Manmohan Singh *Editor*

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Preface

Recent advances in our understanding of innate immunity have fueled the field of drug discovery with emphasis on developing better immune potentiators that can boost the host innate immune system. Targeting the host innate compartment has the unique advantage of triggering a rapid mobilization of key effector mechanisms to engender a strong immune response to a vaccine antigen. Several new class of molecules that target the innate immune system have been recently tested as potential vaccine adjuvants. These novel adjuvants also require rationally designed vaccine formulations and delivery systems that can provide maximum potency with acceptable safety in a prophylactic setting. These delivery systems contribute greatly on modifying and controlling the level of systemic exposure, avoiding the potential production of proinflammatory cytokines, improving safety and/or tolerability of the novel adjuvant.

One of the fascinating aspects of vaccine delivery for several decades now has been fully exploring the benefits and limitations of mucosal delivery. Exciting new advents have been made in this regard using gene-based and attenuated oral vaccines. Immunization through the skin as the route of delivery of antigens holds great promise in making vaccines more patient compliant and needle free. Since most vaccines are complex compositions, new medium and high throughput tools have now emerged that help screen rapidly for excipients and stabilizers prior to running expensive preclinical animal studies. Several biophysical tools and assays are now being adapted to better characterize vaccine formulations.

In this book we have made an effort to cover new vaccine delivery technologies and discuss some of the next generation immune potentiators that could potentially be part of licensed products in the future. Detailed description of all leading vaccine technologies with their limitations should be of great help to researchers and students to enhance their understanding of these novel concepts. The book also has chapters on clinical and non-clinical safety evaluation of vaccine formulations which should be of great value in moving vaccines from research to clinic.

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Section I
Novel Immune Potentiators and Delivery Systems for Enhancing Vaccine Potency

Chapter 1
TLR7/8 Agonists as Vaccine Adjuvants

Mark A. Tomai and John P. Vasilakos

1.1 Introduction

Small molecule TLR7/8 agonists have demonstrated great potential as vaccine adjuvants, since they quantitatively and qualitatively enhance both humoral and cellular immune responses. However, most small molecule TLR agonists evaluated thus far as vaccine adjuvants are highly soluble and have a propensity to rapidly disperse away from the vaccination site, resulting in decreased efficacy and increased systemic adverse effects. Intense effort and progress has been made to increase their ability to maintain close proximity to antigen at the administration site. Here, we will discuss three vaccine approaches utilizing small molecule TLR7/8 agonists as vaccine adjuvants. These approaches are designed to improve the adjuvanticity and to reduce the potential for systemic adverse events associated with these small molecule TLR7/8 agonists when used as vaccine adjuvants. One approach utilizes the TLR7/8 agonist resiquimod gel as a topically applied adjuvant at the vaccination site. The other two approaches utilize novel TLR7/8 agonists in a conventional vaccine format where the adjuvant and antigen are administered together. These novel TLR7/8 agonists are lipid modified or chemically modified for conjugation to antigen—all three approaches are designed to promote retention of the TLR7/8 agonists at the administration site in order to maintain their spatial and temporal proximity to the antigen, resulting in enhanced immune responses and reduced systemic adverse effects.

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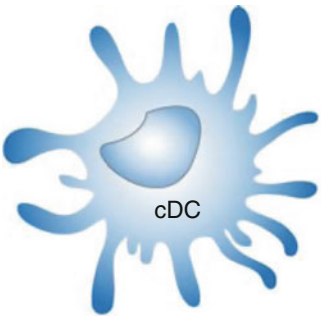
1.2 The Need for New Vaccine Adjuvants

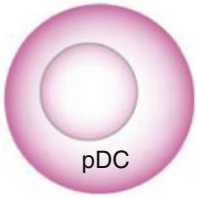
Despite the development of numerous successful vaccines, vaccines do not exist for many pathogens or cancers. Currently, inactivated pathogens, recombinant proteins, purified peptides, and DNA vaccines are being explored in order to address adverse events associated with live vaccines, and in some cases, to address the fact that live infectious agents do not confer protection. The major problem with most protein, peptide, and DNA vaccines is that they are poorly immunogenic or elicit an inappropriate immune response, and don't provide protection against the infectious agent or cancers. The question isn't whether an adjuvant is required, but what type of adjuvant or adjuvant combination will work best with a specific antigen or antigens for a specific disease indication. In addition, each antigen and adjuvant combination must be formulated to provide adequate stability and to ensure that the vaccine maximally stimulates the appropriate immune response in an acceptably safe and tolerable manner. Hence, the three key components of a vaccine are the antigen, adjuvant, and formulation. This chapter will focus on adjuvants, specifically small molecule TLR7/8 agonists.

