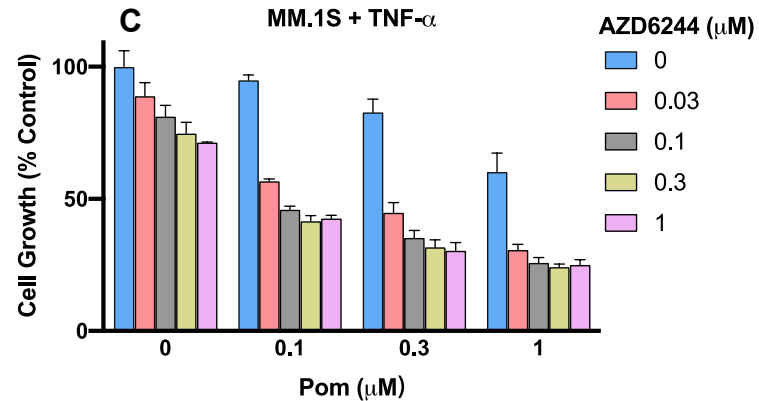
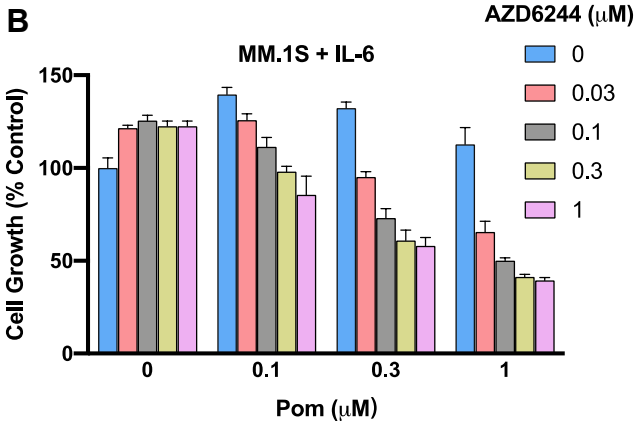
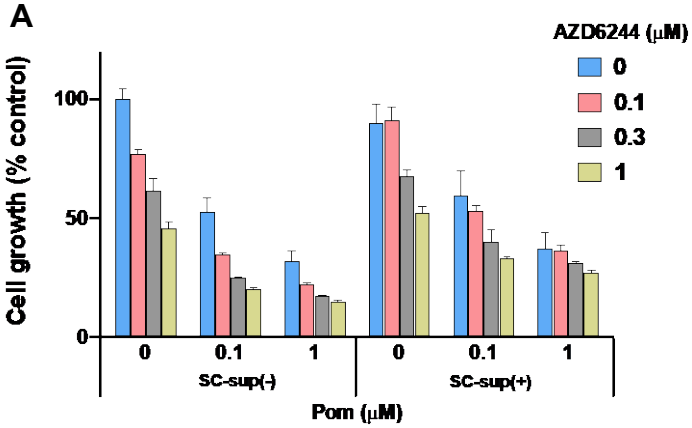


New Therapies for Myeloma

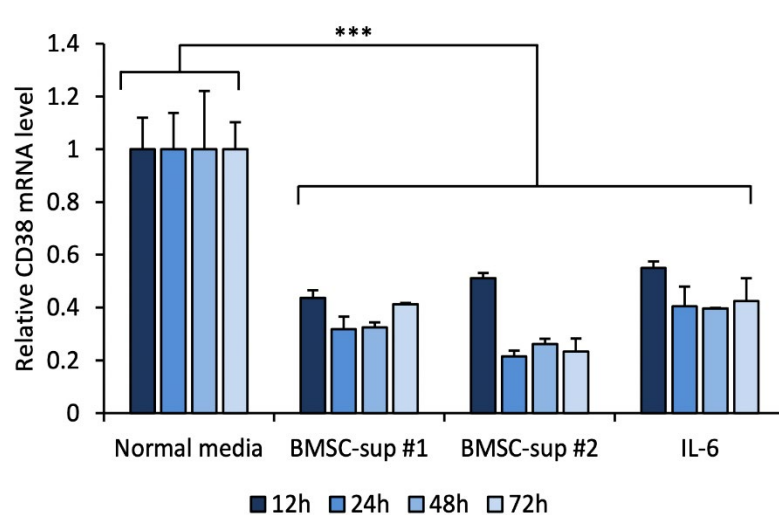
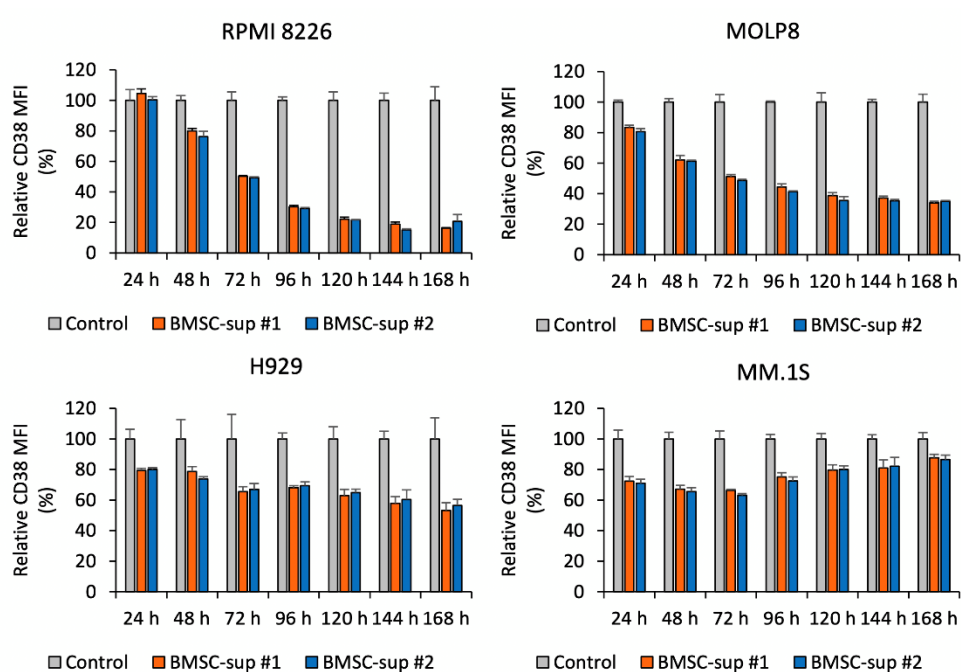
Kenneth Anderson, MD
Director, Jerome Lipper Multiple Myeloma Center
and LeBow Institute for Myeloma Therapeutics
Dana-Farber Cancer Institute
Kraft Family Professor of Medicine
Harvard Medical School

