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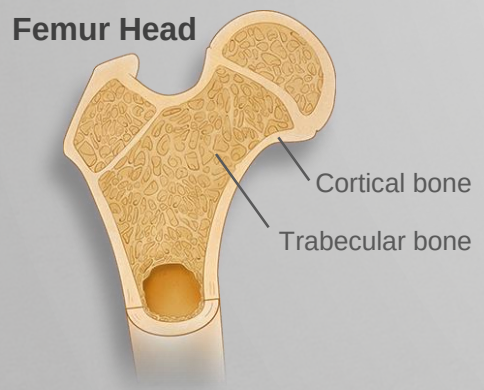

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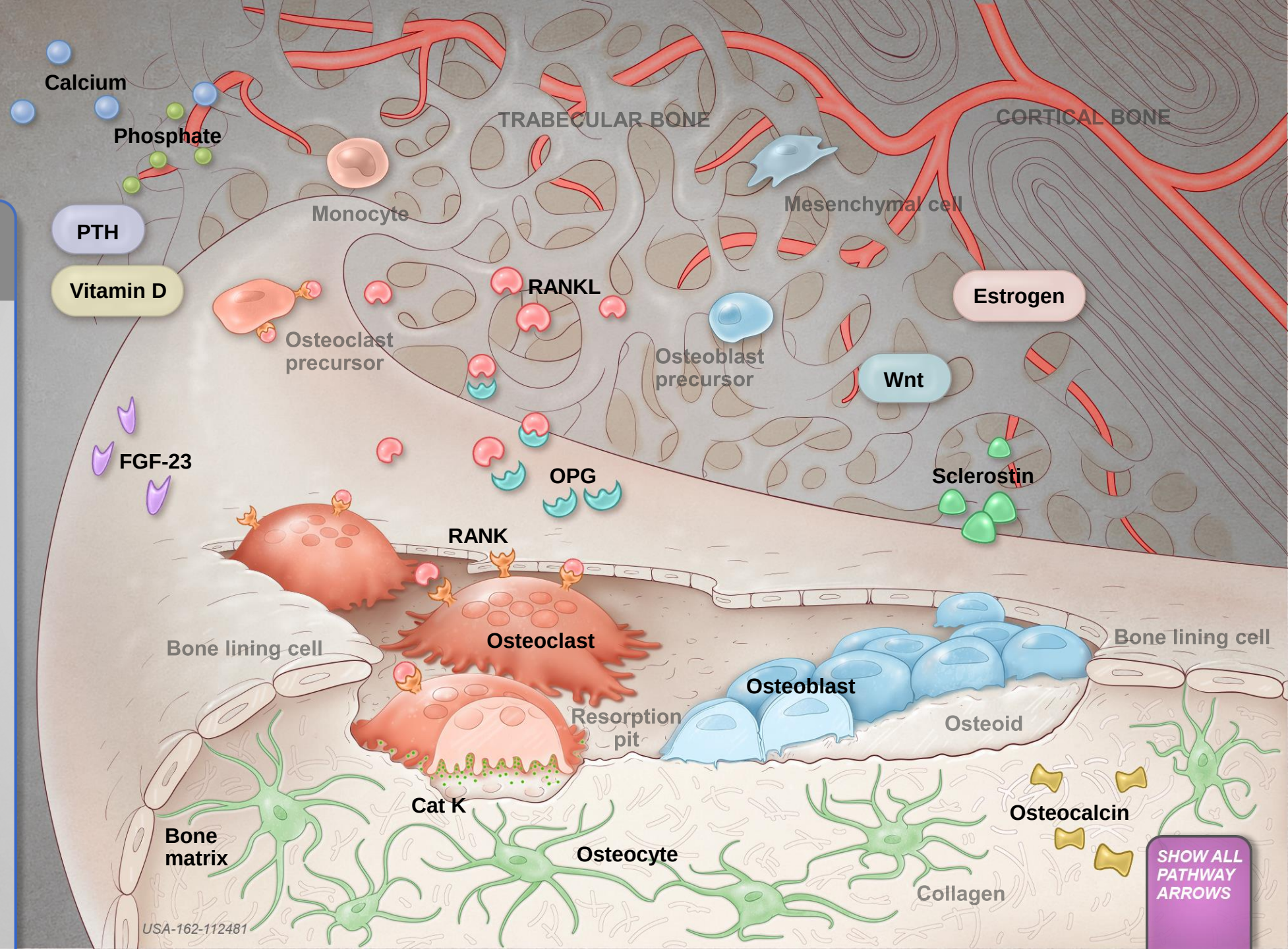

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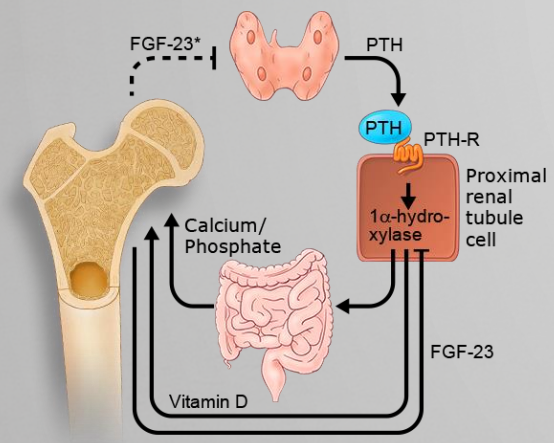
Parathyroid Hormone

Parathyroid hormone (PTH) is secreted by the parathyroid gland and maintains calcium homeostasis[1]

Endogenous PTH stimulates both bone formation and bone resorption[1]



Adapted from Blau JE, et al. *Rev Endocr Metab Disord*. 2015; In press.
*FGF23 suppression on the parathyroid gland was reported in *in vitro* studies only
[1] Bergwitz C, et al. *Ann Rev Med*. 2010;61:91-104.

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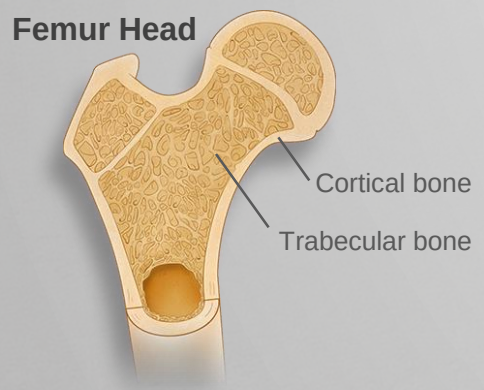

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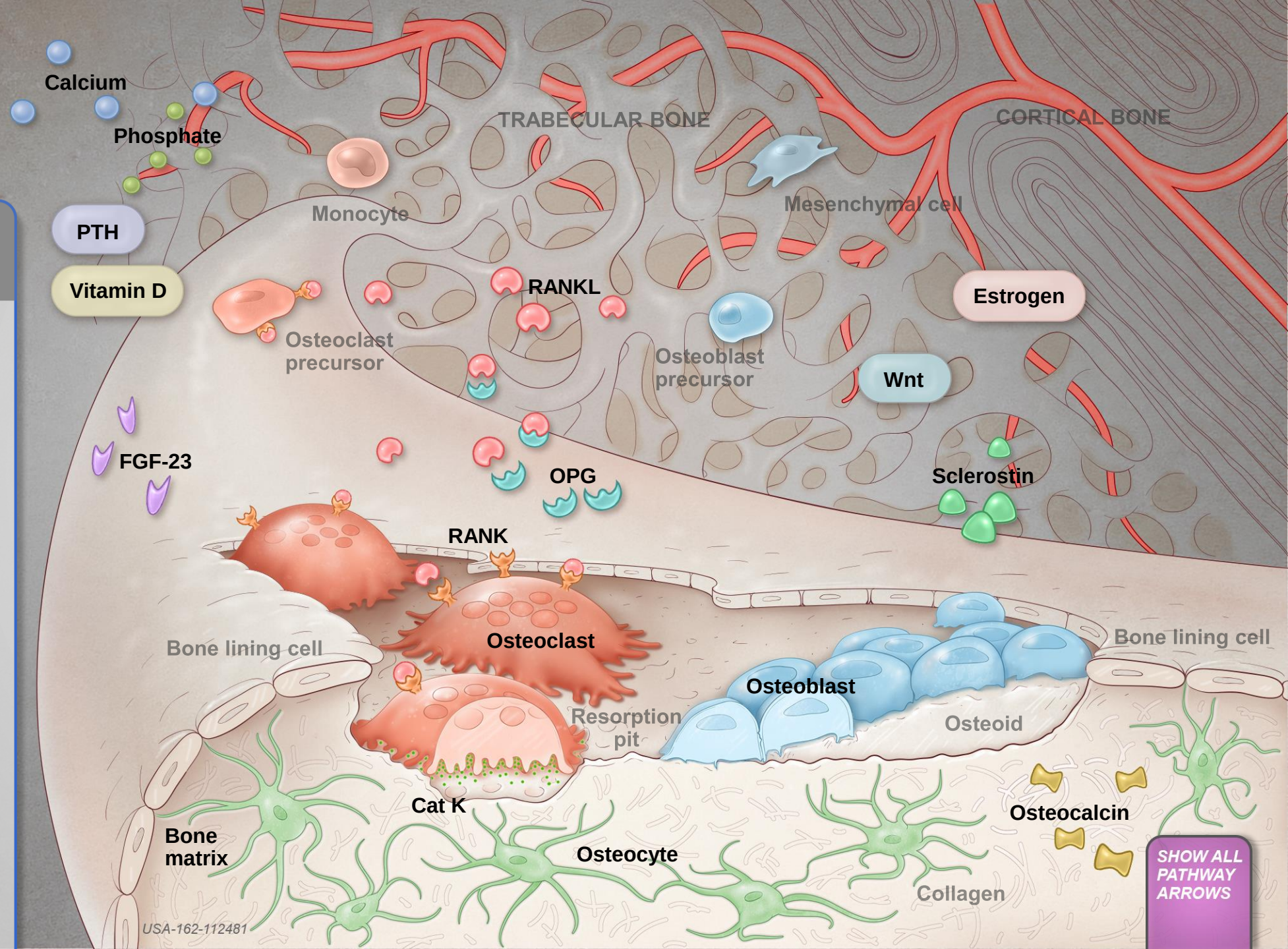

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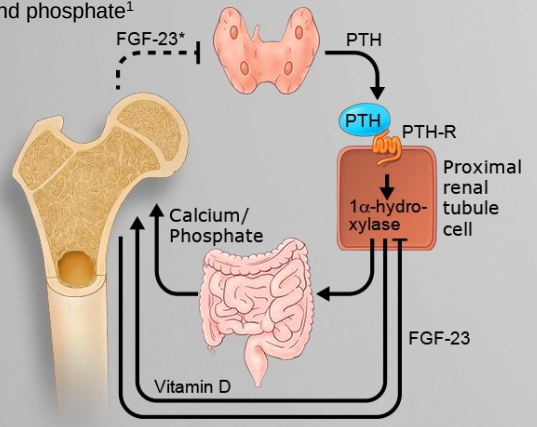
Calcium/Vitamin D

Calcium homeostasis is regulated by PTH and maintained by absorption of dietary calcium in the intestine, reabsorption in the kidney, and release from bone[1]

Vitamin D, produced by the enzyme 1α-hydroxylase, indirectly acts on bone homeostasis by suppressing PTH and increasing intestinal absorption of calcium and phosphate[1]



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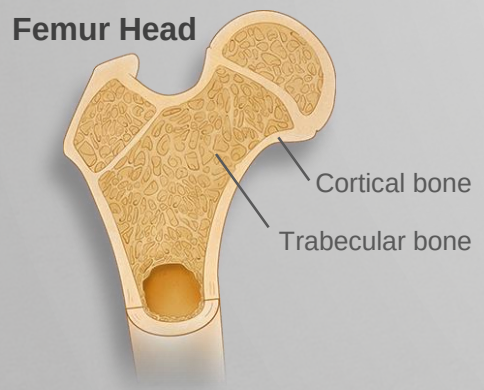

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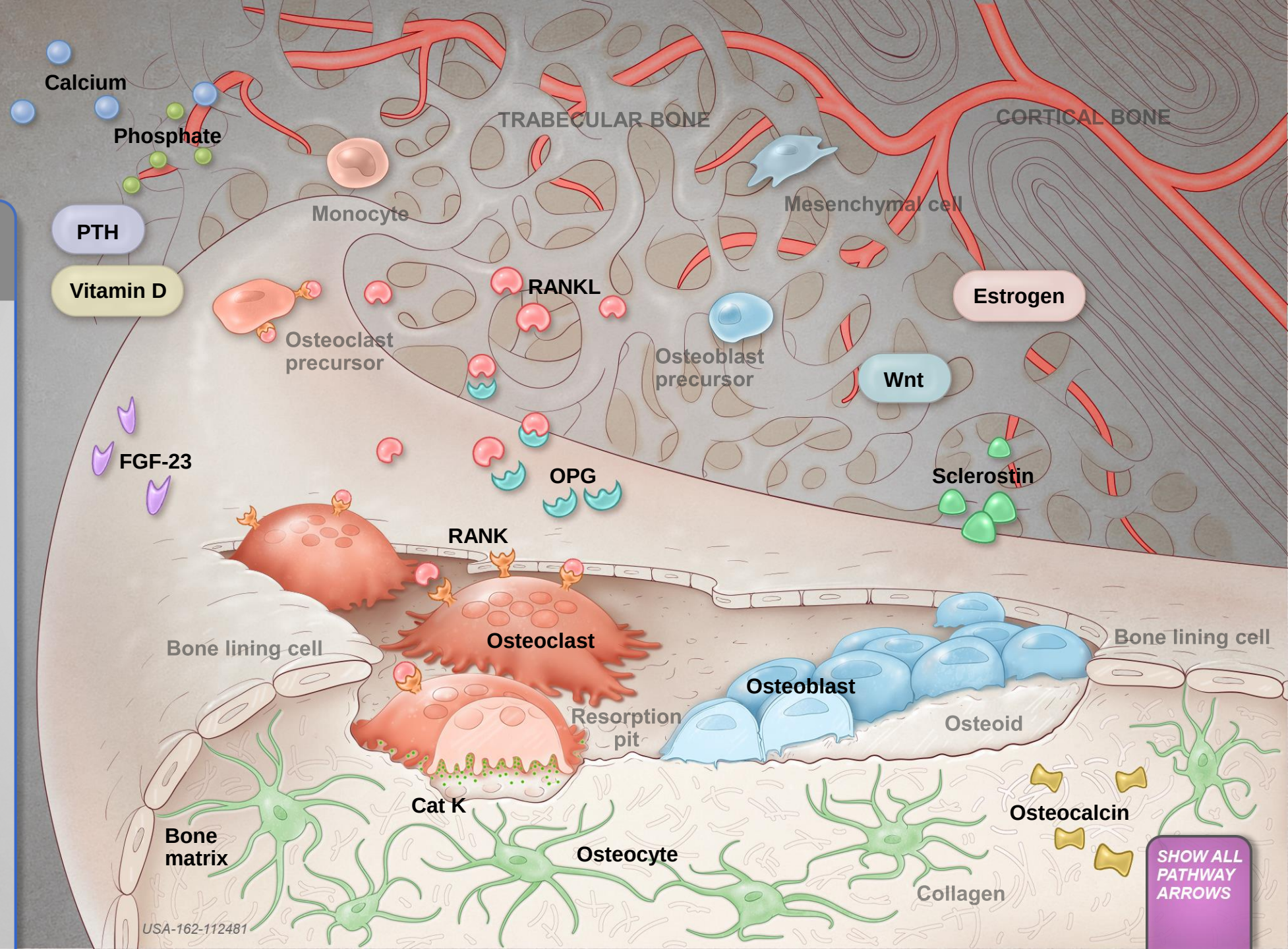

