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Center for Biologics Evaluation and Research (CBER)
Cellular, Tissue, and Gene Therapies Advisory Committee
(CTGTAC)
Meeting #68

OPEN SESSION
ONLINE MEETING

May 8, 2020

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

Lisa Butterfield, Ph.D.	Parker Institute for Cancer Immunotherapy
Kenneth Berns, M.D., Ph.D.	University of Florida
Christopher K. Breuer, M.D.	Nationwide Children's Hospital
Bernard Fox, Ph.D.	Providence Portland Medical Center
Sean J. Morrison, Ph.D.	University of Texas Southwestern Medical Center
Geoffrey Martin Nichol, MB ChB	BioMarin Pharmaceutical
Raymond Roos, M.D.	University of Chicago
Jan Stegemann, Ph.D.	University of Michigan
Michael Streiff, M.D.	Johns Hopkins School of Medicine
Mark C. Walters, M.D.	USCF Benioff Children's Hospital
Joseph Wu, M.D., Ph.D.	Stanford University
Jeannette Yen Lee, Ph.D.	University of Arkansas for Medical Sciences
John Zaia, M.D.	Beckman Research Institute of City of Hope
Sheldon Toubman, J.D.	New Haven Legal Assistance Association
Carolyn Wilson, Ph.D.	Food and Drug Administration
Wilson Bryan, M.D.	Food and Drug Administration
Rachael Anatol, Ph.D.	Food and Drug Administration
Suzanne L. Epstein, Ph.D.	Food and Drug Administration
Chava Kimchi-Sarfaty, Ph.D.	Food and Drug Administration

Raj Puri, M.D., Ph.D.	Food and Drug Administration
Steven Oh, Ph.D.	Food and Drug Administration
Steven Bauer, Ph.D.	Food and Drug Administration
Christina Vert, M.S.	Food and Drug Administration
Joanne Lipkind, M.S.	Food and Drug Administration
Kathleen Hayes, M.P.H	Food and Drug Administration
Monique Hill, M.H.A.	Food and Drug Administration
Prabhakara Atreya, Ph.D.	Food and Drug Administration
Leslie Meltzer, Ph.D.	Orchard Therapeutics

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WELCOME AND CALL TO ORDER

DR. BUTTERFIELD: Well, good morning. Good afternoon and welcome, everyone, to the Food and Drug Administration Center for Biologics Evaluation and Research Cellular, Tissue, and Gene Therapies Advisory Committee meeting. I really appreciate the participation of all the members, the participants, the public today, and the audience joining us all online through Adobe Connect. So I'll turn this over now to Christina to take the roll call.

MS. VERT: Hello, Dr. Butterfield. Do you want to go ahead and start the meeting?

MS. HAYES: I could hear Dr. Butterfield fine. Can you not hear her?

DR. BUTTERFIELD: Yeah. I just did my introduction. We're going to pause here and wait to hear back from Christina about whether or not she and I are hearing each other well.

MS. HAYES: Christina, is your microphone on

mute or your speakers?

MS. VERT: Okay. I just unmuted it. Thank you.

MS. HAYES: Yeah. Dr. Butterfield went ahead and did her introduction, so we can proceed.

ROLL CALL AND CONFLICT OF INTEREST STATEMENT

MS. VERT: Okay. This is Christina. I will now take the roll call of members in alphabetical order. When I call your name, please introduce yourself, your institutional affiliations and expertise. Since Dr. Butterfield probably already went, I'll start with Dr. Berns.

DR. BERNS: Okay. This is Dr. Berns. I'm affiliated with the University of Florida where I'm Professor Emeritus of Molecular Genetics and Microbiology. So my expertise is in molecular virology and gene therapy.

MS. VERT: Thank you. Dr. Breuer?

DR. BREUER: Hi, my name is Chris Breuer. I'm from Ohio State University and the Children's Hospital at Nationwide. I'm the director of the regenerative medicine program, and my expertise is in translational cardiovascular tissue engineering.

MS. VERT: Thank you. Dr. Fox? Okay. We can come back to him later. Dr. Morrison?

DR. MORRISON: I'm Sean Morrison. I'm Director of Children's Research Institute at the University of Texas Southwestern Medical Center where my lab works on stem cells and cancer.

MS. VERT: Thank you. Dr. Nichol?

DR. NICHOL: Yes, I'm Geoff Nichol. I'm currently Chief Medical Officer at BioMarin Pharmaceutical, and my expertise is in general drug development. But I've had experience -- current experience and recent past experience developing cell therapies involving genome editing. And BioMarin is currently involved with AAV gene therapy, and I am the industry representative on the committee.

MS. VERT: Thank you. Dr. Roos?

DR. WU: Yes. This is Joseph Wu. I'm the director for the Stanford Cardiovascular Institute. I last worked on cardiovascular, stem cells, genetics, and genomics.

MS. VERT: Thank you. Dr. Stegemann?

DR. STEGEMANN: Hi, this is Jan Stegemann. I'm a professor in the Department of Biomedical Engineering at the University of Michigan. And my research interests are in biomaterials for cell-based therapies.

MS. VERT: Thank you. Dr. Streiff?

DR. STREIFF: Sorry. Yeah. This is Mike Streiff, Professor of Medicine at Johns Hopkins, and my primary interest is in -- well, clinical and research is in the prevention and treatment of venous thromboembolism. Thanks for the invitation.

MS. VERT: You're welcome.

MS. HAYES: This is Kathleen. Does everyone -- I'm sorry to interrupt you, Christina. If everyone

could just -- if you're on the phone, if you're calling in on the phone, just go up to the top and mute your computer microphone so there's not feedback or echo. That would be great. Thank you.

MS. VERT: Dr. Wu? Okay. We'll come back to him. Thank you. Dr. Lee?

DR. LEE: Yes. This is Jeannette Lee. I'm a professor of biostatistics at the University of Arkansas for Medical Sciences. My area's coordination of clinical trials, primarily in HIV, cancer, and some pediatric trials. Thank you.

MS. VERT: Thank you. Dr. Zaia? Okay. We'll come back to him later.

MR. BONNER: Hi, Christina, this is Derek Bonner with the AV team. We're still working on Dr. Zaia's connection.

MS. VERT: Thank you for letting me know. Okay. We'll move forward with some FDA senior leadership in alphabetical order. I'll read off some names that I have and if you can unmute. Dr. Anatol?

DR. ANATOL: Hi, this is Rachael Anatol, Deputy Director of the Office of Tissues and Advanced Therapies in CBER.

MS. VERT: Thank you. Dr. Bauer?

DR. BAUER: Hi, this is Steve Bauer. I'm the Cell and Tissue Therapy Branch in the Division of Cell and Gene Therapies, Office of Tissues and Advanced Therapies, FDA. One of the presenters today.

MS. VERT: Thank you. Dr. Bryan?

DR. BRYAN: Good afternoon, this is Wilson Bryan. I'm Director of the Office of Tissues and Advanced Therapies.

MS. VERT: Thank you. Dr. Epstein? Okay. We'll move on. Dr. Kimchi-Sarfaty?

DR. KIMCHI-SARFATY: Dr. Kimchi-Sarfaty, Deputy Associate Director for Research at OTGT.

MS. VERT: Thank you. Dr. Marks?

DR. MARKS: Hi, Peter Marks, Director of the Center for Biologics Evaluation and Research. Thanks for doing this today.

MS. VERT: Thank you. Dr. Puri?

DR. PURI: Hi, this is Raj Puri. I'm the Director of the Division of Cellular and Gene Therapies in the Office of Tissues and Advanced Therapies.

MS. VERT: Thank you.

DR. EPSTEIN: Hello, this is Suzanne Epstein. I figured out how to unmute.

MS. VERT: Dr. Oh? Okay. We'll move on. Dr. Wilson? Okay. Did I miss anyone?

MR. TOUBMAN: This is Sheldon Toubman. I am the temporary participant, sort of being borrowed from the Vaccine's Advisory Committee. I have no expertise in the area, but I'm an attorney at New Haven Legal Assistants Association in New Haven, Connecticut. And my area of expertise is Medicaid and access to healthcare. But because I'm the consumer representative on the vaccine's committee, I was asked to participate today. Thank you.

MS. VERT: Thank you. Just give me a second here and we'll move on.

DR. FOX: Hi, afternoon. I'm here.

MS. VERT: Glad you're on, Dr. Fox.

DR. FOX: There we go. Yes, it's great to be on. Sorry I was late. I had technical difficulties.

MS. VERT: Right. That's fine. We understand.

DR. FOX: But I was listening to the great music that the FDA has on the phone line. Anyway. It's very exciting.

MS. VERT: All right. Thanks.

MS. HAYES: Dr. Wu and Dr. Walters, are you online and able to hear us okay?

DR. WU: I'm online. I can hear you.

MS. VERT: Okay. This is Christina Vert. I want to thank our AV contractors today for helping everyone. I'll mention a few names here. Derek and Aaron, thank you very much. All right. Good afternoon, everyone, or good morning if you're on the West Coast. I hope everyone is safe and healthy.

