Discovery and preclinical development of novel CD74-targeting antibody-drug conjugates (ADCs) with significant activity in multiple myeloma (MM) cell lines and xenograft models

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BACKGROUND

Rationale for targeting CD74 (HLA-DR-associated invariant chain) in MM

- CD74 is a type II transmembrane glycoprotein that is rapidly internalized and recycled back to the membrane.
- Functions of CD74, including transport of MHC class II, B-cell maturation via a nuclear factor-kappa (NF-κB) mediated pathway.
- Expression in cell surface and transcytosis.
- Involved in signal transduction of macrophage migration inhibitory factor (MIF).
- Mediation of disease progression in a variety of malignancies.

CD74 Expression

- Normal tissues: HLA class II positive cells, including B-cells, monocytes, macrophages, Langerhans cells, dendritic cells, subsets of activated T cells and thymic epithelium.
- Overexpression in malignancy: Immunohistochemistry (IHC) using the CD74 antibody (1L1) demonstrated 19-22% expression by multiple myeloma specimens stained positively for CD74, with 16 of these specimens demonstrating strong CD74 expression in >95% of the myeloma cells.

Discovery of CD74-targeting ADCs

ADCs are emerging as a promising class of cancer biopharmaceuticals that combine the specificity of monoclonal antibodies with the anti-tumor activity of cytotoxic agents.

We have developed a novel anti-CD74 human IgG1 antibody, SP7219, and conjugated this to specific amino acids to non-cleavable maytansinoid linker-warheads (TCSR296 or SC236) with a drug-to-antibody ratio (DAR) of 2, to generate two potent ADCs, SP7676 and STR0-001.

Development of the CD74-targeting lead antibody and novel, specific and homogeneous ADCs.

RESULTS

Figure 1. Multiple myeloma cell lines express CD74 on the cell surface

A)   B)   C)


Figure 2. STRO-001 ADC targeting of CD74 results in efficient cell killing in vitro

- STRO-001 ADC was used to determine the IC50 and percent of cells killed in MM cell lines. A) Cell survival curve showing percentage of viable cells at different concentrations of STRO-001 for MM cell lines. B) Quantitation of IC50 and cell killing span (% of cells killed). Ni: No Killing.

Figure 3. SP7676 increases survival in the disseminated CAG MM model


Figure 4. STRO-001 and SP7676 significantly reduce tumor burden in disseminated ARPB-1 MM model


Figure 5. SP7676 is a potent inhibitor of tumor growth in the ANBL-6 Melphalan refractory MM subcutaneous disease model


Figure 6. STRO-001 induces dose-responsive ablation of B-cells in cynomolgus monkeys

CONCLUSIONS

- Sutro technology allows for the generation of novel, specific, and homogenous ADCs targeting CD74.
- ADC targeting CD74 can produce efficient cell killing in multiple MM cell lines.
- ADC targeting CD74 led to the suppression of tumor growth in three MM models in vivo: ANBL-6, CAG, and ARP-1.
- Initial toxicology study in cynomolgus monkeys did not produce any unexpected findings; the mean result of treatment with STR0-001 was no B-cell depletion followed by recovery.
- RD-enabling studies are planned.

MATERIALS & METHODS

- All animal work was performed under the IACUC at Sutro Biopharma when this work was conducted.

REFERENCES