Bone Disease: From Pathophysiology to Treatment

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Disclosures for
G. David Roodman, M.D., Ph.D.

- **Consultant: Amgen, Novartis, Celgene, and Onyx**

Bone Involvement in Different Tumor Types

	Disease prevalence (US) (in thousands)	Incidence of bone metastases in patients with advanced disease (%)	Median survival of patients with bone metastases (months)
Myeloma	**51.9**[1]	**84**[3]	**37–58**[7]
Lung	**355**[1]	**30–40**[2]	**8–10**[4]
Breast	**2,357**[1]	**65–75**[2]	**19–25**[5]
Prostate	**1,938**[1]	**65–75**[2]	**30–35**[6]

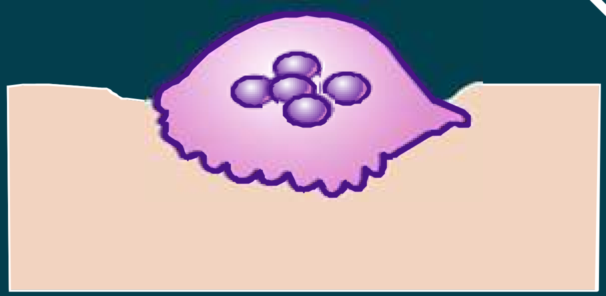
1. Ries LAG et al, eds. SEER Cancer Statistics Review, 1975-2003. Bethesda, MD: National Cancer Institute; 2006.
2. Coleman RE. *Oncologist*. 2004;9(suppl 4):14-27.
3. Kyle RA et al. *Mayo Clin Proc*. 2003;78:21-33.
4. Smith W, Khuri FR. *Semin Oncol*. 2004;31(suppl 4):11-15.
5. Lipton A. *J Support Oncol*. 2004;2:205-213.
6. Tu S-M, Lin S-H. *Cancer Treat Res*. 2004;118:23-46.
7. Palumbo A et al. *Blood*. 2004;104:3052-3057.

Consequences of Increased Bone Resorption

Increased bone resorption → **Hypercalcemia**

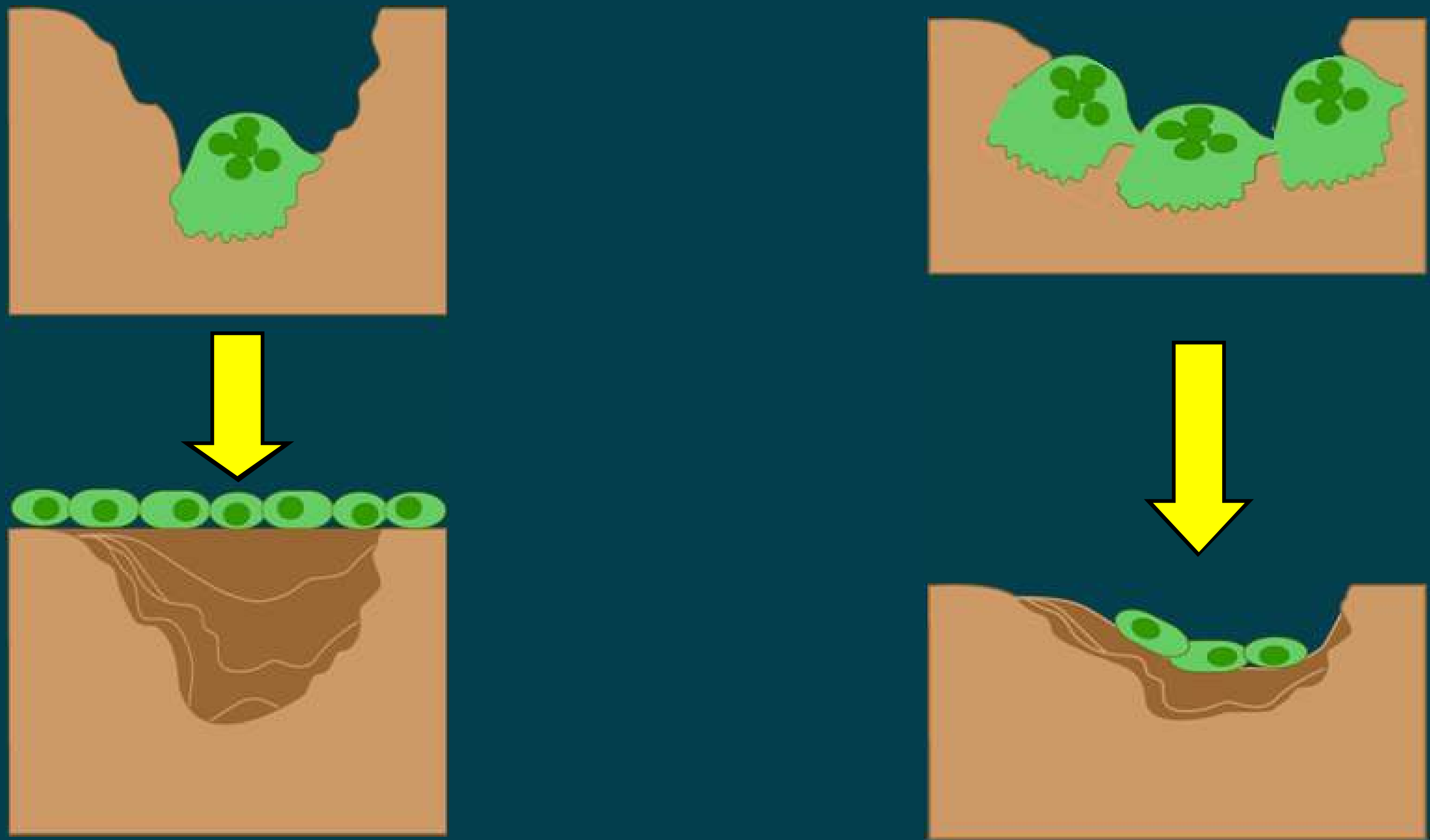
Increased bone resorption → **Fracture** → **Bone pain**

Increased bone resorption → **Bone pain**



Bone

Bone Remodeling is Uncoupled in Myeloma

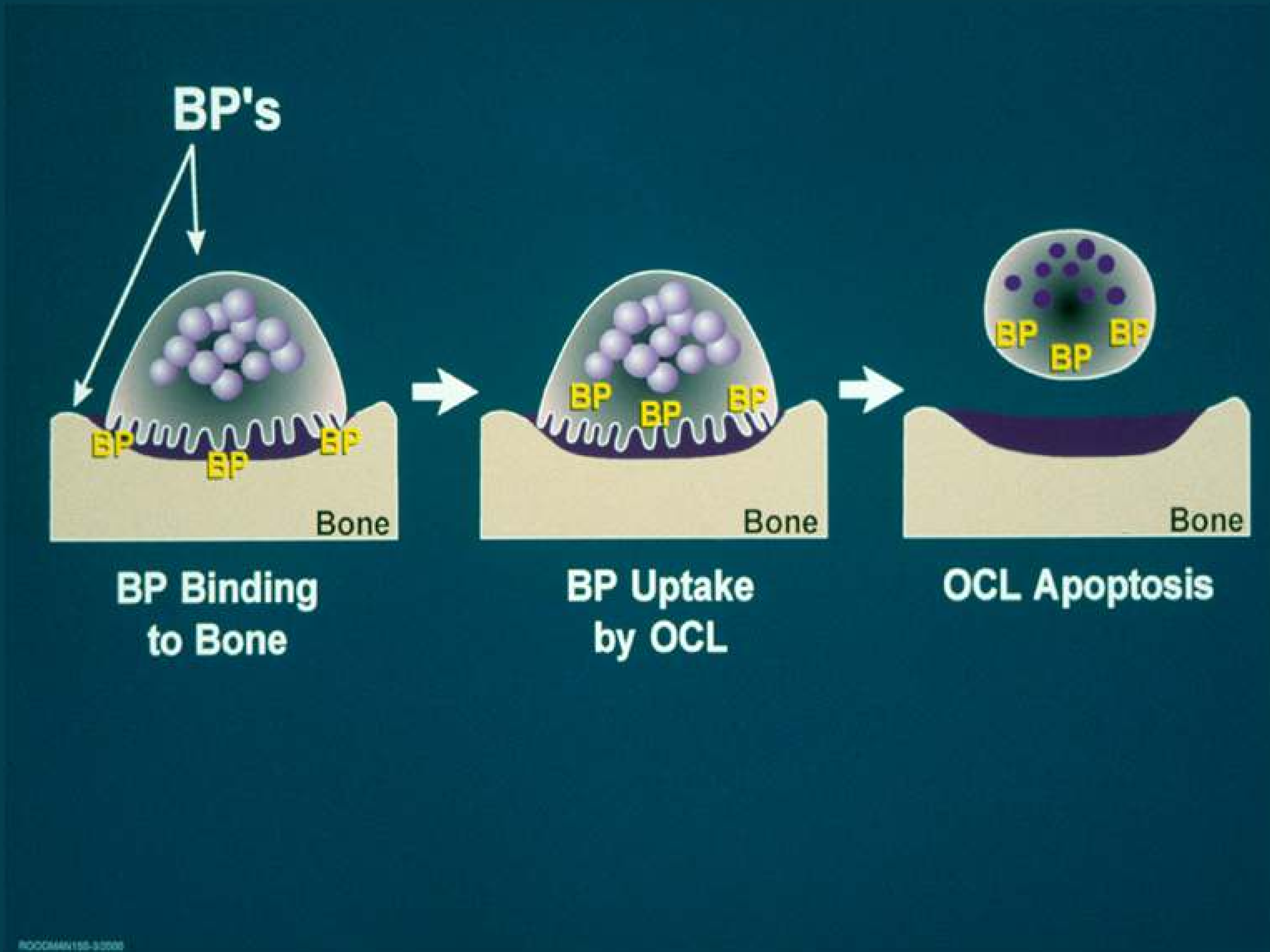


Normal **Myeloma**

Hattner R et al. *Nature.* 1965;206:489.