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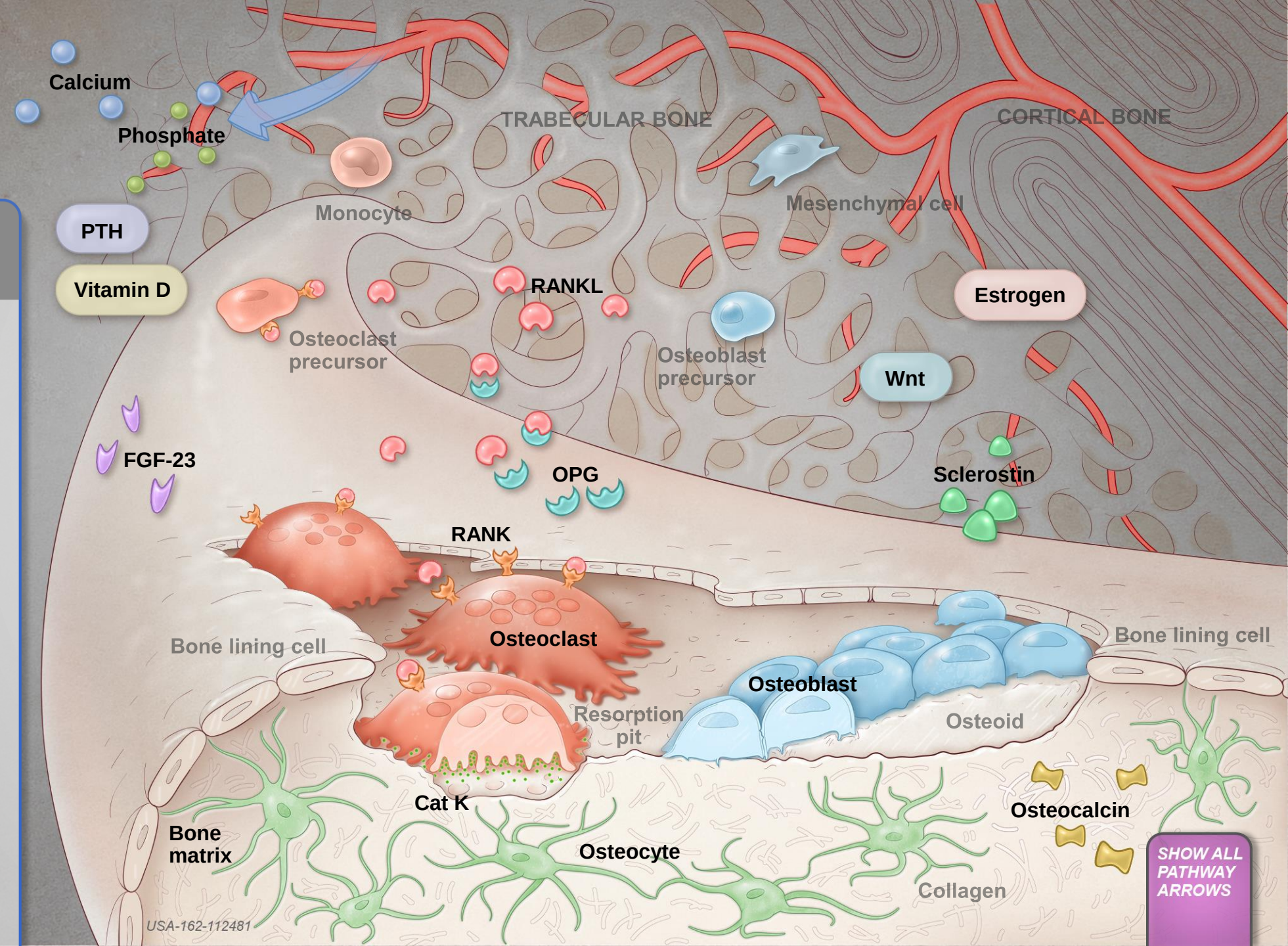
Phosphate

Phosphate homeostasis is maintained by absorption of dietary phosphate in the intestine, reabsorption by the kidney, and movement of phosphate between the extracellular fluid space and the bone and soft tissue[1]

The majority of phosphate retained in the body is deposited in bone as calcium-phosphate hydroxyapatite crystals[2]

Chronic serum phosphate deficiency results in impaired bone mineralization, rickets, and osteomalacia[1]



[1] Berndt T, et al. *Annu Rev Physiol*. 2007;69:341-359.
[2] Farrow EG, et al. *Nat Rev Nephrol*. 2010;6:207-217.

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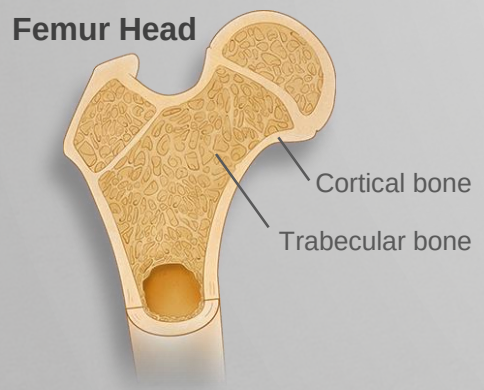

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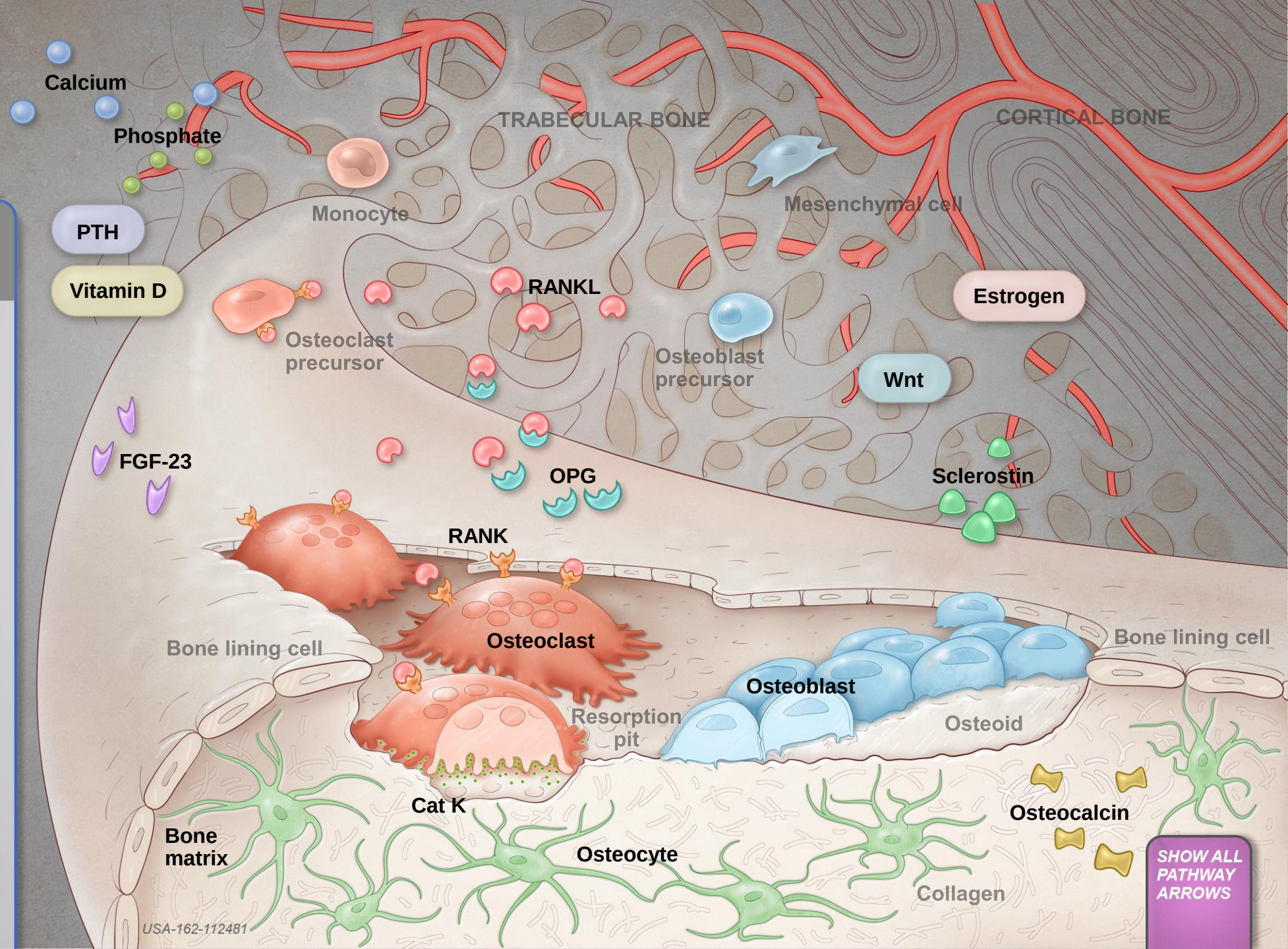

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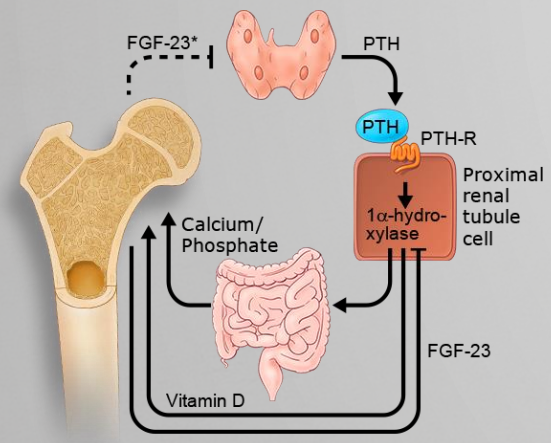
FGF-23

Fibroblast growth factor 23 (FGF-23) is synthesized and secreted by osteocytes.[1] FGF-23 is upregulated by vitamin D and inhibits synthesis of vitamin D in a negative feedback loop.[1, 2] FGF-23 is a phosphaturic hormone that regulates renal phosphate reabsorption and bone mineralization[1]



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*FGF23 suppression on the parathyroid gland was reported in *in vitro* studies only
[1] Martin A, et al. *Endocrine FGFs and Klothos*. Austin, TX: Landes Bioscience;2012:65-83.
[2] Liu S, et al. *J Am Soc Nephrol*. 2006;17:1305-1315.

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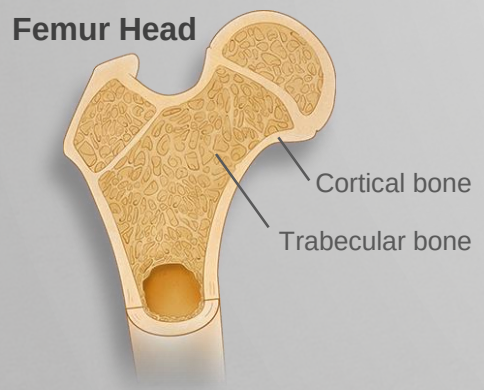

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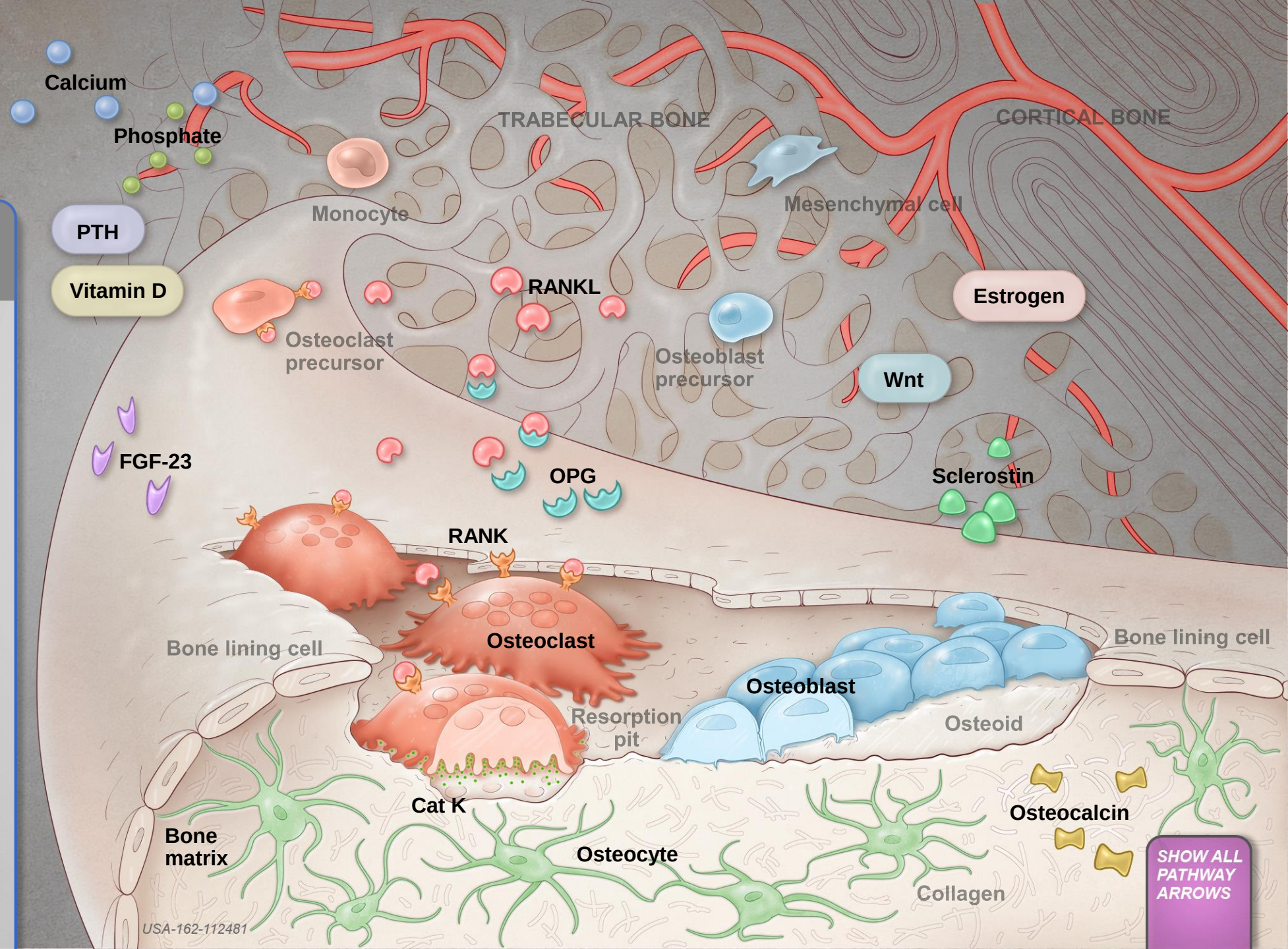

