LICENSED VACCINES AND IMMUNOLOGICAL MECHANISMS

VACCINE-ELICITED PROTECTION

Rolando Pajon, PhD, Vaccine Validation Scientist, Vaccine and Novel Immunotherapeutic Laboratory Solutions at Covance

Recent discoveries and technological breakthroughs have advanced our industry’s understanding of the mechanisms of vaccine-induced immunity and revealed new approaches to improve currently licensed vaccines. There are, however, ongoing challenges in the field, spanning process development to effectiveness monitoring. Making a difference in this dynamic area requires an integrated review of the mechanisms that mediate protection following vaccination against pathogens like *Bordetella pertussis*, measles and serogroup B meningococcus.

In vaccine-mediated protection, antibodies effectively “catch” extracellular or exposed entities, but cell-based effector mechanisms also target intracellular pathogens, and are particularly effective at eliminating tumor cells. Antigen-specific and non-specific cells are also important, as is the integration between humoral and cell-mediated responses. In many cases, the link between both the humoral and cellular sides is reinforced by another major element: the human complement system.

Complex System, Different Outcomes

With more than 30 proteins at different concentrations, and interactions occurring at different rates, complement activation is a very elaborate process. Small changes in the level of a protein, the density of the target, or carried mutations that affect one component’s activity may lead to vastly different outcomes—such as “kill” versus “no kill”, or protection versus susceptibility. In addition, no two individuals have exactly the same complement, meaning that two vaccinated individuals with similar levels of vaccine-elicited antibodies will not necessarily be protected at the same level.

Determining the Correlate of Protection

During vaccine development, researchers learn about the specifics of the immune mechanisms mediating protection. In many cases this involves the discovery of a correlate of protection: an immune marker statistically correlated with efficacy that may or may not be a mechanistic causal agent of protection.

Knowing a correlate of protection for a vaccine has great advantages. For example, when testing a vaccine against a slow-developing disease, it may take years to be able to perform a valid clinical comparison between vaccinated and un-vaccinated groups. A measurable immunological variable, on the other hand, can lead to reportable data in just months.
A correlate of protection also helps during the development of the product, as it will shorten the time to proof of concept, help to define reasonable outcomes when setting up QC and CMC strategies and support testing different doses or formulations in clinical research.

Clear and Practical Correlates: A Double-Edged Sword

Not having a clear and practical correlate of protection has hampered the development of vaccines against pathogens like HIV and diseases like malaria, but this fact can be seen as an opportunity rather than a problem.

In the case of vaccines against *Bordetella pertussis*, the causal agent of whooping cough, there is a lack of a clear correlate. Recent findings suggest that although vaccination with acellular pertussis vaccines prevented disease, no apparent effect was observed on infection, carriage and transmission. One explanation may be that current acellular pertussis vaccines do not induce high levels of opsonophagocytic and/or bactericidal activity. (The disease among vaccinated individuals also occurs due to decreasing antibody levels following vaccination with current acellular vaccines, in part perhaps because of the Th₂-biased response that is elicited, rather than the Th₁ type provided by whole-cell vaccines).

In the case of the pertussis, opsonophagocytosis seems to be a very promising candidate as a possible correlate of protection. Further research is ongoing to explore the likely complex correlate of protection, where multiple immunological markers contribute to the process.

Underestimating Protection Levels

If we use only antibody levels as a correlate of protection, we could be underestimating the protection levels elicited by vaccines in certain individuals. As an example, the current correlate of protection for measles is based on measurements of the vaccine-elicited antibody levels. Early on, the efficacy of the measles vaccine was very clear, and it was found that antibodies elicited by the vaccine were very important in the observed protection. Evidence was also noted that both gamma globulin and maternal antibodies demonstrate protection against measles. In functional assays, combining antibodies with live virus limits the ability of the live virus to infect.

There is, however, growing evidence supporting the role of cellular responses in protection against measles. Therefore, if we solely use antibody levels as a correlate of protection, we could be underestimating protection levels. Understanding cellular responses also presents an opportunity for personalized medicine. Developing novel correlates of protection for diseases such as measles could lead to advances in the rapidly expanding menu of personalized immunity.

Potential Benefits of Investigating Individual Immunity

Understanding individual immune responses, rather than focusing on broad-based population data, may be useful when developing alternative paths for vaccine development. Meningococcal disease is caused by *Neisseria meningitidis*, which periodically colonizes our nasopharynx. Most of us will be colonized several times throughout our lives, however, only a small fraction of individuals will develop symptoms and suffer meningococcal disease. As a highly variable bacterium, it is a pathogen with mechanisms of resistance against the activity of human antibodies, complement and immune cells.

To date, two completely different vaccine approaches have been developed: Conjugate vaccines that elicit protection against serogroups A, C, W and Y and protein-based vaccines (licensed in 2015 in the US) that protect against serogroup B strains.
Immune responses to both types of vaccines can be measured by the enzyme-linked immunosorbent assay (ELISA) to the vaccine antigens, or by quantifying the bactericidal activity of vaccines sera in the presence of complement. We know that such bactericidal activity is the mechanistic correlate of protection and as such, it is captured in the serum bactericidal assay (SBA) where serum and an external source of complement are mixed with a known number of bacteria. The readout of this assay is the serum dilution that kills 50% of bacteria after one hour.

The source of the complement is a complicated technical issue and heavily influences this assay. An external source of complement is used, not the vaccine's own complement. As a consequence: the current serum bactericidal assays are good at telling us about the quality and quantity of the antibodies elicited by the antigens in the vaccine, but they do not ultimately tell us the individual's protection status.

Furthermore, while the SBA is the currently accepted correlate of protection against disease, we do not know the correlate against infection and carriage. We know that protein-based vaccines struggle to confer protection against colonization. Data illustrate that conjugate vaccines provide protection against carriage at the population level; but we don't know if such protection is related to a specific mechanism at the mucosa of vaccinated individuals.

The challenge—and opportunity—resides in developing a complex, multivariate and likely biomarker-based approach for the evaluation and prediction of individual immune status to meningococcal disease and transmission.

**Concomitant Vaccine Testing Challenges**

Each time a novel pediatric vaccine is developed, the vaccine must demonstrate the ability to function concurrently with other vaccines on the immunization schedule without affecting the immune response of the other vaccines. This process, called concomitant evaluation, creates a need for testing and retesting of existing vaccines like MMRV, DTP and Hib.

Concomitant vaccine application testing is challenging due to a high number of samples required, as well as the generally low volume of available test product required to run the tests. The need to perfect new assays and approaches that capture how currently licensed vaccines work, should, therefore, not be understated.

**Opportunities for Emerging Vaccines**

As we know more about the associated immune responses, more robust and high-throughput quantitative assays are needed. We are at a point where multiplexing platforms in the research and developing areas of the vaccine space must move deeper into a clinical testing space. The same holds true for licensed vaccines.

An additional driver is the wave of emerging vaccines and immunotherapies. Multi-marker approaches will assist us in the creation of novel correlates of protection and will create the data needed to advance individualized medicine. Personalized immunity has arrived. In this approach, complexity is not a problem; it is an integral part of a solution.

Learn more about our vaccine solutions at [www.covance.com/vaccines](http://www.covance.com/vaccines)
References:


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The Americas +1.888.COVA NCE (+1.888.268.2623) +1.609.452.4440
Europe / Africa +00.800.2682.2682 +44.1423.500888
Asia Pacific +800.6568.3000 +65.6.5686588
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