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# Enhancing vaccine effectiveness with delivery technology

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Vaccines stand as a very powerful means of disease prevention and treatment. Fundamental to the success of vaccination is the efficient delivery of antigenic cargo needed to trigger an effective immune response. In this article, we will review recent advances in delivery technology with a focus on devices designed to optimally maximize responses to antigen cargo. Included with the review is an overview of traditional vaccine applications and how these approaches can benefit by well-designed delivery methods.

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## Introduction

Vaccines can be divided into two broad groups: live attenuated vaccines and inactivated vaccines. Live attenuated vaccines, which are comprised of weakened forms of disease-causing organisms (pathogens) such as viruses or bacteria, induce immune reactions similar to those resulting from an actual infection [1]. This group of vaccines elicits a strong response and is capable of conferring immunity that can last for decades with a single dose [1]. For example, one vaccination of the smallpox vaccine can maintain substantial immunity to the virus for up to 75 years [2]. Inactivated vaccines, which range from completely inactivated pathogens to the antigen components of those pathogens (including subunit vaccines, toxoid vaccines, carbohydrate vaccines, and conjugate vaccines) induce short-lived protection compared to attenuated vaccines and often require a follow-up booster vaccination to maintain protective immunity [3]. Furthermore, inactivated vaccines typically contain adjuvants, which are additives designed to enhance and shape immune response outcomes [4]. Understanding how to induce protective responses with adjuvants will enable the production of more specific and efficient vaccines, which can confer immunity for longer periods of time [5].

Delivery technology offers advantages in vaccine application by carefully designing the introduction of antigens and adjuvants for a more directed and enhanced immune response. In particular, delivery systems can enhance immunological outcomes by: Firstly, prolonging the deposition of antigens at the site of administration; secondly, recruiting sentinel immune cells (termed antigen presenting cells or ACPs) required for immune response initiation; thirdly, influencing site localization and antigen delivery; and finally, protecting delicate payloads (e.g. nucleic acids) [6,7].

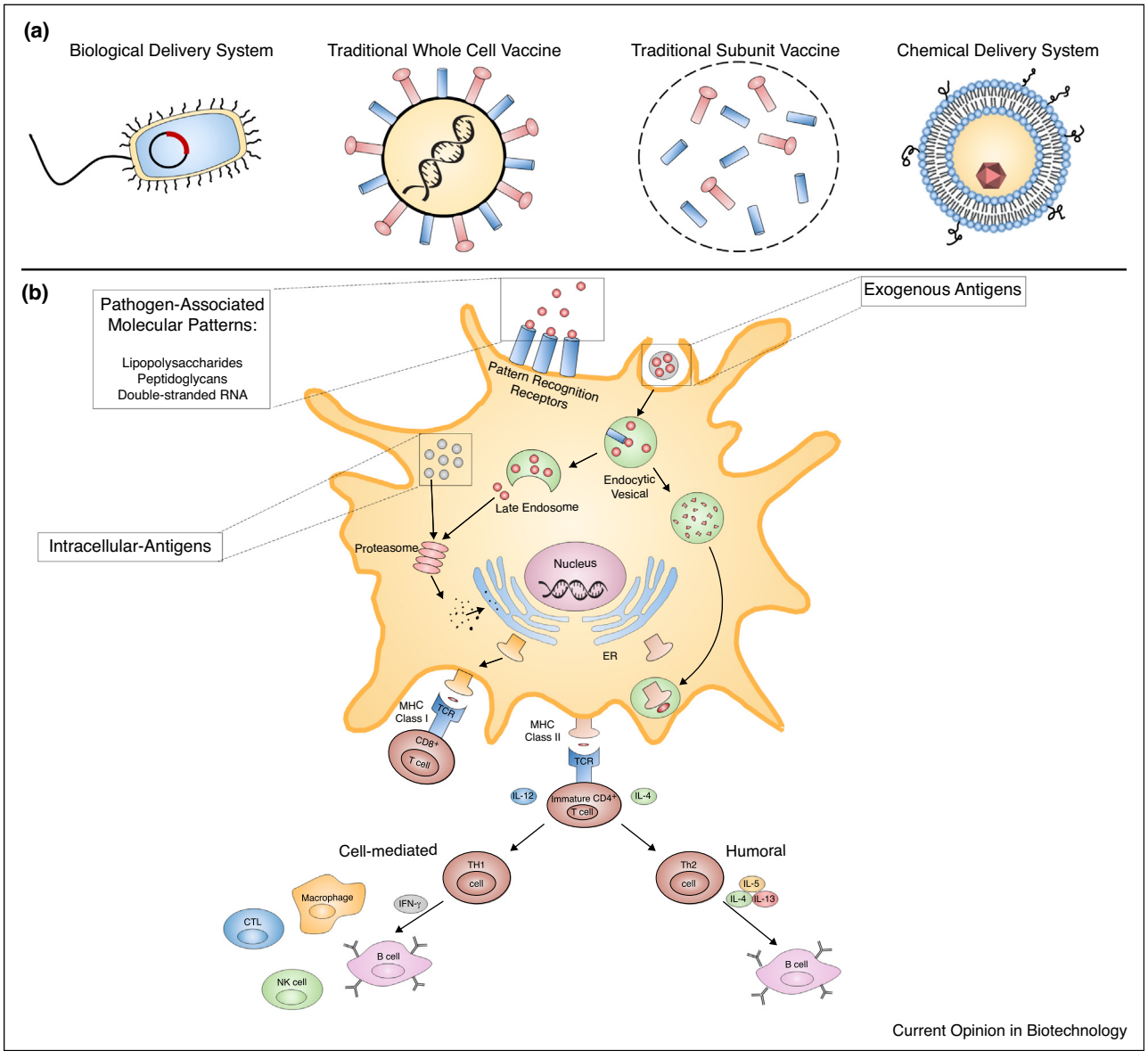
In this review, delivery technology will be evaluated in parallel to traditional vaccines (live attenuated and inactivated whole or component). Emphasis will be placed on how the delivery vector can alter, improve, or accentuate the process of immune response.

