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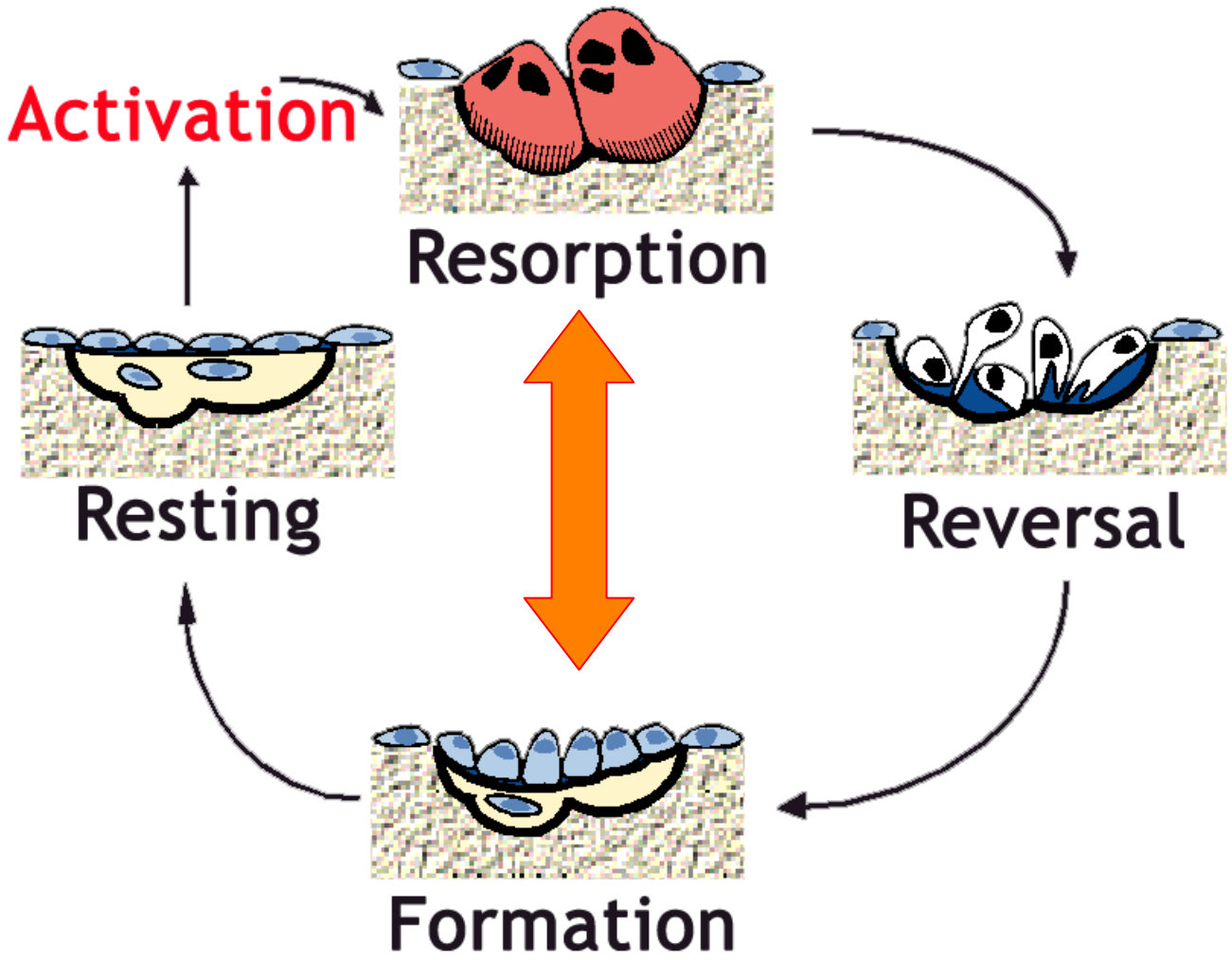
# Osteoclast and gp130 signals that regulate bone metabolism

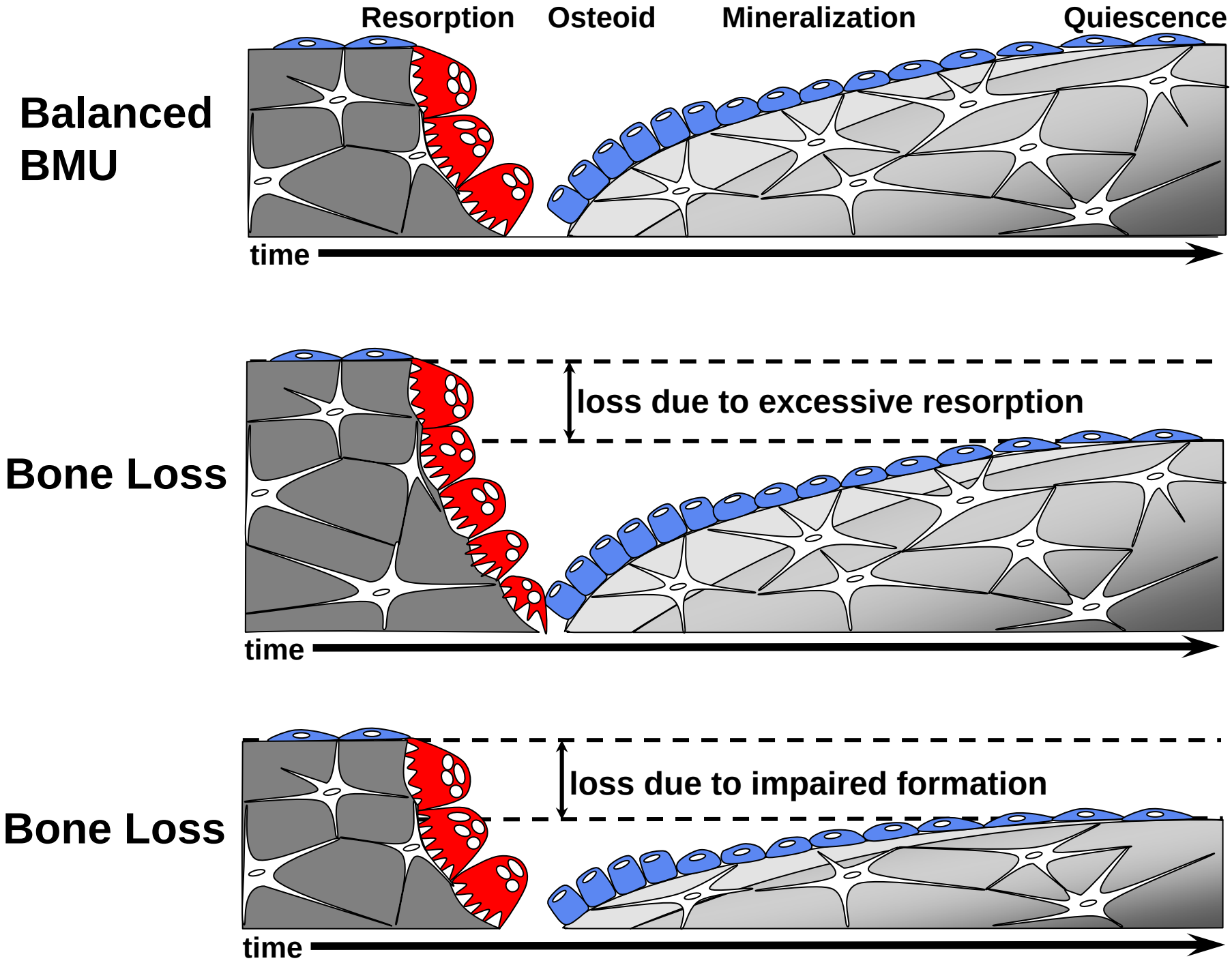

**Natalie A Sims**

**NHMRC Senior Research Fellow**

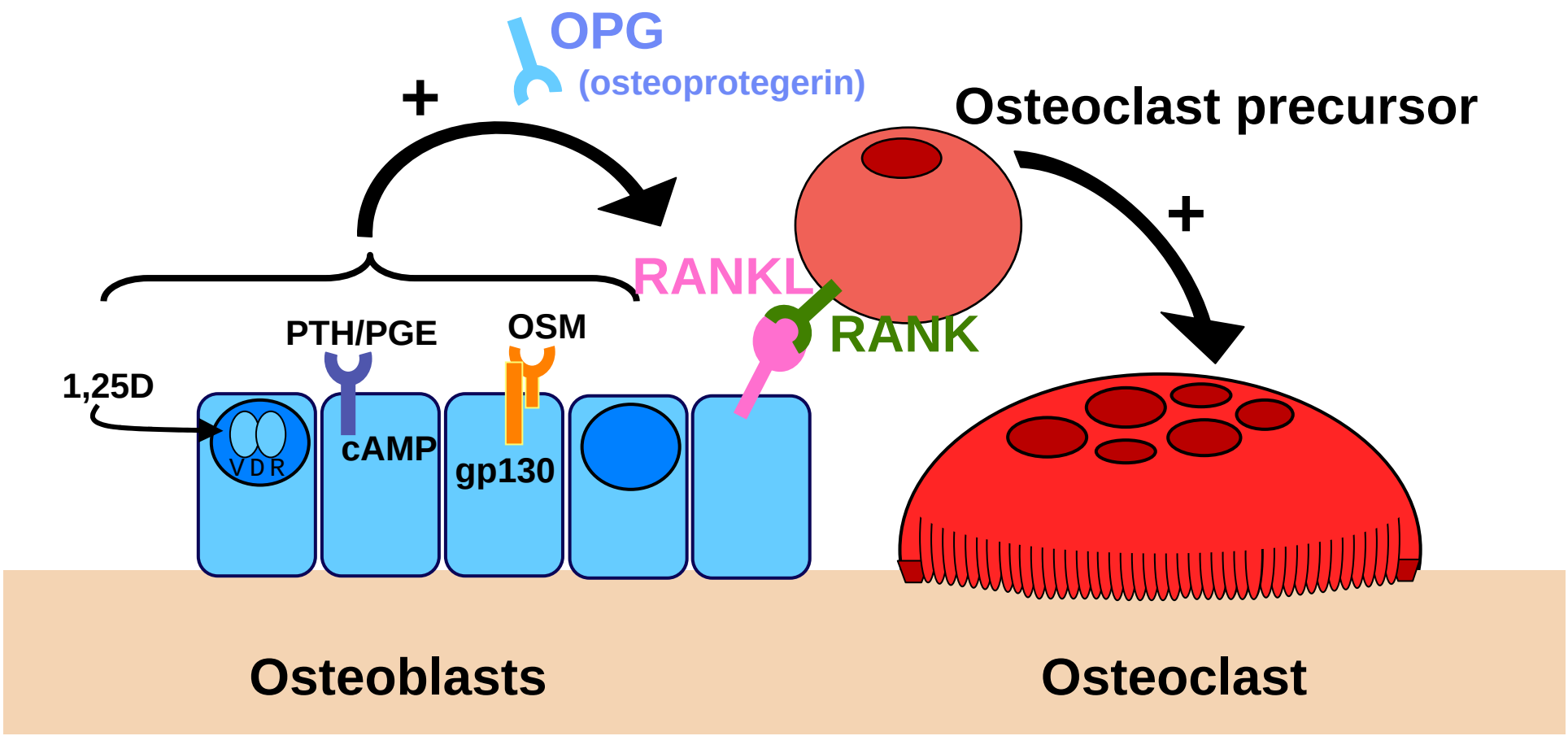
**Bone, Joint and Cancer Unit**

# Bone remodelling determines bone mass

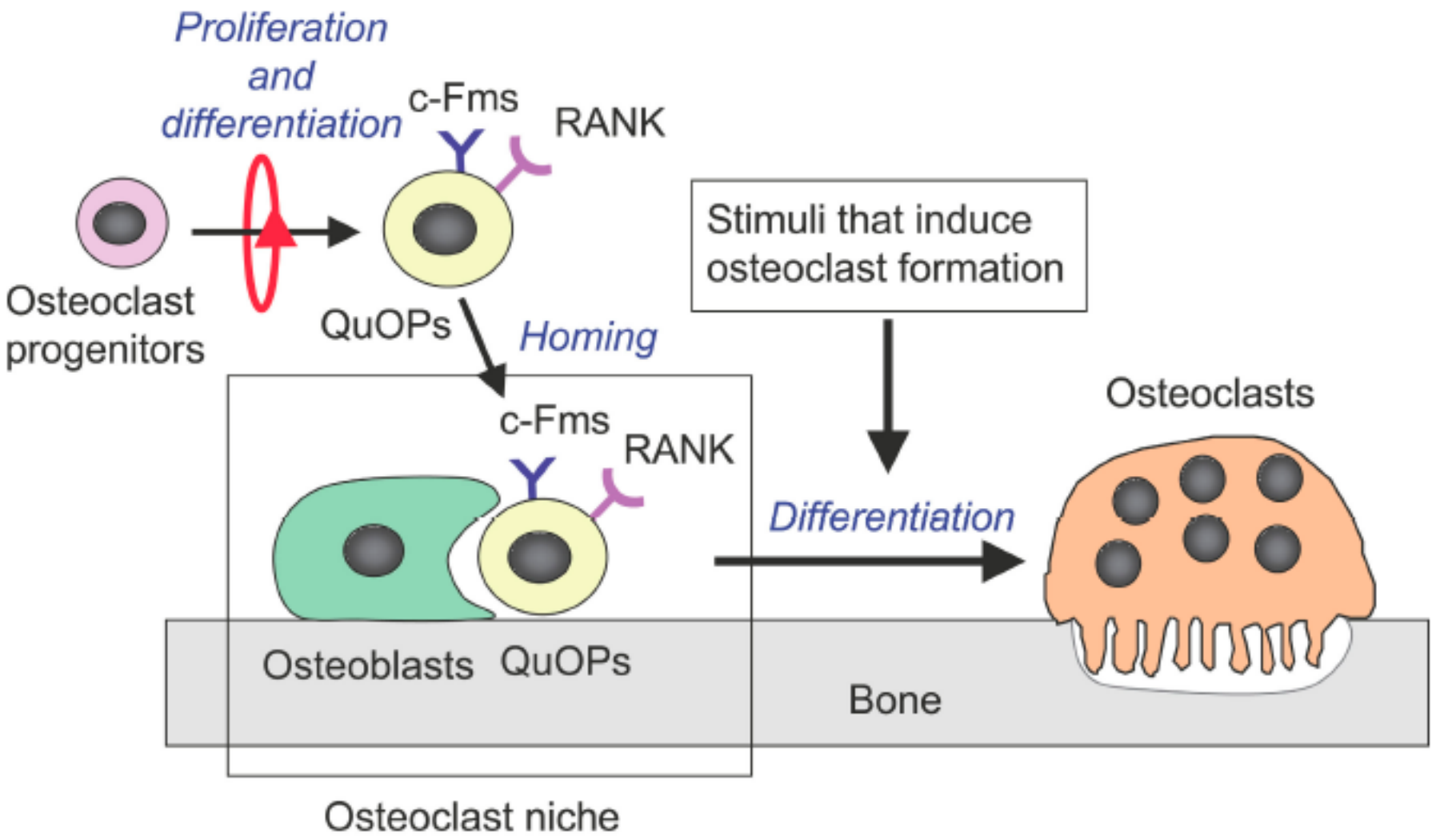



Resorption
Osteoid
Mineralization
Quiescence
Balanced BMU
time
Bone Loss
loss due to excessive resorption
time
Bone Loss
loss due to impaired formation
time

