

New Drugs in Treatment of Osteoporosis

**A Ahmadzadeh, MD
Rheumatologist
Loghman Hospital, SBMU**



Why should we investigate for new drugs?

- By 2050, the worldwide incidence of hip fracture is expected to rise by 240% in women and 310% in men compared to 1990 involving approximately 1.66 million in 1990 to 6.26 million in 2050
- Total cost for treating the prevalent osteoporotic-related fractures in the United States was estimated \$19 billion in 2005 that would be tripled by the year 2040

Schuiling KD, Robinia K. Osteoporosis update. J Midwifery Womens Health. 2011;56:615–27.

doi:[10.1111/j.1542-2011.2011.00135.x](https://doi.org/10.1111/j.1542-2011.2011.00135.x).

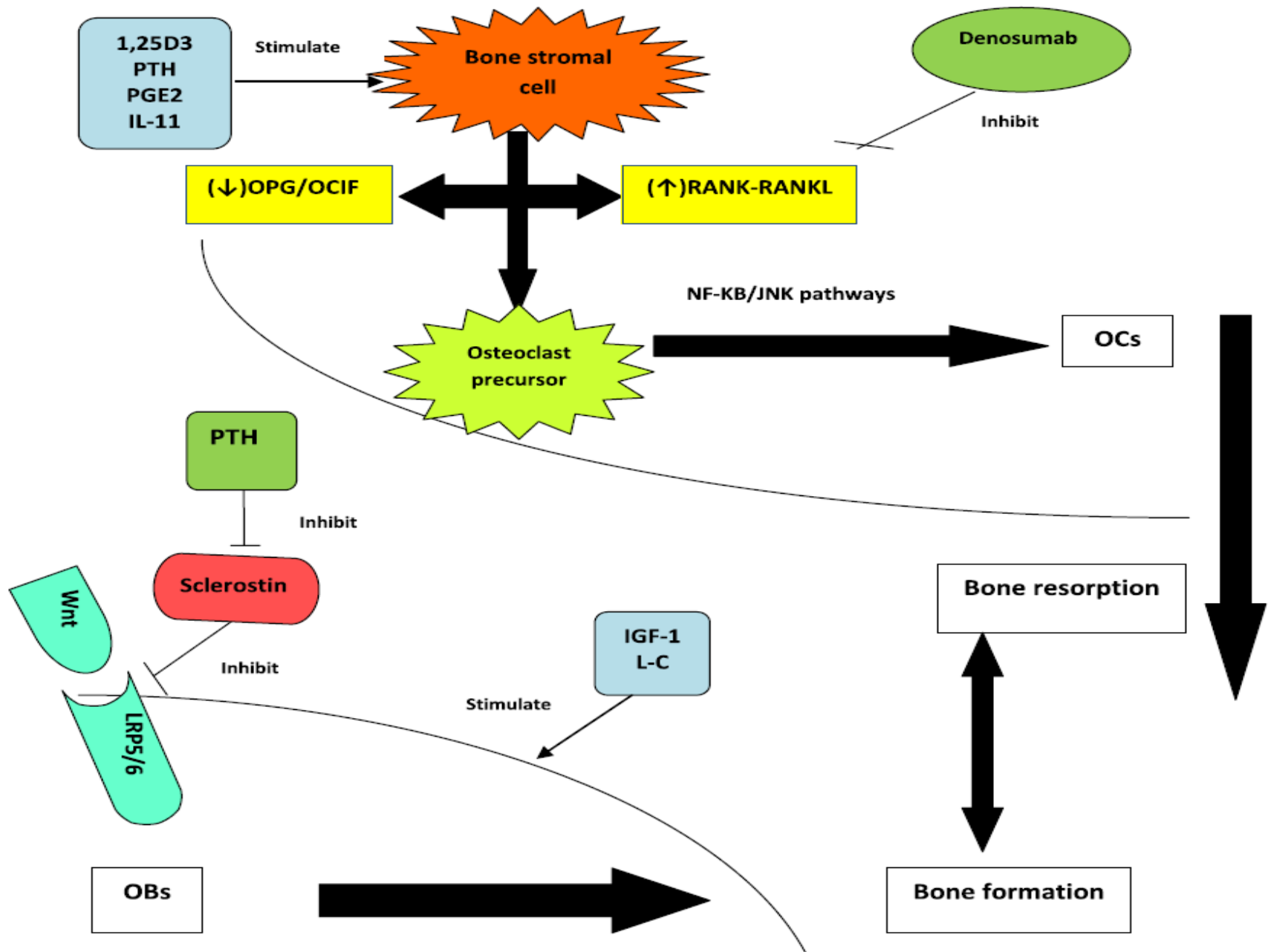
New drugs under investigation

New classes

- Sclerostin inhibitors
- Integrin antagonists
- Cathepsin K inhibitors

New members of traditional groups

- New SERMs
- PTH related peptide



All Content [Advanced Search](#)[< Previous Article](#)

Volume 390, No. 10102, p1585–1594, 30 September 2017

[Next Article >](#) Articles

Romosozumab (sclerostin monoclonal antibody) versus teriparatide in postmenopausal women with osteoporosis transitioning from oral bisphosphonate therapy: a randomised, open-label, phase 3 trial

