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# Graphene oxide as novel vaccine adjuvant

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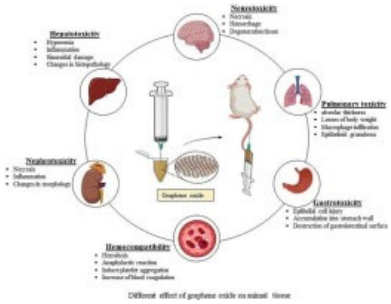
## Abstract

To improve antigen immunogenicity and promote long-lasting immunity, vaccine formulations have been appropriately supplemented with adjuvants. Graphene has been found to enhance the presentation of antigens to CD8+ T cells, as well as stimulating innate immune responses and inflammatory factors. Its properties, such as large surface area, water stability, and high aspect ratio, make it a suitable candidate for delivering biological substances. Graphene-based nanomaterials have recently attracted significant attention as a new type of vaccine adjuvants due to their potential role in the activation of immune responses. Due to the limited functionality of some approved human adjuvants for use, the development of new all-purpose adjuvants is urgently required. Research on the immunological and biomedical use of graphene oxide (GO) indicates that these nanocarriers possess excellent physicochemical properties, acceptable biocompatibility, and a high capacity for drug loading. Graphene-based nanocarriers also could improve the function of some immune cells such as dendritic cells and macrophages through specific signaling pathways. However, GO injection can lead to significant oxidative stress and inflammation. Various surface functionalization protocols have been employed to reduce possible adverse effects of GO, such as aggregation of GO in biological liquids and induce cell death. Furthermore, these modifications enhance the properties of functionalized-GO's qualities, making it an excellent carrier and adjuvant. Shedding light on different physicochemical and structural properties of GO and its derivatives has led to their application in various therapeutic and drug delivery fields. In this review, we have endeavored to elaborate on different aspects of GO.

## Graphical abstract



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## Introduction

Conventional vaccines contain live-attenuated or inactivated variants of the target pathogens, providing strong and prolonged immune responses against infection. Such vaccines usually generate mild symptoms as that observe in people previously have been infected with the related pathogen. Despite all the advantages of the conventional vaccines, the main problem of such vaccines is the potential risk of the restoration of pathogen. Besides safety concerns, these vaccines have not been successfully developed for many pathogens [1], [2]. By contrast, nonliving vaccines containing only the antigenic components of a pathogen, are considered very safe vaccines, although they do not stimulate a robust immune response [3]. To overcome the low immunogenicity of nonliving vaccines, additional components, termed as adjuvants, are added to formulations of vaccines to intensify the immune responses [4], [5]. Adjuvants have been used to improve vaccine efficacy and decrease the number of administration dose of vaccine. Furthermore, they increase the speed of initial immune responses against the infection, which could be important factor against the emergence of pandemics [6]. Adjuvants also channel the immune system to produce the most effective form of the immune response against the pathogen [7]. Aluminum salts is the only human vaccine adjuvant, which has been used for more than 70years [8]. In the last 20years, novel adjuvants have been introduced in the formulation of licensed vaccines [9]. Recent advances in immune biological research have highlighted novel components for the development of novel adjuvants in human vaccination. Generally, adjuvants are classified based on their mechanisms of action (particulate or non-particulate), physicochemical properties, and their origin (synthetic or natural). Particulate adjuvants, including aluminum salts, immunostimulating complexes (ISCOMS), liposomes, and oil emulsions can be used to stimulate immune responses [10]. Non-particulate adjuvants are generally immunomodulators such as cytokines, saponins, carbohydrates, and derivatives of bacteria that could directly activate the immune system [11]. Some adjuvants possess depot effects, which trap or slowly release the antigen at the injection site, providing a sustained antigen supply for local antigen presenting cells (APCs) and stimulating a long-lasting immune response. Other adjuvants enhance the expression of co-stimulatory and major histocompatibility complex (MHC) molecule or attached to pattern recognition receptors (PRRs) and provoke innate immunity. In addition, some adjuvants generate localized pro-inflammatory immunity at the injection site, leading to the recruitment and activation of immune cells. It has been revealed that some adjuvants employ one or two of the above-mentioned mechanisms to stimulate the immune system, including MF59 and alum [12]. To design an ideal adjuvant, some considerations should be taken into account, in particular, their safety, stability, and biocompatibility [13]. As for safety and purity, metabolizable and synthetic adjuvants are preferable. Furthermore, specific B or T cell responses should not be induced by an ideal adjuvant [14]. Although many of the bacterial derived components possess acceptable adjuvanticity, they are highly toxic to humans. Hence, chemical modifications are applied to reduce adjuvant toxicity [15], [16]. To achieve desired immune responses combination of several adjuvants in a single vaccine formulation can be used. The most common example is Freund's complete adjuvant (FCA), a paraffin oil-in-water emulsion containing killed *Mycobacterium tuberculosis,* which is effective in eliciting strong immune responses by attracting macrophages and other immune cells to the injection site. FCA is widely used for experimental studies in animal models; nevertheless, its use in human vaccines is forbidden due to its toxicity [17]. Up to now, few adjuvants have been licensed for use in human vaccines, mainly due to safety issues. In addition to safety, these components should be effective for young children and infants [18]. As the focus has shifted from conventional vaccines to next-generation vaccines, the development of novel vaccine adjuvants is an urgent need [19].

