Understanding Biological Activity to Inform Drug Development in Multiple Myeloma

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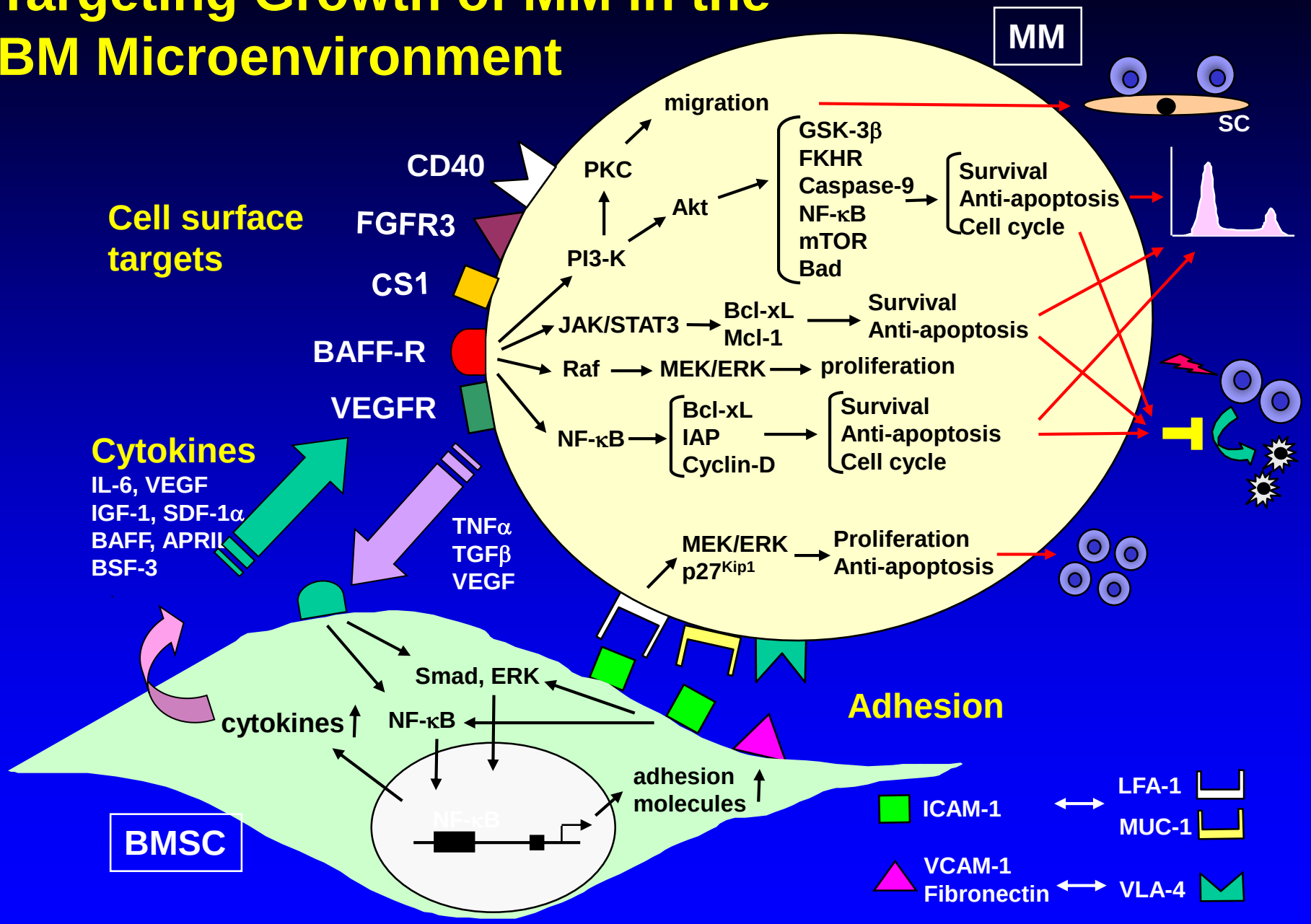
Targeting Growth of MM in the BM Microenvironment



Hideshima T and Anderson KC. Nat Rev Cancer 2007,

Integration of Novel Therapy Into Myeloma Management

Proteasome inhibitors: Bortezomib, carfilzomib, ixazomib; **immunomodulatory drugs:** thalidomide, lenalidomide, pomalidomide; **HDAC inhibitor:** panobinostat; **monoclonal antibodies:** elotuzumab and daratumumab

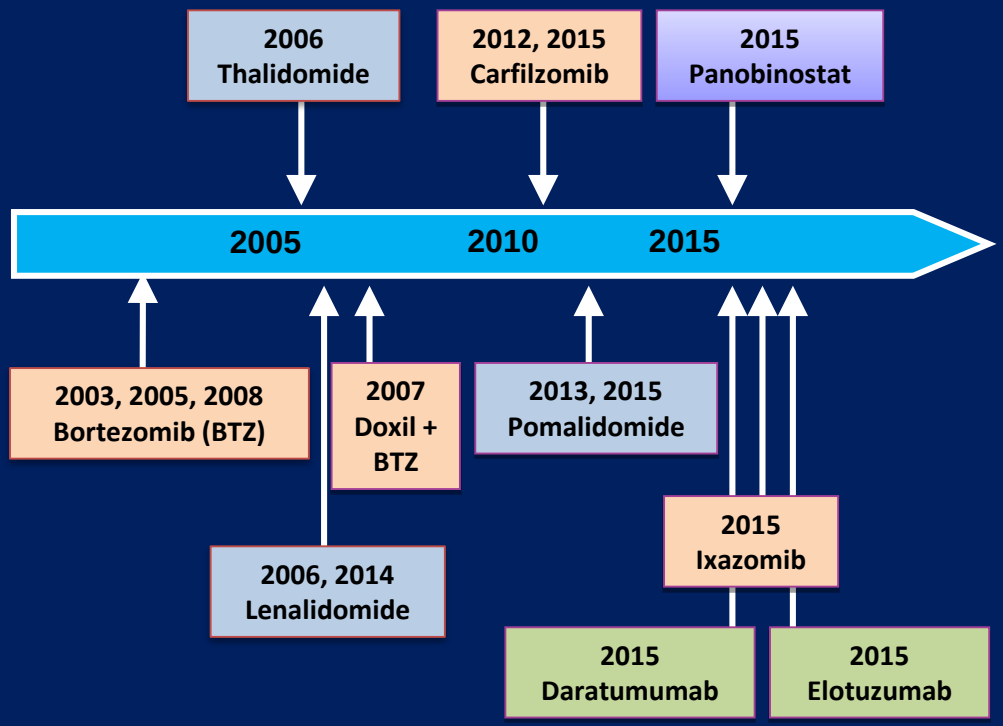
Target MM in the BM microenvironment, alone and in combination, to overcome conventional drug resistance *in vitro* and *in vivo*

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

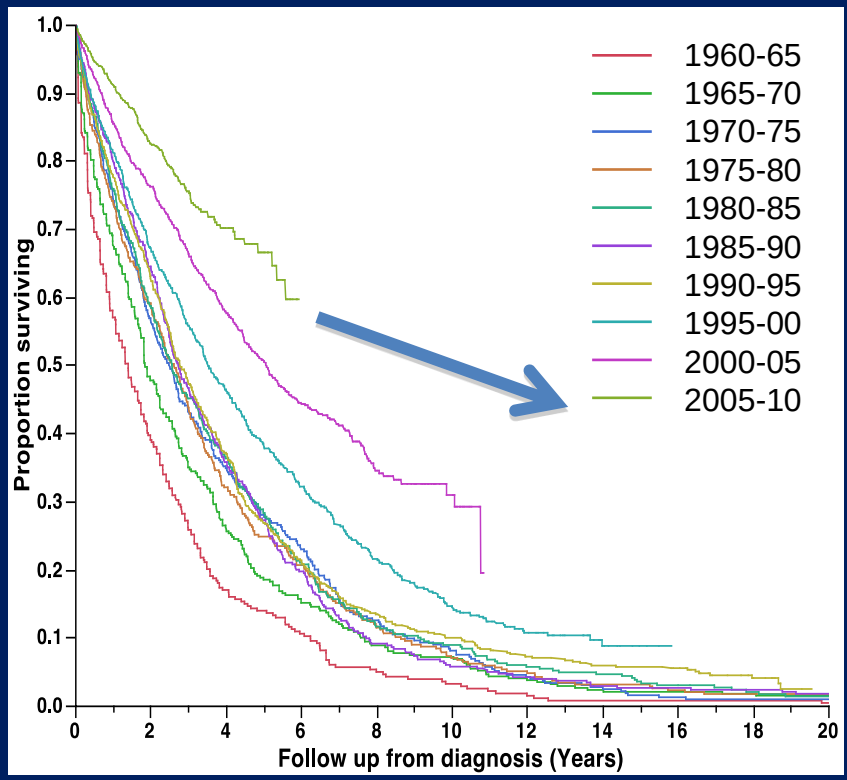
18 FDA approvals and median patient survival prolonged 3-4 fold

