U.S. FOOD & DRUG ADMINISTRATION

Overview of the Laboratory of Immunoregulation

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Research Program Site Visit on September 5, 2024

VRBPAC presentation on December 12, 2024

Lab of Immunoregulation (LI)

- Staff structure
- Regulatory activities
- Research programs
- Research highlights and impact

LI Staff and collaborators

- Carol Weiss, M.D., Ph.D., PI, Lab Chief
  - 1 Lab manager (both PI teams) (FTE)
  - 2 Staff Scientists/Fellows (FTEs)
  - 1-2 post-bac/post-doc fellows supported by awarded competitive grants
- Ira Berkower, M.D., Ph.D., PI
  - 1-2 post-baccalaureate or post-doctoral fellows
- Many collaborators
  - COVID-19 response efforts: HHS agencies (NIH, CDC, BARDA/ASPR)
  - DoD Clinical trials: Uniformed Services University (USU) and DoD partners
  - Antigenic cartography analyses: NIH/NIAID
  - Specific influenza and SARS-CoV-2 virology studies: CBER PIs

Regulatory review responsibilities

- Provide expert scientific review of FDA submissions for experimental and licensed vaccines for preventing viral infectious diseases

  - ***Product review:*** CMC (chemistry/manufacturing/controls)
    - Product quality, purity, and potency
    - Manufacturing process consistency

  - *Clinical review*
    - Clinical protocols, safety, immunogenicity, and efficacy data
    - Experimental HIV vaccines for treatment and cure strategies with trial designs that include antiretroviral treatment interruptions

Regulatory activities

- Review of submissions
  - Files and associated sponsor meetings: PreINDs, INDs, Master Files, BLAs, BLA supplements for post-approval manufacturing changes, inter-center consults
  - Review portfolio includes experimental vaccines for HIV, influenza, and coronavirus, and approved vaccines for influenza and human papilloma virus
- Advisory meeting preparations
  - Discussions with stakeholders
  - Data contributions
  - Briefing material preparations

Other public health activities

- COVID-19 response efforts
  - Operation Warp Speed, Therapeutics Research Team
  - HHS Interagency Working Groups—contributed data, presentations, and risk assessments
    - Working groups for Assays, Therapeutics, and Vaccines
    - NIH SARS-CoV-2 variant evolution (SAVE) program for responding to latest SARS-CoV-2 variants
    - Risk assessments committees: 1) therapeutic antibodies and 2) SARS-CoV-2 BSL level re-evaluations
  - DoD/Uniformed Services University working group research meetings
- International biological standards and regulatory harmonization efforts
  - WHO International Standard for anti-SARS-CoV-2 immunoglobulin and reference panel for VOCs
  - SARS-CoV-2 assay comparison studies involving different consortia (Duke, NIH, USU/DoD)
  - FLUCOP study: cross laboratory comparison of hemagglutinin inhibition and microneutralization assay performance for seasonal influenza vaccines

Laboratory expertise informs all components of product regulatory review

- Review of manufacturing process steps to assure product safety and consistency
  - *Virus growth steps*
  - *Purification steps*
  - *Methods validation*
  - *Detection of adventitious agents*
  - *Product comparability studies after manufacturing changes*
- Review of viral inactivation steps to assure product safety
  - *Inactivation procedures*
  - *Methods for detecting residual infectious virus*
- Review of assessments of replicating vector stability and antigenicity to assure safety and potency
- Review of potency assays to assure product lot-to-lot consistency and potency
- Review of immunogenicity measurements and assays that support licensure

LI research programs

- Weiss lab
  - Overall theme: basic and applied studies of virus entry into cells and its neutralization by antibodies
  - Influenza studies since last site visit
    - Antibody correlates of protection during an H3N2 influenza outbreak in military recruits
    - Comparing antibody responses elicited by different approved seasonal influenza vaccines manufactured using eggs, cells, and recombinant protein methods
    - Generation of a novel antibody targeting a conserved region of influenza hemagglutinin (HA)
  - SARS-CoV-2 studies since last site visit
    - Variant characterization and immune escape
    - Mutations conferring resistance to therapeutic antibodies and post vaccination sera
- Berkower lab
  - Live-attenuated rubella vector for antigen delivery and protection
  - Vector prime-protein boost vaccine strategies for HIV protection and cure

Selected research highlights

- **Influenza studies**
  - For 2018-2019 seasonal influenza vaccines showed that egg- and cell-based vaccines elicited similar neutralization titers against vaccine viruses, and that titers elicited by the recombinant HA vaccine were higher

- **SARS-CoV-2 studies**
  - Quickly established a safe pseudovirus assay for characterizing SARS-CoV-2 variants and measuring antibody neutralization
  - Identified mutations that conferred resistance to therapeutic antibodies and post-COVID-19 vaccination sera
  - Showed that primary mRNA COVID-19 vaccination series elicited broader and higher neutralization response against variants than infection alone by a single variant
  - Characterized antigenic changes in variants that informed decisions about variant composition updates to COVID-19 vaccines

Overall research contributions

- **Provided laboratory expertise for supporting scientific regulatory review**
  - Assessments of manufacturing processes and testing methods
  - Technical communications with vaccine developers
  - Agility for adapting to changing priorities
- **Generated materials & methods for facilitating the development of vaccines**
  - New cell lines, assays, and references materials
  - Multi-laboratory, harmonization of methods for vaccine evaluation
- **Contributed data for science-based regulation**
  - Internal discussions and meetings with vaccine stakeholders
  - Many peer-reviewed, scientific publications for widespread dissemination

Thank you