Preclinical Basis for 2nd Generation Proteasome Inhibitors

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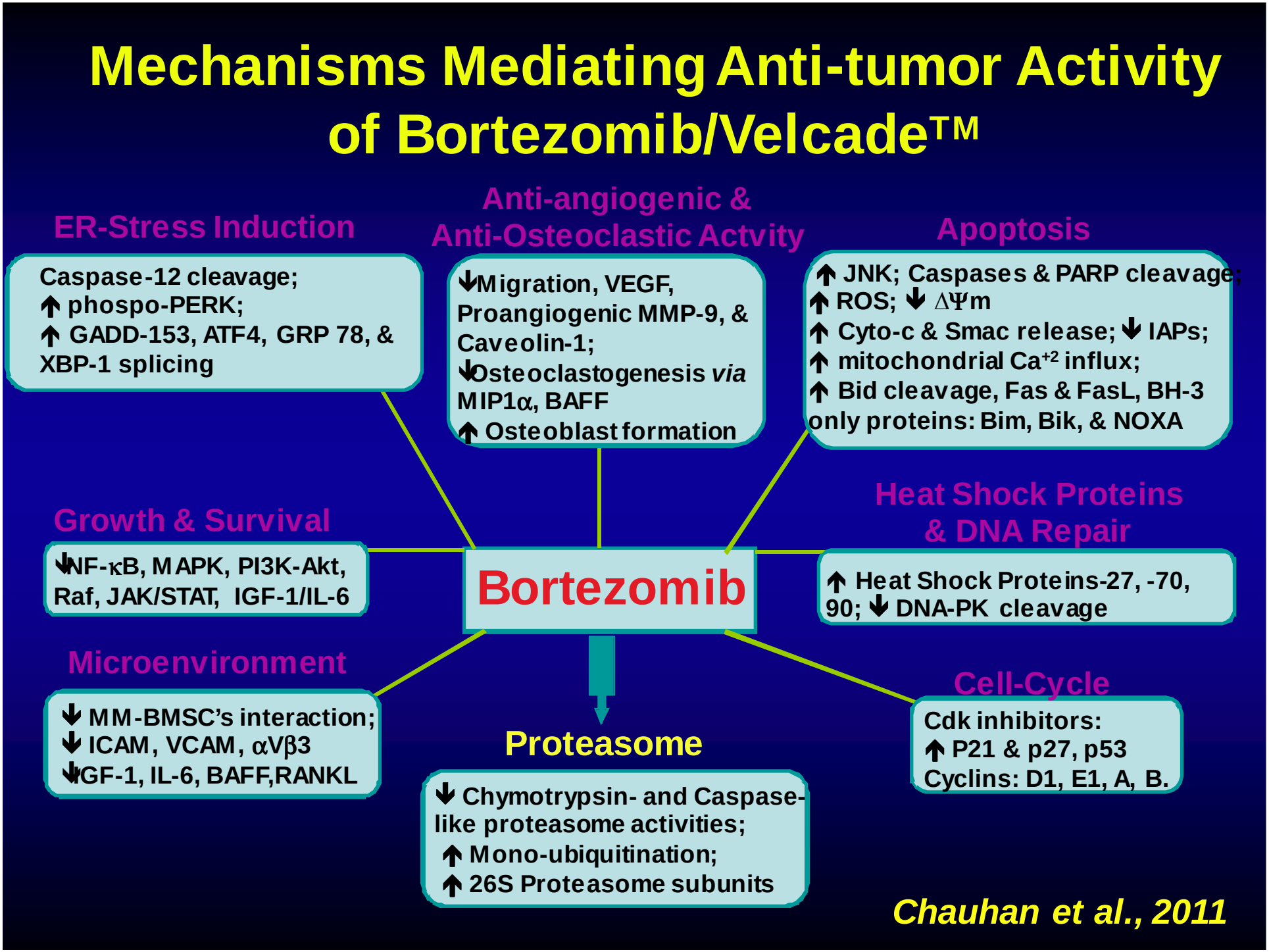
Rationale for Targeting Proteasomes as Anti-Cancer Therapy

- Cancer cells are more sensitive to proteasome inhibition than normal cells likely due to higher proliferation rate and enhanced requirement for protein synthesis and degradation
- *Palombella et al., 1995* showed that proteasome inhibitor MG-132 targets NF-κB
- NF-κB is a key player in the growth & survival of MM

  Chauhan et al., 1996 Blood 87:1104-1112

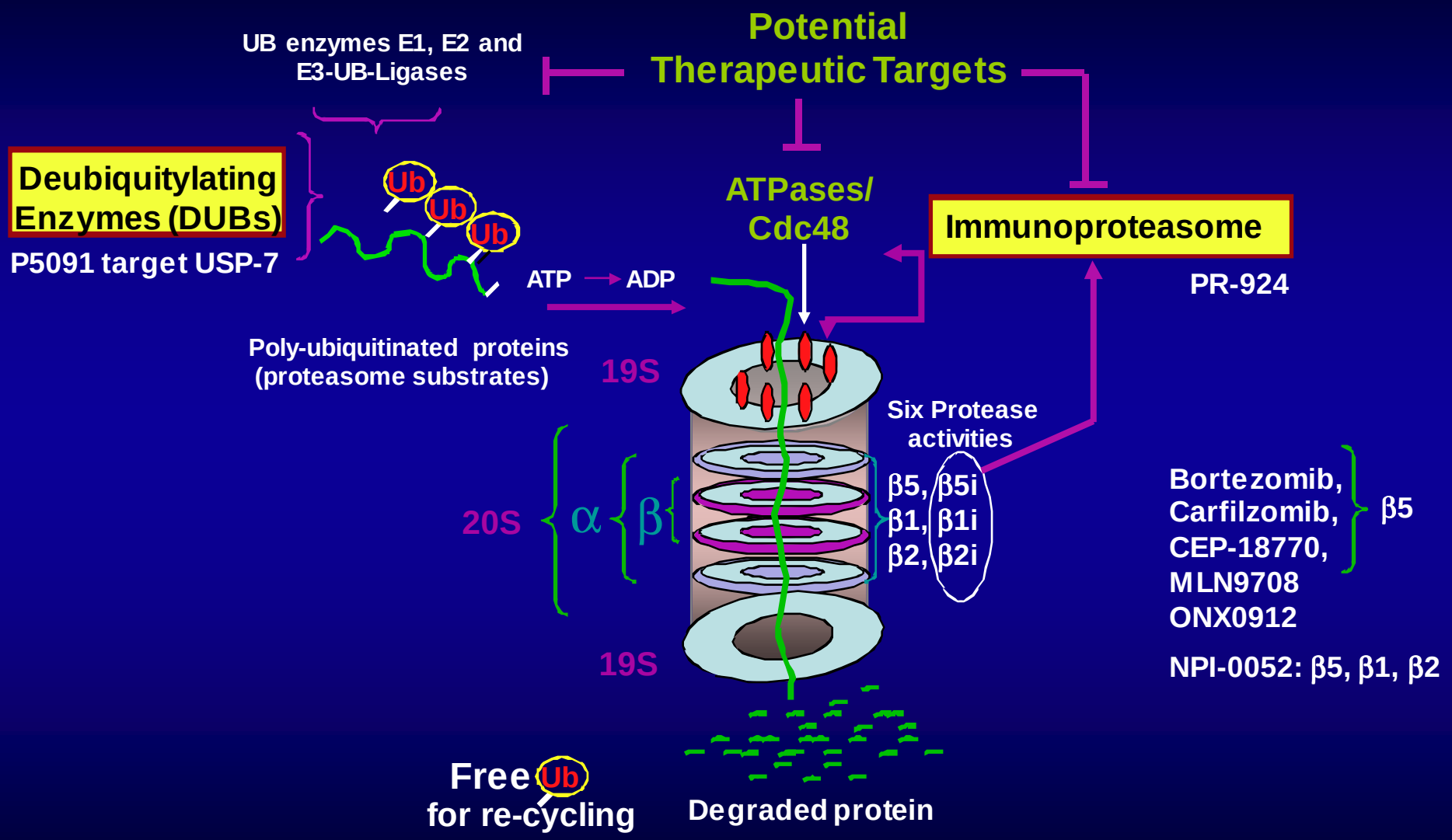
  Feinman et al., 1997 Blood 93:3044

Mechanisms Mediating Anti-tumor Activity of Bortezomib/Velcade™



Chauhan et al., 2011

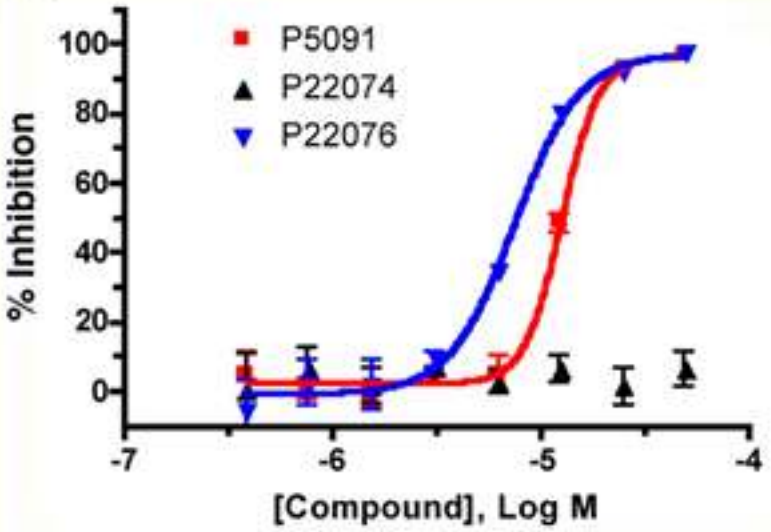
Proteasome: Present and Future Therapies



Chauhan et al., 2011

P5091 Selectively Blocks USP-7 Function

A.



B.

