

Opportunity

To accelerate the development of therapeutic and/or prophylactic rabies vaccines through licensing or direct investment, contact:

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Attenuation strategies for live rabies vaccine

Developing live rabies vaccines based on attenuating virus with amino acid substitutions

The Technology

- Live viral vaccines can overcome the limitations of inactivated vaccines, providing long-term prophylactic protection from simple regimens, including single dose delivery.

Market Need

- Rabies is a vaccine preventable disease; however, there is no cure, and it is usually fatal once symptoms appear. While inactivated rabies vaccines have multiple disadvantages, the development of new and improved vaccines is a priority for the control of rabies.

Technology Status

- Introducing attenuating mutations in the highly conserved lyssavirus phosphoprotein (P-protein) ablates the critical activity of P-protein in facilitating viral evasion of the host immune through inhibition of the STAT1/2 transcription factors. Using a combination of such mutations in a live virus vaccine offers the opportunity for a 'best in class' live rabies vaccine with safety and immunogenicity profile.



Market Need

Currently Rabies is an invariably fatal viral disease in animals and humans. Nearly 59,000 human deaths worldwide are attributable to rabies annually.

The mass vaccination of domestic animals has been the most effective factor in reducing human rabies. However, inactivated rabies vaccines have multiple disadvantages. They are difficult to manufacture and store, have low immunogenicity, and require multiple injections.

Moreover, they are expensive and thus beyond the reach of most people who need to use the vaccines, such as in developing countries. In addition, these inactivated vaccines typically include adjuvants which may cause unwanted side effects.

Live viral vaccines can overcome the limitations of the inactivated vaccines, often providing long-term prophylactic protection from simple regimens, including single dose delivery. However, live rabies vaccines that are currently available have several issues that require improvements in areas such as:

- need for even higher immunogenicity
- residual pathogenicity problems
- risks of reversion to virulence

Solution

UoM researchers have identified a combination of 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 antiviral 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*. The use of multiple attenuations across a distinct viral gene(s) in a live virus vaccine offers the opportunity for a 'best in class' safety profile, with a probability of spontaneous reversion at almost zero.

Technology and IP Status

UoM researchers have performed structural analysis of the full-length STAT1 protein binding to an interferon antagonist of a rabies virus. They identified a complex interface comprising several distinct sites and demonstrated

that targeted modifications of these sites can significantly attenuate the pathogenic virus. It has been shown in the two distinct RABV strains (Tha street strain and ERA strain) that a combination of mutants can be introduced to make a viable vaccine strain that is safe and protective *in vivo*.

Introduction of mutants to ERA live vaccine strain (previously used for wild animals) for testing in mice indicated:

- greatly enhanced safety: wild-type ERA remained pathogenic in mice, but mutant strain was non pathogenic
- effectiveness as a vaccine: infection with an attenuated mutant ERA strain protected 100% of mice from a standard pathogenic rabies virus challenge.

These novel mutations can be used independently or combined with other attenuating mutations affecting other viral proteins/mechanisms. This creates an opportunity to generate a 'best-in-class' live vaccine with safety and immunogenicity profile that is not provided by the current rabies virus vaccines on the market.

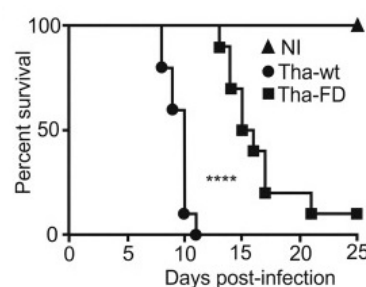


Figure 1. Survival data for BALB-c mice infected with either RABV Tha-WT Street strain or Tha-FD (F209A/D235A-mutated) Street strain. Tha-FD showed significantly impaired pathogenesis compared with Tha-WT following intramuscular inoculation of mice.

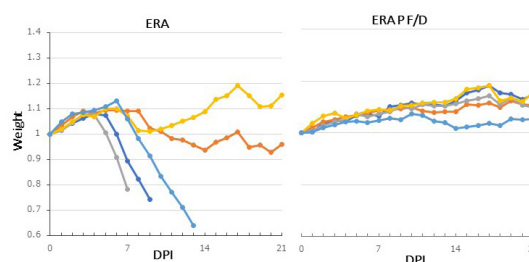


Figure 2. ddY mice were intramuscularly inoculated with the indicated virus (ERA virus, ERA virus containing the mutations (ERA P F/D)). Weight and health was monitored for 21 days; >50% of mice inoculated with ERA strain reached the end point within 14 days. No specific symptoms were evident for mice infected by ERA P F/D virus.

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Researchers	Prof Paul Gooley, Assoc Prof. Gregory Moseley
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Patents	National phase patent applications in Australia, USA, India and Japan. International Publication NO.: WO 2020198776 A1, priority date 3 April 2019.
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