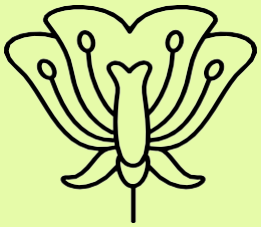
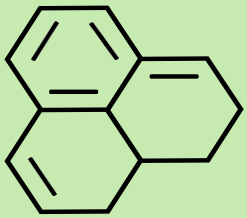
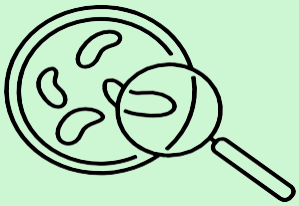
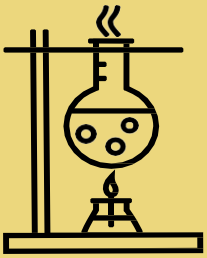
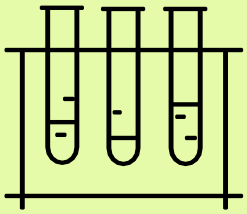


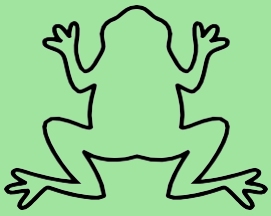
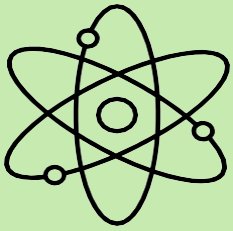
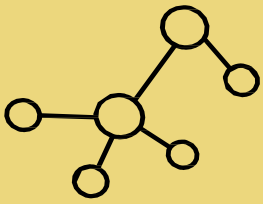
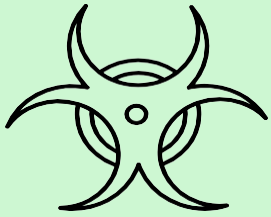
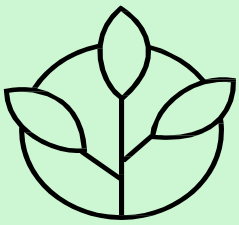
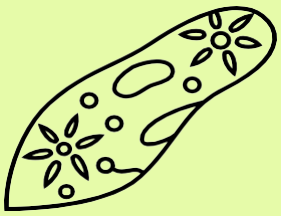
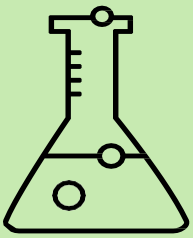
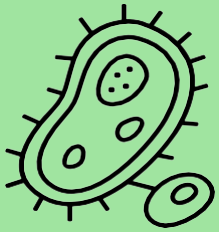







CBER Science Symposium

Program Book

Agenda, Speaker Abstracts & Bios

September 16-18, 2024 - 9:30 AM – 4:30 PM

FDA White Oak Great Room

Contents

WELCOME

Welcome to the 2024 CBER Science Symposium! We are thrilled to return this year's symposium to an in-person event, complemented by a virtual option to maximize access to the rich science that will be shared during these three days. The global COVID-19 pandemic was yet another event that validated the importance of conducting research related to the products that the center regulates. Indeed, the researcher-reviewer model remains an integral part of what we do at the Center to support the development of important biologic products that advance public health. This symposium provides us with the opportunity for scientific exchange and dialogue across the spectrum of the products regulated by the Center. The discussions that occur as part of this symposium may well lead to new insights and approaches for both existing and future research projects. We hope that through this exciting opportunity for communication and collaboration, CBER will continue to increase the contribution of its work toward the improvement of public health.

Thank you very much for taking the time to participate in the symposium. We hope that you will find the program informative, inspiring, and enjoyable.

Sincerely,

Peter Marks, MD, PhD, Director, CBER

Dear colleagues,

Welcome to the 2024 CBER Science Symposium! Thank you for choosing to spend time with us over this week to share the latest scientific advances within CBER and in the greater biomedical research community. Our common goal is to focus on new knowledge that supports biological product development and CBER's regulatory mission, to the benefit of public health in the U.S. and globally.

The COVID-19 pandemic changed many things, including the way we communicate science. We have renewed appreciation for the importance of in-person scientific meetings, the format that returns for the 2024 CBER Science Symposium. We are especially grateful for the presence of our external speakers who are traveling from near and far to join us. But we have also learned to embrace the advantages of a virtual platform. The hybrid format will allow even more speakers at a distance to share their science, and the hybrid approach will make the meeting accessible to all. No matter how you participate, we very much hope you'll find the scientific sessions stimulating and informative, such that you gain new knowledge, new ideas for lines of investigation, and new options for collaboration.

No scientific meeting comes to fruition without a dedicated group to plan the event and coordinate its many logistics*. I am so grateful to the dedicated people from across CBER who labored long and hard on Planning and Execution Committees to bring you this year's symposium. In particular, I want to recognize and thank Dr. Monica Young for her terrific leadership in working across the Center and with our external colleagues to organize and implement all aspects of this biannual event.

So please learn, communicate, collaborate, and most of all, enjoy!

Kind regards,

Karen Elkins, PhD, Associate Director for Science, CBER

*see pages 6-7 for complete listing

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Maryland Hatch, CBER IT Liaison/IT AE Project Manager

AGENDA

FDA Headquarters, White Oak Great Room, Building 31
September 16 -18 - 9:30am - 4:30pm

September 16, 2024

WELCOME & HISTORICAL PERSPECTIVE

9:30 AM	Peter Marks, MD, PhD	Director, CBER

SESSION 1: CELL, TISSUE & GENE THERAPY

Session Chairs: Alexander Zhovmer, PhD & Ronit Mazor, PhD

10:10 AM	Session Keynote: "Hematopoietic Stem Cell Gene Therapy for Inherited Blood Cell Diseases" **Donald Kohn, MD,** Distinguished Professor, Pediatrics, Hematology/Oncology, Distinguished Professor, Molecular and Medical Pharmacology, University of California, Los Angeles
10:45 AM	Q & A for Donald Kohn
10:55 AM	"Immunogenicity monitoring and mitigation of AAV Vectors in Gene Therapy" **Ronit Mazor, PhD,** Principal Investigator, Office of Gene Therapy, Center for Biologics Evaluation and Research
11:15 AM	"Understanding and navigating immune responses to Cas proteins used in gene editing" **Zuben Sauna, PhD,** Principal Investigator/Director, Division of Hemostasis, Office of Plasma Protein Therapeutics, Center for Biologics Evaluation and Research
11:35 AM	Q & A for Ronit Mazor & Zuben Sauna
11:45 AM	LUNCH

SESSION 2: ADVANCED MANUFACTURING AND ANALYTICS, INCLUDING NEW AND EMERGING TECHNOLOGIES

Session Chairs: Carlos Villa, MD, PhD & Amir Khoshi, PhD

12:45 PM	Session Keynote: "Single-shot, Multi-Dose Vaccines Prepared with Atomic Layer Deposition Techniques" **Theodore Randolph, PhD,** Gillespie Professor/Co-Director, Center for Pharmaceutical Biotechnology, University of Colorado Boulder
1:20 PM	Q & A for Theodore Randolph
1:30 PM	Session Keynote: "Self-Tolerance and Immunoregulation after Traumatic Soft Tissue Injury" **Kaitlyn Sadtler, PhD,** Earl Stadtman Tenure-Track Investigator, Chief of the Section for Immunoengineering, NIH, National Institute of Biomedical Imaging and Bioengineering
2:05 PM	Q & A for Kaitlyn Sadtler
2:15 PM	"Evaluation of 405 nm visible blue light as a novel pathogen reduction technology for plasma and platelets" **Joseph Jackson, PhD,** Staff Fellow, Office of Blood Research & Review, Center for Biologics Evaluation and Research
2:30 PM	"Advanced In Vitro Systems for Enhancing Functional Assessment of Cell Therapy Products" **Kyung Sung, PhD,** Principal Investigator/Chief of Cellular and Tissue Therapy Branch, Office of Cellular Therapy and Human Tissues, Center for Biologics Evaluation and Research
2:45 PM	"Use of advanced cell culture systems for immunotherapy testing" **Alex Zhovmer, PhD,** Principal Investigator, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research
3:00 PM	Q & A for Joseph Jackson, Kyung Sung & Alex Zhovmer
3:15 PM	BREAK

3:30 PM	**Symposium Keynote Address** "How will CRISPR genome editing become a standard of care?" **Jennifer Doudna, PhD,** Nobel Laureate in Chemistry; Professor; Li Ka Shing Chancellor's Chair in Biomedical and Health Sciences, University of California, Berkeley (virtual presentation)

September 17, 2024

SESSION 3: EMERGING AND RE-EMERGING DISEASES
Session Chairs: David McGivern, PhD & Ranadhir Dey, PhD

9:30 AM	Session Keynote: "Clinically Validated Metagenomic Sequencing Assays for Infectious Disease Diagnosis and Characterization of Emerging Pathogens" **Charles Chiu, MD, PhD,** Professor of Laboratory Medicine and Medicine, Division of Infectious Diseases, University of California, San Francisco
10:05 AM	Q & A for Charles Chiu
10:15 AM	Session Keynote: "Anticancer pan-ErbB inhibitors reduce inflammation and tissue injury and exert broad-spectrum antiviral effects" **Shirit Einav, MD,** Professor of Medicine (Infectious Diseases) and of Microbiology and Immunology, Stanford University
10:50 AM	Q & A for Shirit Einav
11:00 AM	"Unbiassed metagenomic exploration of Transfusion-Transmitted infections with Nanopore sequencing" **Viswanath Ragupathy, PhD,** Staff Scientist, Office of Blood Research & Review, Center for Biologics Evaluation and Research
11:20 AM	"Outflanking Norovirus Antigenic Evolution for Vaccine Design" **Gabriel Parra, PhD,** Principal Investigator, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research
11:40 AM	Q & A for Viswanath Ragupathy & Gabriel Parra

