Managing the Microenvironment Matters

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Disclosures

Consulting fees from: Bristol-Myers Squibb, Celgene, Millennium, and Onyx

Fees for non-CME services such as Speaker's Bureau from: Celgene

New Treatments and Outcome in Myeloma

Single Transplant

Tandem Transplant

Thal/Len/Btz Combinations + Transplant

Thal/Len/Cfz Combinations +/- Transplant

1990s

2000 - 2010

2011 - present

MP prevails

Thalidomide

Bortezomib

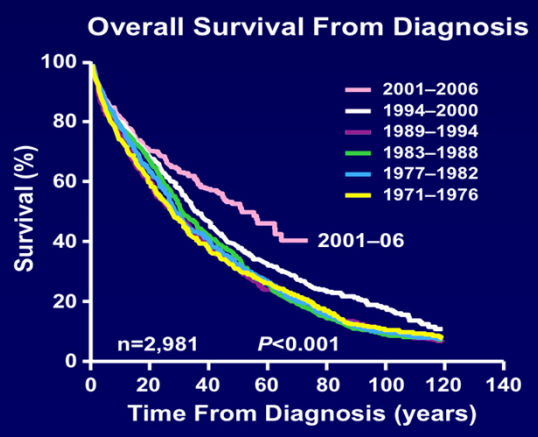
Lenalidomide

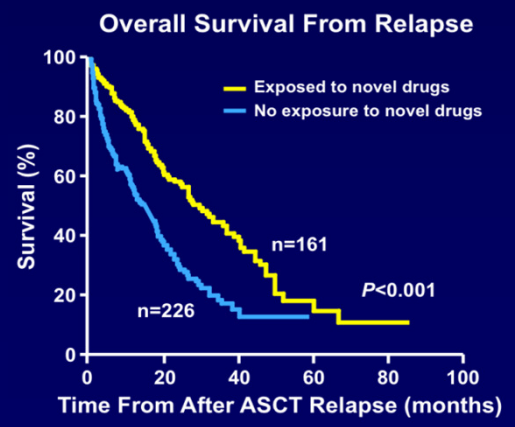
Thal/Len/Btz combinations

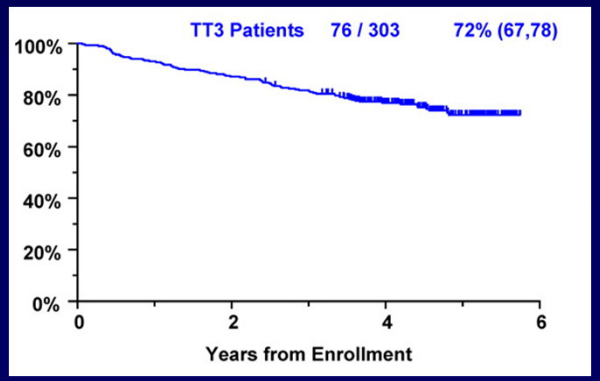
Carfilzomib

Pomalidomide

Pom/Btz/Cfz combinations





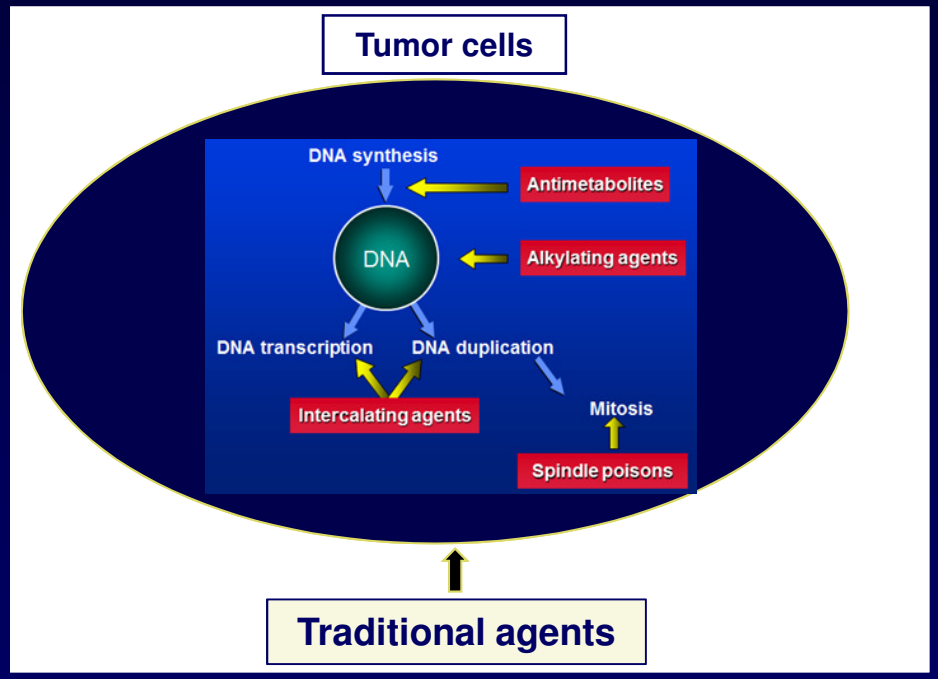


Kumar SK et al. *Blood.* 2008;111(5):2516-2520.

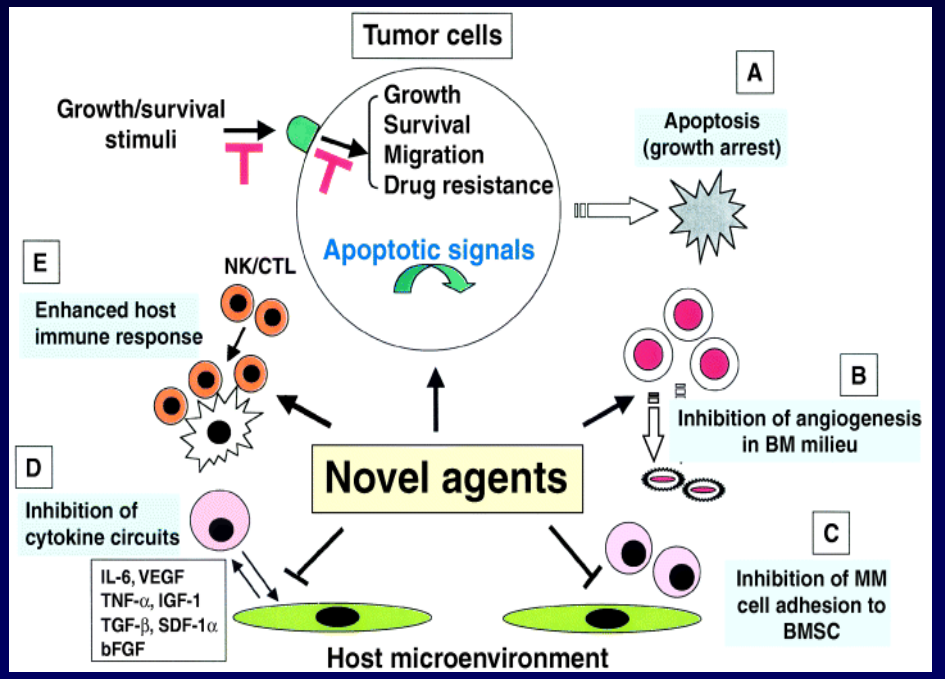
Van Rhee et al. *Blood.* 2010;116(8):1220-1227.

New Drugs and New Approach

Traditional Chemotherapy



Novel Agents

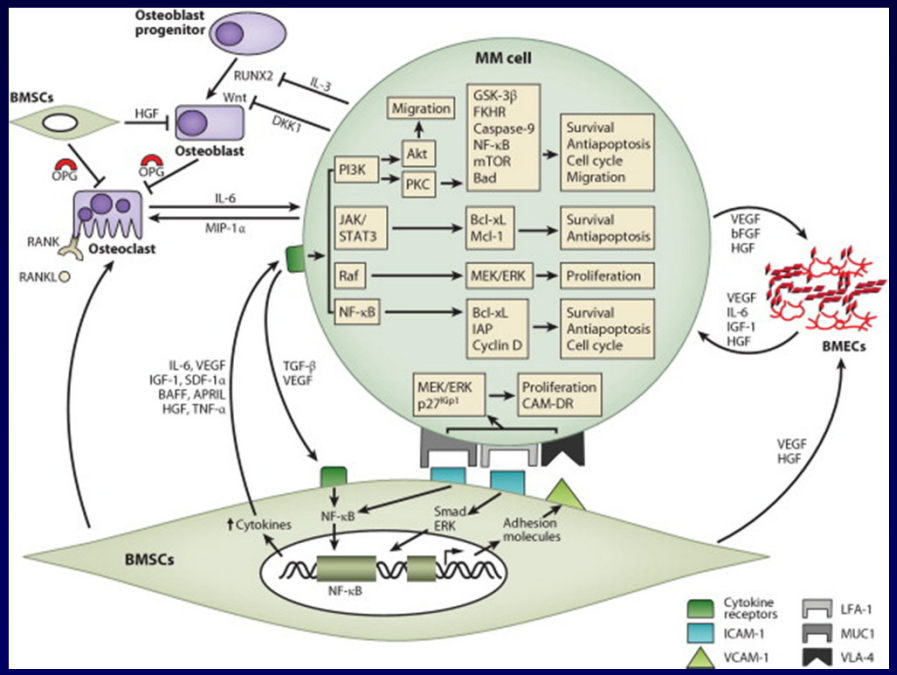


Hideshima T, et al. *Immunological Rev.* 2003;194(1): 164-176.

