A novel T cell engager targeting BCMA and GPRC5D showed promising preclinical activity with low toxic risk for multiple myeloma treatment

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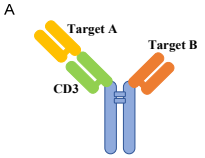
Abstract #1883

INTRODUCTION

- BCMA and GPRC5D are independently expressed in Multiple myeloma (MM) cells. The percentage of MM patients with single or co-expression of BCMA and GPRC5D is close to 90%, so they are the ideal MM Therapeutic targets.
- SCR-8572, A novel T cell engager targeting both BCMA and GPRC5D showed promising preclinical activity with low toxic risk for MM treatment，has the potential to cover a larger population of MM.
- Anti-human GPRC5D mAb was generated from mouse hybridoma whereas anti-human BCMA Ab was discovered from Alpaca as single-domain antibody (sdAb). The two lead TAA antibodies were assembled to anti-CD3 antibody with low binding activity. SCR-8572 was selected from dozens of different formats of triple-specific antibodies.
- SCR-8572 showed good binding activity with several MM cell lines and the weak binding to PBMC can decrease the sink effect in peripheral blood. *In vitro* functional studies revealed that SCR-8572 showed very good tumor-induced T cell activation against three MM tumor cell lines. And the cytotoxicity to tumor cell lines was much stronger than that of BCMA-CD3 (Teclistamab analogue, JNJ7957) and/or GPRC5D-CD3 (Talquetamab analogue, JNJ7564) treatment.
- In consistent with in vitro results, SCR-8572 displayed better anti-tumor efficacy in vivo in two MM cell-derived-Xenograft mice models with PBMC reconstitution compared to Teclistamab and/or Talquetamb groups.
- SCR-8572 was well tolerated in cynomolgus monkeys with high dosage in preliminary toxicity test warranting further investigation.

RESULTS

BCMA and GPRC5D binding affinity of SCR-8572



B

TriAb	Antigens	Binding Kinetics KD (M)
SCR-8572	humanBCMA-his	4.13E-11
	humanGPRC5D-biotin	2.41E-11

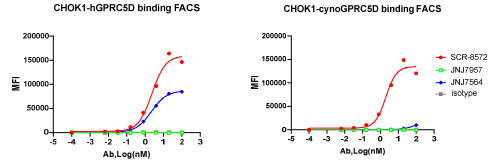


Figure 1. (A) Schematic diagram of the structure of SCR-8572. Target A and Target B represent BCMA or GPRC5D. (B) SCR-8572 shows strong binding affinity to humanBCMA and humanGPRC5D protein by SPR. (C) SCR-8572 shows strong binding affinity to CHOK1 cells overexpressing human GPRC5D and cyno GPRC5D by FACS. JNJ7957 is Jassen's Teclistamab analogue and JNJ7564 is Jassen's Talquetamab analogue.

SCR-8572 shows better binding to MM cell lines but weaker binding to PBMC than BCMA-CD3 BsAb JNJ7957 or GPRC5D-CD3 BsAb JNJ7564

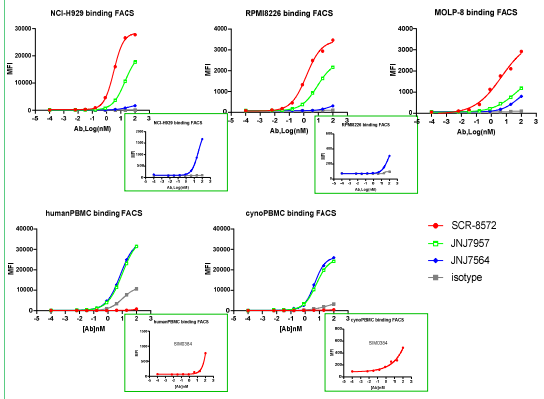


Figure 2. The ability of antibodies binding to three MM cell lines (NCI-H929, RPMI8226, MOLP-8), humanPBMC and cynoPBMC was assessed by FACS.

SCR-8572 shows very good tumor-induced T cell activation against three MM cell lines.

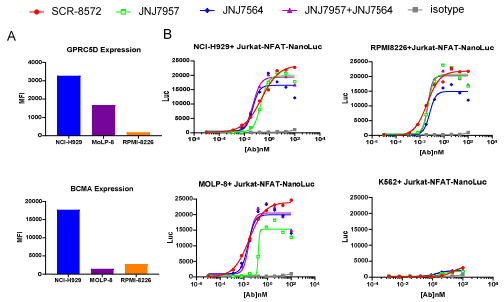


Figure 3. (A) The expression of BCMA and GPRC5D on different MM tumor cells was assessed by FACS. (B) Activation of CD3 signaling in Jurkat reporter cells co-cultured with MM cell lines in the presence of different concentrations of antibodies. The CD3 signaling activation was evaluated by NFAT driven Nano-luciferase activity in Jurkat cells.

