Melorheostosis
Current Understanding and Recent Developments: 2006

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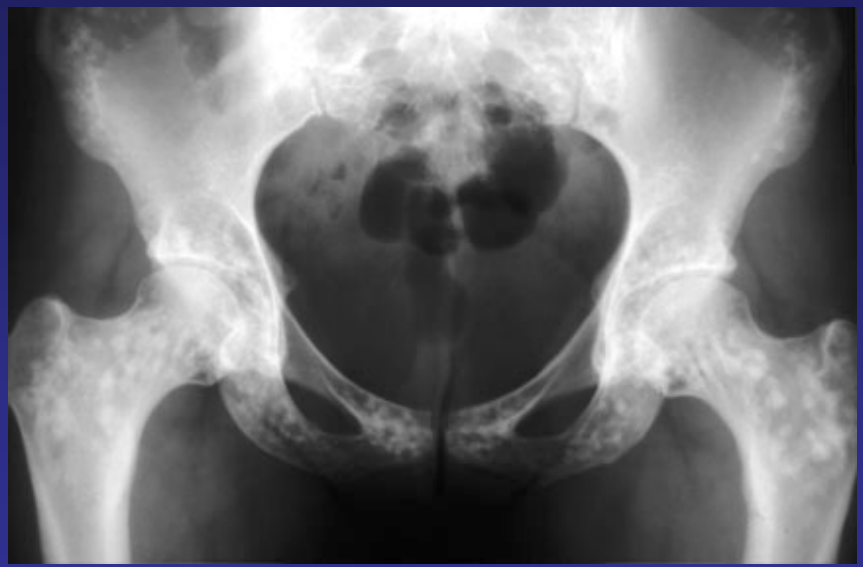
Clinical Diagnoses

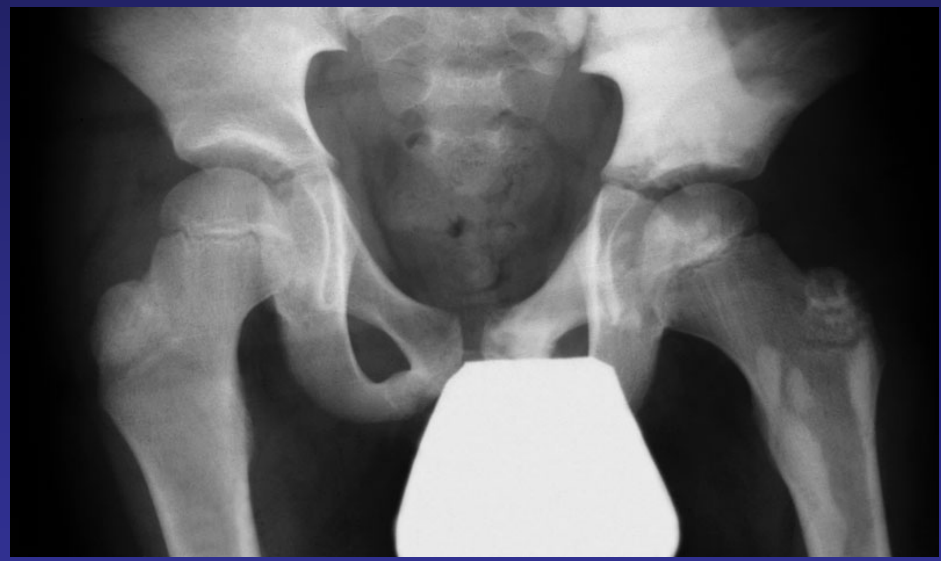
- Osteopoikilosis
  - Autosomal Dominant Inheritance
  - Multiple hyperostotic areas
- Buschke-Ollendorff Syndrome
  - Autosomal Dominant Inheritance
  - Osteopoikilosis with Connective tissue nevi
- Melorheostosis
  - ? Somatic mutation (Segmental type II)
  - Flowing hyperostosis with adjacent soft tissue abnormalities

Radiographic Appearance

Ostopoikilosis

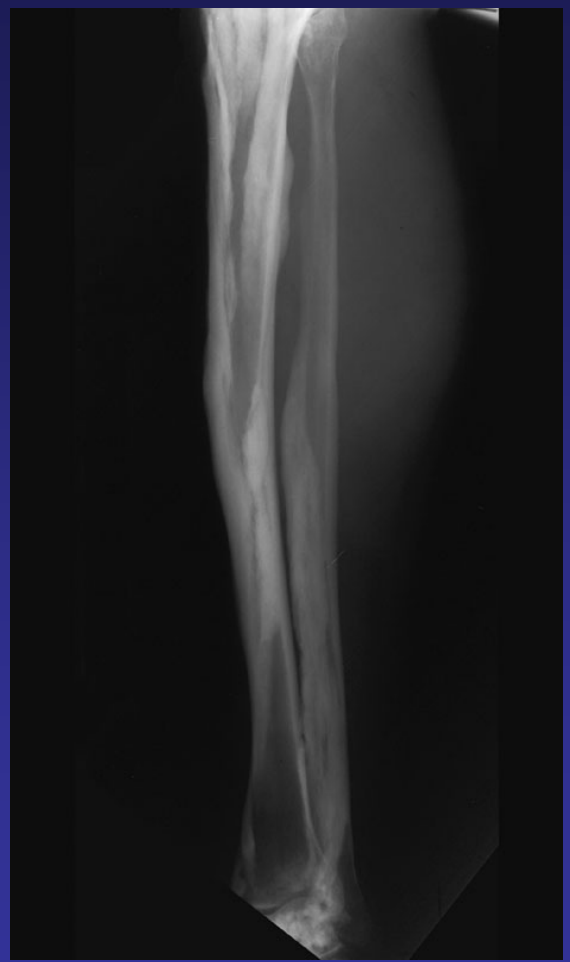


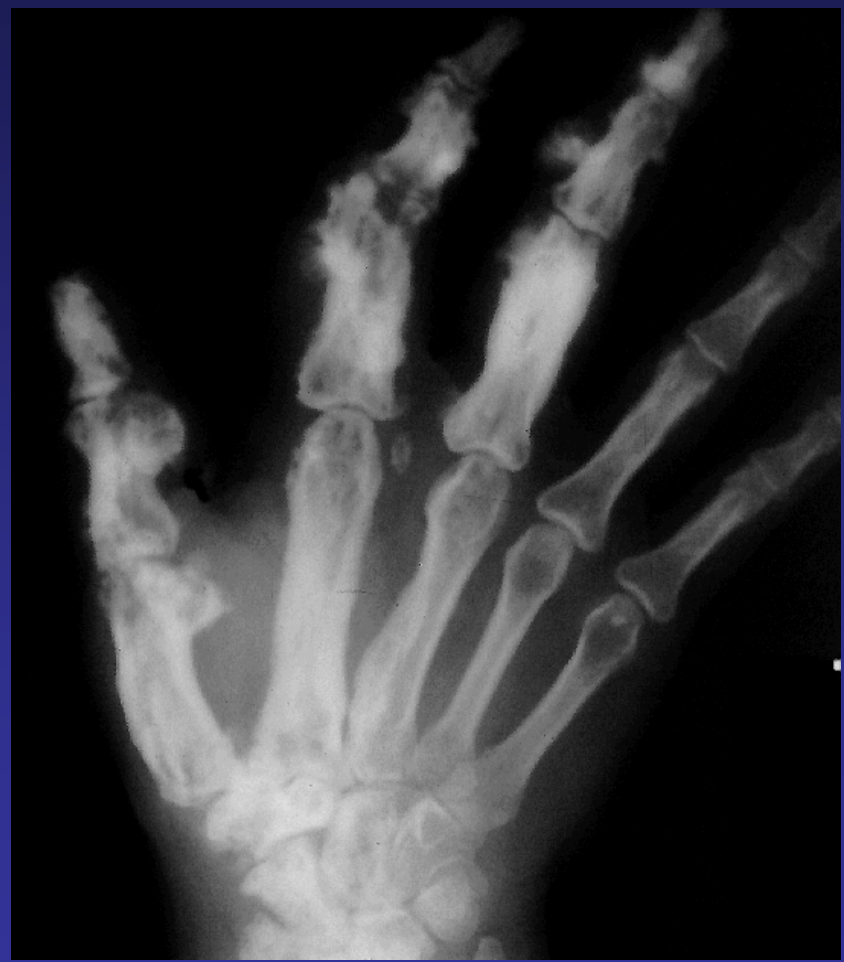
Melorheostosis



www.rad.washington.edu/ mskbook/dysplasia.html

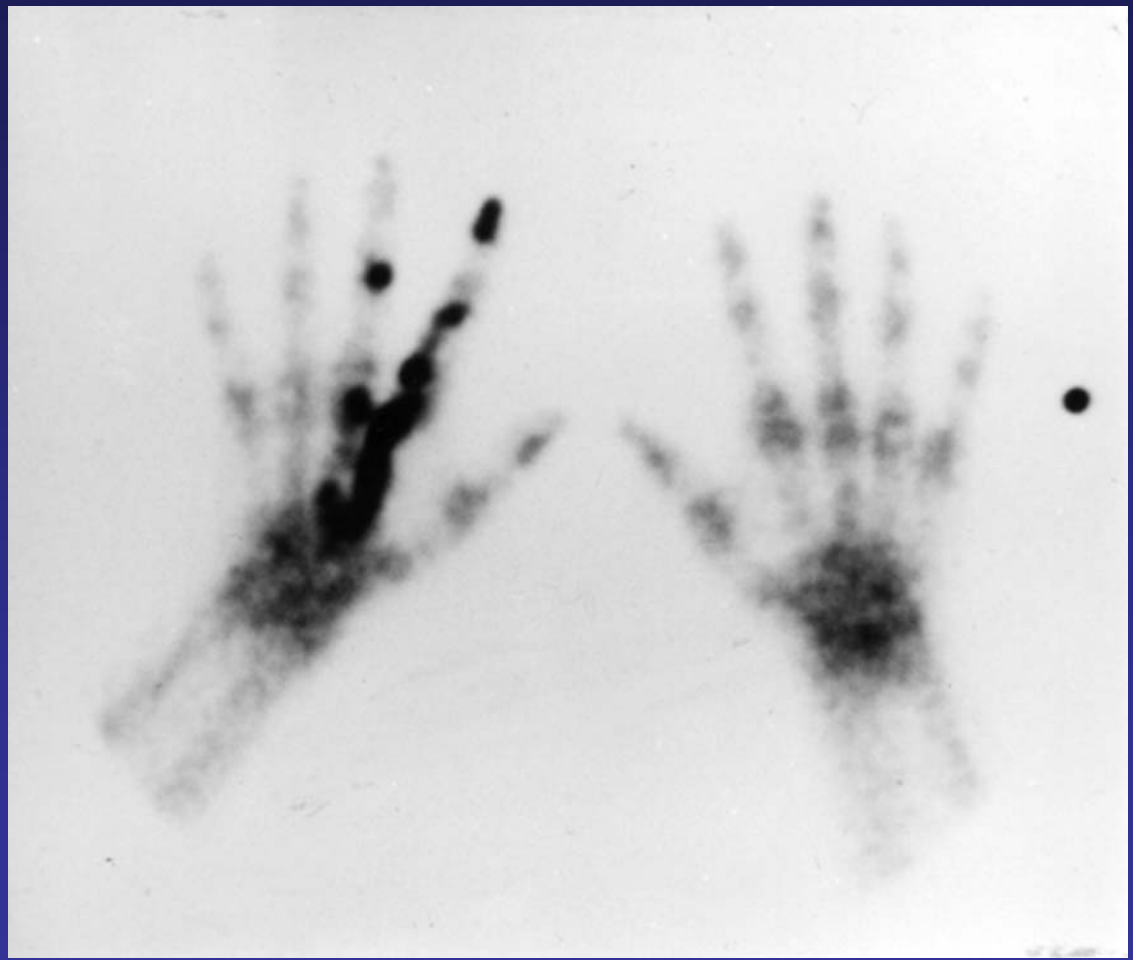
Melorheostosis "Candle Wax" Appearance





www.stevensorenson.com/ residents6/melorh9.gif

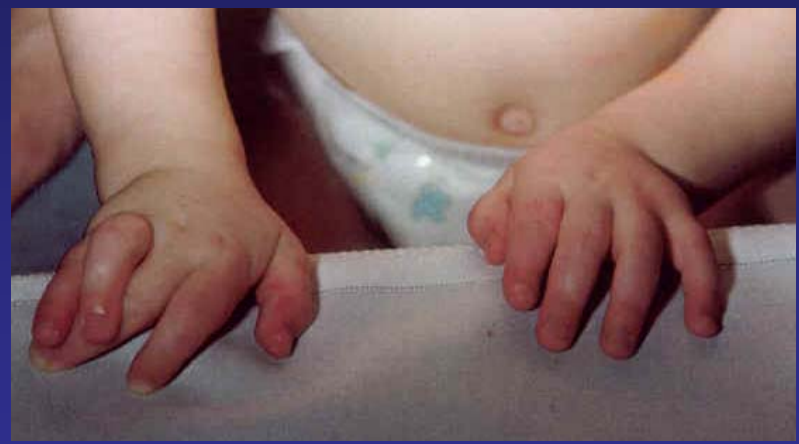
Bone Scan Findings



http://ard.bmjjournals.com/content/vol57/issue8/images/large/98133.f3.jpeg

Associated Problems

- Joint contractures
- Sclerodermatous skin lesions
- Muscle atrophy
- Hemangiomas
- Lymphoedema



