Abstract #1882

SCR-9171, a MUC17-targeted bispecific T cell engager molecule for gastrointestinal cancer

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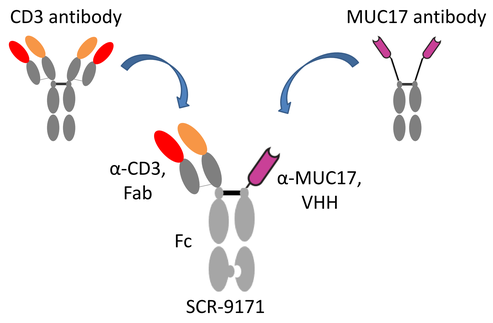
Introduction

- Although advances treatment have significantly improved the survival of patients with gastrointestinal cancer in recent decades, there is still an unmet medical need for more effective treatments. A promising strategy is the use of bispecific antibodies (bsAb) that recruit T cells to kill cancer cells by simultaneously binding to CD3 on T cells and tumor associated antigens.
- CD3-based T cell engagers are highly potent therapeutic molecules with T cell cytotoxicity activities. But high CRS risk and T cell exhaustion has been observed for high affinity CD3-based T cell engagers in clinicals. Effective and safe use of these therapeutics depends on selective targeting of cancer cells and optimal CD3 affinity.
- MUC17, a member of the mucin family, is a transmembrane glycoprotein only expressed on the apical membrane of normal gastrointestinal mucosal epithelial cells. MUC17 is overexpressed in 23%-52% of patients with gastric cancer. Compared to the adjacent normal tissues, the expression of MUC17 protein is consistently higher in gastric cancer tissues, suggesting that MUC17 is an attractive therapeutic target for gastric cancer.
- We created MUC17 x CD3 T cell engaging bispecific antibodies by starting with a single-domain antibody humanized from camel and a low affinity CD3 antibody. Here we report the design and the promising preclinical activity of SCR-9171 molecule in vitro and in vivo.

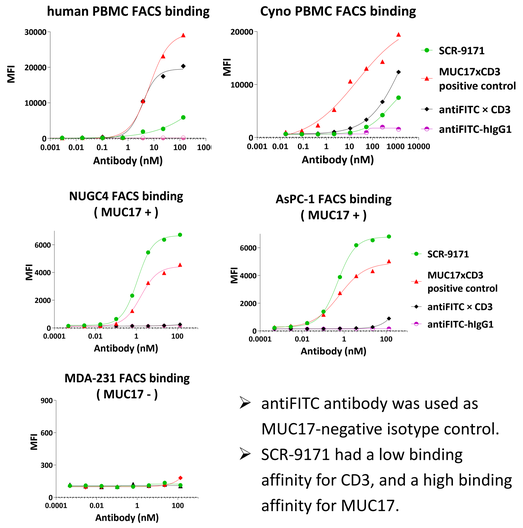
SCR-9171 molecular structure



- Fab, fragment antigen-binding
- VHH, single domain antibody derived from camel
- SCR-9171, 1+1 bispecific antibody.

MUC17xCD3 bsAb Binding

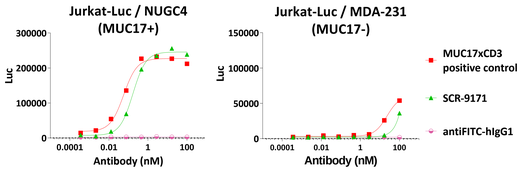
SCR-9171 Binds to T Cells and MUC17-Positive Target Cells



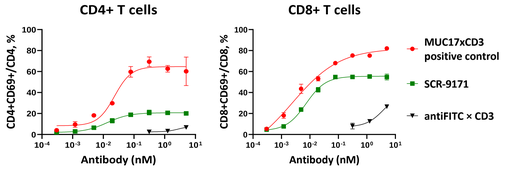
- antiFITC antibody was used as MUC17-negative isotype control.
- SCR-9171 had a low binding affinity for CD3, and a high binding affinity for MUC17.

