Bone & Musculoskeletal Disease

BCH 130 — Advanced Human Biochemistry · Dr. Radi

By the end of this unit, you can…

- Explain bone remodeling (osteoblast/osteoclast coupling, RANKL/RANK/OPG, Wnt/sclerostin) as the framework for osteoporosis.
- Connect estrogen deficiency, aging, and glucocorticoid excess to net bone loss, and interpret DXA/T-score and bone-turnover markers.
- Explain osteoporosis pharmacology by target
- Describe sarcopenia and the muscle-bone unit — anabolic resistance, myostatin, and the biochemistry of age-related muscle loss.

Today's route

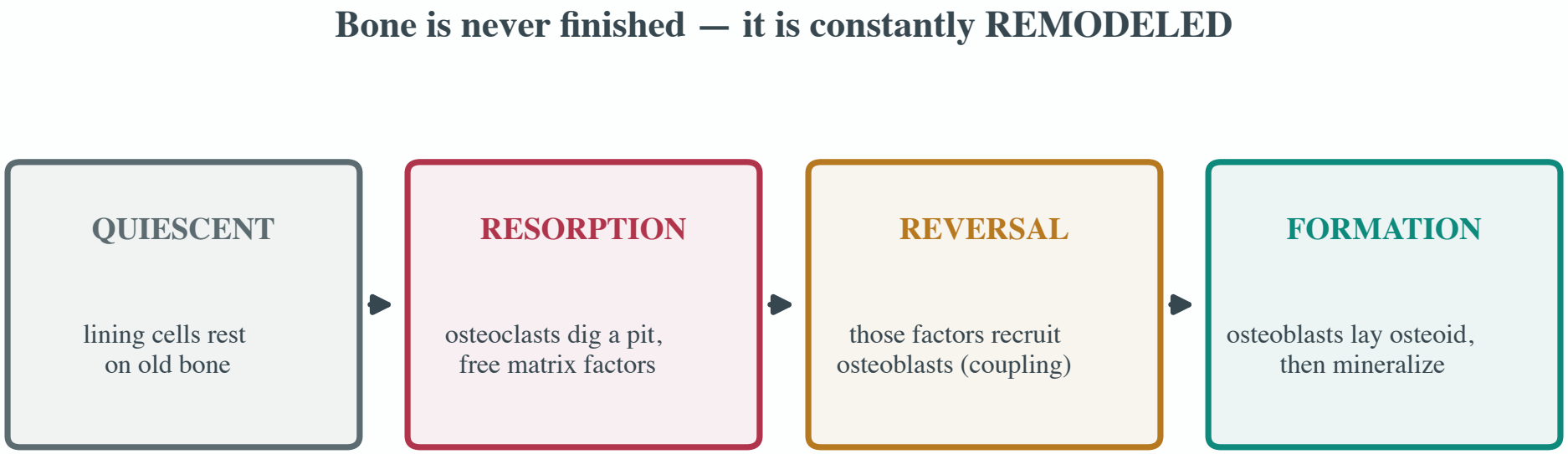
1. Osteoporosis – How Bone Is Lost
2. Osteoporosis Drugs & Sarcopenia

1 · Osteoporosis — How Bone Is Lost

"Bone looks like dead scaffolding, but it's the most alive tissue you own — torn down and rebuilt your whole life. Osteoporosis is what happens when the tearing-down team quietly out-works the rebuilding crew. Let's meet the two cells, the molecular dials that referee them, and the three forces that tip the fight toward loss."