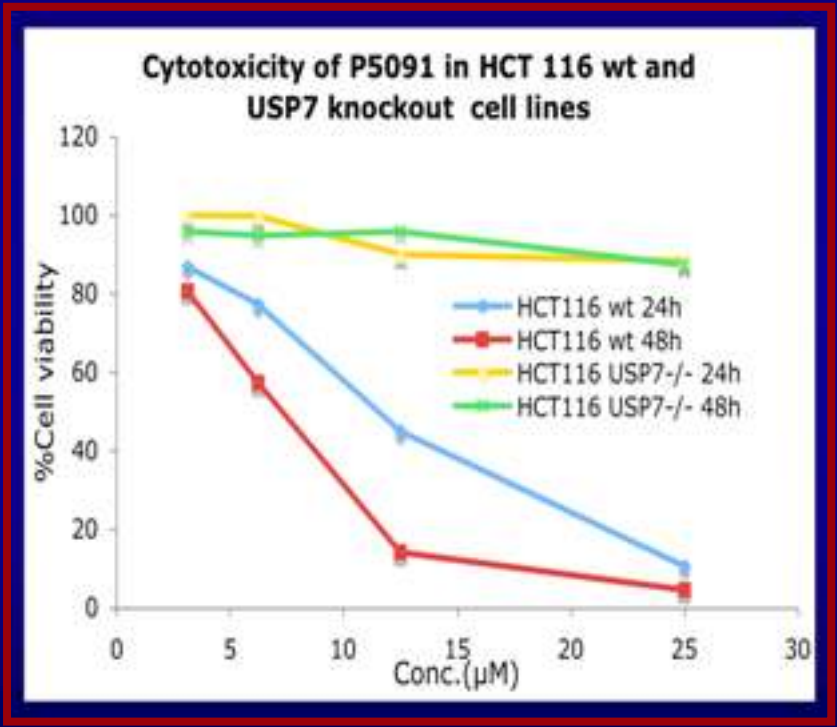
Compound	EC50 (μM) Mean ± SD	% Inhibition Mean ± SD
P5091	10.8±2.3	92±5
P22074	>50	9±5
P22076	6.6±3.2	96±3

C.

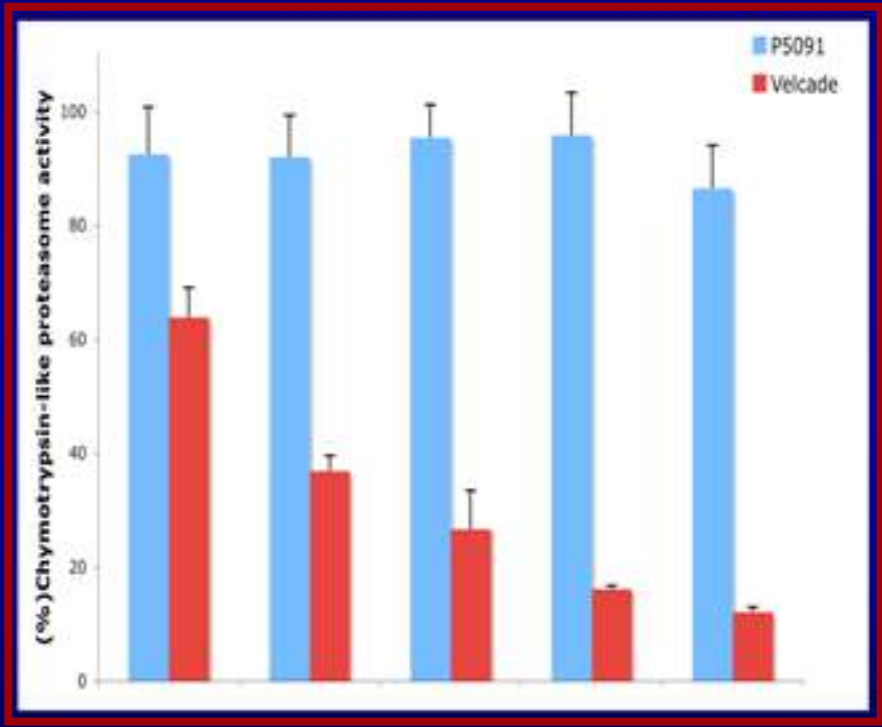
Compounds	EC50 (μM), mean										
	USP7	USP2	USP8	USP20	USP34	UCHL5	JOSD2	SENP6	PLpro	PLP2	Caspase 3
P5091	10.8	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50
P22074	>50	>50	ND	ND	ND	ND	ND	ND	ND	ND	>50
P22076	6.6	>50	>50	>50	>50	>50	>50	>50	>50	>50	>50

