Food and Drug Administration

Center for Biologics Evaluation and Research (CBR)

Cellular, Tissue and Gene Therapies

Advisory Committee (CTGTAC)

September 7, 2016

OPEN SESSION

FDA White Oak Conference Center
Great Room, Salon B
Silver Spring, Maryland

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PROCEEDINGS

Agenda Item: Welcome, Call to Order and Roll Call, Timothy Cripe, MD, PhD, Chair

DR. CRIPE: I think we are still missing Dr. Byrne, but as long as you are okay with us proceeding at not the full complement of the committee.

DR. KIM: Yes.

DR. CRIPE: Hopefully he will dial in. So again, just to make sure everyone is on the right airplane, this is the CBER Cellular Tissue Gene Therapy Advisory Committee meeting teleconference number 66.

So I would like to welcome everybody and call the meeting to order. The goal of this meeting is to discuss the research programs in the Office of Cellular Tissue and Gene Therapies and the Gene Transfer and Immunogenicity Branch specifically, regarding a site visit we had earlier this year.

Before we get into the presentations that give us an overview of that office and the branch, our designated federal officer, which is Janie Kim, will make administrative remarks, read a conflict of interest statement, and then she will also take a roll call. Go ahead, Janie.

Agenda Item: Conflict of Interest Statement, Janie Kim, Pharm.D., Designated Federal Officer

DR. KIM: Thanks, Dr. Cripe.

Good morning, everyone. My name is Janie Kim. I'm the designated federal officer for this committee for today's meeting of the Cellular Tissue and Gene Therapies Advisory Committee meeting. Ms. Denise Royster is the committee management specialist, and we also have Joanne Lipkind, also committee management specialist, who will be assisting her today.

On behalf of the FDA and the Center for Biologics Evaluation and Research and the Office of Cellular Tissue and Gene Therapy, we would like to welcome everyone to this meeting. Members are participating today via the phone and also online. They can view what's going on in the room today, which is being telecast via the web.

Today's meeting will begin with a session that is open to the public, followed by an open public hearing session, both of which will be webcast live on the internet. If there are no comments from the public, the meeting will go to a closed session that will not be webcast. For the closed session, FDA staff being evaluated will leave the room and industry representative Dr. Dale Ando will also leave the call.

For those on the phone, please remember to identify yourself before you speak and to mute your phone when you are not speaking to minimize any background

noises. Participants in the room also are requested to state their name and to speak clearly and loudly into the microphone so that the transcriber and attendees on the phone are able to hear their comments.

We also caution everybody in the room today against discussing personnel actions or any other confidential information in this public forum. We would also like to remind everyone to please silence your cellphones and other devices.

I will now take roll and read the conflict of interest meeting statement.

So Dr. Cripe, if you could announce yourself and your professional affiliation, where you work currently.

DR. CRIPE: Tim Cripe. I am chief of heme/onc at Nationwide Children's Hospital, affiliated with Ohio State University in Columbus, Ohio.

DR. KIM: Dr. Ando?

DR. ANDO: Yes, this is Dale Ando. I'm the chief medical officer of Sangamo Biosciences in the Bay Area in California.

DR. KIM: Dr. Bartlett?

DR. BARTLETT: Dave Bartlett. I'm a surgical oncologist at the University of Pittsburgh.

DR. KIM: Dr. Byrnes? Still not on the phone.

DR. BYRNES: (No response.)

DR. KIM: Dr. Bollard?

DR. BOLLARD: Yes, it's Cath Bollard. I'm the division chief of allergy and immunology at Children's National and the George Washington University in Washington, D.C.

DR. KIM: Dr. Bugbee?

DR. BUGBEE: Hi, William Bugbee, I am at Scripps Clinic in La Jolla, California, chief of joint reconstruction and cartilage transplantation.

DR. KIM: Dr. Pluhar?

DR. PLUHAR: Hi, I'm Liz Pluhar. I am a professor at the College of Veterinary Medicine at the University of Minnesota and Minneapolis, Minnesota, and I'm director of the Canine Brain Tumor Clinical Trials Program here.

DR. KIM: Dr. Rose?

DR. ROSE: I'm Stephen Rose. I'm the chief research officer at the Foundation Fighting Blindness in Columbia, Maryland.

DR. KIM: Dr. Stegman?

DR. STEGMAN: This is John Stegman. I am a professor of biomedical engineering at the University of Michigan in Ann Arbor.

DR. KIM: Dr. Wittes?

DR. WITTES: This is Janet Wittes. I am the president of Statistics Collaborative in D.C., and I am a

statistician.

DR. KIM: And Dr. Zovein?

DR. ZOVEIN: Hi, this is Dr. Zovein. I am a physician scientist, professor at Cardiovascular Research Institute and also appointed in neonatology and pediatrics.

DR. KIM: Thank you. Now I will read the conflict of interest meeting statement.

The Food and Drug Administration, FDA, is convening today's meeting of the Cellular Tissue and Gene Therapies Advisory Committee under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and temporary voting members are special government employees or regular federal employees from other agencies and are subject to the federal conflict of interest laws and regulations.

The following information on the status of today's compliance with the federal ethics and conflict of interest laws covered by but not limited to 18 USC Section 208, is provided to participants in today's meeting and to the public. FDA has determined that members and temporary voting members of this committee are in compliance with all federal ethics and conflict of interest laws and regulations. This open session's agenda includes an overview of the research programs in the Gene Transfer and Immunogenicity Branch of the Division of Cellular and Gene

Therapies in the Office of Cellular Tissue and Gene Therapies at the Center for Biologics Evaluation and Research.

This overview is a non-particular matter and based on the agenda, it has been determined that the overview presents no actual or appearance of conflict of interest. In closed session, the committee will review and discuss the draft site visit report from the site visit concluded on May 19, 2016.

Dr. Dale Ando is serving as the industry representative, acting on behalf of all related industry. He is employed by Sangamo Biosciences. Industry representatives are not special government employees and do not vote. The conflict of interest statement will be available for review at the registration table.

This concludes the meeting statement.

Dr. Cripe, I now hand over the meeting to you so that you can introduce the next speaker.

DR. CRIPE: Thank you, Janie. Our first speaker is Carolyn Wilson, PhD, associate director for research from CBER.

So Carolyn, do you want to take over, please?

