Moving Scientific Advances From Bench to Bedside

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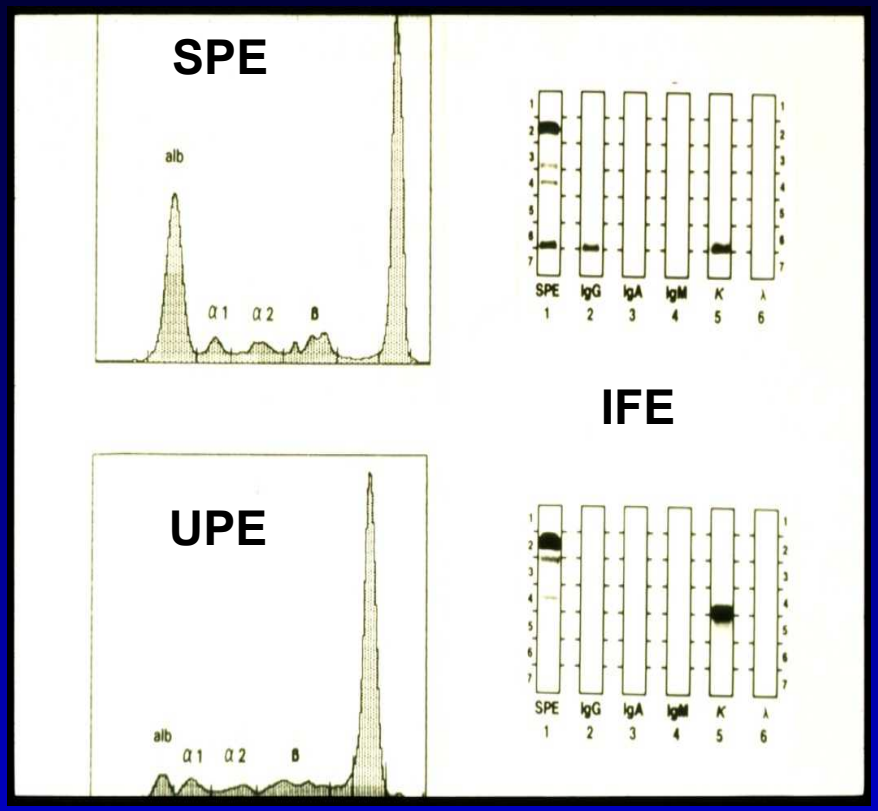
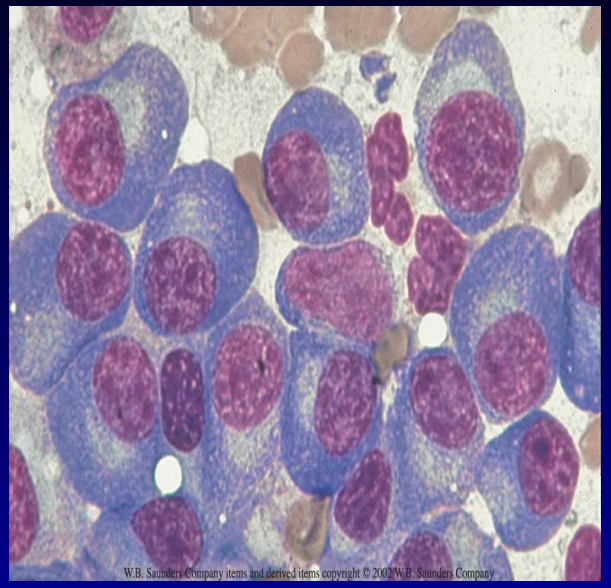
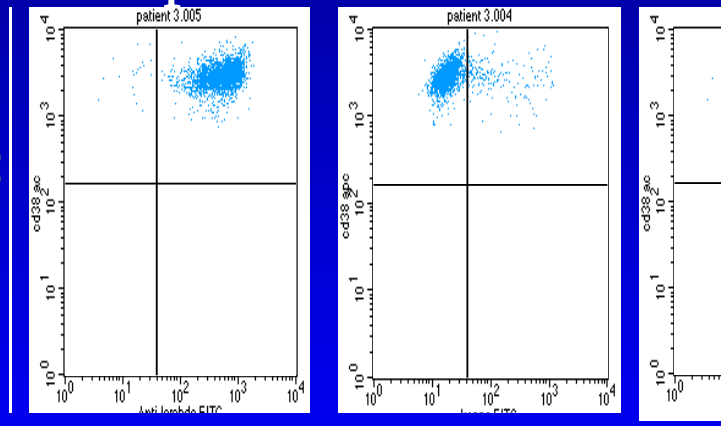
Multiple Myeloma



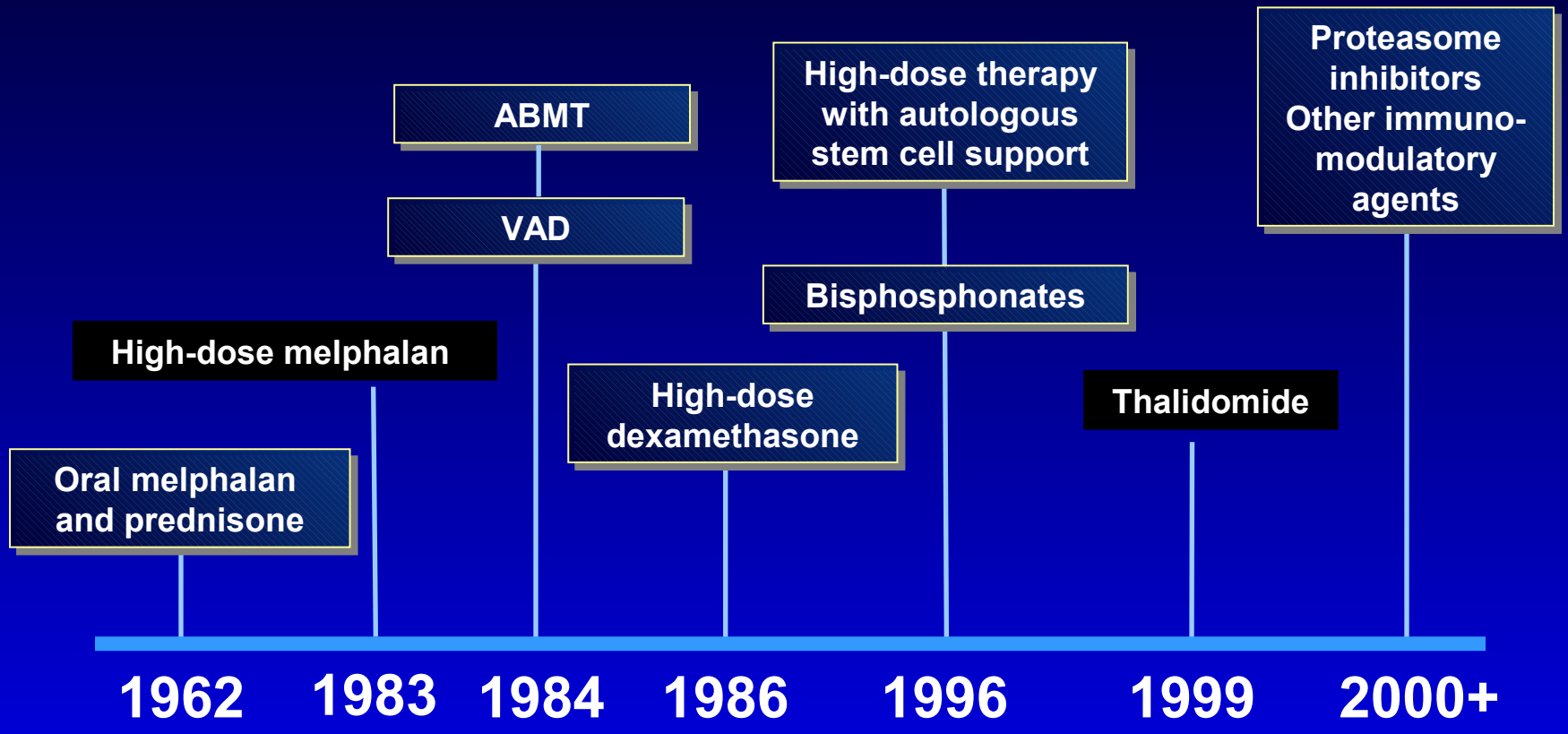
Monoclonal
Protein in blood and/or urine



Monoclonal CD138+
BM plasma cells



Historical Perspective of Multiple Myeloma

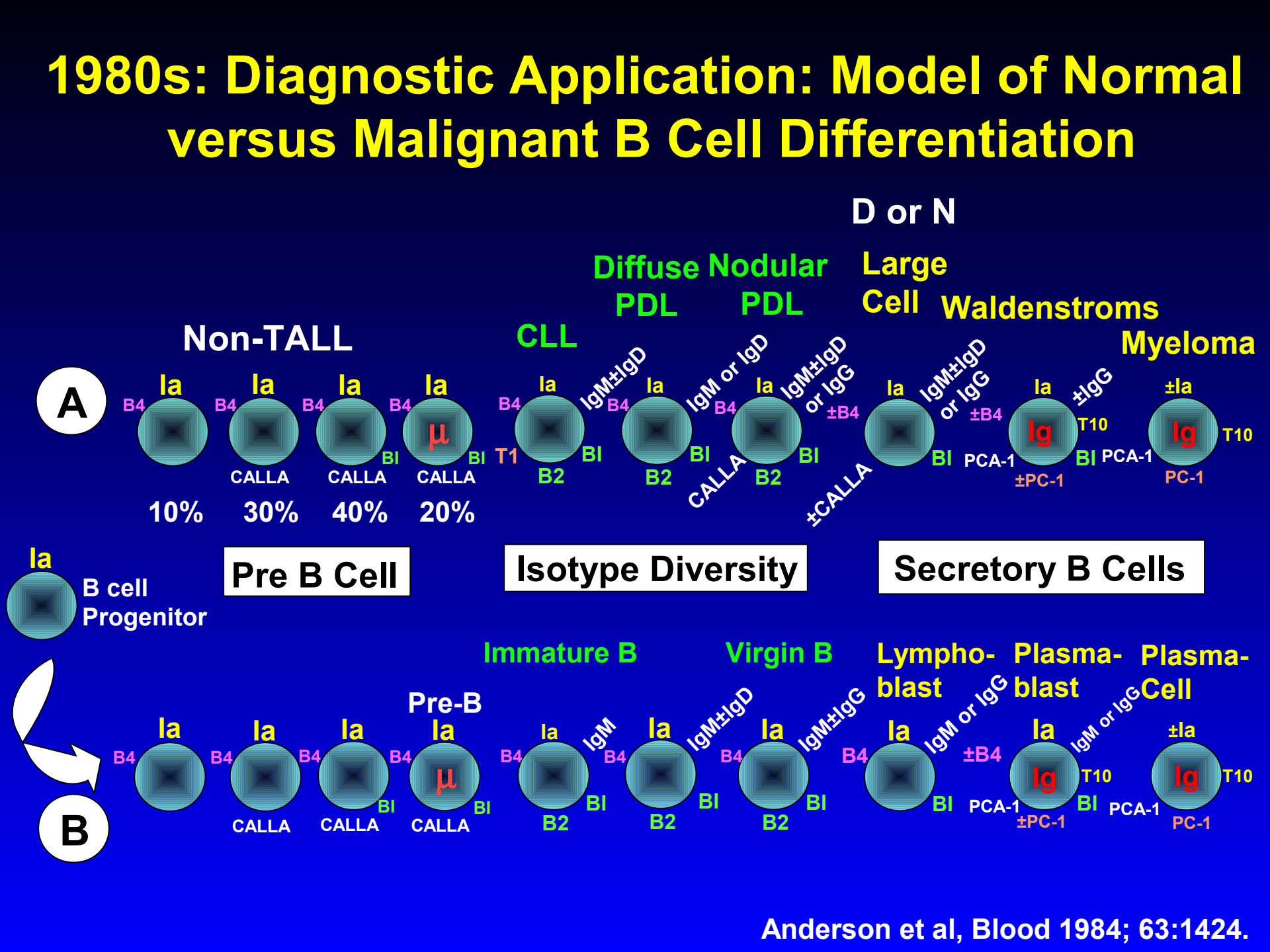


1980s: Characterization of New Lineage Reactive MoAbs

	Old Criteria	New Criteria
Pre-B cell	cyto μ	B4 (CD19)*
B cell	surface Ig	B1*, B2 (CD21)*, B5 *
Plasma cell	cytoplasmic Ig	PCA-1*, T10 (CD38)*
T cell	E-rosette	T3 (CD3), T4 (CD4), T8 (CD8)
Monocyte	phagocytosis	MO1 (CD11b), MO2 (CD14)

*KA contribution to B lineage markers

1980s: Diagnostic Application: Model of Normal versus Malignant B Cell Differentiation



Anderson et al, Blood 1984; 63:1424.

