Max-Planck-Innovation

Technology Offer

Broad-spectrum vector-based antiviral and potential live vaccine

Our scientists developed a vector-based high tolerable and efficient antiviral (plasmid-derived defective interfering particles) to support IAV pandemic preparedness. The DIP also shows a broad-spectrum antiviral activity against other respiratory viruses, e.g. RSV and SARS-CoV-2 and is Intended for intranasal administration (droplet spray) for human use. A state-of-the-art, high-yield production process in a GMP-ready controlled and sterile environment in animal cell culture.

Background

Influenza A viruses (IAVs) cause annual epidemics, and pandemics with millions of deaths can occur. The timing of such events is almost impossible to predict, and the COVID-19 pandemic clearly demonstrated the need to improve pandemic preparedness. New antiviral therapies – ideally with broad-spectrum antiviral efficacy – need to be developed to contain pandemics at an early stage and to protect vulnerable populations, especially when vaccines or other measures are not yet available. This applies, in particular, for the growing proportion of elderly, chronically ill and/or multimorbid individuals who are highly susceptible to severe outcomes from respiratory viral infections.
Current countermeasures against IAV infections include the use of vaccines and antivirals. While vaccination is the most effective way to prevent and control influenza disease, it takes time to develop and manufacture new vaccines for each influenza season. Therefore, antivirals are essential as a first line of defense for pandemic preparedness and to complement annual vaccination programs. As circulating human IAV strains have developed resistance against many commonly used antivirals, new antiviral treatment options are urgently needed.

Technology

Defective interfering particles (DIPs) of IAV, i.e., vector-based antivirals, are a promising new class of antiviral agents. Conventional DIPs carry deletions in their genome. The technology covers a **newly identified type of IAV-DIP "OP7"** (patent: MI1402-5459) that carries a novel, previously unknown genomic structure. OP7 shows **significantly higher antiviral efficacy** than conventional DIPs both *in vitro* and *in vivo*.

OP7 could be **administered intranasally as a droplet spray** to the initial site of infection (pharynx) as a prophylactic and/or therapeutic antiviral agent **for human use** (Figure 1).

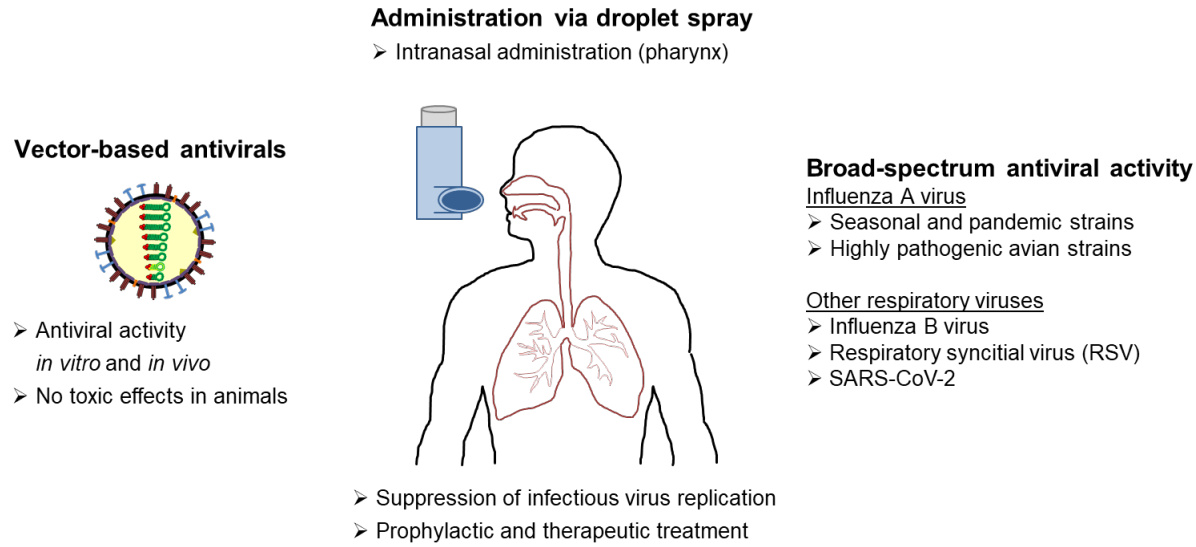

Figure 1. Concept of OP7 administration for antiviral treatment.

Max-Planck-Innovation GmbH
Arnulfstr. 58
80335 München
www.max-planck-innovation.de

IAV DIPs show potent antiviral activity against IAV infection in various animal models, including mice and ferrets. IAV DIPs typically suppress a wide range of IAV strains, including current human epidemic, pandemic and highly pathogenic avian IAV. In addition, IAV DIPs can also suppress non-homologous virus replication including that of several respiratory viruses such as respiratory syncytial virus (RSV) and SARS-CoV-2 (patent: MI1402-6192). Taken together, IAV DIPs, in particular OP7, are a **new class of broad-spectrum antivirals** to treat respiratory viral infections as a rapid countermeasure to protect at-risk individuals and limit virus spread.