FLASH Talks

12:00 PM	**Poster Title**	**Presenter**
	Identification of a novel strategy to modify AAV vector capsid to reduce immunogenicity	Winston Colon-Moran, MSc
	Developing a novel manufacturing platform for adeno-associated virus (AAV)-based vectors for gene therapy	Alan Baer, PhD
	Use of Bacteriocins to Improve Live Biotherapeutic Product Purity Assays	Robert Dorosky, PhD
	Efficient and robust generation of functional hematopoietic cells from human pluripotent stem cells in albumin-free conditions	Byung Woo Kim, PhD
	Investigation of the reversal potential of engineered Factor Xa agents in plasma treated with Factor Xa inhibitors	Stepan Surov, PhD
	Analyzing interactions of Influenza HA vaccine-elicited monoclonal antibodies using cryo-electron microscopy	Tapan Kanai, PhD
	Comparison and characterization of myeloid cell line models for *Anaplasma phagocytophilum* infection	Sabarinath Neerukonda, PhD
	A Machine Learning Driven Investigation of the Association between HLA and Asymptomatic SARS-CoV-2 Infection	Atul Rawal, PhD
	Single-cell transcriptomics reveals the immune landscape of the mouse colon during chronic *Trypanosoma cruzi* infection	Erica Silberstein, PhD
	Investigation of novel bacteriophage resistance mechanisms in vancomycin-resistant Enterococcus (VRE)	Emily M. Smith, PhD
	Characterization of hepatitis B virus (HBV) from deferred potential blood donors and infectivity in primary human hepatocytes cultures	Bryan Visser, PhD

12:30 PM	**POSTER PRESENTATIONS & LUNCH** ODD Numbered Posters for Sessions: • CELL, TISSUE & GENE THERAPY • ADVANCED MANUFACTURING AND ANALYTICS, INCLUDING NEW AND EMERGING • EMERGING AND RE-EMERGING DISEASES

SESSION 4: ADVANCES IN COMPUTATIONAL SCIENCE SUPPORTING BIOLOGICS' EVALUATION **Session Chairs:** Darón Freedberg, PhD & Marisabel Rodriguez, PhD	
2:00 PM	"Computational Microscopy of Viruses" Session Keynote: **Rommie Amaro, PhD,** *Professor*, Molecular Biology, University of California, San Diego (virtual presentation)
2:35 PM	Q & A for Rommie Amaro
2:45 PM	"Chemometrics and Machine Learning to Enable Applications of NMR in Biomanufacturing" **Frank Delaglio, PhD,** Principal Investigator, University of Maryland/National Institute of Standards and Technology
3:20 PM	Q & A for Frank Delaglio
3:30 PM	"Computational approaches for evaluating the effects of synonymous variants: Implications in human diseases, drug development and regulation" **Nobuko Katagiri, PhD,** Staff Scientist, Office of Plasma Protein Therapeutics, Center for Biologics Evaluation and Research Center for Biologics Evaluation and Research
3:45 PM	"Pythonic Applications for the Study of Glycans" **Lisa Parsons, PhD,** Staff Scientist, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research
4:00 PM	"Improving and Expediting Biologics Adverse Event Surveillance using a FHIR-based Platform" **Hussein Ezzeldin, PhD,** Senior Staff Scientist, Office of Biostatistics and Pharmacovigilance, Center for Biologics Evaluation and Research
4:15 PM	Q & A for Nobuko Katagiri, Lisa Parsons & Hussein Ezzeldin

September 18, 2024

SESSION 5: METHODS AND BIOMARKER DISCOVERY FOR PRODUCT SAFETY AND QUALITY
Session Chairs: Daniel Lagasse, PhD & CD Atreya, PhD

9:30 AM	"Microengineered Biomimicry of Human Physiological Systems" **Dan Dongeun Huh, PhD,** *Professor* of Bioengineering, University of Pennsylvania
10:05 AM	Q & A Dan Dongeun Huh
10:15 AM	Session Keynote: "Immunogenicity of Biologics – Prediction and Mitigation" **Sathy Balu-Iyer, PhD,** *Professor* of Pharmaceutical Sciences, University of Buffalo
10:50 AM	Q & A for Sathy Balu-Iyer
11:00 AM	"Evaluating factors affecting genome editing efficiency and specificity" **Zhaohui Ye, PhD,** Principal Investigator/Chief, Gene Transfer and Immunogenicity Branch, Office of Gene Therapy, Center for Biologics Evaluation and Research
11:20 AM	"Influenza Neuraminidase Active Site Proximity Assay (NAspa) for Rapid Profiling of Inhibitory Antibody Titers and Antigenic Drift" **Robert Daniels, PhD,** Principal Investigator, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research
11:40 AM	Q & A for Zhaohui Ye & Robert Daniels

FLASH Talks

12:00 PM	Poster Title	Presenter
	Revealing the role of micro-RNAs as post-transcriptional regulators of ADAMTS13 through binding to its coding region and understanding the effects of synonymous mutations on ADAMTS13 functionality	Katarzyna Jankowska, PhD
	Heterogeneity in pathogenic brain sequestered CD8+ T cells during experimental cerebral malaria revealed by single cell sequencing	Miranda Oakley, PhD
	Metabolite profiles distinguish exposure to Zika and Dengue flaviviruses in human induced pluripotent stem cells (hiPSCs)	Tahira Fatima, PhD
	Evaluation of the Leishmanin Skin Test antigen as a biomarker of vaccine immunogenicity and disease surveillance	Laura Klenow, PhD
	Exploring host microRNAs in plasma as non-immune biomarkers for differential diagnosis between Dengue and Zika	Krishnamurthy Konduru, PhD
	High-throughput APTT and one-stage APTT-based FVIII potency assays in low volume of mouse plasma	Catherine Jean
	A Live-Attenuated Leishmania Vaccine Shapes the Cellular Response in The Bone Marrow	Thalia Pacheco-Fernandez, PhD
	Defining Humoral Immunity and Antibody Immunodominance Following Human Norovirus Challenge	Kelsey Pilewski, PhD
	Qualitative analysis of immune responses to hepatitis C virus E2 protein induced with viral vector versus recombinant protein	Naveen Rajasagi, PhD

12:30 PM	**POSTER PRESENTATIONS & LUNCH** Even Numbered Posters for Sessions: • ADVANCES IN COMPUTATIONAL SCIENCE SUPPORTING BIOLOGICS' EVALUATION • METHODS AND BIOMARKER DISCOVERY FOR PRODUCT SAFETY AND QUALITY • EMERGING AND RE-EMERGING DISEASES • IMMUNE RESPONSE TO VACCINATION

SESSION 6: IMMUNE RESPONSE TO VACCINATION

Session Chairs: Hana Golding, PhD & Sherry Kurtz, PhD

2:00 PM	Session Keynote: "Challenge of Incompatible Requirements for SARS-CoV-2 and HIV-1 Neutralizing Antibody Assay Method Validation" **David Montefiori, PhD,** Professor in Surgery, Duke University
2:35 PM	Q & A for David Montefiori
2:45 PM	Session Keynote: "The study of adaptive immunity to viruses of pandemic concern" **Alessandro Sette, Dr.Biol.Sci.,** Professor, La Jolla Institute for Immunology
3:20 PM	Q & A Alessandro Sette
3:30 PM	"Unique attributes of early age immune responses to vaccines" **Mustafa Akkoyunlu, MD, PhD,** Principal Investigator, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research
3:45 PM	"Antigenic Assessments of Recent SARS-CoV-2 Variants for Guiding COVID-19 Vaccine Variant Composition Updates" **Carol Weiss, MD, PhD,** Principal Investigator/*Chief,* Lab of Immunoregulation, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research
4:00 PM	Q & A for Mustafa Akkoyunlu & Carol Weiss

CLOSING REMARKS

4:15 PM	Karen Elkins, PhD	Associate Director for Science, CBER

SPEAKER ABSTRACTS & BIOGRAPHIES

CBER Science Symposium

September 16-18, 2024 - 9:30 AM – 4:30 PM EST

Session 1: Cell, Tissue & Gene Therapy

September 16, 2024 – 10:10 AM – 11:45 AM EST

"Hematopoietic Stem Cell Gene Therapy for Inherited Blood Cell Diseases"

Donald Kohn, MD, Distinguished Professor, Pediatrics, Hematology/Oncology, Distinguished Professor, Molecular and Medical Pharmacology, University of California, Los Angeles

