CLAYTON
BIOTECHNOLOGIES

PG1180

Prevention and treatment of post-menopausal osteoporosis and obesity.

Post-menopausal osteoporosis and obesity

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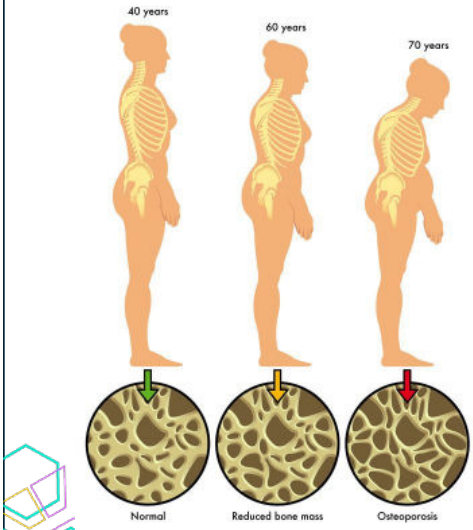
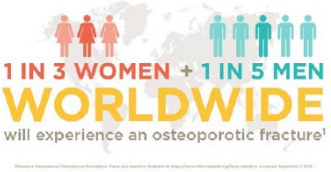


Image: Endocrineweb.com

- **Osteoporosis** is the most prevalent metabolic bone disorders, characterized by low bone mass and microarchitectural deterioration
- Most common type of primary osteoporosis is due to the **post-menopausal** estrogen deficiency
- **Menopause** associated with reduced estrogen levels promotes **abdominal / visceral fat storage**, linked to insulin resistance, type 2 diabetes, cardio-vascular disease

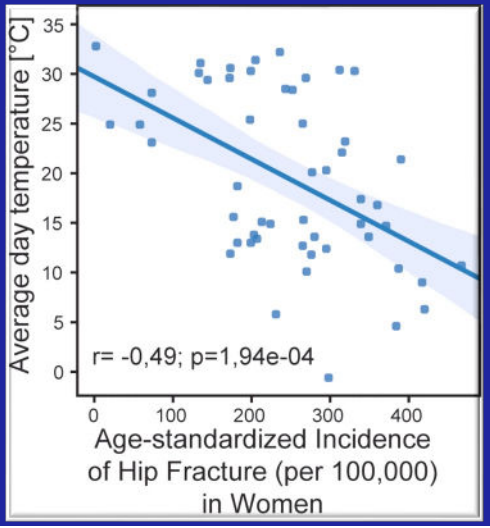
Existing treatments for Post-menopausal osteoporosis



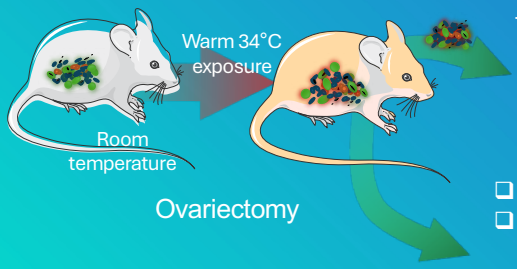
- **Existing treatments for osteoporosis** (Bisphosphonates, raloxifene and bazedoxifene, teriparatide and abaloparatide, denosumab, romozumab, Menopausal Hormone Therapy) ***are either not fully effective, costly or associated with side effects***.
- **New antibody therapeutics (Prolia and Evenity) are costly.**
- **Standard of care bisphosphonates (such as Alendronate or Fosamax)** have numerous **side effects** and do **not address other menopause related changes such as weight gain**

➢ Clear unmet need for better treatments to prevent and cure osteoporosis!

Higher ambient temperatures decreases osteoporosis



Correlation between higher ambient temperatures and decreased osteoporosis



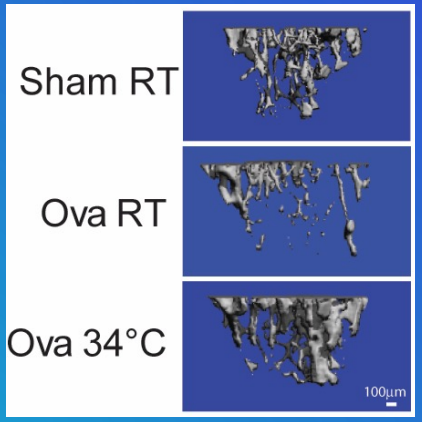
- **Human metadata analysis:** inverse correlation between osteoporotic hip fractures and average temperatures
- Mice **adapt to increased temperatures** partly by increasing tail length

???

