

Immunotherapy with Long-Lived Anti-CD123 × Anti-CD3 Bispecific Antibodies Stimulates Potent T Cell-Mediated Killing of Human AML Cell Lines and of CD123⁺ Cells in Monkeys: A Potential Therapy for Acute Myelogenous Leukemia

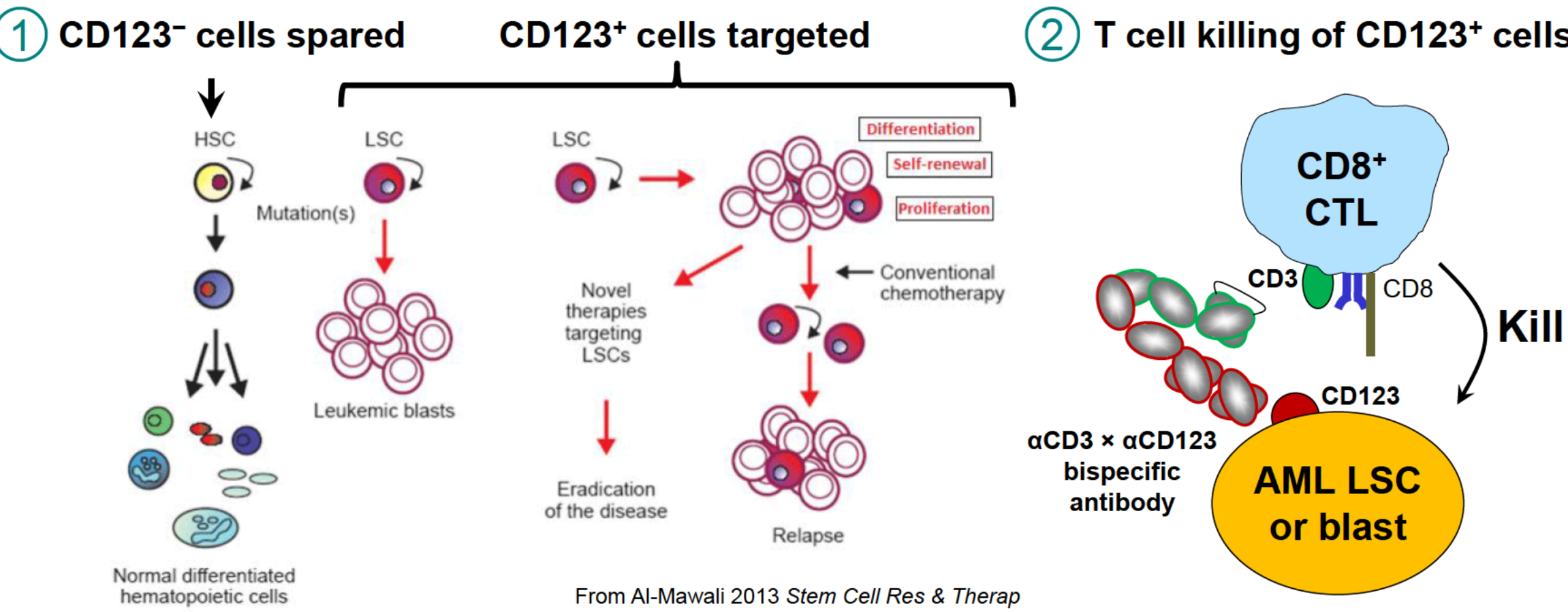
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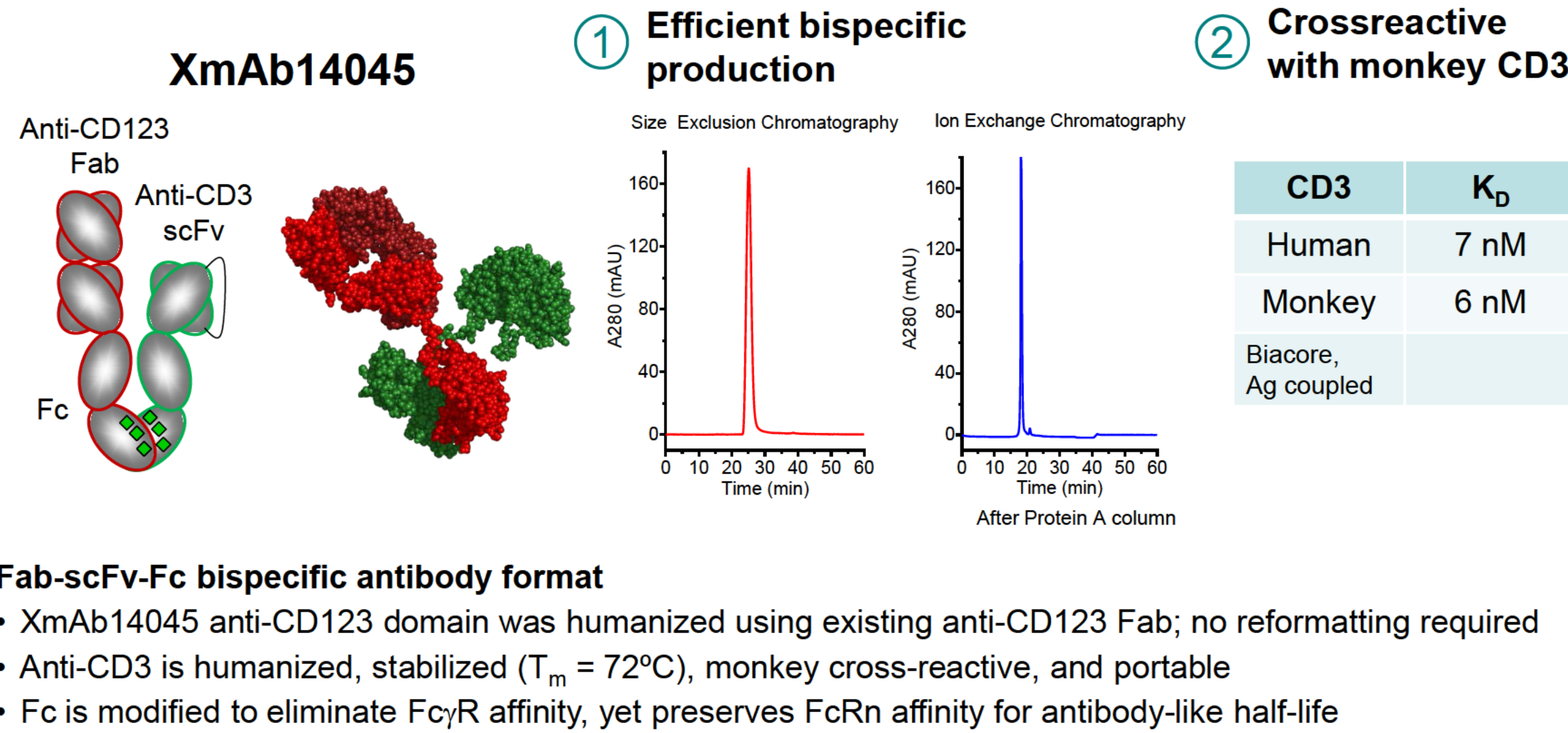
Introduction

- 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 manufactured.