Bone is a construction site

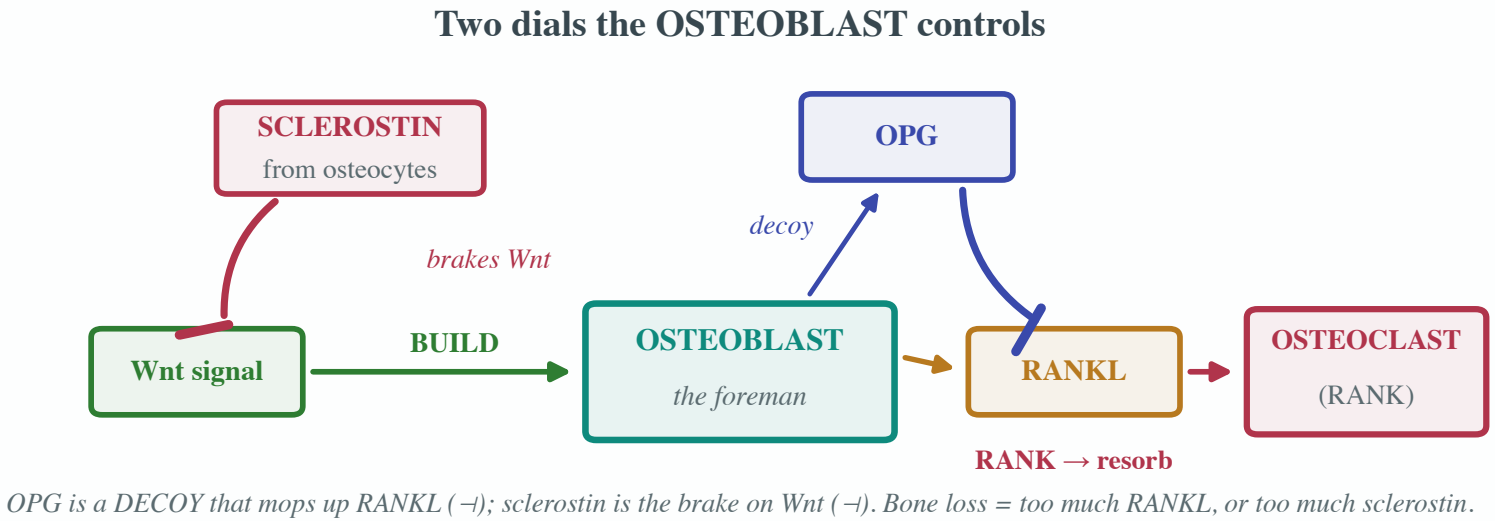
Here's the surprise: your skeleton is **rebuilt** constantly. Bone-eating **osteoclasts** dig a pit and release the growth factors stored in the matrix; those factors **recruit osteoblasts** to fill the pit back in. That's **coupling** — resorption and formation chained together. When the two crews stay balanced, bone mass holds steady. Osteoporosis is a coupling that has quietly gone lopsided.



Osteoclasts and osteoblasts are COUPLED — resorption and formation are chained. Balanced = no net loss.