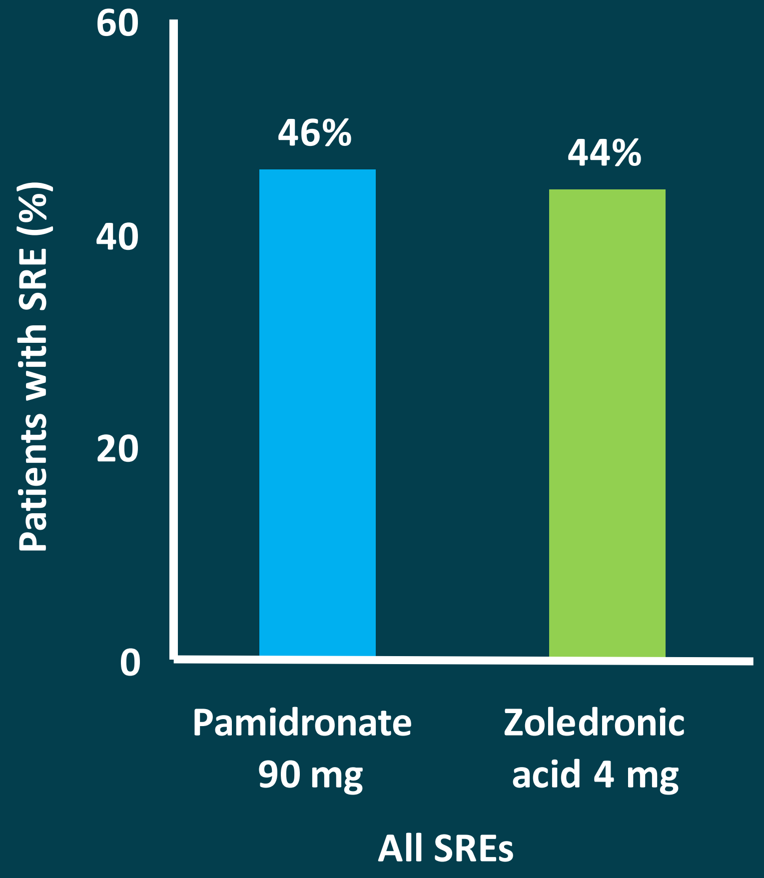
Current Treatment of MM Bone Disease

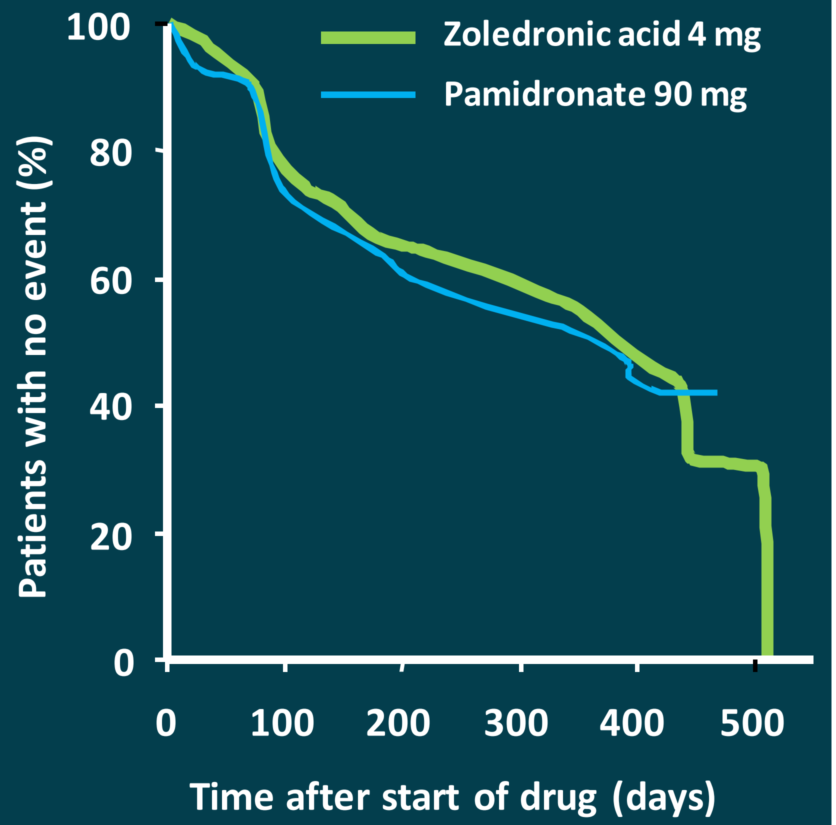
- Bisphosphonates
- Surgical procedures
  - Vertebroplasty
  - Balloon Kyphoplasty
- Radiotherapy
- Treatment of myeloma



Hughes DE et al. *J Bone Miner Res*. 1995;10(10):1478-1487.

Zoledronic Acid and Pamidronate in Multiple Myeloma





SREs=skeletal-related events.

Rosen LS et al. *Cancer J.* 2001;7:377-387.

MRC Myeloma IX Study

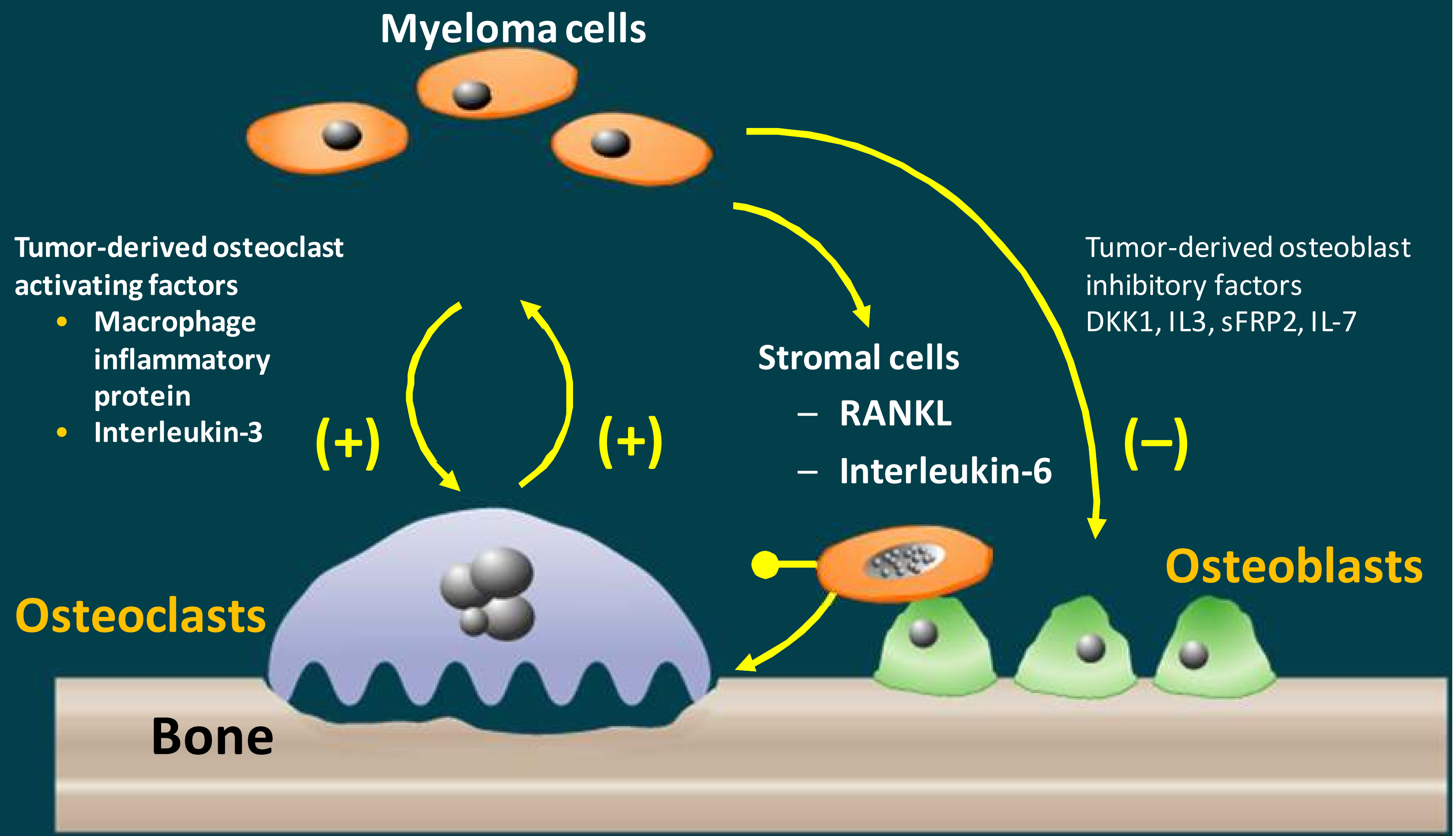
- 1,970 newly diagnosed MM patients randomized to Zol vs CLO plus anti-MM RX
- Rx until disease progression
- Median F/U 3.7 yrs
- Zol reduced no. of pt. with SREs (27% vs. 35%,p=.0004)
- Zol increased OS (5.5 months , p<.05) independent of time to first SRE
- ONJ for Zol vs CLO was 3.5% vs. 0.3%