ABSTRACT

Treatment of inherited blood cell diseases using autologous transplantation of gene-modified stem cells (gene therapy) has been advancing over the past 3 decades. Adenosine deaminase Severe Combined Immune Deficiency (ADA SCID) was the first disorder approached by gene therapy. In studies done in collaboration with investigators at University College London/Great Ormond Street Hospital (UCL/GOSH), we treated 50 ADA SCID patients with the EFS-ADA lentiviral vector (LV) and busulfan reduced intensity conditioning (RIC)h busulfan. 48/50 (96%) achieved sustained engraftment of ADA gene-corrected stem cells with immune reconstitution (Kohn, Booth et al *NEJM*, 2021). Similar high frequencies of immune reconstitution have been achieved in a trial using a LV and RIC for X-linked SCID (XSCID) in a trial performed at UCL/GOSH, Boston Children's Hospital and UCLA with all 15 patients achieving sustained immune reconstitution. We have also performed clinical trials of gene therapy for two disorders of neutrophil dysfunction, X-linked Chronic Granulomatous Disease (XCGD) and Leukocyte Adhesion Deficiency I (LAD I). Both trials used the same LV backbone with a chimeric myeloid enhancer/promoter driving expression of the relevant cDNA (*CYBB* and *ITGB2*, respectively) and cytoablative busulfan conditioning (target AUC 65-75 mg/L*hr.). While the 5 adult patients with XCGD achieved sustained engraftment of gene-corrected HSC with >10% oxidase (DHR)+ neutrophils and absence of subsequent opportunistic infections, all 4 pediatric patients suffered significant decline in gene-marked cells in peripheral blood cells and BM CD34, 3-6 months after gene therapy, stabilizing at ~0.5% DHR+ neutrophils. The basis for the decline in gene-marked cells in the pediatric patients is unknown. In contrast, all 9 of the LAD I patients, treated between 0.5-9 years of age, have shown stable persistence of gene marked blood cells and ~20-70% CD18-expressing neutrophils. We are currently investigating the use of adenine base editing in HSC to correct a founder mutation in the *CD3D* gene that causes SCID in a Mennonite population; base editing in HSC is highly efficient and restores the ability of the corrected HSPC to produce mature T lymphocytes in vitro in an Artificial Thymic Organoid system. These studies demonstrate the potential to apply HSC gene therapy for the treatment of blood cell diseases.

"Immunogenicity monitoring and mitigation of AAV Vectors in Gene Therapy"
Ronit Mazor, PhD, Principal Investigator, Office of Gene Therapy, Center for Biologics Evaluation and Research

ABSTRACT
Adeno associated viruses (AAV) are potent vectors used for gene delivery in gene therapy products. Recent clinical findings revealed immunogenicity related challenges including pre-existing antibodies, formation of neutralizing antibodies after the first administration, innate activation and formation of a cytotoxic immune response against transfected cells. Here, we provide a review of current state of the art of immunogenicity of AAV vectors and strategies for mitigating it.

"Understanding and navigating immune responses to Cas proteins used in gene editing"
Zuben Sauna, PhD, Principal Investigator/Director, Division of Hemostasis, Office of Plasma Protein Therapeutics, Center for Biologics Evaluation and Research

ABSTRACT
Immunogenicity refers to immune responses to proteins used in therapeutic applications. Immunogenicity is of concern during drug development and licensure as it can affect the safety and/or efficacy of drug products. The Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR)-Cas9 system is an efficient genome editing tool with the potential to treat inherited human diseases. Development of safe and effective in vivo delivery remains a potential challenge for the widespread clinical use of CRISPR-Cas9. We and others have demonstrated that Cas9 is immunogenic in humans and have identified pre-existing adaptive immune responses against Cas9 derived from Staphylococcus aureus and Streptococcus pyogenes. The presentation will provide: (1) An overview of tools available for immunogenicity risk-assessment during drug-development and licensure. (2) Specific examples that illustrate the use of *in silico*, *in vitro* and *ex vivo* methods for immunogenicity risk-assessment of the Cas proteins when they are used *in vivo* for gene editing.

SPEAKER BIOS:

Dr. Donald B. Kohn is a Distinguished Professor at the University of California, Los Angeles in the Departments of Microbiology, Immunology & Molecular Genetics (MIMG) and Pediatrics. He is a pediatric bone marrow transplant physician and a member of the UCLA Broad Stem Cell Research Center and the Jonsson Comprehensive Cancer Center. He performs laboratory and clinical studies of gene therapy for blood cell diseases, especially primary immune deficiencies and hemoglobinopathies. His research is focused on developing improved methods for adding or editing genes in human hematopoietic stem cells and evaluating these approaches in early phase clinical trials.

Dr. Ronit Mazor is a Principal investigator in the office of gene therapy (OGT), Office of Therapeutic Products (OTP) at the Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA). She leads a research group that focuses on cellular and humoral immune response to gene therapy vectors. Ronit performs CMC reviews for BLA and IND submissions of biological products focusing on viral vector gene therapies. Before joining the FDA, Ronit worked as a senior scientist in Medimmune/AstraZeneca in their Antibody discovery and protein engineering focusing on prediction and mitigation of immunogenicity of therapeutic proteins. Dr. Mazor completed her graduate work in immunology from Tel Aviv University in Israel and her Post-doctoral training in the National Cancer Institute in Bethesda.

Dr. Zuben E. Sauna is a Principal Investigator and Director, Division of Hemostasis in the Office if Therapeutic Products (Center for Biologics at the US Food and Drug Administration. His research interests lie in understanding the pharmacogenetic basis of the immune response to proteins used in therapeutic interventions, including new modalities such as gene editing. His laboratory exploits a combination of computational, in vitro and ex vivo approaches to understand why some individuals and/or sub-populations develop immune responses while others do not. Work from his laboratory has been published in high impact journals such as Nature Biotechnology, Nature Medicine, Nature Communications, Science, and Science Translational Medicine. He received his Ph.D. from Poona University, India with subsequent training at the National Cancer Institute, Bethesda, USA.

Session 2: Advanced Manufacturing and Analytics, including New and Emerging Technologies

September 16, 2024 – 12:45 PM – 3:00 PM EST

"Single-shot, Multi-Dose Vaccines Prepared with Atomic Layer Deposition Techniques"

Theodore Randolph, PhD, Gillespie Professor/Co-Director, Center for Pharmaceutical Biotechnology, University of Colorado Boulder

ABSTRACT

It is an obvious statement, but vaccines are only beneficial when people get vaccinated! Unfortunately, the logistics of vaccination are complicated by the instability of vaccine antigens and adjuvants, and requirements for multiple vaccine doses. Effective delivery of vaccines to patients requires formulations that provide stability during storage, transportation, and delivery to patients. Vaccine components typically are only marginally stable, requiring degradation to be controlled by maintaining the vaccines within carefully prescribed, narrow temperature ranges. Maintenance of this "cold-chain" at each stage of delivery, storage and administration imposes serious logistical burdens and costs, especially in resource-limited areas. Furthermore, to generate

robust protective immune responses, many vaccines require administration of multiple doses at specific time intervals, resulting in poor patient compliance and additional logistical challenges.
To address challenges associated with delivery of multiple doses, a new process will be described that uses atomic layer deposition (ALD) techniques to deposit highly controlled, nanoscopic layers of alumina on the surface of spray-dried, glassy vaccine formulations. The resulting dry powders are remarkably thermostable, and suspensions of the powders upon injection provide controlled, pulsatile release of the vaccine where the time of that release can be "dialed in" by specifying number of applied ALD cycles. This allows single-shot injections of the ALD-coated powders to mimic the effect of multiple injections of conventional formulations. ALD-coated powders incorporating rabies virus vaccines retained full immunogenicity after storage for at least three months at 50°C, with single doses yielding both total antibody responses and neutralizing antibody responses almost an order of magnitude higher than those resulting from a typical prime-boost two dose series of conventionally formulated rabies vaccines.

"Self-Tolerance and Immunoregulation after Traumatic Soft Tissue Injury"
Kaitlyn Sadtler, PhD, Earl Stadtman Tenure-Track Investigator, Chief of the Section for Immunoengineering, NIH, National Institute of Biomedical Imaging and Bioengineering

ABSTRACT
During trauma and surgical reconstruction there is a disruption of homeostasis, release of self-antigen, and induction of inflammatory processes. This inflammation is meant to clear debris, prevent infections, and initiate wound healing. With the increased inflammation and release of self-antigen, central and peripheral tolerance are at play to prevent autoimmunity. As such we investigated the communications between innate and adaptive immunity to identify potential mechanisms of self-tolerance and how they are modulated in biomaterial-mediated muscle regeneration. Through use of a volumetric muscle loss (VML) model the lab has discovered that NK cells, cDC1s, pDCs, and regulatory CD8+ T cells play a central role in post-trauma self-tolerance. Through this study we have identified a new pathway mediating muscle wound healing and tissue regeneration with implications in future development of therapeutics both for tissue engineering and medical device development. This pathway has been found to be mis-regulated in a variety of autoimmune-like conditions suggesting a possible mechanism that links traumatic tissue injury with pathologies seen with more minor tissue damage. Work in human patients has identified multiple cytokine and chemokine changes after traumatic injury that are associated with autoimmune and tolerogenic responses including identification of a novel predictor of patient survival.