Bench to Bedside Translation of Novel Agents in Myeloma

Preclinical and Clinical Studies leading to FDA Approvals in MM

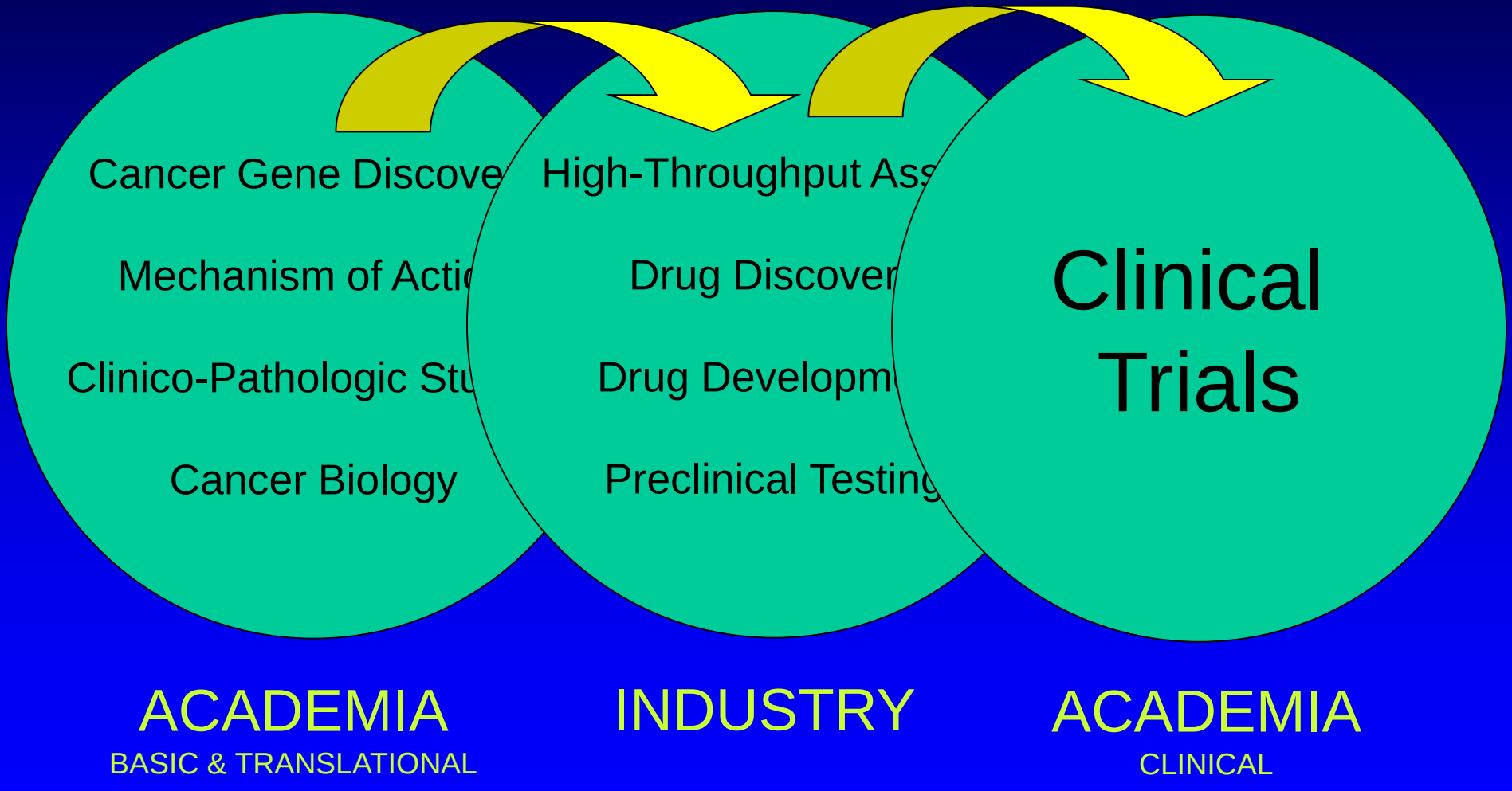


Improvement in overall survival from median of 3 to 8-10 years

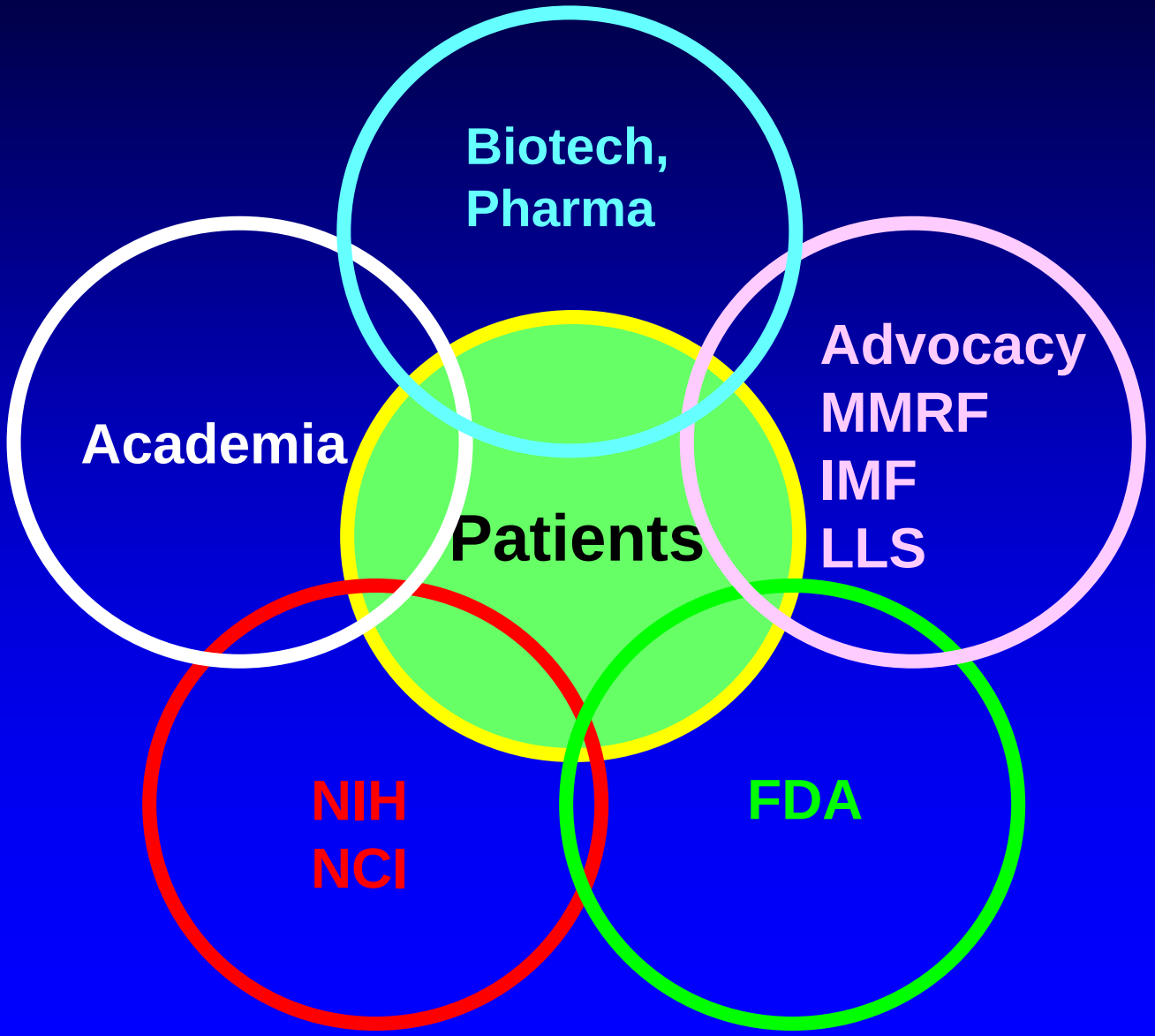


Immunomodulatory agent
Monoclonal Antibody
Proteasome inhibitor
HDAC inhibitor

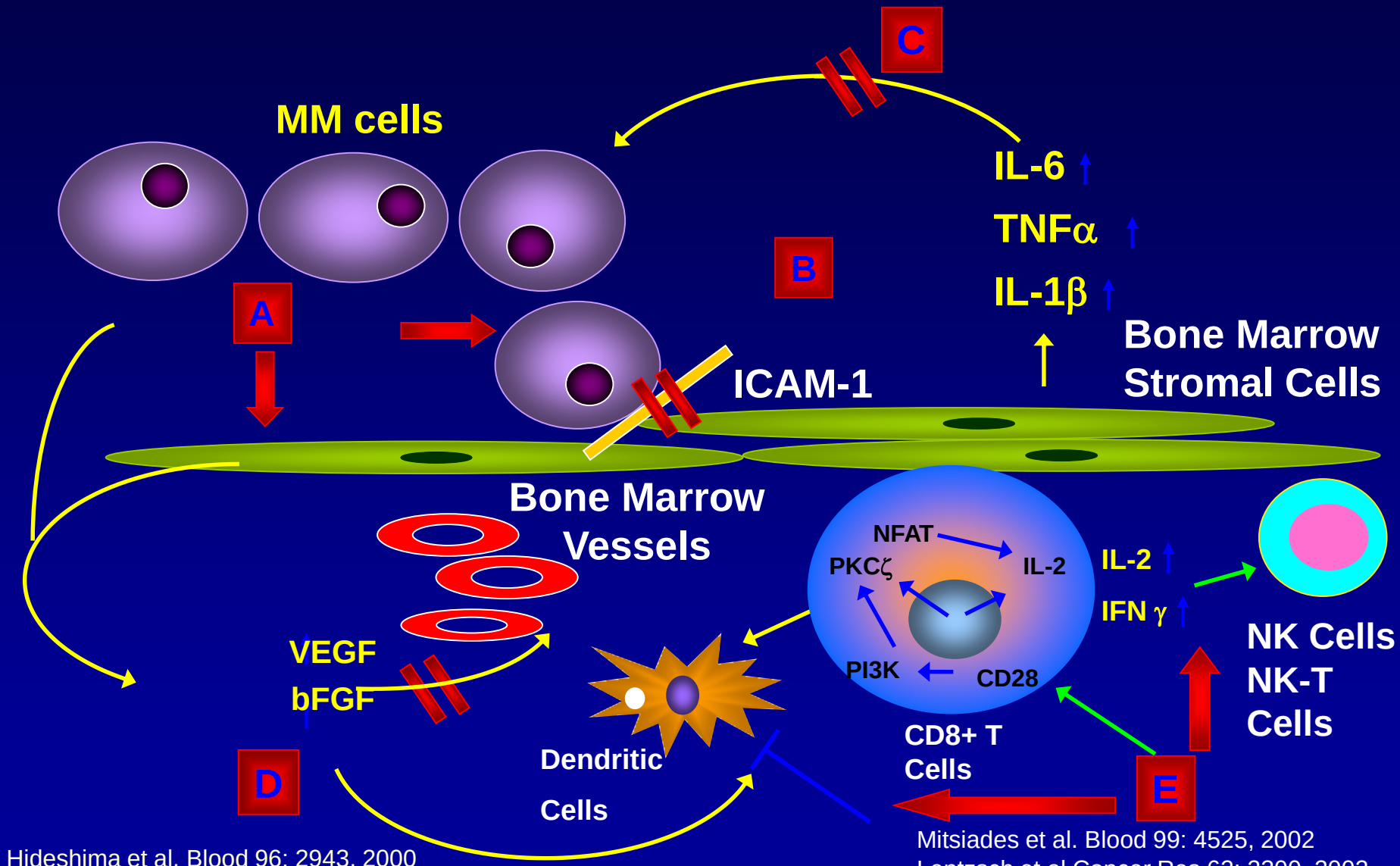
Myeloma Model to Link Partners to Overcome Obstacles in Traditional Drug Development