Inhibition of MEK Overcomes IMiDs Resistance Induced by BM Microenvironment



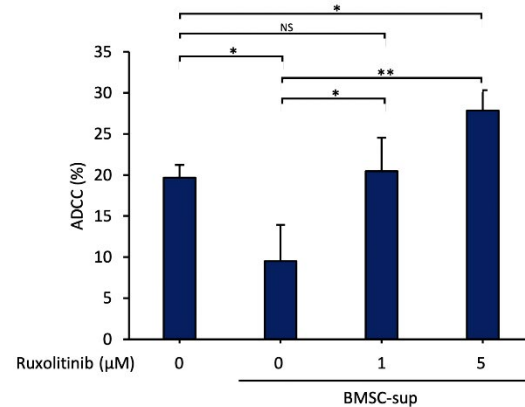
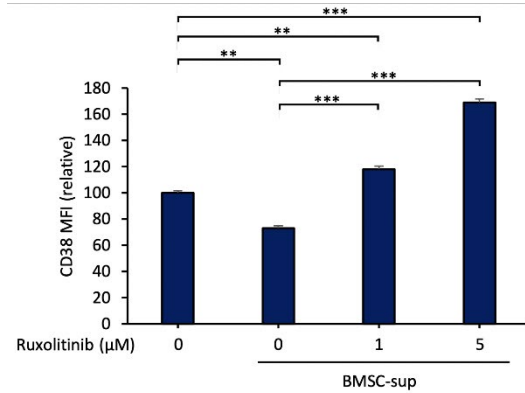
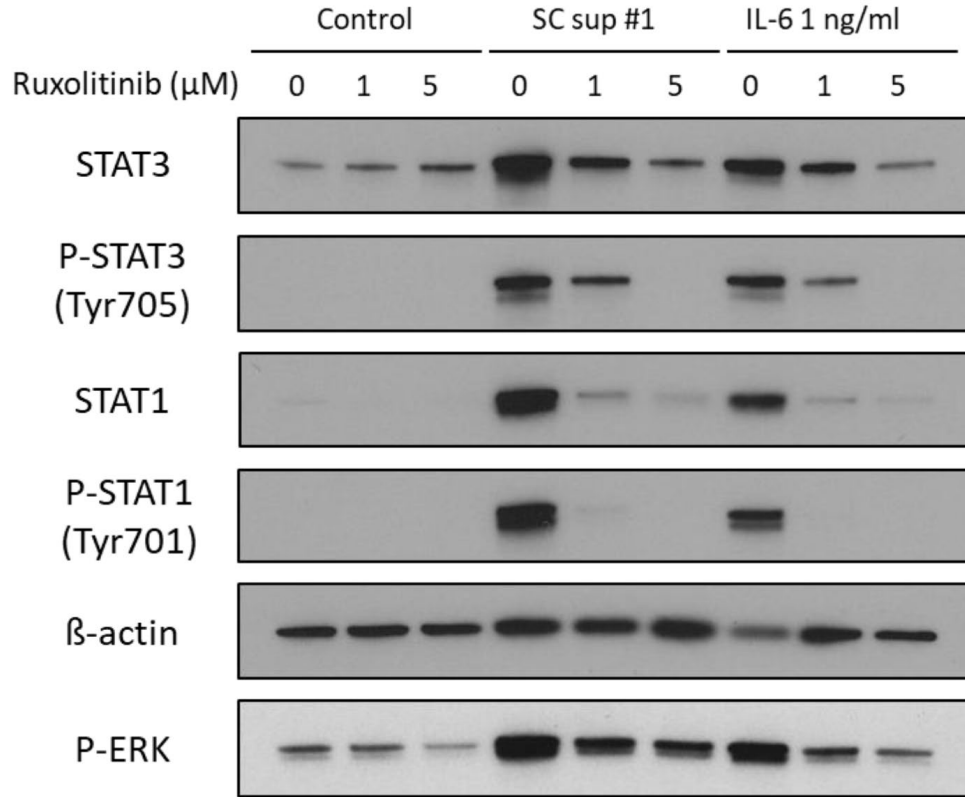
Targeting MEK/ERK can overcome IMiDs resistance due to TRAF2 downregulation intrinsic to MM cells, as well as resistance induced by BM milieu

Bone Marrow Stromal Cell Supernatants (BMSC sup) or IL-6 Decrease CD38 on MM Cells and Confer Resistance to CD38 MAb Therapy



Ogiya et al, Blood 2020; 136: 2334-45

BMSC-sup or IL-6 Trigger p-STAT3 and CD38 Downregulation; Ruxolitinib Restores CD38 Expression and ADCC in the BM Milieu

