TARGETING WILDTYPE IL-2 TO CD8 T CELLS INDUCES POTENT ANTI-TUMOR IMMUNE RESPONSES AND DECREASES IL-2 MEDIATED TOXICITY

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Background High dose IL-2 treatment in metastatic renal cell carcinoma and metastatic melanoma patients induced complete remission in 5%–10% of patients without recurrence for over 25 years and potentially cured 70% of these patients.1 Although FDA approved for treatment of metastatic melanoma and renal cell carcinoma, the clinical utility of high-dose IL-2 is limited by significant multisystem toxicity, treatment-related mortalities in up to 4% of patients, and a lack of response in some patients. As a pleiotropic cytokine, IL-2 not only boosts the desired proliferation and effector function of T and NK cells, but also enhances detrimental immune suppression by expanding high affinity IL-2R(αβγ) expressing Treg cells. Contributing to its toxicity, IL-2 also activates innate lymphoid cells (ILC) and IL-2Rα+ endothelial cells to cause vascular leak syndrome. A key challenge in developing IL-2 as a safe and efficacious cancer therapeutic is uncoupling its efficacy from its toxicity. Here, we present data to support that this could be achieved by linking wildtype IL-2 to an anti-CD8 antibody and selectively delivering IL2 to CD8 T cells.

Methods We separately linked wild type human IL-2 to anti-murine and anti-human CD8 or untargeted RSV antibodies for studies in murine and human systems, respectively. In vitro pharmacology was studied with mouse splenocytes and human PBMC. In vivo pharmacodynamics, efficacy, and toxicity were assessed in naïve mice, B16F10 and MC38 syngeneic tumor models.

Results Incubating respective CD8-IL2s with mouse splenocytes and human PBMC selectively loaded IL2 on CD8 T cells. This resulted in potent pSTAT5 activation downstream of the IL-2R and CD8 T cell expansion compared to incubating with untargeted IL-2 antibody fusions. CD8-IL2 localization is driven by CD8 antibody affinity where as untargeted IL2 localization is driven by IL-2 affinity for its receptors. In naïve mice, CD8-IL2 preferentially expanded CD8 T cells over Treg and NK cells. In contrast, untargeted IL-2 primarily expanded high-affinity IL-2R positive Treg and NK cells. In B16F10 syngeneic tumor bearing mice, untargeted IL-2 induced a dose dependent increase in inflammatory cytokines responsible for high toxicity and body weight loss. In contrast, treatment with CD8-IL2 significantly reduced toxicities but potently inhibited B16F10 and MC38 syngeneic tumor growth.

Conclusions Our data supports that selective targeting of IL-2 to CD8+ T cells minimizes exposure of other cell types to IL2 and reduce IL2 mediated toxicity. CD8-IL2 is expected to be a safe and effective cancer immunotherapy.

REFERENCE

Ethics Approval All experimental animal procedures were approved by the Institutional Ethics Review Board.