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Editorial

Nanovaccine Delivery Systems in Vaccine Formulations

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Editorial

The important biological molecules such as polysaccharides, proteins, allergens and Pathogen Associated Molecular Patterns (PAMPs) are of nanometer in size. Hence, the size, charge, hydrophobic properties will influence their effects on the immune system by way of specific and varied response. Vaccines play a pivotal role in disease containment and prevention. One of the bottle necks is the vaccine administration system. Earlier vehicles and adjuvant systems pose unwanted reactions due to the nature of delivery system used in the vaccine. Delivery systems are those materials used for the administration of vaccines s in a controlled manner aimed to achieve a therapeutic effect. These systems provide: cell or tissue targeted delivery of the antigen, improved antigen presentation, solubility, sustained release and protection of the prophylactic agent from degradation.

Incorporation of adjuvants to vaccine to improve the quality of cellular and humoral response could be swapped for the recent intended use of nanoparticles that also provide adjuvant activity by enhancing the delivery of antigens to the immune system or by potentiating innate immune responses. Some of the proven nanoformulations include the concept of virus like particles which are cages into which the payload of antigens can be stuffed, such as the MF59 (Novartis). Other formulations using nanoscale materials such as dendrimers, spherical fullerence, cylindrical fullerence, micelle, liposomes, oil-in-water emulsion, and synthetic virus particles are either in the developmental or on the testing stages [1].

Nanoencapsulation involves forming antigen loaded particles with diameters ranging from 1 to 1000 nm, although other stricter definitions refer only to structures in the 1-100 nm range. This size property enables the nanoscale devices to readily interact with biomolecules, such as enzymes and receptors, both on the surface and inside the cells. Since the dawn of 1960, the initial liposomes mediated delivery systems gained momentum followed by complex delivery systems that took care of pH variations and targeted drug release.

Now a days, nanoparticles can be easily tuned to have unique physical characteristics in size, shape, surface chemistry, or targeted surface ligand/receptor. The benefits of nanoparticles as delivery tools are the reduction of the doses, tissue specific targeting, reduction of the toxic or secondary effects of the drug and increase in the delivery efficiency. The encapsulated molecules will generally have completely different properties (e.g., solubility or circulating half-life) compared to the non-encapsulated ones. Thus, it is very important to understand and control the *in vivo* behavior on cells or tissues of these bioactive compounds once encapsulated, to know their efficacy and side effects. The size of the nanoparticle is not only important for the interaction with biomolecules but also because it will influence its bio-distribution *in vivo*. In mammals it has been extensively studied that particles of less than 5 nm are cleared from the circulation through extravasation or renal clearance, whereas bigger nanoparticles (up to 15 μm) accumulate in the spleen, liver, and bone marrow. The particle size also influences the preferred mechanism of cellular internalization, such as phagocytosis, macropinocytosis, caveolae-mediated-endocytosis, or others. Nanoparticles can also facilitate the interaction of the delivered antigens with Antigen Presenting Cells (APCs), increasing the immune responses to antigens. Accordingly, nanovaccines have recently attracted a lot of interest owing to their unique properties to overcome the limitations of immunotherapeutics, including inherent instability of biomacromolecules, low interaction with APCs, and lack of cross-presentation to T lymphocytes. The immunostimulative biomolecules can be either encapsulated within or conjugated on the surface of polymeric nanoparticles.Different studies using the same nanoparticle with different surface charges have shown that those with cationic groups were internalized more efficiently, mostly due to the high affinity for the negatively charged proteoglycans present on the surface of cells [2].

Major delivery systems include the alginate a naturally occurring brown algae based polysaccharide which is formed by unbranched polyanionic polysaccharides. Chitosan particles and carbon nanotubes have been widely used for both bacterial and viral formulations. PLGA,

Poly (Lactic-co-Glycolic Acid) a biodegradable polymer are the most extensively investigated carrier for delivery systems. They can be packed as nano or microparticles based on the nature of delivery and formulations. Approach to develop new nanomaterials for *in vivo* delivery includes the calcium phosphate nanoparticles and solid lipid nanoparticles.

