Overview of Skeletal Remodeling and Bone Mass

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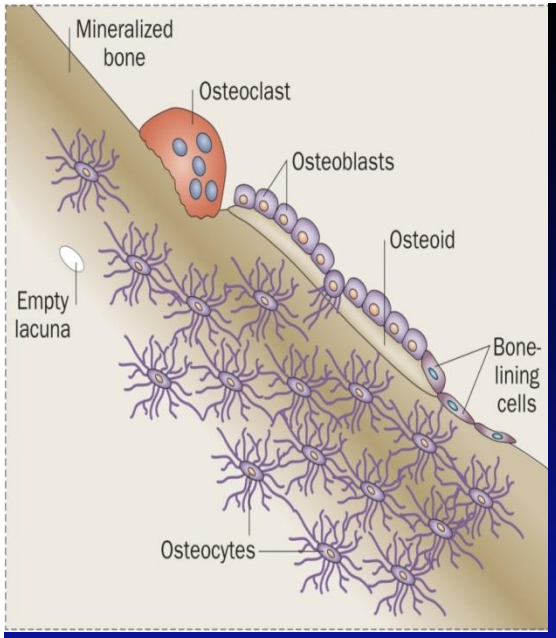
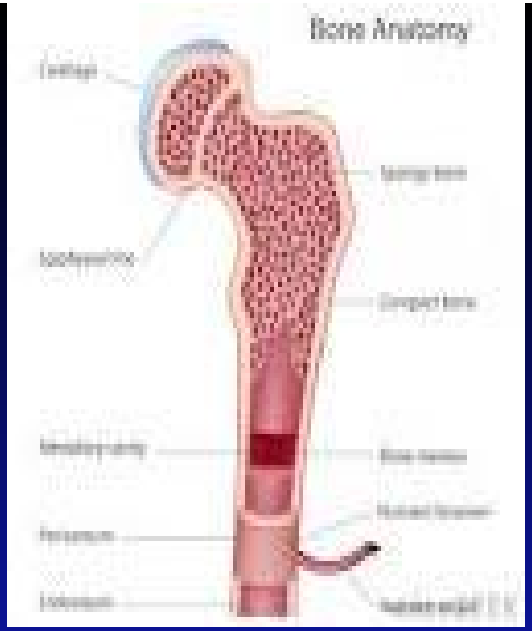
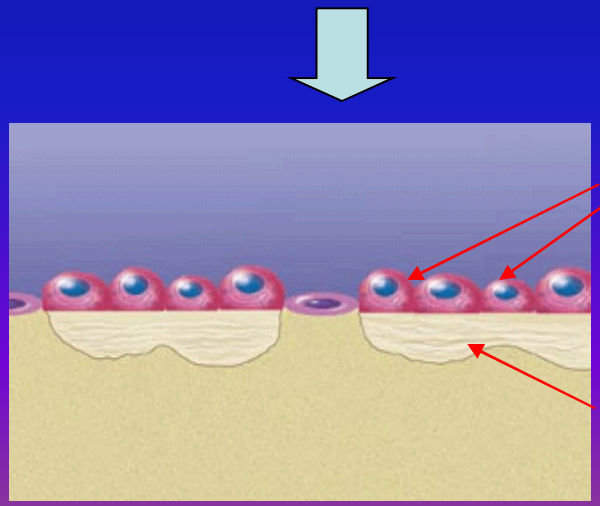
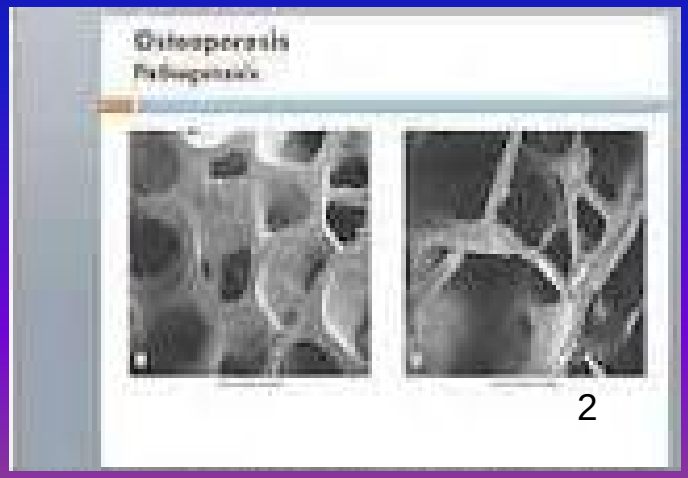




