New Drugs and Therapeutic Approaches

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Integration of Novel Therapy Into Myeloma Management

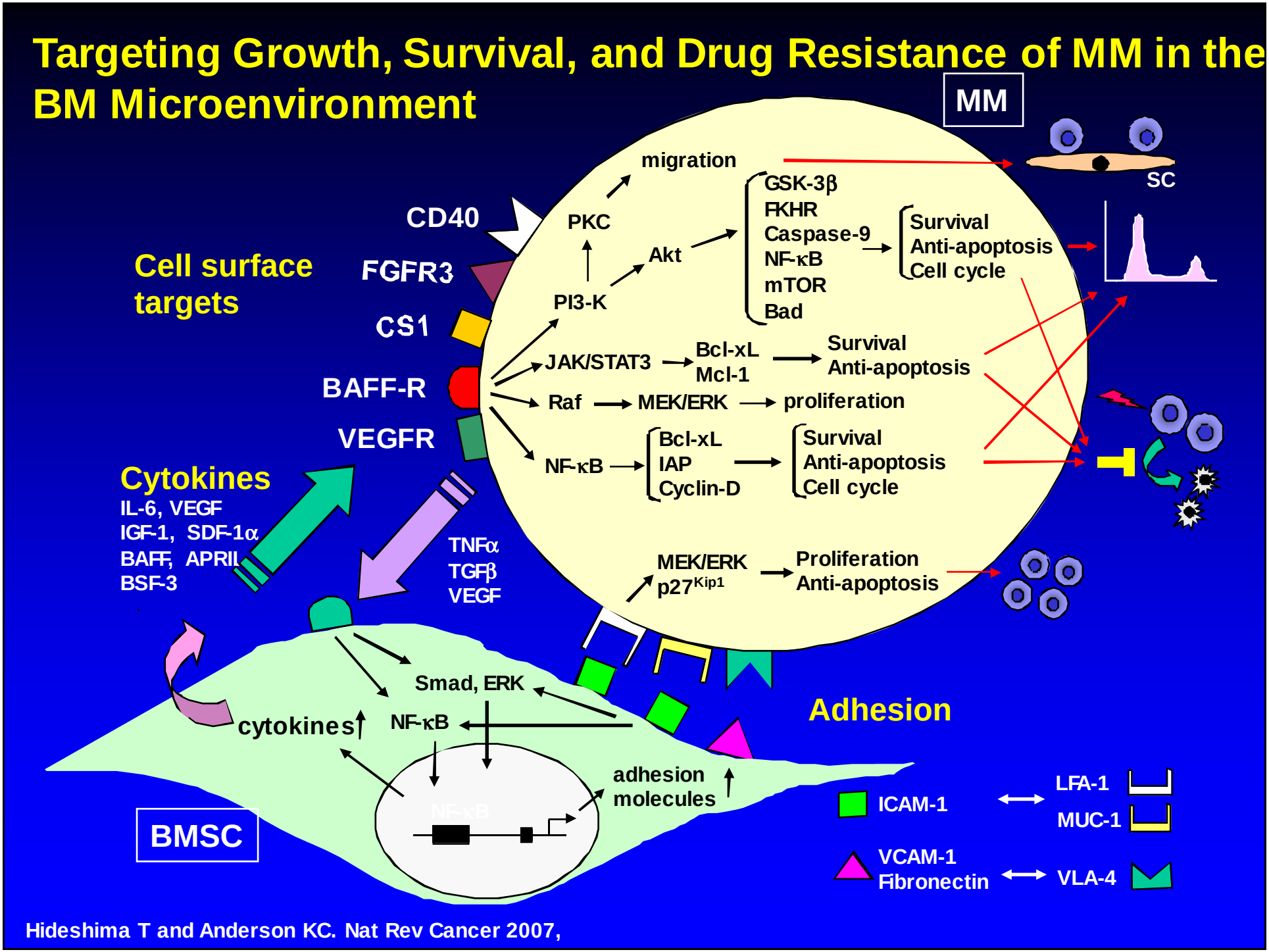
Bortezomib, Lenalidomide, Thalidomide, Doxil

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

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

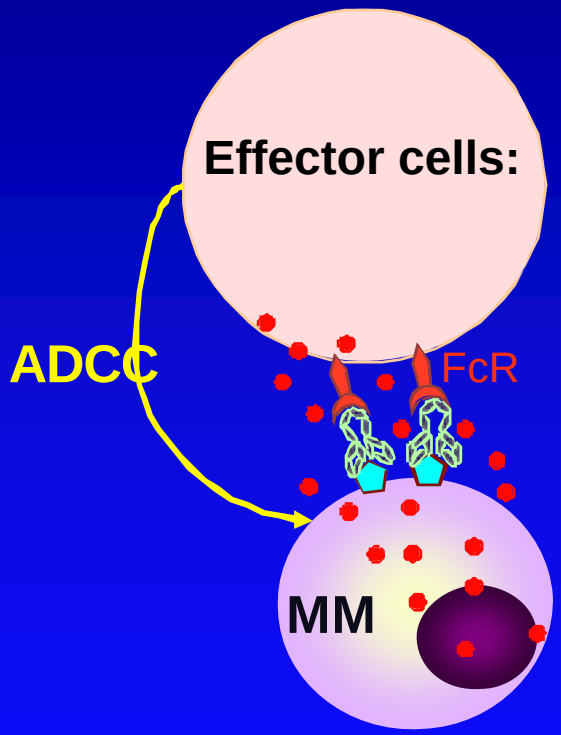
Targeting Growth, Survival, and Drug Resistance of MM in the BM Microenvironment



Hideshima T and Anderson KC. Nat Rev Cancer 2007,

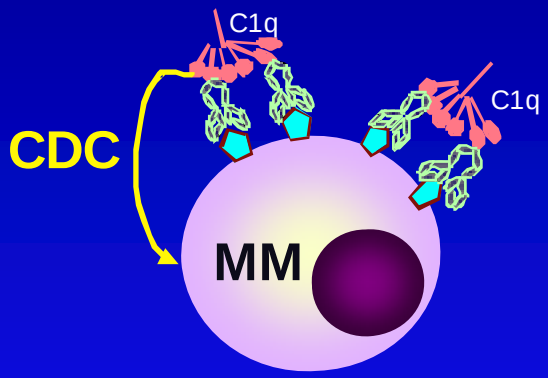
MAb-Based Therapeutic Targeting of Myeloma

Antibody-dependent Cellular cytotoxicity (ADCC)



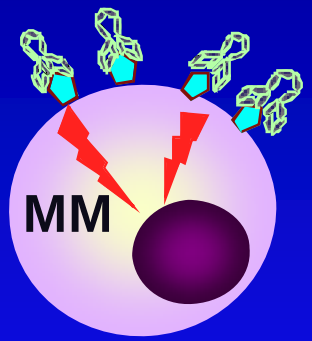
- Lucatumumab or Dacetuzumab (CD40)
- Elotuzumab (CS1)
- Daratumumab (CD38)
- XmAb 5592 (HM1.24)

Complement-dependent Cytotoxicity (CDC)



- Daratumumab (CD38)

Apoptosis/growth arrest via targeting signaling pathways



- huN901-DM1 (CD56)
- nBT062-maytansinoid (CD138)
- 1339 (IL-6)
- BHQ880 (DKK1)
- RAP-011 (activin A)
- Daratumumab (CD38)

Tai & Anderson Bone Marrow Research 2011

Elotuzumab Anti-CS MoAb in MM

- CS1 is highly and uniformly expressed on MM cells
- Elotuzumab (Elo) is a humanized monoclonal IgG1 antibody targeting CS1
- Clinical trial of Elo in MM achieved SD
- Anti-MM activity of Elo enhanced by lenalidomide (len) in preclinical models
- Phase I/II trials: 80-90% response to len dex elo in relapsed MM
- Phase III trial of len dex elo versus len dex in relapsed MM for new drug approval

- Hsi ED et al. Clin Cancer Res. 2008;14:2775-2784; Tai YT et al. Blood. 2008;112:1329-1337; Van Rhee F et al. Mol Cancer Ther. 2009;8:2616-2624; Lonial S et al. Blood. 2009;114:432; Richardson et al Blood 2010:864
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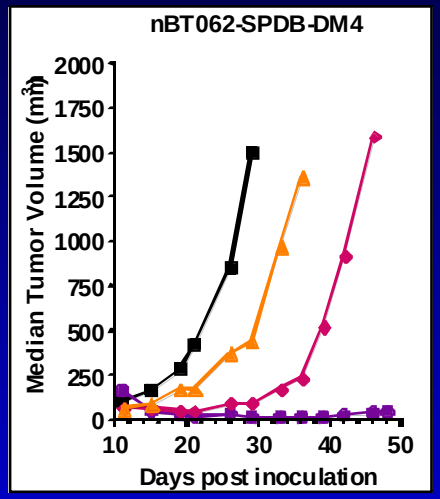
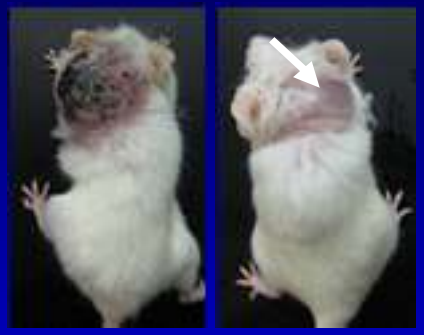
nBT062-SPDB-DM4 (CD 138 Immunotoxin) Inhibits Human MM Cell Growth In Vivo

A



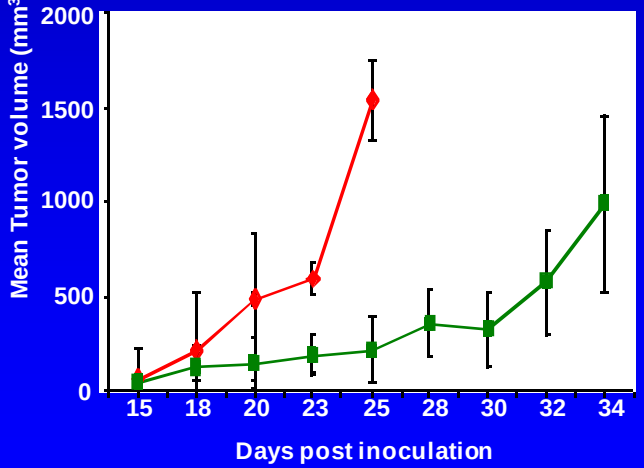
PBS
100ug/ml
250ug/ml
450ug/ml

B

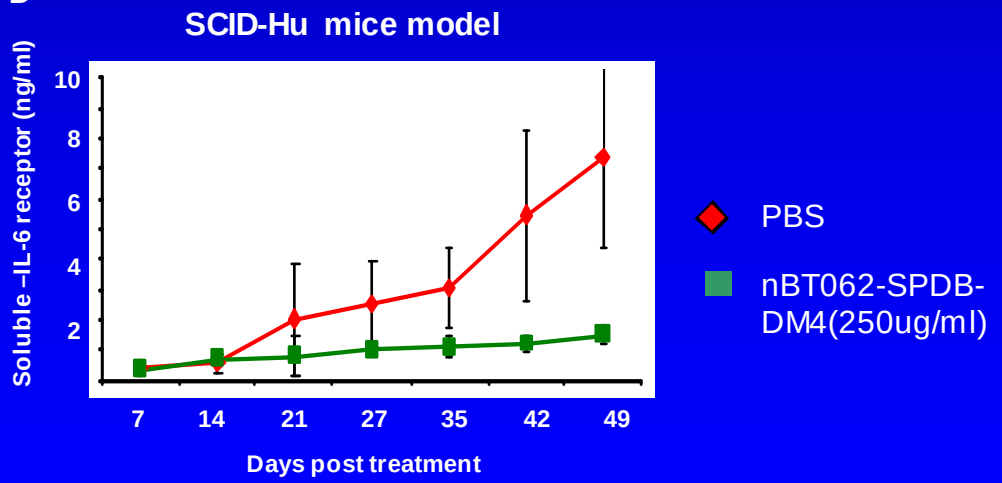


PBS BT062-SPDB-DM4

C



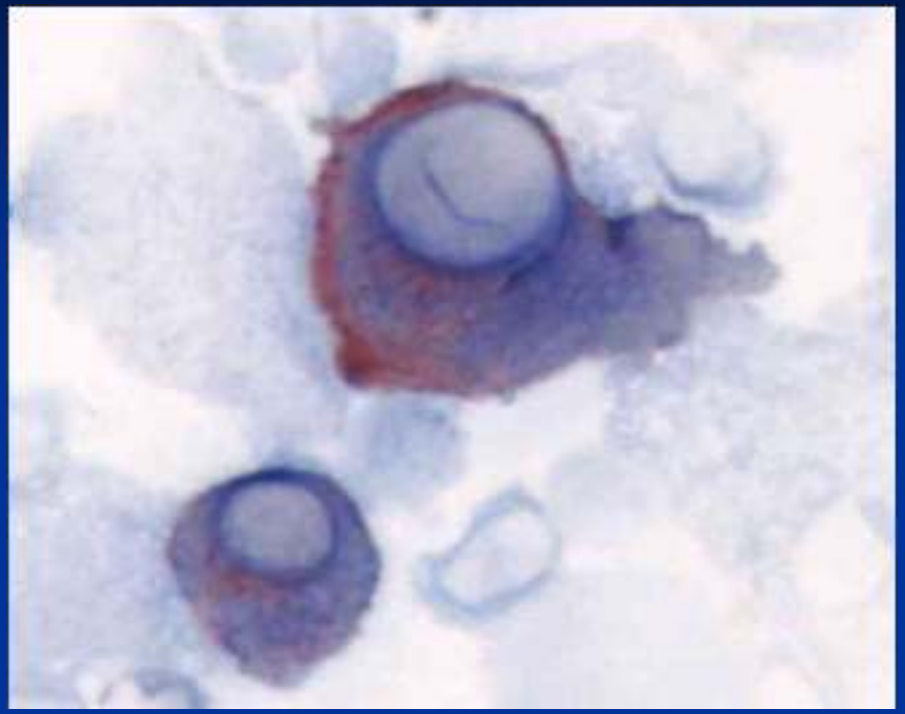
D



Clinical Trials Ongoing

Ikeda et al, Clin Can Res 2009; 15: 4028

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. BritJHematol 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.