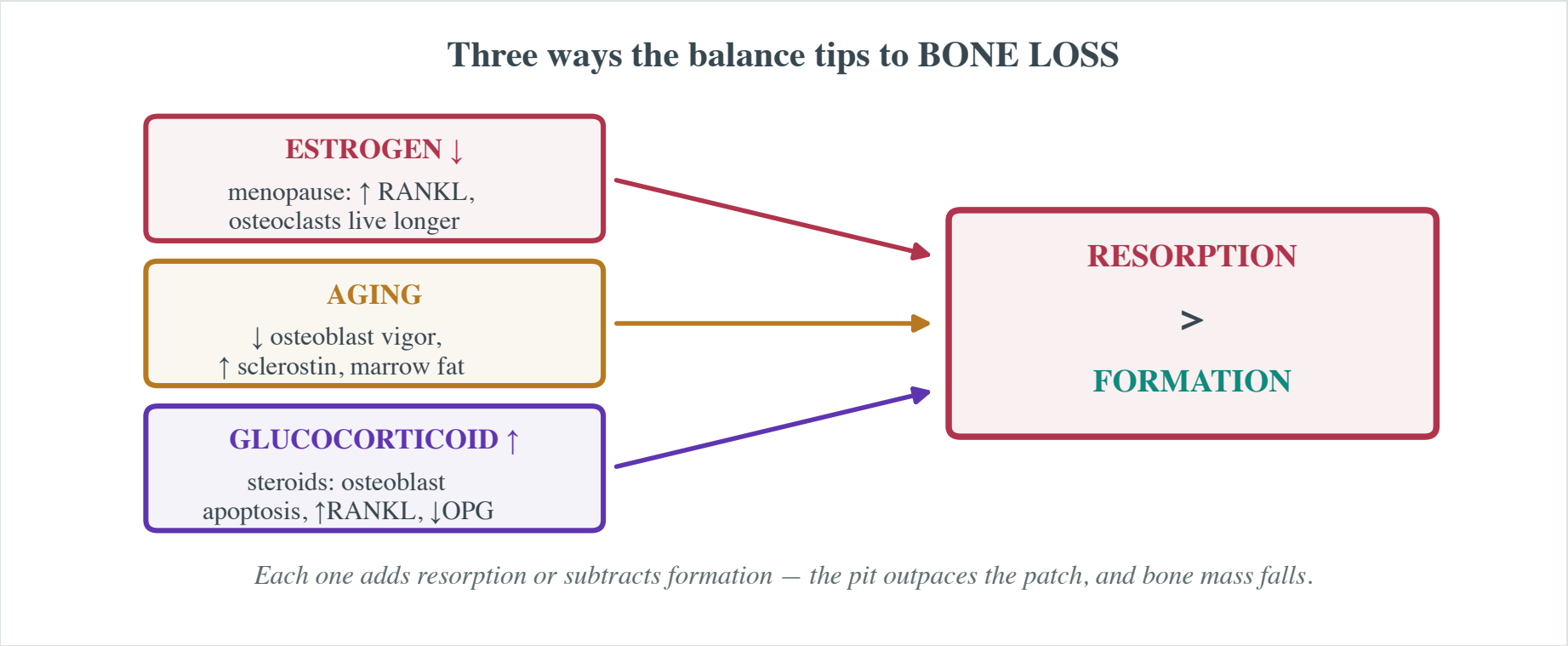
The two dials the osteoblast runs

The osteoblast is the foreman, and it works **two dials**. On the resorption side: it makes **RANKL**, which docks on **RANK** to wake up osteoclasts — and it makes **OPG**, a decoy receptor that mops RANKL up (**OPG ⊣ RANKL**). On the formation side: **Wnt** tells the osteoblast to build, and **sclerostin** is the brake on Wnt (**sclerostin ⊣ Wnt**). Bone loss = too much RANKL, or too much sclerostin.