My name is Christina Vert, and it's my

pleasure to serve as the Acting Designated Federal Officer for the 68th Cellular, Tissue, and Gene Therapies Advisory Committee, known as CTGTAC. Kathleen Hayes is a designated federal officer as well and is also supporting this meeting. The Committee Management Specialists for this meeting are Ms. Joanne Lipkind and Ms. Monique Hill. The Committee Management Officers for this meeting are Dr. Jeannette Devine and Ms. Casey Stewart. And our Director is Dr. Prabha Atreya.

On behalf of the FDA, the Center for Biologics Evaluation and Research, and CTGTAC, we would like to welcome everyone to this 100 percent virtual Adobe Connect teleconference meeting. Today's session has two topics that will first be discussed in open session, and then we'll have the open public hearing. After the open public hearing, the meeting will move to the closed session. For the closed session, FDA staff being evaluated will leave the teleconference, as well as the industry rep, Dr. Nichol. This open session

will be recorded by Adobe Connect.

The meeting topics are described in the federal register notice that was published on March 16, 2020. The FDA CBER press/media representatives for today's meeting are Ms. Meghan McSeveney and Ms. Monique Richards. The transcript for the meeting today is Ms. Linda Giles.

Since this is an Adobe Connect meeting, I have some points to emphasis. If you need assistance, you may refer to the technical notes or chat with the AV staff in the host box. Regarding audio, most members and FDA staff have been able to call in using their phone. If this is the case, please mute your phone when not speaking and mute your computer audio to minimize feedback from having both going at the same time. If you're using audio on your computer, please mute the speaker if we have not already done so.

Regarding speaking and asking questions, before speaking, please first state your name and speak up so that your comments are accurately recorded for

transcription. When members want to ask a question or comment, please unmute yourself and ask to speak or use the hand raise or chat feature in Adobe Connect to let us know. Either the chair, Dr. Butterfield, or I will recognize the person by stating the person's name so they can speak.

The public should hold all their questions and comments for the open public hearing time slot. Let me know if you want to speak, and you'll be unmuted at that time. And for those that are just calling in, it may be good for the speakers to state the number of your slide every few slides so that those on the phone can keep track. We also caution everyone on the teleconference today against discussing personal actions or any other confidential information during the open session. Thank you.

I will now proceed to read the conflict of interest statement for this meeting. I'm going to wait for my slides to come up. Okay. Thank you. Okay. I'm going to start.

The Food and Drug Administration is convening virtually today, May 8, 2020, for the 68th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) under the authority of the Federal Advisory Committee Act (FACA) of 1972. As this May 8, 2020 meeting is being held virtually, please direct your attention to the conflict of interest slides as I continue to read the first conflict of interest statement into the public record. The meeting today will have two conflict of interest disclosure statements read, one during the open session and one during the closed session.

Please note that Dr. Butterfield is serving as the Chair for both the open and closed sessions for this meeting. The first part of this May 8, 2020 virtual held meeting will meet in an open session to hear an overview and updates of two research programs. Topic I will be the Tumor Vaccines and Biotechnology Branch (TVBB), and Topic II will be the Cellular and Tissue Therapy Branch (CTTB.) Both programs are in the

Division of Cellular and Gene Therapies, Office of Tissues and Advanced Therapies, CBER, FDA. These topics have been determined to be Non-Particular Matters and, as such, do not focus their discussion on any particular products.

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 provided to participants at this meeting and to the public. With the exception of the industry representative, all participants of the Committee are 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 Topic I and II of this meeting are determined to be Non-Particular Matters, it has also been determined that the overview and updates of this meeting present no actual appearance of financial conflicts 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 od not vote and do not participate in the closed sessions.

Mr. Sheldon Toubman is serving as a Temporary Voting Member as well as the Acting Consumer Representative for this Committee. Temporary Voting Members and 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 sessions.

At this meeting, there may be regulated industry speakers and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and

with other regulated firms. The FDA asks in the interest of fairness that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest. Okay.

FDA encourages all other participants to advise the Committee of any financial or professional relationships that they may have with any firms, its products, and, if known, it's direct competitors. We would like to remind members, consultants, and participants that, if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such discussions, and their exclusion will be noted for the record. This concludes my reading 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. BUTTERFIELD: Thank you very much. And I also apologize for not fully introducing myself when I made my introductory comments. I'll do so now. My name is Lisa Butterfield. I'll serve as Chair today. I'm a vice president at the Parker Institute for Cancer Immunotherapy. I'm also an adjunct professor at the University of California San Francisco. I work in cancer vaccines and cellular therapies.

So with that being completed, it's now my pleasure to introduce our first speaker, Dr. Carolyn Wilson, Associate Director for Research at CBER. Dr. Wilson.

OVERVIEW OF CBER RESEARCH PROGRAMS

DR. WILSON: Does everybody hear me? Oops. Sorry.

MS. HAYES: Dr. Wilson, we could hear you just now when your phone was unmuted, but there was a little bit of feedback. So, I'm not sure if your computer mic

may be picking up as well at the top of your screen.

DR. WILSON: Hi, good afternoon. Can you hear me now?

MS. HAYES: We can hear you just fine. We're having trouble seeing your slides.

DR. WILSON: I see them. I don't know why other people don't see them.

UNIDENTIFIED MALE: I see them.

MS. VERT: Yeah. We do see the slides.

MS. HAYES: Okay. Great.

DR. WILSON: Okay. Great. Okay. Well, I apologize for my rather uncomfortable entry into this conference. But I want to start by thanking DSAC, as well as adding my thanks to the FDA technical support for doing this all virtual Advisory Committee. As you probably can perceive, this isn't straight forward or simple. So, we really appreciate everybody's patience as we all get up to speed on figuring out how to use these tools in the optimal way.

I also want to start by thanking the chairs

and co-chairs of the two site visits that are going to be presented later today. For CTTB, that was Dr. Zaia and Dr. Stegemann. And for TVBB, that's Drs. Butterfield and Morrison. So, we are always grateful to the members of the Advisory Committee who are willing to share their time and expertise to chair these site visit reviews of our research programs as they're really critical for us to ensure relevance and rigor in our scientific program. So, I will go on to the next slide, which is just -- oh, now I have control. Okay. There we go.

So, this is just an introduction to show you the types of products that we regulated. Obviously, on this Committee you're quite familiar with the cell and gene therapies, as well as potentially human tissues and xenotransplantation products. But the Center as a whole regulates a variety of other products, like blood and blood components, blood derivatives and various related devices. In addition to vaccines, we also regulate live biotherapeutic products and allergenic

products. Okay.

So, we think of research as very important to advance product development, and it really goes side by side with the regulatory authorities that we are given by Congress. And the way we view it is that, when there's a public health issue -- so for example, right now, it's very relevant, COVID-19 pandemic -- obviously, there's a great deal of novel product development. But sometimes there's regulatory challenges.

So, as you probably know with COVID-19 we're still -- you know, there's rapid discovery on what might be the best animal model to assess products, as an example, again, just to stay current. Those challenges can then be meet through regulatory science, which is a combination of both discovery science and targeted development and new tools that help to create new knowledge that informs regulatory policies and decision making and may then allow us to get improved data from sponsors with regard to making benefit-risk

decisions. The idea is, at the end, we have a licensed product with a positive impact on the initial public health need. And of course, it doesn't stop there because we also have a very robust post-market surveillance program as well.

We have four research goals within -- for Center for Biologics, which are supporting the advancement of the scientific basis for regulations of biologics, human tissues, and blood by developing and evaluating technology, reagents, and standards to inform and improve chemistry, manufacturing, and controls. The second is to develop and assess nonclinical models and methods predictive of clinical performance with respect to toxicity and effectiveness. The third is to improve clinical evaluation pre- and post-licensure through use of big data, innovative designs, and statistical, analytical, and modeling approaches. And the fourth is to prepare for future regulatory and public health challenges.

A couple of new scientific initiatives to

mention, which are really targeting both expanding our intramural capacity as well as some new extramural opportunities that are being funded through grants and contracts, the first being advanced manufacturing, which is -- in addition to the extramural grants and contracts that are being funded, we have stood up two new intramural programs in the areas of influenza vaccine manufacture and improving the robustness of hematopoietic stem cell-derived therapy manufacture. And then a new area that we just launched this year is pathogen reduction technologies. And that is really to expand technologies that are currently licensed for plasma and platelets to be able to do that in whole blood. So, we're excited about those new scientific initiatives.

As you may know, the expertise within the Center is relatively diverse yet also very applied towards the needs of our regulated products. So, we have a lot of expertise in certain technologies that are very important for evaluating products, such as

NMR, mass spectrometry, flow cytometry, microarray, high throughput sequencings. And we also have a bioinformatics and non-key core to support that sequencing component.

