Myeloma as a Paradigm for Bench to Bedside Research

Kenneth C. Anderson, M.D.

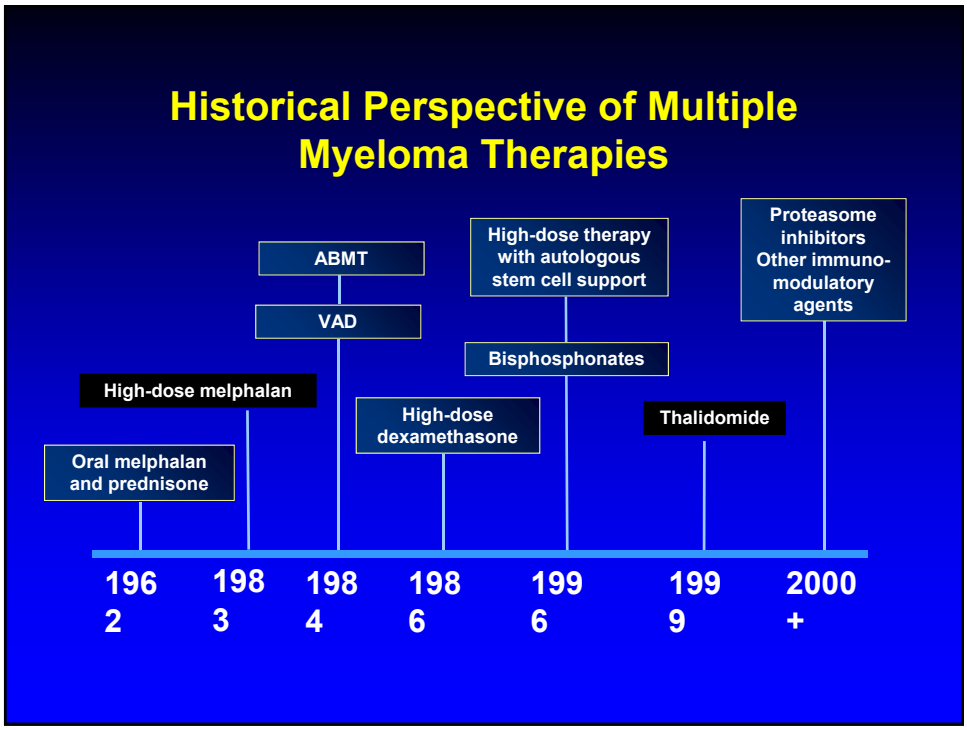
Jerome Lipper Multiple Myeloma Center
Dana-Farber Cancer Institute
Harvard Medical School

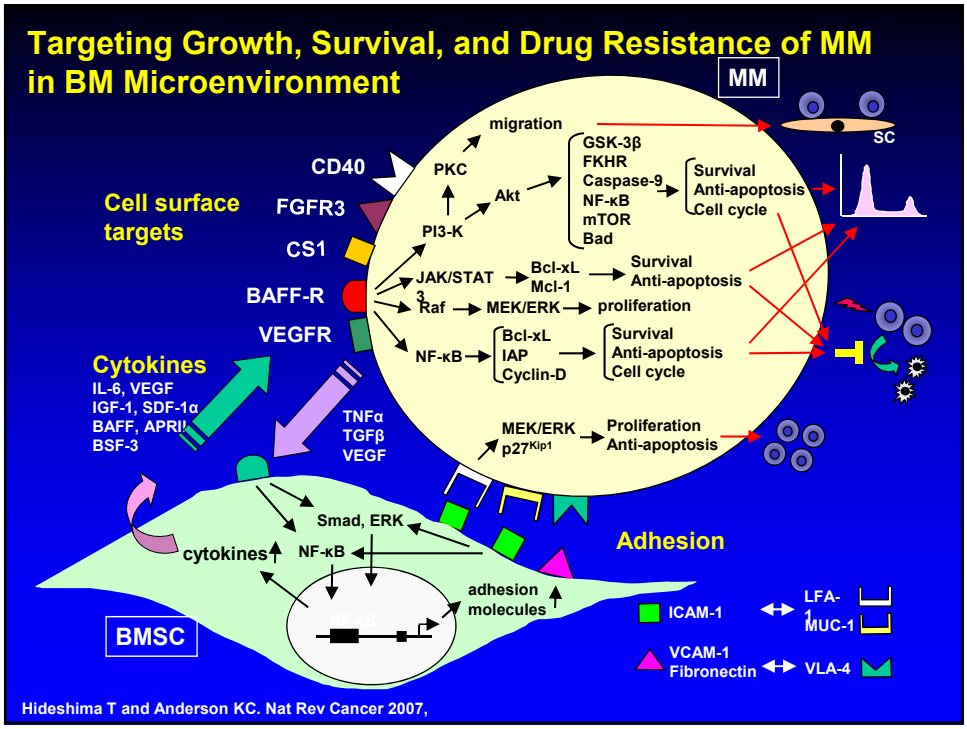
Conflict of Interest: Kenneth C. Anderson, M.D.

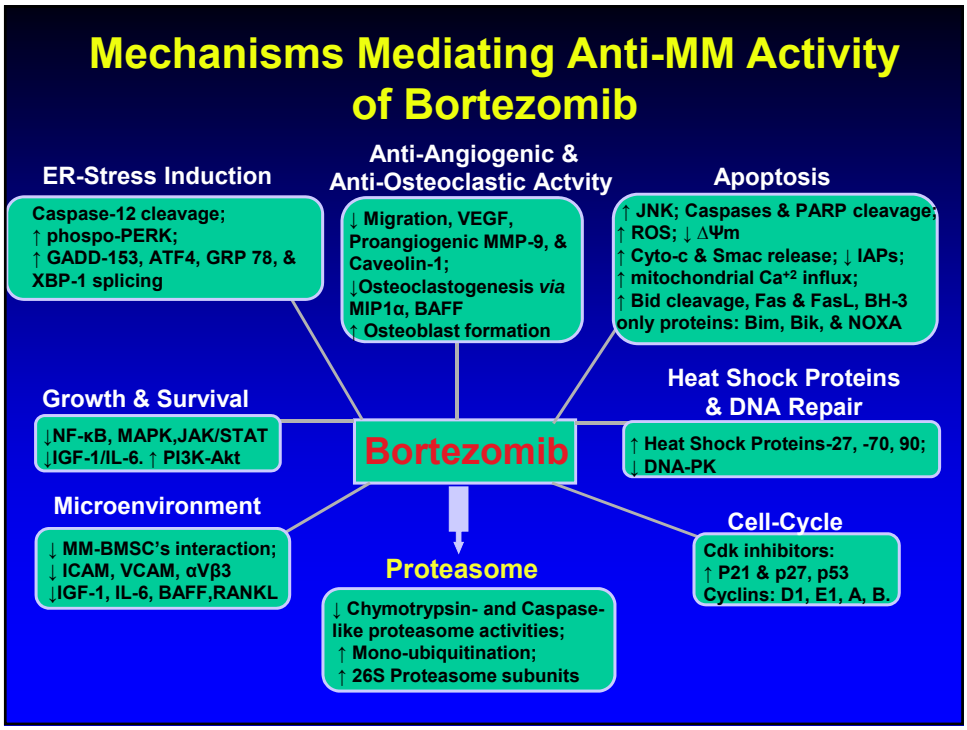
Consultancy: Celgene, Onyx, Sanofi Aventis, and Gilead

Scientific Founder: Acetylon, Oncopep

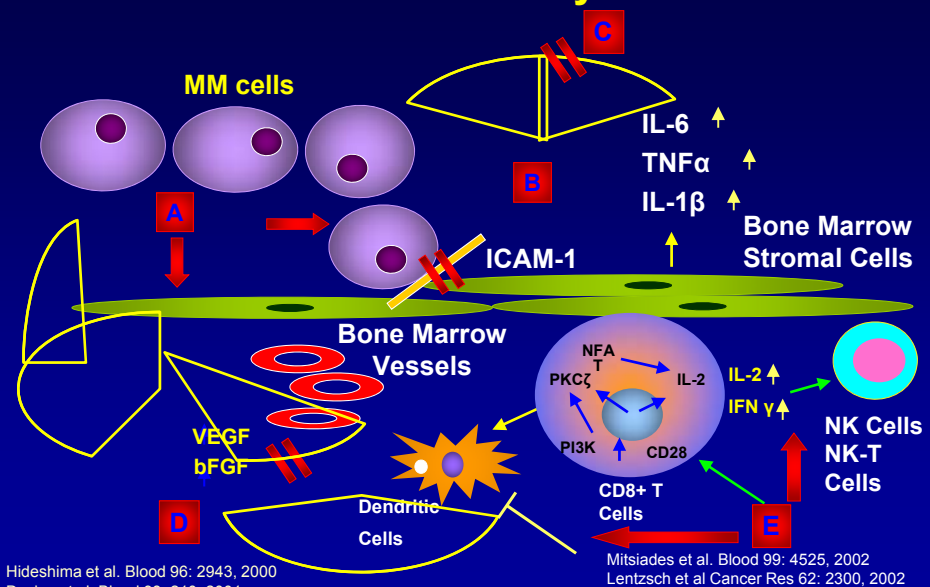

Kenneth Anderson
MD
FACULTY


Historical Perspective of Multiple Myeloma Therapies
Oral melphalan and prednisone
High-dose melphalan
VAD
ABMT
High-dose dexamethasone
Bisphosphonates
High-dose therapy with autologous stem cell support
Thalidomide
Proteasome inhibitors
Other immuno-modulatory agents
1962
1983
1984
1986
1996
1999
2000+


