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Review

New generation adjuvants – From empiricism to rational design

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ABSTRACT

Adjuvants are an essential component of modern vaccine development. Despite many decades of development, only a few types of adjuvants are currently included in vaccines approved for human use. In order to better understand the reasons that development of some adjuvants succeeded while many others failed, we discuss some of the common attributes of successful first generation adjuvants. Next, we evaluate current trends in the development of second generation adjuvants, including the potential advantages of rationally designed synthetic immune potentiators appropriately formulated. Finally, we discuss desirable attributes of next generation adjuvants. Throughout, we emphasize that the importance of formulation and analytical characterization in all aspects of vaccine adjuvant development is often underappreciated. We highlight the formulation factors that must be evaluated in order to optimize interactions between vaccine antigens, immune potentiators, and particulate formulations, and the resulting effects on safety, biological activity, manufacturability, and stability.

1. Empirical vaccine adjuvants – the first generation particulates

The first generation of adjuvants that have been widely available for many years and some of which are included in the currently licensed vaccine products, have been described by Steve Reed (in this issue). These adjuvants are essentially particulate 'carriers', which although are often compositionally and structurally very different, have broadly similar dimensions (Fig. 1) and closely related mechanisms of action. Adjuvants based on insoluble aluminium salts, oil in water emulsions and liposomes have been used in human vaccines for some considerable time and have enjoyed significant success as components of licensed products. In contrast some alternative particulate adjuvants described in more recent decades, e.g. ISCOMs and polymeric particles, have made more limited progress into clinical testing, and have not yet been included in vaccine products.

Since only a few adjuvant technologies have succeeded, while many others have failed, we would like to use our experience and insights to highlight what might have made the difference and importantly, to try to improve success rates in the future. In thinking about why so many have failed, perhaps an important consideration is that those which succeeded usually had an alternative medical use prior to their utilization in vaccines (Table 1). Moreover, the alternative uses often continued and expanded alongside their use in vaccines, which meant that many key technical attributes were in place, which could also be exploited for vaccines. For example, the manufacturing of formulations suitable for clinical evaluation was established, using materials that had been resourced through a supply chain which was appropriate for a medical product. Moreover, the use of these technologies (e.g. liposomes/emulsions) in vaccines could directly benefit from process or manufacturing improvements that were implemented due to alternative uses of the technologies. We believe that perhaps this point has been under-appreciated, and that it should be an important consideration as we consider the question of 'which are the best adjuvant technologies for the future?' The economics of vaccine development has traditionally been challenging and the market realities have made it difficult to support large and expensive manufacturing investments for new technologies. Therefore, it is attractive if within the pharmaceutical industry an alternative product opportunity outside the vaccine arena could support the development process for a new adjuvant, particularly since the vaccine industry operates substantially within the allied pharmaceutical industry. Unfortunately, this may suggest that many of the new adjuvants currently under investigation are likely to fail, like many more before them.

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Table 1
Alternative use of clinical phase adjuvants.

Delivery system/adjuvant	Early medical use	Licensed for drugs
Aluminium salts	Oral ~1915	Yes – oral antacids
Emulsions (o/w)	Intralipid TPN–1962	Yes – Propofol (1989)
Liposomes/virosomes	Artificial membranes – 1964	Yes – Doxil (1995) now >10
Topical cream w/TLR7 agonist	Genital warts, actinic keratosis, carcinoma	Yes – Aldara (1997)
Microparticles (PLG)	Steroid hormones – 1980	Yes – hGH (1999), sutures (1970)
Saponins (ISCOMs, etc.)	Veterinary vaccines – 1951	Yes – veterinary vaccines (1951)

2. Second generation adjuvants – exploiting synergy between the first generation and added immune potentiators

The majority of second generation adjuvants currently under investigation have exploited the successes of the first generation, while adding an 'immune potentiator' to improve potency. The added immune potentiators are usually TLR agonists, as discussed by Steve Reed (in this issue), although alternative pattern recognition receptor (PRR) ligands are also available to potentially exploit additional or alternative pathways of innate activation, including NLR, RIG-I or STING. The addition of TLR agonists is not a new concept, since combined vaccine adjuvants have been evaluated since the 1930s, when whole bacterial cells were added to water-in-oil emulsions to create Freunds' complete adjuvant. Nevertheless, successful licensure of a product containing a purified bacterial component as a component of a second generation adjuvant was not achieved until 2005 [1]. Monophosphoryl lipid A (MPL®), a TLR4 ligand, was the first TLR agonist included in a licensed human vaccine. Although MPL® is a natural product, there are now various synthetic TLR4 agonists available with potential advantages over the original natural product, including GLA (Reed et al., in this issue). Moreover, besides TLR4 ligands, there are various other TLR agonists at various stages of clinical development. Overall, there is a gradual and logical shift from the use of natural products to more rationally defined and synthetically created TLR agonists and others for inclusion in second generation adjuvants.

