Blood Products Advisory Committee (BPAC)
Center for Biologics Evaluation and Research
123rd Meeting of the Blood Products Advisory Committee
December 8, 2022

Final Agenda
BPAC - Final Transcript
AABB Joint Statement in Support of FDA's Research Programs

Topic: Overview of the Research Programs of the Laboratory of Emerging Pathogens (LEP) and the Laboratory of Molecular Virology (LMV), Division of Emerging and Transfusion Transmitted Diseases (DETTD), Office of Blood Research and Review (OBRR), Center for Biologics Evaluation and Research (CBER)

Meeting Summary

I. The meeting opened with a welcome to all presenters, members, FDA, and the general public and instructions on how to ask questions during the proceedings. Additionally, an overview of the presentations taking place during the meeting was reviewed. Next, a formal roll call of the committee members was conducted. Finally, the reading of the Conflict of Interest statement was conducted and the agenda for the session was read.

II. Presentation #1: Overview of CBER Research Programs – Monica L Young, PhD

An overview of the areas regulated by CBER, along with CBER goals was given. The second CBER goal is to conduct biologics research to address challenges in the development and laboratory evaluation of medical products. This is achieved by taking a collaborative approach to regulation of biologics, including the review of data submitted by sponsors, internal discussions, first market surveillance, and active research. The research program and its structure helps ensure the understanding of advanced techniques that are the source of data in regulatory submissions and decisions.

CBER's Approach to Regulating Biologics
- Investigator-initiated research in the context of regulatory review work
- Active research programs
- CBER's research and review are integrated

CBER's Role in Regulatory Review Teams
- Chemistry, manufacturing, and control (CMC) product reviewer
  - Scientific rationale, data for proof-of-concept
  - Production techniques and resulting product
  - Quality control testing
  - Clinical assays

Science and regulation are used to advance product development from the introduction of a novel product all the way through the licensing of the product and post-market surveillance.

CBER's White Oak Lab Facility encompasses 450,000 square feet, with approximately 150 BSL-1 to BSL-3 laboratories and offices for more than 500 research staff. The core technologies used at the facility include:

- Flow cytometry
- Confocal microscopy
- High-performance Integrated Virtual Environment (HIVE)
- Biotechnology core facility

The facility also includes a state-of-the-art vivarium with a complete imaging facility and transgenic derivation facility.

CBER research program benefits:

- Allows CBER scientists to prepare for future innovative products and public health challenges
- Develops tools and data that are available to stakeholders
- Develops of all product classes
- Attracts and maintains highly trained scientists

CBER's research program is evaluated through:

- Reporting
- Peer review of new projects
- External review of research program
- Annual review of the research program at a project level
- Evaluation of program alignment

Site Visit Report

- Site visit team composed of members of the Advisory Committee
- Draft report is developed and distributed to the full Advisory Committee for review and evaluation
- Report is either accepted or rejected and sent back to the site visit review team for review and revision.

III. Overview of Research and Regulatory Program of Division of Emerging and Transfusion Transmitted Diseases (DETTD) – Hira Nakhasi, PhD, FASTMH

Mission: Ensuring Blood Safety and Availability

Statistics

- Approximately 14M units are transfused annually (10M RBC; 2M PLT, 2.4M plasma)

- Risk of transfusion-transmitted infections has been significantly reduced with the introduction of FDA-licenses or cleared screening tests

Overview of DETTD Laboratories/Branches

- Laboratory of Molecular Virology (LMV) – focus on pathogenesis of retroviruses
- Laboratory of Emerging Pathogens (LEP) – focus on emerging and re-emerging blood-borne parasitic, viral agents and tick-borne pathogens
- Product Review Branch (PRB) – focus on review of regulatory submissions

DETTD Research and Regulatory Activities

- Plan and conduct mission-related research on pathogenesis of transfusion-transmitted infection of blood-borne agents (e.g. HIV, Hepatitis, tick-borne agents, etc.)
- Proactively ensure the safety of the blood supply by reviewing regulatory submissions, evaluating new technologies, and development policy and guidance documents
- Provide source material for blood-borne pathogens to develop reference materials

- Provide scientific and technical advice to other agencies and government components (e.g., CDC, DOD, DHHS)
- Outreach to stakeholders (e.g. Blood Product Advisory Committee, WHO, etc.)

Examples of recent significant research publications were reviewed, as were the research and regulatory accomplishments of FY21-22. A Review of LMV and LEP PI's Research programs was held on May 12, 2022.

IV. Summary of Viral Diseases Research Programs of Laboratory of Emerging Pathogens – Sanjai Kumar, PhD, FASTMH

Three main areas covered in presentation:

- Diagnosis and Pathogenesis of Filoviruses (FV) and Hepatitis A Virus (HAV) – Gerardo Kaplan, PhD
- Diagnosis and Pathogenesis of Hepatitis Viruses that Threaten the Safety of Blood and Related Projects – David McGivern, PhD
- Evaluating Pathogenesis and Markers of Arbovirus Infections and Developing Reference Reagents to Improve Blood Safety – Maria Rios, PhD

Diagnosis and Pathogenesis of FV and HAV
Rationale for the work in FV and HAV was reviewed. Projects under this research program include:

- Filovirus Program (plan to discontinue program in near future)
- HAV Program

The four-year accomplishments of this program were reviewed; this included publications for both Filovirus and HAV.

