

## Development of a Transgenic Murine Model for Human Herpesvirus-6 Infection

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Several clinical studies have correlated human herpesvirus 6 (HHV-6) infection to the pathogenesis of different diseases, including the neurological autoimmune disease multiple sclerosis (MS). However, a direct link of causality between HHV-6 and MS is still missing, and the lack of suitable small animal models for HHV-6 infection has considerably

hampered the study of the viral infection in the central nervous system. Human CD46 molecule was identified as a receptor for HHV-6, opening new perspectives for experimental approaches. We have generated several lines of transgenic mice, expressing one or both isoforms of CD46 (Cyt1 and/or Cyt2), crossed or not into an interferon type 1 receptor deficient background, and analyzed their susceptibility to HHV-6 infection. We first generated primary brain cell cultures from these mice and infected them with HHV-6A (strain GS) or HHV-6B (strain Z29). We detected expression of viral transcripts only in cultures from CD46-expressing mice and not from wild type mice, after HHV-6A, but not HHV-6B infection. These mice were also infected *in vivo* with both variants of HHV-6 and were monitored for up to 3 months. In agreement with *in vitro* results, HHV-6A DNA persisted for up to 2 months in the brain of CD46-expressing mice but not in the non-transgenic littermates, whereas HHV-6B DNA levels decreased rapidly after infection in all mice. Although infected mice did not show clinical signs of disease, histological studies revealed the presence of demyelinated areas and infiltrating cells in the brain. Finally, preliminary experiments with experimental autoimmune encephalomyelitis (EAE), the animal model for MS, suggested that HHV-6 infection prior to EAE induction could significantly increase the severity of the disease, implying a possible effect of HHV-6 on MS-like disease development *in vivo*. Our results present the first murine model for HHV-6A infection, opening novel perspectives for the study of virus-associated pathologies.