Multiple Myeloma Collaborative Model for Bench to Bedside Research



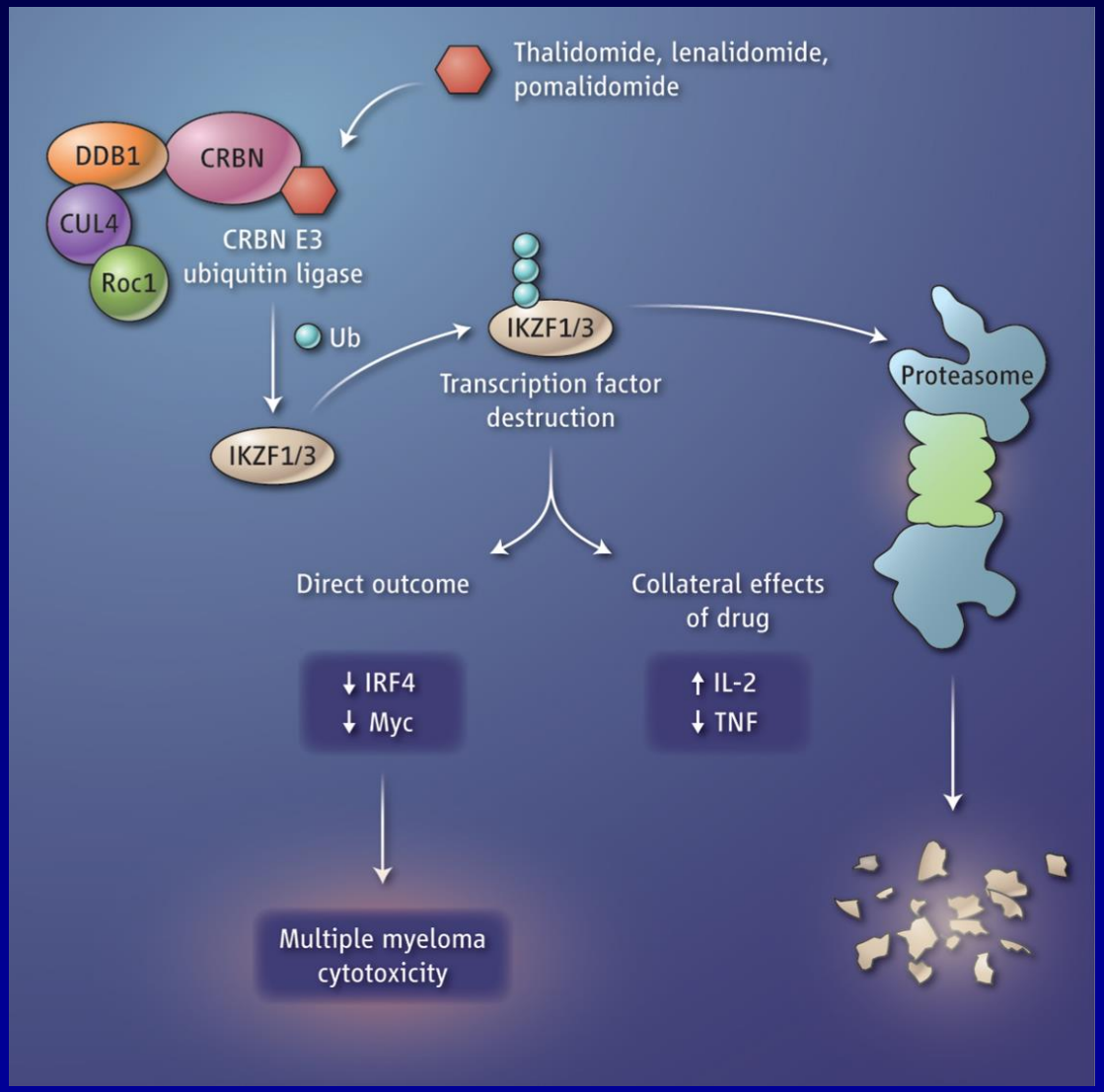
Immunomodulatory Drugs in Myeloma



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

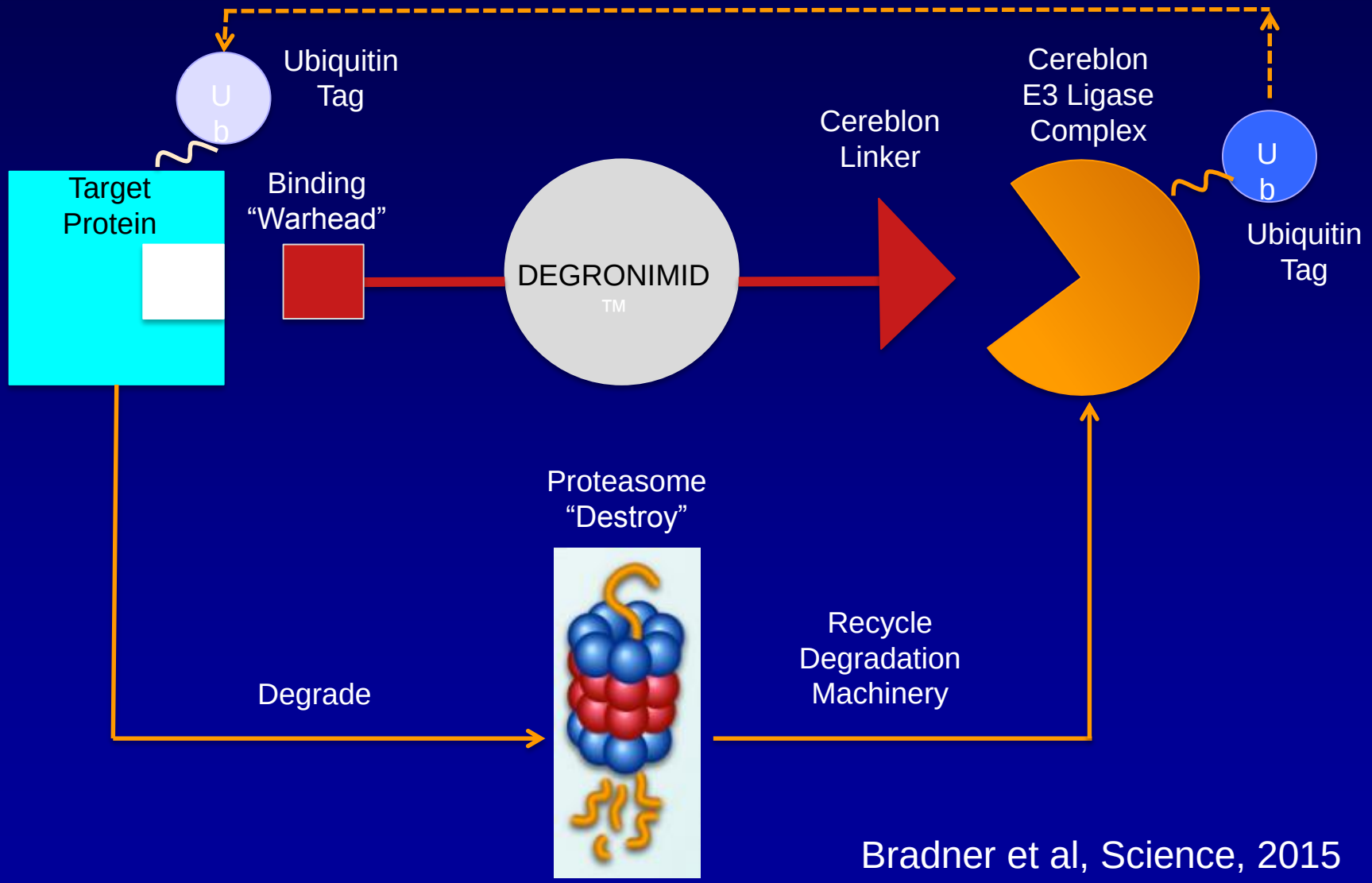


Degronimids:
Link to ubiquitin
3 ligase complexes

Kronke et al, Science, 2014

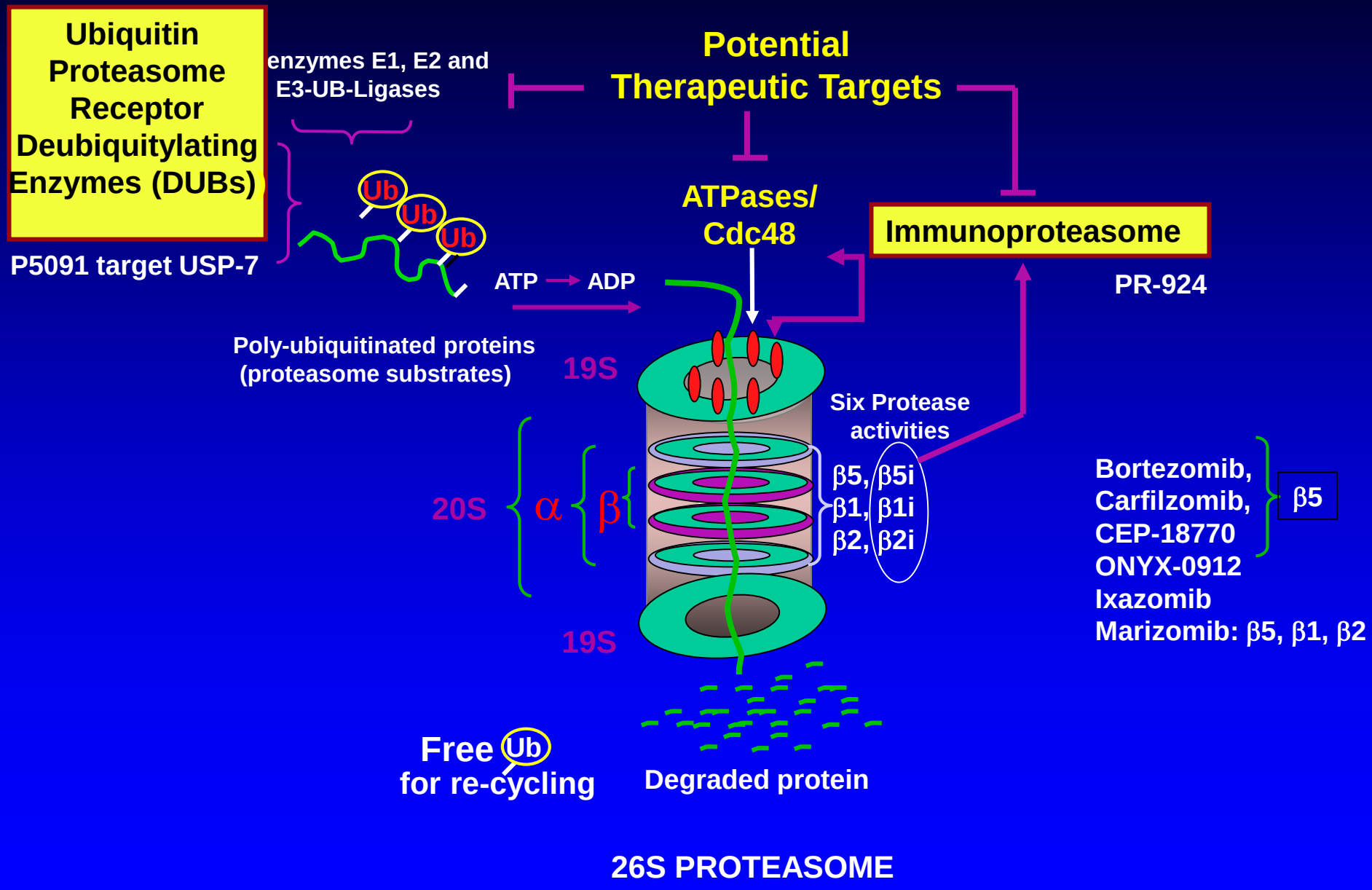
Lu et al, Science, 2014

Degronimids Trigger Degradation of Selective Substrates

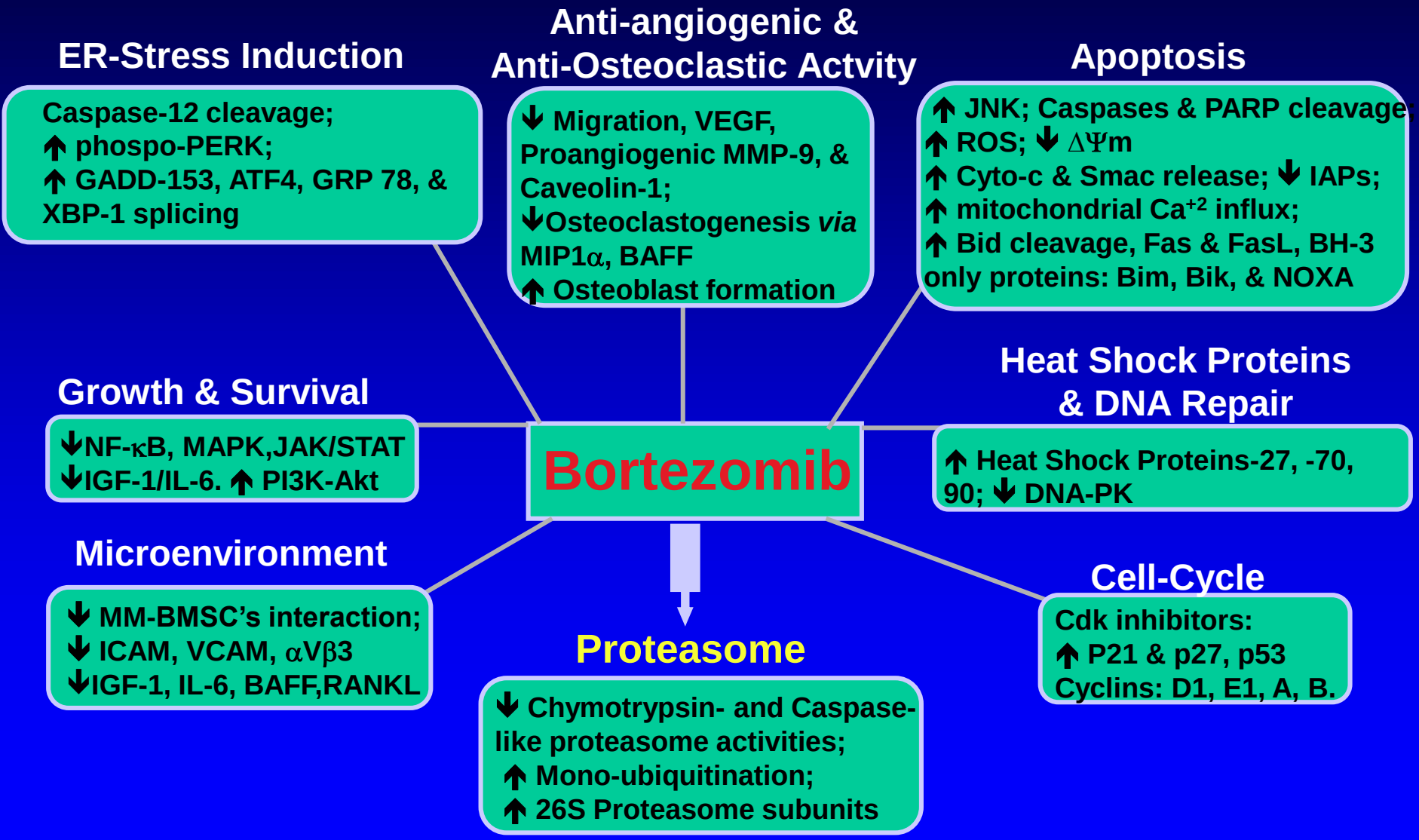


Bradner et al, Science, 2015

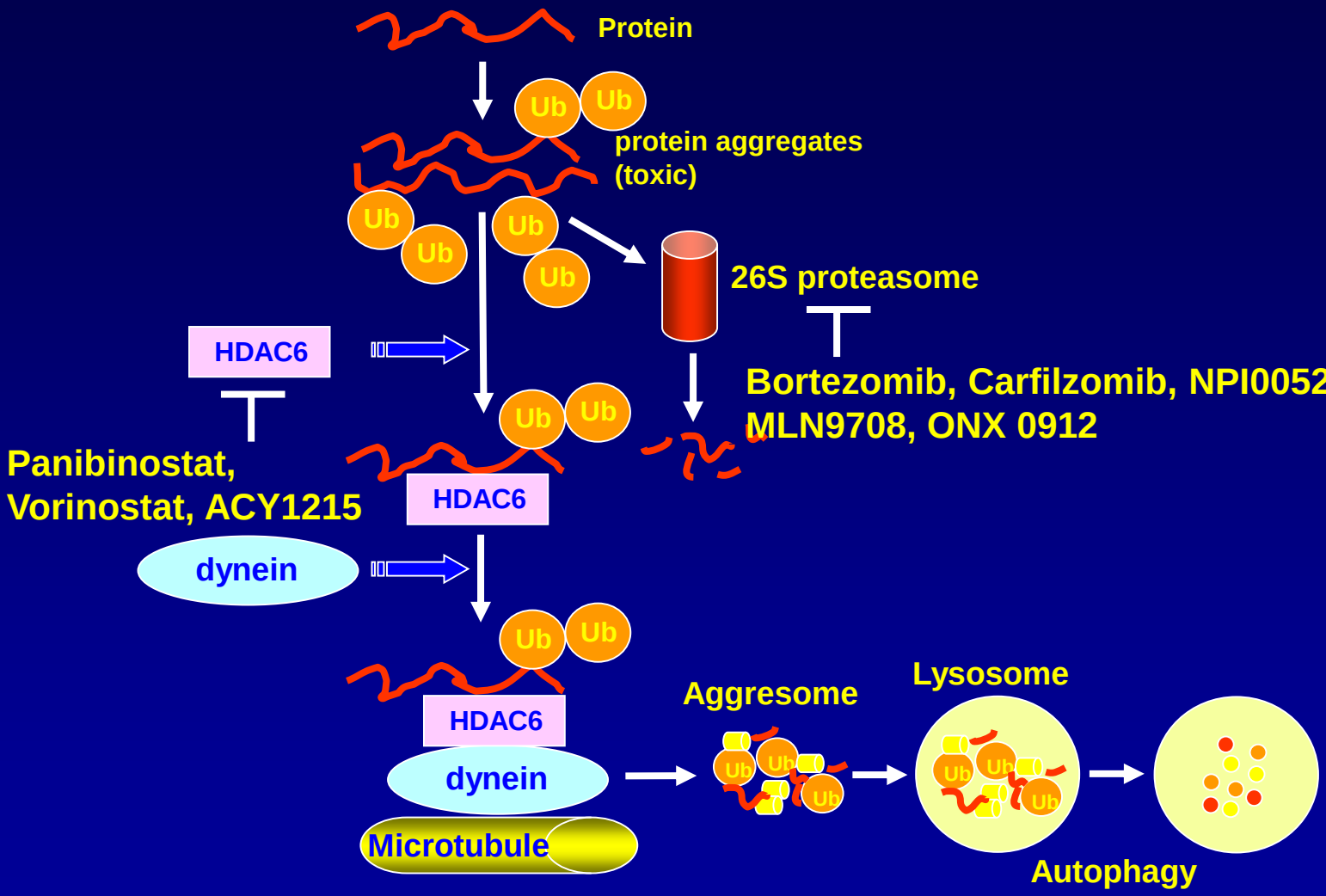
Proteasome: Present and Future Therapies



Mechanisms Mediating Anti-MM Activity of Bortezomib



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.

Panobinostat or Placebo Plus Bort/ Dex in Relapsed or Relapsed/ Refractory MM

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 3/4 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%).

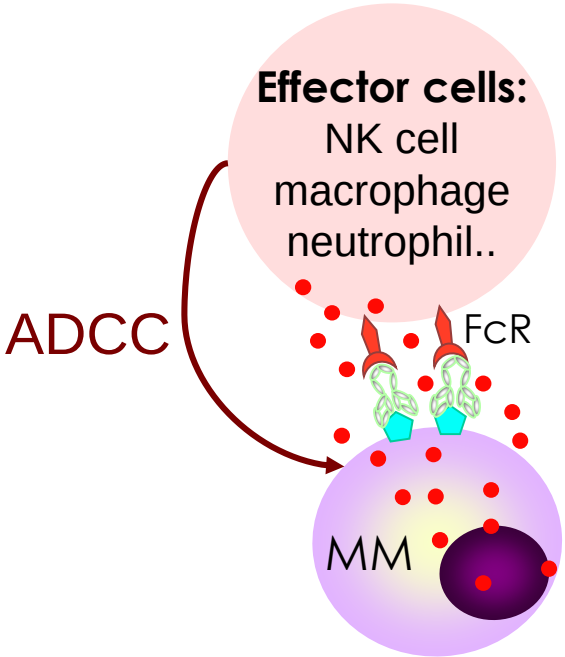
FDA approved for relapsed refractory MM exposed to bortezomib and IMiD

Need for less toxic more selective HDACi that can be given with PI to exploit synergistic cytotoxicity, ACY 241.

Richardson PG, et al. Blood. 2013;122:2331-2337
San Miguel J, et al. Lancet Oncol. 2014

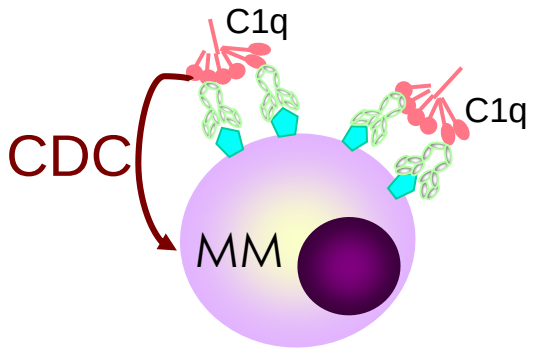
MAb Based Therapeutic Targeting of MM

Antibody-dependent Cellular Cytotoxicity (ADCC)



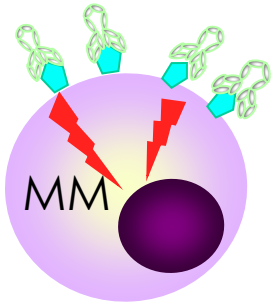
- Lucatumumab or Dacetuzumab (CD40)
- **Elotuzumab (CS1)**
- **Daratumumab (CD38)**
- XmAb®5592 (HM1.24)
- **SAR650984 (CD38)**

Complement-dependent Cytotoxicity (CDC)



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

