During the past decade, a dramatic shift has occurred in immunological theory, which has found its most practical application in the discovery and design of novel vaccine ADJUVANTS. This change in thinking has been driven by an increased appreciation that activation of the INNATE IMMUNE SYSTEM initiates, amplifies and drives antigen-specific immune responses. Moreover, the identification of discrete cell types, specific receptors and the signalling pathways involved in activation of innate immunity has provided a multitude of new targets for exploitation by the development of novel adjuvants (IMMUNE POTENTIATORS and DELIVERY SYSTEMS). Combined with these factors, there has been an increasing emphasis in the field of vaccines on the need for improved safety (for example, subunit vaccines), along with improved efficacy against particularly insidious pathogens (for example, human immunodeficiency virus (HIV) and hepatitis C virus (HCV)). More recently, the threat of a bio-terrorist attack has added an even greater sense of urgency to these efforts. As a result, there has been a dramatic increase in efforts to target and manipulate the innate immune response with improved vaccine adjuvants, which has coincided with a greater mechanistic understanding of how this might be optimally achieved.

RECENT ADVANCES IN THE DISCOVERY AND DELIVERY OF VACCINE ADJUVANTS

Derek T. O’Hagan and Nicholas M. Valiante

Adjuvant design has historically had a touch of alchemy at its heart due to its reliance on the complex biology of innate immune activation. However, a new mechanistic understanding of innate immunity, combined with new adjuvant and delivery platforms for exploiting this knowledge, has led to significant advances recently. Although many challenges remain, the field is moving rapidly and the proper tools and methodologies are in place for the use of traditional drug discovery engines in guiding the development of vaccine adjuvants. In this review, we outline the current trends in immune potentiator, delivery system and adjuvant design that will shape the vaccines of the future.

Vaccines from practice to theory

Vaccination is considered by the World Health Organization to be the most cost-effective strategy for controlling infectious disease. In terms of direct effects on public health, the development of the presently available vaccines is second only to the introduction of a clean water supply. Vaccination works by manipulating the body’s immune system, preparing it for the rapid elimination of infectious agents and/or their toxic products. From a mechanistic perspective, vaccines select, activate and expand memory B and T cells of the immune system, which are then poised to respond rapidly and specifically to subsequent pathogen exposure.

Since Edward Jenner’s first successful vaccination against smallpox, which can be considered the birth of immunology as a scientific discipline, vaccine design and discovery has been dominated by pragmatic considerations — one uses what works, regardless of understanding why it works. In recent years, however, basic immunological research has started to make a greater contribution to the vaccine development process. There are many factors driving this re-invigorated search for the theoretical and mechanistic underpinnings of vaccination, including the need for the development of vaccines from practice to theory.
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Figure 1 | The three components of optimal subunit vaccines. It is well known that subunit vaccines elicit more potent and durable antigen-specific immunity if combined with an adjuvant. The in vivo adjuvant effect can be divided into two principal components: delivery and immune potentiation. Delivery systems localize antigens and target them to the appropriate cell types of the innate immune system. Delivery can also be optimized for immune potentiator targeting. Immune potentiators directly activate innate immune cells providing the pro-inflammatory context for antigen recognition. Antigens provide the specific pathogen epitopes necessary to generate long-lived immunological memory. These three components are intrinsic to naturally occurring infections and whole-cell vaccines, whereas they must be combined in subunit vaccine formulations.

of safer, better defined and more effective vaccines against a number of important diseases for which vaccines do not presently exist (for example, HIV, HCV, Neisseria meningitides and severe acute respiratory syndrome (SARS)). Furthermore, recent breakthroughs in immunology have revealed numerous new targets and mechanisms of the innate arm of the immune system that can be manipulated by improved adjuvants to produce better vaccines.