Targeting Growth, Survival, and Drug Resistance of MM in BM Microenvironment
MM
migration
SC
PKC
Akt
GSK-3β
FKHR
Caspase-9
NF-κB
mTOR
Bad
Survival
Anti-apoptosis
Cell cycle
PI3-K
CD40
FGFR3
CS1
BAFF-R
VEGFR
Cell surface targets
JAK/STAT 3
Bcl-xL
Mcl-1
Survival
Anti-apoptosis
Raf
MEK/ERK
proliferation
NF-κB
Bcl-xL
IAP
Cyclin-D
Survival
Anti-apoptosis
Cell cycle
Cytokines
IL-6, VEGF
IGF-1, SDF-1α
BAFF, APRIL
BSF-3
TNFα
TGFβ
VEGF
MEK/ERK
p27Kip1
Proliferation
Anti-apoptosis
Smad, ERK
cytokines
NF-κB
adhesion molecules
Adhesion
BMSC
ICAM-1
LFA-1
MUC-1
VCAM-1
Fibronectin
VLA-4
Hideshima T and Anderson KC. Nat Rev Cancer 2007,


Mechanisms Mediating Anti-MM Activity of Bortezomib
ER-Stress Induction
Caspase-12 cleavage;
↑ phospo-PERK;
↑ GADD-153, ATF4, GRP 78, & XBP-1 splicing
Anti-Angiogenic & Anti-Osteoclastic Actvity
↓ Migration, VEGF, Proangiogenic MMP-9, & Caveolin-1;
↓Osteoclastogenesis *via* MIP1α, BAFF
↑ Osteoblast formation
Apoptosis
↑ JNK; Caspases & PARP cleavage;
↑ ROS; ↓ ΔΨm
↑ Cyto-c & Smac release; ↓ IAPs;
↑ mitochondrial Ca+2 influx;
↑ Bid cleavage, Fas & FasL, BH-3 only proteins: Bim, Bik, & NOXA
Growth & Survival
↓NF-κB, MAPK,JAK/STAT
↓IGF-1/IL-6. ↑ PI3K-Akt
Bortezomib
Heat Shock Proteins & DNA Repair
↑ Heat Shock Proteins-27, -70, 90;
↓ DNA-PK
Microenvironment
↓ MM-BMSC's interaction;
↓ ICAM, VCAM, αVβ3
↓IGF-1, IL-6, BAFF,RANKL
Proteasome
↓ Chymotrypsin- and Caspase-like proteasome activities;
↑ Mono-ubiquitination;
↑ 26S Proteasome subunits
Cell-Cycle
Cdk inhibitors:
↑ P21 & p27, p53
Cyclins: D1, E1, A, B.

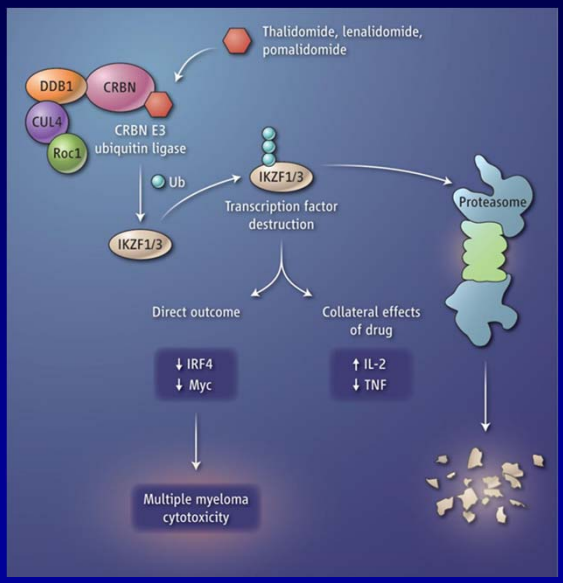
Lenalidomide in Myeloma



Hideshima et al. Blood 96: 2943, 2000
Davies et al. Blood 98: 210, 2001
Gupta et al. Leukemia 15: 1950, 2001

Mitsiades et al. Blood 99: 4525, 2002
Lentzsch et al Cancer Res 62: 2300, 2002
LeBlanc R et al. Blood 103: 1787, 2004
Hayashi T et al. Brit J Hematol 128: 192, 2005

Mechanism of Action of Immunomodulatory Drugs



Kronke et al, Science, 2014

Lu et al, Science, 2014

Integration of Novel Therapy Into Myeloma Management

Bortezomib, Lenalidomide, Thalidomide, Doxil, Carfilzomib, Pomalidamide

Target MM in the BM microenvironment to overcome conventional drug resistance in vitro and in vivo

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

Nine FDA approvals and median survival prolonged from 3-4 to 6-7 years, with additional prolongation from maintenance

New approaches needed to treat and ultimately

Bortezomib, Lenalidomide and Dex Therapy

Lenalidomide induces caspase 8 mediated apoptosis of MM cells in BM *in vitro* and *in vivo*; Dex (caspase 9) enhances response

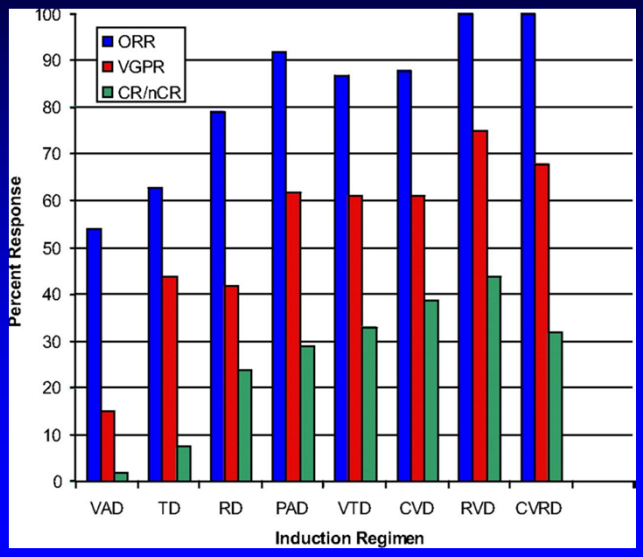
Synergistic MM cell toxicity of lenalidomide (caspase 8) with Bortezomib (caspase 9>8) *in vitro* and *in vivo* (dual apoptotic signaling)

Phase I-II trials show that majority (58%) of patients refractory to either agent alone respond to the combination

Phase I-II trials show 100% response with 74% CR/VGPR and 52% CR/nCR when used as initial therapy, including molecular responses.

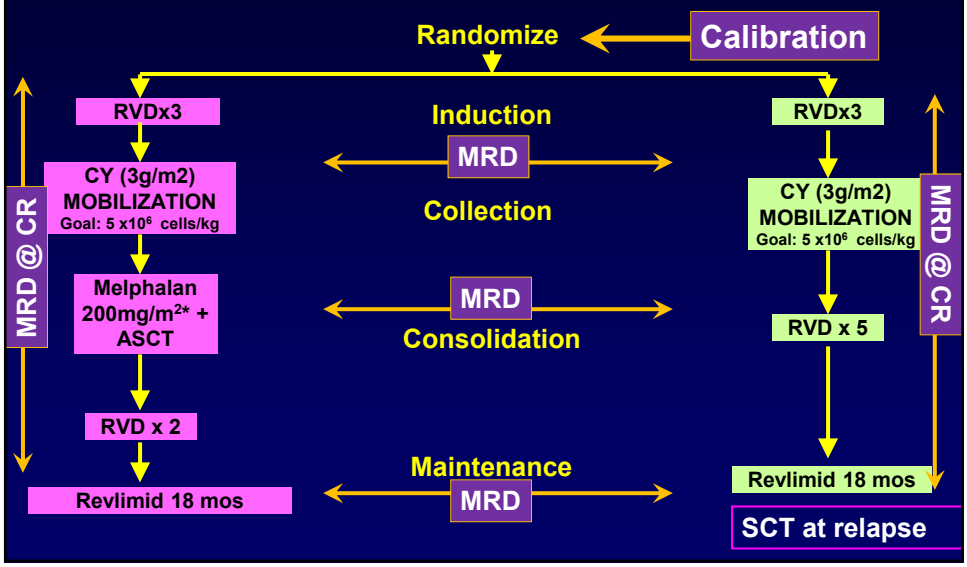
Richardson et al JCO 2009; 27:5713-19.
Richardson et al Blood 2010; 116:679-86.

