Bispecific anti-CD123 x anti-CD3 ADAPTIR™ Molecules for Redirected T-cell Cytotoxicity in Hematological Malignancies

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Introduction

CD123 is a component of the IL-3 receptor expressed in several hematological malignancies including AML, ALL, HCL, and MDS. CD123 is a compelling target in AML due to its overexpression on AML blasts as well as leukemic stem cells, which are thought to be resistant to chemotherapy and may be responsible for relapse of disease following treatment.1,2 While CD123 is expressed by some normal leukocyte populations in circulation and hematopoietic progenitor cells in the bone marrow,3 the low frequency of expression on normal cell types provides a therapeutic window for targeting CD123 in tumor settings with the potential for durable responses and reversible side effects. We have developed bispecific anti-CD123 x anti-CD3 ADAPTIR molecules APVO436 and APVO437 for redirecting T-cell cytotoxicity against CD123 expressing tumor cells. Results are presented that examine the in vitro and in vivo activity of these molecules in preclinical models of AML.

APDARTIR Molecules Targeting CD123 and CD3

APDARTIR molecules are bispecific antibody-like therapeutics containing two binding domains linked to immunglobulin Fc domains to extend the half-life of the molecule in vivo. The anti-CD123 x anti-CD3 ADAPTIR molecules bind both CD123 and CD3 to redirect T-cell cytotoxicity against CD123 expressing tumor cells. The anti-CD123 binding domain is a fully human single chain variable fragment (scFv) that binds human and non-human primate (NHP) CD123. The anti-CD3 binding domain is a humanized scFv adapted from a murine antibody that binds human and NHP CD3. In order to avoid interactions with other components of the immune system that could lead to CD3 clustering and non-specific T-cell activation, the Fc region has been engineered to minimize complement fixation and interaction with Fc receptors.

Redirected T Cell Cytotoxicity (RTCC) by anti-CD123 and anti-CD3

In Vitro: APVO436 and APVO437 Have Antibody-Like Half-Lives in Bablic Mice

In Vivo: APVO436 and APVO437 Inhibit Molm-13 Tumor Growth

Summary and Conclusions

• APVO436 and APVO437 bound human and cynomolgus CD123-expressing cells with EC50 values in the low nM range and SFC studies demonstrated the binding of both ADAPTIR proteins bound human CD123 protein with high affinity. Both APVO436 and APVO437 reduced concentration-dependent loss of CD123+ AML cell lines with human primary effector T-cells, accompanied by T-cell activation and proliferation. Comparable redirected T-cell cytotoxicity function was observed using primary cynomolgus macaque T-cells. These activities were dependent on the expression of CD123 by the tumor target cells.

• In vivo, pharmacokinetic analysis demonstrated serum half-lives of 12.5 days for APVO436 and 8.5 days for APVO437 in Bablic mice and growth of AML tumor cells was inhibited by treatment with low doses of APVO436 and APVO437, significantly improving host survival.

Conclusion: These studies demonstrate the anti-CD123 x anti-CD3 ADAPTIR molecules APVO436 and APVO437 are capable of potentially inducing redirected T-cell killing of AML tumor lines both in vitro and in vivo and suggest further investigation of these proteins as potential therapeutics in hematological malignancies is warranted.