FOOD AND DRUG ADMINISTRATION (FDA)
Center for Biologics Evaluation and Research (CBER)
122nd Blood Products Advisory Committee (BPAC) Meeting

OPEN SESSION

Web-Conference

November 4, 2021

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

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Rachael F. Anatol, Ph.D.	Food and Drug Administration
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OPENING REMARKS: CALL TO ORDER AND WELCOME

MR. MICHAEL KAWCZYNSKI: Good morning and welcome to the 122nd meeting of the Blood Products Advisory Committee, BPAC. I'm Mike Kawczynski, and I will be help moderating today's meeting. Along with me is Dr. Richard Kaufman, who is today's chair. Just know periodically, you know, our job is to keep this meeting live. We are live, so if at any times we have any unexpected audio issues or any technical issues at all, you may see me jump in and assist our members at that time. So let's have a great meeting and, Dr. Kaufman, are you ready to start?

DR. RICHARD KAUFMAN: Yes, I am. Thanks.

MR. MICHAEL KAWCZYNSKI: All right. And just a reminder to all my members, let's make sure you keep yourselves muted when you are not speaking so we don't disrupt any of the others. So, all right, Dr. Kaufman, take it away.

DR. RICHARD KAUFMAN: It's my pleasure to welcome everyone to today's meeting. The members, both

returning members and we have some new members as well to BPAC -- as well as our participants from FDA and anyone from the public who may be viewing this remotely. I would just like to remind the Committee members and participants to use the raise your hand feature on the system. So if you have a question or comment to make -- and then I can call on you to speak. So for today's meeting we will be reviewing three research programs that take place within CBER.

So FDA's tasked with regulating a wide range of different biomedical activities that are always changing and advancing. And in order to complement the regulatory work that they do, various offices within CBER maintain basic and translational research programs that are meant to align with their regulatory mission. So, as I mentioned, we'll be reviewing three such programs today, and each of these underwent detailed external review earlier in the year. And so I would like to at this time hand the meeting over to Christina Vert for administrative announcements, rollcall, and Conflict of Interest statement.

ADMINISTRATIVE ANNOUNCEMENTS, ROLL CALL, AND CONFLICT OF INTEREST STATEMENT

MS. CHRISTINA VERT: Thank you, Dr. Kaufman. My name is Christina Vert, and it is my pleasure to serve as the Designated Federal Officer for today's 122nd BPAC Meeting. On behalf of the FDA, the Center For Biologics Evaluation and Research, and the Committee I would like to welcome everyone to today's virtual meeting. The meeting for today will be to hear an overview of the research programs of the Plasma Derivatives Branch, Laboratory of Cellular Hematology, and the Laboratory of Emerging Pathogens. Today's meeting topic was described in the federal register notice that was published on September 13th, 2021.

I would now like to acknowledge the contribution of a few other members of the Division of Scientific Advisors and Consultants, including our director, Dr. Prabha Atreya, Ms. Joanne Lipkind, Ms. Karen Thomas, and Ms. Kathleen Hayes who have assisted

in preparing for this meeting. I would also like to express my many thanks to Mr. Mike Kawczynski for facilitating the meeting today.

For any media or press-related questions, you may contact FDAs Office of Media Affairs at FDAOMA@FDA.hhs.gov. The transcriptionist for today's meeting is Ms. Linda Giles and Ms. Erica Denham. We will begin today's meeting by taking a roll call of the Committee members. When it is your turn, please turn on your video camera and unmute your phone, then state your first and last name, your expertise, and your organization. And when finished, please turn your camera off, and we will proceed to the next person. We will begin the roll call with the chair, Dr. Richard Kaufman. Dr. Kaufman, please go ahead and introduce yourself.

DR. RICHARD KAUFMAN: Hi, I'm Richard Kaufman. I'm the medical director for the Transfusion Service at the Brigham and Women's Hospital. And I'll be chairing the BPAC Meeting today.

MS. CHRISTINA VERT: Thank you. Dr. Marc

Ballow.

DR. MARC BALLOW: Good morning. I'm Marc Ballow. I'm at University of South Florida and also Children's Hospital in St. Petersburg. I'm an allergist, immunologist (audio skip) with a special interest in immunoglobulin replacement products.

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

DR. SRIDHAR BASAVARAJU: Hi, I'm Sridhar Basavaraju. I'm the Director of the CDC Office of Blood, Organ, and Other Tissue Safety.

MS. CHRISTINA VERT: Thank you. Dr. Bloch. Are you muted? That's great, go ahead.

DR. EVAN BLOCH: I'm Evan Bloch. I'm Associate Director of Transfusion Medicine at Johns Hopkins Hospital and Director of Apheresis.

MS. CHRISTINA VERT: Thank you.

DR. EVAN BLOCH: Thanks.

MS. CHRISTINA VERT: Dr. Cumming or Ms. Cumming.

MS. MELISSA CUMMING: Good morning. My name's

Melissa Cumming. I am a senior epidemiologist with Massachusetts Department of Public Health, and I currently oversee our healthcare associated infections and antibiotic resistance program along with our hemovigilance program.

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

DR. BRENDA GROSSMAN: Hi, I'm Brenda Grossman. I'm the Medical Director of the transfusion service at Barnes-Jewish Hospital, Washington University in St. Louis.

MS. CHRISTINA VERT: Thank you. Dr. Marques. Oh, you're muted. Oh, okay. Well, we'll move along. Dr. Perez. That's okay.

DR. ELENA PEREZ: Hi, good morning. I'm Dr. Elena Perez. I'm a clinical allergy and immunologist with an interest in immune deficiency and immunoglobulin products. Thank you.

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

DR. JEREMY PERKINS: Allergist at Walter Reed --

MS. CHRISTINA VERT: You're good.

DR. JEREMY PERKINS: Thank you for turning on my microphone. Jeremy Perkins, I'm a hematologist/oncologist at Walter Reed National Military Medical Center. I'm the DOD representative of this Committee with clinical focus and a lot of experience on operational transfusion medicine.

MS. CHRISTINA VERT: Thank you. Dr. Rossman. We can't hear you. Oh, you were muted.

DR. SUSAN ROSSMAN: Now?

MS. CHRISTINA VERT: That's good. Go ahead.

DR. SUSAN ROSSMAN: Okay. I'm the Chief Medical Officer at Gulf Coast Regional Blood Center in Houston and representing a variety of interested industries related to BPAC. By training I'm a pathologist with interest in transfusion medicine.

MS. CHRISTINA VERT: Thank you. Dr. Shapiro. Go ahead.

DR. AMY SHAPIRO: I'm Amy Shapiro. I'm a pediatric hematologist. I'm CEO and Medical Director of the Indiana Hemophilia and Thrombosis Center. My interest and background is in clinical hemostasis and

thrombosis.

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

DR. ABDUS WAHED: Hello, this is Abdus Wahed. I am a biostatistician. I am an associate in the biostatistics department at the University of Pittsburgh.

MS. CHRISTINA VERT: Thank you. All right. Does anyone else want to do roll call? Okay. But let's go to the TVMs, yes. Dr. Baker.

DR. JUDITH BAKER: Hi, good morning. My name is Judith Baker. I'm the Director of Public Health with the Center for Inherited Blood Disorders in Orange, California. I'm serving as the consumer representative for this meeting, and my areas of expertise are public health matters as they relate to rare blood disorders.

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

DR. ALFRED DEMARIA, JR.: Good morning. I'm Al DeMaria, formerly state epidemiologist and medical director of the Bureau of Infectious Disease and Laboratory Science at the Massachusetts Department of

Public Health, currently Medical and Laboratory Consultant. And my background is in infectious disease and public health.

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

DR. JACK STAPLETON: Hi, I'm Jack Stapleton. I'm a professor of internal medicine, infectious diseases, and microbiology and immunology at the University of Iowa. My area of work is clinical HIV and virology of several virus now, now including SARS-CoV-2.

MS. CHRISTINA VERT: Thank you. Thank you for your introductions. I would now like to acknowledge CBER leadership and management, including Dr. Marks, Dr. Witten, Dr. Elkins, Dr. Bryan, Dr. Anatol, Dr. Epstein, Dr. Kimchi-Sarfaty, Dr. Golding, Dr. Farshid, Dr. Verdun, Dr. Eder, and Dr. Chintamani Atreya, Dr. Illoh, Dr. Paul, Dr. Nakhasi, and Dr. Hobson, some of whom will be joining the meeting later today and others who will be providing overview presentations shortly.

Before we begin with reading the Conflict of

Interest statement, I would just like to briefly mention a few housekeeping items related to today's virtual meeting format. For member speakers, FDA staff, and anyone else joining us in the Adobe Room, please keep yourself on mute unless you are speaking to minimize feedback. If you have raised your hand and are called upon to speak by our chair, Dr. Kaufman, please speak slowly and clearly so that your comments are accurately recorded for transcription and captioning. I will now proceed with the Conflict of Interest statement. Thank you.

The Food and Drug Administration is convening virtually today, November 4th, 2021, for the 122nd Meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act, FACA, of 1972. Welcome to the November 4th, 2021, Meeting of the Blood Products Advisory Committee, BPAC. The BPAC Committee will meet in open session to hear an overview and updates of three research programs. Topic I will be an overview of the Research Programs of the Plasma Derivatives Branch in the Division of Plasma

Protein Therapeutics in the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research.

Topic II will be an overview of the Research Programs of the Laboratory of Cellular Hematology in the Division of Blood Components and Devices in the Office of Blood Research and Review, Center for Biologics Evaluation and Research. Topic III will be an overview of the Research Programs of the Laboratory of Emerging Pathogens in the Division of Emerging and Transfusion Transmitted Diseases in the Office of Blood Research and Review, again, in the Center for Biologics Evaluation and Research.

Per Agency guidance, these topics are determined to be non-particular matters which would have no input on the outside financial interests. Hence, no effected firms are identified, and members are not screened for this topic. Today's meeting will also have three closed sessions from 11:30 a.m. to 12:20 p.m., from 2:10 to 3:00 p.m., and from 4:30 p.m. to 5:20 p.m. Eastern Time to permit discussions where

disclosure would constitute a clearly unwarranted invasion of personal privacy under (5 U.S.C. 552b(c)6)).

Dr. Richard Kaufman is serving as the chair for both the open and closed sessions for this meeting. The following information on the status of this Advisory Committee's compliance with federal Ethics and Conflict of Interest laws including, but not limited to, 18 U.S. Code §208 is being provided to participants at this meeting and to the public. With the exception of the industry representative, all participants of the Committee are either Special Government Employees (SGEs)or Regular Federal Government Employees (RGEs)from other agencies and are subject to the federal Conflict of Interest laws and regulations.

Given that Topic I, II, and III 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 or appearance of financial conflicts of interest. Dr. Susan Rossman is currently serving as the Industry representative to

this Committee. Dr. Rossman is employed by the Gulf Coast Regional Blood Center. Industry representatives act on behalf of all related industry and bring general industry perspective to the Committee. Industry representatives are not special government employees and do not vote and do not participate in the closed sessions.

Today, we have three consultants serving as temporary voting members: Dr. Judith Baker, Dr. Alfred DeMaria, Jr., and Dr. Jack Stapleton. Dr. Judith Baker is serving as a temporary voting member, as well as 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.

FDA encourages all meeting participants, members, or consultants, including open public hearing speakers, to advise the DFO and this Committee if they

realize they have any financial, professional, or regulatory relationships with any of the topics or individuals being discussed today that were not previously disclosed and recuse themselves from Committee discussions, and their absence will be noted for the record. This concludes my reading of the open session Conflict of Interest statement for the public record. At this time, I would like to hand over the meeting to Dr. Kaufman. Thank you.

OVERVIEW OF CBER RESEARCH PROGRAM

DR. RICHARD KAUFMAN: Thanks Christina. So it's my pleasure to introduce Dr. Karen Elkins, who's Associate Director for Science at FDA. Dr. Elkins, I have to remind you to turn on your camera and unmute your phone.

DR. KAREN ELKINS: Right. Can you hear me now?

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

DR. KAREN ELKINS: All righty. And I'll preface this by saying I have a notice from OITM that my computer has to restart, so I'm going to hope it'll give me 20 minutes on this side. But if I disappear, there you have it. So, on behalf of the Center, I'd like to welcome all of you to today's meeting and especially for your ongoing service on this Advisory Committee, which is critical to all of our operations. Today's is particularly of interest in relationship to the research program, and several of you served, of course, on the site visits themselves that are the subject of today's meeting. But we are particularly grateful for your time and energy on that. I'd like to give you a brief overview of our research program in general to provide you with some context for today's deliberations. I will focus on the big picture at the center level, and then, my colleagues will also give you further information on the particular units that are the subject of today's review.

So CBER is responsible for regulating biological products. They are complex. There is a

formal definition in law of a biological product, but in general, this means that we are responsible for oversight of vaccines, both preventative and therapeutic; allergenic products; live biotherapeutic products; xenotransplantation products, a suite of cell, gene, and tissue therapies; and, of course, the topic that's near and dear to this groups heart, blood and blood products. And that, in turn, requires a large amount of expertise. The word cloud is drawn from some of the key words of the disciplines in which our scientists were trained. And they are all related to the -- directly related to the products that we regulate.

CBER recently released a new strategic plan. Conducting research is one of our explicit goals, specifically to address challenges in the development and regulatory evaluation of our biological products. And we do business by having the so-called researcher-reviewer model. We have about 75 PIs in the Center that director laboratory groups that look like the format and approach that you are probably familiar

with. They propose investigator-initiated research, but those programs are not just anything. They are not that strictly investigator-initiated. They are in topics that are related directly to the products that the investigators in question regulate.

