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Promising cutting-edge technologies and tools to accelerate the discovery and development of new vaccines

Jeffrey B Ulmer, PhD and
Novartis Vaccines & Diagnostics, Cambridge, MA 02139, USA

Marcelo B Sztein, MD
Center for Vaccine Development, University of Maryland, Baltimore, MD 21201, USA

Jeffrey B Ulmer: jeffrey.ulmer@novartis.com; Marcelo B Sztein: msztein@medicine.umaryland.edu

Background

There has been a long and successful history of vaccine use. Although the concept of marshalling the host's immune system to fight off infections via vaccination is widely attributed to Edward Jenner in the 18th century, recorded evidence of inoculation in China and India dates back more than two millennia. Today, vaccines prevent >99% of cases of many childhood diseases, such as polio, diphtheria, rubella, mumps and measles. As such, vaccines are considered to be one of the most effective medical interventions available. Sadly, however, more than 10 million people die each year from infectious diseases, approximately half of whom are under the age of 5 years. These diseases, including AIDS, tuberculosis, malaria, diarrheal diseases, and acute respiratory infections, could in principle be prevented by effective vaccines. So what is preventing the successful discovery and development of vaccines to prevent these diseases? There are two main types of barriers. First, there are practical issues that increase the risks, costs, and timelines associated with developing a vaccine. Unlike traditional pharmaceuticals, which are often synthetic molecules typically used to treat acute or chronic ongoing conditions, vaccines are biologics administered to healthy people to prevent diseases that may or may not be a threat at some point in the future. As a consequence, high safety and regulatory standards are critical but contribute to lengthy and costly evaluation of vaccines before registration. Second, there are substantial technical hurdles that must be overcome to address the remaining major unmet medical needs. In most cases, we have an incomplete understanding of the biology of disease associated with microbial infections. Hence, the choice of antigen(s) to target, the type of immunity needed for protection, and the best suited vaccine technology to apply are often not clear. Furthermore, our ability to predict vaccine safety and efficacy in humans using animal models is an inexact science at best. These limitations severely hamper the selection of the best vaccines to advance to human clinical trials and create uncertainty in predicting the chances for success.

Addressing large unmet medical needs

In this special issue of *Current Opinion in Immunology*, we have compiled nine chapters that highlight many of the key challenges remaining in the discovery and development of vaccines. These chapters touch on several of the largest unmet medical needs for vaccines

against infectious and non-infectious diseases for which there are no current vaccine solutions, such as malaria (see Rollier *et al.*), AIDS (see Verkoczy *et al.*; Rollier *et al.*), dengue (see Coller and Clements), and cancer (see Kreiter *et al.*). In addition, improved vaccines are urgently needed to replace existing, but suboptimal vaccines against certain infectious diseases. For example, the widely used BCG vaccine for tuberculosis (Tb) is effective in infants, but immunity wanes over time. BCG is not effective as a booster, hence a new type of Tb vaccine is needed to extend immunity and thereby prevent the millions of new cases to Tb that arises every year. Rollier *et al.* describe the concept of recombinant viral vectors to elicit antigen-specific immunity, which is one of the several promising approaches currently undergoing clinical evaluation to boost immunity in individuals who have received BCG at birth. Similarly, while the current pneumococcal vaccine is very effective against the bacterial strains covered by the vaccine, an ideal vaccine should be broadly protective against all circulating pneumococcal strains. The conventional vaccine already in use targets the polysaccharide capsule of the bacteria, which consist of variable antigens across different strains. Potential next generation vaccine approaches that target conserved protein antigens of the bacteria may provide broader protection, as reported by Moffitt and Malley.

Technologies for new and improved vaccines

Most conventional vaccines have been developed over the past two centuries based on the principles of Louis Pasteur. That is, to identify the organism causing disease, render the organism harmless, and administer it to the individual as a means to elicit protective immunity. Vaccines developed in this way include inactivated (e.g., by chemical treatment) or attenuated (i.e. a live organism but genetically modified to make it safe for humans) viruses and bacteria. Other approaches being explored involve the use of live vector vaccines consisting of attenuated organisms carrying genes expressing foreign antigen(s) presumed to be important in protection to other infectious microbes in an attempt to elicit protective immunity to both the attenuated vector and the microbe(s) from which the foreign antigen(s) were derived. This general approach has been very successful so far, but has limitations in its application to many of the remaining vaccine targets. These include practical issues of culturing certain microbes (e.g., HCV) and safety issues for highly pathogenic organisms (e.g., HIV). Therefore, a preferred alternative widely used today for many vaccines in development is the subunit approach, where the immune response is focused on one or only a handful of antigens either purified from the organism (e.g., influenza vaccine) or recombinantly produced (e.g., hepatitis B vaccine). Such subunit vaccines, because they are highly purified and sometimes are not inherently immunogenic, often require a supplementary immune stimulus to increase potency, in the form of an added adjuvant. So far, vaccines containing such adjuvants are very effective, but currently limited to injection for induction of systemic immunity (mostly resulting in enhanced antibody responses). Since most microbes gain entry into humans via mucosal surfaces, a strong local immune response at these surfaces could provide a first line of defense. To this end, adjuvants able to enhance mucosal immunity are needed. Lawson *et al.* describe the encouraging status for development of novel adjuvants and carrier formulations designed for mucosal administration.

