Koup: Comprehensive Cellular Vaccine Immune Monitoring Consortium

OVERVIEW

The Comprehensive Cellular Vaccine Immune Monitoring Consortium (CCVIMC) is a Central Service Facility (CSF) within the CAVD providing a variety of cellular assays in support of pre-clinical and clinical HIV vaccine trials. Beyond providing exploratory, qualified, standardized and GCLP-compliant cellular assays, the CCVIMC consults with the Vaccine Discovery Consortia (VDCs) on both pre-trial design and as well as post-trial/assay assessments. The goal of these efforts is to facilitate the development and licensure of a safe and effective HIV vaccine.

RESEARCH OBJECTIVES

1.) Maintain a Clinical Trial Testing Core (CTTC) with GCLP-compliant laboratories at the Fred Hutchinson Cancer Research Center (FHCRC) and the Vaccine Immunology Testing Laboratory (VITL) in the Vaccine Research Center (VRC) at the National Institute of Allergy and Infectious Diseases (NIAID).

2.) Maintain a Nonhuman Primate Core (NHPC) providing standardized and exploratory assays at the VRC.

3.) Maintain a Transcriptomic Core (TC) provide enabling transcriptomic technology, systems biology expertise, and bioinformatics consultation in order to generate biomarkers of vaccine protection and testable hypotheses for improving vaccine regimens.

4.) Develop and optimize exploratory cellular assays and technologies for monitoring cellular immune responses in clinical and pre-clinical trials.

5.) Enable efficient technology transfer and deployment of new and improved exploratory assays for availability to CAVD community as standardized, qualified, validated, or GCLP-compliant assays.

6.) Supply the CAVD community with quality-controlled, well characterized PBMC samples for use in the assay development and standardization.

7.) Investigate vaccine-related scientific questions that are not being addressed by individual VDCs.

8.) Maintain an Administration and Management Core (AMC) responsible for grants management, compliance oversight, and initiating and facilitating inter- and intra-consortium communications within the CAVD.

SERVICES

The CCVIMC provides both standardized, and a variety of research, assays—including an expanding repertoire of B cell, tissue imaging, and immune complex assays—to CAVD investigators for both human clinical trials and NHP studies. Our preference is to begin working with VDC investigators early in the study design process so that we can provide expertise and experience in assay and sampling selection (both time points and tissue selection), perform QA/QC for sample processing (collecting, storing and shipping), and assure the timely procurement and validation of assay reagents. Our partnership with each VDC continues throughout the study, convening interim calls as necessary, and lending our collective expertise to investigators as they interpret assay data.

Our standardized assays include:

- Intracellular cytokine staining (ICS), with several panels available to measure both CD8 and CD4 responses and a variety of other markers in monkeys and humans.
- A standardized IFN-g ELISpot assay is also available from our core of clinical and NHP labs.
- B cell phenotyping is a standardized assay for NHP trial.
- Transcriptomic analysis – RNAseq (or microarray for historic comparisons) is available including systems biology analysis.
- Secreted cytokine assay to measure factors linked to variety of immune functions, such as Th1, Th2, pro-inflammatory, regulatory, and chemotactic responses;
- Clinical Virus Inhibition Assay for measuring CD8-mediated virus replication inhibition.

Our research assays, which serve as secondary endpoints, include:

- Epitope mapping, using either ELISpot or ICS platforms to define which epitopes are targeted by a T cell response;
- B cell, T cell, and NK phenotyping using multi-parameter flow cytometry to define representation and activation state of lymphocyte subsets;
- Fluidigm assays (multiplexed qPCR) for T and B cell interrogation, both nanoarray and single cell, to quantify gene expression profiles;
- Transcriptomics to identify gene expression profile signatures of cell/tissue subsets;
- TCR clonotyping to define the repertoire of epitope (peptide) specific responses.

Grant at a Glance

Principal Investigator
Richard Koup, MD, NIAID, Vaccine Research Center

Grantee Institution
Foundation for the NIH, USA

Project Title
Comprehensive Cellular Vaccine Immune Monitoring Consortium

OPPID
1147555

Grant Award
Up to $11.5 Million, awarded in July 2016

Collaborating Institutions
- ◊ Case Western Reserve University, USA
- ◊ Duke University, USA
- ◊ Fred Hutchinson Cancer Research Center, USA
- ◊ National Institute of Allergy and Infectious Diseases, NIH, USA

External Scientific Advisory Board
- ◊ Jaap Goudsmit, Harvard
- ◊ Danilo Casimiro, Sanofi Pasteur
- ◊ Quentin Sattentau, Oxford University
- ◊ Nelson Michael, Walter Reed Army Institute of Research
- ◊ Louis Picker, Vaccine Gene Therapy Institute, Oregon Health & Science University
- ◊ Susan Barnett, Bill & Melinda Gates Foundation (ex officio)
- ◊ David Montefiori, Duke University Medical Center (ex officio)
- ◊ Patricia D'Souza, National Institutes of Health (ex officio)
- ◊ Raphael Gottardo, Fred Hutchinson Cancer Research Center (ex officio)
- ◊ Jean Patterson, National Institutes of Health (ex officio)

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Additional assay development efforts include multiplexed confocal imaging to assess the anatomic and structural features of germinal centers in response to vaccine strategies or SIV/SHIV infections.

The CCVIMC also provides CAVD investigators with a variety of clinical and NHP PBMC specimens, and some NHP tissue specimens to support assay development initiatives.

PROGRESS

Standardized assays as well as research assays have been provided for both clinical and pre-clinical (NHP) vaccine trials within the CAVD. The data generated from these assays are provided to the Vaccine Immunology Statistical Center (VISC) for statistical analysis and reported directly to the Vaccine Discovery Consortia (VDC) for the evaluation of the impact of data on the results of the trial.

The CCVIMC continues to expand services to include more advanced research assays and broaden the role of data analysis and interpretation. We continue to adapt our services to meet and anticipate the changing landscape of HIV vaccine design.

High-throughput processes have been established to interrogate antigen-specific B cell populations. The sensitivity and throughput capabilities in our laboratories have opened the door for exploring novel vaccine strategies based on targeting specific naïve B cell populations, stimulating the expansion and maturation of genotypic lineages that serve as precursors to broadly neutralize antibodies.

High parameter flow cytometers (BD Symphony) are established at the VRC and the FHCRC. New panels developed for these instruments are available for use by the CAVD through the CCVIMC with ongoing expanded-panel development underway to offer the capability to interrogate a wide array of immune responses.

Our integrative systems biology approach combines, plasma cytokine/chemokines levels with RNA-Seq analysis, FCM phenotypic and other functional measurements to identify correlates of protection (including pre-vaccination markers of vaccine conferred immunogenicity and protection).

The CCVIMC provides the analysis of tissue immunodynamics by advanced confocal microscopy and quantitative image analysis. We engage in the development, optimization and application of cutting-edge imaging assays that can be applied as part of a comprehensive analysis of tissues of interest for further understanding of T and B cell dynamics in secondary lymphoid organs in natural infections (HIV/SIV) and after vaccination. This type of analysis provides critical information for the cellular and molecular mechanisms underlying i) the vaccine or pathogen-induced B cell responses and ii) the formation of “persistent viral reservoirs” at the tissue level.

We work in concert with our VISC and CAVIMC collaborators, convening joint VIMC Scientific Advisory Board annual meetings to showcase our collaborative efforts, enabling combined assessments of cellular and antibody responses observed in CAVD sponsored studies.