PATHWAYS IN OSTEOPOROSIS

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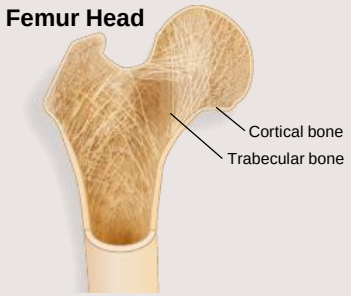
THE SKELETON is a dynamic organ that is constantly regenerating. Bone is made up of a matrix and highly specialized cells, including osteoblasts, osteoclasts, osteocytes, and bone lining cells.[1] These specialized cells carry out bone modeling and remodeling in a tightly regulated process that maintains the integrity of bone. Numerous factors regulate the activity of osteoblasts and osteoclasts in bone modeling and remodeling.[2] An imbalance or alteration in these pathways may lead to increased bone loss and contribute to the pathogenesis of osteoporosis.[3]



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

Vitamin D
TRABECULAR BONE
PTH
CORTICAL BONE
Monocyte
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RANKL
Mesenchymal cell
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OPG
Osteoblast precursor
Sclerostin
Differentiated osteoclast
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Activated osteoclast
Bone lining cell
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Collagen
Osteoid
Phosphate
Resorption pit
Sclerostin
BONE MATRIX COMPONENTS
Osteocytes

BONE REMODELING PROCESS | Premenopausal | Postmenopausal Osteoporosis | SHOW ALL PATHWAY ARROWS

PATHWAYS IN OSTEOPOROSIS

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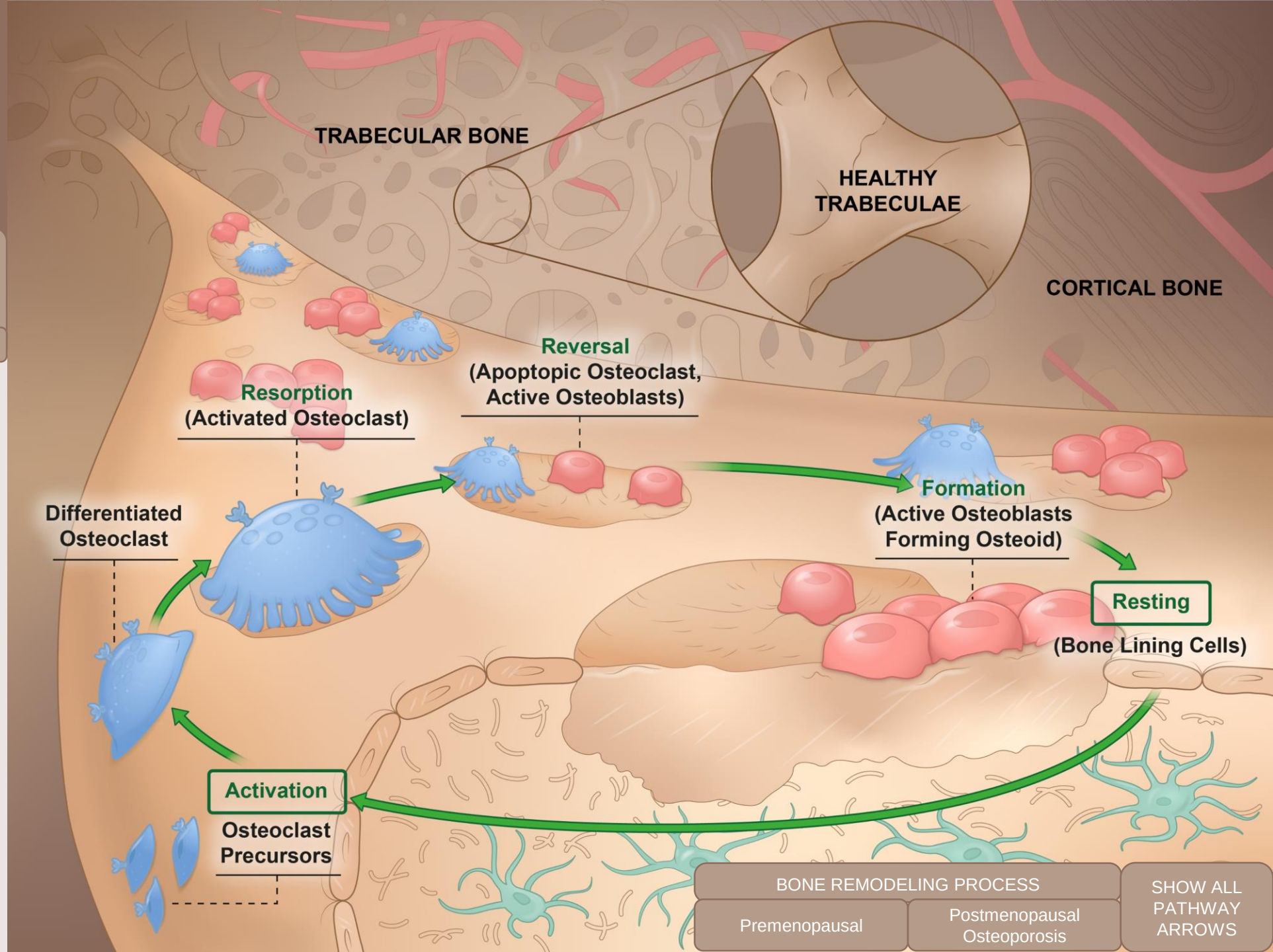
Premenopausal Bone Remodeling

Normal bone remodeling before the menopause consists of five main phases:

- *Activation phase*: Osteoclast precursors differentiate into osteoclasts which are recruited to the remodeling site[1]
- *Resorption phase*: Osteoclasts resorb bone at the site of remodeling[1]
- *Reversal phase*: After resorption, the osteoclasts undergo apoptosis and osteoblasts are recruited[1]
- *Formation phase*: Osteoblasts lay organic bone matrix which later undergoes mineralization[1]
- *Resting phase*: Bone lining cells remain dormant until the next cycle of remodeling starts[2]



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2. Raggatt LJ, et al. J Biol Chem. 2010;285:25103-25108.

