'll refer to it as OTAT; OTAT mission and regulated products, research goals, research reviewer model; organizational structure of Division of Cellular and Gene Therapies, which I'll be

referring to it as DCGT; DCGT activities, research, and resources.

So OTAT is directed by Dr. Wilson Bryan and has five divisions. Most divisions have several branches. DCGT and Division of Plasma Protein and Therapeutics also have branches that have lab research components, which I'll get into in a little more detail later on. OTAT's mission is to promote public health and to facilitate the development of biological drugs that ensure safety, quality, and effectiveness.

The office evaluates and regulates a wide variety of products such as gene therapy products, including ex vivo and genetically modified cells such as CAR T-cell and various viral vector-based therapeutics. We also have cell therapy products including stem cells, stem cell-derived products, and thematic cells, therapeutic vaccines and cellular immunotherapy products. We have also tissue engineered medical products, human tissues and veno transplantation products, and blood and plasma-derived therapeutics.

The research goals in our office are in three

folds. The first goal is chemistry manufacturing and controls, which is to develop and evaluate methods and standards for improving characterization and (inaudible) of our products including critical quality attributes. We also develop and establish pre-clinical models to better understand the underlying biology to enhance the safety and effectiveness of the therapeutics.

We conduct analysis to gain increased understanding of clinical trial design issues and patient characteristics. Lastly, we study safety issues related to human tissues. Cell and gene therapy products that we review and regulate are extremely diverse, rapidly evolving, and often use nontraditional regulatory paradigm, which raises extraordinarily complex scientific and regulatory issues.

To address these challenges, we have not only regulatory reviewer scientists in DCGT but a large number of researcher reviewer scientists who perform regulatory reviews, participate in developing policies and guidance documents, as well as performing research in key areas of development relevant to our products to

support the FDA mission. The research review model has been already discussed by Dr. Elkins, so I'll not get into too much detail in the interest of time.

So, we have in DCGT 14 principal investigators who are researcher reviewers, and a majority of them are permanent. We also have staff scientists and staff fellows who are also researcher reviewers supporting their PI's research program. They are fairly independent in the lab but also carry out a large amount of regulatory activities as well. We have technical staff that primarily do research, but some technicians voluntarily wish to do review work as well. So that is also happening on a case-by-case basis.

Between FDA and NCI, we have Inter Agency Oncology Task Force, IOTF, fellows. We also have National Standards for Advanced Translational Science, NCATS, fellows. These fellows conduct research in the lab, and they are also trained to do some review work with their PIs. In addition to all that, we have postdoctoral fellows who are funded by Oak Ridge Institute for Science and Engineering. The research funding is provided to the PI, and the PIs are expected

to build and lead FDA mission-relevant research programs. And that's been already discussed by Dr. Elkins.

The responsibility of the PIs include product review, product development, outreach to give pre-submission advices, scientific and regulatory talks, refereeing and editing journals, chairing sessions at scientific conferences, and scientific collaborations. They also manage the lab activities, obviously, and involved in training, mentoring, and supervising, publishing papers and writing grants. As part of regulatory work duties, they also participate in compliance and enforcement actions.

OTAT has 21 research labs in the two divisions, namely DCGT and the Division of Plasma Protein and Therapeutics, who have published 51 research articles in 2021, given 47 external scientific research presentations, and there are seven COVID-related ongoing research projects at the moment.

So, here's a closer look at the structure of DCGT. As I mentioned earlier, I serve as interim Division Director, and I'm also the Deputy Director.

We have three associate directors in this division. On the left side of the org chart you'll see four regulatory branches dedicated to regulatory work full-time. Whereas on the right side you'll see three research regulatory branches, namely Cellular and Tissue Therapy Branch, Gene Transfer and Immunogenicity Branch, and Tumor Vaccine and Biotechnologies Branch. And in these three branches all research reviewers carry out their mission-relevant research, as well as regulatory work in parallel.

DCGT played a critical role in review and approving first gene therapy product, Kymriah, in the United Sates in 2017. It's a CAR T-cell product for the treatment of certain children and young adults with B-cell acute Leukemia. In the same year we also licensed another CAR T-cell product, Yescarta, for treatment of adult patients with relapsed or refractory large B-cell lymphoma.

Since 2017 we have licensed additional gene therapy products as shown in this slide. These include first in class and adeno-associated viral vector expressing the gene for human RPE65 protein for the

treatment of patients with biallelic RPE65 mutation associated retinal dystrophy. Most recently, in fact only 10 days ago, we have licensed a B-cell maturation antigen-directed genetically modified autologous T-cell immunotherapy. And this was for treatment of adults with relapsed or refractory multiple myeloma.