As you would imagine, with our agreement we have a robust microbiology, immunology, biochemistry, and molecular biology expertise. We also have -- especially you'll hear about today a lot of work in cell and developmental biology and relatively new tissue engineering and microphysiologic systems. Epidemiology scientific expertise is obviously important for the post-marketing evaluations and meta-analyses biostatistics for looking at clinical trial design and analysis and, of course, the bioinformatics again.

We do have at the White Oak facility a number of core facilities to support the laboratory program, and these provide equipment that would be really expensive to invest in any one single laboratory. And so, we leverage these fairly large capital expenses to

support as many investigators as are interested in using these technologies. So, you can see the list here. It's a combination of traditional biotechnology, as well as other more targeted areas that are really critical to our research programs. We also have a state-of-the-art vivarium with a robust array of imaging, including MRI, as well as animal biosafety level 2 and 3 lab procedure rooms and transgenic derivation. Okay. I apologize. That was me doing that.

I wanted to mention we also have over the last several years had a PI networking and information group which provides peer mentoring and information sharing that's open to all PIs. They meet once a month. It's informally mentored by senior principle investigators, and it's really been a great forum for discussing a variety of issues relating to managing the laboratories, as well as how to deal with very specific things like budget and personnel issues. Okay.

So, we also do a lot of external

collaboration. Obviously, we can't have all the expertise that we need in-house, so we collaborate broadly throughout the United States, internationally. Let's see. Okay. There we go -- internationally -- sorry. There we go. And the collaborations represent a variety of different sectors, and we use a number of different formal, external mechanisms to leverage these types of external partnerships and collaborations. And then this also just shows that we also bring in additional funding through these mechanisms.

The research management processes, we have a governance council called the Regulatory Science Council. That's the body that's composed of the Center director and deputy. It's chaired by myself, and we also have all the office directors, all the office associate directors for research. And that's where we develop a consensus about our research goals and objectives. Offices also develop their own goals and objectives, which are reviewed by the Regulatory Science Council and endorsed there. We develop

evaluation framework and criteria to measure scientific and regulatory impact, and we do portfolio level review of the research programs periodically, as well as discussion of future research needs. Excuse me.

In addition to that, there's management evaluation of the research program, as well as peer review. And we do that, excuse me, internally as well as externally. And of course, today is the outcome of an external peer review, which we call a site visit. This goes into a little bit more details about the different types of management review that are done at different periodicity, as well as the peer review. But importantly, the site visit program -- site visits are reviewing program level information. And that feeds into the report that you'll be reviewing later today in closed session into the Committee for Promotion Evaluation of Researcher-Reviewers, which looks at this for promotions and other actions as far as salary adjustments.

We developed an evaluation framework, as I

mentioned earlier. We created that around four big buckets, the first being mission relevance. How is the work aligned with goals and objectives? How is it supporting our review and scientific capabilities? The second is dissemination, which is the program presenting at scientific meetings and publishing in peer reviewed journals? And then impact we distinguish from dissemination as really a measure of uptake by the scientific community and regulated stakeholders. And then the unique contribution to regulatory practice is for those things that really enhance our regulatory mission.

So, I know that, again, in closed session, not in the open session, we'll be discussing some of the types of questions around promotions or salary adjustments. This is just to orient you to the various terms that you may have seen in the site visit report as far as that goes. So, we have researcher-reviewers, a few different flavors. There are independent scientists, and there are two types of independent

scientists, temporary positions through the service fellowship program, also called senior staff fellows -- excuse me -- as well as permanent staff, which we call principle investigators. We also have support scientists, and likewise, we have temporary positions through service fellowship program and permanent staff, who are called staff scientists. And all of these different types of positions need to undergo at least one site visit in order to achieve certain milestones in their career development as it relates to career advancement of salary or GS scale.

So, the report that you'll be reviewing today is a draft report that was developed by the site visit team. You have three options ahead of you. One is to accept the report as written. Second is to amend the report, and the third is to reject the report and send it back to the site visit team. Assuming that it is approved by the whole Advisory Committee at some point, that final report is then used in many ways for internal peer review of the research PI by committee

for a promotion evaluation of Researcher-Reviewers for various personnel actions -- the PIs, of course, take the recommendations for their scientific direction and other aspects of the research very carefully into account as they plan their research going forward -- and then by management when it comes to resource allocation decisions, assuming resources are available.

The benefits of the research programs, to really summarize, are to integrate research and review. It ensures relevance, expertise, timeliness, and usability. It fosters rational policy and decisions based on sound science, law, and public health impact. It helps us to prepare for future innovative products and public health challenges. It helps develop specific tools and data available to all stakeholders to support development of product classes and recruit and maintain highly trained scientists with the necessary expertise to review regulatory submissions.

So, I will finish, again, with a thank you to everybody who participated in the two site visits we'll

be hearing about today, as well as you, the Advisory Committee, for your time to consider the issues and the questions before you. So, thank you. I'm happy to answer any questions, and I apologize again for my bumpy start.

DR. BUTTERFIELD: Thank you very much, Dr. Wilson. We do have a couple of minutes for Q&A. Do we have any questions? I am not seeing anything.

MS. VERT: Thank you, Dr. Wilson.

DR. BUTTERFIELD: Christina, do you see any questions? All right. So, if there are no questions, then it's a pleasure to introduce our next speaker, Dr. Raj Puri, Director of the Division of Cellular and Gene Therapies. Dr. Puri.

OVERVIEW OF OTAT AND DCGT RESEARCH PROGRAMS

DR. PURI: Christina, can you please load my slides? Good afternoon. My name is Raj Puri. I'd like to thank Dr. Butterfield and the subcommittee co-

chairs, Dr. Butterfield and Dr. Morrison, the Advisory Committee members, and the Advisory Committee staff and the IT technical team for your help in today's virtual presentation. We appreciate your time and effort in reviewing the intermural research program in two branches of the Division of Cellular and Gene Therapies. In my presentation, I will discuss the organizational structure of the Office of Tissues and Advanced Therapies, OTAT. I'll talk about the mission, the regulatory portfolio and activities, and then I'll talk about Division of Cellular and Gene Therapies research program, regulatory scientists and researcher-reviewer model and resources and the staff responsibilities.

Our Office of Tissues and Advanced Therapies, OTAT, is directed by Dr. Wilson Bryan, and it has five divisions. Division of Cellular and Gene Therapies has five branches. The folks in the gene therapy branch and cell therapy branch on the left side of your graph, they are the full-time regulatory scientists. They

review the applications and also do significant amount of outreach, develop policies and guidance documents.

Folks in these three branches on the right side of the graph also do the same thing but 50 percent of the time. The other 50 percent of the time they do mission relevant research. There are 14 PIs in these three branches that include branch chiefs, associate director of research of OTAT, and a division director.

The mission of our office is to ensure the safety, potency, and effectiveness of a wide variety of products that includes cell and gene therapies, tissue products, tissue engineering and genome products for the prevention, diagnoses, and treatment of human diseases and conditions. We evaluate a few of other products that include stem cell, stem cell-derived products, somatic cells, therapeutic vaccines, and other antigen-specific active immunotherapies that include cancer vaccines, immunotherapies such as cells, lymphocyte-based therapies, et cetera. We evaluate a variety of gene therapy products that includes

genetically modified cells, such as CAR-T cells, different types of viral vectors, oncolytic viruses, xenotransplantation products, combination products and devices that are used to process cells and tissue or delivery of cells or genes.

I want to show you this chart just to highlight that the work that we folks do in the Office of Tissue and Advanced Therapy -- is to highlight that we have been extremely busy in the last several years. And I just point your attention to particularly two years -- two years, 2017 to 2019. You can see the total number of INDs and the IDEs submitted to our office has increased from 223 from 2017 to 453 in 2019. It's an increase of about 103 percent. And these INDs include the research INDs, which are product development programs of 142 to 277 for INDs and IDEs. That increased about 95 percent.

In 2017, we were the first to approve the first gene therapy product in the United States. That was Kymriah. It's a CAR T-cell therapy for the

treatment of certain children and young adults with B-cell acute lymphocytic leukemia. In the same year, we licensed another product, Yescarta. That is what is approved for the treatment of adult patients with relapsed or refractory large B-cell lymphoma.

Since the original approval, Kymriah has also been approved for the treatment of adult patients with the relapse or refractory large B-cell lymphoma after two or more lines of systemic therapy. In 2017 also we licensed yet another gene therapy, the first in class, an adeno-associated viral vector expressing the gene for human RTE 65 protein for the treatment of patients with confirmed biallelic RPE65 mutation-associated retinal dystrophy. And last year, in May, we licensed Zolgensma, Onasemnogene abeparvovec, for the treatment of patients less than two years of age with a spinal muscular atrophy with confirmed biallelic mutations in the survival motor neuro 1 gene. In all the years, we have licensed a variety of cell therapy products that includes Provenge, one of the first cancer vaccine

products, an autologous antigen presenting cells for the treatment of asymptomatic or minimally symptomatic metastatic castrate resistant hormone refractory prostate cancer. Over the years, we have also licensed eight cord blood biocenters in the United States for the HPC cord blood.

