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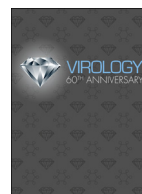
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## Review

## Ferret models of viral pathogenesis



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## ABSTRACT

Emerging and well-known viral diseases remain one of the most important global public health threats. A better understanding of their pathogenesis and mechanisms of transmission requires animal models that accurately reproduce these aspects of the disease. Here we review the role of ferrets as an animal model for the pathogenesis of different respiratory viruses with an emphasis on influenza and paramyxoviruses. We will describe the anatomic and physiologic characteristics that contribute to the natural susceptibility of ferrets to these viruses, and provide an overview of the approaches available to analyze their immune responses. Recent insights gained using this model will be highlighted, including the development of new prophylactic and therapeutic approaches. To provide decision criteria for the use of this animal model, its strengths and limitations will be discussed.

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## Ferrets as experimental animals

Domestic ferrets (*Mustela putorius furo*) are small carnivores belonging to the *Mustelidae* family. Their closest wild relatives are wild European ferrets (*M. putorius*), European polecats (*M. furo*) and the steppe polecat (*M. eversmannii*), and interbreeding among these species produces fertile offspring, illustrating the close relationship (Lewington, 2007). Due to their relatively small size

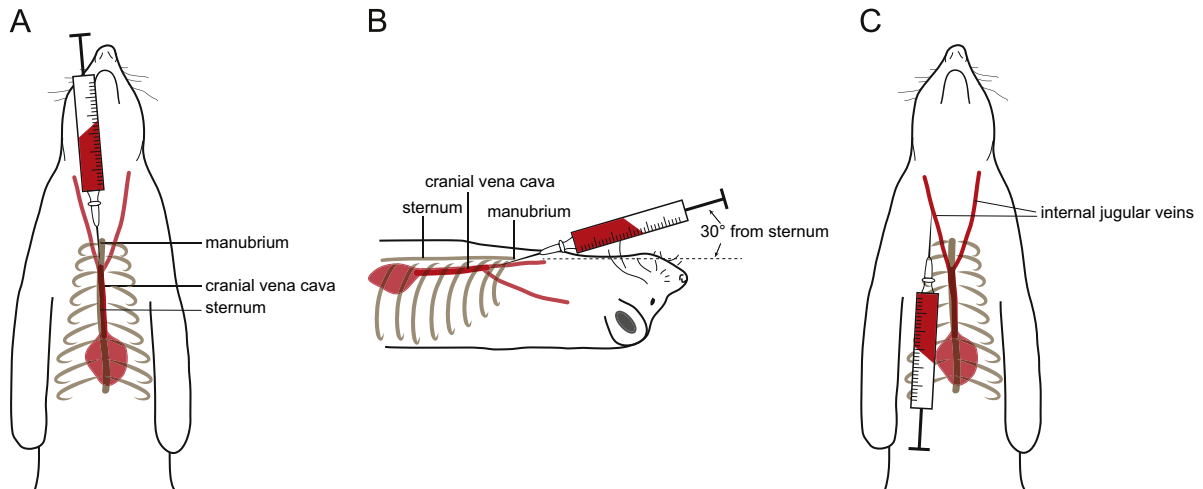
and their similarity to humans with respect to aspects of their anatomy, physiology, and metabolism, they are increasingly considered an alternative to larger animal models such as dogs and non-human primates (Clingerman et al., 1991). Ferrets are available from different commercial breeders, some of which are even offering specific pathogen free (SPF) animals. Seronegative animals, while of particular interest for the infectious disease community, are difficult to maintain due to the natural susceptibility of ferrets for human respiratory viruses. Breeders offer pre-testing of animals prior to purchase and use HEPA-filtered transport cages to minimize risk of exposure during shipping, but the serostatus of all animals has to be verified after arrival. In addition, personal