Summary of main findings:

- Discovery of the exosome mimicry model of HAV infection: cargo delivery of
- exosomes requires two lipid receptors, HAVCR1 and NPC1, but not a viral envelope.
- Infectivity of exosomes from HAV-infected cells is mediated by cargo delivery of free viral RNA and not intracellular uncoating of viral particles.
- This exosome mimicry pathway can be targeted for therapeutic interventions to prevent viral infection, modulate exosome-mediated treatments, and
- enhance mRNA vaccine delivery

Proposed Future Work:

- Extend our knowledge on HAV cell entry to develop methods for pathogen reduction of non-enveloped viruses.
- Analyze clinical markers of HAV infection in plasma from serial donations obtained during the current HAV epidemic in the US.

Diagnosis and Pathogenesis of Hepatitis Viruses that Threaten the Safety of Blood and Related Products

Development of reference reagents and standards for assays intended to detect viral nucleic acids. Covered under this section were:

- Background and rationale
- Hepatitis E virus (HEV) secondary standards
- References Panels for SARS-CoV-2

Understanding the prevalence and disease impact of viral hepatitis in North America. Covered under this section were:

- Background and Rationale
- Research Progress

Novel models for studying hepatitis virus infectivity and pathogenesis. Covered under this section were:

- Background and Rationale
- Research Progress

Finally, a review of the accomplishments 2018-2022 was done, including a list of selected publications from a total of 10 papers, as well as a discussion of the future directions being taken.

Evaluating Pathogenesis and Markers of Arbovirus Infections and Development Reference Reagents to Improve Blood Safety

Research Project 1: Development Reference Reagents to Evaluate and Harmonize Nucleic Acid Test (NAT) Assays. Covered under this topic were:

- Mission Relevance

- Project Accomplishments

Project 2a: Study on DENV, WNV, and ZIK using primary isolates: Impact of genetic variation in flavivirus infectivity and pathogenesis. Covered under this topic were:

- Mission Relevance
- Rationale
- Major Findings on ZIKV

Project 2B: Identification of differential biomarkers for DENV, WNV and ZIKV infections. Covered under this topic were:

- Mission Relevance
- Rationale
- Major Findings
- Ongoing Study

Finally, additional discussion of accomplishments 2018-2022 and future directions was held.

V. Overview of OBRR and Research Programs – CD Atreya, PhD

An organizational chart of the Office of Blood Research and Review (OBRR) was shown. Following that brief discussion, a review of the OBRR mission (Ensure the safety, efficacy, and availability of blood and blood products through regulation) and OBRR functions.

Next, an overview of the OBRR Vision for Research was made, leading into the OBRR Research Goals.

- OBRR Research Goal 1: Assess and promote safety and effectiveness of transfusion products and related devices and technologies
- OBRR Research Goal 2: Assess and promote safety and effectiveness of Transfusion-Transmitted Infectious Disease (TTID) agent donor screening and supplemental tests, and retroviral diagnostics

OBRR research resources include subject expertise, including virology, retrovirology, bacteriology, parasitology, prions, cell biology, immunology, biochemistry, and physiology. Program funding comes from both internal and external sources. Fifteen Investigator (Research-Reviewer) initiated programs are located in two divisions under four laboratories.

OBRR global outreach includes OBRR staff who participate either as a Member or Observer in:

- WHO initiatives
- European Directorate for the Quality of Medicines & Healthcare, Blood Transfusion Sector
- International Society of Blood Transfusion Working Groups on Transfusion Transmitted Diseases, Hemovigilance, and Global Blood Safety

- FDA/EMA/Health Canada Blood Cluster

VI. Overview of Laboratory of Molecular Virology (LMV) Research Programs – Indira K Hewlett, PhD

An overview of mission relevance – OBRR research priority, and the LMV mission of Regulatory and Research was reviewed, moving into an organizational chart.

Projects under HIV and Retrovirus Section include:

- Molecular diversity of HIV, impact on diagnosis and pathogenesis
- Novel, emerging diagnostic technologies, bioinformatics for retrovirus detection and characterization
- Pathogen reduction technologies for HIV and retroviruses

The following topics were covered during the presentation:

- Molecular Characterization of Highly Diverse HIV-1 Viruses for reference panel development (included results, summary, and future directions)
- HIV-1 drug resistance mutation (DRM) data analysis app for review of sponsor NGS data (included rationale, results, and future work)
- Disease stage specific host biomarkers of HIV infection (included rationale for work, study design for identification of plasma miRNA biomarkers of early HIV-1 infection, summary, and future directions)
- Studies on Pathogen Reduction Technologies (PRT): HIV-1 inactivation in plasma by 405nm visible blue light (included rationale, summary, and future work)
- Bacterial and TSE Section Research Goals (included rationale for TSE research, results, and future work)

A comprehensive list of acknowledgements of all those who contributed to this presentation was made.

At the conclusion of this presentation, the BPAC went into a closed session.