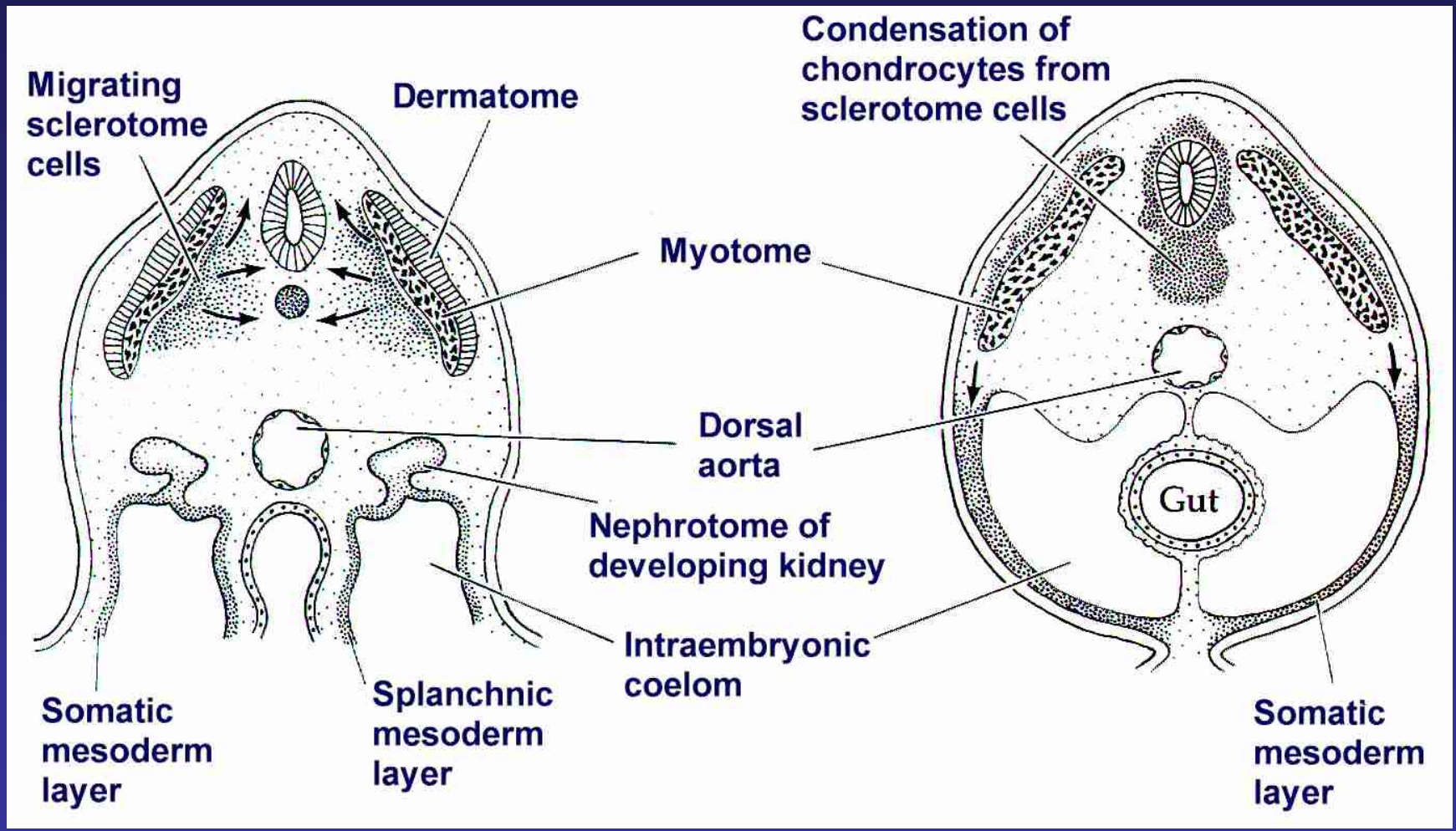
www.melorheostosis.org/ PIF_Monica.htm

“Segmental” Distribution

- Melo. lesions may correspond to a “sclerotome”
- Sclerotomes reflect the segmental pattern of early development

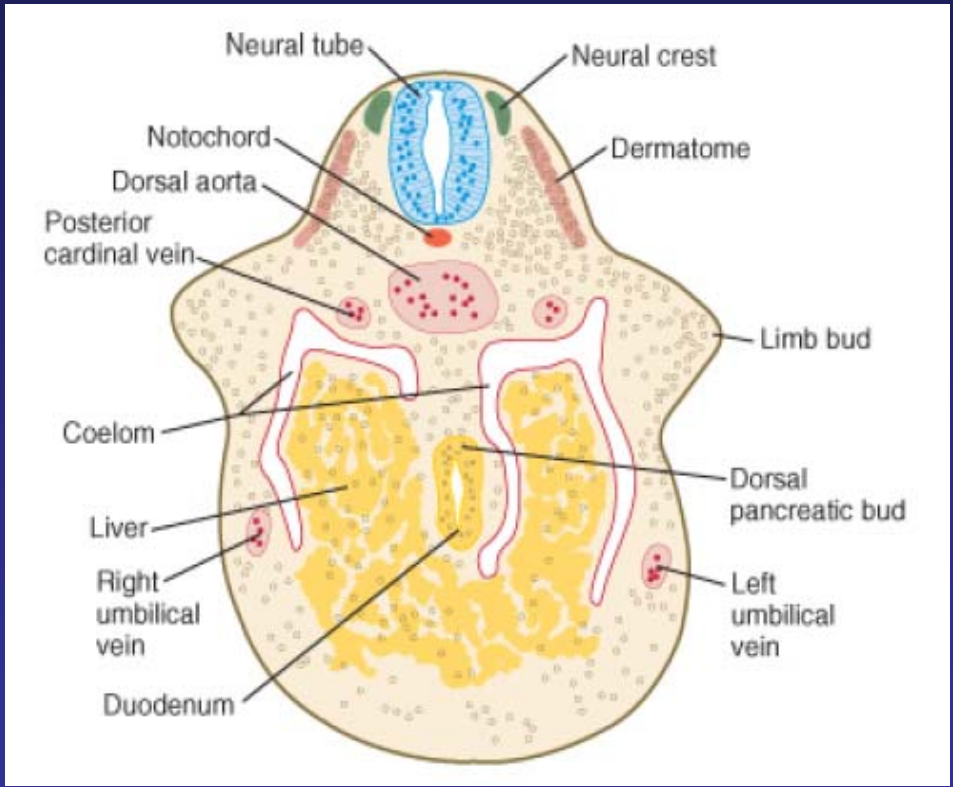
http://focus.hms.harvard.edu/2003/May2_2003/research_briefs.html

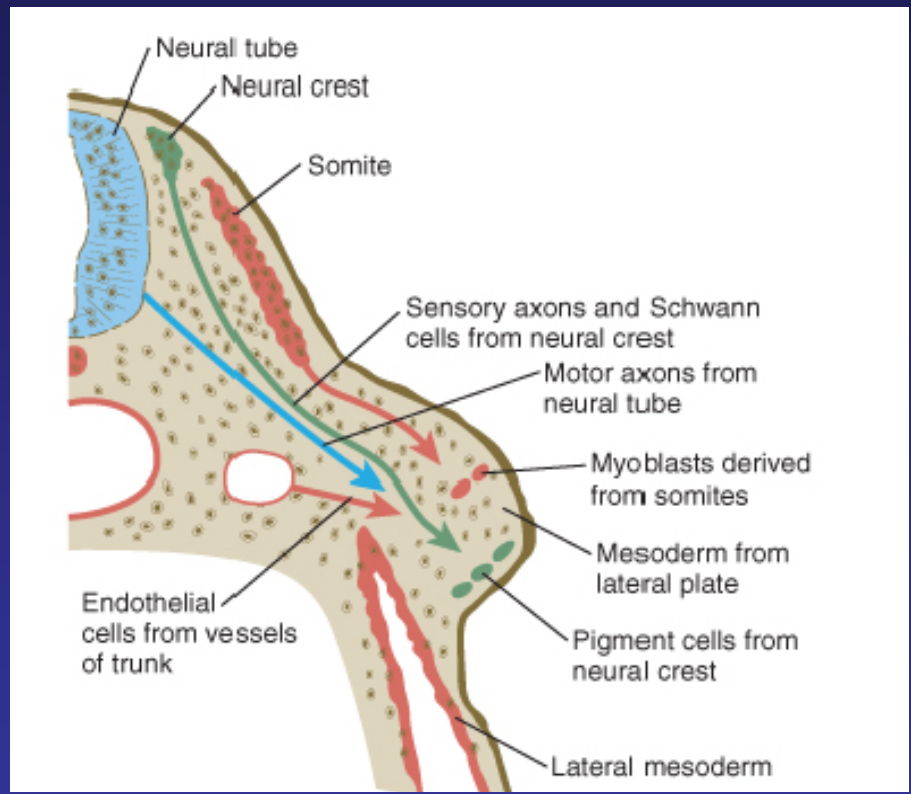
The Sclerotome Forms Cartilage and Bone



http://classes.aces.uiuc.edu/AnSci312/Bone/Gil%209%205%20Somites%20migration%20human.jpg

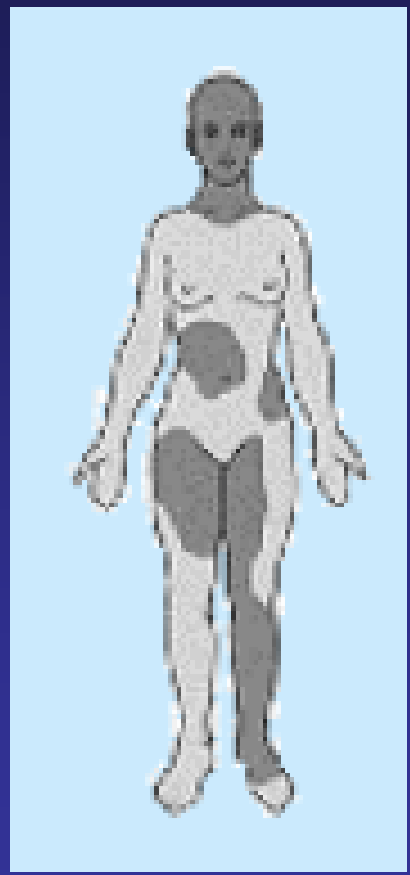
Cartilage-Forming Cells Migrate from the Sclerotome to the Limb Buds





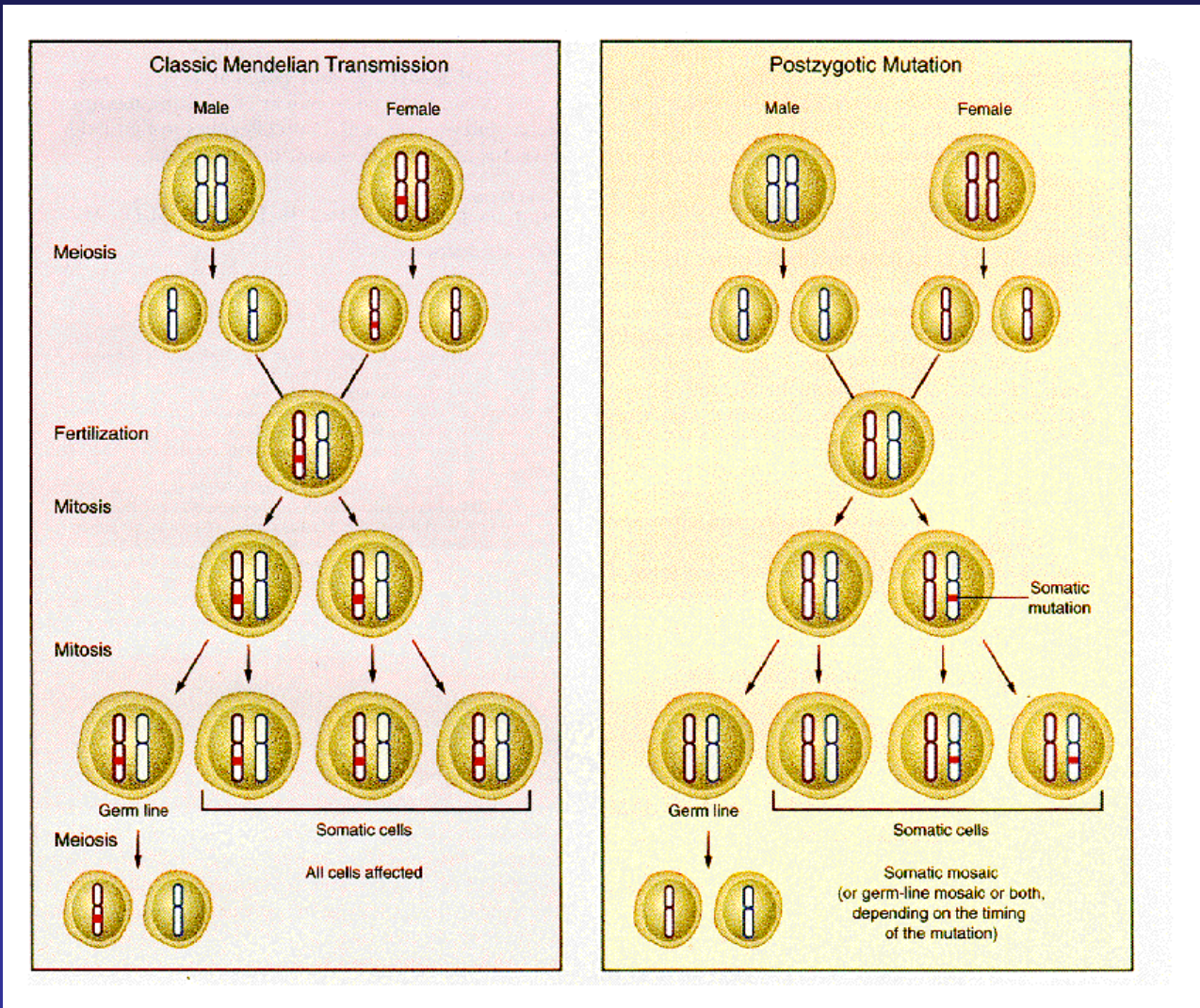
Segmental Distribution Suggests a Somatic Mutation

Anomalies found only in certain segments of the myotome, dermatome, or sclerotome may be due to a “somatic mutation,” i.e. a mutation that occurred *after* embryonic development has begun.