And so that gives us a menu of research programs that look from -- range from something you might describe as relatively basic research to very targeted studies that are directly tied to our regulated products. We think this way of doing business ensures that the people performing regulatory review and research have direct hands-on understanding of the techniques that are the source of data we see in regulatory decisions, that it ensures an effective, efficient, and credible review, and that, in general, it fosters decisions based on sound science. So our research and activity -- research and review activities are integrally linked.

And, specifically, our laboratory scientists, who are the subject of today's review, participate directly in regulatory review teams. Most of our lab-

based people are responsible for the product review. In the business this is often described as CMC or chemistry, manufacturing, and control reviewer. Our folks look directly at the scientific rationale and evaluate any data that is provided in proof-of-concept to support entry into human trials.

But they focus especially on the product itself. That means the production techniques, the manufacturing techniques, and the end product and its quality control testing. Obviously, most QC testing is laboratory-based, and laboratory-based expertise is important in that.

If there are clinical samples obtained in the course of the trial and those are assessed in a laboratory technique, the product reviewers also evaluate the quality of the clinical assays. And I tell you all this to make the point that up to 50 percent of time from the laboratory-based staff is spent in regulatory review. The amount of time spent in regulatory review varies with specific subject matter expertise, with the seniority and level of

training of individual people, and, of course, with the workload related to what sponsors submit to us. But the usual description for an established PI is that up to 50 percent of their time will be devoted to regulatory review, relatively less to the more junior staff members.

Product reviewers function in the context of an overall team. And that is typically comprised of other people like a project manager, who oversees the entire operation, a pharm/tox reviewer, a clinical reviewer who focuses on the clinical trial design, and on resulting clinical data as the studies progress. And a statistical reviewer who analyzes all of the numbers. So we think this approach means that throughout the development of a product and its lifecycle, from its very start to the challenges it presents to its progression through clinical trials, and in the licensure is informed by science and scientific activity's.

You are not today at our White Oak facility. In normal times you would have been. On the campus in

Silver Spring, we have about 450,000 square feet of lab space, over 150 labs ranging from BSL-1 to BSL-3, and about 500 research staff at the moment. On our campus we have the luxury of several core facilities including ones for flow cytometry, for imaging, for bioinformatics computing, and for molecular biology, as well as a state-of-the-art vivarium.

Our researchers are integrated into the larger scientific community in a number of ways. Most of our external collaborations, as you might expect, are with academia and with other government agencies, including other parts of FDA. But we do have in some examples, direct collaboration with regulated industry. As you might expect, those have rather careful oversight and management for conflict of interest.

Our external collaborations often result in formal agreements, such as CRADAs, contracts. We do have some external grant funding, and intellectual property activities, and, particularly in the COVID days, a whopper number of material transfer agreements. We think our research program has a number of benefits.

It prepares us for future challenges, and it facilitates the recruitment and retention of highly trained scientists who have direct expertise. We are living those two bullets during the current COVID-19 pandemic because we have a cadre of virologists, immunologists, those with expertise in convalescent plasma and the like, ready to go when the pandemic hit.

In some cases, the research efforts directly developed data and tools that support the development of classes of products and fills knowledge gaps that inform our policy development and our regulatory decision-making. Our research programs are evaluated in a number of different ways. We have an extensive annual report process in which investigators provide a number of -- a lot of information about the progress of their research, and that is reviewed by all the relevant supervisory levels annually. We have a formal horizon scanning process that takes place about every four years on a rotating basis for each product area in which office staff and Center staff look forward and try to anticipate what is coming down the pike in needs

of product development. New projects that are proposed for addition to the portfolio are specifically reviewed intramurally at the office in the center level before they are initiated -- and then, the topic of today's discussions, our external subject matter expert committee-based reviews in the form of site visits.

If you're familiar with the NIH site visit, this was originally modeled along those lines. And those are intended to take place every four years. The timeline has slipped a little bit with the pandemic, like a lot of timelines, but the intent is that these are periodically reviewed for quality. The criteria for evaluation include mission relevance. We understand that you may not be familiar with the details of the product development side, but we are sure that you can judge the relevance of the work in a general and useful way.

Like everybody, we consider the productivity and dissemination of research results in terms of presentations, publications, and occasionally tech transfer agreements. Probably the main criteria is the

scientific impact of our research efforts, that is whether it is taken up by the scientific community, is useful to the scientific community, and is important to our regulated stakeholders. The unique aspects of the regulatory mission and practice part of it, we don't expect you to be down in the weeds with, and that is primarily reviewed internally.

The site visit is a one- or two-day gathering in which staff provide presentations, take questions, and have one-on-one interviews with the subject matter Committee members. And that results in a report, and you have a draft of that report that has been distributed to the full Advisory Committee that is associated with the subject matter. And so your outcomes for today are three-fold: to take that report and accept it as-is, to request amendments, or to reject it and send it back to the site visit team for further work.

When it is at the stage of being -- of nearing approval, you will vote on that approval. And once it is approved, the finalized approved report is used in a

number of ways. The feedback goes back directly to individual PIs, and I assure you that they take your constructive criticism to heart to improve their research program.

Supervisors at all levels review the report and have further discussions on the program's progress and new directions. And up and down the chain, the report is considered during resource allocations in terms of internal budget space and people. So, with that, I'm happy to answer any questions, but mostly I want to thank you for your work. This is a critical part of reviewing our research programs and integral to maintaining the quality of our research program and fulfilling our regulatory missions. Thank you so much. And what else can I tell you?

DR. RICHARD KAUFMAN: Thanks, Dr. Elkins. Any questions from the group?

DR. KAREN ELKINS: And it's not your last chance. I and all my colleagues are available to you through the day. And, as I mentioned, the organizational units that are closer to the subject of

today's reviews will also be providing further information.

DR. RICHARD KAUFMAN: Okay. Well, I'm seeing no hands going up, so --

DR. KAREN ELKINS: All right.

DR. RICHARD KAUFMAN: -- I think we're good for now. Thank you.

DR. KAREN ELKINS: Thank you all.

TOPIC I: OVERVIEW OF OTAT AND DPPT RESEARCH PROGRAMS

DR. RICHARD KAUFMAN: All right. So our next speaker will be Dr. Basil Golding, who's Director of the Division of Plasma Protein Therapeutics, of OTAT, and FDA. So, Dr. Golding.

DR. BASIL GOLDING: Good morning and welcome, and I just want to add my thanks to that of Dr. Elkins for the work done by the site visit group that came and spent a lot of time with us and prepared this report and also, to the Advisory Committee for spending this time today to review that. So my task today is to

present an overview of the Office of Tissues and Advanced Therapies and the Division of Plasma Protein Therapeutics. Next slide. So, first of all, an overview of the Office of Tissues and Advanced Therapeutics. As you can see from the slide, the office director is Dr. Wilson Bryan. His deputy is Rachael Anatol. And you can see there are five divisions. The two divisions on the left are the DMC divisions that review manufacturing.

So the first division on the left, Division of Cellular and Gene Therapy, is headed by Dr. Raj Puri. And the next division over is my division, Division of Plasma Protein Therapeutics. And the division in the middle is the Division of Clinical Evaluation and Pharmacology and Toxicology.

The next division is the Division of Human Tissues, and the one on the right is the Division of Regulatory Product Management. Sorry, I meant to mention Division of Human Tissue is headed by Dr. Scott Bruebaker and then the Division of Regulatory Project Management headed by Ramani Sista. That division is

involved with administration and making sure that all the admissions are signed property and reviewed in a timely way and that communications with the industry go out in an expeditious way.

So you'll also notice on the slide that there are two rectangles. Those are the -- the two rectangles include the research branches. So in the Division of Cellular and Gene Therapy there are three research branches and in my division two research branches. And the Plasma Derivatives Branch is the one that was being looked at today for its site visit report. Next slide, please.

So what products do we review? So this is OTAT products, excluding the products in my division. So the OTAT products includes stem cell and stem cell-derived products, thermally-differentiated cell therapies, and therapeutic vaccines and other antigen-specific active immunotherapies. Next slide, please.

Here we have gene therapies. We have xenotransplantation products, tissues and tissue-based products, and some devices and combination products, a

lot of them involved with delivery of cells and tissues. Next slide, please. Just to give you a flavor of the workload in OTAT, so this is for all the divisions, including my division. So you see the number of INDs on this slide gradually increasing since 1963. But as you get closer to today, you see an exponential increase with a tripling from 2017 to 2019. I guess it's 2020. Next slide, please.

So these are the recent BLA approvals. As you can imagine, an actual license approval is a huge amount of work and is important, obviously, to getting products to the market. So these are approvals in the last year and up to October this year.

The top one is SEVENFACT. That's a recombinant factor VIIa approved in my division. And the next three are CAR T cells directed against B cell marker CD19 and the B cell maturation antigen expressed on myeloma cells. So those were approved in the other division -- Dr. Puri's division. RYPLAZIM, plasminogen was also approved in our division. It's a plasma-derived product. And then we have these more recent

ones, STRATAGRAFT, which is human skin, treatment of burns and the RETHYMIC, which was human thymic tissues for treatment of athymic infants. Next slide, please.

To just give you an idea also of BLA supplements in 2020 and this year, so the 2020 and until October 2021, separated by this forward slash -- so you see the numbers there: 15 and 3, 28/16, but most of the supplements were actually manufacturing supplements -- a huge number. And the reason for this primarily is we have a large number of products in DPPT alone. We have over 100 products that have been approved. Next slide, please.

So these are device applications in the same period. And you can see the numbers there of original applications, 510(k)s, IDEs, and then IDE Amendments. Again, the bulk of the work is in the amendments for already approved devices. And you also see information about PMA supplements, HDE supplements, and Qsub submissions. Next slide, please.

Getting into the research or regulatory science, OTAT has 22 laboratories. There were 31

publications in 2020, 40 plus external conference presentations, and we've developed 7 COVID-related research projects. Next slide, please. Now I'm switching to my division, the Division of Plasma Protein Therapeutics. Next slide.

This is the organization of my division. On the left you can see I'm the director. Underneath me is Mahmood Farshid, the deputy director. And then one column over you see the two branch chiefs, Dr. Timothy Lee with his PIs on the right. He has four PIs. And Dr. Scott underneath him, she is the branch chief, and she'll be presenting, right, more detail the research of the plasma derivatives branch. And that branch has three PIs.

Underneath that is Chava Kimchi-Sarfaty, who's the deputy associate director for research for the office and really helpful in our division in determining policy or helping with policy issues related to research. And underneath that are the two administrative employees, Trevor Pendley and Esther Saintilaire. Next slide, please.

So the DPPT workload, just to give you a quick understanding of how much work is devoted to research and how much to review -- so the regulatory scientists, we have 10 of them. They spend all their time doing review. The PIs, the principal investigator -- there's seven of them -- split their time between research and review the same with the research scientists and staff fellows. And the ORISE fellows and contractors spend a hundred percent of their time doing research, no review. Next slide, please.

So what is the regulatory function? What do we do in DPPT in terms of regulation? Well, obviously we review applications for products, and this is very diverse. So it includes biologics, drugs, and devices. And the evaluation process of products includes scientific review, laboratory investigation assay and standard development, and we are also involved in surveillance. This involves inspections, especially pre-approval inspections.

We file adverse event reports and investigate them. And we also investigate product failures. And

all of this is done under the legal framework of the federal -- code of federal regulations and different acts of Congress, the user fee for drugs or user fee for devices, and the FDC and PHS Acts. Next slide, please.

So what other tasks do we have? We are involved in policy and developing guidance documents, harmonization with other regulatory agencies -- the ICH is the International Council for Harmonization. And we have quarterly meetings with the European Medical Authority, EMA, and the Canadian Health Authority. We also have liaison meetings with different government agencies, with industry, with patient groups, and we communicate by websites postings and letters with industry. We have workshops to deal with scientific issues. And we also have representatives of multiple scientific committees inside the FDA, outside the FDA. And we sometimes have to answer citizen petitions. Next slide, please.

So other committees and working groups, we work closely with the NIBSC, National Institute of

Biological Standards and Control in the U.K., and with WHO, and this is related to -- mainly related to development of assays and standards for our products, which is very critical, especially, for example, to determine potency of our products. This has to be standardized and validated. We also participate in the EDQM, which is a European Pharmacopoeia Expert Group, which deals with plasma-derived products. And we attend as observers. Next slide, please.

In addition, other committees and working groups, we have working groups within the FDA, within CBER, with CDER, and these working groups have multiple functions -- container closure, genomics working group, the HIVE, which is an informatics group. And we have representatives in business process committees. These are coordinating with committees for research, for information management, and for regulation management. And we participate in multiple USP committees and working groups, and multiple industry education groups such as PDA, CASSS, and DIA. Next slide, please.

So how does the regulatory process work? The

decisions are based on scientific data showing safety, efficacy, and purity. The decision-making process involves internal review, presentations to advisory committees, and multiple meetings with manufacturers during the course of product development, including pre-IND/IDE meetings, INT meetings, pre-license application meetings, and after the license is submitted, several meetings including mid and late cycle meetings. Next slide, please.

Just to give you a sense of the workload in DPPT, this shows the different types of license applications. So at the bottom of each bar, you see a -- you may be able to see a slight blue bar which is the new original BLAs. We have about five to eight per year. In this year alone -- and it's not easily seen on the slide, but in this year alone we approved two products, the plasminogen and the SEVENFACT. From the bottom up we, so the bottom is the new original BLAs, then supplements, which is a major part of our work, then annual reports, then product correspondence, and then post-marketing commitment submissions. Next

slide, please.