Microenvironment in Myeloma

Components

- Extracellular matrix
- Stromal cells
- Osteoclasts
- Osteoblasts
- Immune cells
- Other hematopietic cells
- Endothelial cells



Role

- Homing
- Adhesion
- Cytokine release
- MM cell molecular profile
- Angiogenesis
- Bone metabolism and turnover

Anderson KC, et al. *Annu Rev Pathol.* 2011;6:249-274.

Bone Marrow Microenvironment and Pathogenesis of Myeloma

- Tumor cell growth and survival
- Development of resistance to therapy
- Tumor angiogenesis
- Myeloma bone disease

Myeloma and Angiogenesis

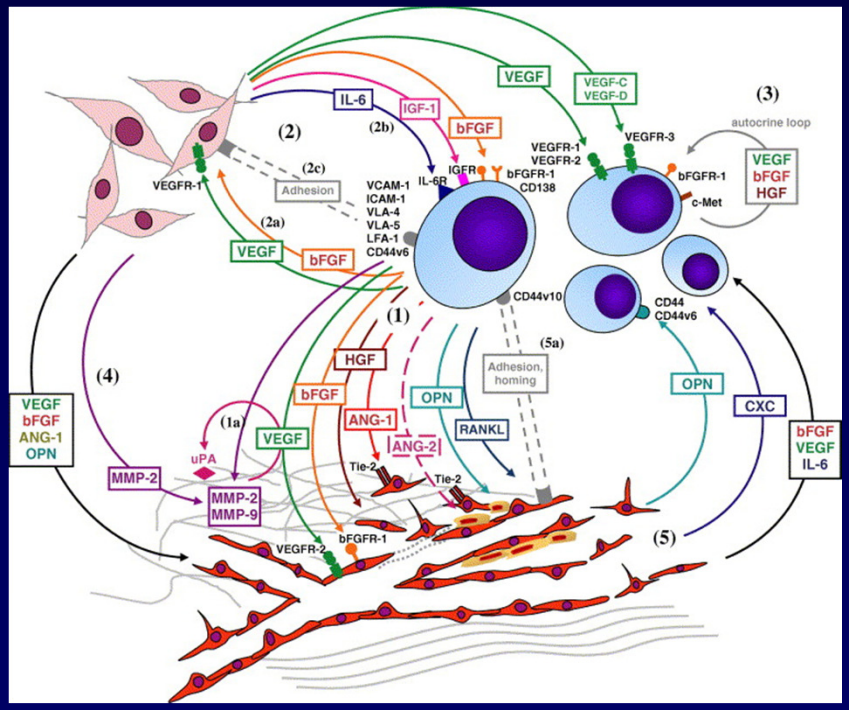
BMEC – VEGF, IL-6

IGF-1 – MM cell growth

BMEC – SDF-1α – CXCR4

Cytokines – angiogenic activity

MM cell growth



MM oncogene transformation

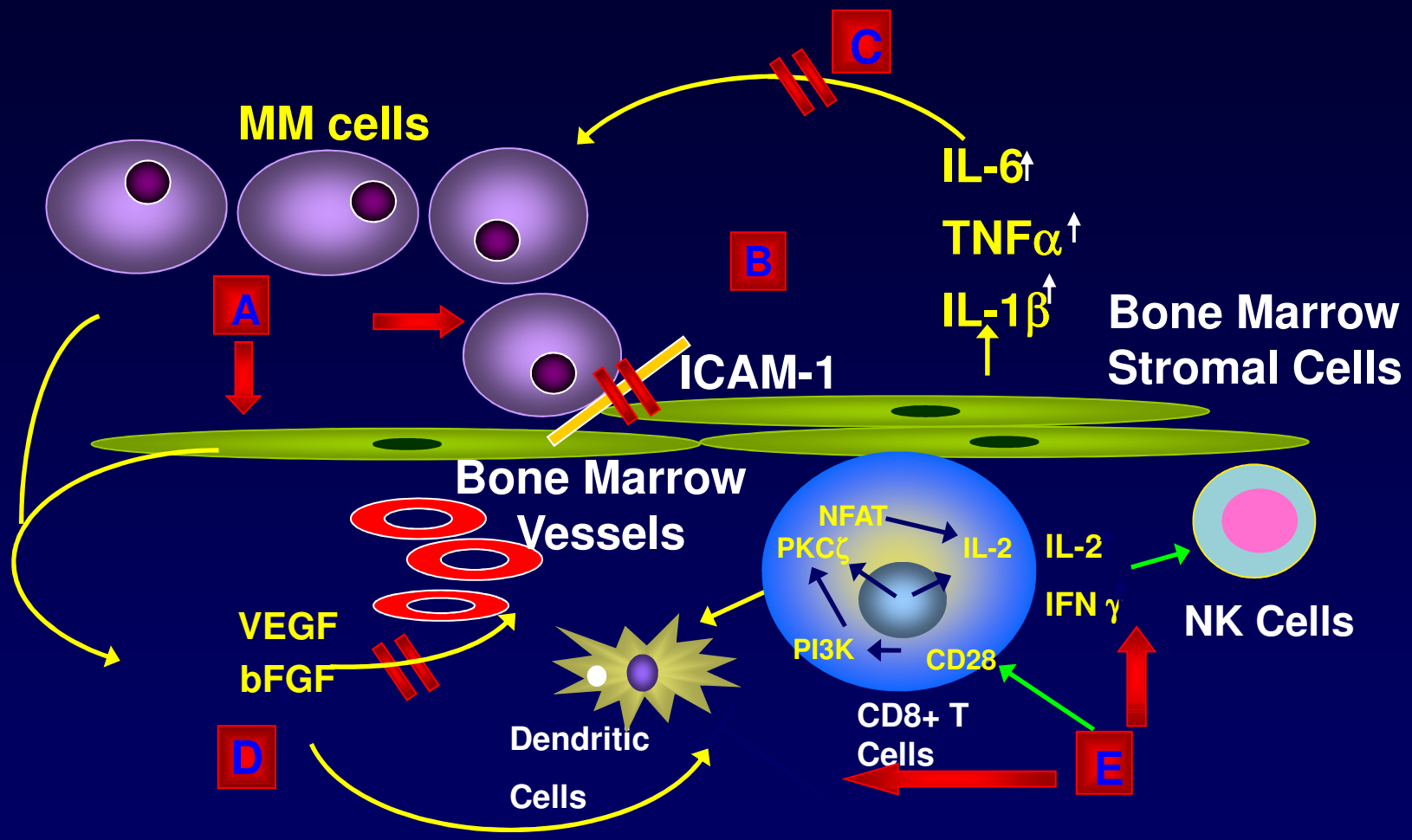
Increase of VEGF, bFGF, MMPs

Increased angiogenic activity

Increased angiogenesis

BM angiogenesis and MVD correlate with status of disease

Thalidomide and Other IMiDs



Hideshima T, et al. *Blood.* 2000;96(9):2943-2950; Davies FE, et al. *Blood.* 2001;98(1):210-216; Gupta D, et al. *Leukemia.* 2001;15(12):1950-1961; Mitsiades N, et al. *Blood.* 2002;99(12):4525-4530; Lentzsch S, et al. *Cancer Res.* 2002;62(8):2300-2305; LeBlanc R, et al. *Blood.* 2004;103(5):1787-1790; Hayashi T ,et al. *Brit J Hematol.* 2005;128(2):192-203.

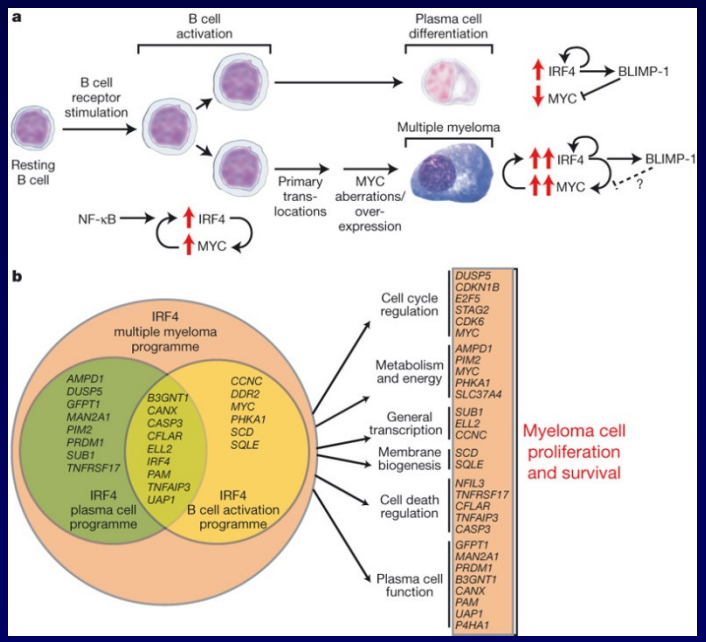
IMiDs and Microenvironement Indirect anti-MM Effects

- Inhibition of angiogenesis
- Decreased binding MM cell to BM
- Inhibition of osteoclast maturation
  - Directly (PU.1) and indirectly (reducing MM)
- Immunomodulatory activity
  - Enhancing CD4+ and CD8+ costimulation (Pom/Len > Thal)
  - T-cell proliferation and enhancing IL-2 and IFNγ
  - Inhibition of Tregs (Pom and Len)
- Stimulation of NK and NK-T immunity
  - Enhancing NK cell mediated cytotoxicity and ADCC
- Inhibition of production of TNF-α, IL-1, IL-6, and IL-12

