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

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Background

VAXIMM's oral T-cell vaccine platform is based on the approved live attenuated Salmonella TYS strain Ty21a vaccine, which has been shown to elicit potent immune responses in animal models and in several clinical studies. The murine analogue of VXM01 has shown consistent anti-angiogenic activity in different tumor models1,2 and in several animal studies. VXM01 is currently in clinical development as a broad-spectrum cancer vaccine.

The current study summarizes the pre-clinical safety profile, the immuno-genicity and the anti-cancer efficacy of the live attenuated Salmonella Typhimurium strain SL2207 based murine DNA vaccines VXM04, VXM06, VXM10 and VXM02 which encode Mesothelin, WT1, PD-L1 full-length or truncated proteins, and multi-epitope constructs respectively.

Immuno-genicity

Immunokinetic studies were performed in C57Bl/6 mice (n=5 per group) immunized 4 times every other day via the oral route with doses of 10^6 CFU of either VXM01, VXM04, VXM06 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 an influenza-A/PR8 specific mAb. Immunogenicity results (Figure 3). The anti-vaccine efficacy of VXM01 and VXM04 was evaluated in a prophylactic setting in the Panc02 syngeneic model of pancreatic adenocarcinoma expressing MSLN3. Vaccination with VXM01 and VXM04 resulted in markedly reduced tumor growth (Figure 4). At the end of the study, the tumor growth inhibition relative to the control groups reached 60.6% and 92.8% in the VXM01 and VXM04 vaccinated groups respectively.

Immunity to PD-L1

Live attenuated Salmonella Typhimurium DNA vaccines VXM10 and VXM14 are transformed with eukaryotic expression plasmids encoding short hairpin RNA (shRNA)-mediated PD-L1 protein and a truncated form of PD-L1 respectively. The deletion of the signal peptide in VXM10A promotes the proper localization of the native PD-L1 protein to the cell membrane.

The antibody response was evaluated in the sera of FBL3-bearing animals, collected 79 days after the final immunization. Anti-PD-L1 antibodies were detected in animals vaccinated with VXM10A and VXM10B, and the response was more pronounced in the highest dose vaccination groups, with 50% of the animals showing signal-to-background ratio (SBR) above cut-off value (Figure 6).

Multi-epitope vaccines

VXM06 vaccines induced a substantial systemic T-cell response for up to 6 out of 9 CD8 epitopes. Importantly, the dose, treatment schedule, and linkage strategy greatly influence the immunogenicity of the encoded polyepitope (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 effects.

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

VXM06 and VXM10 vaccines induced a rapid and sustained anti-leukemia activity in the BALB/c model.

The oral route with doses up to 10^10 CFU of different VXM06 constructs.

Anti-leukemia activity

The anti-leukemia activity of VXM06 was evaluated in the BFL-3 disseminated model of leukemia, which also expresses a high level of PD-L1. Prophylactic vaccination with VXM01 and VXM04 generated and sustained anti-leukemia effect with 100% of surviving animals 80 days after leukemia challenge (Figure 5A). Importantly, 100% of surviving mice resisted re-challenge with BFL-3 cells at least 100 days after the final immunization (Figure 5B). Prophylactic vaccination with VXM06 generated a potent memory T cell response against the leukemia (Figure 5A). Therapeutic vaccination with VXM06 induced the full regression of surviving animals 94 days after leukemia challenge (Figure 5B).

References


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