Table 1 The Role of Adjuvants in Vaccine Development

1.	Increase antibody titers, e.g., bactericidal, opsonizing or neutralizing antibodies.
2.	Decrease the dose of antigen.
3.	Decrease the total number of doses.
4.	Overcome competition in combination vaccines.
5.	Enhance responses in the young or old.
6.	Increase the speed and duration of the response.
7.	Induce potent cell mediated immunity, including Th1 responses.

effects (Table 1). Historically, adjuvants have been crucial to the development of vaccines, and they are likely to prove even more so in the future. Many vaccines currently in development are comprised of highly purified recombinant proteins, or peptides, usually representing subunits of pathogens. Unfortunately, these vaccines lack most of the features of the original pathogen from which they were derived and are often poorly immunogenic. Therefore, the need for vaccine adjuvants is great. The preferred strategy for the development of new generation vaccines is to add highly purified synthetic adjuvants, which will activate only the elements of the immune response required for protective immunity against the pathogen and will not trigger a more generalized activation of the immune response. Generally, vaccines comprised of attenuated live organisms or whole inactivated organisms do not require adjuvants, as these are sufficiently similar to the native pathogens and usually comprise many inherent adjuvant active molecules.

Since adjuvants are defined by the effects they achieve rather than what they actually are, a diverse range of compounds and materials can achieve an adjuvant effect. To define more precisely how adjuvants achieve their effects, it is necessary to reduce the complexity of the immune response down to some simple basic concepts. One concept is to consider the ''signals'' necessary to induce a successful immune response. With this approach, it is possible to define how adjuvants make important contributions to vaccines, and one can place different kinds of adjuvants into broad groupings to understand how they achieve their effects.

The signals necessary for a successful immune response to a vaccine can be summarized as follows:

Signal 1—antigen
Signal 2—costimulation of immune cells, including APC
Signal 3—immune modulation/manipulation
Signal 0—activation of the innate immune response

Adjuvants contribute directly to all these signals, but different adjuvants do so in different ways. Some adjuvants are better defined as antigen delivery systems; these are particulate carriers to which antigens can be bound, adsorbed, or associated. This allows the antigens to be stabilized against degradation and clearance, and allows them to be present for extended periods of time. The long-established adjuvant, alum, which is based in insoluble aluminum salts, is thought to work predominantly in this way. Although speculation continues more than 70 years after approval, it is still not entirely clear how alum works (5–7). Nevertheless, it is thought that antigen delivery system–based adjuvants often prolong signal 1 by making the antigen present for extended periods. Prolongation of signal 1 has also been called a ''depot effect,'' in relation to the mechanism of action of alum. It has been shown that the duration of antigen persistence is important in triggering protective T-cell responses (8). Because antigen delivery systems are generally particulates with similar dimensions to pathogens, they are usually taken up efficiently by phagocytosis into APC, the key cells involved in immune response induction. Hence, delivery systems can also contribute to signal 2, through indirect activation of APC due to the particulate uptake process and can sometimes more directly activate APC. In contrast to delivery systems, immune potentiators are a different broad class of adjuvants, which generally exert direct stimulatory effects on immune cells (signals 2 and 3) and can also initiate the immune response through direct activation of innate immunity (signal 0). Although immune potentiators are a very broad class of materials, typical immune potentiators are purified components of bacterial cells or viruses, or synthetic molecules, which mimic their structure. Consequently, they are recognized as ''danger signals'' by the cells of innate immunity and can be said to express ''pathogen-associated molecular patterns,'' or PAMPs. There are a number of receptor systems present on and in innate immune cells, which are present to ''sense'' when an organism is infected. Once these receptors are activated by their ligands, the cells respond accordingly through activation of the innate immune response, which provides a first line of defense against pathogens. These cell-associated receptors, which have been termed pattern recognition receptors (PRRs), have specificity for PAMPs and act to initiate innate immunity. It has recently been proposed that a ''trinity'' of pathogen sensors is present to activate the innate immune response following exposure to pathogens; namely, the NOD-like receptors, the RIG-like receptors, and the Toll-like receptors (TLRs) (9). Although diverse in their expression patterns and response to different bacterial and viral components, it is apparent that there is significant complementation and overlap between these PRRs in terms of the consequences of individual receptor activation (10). Furthermore, it is increasingly apparent that these and perhaps additional not yet recognized PRR work in harmony to ensure the appropriate activation of the adaptive immune response and the necessary level of immunological activation and memory. The key cells responsible for these activities are the various populations of professional APC, the dendritic cells (DCs), which have a key role to play in linking innate and adaptive immune responses. Peripheral immature DCs, in particular, possess highly effective mechanisms to detect, capture, and respond to pathogens, which may have breached the protective barriers of the skin and mucosal surfaces. Such an encounter triggers maturation and migration of the DCs to key areas of the local lymph nodes, where they can interact with T cells to initiate adaptive immunity. However, DCs are a very heterogeneous population of cells, with different subtypes responsible for different roles in the immune response at different stages of their life cycles (11). The most well known of the PRRs associated with DCs are the rTLR family (12), which recognize diverse components derived from bacteria and viruses and play a key role in initial proinflammatory responses following pathogen exposure. So far, 13 TLRs have been identified in mammals (13), which recognize different microbial components. While some TLRs are located within cell membranes (TLR1, 2, 4, 5, and 6), others are situated within the endoplastic reticulum and endosomes (TLR3, 7, 8, and 9) and recognize various forms of nucleic acids. The expression of TLR can be distinctive to particular cell types of the immune system, or even to nonimmune cells, and TLR expression may be altered in response to cytokines or the presence of distinct kinds of pathogens. In addition to the