Agenda Item: Overview of CBER Research Program, Carolyn Wilson, Ph.D., Associate Director for Research, CBER

DR. WILSON: Yes, thank you, Dr. Cripe. I am ready.

So I am going to give you a quick overview about the Center for Biologics and then drill down into how we review and manage research, some of the new processes we have put in place as FYI for where we are going, recognizing that not all of the processes were in place during the four-year period that this group was reviewed for, but just wanted to make you aware, and I want to start by thanking both Dr. Cripe and Dr. Byrne who served as cochairs for the site visit team that came last May. This is a really important aspect of the membership on our advisory committees. We often do tap members of the committees to serve in this capacity, and we are really grateful when they do.

So next slide. So this is just to give you an overview of the types of products that we regulate here in the Center for Biologics, and obviously you are mostly familiar with cell and gene therapies and xenotransplantation products and probably the human tissues part of the portfolio, but we also regulate all blood and blood components and various derivatives, vaccines, both preventive and therapeutic, new areas like live biotherapeutics, which includes things like fecal transplantation, and allergenic products that include

actually over 1,300 different extracts that are used both for diagnosis and treatment of allergies. And then we also have oversight of various related devices.

We like to think of our research program as playing an integral part in the life cycle of product development, and we think of it as starting with the public health concern that usually drives the development of a novel product, and these novel products, especially as you know in the areas of cell and gene therapies, often pose regulatory challenges, because we don't always have the science available to help us assess the risks and the potential for benefits, and this is where regulatory science, through a combination of discovery research and targeted development of new tools, can play a role in helping to fill some of these scientific gaps.

As we understand the science better, we as a regulatory agency are in a better position to develop regulatory policy and support our science based decision-making and then hopefully at the end of the day we have better data from our sponsors that will allow us to make benefit risk decisions to license those products, to have a positive impact on the initial public health problem, but it doesn't stop there, and the post-market surveillance is a really critical component after products are licensed to ensure safety of these marketed products, and oftentimes we

often continue to gather efficacy data as well.

In Center for Biologics, we have what's called the researcher reviewer model, where about 20 percent of our staff are research scientists who perform their own original research, and it is investigator initiated, but they also have regulatory and review responsibilities, and what this means is it's not just that they are an occasional consult on a regulatory file but that they actually are spending up to 50 percent of their time doing all the same activities as a fulltime reviewer. This means reviewing regulatory submissions, going out on inspections, participating in organizing and presenting at advisory committees, workshops, writing guidance documents, and so on.

So because these scientists have one foot firmly in the research community going out to their scientific and professional meetings and one foot firmly within the regulatory component of the agency, it really helps to marry these two components into one person so that we can make sure we are addressing the most important problems with our research program. Reviewers often see across a whole class of products and can identify gaps that would help to move a whole class of products forward more rapidly.

So we do this by having a wide variety of

scientific expertise within the center. As you can see, we have a variety of important technologies that are helping us to understand how best to characterize the types of complex products we regulate. As you can imagine with our portfolio, microbiology pretty much every type, including working on transmissible spongiform encephalopathies. Immunology is critically important, biochemistry, molecular biology, cell and developmental biology, and a relatively new program in tissue engineering.

Epidemiology to support post-market surveillance, including development of new methods to do meta-analyses of large healthcare databases, and of course biostatistics, and we have also recently enhanced and grown a new group in bioinformatics.

So we don't do this alone. We actually collaborate across the country, as well as globally, and these maps that are from the 15 research reporting database show the types that we collaborate, not just across the United States but also globally. We do a lot of interactions with other regulatory authorities, with other standard setting organizations, and with the World Health Organization.

We do this through collaborations with academia, other government agencies, nonprofit organization, and with very careful oversight, at times we also collaborate with

industry.

So I am going to finish with a little bit of chat about some new things that are going on within the Center for Biologics. We stood up a peer mentoring group. One of the concerns that has come up repeatedly in a number of site visits is do we do enough mentoring of our younger scientists, and so because we are fairly thin, we decided that one way to address this is to do what's called peer mentoring.

So we have a monthly group that is open to any PI within the center, and we always make sure there's at least one senior PI who is there to oversee and participate and facilitate the discussion, and its open topics for whatever scientists would find useful to share in terms of a variety of different issues about how to manage a research program. We did move to the White Oak campus about two years ago, and then I'll also talk about this new research management process that we are standing up.

One of the -- two components that are very important are two new governance bodies that oversee setting up research priorities as well as budget and resource planning. So the regulatory science council has leadership from across the center that helps to develop center-level goals as well as oversee and approve office-level goals and objectives, and they also are the body that

will undertake a portfolio review at a higher level of the research program. Then the resource committee looks at annual budget and resource planning to determine how funds should be allocated to the offices. Both of these bodies are advisory to the center director and deputy.

This year, the regulatory science council adopted the following four regulatory science and research goals. The first is to advance the scientific basis for regulation of biologics, human tissues, and blood to enhance safety, effectiveness, quality, and consistency through development and evaluation of new concepts, methods, models, and reagents. Second is to develop and assess nonclinical models and methods with improved predictive value, and as feasible apply the three Rs to the use of animals for evaluation of safety and effectiveness of our products.

The third is to improve clinical evaluation of our products through use of new biomarkers, large healthcare datasets, innovative design and analysis, applying new statistical epidemiological and mathematical modeling approaches, and considering patient input to inform benefit risk assessment of general and special populations.

Finally, but very important, is also to be thinking about future regulatory and public health challenges through investments in emerging science and

technology and to develop and sustain varied scientific expertise.

So starting in FY2017, we are changing how we are reviewing our research programs on an annual basis. Twenty-five percent of research programs will undergo peer review. These are ongoing research programs, and the new project proposals would be reviewed. This way in every four-year cycle, we touch on every research program.

Then in addition, there is supervisory division and office level review of the annual research report, and that's done on an annual basis for all of the programs and projects, and then there's a portfolio level review by the regulatory science council.

In FY2017, we are doing a onetime look across the entire portfolio and then subsequent to that, we will be looking at one office per year. So again, we have four offices that have a research component. So that will be doing a portfolio look once -- we will get through the entire center over a four-year period. We developed a new research impact framework that can be used for all aspects of review.

