Introduction

- CD123 (IL-3 receptor alpha) is highly expressed on acute myelogenous leukemia stem cells and blasts, and represents a promising target of antibody therapies for AML.
- Anti-CD123 antibodies such as CSL362 and KHK2823 are currently in clinical development; however, a limitation of these molecules is that they are unable to stimulate T cell-mediated killing of CD123+ AML cells.
- To exploit the potent activity of T cell immunotherapy while maintaining the favorable dosing regimen of a therapeutic antibody, we designed XmAb14045, a novel bispecific antibody that recruits T cells to attack CD123+ AML stem and blast cells.
- XmAb14045 acts via "redirected T cell cytotoxicity" (RTCC), a mechanism that stimulates targeted T cell-mediated killing regardless of T cell antigen specificity.
- Unlike other bispecific formats, XmAb14045 possesses an Fc domain that binds to human FcRn (to maintain long serum half-life) and spontaneously forms stable heterodimers that are readily manufacturable.

Bispecific mechanism recruits cytotoxic T cells to kill AML stem cells & blasts

1. CD123+ cells spared
2. CD123+ cells targeted
3. T cell killing of CD123+ cells
4. DCs
5. CTL
6. Leukemia Blasts
7. CD8+ T cells
8. CD4+ T cells
9. Natural killer cells
10. Monocytes
11. Eosinophils
12. Neutrophils
13. Basophils
14. pDCs
15. B cells
16. AML LSC or blast

Novel bispecific format enables efficient manufacturing & purification

1. Efficient bispecific production
2. Crossreactive with monkey CD3
3. Anti-CD123
4. Fab
5. Anti-CD3
6. scFv
7. Fc
8. Fc-scFv
9. Bispecific antibody format

XmAb14045

1. Anti-CD123
2. Fab
3. Anti-CD3
4. scFv
5. Fc

Fab-scFv: Fc-bispecific antibody format

- XmAb14045 anti-CD123 domain was humanized using existing anti-CD123 Fab, no refactoring required
- Anti-CD3 is humanized, stabilized (T₄ + T2C), monkey cross-reactive, and portable
- Fc is modified to eliminate FcR affinity, yet preserves FcRn affinity for antibody-like half-life

Bispecific antibody binds to human & monkey CD123

1. Human AML cell line
2. Primates and pDCs
3. Basophils
4. pDCs
5. CD123+ antigen
6. XmAb14045 binds to CD123 on basophils & plasmacytoid dendritic cells (pDCs) of cynomolgus monkeys

Bispecific antibody kills human AML cell lines

1. Killing of CD123+ AML cell line
2. T cells are serial killers

Fc-containing bispecifics have long half-lives in mice

1. Single dose of XmAb14045 depletes CD123+ cells in monkeys

CD123+ cell depletion correlates with T cell redistribution & activation

1. T cell redistribution
2. T cell activation
3. Cytokine release

Summary

The anti-CD123 × anti-CD3 bispecific antibody XmAb14045:

- Incorporates a human Fc domain for long serum half-life
- Effectively recruits T cells to kill CD123+ AML cells in vitro at ~1 ng/ml potency
- Safety & effectively depletes CD123+ cells in monkey blood & bone marrow at doses of 1 & 10 μg/kg
- Is efficiently manufactured using standard antibody production methods

These results support clinical testing of XmAb14045 in patients with AML and other CD123+ malignancies, using basophils & pDCs as biomarker populations

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