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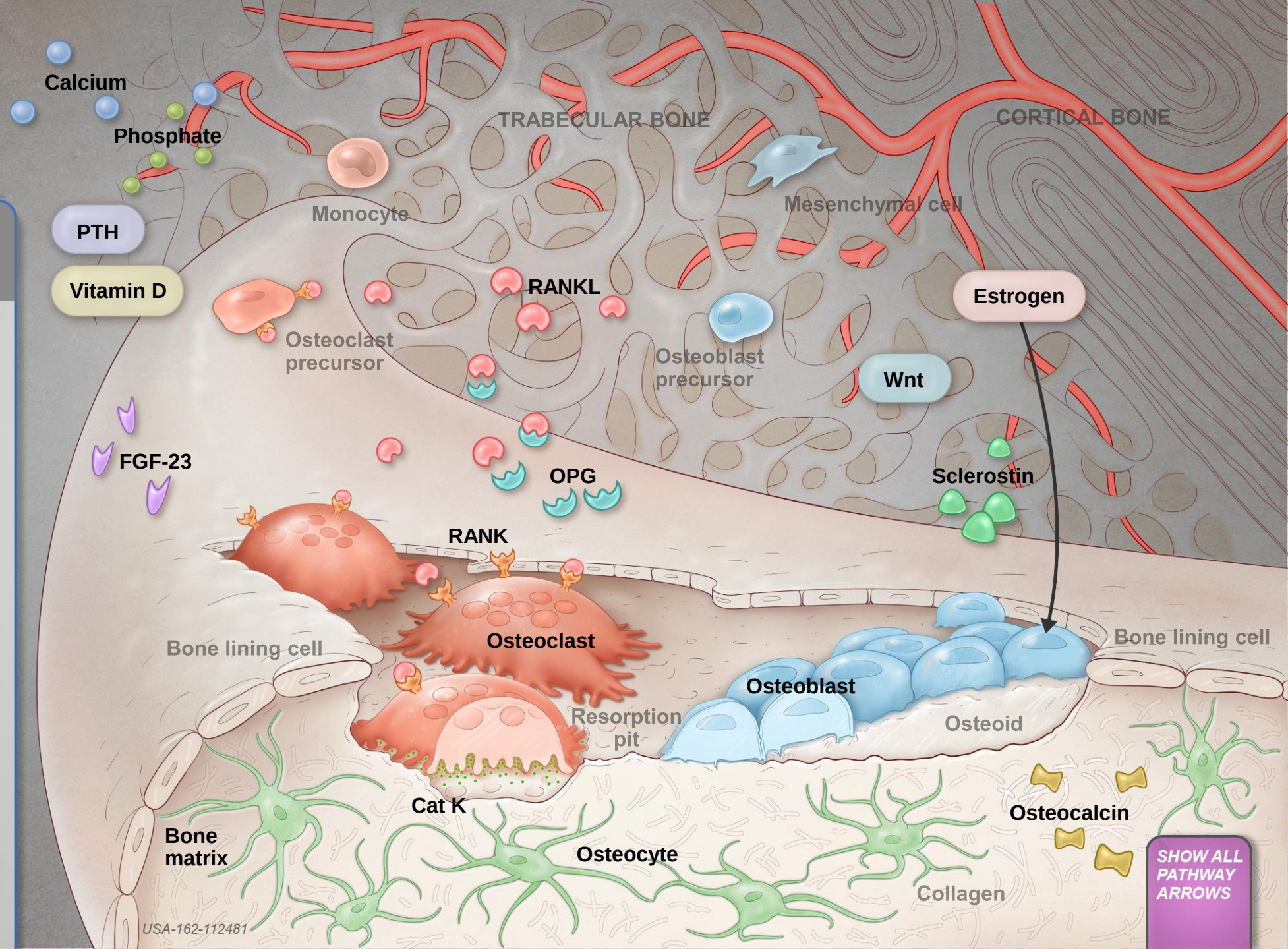
Estrogen

Estrogen regulates bone metabolism by inhibiting bone remodeling, stimulating osteoclast apoptosis, and promoting osteoblast survival[1]

Estrogen deficiency has been identified as the cause of bone loss in postmenopausal women and aging men[2]



[1] Khosla S, et al. *J Bone Miner Res*. 2011;26:441-451.
[2] Riggs BL, et al. *J Bone Miner Res*. 1998;13:763-773.

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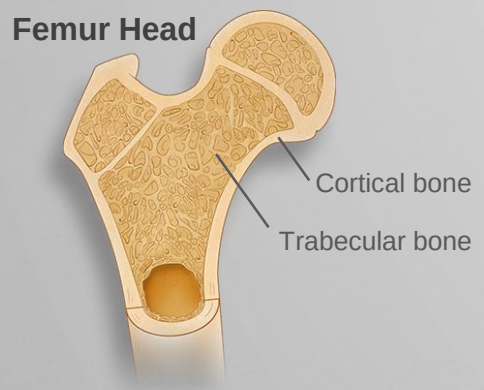

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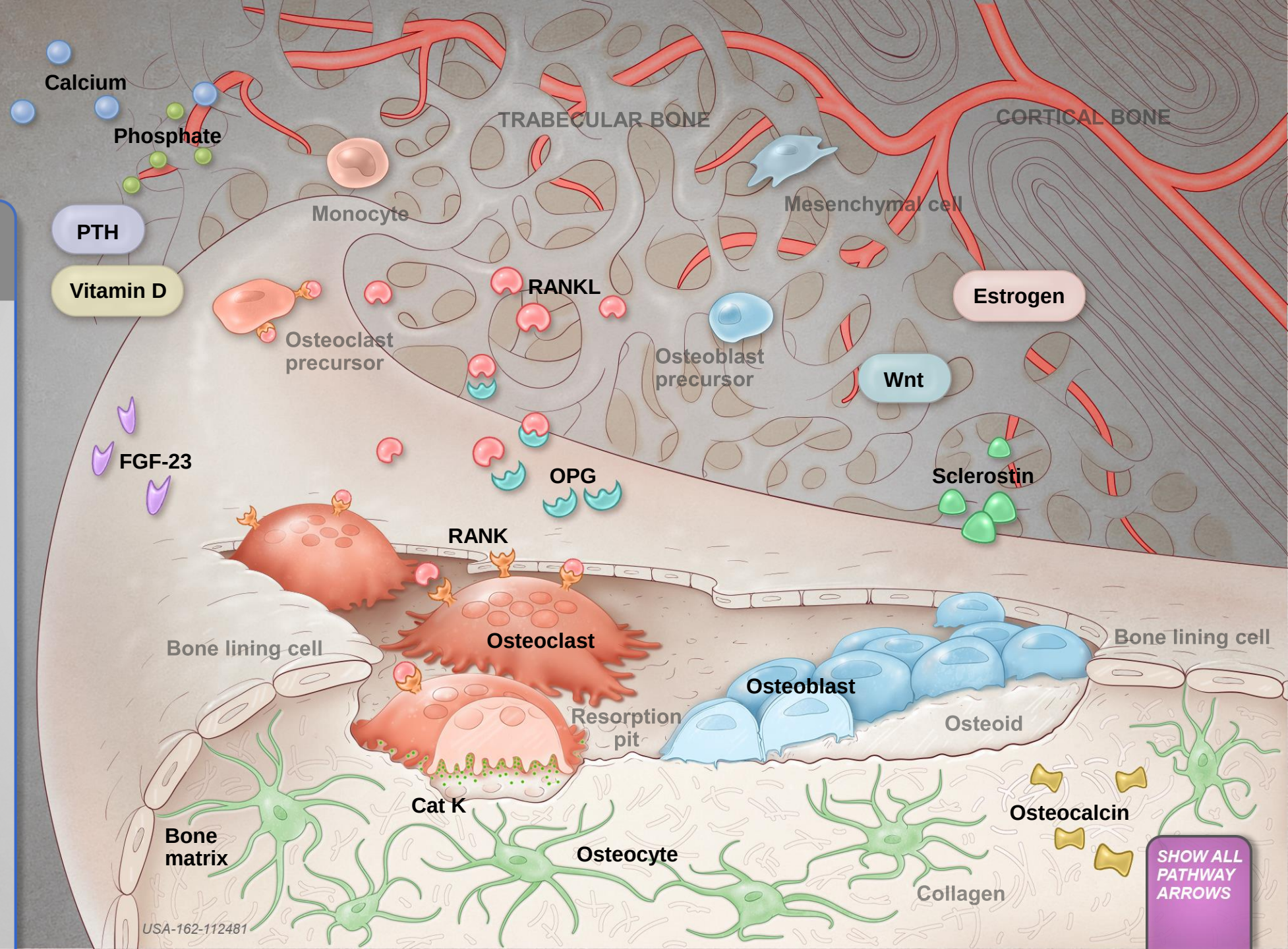

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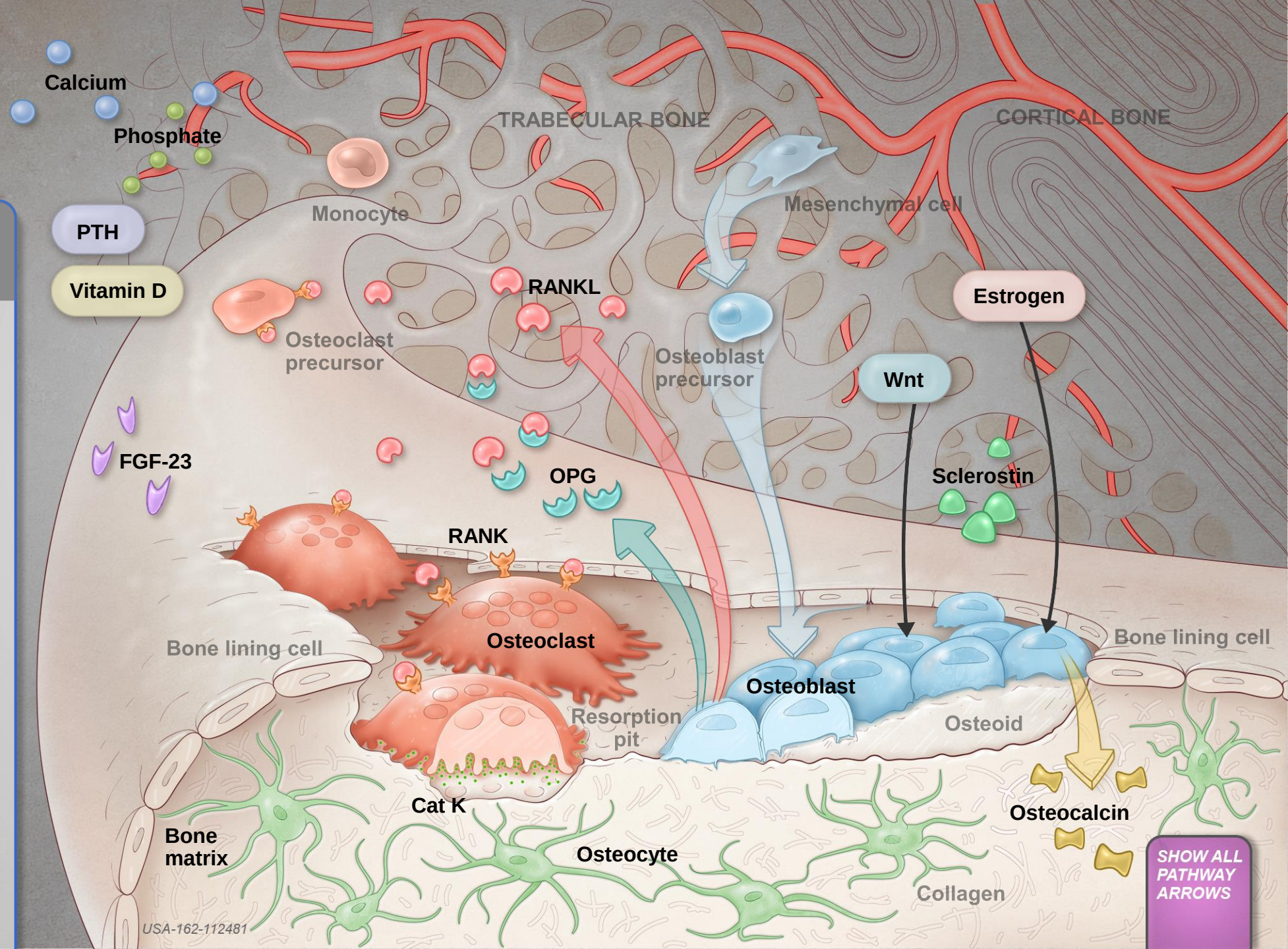
Osteoblasts

Osteoblasts, which originate from mesenchymal stem cells, synthesize and secrete proteins that regulate extracellular matrix formation and mineral deposition[1]

Bone formation begins when osteoblasts lay down osteoid, which becomes mineralized into new bone[1]



[1] Manolagas SC. *Endocrine Reviews*. 2000;21:115-137.

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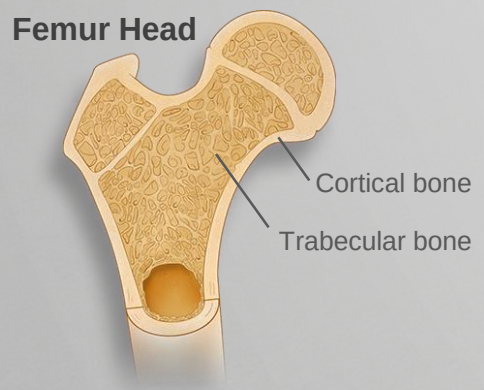

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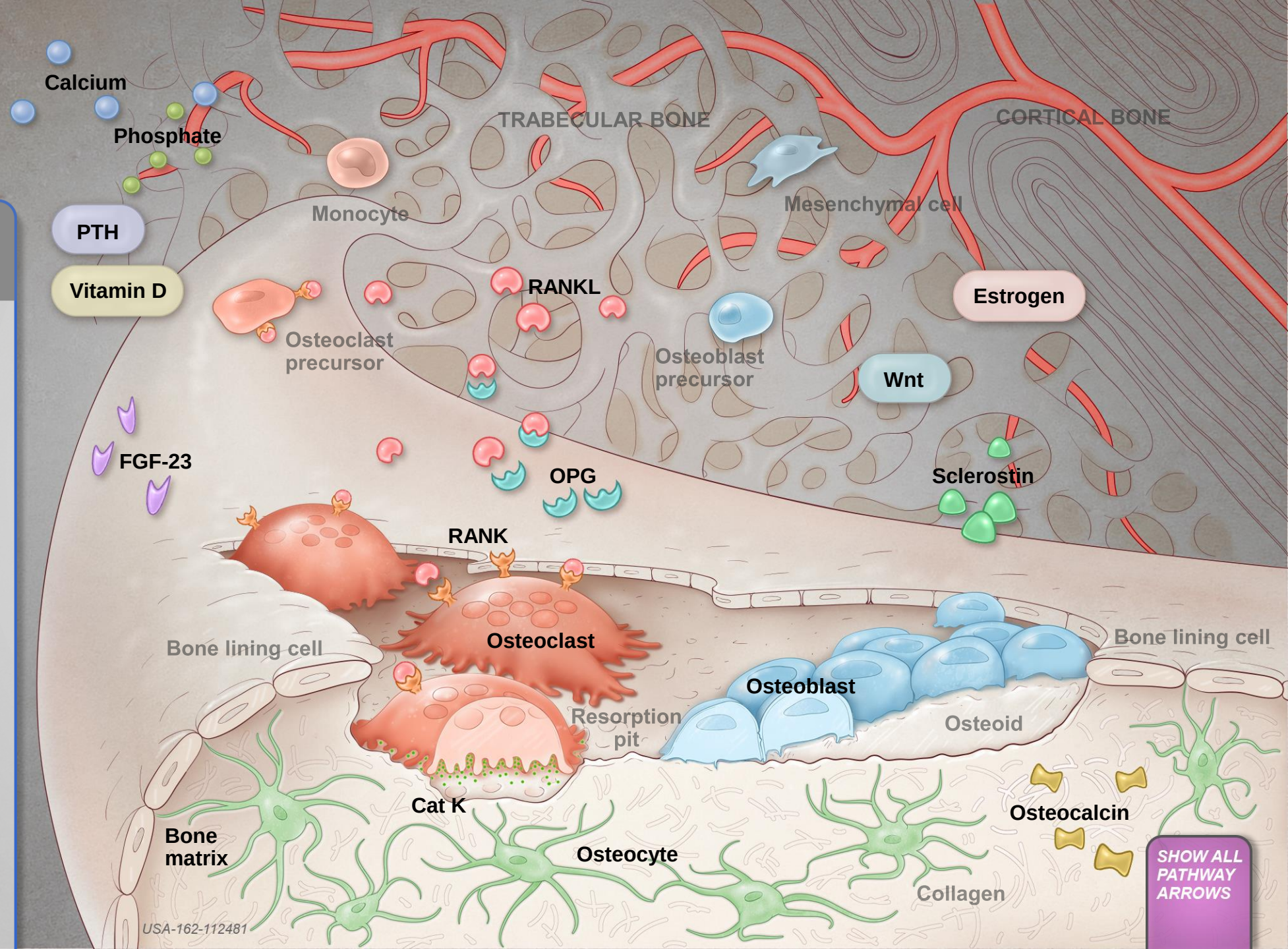

