Development of Novel Vaccines

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Adults and children today are the benefactors of more than a century of research and development that has resulted in a great variety of licensed vaccines. Vaccine coverage in developed countries is, on the whole, exceptional, and has led to an expectation of a long and healthy life for most children born in this setting. However, it is possible to falsely conclude that the major infectious disease challenges are addressed and few novel vaccine targets remain. There is in fact an endless variety of common pathogens, emerging infections and potential pandemics that will continue to plague humans and drive the need for further discovery, and innovation. The past successes and new challenges will undoubtedly stimulate the vaccinologists of the world to move new ideas down the long and hard slog to testing and approval. These past successes and current challenges, and, the general momentum of vaccine science today, has stimulated an unprecedented level of R&D surrounding novel and existing vaccines. The growth of international markets, more sophisticated and complex regulatory pathways, NGO commitments to the developing world unmet needs have made vaccine licensure ever more a daunting challenge. With this setting in mind, the new book, *Development of Novel Vaccines* by von Gabain and Klade is a welcome resource.

This small book covers a great deal of ground for readers with respect to novel vaccine development, but as happens with books of this nature, it is dated due to recent progress, and thus its time to work on the next edition. Organizationally, it begins with a review of relevant immunology,

sweeps through antigen identification, adjuvants, delivery and ends with discussions of novel licensed vaccines and regulatory/licensure of vaccines. Recognizing that one reads with their own rose colored glasses, I found the last chapter to be the most illuminating among a collection of very good essays. Here, the author Fleiderer lays out succinctly the landscapes of challenges and hurdles that vaccine development to licensure faces. In a sober assessment, he suggests that only large Pharma is capable of crossing the goal line of product licensure and maintaining the systems required for continued supply of quality product to those who need it. The bias for licensure success only by large biotech however is not a fixed rule, as evidenced by the preceeding chapter in which the licensing pathway for the Japanese Encephalitis vaccine is documented. This vaccine, simultaneously licensed in the US and Europe, was discovered initially conceived in academia and further developed through licensure in a small Biotech company, resulting in simultaneous approval in the US and Europe, a remarkable achievement. The same chapter also reviews the clinical development of HPV, done in the context of Large Pharma but again founded on classic discoveries made in basic science. For both programs, there is an instructive and detailed assessment of the clinical strategy and data generated during the path to licensure and beyond. The complexity, number of questions addressed and subjects in the trials reinforces the sober assessment of Fleiderer that vaccine development is at least a monumental task.

Returning to an ordered survey of the chapters, in Chapter 1, Alkan reviews the fundamentals of immunology, new

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technologies and a systems biology approach to understanding immunity as it relates to vaccines. However, there are two pre-suppositional flaws to this and many other reviews of immunology and discovery work in general as it relates to vaccines. First, so little of what is known about immunology or might be described during a vaccine-induced immune response is actually employed in licensing a vaccine. Thus, the details discussed here might relate to preclinical mechanism of action studies, but are not as relevant to the process of licensing a human vaccine. The point in case is the JEV vaccine, where antibodies were the basis for licensure. Second, few review(er)s draw clear lines between mouse immunology and human immunology. Thus, the statement that “the new technologies and computational tools permit the comprehensive and quantitative analysis of all the components of immunity over time...and is expected to provide relevant and novel insights,” is an overreach as human vaccinologists more narrowly approach the measures of immunity when planning for licensure studies. Thus, while applied immunology, including mouse immunology, should not be ignored, more ink could have been provided to the principles of human immune assay development, and the less glamorous topics of qualification and validation of such assays. Similarly, the interesting chapter on “Finding Bacterial Antigens,” is plagued by the utility of its presupposition that finding a match between genomically displayed antigens and human immune responses to pathogens in the natural setting, will lead to important vaccine targets. There are for example, many decoy responses and worse, responses that lead to immune pathology. Similarly, the use of animal model data seldom readily translates to human efficacy. The recent adverse outcomes of the IsdB *S. auerus* vaccine, where it appears that the vaccine antigen caused disease enhancement in a Phase 3 trial, is a recent and sobering example that translation can be very

unpredictable. Antigen discovery should pay more homage to pathophysiology and human pathology, which to be fair, is given some importance. The recent approval of the Meningitis B vaccine in Europe and its pathway from discovery to licensure could have been covered upfront and will warrant future preeminence in the next edition. The chapter on adjuvants is informative yet will similarly need to be updated. The very recent applications for US licensure of H5N1/ASO3 and Hepislay, indicate that the use of novel adjuvants have begun to make their case for utility in the US regulatory environment, yet continue to be very challenging to license due to safety (Hepislay). Novel adjuvants need to seriously considered in any novel vaccine development program. However, as alum salts continue to be a mainstay in old and new vaccines, it is rightly discussed upfront. Possibly, more pragmatic advice on alum formulations, details on the role of binding, stability and dosage might have made this chapter more informative. The chapter on vaccine delivery to the skin is interesting but narrow focused on a single technology, without paying heed to other skin delivery approaches. There is today a great deal of research activity surrounding methods of delivery, the immunology of the skin and adjuvant use. This chapter will need to be updated due to cover the successfully licensed intradermal flu vaccine (Intanza), a device and vaccine story success story, and the unsuccessful Phase 3 trial of the traveler’s diarrhea vaccine, a novel vaccine and delivery effort. In addition other routes of delivery might be reviewed, recognizing that the editors and authors walk a tightrope between brevity, scope and thoroughness.

Chapters 6 and 7 are important topics for the vaccine developer. Those who are experienced in these specific disciplines will find the sections simplistic, but this book caters to a broad audience and the authors found a good balance at

the technical level for such an audience. Upstream manufacturing of a biologic product in microbes combines art and science and the authors rightly state that “the choice of the cell substrate is critical...” and no doubt complex. Returning to the idea that only large pharma is capable of licensing the vaccine, the efforts required to manufacture and purify vaccines are fraught with many failures that small companies are unlikely to be able to absorb. Smart choices, and investment in running the systems early and making wise choices increase future success. Whereas, Wacker and Casiro cover the biologic systems that could be used with brevity and precision, they give little guidance on decision trees making choices and this would be a helpful opinion, possibly best rendered by those who have licensed a vaccine. Similarly, Schlegal and Hahn cover antigen purification in detail and the reader should wrestle with the math and the concepts therein, as it is relevant and informative. Chapters 8 and 9 are strangely given the same title and give the least broad scope to their topics, which is unfortunate as influenza is a relevant, ever-changing and challenging vaccine field. Of all the chapters, these two most narrowly tout their own approaches and give little room to other approaches such as VLPs or soluble HA, which are innovations well down the path to licensure.

In summary “Development of Novel Vaccines” is well worth reading. The editors have for the most part chosen topics well, but should ask the future contributors to cover the issues with more balanced and broader views in the next edition. This is the frequent flaw of a special issue book, and a universal complaint of the reviewers of such books! The editors or their successors should provide an update of the topics, consider adding issues and discovery priorities for lesser developed countries, and emerging infections in a future edition, which this reviewer hopes will soon be forthcoming.