So just to look on the left -- concentrate on the left, these are INDs, IDEs, and master files that were submitted. Right at the bottom -- it's hard to see -- are original applications. We get about 20-25 a year. And then the rest of it are amendments to those IND applications. I've already dealt with the BLAs on the right, so let's go to the next slide.

So what are the licensed products in the plasma derivative branch -- the branch that you are reviewing today in terms of research? So the products include polyclonal immune globulins used for immunodeficiencies and various autoimmune diseases and neurological diseases; then specific immune globulins or hyper-immunes; again, infectious diseases. We also review anti-toxins, anti-venoms, anti-T cell therapies for prevention of transplant rejection, and enzymes for enzyme deficiencies such as Alpha-1 proteinase inhibitor and C1 esterase inhibitor. Next slide, please.

We also regulate coagulation factors in the

hemostasis branch not under review today, so these are coagulation factors VIII and IX; von Willebrand factor; fibrinogen factor; factor X; factor XIII; anti-coagulants, including protein C; antithrombin; bypassing agents, such as anti-inhibitor coagulant complex; recombinant activated factor VII; hemostatic agents used in surgery, thrombin, fibrin and CryoSeal; fibrin sealant; and reversal agents for anticoagulants for prothrombin complex concentrate; and recombinant factor Xa variant, which is inactivated. Next slide, please.

So what is the scope of the DPPT Research? Obviously, this is mission related. It's we're looking at the efficacy of the immune globulin products in relation to various infectious diseases, including COVID. We study the regulation of blood coagulation of factors VIIa, IXa, and XIa. Aggregates are a problem in protein products, and we study that and develop more sophisticated methods to see that, to detect them. We have projects on immunogenicity, Fc-fusion proteins, Factor VIIa, and CRISPER/Cas9. We have projects on

pharmacogenomic and codon optimization studies of proteins, materno-fecal transfer of antibodies, assay and standard development, and counterterrorism and pandemic research related to products. Next slide, please.

So what about productivity? So you see highlighted here the 52 publications and 84 presentations in the last nearly three years. The publication topics include immune responses to SARS-CoV-2 vaccine, Fc-fusion drugs, protein immunogenicity, HLA donor optimization, synonymous mutations, published in various journals -- some of them very high-impact. And the presentation topics on the right, these are presented at meetings. You have some examples there, and then you have examples of meetings that are -- which we attend and present at often on an annual basis. Next slide, please.

So what about COVID? What have we done regarding COVID? Next slide, please. The research that has addressed the COVID dosing considerations for hyperimmune based on Hamster Challenge Studies, which

has been published; investigating coagulopathies that are associated with mortality following COVID infection; developing methods for rapid screening of convalescent plasma and immune globulin products; designing codon-modified versions of the SARS-CoV-2 virus to attenuate for vaccine use; testing of antibodies that neutralize COVID; and examining binding of coagulation-related proteins to the SARS-CoV-2 -- coronavirus 2. Next slide, please.

So just to give you a sense of the recognition -- so you may not know this, but we are not able to apply for NIH RO1 grants. But we do apply for competitive grants. We do get money internally, non-competitive money, which is baseline money for research. But in addition, we apply for grants from government agencies and agencies within the FDA. So BARDA is one example where we received grants and OCET, which is for counterterrorism and emerging threats. We've received several grants and we received grants from, challenge grants that have been available through the FDA. At the bottom you see some CRADA agreements.

These are contracts that we have with academia, with the Boston Children's Hospital, and Cleveland State University. Next slide, please.

So looking ahead, DPPT has identified and has plans to address the following gaps in regulatory research. So this is similar to what Dr. Elkins called horizon scanning. So what we think we need to do in the future is improve our ability to perform bioinformatics to examine immunogenicity and introducing DNA sequence changes for optimizing product yield; looking at next generation immune globulins, such as recombinant polyclonal immunoglobulins, modified immunoglobulins, and novel immunoglobulins against emerging pathogens and toxins; and looking at safety issues related to platform technologies for protein modification, such as Fc and albumin fusion and pegylated proteins. Next slide, please.

What are the anticipated new products? This is also part of horizon scanning. So we think that we're going to see proteins with improved pharmacological properties, new recombinant coagulation

factors, new PEGylated products, new fusion proteins of coagulation factors with XTEN or CTP to prolong half-life -- and then the second bullet, plasma-derivatives and their recombinant analogs for factor deficiencies and other disorders in hemostasis, such as coagulation factors for deficiencies, heme scavengers for treatment of sickle cell disease, recombinant variants for the treatment of arterial thrombosis and thromboembolism, reversal agents for anticoagulants, and metalloprotease to treat TTP. That's atom TS13. Next slide, please.

So we also anticipate HDL-type products for the reduction of atherothrombotic events. And under immune globulins, we will be expecting COVID-19 hyper immune globulins, new INDs, recombinant polyclonal immune globulins, glycosylation variants of immune globulins, and oral milk or colostrum-derived bovine immune globulin treatments for GI diseases, and new equine antibodies for treating toxins from spiders and snakes. And indeterminates of serine proteases, we are expecting recombinant products, subcutaneous formulations, and inhalational formulations. Next

slide, please.

So with that I just want to thank the people that helped me put all these slides together, Dr. Bryan, Rachael Anatol, Sue Epstein, Chava Kimchi-Sarfaty, Timothy Lee, Trevor Pendley, and Robert McElwain. And I want to thank you for your attention.

OVERVIEW OF PDB RESEARCH PROGRAMS

DR. RICHARD KAUFMAN: Thank you, Dr. Golding. Are there any questions from the group? Okay. Well, hearing none, I will move on then. Our next speaker will be Dr. Dorothy Scott, who's the Chief of the Plasma Derivatives Branch of OTAT.

DR. DOROTHY SCOTT: Good morning, everyone. I'm here today to present some highlights --

MR. MICHAEL KAWCZYNSKI: Dr. Scott, do you mind turning your camera on for us?

DR. DOROTHY SCOTT: Yeah. I don't mind at all.

MR. MICHAEL KAWCZYNSKI: Top of the screen --

oh, there you go. Perfect. Now we see you. Take it away.

DR. DOROTHY SCOTT: Yep. Okay. All right. I'd rather not see me, but that's okay. So, as I was saying, I'm going to try to give you a flavor of five projects in 20 minutes, so I need you to hold onto your hat while we proceed forward. Next slide, please.

I got it. The Plasma Derivatives Branch mission statement is to meet the public health needs for safe and effective products by performing high quality research that directly impacts safety, effectiveness, and availability of Plasma Derivatives. I'm sorry, I'm trying to advance the slide now. Could I have the next slide, please?

MR. MICHAEL KAWCZYNSKI: Sure.

DR. DOROTHY SCOTT: This is our branch, we have three sections, immunology, and (audio skip) safety and quality section, Pei Zhang as the PI, and we'll be presenting work from all three of those groups. I do want to point that without the people listed under us, this work would not be possible. They

do a lot of the bench work, almost all of the (audio skip) amazing what they're able to accomplish even though (audio skip). Next slide, please.

I'm going to present two projects of Dr. Goldings: New approach for treating people with hemophilia with inhibitors using Fc-fusion proteins and NK cells. Dosing considerations for use of hyperimmune SARS-CoV-2 and immune globulin in the treatment of COVID-19.

We're just going (audio skip). All right, so this is our data slide for this (audio skip). What Dr. Golding and Dr. Lagassé, first doctor on the (audio skip) in this work did is they took Syrian Golden hamsters and are asking the question of how the Fc-fusion protein impacts B cells. So what you see here is rituximab on the left, and the kinds of cells it would use are Raji cells are the cell type and at a B cell line that is specific for factor VIII proteins. (audio skip) positive control, rituximab, will bind to both of these and in the presence of natural killer cells there's a little plus here under the cell lysis.

But when you look -- when you add instead recombinant factor XI Fc, it has no impact on Raji cell lysis, even if NK cells are present. But, for the specific cell line, you see lysis, so this recombinant fusion protein is used as a therapy for factor VIII. And the idea, obviously, is to increase the half-life, but it turns out that there are some other things that are happening, at least in vitro, that Dr. Lagassé and Dr. Golding were able to show. The peak of the fusion protein-induced lysis is at a concentration of about 25 nM of the fusion protein. And this is achievable during immune tolerance induction regiments.

So the conclusions from this project are that the recombinant fusion protein activates CD16 NK cells. The infusion protein induces interferon gamma secretion, which you didn't see, from primary preferable blood monocytes and also from NK cells. And this lysis is particularly associated with presence of a high affinity CD16 allotype, and recombinant fusion protein induces factor VIII-specific B cells to be lysed in the presence of NK cells.

So, obviously, what is happening in the gray you can see the fusion protein -- the Fc portion of it binds to Fc receptor on NK cell CD16, to be precise, and the antigen portion, the factor VIII itself, is bound to these factor VIII-specific B cells. And this brings the cell -- it bridges the cells together so that the NK cells can destroy cells which you don't want to have making inhibitor.

So Dr. Goldings' second project that I'm showing today is considerations for antibody therapies against COVID-19. This based on some work that he did with others using the Golden Syrian Hamster Model of SARS-CoV-2 infection. The hypothesis was that in order to achieve optimal dosing the viral load needs to be taken into account. In this second project -- and I apologize that this is kind of small -- what they did is they looked at the changes in pharmacokinetic parameters based on viral loads. And these viral loads were determined by collection of samples -- nasal pharyngeal samples from the animals after injection.

So first, they infected the hamsters with

SARS-CoV-2, and two days later, they gave these same hamsters immunoglobulin that is specific for SARS-CoV-2. And that immunoglobulin was derived from plasma of people who had had SARS-CoV-2 infection. This is convalescent plasma.

And what they saw was that as you -- well, in the left-hand side, you can see that there's a control. That's an animal that got immunoglobulin and was not (audio skip) animals with a low viral load that were infected and received immune globulin and some with the higher viral load. And the clearance of the immunoglobulin appears to be increasing with increased viral load, and you can see this also in Graph C. And there are a lot of pharmacokinetic parameters here, including area under the curve, which was lower in the presence of (audio skip).

The conclusions were that virus presence reduces antibody concentration due to immune complex clearance. And viral load needs to be taken into account when treating patients that have COVID-19 with a hyperimmune SARS-CoV-2 immune globulin.

Next project -- and we're switching gears a bit -- is -- the next several projects are by Pei Zhang in his lab. They focus on evaluation and characterization of neutralizing antibodies against viruses that are relevant to blood-derived products. The regulatory relevance is we are tasked with developing and evaluating technologies, reagents, and standards that may improve the chemistry, manufacturing, and controls of plasma-derived immunoglobulin products. Some of the goals here of Dr. Zhang's projects are to facilitate improvement of the immunoglobulin products to increase their clinical efficacy, and to help immunoglobulin manufacturers develop reliable and better assays to measure product quality and characterize their products.

This slide looks complex, and I will do my best to explain it. But it's very elegant work that was recently published in PNAS by Dr. Zhang with Lu Deng as the first author. And what they did is they're looking at the hepatitis C virus epitope and its structural dynamics. First of all, there's an epitope

called epitope III in the E2. That's an envelope protein of hepatitis C virus. And that is a neutralizing epitope. What you're seeing in the left-hand panel are two arms of a neutralizing antibody.

So this -- a monoclonal antibody neutralizes HCV, and they co-crystalize this with epitope III. And what they found was a unique conformational structure that epitope III has to attain in order to be bound by this antibody. And this unique structure is obviously different from sort of a classical or typical structure, so what epitope III is responsible for is binding to -- of the virus to CD81, the virus receptor, and allowing entrance of HCV into the cell.

What they found is that these two conformations give more or less mutually exclusive functions, so in the unique epitope that is recognized by the neutralizing antibody, the antibody neutralizes it and prevents it from binding to CD81 because structure in general has now become different as a result of conformational change. Whereas this other form of the protein can bind CD81 and is not found by

the antibody. So by changing the conformation, the HCV E2 protein can avoid antibody recognition without varying its amino acid sequence. And it combines to host cell receptor for CD81 (audio skip).

Dr. Zhang's second project was on hepatitis B virus where he studied -- or analyzed the specific sites on the HB surface antigen protein that are bound by the therapeutic antibodies hepatitis B and hepatitis B immune globulin -- a hyper immune globulin that's used for prevention, post-exposure prophylaxis, and ISB. And it's also used post-liver transplant for people with hepatitis C to prevent recurrence of HBV disease. So he mapped these five major epitopes that are recognized on the HBsAg protein.

Then, he looked for clinically important escape variants of the virus. And what he found is that these are generally located -- or many of them are located in these specific areas. And he proved that replicating those mutations in the HBV protein also diminished the binding of hepatitis B immune globulin.

This has some implications. For HCV -- sorry,

there's a typo here. For HBV, further studies will determine whether the current HBIG treatment could be improved by supplementing it with site-specific neutralizing monoclonal antibodies that target clinically observed mutations for control of HBV infections. This would be used in people with more chronic infections or possibly transplant patients or immunocompromised people who can't necessarily control the infection themselves -- who have chronic infection to suppress any (audio skip). And for product improvement, further experiments will be designed based on the data to help immunoglobulin manufacturers to develop reliable and more comprehensive assays for better product quality characterization. So that would be, for example, potency assays for virus-specific immunoglobulin production.