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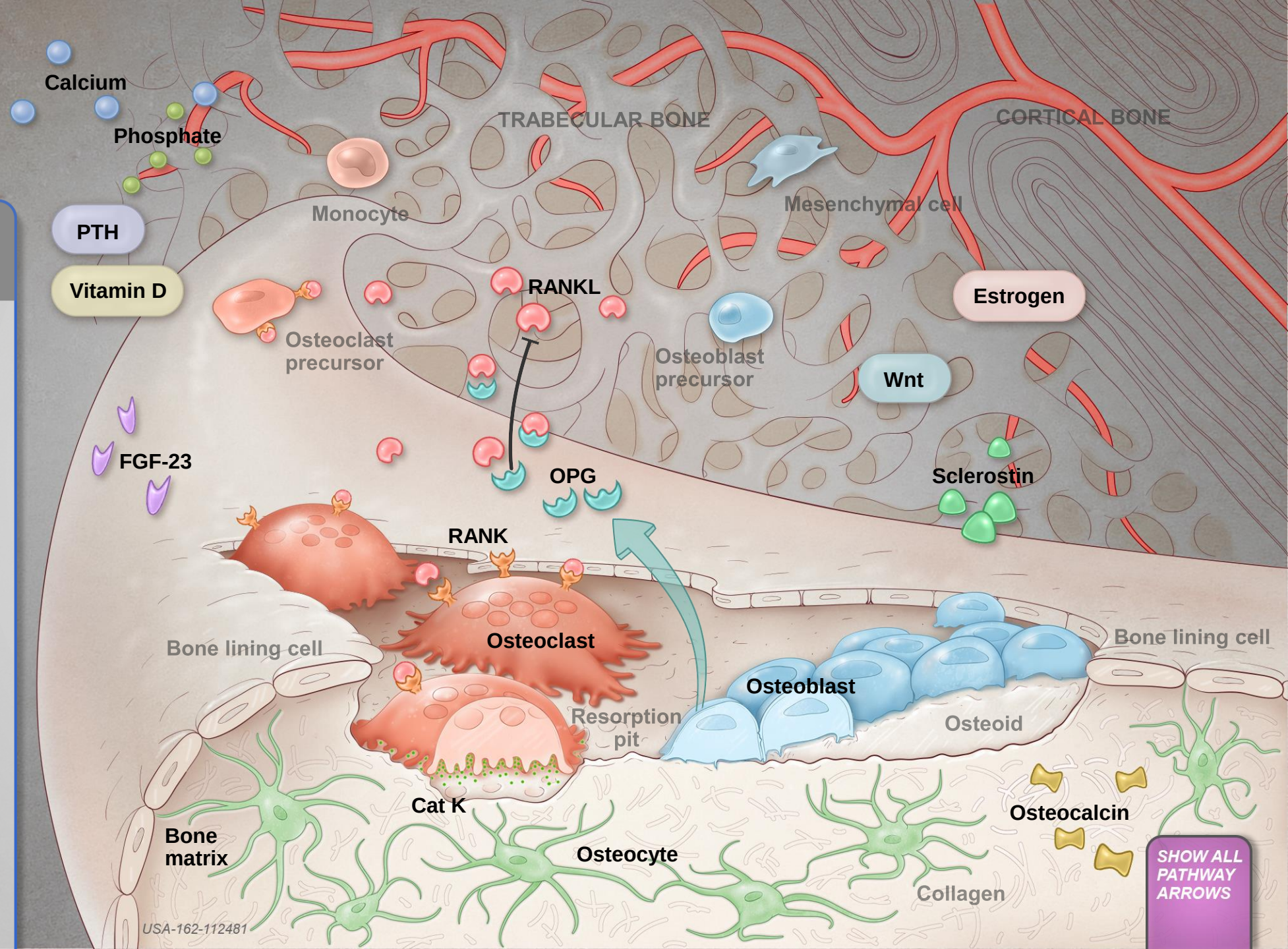
Osteoprotegerin

Osteoblasts produce a glycoprotein called osteoprotegerin (OPG), which binds to RANKL and prevents it from binding to RANK[1]



[1] Hofbauer LC, et al. *JAMA*. 2004;292:490-495..

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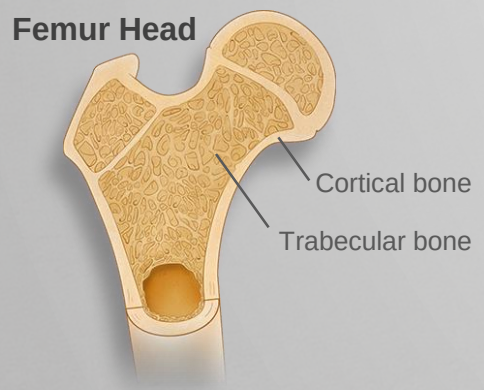

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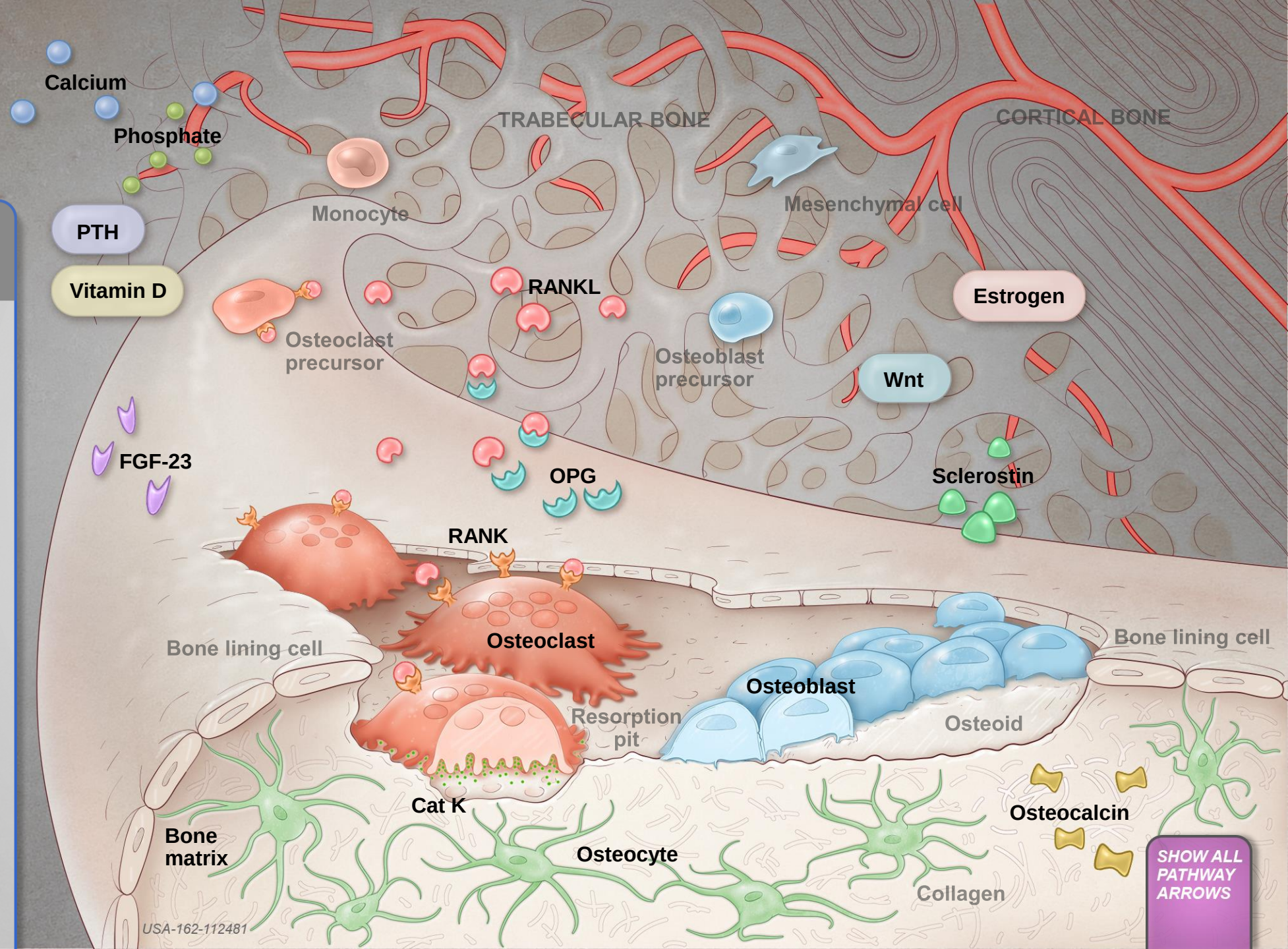

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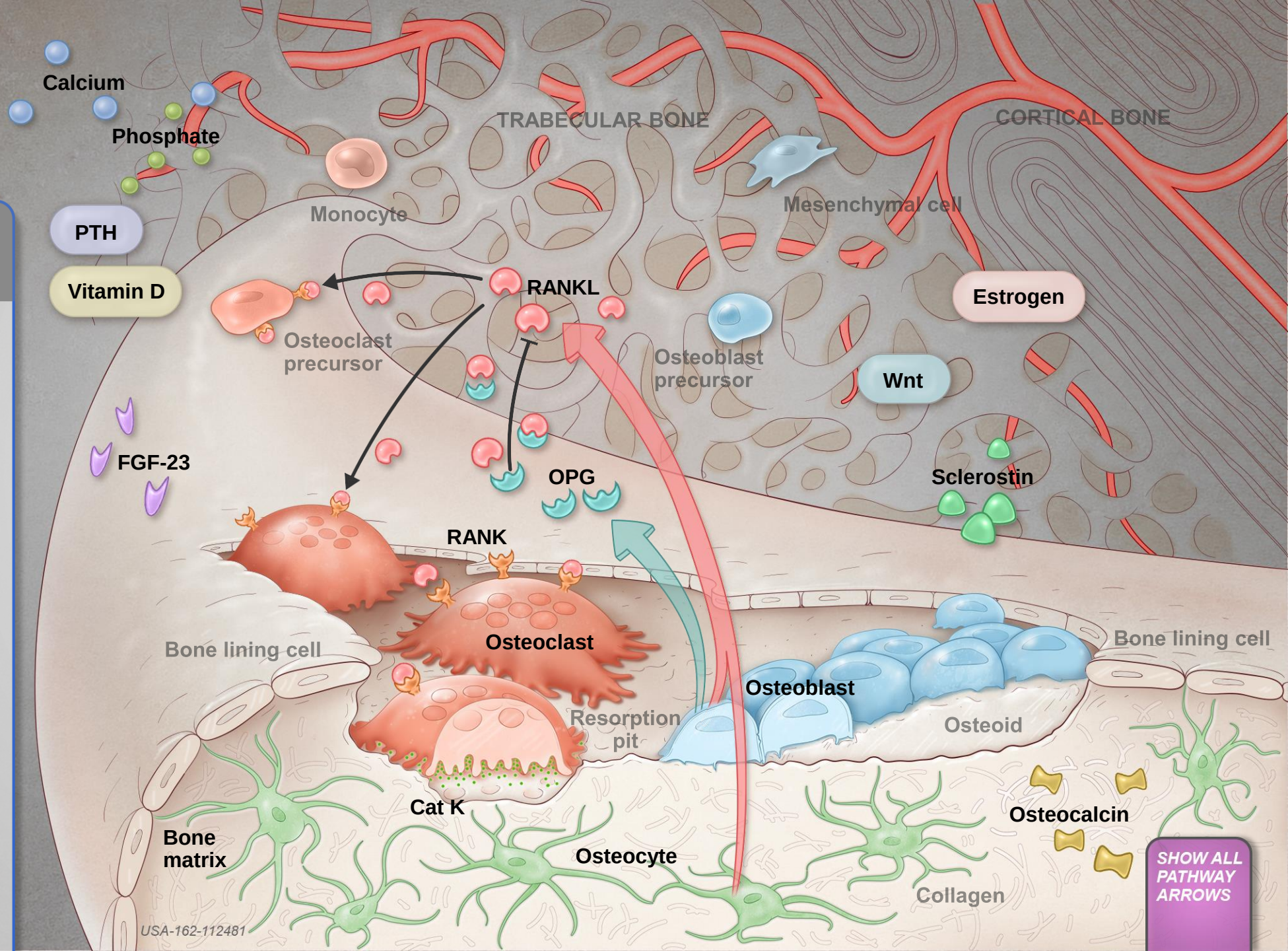
RANKL

Osteoblasts, osteocytes, and T-cells produce RANKL[1], which binds to and activates its receptor, RANK, on immature and mature osteoclasts[2]

Binding of RANKL to RANK promotes osteoclast formation, function and survival[2]



[1] Nakashima T, et al. *Nat Med*. 2011;17:1231-1234.
[2] Dempster DW, et al. *Clin Thera*. 2012; 34:521-536.

PATHWAYS IN OSTEOPOROSIS

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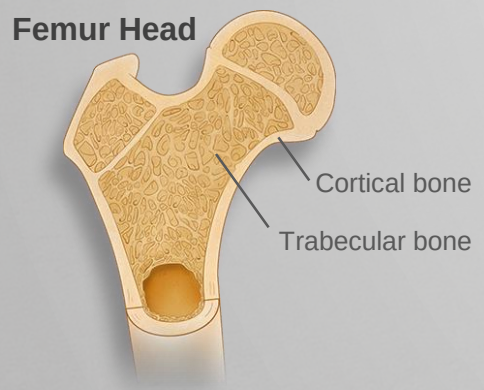

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[2] Manolagas SC. *Endocr Rev*. 2000;21:115-137.
[3] Raisz L. *J Clin Invest*. 2005;115:3318-3325.

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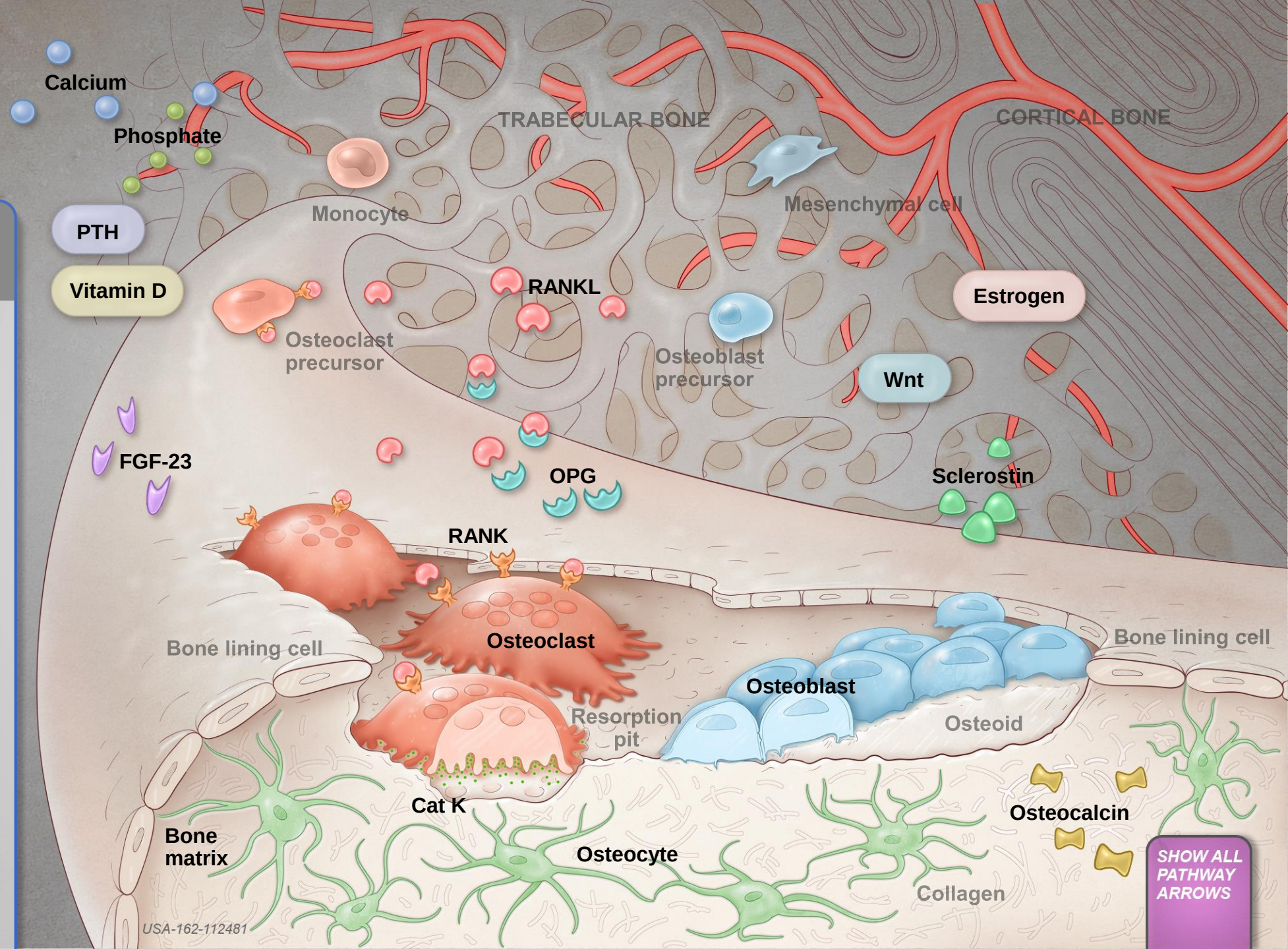