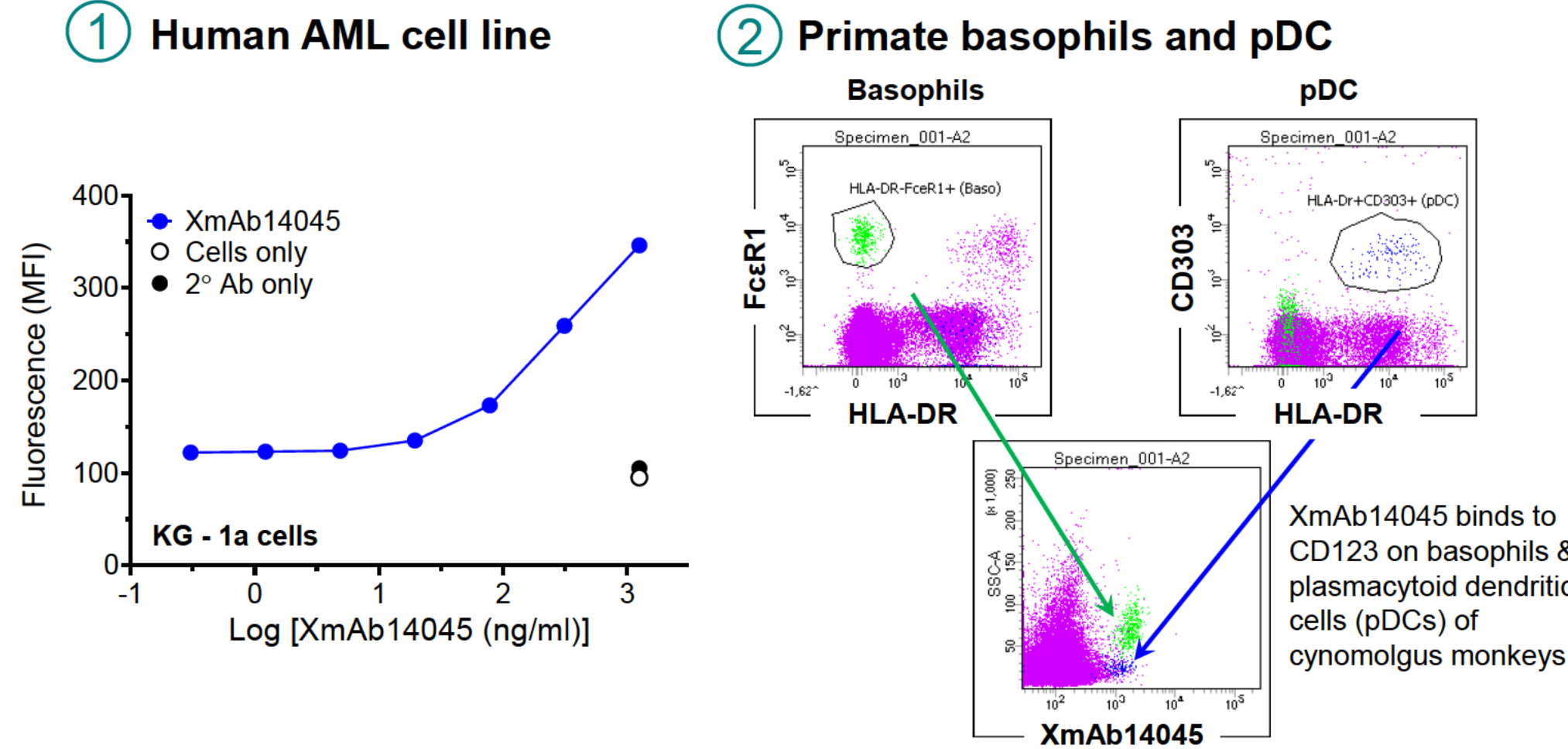
A Bispecific mechanism recruits cytotoxic T cells to kill AML stem cells & blasts



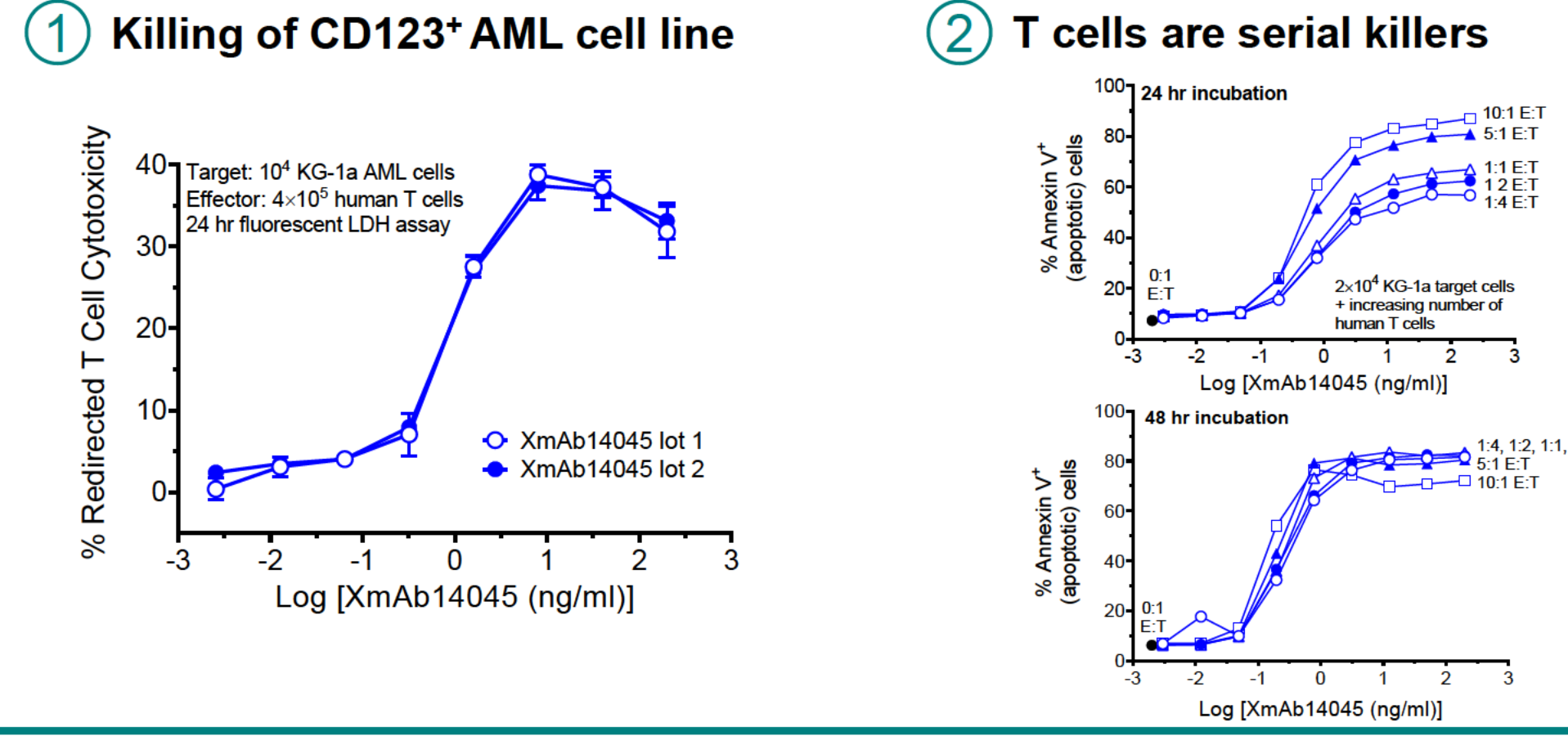