## Immune response cascade and lessons in vaccine design

Upon administration of a live attenuated vaccine, an immune response similar to that of a natural infection is elicited. First, specialized receptors on the surface of dendritic cells (DCs), such as toll-like receptors (TLRs), identify an antigen as a potential threat via pathogen-associated molecular patterns (PAMPs) [1]. The antigen is then internalized by DCs, which differentiate into antigen presenting cells after either destroying or partially degrading the antigen [1]. In a natural infection, DCs may be able to eradicate the pathogen [8]. For an efficient vaccine, however, APCs must activate the adaptive immune system [9] which consists of antibody producing B cells and cytokine/cytolytic molecule producing T cells [1,10] (Figure 1).

While a T cell-independent immune response can occur, an effective vaccine must induce a T cell-dependent response. This occurs when T cells interact with the APCs, differentiate into T-helper (Th) cells, such as $CD4^+$ T cells, and begin to secrete cytokines that then affect the behavior of B cells [1,8]. For example, continuously replicating live attenuated vaccines constantly present proteinaceous antigens that are recognized by Th cells. These Th cells trigger a humoral (B cell) response, allowing for the formation of memory B cells that can be reactivated rapidly upon re-infection without further aid of T cells [1,11,12].

**Figure 1**




Vaccine types, delivery devices, and immune response outcomes. **(a)** A pictorial representation of different vaccines and delivery devices. Biological delivery systems include avirulent and attenuated recombinant bacterial vectors capable of delivering genetic and protein antigens. Traditional whole cell vaccines, such as the live attenuated vaccine depicted, contain weakened versions of pathogens that do not cause disease but can continue to replicate. Unlike whole cell vaccines, subunit vaccines only contain the most antigenic regions of a pathogen. Liposomes, a type of chemical delivery system, can provide a high degree of multivalent surface antigens. **(b)** Diagram representing the processing and presentation of antigens in dendritic cells (DCs). Pattern recognizing receptors on the surface of DCs identify pathogen associated molecular patterns (PAMPs) which initiate DC activation. Exogenous antigens are internalized by DCs and processed in endocytic vesicles before being loaded onto MHC Class II molecules, forming a peptide-MHC II complex that is presented to immature T cells that can then stimulate either a humoral or cell-mediated (CTL, cytotoxic T cell; NK, natural killer cell) response. Endogenous, as well as exogenous, antigens can also be loaded onto MHC I molecules; the resulting complex then interacts with $CD8^+$ T cells, which have cytotoxic activity.

Another main component of the adaptive immune system, cytotoxic T cells ($CD8^+$ T cells or killer T cells), secrete cytotoxic factors and cytokines upon interacting with ACPs, which allows them to kill cells that display pathogen-derived proteins [8]. $CD8^+$ T cells are often activated by ACPs displaying antigens derived from foreign or altered nucleic acid content, resulting from cancer aberrations or viral infections, for example, in what is known as a cell-mediated response [13]. It should be noted that a $CD8^+$ response has recently been demonstrated to be