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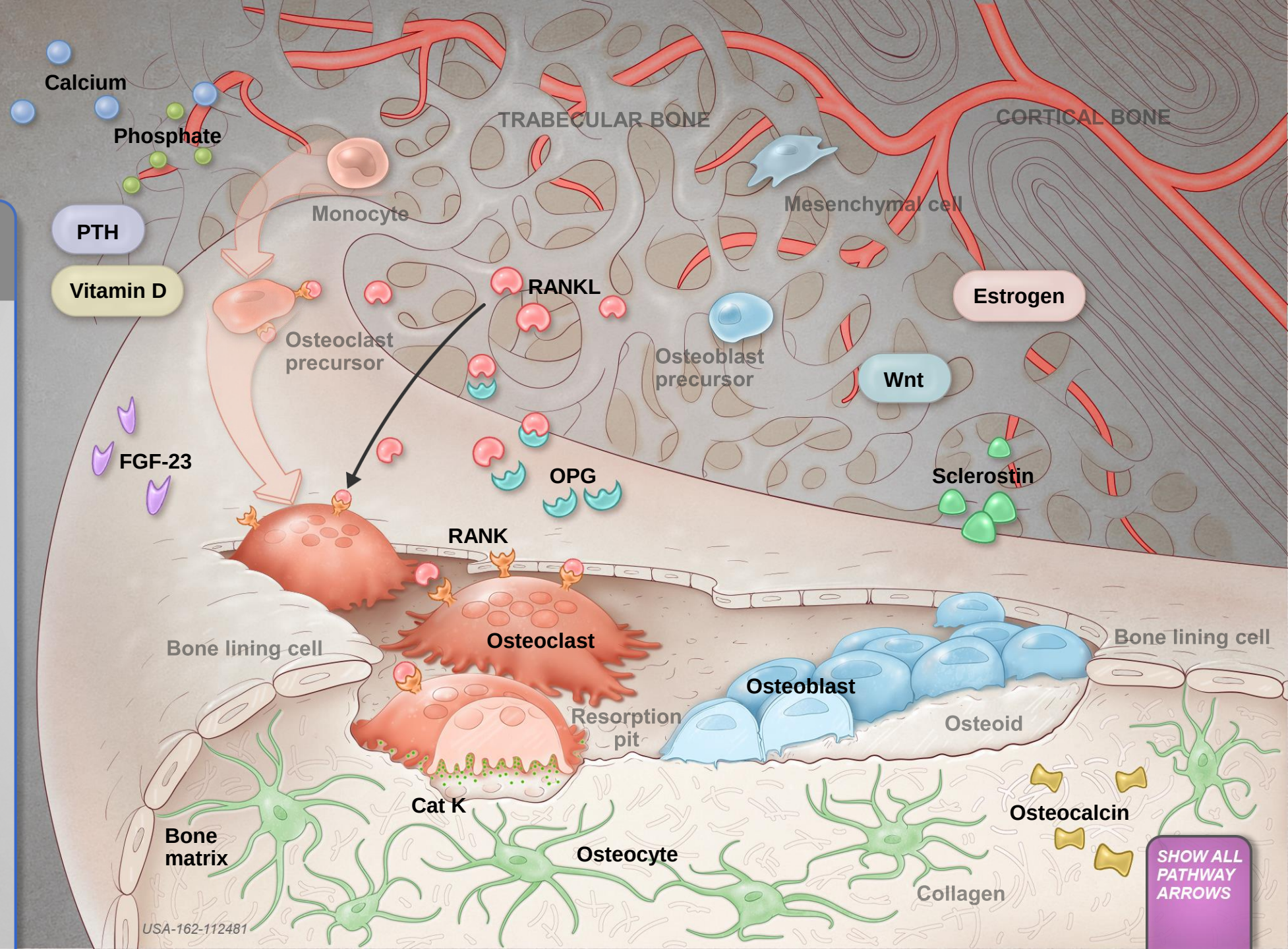
Osteoclasts

Osteoclasts are large, multi-nucleated cells derived from monocyte/macrophage precursors[1]

Osteoclasts attach to bone matrix, then secrete acid and enzymes that degrade bone[1]



[1] Boyle WJ, et al. *Nature*. 2003;423:337-342.

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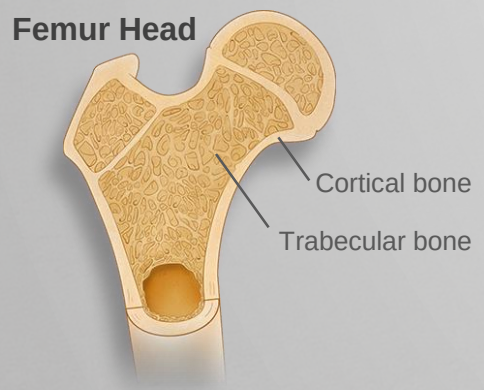

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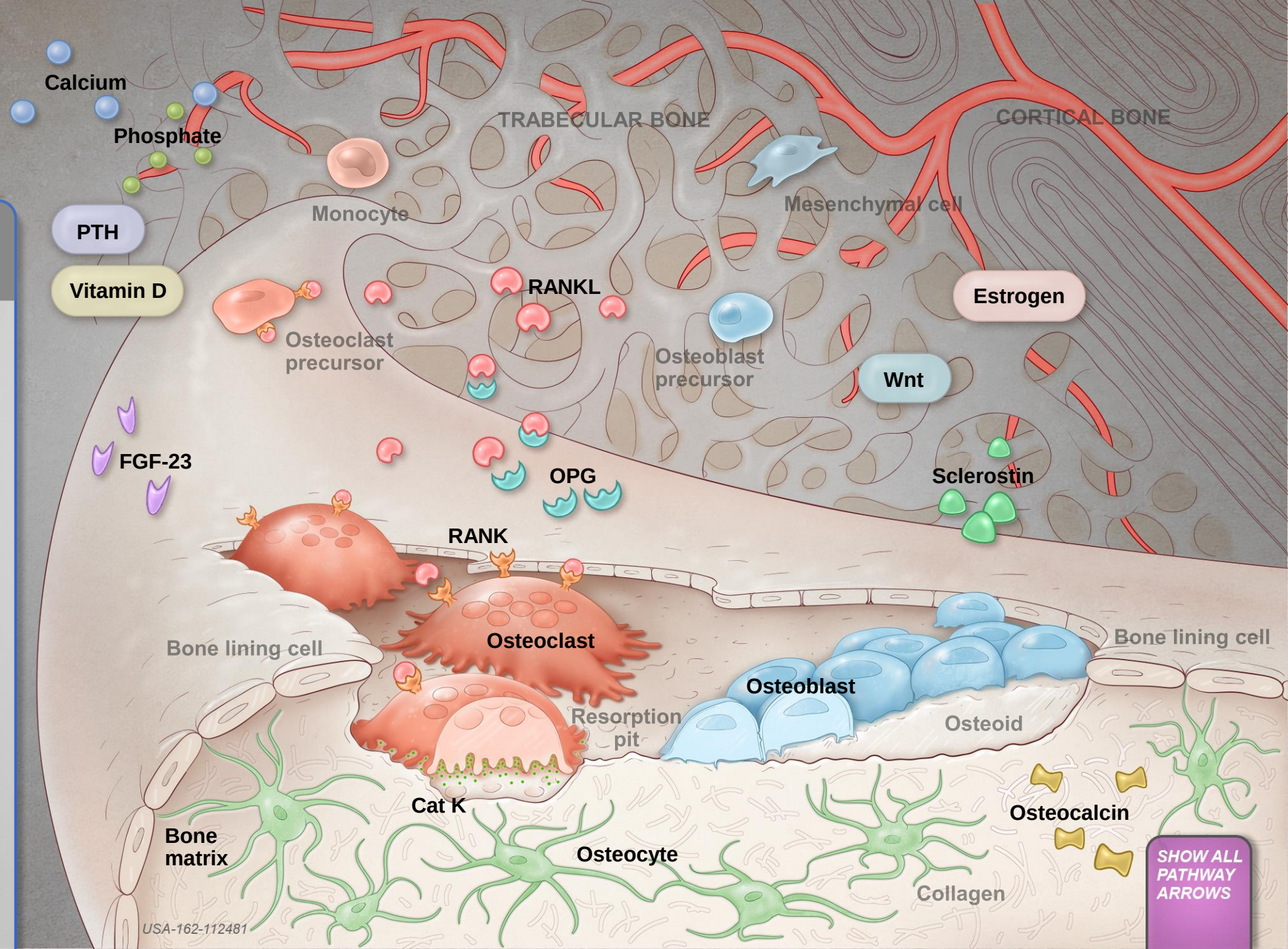

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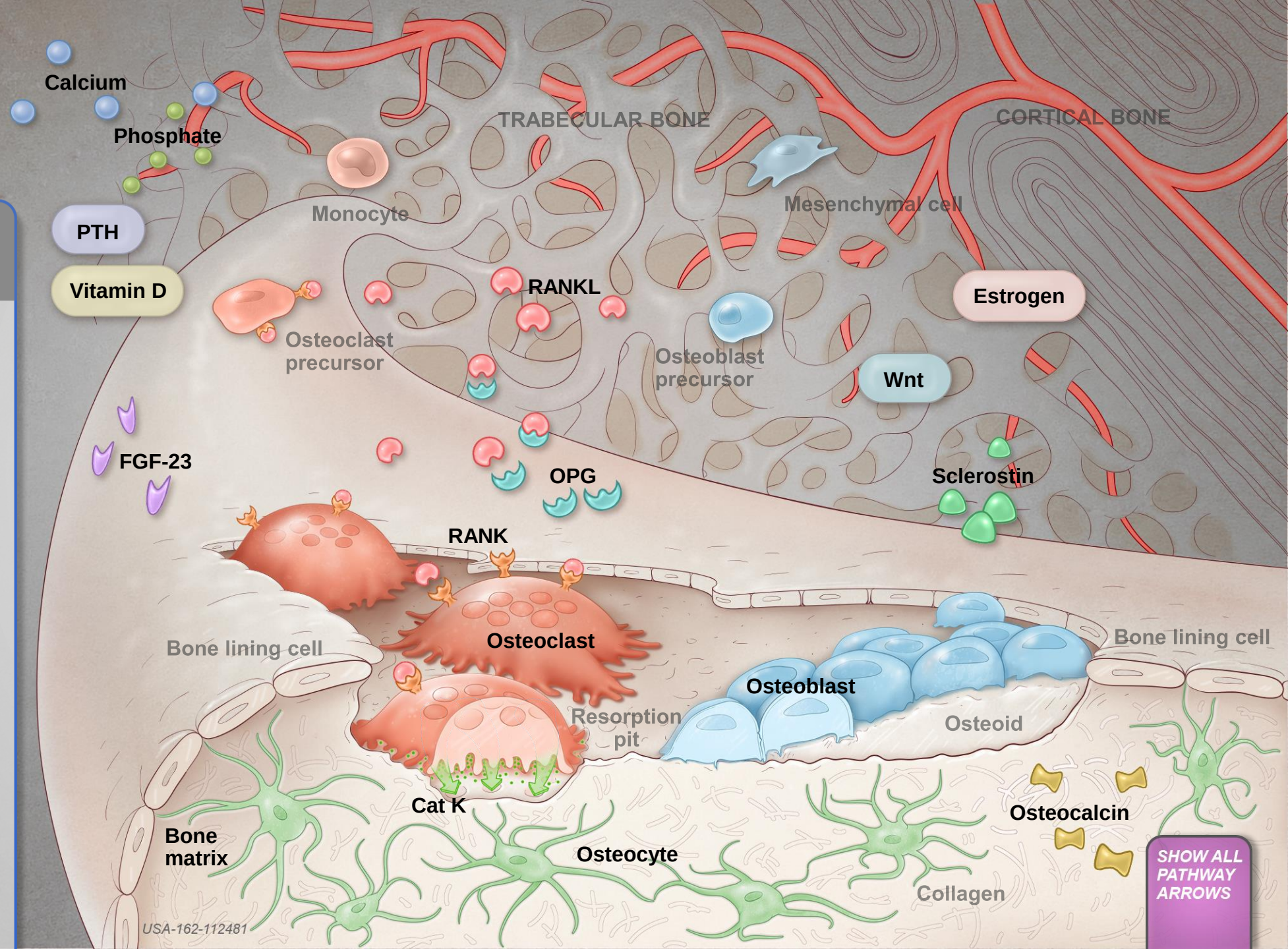
Cathepsin K

Cathepsin K is a cysteine protease that is highly and selectively expressed in osteoclasts[1]

Active proteases released from osteoclasts into the resorption lacunae degrade bone-matrix proteins and type I and type II collagen[2–4]



[1] Drake FH, et al. *J Biol Chem*. 1996;271:12511-12516.
[2] Baron R, et al. *J Cell Bio*. 1985;101:2210-2222.
[3] Bossard MJ, et al. *J Biol Chem*. 1996;271:12517-12524.
[4] Kafienah W, et al. *Biochem J*. 1998;331:727-732.