The integrated model of host defence
Protective immunity against pathogen exposure is achieved by the integration of two distinct arms of the immune response, the innate and antigen-specific (also called adaptive) responses. The innate response acts early after infection (within minutes), detecting and responding to broad cues from invading pathogens. By contrast, the adaptive response takes time (days to weeks) to become effective, but provides the fine antigenic specificity required for complete elimination of the pathogen and the generation of immunological memory. Antigen-independent recognition of pathogens by the innate immune system leads to the immediate mobilization of immune effector and regulatory mechanisms that provide the host with three crucial survival advantages: rapid initiation of the immune responses (both innate and adaptive) and creation of the inflammatory and co-stimulatory context for antigen recognition; establishment of a first line of defence, which holds the pathogen in check during the maturation of the adaptive response; and steering of the adaptive immune response towards the cellular or humoral elements that are most appropriate for protection against the particular infectious agent. So, although the overall objective of vaccination is the activation of antigen-specific immunity, vaccines cannot optimally achieve this goal without effectively activating the pathogen-detection mechanisms of the innate immune response.

Vaccine adjuvants are broadly defined by their functional ability to enhance in vivo immunogenicity (that is, antigen-specific responses) of the antigens with which they are co-administered. As such, adjuvants represent important components of most of the successful vaccines, particularly those based on sub-units of pathogens, including isolated fractions of the killed pathogens, or recombinant antigens. However, as a consequence of the growing appreciation of innate immune mechanisms, and the details of antigen processing and presentation, more sophisticated definitions of adjuvants are required. Therefore, we have begun to separate both traditional and novel adjuvants into two main categories (immune potentiators and delivery systems) on the basis of their dominant mechanism(s) of action. Whereas delivery systems mainly function to localize vaccine components and to target vaccines to antigen-presenting cells (APCs), immune potentiators directly activate these cells through specific receptors (for example, Toll-like Receptors (TLRs)). So, delivery systems are used to promote the interaction of both antigens and immune potentiators with the key cells of the innate immune system. Immune potentiators provide the inflammatory context necessary for optimal antigen-specific immune activation by activating APCs and amplifying the innate immune response (Fig. 1).