Next slide. That's shown here. There are several elements that are more relevant to the portfolio management but can also be applied to some extent at the individual project and program level. And then there are things that

are clearly obviously important to evaluate at the project level. So the first is is the research aligning with center- or office-wide initiatives and priorities? Is the research building a world-class review capability, because as I mentioned our research scientists do participate in the review, and their expertise as research scientists is critically important to bring to the table in the review capacity, and does it also provide an agile set of internal capabilities to address unexpected urgent public health needs? Good examples from the last couple of years are Ebola and Zika where we have actually had to fairly quickly stand up internal research capacity in those areas.

Then on the individual project level, are we using our unique perspective as a regulatory agent to address the scientific gaps and questions that are important to fulfill our regulatory mission and obviously what underlies all of it is the scientific merit and feasibility and the PI's prior productivity.

So at the program level, the PI submits to the research reporting base on an annual basis an overview. There is a pulldown list for expertise so that there is common nomenclature used to collect that information. They have to also pick list their CBER goals and FDA priorities, listing staffing collaborators, lab space, major equipment, and other resources that they have, and then we also

collect there all publications, presentations; other output might include things like employee invention reports or patent applications.

At the project level, we collect how is it relevant to the specific office goal and objective. We get an executive summary and background for the project, and then the PI needs to speculate on how this is going to support review capability, what are the expected outcomes and impact, and then one to three specific aims under which each you provide an experimental approach and if it's an ongoing project, the progress and the plans for the next year, as well as they anticipated results.

We also collect there and keep track of a variety of different administrative information, like personnel working on the project, how much funds they are requesting, the relevant IBC applications, risk applications, ACUC, animal care and use committee, and a new element which is falling out of an OSTP mandate for all government agencies is to have a data management plan for all funded research.

So what we are talking about today is what happened in May, which is an external site visit where we bring in every four years a team of peer scientists who review at the lab or branch level a group of principal investigators. The output of that is the report which you will be reviewing in closed session, and that report goes

to the internal promotion, conversion, and evaluation committee, which is an internal peer review committee that does exactly what it says. Sometimes they are looking at promotions. Sometimes it is a conversion from temporary to permanent status.

So what you have before you today is the draft report that came out of the site visit team. The site visit team is essentially set up as a subcommittee to this advisory committee. So you have one of three options. You can review the report and approve it in its current form, or you can amend the report, or you can send it back to the original site visit team for additional changes. It is up to you to decide, depending on the discussion.

But I want to point out how important these reports are. As I mentioned already, they are part of a larger package for various personnel actions. The PIs obviously take this opportunity to get external expert input very seriously so that this is an opportunity to improve the direction and experimental design of their research program, and then management also takes these into account when thinking about resource allocation decisions or other issues. So as I mentioned already, you have three different outcomes of today's meeting.

So again, I just want to thank Dr. Cripe and Byrne for their participation as chair and cochair, as well

as the rest of the site visit team and to you today for your attention and interest and input into the final report, and just as a reminder, we don't discuss the final report, any of that, those particulars, in this open session, but there will be an opportunity to go through that in detail in the closed session.

So thank you, and I'm happy to answer any questions.

DR. CRIPE: Thanks, Dr. Wilson. I actually have a question. You mentioned that in fiscal year 2017, you were instituting a new peer review process. Is that separate from this process? Is that an internal process? Or did I misunderstand that?

DR. WILSON: No, thank you for asking. I wasn't clear. That is an internal peer review, and I do want to say that we have had an internal peer review of a portion of projects over at least the last 10 years, but this is a more systematic approach to doing peer review throughout the center, and it's an internal peer review. So it complements the external peer review. So we will continue our external site visits as well.

DR. CRIPE: Will the external site visits have access to those internal reports?

DR. WILSON: That is an excellent question. We haven't gotten through the first round of this. So I will

keep that in mind, and we are going to sort of do a big -- we are setting in place a lot of new processes that are carrying over from the end of 2016 into the 2017 cycle, and we are going to sort of stop mid-cycle in 2017 after we have gotten through everything once and reassess and think about how to improve things going forward, and that is certainly an interesting suggestion for us to keep in mind as we look at the output of the peer review.

DR. BYRNE: Hi, Tim, this is Barry Byrne. I was just going to maybe echo the comment that it was really useful in that it was a bidirectional exchange of information. So I hope that the site visit team was helpful to the internal group, because I thought certainly as a reviewer that I learned a lot about what was being done in the agency and particularly by this particular group.

DR. CRIPE: Great, thanks, Barry. Great to have you on. Any other questions about CBER, the CBER overview?

DR. WILSON: Okay, thank you.

DR. CRIPE: Great, thank you, Dr. Wilson.

Next up is Dr. Raj Puri, who is the director of the Division of Cellular and Gene Therapies, and he will give us an overview of the Office of Cellular, Tissue and Gene Therapy research programs.

Agenda Item: Overview of Office of Cellular, Tissue and Gene Therapies, Raj Puri, M.D., Ph.D., Director,

Division of Cellular and Gene Therapies

DR. PURI: Okay, good afternoon. I am Raj Puri. I am the director of the Cellular and Gene Therapies and the Office of Cell, Tissue, and Gene Therapy, but before I begin, I would like to thank the committee for your time and efforts in reviewing the research program in the Division of Cellular and Gene Therapies.

In my discussion, I will talk about the organizational structure of the Office of Cell Tissue and Gene Therapy, I'll talk about mission and activities, regulatory portfolio, and researcher reviewer model, and the summary of the site visit of the lab activities in Gene Transfer and Immunogenicity Branch will be provided to you by Dr. Andrew Byrnes.

In slide number three is a chart that lists that our office is headed by Dr. Celia Witten who is unfortunately not able to attend this afternoon, due to other urgent commitment. Dr. Witten has recently been selected as a deputy center director of CBER.

In this office we have three divisions, the Division of Cellular and Gene Therapy that I direct, and in collaboration with the Division of Clinical Evaluation and Pharm/Tox folks, we do all the premarket review of all the applications in the product area that we oversee are submitted to our office. Our colleagues in the Division of

Human Tissues are involved in human tissue safety for transplantation.

Slide four lists the organizational structure of the Division of Cell and Gene Therapies, DCGT. We have five branches. Branches on your left, Gene Therapies Branch and Cell Therapies Branch, are fulltime review branches where these colleagues perform the premarket review of all the applications, as well as they develop policy and guidance documents, and do a large amount of outreach effort with our stakeholders.