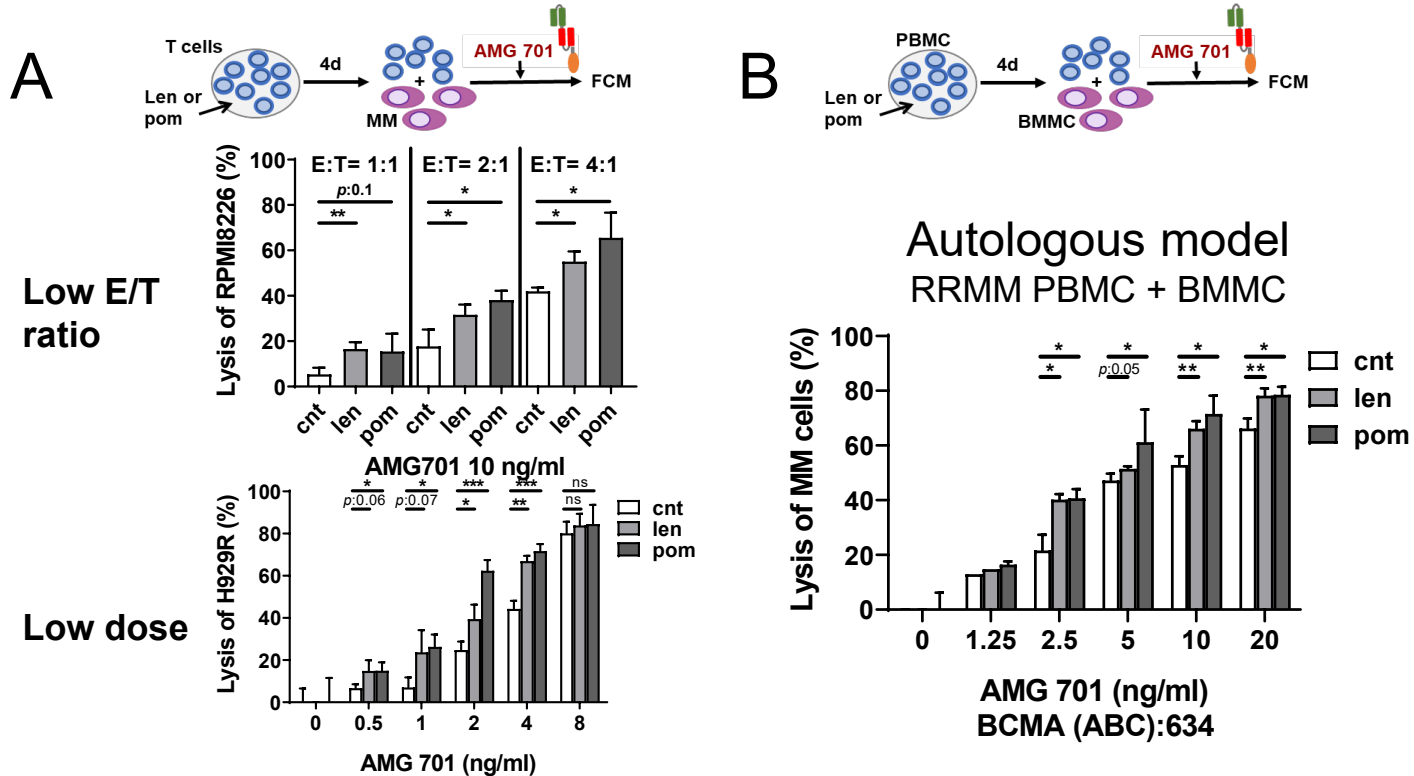


Bispecific T Cell Engagers (Bites) in Multiple Myeloma

	Tesclistamab Ph1 N=149	AMG-701 Ph1 N=85	REGN5458 Ph1 N=49	PF-3135 Ph1 N=30	Talquetamab Ph1 N=157	Cevostamab Ph1 N=53
Target	BCMA-CD3	BCMA-CD3	BCMA-CD3	BCMA-CD3	GPRC5D-CD3	FcRH5-CD3
Dosing Schedule	Q2W→QW IV or SC IV: 0.3-19.2 µg/kg SC: 80-3000 µg/kg	QW IV (0.005-18 mg)	QW→Q2W IV (3-96mg)	QW SC (80-1000µg/kg)	QW or Q2W IV: 0.5-180 µg/kg SC: 5-800 µg/kg	Q3W IV (0.05-160mg)
CRS, % Any grade Grade ≥3	55% 0	65% 9%	39% 0	73% 0%	54% 3%	76% 2%
NT, % Any grade Grade ≥3	5% 1%	Not reported	12% 0	Not reported	6% 2%	Not reported
ORR	At RP2D (1500 µg/kg SC): 73% (≥CR, 23%)	26% (≥CR, 10%)	39% (≥CR, 16%)	80%	At RP2D (405 µg/kg SC): 69% (≥CR, 15%)	In ≥20 mg cohorts: 53% (≥CR, 18%)
Median follow-up	At RP2D: 3.9 mo	6.5 mo	2.6 mo	Not reported	≥60 µg/kg: 7.4 mo ≥405 µg/kg: 3.7 mo	8.1 mo
Median DOR	Not reached	Not reached	6.0 mo	Not reported	Not reached	8 patients ≥6 mo
Median OS	Not reached	Not reported	Not reported	Not reported	Non reported	Not reported

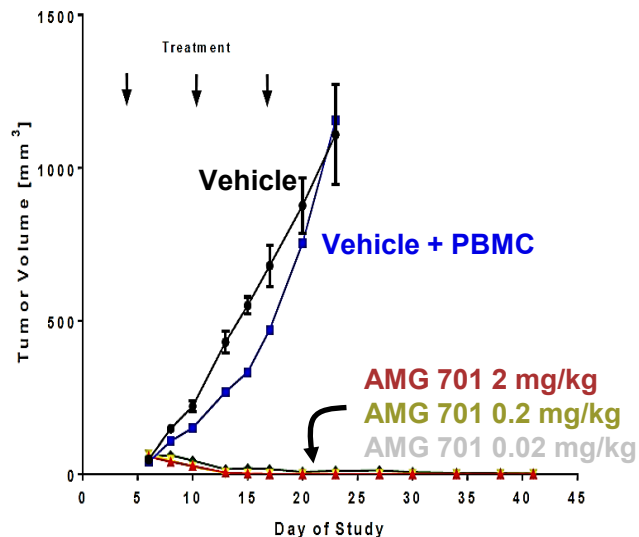
Garfall et al; Harrison et al; Madduri et al Chari et al; Cohen et al ASH, ASCO 2020

Combination Immunotherapy: IMiDs Enhance AMG 701 BiTE-Mediated MM Cytotoxicity



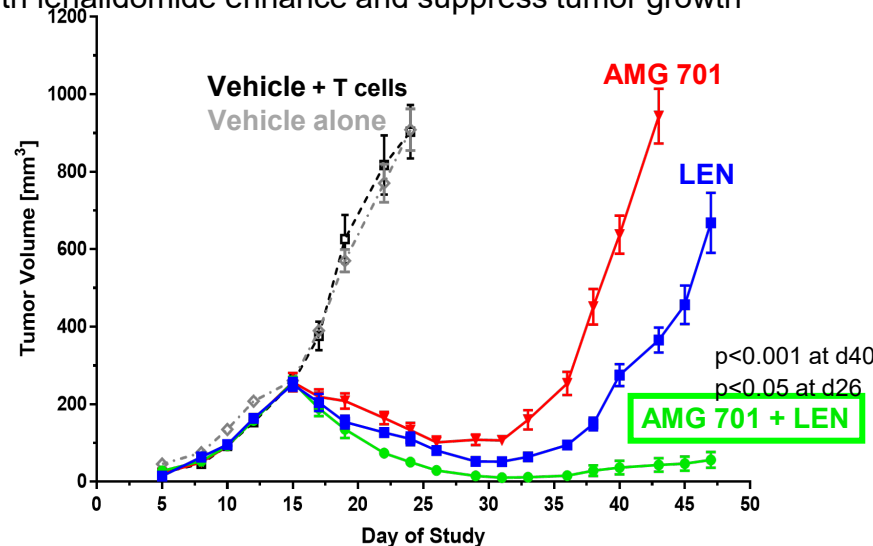
Combination AMG 701 and Lenalidomide Enhanced Anti-tumor Activity in a Mouse Model of Established MM (Clinical Trial Ongoing)