# Osteoblast: osteoclast communication

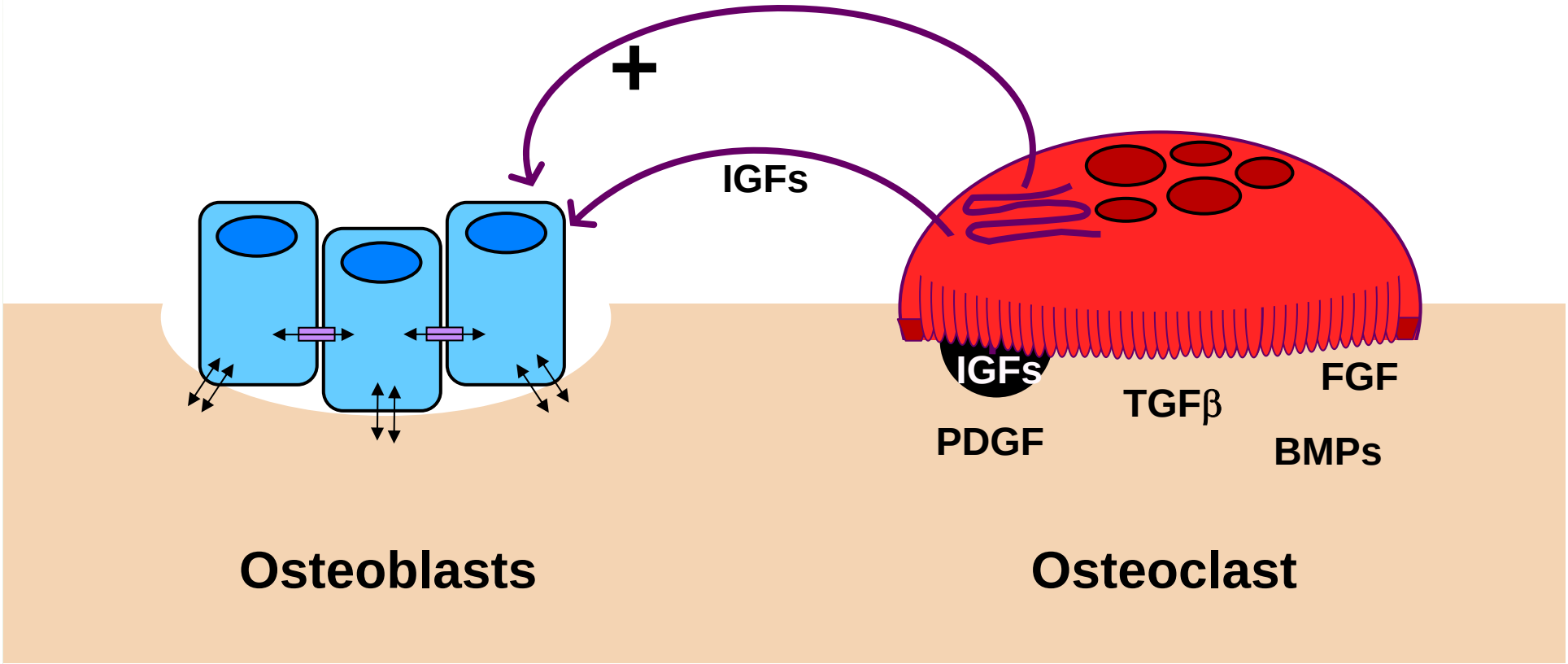


# The Osteoclast Niche



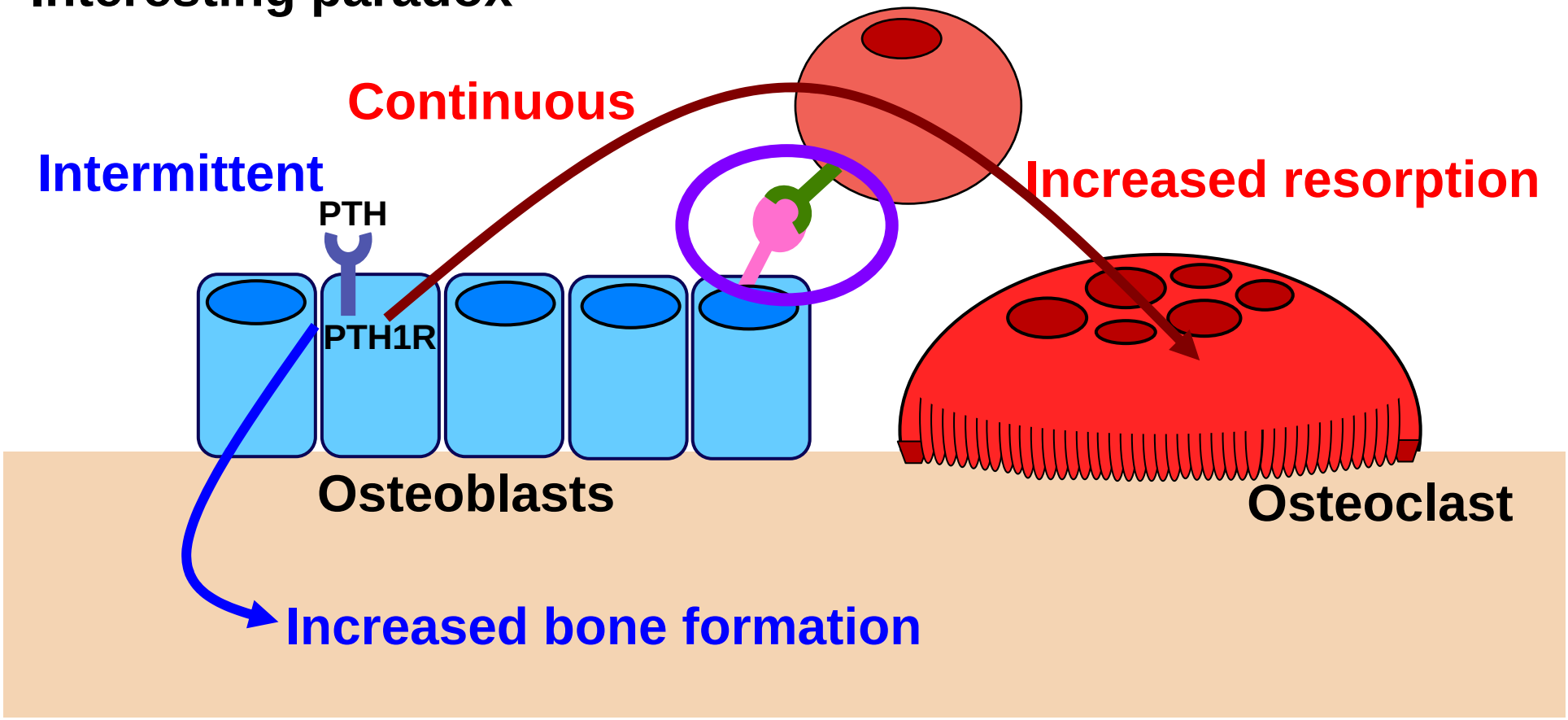

*Mizoguchi et al, J Cell Biol 184:541, 2009*

# Signals from the osteoclast to the osteoblast

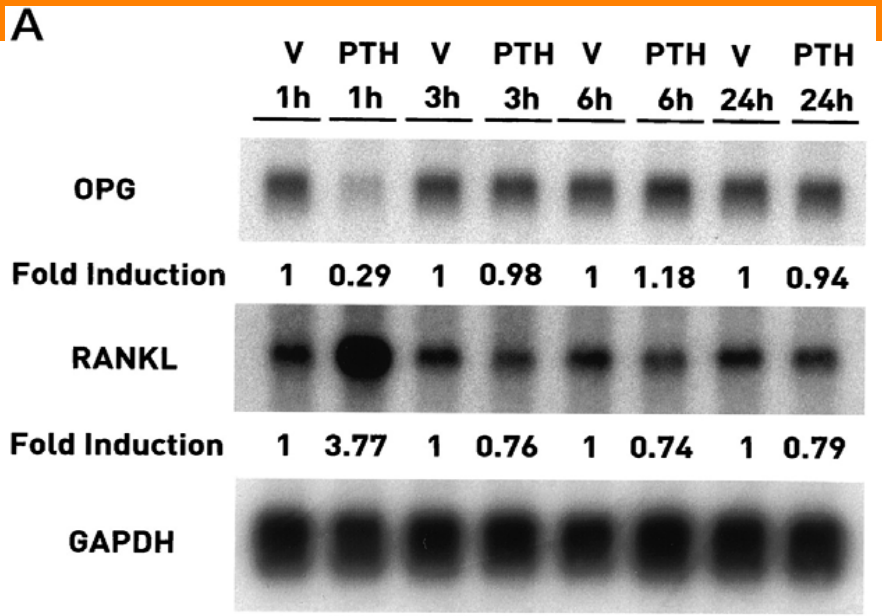


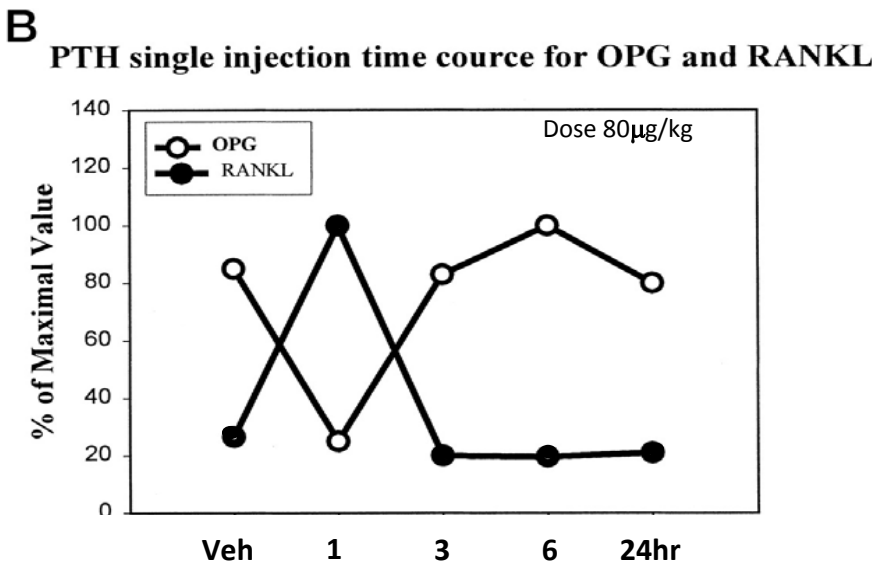
# PTH treatment has two possible effects both mediated through a receptor in the osteoblast