Apoptosis/growth arrest via intracellular signaling pathways



- **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**

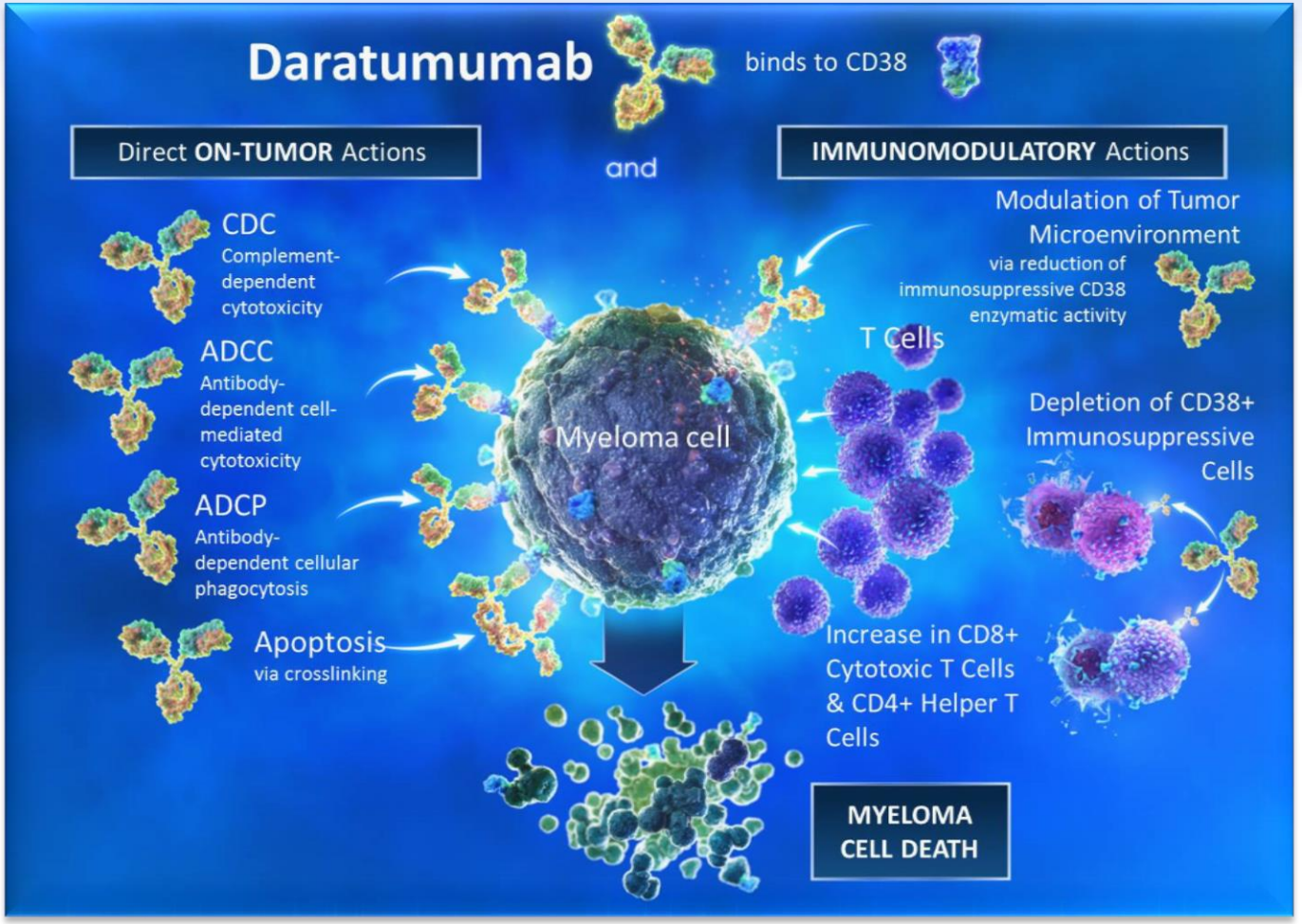
Updated from
Tai & Anderson Bone Marrow Research 2011

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

- SLAMF7 (CS1) is highly and uniformly expressed at gene and protein level on patient MM and NK cells
- Elotuzumab (Elo) is a humanized monoclonal antibody targeting CS1, activates NK cells via CD 16 and ADCC
- 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 II trial: 92% response to len dex elo in relapsed MM, PFS 32.5 months
- Phase III trial shows len dex elo prolongs prolongs PFS in relapsed MM by 5 months compared to len dex, leading to FDA approval

Daratumumab: Mechanism of Action

- Human CD38 IgGκ monoclonal antibody
- Direct and indirect anti-myeloma activity[1-5]
- Depletes CD38+ immunosuppressive regulatory cells[5]
- Promotes T-cell expansion and activation[5]



1. Lammerts van Bueren J, et al. *Blood*. 2014;124:Abstract 3474.
2. Jansen JMH, et al. *Blood*. 2012;120:Abstract 2974.
3. de Weers M, et al. *J Immunol*. 2011;186:1840-8.
4. Overdijk MB, et al. *MAbs*. 2015;7:311-21.
5. Krejcik J, et al. *Blood*. 2016. Epub ahead of print.

Dara, Len, and Dex (DRd) Versus Len and Dex (Rd) in RR MM

- Daratumumab-Rd significantly improved PFS in comparison with Rd alone: **63% reduction in progression/death**
- DRd doubled CR/sCR rates and quadrupled MRD-negative rates,with safety profile of daratumumab or Rd alone
- Dimopoulos et al, EHA 2016, NEJM 2016

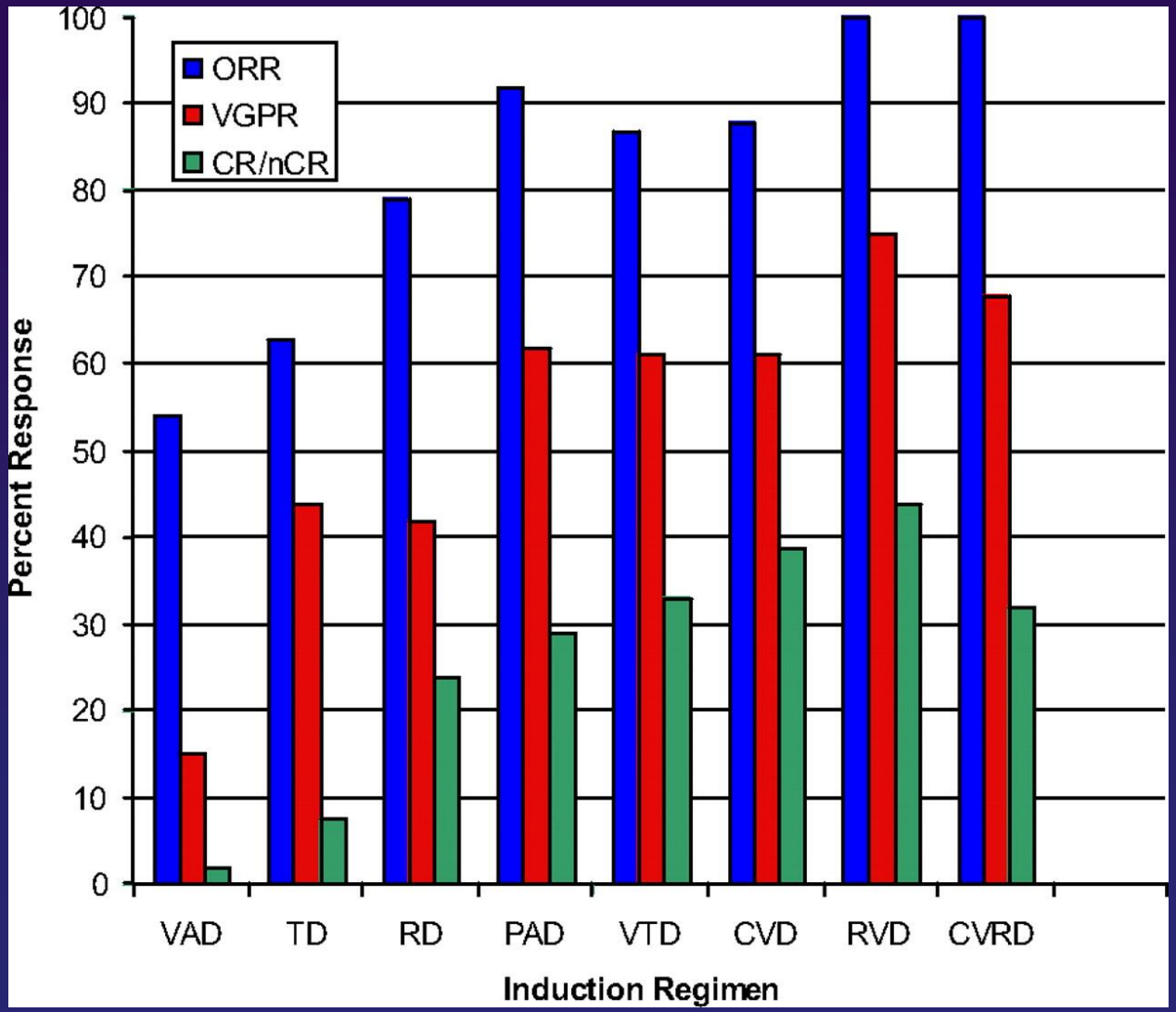
Dara, Bort and Dex (DVd) versus Bort and Dex (Vd) in R/R MM