PATHWAYS IN OSTEOPOROSIS

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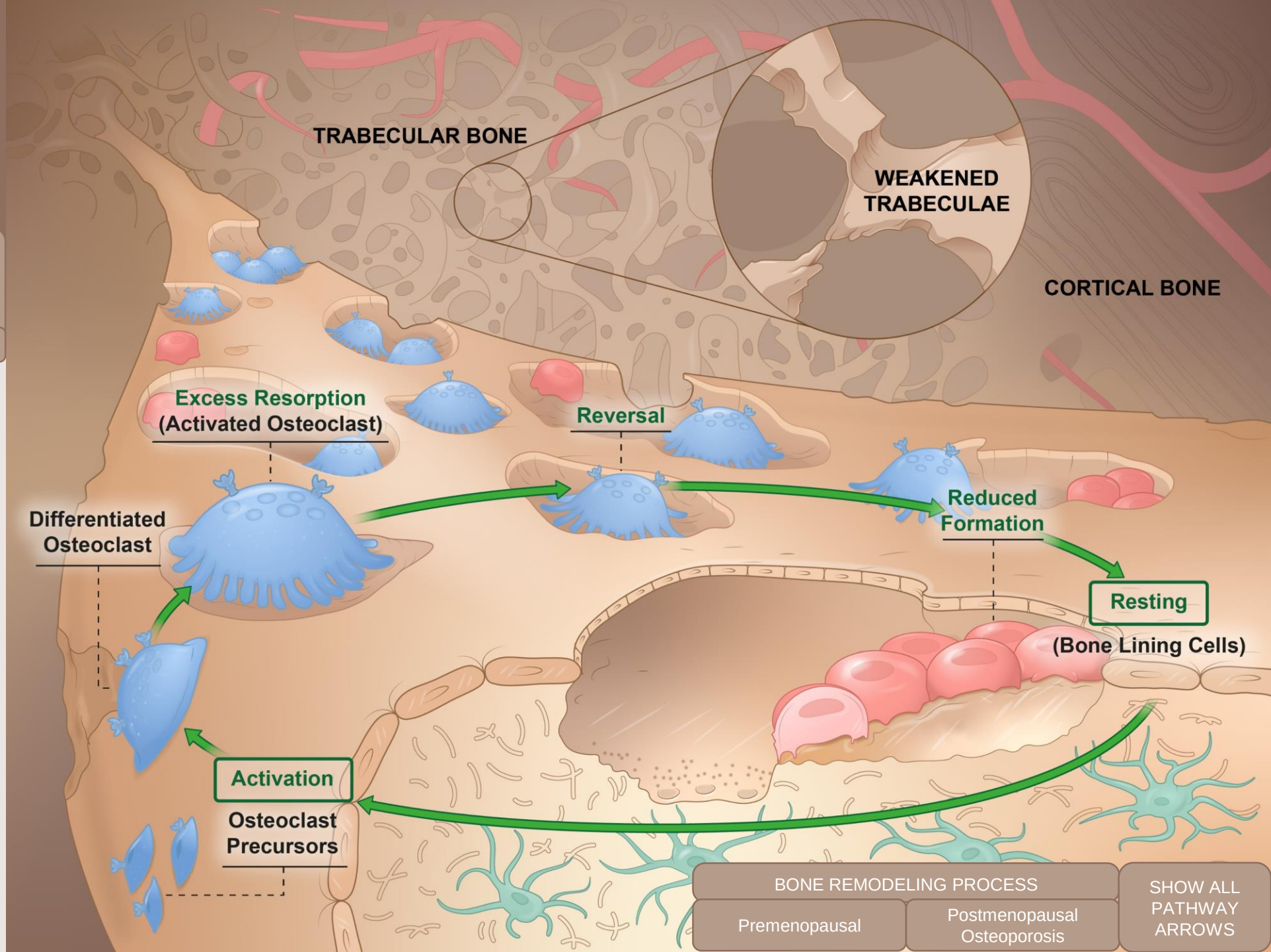
Postmenopausal Osteoporosis Bone Remodeling

Estrogen deficiency during menopause greatly affects bone turnover cycle. Osteoclast resorption activity increases while the activity of osteoblasts decreases. This results in more resorption than deposition of bone, leading to net bone loss[1]

Postmenopausal women undergo two stages of bone loss. During the first, trabecular bone is predominantly affected, where bone resorption exceeds bone formation, called menopause-related bone loss. During the second, there is slower persistent loss of both trabecular and cortical bone, caused by reduced bone formation, called age-related bone loss[1]

Not all postmenopausal women develop osteoporosis. Bone mineral density (BMD) is used to identify osteoporosis and fracture risk. An individual's BMD is compared to the mean value in young healthy individuals. A standard deviation value between -1 to +1 indicates normal bone, while a value between -1 and -2.5 indicates osteopenia and ≤-2.5 indicates osteoporosis[2]

1. Ji MX, et. al. *Chronic Dis Transl Med*. 2015;1:9-13.
2. U.S. Department of Health and Human Services. *Bone Health and Osteoporosis: A Report of the Surgeon General*. 2004.



PATHWAYS IN OSTEOPOROSIS

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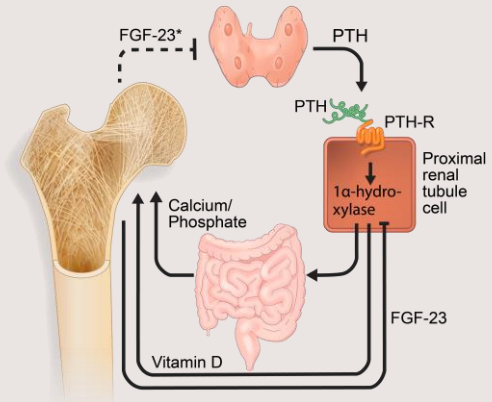
Parathyroid Hormone

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;16:165-174.
*FGF-23 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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PATHWAYS IN OSTEOPOROSIS

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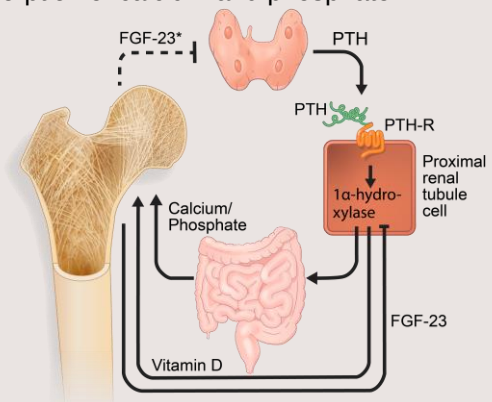
Calcium / Vitamin D

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

Vitamin D indirectly acts on bone homeostasis by suppressing PTH and increasing intestinal absorption of calcium and phosphate[1]



Adapted from Blau JE, et al. *Rev Endocr Metab Disord*. 2015;16:165-174.
*FGF-23 suppression on the parathyroid gland was reported in in vitro studies only

