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The economics of virus-like particle and capsomere vaccines☆

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ABSTRACT

Effective control of infectious diseases relies on new vaccine technologies that can quicken and broaden vaccine delivery. Novel modular virus-like particle (VLP) and capsomere technologies have been recently reported. These technologies utilize murine polyomavirus (MuPyV) VLPs and capsomeres as potent delivery systems to carry and display antigenic modules consisting of heterologous peptides, in the form of modular constructs capable of inducing high levels of specific antibodies against bacterial or viral antigens. These constructs are prepared using high-yield microbial synthesis, potentially enabling low-cost, rapid and scalable manufacture of new vaccines. To evaluate this potential, this study analyzes the economics of capsomere and VLP production using process simulation. Data here show that the unit production cost (UPC) for capsomere is up to 69% lower than that for VLP at the comparison scale (500 L fermentor), due to a simpler downstream process and a higher product yield. For VLP production, reactive diafiltration assembly was shown to have a UPC 30% lower than dilution assembly. Sensitivity analysis of uncertain process inputs with Monte Carlo simulations revealed a significant influence of final biomass concentration on UPC, contributing up to 50% of variance observed in the UPC probability distribution. Despite such process variability, optimized capsomere or VLP vaccine production, using a 500-L or 1500-L fermentor respectively, has more than 80% chance of producing vaccine at a cost less than 1 cent per dose based on a conservative assumption of 50 μg protein per vaccine dose. With a 10-kL fermentor, both the capsomere and VLP processes have productivity that could allow manufacture of 320 million vaccine doses in 2.3 and 4.7 days, respectively. This study confirms with quantitative data the possible economic, speed and scale benefits of the modular capsomere and VLP vaccine technologies, which can potentially redefine current vaccine distribution landscape and time-scale benchmarks.

1. Introduction

Vaccination is critical in reducing the global burden of infectious diseases underscored by the 15 million disease-related deaths recorded annually, half of which were of children under 5 years of age in 2004 [1]. The introduction of smallpox, polio and measles vaccines has generated a substantial public health impact in the past [2–4], and continued immunization programs are forecast to avert more than 23.3 million deaths in low-income countries (LICs) over 2011–2020 [5]. However, significant challenges remain, particularly due to high production cost limiting vaccine access and slow manufacture leading to vaccine shortages during pandemics [6]. The cost factor affects primarily developing countries while the deficiency in technological response to pandemic emergence impacts both developing and developed nations.

An approach to engineer and manufacture modular murine polyomavirus (MuPyV) virus-like particle (VLP) [7] or capsomere [8] vaccines has been reported with promising pre-clinical results [6,9–11]. These vaccines could potentially be delivered to the society rapidly and economically as they are synthesized with a fast and scalable microbial platform at grams-per-liter levels [12,13]. MuPyV VLPs are virus-mimicking structures (45–50 nm [14]) assembled from 72 subunits known as capsomeres, which are in turn pentamers of the MuPyV major structural protein VP1. The MuPyV VLPs and capsomeres were engineered in this approach as delivery systems for heterologous antigenic peptide modules which are usually non-immunogenic on their own [15,16]. The VLP and capsomere delivery systems are potent as they possess the viral structural signatures, and for VLP, the optimum size for immune cell uptake [15]. When evaluated *in vivo*, high levels of peptide-specific

☆ The University of Queensland (UQ) filed patents on the use of MuPyV as a vaccine platform. L.H.L.L. and A.P.J.M. contributed to those patents and, through their employment with UQ, hold an indirect interest in this intellectual property.

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Table 1
Process economics of CAP, VLPDIL and VLPDIA based on a 500-L fermentor.

	CAP	VLPDIL	VLPDIA
Investment ($)	17 285 008	25 065 686	19 693 170
Unit production cost, (UPC) ($ kg^{-1})	81 608	266 069	187 658
Production rate (kg yr^{-1})	115.7	48.3	56.7
Operating cost ($ yr^{-1})	9 441 621	12 855 169	10 631 488
Operating cost component ($ yr^{-1})			
Raw materials	2 594 825 (27%)	3 110 965 (24%)	2 894 086 (27%)
Equipment dependent	2 999 110 (32%)	4 365 016 (34%)	3 419 720 (32%)
Labor	2 686 547 (28%)	3 812 435 (30%)	2 951 365 (28%)
Consumables	483 142 (5%)	593 025 (5%)	587 849 (6%)
Quality control (QC) and assurance (QA)	402 982 (4%)	571 865 (4%)	442 705 (4%)
Utilities	5221 (<1%)	6195 (<1%)	5709 (<1%)
Waste treatment and disposal	269 794 (3%)	395 669 (3%)	330 055 (3%)
Operating cost by section ($ yr^{-1})			
Fermentation	3 753 247 (40%)	3 753 976 (29%)	3 746 878 (35%)
Primary recovery	2 120 462 (22%)	2 113 198 (16%)	2 120 027 (20%)
Chromatography	3 285 807 (35%)	3 271 164 (25%)	3 285 730 (31%)
Assembly	0	1 739 011 (14%)	425 328 (4%)
Aggregate removal	0	1 485 718 (12%)	803 406 (8%)
Formulation	282 105 (3%)	510 120 (4%)	250 120 (2%)

antibodies were achieved using modular VLPs without adjuvant [6,10,11], or with adjuvanted modular capsomeres [9,10].