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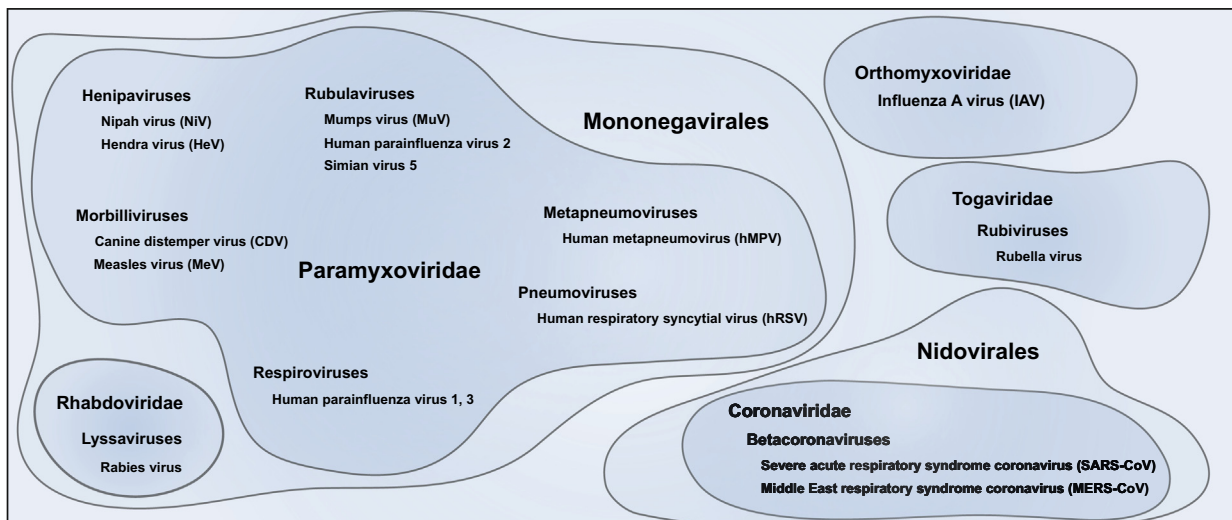
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**Fig. 1.** Examples of different cage types for ferret housing. Longterm free-range housing in same sex groups. Environmental enrichment like hammocks, tubes, and additional levels for climbing are provided (A, B). During ongoing experiments the animals are housed in pairs in different cage types connected by tubes or openings in separating walls (C, D).



**Fig. 2.** Large volume blood collection sites. The anterior vena cava (A, B) and the internal jugular vein (C) allow collection of larger blood volumes.



**Fig. 3.** Viruses investigated in ferrets. Viruses from different families discussed in this review that have been studied in ferrets.

protective equipment such as N95 masks or powered air purifying respirators (PAPRs) should be worn for all interactions with the animals to prevent accidental exposure by infected staff.

The animals are social and should be housed in same sex groups whenever possible (Fig. 1A and B). Many of the standard rabbit caging systems can be used to house ferrets during experiments (Fig. 1C and D). The spacing of the grid walls and food receptacles may have to be adapted to prevent escape, and hiding places such as tubing or tunnel, hammocks, or nesting boxes have to be provided (Ball, 2002). Because of their value for pathogenesis studies with viruses requiring high containment, different individually ventilated cage (IVC) systems have been also developed. An adult female ferret weighs 700–1000 g, while males weigh 1400–2000 g, thus allowing repeat blood sampling at volumes sufficient for immunological analyses over the course of an infection (Bixler and Ellis, 2004). While small blood samples can be obtained from the tail or leg veins, larger volumes required for the isolation of peripheral blood mononuclear cells are best collected from the anterior vena cava (Fig. 2A and B) or the internal jugular vein (Fig. 2C). The sexual weight dimorphism together with the requirement for inducing ovulation in female ferrets in estrus has led many researchers to preferentially use males (Fox, 1998; Sherrill and Gorham, 1985).

Following the fortuitous discovery of the natural susceptibility of ferrets to human influenza viruses in the 1930s (Smith et al., 1933), they were found to reproduce the human course of disease of a number of human respiratory viruses including respiratory syncytial virus (RSV), parainfluenzaviruses (PIV), and severe acute respiratory syndrome (SARS)-coronavirus (Fig. 3). In addition to the presence of the respective receptors, the fact that anatomic proportions of the ferret upper and lower respiratory tracts, the density of submucosal glands in the bronchial wall and the number of generations of terminal bronchioles are all reproduce the situation in the human respiratory tract likely contributes to this effect (Johnson-Delaney and Orosz, 2011; Robinson et al., 1986). With technical developments enabling infection via the ocular route or by aerosol, the impact of the inoculation route and volume on pathogenesis have been increasingly recognized (Belser et al., 2014, 2012; Bodewes et al., 2013; Kreijtz et al., 2013; Moore et al., 2014). For most studies however, the animals are inoculated intranasally with volumes ranging from 0.1 to 1 ml.

## Influenza virus

In the context of infectious disease research, ferrets are most widely known as model for the study of influenza viruses, which belong to the *Orthomyxoviridae* family (Palese and Shaw, 2007). Influenza A, and to a lesser extent influenza B, viruses cause annual epidemics with an estimated 250,000–500,000 deaths worldwide. While humans are the only natural reservoir for influenza B, influenza A infects a broad range of avian and mammalian species with aquatic birds acting as principal reservoir. Among livestock, infections in poultry and pigs have the greatest economic impact, but horses, and more recently dogs, can also be affected. Avian and swine influenza A viruses are of particular public health relevance because their close contact with humans provides multiple opportunities for interspecies adaptation and transmission (Palese and Shaw, 2007).

