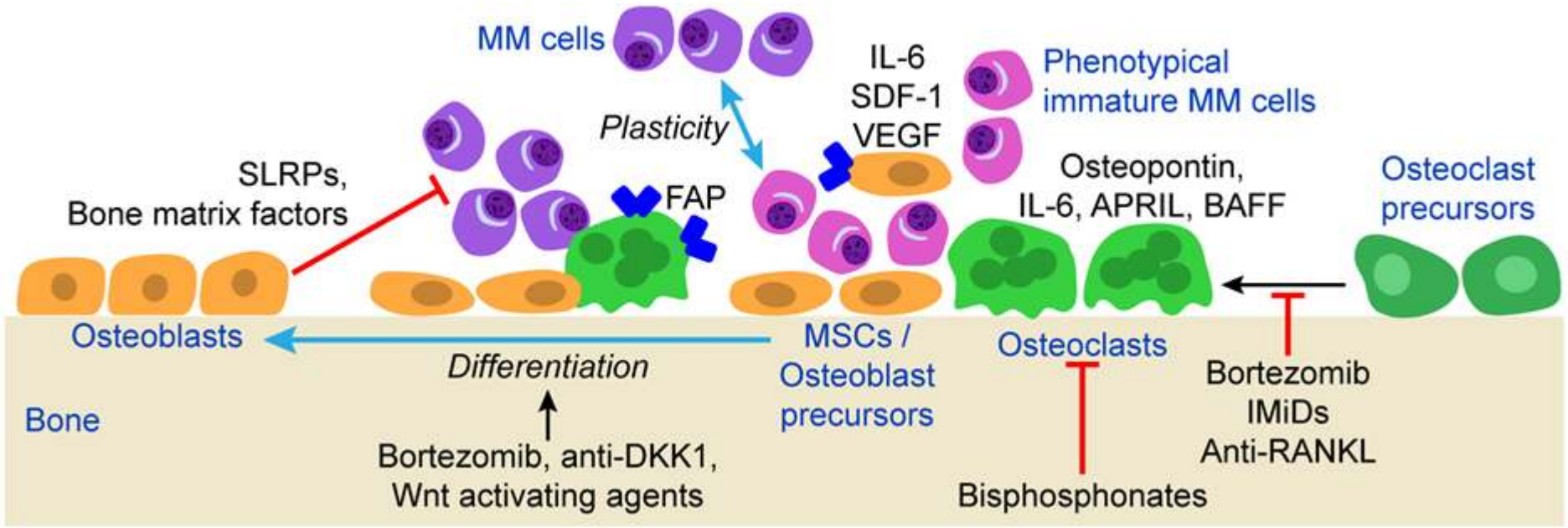
# Bone Anabolism and Tumor Growth in Myeloma

Shmuel Yaccoby, PhD
Myeloma Institute for Research and Therapy
University of Arkansas for Medical Sciences

# Disclosure

No conflicts of interest

# Contrasting Effects of Bone Resorption and Bone Formation on MM




***Yaccoby, BJH 2010***

# Consequences of Osteoblast Activation

## MM Suppression:

1. Restoring “coupling” may reduce osteoclast activity.
2. Increased production of MM restraining factors.
3. Recovering hematopoiesis and immune function.
4. Reconstructed osteoblastic niche replaces the MM osteoclastic/reactive stroma niche.

# Consequences of Osteoblast Activation

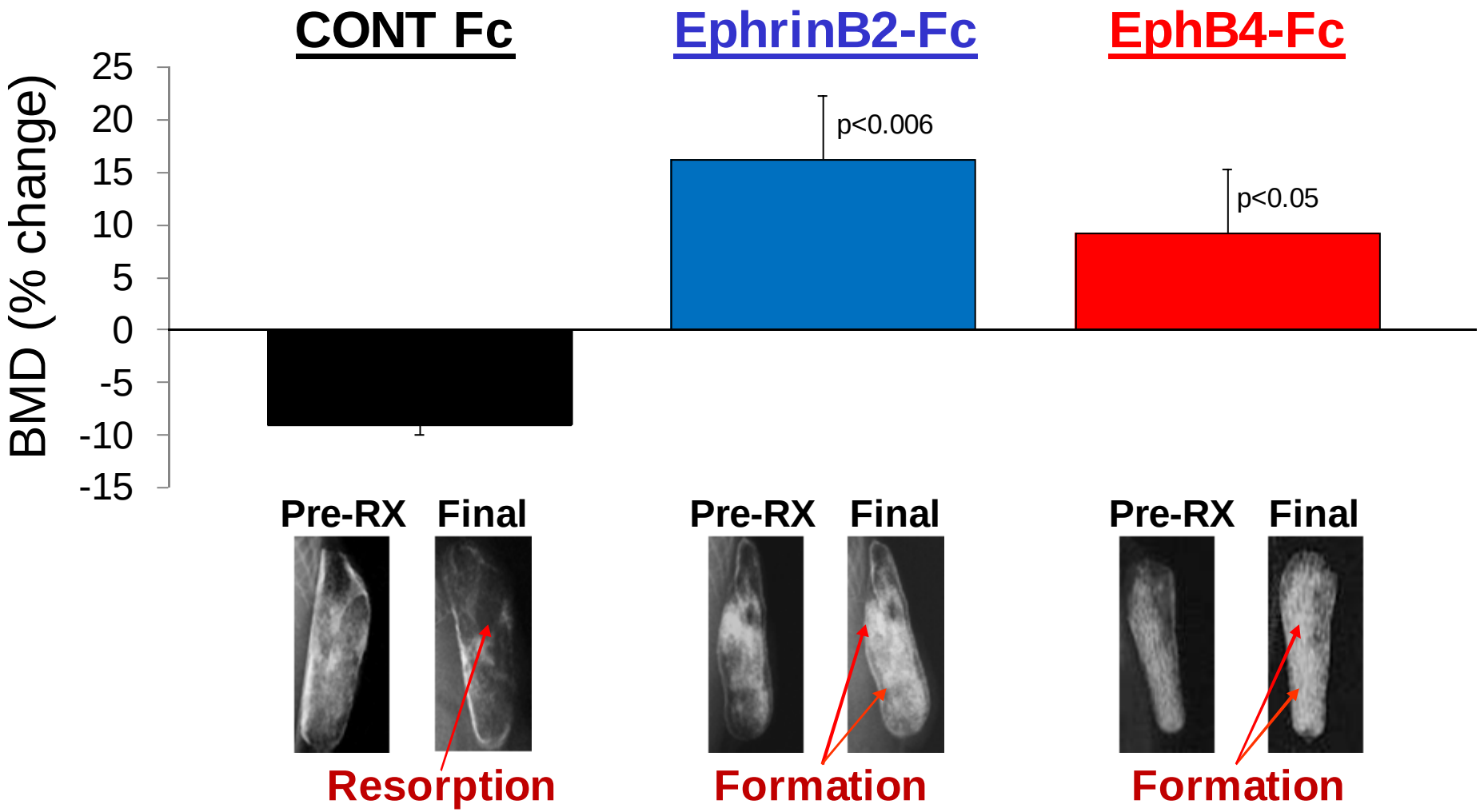
## MM Stimulation:

1. Increasing MSC pool may also increase pool of reactive stroma.
2. Osteogenic cells produce MM growth factors.
3. MM “stem cells” may compete with HSCs on the restored osteoblastic niche.