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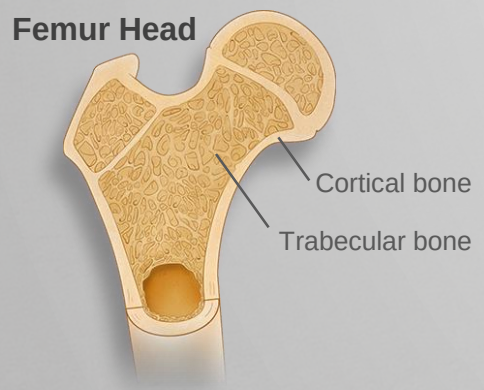

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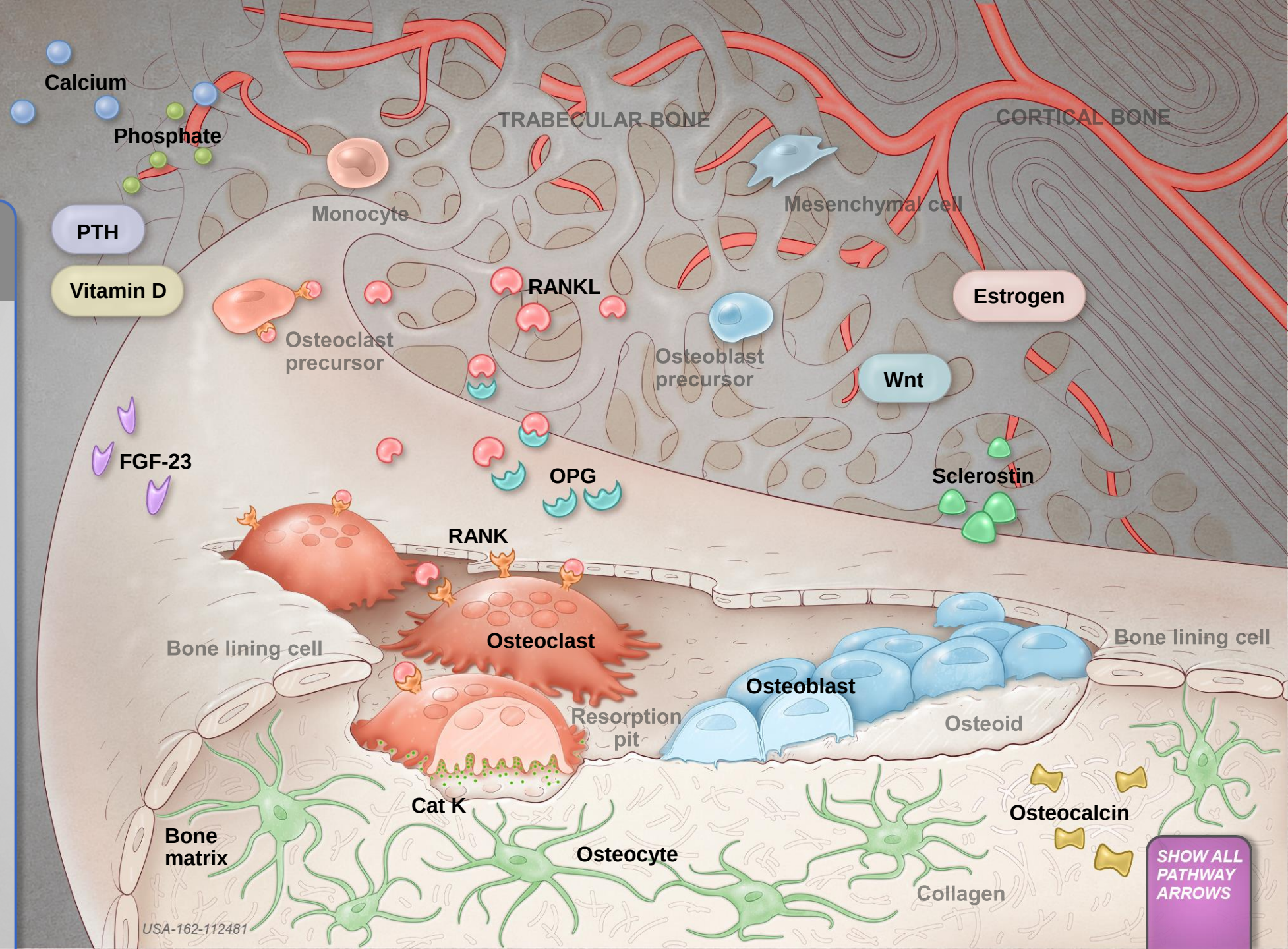

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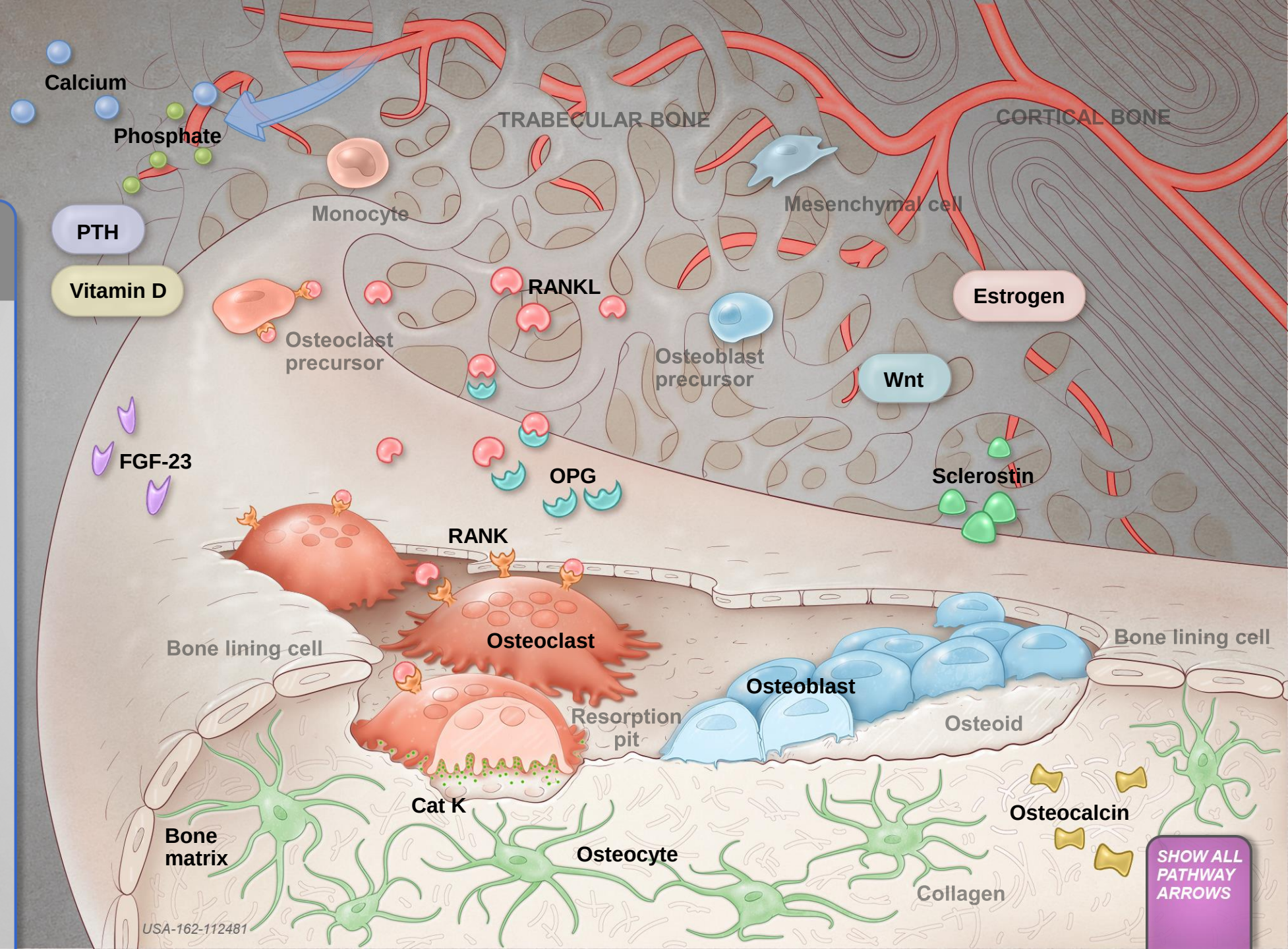
Bone Matrix

Osteoblasts secrete collagen, which composes the majority of the organic component of bone[1]

The inorganic bone matrix consists primarily of mineralized calcium and phosphate[1]



[1] Downey PA, et al. *Phys Ther*. 2006;86:77-91.

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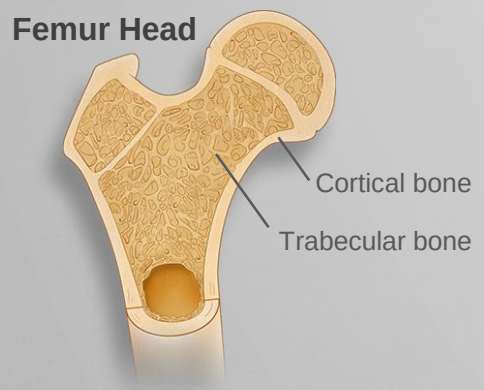

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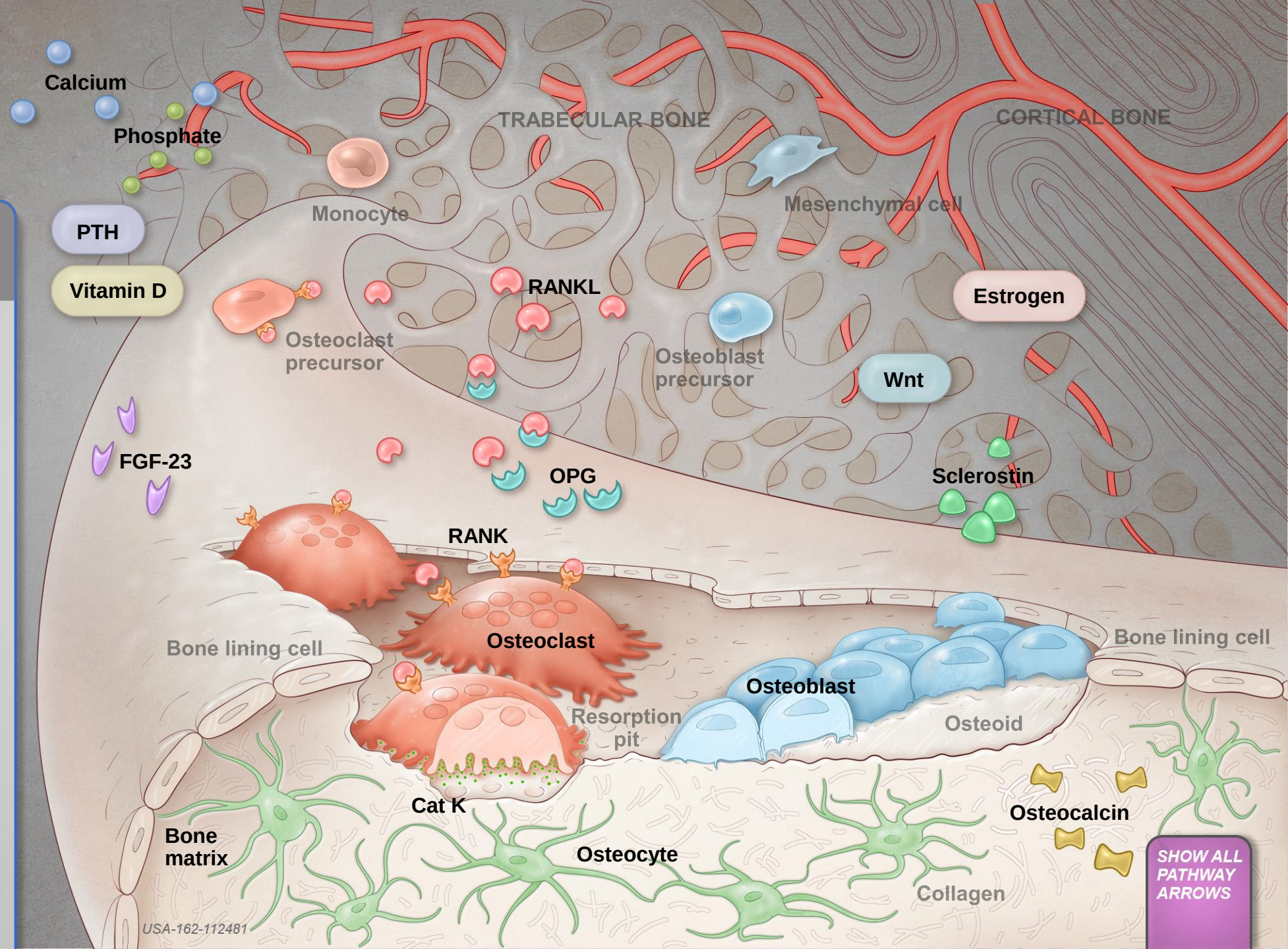

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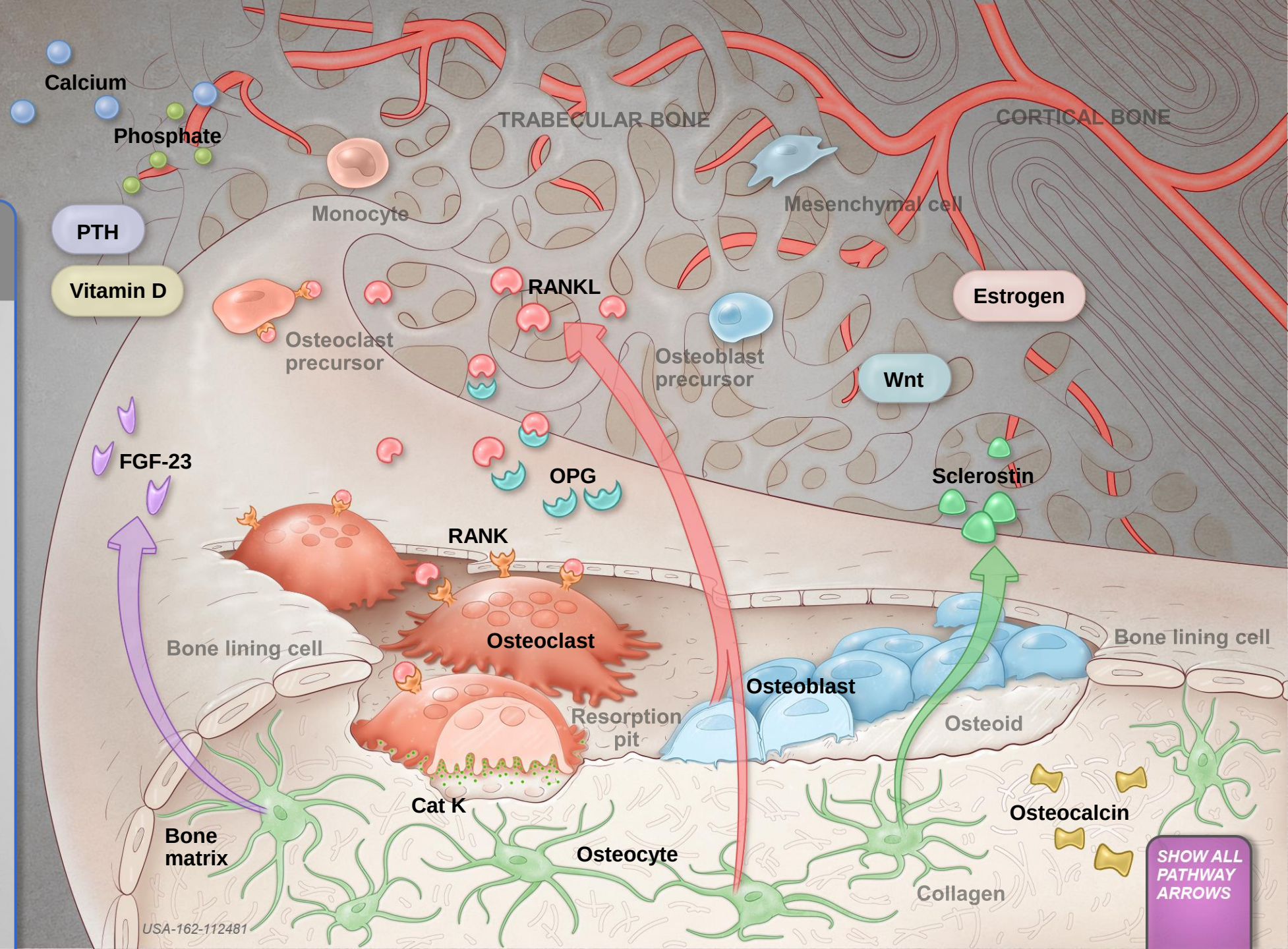
Osteocytes

Osteocytes are terminally-differentiated osteoblasts embedded in the bone matrix[1]

Osteocytes respond to mechanical and environmental stimuli to modulate the process of bone formation and resorption[1]



[1] Bellido T. *Calc Tiss Int*. 2014;94:25-34.