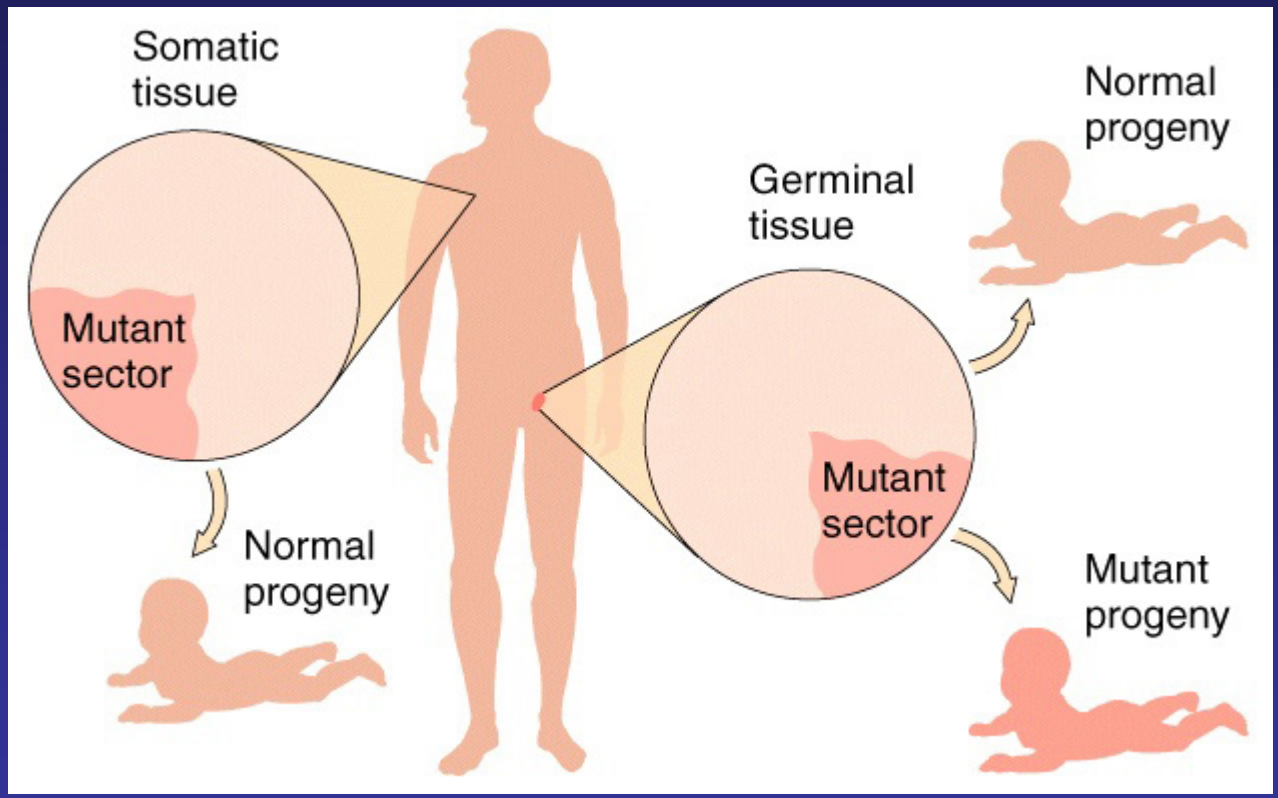


http://members.shaw.ca/copingwithillness/april02Xinact2/sld014.htm

Somatic (Postzygotic) Mutations Lead to "Mosaicism"



Somatic Mutations Are (Generally) Not Transmitted



MAN1/LEMD3 Mutations and Osteopoikilosis

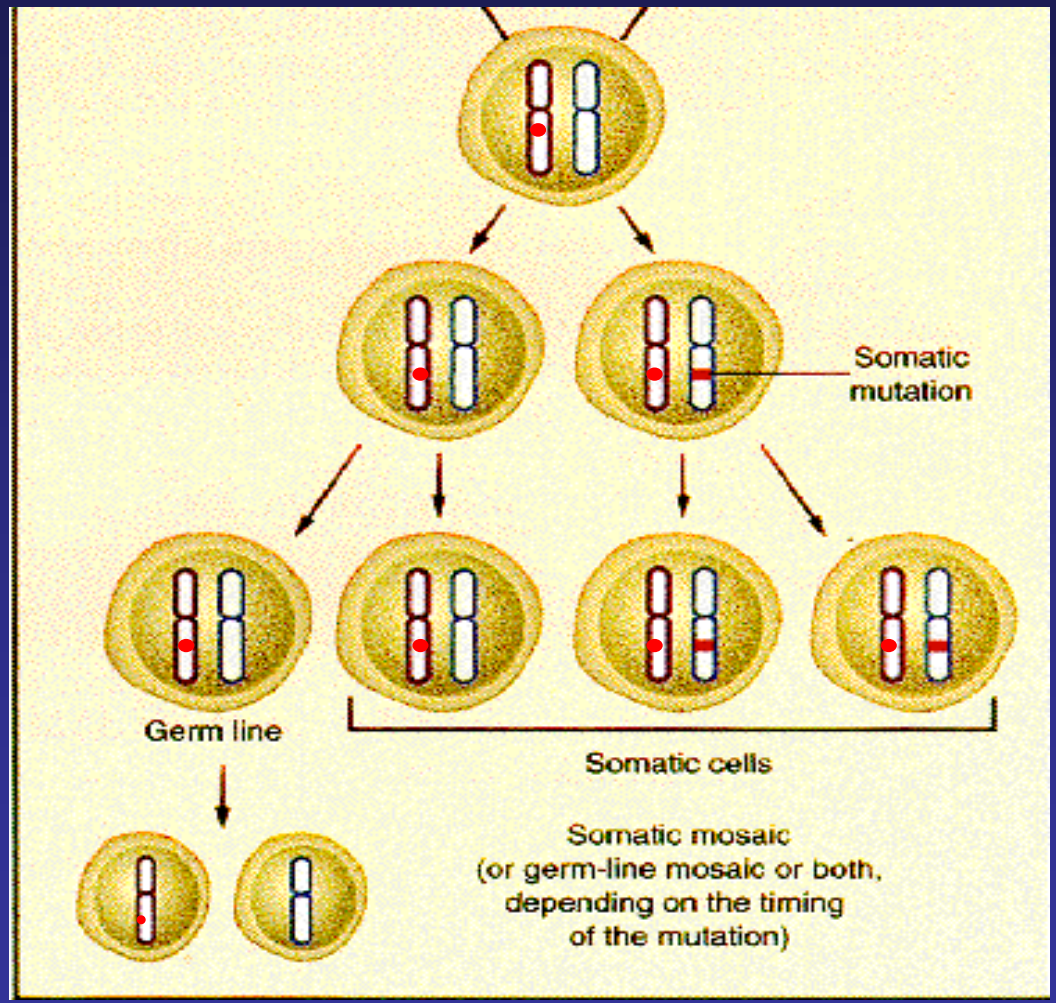
- Mutations resulting in “loss of function”
- Identified in the LEMD3 gene
  - Also known as the MAN1 gene
  - Also known as XMan1 or SANE in the Xenopus frog
- In patients with:
  - Osteopoikilosis
  - Buschke-Ollendorff Syndrome
  - Osteopoikilosis + Melorheostosis

Hellemans et al Nature Genetics 36: 1213-1218, 2004

MAN1/LEMD3, Osteopoikilosis, and Melorheostosis: A Theory

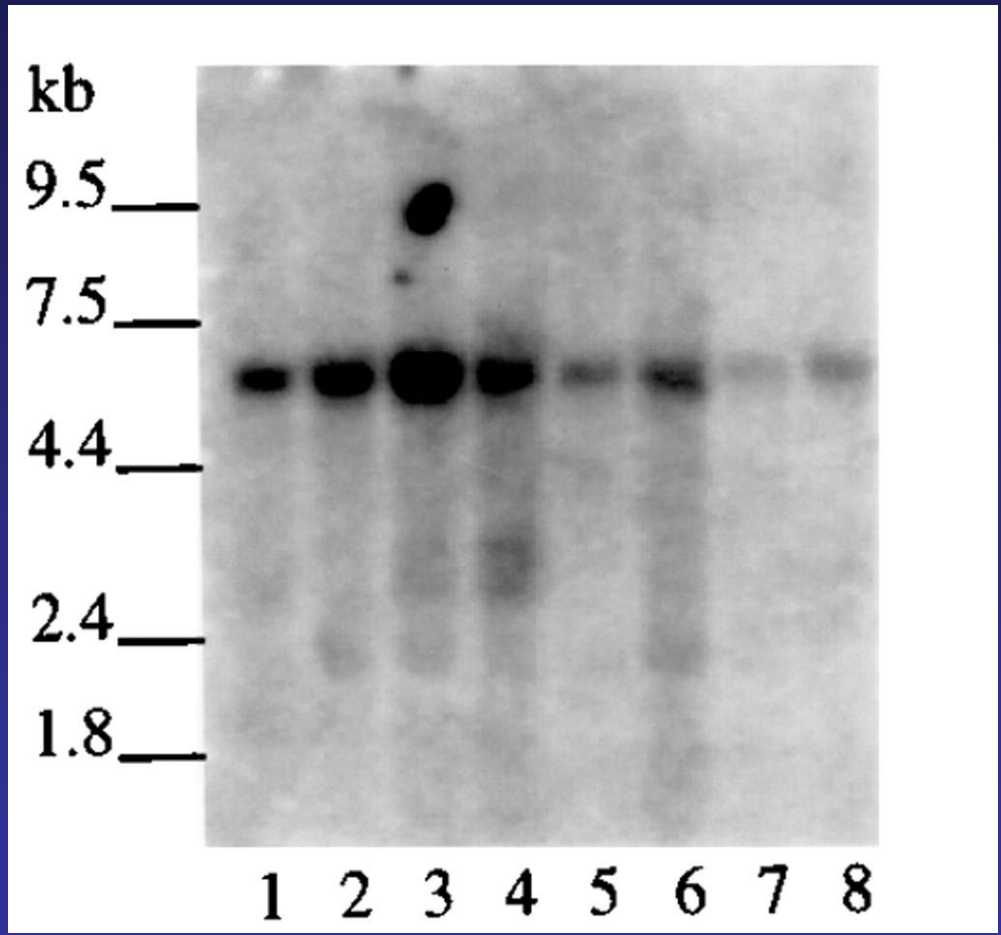
- Germline-transmitted mutations in MAN1/LEMD3 cause osteopoikilosis
- A second “somatic” mutation in MAN1/LEMD3 causes melorheostosis in bones and tissues derived from the involved segment (“second hit”)
- This second mutation is only expected in the involved tissue

Testing the "2nd Hit" Theory



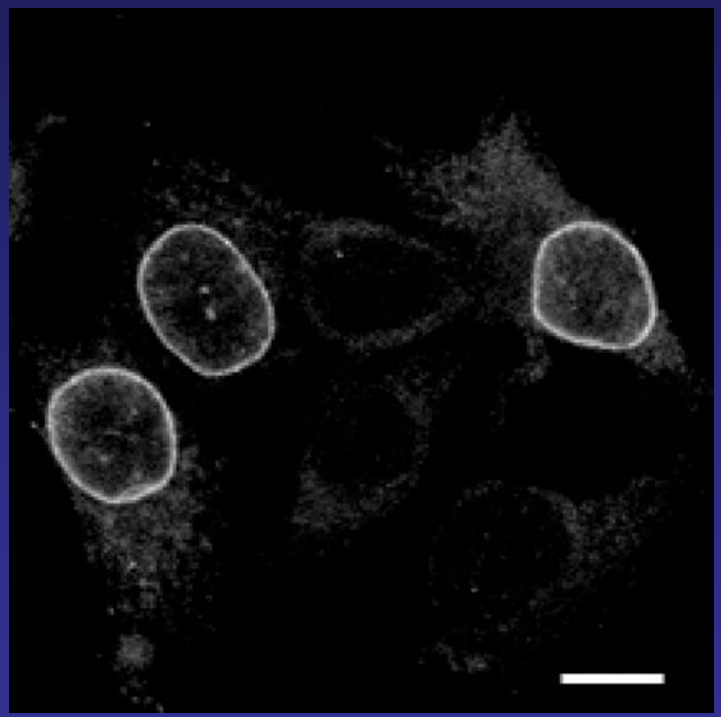
- Tested theory: No "second hit" found in involved skin tissue
- Osteoblasts not tested
- Entire gene not sequenced
- Second hit gene not MAN1/LEMD3?