# Osteoblast Activating Agents Attenuate MM Growth in Bone

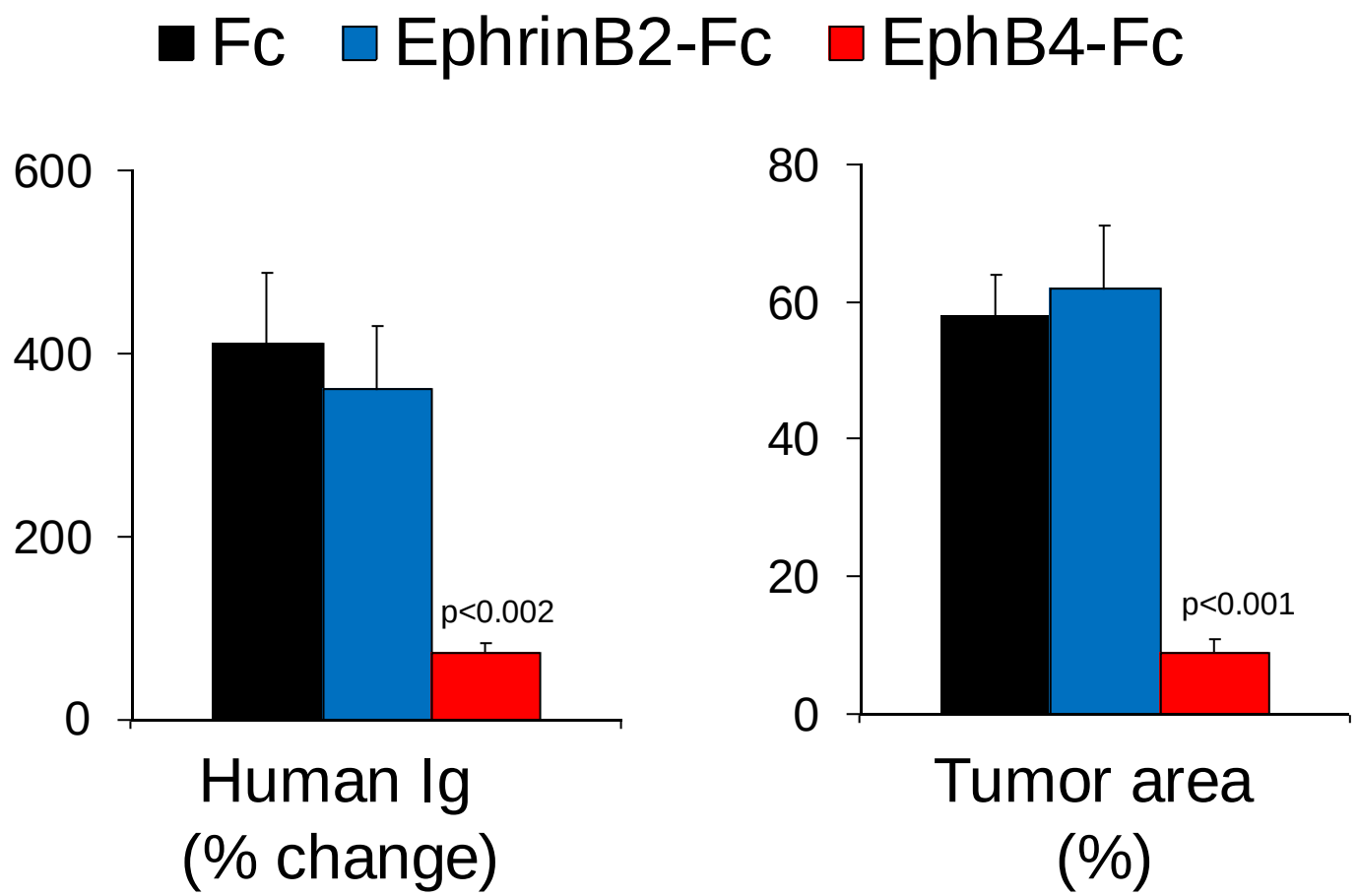
- **Anti-DKK1** (Yaccoby et al., Blood 2007; Fulciniti et al, Blood 2009)
- **Wnt3a** (Qiang et al., Blood 2008)
- **Lithium Chloride** (Edwards et al., Blood 2008)
- **EphB4-Fc** (Pennisi et al., Blood 2009)
- **TGF-β inhibition** (Takeuchi et al., PLoS One 2010)
- **Activin A inhibition** (Vallet et al., PNAS 2010; Chantry et al., JBMR 2010)
- **PTH** (Pennisi et al., PLoS One 2010)
- **Bortezomib** (Edwards et al., AJH 2009; Pennisi et al., AJH 2009)
- **MSC cytotherapy** (Yaccoby et al., 2006; Li et al., Stem Cell 2011)

# EphrinB2-Fc and EphB4-Fc Stimulate Bone Formation in MM Bones




*Pennisi et al., Blood 2009*

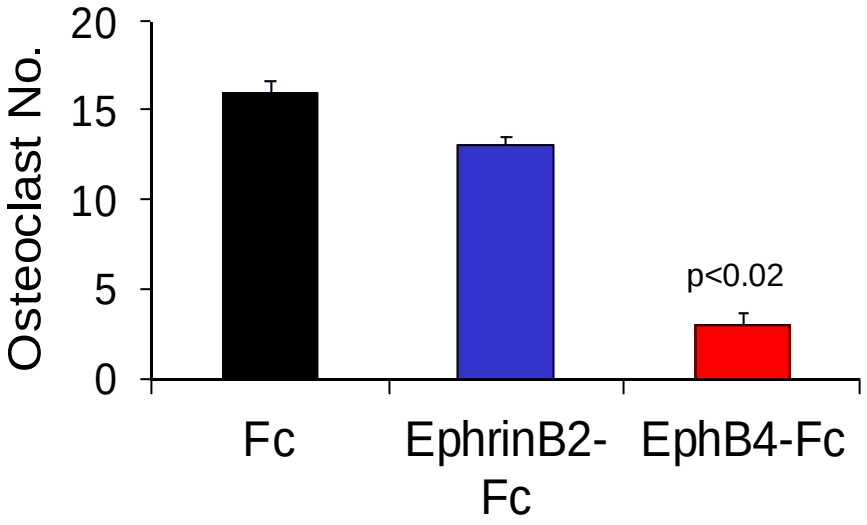
# EphB4-Fc but Not EphrinB2-Fc Inhibits MM Growth



