Universal SLAMF7-specific CAR T-cells as treatment for multiple myeloma

Rohit Mathur[1], Zheng Zhang[1], Jin He[1], Roman Galetto[2], Gouble Agnes[2], Isabelle Chion-Sotinel[2], Stephanie Filipe[2], Annabelle Gariboldi[2], Tanooha Veeramachaneni[1], Elisabet E. Manasanch[1], Sheeba K. Thomas[1], Hans C. Lee[1], Krina K. Patel[1], Donna M. Weber[1], R. Eric Davis[1], Robert Z. Orlowski[1], Julianne Smith[3], Jing Yang[1] and Sattva S. Neelapu[1]

[1]Department of Lymphoma and Myeloma, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, USA
[2]Cellectis SA, 8 rue de la croix Jarry, 75013 Paris, France
[3]Cellectis Inc, 430 East 29th Street, 10016 New York, NY, USA

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Rationale for targeting SLAMF7 with CAR T cells in MM

- Despite development of novel therapies, multiple myeloma (MM) remains an incurable disease
- Recent studies with autologous chimeric antigen receptor (CAR)-T cells targeting BCMA have shown promise in the treatment of patients with relapsed/refractory MM. (Ali et al, Blood 2016; Cohen et al, Ash 2016 abstract # 1147; Berdeja et al, ASCO 2017 abstract # 3010; Fan et al ASCO 2017 abstract # LBA3001)
- Signaling lymphocytic activation molecule F7 (SLAMF7, also called CS1) is highly expressed on MM tumor cells and is present in only a subset of T cells, B cells and NK cells among normal tissues (Y. Tai et al, Blood 2009; His ED et al, Clin Cancer Res. 2008)
- Elotuzumab, a monoclonal antibody targeting SLAMF7 has been found to be safe and effective in patients with MM (Sagar Lonial, NEJM 2015)
- Together, these studies suggested that SLAMF7 is likely to be a good therapeutic target for CAR-T cell therapy in MM.
- Currently, most CAR-T cell therapy products are generated from autologous T cells, which is a major limitation logistically and likely difficult to do for lymphopenic and most critically ill patients.

Benefits and challenges of allogeneic CAR-T cells

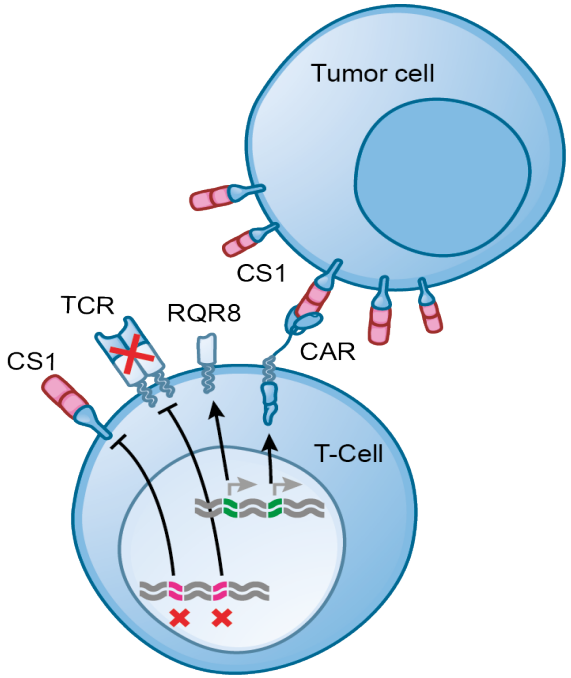
Benefits

- Universal or “off-the-shelf” product
- CAR-T cells are prepared from T cells of healthy donor and therefore likely more functional
- Allows therapy with CAR-T cells in patients who are critically ill or profoundly lymphopenic
- Decreases production time, delays, and cost

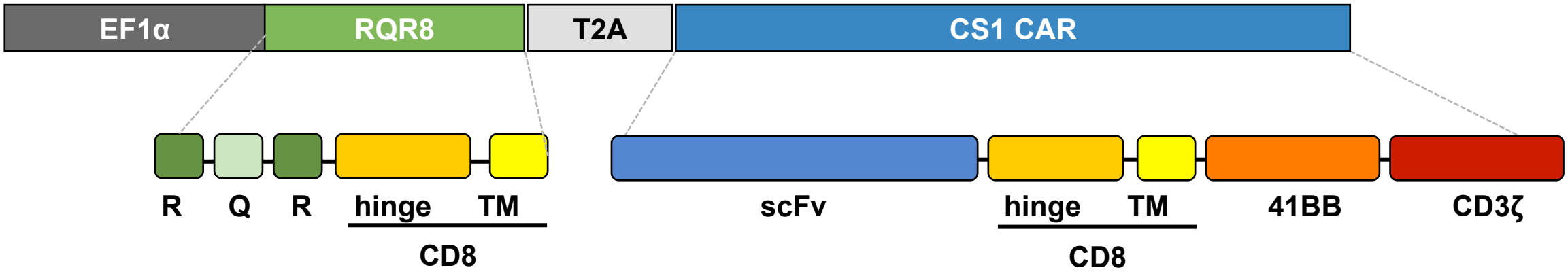
Challenges

- Potential induction of GvHD
- Potential for rejection of allogeneic CAR-T cells
- Since SLAMF7/CS1 is expressed on activated CD8+ T cells, fratricide of CAR-T cells may occur

“Off-the-shelf” allogeneic SLAMF7-specific CAR-T cells



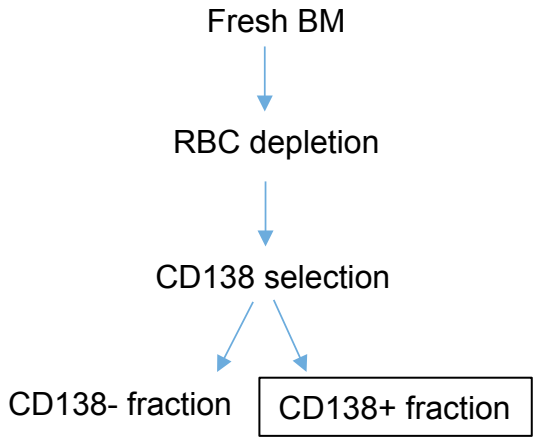
- Anti-SLAMF7 CAR expression to redirect allogeneic T cells against MM
- TRAC gene inactivation using TALEN® gene-editing technology to knock-out TCR and minimize GvHD
- SLAMF7 inactivation using TALEN® to prevent fratricide
- Elimination gene (RQR8) for safety → Rituximab