Innate defence strategies are designed to detect broad and conserved patterns which differ between pathogenic organisms and their multicellular hosts. This non-antigen-specific detection strategy is mediated by diverse and evolutionarily conserved families of pattern-recognition receptors (PRRs). An increasing number of PRRs are being identified, with the ten recently discovered members of the TLR family attracting the most interest at present. The pathogen-associated molecular patterns (PAMPs) which they recognize are structurally and chemically diverse compounds, but they share the common feature of being highly conserved in pathogens and absent from multicellular organisms. This broad recognition strategy allows the innate immune system to respond rapidly to infection in advance of the more delayed activation of antigen-specific immunity. As such, the key advantage of an integrated system of pattern recognition and antigen-specific responses is that the immune system divides the responsibility of recognizing and eliminating infectious agents by fulfilling two mutually exclusive goals of the primary immune response: speed and specificity. It is important to note that the optimal immune response required for long-term protective immunity — immunological memory — represents the merger of these two competing goals and that vaccination exploits this union with remarkable success (Fig. 2).
Various cell types of the immune system are capable of presenting antigens to T cells, providing a crucial bridge between the innate and adaptive responses. Among these, dendritic cells (DCs) are considered 'professional APCs' because they are highly efficient and are specialized for this function. DCs and other APCs constantly sample their environment through pinocytosis and/or phagocytosis, and use their PRRs to detect infectious agents. This constitutive process is thought to provide the mechanism by which the immune system not only mobilizes both innate and antigen-specific defences to infection or following vaccination, but also maintains tolerance (non-responsiveness) to autologous or benign agents. The dual activation/tolerization function of DCs is mediated by their capacity to change the context of antigen presentation and to communicate to T cells the nature of the antigens they are presenting. They do this by responding to PAMPs or synthetic immune potentiators, and producing pro-inflammatory cytokines and expressing co-stimulatory molecules (for example, CD80/86) which induce full activation of antigen-specific T cells. In the absence of these pro-inflammatory cues, T-cell responses are shut down. It is this better understanding of antigen presentation and APC biology that has provided opportunities for future improvements in vaccine development, as more selective and sophisticated immune potentiators and delivery systems are developed. Among other emerging targets of immune potentiators and delivery systems is the B cell. The direct adjuvant effects on B cells are particularly intriguing and seem to act at three levels. First, delivery systems, especially particulate ones, facilitate an ordered and repetitive array of B-cell epitopes, which results in more efficient B-cell activation through their antigen receptors. Second, although B cells are considered part of the antigen-specific immune system, they also express PRRs (for example, TLRs), and, therefore, can be activated by PAMPs or immune potentiators in ways that modify both the quantity and quality of their antibody responses. Last, B cells can also act as APCs, and B-cell...
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The intimate interactions (cognate recognition) between antigen-presenting cells (APCs) and antigen-specific T cells initiate and amplify pathogen-specific responses. A dendritic cell (DC) is depicted here. The key interaction is driven by the recognition of antigenic peptide–major histocompatibility complex (MHC) dimers by T cells bearing T-cell receptors (TCRs) with high affinity for the complex. However, this signal alone is not sufficient for initiation and amplification of specific T-cell responses. Co-stimulatory signals (that is, CD80/CD86 recognition of CD80/CD86 and the production of pro-inflammatory cytokines) provide the ‘infectious context’ by which the full activation of antigen-specific T cells is achieved. The expression of co-stimulatory molecules and cytokines by APCs is tightly regulated and induced only when the APC encounters antigens associated with pathogen-associated molecular patterns. From the perspective of adjuvant design, the APC is a high-priority target. Delivery systems increase antigen uptake and presentation, and can also target immune potentiators more efficiently to APCs. Immune potentiators induce co-stimulatory signals and cytokine production, and the antigens select the highly specific T cells leading to the initiation and amplification of antigen-specific immunity. CD40L, CD40 ligand.

activation by antigen and immune potentiators enhances their efficiency of antigen presentation to T cells, as well as inducing the production of cytokines. Given that antibody responses are traditionally considered the correlate of protection for most vaccines, further efforts to selectively target B cells with immune potentiators and delivery systems hold great promise.

It is important to keep in mind that infectious agents and most licensed vaccines, particularly live attenuated or killed whole-cell products, contain all of the components necessary for activating an integrated immune response. This is because the pathogens used in the vaccines possess all of the relevant antigens in a particular form — a whole cell — which also contains many potent immune potentiators (that is, PAMPs). However, the trend in vaccine development is to move away from these whole-cell products towards safer and better-defined subunit vaccines, produced as highly purified recombinant proteins. Unfortunately, these recombinant antigens are often poorly immunogenic, because they lack intrinsic immune-potentiating activity. So, the challenge in subunit vaccine development is to reintroduce selective signals for activation of the innate immune response, which will be sufficient to mimic natural infection or traditional vaccination. The immune potentiators and delivery systems used to improve the potency of subunit vaccines will need to be low cost, but more effective and safer than whole-cell vaccines.

