MULTI-EPIPOTE DNA VACCINE TARGETING CANCER NEOANTIGENS ENHANCES EFFICACY OF ANTI-PD1 THERAPY

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Background Immune checkpoint inhibition (ICI) has revolutionized cancer therapy and significantly improved survival of patients across several cancer types. However, ICI is only effective in some patients and most patients don’t respond to ICI.1,2 Neoantigens are tumor specific antigens derived from either point mutations or gene/RNA fusions in cancer cells, and can be recognized by the host immune system as foreign antigens. Several studies have shown that the success of ICI is linked to the number of neoantigens in the patient’s tumor.[3][4] Here, we demonstrate that DNA immunogens designed to target 40 neoantigens derived from MC38 mouse model of colon cancer synergizes with anti-PD1 antibody and improves the efficacy of anti-PD1 therapy.

Methods We performed whole exome sequencing on MC38 tumors to identify neoantigens. Through the sequencing data, we identified 40 neoantigens based on predicted affinity to class I MHC binding. All 40 neoantigens were encoded into a single plasmid vector, we designed each neoantigen separated by a furin cleavage site. Immune responses were measured in C57/Bl6 mice via IFN-γ ELISPOT assay and flow cytometry. Finally, we tested immunization with MC38vax to impact tumors in vivo and whether co-treatment with anti-PD1 antibody treatment further impacted tumor control.

Results In ELISPOT data, we observed that 11/40 neoantigens generated immune responses in mice. We also studied immune response to WT peptides and observed that the immune response was specifically induced against mutated peptides. Using flow cytometry, we observed that the vaccine induced predominantly CD8+ T cell responses, although CD4+ T cell responses were also observed. In a therapeutic tumor challenge, both anti-PD1 antibody and MC38vax as single treatment partially controlled the growth of MC38 tumors. However, co-treatment with both therapies was synergistic, demonstrating a 100% tumor control rate and improved animal survival.

Conclusions Large collections of neoantigens in a DNA immunization platform drive CD8+ T cell immunity against a diverse set of tumor antigens resulting in significant impact on tumor growth and improving survival. In combination with anti-PD1 these vaccines allow for tumor clearance and 100% survival from challenge, significantly improving the outcome of anti-PD1 therapy alone. These studies establish the importance and feasibility of improving patient specific T cell immunity, providing new tools for improving immunotherapy of, in this case colon adenocarcinoma, that is worth considering in other cold tumors that respond poorly to ICI.

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REFERENCES