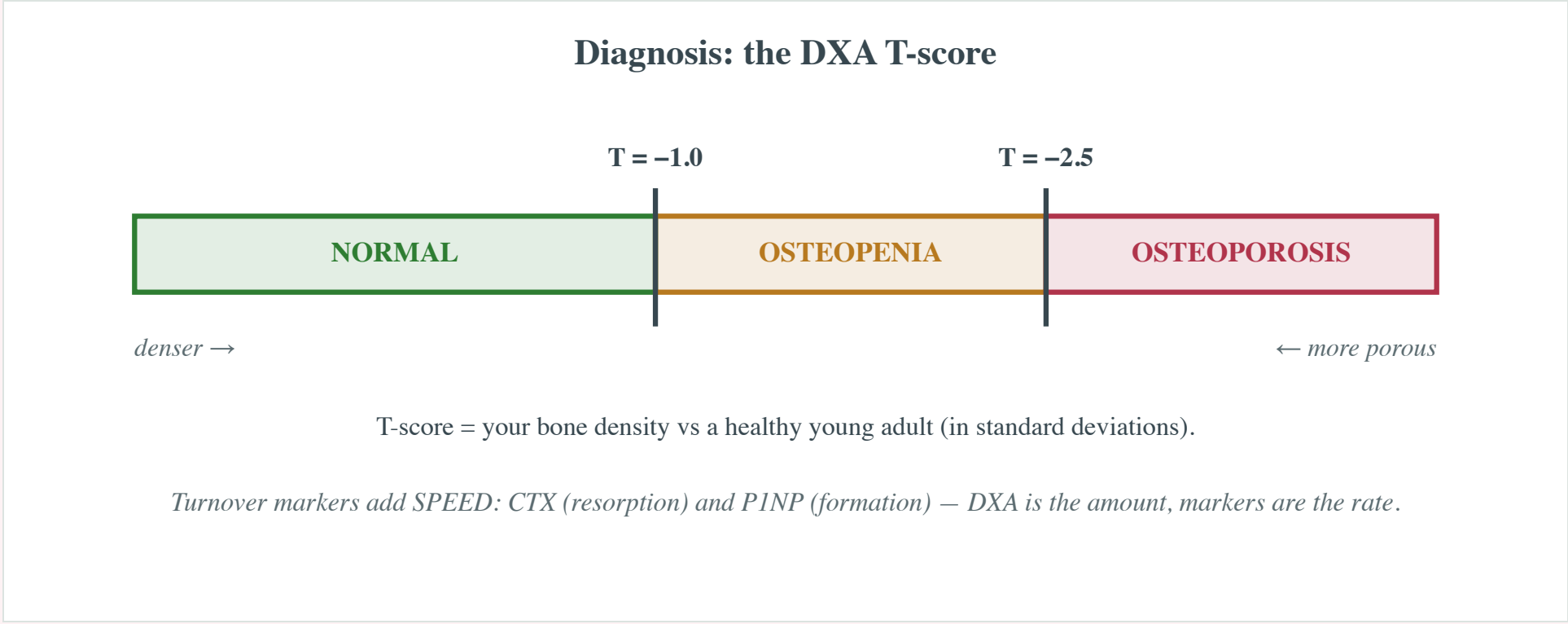
Three ways the balance tips

Now the villains. **Estrogen deficiency** (menopause) is the big one — estrogen normally restrains RANKL, so its loss unleashes osteoclasts and lets them live longer. **Aging** dulls the osteoblasts and raises sclerostin. **Glucocorticoid excess** — steroids — is brutal on both dials: it kills osteoblasts, pushes RANKL up, and drops OPG. Each one lets the pit outpace the patch.



Reading the bone

We measure it two ways. **DXA** gives a **T-score** — your density against a healthy young adult, in standard deviations. **Normal** is above −1; **osteopenia** sits between −1 and −2.5; **osteoporosis** is **−2.5 or below**. DXA tells you the **amount**. **Bone-turnover markers** add the **rate**: **CTX** tracks resorption, **P1NP** tracks formation — a fast, cheap readout of whether treatment is working.

