Immunotherapy with Long-Lived Anti-CD38 × Anti-CD3 Bispecific Antibodies Stimulates Potent T Cell-Mediated Killing of Human Myeloma Cell Lines and CD38⁺ Cells in Monkeys: A Potential Therapy for Multiple Myeloma

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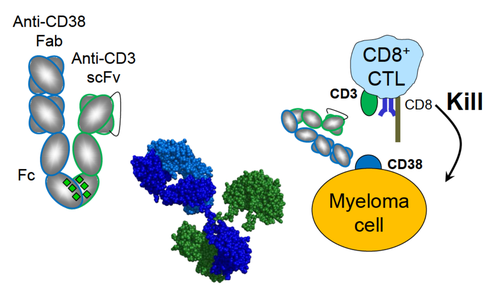
Introduction

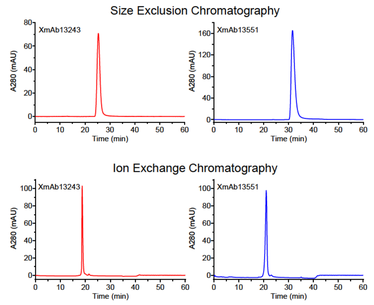
- CD38 is highly expressed on malignant plasma cells and is an attractive target of new therapies for multiple myeloma (MM).
- Several anti-CD38 antibodies such as daratumumab are in clinical development; however, one limitation of these monospecific antibodies is their inability to stimulate cytotoxic T cell killing of myeloma cells.
- To exploit the potent mechanism of T cell immunotherapy yet preserve the favorable drug and dosing properties of therapeutic antibodies, we designed XmAb13243 & XmAb13551 as Fc-containing bispecific antibodies that recruit T cells to CD38⁺ myeloma cells.
- XmAb13243 and XmAb13551 are highly effective at killing CD38⁺ cells, are readily manufactured, and have prolonged serum half life.

A CD38 x CD3 bispecific antibodies are readily produced & purified

① **Portable T cell-recruiting design**



② **Efficient bispecific production**



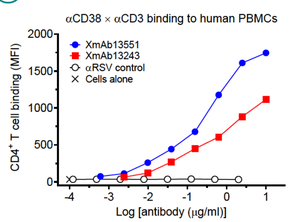
After Protein A column

Fab-scFv-Fc bispecific antibody format

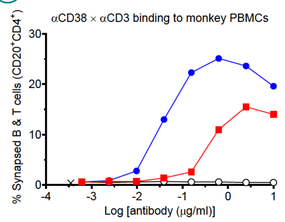
- XmAb13243 & XmAb13551 are designed with low & high affinity, respectively, for CD38
- Both were humanized using an existing anti-CD38 Fab; no reformatting required
- Anti-CD3 is humanized, stabilized (T_m = 72ºC), highly expressed, monkey cross-reactive, & portable
- Fc domain is modified to eliminate FcγR affinity, yet preserves FcRn affinity for antibody-like half-life

B Bispecific antibodies bind to human & monkey CD38 & CD3

① **Human**



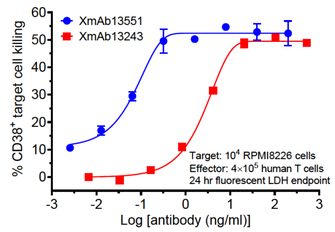
② **Cynomolgus monkey**



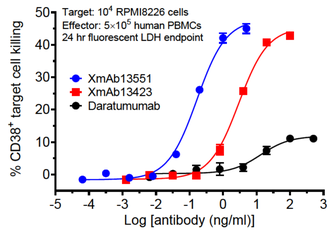
K_D	Human CD38	Cyno CD38	Human CD3	Cyno CD3
XmAb13243	16.8 nM	16.2 nM	5 nM	5 nM
XmAb13551	0.20 nM	0.28 nM	4 nM	2 nM
Biacore, Ag coupled				