The colleagues in the remaining three branches on the right, these colleagues also do the same activity on those regulatory branches, but 50 percent of the time. The other 50 percent of the time, they spend in performing the mission relevant research supporting the medical product development submitted to FDA. The branch which is being reviewed here today is Gene Transfer and Immunogenicity Branch.

Slide five, the mission of our office is to ensure the safety, potency, and effectiveness of cell tissue and gene therapy products which are used for prevention, diagnosis, and treatment of human diseases.

Next slide is we regulate a plethora of products listed in this slide that includes cell therapy, including adult or embryonic or induced pluripotent stem cells,

cancer vaccines and immunotherapy products, gene therapies, tissue and tissue based products, xeno products, combination products where the cells and genes are combined with the device or the drugs. We also evaluate devices that are used to select cells and tissues and of course evaluate the donor screening test for tissue safety.

Slide number seven lists the trend of the submissions that we receive each year, and as you can see, that over the years the number of submissions in our product areas have been on the rise, and if you look at the last five years alone, the number of submissions has almost doubled in our office. Most submissions include cell therapy, followed by gene therapy, and other files.

Slide eight lists the -- so the number of submissions coming from commercial sources or research sources, research applications, that are predominantly coming from academic investigators, government investigators, and startup companies that requires significant effort, our staff's time spent in helping initiate the IND and further product development.

Slide nine lists the OCTGT activities that include the review and evaluation of the various product applications that includes BLA and their supplements. Our staff performs a large amount of pre-IND meetings with the sponsors, pre-pre-IND, pre-IDE, presub advice. We

participate in the inspection of the manufacturing facilities for compliance with applicable standards and other compliance activities including court cases. We develop policy and procedures governing the premarket review and evaluation of cell and gene therapy products, in keeping with the provisions of the Public Health Service Act and Food and Drug Cosmetic Act.

In slide 10, continuing listing of OCTGT activities, our staff develop FDA guidances for the regulation of our product areas. We provide consult and education to various CBER offices, FDA centers, government agencies, sponsors, and our staff participate in organizing and presenting at the advisory committee meetings.

We do a large amount of community outreach to professional societies and patient advocacy and the list is provided to you in my handout that lists all these activities that we do. Similarly, we have partnership with the standard determining organizations, NIH, and global regulatory authorities, and this list is also provided in additional slides in your handout. Our staff is involved in performing research to support the review and progress towards a safe and effective medical product development.

Slide 11, our staff in the Office of Cellular Tissue and Gene Therapy has been very prolific. In the last 4 years alone, they have published 13 guidance documents,

and the list is provided to you in additional slides, and these are important documents that include potency, cancer vaccine considerations, pharm/tox, early phase clinical trials, shedding studies, environmental assessment in gene therapy, cord blood guidance, cartilage guidance, adipose tissue, and minimal manipulation.

The research program as listed in slide 12 has three important goals, which have been recently refined. These goals are aligned with the center's goals, and the objective under these goals are provided to you in your handout in additional slides. The major goals include in research involving chemistry, manufacturing, controls, and assay development, lot release testing, identifying critical quality attributes that could be predictive of safety, effectiveness, and consistency of the product performance.

The second goal involves preclinical and clinical investigation, that includes animal models, pharm/tox model, proof of concept studies, and clinical study issues, and the goal of improving the safety and efficacy of our products. The third goal involves the safety issues related to human tissues.

Slide number 13 lists a variety of different projects, areas, general areas of research that our 13 principal investigators undertake in DCGT. Areas include

virology, immunology, cell and development biology, cancer biology and immunology, and we are very fortunate that we have expertise and equipment and knowhow in a variety of cutting edge areas of research that includes genomics, flow cytometry, proteomics, transgenics, tissue engineering, pyrosequencing, and whole genome sequencing.

Slide number 14 gives an example of a collaboration between seven principal investigators in the Division of Cellular and Gene Therapy, and this group of investigators chose a model cell type, MSC, which is a multipotent stromal cells, or another name is mesenchymal stem cells, and trying to characterize the various different biological characteristics of this cell type with the hope of relating the biological characteristic to the outcome, which is biological activities, potency, safety, and efficacy.

These investigators are listed in this slide dealing with the gene expression, proteomics, epigenetics, genomics, and various biological activities in vitro and in vivo models.

Now I will switch to some of the -- in explaining the researcher reviewer model that you heard from Dr. Wilson and providing the DCGT perspective that our product areas are diverse and rapidly evolving. They use new regulatory paradigms that are developing rather than

established. These products raise extraordinarily complex issues, and to address some of the scientific challenges and to understand the science behind it to be able to communicate that we seek to foster a cadre of researcher reviewer scientists who perform regulatory review, participate in the development of policy and guidance documents, they perform research in key areas to support the FDA mission, and help sponsors solve product development problems to advance the products to the marketplace.

We are not trying to reproduce industry, academia, or NIH expertise here. However, we need scientists in key areas that can engage in constructive and informed evaluation of files and productively interact with the industry and academia including their cutting edge scientists.

We have principal investigators; I indicated that we have 13 PIs in the division. They are tenured, or some of them are tenure track researcher reviewers. We have staff scientists, which are tenured researcher reviewers support the PI program. They do both research and review. We have technical staff do primarily research supporting PIs, some do limited amount of regulatory work.

We have staff fellows. We have Commissioner's Fellows. We have FDA, NCI, interagency oncology task force

fellows. They do review and research work. And we have postdoctoral fellows through the ORISE mechanism. They do primarily research, and the funding is provided to PIs and they are expected to lead and promote FDA mission relevant research program.

Slide 17 talks about responsibilities of PIs. They do product review of various regulatory pathways. They participate in inspection, and the regulatory mentoring for the reviews of PIs is provided there, branch chiefs, in addition to regulatory branch chiefs that we have in the division.

These PIs are involved in policy development, writing the guidance documents, advisory committee participation, and they do quite a bit of outreach effort and pre-submittal advice, scientific and regulatory talks, refereeing and editing for journals, chairing the scientific conferences, and do scientific collaboration. They are expected to manage their research program. They provide training and mentoring supervising, publishing papers, writing grants, expert peer reviewers or journal articles, and they are engaged into compliance and enforcement actions.

The budget for these PIs is provided. A core budget is provided from the division each year and in addition, too, all PIs have an opportunity to apply for

additional grants through the Office of Science and Health Coordination Office of the Commissioner, Chief Scientist Challenge Grants, and in the past they used to be, as you heard from Dr. Wilson, we used to have an additional mechanism of internal peer review in three different pathways of research proposal that PIs used to get additional funding for their program.