Morgan,G J Clin Oncol 28:7s 2010 (suppl;abstr 8021)

Issues with BP Therapy

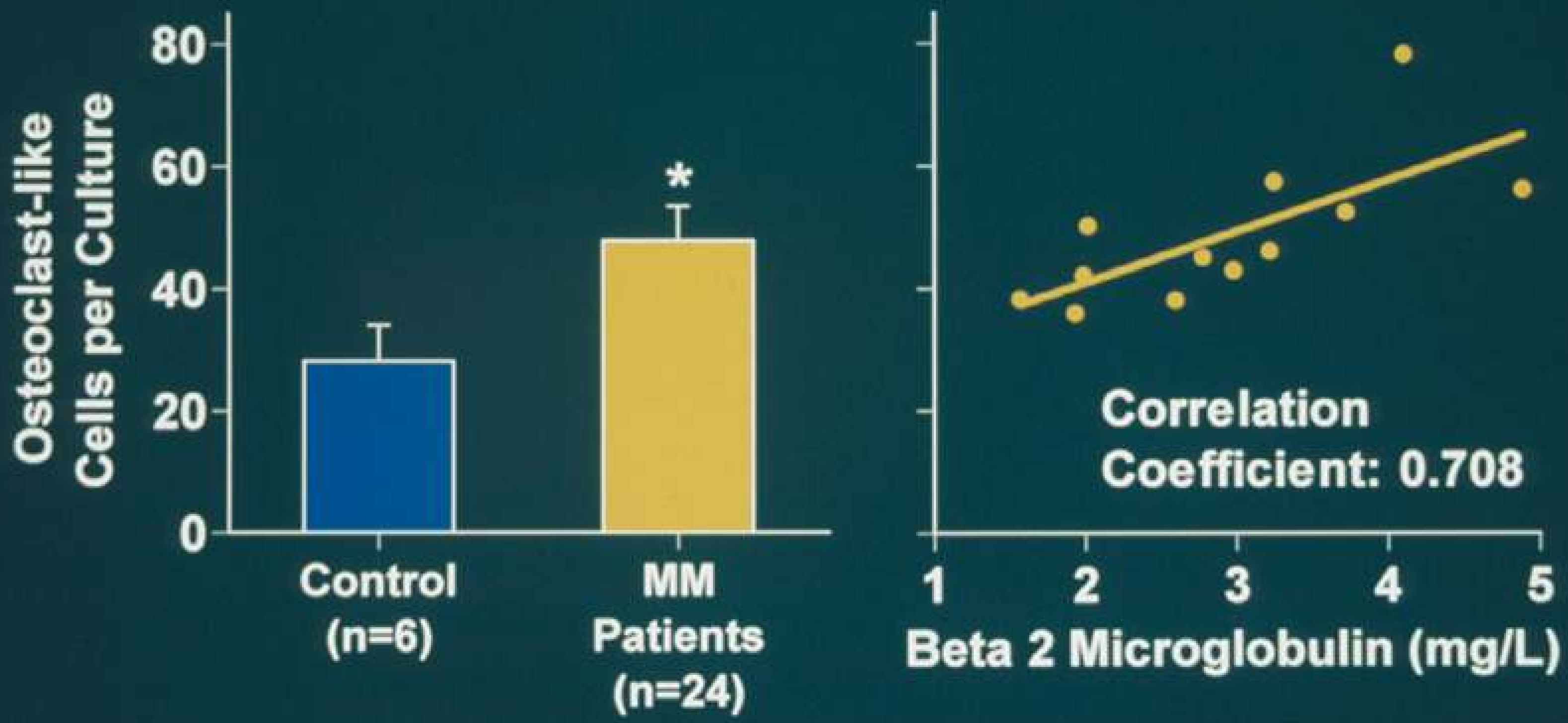
- Renal Toxicity
- Osteonecrosis of the jaw
- Decreases skeletal events by 50%; patients still progress but at a slower rate
- No clear anti-tumor activity previously reported

Myeloma Bone Disease



Roodman GD. *N Engl J Med.* 2004;350(16):1655-1664.

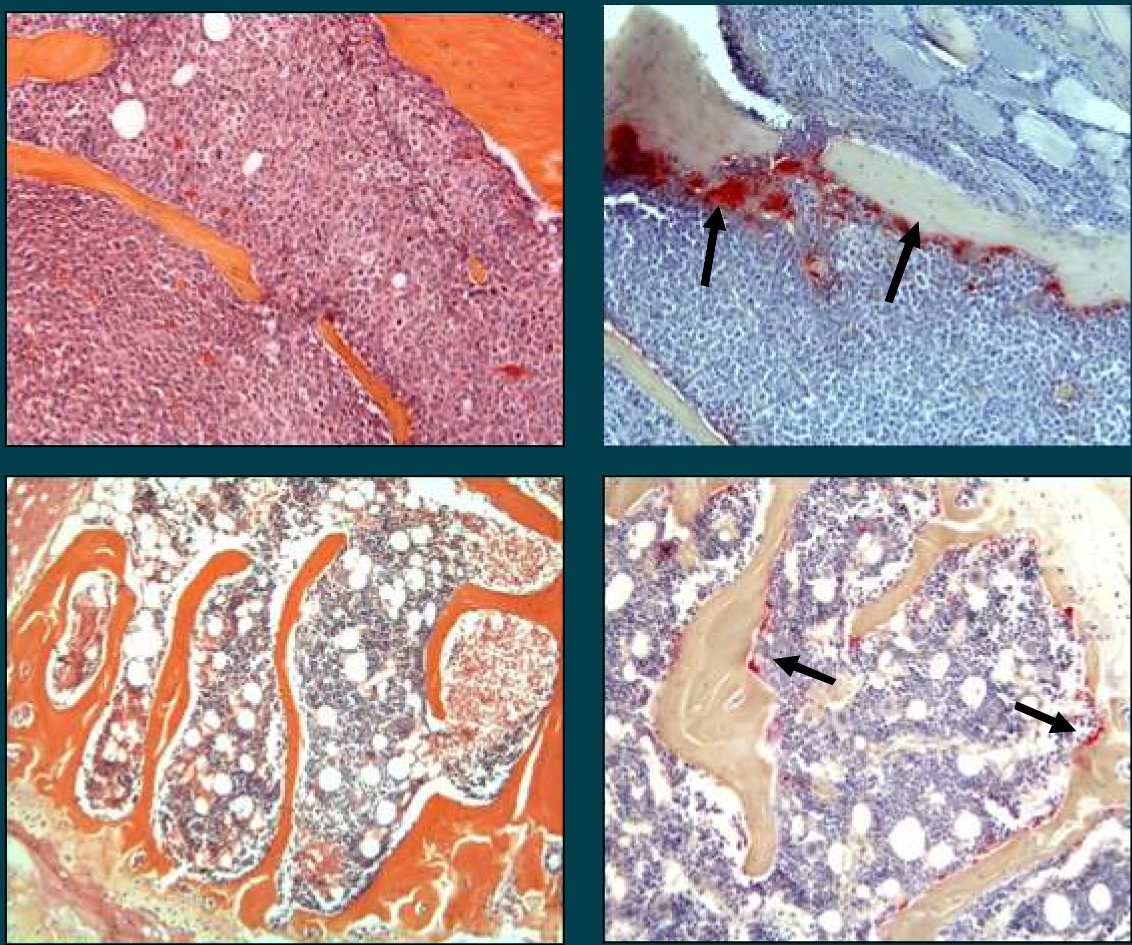
Multiple Myeloma Bone Marrow Plasma Stimulates Osteoclast Formation



* p<0.003 compared with controls

Choi SJ, Cruz JC, Craig F, Chung H, Devlin RD, Roodman GD, Alsina M. Blood. 2000 Jul 15;96(2):671-5

Antisense to MIP-1α Decreases Tumor Burden and Bone Destruction in ARH Mice



EV

AS

H & E

TRAP stain

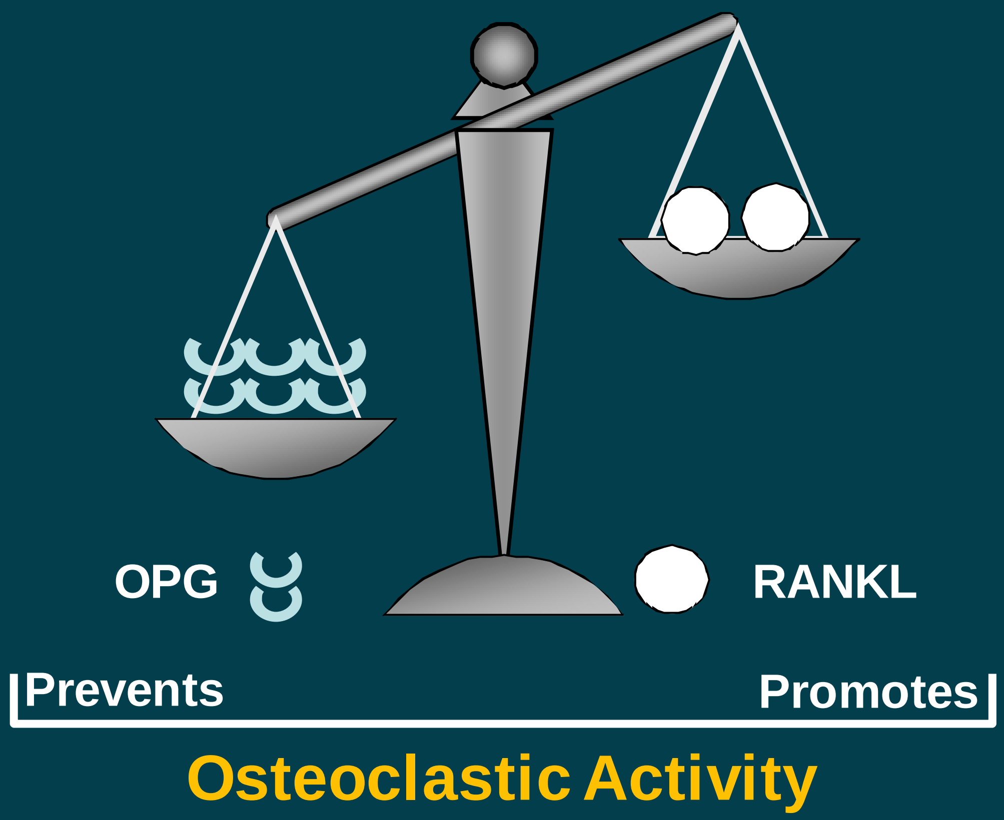
Choi SJ, .J Clin Invest. 2001 Dec;108(12):1833-41.