**Understanding PTH therapy**
**Local role of PTHrP**
**Interesting paradox**



# Intermittent PTH stimulates RANKL expression



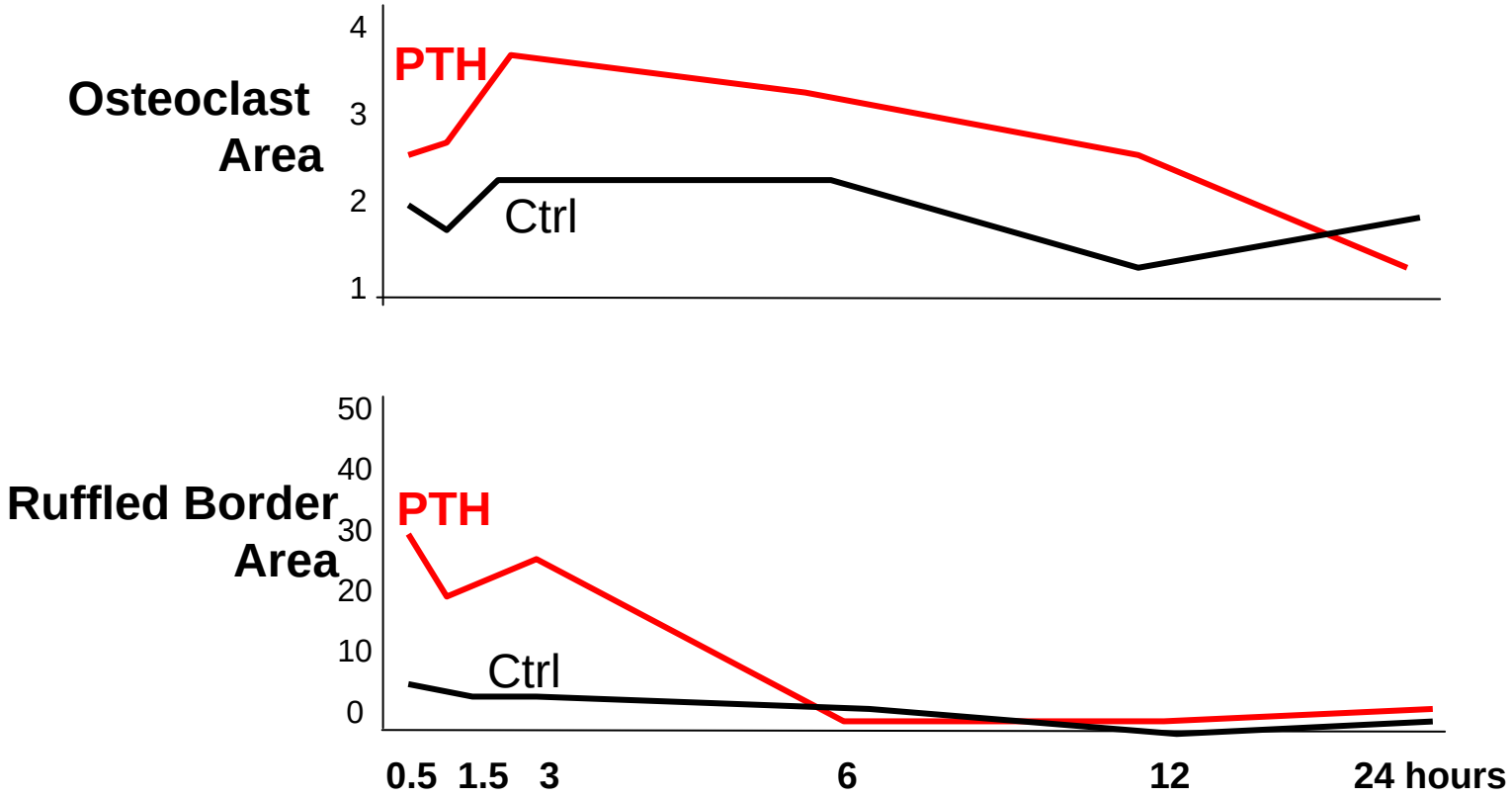




**Transient activation of osteoclasts?**

RNA: Femoral Metaphysis

*Ma, et al. Endocrinology, 2001*

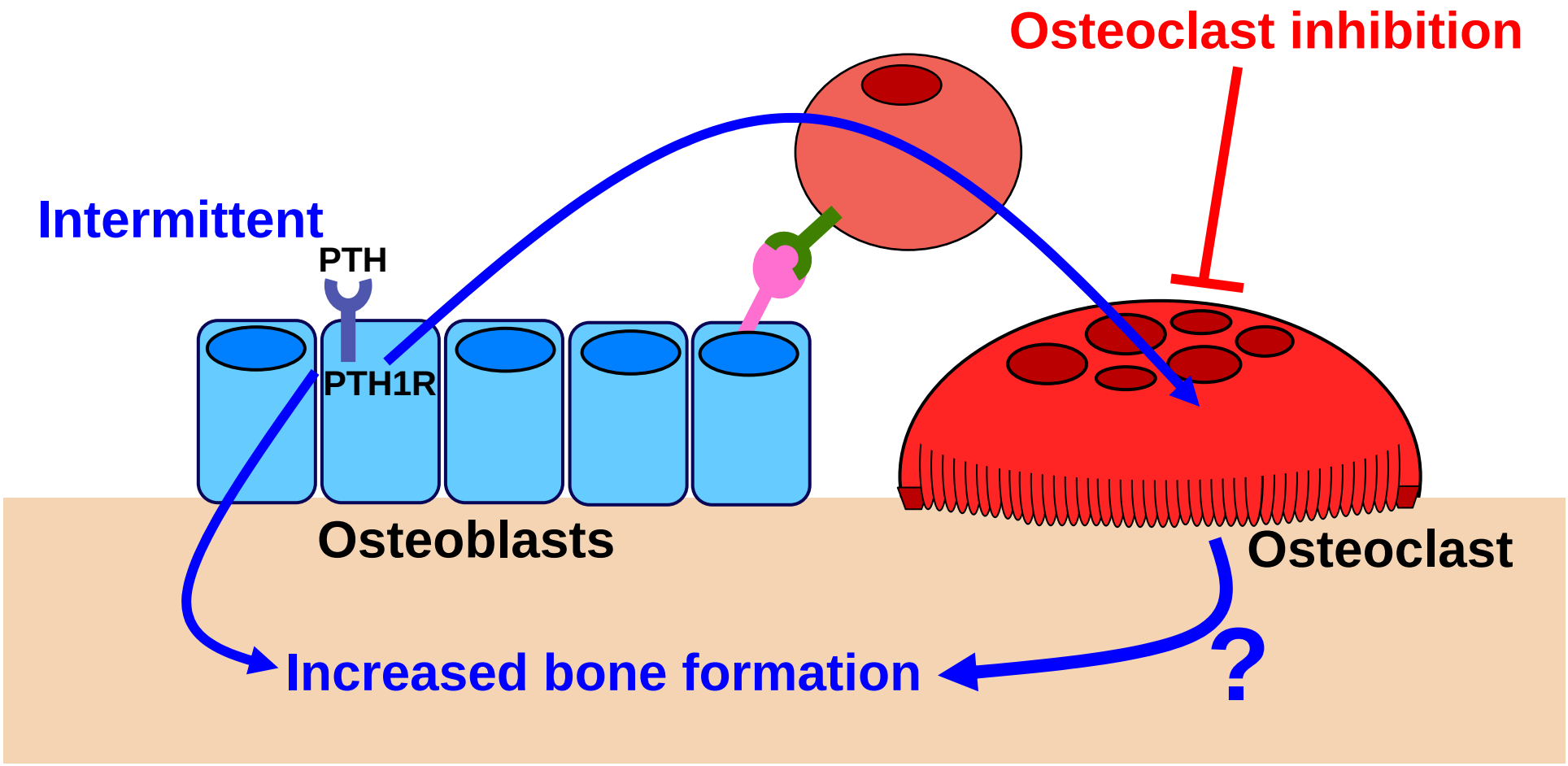
# Rapid effect of PTH on osteoclasts



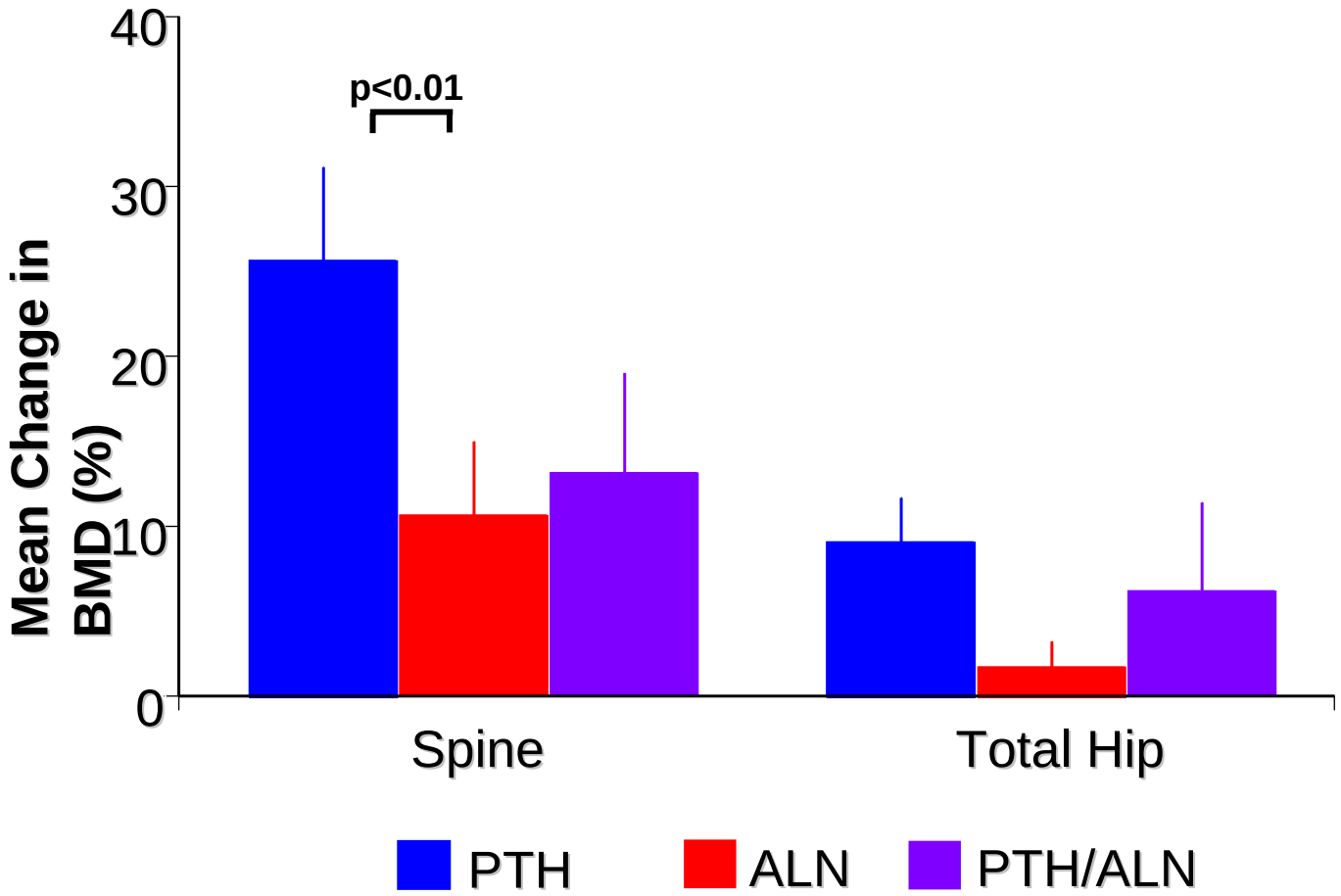

*(Holtrop ME, et al. Calcif Tissue Int. 1979;27:129-135)*

# Is the osteoclast required for the anabolic action of PTH?

**Evidence for osteoclast requirement: PTH + bisphophonates**

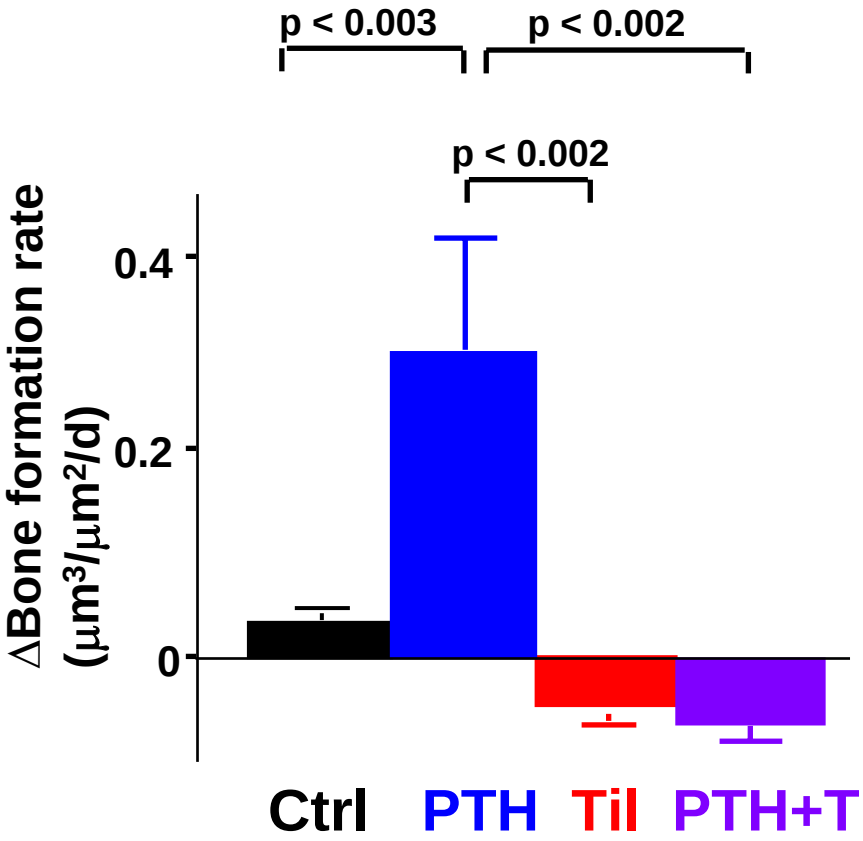


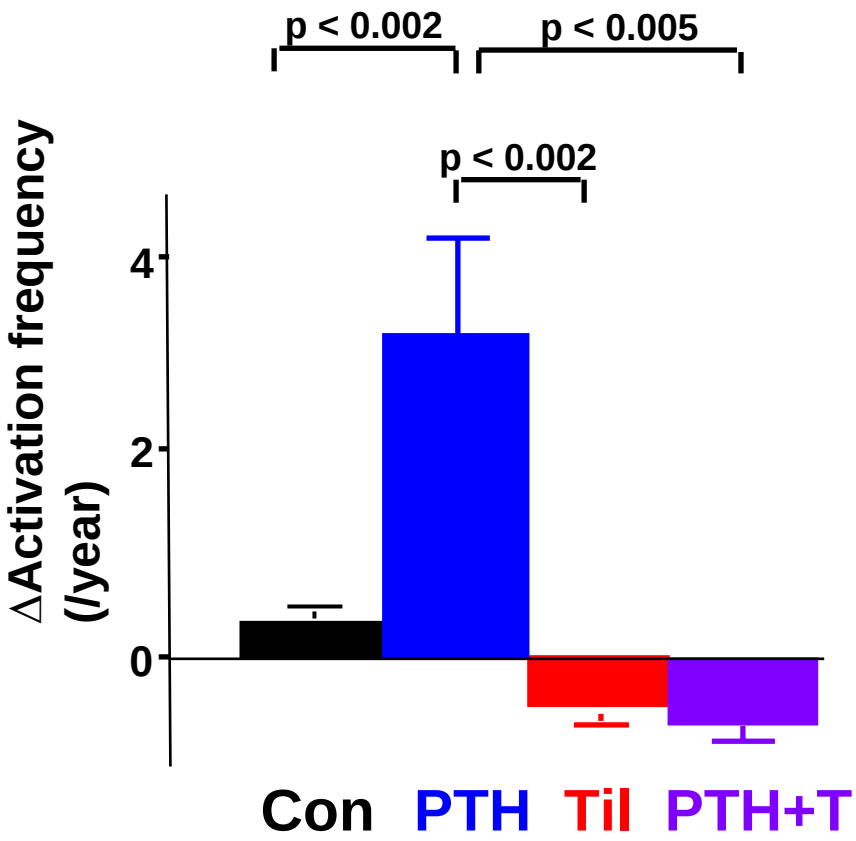
# Alendronate inhibition of osteoclasts reduces the anabolic effect of PTH




*(Black DM, et. al. N Engl J Med. 2003;349:1207-1215)*

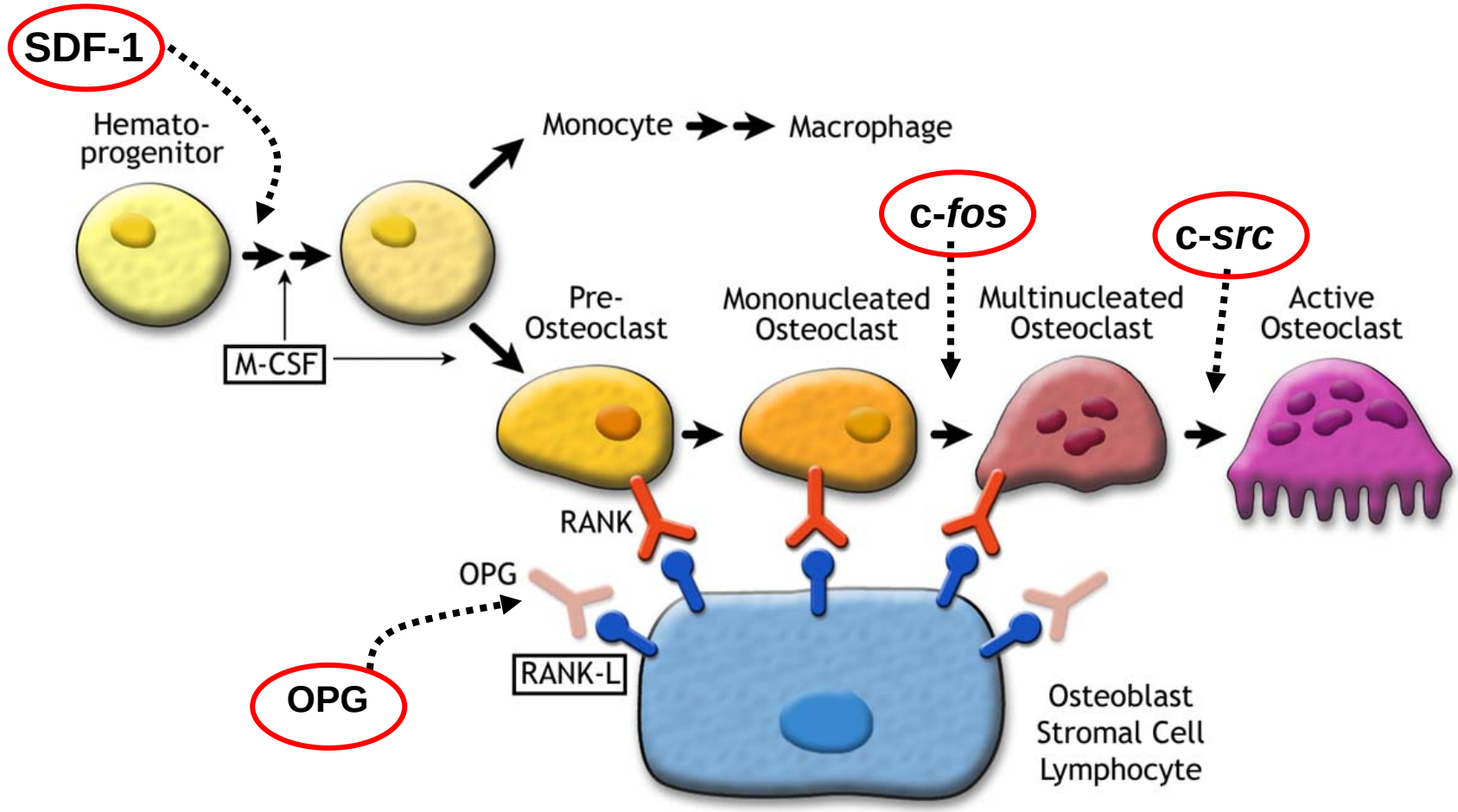
# Tiludronate inhibition of osteoclasts blocks the anabolic effect of PTH




*(Delmas 1993)*

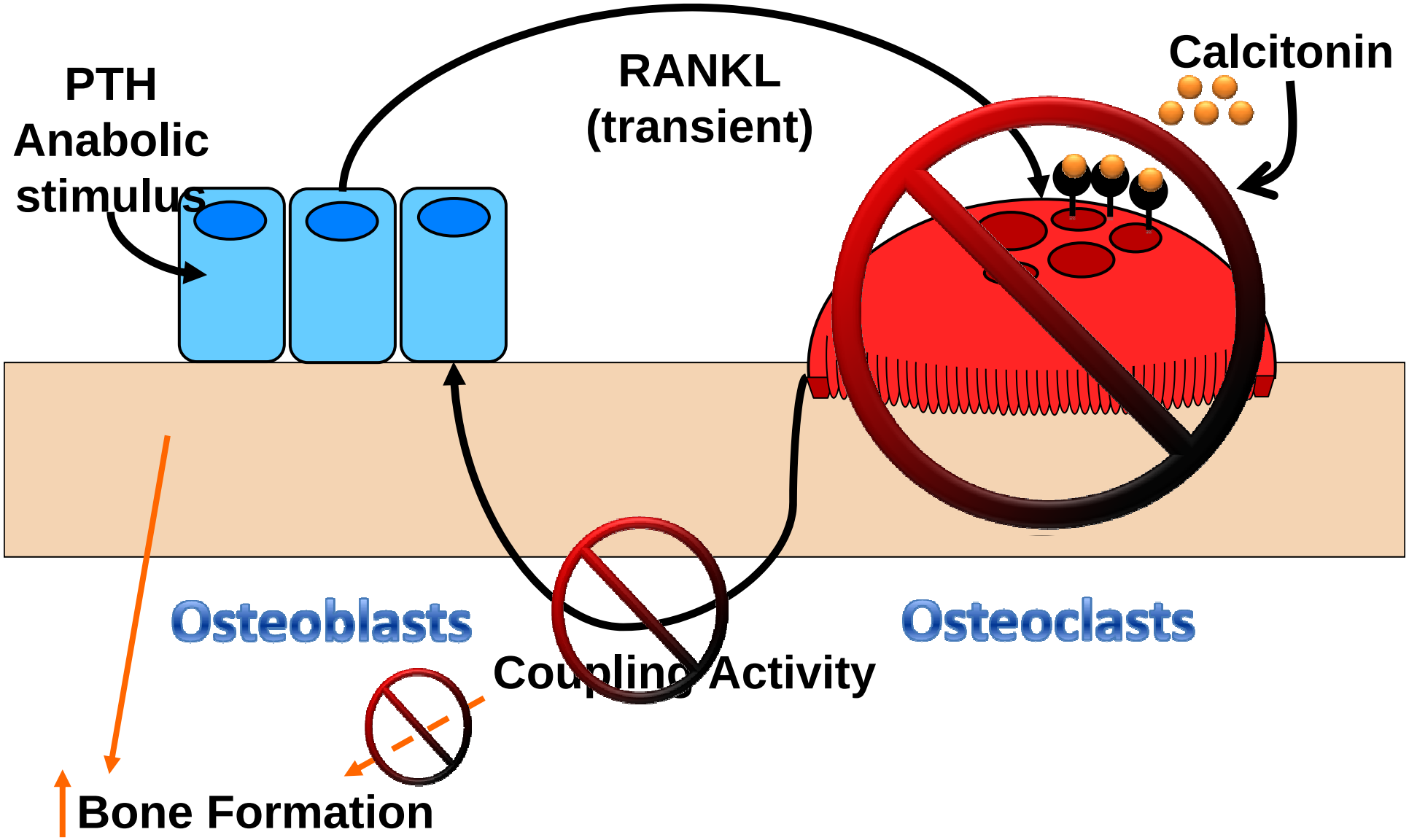
# Is the osteoclast an integral mediator of the anabolic actions of PTH?



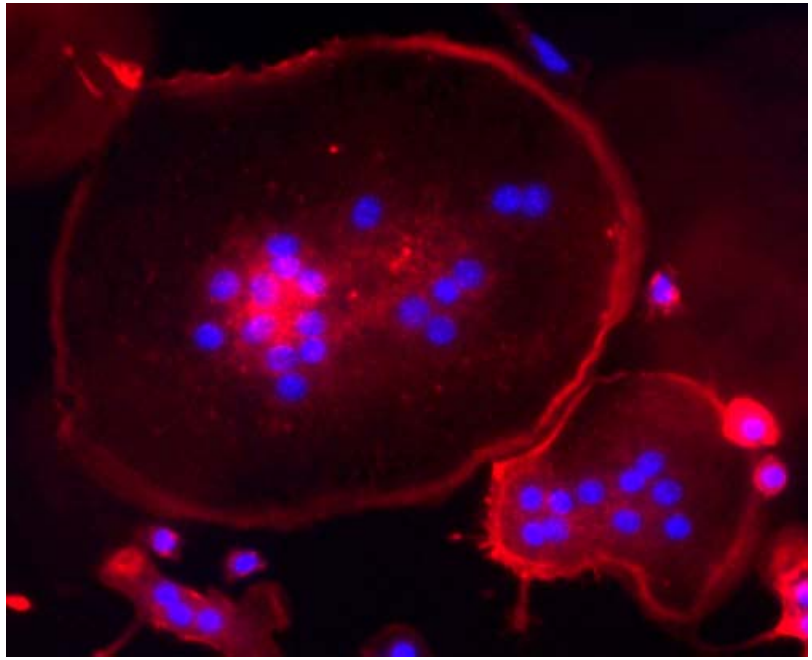

**Altering SDF-1, OPG, or c-fos but not c-src inhibited the anabolic action of PTH**

*Courtesy of L. McCauley*

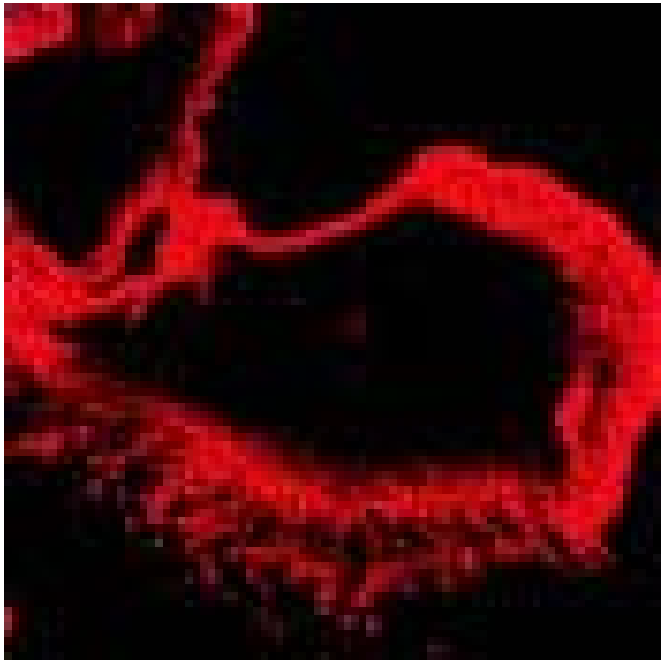
# Does transient osteoclast inhibition reduce the anabolic action of PTH?