Targeting TAAs with Cocktails of Specific Peptides

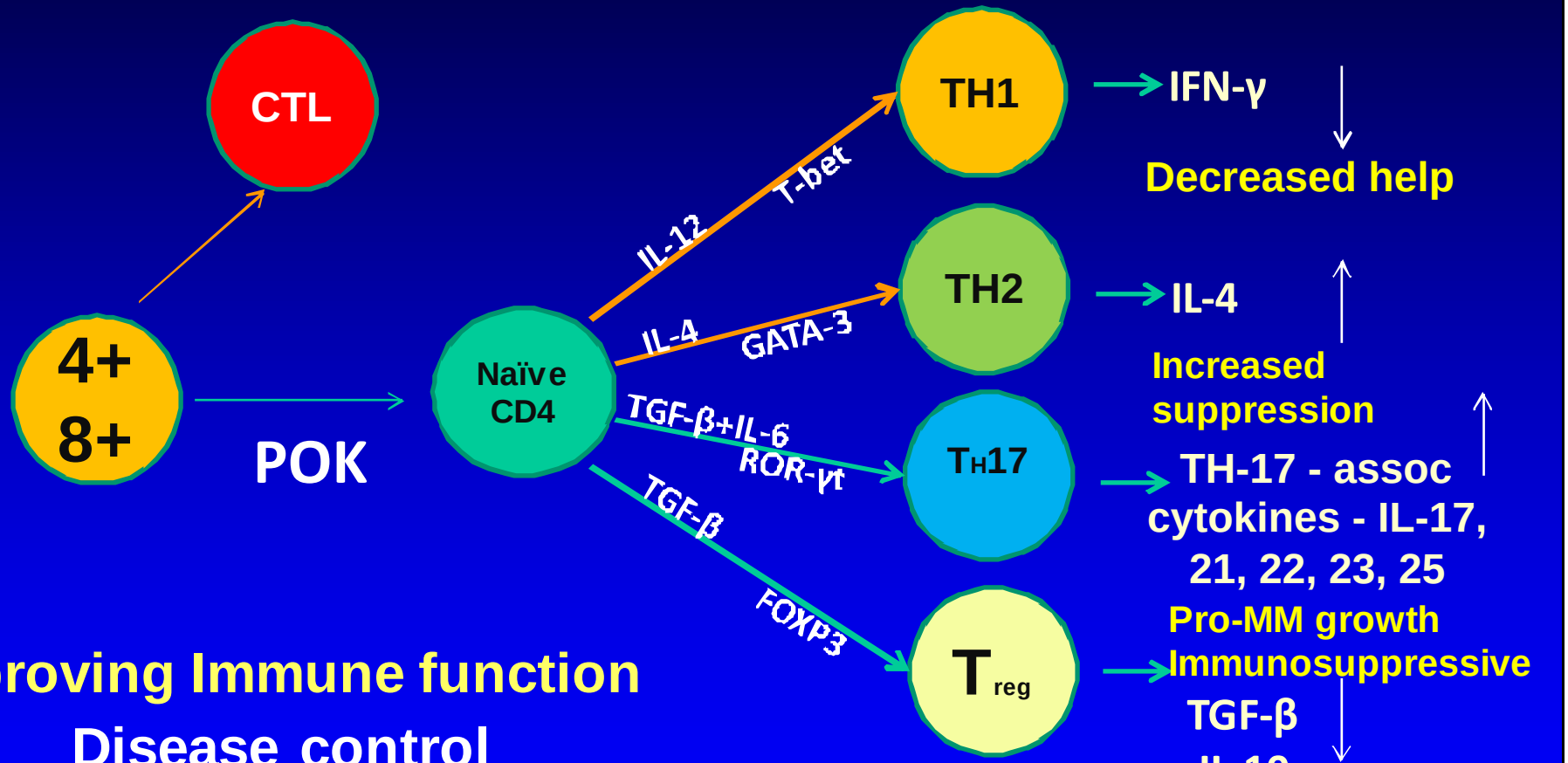
- Using immunogenic HLA-A2-specific XBP1, CD138, CS1 peptides to induce MM-specific and HLA-restricted CTL responses against several MM antigens

Polyfunctional responses: IFN-γ, cytotoxicity, proliferation, CD107a degranulation to primary MM cells and cell lines

Peptide-specific responses: Individual differences in specificity, more broad response to cocktail

Bae et al, Leukemia 2011, in press

Immune Dysfunction in Myeloma
TH Subset Abnormality

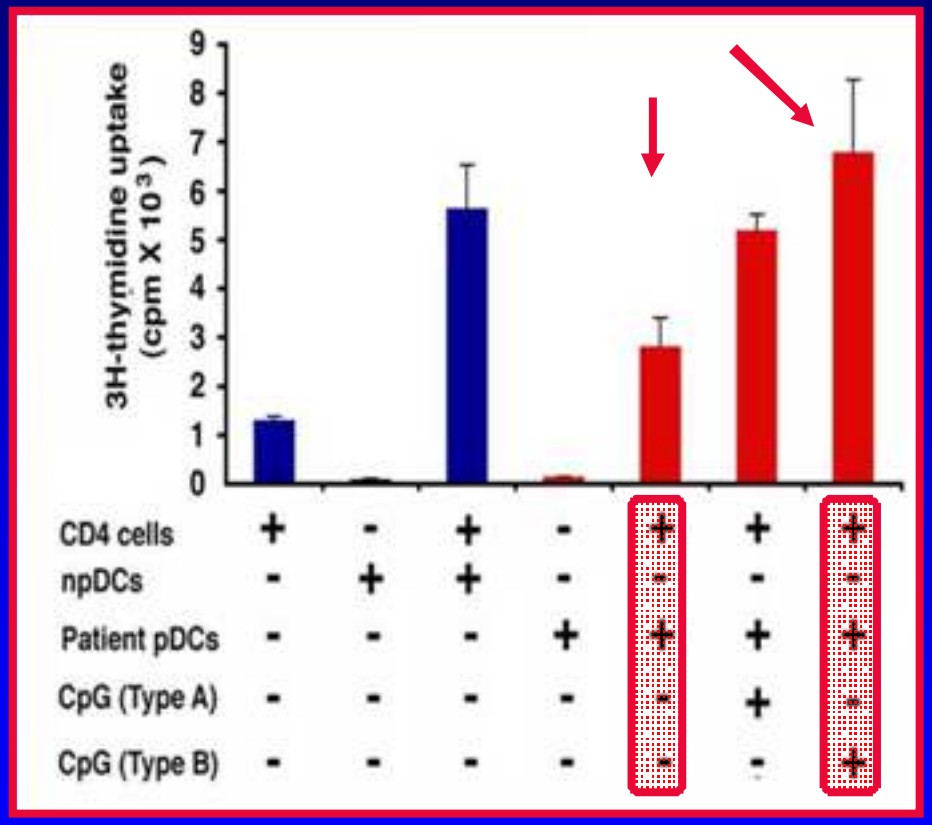


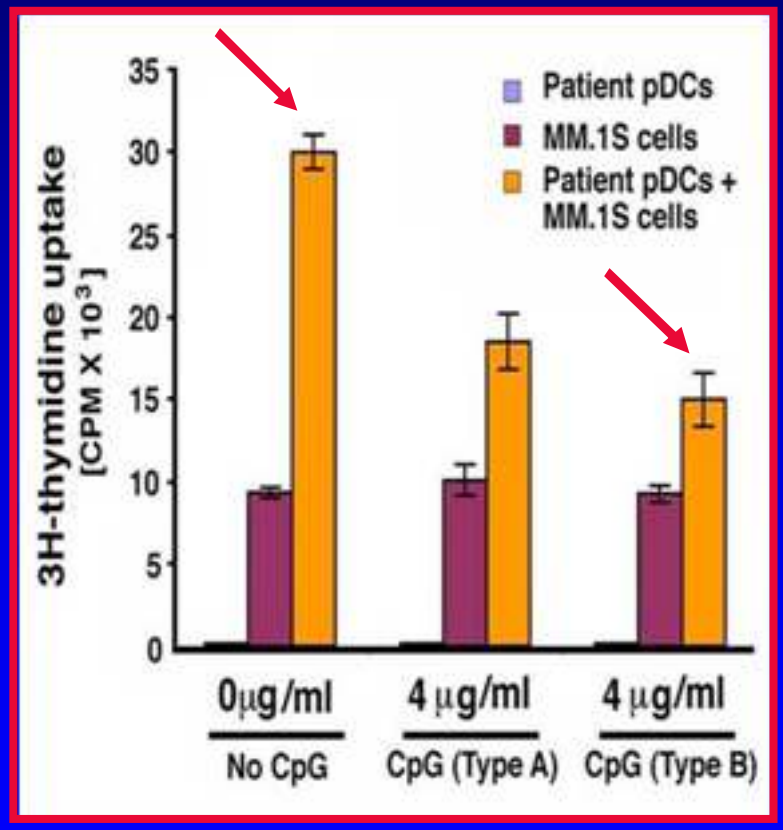
Improving Immune function

- Disease control
- Immune modulation: Lenalidomide, cpg
- Cytokine modulation: Anti-IL6, anti-IL-17

Rao et al, Blood 2010; in press.

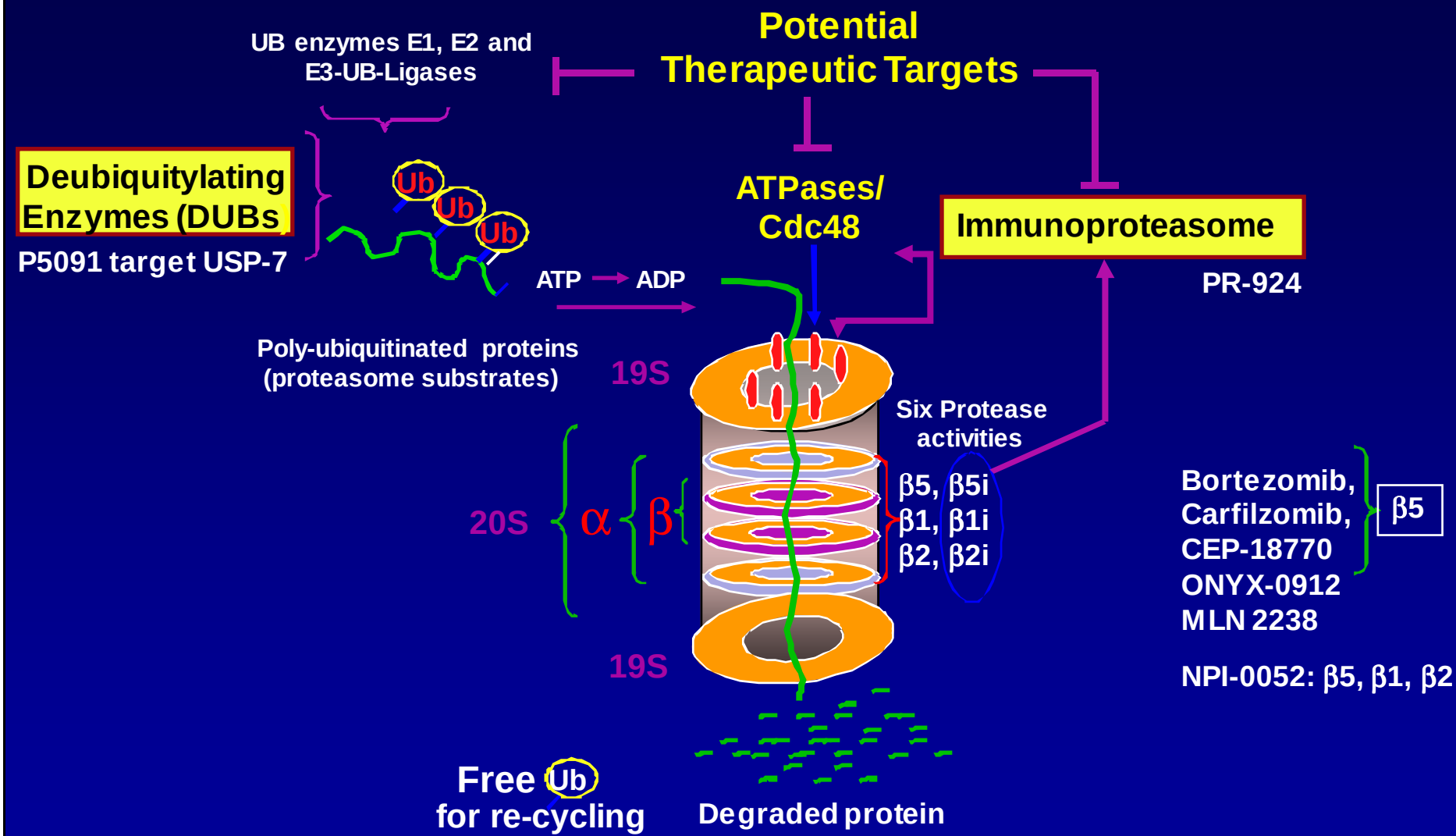
CpG ODNs Restore MM Patient-pDCs Immune Function and Block pDC-Induced MM Cell Growth