P5091 Specifically Target USP-7 and does not alter Proteasome Activity

USP-7 Knockout



Proteasome Activity Assay

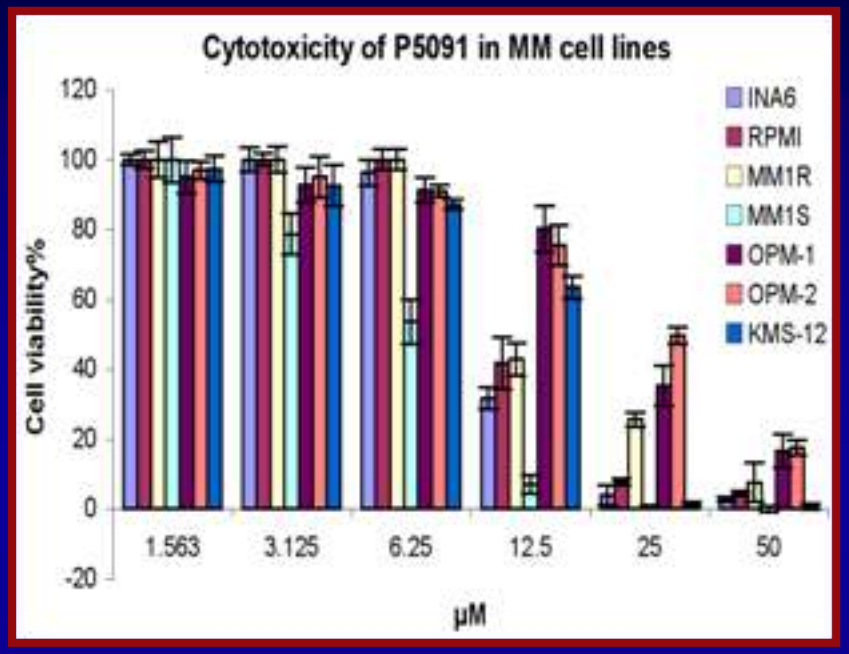


P5091 (μM)	2.5	5	7.5	10	12.5
Velcade (nM)	1	3	5	7	9

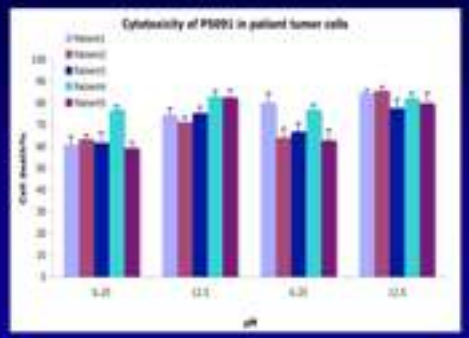
Chauhan et al., 2011

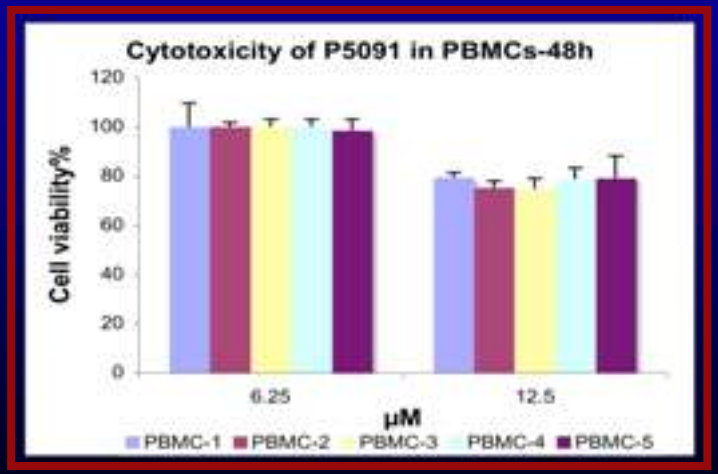
Anti-MM Activity of P5091

% Viable cells

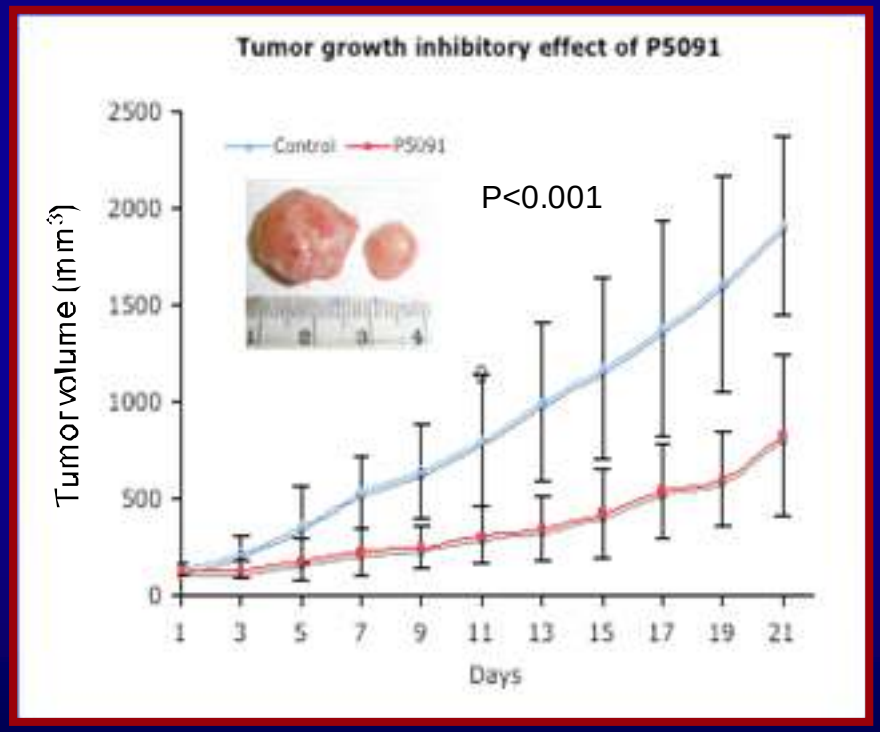


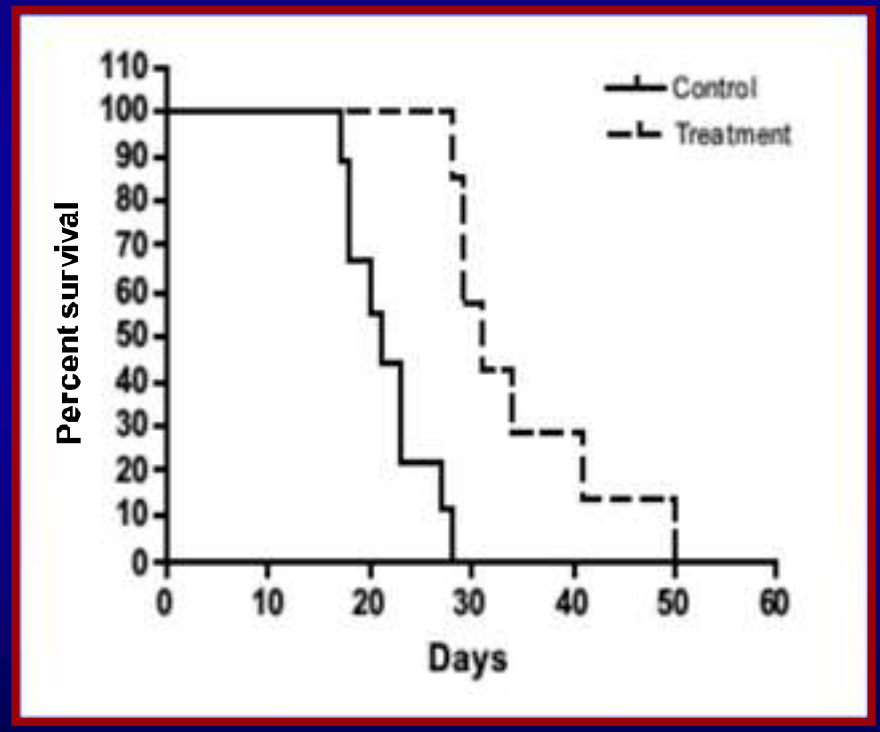
% Dead cells





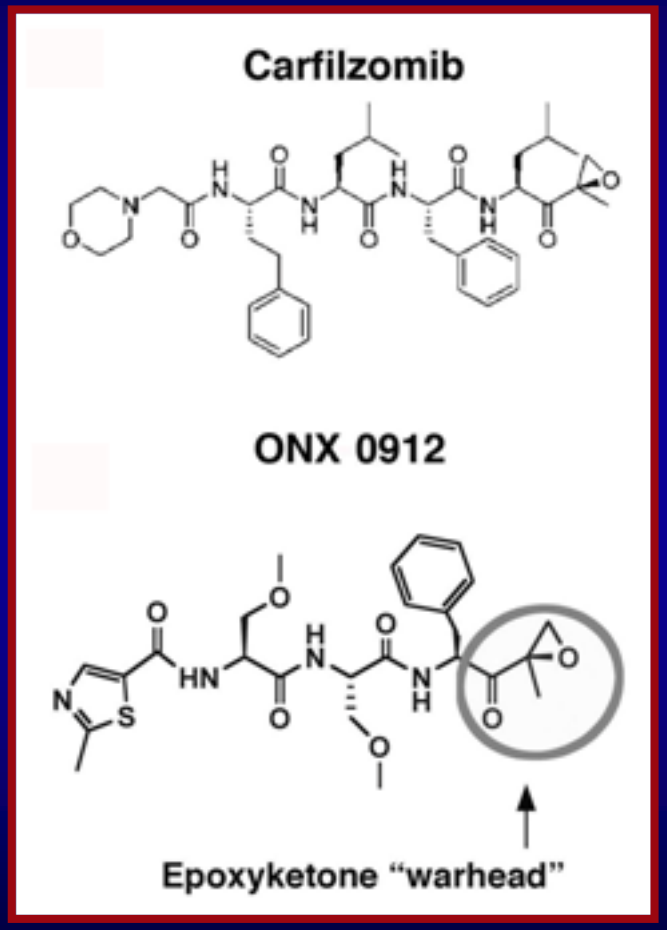
P5091 Inhibits Tumor Growth and Prolongs Survival in Human Plasmacytoma Xenograft Model

