Preface

Modern vaccines increasingly rely on administration with additional substances—adjuvants—in order to stimulate effective immune responses. Although the concept of adjuvants has been recognized for at least 80 years, their mechanism of action has been only partially understood, and the pathway to rational design of safe and effective adjuvants has been unclear. There have been few principles to guide adjuvant research, relying largely on increasing antigen uptake by macrophages and based heavily on empirical approaches.

However, by the mid- to late-1990s, major advances in basic immunology forever changed the strategies for discovery, design, development, and use of vaccine adjuvants. First, discoveries of receptors that rapidly signal the presence of invading viruses, bacteria, and parasites pinpointed the innate immune system as the target of adjuvants. That is, adjuvants serve an absolutely essential function for the development of B- and T-cell responses by triggering antigen-presenting cells, in particular dendritic cells, to upregulate co-stimulatory molecules, to process and present antigens, migrate to lymph nodes, and secrete cytokines that trigger appropriate Th1 (cell-mediated) or Th2 (antibody-dominated) responses. The concept that adjuvants trigger innate immune receptors that are hard-wired to detect microbial molecules underlies all of the chapters in this volume. Microbial molecules include bacterial cell wall compounds, viral and bacterial nucleic acids, parasite sugars, and proteins and lipoproteins that are generally essential components of pathogens. In addition, there are increasingly refined technologies available to monitor the immune system in response to infection, including "chip" analyses of gene expression, proteomic approaches, and peptide-major histocompatibility complex tetramers to monitor antigen-specific T cells. Together, these advances raised the exciting prospect not only for the development of safer and more effective adjuvants to trigger powerful immune responses, but also to design adjuvants that manipulate the direction of the immune response to yield Th1, Th2, cytotoxic T cell, or combinations of desired responses.

Vaccine Adjuvants comprises a highly select group of chapters that detail major research areas in this new era of adjuvant discovery, design, development, and use. Articles include a focus on specific receptor–ligand interactions, including the molecular features needed for a compound to possess adjuvant activity. The critical interface zone between

the innate and adaptive immune systems is analyzed to show how adjuvants exert their effects on T- and B-cell activation.

Vaccine Adjuvants: Immunological and Clinical Principles also addresses why there is a need for developing a variety of distinct adjuvants. In the future, no single adjuvant will fit all needs. Chapters detail specific properties and uses of such diverse adjuvants as modified bacterial toxins, synthetic mimetics of bacterial cell wall lipids, parasite sugar moieties, plant saponins, microparticles, and CpG-containing nucleic acids. This developing repertoire is contributing toward eventually having an arsenal of such compounds that can function specifically to direct immunity to Th1 or Th2 responses, that can work optimally in the gut, lung, skin, or other desired route of vaccination, and which potentially may be optimized for distinct age groups or individuals with different needs. For example, as we gain insight into the genetic makeup of different human populations and the genetic influences on immune responses, it may be possible to tailor adjuvants to specific genotypes to yield optimally safe and effective responses. These chapters address key areas that underpin a new era of research that will lead to the rational design of new adjuvants and a new set of principles for their use.

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