Direct Anti-MM Effects of IMiDs

- Lenalidomide (LEN) , Pomalidomide (POM), and to lesser extend thalidomide (THAL), induce cell cycle arrest and apoptosis
  - Up-regulation of p21
  - Inactivation of NF-κB
  - Activation of caspase-8
- Additive toxicity with agents triggering apoptosis via both capase-8 and caspase-9

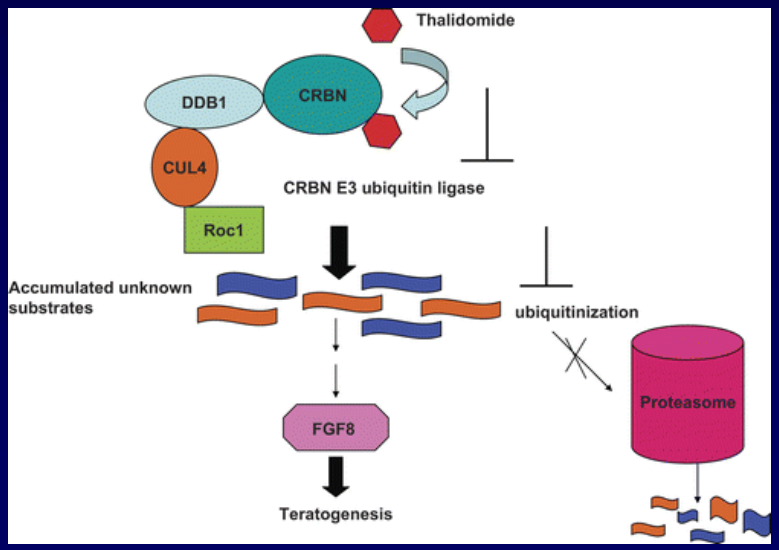
LEN and POM, inhibit expression of IRF4



Shaffer et al, *Leukemia* 2008; 26, 2326–2335

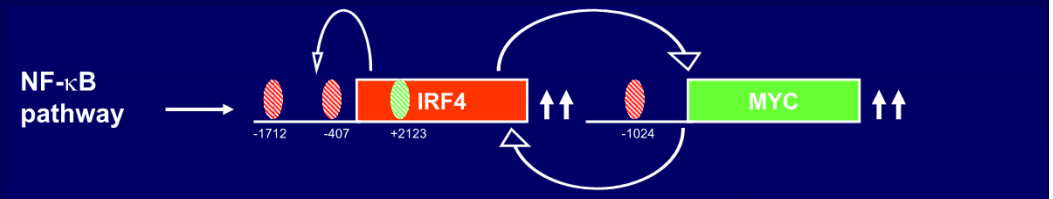
Cereblon (CRBN) and IMiDs

- **Anti-myeloma activity of IMiDs is dependent on CRBN function**
  - **E3 ubiquitin ligase**
  - **AMPK**



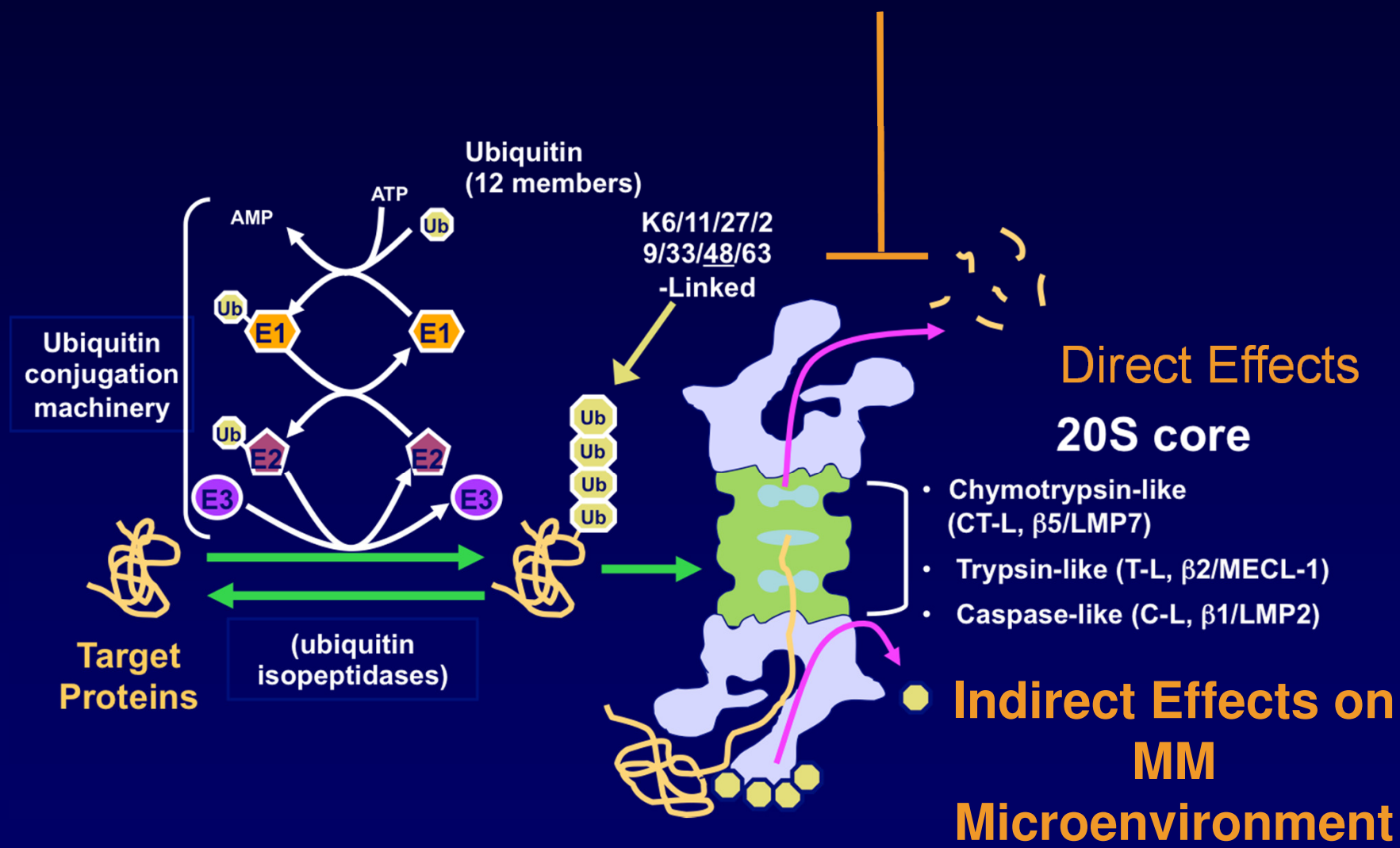
Zhu et al, *Leuk Lymphoma*. 2013 Apr;54(4):683-7

Interference with IRF4/MYC positive autoregulatory loop



Adopted from Shaffer et al, *Leukemia* 2008; 26, 2326–2335

Proteasome Inhibitors (PIs)



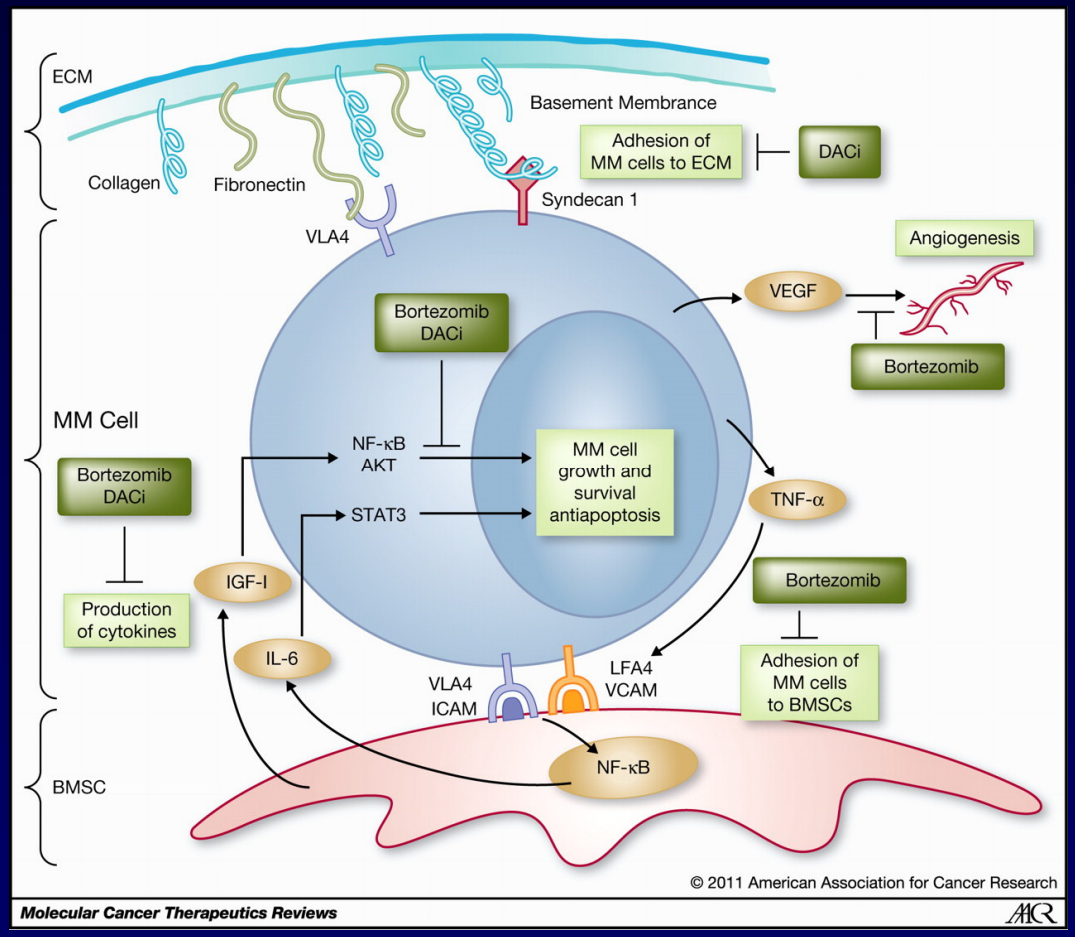
PIs and Microenvironment Indirect anti-MM Effects

