骨の重力応答とその制御

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分子薬理学

Unloading Causes Rapid Bone Loss

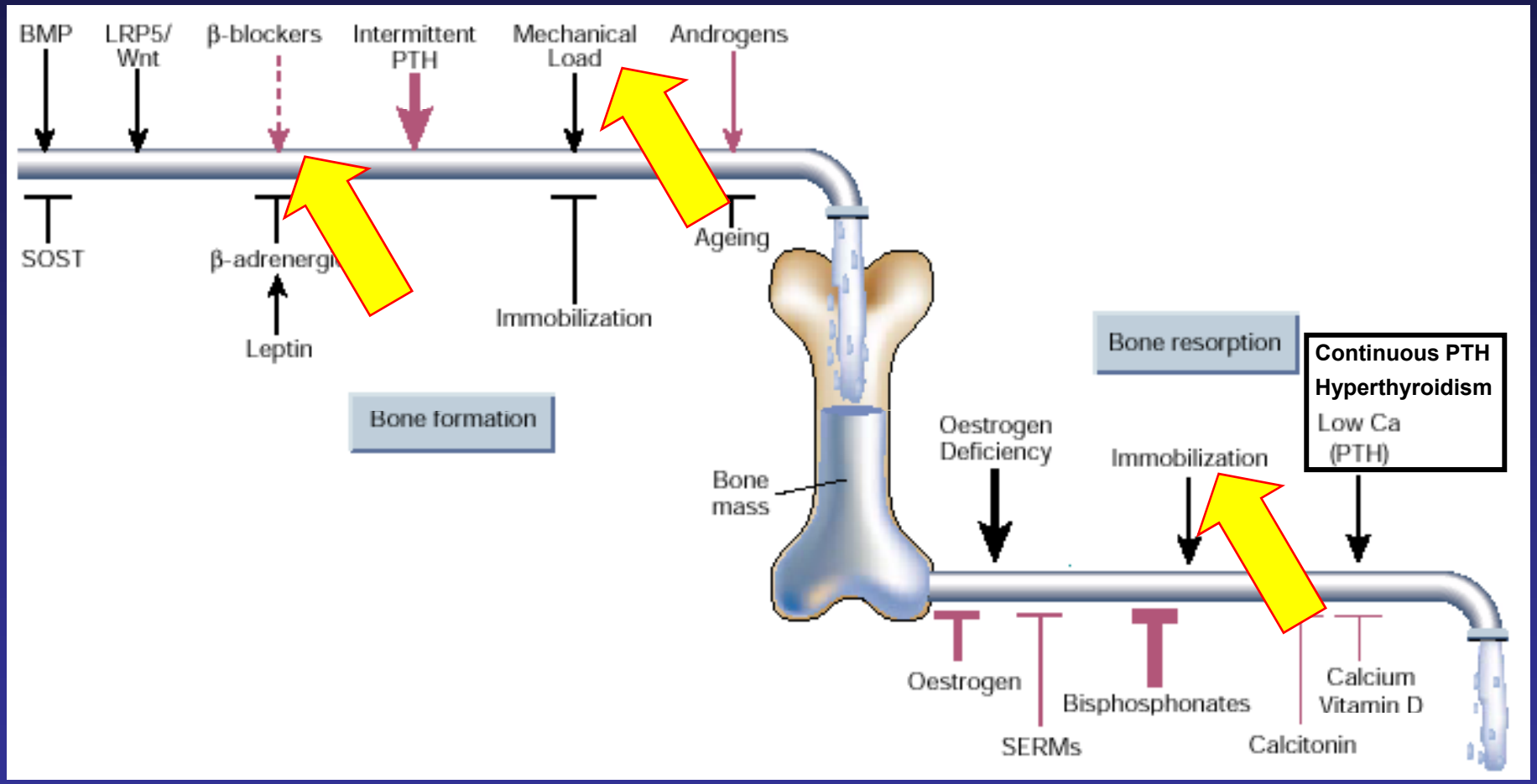
Bed-Ridden Patients

Astronauts

↓ Mechanism?

Osteoporosis

骨形成と骨吸収

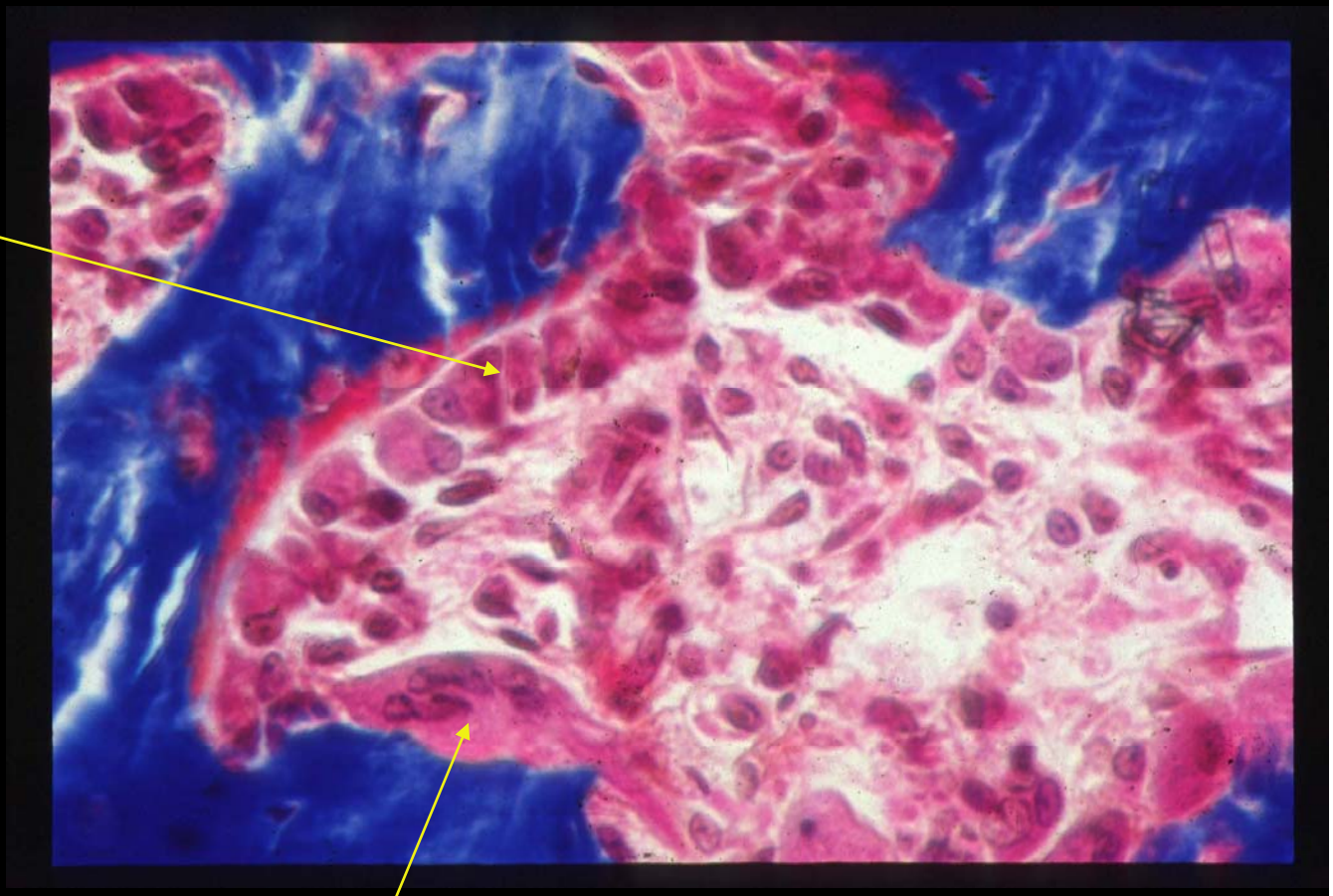


Physiological (black) and pharmacological (pink) stimulators and inhibitors of bone formation and resorption

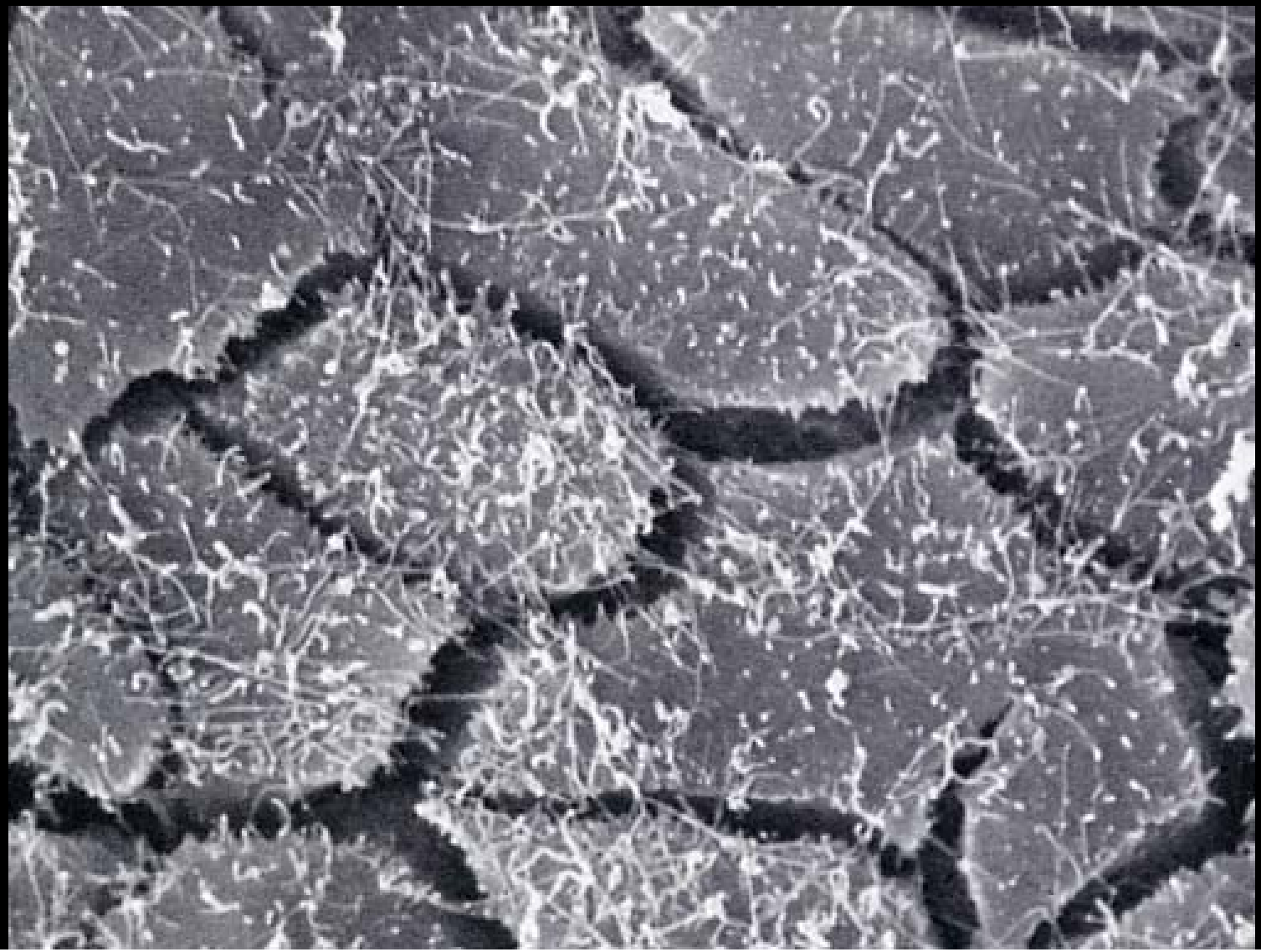
Determinants of skeletal homeostasis and bone mass

(Harada & Rodan, Nature 2003)