On the cell therapy side, we have licensed a variety of cell therapy products. That includes Provenge, one of the first cancer vaccine products in autologous antigen presenting cells for the treatment of asymptomatic or minimally symptomatic metastatic caspase-resistant and hormone refractory prostrate cancer. Over the years we have also licensed eight cord blood centers in the United States for the hematopoietic regenerative cell cord blood.

Activities of DCGTs are numerous, and I would like to summarize some of them in the next two slides. Our staff reviews, evaluates, and takes appropriate actions on product applications, some of these through various regulatory pathways such as INDs, IDEs, HDEs, BLAs, PMAs, NDAs, and 510(k)s. We also hold a lot of meetings that includes CATT, INTERACT, pre-IND meetings

and pre-IDE meetings, and other variety of milestone meetings such as end of Phase 2 pre-BLA meetings during the product development lifecycle.

Our staff participates in facility inspections for compliance and pre-licensure of the products. We also develop policies and procedures governing the pre-market review and the evaluation of our products. And these efforts include developing over 11 FDA guidance documents for our products in the last two years alone. We've provided scientific and technical advice to other CBER offices, other FDA centers, government agencies, and sponsors.

We hold advisory committee meetings like this one and typically DCGT staff chairs the OTAT advice committee events. We are extensively involved in community outreach. We give numerous regulatory talks in conferences organized by various professional societies, for example, American Society for Gene and Cell Therapies, International Society of Stem Cell Research, International Society for Cell and Gene Therapies, Society for Immunotherapy of Cancer, patient advocacy groups, and so on.

We also participate in standard development organizations, NIH activities, National Institute Standards and Technology, NIST, Activities, and global regulatory authorities on various regulatory science matters. Lastly and not least, we conduct research to support review and expand the field towards developing safe and effective products.

I'd like to show two charts in the next two slides to highlight how busy we have been with regulatory work in DCGT. Clearly in the last five years, this bar graph shown here shows the total new INDs received in our office each year since 1963. You may note that in year 2016 we received a total of 263 new INDs. But since then, the annual rate of increase has become much steeper. And in four years, in 2020, the number has nearly tripled to 666 new INDs. This is a sharp increase of regulatory work, almost looking like an exponential increase. In 2021 and '22, although those numbers are not in the chart, we expect the numbers will match this trend.

Now in this chart, the total number of sponsor meetings on regulatory matters are shown. And relative

to the previous bar graph the rate of increase from 2016 has become much steeper, and the total number of meetings has doubled again in 2020 as compared to 2016.

In addition, cell and gene therapy products and tissue engineered products are eligible for expanded development pathways known as Breakthrough Therapy Designation and Regenerative Medicines Advanced Therapy Designation. And this can happen as early as gene Phase I study. OTAT has reviewed several hundreds of breakthrough designation and RMAT designation requests and granted these designations to numerous INDs.

When breakthrough designation or RMAT designation has been granted to an IND, DCGT reviewers are involved in providing extensive advice and interactions with sponsors to facilitate efficient CMC development. This activity involves the reviewers time and effort that go beyond what would be typically expect of an IND without such a designation.

The research areas in DCGT are many. Our PIs perform research in virology, immunology, stem cell and developmental biology, cancer biology and cancer

immunology. The division also fosters expertise in various advanced technologies such as genome editing, advanced manufacturing, genomics, proteomics, transgenics, flow cytometry, and tissue engineering. Notably, seven PIs in DCGT form the Multipotent Stromal Cell, MSC, Consortium and have been using MSC, also known as mesenchymal stem cells, as a model cell and taken a systems biology approach to look at the analytical attributes of MSCs to link them to the safe and effectiveness of MSC-based products. And lastly, we have been pursuing various projects related to pyrosequencing and whole genomic sequencing of cell therapy or tissue products.

The bulk of research for research labs comes from budget authority, and Dr. Elkins has already explained to some extent. Each year, each PI in CBER is expected to provide their annual report in CBER's PI annual report database. In addition, we collaborate with Dr. Sue Epstein who is the associate director of research in our office, DCGT, to collect information regarding PIs productivity each year. We look at this data in assigning additional resources to PIs based on

their accomplishments. I would also note that some PIs may receive supplemental research funding from various grants such as Chief Scientist Challenge Grant, 21st Century Cures Fund, Defense Manufacturing Fund, COVID Fund, Cooperative Research Development Agreement, and other resources.