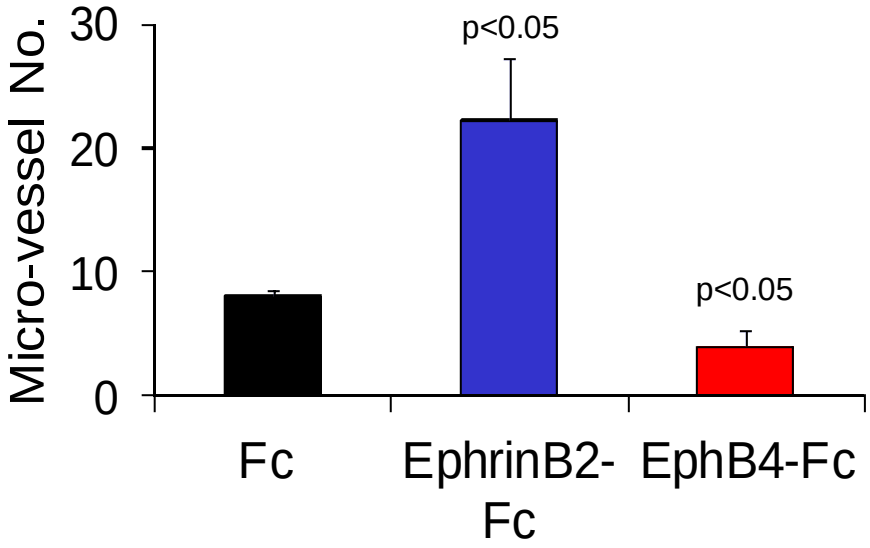

*Pennisi et al., Blood 2009*

# Osteoblastogenesis Alone May Not Be Sufficient For Restraining MM

## Osteoclasts

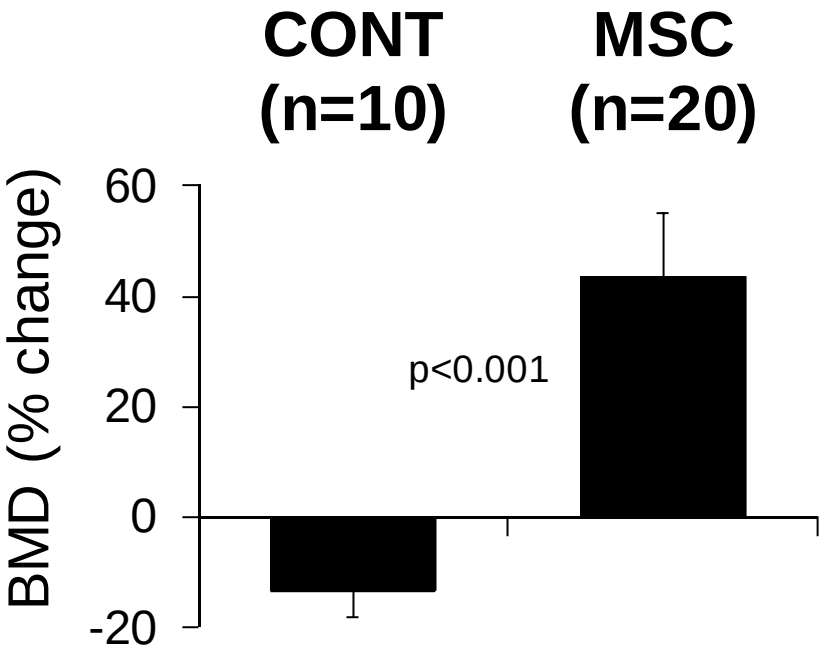


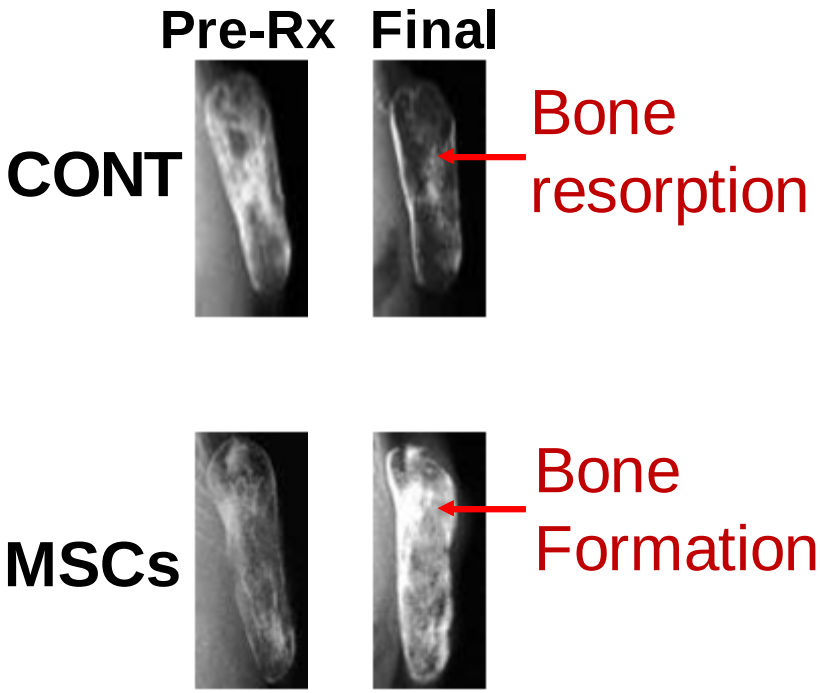

## Angiogenesis




*Pennisi et al., Blood 2009*

# Intra-Bone Injected MSCs Promote Bone Formation in MM Bone

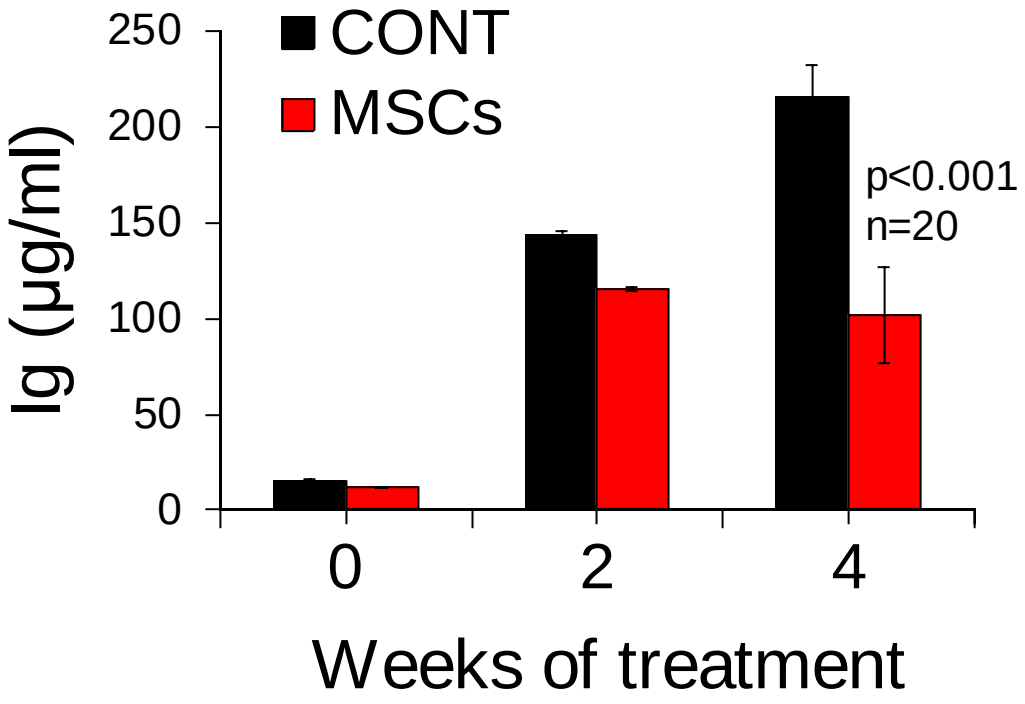


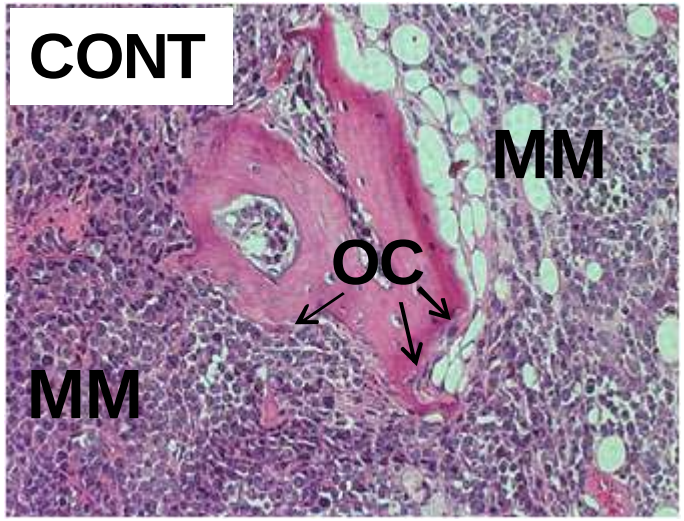



