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

Disclosures

Consultant: Pfizer, Amgen, Astrazeneca, Janssen, Precision Biosciences, Mana, Window

Speaker’s Bureau: none

Grant/Research Support: none

Stock Shareholder: C4 Therapeutics, Oncopep, Raqia, NextRNA

Honoraria: As per consultants above

Full-time/Part-Time Employee: none

Other: none

Therapeutic Advances in Multiple Myeloma

Proteasome inhibitors: bortezomib, carfilzomib, ixazomib; immunomodulatory drugs: thalidomide, lenalidomide, pomalidomide; HDAC inhibitor: panobinostat; monoclonal antibodies: elotuzumab daratumumab, and isatuximab; nuclear transport inhibitor: Selinexor; Immunotoxin: belantomab mafodotin; peptide drug conjugate: melflufen; CAR T cell: Idecel

Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

Effective in relapsed/refractory, relapsed, induction, consolidation, and maintenance therapy

30 FDA approvals (14 agents) and median patient survival prolonged 3-4 fold, from 3 to at least 8-10 years, and MM is a chronic illness in many patients.

Future: 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.

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, CFT7455, degronimids

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

Combination immunotherapies to overcome resistance

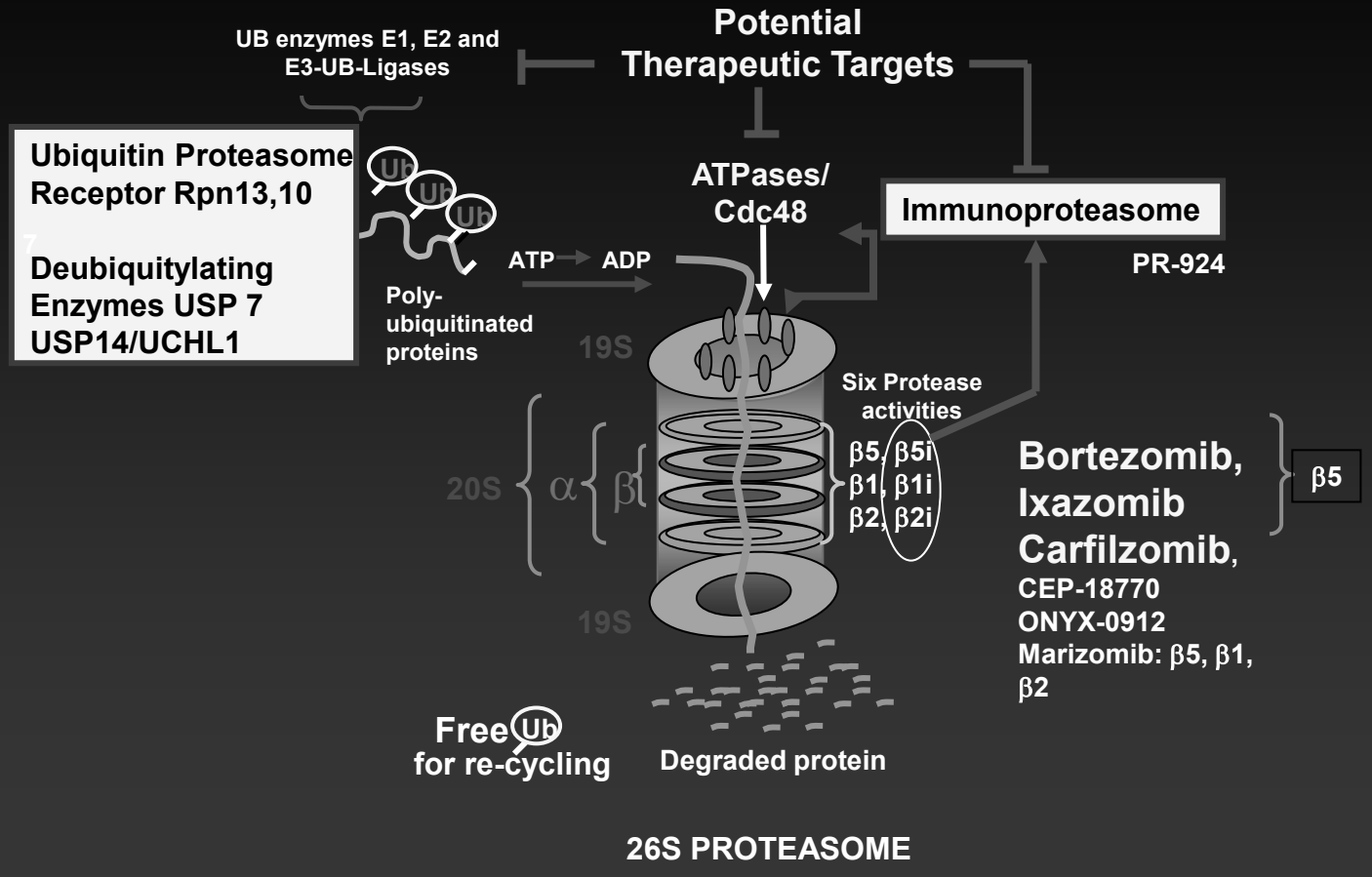
MEK inhibitors to overcome IMiDs resistance

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

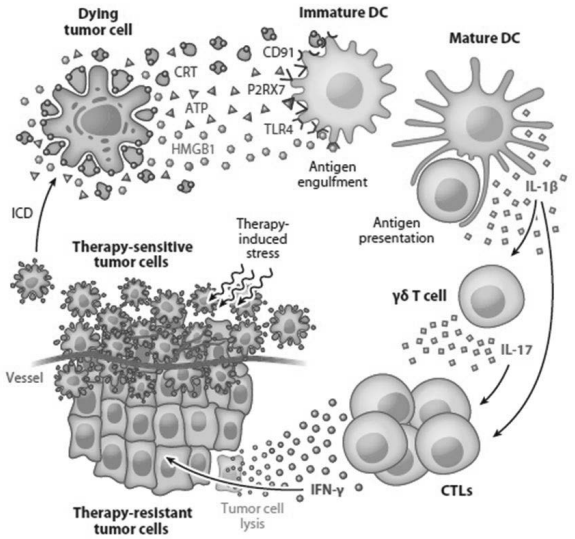
Targeting Vulnerabilities: The Ubiquitin Proteasome System in MM



Blocking Ubiquitin/Proteasome Cascade (Proteasome, Ubiquitin Receptor) Induces Immunogenic Cell Death (ICD) in Myeloma

Damage-associated molecular patterns (DAMPs)

- **CALRETICULIN: “eat-me signal”**
- **ATP: “find-me signal”**
- **HMGB1: tumor antigen processing**

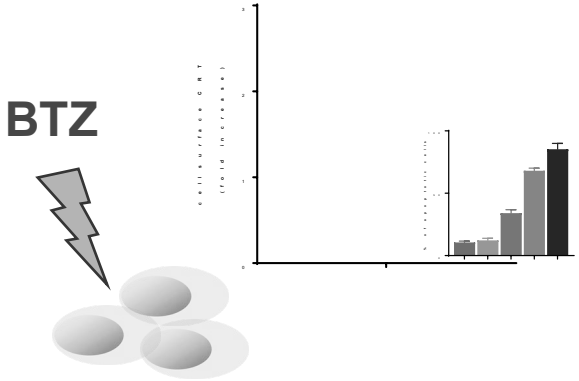


Galluzzi L. et al. (2016) Nat. Rev. Immunology

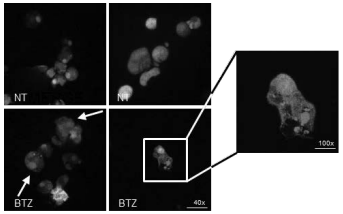
Bortezomib (BTZ) Triggers ICD and Induces Anti-MM Immune Response

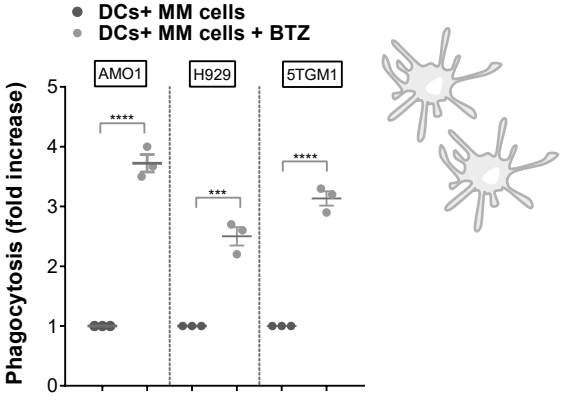
1. MM cells expose CALR on cell surface

BTZ

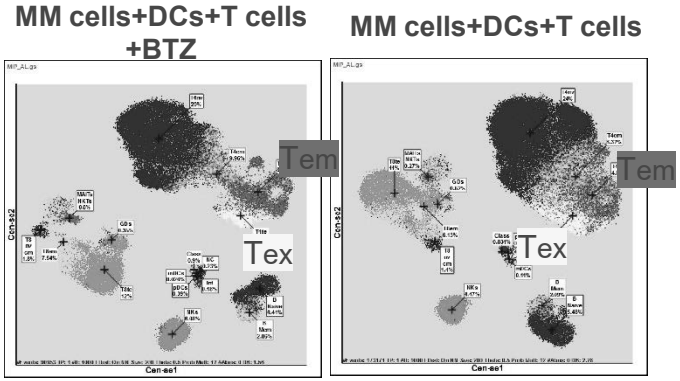


2. Dendritic cells become functionally mature

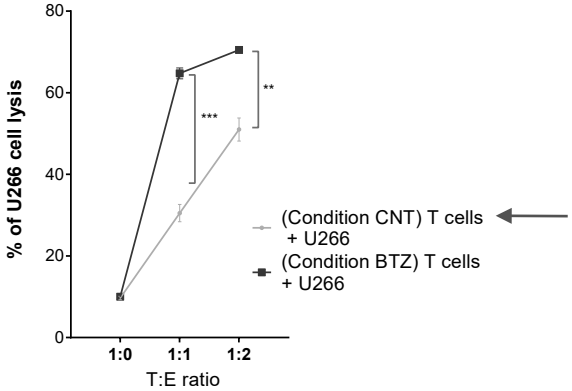




3. T cells are primed against MM



4. MM cell lysis

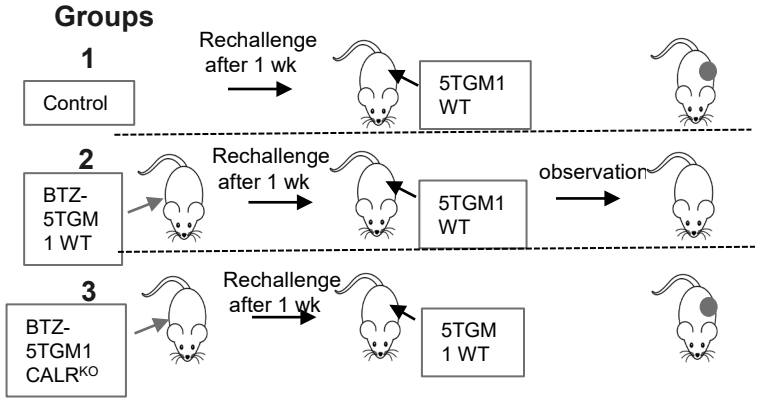


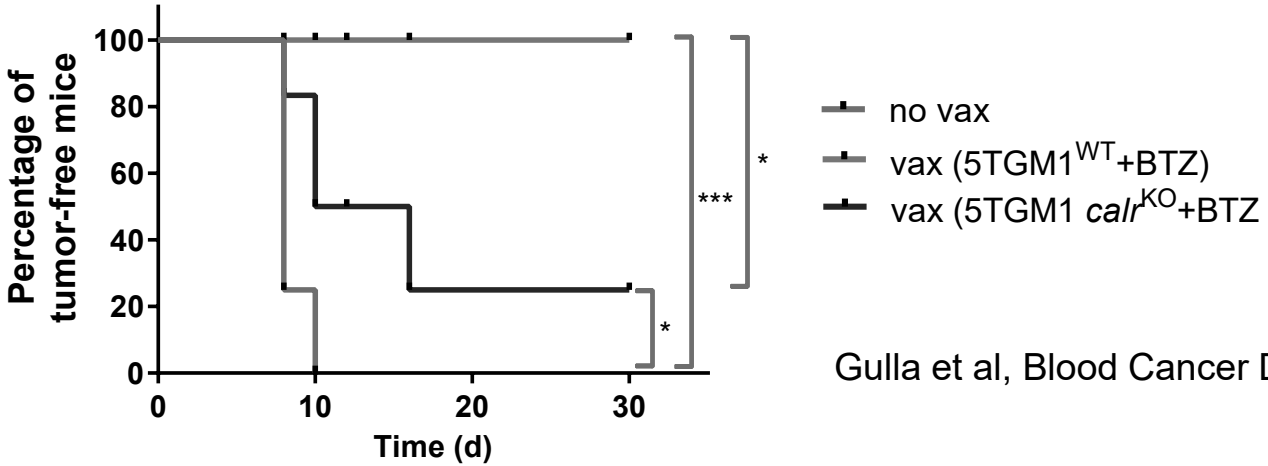
Gulla et al, Blood Cancer Discovery, in press