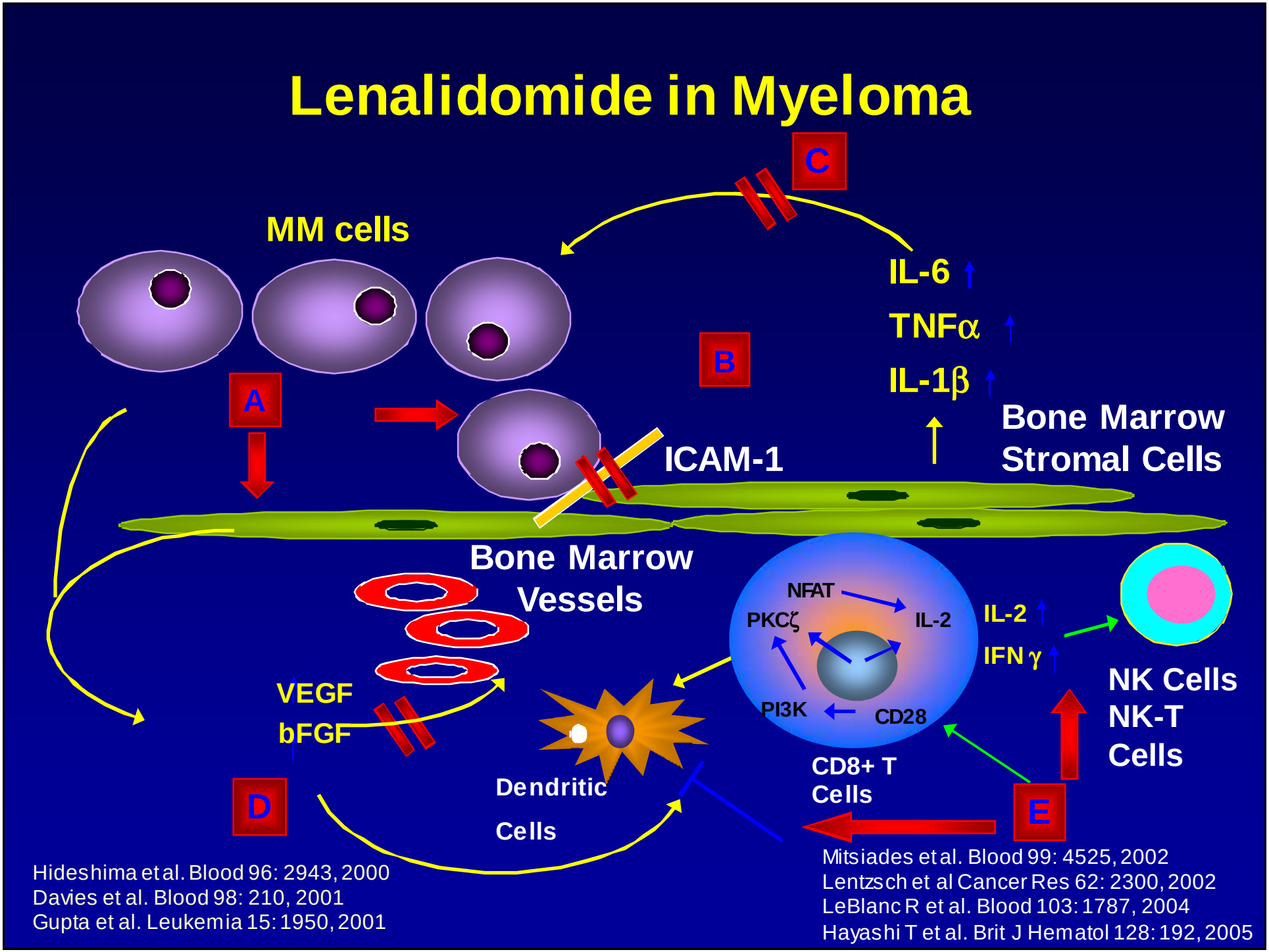


Chauhan et al: Cancer Cell 2009; 16:309-23.

Proteasome: Present and Future Therapies

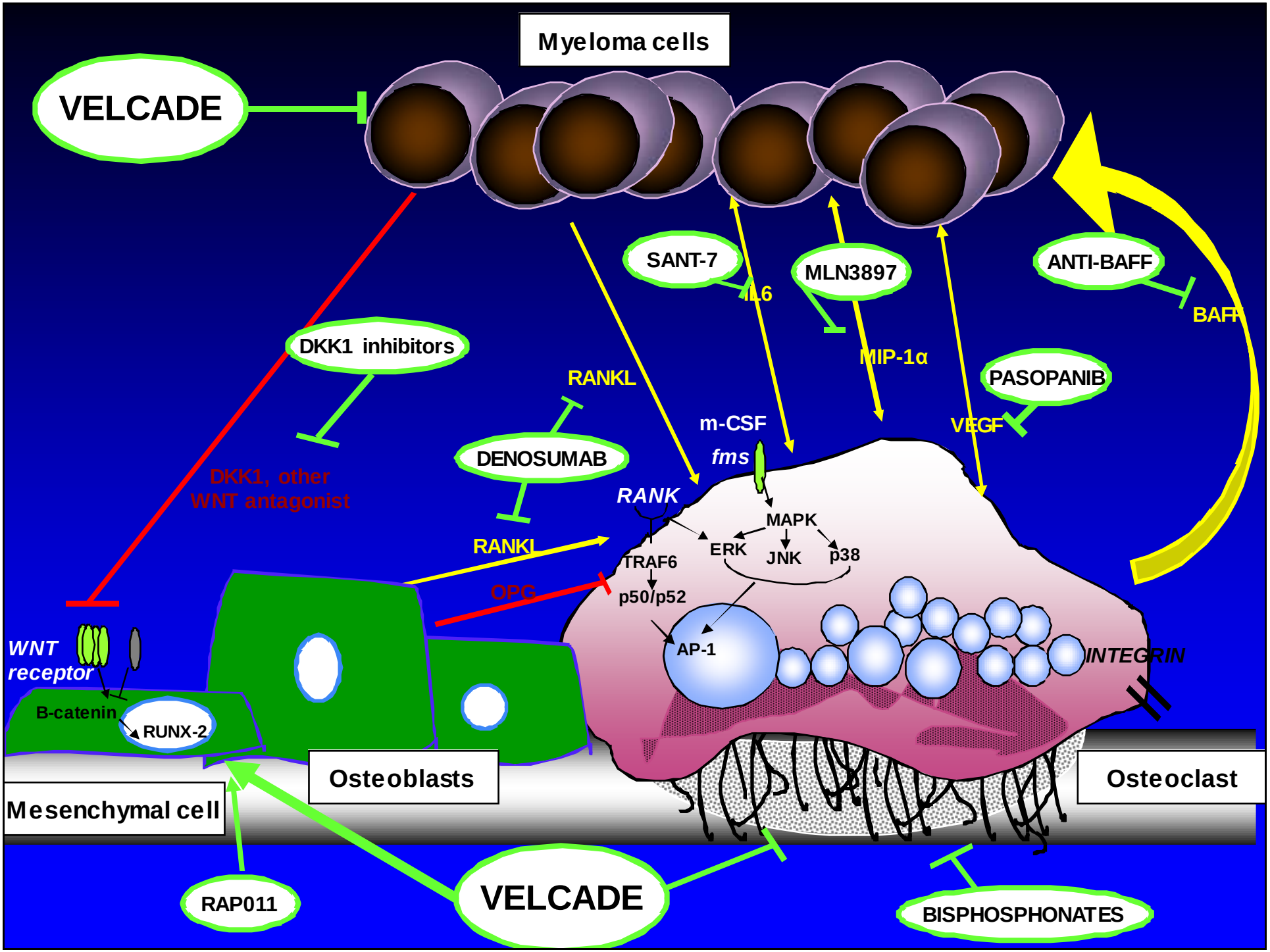


Lenalidomide in Myeloma

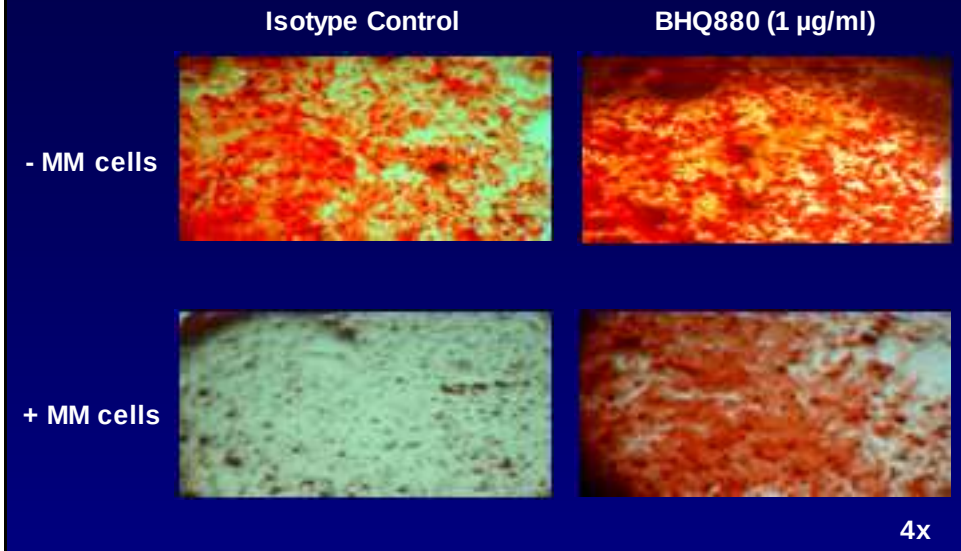


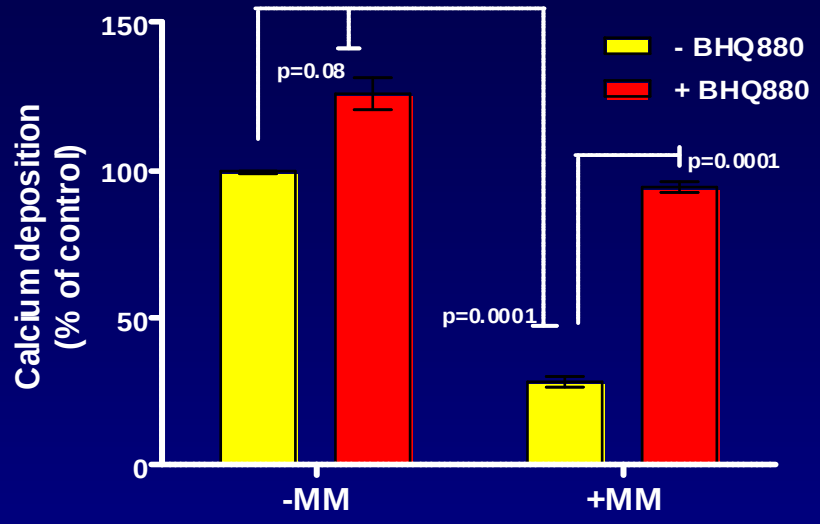
Hideshima et al. Blood 96: 2943, 2000
Davies et al. Blood 98: 210, 2001
Gupta et al. Leukemia 15: 1950, 2001

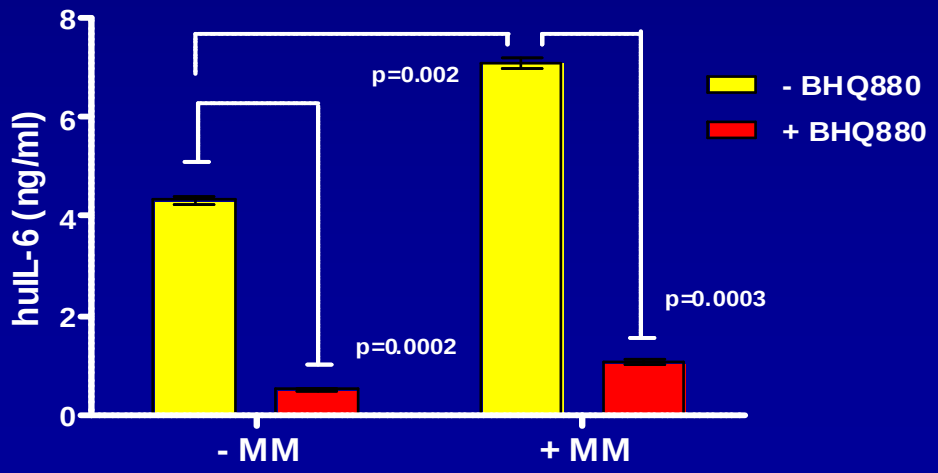
Mitsiades et al. Blood 99: 4525, 2002
Lentzsch et al Cancer Res 62: 2300, 2002
LeBlanc R et al. Blood 103: 1787, 2004
Hayashi T et al. Brit J Hematol 128: 192, 2005