So in summary, our research provides in-house, hands-on expertise in cutting edge areas. We facilitate product development by addressing challenges encountered and by helping develop approaches and guidance documents. We believe these activities, by addressing concerns, provide increased public confidence in and acceptance of these novel technologies.

I would like to acknowledge all my colleagues in DCGT for their incredible work every day collaboratively to promote the public health. I'd also like to thank the colleagues whose names are shown here on this slide for their help with the preparing of this presentation. And thank you for your attention.

DR. LISA BUTTERFIELD: Super. Thank you so much, Dr. Oh. We appreciate that detailed overview and

all the information. So, we do also have a few minutes here for questions from the Committee for Dr. Oh. Geoffrey Nichol, please.

MR. MICHAEL KAWCZYNSKI: Let's get you unmuted, Dr. Nichol. Hold on a minute.

DR. GEOFFREY NICHOL: Yep.

MR. MICHAEL KAWCZYNSKI: Go ahead, sir.

DR. GEOFFREY NICHOL: Okay. We good?

MR. MICHAEL KAWCZYNSKI: Yep, we're good.

DR. GEOFFREY NICHOL: Great. Thank you, Dr. Oh, for a great overview. Just one question for clarification. On slide 11 you mentioned two gene therapy branches, branches one and two. What are the differences between those two branches?

DR. STEVEN OH: Are you talking about the ones that are shown on the left side and the right side?

DR. GEOFFREY NICHOL: Correct.

DR. STEVEN OH: Okay. So, we have two types of branches for the lack of better word. If you could show that slide 11. I'll move it over there. Yes, thank you. So, the ones on the left are primarily for full-time reviewing of information -- the regulatory

information. So, people in those four branches -- the branches are cell therapy branches, gene therapy branch one and gene therapy branch two, and tissue engineering branch. Staffing those branches are full-time reviewers, and their primary responsibilities would be reviewing regulatory submissions.

Whereas the ones -- the three branches on the right side, those are cellular and tissue therapy branch, gene transfer and immunogenicity branch, and tumor vaccine and biotechnology branches. Those are the lab-based branches where most of the people in the branch are research regulatory, in other words, researcher or reviewer in terms of their duty. So roughly their role is 50 percent research and 50 percent regulatory reviewer. Does that answer your question?

DR. GEOFFREY NICHOL: Thank you. Thank you very much.

DR. STEVEN OH: Great.

DR. LISA BUTTERFIELD: Thank you. And we have several other questions. Dr. Wu. And we can't hear you yes, Dr. Wu.

MR. MICHAEL KAWCZYNSKI: Yep, hold on a second, sir. I'll make sure you're unmuted.

DR. JOSEPH WU: So sorry, I just unmuted myself. So, great presentation, Dr. Oh. I have a question about the intermural programs that you have. Are they mostly for basic research and pre-clinical research, or are the investigators trying to push some of this research into clinical and even into a phase 1 clinical trial? And if you were to do that who would be reviewing the product profiles given that there's a potential conflict of interest?

DR. STEVEN OH: Yes, that's a great question. The scope of the research is based on PI initiated projects. Having said that, most of the research projects that's ongoing are rather in the pre-clinical or translational side of the research spectrum. And the goal of the research is really to bridge the gap that's in the research arena, where the scientific, the academic research, or the industry research has their own niche where we see some gaps in that particular area of science. And PIs in the labs are developing projects that would bridge those types of gaps. And we

would therefore focus more on the regulatory science aspect of the projects.

DR. JOSEPH WU: Maybe as a follow-up question, do you have programmatic reviews so that the research that you're doing are more aligned with the industry? For example, if the industry is currently working on product A, B, C, but yet the FDA is working on product X, Y, Z, that this will really relate to what the industry currently are doing? And there might not be so much relevance in terms of what the FDA is doing versus what the current biotech companies or companies are doing. So just wondering how do you kind of link the two -- you know, how do you link your programs and make them relevant as to what's going on as of 2020, 2030?

DR. STEVEN OH: Yeah, those are great questions. So, we have projects ongoing, for example, on MSC, mesenchymal stromal cells or multiple stromal cells. And while there are a lot of MSC-based products that are being developed by the sponsors or the industry, we do not necessary duplicate any of those efforts. Rather we would look for areas where there's

a gap and try to delegate projects that would help -- to help the industry and to really cover the areas where there's a greater need from the regulatory science point of view.

So, I guess to answer your question in a different way, we do not try to develop actual therapeutic products for clinical use. Whereas we try to develop tools and methods that we can publish which will be useful for any cell therapy or gene therapy manufacturers. We also have projects that are based on AAV vectors. We have projects that are based on CAR T-cells, but we don't necessarily -- our interest is in developing actually therapeutic products.