Dana-Farber Cancer Institute

Mice Vaccinated with Bortezomib-Treated WT 5TGM MM cells, but not *Calr*^{KO} 5TGM MM cells, were Protected Against Tumor ReChallenge

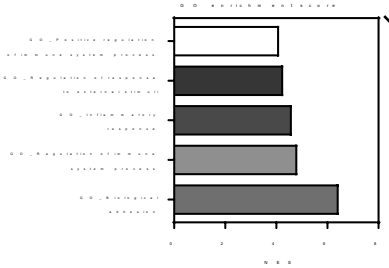
VACCINATION STUDY





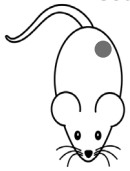
Gulla et al, Blood Cancer Discovery, in press

BTZ-Induced ICD-Type 1 IFN Signature Correlates with Clinical Outcome

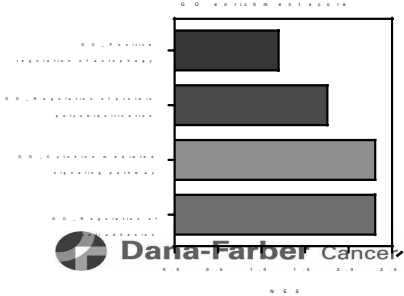


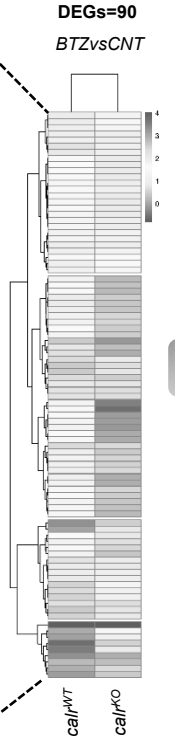
Enriched in *calr*^{WT} tumors

RNA-seq



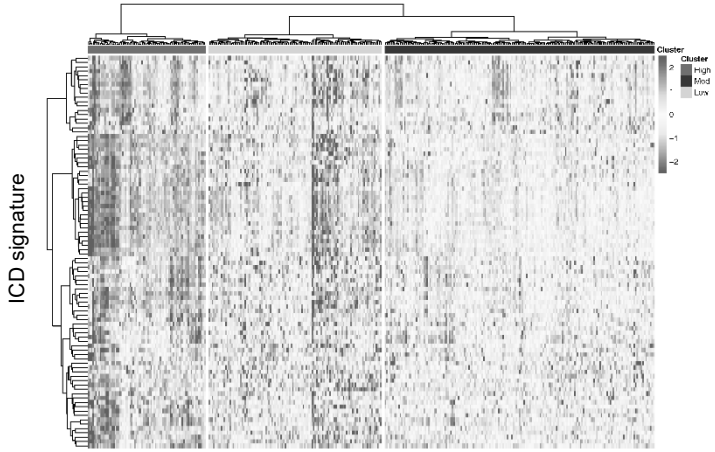
Enriched in *calr*^{KO} tumors

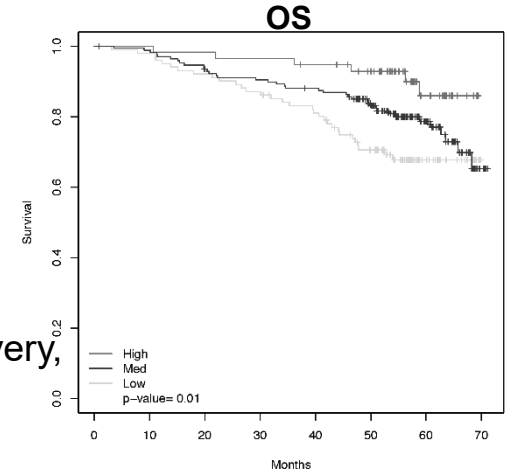




ICD SIGNATURE

IFM-DFCI 2009 clinical trial





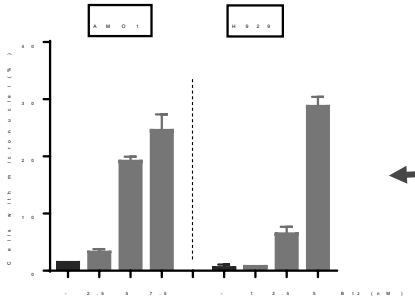
Gulla et al, Blood Cancer Discovery, In press

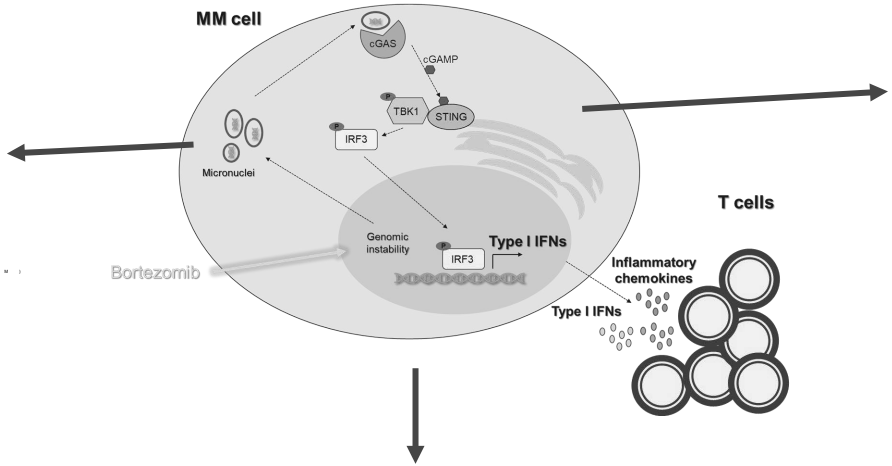
Dana-Farber Cancer Institute

BTZ Induces ICD via cGAS/STING Pathway and Type I IFN Response

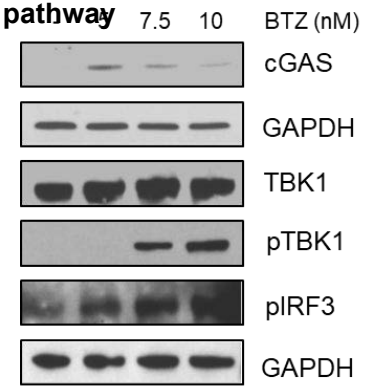
Sting Agonist as a Novel Targeted Therapy

Micronuclei

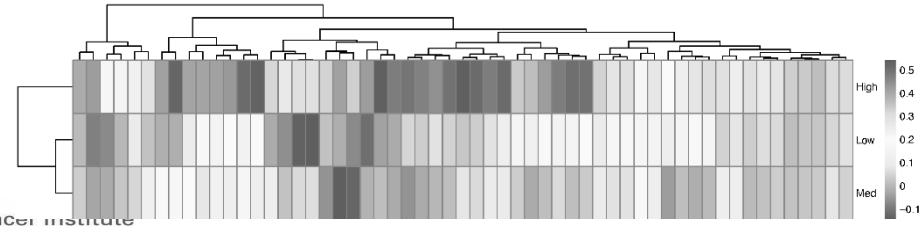




cGAS/STING pathway

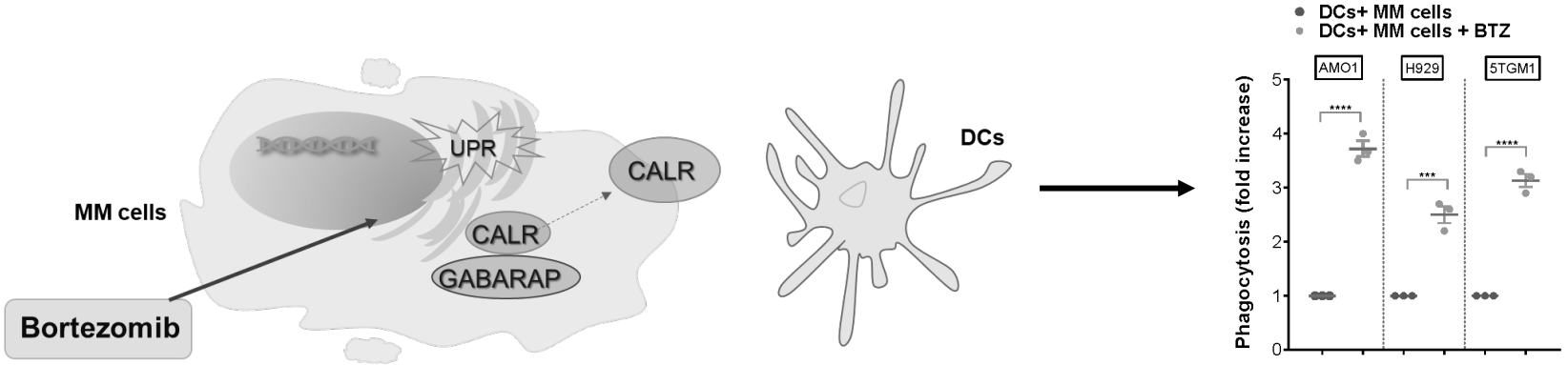


STING correlates with ICD-signature in MM patients

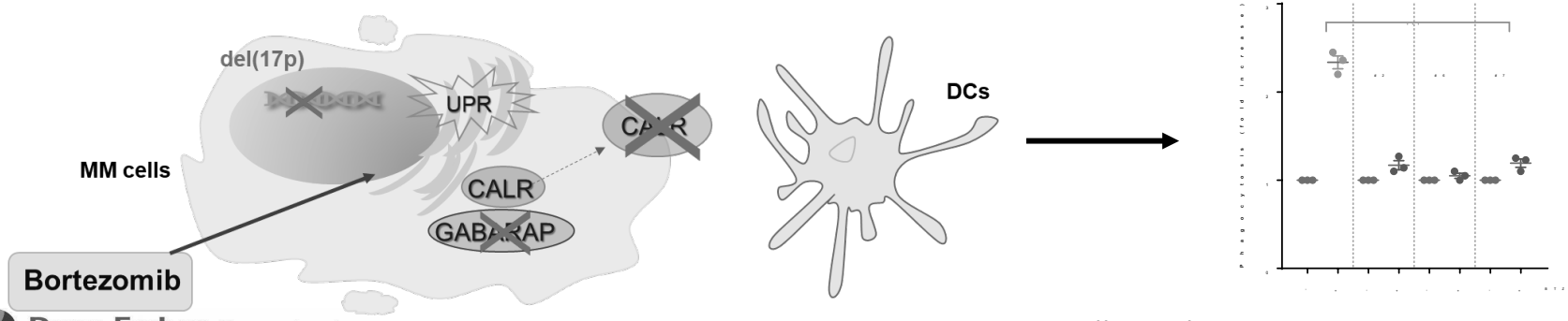


Gulla et al, Blood Cancer Discovery, in press

Loss-of-function of GABARAP (on 17p) in High Risk MM Abrogates Induction of ICD



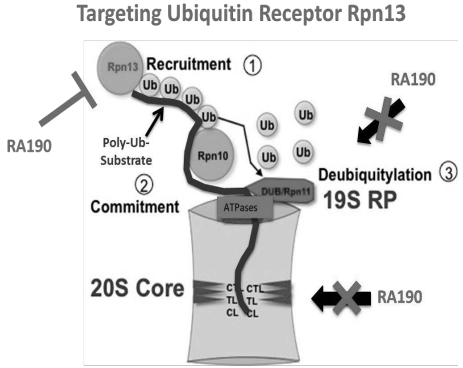
Novel Therapies to Restore GABARAP and ICD



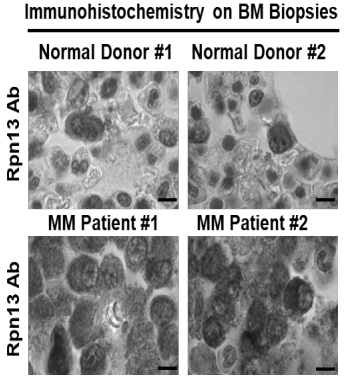
Dana-Farber Cancer Institute

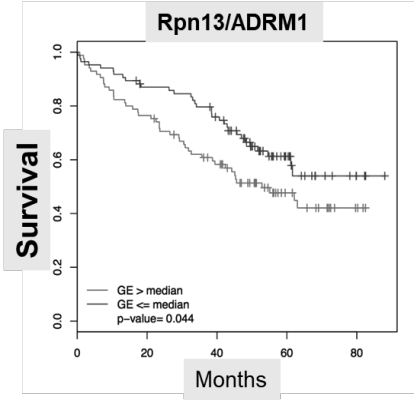
Gulla et al, IMW 2021

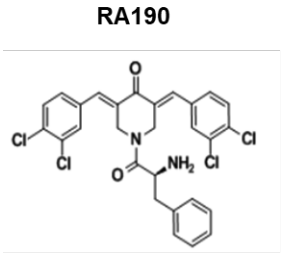
Targeting Ubiquitin Receptor Rpn13 (RA190) Inhibits Growth and Overcomes Proteasome Inhibitor Resistance in MM

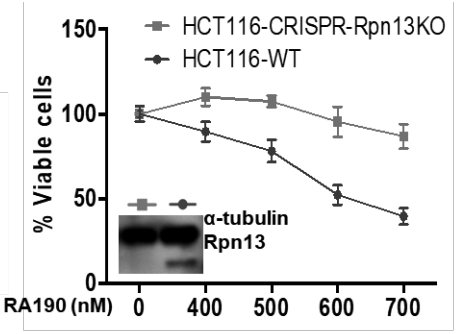


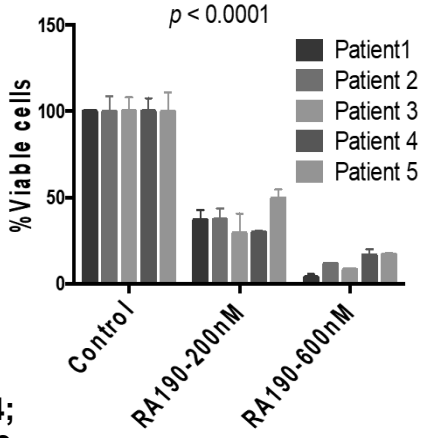
Song et al, Leukemia 2016; 30:1877-86.











