342 IMPROVING TCR-T CELL FUNCTION AGAINST SOLID TUMORS WITH IMMUNE ENHANCING EDITS

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Background The success of T cell therapies for the treatment of solid tumors has been limited. Factors limiting efficacy in solid tumors are poor infiltration, exhaustion, and an immunosuppressive tumor microenvironment (TME).

Methods To address these issues, we developed multiple mouse syngeneic tumor models to conduct *in vivo* CRISPR screening to identify Immune Enhancing Edits (IEEs) that augment CD8+ T cell function across TMEs. Several IEEs were validated in multiple mouse syngeneic solid tumor models, displaying significant *in vivo* tumor control. To better understand the therapeutic potential in human T cells, we engineered Wilms Tumor 1 (WT1)-specific TCR-T cells with these IEEs and tested them against WT1-expressing human solid tumor xenografts.

Results WT1-specific TCR-T cells with either single IEE or a combination of IEEs induced tumor regression across multiple human tumor models. These IEE targets were also able to enhance CAR-based T cell therapies against solid tumors, adding to the broad applicability of this platform.

Conclusions Coupling CRISPR-engineered immune enhancements with our allogeneic platform, Intellia is creating next-generation cell therapies for the treatment of solid tumors.

Ethics Approval The mouse studies described here have been performed in compliance with protocols approved by Intellia Therapeutics' IACUC (Institutional Animal Care and Use Committee). (Mainly protocol number IT008)

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