REVIEW ARTICLE

# Virus-like Particles-Application in Nano Vaccines: A Review

Ghassaq Tariq Alubaidi*

*Medical Research Unit, College of Medicine, Al-Nahrain University, Baghdad, Iraq*

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**ABSTRACT**

Nanomaterials are increasingly applied to develop new vaccines with new strategies. Implementation of such substances in vaccines will enhance vaccine formula immunogenicity, target delivery, and antigen stability control release. Genetically engineered virus-like particles (VLPs), structurally mimic the viruses and had been successfully used as nano vaccines. VLPs-based vaccines possess the advantage of being safe, effective, and non-infectious. Moreover, due to the optimized nano-size and repetitive structural units of the VLPs, it is suspected that those particles are highly immunogenic, even in absence of adjuvant substances. VLPs could be formulated to carry an array of heterogeneous antigens of different viruses. For all, they are considered as ideal nano vaccine model.

**Keywords:** Immunity to VLP, Nano vaccines, Virus-like particle (VLP).

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## INTRODUCTION

Vaccines possess a proud history as a successful prophylactic intervention to control disease outbreaks. According to the World Health Organization (WHO), vaccination is recognized as a substantial concept of human health rights, that it saves 2.5 million deaths annually.[1]

The concept of vaccination was first started in the late 18th century and continued to develop until the 21st, where molecular biology and genetic engineering paved the way to establish a new strategy in vaccine designation. Genome-based immunogen identification technologies have played a potential role in vaccine formulation through the screening of the whole potential antigens repertoire of the pathogen.[2] Most candidate vaccines represent minimalists compositions with inadequate immunogenicity, therefore, immune response stimulators and delivery systems are increasingly needed to get more efficient vaccines.[3]

Nanotechnology, which is the science that implies the application of particles in the nano-scale level (1–100 nm), would offer the opportunity to manufacture vaccines with unique properties regarding structure, size, shape, and surface properties. This will improve vaccines' intracellular delivery through the endocytosis mechanism, mainly pinocytosis. Such an application had led to the birth of a new branch in nanomedicine named "nanovaccinology".[4,5]

Nano vaccines typically comprised of antigens and nanoparticles, those materials conformational strategy could simply occur by physical adsorbance, such interaction is usually weak and dissociation easily occurs *in vivo* or could be in a more complex and stronger manner by chemical conjugation or antigens encapsulation inside nanoparticles.[6]

Nano vaccines can generally be classified according to the nanoparticle role. In some nano vaccines, nanoparticles act as a delivery vehicle to the immune cells, while in others, nanoparticles act as immune stimulator agents that will stimulate certain immune pathways to reach desirable immunogenicity.[7]

## VLPS STRUCTURE

The VLPs are self-assembly, non-replicative, and biocompatible nanoparticles, ranging in size between 20–800 nm in diameter, made of viral capsid proteins. VLPs could be of anthroponotic or zoonotic origin. They simulate natural viral vaccines regarding their interaction and stimulation for the immune response, with the further advantage of losing the infectious viral genome. Moreover, they possess the capability of delivering multiple immunogenic epitopes of different pathogens simultaneously.[8,9]

Structural proteins generating the VLPs architecture varies according to the biology of the virus: simple viral capsids one-two structural proteins, like human papillomavirus (HPV) and hepatitis-E virus (HEV), complex viral capsids with multiple layers of structural proteins could be translated from different mRNA or developed from single polypeptide (picornavirus), enveloped viral capsids, which is derived from host cellular membrane during the budding process, such capsid may further contain surface glycoprotein spikes (influenza virus).[10]

*Author for Correspondence: ghasaqtariq119@gmail.com

Although implying a variety of manufacturing technologies for VLP preparation, the traditional approach is the *in vivo* approach, that involves the self-assembly of capsid proteins inside the expression host. The assembled product (VLP) is then purified from the contaminants attached on its surface or encapsulated inside it. For extensive purification sometimes it is important to disassemble and reassemble the VLP.[11]

Recently, VLP-based vaccines are manufactured *in vitro* cell-free regimen; this technique implies, first a large scale of purification to the VLP building blocks from contaminants, followed by their *in vitro* assembly, by this avoiding the disassemble-reassemble step.[12]

VLP was confirmed to have excellent immunogenicity, for instance, the VLP vaccine made of major capsid structural protein L1 of HPV-16 was reported to induce high titer of neutralizing antibodies leading to protection against this virus, which is associated with cervical cancer.[13] For further potentiation of VLPs immunogenicity, they are linked to immunostimulators. For instance, the non-toxic subunits of cholera toxin-B (CTB), when chemically conjugated to VLP via biotin-streptavidin, induced higher titer of serum specific IgG1 antibodies, secretory IgA antibodies, and cellular immune response compared to the free or co-injected CTB.[13]

