Personalizing Salvage Approaches for Relapsed Multiple Myeloma following CAR T Cell Therapy

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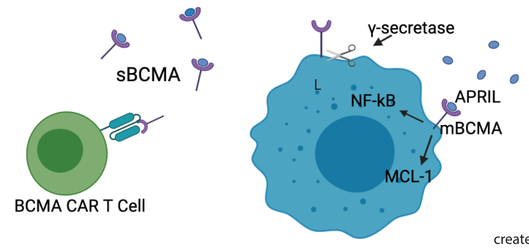
Introduction

B cell maturation antigen (BCMA) has become the second FDA-approved CAR-T cell therapy target through the approvals of idecabtagene vicleucel (ide-cel) and ciltacabtagene autoleucel (cilta-cel) for patients with multiple myeloma (MM), a plasma cell (PC) malignancy. Multiple myeloma has a uniquely challenging disease course, as patients go through cycles of initial response to therapy and subsequent relapse. Despite the initial effectiveness of novel CAR-T cell therapies, relapse still remains inevitable. Thus, it is necessary to understand mechanisms of resistance to anti-BCMA CAR-T and identify effective therapies, such as bispecific antibodies that engage T-cells with MM cells via BCMA or alternative targets.

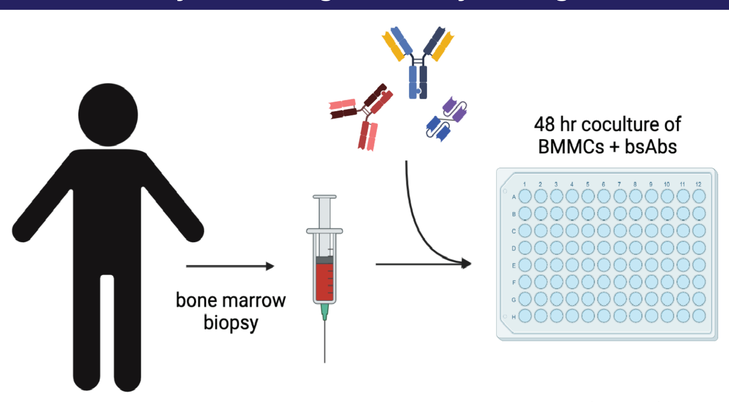
BCMA is critical for development and survival and proliferation of long-lived PCs and overexpressed in MM. PC homeostasis is maintained by cleavage of BCMA by the ectoenzyme y-secretase, releasing soluble BCMA (sBCMA) into the serum. This may act as a drug sink for CAR-Ts and aid MM resistance to therapy.



Materials and Methods

To study CAR-T resistance, we are collecting bone marrow and peripheral blood samples from patients treated with CAR-T cells for MM at the University of Colorado. Samples are collected pre-treatment, on-treatment and at the time of eventual relapse. To investigate downregulation of BCMA target protein, we are using flow cytometry panel that simultaneous monitors other potential targets for novel immunotherapies, such as bispecific antibodies. Simultaneously, we measure soluble BCMA (sBCMA) by ELISA (abcam) to evaluate if increased cleavage may also contribute to CAR-T resistance. Lastly, to investigate efficacy of novel immunotherapies post-CAR-T, we are using \Myeloma Drug Sensitivity Testing (MyDST) ex vivo drug sensitivity profiling to evaluate the effects of bispecific antibodies to decrase primary MM cell viability.

Myeloma Drug Sensitivity Testing



Flow Gating Schemes

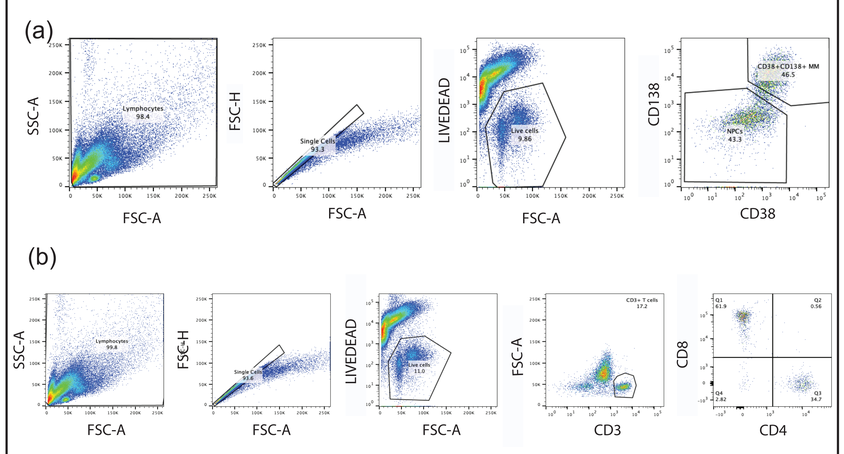


Figure 1. (a). gating scheme for identification of CD38+CD138+ MM vs. non plasma cell (NPC) populations (b). gating scheme for identification of CD3+ T cell subpopulations