Influenza A viruses are grouped into different subtypes according to the antigenicity of their surface glycoproteins, which are the principal targets of the neutralizing antibody response (Gerhard, 2001; Palese and Shaw, 2007). So far, 18 hemagglutinin (HA, H1–H18) and 11 neuraminidase (NA, N1–N11) subtypes have been identified (Tong et al., 2012, 2013). Introduction of a new influenza A subtype into the human population can result in a pandemic with increased morbidity and mortality (Belser et al., 2009;

Johnson and Mueller, 2002). Avian influenza viruses are further classified in low pathogenic (LPAIV) and highly pathogenic avian influenza viruses (HPAIV), according to their HA cleavage site: LPAIV HAs carry a monobasic cleavage site, which can only be activated by proteases present in the avian respiratory tract, while HPAIV HAs are activated by subtilisin-like proteases present in every cell due to their polybasic cleavage site (Bertram et al., 2010).

Ferrets became the animal model of choice for influenza research when the first isolation of an influenza virus succeeded in this species (Smith et al., 1933), and they have made remarkable contributions to our understanding of influenza biology ever since. In addition to being naturally susceptible to human influenza A strains, the clinical course of disease in ferrets reproduces key aspects of human disease including fever, lethargy and signs of upper and sometimes lower respiratory infection (Bouvier and Lowen, 2010; Smith and Sweet, 1988). The similar influenza receptor distribution in the human and ferret respiratory system likely represents an important contributing factor: in the upper respiratory tract of both species, there is a high density of alpha 2,6-linked sialic acids (SA $\alpha$ 2,6), while SA $\alpha$ 2,6 as well as alpha 2,3-linked sialic acids (SA $\alpha$ 2,3) are present in the lower respiratory tract (Shinya et al., 2006; van Riel et al., 2007). As seen in adult human patients with uncomplicated influenza, infection of ferrets with seasonal H1N1 and H3N2 strains, which preferentially bind to SA $\alpha$ 2,6, results in a mild to moderate disease characterized by extensive infection of the upper respiratory tract with limited spread to the lung (Huang et al., 2011; van den Brand et al., 2012). In contrast, highly pathogenic influenza viruses, which have a higher affinity to SA $\alpha$ 2,3, are always associated with severe pneumonia and widespread infection throughout the lung (Belser et al., 2009; Kumlin et al., 2008; Nicholls et al., 2008; Shinya et al., 2006; van Riel et al., 2007), and in the case of certain strains also lead to neurologic and gastrointestinal involvement (Gambotto et al., 2008). The assessment of the reconstructed pandemic H1N1 1918 virus in ferrets not only demonstrated the high virulence of this historic virus compared to a seasonal human H1N1 strain (Taubenberger et al., 1997; Tumpey et al., 2005), but also revealed that two amino acid changes in the HA protein were sufficient to switch the receptor specificity from SA $\alpha$ 2,6 to SA $\alpha$ 2,3 and abolish respiratory droplet transmission (Tumpey et al., 2007), illustrating the important role of receptor specificity in influenza pathogenesis.

The similarity in influenza susceptibility between humans and ferrets is increasingly exploited to gain insights into the transmissibility and virulence of new isolates. Human-adapted seasonal influenza viruses spread through direct or indirect contact or respiratory droplets (Brankston et al., 2007), while infections with avian viruses are usually associated with close contact to infected poultry and are rarely transmitted. Transmissibility assessments of different HPAs in ferrets have confirmed the poor transmissibility observed in the field (Maines et al., 2006). However, there is great concern that one of these viruses acquires the capacity for aerosol spread and causes a pandemic (Matrosovich et al., 2000; Stevens et al., 2008). Characterization of transmission determinants using genetically modified H5N1 viruses revealed that only five amino acid changes in the HA, PB1, and PB2 proteins were sufficient to enable efficient respiratory droplet transmission between ferrets (Herfst et al., 2012; Imai et al., 2012; Linster et al., 2014). Most of these mutations had already been described to play an important role in influenza virulence in ferrets and mice by either affecting replication efficiency or altering virus tropism (Chen et al., 2007; Hatta et al., 2001; Maines et al., 2011; Shinya et al., 2004). In contrast to HPAI H5N1, the recently emerged human H7N9 isolates display a natural affinity for both SA $\alpha$ 2,6 and SA $\alpha$ 2,3 receptors. Even though they replicate efficiently in the upper and lower respiratory tract of humans and ferrets, transmission studies have so far yielded contradictory results ranging from reports of



efficient airborne transmission over reduced aerosol transmission compared to seasonal and pandemic H1N1 strains to contact transmission only (Belser et al., 2013; Richard et al., 2013).