In general, we believe that the key role of formulation science has traditionally been underappreciated in adjuvant development. Moreover, it is within the context of the development of second generation adjuvants that this role becomes most crucial. Since there are a range of particulate adjuvants available, which can now be combined with a range of immune potentiators (TLR agonists and others), it is the crucial and distinctive role of formulation science to determine how best these can be optimally combined. In addition, the combination (2nd generation) adjuvants can be linked to vaccine antigens in a variety of ways including adsorption, encapsulation, conjugation, complexation, chelation, dispersion or simple co-administration. Unfortunately, the actual need for physical association between individual components needs to be determined empirically, and remains both antigen and immune potentiator dependent. Extensive studies need to be undertaken to address this question for each new adjuvant, and these need to be driven by insightful formulation science. The objective of these

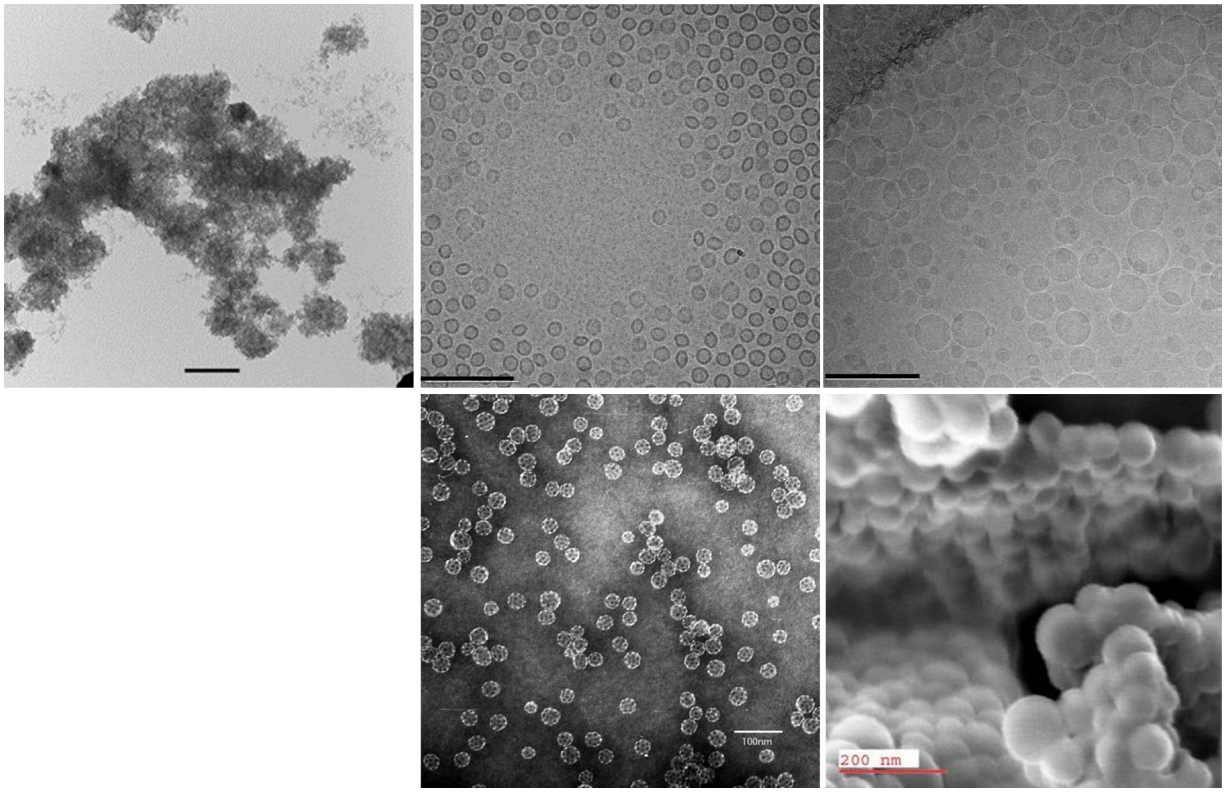

Fig. 1. Electron micrographs of adjuvant formulations demonstrate the complexity and diversity of particulate structures. (a) Unstained TEM of aluminium oxyhydroxide (scale bar 2 μm), (b) cryo-TEM of GLA-liposomes (scale bar 200 nm), (c) cryo-TEM of GLA-SE, (d) negative stained TEM of ISCOMs (scale bar 100 nm), (e) SEM of PLG nanoparticles (scale bar 10 μm). (a) Reprinted from Harris et al. Micron 2012, 43:192–200, with permission from Elsevier. (b and c) Reprinted from Fox et al. [3], with permission from Elsevier. (d) Reprinted by permission from Macmillan Publishers Ltd: Sanders et al. Immunol Cell Biol 2005, 83:119–128.