Daratumumab-Vd significantly improved PFS, TTP, and ORR in comparison with Vd alone: **61% reduction in progression/death**

Daratumumab-Vd doubled VGPR and CR rates, w/o toxicities

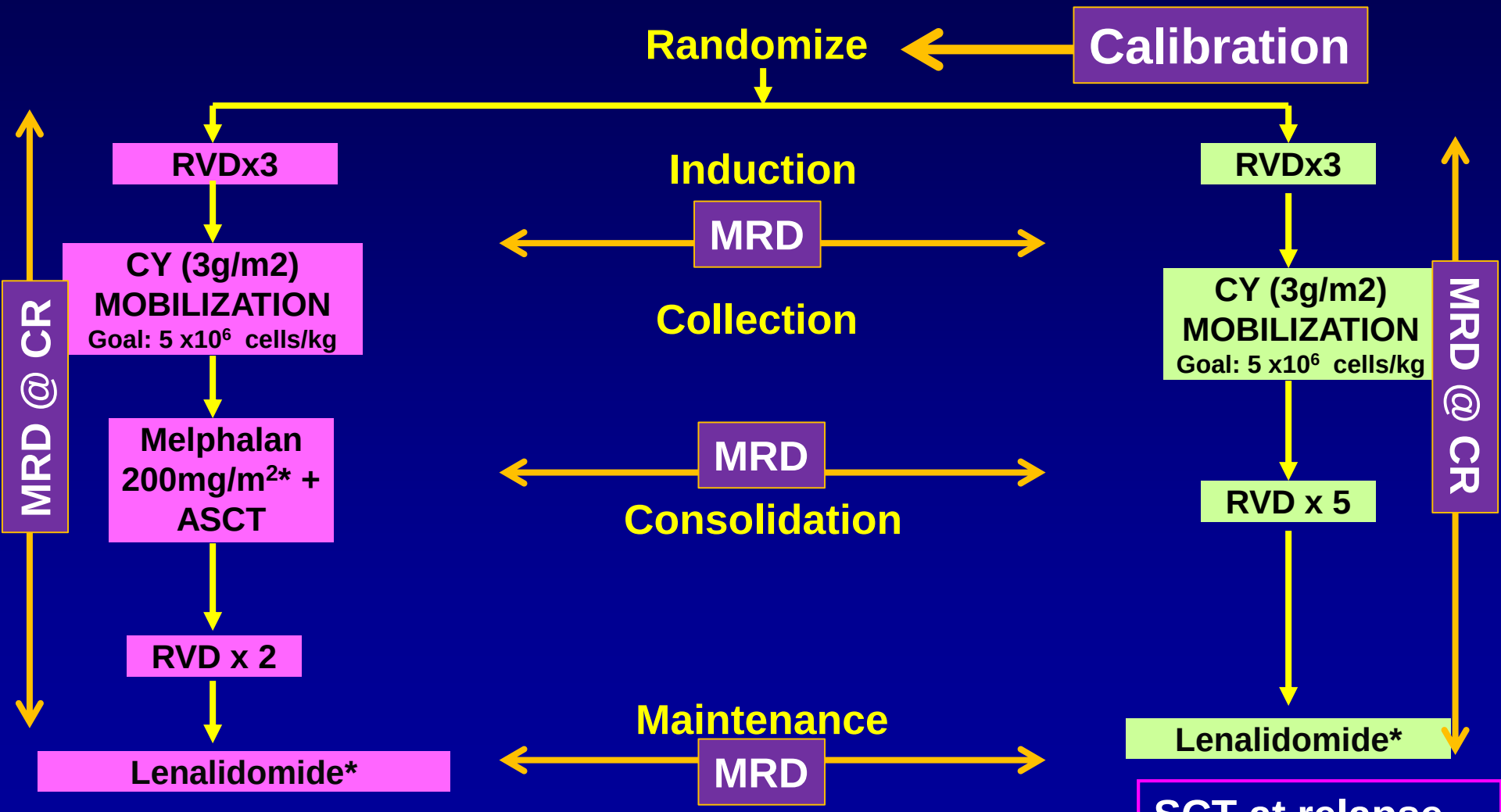
Palumbo et al, ASCO 2016, NEJM 2016

Combinations in the Upfront Treatment of MM



Stewart AK, Richardson PG, San Miguel JF Blood 2009

Is Early Transplant Needed?
IFM/DFCI 2009 (N=1,360)



Richardson et al, ASH 2014

*IFM vs. US: 1yr vs. Continuous

IFM: RVD and Early vs Late ASCT

	RVD arm N=350	Transplant arm N=350	p-value
CR	49%	59%	
VGPR	29%	29%	0.02
PR	20%	11%	
<PR	2%	1%	
At least VGPR	78%	88%	0.001
Neg MRD by FCM , n (%)	228 (65%)	280 (80%)	0.001

Attal et al, ASH 2015

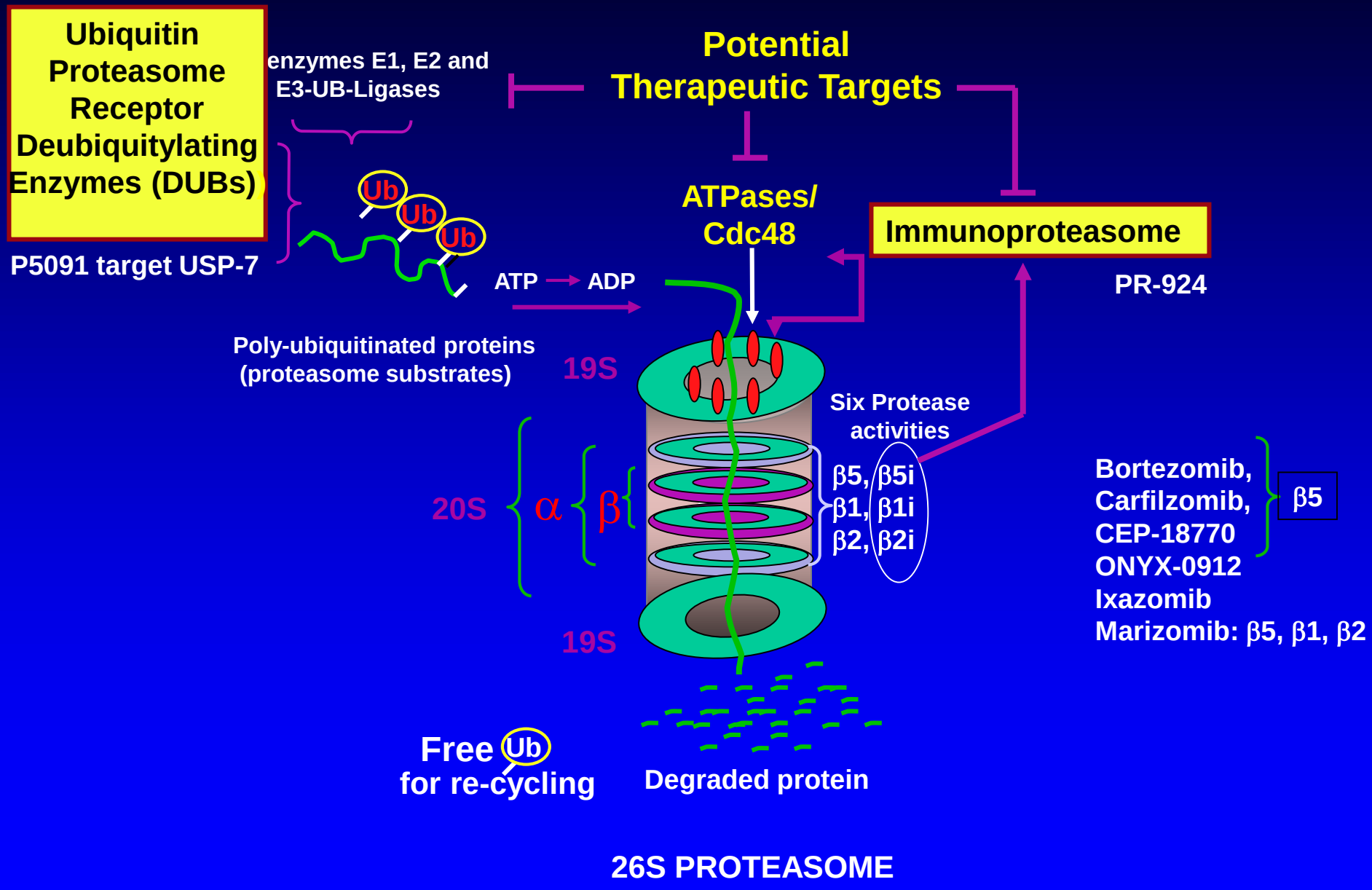
Achilles Heals: Hallmarks of the Disease that are Vulnerabilities

Excess Protein Production:
Target protein degradation
Trigger selective protein degradation

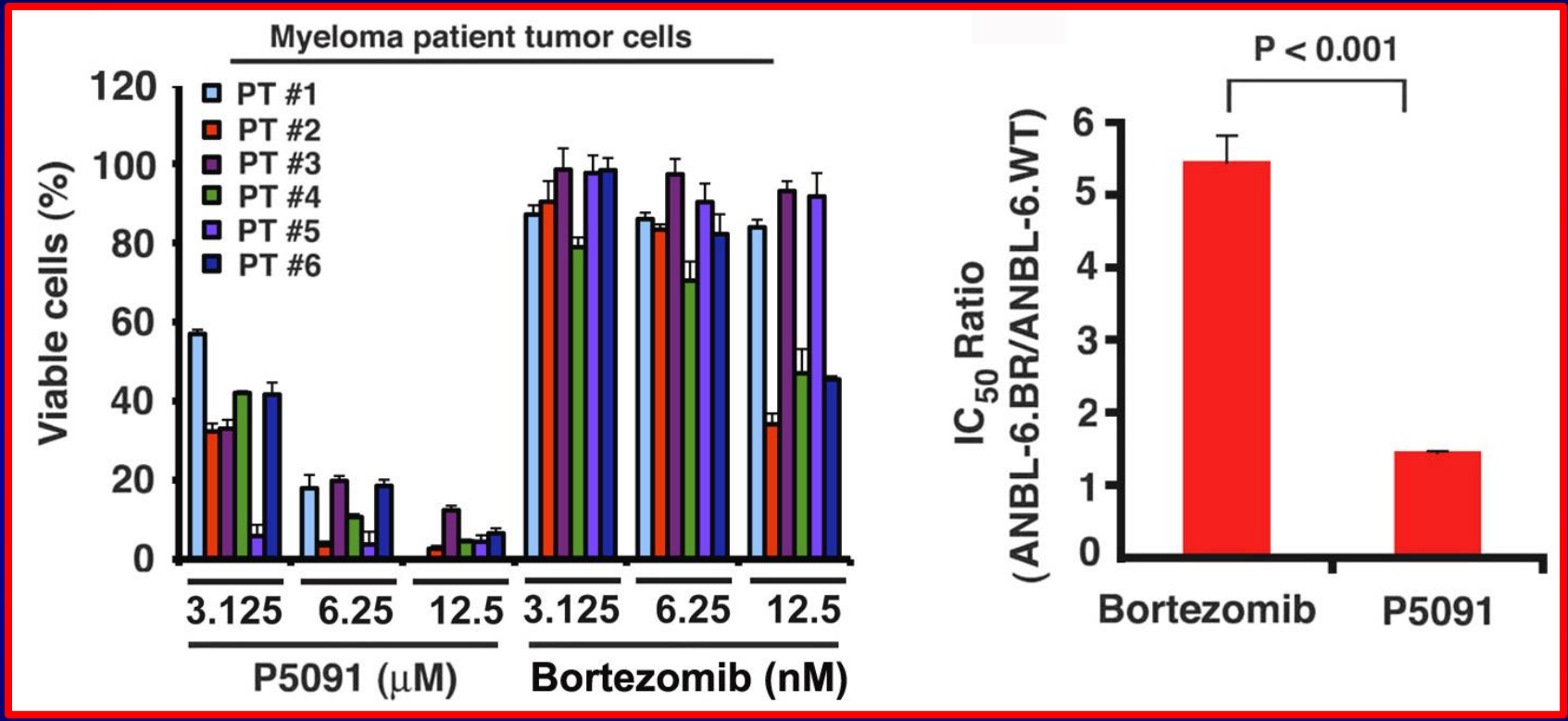
Immune Suppression:
Restore anti-MM immunity