In addition, too, many DCGT PIs have been successful in obtaining grants from Department of Defense, from BARDA, and getting some funds from Cooperative Research Development Agreements and royalties from their patents.

As you heard from Dr. Wilson, the research program is managed and there are quite a few new processes, but in the past, we looked at the productivity and alignment with our office's goals. Every two to three years, Dr. Sue Epstein, who is the associate director of research in our office, she does horizon scanning, getting the input from our medical officers, pharm/tox reviewers, product reviewers, regulatory folks, and researcher reviewers to identify the new areas of hopefully developing a new program in the future.

We track outside resources our PIs received and you heard already that each PI is expected to provide their -- some meet at the CBER research center, their annual

report, and providing their research goals and the progress of the research, and some of them refocus and adjust their ongoing research program.

Slide 20 talks about the mentoring of PIs and you heard about it in detail from Dr. Wilson. We also get, in addition to input from the PCE you heard an advisory committee and site visit, we have also gotten advice and review of our research program under the umbrella of office of commissioners, CERSI program, which is Center for Excellence in Regulatory Science Initiative. We brought experts, the world's expert in the area of MSC to get input in MSC consortium projects. I would also like to mention, in addition to what you heard before from Dr. Wilson, that each staff in the DCGT undergoes a cyclical review every five years.

Slide 21 lists the review of the productivity of each PI and how we allocate the division resources, and we have been doing this for the past more than a decade, where Dr. Epstein has been collecting information from each PI, their scientific publication in the peer review journal, their impact factor, their authorship role, their regulatory workload and quality, and the review articles, regulatory articles, any patents, patents files, any invited presentations, and recognition by peers.

We look at all of this in coming up with the

numbers to reward high performers, medium performers, and low performers for additional small amounts of funding that the DCGT gives out to the PIs.

My last slide, slide 22, I would like to thank Dr. Celia Witten and Dr. Epstein for support and the entire staff in the Division of Cell and Gene Therapy for their outstanding health work in promoting and protecting public health and I would like to thank you for providing your insights. Your input is critical to fulfilling our regulatory mission at the FDA. I would like to stop here and if you have any questions, I would be happy to answer.

DR. CRIPE: Thank you, Dr. Puri. We will open it to questions. I'm going to start again. I noticed on your slide that the scientists are eligible to apply for Department of Defense funding but my recollection is you can't apply for NIH funding. Can you confirm that's true and why the difference?

DR. PURI: Yes, confirming yes.

DR. WILSON: The difference is a congressional restriction on applying for another DHHS agency. Because DoD isn't DHHS, we can apply for their grants. We're not eligible for all of their grant programs, but certain ones.

DR. CRIPE: Okay, thanks. Any other questions from other committee members for Dr. Puri?

DR. ROSE: Yeah, Steve Rose. I may have missed it

and I apologize if I did, but in looking at slide number 4, which is the DCGT structure, can you explain the difference between Gene Therapies Branch and the Gene Transfer and Immunogenicity Branch, and then the Cell Therapies Branch and the Cellular and Tissue Therapy Branch? What is the overlap and what's the distinction?

DR. PURI: The main distinction is that in Gene Therapy Branch, we have fulltime review scientists. They do not do any research. In Gene Transfer Immunogenicity Branch, we have researcher reviewer, that model I described. These folks do 50 percent of the time of the regulatory activities as well and the other 50 percent they spend in research.

The regulatory activities take the precedence over the other activities. So when we have applications are submitted at the time, each PI and staff in their branches are expected to meet those PDUFA Prescription Drug User Fee Act timelines and with remaining time, they continue their research.

Similarly, in the Cell Therapy Branch, we have a regulatory scientist. They do not do research but in Cell and Tissue Therapy Branch, we have scientists who do both research and regulatory. That's the key difference between the two.

DR. ROSE: What is the interaction between them

because obviously the Gene Therapies Branch, I would guess, has some information that could be useful for the Gene Transfer and Immunogenicity Branch, the same thing with the cell.

DR. PURI: Yes. So there is quite a bit of interaction between these branches. We will start from every two weeks, the Division of Cell and Gene Therapy holds a regulatory meeting. They spend two hours going over all the regulatory submissions during that time period. That includes pre-IND, pre-pre-INDs, any BLAs or any end of phase II or phase III three submissions.

In addition, too, we invite speakers from outside who are within the FDA. We talk about specific areas. For example, in manufacturing and quality testing, and et cetera. In addition to that, all the reviews that are being done from Gene Transfer Immunogenicity Branch and Cell and Tissue Therapy Branch, which our research regulatory branch is, the reviews are looked at by their immediate branch chief, in Gene Transfer and Immunogenicity Branch, by Dr. Andrew Byrnes.

And then for the consistency of all of the reviews, the final signoff is by the branch chief in gene therapy branch. So any IND or applications other than INDs, such as IDE, 510(K)s, pre-BLA reviews, they are reviewed by Andrew, plus they are finally reviewed by Denise Gavin. So

that ensures the consistency for review as well as the comments that we provide, and guidance, that we provide to our sponsors.

In addition to that, we have branch chief meetings. So every two weeks, very cross-cutting discussions. In addition, too, we have a working group, cell therapy working group, gene therapy working group, they get together, focused area of expertise, and folks who are reviewing cell therapy, they all get together and interact significantly with each other and cross communication of ideas and expertise. Dr. Epstein would like to add additional things here.

DR. EPSTEIN: Just to add that the full time review staffer is always invited to the research work in progress talks and to the site visit rehearsals and other events where they can learn more about the research, the impacts, series of presentations, and they can provide input to those speakers.

DR. CRIPE: Other questions for Dr. Puri?

(No response.)

I don't hear any, so thank you, Dr. Puri.

We will move on to our next speaker, Dr. Byrnes, who is the chief of the Gene Transfer and Immunogenicity Branch and will give us a summary of that branch.

Agenda Item: Summary of Gene Transfer and

Immunogenicity Branch (GTIB) Research Programs, Andrew Byrnes, Ph.D., Chief, GTIB, OCTGT, CBER

DR. BYRNES: All right, good afternoon, everybody. I would like to start by thanking the advisory committee and also the site visit committee for their feedback. We are really looking forward to it. It's always extremely helpful in improving the quality of our research programs. So we value it highly.