Myeloma cells
VELCADE
SANT-7
IL-6
MLN3897
MIP-1α
ANTI-BAFF
BAFF
DKK1 inhibitors
DKK1, other
WNT antagonist
RANKL
DENOSUMAB
RANKL
OPG
m-CSF
fms
RANK
MAPK
ERK
JNK
p38
TRAF6
p50/p52
AP-1
PASOPANIB
VEGF
INTEGRIN
WNT
receptor
B-catenin
RUNX-2
Osteoblasts
Osteoclast
Mesenchymal cell
RAP011
VELCADE
BISPHOSPHONATES

Anti-DKK-1 MAb BHQ880 Abrogates the Inhibitory Effect of MM Cells on Osteoblastogenesis



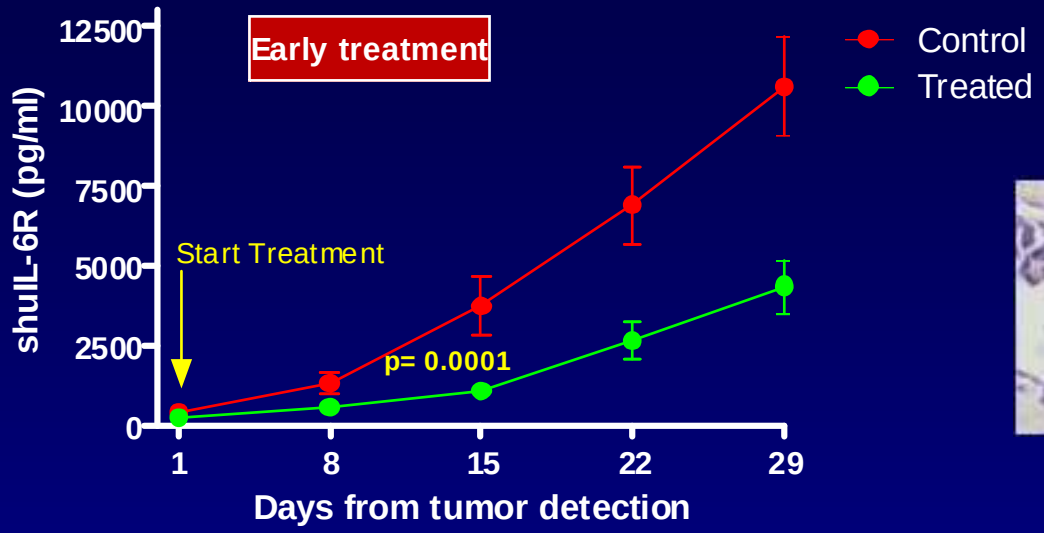


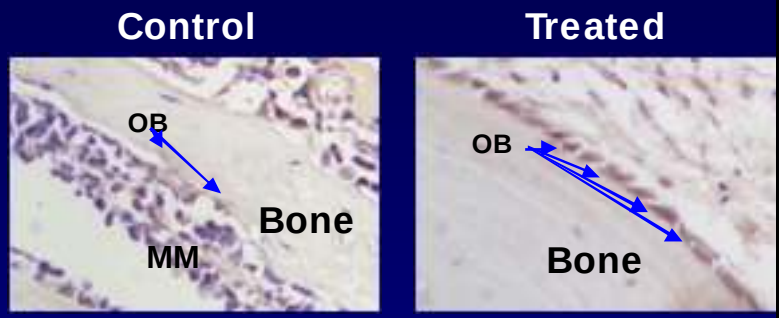


Clinical Trial Ongoing in MM

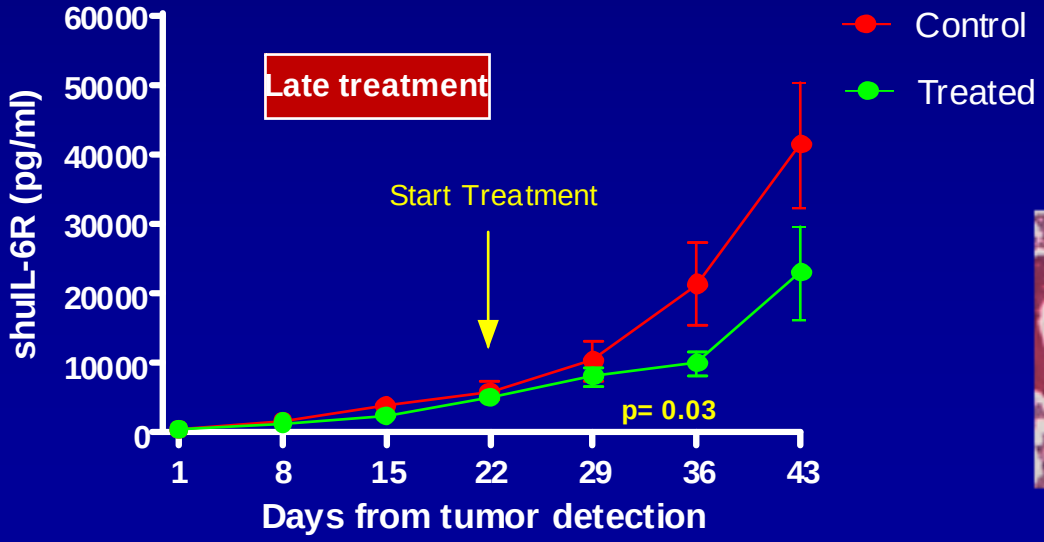
Fulciniti et al Blood 2009; 114;371-9

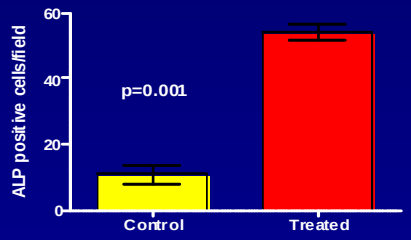
BHQ880 Inhibits Myeloma Cell Growth in SCID-hu Mice

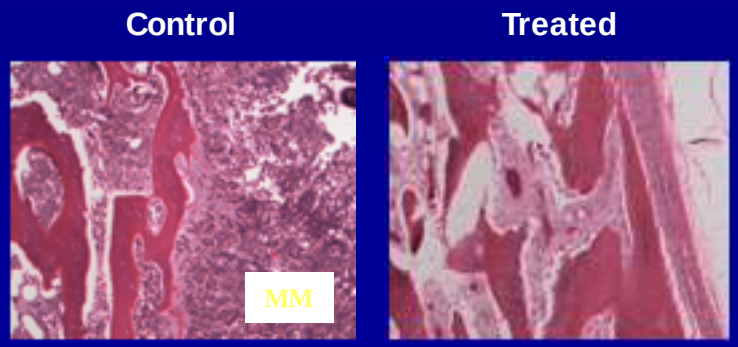




Treatment= 200ug/mouse ip 3x/wk



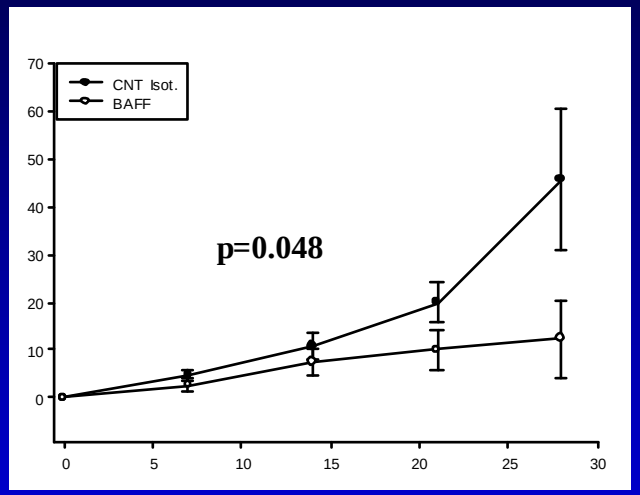




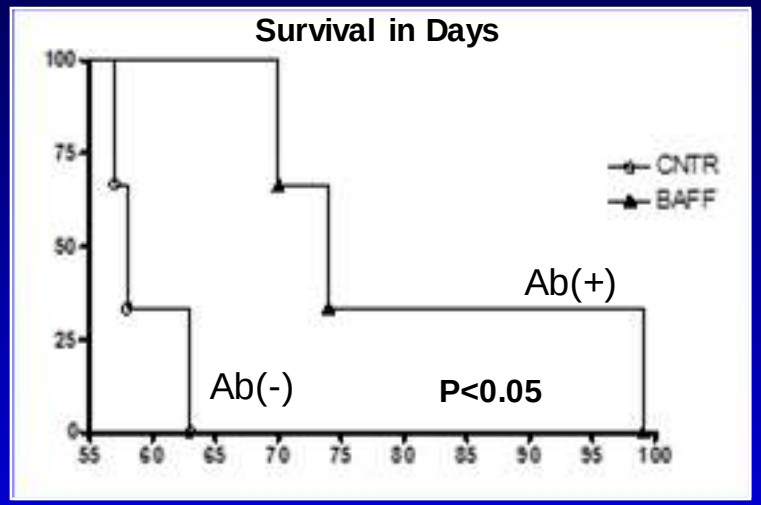
Fulciniti et al Blood 2009;114;37-91

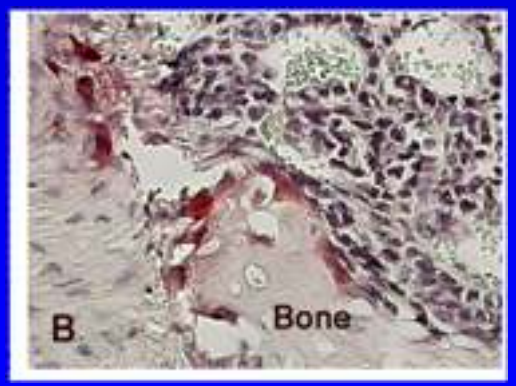
Anti-BAFF MAb Inhibits Osteoclasts and Prolongs Survival in SCID-Hu Model of MM