"Evaluation of 405 nm visible blue light as a novel pathogen reduction technology for plasma and platelets"
Joseph Jackson, PhD, Staff Fellow, Office of Blood Research & Review, Center for Biologics Evaluation and Research

ABSTRACT
The safety of blood products stored for transfusion, such as platelet concentrates, are accomplished by reducing risk of transfusion-transmitted infections (TTIs) in a variety of ways. A proactive approach to mitigate this risk is utilizing pathogen reduction technologies (PRTs) that play a pivotal role in inactivating a variety of pathogens, including bacteria, viruses, and parasites. Currently approved PRTs utilize chemical and UV-light based methods, and while these are effective in the inactivation of pathogens, exposure to UV-light is reported to cause tolerable

but unintended consequences to the quality of blood products. We and others have characterized an alternative approach to pathogen inactivation via exposure to 405 nm visible blue light. We have demonstrated that 405 nm blue light exposure inactivates gram positive and negative bacteria, viruses, and parasites in platelet concentrates stored in plasma. Furthermore, exposure to 405 nm blue light yields little effect or no effect on platelet in vitro quality and survival and recovery in SCID mice, and retains the activity of plasma coagulation factors tested to date. The successful pathogen inactivation capability and limited effect on platelets and plasma quality warrant continued exploration of the potential of 405 nm blue light as a novel and effective PRT.

"Advanced In Vitro Systems for Enhancing Functional Assessment of Cell Therapy Products"

Kyung Sung, PhD, Principal Investigator/Chief of Cellular and Tissue Therapy Branch, Office of Cellular Therapy and Human Tissues, Center for Biologics Evaluation and Research

ABSTRACT

The characterization of cell therapy products is often challenged by their inherent heterogeneity, leading to variability in product consistency and functional outcomes. Developing reliable and sensitive in vitro assays is crucial for identifying functional subpopulations within these products, thereby ensuring consistent and functional outcomes. Advanced in vitro systems, such as microphysiological platforms, offer powerful tools for this purpose. These systems can improve throughput, relevance, and reliability in assessing cellular function, particularly for cell therapy products that are difficult to characterize using conventional methods. Our recent studies have demonstrated how a microphysiological system was used to create a three-dimensional (3D) environment *in vitro*, thereby enhancing the sensitivity and reproducibility of cell functional behavior assessment. This system enabled the identification of lots that exhibited enhanced functional activity of mesenchymal stromal cells in inducing angiogenesis and vasculogenesis. Enhancing functional assessment through these advanced tools could lead to significant advancements in the manufacturing process and product release strategy for cell therapy products.

"Use of advanced cell culture systems for immunotherapy testing"

Alex Zhovmer, PhD, Principal Investigator, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research

ABSTRACT

Current options for treatment of food allergies are limited. However, recent advances in preclinical and clinical immunotherapy studies have greatly broadened the potential to manipulate immune system in patients with allergies, counteracting pathological immune responses. These new approaches include allergen immunotherapy, DNA and viral-like particle vaccines, biologics such as anti-IgE antibodies, as well as gene and cell therapy with gene-modified immune cells. While animal models can provide accurate and comprehensive characterization of safety and performance of emerging therapies, non-animal alternatives to animal studies are needed to reduce use of animals and cost of therapy testing. To facilitate initial evaluation of emerging immunotherapies, we develop advanced cell culture systems with tissue-like mechanics and structural properties. Here, we discuss how these tools may allow us to study physiological- and pathological-like behavior of immune cells, therapeutic effects and potential adverse reactions to prototype immunotherapies, and the potential for establishment of permanent immunologic tolerance to common foods by using gene and cell therapy approaches.

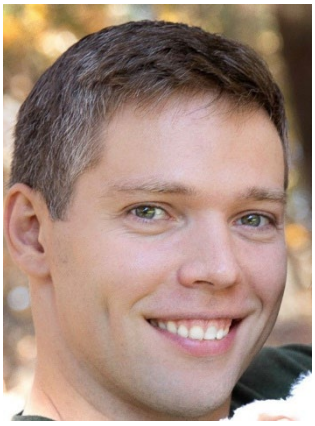
SPEAKER BIOS:

Dr. Ted Randolph received his Ph.D. in Chemical Engineering at the University of California, Berkeley. He worked as a post-doctoral fellow at the Ecole Polytechnique Federale de Lausanne, and then joined the Department of Chemical Engineering at Yale University as an Assistant Professor. After promotion to Associate Professor, he was named to Yale's first John J. Lee Junior Professorship Chair in Chemical Engineering. In 1993, Dr. Randolph accepted the Patton Associate Professorship Chair in the Department of Chemical Engineering at the University of Colorado. He currently serves as the Gillespie Professor of Bioengineering, co-Director of the University of Colorado's Center for Pharmaceutical Biotechnology. Dr. Randolph is a Fellow of the National Academy of Inventors, a National Science Foundation Presidential Young Investigator, received the AIChE Professional Progress Award and has twice received the American Pharmacists' Association Ebert Prize. He is an author of more than 260 peer-reviewed journal articles in the areas of biopharmaceutical formulation, lyophilization of proteins, protein-solvent interactions in non-aqueous environments, and protein refolding. Dr. Randolph is an inventor on 30 US patents, and has co-founded three companies, RxKinetix Inc., Barofold, Inc. and VitriVax Inc.

Dr. Kaitlyn Sadtler is a scientist and Chief of the Section on Immuno-Engineering at the National Institutes of Health. She began her lab at the National Institute of Biomedical Imaging and Bioengineering after a postdoctoral fellowship at the Massachusetts Institute of Technology in the Department of Chemical Engineering working on the molecular mechanisms of immune activation in the foreign body response. She completed her Ph.D. at the Johns Hopkins University School of Medicine where she showed a role for immune cells in biomaterial-mediated muscle regeneration. She has led research that has been published in journals such as Science, Nature Communications, Nature Materials, and Science Translational Medicine. She was recognized as a TED Fellow and delivered a TED talk that was listed as one of the top-viewed talks of 2018. Dr. Sadtler was selected for the Forbes 30 Under 30 List in Science, the MIT Technology Review 35 Innovators Under 35, the World Economic Forum Young Global Leaders, and the National Academies of Science Engineering and Medicine New Voices Program. She also received the 2021 Outstanding Recent Graduate Award from Johns Hopkins University and an honorary doctorate from her undergraduate university, UMBC. At NIH, Dr. Sadtler has lent her lab's expertise to the fight against COVID-19, leading a study that detected 16.8 million undiagnosed SARS-CoV-2 infections in the US after the first pandemic wave in the US. She continues her work on immunoengineering in the context of traumatic injury focusing on the balance of tolerance and autoimmunity during tissue reconstruction, recently implicating a new immune cell type in self-tolerance after volumetric muscle loss.

Dr. Joseph Jackson is a Staff Fellow in the Laboratory of Cellular Hematology, Division of Blood Components and Devices, Office of Blood Research Review, Center for Biologics Research and Evaluation at the US Food and Drug Administration. He has been actively contributing to the field of platelet biology and hematology through several publications in peer-reviewed journals and also contributes to the regulatory review of devices intended for blood collection, storage, and treatment. Dr. Jackson received his PhD from the Department of Microbiology and Immunology, University of Rochester, NY, USA where he elucidated the activity of platelets in HIV-induced inflammation. He subsequently received postdoctoral training at the National Cancer Institute, NIH, where he deciphered the role of heat shock proteins in platelet activity, followed by postdoctoral training in the Office of Therapeutic Products, CBER, US FDA, where he studied various aspects of blood coagulation relevant to regulation.

Dr. Kyung Sung is the Chief of the Cellular and Tissue Therapies Branch in the Office of Cellular Therapy and Human Tissue at the Center for Biologics Evaluation and Research, U.S. Food and Drug Administration. In this role, she oversees regulatory science research programs and the regulatory review process for cell and tissue therapeutic products, as well as medical devices. Her research focuses on the interactions between living cells and biomaterials, developing novel quantitative assays using advanced biomedical engineering tools. The overarching goal of her work is to understand how these interactions influence the production and characterization of regenerative medicine cellular products. Dr. Sung earned her Ph.D. in Chemical Engineering from the University of Michigan, Ann Arbor, and completed her postdoctoral training at the University of Wisconsin, Madison. Prior to joining the FDA in 2015, she worked as a Biotechnology Patent Examiner at the U.S. Patent and Trademark Office.



Dr. Alex Zhovmer became interested in immunology during his master's studies, working on cancer immunology at the Institute of Clinical Immunology in Novosibirsk, Russia. During his PhD and postdoctoral work, he studied molecular mechanisms of gene expression and cell signaling at the Institute of Genetics and Molecular and Cellular Biology in Illkirch, France, and at the Memorial Sloan Kettering Cancer Center in New York, US. He was able to combine these research experiences, studying basic mechanisms of immune cell motility and cell polarization during his work with Dr. Robert Adelstein at the National Heart, Lung, and Blood Institute, Bethesda, US. Currently, he serves as a Principal Investigator in the Laboratory of Immunobiochemistry, Center for Biologics Evaluation and Research, FDA, Silver Spring, US. His group uses animal models to study perspective immunotherapies for food allergy, trying to uncover mechanisms of coordinated actions of immune cells in tissues.

Symposium Keynote Address

September 16, 2024 – 3:30 – 4:00 PM EST

"How will CRISPR genome editing become a standard of care?"
Jennifer Doudna, PhD, Nobel Laureate in Chemistry; Professor; Li Ka Shing Chancellor's Chair in Biomedical and Health Sciences, University of California, Berkeley

ABSTRACT

Fundamental research to understand how bacteria fight viral infections uncovered the function of CRISPR-Cas programmable proteins that detect and cut specific DNA or RNA sequences. CRISPR technology is now an indispensable tool in human, animal, and agricultural research. Furthermore, the FDA's approval of a CRISPR therapy for sickle cell disease marked the beginning of a new era in healthcare. I will discuss the scientific and societal advances that will expand both the applications and impact of genome editing across the globe.

