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Bioengineering towards self-assembly of particulate vaccines

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There is an unmet demand for safe and efficient vaccines for prevention of various infectious diseases. Subunit vaccines comprise selected pathogen specific antigens are a safe alternative to whole organism vaccines. However they often lack immunogenicity. Natural and synthetic self-assembling polymers and proteins will be reviewed in view their use to encapsulate and/or display antigens to serve as immunogenic antigen carriers for induction of protective immunity. Recent advances made in *in vivo* assembly of antigen-displaying polyester inclusions will be a focus. Particulate vaccines are inherently immunogenic due to enhanced uptake by antigen presenting cells which process antigens mediating adaptive immune responses. Bioengineering approaches enable the design of tailor-made particulate vaccines to fine tune immune responses towards protective immunity.

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Introduction

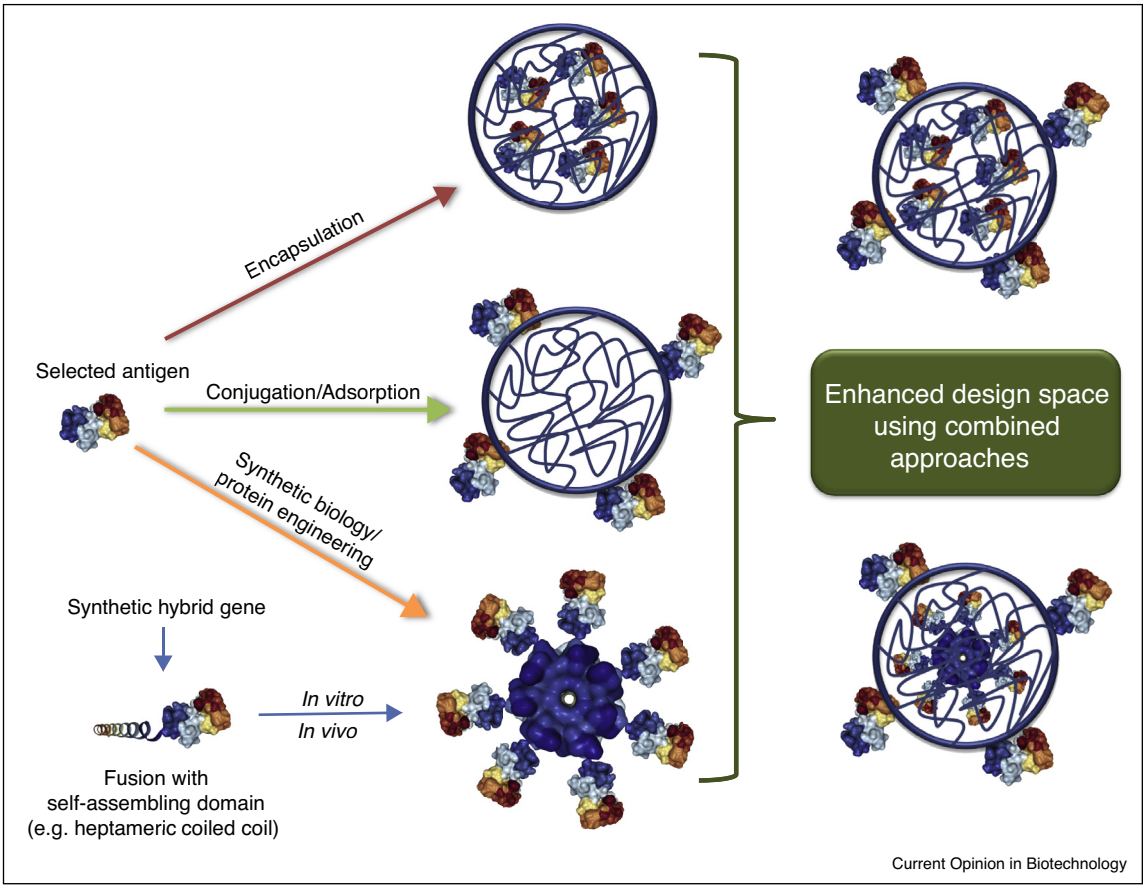
Vaccines represent effective means to control and prevent infectious diseases in humans and animals. Vaccination has successfully eliminated the human disease small-pox [1] and the livestock disease rinderpest [2]. Traditional vaccines are based on live-attenuated whole-organisms and inactivated whole-organisms/viruses [3]. Live vaccines can induce protective immunity lasting for decades; while inactivated vaccines including pathogen derived antigenic components (subunit vaccines) often only induce short-term immunity requiring additional booster vaccinations for continuous protective immunity [4]. Increasing safety concerns in regard to using whole-organism/virus-based vaccines have shifted the focus towards development of safe and efficient subunit vaccines [5•]. Antigens for subunit vaccines had been selected based on their localization at the surface of the pathogen in order to stimulate the production of neutralizing and/or opsonizing antibodies. In the last decade reverse vaccinology, a pathogen genome-based mining approach, emerged as powerful tool to identify key antigens for subunit vaccines [6,7]. Inherently subunit vaccines, mostly based on specific proteins/peptides or carbohydrates, are less immunogenic than whole-organism vaccines. Thus additional immunostimulatory components are required, so-called adjuvants [8]. Except for the licensed adjuvant AS04, monophosphoryl lipid A (MPL) adsorbed to aluminium hydroxide, the few currently approved adjuvants are effective in inducing antibody responses, but are less successful in inducing cell-mediated immunity. The latter is required to protect against intracellular pathogens and viruses as well as is being considered as relevant for treatment of cancer and autoimmune diseases. Vaccines that induce strong and long-lasting cell-mediated immune responses are still needed to control and prevent certain infectious diseases such as hepatitis C [9] and tuberculosis [10] and as therapies for cancer [11].