Listed here are the three labs that were under review. My lab, where Zhili Xu is also a visiting associate, Suzanne Epstein's lab, where Graeme Price is a staff scientist, and Jakob Reiser's lab. So this afternoon I'm just going to give you a bit of overview about the branch in general and then very briefly go through each of the three labs just to give you an idea of what we do and why it's important to the FDA and then at the end, we'll all be available for questions if anybody has any particular specialized questions.

So on slide 2, just a reminder that everybody in this branch that is being reviewed today is a researcher regulator. We do both laboratory work and regulatory work. We review manufacturing and testing of both gene therapies and cell therapies, and this includes an increasing number of late phase clinical trials in both gene therapy and cell therapy. In addition, we are involved in policy and

guidance development, as you heard from Dr. Puri, and also outreach to professional societies.

On slide 3, our research and our branch is focused on gene therapy, virology, and immunology, and the mission relevance is to try to improve product safety and efficacy, try to develop new ways of characterizing these extremely complicated products, developing better preclinical animal models is a big effort, and also FDA and HHS have overarching priorities for certain issues such as pandemic influenza as one example.

These are the three branches. We all work on different viral systems. These are the three labs within the branch. I just wanted to, on slide 5, mention that we've expanded recently just within the past few months. We have two new labs. We have recruited two new PIs from outside the FDA, outside the government.

The first is Nirjal Bhattarai who will be studying viral manipulation of T cell signaling. This is very relevant to the large number of T cell products that we are regulating currently. He joined us from the University of Iowa. And then Zhaohui Ye, who is joining us from Johns Hopkins University, is working on development of hematopoietic cells from induced pluripotent stem cells as well as gene editing. Both of these, again, are very up and coming topics in the products that we're receiving in IND

form.

I wanted to expand a little bit on mentoring for new PIs. You heard a little bit about that already. Within our branch, we have mentoring of new PIs by both the branch chief, myself, and the OCTGT ADR, Dr. Epstein. Regulatory review mentoring by the branch chief and others, including Denise Gavin, for example, the branch chief of the Gene Therapies Branch.

In addition, each new PI is paired with an independent, experienced mentor PI, either from within the FDA or from outside the agency. This is to give them some independent advice and feedback on both their research and on administrative issues. There is also the new informal monthly CBER PI peer group that Dr. Wilson mentioned earlier. Also, starting in October, we are going to have a series of six lecture-based trainings for new PIs in lab management. These topics include how to manage projects, how to hire good people, publications, presentations, topics like that, lab budget management.

All right, so I'm going to start by telling you a bit about Dr. Epstein's program and again, we are on slide 7 now, Dr. Price is a staff scientist in Dr. Epstein's lab and I will be pointing out the work that he contributed to, as well.

Slide eight now. As you all are aware, influenza

is a very serious public health problem, both the seasonal influenza strains but also a special concern about emerging strains or pandemic strains. Even with the seasonal influenza strains, the strain match vaccine may be delayed or insufficient because of shortages of manufacturing or difficulties of manufacturing. As you also know, you have to predict the strain that is going to be needed for the vaccine a long time in advance. Unexpected drift or shift in the strains that are circulating can means that the vaccine is no longer a good match.

So for all these reasons, there is a lot of interest in developing universal influenza vaccines that have wider protection than just a single strain. So the Epstein lab has been working on that for a long time and they primarily work in animals showing protection with vaccines that express conserved influenza proteins. These vaccines are based on plasmids and adenoviruses mainly, but also on adeno-associated virus vectors.

I'll go through three research projects that the Epstein lab has been doing recently, two of them in animals. One of them is whether universal influenza vaccines of the type that they work on can protect elderly mice. This is a big issue because in the elderly, influenza is often more severe than in other populations, but also in the elderly, vaccines may not work as well. So it is an

important question whether these universal influenza vaccines can protect the elderly.

The second question is whether these vaccines not only protect the recipient, which they have shown already, but whether they can inhibit transmission of influenza and possibly inhibit spread within the population.

The final topic that I am going to talk about is whether there is pre-existing cross-protective immunity in the human population against new strains of influenza. This took advantage of the H1N1 pandemic outbreak in 2009 to do a prospective study looking at whether the population already had some pre-existing protective immunity against H1N1.

The relevance to CBER's public health mission, as I mentioned, the CBER and FDA and HHS in general are very interested in control of epidemic and pandemic influenza from both a public health perspective and a counter-bioterrorism perspective, but just within our own office, we have a great many products that are based on adenovirus and plasmids where many of the same issues arise. We need to understand immune responses to these products, whether they are used as vaccines or gene therapies or oncolytic viruses. It's all very important in how we regulate them and how we make sure that they are safe and effective.

So on slide 10 now, this is the study that was

recently published by the Epstein lab on protection by universal influenza vaccines in elderly mice. So in this study, they used two vaccines based on adenoviruses, one expressing influenza nucleoprotein, the other expressing influenza M2 protein, and found that they protect elderly mice from lethal influenza infections. So elderly is 20 months old. The mice were primed and boosted and then challenged at 22 months.

On the left is morbidity as measured by body weight, and on the right is mortality. You can see in the filled in circles, the dark circles, a combination of both of the NP and the M2 vaccines was effective at protecting mice from a lethal influenza challenge, more effective than each of the vaccines individually. So this shows that these types of vaccines can be effective in elderly mice.

On slide 11, the question is whether these vaccines protect against, can impact transmission of the virus. Graeme Price was the primary driver of this work and he developed a new assay to look at transmission of influenza within mice. So on the left, you can see the red mice. These are mice that have been vaccinated with the universal influenza vaccine and then infected with influenza. One day later, the mice are placed in cages with naive contact mice that have never been vaccinated, the white mice, and then three days later, all of the mice are

sacrificed and then collected tissues to determine whether the uninfected mice have become infected or not, to look at whether the vaccine was effective at reducing the spread from the red mice to the white mice.

The finding was very strong, that the universal vaccines, the same NP and M2 vaccines reduce transmission of influenza from infected mice to naive contacts. So not only are these vaccines protecting the recipients, but they are protecting the contacts as well. This is important because these vaccines don't provide sterilizing immunity. Mice that have been vaccinated with these vaccines can still become infected with influenza, but they seem to shed a bit less virus and transmission is greatly reduced.