**Innate immune-potentiating compounds**

With the discovery of the TLR family of receptors, many pathogen products with known immune-potentiating activity (adjuvants) have now been shown to activate innate immunity via TLRs, or through an increasing number of non-TLR PRRs, including CD14, Dectin1, TREM1 and 2, RNA-dependent kinase (PKR) and CD91 (REFS 4,15–18). For example, bacterial lipopolysaccharide (LPS), the epitope of a pro-inflammatory agent, is now known to interact specifically with TLR4, which acts together with other receptors (for example, CD14) found on LPS-responsive cell types (for example, monocytes, macrophages, DCs and B cells). Other examples of pathogen products with corresponding TLR-dependence include tri-acyl lipopeptides (TLR1); lipidated peptides, proteins and carbohydrates (TLR2); double-stranded RNA (Poly I:C) (TLR3); flagellin (TLR5); di-acyl lipopeptides (TLR6); and CpG DNA (TLR9). Of the ten TLR family members, only TLR7, 8 and 10 have yet to have a natural pathogen-derived product identified. Cooperation between individual TLRs and other PRRs also seems to be a general rule for natural infections and traditional whole-cell vaccines19,20. Moreover, some TLRs seem to be highly promiscuous (for example, TLR2 and TLR4) and participate in responses to numerous and diverse pathogen products. Intriguingly, TLR2 and 4 have also been implicated in stress-induced responses to both pathogen- and host-derived heat-shock proteins5. These observations indicate that TLR2 and 4 play a more general role in initiation/amplification of the early immune response, whereas other TLR family members, and perhaps other PRRs, have evolved more specialized functions.

Given the plethora of natural products capable of activating innate immune mechanisms, research and development efforts to exploit these immune potentiators as adjuvants have been aggressive. Although in vivo proof of concept has been established for the use of many natural PAMPs as adjuvants, and a number of these have been advanced into clinical trials, the trend for the future indicates an increased reliance on synthetic analogues. This is due mainly to the lower manufacturing and regulatory hurdles associated with synthetic immune potentiators that are highly defined and standardized. In addition, a synthetic platform allows for a more rational approach to the optimization of next-generation compounds possessing greater potency and decreased toxicity. From this perspective, perhaps the most promising adjuvant/immune potentiator platform recently identified is based on a small-molecule approach. The identification of imidazquinolines as TLR7- and 8-dependent small-molecule immune potentiators (SMIPs) indicates that more traditional pharmaceutical-based or drug-like molecules can be exploited as vaccine adjuvants21,22. Indeed, imidazquinolines
have been shown to enhance antigen-specific responses in mouse models and, therefore, have the potential to be developed as adjuvants for humans.

An SMIP-based platform for adjuvant design and discovery holds significant potential for the future of vaccine development. There are numerous advantages that can be realized throughout the vaccine R&D pipeline if SMIPs rather than other natural or synthetic immune potentiators are chosen for optimization and development as adjuvants. For discovery efforts, the incredible diversity of scaffolds generated through combinatorial chemistry, the ability to target with exceptional selectivity innate immune mechanisms, and the tried and tested drug discovery engines of high-throughput screening and hit-to-lead optimization can now be applied to vaccine adjuvants. Later in development and manufacturing, an SMIP-based adjuvant provides a low cost, highly pure and standardized alternative to all other existing candidate immune potentiators. Given these advantages, and the likelihood that more and diverse families of SMIPs will be discovered, it seems that the imidazquinoline TL7/8 agonists represent only the first in a long line of future small-molecule-based vaccine adjuvant candidates.

Development of vaccine delivery systems

Although the terms ‘adjuvant’ and ‘delivery system’ have often been used interchangeably in relation to vaccines, a clear distinction can often be made and the respective roles of each can be more clearly differentiated, particularly when a delivery system is used for a vaccine adjuvant. Included in lists of vaccine adjuvants are a number of particulate delivery systems (for example, emulsions, liposomes, iscoms, virus-like particles and microparticles), whose principal mode of action is to promote the uptake of antigens into the key APC responsible for the induction of immune responses. However, the potency of these delivery systems can be significantly improved by the addition of a vaccine adjuvant, or immune potentiator. Adjuvants are included in delivery systems to focus their effects onto the APCs, and to minimize effects on non-immune cells. Hence, delivery systems can improve the therapeutic ratio of adjuvants.