- Inhibition of NFκB – dependent upregulation of IL-6 by BMSC
- Blockade of the TNF-α-induced upregulation of NFκB leading to decrease of expression of ICAM1 and VCAM1 on MM and BMSC
- Inhibition of expression of pro-angiogenic factors (i.e. VEGF)

→

- Inhibition of cytokine secretion
- Suppression of expression of adhesion molecules
- Inhibition of angiogenesis

Combining PIs and DACi



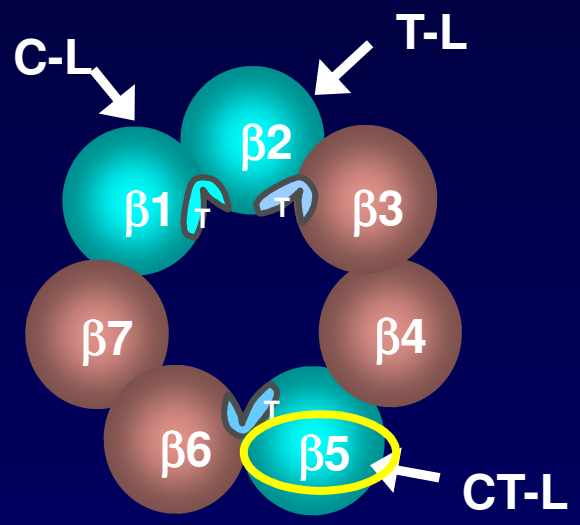
Hideshima T, et al. *Mol Cancer Ther.* 2011;10(11):2034-2042.

Different PIs
Different Impact on Microenvironment?

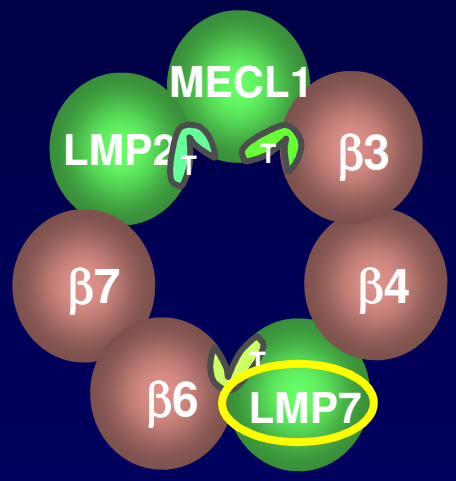
Peptide Boronates
Borezomib
Ixazomib (MLN9708)

Peptide Epoxyketones
Carfilzomib
Oprozomib (ONX0912)

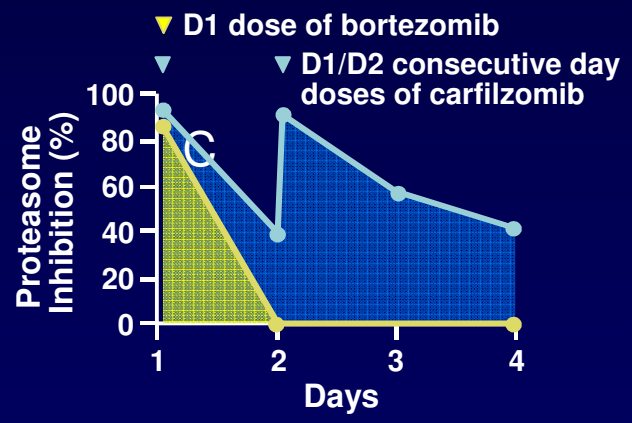
β-Lactones
Marizomib (NPI-0052)



Constitutive proteasome



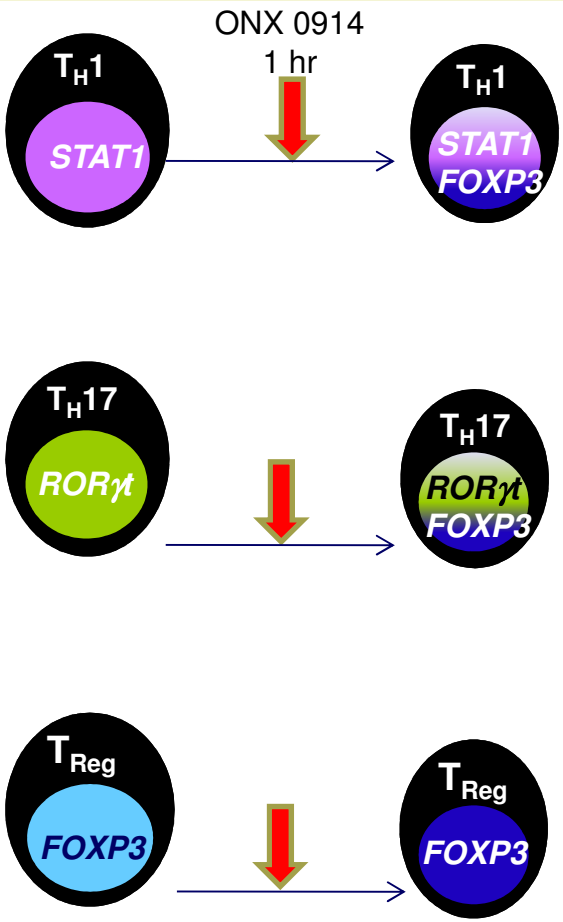
Immunoproteasome

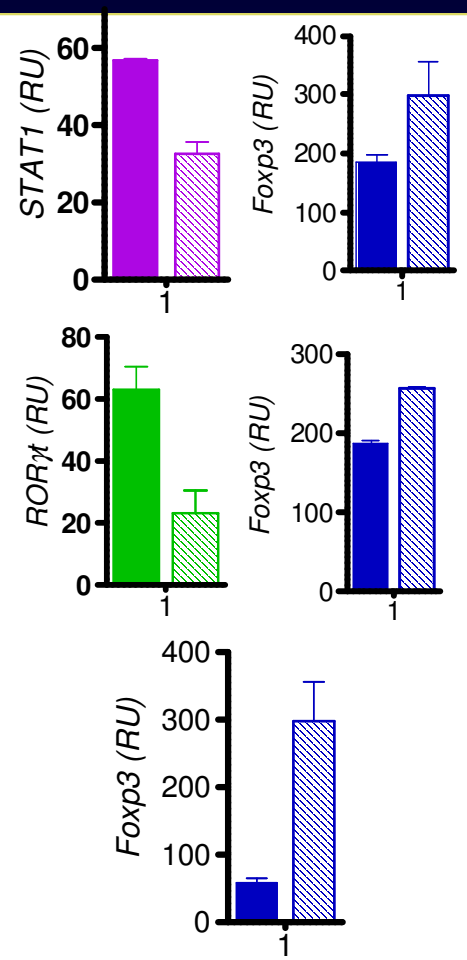


Demo SD et al. *Cancer Res.* 2007;67:6383.

- CT-L subunits are primary target of BTZ and CFZ
- CT-L inhibition sufficient to induce cell death
- Secondary site inhibitors potentiate CFZ and BTZ