Song et al, Leukemia 2016; 30:1877-86; Song et al Leukemia 2019; 33:2685-94; Blood Cancer J 2019; 9: 64; Leukemia 2021; 35: 550-61; Blood Cancer J 2021; 11: 13.

Targeting Ubiquitin Receptor Rpn13 Triggers T and NK Cell Anti-MM Immunity (Immunogenic Cell Death)

Blockade of Ubiquitin Receptor Rpn13
(RA190 or siRNA)

Tolerogenic Immature pDCs

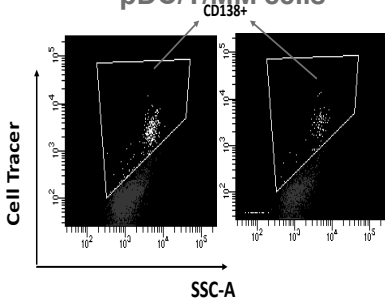
CD80, CD83,
CD86, HLA-DR

Activation/Maturation of pDCs

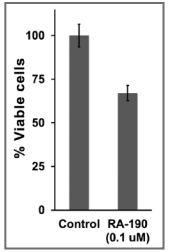
NK cell-
Anti-MM Activity

T-Cell
Anti-MM Activity

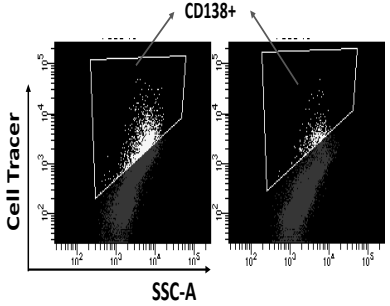
Autologous patient
pDC/T/MM cells



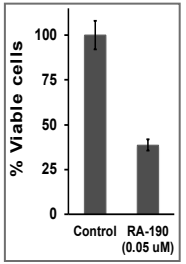
MM cell lysis



Autologous patient
pDC/ NK/MM cells



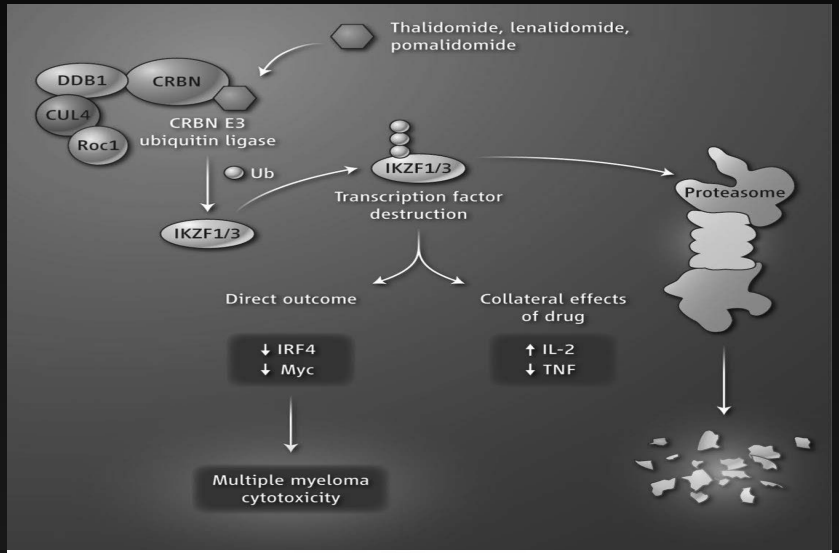
MM cell lysis



Ray et. al. Blood Cancer Journal 2019; 9:64

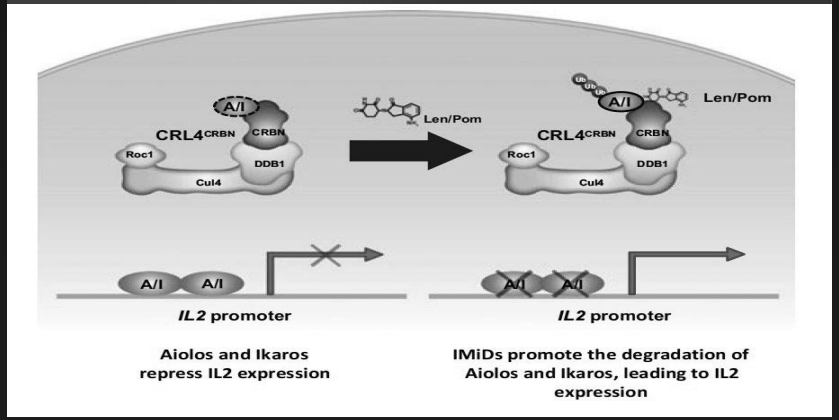
Immunomodulatory Drugs Target Cereblon in Tumor and Microenvironment

CELMoDs: increased CRBN affinity, CC220, CC92480) 30-50% responses In len/pom resistant MM (Lonial et al, Richardson et al ASCO, ASH 2019, 2020, 2021)



Kronke et al, Science, 2014

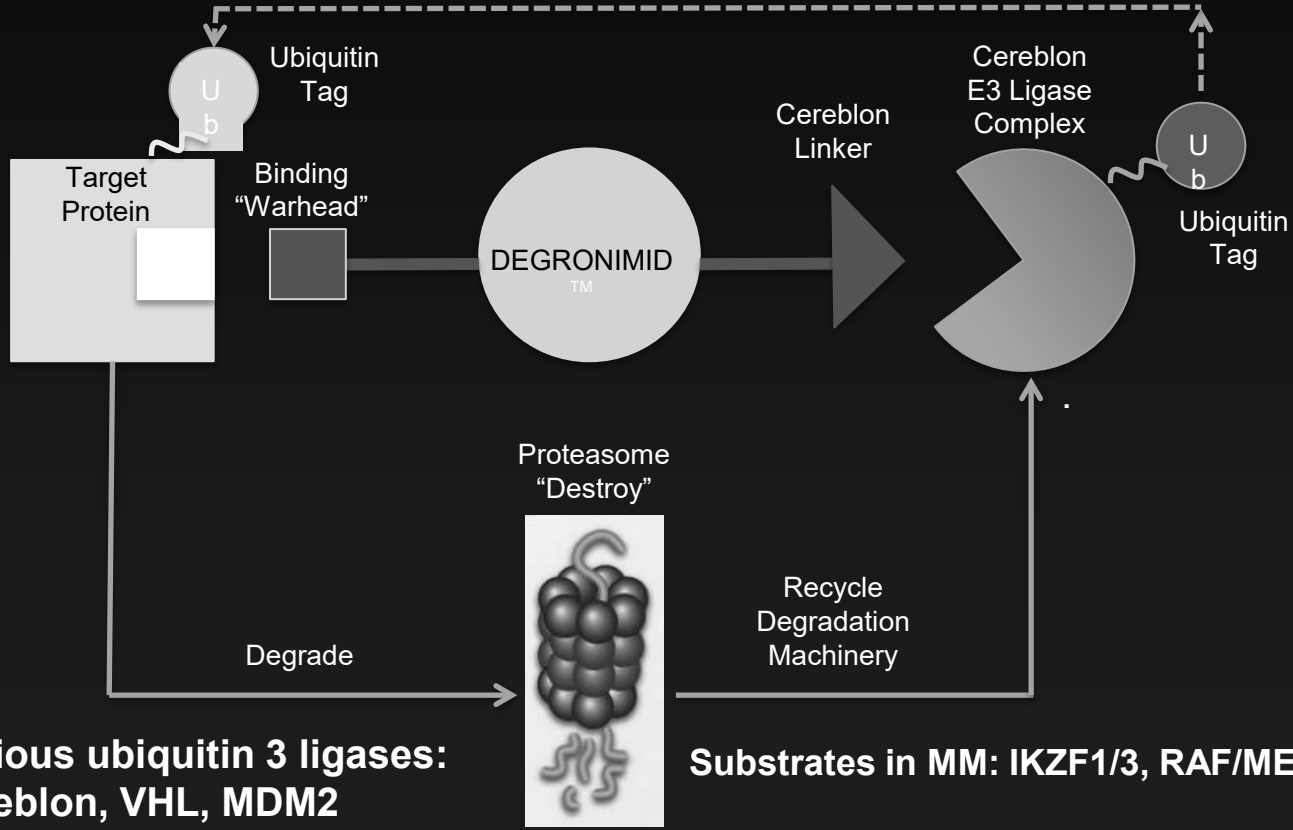
Lu et al, Science, 2014



Gandhi AK et al. Brit J Haematol, 2014;164: 811-21.

Degronimids Trigger Degradation of Selective Substrates (ie IKZF1/3 and RAF/MEK/ERK in MM)

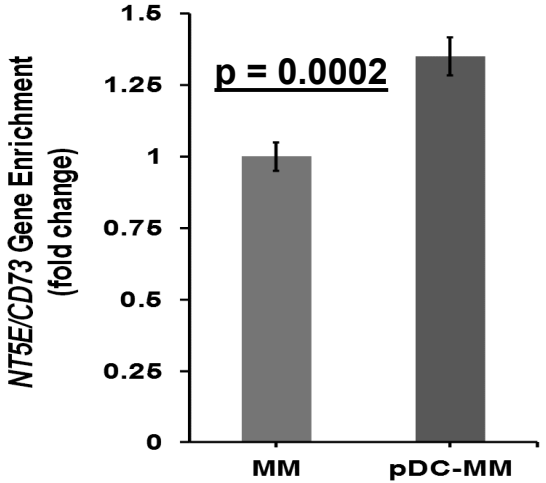
Winter, Bradner et al, Science,2015; 348: 1376-81.

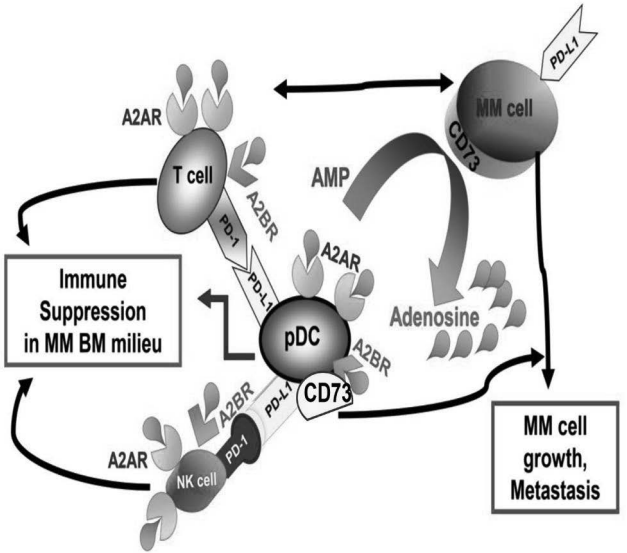


Various ubiquitin 3 ligases: cereblon, VHL, MDM2

Substrates in MM: IKZF1/3, RAF/MEK/ERK

Plasmacytoid Dendritic Cell (pDC)-MM Interaction Upregulates *CD73* on MM Cells, Increasing Adenosine in BM, Activating Adenosine Receptor on T cells, and Conferring Immunosuppression





CD73 cell surface enzyme converts AMP to adenosine in the bone marrow milieu

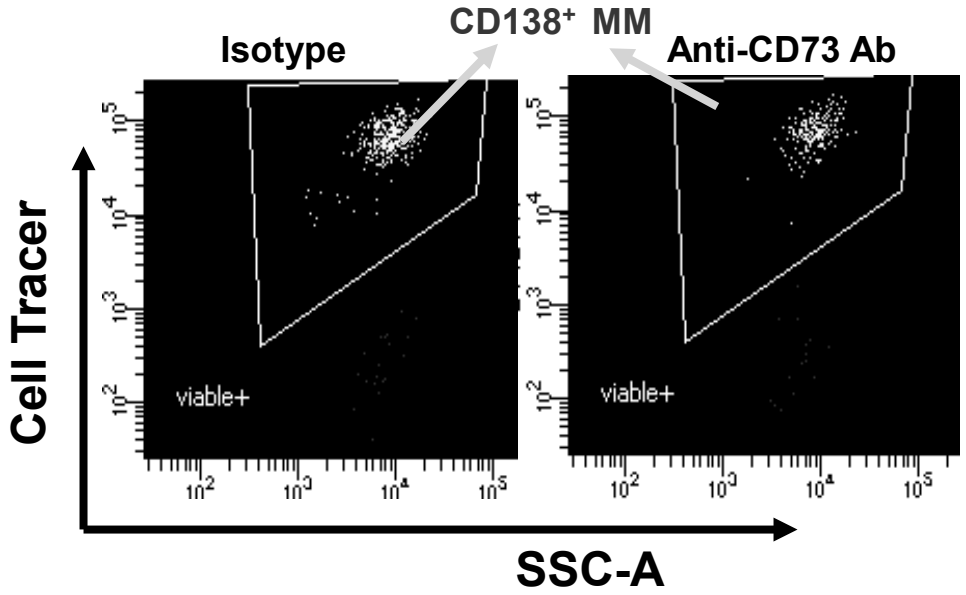
CD73 promotes tumor growth and triggers immune suppression via activation of adenosine receptors on on CD8+ T and NK cells.