The activities of OTAT are numerous. I would like to highlight some of those. Our staff reviews, evaluates, and takes appropriate action on product applications submitted at various regulatory paths, such as INDs, IDEs, HDEsPMAs, BLAs, NDAs, and certain banks. We hold a lot of meetings that include INTERACT, which is formally known as pre-pre-IND, pre-IND, pre-IDE, mission advised, and a variety of milestone meetings during the lifecycle of product development.

Our staff participate in inspections of many section facilities for compliance and pre-licensure of the products. We develop policy and procedures combining the pre-market review and evaluation of our

products. We develop policy and guidance documents for the regulation of our products. And I must say that our colleagues have been extremely prolific, developing 14 guidances in the last four years alone.

We provide scientific and technical advice to other CBER offices, FDA centers, government agencies and sponsors. We hold Advisory Committees. We chair the Advisory Committee events. We do a huge amount of community outreach. We have -- through various professional societies that includes, for example, American Society of Gene and Cell Therapy, International Society of Stem Cell Research, International Society of Cell Therapies, Society for Immunotherapy for Cancer and so on. And we do quite a bit of outreach to the patient advocacy groups. We do partnership with the standard developing organizations: NIH, NIST, global regulatory authorities. We do a variety of activities and perform research to support review and progress towards safe and effective medical product development.

The research goals in our office are threefold. The first is chemistry, manufacturing, and controls, which is to develop and evaluate methods and standards for improved characterization of our products and lot release testing that's including the critical quality attributes. We perform pre-clinical and clinical -- and the pre-clinical model is through understanding -- a further understanding of the underlying biology of in vitro and in vivo preclinical models. And we research on the safety issues related with human tissues.

The research areas in DCGT are many. Our PIs perform research in virology, immunology, cell and developmental biology, cancer biology and immunology. And we are very fortunate that we have an expertise in our division in various advanced technologies, such as genome editing, advanced manufacturing, genomics, flow cytometry, proteomics, transgenics, and tissue engineering. We have been -- seven PIs in a consortium called MSC Consortium have been taking a model cell,

MSC, multipotent stromal cell, also known as mesenchymal stem cell, in a system biology approach to look at the analytical attributes of MSC to link to the safety and effectiveness of these products. And we have been pursuing various projects related to pyrosequencing and whole genomic sequencing of the cell therapy or tissue products.

Our products are diverse and rapidly evolving. They use new regulatory paradigms that are developing rather than established. The issues are extraordinarily complex. To address these challenges, we have regulatory reviewer scientists, and we also foster a cadre of researcher reviewer scientists who perform regulatory review, participate in the development and policy and guidance documents, and perform research in key areas to support the FDA mission and help sponsors solve product development problems to advance their products to the marketplace.

We have 14 principle investigators. The majority of them are permanent. Some of them are

service fellows, as you heard from Dr. Wilson. We have staff scientists who are researcher-reviewers supporting the PIs program. They are fairly independent and do a large amount of regulatory activity. We have technical staff that primarily research, but some of the technicians are voluntarily -- like to do the review work as well.

We have staff fellows. We used to have commissioner's fellows. We have Interagency Oncology Task Force fellows, which is an FDA and NCI task force. These folks do both the review and research activities. We have postdocs in our labs that -- they're funded through the ORISE, Oak Ridge Institute for Science and Engineering, and they do primarily research. The funding is provided through PIs, and PIs are expected to build and lead FDA mission-relevant research program.

The responsibilities of PIs include products review, policy development, outreach in the pre-submittal advice, scientific and regulatory talks,

refereeing and editing for journals, chairing sessions at scientific conferences, and scientific collaborations. They manage the lab activities, training and mentoring, supervising, publishing papers, grant writing, and various research related activities. And they participate in the compliance and enforcement actions.

Each year each PI in CBER is expected to provide their annual report in CBER PI annual report database. In addition, in collaboration with Dr. Sue Epstein, the associate director of research in our office, we collect the PI productivity each year. And Dr. Epstein collects this information, and we look at this data in assigning additional resources to these PIs based on their accomplishments in that year.

To summarize then, our research provides in-house, hands-on expertise in cutting-edge areas. We facilitate product development by addressing challenges encountered and helping develop approaches and guidance documents. And these activities provide increased

public confidence in and acceptance of novel technologies and addressing concern. Our PIs participate to the public health emergencies, such as COVID-19 pandemic, where one PI with a proposal to study this potential treatment of COVID-19 infection.

Lastly, but not the least, I'd like to acknowledge the colleagues in the Division of Cellular and Gene Therapy for their incredible amount of activity on a daily basis. I'd like to thank my colleagues for providing me slides and help in preparing this presentation. I'll stop here for the first part of my presentation and see if there are any questions.

Q&A

DR. BUTTERFIELD: Thank you, Dr. Puri. We do have one question. We have two questions. The first one: does OTAT and your division interact with or coordinate reviews of cancer vaccines with the FDA

Oncology Center of Excellence?

DR. PURI: Yes. The answer is yes. The Division of Cellular and Gene Therapies is a CMC division. It deals with the CMC aspects of all the submissions. Our colleagues in the Division of Clinical Evaluation Pharm/Tox, which is headed by Dr. Tejashri Purohit-Sheth. Her division collaborate with Oncology Center for Excellence in review of applications in a collaborating way as a consult for all the applications.

DR. BUTTERFIELD: Thank you. And Christina is clarifying that only members should ask questions right now. So Christina, are either one of these other questions things that we should bring forward now?

MS. VERT: Dr. Roos can go.

DR. BUTTERFIELD: And Dr. Roos' question: was there an increase in staff over the last three years since there was an increase in regulatory activity?

DR. PURI: Yes, we did receive some staff in the last two years. Our division was able to recruit

some new reviewers, full-time regulatory reviewers in the division. We also recruited a new PI in advanced manufacturing, and I will mention that in my second presentation later on.

DR. BUTTERFIELD: Thank you. Christina, other questions for right now?

MS. VERT: I'm just checking. Hold on.

DR. BUTTERFIELD: Thank you.

MS. VERT: No, I think we're good.

DR. BUTTERFIELD: Okay. Then, Dr. Puri, I welcome you again to continue presenting, this time as Chief of the TVBB, please.

OVERVIEW OF TVBB RESEARCH PROGRAMS

DR. PURI: Thank you and, Christina, can you please load my presentation. It's the same presentation.

MS. VERT: We'll get them up.

DR. PURI: Yes. Mine is the same

presentation, and the slides continue. Can you please bring my previous presentation?

MS. VERT: I can hear you, Dr. Puri.

DR. PURI: Can you bring my previous -- yes, thank you. Yes, after this I will read -- now, thank you. I will be able to manage it from here. Okay. So, Dr. Butterfield, should I start?

DR. BUTTERFIELD: Yes, please.

DR. PURI: Okay. So now I will talk about the -- and summarize the overview of the research programs in the Tumor Vaccines Biotechnology Branch, which I'm also the branch chief of. This branch has two PIs, myself and Dr. Shyh-Ching Lo. And in the recent PI presentation that the site visit did, we had two additional senior staff scientists follow my group, Dr. Bharat Joshi and Dr. Rafat Husain, who also presented their research. And I will summarize their work, as well.

At the time of the site visit, we had been recruiting a new PI, which I mentioned before, Dr.

Pankaj Mandal, an advanced manufacturing PI. I'm hearing a lot of background. Will someone please mute your phone? Thank you.

The research in our lab is focused on targeting human cancer. Cancer is a very difficult public health problem. To target cancer, it is important to identify a target that is specific for cancer by not a normal cell and develop a strategy to target not only tumor but also tumor microenvironment and overcome immune tolerance. There are a large number of cancer vaccines, and immunotherapy products are under development. These products are complex --

MS. VERT: Dr. Puri, can you wait a minute? I think there's a technical issue. I hear you, but some people may not hear you. Just pause, please.

DR. PURI: Okay.

MS. HAYES: I believe the issue was resolved.

DR. PURI: Okay. So, to continue, to target cancer, it is important to identify a target that is a specific for cancer but not in normal cells and develop

strategies to target not only tumor but also tumor microenvironment and overcome immune tolerance. There is a large number of cancer vaccines and immunotherapy products that are under development. These products are complex and often consist of mature cells, proteins, or peptide antigens, neoantigens, gene modified cells. Therefore, identification of appropriate critical quality attributes, which are critical for product development, is often challenging.

Animal models of safety and efficacy are important to determine safety, starting dose, frequency of dosing, dose escalation and prediction of response in clinical trials. Appropriate animal models of human disease may help guide these parameters. Similarly, immune biomarkers or other markers of response in safety are rare. These biomarkers may predict clinical outcome, good or bad, and may be identified in pre-clinical animal studies in early phase clinical trials. Our research program is addressing some of these challenges in our lab.