Genomic abnormalities:
Target and overcome
genomic abnormalities

Proteasome: Present and Future Therapies

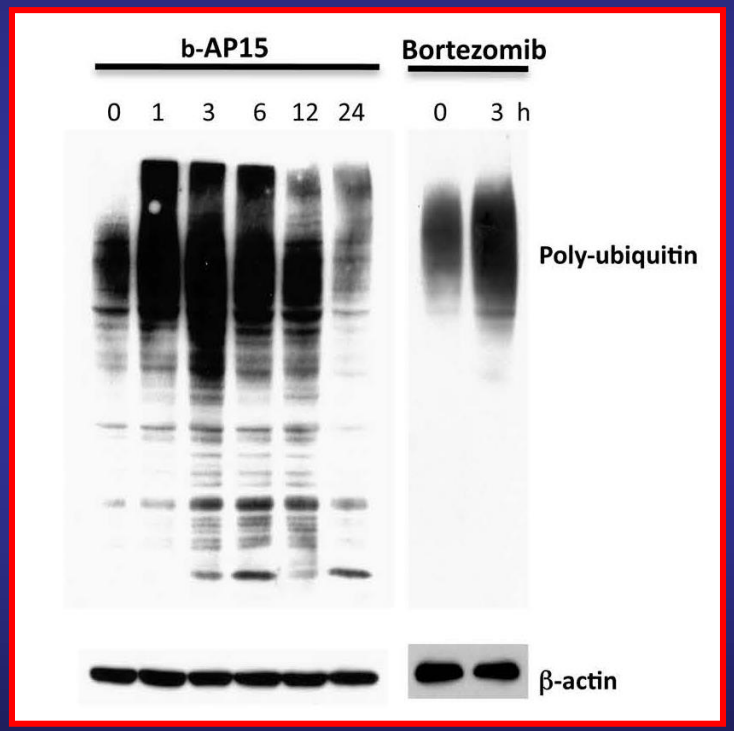


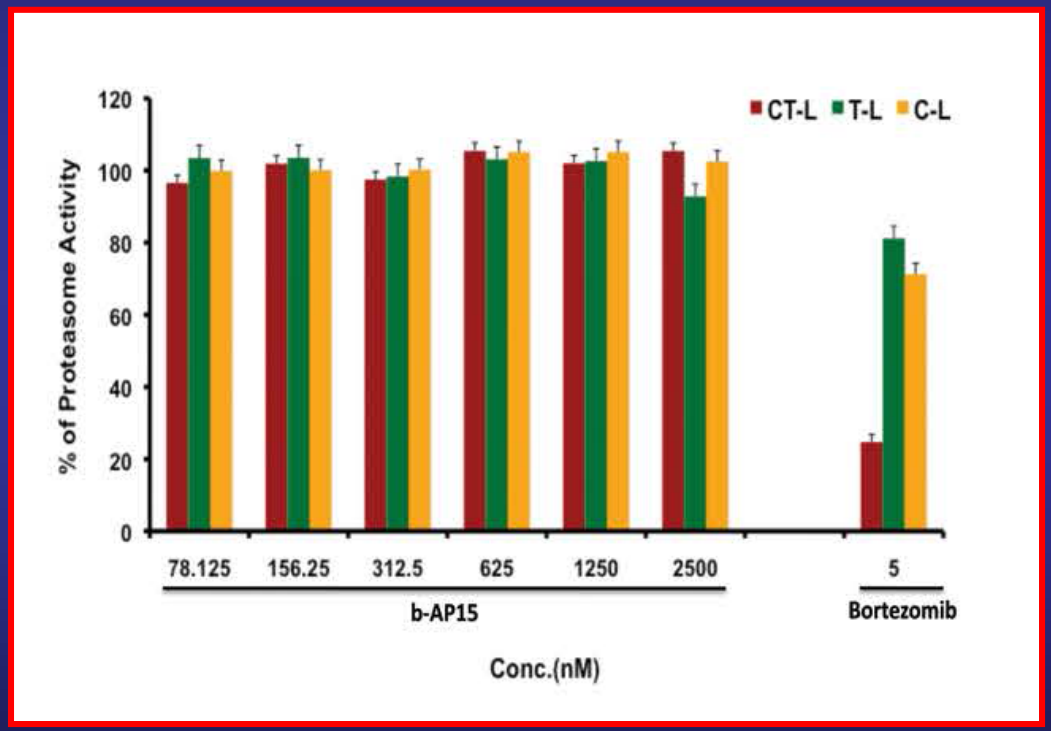
USP 7 (DUB) Inhibitor P5091 Overcomes Bortezomib-Resistance in MM



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

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

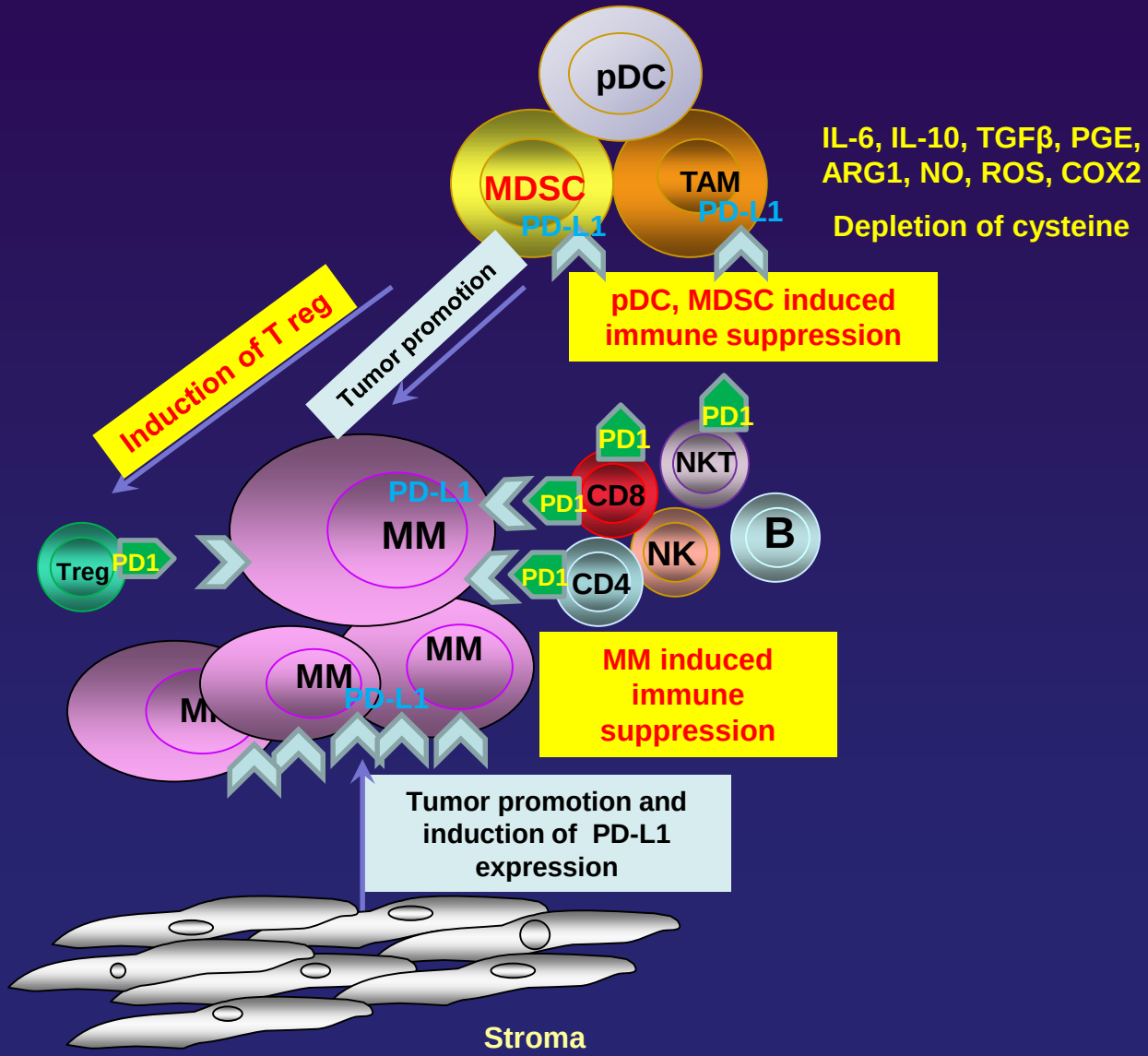




Clinical Trial Ongoing

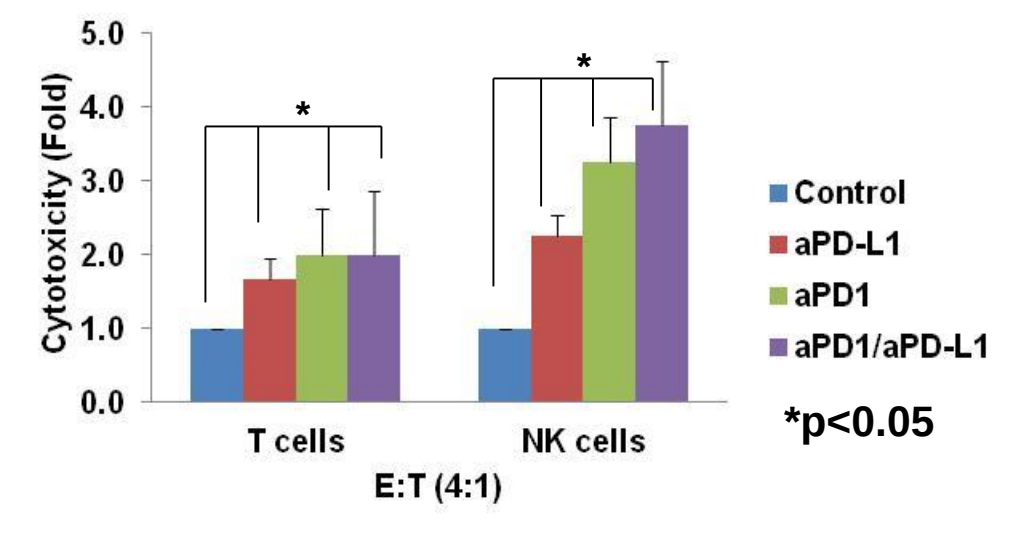
Tian et al. Blood 2014; 123: 706-16

Immune Suppressive Microenvironment in MM



Görgün GT, et al. Blood 2013;121:2975-87

Checkpoint Blockade Induces Effector Cell Mediated MM Cytotoxicity



Effector: Autologous effector cells (CD3T cells, NK cells)