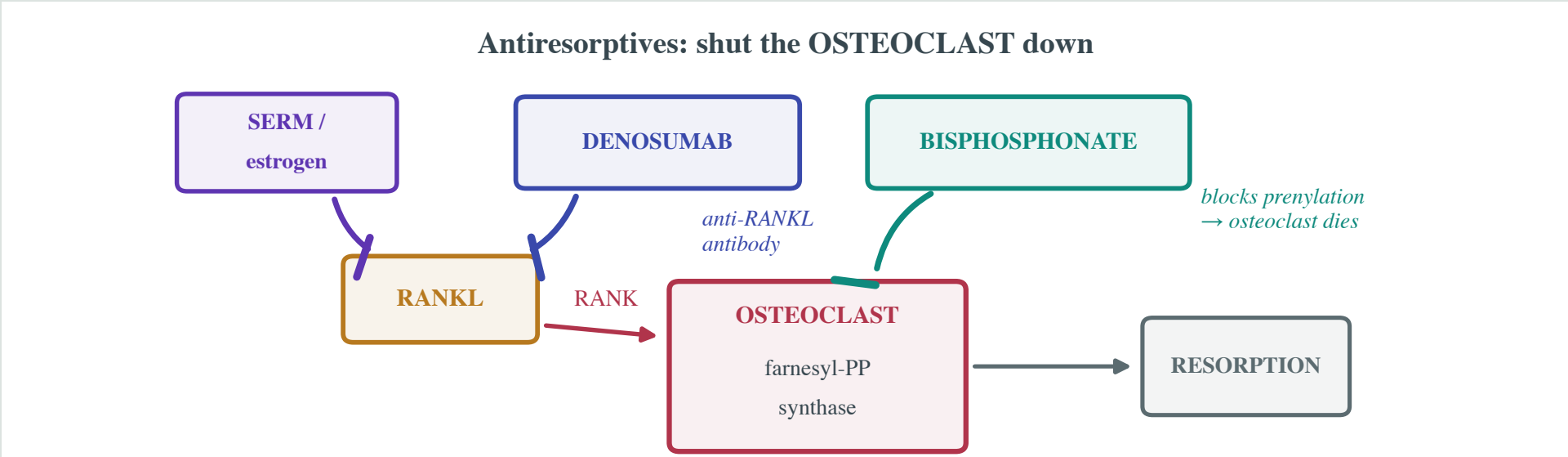


2 · Osteoporosis Drugs & Sarcopenia

"Here's the payoff of learning the remodeling dials: every osteoporosis drug grabs one of them. Some slam the brakes on resorption, others floor the accelerator on formation — and once you know the target, the drug name explains itself. Then we turn to muscle, because bone never ages alone: its lifelong partner is wasting right beside it."

Antiresorptives: shut the osteoclast down

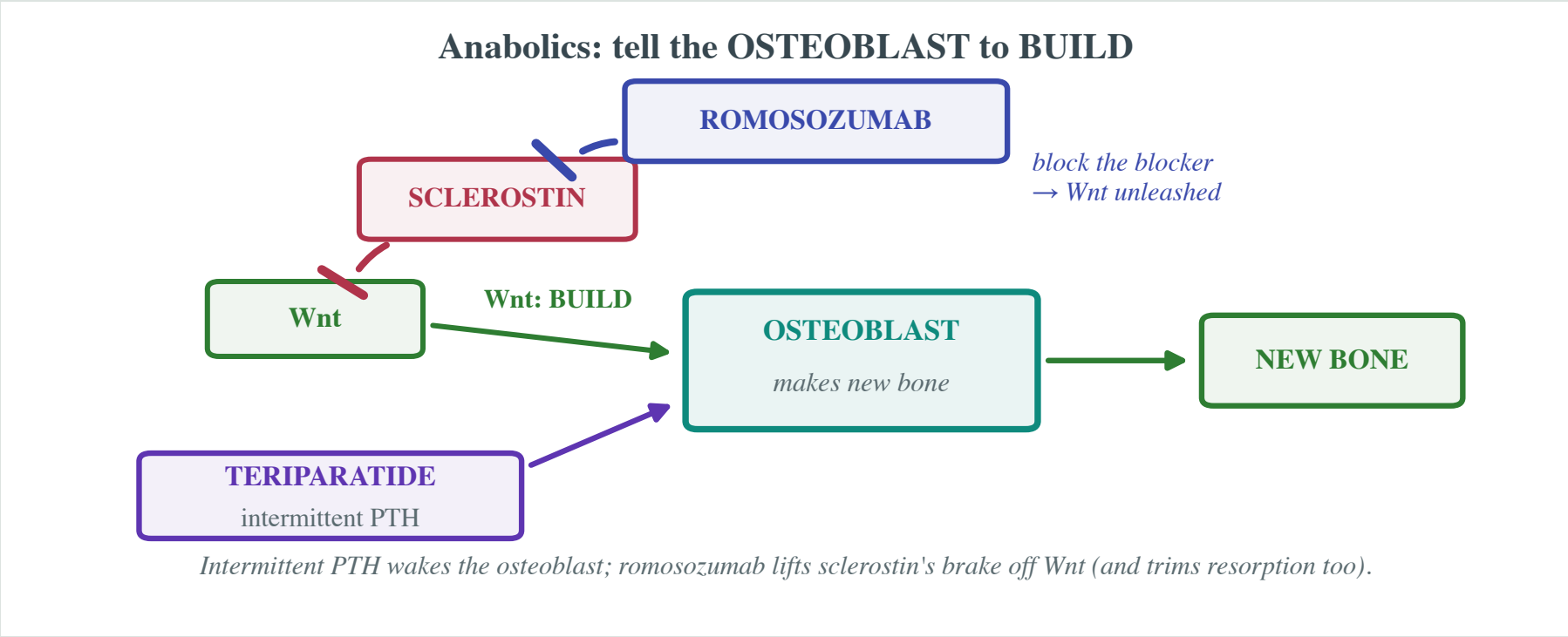
The first family just **stops the tearing-down**. **Bisphosphonates** are swallowed into the osteoclast and block **farnesyl-PP synthase** in the mevalonate pathway — no prenylation, so the cell can't work and dies. **Denosumab** is an antibody that blocks **RANKL** — it's basically OPG in a syringe. **SERMs** (raloxifene) and estrogen lower RANKL too. Different doors, same room: less resorption.