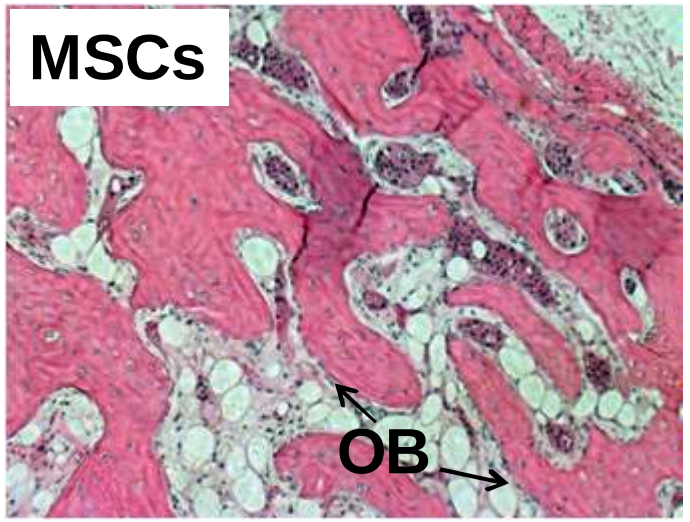

*Li et al., Stem Cells 2011*

*Yaccoby et al., 2006*

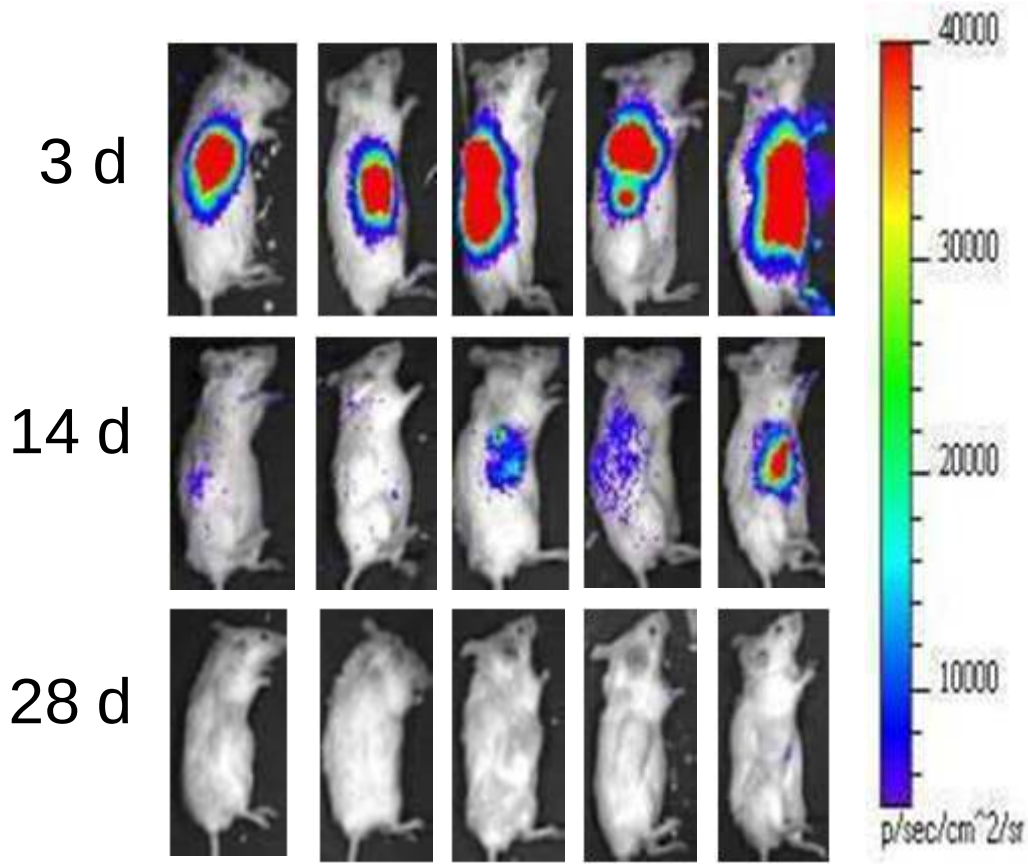
# Intra-bone Injected MSCs Inhibit MM Growth in Bone



# Intra-Bone Injected MSCs Disappear Within 4 Weeks

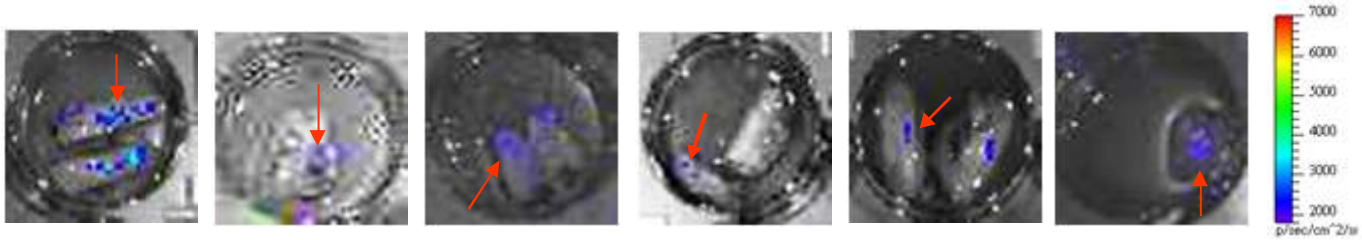



*MSCs infected with luciferase-expressing lentivirus.

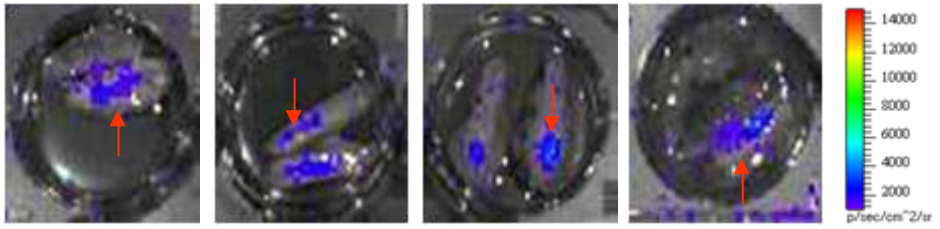
# Intravenously or Intracardiacly Injected MSCs Home to MM Bone