The value of the ferret model to rapidly gauge the virulence of a newly emerging virus first became apparent during the H1N1 2009 pandemic. Evaluation of early isolates indicated an increased morbidity and higher pathogenicity compared to seasonal H1N1 strains but similar transmission efficiency (Maines et al., 2009; Munster et al., 2009), thereby providing valuable information to public health officials. A large body of work investigating the pathogenesis and transmissibility of HPAI H5N1, H7N1, and H9N1 strains isolated from human cases or poultry provides a framework for the pandemic risk assessment of new viruses emerging from the animal reservoir (Kimble et al., 2014; Lipatov et al., 2009; Maines et al., 2006; Sutton et al., 2014; Yen et al., 2007). Recently, avian H3N8 influenza viruses isolated from seals were found to have naturally acquired mutations known to increase transmissibility, demonstrated increased affinity for mammalian SA $\alpha$ 2,6 receptors, and were transmitted via respiratory droplets between ferrets (Karlsson et al., 2014), suggesting a pandemic potential for these viruses. This year, a novel highly pathogenic H5N8 virus was isolated from outbreaks in poultry first in Korea and China, and more recently also in Europe and Canada (Fan et al., 2014; Ku et al., 2014; Wu et al., 2014). The virus causes moderate to severe disease in ferrets, but so far no avian-to-human transmission has been observed (Kim et al., 2014). This continued emergence of new influenza strains in birds and mammals not only requires active surveillance but also the need for systematic characterization of their pandemic potential including pathogenesis studies in ferrets.

Despite the limited availability of ferret-specific immunological reagents, investigation of innate host responses based on mRNA expression levels, either by quantitative real-time RT-PCR or using a canine microarray, revealed profiles similar to those seen in patients, thereby illustrating the value of this animal model not only for virulence assessment but also the characterization of host responses (Cameron et al., 2008; Kang et al., 2011; Maines et al., 2012; Meunier et al., 2012). While seasonal influenza strains are generally associated with a rapid rise and fall of type I and II interferons and TNF $\alpha$  during the first days after infection (Rowe et al., 2010; Svittek et al., 2008), highly pathogenic H5N1 strains lead to a more sustained expression of interferon response genes and higher expression levels of cytokines and inflammatory mediators in the lungs (Cameron et al., 2008). Since such a hypercytokinemia or cytokine storm is also observed in H5N1 patients (de Jong et al., 2006; Peiris et al., 2009; To et al., 2001) a more detailed characterization of the underlying pathomechanism in ferrets, using newly developed tools and assays and including more detailed kinetics of lymphocyte subsets, hematological parameters and serum chemistry profiles (Belser et al., 2011), may yield innovative therapeutic approaches.

The ferret model also remains the gold standard for efficacy assessments of new vaccine strategies and therapeutic approaches. These studies are usually performed using seronegative animals to eliminate additional confounding factors, even though this does not reflect the epidemiological situation in the human population, where most adults have been exposed to at least one, but likely several, strains of the circulating subtypes (Bodewes et al., 2011; Fonville et al., 2014; Hoschler et al., 2013). At this time, inactivated influenza vaccines and live-attenuated influenza vaccines (LAIV) are licensed in most countries (Lambert and Fauci, 2010). While LAIV induce a stronger immune response in naïve individuals, inactivated vaccines are more immunogenic in the presence of pre-existing immunity. In the context of the annual vaccination campaigns, LAIV are thus primarily given to children and young adults (Rodgers et al., 2015). The potential of LAIV to induce a broader and more efficient immune response against newly emerging strains has been investigated extensively. Studies in

ferrets demonstrated that a recombinant H5N1 LAIV elicited a broad cross-protection against different H5N1 sublineages (Li et al., 1999; Suguitan et al., 2006). More recently, it was shown that immunization with LAIV H7N3 and H7N7 resulted in cross protection against the newly emerged H7N9 virus (Xu et al., 2013b).

The immunogenicity and extent of cross-protection have also been investigated for inactivated pandemic vaccines. In general, whole-virus inactivated vaccines induce robust responses after a single dose and may even protect against antigenetically mismatched viruses (Govorkova et al., 2006; Poland and Sambhara, 2008; Subbarao and Luke, 2007). In contrast, split-virus or subunit vaccines are less immunogenic, and more than one dose or the addition of an adjuvant are required to protect naïve individuals (Bresson et al., 2006; De Groot et al., 2013; Duan et al., 2014; Lin et al., 2006). The development of safe and efficacious adjuvants is of great relevance in the context of pandemic preparedness, since the use of adjuvants reduces the amount of antigen needed per dose (Clegg et al., 2014; Onishi et al., 2014). In addition, the development of adjuvanted seasonal vaccines is considered for seniors, who often respond poorly to the currently used non-adjuvanted inactivated vaccines (Ann et al., 2014; van den Brand et al., 2011).

A comprehensive overview of innovative vaccine approaches against influenza is beyond the scope of this review. Among the most promising candidates are virus-like particles (VLPs) composed of the M1 matrix protein together with the HA and NA proteins. Intranasal or intramuscular vaccination with such VLPs containing H5, H7 and H9 proteins, or the H1 protein alone, induced an immune response against all HAs present and protected ferrets from challenge with multiple avian influenza viruses (Mahmood et al., 2008; Pushko et al., 2011; Ross et al., 2009; Tretyakova et al., 2013). Different viral vector-based approaches have also been developed to the clinical trial stage. Among those, recombinant modified vaccinia virus Ankara (MVA) expressing different HA subtypes have demonstrated efficacy in ferrets and recent in first-in-man clinical trials have confirmed the immunogenicity in humans (Kreijtz et al., 2014, 2010; Rimmelzwaan and Sutter, 2009). DNA- and more recently RNA-based vaccine candidates have great appeal in a pandemic context, since they can be produced rapidly and at large scale. DNA vaccines expressing single or multiple HA proteins alone or in combination with NA induce protective T and B cell responses in different animal models, especially in the context of prime-boost regimen with other vaccine candidates (Bragstad et al., 2011; Lin et al., 2012; Pillet et al., 2011; Rao et al., 2010; Suguitan et al., 2011). In a first proof-of-concept study, a PR8-HA-expressing RNA vaccine induced an immune response similar to approved influenza vaccines in ferrets and pigs (Petsch et al., 2012), indicating the feasibility of this approach. However, despite recent progress using *in vivo* electroporation or gene guns (Laddy et al., 2008; Yager et al., 2013), efficient DNA or RNA delivery remains a major obstacle for the implementation of this technology.