Currently, there are very few vaccine adjuvants approved for human use. Aluminum salts (i.e., ALUM) are one of few US Food and Drug Administration approved adjuvants and is the most widely used adjuvant [1]. Additionally, MF59, an oil-in-water squalene emulsion, has been approved in some countries [2]. More recently, AS03 adjuvant (DL-a-tocopherol, squalene, polysorbate 80) and AS04 adjuvant (ALUM and monophosphoryl lipid A) have also been approved in some countries [3, 4]. These adjuvants are safe, but they do not uniformly or sufficiently enhance cell-mediated immune responses that are required for elimination of many intracellular organisms and cancers. Hence, adjuvants that drive cellular immunity, both CD4 and CD8 responses, are being investigated.

1.3 Toll-Like Receptors and Toll-Like Receptor Agonists

In order to understand how vaccines induce adaptive immune responses, we first must begin with how the innate immune system recognizes microorganisms. Several recognition strategies have been developed by the innate immune system to deal with the problem of detecting a broad range of heterogeneous and rapidly evolving pathogens. Specifically, the innate immune system possesses receptors, broadly classified as pattern recognition receptors (PRR), which specifically recognize conserved microbial molecular patterns [5, 6]. PRRs are predominantly expressed on or in phagocytic cells, such as dendrtitic cells, macrophages, neutrophils, monocytes, and to a lesser extent on other cell types. PRRs are germ-line encoded receptors, and unlike T-cell or B-cell receptors, don't undergo somatic mutation and clonal distribution. As such, PRRs are "hard-wired" to recognize conserved microbial molecular patterns known as pathogen-associated molecular patterns (PAMPs). PAMPs are classically characterized as a limited set of conserved molecular patterns unique to the microbial world and invariant among entire classes of pathogens [7]. Engagement of PRRs with PAMPs results in antimicrobial and inflammatory responses, including the production of





TLR	TLR Ligand
3	Poly (I:C)
4	MPL
5	Flagellin
8	Resiquimod

TLR	TLR Ligand
7	Resiquimod
9	CpG

IL-12

IFN-α

Fig. 1.1 Conventional DC express TLR3, 4, 5, and 8, and when ligated with specific agonists, produce IL-12. Plasmacytoid DC express TLR7 and TLR9, and when ligated with their specific agonists, produce IFN-α. Adapted from Coffman et al. [3]

cytokines and chemokines that affect innate and adaptive immune responses. Indeed, it has become clear that innate immune cells and their PRRs are usually critical for the induction, magnitude, and quality of adaptive immune responses.

Toll-like receptors (TLRs) are one type of PRRs utilized by the innate immune system to recognize microbial pathogens. There are ten human TLRs; they are transmembrane-signaling proteins expressed on surface of the plasma membrane or endosomes. TLR1, 2, 4, 5, 6, and 10 are cell surface expressed, and TLR3, 7, 8, and 9 are expressed in endosome/lysosome membranes. Although innate immune cells express TLRs, all innate immune cells do not express the same TLRs. As an example, the majority of human dendritic cells (DC) can be classified as conventional DC (cDC) or plasmacytoid DC (pDC). Conventional DC express TLR3, 4, 5, and pDC express TLR7 and 9. Ligation of cDC TLRs results in the production of numerous cytokines including IL-12. In contrast, ligation of pDC TLRs results in the production of interferon alpha. Therefore cell-specific TLR expression results in differences in cytokine responses induced by various TLR agonists (Fig. 1.1).

Although the schematic in Fig. 1.1 is an oversimplification of the complexities of TLR expression patterns and cytokine responses resulting from TLR ligand