SPEAKER BIO:

Dr. Jennifer A. Doudna is the Li Ka Shing Chancellor's Chair and a Professor in the Departments of Chemistry and of Molecular and Cell Biology at the University of California, Berkeley. Her groundbreaking development of CRISPR-Cas9 as a genome-engineering technology, with collaborator Emmanuelle Charpentier, earned the two the 2020 Nobel Prize in Chemistry and forever changed the course of human and agricultural genomics research.

This powerful technology enables scientists to change DNA — the code of life — with a precision only dreamed of just a few years ago. Labs worldwide have re-directed the course of their research programs to incorporate this new tool, creating a CRISPR revolution with huge implications across biology and medicine.

In addition to her scientific achievements, Doudna is a leader in public discussion of the ethical implications of genome editing for human biology and societies, and advocates for thoughtful approaches to the development of policies around the safe use of CRISPR technology.

Doudna is an investigator with the Howard Hughes Medical Institute, senior investigator at Gladstone Institutes, and the founder of the Innovative Genomics Institute. She co-founded and serves on the advisory panel of several companies that use CRISPR technology in unique ways.

She is a member of the National Academy of Sciences, the National Academy of Medicine, the National Academy of Inventors, and the American Academy of Arts and Sciences. Doudna is also a Foreign Member of the Royal Society, a member of the Pontifical Academy of Sciences, and has received numerous other honors including the Breakthrough Prize in Life Sciences (2015), the Japan Prize (2016), Kavli Prize (2018), the LUI Che Woo Welfare Betterment Prize (2019), and the Wolf Prize in Medicine (2020). Doudna's work led TIME to recognize her as one of the "100 Most Influential People" in 2015 and a runner-up for "Person of the Year" in 2016. She is the co-author of "A Crack in Creation," a personal account of her research and the societal and ethical implications of gene editing.

Session 3: Emerging and Re-emerging Diseases

September 17, 2024 - 9:30 AM – 12:00 PM EST

"Clinically Validated Metagenomic Sequencing Assays for Infectious Disease Diagnosis and Characterization of Emerging Pathogens"

Charles Chiu, MD, PhD, Professor of Laboratory Medicine and Medicine, Division of Infectious Diseases, University of California, San Francisco

ABSTRACT

Recent outbreaks, including the 2019 COVID-19 pandemic from SARS coronavirus 2 (SARS-CoV-2) and the 2022 monkeypox outbreak, have underscored the importance of broad-based diagnostic tests for emerging infectious diseases. Accurate microbiologic diagnosis in patients with presumptive infectious disease syndromes, including meningoencephalitis, sepsis, and pneumonia, are needed to guide appropriate treatment with antimicrobial agents and improve clinical outcomes. Early detection and rapid characterization of pathogens are also critical to informing public health interventions, disease containment, and test development. Metagenomic next-generation sequencing (mNGS) is a powerful approach for detection of nearly all potential pathogens, including viruses, bacteria, fungi, and parasites, in a single assay without *a priori* knowledge of target sequences and the use of specific primers or probes. Furthermore, mNGS can be leveraged to monitor host gene expression by machine learning based analyses of RNA sequencing (RNA-Seq) data and develop classifiers to discriminate between infectious and non-infectious syndromes. Here the challenges in developing and validating mNGS assays for routine use in diagnosis of infections and investigating emerging pathogens will be described.

"Anticancer pan-ErbB inhibitors reduce inflammation and tissue injury and exert broad-spectrum antiviral effects"

Shirit Einav, MD, Professor of Medicine (Infectious Diseases) and of Microbiology and Immunology, Stanford University

ABSTRACT

Targeting host factors exploited by multiple viruses could offer broad-spectrum solutions for pandemic preparedness. Seventeen candidates targeting diverse functions emerged in a screen of 4,413 compounds for SARS-CoV-2 inhibitors. We demonstrated that lapatinib and other approved inhibitors of the ErbB family of receptor tyrosine kinases suppress replication of SARS-CoV-2, Venezuelan equine encephalitis virus (VEEV), and other emerging viruses with a high barrier to resistance. Lapatinib suppressed SARS-CoV-2 entry and later stages of the viral life cycle and showed synergistic effect with the direct-acting antiviral nirmatrelvir. We discovered that ErbB1, ErbB2, and ErbB4 bind SARS-CoV-2 S1 protein and regulate viral and ACE2 internalization, and they are required for VEEV infection. In human lung organoids, lapatinib protected from SARS-CoV-2–induced activation of ErbB-regulated pathways implicated in non-infectious lung injury, proinflammatory cytokine production, and epithelial barrier injury. In mice infected with mouse adapted SARS-CoV-2, lapatinib protected from mortality and reduced viral load in nasal tribunates and lungs. Similarly, lapatinib suppressed VEEV replication, cytokine production, and disruption of blood-brain barrier integrity in microfluidics-based human neurovascular units, and reduced mortality in a lethal infection murine model. We validated lapatinib-mediated inhibition of ErbB activity as an important mechanism of antiviral action. These findings reveal regulation of viral replication, inflammation, and tissue injury via ErbBs and establish a proof of principle for a repurposed, ErbB-targeted approach to combat emerging viruses.

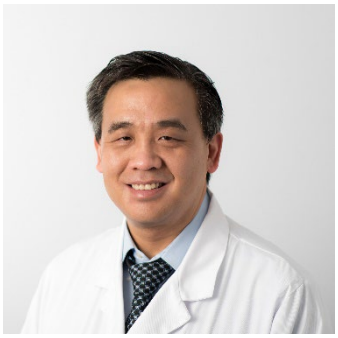
"Unbiassed metagenomic exploration of Transfusion-Transmitted infections with Nanopore sequencing"
Viswanath Ragupathy, PhD, Staff Scientist, Office of Blood Research & Review, Center for Biologics Evaluation and Research

ABSTRACT
We evaluated plasma samples from individuals with natural infections of HBV, HCV, HIV, and WNV. Additionally, we determined the limit of detection (LoD) and precision of our metagenomic sequencing approach using representative viruses. Briefly, sample preparation and analysis process include DNA/RNA extraction, cDNA synthesis, barcoded library preparation for Nanopore sequencing, followed by use of core bioinformatics tools, algorithms, and microbial databases were employed for data analysis. Targeted sequence analysis was conducted using CLC Genomic Workbench v21.0. This study uncovered a diverse microbial landscape, with a majority of reads being host or run control, leaving about 3% for virus-specific analysis. WNV, HIV, and HCV were identified, and modified sample preparation enabled HBV detection. High viral loads provided extensive genome coverage, while low viral loads yielded limited hits. Notable findings included HCV genotype 4a, HIV genotype B, and high similarity in WNV sequences to Lineage 1A. Co-infections such as human pegivirus 1 (HPgV-1) in HCV and Torque Teno Virus (TTV) in HBV cases were also observed. The virus panel showed hits at 10^3 copies, but consistent hits with full genome coverage were seen at 10^4 copies. These results demonstrate the effectiveness of the methods in detecting and characterizing various viruses and co-infections. The application of metagenomic characterization studies for agnostic viral detection opens a new opportunity towards identification of both known and unknown viruses for blood safety. The LoD for nanopore metagenomic sequencing approach is 10^4 copies/ml for the representative viruses tested. This approach enhances public health security by offering a comprehensive method for pathogen detection.

"Outflanking Norovirus Antigenic Evolution for Vaccine Design"
Gabriel Parra, PhD, Principal Investigator, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research

ABSTRACT
The fast-evolving nature of RNA viruses facilitates the emergence of new human pathogens and constitutes a major obstacle for vaccine design and implementation. One such fast-evolving viruses, norovirus, is a major cause of acute gastroenteritis in all age groups. In this talk, I will first discuss how viral population genomics enable us to determine the antigenic sites involved in the antigenic diversification of human noroviruses. I will then demonstrate that cross-reactive antibodies can be elicited against these variable antigenic sites, providing novel insights for the development and review of norovirus vaccines.

SPEAKER BIOS:



Dr. Charles Chiu is Professor of Laboratory Medicine and Medicine, Division of Infectious Diseases at University of California, San Francisco and Director of the UCSF Clinical Microbiology Laboratory. Chiu currently leads a translational research laboratory focused on the development and clinical validation of metagenomic next-generation sequencing (mNGS) and host response profiling assays for diagnosis of infections, outbreak investigation, and pathogen discovery. He is a principal developer of a CRISPR-Cas12a based assay for the diagnosis of COVID-19, for which FDA Emergency Use Authorization was obtained in July of 2020, and has achieved FDA breakthrough device designation for mNGS assays for pathogen identification from cerebrospinal and respiratory fluids. Chiu also leverages machine learning based approaches to develop host response classification models based on RNA gene expression for differential diagnosis of central nervous system infections, infection-associated chronic illnesses (Lyme disease, chronic fatigue syndrome, and long COVID), and hyperinflammatory syndromes such as sepsis and multi-systm inflammatory syndrome in children (MIS-C). Chiu's work is supported by funding from the National Institutes of Health (NIH), US Center for Disease Control and Prevention (CDC), Biomedical Advanced Research and Development Authority (BARDA), Abbott Laboratories, Chan-Zuckerberg Biohub, the Steven and Alexandra Cohen Foundation, and the California Initiative to Advance Precision Medicine. Dr. Chiu has authored more than 200 peer-reviewed publications, holds over 15 patents and patent applications, is a co-founder of Delve Bio, and serves on the scientific advisory board of Delve Bio, Biomeme, Mammoth Biosciences, Flightpath Biosciences, Biomesense, and Poppy Health.