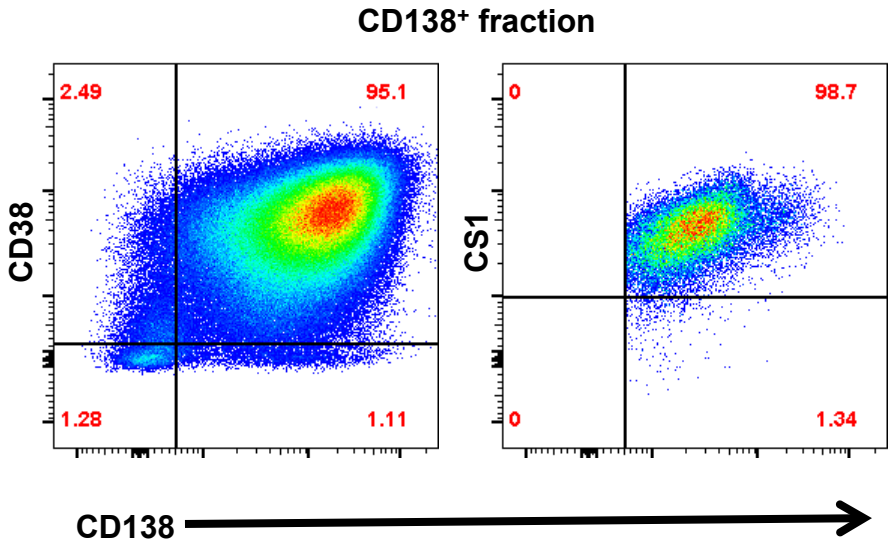


R= CD20 mimetope (rituximab)
Q= CD34 epitope (Qben10)

Galetto et al, ASH 2015, Abstract # 116

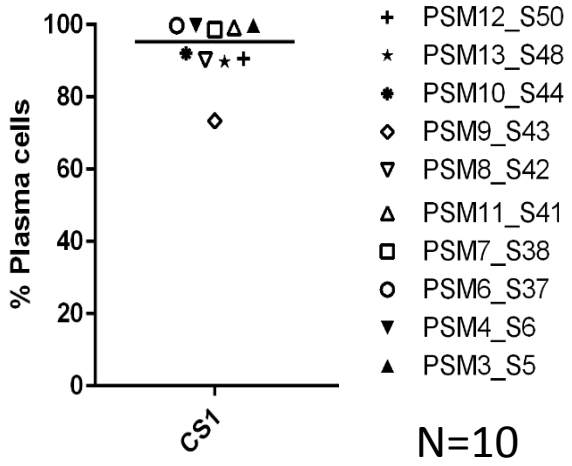
Isolation of primary MM tumor cells and expression of SLAMF7/ CS1





Sample ID	Age/ Sex	Treatment status	Risk
PSM1_S1	74/M	Untreated	High
PSM2_S2	62/F	Untreated	High
PSM3_S5	67/F	Untreated	High
PSM4_S6	55/M	Treated	Standard
***PSM5_S29**	77/M 78/M 69/M	Treated Treated Treated	N/A
PSM6_37	84/F	Treated	High
PSM7_S38	67/M	Untreated	N/A
PSM8_S42	67/M	Untreated	High
PSM9_S43	41/F	Untreated	High
PSM10_S44	58/M	Untreated	Standard
PSM11_S41	49/M	Treated	High
PSM12_S50	65/F	Untreated	High
PSM13_S48	71/M	Untreated	High
PSM_S53	61/M	Untreated	Standard
***PSM_S32**	77/M 72/M	Treated	High

* Patient samples were combined together



High risk – p53 deletion; del 1p32; 1q21 gain; monosomy 13
Standard risk – t(11;14); RB1 deletion