Results from animal trials

In animal studies (mice), intranasal administration of OP7 alone did not result in any disease symptoms and other toxic or pathological changes. Thus, it was clearly demonstrated that **OP7 is well tolerated**. In addition, mice were infected with a lethal dose of IAV and co-treated with OP7. All animals survived the infection and showed no signs of disease, demonstrating the **remarkable antiviral efficacy of OP7** (Figure 2).

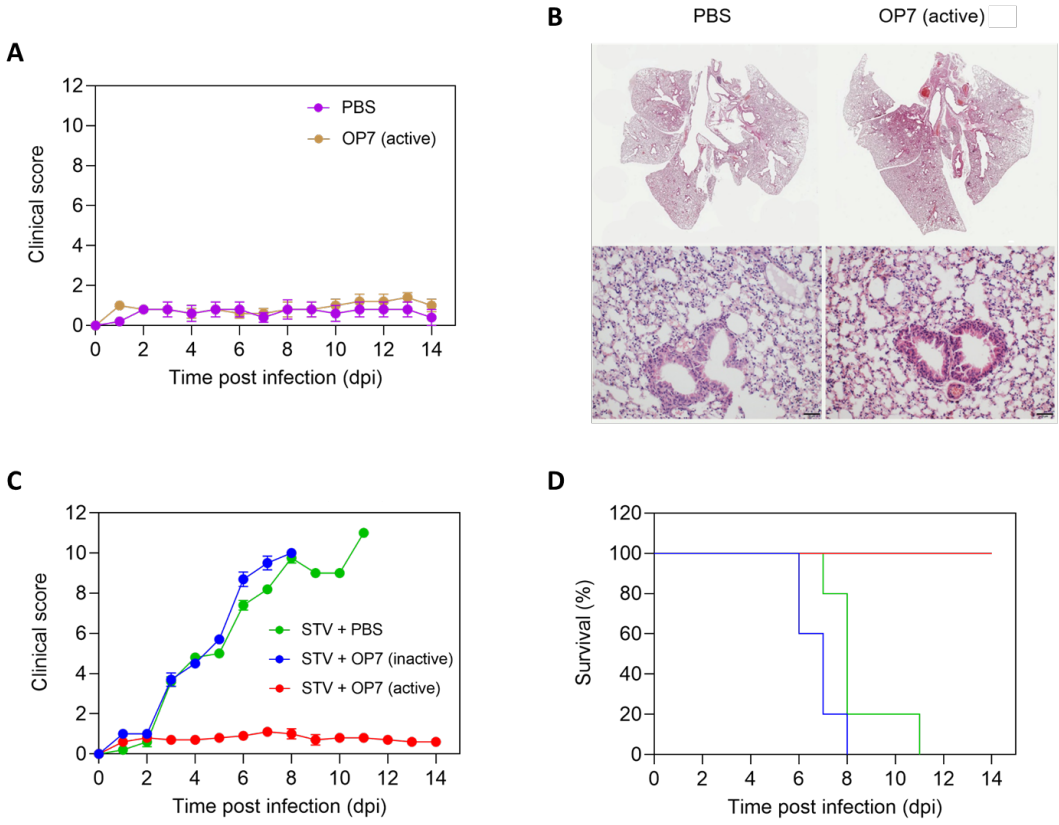

Figure 2. Antiviral efficacy of OP7 in a mouse infection model. A) and B) OP7 or PBS was intranasally administered to mice. A) Clinical score. B) Histopathological changes in mouse lung after H&E staining. C) and D) Mice were inoculated with a lethal dose of IAV and co-treated with OP7. C) Clinical score. D) Kaplan-Meyer curve representing the survival rate.

Improvements made on the technology (OP7) compared to conventional IAV DIPs

So far, IAV DIPs were produced in embryonated chicken eggs. By contrast, previous efforts of the BPE group are **cell culture-based production processes** for DIPs, allowing for an improved scalability and flexibility, better defined process conditions and reproducible product quality.
Previously, DIPs were produced in the presence of infectious virus to complement for the defect in virus replication of DIPs. In order to inactivate STVs that can cause harm in a potential application, UV irradiation was used. This, however, would potentially raise safety and regulatory concerns due to

Max-Planck-Innovation GmbH
Arnulfstr. 58
80335 München
www.max-planck-innovation.de

residual infectious viruses in the medical product. In addition, efficacies of DIPs are reduced by UV treatment.
We developed a **genetically engineered cell line** to **propagate OP7 preparations** that are completely **free of infectious virus**, alleviating potential safety and regulatory concerns. Thereby, we also avoid the necessity for UV irradiation that reduces antiviral efficacies of OP7. As mentioned above, OP7 displays a significantly higher antiviral efficacy than conventional DIPs. The higher efficacy allows for a more economic production process.