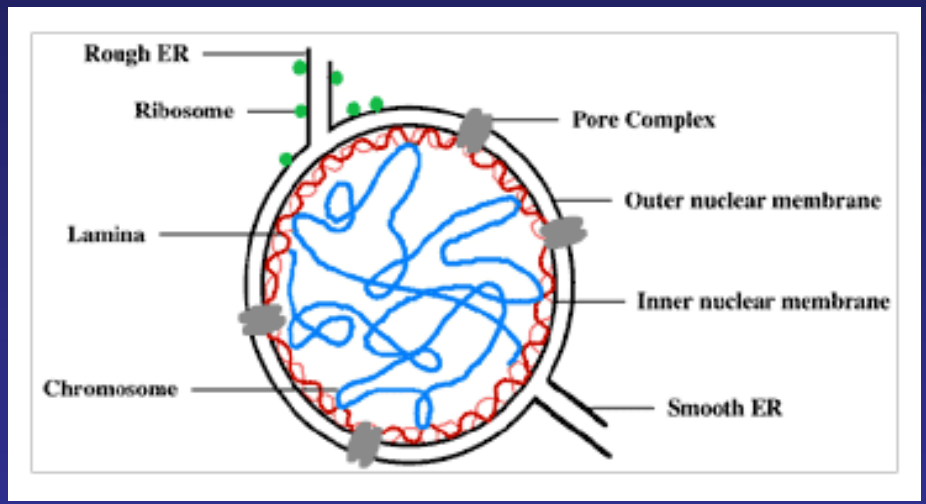
MAN1/LEMD3 is Expressed in Multiple Tissues



Lin, F. et al. J. Biol. Chem. 2000;275:4840-4847

MAN1/LEMD3 is an Inner Nuclear Membrane Protein





Lin, F. et al. J. Biol. Chem. 2000;275:4840-4847

Regions Identified in the MAN1/LEMD3 Protein

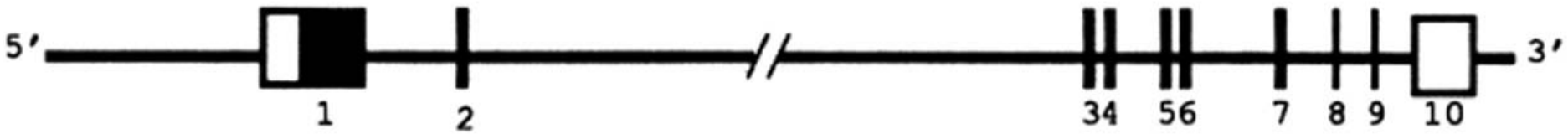
- 754 amino acids long
- Has a LEM domain
  - Region identified in three different proteins: LAP2, emerin, MAN1
  - LEM is 40 amino acids long
  - Function of LEM domain is unknown
- Has two membrane-spanning domains
  - Predicted to fold across a membrane

Lin, F. et al. J. Biol. Chem. 2000;275:4840-4847

MAN1/LEMD3 Mutations in Different Osteopoikilosis Patients

Hellemans et al Nature Genetics 36: 1213-1218, 2004

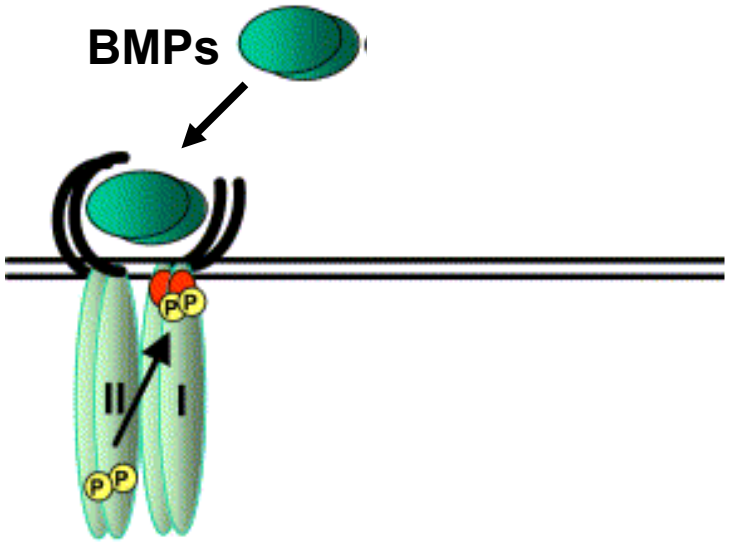
What is the MAN1/LEMD3 gene structure?



- 10 exons (rectangles) make up the mRNA
- 9 of these contain sequences encoding amino acids (black rectangles)

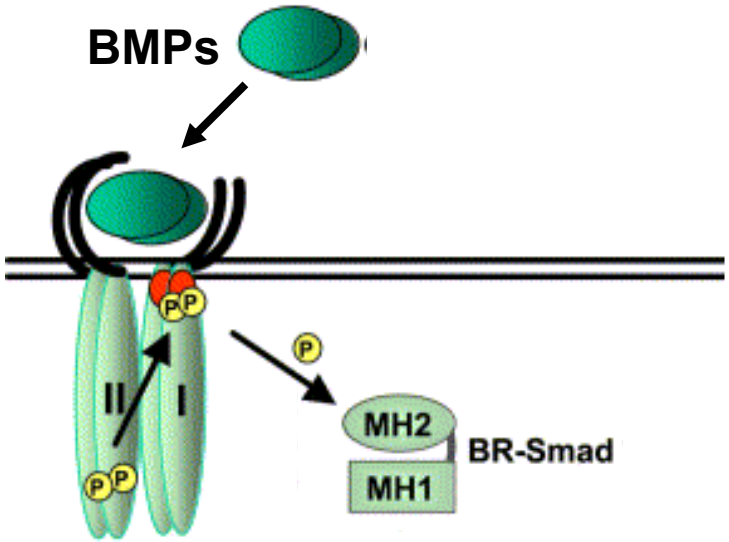
What Does MAN1/LEMD3 Do?

- Blocks the signal from Bone Morphogenic Proteins (BMPs) and from TGF-beta
- By Binding to SMAD proteins
- Preventing SMAD proteins from activating certain genes involved in bone formation
- Thus, loss of MAN1/LEMD3 leads to excess bone formation



Cell Membrane

Modified from:
Zwijsen, et al FEBS Letters 546:133-139, 2003



Cell Membrane

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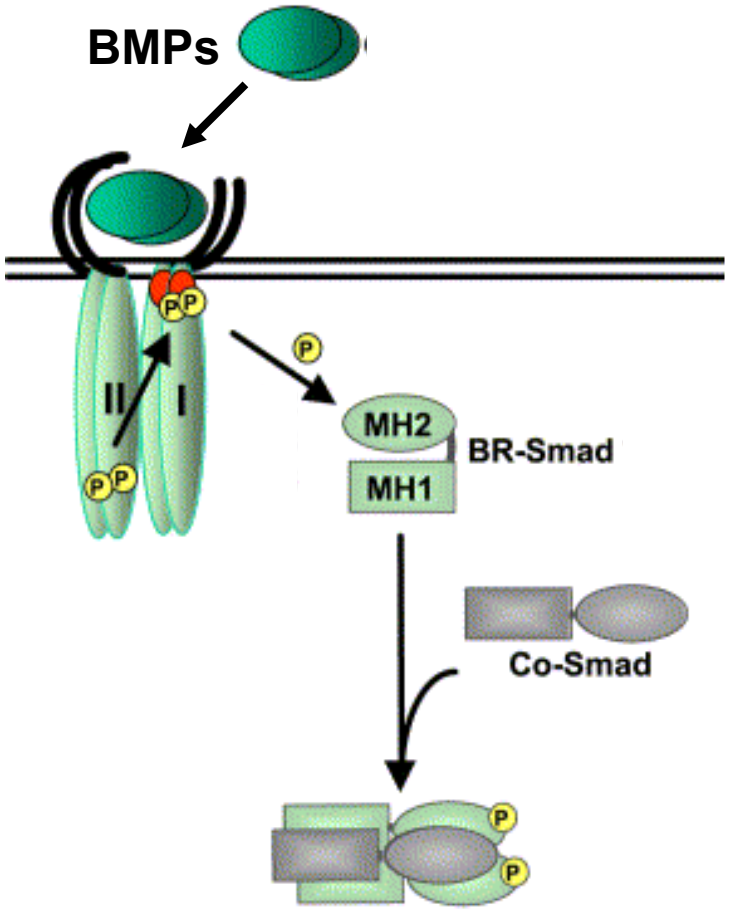

Cell Membrane

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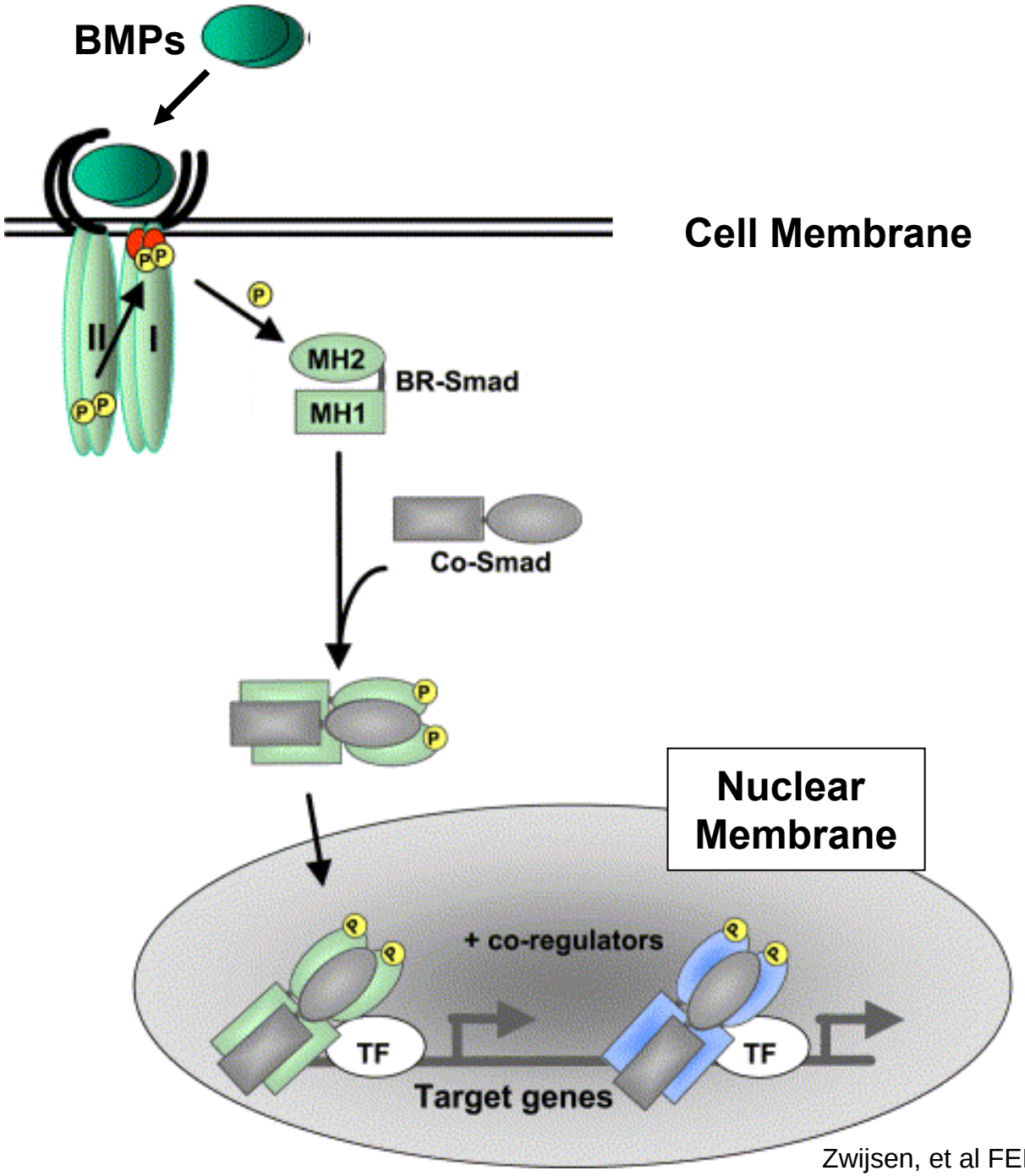