# Calcitonin is a transient inhibitor of osteoclast activity



Osteoclast

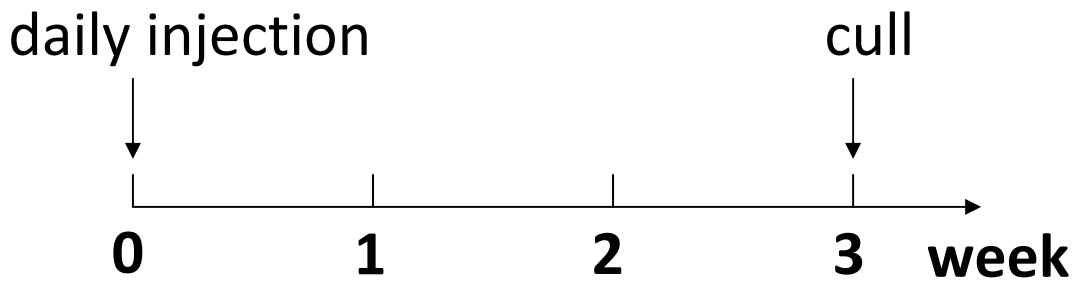


Osteoclast + Calcitonin

# Does calcitonin modify the bone-building effects of PTH?

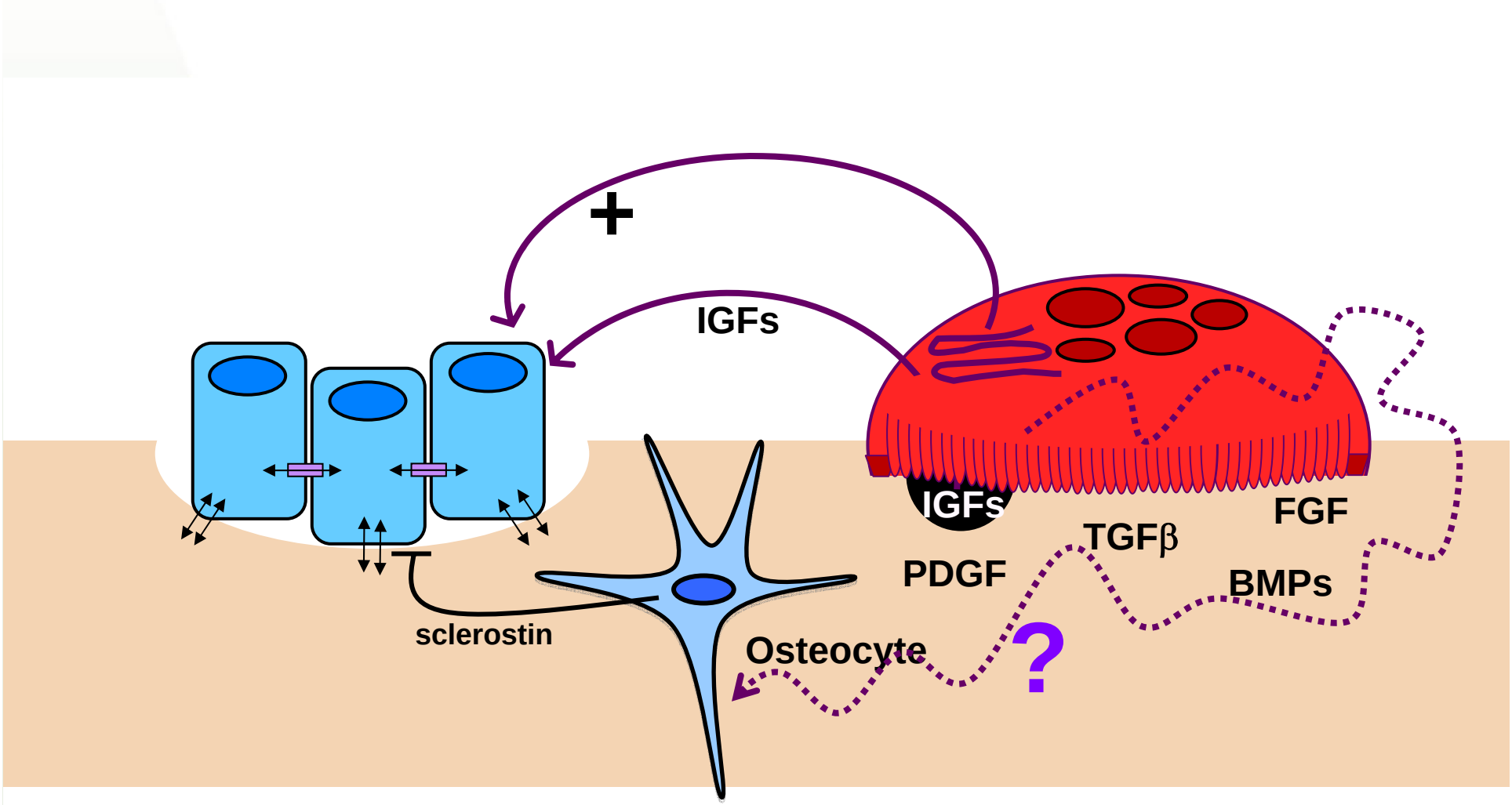
**Combine CT blockade of osteoclast activation with daily PTH treatment over 3 weeks.**

- **Vehicle**
- **PTH alone (30μg/kg)**
- **CT alone (0.5μg/kg)**
- **PTH + CT simultaneously**



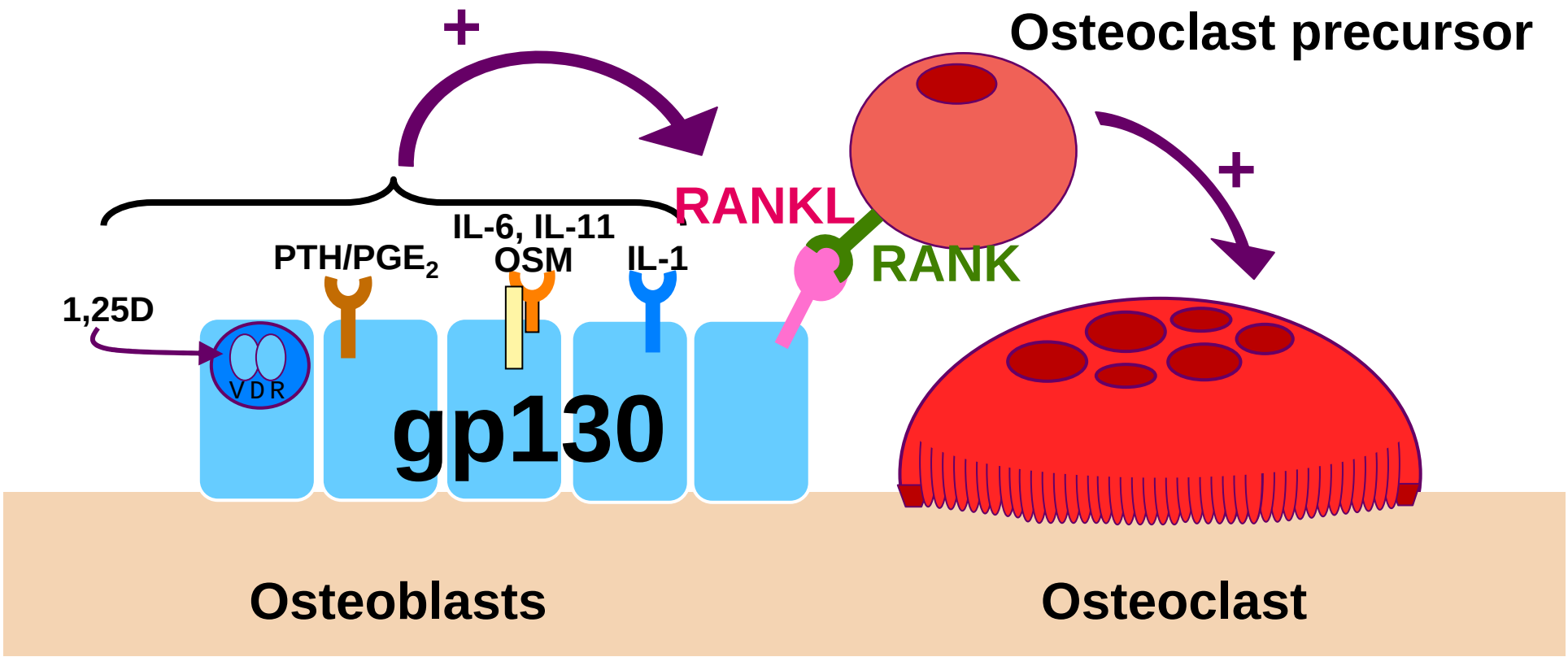
Unpublished data slide removed

# Signals from the osteoclast to the osteocyte



# Finding osteoclast derived factors that influence osteoblasts and osteocytes….

# gp130 plays a critical role in intercellular communication in bone

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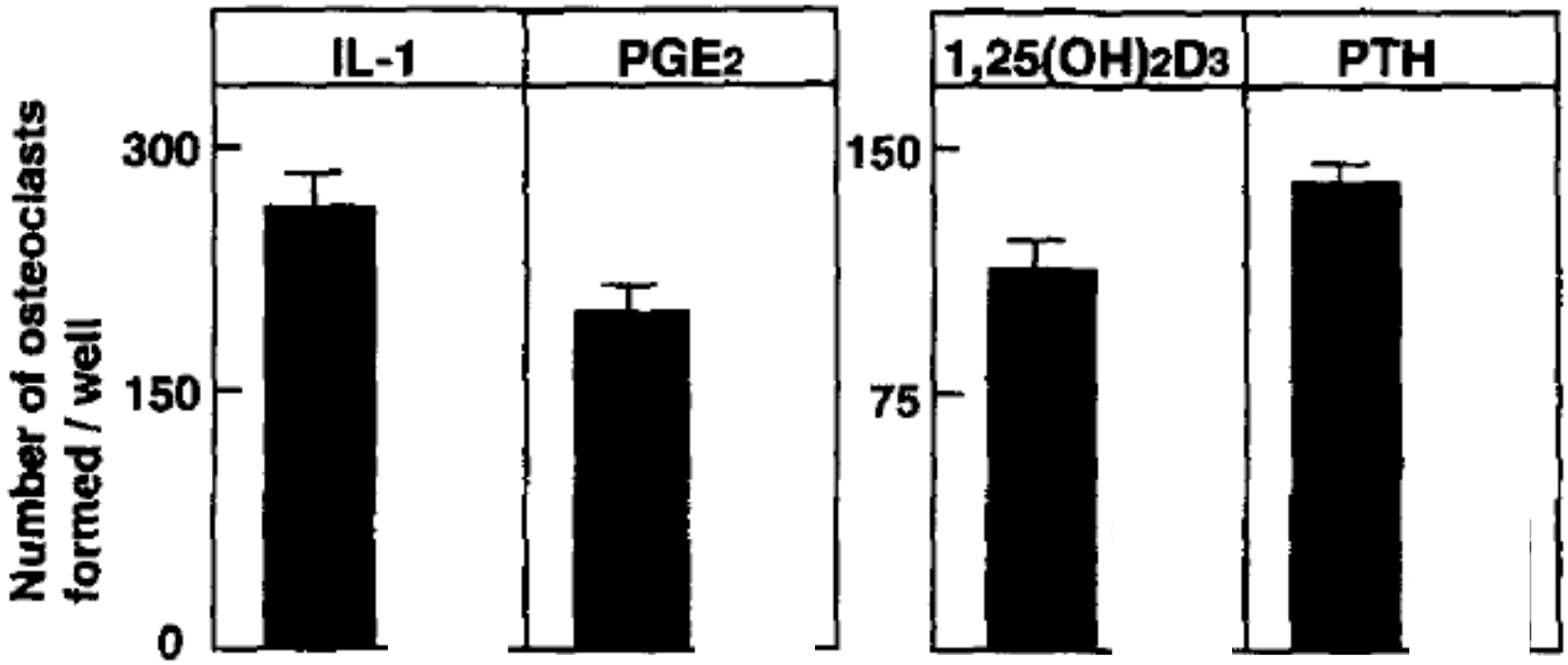
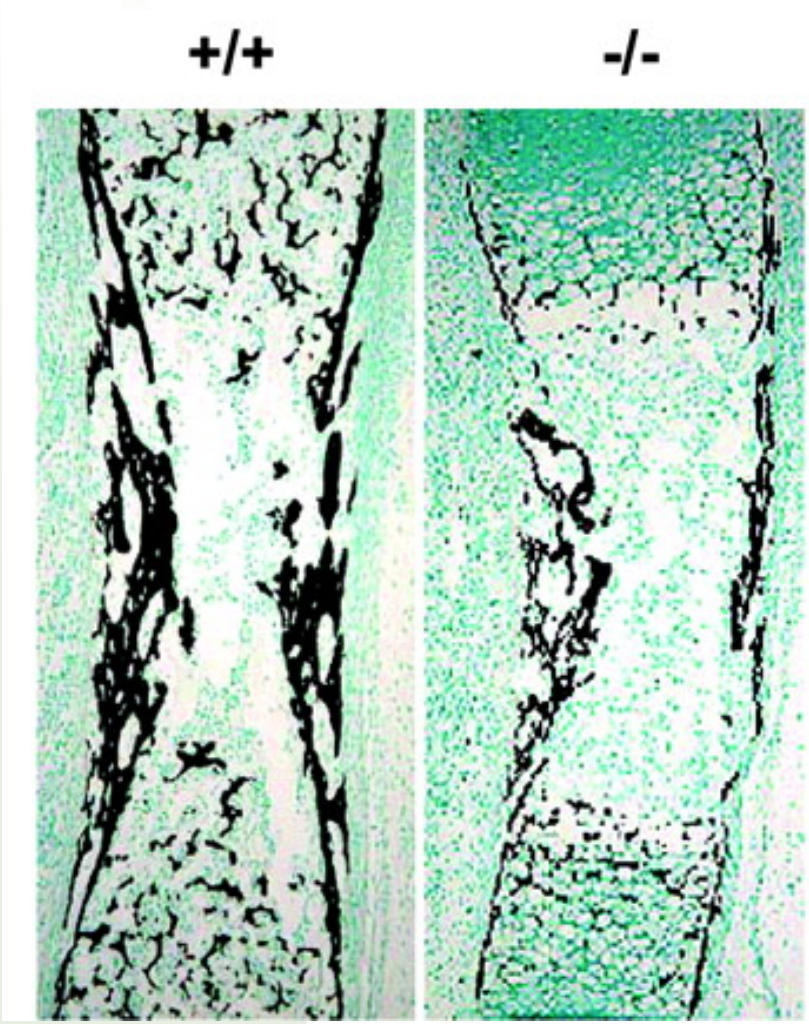
# gp130 mediates osteoclast formation in response to:




*(Romas JEM 1996)*

# gp130 knockout: low bone mass




Neonatal lethal

- Many large osteoclasts
- Few osteoblasts

Coupling disrupted!

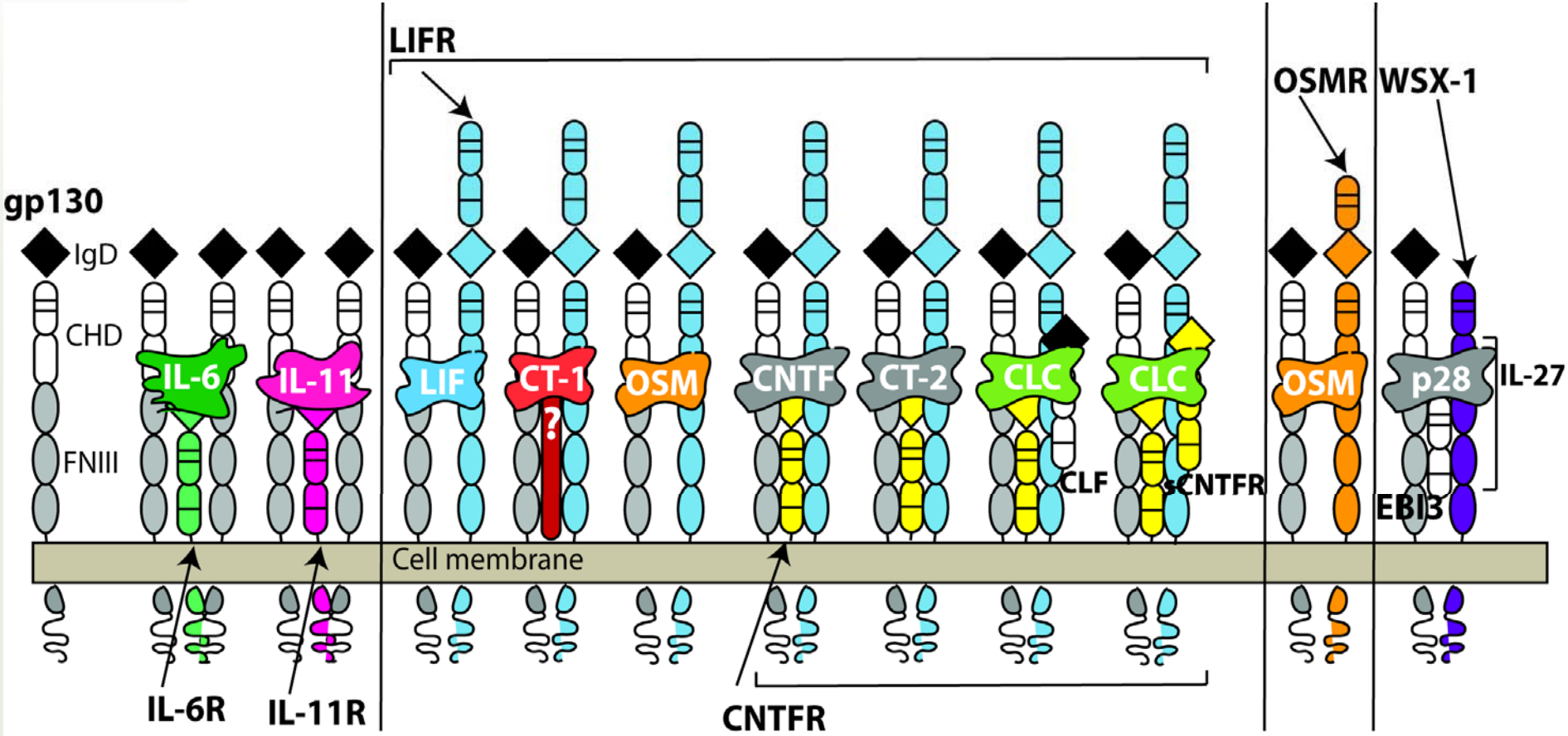
Balance shifted in favour of resorption - bone mass reduced

Almost identical phenotype observed in LIFR KO (Ware 1995)



