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Editorial overview: Preventive and therapeutic vaccines

Mansun Law

Department of Immunology and Microbial Science, The Scripps Research Institute, La Jolla, CA, USA.

During the preparation of this issue of Current Opinion in Virology, we have experienced a number of unusual, but not unexpected viral outbreaks. The Ebola epidemic began in late 2013 and has ravaged several countries in West Africa, claiming more than 11 000 lives and is still ongoing. A vaccine to stop the virus from spreading is unavailable. As herd immunity to Ebola in unexposed regions is mostly non-existent, it is just a matter of time for this devastating virus to cross over to new territories. In this part of the world, we are witnessing an increasing number of measles cases, a disease that was declared eliminated from the United States in 2000. The MMR vaccine is safe and effective but the irrationality of vaccine refusal prevents it from protecting our society against imported measles. Owing to the high efficiency of global air travel, we are destined to witness more emerging viral outbreaks in the near future. Vaccination will be the most cost-effective answer to prepare for this imminent threat. We shall capitalize on the many recent technological breakthroughs in biomedical sciences to accelerate vaccine discovery and improve existing vaccines.

The twelve reviews in this issue focus on the conceptual and technological aspects of vaccine design, especially on the induction of anti-viral antibodies. This is not to disregard the importance of cellular immune response which works hand-in-hand with antibodies in vaccine protection and deserves another issue for an in-depth discussion. With this in mind, we will explore the concept and feasibility of 'B cell epitope vaccines' from multiple angles. A common theme is the emphasis on the prediction, discovery, characterization and utilization of protective antibody epitopes in vaccine development. Thanks to the repeated demonstrations of *in vitro* and *in vivo* efficacy of broadly neutralizing antibodies (bnAbs) against different antigenically variable viruses, the antibody epitope-focused approach has gained significant traction in contemporary vaccine research effort. It also provides a platform to apply structural and computational biology to immunogen design, and high-throughput single-cell analysis to study vaccine responses in a highly specific manner. This issue starts with two success stories:

mlaw@scripps.edu.

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Mansun Law is an Associate Professor in the Department of Immunology and Microbial Science, The Scripps Research Institute. He received his B.Sc. in Biotechnology from The University of Hong Kong and his D.Phil. in Virology/Pathology from Oxford University. His research focuses on understanding viral surface proteins, their antigenicity and immunogenicity for rational vaccine design.

Luca Bruno *et al.* (doi: 10.1016/j.coviro.2015.03.001) review the concept and development of ‘reverse vaccinology’ (RV), followed by synthetic and structural vaccinology. RV was pioneered by Rino Rappuoli and colleagues to identify bacterial antigens from genomic sequences that can induce protective immunity in vaccination. RV seems suitable for large complex viruses in which the targets of protective immunity are not fully understood (e.g. human cytomegalovirus and African swine fever virus). The advantages and limitations of RV for viruses and other modern vaccine concepts are discussed.

Shaowei Li *et al.* (doi: 10.1016/j.coviro.2015.04.003) explain the science behind the development of the first licensed vaccine to hepatitis E virus, Hecolin. Their team succeeded in developing a subunit component of HEV, p239, that forms nanoparticles in the manufacturing process. The nanoparticles are highly immunogenic and elicit high level of nAb response. Subsequent biochemical and structural characterization of the nAbs in the context of virus and nanoparticles shed light on the protective epitopes shared by all four HEV genotypes and the broad activity of the vaccine.

We then examine the neutralizing epitopes of four viruses [respiratory syncytial virus (RSV), hepatitis C virus (HCV), influenza virus and human rhinovirus (HRV)] and epitopes that involve host glycans. Jason McLellan (doi: 10.1016/j.coviro.2015.03.002) reviews the studies of RSV fusion (F) protein at the pre- and post-fusion states, and its structural implication in vaccine development. In natural infection, most nAbs in human sera directs to the pre-fusion form. During viral fusion, structural reorganization of the F protein drastically alters its antigenic surface, resulting in the loss of important neutralizing epitopes. This new information is now guiding the field to develop vaccine candidates based on pre-fusion F, reigniting hope for an RSV vaccine.

Leopold Kong *et al.* (doi: 10.1016/j.coviro.2015.04.001) review recent research on HCV nAbs. HCV is one of the most genetically diverse human viruses for which many think a vaccine may not be feasible. Surprisingly, bnAbs to diverse viral genotypes were isolated recently by several laboratories and some of them were found to protect animal models against heterologous viral challenge. Several structures of bnAbs in complex with the viral antigens, including the E2 core domain, were determined, revealing a conserved and accessible antigenic surface on the virus for structure-based vaccine design.

Gillian Air (doi: 10.1016/j.coviro.2015.03.006) provides a concise overview of nAbs to different surface antigens of influenza virus. The Flu vaccine requires update nearly every year to match the influenza A and B strains forecasted to circulate in the coming flu season. Therefore, a “future-proof” universal flu vaccine is the holy grail in modern vaccine research. Several recently identified antibodies to the head or stem region of flu hemagglutinin were found to be broadly effective against different influenza A subtypes and/or influenza B, providing critical information for the design of such universal vaccines.

