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Publication date:
2014

Document Version
Publisher's PDF, also known as Version of record

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Citation (APA):
Gullberg, M., Polacek, C., Bøtner, A., & Belsham, G. (2014). *Targeted modifications of foot-and-mouth disease virus; towards improved vaccine candidates*. Abstract from 8th Annual Meeting of Epizone, Copenhagen, Denmark.

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Targeted modifications of foot-and-mouth disease virus; towards improved vaccine candidates

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Foot-and-mouth disease virus (FMDV) is responsible for one of the most economically important diseases of farm animals (estimated annual costs are about US\$10 billion globally). The virus is the prototypic *Aphthovirus* within the family *Picornaviridae* and has a positive sense RNA genome (ca. 8.3kb) encoding a single large polyprotein that is processed to generate about 15 mature proteins plus precursors. The virus particle comprises 60 copies of 4 separate capsid proteins (VP1-VP4) plus a single copy of the genome. By modifying full length cDNAs, producing RNA transcripts *in vitro*, and introducing these into susceptible cells it is possible to rescue specifically altered FMDVs. We have used this approach to generate modified viruses that have particular properties; these studies can assist in the development of improved and safer vaccines to protect against FMDV. For example, we have made changes to the leader (L) protein coding sequence. The L protein is the first component of the viral polyprotein and is produced in two forms, termed Lab and Lb as the result of use of alternative initiation codons, 84 nt apart. Both forms have protease activity (which separates the L protein from the capsid precursor) and induce the shut-off of host cell protein synthesis. When the shorter form, Lb, is precisely deleted then FMD viruses that grow well in cell culture are produced (Belsham, 2013). However such viruses are attenuated within cattle. In contrast, when the entire Lab coding sequence is deleted then no viable viruses are generated. In an alternative approach, we have modified a processing site within the viral polyprotein so that incomplete processing occurs. It has been shown that a single amino acid substitution that blocks cleavage of the VP1/2A junction within the capsid precursor results in the production of modified "self-tagged" virus particles that contain the VP1-2A precursor (Gullberg et al., 2013). This approach works for two of the most common FMDV serotypes (O and A) and offers the possibility of a single approach to purifying virus particles from different serotypes using reagents targeted to the conserved 2A peptide.

(340 words)

Belsham, GJ. (2013). Influence of the Leader protein coding region of foot-and-mouth disease virus on virus replication. *J. Gen Virol.* 94, 1486-1495.

Gullberg, M, Polacek, C, Bøtner, A & Belsham, GJ. (2013) Processing of the VP1/2A Junction is not necessary for production of foot-and-mouth disease virus empty capsids and infectious viruses: characterization of "self-tagged" particles. *J. Virol.* 87, 11591-11603.