Experimental plan/ Methods

In vitro efficacy studies of UCARTCS1 against MM tumor cells

- Proliferation assay
- Cytokine induction
- Cytotoxicity
- Degranulation

In vivo efficacy studies of UCARTCS1 against MM xenografts

- SCID-Hu orthotopic mouse model

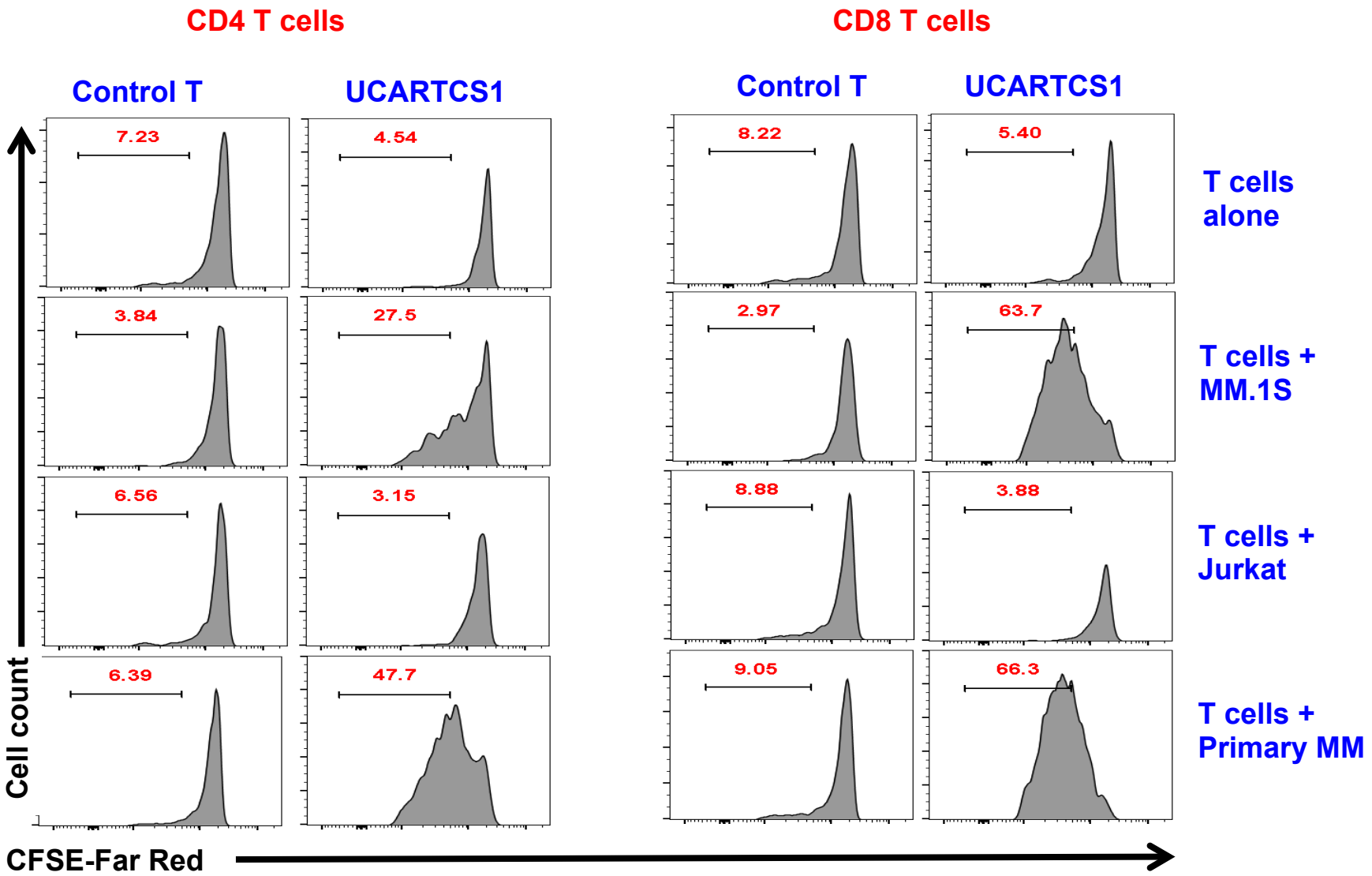
Tumor cells used

- Positive Cell line: MM.1S
- Negative Cell line: Jurkat
- Primary MM tumor cells

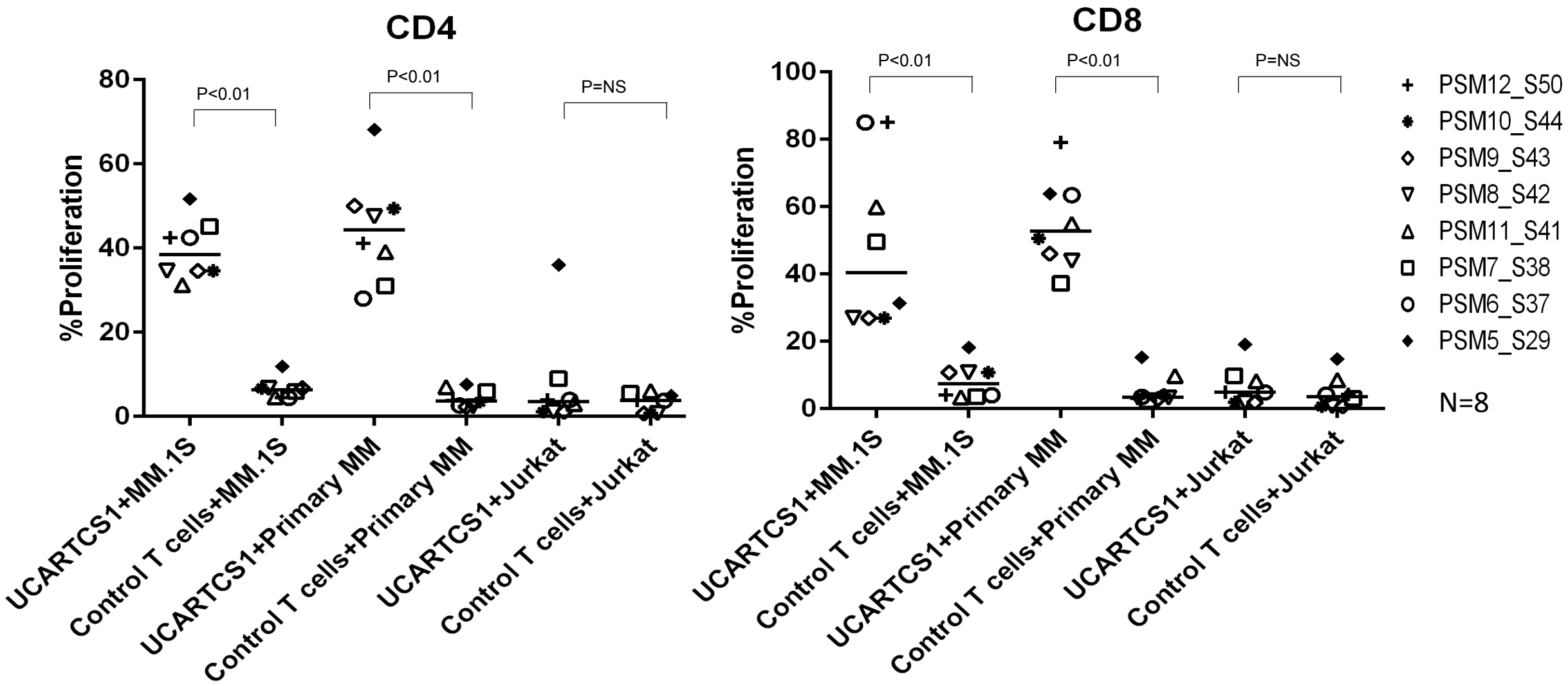
T cells used

- CAR-T cells against SLAMF7: UCARTCS1
- TCR and SLAMF7 double-knockout T cells: Control T-cells