Prof Bente L Langdahl, DMSc  , Cesar Libanati, MD, Daria B Crittenden, MD, Michael A Bolognese, MD, Jacques F Brown, MD, Nadia S Daizadeh, PhD, Eva Dokoupilova, MD, Klaus Engelke, PhD, Prof Joel S Finkelstein, MD, Harry K Genant, MD, Stefan Goemaere, MD, Lars Hyldstrup, MD, Prof Esteban Jodar-Gimeno, MD, Prof Tony M Keaveny, PhD, Prof David Kendler, MD, Prof Peter Lakatos, MD, Judy Maddox, DO, Jorge Malouf, MD, Fabio E Massari, MD, Jose Fernando Molina, MD, Maria Rosa Ulla, MD, Andreas Grauer, MD

methods

- This randomised, phase 3, open-label, active-controlled study was done at 46 sites in North America, Latin America, and Europe. women (aged ≥ 55 to ≤ 90 years) with postmenopausal osteoporosis who had taken an oral bisphosphonate for at least 3 years before screening and alendronate the year before screening; an areal BMD T score of -2.5 or lower at the total hip, femoral neck, or lumbar spine; and a history of fracture were enrolled.
- Patients were randomly assigned to receive subcutaneous romosozumab (210 mg once monthly) or subcutaneous teriparatide (20 μg once daily)
- The primary endpoint was percentage change from baseline in areal BMD by DXA at the total hip through 6-12 mo(a mean treatment effect at months 6 and 12 was measured)

results

- Between Jan 31, 2013, and April 29, 2014, 436 patients were randomly assigned to romosozumab (n=218) or teriparatide (n=218)
- 206 patients in the romosozumab group and 209 in the teriparatide group were included in the primary efficacy analysis
- Through 12 months, the mean percentage change from baseline in total hip areal BMD was 2.6% (95% CI 2.2 to 3.0) in the romosozumab group and -0.6% (-1.0 to -0.2) in the teriparatide group; difference 3.2% (95% CI 2.7 to 3.8; $p < 0.0001$)

interpretation

- Transition to a bone-forming agent is common practice in patients treated with bisphosphonates, such as those who fracture while on therapy. In such patients, romosozumab led to gains in hip BMD that were not observed with teriparatide
- These data could inform clinical decisions for patients at high risk of fracture

Adverse events

- Serious adverse events were reported in 17 (8%) patients on romosozumab and in 23 (11%) on teriparatide; none were judged treatment related
- There were six (3%) patients in the romosozumab group compared with 12 (6%) in the teriparatide group with adverse events leading to drug withdrawal
- The most frequently reported adverse events were nasopharyngitis (28 [13%] of 218 in the romosozumab group vs 22 [10%] of 214 in the teriparatide group), hypercalcaemia (two [$<1\%$] vs 22 [10%]), and arthralgia (22 [10%] vs 13 [6%])



The NEW ENGLAND JOURNAL of MEDICINE

[HOME](#)[ARTICLES & MULTIMEDIA ▾](#)[ISSUES ▾](#)[SPECIALTIES & TOPICS ▾](#)[FOR AUTHORS ▾](#)[CME >](#)

Free Preview

[PRINT](#)[E-MAIL](#)[DOWNLOAD CITATION](#)[PERMISSIONS](#)

ORIGINAL ARTICLE

Romosozumab or Alendronate for Fracture Prevention in Women with Osteoporosis

Kenneth G. Saag, M.D., Jeffrey Petersen, M.D., Maria Luisa Brandi, M.D., Andrew C. Karaplis, M.D., Ph.D., Mattias Lorentzon, M.D., Ph.D., Thierry Thomas, M.D., Ph.D., Judy Maddox, D.O., Michelle Fan, Ph.D., Paul D. Meisner, Pharm.D., and Andreas Grauer, M.D.

N Engl J Med 2017; 377:1417-1427 | [October 12, 2017](#) | DOI: 10.1056/NEJMoa1708322

Methods

- 4093 postmenopausal women with osteoporosis and a fragility fracture were randomly assigned them in a 1:1 ratio to receive monthly subcutaneous romosozumab (210 mg) or weekly oral alendronate (70 mg) in a blinded fashion for 12 months, followed by open-label alendronate in both groups
- The primary end points were the cumulative incidence of new vertebral fracture at 24 months and the cumulative incidence of clinical fracture (nonvertebral and symptomatic vertebral fracture) at the time of the primary analysis (after clinical fractures had been confirmed in ≥ 330 patients). Secondary end points included the incidences of nonvertebral and hip fracture at the time of the primary analysis

Results

- in 24 months, a 48% lower risk of new vertebral fractures was observed in the romo. to Alend. group (6.2% [127 of 2046 patients]) than in the Alend.to Alend.group (11.9% [243 of 2047 patients]) ($P<0.001$)
- Clinical fractures occurred in 198 of 2046 patients (9.7%) in the romo. to alend. group versus 266 of 2047 patients (13.0%) in the alend.to alend. group, representing a 27% lower risk with romosozumab ($P<0.001$)
- The risk of nonvertebral fractures was lower by 19% in the romo.to alend. group than in the alend. to-alend.group (178 of 2046 patients [8.7%] vs. 217 of 2047 patients [10.6%]; $P=0.04$), and the risk of hip fracture was lower by 38% (41 of 2046 patients [2.0%] vs. 66 of 2047 patients [3.2%]; $P=0.02$)

Adverse events

During year 1, positively adjudicated serious cardiovascular adverse events were observed more often with romosozumab than with alendronate (50 of 2040 patients [2.5%] vs. 38 of 2014 patients)

During the open-label alendronate period, adjudicated events of osteonecrosis of the jaw (1 event each in the romo.to-alend. and alend.to-alend. groups) and atypical femoral fracture (2 events and 4 events, respectively) were observed

Conclusions

- In postmenopausal women with osteoporosis who were at high risk for fracture, romosozumab treatment for 12 months followed by alendronate resulted in a significantly lower risk of fracture than alendronate alone

FDA has rejected the drug (romosozumab)

decision was expected when a higher rate of serious adverse cardiovascular events with the drug reported compared with alendronate in the [ARCH study](#) in May.

Amgen and UCB Pharma announced that FDA now wants to see data from the ARCH study as well as from [BRIDGE](#), a trial of romosozumab in men with osteoporosis.

- The agency had already been considering data from the phase 3 [FRAME](#) study with romosozumab. In FRAME, reported at the [American Society of Bone and Mineral Research 2016 Annual Meeting](#) and simultaneously [published online](#) in the *New England Journal of Medicine*, romosozumab reduced the rate of vertebral fractures by 73% compared with placebo
- The data were called "unprecedented" by the lead investigator. However, romosozumab did not significantly reduce the risk of nonvertebral fractures, a key secondary end point of FRAME

[J Bone Miner Res.](#) 2015 Feb;30(2):216-24. doi: 10.1002/jbmr.2351.

