MESOTHELIN (MSLN) TARGETING ALLOGENEIC CAR T CELLS ENGINEERED TO OVERCOME TUMOR IMMUNOSUPPRESSIVE MICROENVIRONMENT

Cecile Schiffer-Mannioui, Sophie Leduc, Isabelle Chion-Sotinel, Diane le Clerre, Valérie Guyot, Marco Rotondi, Roman Galetto*, Agnès Gouble. *Collectis SA, Paris, France*

Background Chimeric Antigen Receptor (CAR) T cell therapy is emerging as a potential treatment for solid tumors, even if only limited activity has been observed for CAR T therapies to date. Cellular therapies face indeed many hurdles in solid tumors, such as the immunosuppressive microenvironment. TGF β is an important growth factor of the tumor microenvironment and has been shown to suppress anti-tumor immunity. Gene editing represents a powerful way to enhance properties of CAR T cells and can be used to circumvent the effect of TGF β signaling. The tumor associated antigen mesothelin (MSLN) is an attractive target for cellular therapy; being expressed at high levels in several tumor types (e.g., pleural mesothelioma and pancreatic cancer) while only modestly expressed in healthy tissues.

Methods UCARTMeso, an allogeneic CAR T cell product targeting MSLN expressing cells is being developed by Collectis. UCARTMeso bears an anti-MSLN CAR and a triple gene knock-out (KO) for TRAC, CD52 and TGFBR2 genes, all generated using TALEN® gene-editing technology. TRAC KO limits the risk of GvHD, while CD52 KO allows the use of alemtuzumab in the preconditioning regimen. The additional KO of TGFBR2 confers resistance to the immunomodulatory effects of TGF β within the solid tumor microenvironment.

Results Preclinical studies showed high specificity of the anti-MSLN CAR, as well as potent anti-tumor activity in vitro against different cell lines expressing MSLN. In addition, this activity was confirmed in mouse studies against pancreatic and pleural mesothelioma tumor models, with comparable activities observed in the latest model upon i.v. or intra-pleural administration of UCARTMeso. Also, we observed that TGFBR2 edited anti-MSLN CAR T cells displayed a blockade in the TGF β signaling pathway, being able to respond to antigen stimulation in the presence of TGF β (figure 1).

Conclusions Altogether, we have demonstrated potent antitumor activity in vitro and in vivo, and that addition of the third knock-out of TGFBR2 gene provide valuable additional properties to UCARTMeso cells, representing a very attractive strategy for their use in the treatment of solid tumors.

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