Combinations in the Upfront Treatment of MM



Stewart AK, Richardson PG, San Miguel JF *Blood* 2009

IFM/DFCI 2009 Study
Newly Diagnosed MM (N=1,000)

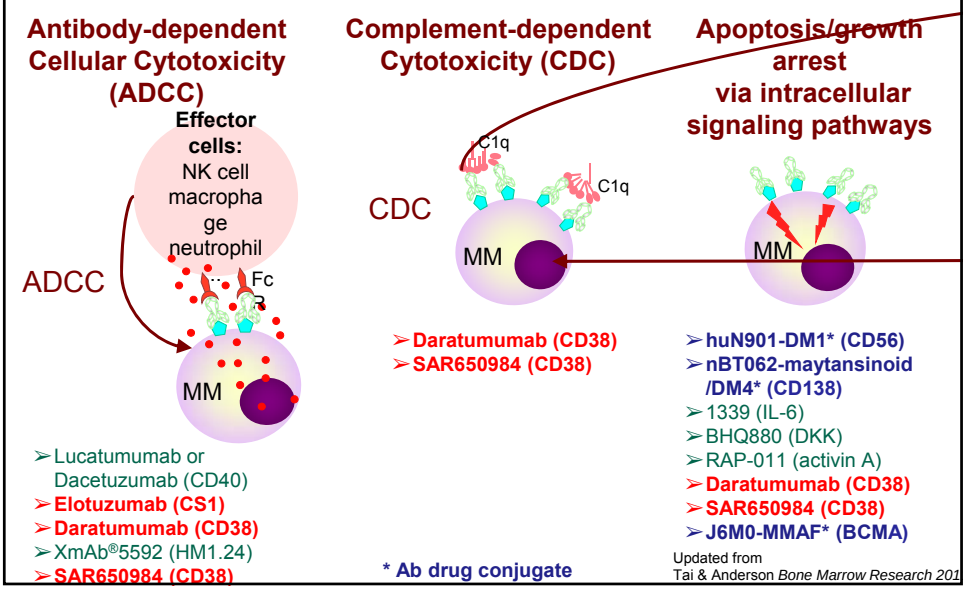


Current and Future Directions

1. immune therapies
1. Targeting the myeloma microenvironment
1. Targeting protein degradation
4. Targeting the myeloma epigenome
5. Targeting the myeloma genome

Myeloma will be a chronic illness, with sustained CR in a significant fraction of patients.

MAb Based Therapeutic Targeting of MM



- Lucatumumab or Dacetuzumab (CD40)
- **Elotuzumab (CS1)**
- **Daratumumab (CD38)**
- XmAb®5592 (HM1.24)
- **SAR650984 (CD38)**

- **Daratumumab (CD38)**
- **SAR650984 (CD38)**

- **huN901-DM1* (CD56)**
- **nBT062-maytansinoid /DM4* (CD138)**
- 1339 (IL-6)
- BHQ880 (DKK)
- RAP-011 (activin A)
- **Daratumumab (CD38)**
- **SAR650984 (CD38)**
- **J6M0-MMAF* (BCMA)**

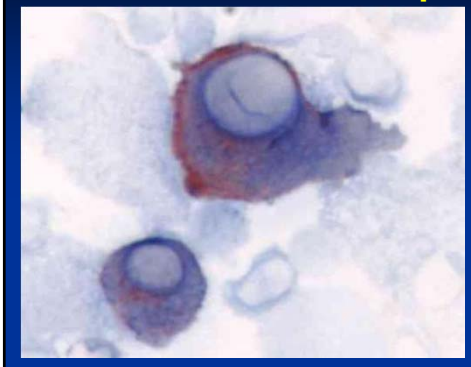
*** Ab drug conjugate**

Updated from
Tai & Anderson *Bone Marrow Research 201*

Iterative Bedside to Bench and Back Development of Elotuzumab and Lenalidomide Dexamethasone

- CS1 is highly and uniformly expressed at gene and protein level on patient MM cells
- Elotuzumab (Elo) is a humanized monoclonal antibody targeting CS1 in preclinical models
- Clinical trial of Elo in MM achieved stable disease
- ADCC activity of Elo against MM enhanced by lenalidomide (len) in preclinical models (Tai et al, Blood 2008)
- **Phase I/II trials: 80-90% response to len dex elo in relapsed MM, PFS >33 months**
- Phase III trial of len dex elo versus len dex ongoing in relapsed MM for new drug approval

Phase I Trial of Vaccination with DC/MM Fusions in Relapsed Refractory MM

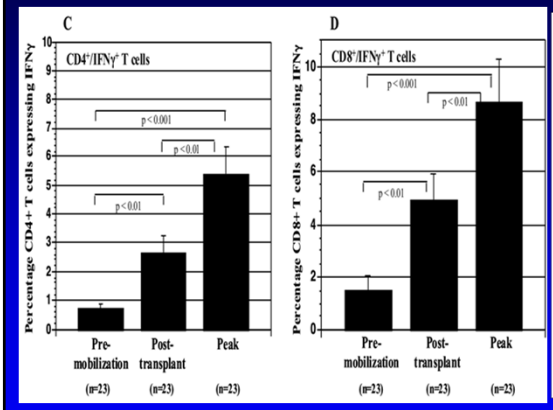


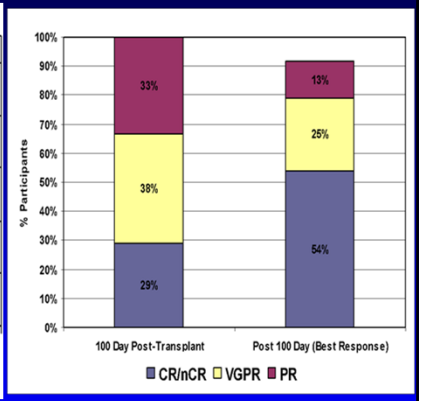
- DC/MM fusions induce anti-MM immunity in vitro and inhibit MM cell growth in vivo in xenograft models
  - Vasir et al. Brit J Hematol 2005; 129: 687-700

- Well tolerated, no autoimmunity
- Induced tumor reactive lymphocytes in a majority of patients
- Induced humoral responses to novel antigens (SEREX analysis)
- Disease stabilization in 70% of patients

Rosenblatt et al Blood 2011; 117:393-402.

Background: MM/DC Vaccination following Autologous PBSCT for Myeloma

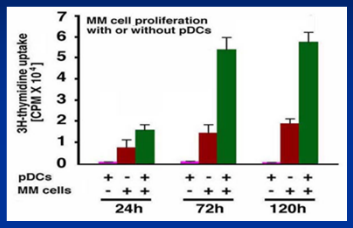


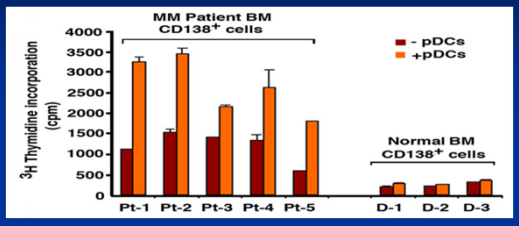


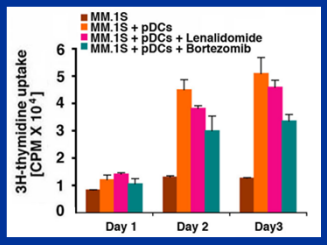
Rosenblatt et al, CCR 2013; 19: 3640-8.

