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Editorial overview: Vaccine immunology: what is seen and not seen

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Prof. Shane Crotty's lab studies the fundamental immunology underlying the functions of vaccines. The lab focuses on the biology of T follicular helper (Tfh) CD4 T cells (*Science* 2009, *Immunity* 2019), the central roles of germinal centers and memory in vaccine immunology (*Immunity* 2018, *Cell* 2019), and understanding the human B cell repertoire (*Science* 2016).

Vaccines have saved innumerable lives and been one of the most successful medicines in the 120 years since the turn of the 20th century [1]. The measles vaccine alone has saved an estimated 21 million lives in the past 17 years [2]. The polio vaccine eliminates more than 350 000 cases of pediatric poliomyelitis paralysis every year [3]. Vaccines are probably the most powerful economic investment low income countries can make for the health and stability of their citizens [4,5]. Clearly, developing more vaccines would be of value to healthy lives in countries around the globe. There are only successful human vaccines for approximately 27 pathogens [6]. There has been great public health value—both short-term and long-term—for each successful vaccine so far. Scientists have found that developing new vaccines is hard. There are multiple reasons for this, but two reasons are 1) the direct study of human immunology in general has been insufficiently robust, and 2) the underlying immunology of the mechanisms of how vaccines function has been insufficiently studied; but now research is illuminating those topics more and more each year. The articles in this collection have been chosen because of their insights into these topics.

Most licensed vaccines work on the basis of protective antibody responses [6]. Therefore, the bulk of these articles focus on how protective antibody responses are elicited to licensed vaccines (Heineman; Ueno), or how they might be elicited by vaccine candidates that are in clinical trials (Graham) or in early development (Kulp; Teyton). Nevertheless, there is a clear emphasis in this volume on the potential value of combined roles of T cells and antibodies in vaccine protective immunity. Most antibody responses depend on T cells of course [7], in the form of T follicular helper (T_{FH}) CD4 T cells [8]. Other required roles of T cells in the protective efficacy of human vaccines are not well demonstrated. The whole cell pertussis vaccine was extremely effective, resulting in a nadir of ~400 annual cases of pertussis in the USA in the 1970s. The newer acellular pertussis vaccine, however, has been substantially less successful. Merkel et al. provide insights into why this may be the case, including evidence that Th17 cells combine with antibody responses to the whole cell vaccine to control pertussis infections, but that the acellular pertussis vaccine elicits other CD4 T cell responses that are less protective. Sullivan et al. discuss how the protective immune response to the Zostavax vaccine are thought to be T cell driven, even though Zostavax elicits antibodies and the related Shingrix vaccine works on the basis of neutralizing antibodies (Heineman). Shresta et al. explain why an antibody-only vaccine against Dengue or Zika is not a good idea, and they propose a combined T cell — antibody approach that may avoid the antibody-dependent enhancement disease that is a peculiarity of dengue.

There is a focus here on direct human vaccine immunology. While it is clear that mouse models are useful for understanding aspects of immunology, it is also clear that mouse models fail to be predictive of human immunology in many cases. The massive success of the human papillomavirus (HPV) vaccines (against cervical cancer) and the human shingles vaccines (Sullivan; Heineman) (against the 'shingles' or 'zoster' disease caused by varicella-zoster virus (VZV) recrudescence in adults) has been without specific mouse models of those diseases. More importantly, those vaccines were developed in spite of widespread consensus that antibody-based vaccines against herpes viruses and papillomaviruses would fail, on the basis of animal models. Given that the Shingrix vaccine has been recently licensed on the basis of its 97% protective efficacy in clinical trials [9], this COI volume was a good opportunity to compare and contrast the Shingrix vaccine against shingles (Heineman) and the earlier licensed Zostavax vaccine against shingles (Sullivan). Both articles provide insights into what we understand and do not understand about protective immunity to chronic herpes virus infections, as well as the approaches those vaccine programs took for developing protective immunity.

One persistent problem with human vaccine immunology has been the accessibility of the immune system. To paraphrase Ueno, it is an issue of what is seen and not seen in blood. Blood is a convenient—and usually the only—source of human cells from vaccine trials. Unfortunately, most high-affinity antibody responses come from germinal centers, and there are no germinal centers in blood. Germinal center biology is restricted to lymph nodes and spleen. Without directly studying germinal center responses, most vaccine trials are left guessing about what immune responses a given antigen and adjuvant elicit. More and more there is recognition of the importance of directly studying immune responses in the tissues that they occur. Ueno and Merkel each discuss this topic in different contexts. My own lab has been using lymph node fine needle aspirates as a method to assess germinal center and T_{FH} cell responses to candidate vaccines [10,11], which has provided insights into adjuvants, B cell immunodominance, germinal center kinetics, and neutralizing antibody development to a difficult pathogen protein [12].

Technology frequently drives advances in science, and new vaccine technologies are highlighted here. Protein engineering to enhance epitopes of interest and hide distracting epitopes is a topic of great interest for pathogens with difficult antibody targets [13,14]. Kulp reviews the field of protein engineering for vaccine development. Teyton reviews the special challenges presented by glycans for vaccines and technologies that can potentially overcome those important challenges. Sander reviews our understanding of innate sensors that at targeted by adjuvants, and how a better understanding of human innate sensors may lead to better adjuvants.

Finally, currently human vaccines only exist for infectious diseases, but non-infectious diseases are being considered for potential vaccine development. Here, Ley et al. highlight interesting approaches to a heart disease vaccine—an atherosclerosis vaccine—using either antibody or T cell focused approaches, and how monoclonal antibody clinical trials can provide insights for candidate vaccine development. It is a helpful summary of how scientists are trying to apply vaccine immunology in new contexts.

With a nod to Kedl and Seder, I thank the authors of this volume for their scholarly attention devoted to these excellent articles, and I hope these articles guide current and future investigators in their efforts to make successful vaccines.

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