I'm switching to Dr. Struble's work. Dr. Struble is a staff scientist and a research pharmacologist, who also is a marvel at regulating the pharmacology and toxicology in pre-clinical models that we see in regulatory submissions. So I'm going to

present her animal studies to assess immune globulin treatments when used during pregnancy. And, again, the mission relevance is to address challenges in development and regulatory evaluation of biologics.

So maternal-fetal partitioning of hyperimmune globulin, so this HIG means hyperimmune globulin -- Dr. Struble first noted that hyperimmune globulins are proposed to treat pregnant women and to prevent vertical transmission of viral disease to the fetus. And these have been studied for hepatitis B virus, cytomegaly virus, and Zika virus. And we expect that other viruses may be studied in a similar fashion. So can you give the mother a hyperimmune globulin and prevent transmission to her baby?

In humans, placental transfer of IgG occurs during the second and third trimesters. And here we're looking at the maternal to fetal ratios of immune globulin in pregnant humans as pregnancy progresses. And you can see that that ratio changes over time and there's less immunoglobulin in the mother compared to the babies. So placental transfer that occurs during

the second and third trimesters, the questions came up, how does that affect the efficacy of hyperimmune globulin therapy in pregnant women? And is hyperimmune globulin therapy during pregnancy effective in preventing vertical transmission of viral disease to the fetus and the newborn? And the clinical data have not provided clear answers.

And there are some studies that have been attempted, which have not yielded positive results. And there are several interesting reasons for that, one of them being dose, one of them being timing. So in the study I'm going to show you, she looked at placental transfer in an animal model using hepatitis B immune globulin. This situation -- and I should say that Dr. Struble developed this animal model for this purpose in the guinea pigs and injected them with immune globulin at gestation day 21, 30, 40, 50, and 60, with the hepatitis B immune globulin. What she found is that as time went by in the pregnancy, the fetal to maternal ratio of immune globulin -- human immune globulin went up. And so this is consistent

with what you saw for people, only it was maternal/fetal ratios in the first slot.

So what she also found were differences in pharmacokinetic parameters. So the area under the curve and first bar is control. The second bar is pregnant guinea pigs. The area under the curve for the human immunoglobulin you can see here is higher when animals are not pregnant and lower when animals are pregnant. And this is seen at two different doses of hepatitis B immune globulin.

Compatible with that, she also looked at the AUC in these guinea pigs at first, second, and third trimester equivalents, and you can see that the AUC is going down -- the maternal AUC. (Audio skip). So the conclusions here are that the maternal-to-fetal (audio skip) reduction of maternal exposure, exposes the fetus to progressively higher concentrations with increased gestational age results in fetal neutralizing activity against HBV in amounts associated with protection in people against HBV. So the potential for reduced maternal exposure, for the decreased half-life and

increased clearance in pregnant women should be taken into consideration on the selection of the dosing regimen during pregnancy.

And now I'm going to go on, we're at our last couple of projects, and I think I'm doing a little better than I expected. This project was initiated by Yonggang Wang in my lab, and the topic is hemolytic activity of licensed immune globulins. I'm sorry this slide is so busy, but I won't go through it all. We wanted to address hemolytic activity in IGIV products -- or IVIG products. And we had been receiving increased numbers of hemolysis reports in IVIG recipients from products that passed a lot release test, which is direct hemagglutination test.

And it has the specifications as the European pharmacopeial test, and it's used for all of our products to diminish the amount of isoagglutinin in those products, that is antibodies to the A and B determinants on red cells. We developed a compliment-mediated hemolysis assay, a compliment-dependence called the CBHA for IVIG products. We also identified

antibody subclasses in IVIG that mediate hemolytic activity. And, again, this research addresses challenges in developments and regulatory evaluation of products. And I'll keep going here.

The CDHA we developed in order to improve detection of hemolysins in IVIG. So the current direct hemagglutination assay that is used for lot release in all of our IVIG lots, it is somewhat imprecise. It has a large titer variation. It does not screen out hemolytic IVIG lots. There's a subjective readout, and it measures binding of antibody to RBC but not really the functional activity of those antibodies that are binding.

So we modified and somewhat modernized classical methods used to detect hemolytic activity in general of antibodies against red cells. And I'm not going to go through how we did all of this. It looks simple, but it was complex because there are a number of different parameters that have to be controlled.

And, well, it was more work than it looks like here. But it's adding antibody to the red cells,

followed by human compliment, and measuring the amount of hemoglobin that is released, which is evidence of (audio skip). We looked at a number of different brands of immune globulin product, and we found different amounts of hemolytic activity using the CDHA. Here, what you're looking at on the Y-axis is specific lysis and on the X-axis is the volume or concentration of the immunoglobulin that was used in this in vitro assay. And this curve up at the top of all of these is a positive control from a highly hemolytic lot -- clinical lot.

So what you can see is we came up with three patterns, basically: a relatively high hemolytic activity, somewhat lower hemolytic activity, and undetectable hemolytic activity. Now, to show you what high means, we also have a graph down here of the hemolytic activity of product lots that cause clinically significant hemolysis and had at least several reports of hemolysis for these spontaneous adverse event reporting system. So these are definitely implicative lots, and you can see that their

hemolytic activity appears to be reasonably high.

Now, this can be quantitated by using an EC50, and I'm just showing you how we do that here. What we found is that hemolytic activity differs across product brands, but it's consistent for individual product brands. And the CDHA testing itself was more quantitative, and it was reproducible the way in which we did it. And we also identified clinically hemolytic lots that it passed direct to agglutination testing at the manufacturer and also in our hands.

Just very briefly I'll show you the contribution of antibody subclasses to hemolytic activity. And the first thing we did is we looked at monoclonal antibodies that Dr. Wang generated, which bind the A antigen on red cells, and he made subclass switched recombinant anti-A antibodies. This is a positive control and negative control for the assay. And what we saw is that all of these antibodies had a bit of hemolytic activity but not a lot. IgG3 had the most, and that's kind of what you would expect because IgG3 is especially good at finding compliment by virtue

of its long stem and of complexing. So, then, he took immunoglobulin that was known to be hemolytic in vitro and to in vivo in susceptible patients.

And he purified the IgG subclasses from it, and this is not so easy to get at least 90 percent or higher purity of the subclasses. But at any rate, it can be done with chromatographic methods. And he found that IgG2 purified from the immune globulin has the highest hemolytic and hemagglutinating activity.

So the outcomes of this is that we became proficient in product testing, and we do test our products with the CDHA as well as the direct hemagglutination assay. In the past year there have been seven pre-IND or IND products that we've looked at, and the reason we look at these is we're seeing new methods of manufacturing and the need to understand impurities, particularly this one because it requires certain conditions to be got rid of. And we also tested for licensed products after they underwent major manufacturing changes that might alter the partitioning of isoagglutinin's during manufacturing.

We participated in WHO international standards and methods studies by virtue of this expertise. We identified and assisted in NIBSC to obtain a high titer anti-A, anti-B immune globulin product to use as a reference standard, which became NIBSC 14/160. And we've just submitted a manuscript for the CDHA method. Our future plans are to look more at the pathogenesis of extravascular -- or to look at all at the in vitro method of trying to measure or replicate extravascular hemolysis so that we can look at the contribution of our new globulin products via this route to hemolytic activity testing in patients. And we'll continue our international standards and other work. I want to thank everybody -- oops, I'm sorry. I have one more. I'm almost finished.

And that's treatment and prophylaxis efficacy of FLUIGIV murine animal models. So this is another hyperimmune globulin, this time against influenza. And I'll just -- it's consistent with CBER's regulatory mission to increase preparedness for emerging threats and promote global public health. The specific goals

were to study a human hyperimmune globulin we call FLUIGIV against influenza A in normal and immunocompromised mice. Compare the efficiency or efficacy of different FLUIGIV treatment regimens with respect to timing relative to influenza challenge and single versus repeat dose regimens, and also to assess FLUIGIV, which was made against the pandemic H1N1 influenza back from the early 2000s -- to assess the cross-reactivity of this FLUIGIV and its protection potential against highly pathogenic avian influenza strains. Actually, we use reassortant virus on a PR8 backbone, so we'll just -- it's very attenuated.

What Dr. Khalenkov found was that there was in vivo cross-reactivity of FLUIGIV with different pandemic influenza strains, specifically H1 -- I'm sorry, H1N1 is already there -- H5N1 completely protected the BALB/c mice when given prior to, or at the same time, as FLUIGIV. And H7N9, there was partial protection there. So FLUIGIV protected 100 percent of animals from H1N1 and H5N1 group, and partial protection was observed in the H7N9 group.

He also looked at time-dependent FLUIGIV prophylaxis and treatment in BALB/c and SCID mice. And what you can see here is that giving pre-exposure prophylaxis or day zero treatment fully protected BALB/c mice from lethal challenge. But post-exposure treatment failed to protect the BALB/c mice from lethal challenge.

It's more complicated with SCID mice, but he showed that pre-exposure prophylaxis and post-exposure treatment prolonged survival in SCID mice in a time-dependent manner but did not ultimately provide protection from lethal challenge. Well, every now and then a mouse survived. And you can see that partial protection was seen especially with pre-exposure prophylaxis in the mice groups there.

So, in 2019, there was a publication of an NIH-sponsored trial of an anti-influenza hyperimmune globulin for adults with influenza A or B infection. And this trial showed no difference in the composite safety outcome of death, serious adverse event, or grade three or four adverse event between placebo and

treatment groups. I should point out that the people who were treated already were seriously ill and were expected to be in the hospital for more than 24 hours. And they had certain warning signs that they were going to have a difficult course.

The BALB/c experimental data that we showed is in concurrence with these clinical trial results. And the BALB/c results predict that pre-exposure prophylaxis with FLUIGIV could be beneficial. And based on the SCID mouse experiments, there could be potential benefits of a FLUIGIV for treatment of severely immunocompromised patients infected with influenza A.

And the future studies that are planned are to obtain a detailed PK and PD of the FLUIGIV normal and SCID murine models, to evaluate host-dependent immunological determinates of protection -- and we actually have tissues from a lot of our experiments so that we can do that -- and to start some combination studies in the SCID mice and the BALB/c post-exposure treatment mice with currently approved drug therapies

for influenza disease. Now, I want to thank you for your attention.

I'm sorry it has been a whirlwind, and I'm sorry I ran a little late. But it's very much appreciated, your evaluation, critiques, and we look forward to seeing the site visit report. Thank you very much.

Q&A SESSION

DR. RICHARD KAUFMAN: All right. Thank you, Dr. Scott. Are there any questions from the Committee? And I'll just ask people to use their raise your hand button if there's anything you'd like to ask. Dr. Ballow.

DR. MARC BALLOW: Good morning, doctor. It's nice to see you again.

DR. DOROTHY SCOTT: Hi. Likewise.

DR. MARC BALLOW: I wanted to ask you about Basil's SARS-CoV-2 experiments. I think, was it hamsters, I believe? The immunoglobulin that was

derived from the post (inaudible) bodies to try to detect what kind of antibodies were in the post-infectious immunoglobulin product that was used in those animal models? Because obviously there's a broader range of antibodies. There's neutralizing antibodies, and there's, you know, antibodies of -- perhaps other components that may be less effective or perhaps even more effective in that animal model.

DR. DOROTHY SCOTT: So I think you're asking about the -- how were the COVID-19 -- or how were the SARS-CoV-2 antibodies characterized in that immunoglobulin product; is that right?

DR. MARC BALLOW: Right. And whether that may have made any difference in the results -- in the experimental results.

DR. DOROTHY SCOTT: I think that those antibodies generally are characterized by neutralization mainly, not by other particular characteristics like ADCC or other mechanisms of action.

DR. MARC BALLOW: Okay.

DR. DOROTHY SCOTT: They're all derived from convalescent plasma.

DR. MARC BALLOW: So those antibodies actually penetrate the nasal epithelium?

DR. DOROTHY SCOTT: That's a very good question. I don't know. Dr. Golding is actually here, and he could answer that.

DR. BASIL GOLDING: Can I just weigh in?

DR. DOROTHY SCOTT: Yeah, absolutely.

DR. BASIL GOLDING: Dr. Ballow, yeah, those are obviously good questions. The antibody we used -- you know I can't divulge the company, but it was used in the clinical trials. And we do have neutralizing titers that were in the 300 to 600 range, using a pseudo-virulent assay that was a standard -- a WHO standard. So that's the information we have. They weren't characterized in terms of how much non-binding antibodies there are.

And we don't know in the hamster model to what extent the antibodies that were effective were neutralizing or not but based on a lot of evidence in

the literature, I would expect that the neutralizing antibodies did play a role. And I don't know if you saw it in the slides that Dr. Scott presented. The hamsters that received the product did have a quicker recovery time and less loss of body weight compared to hamsters who did not receive the antibodies.

DR. DOROTHY SCOTT: Yeah.

DR. BASIL GOLDING: There was something else you asked?

DR. MARC BALLOW: No, I just -- I was just asking about the penetration of those antibodies into the --

DR. BASIL GOLDING: Nasal tissues. Yeah, so that's problematic. We did look at that. The antibody levels in the nasal tissues were particularly low in our hands. So this was antibody given intravenously to these hamsters through a catheter in the jugular vein. So the levels in the nasal tissues were low, which was in keeping with what other people have seen in animal and human studies.

And also I would point out that when we looked

at viral loads in the lung and in the nasal tissues, the viral loads in the lung were decreased in the presence of the antibody, but the viral loads in the nasal tissues were not -- they were slightly decreased, but it was not significant. So if the point you're making is that do they reach the nasal tissues? Well, they do but in much lower amounts than they do in --

DR. DOROTHY SCOTT: Small.

