

TARGETING HUMAN OVARIAN CANCER WITH IMMUNE CELLS DERIVED FROM THE PATIENT OR FROM HOMOZYGOUS HLA HAPLOTYPE IPS CELLS

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Chimeric antigen receptors (CARs) have been used for efficient destruction of B cell tumors but have been relatively ineffective as therapy for solid tumors. Ovarian cancer is a difficult cancer to treat, with five-year survival rates commonly around 25% of patients at diagnosis. The oncofetal glycoprotein antigen TAG-72 is commonly expressed on adenocarcinomas and is present on >95% of serous and >85% of clear cell ovarian cancers. We designed a novel TAG-72 CAR to increase antigen binding and lower antigenicity over other TAG-72 CARs.

Our TAG-72 CAR-T cells are extremely active in killing TAG-72 expressing human ovarian cancer cells in vitro and in vivo (NOD-SCID gamma (NSG) mice xenografted human ovarian cancer cells – e.g. Ovar3) but were less effective against low TAG-72 expressing tumour cells (e.g. Mesov). In vivo relapse in mice was often observed after 30-40 days of CAR-T cell treatment. Anticipating that treatment of solid tumors will require more than just a conventional CAR-T cell, we investigated a panel of key genes purportedly linked to immune suppression. By deleting them individually by gene editing in TAG-72 CAR-T cells, we identified potent novel genes as prime candidates for boosting CAR-T cell function and longevity. When the TAG-72 CAR-T cells with these gene knockouts (KO) were tested in our NSG mouse model the ovarian cancers were eradicated. At 100 days post treatment with TAG-72+gene KO CAR-T cells, human CD3+ T cells were still present at the site of the tumor, in contrast to their absence in non-gene edited human TAG-72 CAR-T cells.

We have also explored the generation of TAG-72 CAR cells from induced pluripotent stem (iPS) cells. Homozygous HLA haplotype iPS cells differentiated into natural killer cells (iNK cells) are able to kill human ovarian cancer in vitro and in vivo. iNK cells gene edited to knock-in TAG-72 CAR, killed ovarian cancer cells more efficiently than the iNK cells without a CAR. The TAG-72 CAR-iNK cells kill both high and low expressing TAG-72+ human ovarian cancers. The redesign of TAG-72 CAR-T cells and the gene edited KO produces a very effective therapeutic for eradication of ovarian cancer in mice. The development of CAR-iNK cells with enhanced cancer killing capacity and potential longevity may be an important development in stem cell based immune cancer therapies.