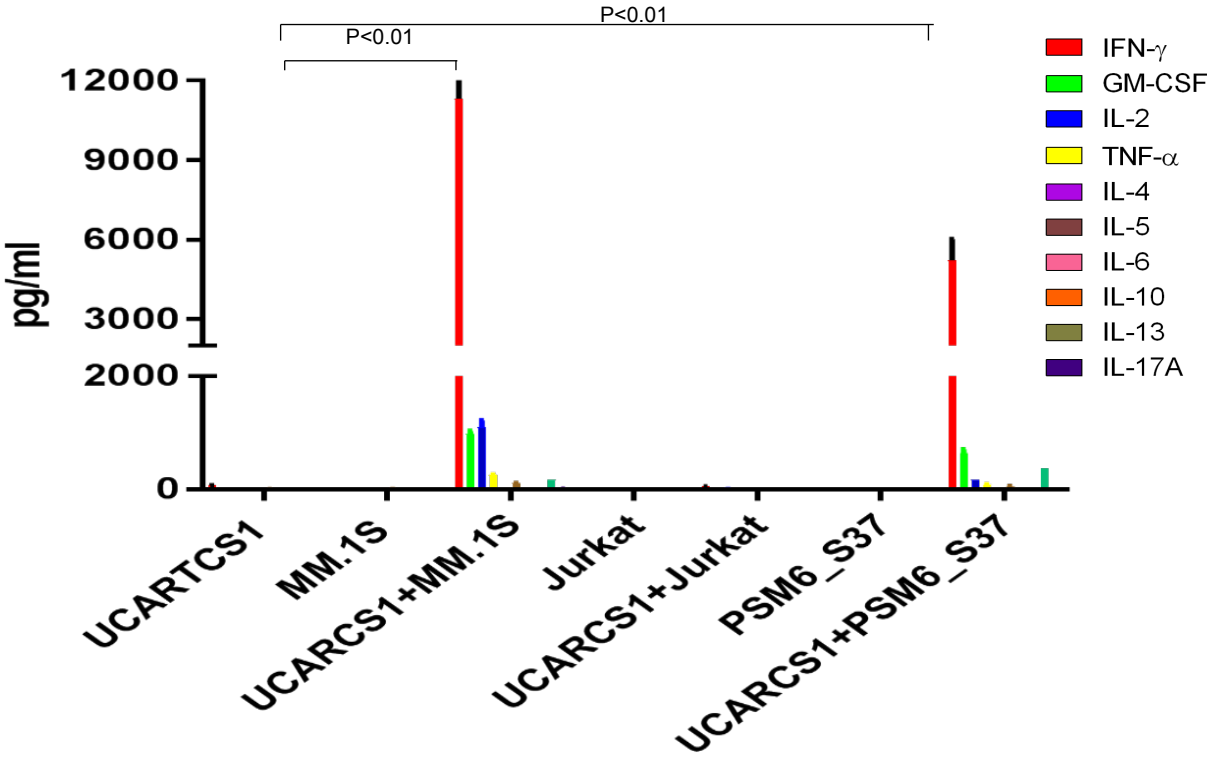
UCARTCS1 CD4+ and CD8+ T cells proliferate in response to myeloma tumor cells but not Jurkat cells