Bone Is a Dynamic Organ

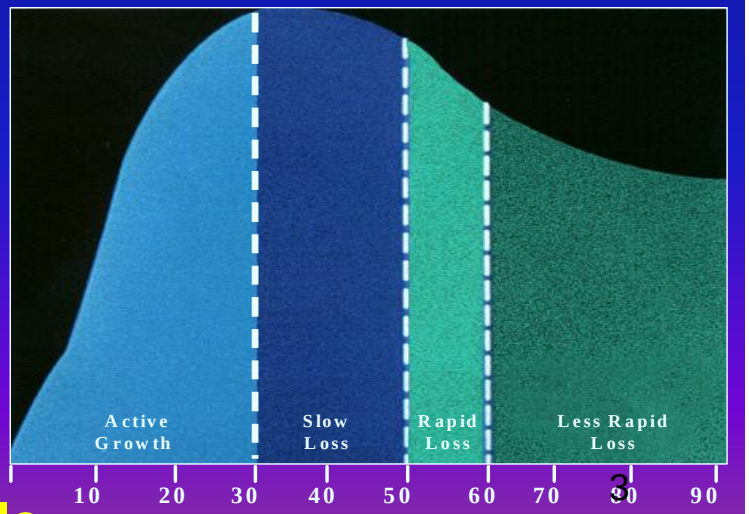


Osteoporosis

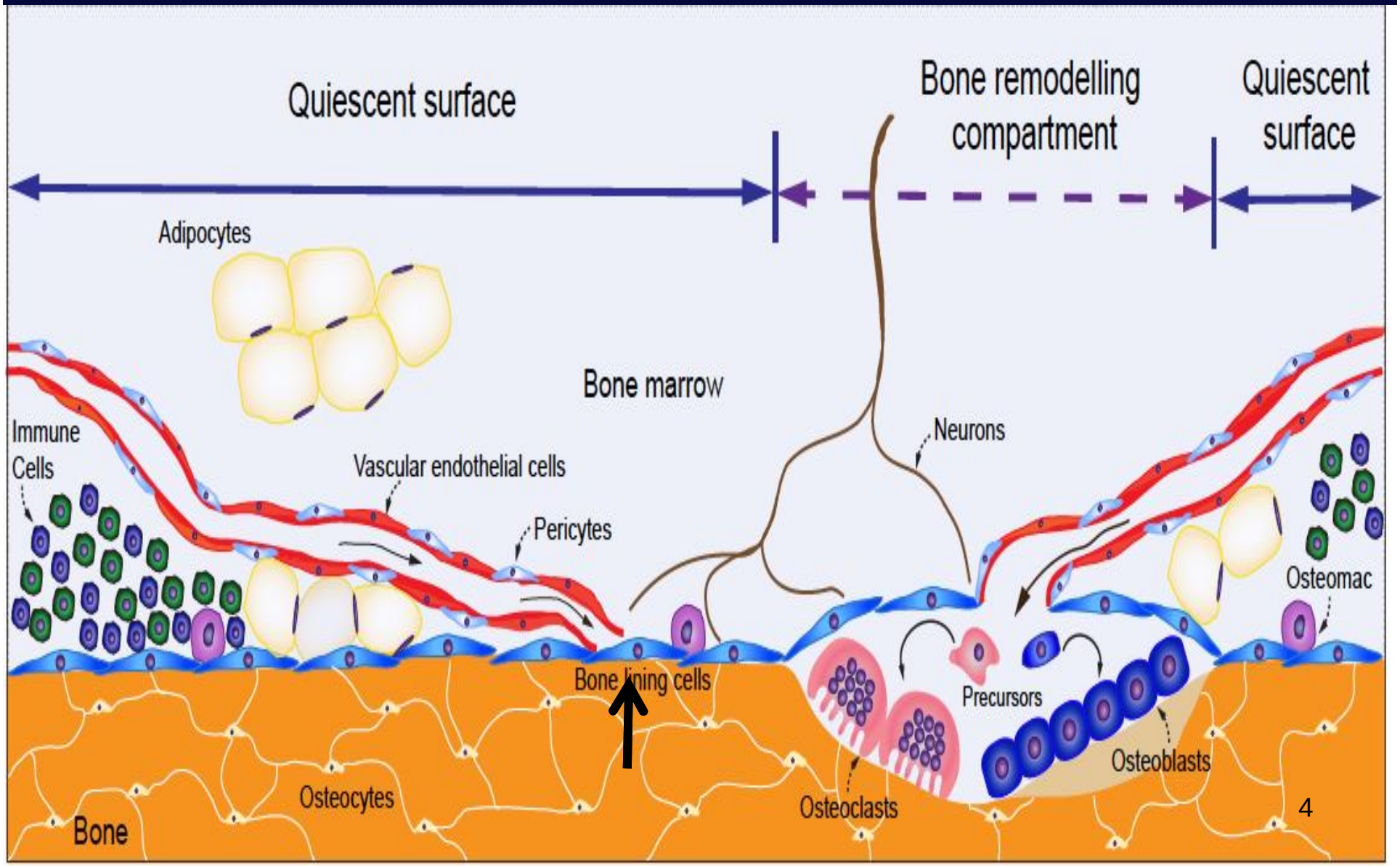


SKELETAL PHYSIOLOGY: Critical Phases

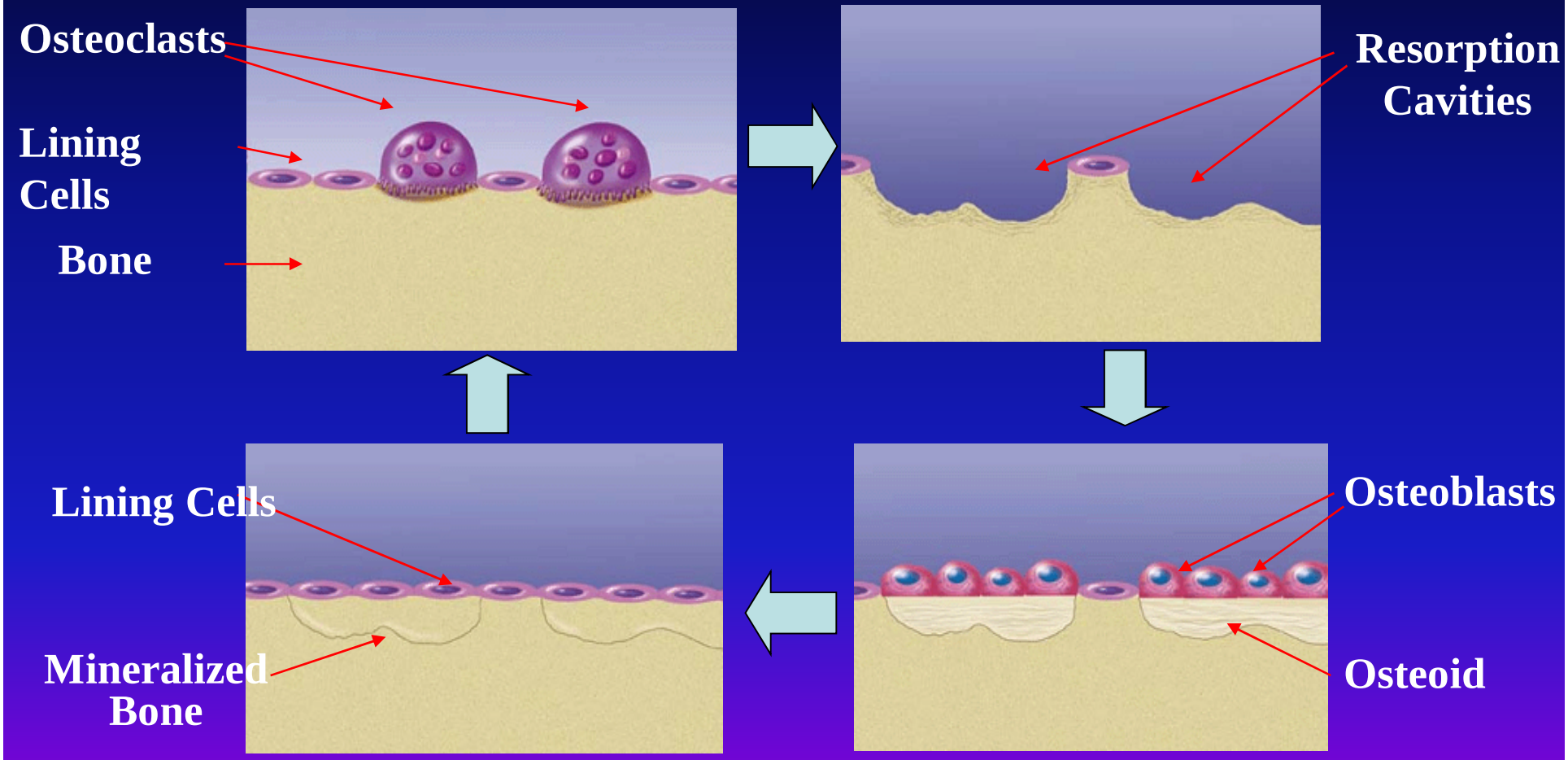
- **Skeletal Growth**
  - Prenatal to Adolescence
  - Modeling and remodeling
  - Early and Rapid linear growth which then slows before increasing with adolescence
- **Peak Bone Acquisition**
  - Ages 12-18
  - Gender and compartment specific!!!!
  - Strong genetic determinants
  - Phased with linear growth
- **Bone Maintenance**
  - Ages 20-50: Remodeling 10% of the skeleton/yr
- **Bone Loss**
  - Gender and compartment specific
  - Genetic determinants may play a role

