712 PRECLINICAL CHARACTERIZATION OF GT-00A X IL15: A NOVEL IL-15-BASED IMMUNOCYTOKINE WITH UNIQUE TUMOR TARGETING PROPERTIES

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Background IL-15 is a potent pro-inflammatory cytokine that enhances the differentiation, proliferation and cytolytic activity of NK cells and T cells. Due to the huge potential of IL-15 to activate both innate and adaptive anti-tumor immunity, several IL-15-based immunocytokines are currently in clinical development. However, all of them preferentially act in the periphery and not locally within the tumor. To further increase the efficacy and safety of IL-15-based immunocytokines, we developed GT-00A x IL15, an immunocytokine targeting a tumor-associated, glycosylated epitope of MUC-1 (TA-MUC1). GT-00A x IL15 was designed to induce anti-tumor responses directly within the tumor microenvironment for the treatment of solid tumors.

Methods GT-00A x IL15 was extensively studied in vitro and in vivo to adequately characterize its complex mechanisms of action and to analyze its anti-tumor efficacy. The relevance of TA-MUC1 binding as differentiation criteria against untargeted IL-15 (super)agonists was investigated in detail. In vitro cytotoxicity and 3D tumor spheroid immune cell infiltration mediated by GT-00A x IL15 was compared to the parental antibody GT-00A and an untargeted IL-15 control. In vivo, several pharmacokinetic, pharmacodynamic, biodistribution and efficacy studies were performed in tumor-free or tumor-bearing mice.

Results We could show in vitro that GT-00A x IL15 increased the cytotoxic activity of PBMC against TA-MUC1-positive tumor cell lines compared to parental GT-00A and an untargeted IL-15 control construct. Additionally, dose-dependent infiltration of NK and T cells into MCF-7 tumor spheroids is mediated by GT-00A x IL15 but not the untargeted IL15 control construct or parental GT-00A. In vivo single agent efficacy of GT-00A x IL15 was shown in different tumor models by means of tumor growth inhibition and increased survival. Subsequent flow cytometric analysis of tumor samples confirmed activation and expansion of tumor-infiltrating NK and CD8+ T cells. Furthermore, in a biodistribution study using radioactively labelled GT-00A x IL15 we observed significantly increased enrichment in the tumor compared to the untargeted IL-15 control construct.

Conclusions Our results confirm the relevance of TA-MUC1-mediated tumor cell binding for the mechanisms of action of our immunocytokine. GT-00A x IL15 shows increased accumulation in the tumor and mediates enhanced cytotoxicity and immune cell infiltration compared to an untargeted IL-15 control construct highlighting the potential to increase the efficacy and safety of IL-15-based immunocytokines by tumor targeting. GT-00A x IL15 shows great promise for the treatment of TA-MUC1-positive solid tumors either as monotherapeutic agent or as valuable combination partner.

http://dx.doi.org/10.1136/jitc-2021-SITC2021.712