In unpublished work down at the bottom of this slide 11, Graeme Price has done some recent work on the mechanism and found interestingly enough that antibodies in the vaccinated animals are not required for reduction of transmission. Cellular immunity, T cell immunity, is sufficient. So T cells in the vaccinated animals are not only for protecting the animals themselves, but they are also reducing transmission of the virus to new contact animals.

On slide 12 is the human study that I mentioned that took advantage of the 2009 H1N1 pandemic to ask the question whether, if people have been exposed to influenza

previously, whether they have some degree of T cell immunity in particular that might protect them against subsequent strains of influenza even if they've never seen those strains before.

So this is an example of a very comprehensive look at different T cell reactivity against different influenza antigens. This is before the pandemic hit and then as it turned out, the pandemic was fairly limited. So only a few people got infected in this study. It was too limited to draw statistical conclusions about whether this pre-existing immunity protected against the virus or not.

Even so, there were some novel observations, including about the antibody responses that happened after an infection, and a new T cell marker of infection that was identified. So this work is currently being written up for publication.

So in sum, on slide 13, these universal influenza vaccines have broad public health implications. They can provide cross-protective immunity that might be useful early in an outbreak before match vaccine strains, the traditional influenza virus, before those are available. They have the potential to reduce not just illness and death but also viral titers and the spread of the infection within the population. Perhaps someday they could even be used routinely, probably as an add-on to the traditional

influenza vaccine.

All right, now, on slide 14, we are going to move to Jakob Reiser's research program. He worked on safety-enhanced lentiviral vectors for gene therapy. Lentiviral vectors are a big class of products that we regulate here at our division.

So his background, the goal of the Reiser lab is to develop safer vectors by two aspects. One is by narrowing the vector's tissue tropism, so controlling what receptors the vectors bind to. The second is once the vector has gotten into the cell, to control how the vector integrates, where it integrates into the genome, and to try and target that to make safer and more effective products.

We are going to focus first on narrowing the vector's tissue tropism. The approach that Dr. Reiser has taken is to pseudotype these lentiviral vectors with H and F proteins from paramyxovirus. So measles virus and tupaia paramyxovirus. The receptor binding of these viruses is fairly well understood. You can mutate the H protein so that it no longer binds to the normal receptors and then you can add on various tags to try and change the tropism of the vector to bind to new receptors.

So on slide 17, we have an example of how this is done. Dr. Reiser's lab has targeted both the IL-13 receptor alpha 2 and the EGF receptor. Both of these receptors are

expressed on certain types of tumors, and it will be very useful to have lentiviral vectors that could specifically target tumors that express these proteins.

So we have receptor-blind H proteins that can be modified in a couple different ways. One is by putting protein ligands on them. So the IL-13 protein itself or the EGF protein will target their respective receptors. The other way of doing this is to use RNA aptamers. These aptamers can be evolved to have very high affinity against various proteins. So the Reiser lab has taken an EGF receptor aptamer that binds to the EGF receptor and figured out how to attach this RNA to the H protein and retarget the vector to cells that are EGF receptor-positive.

On slide 18, the other aspect of the Reiser lab's research is to look at how to target vector integration to specific sites in the chromosome. So their approach is to use integrase-defective lentiviral vectors with homology arms that have DNA that will target it to specific sites. In the case of these examples, the AAVS1 safe harbor locus where AAV integrates is being used as the target. This is thought to be a safe site for DNA integration.

So the Reiser lab is combining site-specific nucleases with homology-directed repair to try and improve the efficiency of editing of these sites. In some cases, these nucleases cleave the DNA entirely. In some cases,

they may just make a single strand.

Here on 19 in cartoon form is the illustration of how this works. You need two vectors. One vector, the donor vector, has the donor sequences including homology arms and whatever sequence you wish to integrate. If you just use this donor vector by itself, the process is extremely inefficient because there is no integrase. The vector doesn't integrate well in either, to the target site or anywhere else for that matter.

However, if you combine this with a vector that expresses a site-specific nuclease that is specific for the AAVS1 locus, this can greatly enhance the efficiency by bringing in the cellular DNA repair machinery. So when the nuclease targets that specific locus, the repair machinery comes in and that increases the efficiency of homology-directed repair. So the Reiser lab is working to try to improve the efficiency of this process. They are using novel nucleases to try to do that and also to try to improve the safety of the process by making sure it integrates in the correct location.

So future plans from the Reiser lab, to design improved strategies to target both the IL-13R alpha 2 and the EGF receptor and do this by high-affinity aptamers and also by evolving vector variants that have higher targeting to either of these receptors. This will be done both in

vitro and in vivo, in vivo using mouse models of human lung cancer. Then the other aspect of the work, again, is to design safer strategies for genome editing using site-specific recombinases, new strategies with novel recombinases.

Then finally, for my lab, Dr. Zhili Xu is a visiting associate at my lab and I will be pointing out the work that he was involved in as well.

So my lab, on slide 22, we focus on adenovirus vectors. This is an extremely popular vector in clinical trials. We have a large number of active INDs in our division, about 60 gene therapies and oncolytic adenoviruses. Almost all of these are based on serotype 5. So most of our research today has been done on serotype 5, but the field is gradually expanding to other serotypes and we are as well in response to that, expanding to other serotypes as well.

Over in the Office of Vaccines, there are about 40 adenovirus-based vaccines, mostly vector vaccines against other infectious diseases. So this is very active area of research of both Office of Vaccines and in our office.

On slide 23, so our focus in our lab is on systemic delivery of gene therapy with adenovirus vectors. We use rodent models, non-replicating adenovirus 5 vectors.

So our question is what happens when you inject these intravenously? Where do these vectors go? What types of tissues do they transduce and why? What receptors do they use?

The potential of this systemic delivery is that you could deliver the vector, in theory, to any organ or tumor. However, the reality is that these vectors have very poor pharmacokinetics. They are cleared extremely rapidly from the circulation and there is toxicity as well because of activation of the innate immune system, primarily, and the liver in particular is a target for that. So we have been studying the liver for quite a while now.

So on slide 24, here is a diagram of the liver and the cells that we study. We have been studying clearance of the vector by Kupffer cells for quite a few years and trying to understand the receptors that are used for that. Kupffer cells are macrophages that clear very large amounts of adenovirus vectors.