1. Lieben L, et al. *Best Pract Res Clin Endocrinol Metab*. 2011;25:561-572.

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BONE REMODELING PROCESS

Premenopausal | Postmenopausal Osteoporosis

SHOW ALL PATHWAY ARROWS

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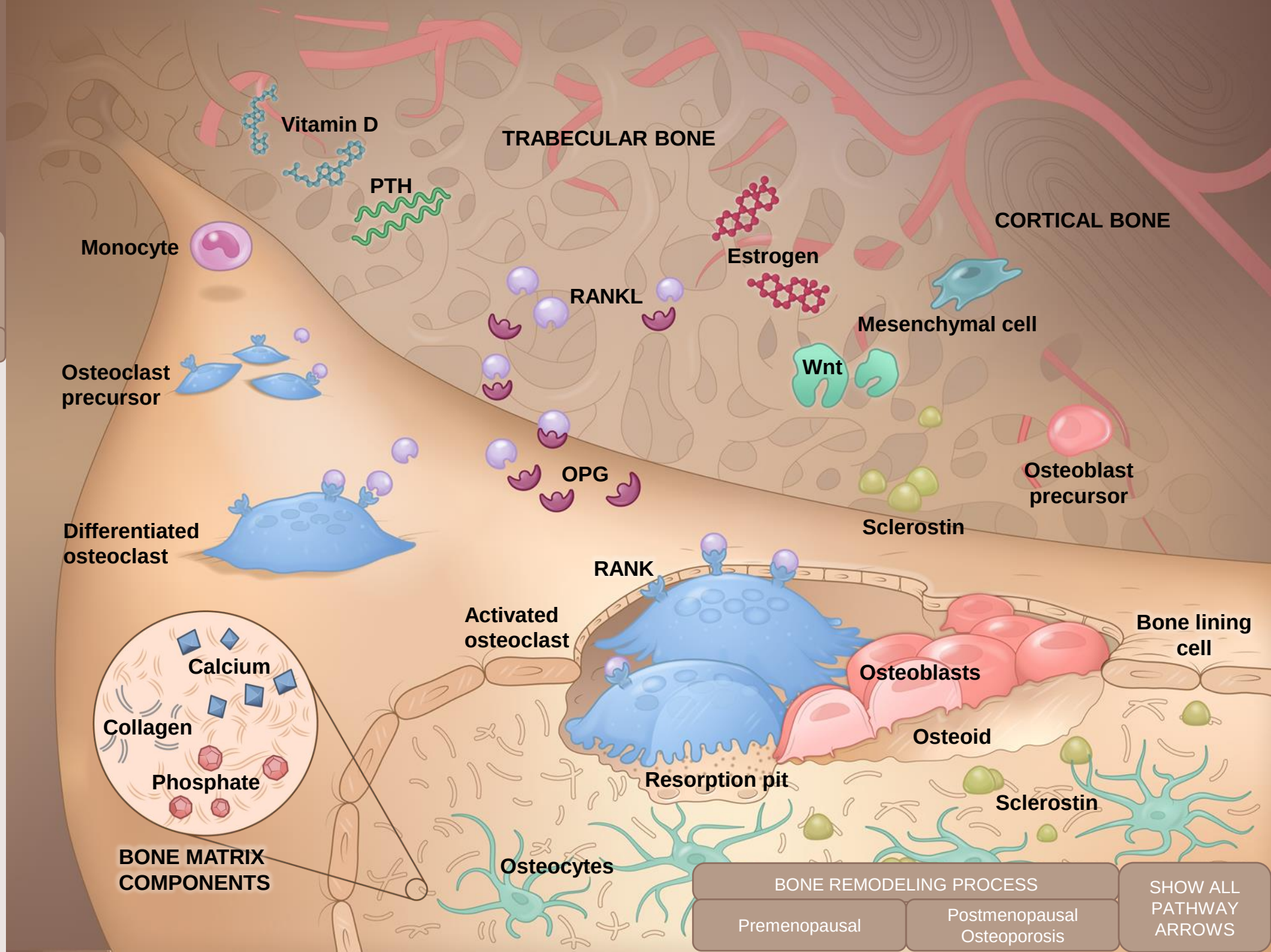
Phosphate

Phosphate homeostasis is maintained by absorption of dietary phosphate in the intestine, excretion by the kidney, and movement of phosphate between the extracellular 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.

PATHWAYS IN OSTEOPOROSIS

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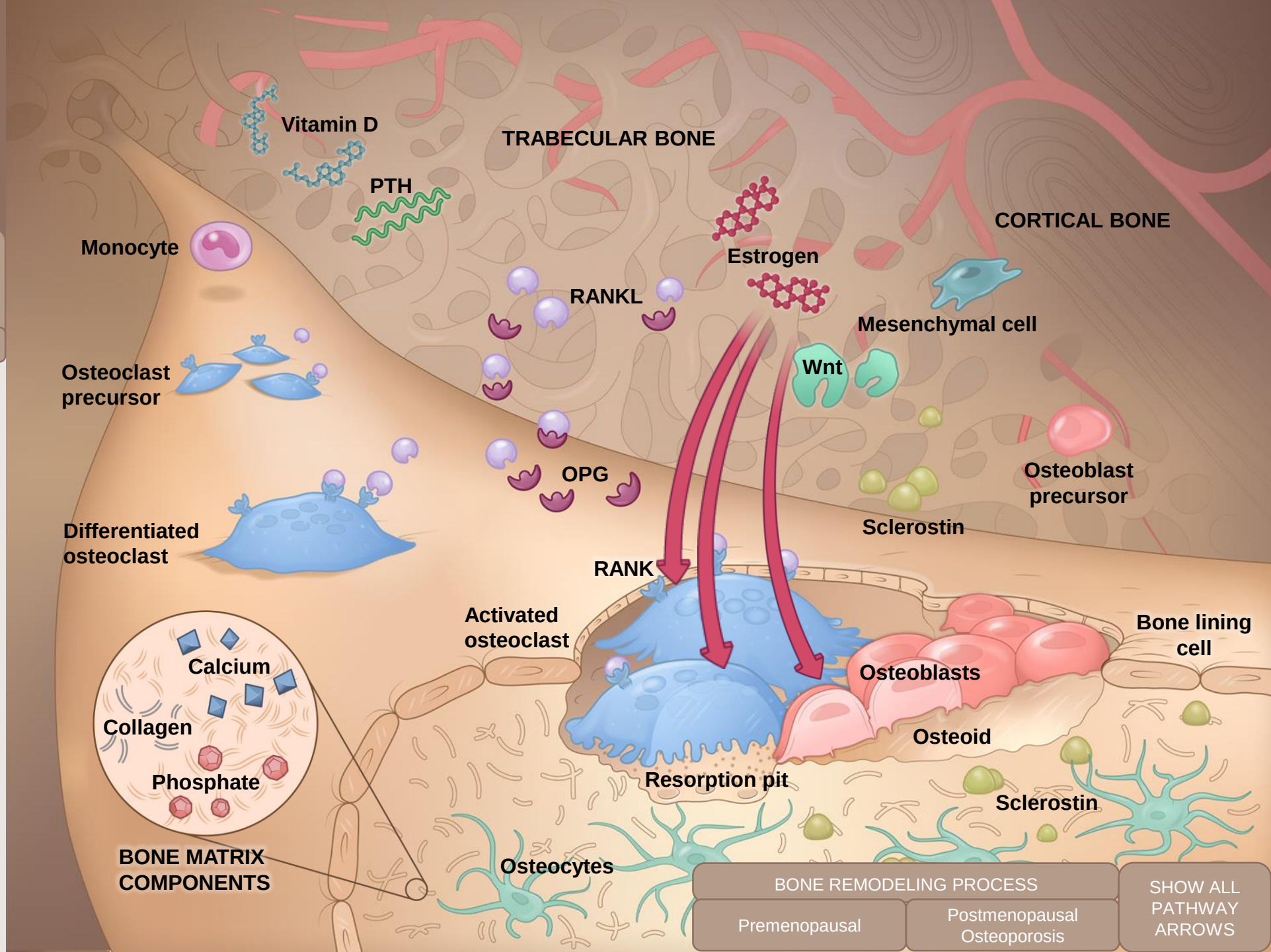
Estrogen