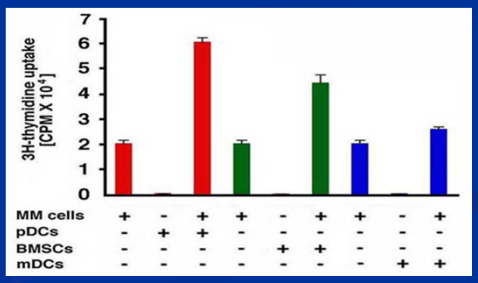
CTN Randomized trial of lenalidomide with or without vaccine posttransplant this year
Avigan et al

Plasmacytoid DCs Promote Growth, Survival, and Drug-Resistance in Myeloma



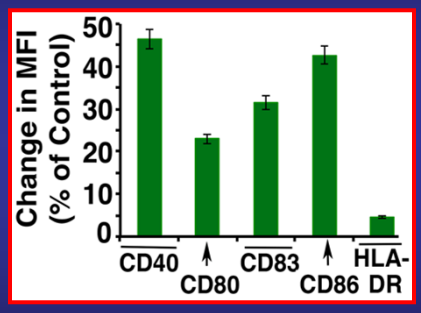


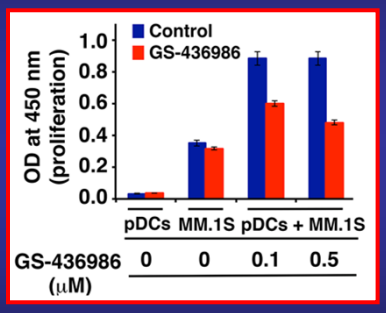




Chauhan et al: Cancer Cell 2009; 16: 1-15

Targeting TLR-7 with GS-4369869 Triggers pDCs Maturation and Blocks pDC-induced MM Cell Growth

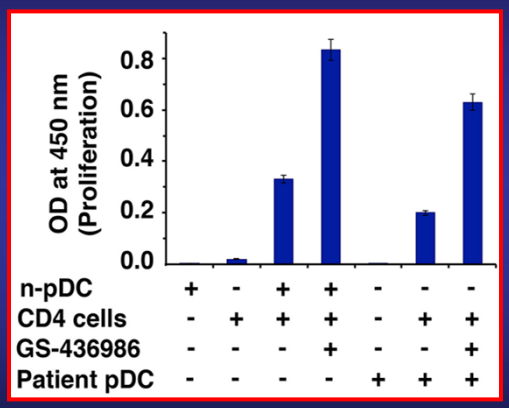


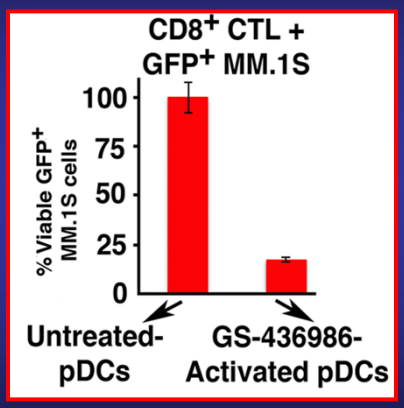


Phase I Clinical Trial

Chauhan et al, 2014

Targeting TLR-7 with GS-4369869 Triggers MM-specific CTL Activity

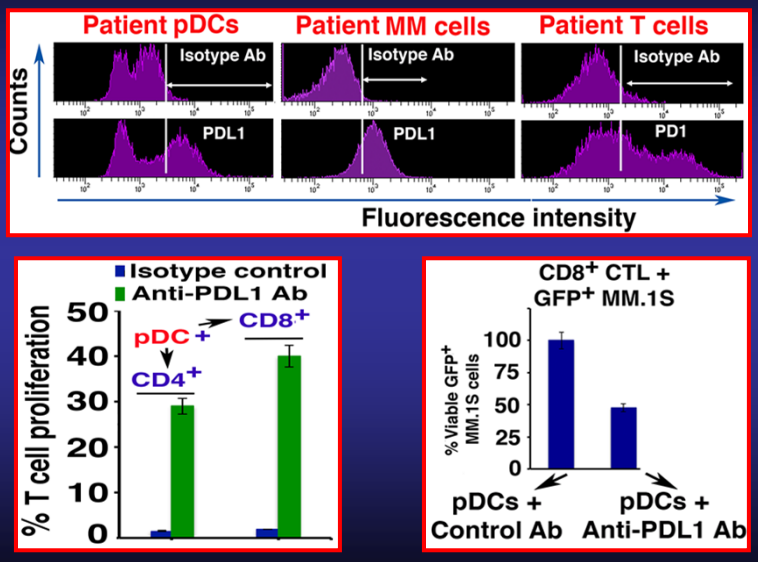




Phase I Clinical Trial

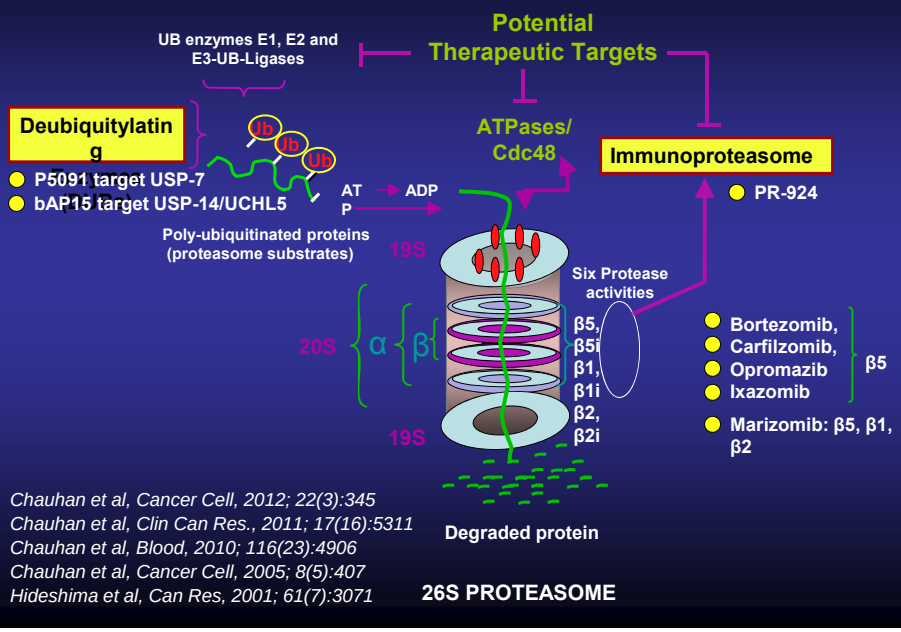
Chauhan et al, 2014

Targeting PD1-PDL1 Immunologic Checkpoint in pDC-T Cell and pDC-MM Cell Interactions



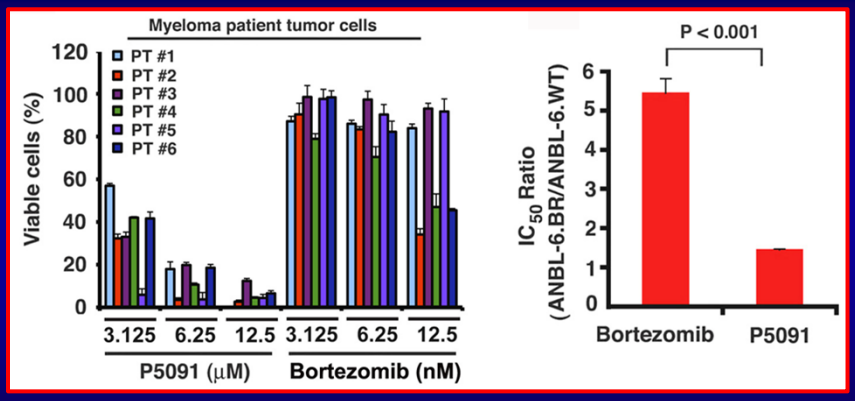
Chauhan et al, 2014

Targeting Ubiquitin Proteasome System



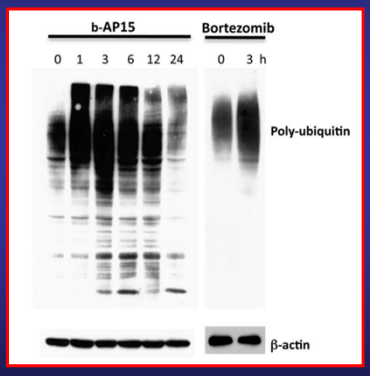
Chauhan et al, Cancer Cell, 2012; 22(3):345
Chauhan et al, Clin Can Res., 2011; 17(16):5311
Chauhan et al, Blood, 2010; 116(23):4906
Chauhan et al, Cancer Cell, 2005; 8(5):407
Hideshima et al, Can Res, 2001; 61(7):3071