AMG 701 prevents tumor growth in a xenograft model at all doses tested



Monotherapy: 3 separate dosing

Combination of minimally effective doses of AMG 701 with lenalidomide enhance and suppress tumor growth

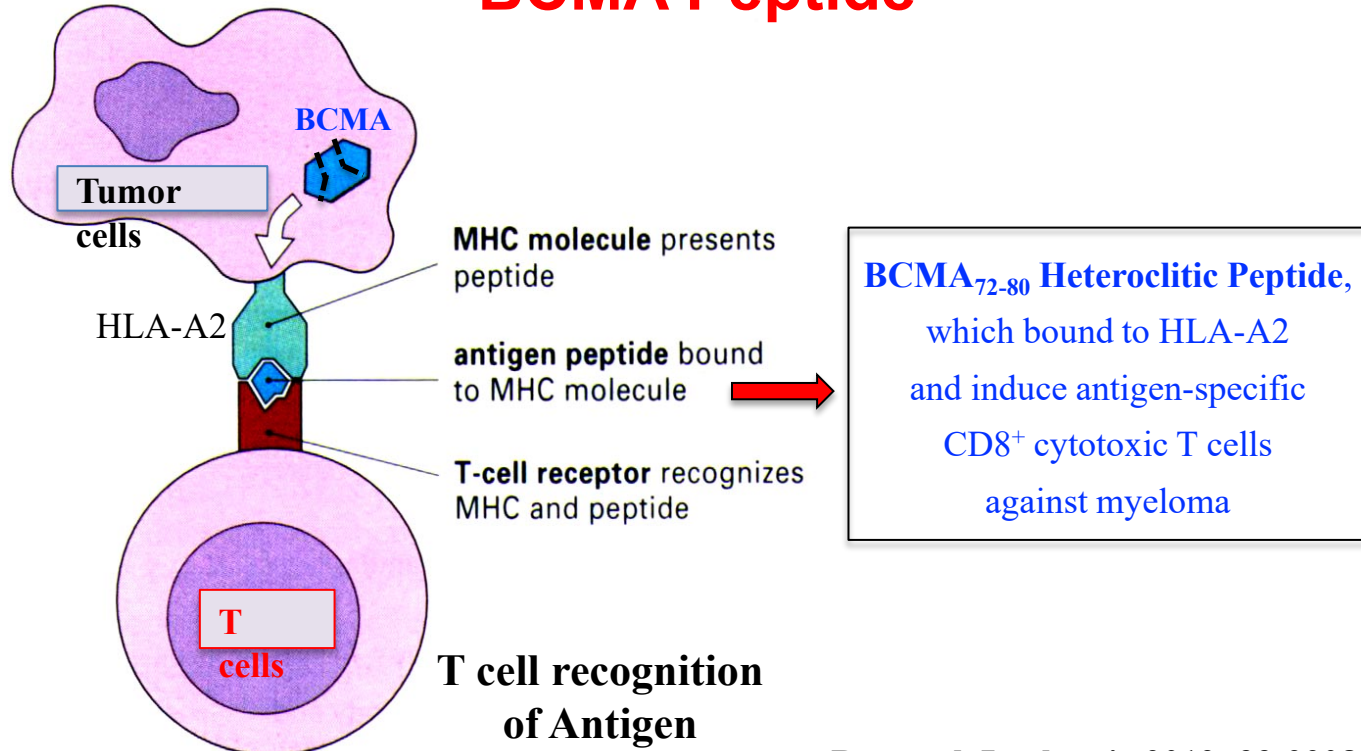


Vehicle (+DMSO); IP

AMG 701 (0.25 mg/kg); IV

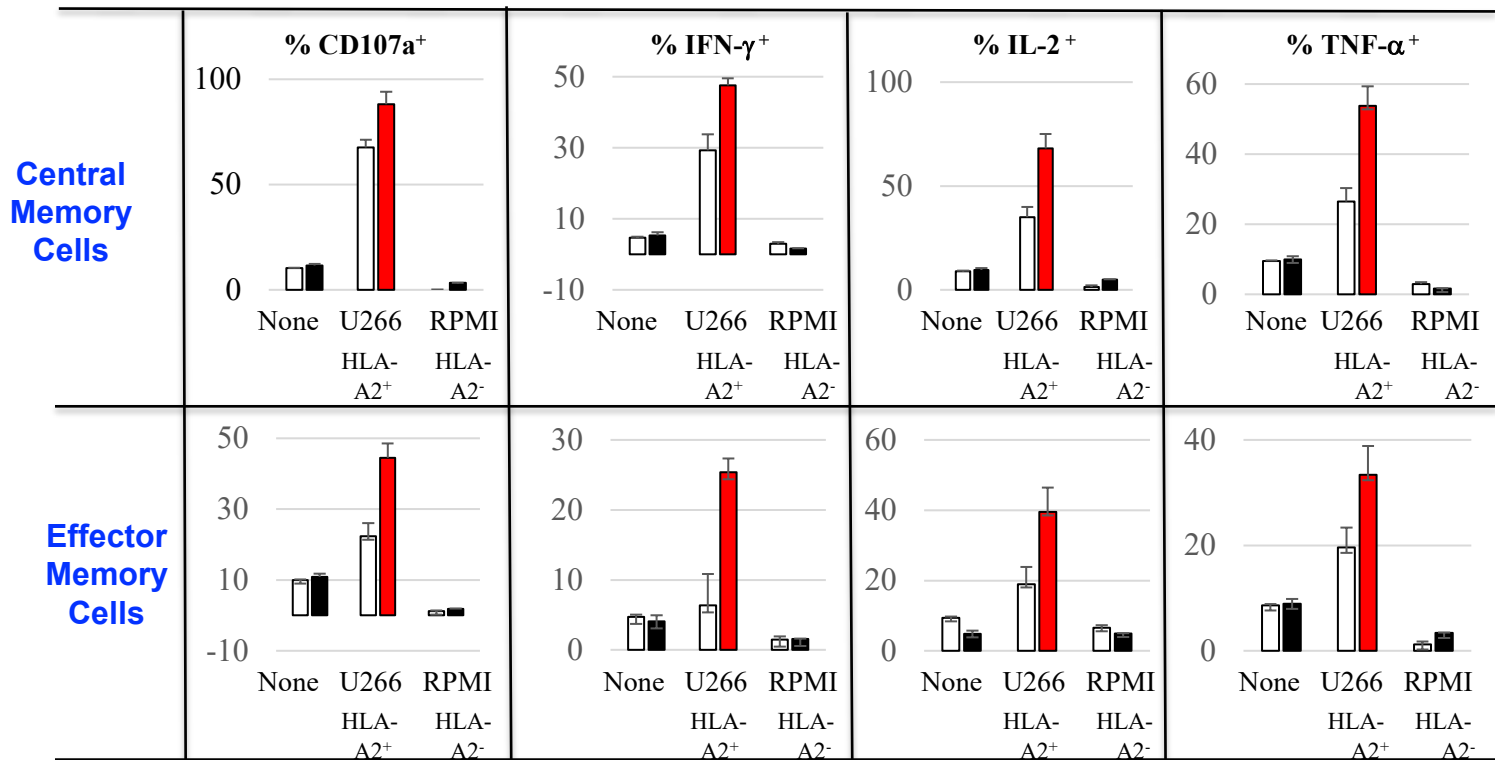
Lena (0.2 mg/kg); IP

Incorporating Vaccination into BiTE Treatment Paradigm: HLA-A2-Specific BCMA Peptide



PLGA/ Heteroclitic BCMA₇₂₋₈₀ Peptide Induces HLA-A2 Restricted Central and Effector Memory CTLs

