vaccines currently available reside in the upper right quadrant and have been developed using well-established technologies.

Modern preventive vaccines required for more difficult infectious organisms can build on expanding new technologies and immunological knowledge. Good examples are the several recombinant and conjugate vaccines already licensed, and several vaccines developed using genomics (reverse vaccinology) that are in development. Reverse vaccinology represents a revolution in vaccinology and a milestone in biotechnology. It illustrates how a complex biological problem such as vaccine design can be solved by addressing and integrating in silico predictions and high-throughput in vitro experimental analysis for the identification of optimal vaccine antigen formulations. Beyond the pioneering work with MenB, we see the development and maturation of the technique, as it has been adapted to other biological systems with their inherent difficulties (such as GBS). We also see how newly emerging bioinformatic and immunoinformatic technologies can be integrated with functional genomics approaches to hone down the targets (Fig. 1). With many more antigens discovered for each pathogen, it is now possible to select antigens that respond to validated principles, such as antibody-mediated protection, and with limited or absent antigenic variability.

An important minority of the vaccines described in this book reside in the middle or left quadrant of Figure 3. These are the vaccines for which today's technologies have not yet succeeded, and developing these vaccines requires bridging scientific gaps such as learning to develop vaccines based on T cell–mediated protection. Today, development of these vaccines is being addressed using innovative immunostimulatory molecules and adjuvants, replicating or nonreplicating viral vectors, prime-boost regimens, etc. An alternative approach could be to bring them to the ''comfort zone'' of the upper right quadrant of Figure 3 by learning how to engineer immunologically silent conserved epitopes into immunodominant epitopes. A good example of this is HIV, where antibodies such as B_{12} that recognize the conserved CD4-binding site could be able to protect from infection if this epitope were immunodominant.

In conclusion, the majority of the new vaccines addressed in this book are within the reach of today's technologies. Rather, the question is therefore whether or when they will be developed. Unfortunately, technical feasibility is only one of the hurdles in vaccine development. Even more important is often whether there is a market that can justify the huge investment that is necessary to bring vaccines to licensure. Many of the vaccines described in this book are at the ''discovery'' stage. However, the clinical development phase, during which a discovery is transformed into a potential product, is a long and expensive process. New vaccines today are developed by a few global vaccine manufacturers that can only afford to invest in vaccines that have a high probability of success in the market. In addition, the half dozen largest vaccine manufacturers have the traditional knowledge and the necessary investment to carry out clinical vaccine testing and manufacturing process development of candidate vaccine products. Many of the failures in vaccine development are due to the poor understanding and underestimation of the complexity of this phase.

Thanks to the impressive progress in biotechnology, the vaccine field is embarking on a new post–genomic era: harnessing genome data, and using genomics, proteomics, and immunology techniques in a new interdisciplinary realm of inquiry (Fig. 1). Vaccines targeting hypertension, drug addiction, and cigarette smoking are examples of how vaccines are being evaluated to target diseases that are not traditionally tackled by vaccination. Vaccines today are usually given to prevent diseases that parents and pediatricians have never seen, and in their minds, they are no longer immediate lifesavers but tools that improve the quality and duration of life.

REFERENCES

1. Rappuoli R. Bridging the knowledge gaps in vaccine design. Nat Biotechnol 2007; 25(12):1361–1366.
2. Cutts FT, Franceschi S, Goldie S, et al. Human papillomavirus and HPV vaccines: a review. Bull World Health Organ 2007; 85(9): 719–726.
3. Plotkin SA. Six revolutions in vaccinology. Pediatr Infect Dis J 2005; 24(1):1–9.
4. Valenzuela P, Medina A, Rutter WJ, et al. Synthesis and assembly of hepatitis-B virus surface-antigen particles in yeast. Nature 1982; 298(5872):347–350.
5. Pizza M, Covacci A, Bartoloni A, et al. Mutants of pertussis toxin suitable for vaccine development. Science 1989; 246(4929):497–500.
6. Greco D, Salmaso S, Mastrantonio P, et al. A controlled trial of two acellular vaccines and one whole-cell vaccine against pertussis. Progetto Pertosse Working Group. N Engl J Med 1996; 334(6): 341–348.
7. Blaney JE Jr., Durbin AP, Murphy BR, et al. Development of a live attenuated Dengue virus vaccine using reverse genetics. Viral Immunol 2006; 19(1):10–32.
8. Buchholz UJ, Nagashima K, Murphy BR, et al. Live vaccines for human metapneumovirus designed by reverse genetics. Expert Rev Vaccines 2006; 5(5):695–706.
9. Subbarao K, Chen H, Swayne D, et al. Evaluation of a genetically modified reassortant H5N1 influenza a virus vaccine candidate generated by plasmid-based reverse genetics. Virology 2003; 305 (1):192–200.
10. Webby RJ, Perez DR, Coleman JS, et al. Responsiveness to a pandemic alert: use of reverse genetics for rapid development of influenza vaccines. Lancet 2004; 363(9415):1099–1103.
11. Daudel D, Weidinger G, Spreng S. Use of attenuated bacteria as delivery vectors for DNA vaccines. Expert Rev Vaccines 2007; 6(1): 97–110.
12. Mercenier A, Müller-Alouf H, Grangette C. Lactic acid bacteria as live vaccines. Curr Issues Mol Biol 2000; 2(1):17–25.
13. Levine MM. Use of vaccines for the prevention of typhoid fever. Indian Pediatr 2003; 40(11):1029–1034.
14. Cheminay C, Hensel M. Rational design of *Salmonella* recombinant vaccines. Int J Med Microbiol 2008; 298(1–2):87–98.
15. Loessner H, Endmann A, Leschner S, et al. Improving live attenuated bacterial carriers for vaccination and therapy. Int J Med Microbiol 2008; 298(1–2):21–26.
16. Center KJ. Prevenar vaccination: review of the global data, 2006. Vaccine 2007; 25(16):3085–3089.
17. Verez-Bencomo V, Fernandez-Santana V, Hardy E, et al. A synthetic conjugate polysaccharide vaccine against *Haemophilus influenzae* type b. Science 2004; 305(5683):522–525.
18. Ludwig C, Wagner R. Virus-like particles-universal molecular toolboxes. Curr Opin Biotechnol 2007; 18(6):537–545.
19. Bazhan SI, Karpenko LI, Lebedev LR, et al. A synergistic effect of a combined bivalent DNA–protein anti-HIV-1 vaccine containing multiple T- and B-cell epitopes of HIV-1 proteins. Mol Immunol 2008; 45(3):66166–66169.
20. Maurer P, Bachmann MF. Vaccination against nicotine: an emerging therapy for tobacco dependence. Expert Opin Investig Drugs 2007; 16(11):1775–1783.
21. Robert-Guroff M. Replicating and non-replicating viral vectors for vaccine development. Curr Opin Biotechnol 2007; 18(6):546–556.
22. Liniger M, Zuniga A, Naim HY. Use of viral vectors for the development of vaccines. Expert Rev Vaccines 2007; 6(2):255–266.