Development of Live attenuated Langat virus infectious clone as potential new TBEV vaccine candidate: Study of cellular and humoral immune response in mice

Rita Jaafar[1], Naveed Asghar[1], Karl Ljunberg[2], Wessam Melik[1], Magnus Johansson[1], Developvaccines@oru [1, 2, 3]

[1] *School of Medical Science, Örebro University, Örebro, Sweden*
[2] *Eurocine Vaccines AB, Solna, Sweden*
[3] *Academy of Quality in Pharm Science AB (AQPS), Södertälje, Sweden; Adlego Biomedical AB, Solna, Sweden; GU Ventures AB, Göteborg, Sweden; Karolinska Cell Therapy Center (KCC/ Vecura), Huddinge, Sweden; Karolinska Institutet, Department of Laboratory Medicine, Huddinge, Sweden; MIVAC Development AB, Göteborg, Sweden; Nordic BioAnalysis AB (NBAB), Södertälje, Sweden; Probi AB, Lund, Sweden; Svenska Vaccinfabriken produktion AB (SVF), Sollentuna, Sweden; Valneva SE, Solna, Sweden*

Tick-borne encephalitis (TBE) is one of the most important tick-transmitted diseases in Europe and Asia. The incidence of TBE cases showed a remarkable elevation in recent years probably due to the geographic expansion of TBEV and its vectors, which is concerning in the absence of a specific antiviral treatment. Vaccination remains the best protective measure against TBE. However, currently available vaccines have a burdensome immunization schedule, and poor immunogenicity in the elderly, which may contribute to observed vaccine failures, i.e., TBE occurrence in vaccinated people. One aim within the Developvaccines@oru project is to develop a novel TBE vaccine that could provide improved immunogenicity using fewer doses. Our strategy is to induce an immune response at possible sites of virus infection by a modified live attenuated vaccine based on Langat virus (LGTV). Infectious clones of Langat virus (LGTV IC) based on the strain available in our laboratory are created followed by the generation of modified LGTV IC as potential attenuated virus. Then, we compare them with the ¨original¨ LGTV strain using cell based and animal models. In our laboratory, we f successfully created LGTV IC. In order to establish a baseline for animal experiments with our vaccine candidates, we planned a pilot study using the “original” LGTV and LGTV IC strains. First, we conducted a pre-pilot experiment to optimize the study design and evaluation methods. Our preliminary data shows that intramuscular administration of both strains was well tolerated in mice. In contrast to the original LGTV, LGTV IC was found to cause a transient, but significant reduction in body weight. ELISA results showed that mice antibodies after LGTV IC infection cross reacted with TBEV antigens. The T lymphocytes, isolated from these mice spleens, showed Interferon gamma secretion when stimulated with both LGTV and TBEV peptides. However, this cellular response revealed higher in original LGTV infected mice. Moreover, we confirm that LGTV IC show lower viraemia peak than original LGTV, both occurring at 2 days post infection. Besides, we have successfully rescued modified LGTV infectious clones with individual or combined mutations in genomic regions coding for NS3, NS5 and/or 3’non-coding region of LGTV genome. Further in-vitro and in-vivo investigation of the modified and potentially attenuated LGTV clone, seems interesting in the development approach of new TBEV vaccine candidate.