1980s : Therapeutic Applications

1. Monoclonal Ab purging of autografts (CD 10, CD20, PCA-1)

2. T cell depletion of allografts (CD6)

3. Immunotoxins (CD19, CD38 blocked ricin)

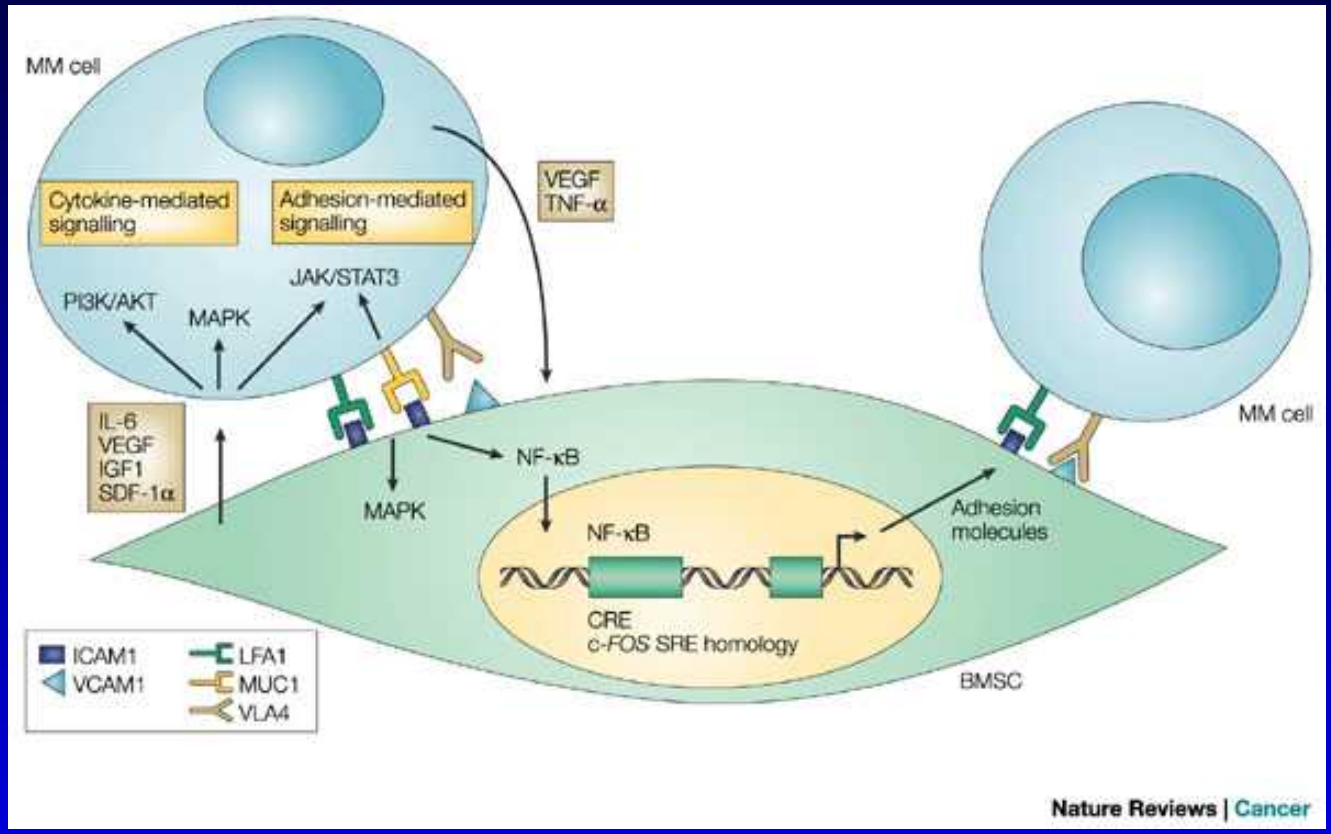
1990s : Bench to Bedside

1. Importance of tumor-host interaction and microenvironment in pathogenesis

2. Cytokines - IL-6, IGF-1, TGF-β,TNFα, IL-11, OSM, VEGF, SDF-1α, BAFF

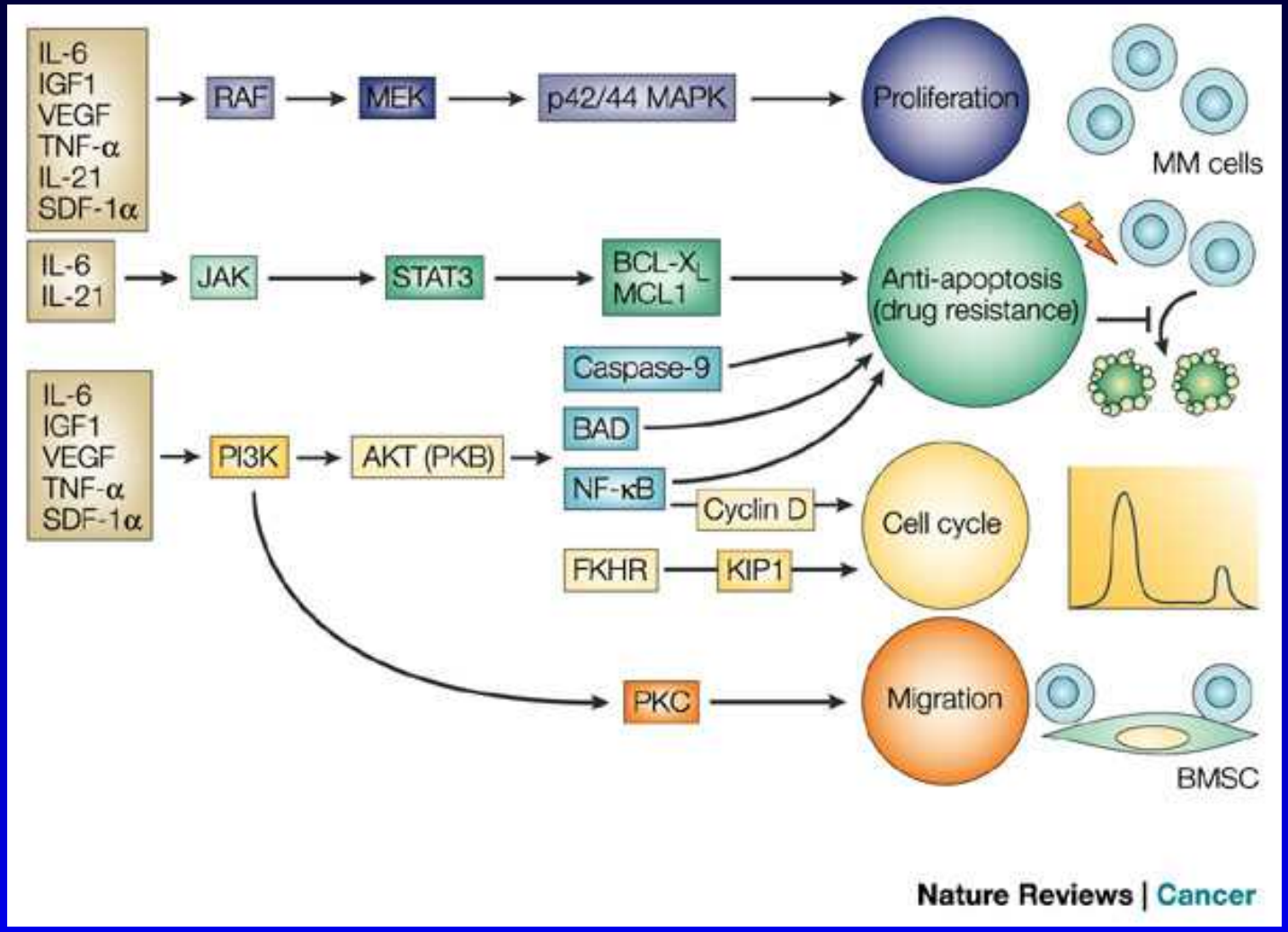
3. Growth, survival, drug resistance, and migration signaling cascades

Interaction of MM Cells and Their BM Microenvironment



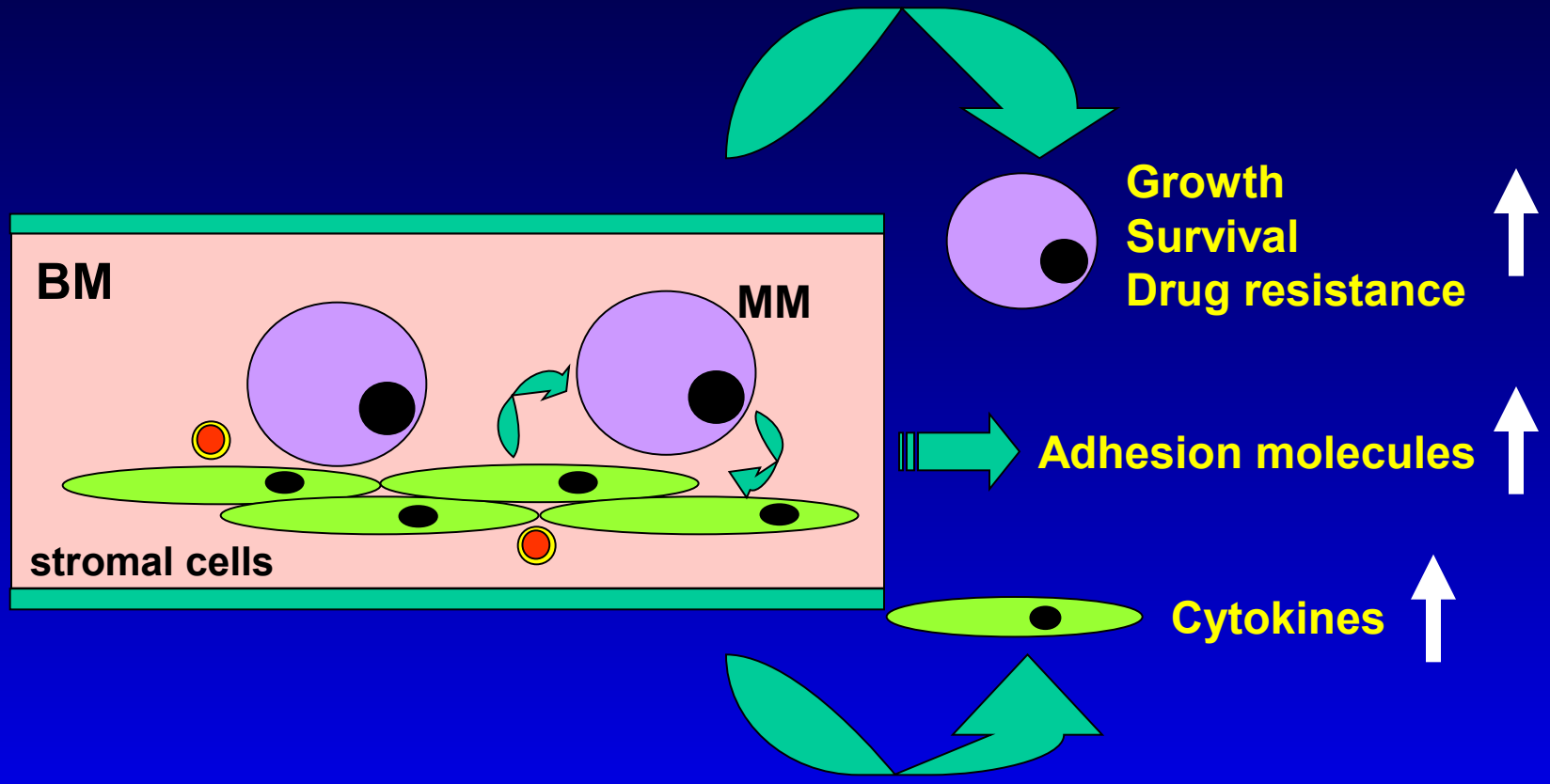
Hideshima T & Anderson KC Nat Rev Cancer 2002 2:927-937

Signaling Cascades Medating Growth, Anti-Apoptosis (Drug Resistance) and Migration in MM

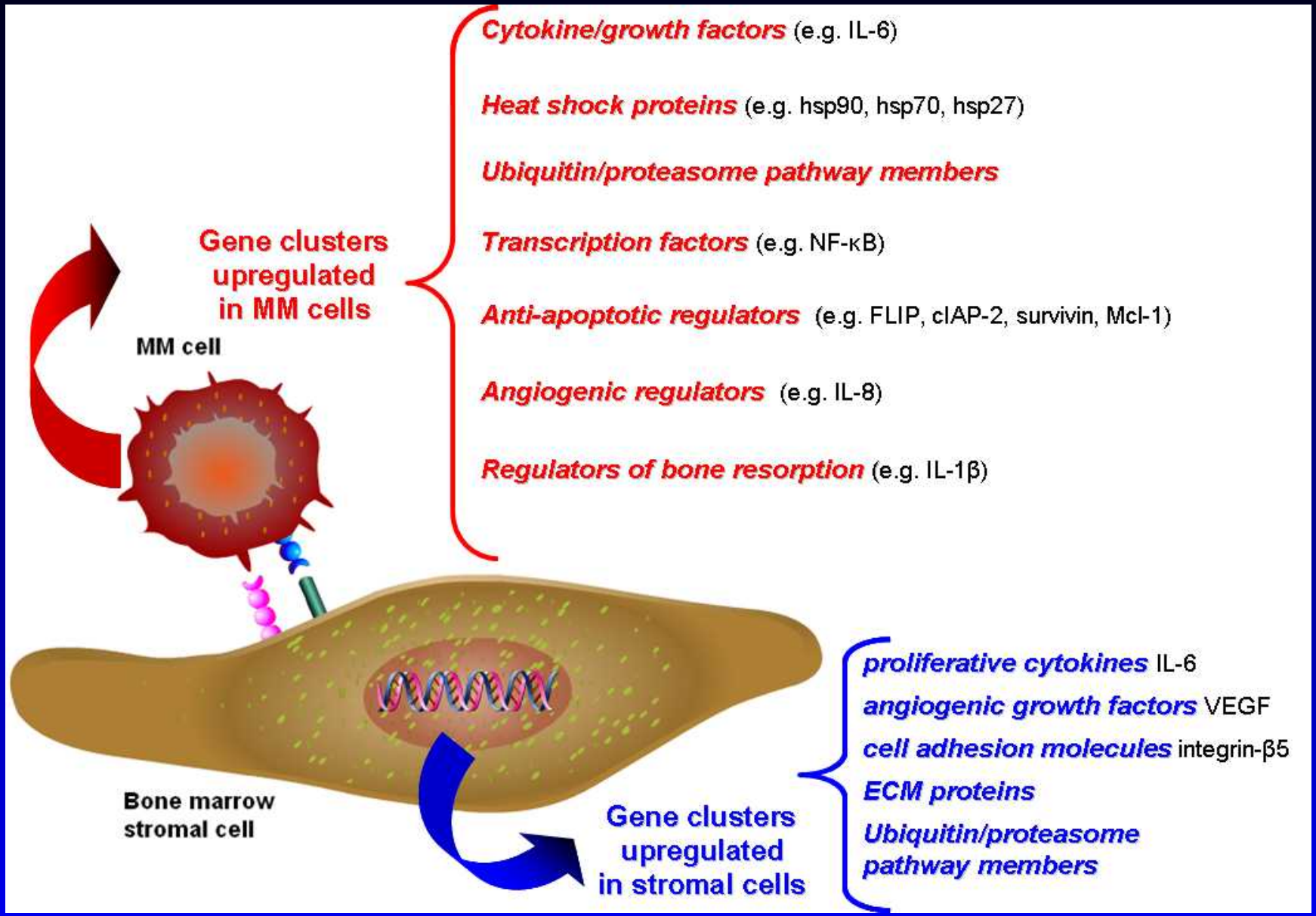


Hideshima T & Anderson KC Nat Rev Cancer 2002 2:927-937

Myeloma as a Model for Targeting Tumor Cells in the Microenvironment

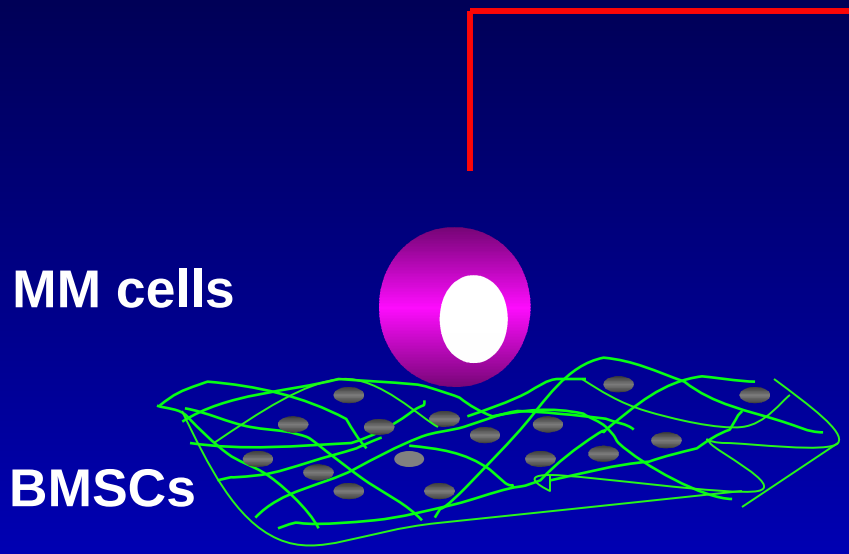


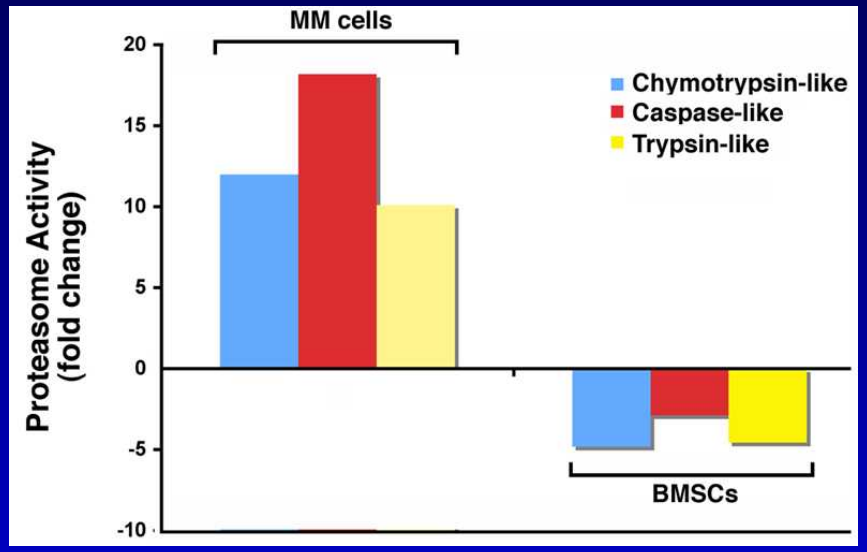
Gene Clusters Modulated by MM-BMSC Interactions



