New approaches to VLP-based vaccines

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Vaccination is a long and established field of research, and outputs from the research have saved countless millions of lives. The early vaccines were developed with scant regard for the immunological mechanisms at play, largely because they were unknown. We are now in a position to use our knowledge of immunology to rationally design vaccines. This article focusses on the use of virus-like particles (VLPs) as vaccines.

VLPs successfully prevent human papilloma (HPV) and hepatitis B virus (HBV) infections, but they may be exploited for novel uses as shown in Figure 1. VLPs are empty protein capsids formed by the self-assembly of viral proteins without any viral nucleic acids: therefore there is little chance of pathogenicity[1]. The primary prerequisite for the production of VLPs is to produce viral proteins which have the capacity to self-assemble into VLPs[2]. Bacterial, yeast, insect and plant expression systems are used depending on the nature of protein being produced. Proteins which do not require any post translational modifications can be expressed in a prokaryotic host like *E. coli*, and those requiring these modifications can be expressed in eukaryotic hosts such as yeasts (e.g. *S. cerevisiae* and *P. pastoris*). Two commercially available VLP-based vaccines are those for HBV and HPV. Despite WHO recommendations to incorporate HBV vaccine in the childhood immunisation schedule, only 76% of countries implemented it by 2003[3]. This percentage was increased to 90% by 2013 due to its displayed success in HBV prevention[4]. The first quadrivalent HPV vaccine, Gardasil was licensed in 2006 with considerable success in prevention, despite some ongoing debate on its side-effects[5]. The possible reason for the success of the HPV vaccine is that its prolonged infectious cycle enables the induction of strong inhibitory humoral responses[6]. VLPs are also being trialled in gene therapy and DNA vaccine delivery. Yeast transposon VLPs (Ty-VLPs) are native transposition intermediates in various species of *Saccharomyces* and are similar to that of retroviral cores[7]. Their application for HIV-1 p24 antigen delivery as a subunit vaccine was successful *in vivo*, eliciting specific immune responses[8]. Ty-VLPs are capable of holding 5.7 kb Ty1-RNA[9], hence they might have gene delivery ability also. This application was not explored previously. Therefore we investigated the efficiency of these Ty-VLPs to deliver plasmid DNA to dendritic cells[10], and an increased transfection efficiency was observed compared to naked plasmid (Figure 2). Dendritic cells were chosen for *in vitro* study as they are the main antigen presenting cells in the mammalian immune system[11]. They preferentially take up nanoparticles within the viral size range of 20–200 nm[12]. Some other types of VLPs such as polyoma[13] and various types of papilloma VLPs[14,15] were reported for their gene and DNA delivery abilities.

Chimeric or hybrid VLPs produced by the engineering of surface exposed amino acids on VLPs are also under study, as well as chimeric VLPs loaded with drugs[16], and multiple antigens[17].

The main criteria for a successful VLP-based vaccine is the ease of efficient scale up and approval by the FDA for use in humans. A 'selective flocculation and precipitation method' for scaling up of virus yield at the commercial level was developed with a significant improved yield[18]. The effects of sparging, agitation and bioreactor scale on baculovirus-insect cell line growth, infection kinetics and productivity of *Porcine parvovirus* VLP production at the commercial scale was studied and highlighted their importance[19].

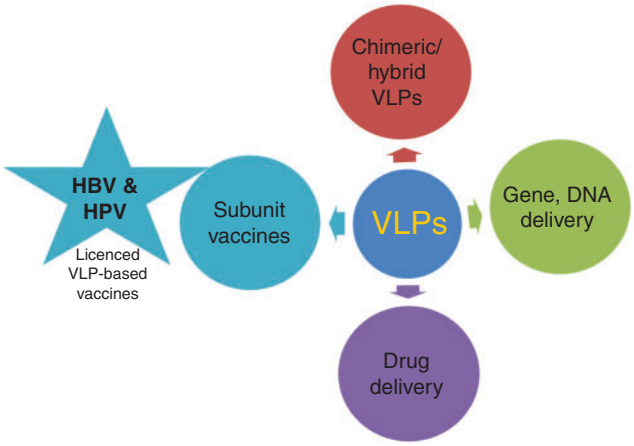

Figure 1. Main applications of VLPs.

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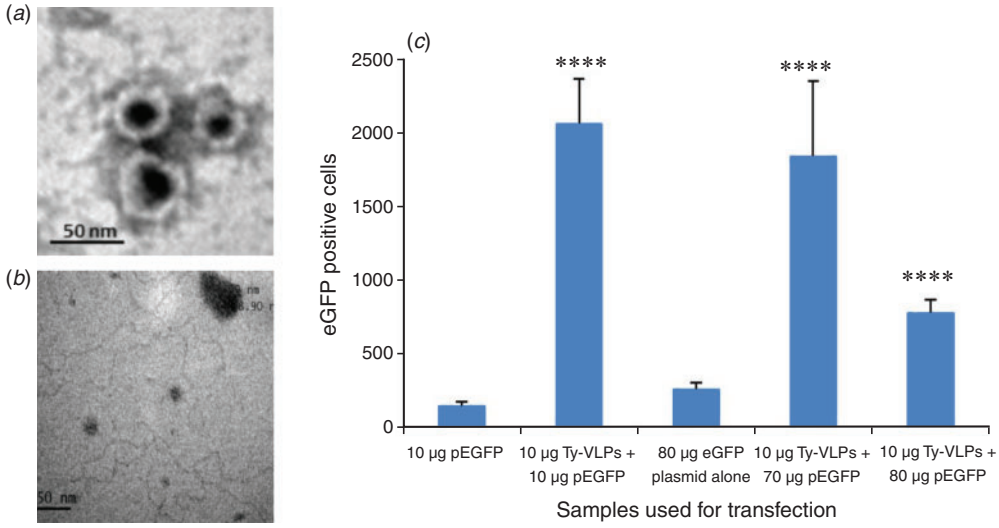

Figure 2. (*a*) TEM image of Ty-VLPs, (*b*) TEM image of Ty-VLP/DNA complexes, (*c*) *in vitro* transfection of DC2.4 cells with various ratios of Ty-VLP/DNA complexes.

Many VLP-based vaccines are at various stages of clinical trials and the chances of their success seems high judging from their laboratory level efficiency. Interestingly a VLP vaccine designed for hypersensitivity[20] was successful in pre-clinical and phase-I trials and is under further clinical trials. The practical utility of many VLP-based vaccines is being restricted due to their limitation to incorporate large antigens and difficulties in commercial scale production[21]. Therefore, more research needs to be undertaken in terms of developing commercial scale-up methods and choosing suitable protein subunits of the virus to produce effective VLPs, which may elicit robust immunity.

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Biographies

Alekhya Penumarthi is a PhD candidate in Professor Peter Smookers' Biotechnology lab in RMIT University, who is currently writing her thesis. She completed her Master's degree in Virology from Sri Venkateswara University, Tirupati, India. Her research interest is in utilising virus like particles and nanoparticles in vaccine development, particularly for DNA vaccine delivery.

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