## Implanted myelomatous bones

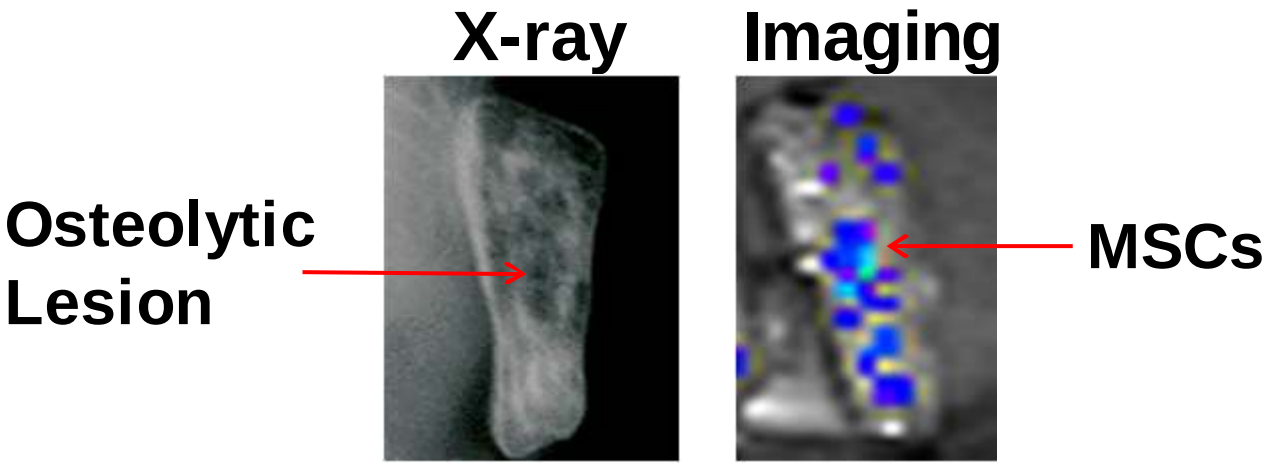
IV

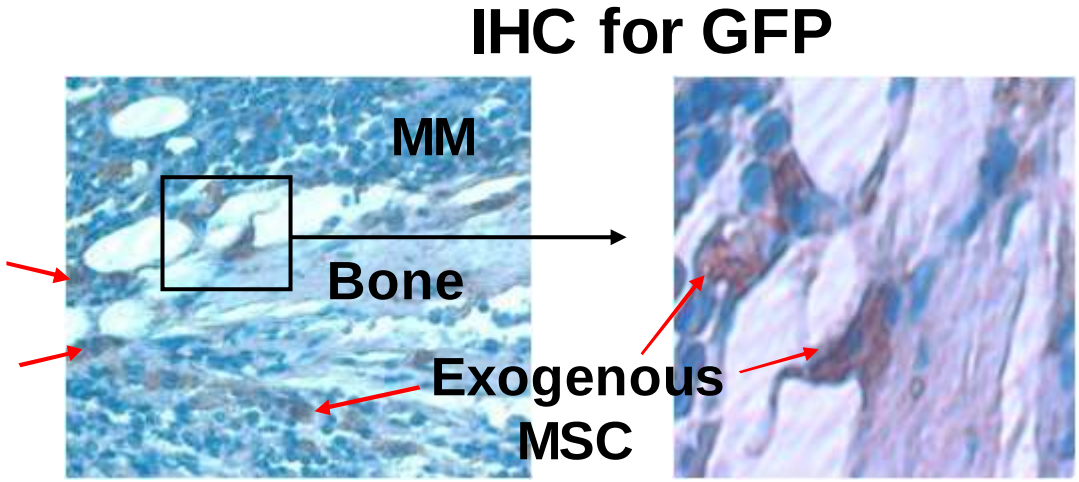



IC



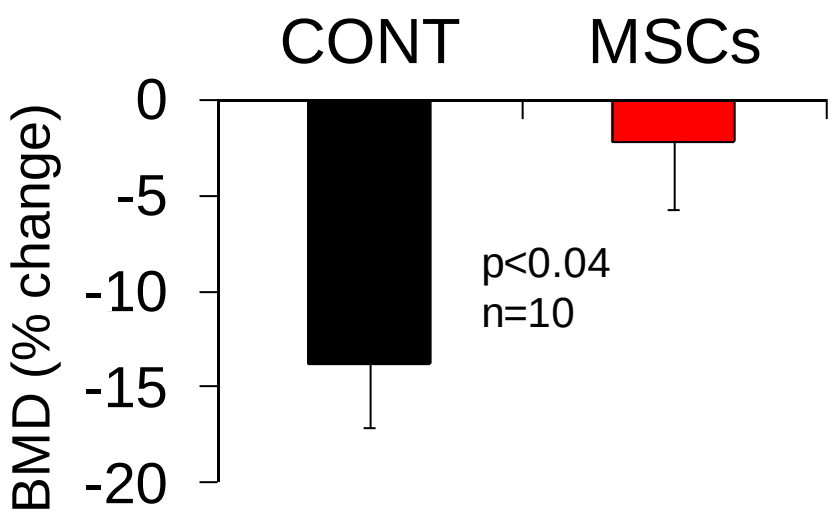
# MSCs Home to Lytic Lesions in MM Bone

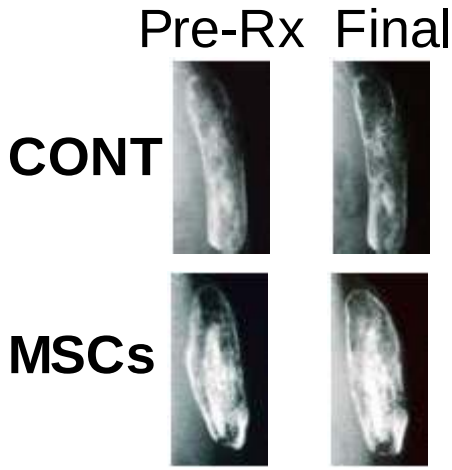


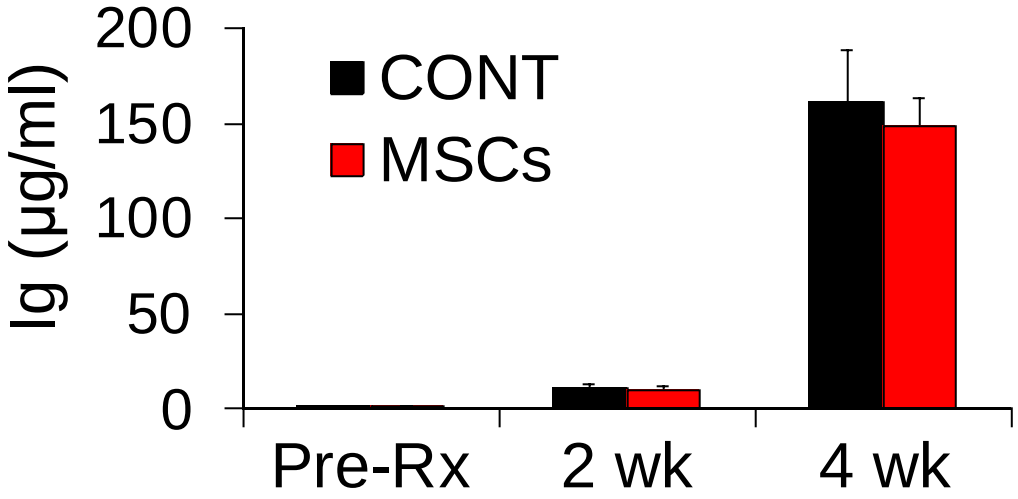
# Weekly IV Injected MSCs Inhibit MM Bone Disease