DR. BASIL GOLDING: So the antibody treatment may be effective in reducing lung disease, but it won't be very effective in reducing nasal viral loads and transmission.

DR. MARC BALLOW: Great, thanks. And then, Dorothy, I wanted to make a comment about your hyperimmune flu antibody studies. In conjunction with Immune Deficiency Foundation, we actually published a paper. It was based on a questionnaire to patients with a variety of types of antibody deficiency, and, as you know, there's a lot of (audio skip) that present immunoglobulin products contain cross-reacting antibodies and --

DR. DOROTHY SCOTT: Yeah.

DR. MARC BALLOW: -- and flu that range back many, many years ago depending on the donor pool. And we actually found that patients with (inaudible) anemia who, obviously, can't make antibodies because their own specific antibodies -- but there are immunoglobulin replacement therapy -- had the lowest -- again, this is not by culture but by report of the parents whether those patients got sick with flu -- had the lowest flu symptomatology than some of the other groups of patients. So, you know, in other words, immunoglobulin products that we use today may actually have enough cross-reactive antibodies so it's prophylaxis in our patients with primary antibody (audio skip).

DR. DOROTHY SCOTT: Well, that's -- I remember that. I remember calling IDF even and asking if that -- if they think that chronic administration is good. And I think that patients might be happy to know that immunoglobulins now also contain -- or many of them contain some antibodies against SARS-CoV-2 because that's obviously been -- people are vaccinated and

convalescent, and there's a whole lot of them. And some of those, maybe even a lot of those -- the donor population has now got those antibodies, and they have worked their way through the system. And the plasma's been manufactured. And we're rather eager to look at some immunoglobulins that we've purchased to see how much COVID-19 antibody is there.

There's one publication already by Thomas Cryal (phonetic) from Takeda (phonetic) where he's looked at the Takeda products and found, you know, neutralizing antibodies. So, yes, you might say -- also for CytoGam a long time ago, I remember the children who received it had fewer upper respiratory tract infections in general or had fewer ear infections to be specific. And so the -- and they had a pretty hefty dose of the immune globulin.

DR. RICHARD KAUFMAN: Well, listen. Thanks very much. Just in the interest of time, I want to give everybody a break. So we will -- let's just reconvene at 11:20. So thanks very much, Dr. Scott.

DR. DOROTHY SCOTT: Bye-bye.

[BREAK]

OPEN PUBLIC HEARING

DR. RICHARD KAUFMAN: All right, so --

MR. MICHAEL KAWCZYNSKI: All right.

DR. RICHARD KAUFMAN: -- our next session, it says open public hearing. However, due to no formal oral requests being received, we'll be moving on to the closed session for Topic I. And this closed session will allow for the Committee members to have internal discussions about the research program and discuss the draft site visit report.

BREAK FOR TOPIC I CLOSED SESSION

MR. MICHAEL KAWCZYNSKI: All right. Welcome back from that long break, but we are now going to start our middle portion of the agenda, and I'm going

to hand it back to Dr. Kaufman.

Dr. Kaufman, take it away.

DR. RICHARD KAUFMAN: All right. Thank you.

Welcome back, everyone. Our next speaker will be Dr. Orieji Illoh from OBRR. She'll be talking about the DBCD. Thank you.

TOPIC II: OVERVIEW OF OBRR AND DBCD RESEARCH PROGRAMS

DR. ORIEJI ILLOH: Hi. Good afternoon, everyone. Just confirming that the audio is good.

MR. MICHAEL KAWCZYNSKI: Yes. You're good.

DR. ORIEJI ILLOH: Yeah. All right. Thank you.

So, good afternoon. My name is Orieji Illoh. Welcome to our discussion this afternoon of the LCH site visits. So, my name is Orieji Illoh. I'm the Director of the Division of Blood Components and Devices. In my talk today, I'll be giving an overview of the Office of Blood first, followed by an overview of my division, the Division of Blood Components and

Devices, and our research programs.

So, within the office of Blood Research and Review, OBRR, we have the Office of the Director and then two divisions: the Division of Emerging and Transfusion Transmitted Diseases, which is DETTD, and the Division of Blood Components and Devices, which is DBCD.

Within DETTD, there are four groups. There's one group that does complete review, where everyone there does complete reviews. And then we have three research branches, and within those three research branches, they do both research and regulatory review.

Within the Division of Blood Components and Devices, we have five groups. Three do review work, and the other two do a combination of research and regulatory review work.

So, this slide just kind of gives us names to the groups. And within the Office of the Director, our director is Dr. Nicole Verdun. Our deputy director is Dr. Anne Eder. Dr. C.D. Atreya is Associate Director for Research.

And also within the Immediate Office of the Director, we also have our administrative staff housed there, our regulatory project managers. Our quality staff are all within that group, too, and also our policy staff.

So, DETTD is directed by Dr. Hira Nakhasi, who you will hear from later on, who will give a more expanded overview of DETTD. And his deputy is Dr. John Hobson. Now, within that group, like I mentioned earlier, there are three research groups, research labs. We have the Laboratory of Molecular Virology, led by Dr. Indira Hewlett; the Laboratory of Bacterial and TSE Agents, led by Dr. David Asher; and the Laboratory for Emerging Pathogens, led by Dr. Sanjai Kumar.

Within the Division of Blood Components and Devices, other than the three groups that do regulatory review, we have two research groups, which is the Laboratory of Cellular Hematology, led by Dr. Jaro Vostal, and also the Lab of Biochemistry and Vascular Biology, led by Dr. Abdullah Alaysah.

So, the OBRR's mission is to ensure the safety, efficacy, and availability of blood and blood products through the regulation of blood and blood components for transfusion, and also, we oversee the collection of source plasma, which is plasma for refractionation.

We oversee blood collection containers, storage solutions, devices used in the manufacture of blood and blood components. We also oversee plasma volume expanders and oxygen-carrying solutions, assays used to test for transfusion-transmissible agents, and diagnostic tests for human retroviruses.

In addition, as we all know, we also conduct research. And our vision for research is to conduct mission-relevant research to facilitate the development, manufacture, and evaluation of the products that we regulate. Our goals include to address scientific questions critical to effective regulation and review of the products and also to advance innovation in research areas that enrich our regulatory science base.

So, within OBRR, we have several research resources, which includes 16 investigator/research-reviewer programs. The expertise varies within these groups and includes expertise in virology, retrovirology, bacteriology, parasitology, prions, cell biology, immunology, biochemistry, and physiology.

The programs are mostly funded, as you heard earlier today, by internal resources, which is from CBER and also resources from FDA. But some of our programs do obtain external resources or collaborations with other federal agencies such as the NIH, NHLBI, NCI, and DoD. But in addition, a few of the programs also get non-government funding through CRADAs, and CRADAs mean cooperative research and development agreements.

Periodically, the Office of Blood evaluates their research goals and makes sure that they are in line with our mission and our priorities. Currently, we have two broad research goals. Goal 1 is to assess and promote safety and effectiveness of transfusion products and related devices and technologies.

Some of the objectives include evaluation of ex vivo stored platelets and red cells for safety and efficacy. We do this through studies of toxicokinetics, development of biomarkers of product quality, microparticle-associated toxicities, both of which you'll hear about today.

We also evaluate the safety and effectiveness of oxygen-carrying solutions, platelet-like products, and related biologics. We develop and evaluate reference panels for molecular typing methods for blood groups and HLA antigens. And we also facilitate the development of pathogen reduction technologies applicable to whole blood and blood components.

Our second research goal is to assess and promote safety and effectiveness of transfusion-transmitted infectious disease agents, donor screening and supplemental tests, and retroviral diagnostics.

Some of the objectives include to evaluate screening and confirmatory technologies for detection of TTID agents for assurance and enhancement of blood safety, develop and evaluate reference panels for

screening and confirmatory tests for TTID agents and retroviral diagnostics, and finally, facilitate preparedness for blood safety from emerging infectious agents and other pathogens of global significance through investigations of mechanisms of transmission and pathogenesis.

In addition to the regulatory work and research work that our staff do, a lot of our staff are also involved in global outreach opportunities. The OBRR staff participate either as members or observers in different groups, and this includes WHO initiatives such as the Collaborating Center for Biological Standardization, the Expert Committee on Biological Standardization, the Blood Regulators Network, and the Prequalification Program for diagnostics.

We also participate with the European Directorate for the Quality of Medicines and HealthCare, typically called just EDQM. Within the blood transfusion sector, there are several workgroups that our staff participate in. We also participate in the International Society for Blood Transfusion Working

Groups on Transfusion Transmitted Diseases, Hemovigilance, and Global Blood Safety. Finally, we also participate in the FDA/EMA/Health Canada Blood Cluster.

So, that's a general overview of the Office of Blood. And now I'll go to an overview of the Division of Blood Components and Devices.

Within the Division of Blood Components and Devices, like I mentioned earlier, I'm the director. My deputy is Dr. Wendy Paul. And we have five groups, like I mentioned, and I'll just go over these briefly.

The Device Review Branch, where the staff do regulatory reviews, is responsible mainly for the oversight of reagents for immune hematology testing, for example, reagents for HLA testing, and also blood establishment computer software, among a host of other things that they do. They also oversee molecular test methods for red cell antigens and platelet antigens and neutrophil antigens. That group is led by Dr. Jason Liu.

Within the Clinical Review Staff, the team

lead there is Dr. Salim Haddard. And that group comprises mainly medical officers and some individuals of expertise in pharmacotoxicology. And this group reviews clinical studies and investigational studies related to devices or drugs.

Within the Blood and Plasma Branch, this group consists of mainly individuals with medical technology training and blood collection or blood banking. And this group is responsible for the oversight of the manufacturing of blood components within our different blood centers. This group is led by Richard McBride.

Now, we have two groups that do research and review activities. The first is the Laboratory of Biochemistry and Vascular Biology, led by Dr. Abdu Alayash. In this group, they evaluate things like the blood substitute, like the oxygen-based carriers, albumin solutions and other plasma expanders, additive solutions for blood components, and anticoagulants. There's a host of things that they look at there. There are two PIs in that group, Dr. Alayash and Dr. D'Angillo. There's actually a vacant position in that

group for a PI.

Now, within the Laboratory of Cellular Hematology, which we'll be discussing more today, that group is led by Dr. Jaro Vostal. And Dr. Vostal will give more information about his group, but that group oversees mainly devices used for blood collection and processing, such as apheresis devices for blood collection, leukocyte reduction filters, for example, blood warmers, pathogen reduction devices, also a host of other things.

And within that group, there are three PIs. In addition to Dr. Jaro Vostal, there's also Dr. Jan Simak and Dr. Atreya, who perform research work in that group.

The mission of DBCD is to assure the safety, efficacy, and availability of blood and blood components and related biological products. As you all know, blood transfusion involves multiple processes, including donor screening, testing, collection, storage, and compatibility testing. And so, a lot of our work revolves around these different stages of

blood collection and storage.

We also look at biological products, which include hemoglobin-based oxygen carriers and volume expanders such as albumin. Our review activities include the review of applications and inspections related to the manufacture of blood and blood components for transfusion and source plasma for further manufacture into derivatives.

We look at devices used in the manufacture of blood and blood components, immunohematology reagents for blood compatibility testing, HLA reagents also. We also look at plasma volume expanders and, as I mentioned earlier, the hemoglobin-based oxygen solutions and therapeutics and fluorocarbon-based oxygen solutions.

In addition, our group is involved in the review of investigational new drug and investigational device reviews as they come in and other pre-marketing activities. This might include meetings with sponsors to discuss their drug development plans or device development plans.

Our regulatory review process -- our regulatory decisions are based on scientific data showing safety, efficacy, and purity. Generally, the review entails an internal review by a group of reviewers or research review staff. And this might be an individual reviewer or a team of reviewers from different areas of expertise as needed.

We also, as supervisors, participate in evaluating these reviews and making regulatory decisions. As needed, there might also be facility inspections or presentations to the Advisory Committee, for example, if it were looking at a novel blood product or a novel device. And as necessary, we might conduct public workshops as part of our regulatory review process.

So, in addition to regulatory work, our staff are involved in many other activities. This includes developing policies governing practices related to blood donor eligibility and product manufacturing. So, we're involved in the development of regulations and guidance document development as relevant to our

products.

We also serve as liaisons with many industry government agencies such as the NIH/CDC, regulatory agencies of foreign governments, and international bodies. In addition, we conduct mission-relevant research to facilitate the development, manufacture, and evaluation of products that we regulate.

In terms of our research goals, this is tied to the overall office research goals. And our goal is to assess and promote the safety and effectiveness of transfusion products, explore novel methods for blood product processing and evaluation.

Examples of some of the things that we do are evaluation of pathogen reduction technologies, the development of animal models to evaluate cellular blood product quality, assessing the role of different biomarkers in blood product storage and quality, the development of novel methods to evaluate microparticles in blood products, and evaluation of the safety and effectiveness of oxygen-carrying solutions.

So, in summary, our research complements the

regulatory mission of our office and our division. This enhances our ability to advance the review and development of safe blood products and related devices, and our efforts contribute to the development of regulatory policies for product development and review.

Our research staff have made significant contributions to the field and are recognized internationally for their work. So, this is my last slide, I believe. And I will be happy to take any questions.

DR. RICHARD KAUFMAN: Thanks, Dr. Illoh.

Any questions for her? Okay. It looks like not. Well, thanks very much.

DR. ORIEJI ILLOH: All right. Thank you.