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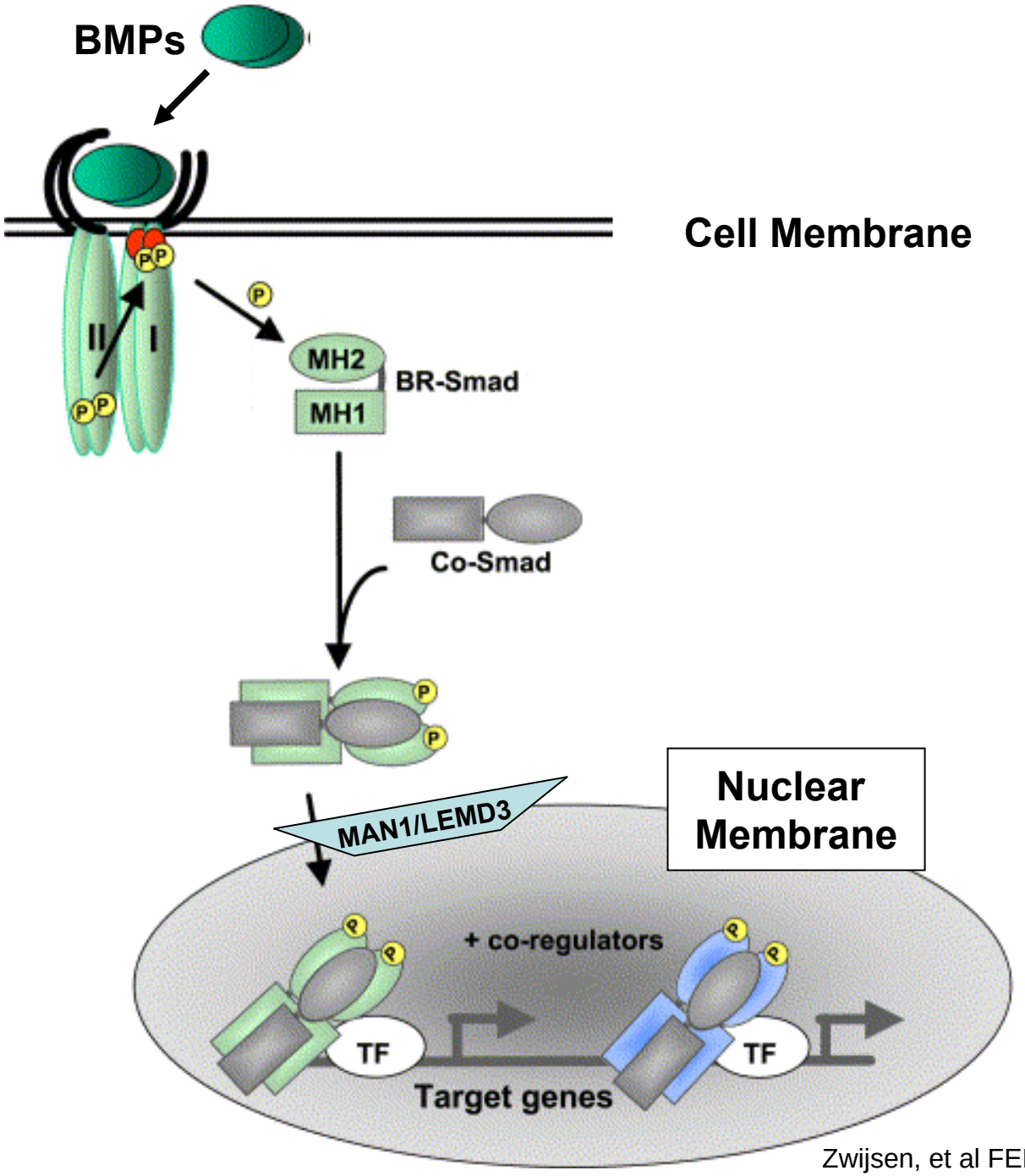

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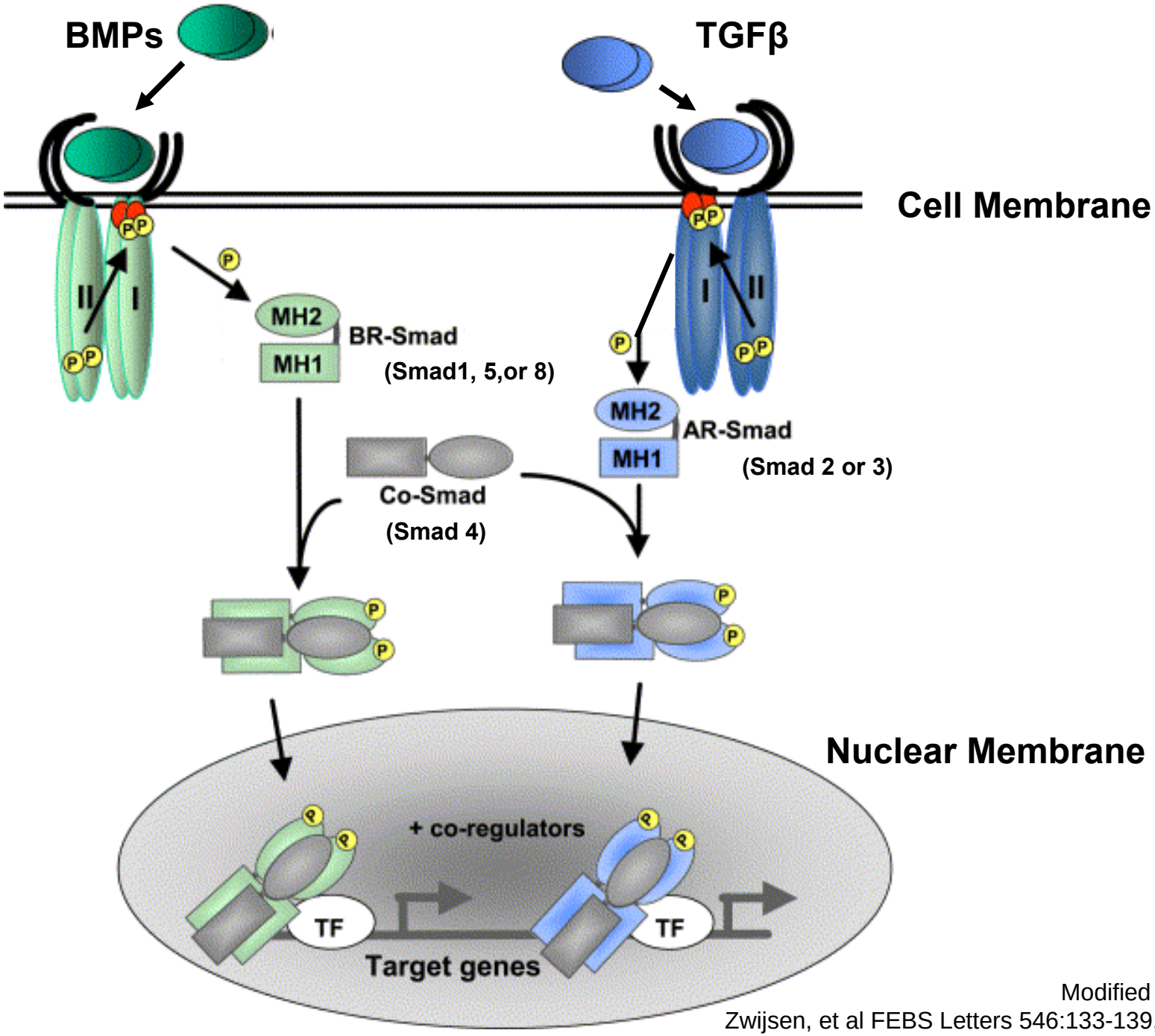

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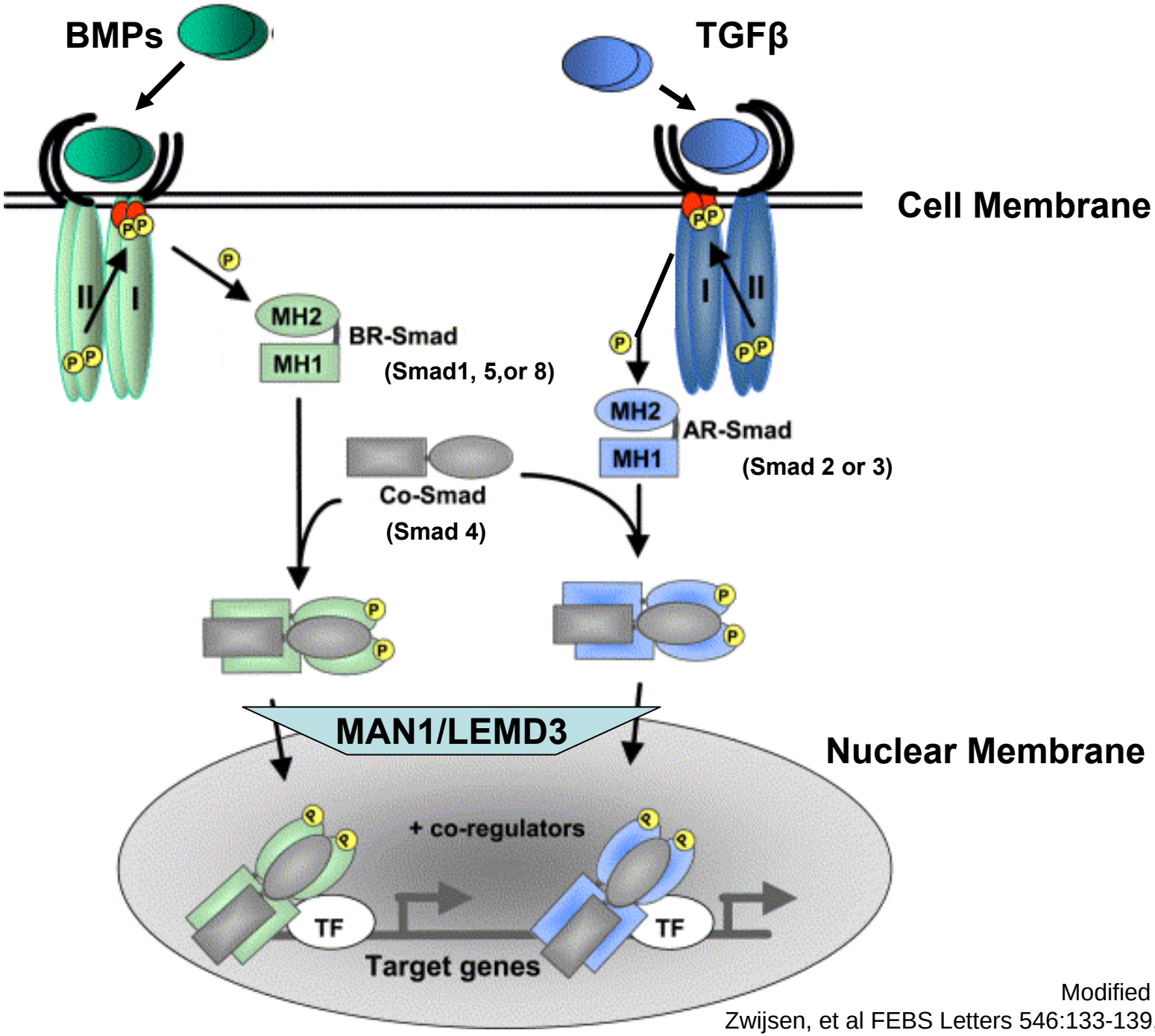


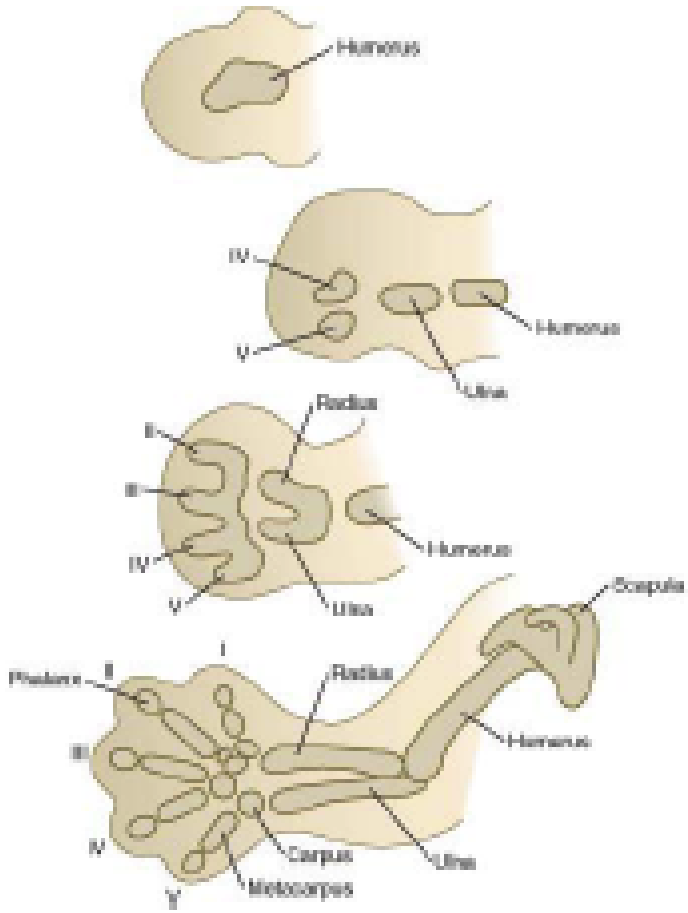
Modified from:
Zwijsen, et al FEBS Letters 546:133-139, 2003

