A novel CAR-T cell therapy strategy to inhibit hepatocyte growth factor in solid tumor

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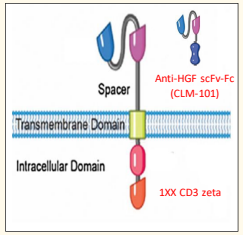
CellabMED platform - OD CAR-T (Offense and Defense CAR-T)

Offense : CD3 zeta ITAM 2 and 3 tyrosine (T) are point mutation to phenylalanine (F)

Defense : Secretion of anti-Hepatocyte growth factor single-chain variable fragment, scFv -Fc



Abstract

Chimeric antigen receptor (CAR) T cell therapy for solid tumors has not been nearly as successful and remains very challenging. One of the reasons limiting the efficacy of CAR-T in solid tumors is that various factors in the tumor microenvironment inhibit the activity of immune cells including CAR-T cells.

Hepatocyte growth factor (HGF) is a multifunctional cytokine that promotes the proliferation, invasion, metastasis and angiogenesis by its autocrine and paracrine signaling in diverse solid tumors including breast, lung, glioblastoma and ovarian tumor. In addition to these cancer-promoting properties of HGF, recent studies reported that HGF interacts with CD8 cytotoxic T cells expressing its receptor c-MET, resulting in reduced cytotoxicity and decreased infiltration to tumor region. Here, we investigated whether anticancer efficacy of CAR-T is improved in combination with anti-HGF monoclonal antibody, CLM-101. We also developed a CLM-101 single chain variable fragments (scFv)-secreting CAR-T

Methods and Materials

CLM-101 : Anti-HGF monoclonal antibody

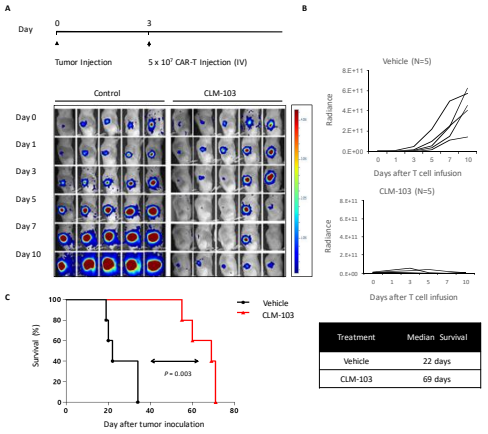
CLM-103 : IL13Ra2-specific CAR-T

CLM-103-1XX : IL13Ra2-sepecifc CAR-T (ITAM2 and 3 mutant CD3 zeta chain)

OD CAR-T : CLM-101 scFv-secreting CLM-103-1XX CAR-T

To evaluate the in vivo efficacy of CLM-103 CAR-T, CLM-103-1XX CAR-T and OD CAR-T cells, NSG mice received an orthotopic injection of 1 × 10^5 A2780-luc cells. For i.v. injection, 1.5 × 10^7 or 5 x 10^7 of CAR-T or UnTd T cells were infused into NSG mice 3 days after xenograft.

A. CLM-103



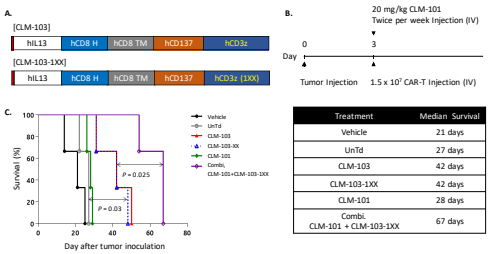
Treatment	Median Survival
Vehicle	22 days
CLM-103	69 days

Figure 1. CLM-103 improved survival rates in orthotopic mouse model

Results

The efficacy of IL13Rα2-directed CAR-T (CLM-103) cells was improved in combination with CLM-101 compared to CAR-T alone. Interestingly, *in vivo* efficacy of CLM-101 scFv-secreting OD CAR-T was better than combination of CLM-103 CAR-T cells with CLM-101 antibody in orthotopic xenograft model. This improved efficacy of CLM-101 scFv-secreting OD CAR-T may probably due to overcoming the immunosuppressive environment caused by HGF in the tumor microenvironment by blocking HGF released from the target cells.

B. Combination of CLM-103 with CLM-101



Treatment	Median Survival
Vehicle	21 days
UnTd	27 days
CLM-103	42 days
CLM-103-1XX	42 days
CLM-101	28 days
Combi. CLM-101 + CLM-103-1XX	67 days

Figure 2. Combination of CLM-103 with CLM-101 improved survival rate

C. Construct and Expression of OD CAR-T

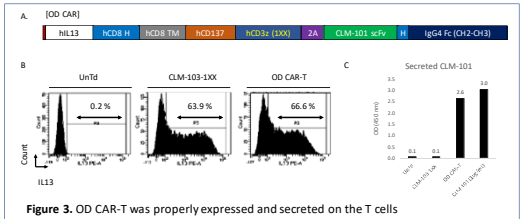
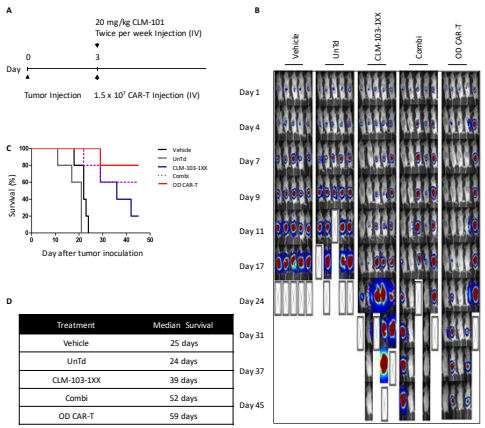


Figure 3. OD CAR-T was properly expressed and secreted on the T cells

D. Anti-cancer effect of OD CAR-T



D

Treatment	Median Survival
Vehicle	25 days
UnTd	24 days
CLM-103-1XX	39 days
Combi	52 days
OD CAR-T	59 days

Figure 4. OD CAR-T improved the survival on orthotopic ovarian tumor.

Discussion

Our experimental results showed that Combination of CAR-T with CLM-101 antibody treatment may be effective with minimizing toxicity by CRS and ICANS because low dose treatment of CAR-T cells is possible. Interestingly, the anti-cancer efficacy of OD CAR-T was better than the combination therapy.

In tumor microenvironment, the infiltration of OD CAR-T cells to tumor region might be increased by blocking binding of CAR-T cells and HGF. These results demonstrated that CAR-T which is secreting HGF antibody may be a strategy to overcome CAR-T dysfunction

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