DR. JOSEPH WU: Got it. Thank you very much.

DR. LISA BUTTERFIELD: All right. Let's see if we can have a couple more short questions. Dr. Shah.

DR. NIRALI SHAH: Hi. My video take is slow. But the question that I have -- you know, you showed that really beautiful slide about the number of INDs that are being requested. A fair portion of those in recent years seem to be distributed towards expanded

access. Can you explain in more detail what those expanded access studies are and, you know, if they are typically representing a particular single patient access or single product? Thank you.

DR. STEVEN OH: Yes, a great question. And I have to admit that I didn't go through that slide in detail. Could we pull up Slide 17? So, if you look at that slide, yes, each bar is color coded. And the reddish part of the bar is for expanded access, whereas the blue part is what you call research INDs, where you would typically have a study design meant to provide a clinical study output based on set objectives. So, we do have expanded access there.

That expanded access could include single patient IND or expanded access that goes beyond just treating single patients. So that's included in the bar. If you take away the expanded access and just look at the blue part of the chart there in each bar, you would see about doubling of the number of INDs from 2016 to 2020. Can you hear me? I think I --

DR. NIRALI SHAH: Yep, I can hear you.

DR. STEVEN OH: Okay. Do I still have video?

I'm seeing something --

MR. MICHAEL KAWCZYNSKI: No, sir. No sir, your camera came off. Your camera came off, sir.

DR. STEVEN OH: Okay. It looks like I'll have to re-log in, but in the interest of time I'll just keep my audio and log in back later on. Will that be okay?

MR. MICHAEL KAWCZYNSKI: That's fine. That's fine.

DR. LISA BUTTERFIELD: Thank you. And we've got two more questions if we can wrap this one up.

DR. NIRALI SHAH: That answers my question. Thank you.

DR. LISA BUTTERFIELD: Perfect. Dr. Fox.

DR. BERNARD FOX: Yeah. Just a quick question for Dr. Oh. In that doubling of sort of the blue bar, the INDs from 2016 to 2020 and when it continued to increase, how many new reviewers have you been able to add to take care of that workload?

DR. STEVEN OH: Great question, Dr. Fox. And thank you for the question. We are able to add a number of new reviewers but not at the rate of what we

see in that chart.

DR. BERNARD FOX: And I guess just in terms of working to leverage support for additional reviewers given the interest of the field in this area are there -- and it may be something for offline, but I just wonder what it is that we can do to help support getting FDA additional funding to support that type of development? Because I think as you noted it's going to continue, or it is continuing to increase. But thank you for your efforts and congratulations on being names interim director.

DR. LISA BUTTERFIELD: Thank you for those comments, Dr. Fox. So why don't we go to our last question from Dr. Hawkins.

DR. RANDY HAWKINS: Thank you, Dr. Oh. And I'm not sure if this question applies here. I notice there are a couple open position interim directors. How are we doing with recruiting, realizing that staff actually are critical to a division or department's function? Thank you.

DR. STEVEN OH: So, we are actually recruiting around the clock. That's been one of the major

challenges that we face on a daily basis. So that's a great challenge. I think that's true for not just FDA but a lot of other employees who are in this space.

DR. LISA BUTTERFIELD: Well, terrific. Thanks again, Dr. Oh, for all of the questions and answers. And so now we're going to move to the presentation from Dr. Andrew Byrnes, who is the Chief of the Gene Transfer and Immunogenicity branch. Looking forward to your presentation, Dr. Byrnes.

OVERVIEW OF GTIB RESEARCH PROGRAMS

DR. ANDREW BYRNES: All right. Good morning, everybody. It's a pleasure to be here. And I'm going give you a very brief, whirlwind 20-minute overview of the six labs and the research we do and the mission relevance. And I'd like to start by thanking the site visit committee and the Advisory Committee. Your feedback is so valuable to us as we review the quality and the mission relevance of our research programs. So, thank you so much for being here today and to our FDA colleagues in GTAC and elsewhere who have put this

Advisory Committee meeting together today.

So, we have six laboratories focused on cell and gene therapy, immunology and virology, so very related topics. And the relevance to FDA's mission broadly is by improving the safety and efficacy of cell and gene therapy products, and that includes characterizing complex products. These are some of the most complicated therapeutics ever manufactured in many cases -- mitigating and measuring immune responses to these products, developing better pre-clinical models, and understanding what are the differences between pre-clinical model in humans, and then other overarching FDA and HHS priorities including pandemic influenza and now COVID-19.

