Integrated production of an influenza A vaccine candidate with MDCK suspension cells

Thomas Bissinger[1], Yixiao Wu[1], Pavel Marichal-Gallardo[1], Dietmar Riedel[2], Xuping Liu[3], Y Genzel[1], wen Tan[3], and Udo Reichl[1]

[1]Max Planck Institute for Dynamics of Complex Technical Systems
[2]Max Planck Institute for Biophysical Chemistry
[3]East China University of Science and Technology

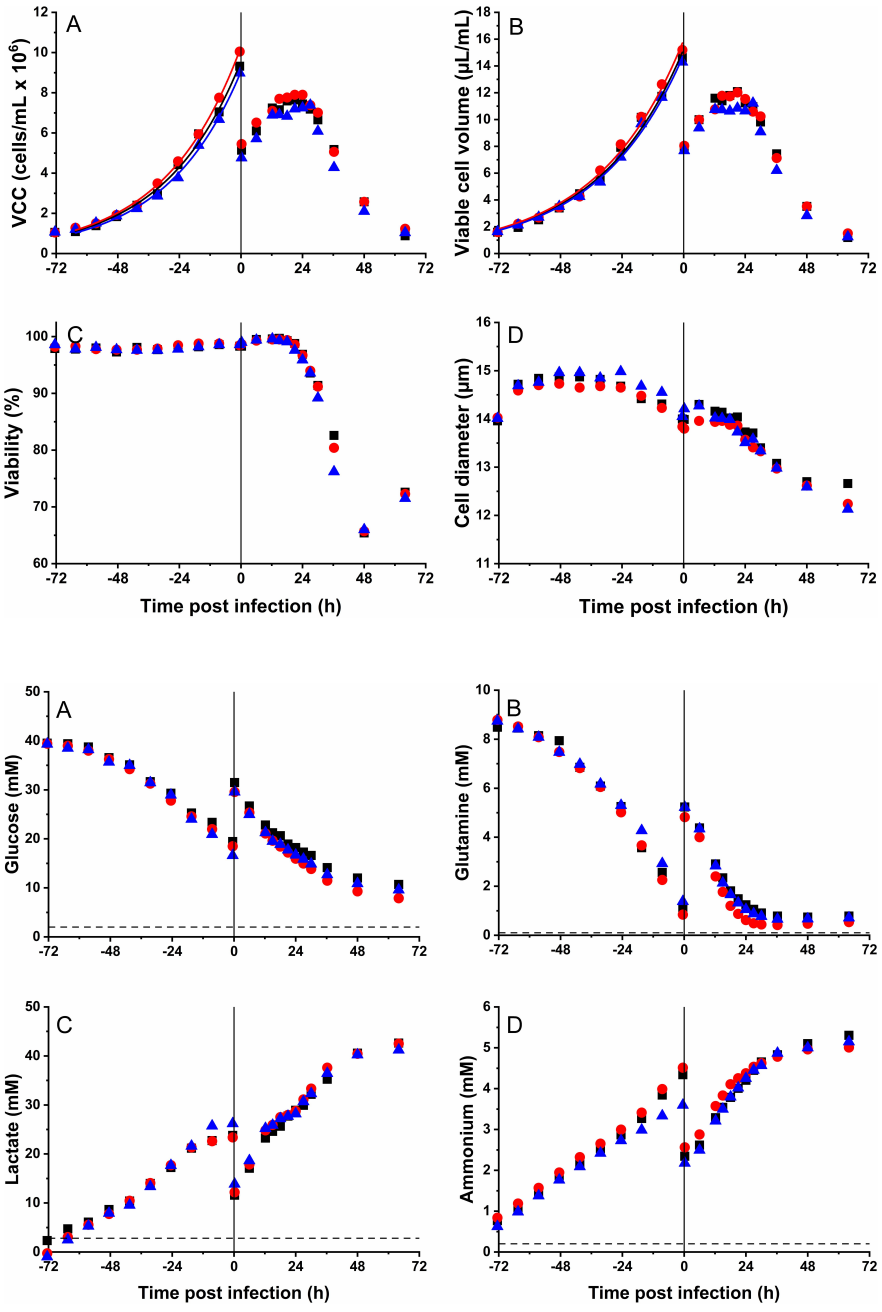
March 3, 2021

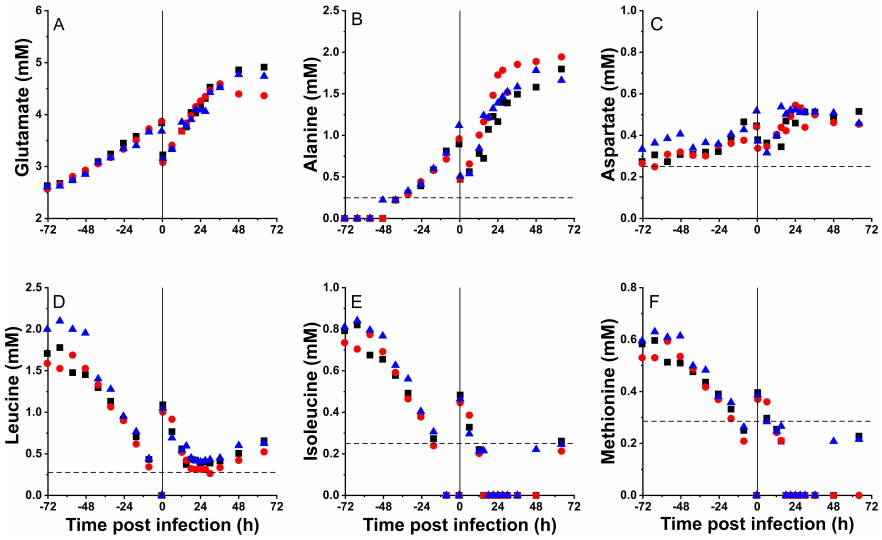
Abstract

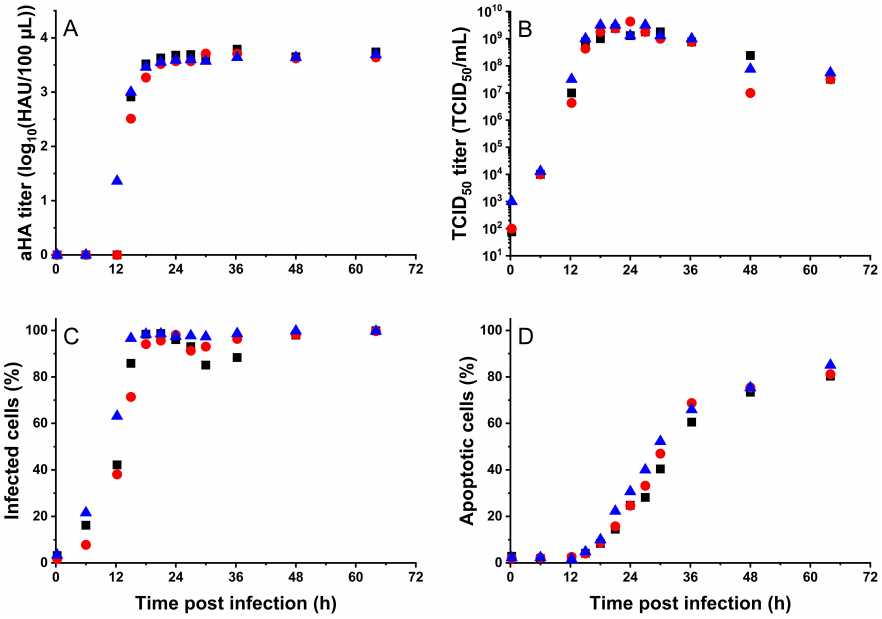
Seasonal influenza infection waves occur both in northern and southern hemispheres every year. Despite the differences in influenza virus surface antigens and virulence of seasonal subtypes, manufacturers are well-adapted to respond to this periodical vaccine demand. Due to decades of influenza virus research, the development of new influenza vaccines is relatively straightforward. Nevertheless, compared to the recent Covid-19 pandemic where a vaccine is not yet available, influenza vaccine manufacturing would be a major bottleneck for the rapid supply of billions of doses required worldwide. In particular, egg-based vaccine production would be difficult to schedule and shortages of other egg-based vaccines with high demands also have to be anticipated. Cell culture-based production systems enable manufacturing of large amounts of vaccines within a short time frame and expand significantly our options to respond to pandemics and emerging viral diseases. In this work, we present an integrated process for the production of inactivated influenza A virus vaccines based on a MDCK suspension cell line cultivated in a chemically defined medium. Very high titers of 3.6 log10(HAU/100 µL) were achieved using fast growing MDCK cells at concentrations up to 9.5 × 106 cells/mL infected with influenza A/PR/8/34 H1N1 virus in 1 L stirred tank bioreactors. A combination of two membrane-based chromatography steps enabled full recovery for the virus capture and up to 80 % recovery for the virus polishing step, respectively. Purified virus particles showed a homogenous size distribution around a mean diameter of 80 nm. Based on a monovalent dose of 15 µg hemagglutinin (SRID assay), the level of total protein was 58 µg and the level of host cell DNA contamination was below 10 ng. Furthermore, all process steps can be fully scaled up to industrial quantities for commercial manufacturing of either seasonal or pandemic influenza virus vaccines. Fast production of up to 300 vaccine doses per liter within 4 to 5 days makes this process competitive not only to other cell-based processes, but to egg-based processes as well.