In the quest for immunogenic subunit vaccine formulations which can induce cell-mediated responses, particulate antigen assemblies offer an exciting alternative. Antigens processed into and/or attached to particles which mimic the size of a virus or pathogen are efficiently taken up by antigen-presenting cells (APCs) which represents a critical initial step towards induction of an adaptive immune response [12•].

Immunological properties of particulate antigen formulations

Antigens can be rendered insoluble, i.e. processed into particles, using a variety of approaches including self-assembly, attachment and/or encapsulation into carrier materials (Figure 1). Particulate antigen delivery systems are desirable as they are in general more immunogenic than their soluble counterparts due to facilitated uptake by APCs. APCs are often designated as the sentinels of the immune system that recognize and efficiently take up nano-/microparticles, as they mimic the size of a pathogen (~0.1–10 μm), initiating adaptive immune responses. The size, the most prevalent physical property of the particulate delivery system, was shown to significantly impact on immunogenicity and the mode of immune response as previously reviewed [13]. In contrast to soluble antigens which are taken up by endocytosis [14],

Figure 1



Processing of antigen into a particulate vaccine. The different modes of antigen assembly and/or loading are depicted. As an example the TB antigen Rv1626 was selected. The depicted structural models were obtained from the protein data bank (PDB) as follows: 1S8N, crystal structure of Rv1626 from *Mycobacterium tuberculosis* and 5EZ8, a *de novo* designed heptameric coiled coil CC-Hept-I-C-I. See Table 1 for a list of carrier materials, antigen loading mode and relevance to immune response.

particles are phagocytosed [15]. The uptake of particles by phagocytosis into phagosomes has major consequences for antigen processing as it facilitates cross-presentation of antigen derived epitopes via MHC class I (stimulating naïve $CD8^+$ T cells) and MHC class II (stimulating naïve $CD4^+$ T cells) pathways [16]. Such cross-presentation not only stimulates $CD4^+$ Th1 and Th2 cells to induce B cells to initiate antibody responses but Th1 cells can also facilitate differentiation of $CD8^+$ T cells towards cytotoxic T cell responses i.e cell-mediated immune responses. Induction of Th1 cells is presumed to play a critical role for phagocytic responses via the production of pro-inflammatory cytokines.

Soluble antigens are predominantly loaded onto MHC class II molecules and hence are less likely to induce cytotoxic T-cell responses which also require MHC class I display [17]. These cell-mediated responses associated with stimulation of Th1 cells are important for protective immunity against intracellular pathogens such as *Mycobacterium tuberculosis* or viruses. The display of epitopes on MHC class II primes $CD4^+$ T cells to differentiate into Th1 and Th2 cells with the latter mediating antibody responses via stimulation of B lymphocytes i.e leading to humoral response. Such an antibody response is in particular relevant for protection against extracellular pathogens such as *Streptococcus pneumoniae*.

Particulate vaccines less than 200 nm in diameter can traffic to lymph nodes enabling direct interaction of displayed antigen with B cells. The possibility of designing particulate vaccines to display multiple repeats of antigens/epitopes enhances the interaction with naïve B cells via binding to the cognate B cell receptor (BCR) inducing antibody production i.e. a humoral immune response. These repetitive multivalent antigens efficiently activate B cells at much lower antigen concentrations than their monomeric counterparts likely avoiding the requirement for exogenous adjuvants [18].