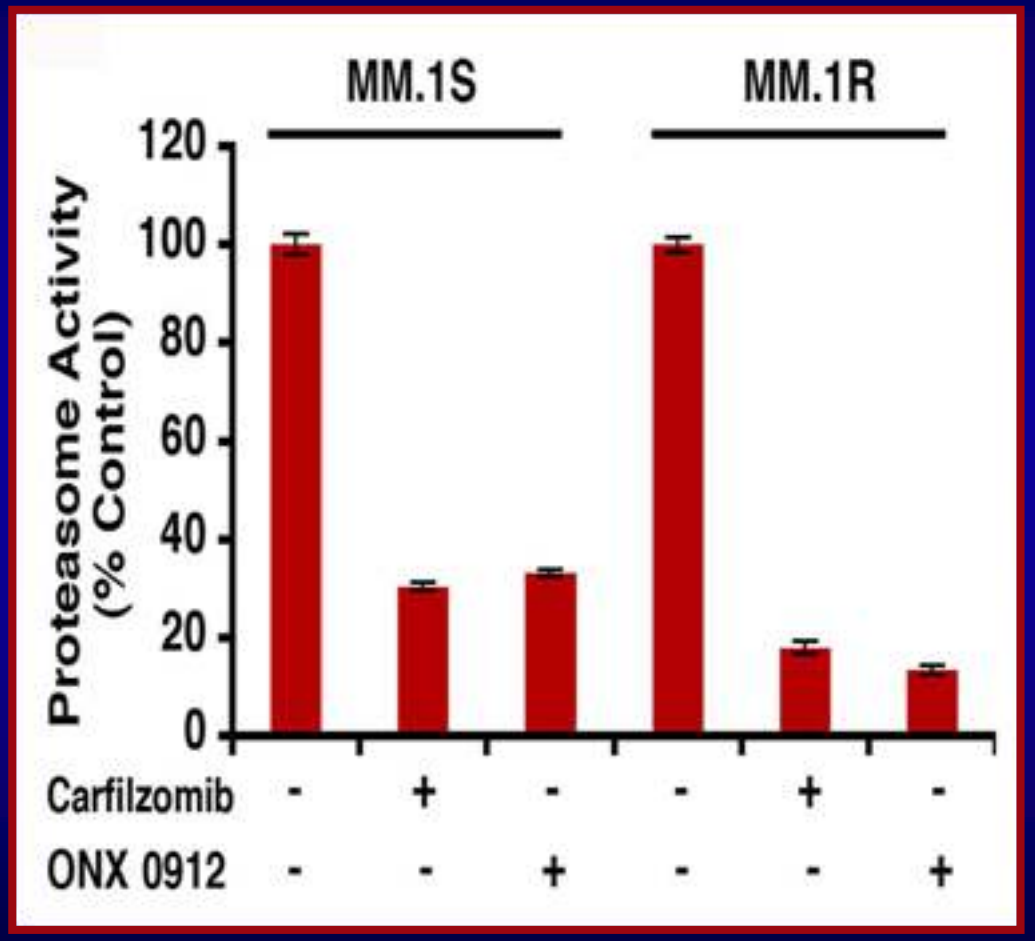




Chauhan et al., 2011

ONX 0912, a Novel Orally Active Form of Proteasome Inhibitor Carfilzomib

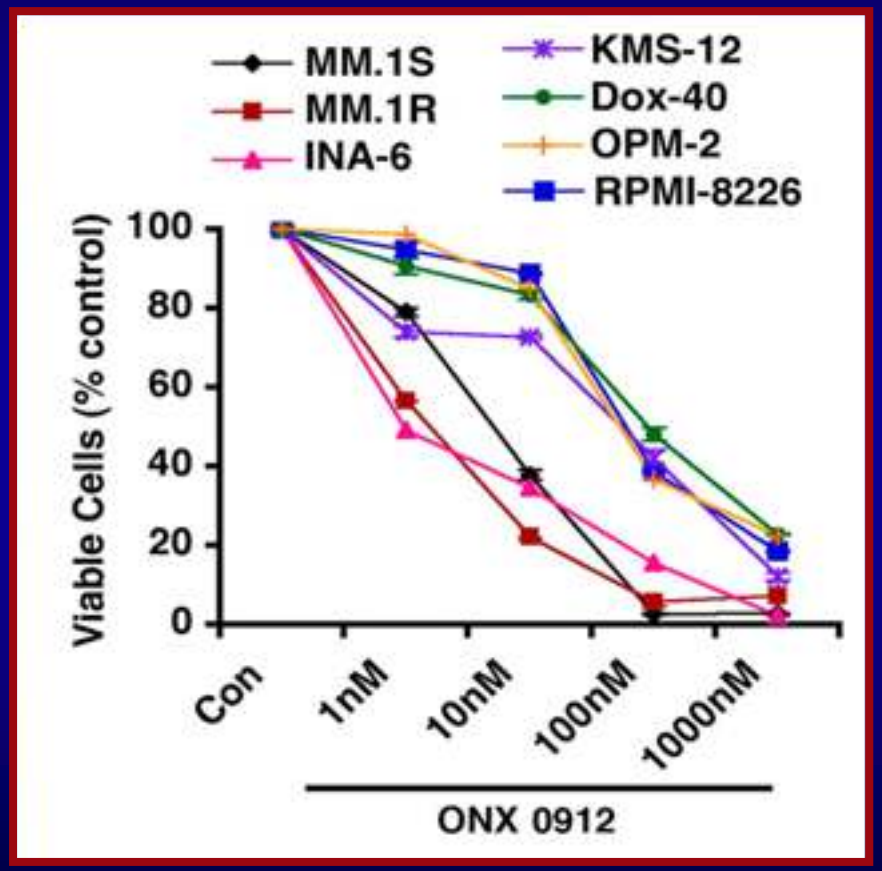




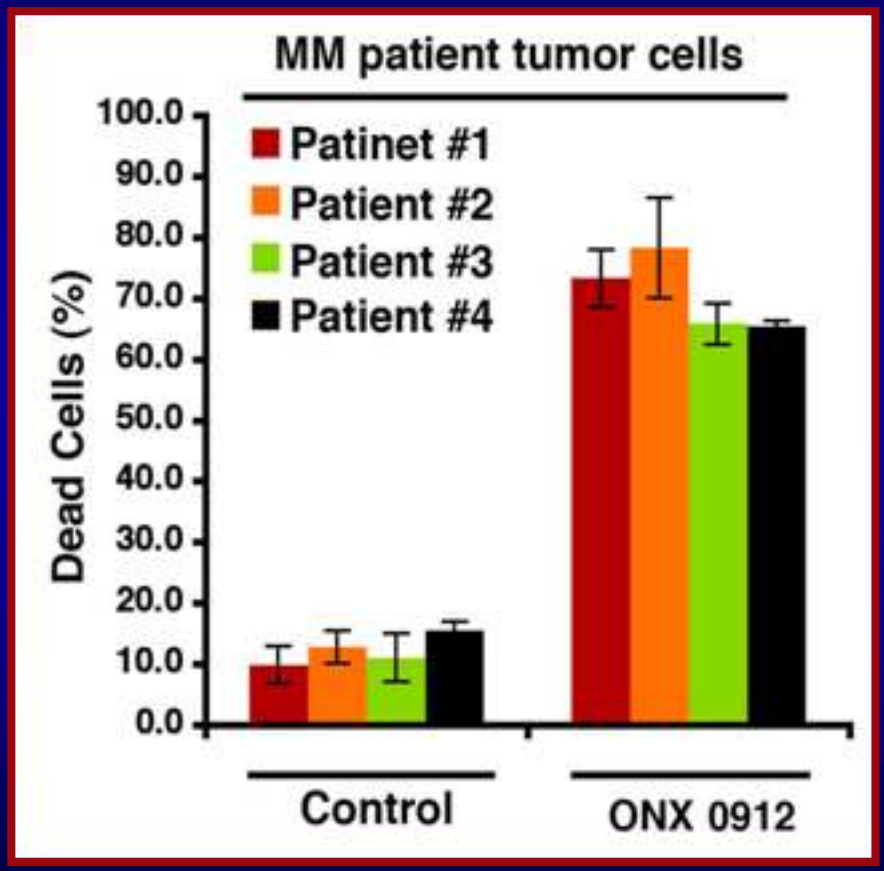
Chauhan et al., Blood 2010, 116: 4906-4915

Anti-Myeloma Activity of ONX 0912 *in vitro*

Myeloma Cell Lines

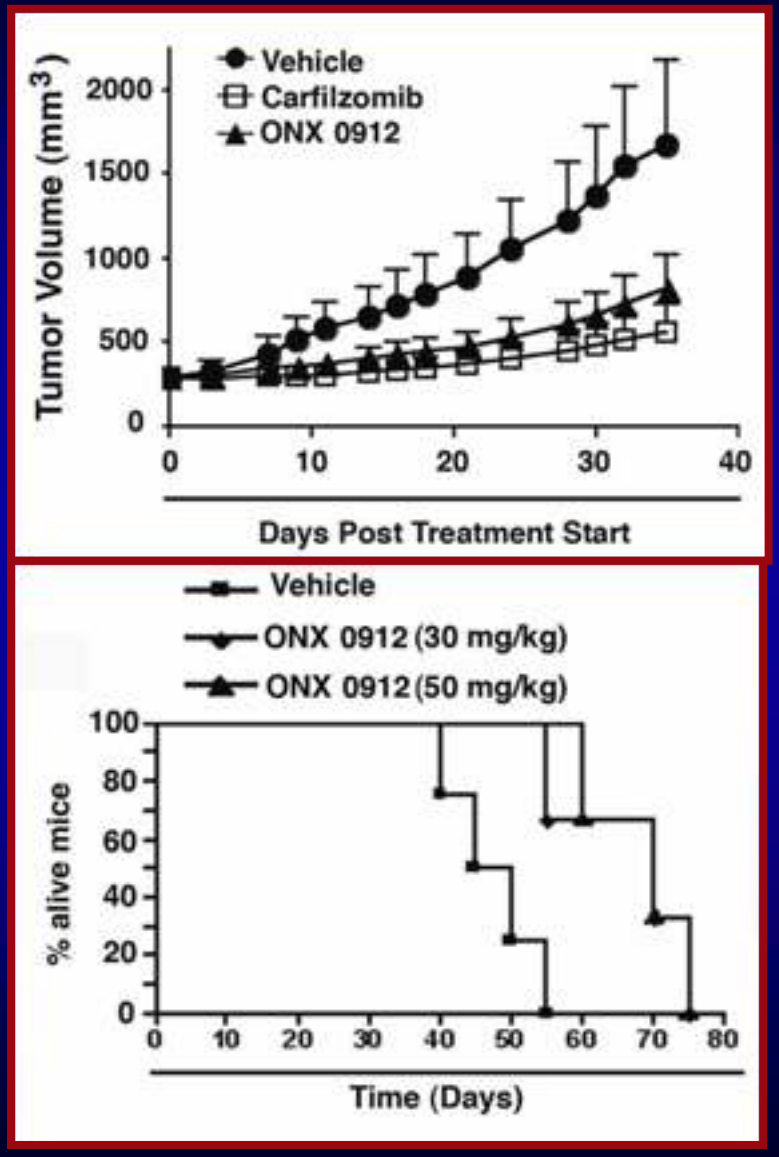


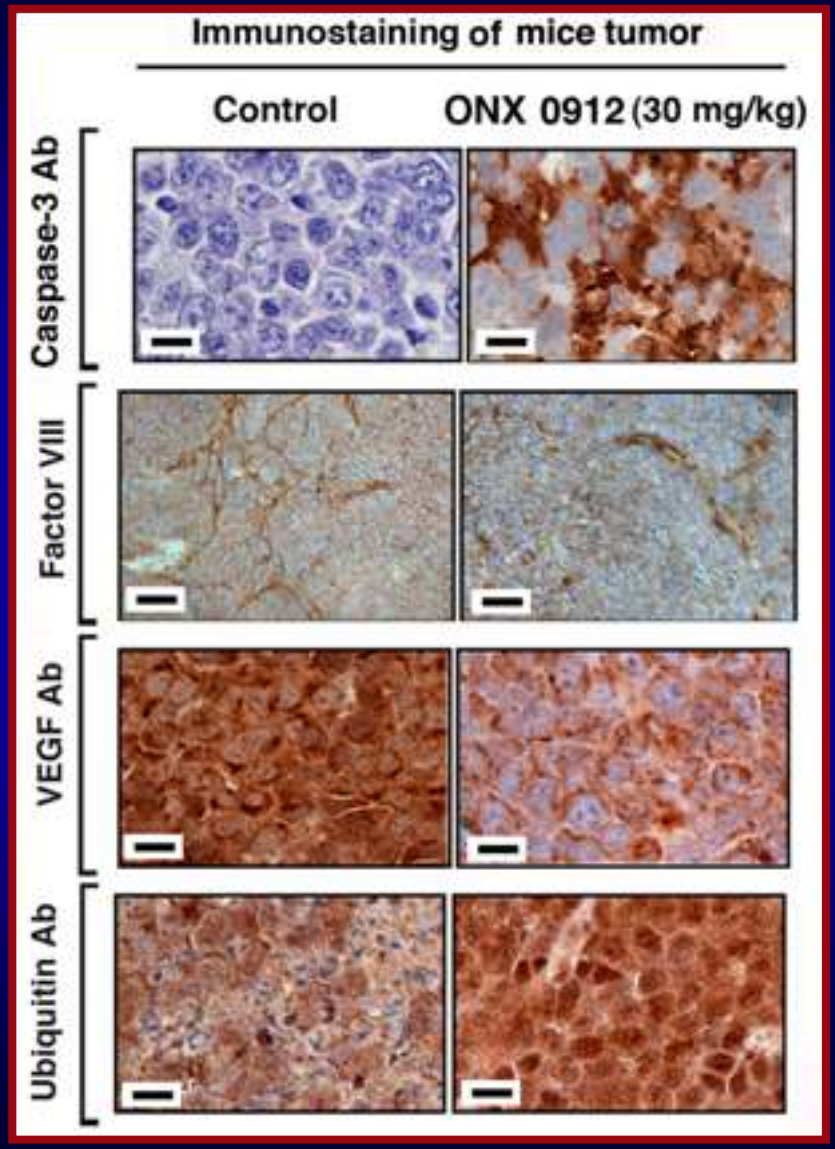
Patient Tumor Cells



Chauhan et al., Blood 2010, 116: 4906-4915

Anti-Myeloma Activity of ONX 0912 *in vivo*

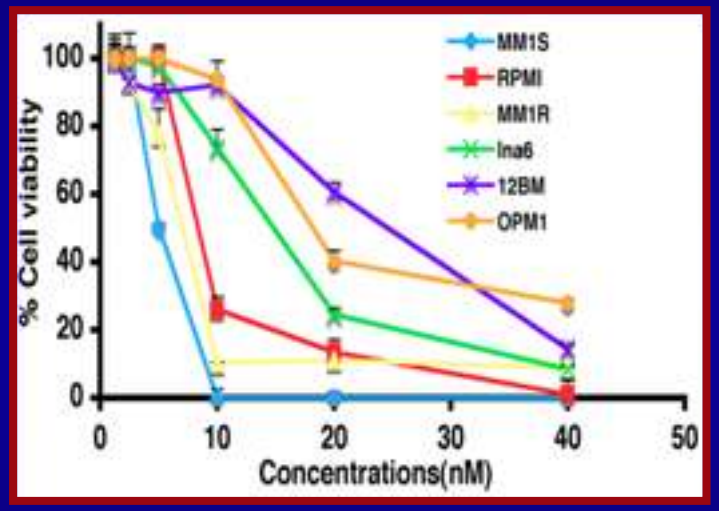




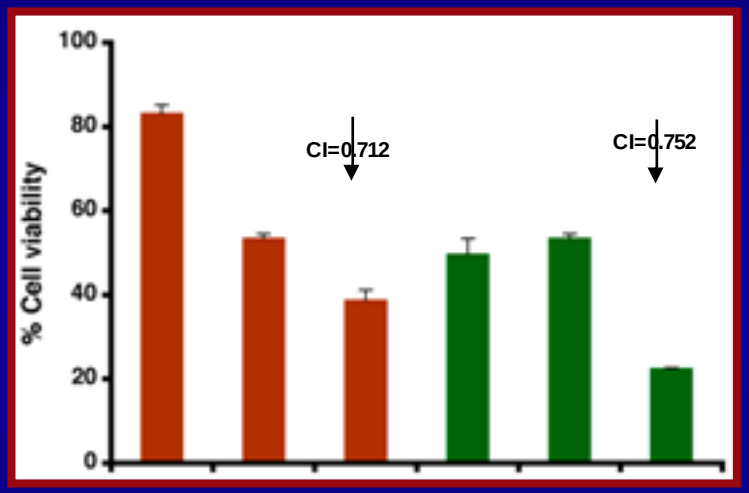
Chauhan et al., Blood 2010, 116: 4906-4915