SCR-9171 mediates T cell activation in vitro

SCR-9171 induced Activation of Jurkat-Luc reporter cell

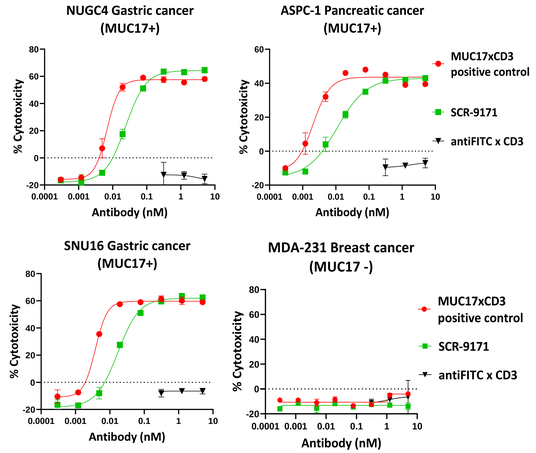


SCR-9171 mediates CD4+ and CD8+ T cell activation



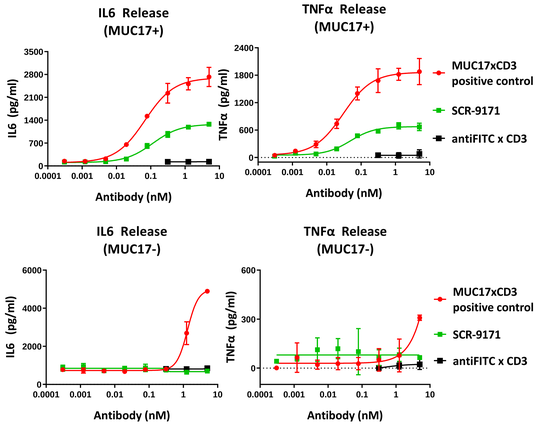
- Activation of CD4+ or CD8+ T cells were determined by FACS after 48 hours of co-culture with MUC17 positive SNU16 cells.

SCR-9171 induces T cell-mediated lysis of MUC17+ cells



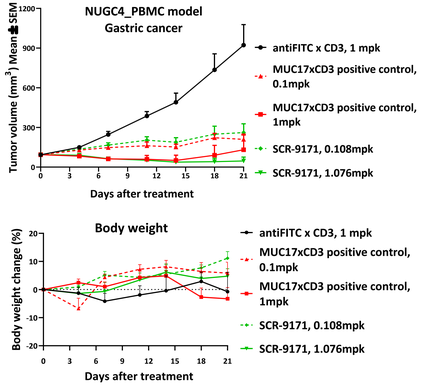
- Cell viability was measured by the Cell Titer-Glo Assay after the indicated antibody and cells were cultured for 48 hours.

SCR-9171 mediates cytokine release in vitro



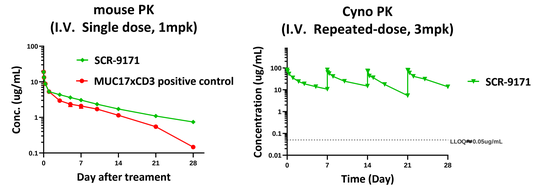
- PBMCs were co-culture with NUGC4 (MUC17+) or MDA-231 (MUC17-) cells.
- The co-culture supernatant was collected after 48h incubation, and cytokines secretion were detected by ELISA kit.

Anti-tumor Activity in CDX Model



- PBMC and tumor cells were co-implanted in NPG mice.
- Mice were dosed with the indicated antibody twice weekly, iv.

Plasma PK



- half-life of SCR-9171 was about 10 days in mouse, and 5 days in cyno monkey.
- SCR-9171 was well tolerated in cyno monkey, no indication of target-dependent toxicity in MUC17 expressing tissues.

Summary

- Binding to MUC17 on tumor cells and to CD3 on T-cells, thereby utilizing MUC17 to redirect T-cell effector function to cancer cell.
- Novel low affinity CD3 antibody used for bsAb results in reduced cytokine secretion.
- Effective anti-tumor efficacy in a dose-dependent manner in PBMC reconstituted model.
- Well-tolerated in non-human primates with favorable PK.
- SCR-9171 is a promising candidate for further development in clinical.

References

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