# Preclinical development of UB-VV500, an in vivo potency-enhanced CAR T cell product targeting BCMA and GPRC5D for multiple myeloma

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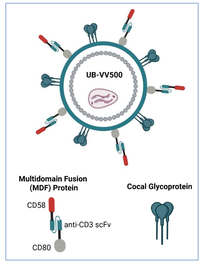
## Introduction

Autologous, ex-vivo manufactured chimeric antigen receptor (CAR) T cell therapies targeting BCMA have revolutionized the treatment of relapsed or refractory (R/R) multiple myeloma (MM), with two FDA-approved CAR T cell products. While effective, ex vivo CAR T cells have limitations including complex manufacturing and the requirement for lymphodepleting chemotherapy which substantially limit patient access to these transformative therapies. Furthermore, patients receiving BCMA-directed therapies may relapse, or not respond due to heterogeneity of BCMA expression within tumors and through BCMA loss via genetic deletion, surface downregulation/cleavage, or mutations resulting in epitope loss.

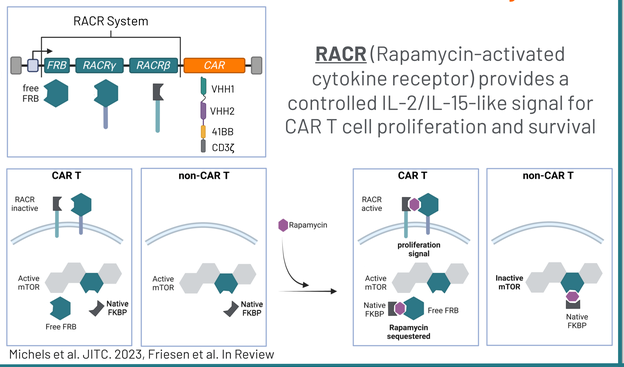
To address these limitations, Umoja is developing UB-VV500, an off-the-shelf lentiviral vector product based on VivoVec™ technology designed to engineer fully-human anti-BCMA/GPRC5D dual-targeting CAR T cells in vivo, without the need for lymphodepleting conditioning. Like BCMA, GPRC5D is highly expressed on MM cells with limited expression in other tissues, making it a promising target. In addition, UB-VV500 also encodes a Rapamycin-Activated Cytokine Receptor (RACR™), designed to enable small-molecule controlled IL-2/IL-15-like signaling within the CAR+ cells, promoting CAR T cell expansion and antitumor activity. Here we detail in vitro and in vivo preclinical studies demonstrating UB-VV500 efficiently generates anti-BCMA/GPRC5D dual-targeting CAR T cells, which exhibit potent antitumor effector functions (cytokine secretion, proliferation, cytotoxicity) against multiple myeloma tumor cells that are greatly augmented by RACR activation with rapamycin.

## Fig 1. UB-VV500 delivers an anti-BCMAxGPRC5D CAR and RACR system to T cells in vivo

**VivoVec** activates and transduces T cells in vivo



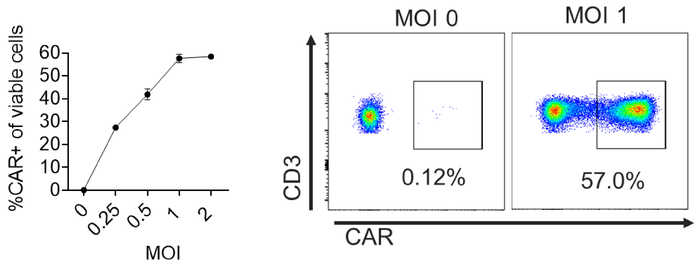

Nicolai et al. Blood. 2024




**RACR** (Rapamycin-activated cytokine receptor) provides a controlled IL-2/IL-15-like signal for CAR T cell proliferation and survival

