SELECTIVE ACTIVATION OF CD8+ T CELLS BY A CD8-TARGETED IL-2 RESULTS IN ENHANCED ANTI-TUMOR EFFICACY AND SAFETY

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Background High-dose IL-2 induces complete responses in a subset of cancer patients, but severe toxicity, including vascular leak syndrome (VLS), limits its clinical potential. Insights into IL2R α 's role in the development of VLS sparked a wave of second-generation IL-2 molecules referred to as “not- α ” IL-2s. Emerging clinical data suggests that although not- α IL-2s avoid VLS, they induce suboptimal monotherapy activity in patients. Given the observation that CD8+ T cells are the dominant effector cells with IL-2-based therapies,^{1 2} we hypothesized that maximizing the activity of IL-2 on CD8+ T-cells and limiting its activity on immunosuppressive Tregs and highly IL-2-sensitive innate populations would improve IL-2's efficacy and tolerability. We developed cis-targeted IL-2 (CD8-IL2) fusion proteins that selectively activate CD8+ T cells and have minimal activity on CD8-negative cells.

Methods In vitro selectivity of CD8-IL2 molecules was tested on primary immune cells including mouse splenocytes and human PBMCs. In vivo activity was evaluated in syngeneic tumor models and non-human primates.

Results Due to the 10–20x higher expression of IL2R β on NK cells over other lymphocytes, not- α IL-2 induced preferential NK cell expansion in mice. Toxicity-induced body weight loss with not- α IL-2 treatment was dependent on cells expressing NK1.1 but not CD8. To avoid overt activation of IL2R β high NK cells, IL-2R α -associated toxicity, and Treg activation, we generated cis-targeted fusion proteins consisting of anti-CD8 antibodies and IL-2 muteins with attenuated binding to IL2R α and IL2R β . We demonstrated that CD8-IL2 fusions preferentially activated CD8+ T cells within mouse, human, and cynomolgus immune populations, with 100–1000 fold selectivity over NK cells and Tregs for all three species. Selective expansion of CD8+ T cells over NK cells and Tregs was demonstrated in tumor and peripheral blood compartments in mice. Selective CD8+ T cell expansion was also demonstrated in cynomolgus monkeys. Furthermore, a single dose of CD8-IL2 in mice elicited strong monotherapy efficacy in MC38 tumors, with a majority of mice demonstrating complete responses without detectable body weight loss at doses that were well tolerated in cynomolgus monkeys. In contrast, not alpha IL-2 induced >10% body weight loss prior to reaching efficacious doses in mice and did not drive any complete anti-tumor responses.

Conclusions CD8-targeted IL-2 has superior efficacy and lower toxicity compared to second-generation not- α IL-2. Development of AB248, a novel CD8-targeted IL-2 molecule is underway.

REFERENCES

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