RANKL

- TNF superfamily member, expressed on surface of marrow stromal cells and osteoblasts
- Binds with and activates RANK on osteoclast and osteoclast precursor cells
- Induces differentiation and fusion of precursors into mature, active, functional osteoclasts

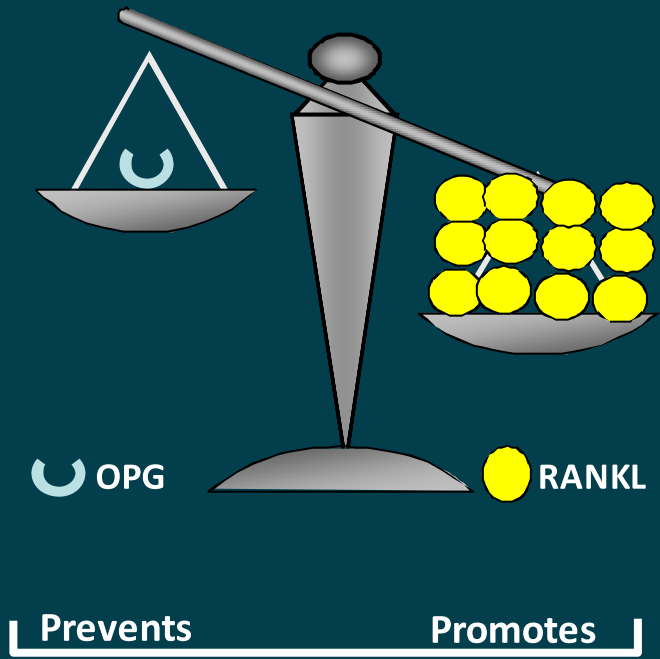
Kostenuik PJ. *Curr Opin Pharmacol*. 2005;5(6):618-625.

RANKL/OPG Ratio: Maintains Bone Homeostasis



Hofbauer LC, Schoppet M. *JAMA*. 2004;29294):490-495.

The RANK/RANKL/OPG Pathway in Osteolytic Bone Disease



Increased Osteoclastic Activity and Decreased OPG May Lead to Increased Bone Destruction

Roodman GD. *N Engl J Med.* 2004;350(16):1655-1664.

Denosumab (AMG 162)

- Human monoclonal antibody that binds RANKL
- High affinity for human RANKL
- Specific: does not bind to TNFα, TNFβ, TRAIL, or CD40L
- Inhibits formation and activation of osteoclasts

Lipton A, Jun S. *Curr Opin Support Palliat Care.* 2008;2(3):197-203.

Phase 2 Study of Denosumab in Relapsed and Plateau-Phase MM

Effective for myeloma bone disease

Median changes in bone resorption markers were -70% and -52% for relapsed and PP patients.

Vij R et al. *Am J Hematol*. 2009 Jul 25. [Epub ahead of print]

Denosumab vs. Zoledronate

- Phase 3 trial in 1,776 patients with solid tumors (not breast or prostate) or myeloma. Primary endpoint median time to first SRE

- Delay in time to first SRE or subsequent SRE was not statistically different

- SAEs were similar

- ONJ infrequent and similar (10 vs 11 patients)

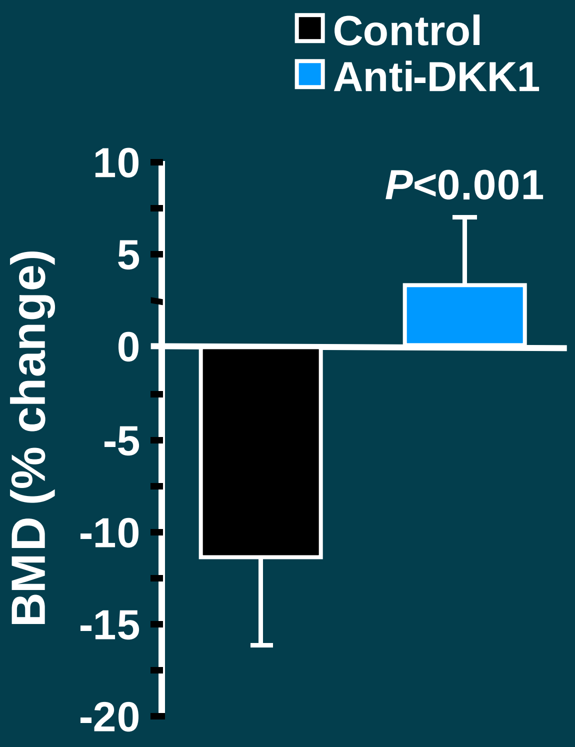
Henry D et al. *EJC Supplements*. 2009;7(3):12. Abstract 20LBA.

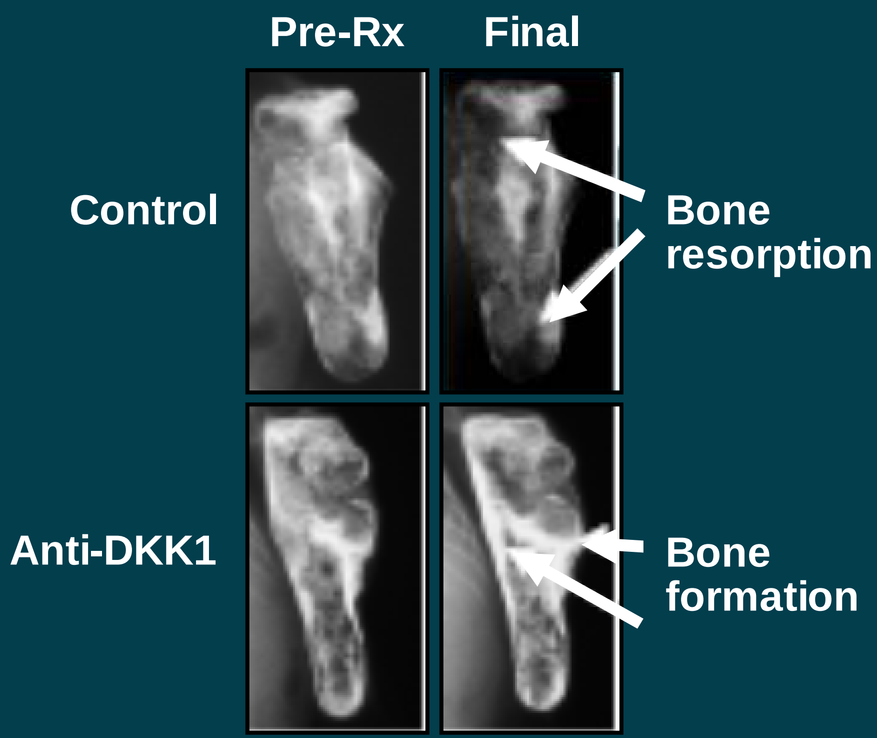
DKK1 and sFRP-2 in Myeloma Bone Disease

- **Inhibitors of the WNT signaling pathway**
- **WNT signaling is a critical pathway for OBL differentiation**
- **Secreted by myeloma cells**
- **Marrow plasma from patients with high levels of DKK1 or sFRP-2 inhibit murine OBL differentiation**
- **DKK1 gene expression levels correlated with extent of bone disease in MM patients**

