

VIRUS-LIKE PARTICLES: A FLEXIBLE PLATFORM FOR UNIVERSAL INFLUENZA VACCINE DEVELOPMENT

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Key Words: Virus-like particles, *Pichia pastoris*, Tandem core, Hepatitis B core protein (HBcAg)

Human influenza remains a global public health threat, namely due to its evolutionary adaptability, which hinders effective prevention. Vaccination is currently the predominant tool in the prevention of infectious disease. However, current production methods for influenza vaccines are not only logistically inadequate in the face of a pandemic, but also rely on targeting two surface proteins on the influenza virus, which are prone to antigenic drift. As a consequence, a new vaccine needs to be developed for each new seasonal epidemic. Additionally, the vaccine strain needs to be selected around eight months prior to administration and can often be mismatched leaving the population unprotected. A 'universal' vaccine, effective irrespective of the surface proteins, would be desirable to offer cross-protectivity across strains.

Tandem core virus-like particles (VLPs), expressed in methylotrophic yeast *Pichia pastoris*, are an exciting alternative to current manufacturing methods. VLPs, due to their inherent safety profile and advances in genetic engineering, have excellent potential both as standalone vaccines for the virus from which they are derived, or as platforms for the display of foreign antigens. The hepatitis B core antigen (HBcAg) is able to spontaneously self-assemble, forming icosahedral particles that are inherently immunogenic. Moreover, the HBcAg is capable of carrying antigen inserts in the major insertion region (MIR) which are displayed on the particle surface. In order for VLPs to be considered a viable alternative, their bioprocessing must be optimized. Currently, various issues are at play including problems with formation, solubility and immunogenicity, often clone dependent. In this work, two genetically linked HBcAg monomers, carrying different inserts in the MIR, were used to study the effects on fermentation efficiencies using two different induction strategies. Rationalizing an induction strategy would enable the development of an efficient process to produce and purify VLPs. Results indicate that increased biomass is not always synonymous with increased protein expression. Moreover, protein expression and solubility appear to be linked with the complexity of the inserts displayed on the VLP surface.

The aim of this work is to improve the bioprocessing of VLPs in a microbial expression system, using tandem core technology. This proposed method is cheap and rapidly scalable, reduces the cost per dose and eliminates the long production timelines associated with current manufacturing. The very nature of VLPs and the comparable ease of production would enable this to be promoted as a platform process, for a myriad of disease targets.