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

Estrogen suppresses bone resorption in part through increased osteoprotegerin and decreased RANKL expression by osteoblasts, and by modulating RANK signaling in osteoclasts[1]

Estrogen deficiency has been identified as the cause of bone loss in postmenopausal women and aging men[1]



1. Khosla S, et al. *J Bone Miner Res*. 2011;26:441-451.

PATHWAYS IN OSTEOPOROSIS

Select text on the image to access detailed information

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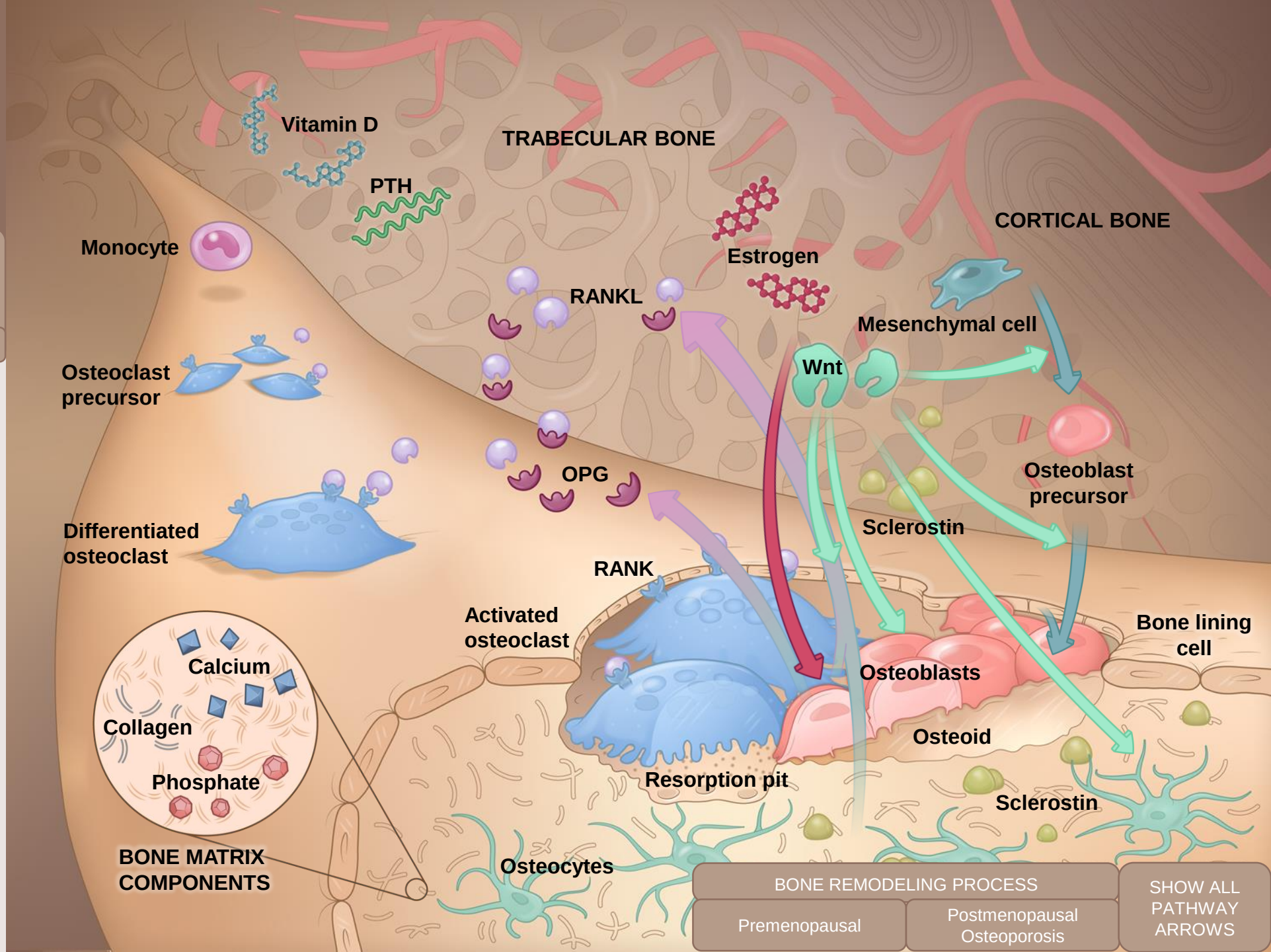
Osteoblasts

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. *Endocr Rev*. 2000;21:115-137.

