

Development of a Production Process of Viral Particles –Kinetic Studies of Measles Virus Production in Vero Cells

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Tissue culture–adapted Edmonston strains of measles virus (MV) have altered its receptor specificity and became selectively oncolytic with attenuated pathogenicity. This property of the MV eventually leads to selective tumor cell killing. According to the dose needed for measles vaccination in cancer therapy a much larger amount of the MV is needed. The subject of this project is to scale up the production of MV in Vero cells in order to achieve an optimized fermentation process by providing more MV particles for the use in cancer therapy. First results of the work are presented here.

MV production was carried out in spinner system and bioreactor cultivation. The offline tracking of cell growth was performed by fluorescence-based and activity-based assays. Metabolite concentrations of glucose, lactate, glutamine and ammonia were determined with enzymatic kits. The MV concentration was estimated by the TCID₅₀ method.

The cells have been adapted to a commercially available serum-free medium. In addition, all products of animal origin have been replaced. The growth surface was provided by micro carriers for the cultivation of adherent cells in stirred systems. Similar maximum titers were reached for cell-associated and extracellular MV. Repeated harvesting of the extracellular MV showed no negative influence on MV yields, but raised cumulative virus titers. In addition research on the temperature stability of the MV was carried out and it has been shown that the MV in the supernatant under culture conditions was very unstable due to temperature inactivation.

After infection cell metabolism changed for MV production and therefore cells stopped growing but still consumed substrates. These kinetics were investigated and described including concentration of glucose, lactate, glutamine and ammonia, additionally extracellular and cell-associated MV titers and MV decay due to temperature depend inactivation were considered. Using extended Monod kinetic the kinetic constants were determined.

To meet commercial and regulatory requirements, this process must be high yielding, scalable and reproducible. These requirements are met by establishing a cell culture process employing stirred system and serum-free cell culture medium. A first description of MV production kinetics is promising for a successful optimization of the process.