*Shin et al, Endocrinology 145:1376-1385, 2004*

# gp130-signalling cytokines



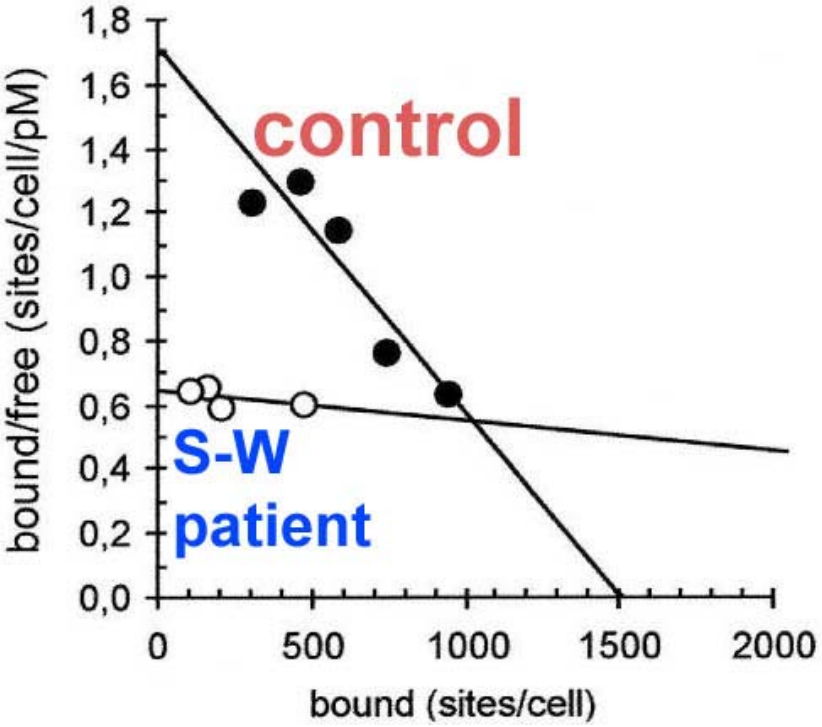



*(Sims, Molecular and Cellular Endocrinology, In Press)*

# Human LIFR mutation - Stüve-Wiedemann / Schwartz-Jampel Type 2 Syndrome

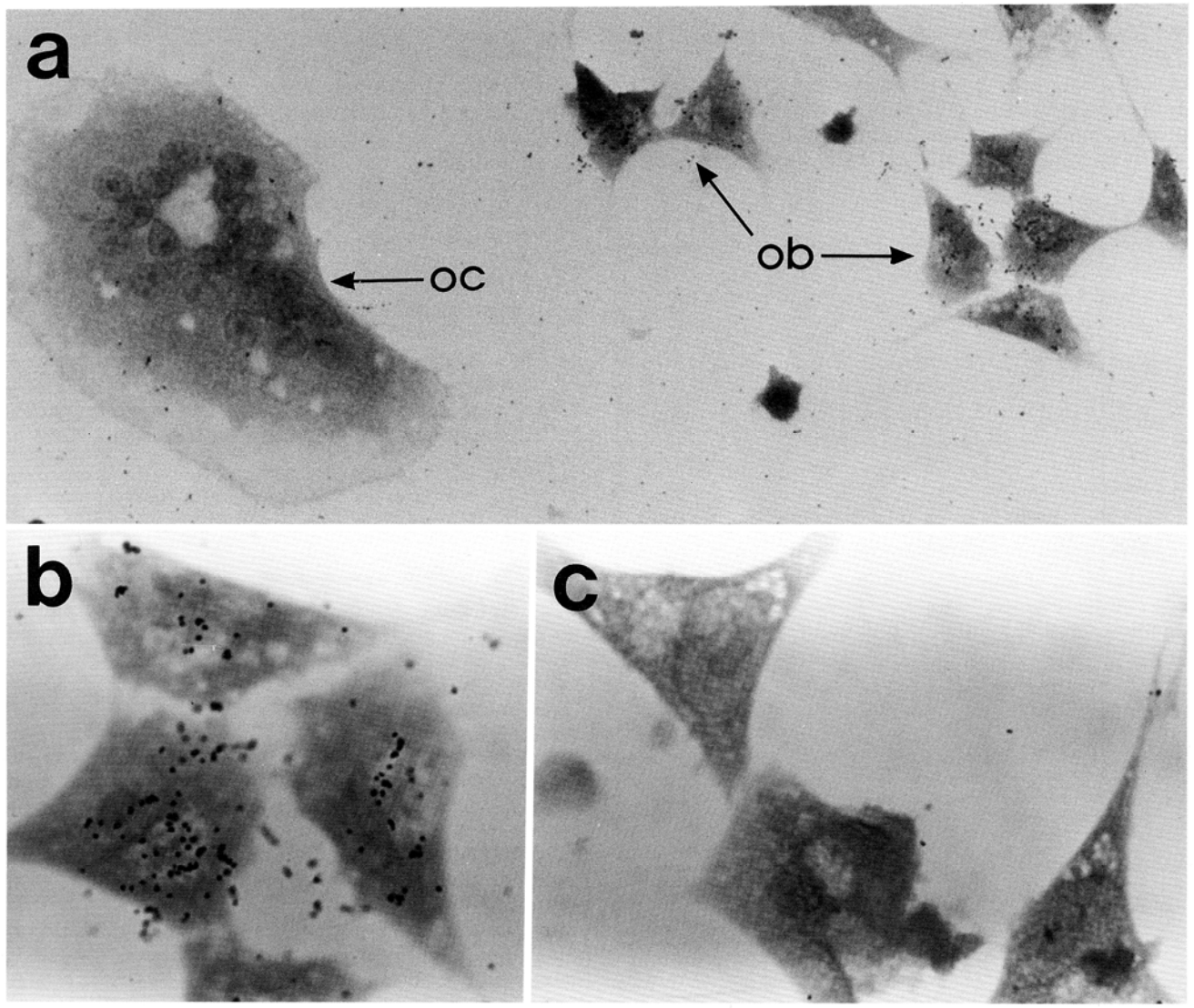
**Bent-bone dysplasia** - death within the first few months of life - respiratory / swallowing difficulties, hyperthermic episodes

**Mild forms** - longer lifespan, progressive scoliosis, spontaneous fractures, flared joints, abnormal trabecular bone




*(Dagoneau et al, Am J Hum Gen 2004)*

# LIFR expression in osteoblasts

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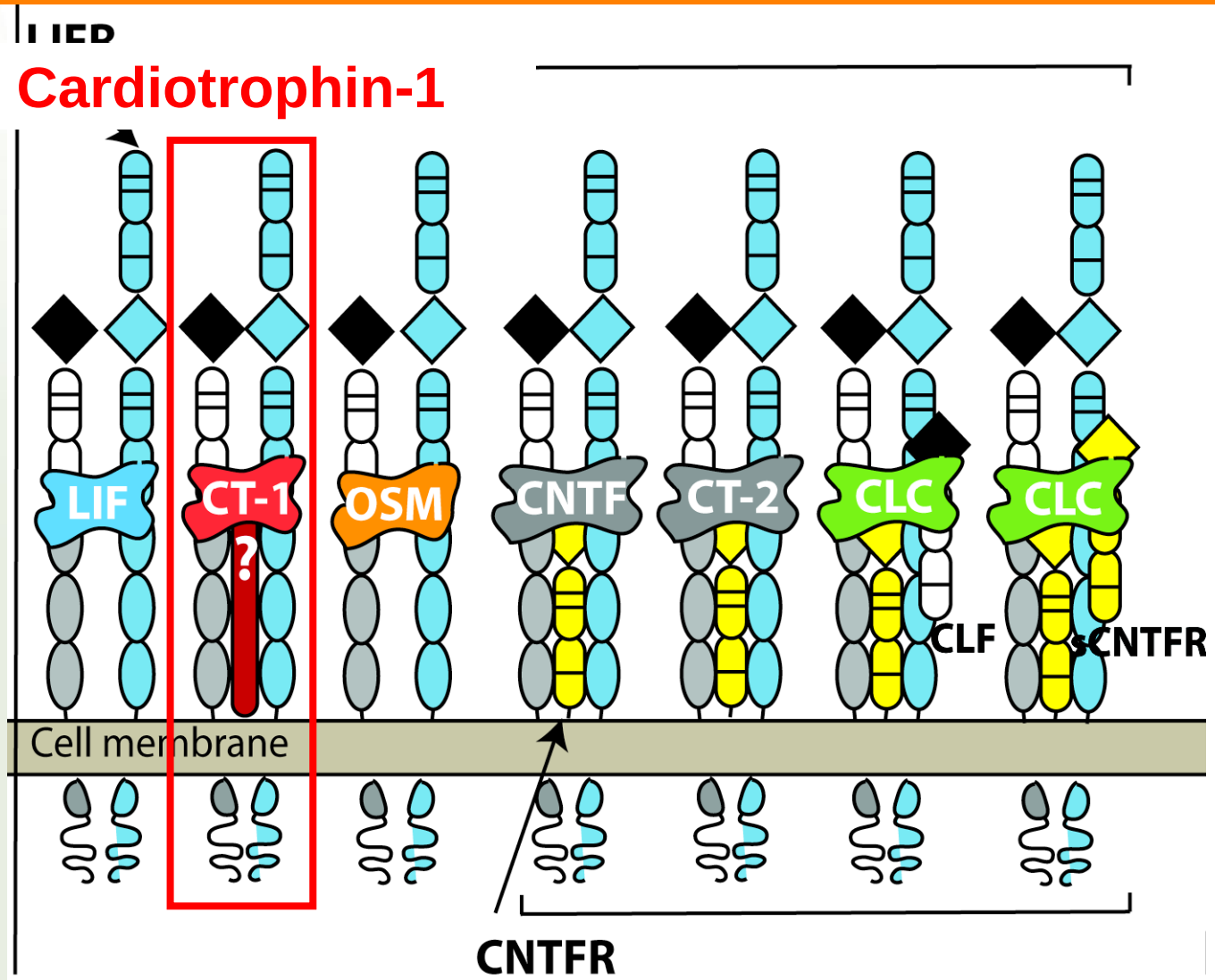
*(Allan J Cell Physiol 1990)*

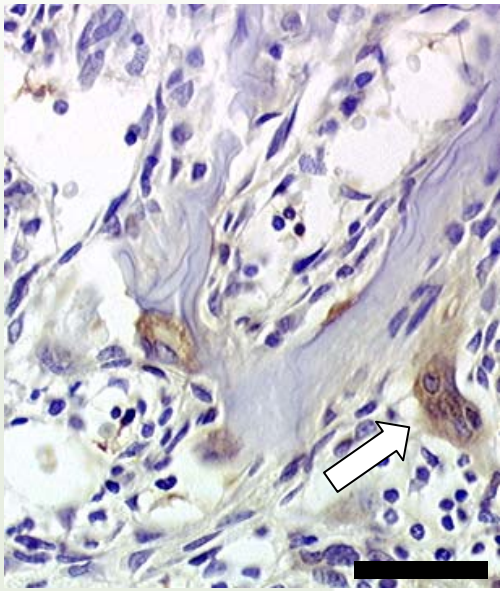
# gp130:LIFR-signalling cytokines



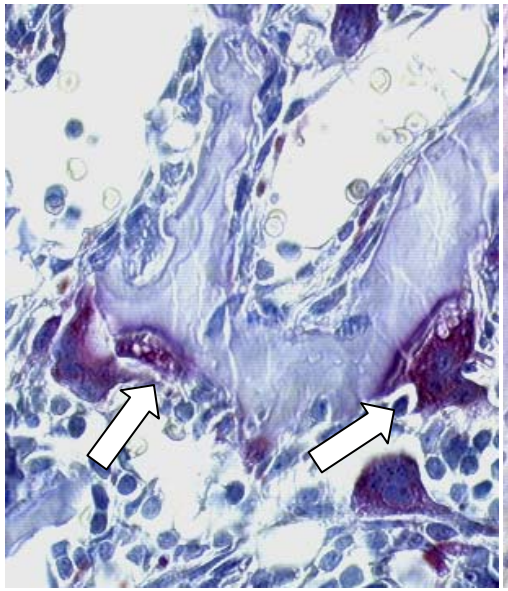



*(Sims, Molecular and Cellular Endocrinology, In Press)*

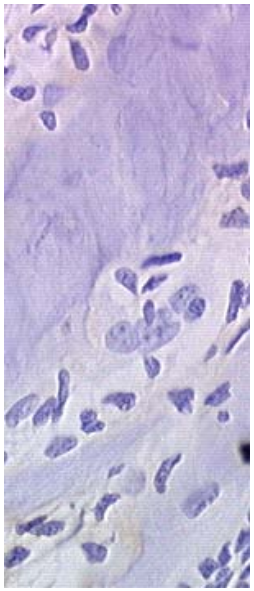
# CT-1 is expressed by osteoclasts

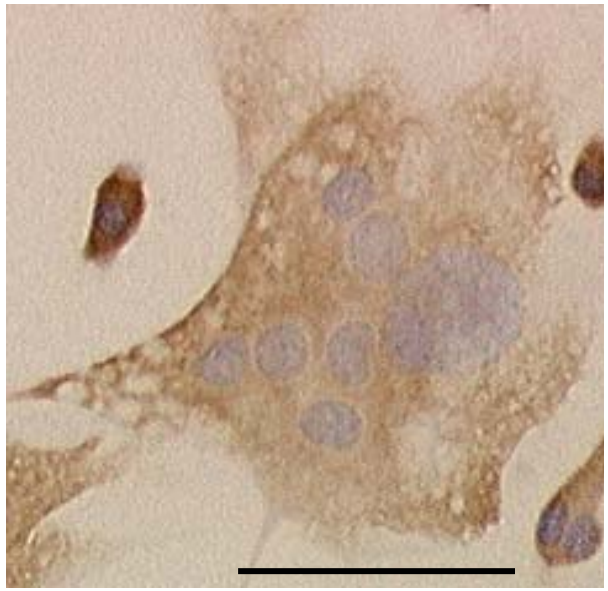


CT-1 in bone



TRAP
(OC marker)