- ❑ *Does elevated environmental temperature increase bone strength?*
- ❑ *Does elevated environmental temperature impact the microbiota composition?*
- ❑ *Do microbiota alterations influence bone morphology and strength?*
- ❑ *What are the metabolic effects of warm-adapted microbiota on "post-menopausal" mice?*

Warm applied post-development and warm-adapted microbiota improve bone strength and prevent osteoporosis

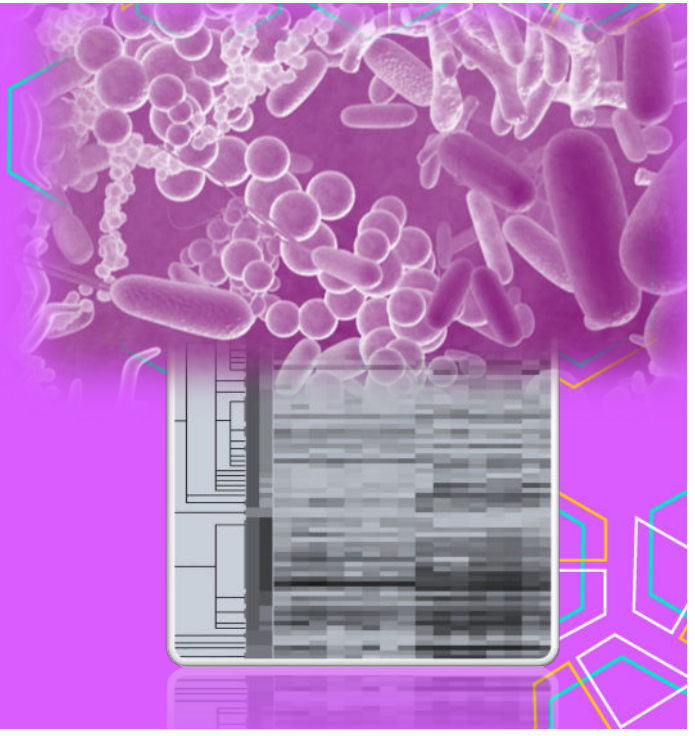
- Transplantation of the warm–adapted microbiota **prevents osteoporosis** in ovariectomized (post-menopausal) mice.
- Warm adapted microbiota transplantation **reverts changes of the tibia** and **increases periosteal bone formation**.



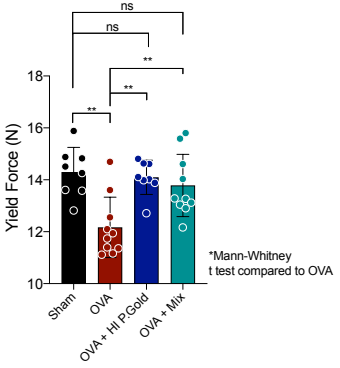
What bacterial strains prevent osteoporosis?

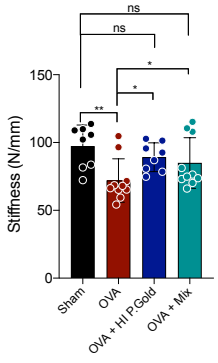
Conducted a **combinatorial metagenomics/ metabolomics analysis**

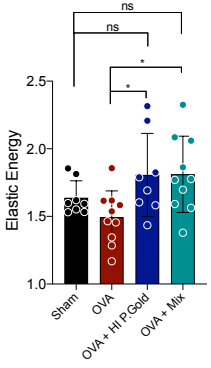
- Identified several strains
  - *L. reuterii*
  - *L. gasseri*
- **A novel bacterial strain that, even when inactivated, can reduce or prevent both osteoporosis and weight gain:**
  - ***PG1180 (P. goldsteinii)***



PG1180 alone or in combination with other microbiome strains improves bone strength







PG1180 prevents ovariectomy-induced bone deterioration.

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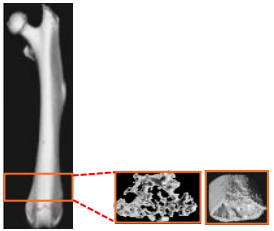
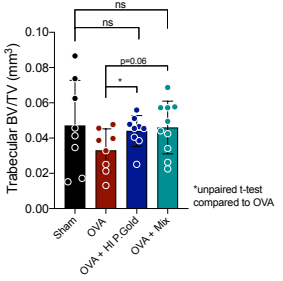
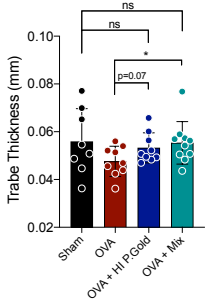
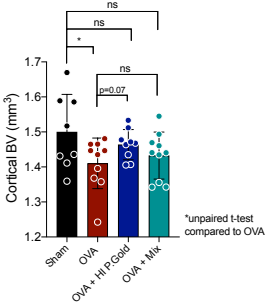
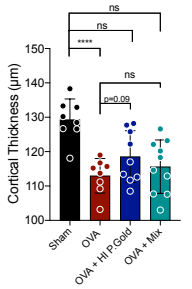
Femur