McMillin et al, ASH 2008

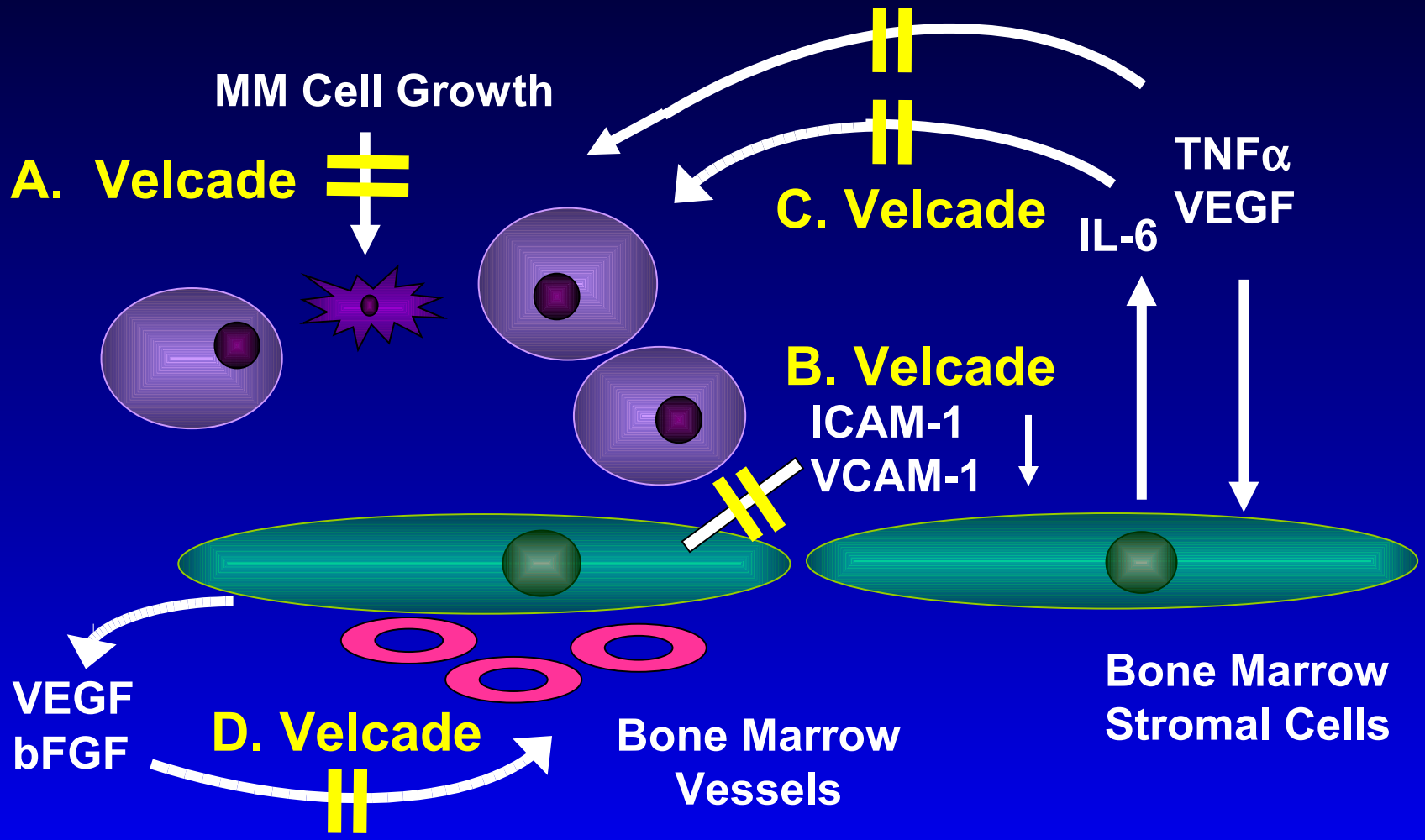
BM Microenvironment Triggers Proteasome Activity in MM Cells





Chauhan et. al., 2006

Bortezomib Targets MM Cells in the BM Microenvironment



Also blocks bone resorption and triggers new bone formation

Bortezomib Effects on Myeloma Cells

1. Downregulates adhesion molecules, caspase dependent cleavage of IL-6R
2. Activates JNK, increased ROS, mitochondrial release of cyto C/Smac, caspase 9>8, 3 cleavage
3. Induces p53+/- apoptosis
4. Induces cleavage of Mcl-1
5. Inhibits DNA repair (ATM, DNA PKcs cleavage)
6. Induces apoptosis of endothelial cells, osteoclasts
7. Induces osteoblasts and new bone formation

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 MM

Effective as Induction/First-line Therapy

Transplant/Maintenance

Integration of Novel Therapy Into Myeloma Management

Six FDA/EMEA Drug Approvals
in Last Five Years

Median survival prolonged from 3-7 years
(especially in younger patients)

Three phase III trials of novel agents
ongoing for FDA approval

Bortezomib and Lenalidomide Therapy

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

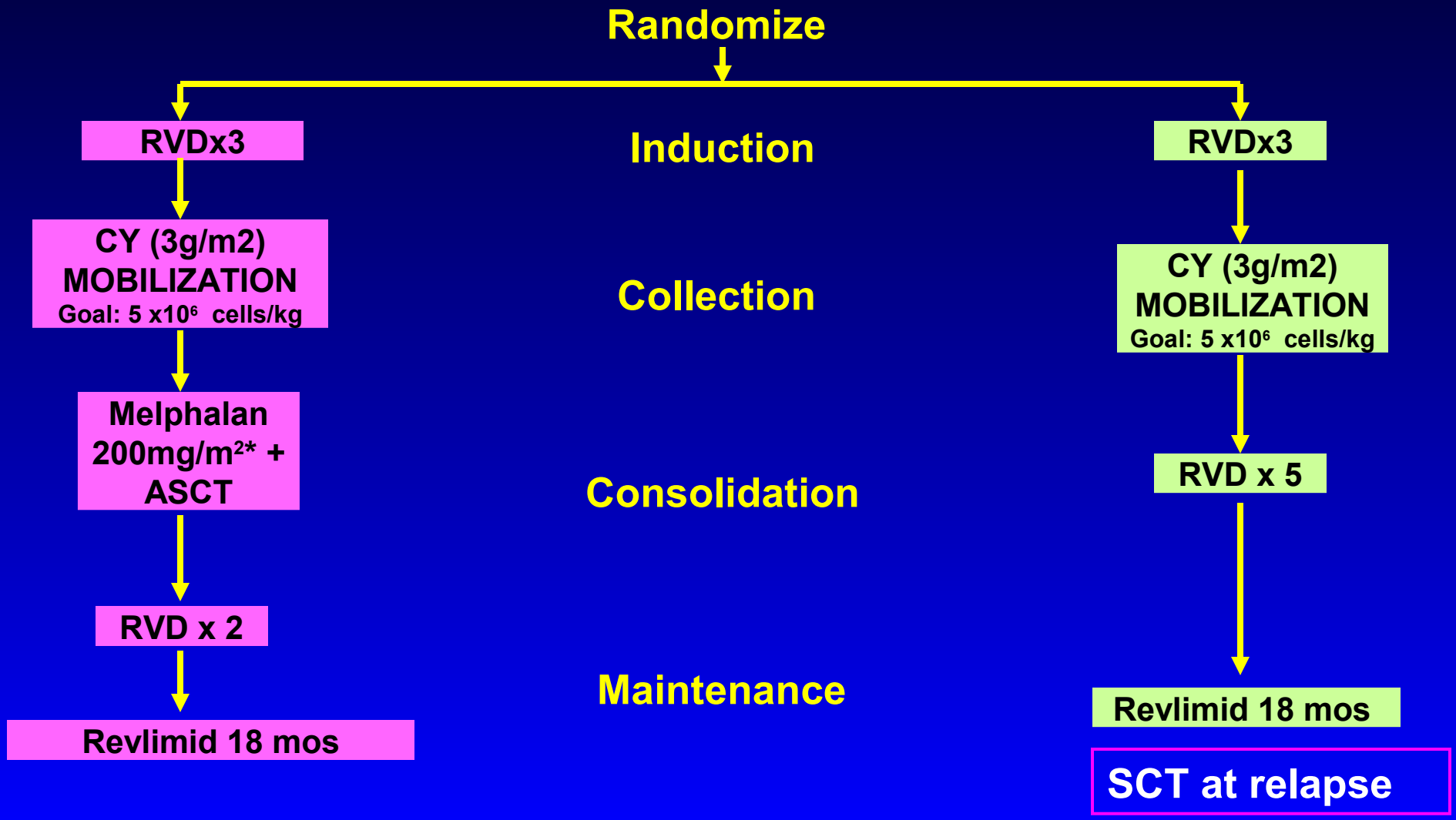
Synergistic MM cell toxicity of lenalidomide (caspase 8) with Bortezomib (caspase 9>8) in vitro and in vivo (dual apoptotic signaling)

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 71% CR/VGPR when used as initial therapy.

Richardson et al, ASCO, ASH 2008

IFM/DFCI 2009 Study
Newly Diagnosed MM (SCT candidates)



Current and Future Directions

1. Improved classification and development of personalized therapy

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

3. Development of immune therapies

4. Development of rationally-based combination therapies

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

Global View of Myeloma Genome/Proteome

DNA

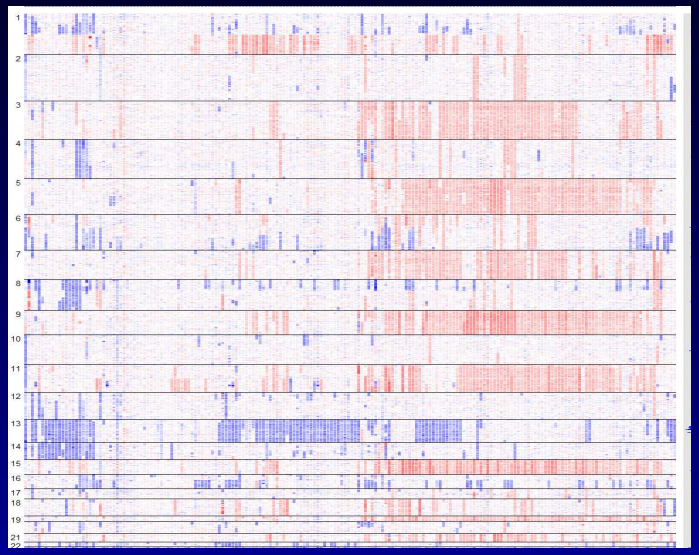
- Amplification and Deletion – array CGH
- Single Nucleotide Polymorphism – 500K SNP array

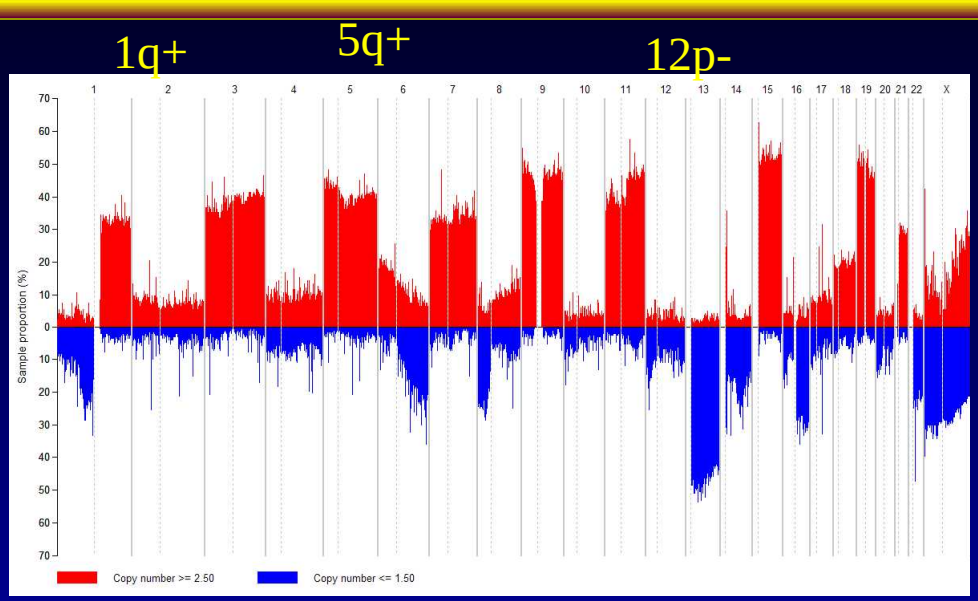
RNA

- Expression changes – expression profile with GeneChip® Human Exon 1.0 ST
- Alternate splicing - genome-wide Exon analysis with GeneChip® Human Exon 1.0 ST
- microRNA – qRT-PCR based microRNA array