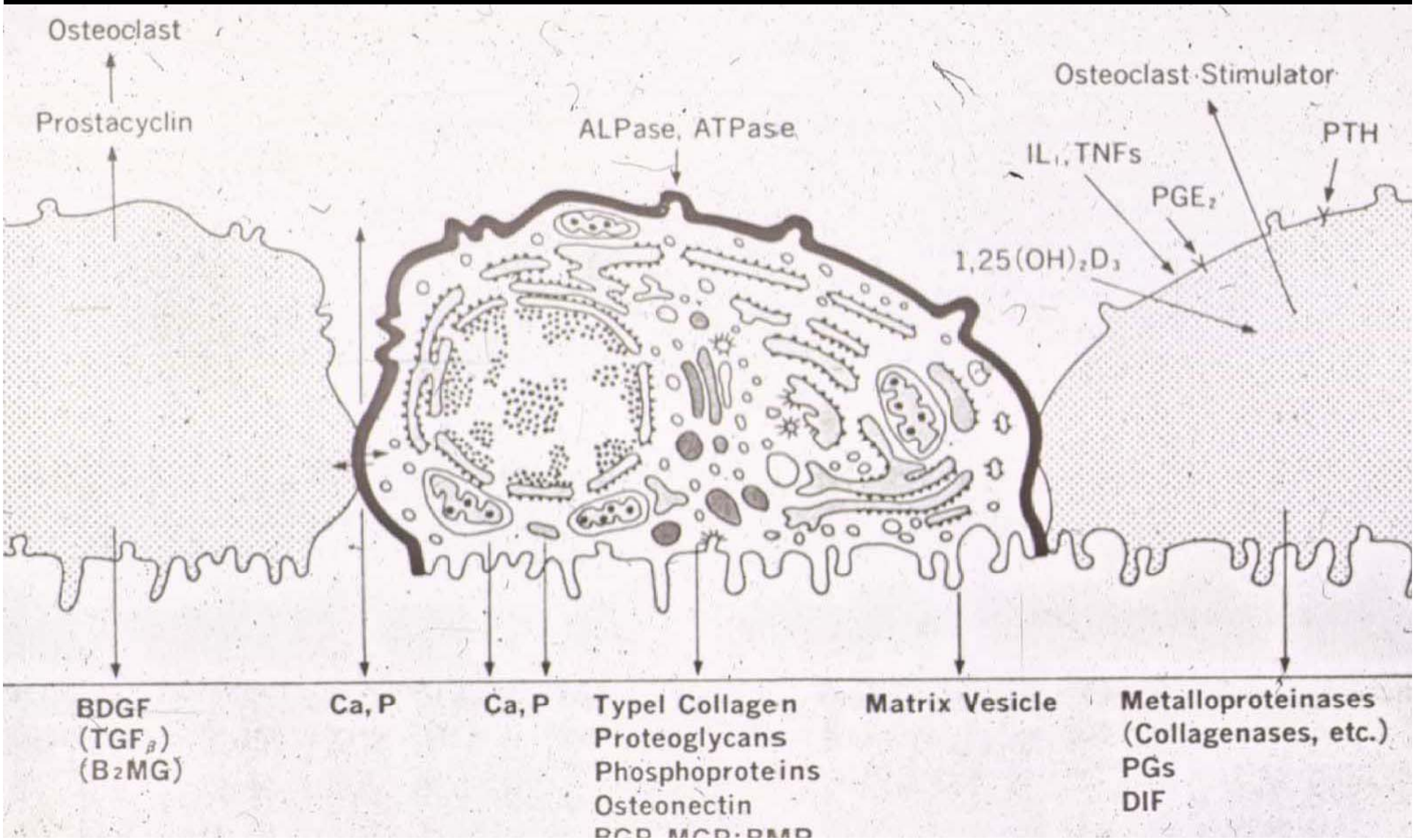
骨芽細胞と破骨細胞の共同作業の場



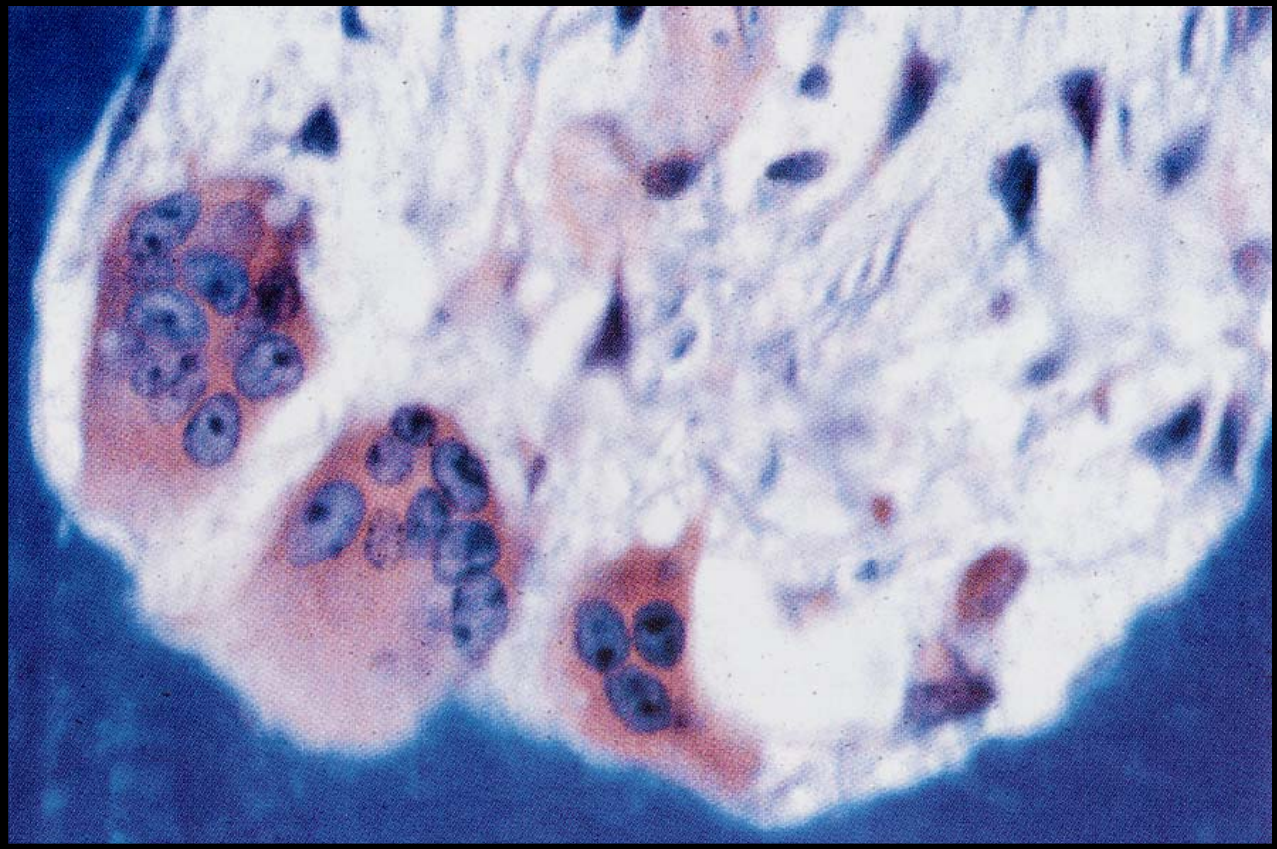
骨芽細胞



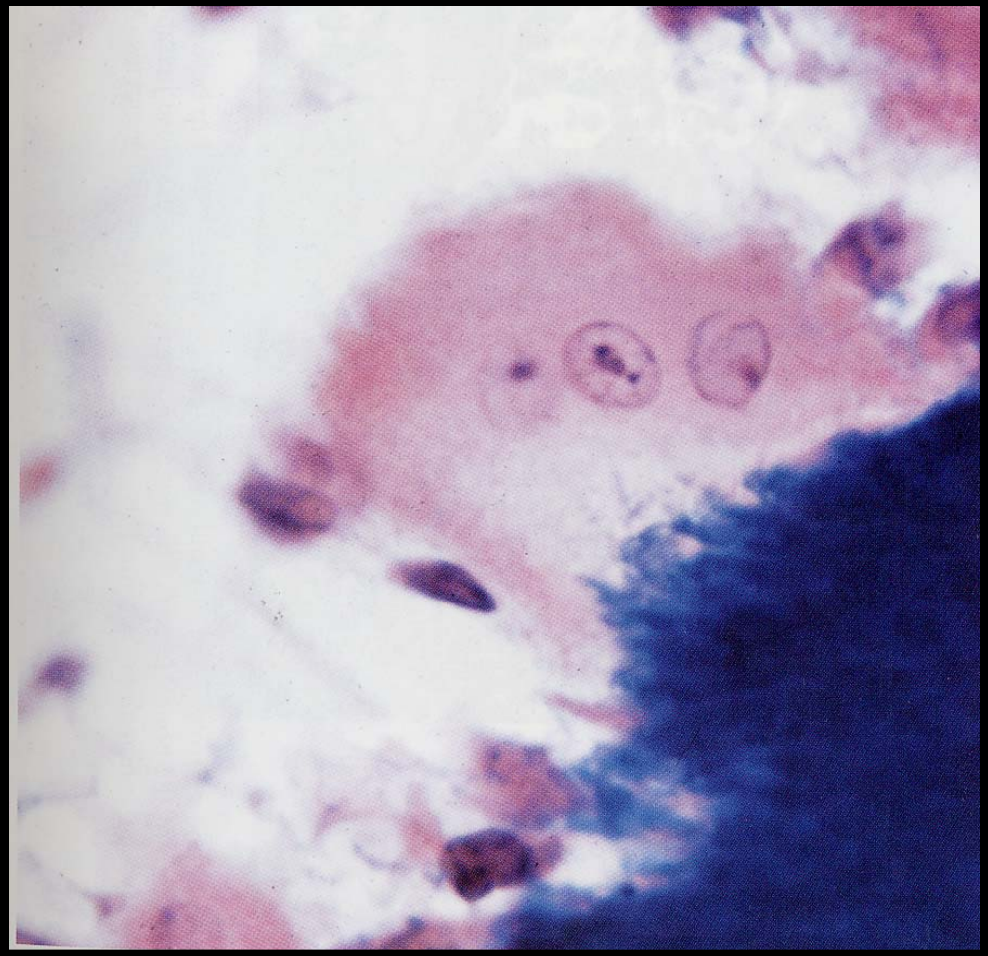
骨芽細胞


Osteoclast
Prostacyclin
ALPase, ATPase
Osteoclast-Stimulator
IL1, TNFs
PGE2
PTH
1,25(OH)2D3
BDGF
(TGFβ)
(B2MG)
Ca, P
Ca, P
Typel Collagen
Proteoglycans
Phosphoproteins
Osteonectin
Matrix Vesicle
Metalloproteinases
(Collagenases, etc.)
PGs
DIF

