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Review

A treatment for and vaccine against the deadly Hendra and Nipah viruses

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ABSTRACT

Hendra virus and Nipah virus are bat-borne paramyxoviruses that are the prototypic members of the genus *Henipavirus*. The henipaviruses emerged in the 1990s, spilling over from their natural bat hosts and causing serious disease outbreaks in humans and livestock. Hendra virus emerged in Australia and since 1994 there have been 7 human infections with 4 case fatalities. Nipah virus first appeared in Malaysia and subsequent outbreaks have occurred in Bangladesh and India. In total, there have been an estimated 582 human cases of Nipah virus and of these, 54% were fatal. Their broad species tropism and ability to cause fatal respiratory and/or neurologic disease in humans and animals make them important transboundary biological threats. Recent experimental findings in animals have demonstrated that a human monoclonal antibody targeting the viral G glycoprotein is an effective post-exposure treatment against Hendra and Nipah virus infection. In addition, a subunit vaccine based on the G glycoprotein of Hendra virus affords protection against Hendra and Nipah virus challenge. The vaccine has been developed for use in horses in Australia and is the first vaccine against a Biosafety Level-4 (BSL-4) agent to be licensed and commercially deployed. Together, these advances offer viable approaches to address Hendra and Nipah virus infection of livestock and people.

1. Introduction

Hendra virus and Nipah virus are recently recognized bat-borne paramyxoviruses, each of which have repeatedly emerged causing significant morbidity and mortality in both animal and human populations since the mid to late 1990's. Hendra virus was isolated in Australia from fatal cases of severe respiratory disease in horses and one person in the Brisbane suburb of Hendra in September, 1994, and was shown to be distantly related to measles virus and other morbilliviruses (Murray et al., 1995). The same virus had also caused fatal infections in horses a month prior in Mackay, Australia, but this emergence was only recognized when one individual who was unknowingly exposed to the infected horses at that time developed a recrudescence of fatal meningoencephalitis 13 months later (O'Sullivan et al., 1997; Wong et al., 2009). Hendra virus' close relative, Nipah virus, emerged in peninsular Malaysia in 1998–99, in a large outbreak of respiratory disease in pigs along with numerous cases of encephalitis among pig farmers, eventually resulting in more than 100 human fatalities. Genetic and serological studies revealed the relatedness of this new virus to Hendra virus (Chua et al., 2000). Hendra virus and Nipah virus now represent the prototype species of the new genus *Henipavirus* within the paramyxovirus family (Wang et al., 2013).

Since their discovery, both Hendra virus and Nipah virus have continued to repeatedly cause spillover events into animals and/or people. Hendra virus infection among horses in Australia has occurred annually since 2006 and in total there have now been 7 human cases of which 4 have been fatal (Anonymous, 2009b; Playford et al., 2010). In all 7 human cases, Hendra virus was trans-

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mitted from infected horses to humans. Of note, in 2011 from the months of June to October, a significant increase in the number of Hendra virus spillovers occurred with 18 separate episodes of infection in horses in Australia, including the first recognized case of infection in a dog (reviewed in (Broder, 2012)). There were 8 cases of Hendra virus spillovers into horses in 2012 (Anonymous, 2012b) and a further two cases of Hendra virus infection in horses in early 2013 (Anonymous, 2013b). In all, a total of 42 Hendra virus spillover events have occurred since 1994 and 28 of these have occurred in just the past 2 years. Likewise, following the Malaysian outbreak in 1998, nearly annual outbreaks of Nipah virus infection, occurring primarily in Bangladesh but also India have occurred since 2001. The most recent outbreak occurred in early 2013, with apparently 10 fatalities of 12 cases (Anonymous, 2013c). Compared to the original Malaysian outbreak, these Nipah virus spillovers have been smaller in case number, however the fatality rates in people overall have been notably higher, ranging from 75–100%. Importantly, direct transmission of Nipah virus from bats to humans and significant human-to-human transmission have also been documented during outbreaks in India and Bangladesh. The epidemiological details of the spillovers of both Hendra virus and Nipah virus into people since their emergence and recognition have recently been reviewed and summarized in detail (Luby and Gurley, 2012). There have been an estimated 582 cases of Nipah virus infection with 315 human fatalities (Anonymous, 2013c; Luby and Gurley, 2012; Luby et al., 2009; Pallister et al., 2011a).

