Immunotherapy with Long-Lived Anti-CD20 × Anti-CD3 Bispecific Antibodies Stimulates Potent T Cell-Mediated Killing of Human B Cell Lines and of Circulating and Lymphoid B Cells in Monkeys: A Potential Therapy for B Cell Lymphomas and Leukemias

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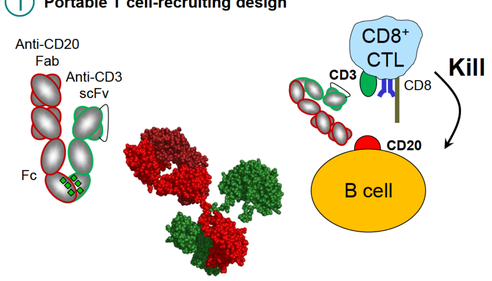
Introduction

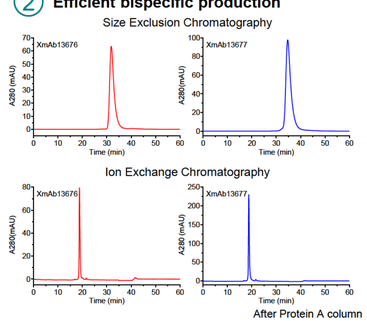
- CD20 is highly expressed on normal and malignant B cells, and is a well-established target of antibody therapeutics for B cell leukemias and lymphomas.
- However, one limitation of approved anti-CD20 antibodies such as rituximab, ofatumumab, and obinutuzumab is that they are unable to stimulate T cell-mediated killing of CD20$^+$ B cells.
- To exploit the potent activity intrinsic to T cell immunotherapy while maintaining the favorable dosing regimen of a therapeutic antibody, we have designed novel humanized bispecific antibodies that bind to both CD20$^+$ B cells and CD3$^+$ T cells.
- Such bispecific antibodies act 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, these antibodies possess a full Fc domain that binds to human FcRn (to maintain long serum half-life) and spontaneously forms stable heterodimers that are readily manufactured.

A CD20 x CD3 bispecifics are readily produced & purified

① Portable T cell-recruiting design



② Efficient bispecific production



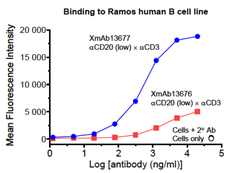
After Protein A column

Fab-scFv-Fc bispecific antibody format

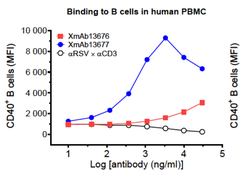
- XmAb13676 & XmAb13677 were designed with low & high affinity, respectively, for CD20
- Both were humanized using an existing anti-CD20 Fab; no reformatting required
- Anti-CD3 domain is humanized, stabilized (T_m = 72ºC), highly expressed, monkey cross-reactive, & portable
- Fc domain is modified to eliminate FcγR affinity, yet preserves FcRn affinity for antibody-like half-life

B Bispecific antibodies bind to human & monkey CD20 & CD3

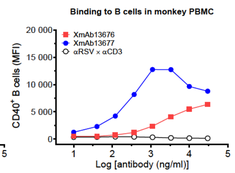
① Human B cell line



② Human PBMCs



③ Monkey PBMCs

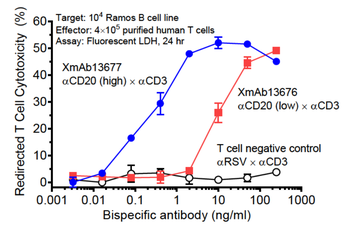


④ CD3 binding

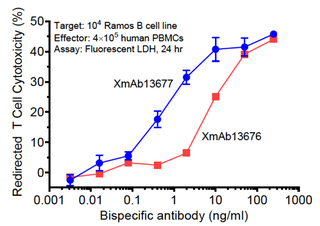
CD3 Binding (K_D)	XmAb 13676	XmAb 13677
Human	7 nM	5 nM
Cyno	7 nM	5 nM
Biacore, Ag coupled		

