TUMOR-INFLTRATING LYMPHOCYTES (TIL) WITH INDUCTIBLE AND MEMBRANE-BOUND IL-12 EXHIBIT SUPERIOR ANTITUMOR ACTIVITY IN VITRO

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Background TIL cell therapy has shown clinical benefit for patients with solid tumors. However, an immunosuppressive tumor microenvironment (TME) may abrogate the full potential of TIL cell therapy. The proinflammatory cytokine IL-12, known for its capability to increase IFN-γ production and promote type 1 immune responses, reshapes the TME and has a potential to augment antitumor activity. Here, we report genetic engineering of TIL with an inducible and membrane-bound IL-12, incorporated into a 22-day manufacturing process, which showed superior cytotoxic function in vitro.

Methods Tumor tissue from several solid tumor types, including non-small cell lung, breast, head and neck, and ovarian cancers, was fragmented and cultured, followed by transduction with lentivirus containing a gene encoding membrane-bound IL-12 via an NFAT-promoter (TeIL-12), and a rapid expansion protocol (REP). Expression, biological function, and shedding of IL-12 molecule were assessed in vitro. Immune phenotype and in vitro cytotoxic activity of TeIL-12 gene-engineered TIL were examined in various assays.

Results Lentiviral gene transfer resulted in TIL expressing IL-12 on their surface via a membrane anchor. This modification potentiated IL-12 receptor downstream signaling activation in a contact-dependent manner in assays using HEK-IL-12-Blue reporter cells. TeIL-12-TIL exhibited increased IFN-γ production and superior cytotoxicity in a KILR assay. An xCELLigence-based cytotoxicity assay further confirmed increased killing with TIL that were unstimulated or stimulated. Moreover, phenotype profiling revealed TeIL-12-TIL were less differentiated, with reduced expression of immune-inhibitory receptors and increased production of cytotoxic molecules associated with antitumor activity. IL-12 shedding in the coculture supernatant was minimal.

Conclusions The enhanced in vitro killing activity, combined with a less-differentiated phenotype of TIL with inducible and membrane-bound IL-12 suggests a potential for increased clinical efficacy. Further, minimal IL-12 shedding supports reduced potential for IL-12-associated toxicity. Together, these data support investigation of TeIL-12 in vivo and subsequent clinical development.

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REFERENCES

Ethics Approval The study was approved by the institutional review board at each site and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines of the International Conference on Harmonization. All patients provided written informed consent.

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