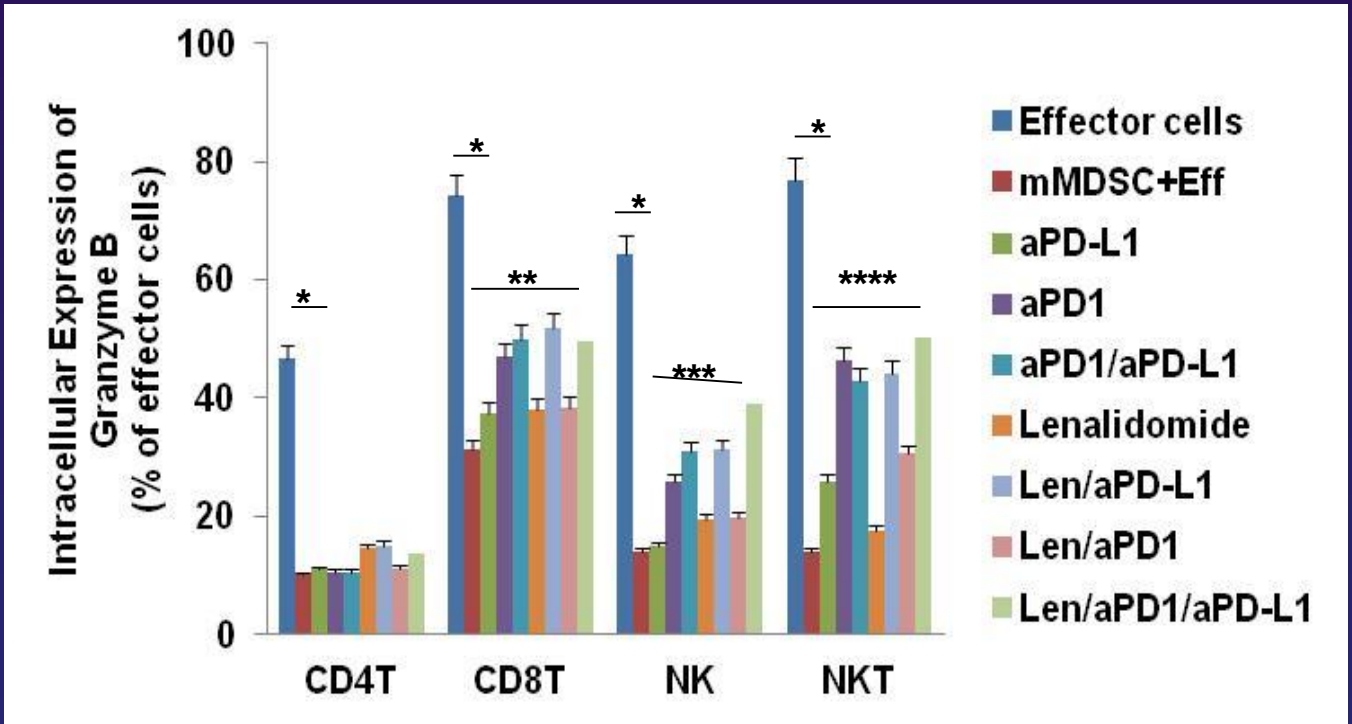
Target: CD138^{+} MM cells from Rel/Ref MM-BM

Görgün G. et al. Clin Cancer Res 2015; 21: 4607-18.

Lenalidomide with Checkpoint Blockade Reverses MDSC Induced Immune Suppression in MM

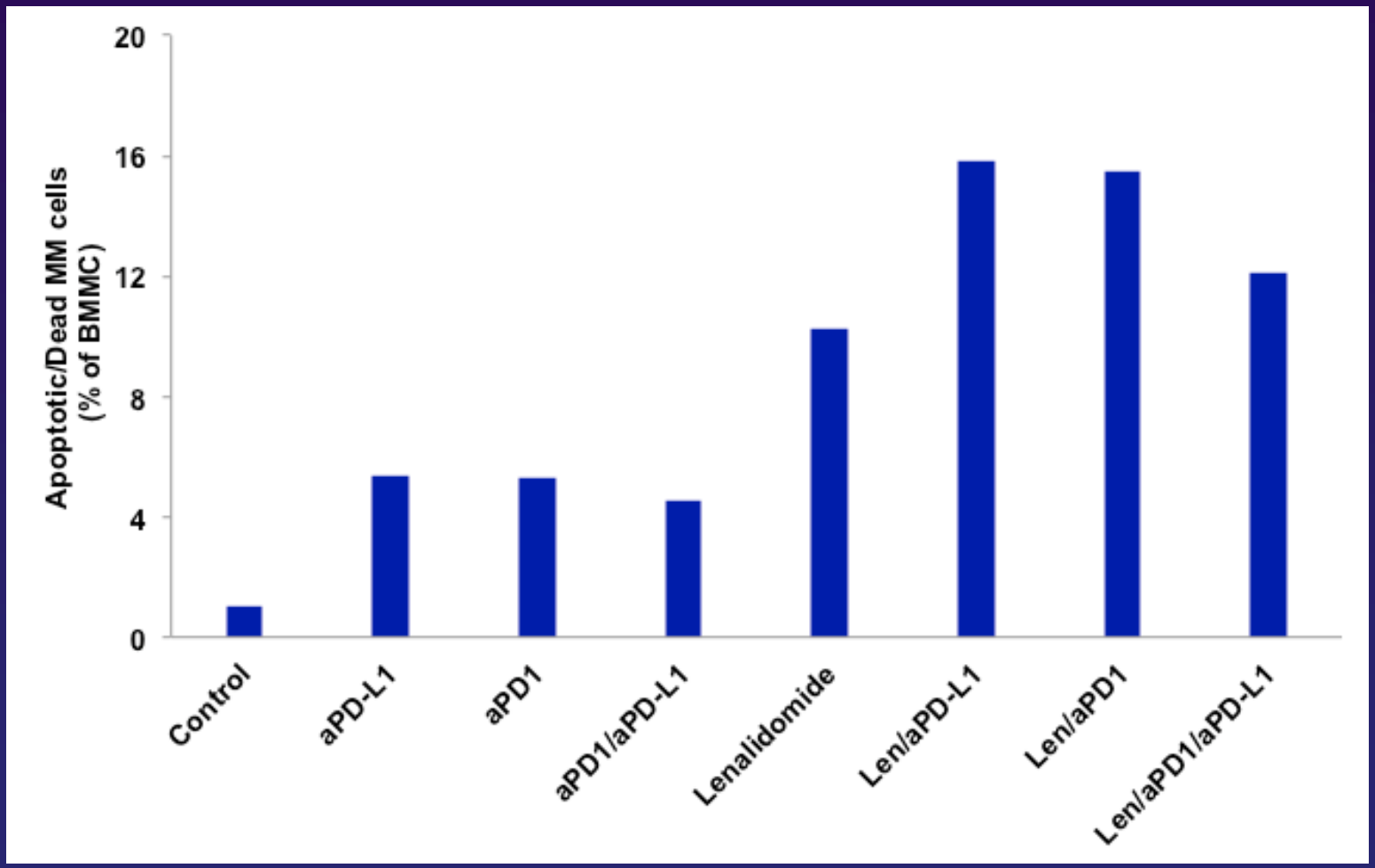
Autologous effector cells cultured with MDSC

of RR-MM bone marrow



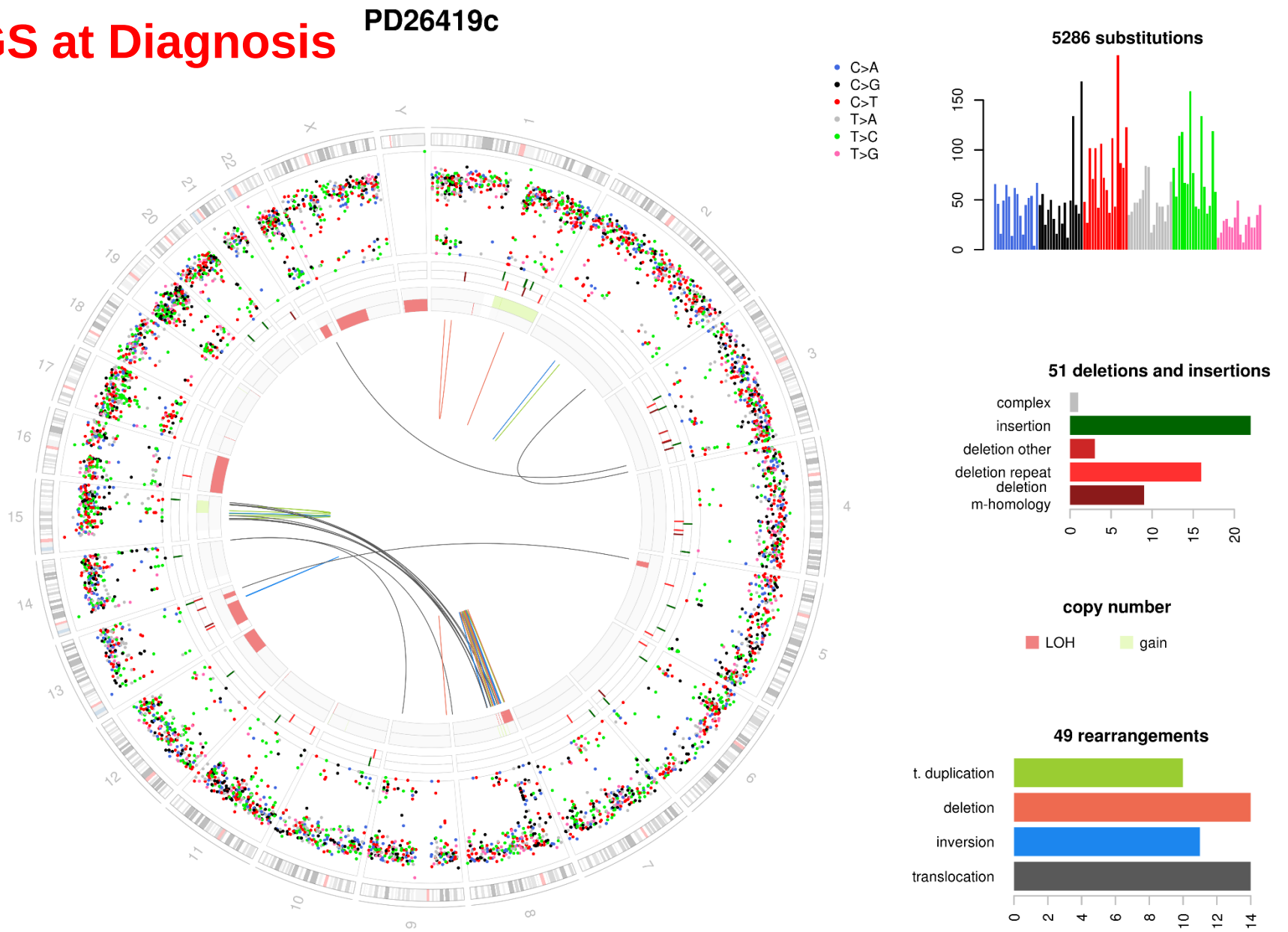
Görgün G. et al. Clin Cancer Res 2015; 21: 4607-18.