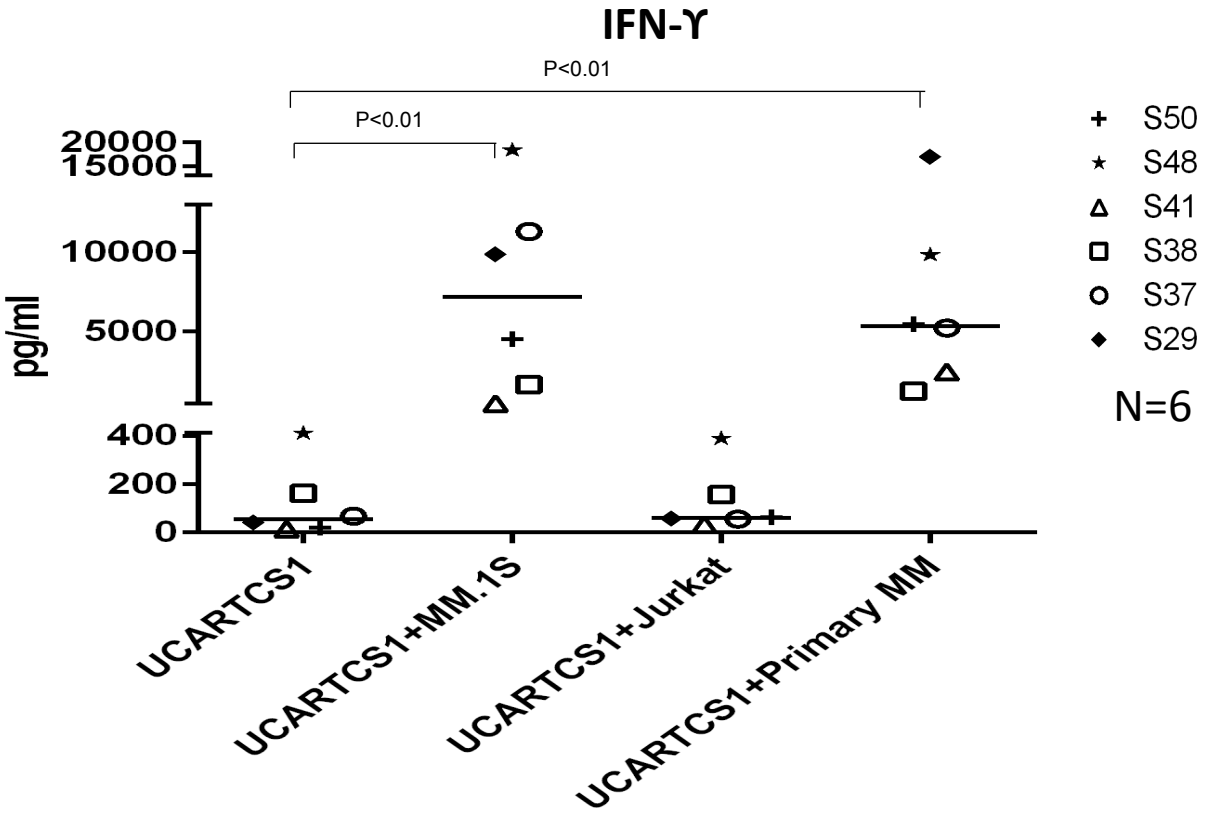


UCARTCS1 CD4+ and CD8+ T cells but not control T cells proliferate in response to primary myeloma tumor cells



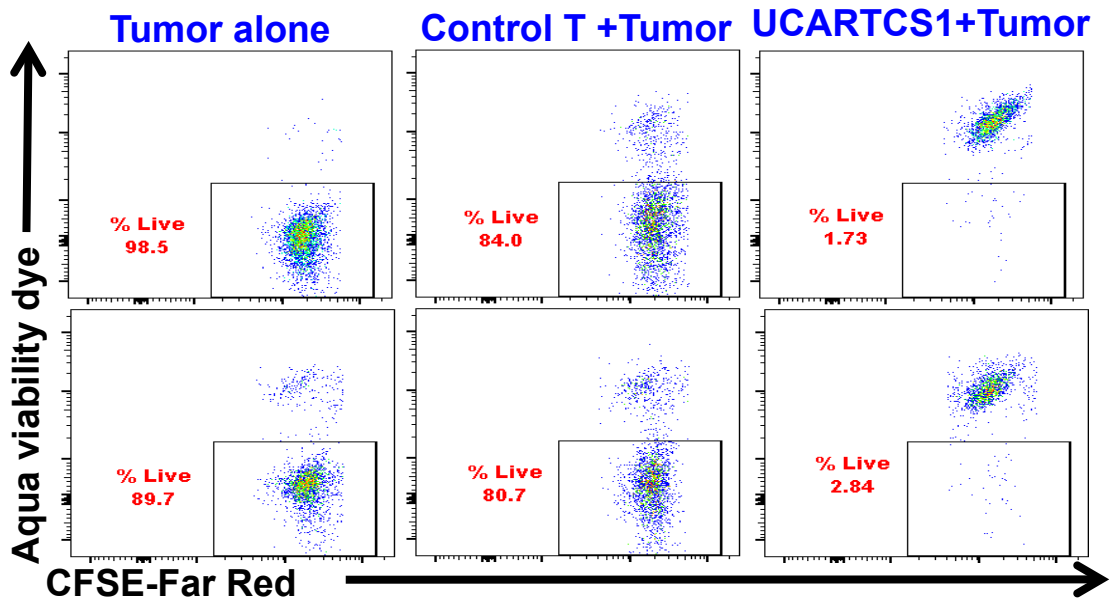
UCARTCS1 cells produce Th1 cytokines in response to MM





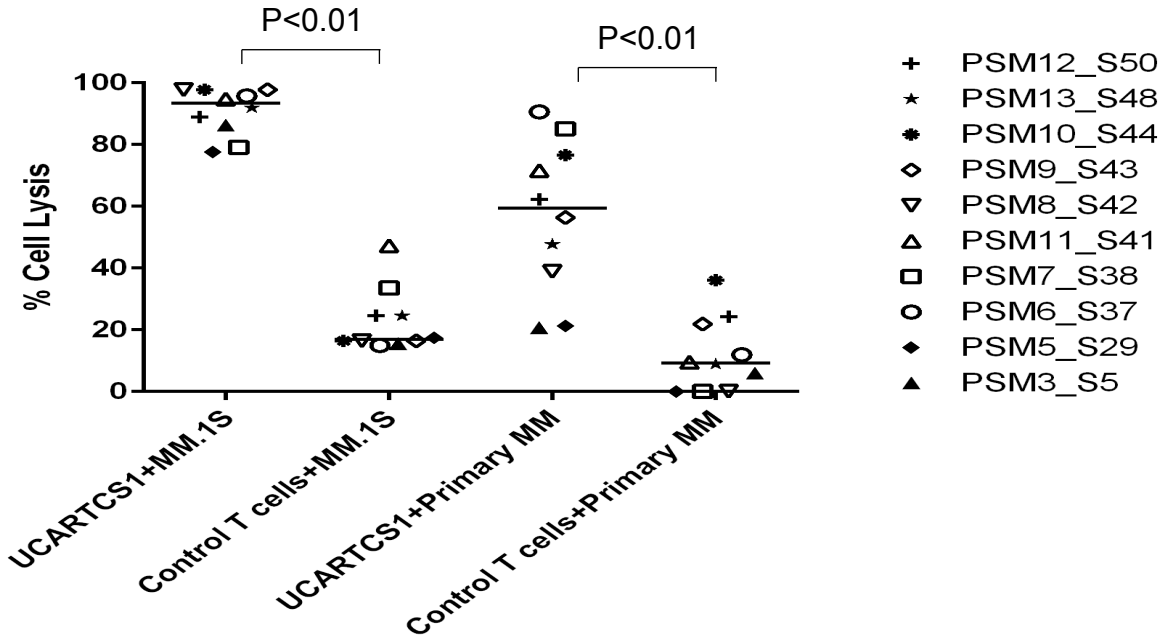
Specific Th1 cytokine response was observed with UCARTCS1 cells but not control T-cells (data not shown) in co-cultures with MM cell line or primary samples