DR. RICHARD KAUFMAN: All right. So, our next speaker will be Dr. Jaro Vostal, and he'll be talking about research programs in the Laboratory of Cellular Hematology (audio skip).

OVERVIEW OF LCH RESEARCH PROGRAMS

DR. RICHARD KAUFMAN: Oh, sorry. You're on mute.

MR. MICHAEL KAWCZYNSKI: You're still muted, sir, yep, on your own phone.

DR. JAROSLAV VOSTAL: All right. Is this better?

MR. MICHAEL KAWCZYNSKI: Yep. There you go.

DR. JAROSLAV VOSTAL: All right. Well, thank you. So, again, my name's Jaro Vostal, and thank you for coming to review our laboratory and our research program. I'm going to give you a brief presentation of the site visit and the work that we've done in the last four or five years.

So, as you heard already, we have regulatory as well as research responsibilities in our laboratory. And since we've already gone over this previously, I'm just going to briefly summarize. We review biologic products, specifically transfusion products, including red cells, platelets, and whole blood, as well as plasma. These products come in a number of varieties and configurations, as we can see over here.

We also review the devices that are used to collect, process, and store transfusion products. These include collection bags, storage bags, apheresis equipment, leukocyte reduction filters, leukocyte counting devices, pathogen reduction processes, bacterial detection, which is culture-based or rapid, blood bank counters, sterile connectors, and so on -- pretty much all the devices you would be expected to encounter in a blood bank or a blood collection center.

So, the scope of the regulatory review is we look at preclinical evaluation of products and devices, and specifically for safety and efficacy of these products. We review in vitro tests of processed transfusion products, platelets, red cells, and plasma. We look at the biochemistry of these cells, the cell physiology. We pay attention to platelet activation and similar types of cell responses.

We also look at the medical device design, the performance and their impact on transfusion products, the software that are on these devices, and we also participate in the post-market failure and adverse

event investigations.

The other responsibility that we have is to carry on mission-related research. And mission-related is that we're trying to align with the strategic research goals for the Center for Biologics. One of these goals is to facilitate the development and availability of safe and effective medical products through the integration of advances in science and technology.

Another goal is to conduct research to address the challenges in the development and the regulatory evaluation of medical products. Our research products are covered in this column here. We've looked at or we are looking at improved and novel pathogen reduction methods, including expanded efficacy against pathogens and methods of potential for less toxicity.

We look at new transfusion products with safer profiles, and that will be cold-stored platelets and temperature cycled platelets for lower bacterial contamination and septic transfusion rates. We look at improved product availability with products such as

frozen platelets and extended cold storage of platelets.

And we seek to better understand the storage and processing lesions, and specifically, we've been looking at changes in platelet and red cell microRNAs. And we're also developing animal models for human transfusion product efficacy, and we have models in the area of oxygen delivery and also in the area of hemostasis.

There are three principal investigators in the lab, and I'm going to go through the presentation that they gave. I'll start with my own program. My program is called the Safety and Efficacy of Cellular Transfusion Products, and the objective of this program is to address issues of safety in current transfusion products and develop methods to evaluate efficacy of novel transfusion products.

The accomplishments we have for the last five years are in the area of pathogen reduction, cold platelet storage, and animal model development. For pathogen reduction, we've been able to develop five new

photosensitizers for UVA-light-based, naturally occurring molecules with bactericidal pathogen reduction efficacy in plasma with up to six log reduction of the pathogens.

The photosensitizers include vitamins K3, K5, and vitamins B1 and B6, and also the naturally occurring molecule benzophenone. These results were published in 2018 and 2020. We've also introduced a new concept of synergy by pairing photosensitizers that can increase antibacterial efficacy by up to ten thousandfold, and this was published in 2020. We've also demonstrated viral reduction in whole blood with vitamin K5 and UVA. That was a recent publication in 2021.

In the area of platelet cold storage, we've looked at improvements to platelet quality after storage, and we conducted a clinical trial in healthy humans to demonstrate improved in vivo recovery and survival of temperature-cycled platelets compared to cold-stored platelets after they've been stored for seven days. So, temperature cycling is 11 and a half

hours in the cold with a half-hour warm-up to 37 degrees. And this is then cycled for the duration of the seven days.

In the results, the temperature cycling increased the in vivo area under the curve two-and-a-half-fold over the cold-stored platelets, so a major improvement in terms of performance of the platelets with minimal changes in blood bank practice. This study was done in collaboration with American Red Cross Laboratories and was published in 2018.

We've also used the pharmacological inhibition of MAP kinase in platelets with a drug called VX-702 to reduce the cold-storage-induced platelet lesions. And this study was published in 2021.

So, in the area of models of transfusion, we have validated a mouse model of in vivo human platelet circulation against the humans in our clinical trial. This model is an immunodeficient mouse. It's a SCID mouse that can accept human platelets. And based on a validation we did, the SCID mice can be used to predict platelet in vivo recovery in humans. This study was

published in 2020.

We also have a model of chronically anemic and immunodeficient beta-thal SCID mouse for demonstration of oxygen delivery by human red cells. Because it's immunodeficient, it can accept human red cells. And the endpoint is the reduction of exercise-induced lactate buildup by transfusion of human red cells. And this study was published in 2016.

And then we also have a model of human platelet transfusion outcomes in a septic rat model. This is an immunodeficient rat that accepts human platelets. And this model was able to demonstrate that macrophage-mediated platelet aggregates in the spleen once the platelets were transfused. This publication was in 2019.

The future plans in my plan are for pathogen reduction. We're going to look at pathogen reduction of red cells and whole blood with pairs of photosensitizers to improve the efficacy, and we're also going to evaluate the quality of the treated cells.

For platelet cold storage, we're looking to extend cold storage up to 21 days with temperature cycling and also with pharmacological inhibitors of platelet activation. We're looking to plan a collaboration for a clinical trial of cold-stored platelets with the drug Vx-702 to define the kinetics of platelets stored under those conditions in healthy humans. For animal models, we're now working on humanized mice to evaluate human platelet hemostasis.

So, this is the next program, and it's under the direction of Dr. Jan Simak. The title of the program is Investigation of Potential Toxic Effects of Biologic and Engineered Nanoparticles and Microparticles in Blood and Blood Products and their Biomarker Applications.

There are two objectives and research projects under this title. The first one is in vitro evaluation of effects of engineered nanomaterials on vascular endothelial cells, and that's part of the Nanotechnology CORES Grant. And the second one is investigation of cell membrane and protein

microparticles in blood and blood products, their biomarker applications, and potential role in vascular injury.

The accomplishments of this program are -- for Project 1, they're the PAMAM dendrimer model of effects of spherical nanoparticles on cultured endothelial cells -- and this was published in 2019 -- and the design and ongoing validation of a panel of in vitro assays -- and this was published in a series of publications from 2016 to 2018 -- and also a protein particle model using protein corona on engineered nanoparticle core for investigation of adverse effects for protein particles in biologics. And this work is done in collaboration with Dr. Scott's labs in OTAT.

The accomplishments for Project 2 are the comprehensive analysis of platelet extracellular vesiculome using a panel of high-resolution analytical and imaging methods -- and this was published in 2018.

This publication also distinguished four different pathways for platelet extracellular vesicles released from activated platelets, and as well as

characterization of six percent DMSO cryopreserved platelets with a focus on platelet membrane disintegration, irreversible platelet damage, and marked release of platelet extracellular vesicles with thrombin generation procoagulant activity.

And these vesicles contribute about 25 percent of procoagulant activity of cryopreserved platelet products. And this was published in 2016.

The future plans for Dr. Simak's program are a development of assays for characterization of membrane and protein submicron particles in biologics with a focus on nanoparticle tracking analysis, atomic force microscopy, asymmetric flow field flow fractionation, and high-resolution flow cytometry; also to develop new methods of platelet cryopreservation to achieve preservation of fully functional platelets -- and this is with investigation of different cryoprotectants and ice recrystallization inhibitors -- also, to investigate cryoprotective effects of various engineered nanomaterials for platelet cryopreservation, and to investigate the cold resistance of platelets

from cold and freeze-tolerant species.

The third program is under the direction of Dr. C.D. Atreya, and it's titled Ex Vivo Stored Blood Component Safety and Quality: Evaluation of Novel Methods for Pathogen Reduction and Functional Regulation in Blood Components. The objective of this program is to identify and evaluate promising methods and technologies effective in pathogen inactivation while preserving functional properties of the treated blood components.

The accomplishments under this program are evaluation of 405 nanometer light as a novel pathogen reduction technology for blood component safety. This research project generated seven publications in peer-reviewed journals, one patent application that was filed by the FDA, and also one cooperative research and development agreement, or CRADA.

Also under these accomplishments are the evaluation of microRNA-based regulatory mechanisms in ex vivo-stored blood cells with reference to platelet functions. And this resulted in nine publications in

peer-reviewed journals, and also a whole blood microRNA analysis of hemophilia A patients, and led to discovery of microRNA regulation as a mechanism for hemophilia A. And this resulted in five publications in peer-reviewed journals.

The rationale for the 405-nanometer light as a tool for blood safety is summarized here. Microbicidal efficacy of 405-nanometer light has been well established as an alternative to UV light. It can be used at levels that are lethal to microorganisms without harming the exposed mammalian cells.

In situ pathogen reduction treatment without external photosensitizers is thus possible, unlike with UV-A or UV-B light. The light-excited endogenous porphyrins produce reactive oxygen species, including hydrogen peroxide and singlet oxygen, leading to oxidative damage and microbial cell death.

The proof of concepts for the 405-nanometer light effect are summarized on this slide. This group tested a number of pathogens, including gram-positive bacteria and gram-negative bacteria, several viruses,

and also protozoa. And they were able to show that there's up to a greater-than-five-log reduction of these pathogens with a reasonable dose of UV light in the 200 joules per centimeter range.

The effect on blood components was that it did not alter platelet in vitro metabolic parameters, and the treated platelets were able to retain their platelet aggregation potential. The treatment also preserved plasma protein integrity -- and these studies are ongoing -- and preserves human platelet in vivo survival and recovery function in the SCID mouse model. Studies of this treatment on red cell is currently ongoing.

So, in summary, studies with 405-nanometer light provided proof of concepts on microbicidal efficacy and preservation of plasma integrity and platelet functional parameters. And overall, these concepts warrant further comprehensive evaluations towards an alternative to the existing pathogen reduction technologies.

Okay. So, another project in this group is

the evaluation of microRNA-based regulatory mechanisms in ex vivo stored platelets. The objective here is to identify platelet functions relevant to in vitro quality that are regulated by microRNAs.

And as way of background, platelets are terminally differentiated and enucleated, do not have gene transcriptional regulatory mechanisms, but they have abundant microRNAs, which are the small noncoding regulatory RNAs.

The existence of microRNA-based post-transcriptional regulation of messenger RNA is known in platelets. Preservation of platelet shape, activation potential, and ATP conservation in storage are important for platelet in vivo functions. And how these functions are regulated in stored platelets is currently not known.

So, in summary, this group identified microRNA-223 regulation of platelet septine-2 and -6, which are important for preserving platelet shape. It identified microRNA-320c and microRNA-181a, a regulation of platelet activation through regulation of

RAP1b protein, which is Ras-related and important for platelet activation.

It also identified microRNA-570 interaction with mitochondrial ATPase Subunit G, ATP5L, in stored platelets. And these publications range from 2017, 2018, and 2020.

So, future plans for Dr. Atreya's program are in the evaluation of 405 nanometer light as a novel pathogen reduction technology for blood component safety, and these plans include, based on the proof of concept developed so far, further comprehensive evaluations following additional bloodborne pathogens will be evaluated. And there's a series of viruses and protozoa that will be tested.

The plan is to identify the optimal light dose that effectively inactivates pathogens, to evaluate platelet and plasma coagulation function following treatment with the optimal light dose, and to examine pathogen reduction capability in stored red blood cells.

In the area of evaluation of microRNA-based

regulatory mechanisms in ex vivo stored blood cells with reference to platelet functions, the plans are to continue examining the role of microRNAs and messenger RNAs identified in our microRNA/messenger RNA profiling with a reference to platelet function and quality, and also to evaluate the platelets after exposure to 405 nanometer light to identify potential microRNA biomarkers of in vitro quality.

So, that concludes my presentation. I'd be happy to answer any questions.

DR. RICHARD KAUFMAN: Thanks very much.

Q&A SESSION

DR. RICHARD KAUFMAN: Are there any questions from the group? Srid.

DR. SRIDHAR BASAVARAJU: Hi. Thanks for presenting that. That was interesting. The question I had was there's only one PRT technology on the market right now, as you know, the Cerus technology. And it appears that you're trying to develop, potentially,

another one, right?

How long do you think before any of these would actually be available in clinical settings if you had to guess? I know that's just speculative. I'm just kind of curious. That's all.

DR. JAROSLAV VOSTAL: Well, it's really hard to tell. I can tell you for reference that it took about 20 years to build up the Cerus product from the original concept through the clinical trials and eventual approval. So, there's a lot of efficacy and safety issues that have to be covered with the chemical treatments of the cells.

DR. SRIDHAR BASAVARAJU: So, would you guys see that that through, or at some point, do you license it out to another company or something like that?

DR. JAROSLAV VOSTAL: So, I think we would -- what we try to do is develop proof of concepts that things can be done, like for example, pathogen reduction whole blood or red cells. And we're hoping that there's somebody else out there in the marketplace who will be able to pick up on that and take it further

and commercialize it. Our goal is not to commercialize anything that we develop.