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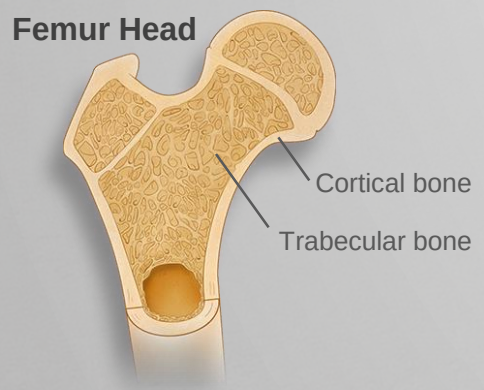

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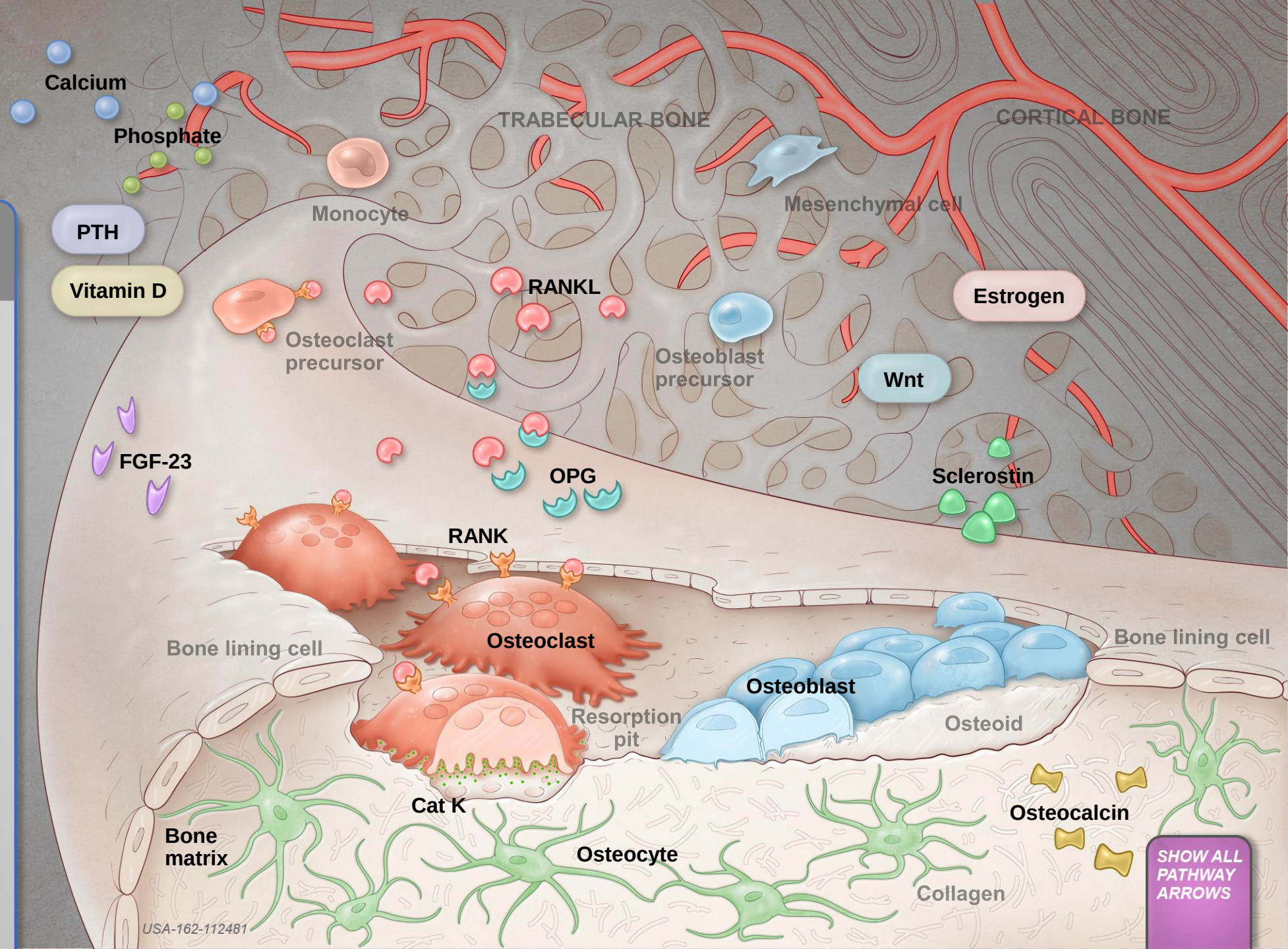

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Wnt

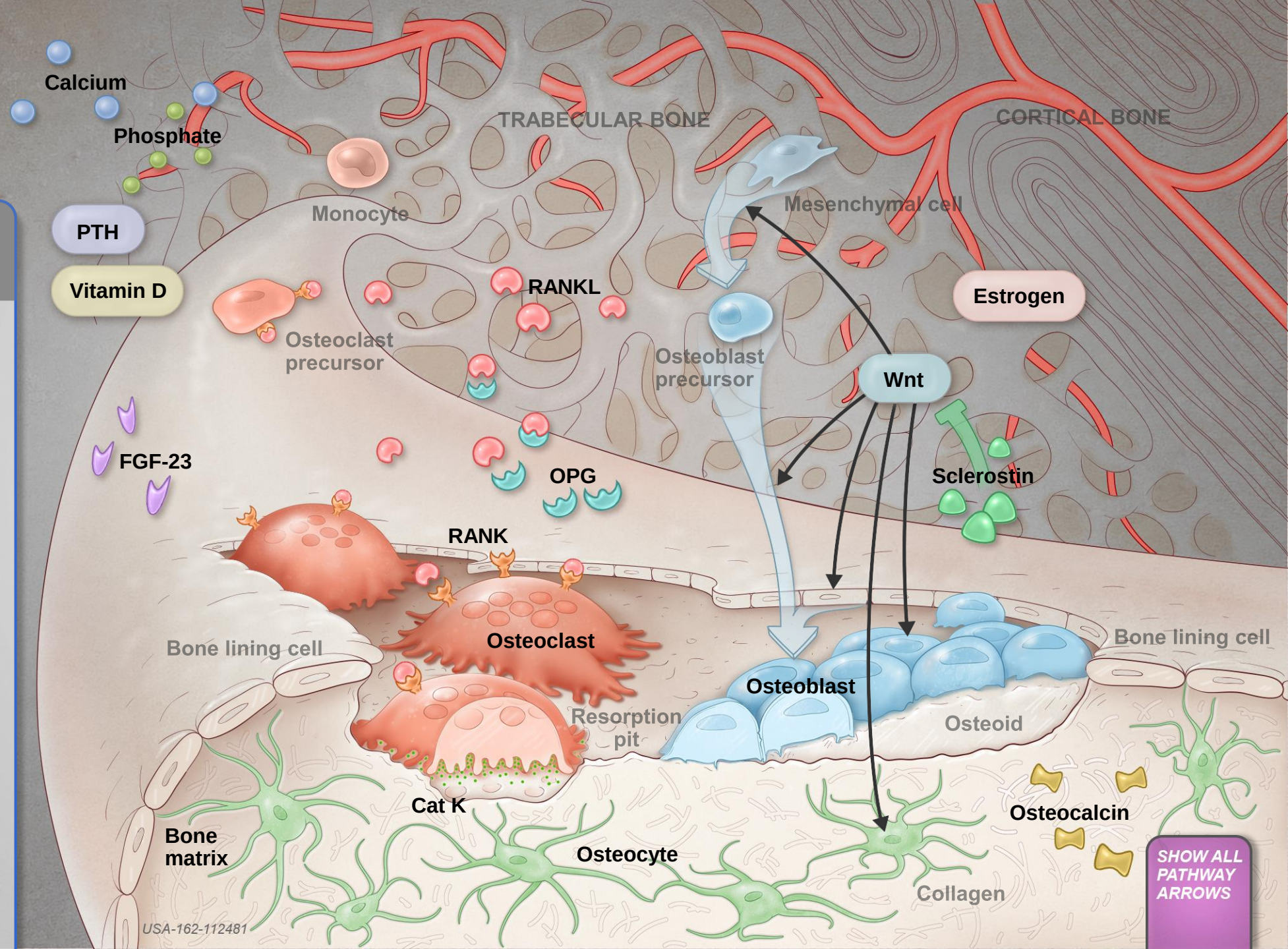
Wnt proteins are key signaling molecules in tissue development and regeneration[1]

Wnt binds to co-receptors LRP 5/6 and frizzled, forming a complex that stabilizes intracellular β-catenin. Stabilized β-catenin translocates to the nucleus and mediates gene transcription, resulting in increased bone formation[1]

Canonical Wnt signaling increases bone formation through multiple mechanisms:

- Increased differentiation of mesenchymal stem cells to osteoblasts[2]
- Increased osteoblast activity[3]
- Stimulation of the conversion of bone lining cells into osteoblasts[4]
- Regulation of osteoblast and osteoclast activity via osteocyte signaling[5, 6]

[1] MacDonald BT, et al. *Developmental Cell*. 2009;17:9-26.
[2] Hu H, et al. *Development*. 2005;132:49-60.
[3] Kato M, et al. *J Cell Biol*. 2002;157:303-314.
[4] Nioi P, et al. *J Bone Miner Res*. 2015;30:1457-1467.
[5] Tu X, et al. *Proc Natl Acad Sci*. 2015;112:e478-486.
[6] Kramer I, et al. *Mol Cell Bio*. 2010;30:3071-3085.



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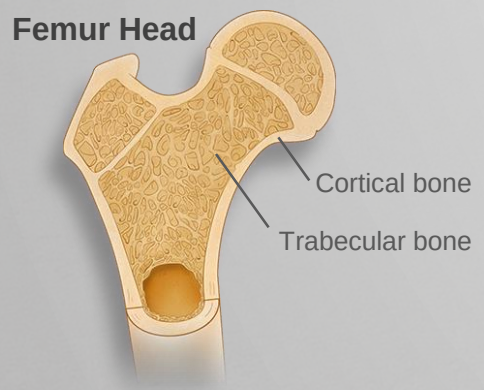

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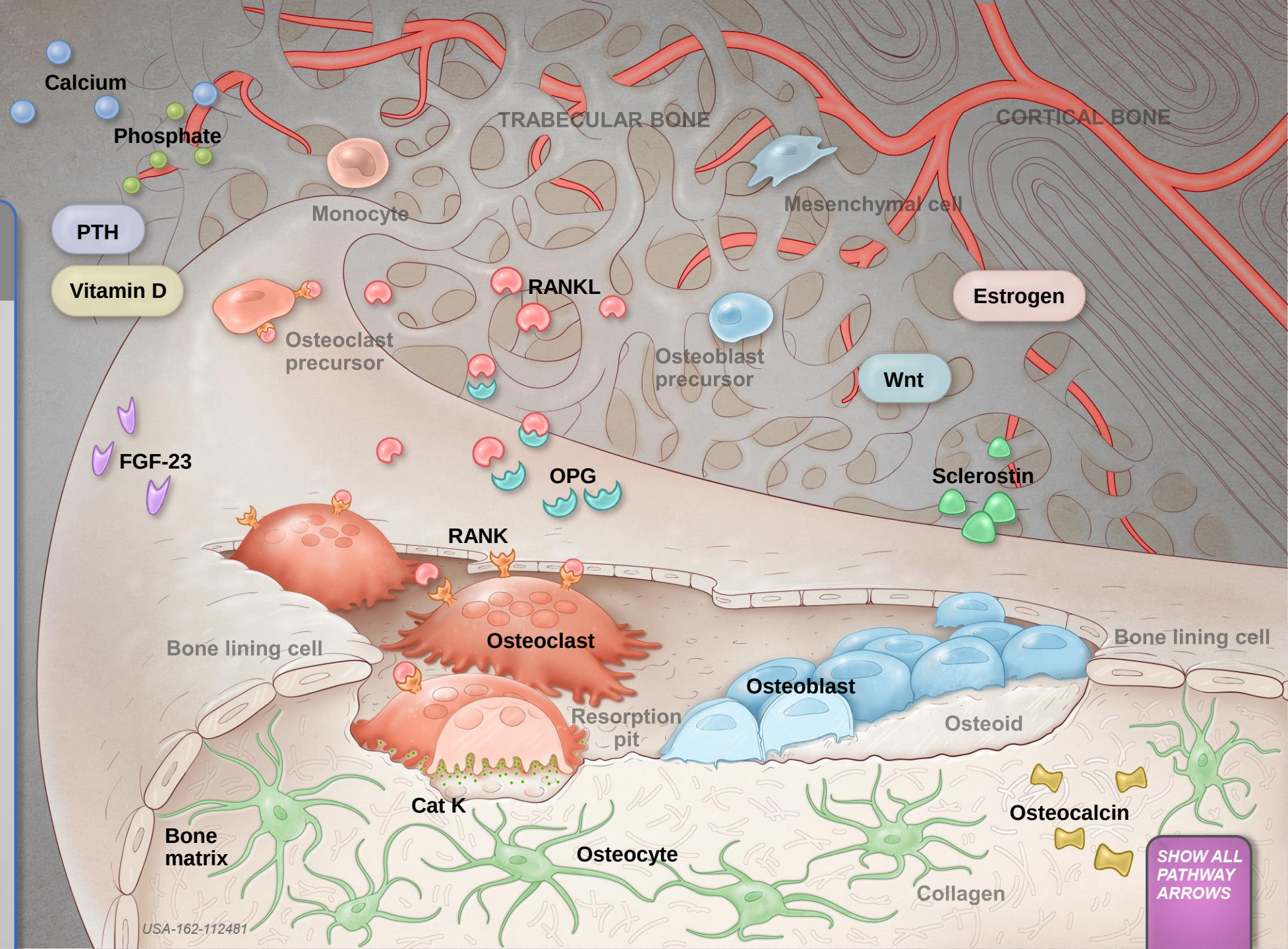

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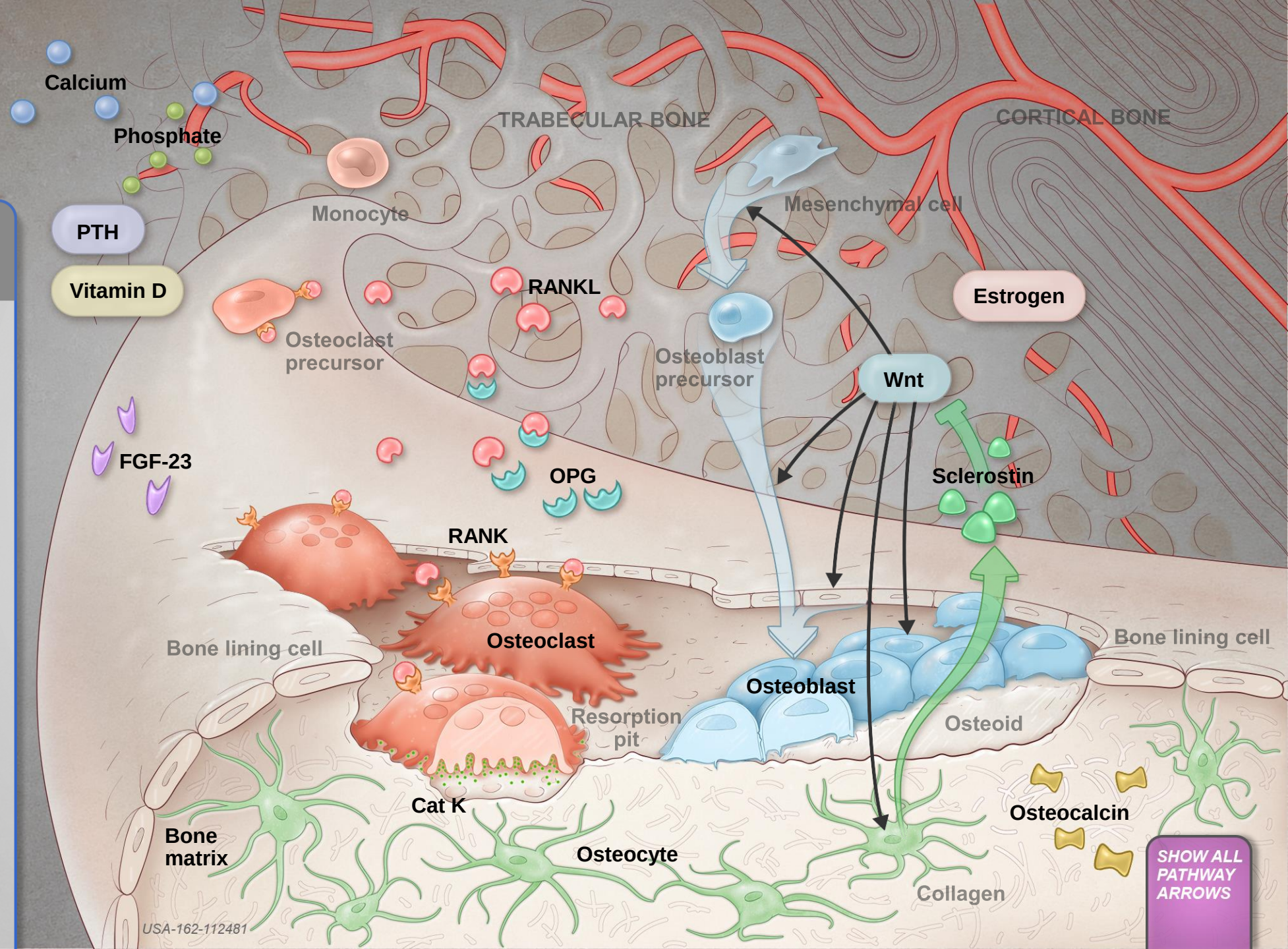
Sclerostin

Sclerostin is a protein secreted predominantly by osteocytes in bone[1]

Sclerostin binds to low density lipoprotein receptor-related proteins (LRP4, LRP5, LRP6) and inhibits canonical Wnt-β-catenin signaling[2, 3]

In human disease, loss-of-function mutations in the sclerostin gene (*SOST*) result in high bone mass phenotypes, e.g., sclerosteosis[4]



[1] Winkler DG, et al. *EMBO J*. 2003;22:6267-6276.
[2] Li X, et al. *J Biol Chem*. 2005;280:19883-19887.
[3] Choi HY, et al. *PLoS One*. 2009;4:e7390.
[4] Balemans W, et al. *Hum Molec Genet*. 2001;10:537-543.