Adenovirus vectors also transduce hepatocytes extremely efficiently and we are trying to understand what receptors are used and the mechanisms for that for two reasons. One is to be able to manipulate it and try to either decrease or increase targeting hepatocytes and the other is to try to avoid hepatocytes if we can with certain vectors.

What we're finding is that the receptors for the adenovirus turn out not to be so important for this process for either targeting Kupffer cells or hepatocytes. It turns out that what is important is when you inject things intravenously, they immediately get coated by all sorts of plasma proteins and that really controls the tropism of the vector.

So the importance of our research is how to improve vector biodistribution for both safety and efficacy reasons, try to understand how hepatotoxicity occurs, and also to try and understand how accurate these rodent models really are for predicting humans, whether there are differences in the proteins that opsonize the bars between humans and mice and how that might affect the predictive power of the mouse model.

Here are some examples on slide 25 of plasma proteins that opsonize adenovirus. One worth pointing out is coagulation factor X. Interestingly enough, the virus hexon protein, which is in purple here, has very high-affinity binding to coagulation factor X. So as soon as you inject it intravenously, the virus gets immediately coated by coagulation factor X. In addition, other proteins of the innate immune system, immune globulin M, complements of proteins interact with the virus as well and this can have a big impact on the tropism of the virus.

On slide 26, some work that Zhili Xu led on coagulation factor X and its importance in the tropism of the virus. What we found is that coagulation factor X shields the virus from natural IGM antibodies and from the complement system. So the way this works is the virus becomes coated with factor X and this acts as a shield against the antibodies and complement. This has a very large impact on liver transduction. When the shield is absent, so when the virus is not able to bind to factor X, the vector becomes very poor at transducing the liver.

So our ongoing and future work, on slide 27, as I mentioned earlier, we are moving beyond Ad5 to study other Ad serotypes. We are finding that factor X doesn't bind to all Ad serotypes and that when it does, factor X doesn't affect all the Ad serotypes the same way it does Ad5. So this is quite interesting. There is a large number of different serotypes and it is giving us a lot of interesting tools to work with.

In the long run, the goal is to be able for us or for others to be able to design vectors that have tailored interactions with plasma opsonins and allow us to better control where the vector goes and target it. We are studying additional coagulation factors besides factor X. Factor X is not the only coagulation factor that interacts with viruses.

We are also studying how mouse studies relate to humans. So for example, we are finding that human and mouse coagulation factors don't always bind the same way to all vectors. They have different affinities and we are also studying both mouse serum and human serum to compare how they neutralize the vector and how coagulation factors can protect the vectors.

All right, so that concludes the talk and I will be happy to take any questions or direct any questions to any of the other people that are under review today.

DR. CRIPE: Thank you, Dr. Byrnes. Any questions?

DR. ROSE: Yes, Steve Rose again. I'm interested in -- I don't see adeno-associated virus on your list. Is that not something you are looking at?

DR. BYRNES: So Dr. Epstein has done some work on AAV vaccines and Dr. Reiser also has a small research program that he is starting on AAV vaccines, but it's not a focus of any of our programs right now, but I'll let Dr. Epstein talk.

DR. EPSTEIN: I will just add one point, that in the future plans presented to the committee, in the report we proposed an additional project that included some AAV vectors from Jay Chiorini's lab at NIH that we looked at for impact on the lungs.

DR. ROSE: So this is the research and review

branch. Am I remembering correctly?

DR. BYRNES: That is correct.

DR. ROSE: So when an AAV IND comes in, is that strict -- who covers that from the vectorology point of view?

DR. BYRNES: Well, we don't have enough positions to have research programs in every possible vector, and we use -- many of us have general background educations as virologists and are able to cover a number of systems. So I review adenovirus vectors, I review herpes vectors, AAV vectors, I review cell therapy, so we have some general expertise. We do have a lot of AAV vectors in our portfolio. Also, Denise Gavin trained with Jude Samulski so she has particular expertise in AAV vectors.

DR. ROSE: That's fine, I just didn't see them listed and was just confused. Thanks.

DR. CRIPE: Other questions?

DR. ZOVEIN: Hi, this is Ann Zovein. I just had a quick question. A lot of the focus on targeting is therapeutic which is great, but I was just curious how the different groups look at off-target effects of some of the vectors that they're engineering.

DR. BYRNES: So in my own research program, Kupffer cell uptake would be an example of off-targeting because that's undesirable. The vector that ends up in

Kupffer cells is essentially wasted, and that can contribute to the inflammatory response. Dr. Reiser is also interested in off-targeting in a different sense. How efficiently can you integrate into one specific area of the chromosome and direct it to that area and not to others?

As I mentioned, also in the new research program, Zhaohui Ye has been studying off-targeting effects of CRISPR/CAS nucleases and other types of nucleases as well. So he has some expertise in that as well and will continue in that type of research.

DR. ZOVEIN: Then how are those measured? Do you guys have access -- I assume you have to do a lot of sort of downstream sequencing of different cell types and stuff to look at some of these either abnormal integration or abnormal cellular uptake. Are those resources readily available or is there some sort of plan to integrate that into some of the work?

DR. BYRNES: Yes, our biotechnology core here has deep sequencing apparatus available and people also use commercial services as well.

DR. WILSON: I just wanted to add to that, if I might, that in addition to the actual physical sequencing capability with Illumina HiSeq and MiSeq, we also have developed a core bioinformatics group that uses highly parallelized computational analysis to allow for evaluation

of next gen sequencing data.

DR. CRIPE: Thanks, Dr. Wilson.

Other questions from the committee?

(No response.)

Hearing none, the next thing on the agenda is supposed to be an open public hearing. As prior to this meeting, we didn't have anyone registered to speak. I assume there is no one in the room there that wants to come forward. I guess we can ask for anyone who would like to, might have dialed in from the public that has questions or wants to make a comment.

Agenda Item: Open Public Hearing

DR. KIM: We had no walk-ins for the OPH sessions.

DR. CRIPE: Great. So that will then conclude the open session of this meeting. We now move to a closed session. So committee members, don't hang up, but I believe that there will be some shifting of personnel in the room there.

DR. KIM: Yes, we are going to be taking a five-minute break so that we can clear the room and allow Dr. Ando to exit the call. Thank you for participating, Dr. Ando.

(Whereupon, at 2:20 p.m., the open session was adjourned, to reconvene in closed session at 2:30 p.m.)