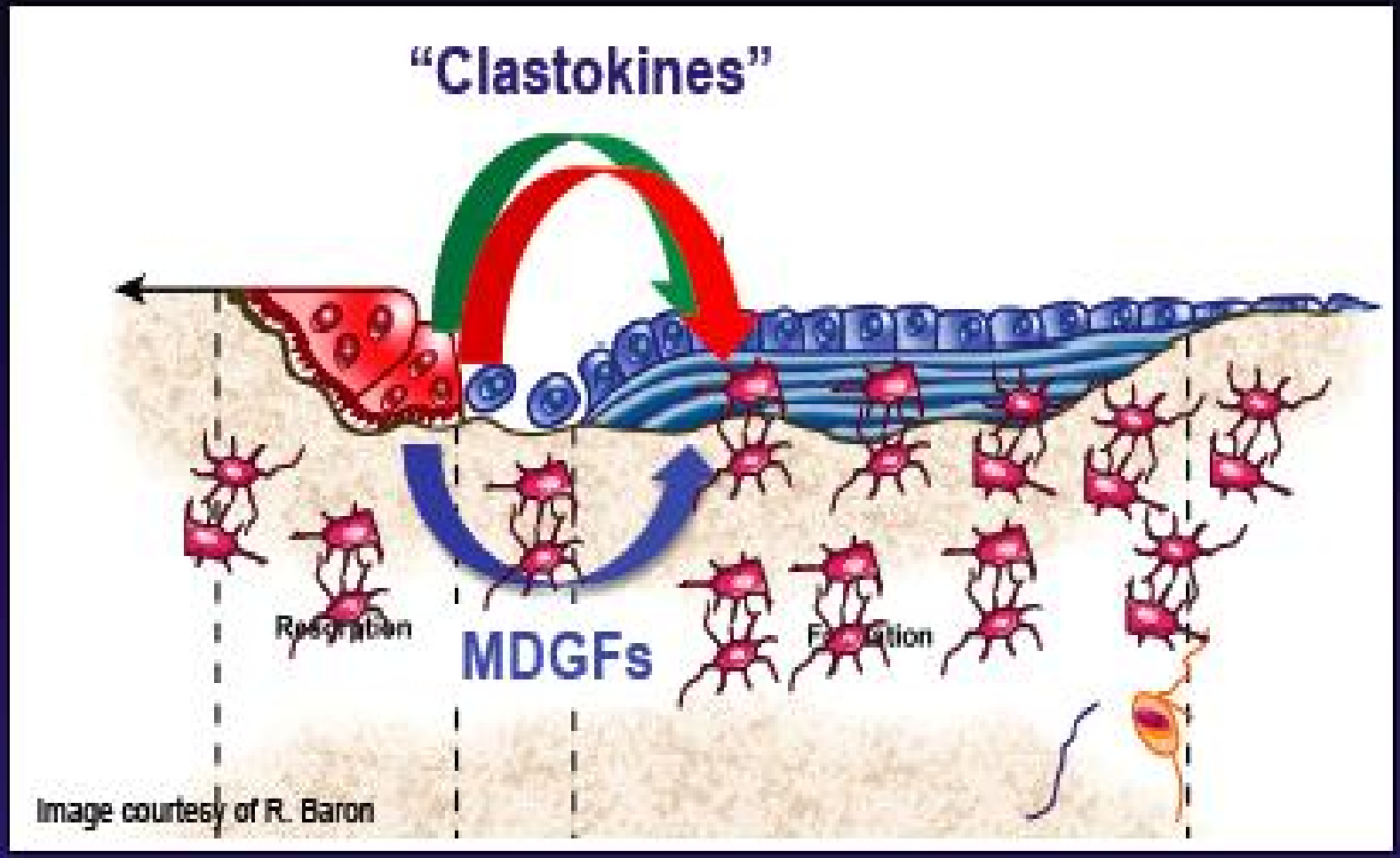


Cellular Complexity in the Bone Marrow N



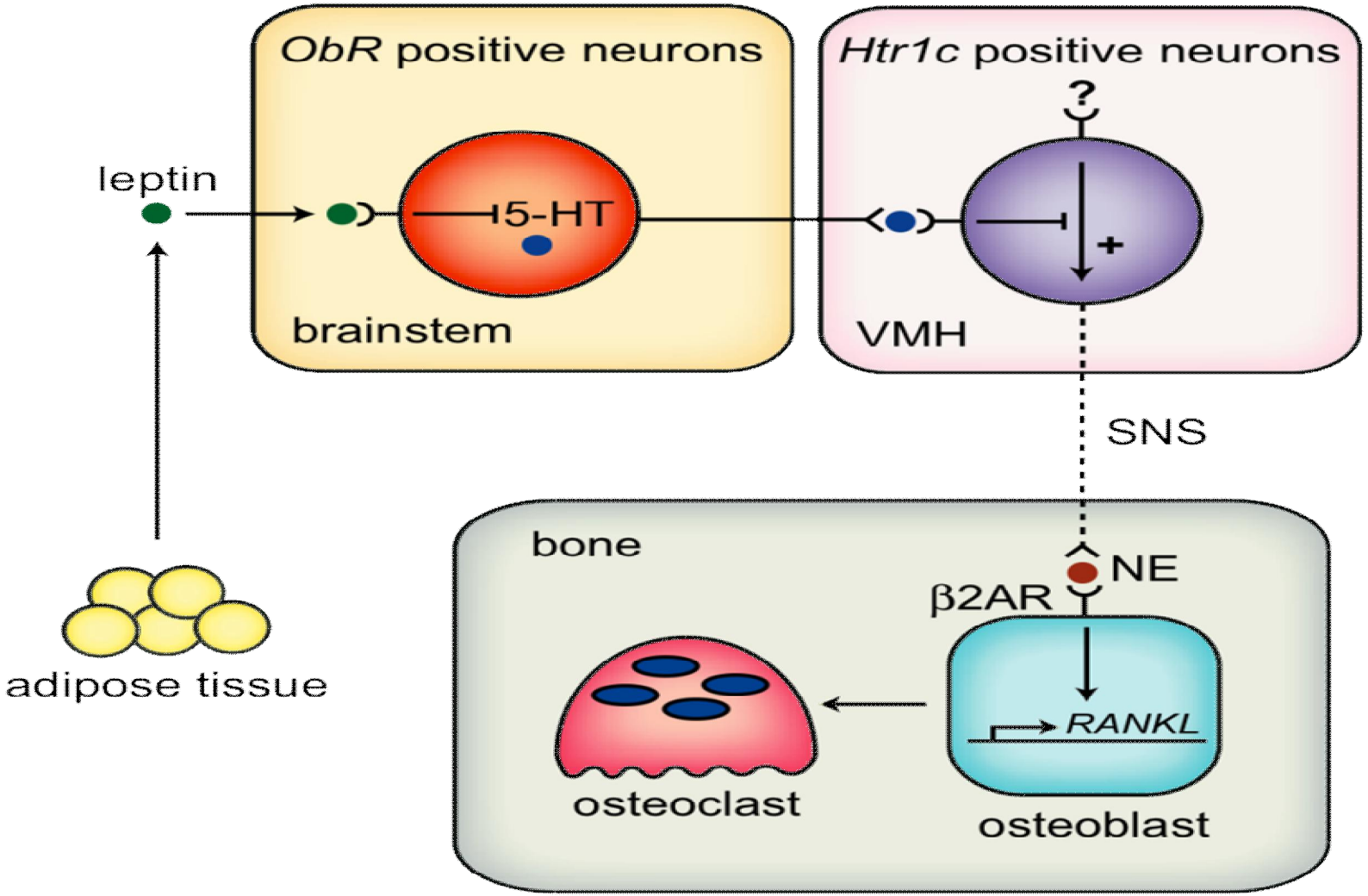
Bone Remodeling Process





- Direct effects on osteoblasts?
- Indirect effects via the osteoclasts and coupling?

The CNS Regulates Bone Turnover



Common Circuits:

Bone is Connected to Metabolic Homeostasis

SNS

SNS

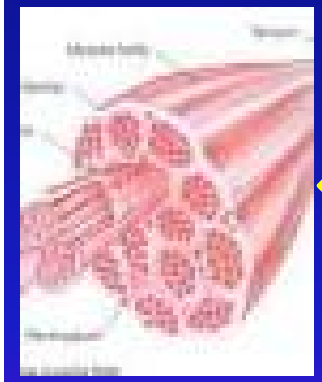
BDNF

Muscle

Bone

BAT

"Beige or Bright"