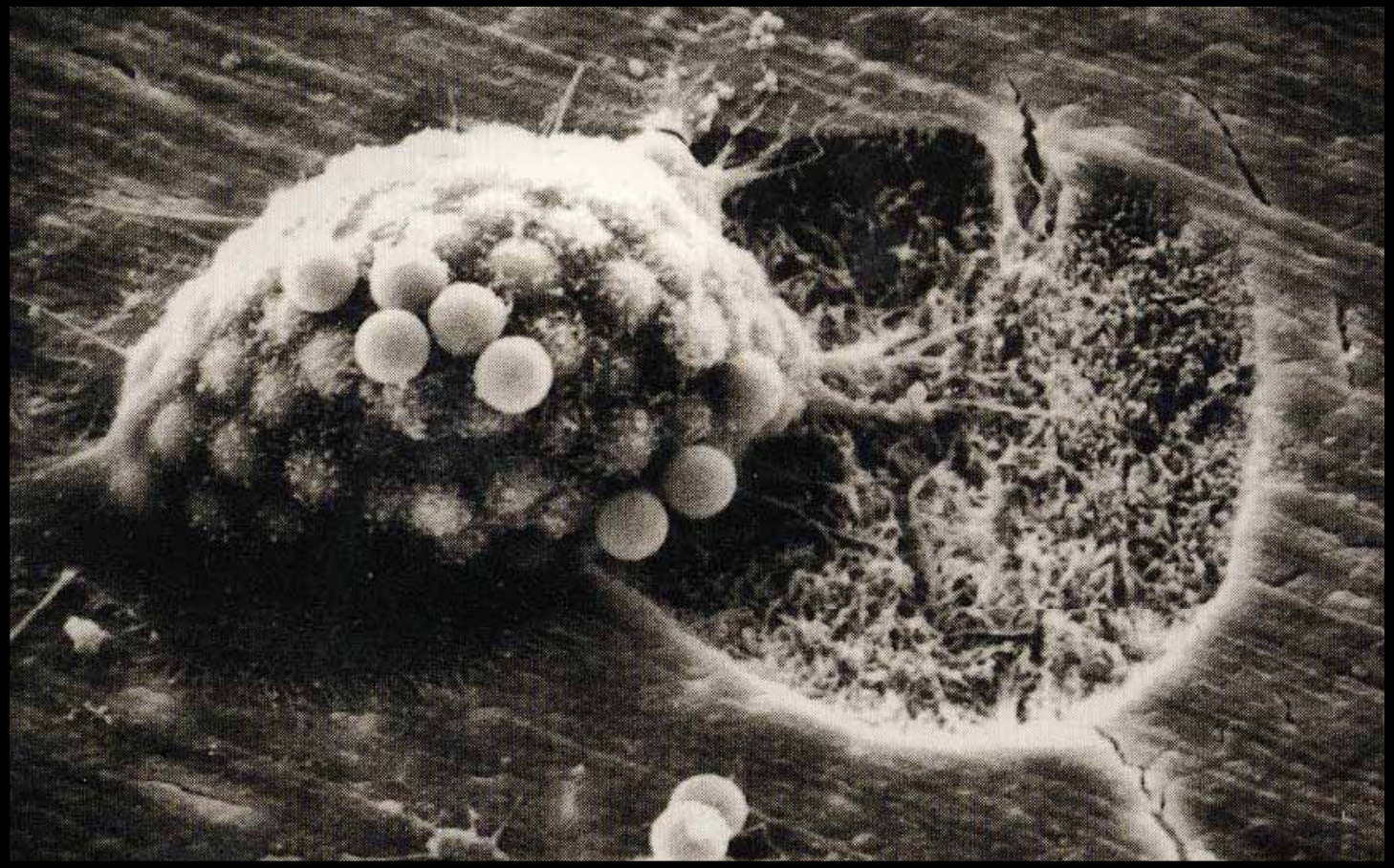
破骨細胞



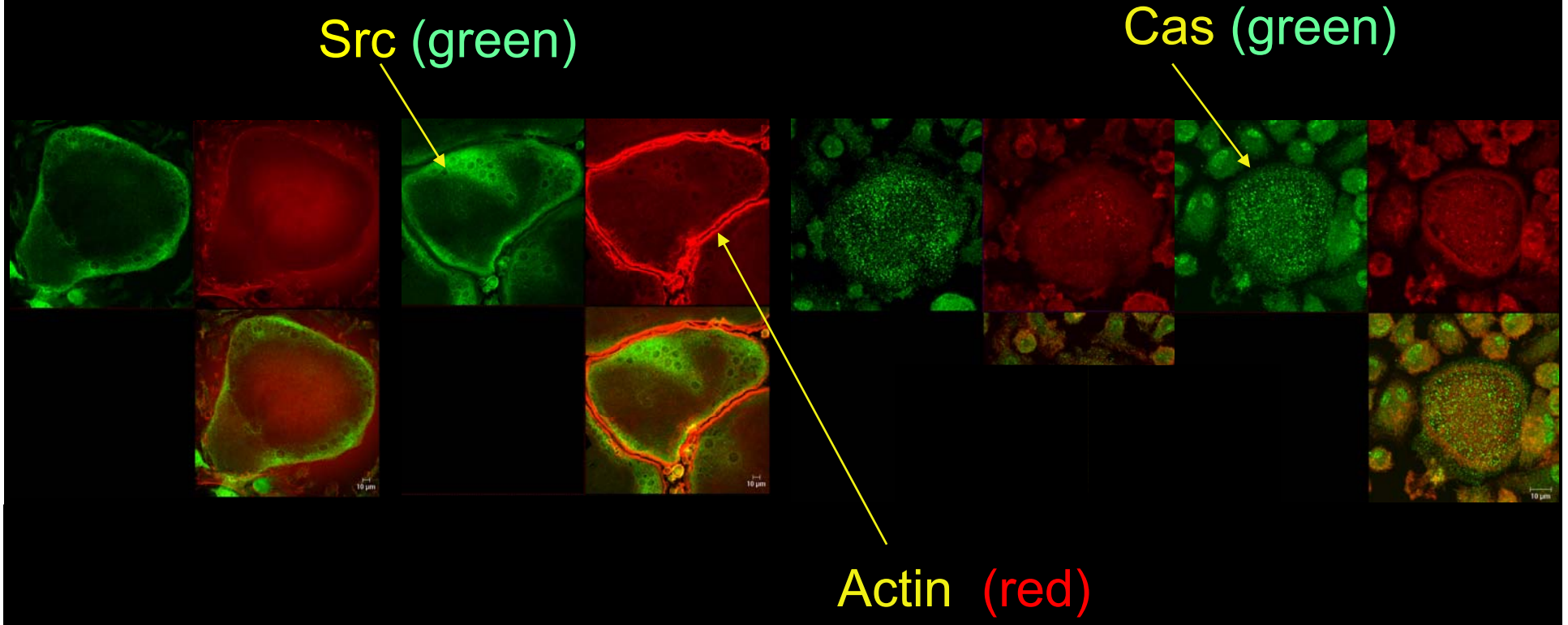
破骨細胞

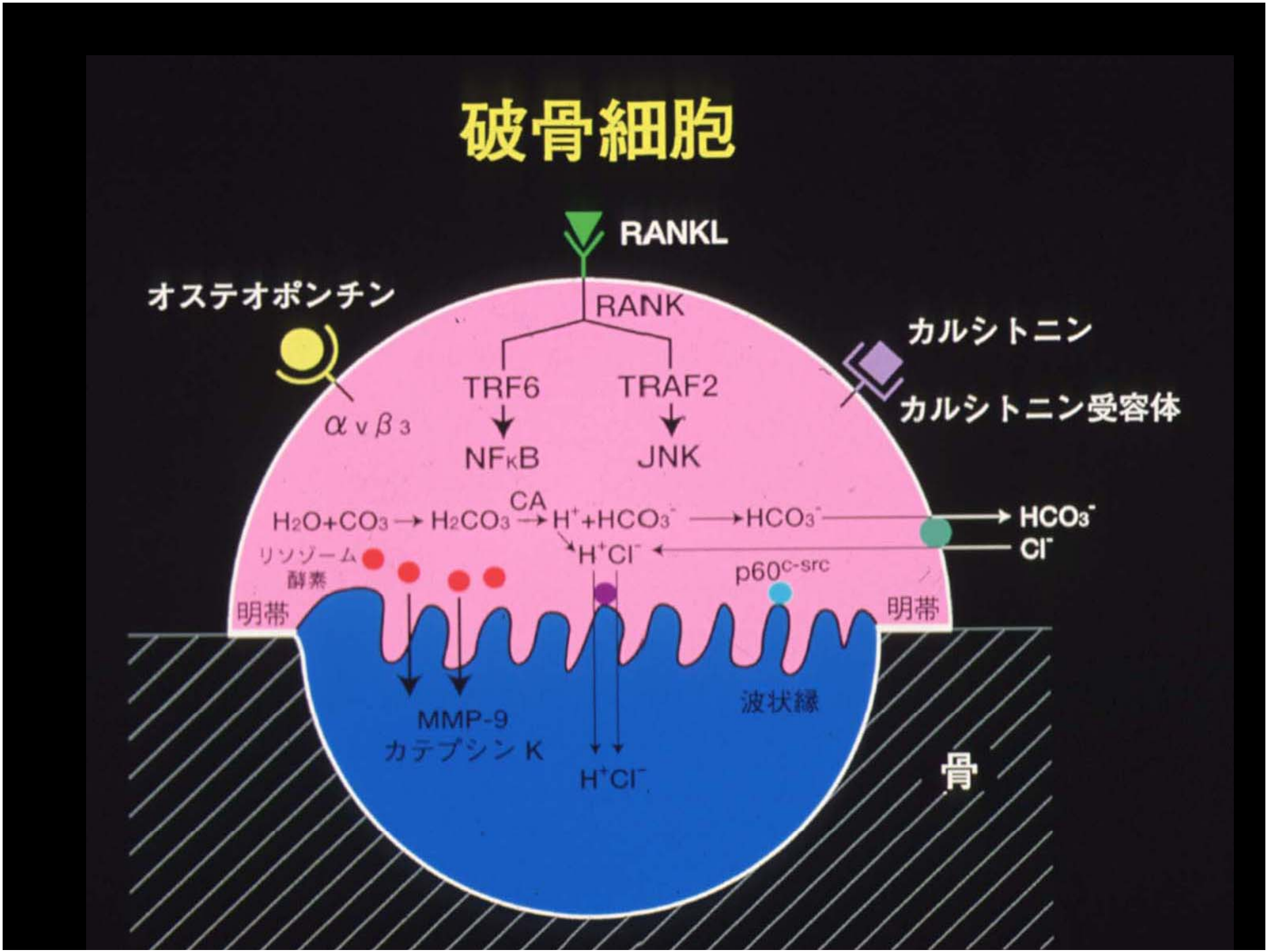


破骨細胞の骨吸収

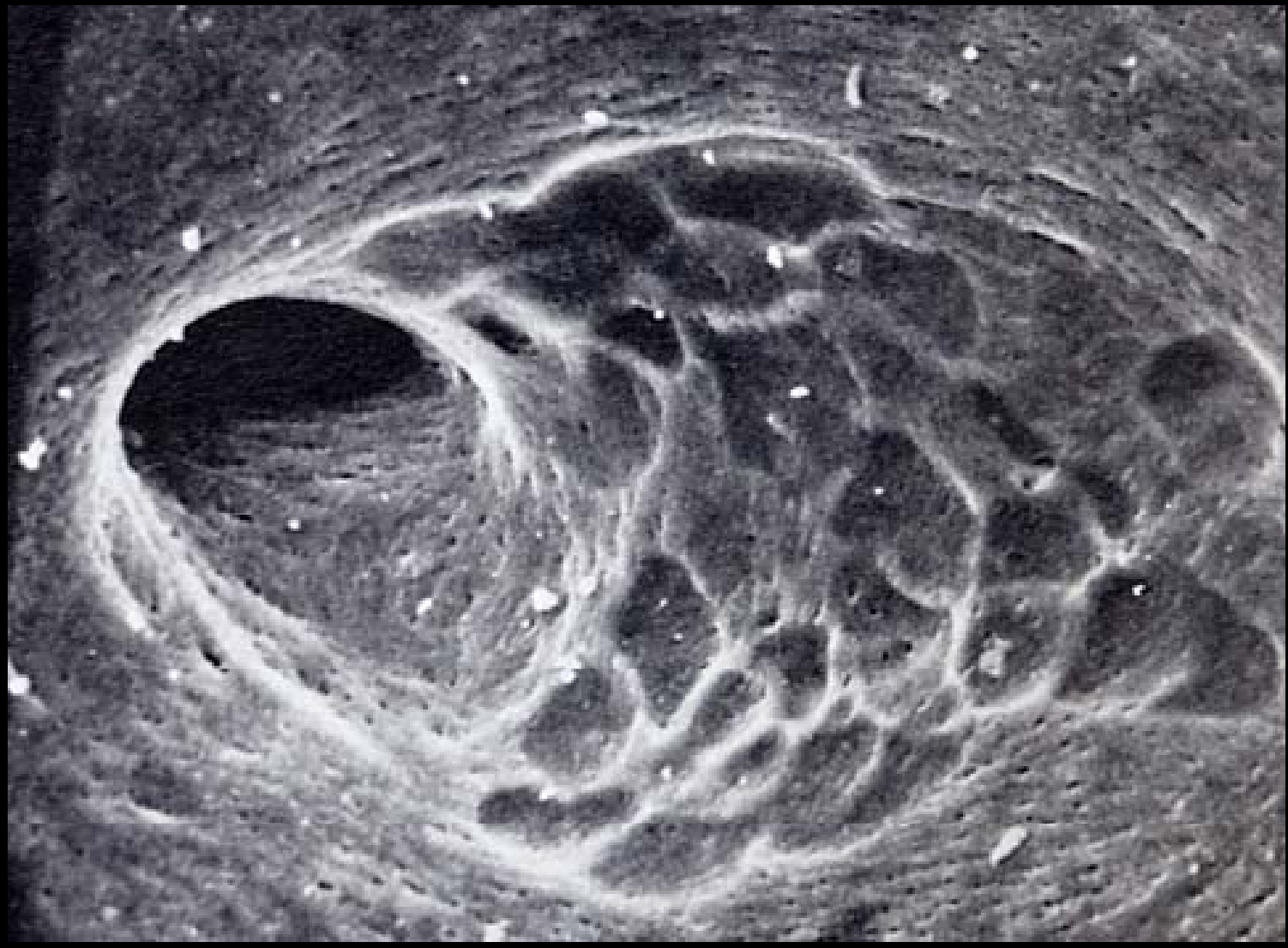


破骨細胞は細胞骨格により閉鎖腔を構成する

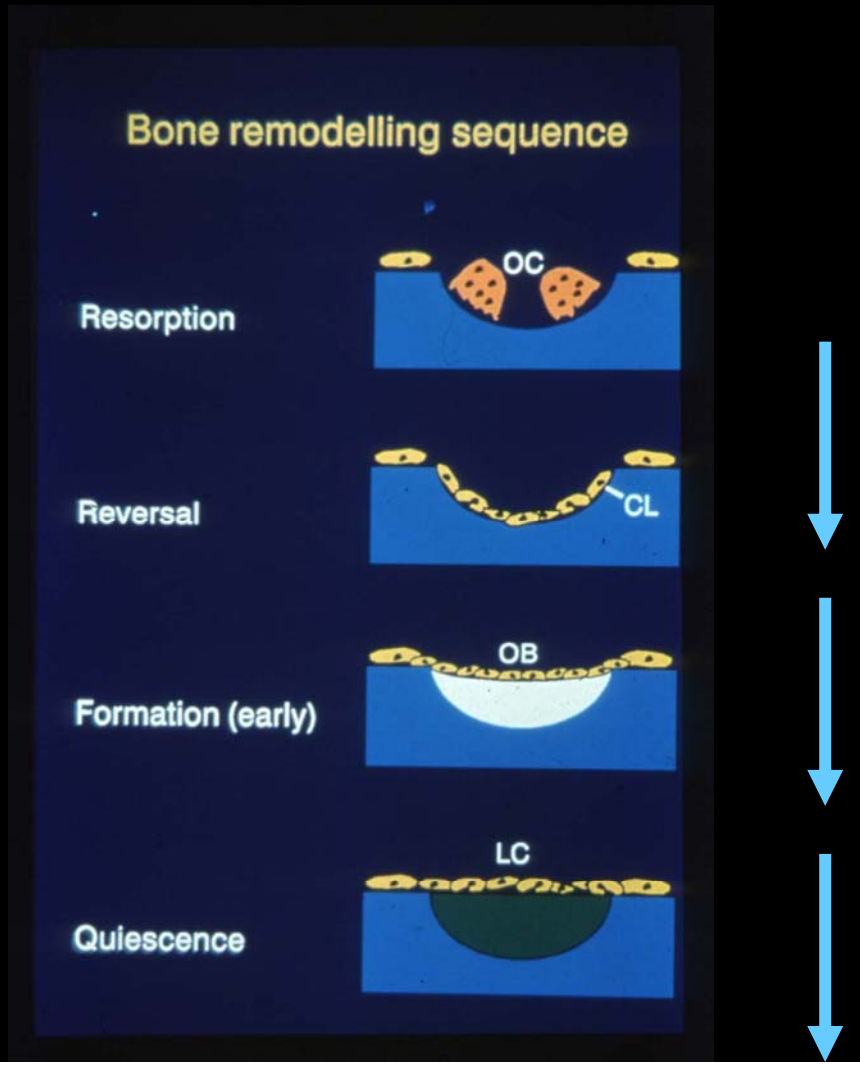


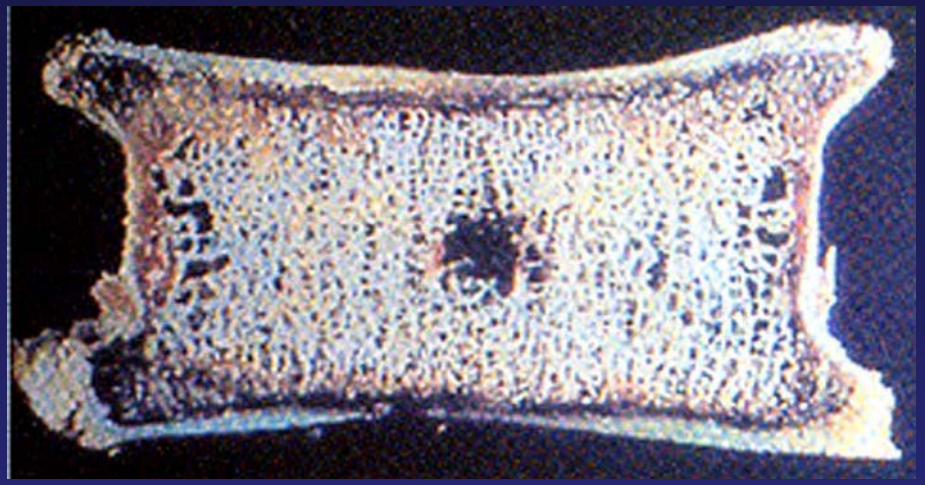

破骨細胞
RANKL
RANK
オステオポンチン
カルシトニン
カルシトニン受容体
TRF6
TRAF2
αvβ3
NFκB
JNK
CA
H2O+CO3 → H2CO3 → H+HCO3- → HCO3-
HCO3-
Cl-
H+Cl-
リソゾーム酵素
p60c-src
明帯
明帯
MMP-9
カテプシンK
