

Table 1 Classes of Modern Vaccine Adjuvants, Carriers, and Vehicles

Adjuvants			
Mineral salts	Mycobacterial, bacterial, and plant derivatives	Surface-active agents and microparticles	Polymers
Aluminum hydroxide (<i>Alhydrogel</i> TM ; <i>Rehydrigel</i> TM), aluminum and calcium phosphate gel	Complete Freund's adjuvant (killed <i>M. tuberculosis</i>), <i>DETOX</i> TM (MPL plus cell wall skeleton of <i>Mycobacterium phlei</i>), BCG, muramyl dipeptides and tripeptides, dipalmitoyl phosphatidyl ethanolamine-MTP (MTP-PE), MPL, γ -inulin/aluminum salts (algammulin), <i>Klebsiella pneumoniae</i> glycoprotein, <i>Bordetella pertussis</i> , <i>Corynebacterium parvum</i> , cholera toxin, <i>E. coli</i> LT, QS-21	Saponin (<i>Stimulon</i> TM QS-21, Quil-A), immune-stimulating complexes (<i>ISCOMS</i> TM), <i>Avridine</i> TM , nonionic block copolymers (CRL1005, pluronic L121), virosomes, DDA	Dextran, double-stranded polynucleotides (Poly rA:Poly rU), acetylated polymannose (Acemannan), sulfolipopolysaccharide, PMMA, acrylic acid-allyl sucrose (Carbopol), polyphosphazene (<i>Admumer</i> TM), β -glucan (pleuran, algal glucan)
Cytokines, vitamins, and hormones	Synthetic constructs	Carriers	Vehicles
GM-CSF, IFN- γ , IL-1, IL-2, IL-6, IL-7, IL-12, cytokine-containing liposomes, vitamin A, D ₃ (calcitriol), E, human growth hormone, DHEA	Imidazoquinolines (imiquimod, S-28463), glycolipid Bay R1005, stearyl tyrosine DTP-GDP (<i>ImmTher</i> TM) DTP-DPP (<i>Theramide</i> TM) Threonyl-MDP 7-allyl-8-oxoguanosine (Loxoribine) Multiantigen peptide (MAP) system Linear polymerization of haptenic peptides Peptide linkage to T cell or B cell epitopes	Bacterial toxoids (tetanus, diphtheria, <i>Pseudomonas aeruginosa</i> A exotoxin, pertussis), Meningococcal outer membrane proteins (proteosomes), Fatty acids, Ty virus like particles, Nucleic acid vaccines, living vectors (vaccinia virus, adenovirus, canarypox, poliovirus, BCG, attenuated <i>Salmonella</i> , <i>Vibrio cholerae</i> , and <i>Shigella</i>), protein cochleates	Mineral oil (IFA, <i>Montanide</i> TM ; Specol) and vegetable oil (peanut, olive, sesame) emulsions, squalene and squalene emulsions (MF59, SAF, SPT), lipid containing vesicles (liposomes, DMPC, DMPG), sendai proteoliposomes, virosomes (IRIV), biodegradable polymer microspheres (lactide and glycolide polymers (PLGA, PGA, PLA), proteinoid microspheres (<i>PODDS</i> TM), polyphosphazene, protein cochleates, transgenic plants, chitosan polysaccharide

Abbreviations: BCG, bacillus Calmette-Guérin; PMMA, polymethyl methacrylate; DHEA, dehydroepiandrosterone; DDA, dimethyl dioctadecyl-ammonium bromide; MPL, monophosphoryl lipid A; LT, heat-labile toxin; GM-CSF, granulocyte-macrophage stimulating factor; IL, interleukin.

adjuvants over the past decade. Mammalian homologues or toll-like receptors (TLRs) have been discovered that provide a means to activate immune cells such as macrophages and dendritic cells with microbial "danger signals" (9). Bacterial lipopolysaccharide (LPS), which has long been known to be inflammatory if injected in very small quantities or if present as a trace contaminant in vaccines, was found to be a ligand for the TLR4 receptor (10). Since then, lipopeptides, flagellin, single- and double-stranded RNA, and CpG DNA found principally in bacteria and viruses have been linked to individual TLRs and provide a scientific basis for the development of adjuvants (11–13). However, many existing adjuvants may not function via the TLRs, and their mechanisms remain unknown (14).

It is known that adjuvants can select for or modulate humoral or cell-mediated immunity, and they do this in several ways. First, antigen processing can be modified, leading to vaccines that can elicit both helper T cells and cytotoxic lymphocytes (CTLs) (reviewed in Ref. 15). Second, depending upon the adjuvant, the immune response can be stimulated in favor of type 1 or type 2 immune responses (16). For example, complete Freund's adjuvant and the QS-21 adjuvant can elicit DTH and MHC class I CTL responses when mixed with protein antigens, peptides, or inactivated viruses (17). Many other adjuvants, such as aluminum salts (16) and nonionic block polymers (18) elicit principally antibody responses when combined with protein

antigens or inactivated organisms, perhaps by activating APCs by an IL-4-dependent mechanism (19). Third, adjuvants can augment the immune response by preferentially stimulating Th1 or Th2 CD4⁺ T-helper cells (20). The Th1 response is accompanied by secretion of interleukin-2 (IL-2), interferon- γ (IFN- γ), and TNF- α leading to a CMI response, including activation of macrophages and CTL and high levels of IgG2a antibodies in mice. The Th2 response is increased by secretion of IL-4, IL-5, IL-6, and IL-10, which provide better help for B cell responses, including those of IgG1, IgE, and IgA isotypes in mice. Aluminum salts and MF59 principally stimulate the Th2 response (21,22), while the Th1 response is stimulated by many adjuvants, such as muramyl dipeptide, monophosphoryl lipid A (MPL), and QS-21 (3). Vaccine adjuvants can modulate antibody avidity, specificity, quantity, isotype, and subclass against epitopes on complex immunogens (23–26). For example, only certain adjuvants, vehicles, and adjuvant formulations can induce the development of the protective IgG2a antibody isotype against *Plasmodium yoelii* (27), a mouse model of malaria.

While an adjuvant's effect on immunogenicity can be studied preclinically in animals, the models do not always anticipate their level of efficacy or safety in humans (28,29). However, decades of basic cellular research, preclinical experiments, and clinical safety and immunogenicity studies have led to a significant expansion in the understanding of the mode of