A randomized, double-blind phase 2 clinical trial of blosozumab, a sclerostin antibody, in postmenopausal women with low bone mineral density.

[Recker RR¹](#), [Benson CT](#), [Matsumoto T](#), [Bolognese MA](#), [Robins DA](#), [Alam J](#), [Chiang AY](#), [Hu L](#), [Krege JH](#), [Sowa H](#), [Mitlak BH](#), [Myers SL](#).

Blosozumab

- Postmenopausal women with a lumbar spine *T*-score -2.0 to -3.5 , inclusive, were randomized to subcutaneous blosozumab 180 mg every 4 weeks (Q4W), 180 mg every 2 weeks (Q2W), 270 mg Q2W, or matching placebo for 1 year, with calcium and vitamin D
- Serial measurements of spine and hip BMD and biochemical markers of bone turnover were performed
- Overall, 120 women were enrolled in the study (mean age 65.8 years, mean lumbar spine *T*-score -2.8). Blosozumab treatment resulted in statistically significant dose-related increases in spine, femoral neck, and total hip BMD as compared with placebo. In the highest dose group, BMD increases from baseline reached 17.7% at the spine, and 6.2% at the total hip

Parathyroid hormone-related protein

- **PTHrP** shares some of the actions of PTH, including stimulation of renal tubular calcium reabsorption and bone resorption
- minimal effect on intestinal calcium absorption due to weak stimulation of $1,25(\text{OH})_2 \text{D}_3$ production
- PTHrP regulates cellular proliferation and is an important component of fetal calcium regulation, placental calcium transfer, and lactation
- PTHrP is produced by some cancers and is the primary cause of humeral hypercalcemia of malignancy

- The classical parathyroid hormone receptor, PTH1R, recognizes both PTH and PTHrP due to the substantial degree of homology in the N-terminal parts of these two peptides
- The first two amino acids in the N-terminal region of the molecule are obligatory for activation of PTH1R
- Chronic exposure to PTH or PTHrP (primary or secondary hyperparathyroidism or hypercalcemia of malignancy, respectively) results in bone resorption
- intermittent administration of recombinant human PTH (either full-length 1-84 or fragment 1-34) or PTHrP 1-34 has been shown to stimulate bone formation more than resorption and reduce fractures

What makes abaloparatide more attractive

- studies have shown that teriparatide therapy can lead to a mild degree of hypercalcemia (serum calcium > 10.6 mg/dL) attributed to a mild increase in bone resorption, which limits the BMD gains at cortical sites
- It was also shown that abaloparatide has resulted in a greater increase in hip BMD as compared to teriparatide

Effects of abaloparatide, a human parathyroid hormone-related peptide analog, on bone mineral density in postmenopausal women with osteoporosis. Leder BZ, O'Dea LS, Zanchetta JR, et al. J Clin Endocrinol Metab. 2015;100:697–706.

advantage

- Abaloparatide has 41% homology to parathyroid hormone (PTH) (1-34) and 76% homology to parathyroid hormone-related protein (PTHrP) (1-34). The molecule was meticulously selected to retain stability and potent bone anabolic activity, and it has a limited effect on bone resorption (hence, a low calcium-mobilizing potential)
- In clinical trials to date, abaloparatide appears to have a good safety and tolerability profile with a significantly lower degree of hypercalcemia compared to that of teriparatide

Abaloparatide (Tymlos)

- PTH analogue, abaloparatide was approved by the FDA in April 2017. based on results at 18 months from the Abaloparatide Comparator Trial in Vertebral Endpoints (ACTIVE) trial and first 6 months of the ACTIVEExtend trial
- In the ACTIVE trial of more than 2000 women, subcutaneous abaloparatide was associated with significant reductions in the relative risk for new vertebral fractures (86% reduction) and nonvertebral fractures (43% reduction) compared with placebo.
- The absolute risk reductions were 3.6% and 2.0%, respectively. The benefits were evident regardless of age, years since menopause, presence or absence of prior fracture (vertebral or nonvertebral), and bone mineral density (BMD) at baseline. ^[159]
- In the ACTIVEExtend trial, roughly 1100 patients who completed 18 months of abaloparatide or placebo in ACTIVE received open-label alendronate for up to 24 additional months. Data from the first 6 months of ACTIVEExtend showed improved BMD and reduced fracture risk throughout the skeleton

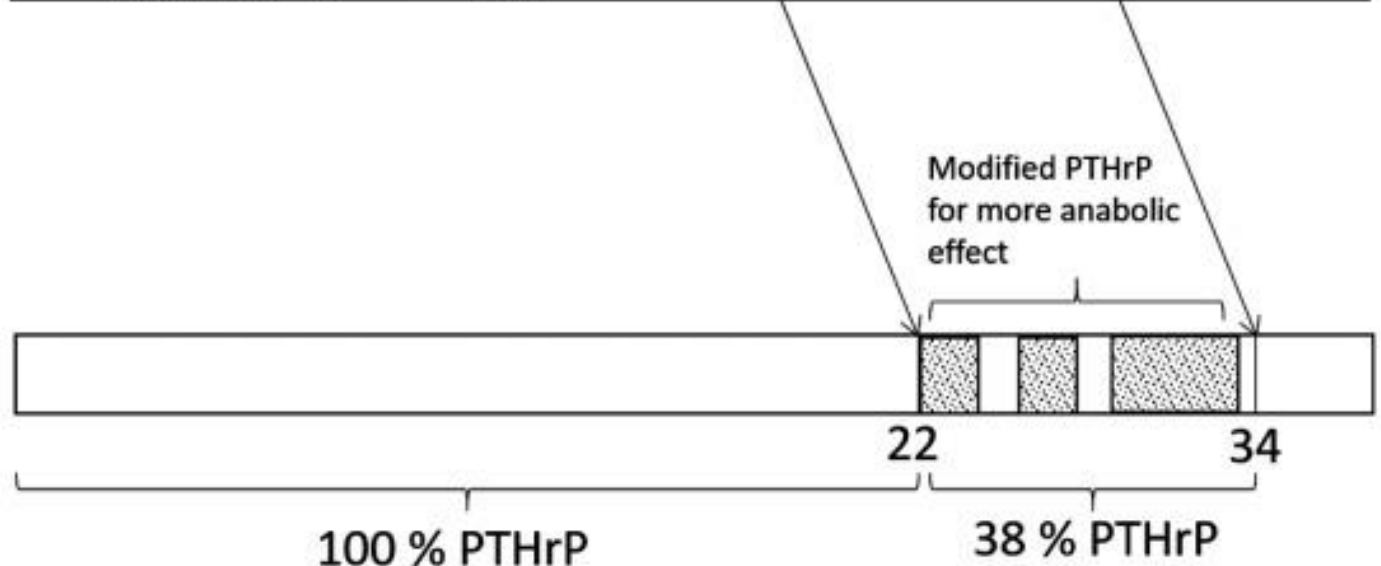
hPTH 1-34
(Forteo)