PROTEINS- SELDI, MALDI-TOF

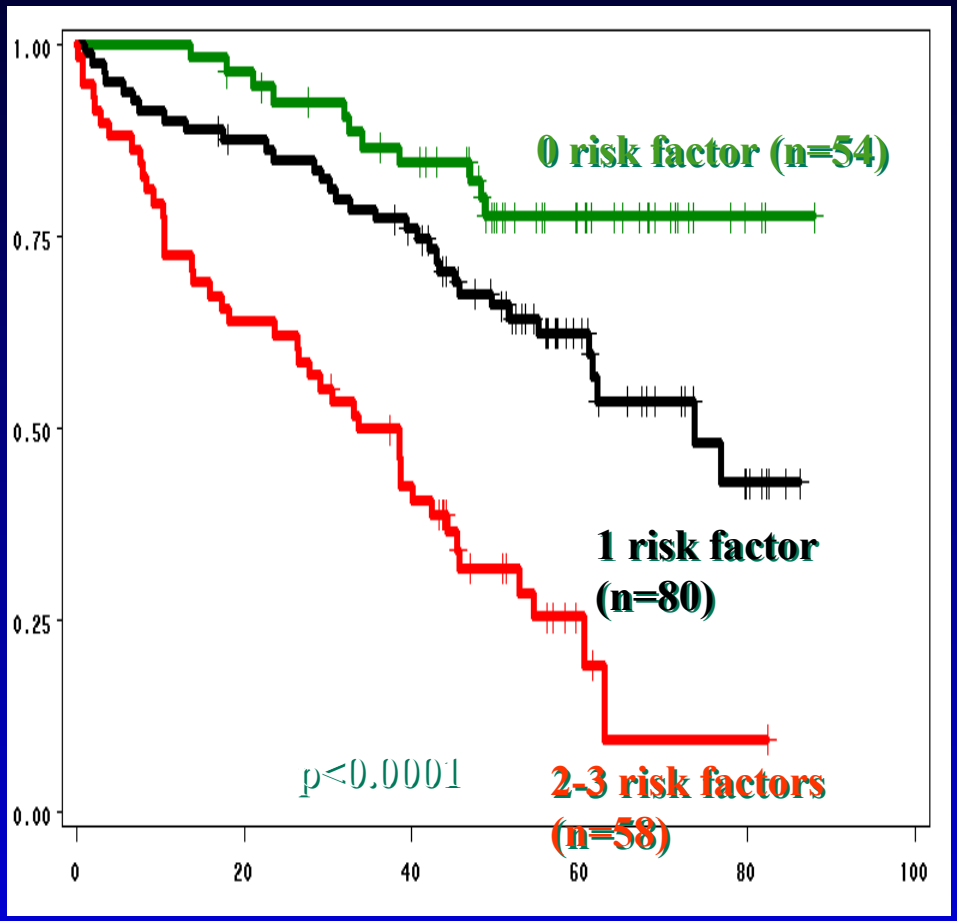
SNP Array Based Prognostic Model





Multivariate analysis (stepwise Cox model)		
Prognostic variables	**Hazard ratio [95% CI*]**	**p**
Amp(1q23.3) Yes vs. No	1.90 [1.23-2.94]	0.004
Amp(5q31.3.) Yes vs. No	0.37 [0.22-0.63]	0.0002
Del(12p13.31) Yes vs. No	2.32 [1.33-4.06]	0.003

Chromosomal Multivariate Analyses

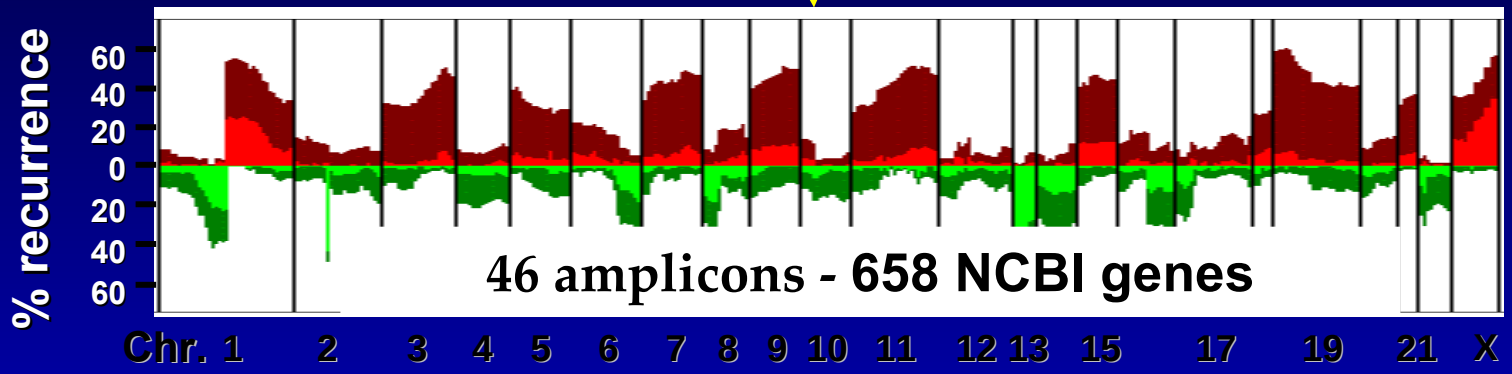


- Copy number analyses reveal novel prognostic classification
- Identifies regions of clinical importance especially del12p and amp 5q
- SNParrays highlight few regions with bi-allelic deletions
- SNP analysis may ultimately lead to an individual therapeutic approach.

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.

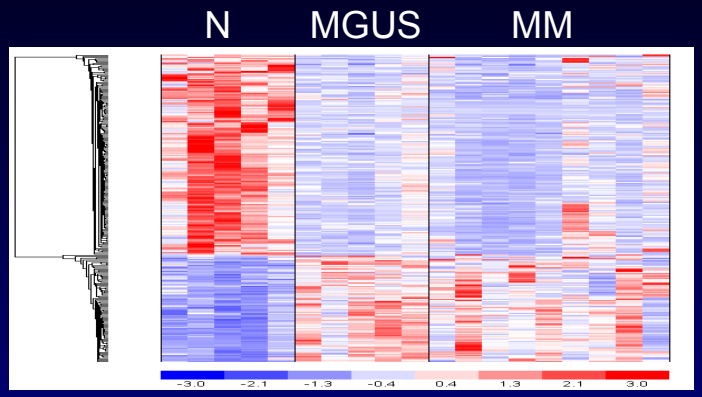
Small molecule

New models

Carrasco et al. Cancer Cell, 2006 9:313-325

Monoclonal Abs
Vaccines

Molecular Pathogenesis of Myeloma



UPREGULATED

91 GENES
Oncogenes – BCL2, LAF4
Transcription – FOXG1A, RING1
Development – SHH, WNT

22 GENES
Transcription – RING1
Development - FRZB

CELL PROLIFERATION

N → MGUS → MM → PCL

DOWNREGULATED

172 GENES
Membrane – CD38, CD27
Tumour Supressor – RB, ARMET
Transcription – XBP-1, ZFP
Death – TAX1BP1, TXNL

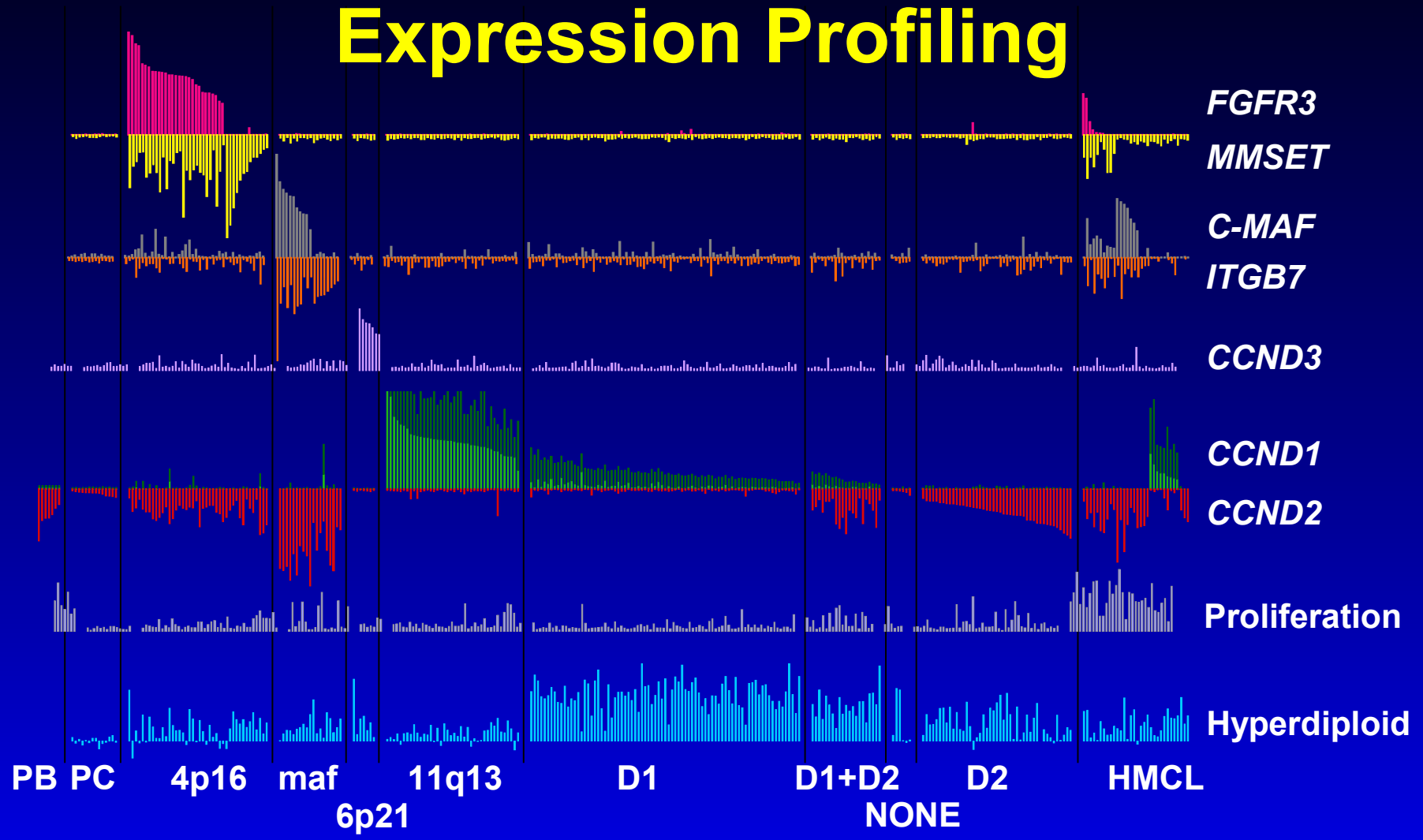
52 GENES
Survival – TNFSF7
Signalling – MD2, MACS
Structural – ADD1, VCL

ADHESION

DNA REPAIR

Davies et al. Blood 2003;102:4504.

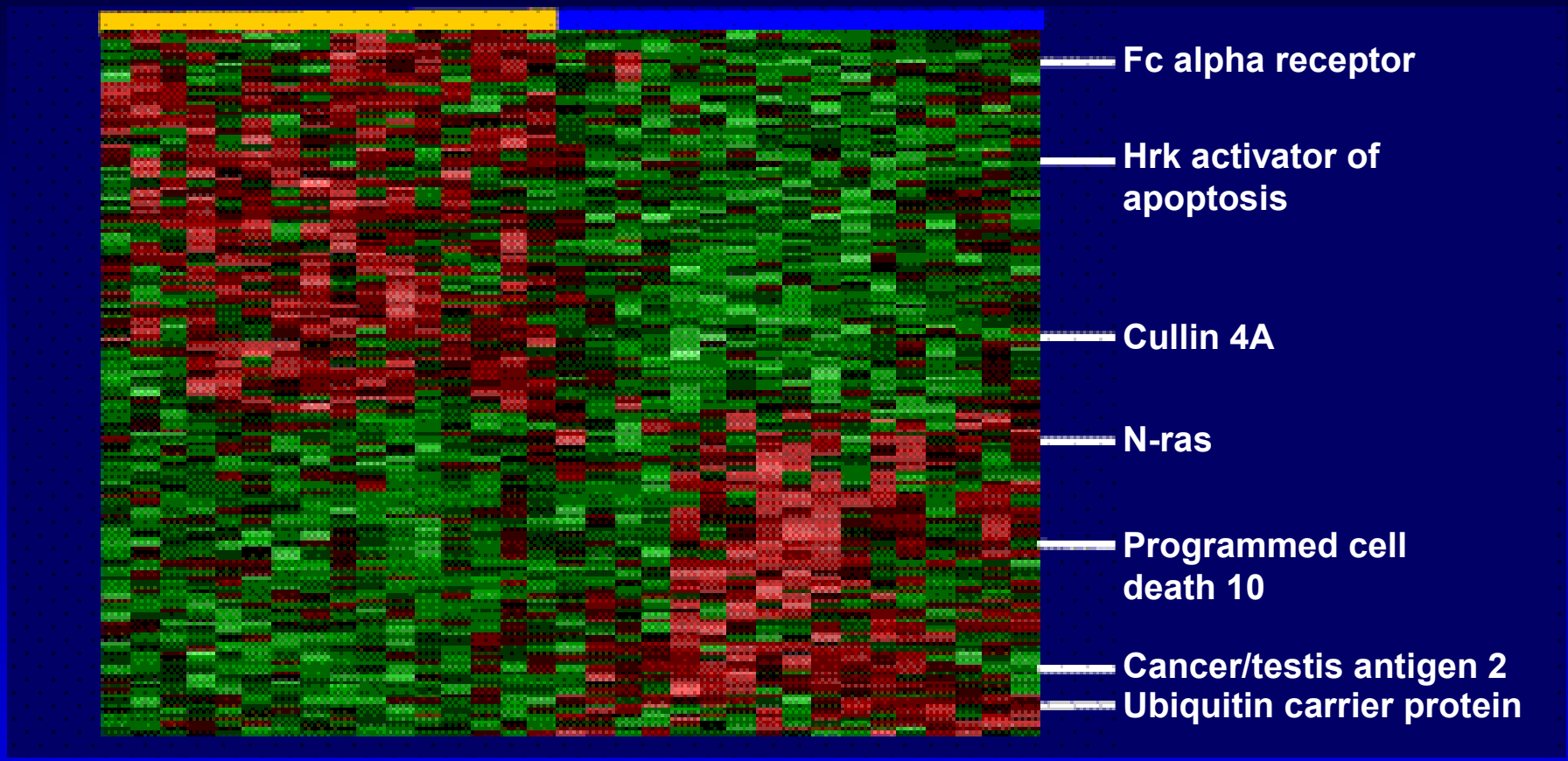
Classification Based upon Expression Profiling