**Prevention of Bone Loss**

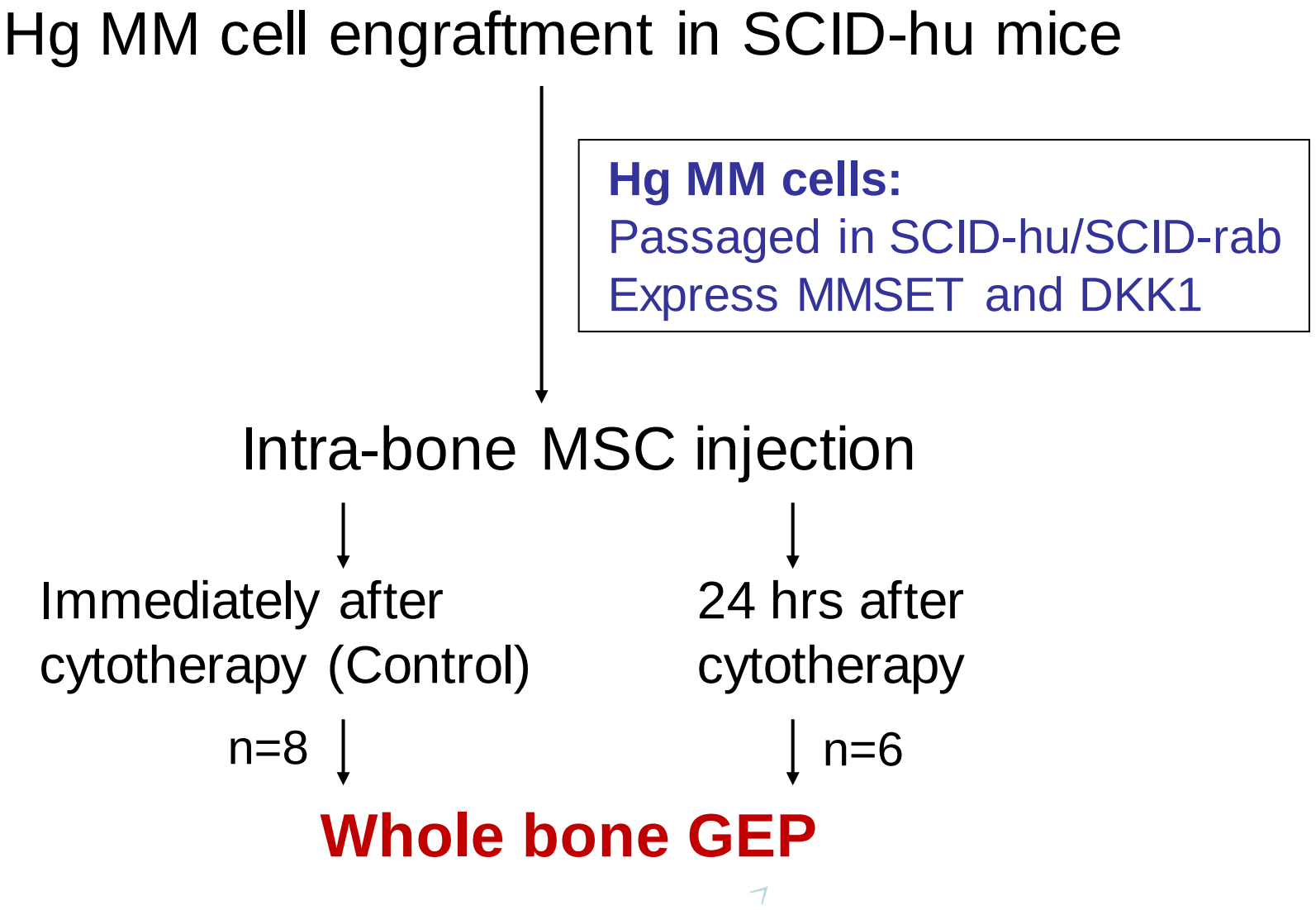



**No Effect on MM Burden**



# Molecular Mechanism Study Design



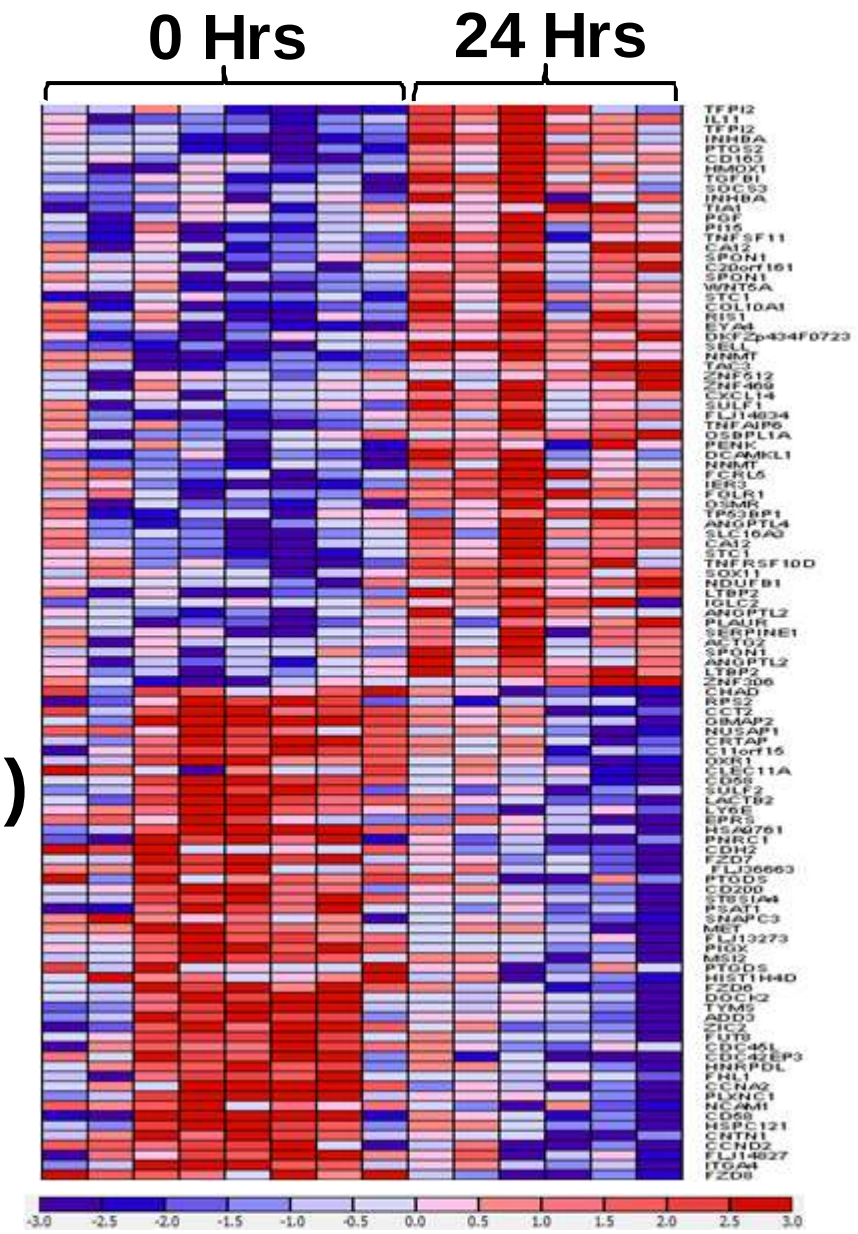
# GEP Criteria and Overall Findings

## Overexpressed (~60 genes)

p<0.05
≥2 folds increase
≥500 mean signal in 24 hrs

## Underexpressed (~50 genes)

p<0.05
≥2 folds reduction
≥500 mean signal in 0 hrs



# Factors Affected by MSC Cytotherapy

- **Anti-inflammatory**: *TNFAIP6, CXCL14, PTGS2*
- **Proteases inhibitors**: *TFPI2, PI15*
- **Antioxidants**: *HMOX1*
- **TGFβ signaling**: *SPON1, INHBA, TGFBI*
- **Macrophages (osteomacs)**: *CD163*