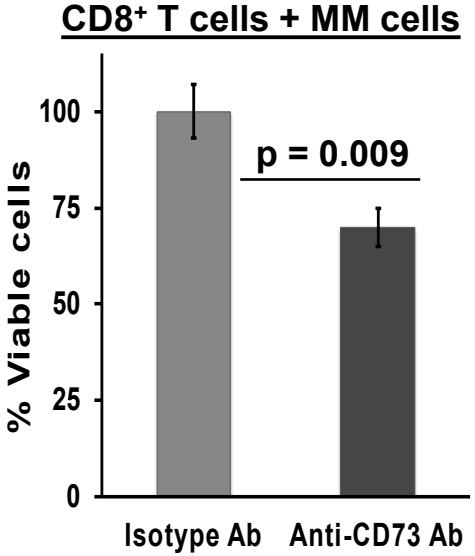
Ray et al Submitted

Blockade of CD73 Overcomes Immunosuppression and Triggers T cell- Mediated Autologous MM-Specific Cytotoxic Activity

Patient MM-BM: Autologous pDCs/T/MM cells

MM Patient (7) BM Samples

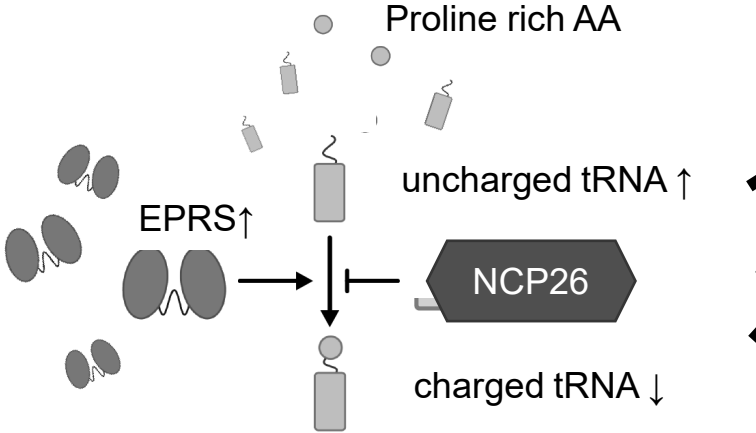




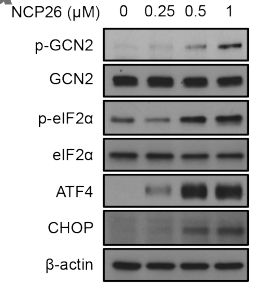
Oral CD73 Inhibitor Clinical trial in MM

Ray et al Submitted

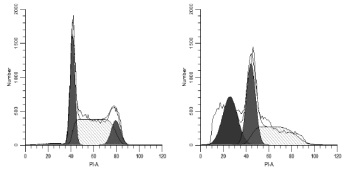
Glutamyl-Prolyl-tRNA Synthetase (EPRS, Catalyzes Ligation of Glutamic Acid or Proline to Cognate tRNAs): A Novel Target in Myeloma

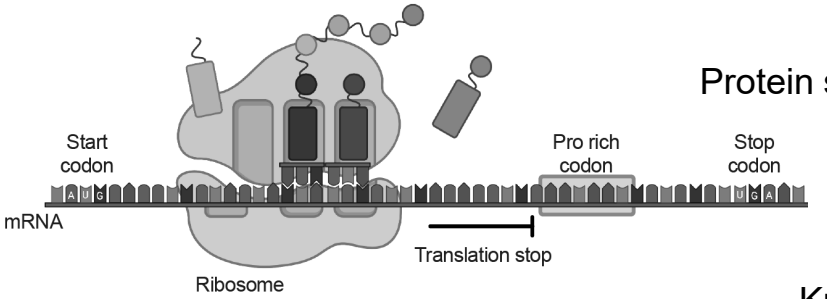


Amino acid starvation response



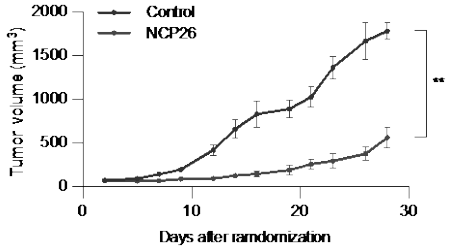
Cell cycle arrest/ Apoptosis





Protein synthesis ↓

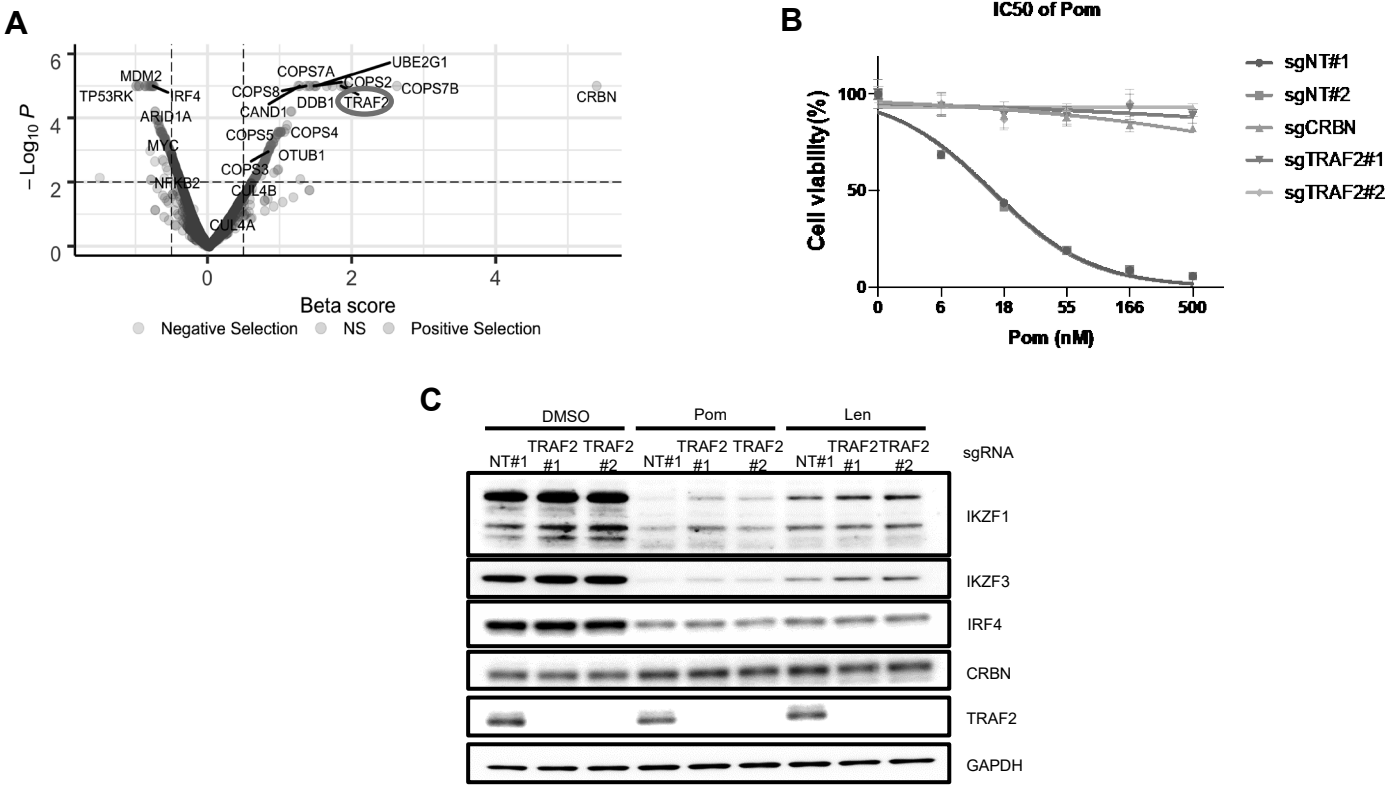
in vivo growth inhibition



Kurata et al, 2021

Novel Targeted Therapies to Overcome IMIDs Resistance

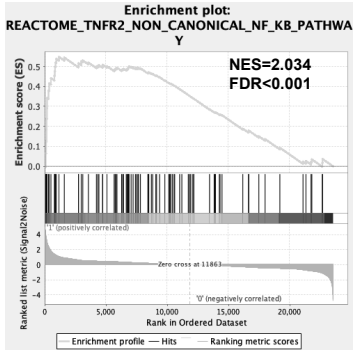
Genome-Wide CRISPR-Cas9 Screening Identifies TRAF2 Mediating IMiDs Sensitivity

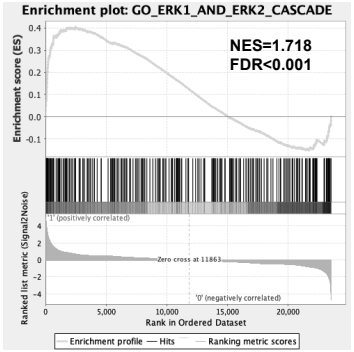


Liu et al, Science Adv 2021;7(23):eabg2697

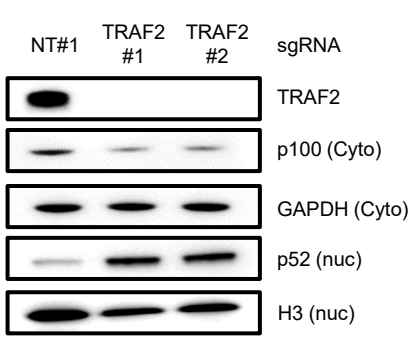
TRAF2 KO Induces Activation of Non-canonical NF-κB and ERK Pathways

A

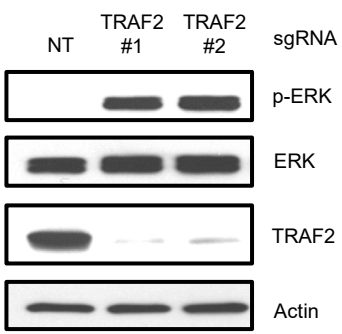




B



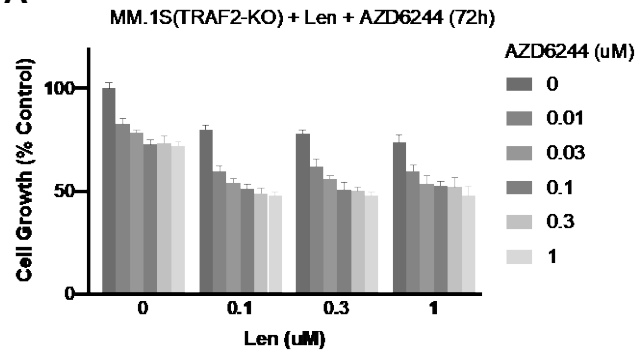
C



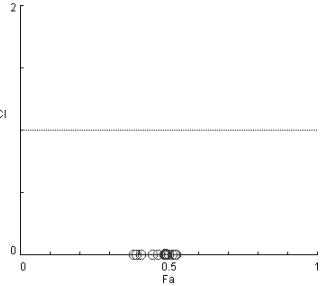
Liu et al, Science Adv 2021;7(23):eabg2697

Inhibition of MEK-ERK Overcomes IMiDs Resistance Induced by *TRAF2* Knock Down *in Vivo*

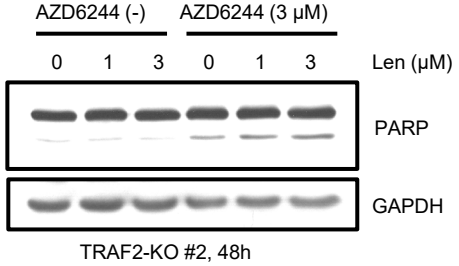
A



Dose Len	Dose AZD	Effect	CI
0.1	0.01	0.407	9.02E-4
0.1	0.03	0.465	4.94E-4
0.1	0.1	0.492	7.86E-4
0.1	0.3	0.513	0.00135
0.1	1.0	0.525	0.00327
0.3	0.01	0.383	0.00258
0.3	0.03	0.447	8.72E-4
0.3	0.1	0.495	7.38E-4
0.3	0.3	0.502	0.00181
0.3	1.0	0.524	0.00336
1.0	0.01	0.392	0.00380
1.0	0.03	0.447	0.00112
1.0	0.1	0.486	9.98E-4
1.0	0.3	0.49	0.00254
1.0	1.0	0.488	0.00873