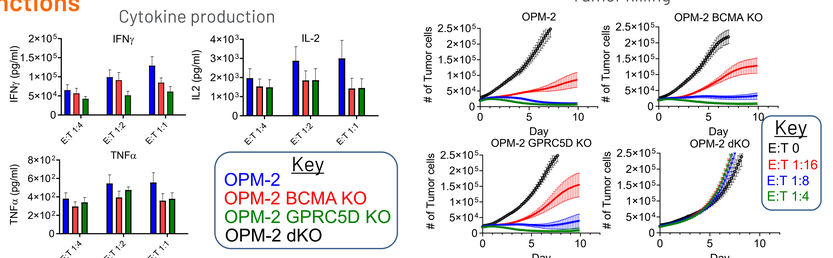
Michels et al. JITC. 2023, Friesen et al. In Review

## Fig 2. UB-VV500 efficiently transduces resting T cells in vitro



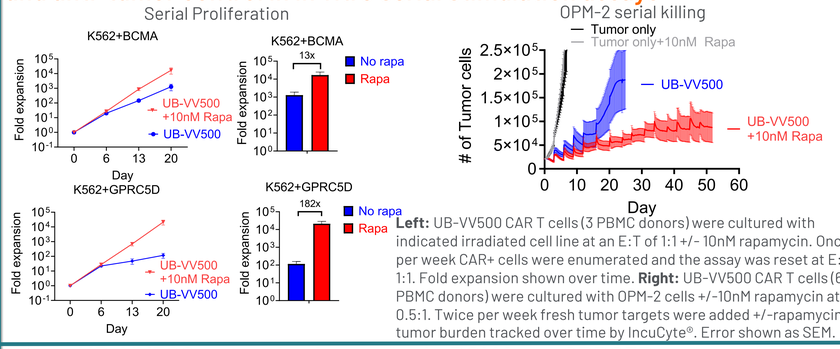

**Above**: UB-VV500 was added to PBMCs from 3 donors at several MOIs. 7 days later CAR expression was assessed on viable, CD3+ T cells. Representative flow plot shown. Error bars shown as SEM.

## Fig 3. UB-VV500-generated CAR T cells exhibit antigen-dependent effector functions



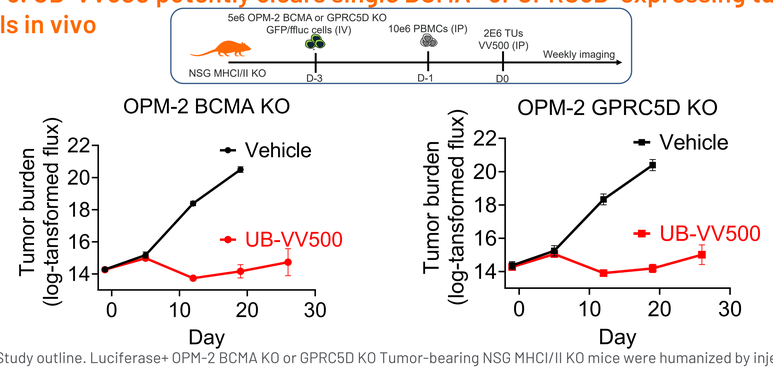

**Left**: VV500 CAR+ T cells (6 PBMC donors) were generated and cultured at the indicated E:T ratios with parental, BCMA KO, GPRC5D KO, or double KO OPM-2 tumor cells for 18 hours followed by supernatant cytokine analysis by MSD®. **Right:** VV500 CAR+ T cells (6 PBMC donors) were generated and cultured at the indicated E:T ratios with parental, BCMA KO, GPRC5D KO, or double KO OPM-2 tumor cells. Total tumor cells were tracked over time on an IncuCyte®. Error shown as SEM.

## Fig 4. Rapamycin enhances UB-VV500-generated CAR T cell proliferation and anti-tumor control in in vitro serial stimulation assays