UCARTCS1 cells lyse MM cell line and primary MM samples



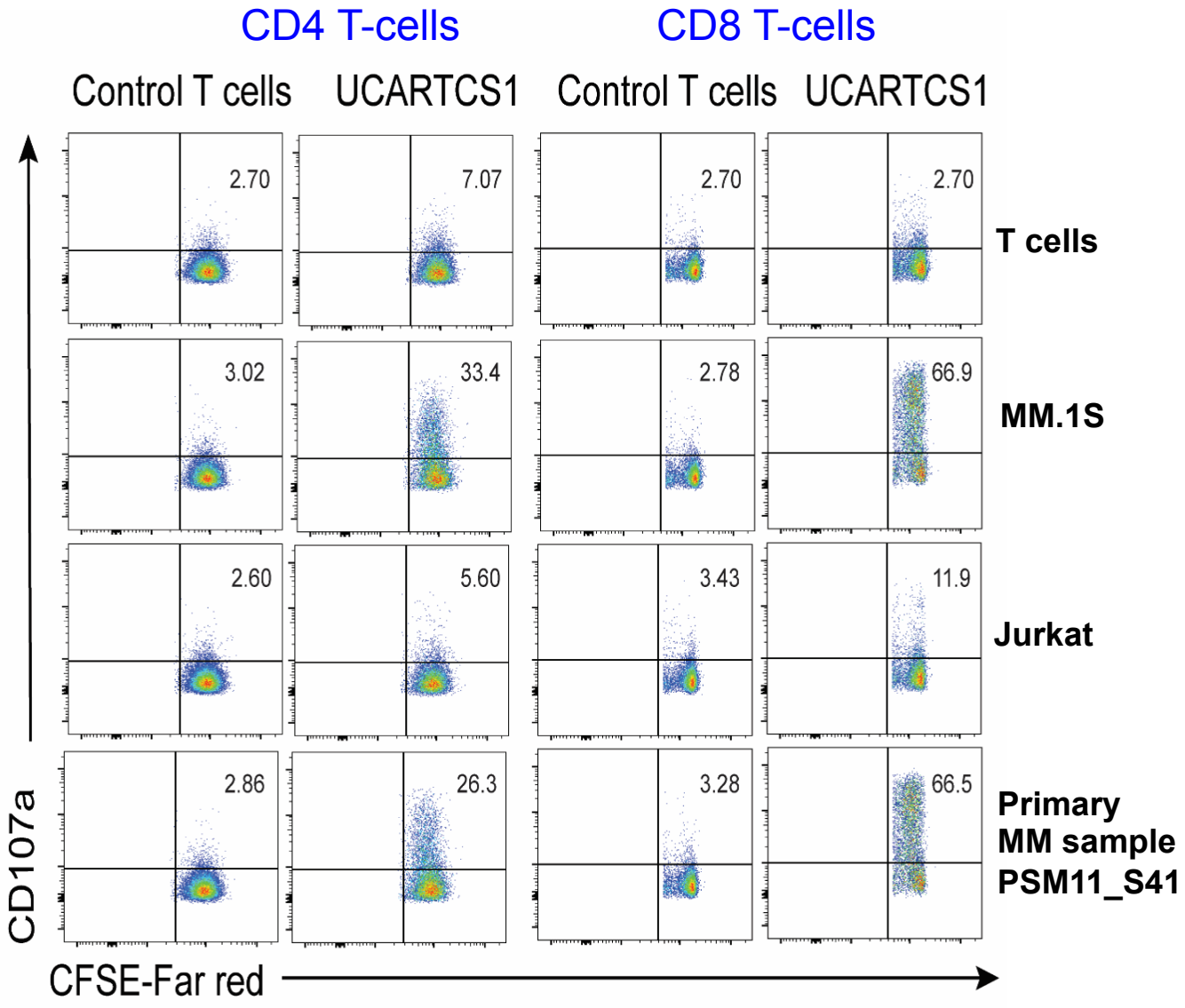
MM.1S cell line

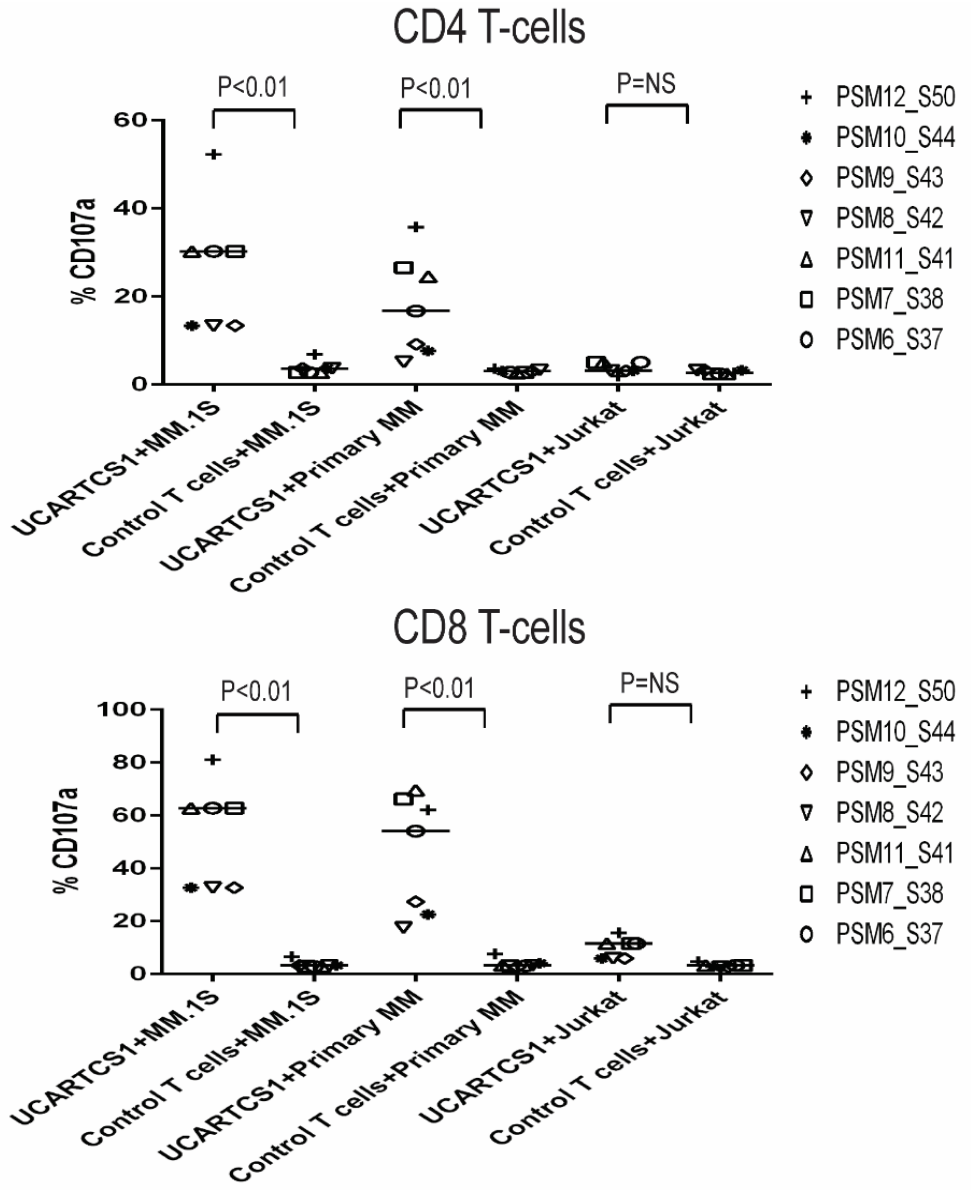
Primary MM sample PSM6_S37



N=10