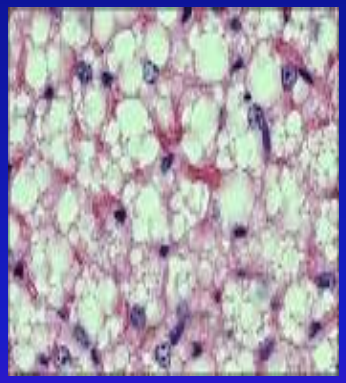


Pgc1a

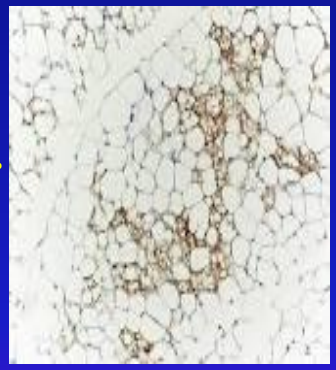
irisin

unOC

Wnt10b
Igfbp2



adiponectin



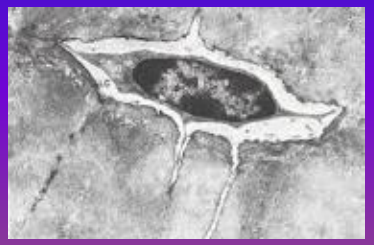
Sarcopenia

Osteopenia

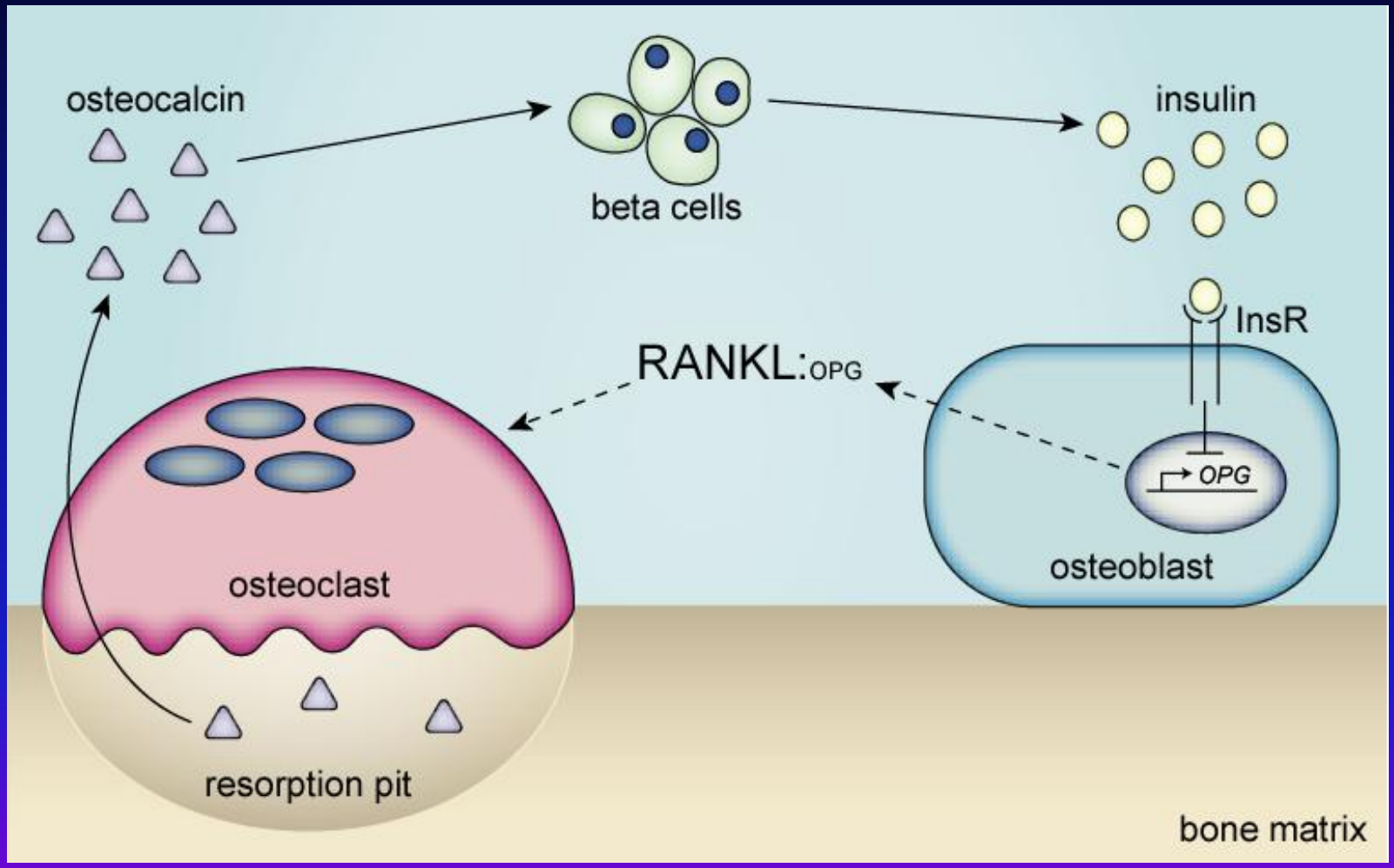
Cthrc1

BAT dystrophy

Lipoatrophy

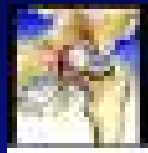


The Beta Cell, Osteoblast-Osteoclast Connection



Karsenty revised

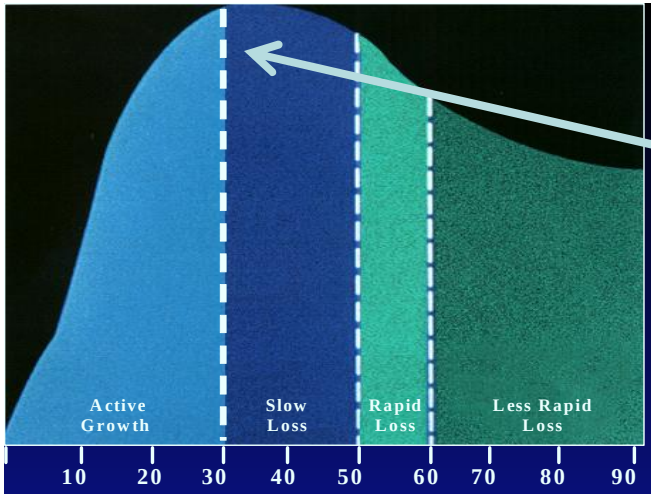
Definition of Osteoporosis From BMD



WHO Classification of BMD

Classification	T-score
Normal	-1.0 or greater
Low Bone Mass (Osteopenia)	Between -1.0 and -2.5
Osteoporosis	-2.5 and below
Severe Osteoporosis	-2.5 and below with history of fragility fracture