Nucleic acid-based vaccines consist of expression vectors that encode the antigen(s) of interest. These constructs come in various forms. Plasmid DNA vaccines have shown great promise in animal models, but are not sufficiently potent in humans to elicit protective, long-lasting immunity. A potentially enabling technology for DNA vaccines is *in situ* electroporation, which markedly facilitates delivery of DNA directly into cells and enhances immunogenicity, as summarized by Sardesai and Weiner. In another nucleic acid approach, Kreiter *et al.* describe the use of RNA as vaccines, including mRNA as well as engineered replicon RNAs derived from certain RNA viruses such as alphaviruses. Finally, recombinant replication-defective viral vectors, such as those derived from poxviruses and adenoviruses, are discussed by Rollier *et al.* Each of these technologies has its relative merits and limitations, but the concept is the same, namely to mimic the properties of a live infection (i.e. *in situ* production of antigen), without the practical and safety issues associated with the administration of live organisms.

Tools to facilitate rational vaccine design

At the outset of a vaccine discovery and development program, the key questions that need to be addressed are: firstly, what antigen(s) to target with the vaccine; secondly, what type of immunity is needed for protection; thirdly, what technologies to apply in order to achieve the desired immune response; and fourthly, how to translate preclinical information to guide clinical application. The development of novel vaccines using the traditional empiric approach continues to show that this tactic is less than satisfactory and the outcome difficult to predict. Fortunately, novel technologies and strategies are emerging that promise to revolutionalize the strategies to develop vaccines using more rational approaches. In this issue, three chapters are focused on reviewing the prospects of using these sophisticated technologies and strategies to provide insight into the above questions, in order to facilitate rational approaches to vaccine discovery and development. Corti *et al.* have described high throughput methods designed to study B and T cell repertoires to evaluate the fine specificity of humoral and cellular immune responses to vaccination necessary to adequately assess the diversity of the human immune response. The authors discuss the likelihood that these methods will accelerate the development of vaccines through the identification of, for example, broadly reactive antibodies, or by eliciting T cell responses by the most appropriate cell subsets and to the most favorable antigens. Verkoczy *et al.* have explored the intricacies of the antibody response to HIV and provide clues to how induction of potent, broadly cross-reactive, and protective virus neutralizing antibodies may be achievable. The output of these strategies not only has the potential to yield valuable information about the quantity and quality of vaccine-induced immune responses, but also may provide the means to generate effective monoclonal antibodies for preventive and therapeutic use. Finally, Oberg *et al.* illustrate a promising systems biology approach to interpreting the complexities of the broader host response to vaccination, as probed by profiling at the genomic, transcriptomic, proteomic, and network levels. Approaches such as those described, will be necessary for an informed, iterative vaccine optimization and development program.

Prospects for success

The previously mentioned practical and technical hurdles for vaccine development have historically minimized investment in research and development, and posed a high barrier to entry for new vaccine initiatives. However, the landscape is changing. Until the recent past, there were few major vaccine players, visibility was low, technical and regulatory risks were viewed as unacceptably high, and return on investment was considered lower than traditional pharmaceutical drugs. Today, many major pharmaceutical companies have significant vaccines R&D activities, vaccines have much higher visibility than before, new technologies have enabled the advancement of promising vaccine candidates, and there have been several recent blockbuster vaccine success stories (e.g., to prevent diseases associated with pneumococcal and papilloma virus infections). Together, these factors have set the stage for an exciting period of rapid growth for vaccines.

Biographies

Jeffrey B. Ulmer, PhD, is the Global Head of External Research for Novartis Vaccines & Diagnostics. He is responsible for identifying and creating new strategies and opportunities for external collaborations in vaccines discovery and development.

Marcelo B. Sztein, MD, is a Professor, in the Department of Pediatrics, and the Associate Director for Immunologic Studies, Leader of the Immunology Group and Chief of the Cellular Immunology Section and Flow Cytometry Core Laboratory at the Center for Vaccine Development, with adjunct appointments in the Departments of Medicine and Microbiology and Immunology, University of Maryland, Baltimore, MD. His lab works on understanding the mechanisms underlying the generation of protective immune responses to infectious agents in the context of vaccine development in humans and animal models through the study of cellular, humoral, innate and mucosal immunity.