Dr. Shirit Einav is a physician-scientist in the Department of Medicine (Division of Infectious Diseases) and the Department of Microbiology and Immunology at Stanford University School of Medicine. After obtaining her MD from Tel-Aviv University in Israel, Shirit pursued Residency in Internal Medicine at Harvard University (Beth Israel Deaconess Medical Center) followed by fellowship in Infectious Diseases at Stanford University. She joined the faculty at Stanford in 2011. Her basic research program focuses on understanding the roles of virus-host interactions in viral infection and disease pathogenesis. This program is combined with translational efforts to apply this knowledge for the development of broad-spectrum host-centered antiviral approaches to combat emerging viral infections and means to predict their progression to severe illnesses. Shirit is an Investigator at the Chan Zuckerberg Biohub in San Francisco and a Fellow of the Infectious Diseases Society of America (FIDSA).

Dr. Viswanath (Vishy) Ragupathy is a virologist with 28 years of experience in HIV/AIDS research and diagnostics. He has published several articles in high-impact scientific journals and has been actively involved in international collaborative research studies, including those focused on the use of NGS and AI/ML technologies. As a Lead Reviewer for IVD applications at the FDA, he plays a crucial role in reviewing and approving diagnostic device applications. His expertise spans clinical trials, IVD regulatory pathways, and advanced technologies such as AI/ML and next-generation sequencing. Dr. Ragupathy has made significant contributions to HIV panel development through collaborations with the NIH and Duke University. These panel materials are currently

used for both vaccine and assay development by various commercial manufacturers. His work in preventing mother-to-child HIV transmission in rural settings underscores his commitment to global health. A skilled mentor and communicator, Dr. Ragupathy continues to drive innovation in HIV diagnostics and research.

Dr. Gabriel I. Parra is a Principal Investigator at the Division of Viral Products, Food and Drug Administration, USA. He received his degree in Biology from the School of Sciences, Paraguay, his PhD in Microbiology from the School of Sciences, Uruguay, and completed his postdoctoral training at the National Institutes of Health, USA. His research is focused on epidemiology, genomics, evolution, and immunity of viruses associated to gastroenteritis.

Session 4: Advances in Computational Science Supporting Biologics' Evaluation

September 17, 2024 – 2:00 PM – 4:30 PM EST

"Computational Microscopy of Viruses"
Rommie Amaro, PhD, Professor, *Molecular Biology, University of California, San Diego*

ABSTRACT

I will discuss our lab's efforts, together with collaborators, to use data-driven molecular dynamics simulations as a "computational microscope" in order to understand SARS-CoV-2 and influenza viruses in atomic detail. I will focus on our studies of viral glycoproteins, their glycan shields, interactions with various host cell receptors, and other features. I will highlight how molecular simulations can help understand biologics mechanism of action and as well as drive immunogen design.

"Chemometrics and Machine Learning to Enable Applications of NMR in Biomanufacturing"
Frank Delaglio, PhD, Principal Investigator, University of Maryland/National Institute of Standards and Technology

ABSTRACT

Nuclear magnetic resonance spectroscopy (NMR) is powerful and diverse tool to characterize higher order structure (HOS) of protein therapeutics, because NMR spectra are sensitive to molecular shape and intermolecular interactions as well as chemical structure, and NMR can reproducibly probe this information at atomic resolution. Furthermore, NMR has the advantage that it can be applied non-destructively to protein therapeutics as-formulated, with little or no sample preparation. Intriguingly, since NMR can also be applied to quantify the small molecule mixtures comprising the metabolome, NMR has the potential to characterize the metabolomics of bioreactor production of proteins and live cell therapeutics, with a time resolution of hours or minutes. Exploiting NMR for these biomanufacturing needs leads to a series of computational challenges which we review, including metrics of spectral similarity, data handling for applications of principal component analysis (PCA), spectral analysis of mixtures, and identification of spectral features by machine learning.

"Computational approaches for evaluating the effects of synonymous variants: Implications in human diseases, drug development and regulation"

Nobuko Katagiri, PhD, Staff Scientist, Office of Plasma Protein Therapeutics, Center for Biologics Evaluation and Research

ABSTRACT

Due to the redundancy of the genetic code, many gene variants do not alter the amino acid sequence of the translated protein. These synonymous mutations were termed "silent mutations", assumed to be benign, and have been overlooked in the clinical genetic testing pipelines. A critical mass of literature from diverse disciplines has now conclusively demonstrated that synonymous variants can affect folding of both mRNA and protein via multiple mechanisms, alter protein levels and function, and cause numerous human diseases. Deliberate recoding of genes, often referred to as "codon optimization", leverages synonymous variation as an emerging technology for increasing protein yield. This technology is rapidly penetrating all aspects of therapeutic protein development and the design of gene therapy vectors. Dr. Katagiri will draw from studies of her own and other researchers, such as those on codon and codon-pair usage, mRNA stability, splicing regulation, miRNA binding, and codon conservation, to discuss computational approaches to evaluate the consequences (both desirable and undesirable) of gene recoding by considering parameters on nucleotide and protein levels. Dr. Katagiri's collaborative research on establishing computational methods, including tools for predicting functional co-occurring mutations and analyzing codon conservation and publicly accessible databases, such as CoCoPUTs have applications in clinical diagnoses, drug development and regulation.

"Pythonic Applications for the Study of Glycans"

Lisa Parsons, PhD, Staff Scientist, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research

ABSTRACT

Saccharides (glycans) and glycoconjugates are essential for life in nearly every organism on Earth. CBER regulated biologics products often contain glycoconjugate or saccharide components crucial to the function of the active pharmaceutical ingredient. For example, capsular polysaccharides excreted by *Haemophilus*, *Streptococcal*, and *Meningococcal* bacterial species are the primary antigenic components of several vaccines. Glycosylation of viral protein antigens, such as the spike protein of SARS-CoV-2 and flu hemagglutinin, serves vital roles including but not limited to: proper folding, modification of antigenic sites, and presentation to the immune system. Mass spectrometry is a useful tool for examination of glycan and glycoconjugate composition and fine structural features. However, analysis of these compounds presents some unique challenges not met by mainstream proteomic software. This talk presents an overview of ways we have used Python to develop applications to meet these challenges with special attention to the publicly available AssignMALDI program.

"Improving and Expediting Biologics Adverse Event Surveillance using a FHIR-based Platform"
Hussein Ezzeldin, PhD, Senior Staff Scientist, Office of Biostatistics and Pharmacovigilance, Center for Biologics Evaluation and Research

ABSTRACT

The Office of Biostatistics and Pharmacovigilance (OBPV) in the Center for Biologics Evaluation and Research (CBER) is responsible for ensuring postmarket safety of CBER-regulated products utilizing both active and spontaneous surveillance systems. National spontaneous safety surveillance systems like the FDA Adverse Events (AE) Reporting System (FAERS) and the Vaccine AE Reporting System (VAERS) are the first line for detecting possible signals of AE for regulated products. These AE reporting systems have multiple challenges including inefficient manual reporting processes, disconnected data subsystems, underreporting for certain products, and inconsistencies in reporting quality. To address some of these challenges, CBER established the Biologics Effectiveness and Safety (BEST) Platform, an HL7® Fast Healthcare Interoperability Resources (FHIR)-based infrastructure aiming to enhance postmarket AE reporting while minimizing reporting burden. BEST partnered with eHealth Exchange (eHx), a national health information exchange (HIE), to conduct two pilot studies with eHx member providers and explore validation and automated AE detection. The BEST pilot studies assessed the status of the FHIR® implementation in the U.S. healthcare system and its fitness-for-purpose for specific public health use cases on detecting AE. We will describe the Platform's components and summarize the results from these pilot studies. We will also share the challenges and potential long-term solutions for adopting a national implementation of the Platform that can better promote patient safety surveillance while reducing the burden on providers.

SPEAKER BIOS:

Dr. Rommie E. Amaro holds the Distinguished Professorship in Theoretical and Computational Chemistry at the University of California, San Diego. She grew up on the south side of Chicago and received her B.S. in Chemical Engineering (1999) and her Ph.D. in Chemistry (2005) from the University of Illinois at Urbana-Champaign. Rommie was a NIH postdoctoral fellow with Prof. J. Andrew McCammon at UC San Diego from 2005-2009 and started her independent lab at the University of California, Irvine in 2009. In 2011 she moved to UC San Diego. She is the recipient of an NIH New Innovator Award, the Presidential Early Career Award for Scientists and Engineers, the ACS COMP OpenEye Outstanding Junior Faculty Award, the ACS Kavli Foundation Emerging Leader in Chemistry, the Corwin Hansch Award, and the 2020 ACM Gordon Bell Special Prize for COVID19. Rommie's scientific interests lie at the intersection of computer-aided drug discovery and biophysical simulation. Her scientific vision revolves around expanding the range and complexity of molecular constituents represented in atomic-level molecular dynamics simulations and the development of novel multiscale methods for elucidating their time dependent dynamics.

Dr. Frank Delaglio is a Principal Investigator at the National Institute of Standards and Technology, developing computational methods for Nuclear Magnetic Resonance (NMR) data to support development and manufacturing of drugs and vaccines, and to support basic research in structural biology. His career includes commercial software development, extensive pharma consulting, and regular participation as an advanced course instructor for the European Molecular Biology Organization. He earned a BA in Chemistry from Syracuse University, and a PhD from the Osaka University Graduate Department of Pharmaceutical Sciences.