Our research program began from the discovery of overexpression of T helper 2-derived cytokine receptors in human tumors. We first discovered Interleukin-4 receptors in human tumors and later Interleukin-13 receptors. Over the years, we have studied these receptors on human cancer, and we have reported a large number of publications. In the last reporting period, we focused our attention to anaplastic thyroid and ovarian cancer for IL-4 receptors and on pancreatic ductal adenocarcinoma (PDA), glioblastoma multiforme, and adrenocortical cancer for IL-13 receptors.

Our research program is divided into two major program areas: cancer vaccines and adoptive cellular immunotherapies. And I will discuss some of the work here -- summarize it here. I would also like to highlight that the work presented and being undertaken by staff scientist Dr. Rafat Husain and Dr. Joshi -- these folks not only perform fairly independent research but perform large amount of regulatory

activities similar to any other PI in the Division of Cell and Gene Therapy. Somehow, I have lost the control of my slides. Okay. Now I do have it.

And the second program area, this is the application of genomics technology. And I will touch upon -- summarize this program as well, particularly in the area of cytokine receptors as potential biomarker of disease prognosis and response. I would also like to mention here that Dr. Ramavati Pal, listed in the slide, is a staff fellow. I inherited her from a PI in the division who departed to direct the center. And that PI and Dr. Pal was pursuing the proteomics of the mesenchymal stem cell. And her project also studied the secretome of human multipotent stromal cell as part of the MSC consortium to identify the specific proteins in MSC. And she also presented at the site visit subcommittee.

The IL-4 receptor expression that I'm going to talk about -- we focus our attention in thyroid cancer. There are two major types of malignant tumors that

originate from the thyroid epithelium: the well differentiated papillary thyroid carcinoma, WDPC, well differentiated follicular thyroid carcinoma, WDFC, and anaplastic thyroid carcinoma, ATC. Anaplastic thyroid carcinoma is most highly aggressive and invasive tumor with a poor prognosis and a median survival of less than six months after the diagnosis. And the thyroid survival rate is less than 7 percent.

Using an antibody to envelope the receptor, immunofluorescent, Dr. Joshi in the lab found that the anaplastic thyroid carcinoma express high levels of Interleukin-4 receptor, followed by follicular carcinoma and capillary carcinoma of the thyroid. These results have been reported in *Discovery Medicine Journal* in 2015.

To target human tumors, we have developed two immunotoxins, Interleukin-4 pseudomonas exotoxins, that is not presented here, with Interleukin-13 pseudomonas exotoxins. Both are recumbent immunotoxins. They are highly specific to the (Inaudible) -13 target tumor

cells. And we have reported large number of studies using these molecules, and both these molecules are in clinical trials at present.

Using Interleukin-4PE, we show that Interleukin-4PE has a remarkable anti-tumor effect if we're looking at the tumor size and the survival of the animals as we followed in the tumor bearing animals. In the case of IL-13 receptor expression and the relationship to the -- as a potential as a biomarker in GBM, what we observed that the animal models would be -- for this, when the IL-13 receptors that are expressing tumors are administered -- are injected into the mice, the survival of these animals are less, and these tumors metastasize. And so, we wanted to look at that, if IL-13 receptor has a similar prognostic biomarker in brain tumors.

So Jing Han, before he departed from our lab, looked at the TCGA database, which is NCI's database. It is one of the largest database which contains a wealth of information on the genomics, proteomics,

sequencing, RNAseq, the clinical information, the treatment the patients have received. So, it's an incredible amount of information which has been now incorporated in the Moonshot Initiative, and now it's called Global Data Commons.

By looking at the IL-13 receptor expression in brain tumors in GBM, Jing Han, what he found that tumor cells -- tumor sample that expresses high level of IL-13 alpha 2, as you can see in the graph on the left in red, and the median survival of these subjects are 337 days. Compared to the tumors with the receptor expression of low or no expression, the median survival was 386 days. It's a statistical significant difference between the two.

On the right side of the graph, when we look at both genes of IL-13 receptor, IL-13 binds to two proteins, IL-13 alpha-1 and IL-13 alpha-2. And when we look at both of them, as you can see, the red line again, the median survival is 342 days. But when both of them are low or no expression in the tumors, the

survival has gone up to 1,255 days. That's four times higher compared to that high expressor of the IL-13 receptor. In addition, IL-13 alpha-2 expression in GBM is associated with resistance to temozolomide chemotherapy, which is a standard treatment along with the radiation therapy for this disease.

Dr. Joshi in the lab had started a couple years ago -- he began a project where he used fused a single chain FV against the IL-13 receptor alpha-2. It took about two postdocs before we identified a single chain FV using phase display technology, the human library. And Dr. Joshi "optimized" it. He chose a gene with the single one, CD3 zeta and single two, 41BB with CD28 cytoplasmic domain and created this concept using a lentiviral vector. And he transfused Jurkat cells, which he did from (inaudible) T-cell line of peripheral-derived lymphocytes and created CAR-T cells. And tested, these cells expressed the construct on the cell surface by facts analysis.

And then this slide shows that these cells

were viable and they proliferate in a time dependent manner. And these cells are highly potent, as you can see in the C graph on the left. Below, these CAR-T cells, they only kill the tumor cells that express IL-13 alpha-2. And these are glioma cell line, human GBM cell line.

But if you knock down the receptor by RNA-I technology, these cells actually do not get killed by the CAR-T cell; as you can see the green and the black lines, suggesting that these are IL-13 receptor alpha-2 targeted CAR-T cells. Another way to look at the potency of the CAR-T cells was looking at the gamma interferon release assay, which is -- both these assays are very common assay being used in CAR-T cell therapy trials. And the CAR-T cells produce IL -- the Interferon gamma only when they're exposed to IL-13 receptor alpha-2 part of the GBM cell line, as you can see the tall bar graph compared to the small graph on the right side, which is G98 G cell line, which expresses no IL-13 receptor. Dr. Joshi is now pursuing

this experiment in looking at the safety and efficacy and also in collaboration with the -- in the Hopkins collaborators, Johns Hopkins collaborators are looking at the biodistribution of these cells in the animal model.

Dr. Husain in the lab, he's been pursuing his work in creating cancer vaccines area. And Dr. Yuki Sato (phonetic) working in our lab, a post-doctoral fellow from Japan, she spent several years in creating a modified vaccinia Ankara virus that expresses IL13 receptor alpha-2 chain. And here is in vitro study showing that this vector -- this virus when it's expected to be infected the T98 glioma cell line, they do not express IL-13 alpha-2. The Western Blot analysis after the virus infection they expression alpha-2. But fluorescence of GFP stating -- they show that GFP is expressed. Using the antibody through IL-13 alpha-2 by immunostaining, you can see they express on the cell surface and some cytoplasm.

Through FACS analysis we see that IL-13

subalpha-2 is expressed on these cells. MVA virus can infect tumor cells to express Il-13 receptor alpha-2 on the cell surface. Dr. Husain now has been pursuing this vector in looking at the animal models, and we have recruited a new staff fellow, Dr. Karen Knudsen from NCI. And this will be one of their major projects to look at the safety, effectiveness, and biodistribution of this cancer vaccines in the animal model.

So, in summary, we have reported that human tumors express high levels of Interleukin-4 receptors and Interleukin-13 receptors. The old expression of IL-13 receptor is associated with poor patient prognosis and resistant the temozolomide therapy. Both IL-4 receptors and IL-13 receptors can be targeted with immunotoxin. We have generated a vaccine -- a modified vaccinia Ankara recumbent virus expressing IL-13 alpha-2 for its use in the animal models of cancer. And we have created a third generation CAR-T cells that express a single chain IL-13 alpha-2 to be used for the

targeting human cancer in the animal model.

Now, I'd like to shift my gears towards the summary of the project from Dr. Shyh-Ching Lo's lab. An increasing number of human tissues are recovered, processed as grafts by industry and used by medical practice each year in the United States. Our office regulates human cells, tissue, and cellular and tissue-based products, or HCT/Ps, in order to prevent the transmission of communicable diseases. This laboratory has been established -- and this is in my division -- along with the collaboration with GBM human tissue in our office to enhance both the safety and availability of high-quality human tissue grafts and HCT/Ps for therapeutics.

The specific aim and research area in this laboratory include to establish and maintain the required scientific capabilities to directly support regulatory needs for tissue safety and to adopt new molecular technologies for rapid detection of target infectious pathogens with high sensitivity and

specificity, to develop highly effective genomic sequencing capabilities for identification and characterization of infectious agents that would likely threaten the safety of human HCT/P, and to explore new scientific approaches for detection and characterization of previously unknown or newly emerging infectious pathogens. Infections cause by normally cytolytic Flavivirus such as West Nile Virus or Zika virus could often lead to viral persistence in the infected host. There were incidents of transmitting fatal infections of West Nile flavivirus through organ transplantation from donor and persistent West Nile virus infection. Zika virus were reported to persist in the infected host months after infected host were no longer viremic by Zika virus.