The encapsulated antigens modify the physico-chemical characteristics of the nanodelivery system so that the results of the assays on stability, size, surface charge, and organ biodistribution cannot be extrapolated from one molecule to another using the same encapsulating particle. Similarly, the characteristics of the antigen can be changed when it is encapsulated, and thus the functional structure, stability, and immunogenicity of the antigen need to be verified. For example, the size and the surface charge are extremely important for interaction with cells and should be characterized in the loaded system because they can change easily. Overall, the administration of nanoparticles by intraperitoneal injection in lab animal testing achieve good protection levels against infections compared to oral administration which is less efficient. One of the exceptions is the system developed with alginate or chitosan to encapsulate DNA vaccines. DNA vaccines are still under development and only one commercial vaccine has been licensed in Canada. They are the most promising tools to fight viral infections and thus, the development of novel encapsulation systems to improve their administration and the efficiency is very important [3].

Several new nanomaterials such as carbon nanotubes or solid lipid NP are still in the early steps of development but have shown promising results. It is important to mention that in some studies, the adjuvant effect of the nanodelivery system is almost as potent as the loaded antigen itself. The adjuvant effect of the system itself has been extensively reported in mammals in the use of liposomes. Currently, alum salts are the most widely used immune adjuvants, owing to their ability to trigger the so-called "inflammasome" mechanism in the cells. This mechanism leads to the increased release of danger signals from the cells and subsequent generation of a proinflammatory environment that cause the activation of the immune system. Despite the popularity of alum salts as immunadjuvants during the last few decades, they have some major limitations, such as adverse local reactions, lack of inducing cellular immune responses, degradation upon freeze-drying, and necessity of multiple administration for long lasting protection. These limitations have motivated scientists to find new vaccine delivery systems with the potential to circumvent the limitations of present immunoadjuvants and vaccines to effectively address these limitations, emulsions are among the suggested systems which may be applied in immunotherapy. Although some water-in-oil emulsions with the ability of forming depot at the injection site and attracting immune cells have already been developed, the adverse reactions associated to these adjuvants and its uncertain success have limited their application. Conversely, Oil-in- Water (O/W) emulsions have more suitable properties to be used as alternative vaccine adjuvants. MF59™ is considered as the first O/W emulsion with high safety profile approved in 1997 as adjuvant for influenza vaccine. This emulsion renders high efficiency to vaccines owing to immune adjuvanticity. In addition to emulsions, liposomes have also been proposed as alternative for the stimulation of the immune system. These particles are composed of vesicular phospholipid bilayers that are able to efficiently encapsulate antigens, deliver them to the APCs, facilitate the cross presentation of antigens, and promote cellular immune responses. Moreover, one of the unique benefits of these carriers is the possibility of co-encapsulation of immunostimulants.

Currently, virosomes are the most advanced liposomal structures developed as nanovaccines. One of the virosome-based nanovaccine licensed for influenza is called Inflexal V. where, two glycoproteins of influenza, including Hemagglutinin (HA) and neuraminidase are integrated onto the surface of liposomal structures by covalent or electrostatic interactions, increasing the chance of antigen capture and processing by APCs. The high immunotherapeutic effect of this compound is related to the ability of HA protein to fuse with the endosomal membrane and facilitates the escape of the virosome, thereby avoiding the destruction of the antigen. This property helps the antigen to be available for class I antigen presentation. Overall, despite the great versatility and promising features observed for the therapeutic potential of nanovaccines, intensive research studies are still needed in order to develop proper nanoformulations for immunotherapeutic applications that can be applied in the clinic [4].

The use of nanoparticles does also have some limitations. For example, their small size and large surface area can lead to particle aggregation and result in limited drug loading and burst release, making physical handling of nanoparticles difficult in liquid and dry forms. Another issue is the safety, not only of the delivery system itself but also of the degradation products of the nanoparticles. These biosafety issues should be carefully addressed to avoid environmental contamination that can provoke detrimental effects on human health.

Nanotechnology is currently being the most sought technology to engineer specific immune responses for prophylactic and therapeutic effects. In the future, the use of nanoparticles that have unique immunological properties determined by their size, shape, charge, porosity and hydrophobicity will enable researchers to 'customize' immune responses in new and unexpected ways. Nano-encapsulation is a very promising strategy with a potential to substantially improve the development of effective vaccines. The research on the delivery of viral vaccines using nanoparticles will be the more important milestone in vaccinology.

Despite the huge number of studies focusing on nano-based delivery system there are very low numbers of commercialized products as the formulations are in the testing state either in vitro or at *in vivo* lab animal trials. Nanovaccine formulations in theory may do not need any booster doses or to be maintained in a cold chain. Thus in future, more preclinical approach will facilitate development of these nanovaccines.

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