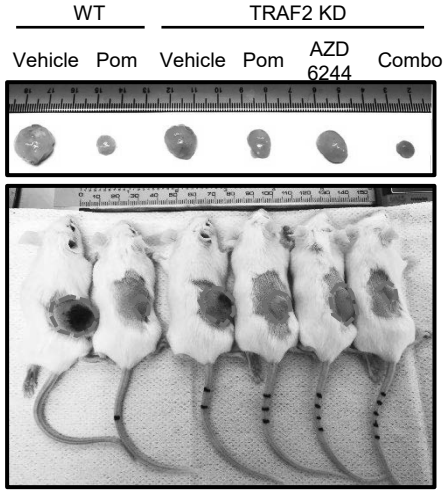


B

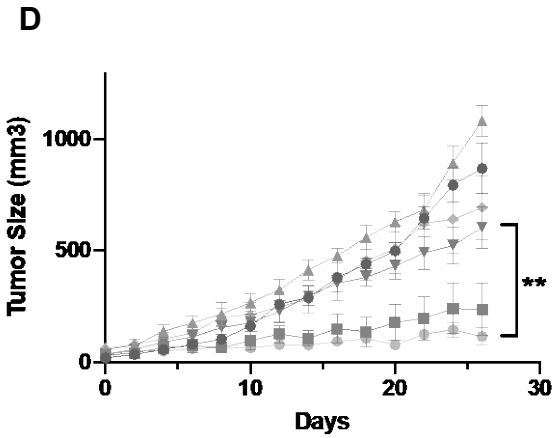


TRAF2-KO #2, 48h

C

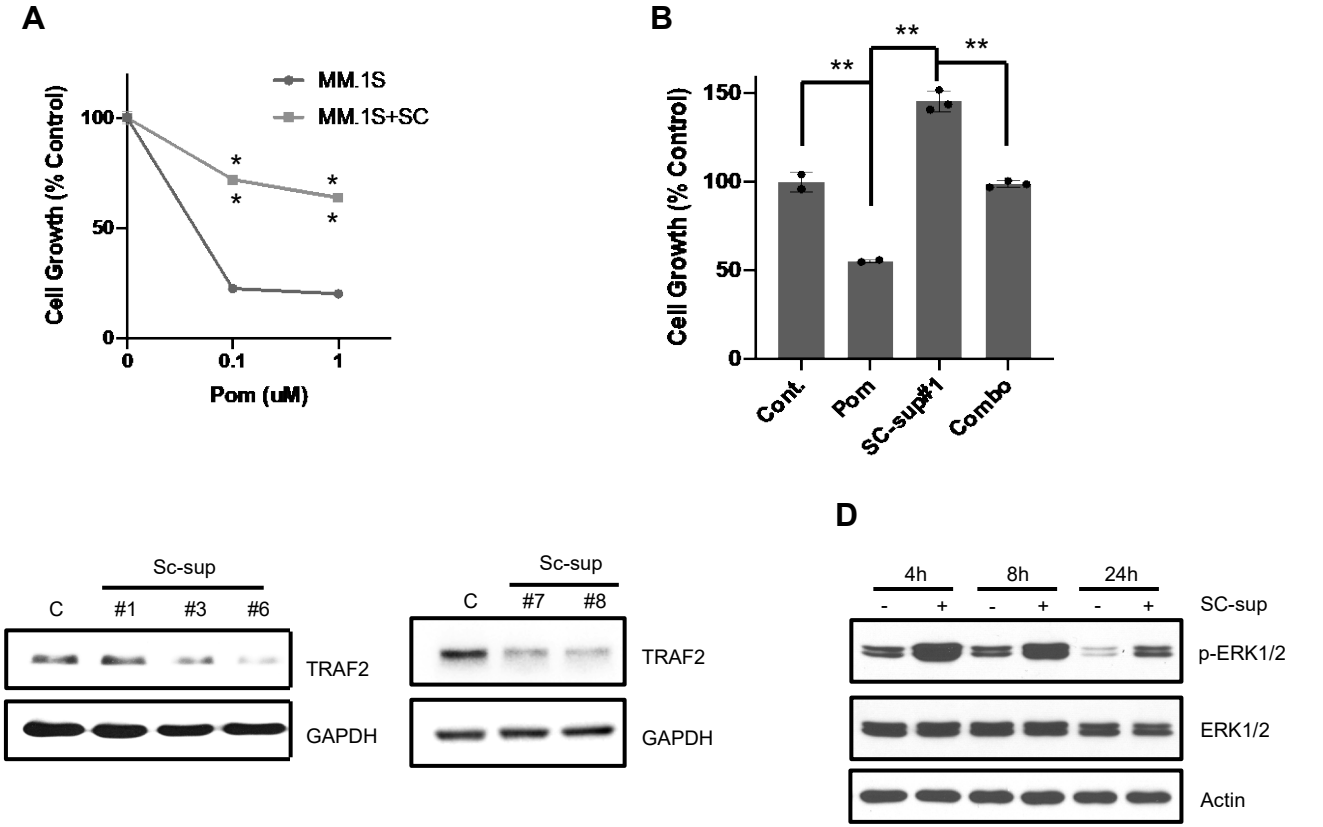


D



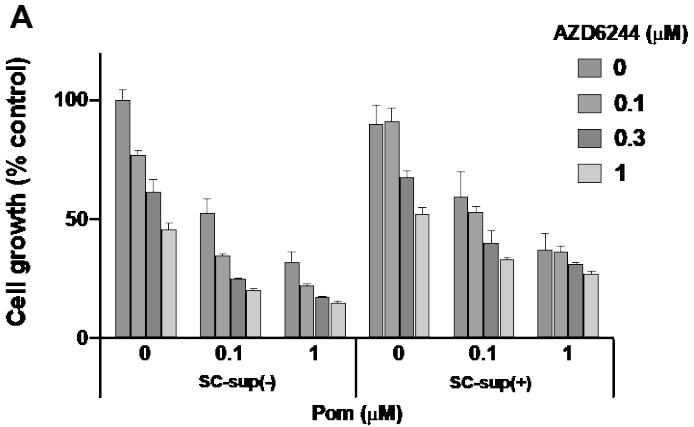
Liu et al, Science Adv 2021; 7(23):eabg2697

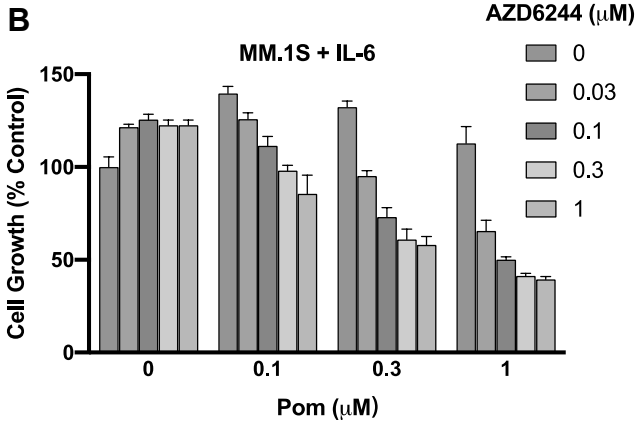
Bone Marrow (BM) Microenvironment Induces IMiDs Resistance, Associated with Downregulation of TRAF2 and ERK Activation

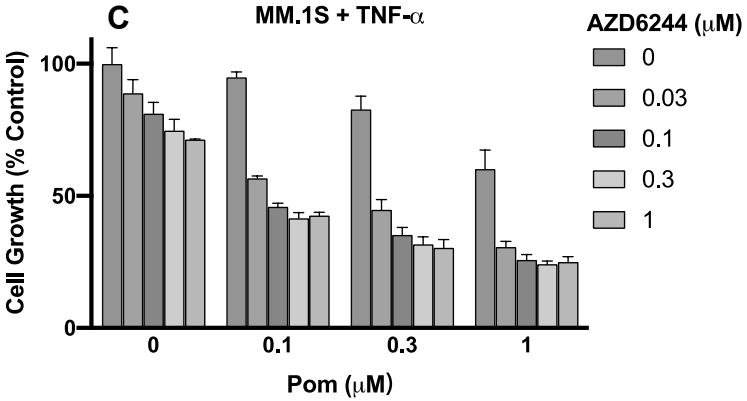


Liu et al, Science Adv 2021;7(23):eabg2697

Inhibition of MEK Overcomes IMiDs Resistance Induced by BM Microenvironment



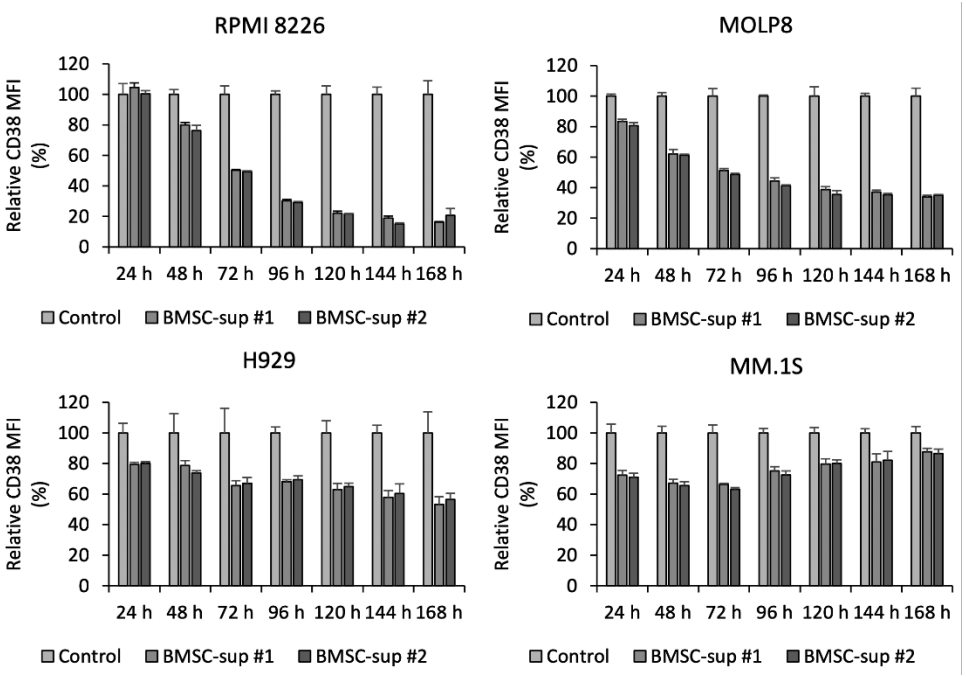


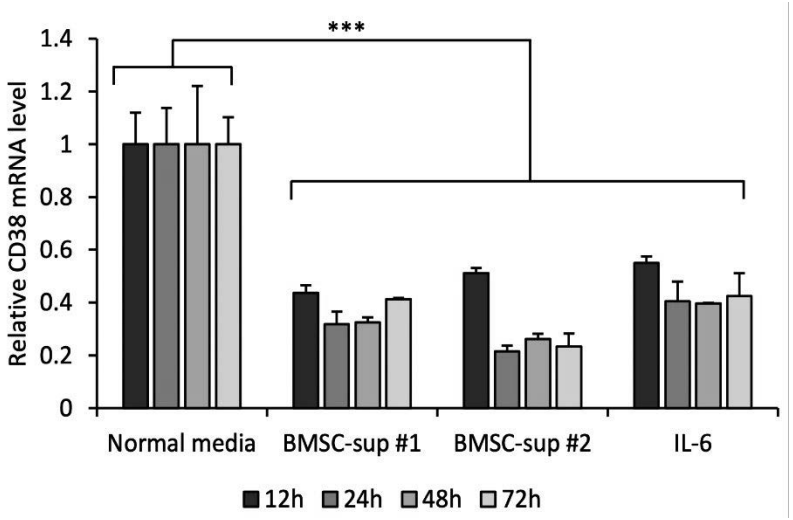


Targeting MEK/ERK can overcome IMiDs resistance due to TRAF2 downregulation intrinsic to MM cells, as well as resistance induced by BM milieu