LEMD3 Unsolved Mysteries

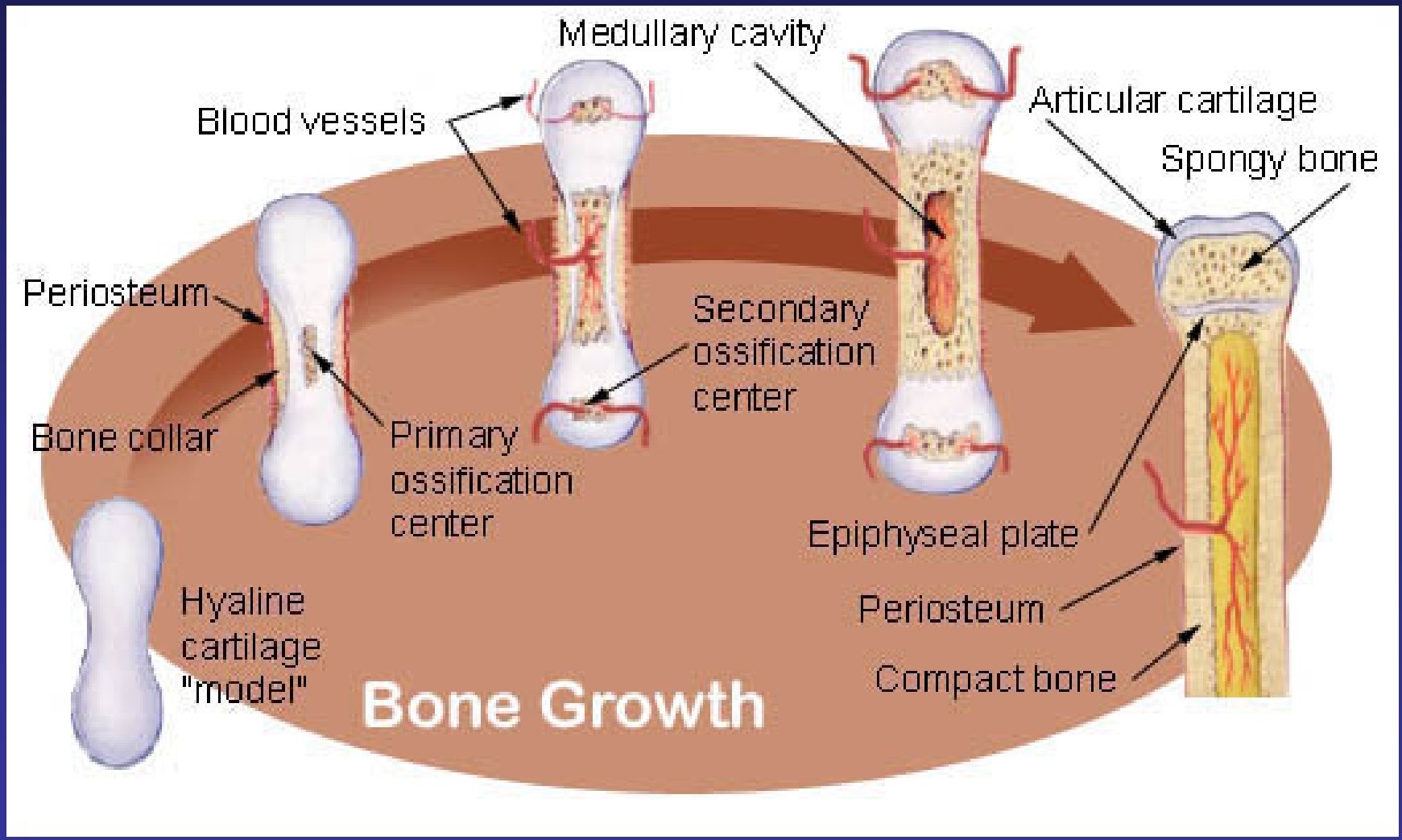
- Is LEMD3 the melorheostosis gene?
- Is melorheostosis due to a somatic mutation?
- Does everyone with a LEMD3 mutation get bone changes?
- What genes are down-regulated by LEMD3?
- What are the compensatory mechanisms in the cell for loss of LEMD3?

BMPs Play a Central Role in Limb Development

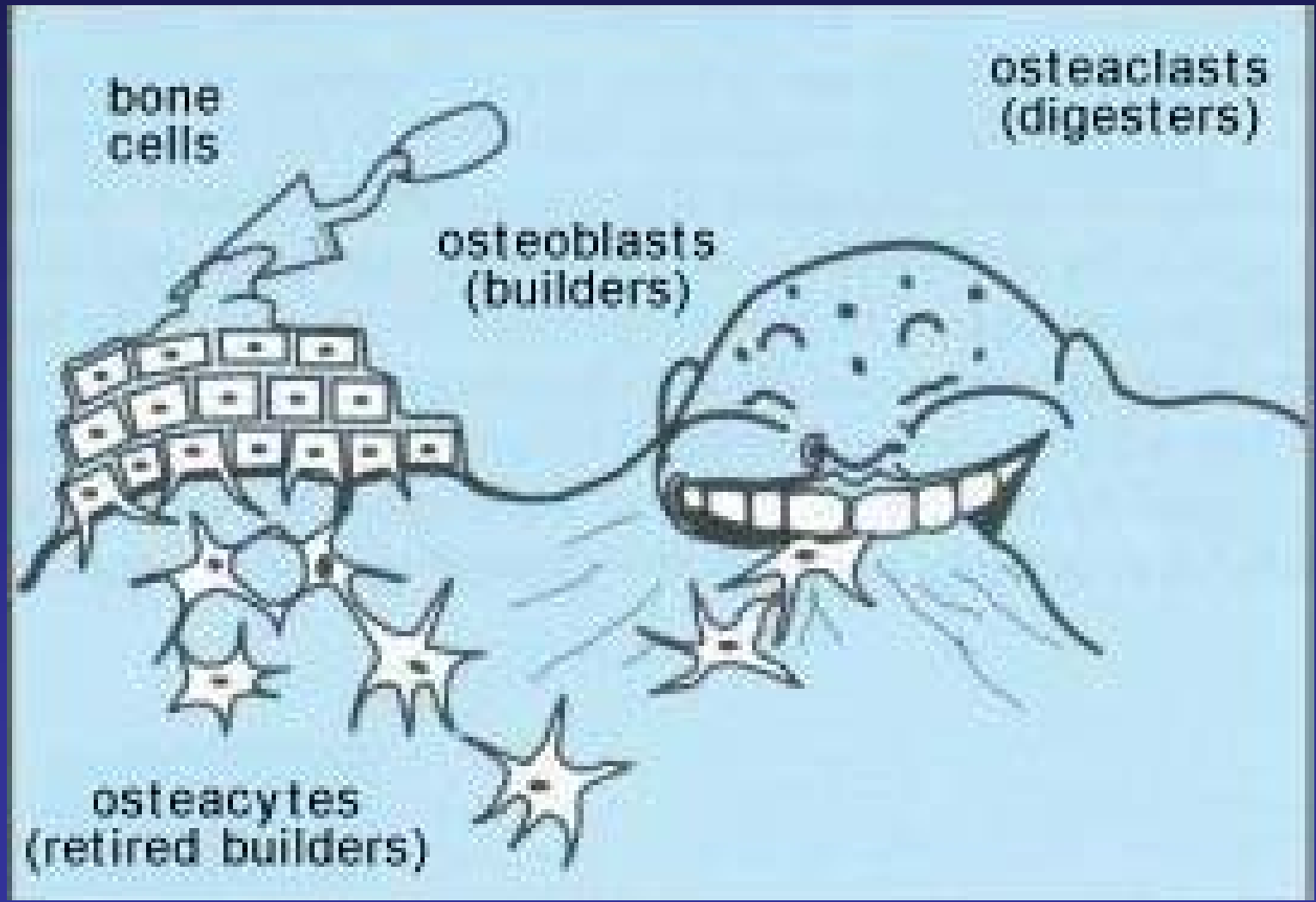
- Skeletal structures are first to differentiate (recognizably) in the limb.
- Differentiation into pre-cartilaginous condensates happens centrally, partly because ectoderm inhibits cartilage differentiation. These aggregates begin expressing BMP2 and BMP4, but that expression gradually is restricted to periosteum or perichondrium surrounding the bones. Similarly BMP3 starts in differentiated chondrocytes, but is also restricted to perichondrium as the bones develop.
- BMP-6 (possibly induced by Ihh) is expressed in hypertrophic maturing cartilage.

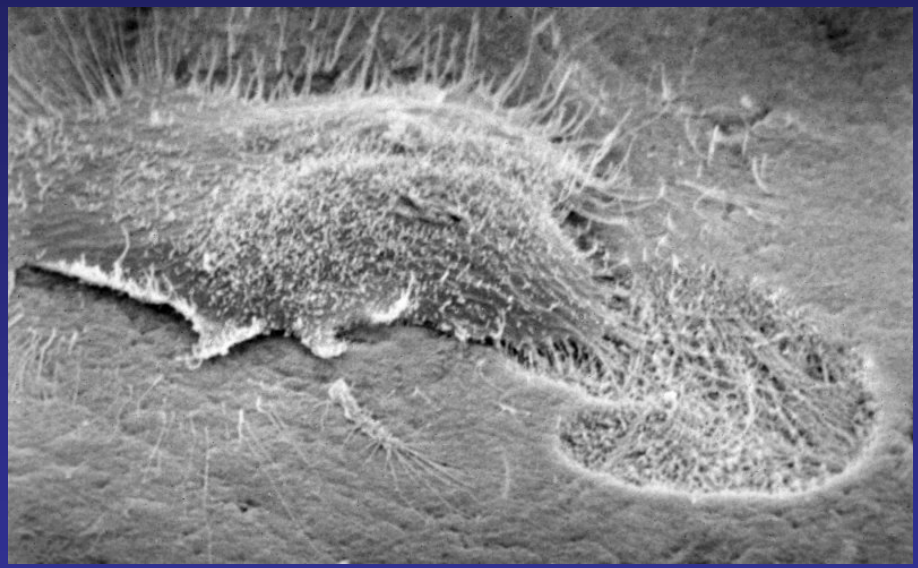


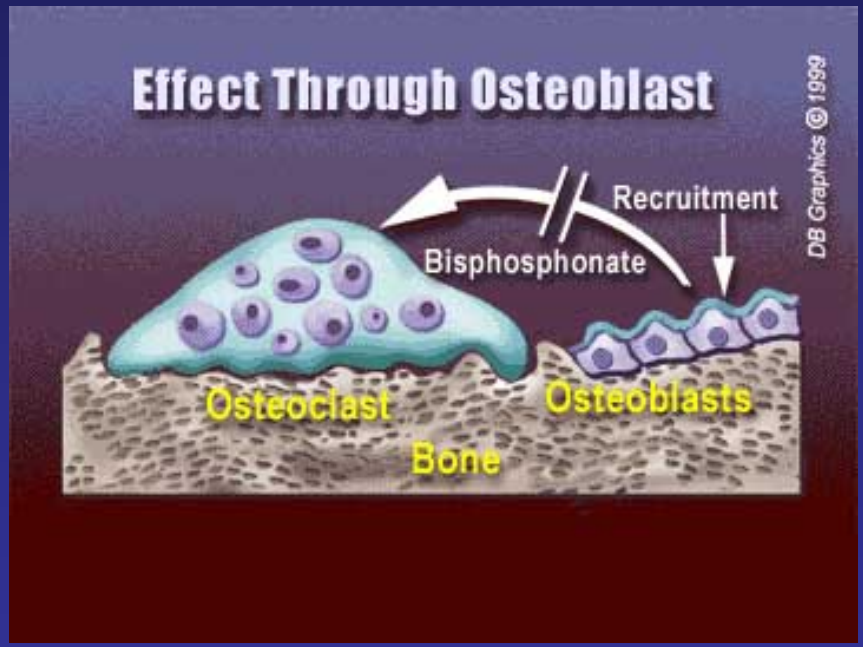
Endochondral Bone Formation



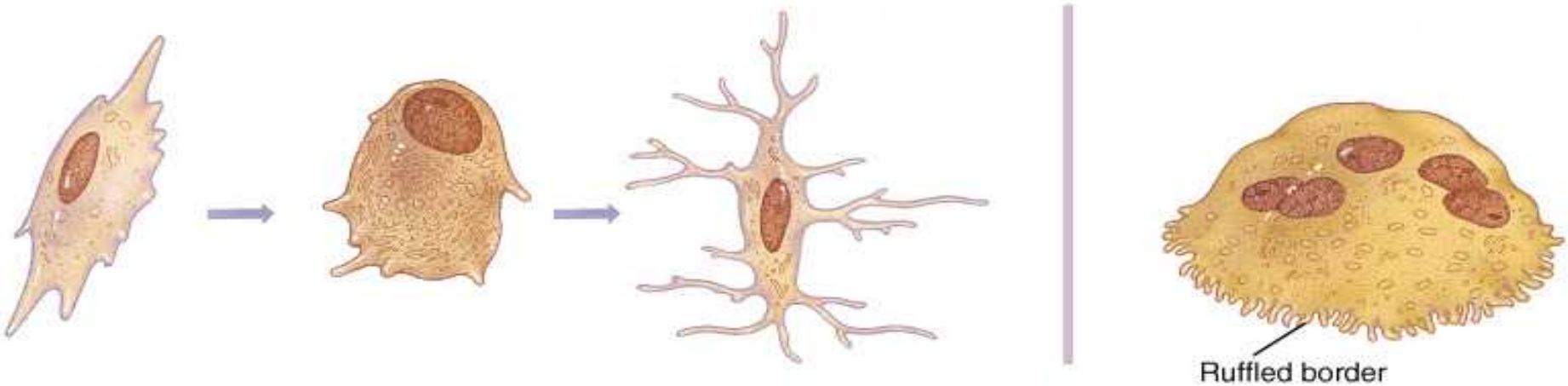
Types of Bone Cells






Effect Through Osteoblast
Recruitment
Bisphosphonate
Osteoclast
Osteoblasts
Bone
DB Graphics © 1999