Tian et al NEJM 349:2483,2003, Oshima T. et al.Blood.;106:3160, 2005

Anti-DKK1 Increases Bone Formation in the SCID-Rab Multiple Myeloma Model



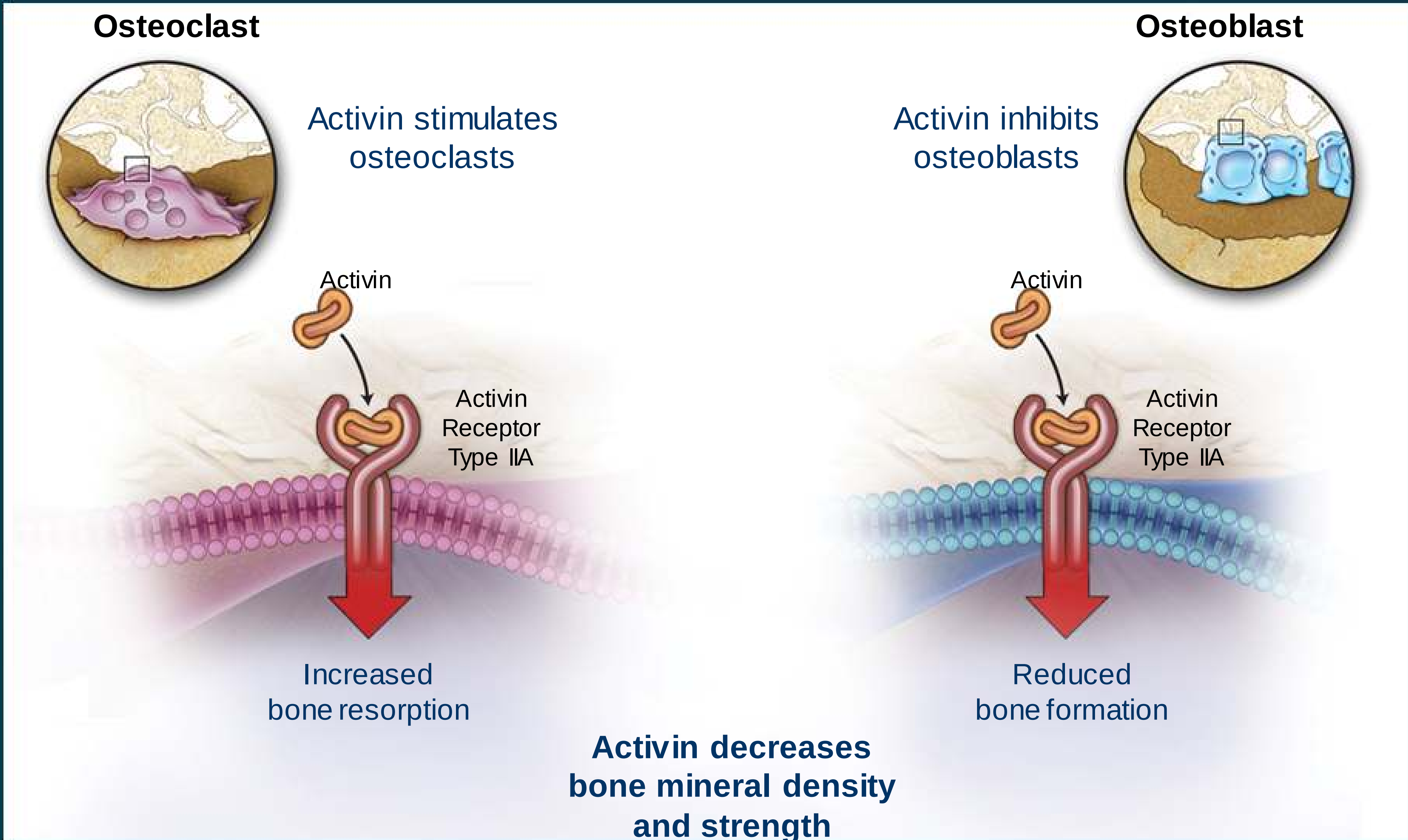


Yaccoby S et al. *Blood.* 2007;109:2106-2111.

BMD, bone mineral density

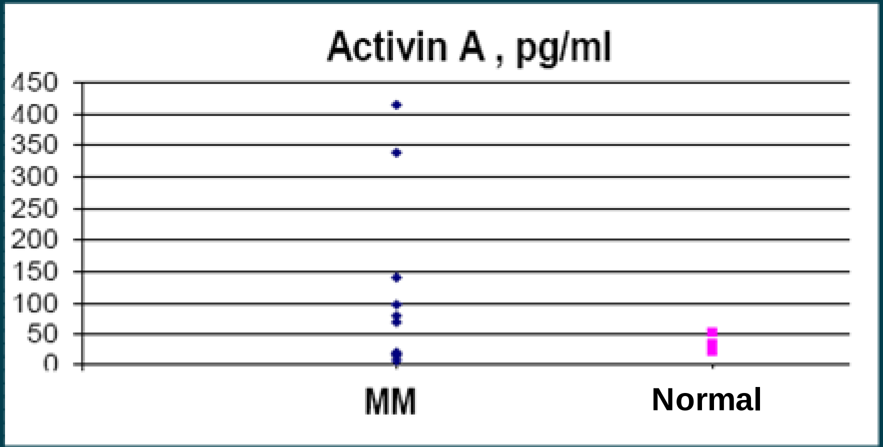
Phase I/II Study of BHQ880, an Anti-DKK1 Human Monoclonal Antibody, in Relapsed/Refractory MM Patients Treated with Zoledronic Acid and Anti-Myeloma Therapy is ongoing

Activin and Bone Growth



Activin A Levels are Elevated in Patients with MM

Activin A Levels are Increased in Bone Marrow Plasma of MM Patients

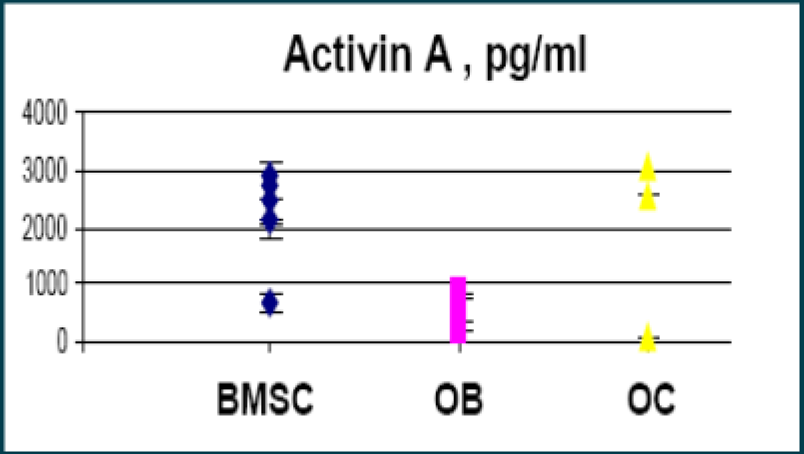


Average Levels of Activin A in BM Sera of MM Pts:

MM: 119 +/- 143 pg/ml

Normal: 33 +/- 14 pg/ml

Activin A is produced by the microenvironment, notably BMSCs and Osteoclasts



Median Levels in 72h Culture Supernatants:

