Monash University researchers have created a novel strategy for developing a live and attenuated rabies vaccine with a 'best in class' safety profile that could support the expanded use of live rabies vaccines in the domestic animal and human pharmaceuticals markets.

Benefits over existing treatments:
- 'Best in class' safety profile for live attenuated rabies vaccines.
- Potential expansion into the domestic animal market.
- Potential prophylactic and/or post-exposure vaccine in humans.
- Applicable in live vaccines for other lyssaviruses.

Background
Rabies is a zoonotic viral disease caused by members of the lyssavirus genus that cause acute encephalitis in warm-blooded animals. Lyssaviruses, the most common of which is the rabies virus, are usually transmitted through a bite from an infected or 'rabid' animal.

In humans, rabies is almost invariably fatal if post-exposure prophylaxis using vaccine and rabies immunoglobulins is not administered prior to the onset of symptoms. Rabies causes > 55,000 human deaths p.a. mostly in Asia and Africa, with almost 100% of these cases arising from rabid dog bites. The estimated annual cost of rabies infections, when including domestic and agricultural animal populations, is US$6 billion (WHO).

Inactivated viral vaccine products are on the market but only offer short-term (1-3 years) partial protection in domestic animals and humans, and require multiple inoculations both before and after virus exposure. Additional major limitations are cost and deliverability – particularly in the developing world.

Live viral vaccines can overcome these limitations, often providing long-term prophylactic protection from simple regimens, including single dose delivery. For rabies virus, these products encompass poxvirus-vectors expressing the immunoprotective rabies virus glycoprotein (G-protein), and live rabies virus attenuated via a single mutation/amino acid substitution in the G-protein.

However, live rabies virus vaccines have been limited by a generally poor immunogenicity of the poxvirus-vectors (especially in dogs – the main vector to humans), and a residual pathogenicity of attenuated rabies virus in some species. There is also the potential for reversion of the single attenuating mutation. Therefore, attenuated viral vaccines have been used only in select wild-animal populations in "live" baits.

The opportunity
Monash University researchers have recently identified at least 2 novel attenuating site-specific mutations in the highly conserved lyssavirus phosphoprotein (P-protein). These mutations ablate the critical activity of P-protein in facilitating viral evasion of the host immune response by preventing signalling by interferon (an anti-viral cytokine) through inhibition of the STAT1/2 transcription factors. However, these mutations do not affect P-protein-mediated viral genome replication functions, allowing the virus to be generated at high titres in the absence of interferon.

Rabies virus containing these novel mutations has been shown to be profoundly attenuated in vivo (see Figure 1). The use of multiple attenuations across distinct viral genes (i.e. P-protein and G-protein) in a live virus vaccine offers the opportunity for a 'best in class' safety profile, with a probability of spontaneous reversion at almost zero.

This safety profile is a point of differentiation that expands the potential use of live attenuated rabies vaccines to the domestic animal (companion and livestock) and human pharmaceutical markets. These attenuations could also form the basis of the first live vaccines in animals and humans against lethal lyssavirus species (such as Duvenhage or Mokola virus) that are not prevented by the current rabies virus vaccines.

Key contact:
Dr Michael Bettess
Senior Business Development Manager
Industry Engagement and Commercialisation
michael.bettess@monash.edu
+61 3 9905 6243
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Figure 1. Mutated rabies virus is strongly attenuated in vivo. Mice were infected with 10⁴ focus forming units of attenuated or wildtype virus (12 mice/group) and disease symptoms monitored for 21 days. All mice infected with wildtype virus died (†) by 12 days post-infection (dpi), but mice infected with attenuated virus showed no major symptoms. The graph indicates mean body weight change.