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# Sequential administration of a MVA-based MUC1 cancer vaccine and the TLR9 ligand Litenimod (Li28) improves local immune defense against tumors

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TG4010 is an immunotherapeutic vaccine based on Modified Vaccinia Ankara (MVA) encoding the human tumor-associated antigen MUC1 and human IL-2. In combination with first-line standard of care chemotherapy in advanced metastatic non-small-cell lung cancer (NSCLC), repeated subcutaneous injection of TG4010 improved progression-free survival in phase 2b clinical trials. In preclinical tumor models, MVATG9931, the research version of TG4010, conferred antigen-specific responses against the weak antigen human MUC1. The combination of a suboptimal dose of MVATG9931 and the type B TLR9 ligand Litenimod (Li28) markedly increased survival in a subcutaneous RMA-MUC1 tumor model compared to the treatment with MVATG9931 or Li28 alone. The requirements for this protection were: 1) de novo synthesis of MUC1, 2) Li28 delivered several hours after MVATG9931 at the same site, 3) at least two vaccination cycles, and 4) implantation of MUC1-positive tumor cells in the vicinity to the vaccination site. Subcutaneously injected MVATG9931 allowed transient local gene expression and induced the local accumulation of MCP-1, RANTES, M-CSF, IL-15/IL-15R and IP-10. After repeated injection, CD4+ and CD8+ T lymphocytes, B lymphocytes, NK cells, pDCs, neutrophils, and macrophages accumulated around the injection site, local RANTES levels remained high. Delayed injection of Li28 into this environment, led to further accumulation of macrophages, the secretion of IL-18 and IL-1 beta, and an increase of the percentage of activated CD69+ NK cell. Combination treatment augmented the number of activated CD86+ DCs in the draining lymph nodes and increased the percentage of KLRG1+ CD127-CD8+ T cells at the injection site. In vivo depletion of macrophages around the injection site by clodronate liposomes reduced local IL-18 levels and diminished survival rates significantly. Thus, sequential administration of MVATG9931 and Li28 improves local innate and adaptive immune defense against tumors, arguing for intra-tumoral delivery of this peculiar sequential combination therapy.

## Biography

Karola Rittner is a creative team player with long term experience in a biopharmaceutical company, developing products from bench to bedside. Areas of experience: Virology (HIV, AAV, Adeno and MVA), RNA technologies (antisense RNA design, screening), therapeutic vaccination with MVA vectors, in combination with immune modulators (RLR ligands) and immune check point inhibitors.

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