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Comparative neuropathogenesis and neurovirulence of attenuated flaviviruses in non-human primates

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Tick-borne encephalitis (TBE) is a debilitating and often fatal neuroinfection caused by RNA viruses belonging to the *Flaviviridae* family. Licensed inactivated TBE vaccines are currently available in Europe and Russia, however, three doses of vaccine are required for primary immunization, and subsequent booster vaccinations every 3 years are needed to maintain protective immunity. Despite immunization of populations living in endemic areas using inactivated TBE vaccines, TBE remains a pressing public health problem. A less expensive live TBE vaccine that induces more durable immunity is needed.

Based on previous preclinical evaluation in mice and monkeys, the chimeric TBEV/DEN4Δ30 virus, carrying the prM and E protein genes from a highly virulent Far Eastern strain of tick-borne encephalitis virus (TBEV) on the backbone of a non-neuroinvasive dengue type 4 virus (DEN4), has been identified as a promising live attenuated virus vaccine candidate against disease caused by TBEV. However, prior to use of this vaccine candidate in humans, its neurovirulence in non-human primates needed to be evaluated.

In the present study, we compared the neuropathogenesis of the chimeric TBEV/DEN4Δ30 virus, Langat virus (LGTV), a former live TBEV vaccine, and yellow fever 17D virus vaccine (YF 17D) in rhesus monkeys inoculated intracerebrally. TBEV/DEN4Δ30 and YF 17D demonstrated remarkably similar spatiotemporal profiles of virus replication and virus-associated histopathology in the CNS that were high in cerebral hemispheres but progressively decreased toward the spinal cord. In contrast, the neurovirulence of LGTV exhibited the reverse profile progressing from the site of inoculation toward the cerebellum and spinal cord. Analysis of the spatiotemporal distribution of viral antigens in the CNS of monkeys revealed a prominent neurotropism associated with all three attenuated viruses. Nevertheless, TBEV/DEN4Δ30 virus exhibited higher neurovirulence in monkeys compared to either LGTV or YF 17D, suggesting insufficient attenuation.

Our results provide insight into the neuropathogenesis beyond the most often analyzed time point on day 30 post-inoculation and demonstrate that attenuated flaviviruses can be more reliably discriminated by their histopathological profile at earlier time points, such as day

14 to 21. These findings and our modified methodology of histopathological evaluation of neurovirulence associated with attenuated flaviviruses may guide the design of safe vaccines against neurotropic flaviviruses.

We are currently performing a computerized morphometric analysis of the cellular inflammatory responses within the CNS of monkeys to investigate their role in the neuropathogenesis and contribution to the outcome of neuroinfection. Results of these studies will be presented.