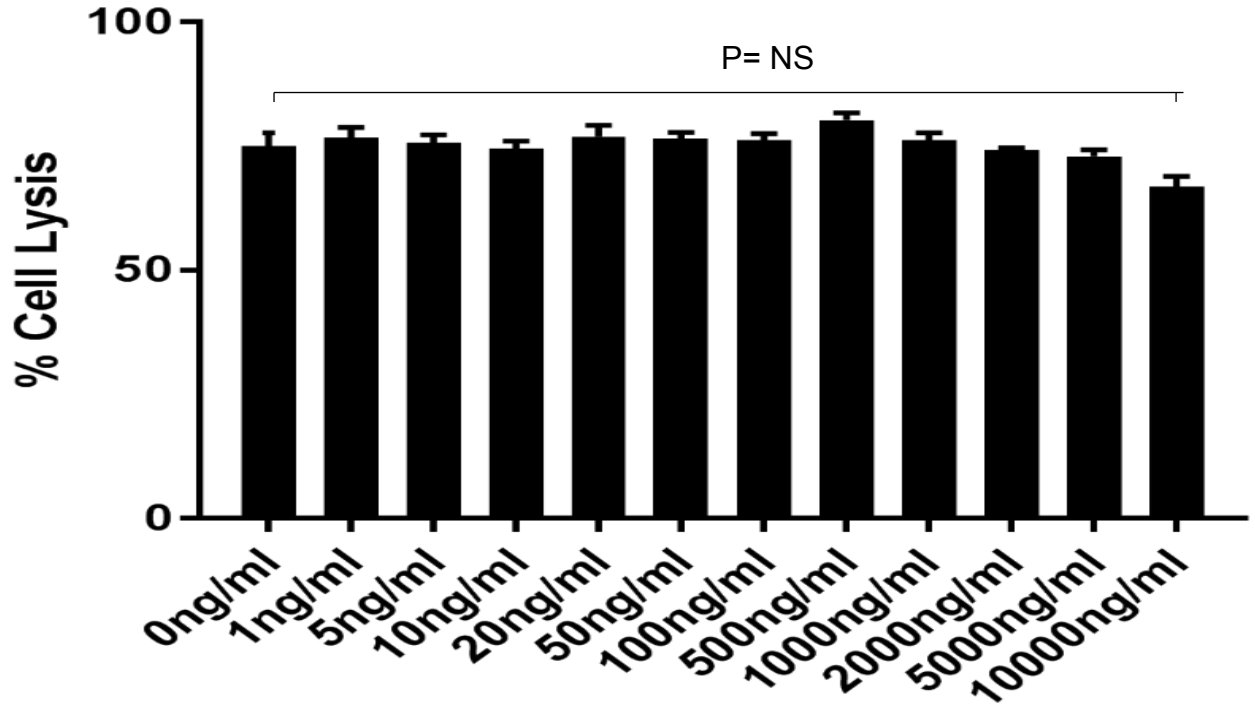
UCARTCS1 cells degranulate against MM cell line and primary MM samples





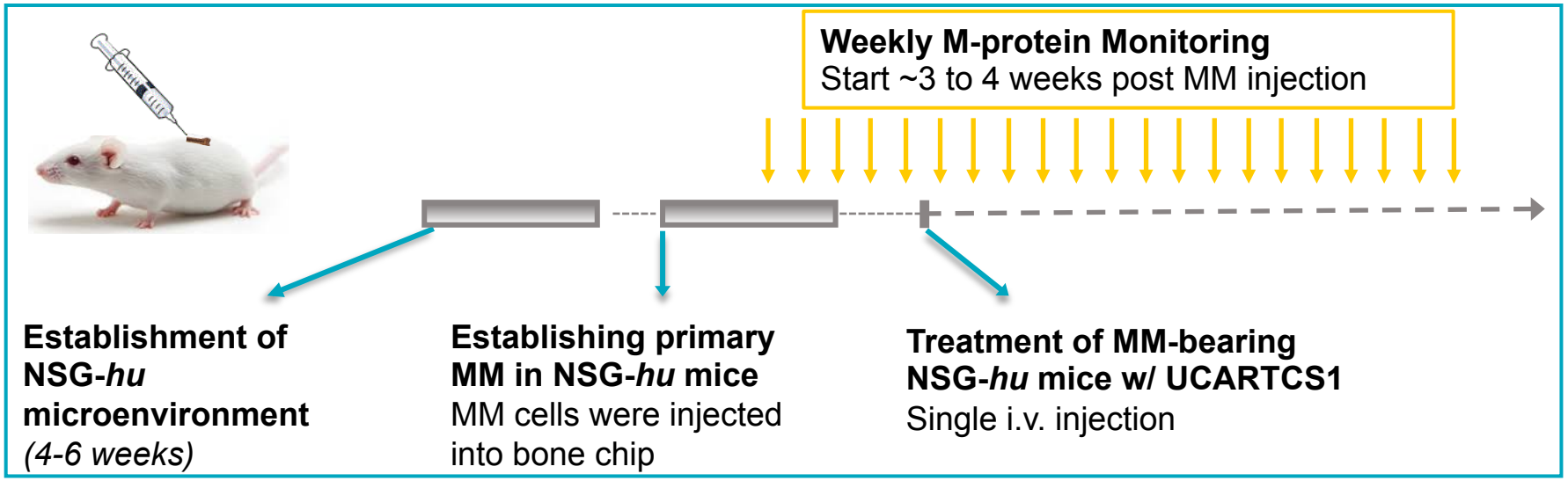
Soluble SLAMF7 did not affect cytotoxic activity of UCARTCS1

