TUMOR TARGETED SUPERANTIGEN (TTS) ENHANCES CAR-T CELL ACTIVITY AGAINST SOLID TUMORS IN VIVO

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Background Chimeric antigen receptor (CAR) T-cell therapy has shown limited efficacy against solid tumors primarily due to low trafficking to the tumor, restricted cell expansion, tumor antigen heterogeneity, and immunosuppressive tumor microenvironment. TTSs are fusion proteins that consist of genetically engineered superantigens linked to fragment antigen-binding moieties directed to tumor-associated antigens. It was previously shown that TTS turns ‘cold tumors hot’,1 induces long-term memory responses in preclinical models,2 and activates CAR-T cells, enhancing their anti-cancer efficacy in vitro.3 Here we present new preclinical data demonstrating the synergistic anti-tumor effect of TTS in combination with CAR-T cells in the poorly immunogenic B16F10 tumor model, highlighting the potential of TTS to overcome existing limitations of CAR-T therapy.

Methods C57BL/6 mice were engrafted subcutaneously with B16F10 cells expressing both human 5T4 and EpCAM antigens. Seven days after tumor inoculation, mice were intravenously injected with murine CAR-T cells targeting the 5T4 antigen (h5T4-CAR-T) or control non-transduced T cells (NTD). Three days later, TTS targeting the hEpCAM antigen (C215Fab-SEA), was administered via intraperitoneal injection for four cycles of four consecutive days. Throughout the study, tumor volume, weight, and survival of the mice were monitored. Additionally, spleen, tumors and draining lymph nodes (DLNs) were harvested for immune analysis.

Results h5T4-CAR-T cell monotherapy showed limited transient anti-tumor activity, while C215Fab-SEA demonstrated some effectiveness against the B16F10 poorly immunogenic solid tumor. Notably, when h5T4-CAR-T therapy was combined with C215Fab-SEA, a synergistic effect was observed. This combination resulted in a substantial reduction in tumor size (90% growth inhibition), significantly prolonged mouse survival compared to monotherapies and even led to 20% complete remission. The combination treatment was well-tolerated with no signs of adverse events. Furthermore, ex-vivo analysis of the h5T4-CAR-T cells from spleens and DLNs revealed significant improvements in persistence, proliferation, and activity of the CAR-T cells following TTS treatment.

Conclusions Our preclinical results demonstrate the potential of TTS to enhance CAR-T cell activity against solid tumors. The synergistic effect observed in the B16F10 tumor model suggests that TTS can effectively address the limitations of current CAR-T therapy. The ex-vivo analysis further elucidates the positive impact of TTS on CAR-T cell persistence, proliferation, and activity. These results provide valuable insights for the development of improved strategies combining TTS with CAR-T therapy, paving the way for enhanced treatment options in solid tumors.

The 5T4-targeted TTS, naptumomab estafenatox, is currently being evaluated in clinical studies in combination with durvalumab [NCT03983954] and docetaxel [NCT04880863].

REFERENCES

Ethics Approval Studies were carried out in accordance with the Guide for the Care and Use of Laboratory Animals of Tel Aviv University (TAU; Tel Aviv, Israel); study approval # : 01-20-075

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