C Bispecific antibodies kill myeloma cells

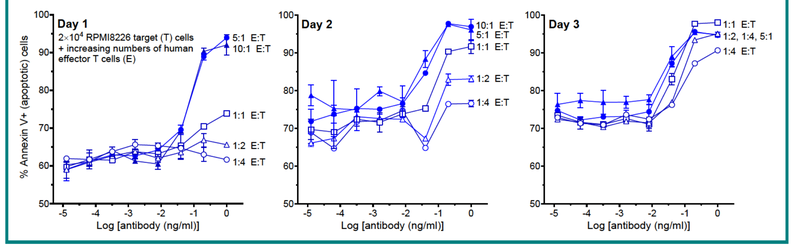
① **RTCC by purified human T cells**



② **More potent than daratumumab**

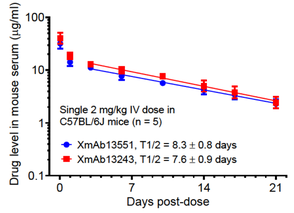


③ **T cells are serial killers even when outnumbered by target cells**

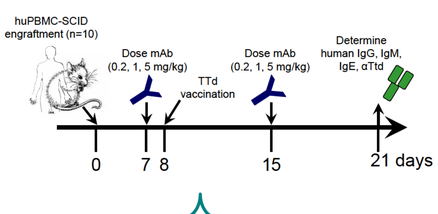


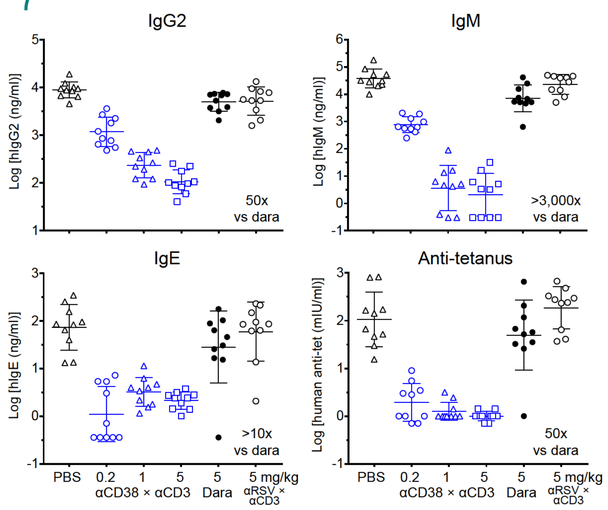
D Bispecifics have long half-life & suppress human Igs in mice

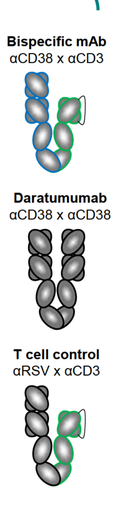
① **Fc domain prolongs half-life**



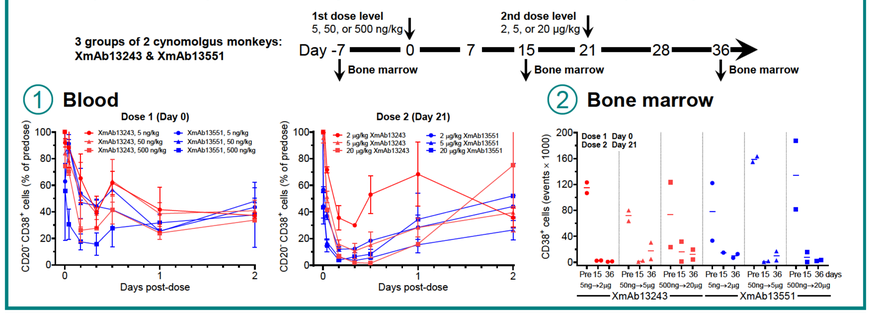
② **Greater hIg depletion vs daratumumab**



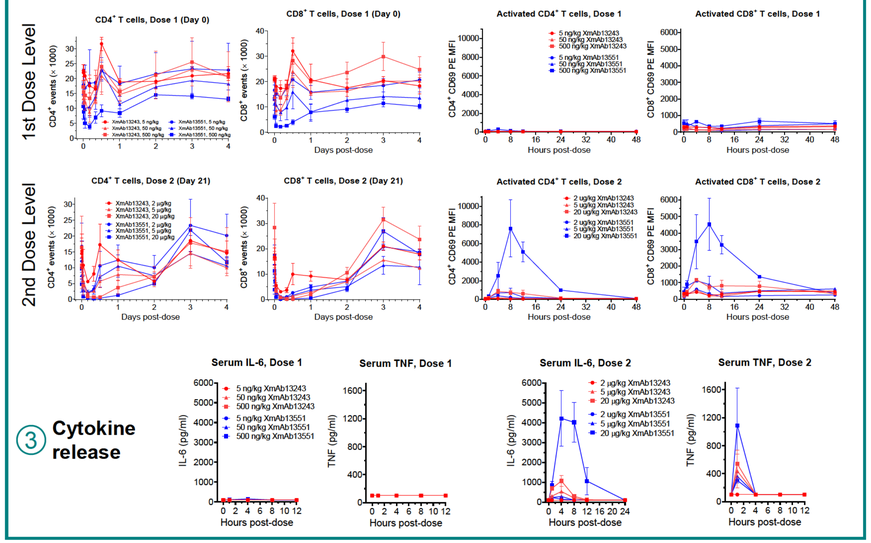




E Bispecifics deplete monkey CD38⁺ cells in blood & especially bone marrow



F CD38⁺ cell depletion correlates with T cell redistribution & activation



Summary

The anti-CD38 × anti-CD3 bispecific antibodies XmAb13243 & XmAb13551:

- Incorporate a human Fc domain for long serum half-life
- Effectively recruit T cells to kill CD38⁺ multiple myeloma cells in vitro
- Deplete human CD38⁺ cells and suppress human IgG, IgM, IgE, & anti-tetanus production in human PBMC-engrafted SCID mice
- Safely & effectively deplete CD38⁺ cells in blood & particularly in bone marrow of monkeys at doses from 0.5 to 20 μg/kg, with bone marrow depletion persisting to study end (Day 36, 2 weeks after last dose)
- Possess greatly increased efficacy & potency against myeloma cell lines & humanized mice compared to daratumumab, a monospecific anti-CD38 antibody
- Are efficiently manufactured using standard antibody production methods

These results support clinical testing of these bispecific antibodies in patients with multiple myeloma and other CD38⁺ malignancies.

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