AB821 IS A CD8+ T CELL SELECTIVE IL-21 WITH ENHANCED BIOAVAILABILITY THAT REDUCES CD8+ T CELL EXHAUSTION TO INDUCE POTENT ANTI-TUMOR ACTIVITY

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Background IL-21 is a clinically validated cytokine with monotherapy activity in melanoma1 and renal cell carcinoma.2 Further clinical development of IL-21 was discontinued, likely due to limitations including short half-life and poor bioavailability resulting from IL-21’s low molecular weight and highly positively charged nature. We designed AB821, a cis-targeted IL-21, to selectively act on CD8+ T cells and demonstrated that AB821 enhanced the anti-tumor responses compared to recombinant IL-21 in multiple preclinical mouse models.1,4 Previously, IL-21 has been shown to sustain effector function and reduce exhaustion.5–7 Here, we provide mechanistic insight into how AB821 enhances the functionality of CD8+ T cells in tumor infiltrating lymphocytes (TILs), thereby facilitating the antitumor effects of IL-21.

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. Activity of AB821 and its murine surrogate, muAB821, were characterized in human primary tumor culture models and syngeneic tumor models, respectively, by flow cytometry, single cell RNAseq, and antitumor activity studies.

Results In mouse tumor models, muAB821 demonstrated monotherapy activity against sizable tumors that show resistance to anti-PD-1 monotherapy and synergized with anti-PD-1 to treat multiple checkpoint inhibitor refractory models including tumors at advanced stages of development. Characterization of CD8+ T cells by single cell RNAseq in mouse tumors revealed that the exhausted CD8+ T cell subset expressed high levels of IL-21R, suggesting that they are a target for AB821 therapy. Treatment with muAB821 resulted in replacement of exhausted CD8+ T cells with CD8+ T cell populations with distinct functionality, including enhanced cytotoxicity. Likewise, we observed high expression of IL-21R on antigen-reactive and exhausted CD8+ T cells in human TILs; these populations are highly responsive to AB821 as measured by pSTAT3 sensitivity. In human TILs cultured with AB821, exhausted CD8+ T cells increased expression of granzyme B and perforin, indicating improved functionality.

Conclusions AB821 is a next generation IL-21 with superior nonclinical anti-tumor activity over wild type IL-21. AB821 reduced CD8+ T cell exhaustion, resulting in potent anti-tumor activity in PD-1 refractory models both as monotherapy and in synergy with anti-PD-1. The exhausted CD8+ T cell subset is a prime target for AB821 activity based on high expression of IL-21R. Overall, data from mouse and human tumors demonstrated that AB821 can specifically restore cytotoxic potential to IL-21R-expressing, exhausted CD8+ T cells. Clinical development of AB821 is planned.

REFERENCES

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