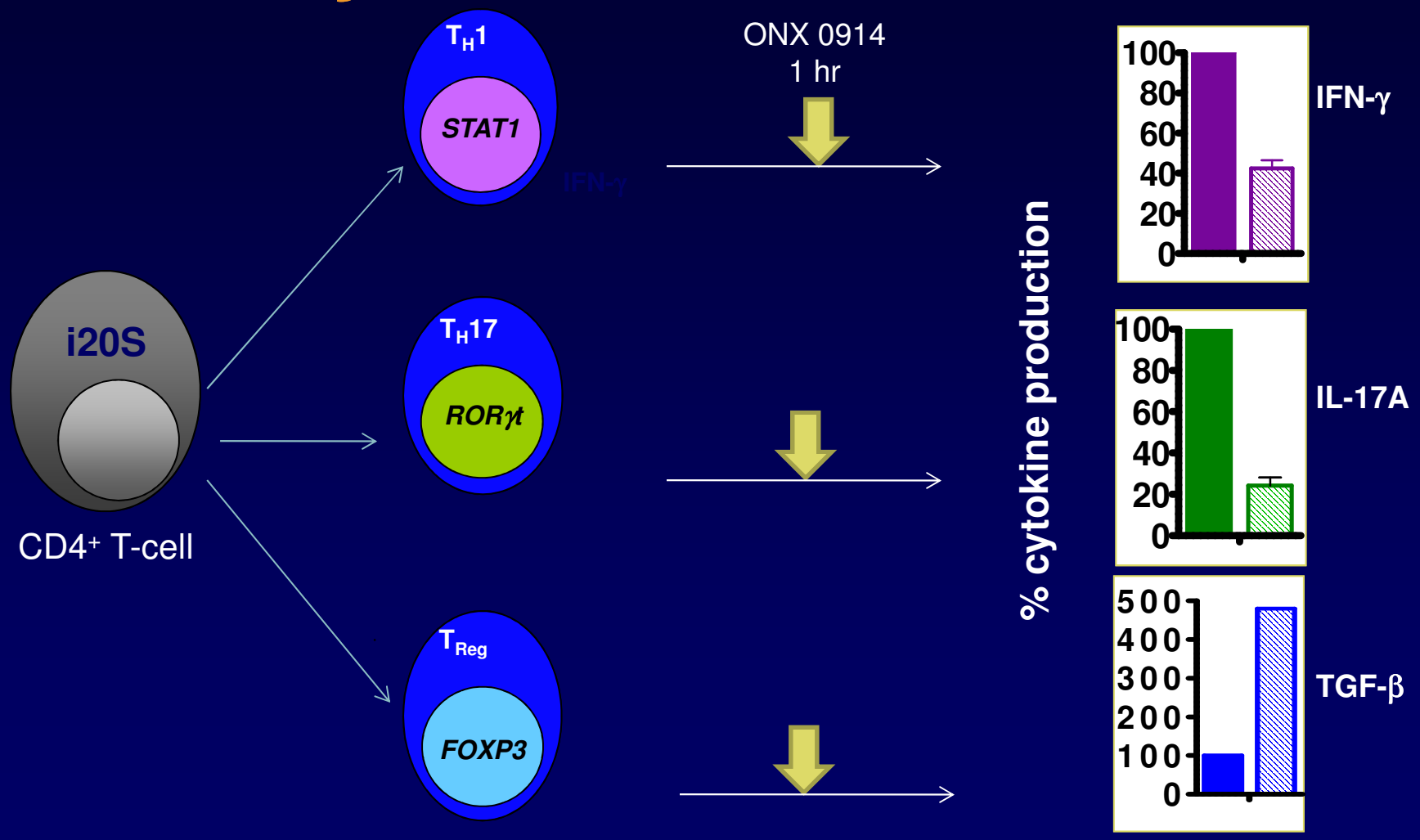
Immunoproteasome Inhibition Induces Regulatory Phenotype





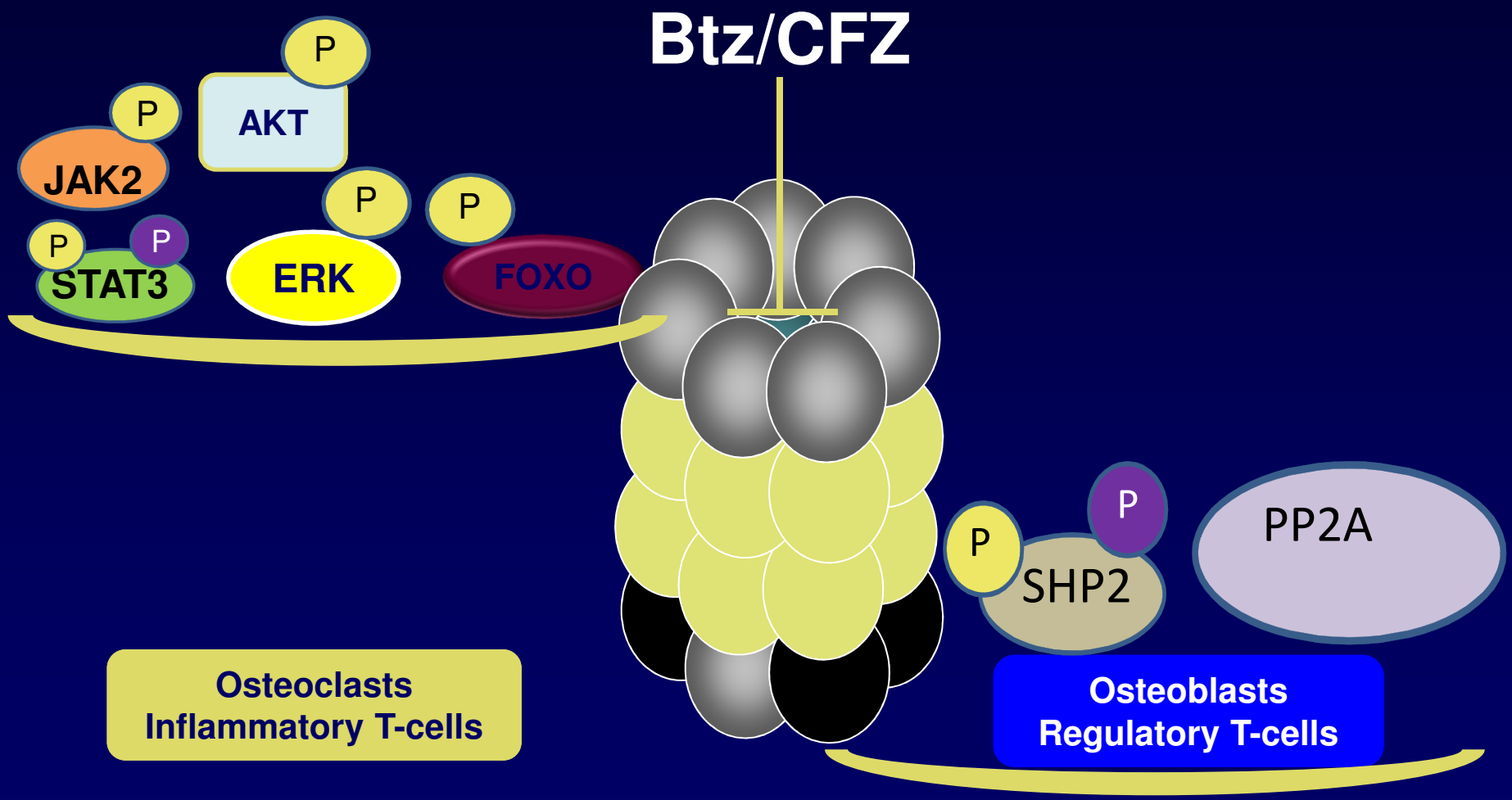
E. Suzuki, manuscript in preparation, courtesy Christopher Kirk

Immunoproteasome Regulates Cytokine Production



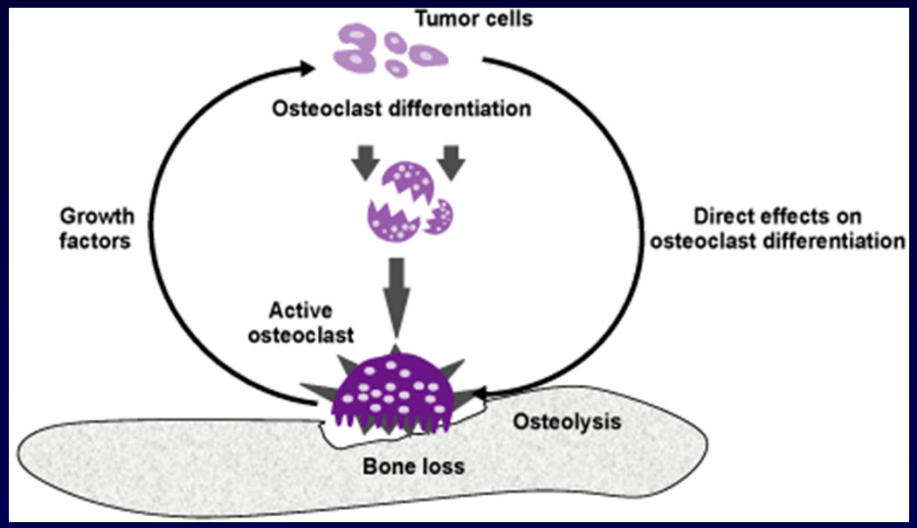
E. Suzuki, manuscript in preparation, courtesy Christopher Kirk

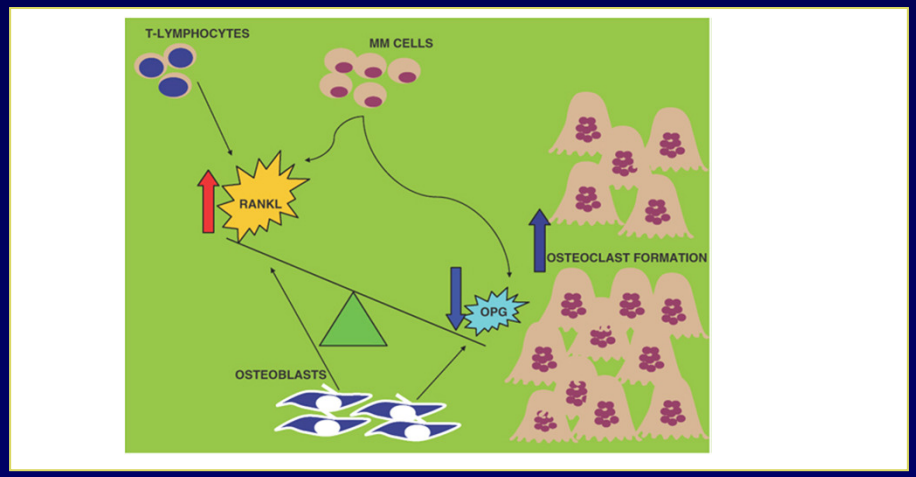
Resetting the Signaling Balance in Accessory Cells