These are some of the recent publications from Dr. Lo's lab in Zika virus research, studying the processes and mechanisms that lead to Zika virus persistence in human cells to prevent possible transmission of Zika virus through therapeutic

biologics. The tissue micro lab under the direction of Dr. Shyh-Ching Lo conducted whole genome expression profiling analysis of the persistently Zika virus infected U937 cells to identify their crucial metabolic pathways, biological functions in the infected human host cells that confer the viral persistence.

So, the summary of this lab includes that they have developed the rapid, highly sensitive technology for the detection of pathogens, and their focus is Candida in the cornea tissues for transplantation. They've developed high-throughput genomic sequencing capability for detection and characterization of established and newly emerging infectious pathogens, such as Epstein-Barr virus and Zika virus present in human tissue, cells, or tissue-base products. They have developed significant expertise in transcriptomics, whole genome expression profiling capability for identification of key molecules, metabolic pathways and biological functions in the human host cells and confer Zika virus persistence.

Now will I talk about Dr. Pankaj Mandal, who was a new PI -- is a new PI who's recruited during the time of the site visit in September of 2019. Dr. Mandal's work includes the advancement in testing of genome edited hematopoietic stem cells. Hematopoietic stem cells are at the forefront of regen medicine, and hematopoietic stem cell-based therapeutics are one of the leading advanced therapies. Though hematopoietic stem cell therapy are routinely performed in a clinic, more than a million transplantations have been performed worldwide. HSCT is underutilized as a blood disorder, as it has high risk of seizure.

With the advancements of gene therapy and genome editing technologies, the scope of hematopoietic stem cell therapy has been broadened and could potentially be used to treat a variety of blood disorders and other conditions. In recent years, using genome editing, particularly crystal and cast-mined tools, highly efficient and therapeutically meaningful genome editing can be achieved in hematopoietic stem

cells. Because optimized methods for hematopoietic stem cell expansion ex vivo have yet to be established, this will lead to large scale manufacturing of hematopoietic stem cell-based therapies with acceptable critical quality attribute remains bottlenecked for wider applicability of HSC-based therapeutics.

Using FGB, fibrinogen reporter mouse that Dr. Mandal developed in his previous lab, and human hematopoietic stem cells and CRISPR tool, Mandal Lab is planning to study the advanced manufacturing of genome edited hematopoietic stem cell-based therapeutics, with specific aims as shown in this slide: A) optimizing the large scale manufacturing of HSC-based products, developing novel approaches for HSC derivation and expansion using CRISPR's training and functional genomics approach, evaluating the potency and safety of genome-edited HSC, and last, but not the least, help develop reference reagents for HSC-based products and derivation that will help in developing regulatory guidance for this product class. Christina, somehow

I'm unable to move the slide. It's covering the arrow. The closed-captioning is covering the -- okay. Thank you.

Lastly, but not the least, I'd like to thank you for reviewing the DCGT's research programs and providing your insights. Your input is very critical to fulfilling our regulatory mission. I'll stop here, and I'll be glad to answer any questions.

Q&A

DR. BUTTERFIELD: Thank you very much, Dr. Puri. Do we have members who have questions, please? We have a couple of minutes. Okay. I'm not -- I'm not hearing any questions for Dr. Puri, so we're going to move ahead. And it's now my pleasure to introduce Dr. Stephen Bauer, Chief of CTTB. Dr. Bauer, please.

OVERVIEW OF CTTB RESEARCH PROGRAMS

DR. BAUER: Thank you, Dr. Butterfield, and I want to add my thanks to those that others have expressed already earlier. But my colleagues and I in CTTB really deeply appreciate the efforts by DSAC, Christina Vert, Kathleen Hayes, Prabha Atreya and others and IT support getting this meeting coordinated. Also to our OTAT management and CBER for the tremendous support we receive and have received over the years for our research and to the Advisory Committee meeting today virtually. We very much appreciate that but especially the efforts of our site visit team.

So, my slides still aren't loaded, or at least I don't see them. But our site visit occurred on November 1st. And actually my first slide says 2020. I'm a year ahead, but it was in 2019. In the branch, we have 26 staff members. 16 of them are FTEs who are engaged in research and review. And listed here you see the five PIs, and some of us have staff fellows who were also evaluated in the site visit. In total, we have 11 staff fellows, and we also have 10 contract

researchers who help us out in our investigations. Let's see if I can control these slides. I'm not sure how to advance the slide, so let's go to slide number two.

MS. VERT: There's two arrows on the lower left corner.

DR. BAUER: Oh, okay. Thank you. Thank you. The people who do review, including the people under review for the site visit, are engaged in (inaudible) 50 percent of our time in the regulatory review. And we review products that are primarily focused, as I show here, on stem cells, adult cell therapy products, combination products, which involve tissue engineering with cells. Some of us do gene therapy review, and some of us do device review, as well, including diagnostic and cell purification. And I might mention as well that some of our technical expertise is leveraged by other centers, and we do collaborative reviews, particularly in flow cytometry but also in other areas.

So, our research addresses some of the challenges I've listed on this slide that we encounter through our review and also through our research. And one of the primary areas of concern is that oftentimes we see that the markers that people use to evaluate their products are inadequate in terms of prediction of the cell state and cell fate. So, our work is aimed at showing strategies, showing approaches about how one might go about finding perhaps more predictive measurements that one could make that would correlate to both in vitro biology and clinical effectiveness and safety.

This reflects a relatively poor understanding of how cells interact with their microenvironment. Manufacturing is another microenvironment. It does affect how cells behave. And the assumption that the in vivo biology that we want will be maintained through manufacturing in an ex vivo microenvironment is something we want to investigate and understand better. And we engage in some research that we hope to

understand better how our characterization that we do for cells will lead us to understand cell fate and survival post transplantation.

In order to do this, we use complementary systems from frog, fruit flies, and mouse and man. We look at such things as gene and protein, cell, tissue, and microenvironmental interactions that happen in manufacturing and as they might affect the performance of products in the patient and also in pre-clinical settings in animal models. So, we look at in vivo and in vitro development. And one of the themes that you'll hear more about is we hope to increase knowledge and manipulation of growth factor pathways as it relates to product characterization and understanding.

So, I'm going to now summarize some of the research that was presented at the site visit, and the first one, my project, which has been focusing on improved characterization of multipotent stromal cells as a way to illustrate ways -- new strategies to assure the safety and efficacy of stem cell-based products.

And primarily what you'll hear about today is our efforts in developing quantitative approaches to measure biological activity of cell-based products. So, this is fit into the MSC consortium, which you heard a little bit about before.

Our role in the MSC consortium was to make a lot of MSCs to hand out to our partners in the consortium and also to, in parallel, develop these in vitro quantitative bioassays that I'll be talking about. What we did was to take cells that were commercially available from eight different human bone marrow donors and passage them out to passages three, five, and seven. So, we got a picture of what happens during the duration of cell expansion in a typical manufacturing scheme. We handed out cells at those three passages to members of the consortium.

One of the things that I want to emphasize is that there are community consensus characterization schemes for MSCs that rely on just a few cell surface markers and a qualitative demonstration of some kind of

development. But the theme that you'll hear from me -- and, you know, there's awareness in the community as well -- is that those -- that manufacturing scheme, that set of what you might hope are critical quality attributes do not capture the functional heterogeneity, the biology of the cells that have undergone manufacturing. So, we focused -- or my focus today will be mostly talking about our efforts in quantitative MSC differentiation assays.

And shown here is an illustration of a preparation of MSCs. You can get them to undergo a trilineage differentiation and undergo adipogenesis or chondrogenesis or osteogenesis with appropriate stimulation. You can look at inherent immunomodulatory effects of these cells, or you can stimulate increased immunomodulatory activity through what's popularly called licensing or treating with interferon gamma or other growth factors. And Dr. Sung's lab -- you'll hear more about this later -- helped develop the chondrogenesis assay.

So, without going into a lot of details about what we've done and how we've done it over the years, this is sort of a summary slide of the quantitative measures that we've actually been able to develop, looking at such things as changes in proliferation or cell size or colony forming unit activity or adipogenic activity. And all of those change over time with duration, and, generally, the differentiation and the proliferation decrease with cell cultured duration. And the cell sizes increase.

In more recent times, including the time covered by the site visit, we've shown that we could develop osteogenic and immunosuppressive activities and the chondrogenic activity assays. And all of these assays are able to detect differences among MSCs from different donors, cultured for different lengths of time, and manufactured under different conditions. So that was our hope.

And I'm just going to go into this last slide of what -- my research and talk about some effort in

the immunosuppression realm. So, we were able to develop a quantitative assay that would detect differences between cells from different donors since they showed decrease over time of culture. And we could show that a morphological profile gathered looking at many, many morphological parameters could be develop and that would correlate with our activity in the in vitro immunosuppression assay. And then we further developed that by showing that we could take that high density, high multiparameter data and use machine learning on the morphological parameters to correlate with that immunosuppressive activity and, furthermore, to use those morphological data to look at subpopulations.