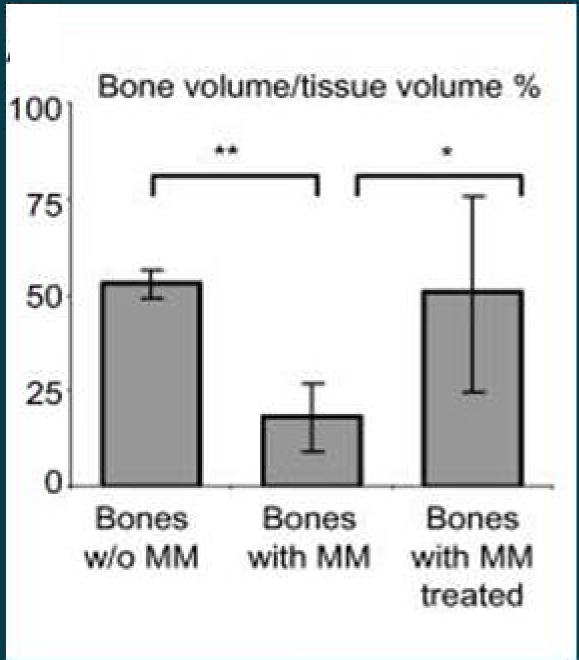
BMSCs: 2094 pg/ml

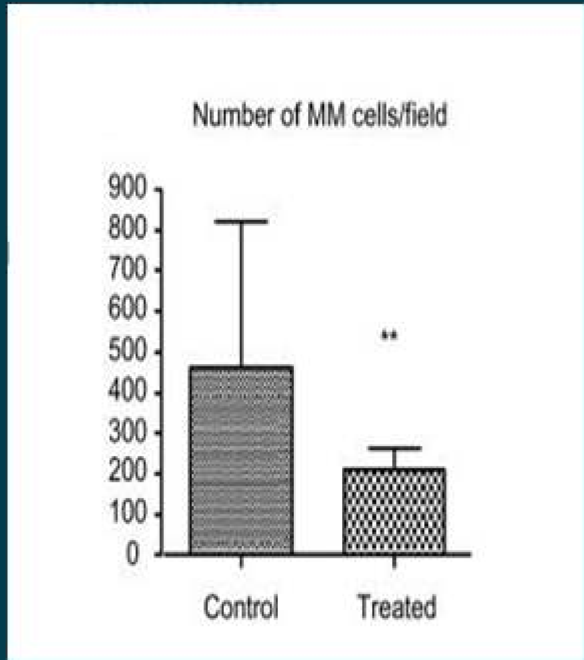
OCs: 1396 pg/ml

OBs: 200 pg/ml

N Raje et al. *2008 AACR Annual Meeting* Abstract #1521

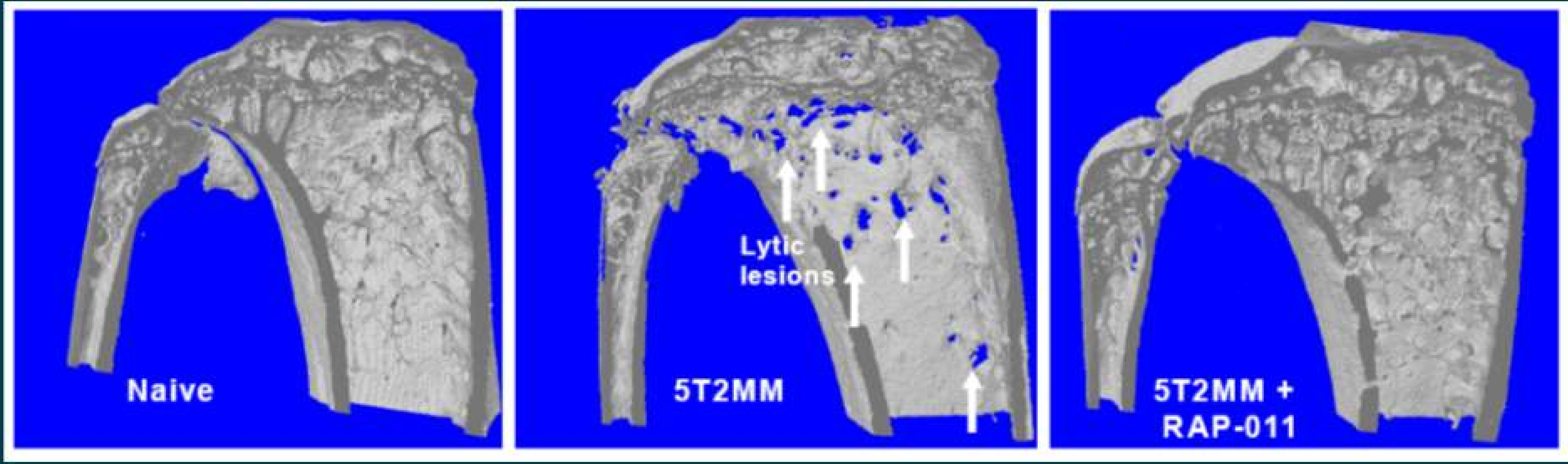
Activin A Receptor Antagonist Increases Bone Volume and Decreases MM Tumor Burden





Vallet, S et al PNAS 2010 Mar 16;107(11):5124-9

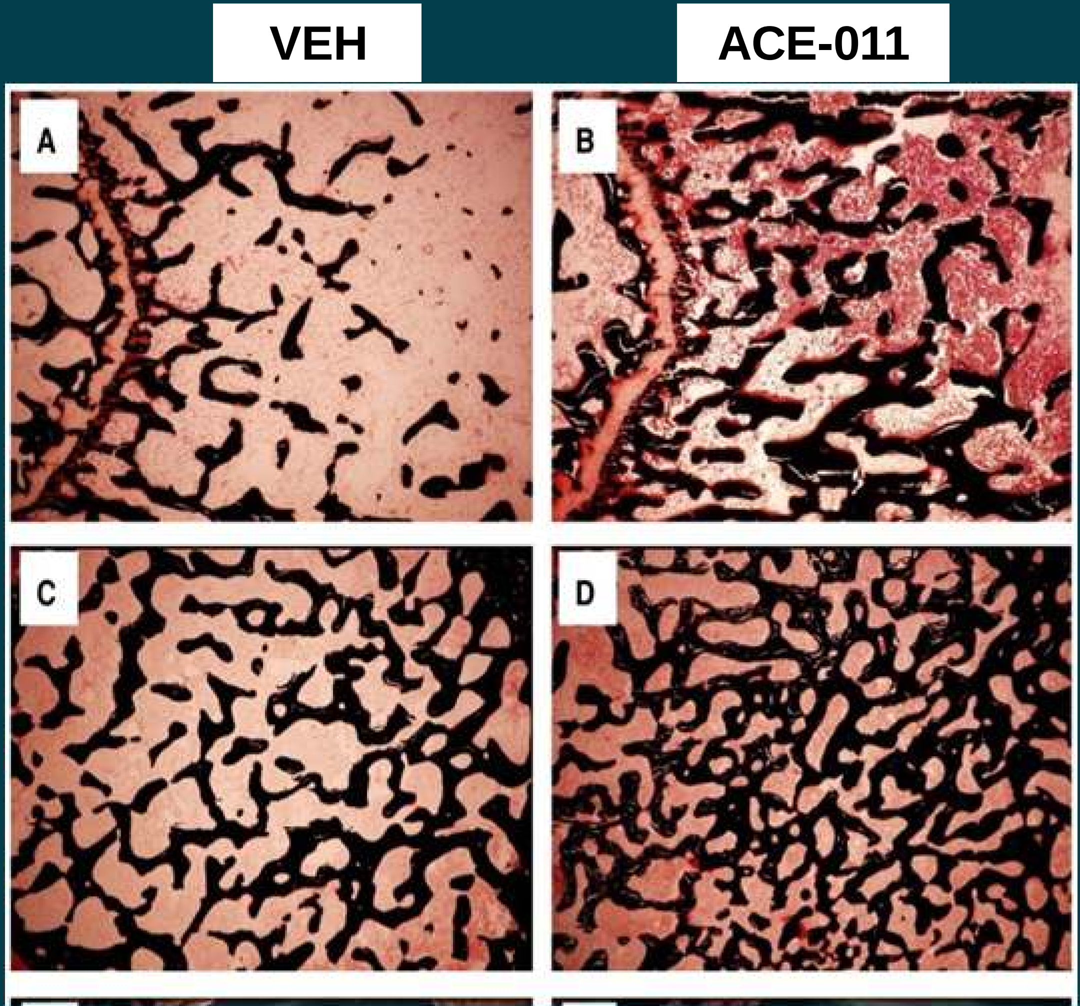
RAP-011 Prevents Development of Myeloma Bone Lesions

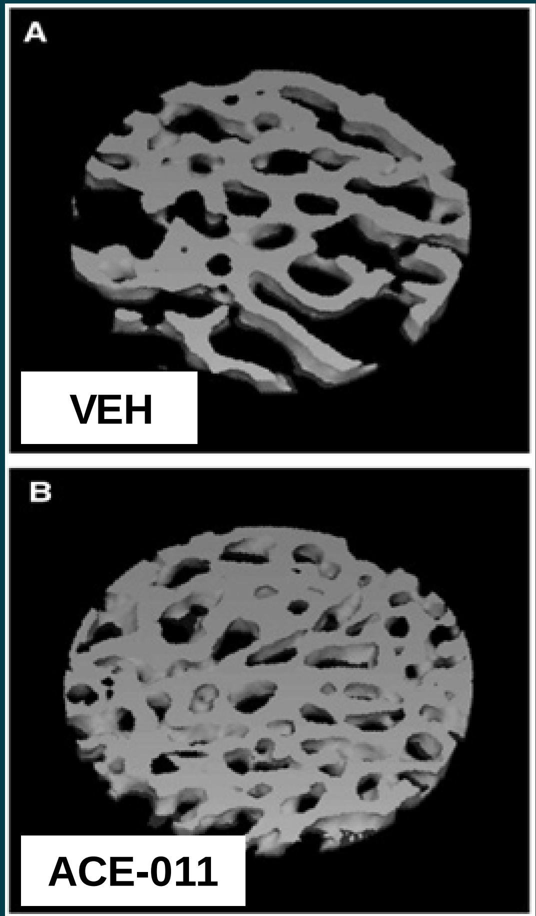


Normal Mice | **Mice + tumor** | **Mice + tumor + RAP-011**

Croucher et al. *2007 XIth International Myeloma Workshop*

Activin Receptor Antagonist Increases Bone in Macaques

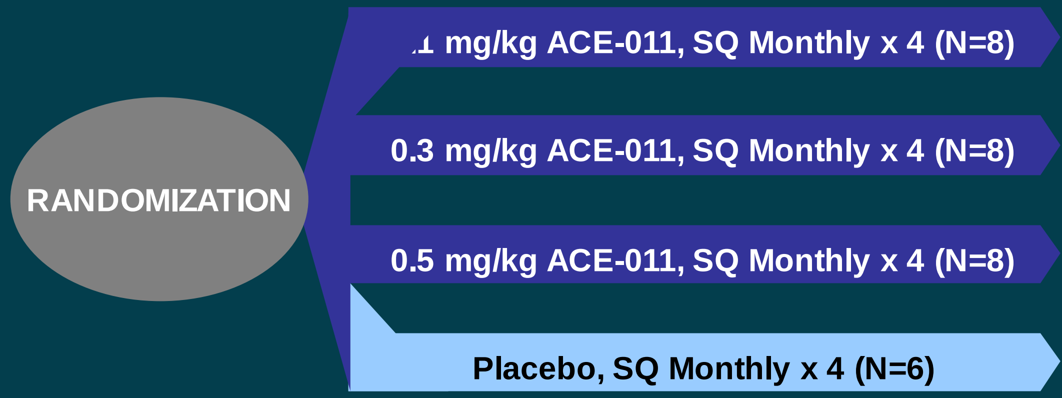




Lotinun S, et al Bone. 2010 Jan 18.