2. The henipavirus transboundary threat

The natural reservoir hosts of Hendra virus and Nipah virus are several species of pteropid fruit bats among which they are not known to cause disease (Halpin et al., 2011). However, Hendra and Nipah viruses possess an exceptionally broad species tropism and both natural and experimental infections have demonstrated their capacity to cause disease which can often be fatal in horses, pigs, cats, dogs, ferrets, hamsters, guinea pigs, monkeys, and humans, spanning 6 mammalian Orders (reviewed in (Geisbert et al., 2012)). In disease susceptible animal hosts and people, Nipah virus and Hendra virus cause a systemic infection that is characterized as a wide-spread vasculitis and endothelial cell tropism. Though this pathology is not unique to these henipaviruses, an understanding of Hendra and Nipah virus cellular tropism on the molecular level has provided an explanation to this disease feature which includes the appearance of syncytia, thrombosis, ischemia and necrosis, with parenchymal cell infection and associated pathology in many major organ systems, and prominently in the brain and lung (reviewed in (Weingartl et al., 2009; Wong and Ong, 2011)). The major involvement of the lung and brain in Hendra and Nipah virus infection often manifests as an acute severe respiratory syndrome, encephalitis or a combination of both. Disturbingly however, infection in people can also have longer term consequences, and in addition to an acute symptomatic infection, Hendra and Nipah virus infection can also take a protracted course following recovery from an initial infection. Individuals in these cases can later undergo a recrudescence of virus replication in the central nervous system (CNS) causing a relapse of encephalitis, a process that was first noted in the second fatal case of Hendra virus human infection (O'Sullivan et al., 1997; Wong et al., 2009). Quite remarkably, relapsed-encephalitis caused by Nipah virus has been reported in people from several months to as long as 11 years following infection (Abdullah et al., 2012) (reviewed in (Wong, 2010)). How the henipaviruses survive immune-mediated clearance and can later cause a recrudescence of replication in the CNS is unknown, but this virological feature clearly has important implications for anti-henipavirus therapeutics development.

Given the virulence of Hendra and Nipah virus and the increase in their spillover occurrences over the past decade, strategies to mitigate the risk of Hendra and Nipah virus exposure have become paramount. Both Hendra virus and Nipah virus reside in large wild bat populations, which make controlling virus in the reservoir host or influencing the reservoir host population dynamics difficult to impossible. In extreme instances, bat culling has been proposed to minimize exposure; however, the ecological importance of bats as a whole makes this an unrealistic option. In Malaysia and Australia efforts have been made to reduce livestock interactions with bats; for example, restricting livestock access to areas under fruit trees, covering water and feed containers to prevent contamination and not placing water and feed under fruit trees (Anonymous, 2013a). However, the significant numbers of fruit trees and roosting flying foxes on or near properties containing livestock makes complete separation of the wildlife and livestock populations near impossible. In Bangladesh, measures have been employed to prevent flying foxes access to date palm sap collectors in hopes of preventing contamination with Nipah virus (Luby and Gurley, 2012). Unfortunately, Nipah outbreaks continue to occur every year reflecting the difficulty of implementing a new practice culturally to prevent such a disease that is still considered to be rare. Developing vaccines and antiviral therapies for Hendra and Nipah virus are also viable alternatives for mitigating disease risk. As livestock have been identified as intermediate hosts for both Hendra and Nipah virus, antiviral therapies seem less attractive given the size of horses and pigs and the significant costs associated with producing large quantities of any possible drug. Conversely, vaccination of livestock populations is a highly attractive mitigation strategy since both disease in the target species as well as secondary transmission of virus to humans would be prevented. In areas such as Bangladesh, where no intermediate host has been definitively identified, there is a real need for the development of effective therapies and vaccine strategies to prevent infection. Similarly, for individuals who have potential occupational exposure to Hendra and Nipah virus infection, such as pig farmers and equine veterinarians, therapeutic agents and/or a vaccine to prevent infection would significantly reduce morbidity and mortality associated with Hendra and Nipah viruses.

Hendra and Nipah virus attach to host cell-surface displayed ephrin-B2 or -B3 proteins and infect host cells by the coordinated activity of their attachment (G) and fusion (F) glycoproteins (reviewed in (Aguilar and Iorio, 2012; Lee and Ataman, 2011)). The G glycoprotein monomer consists of a stalk and globular head (Fig. 1) and the atomic structures of both the Nipah and Hendra virus G glycoprotein's globular head domain have been determined alone and in complex with ephrin proteins (reviewed in (Xu et al., 2012a)). The F glycoprotein mediates the membrane fusion process between the viral and host cell membranes by a Class I fusion mechanism that is initiated following the G glycoprotein engagement of ephrin receptor (Lee and Ataman, 2011). The susceptible host species and associated cellular tropism and pathology of Hendra and Nipah virus has in large part been explained by their use of the highly conserved ephrin-B2 and -B3 proteins as entry receptors (reviewed in (Pernet et al., 2012; Wong and Ong, 2011)). In addition and of importance to countermeasure development, the henipavirus G and F envelope glycoprotein spikes are major targets of virus-neutralizing antibodies and as discussed below, the development of potential vaccines have largely focused on these important structural components of the virion (reviewed in (Broder, 2010)).

The development of medical countermeasures for use in humans is a time-consuming process, especially for highly pathogenic