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Dynamic oncolytic measles virus production

Tanja Grein

University of Applied Sciences Mittelhessen, Institute of Bioprocess Engineering and Pharmaceutical Technology,
tanja.a.grein@kmub.thm.de

Denise Salzig

University of Applied Sciences Mittelhessen, Institute of Bioprocess Engineering and Pharmaceutical Technology

Michael Muehlebach

Oncolytic Measles Viruses and Vectored Vaccines, Paul-Ehrlich-Institut, Langen, Germany

Peter Czermak

University of Applied Sciences Mittelhessen, Institute of Bioprocess Engineering and Pharmaceutical Technology

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Tanja A. Grein, University of Applied Sciences Mittelhessen, Institute of Bioprocess Engineering and Pharmaceutical Technology, Wiesenstrasse 14, Giessen, Germany
Tanja.a.grein@kmub.thm.de

Denise Salzig, University of Applied Sciences Mittelhessen, Institute of Bioprocess Engineering and Pharmaceutical Technology, Wiesenstrasse 14, Giessen, Germany

Michael M. Muehlebach, Oncolytic Measles Viruses and Vectored Vaccines, Paul-Ehrlich-Institut, Langen, Germany

Peter Czermak, University of Applied Sciences Mittelhessen, Institute of Bioprocess Engineering and Pharmaceutical Technology, Wiesenstrasse 14, Giessen, Germany and Kansas State University, Department of Chemical Engineering, Manhattan, Kansas, United States and Justus Liebig University, Faculty of Biology and Chemistry, Giessen, Germany and Fraunhofer Institute for Molecular Biology and Applied Ecology (IME), Project group Bioresources, Giessen, Germany

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Oncolytic viruses can be effective weapons against cancer with few treatment options. For example the tissue culture–adapted Edmonston strains of measles virus (MV) have altered its receptor specificity and became selectively oncolytic with attenuated pathogenicity. Russel et al. showed in 2014 full remission in an advanced stage multiple myeloma patient after systemic application of genetically modified MV. In this clinical trial, the patient was treated by intravenous infusion of 10^{11} TCID₅₀ (50% tissue culture infectious dose) - of an engineered MV encoding human sodium iodide symporter. Appropriate medical treatment with oncolytic viruses calls for high concentrations and absolute product purity.

The main challenge in the field of viral bioprocess design is the low product stability. Although oncolytic MV production is feasible in a stirred tank bioreactor, the poor knowledge about the virus release and inactivation process hampers oncolytic MV production in industrial scale. As published by Weiss et al. already a simple transfer of the MV production process from a static cultivation system (e.g. T-Flask) into a dynamic system (e.g. STR) can dramatically reduce MV yield. As static systems are only suitable for small-scale processes, the process transfer into scalable dynamic systems is a bottleneck for a broad application of MV as cancer drugs. Beside their limited scalability, T-flasks or cell factories only allows the MV production in a batch mode. Through this process mode, the MV particles can be harvest only once and at an assumed time of harvest (TOH). In consideration of the short MV half-life of one and two hours at 37°C and 32°C respectively, the TOH is a critical point in bioprocessing. But measles viruses are known to be sensitive against the production temperature. Therefore an infection cycle adapted virus harvest with related synchronal purification is required. Virus membrane filtration represents a beneficial trade-off. Membrane-based filtration like cross flow filtration can process potentially large volumes and yielding high host cell concentration in the bioreactor. On the other hand, membrane based filtration processes are very unspecific. To remain the advantages of membrane filtration and increase the selectivity of the purification, membrane chromatography is a true alternative. Application of adsorptive membranes based on the electric interaction between charged components of the liquid phase including viruses and ionic groups immobilized on the solid membrane matrix, ion exchange membrane chromatography (IEMC) is a potentially simple and efficient method for MV concentration and purification. In present work, a continuous bioprocess concept for oncolytic MV production and purification for the use in cancer therapy will be presented.

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