WHO Study Group 1994



Genetics 60%

Nutrition

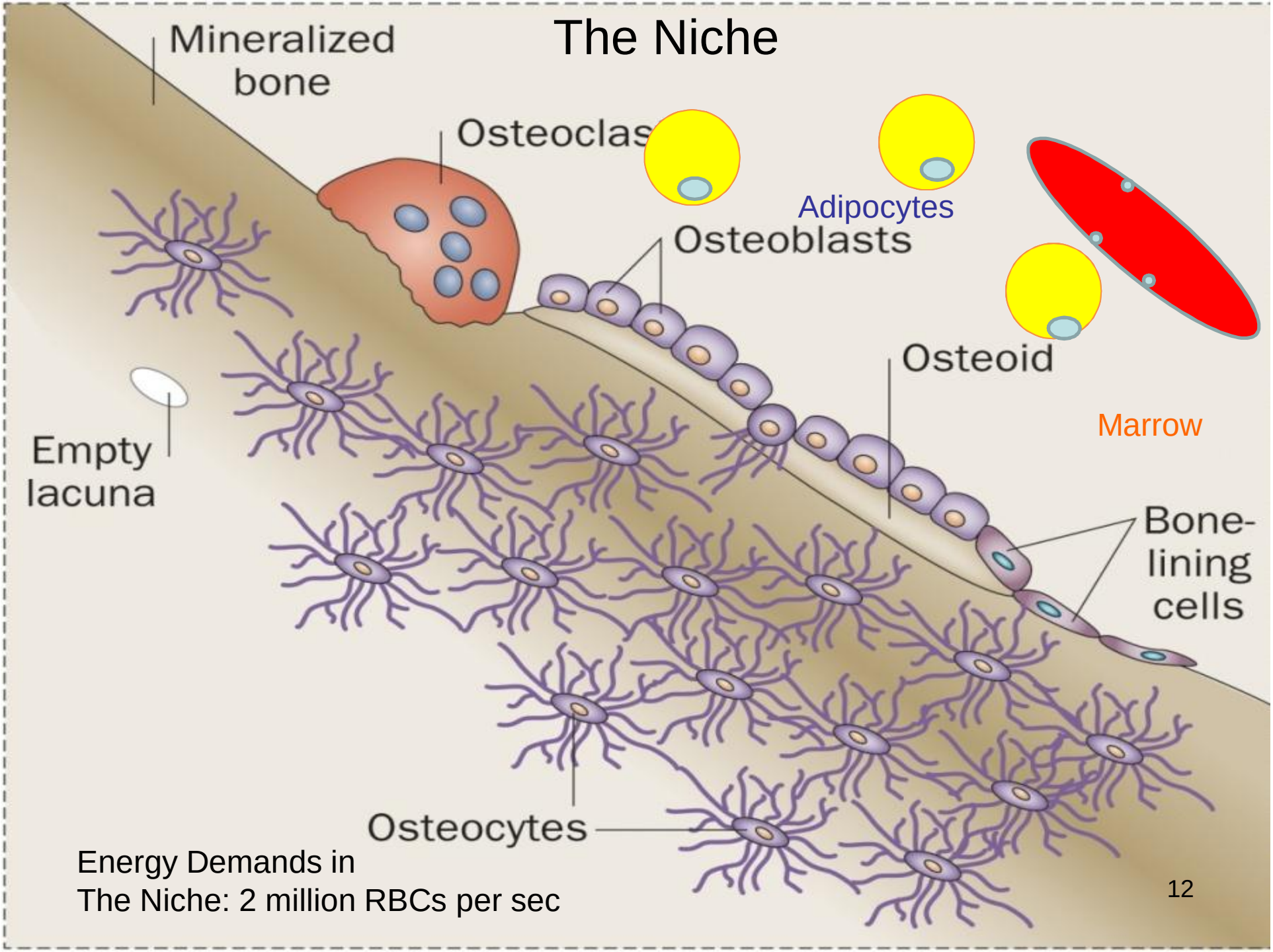
PEAK BONE MASS
12-22 years of age

Hormones

Lifestyle

- **PBM is a determinant of lifetime BMD**
- **BMD is the major determinant of future fracture**
- **Multiple factors contribute to PBM**