At this time, there are two classes of commercially available drugs against influenza, adamantane-derivatives, which inhibit the M2 ion channel, and neuraminidase inhibitors. In addition, the viral polymerase inhibitor favipiravir has received regulatory approval in Japan for use against influenza in 2014 (Furuta et al., 2013; Nagata et al., 2014). Early on, ferret studies demonstrated the rapid emergence of antiviral resistance against adamantanes and the transmission of drug-resistant strains without loss of virulence (Herlocher et al., 2003; Sweet et al., 1991), thereby predicting today's resistance of all circulating seasonal influenza strains (Bright et al., 2005; Bright et al., 2006). Nonetheless, adamantanes may still be useful in the context of a pandemic strain carrying a non-resistant M segment of animal origin (Nguyen et al., 2012). Ferret studies also demonstrated the efficacy

of neuraminidase inhibitors against lethal infection with different H5N1 strains (Boltz et al., 2008a, 2008b; Govorkova et al., 2007), which are now an integral part of pandemic preparedness strategies. After the emergence of oseltamivir-resistant strains, studies in ferrets have been used to characterize the impact of the mutations involved and to investigate the fitness cost associated with this resistance (Watanabe et al., 2013). Ferret studies thus remain an integral part in the development of new prophylactic and therapeutic strategies against influenza.

## Paramyxoviruses

### Henipaviruses

Hendra (HeV) and Nipah (NiV) viruses belong to the genus Henipavirus within the *Paramyxoviridae* family. Their natural hosts are fruit bats of the family *Pteropodidae* that can be found in South-East Asia, Australia and Africa (Hayman et al., 2008; Olson et al., 2002; Young et al., 1996). Infected bats shed the virus in urine, thereby infecting other species. Transmission to humans occurs through intermediate hosts like pigs (NiV) and horses (HeV) (Luby et al., 2009). Ephrin B2, which has been identified as the cellular receptor of henipaviruses, is highly conserved and present on endothelial cells, smooth muscle cells, and neurons (Gale et al., 2001), and thus thought to contribute to the broad species and tissue tropism (Bonaparte et al., 2005). In humans, the Henipavirus case fatality rate is approximately 70%. The disease starts with influenza-like symptoms such as fever, dry cough, sore throat, and lymphadenopathy, often leading to acute respiratory distress symptom (ARDS) (Hossain et al., 2008). There is a high incidence of neurologic symptoms and survivors often experience neurologic sequelae months and even years after the acute infection (O'Sullivan et al., 1997; Playford et al., 2010; Tan et al., 2002; Wong et al., 2009).

Ferrets experimentally infected with NiV or HeV develop the full spectrum of disease seen in humans. First clinical signs occur 6–10 days after infection, starting with fever, coughing, nasal discharge, shortness of breath, and depression, sometimes followed by limb paralysis and meningitis (Bossart et al., 2009; Pallister et al., 2009, 2011). Comparison of NiV strains isolated from patients in Bangladesh and Malaysia revealed differences in the amount of virus shed in oral secretions of infected ferrets, which may explain the increased human-to-human transmissions seen during outbreaks in Bangladesh (Clayton et al., 2012). However, more extensive pathogenesis and transmission studies are limited by the high containment requirements for the work with these viruses. A recently generated recombinant HeV expressing GFP or luciferase from an additional open reading frame retained the ability to cause fatal disease in ferrets, thus constituting a valuable tool to directly characterize dissemination and to visualize virus–host interactions (Marsh et al., 2013).

While there is currently no vaccine or antiviral treatment approved for humans, a HeV vaccine for horses based on soluble HeV glycoprotein has been available since 2012. Efficacy studies in ferrets were instrumental in the development of this vaccine (Bossart et al., 2005; Middleton et al., 2014; Pallister et al., 2011), and the analogous approach against NiV protected ferrets from NiV challenge for more than 12 months (Broder et al., 2013; Pallister et al., 2013). A vesicular stomatitis virus pseudotyped with the NiV glycoproteins was equally protective in ferrets, indicating that the development of an efficient and safe vaccine against these viruses is feasible (Mire et al., 2013). In addition, the potential of monoclonal antibody treatment has also been demonstrated in ferrets using a monoclonal antibody, which blocks the receptor-binding domain of the HeV and NiV G glycoproteins

(Bossart et al., 2009), further validating ferrets as animal model for these viruses.