B Novel bispecific format enables efficient manufacturing & purification



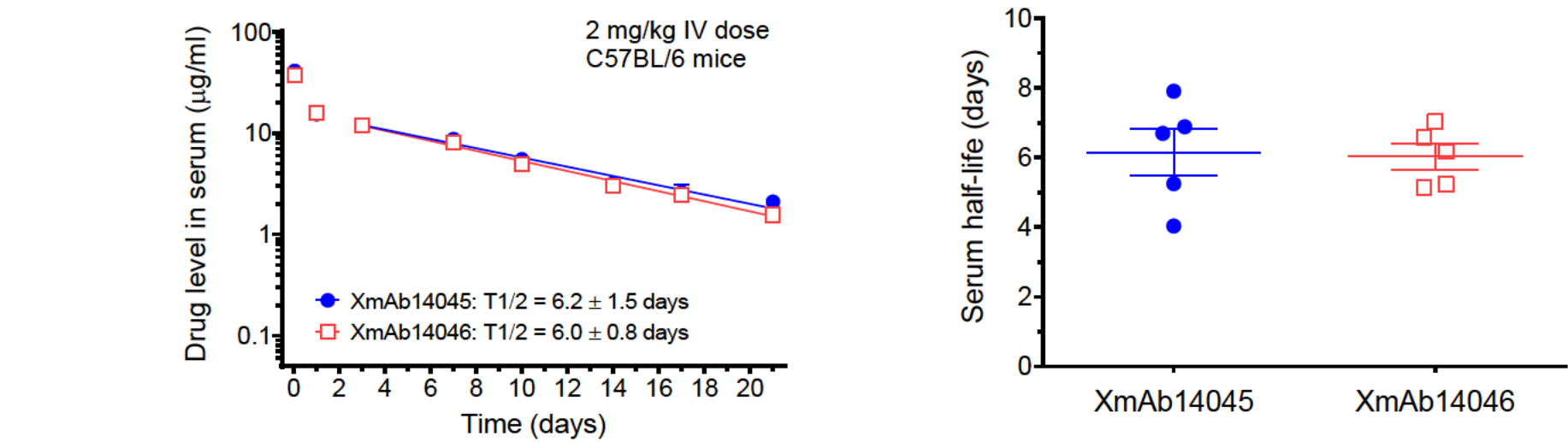
C Bispecific antibody binds to human & monkey CD123



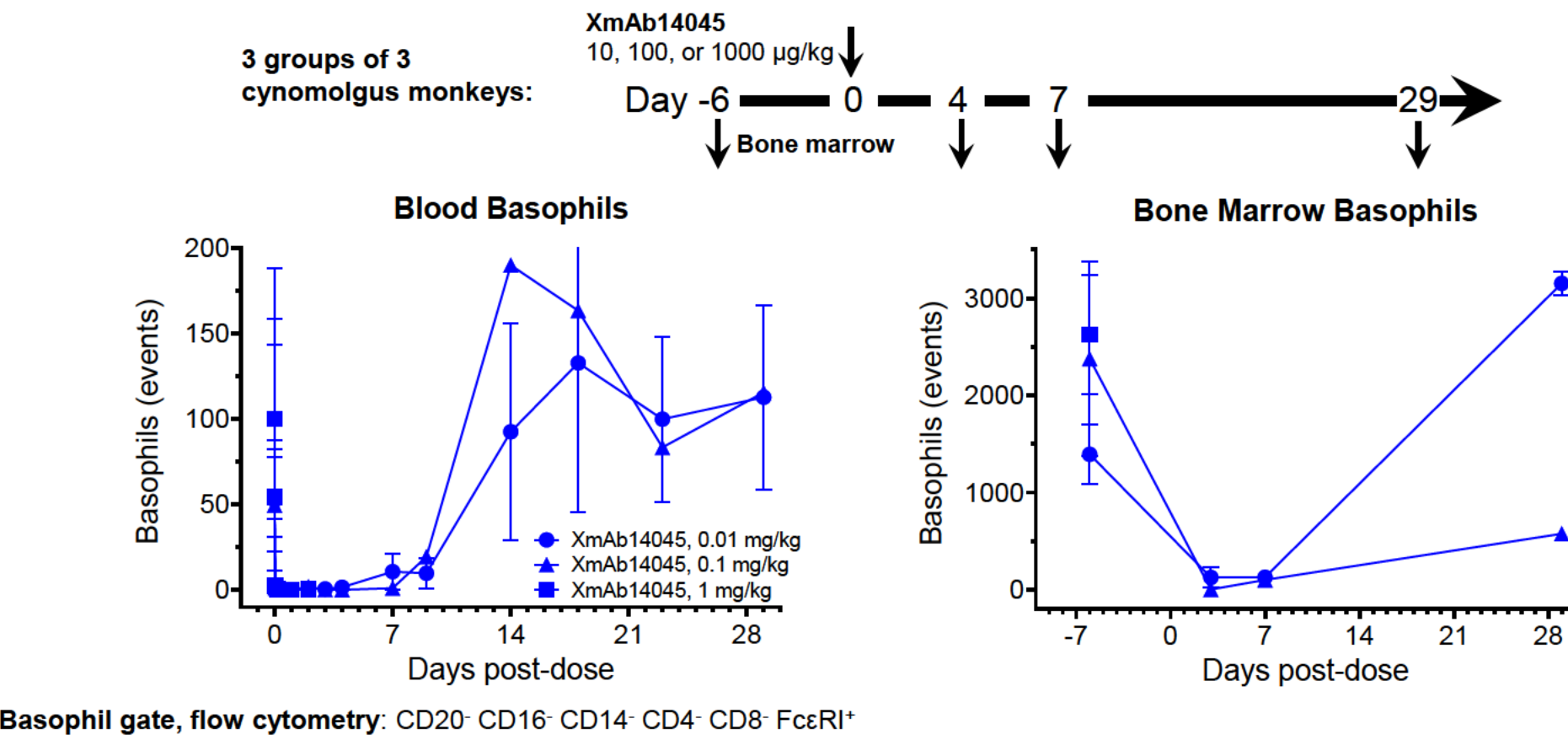