Types of Bone Cells



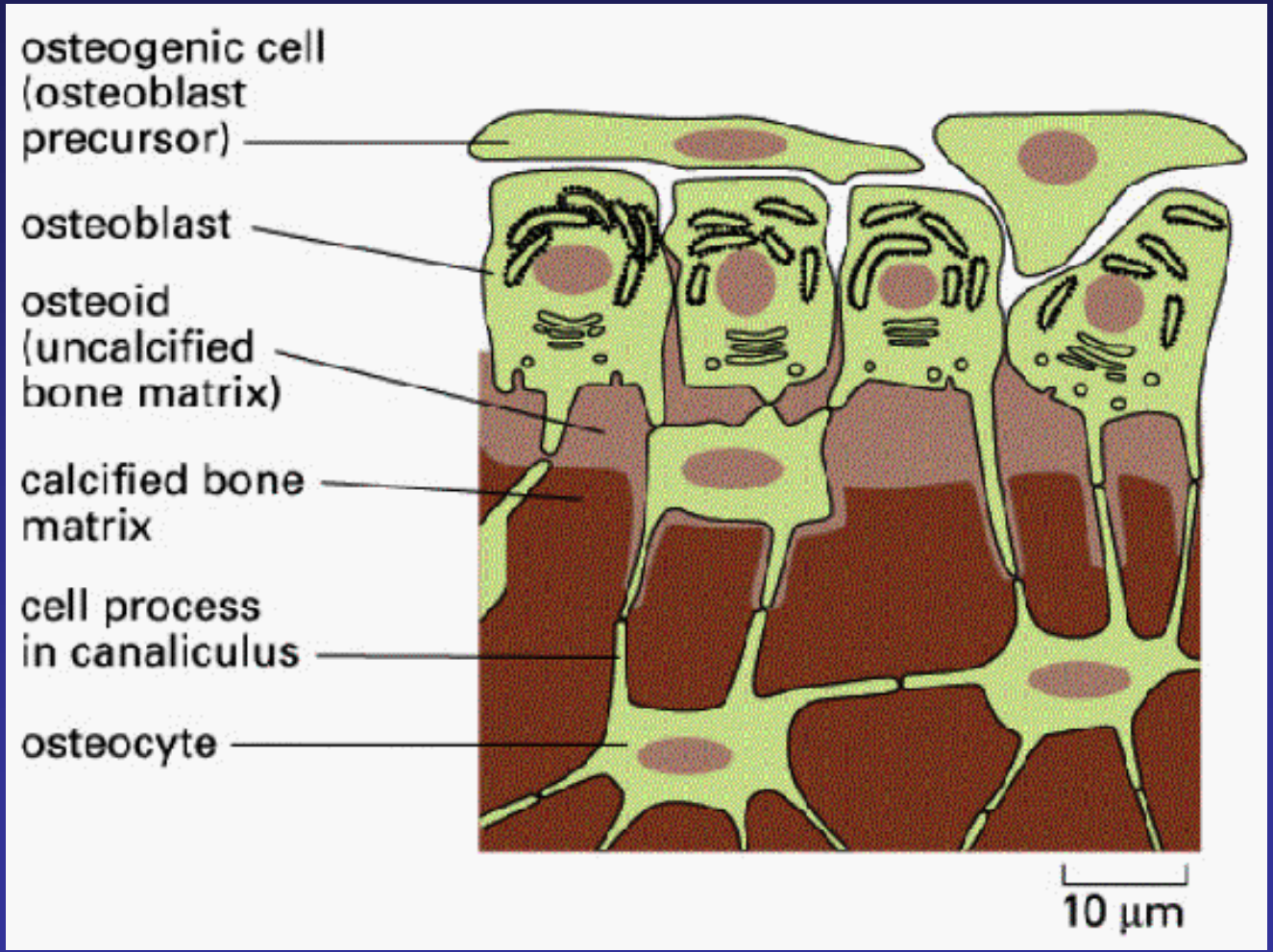
Osteogenic cell (develops into an osteoblast)

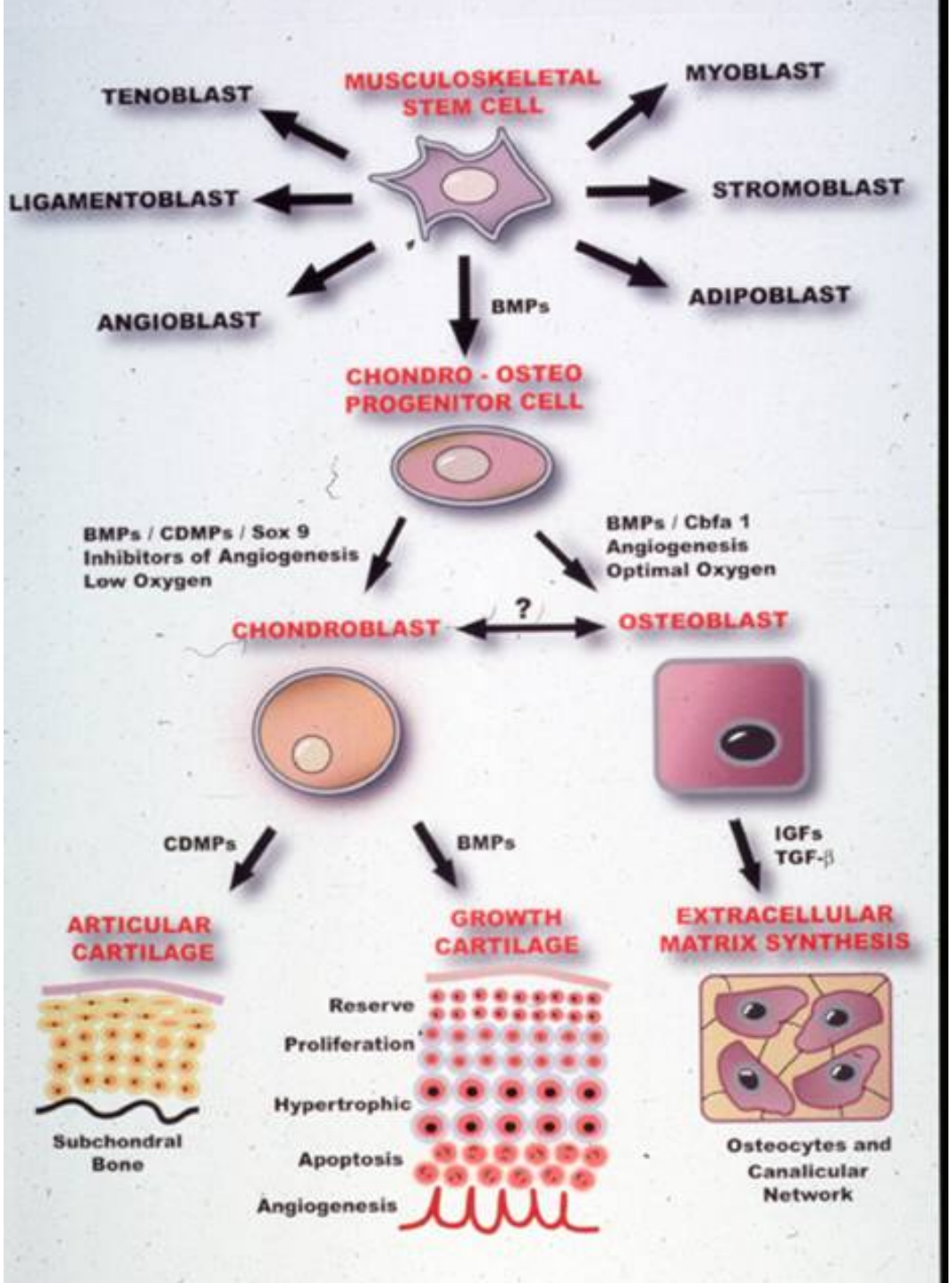
Osteoblast (forms bone tissue)

Osteocyte (maintains bone tissue)

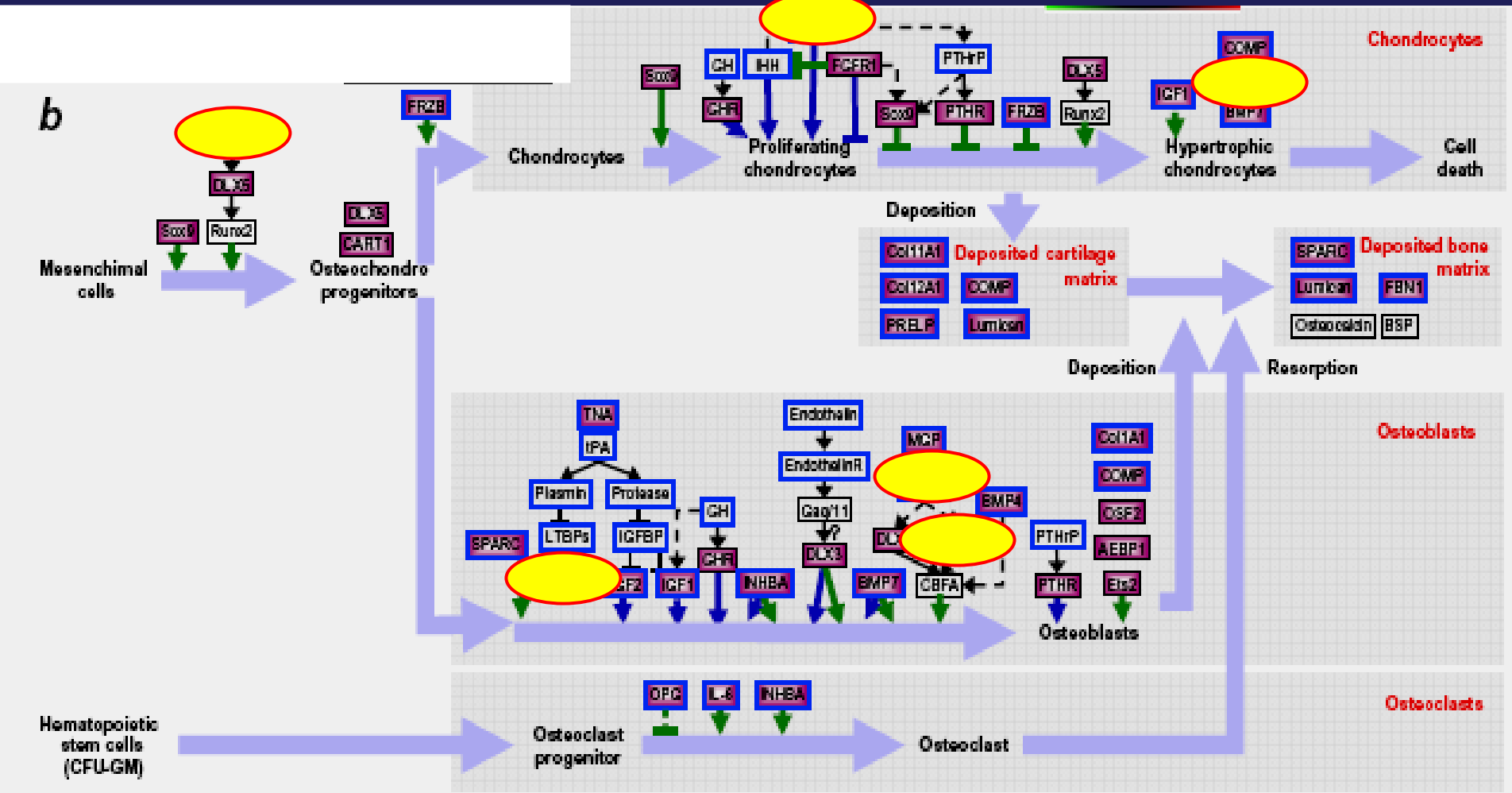
Osteoclast (functions in resorption, the destruction of bone matrix)