# Potential Extracellular Factors Mediating MSC Cytotherapy

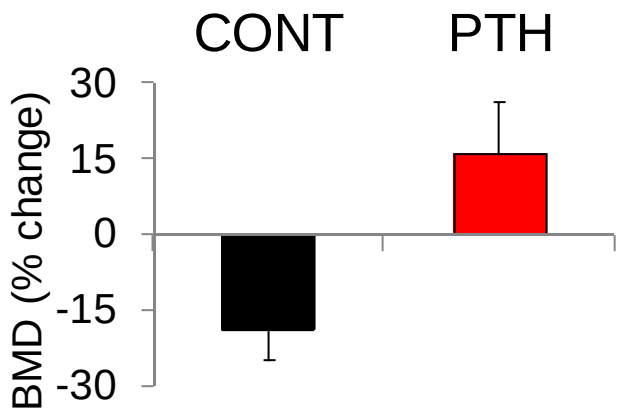
- ***TFPI2*** (Tissue factor pathway inhibitor 2)
- ***SPON1*** (F-spondin)
- ***CXCL14*** (Chemokine C-X-C motif ligand 14)
- ***TNFAIP6*** (TNFα–induced protein 6)
- ***ANGPTL2 & 4*** (Angiopoietin-like 2 and 4)
- ***PI15*** (Peptidase inhibitor 15)

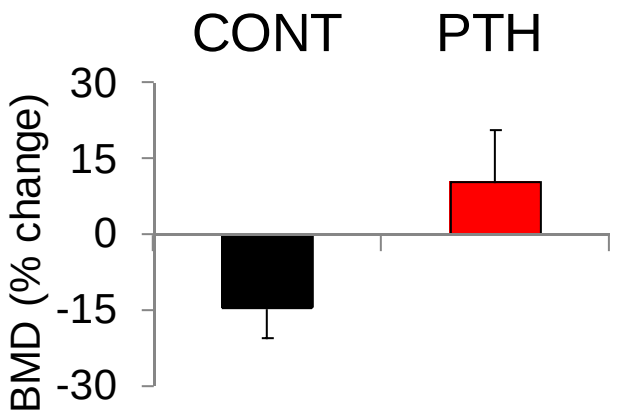
# PTH Promotes Bone Formation and Attenuates MM Growth

**Primary MM (n=10)**

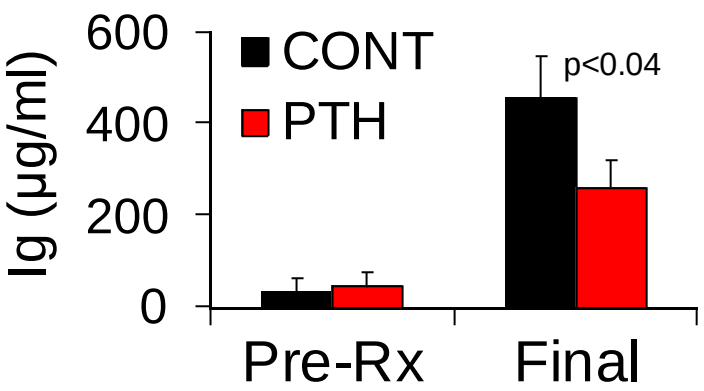
**Hg MM Line**

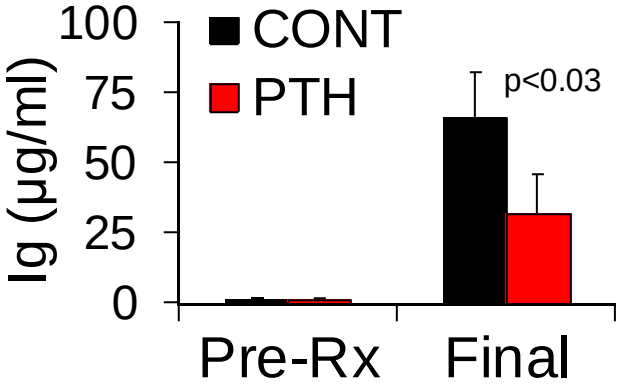
**Bone Formation:**




**MM Growth:**




*Pennisi et al., PlosONE 2010*

# Environmental Pathways Targeted by PTH

**Osteogenesis**

- RUNX2 ↑
- BGLAP ↑
- **DECORIN** ↑
- SPARC ↑

**WNT**

- **DKK1** ↓
- LRP4 ↑
- ROR2 ↑

**cAMP/PKA**

- RGS1 & 2 ↑
- Phosphodiesterases ↑

**Others**

- FGFR2 ↑
- PDGFA ↑
- TGFB2 ↑
- FOXC1 ↑
- MSX1 ↑

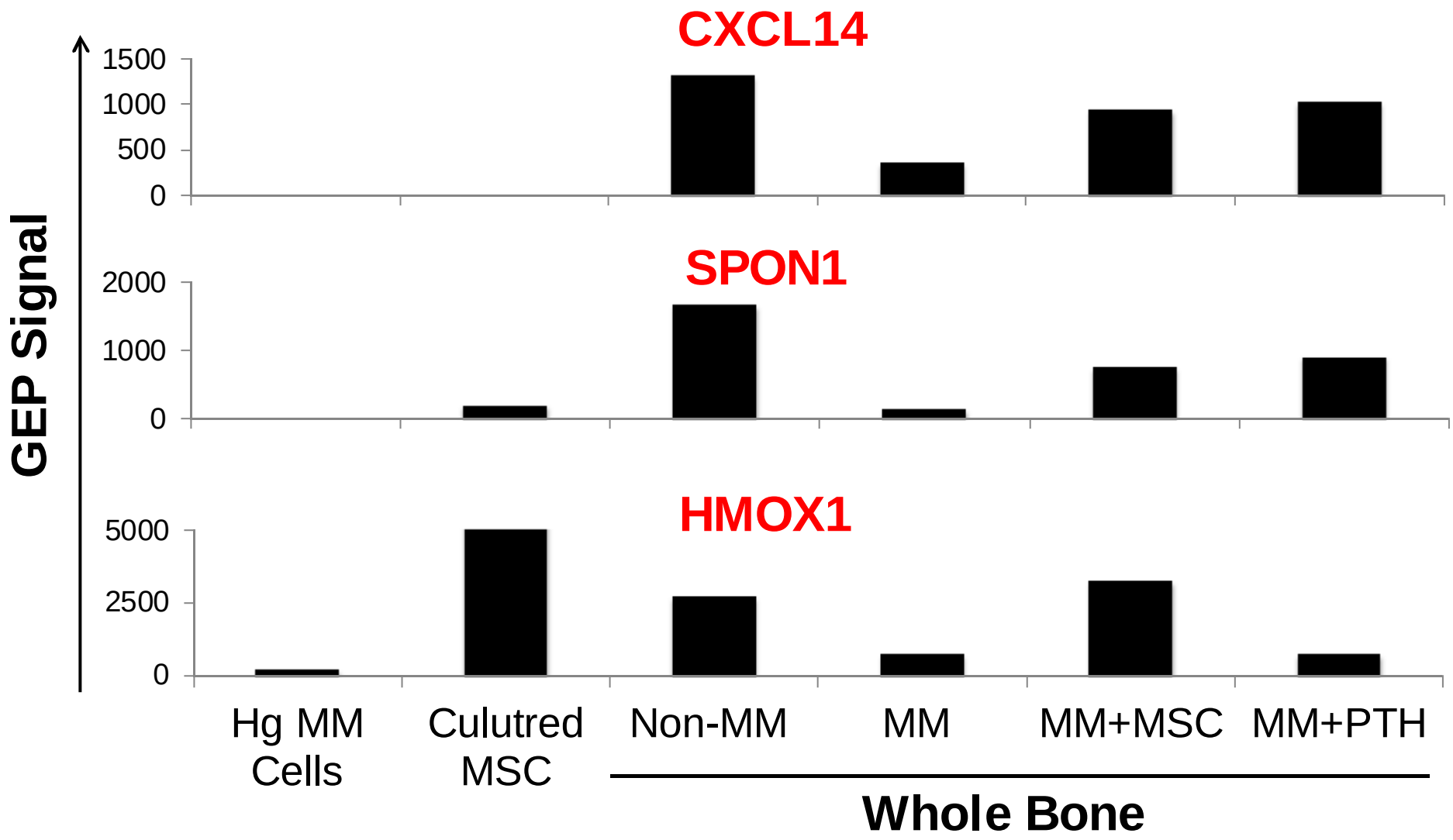
*Pennisi et al., PlosONE 2010*

# Anti-Inflammation Mediators are Among Top Upregulated Genes by PTH

| | Fold Increase |
|---|---|
| • **CXCL14** | 4 |
| • **F-Spondin** | 4 |
| • **ANGPTL2** | 4 |
| • **ANGPTL4** | 3 |
| • **PTGE3** | 3 |
| • **TNFAIP6** | 2 |