Delivery systems in vaccine design

If the geographical concept of immune reactivity, in which antigens that do not reach local lymph nodes do not induce responses, is accepted, then the role and importance of delivery systems becomes clear. Delivery systems serve to maximize the concentration of antigen in local lymph nodes either by directly promoting antigen uptake into lymphatics, or by promoting antigen uptake into motile APCs that will then migrate to the lymph nodes. As such, the role of a vaccine delivery system is to enhance the amount of antigen reaching the cells or tissues responsible for immune response induction.

Alternative vaccine delivery systems

Particulate vaccine delivery systems (for example, emulsions, microparticles, iscoms, liposomes, virosomes and virus-like particles) have comparable dimensions to the pathogens that the immune system evolved to combat. Therefore, these particulates are normally taken up efficiently by APCs and function mainly to deliver associated antigen into these cells.

The main hurdle to the development of new and improved adjuvants has been safety, because vaccines that are to be used in healthy individuals will need to induce minimal adverse effects to prove acceptable for use. So, although many adjuvants have been extensively evaluated both preclinically and clinically, only aluminium salts (generically called ‘alum’) have been successfully licensed for use as vaccine adjuvants in North America and Europe. However, an alternative particulate delivery system, the microemulsion MF59 (REF. 28), was successfully introduced onto the market in Europe in 1997 to be used in conjunction with an influenza vaccine (Fluad; Chiron). MF59 seems to function as an adjuvant mainly through promoting the uptake of co-administered vaccine antigens into APCs. Although MF59 has been shown to be safe and efficacious in a wide range of clinical trials, its early clinical development yielded a number of important lessons. Originally, microemulsions such as MF59 were used as delivery systems for a potent adjuvant active molecule — a lipiodated muramyl tripeptide (MTP-PE) — that was a novel synthetic derivative of mycobacterial cell wall. However, the MF59/MTP-PE combination proved too reactogenic for routine clinical use, although MF59 alone was well-tolerated and had comparable immunogenicity to the MF59/MTP-PE combination. Consequently, MF59 alone was used subsequently and proved sufficiently potent and safe to allow successful product development. Our clinical experiences with microemulsions served to highlight the need for careful selection of immune potentiators to be included in vaccines. Overall, although MF59 is normally a more potent adjuvant than alum, like alum, it cannot be expected to be appropriate for use with all vaccines. MF59 works well with a variety of antigens to enhance antibody and T-cell proliferative responses. However, it is unable to induce potent T-cell responses of the Th1 type, defined by the production of the cytokine interferon-γ, which might be required to provide protective immunity against some intracellular pathogens. So, it is clear that additional adjuvant and delivery approaches will be needed for some vaccines.

In the recent past, we have focused on an alternative particulate delivery system for vaccines, comprising biodegradable microparticles prepared from the polymer poly(lactide-co-glycolide) (PLG). Because PLG polymer has already been used for a variety of biomedical purposes, including the preparation of a controlled-release delivery system for the therapeutic protein human growth hormone, it was an excellent choice as a vaccine delivery system. In addition, microparticles of the appropriate size (~1 μm) have been shown to be taken up by APCs in vivo, which migrated to the T-cell area of local lymph nodes and differentiated into mature DCs. Initial work focused on the use of microparticles for controlled release of trapped antigens, with the objective of making single-dose vaccines.

MICROPARTICLES
Particulate carrier systems in the micron size range, normally prepared with synthetic polymers, which can be used as delivery systems for drugs or vaccines that are usually trapped within the particles.