hPTHrP 1-34



Abaloparatide



-  = Empirically inserted amino acids to maximize anabolic effect
-  = Homology of amino acids between PTH and PTHrP

Abaloparatide Vs. teriparatide

Head to head

- in an 18-month randomized, multicenter trial 2,463 postmenopausal women with osteoporosis were randomized to receive abaloparatide(80 mcg) and teriparatide(20 mcg) or placebo
- both abalop. & terip. groups showed a significant increase in bone formation and resorption markers ($p < .001$)
- However, abaloparatide and teriparatide differed in the pattern of bone turnover marker changes
- The increase in CTx was much less in the abaloparatide group (46%, 56%, and 69% less at 6, 12, and 18 mo. respectively; $p < .001$ for all months), while the differences in the formation marker between abaloparatide and teriparatide were much closer

Effect of Abaloparatide vs Placebo on New Vertebral Fractures in Postmenopausal Women With Osteoporosis: A Randomized Clinical Trial. Miller PD, Hattersley G, Riis BJ, Williams GC, Lau E, Russo LA, Alexandersen P, Zerbini CA, Hu MY, Harris AG, Fitzpatrick LA, Cosman F, Christiansen C, ACTIVE Study Investigators. JAMA. 2016 Aug 16; 316(7):722-33

LASOFOXIFENE

the drug acts as a skeletal agonist and breast and uterine antagonist

In the Postmenopausal Evaluation and Risk-Reduction With Lasofoxifene (PEARL) trial 8500 postmenopausal women with osteoporosis (T-score < -2.5) were randomly assigned to lasofoxifene (0.25 or 0.5 mg daily) versus placebo

All subjects received calcium (1gr.) and vitamin D (400 to 800 iu) daily

The primary endpoint for the first three years of the five-year trial was radiographic vertebral fractures. Nonvertebral fracture and estrogen receptor (ER)-positive breast cancer were coprimary endpoints through five years



The NEW ENGLAND JOURNAL of MEDICINE

**SUBSCRIBE
OR RENEW >**

ORIGINAL ARTICLE

[A Correction Has Been Published >](#)

Lasofexifene in Postmenopausal Women with Osteoporosis

Steven R. Cummings, M.D., Kristine Ensrud, M.D., Pierre D. Delmas, M.D., Ph.D., Andrea Z. LaCroix, Ph.D., Slobodan Vukicevic, M.D., Ph.D., David M. Reid, M.B., Ch.B., M.D., Steven Goldstein, M.D., Ph.D., Usha Sriram, M.D., Andy Lee, M.A., John Thompson, Ph.D., Roisin A. Armstrong, Ph.D., David D. Thompson, Ph.D., Trevor Powles, M.D., Jose Zanchetta, M.D., David Kendler, M.D., Patrick Neven, M.D., Ph.D., and Richard Eastell, M.D., for the PEARL Study Investigators*

N Engl J Med 2010; 362:686-696 | [February 25, 2010](#) | DOI: 10.1056/NEJMoa0808692

Lasofoxifene results

- After three years, patients treated with either dose of lasofoxifene had fewer vertebral fractures (13.5 versus 23 per 1000 patient-years in the 0.5 mg and placebo groups, [HR] 0.58, 95% CI 0.45-0.73)
- After five years, the reduction in vertebral fracture was continued, and patients who took 0.5 mg daily had significantly fewer nonvertebral fractures (18.7 versus 24.5 per 1000 person-years, HR 0.76, 95% CI 0.64-0.91). **There was no effect on the incidence of hip fracture**

Coprimary outcomes of lasofoxifene

- After five years, there was a reduction in the incidence of ER-positive breast cancer (0.3 versus 1.7 per 1000 person-years in the 0.5 mg and placebo groups, respectively, HR 0.19, 95% CI 0.07-0.56)

SERMs new comers

- **Arzoxifene** as a long acting raloxifene and **ospemifene** (Ophena[®]) that is structurally tamoxifene like are new SERMs with beneficial effects on bone such as increased BMD, decreased bone turnover, and fracture risk
- clinical studies with ospemifene and arzoxifene are proceeding that are not approved by FDA, yet

To pay respect to the fallen comrades

Cathepsin K inhibitors

- Cathepsin K is a protease expressed in osteoclasts that plays a role in osteoclast-mediated bone resorption. Cathepsin K degrades organic bone matrix, primarily type 1 collagen.
- Cathepsin K inhibitors (eg, odanacatib) inhibit matrix dissolution, decrease bone resorption, and improve BMD in postmenopausal women.
- In a phase III trial (The Long-term Odanacatib Fracture Trial, LOFT), there was significant fracture risk reduction for both spine and nonvertebral fractures but a higher and statistically significant increase in stroke events. The current development program for odanacatib has been halted and, therefore, the agent will not be going to the US Food and Drug Administration (FDA) for further evaluation and approval.

Odanacatib, a cathepsin-K inhibitor for osteoporosis: a two-year study in postmenopausal women with low bone density. AUBone HG, McClung MR, Roux C, Recker RR, Eisman JA, Verbruggen N, Hustad CM, DaSilva C, Santora AC, Ince BA. SOJ Bone Miner Res. 2010;25(5):937.