Phase 2 Study of hActRIIA-IgG1 *in* Patients With Osteolytic Lesions *Multiple Myeloma*

- **Randomized, Double-Blind, Placebo Controlled**
- **Dose-Ranging, Multiple Dose, Parallel-Assignment**
- **N=30**
- **All patients receiving backbone MPT regimen**



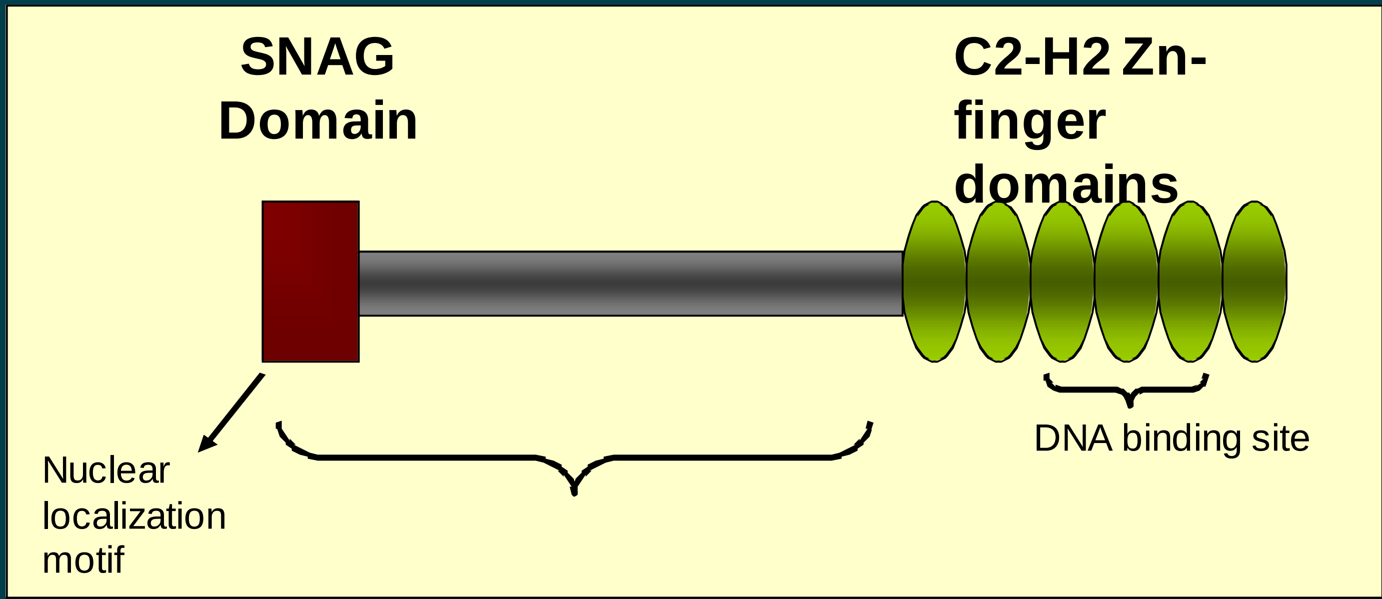
www.clinicaltrials.gov (NCT00747123)

Results

- 28 patients had at least one prior Rx
- 13 patients on bisphosphonates
- 75% of patients had hgb increase of 1.5 gm/dL vs. 17% on placebo
- Increased BSAP and slightly decreased S-CTX levels among BP-naïve patients

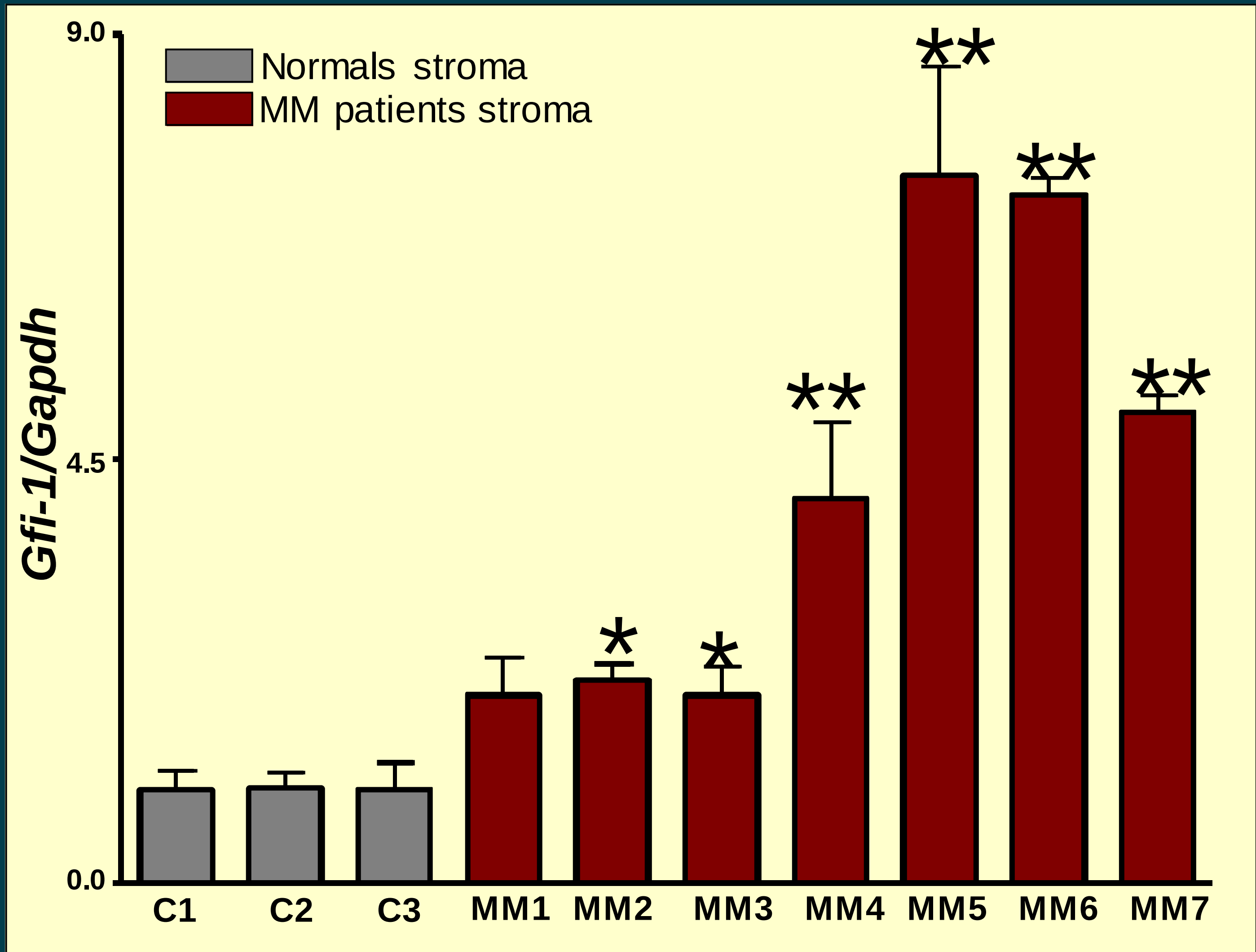
Abdulkadyrov, KM et al, ASH abstract 749 2009

Growth Factor Independence 1 (GFI-1)



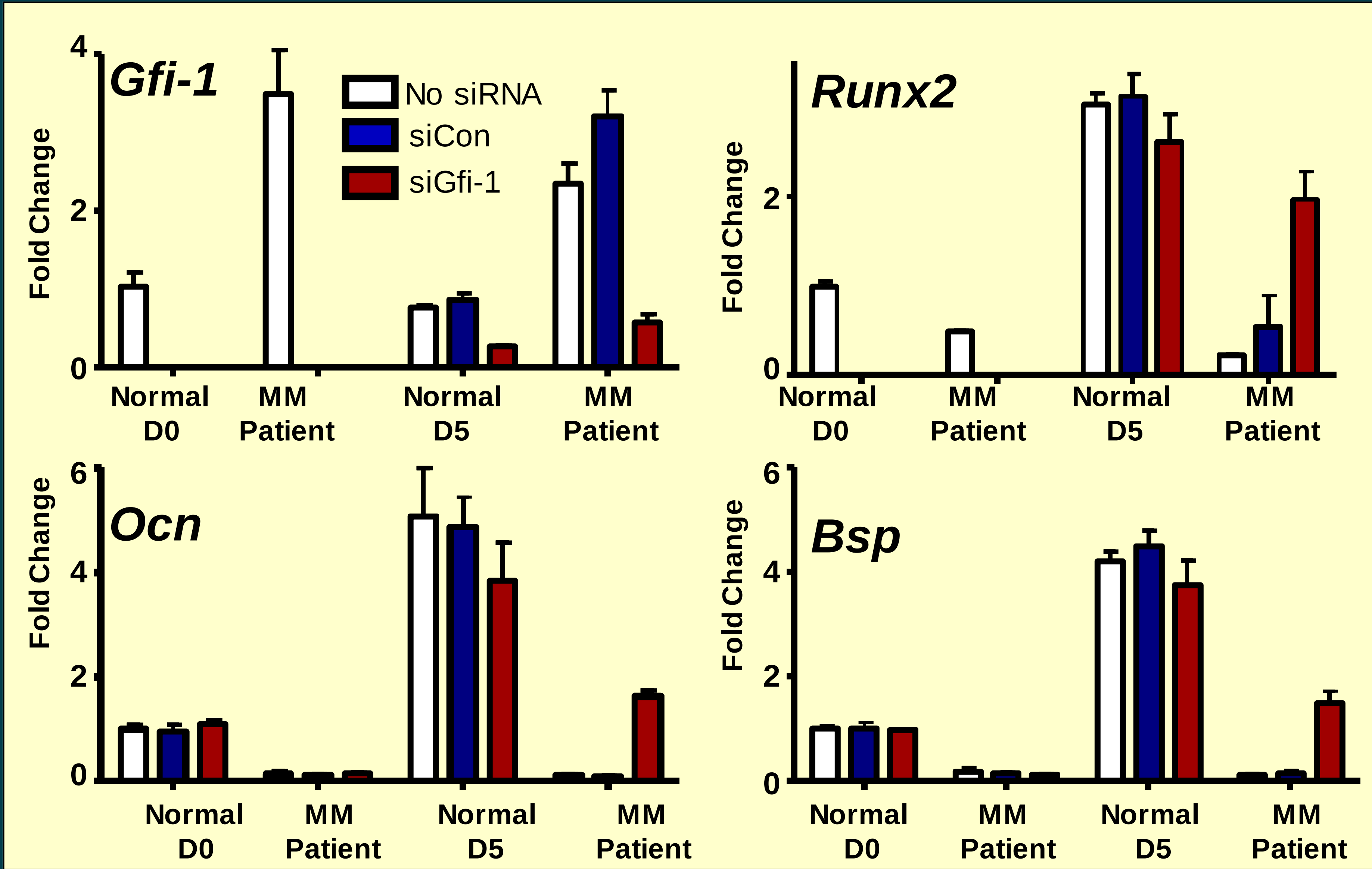
1. 55 kD transcriptional repressor
2. Recruits histone modifying enzymes and corepressors to target genes