And before I get into the research programs, just one slide on the regulatory review responsibilities of staff in this branch because as you've heard, it is a very significant amount of our time, approximately 50 percent, although that varies. And these duties include review of investigational products. So, some of the types of products that we review in this branch, gene therapy vectors, especially

adenovirus, AAV, and lentiviral vectors, T-cell therapies like CAR T-cells, CD34 positive hematopoietic stem cell therapies, and genome editing products, which is a very rapidly increasing product category. And then when it comes time for license applications, so BLAs, we serve on those BLA committees. In many cases a number of us have chaired those BLA review committees.

These are many first in class products that raise complicated scientific and regulatory issues. So, our scientific backgrounds really come into play here. And then even after our products are licensed, we're finding that because these products are so new in part, there's many manufacturing improvements and changes that need to occur after licensure. So, we're constantly reviewing BLA supplements as manufacturers expand their manufacturing or improve their manufacturing processes.

We also participate as team members on GMP inspections of manufacturing facilities across the United States and internationally. And then we participate in a variety of policy guidance writing

activities, meetings with sponsors, and outreach at conferences and workshops and training as well. So, these are very important duties that we do here. However, they do impact our productivity in the lab. And also, the COVID pandemic in the past two years, especially in 2020, had a very major impact on productivity as well.

All right. So, I'd like to start my overview of the six labs' research with the Epstein lab. Dr. Epstein works on recombinant vectors used as vaccines for influenza virus. And the relevance of this work to our regulatory mission, of course, with the interest in influenza across the HHS, the Epstein lab is developing approaches that could potentially serve as universal influenza vaccines that could protect against a variety of strains of influenza without having to have the strain match type.

But beyond the relevance to influenza, these projects from the Epstein lab are very relevant to cell and gene therapies, particularly gene therapy vectors. The vectors used by the Epstein lab include many of the same vectors that are used for gene therapy including

plasmid, adenovirus which I'll be telling you about today, AAV vectors, and poxvirus vectors. And it's very important to understand the immune responses, how to measure those and evaluate them in both pre-clinical animal models and clinical trials. And it's worth noting that we also regulate several immune-based therapies for influenza and other respiratory viral infections.

So just briefly, some work that was done in the past few years from the Epstein lab with recombinant adenovirus vectors that express conserved influenza A or influenza B proteins as a potential (audio skip). So, the findings in recent years include that after a single intra-nasal administration with these adenovirus vectors expressing flu antigen, you get antibody and T-cell responses against the flu antigens that can persist for more than a year. And that also gives broad protection against a variety of influenza virus strains for more than a year. And despite pre-existing immunity to the vector after a first injection, you can give a second injection of the vector that expresses a different antigen a year later

and still get a good immune response against that antigen.

And then the Epstein lab has developed a very interesting mouse model of influenza transmission. And they've shown that this intra-nasal vaccine can protect against flu transmission for up to a year. And then they have been looking more recently at whether this intra-nasal administration has any damaging effects on the lungs or the immune response. So, they've shown recently that mucosal immunization by the intra-nasal route with adenovirus vectors dose not impair lung function.

And to follow up on that, their current ongoing research is to analyze those immune responses in more detail and just make sure that there are no damaging effects, for example, excess cytokine secretions or very severe cytotoxic T-cell responses. And again, this work has very broad public health implications. You could use potentially universal influenza vaccines to protect against any influenza strain. And although they may not prevent infections of individuals by influenza, they do have the potential

to reduce illness and death and transmission of infection.

I would like to speak briefly about the lab of Nirjal Bhattarai and Alan Baer as a staff fellow in the Bhattarai lab. And they work on both cell and gene therapies to understand mechanisms for immunotoxicity, immunogenicity, and inflammatory toxicity. So, the Bhattarai lab aims to improve manufacturing and decrease immunogenicity of cell and gene therapies.

And there's two main areas that I'll tell you about next. The first broad area is cell-based gene therapies, including CAR T-cells. They work on manufacturing challenges, developing methods to make products of better quality, and also understanding the mechanisms that contribute to toxicity, especially cytokine release syndrome and developing strategies to reduce those toxicities.

And then in the area of viral vectors, they use AAV as a model system. They're studying innate immune responses in in vitro systems and working also on developing in vivo systems as well. And they've recently developed novel strategies to reduce T-cell

responses to AAV vectors. And this work has obvious mission relevance because it addresses important challenges with cell and gene therapy products to improve the safety and efficacy of the products.

