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P03 Vaccine Therapy

P03.01 HIGH IMMUNOGENIC VLP-BASED VACCINES ELICIT NEW T CELL SPECIFICITIES AGAINST MELANOMA NEOANTIGENS IN MICE

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Background Neoantigens' (neoAg) identification, which determines T-cell responses against tumors, has fostered the development of personalized vaccines with promising results. While the ranking of the most immunogenic neoAg can be addressed using predictive techniques, their formulation as vaccines needs to be improved. To maximize their therapeutic potential, optimal neoAg-based vaccines should be manufactured in a superb delivery platform that enhances robust new immune responses, able to bypass thymic tolerance and the humoral immunosuppressive microenvironment. These novel T cell responses generated at the periphery will not be exhausted, opposite to TILs. We aim to develop a highly immunogenic vaccine platform, based on engineered HIV-derived Virus-Like Particles (VLP) expressing approximately 2500 copies of each selected neoAg. We tested different neoAgs loaded VLPs (neoVLP) in a melanoma mouse model to evaluate their capability to generate new immunogenic specificities.

Material and Methods Specific non-synonymous mutations from B16F10 cells were identified, selected and used to generate a list of prioritized peptides. NeoAgs were classified as: Tier1, acquiring a mutation that creates an anchor residue to the MHC-I, not present in the WT peptide; Tier2, acquiring a mutation in a position that largely impacts contact with the TCR respect to WT; and Tier3, acquiring a mutation in the TCR contact region but inducing a less drastic change than in Tier2. Frame shift (FS) mutations, expected to be highly immunogenic, were also included.Thirteen to fifteen selected neoAgs from each group were loaded on highly immunogenic neoVLPs. Their immunogenicity was evaluated in C57bl/6 mice by immunization with a neoVLP-coding plasmid DNA (prime) and purified neoVLPs as soluble particles (boost). Splenocytes were used to evaluate neoAg-specific T cell responses.

Results We have successfully generated and purified neoVLPs, exposing neoAgs from all groups by transient transfection of Expi293 cells. Protein integrity and VLP morphology were confirmed by western blot and cryo-EM. When used for immunization assays, neoVLPs, containing neoAgs from Tier2, Tier3 and FS groups, were capable of generating humoral responses against viral proteins and T cell responses against neoAgs present in the neoVLP. B16F10 inoculated animals, but not vaccinated, did not develop detectable T cell responses against neoAgs present in any tested neoVLP, suggesting that the vaccination with neoVLPs promoted new specificities against selected neoAgs that might contribute to tumor control and eradication.

Conclusion Our data show that the neoVLPs promote the generation of new antitumor-specific immune responses against selected neoepitopes, suggesting that neoVLPs vaccination could be an alternative to current therapeutic vaccine approaches and a promising candidate for future personalized immunotherapy.

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P03.02 PROTEIN-BASED CANCER VACCINE COMBINED WITH AN ONCOLYTIC VACCINE PROMOTES POTENT ANTITUMOR IMMUNITY

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Background KISIMA^{TM} platform allows the development of protein-based cancer vaccines able to induce a potent, tumor-specific CD8 and CD4 T cells response. While the cell penetrating peptide and peptide agonist for Toll like receptor (TLR)-2 and TLR-4 confer, respectively, the cell delivery and self-adjuvanticity properties, the multiantigenic domain allows the targeting of different cancer antigens, resulting in antitumoral efficacy in different murine models. Oncolytic viruses exert their therapeutic effects by a prolonged oncolytic action and the associated intratumoral inflammation as well as general immune activation. Arming oncolytic virus with tumor associated antigens can additionally enhance the tumor-specific T cell portion and therefore positively affect the balance of antitumor versus antiviral immune responses. The protein vaccine KISIMA^{TM} and the recombinant oncolytic virus VSV-GP-TAA (vesicular stomatitis virus pseudotyped with LCMV GP expressing tumor-associated antigens) are both promising vaccine candidates that offer a new