- **Genetic determinants are critical but are modifiable by environmental factors**

The Niche



Energy Demands in
The Niche: 2 million RBCs per sec

The Marrow is Far From Inert

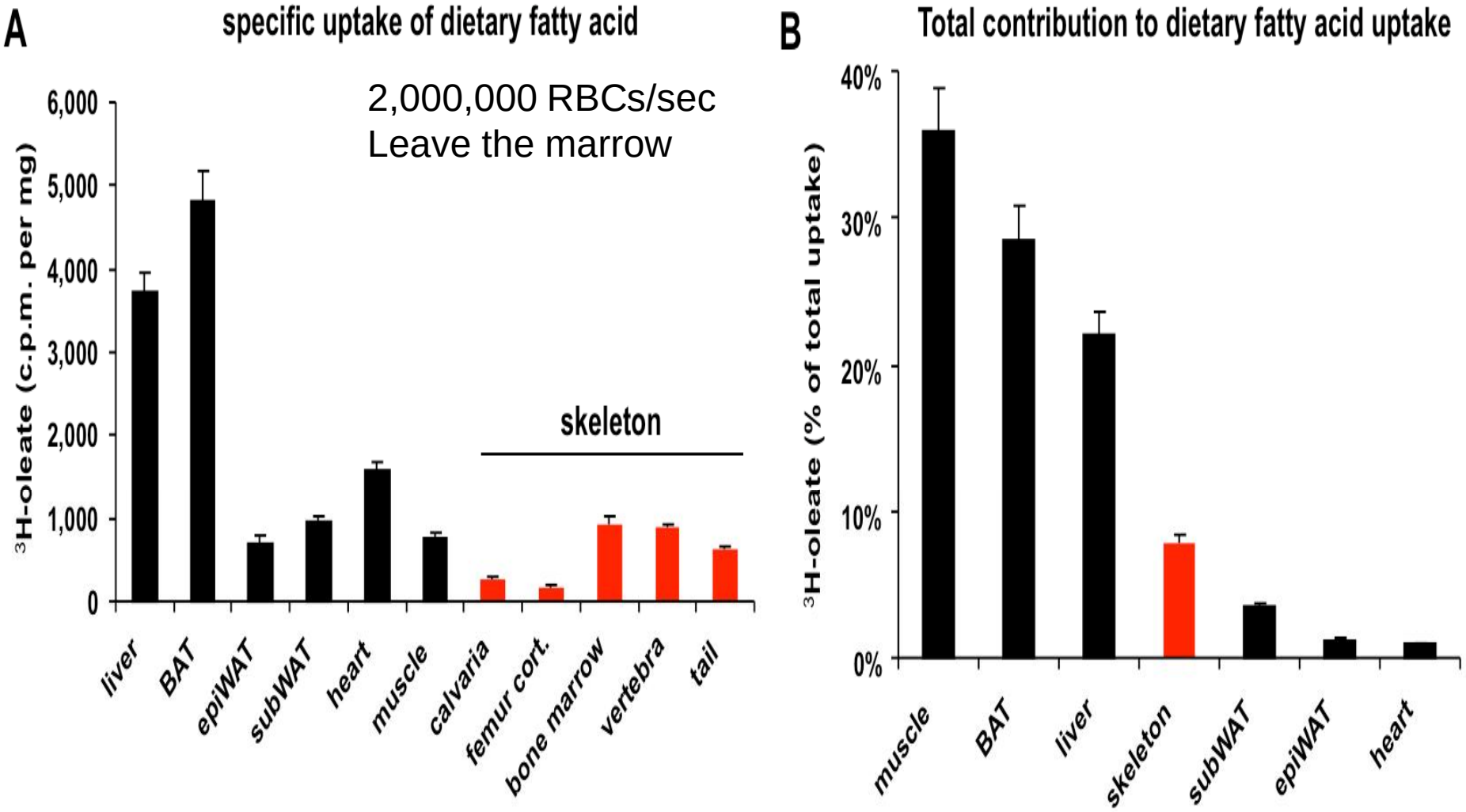
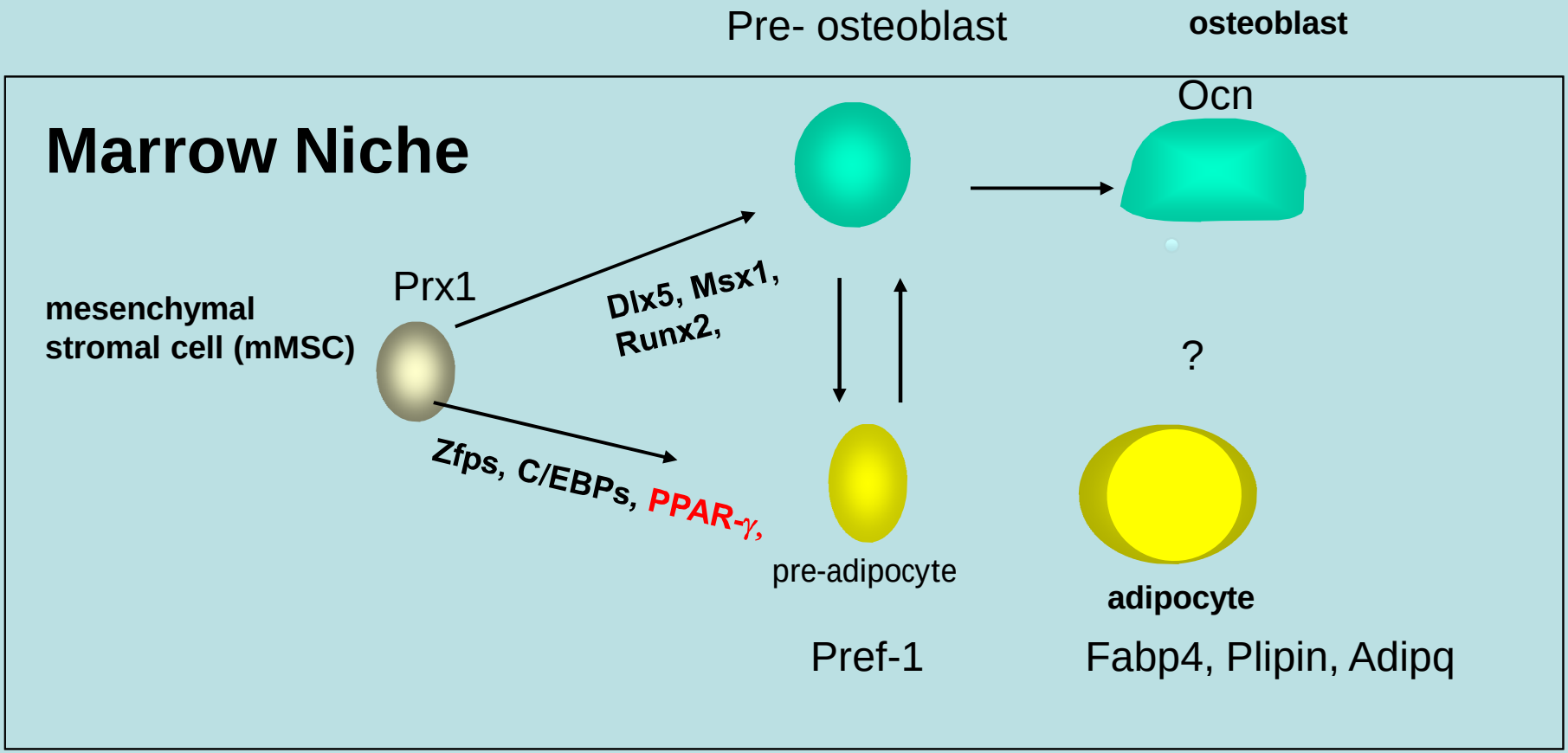