Merck&Co. drops osteoporosis drug odanacatib. AUMullard A. SONat Rev Drug Discov. 2016 Sep;15(10):669.

Levormeloxifene

- is a selective estrogen receptor modulator that was developed as an alternative to estrogen replacement therapy for the treatment and prevention of postmenopausal bone loss
- In animal models, levormeloxifene prevented increased bone turnover and vertebral bone loss following ovariectomy. Studies of healthy postmenopausal women showed that levormeloxifene 1.25–20 mg/day decreased bone turnover and increased bone mineral density to a comparable extent to that observed during conventional hormone replacement therapy
- in the phase II and III studies, the effect on bone turnover and bone mineral density was similar for each dose of levormeloxifene and the minimal effective dose was never established
- The development of levormeloxifene was discontinued during the phase III trial due to a significant incidence of gynecologic adverse events in the levormeloxifene-treated groups

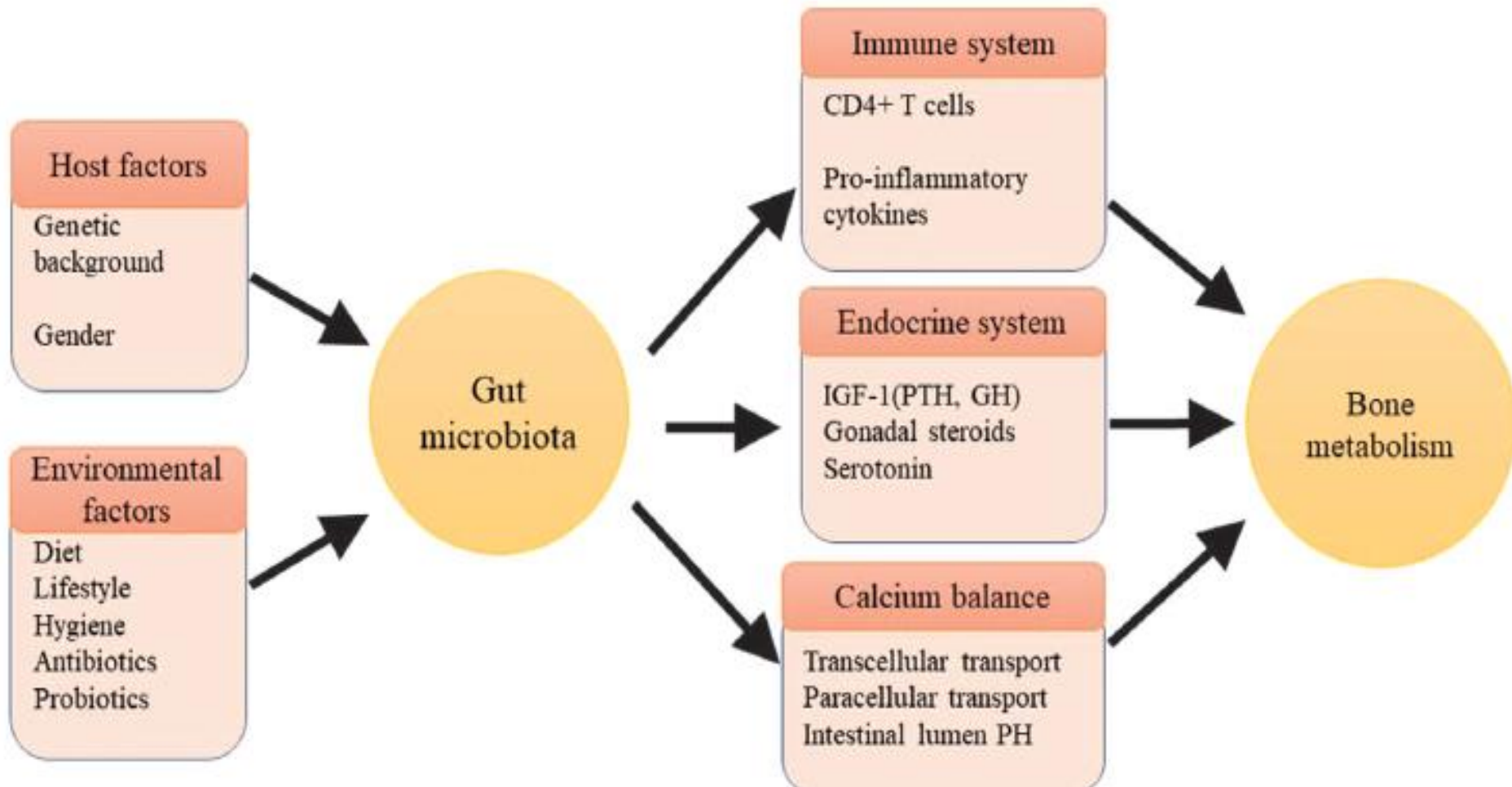
REVIEW ARTICLE

Intestinal microbiota: a potential target for the treatment of postmenopausal osteoporosis

Xin Xu^{1,2}, Xiaoyue Jia^{1,2}, Longyi Mo¹, Chengcheng Liu^{1,3}, Liwei Zheng^{1,4}, Quan Yuan^{1,5} and Xuedong Zhou^{1,2}

Postmenopausal osteoporosis (PMO) is a prevalent metabolic bone disease characterized by bone loss and structural destruction, which increases the risk of fracture in postmenopausal women. Owing to the high morbidity and serious complications of PMO, many efforts have been devoted to its prophylaxis and treatment. The intestinal microbiota is the complex community of microorganisms colonizing the gastrointestinal tract. Probiotics, which are dietary or medical supplements consisting of beneficial intestinal bacteria, work in concert with endogenous intestinal microorganisms to maintain host health. Recent studies have revealed that bone loss in PMO is closely related to host immunity, which is influenced by the intestinal microbiota. The curative effects of probiotics on metabolic bone diseases have also been demonstrated. The effects of the intestinal microbiota on bone metabolism suggest a promising target for PMO management. This review seeks to summarize the critical effects of the intestinal microbiota and probiotics on PMO, with a focus on the molecular mechanisms underlying the pathogenic relationship between bacteria and host, and to define the possible treatment options.