Nicholas Glanville and Sebastian Johnston (doi: 10.1016/j.coviro.2015.03.004) discuss the challenges in vaccine development to human rhinovirus (HRV), a major cause of common cold which is also associated with asthma development. With >100 serotypes and >150 genotypes circulating concurrently and ubiquitously throughout the world, HRV represents

one of the most difficult challenges in vaccine development. Despite the great genetic diversity, recent studies suggest there are conserved regions in the viral structural proteins that can possibly be targeted by T and B cells. It is yet to be determined if cross-neutralizing monoclonal antibody to HRV exists and can be isolated from infected humans to facilitate the structure-based approach of vaccine design.

In addition to protein-based neutralizing epitopes, Max Crispin and Katie Doores (doi: 10.1016/j.coviro.2015.02.002) review the unique properties of viral glycans that may be explored for vaccine design. Enveloped viruses are known to utilize host glycans to shield their envelope proteins from nAbs. Interestingly, the high density of glycosylation on certain viral envelope proteins, notably for HIV-1, can inhibit efficient processing of the glycans in cells, resulting in patches of oligomannose-type glycans on the virus that are seen as “non-self” by the immune system. Highly potent bnAbs interacting with the mannose patches have been isolated and their structures provide clues in the design of glycan-based vaccine antigens.

With the increased understanding of antigen-antibody interactions at the atomic level, tremendous opportunities in the prediction and modeling antibody epitopes arise with the aid of relevant bioinformatics and computational tools. Inbal Sela-Culang *et al.* (doi: 10.1016/j.coviro.2015.03.012) review the history of B cell epitope prediction and suggest that the immune system will likely be able to generate antibodies to any given antigenic surface. The other side of the coin is that one may predict and define the epitope of any given antibody computationally if sufficient information on the antigen structure and related antibody sequences is available. This concept is echoed by the review of Karthik Viswanathan *et al.* (doi: 10.1016/j.coviro.2015.03.019) on the application of atomic interaction network (AIM)-based approach to the prediction of amino acid residues on viral antigen surfaces that are clustered and have low mutational potential. Combining structural data available for the antigen, antibodies can be engineered to achieve high specificity and potency to the predicted site. It will be interesting to know whether the conserved ‘antigenic sites’ predicted by AIM are immunogenic and applicable to the design of novel immunogens.

To develop epitope-focus immunogens, John O’Rourke *et al.* (doi: 10.1016/j.coviro.2015.03.005) add a new twist to the virus-like particle (VLP) technology. Due to its optimal size and surface repetitiveness, VLP is a highly effective platform to present immune epitopes to elicit potent and long-lasting antibody responses in the immunized subjects. By linking the phenotype to genotype analogous to filamentous phage display, the authors outlined a strategy for the rapid generation of VLPs displaying epitope mimics (mimotopes) ready for immunization studies. The recombinant VLPs are selected by a bnAb of interest from a pre-made library of icosahedral bacteriophage engineered to display a randomized peptide or loop on its surface.

Another approach to develop epitope vaccines is by scaffolding. Linling He and Jiang Zhu (doi: 10.1016/j.coviro.2015.03.013) discuss how the many computational tools originally developed for protein structure prediction can be repurposed for immunogen design. For highly variable viruses (e.g. HIV-1, HCV), the full-length envelope proteins often contain viral features to misdirect antibody response to non-neutralizing and/or isolate-specific

regions of the proteins. By grafting a target epitope onto a heterologous protein background and constraining its fold resembling the structure in the antigen-antibody complex, it will eliminate those viral features and have a better chance to elicit antibody response to the conserved epitopes. Furthermore, it is now possible to follow the antibody responses at the genetic level by deep sequencing. This combined strategy can provide a feedback loop for iterative improvement of the candidate vaccine antigens to elicit bnAbs.

The last review by Nicole Doria-Rose and Gordon Joyce (doi: 10.1016/j.coviro.2015.04.002) consider the antibody affinity maturation process in vaccine design. Although highly potent bnAbs have been identified for multiple highly variable viruses, it is unclear how such antibodies may be elicited through vaccination. During an immune reaction to infection or vaccination, specific antibodies are created by selective accumulation of mutations in the antibody genes. Attention has now been drawn to the ability of the candidate vaccine antigens to interact with the parental germline and the progeny intermediate B cell receptors along the antibody maturation pathway. The authors discuss a number of vaccination strategies to guide B cell maturation along the right path to produce those rare potent bnAbs. In the HIV vaccine field, a lot of excitement and technological capacity are being built to analyze and optimize nearly every aspect in the vaccination process.

As vaccine research effort is taking a rational approach to define individual components important for protection, it is my hope that one day we can fully realize the potential of the epitope vaccine approach to overcome the scientific challenges discussed in this issue. It is also my dream that the different vaccine components for protection may someday be combined to generate a multiplex vaccine that can protect the world's population from most major and emerging human pathogens through a simple immunization regimen.

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