Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Platform technologies for modern vaccine manufacturing

Hayley K. Charlton Hume, Linda H.L. Lua *

The University of Queensland, Protein Expression Facility, St Lucia, QLD 4072, Australia

ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Virus-like particle
Liposome
Vaccine design
Modular
Platform technology

ABSTRACT

Improved understanding of antigenic components and their interaction with the immune system, as supported by computational tools, permits a sophisticated approach to modern vaccine design. Vaccine platforms provide an effective tool by which strategically designed peptide and protein antigens are modularized to enhance their immunogenicity. These modular vaccine platforms can overcome issues faced by traditional vaccine manufacturing and have the potential to generate safe vaccines, rapidly and at a low cost. This review introduces two promising platforms based on virus-like particle and liposome, and discusses the methodologies and challenges.

1. Advancing from traditional vaccine production

Vaccination continues to be a leading defense strategy against infectious pathogens. Traditional vaccines that employ whole-cell antigens to raise an immune response have been irrefutably successful in the control or localized eradication of diseases such as poliomyelitis, measles, mumps, rubella, influenza and hepatitis A and B [1–3]. Eradication of smallpox was declared in 1980 after a global immunization effort by WHO [4]. Rinderpest was the second disease globally eradicated by traditional vaccine means as declared by the World Organization for Animal Health in 2011 [5]. Despite this success, live attenuated and inactivated vaccines possess several major drawbacks. Both live attenuated and inactivated vaccines require the production of large volumes of pathogens in the form of viruses and bacteria. This lengthy culturing process contributes to a considerable lag time between antigen production and vaccine delivery. Furthermore, it demands specialized containment facilities and poses considerable risk to the operators and environment due to the infectious nature of the material [6,7]. Despite adequate passaging to diminish virulence, live attenuated pathogens are capable of reverting to virulent strains as evidenced with simian immunodeficiency virus [8], African horse sickness [9] and infectious bronchitis virus vaccines [10]. The genuine threat of vaccine-derived polio associated with Sabin's oral polio vaccine has hindered immunization programs worldwide [11,12]. Inactivated polio vaccine has less of a biosafety risk to vaccine recipients as inactivated poliovirus is incapable of replication, thereby eliminating the possibility of vaccine-derived polio. However, inactivation of microorganisms can compromise the native conformation of antigenic epitopes resulting in reduced immunogenicity [13]. Pathogens that display high levels of antigenicity owing to high mutation rates (e.g. RNA viruses such as influenza and human immunodeficiency virus [14,15]) or existing as multiple genotypes and serotypes (e.g. rotavirus [16,17], enterovirus [18] and the Group A Streptococcus [19]) present a challenge for developing efficacious vaccines. While this is an important consideration for all vaccine manufacturing platforms, the current timescale of traditional vaccine manufacturing highlights their inadequacy.

Outbreaks of H1N1 influenza, Middle East Respiratory Syndrome, Ebola and Zika over the last decade, are timely reminders that improved modern vaccine technology is necessary to shorten the developmental and production time of vaccines. Vaccine platform technologies, the formulation of antigens of choice with a pre-defined platform base, have the potential to address vaccine manufacturing challenges such as speed, safety and efficacy. Platforms based on virus-like particle (VLP) and liposomes are discussed, with a focus on the challenges and opportunities offered by these vaccine platform technologies.

2. Modular vaccine approach

A tailorable platform that supports safe and simple manufacture of target antigens at high capacity has the potential to rapidly respond to an emerging disease. Most vaccine platform technologies consist of a platform base carrier (Fig. 1) that is amendable to modularization with target antigenic components of pathogens (known as modules). Independently, these components exhibit weak immunogenicity and poor stability. To harness the

* Corresponding author.
E-mail address: l.lua@uq.edu.au (L.H.L. Lua).