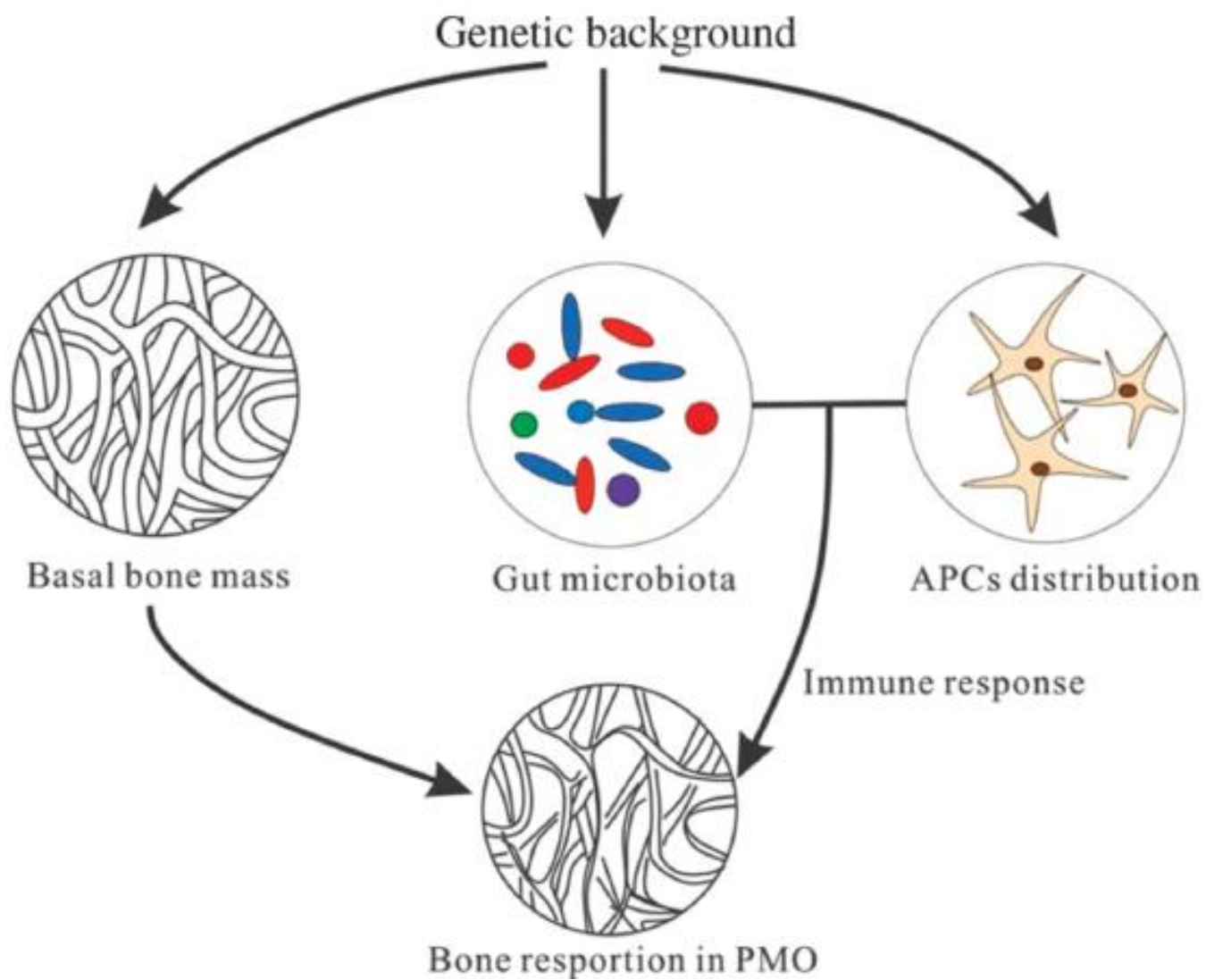
Bone Research (2017) 5, 17046; doi:10.1038/boneres.2017.46; published online: 4 October 2017



Regulators of the gut microbiota and mechanisms by which the gut microbiota regulates bone metabolism. Shaped by both host and environmental factors, the gut microbiota regulates bone metabolism through various pathways, including the immune system, endocrine system, and influences on calcium balance