The major findings, with the CAR T-cells they've identified a novel role for Src-kinases in CAR-T-cell activation. And this has led directly to a strategy to improve the quality of CAR T-cells during manufacturing by using a Src-kinases inhibitor. And this was published recently in *Journal of Immunotherapy*. And then to address the safety concerns, they've identified a novel inflammatory factor that's released by T-cells and that activates bystander cells and contributes to CAR T-cell toxicity, in vitro at least. And then they're also working on AAV vectors. They've identified a novel peptide from hepatitis C virus that suppresses T-cell responses and shown that this works when you put it into an AAV vector to suppress T-cell responses.

So ongoing work and future directions, with the CAR T-cell project they're going to be characterizing this inflammatory factor that's related

by T-cells in more detail, including in vivo models of cytokine release syndrome and neurotoxicity in mice and then to develop strategies to prevent toxicity or reduce toxicity by modulating this inflammatory molecule that's released by the CAR T-cells. And then the viral vector immunogenicity project, they're studying the immunogenicity of these AAV vectors in vivo, as I mentioned, in mice but also developing strategies to reduce vector-induced innate immune responses in addition to T-cells.

Now the lab of Jakob Reiser. And Takele Argaw is the Staff Scientist in this lab. And this lab works on safety enhanced lentiviral vectors for gene therapy. Now, there's a number of important potential safety issues with lentiviral vectors that I'm sure you're all aware of. They have the potential to form replication competent lentiviruses. They can also potentially cause insertional gene activation or inactivation, and this could lead to genotoxicity or oncogenesis. And there's also the potential for off target transductions. So, the lentiviral vectors might transduce the wrong cells.

So, the Reiser lab is working on theses last two safety issues with lentiviral vectors. I'll take these topics one by one on the next two slides. But the overall goal is to develop safer lentiviral vectors by directing vector integration to genomic safe harbor sites and then narrowing the vector's cell tropism to make sure the vector gets to the right cells in the first place.

So, on the topic of directing vector integration to genomic safe harbor sites, the Reiser lab is using engineered recombinases to target lentiviral integration without causing double stranded DNA breaks and to target safe harbor sites that won't disrupt the central genes or raise the risk of oncogenesis. They're also using a strategy with the Rhabdovirus vector, so Vesicular Stomatitis Virus or VSV, to use directed evolution to evolve recombinases that have better specificity and activity. And then finally, they're using Gag protein from HIV either in lentiviral vectors or nanoparticles as tools for transient delivery of recombinases either in the form of protein or RNA. So, you can attach these either

proteins or RNA to Gag and use that as the delivery mechanism.

And next in the topic of narrowing the vectors cellular tropism by engineering the envelope proteins of lentiviral vectors to bind to new receptors, so the Reiser lab has worked for many years now on rational design of targeting envelope proteins. And they're also starting to work on directed evolution using this VSV system with the various envelope glycoproteins. You can put them into the VSV system and evolve them to improve cell targeting and then to test these re-targeted vectors, both in vitro and in vivo in mouse models, characterize their cellular tropism. There's the potential that these vectors or nanoparticles with these re-targeted envelope proteins could also be used to transiently deliver protein or RNA to specific cells.

Next, I'll turn to the lab of Zhaohui Ye who is working on development and evaluation of cell engineering technologies. And the Ye lab works on two areas that I'll explain on the next two slides. The first area is making hematopoietic stem cells from

induced pluripotent stem cells, which would ultimately allow reconstituting a patient's hematopoietic system from any cell type. And then the second area is understanding the safety of genome editing technologies to understand how to evaluate whether genome editing causes unintentional mutations.

So, in the area of iPSCs the lab is developing methods to optimize hematopoietic differentiation conditions as well as to develop characterization methods for iPSC generated cell types. So, we have many hematopoietic products that we regulate and many iPSC derived products. And this is an area of huge interest and rapidly growing and complicated science.

So, the mission relevance is quite clear. This knowledge gained from these projects can be used to support development of manufacturing platforms that use iPSCs but also improve methods for quality assessment of stem cell derived products. And then in the area of evaluating genome editing technologies the Ye lab works on novel CRISPR-based genome editing tools. And this is a huge area of interest right now.

So, they work on developing technology to

improve product manufacturing and also improving safety evaluation of gene therapies incorporating genome editing. So, in this example here from a recently published work the Ye lab used genome wide sequence analysis to look at mutations caused by Cas9-based cytosine-based editors in human stem cells. And these mutations they found have a random chromosomal distribution. So, it's not targeted to specific areas.