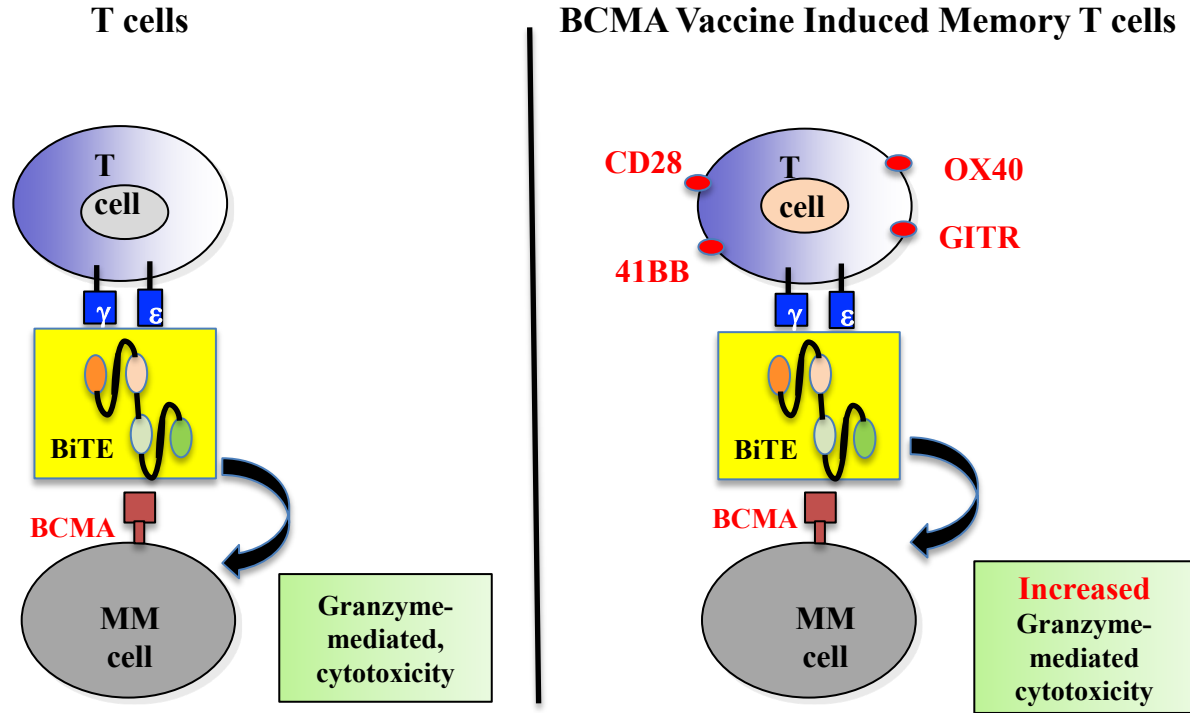
BCMA-specific CTL generated with:
 Free BCMA peptide PLGA /BCMA peptide



Target Cells

Bae et al Leukemia 2020: 34: 210-23.

Combination BCMA Peptide Nanoparticle Vaccine and BCMA BiTE to Enhance Engagement and Anti-Myeloma Activity of Memory CTL



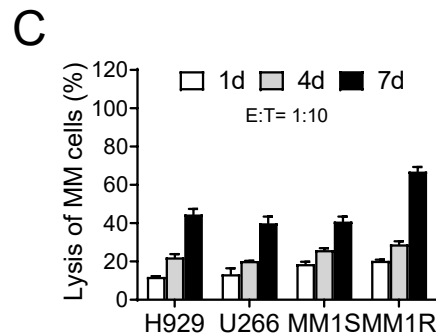
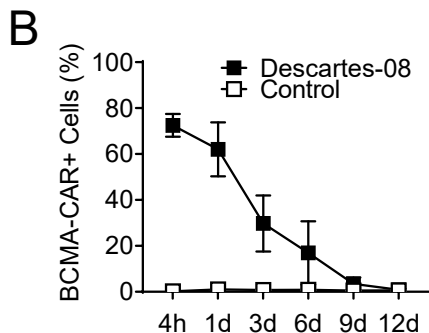
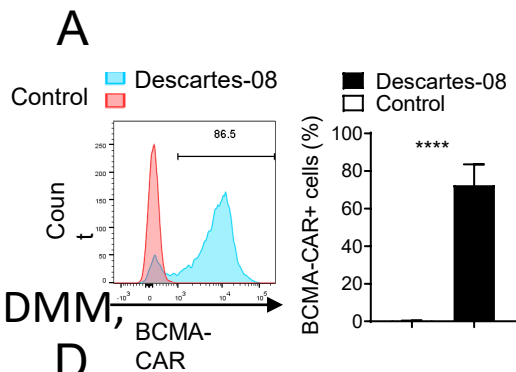
CAR T-Cell Therapy in Multiple Myeloma