Gfi-1 is Upregulated in Stromal Cells from MM Patients



(*,p<0.05; **,p<0.001)

siGfi-1 Partially Rescues Runx2, Bsp, Ocn Expression in MSC from MM Patients



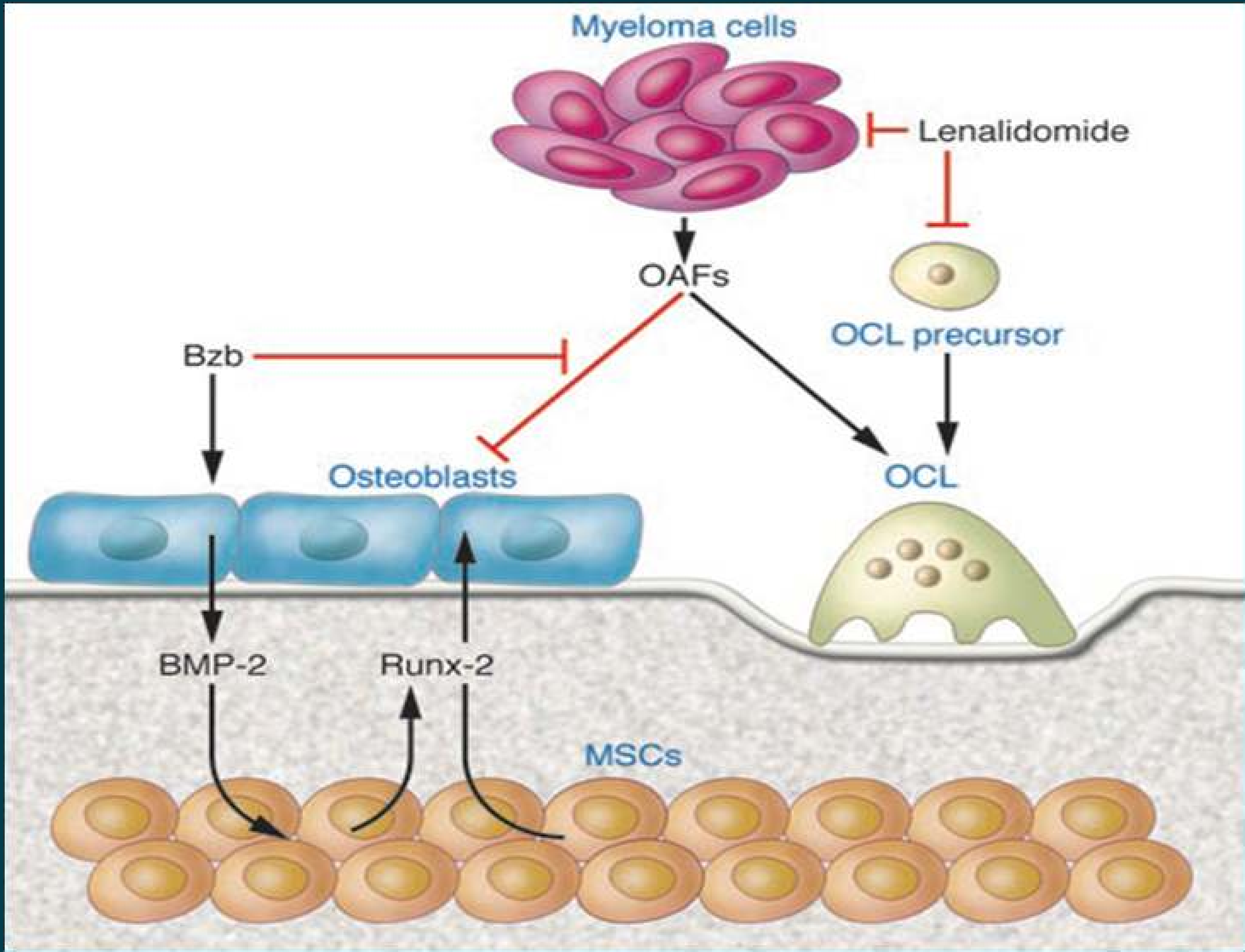
New Agents for Treating Myeloma

Thalidomide

Lenalidomide

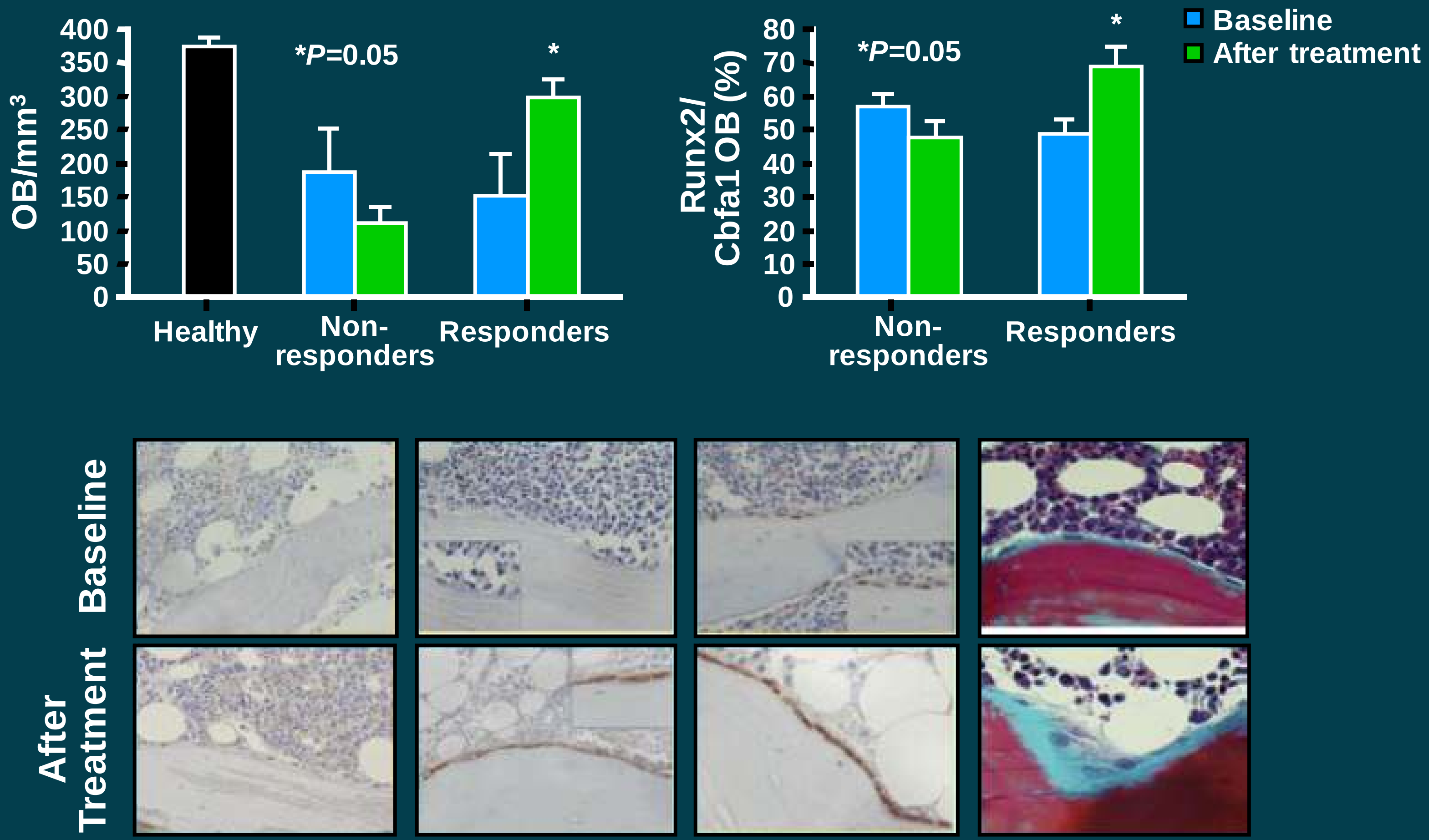
Bortezomib

Bortezomib / Lenalidomide in MBD



Roodman GD JCI 2008 118:462-4

Effect of Bortezomib on Bone Formation in Multiple Myeloma Patients



Multiple myeloma "nonresponder"

Multiple myeloma "responder"

Multiple myeloma "responder"

Giuliani N et al. Blood. 2007;110:334-338.

Novel Therapeutic Targets for MM Bone Disease

Target	Potential Therapy
MIP-1α	CCR1 antagonist
RANKL	Anti-RANKL
DKK1/sFRP-2	Wnt Agonist, Anti-DKK1, Bortezomib
Activin A	ACE-011