And I think the theme of subpopulations and tying that to the heterogeneity is an important one. And in this work, we were able to show that we could manually gate based on morphological data but look at cells with visibly different morphologies and correlate subpopulations specifically with activity of those

different MSC preparations. And the hope here is that we will be able to look at the subpopulations in a molecular sense and correlate molecular signatures that would be relatively robust, easy to measure and correlate that with product activity.

And next, I'm going to go and talk about work that was presented by Dr. Hursh and Dr. Vallabhaneni, and their major theme is to develop predictive indicators of genome stability, which is a safety criteria in cell maturation and efficiency or efficacy of cells as measures of cell therapy product efficacy and safety. A lot of their work looks at induced pluripotent stem cells, which, of course, have great potential. And the question is how do we assess the quality of stem cell products and their sources?

And Dr. Hursh's lab is working on ways to develop methods to assess the cell quality and genome stability. One of the areas they've investigated is looking at the mitochondria as indicators of cell quality and using a histone marker, gamma H2AX, to look

at DNA breakage, looking at in vitro culture methods to expand pluripotent stem cells. And also, an in vivo model using persopholate (phonetic) to look at a very important cell state determining signaling pathway, TGF-theta/BMP.

This slide is a summary of some of the work showing that mitochondria -- so the experiment was to look at how iPSCs grown under physiological oxygen 3 percent versus 20 percent might differ -- if that might affect their quality. And the observation was there is greater mitochondrial mass in the cells that are grown under lower or physiological oxygen. I'll point out that this was a fibroblast line as control, but it was the origin of three different iPS cell lines that were used for these experiments.

Interestingly, the mitochondrial activity is not increased on a cell basis, but literature suggests that mitochondria might play a rule in pluripotency. So, they looked at pluripotent markers and looked at embryoid body formation as indices of pluripotency.

And they were able to show that the pluripotent stem cells show increased differentiation potential when grown under these conditions.

On the safety side of the equation and the understanding of the potential for DNA damage during cell culture, they looked at this histone marker of DNA damage and found that it was mostly associated with replication. It was enhanced in positivity and iPSCs compared to MSCs. But in the end, it seemed that most of this was relative to proliferation and not necessarily an increased sensitivity in iPS cells for this kind of damage. But the work is important in increasing understanding of how mutations might collect in iPSC cell lines and other cell products.

Dr. Vallabhaneni has been investigating different systems for meeting the goal of having large numbers of pluripotent stem cells during manufacturing and looked at various bioreactor and culture systems to assess their capability to make high-quality cells and did a variety of characterizations shown here in the

blue box to look at the quality of these cells. And there are studies today that have shown you can get a 20-fold expansion of cells in these different bioreactor formats and maintain high levels of pluripotency markers, indicating that these are going to be quality cells for further uses in manufacturing.

Now, I'm going to turn to Dr. McCright and their efforts to develop measures of safety and efficacy for tissue engineered products. And Dr. McCright is engaged in both the cell signaling pathway paradigm of research, as well as cell distribution in these two different projects I'll briefly mention. The first is looking at protein phosphatase 2A function and how it's controlled by regulatory subunits and then technology developing in his lab to use MRI to track transplanted cell therapies and improve anatomical imaging -- and Dr. Ma, whose work is on identifying molecular and morphological indicators of neural stem cell differentiation capacity.

Just a brief summary, protein phosphatase 2A

is a heterotrimeric complex, and Dr. McCright's work has investigated the B subunit primarily, which controls intracellular localization, substrate specificity, and kinetic activities. And they are -- have been shown to be in regulators of developmental signaling and cancer signaling pathways. So, the goal is to identify functional requirements for this regulatory subunit during formation of tissues and cells used for cell therapies.

And this work is also led to some insights in genomic stability. Showing here, loss of the B56 gamma subunit can cause chromosome instability in fibroblasts where that gene has been ablated. And the yellow arrows show areas where you see abnormalities in chromosome formation and, in the bottom, chromosome segregation.

The next slide -- this is slide 20 now -- is showing the work on neuronal stem cells. And they're often cultured extensively to make cell therapy products. And the question is what characteristics

should we be using to evaluate neural stem cells? We have the observation that when you use iPSC derived neuronal stem cells they develop morphological subpopulations, some of which express Notch and Sox2 better or at a higher level and that you can see differences in neurosphere formation that correlate with those Notch and Sox2 expressions.

So, this is also related to looking at changes during duration of culture. You can see in the population at the lower left gene expression is shown there. You can see decreasing ability to form neurospheres and decreasing expression of these two markers.

And then on the next slide, this was to illustrate development of improvements in magnetic resonance imaging using a technique called inductive resonance. Using a contrast reagent, 19-fluorine, you can look in panel B, and the boxes in red are showing sharper images from histological areas that are evaluated at day 2 or day 40 after implantation of

encapsulated neuro stem cells. I think this is a nice technological advance that will help us track cells and understand their cell fate after transplantation.

Next, I'll summarize work from Dr. Malcolm Moos on SMOC modulation of the BMP/Wnt signaling, again looking at how Wnt signal pathways affect cells in vitro and in vivo, and single cell mRNA sequencing to identify and characterize cell product subpopulations. I think this theme of heterogeneity in populations is an important one and will describe a little bit more Dr. Moos' efforts here.

Slide 24 shows a representation of what happens using a SMOC protein that Dr. Moos' lab purified -- SMOC protein and was able to use what's called an animal cap assay using xenopus embryos; taking an animal cap, putting it in vitro, exposing it to that SMOC protein and then looking at what happened in using RNAseq in these explants.

And you can see here a summary of data showing upregulation of 25 genes, more than fivefold, and 44

genes down regulated greater than fivefold. So, you can start to get a picture of the gene expression networks that are influenced during the renal induction via SMOC and that signaling pathway.

In the next slide -- shows some data from trying to understand how RNAseq can be used to understand population substructure in a bone marrow or adipose derived stem cells. And you can see here bone marrow on the left versus adipose and the subpopulations that were identifiable using RNAseq on single cells. So, you can start to understand the complexity and the heterogeneity in these kinds of populations using this sort of (inaudible).

DR. BUTTERFIELD: Dr. Bauer, this is Dr. Butterfield. I just wanted to confirm that's 20 minutes for the entire presentation. I know there's a lot of great data to show.

DR. BAUER: Okay. I'll try to get through it very quickly here. This slide shows an important consideration that using single cell seq you can see

that there are what are called batch effects. So, on the left, you see a correlation of subpopulations with the institutions where that analysis was done. On the right, you show that there are computational ways to correct for those problems.

So, I'll just go on to the last section of my talk. This was from Dr. Sung's lab investigating the effect of cell materials interaction on safety and effectiveness. I'll skip this one which is talking about how important biomaterials are in the tissue engineering realm and that these folks are developing flexible systems to increase our understanding of cell-cell biomarker interactions in that microenvironment. The goal I just expressed, but their systems have been using multipotent stem cells derived from iPS cells to understand those cell-cell interactions in that kind of microenvironment.

This is a scheme showing that they looked at 3D aggregates for quantitative assessment of MSC capacities to undergo chondrogenesis. This is from a

paper that showed you could look at the size of the aggregates and correlate the size of the aggregates with early or late passage and derive a gene expression profile that would predict the amount of chondrogenesis based on the size of the pellets that were formed. And they went on to look at immunosuppressive activity of MSCs in some of these microphysiological systems to look at the role of integrins and cell-cell contact versus paracrine influences in MSC immunomodulatory activity and found some interesting correlation with various integrins and whether or not the cells were in contact or not.

And then they have developed a nice system to look at interactions between endothelial cells and MSCs. And in this slide they're summarizing morphological parameters that were different between MSC preparations and were also passage dependent, a theme that I've talked about extensively. So, the research in the branch addresses cell therapy challenges using these different complementary in vivo

and in vitro systems to look at all these complex biological interactions.

And our findings are -- our goal is to reveal cell product quality attributes that lead to improved characterization of cell-based therapies, methods to monitor manufacturing differently, perhaps the ability to choose appropriate donors better, and serve as a scientific basis for policy development, guidance for sponsors, and standards development. I just want to thank all the collaborators and apologize for going over time. And with that, I'll stop, and we can take some questions if we have time.

Q&A

DR. BUTTERFIELD: Thank you very much, Dr. Bauer. I appreciate it. So, we do have a few minutes for questions from the members. Dr. Morrison?

DR. MORRISON: Dr. Bauer, I really appreciated you making the point about there being biological

heterogeneity among the MSCs that's not captured by markers. I just wanted to explore that idea a little further because I think this is a major issue in this field where not only are people using the same term, MSC, to describe cells from bone marrow and adipose and other sites, but there's been an explosion in science recently that, even within the bone marrow, the fate Noching studies show that there's an enormous diversity in different kinds of mesenchymal progenitors that have different fates in vivo, different biological characteristics that not only are not well understood in terms of markers but also that may not even be picked up in terms of in vitro assays. So how do you think about this?