H+Cl-
波状縁
骨

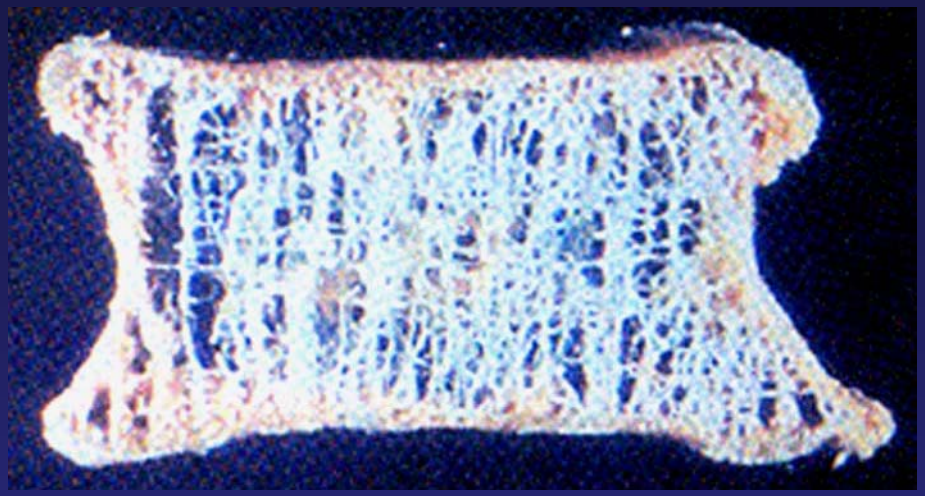
破骨細胞により形成された骨吸収窩



骨芽細胞･破骨細胞による骨のリモデリングの進行







Normal Osteopo

Remodeling / Mechanical Stress

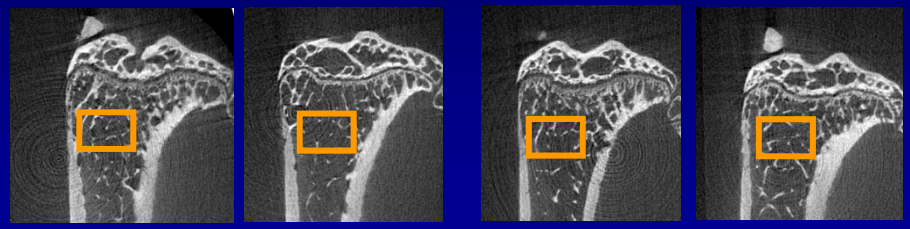
Load

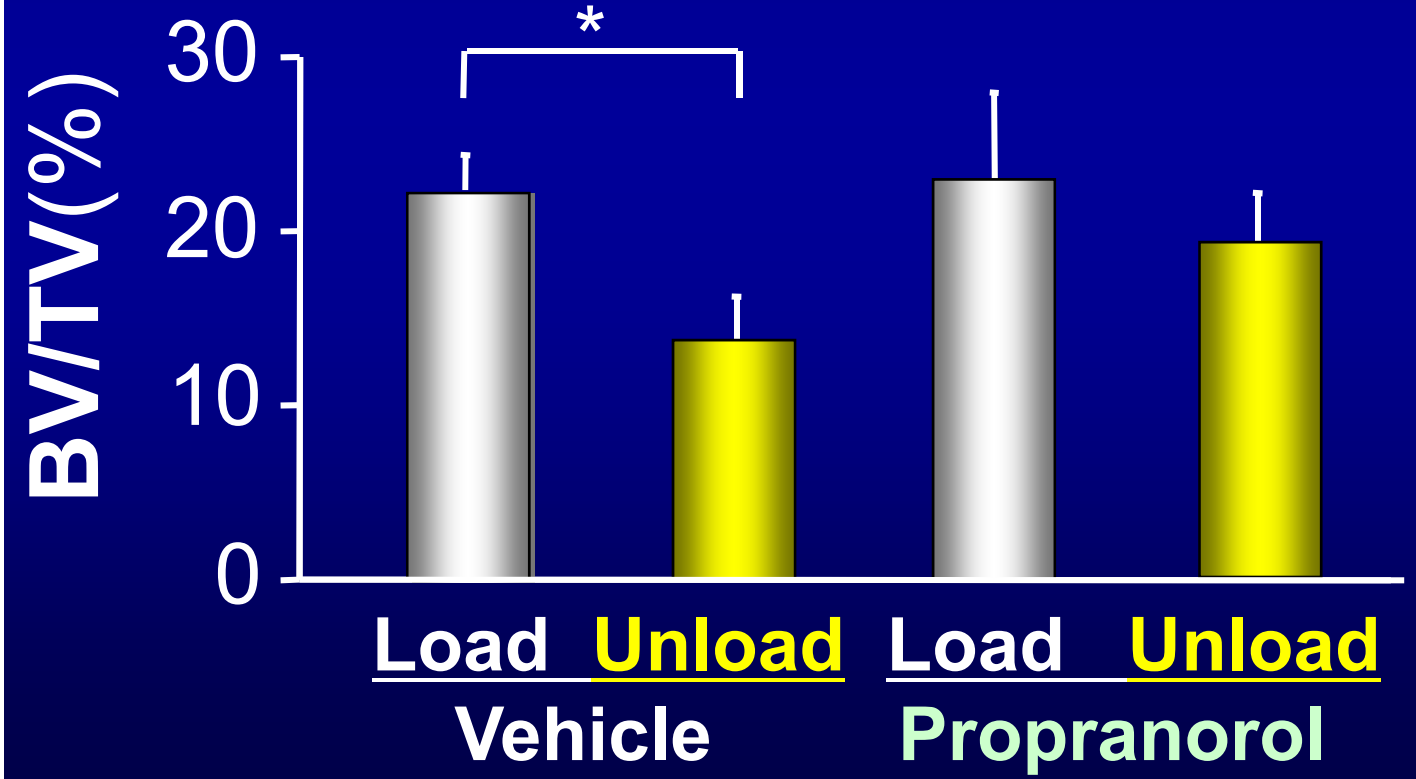
Unload

Vehicle

Propranolol

Propranorol Suppressed Unloading-Induced Bone Loss

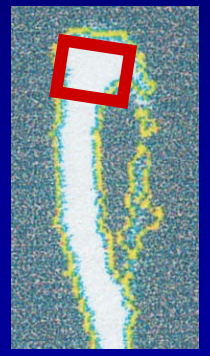




*p<0.001

10 days unload

Propranorol Suppressed Unloading-Induced Bone Loss



(g/cm^2)