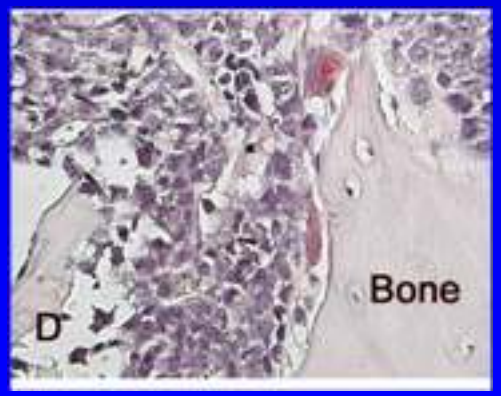
Control



Anti-BAFF Ab-Treated



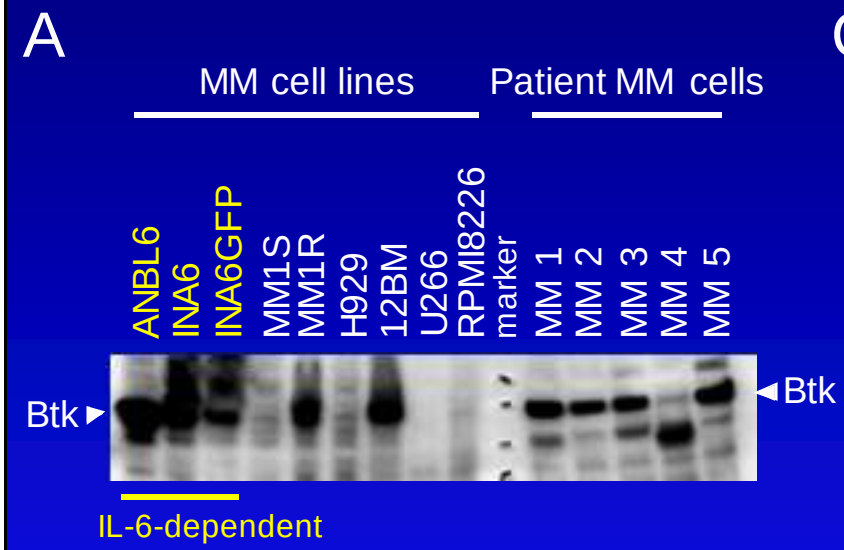


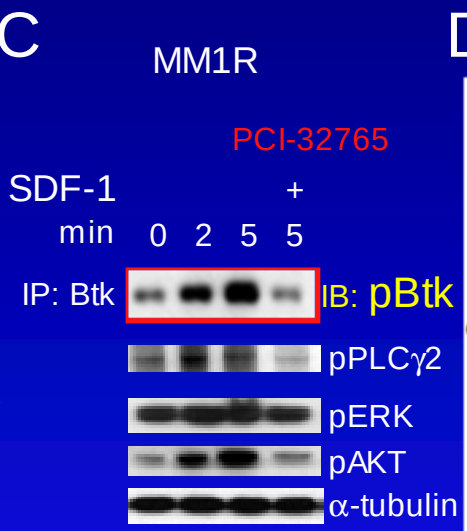


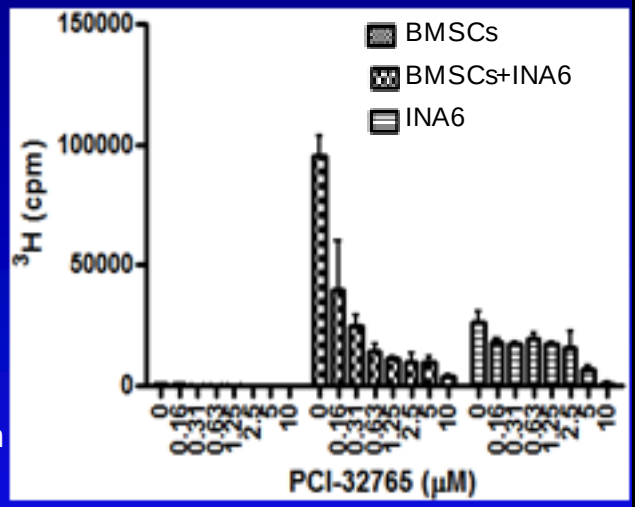
Clinical Trial Ongoing

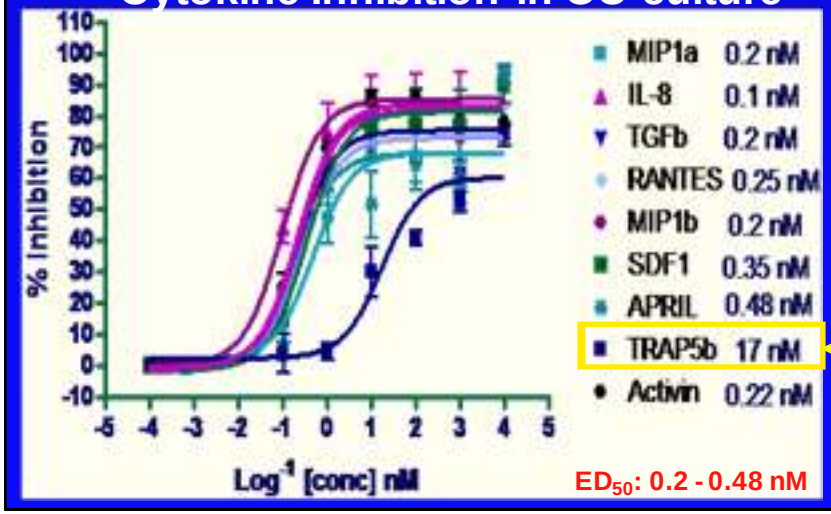
Neri et al: Clin Can Res 2007; 13: 5903.

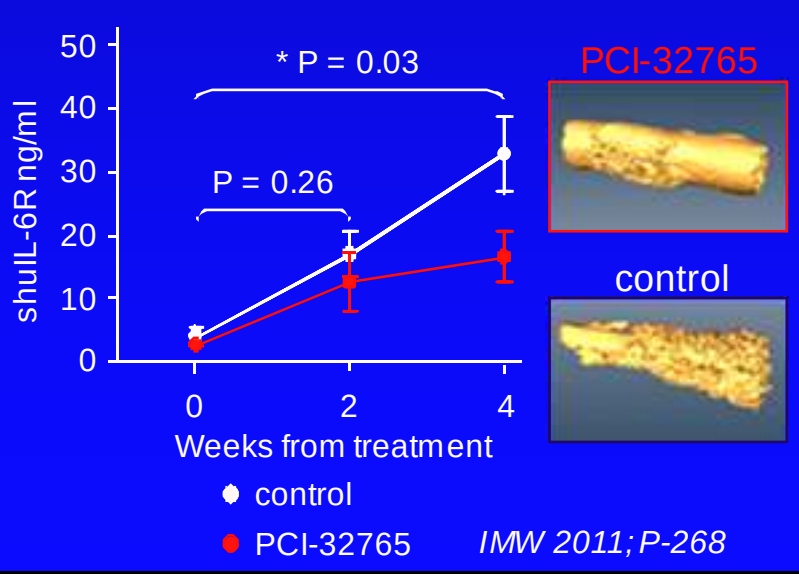
Targeting BTK with PCI-32765 Blocks Osteoclast Formation & MM Cell Growth In BM











EVALUATION OF CDKIs IN MM

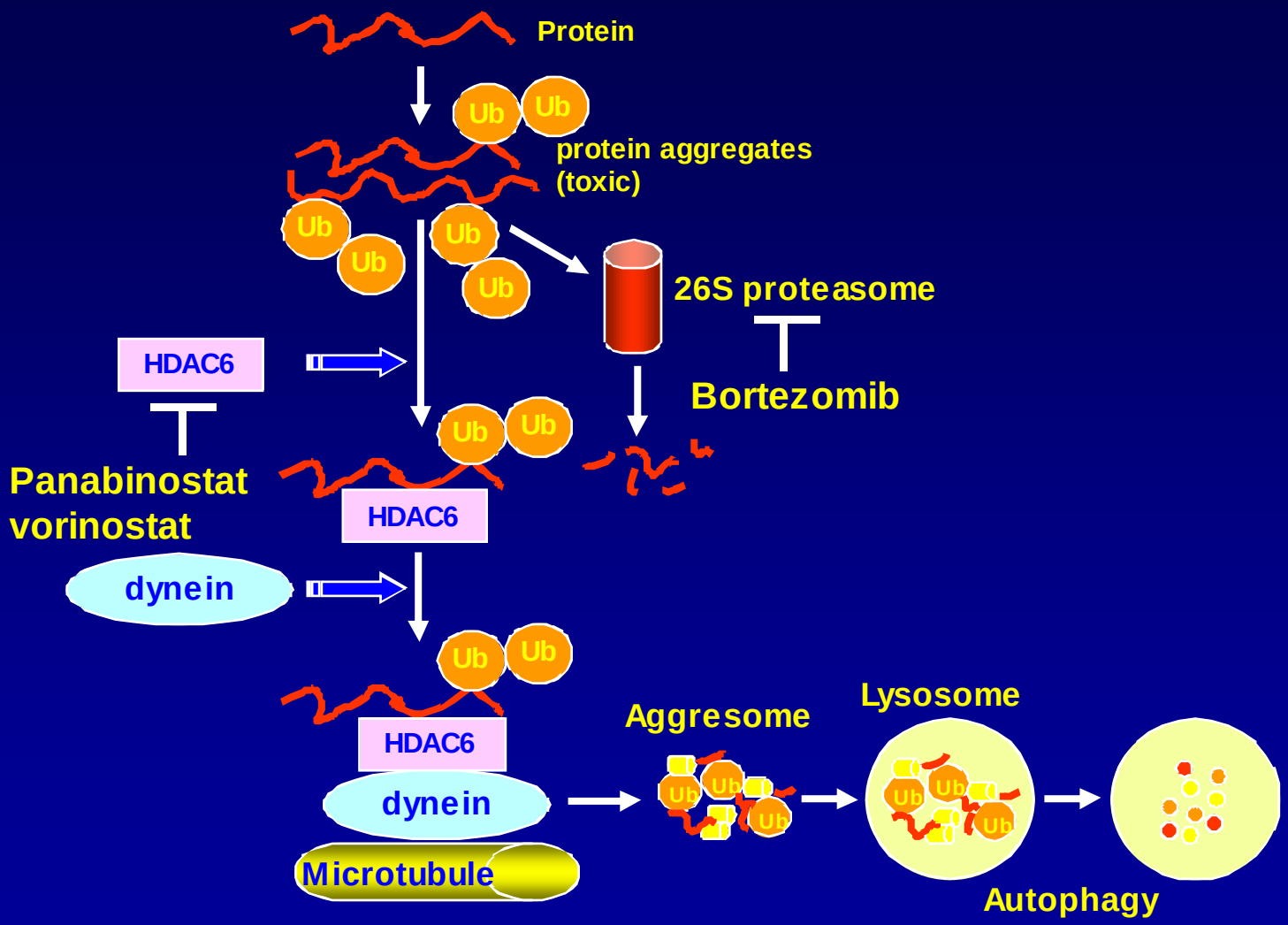
CDKI ID/ code number	Reported CDK activity	Other kinase activity	Phase of development	References
I. Selective CDKs activity				
PD 0332991	CDK4,6/cyclin D	—	Phase I/II in combination with bortezomib and dexamethason in R/R MM	Baughn L et al. *Cancer. Res.* 2006
II. Multi-CDKs activity				
Seliciclib	CDK2/cyclin A ,E CDK7/cyclin H CDK9/cyclinT1	—	Preclinical testing	Raje N et al. *Blood.* 2005.
P276-00	CDK1/cyclin B CDK4/cyclin D CDK9/cyclinT1	—	Phase I multicenter study in R/R MM (India)	Raje N et al. *Leukemia.* 2009.
III. Multi-CDKs and additional targeted kinase activity				
AT-7519	CDK1/cyclin B CDK2/cyclin A, E CDK4,6/cyclin D CDK7,9/cyclin H, T	GSK-3β	Phase I/II alone and in combination with bortezomib	Santo L et al. *Oncogene* . 2010

PI3K/AKT/mTOR Inhibitors in MM

≥ *MR*	Target	+/- Dex	Bort + Dex (n=73)*	Len +/- Dex
Perifosine	AKT	*38%*	*38%* [2**]	*70%*[3]
Everolimus	mTORC1	7%[4]		*63%*[5]
Temsirolimus	mTORC1	*37%*[6***]	*73%* [7]	*24%*[8]

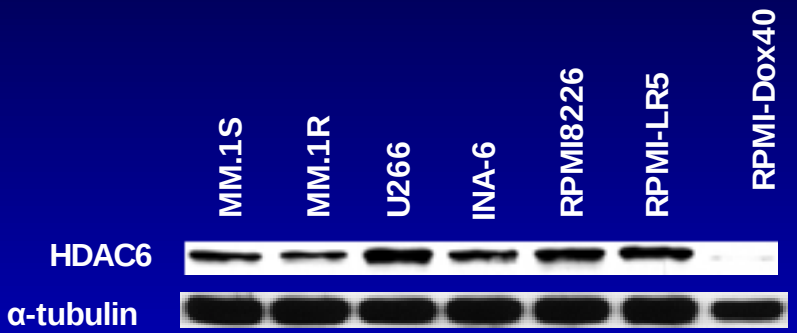
1. Richardson P et al. ASH 2007. Abstract 1164; 2. Richardson PG et al. IMW 2009. Abstract A349;
3. Jakubowiak AJ et al. IMW 2009. Abstract A347; 4. Guenther A et al. ASCO 2010. Abstract 8137;
5. Mahindra AK et al. ASCO 2010. Abstract 8032; 6. Farag SS et al. *Leuk Res.* 2009;33:1475;
7. Ghobrial IM et al. ASH 2009. Abstract 748; 8. Hofmeister CC et al. ASH 2009. Abstract 2884.

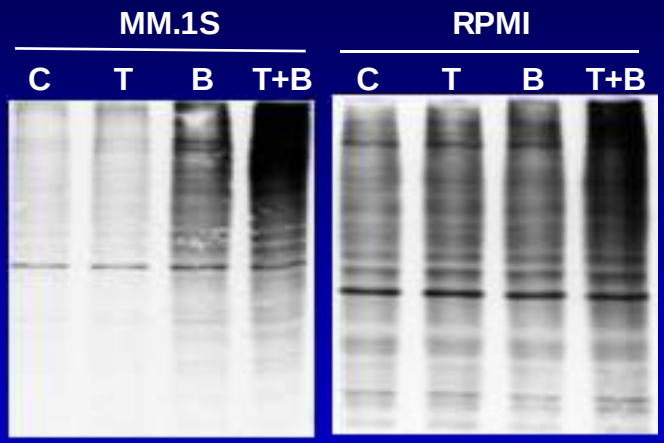
Blockade of Ubiquinated Protein Catabolism



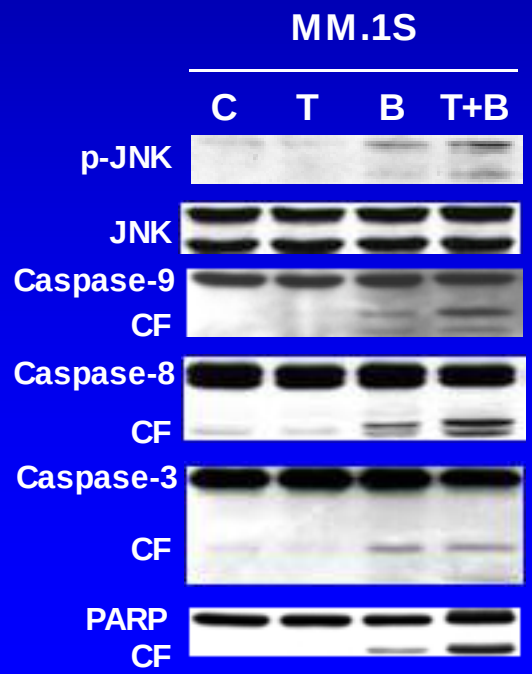
Hideshima et al, Clin Cancer Res;2005; 11: 8530
Catley et al, Blood 2006; 108: 3441-9.