Anti-Myeloma Activity of Novel Orally-active Proteasome inhibitor CEP-18770

CEP18770 Cytotoxicity in MM cell lines



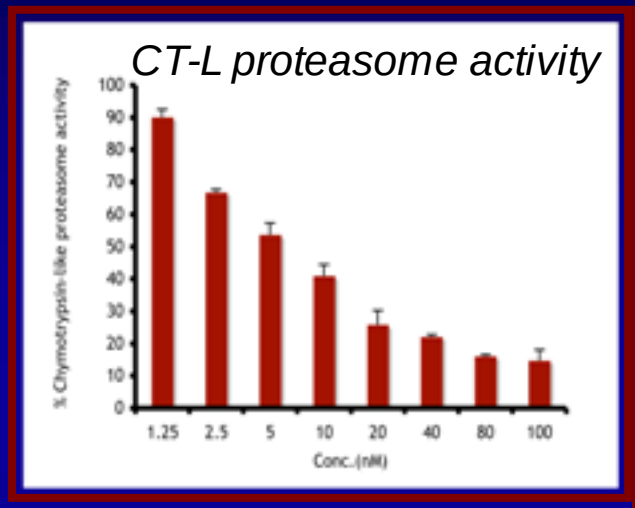
CEP18770 plus Dexamethasone trigger Synergistic cytotoxicity in MM.1S cells

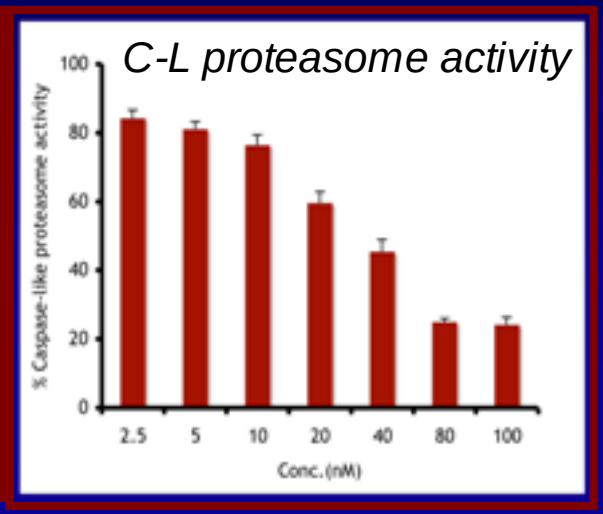


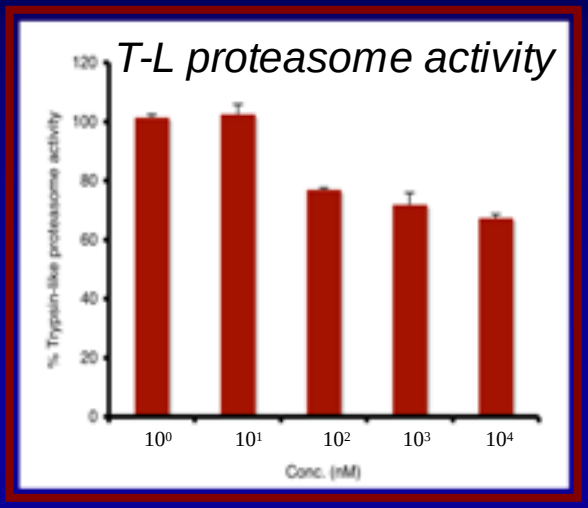
Cep-18770 (3nM)	-	-	+	-	-	-
Cep-18770 (5nM)	-	-	-	+	-	+
Dex (10nM)	-	+	+	-	+	+

Chauhan et al., 2011

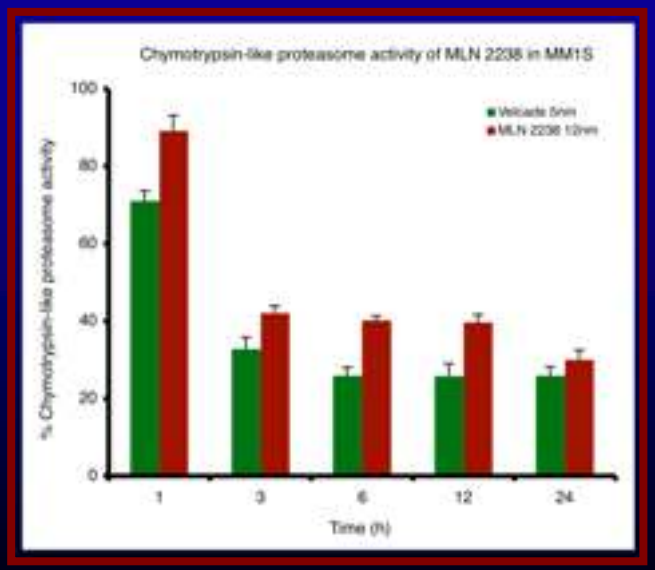
MLN9708/MLN2238 Blocks Proteasome Activity in MM Cells





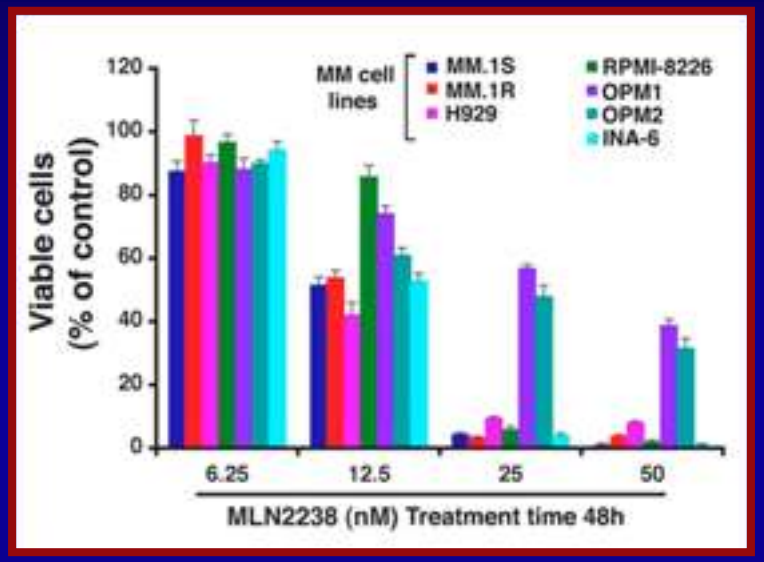


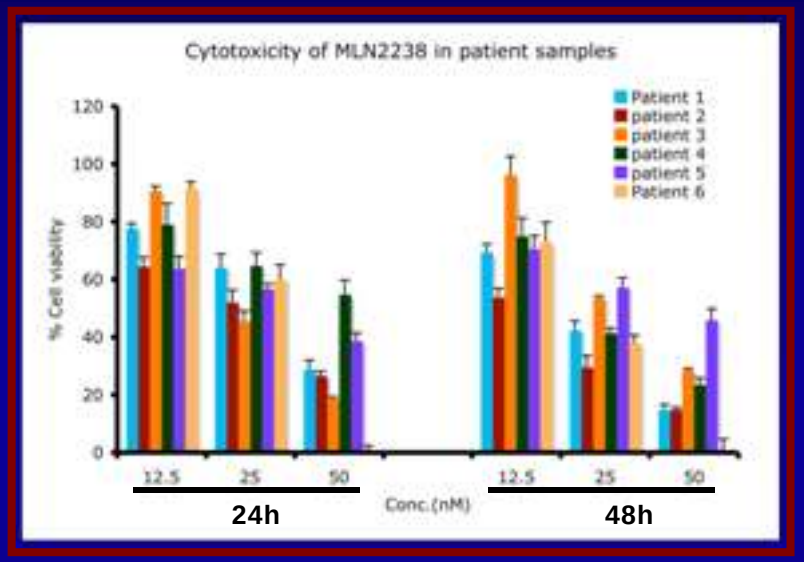
Comparative effects of MLN2238 vs. bortezomib on CT-L proteasome activity

