

DISCOVERY OF VACCINE ADJUVANTS

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1 INTRODUCTION

Vaccination has had a profound effect in alleviating human morbidity and mortality since the approach was widely introduced in the nineteenth century. The objective of vaccination is to administer a vaccine in such a way as to induce a protective immune response against the corresponding pathogen. Live attenuated and inactivated viral and bacterial vaccines were successful against a number of major pathogens including smallpox, polio, measles, and pertussis. However, together with the major advances in molecular genetics and immunology, safety concerns associated with live and whole-cell killed vaccines have driven a quest for “subunit” vaccines that are based on isolated components of microbes. Despite their advantages in terms of safety, these vaccines are generally ineffective when administered alone, necessitating the use of substances (adjuvants) that can enhance immunity. Alum is the most widely used vaccine adjuvant and is very effective at promoting antibody responses and Th2 type T cell responses. However, it is now recognized with a number of major diseases, including tuberculosis and malaria, that strong cell-mediated immunity is important for protection so adjuvants that can effectively drive such responses and not only antibody responses are required [1]. The global vaccine market is projected to grow very strongly over the next decade so there will be an increasing demand for a range of potent and effective vaccine adjuvants.

2 HISTORY OF ADJUVANT DISCOVERY

Adjuvants were originally defined as “substances used in combination with a specific antigen that produce more immunity than the antigen alone” [2]. The modern field of adjuvant research emanated from studies carried out by Gaston Ramon at the Pasteur Institute in the early 1920s that demonstrated that the injection of an eclectic variety of substances including tapioca, inorganic salts, oil, and pyogenic bacteria with diphtheria toxoid enhanced antibody responses to the toxin [3, 4]. Soon afterward Glenny and co-workers reported that injection of diphtheria toxoid as an alum precipitate induced significantly higher antibody responses than injection of the toxoid alone [5–7]. This seminal observation on the adjuvant properties of aluminum compounds ushered in the use of these mineral salts, and these still form the basis of the most widely used adjuvants today. Indeed these remain the only vaccine adjuvants currently licensed by the U.S. Food and Drug Administration (FDA).

The next significant advance in adjuvant research was the description by Jules Freund of a water-in-mineral-oil emulsion containing killed mycobacteria [8]. This is commonly known as Freund's complete adjuvant (FCA) and is a highly potent adjuvant although associated with unacceptable side effects. As a result, a formulation without the killed bacteria was developed and has been used clinically [9, 10]. However, newer emulsions have since been developed and Freund's