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Recent Developments in Nonliving Antigen Delivery Systems

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THE SAFETY OF VACCINE ADJUVANTS

While complete safety for any medical intervention is impossible, with almost 100 years of accumulated data involving many billions of doses, it is clear that vaccines, including adjuvants, have an excellent safety profile. Recently the safety of long-established vaccine adjuvants based on insoluble aluminum salts (alum) was readdressed (1). The conclusion was that alum was safe and effective, although local reactions can be common. However, since vaccines are administered to hundreds of millions of individuals on an annual basis, the safety hurdles applied to new vaccines and new vaccine adjuvant technologies will be high, with rigorous evaluation the established practice. It is in this very conservative context that the merits and advantages of novel adjuvants need to be considered.

This chapter will focus on a subset of vaccine adjuvants, which can be more accurately described as ''antigen delivery systems,'' including emulsions, polymeric particles, immune-stimulating complexes (ISCOMs), liposomes, and virus-like particles (VLPs). These well-established vaccine adjuvants function primarily through a mechanism that promotes the uptake and processing of associated antigens by important antigen-presenting cells (APCs). However, vaccine adjuvants are generally described by what they do, which is to enhance immune responses to coadministered antigens, rather than what they actually are. Hence adjuvants are a very broad class of compounds, which defy easy descriptions and explanations, so it will be necessary to diversify within this chapter, to include discussions of additional kinds of adjuvants, to allow a full description of the ''delivery system''–based adjuvants. The mechanisms of action of most adjuvants are often poorly understood, mainly because they are rarely simple, involving many factors, cells, receptors, and processes, which often cooperate in complex cascades with unclear triggers, activators, and feedback loops. Nevertheless, wherever possible within this chapter, simple definitions and descriptions will be offered to add clarity, but this will inevitably result in some necessary over simplifications.

Any review on the future development of nonliving antigen delivery systems, inevitably has to begin with a discussion of safety. Many hundreds of different adjuvants have been described in preclinical studies over many years, but only a very few have progressed as far as inclusion into licensed vaccine products, which have survived in the market place. The principal reason for the slow progress of adjuvant development is safety. Approximately 70 years passed between the licensure of insoluble aluminum salts as an adjuvant for vaccines in the 1920s until the licensure of MF59 in the 1990s. In addition to safety concerns, obstacles in manufacturing have contributed to the slow development of new vaccine adjuvants, including scarcity and high cost of certain raw materials, problems in scale-up, and lack of process reproducibility. However, while it has been possible to overcome many of the manufacturing problems, the issue of adjuvant safety has proven more intractable and often impossible to resolve, despite the expenditure of enormous resources.

THE NEED FOR NEW AND IMPROVED VACCINES

There is a clear need for the development of new vaccines against a number of infectious diseases for which vaccines are not yet available, or are inadequate, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), group B *Neisseria meningitidis*, tuberculosis (TB), and malaria. Unfortunately, these pathogens have proven exceptionally difficult to control, and novel approaches are required. While new technologies are playing a role in the development of vaccines against these difficult targets, including genome-based antigen discovery (2), new vaccine adjuvants also have a key role to play, through their ability to enhance and diversify immune responses (Table 1). New vaccines may also be needed to protect against a number of emerging or reemerging infectious diseases, including Ebola, Hanta, and Dengue viruses. In addition, improved vaccines are necessary to protect against the emergence of pandemic strains of influenza and the continued growth of drug resistant organisms. Moreover, vaccines may be required to protect against the threat of bioterrorism (3). Moving beyond the traditional use of vaccines to prevent infectious diseases, there is an increasing awareness that infectious agents are often the cause of chronic diseases, which might be prevented or treated with novel vaccines. The ability of adjuvants to activate and manipulate the immune response will almost certainly be key to the successful development of therapeutic vaccines against infectious organisms and other causes.

ALTERNATIVE APPROACHES TO IMPROVED VACCINE ADJUVANTS

Vaccine adjuvants were first described by Ramon more than 80 years ago (4) and have been used to improve the immunogenicity of most nonliving vaccines ever since. Although the role of an adjuvant is to improve the immunogenicity of antigens, and indeed, this is how they are defined, adjuvants are often included in vaccines to achieve a range of much more specific