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

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Background IL-21 is a clinically validated cytokine that showed monotherapy activity in melanoma1 and renal cell carcinoma2. 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 have also 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, respectively3,4. 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