Bergsagel et al, Blood 2005

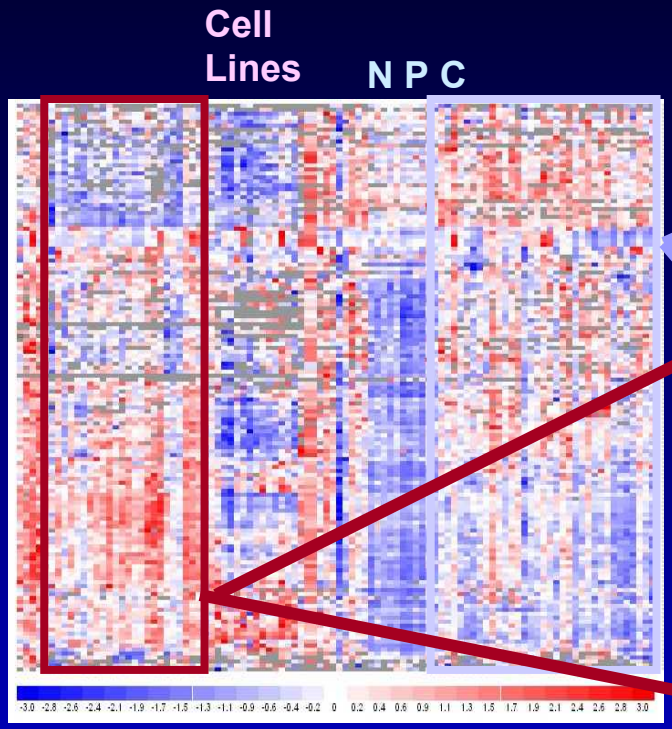
Development of Personalized Medicine

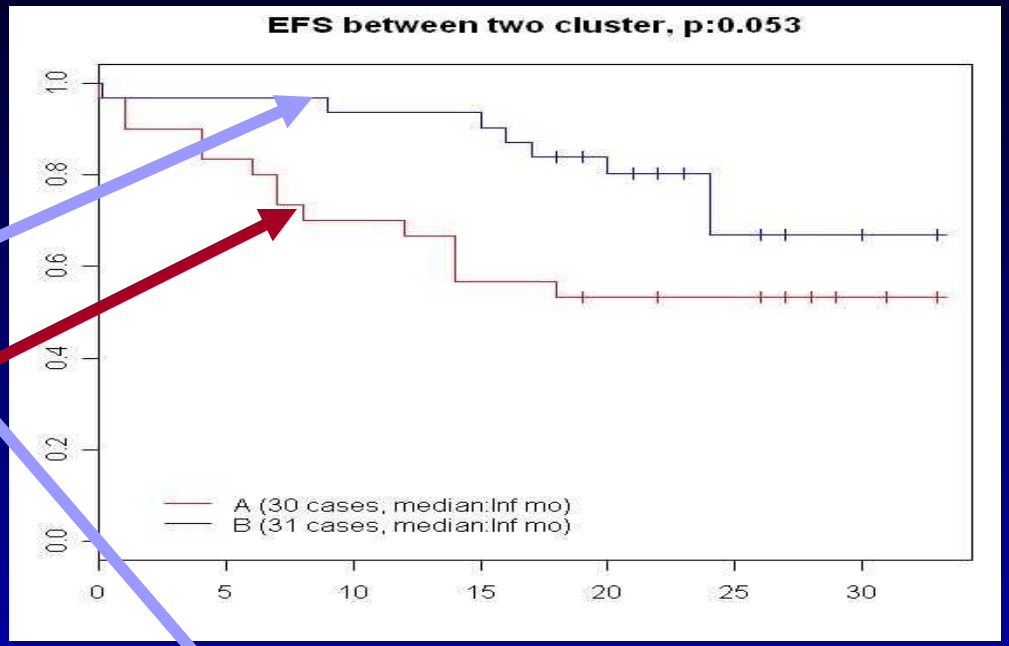
Genes Correlated With Response (Bortezomib)

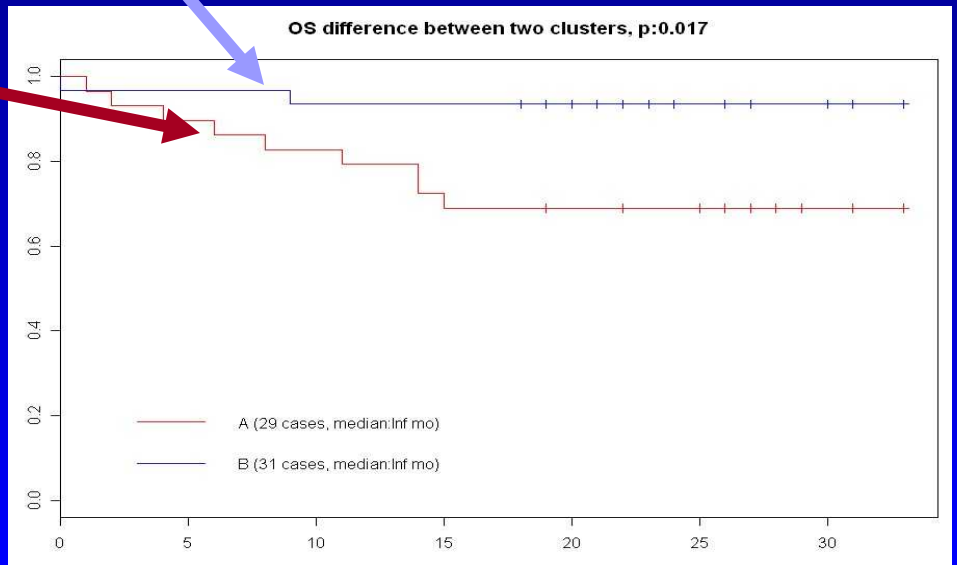


Richardson et al. N Engl J Med. 2003; 348:2609-2617

Micro RNA Profile Identifies Clinical Sub Groups With Different Survival



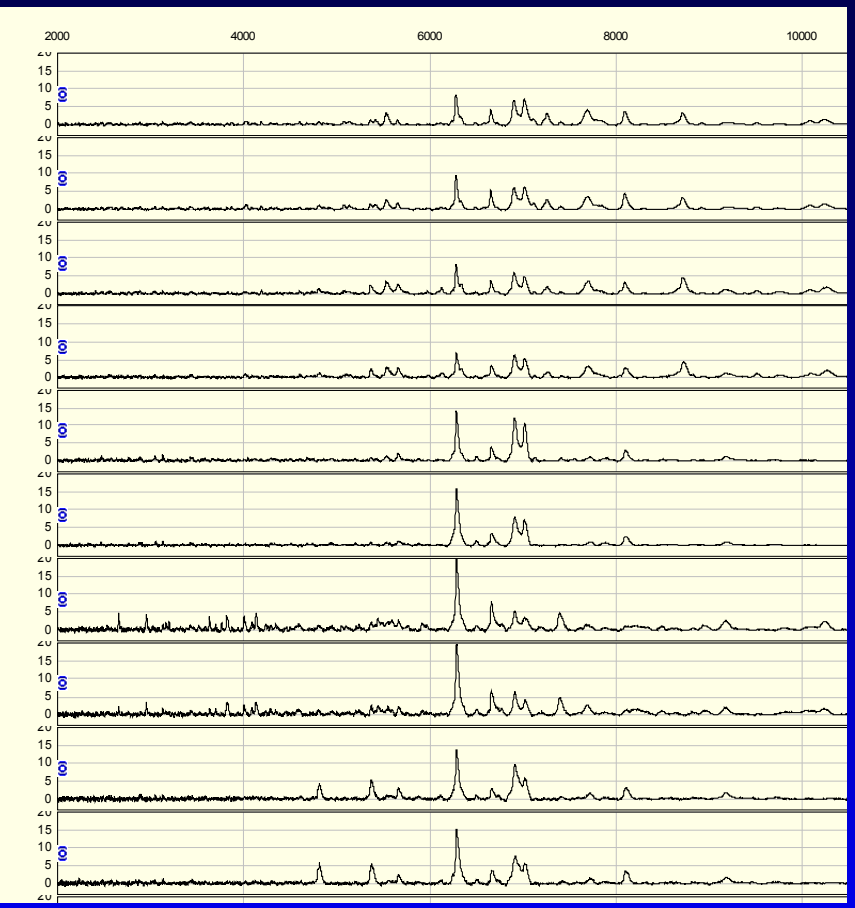




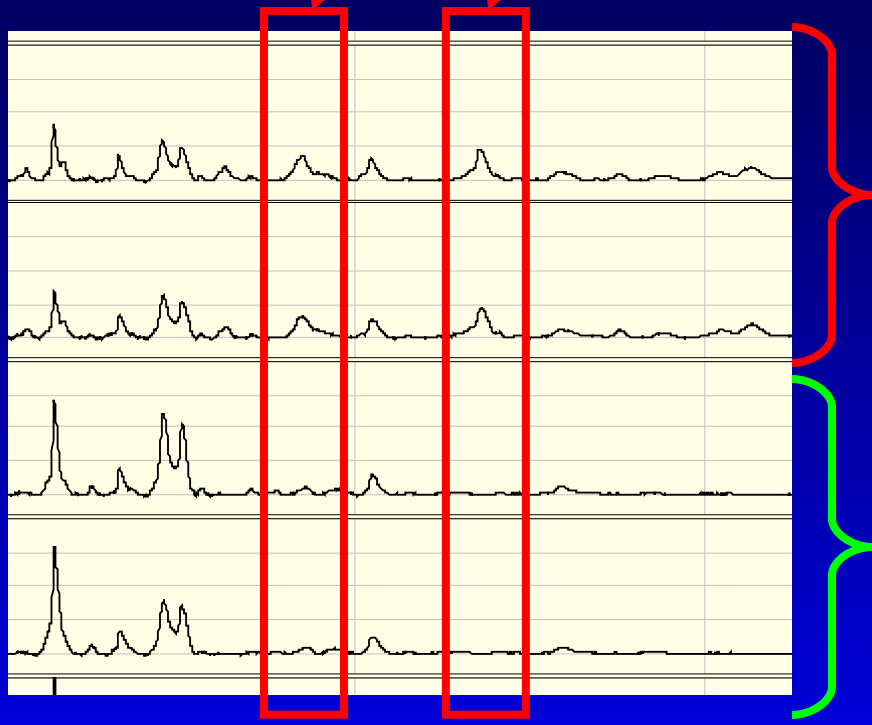
- 79 uniformly treated MM patients
- 11 MM cell lines and
- 9 healthy donors
- microRNA profiling

Proteomic Profiles Distinguish Drug Sensitive versus Resistant MM Cells

SELDI Platform

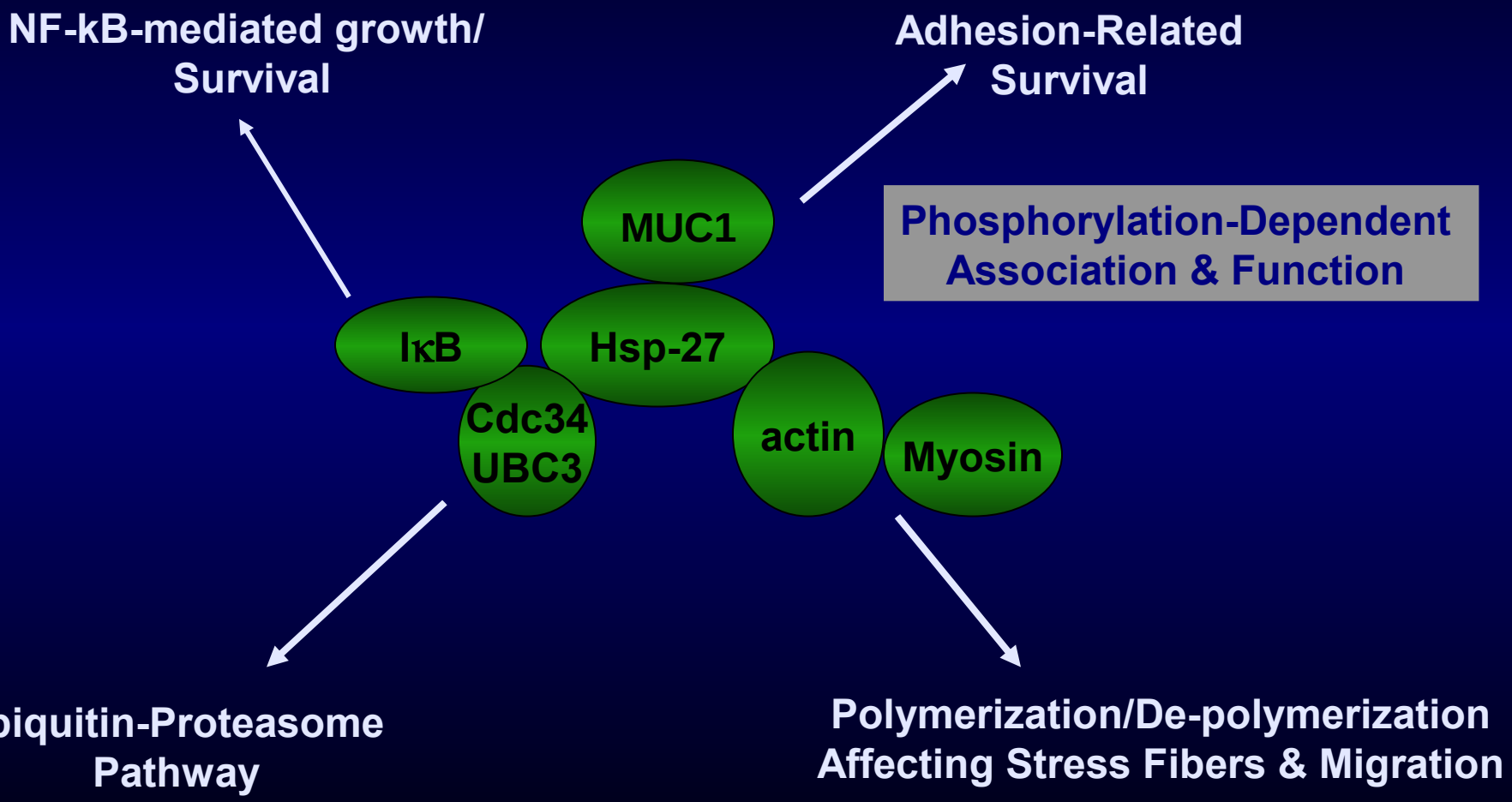


Proteins upregulated in chemoresistant MM cells



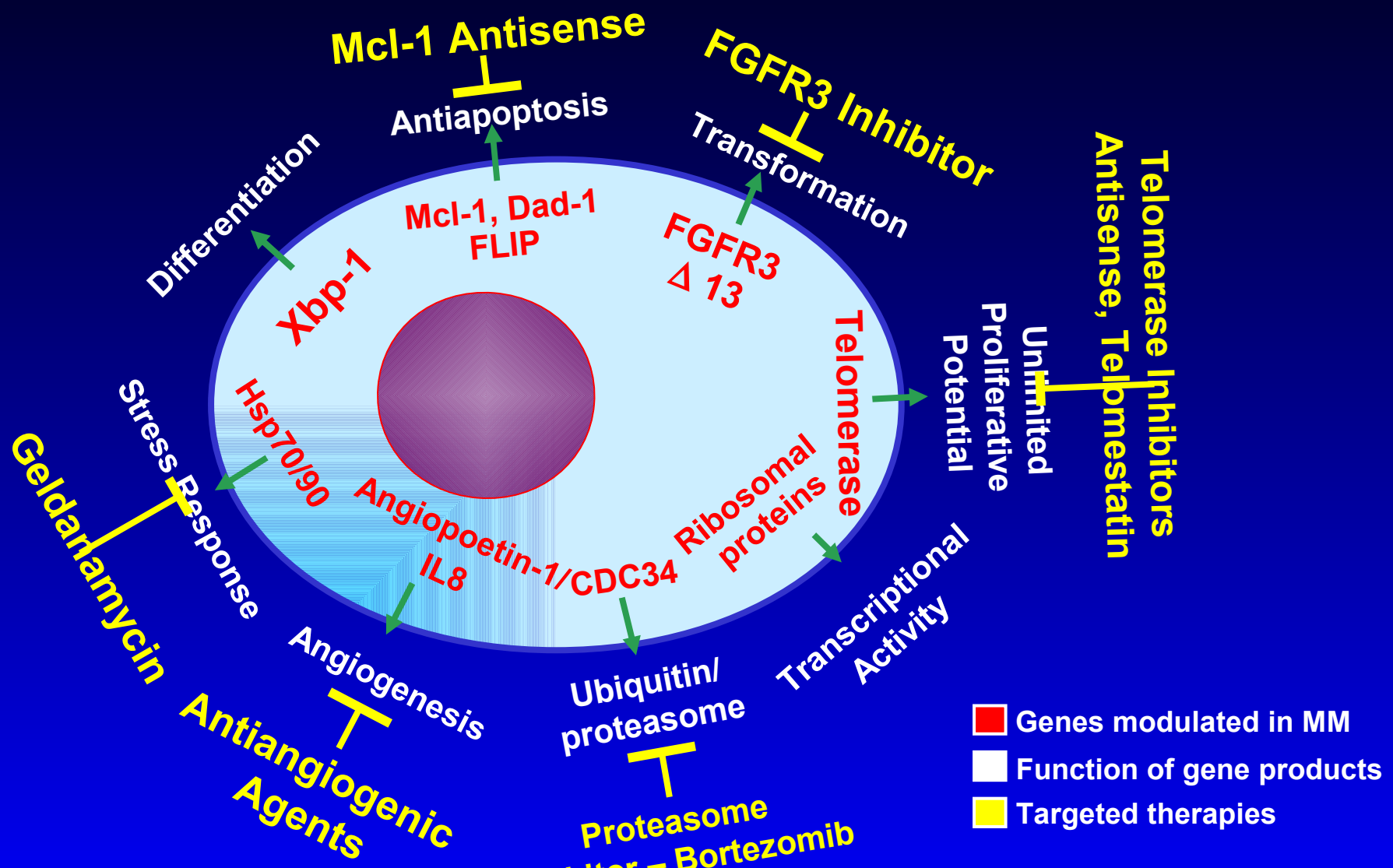
Mitsiades CS et al.