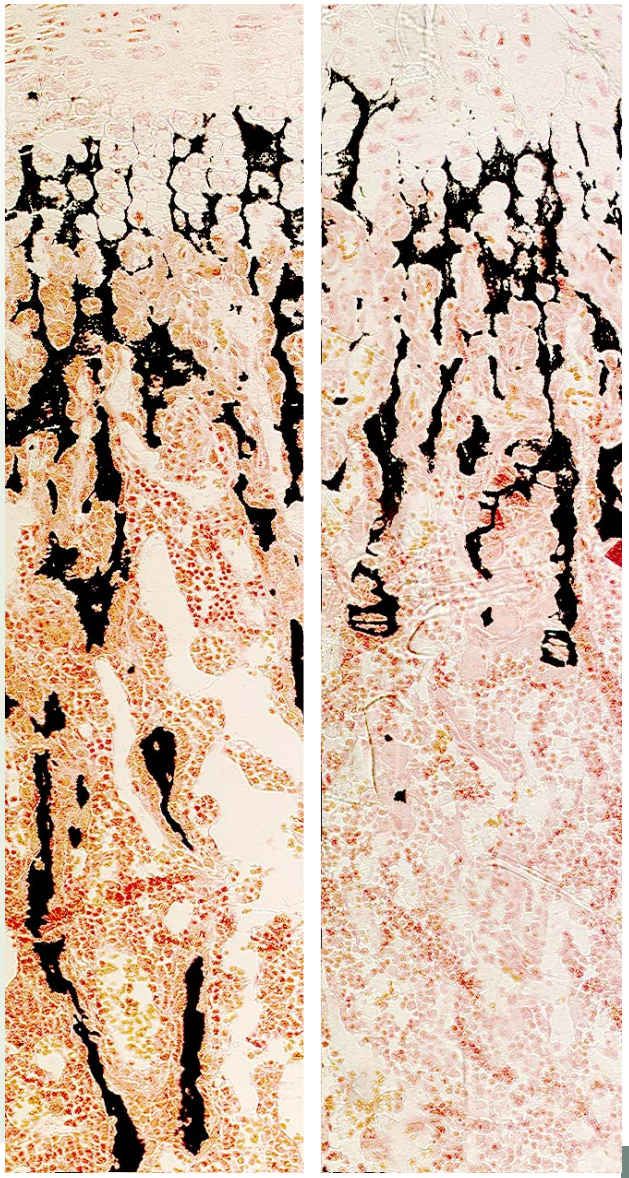


CT-1 in cultured OC

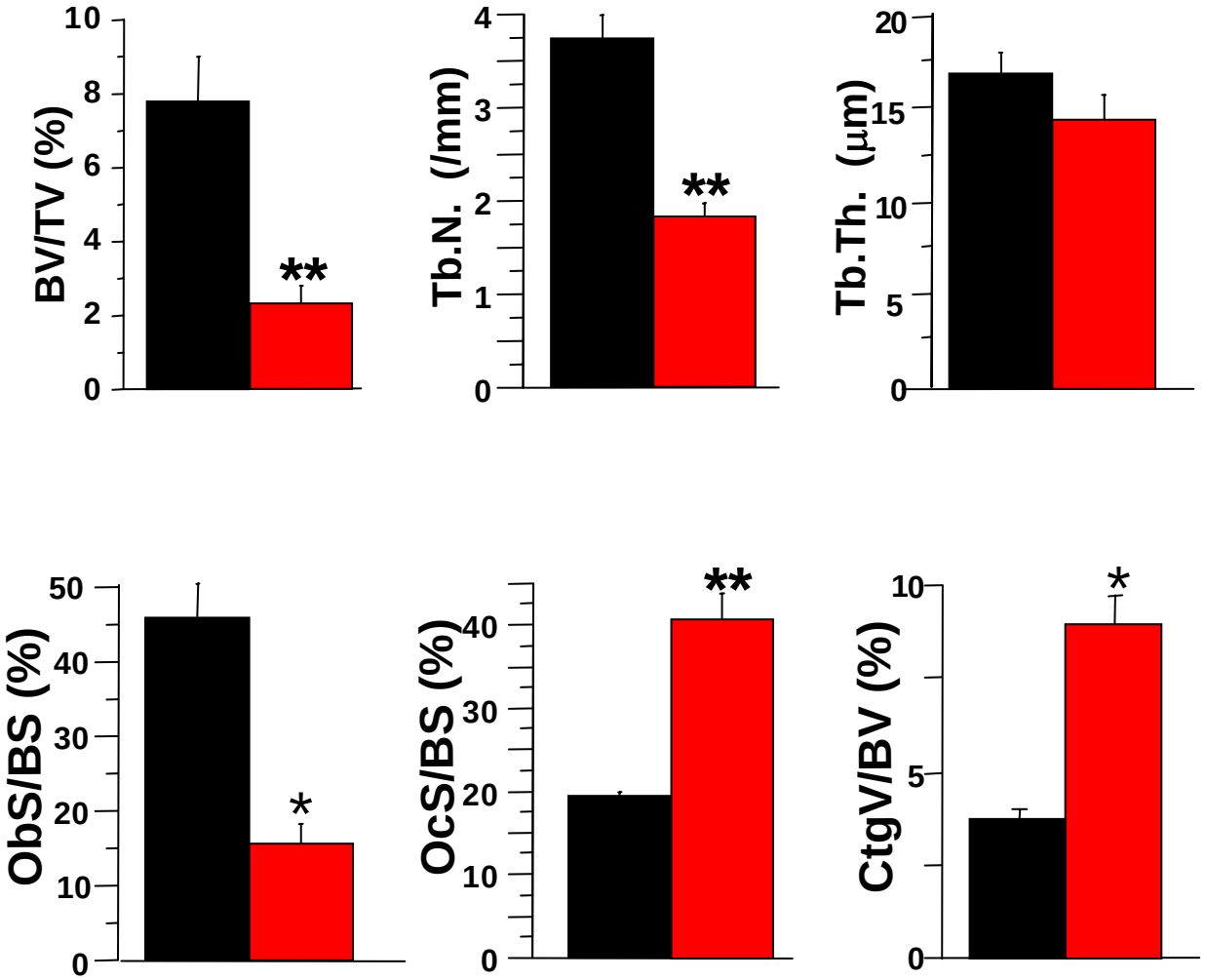


*Walker JBMR 2008*

# CT-1 KO phenotype (4 days)

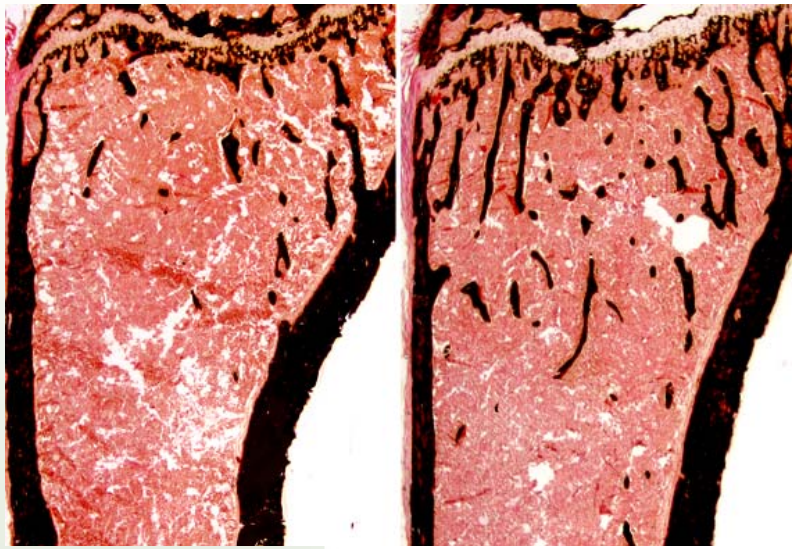


wild type CT-1 KO

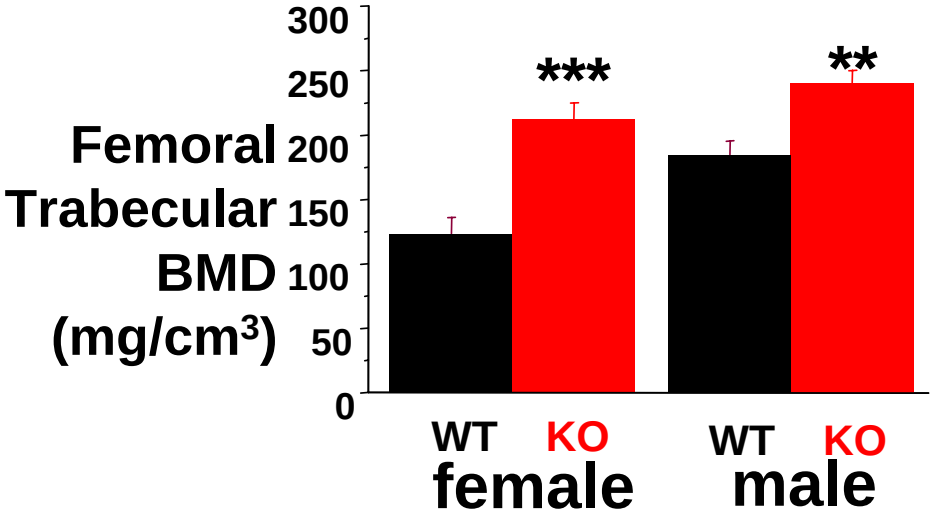


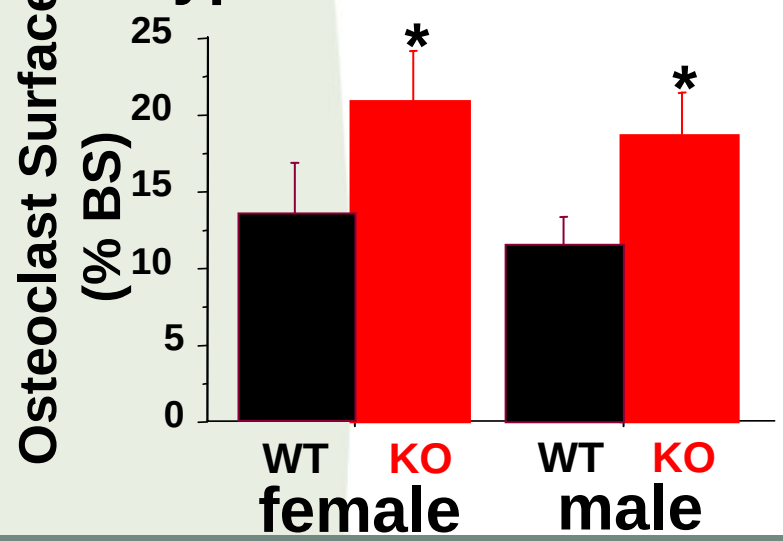

*Walker JBMR 2008*

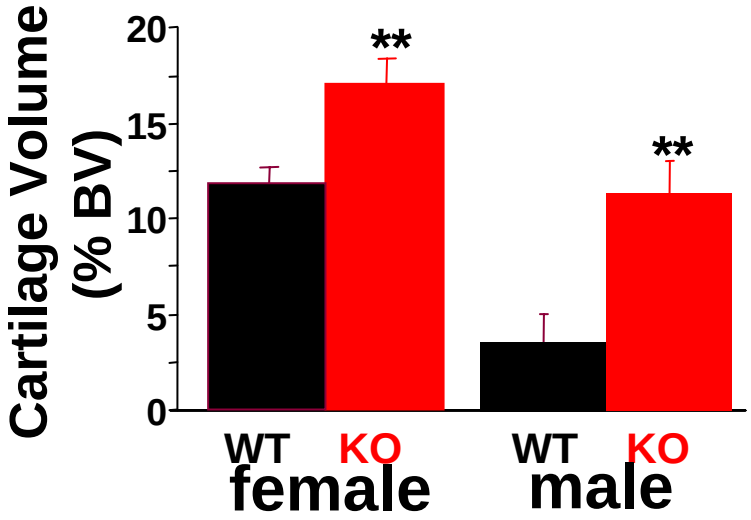
# CT-1 KO phenotype (adult)



wild type CT-1 KO

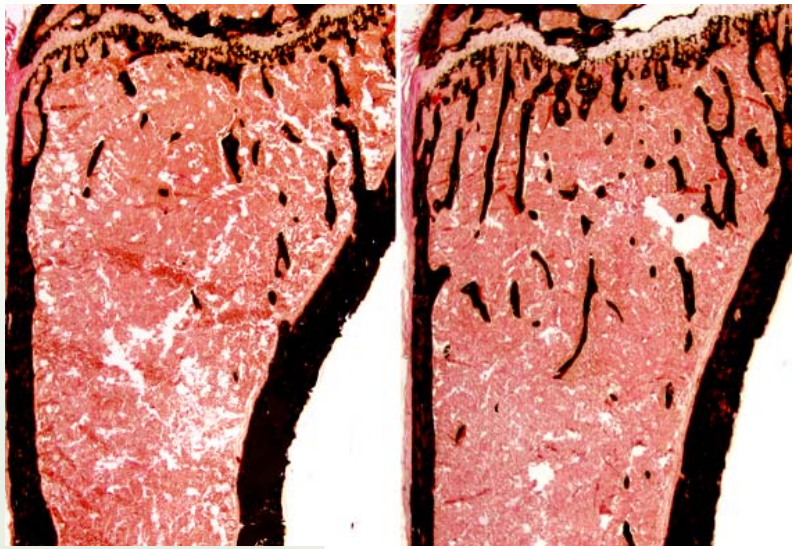


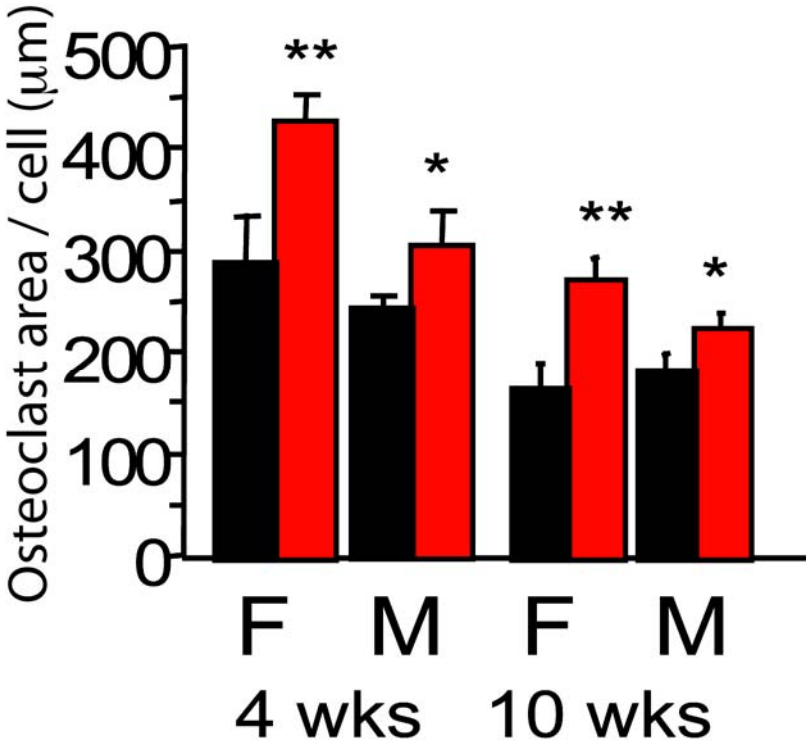




*, p<0.05; **, p<0.01; ***, p<0.001 vs wild type
Walker JBMR 2008

# CT-1 KO phenotype (adult)

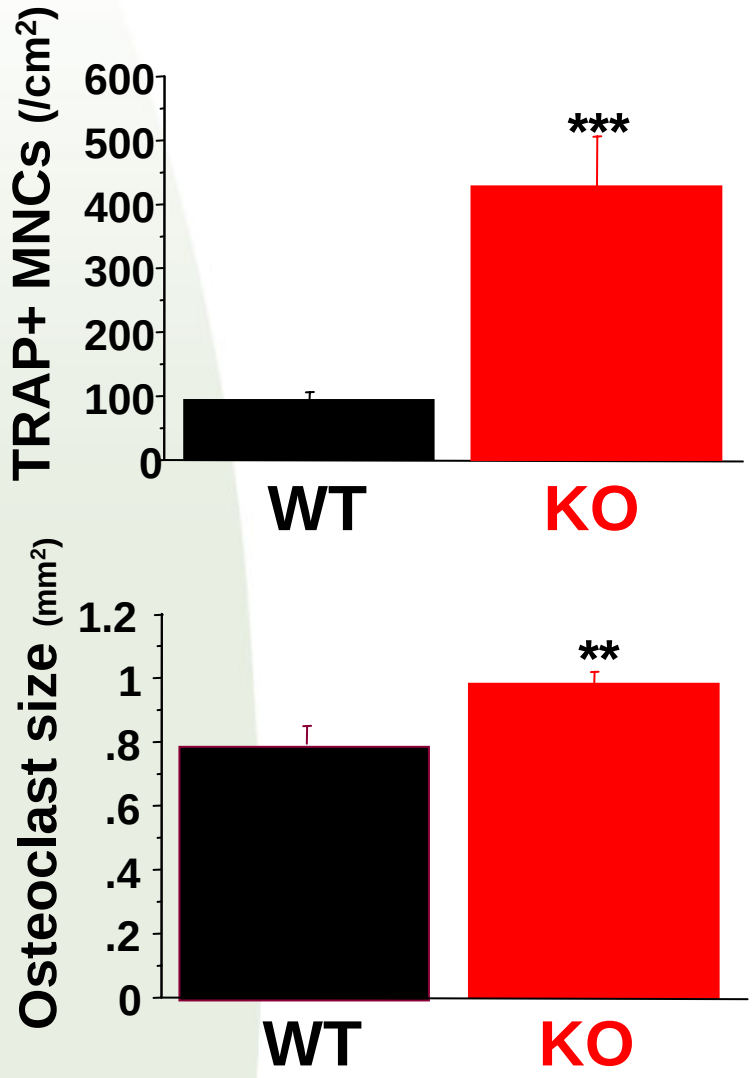


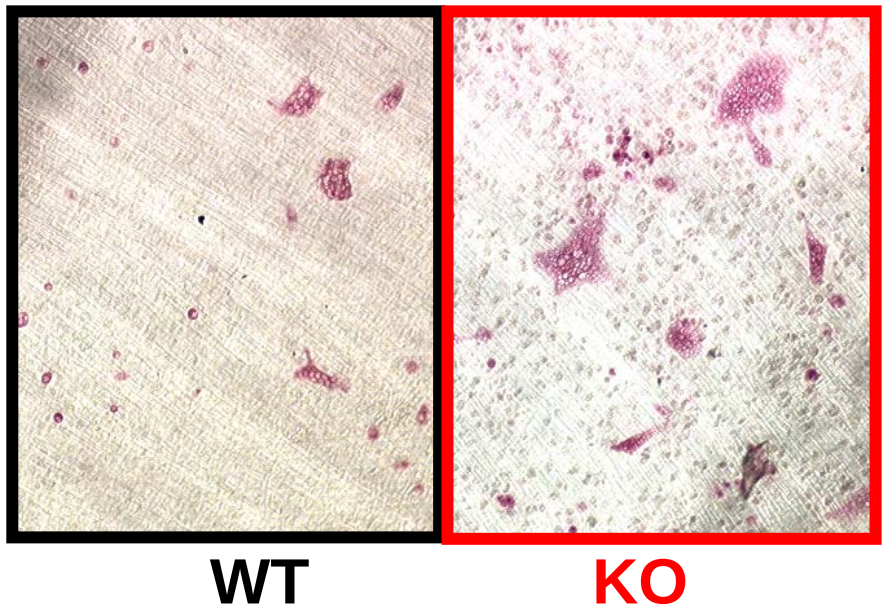
wild type CT-1 KO




*, p<0.05; **, p<0.01; ***, p<0.001 vs wild type
Walker JBMR 2008

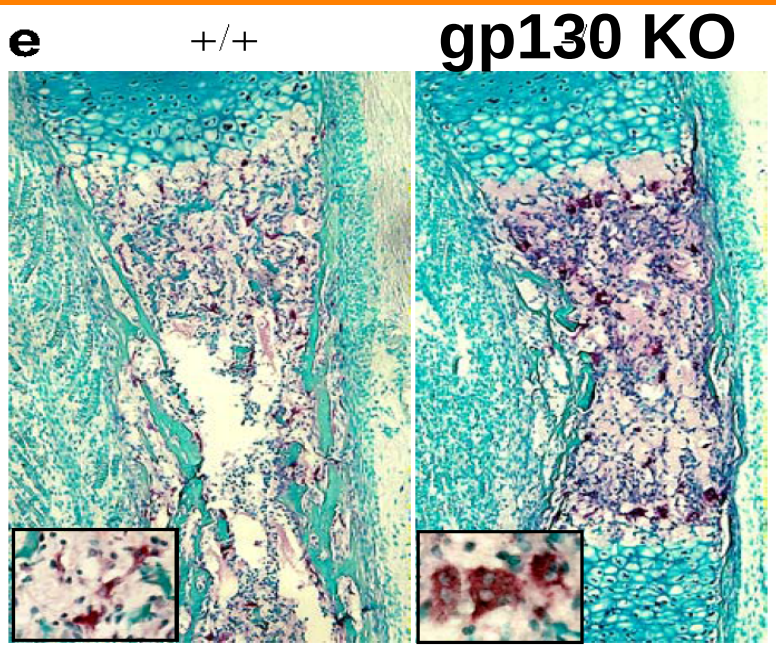
# Many large osteoclasts from CT-1 KO BMM+RANKL

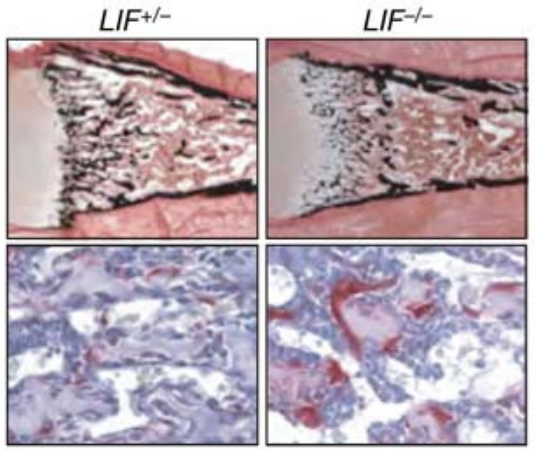


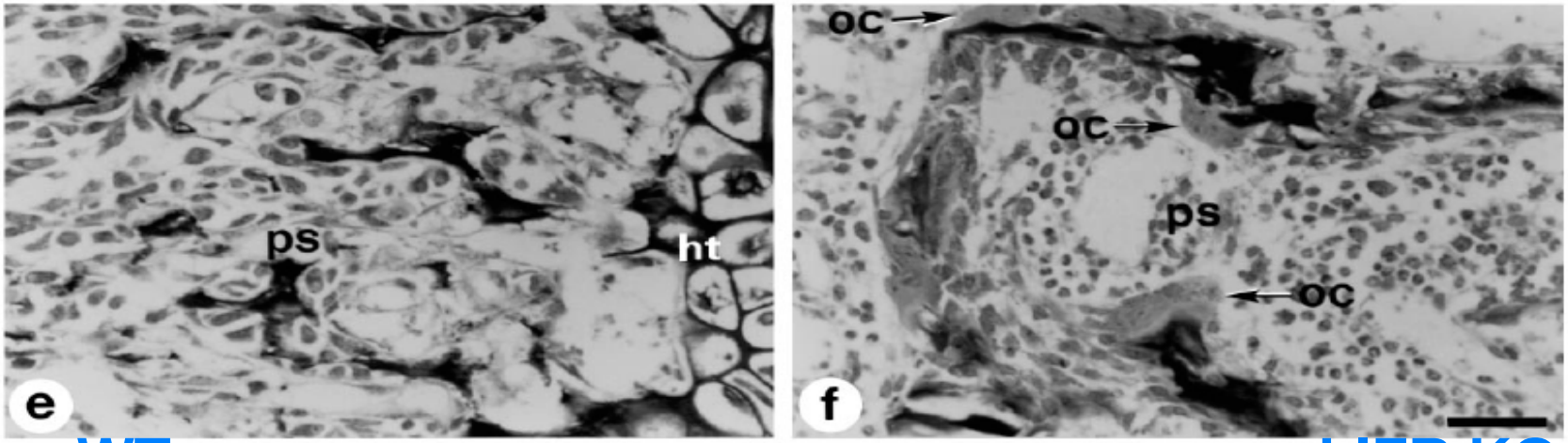

*Bone marrow + RANKL/M-CSF, males only*
*7 day cultures; **, p=0.01 vs wild type*
*Data from >/=4 wells each of 4 expts*