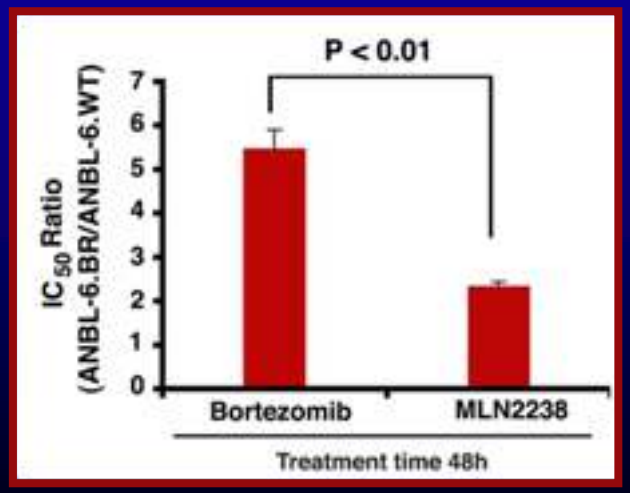


Chauhan et al., Clin Cancer Res, 2011

MLN2238 Decreases Cell Viability in MM Cells and Overcomes Bortezomib-Resistance



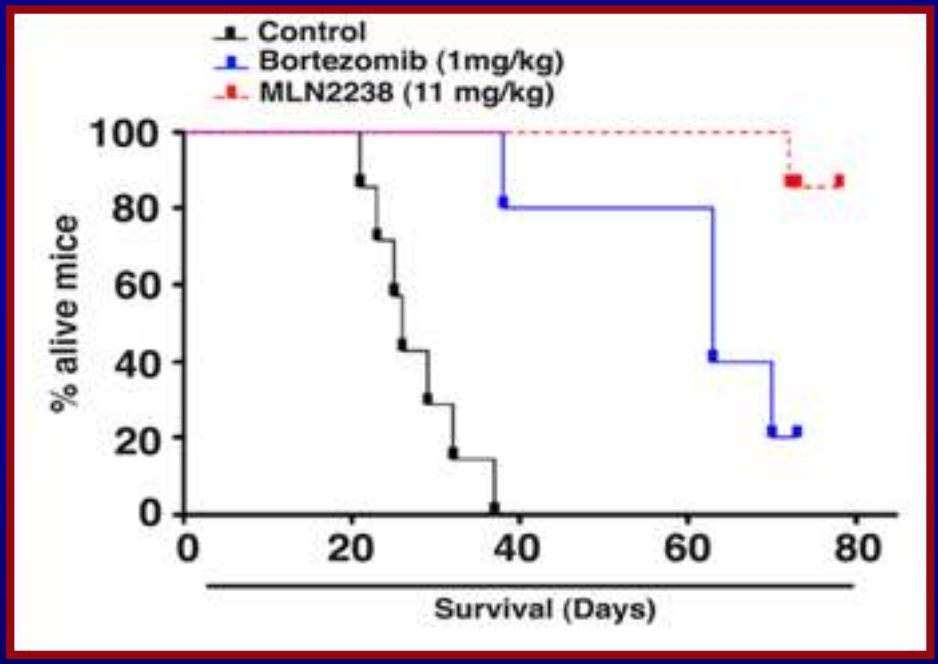




Chauhan et al., Clin Cancer Res, 2011

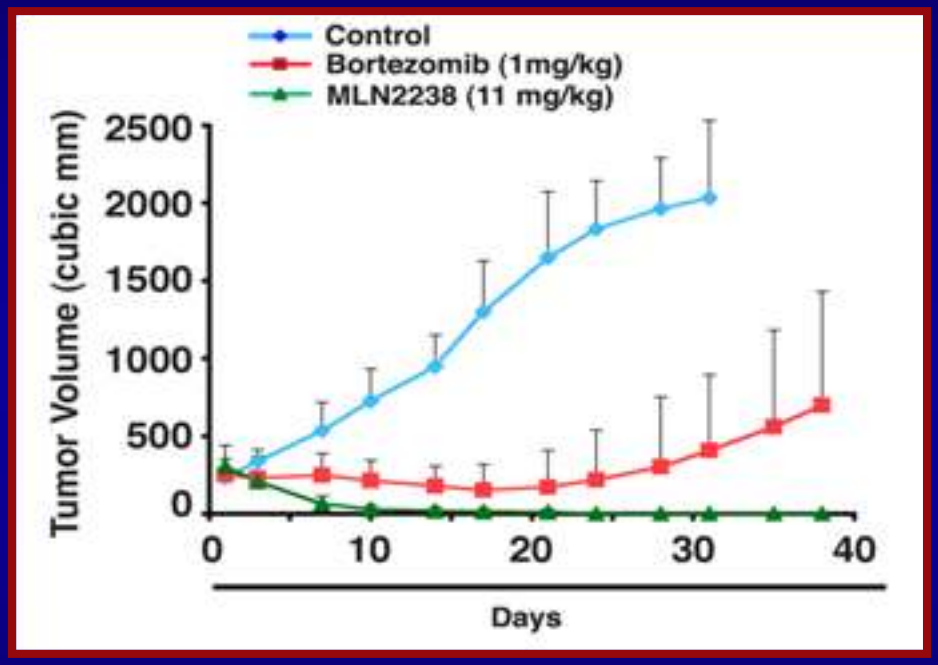
In Vivo Anti-MM Activity of MLN2238 *vs.* Bortezomib

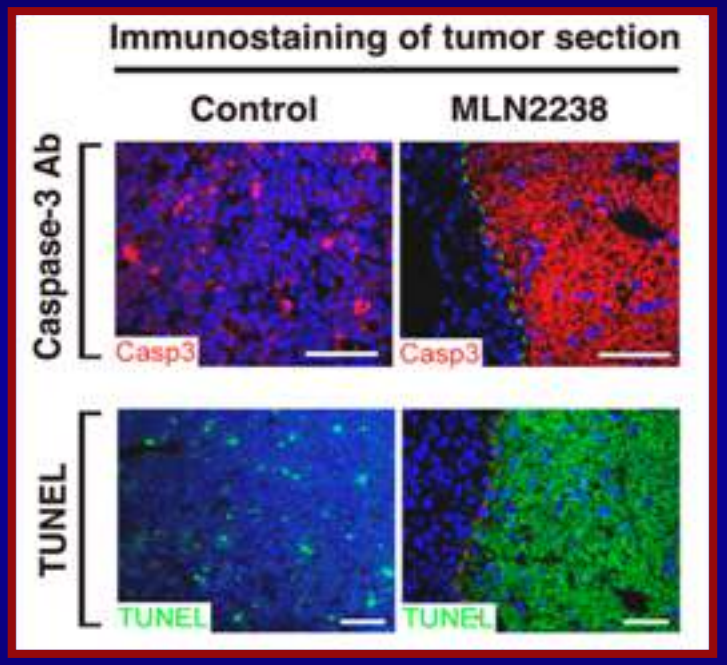
A longer survival time was observed in mice treated with MLN2238 than mice receiving bortezomib



Chauhan et al.,
Clin Cancer Res, 2011

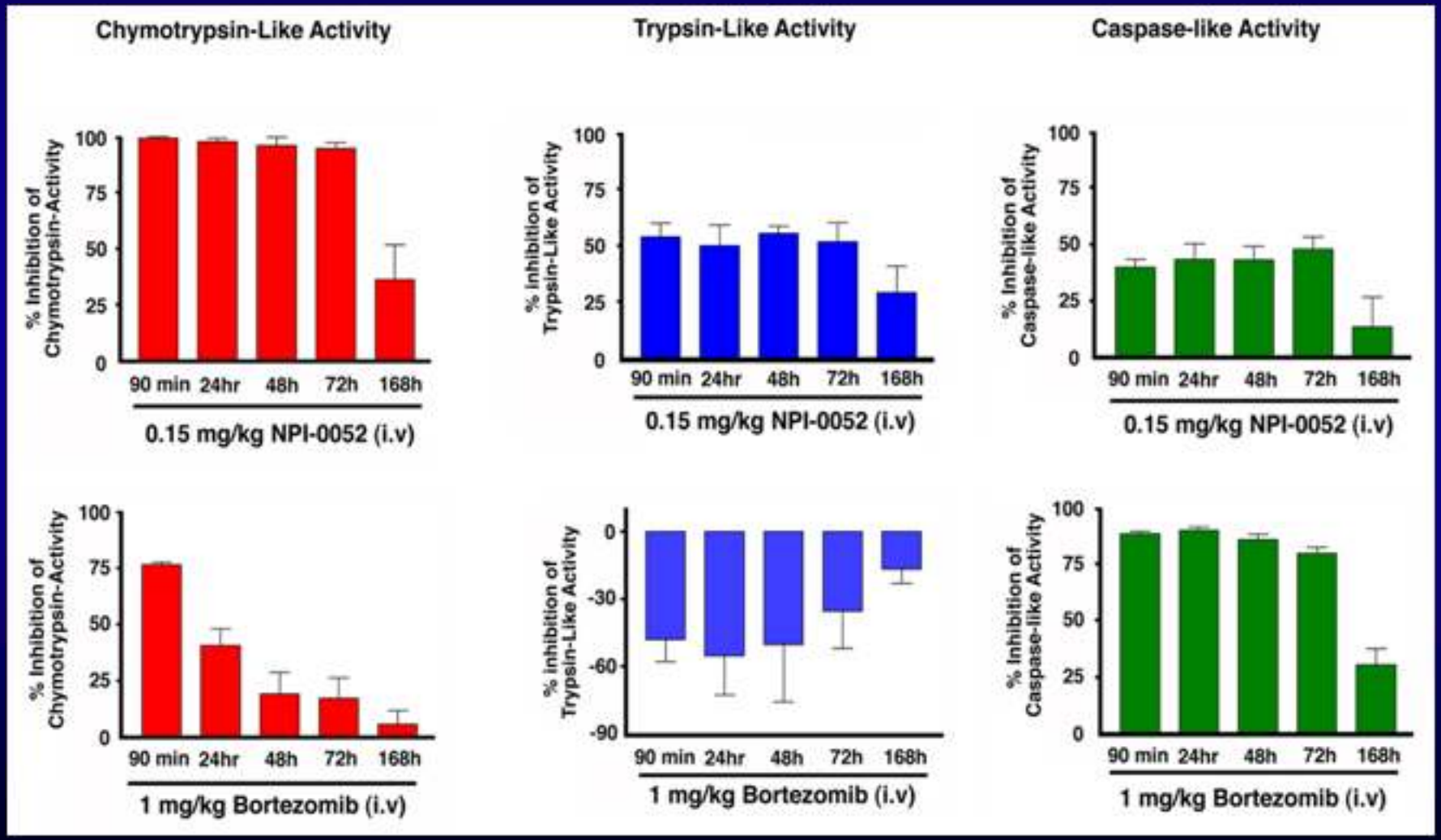
MLN2238 Inhibits MM Cell Growth *In Vivo*



