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CONTINUOUS PRODUCTION OF VIRAL VACCINES WITH A TWO-STAGE BIOREACTOR SYSTEM

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Continuous processes can be particularly efficient for production of biologicals that are required in large amounts such as viral vaccines. One virus that has received much clinical attention is Modified Vaccinia Ankara virus (MVA), which is a potential platform for expression of recombinant viral antigens and can be used as a vector in gene therapy [1]. Recently, a new MVA virus strain has been successfully propagated at high yields in non-aggregated avian suspension cells [2] allowing the production of MVA virus in continuous bioreactors. MVA is a lytic DNA virus and therefore, continuous production strategies can be implemented using two-stage bioreactor systems, where cell growth and virus propagation occur in separated vessels [3]. However, a possible drawback for continuous virus production is the presence of defective interfering particles among the virus population that cause oscillations in virus levels and low production yields [3], known as Von Magnus effect.

In this work, continuous production of MVA virus in a two-stage bioreactor (TSB) set-up (two 1 L stirred tank bioreactors) was evaluated. Subsequently, the set-up was scaled down to a non-instrumented semi-continuous cultivation system (two shaker flasks; small-scale culture, SSC) as approximation to a continuous cultivation [4] that would facilitate TSB screening. The virus strain MVA.CR19 and the duck cell line AGE1.CR.pIX (both from ProBioGen, Berlin) were used. The TSB system involved a bioreactor for cell growth and a second bioreactor in series for virus propagation [3]. The SSC system consisted of two shaker flasks, one for cell growth (120 mL working volume) and another for virus propagation (different residence times). Harvest, cell transfer, and addition of fresh medium were done manually twice a day.

Continuous production of MVA-CR19 was maintained for 18 d with the TSB system. Virus titers showed 7 d of transient phase, followed by stable titers that suggested the absence of a Von Magnus effect over 18 d. A total production capacity of $2x10^{10}$ viruses/day was estimated ($4x10^{10}$ viruses/day estimated for batch). The space-time yield of the TSB approached that of 2 parallel batches at 11 d post infection. The process was scaled down to the SSC system that resulted in stable production of cells, and virus titers that approached the dynamics and values obtained with the TSB system. Additional cultivations with the SSC system showed that different residence times in the virus bioreactor could influence virus titers.

Overall, it was demonstrated that continuous production of MVA.CR19 virus in a TSB system is feasible. Also, a small scale two-stage semi-continuous cultivation was successfully established as a faster and cheaper tool for screening the TSB systems before scale-up.

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