# Large osteoclast phenotype in gp130 KOs




**But LIFR not in osteoclasts!**




WT

LIFR KO

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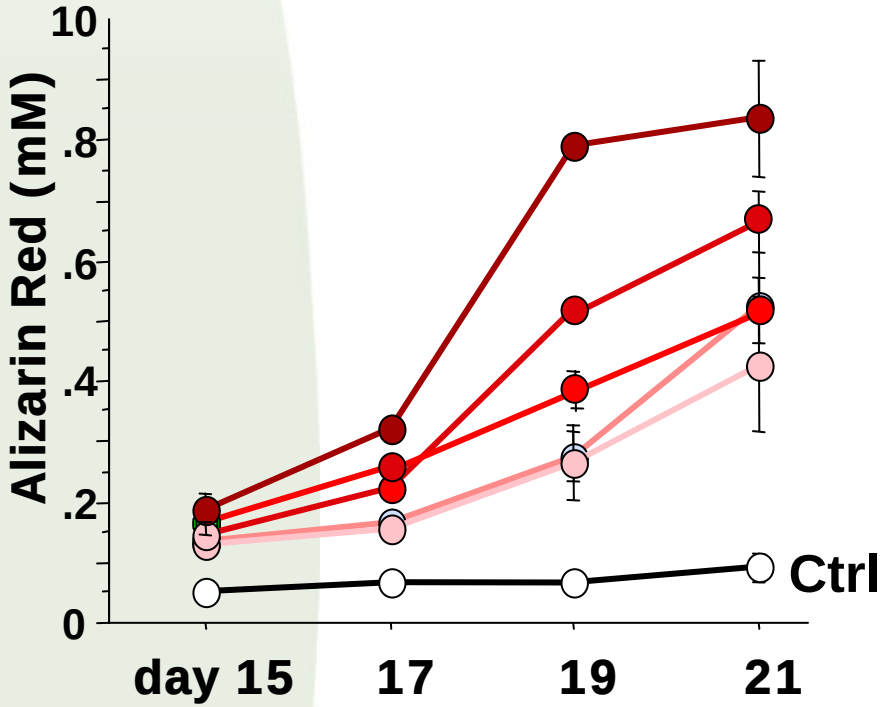
*(Ware 1995, Shin, Endocrinology 2004; Bozec, Nature 2008)*

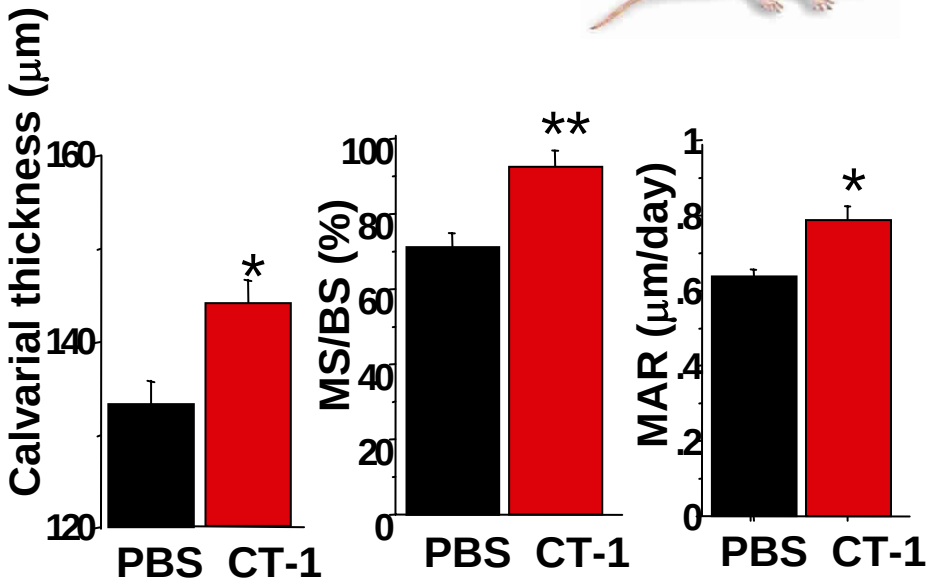
# CT-1 stimulates mineralisation *in vitro* and *in vivo*

