Bridging the Clinical Gap for DNA-based Antibody Therapy through Translational Studies in Sheep

Kevin Hollevoet[1*], Stéphanie De Vleeschauwer[2], Elien De Smidt[1,3], Giles Vermeire[1], Nick Geukens,[3] Paul Declerck[1]

Abstract

Clinical translation of DNA-based administration of monoclonal antibodies (mAbs) is uncertain due to lack of large animal data. To bridge the clinical gap, we evaluated a panel of novel plasmid DNA (pDNA)-encoded mAbs in 40-70 kg sheep with a clinical intramuscular electroporation protocol. Injection of 4.8 mg of pDNA, encoding ovine anti- CEA mAb (OVAC), led to peak plasma mAb titers of 300 ng/ml. OVAC remained detectable for three months and was boosted by a second pOVAC administration. Hyaluronidase muscle pretreatment increased OVAC concentrations up to ten-fold. These higher plasma titers, however, led to anti-drug antibodies (ADAs) towards the OVAC variable regions, resulting in loss of mAb detection and of adequate re-dosing. Transient immune suppression avoided ADA formation, with OVAC peaking at 3.5 µg/ml and remaining detectable for 11 months after pOVAC injection. DNA-based delivery of ovine anti-EGFR mAb (OVAE), identical to OVAC except for the variable regions, preceded by hyaluronidase, allowed for at least three consecutive administrations in an immune-competent sheep, without ADA response. When tripling the pOVAE dose to 15 mg, transient ADAs of limited impact were observed; plasma OVAE peaked at 2.5 µg/ml and was detected up to seven months. DNA-based anti-HER2 trastuzumab in sheep gave no detectable mAb concentrations despite previous validation in mice, highlighting the limitations of relying on small-rodent data only. In conclusion, our results highlight the potential and caveats of clinical DNA-based antibody therapy, can expedite pre-clinical and clinical development, and benefit the field of gene transfer as a whole.

Plasma trastuzumab in sheep #4409 and #0999 was also quantified with a commercial HER2-coated SHIKARI® Q- TRAS ELISA (Matriks Biotek) following manufacturer's instructions.