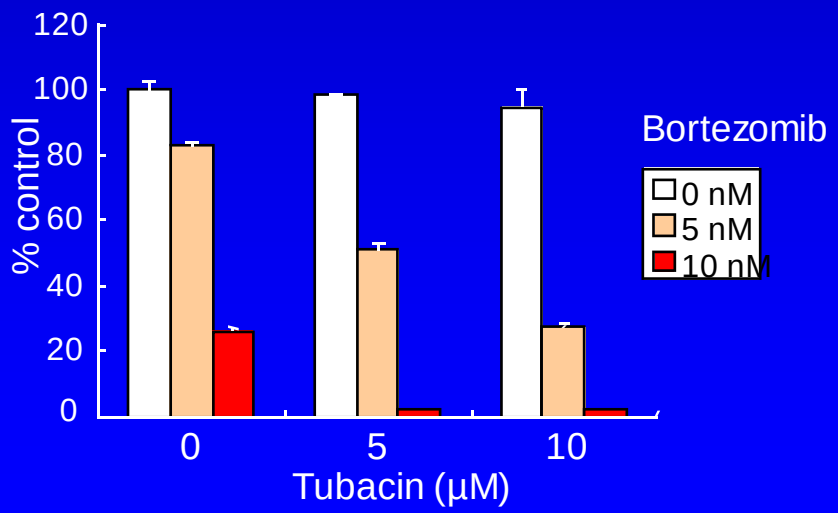
Targeting Proteasome and Aggresome Triggers Synergistic MM Cytotoxicity





C: control T: tubacin (5μM)
B: bortezomib (5 nM)

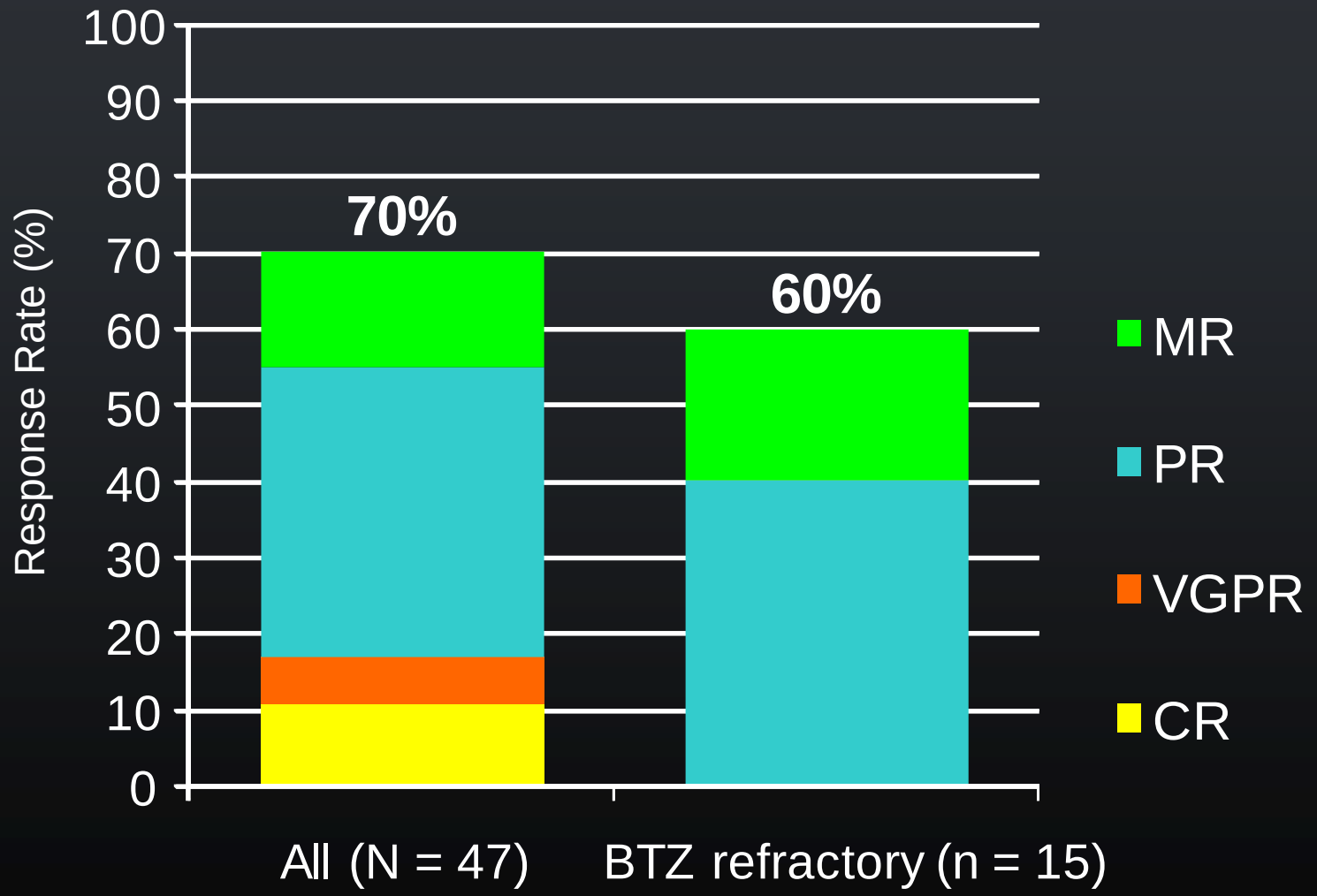




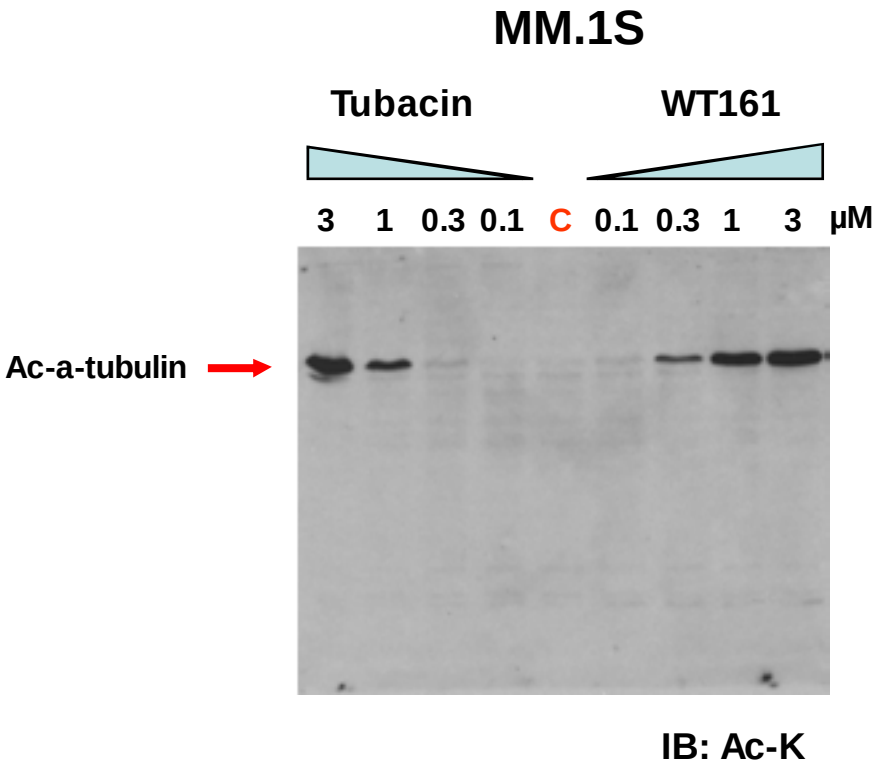
Hideshima et al. PNAS 2005; 102: 8567.

Panobinostat + Bortezomib to Inhibit Aggresome and Proteasome In Relapsed Refracory MM

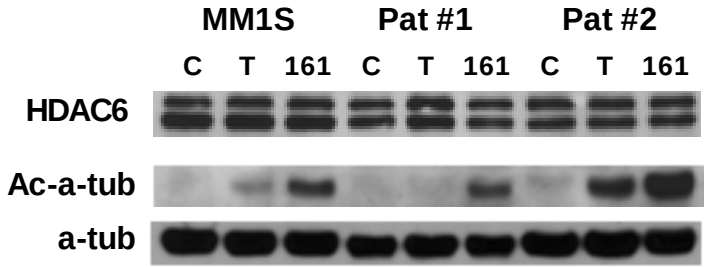
San Miguel et al, ASCO 2010

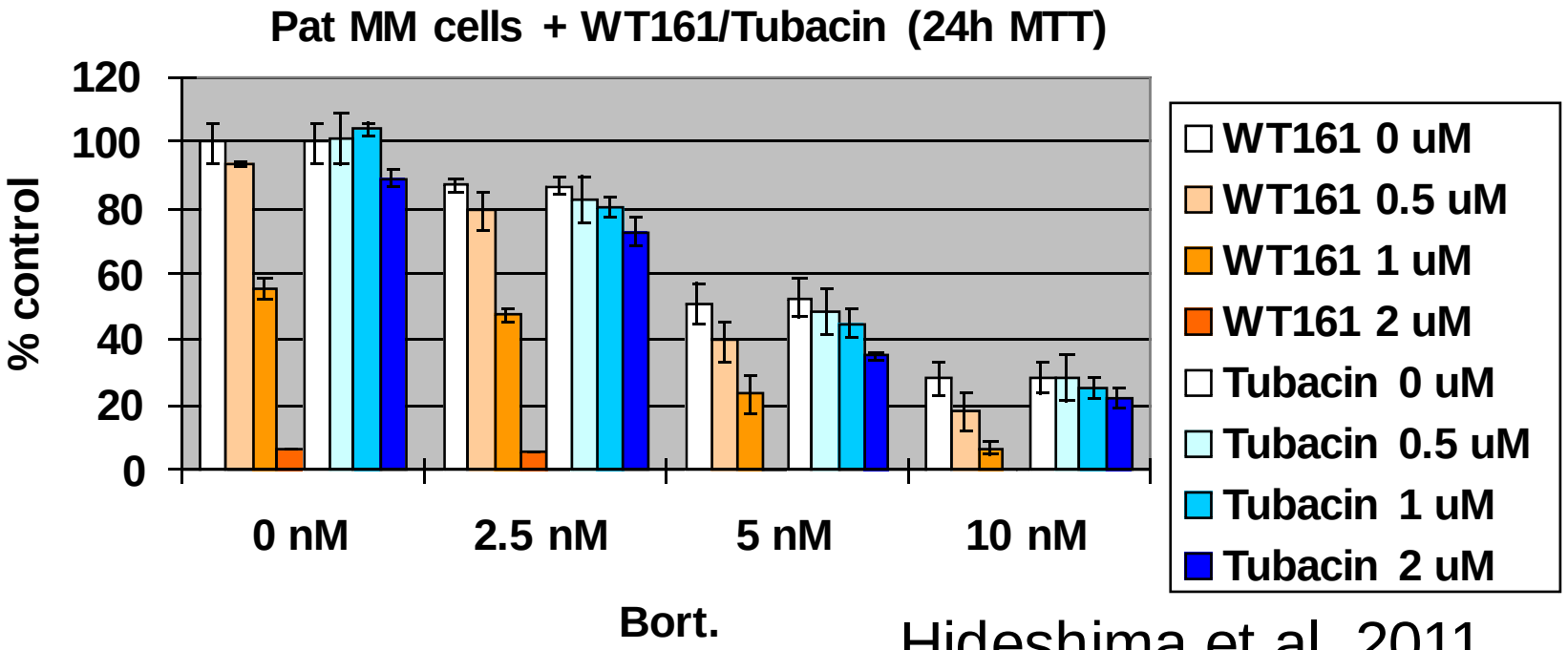


WT161 is More Potent Selective HDAC6 Inhibitor Than Tubacin



HDAC 6 Selective Inhibitor WT161 Enhances Bortezomib-Induced Cytotoxicity in Patient MM Cells





Hideshima et al, 2011

Bench to Bedside Translation of HDAC 6 Selective Inhibitor ACY 1215

Orally bioavailable, highly potent, selective inhibitor of HDAC 6 synthesized in fall 2009

Synergistic MM cytotoxicity with Bortezomib in vitro and in vivo

Favorable PK/PD, toxicity profile

Highly favorable FDA regulatory process from pre-IND through IND allowance

Phase Ia/Ib/II clinical trial of ACY1215, alone and with Bortezomib, beginning spring 2011