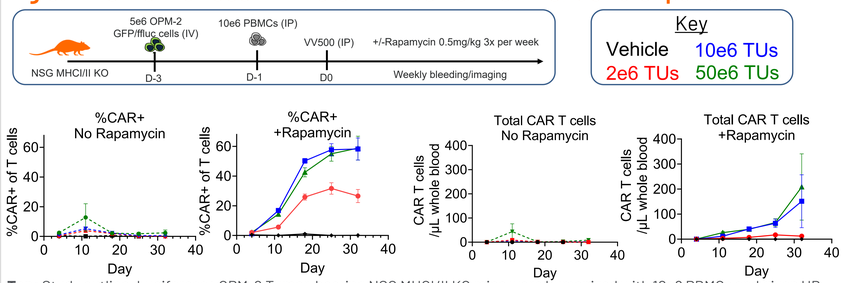

**Left:** UB-VV500 CAR T cells (3 PBMC donors) were cultured with indicated irradiated cell line at an E:T of 1:1 +/- 10nM rapamycin. Once per week CAR+ cells were enumerated and the assay was reset at E:T 1:1. Fold expansion shown over time. **Right:** UB-VV500 CAR T cells (6 PBMC donors) were cultured with OPM-2 cells +/-10nM rapamycin at E:T 0.5:1. Twice per week fresh tumor targets were added +/-rapamycin and tumor burden tracked over time by IncuCyte®. Error shown as SEM.

## Fig 5. UB-VV500 potently clears single BCMA- or GPRC5D-expressing tumor cells in vivo



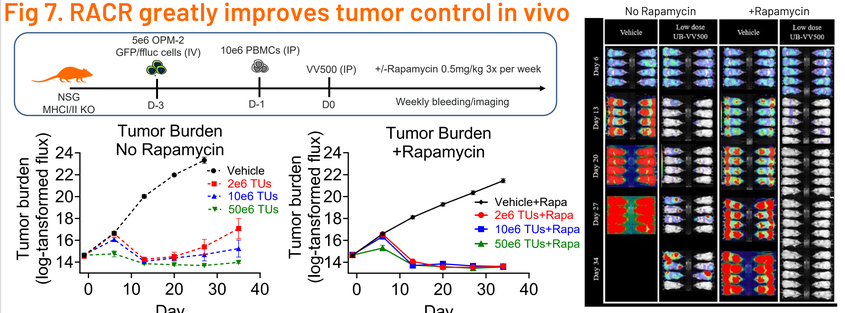

**Top:** Study outline. Luciferase+ OPM-2 BCMA KO or GPRC5D KO Tumor-bearing NSG MHCI/II KO mice were humanized by injecting 10e6 PBMCs into the intraperitoneal cavity. Mice received 2E6 TUs of UB-VV500. **Bottom:** Tumor burden was assessed over time as total flux and tracked over time using an *In vivo* imaging system (IVIS®). Error shown as SEM.

## Fig 6. RACR enhances in vivo CAR T cell enrichment and expansion




**Top:** Study outline. Luciferase+ OPM-2 Tumor-bearing NSG MHCI/II KO mice were humanized with 10e6 PBMCs and given UB-VV500 at 3 doses. Some animals were additionally treated with rapamycin at 0.5mg/kg 3x per week. **Bottom:** %CAR (left) and total CAR T cells (right) in the blood over time +/- Rapamycin. Error shown as SEM.

## Fig 7. RACR greatly improves tumor control in vivo




**Top:** Study outline. Luciferase+ OPM-2 Tumor-bearing NSG MHCI/II KO mice were humanized with 10e6 PBMCs and given UB-VV500 at 3 doses. Some animals were additionally treated with rapamycin at 0.5mg/kg 3x per week. **Bottom Left:** OPM-2 tumor burden after treatment with UB-VV500 +/- rapamycin. Tumor burden tracked over time using an *In vivo* imaging system (IVIS®). **Bottom Right:** IVIS® images of tumor burden over time. Error shown as SEM.

## Summary

- UB-VV500 transduces resting T cells, efficiently generating dual BCMA/GPRC5D-targeting CAR T cells.
- UB-VV500 CAR T cells are highly functional against BCMA and GPRC5D expressing cell lines in an antigen-dependent manner.
- UB-VV500 CAR T cell in vitro proliferation and serial killing are greatly enhanced via the RACR system.
- UB-VV500 potently clears BCMA and GPRC5D-expressing tumor cells in vivo, and CAR T cell persistence and tumor clearance is greatly enhanced through rapamycin-dependent RACR activation.

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