Two routes to the same end: cut the RANKL signal (denosumab, SERM) or poison the osteoclast's mevalonate enzyme (bisphosphonate).

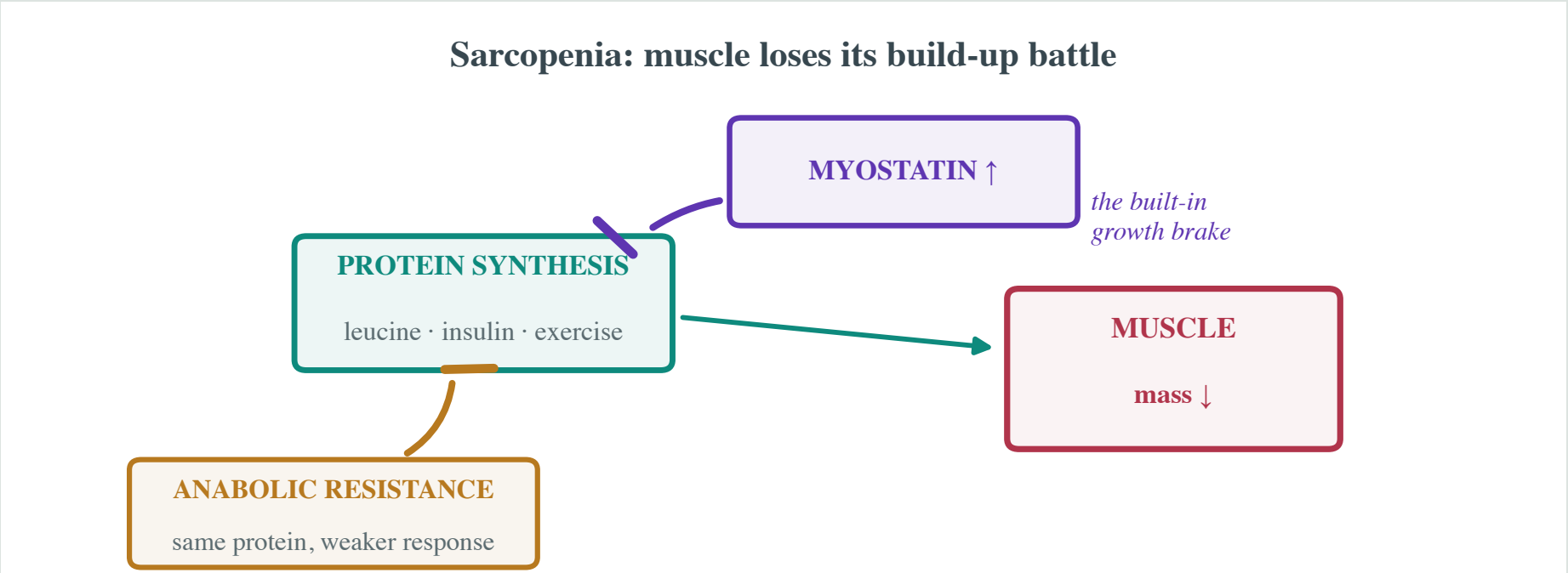
Anabolics: tell the osteoblast to build

The second family **adds new bone**. **Teriparatide** is PTH given as a daily pulse — and here's the trick: **intermittent** PTH is **anabolic**, waking osteoblasts, even though chronic high PTH would strip bone. **Romosozumab** is an antibody against **sclerostin** — block the blocker, and Wnt is unleashed to build (it trims resorption at the same time). These are the drugs that grow a skeleton back.