Proteomic Analysis (MALDI-TOF): Complex Protein-Protein Association Confers Drug-Resistance



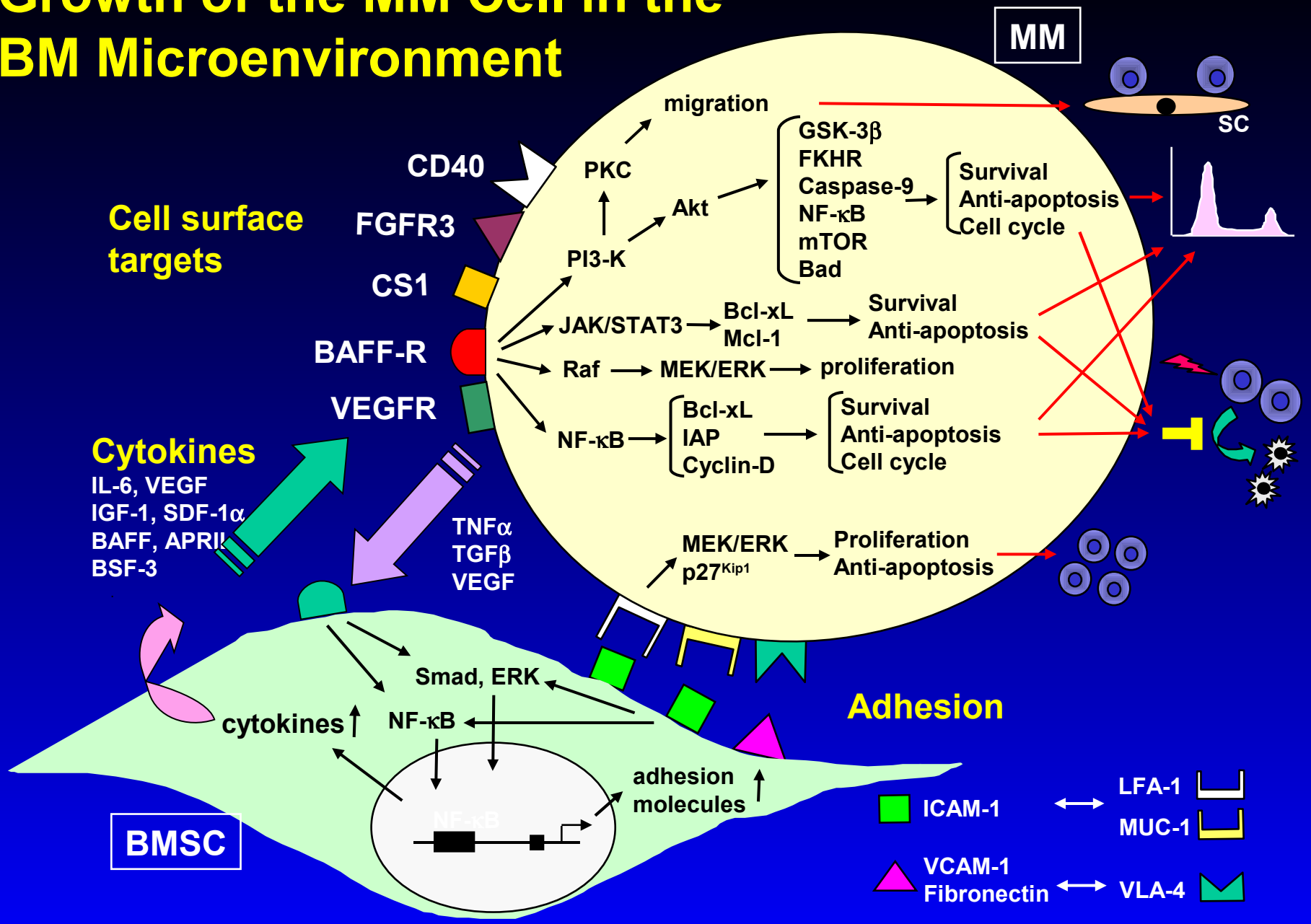
Chauhan et al

Individualized Targeted Therapy



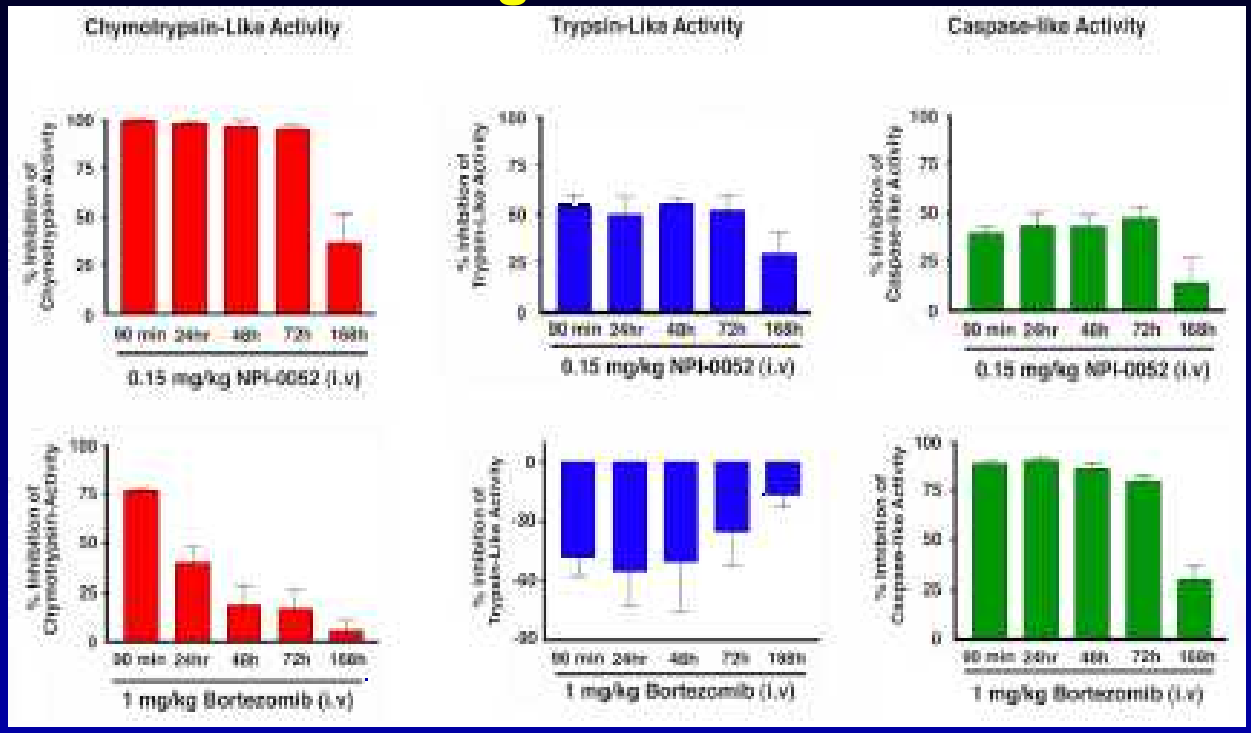
Munshi NC et al. *Blood*. 2004;103:1799.

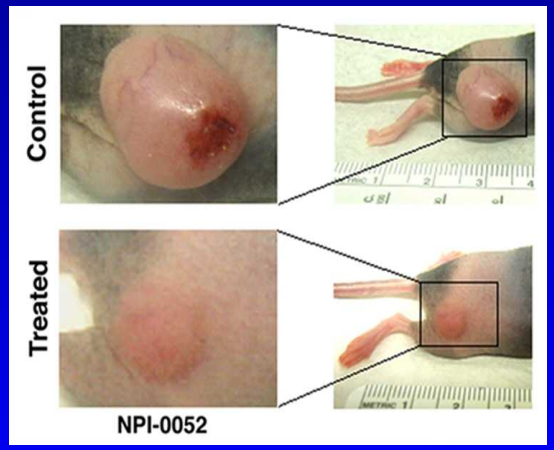
Growth of the MM Cell in the BM Microenvironment

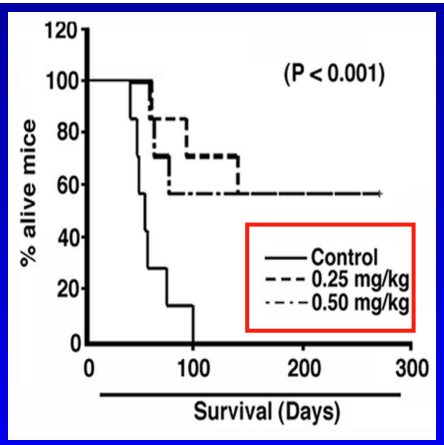


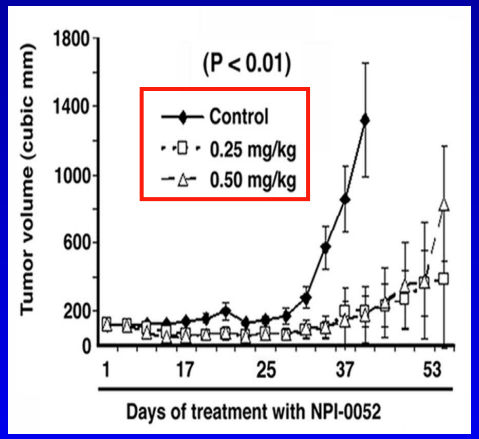
Hideshima T and Anderson KC. Nat Rev Cancer 2002, 2:927. Hideshima T et al. 2004, Blood 104:607

Novel Proteasome Inhibitor NPI-0052 Inhibits Human MM Cell Growth and Prolongs Survival in a Murine Model



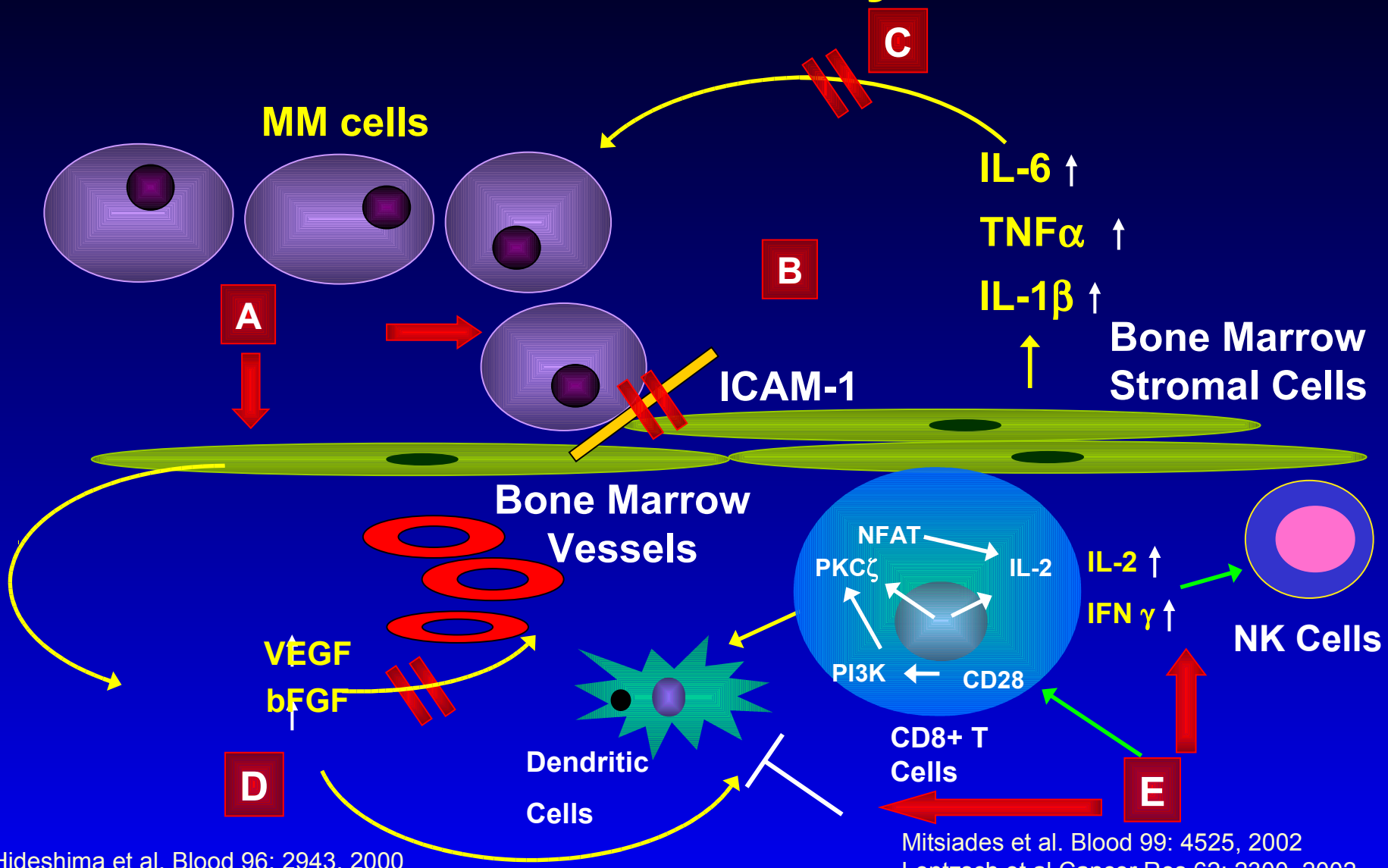






Chauhan et al, Cancer Cell, 2005.