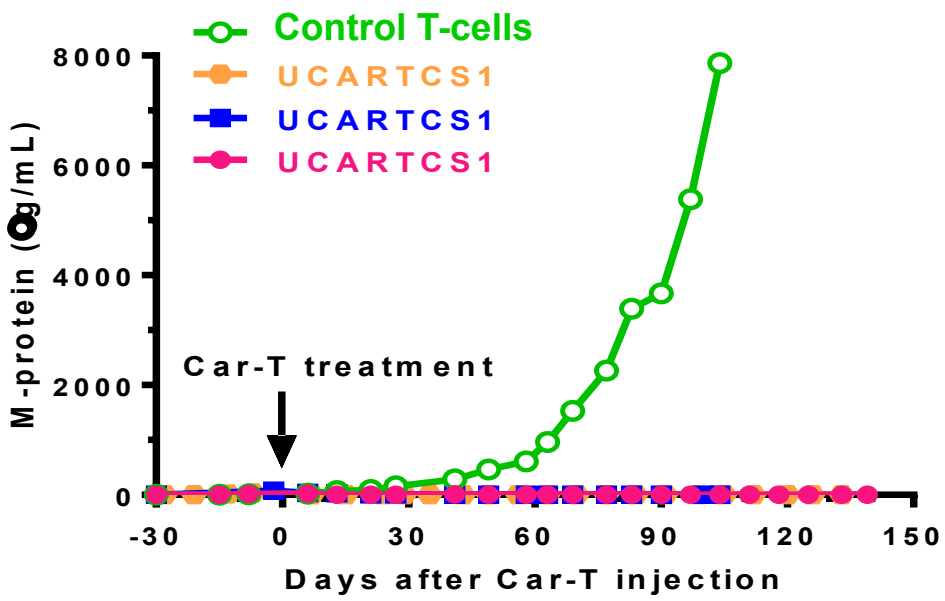
MM.1S cells were supplemented with recombinant SLAMF7 protein

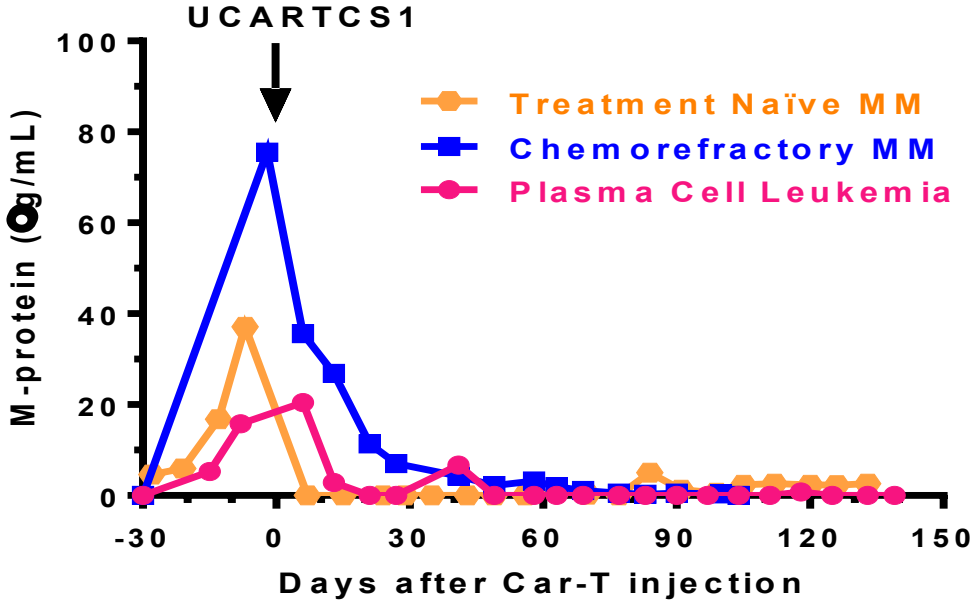


- Serum SLAMF7 levels in MM patients: Up to 20ng/ml
- Presence of soluble SLAMF7 even up to 500 fold higher than serum concentrations observed in MM patients did not affect the cytotoxic potential of UCARTCS1 cells

UCARTCS1 exhibit durable in vivo efficacy in high-risk MM







Summary

- UCARTCS1 is an off-the-shelf product with a novel design that lacks TCR and SLAMF7 (to reduce the risk of GvHD and prevent T cell fratricide).
- UCARTCS1 cells proliferate, produce IFN-ϒ, and exhibit marked cytotoxic activity against MM cell lines and primary MM tumor samples.
- More importantly, UCARTCS1 eradicated established MM and induced durable remission in an orthotopic mouse xenograft model.
- These results support further development and testing of this universal “off-the-shelf” allogeneic SLAMF7-specific CAR-T product in patients with MM