*Pennisi et al., PlosONE 2010*

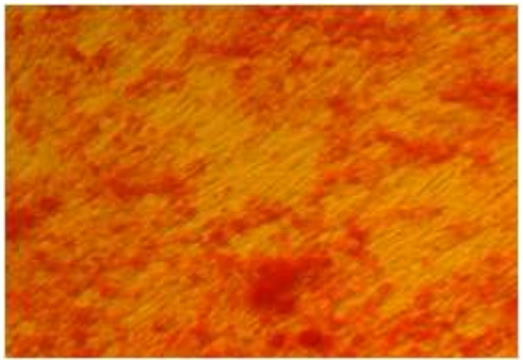
# MSC Cytotherapy or PTH Restore Expression of Anti-MM Mediators



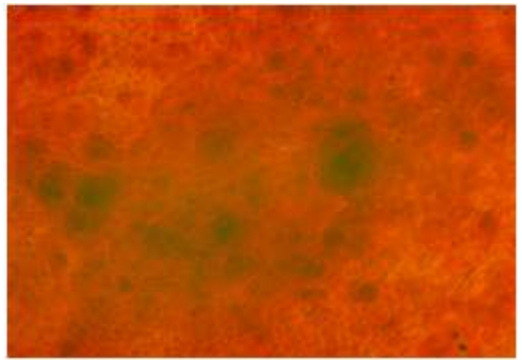
# HMOX1 Inducer, Hemin, Promotes Osteoblast Differentiation and Inhibits Osteoclast Formation

**Osteoblast Differentiation**

**Control**

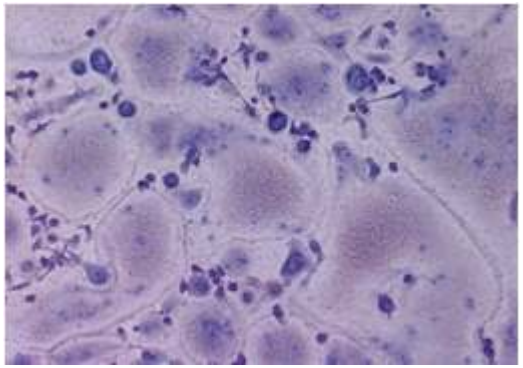


**Hemin**

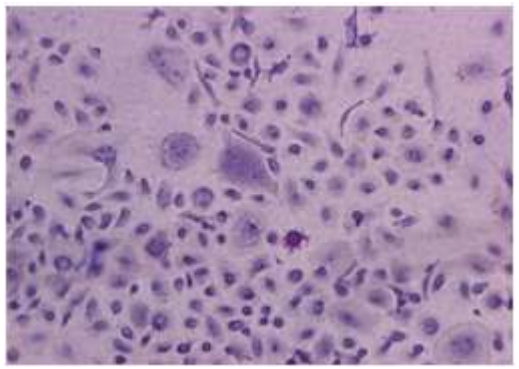


**Osteoclast Formation**

**Control**



**Hemin**

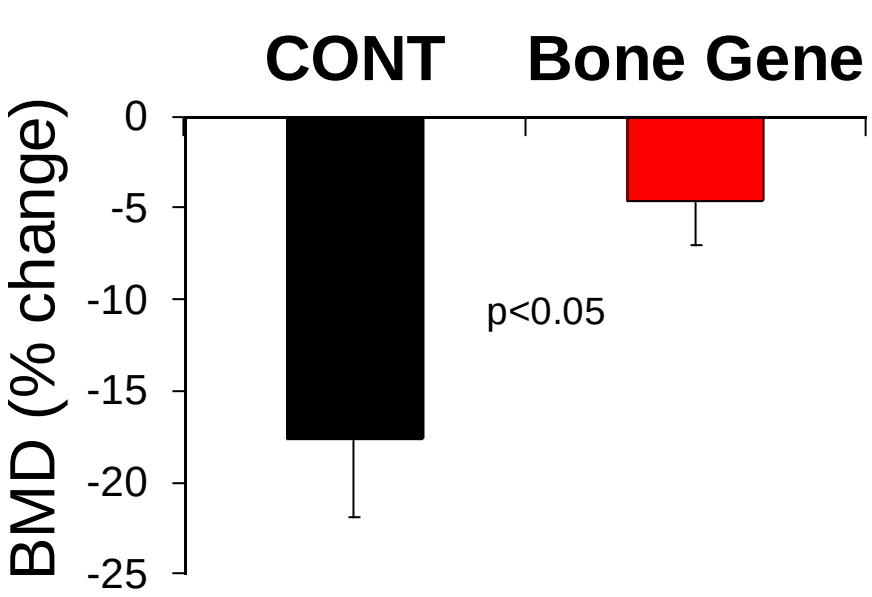


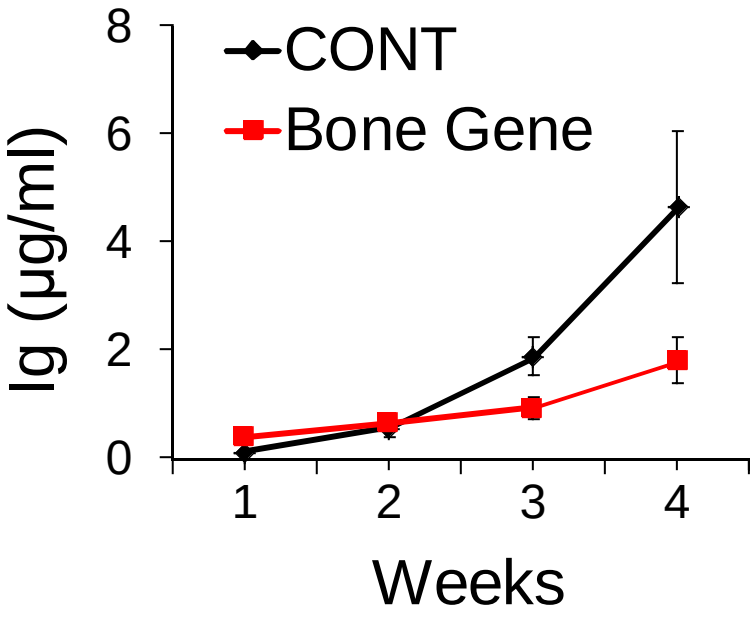
**110±3**

**51±2**

**p<0.001**

# “Bone” Anabolic Protein Inhibits Osteolysis and MM Growth




H929 MM cells transduced with “bone” gene were engrafted in SCID-hu mice.

# Summary and Conclusions

1. **Bone anabolic therapies upregulate anti-inflammatory, anti-osteoclastogenic and anti-angiogenic factors.**
2. **Source of these factors are mature osteoblasts and/or certain hematopoietic cells (e.g. BM macrophages).**
3. **These factors may restrain MM directly ("immediate effect") and indirectly ("long-term effect") by altering bone remodeling and BM cellularity.**

# Acknowledgment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