Pomalidomide 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

Phase II trial of Pomalidomide in Relapsed/Refractory Myeloma

Median follow-up 4 months

Confirmed Response	N =60
sCR	1 (2%)
VGPR	14 (23%)
PR	20 (33%)
SD	11 (18%)
PD	13 (22%)
NE	1 (2%)

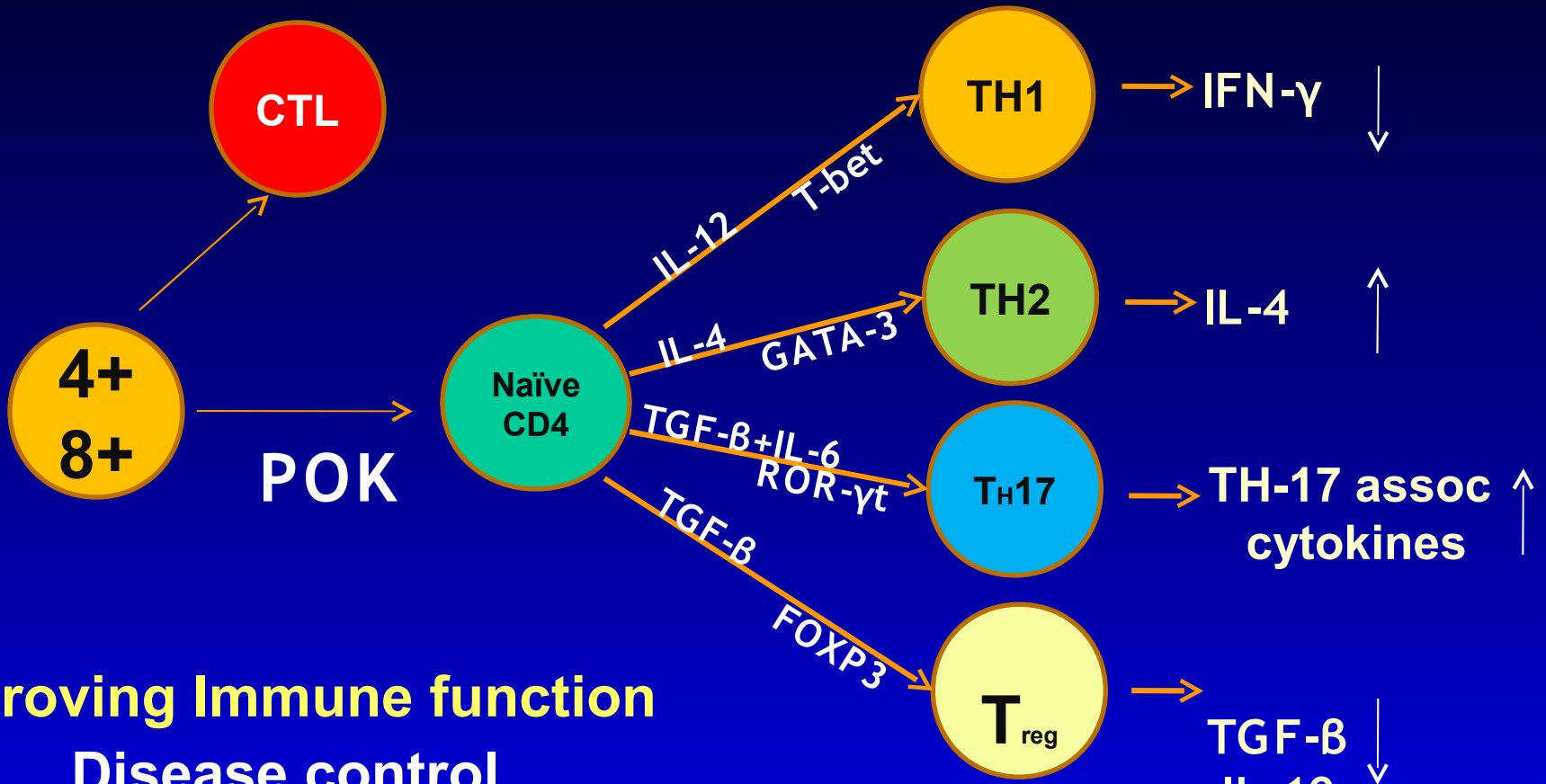
ORR 58%

CR +VGPR 25%

Among the first 37 patients, there were 13 lenalidomide refractory patients, with responses seen in 29%

Lacy et al, ASH 2008

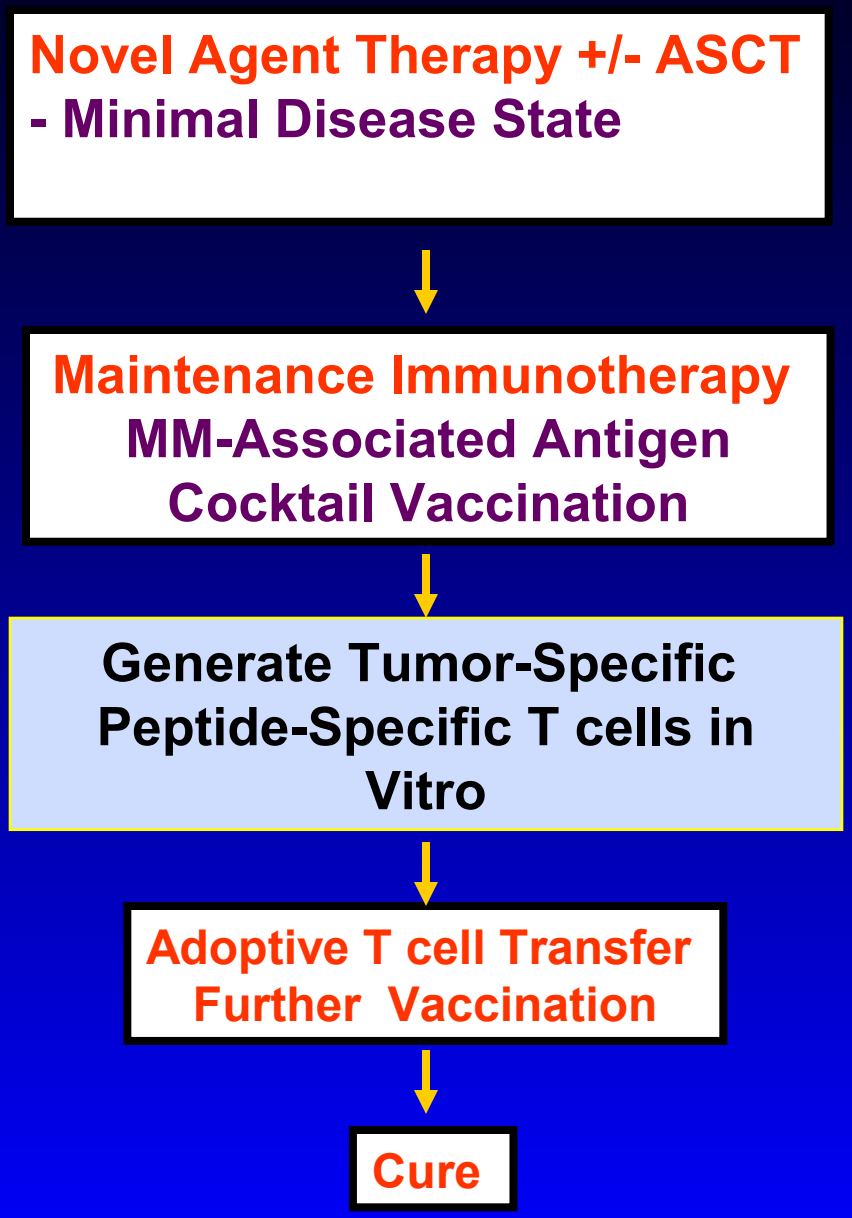
Immune Dysfunction in Myeloma
TH Subset Abnormality



Improving Immune function

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

Long-Term Goal of Immunotherapy



Rationally Based Combination Therapies

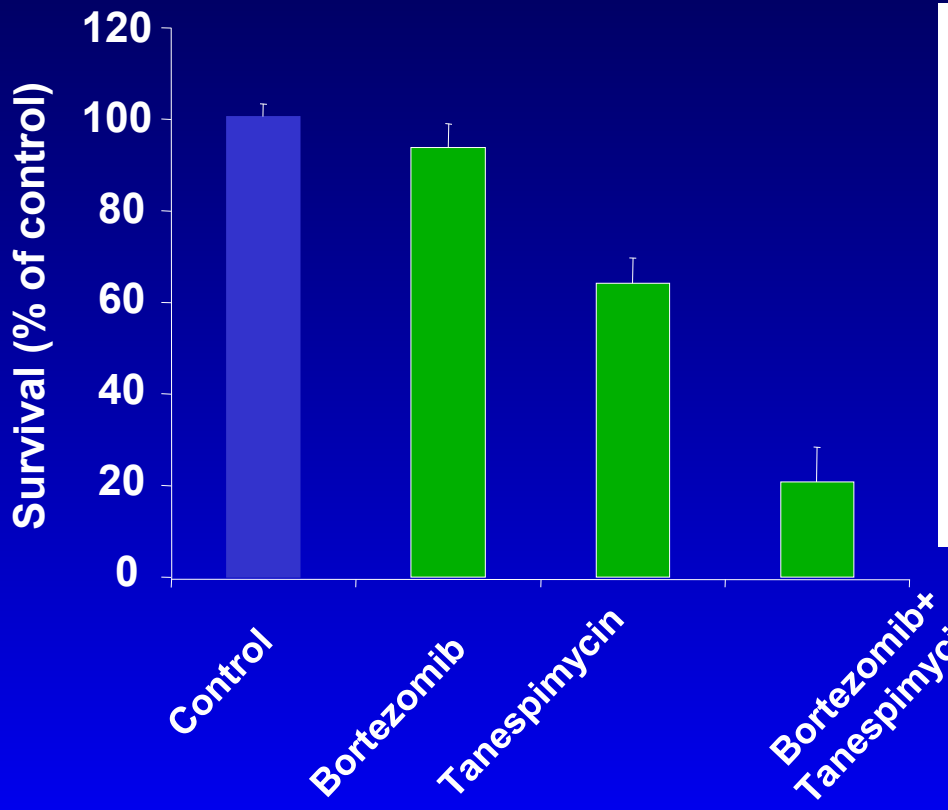
- Bortezomib and doxil
- Bortezomib, melphalan
- Bortezomib and Hsp 90 inhibitor
- Bortezomib and NPI-0052
- Bortezomib and perifosine
- Bortezomib and LBH 589
- Bortezomib and Smac peptides
- Bortezomib and Bcl 2 inhibitor
- Bortezomib and p38 MAPK inhibitor
- Bortezomib and HuLuc63

- Lenalidomide and mTOR inhibitor
- Lenalidomide and Anti-CD40 antibody
- Lenalidomide and doxil
- Lenalidomide and HuLuc63
- Lenalidomide and LBH 589
- Lenalidomide and perifosine
- Lenalidomdide and Bevacizumab
- Lenalidomide and Vaccine

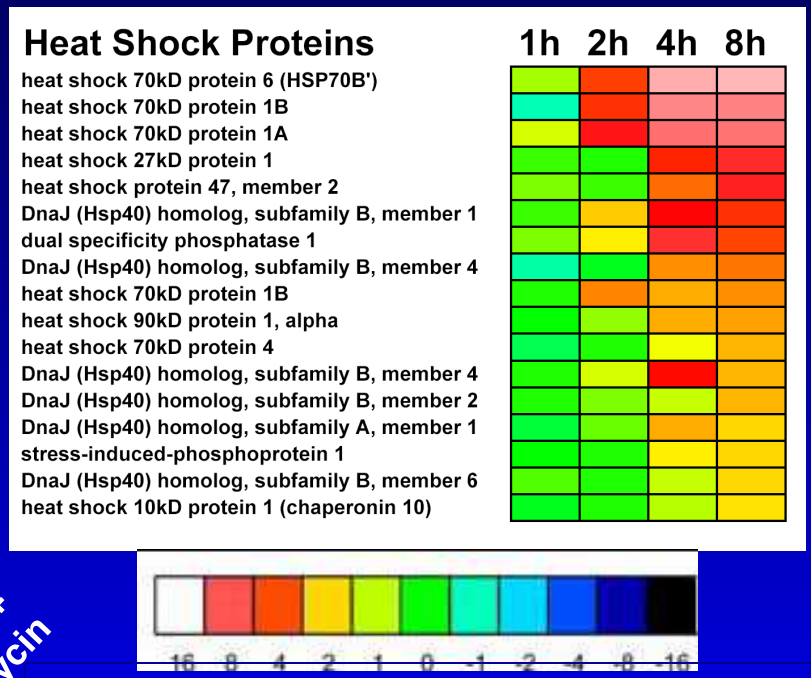
Lenalidomide and Bortezomib

Tanespimycin + Bortezomib Synergistic Anti-MM Activity

In vitro **cytotoxicity model using MM cell lines suggests synergy**



Induction of Hsp70 seen at 2 hrs; Hsp90 transcription increase ~4-8 hrs following tanespimycin/BZ



Mitsiades CS et al. Blood 2006 Feb 1;107(3)

