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Lonafarnib inhibits cell entry of Human Respiratory Syncytial Virus (hRSV)

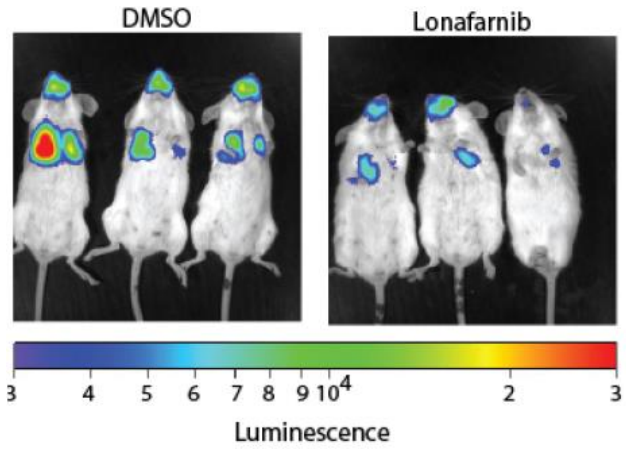
Keywords: RSV, cell entry inhibitor, fusion protein, treatment, prophylaxis, antiviral, high-risk patients

INVENTION NOVELTY

Human respiratory syncytial virus (hRSV) causes infections of the upper and lower respiratory tract. While the course of infection is predominantly mild, severe infections can be fatal. Risk groups for severe courses are infants (especially preterm babies), the elderly and immunocompromised patients. Since effective directly acting agents against RSV infection are not yet available for clinical use, treatment options are limited to symptomatic therapy. Scientists of TWINCORE – Centre for Experimental and Clinical Infection Research and Hannover Medical School in a repurposing screen now identified lonafarnib as a novel antiviral agent against hRSV.

VALUE PROPOSITION

In the group of infants under 5 years of age, there are about 3.4 million severe hRSV infections annually, causing up to 199,000 deaths. While Ribavirin shows antiviral activity *in vitro,* it has limited efficacy in patients and is therefore no longer recommended. Monoclonal antibody palivizumab is used as prophylaxis in children at high risk of severe disease progression, however, it reduces hospitalization rates by only 55%, cannot be broadly applied, and is further restricted by rapid development of resistance mutations. Lonafarnib is an approved drug to treat Hutchinson-Gilford progeria syndrome (Zokinvy®). It furthermore is under development for hepatitis delta virus (HDV) therapy in a phase III study. While it is known to act as farnesyltransferase inhibitor, it surprisingly also binds to viral fusion protein (F protein), thereby inhibiting hRSV cell entry. In this regard, lonafarnib might prove to be of great value in treatment of high-risk patient populations.



Significantly reduced reporter virus signal in lung and nose of treated animals on days 2-4 post-infection
Source: Pietschmann et al, unpublished manuscript

TECHNOLOGY DESCRIPTION

Binding to viral F protein was confirmed by testing cell entry inhibition of F-carrying lentiviral pseudotypes, surface plasmon resonance, and co-crystallography. Inhibition of RSV infection was confirmed in differentiated human lung cells and in a mouse infection model. BCi-NS1.1 cells were differentiated into a pseudostratified ciliated epithelium and infected with RSV GFP reporter virus. Treatment of these cells with lonafarnib dose-dependently inhibited RSV infection (10-15-fold reduction of viral load in infected cells). Balb/c mice were perorally treated with 60mg/kg lonafarnib and two hours later were infected with a recombinant RSV luciferase reporter virus. Bioluminescence was measured on days 2-4 post infection. Results showed a significantly reduced reporter signal in the lung and nose of treated animals and a dose-dependent decline of viral DNA in the lungs of treated animals at day 4. Furthermore, lonafarnib-treated animals suffered less weight loss from the infection compared to untreated animals.

COMMERCIAL OPPORTUNITY

The technology is available for co-development or licensing.

DEVELOPMENT STATUS

Proof of concept of antiviral activity in a mouse model of RSV infection. Antiviral activity with recent RSV subtype A and B clinical isolates confirmed.

PATENT SITUATION

Applications in US and EP based on PCT/EP2022/051377 with priority of January 2021 are pending.

FURTHER READING

Sake et al. Drug repurposing screen identifies lonafarnib as respiratory syncytial virus fusion protein inhibitor. Nat Commun. 2024 Feb 8;15(1):1173.

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