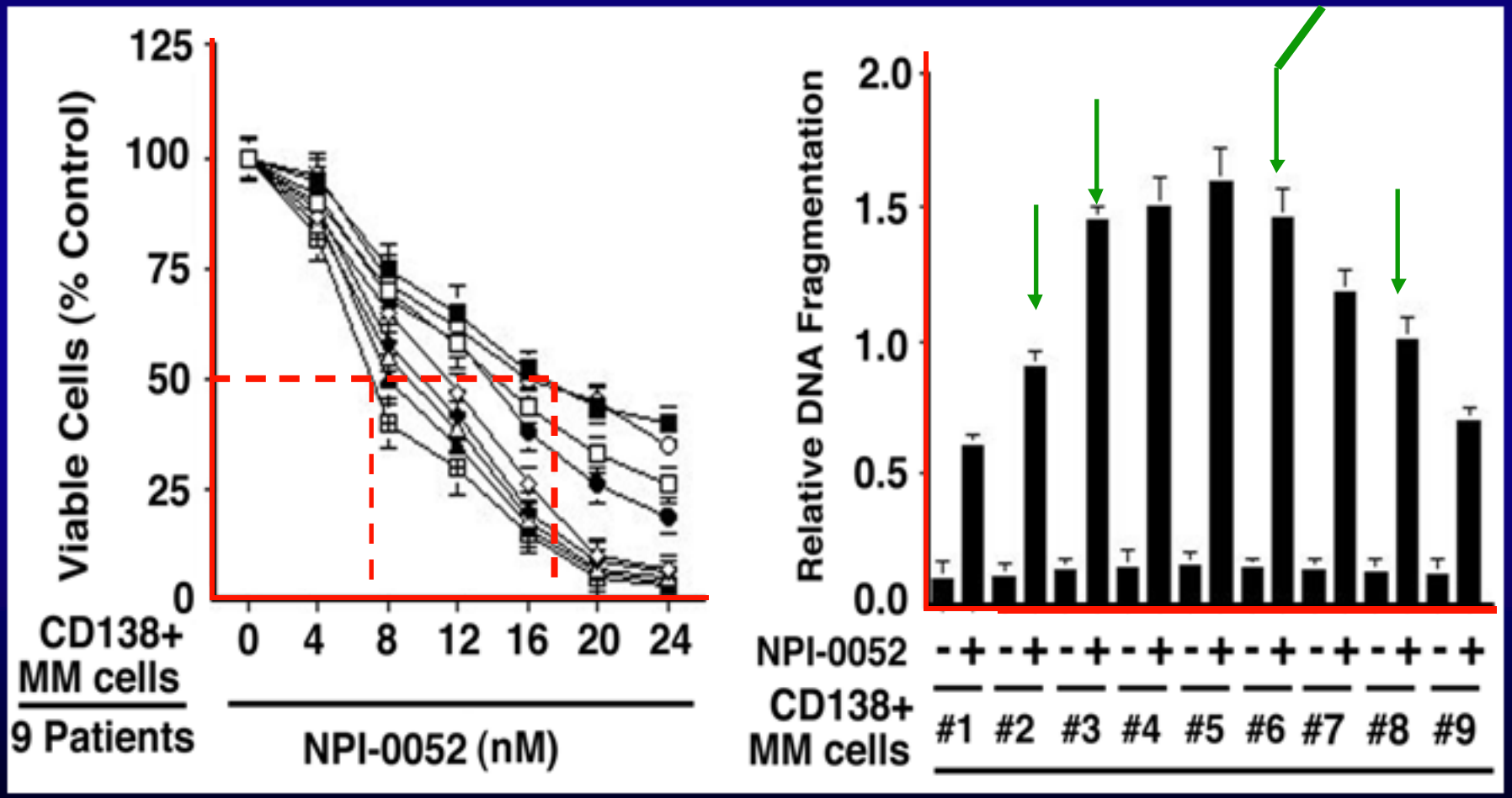


Chauhan et al.,
Clin Cancer Res, 2011

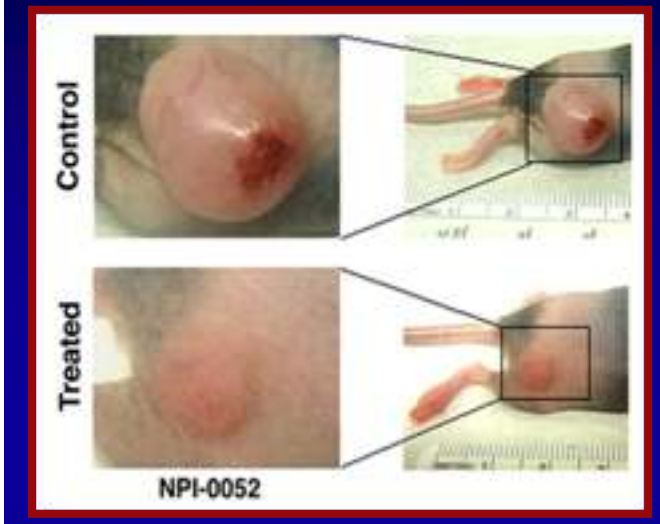
In Vivo Proteasome Activity Profiles of NPI-0052 and Bortezomib

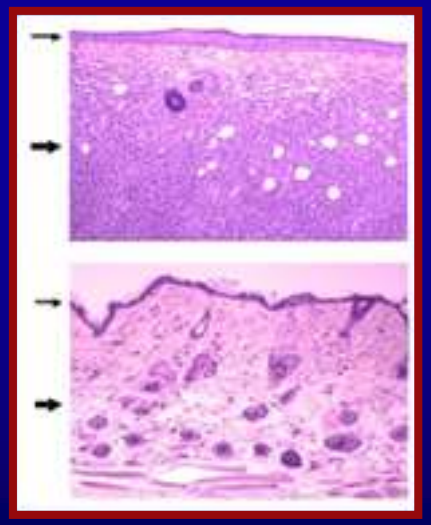


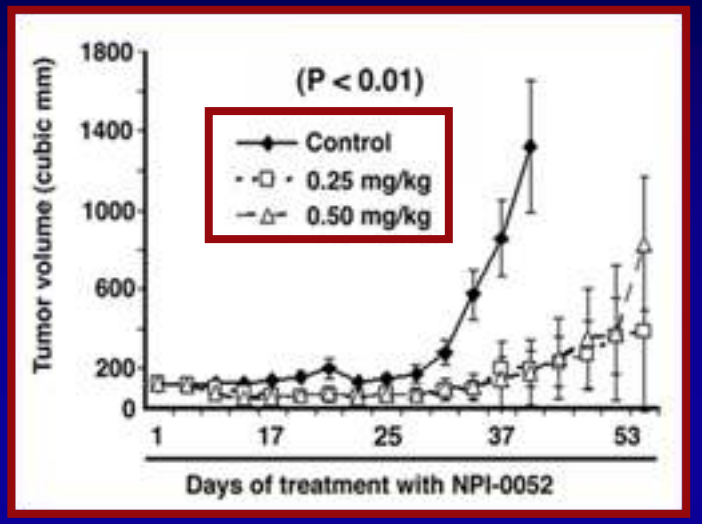
NPI-0052 Inhibits Growth and Triggers Apoptosis in Purified MM Patient Cells

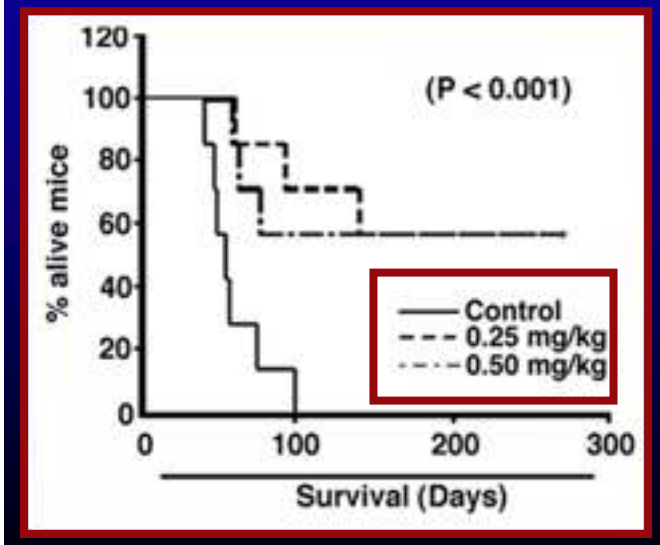


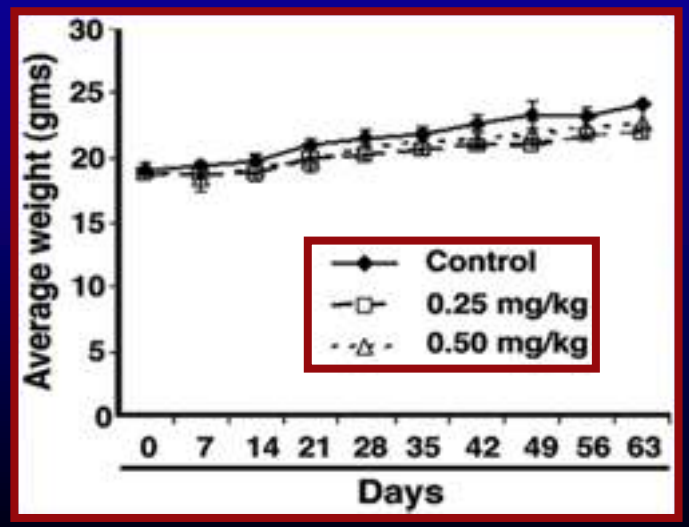
NPI-0052 Inhibits MM Cell Growth *In Vivo* and Prolongs Survival in a Murine Model



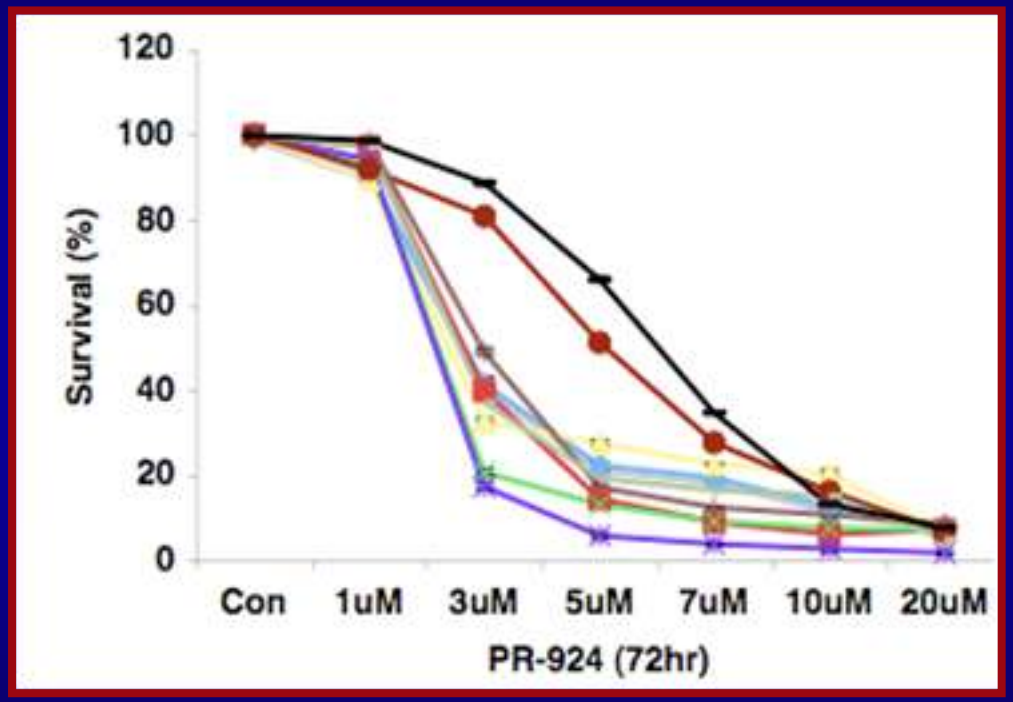


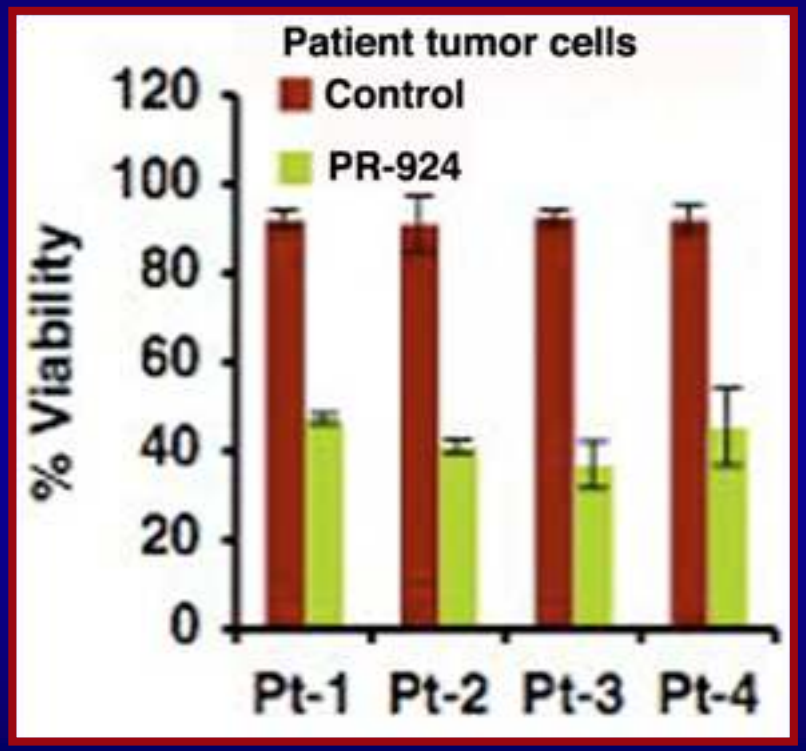






PR-924, a Selective Inhibitor of Immunoproteasome Subunit LMP-7, Blocks MM Cell Growth *in vitro*