Bortezomib and Hsp 90 Inhibitor Therapy

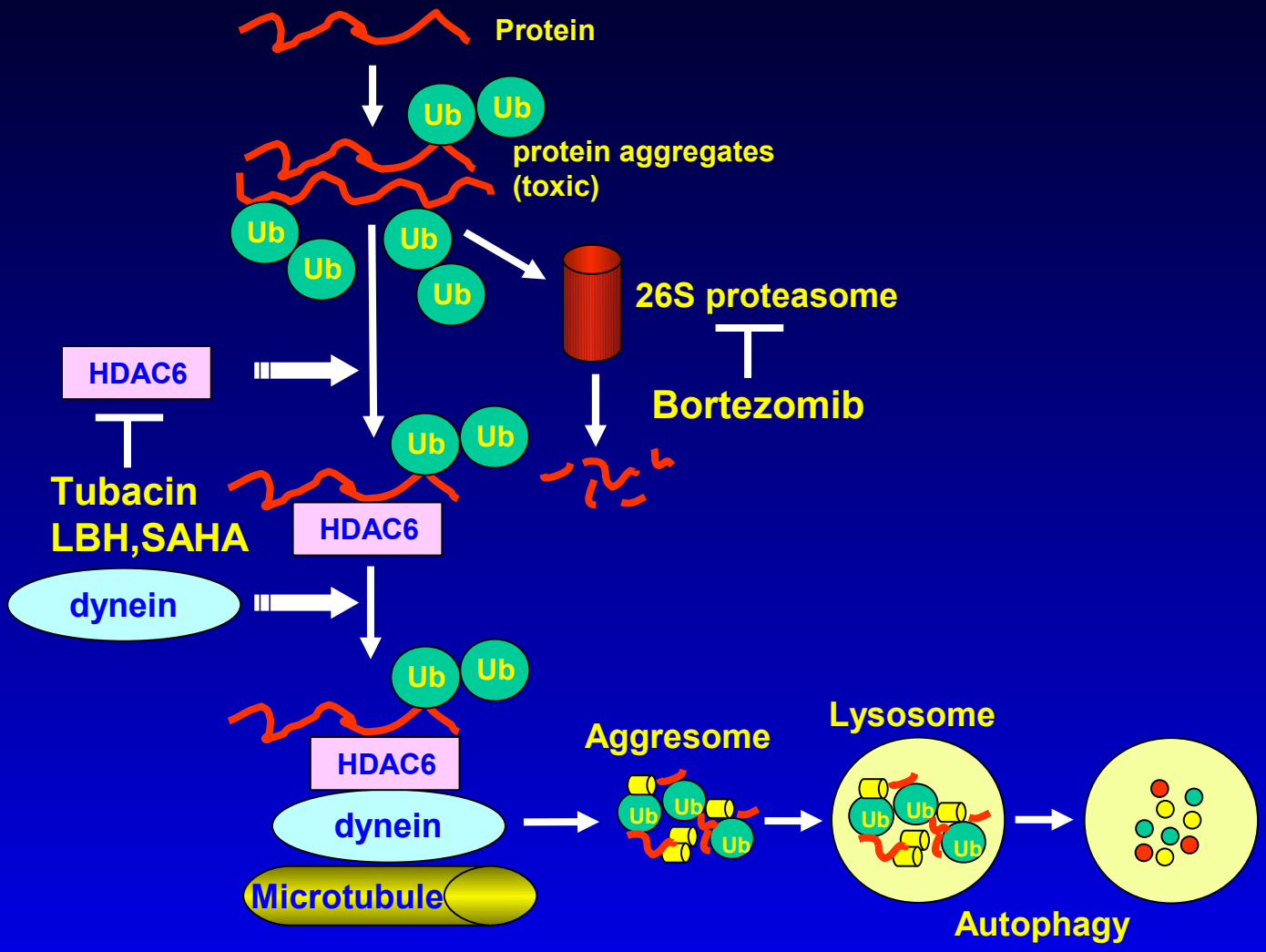
Hsp 90 gene and protein overexpressed in MM; Bortezomib further upregulates hsp 90 (2002)

Hsp90 inhibitor and Bortezomib induces synergistic cytotoxicity and overcome Bortezomib resistance in vitro and in vivo (2003-4)

Phase I/II clinical trials show safety and that hsp90 inhibitor can sensitize or overcome resistance to Bortezomib (2005-6) (Richardson et al, ASH 2006)

Phase III trial of Bortezomib/hsp90 inhibitor versus Bortezomib in relapsed MM for FDA approval

Blockade of Ubiquinated Protein Catabolism



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

Vorinostat-Bortezomib

Weber et al ASH 2008 Abstr 871

Effective for treatment of relapsed/refractory MM

- Overall response (PR + CR) ~38-43%
- ≥ SD ~90%

Effective despite prior bortezomib therapy

- Overall response ~29-35%
- SD ~41-53%
- Overall response refractory pts ≥ PR ~29-38%
- SD refractory pts ~42-50%

Well Tolerated Fatigue, Diarrhea, thrombocytopenia

Phase III trial of Bortezomib and SAHA versus Bortezomib in relapsed MM ongoing for FDA approval

Panobinostat-Bortezomib

Active for treatment of relapsed / refractory MM

- Overall response (PR + VGPR + CR) = 50%

Active despite prior bortezomib therapy

- 7 responses in patients with prior bortezomib
- 5 of these responders were refractory to their last bortezomib based therapy

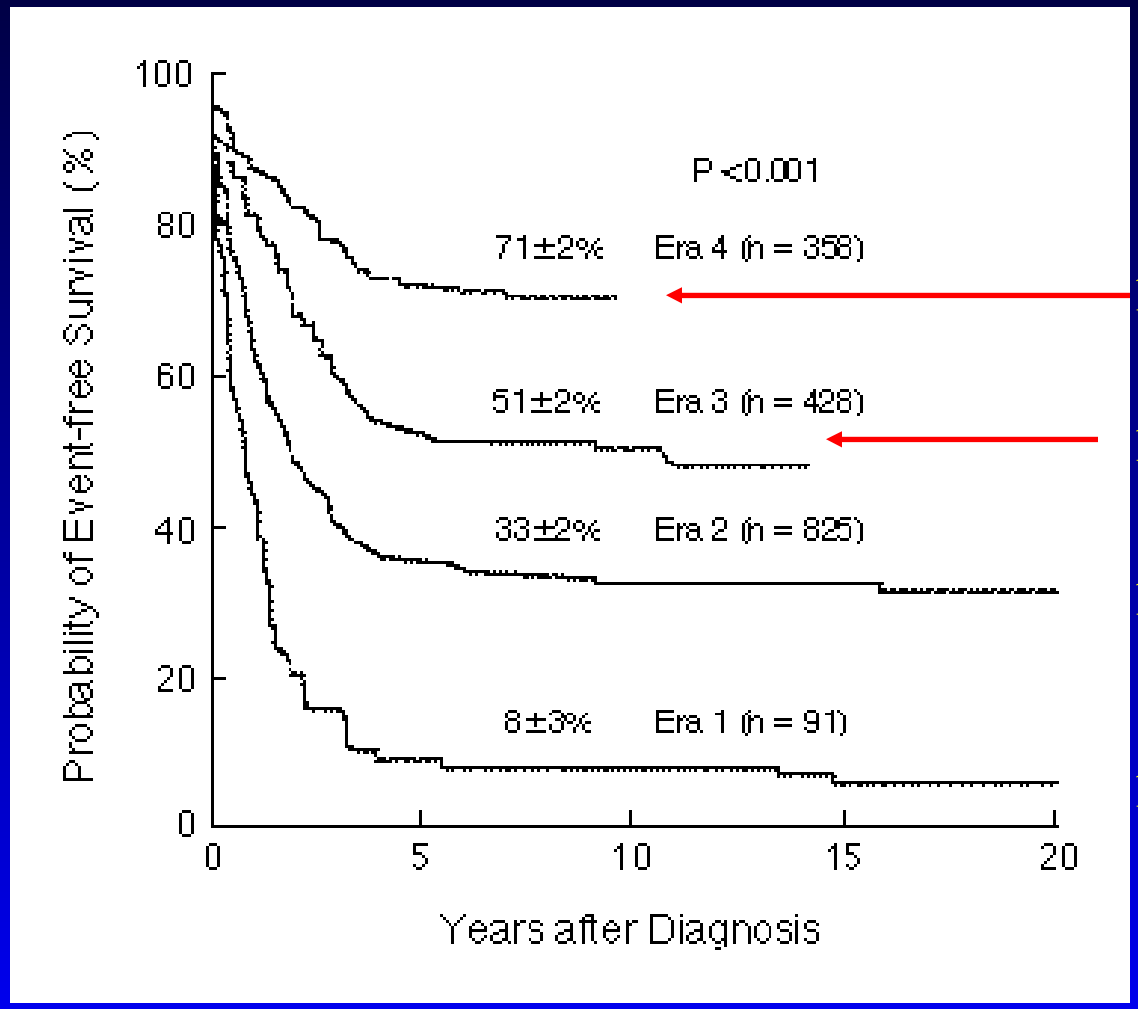
Well tolerated

- Fatigue, Diarrhea, Thrombocytopenia

Trial ongoing

Sezerer et al IMW 2008

Curative Combination Chemotherapy in Childhood ALL as a Model for Progress in MM



Pui, NEJM 1995; 332: 1618

Conclusions and Future Directions

1. A new treatment paradigm targeting both the tumor cell and its microenvironment has already markedly improved OR, CR, EFS and OS.

2. Ongoing oncogenomic and proteomic studies are informing clinical protocol design and identifying novel therapeutic targets.

3. Future moleculary based rationally designed combination therapies (ie immunomodulatory drug, proteasome inhibitor, hsp 90 inhibitor, HDAC inhibitor, and MoAb) will achieve durable CR in the majority of patients.

United Nations Against Myeloma

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Japan

Taiwan

UK

Germany

Turkey

Italy

India

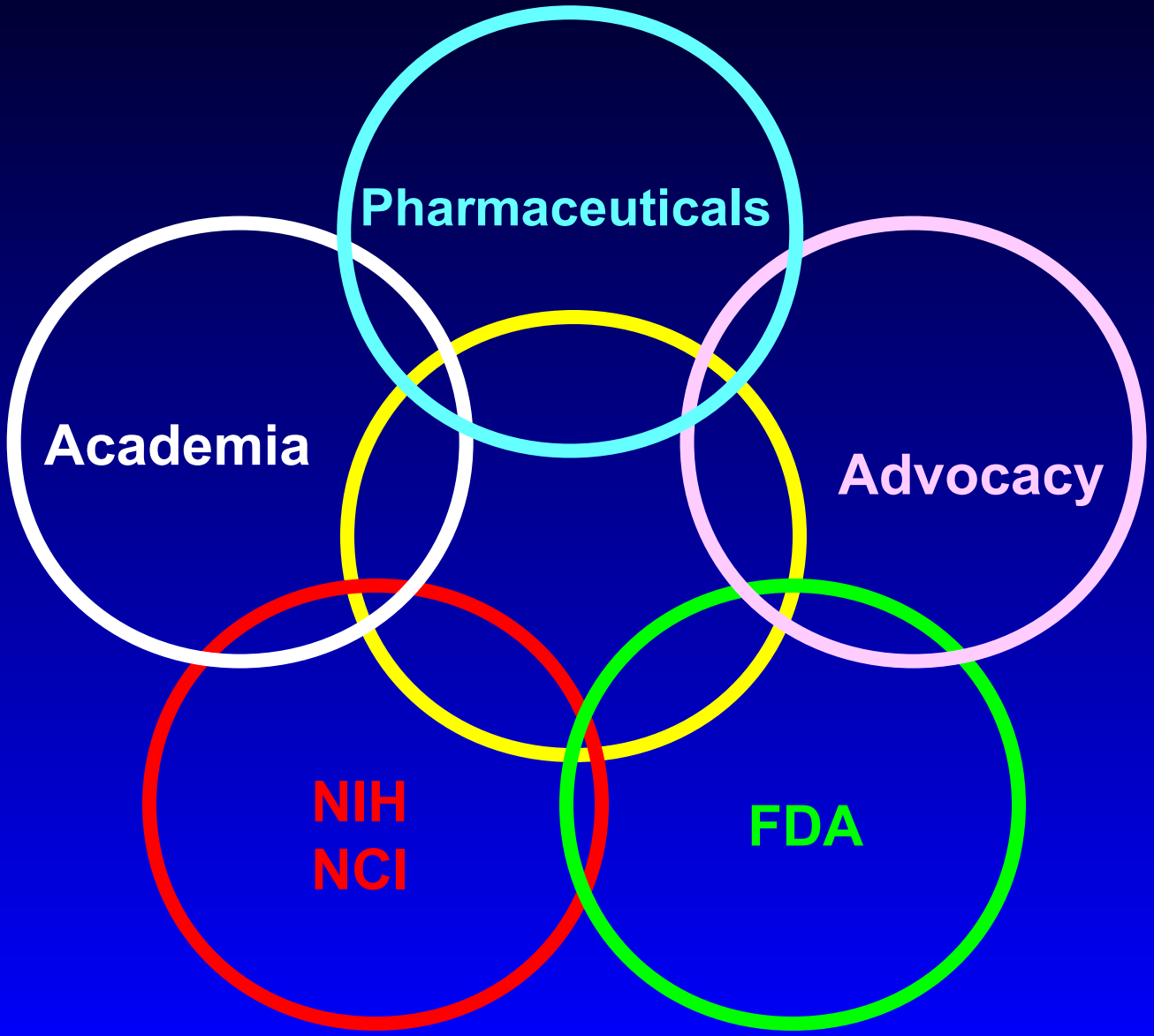
Australia

Israel

USA

Ireland

Collaborative Models for Rapid Translation of Novel Drugs from Bench to Bedside

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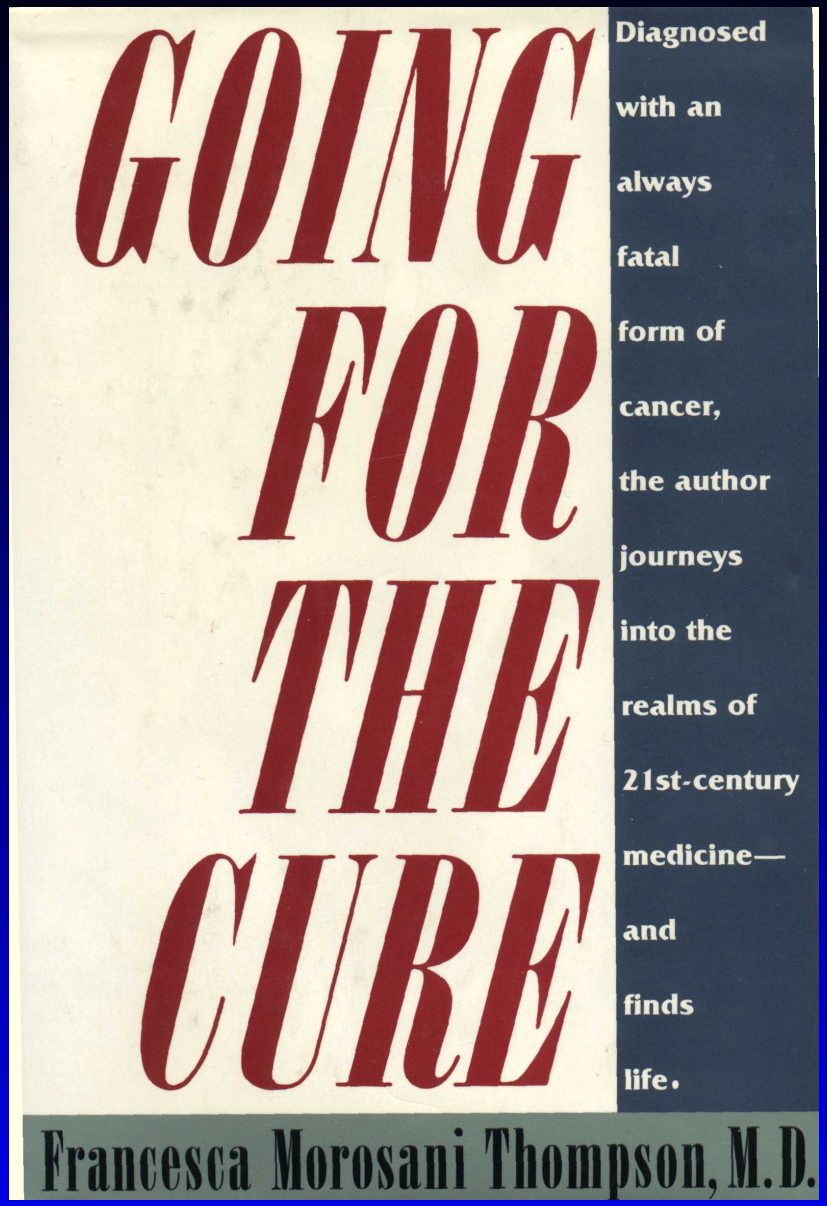
Learn from and be Inspired by Patients



Cure means growing old and dying from something else