Anti-SSTR2 × anti-CD3 bispecific antibody induces potent killing of human tumor cells in vitro and in mice, and stimulates target-dependent T cell activation in monkeys: A potential immunotherapy for neuroendocrine tumors

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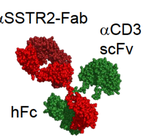
Introduction

- Somatostatin receptor 2 (SSTR2), a GPCR, is highly over-expressed in neuroendocrine tumors (NETs) and small cell lung cancer (SCLC).
- Somatostatin analogs and radionuclide therapies have clinical liabilities including short half-life, modest efficacy, administration challenges, and adverse side effects due to non-selective inhibition of other SSTRs.
- To exploit the potent mechanism of T cell immunotherapy for SSTR2+ cancers, we designed XmAb®18087, a humanized and affinity-optimized anti-SSTR2 × anti-CD3 bispecific antibody that possesses a full Fc domain to maintain long serum half-life and facilitate efficient manufacturing.
- XmAb18087 eliminates SSTR+ tumor cells by stimulating redirected T cell-mediated cytotoxicity (RTCC) in vitro and in a mouse model.
- In monkeys, XmAb18087 stimulates T cell redistribution and activation and cytokine induction via an SSTR2 target-dependent mechanism.

A Anti-SSTR2 × anti-CD3 bispecific XmAb18087 is readily manufactured

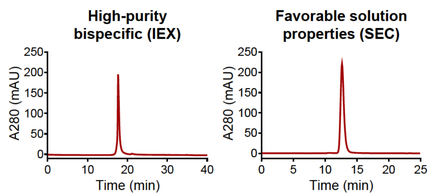
① Portable T cell-recruiting bispecific antibody was designed using Fab-scFv-Fc format

- Modified Fc domain eliminates FcγR affinity but preserves FcRn affinity for antibody-like half-life.
- Fc substitutions promote heterodimer formation and facilitate purification by standard methods.
- An αSSTR-Fab was humanized, affinity-matured, and inserted into a CD3 bispecific platform.

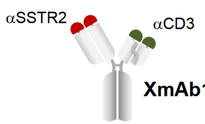


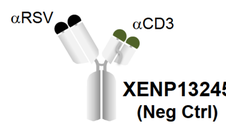
XmAb18087

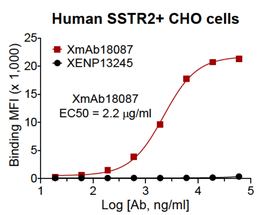
- High-yielding stable cell lines (>2 g/L)
- Protein A + ion-exchange chromatography

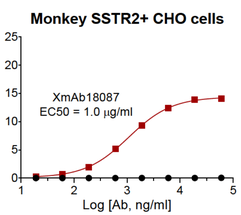


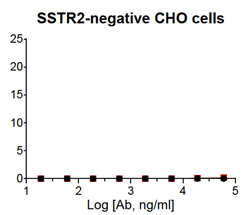
② XmAb18087 binds to human and cynomolgus monkey SSTR2





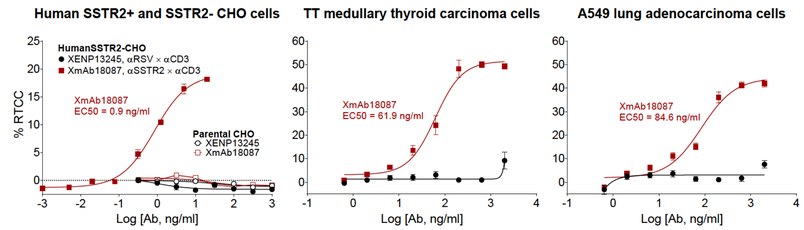




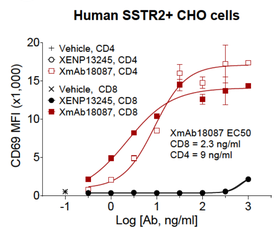


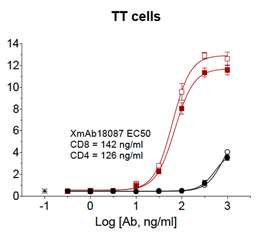
B XmAb18087 mediates T cell killing of SSTR2+ target cells in vitro