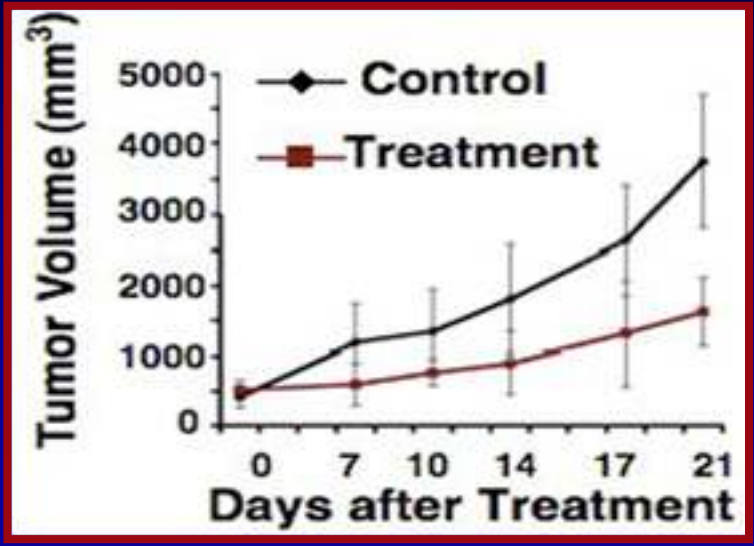


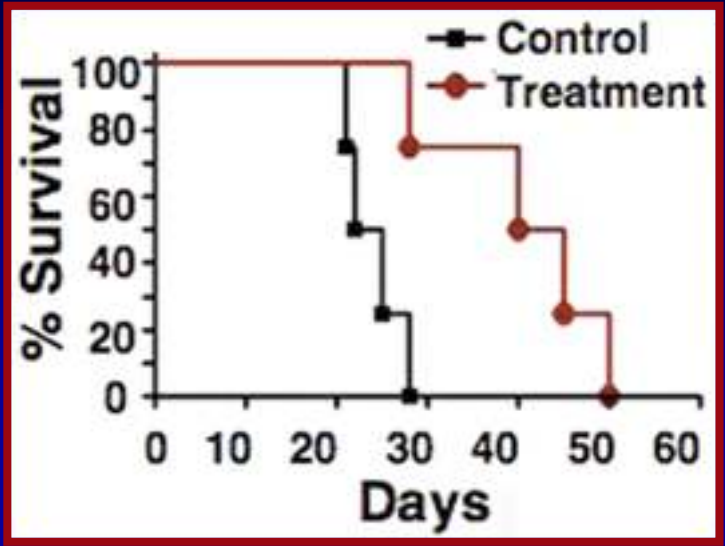


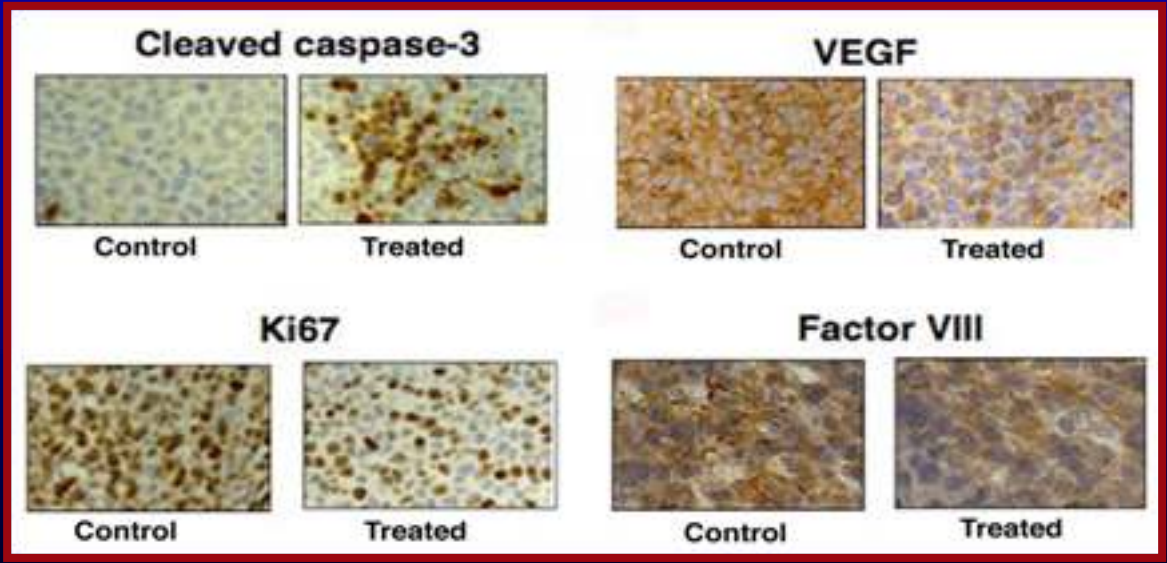
MM1S
MM1R
RPMI
KMS
LR5
Dox40
INA6
OPM1
OPM2

Singh and Chauhan et al., Br J Hematol 2010, 152: 155-163

PR-924 Blocks MM Cell Growth *in vivo*







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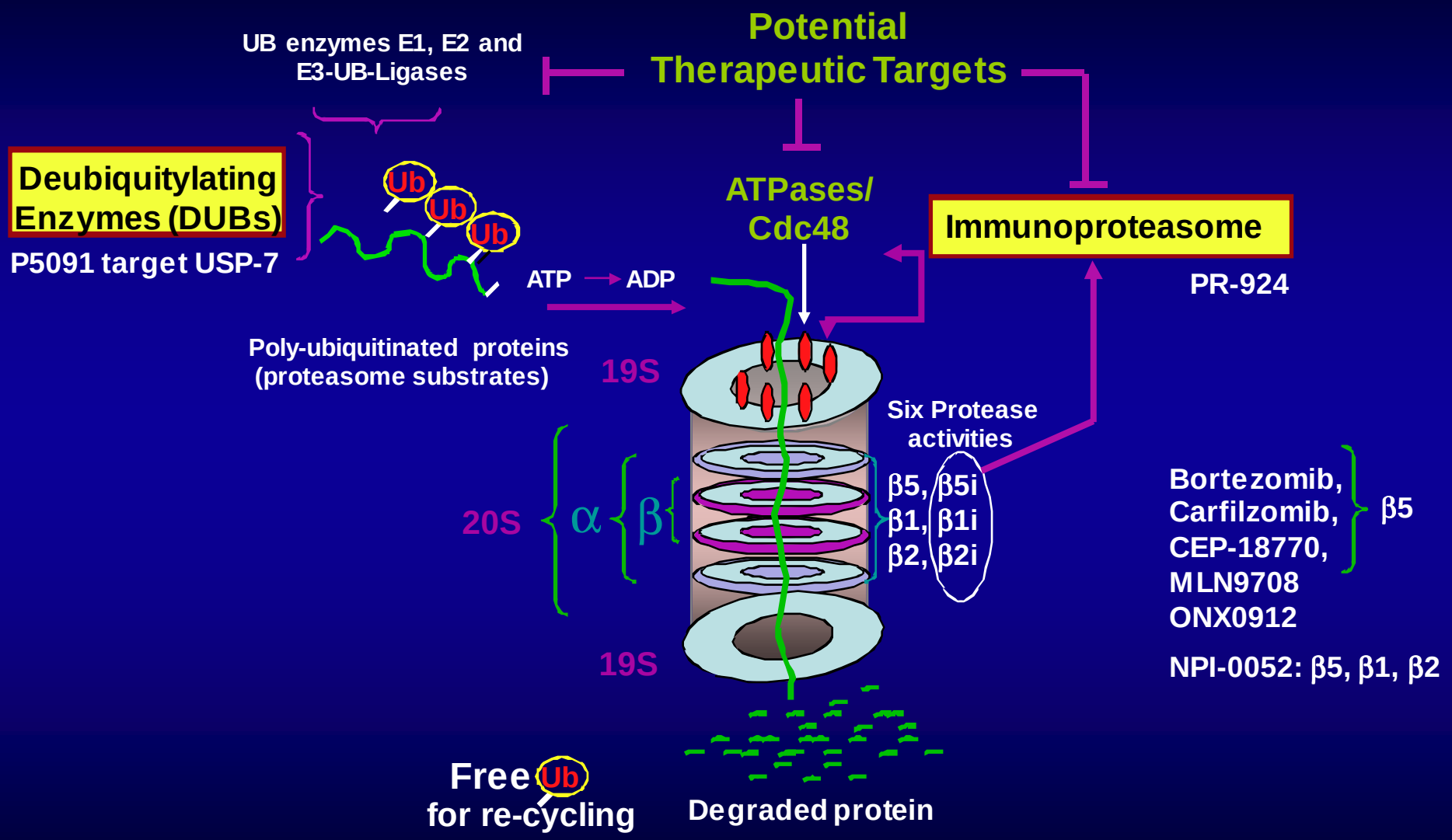

Chauhan et al., 2011