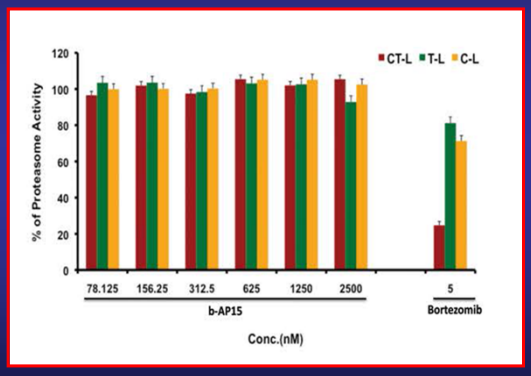
P5091 Overcomes Bortezomib-Resistance in Patient MM cells and Cell Lines



Chauhan et al, Cancer Cell 2012; 22: 345-58.

b-AP15, a Novel USP14/UCHL5 Inhibitor, Induces Polyubiquitination Without Blocking Proteasome Catalytic Activities

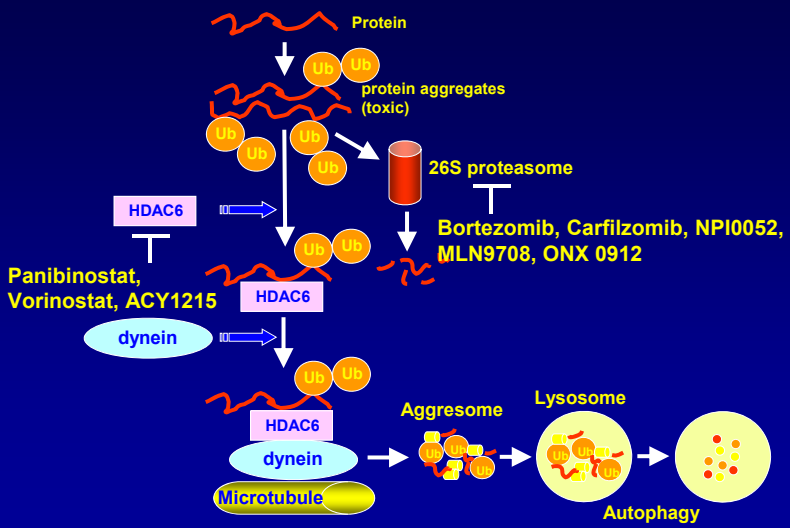




Clinical Trial in Relapsed /Refractory MM

Tian et al. Blood 2014; 123: 706-16

Development of Rationally-Based Combination Therapies (HDAC and Proteasome Inhibitors)



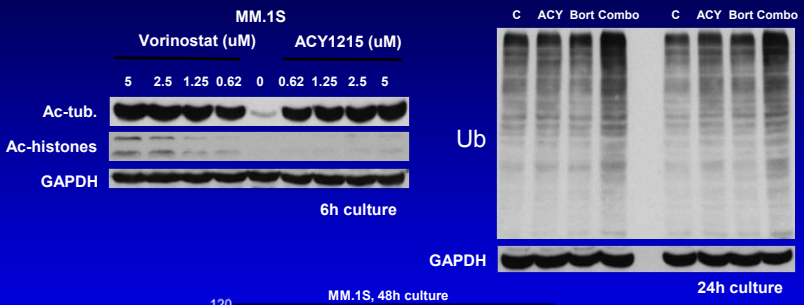
Hideshima et al. *Clin Cancer Res*. 2005;11:8530.Catley et al. *Blood*. 2006;108:3441-9.

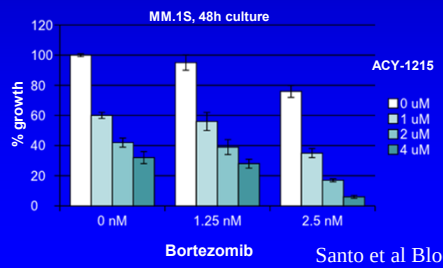
PANORAMA 1: A Randomized, Double-Blind, Phase 3 Study of Panobinostat or Placebo Plus Bortezomib and Dexamethasone in Relapsed or Relapsed and Refractory Multiple Myeloma

- Improvement in median PFS of 4 mos w/o difference in ORR or OS
  - Two-fold increase in nCR/CR rate (28% vs 16%)
- Higher rate of Grade ¾ diarrhea (25.5% vs 8%), fatigue (23.0% vs 11.9%), thrombocytopenia (67.4% vs 31.4%), and leucopenia (34.5% vs 11.4%), discontinuation due to AE (33.6% vs 17.3%).
- Confirms the efficacy of PAN-BTZ-Dex observed in heavily pretreated, BTZ-refractory pts (PANORAMA 2): ORR: 34.5%; CBR: 52.7%; median PFS: 5.4 mos; median OS: 17.5 mos[1,2]
- Need for less toxic more selective HDACi that can be given with PI to exploit synergistic cytotoxicity.

1. Richardson PG, et al. Blood. 2013;122:2331-2337
2. Richardson PG et al. Blood 2013; 122:Abstract 1970

HDAC6 Selective Inhibitor ACY-1215 (Ricolinostat) Enhances Bortezomib-Induced Cytotoxicity





Santo et al Blood 2012;119:2579-89

ACY1215 Alone and With Bortezomib in Relapsed/Refractory MM

- **Monotherapy**
  - 6/15 patients had stable disease (SD) as their best response.
- **Combination with bortezomib and dexamethasone**
  - 20/22 were evaluable for response assessment in six combination cohorts

Raje et al, ASH 2013

  - Overall response rate (≥PR): 25% in heavily pretreated patients
  - 5 patients withdrew after one cycle and 3 had progressive disease after 2 cycles
  - Clinical benefit rate (≥SD): 60%
  - 6/10 patients refractory to bortezomib had ≥SD (1 VGPR, 1 MR, 4 SD)
  - Responding patients have been on study 2 to 16 cycles
  - All 3 patients treated 240 mg QD cohort had MR or better

VGPR	2
PR	3
MR[1]	2
SD	5

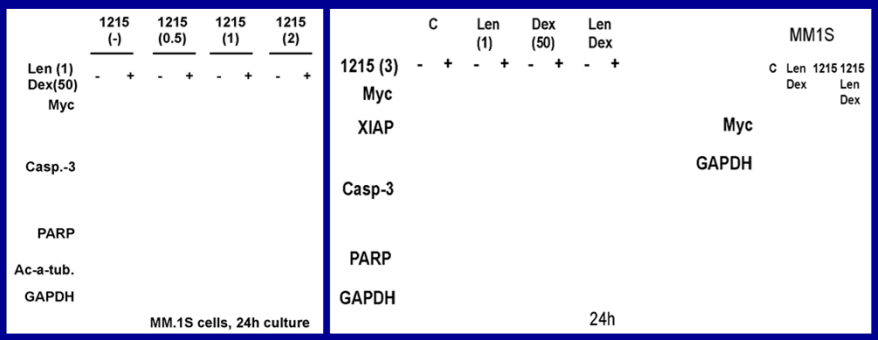
Monotherapy response data from Final CSR. Combination response data pulled from live database Nov 8, 2013

[1] One patient had a 26% decrease in M Protein after Cycle 2 and withdrew after two subsequent cycles with SD

MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

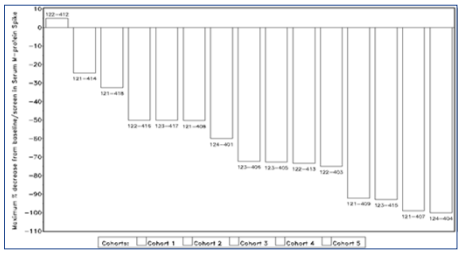
ACY-1215, Lenalidomide and Dexamethasone Inhibits c-Myc Expression

Hideshima et al, 2013



ACY-1215 in Combination with Len and Dex in Relapsed/Refractory MM

M protein % change



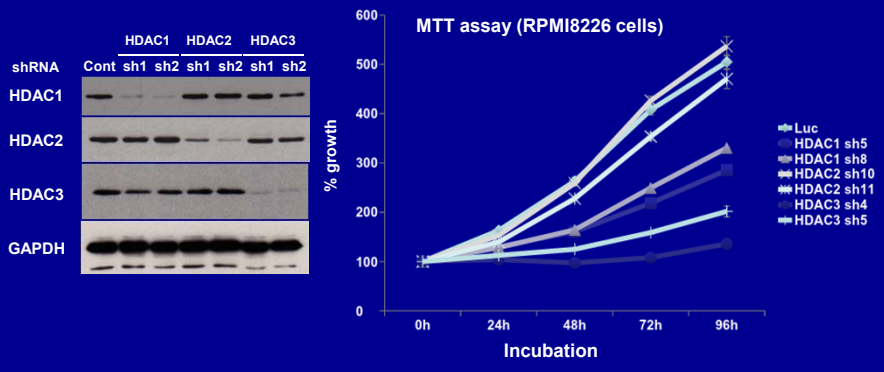
CR	1
VGPR	3
PR[1]	7
MR	2
SD	3

- 11/16 pts (69%) had PR or better
- 16/16 pts (100%) had clinical benefit (including MR and SD)