Liu et al, Science Adv 2021;7(23):eabg2697

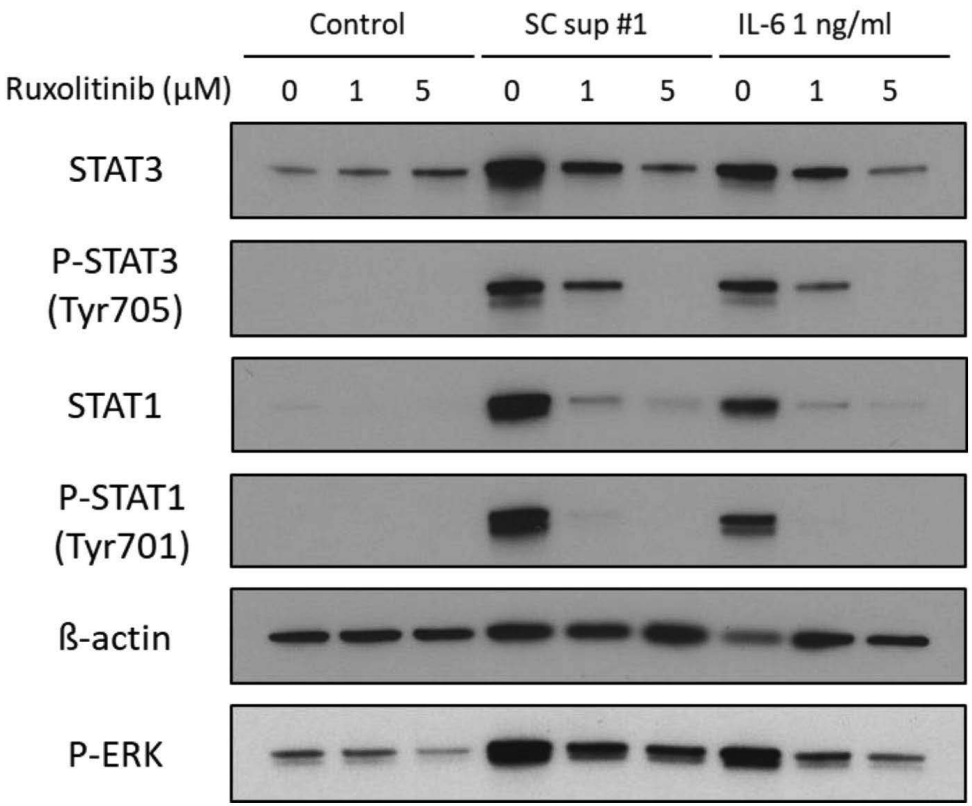
Bone Marrow Stromal Cell Supernatants (BMSC sup) or IL-6 Decrease CD38 on MM Cells and Confer Resistance to CD38 MAb Therapy

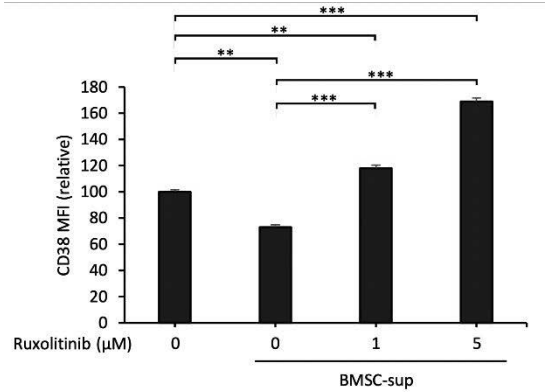


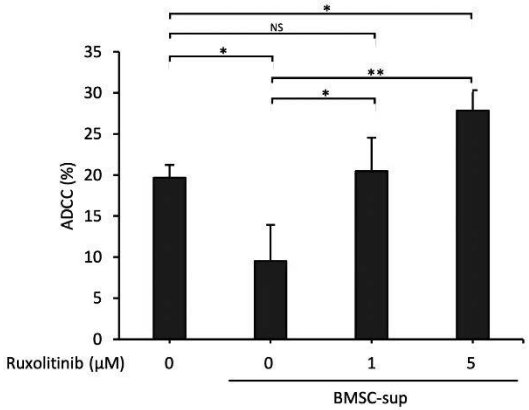


Ogiya et al, Blood 2020; 136: 2334-45

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







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

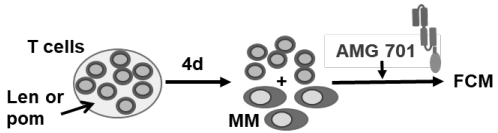
Bispecific T Cell Engagers (Bites) in Multiple Myeloma

	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

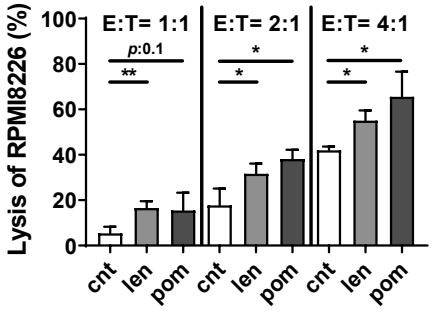
Garfall et al; Harrison et al; Madduri et al Chari et al; Cohen et al ASH, ASCO 2020

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

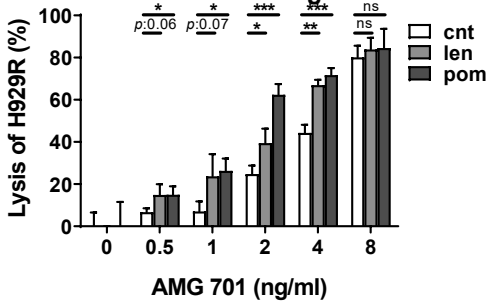
A



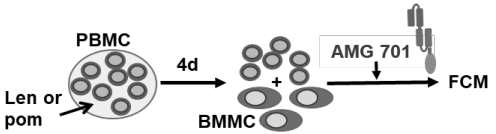
Low E/T ratio



Low dose

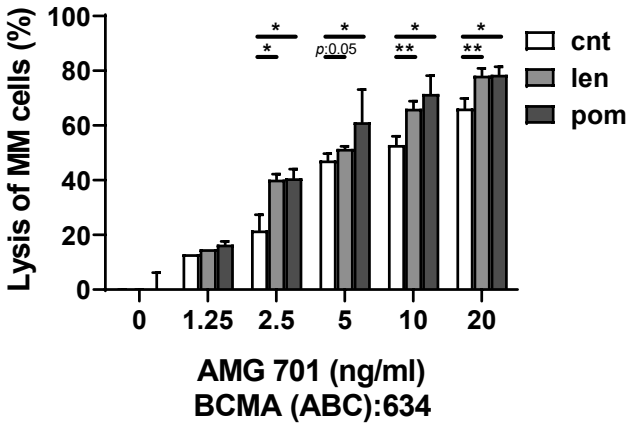


B



Autologous model

RRMM PBMC + BMMC



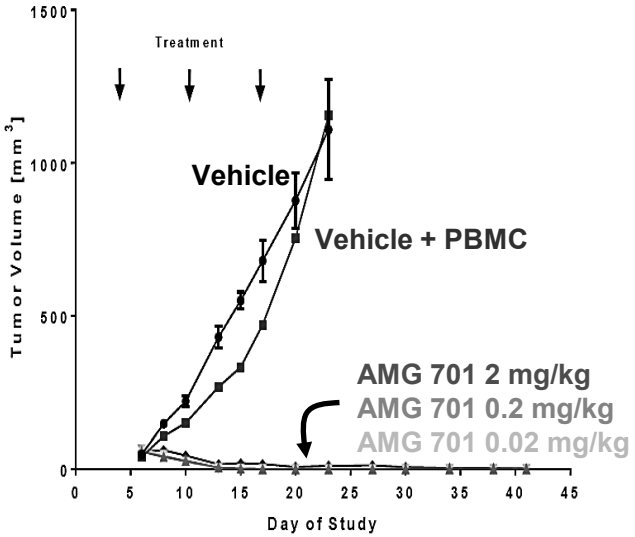
Cho et al Blood Advances 2020; 4: 4195-4207.

Dana-Farber Cancer Institute

HARVARD MEDICAL SCHOOL

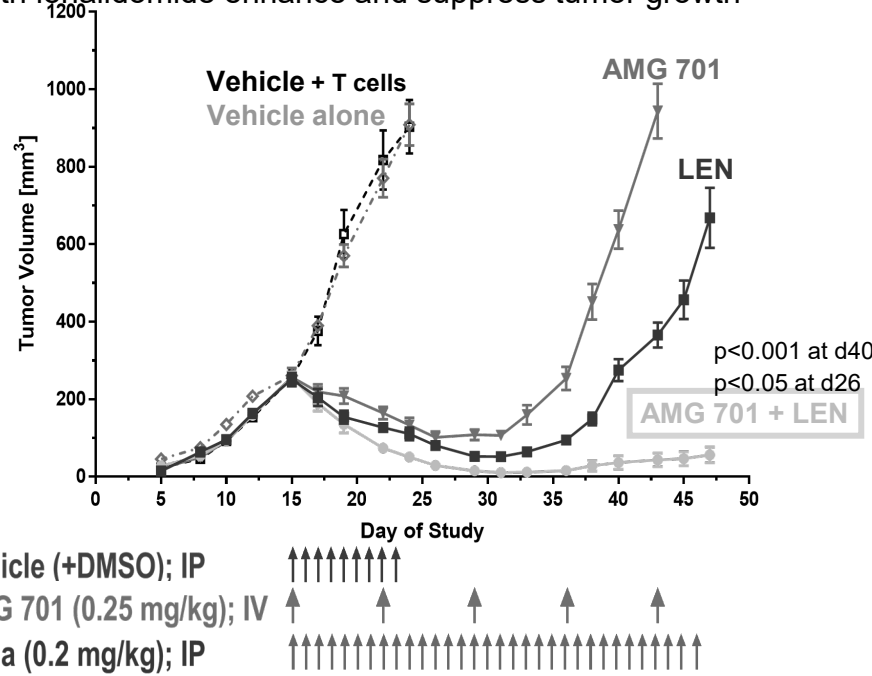
Combination AMG 701 and Lenalidomide Enhanced Anti-tumor Activity in a Mouse Model of Established MM (Clinical Trial Ongoing)

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



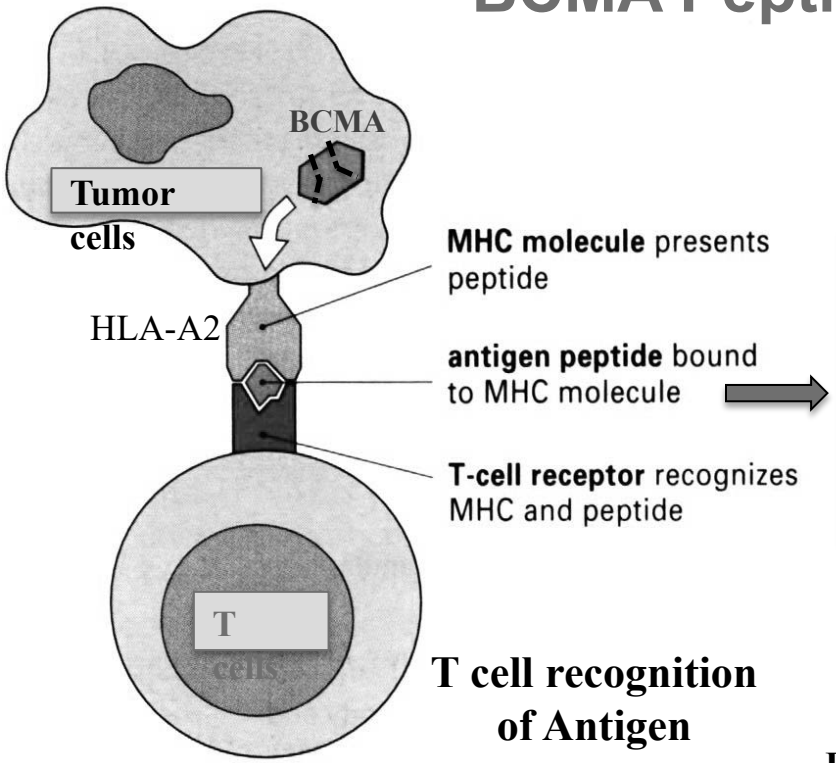
Monotherapy: 3 separate dosing

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



Cho et al Blood Advances 2020; 4: 4195-4207.