0 0.6 1.25 2.5 5 10

day19 CT-1



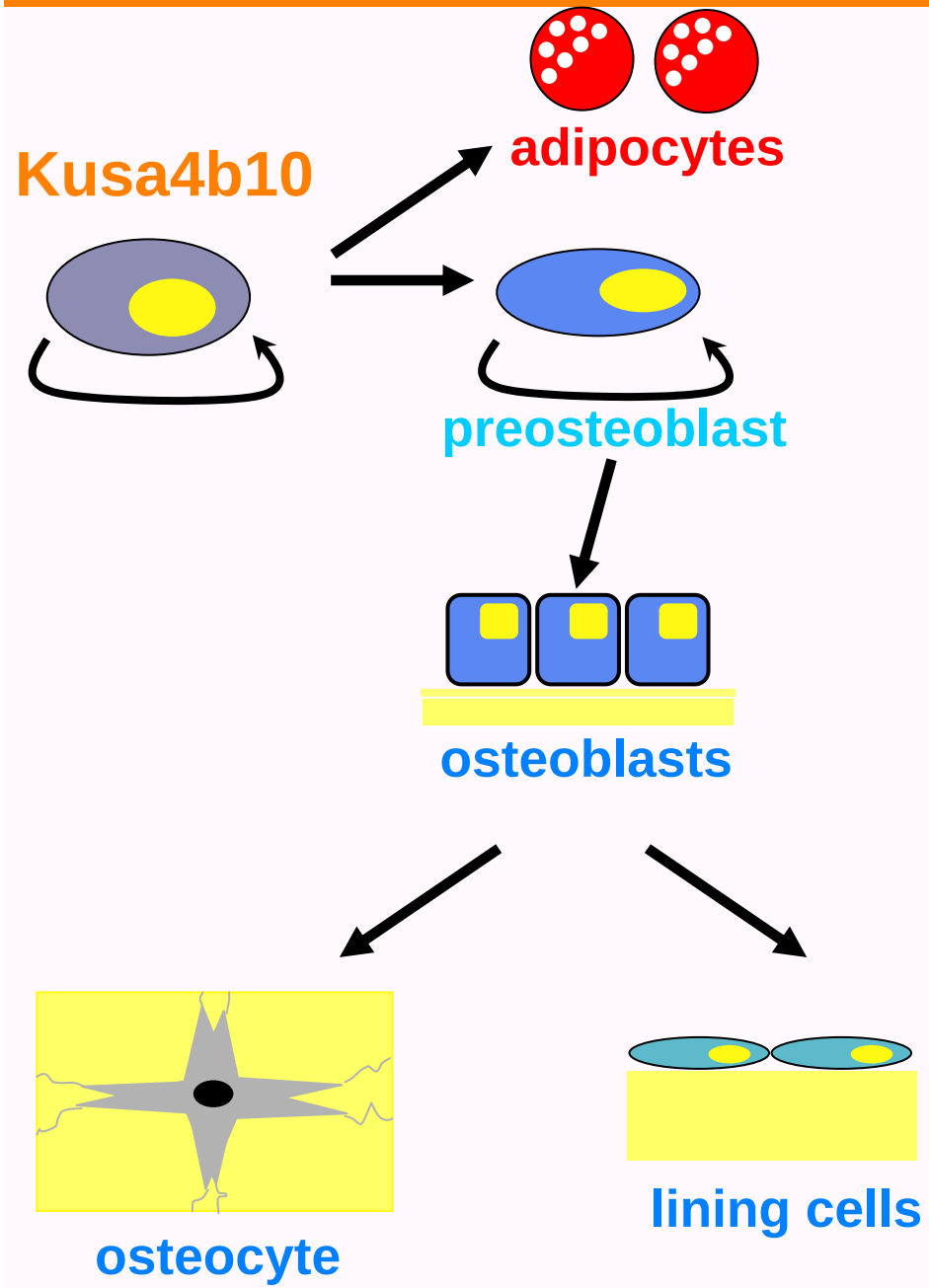

**5 days consecutive treatment**
**Fluorochrome labelled**
**Calvarial bone**

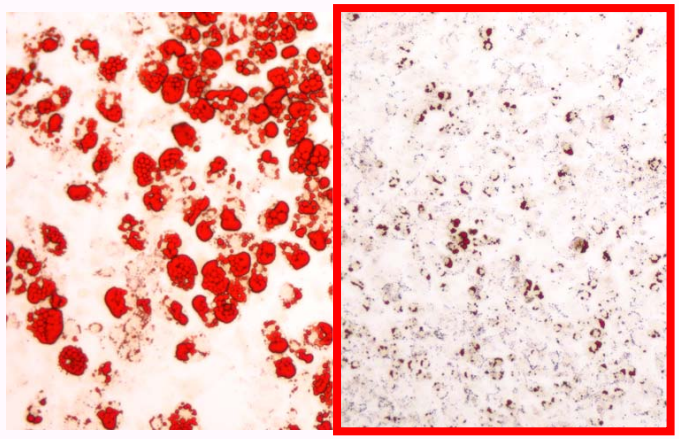


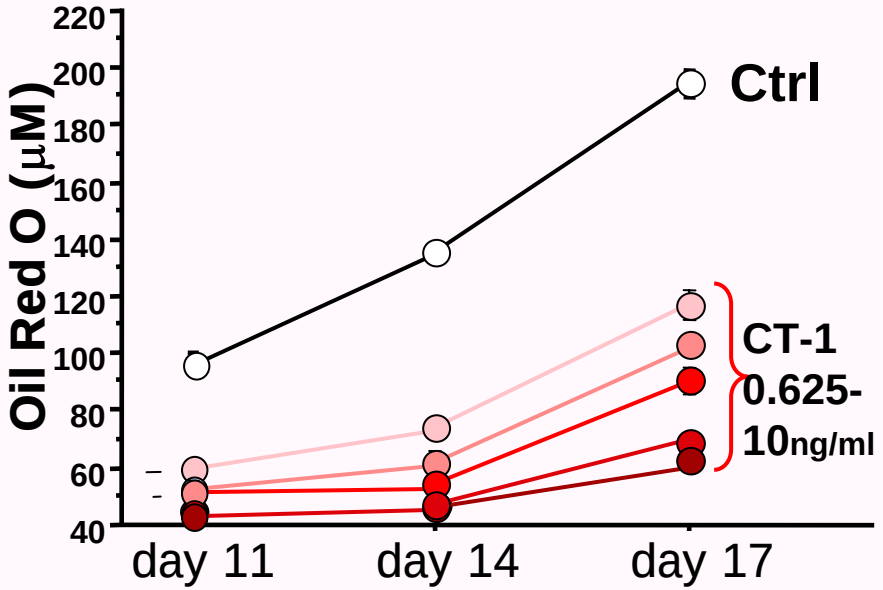

*Mean+SEM, n=3, all CT-1-treated sig>ctrl, p<0.05*

*Mean+SEM, n=6/group, *, p<0.05; **, p<0.01*
*Walker JBMR 2008*

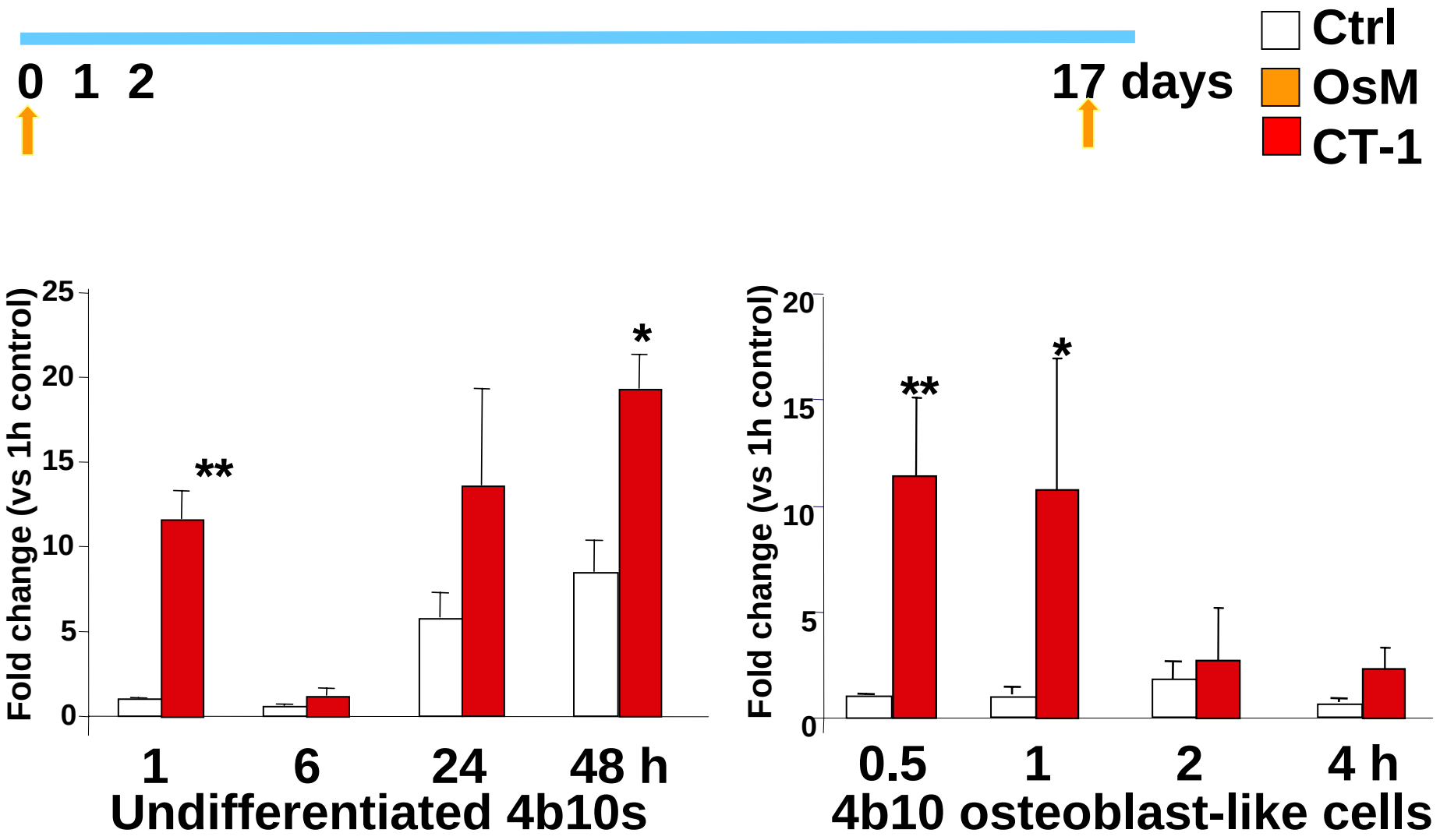
# CT-1 inhibits adipogenesis *in vitro*



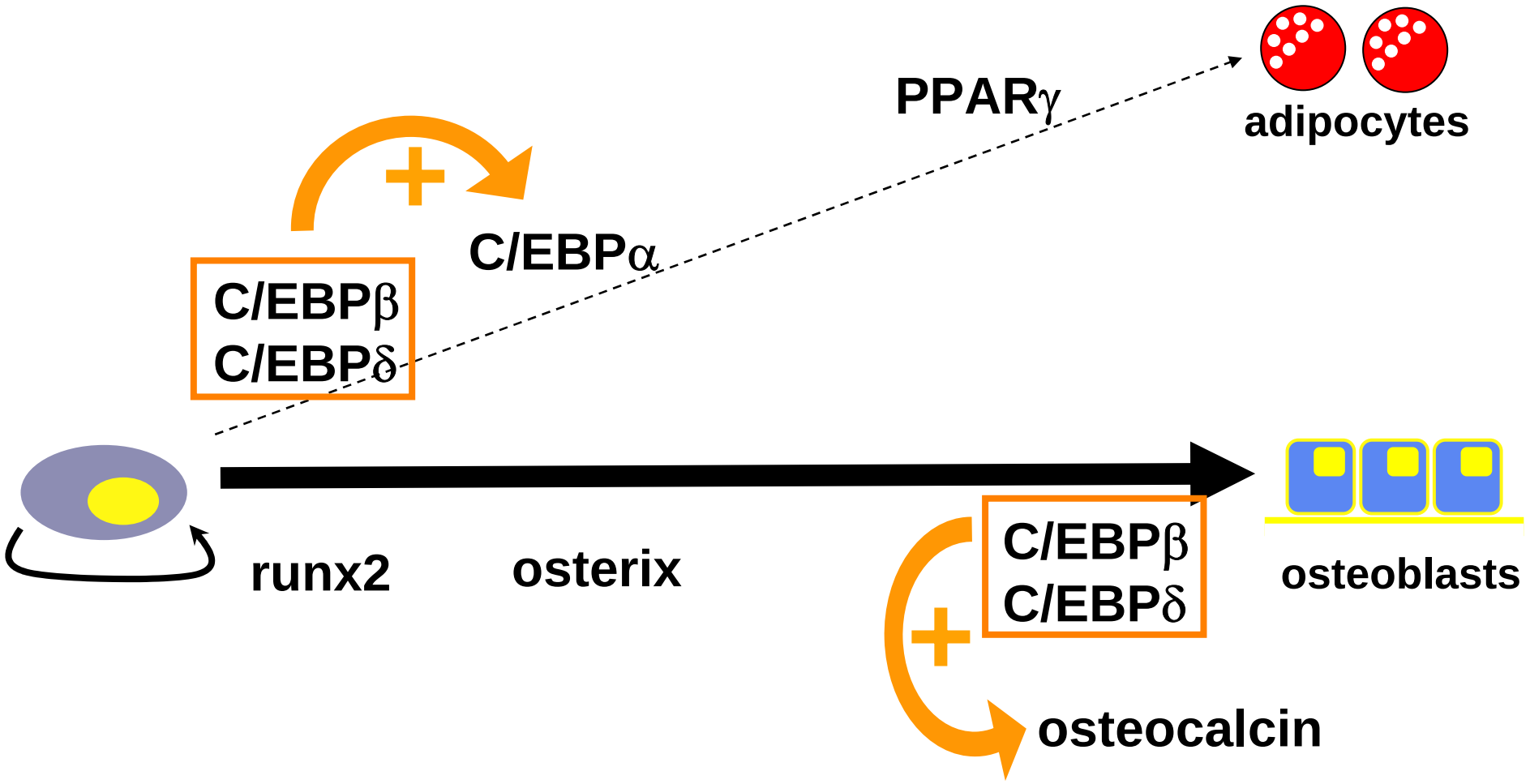



# CT-1 increases C/EBPδ expression in Kusa4b10 cells (qPCR)



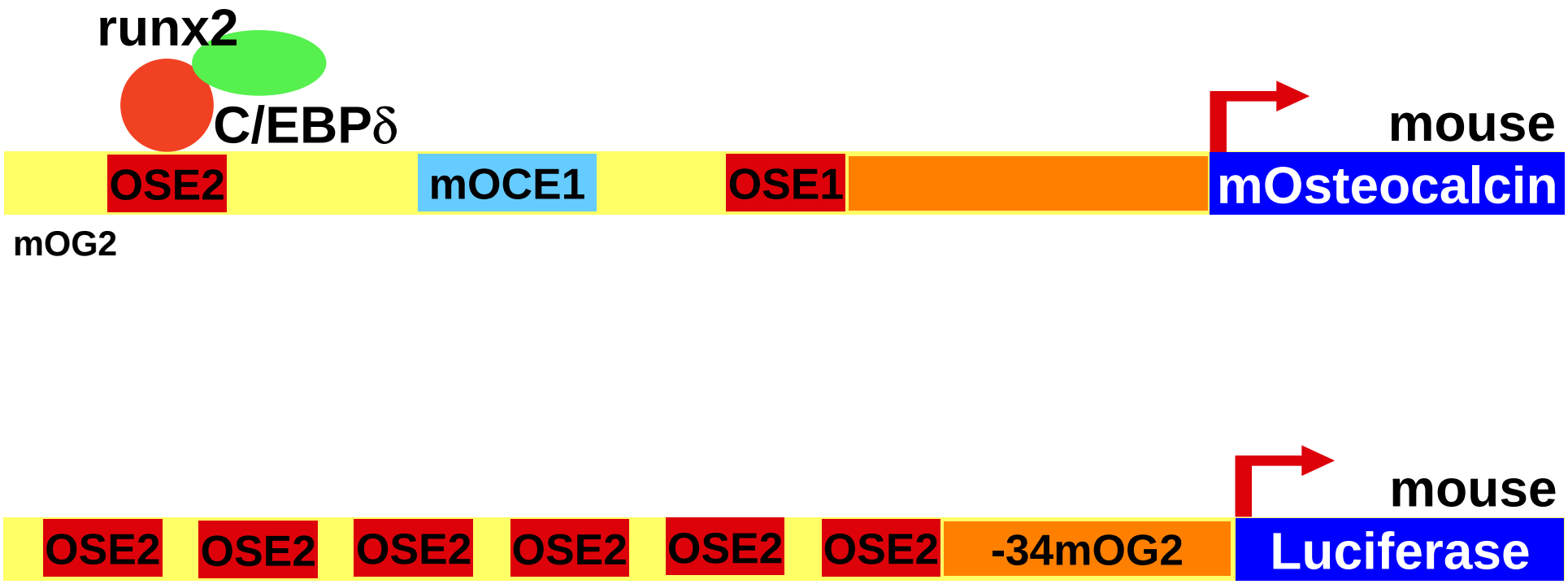

*N=3 independent experiments, *, p<0.05; ***, p<0.001*

# OsM stimulates osteoblast differentiation at the expense of adipogenesis



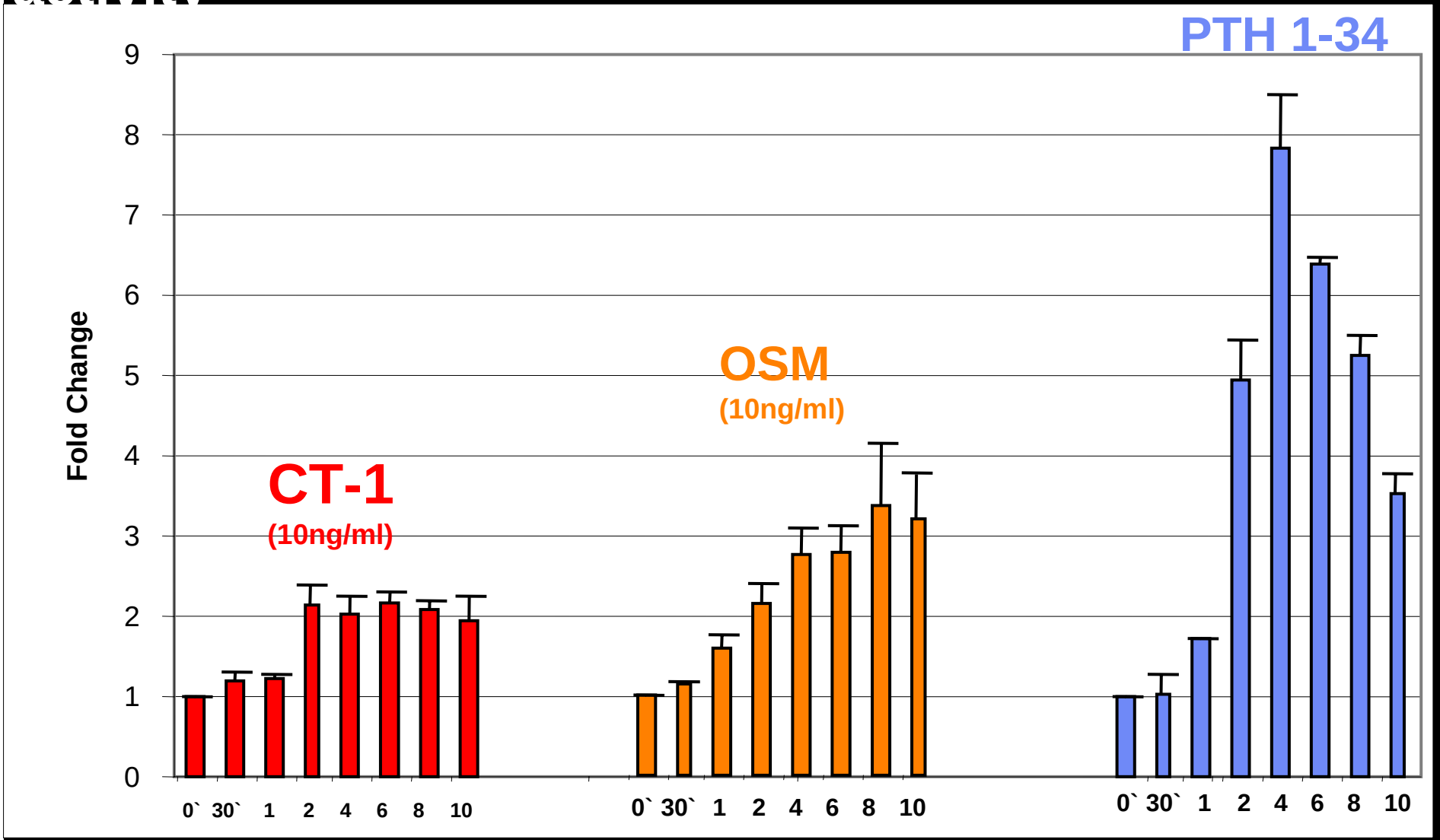

*Guiterrez 2002, Lane 1999*

# C/EBPδ activates osteocalcin transcription




*Ducy MCB 1995; Shin J Mol Endocrinol 2006*

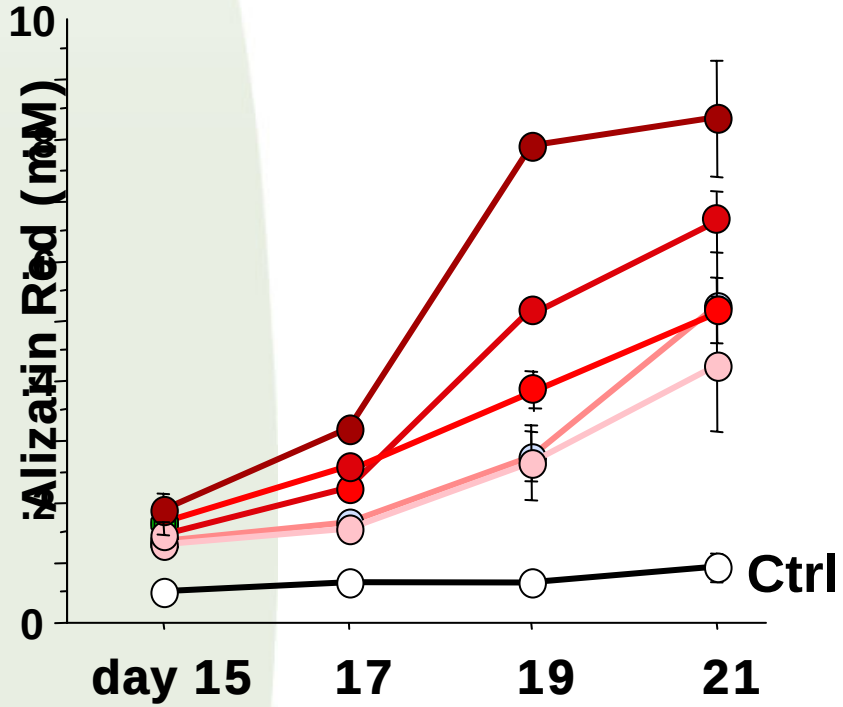
# CT-1 and OSM enhance osteocalcin promoter activity



# CT-1 stimulates mineralisation *in vitro* and *in vivo*

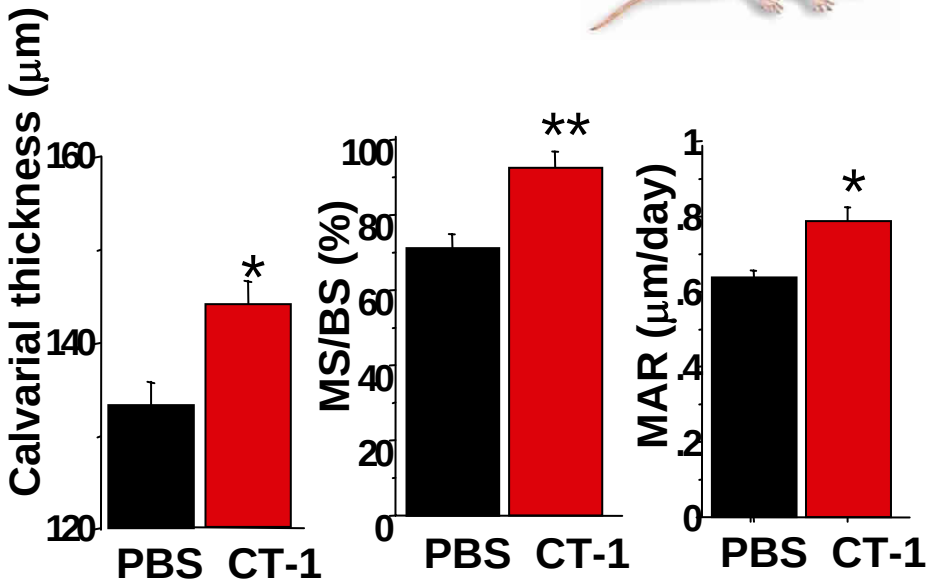
0 0.6 1.25 2.5 5 10

day19 CT-1




*Mean+SEM, n=3, all CT-1-treated sig>ctrl, p<0.05*

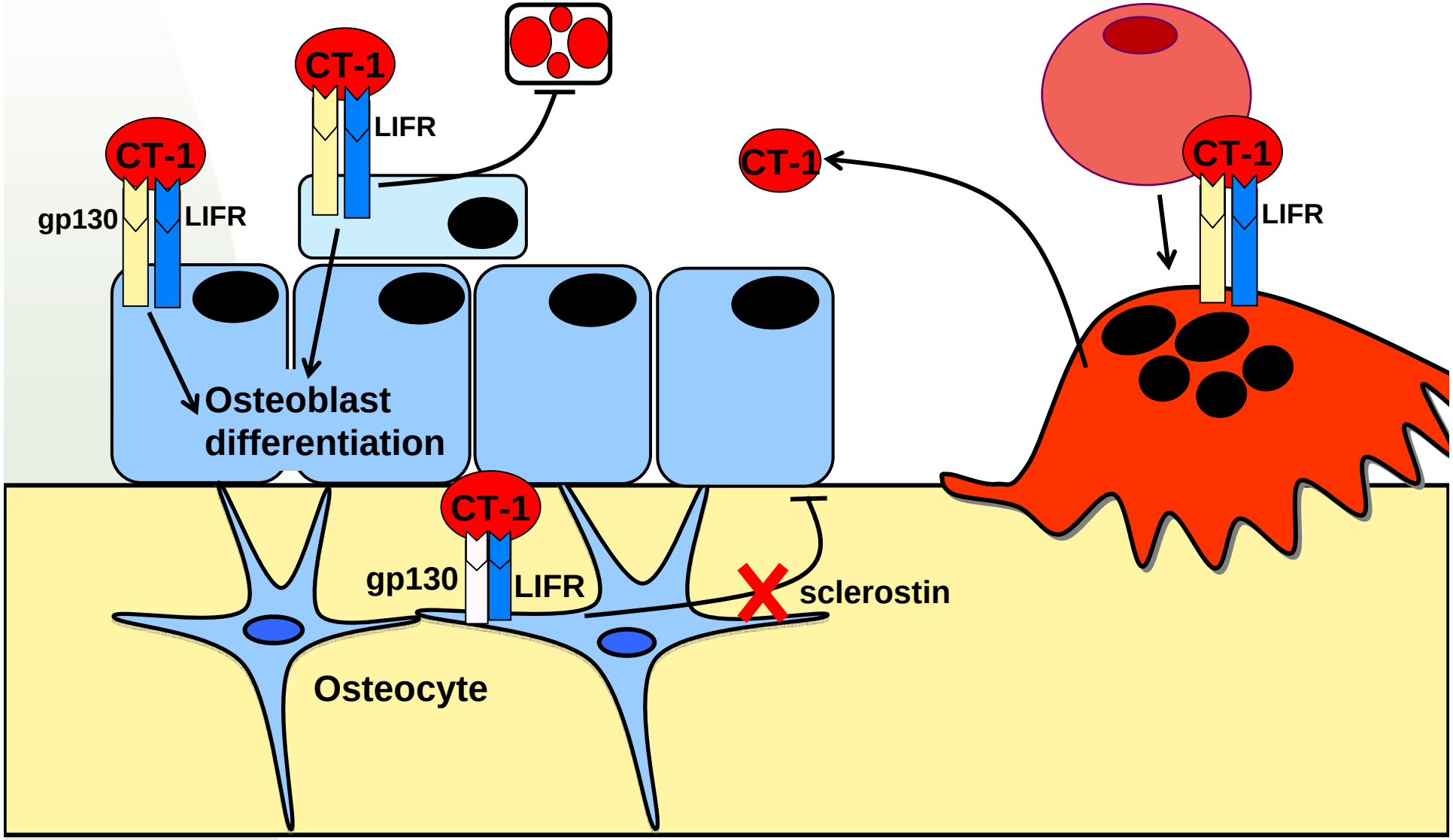
**5 days consecutive treatment**
**Fluorochrome labelled**
**Calvarial bone**




*Mean+SEM, n=6/group, *, p<0.05; **, p<0.01*
*Walker JBMR 2008*

# Unpublished data slide removed

# Influence of CT-1 on the BMU

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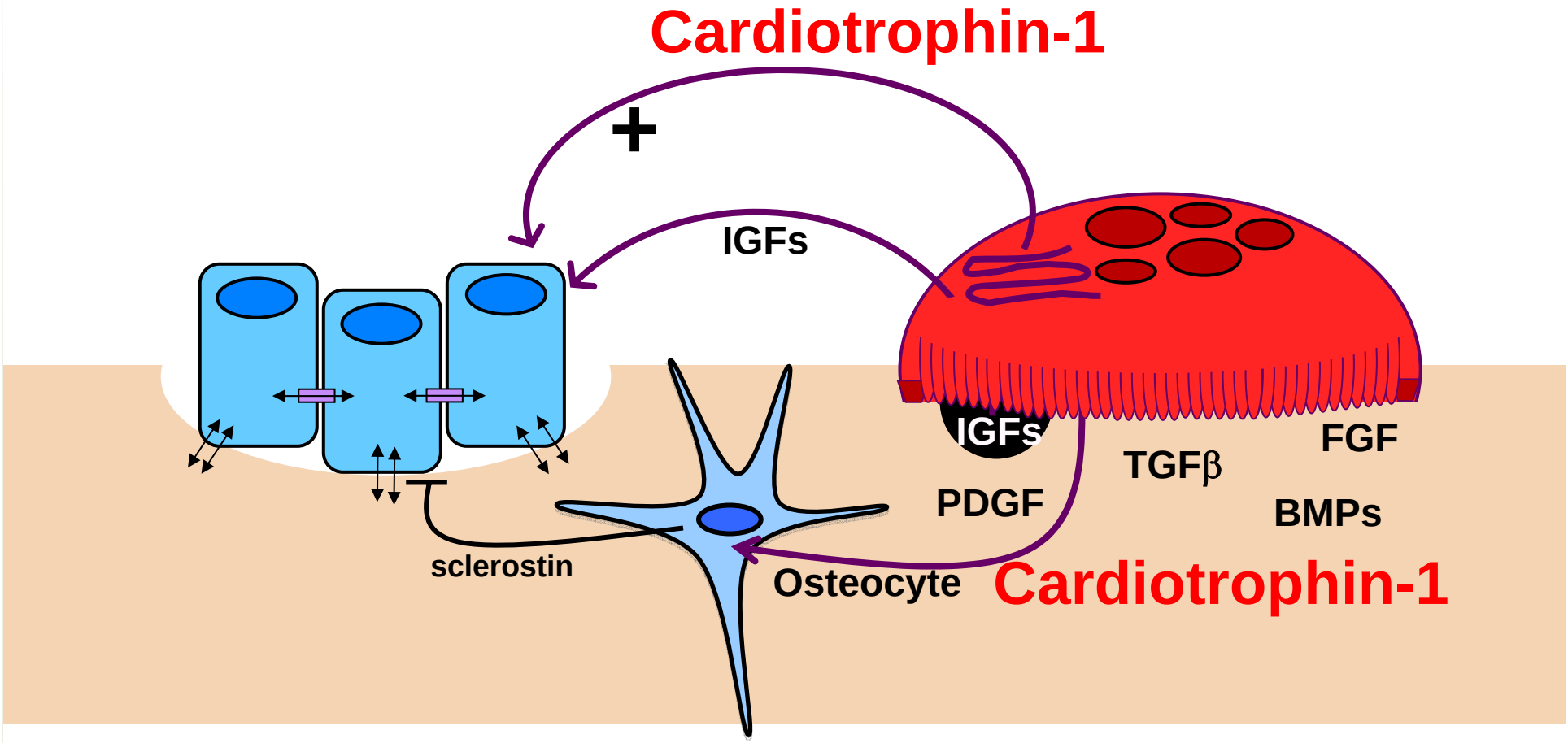
*Walker JBMR 2008*

# Signals from the osteoclast to the osteocyte



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