Severe lung damage caused when flu is followed by infection with measles-like virus, study finds

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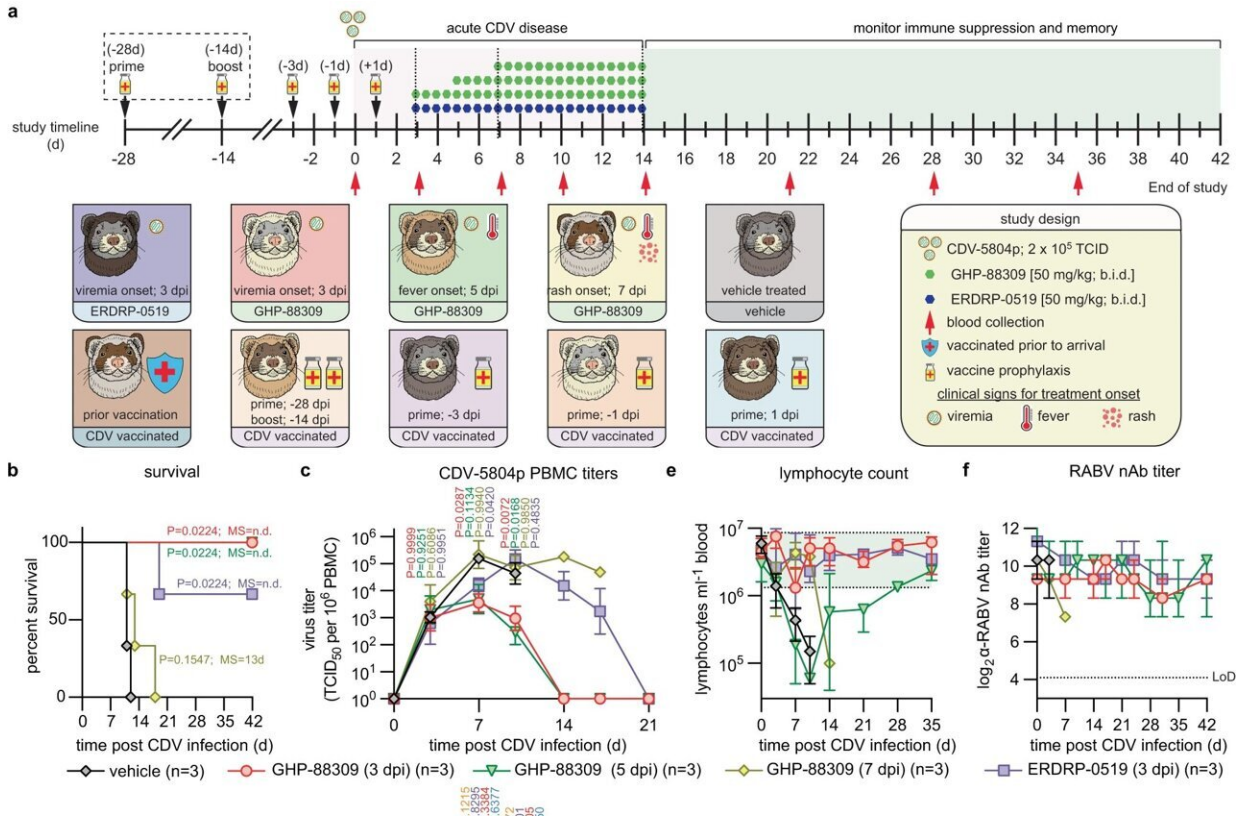

Therapeutic treatment of lethal CDV infection in ferrets. Ferrets were infected with a lethal challenge of CDV and treated with GHP-88309, ERDRP-0519, or therapeutic vaccination. **a** Schematic of the study design. Ferrets were infected with wild-type recCDV-5804p and monitored for 6 weeks. Symbols in the different boxes show clinical presentation of animals when treatment of the respective group was initiated. **b** Survival curves of ferrets infected in (**a**). log-

rank (Mantel-Cox) test, median survival is stated. **c** PBMC associated viremia titers of CDV infected ferrets shown in (**a**). 2-way ANOVA with Dunnett's post-hoc test. **d** Images of ferrets taken 12 days after infection with recCDV-5804p. **e** Lymphocyte counts from infected ferrets measured during the duration of the study detailed in (**a**). Green shading denotes normal range. **f** RABV neutralizing antibody titers from CDV infected ferrets. Symbols (**c**, **e**, **f**) represent geometric means ± geometric SD, lines intersect means. In (**b–e**), top row shows results for inhibitor-treated groups, bottom row for vaccinated animals; LoD, limit of detection; *n* = 3. Source data are provided as a Source Data file. Credit: *Nature Communications* (2024). DOI: 10.1038/s41467-024-45418-5

Infection with a measles-like virus causes catastrophic lung failure in ferrets previously infected with influenza virus or respiratory syncytial virus, according to a study by researchers in the Center for Translational Antiviral Research at Georgia State University.

In the study published in *Nature Communications*, the researchers studied ferrets infected with a common respiratory virus such as respiratory syncytial virus or influenza virus, which results in flu-like illness in the animals. One month after full recovery, animals received a non-lethal strain of canine distemper virus (CDV), which is closely related to human measles virus and causes a measles-like disease in ferrets. Two weeks later, animals developed lethal hemorrhaging pneumonia.

"Acute lung failure after consecutive infection with two non-lethal respiratory viruses was unprecedented," said Richard Plemper, senior author of the study, Regents' Professor at the Georgia State Institute for Biomedical Sciences, and director of the Center for Translational Antiviral Research. "We found that these animals did not succumb to the viral infection, but to bacterial pneumonia because they became unable to prevent lung invasion by commensal bacteria."

Screening for differences in gene expression between animals that had been infected with the influenza virus or not, the study found that canine distemper infection results in the expression of a group of protective host proteins in the lung called trefoil factors.

"When the animals had recovered from influenza, trefoil factors were not upregulated, leaving the animals unprotected against normally harmless bacteria," said Robert Cox, assistant professor in the Center for Translational Antiviral Research and first author of the study. "Usually, these animals would recover, but when exposed to CDV, this decrease in the levels of protective host proteins resulted in the development of severe bacterial pneumonia."

Using an experimental antiviral drug, GHP-88309, that Plemper has developed in recent work, they were able to prevent lethal bacterial pneumonia even when treatment was started very late after CDV infection.

"We currently do not know whether measles virus causes enhanced disease when following unrelated earlier viral infections, but it very much adds to the concerns related to the resurgence of measles that we have seen in recent years globally," Plemper said. "Measles is frequently followed by bacterial otitis media or bacterial pneumonia. Viral disease history of a child could be an underappreciated risk factor for developing these secondary sequelae."

"In addition to discovering that previous infections may play a critical role in disease severity, we were able to experimentally identify the window of opportunity to treat these viral infections and prevent the long-term immune suppression associated with measles-like disease," Cox said.

The researchers demonstrated benefit of treatment with GHP-88309 for

over seven days after the window for therapeutic vaccination has closed, "which introduces a novel additional option to mitigate severe complications of measles-like disease," Plemper said.

More information: Robert M. Cox et al, Therapeutic mitigation of measles-like immune amnesia and exacerbated disease after prior respiratory virus infections in ferrets, *Nature Communications* (2024). DOI: 10.1038/s41467-024-45418-5

Provided by Georgia State University

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