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

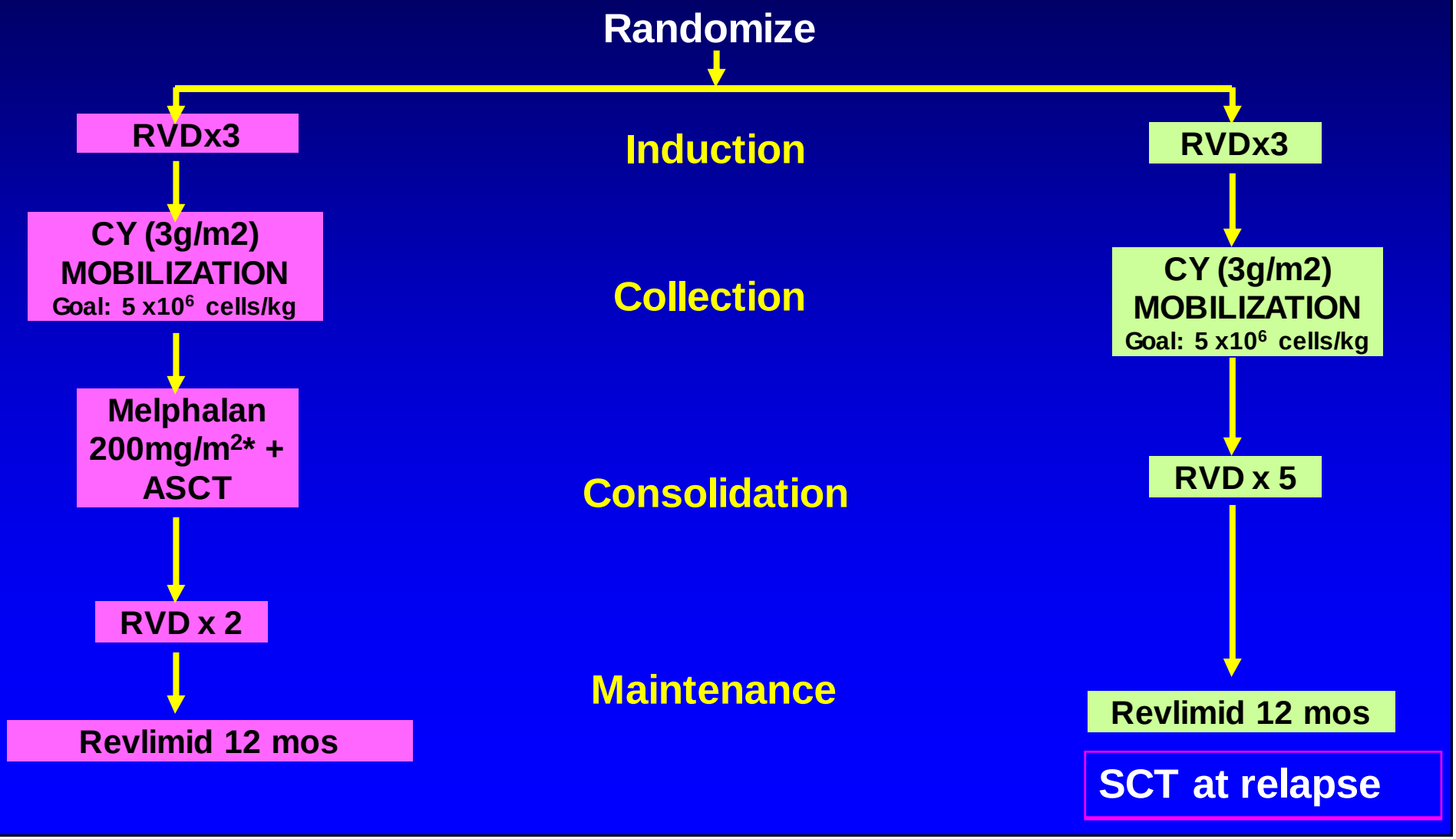
Synergistic MM cell toxicity of lenalidomide (caspase 8) with Bortezomib (caspase 9>8) in vitro and in vivo (dual apoptotic signaling)

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

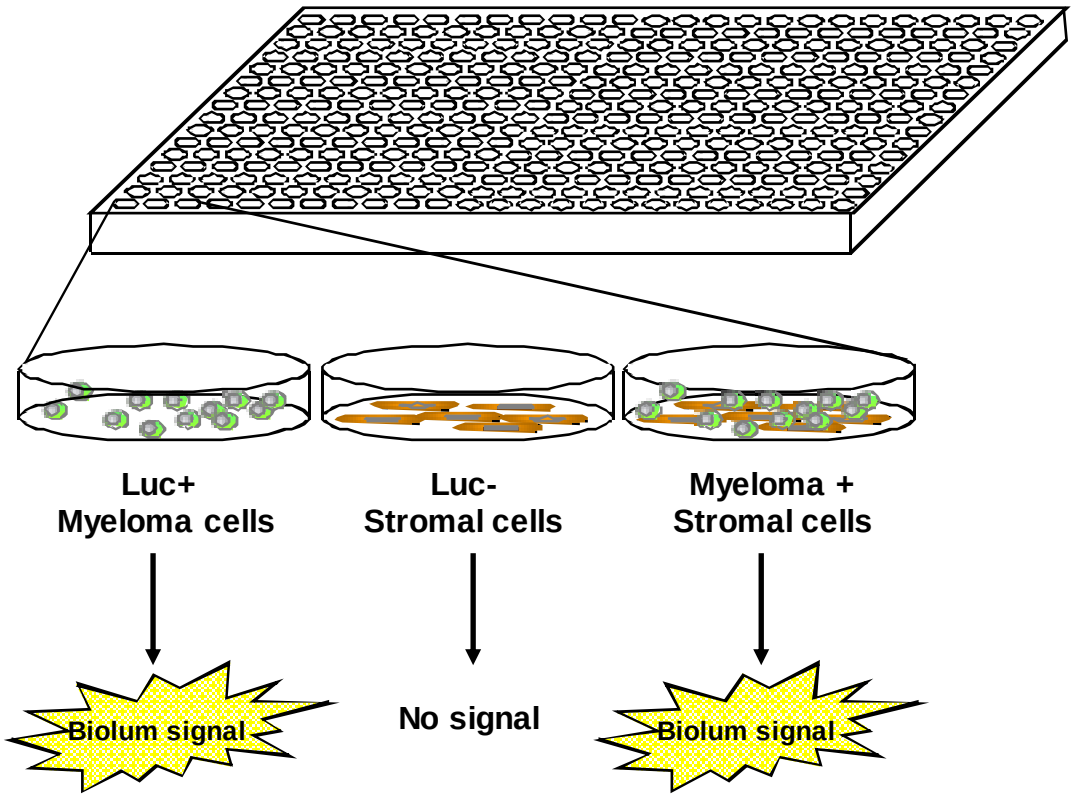
Phase I-II trials show 100% response with 74% CR/VGPR and 52% CR/nCR when used as initial therapy, including molecular responses.

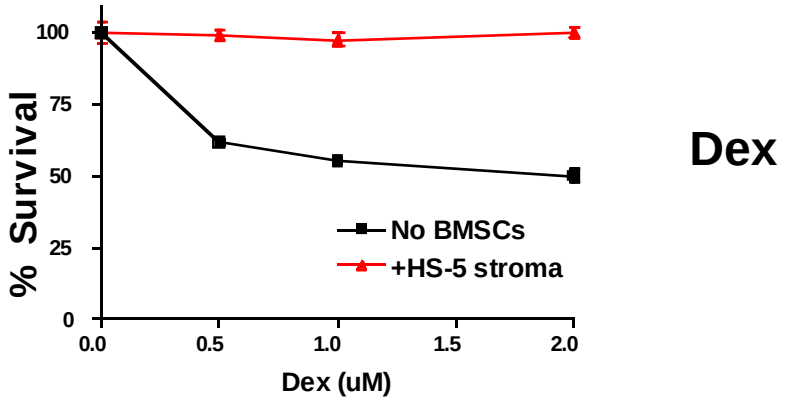
Richardson et al JCO 2009; 27:5713-19.
Richardson et al Blood 2010; 116:679-86.

IFM/DFCI Study in Newly Diagnosed MM Stem Cell Candidates

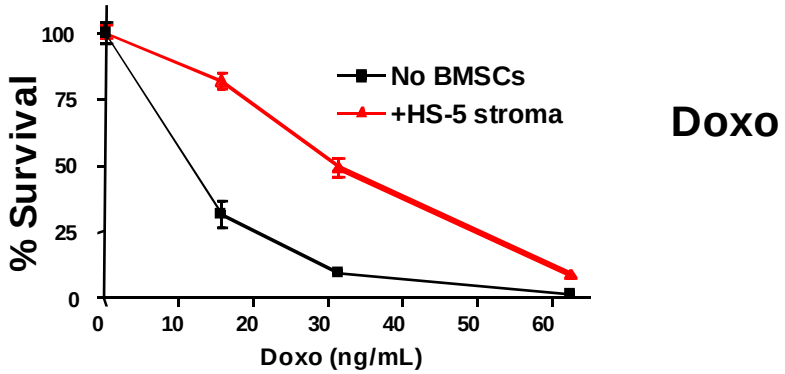


High-Throughput Screening of MM with BMSCs to Define Optimal Single Agents/Combinations

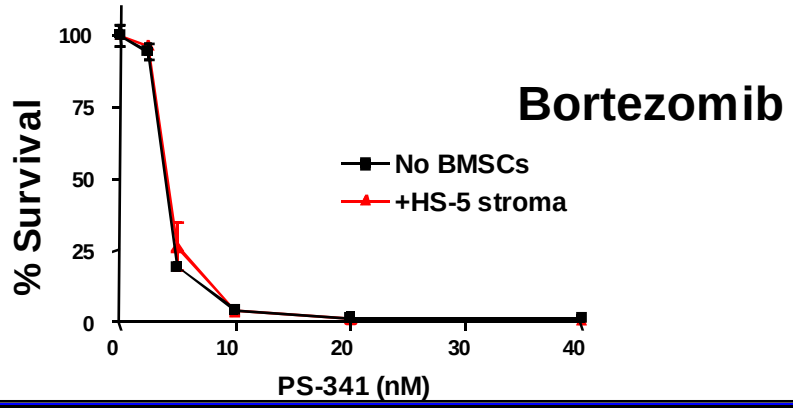




Dex



Doxo



Bortezomib

McMillin et al. Nat Med 2010; 16: 483.

New Drug Screening in Presence of BMSCs

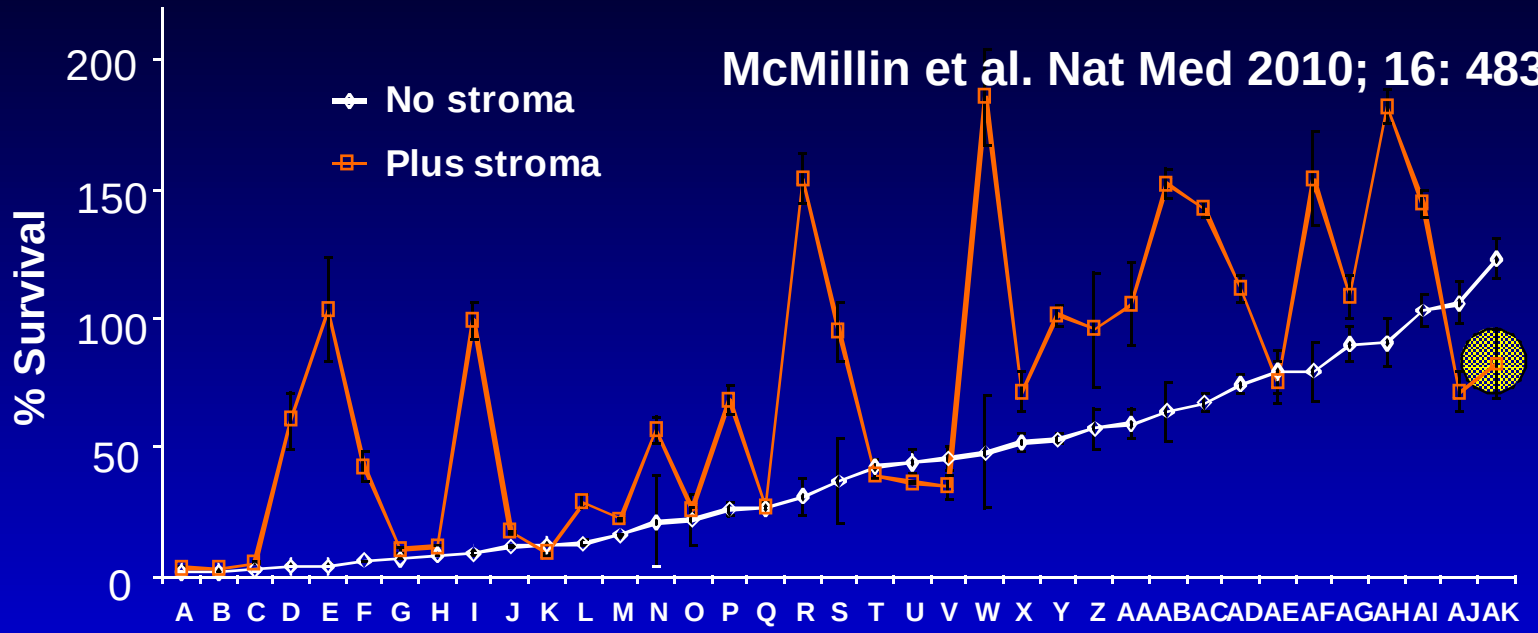
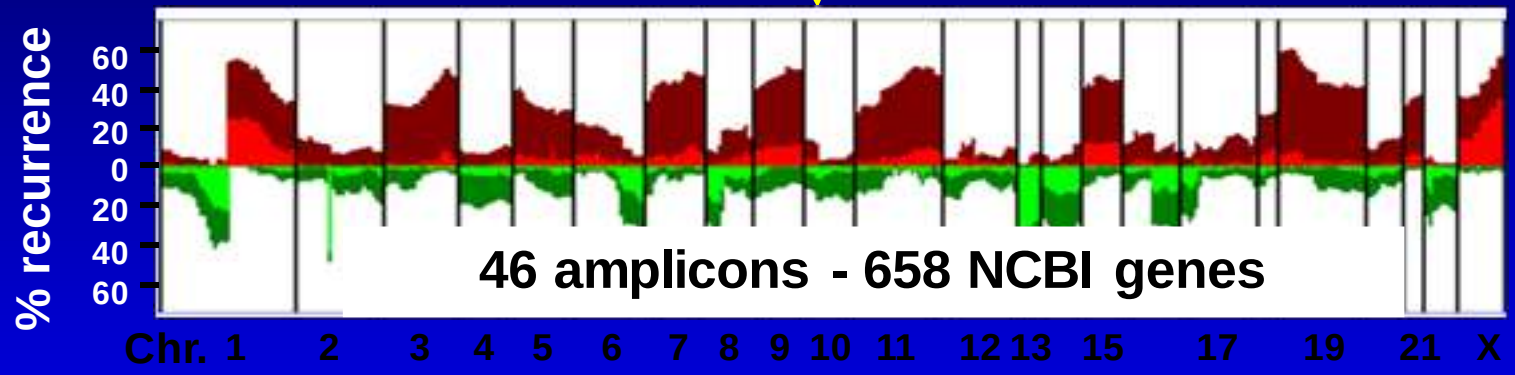


