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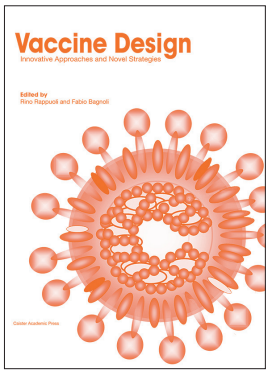

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Vaccines, vaccine research and vaccination have become increasingly popular with an ever-increasing number of international meetings and symposia. It is evident that the breadth of these endeavors as addressed in these many meetings cannot be readily covered in a single book with the depth of discourse and analysis necessary to provide a foundation of understanding for those entering or dedicated to all that encompasses modern vaccinology. Instead of a broad, probably shallow and superficial treatment of vaccine research, Rappuoli and Bagnoli and colleagues have logically focused on evolution of vaccine design strategies for bacterial pathogens dependent on new tools in molecular genetics, high-throughput screening and especially genomic analyses, and then included chapters that detail success and progress in vaccine design in development of safe, efficacious vaccines directed towards induction of antibody-dependent protective immunity.

The highlight of this book is chapter 2 by Bagnoli and colleagues that describes the 10-year effort to develop the innovative 'reverse vaccinology' (RV) technologies, detailing the steps using genomic information from multiple globally distributed strains of a specific bacterial pathogen coupled with ever-improving bioinformatic means of analysis to identify candidate protective antigens. These analyses start with the *in silico* identification of all open-reading frames in the core genome (genes present in every strain within the species) versus the pangenome (every gene present in one or more strains within a species), the identification of encoded gene products likely located on the bacterial cell surface and the presence of these gene products and their homogeneity versus heterogeneity in representative globally distributed strains. The use of proteolytic enzymes to 'shave off' the exposed portions of surface antigens followed by mass spectrometry analyses can confirm surface localization as well as identify surface antigens not identified as surface-localized by current software programs. Evaluations of the importance of the gene product on the ability of the pathogen to colonize and/or cause disease (as deduced by analysis of deletion mutants) and to induce protective immunity in a suitable animal host are then performed. The use of proteomic methods is also detailed, but the problem of distinguishing pathogen proteins synthesized *in vitro* from those induced so as to be synthesized *in vivo* was not well addressed, except the suggested use of culture conditions that might reveal some genes expressed in response to an *in vivo*-encountered stress. While extolling these RV technologies to identify protective antigens, the listed classical approaches used historically to develop many of our existing vaccines still have validity and value. Thus, research on mechanisms of bacterial pathogenesis often identify and characterize virulence attributes that can become important vaccine components. Thus, collaborations between these largely academic-based research efforts and the vaccine industry's use of RV technologies need to continue. The RV approach could benefit from screening bacterial expression gene libraries for products identified by reactivity to antibodies induced following infection that fail to react with gene products produced during *in vitro* cultivation. Similarly, one can use high-throughput selected capture of transcribed sequences (SCOTS) to identify

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pathogen genes uniquely expressed *in vivo* that are not expressed *in vitro* as likely to be important in pathogen success and thus worth investigating as potential protective antigens [1,2]. Another class of protective antigens missed by existing software screens represent enzymes seemingly localized to the cytoplasm, at least during *in vitro* growth, that in the absence of any known secretion mechanism escape the pathogen cell *in vivo* to contribute to virulence and disease. Such *in vivo*-exported antigens that can induce protective immunity, including glutaraldehyde-3-phosphate dehydrogenase, enolase and aldolase, for example, are present in pneumococci (see chapter 14) and other bacterial and parasite pathogens.

Chapter 9 by Adu-Bobie *et al.* details the history and importance of vaccines to prevent *Neisseria meningitidis* infections, and gives the historical development and implementation of RV technologies to successfully yield a vaccine against serotype B (MenB), which is causing an increasing proportion of meningitis cases globally owing to the inability to produce a MenB capsular polysaccharide–protein conjugate vaccine. This is because the MenB capsular polysaccharide contains *N*-acetylneurominic acid repeats that are present in humans. The chapter also details the importance and contributions to immunity afforded by including several protein antigens identified by RV methodologies. This chapter is thus of historical value but is also instructive of important means of MenB pathogenesis and means by which animal and human hosts attempt to contend with MenB infection. Chapter 13 by Cozzi *et al.* describes the evolution of attempts to develop a universal vaccine to prevent group B *Streptococcus* (GBS) infections and the beginnings of successes using the RV approach are described to augment the progress being made with protein conjugate polysaccharide vaccines. Since early onset GBS disease is experienced by newborns during the first week of life, immunization of mothers will probably be important. However, even with the progress in developing a combined protein and conjugate polysaccharide vaccine against GBS infections, there is a difficulty in designing clinical trials to reveal safety and efficacy since little is known about transfer of and protective effectiveness of maternal immunity.