Fig. 2: The skeleton contributes to dietary fat clearance

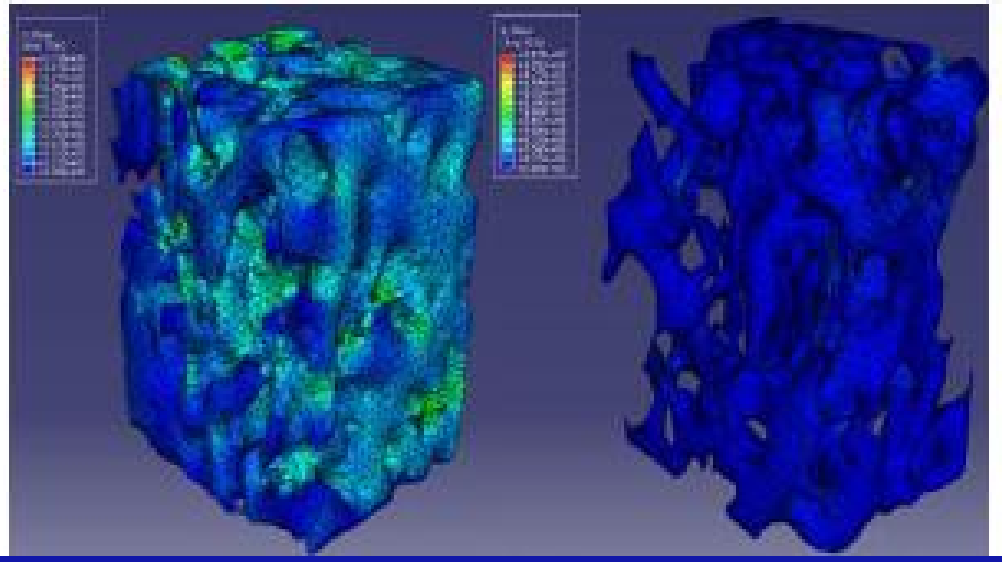
12 weeks-old male C57BL/6J wild-type mice received a lipid gavage (olive oil) with tracer amounts of ^{3}H-triolein. Fatty acid organ uptake 2 h after gavage was determined by scintillation counting. (**A**) Liver and brown adipose tissue (BAT) display the highest specific uptake of all organs analyzed. Parts of the skeleton (indicated in red) display specific uptake comparable to white adipose tissues, the major specialized lipid storage organ. epiWAT: epididymal white