PATHWAYS IN OSTEOPOROSIS

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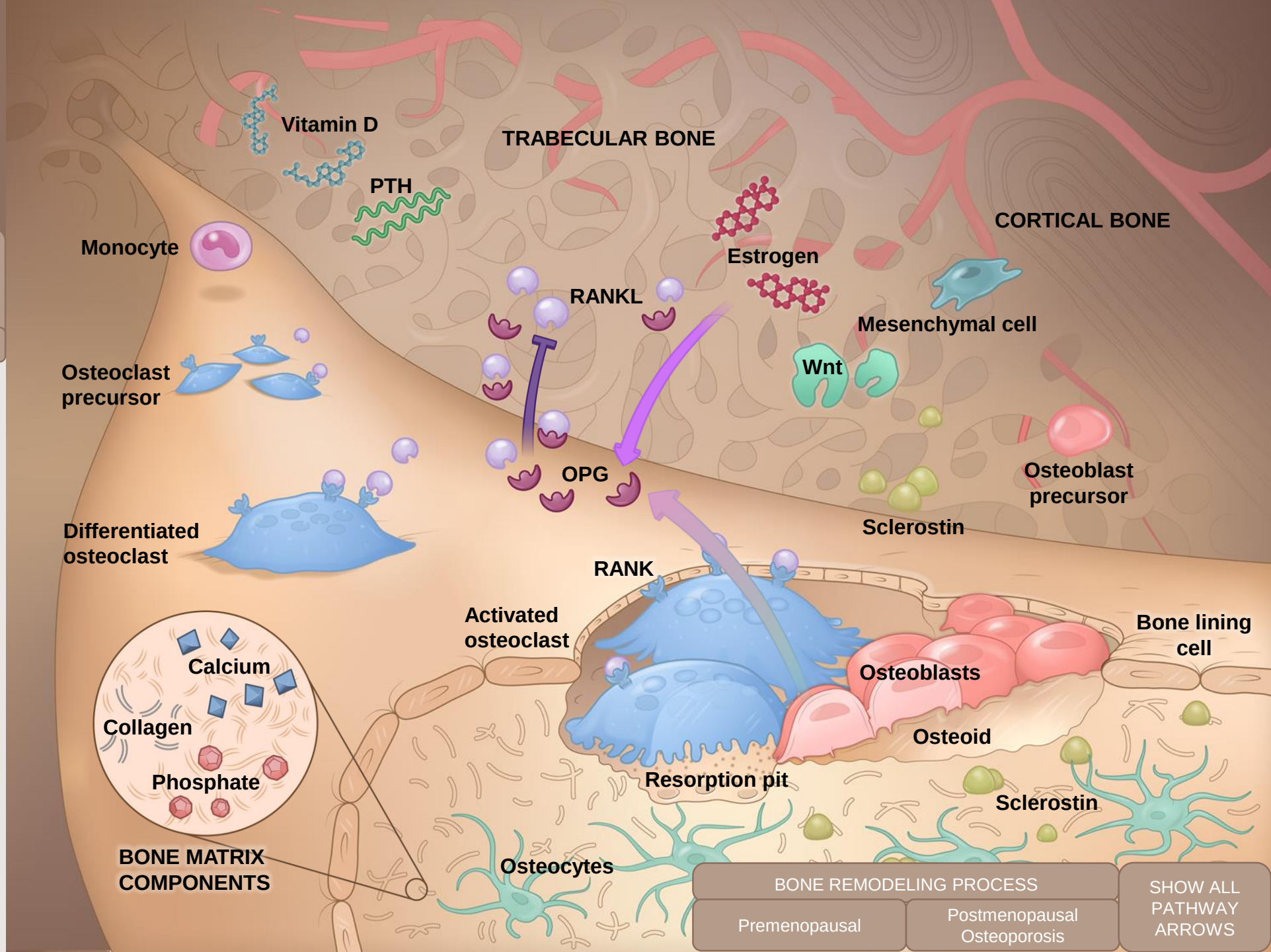
Osteoprotegerin

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

Estrogen directly influences osteoblastic cells to increase the secretion of OPG and inhibit bone resorption[2]



1. Hofbauer LC, et al. *JAMA*. 2004;292:490-495.
2. Hofbauer LC, et al. *Endocrinology*. 1999;140:4367-4370

PATHWAYS IN OSTEOPOROSIS

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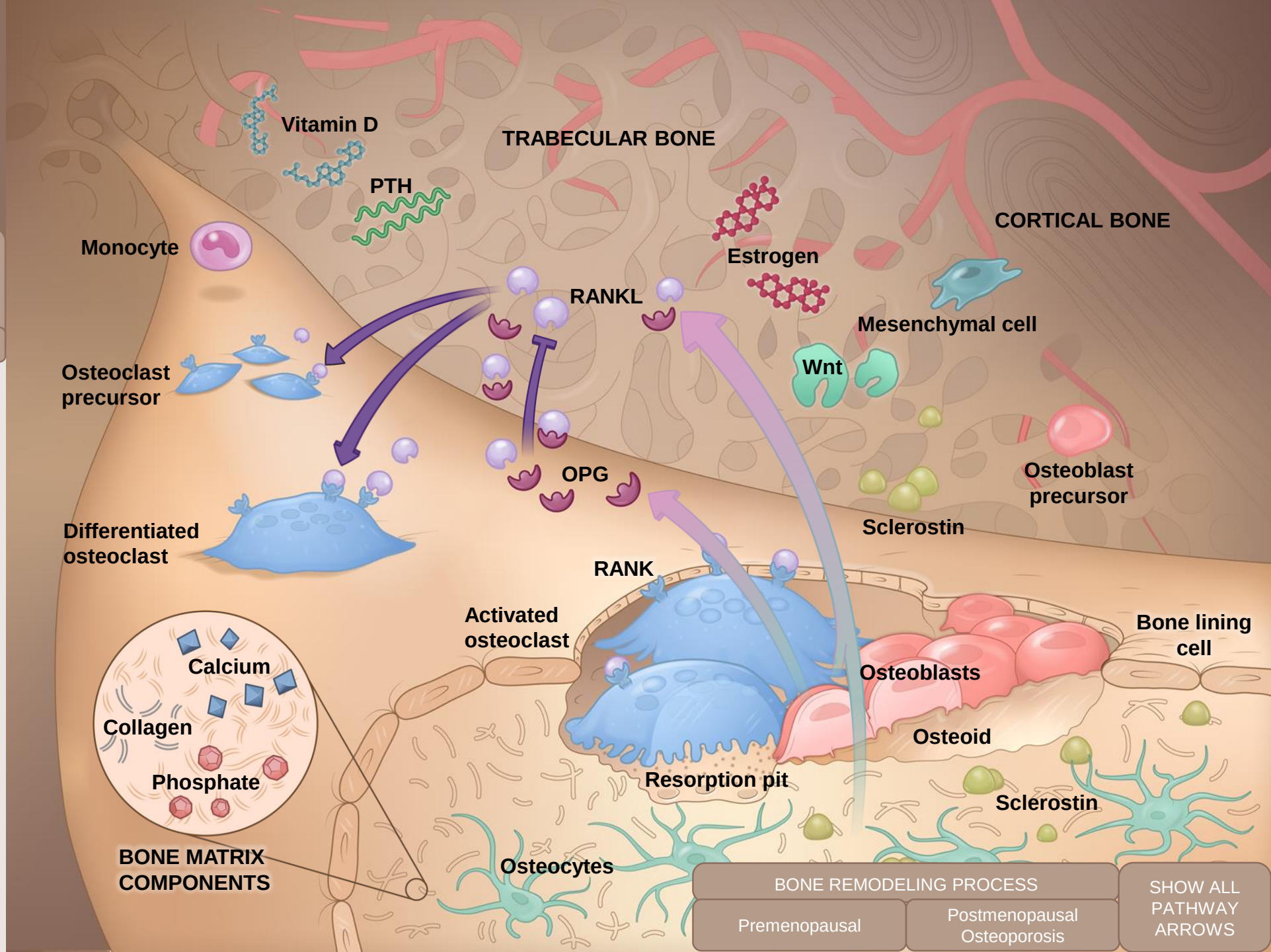
RANKL

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 Ther.* 2012;34:521-536.