The distribution of mutations, in fact, is not predicted by in silico algorithms and is independent of Cas9 binding to DNA. So, you can see in blue the Cas9 that has no guide RNA produces the same pattern of mutations across the chromosomes as Cas9 that does have the guide RNA. So, this is independent of the Cas9 binding to DNA. This is a very good example of how to assess the safety of base editors using genome sequencing. And this result also highlights that there's room for improvement in these base editing tools and also room for improvement in the method for assessing the safety of these tools.

Next, I'll turn to the lab of Ronit Mazor who works on immunogenicity of AAV vectors using gene

therapy. And as you all know, AAV vectors are a very active category right now of the products that we regulate. There is at least 170 active INDs here across multiple indications.

We have two FDA licensed AAV products, as Dr. Oh mentioned. And this is an increasing category of the meetings that we have with sponsors and the INDs that we have that are active. The goals of the Mazor lab include developing platform technologies to investigate, monitor, and mitigate the adaptive immunogenicity, so the T-cell responses to AAV vectors. So, their ongoing projects include identifying T-cell epitopes in AAV vectors, in both mice and humans but mainly in humans.

And then they design novel controls for immune monitoring assays. For example, they plan to design a human T-cell line that could be used as a control in assays to monitor clinical T-cell responses against AAV vectors. They also work in the long-term on developing AAV vectors that have reduced immunogenicity. So, once you identify the T-cell epitopes, you can potentially mutate them to reduce the ability of the T-cells to

detect the AAV vectors.

And then once those T-cell epitopes have been mutated, they can be put back into the capsids and see how that affects the activity and the tropism of the AAV vectors as well as their immunogenicity. And here's an example from the Mazor lab of some recently published work looking at the effect of amidation. So deamidation is a chemical modification of amino acids that occurs spontaneously. And this type of modification to the AAV capsid proteins might cause changes in the ability of T-cells to react these capsid proteins.

So, what's shown here on the top is the amount of protein deamidation in the AV capsids increases with the amount of time after manufacturing. So, this modification happens spontaneously. So why is this important? It's because the T-cells can potentially change how they recognize these epitopes if they have an amino acid that's modified by deamidation. So, if the amino acids in these proteins are changing chemically, it can potentially alter the T-cell responses. And that's basically what the Mazor lab

found in this study.

So, they looked at anti-AAV T-cell responses from a panel of human donors, and they found that deamidation increased T-cell reactivity for some humans. But interestingly, it also decreased it for other donors. So, these differences in T-cell reactivity amongst humans were related to genetic differences in MHC II alleles. So, this work has implications for how to monitor T-cell responses as well as how deamidation might affect immunogenicity of AAV therapies.

And then finally, my lab works on adenovirus vectors and the biodistribution and toxicity of these vectors. Adenovirus remains -- so it's one of the older products classes that we regulate, but it remains one of the most popular. There's currently over 90 active gene therapy and oncolytic adenovirus clinical trials regulated by our office, most of them for cancer. Now, these vectors can be engineered to either replicate or not replicate. The work in our lab is done with non-replicating adenovirus vectors.

And we study systemic IV gene therapies. So,

this could be a very potentially advantageous route for administering adenovirus vectors to target a variety of organs or a variety of metastatic tumors. But there's a big problem because these vectors are cleared very rapidly from the circulation. They end up in the liver where they cause toxicity. So, we're looking at what are the routes and the mechanisms for the immediate clearance of the vector by the liver and how to prevent that.

And we're also very focused on differences between animal models and humans. In some cases, we found that mice may mimic what happens in a human, and in other cases we found that the protein interactions of mouse proteins and human proteins with adenovirus vectors are completely different. So, this has very clear implications for the use of mouse models and other models for preclinical studies.

Now I don't have time to go into detail, but here's just some of the things that we've been working on. And overall, what we've found is that as soon as you expose adenovirus vectors to plasma, they immediately get coded by a variety of host proteins

that interact with the virus and with other host proteins in very complicated ways. So, for example, you could have antibodies bind to the vector that could activate complement, the classical complement cascade. And this can actually neutralize the virus under some circumstances.

And coagulation factors, like Factor X, can bind to specific binding site on the capsid and actually prevent this neutralization. And so again, these proteins interact with each other and with the virus in complicated ways. In some cases, we found that coagulation factors for mice and humans interact in different ways with these adenovirus vectors. So again, that's very relevant to preclinical studies.

So, our ongoing work in my lab and future directions are focused on host proteins that interact with Ad vectors. How do these proteins influence vector via distribution toxicity? And again, how do they differ between mice and humans? We're currently expanding our studies to many different adenovirus serotypes following trends in the field where people are expanding beyond Ad V vectors. And these different

vectors have very different properties as gene therapy vectors.