Yee, et al, ASH 2013

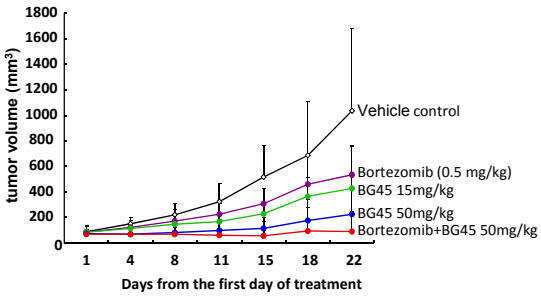
MASSACHUSETTS GENERAL HOSPITAL CANCER CENTER

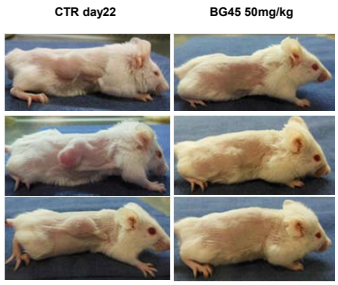
HDAC3 Knockdown Induces MM Cytotoxicity



Minami et al. Leukemia 2014;28: 680-9.

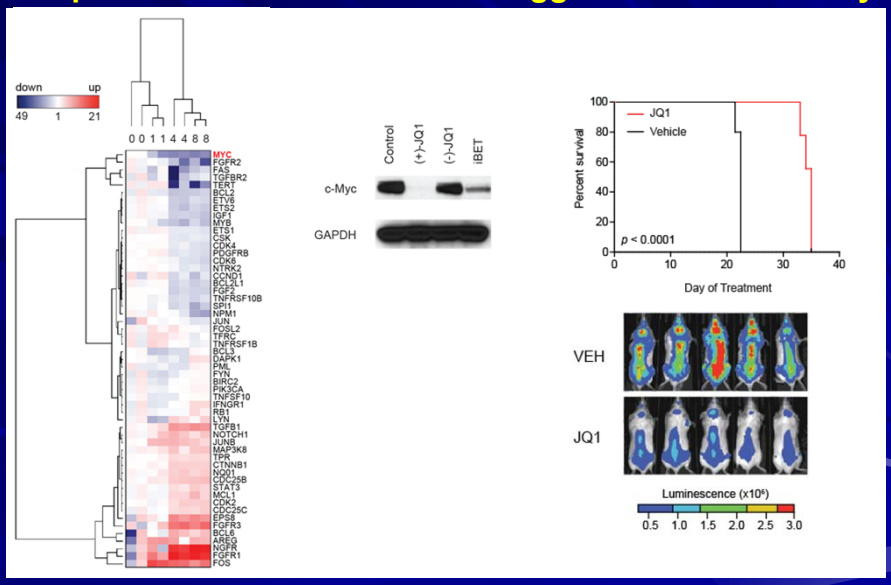
In Vivo Anti-MM Activity of HDAC 3 Inhibitor BG45





Minami et al. Leukemia 2014;28: 680-9

BET Bromodomain Inhibition Suppresses c-myc Expression and Function and Triggers Anti-MM Activity



Clinical Trial Ongoing

Delmore JE., Issa GC, et al Cell 2011; 146:904.

Mutations in Myeloma

19 patients each with newly diagnosed and relapsed MM

Chapman et al Nature 2011; 471: 467-72.

- **Protein homeostasis**: 42% including FAM46C, RPL10, RPS6KA1, EIF3B, XBP1, LRRK2
- **NF-κB signaling:** 10 point mutations, 4 additional structural re-arrangements affecting coding
  Confers bortezomib sensitivity
- **Histone methylating enzymes:** WHSC1, UTX, MLL
- **BRAF:** 4% activating Single patient MM response

Andrulis et al Cancer Discovery 2013; 3: 862-9.

PSMB5 β5 proteasome subunit mutation confers proteasome inhibitor resistance in laboratory, not identified in clinic

Lichter et al Blood 2012: 120: 4513-16.

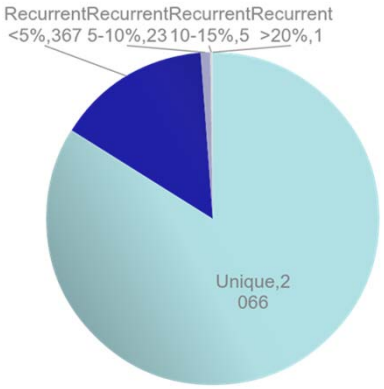
Heterogeneity of Somatic Variants

Total n. of genes found in screen	2462
Cancer Census* Genes	83
Non Cancer Census Genes	2379
Recurrent ≥2	396
Unique	2066

Non-synonymous variant recurrence

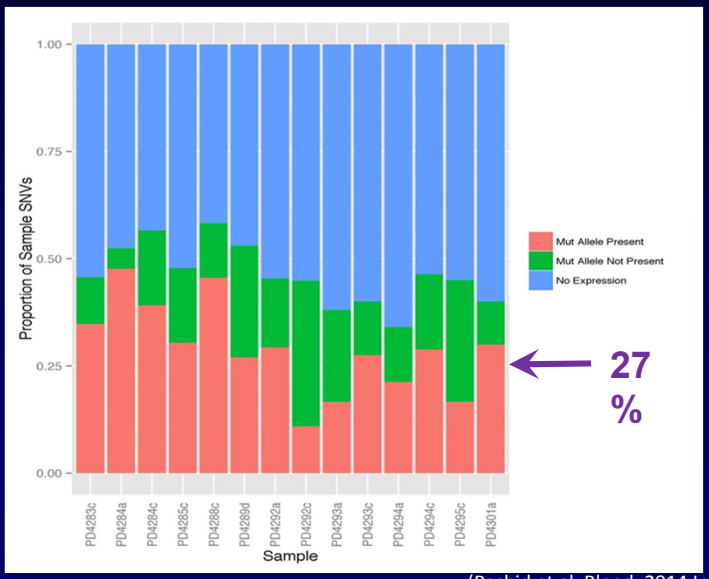
Gene	n. of cases	% recurrent
KRAS	16	23.9%
BRAF	9	21.4%
NRAS	8	11.9%
RYR2	8	11.9%
FSIP2	7	10.4%
TP53	7	10.4%
FAT4	5	7.5%
HMCN1	5	7.5%
DNAH5	5	7.5%
ZFHX4	5	7.5%
PEG3AS	5	7.5%
FLG	4	6.0%
PTPRZ1	4	6.0%
DNAH9	4	6.0%
GPR98	4	6.0%

Distribution of genes



*Futreal A.P. et al, Nat Rev Cancer (2004) 4,177-183

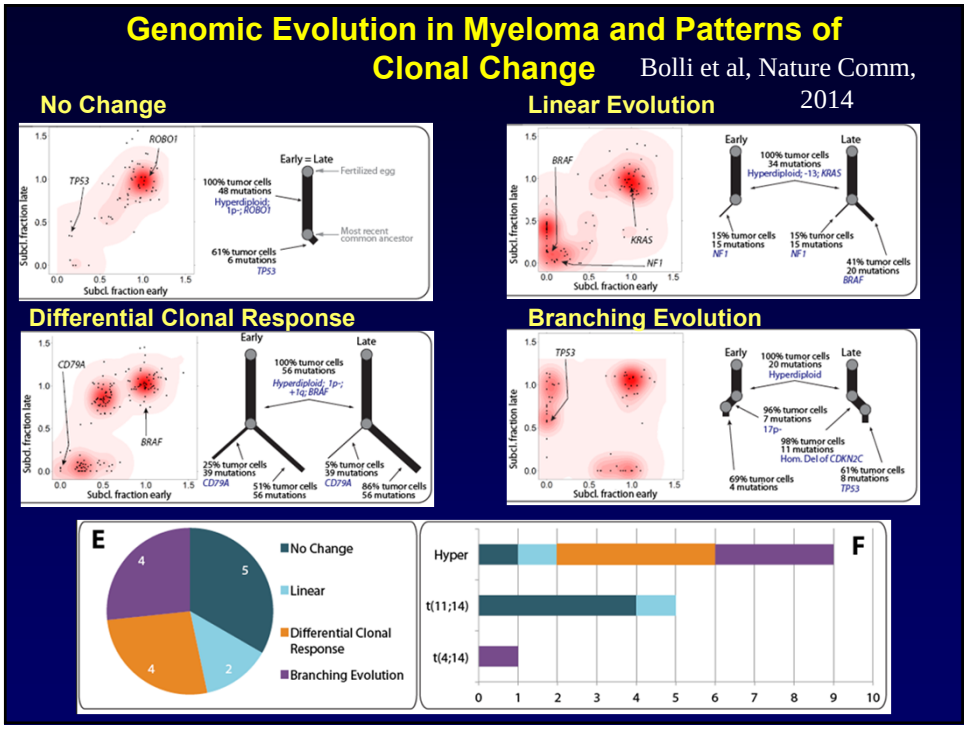
Limited Expression of Mutated Genes
What Mutations Are Relevant?