### Pneumoviruses

Human respiratory syncytial virus (hRSV) and human metapneumovirus (hMPV) belong to the *Pneumovirinae* subfamily in the *Paramyxoviridae* family. They are one of the leading causes of respiratory disease in children worldwide, each year affecting more than 33 million children under the age of five as well as elderly and individuals with pre-existing respiratory conditions (Falsey et al., 2005; Nair et al., 2010; van den Hoogen et al., 2001). These viruses are transmitted via respiratory droplets or through direct contact with respiratory secretions (Hall et al., 1981). The infection is limited to respiratory epithelial cells (Lotz and Peebles, 2012), and the disease is mostly characterized by coughing, sneezing and fever. However, newborns, especially prematurely born infants, can progress to apnea, feeding difficulties, and periodic breathing (Collins and Graham, 2008; Dahlem et al., 2003; van den Hoogen et al., 2003). In elderly patients, the infection often leads to pneumonia and chronic pulmonary disease, asthma, and congestive heart failure (Falsey et al., 2003, 2005). There is currently no vaccine against hRSV or hMPV, and the only approved antiviral drugs are ribavirin and a humanized monoclonal antibody directed against the RSV F glycoprotein (Johnson et al., 1997).

Ferrets are susceptible to hRSV and hMPV infection, and the viruses replicates to high titers in the nasal tissues (Coates and Chanock, 1962). However, hMPV-infected ferrets show no signs of disease (MacPhail et al., 2004). When animals were infected early in life, hRSV causes acute and chronic changes in the neural control of the airways that persist long after the virus was cleared (Colasurdo et al., 1998; Larsen and Colasurdo, 1999). Ferrets were also used to investigate the potential of recombinant adenoviruses expressing the RSV fusion and attachment glycoproteins individually or in combination. After intranasal administration, strong RSV-specific antibody responses were observed, and the animals were protected from subsequent RSV challenge (Hsu et al., 1994). Since replication in the lung only takes place in infant ferrets (Prince and Porter, 1976), their use as animal model for pneumovirus pathogenesis studies has been limited and little is known about the cellular receptors or mechanisms involved, even though ferrets reproduce the age-dependent differences in disease severity seen in humans.

### Morbilliviruses

Ferrets are not susceptible to measles virus (MeV), the member of the Morbillivirus genus infecting humans and certain non-human primates. However, they are very sensitive to canine distemper virus (CDV), which infects a broad range of terrestrial and aquatic carnivores, and the disease reproduces all key elements seen in MeV-infected patients (Ludlow et al., 2014). Because of the high degree of genetic, structural, and functional conservation among morbilliviruses and the consistent course of disease caused by CDV in ferrets, this model is frequently used to characterize common morbillivirus pathogenesis mechanisms. Upon infection with a CDV wild type strain via the respiratory route, virus can first be isolated from peripheral blood mononuclear cells (PBMC) after 2–3 days, and most T and B lymphocytes in lymphatic organs are CDV-positive within one week (Pillet and von Messling, 2009). This coincides with a dramatic drop in white blood cell numbers and the loss of PBMC proliferation activity upon non-specific stimulation (von Messling et al., 2003). While the decrease in white blood cells is seen in all infections, the extent of inhibition of PBMC proliferation activity and of innate

immune activation correlates with disease severity (Svitek and von Messling, 2007). The latter is controlled by the accessory V protein (Ramachandran et al., 2008; Rothlisberger et al., 2010), and a recent study in ferrets revealed that inhibition of STAT2 and mda5 signaling is essential for morbillivirus-mediated interference with the innate immune response (Svitek et al., 2014). After the signaling lymphocyte activation molecule (SLAM) was identified as morbillivirus immune cell receptor (Tatsuo et al., 2000; Tatsuo et al., 2001), pathogenesis studies with SLAM-blind viruses, first with CDV in ferrets and then with MeV in macaques, revealed that immune cell infection is essential for immunosuppression and clinical disease, thereby confirming the “immune cells first” hypothesis (Leonard et al., 2010; von Messling et al., 2005).

After amplification in lymphatic organs, the virus spreads to epithelial tissues throughout the body. If the immune response is not sufficient to control and subsequently clear the virus, the loss of epithelial integrity eventually leads to septicemia and death within three to five weeks after infection. The recently identified epithelial cell receptor nectin-4 (Muhlebach et al., 2011; Noyce et al., 2011) has enabled the generation of nectin-4-blind viruses, which subsequently not only illustrated the importance of epithelial cell infection for clinical disease but also demonstrated that acute immunosuppression requires immune but not epithelial cell infection (Frenze et al., 2013; Sawatsky et al., 2012). Since the incidence of neuroinvasion in ferrets can reach 100% for some strains, they have also been used to investigate morbillivirus neuropathogenesis mechanisms. In addition to the previously known entry routes via the choroid plexus and small blood vessels, the anterograde infection along the olfactory nerves was identified as an additional entry pathway (Rudd et al., 2006). Comparative studies with different strains revealed a correlation with longer disease duration and less severe immunosuppression (Bonami et al., 2007).