Dr. Nobuko Katagiri is currently a researcher-regulator at the Office of Plasma Protein Therapeutics (OPPT), Office of Therapeutic Products (OTP). Her research work in the Kimchi-Sarfaty lab focuses on investigating the effects of sequence variation, especially those of synonymous mutations, on protein characteristics and their mechanisms using both in silico and in vitro methods. In parallel, Dr. Katagiri reviews chemistry, manufacturing, and control (CMC) for a variety of therapeutic proteins, mostly coagulation therapeutics in INDs, BLAs and supplements. Dr. Katagiri acquired her Ph.D. from Tokyo Institute of Technology, Japan and she performed postdoctoral research at the National Institute of Health and University of Maryland.

Dr. Lisa Parsons is a Staff Scientist and Chemistry, Manufacturing and Controls (CMC) reviewer in the Laboratory of Bacterial Polysaccharides (LBP) in the Division of Bacterial, Parasitic, and Allergenic Products (DBPAP), Office of Vaccines Research and Review (OVRR). She received her PhD from the University of Maryland and completed a PRAT fellowship in protein NMR spectroscopy under Dr. Ad Bax at the NIH and an ORISE fellowship in mass spectrometry of glycans under Dr. John Cipollo at the FDA. She currently works for Dr. Cipollo studying the glycosylation of viruses and bacterial glycosylation enzymes.

Dr. Hussein Ezzeldin is a Senior Digital Health Expert in the Office of Biostatistics and Pharmacovigilance (OBPV). During the 10 years with OBPV, he has worked on wide range of modeling, risk assessment, policy, and research projects. Currently he is the team lead for the digital health technology review team (DHTRT), supporting the use of DHTs in regulatory submissions. In addition, Dr. Ezzeldin co-leads the Biologics Effectiveness and Safety Innovative Methods Initiative (BEST IM), which aims to develop new and innovative methods for a semi-automated adverse events (AEs) reporting system for CBER-Regulated Biological Products. Also, Dr. Ezzeldin has a passion for advancing the science of patient input, and he is leading the natural history study for metachromatic leukodystrophy, HOME. Dr. Ezzeldin led the development of the open-sourced SHAPE (Survey of Health And Patient Experience) platform, a versatile Data Collection platform for Patient-Centered Studies.

Session 5: Methods and Biomarker Discovery for Product Safety and Quality

September 18, 2024 - 9:30 AM – 12:00 PM

"Microengineered Biomimicry of Human Physiological Systems"
Dan Dongeun Huh, PhD, Professor of Bioengineering,
University of Pennsylvania

ABSTRACT

Remarkable progress in life science and technology in the past century has advanced our understanding of the human body beyond our imagination. The ever-increasing knowledge of human biology, however, has done surprisingly little to change and improve the way we emulate the complex inner workings of human health and disease in experimental models. Even today, our ability to mimic and study the key aspects of human physiological systems relies on the century-old practice of cell culture or animal experimentation that often raises significant scientific and ethical concerns. This lack of realistic and human-relevant model systems with high predictive capacity is emerging as a critical impediment to our scientific endeavors for a wide variety of biomedical applications. Motivated by this major problem, this talk will present interdisciplinary research efforts in my laboratory to develop and translate advanced in vitro models and preclinical research platforms that leverage the power of microengineering technologies to emulate the complexity of human tissues and functional elements of human organs for biomedical and environmental applications.

"Immunogenicity of Biologics – Prediction and Mitigation"
Sathy Balu-Iyer, PhD, Professor *of Pharmaceutical Sciences, University of Buffalo*

ABSTRACT

The efficacy and safety of therapeutic proteins are undermined by immunogenicity driven by anti-drug antibodies (ADA). Proteins administered subcutaneously can suffer from enhanced immunogenic potential compared to intravenous administration. The talk will cover mechanistic insight into the subcutaneous immune response, the development of a novel preclinical tool to predict clinical immunogenicity and novel mitigation strategies.

"Evaluating factors affecting genome editing efficiency and specificity"
Zhaohui Ye, PhD, Principal Investigator/Chief, Gene Transfer and Immunogenicity Branch, Office of Gene Therapy, Center for Biologics Evaluation and Research

ABSTRACT

Genome and epigenome editing tools, including those engineered from designer nucleases such as zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and CRISPR, are transforming medicine due to their unprecedented efficiency in altering nucleic acid sequences and epigenetic marks in living cells. There has been significant effort in editor protein engineering in recent years. In addition, studies have revealed that host cell intrinsic factors and environmental factors can potentially play important roles in editing efficiency and specificity. Understanding the mechanisms underlying these factors are important for developing safe and

effective gene therapies incorporating genome editing. In previous studies using genome-wide analysis approaches, we have analyzed TALEN and CRISPR/Cas-based editor targeting specificity that is affected by DNA binding and non-DNA binding activities. In this study, we examined the utility of combining a genome editing reporter system and droplet digital PCR (ddPCR) method in assessing how editing conditions and environmental factors affect editing efficiency. While ddPCR provides sensitive and quantitative molecular measures of editing frequency, the fluorescence-based reporter evaluates functional outcomes of genome editing at a cellular level. We show that this approach is capable of evaluating editing through homology-directed repair (HDR) of DNA double strand breaks (DSBs) and through prime editing, which can achieve desired DNA sequence alterations independent of DSBs. Using this approach, we identified small molecules that can enhance both the traditional HDR-based DNA repair and prime editing-based repair. Some of these molecules belong to the class of gut microbiota metabolites, suggesting a potential connection between gut microbiome, diet and genome editing outcomes.

"Influenza Neuraminidase Active Site Proximity Assay (NAspa) for Rapid Profiling of Inhibitory Antibody Titers and Antigenic Drift"

Robert Daniels, PhD, Principal Investigator, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research

ABSTRACT

Identifying suitable vaccine strains for the influenza neuraminidase (NA) antigen remains a significant barrier to the incorporation of NA antigens into seasonal vaccines. This presentation will introduce a new NA active site proximity assay (NAspa) that my lab developed for measuring NA activity inhibitory (NAI) antibodies in solution with two reagents and common lab equipment. The talk will focus on results showing how NAspa could help to select seasonal vaccine strains for NA antigens and for profiling anti-NA antibody responses in humans.

SPEAKER BIOS:

Dr. Dan Huh is a Professor in the Department of Bioengineering at the University of Pennsylvania. He is a pioneer of organ-on-a-chip technology, and his research group at Penn focuses on developing microengineered models of human physiological systems for biomedical and environmental applications. Dr. Huh has won several honors and awards including the PCI Inventor of the Year Award, the Bernard Langer Distinguished Lecture-ship, Lush Prize, the McPherson Distinguished Lectureship, CRI Technology Impact Award, John J. Ryan Medal, Design of the Year Award and Best Product of the Year Award from London Design Museum, NIH Director's New Innovator Award, Analytical Chemistry Young Innovator Award, TEDx Fellow, NC3Rs Annual Award, Lifetime Membership from MOMA, SLAS Innovation Award from the Society for Lab Automation and Screening, Scientific Breakthrough of the Year Award from American Thoracic Society, Best Publication Award from the Society of Toxicology, Wyss Technology Development Fellowship from Harvard, and Distinguished Achievement Award from the University of Michigan.

Dr. Sathy Balu-iyer is a Professor in the Department of Pharmaceutical Sciences at SUNY – University at Buffalo and is an Associate Dean for Research, School of Pharmacy and Pharmaceutical Sciences. He is an elected fellow of American Association of Pharmaceutical Scientists (FAAPS). His interdisciplinary research involves biophysical, immunological and Pharmacokinetic/dynamic approaches to rationally develop immunotherapy modalities. He is recipient of NIH sponsored projects as principal investigator. He has authored about 100 peer-reviewed publications, over 200 meeting abstracts/presentations and is an inventor on 30 patents/patent applications. The Awards he received include Biotechnology Innovation Award from American Association of Pharmaceutical Scientists (AAPS) and Inventor of the year Award from Niagara Frontier Intellectual Property Law Association. His University awards include University at Buffalo Sustained Achievement Award and Teaching innovation Award. He is one of the Editors of Journal of Pharmaceutical Sciences and serves on editorial boards of several international journals including Biodrugs. He is a member of American Association of Pharmaceutical Scientists AAPS and American Association for the Advancement of Science AAAS.

Dr. Zhaohui Ye joined CBER FDA in 2016 as a principal investigator. He is currently the Chief of Gene Transfer and Immunogenicity Branch in the Office of Gene Therapy (OGT), Office of Therapeutic Products (OTP) at CBER. In his role, he is responsible for chemistry, manufacturing and controls (CMC) review and policy development in cell and gene therapy products. Dr. Ye received a PhD degree in Immunology from Johns Hopkins University. Prior to joining the FDA, he held faculty positions at Johns Hopkins School of Medicine. Dr. Ye maintains an active research program on stem cell engineering in OGT at CBER.

Dr. Robert Daniels is a Principal Investigator in the Laboratory of Pediatric and Respiratory Viral Diseases in the Division of Viral Products (DVP) at the FDA. He received his Ph.D. degree in Molecular and Cellular Biology from the University of Massachusetts-Amherst in 2007 and performed his post-doctoral work at the Karolinska Institute in Stockholm. In 2010 he was hired as an Assistant Professor of Biochemistry and Biophysics at Stockholm University where he started his work on influenza neuraminidase and received the 2018 Stockholm University Teacher of the year award. He joined DVP in 2019 and his group is part of the WHO Essential Regulatory Labs for influenza vaccines. The primary focus of his research is to increase the breadth and efficacy of annual influenza vaccines by developing approaches to introduce neuraminidase (NA) antigens into influenza vaccines.