D Bispecific antibody kills human AML cell lines



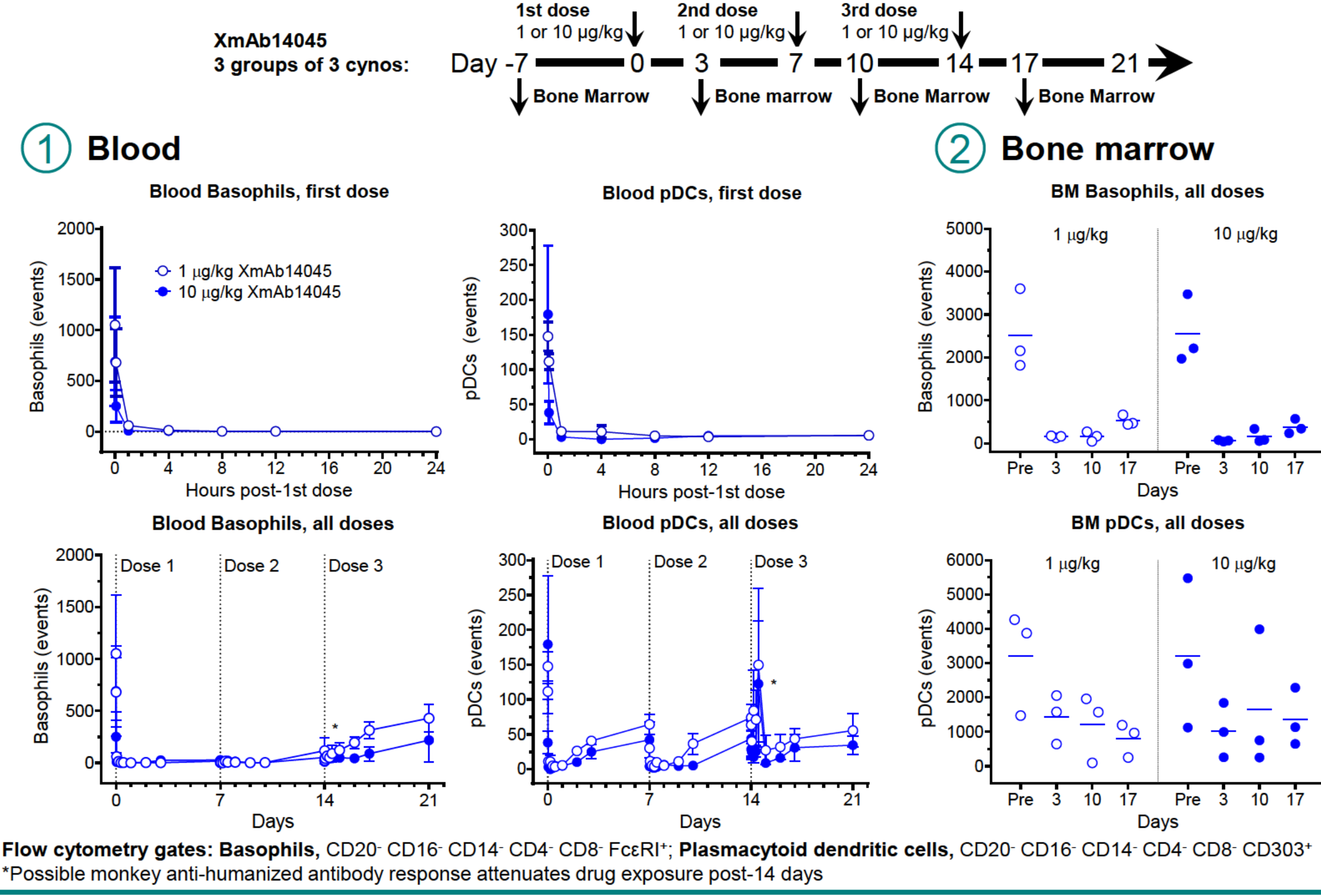
E Fc-containing bispecifics have long half-lives in mice



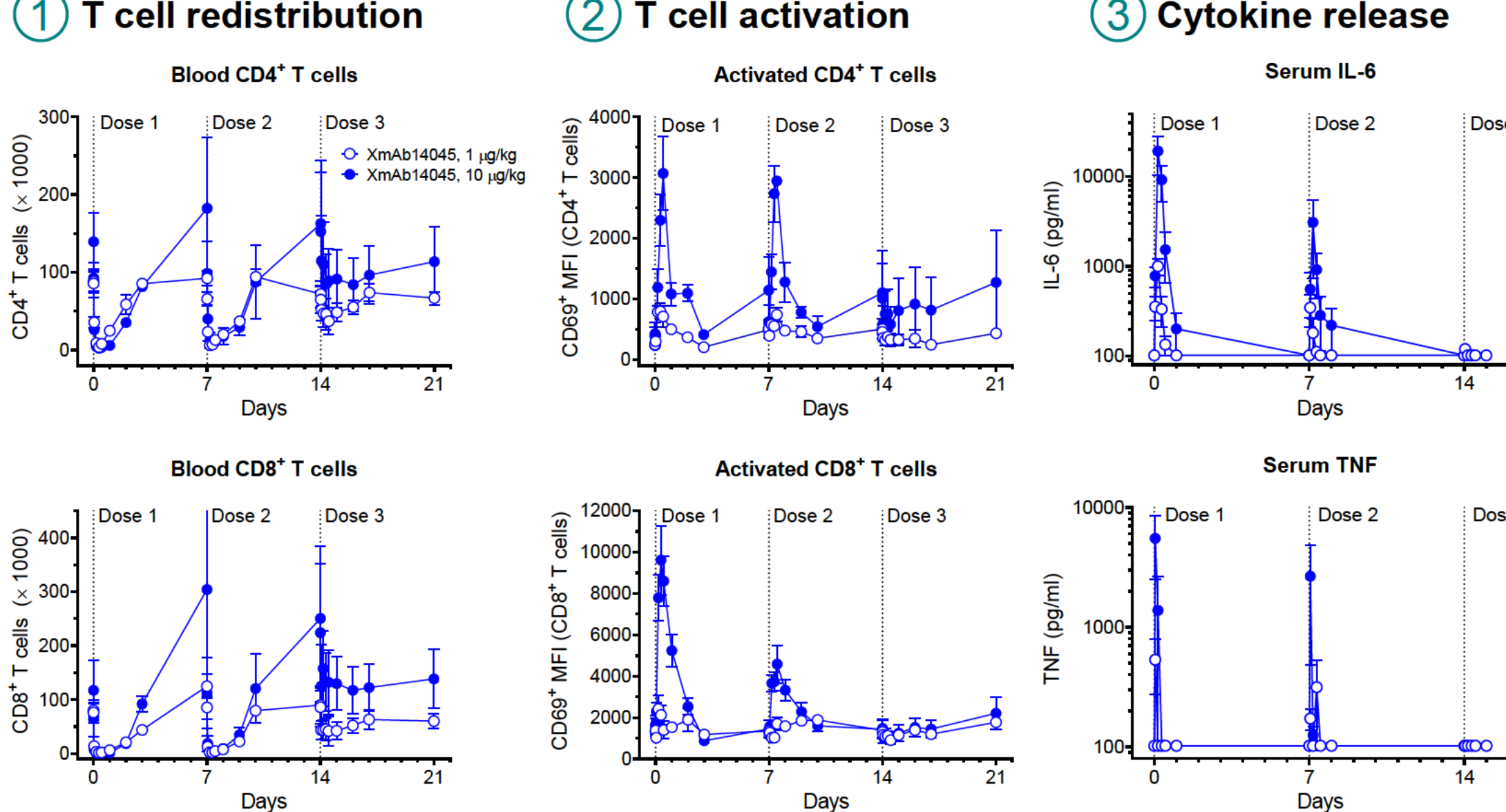
F Single dose of XmAb14045 depletes CD123⁺ cells in monkeys



G Repeat low dose of XmAb14045 depletes CD123⁺ cells in monkeys



H CD123⁺ cell depletion correlates with T cell redistribution & activation



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
- Safely & 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 & pDC as biomarker populations