On Demand Talks: Combination Therapy

**06**  
**EXPRESSION OF ANTI-APOPTOTIC GENE CFLIP TO ENHANCE PERSISTENCE IN CAR T CELLS**

GMY Tan*, SMAR Hosseini, A Poudel, AD Mclellan. University of Otago, North Dunedin, New Zealand

10.1136/jitc-2020-ITOC7.11

**Background** CAR T cell therapy has been successful for targeting blood cancers, but treatment of solid cancers has been limited due to the heterogenous nature of tumour-associated antigen expression on solid cancers, and the suppressive tumour microenvironment.1 Further major obstacle to CAR T cell therapy is activation-induced cell death (AICD) of the CAR T cells.2 In this study, we expressed the anti-apoptotic cellular FLICE-like inhibitory protein (c-FLIP short; c-FLIPs) together with the CAR construct to enhance CAR T cell persistence.3

**Materials and Methods** The anti-Her2 FRP5 CAR T construct with P2A-linked cFLIPs or cFLIPp43 was cloned into the Sleeping Beauty (SB) transposon vector (pSBtet-GP) or lentiviral vector, under the control of a tet-on or a constitutive promoter. Construct expression was validated by qPCR and immunoblot analysis. CAR T cells were generated by SB transposition or lentiviral transduction of CD3/CD28 stimulated primary human T cells with elevated levels of non-peptide phosphoantigens (pAg), induced by cell stress or malignancy. To date, V9V82-T cell based cancer immunotherapeutic approaches were well tolerated and in some cases capable of inducing relevant clinical responses. In an effort to improve the efficacy and consistency of V9V82-T cell based cancer immunotherapy, we designed a bispecific VHH that binds to both V9V82-T cells and EGFR expressed by tumor cells and results in the target-specific activation of V9V82-T cells and subsequent lysis of colorectal cancer cell lines and primary colorectal cancer samples both in vitro and in an in vivo mouse xenograft model. Of note, tumor cell lysis was independent of mutations in KRAS and BRAF that are known to impair the efficacy of clinically registered anti-EGFR monoclonal antibodies as well as in melanoma TME. Ultimately, this model predicted an induction of T cells to target tumors containing high levels of nonpeptide phosphoantigens, which may assist in the precise selection of CAR T cell targets for clinical trials.


**07**  
**A BISPECIFIC VHH APPROACH TO LEVERAGE THE POTENT AND WIDELY APPLICABLE TUMOR CYTOLYTIC CAPACITY OF V9V82-T CELLS**

1LA King*, R Lameris, RC Roovers, P Parnen, T D de Gruijl, 1,12HI van der Vliet. 1AUMC – Cancer Centre Amsterdam, Amsterdam, Netherlands; 12LAVA Therapeutics, Utrecht, Netherlands

10.1136/jitc-2020-ITOC7.12

V9V82-T cells include a unique and potent subset of T cells which play an important role in tumor defense. V9V82-T cells recognize and can lyse butyrophilin 3A1-expressing target cells with elevated levels of non-peptide phosphoantigens (pAg), induced by cell stress or malignancy. To date, V9V82-T cell based cancer immunotherapeutic approaches were well tolerated and in some cases capable of inducing relevant clinical responses. In an effort to improve the efficacy and consistency of V9V82-T cell based cancer immunotherapy, we designed a bispecific VHH that binds to both V9V82-T cells and EGFR expressed by tumor cells and results in the target-specific activation of V9V82-T cells and subsequent lysis of colorectal cancer cell lines and primary colorectal cancer samples both in vitro and in an in vivo mouse xenograft model. Of note, tumor cell lysis was independent of mutations in KRAS and BRAF that are known to impair the efficacy of clinically registered anti-EGFR monoclonal antibodies as well as in melanoma TME. Ultimately, this model predicted an induction of T cells to target tumors containing high levels of nonpeptide phosphoantigens, which may assist in the precise selection of CAR T cell targets for clinical trials.