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

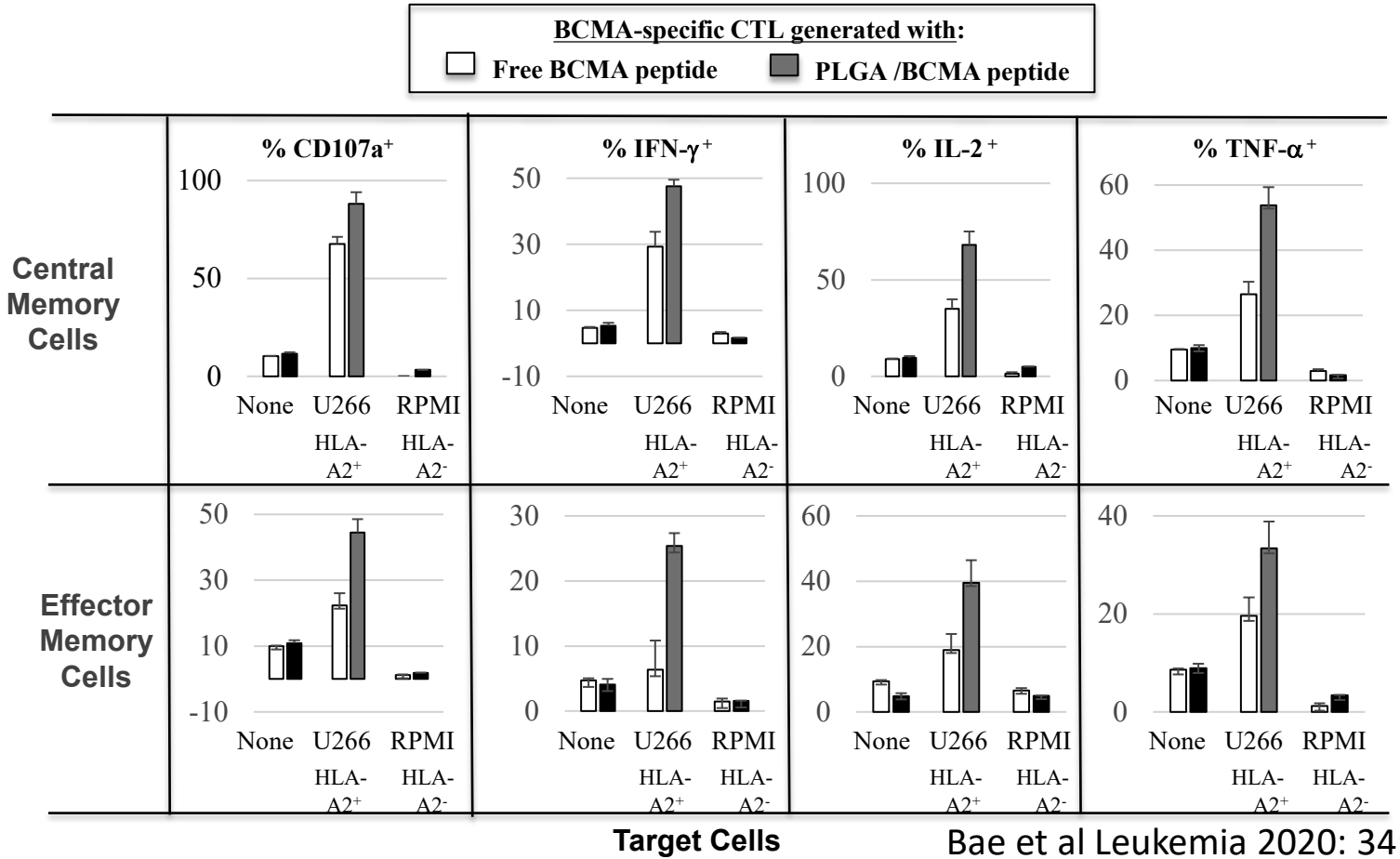


T cell recognition of Antigen

$BCMA_{72-80}$ Heteroclitic Peptide, which bound to HLA-A2 and induce antigen-specific $CD8^+$ cytotoxic T cells against myeloma

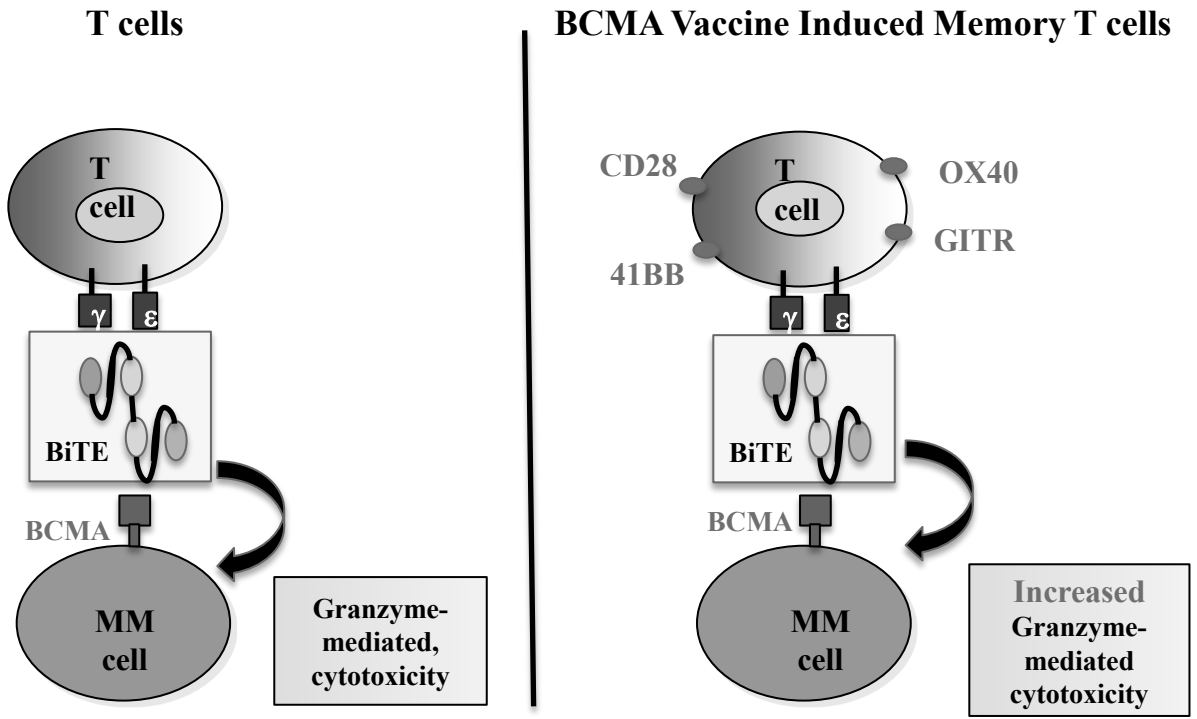
Bae et al. Leukemia 2019; 33:2208-26.

PLGA/ Heteroclitic $BCMA_{72-80}$ Peptide Induces HLA-A2 Restricted Central and Effector Memory CTLs



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



Bae et al, 2020

CAR T-Cell Therapy in Multiple Myeloma

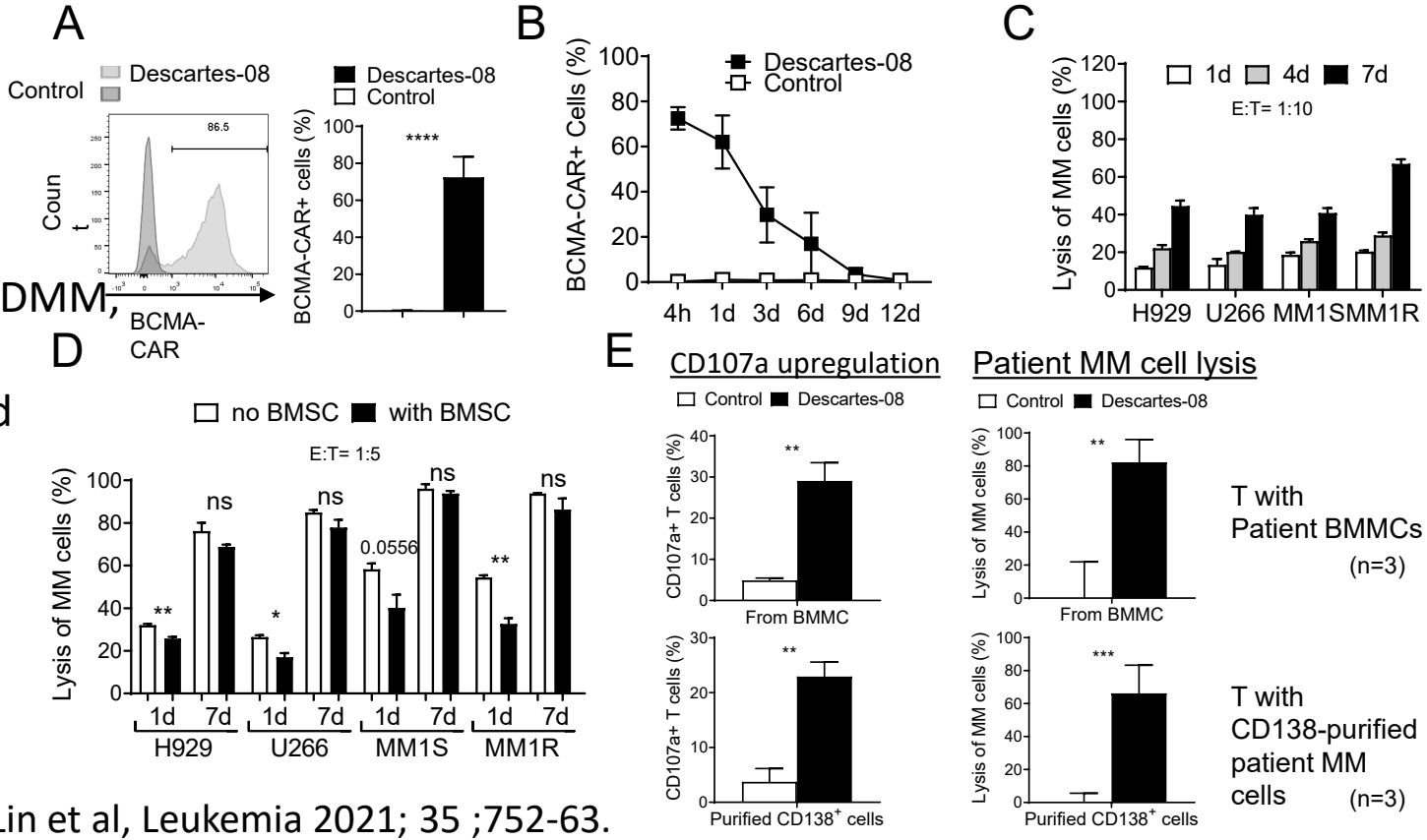
FDA Approved

	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

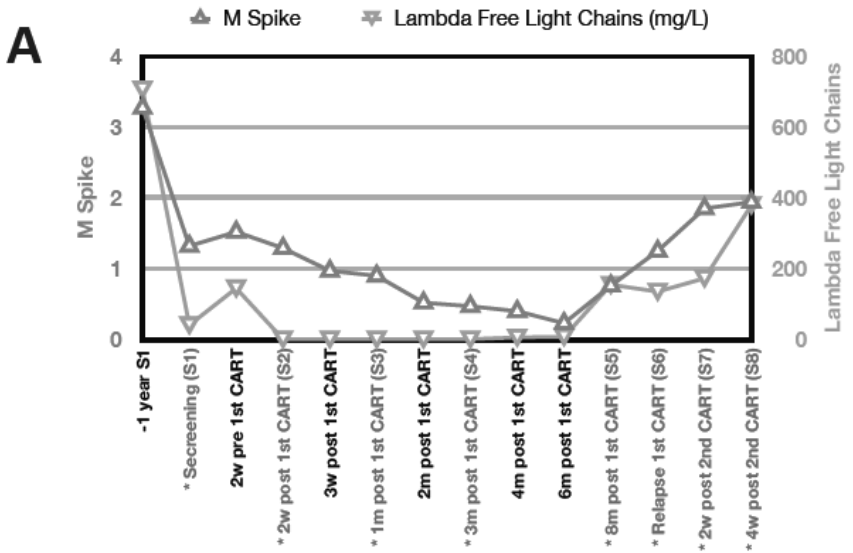
Trial in NDMM, No CRS, Repeated Doses

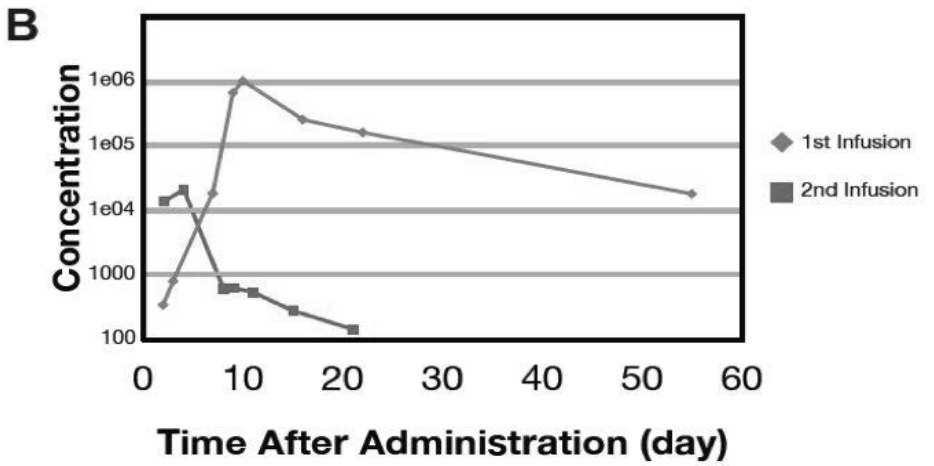


Lin et al, Leukemia 2021; 35 ;752-63.