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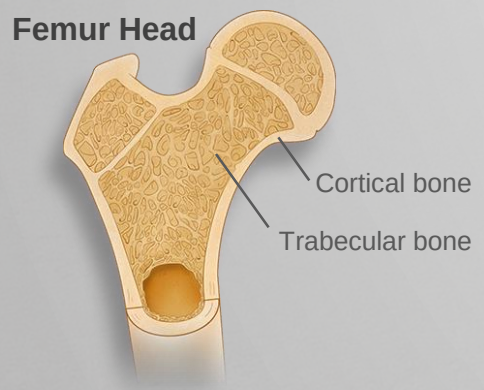

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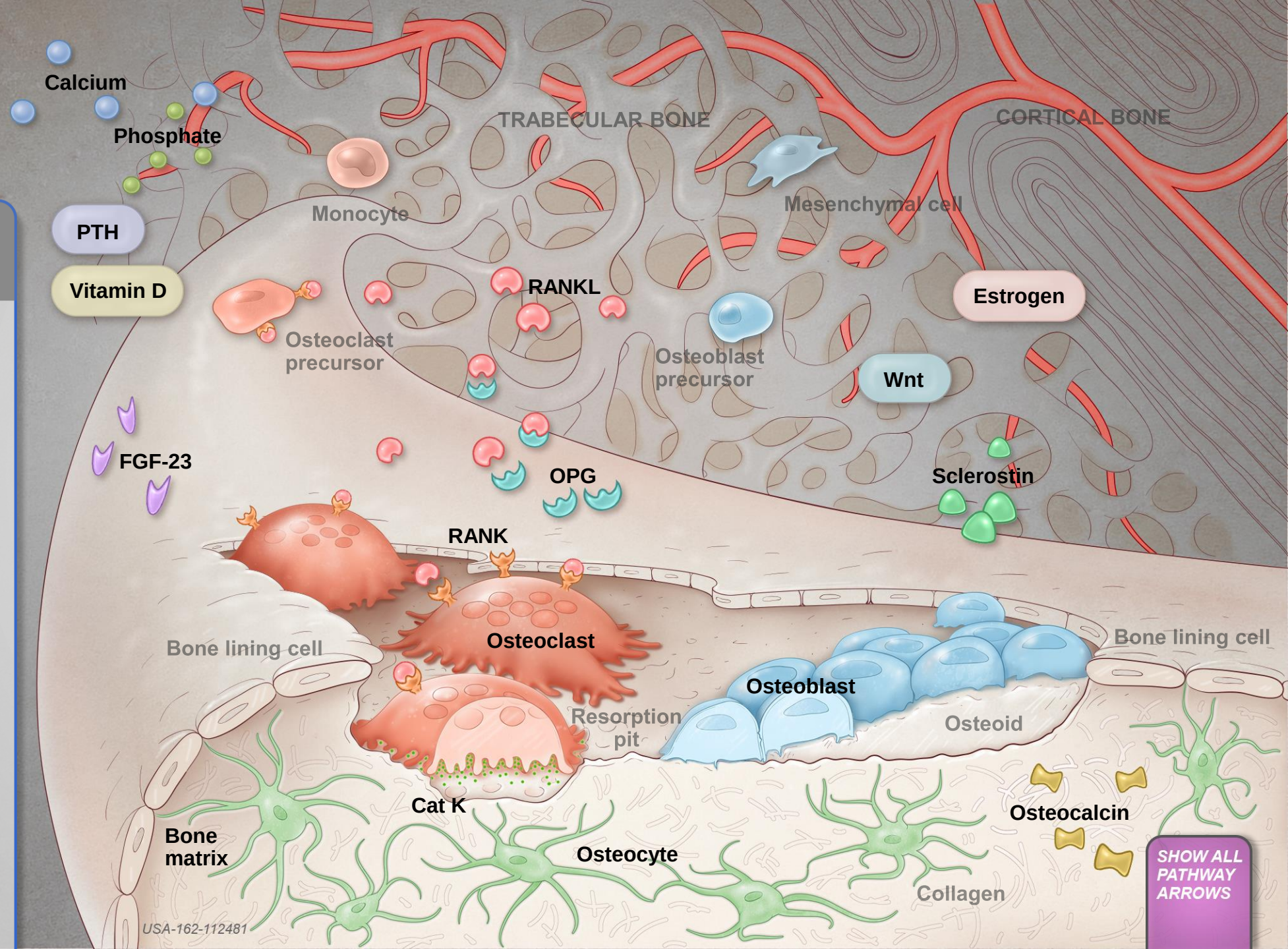

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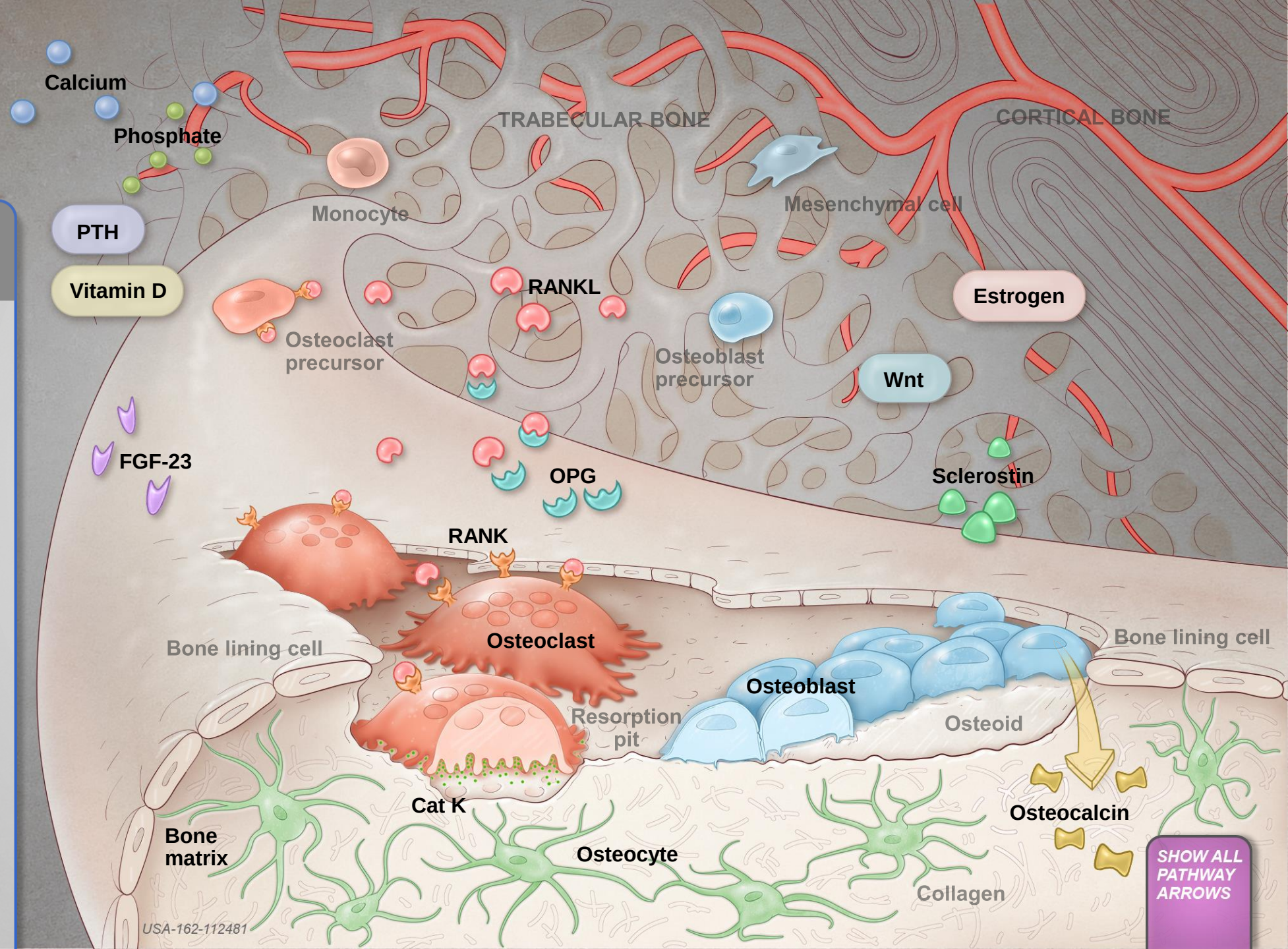
Osteocalcin

Osteocalcin is a calcium-binding protein secreted primarily by mature osteoblasts and used as an osteoblastic-specific marker of bone formation[1]

Recent evidence suggests that under-carboxylated osteocalcin has an endocrine role in the regulation of energy metabolism, e.g., via insulin[2]



[1] Hauschka PV, et al. *Physiol Reviews*. 1989; 69:990-1047.
[2] Ferron M, et al. *Cell*. 2010;142:296-308.

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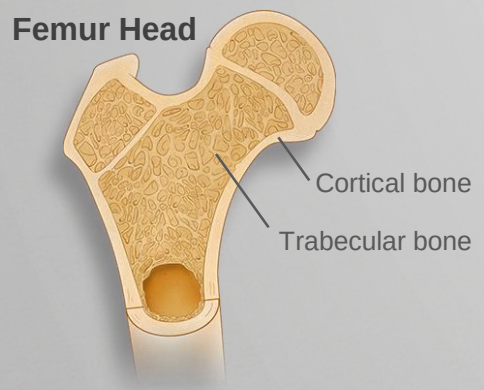

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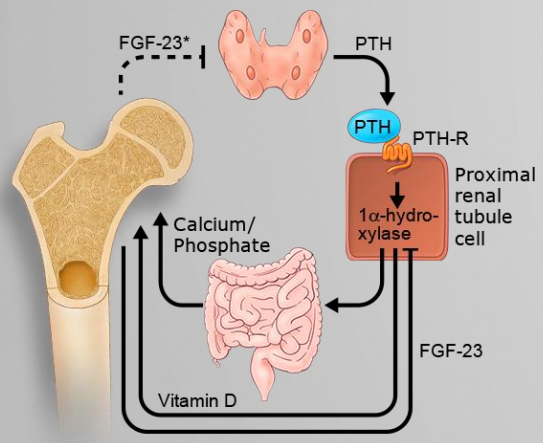

Adapted from Blau JE, et al. Rev Endocr Metab Disord. 2015; In press.
* FGF23 suppression on the parathyroid gland was reported in *in vitro* studies only

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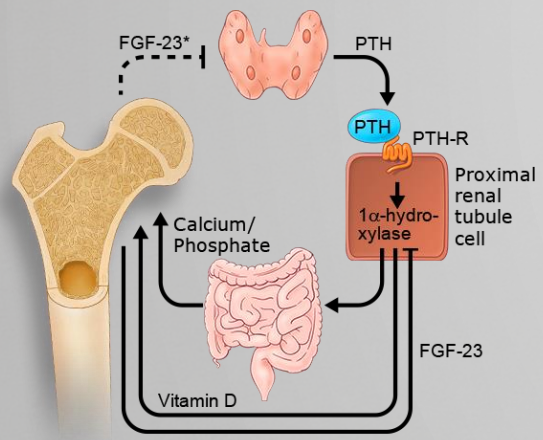
PTH-FGF23 Pathways



Adapted from Blau JE, et al. Rev Endocr Metab Disord. 2015; In press.
* FGF23 suppression on the parathyroid gland was reported in *in vitro* studies only

Calcium
Phosphate
PTH
Vitamin D
TRABECULAR BONE
CORTICAL BONE
Monocyte
Mesenchymal cell
RANKL
Osteoclast precursor
Osteoblast precursor
Wnt
Estrogen
FGF-23
OPG
Sclerostin
RANK
Bone lining cell
Osteoclast
Osteoblast
Bone lining cell
Resorption pit
Osteoid
Cat K
Osteocalcin
Bone matrix
Osteocyte
Collagen
HIDE ALL PATHWAY ARROWS

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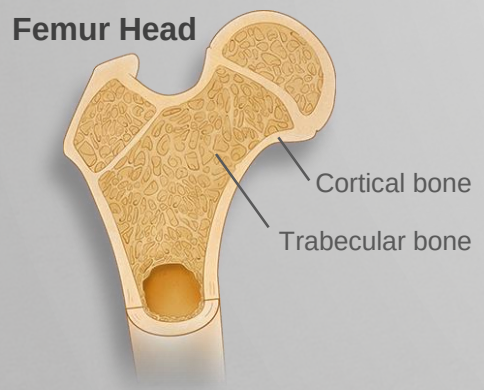
PATHWAYS IN OSTEOPOROSIS

Touch any label on the image to access detailed information

HOME PREVIOUS NEXT

THE SKELETON

is a dynamic organ that is constantly regenerating. Bone is made up of a matrix and highly specialized cells, including osteoblasts, osteoclasts, osteocytes, and bone lining cells. These specialized cells carry out bone modeling and remodeling in a tightly regulated process that maintains the integrity of bone. Numerous factors regulate the activity of osteoblasts and osteoclasts in bone modeling and remodeling. An imbalance or alteration in these pathways may lead to increased bone loss and contribute to the pathogenesis of osteoporosis.[1–3]



[1] Raggatt LJ, et al. *J Biol Chem*. 2010;285:25103-25108.
[2] Manolagas SC. *Endocr Rev*. 2000;21:115-137.
[3] Raisz L. *J Clin Invest*. 2005;115:3318-3325.

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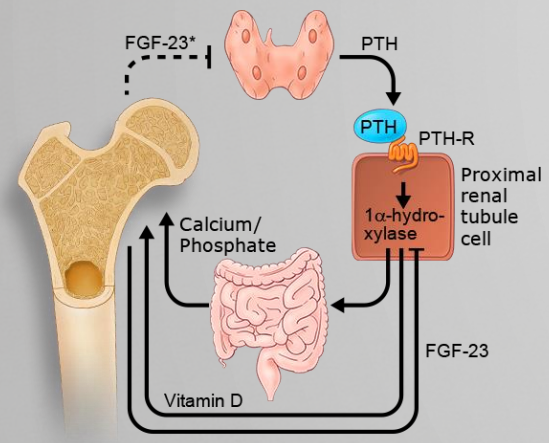

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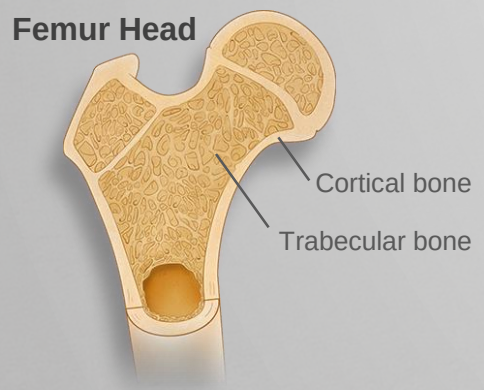

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Medical Approval	Robert Kees Stad Med Director 13-Jun-2019 11:58:31 GMT+0000

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