DR. BAUER: Yeah. I really think that people who are, from a pragmatic sense, isolating bone marrow, as for it's expanding them, might well be having different expansion of some of those subpopulations that you're talking about. Our data seem to indicate that once you have a preparation, if you go back and

assay that over and over again, you get consistent results suggesting there's really not a stochastic stem cell compartment once you've expanded. So I guess our hope is that, from a pragmatic sense, you would be able to have some kind of in vitro biological assay that might discriminate between cells made from a particular donor or made from different manufacturing approaches and that one might try to optimize manufacturing to stimulate certain subpopulations that would correlate with the effect that you want. So that's a kind of -- the application of that sort of knowledge that we're developing here and that sort of perspective.

OPEN PUBLIC HEARING

DR. BUTTERFIELD: Terrific. Thank you very much Dr. Bauer and Dr. Morrison. So, at this point, we are going to move to the open public hearing. So, to begin that, I have a statement to read, after which I'll introduce a speaker who is pre-registered. So

first the statement: I'd like to welcome you to the open public hearing session. Please state your name and your affiliation. Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information gathering and decision making.

To ensure such transparency at the open public hearing session of the Advisory Committee meetings, FDA believes that it is important to understand the context of an individual's presentation. For this reason, FDA encourages you, the open public hearing speaker, as you begin to state if you have any financial, personal, or other professional relationships with any company or group or individual that may be affected by the topic of this meeting. If you do not have any such interests, also FDA encourages you to state that for the record. If you choose not to address this issue of financial, personal, or other professional relationships at the beginning of your statement, it will not preclude you from speaking and you may still

give your comments.

So, with that completed, I would like to introduce Dr. Leslie Meltzer, PhD, Vice President, Head of Global Medical Affairs for Orchard Therapeutics, who has up to ten minutes for her presentation. Dr. Meltzer, please.

DR. MELTZER: Yes. Can you hear me okay?

DR. BUTTERFIELD: Yes.

DR. MELTZER: Okay. Great. Thank you. Hello, everyone, and thank you for having me here today. My name is Leslie Meltzer, and I lead Global Medical Affairs at Orchard Therapeutics. I'm an employee of Orchard Therapeutics.

Today, I will share how ex vivo hematopoietic stem and progenitor cell gene therapy, or HSPC gene therapy, has the potential to address unmet medical needs in monogenic diseases, including neurometabolic disease. Over the next ten minutes, I will discuss the potential for HSPC gene therapy in neurometabolic disease, review the technology platform, and discuss

ongoing clinical development with this approach. HSPC gene therapy offers a highly differentiated approach to the treatment of monogenic disease, including neurometabolic disease.

We can use an integrating viral vector to insert a working company of a gene permanently into the genome of HSPCs. Because HSPCs self-renew, this approach allows for one-time administration that provides the potential for permanent disease correction. Gene corrected HSPCs also give rise to all the cell types of the blood, including white blood cells, red blood cells and platelets, as well as tissue macrophages, which enable this approach to be broadly applicable across a variety of disease states in multiple organ systems. Specifically, today I'm focusing on how HSPCs can differentiate into cells of the monocyte or macrophage lineage that naturally migrate into the tissues. Because these cells naturally migrate into tissues and can express the gene locally, this provides us with a potential mechanism by

which we can genetically correct HSPCs to ameliorate pathophysiology locally in multiple organ systems, including the brain, where I'll focus our discussion today, as well as other organ systems, such as the GI tract and the bones.

Self-inactivating lentiviral vectors have been used to genetically modify HSPCs. These vectors were developed to enhance transduction and minimize the potential risk of insertional oncogenesis that's been observed with other retroviral vectors. Transgene expression itself is driven by mammalian cellular promoters. And the deletion of viral promotors and enhancer sequences and the use of internal promotors minimizes transactivation potential. With current-generation lentiviral vectors, we've seen a 100- to 1,000-fold lower risk of transactivation of adjacent genes in preclinical murine models. And the safety profile in humans is strong, with ten year follow ups showing no signs of oncogenesis.

The manufacturing process for HSPC gene

therapy is outlined on this slide. Patient's HSPCs are procured either from bone marrow or from mobilized peripheral blood. The blood stem cells are then selected and purified, and they're transduced ex vivo with a lentiviral vector to introduce a working copy of the gene.

The product is then cryopreserved in order to allow the necessary release testing to be performed, as well as transportation to the patient's treatment site. After the patient undergoes conditioning to receive the treatment, the gene corrected cells are infused back into the patient intravenously. Aside from some minor variations in individual manufacturing steps and in conditioning protocols, this process is fairly standardized for all HSPC gene therapies in development today.

For the rest of this talk, I'm going to focus on the potential of HSPC gene therapy in neurometabolic disease specifically. HSPC gene therapy enables delivery of proteins to the brain by leveraging the

natural ability of gene corrected HSPCs to migrate across the blood brain barrier. Once they've crossed the blood brain barrier, these gene corrected HSPCs distribute throughout the CNS and engraft and differentiate into microglial-like cells. These cells can express super physiological levels of the relevant enzyme, and this enzyme can then be taken up by the uncorrected cells of the CNS, such as neurons and other glial cells. This process is referred to as cross-correction.

Proof of concept studies in animal models have demonstrated broad cellular distribution and transgene expression after administration of HSPCs transduced ex vivo with a lentiviral vector, such as in this example here where the transduced cells are expressing green fluorescent protein or GFP. These pre-clinical results suggest the potential of the HSPC gene therapy approach in the treatment of multiple neuro metabolic indications. An example of this approach currently under investigation in clinical trials is in the

treatment of metachromatic leukodystrophy, or MLD, which is a devastating neurodegenerative and demyelinating disorder. Children with the most fatal form of MLD experience rapid neurological decline and often do not live past the age of ten.

Presented here are results from an ongoing clinical trial where MLD patients are treated with HSPC gene therapy and then followed for up to eight years after treatment. Neurological function in the treated patients over time is compared with a natural history cohort of untreated MLD patients. On the left, we're showing the time to severe motor impairment or death, and on the right, we're showing cognitive performance by age over time.

In this study, we've observed stabilization of motor function and of cognitive function relative to the natural history in untreated patients with up to eight years of follow up. Similar findings have been seen in clinical studies using HSBC gene therapy in other neurological indications, such as adrenal

leukodystrophy. And studies are also ongoing in MPS1 or Hurler Syndrome, as well as MPS3 or Sanfilippo Syndrome.

So, in summary, HSPC gene therapy has the potential to address high level of unmet medical needs in monogenic diseases, including neurometabolic diseases. HSPC gene therapy offers a highly differentiated approach with one-time administration that provides potential for permanent disease correction. The mechanism of action is broadly applicable across a variety of disease states because the gene corrected HSPCs can address multiple organ systems. HSPC gene therapy has the ability to deliver proteins to the brain through the gene corrected HSPC's ability to naturally migrate across the blood brain barrier. And finally, clinical data in MLD, and other neuro metabolic disease, are demonstrating proof of concept that suggests applicability of this approach potentially in less rare diseases as well. And with that, I thank you for your time.

DR. BUTTERFIELD: Thank you very much. And let's see. So, thanks again and we now in this open session move on to see if there are people who did not register beforehand who wish to make up to a five-minute statement or comment. So again, any people who did not get registered?

DR. BERNS: Is it possible to ask a question?

MS. VERT: Dr. Berns, you can go ahead, just a clarifying question.

DR. BERNS: This is just a factual question, and that is from the speaker. Do we have a good fix on the persistence of transgene expression in the vectors that you're talking about? I thought the results over an extended period of time were very promising, but I just wondered if you'd looked specifically at the persistence of transgene expression.

DR. MELTZER: So, this approach leverages an integrating lentiviral vector, which is directly integrating into the genome. So, the design of the approach is intended for durable expression of the

transgene and maintenance of the transgene in the repository -- in the reservoir of hematopoietic stem cells.

DR. BERNS: Well, in some cases transgenes that get integrated still get turned off, and that's what I'm asking in this case. You don't think that happens here?

DR. MELTZER: So, the results that I showed previously are suggestive of durability out to up to eight years of follow up in our clinical study.

DR. BERNS: Thank you.

DR. BUTTERFIELD: Okay. Any other previously unregistered people who would like to make a statement or comment? So, hearing none, I will confirm, please, with Christina. Do we take a longer break to get us back on schedule?

MS. VERT: We should take a 15-minute break, and then we'll go right into the closed session. I want members to try to log on before the 15 minutes since it will take some time to set up the meeting.

So, the 15 minutes includes your logging on to the closed session.

DR. BUTTERFIELD: Terrific. Thank you very much, Christina. And this ends our open session and we move to break. Speak to you soon in the closed session. Thank you very much to all the speakers and participants.

DR. ROOS: Christina, we sign out of this?

MS. VERT: Yes. You sign out of this meeting, and you go to the closed session link.

DR. ROOS: Thank you.

DR. BUTTERFIELD: And also, the public should log off now. Thank you.

MS. VERT: Yes. The public should log off. The meeting has adjourned. Thanks everyone for coming to the meeting.

[OPEN SESSION ADJOURNED]