MILESTONE 6

Alum adjuvant discovery and potency

Vaccines have been lauded as one of the greatest scientific discoveries, having saved millions of lives from infectious diseases such as smallpox, and measles. Today, the ongoing COVID-19 pandemic is pinning much hope on a vaccine to save more lives. The success of such vaccines depends on their ability to elicit long-lasting immunity and protection from subsequent infections. This potency is highly dependent on adjuvants, which are incorporated in the vaccines to boost the immune response. The word adjuvant is derived from the latin word *adjuvare* meaning 'to aid'. Indeed, adjuvants have been used in vaccines to aid in their efficacy, especially for those using weak antigens.

Today, many vaccines are developed from components of pathogens. As such, adjuvants are required to provoke a strong immune response. The most widely used adjuvant is aluminium salt which was first used by the immunologist, Alexander T. Glenny, in 1926 at the Wellcome Physiological Research Laboratory in London.

In an attempt to purify and concentrate diphtheria toxoids (inactive toxin), Glenny and colleagues used potassium aluminium sulfate in the production of the vaccine. Surprisingly, they found that vaccines developed using aluminium salt precipitation led to better antibody responses in guinea pigs than the soluble toxoids — the first demonstration of aluminium salt adjuvanticity. Glenny aptly stated in his article that "the antigenic value of the emulsion of precipitate appeared greater than that of the toxoid from which it came". Since then, numerous vaccines have been developed with 'alum' salts.

Adjuvants are also important in reducing the dose required for a vaccine. It is now known that combining adjuvants with recombinant proteins can significantly reduce the amount of antigen required to induce sufficient protective antibody production, ultimately reducing the dose administered. In addition, adjuvants can also broaden the immunity from vaccines by providing cross-clade immunity — immunity against different clades of pathogens with related origins. Importantly, adjuvants can also increase the magnitude of antibody responses.

The mechanism of action of adjuvants has been widely contested. In 1931, Glenny and colleagues initially proposed the 'depot theory', which suggests that through adsorption, alum facilitates slow release of the antigen into the injection site, thereby enhancing prolonged stimulation of the immune system. Glenny and colleagues found that alum nodules formed within a few hours in the injection site could be excised from an immunized guinea pig and subsequently implanted into a naive guinea pig, leading to successful immunization. However, work carried out over the past two decades has challenged this depot theory.

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Recent work has suggested that the innate immune system plays a critical role. Following injection into the tissue, particulate adjuvants create a pro-inflammatory response by tissue-resident macrophages. This stimulates recruitment of innate immune cells such as neutrophils and subsequently dendritic cells. The dendritic cells play a crucial role in inducing an adaptive immune response.

In 1994, Polly Matzinger proposed the 'danger hypothesis' whereby localized tissue damage and cell death lead to release of danger signals such as uric acid, which ultimately trigger the innate and adaptive immune responses. Indeed, it has been shown that particulate alum salts lead to release of pro-inflammatory cytokines at the injection site. More recently, numerous studies have focused on the ability of alum adjuvants to activate inflammasomes, which are intracellular sensors that modulate inflammation in response to pathogens. Veit Hornung and colleagues showed that stress associated with phagocytosis of alum can trigger inflammasome activation.

There is a huge effort still required to fully understand the prevailing mechanism by which alum adjuvants regulate immunogenicity. However, it is clear that the pioneering work by Alexander Glenny on acquired immunity has been significant.

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ORIGINAL ARTICLE Glenny, A. T. et al. Immunological notes. XVII–XXIV. *J. Pathol. Bacteriol.* **29**, 31–40 (1926)
FURTHER READING Oakley, C. L. Alexander Thomas Glenny, 1882–1965 (1966) | Reed, S. G., Orr, M. T. & Fox, C. B. Key roles of adjuvants in modern vaccines. *Nat. Med.* **19**, 1597–1608 (2013) | Matzinger, P. Tolerance, danger, and the extended family. *Annu. Rev. Immunol.* **12**, 991–1045 (1994) | Hornung, V. et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat. Immunol.* **9**, 847–856 (2008)