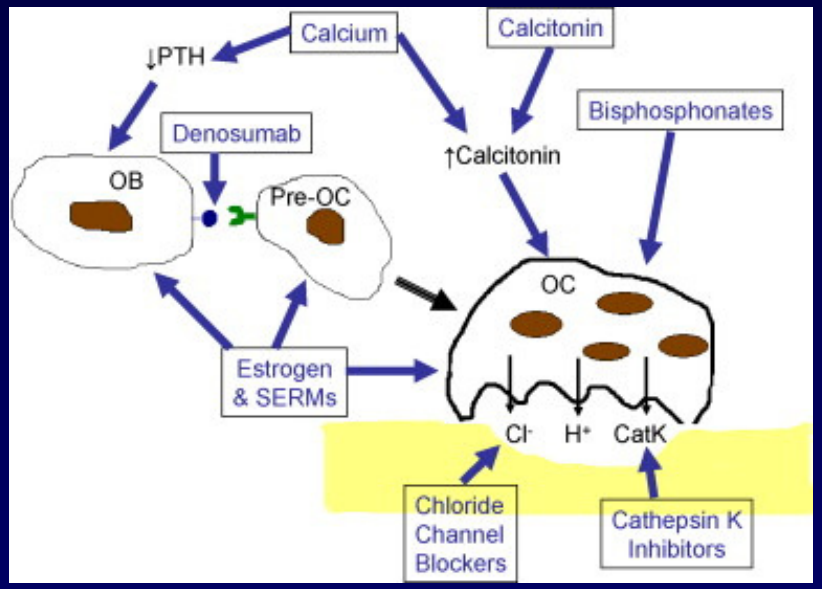
Courtesy Christopher Kirk

Myeloma and Bone Disease





Roodman GD, et al. *Leukemia.* 2009;23(3):435-441.

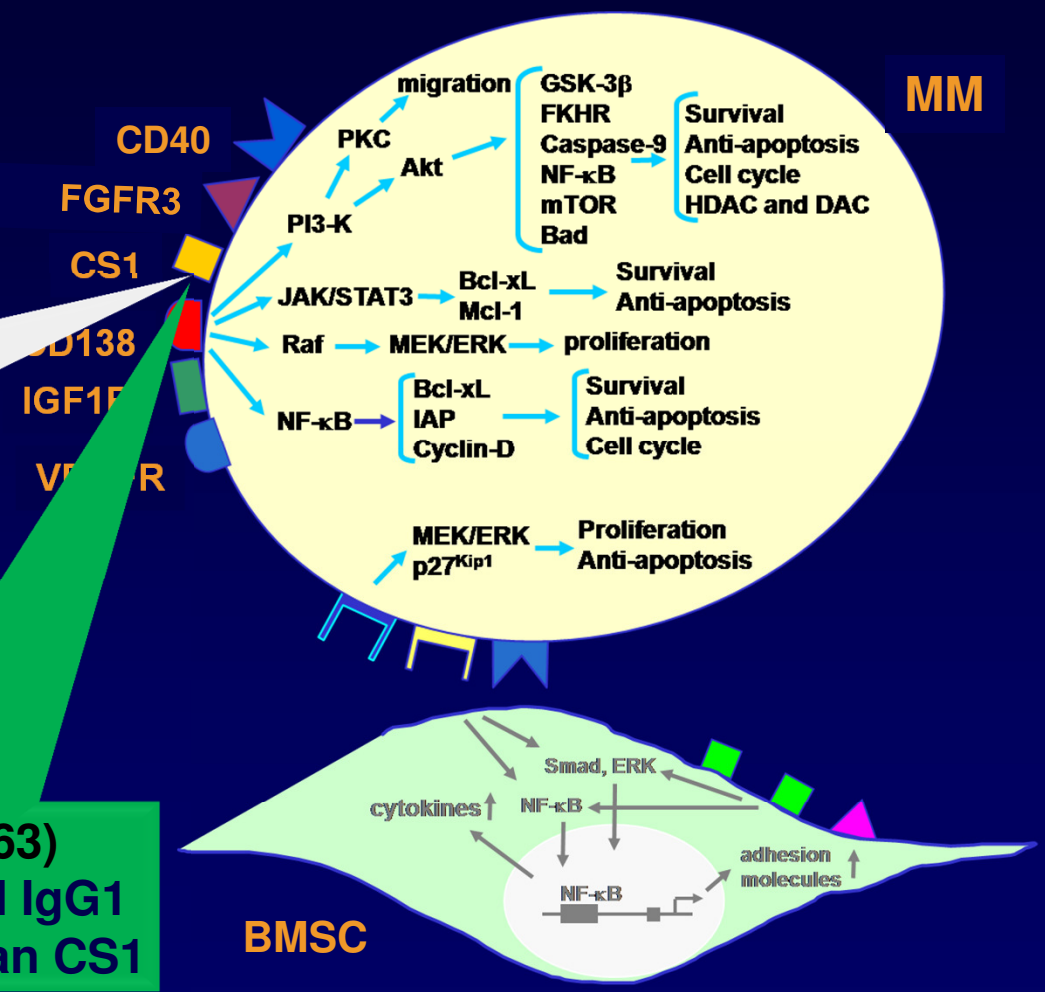


Reid IR, et al. *Semin Cell Dev Biol.* 2008;19(5):473-478.

Targeting Microenvironment with Antibodies

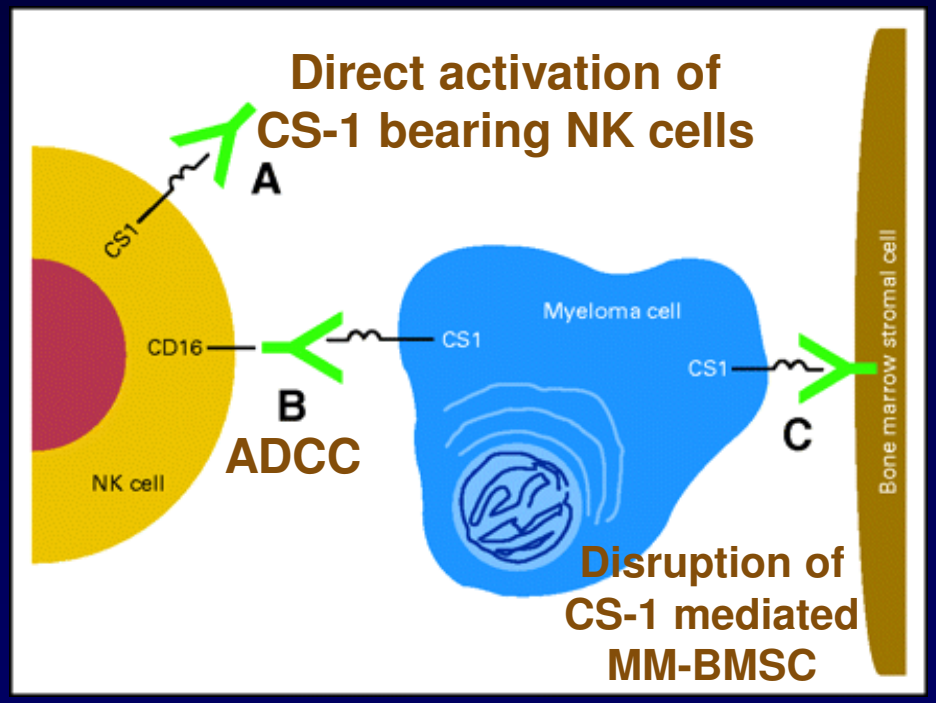
CS1:
Highly expressed on MM cells
Restricted expression on NK cells
Little to no expression on normal tissues

