



Technology Offer

A novel type of influenza A virus-derived Defective interfering Particle for antiviral therapy

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Background

Human influenza A virus (IAV) is responsible for seasonal disease in people and can cause worldwide pandemics. The main lines of defense against IAV are vaccines and antiviral drugs.

Influenza vaccines, including killed and live vaccines, recombinant virus-like particles and viral particles, have been available commercially for many years. Typically, the composition of influenza vaccines is based on the major influenza virus strains causing infection in the previous season. Accordingly, the influenza strains used as the basis of existing vaccines are reassessed from year to year by the WHO and may need to be changed. Furthermore, there is always a time lag between the actual infective influenza strain and the production of the components of the vaccines.

Currently used antiviral drugs act on various known mechanisms of the lifecycle of the viruses. This includes the inhibition of the action of IAV matrix proteins (Amantadine and Rimantadine) or the blocking of neuraminidase (Zanamivir and Oseltamivir). However, the use of antiviral drugs is limited since treatment has to start soon after infection and the resistance to antiviral drugs arises rapidly.

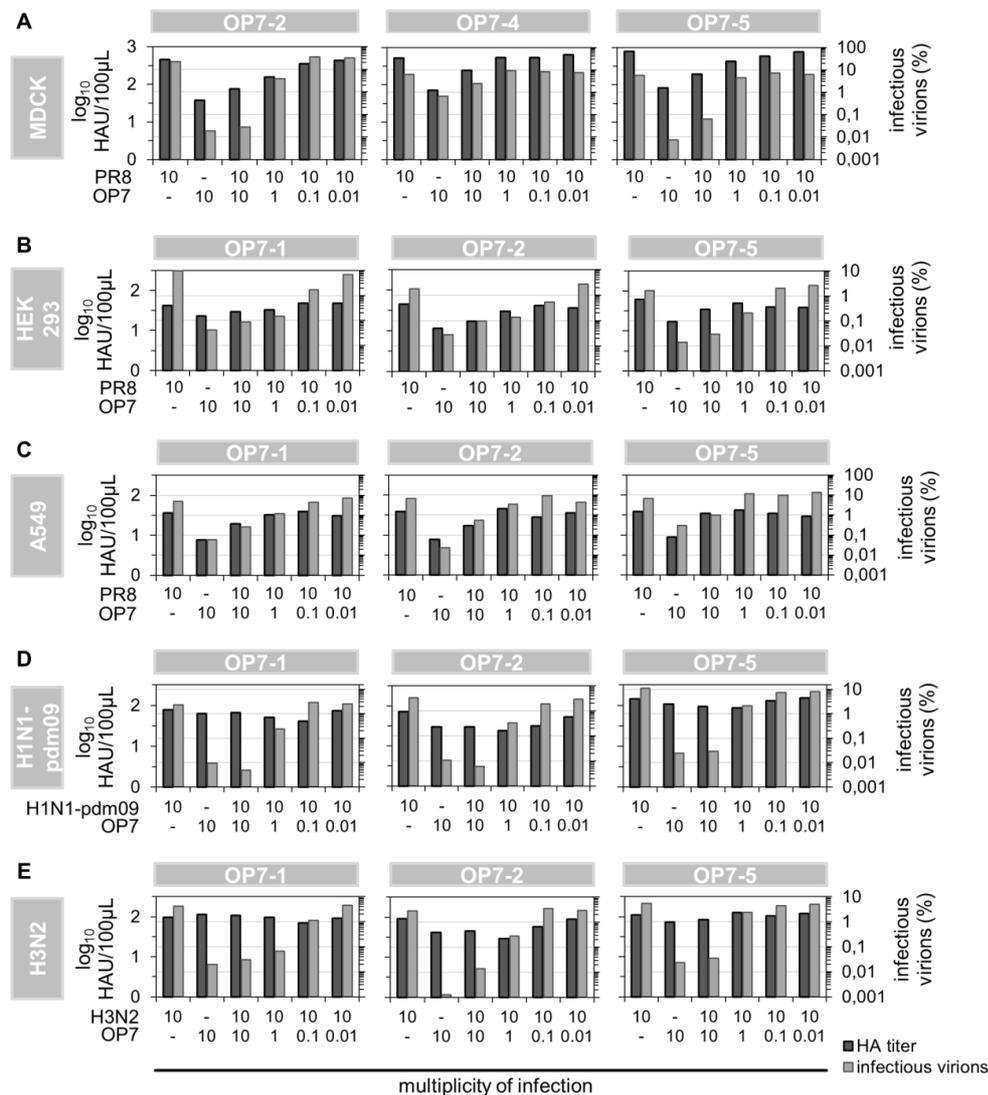
Technology

Recent research indicates that defective interfering particles (DIPs) may also serve as antiviral agents. Conventional DIPs are particles containing a highly deleted form of the viral genome, which renders them non-infectious. The DIPs interfere with the standard virus by replicating at its expense in a co-infection scenario. As a result, mainly non-infectious DIPs are released by the cells. Furthermore, conventional DIPs have been shown to protect mice and ferrets from an otherwise lethal dose of IAV in several previous studies.

So far, DIPs have been primarily identified and characterized on the basis of their large genomic deletions. The present technology covers a novel DIP-type, termed OP7 virus, which contains 37 nucleotide substitutions in its genomic segment number 7 instead of deletions. Moreover, OP7 shows interference *in vitro* against relevant epidemic and pandemic strains, and interference in human cell lines. OP7 also shows a stronger inhibition of virus replication compared to conventional DIPs *in vitro*. Comparative animal studies in mice and in ferrets (conventional DIPs vs OP7) and studies regarding options for cell culture-based production of OP7 show encouraging preliminary results making OP7 viruses promising candidates for antiviral therapy.

Advantages

- Influenza vaccines require two to three weeks for full protection; DIPs operate immediately.
- OP7 shows a stronger inhibition of virus replication compared to conventional DIPs.
- OP7 appears to interfere universally with different IAV strains. Thus, it may not need to be updated and produced again every season.
- Prophylactic treatment (a few weeks before infection) and therapeutic treatment (a few days after infection) are conceivable.



Suppression of influenza A virus replication by OP7 virus co-infection. Cells infected with wild-type (WT) virus at a multiplicity of infection (MOI) of 10 were simultaneously co-infected with OP7 seed virus at the indicated MOIs until 12 hours post infection. Infectious virus titers were quantified by a plaque assay. Fractions of infectious virus were

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calculated using the total virus particle concentration derived from the hemagglutination (HA) titer. HA titers were expressed as \log_{10} HA units (HAU) per 100 μL . **(A)** Interference of OP7 virus with influenza virus A/Puerto Rico/8/34 (PR8) virus replication in Madin-Darby canine kidney (MDCK) cells. **(B and C)** Coinfection of PR8-infected human embryonic kidney 293 (HEK 293) cells (B) and A549 (derived from human lung carcinoma) cells (C) with OP7 seed virus. **(D and E)** Interference of OP7 with virus replication of pandemic influenza virus A/California/7/2009 of H1N1 subtype (H1N1-pdm09) (D) and with influenza virus A/Hong Kong/4801/2014 of H3N2 subtype (H3N2) (E) in MDCK cells. Three independent infection experiments were conducted, each using the WT and one OP7 seed virus (denoted OP7-1, OP7-2, OP7-4 and OP7-5).

Patent Information

Patent application number EP2018159908, filed on March 5th, 2018.

Literature

S. Kupke *et al.*, Journal of Virology 2019 93 (4): e01786-18. doi: 10.1128/JVI.01786-18

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