Self-assembling protein nanoparticles open a new avenue for next generation veterinary vaccines

Abstract
Vaccines are one of the most outstanding innovations in public health. They save millions of lives by the prevention of infectious diseases. Throughout the past two centuries, most vaccines have been formulated by live or killed whole pathogens. Live vaccines have a safety issue that is a risk of reverting back to their virulent state. Kill vaccines have weak immunogenicity and are cumbersome to manufacture. Nanobiotechnology has emerged as a powerful alternative platform in vaccine design, which addresses the safety issue as well as enhancing the immunogenicity of vaccines. Self-assembling protein nanoparticles is one of the most promising platform (SAPN) at nanoscale. In this mini-review, we primarily focus on the discussion of the concept of nanovaccine and the principle of SAPN in vaccine development, and will highlight its applications in designing vaccines for veterinary use.

Keywords: self-assembling, protein nanoparticles, vaccines, avian, influenza, infectious bronchitis

Introduction
Vaccines have been implemented for more than two centuries and have saved millions of lives, which is one of the most outstanding inventions in medicine. The concept of vaccine was conceived two centuries ago by the English physician Edward Jenner, “the father of immunology”. He had initiated the first protective vaccine against smallpox using live cowpox virus in 1798. Many effective vaccines have been developed in the past two hundred years. The majority of them was produced by traditional methods by attenuating live pathogens or by chemically inactivate whole pathogenic organisms. Live attenuated vaccines are highly protective but bear inherent safety concern due to the potential reactivation of virulent state. In contrast, chemically inactivated vaccines cannot regain the virulent state of derivative pathogens and are safe. However, they are poorly immunogenic, and induce weak protection. Besides, tediously labor-intensive efforts are required for formulation preparation of killed vaccines.

The breakthrough progress of genetic engineering in the 1980s allows vaccinologists to address the safety concerns by developing subunit vaccines, which contain one or multiple antigens from a whole pathogen. In this mini-review, we will discuss the application of self-assembled protein nanoparticles in the development of safe subunit vaccines, and will highlight the current progress of its application in poultry vaccines.

Origination of the concept of nanovaccine and its advantages
The vaccine against Hepatitis B is the first successful application of the concept of a nanoparticle-based vaccine. The surface antigen of hepatitis B (HBsAg) was the first antigen synthesized and assembled into nanoparticles (NP) in yeast using recombinant DNA technology, which are similar to 22 nm virus-like particles (VLP) secreted by infected human cells. The genetically engineering vaccine against Hepatitis B was licensed in 1986. Since then, the concept of nanoparticle vaccine or nano scale vaccine has been expanded to the design of immunogens using a wide range of carrier materials at nano scale from 1–1000nm, which include VLPs, virosomes, liposome, emulsion, polymer-copolymer NP, viral vector, immune-stimulating complex (ISCOM) and self-assembling protein nanoparticle. NP vaccines are safe due to their non-replicable nature. They can be easily engulfed by antigen presenting cells because they have well-defined shape and size resembling a virus particle. NP is typically constructed using a repetitive building scaffold. Thru, NP vaccines have repetitive epitopes on their surfaces. This feature constitutes a multivalence, which is able to cross-link B cell receptors and results in the maturation of naïve B cells. In addition, NP vaccines have also been demonstrated induces memory cytotoxic T cell responses against malaria via cross-presentation, which was associated with antigen-associated protein in early endosomes. Most importantly, NP vaccines have demonstrated to be self-adjuvanted by co-displaying immune-stimulatory molecules. Therefore, the application of NP vaccines offers an excellent solution to the long-standing issue of safety versus immunogenicity.

Principle of SAPN as vaccine platform
Among different categories of NP vaccines, self-assembled protein nanoparticles (SAPN), based on coiled-coil folding domains, have emerged as one of most appealing tools in vaccine design. The α-helical coiled-coils are highly versatile protein oligomerization domains characterized by seven-residue repeats called heptad repeats (Figure 1A). Apolar residues preferentially occur in the first (a) or in the fourth (d) position within a unit of heptad repeat whereas the fifth (e) or the seventh (g) position prefers charged residues. A linear peptide chain that containing heptad repeats is able to self-assemble into a left-handed α-helix driven by intramolecularly hydrophobic interaction between ‘a’ and ‘d’ apolar residues (Figure 1A). The α-helix is also stabilized by intramolecular ionic interaction between ‘e’ and ‘g’ charged residues. Coiled-coils consist of two to five α-helices and can self-assemble into supercoils via intramolecular ‘knobs-into-holes’ interaction to form a hydrophobic core, in which the quaternary structure of supercoils is stabilized by intermolecular ionic interactions between side chains of charged residues (Figure 1B). This is the principle of oligomerization of coiled-coil domains, which could be used to produce nanoparticles. It was demonstrated by Peter Burkhard group that chimeric peptides containing two coiled coils...
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