PATHWAYS IN OSTEOPOROSIS

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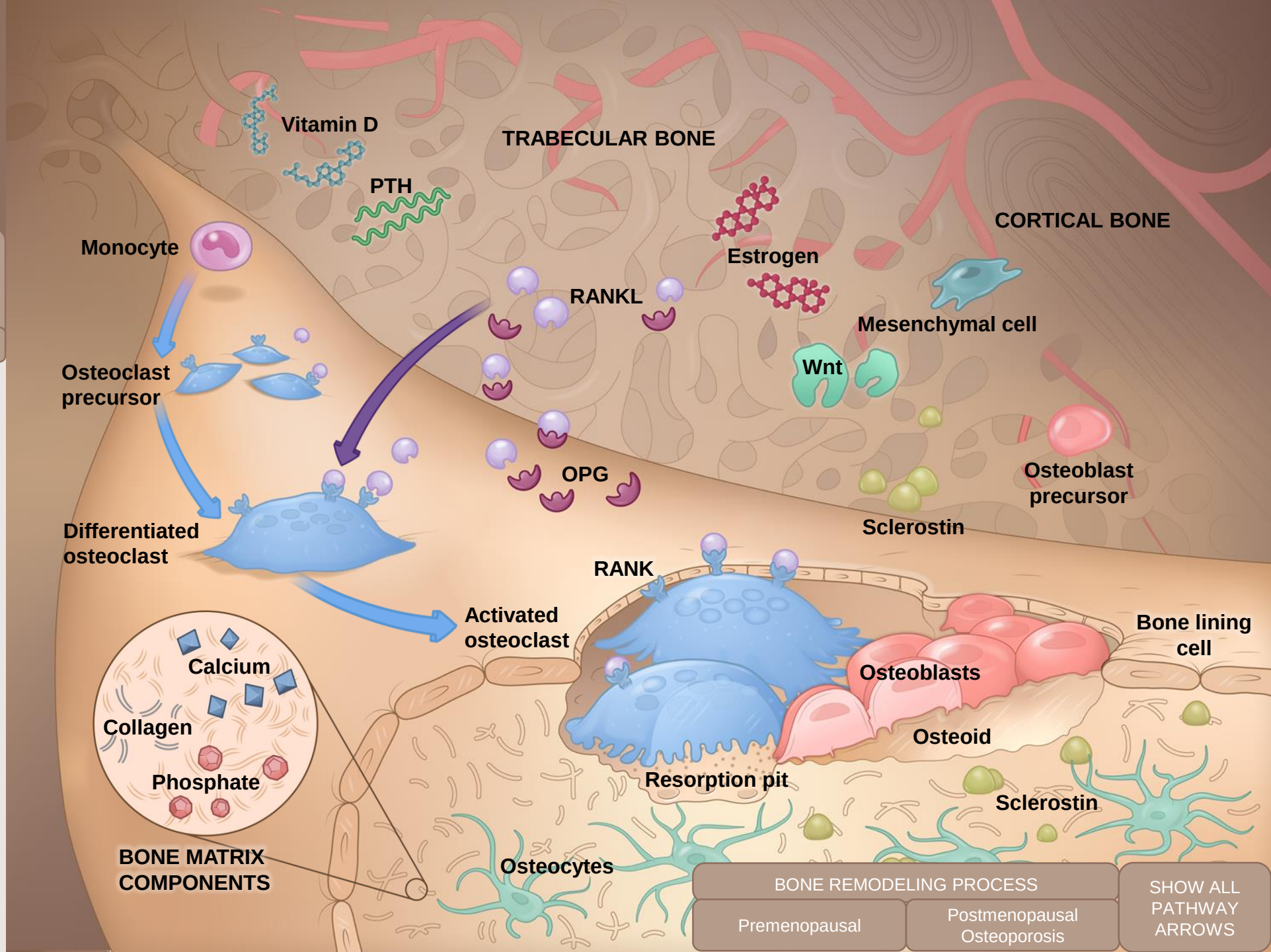
Osteoclasts

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.

PATHWAYS IN OSTEOPOROSIS

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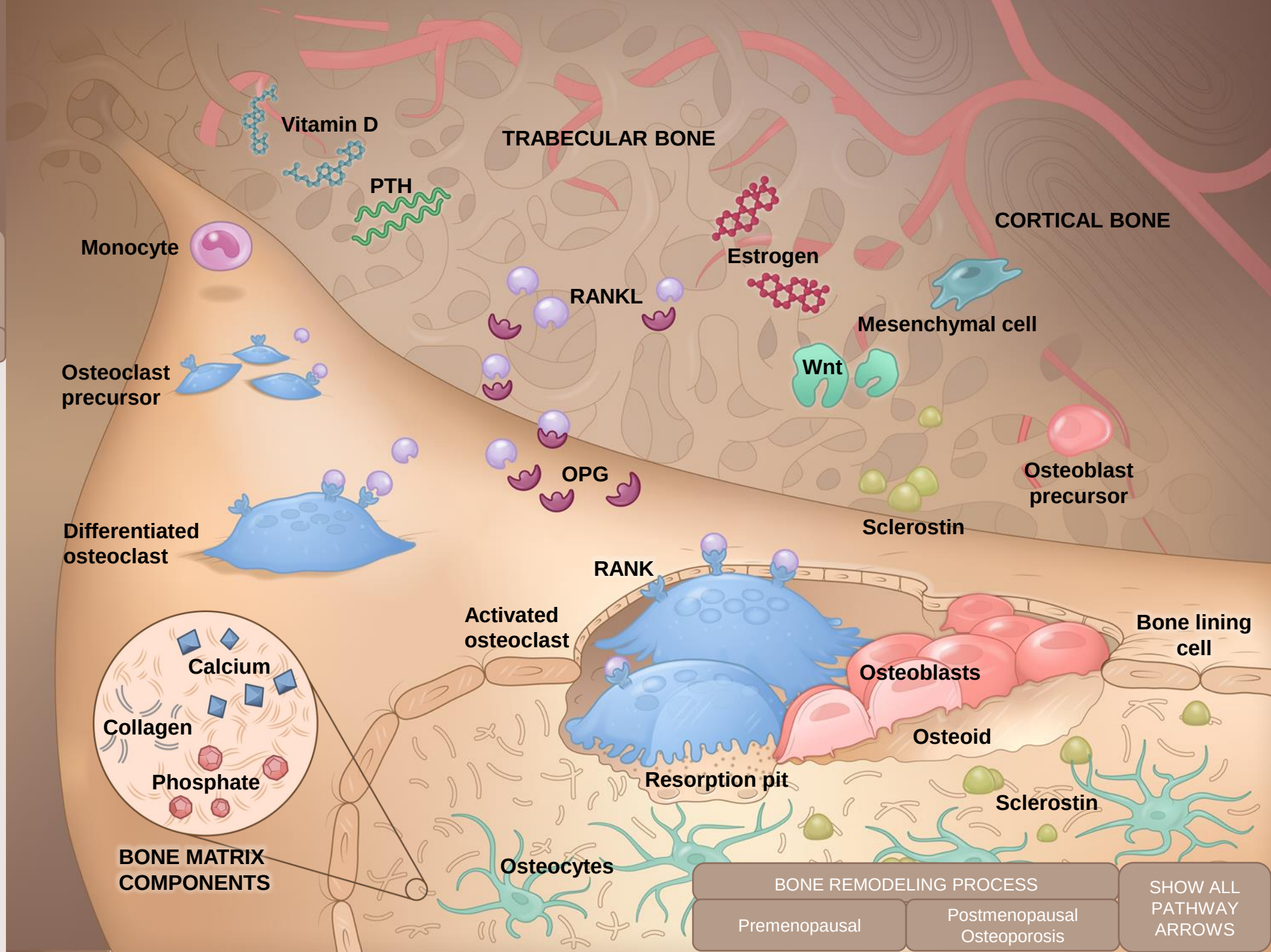
Bone Matrix

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.