Biallelic BCMA Loss Confers Resistance to BCMA CAR T Cells

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

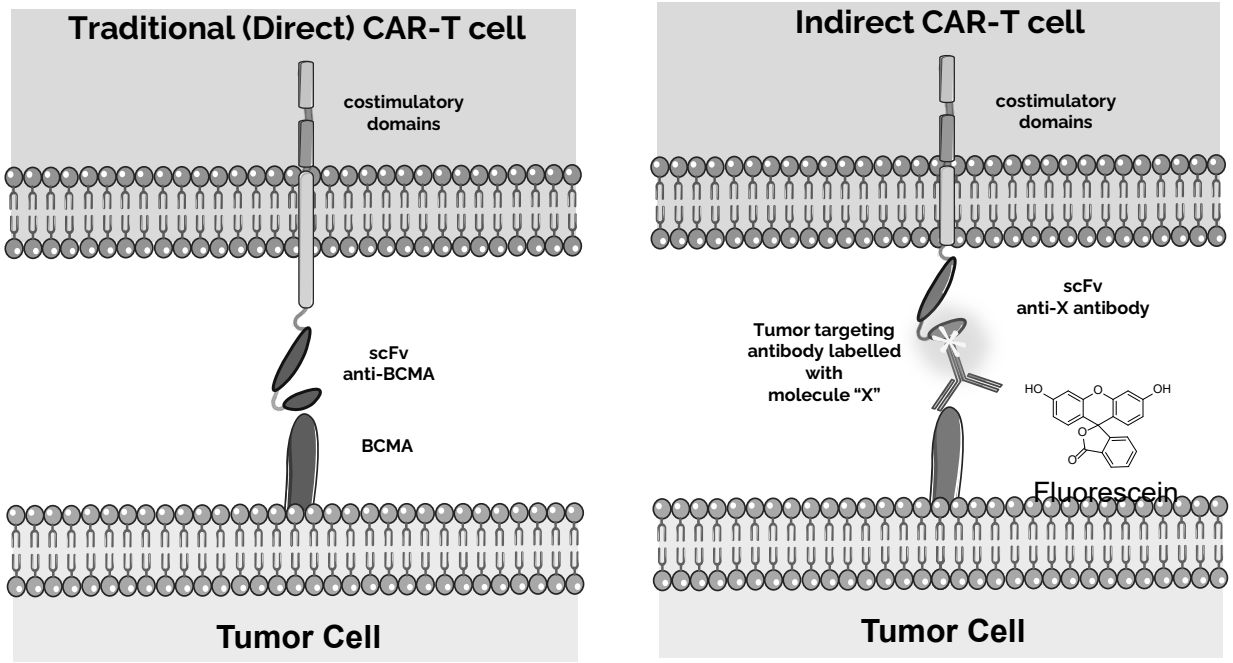




Dual targeting to avoid resistance: GPRC5D, CD19, FcHR5, CD38, CD138, SLAMF-7

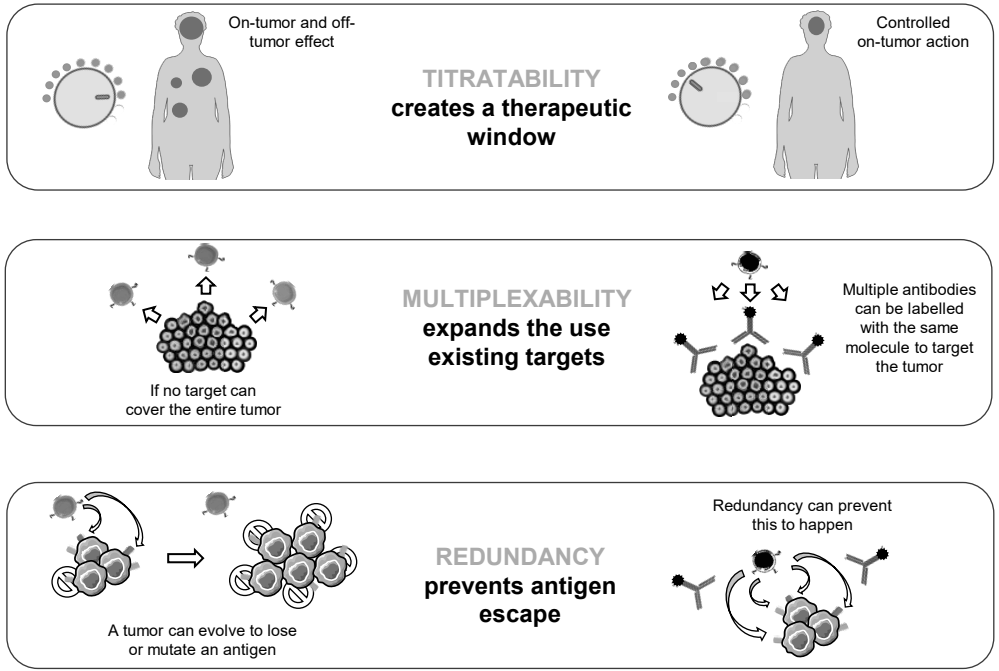
Samur et al Nat Comm 2021

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



Alberto Nobili, PhD and Carl Novina, MD PhD

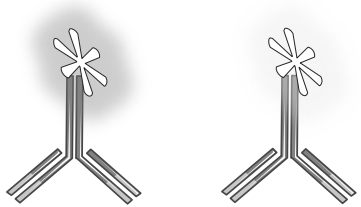
BAT CARs Target Limitations of CAR T Cells



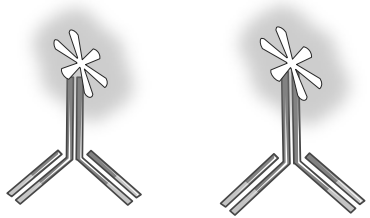
Alberto Nobili, PhD and Carl Novina, MD PhD

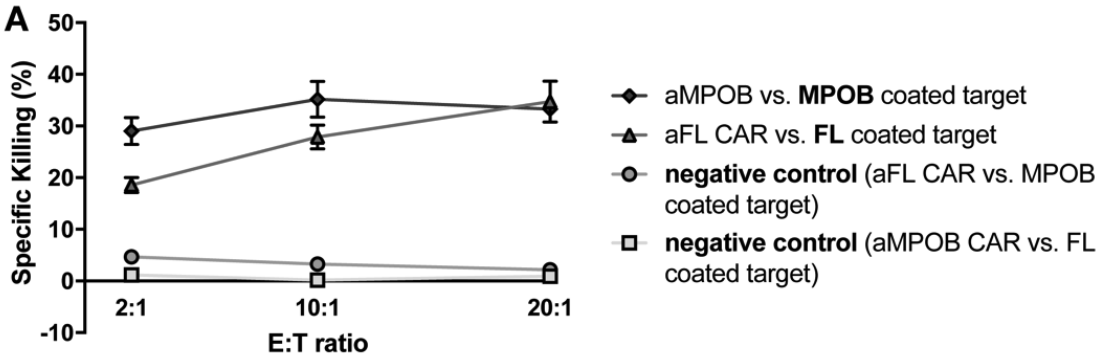
Modular Killing of Multiple Myeloma Cells

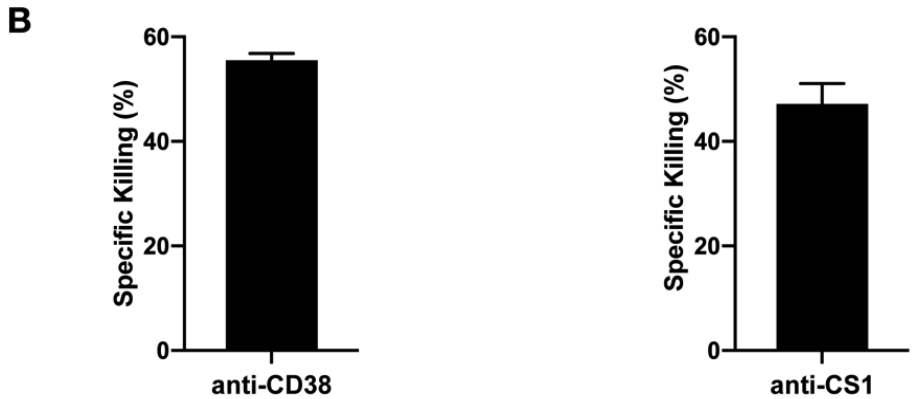
Same target, different small molecule



Same small molecule, different target

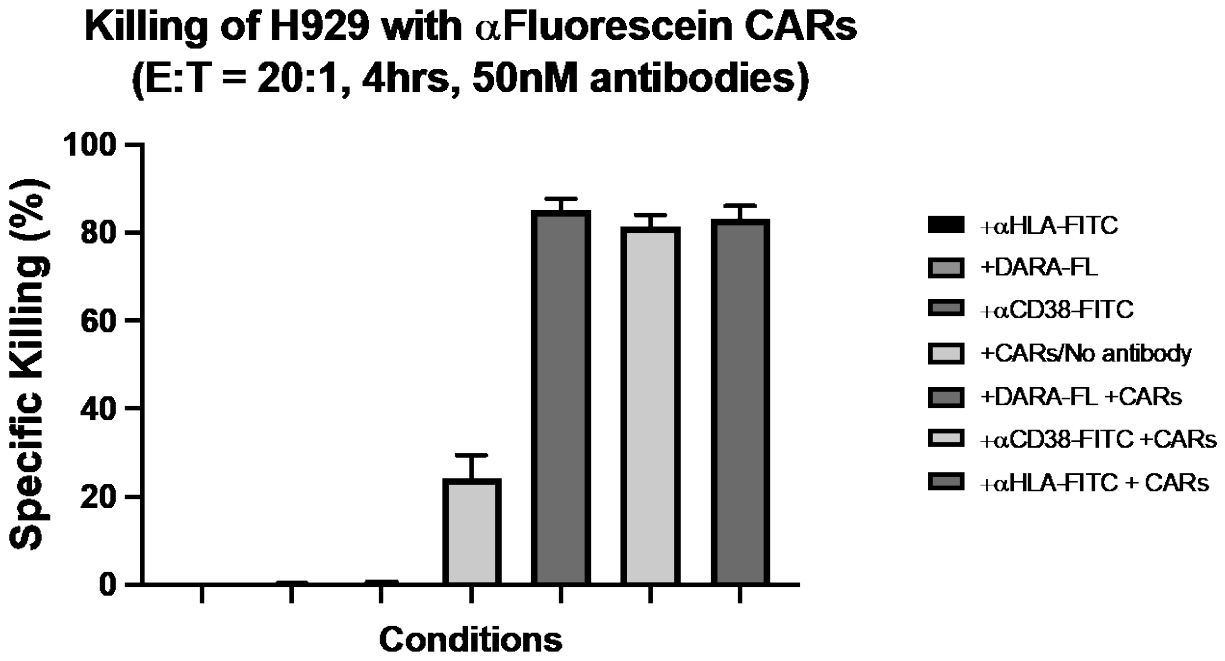




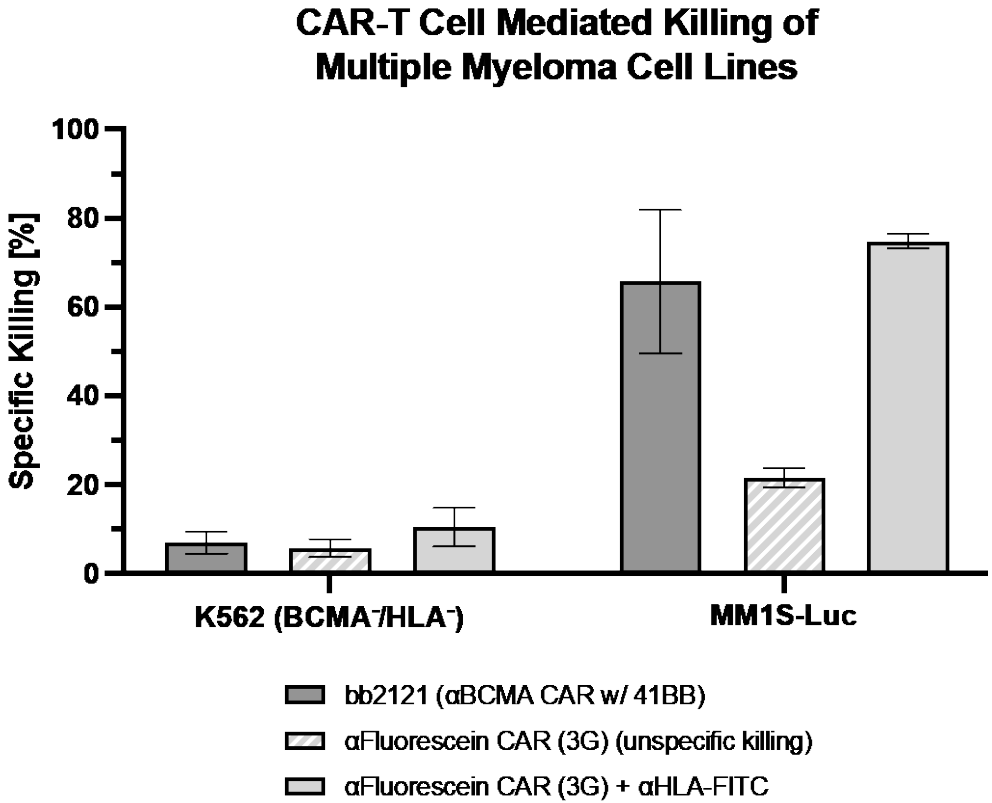


Alberto Nobili, PhD and Carl Novina, MD PhD

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



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