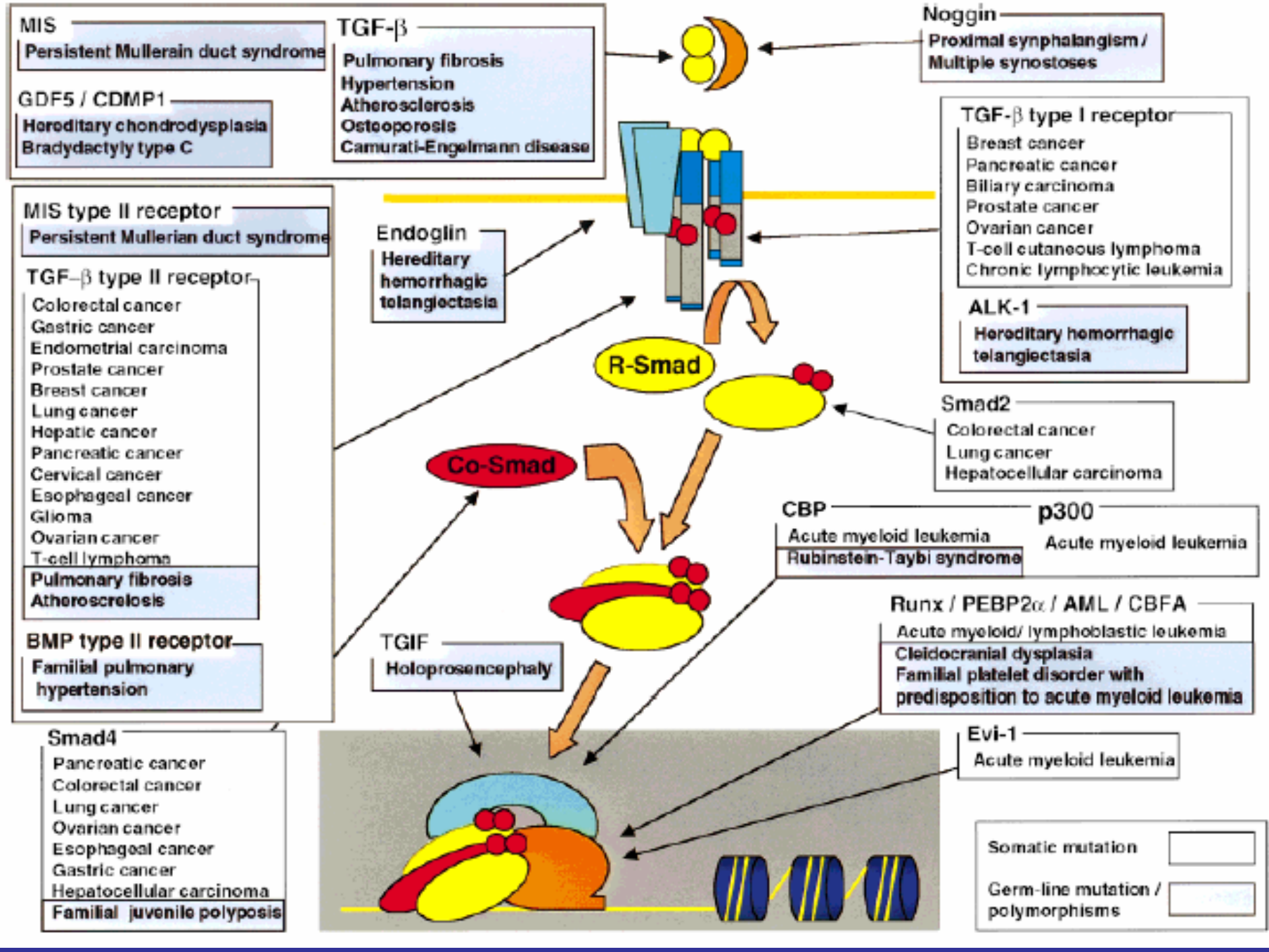
Types of Bone Cells




TENOBLAST
MUSCULOSKELETAL STEM CELL
MYOBLAST
LIGAMENTOBLAST
STROMOBLAST
ANGIOBLAST
BMPs
ADIPOBLAST
CHONDRO - OSTEO PROGENITOR CELL
BMPs / CDMPs / Sox 9
Inhibitors of Angiogenesis
Low Oxygen
BMPs / Cbfa 1
Angiogenesis
Optimal Oxygen
CHONDROBLAST
?
OSTEOBLAST
CDMPs
BMPs
IGFs
TGF-β
ARTICULAR CARTILAGE
GROWTH CARTILAGE
EXTRACELLULAR MATRIX SYNTHESIS
Reserve
Proliferation
Hypertrophic
Apoptosis
Angiogenesis
Subchondral Bone
Osteocytes and Canalicular Network

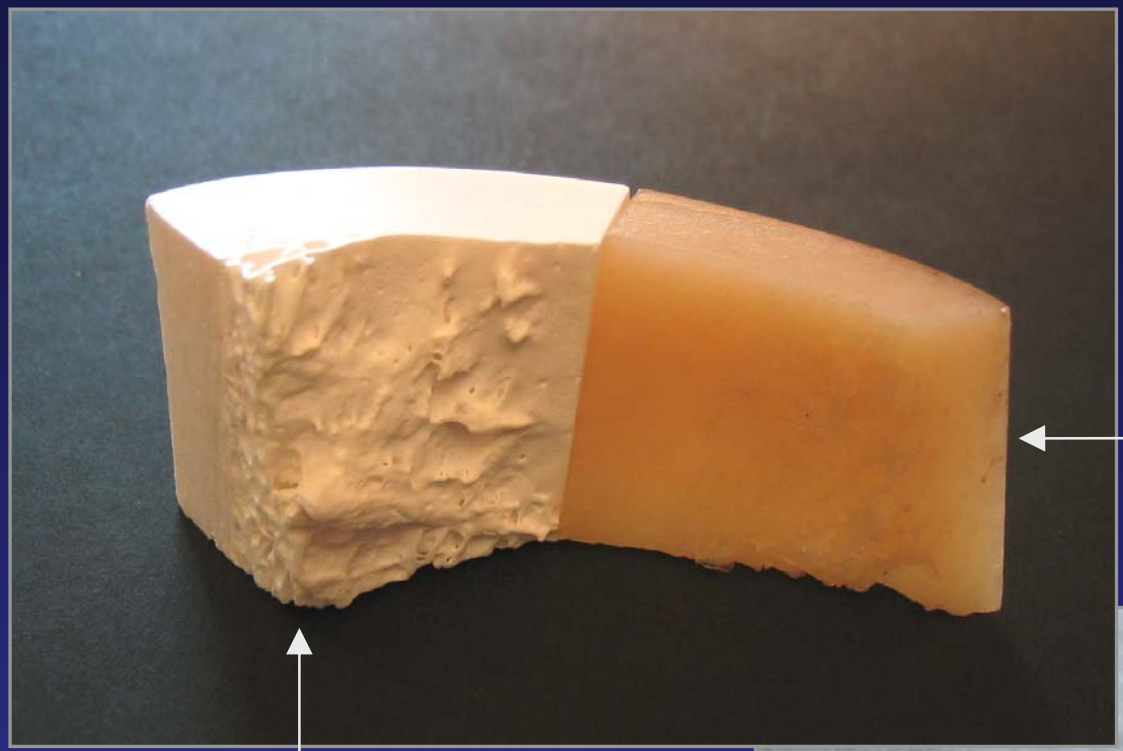
BMPs, TGFb, SMADs Participate in Multiple Steps in Bone Formation





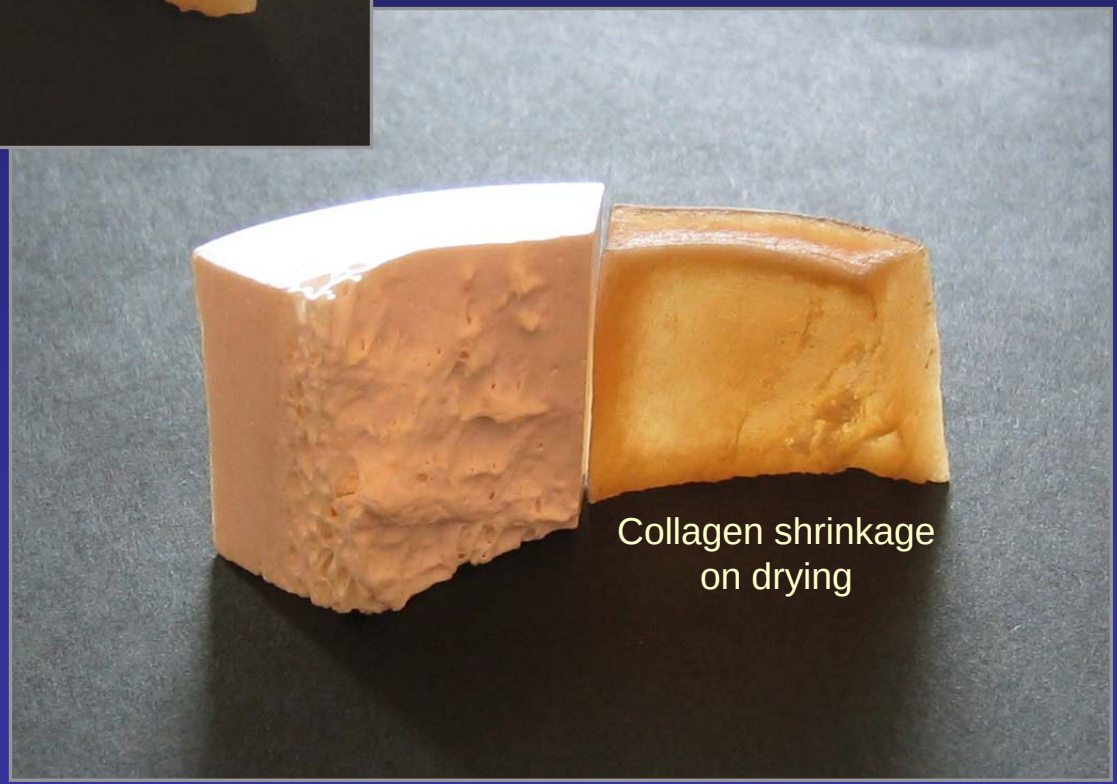
JOURNAL OF CELLULAR PHYSIOLOGY 187:265-276 (2001)

Bone is made of mineral + organic *(mainly collagen)* components



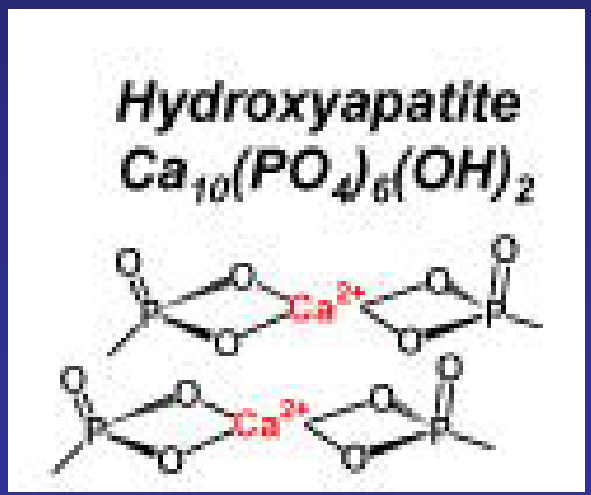
Treated with hydrochloric acid
to dissolve mineral
leaves collagen component intact

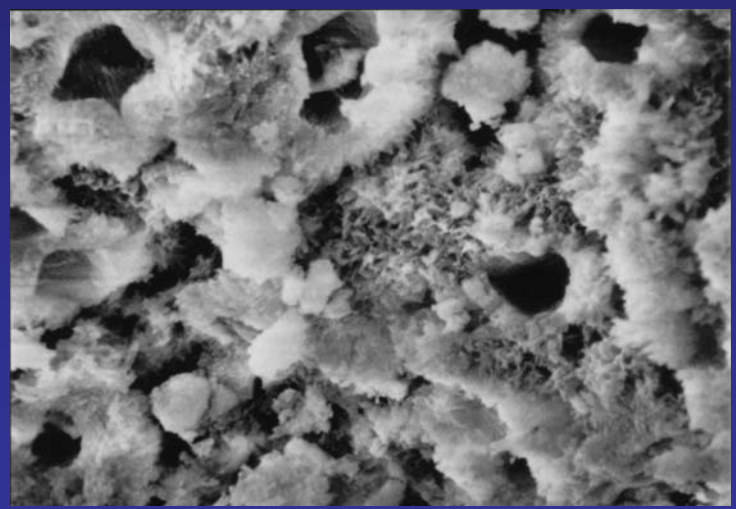
Treated with bleach (hypochlorite)
to digest collagen
leaves mineral component intact



Targeting Therapy to Bone

Enhancement of drug delivery to bone:
Characterization of human tissue-nonspecific alkaline phosphatase tagged with an acidic oligopeptide.

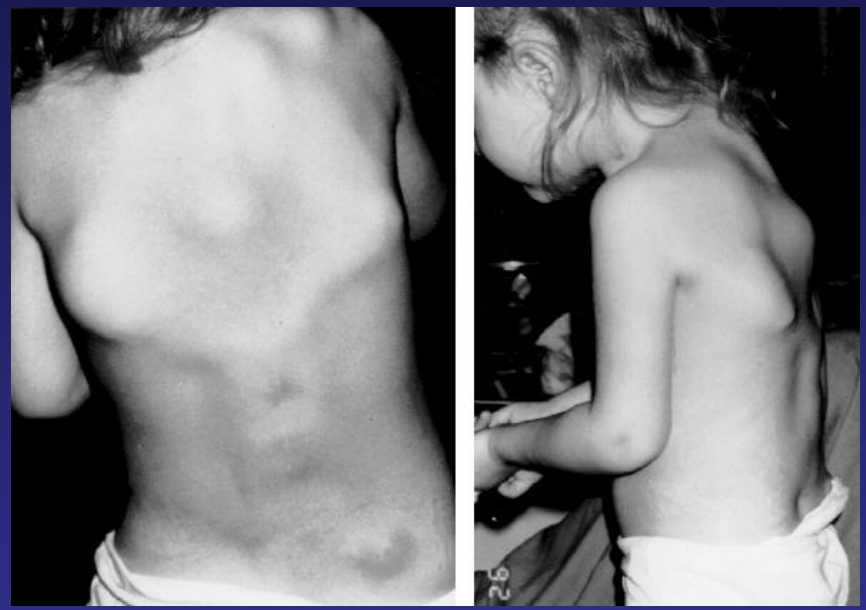


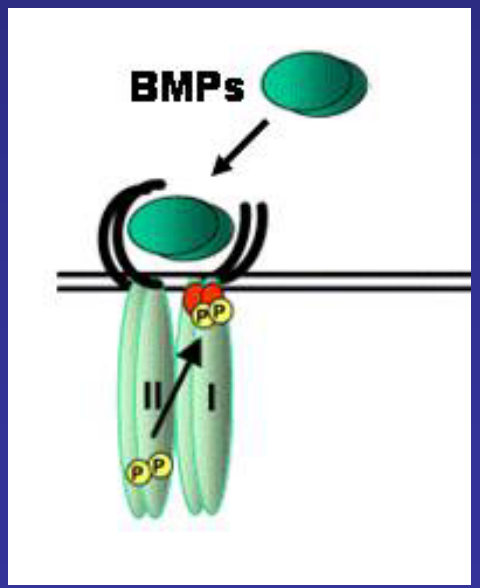


FOP and ACVR1

A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva

Eileen M Shore[1–3], Meiqi Xu[1,2], George J Feldman[1,2], David A Fenstermacher[4–6], The FOP International Research Consortium, Matthew A Brown[7] & Frederick S Kaplan[1,2,8]





The members of the FOP International Research Consortium have been critical in identifying FOP multigenerational families and/or made important contributions to this collaborative effort. We thank the individuals and families with FOP for providing tissue samples for these studies and for their courage and faith;