In regard to clinical trials, chapter 3 by Nahm and Frasch, although brief and focused, makes a good case for development of *in vitro* assays of antibody specificity and effectiveness that could represent correlates of protective immunity. Although not stated, such assays could supplant, or at least modify, the design of clinical trials and facilitate evaluation and validation of vaccines for prophylactic use. Nahm and Frasch thus detail the value of bactericidal and opsonic antibodies as well as multiplex methods to facilitate such screens for use in evaluating meningococcal and pneumococcal vaccines, but surprisingly do not mention quantitative assays to reveal effectiveness of antibodies in blocking binding of complement components, such as factor H. In addition, there are many other means to establish and evaluate correlates of protective immunity using neutralization of toxins, complement-mediated cytotoxicity and blockage of cell invasion, cell-to-cell spread and even growth of bacterial pathogens.

While the introductory chapter 1 by Arnon gives a very broad and complete overview of the many strategies for vaccine design, the remainder of the book's chapters only give a glimpse of some of these efforts. I am concerned, however, with the expression by vaccine researchers of continued apprehension about the genetic instability of live-attenuated and live-recombinant attenuated vectored vaccines as those currently being introduced or developed. In the current era of modern molecular genetics, all such vaccines have multiple gene deletions or multiple base pair changes such that reversion after mutagenesis and exhaustive selection fail to lead to restoration of virulence or toxicity. This standard of genetic stability has been enunciated by researchers developing such vaccines for the last 25 years. It is thus unfortunate to perpetuate these fears in books promoting vaccine development and use.

Of all chapters in this book, chapter 5 on protein toxins by Keith should be a must-read by anyone aspiring to be a vaccinologist. Keith details the history of vaccine development in achieving our current level of success in preventing diphtheria, tetanus and whooping cough with copious literature citations and credits, many in a most generous way. Of note, induction of antitoxin immunity can also reduce the prevalence of exotoxin-producing pathogens. Thus, antibodies against the C-terminal cell-binding portion of the *Clostridium perfringens* α-toxin coat the surface of toxin-producing bacteria to reduce their growth *in vitro* and *in vivo* [3]. The recent contributions of structural biology and molecular genetics in generating stable, nontoxic immunogenic toxins supplants the earlier historical reliance on toxoids but also illustrates the disappointment and frustration when better vaccines never replace the old. This is because trials to validate safety and efficacy are too costly with no financial incentive to conduct them. However, benefit has been realized since genetically engineered nontoxic toxins are being used to construct some protective polysaccharide–protein conjugate vaccines against *S. pneumoniae* and other capsulated pathogens (Bundle, chapter 4). In this chapter on conjugate vaccines that thoroughly presents modern methods of conjugation chemistry, I was disappointed that Avery was not mentioned for having been the first some 80 years ago to make a pneumococcal polysaccharide–protein conjugate vaccine that induced protective immunity nor was there mention of the licensed Vi conjugate vaccine now widely use to confer protective immunity to *Salmonella* Typhi.

Chapter 6 on adjuvants by Skibinski and O'Hagen gives a complete discussion of means by which alum enhances immunogenicity and reduces the necessary antigen doses to affect immunity and gives a similar complete description of the development and efficacy of the MF59 squalene-based adjuvant. However, there is only brief mention of other adjuvants such as MPLA or the use of liposomes, immune-stimulating complexes, CpG and more. Chapter 7 on mucosal vaccines by Ravindran and Pulendran is really much more an excellent account of the mucosal immune system and is rather superficial in terms of mucosal vaccines. The idea that "most mucosal vaccination has traditionally relied on … mucosal delivery of antigens and adjuvants" is misleading since most mucosally delivered vaccines are attenuated viruses and bacteria or their recombinant derivatives used as antigen delivery vectors. The recent investigation of sublingual immunization as a safe, efficacious means to deliver mucosal vaccines was not discussed and this may be important in eliminating safety concerns associated with intranasal vaccination and instability concerns associated with oral administration