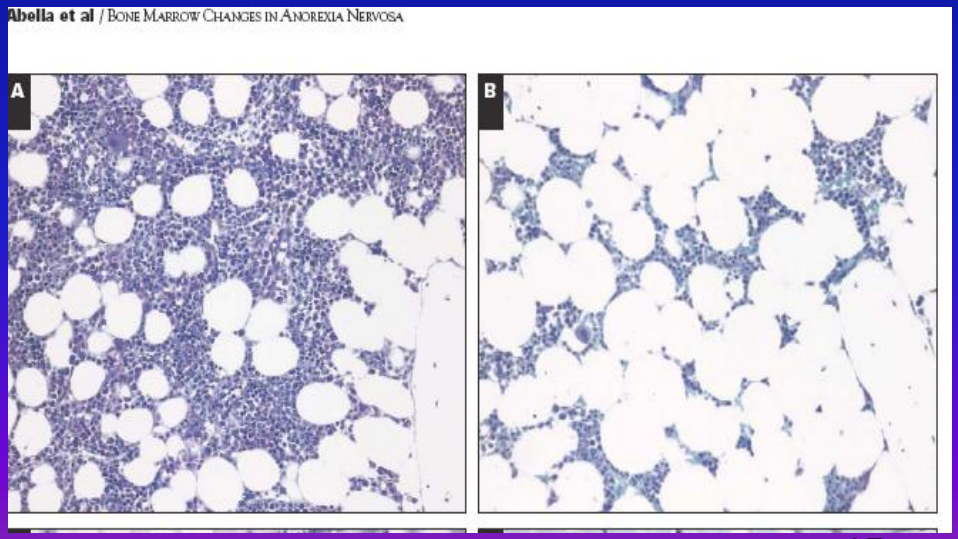
MSC Plasticity in the Marrow Niche:



Hypothesis: Cell Plasticity is fuel dependent

Anorexia Nervosa: A Classic Case of Limited Fuel Availability a marrow lineage shift and skeletal fragility





Bredella et al JCEM, 2009

Osteoporosis- Obesity of Bone

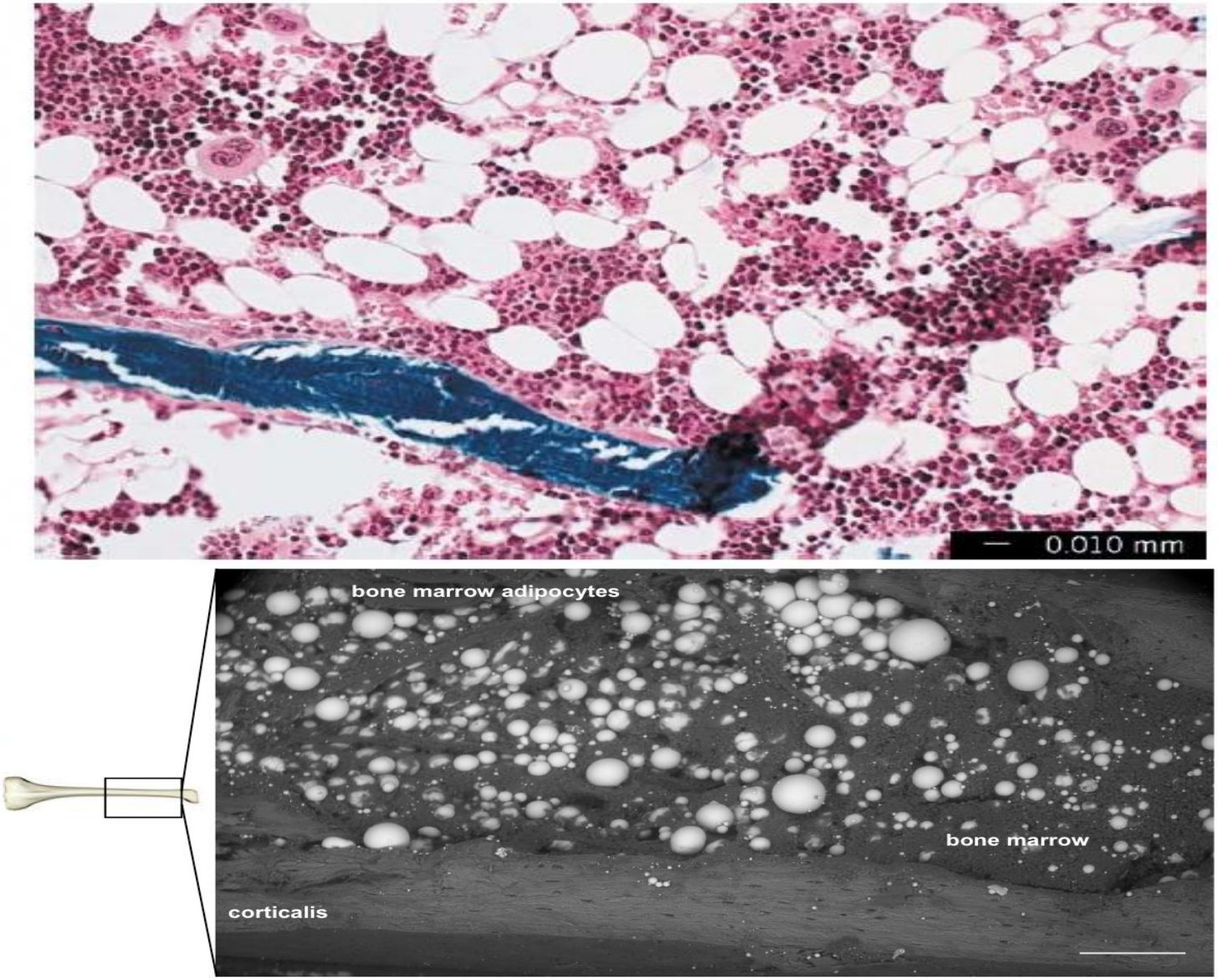


Fig. 1: The skeleton is a lipid storage organ.
Environmental scanning electron microscopy (ESEM) scan from inside a mouse distal tibia. Bone marrow adipocytes appear as large, light spheres. It has long been recognized that the skeleton is a lipid storage organ: "*Good news puts fat on the bones*" (The Bible: Proverbs 15:30) bar: 0,25 mm

Summary

- Bone mass is determined by multiple genetic and environmental factors
- Bone remodeling is a dynamic process and is fuel dependent
- The fate of osteoblasts and adipocytes in the marrow help determine peak bone mass and bone loss
- Nutrient and environmental determinants play a major epigenetic role