BMD

0.06

0.04

0.02

0

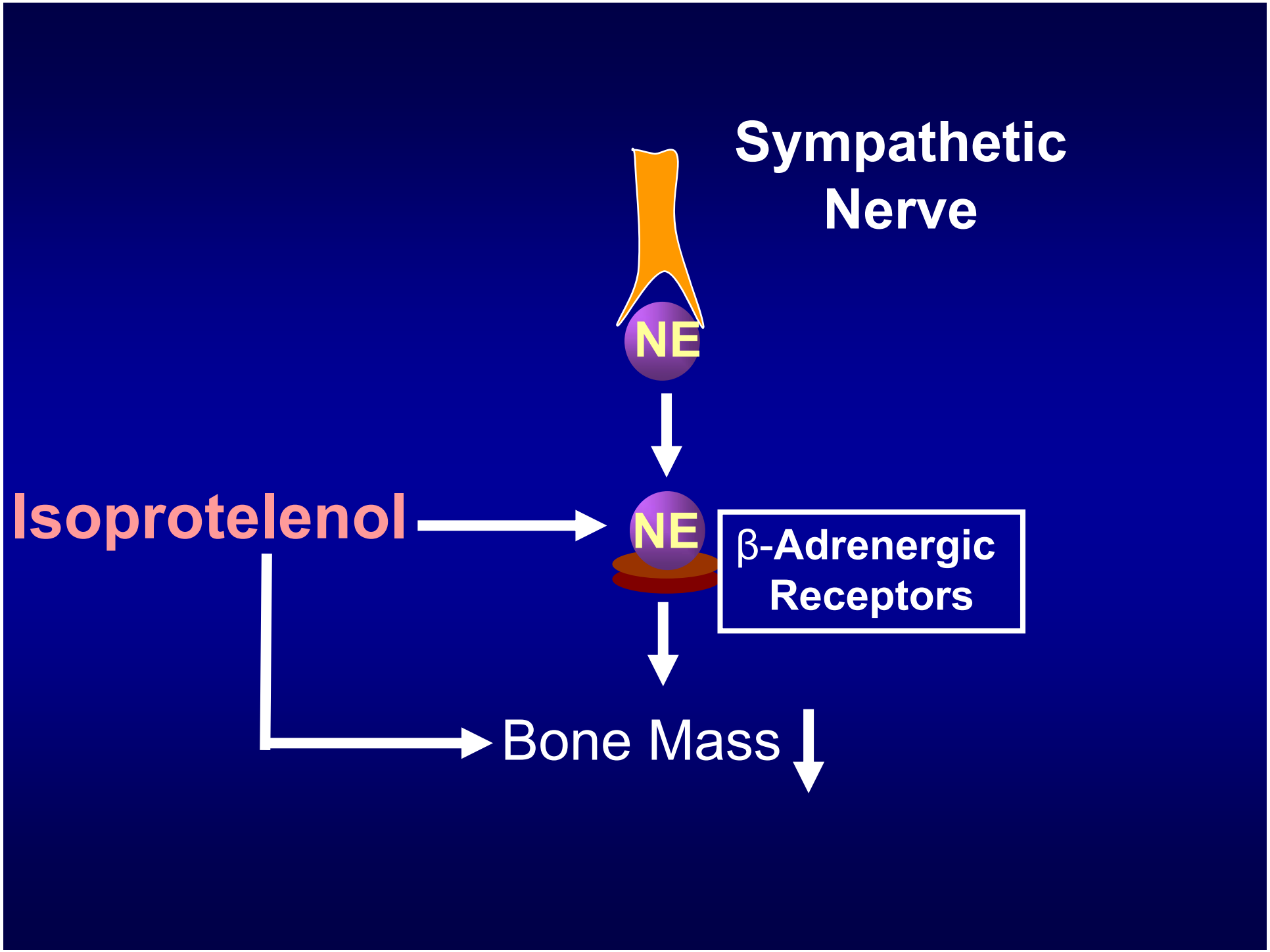
*

*p<0.001

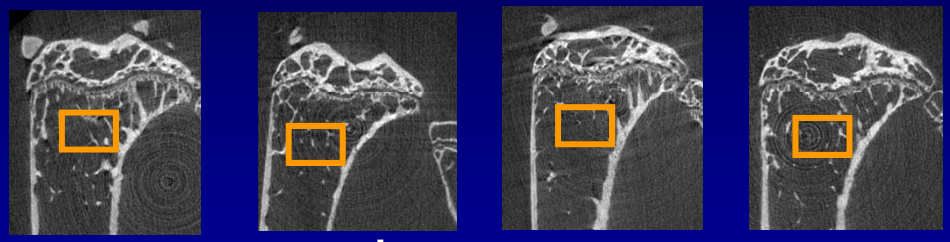
Load Unload Load Unload

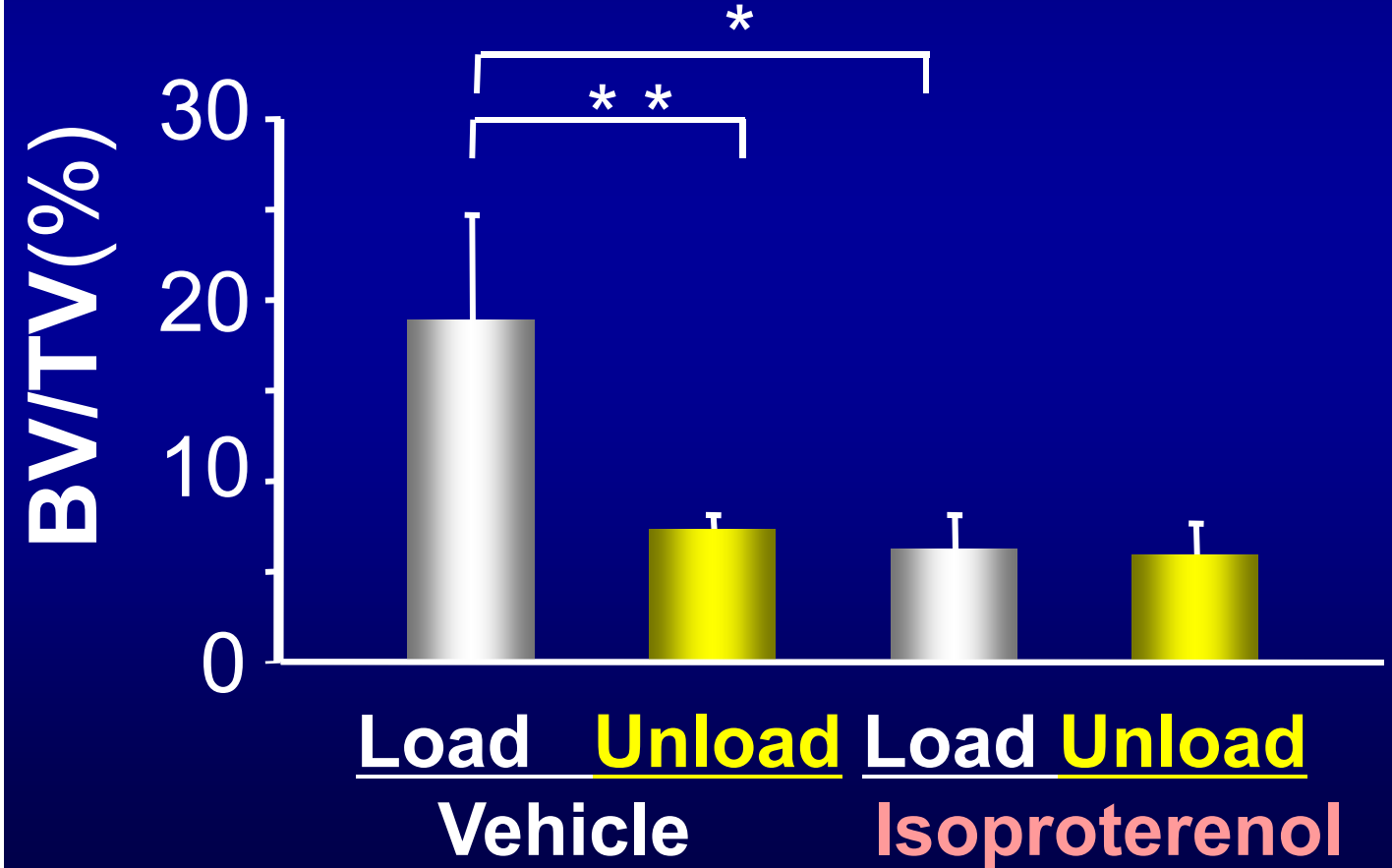
Vehicle Propranorol

Proximal End of Tibiae


Sympathetic Nerve
NE
Isoprotelenol
NE
β-Adrenergic Receptors
Bone Mass

Isoproterenol Decreased Basal Level of Bone Mass



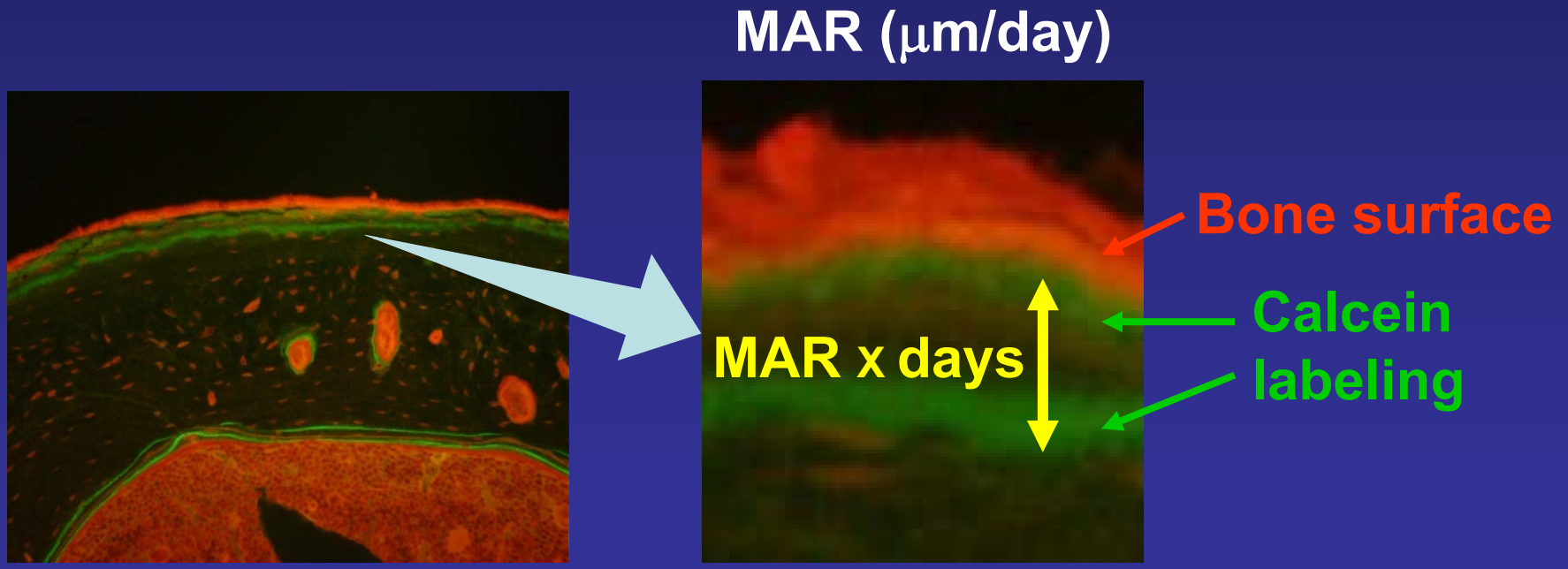


*p<0.05
**p<0.001

10 days unload

Osteoblast parameter

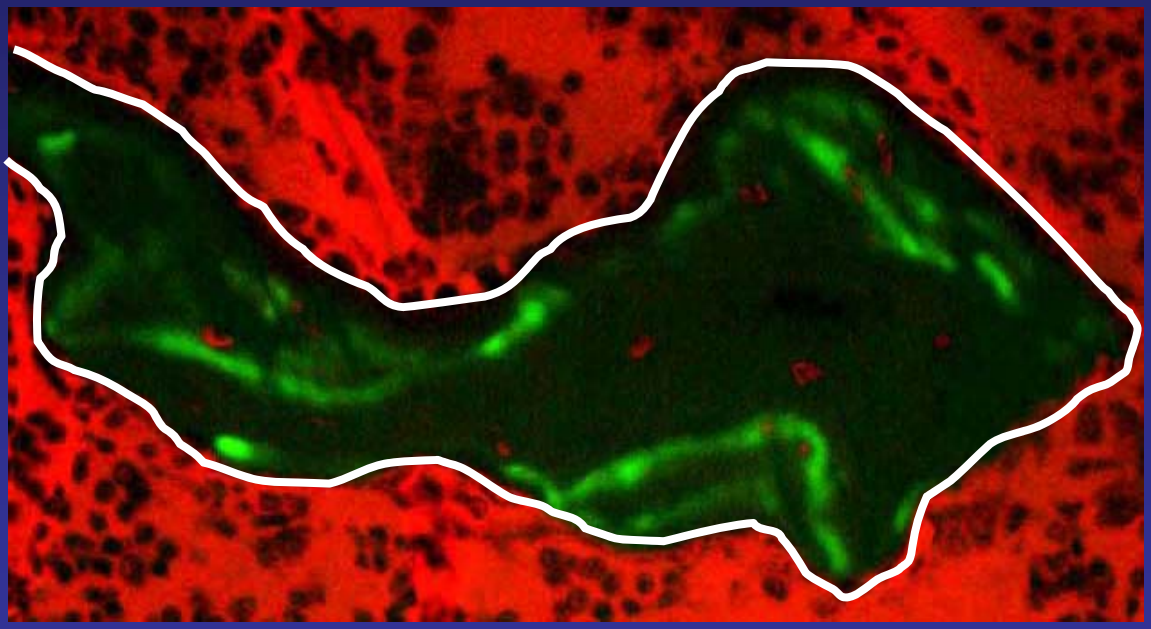
Parameter; Bone Formation Rate (BFR); 骨形成速度
Mineral Apposition Rate (MAR); 骨石灰化速度