DR. RICHARD KAUFMAN: All right. Dr. Perkins, please. Dr. Perkins, are you there?

MR. MICHAEL KAWCZYNSKI: Dr. Perkins, make sure you're unmuted with your own phone.

DR. JEREMY PERKINS: Thank you. That was --

MR. MICHAEL KAWCZYNSKI: There you go.

DR. JEREMY PERKINS: So, for the 405-nanometer light affecting bacterial pathogens through exciting their endogenous porphyrins, does that also affect lymphocytes? I mean, one of the advantages of psoralen-treated UV light is that you also get lymphocyte reduction, which for oncology patients and patients with severe immunodeficiency reduces the risk of transfusion-associated graft-versus-host disease.

DR. JAROSLAV VOSTAL: Well, I think that's a very good question. I don't think that Dr. Atreya's group is focused on that yet. I think maybe they will in the future.

DR. JEREMY PERKINS: Thank you.

DR. RICHARD KAUFMAN: All right. Any other questions?

All right. Dr. Vostal, thanks very much.

DR. JAROSLAV VOSTAL: Okay, thank you.

DR. RICHARD KAUFMAN: So, our next section is designated for the open public hearing.

OPEN PUBLIC HEARING

DR. RICHARD KAUFMAN: However, due to no formal oral requests being received, we'll be moving on to the closed session for Topic II.

MR. MICHAEL KAWCZYNSKI: Do we have an estimated time as to when we will be coming back from the closed session so we can tell the public? Please keep your cameras off for the moment. Hold on.

DR. BRENDA GROSSMAN: Fifty minutes.

MR. MICHAEL KAWCZYNSKI: Okay. All right. So, just give me a second. You said 50 minutes? So, roughly around 2:20. Okay.

So, Studio, if you can make an announcement

and put up there that we should be returning around 2:20, and then cut our feed.

BREAK FOR TOPIC II CLOSED SESSION

TOPIC III: OVERVIEW OF DETTD RESEARCH PROGRAMS

MR. MICHAEL KAWCZYNSKI: Just give me a moment until I get it clear. All right, I'd like to welcome back the public. We just completed our second session. Now we're going into our third for today, so I'm going to hand it back to Dr. Richard Kaufman, today's Chair. Dr. Kaufman, take it away.

DR. RICHARD KAUFMAN: All right, thank you. So I'm delighted to introduce Dr. Hira Nikhasi who's the director of the Division of Emerging and Transfusion Transmitted Diseases. Dr. Nikhasi.

DR. HIRA NIKHASI: Thank you, Dr. Kaufman, and I want to thank all the Committee members on the Advisory Committee as well as the scientific committee who site visited our program. So, I will give you an

overview of our Research and Regulatory Program of the Division of Emerging Transfusion and Transmitted Diseases. I am the director. My name is Hira Nikhasi and I'm the director of the division. Please forgive me because I have an allergy, so I may have to cough in between.

The mission of the Division of Emerging and Transfusion Transmitted Diseases -- hence, I will call it DETDD because it's a mouthful, is to ensure the blood safety and availability of our nation. About 14 million units are transfused annually of which 10 million are red blood cells, approximately 2 million platelets, and approximately 2.4 million plasma.

Now the risk of transfusion-transmitted infections has been significantly reduced with the introduction of FDA licensed or cleared screening tests.

And in those categories, we have a couple nucleic acid tests as well as serological tests. And just to give you an idea of what front we are covering, we have the retroviruses HIV1/2 Group O, for nucleic

acid, hepatitis-wise CMV, West Nile, Babesia, and until recently Zika because we have stopped testing because of -- due to reduced incidents of Zika. Then we also have assays in the serological framework which is, again, retroviruses, hepatitis. In addition to that, we have T. cruzi and Chagas disease, Syphilis, and CMV.

Now, the Division of Emerging and Transfusion Transmitted diseases is organized in immediate office of the director which includes me and Dr. Peyton Hobson, who is the deputy director. Including that, we have deputy associate director Julia Lathrop, and also Dr. Sayah Nedjar, director of Managed Review, as well as program support specialist Mr. Alex Repace. And it is organized into four branches or labs. We have a Product Review Branch, which is staffed with the full-time reviewers.

These are scientists but they are full-time reviewers but they do not do any research. They're headed at the moment by acting chief, Dr. Pradip Akolkar. We are in the process of hiring a permanent chief for that. Then in the other research branches,

we have Laboratory of Bacterial and TSE Agent. Dr. David Asher is the head of that. We have Laboratory of Molecular Virology, and Dr. Indira Hewlett is the head of that laboratory.

And the Laboratory of Emerging Pathogens, Dr. Sanjai Kumar from today, and there are several PI's included in there. And today, you know, you will hear from Dr. Kumar about some of the PI's, not all the PI's research programs or progress which is Dr. Alain Debrabant, Robert Duncan, myself, and Dr. Kumar's personal program.

Now briefly, what are the activities going on in these branches? The Laboratory of Molecular Virology conducts mission-related research on pathogenesis of HIV, HTLV, and emerging retroviruses. Laboratory of Emerging Pathogens conducts mission-related research on emerging and reemerging blood-borne parasitic, viral agents, and tick-borne pathogens.

The Laboratory of Bacterial and Transmissible Spongiform Encephalopathy Agents conducts mission-related research on bacteria such as treponema pallidum

and spongiform encephalopathy like vCJD. The Product Review Branch, which I mentioned, conducts a full-time review of the regulatory submissions.

The mission of the regulatory research activities in the DETTD is to plan and conduct mission-related research on pathogenesis of transfusion-transmitted infections and blood-borne agents such as retroviruses, hepatitis viruses, arboviruses. Most of the agents which are listed, the division are working on it -- parasites, Leishmania, Plasmodium, T. cruzi; tick-borne agents like Babesia. And recently we are in process of hiring a PI to work on other tick-borne agents, for example, in plasma and other relevant pathogens, bacteria, and then also the transmissible spongiform encephalopathy agent.

In addition to conducting the mission-related research, obviously, the research reviewers, as well as the other full-time reviewers, are proactively ensuring the safety of blood supply by reviewing regulatory submissions including biological license applications, pre-market applications, 510(k)s, INDs/IDEs for our

donor screening assays as well as the HIV diagnostic assays.

We are evaluating and the group is evaluating new technologies for rapid and multi-plex screening of blood supplies. And in addition to that, the staff develops policies and guidance documents for blood screening tests and donor screenings and diagnostic assays. In addition, we develop reference materials for validation of the lot release assays and provide scientific technical advice to other agencies such as CDC, DOD, and Department of Health and Human Services, the big department.

Outreach also includes talking to stakeholders. For example, as many of you may have seen in the past, we seek advice from the Blood Product Advisory Committee just like today's one on several issues about testing, implementation, and discussion of any pathogen that we need to in our initial testing for those pathogens to ensure the blood safety. We also serve as liaison to blood establishments and device manufacturers.

We collaborate with the WHO as a collaborating center for individual diagnostics in helping them to develop international standards, sometimes participating in there, or sometimes renewing those IVD standards. And then also, we participate in the Public Health Subcommittee where we participate in horizon scanning new emerging pathogens. I cannot move my slides. Something happened here. Mike? Okay. Thank you, Mike.

So accomplishments in the division are many. And in the next couple of slides, I will talk about the recent publication in the last two years, 2020 and 2021. The staff has published in high-impact journals, for example, in the (inaudible) area, Leishmania or Babesia or even T. cruzi and developed certain models, 3-D models, or talking about the pathogenesis, as well as identifying the isotopes which could be used for better sensitivity of assays.

Or the biomarkers for vaccines in the case of Leishmania here or to prevent the transmission of, if we have a vaccine, then transmission of Leishmania

parasite through blood. Next slide, please.

We also address directly sometimes the regulatory questions which are out there. For example, in the case of the infectious Treponema pallidum, the question was, how long they survive in storage in whole blood and platelets?

And the staff here worked on these questions and developed a model and then responded to that question and published in *Transfusion*. Then the staff is also involved in testing or invalidating new technologies for donor blood detection for diagnostic purposes. We are also looking at changing dynamics for certain arboviruses, for example, Zika virus and, are they over period of changing these sequences? And some of the studies have been done which shows that, over a period of time, there are certain changes in order to make sure that those changes do not affect our assays for the detection. And thank God, so far, we have seen the detection primers and pros which are selected in those regions, they have not changed. Next slide, please.

MR. MICHAEL KAWCZYNSKI: Dr. Hasi, if you could see-- do you see the two arrows right here, down here at the bottom of your PowerPoint?

DR. HIRA NIKHASI: I do, it's not moving. It's not --

MR. MICHAEL KAWCZYNSKI: Go ahead and click on it once.

DR. HIRA NIKHASI: I'm -- I did. Nothing happened; it's stuck.

MR. MICHAEL KAWCZYNSKI: Okay, okay.

DR. HIRA NIKHASI: So, okay. This is the last slide, so you don't have to do anymore after that.

MR. MICHAEL KAWCZYNSKI: That's okay. Go ahead.

DR. HIRA NIKHASI: Thank you for your help, Mike. So this summarizes the regulatory and research accomplishments by the DETTD. And in the area of the applications in last year and a half, we have reviewed approximately 450 applications which includes biological license applications, PMAs supplements, 510(k)s, INDs, IDEs, pre-submissions, which is

basically before any (inaudible) makes a test, they come and talk to us. And there are a lot of meetings with regard to them, and we provide them direction how to develop those assays.

And so, I think that staff has been very busy with that. And then, we have in the last year or so licensed several donor screening assays and cleared some HIV diagnostic assays. The publication for the last one year has been approximately 22 publication. And I gave you a flavor of that publications on previous couples of slides. And then the division has been able to secure funds from both intramural as well as the extramural through collaborations as were mentioned in the beginning by Dr. Orieji Illoh through CRADAs, through NIH CRADAs, but also FDA funding because these are competitive funding in the tune of around $2.5 million.

So I think overall, if I have to summarize, the division has been on the cutting edge of the science of emerging pathogens and is always ready to respond to the pathogens which impact blood safety.

So with that, I will go to the last slide. And I want to thank you all for listening, and I'm here to answer any questions. Thank you.

DR. RICHARD KAUFMAN: Thank you very much. Are there any questions from the group for Dr. Nakhasi? Okay. Well, it looks like none, but thank you again for your presentation.

DR. HIRA NAKHASI: Thank you.

OVERVIEW OF LEP RESEARCH PROGRAMS

DR. RICHARD KAUFMAN: Okay. And our final presenter today will be Dr. Sanjai Kumar. And he serves as chief of the Laboratory of Emerging Pathogens or LEP. Dr. Kumar.

DR. SANJAI KUMAR: Yep, thank you. So, is the timer set now?

DR. RICHARD KAUFMAN: Yep, you're all set.

DR. SANJAI KUMAR: Okay. Thank you, Dr. Kaufman, for the introduction. And as Dr. Nakhasi just said, there are a total of several principal

investigators in the Laboratory of Emerging Pathogens. And of those, I'm going to summarize the research programs of four principal investigators who are conducting research in parasitic diseases. So the -- so those are myself, Dr. Nakhasi, Dr. Debrabant, and Dr. Duncan.

So first I'll begin with my own research program in detection, immunity, and pathogenesis of two in-trial specific parasites of major public health significance. Those are malaria and Babesia.

So I'm going to skip the public health significance of malaria. From our mission perspective, there is no FDA licensed donor screening assay vaccine for malaria. The (inaudible) malaria vaccine is still ongoing.

To this end, we have identified over 200 novel Plasmodium falciparum gametocyte antigens. Of these, one gene, which we call Pfg-17, based on our TPCR assay, this detection target was more than 10-fold sensitive in detecting infectious malaria virus in endemic areas than the gold standard assay using the

female gametocyte gene detection target. So hence, this assay has applications in donor screening for malaria as well.

So next, from the same data set, antibodies against two gametocyte antigens, Pf77 and PfMDV-1, were able to block oocyst development in mosquitos were 93 percent and 84 percent, respectively. These antigens are expressed throughout parasite lifecycle, which is an unusual and unique property because most antigens are still expressed, genetically conserved, and induce naturally occurring antibodies and induce (inaudible) in endemic areas.

And thereby, by any measure, these could be considered ideal vaccine candidates. So in the past few months, I have been able to set up a multi-institution collaboration to produce these antigens in mRNA vaccines (inaudible) studies. So that's where this work is heading now.

Coming to the Babesia projects Babesiosis, another major global health problem with the highest number of (inaudible) transfusion-transmitted

infections occurred in this country, here itself. Again, from mission perspective, FDA has recommended (inaudible) screening for Babesia in year 2020. But we still need assays of superior sensitivity to detect lowest grade asymptomatic infections and understand the mechanism for immunity and pathogenesis.

So what are the accomplishments so far? We identified 56 immunodominant Babesia microti antigens. Most of these were previously not described.

We improved genome annotation, domain architecture, and evolutionary relationships of -- and have identified potential virulent genes. A combination of three antigens improved the sensitivity of ELISA in detecting acute Babesia infections.

And finally, what came out of this work was we developed and finishing work project on a multiplex bead-based antibody assay that highly effectively identifies asymptomatic infections in donor populations. And it improved the detection of low-grade out of the window period cases. So that summarizes this part of our Babesia work.

So the next major aspect of Babesia research, which is more complex to handle, is the deciphering the mechanism of Babesia microti pathogenesis. So there's two major questions here. One is does the Babesia parasite actually sequester? Nobody has shown it so far. I'm talking about Bebasia microti here. And does parasite sequestration and (inaudible) during the tibial cells continue to chronic persistent infections? That's direct relevance to blood safety because those asymptomatic inducers are the one who causes transfusion-transmitted infections.