http://dx.doi.org/10.1016/j.vaccine.2017.02.069
0264-410X/

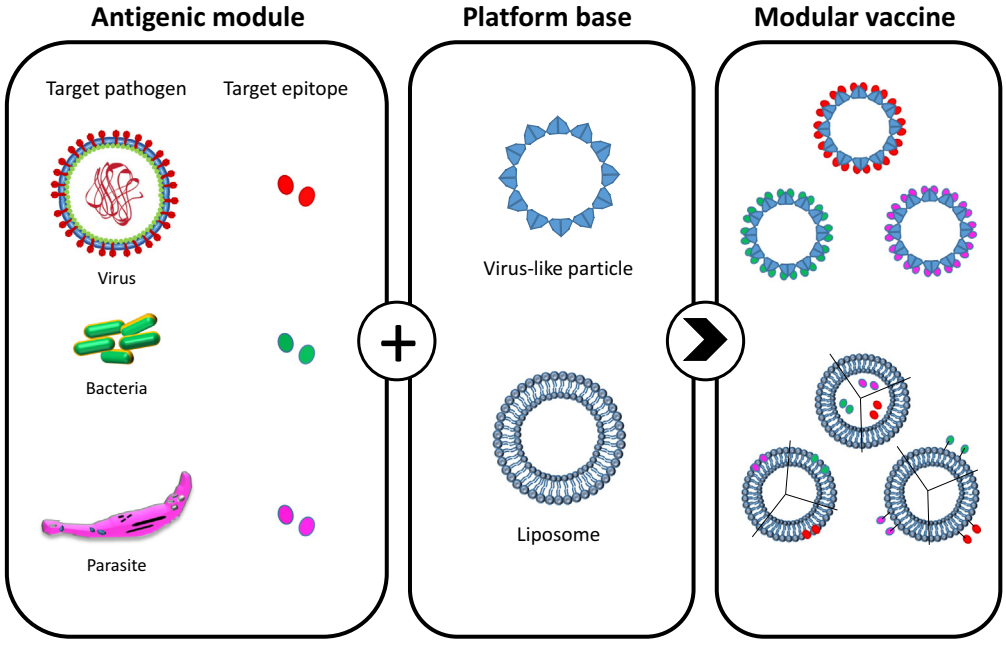

Fig. 1. Modularization of target epitopes onto VLP and liposome vaccine platforms. Antigenic modules from a variety of microorganisms may be modularized onto the surface of VLPs through electrostatic interaction, chemical conjugation or genetic fusion. In liposomes, these antigenic modules may be encapsulated into the aqueous core, adsorbed into the lipid bilayer or conjugated (both covalently or non-covalently) to the vesicle surface.

immunostimulatory properties of such antigens, platform carriers are engineered and developed to enhance the antigenicity but without the infectious trait of pathogens. Such engineering also allows the production of novel vaccine candidates that cannot be obtained through traditional methods (attenuation and inactivation). Basic research to determine suitable modules with antigenic potential is a prerequisite of this modular approach, yet the use of generic platforms supports streamlined and standardized vaccine development, potentially reducing the cost of development.

A well-exploited platform is based on VLP technology. VLPs are highly ordered structures, with varying degrees of complexity, which stimulate both innate and adaptive immune responses [20,21]. These intrinsic properties contributed to the commercialization of VLP-based vaccines against human papillomavirus (HPV), hepatitis B and E [22–24]. The self-adjuvanting properties of VLPs, due to their particulate structure and optimal size for uptake by antigen presenting cells [20,25], makes them an attractive tool for increasing the immunogenicity of antigens. Antigens encapsulated within VLPs can also be used as vectors for drug delivery [26]. Well reported platforms based on self-assembling proteins include HPV L1 [27], Hepatitis B core [28] or surface antigen [29,30], murine polyomavirus VP1 [31,32] and bacteriophages MS2 [33], AP205 [34,35] and Qβ [36]. High antigen-specific antibody titers and protective efficacies have been demonstrated across a range of peptide epitopes and protein domains modularized onto these VLP platforms. As reported, a pre-existing immunity against the VLP proteins from previous exposure to the platform does not diminish the immune response against the antigenic modules [37,38]. Mosquirix™ (RTS,S/ASO1, GlaxoSmithKline), a protein-based malaria vaccine comprising circumsporozoite protein and Hepatitis B surface antigen, has demonstrated safety and protection in children and infants in a Phase III trial [39], and WHO has recently announced the first pilot studies in sub-Saharan Africa [40].

Liposomes are another favorable vaccine platform owing to their natural ability to induce an immune response [41]. Composed of an aqueous core and a uni- or multilamellar phospholipid bilayer, these lipid-based vesicles have immense adaptability and parameters with relation to size, charge, lipid, adjuvant composition and antigen presentation are manipulable [42]. As a result of this versatility, liposomal-based platforms are less well-defined than VLP-based platforms. Surface charge of the vesicle is reported to be an important factor that influences the immune response [42–44]. Cationic formulations are considered the most effective tools in liposomal antigen delivery due to their ability to bind antigen presenting cells through electrostatic interactions and form antigen depots at the site of injection [45,46]. The combination of positively charged dimethyldioctadecylammonium (DDA) with the immunostimulant, trehalose-6,6-dibehenate (TDB) was engineered for the delivery of the tuberculosis antigen, Ag85B-ESAT-6 [45] and is possibly the best characterized. DDA:TDB is also considered as a potential platform for *Chlamydia* vaccines [47].

3. Vaccine design

The strategy for modularizing antigenic peptide or protein module onto the platform base is the key driver for inducing the protective immune response. Maintaining both the native conformational structure of the antigenic module post modularization and the integrity of the immunostimulating platform base are of equal importance. The rules to guide vaccine design are still limited. Although computational simulation tools and structure-based vaccine design are still in their infancy, they offer alternative possibilities to traditional empirical vaccine development [48,49].

Modularization of chosen antigens onto VLPs is achieved through electrostatic interaction [50], chemical conjugation or genetic fusion [51]. Electrostatic interaction requires minimal processing but these non-covalent interactions can be weak and stability is questionable. A variety of linkage chemistries suitable for chemical conjugation result in a more permanent interaction albeit this requires more complex manufacturing processes under potentially harsh conditions that may alter protein structure. Permanent and regular module display is afforded through genetic fusion, eliminating downstream processing yet insertion sites for modules

Please cite this article in press as: Charlton Hume HK, Lua LHL. Platform technologies for modern vaccine manufacturing. Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.02.069