Checkpt modification of BTLA-HVEM-LIGHT signaling by HSV-1 glycoprotein D (gD) improves vaccine-induced CD8+ T cell responses in pre-clinical cancer models

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BACKGROUND

- Checkpoint inhibition by mAbs against PD-1/PD-L1, CTLA-4 and other immunoinhibitors has revolutionized cancer treatment
- Current checkpoint inhibitors target activated T-cells that are differentiating towards exhaustion and fail to rescue exhausted T-cells
- Immunotherapies that can alter CD8+ T cell activation have the potential to enhance and broaden T cell responses to various cancers
- There remains a need to produce novel cancer treatments, alone or in combination that have better safety and tolerability
- Provide more potent and prolonged T cell responses
- Here we present data from several preclinical cancer models investigating a novel immunotherapy platform that uses gD, a genetically encoded checkpoint modifier of early T cell activation

METHODS

The effects of gD on immunogenicity and efficacy of antigens were assessed in a series of preclinical studies in mice:

- HPV-16 associated cancers using early oncoprotein vaccines against transplantable TC-1 tumours in a transgenic adenocarcinoma mouse model
- Melanoma model using an oncoprotein encoded Melapoly against transplantable B16F10 tumours
- Antigens were fused into gD and expressed by adenoviral vectors
- Prime only15 and PrimeBoost vaccines using adenoviral vectors were explored in various studies
- Control vaccinations used either gD alone, a mutated gD that does not bind to HVEM with the antigen or the antigen without gD
- Vaccination with gD-Melapoly vaccine was compared to vaccine with Melapoly alone, Ag alone or the Ag plus gD containing vaccine

RESULTS

- Depigmentation of inbred mice in the melanoma model
- Improved CD8+ T cell responses to various cancers
- Broadened CD8+ T cell responses to subdominant epitopes, which are typically not recognized by the immune system
- Addition of anti-PD-1 mAb treatment further improved the efficacy of gD-containing immunotherapies
- Checkpoint modification by gD of the BTLA-HVEM-LIGHT pathway leads to CD8+ T cell activation throughout and enhances, broadens and prolongs T cell responses
- Clinical studies to evaluate therapeutic vaccination with gD are planned

CONCLUSIONS

Expressing a tumor-associated antigen as a gD fusion protein in preclinical cancer studies shows:

- Consistently enhanced CD8+ T cell frequencies in the draining lymph nodes
- Improved clinical outcomes, including survival and delayed tumor growth
- Broadened CD8+ T cell responses to subdominant epitopes, which are typically not recognized by the immune system
- Addition of anti-PD-1 mAb treatment further improved the efficacy of gD-containing immunotherapies
- Checkpoint modification by gD of the BTLA-HVEM-LIGHT pathway leads to CD8+ T cell activation throughout and enhances, broadens and prolongs T cell responses
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REFERENCES


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ABBREVIATIONS

- Checkpoint: anti-PD-1, anti-PD-L1, anti-CTLA-4
- ICS: intracellular cytokine staining
- INN: International Nonproprietary Name
- SD: standard deviation
- SEM: standard error of mean

DECLARATION OF INTERESTS

- No declaration is necessary for this trial as the study is conducted at the Virion Therapeutics Institute.

FOR MORE INFORMATION

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