Modulating T cell immunity in tumors by targeting tumor-associated antigens, PD-L1 and neoantigens using a versatile attenuated Salmonella vaccination platform

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Background

VAXIMM’s oral T-cell vaccine platform is based on the approved live attenuated Salmonella Typhi strain Ty21a vaccine, which has been shown to be safe and well tolerated. The bacteria are modified to deliver an eukaryotic expression plasmid which encodes the genetic information of a specific target antigen, via the oral route.1 A proposed mechanism of action is described in Figure 1.

Immunogenicity

Immunokinetic studies were performed in C57BL/6 mice (n=5 per group) immunized 4 times every other day via the oral route with 105 CFU of either VXM04, VXM06, VXM03 or the empty vector control. The frequency of antigen-specific T cells was measured at different time points in the spleen by flow cytometry using a fluorescently labelled MHC class I/peptide pentamer.

Vaccination with VXM01, VXM04 and VXM06 induced a significant systemic antigen-specific CD8+ T cell response, with a peak immune response detected 7 to 10 days after the final immunization, with little antigenic stimulation (Figure 3B).

Immunity to PD-L1

Live attenuated Salmonella Typhimurium DNA vaccines VXM10 and VXM10a are transformed with eukaryotic expression plasmids encoding the full-length murine programme death-1 (PD-L1) protein and a truncated form of PD-L1 respectively. The depletion of the signal peptide in VXM10a prevents the proper localization of the native PD-L1 protein to the cell membrane.

The antibody response was evaluated in the serum of animals 79 days after the final immunization. Anti-PD-L1 antibodies were detected in animals vaccinated with VXM10 and VXM10a, and the response was more pronounced in the highest dose vaccination groups, with 50% of the animals showing signal-to-background ratio above 2.0 (Figure 6).

Multi-epitope vaccines

The immunogenicity of different polypeptide vaccines, based on the VXMNEO platform, was assessed in healthy C57BL/6 mice. The frequency of specific CD8+ T cells was measured 10 days after the final vaccination in the spleen by flow cytometry using fluorescently labelled MHC class I/peptide pentamers. The different constructs encode multiple CD8 and CD4 epitopes from VEGFR2 (KDR2 and KDR3), Mesothelin (MSLN), WT1, and Glypican-3 (GPM3), linked via different spacers, e.g. "string-of-beads", and in different orders.

VXMNEO vaccines induced a substantial systemic T-cell response for up to 6 out of 9 CD8 epitopes. Importantly the dose, treatment schedule, ordering and linkage strategy greatly influence the immunogenicity of the encoded polypeptide (Figure 9).

Conclusions

VXM06 was well tolerated at the effective doses.

VXM01, VXM04 and VXM06 induced significant systemic antigen-specific T cell responses in animals, and demonstrated consistent anti-cancer activity.

VXM10 vaccines stimulate both humoral and cellular immunity against the cancer antigens.

VXM06 and VXM10 vaccines induced a rapid and sustained anti-leukemia activity in both the prophylactic and therapeutic settings, and a potent immune memory.

VXMNEO platform can be employed to stimulate T cell responses against multiple antigens encoded by polypeptide constructs, and potentially linked via "string-of-beads".

This study paves the way for advancing the development of tumor-associated antigen vaccines to the clinic, in conjunction with PD-L1 antigen vaccine VXM10 and neoantigens using the VXMNEO platform, and combination thereof, into clinical development.

References


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