PATHWAYS IN OSTEOPOROSIS

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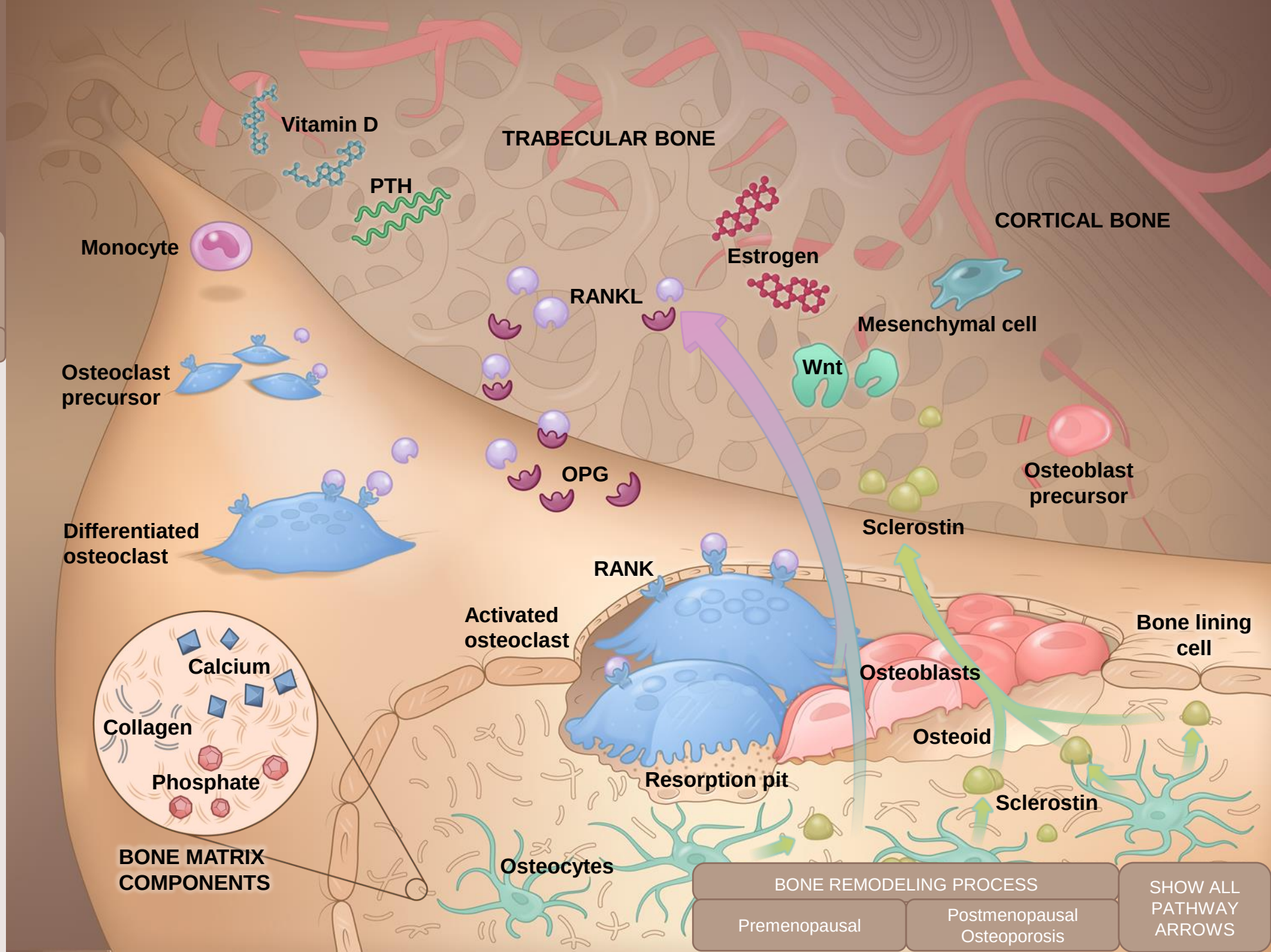
Osteocytes

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. *Calcif Tissue Int*. 2014;94:25-34.

PATHWAYS IN OSTEOPOROSIS

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Wnt

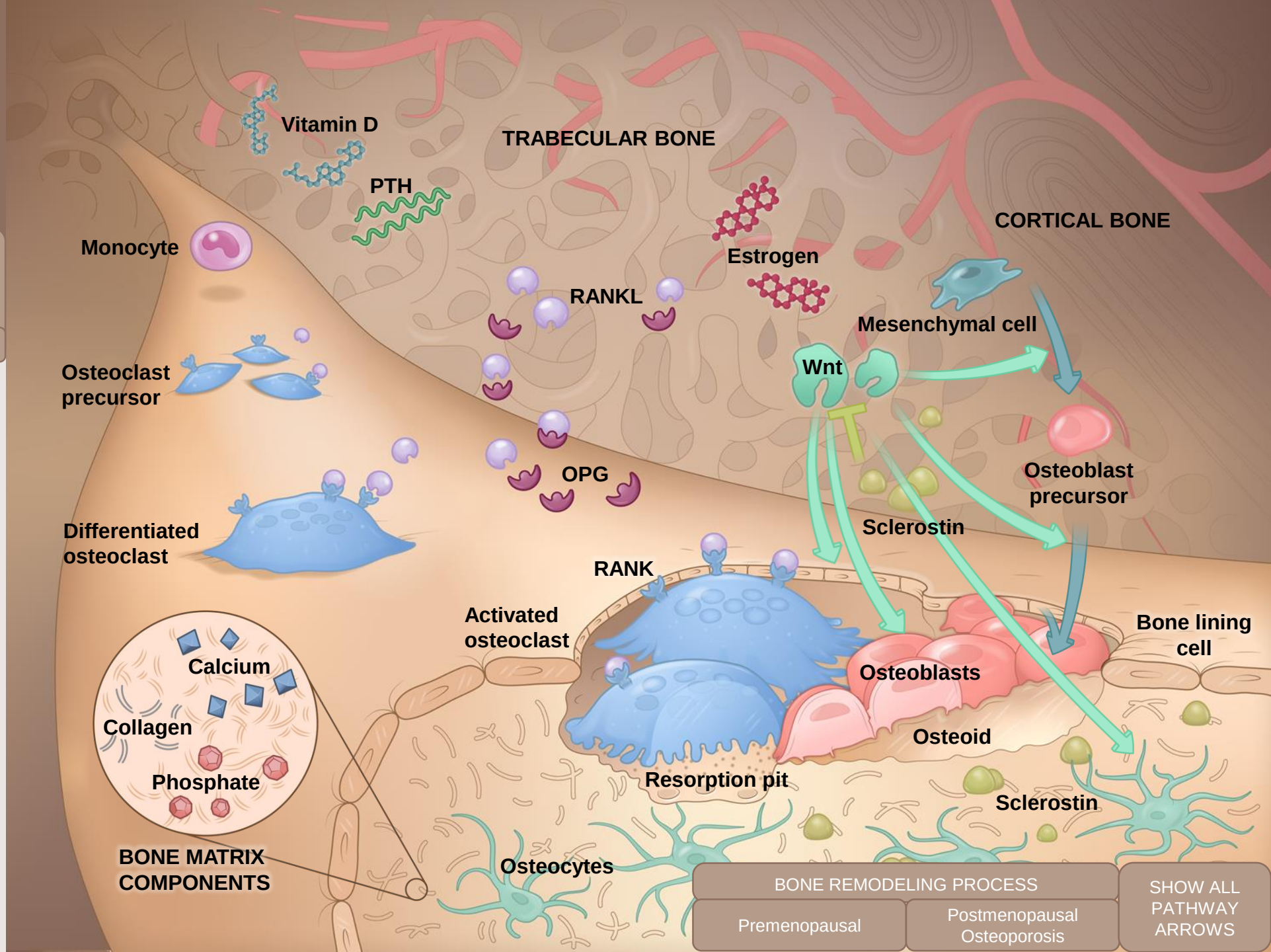
Wnt proteins are key signaling molecules in tissue development and regeneration[1]