FDA
Approved

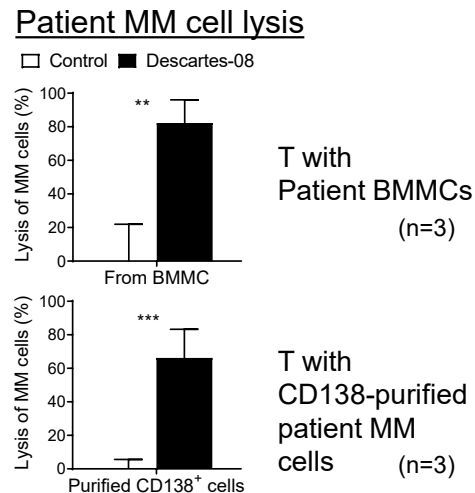
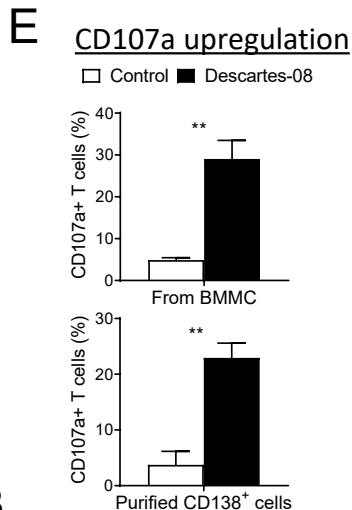
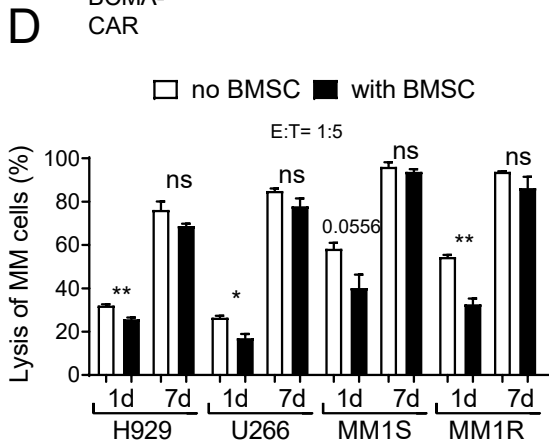
	Ide-cel Ph1 N=128	Cilta-cel Ph1b/2 N=97	Orva-cel Ph1b/2 N=62	bb21217 Ph1 N=69	CT053 Ph1b/2 N=20	P-BCMA-101 Ph1/2 N=55	GC012F Ph1 N=16	ALLO-715 Ph1 N=31
CRS, % All grades Grade ≥3	84% 5%	9% 4%	89% 3%	70% 4%	77% / 83% ^a 0% / 0%	17% 0%	100% 13%	45% 0%
NT, % All grade Grade ≥3	18% 3%	21% 10%	13% 3%	16% 4%	15% / 17% ^a 8% / 0%	4% 4%	0% 0%	0% 0%
ORR CR	73% ≥CR 33% (450: OR 81%, CR 39%)	97% ≥CR 67%	92% CR 36%)	68% (≥CR 29%)	94% (≥CR 28%)	44% - 75% ^b	94% (≥CR 56%)	60% in DL3 (n=10)
Median follow-up	13.3 mo	12.4 mo		5.8 mo	6 mo	120-508 days ^b	7.3 mo	3.2 mo
Median DOR	10.7 mo (450: 11.3 mo)	21.8 mo	Not reported	17.0 mo	Not reported	Not reported	Not reached	Not reported
Median PFS	8.6 mo 12.2 mo 20.2 CR/sCR	22.8 mo sCR: NR	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Median OS	24.8 mo	18 mo OS: 80.9%	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported

Munshi et al NEJM 2021; 384: 705-16; Berjeda et al Lancet 2021; 398:314-24.; Lin et al; Alsina et al; Kumar et al; Costello et al; Jiang et al; Mailankody et al; Anderson et al ASH/ASCO 2020,2021; Usmani et al ASCO 2021

Transiently Active Anti-BCMA mRNA-Electroporated CD8+ CAR T-Cells (Descartes-08) for MM



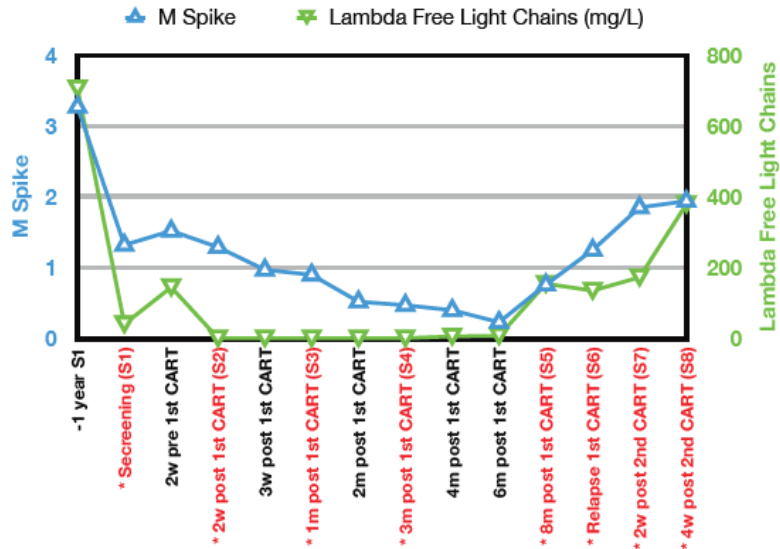
Trial in NDMM,
No CRS,
Repeated
Doses



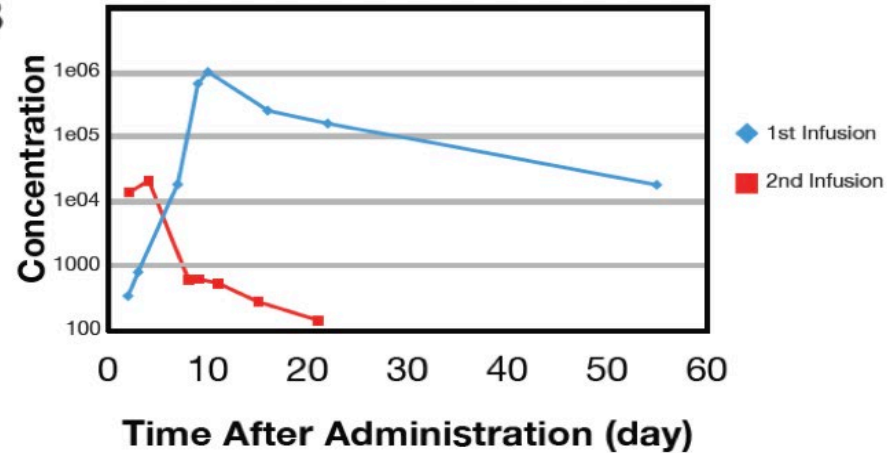
Biallelic BCMA Loss Confers Resistance to BCMA CAR T Cells

BCMA on 16p: should we be screening patients before BCMA therapy?