The overall production methods for modular VLPs and capsomeres are outlined as follows. First, the heterologous antigenic module of interest is fused to the MuPyV VP1 protein at the DNA level [6], and the resultant modular proteins are synthesized intracellularly in *Escherichia coli* (*E. coli*). The synthesized modular proteins are purified as capsomeres [17] and assembled *in vitro* into VLPs [18–20] as the final product. Alternatively, the unassembled capsomeres may be formulated as the final vaccine product [6,9]. For this purpose, the capsomeres are re-engineered for enhanced stability and increased capacity for module display [6,9], and synthesized and purified using the aforementioned procedures. Direct use of capsomeres as vaccines eliminates additional procedures involved in VLP assembly and purification, potentially reducing vaccine costs. This strategy also allows a greater level of antigen incorporation as the N- and C-terminal sites of the MuPyV VP1 protein, normally reserved for VLP assembly, become available for modularization.

This study presents rigorous economic analyses of modular VLP and capsomere vaccine production. Using process models coupled with Monte Carlo stochastic simulations, the probability distribution of each modular system to produce vaccine at a cost below 1 cent per dose was investigated. In particular, uncertainty analysis was performed to interrogate the impact of variability in selected process parameters on unit production cost (UPC). Economic benefits were compared between capsomere and VLP production, and between different methods of VLP production. Additionally the speed- and scale-capabilities of the capsomere and VLP vaccine technologies in responding to a public health emergency were assessed based on a 10 kL fermentor.

2. Methods

2.1. Simulation software and bases

SuperPro Designer® (version 8.5, Intelligen Inc., Scotch Plains, NJ, USA) was used for process simulation, handling material and energy balances, equipment sizing, cost evaluation and process scheduling. Material data and costs in the software database were used where available. Other material costs were estimated based on data available at the ICIS website [21]. The software built-in cost model (2013 prices) was used for economic analysis.

Monte Carlo simulations for uncertainty analysis were performed by integrating Crystal Ball® (version 11.1, Oracle Corporation, Redwood Shores, CA) with SuperPro® via Excel® (version 2007, Microsoft, Redmond, WA). Briefly, uncertain input variables and their probability distributions were first defined in Excel® using the Crystal Ball® add-in. Specifically written Visual Basic for Applications (VBA) scripts were then executed to (i) import the randomly generated values of the uncertain variables from Excel® into SuperPro® as simulation inputs; (ii) instruct material and economic calculations; and (iii) export the calculated unit production cost (UPC) back to Excel®. Outputs from 5000 scenarios (trials) were recorded and analyzed with Crystal Ball® to generate probability distributions and sensitivity analyses. In all simulations reported, the distribution mean standard errors were less than 1%.

Simulation was based on an annual operating time of 79 200 h (330 days), with a production cycle time of 40.7 h, which means that in a multiple batches scenario with staggered scheduling strategy, product can be obtained every 40.7 h. The primary design objective was to lower the UPC to 1 cent per dose of vaccine. For simplicity, capsomeres used for capsomere vaccine formulation and as the precursor for VLP are both assumed to be the same component (molecular weight = 212 500 g mol^{-1}) in simulations. The cost of energy and utilities used for heating or cooling were built-in within each unit operation in the simulation package. The cost of all waste treatment or disposal was considered in the economic analysis and is listed in Tables 1 and 3 as "Waste treatment and disposal". The simulation was performed for a pharmaceutical plant located in New Jersey, USA, home to pharmaceutical industry giants, such Merck & Co. and Johnson & Johnson.

2.2. Process description

Process designs for capsomere and VLP production were based on the processing scheme described previously [6], adapted for industrial-scale production. Fig. 1 shows the process flowsheet which describes production of purified capsomere, and is identical within all processing routes investigated (described below). The flowsheet depicts unit procedures in the: (i) fermentation section for medium preparation, air filtration and bioreaction; (ii) primary recovery section for biomass harvest, cell disruption and filtration to remove cell debris; and (iii) purification section for isolation of capsomeres from host cell proteins (HCPs) using ion-exchange (IEX) chromatography.

Fig. 2 shows the different post-IEX unit procedures in the processing schemes for the production of capsomere and VLP vaccines. The IEX chromatography purified capsomeres could be formulated directly as a vaccine in phosphate buffered saline (PBS) (CAP,