(Rashid et al. Blood, 2014 In Press)

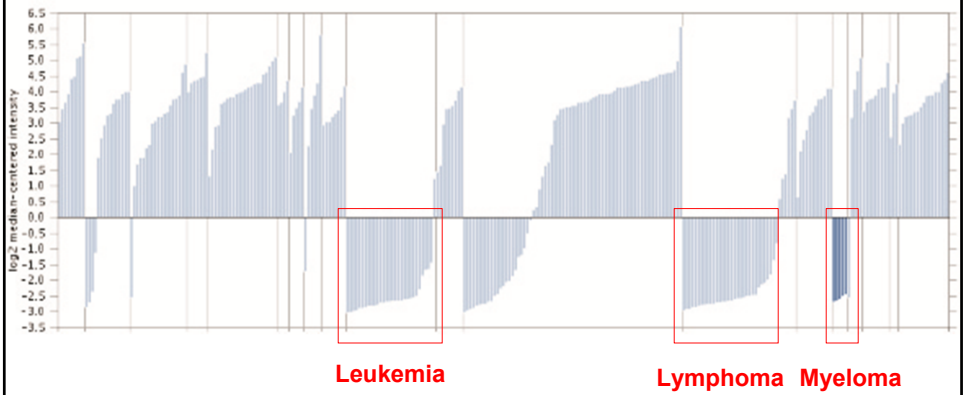
Genomic Evolution in Myeloma and Patterns of Clonal Change

Bolli et al, Nature Comm, 2014



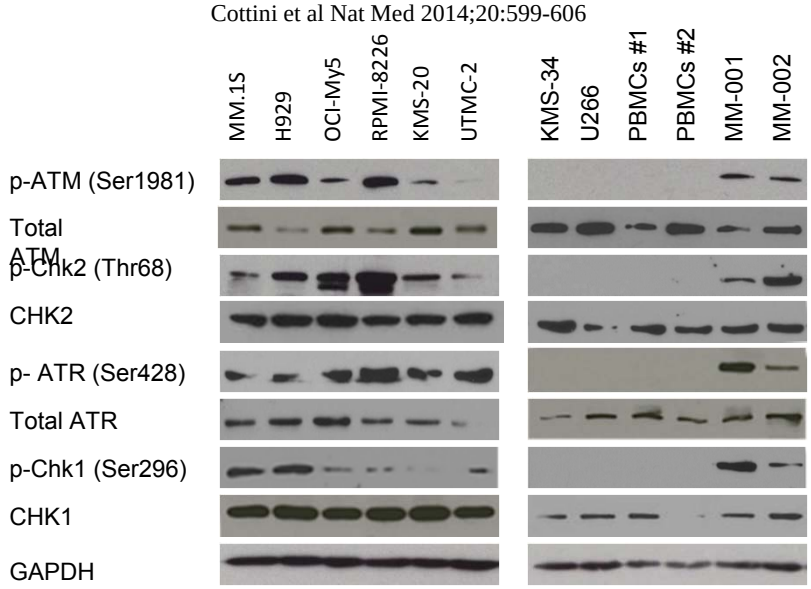
YAP1 low expression correlates with poor clinical outcome in hematological patients

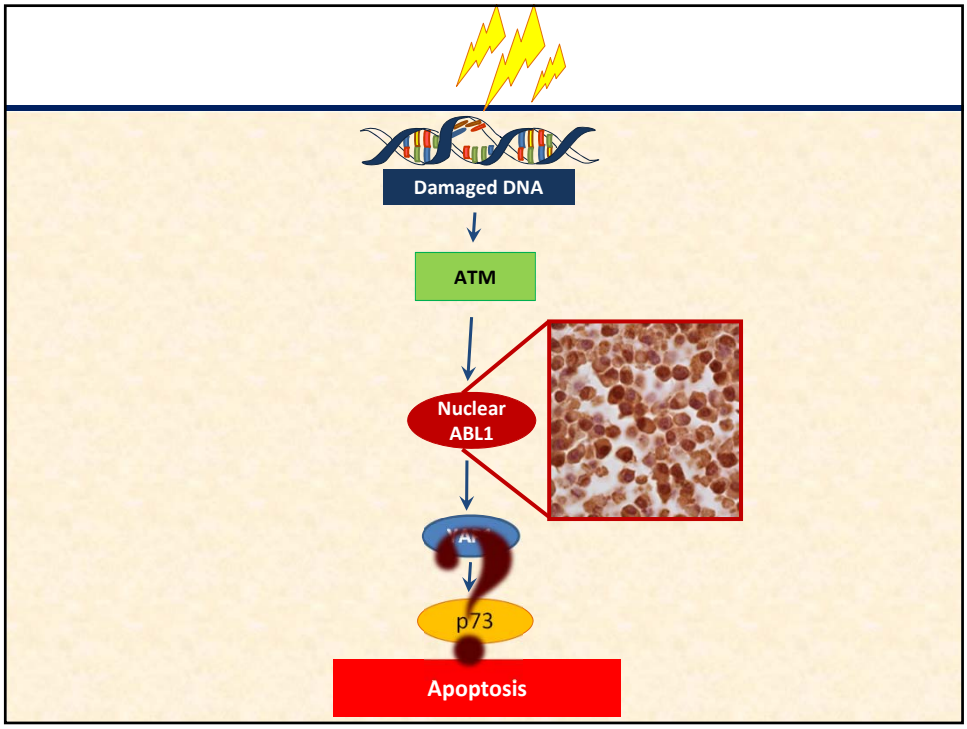
Cottini et al Nat Med 2014;20:599-606



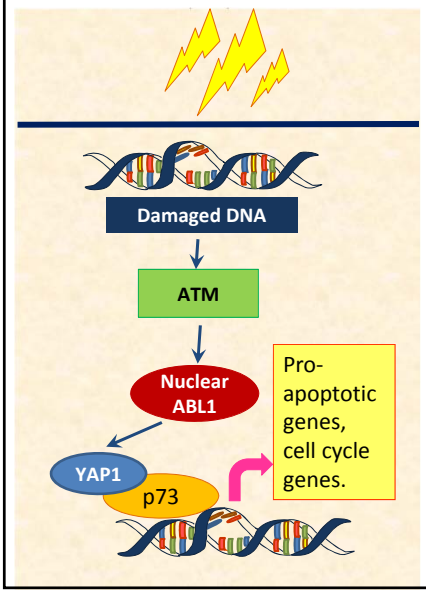
MM cells have DNA damage response (DDR) markers

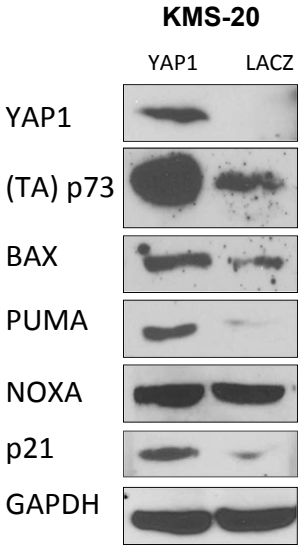
Cottini et al Nat Med 2014;20:599-606





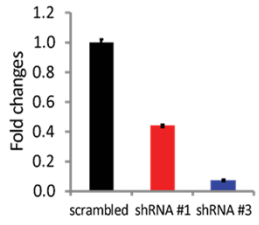
YAP1 overexpression induces p73 and p73-target genes