## Section snippets

### Nano-particulate vaccine adjuvants

Nanoparticles are small solid particles with immunostimulatory effects that are widely applied in vaccine formulation and drug/gene delivery. Due to more permeability and stability in blood circulation, these particles are more efficient in targeted drug delivery [20], [21]. Nano-particulate vaccine adjuvants function by depot effects, thereby enhancing the antigen availability to the immune cells and eliciting long-lasting immunity [22]. Other mechanisms by which nanoparticles trigger immune…

### Different properties of graphene oxide

Graphene is a two-dimensional monolayer with a single atom thick (0.35–1.6nm), and $SP^2$ and $SP^3$ hybridized carbon atoms that form hexagonal structures [43]. Graphene has excellent physicochemical properties and acceptable biocompatibility [44]. This carbon structure has a specific surface area, which has piqued the interest of many researchers due to its potential for high drug loading [45], [46], [47]. However, the hydrophobic and insoluble structure of this carbon structure in water, as well…

### Graphene oxide- based vaccines

GO is made by oxidation of graphene obtained by chemical exfoliation of graphite. It has properties like a soft membrane, liquid crystal, or amphiphilic [110]. The backbone of GO contains many oxygen groups like carboxyl and carbonyl at the sheet edges and epoxy and hydroxyl on the basal plane [111], [112]. Some properties like reactive surface sites and the structure of GO make this material an excellent membrane for water separation. GO structures have different hydrophilicity, for example,…

### Advantages

Graphene is a single atomic layer of $sp^2$ bonded carbon atoms in a hexagonal honeycomb lattice whit a bond length of 0.142nm, a density of $0.77 mg m^{-2}$, and a large theoretical surface area ($2630 m^2 g^{-1}$ [158]. This material has strong fracture strength (125 GPa) [158], which makes it very flexible, brittle and ductile. Simultaneously it has excellent thermal conductivity ($5300 W m^{-1} K^{-1}$), electrical conductivity (2000 S $cm^{-1}$), and electron mobility (200,000cm2 $V^{-1}$ $s^{-1}$ [158], [159]. Graphene is…

### Conclusion

Graphene-based nanomaterials are able to absorb various antigens, as well as they have been introduced as promising vaccine adjuvants in recent years. These nanomaterials have made a tremendous impact on different fields of vaccine design due to their acceptable physicochemical features, large surface area, and functional groups. However, there is much we still have to learn about the GO impacts on immune responses, which involve both adaptive and innate defense mechanisms. From the biological…

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

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