Elotuzumab (HuLuc63)
Humanized monoclonal IgG1 antibody targeting human CS1



Elotuzumab and Microenvironment

MOA



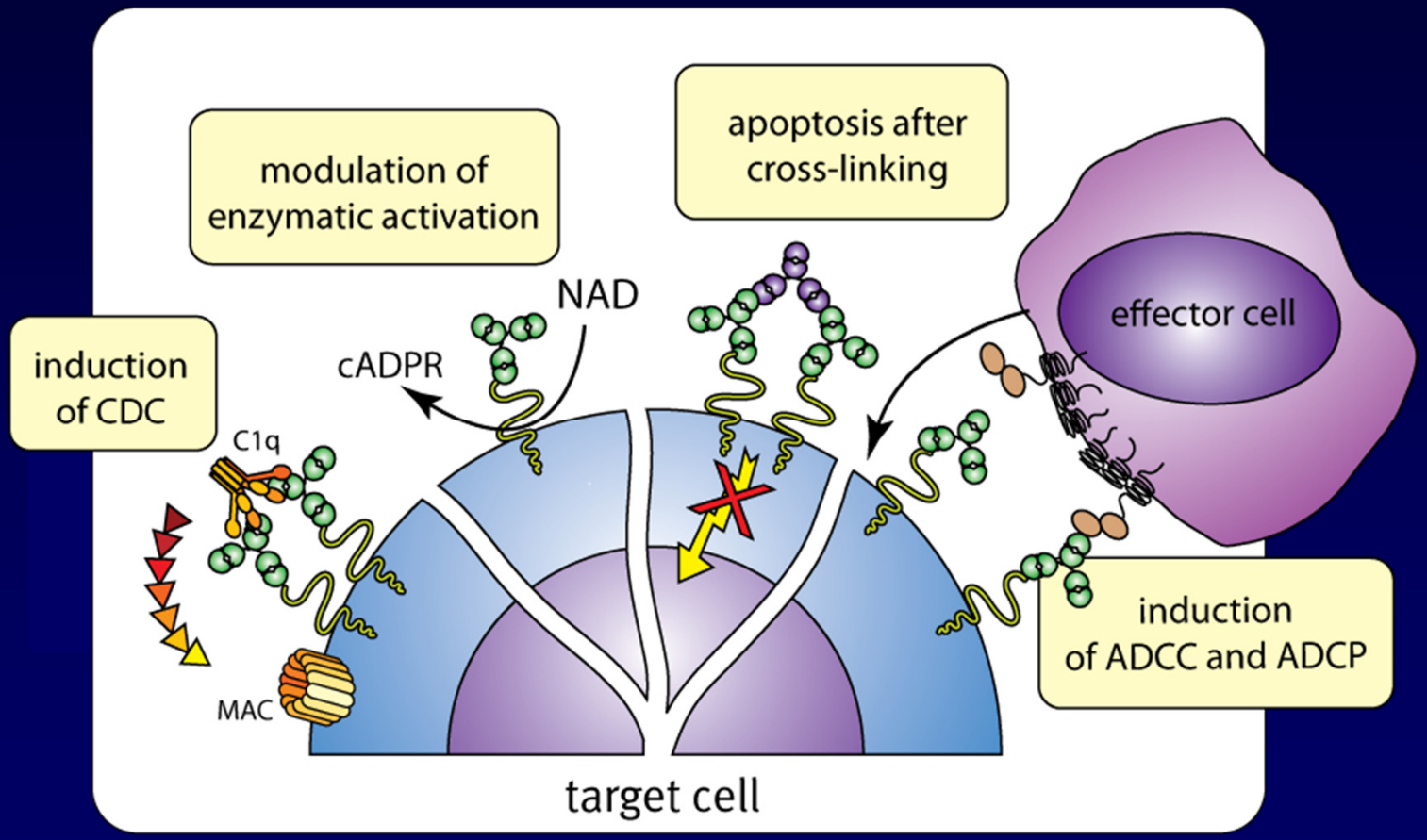
Benson DM, et al. *J Clin Oncol.* 2011;30(16):2013-2015.

Rationale for Combining with IMiDs and PIs

- Lenalidomide
  - Enhances and activates NK cells
  - Inhibits Tregs
- Bortezomib
  - Down-regulates expression of inhibitory NK-cell ligands on MM cells

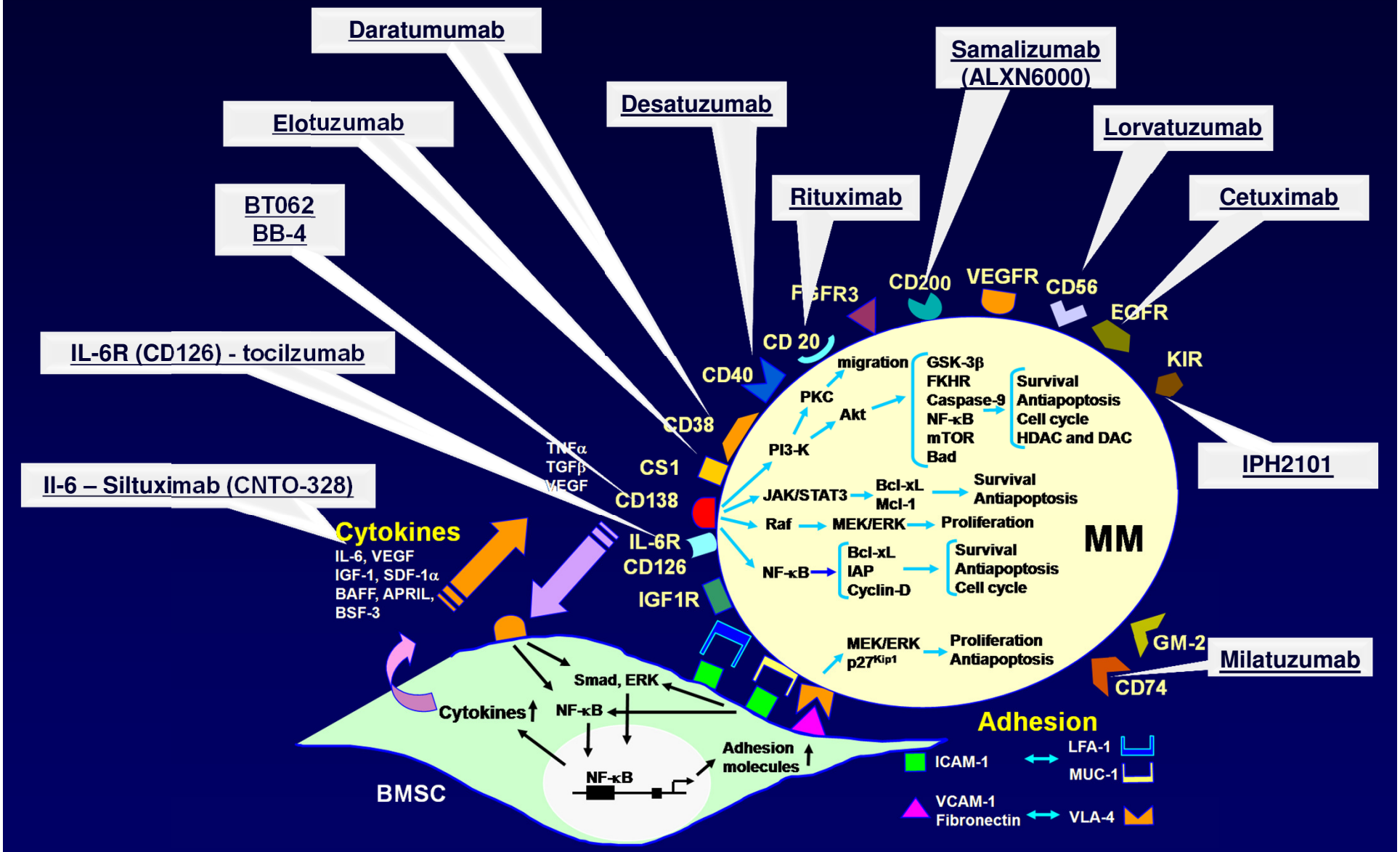
Daratumumab

A human CD38 mAb with broad-spectrum killing activity



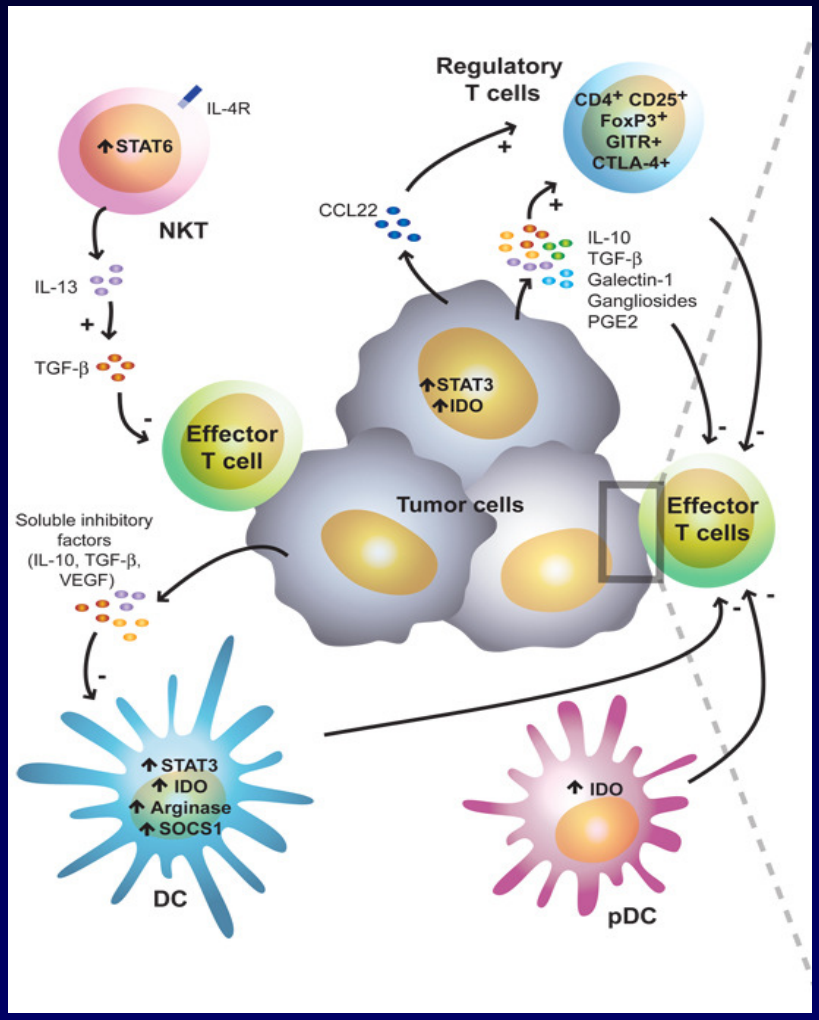
Plesner T, et al. *Blood.* 2012;120: Abstract 73.

