HISTIDYLATED NANOVECTORS FOR MRNA VACCINE FORMULATION: INDUCTION OF A STRONG ANTI-TUMOR T CELL IMMUNITY COMBINED WITH INFLAMMATORY STATE.

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These last years, we are witnessing the emergence of new class of biopharmaceuticals based-on transcribed mRNA. They emerged as an extremely tunable vaccination platform. Formulations made of mRNA and liposomes (lipoplexes) have yielded strong T cell responses, but require induction of cytokines identical to those that have plagued clinical development of siRNA therapeutics. We have developed histidylated Lipid Polymer mRNA nanocomplexes (LPR) that combine the beneficial properties of lipid based and polymer based nanoparticles, including lowered cellular toxicities and improved colloidal stabilities. Immunization with LPR instigated extremely potent T-cell responses and showed superior effectiveness in controlling tumor growth compared to intravenous immunization with antigen mRNA electroporated dendrictic cells. Early innate responses to LPR were characterized by a type I IFN signature in the spleen. Nonetheless, conversely to LR, LPR did not depend on type I IFN responses to generate cytolytic effectors. This unique behavior of LPR enabled the generation of a less pro-inflammatory yet equally potent systemic LPR vaccine by usage of N1-methylpseudo-uridine (N1mψ) modified mRNA required to improve mRNA translatability by avoiding mRNA sensors activation. Overall, our data indicate that LPR can combine excellent immunogenicity with improved inflammatory and they could be an interesting alternative to formulations that are currently explored in early phase clinical trials..

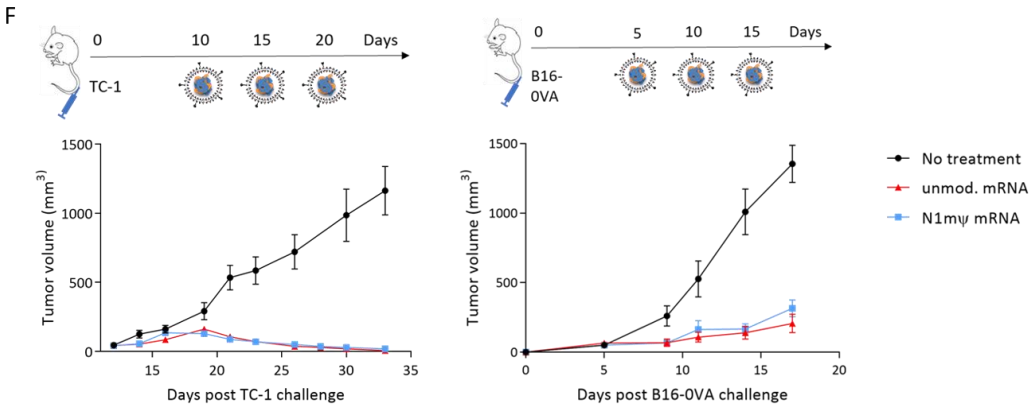

Figure 1 – N1mψ modified mRNA does not hamper antitumor T cell immunity to LPR. Tumor growth curves of TC-1 and *B16-OVA inoculated mice either left untreated or treated by IV immunization with respectively unmodified mRNA LPR or N1mψ modified mRNA LPR. TC-1 mice received three immunizations with E7/ mRNA LPR. B16-OVA mice received three immunizations with OVA/TriMix mRNA LPR.*