Organisms with big genome usually possess genes that induce protective immunity together with genes that inhibit the hosts from elucidating protective immunity, therefore, the right mixture of antigens should be carefully selected and prepared for application. Also, a solution to pathogens with the continuous mutation is the implementation of VLPs that display multiple antigens together.[14] Selection of the appropriate vaccine antigen is recently being revolutionized and improved through the emersion of several technologies, like genomics, transcriptomics, proteomics, immunomics, and bioinformatics analysis. This is conducted through the identification of the target epitopes and virulence factors, and the prediction of the suspected induced immune response.[15]

The *in silico* predicted target proteins are expressed recombinantly as surface antigens, or as secreted in monomeric or oligomeric forms, then purified *in vitro*, and finally evaluate its immunogenicity through its *in vivo* injection to assess the capability to reach protective immune response level.[1]

VLP based vaccines have the strongest evidence-based safe for use in humans, which made them the first nanoparticles class vaccines to reach the market. The first commercialized VLP was in 1986 for Hepatitis B virus (HBV). Newer VLP vaccines for HPV and HEV were approved to be used in humans in 2006 and 2011, respectively. Others, like parvovirus, Norwalk virus, and influenza virus vaccines are still in the preclinical and clinical phases.[12]

## IMMUNE RESPONSE TO VLPS

VLPs can be introduced subcutaneously, intraperitoneally, and intramuscularly. Due to the advantage of the possibility of exposing an array of antigens simultaneously on the VLP surface, those particles are considered as powerful tools for vaccinology. VLPs are more immunogenic than subunit and recombinant proteins. They are capable of inducing both innate and adaptive immune responses, through the induction of innate immunity via toll-like receptors (TLRs) and pattern recognition receptors (PRRs), enhance antigen presenting cell (APCs) maturation, antigens processing, and presentation. They also induce humoral immunity in T-cell independently.[1]

Some VLPs do not need adjuvants since their small size is considered as an inherent self-adjuvant criterion. Upon VLP uptake by the denderitic cell (DC), they will be processed and presented by the MHC-II activating CD-4 T-cell. Moreover,VLPs are able to be cross-presented by the MHC-I that will subsequently activate CD-8 T-cell against intracellular pathogens.[16,17] Activation of DC to produce interferon-gamma and alfa does not require the viral replication, it requires only the intact viral capsid proteins or the non-enveloped VLP as in the HPV-VLP vaccine. This criterion makes VLP vaccine superior to the live attenuated viral vaccine, since viruses that replicate in the DC impede cell maturation and replication via expression of certain viral proteins.[18,19]

In addition to the presentation of an array of target epitopes on the VLPs surface in a high density, imitating the structure of the native virions regarding the spatial construction facilitates, the correct detection of the conformational epitopes by the host immune system will subsequently lead to an upsurge in specific neutralizing antibodies titer. This is mainly true for enveloped VLP displaying structural proteins in a membrane-anchored pattern similar to the native virions. On the other hand, soluble proteins as ectodomains were found to be ineffective.[20,21] VLPs possess the potential for specific-organ transportation since it is composed of capsid proteins of the original viruses, so will have the same tissue tropism.[22]

Pattern recognition receptor ligands could be conjugated to the VLP vaccines as immunostimulators to strengthen the immune response, represented by upsurge germinal center response accompanied with robust production of IgG neutralizing antibodies in a short time; this is accomplished through bypassing T-cell dependency.[23] Hepatitis-B virus vaccine is a successful model for the VLPs. It contains multivalent envelope antigens, thus, mimicking the authentic HBV envelope. This vaccine induces the production of more specific antibodies than traditional vaccines, due to the detection of additional T-cell epitopes that improve the seroprotection rate.[24]

## CONCLUSION

Nanoparticles-based vaccines in different compositions, size, and surface properties are approved for human use, and candidates are increasing. However, challenges remain to exist regarding the poor understanding of the behavior of nanoparticles as a delivery system and as immunostimulators.

The emergence of VLP has revolutionized vaccine development. The novel VLP vaccination technology relays on mimicking the construct of authentic viruses with the further advantage of absent viral genetic material that will make those novel vaccines safer than the traditional viral

vaccines. Moreover, an effective immune response has been recorded following VLP *in vivo* admission. The biofabrication of the repetitive surface of VLP is applied for nano vaccines production, such modular VLP vaccines via their nano-size and unique constructors of certain target antigens, will allow targeting the diseases in a bioengineered pattern. Immunologically, their small size facilitates its entry to the lymphatic vessels and the regional lymph nodes, activating the innate immune response, where they will be processed and presented by the MHC-I and MHC-II of the resident dendritic cells.

Approved VLP is commercially present for several infectious diseases. With further interest to expand the list of applicable VLP, several VLP vaccines are in the preclinical and clinical phases.

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