AB821 IS A CD8+ T CELL SELECTIVE IL-21 WITH ENHANCED BIOAVAILABILITY THAT MEDIATES POTENT ANTI-TUMOR ACTIVITY, CYTOTOXICITY, AND EXPANSION OF MEMORY CD8+ T CELLS

Background IL-21 is a clinically validated cytokine that showed monotherapy activity in melanoma and renal cell carcinoma. Further clinical development of IL-21 was discontinued, likely due to limitations such as short half-life and poor bioavailability, a result of IL-21’s low molecular weight and highly positive charged nature, respectively. The pleiotropic effects of IL-21 may also have limited its effectiveness in the clinic. While IL-21 can activate STAT3 in CD8+ T cells to promote anti-tumor immunity, STAT3 activation in NK cells and myeloid cells may be associated with toxicity and immunosuppression, respectively. To maximize the potential of IL-21, we developed AB821, a cis-targeted IL-21 that selectively activates CD8+ T cells and exhibits improved bioavailability.

Methods AB821 was generated by fusing a CD8 targeting antibody to an IL-21 mutein which has attenuated binding to IL-21 receptor and a reduced positive charge profile. AB821 and its murine surrogate, muAB821, were characterized alongside WT IL-21 in multiple in vitro and in vivo studies.

Results In STAT3 assays with human PBMCs, whereas IL-21 indiscriminately activated CD8+ T cells and non CD8 cells with almost equivalent potency, AB821 demonstrated high potency of 0.5nM on CD8+ T cells and 1000-fold selectivity over other IL-21 target cell types such as B cells, NK cells and CD4+ T cells. Selective activation of STAT3 in CD8+ T cell was also observed following AB821 dosing in cynomolgus monkeys. Besides selectivity, AB821 showed enhanced in vivo exposure with reduced non-specific consumption compared to WT IL-21. Functionally, AB821 largely recapitulated the gene expression signatures of WT IL-21 in both resting and antigen-activated CD8+ T cells. Notably, AB821 induced minimal gene expression changes in resting CD8+ T cells but synergized with antigen stimulation and induced a larger set of genes in activated CD8+ T cells, consistent with IL-21’s primary role in the context of antigen activation. Furthermore, in hematopoietic stem cell-humanized mice, a single dose of AB821 resulted in a persistent increase in Granzyme B+ CD8+ T cells and marked increases in the memory compartment. Finally, muAB821 demonstrated remarkable monotherapy activity in multiple tumor models, with muAB821 significantly outperforming mouse IL-21. Furthermore, muAB821 showed synergistic anti-tumor activity with anti-PD1 antibody in multiple PD1-resistant tumors.

Conclusions AB821 is a next-generation IL-21 with superior anti-tumor activity and enhanced bioavailability over WT IL-21. AB821 promotes cytotoxicity and memory CD8+ T cells in the context of antigen activation and synergizes with PD1 blockade in PD1-resistant tumors. Clinical development of AB821 is planned.

REFERENCES

Ethics Approval All procedures performed on the animals were in accordance with regulations and established guidelines and were reviewed and approved by the Explora’s Institutional Animal Care and Use Committee.

Consent No patient’s data is presented in this abstract.