(Parfitt *et al*., J. Bone Miner. Res. 1987)

Osteoblast parameter

BFR=MAR x (sLS/2+dLS) /BS ($mm^3/mm^2/day$)



BS; Bone surface

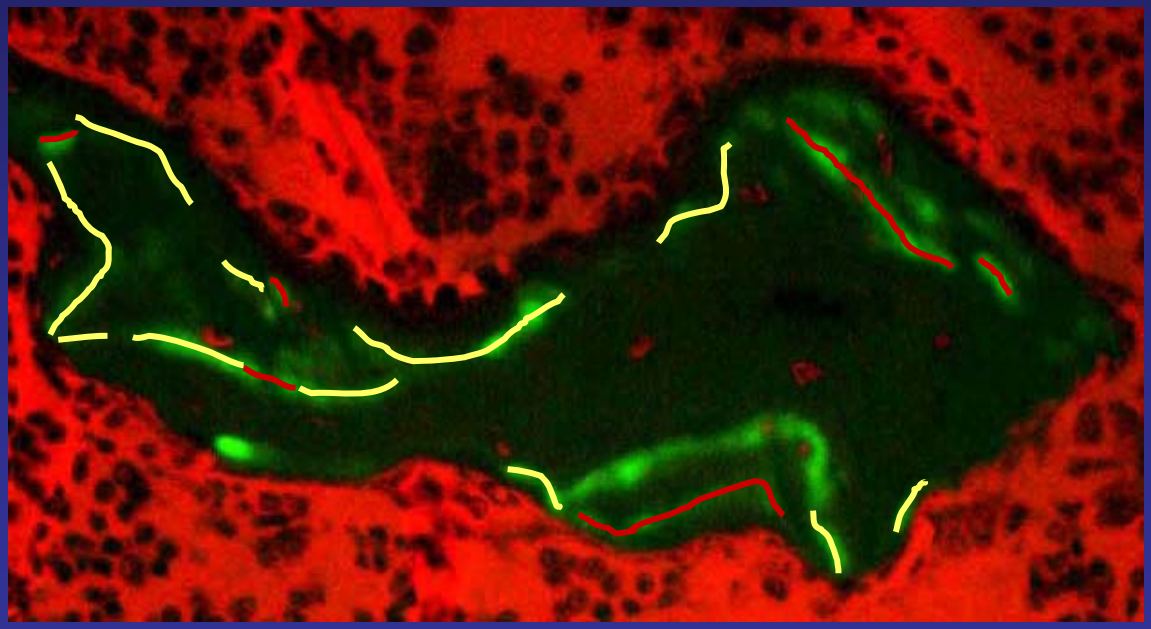
sLS; Single labeled surface

dLS; Double labeled surface

(Parfitt *et al*., J. Bone Miner. Res. 1987)

Osteoblast parameter

BFR=MAR x (sLS/2+dLS) /BS ($mm^3/mm^2/day$)



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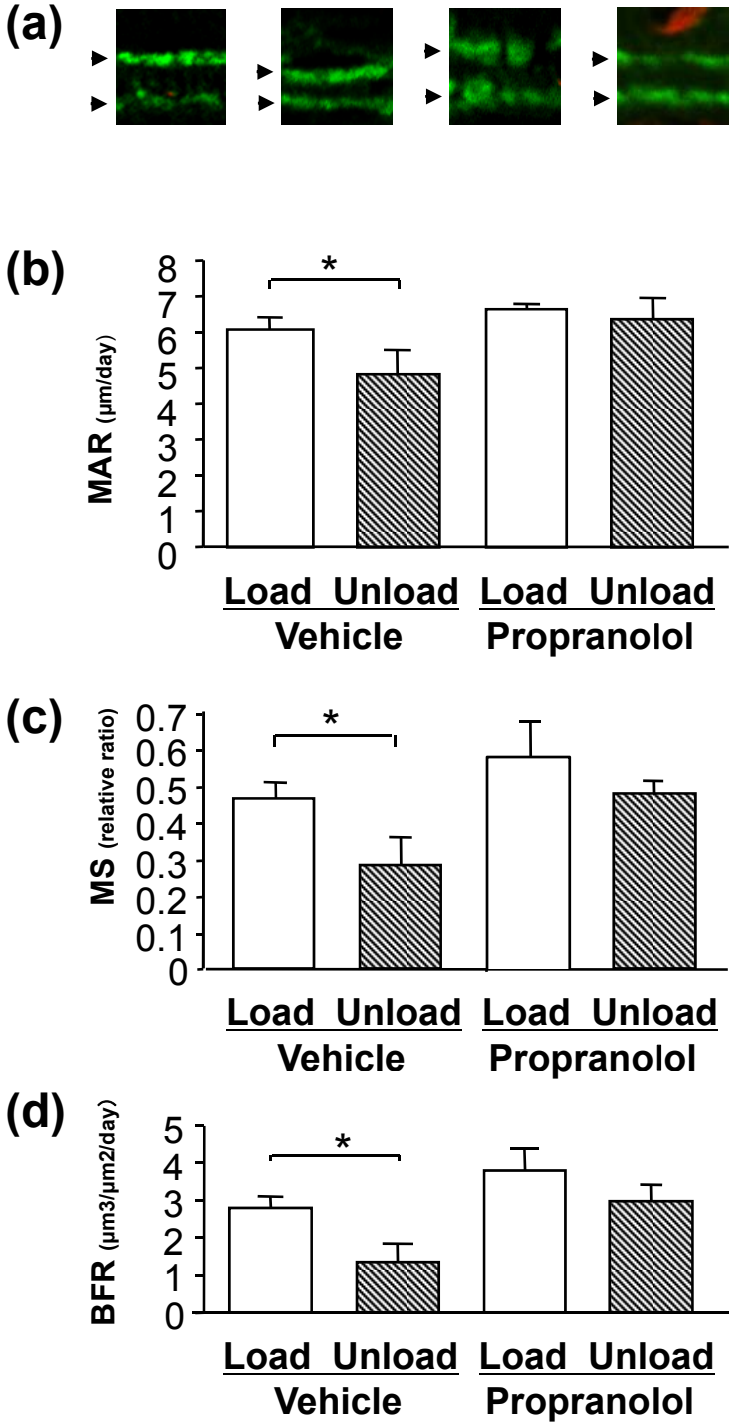
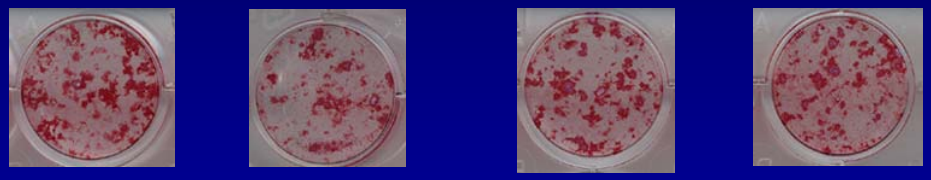
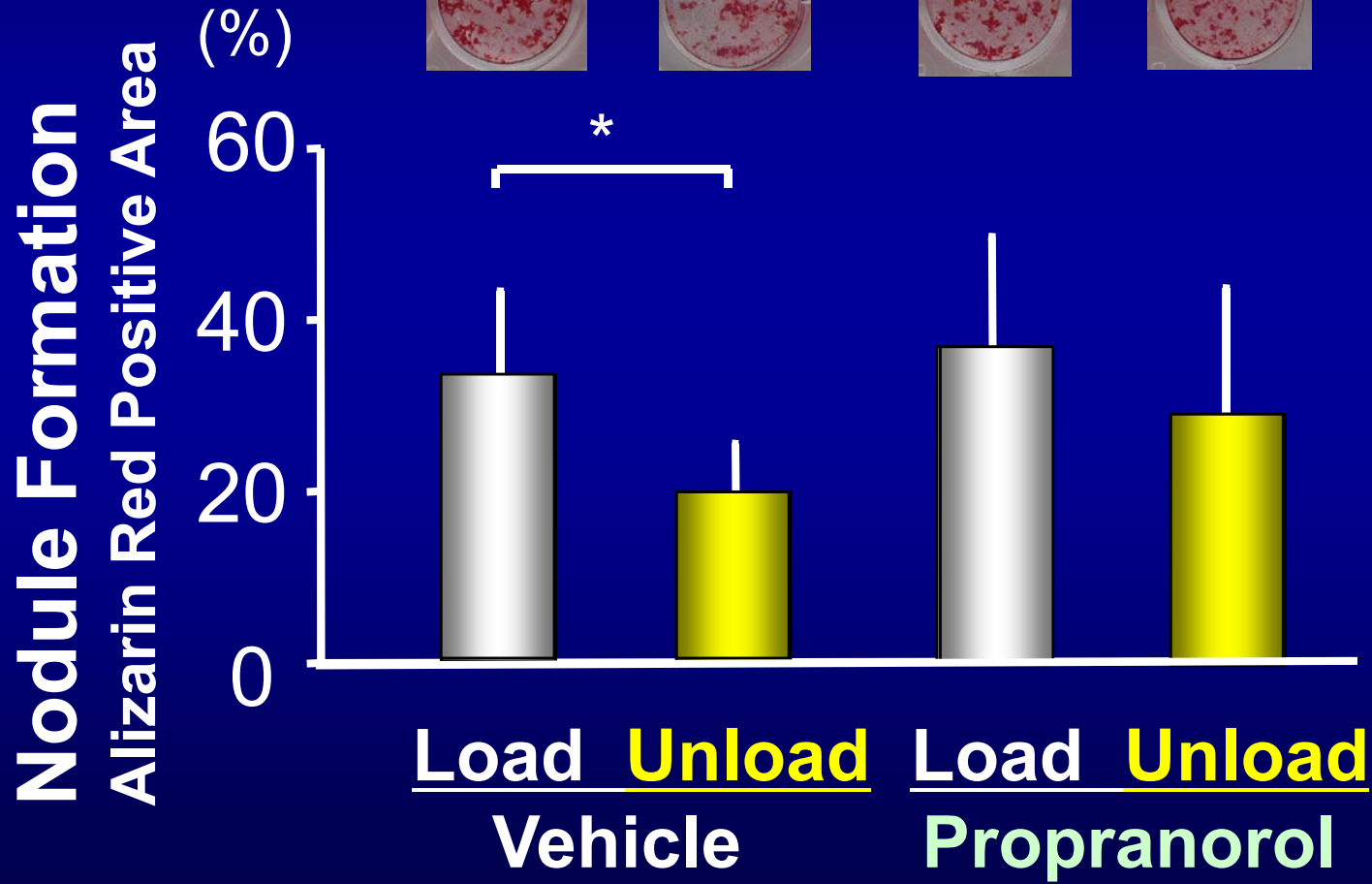
(Parfitt *et al*., J. Bone Miner. Res. 1987)