Enhanced Activity of Combination Immune Therapies

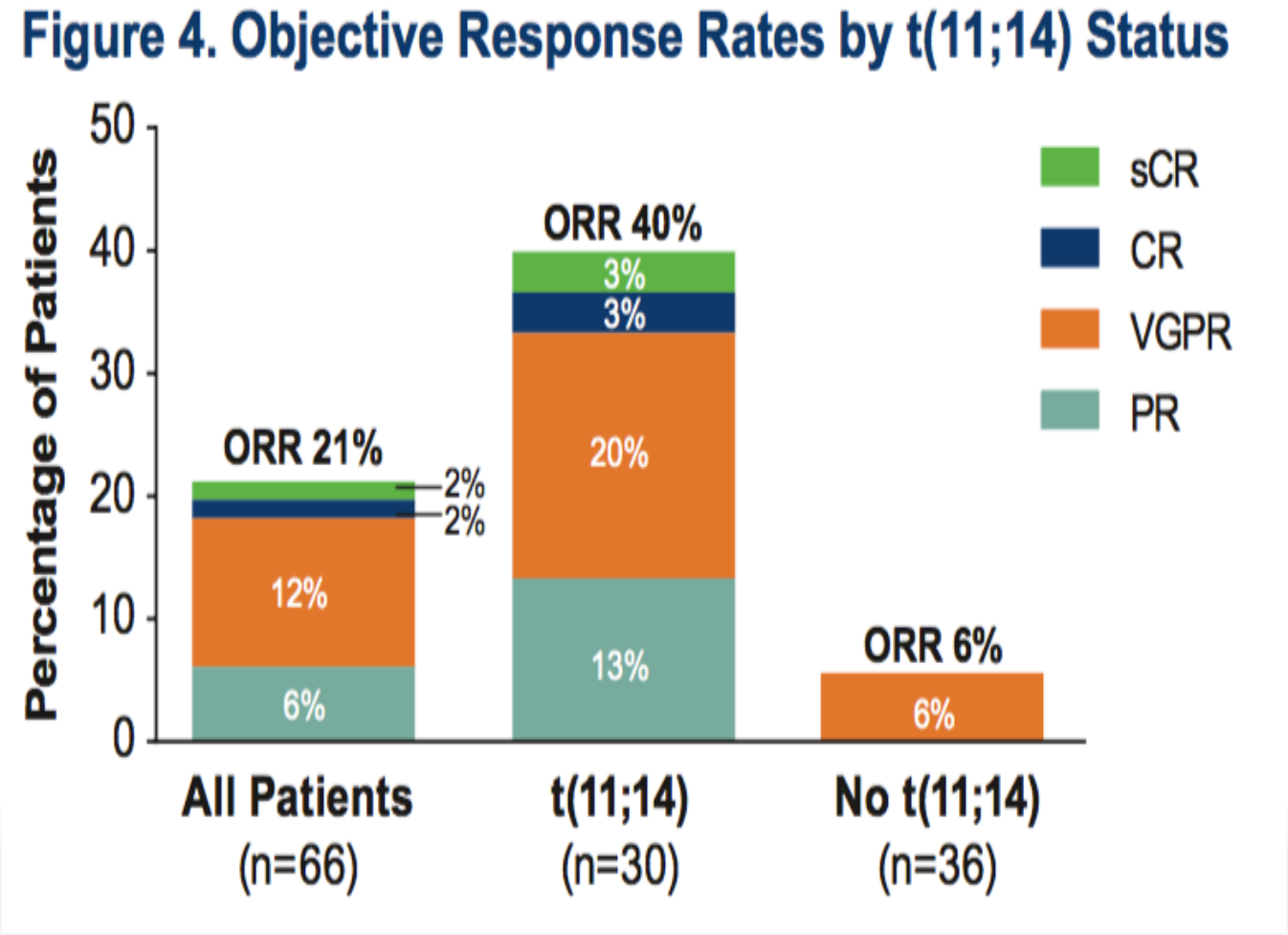


Görgün G. et al. Clin Cancer Res, in press

WGS at Diagnosis



Venetoclax Therapy of Relapsed/Refractory MM

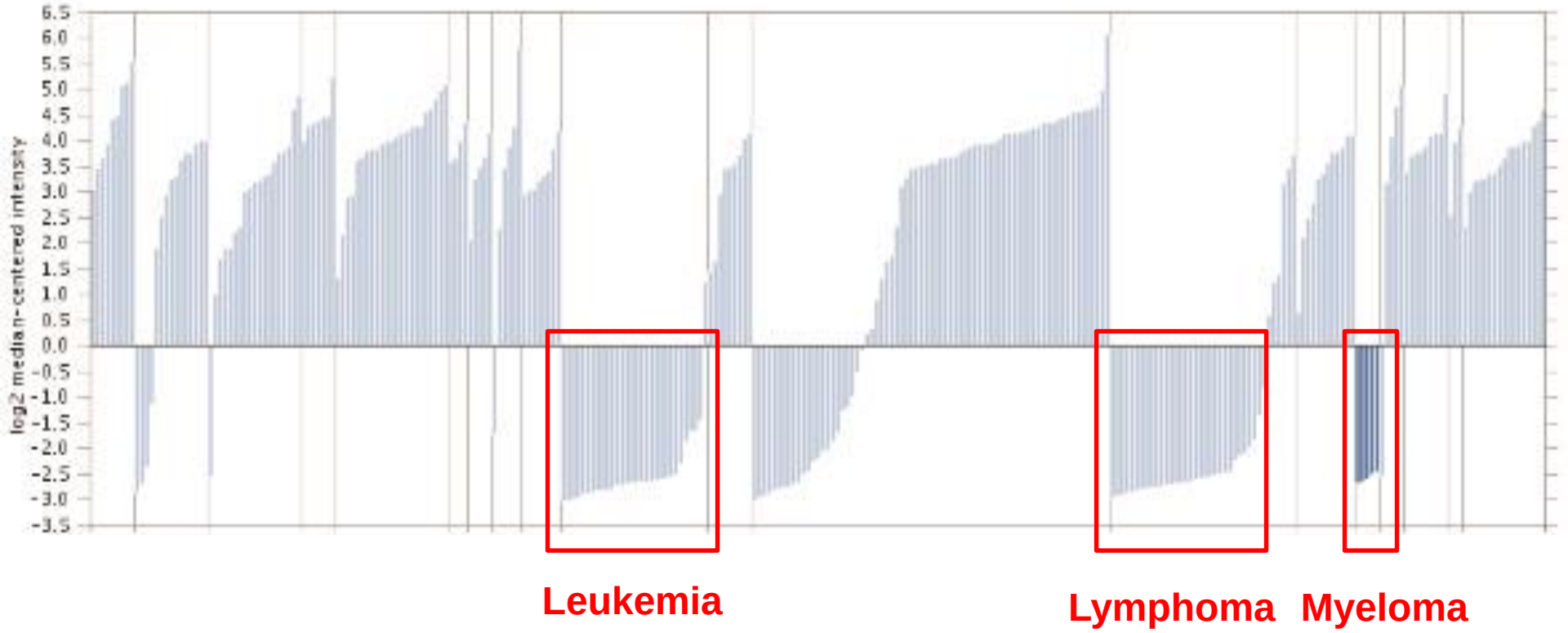


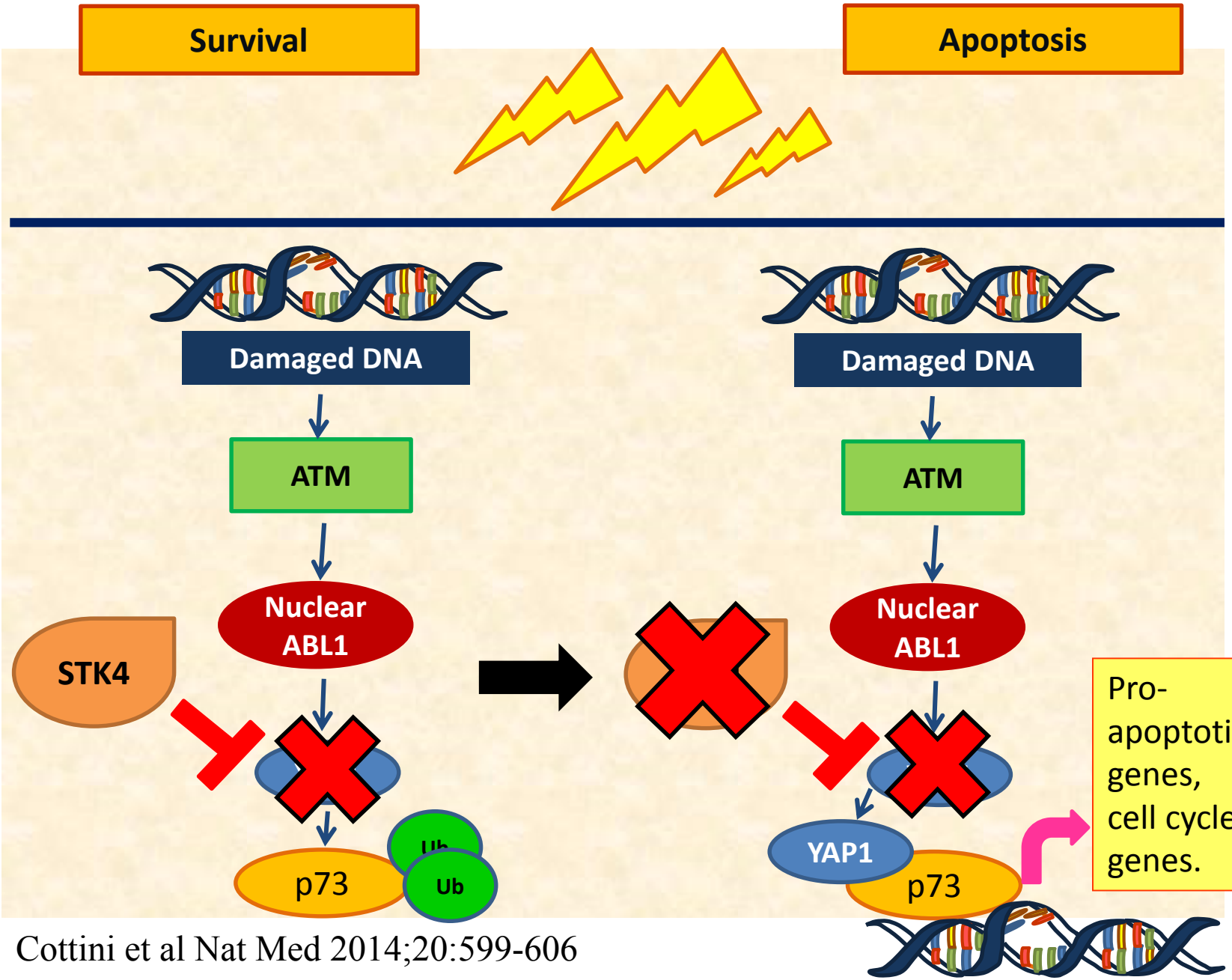
EMORY WINSHIP CANCER INSTITUTE
A Cancer Center Designated by the National Cancer Institute

Kumar et al 2016

Achilles Heal: Low YAP1 Expression in Subsets of Hematological Malignancies

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

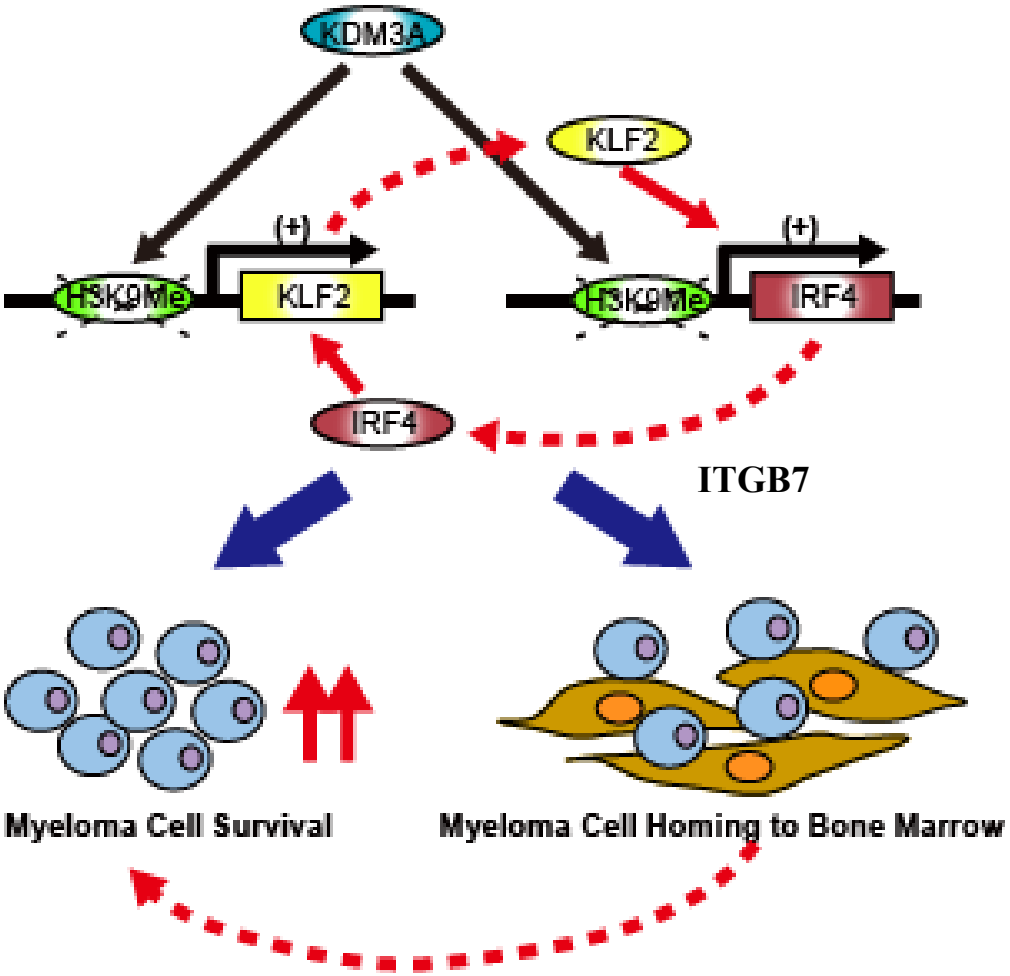




Cottini et al Nat Med 2014;20:599-606

Model of KDM3A-KLF2-IRF4 Axis in MM cells

KDM3A catalyses removal of H3K9 mono- and di-methylation in MM



Ohguchi et al Nat Comm 2016

Summary and Future Directions

Discovery and validation of novel agents, alone and in combination, which can overcome conventional drug resistance using in vivo and in vitro models of myeloma in its bone marrow microenvironment

Clinical trials informed by biomarkers and combinations defined in preclinical studies

Collaborative effort of academia, biotech/pharma, NIH/NCI, FDA, and advocacy

Promising future translational efforts target Achilles heels: targeting protein homeostasis, restoring host anti-myeloma immunity, and targeting genomic abnormalities.