MF59
An oil-in-water microemulsion adjuvant which has been approved in Europe for use in combination with influenza vaccine in the elderly (Fluad).
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However, problems arose as a consequence of the degradation of antigens following microencapsulation and during release from PLG microparticles. We therefore adopted the novel approach of adsorbing antigens onto the surface of microparticles to avoid exposing them to damaging conditions during encapsulation and release. Adsorption was enhanced by using charged surfactants for microparticle preparation, which promoted antigen interaction with the surface of the particles. Consequently, the microparticles were designed to perform as a delivery system to promote the uptake of antigen into APCs, thereby resulting in the induction of potent antibody and T-cell responses in mice and non-human primates. In addition, the adsorption of antigen on microparticles also serves to multimerize the antigens, and so facilitates direct recognition by B-cell antigen receptors. The approach of adsorbing antigens onto charged microparticles has proven sufficiently flexible to allow successful delivery of DNA vaccines, which are adsorbed onto the surface of cationic microparticles. Using cationic microparticles as a delivery system for DNA vaccines resulted in significantly enhanced immune responses in comparison with vaccination using naked DNA in mice and in non-human primates. In mechanistic studies, we showed that the cationic PLG microparticles were able to deliver adsorbed DNA into DCs, whereas naked DNA was unable to transfect DCs. Similar cationic microparticles can also be used as delivery systems for adsorbed adjuvants, including CpG DNA, whereas anionic microparticles have been used for adsorbed protein vaccines. The potential of a broad range of particulate vaccine delivery systems to improve the potency of new generation vaccines has recently been reviewed in more detail.

Delivery systems for mucosal immunization

Although the majority of vaccines have traditionally been administered by injection, mucosal administration of vaccines offers a number of important advantages, including easier administration, reduced adverse effects and the potential for frequent boosting. In addition, mucosal immunization induces local immunity at the sites where pathogens often establish infection. Oral immunization would be particularly advantageous in isolated communities, where access to health care professionals is problematic. Moreover, mucosal immunization would avoid the problem of infection due to the re-use of needles, which is common in the developing world. However, the difficulty of developing mucosal and particularly oral vaccines using non-living approaches should not be underestimated.

The most potent mucosal adjuvants available are the bacterial toxins secreted from Escherichia coli and Vibrio cholerae, called HEAT-LABILE ENTEROTOXIN (LT) and cholera toxin (CT), respectively. Moreover, because these molecules are responsible for traveller’s diarrhoea and cholera, respectively, the native molecules are clearly not appropriate for mucosal administration to humans. Therefore, these molecules have been manipulated to reduce toxicity, while retaining adjuvant activity (FIG. 6). One particular mutant of LT, LTK63, has recently been shown to be safe in a human clinical trial involving intranasal administration, following extensive preclinical toxicity testing. In previous studies, we showed that the potency of LTK63 for intranasal administration could be enhanced by co-administration with bio-adhesive delivery systems in small and large animal models. The bio-adhesive delivery systems were designed to retain the vaccine formulation in the nasal cavity for extended periods and to promote the interaction of the antigen and adjuvant with the mucosal epithelium. Recent data indicate that LTK63 might prove sufficiently potent to allow the mucosal administration of paediatric combination vaccines.

**Figure 4 | Representation of a cationic poly(lactide co-glycolide) (PLG) microparticle (1 µm mean size) with adsorbed DNA on the surface.** The microparticle is cationic because of the presence of the cationic detergent hexadecyltrimethyl ammonium bromide (CTAB), which binds to the surface during microparticle preparation, and allows the efficient adsorption of poly-anionic plasmids. This approach serves to significantly enhance the potency of the antigens encoded by the adsorbed DNA vaccines.

**HEAT-LABILE ENTEROTOXIN (LT).** A bacterial toxin secreted from Escherichia coli which is potently immuno-stimulatory when applied to mucosal surfaces and can also act as an adjuvant for co-administered antigens. However, the molecule is also the causative agent of traveller’s diarrhoea.
TRANSCUTANEOUS IMMUNIZATION
Involves the topical application of vaccines, usually in a specially designed patch, and mediates effective immunization without penetrating the protective layer of the skin with a device or needle.

