



## A Single Amino Acid exchange with the G Protein of a Non-Pathogenic RV

An abstract entitled "An Asn→Lys mutation at amino acid position 194 of the G protein of highly attenuated rabies virus (RV) strains is responsible for reemergence of neurovirulence" was reported by Marie-Luise Faber\*, Milosz Faber\*\*, Jeffrey A. Mattis\*, Koon Yan Pak\*Bernhard Dietzschold\*\*, and Matthias J. Schnell\*\*\* at the American Society for Virology on June 18-22, 2005.

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It is well established that an Arg→Glu exchange at amino acid position 333 of the G protein of several RV strains renders these viruses non-pathogenic and, therefore, RV strains containing such modified G proteins have a great utility as oral vaccines for wild life. However, a potential problem with the use of such live modified RVs for vaccination is the high mutation rate of RNA viruses. To examine the possibility of reversion to the pathogenic phenotype, several attenuated RV strains were passaged in newborn mice. While the Glu333 of G remained unchanged after ten consecutive passages, an Asn→Lys exchange emerged at position 194 of G which was accompanied by an increase in neurovirulence. Site-directed mutagenesis in conjunction with reverse genetics revealed that this Asn194→Lys194 mutation was solely responsible for the reemergence of the pathogenic phenotype. On the other hand, the non-pathogenic phenotype could be stabilized by an Asn194→Ser194 exchange and no mutations or increase in pathogenicity were detected after passaging the Ser194 variant in mice. Interestingly, RVs containing two G genes exhibited the pathogenic phenotype only if Lys194 was present in both G genes, suggesting that neurovirulence requires an Asn194→Lys194 exchange in all G molecules that form the peplomers of the virus particles. In vitro analysis revealed that the enhanced pathogenicity of Lys194 RV variants correlates with a decrease in the time necessary for internalization of RV virions and the capacity of the virus to induce syncytia formation.

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