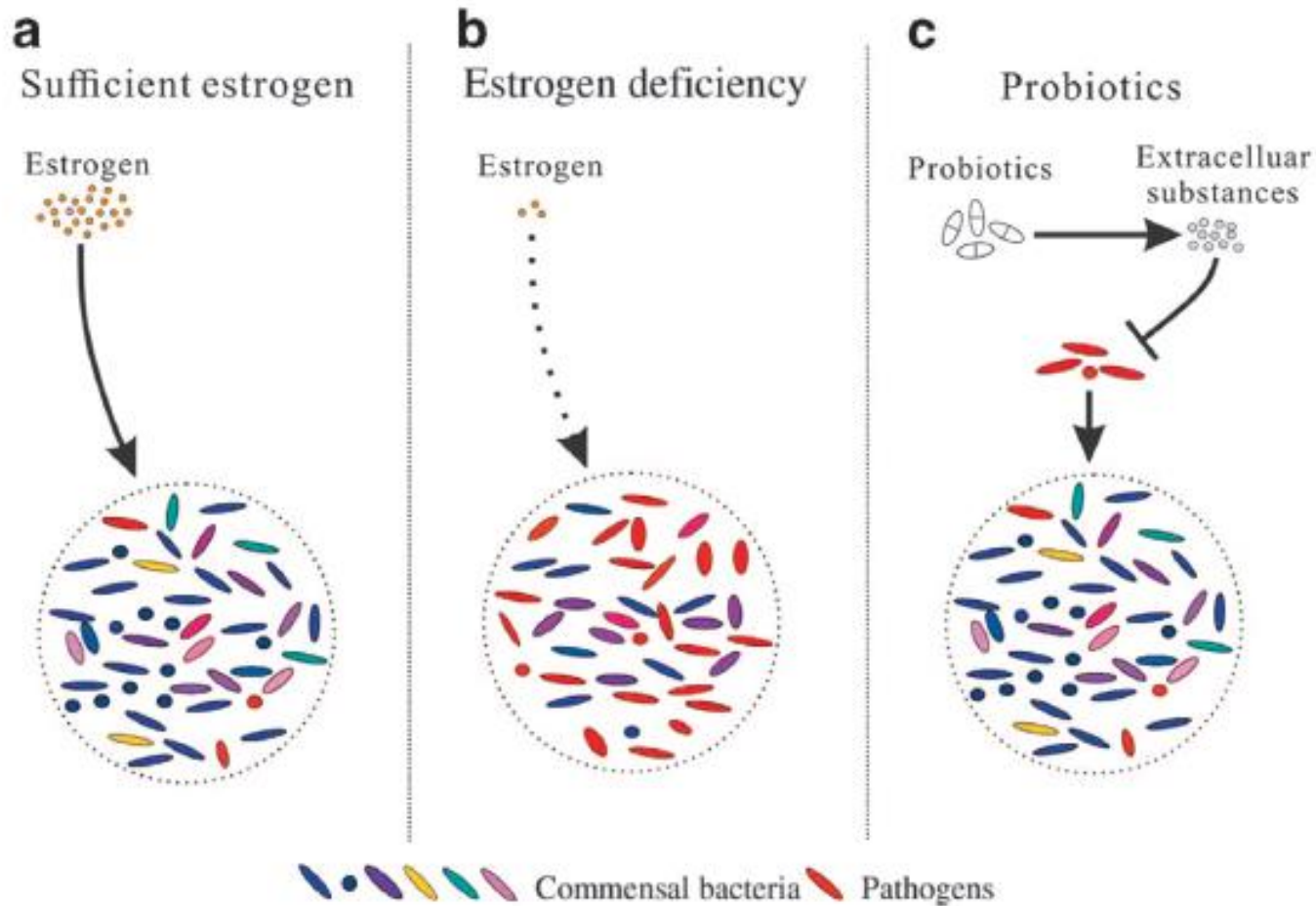
Animal model

- germfree mice showed higher trabecular volume bone mineral density (vBMD) and improved histomorphologic indices in trabecula compared with conventionally raised (CONV-R)mice
- both trabecular BMD and cortical crosssectional area decreased when germ-free mice were recolonized by the gut microbiota, indicating that the gut microbiota is a major regulator of bone mass

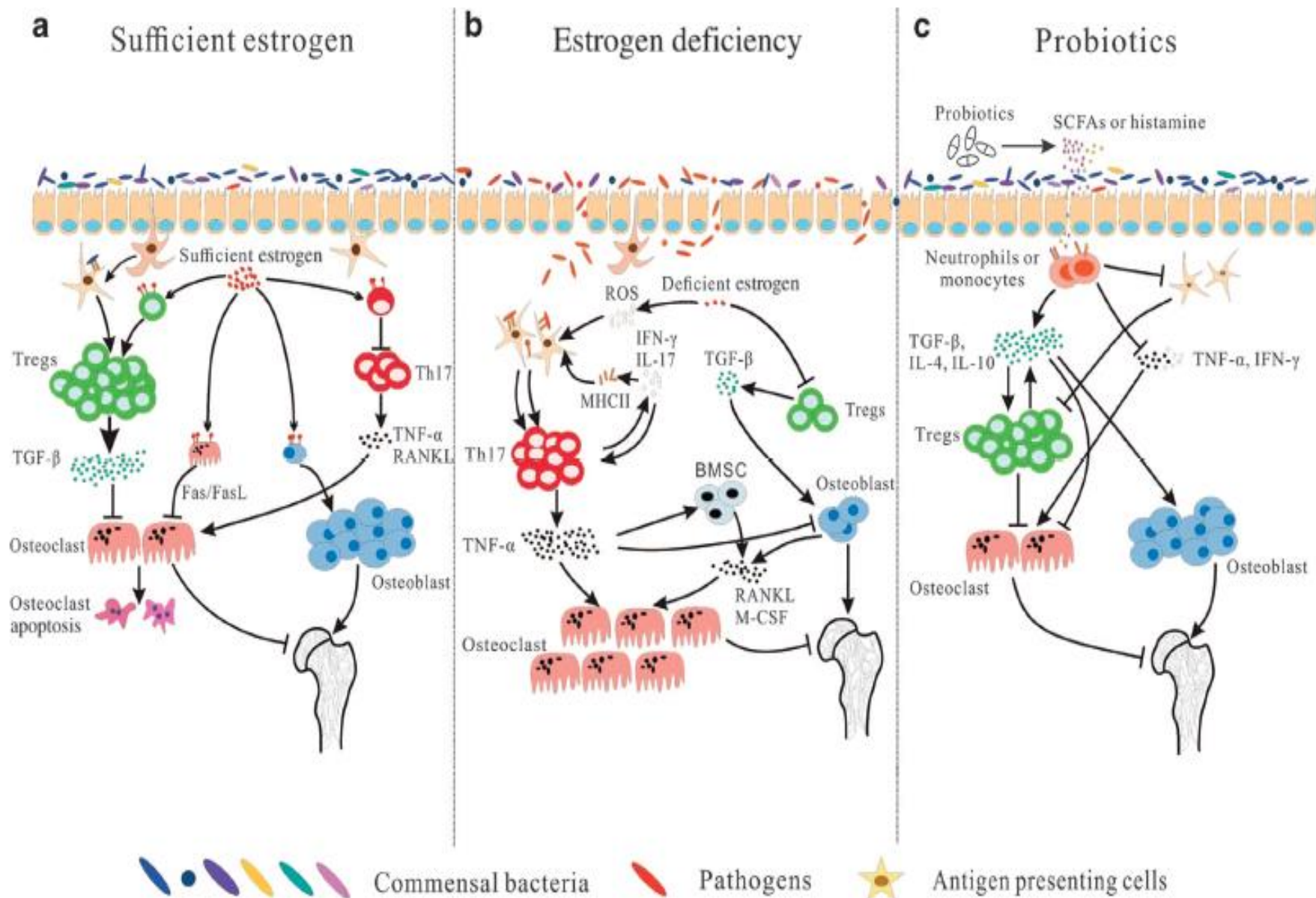


Is it reversible?