Propranolol

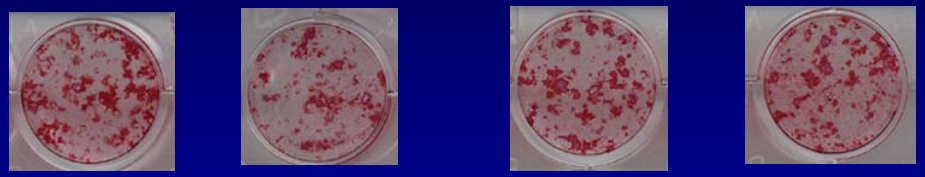
Propranorol Prevented Unloading-Induced Repression of Bone Formation

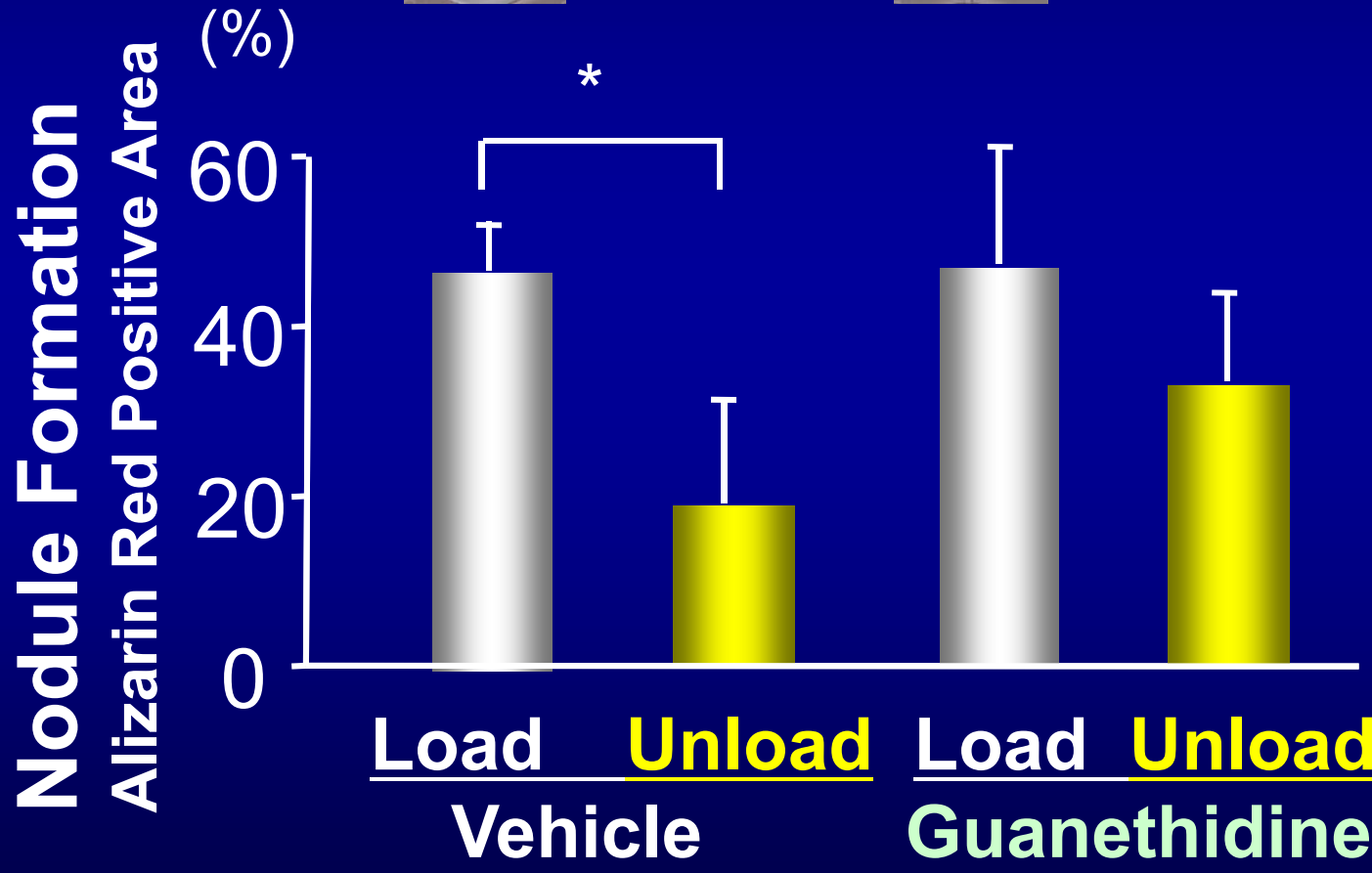




*p<0.05

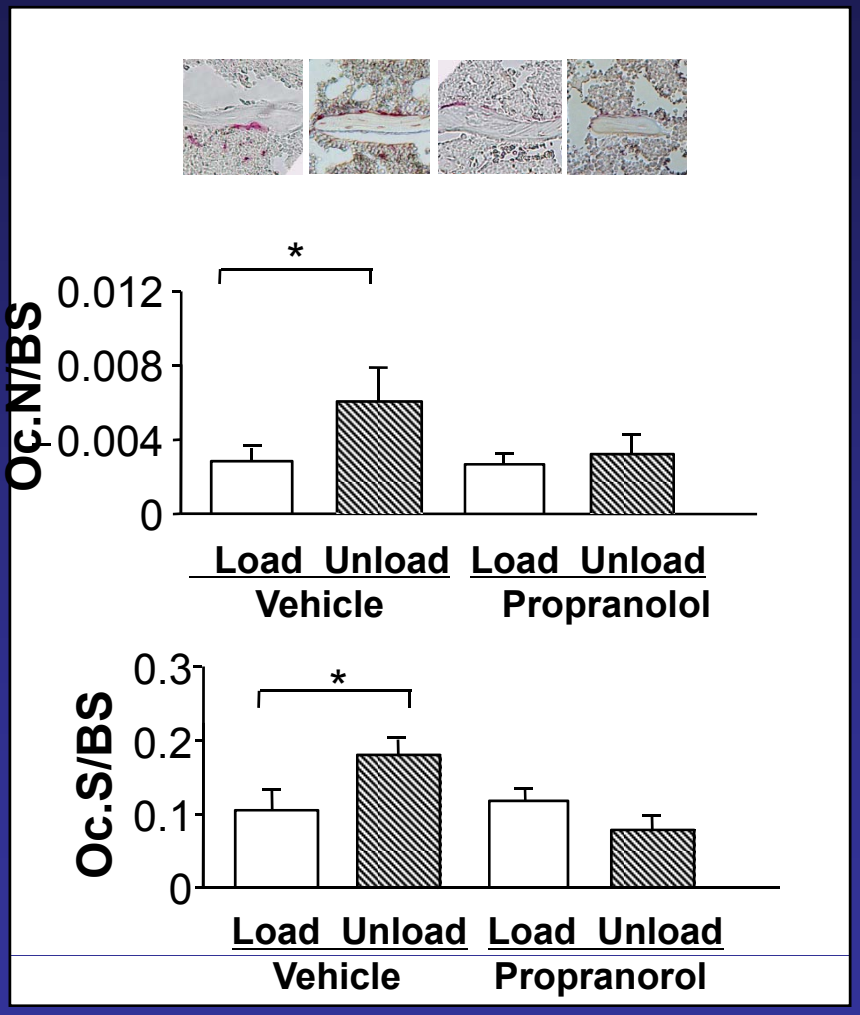
Guanethidine Prevented Unloading-Induced Repression of Bone Formation