The study of CDV in ferrets as a surrogate for MeV in primates has also been used to investigate the potential of novel vaccines and, more recently, an antiviral drug candidate (Krumm et al., 2014; Rouxel et al., 2009; Welter et al., 2000). The consistent pathogenesis together with the availability of robust reverse genetics systems for several vaccine and wild type strains thus make the CDV-ferret model an attractive system to characterize virus-host interactions in the context of lethal disease outcome or survival, and to investigate the impact of interventions at different stages of disease.

## Coronaviruses

In addition to viruses causing a mild upper respiratory tract infection, the *Coronavirinae* subfamily also includes members that lead to severe acute respiratory disease with mortality rates of around 10% for severe acute respiratory syndrome (SARS)-CoV and even higher for Middle East respiratory syndrome (MERS)-CoV (Butler, 2012; Hui et al., 2014). Because of the respiratory tropism, the susceptibility of ferrets was evaluated. In the case of SARS-CoV, the virus was found to replicated efficiently in the upper and lower respiratory tract, and the animals developed clinical disease characterized by nasal discharge, sneezing, fever, and virus shedding including contact transmission to naïve cage mates after intratracheal infection (Chu et al., 2008; Martina et al., 2003). However, no clinical signs were seen after intranasal infection in a different study (Weingartl et al., 2004). This variability may be due to the route of infection, and the age, gender, and genetics of the animals are likely additional contributing factors.

In humans, the SARS-CoV tropism reflects the distribution of the cellular receptor angiotensin-converting enzyme (ACE) 2 (Drosten et al., 2003; Li et al., 2003) in lung alveolar epithelial

cells, enterocytes of the small intestine and tubular cells of the kidney (Ding et al., 2004; Gu et al., 2005; Hamming et al., 2004). The disease can range from mild respiratory signs to severe respiratory failure. After incubation period of 2–14 days patients initially present with influenza-like symptoms, fever, and cough that can progress to atypic pneumonia and respiratory failure (Peiris et al., 2003). The virus can also spread to multiple organs including the gastrointestinal and urinary tract causing a systemic disease. Even though it has been shown that ferret ACE2 interacts efficiently the SARS-CoV receptor-binding spike (S) protein (Zamoto et al., 2006), the tropism of SARS-CoV in ferrets does not match the receptor distribution (Gramberg et al., 2005), which may explain the differences in clinical manifestation observed.

Nevertheless, the ferret represents a useful animal model for the safety and efficacy assessment of SARS-CoV vaccine candidates and therapeutic approaches. While a MVA-based vaccine expressing the SARS-CoV S protein elicited a strong neutralizing immune response and protected the animals from disease, inflammatory lesions were found in the liver of the vaccinated animals (Weingartl et al., 2004). Formalin-inactivated whole-virus vaccines as well as an S-expressing adenovirus-based vaccine also induced neutralizing antibodies and no liver pathology was noted, but the extent of protection varied, indicating that a combination of vaccine strategies may be required for effective protection (Darnell et al., 2007; See et al., 2008). Prophylactic treatment with a monoclonal antibody reduced the replication of SARS-CoV in the lungs of infected ferrets up to one thousand-fold and may thus be useful in protecting contacts thereby limiting the spread of the disease (ter Meulen et al., 2004).

In the case of MERS-CoV, which also causes a severe pulmonary disease in humans, similar to SARS-CoV (Zaki et al., 2012), ferrets were not found to be susceptible. Even though MERS-CoV and SARS-CoV are both members of the genus *Betacoronavirus*, they differ in their receptor usage. MERS-CoV uses dipeptidyl peptidase (DPP) 4 for cell entry (Raj et al., 2013), which can also be found on ferret cells, but the sequence differences between the human and ferret DPP4 protein prevent binding of MERS-CoV (van Doremalen et al., 2014) explaining the lack of infection in this species.

## Others

Even though rabies pathogenesis is mostly studied in dogs, raccoons, or foxes, the protective efficacy of a commercial, inactivated rabies vaccine has also been demonstrated in ferrets (Rupprecht et al., 1990). In the context of a pathogenesis study, experimentally infected ferrets were assessed for susceptibility, incubation period, morbidity, clinical signs, seroconversion, and virus shedding. Interestingly, 17 out of 55 ferrets survived the infection, and rabies virus was isolated only from one of these animals (Niezgoda et al., 1997). Survival of ferrets experimentally infected with rabies virus was also reported in a different study (Hamir et al., 2011), indicating that they might be more resistant than other carnivores. Ferrets were also used to characterize newly discovered lyssaviruses with zoonotic potential and to evaluate the efficacy and cross-protection of available rabies vaccines (Hanlon et al., 2005; Vos et al., 2004).