Vaccine delivery devices
In its broadest sense, the concept of ‘vaccine delivery systems’ can be expanded to include a range of devices and physical delivery systems designed to allow immunization using novel non-invasive routes. Needle-free vaccination is attractive for a number of reasons. In the developed world, there are concerns about the number of vaccinations that are administered to infants and toddlers, and it would be preferable if these could be administered without the use of needles. In addition, ‘needle phobia’ is a significant problem that makes it difficult to convince adults to receive vaccinations. This problem might become particularly acute in the future if it proves necessary to immunize large numbers of individuals in response to a pandemic strain of influenza, or to the threat of a bio-terrorism attack. The problems related to vaccination with needles are even greater in the developing world, where the re-use of needles often results in the transmission of blood-borne pathogens, such as HIV and HCV. Although this problem has been partly remedied through the development of single-use ‘auto-disposable’ syringes, needle-based injections still represent an infectious threat which must be disposed of carefully.

One approach to obviate the problems associated with vaccines administered by needles involves a number of devices that are designed to deliver vaccines through or into the skin, but without the use of needles. Multiple-use jet injector devices that deliver liquid vaccines through the skin were widely used for mass immunization campaigns throughout the 1980s. However, these devices became discredited when it became apparent that they were capable of transmitting blood-borne pathogens such as hepatitis B51. More recently, single-dose jet injector devices have been developed, which are capable of delivering liquid52 or dry powder vaccines53 through the skin using high pressure. In addition, spring-powered liquid injection devices are available and have also been evaluated in the clinic54. However, none of these devices have yet attained broad acceptance in the medical community and their costs will make them difficult, if not impossible, to implement in the developing world. High-pressure-liquid, needle-free devices have also been used for the delivery of DNA vaccines in clinical trials55, as have new needle-free devices designed to deliver gold beads coated with DNA into the skin (‘gene gun’)56. An alternative needle-free approach to vaccine delivery, which could perhaps be described more accurately as ‘needle-lite’, involves the use of microprojection arrays designed to painlessly disrupt the outer layers of the skin to allow the vaccine access to the epidermis and associated Langerhans cells57,58.

Perhaps the most attractive needle-free approach to vaccine delivery being explored at present involves TRANSCUTANEOUS IMMUNIZATION through the topical application of vaccine patches59. This approach has recently provided promising observations in clinical trials60,61. In addition, the ability of a number of different adjuvants to function following topical application with vaccines is encouraging62, as is the ability of a topically applied ‘immunostimulatory patch’ to enhance the immunogenicity of a locally injected vaccine64. However, the available devices need to be made more robust and reliable to be broadly accepted for vaccine administration.
Conclusions

We are entering an exciting and dynamic time in vaccine research in which the principles governing the successful induction of potent and protective immune responses are becoming better understood. At the forefront of this work are discoveries relating to the presence of receptors on innate immune cells, which recognize the characteristic patterns and components present on pathogens. Recognition of the importance of activation of the innate immune system to the eventual induction of antigen-specific immunity has fired enthusiasm to identify pathogen-based ligands for these receptors as potential new-generation adjuvants to be used in combination with recombinant proteins. A significant amount of work is underway in this area and will likely lead to the development of whole new classes of vaccine adjuvants that are able to control and manipulate the immune response in a variety of ways. It is likely that these adjuvants could prove to be sufficiently potent to allow vaccines to be used to treat chronic infectious diseases, autoimmunity and cancer. However, the potency of these adjuvants needs to be carefully balanced with their potential to overactivate the immune system, with damaging consequences. In this regard, vaccine and adjuvant delivery systems might have a role to play in limiting the systemic distribution of adjuvants following administration. Moreover, the main role of vaccine delivery systems is to ensure that the antigens and adjuvants interact optimally with the appropriate immunocompetent cells to induce the desired responses. Nevertheless, for adjuvants capable of initiating potent inflammatory responses, limiting their ability to act on a broad range of cells could prove to be as important as focusing their effect on key immune cells. Overall, it is clear that pharmaceutical scientists have a unique and important role to play in the development of optimal vaccine and adjuvant delivery systems for systemic and mucosal administration.

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Acknowledgements

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