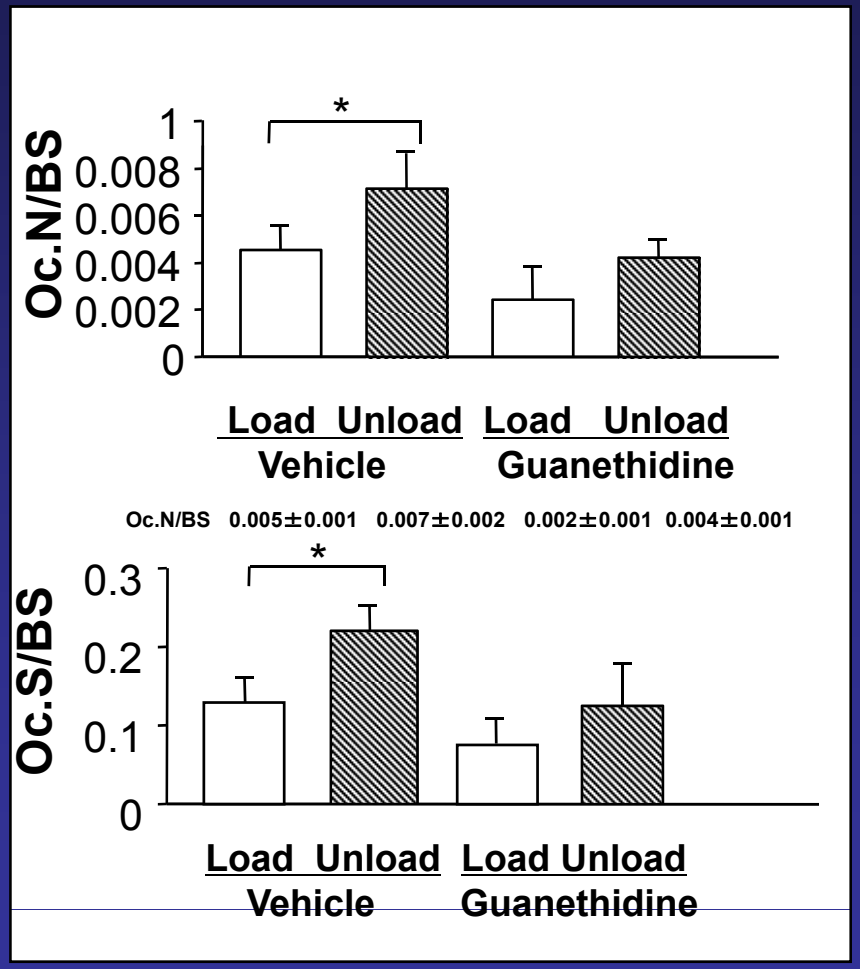




*p<0.001

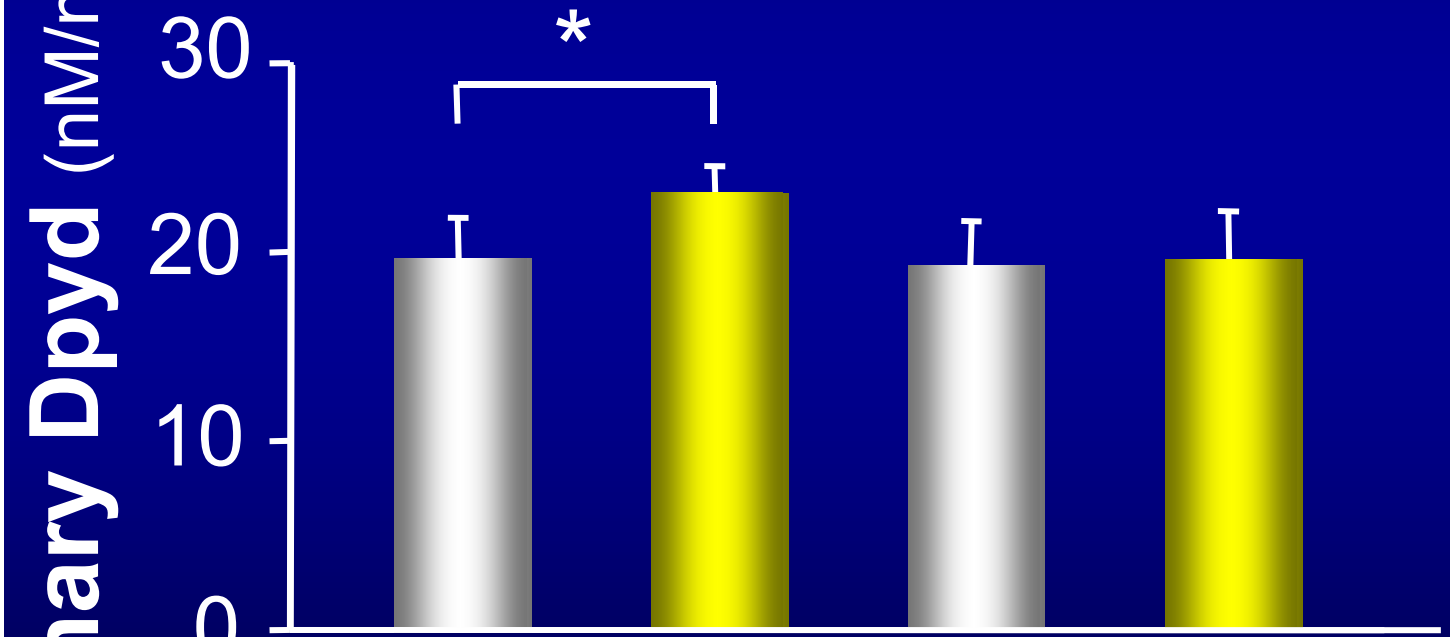
β-antagonists Propanolol and Guanethidine Suppressed Unloading-Induced Enhancement of Osteoclast Number and Surface





Karsenty & Noda et al.: Nature 2005

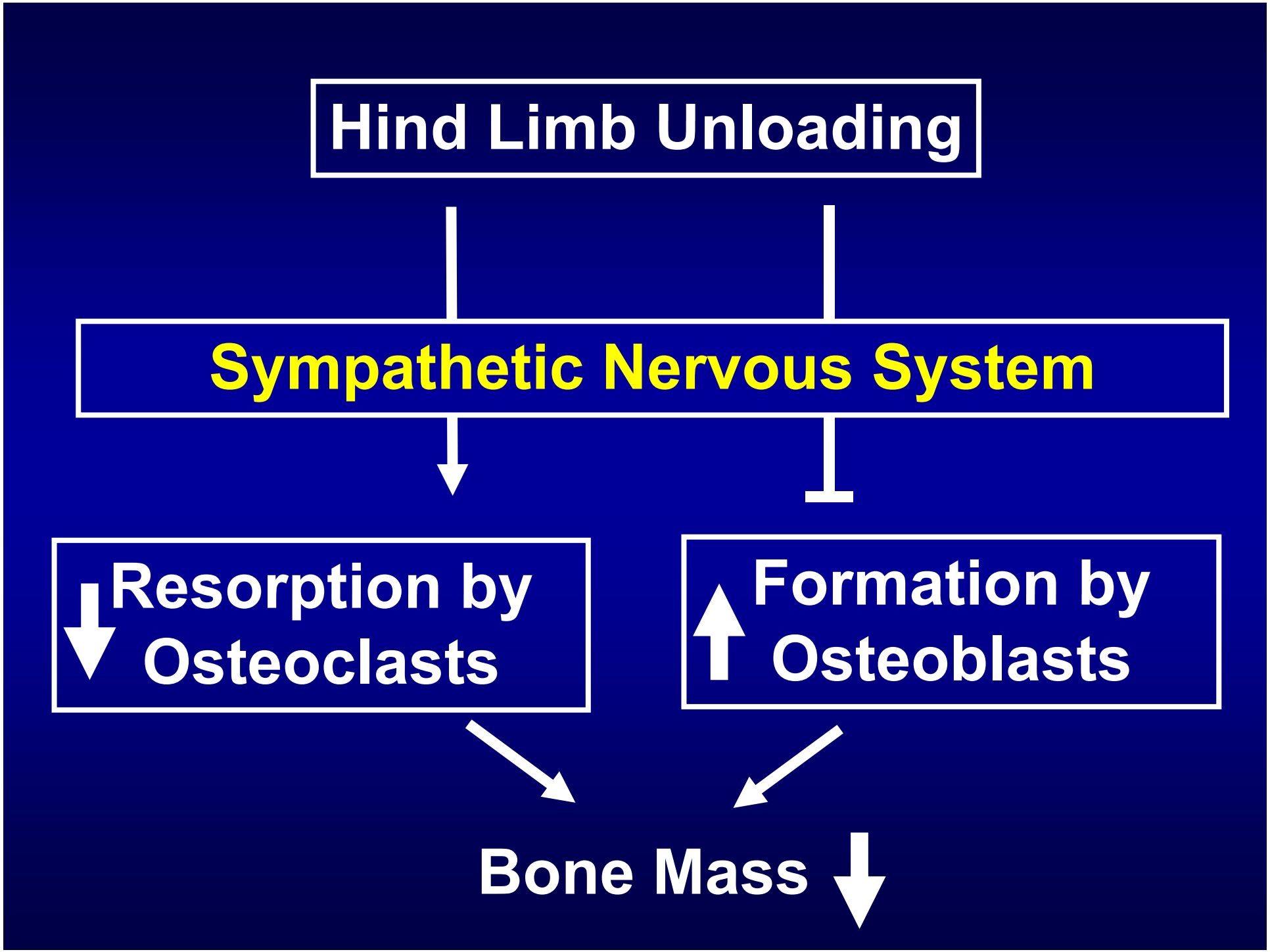
Guanethidine Suppressed Unloading-Induced Enhancement of Urinary Deoxypyridinoline

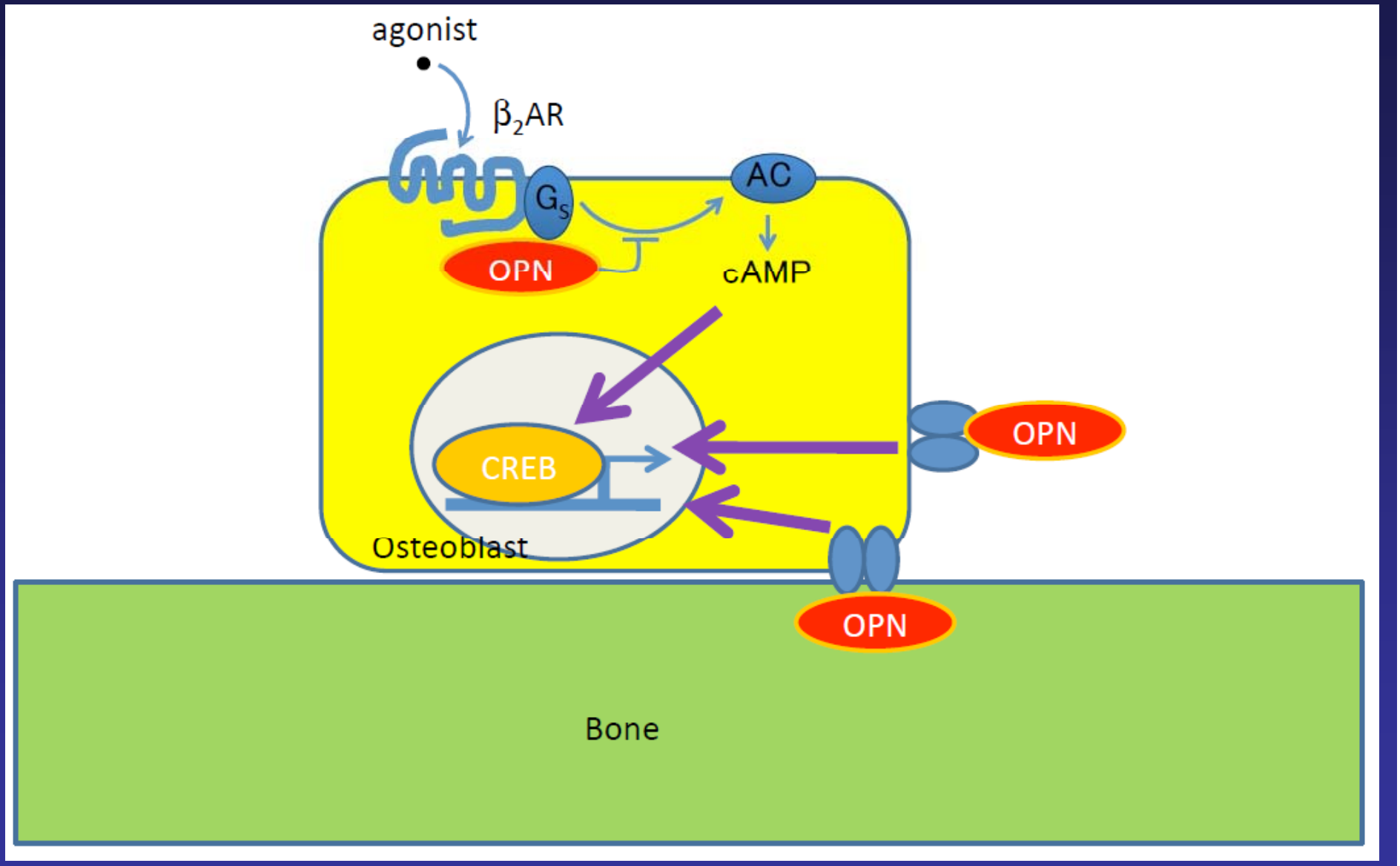


*p<0.05

2 weeks susp

Karsenty & Noda et al.: Nature 2005


Hind Limb Unloading
Sympathetic Nervous System
Resorption by Osteoclasts
Formation by Osteoblasts
Bone Mass



Nagao et al. PNAS 2011