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## **Influence of NT-I7, an engineered long-acting interleukin-7, on CAR T cell therapy in liver cancer**

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**Background and hypotheses:** Glypican-3 (GPC3) is a therapeutic target in liver cancer for chimeric antigen receptor (CAR) T cell therapy since it is expressed in over 70% of hepatocellular carcinomas (HCC). hYP7 is a high affinity humanized monoclonal antibody to GPC3, and CAR T cells derived from hYP7 showed antitumor activity against GPC3-positive HCC cells. As CAR T cell therapy is largely limited by T cell proliferation and survival, interleukin (IL)-7, a non-redundant cytokine crucial for T cell development and homeostasis, has been introduced as an immunotherapeutic agent and was found to enhance immune response in some cancer patients. Here, we introduced NT-I7 (efineptakin alfa), an engineered long-acting IL-7 Fc fusion protein, alongside CAR T therapy, and hypothesized that NT-I7 would enhance the antitumor activity of hYP7 CAR T.

**Study Design and Methods:** In this study, hYP7 CAR T cells were grown in either NT-I7 or IL-2. Mouse models using luciferase expressing Hep3B cells were constructed. NT-I7 was administered one day after hYP7 CAR T infusion. Proliferation, exhaustion, immunophenotype, as well as antitumor activity of hYP7 CAR T was evaluated in vitro and in vivo.

**Results and Conclusions:** We found that NT-I7 enhanced proliferation and inhibited exhaustion of hYP7 CAR T cell both in vitro and in vivo compared to IL-2. The stem -like memory T cells, especially in CD4<sup>+</sup> T cells, increased in the presence of NT-I7 in vitro. hYP7 CAR T also exhibited significantly enhanced antitumor activity against Hep3B with NT-I7 treatment—even with a low dose of CAR T cells and NT-I7. The combination therapy achieves a complete tumor remission in mice.

**Relevance and Importance:** Hepatocellular carcinoma is one of the leading causes of death in Asia and Africa. Our hYP7-derived CAR T cells have previously shown promising effect in reducing the tumor burden in mouse models and demonstrated potential in clinical application. Here, with NT-I7, we look to develop a more effective combination strategy in treating patients with HCC.