of vaccines. This chapter contained a comprehensive description of mucosal adjuvants that were not mentioned in chapter 6. Although safety concerns of using CT and LT as mucosal adjuvants and their unlikely use in humans were noted, I think the induction of Bell's palsy after intranasal administration of an influenza vaccine using LT as the adjuvant should have been discussed [4]. Clearly, one would now use nontoxic derivatives of CT/LT but surmounting regulatory hurdles would be difficult given these previous adverse results. Chapter 8 by Kündig *et al.* on intralymphatic vaccination is useful and informative but I was disappointed in the absence of a thorough treatment of intradermal patch delivery strategies.

Most other chapters dealt with progress toward developing vaccines to protect against specific diseases such as those caused by *Pseudomonas aeruginosa* (chapter 11 by Scarff and Goldberg), *Staphylococcus aureus* (chapter 12 by Cheng *et al.*), *S. pneumoniae* (chapter 14 by Paton), agents of bovine mastitis (chapter 15 by Middleton) and SARS (chapter 16 by Haagmans). The Paton chapter gave a comprehensive and balanced treatment of efforts and successes in developing antipneumococcal vaccines. As appropriate for a chapter in a book on vaccine design, less than a page dealt with pathogenesis and justifying the need for antipneumococcal vaccines. Many of the other chapters dwelled much more on pathogenesis issues without a clear direction for current or future vaccine design efforts to successfully address the disease problems, although some vaccines with specific but limited successes have been developed to control some mastitis pathogens. The chapter by Cheng *et al.*, in noting that immunity is not induced following survival from *S. aureus* infections, gave credence to the belief (not stated in this book) that many pathogens have means to circumvent, suppress, modulate or otherwise avoid inducing immune responses that would lessen their success as pathogens. In these cases, generation of attenuated vaccines is probably precluded until the means by which the pathogens accomplish these immunosuppressive feats are understood and genetically eliminated.

Chapter 10 on vaccines for neglected diseases by Saul is inclusive of the many pathogens causing respiratory and diarrheal diseases as well as the diseases caused by parasites. His overview, although brief, is all-inclusive and the extent and severity of diseases caused by these neglected pathogens is staggering. As such, a complete treatment of these diseases, the causative pathogens and the vaccine development efforts would likely require a two-volume treatise with many chapters. Nevertheless, Saul makes a very telling point that needs to be heard and understood. His point is that with our current economic system, vaccines against these pathogens are not likely to be developed since the economic incentives to undertake these efforts pretty much do not exist. In addition, clinical evaluation is also made difficult since either the disease incidence is so low as to require very large clinical study populations or so prevalent owing to multiple pathogens contributing similar symptoms of disease as to mask the benefit of any vaccine against one causative agent. These problems must be addressed with new means of validating vaccine effectiveness and with public/private partnerships to fund the science, clinical validations and ultimate distribution of approved safe efficacious vaccines.

Although the 16 chapters in *Vaccine Design* add much to our knowledge toward developing vaccines relying on antibody-mediated protection against bacterial diseases, there is an absence of any serious treatment of modern means to induce cellular immunity, which is probably necessary to control HIV, TB, malaria, and a host of other viral and parasite pathogens. A means for developing a RV strategy to succeed in these endeavors would thus be welcomed. In this regard, the use of modern vectored vaccine technologies that offer hope for stimulating all three branches of the immune system and that are designed to be effective in inducing cellular immunity might provide a partial solution to this problem in ensuring public health and an eventual global freedom from infectious diseases.

Throughout this book there are numerous wisdoms that should be enunciated by more vaccinologists. Thus, while stressing the value of protecting the individual, vaccination programs are more important in contributing to community and public health. Even vaccination programs restricted to a country/region can thus diminish the occurrence of global transmission and pandemics. Also, in addition to preventing deaths, widespread vaccination improves the quality of life, especially in the developing world where continual infectious diseases stunt growth and the development of youth. Likewise, widespread vaccination against bacterial pathogens lessens antibiotic use and reduces the pressure for selecting antibiotic resistance, thus enhancing the effectiveness of antibiotics when really needed. The same principle is likely true with regards to antiviral and antiparasite drugs. These thoughts are well developed by Rappuoli and Bagnoli in the introduction and by Arnon in the overview chapter.

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