The potential of ferrets as an animal model has been evaluated for other viral diseases, including mumps virus, simian virus 5, canine or human parainfluenza viruses, and rubella virus. Two recent studies demonstrated that mumps virus-infected ferrets mounted robust humoral and cellular immune response but developed no clinical signs and no virus was shed, indicating that the use of the model is limited (Parker et al., 2013; Xu et al., 2013a). Ferrets infected with simian virus 5 or canine and human parainfluenza viruses, which generally cause a mild and transient

**Table 1**  
Research topics studied in ferrets.

Viruses	Transmission	Pathogenesis	Neurovirulence	Immune response	Vaccination strategies	Antivirals and treatment
<b>Orthomyxoviruses</b>						
Influenza A viruses	+	+	+	+	+	+
<b>Paramyxoviruses</b>						
<b>Morbilliviruses</b>						
Canine distemper virus (CDV)	+	+	+	+	+	+
Measles virus (MeV)	∅	∅	∅	∅	∅	∅
<b>Henipaviruses</b>						
Nipah virus (NiV)	–	+	+	–	+	+
Hendra virus (HeV)	–	+	–	–	+	+
<b>Rubulaviruses</b>						
Mumps virus (MuV)	–	+	–	+	–	–
Human parainfluenza virus (hPIV) 2	–	+	–	+	–	–
Simian virus (SV) 5	–	–	–	+	–	–
<b>Respiroviruses</b>						
Human parainfluenza virus (hPIV) 1, 3	–	+	–	+	–	–
<b>Pneumoviruses</b>						
Human metapneumovirus (hMPV)	–	+	–	–	–	–
Human respiratory syncytial virus (hRSV)	–	+	+	–	+	–
<b>Rhabdoviruses</b>						
<b>Lyssaviruses</b>						
Rabies virus	–	+	+	–	+	–
<b>Togaviruses</b>						
<b>Rubiviruses</b>						
Rubella virus	+	(vertical)	–	–	–	–
<b>Coronaviridae</b>						
<b>Betacoronaviruses</b>						
SARS-Coronavirus (SARS-CoV)	+	+	–	+	+	–
MERS-Coronavirus (MERS-CoV)	∅	∅	∅	∅	∅	∅

+: published.

–: not published.

∅: no infection.

disease in their natural hosts, develop antibody responses and histopathological changes indicative of an infection in the upper respiratory tract similar to those seen in other species, and may thus be an attractive model for the development of vaccines or antivirals (Capraro et al., 2008; Durchfeld et al., 1991; Mascoli et al., 1976, 1975). Finally, during the late sixties, the use of ferrets as an animal model for neonatal rubella was explored but this was ultimately unsuccessful (Elizan et al., 1969; Fabiyi et al., 1967; Rorke et al., 1968).

## Conclusion

Ferrets have been used as animal models in viral research since the beginning of the 20th century, starting with influenza and, as their susceptibility for human respiratory viruses became increasingly apparent, followed by an ever increasing number of additional pathogens (Table 1). Even though their housing requirements are more elaborate than those for rodents, ferrets can still be accommodated in most animal facilities, and animals can be purchased from several commercial sources. The greatest disadvantage of the ferret as an animal model remains the relative lack of species-specific reagents. Although international efforts have been made to improve this situation by generating ferret-specific tools and by identifying cross-reactive reagents (Fang et al., 2010; Rutigliano et al., 2008), ferret immune responses are still poorly characterized. In addition, the potential of the model to characterize the contribution of opportunistic infections and different routes of inoculation, the dynamics of aerosol transmission, and infections in the context of immunosuppression or co-morbidities is just beginning to be explored (Belser et al., 2014; Gustin et al., 2013; Huber and McCullers, 2006; Koster et al., 2012; McCullers et al., 2010; Peltola et al., 2006). Because of its great public health relevance, most of the studies to date have

focused on influenza viruses, but an extension to other pathogens is likely to follow in the near future.

The completion of the ferret genome and the publication of the ferret transcriptome (Bruder et al., 2010; Peng et al., 2014) also open new avenues of experimentation. Not only is it possible to identify transcribed mRNA or activated genes at a given time point of any viral infection, but the ferret genome information also facilitates the development of species-specific genomic and proteomic tools and the mapping of signaling pathways. After succeeding with somatic cell nuclear transfer (Li et al., 2006), the CFTR-knockout ferret as a cystic fibrosis model (Sun et al., 2010) provided proof-of-concept for the generation of transgenic animals with specific phenotypes, and technical advances in the transgenics field such as the use of sleeping beauty transposons (Ivics et al., 2014) and the CRISPR-Cas system (Hai et al., 2014; Tang et al., 2015), will put transgenic ferrets within the reach of the infectious disease research community. As new viruses continue to emerge and additional immunologic, genomic, and proteomic tools for ferrets become available, the importance of this animal model for infectious disease research will likely continue to increase.

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