Ferret models to study clinical intervention strategies against influenza.

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Abstract

Influenza is a moving target. Different influenza virus subtypes circulate across different avian and mammalian populations, drift, reassort, causing disease and spreading rapidly. Ferrets have proven to be indispensable for influenza virus research. Ferrets can be infected with primary and cultured human and avian influenza virus isolates and develop a disease pattern which is very similar to that in humans. Ferrets have shown to be instrumental over a broad spectrum of applications from the production of influenza-specific antisera to the novel highly advanced immunocompromised model. The appropriateness of the different ferret models and their read out parameters for the assessment of clinical intervention strategies for influenza virus infection in humans, such as preventive vaccination and the use of antivirals are presented here in the context of high pathogenic avian influenza A/H5N1, pandemic influenza A/H1N1 and low pathogenic avian influenza A/H7N9 viruses.

Infection dose

The choice of infection dose of the influenza challenge virus in preclinical efficacy studies is important for minimal variation in the test groups in the challenge dose should be sufficiently high, but if the challenge dose is too high it will for instance be too difficult for a vaccine candidate to show protective efficacy and it might be falsely disqualified. The challenge dose influences a number of parameters like mortality, while there are also parameters like the lung viral load that are not influenced. We have carried out dose-finding experiments for pre-2009 influenza A virus H1N1, pandemic H1N1 and highly pathogenic avian influenza virus H5N1 (van den Brand, et al. 2010) and recently also for H7N9 (Kroetz, et al. 2013).

Infection route

Ferrets can be infected with influenza viruses via the respiratory route by intranasal, intratracheal inoculation, and by transmission. The most common route of infection used for ferrets is the intranasal route. Bodelow, et al., who reported that the method of virus inoculation is critical Intratracheal inoculation with T10 TCID50 of influenza A H5N1 (A/Hongkong/3/04) resulted in severe bronchiectasis and pneumonia, while intranasal inoculation with same virus at the same dose induced moderate or severe CTD lesions (Bodelow, et al. 2011 ImmPath). We have shown that Intratracheal challenge can be successfully used for efficacy testing also for intranasal vaccines (Matta, et al. 2014 & Mann, et al. 2014).

Sampling & end points

In studies designed to evaluate the efficacy of antiviral agents against influenza, it is critical to collect respiratory tract samples for virological, pathological and molecular analyses at both the appropriate time point after infection or start of therapy as well as the appropriate location along the respiratory tract This is because influenza virus infection is a highly dynamic process, both temporally and spatially (van den Brand, et al. 2012). Furthermore, experiments with repeated CT scans of the same animals instead of sacrificing multiple animals allows to study respiratory tracts lesions of each individual animal compared with the situation before infection (Veldhuis Kroeze, et al. 2011). We have shown that day-to-day CT monitoring is a valuable tool for the read out of efficacy studies (Veldhuis Kroeze, et al. 2012).

Clinical read-outs

A number of clinical read-outs are relatively easy to obtain and to analyze from ferrets, including body weight and body temperature. However, signs of disease like loss of activity can be difficult to monitor. Therefore, we have developed a very sensitive activity sensor that overcomes the need for time-consuming observations and allows proper analysis of data that are obtained objectively. This activity sensor provides a valuable additional parameter to show the efficacy of countermeasures in the ferret model.

References


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