responses against HPV (135), Norwalk virus (136), and HIV (137). In all these studies, the vaccines proved to be safe, well tolerated, and immunogenic. VLPs from HPV were recently approved as a licensed vaccine (138), and this has ensured that the level of interest in this antigen presentation technology will increase significantly in the near future.

WHAT ARE THE CURRENT OPTIONS FOR IMPROVED VACCINE ADJUVANTS?

Although alum and MF59 adjuvants, and virosomes are all included in licensed vaccines, each of these has some limitations. In preclinical models using naïve animals, neither alum nor MF59 adjuvants induces potent T-cell immune responses of a Th1 type, which is defined as the ability of antigen primed T cells to produce γ-interferon in response to restimulation in vitro. Th1 cells are thought to be particularly important to provide protective immunity against some pathogens, including malaria, HIV, and HCV. Hence the inability of the adjuvants currently included in licensed products to induce potent Th1 responses is thought to be a limiting factor in our ability to develop vaccines against these and other pathogens. Nevertheless, a broad range of immune potentiators are becoming available, which are more able to enhance Th1 responses in preclinical models (99). The first of these, which has been recently included in a licensed vaccine, is called MPL, and is a natural product that is produced by chemically detoxifying bacterial LPS. LPS, which is also known as endotoxin, is very potent at activating the immune system but is too toxic for human use. However, an extensive program in the 1970s identified a reliable and reproducible process for the detoxification of LPS, to allow it to be used as a vaccine adjuvant without significant adverse effects. MPL was first licensed in Europe in early 2005 for use in populations who responded poorly to the existing hepatitis B vaccine, due to renal insufficiency. The product, Fendrix^{TM}, contains the traditional adjuvant alum, to which a recombinant antigen is adsorbed, but also contains MPL. The same adjuvant formulation, with MPL adsorbed to alum, is also undergoing late stage clinical evaluation in other vaccines and likely will gain additional approvals within the next few years. Although MPL has been shown to be a safe and effective adjuvant in clinical trials, alternative new generation adjuvants appear to be much more potent for the induction of Th1 responses. In preclinical studies, synthetic oligonucleotides that mimic signature sequences (CpG) present in bacterial DNA appear to be very potent Th1 adjuvants (139). CpG oligonucleotides are currently undergoing early phase clinical evaluation as new generation vaccine adjuvants. In addition to oligo-based adjuvants, synthetic small molecular weight drugs have also been identified, which are able to induce potent Th1 responses (140).

WHAT IS THE BEST LONG-TERM APPROACH FOR ADJUVANT DEVELOPMENT?

Although there are many natural products, often extracted from bacteria and viruses, which directly activate immune cells, there is also an increasing interest in the use of synthetic analogs of these agents. Synthetic analogs often have lower manufacturing costs and can be obtained in a highly purified form, which is often in sharp contrast to the heterogeneous natural products. One of the most interesting classes of compounds, which have the potential to be exploited as new generation adjuvants are traditional small molecular weight drugs (140). The discovery that traditional drugs can function as vaccine adjuvants required the use of a new terminology, and these drug-like adjuvant active compounds have been called Small Molecular weight Immune Potentiators (SMIPs). The use of SMIPs as adjuvants allows the exploitation of traditional pharmaceutical synthetic approaches, with all the associated advantages, including the ability to manipulate compound structure to control performance, considerable formulation experience with similar compounds, and for some simple and economical synthesis. Hence, there are numerous advantages that can be realized through the use of SMIPs as adjuvants. Given these advantages and the likelihood that many more diverse families of SMIPs will be discovered, it appears likely that a number of SMIPs will become available, to allow better manipulation and control of the immune response. However, it is also clear that new generation delivery systems will be required for SMIP adjuvants to ensure that they are delivered preferentially to key immune cells and that the immune activation signals are not available to a more broad array of cells, due to diffusion of the drugs away from the injection site. Hence, adjuvant formulations will increasingly comprise one or more potent immune potentiators intended to induce the specific kind of immune responses required and formulated into delivery systems designed to maximize potency and minimize potential for adverse events. In this context, the use of microparticles as delivery systems, which were originally developed for the controlled release of small molecular weight drugs, would appear to be a particularly attractive approach. However, extensive research will be necessary to determine the optimal release profiles for different SMIPs and to determine the optimal site for delivery, within a distinctive intracellular compartment, or extracellularly. The preferential site and dynamics of delivery will likely vary extensively, depending on the specific PRR that the SMIP is designed to activate.

CONCLUSIONS AND FUTURE PERSPECTIVE

In the past decade, there have been a number of significant advances in technologies designed to identify, express, and deliver vaccine antigens. As a consequence, many of the vaccine candidates currently under evaluation look very different from traditional vaccines. In particular, there has been a shift away from the use of whole pathogens or inactivated subunits, toward the use of recombinant purified proteins. Although this has improved vaccine safety, it has also resulted in the need to develop novel adjuvants and delivery systems to improve the immunogenicity of these antigens. Many future vaccine candidates will likely contain recombinant protein antigens, purified synthetic adjuvants representing well-defined PAMPs, and a delivery system to ensure that both antigen and adjuvant are targeted efficiently to APC (Fig. 2). Formulation of the vaccine into a delivery system will (*i*) focus the effects of the immune potentiators onto the key cells of the immune system to enhance potency and (*ii*) limit systemic distribution of the immune potentiators to minimize their potential to induce adverse effects. Novel adjuvant and delivery technologies will be required to enable the successful development of vaccines against diseases that have not yet yielded to traditional approaches. The identification of cell surface markers on different DC subsets, which may allow targeting of particulate delivery systems to specific DC