CHART CODE	COMPOUND NAME	TARGET	CONC. (uM)	MM1S AVG no stroma	MM1S AVG with stroma
A, B & G	Staurosporine	Pan-specific	10, 1 & 0.1	1.43	3.32
E	Sphingosine	p38 MAPK	10	4.05	103.34
I	Lavendustin A	EGFRK	10	9.05	99.34
N	Piceatannol	Syk	10	21.11	56.82
P	Ro 31-8220	MEK	1	25.77	68.39
R	HDBA	HER1-2	10	30.71	153.95
W	BAY 11-7082	PKC	1	48.22	185.72
AB	Tyrphostin 51	EGFRK	10	63.83	152.16
AF	Kenpaullone	CaMK II	1	79.46	154.02
AH	U-0127	MEK	1	90.36	181.91
AK	Tyrphostin AG 126	EGFRK	10	132.06	132.40

Oncogenomics to Identify Targeted Therapies

Integrated platform aCGH, SKY and expression profiling

55 MM Cell Lines; 73 Patient Samples



Expressed Genes : **258**

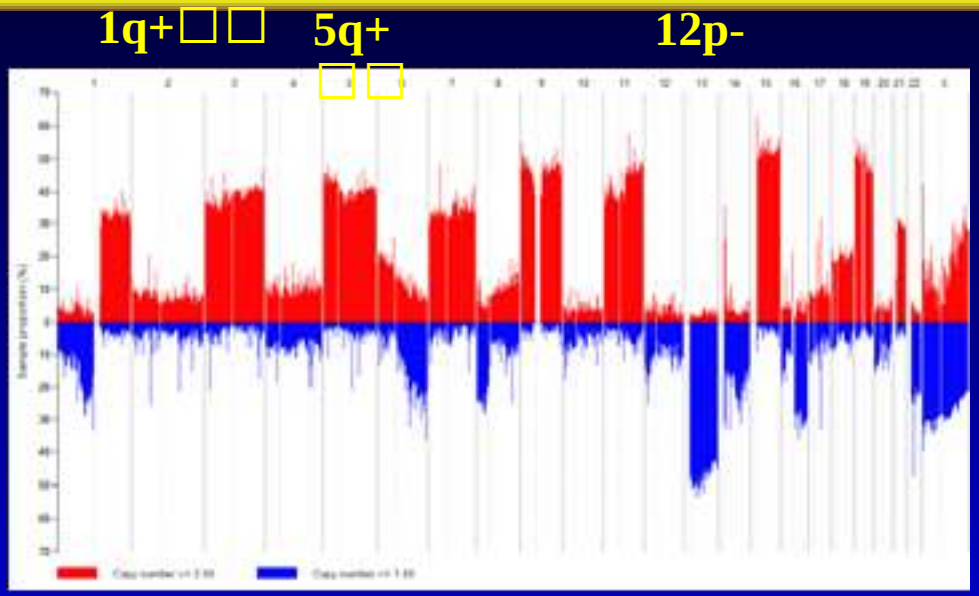
Functional validation of MM candidate genes.

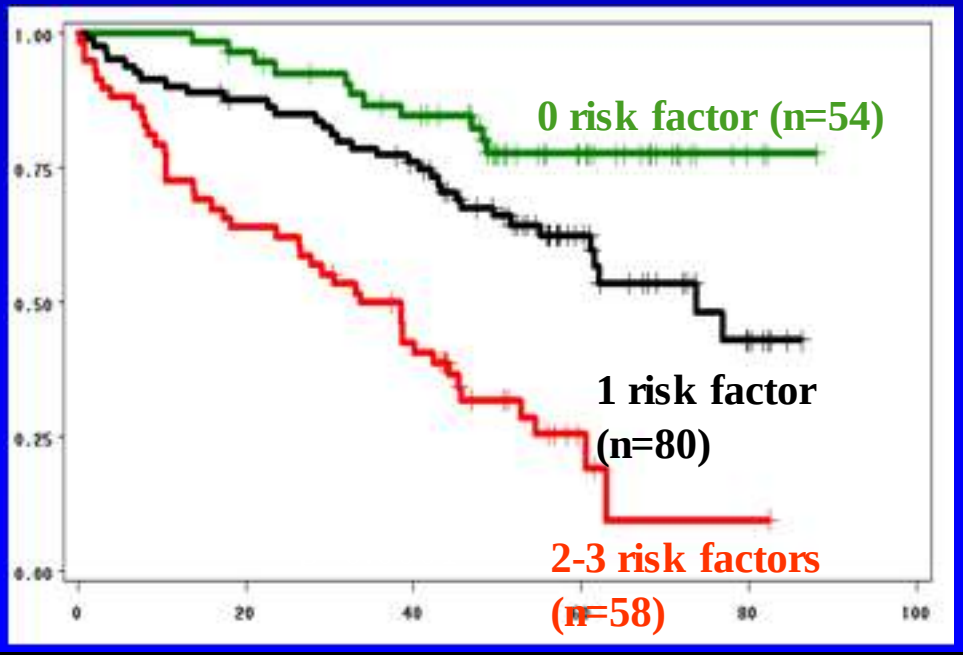
Small molecule
HDAC6

Carrasco et al Cancer Cell 2006; 9: 313

Monoclonal Abs
Vaccines

SNP Array Based MM Prognostic Model





Copy number analyses reveal novel prognostic classification

Identifies regions of clinical importance especially del12p and amp 5q

SNParrays highlight few regions with bi-allelic deletions

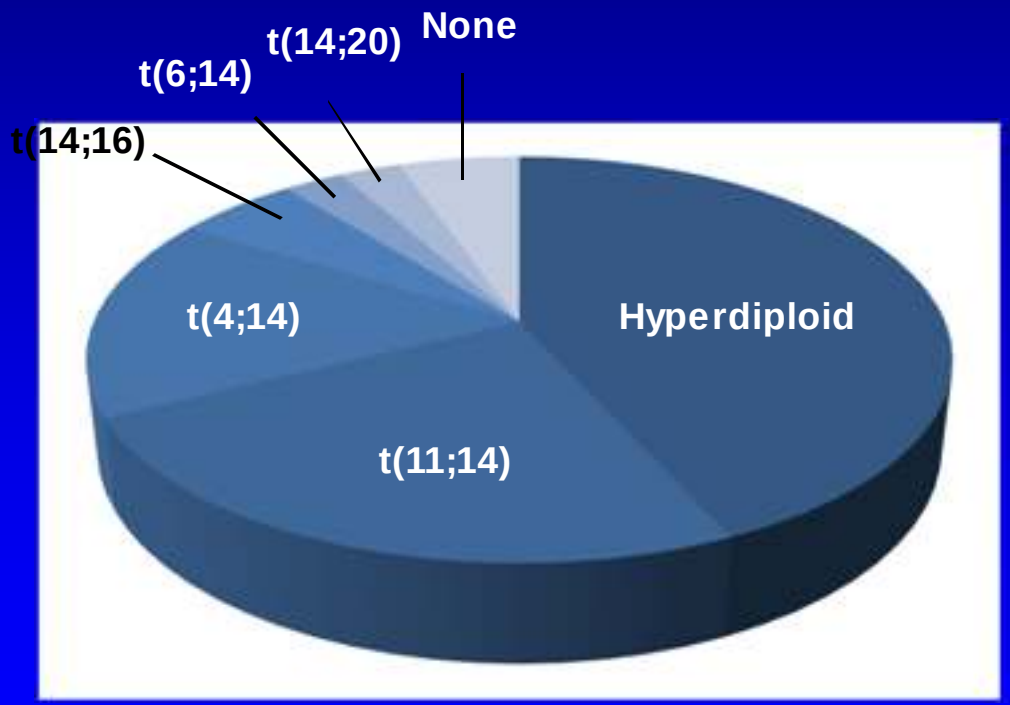
SNP analysis may lead to an individual therapeutic approach.

Avet-Loiseau et al JClin Oncol 2009; 27: 4585-90.

MM Genome Sequencing (MMRF)

19/38 (50%) newly diagnosed

19/38 (50%) received prior treatment



19/38 (50%) del 13q14

2/38 (5%) del 17p13

3/38 (8%) del 1p32

Chapman et al Nature 2011; 471: 467-72

Mutations in Myeloma

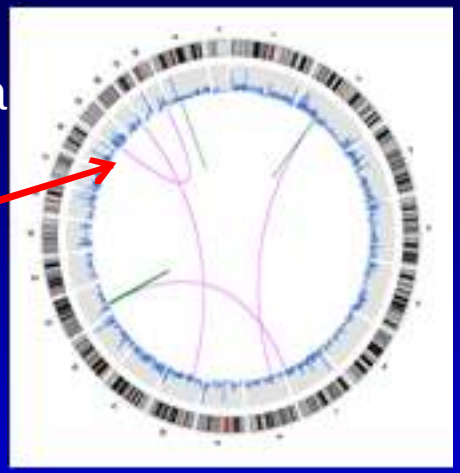
- **Protein homeostasis**: 42% including FAM46C, RPL10, RPS6KA1, EIF3B, XBP1, LRRK2
- **NF-κB signaling:** 10 point mutations, 4 additional structural re-arrangements affecting coding
- **IRF-4, Blimp-1:** 2 mutations each
- **Histone methylating enzymes:** WHSC1, UTX, MLL
- **BRAF:** 4% activating

Chapman et al Nature 2011; 471: 467-72

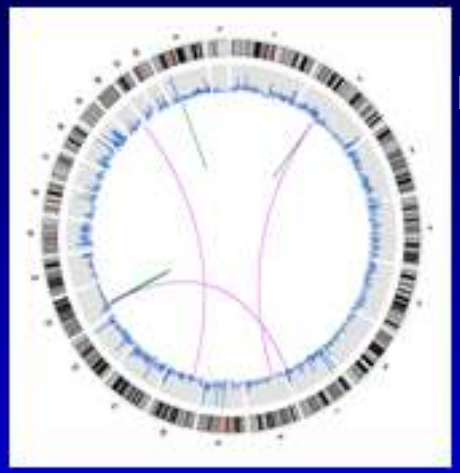
Whole Genome Paired End Sequencing Identifies Genomic Evolution in Myeloma

Early Tumor Circos Plots Late Tumor

PD3823a



PD3823c



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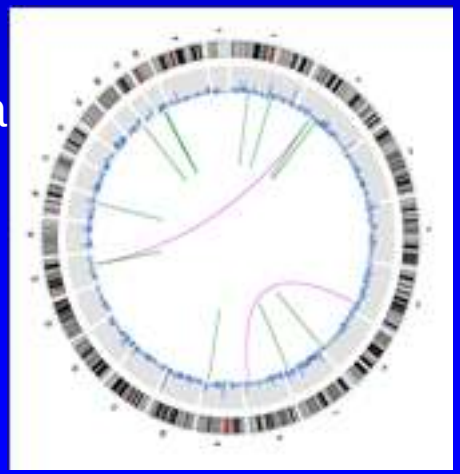

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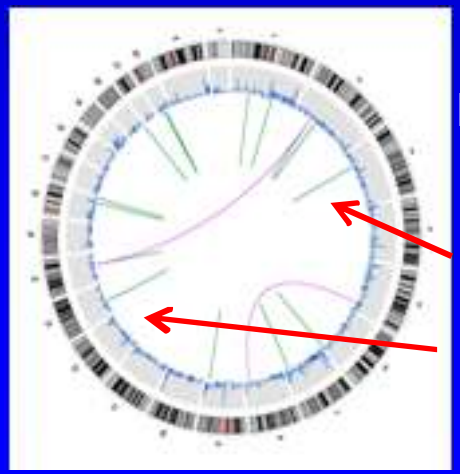

Munshi at al ASH 2009

Current and Future Directions

1. Development of immune (vaccine and adoptive immunotherapy) therapies

2. Development of novel agents targeting the MM cell in the BM microenvironment

3. Development of rationally-based combination therapies

4. Utilization of genomics for improved classification and personalized therapy

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

United Nations Against Myeloma:

Jerome Lipper and Lebow Bench to Bedside Research Team

USA

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Nikhil Munshi
Robert Schlossman
Irene Ghobrial
Steven Treon
Jacob Laubach
Deborah Doss
Kathleen Colson
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Karin Anderson
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Amber Walsh
Samir Amin
Wanling Xie
Parantu Shah
Holly Bartel
Lisa Popitz
Jeffrey Sorrell

UK

India

Italy

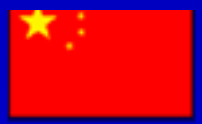
Israel

Japan

Canada

Germany

Austria



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Rao Prabhala
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Avani Vaishnav

Greece

Taiwan

Turkey

Australia

Ireland