And the second question is whether this sequestration also leads to organ damage contributing to severe disease akin to what happens in malaria. So what we have accomplished so far is to identify at least four antigens that have expressed on the surface of infected iRBC and potential (inaudible) cytoadherence host in the tibial cells.

Now we are pursuing this further in cytoadherence assess to determine if Babesia microti cells bind to receptors and host in (inaudible) cells

where these surface antigens such as ligand leading to parasite sequestration that will address a major discussion in the field. And coming to the second question of mechanism of immunopathogenesis, we have finished work on building a complete immuno (inaudible) Babesia microti infection and reinfection immunity is spanning over one year period in mice.

And we are starting pathogenesis studies. And we know (inaudible) model of hamsters, we start to see the disease more as a human disease. And we are conducting studies in terms of human, as understanding pathogens in humans. We are conducting in-depth flow cytometry and animal sequencing in blood samples coming from acute Babesia patients.

So the sum up what was presented. Just looking at the major accomplishments, in last four years, we published total of 21 papers. Some of the examples are here, papers the major publications. Most of the malaria work, especially the vaccine work, was done under the CRADA path and malaria vaccine initiative. And in four years, we received more than

$2 million in direct funding on Babesia. We got one patent actually issued now probably to Babesia microti antigens, U.S. patents. And they have also filed international patent.

We have research collaborative agreement with Griffith University in Australia to work our Babesia vaccines. And here is a list of our major collaborators, which are our most significant accomplishments. And through these collaborations, we are able to do this work at this level.

Now I'm going to present the -- summarize the work of Dr. Nakhasi. So his major objective is to develop methods and animal models to evaluate biomarkers of safety and efficacy of live attenuated Leishmania parasite vaccines. The work he's doing for last, more than 15 years.

So Leishmania and relevance to U.S. public health. So it's a visceral-borne infection but also it can be transmitted through a blood transfusion. So hence, relevant to public health in this country also. It is endemic to certain parts of United States. So

there are major transmission happenings inside the United States. Apparently, donor screening is not an option because it does not meet the incidence threshold that would allow us to implement the universal donor screening in the U.S. donor populations.

So then Dr. Nakhasi has taken this approach actually, alternative approach. And his approach is to reduce or minimize risk to blood safety through vaccination. I mean, you vaccinate people, there is no disease, and there is no risk to blood safety as a consequence. And also, vaccination to U.S. travelers and military personnel. Because the issue came 2-fold in the Iraq war because (inaudible) the military personnel started to come back home. They're stationed in endemic areas and can be an alternative to enhance blood safety. Okay. So next one.

So putting more perspective to the status of vaccination against Leishmania. So there is no FDA licensed vaccine currently, and obviously, there is no successful vaccine so far. In the past, it has been sort of accomplished in some countries through

inoculation with a low dose of wild-type Leishmania parasites. That was Leishmania major species. It's commonly known as Leishmanization process. That provided protection in vaccinated individuals.

But the practice is discontinued now because of flu infections, and it was not safe enough to be the way a wide-type vaccine needs to be. It's just not a long-term option. But it did provide a platform, a proof of concept that vaccination is possible through using whole Leishmania parasite vaccine. So building on that idea, Dr. Nakhasi is developing the genetically modified live-attenuated Leishmania parasite vaccines, although they are extensively profiled for the safety and evaluation of their efficacy and mechanism in human models. This can serve as alternative to unsafe leishmanization process.

Okay. Coming to his actual vaccine work now. The earlier work was done with the Leishmania donor vaccine construct, which is a more virulent form for Leishmania species, and was rather deemed not that safe because it developed infections are insufficient

attenuation in some volunteers that may lead to a more serious form of disease.

So hence, he launched just another program of (inaudible) vaccines the work which will be presented today, here, the summary of each work. So where he replaced -- which the new vaccine defers on the earlier version in two forms. One is the new vaccine is based on the rather benign form of Leishmania, Leishmania major. So the disease, even if it happens in volunteers, will be a more benign, mildly cutaneous disease. And this vaccine is generated using this CRISPR/Cas9 technology. So very well-defined, clean deletion in the centrin gene.

But the cell centrin gene is used as the basis of causing attenuation. And the next thing is it's missing the antibiotic marker which was present in the earlier one. So it's safer for human use. And the subsequent results in safety and immunization and safety profiling have showed the vaccinations in this second-generation vaccine in preclinical study in animal models induced robust immune response.

The vaccine was safe and efficacious against homologous Leishmania major infection, the one which causes the cutaneous version of disease, benign version. And also, surprisingly, and safe and efficacious against the more virulent form visceral Leishmaniasis. So this one singular vaccine live-attenuated should be able to cover both virulent form of the disease and rather more benign form of disease, both which are prevalent in different parts of world. And subsequently should offer a safe alternative to the Leishmanization process which can cause lesions.

So just summing up his accomplishments. A total of 43 publications in high journals. One U.S. patent has been issued, and one patent application has been filed. The work has led to three cooperative research and development agreements. And he has been able to establish a consortium of national and international collaborators.

And the idea being that together they will promote the further preclinical testing in collaboration development of experimental human model

and all these studies together which is across different institutions across many continents. The consortium was able to generate more than $7 million of extramural funding to support this work, and here is the list of those who are part of this consortium listed here. So now I'm going to move on to the work of Dr. Alain Debrabant.

The major objectives of Dr. Debrabant's program are to develop novel biomarker detection assays for Chagas disease and study disease pathogenesis and transmission.

So a bit about the Chagas disease itself and its global and public health relevancy in United States and also the blood transmission. It's caused by Trypanosoma cruzi, which can be bloodborne although it's vector-borne mainly but transfusion-transmission infections do happen. So it's a bit of sufficient problem in this country also.

About 300,000 infected individuals are estimated in the United States including 76 autochthonous cases in southern states here. So there

is a low-level vertical transmission going on here. There's also vertical transmission at a low rate in about one to five percent of pregnant women. So risk of transmission by blood transmission is now significantly reduced. But the risk was deemed sufficient enough that it led to the implementation donor screening for antibody in 2007.

But, even with the donor screening for antibody in place, there's still a need for alternative biomarker detection assays to further include donor testing and for rapid diagnosis and for some of the purposes you'll see. And also, the program aims to address and understand the mechanism of persistent chronic Chagas disease, parasite persistence, and vertical transmission.

So with that, coming to these projects and major findings, so Dr. Debrabant identified and characterized T. cruzi secreted proteins, (inaudible) proteins that could be further developed as novel biomarkers of Chagas disease both of pathogenesis and for diagnosis and subsequently generated high affinity

and specificity detection reagents in the form of aptamers and monoclonal antibodies. These reagents were used to develop new assays in ELISA format and in lateral flow formats that detect the T. cruzi biomarkers of infection in blood from chronically infected mice and in the asymptomatic Chagas infections in endemic areas so those either asymptomatic forms or those experiencing the cardiac symptoms and with the positive T. cruzi infection.

So the idea is to develop a sort of a biomarker for definite diagnosis. One of these biomarkers, T. cruzi-5171-based ELISA detected a reduction in biomarker levels post drug treatment of mice and in patients suggesting its utility to assess efficacy of drugs in pre-clinical and clinical stages of development.

So it allows it to measure drop of this particular biomarker as the successful drug treatment progresses and hence leading to drop in the parasite burden both in the mouse model or in individuals. And so the implications for preclinical evaluation in mice

or in clinical efficacy studies is obvious then. And then collaborative studies are ongoing to further evaluate these assays for treatment efficacy and cure in clinical trials and for rapid diagnosis. So that includes both for diagnostic part and for drug efficacy use of these biomarkers in collaborative studies.

So the next part of this study is Chagas disease pathogenesis and transmission. So by proteomic studies through (inaudible) survey and by live fluorescence studies, Dr. Debrabant's group demonstrated the presence of T. cruzi proteins.

These three proteins are GRP78, HSP70, and Mucin at the surface of infected cells and in the form of extracellular vesicles suggesting their role in pathogenesis. And also using transgenic (inaudible) T. cruzi parasites, they used these parasites to study parasite dissemination in different parts of body and in organs in chronic infection. And what they find is that the gut as a major parasite reservoir in a mouse model of chronic T. cruzi Chagas disease. A finding which has been confirmed by the other groups recently.

In addition, they developed an in vitro 3D culture system of human trophoblasts and showed that 3D-grown JEG-3 cells -- those are trophoblasts aligned -- they were rather refractory to T. cruzi infection and released paracrine factors of resistance to infection, suggesting the role of trophoblasts in limiting parasite vertical transmission. And that goes back to the observation that only one to five percent of pregnant women transmit infection through placental transmission to the child during pregnancy.

So the further study, I think that's going to be the further focus of Dr. Debrabant's work now is to study the mechanisms for immune evasion and parasite persistence. That's how the parasite can invade the endothelial cells and why the immune (inaudible) establish chronic infection.

So again, summing up these accomplishments. There have been publications in each of these major projects here. So the work on the diagnosis both in acute and asymptomatic infection in endemic areas and that drug efficacy is at least based on biomarker

detection, those she is pursuing through collaborations, international collaborations, and also the assay development is also being further progressed both through academia and industry. So that's where it stands now.

I'm going to -- I think my time is ending now also. I'm going to talk about Dr. Duncan's program now, advanced technology for reducing the risk of transfusion transmission of infectious agents. So I'm going to summarize three projects. Two projects are complete, and a third one is still ongoing.

So the first one is Ebola resequencing microarray project. So, the idea around here, resequencing microarray, was designed and developed with the idea to sequence the Ebola virus genome in an efficient and computationally simple process. And the project came into being during this Ebola epidemic in west Africa.

And so as a consequence of this work, three different Ebola virus strains were fully sequenced, Zaire strain, Bundibugyo virus strain, and the Sudan

virus and Taï Forest virus strain. And then further, he confirmed the sequencing to next generation sequencing to make sure there is a sequence validation and no discrepancies.

So the next idea was how to evaluate this assay, will be able to detect a genetic drift during an ongoing epidemic. And that was the main idea to follow that genomic drift. So for that, he relied on his laboratory-generated VSV-Ebola-GP virus to start, and that was subjected to three passages in the presence of neutralizing antibodies. And after three passages, this D amino single test minus a substitution.

This is a dominant mutation that was seen (inaudible), really and Dr. Duncan said this Ebola-RMA device was able to detect this (inaudible). So these studies indicate that Ebolavirus-RMA device can detect genomic drift and is suited for further evaluation as a tool to sequence clinical specimens in epidemiological and surveillance studies. And the device can be modified using this model for any emerging epidemic.

So next is this laser-based detection project

for multiplex pathogen detection in blood. So this was the device developed by Creative LIBS Solutions, and Dr. Duncan was sent this device for the evaluation here. So he was able to use these for two parasites, Gram-negative and Gram-positive bacteria, and HIV-spiked blood samples. And then subsequently, he (inaudible) samples using HIV CV positive and negative samples. And also, I mean, he got sufficient sensitivity results. But the project is now complete now here, and no more further work will be done on this one.

Coming to the last project here, this blood-borne pathogen resequencing microarrays. The two (inaudible) tested in the first one, and then he tested around five pathogens. And then he expanded to 55 blood-borne viruses, 5 bacterial and 16 protozoan species, strains. And they were able to retain sensitivity detection rapid analysis. And also, what he's doing currently is comparing this to the nanopore-based sequencing platform to compare these two sequencing matters. And with that -- so this is the

only part of the project which is still ongoing. The last part comparing the nanopore.

And here are his major publications related to all these three projects. And I'm going to stop here and take any questions if there are any.

DR. RICHARD KAUFMAN: All right. Are there any questions or comments from the group?

MR. MICHAEL KAWCZYNSKI: All right. Just remember, you can please raise your hand. You did such a great job. Oh, here we go. Dr. Stapleton, please.

DR. JACK STAPLETON: Sorry, I meant to not raise it. I was trying to respond.

DR. RICHARD KAUFMAN: No problem.

DR. SANJAU KUMAR: You can still ask a question. Okay, thank you then.

MR. MICHAEL KAWCZYNSKI: All right.

DR. RICHARD KAUFMAN: Thank you, Dr. Kumar. All right.

MR. MICHAEL KAWCZYNSKI: Sir, if you wouldn't mind or Christina. Christina, this is the portion where we are going to conclude the public portion of

today's meeting. Is that correct?

MS. CHRISTINA VERT: Yes. That's -- did you mention the open public hearing?

MR. MICHAEL KAWCZYNSKI: Oh, no, we have to -- sorry, open public hearing. Here you go. Go ahead, sir.

OPEN PUBLIC HEARING

DR. RICHARD KAUFMAN: All right, so our next section is designated for an open public hearing. However, due to no formal oral requests, we'll be moving on to the closed session for Topic III.

MR. MICHAEL KAWCZYNSKI: Okay.

MS. CHRISTINA VERT: Thank you.

MR. MICHAEL KAWCZYNSKI: Is there any formal closeout? We just want to make sure before we end the feed publicly. So just want to make sure if there was any formal steps. This portion of the public session has concluded. So to the studio, you can please end the feed. We thank everybody who has joined us today

and have a great rest of the day. And then in a moment, we will be going back to the closed session which will then run to the conclusion of the meeting.

BREAK FOR TOPIC III CLOSED SESSION

MEETING ADJOURNED AFTER CLOSED SESSION