SCR-8572 shows much stronger PBMC-mediated killing of MM cell lines than the combo of two TCE benchmarks and the cytokine release level is similar with two TCE benchmarks.

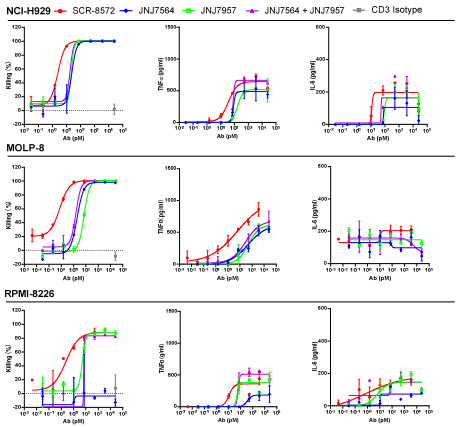


Figure 4. MM cell lines (express luciferase) were incubated with human PBMC at the ratio of 1:5 in the presence of different concentrations of antibodies for 72hrs. Killing was determined by Bright-Glo. Cell culture supernatant was collected for cytokine detection. Cytokine TNFα and IL6 were measured by FACS.

SCR-8572 inhibits tumor growth more effectively in a NCI-H929-hPBMC humanized xenograft mouse model

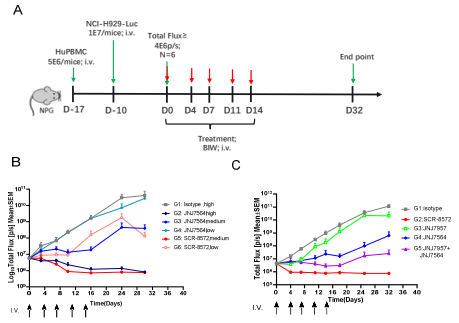


Figure 5. NPG mice were inoculated intravenously with NCI-H929 tumor cells 7 Days after PBMC implantation. Drug administration was initiated when mouse tumor fluorescence reached $5*10^6$p/s. Tumor fluorescence was measured by in vivo imager at the indicated time points. Black arrow heads indicate dosing timepoints.(A) Experimental design diagram. (B) Dose dependence efficacy evaluation of SCR-8572 and JNJ7564 treatment. (C) Efficacy evaluation of SCR-8572 and JNJ7957 and/or JNJ7564 treatment was performed at 0.1mpk dose.

SCR-8572 inhibits tumor growth more effectively than JNJ7957 and/or JNJ7564 treatment in a MOLP-8-hPBMC humanized xenograft mouse model.

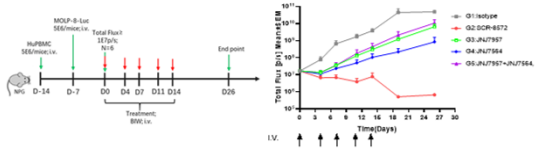


Figure 6. NPG mice were inoculated intravenously with MOLP-8 tumor cells 7 Days after PBMC implantation. Drug administration was initiated when mouse tumor fluorescence reached $1*10^7$p/s，the dose was 1mpk. Drug withdrawal observation was performed from day 14 of administration. Tumor fluorescence was measured by in vivo imager at the indicated time points.

SCR-8572 was well tolerated in cynomolgus monkeys with high dosage in preliminary toxicity test

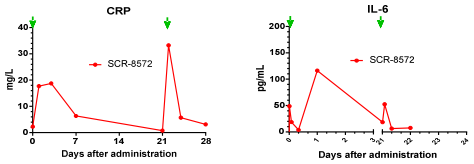


Figure 7. The preliminary toxic effect of SCR-8572 was explored in cynomolgus monkeys by 10mpk followed by 30mpk intravenous injection with 21 days interval. C Reaction Protein (CRP) level increased to 19-33mg/L and recovered to baseline in 7 days. The cytokine IL-6 level was increased to 116.3pg/ml in 24 hours after 10mpk injection and 52.5pg/ml in 2 hours after followed 30mpk injection.

SUMMARY

- SCR-8572 simultaneously bound to human BCMA and GPRC5D with high affinity and has weak binding to PBMC.
- SCR-8572 can induce strong T cell activation against three MM cell lines.
- SCR-8572 shows much stronger PBMC-mediated killing of MM cell lines than the combo of BCMA-CD3 BsAb and GPRC5D-CD3 BsAb.
- SCR-8572 treatment led to significant tumor growth inhibition both in NCI-H929 and MOLP-8-hPBMC xenograft model and are well tolerated in cynomolgus monkeys .

REFERENCES

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