Sarcopenia: the muscle wastes too

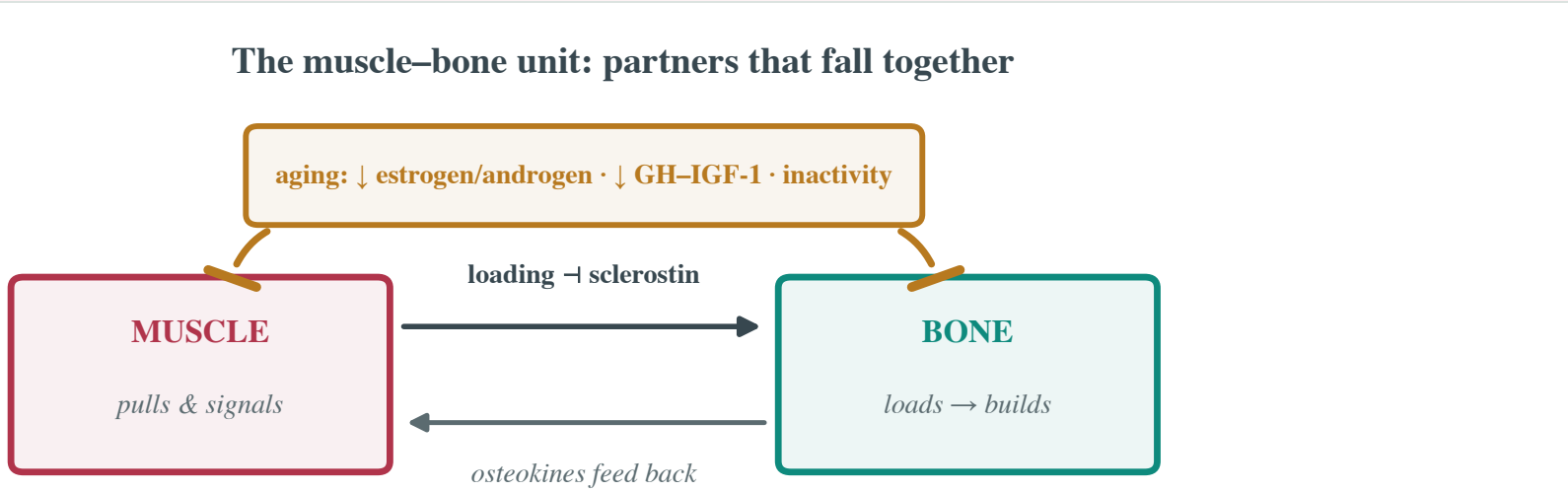
Bone doesn't age alone. **Sarcopenia** is the age-related loss of muscle mass and strength, and it runs on the same imbalance — synthesis falling behind breakdown. Two culprits: **anabolic resistance**, where the same protein or exercise triggers a **weaker** build-up response, and **myostatin**, muscle's built-in growth **brake**, which climbs with age and inactivity. Synthesis can't keep up, and muscle quietly melts away.



Aging blunts the anabolic signal AND lifts myostatin — synthesis can't keep up with breakdown, so muscle wastes.

The muscle–bone unit

Why do they fall together? Because they're **coupled**, just like the two bone cells. Muscle **pulls** on bone, and that mechanical **loading suppresses sclerostin** — so a working muscle literally builds the bone it's anchored to; the two also swap **myokine and osteokine** signals. Then the same aging decline — falling **estrogen, androgen, and GH–IGF-1**, plus inactivity — starves **both**. Treat the unit, not just the scan.



Muscle load builds bone; bone signals back. The same aging decline starves BOTH — so osteoporosis and sarcopenia arrive together.

Can you…?

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If any box stays empty, the practice site has a drill for it.
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