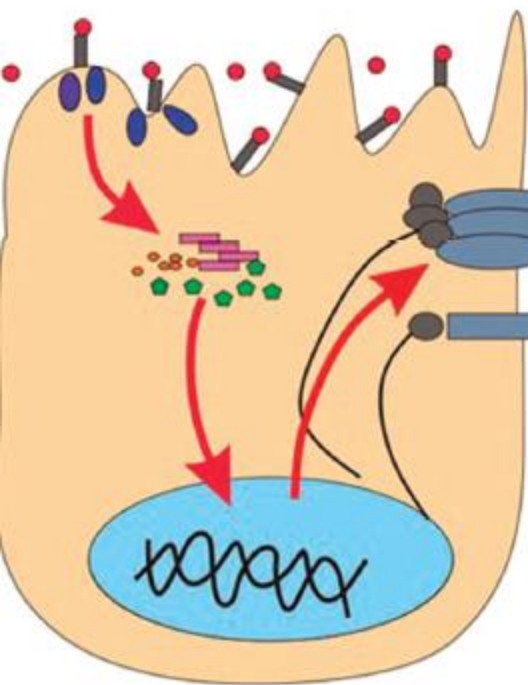
- germ-free mice colonized with immature gut microbiota from donors of different ages or nutritional statuses showed varied femoral phenotypes, suggesting that the impact of the gut microbiota on bone morphologic properties is age/nutrition dependent



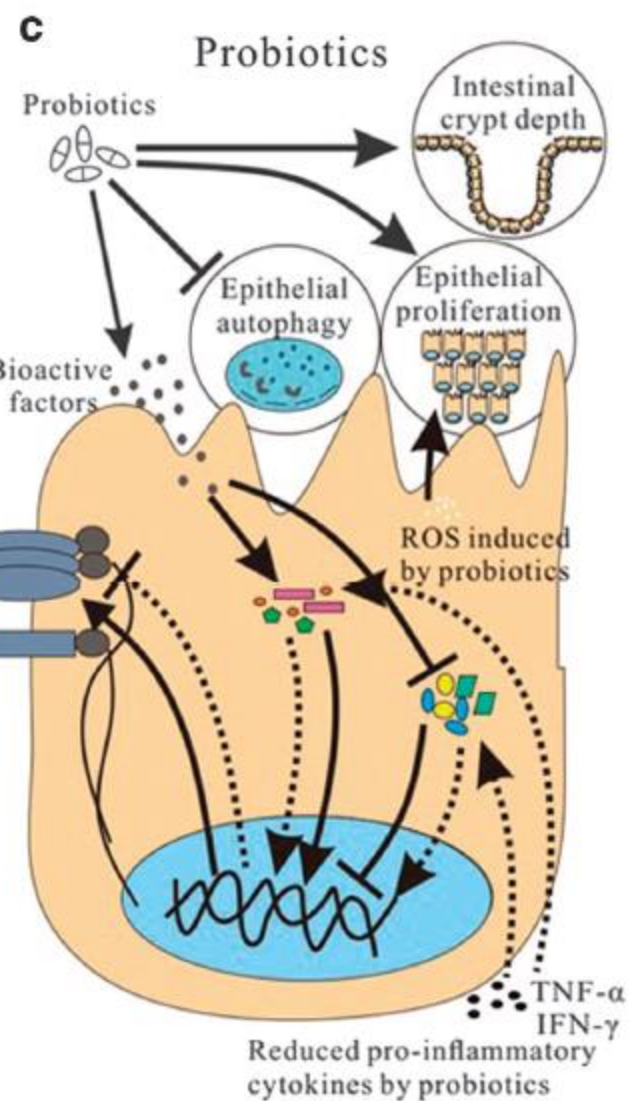
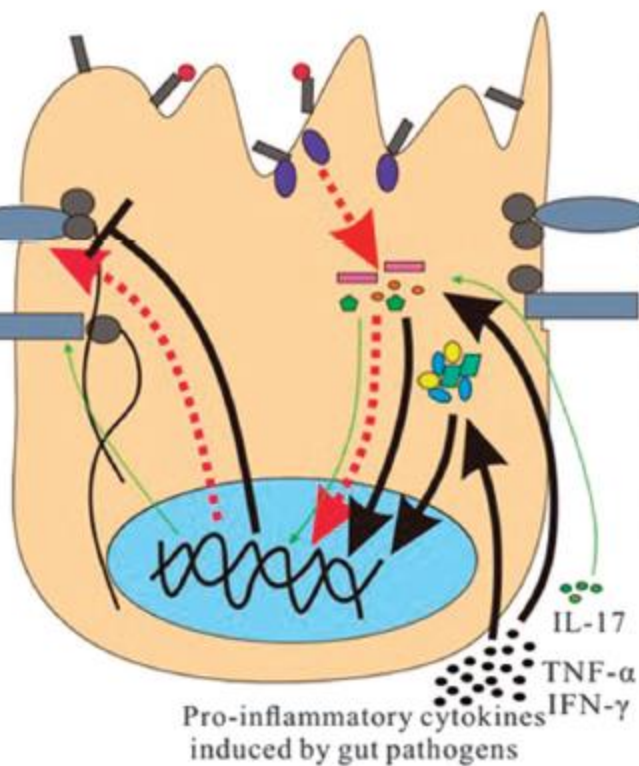
Intestinal microbial diversity in PMO is regulated by estrogen and probiotics. Healthy status can maintain gut microbial diversity and beneficial bacteria, which can activate Tregs to sustain immune homeostasis that is resistant to pathogens (a). Estrogen deficiency reduces gut microbial diversity and beneficial bacteria, while increased pathogens induce inflammation (b). Probiotics can prevent pathogens and increase gut microbial diversity by producing extracellular substances



a Sufficient estrogen



b Estrogen deficiency



Thank you for your attention