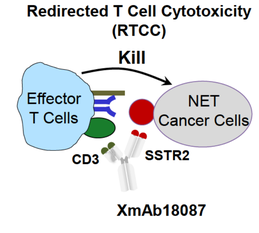
① SSTR2+ cell killing



② CD4 and CD8 T cell activation



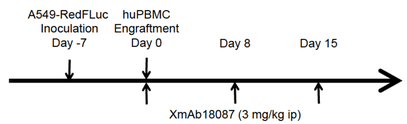




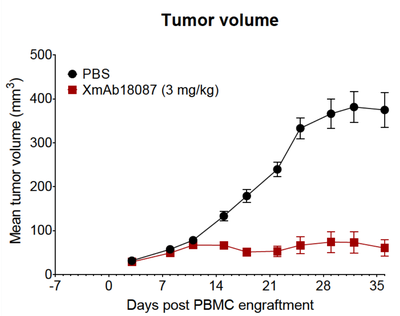
- PBMC effectors plus target cells were incubated 24 hr (E:T ratio = 10:1 or 20:1) and assayed by LDH

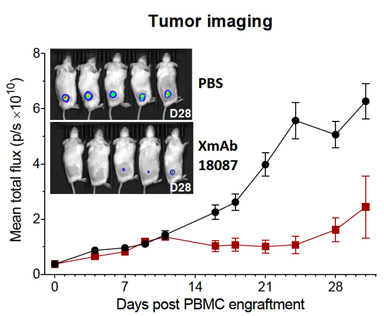
C XmAb18087 stimulates human T cell killing of SSTR2+ A549 lung carcinoma tumors in NSG mice

① Study design



② XmAb18087 suppresses A549 tumor growth

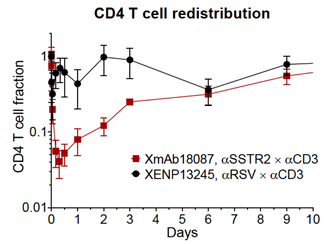


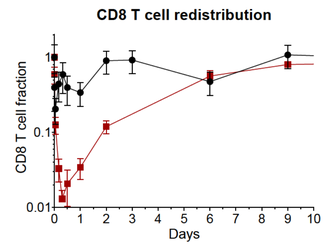


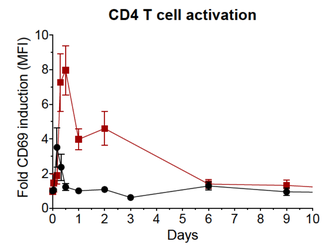
D XmAb18087 stimulates T cell activation in monkeys

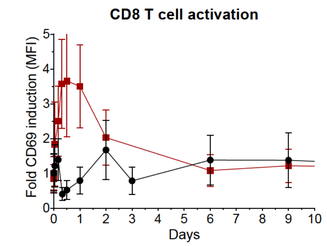
- Cynomolgus monkeys (n=3 per group), single-dose XmAb18087 or XENP13245

① T cell redistribution and activation in monkeys

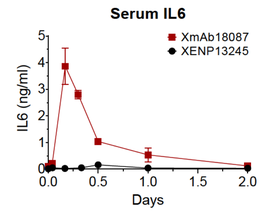


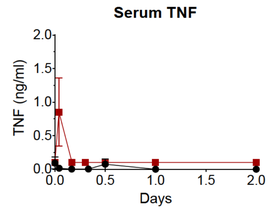






② Cytokine induction





- XmAb18087 induces CD4 and CD8 T cell redistribution and activation
- Cytokine release correlates with T cell activation

Summary

The anti-SSTR2 × anti-CD3 bispecific antibody XmAb18087:

- Is humanized and contains a human Fc domain for long serum half-life.
- Effectively recruits T cells to kill SSTR2+ cancer cell lines in vitro.
- Induces anti-tumor activity in human PBMC-engrafted NSG mice.
- Stimulates SSTR2-dependent T cell activation, T cell margination, and cytokine release in monkeys.
- Is efficiently manufactured using standard antibody production methods.

These results support clinical testing of XmAb18087 as a therapeutic for neuroendocrine tumors and NSCLC.

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