A

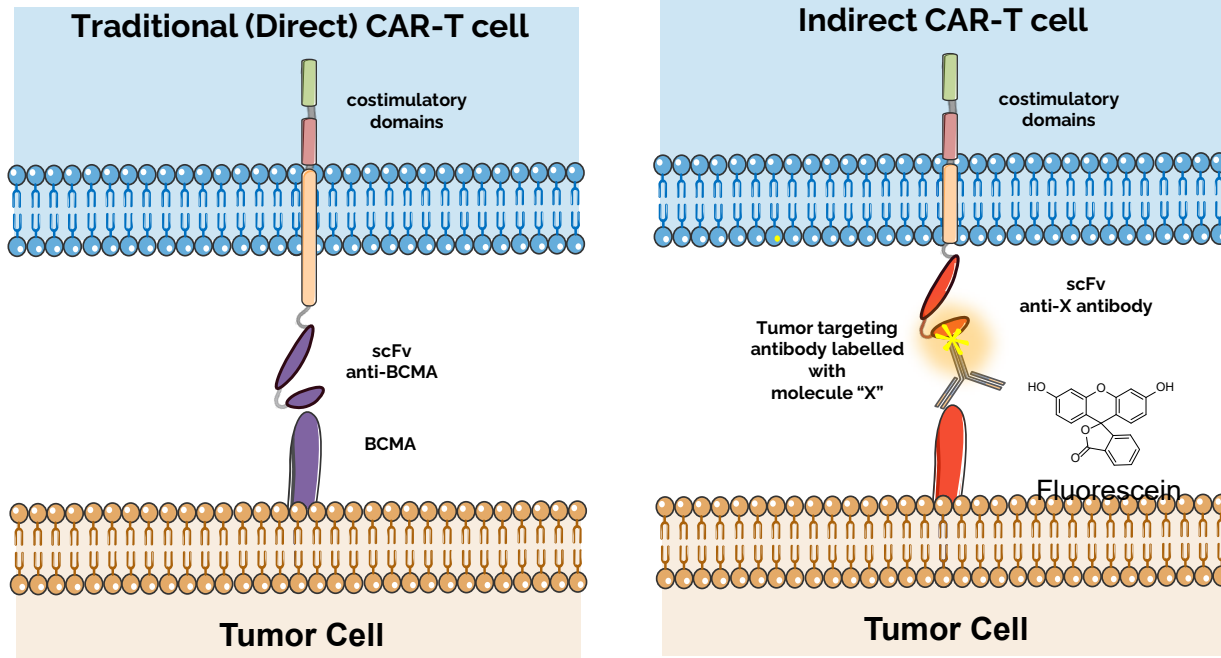


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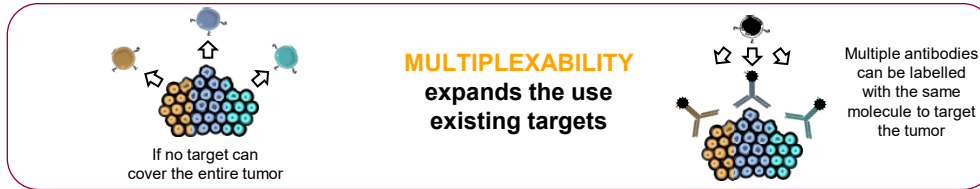
Dual targeting to avoid resistance: GPRC5D, CD19, FcHR5, CD38, CD138, SLAMF-7

BAT-CAR: Binary Activated T Cell with Chimeric Antigen Receptor



Alberto Nobili, PhD and Carl Novina, MD PhD

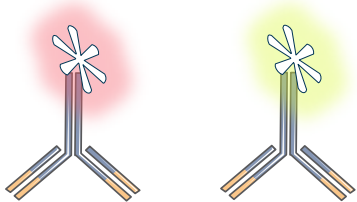
BAT CARs Target Limitations of CAR T Cells



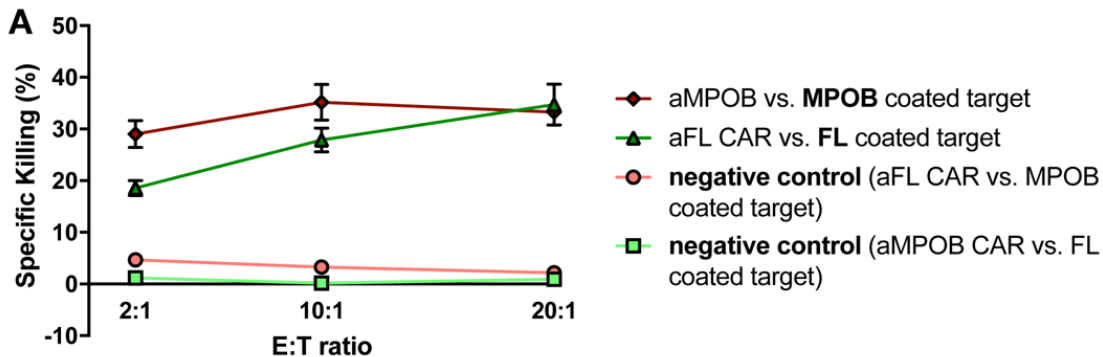
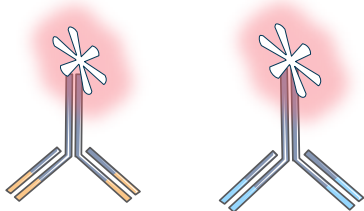
Alberto Nobili, PhD and Carl Novina, MD PhD

Modular Killing of Multiple Myeloma Cells

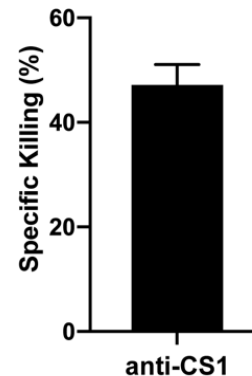
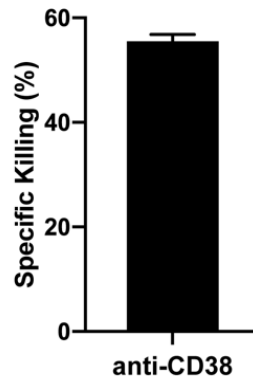
Same target,
different small molecule