SAR442257- a CD38xCD3/CD28 bsAb

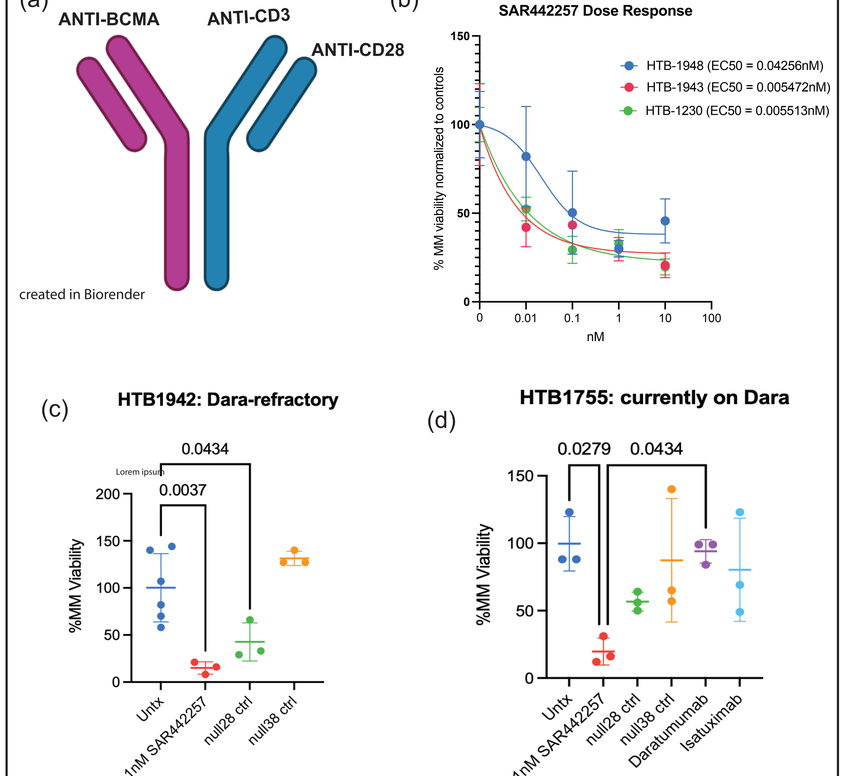


Figure 2. (a) SAR442257 (b) Dose response curves of SAR442257 in three new Dx MM patient bone marrow ex vivo cultures.Y-axis % of viable MM normalized to untreated controls (c) Testing 1nM SAR442257 alongside of identical antibody control missing anti-CD28 arm and identical antibody control missing anti-CD38 arm (null28 and null38 respectively) in daratumumab (anti-CD38 mAb) refractory patient HTB 1942. (d) Testing 1nM SAR442257 against null CD28 and null CD38 controls and daratumumab and isatuximab (both anti-CD38 mAbs) in patient currently on daratumumab; *ANOVA with Tukey's multiple comparison's

SAR442257 increases % CD45+ MM in a dose dependent manner

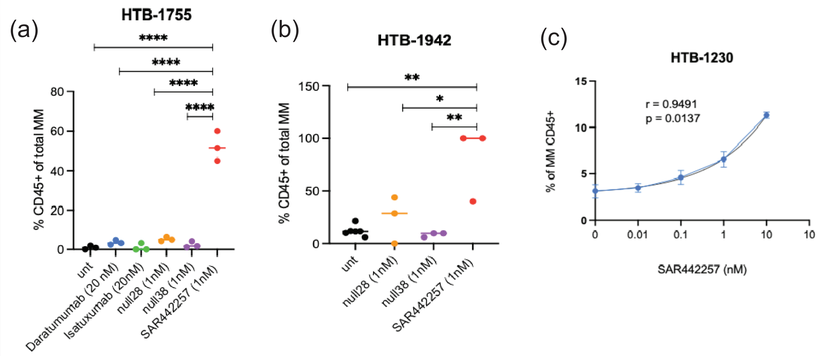


Figure 3. (a) and (b)% of surviving MM that is CD45+ significantly increases with SAR442257.* (c) increase in CD45+ is dose dependent**; *One-way ANOVA with Tukey's multiple comparison's test.; **Pearson's R correlation

serum sBCMA correlates with MM disease burden

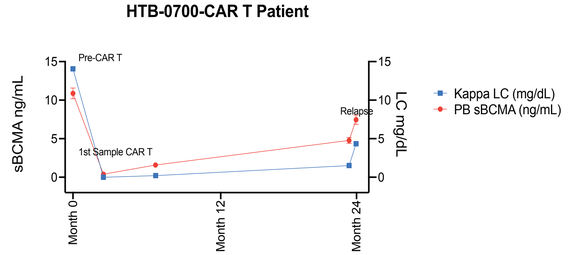


Figure 4. ELISAs were performed on serial timepoints of a patient serum before, during and after BCMA CAR T cell therapy to compare sBCMA (ng/mL) to serum light chain (mg/dL)

Conclusions and Future Directions

-we are capable of measuring immune-mediated effects of therapies using the patient's own endogenous T cells via My-DST

-we have found that SAR442257 increases the percentage of surviving MM that expresses CD45, a marker typically lost with progressisng MM

-we observed correlation between sBCMA levels and MM disease burden

-we are growing a valuable cohort of pre- and post-BCMA CAR-T samples

-to study these, we have established techniques that will be essential to understanding CAR-T resistance in MM, finding the best target for subsequent treatment, and testing out novel agents with a high degree of potential to prolong the lifespan of this important population

Future Directions:

-test bsAbs from Pfizer and Janssen as well and test all bsAbs in patient samples after relapse to BCMA CAR T

-inhibit CD45 alongside SAR442257 therapy & examine isoform specificity

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