Wnt binds to co-receptors LRP 5/6 and Frizzled, leading to the recruitment of dishevelled and Axin. This recruitment disrupts Axin-mediated degradation of β-catenin, thereby allowing β-catenin to accumulate in the nucleus and mediate 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]

1. MacDonald BT, et al. *Dev 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.



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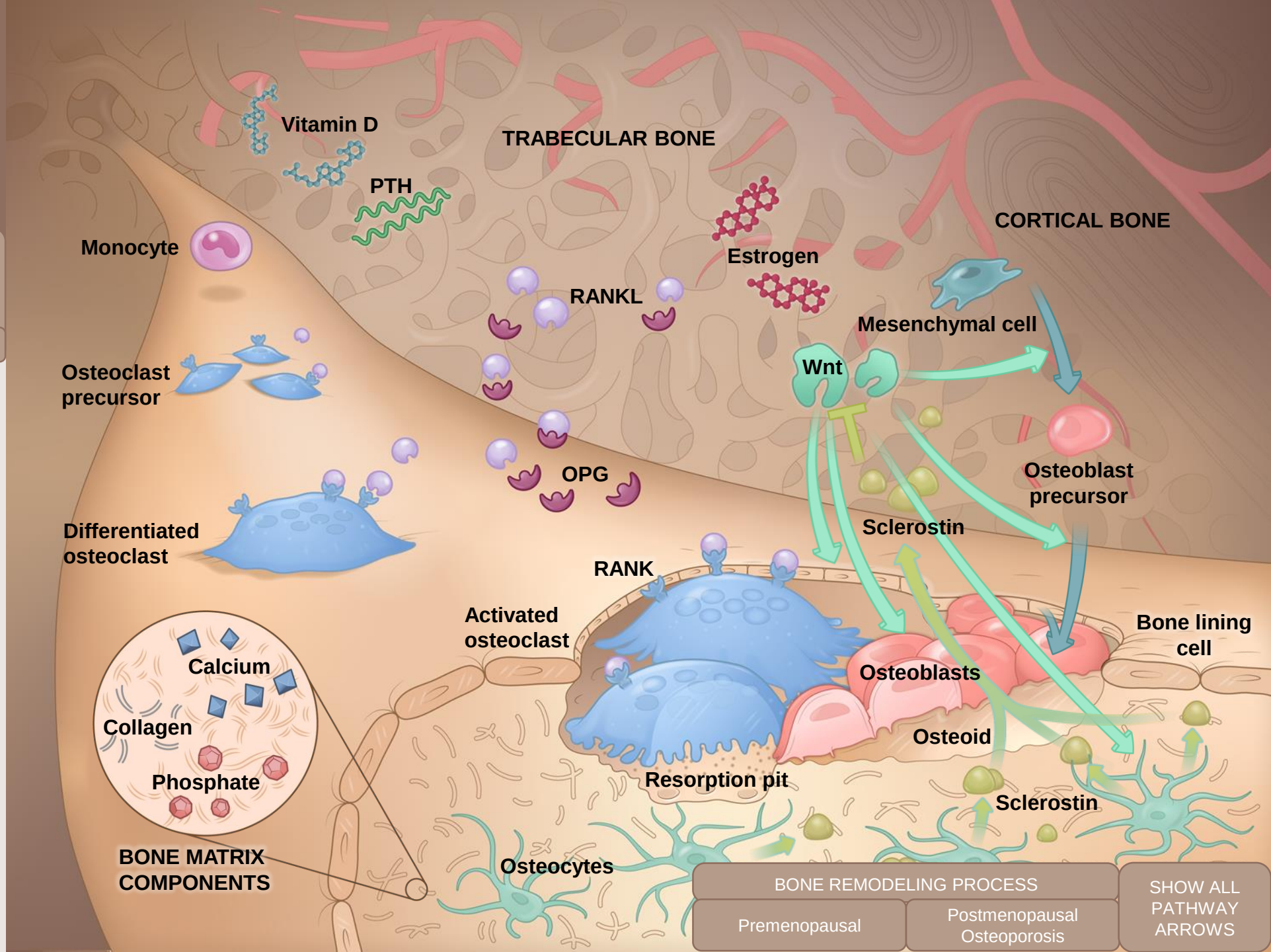
Sclerostin

Sclerostin is a protein secreted predominantly by osteocytes in bone[1,2]

Sclerostin binds to low density lipoprotein receptor-related proteins (LRP4, LRP5, LRP6) and inhibits canonical Wnt-β-catenin signaling[1]

In human disease, loss-of-function mutations in the sclerostin gene (*SOST*) result in high bone mass phenotypes, e.g., sclerosteosis[3]



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2. Winkler DG, et al. *EMBO J.* 2003;22:6267-6276.
3. Balemans W, et al. *Hum Mol Genet*. 2001;10:537-543.

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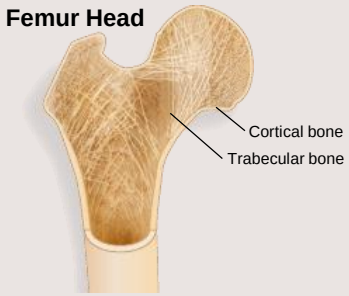

1. Manolagas SC. *Endocr Rev.* 2000;21:115-137.
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