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Conference report

Immune correlates of protection for dengue: State of the art and research agenda

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ABSTRACT

Dengue viruses (DENV1-4) are mosquito-borne flaviviruses estimated to cause up to ~400 million infections and ~100 million dengue cases each year. Factors that contribute to protection from and risk of dengue and severe dengue disease have been studied extensively but are still not fully understood. Results from Phase 3 vaccine efficacy trials have recently become available for one vaccine candidate, now licensed for use in several countries, and more Phase 2 and 3 studies of additional vaccine candidates

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are ongoing, making these issues all the more urgent and timely. At the "*Summit on Dengue Immune Correlates of Protection*", held in Annecy, France, on March 8–9, 2016, dengue experts from diverse fields came together to discuss the current understanding of the immune response to and protection from DENV infection and disease, identify key unanswered questions, discuss data on immune correlates and plans for comparison of results across assays/consortia, and propose a research agenda for investigation of dengue immune correlates, all in the context of both natural infection studies and vaccine trials.

1. Introduction

Dengue is the most prevalent arthropod-borne viral disease globally. The four serotypes of dengue virus (DENV1-4) cause up to approximately 400 million infections annually [1] ranging from asymptomatic infection to severe disease manifested by vascular leak, hemorrhagic manifestations, and shock [2]. A major goal of dengue research is to identify and understand immune correlates of protection and risk (Box 1) of DENV infection, dengue illness, and severe disease, particularly in the context of vaccines (Box 2).

Box 1 Correlates of protection: Summary points.

- An immune correlate of protection is an immune response marker that is statistically associated with protection from disease or infection and may be either mechanistic (causally related to outcome) or non-mechanistic (statistically related to outcome).
- An immune marker that is a correlate of protection is defined for a specific infectious disease endpoint and may be derived from natural or vaccine-induced immunity.
- For some diseases and vaccines, useful non-mechanistic correlates in lieu of true mechanistic correlates of protection are available.
- All currently licensed vaccines work primarily through antibodies, and most vaccines approved in the last 10 years had serological markers as immune correlates measured with validated assays.
- Different aspects of the immune system often perform redundant functions or may be synergistic protective mechanistic correlates.
- Applications and uses of immune correlates of protection and risk include:
  - o helping to define important aspects of infectious disease biology;
  - o identifying the optimal choice of vaccine antigen and establishing criteria for the consistency and potency between vaccine lots;
  - o determining susceptibility to disease at the individual and population level;
  - o providing a way to inform vaccine licensure in cases where establishing efficacy directly through clinical trials is not ethical or feasible; and
  - o helping with bridging from first- to second-generation vaccines [104].
- Types of adaptive immunity that may modify protection include::
  - o serum antibodies and their avidity, neutralization capacity, cytotoxic functionality, and ability to promote opsonophagocytosis;
  - o mucosal antibodies, including local IgA and diffusion of IgG to relevant surfaces;
  - o $CD4^+$ T cells and the degree to which they help activate B and T cells, promote inflammation, release cytokines, lyse cells, and maintain steady-state immunity; and
  - o the avidity of $CD8^+$ T cells and their ability to lyse appropriate target cells and not cause excessive damage [105,106].

Box 2 Correlates of protection for dengue vaccine licensure.

Overview of correlates of protection for vaccine licensure.

- The primary goal of regulators is to establish that biological agents are safe, pure, and potent.
- The traditional method for vaccine licensure requires a randomized clinical trial with comparison between treatment and control arms using a quantitative measure, either disease or an immune correlate.
- Mechanistic and non-mechanistic correlates of protection are used, but immune markers should be measured using functional assays and be regarded by the scientific community as biologically relevant.
- Other fields, such as HIV, received central funding (NIH) to take a harmonized approach for standardization of all measures of immune correlates.
- All assays should be qualified (control for variability due to reagents, the process of conducting the assay, operators, training) so that there can be confidence in the results.
- Validation is a stringent and labor-intensive process, and is important for regulatory submissions [107].

Specific considerations for dengue correlates of protection.

- For dengue, safety, efficacy, and duration of protection are highly interrelated with disease due to immune enhancement.
- Valuable assays for vaccine evaluation include:
  - o second generation neutralization assays, considering different types of cell substrates;
  - o B cell memory assays for inactivated vaccines;
  - o cell-mediated immunity assays;
  - o antibody affinity/avidity;
  - o serotype-specific antibody/depletion assays;
  - o systems immunology; and
  - o isotype/effector function.
- Currently, vaccine developers have each developed their own assays, measuring particular endpoints relevant to their vaccines.
- Attempts to harmonize neutralization assays have been difficult, and lack of a universal correlate of protection across products makes it difficult to know which assays to harmonize [107].

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