C Bispecific antibodies kill human B cells

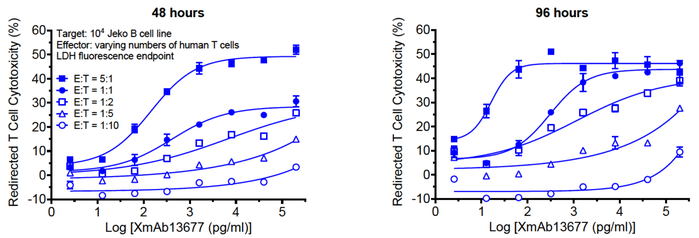
① Killing by purified human T cells



② Killing by human PBMCs

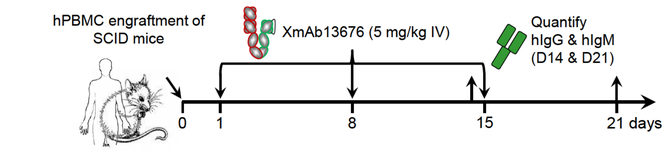


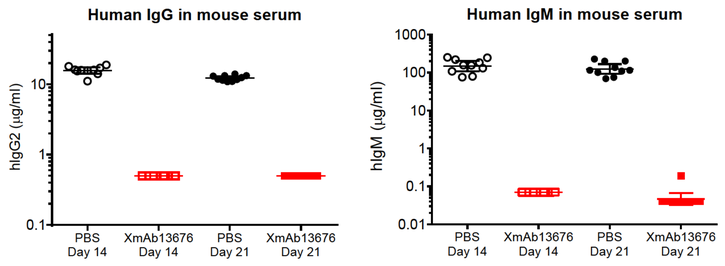
③ T cells are serial killers even when outnumbered by target cells



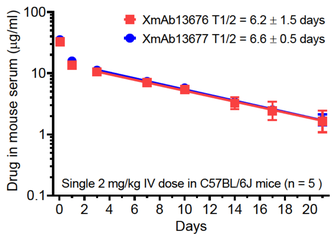
D Bispecific antibodies prevent human immunoglobulin production

① Bispecific antibodies suppress human Igs in hPBMC-engrafted mice



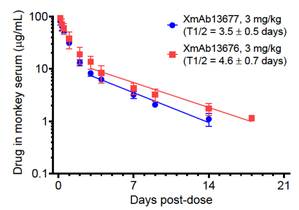


② Fc domain prolongs half-life

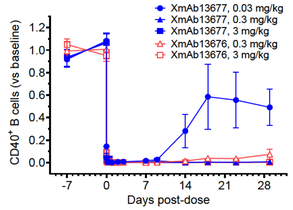


E Bispecifics deplete B cells in blood & lymphoid organs in monkeys

① Long half-life



② Blood B cells

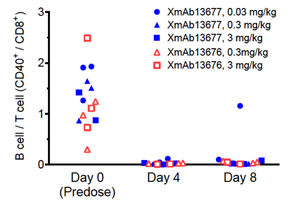


3 cynomolgus per group
Single IV infusion on Day 0:

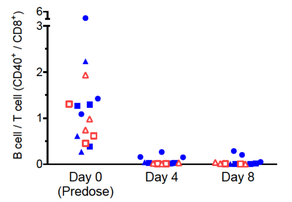
XmAb13676
- Low affinity for CD20
- 300 & 3000 µg/kg doses

XmAb13677
- High affinity for CD20
- 30, 300 & 3000 µg/kg doses

③ Bone marrow B cells

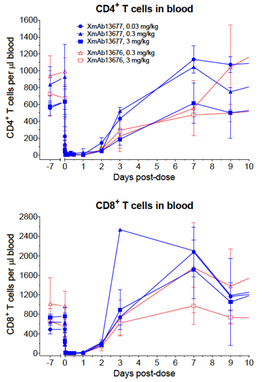


④ Lymph node B cells

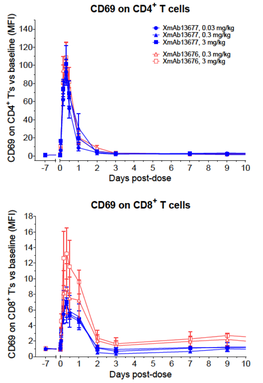


F B cell depletion correlates with T cell redistribution & activation

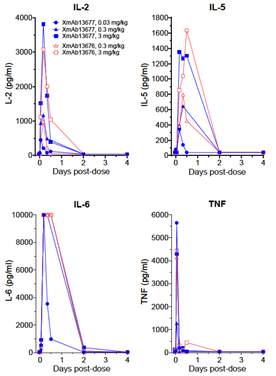
① Redistribution from blood



② CD69 induction



③ Cytokine release



Summary

The anti-CD20 × anti-CD3 antibodies XmAb13676 and XmAb13677:

- Incorporate a human Fc domain for long half-life
- Recruit T cells to kill B cells in vitro with ~50 & ~2 ng/ml potency, respectively
- Safely & effectively deplete B cells in monkeys at single doses as low as 30 µg/kg
- Deplete lymphoid B cells in bone marrow & lymph nodes
- Show T cell-mediated toxicity at higher doses (1 of 3 @ 3 mg/kg XmAb13676; 2 of 3 @ 0.3 mg/kg XmAb13677)
- Are efficiently manufactured using standard antibody production methods

These results support clinical testing of these bispecific antibodies in patients with CD20$^+$ B cell leukemias and lymphomas.

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