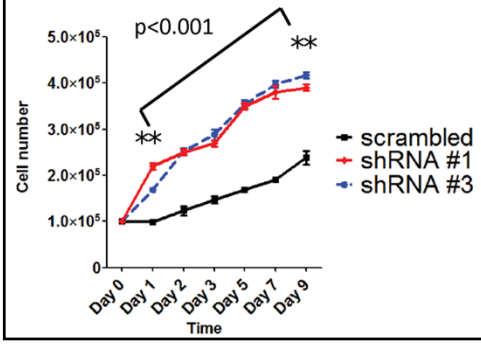


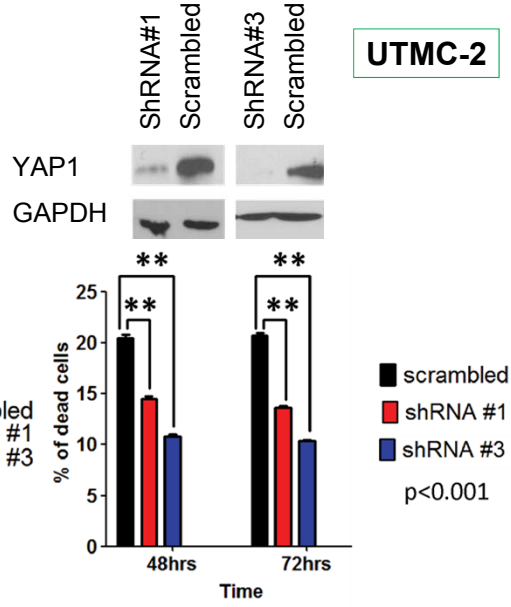


YAP1 silencing increases MM growth

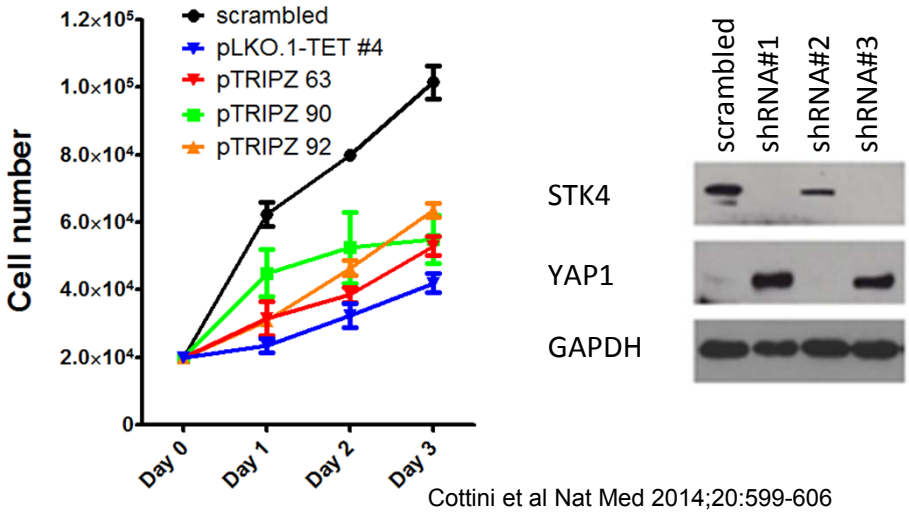
Cottini et al Nat Med 2014;20:599-606





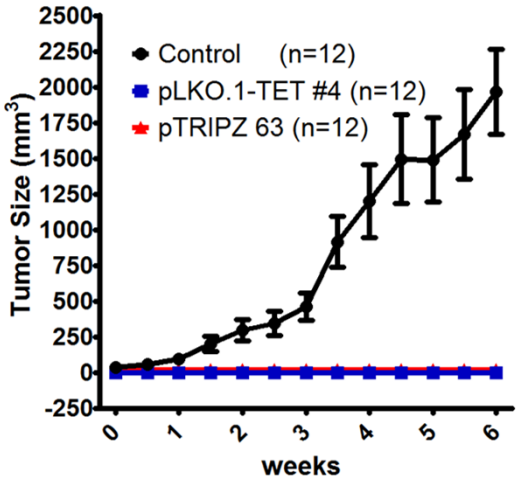


STK4 inhibition blocks MM growth in *in vitro* systems

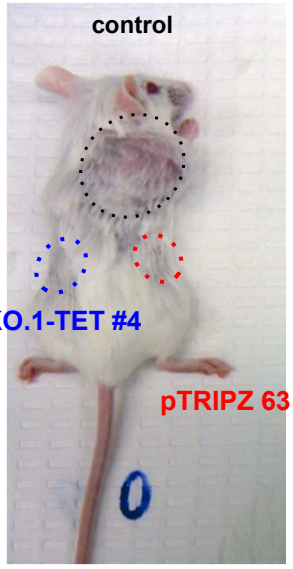


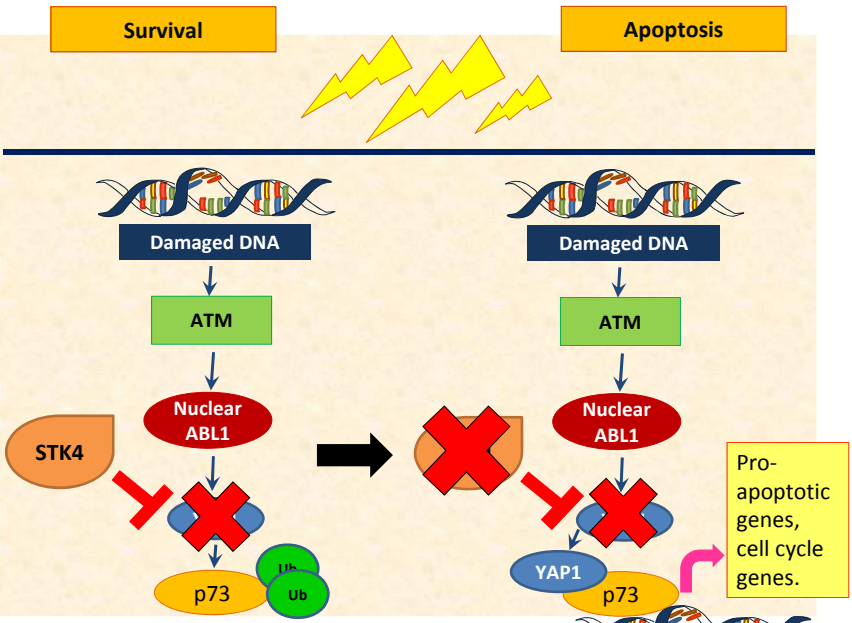
Cottini et al Nat Med 2014;20:599-606

STK4 silencing blocks MM growth in *in vivo* xenograft models



Cottini et al Nat Med 2014;20:599-606





Cottini et al Nat Med 2014;20:599-606

Current and Future Directions

1. immune therapies
1. Targeting the myeloma microenvironment
1. Targeting protein degradation
4. Targeting the myeloma epigenome
5. Targeting the myeloma genome

Myeloma will be a chronic illness, with sustained CR in a significant fraction of patients.

United Nations Against Myeloma:
Bench to Bedside Research Team

USA
Kenneth Anderson
Nikhil Munshi
Paul Richardson
Robert Schlossman
Irene Ghobrial
Steven Treon
Jacob Laubach
Deborah Doss
Kathleen Colson
Mary McKenney
Kim Noonan
Tina Flaherty
Kathleen Finn
Muriel Gannon
Stacey Chuma
Janet Kunsman
Diane Warren
Carolyn Revta
Andrea Freeman
Alexis Fields
Andrea Kolligian
John Feather
Farzana Masood
Nora Loughney
Heather Goddard
Tiffany Poon
Nicole Stavitzski
Ranjit Banwait
Shawna Corman
Heather Goddard
Meghan Marie Leahy
Caitlin O'Gallagher
Christina Tripsas
Karin Anderson
Shannon Viera
Katherine Redman
Amber Walsh
Samir Amin
Wanling Xie
Parantu Shah
Holly Bartel
Lisa Popitz
Jeffrey Sorrell

Japan
Teru Hideshima
Constantine Mitsiades
Dharminder Chauhan
Noopur Raje
Yu-Tzu Tai
Ruben Carrasco
James Bradner
Gullu Gorgun
Jooeun Bae
Francesca Cottini
Michele Cea
Antonia Cagnetta
Teresa Calimeri
Edie Weller
Ajita Singh
Ze Tian
Diana Cirstea
Yiguo Hu
Naoya Mimura
Jiro Minami
Sun-Yung Kong
Weihua Song
Douglas McMillin
Catriona Hayes
Steffen Klippel
Jana Jakubikova
Panisinee Lawasut
Niels van de Donk
Eugen Dhimolea
Jake Delmore
Hannah Jacobs
Masood Shammas
Mariateresa Fulciniti
Jianhong Lin
Jagannath Pal
Samantha Pozzi
Loredana Santo
Claire Fabre
Anuj Mahindra
Rao Prabhala
Jake Delmore
Puru Nanjappa
Michael Sellito
Avani Vaishnav

Canada

Germany

Austria

China

Greece

Taiwan

Turkey

Australia

Ireland

UK

India

Italy

Israel