Same small molecule,
different target

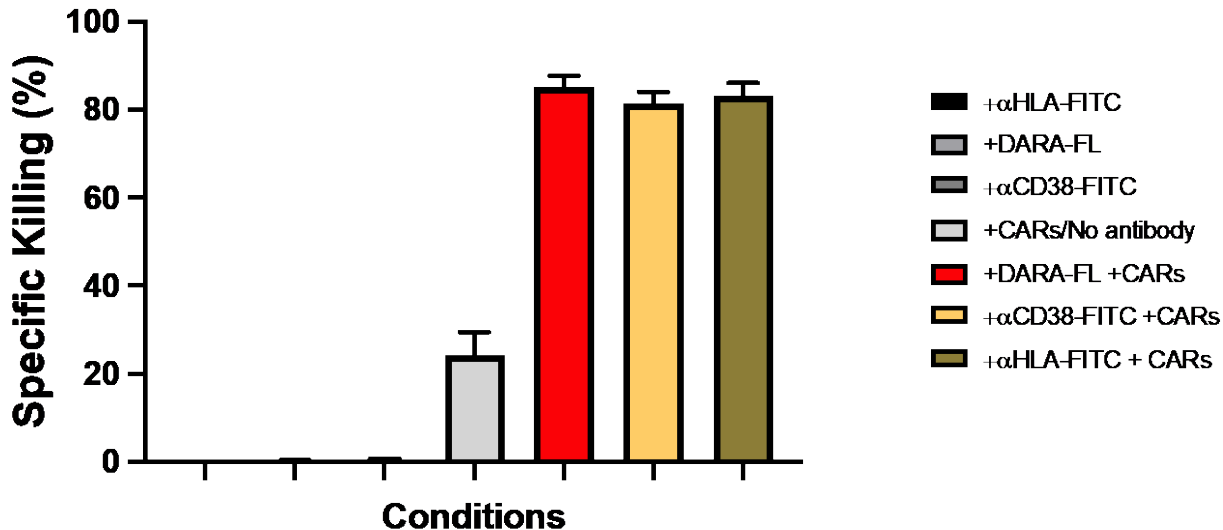


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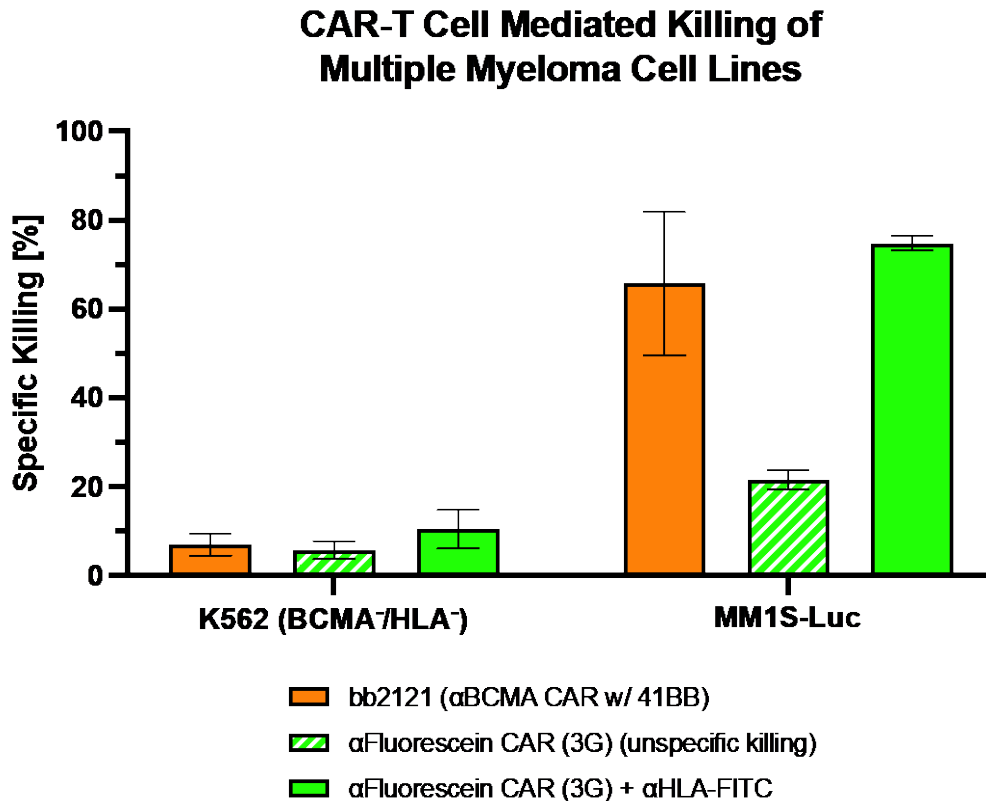


DARA-FL Efficiently Triggers BAT-CAR Killing of H929 cells

**Killing of H929 with α Fluorescein CARs
(E:T = 20:1, 4hrs, 50nM antibodies)**



BAT-CAR Killing Activity of MM Cells Is Comparable to bb2121



Biologically-Based Novel Therapies

Targeting ubiquitin proteasome cascade (PIs, UbRs) for direct toxicity and to trigger immune responses

Novel Targets: STING, GABARAP

Targeting accessory cells (pDCs) and microenvironment to trigger immune responses

Novel Targets: CD73, EPRS

Triggering protein degradation

CELMoDs, degronimids

Novel Targets: IKZF1/3, RAF/MEK/ERK

Combination immunotherapies to overcome resistance

MEK inhibitors to overcome IMiDs resistance

JAK2 inhibitors to overcome CD38MAb resistance

Combination/novel immunotherapies to enhance immune response and improve therapeutic index.

BiTEs with IMiDs, vaccines; mRNA CAR Ts, BAT-CARs

Future Directions

Combination PI, IMiD, Dex, CD38MoAb will achieve high rates MRD negativity in NDMM, including high risk MM

BCMA targeted CAR T cells, BiTEs will then be compared with ASCT to induce long term MRD-with memory anti-MM immune response

Novel uses and next generation of known classes of active agents: inhibiting ubiquitin proteasome cascade/triggering protein degradation to induce anti-MM immunity

Novel targets in the tumor cell (EPRS) and the BM microenvironment (CD73)

Combination novel immunotherapies to enhance response, overcome resistance mechanisms, and improve therapeutic index: JAK2 inhibitors with CD38 MAb; ERK/MEK inhibitors with IMiDs; IMiDs or vaccination with BiTEs, mRNACARs and BAT CARs

Long term disease-free survival and potential cure of MM will be achieved with combination targeted and immune therapies to both achieve MRD negativity and restore host memory anti-MM immunity. These patients will then be free of disease and off all therapy..

Paula and Rodger Riney



Our heroes and inspiration: Giving the gift of hope and of life to myeloma patients and their families around the world