SL-101, a Novel Antibody-Conjugate that Targets Interleukin-3 Receptor Alpha (CD123), Possesses Preclinical Anti-Tumor Activity Against Hodgkin’s Lymphoma

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ABSTRACT

Background: The interleukin-3 receptor alpha chain (CD123) is over-expressed on the tumor bulk and cancer stem cells (CSCs) of multiple hematologic malignancies relative to normal hematopoietic cells. In particular, CD123 has also been shown to be up-regulated on a variety of leukemias and lymphomas, including Hodgkin’s lymphoma (HL). The prognosis for patients with HL who fail to achieve a durable remission with approved Therapeutics or transplantation is poor. Therefore, novel treatment strategies for such patients are needed. SL-101, a novel monoclonal antibody conjugate that targets CD123 with high affinity, was constructed. The potency and activity of SL-101 was evaluated in vitro and in vivo.

Methods: A panel of anti-CD123 monoclonal antibodies was previously screened for binding affinity to CD123 and for receptor internalization. Three antibodies were selected based on relative binding affinity in a fluorescence intensity by flow cytometry and the 1H1 and 1L5 domains of each was sequenced and used to generate scFv constructs. The scFv domains were then genetically fused via covalent linkage to either Pseudomonas exotoxin (P38) or Pseudomonas saporin (saporin), allowing CD123 to be conjugated with either a toxin or saporin. The cytotoxicity of the resulting conjugates was evaluated in vitro using a variety of hematologic malignancies, including HL cell lines.

Results: CD123 expression was up-regulated on the surface of HL cell lines following culture in interleukin-3 (IL-3). CD123 internalization was measured using the Multi-ZAP assay. The sensitivity of CD123 expressing lymphoma cell lines was variable and CD123 binding was more efficacious in vitro compared with in vivo. The IL-3 dependent SL-101 toxicity was dependent on the affinity of the parental antibody, indicating that CD123 efficiently internalized upon binding the anti-CD123 antibody in the presence or absence of IL-3.

Conclusions: These results indicate that SL-101 has demonstrated potent preclinical anti-tumor activity against HL cells.

KEY POINTS

- CD123 is a cell surface receptor expressed on multiple hematologic cancers including Hodgkin’s lymphoma (HL). CD123 is expressed on B and T cell malignant cells in lymphoid malignancies, such as non-Hodgkin lymphoma (NHL), mantle cell lymphoma (MCL), and follicular lymphoma (FL).
- SL-101 is a novel monoclonal antibody conjugate that targets CD123 and is a cytotoxic antibody conjugate that induces receptor internalization upon binding in CD123 expressing hematologic malignancies.
- This panel of anti-CD123 antibodies was previously screened for binding affinity to CD123 and for receptor internalization.
- Three candidate antibodies were chosen for functional screening (clones 32701, 32704, and 32980), which demonstrate high affinity for CD123.
- CD123 internalization was measured using the Multi-ZAP assay. The sensitivity of CD123 expressing lymphoma cell lines was variable and CD123 binding was more efficacious in vitro compared with in vivo.
- The IL-3 dependent SL-101 toxicity was dependent on the affinity of the parental antibody, indicating that CD123 efficiently internalized upon binding the anti-CD123 antibody in the presence or absence of IL-3.