Goals and mission relevance are to build better vectors that can be targeted to specific tissues or tumors and also to understand the benefits and limitations of preclinical animal models. So, I'll stop there. And thank you so much for your time and for participating in this very important process. And I'll be happy to take any questions.

DR. LISA BUTTERFIELD: Super. Thank you so much, Dr. Byrnes. So, we're going to give it a moment for the Committee to see if there are questions. And first we have a question from Dr. Wolfe.

DR. GIL WOLFE: Hi, Dr. Byrnes. Thanks for that presentation. In regard to the first lab you mentioned, Dr. Epstein's lab, this broad spectrum persistent and yet it seemed modifiable immune response to influenza it would seem to have equal, if not even greater relevance on the coronavirus side, specifically SARS CoV-2. And I'm wondering if they're applying any of these findings potentially into the coronavirus sphere?

DR. ANDREW BYRNES: Yeah, that's a great point. So, this is a strategy that's broadly applicable to a variety of respiratory viruses, including coronaviruses. And the Epstein lab is not working on that, but a variety of other labs are very interested in developing coronavirus vaccines that could produce broad immunity against either a variety of SARS-CoV-2, you know, variants or against coronaviruses more broadly. So, it's a very broadly applicable strategy.

DR. LISA BUTTERFIELD: Thank you. And we have one other question from Dr. Nichol, please.

DR. GEOFFREY NICHOL: Hi. Thanks for a great overview, Dr. Byrnes. Just a general observation, but many of these labs are working on things that are of extreme interest to industry sponsors. And it would be great to sort of -- well, to ask you the extent to which it's possible to arrange as much interaction as possible from the scientific front with both industry and academic people. I get from many other presentations that this is ongoing, but it would be very good to encourage as much ongoing scientific

interaction on some of these key questions as possible and certainly to keep industry researchers up with the play of what our FDA scientific interests is in many of these areas.

DR. ANDREW BYRNES: Yeah, that's a good point. So, we both -- we communicate at scientific conferences. We publish our work, and we also hear what's going on at the same time including in scientific conferences but also in venues like our advisory committees. So, for example, we had an Advisory Committee meeting late last year about AAV toxicities, and many of us are very interested in those same problems that were discussed there.

We do have issues, as you might imagine, about collaborating directly with industry being a conflict of interest in many cases. But we are open to collaborating with academic centers, and we do that to large extent.

DR. GEOFFREY NICHOL: Thank you. That's great.

DR. LISA BUTTERFIELD: All right. And let's take just one more minute. Dr. Zaia, a final, final

question.

DR. JOHN ZAIA: Thank you very much for that excellent talk. One of the key goals, I think, of your section will be to stay ahead of the field. You mentioned lipid nanoparticles, in part. There are other areas that are moving quickly. Let's say direct injection gene therapy would be one of them. And I'm asking the question, how do you stay ahead of the field, and where are you on lipid nanoparticle delivery or even direct injection of vectors for gene therapy?

DR. ANDREW BYRNES: I think this is -- so you're mentioning the work in the Reiser lab. And this is one of the main things that they're interested in. And the impetus for studying these is that people are increasingly interested in delivery lentiviral vectors in vivo instead of using them for ex vivo genetic modification. So, this is -- it's still a very early project, but it's in direct response to those changes in the field.

And then because our office regulates such a very wide variety of products, we can't have experts in every single corner. But we do try to -- especially as

we recruit new PIs, we do try to look for areas that will fill gaps. Rather than having people work on the same thing in multiple labs we try to spread out and identify new areas of interest and technology. We call that process horizon scanning. And we do it before we recruit any new PI to our division.

DR. JOHN ZAIA: Thank you.

DR. LISA BUTTERFIELD: All right. Thanks again. We are out of time now for the question and answers. So, thanks again, Dr. Byrnes for that. And so now we are going to take a 10-minute break for the committee before we move to the open public session.

[BREAK]

OPEN PUBLIC HEARING

MR. MICHAEL KAWCZYNSKI: All right. And welcome back to our 71st meeting of the Cellular tissue and Gene Therapies Advisor Committee. I'm going to hand it over to our chair, Dr. Lisa Butterfield.

DR. LISA BUTTERFIELD: All right. Welcome

back, everyone, from our short break. And I would like to welcome everyone to the open public hearing part of our meeting. However, this is a different sort of meeting, and we did not have any requests to speak in the open public hearing. So, I now close the open public hearing because of lack of request. So with that, we are now going to move to the closed session for Committee discussion.

[END OF OPEN SESSION]