Session 6: Immune Responses to Vaccination

September 18, 2024 - 2:00 PM – 4:30 PM EST

"Challenge of Incompatible Requirements for SARS-CoV-2 and HIV-1 Neutralizing Antibody Assay Method Validation"

David Montefiori, PhD, Professor in Surgery, Duke University

ABSTRACT

Valid measurements of vaccine-elicited neutralizing antibodies are often sought by health agencies when evaluating new and updated vaccine products. I will describe FDA requirements for method validation of a pseudovirus-based neutralizing antibody assay for SARS-CoV-2. This assay helped establish neutralizing antibodies as a correlate of protection against symptomatic SARS-CoV-2 infection and is used in clinical studies to acquire essential data for review by the US FDA. I will also describe recent progress in HIV-1 vaccine development and in the development of passively delivered broadly neutralizing monoclonal antibodies for HIV-1 prevention- two very distinct products that rely of valid assessments of neutralization. I will compare and contrast the genetic and antigenic variability of HIV-1 and SARS-CoV-2 to highlight specific FDA requirements for SARS-CoV-2 that are incompatible with HIV-1. Suggestions on how to harmonize method validation of neutralization assays for these two viruses will be discussed.

"The study of adaptive immunity to viruses of pandemic concern"

Alessandro Sette, Dr.Biol.Sci., Professor, La Jolla Institute for Immunology

ABSTRACT

"I will review recent data illustrating the evolution of adaptive responses in the context of repeated SARS vaccinations and breakthrough infections. The lessons learned in the context of the recent pandemic are being applied to the development of a general pipeline to identify regions that are immunogenic in prototype viruses and widely conserved in different members of a viral family of pandemic concern. Finally, I will present recent analysis addressing the potential for preexisting human immunity capable of recognize highly pathogenic avian influenza sequences."

"Unique attributes of early age immune responses to vaccines"

Mustafa Akkoyunlu, MD, PhD, Principal Investigator, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research

ABSTRACT

Infants do not respond to T cell independent (TI) vaccines such as capsular polysaccharides (CPS) from *Haemophilus influenzae* and *Streptococcus pneumoniae*. Although conjugation of CPS to protein carriers converts them to T cell dependent (TD) antigens, CPS-TD vaccines need to be administered 3 to 4 times during the first year of life in order to elicit adult like durable immune responses. The gap in understanding the underlying mechanisms of weaker immune response to TI-CPS and TD-CPS vaccines in infants is an obstacle in improving these vaccines. In adults, the expression of transmembrane activator and calcium-modulator and cyclophilin ligand interactor (TACI) on B cells is essential for the generation of antibody responses against TI-CPS vaccines. We found that TACI expression is severely reduced on neonatal mouse B cells as compared to those of

adults. This severe reduction of TACI on B cells is responsible for the unresponsiveness of neonates to CPS vaccines because immunization of newborns with a CpG containing TI-CPS vaccine elicited antibody responses to CPS by upregulating the expression of TACI on neonatal B cells.

The response to TD-CPS vaccines in adult mice requires the formation of T follicular helper (Tfh) cells for the development of plasma cells and memory B cells. The formation of Tfh cells is severely reduced in TD-CPS vaccine immunized neonates. In adult mice, IL-6 is required for the development of Tfh cells. At the same time, IL-2 inhibits Tfh generation. We found that, despite eliciting significantly higher levels of IL-6 in neonatal mice spleens compared to adult mice, a TD-CPS vaccine induced more IL-2 production and increased expression of IL-2 receptors by neonatal Tfh cells than adult cells. Moreover, immunization of neonatal mice with a TD-CPS vaccine containing IL-6 resulted in further suppression of Tfh cells and enhancing, both IL-2 and IL-2 receptor expression on Tfh cells. Complementing these observations, IL-6 deficient neonatal mice mounted higher antibody response accompanied by significantly increased Tfh cells following the immunization with TD-CPS vaccine. These findings unveil age-specific differences in cytokine mediated vaccine responses and highlight the need to consider age-related immunobiological attributes in designing vaccines.

"Antigenic Assessments of Recent SARS-CoV-2 Variants for Guiding COVID-19 Vaccine Variant Composition Updates"

*Carol Weiss, MD, PhD, Principal Investigator/*Chief, *Lab of Immunoregulation, Office of Vaccines Research & Review, Center for Biologics Evaluation and Research*

ABSTRACT

SARS-CoV-2 continues to evolve, producing new variants that have increased immune evasiveness. At the same time, population immunity has become increasingly complex from different combinations of SARS-CoV-2 variant infections, COVID-19 vaccines, or both. These issues complicate decisions regarding updates to the variant composition of COVID-19 vaccines. This talk will present data on neutralization of recent variants by serum from persons with different infection and vaccination histories. Antigenic assessments of new variants for informing vaccine updates will also be discussed.

SPEAKER BIOS:

Dr. David Montefiori is Professor and Director of the Laboratory for HIV and COVID-19 Vaccine Research & Development in the Department of Surgery, Division of Surgical Sciences at Duke University Medical Center. His major research interests are viral immunology and HIV and COVID-19 vaccine development, with a special emphasis on neutralizing antibodies. Multiple aspects of HIV-1 neutralizing antibodies are studied in his laboratory, including mechanisms of neutralization and escape, epitope diversity among the different genetic subtypes and geographic distributions of the virus, identification and characterization of broadly neutralizing epitopes, requirements to elicit protective neutralizing antibodies by vaccination, optimal combinations of neutralizing antibodies for immunoprophylaxis, and novel vaccine designs for HIV-1. Dr. Montefiori also directs a large vaccine immune monitoring program funded by the NIH and the Bill & Melinda Gates Foundation that operates in compliance with Good Clinical Laboratory Practices and has served as a national and international resource for standardized assessments of neutralizing

antibody responses in preclinical and clinical trials of candidate HIV vaccines since 1988. At the onset of the COVID-19 pandemic, he turned his attention to SARS-CoV-2 with a special interest in emerging variants and how they might impact transmission, vaccines and immunotherapeutics. His rapid response to emerging SARS-CoV-2 variants of concern provided some of the earliest evidence of the potential risk the variants pose to vaccines. In May 2020, his laboratory was recruited by the US Government to lead the national neutralizing antibody laboratory program for COVID-19 vaccines. His laboratory utilizes FDA approved validated assay criteria to facilitate regulatory approvals of COVID-19 vaccines. He has published over 800 original research papers that have helped shape the scientific rationale for neutralizing antibody-based vaccines.

Dr. Alessandro Sette has devoted more than 35 years in biotech and academia to understanding and measuring immune responses, and developing disease intervention strategies against cancer, autoimmunity, allergy, and infectious diseases. Dr. Sette's laboratory is the world leader in the study of the specific structures, called epitopes, that the immune system recognizes. Dr. Sette has overseen the design and curation efforts of the national Immune Epitope Database (IEDB), a freely available, widely used bioinformatics resource. The IEDB catalogs all epitopes for humans and experimental animals for allergens, infectious diseases, autoantigens and transplants, and includes epitope prediction tools to accelerate immunology research around the world. Dr. Sette's lab uses knowledge of epitopes to define the hallmarks of a beneficial immune response associated with effective vaccines, as opposed to immune responses that are ineffective or that cause harm. The laboratory's infectious disease interests include SARS CoV2, dengue, Zika Chikungunya, herpesviruses, poxviruses, lassa fever, HIV and hepatitis viruses, and bacterial pathogens such as tuberculosis and *Bordetella pertussis*. Our investigations outside infectious disease include allergic asthma and Parkinson's disease. Dr. Sette is a Doctor in Biological Sciences from the University of Rome and did postdoctoral work at the National Jewish Center for Immunology and Respiratory Medicine in Denver, Colorado. In 1988, Dr. Sette joined the newly founded company Cytel, in La Jolla, and was also appointed adjunct assistant professor at The Scripps Research Institute. He founded Epimmune in 1997, where he served both as Vice President of Research and Chief Scientific Officer until 2002, when he joined La Jolla Institute for Immunology (LJI) as Head of the Division of Vaccine Discovery. He also heads the Center for Infectious Disease at LJI.

Dr. Mustafa Akkoyunlu is a Senior Investigator at the Laboratory of Bacterial Polysaccharides, DBPAP, CBER. His laboratory investigates the mechanisms of antibody development against bacterial polysaccharide vaccines in neonates and infants. The objective of his research is to help improve vaccine responses in early age and to aid in regulatory review by gaining further insights into the unique features of early age immune responses to vaccines. Before joining FDA in 2002, Dr. Akkoyunlu pursued postdoctoral fellowship at Yale University. He earned his MD degree from Ankara University Medical School, Turkey and his PhD in Microbiology/Immunology from Lund University, Sweden.

Dr. Carol Weiss is a Principal Investigator and Lab Chief in the Division of Viral Products, Office of Vaccines Research and Review, CBER. She has more than 25 years of experience reviewing vaccines for preventing viral infectious diseases. Her research program focuses on basic mechanism of virus entry into cells and neutralization of HIV, influenza, and coronaviruses.