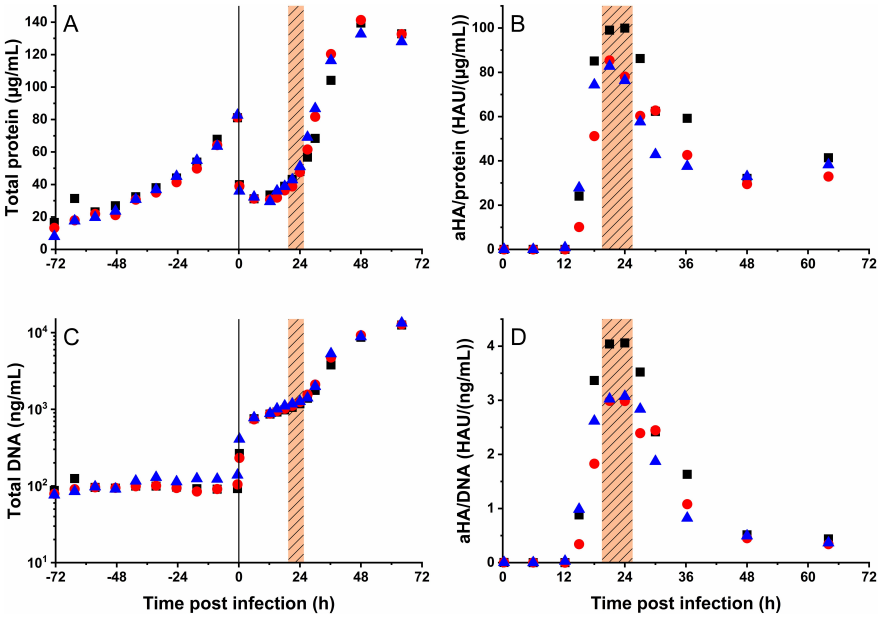
Hosted file

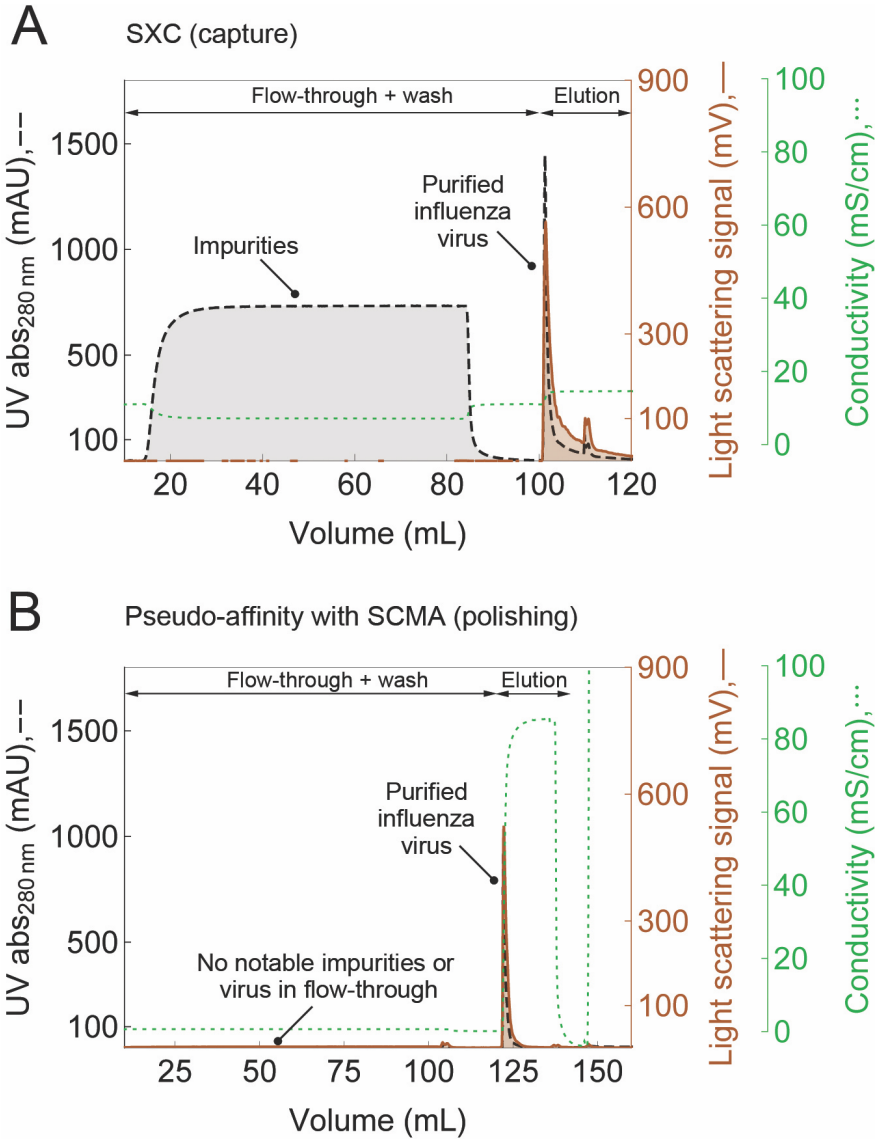
`Manuscript_USP_DSP_IAV_submission_02.pdf` available at https://authorea.com/users/399241/articles/511801-integrated-production-of-an-influenza-a-vaccine-candidate-with-mdck-suspension-cells

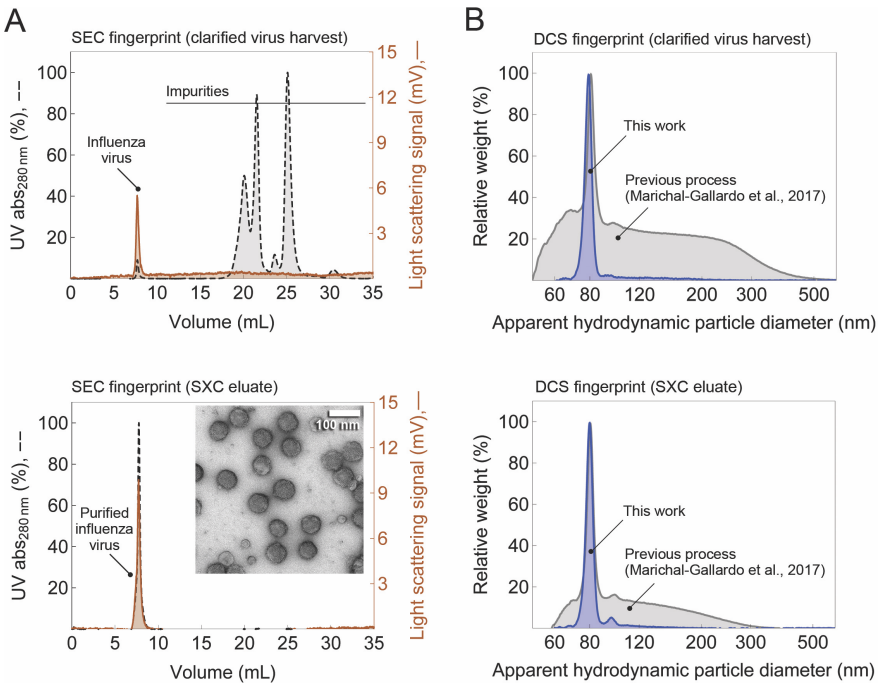












Hosted file

Table_01.pdf available at https://authorea.com/users/399241/articles/511801-integrated-production-of-an-influenza-a-vaccine-candidate-with-mdck-suspension-cells

Hosted file

Table_02.pdf available at https://authorea.com/users/399241/articles/511801-integrated-production-of-an-influenza-a-vaccine-candidate-with-mdck-suspension-cells