Development towards clinical trials

In recent years, **cell culture-based production** and purification processes for OP7 have been developed that are suitable for **GMP-ready large-scale production**. **High production yields of OP7 were achieved** with up to 2.6E+11 OP7 particles/mL. To facilitate GMP manufacturing, Fraunhofer ITEM (Braunschweig, Germany) was hired to establish and store master cell banks and virus seeds under GMP conditions. In addition, MPI-established processes are being transferred to establish GMP-ready upstream processing at ITEM to facilitate pre-clinical and clinical trials (PhD study).

A “scientific orientation discussion” was recently (June 2023) held with the **Paul Ehrlich Institute** to ensure that the qualitative and regulatory requirements for manufacturing and subsequent clinical trials as well as marketing authorization issues are properly addressed. The regulatory authority raised **no critical concerns**.

Outlook

Finally, work is in progress to develop this technology (OP7) towards use as a live vaccine for human use (patent: MI1402-5459). It is anticipated that this vaccine will meet the current demand for the development of **novel mucosal vaccines** as requested since many years by experts. The virus preparation will be a novel **broad-spectrum antiviral that also serves as a live vaccine** for intranasal administration. This would enable a new form of pre- and post-exposure prophylaxis to treat large cohorts, e.g. in the event of local virus outbreaks, to protect people at risk and to contain the spread of the virus, e.g. in the event of a pandemic.

Advantages

- Vector-based antiviral (plasmid-derived defective interfering particles) to support IAV pandemic preparedness, safe for human use
- Production in a controlled and sterile environment in animal cell culture
- Broad-spectrum antiviral activity against other respiratory viruses, e.g., RSV and SARS-CoV-2
- High tolerability and antiviral efficacy demonstrated in animal models
- Intended for intranasal administration (droplet spray) for human use
- A state-of-the-art, high-yield production process

Offered IP

MI1402-5459 "Protective interfering nucleic acid molecule and virus-like particle, viral vector, or virus particle containing the same ..."
Priority application EP3536779 filed on 05.03.2018,
PCT application WO2019170625 filed 05.03.2019, nationalized in EP, US and JP
US11274304B2 and JP7324213B2 granted, EP3762483A1 under examination.

MI1402-6192 "Influenza virus defective interfering particles for use in the prophylactic or therapeutic treatment of coronaviridae infection"
Priority application EP21157812 filed on 18.02.2021,
PCT application WO2022175436 filed 18.02.2022, nationalized in EP, US and JP
EP22706603.2, US18/546,690 and JP2023-548859 under examination.

Max-Planck-Innovation GmbH
Arnulfstr. 58
80335 München
www.max-planck-innovation.de

300 vials master cell bank (MCB), 300 vials work cell bank (WCB) and 100 vials virus seeds (DMS) owned by Max-Planck-Gesellschaft produced and stored under GMP conditions at Fraunhofer ITEM

Extensive qualified knowhow regarding GMP-ready suspension MDCK cell culture-based production and purification processes for OP7 in batch and in perfusion mode. Optimized production conditions yield high product titers (2.6E+11 OP7 particles/mL) and a purity of OP7 chimera DIPs of >99.7%.

Scientific Publications

Kupke *et al.* (2019) *J Virol* 93:e01786-18
Bdeir *et al.* (2019) *PLoS ONE* 14(3): e0212757
Hein *et al.* (2021a) *Appl Microb Biotech* 105:129-146
Pelz *et al.* (2021) *J Virol* 95:e01174-21
Rand and Kupke *et al.* (2021) *Cells* 10,1756
Hein *et al.* (2021) *BMC Biology* 19:91
Rüdiger *et al.* (2021) *PLoS Comp Biol* 17(9):e1009357
Hein *et al.* (2021b) *Appl Microb Biotech* 105:7251-7264
Pelz *et al.* (2023) *Viruses* 15,1872
Dogra et al. (2023) Sci Rep 13:20936
Pelz et al. (2023) Appl Microb Biotech (accepted)

Contact

Dr. Lars Cuypers
Senior Patent- & License Manager
Chemist
Phone: +49 (0)89 / 29 09 19 - 21
eMail: cuypers@max-planck-innovation.de

Max-Planck-Innovation GmbH
Arnulfstr. 58
80335 München
www.max-planck-innovation.de