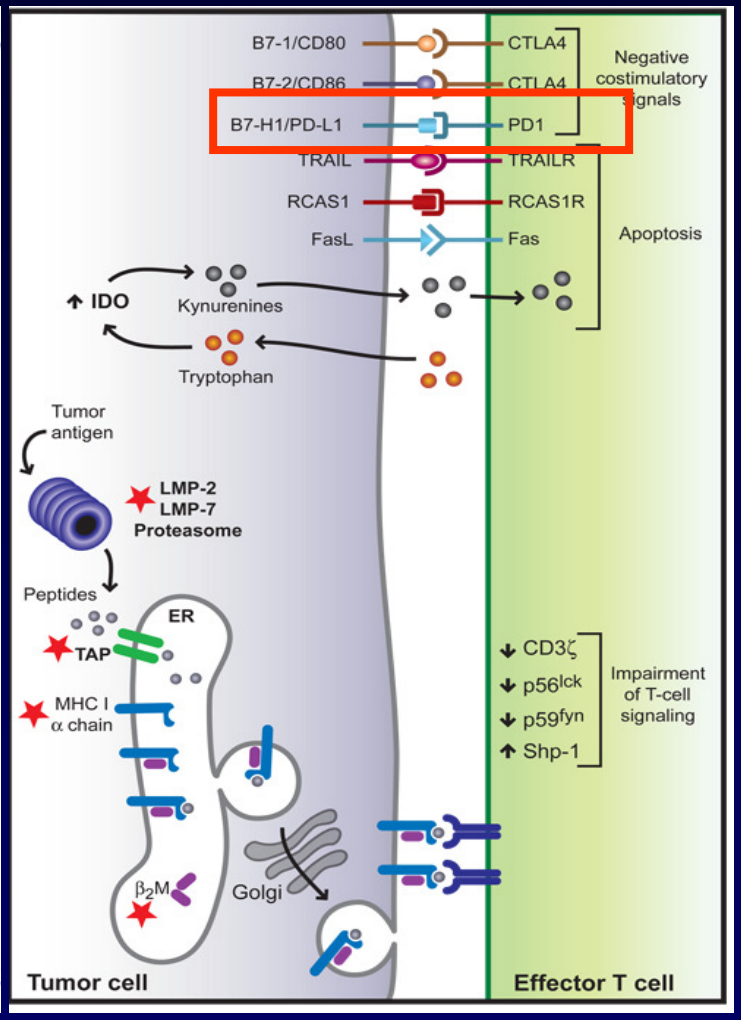
Potential Targets for Immunotherapy



Adapted from HideshimaT, et al. *Nat Rev Cancer.* 2002;2(12):927-937; Hideshima T, et al. *Blood.* 2004;104(3):607-618.

Tumor Mediated Immune Suppression



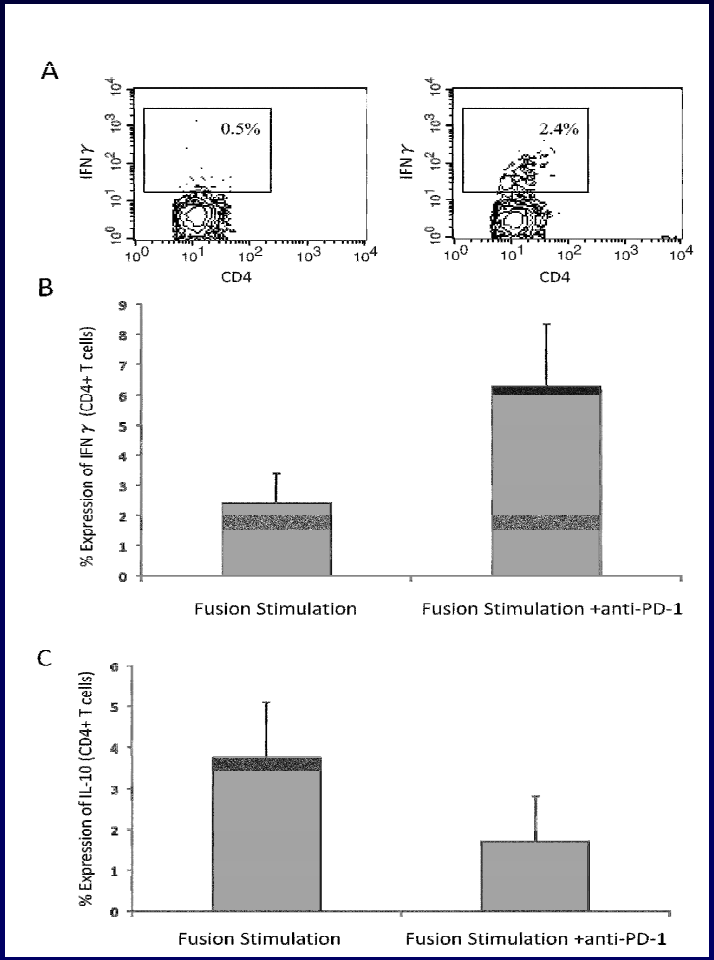


Rabinovich GA, et al. *Annu Rev Immunol.* 2007;25: 267-296.

PD1 blockade enhances immune response to DC/myeloma fusion vaccine in vitro

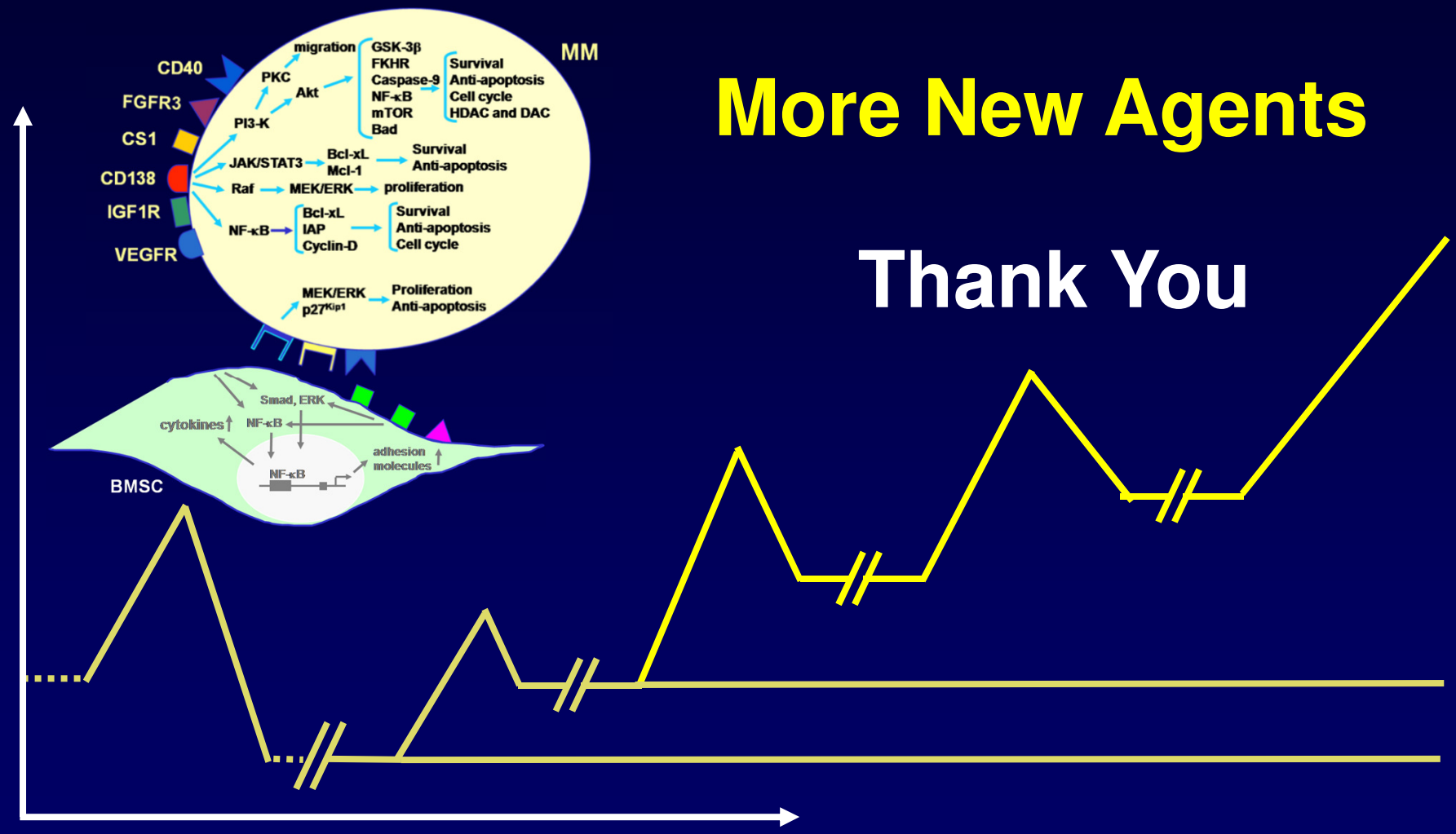
PD-1 blockade in conjunction with DC/myeloma fusion stimulation of T cells in vitro results in:

- increased IFN-gamma secretion
- decreased IL-10 secretion
- decreased expansion of Tregs
- enhanced tumor killing



Rosenblatt J, et al. *J Immunother.* 2011;34(5):409-418.

Race for Cure



More New Agents

Thank You

Adapted from Hideshima T, et al. *Mol Cancer Ther*. 2011;10(11):2034-2042; Ocio EM, et al. *Lancet Oncol.* 2008;9(12):1157-1165.