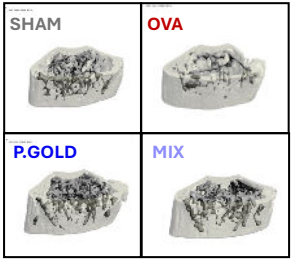












PG1180 decreases body weight gain in osteoporosis mice model

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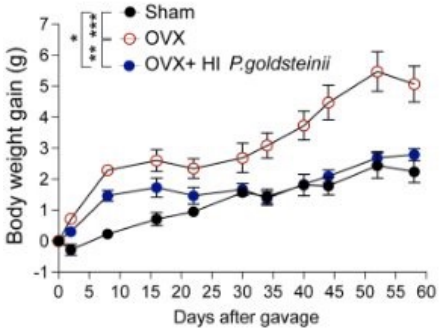
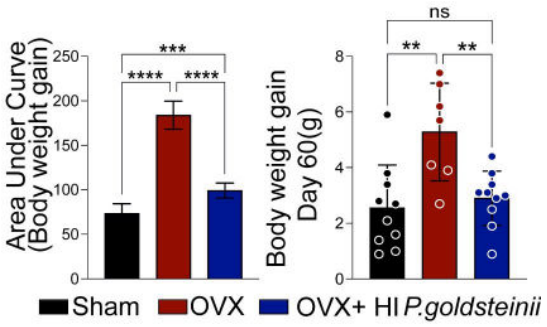
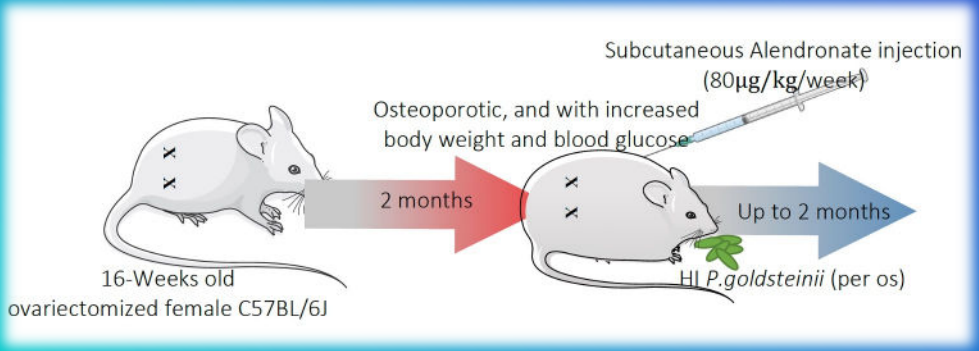




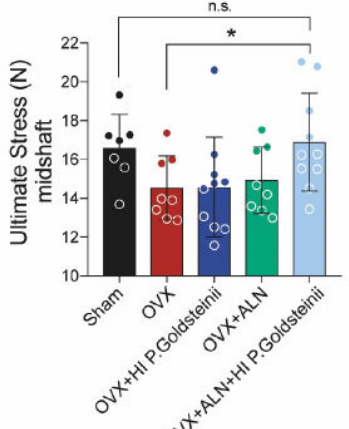
Can PG1180 cure osteoporosis?

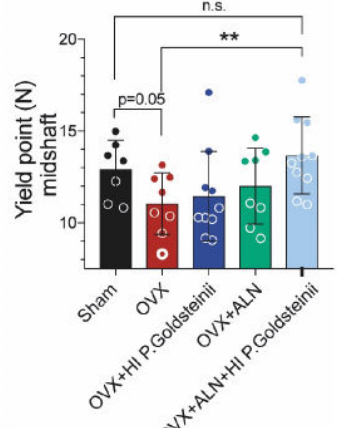
Is there synergy in combination with standard of care? What impact on metabolism of ova mice?



Curative mouse model for osteoporosis. 16 week old female C57Bl/6J mice were ovariectomised and left for 2 months to develop the symptoms of osteoporosis and postmenpausal weigh gain and glucose intolerance. Administration of the respective treatment was initiated following these 2 months after the ovariectomies, i.e., once the mice already developed the symptoms of the respective metabolic disease.

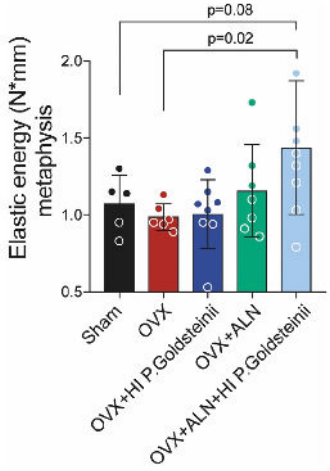
Synergistic effect of alendronate and PG1180 in reverting estrogen-deficiency induced osteoporosis

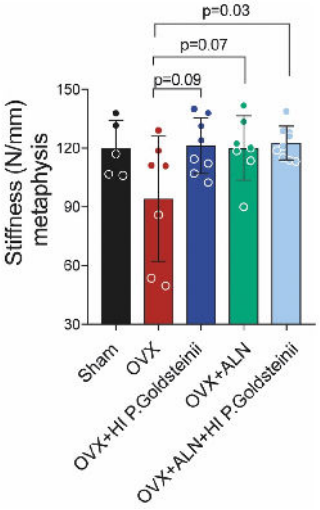




Femur midshaft weakening, revealed through biomechanical analysis of Ultimate Stress and Yield point, is reverted by combined PG1180/Alendronate treatment

Synergistic effect of alendronate and PG1180 in reverting estrogen-deficiency osteoporosis





Femur metaphysis weakening, revealed through biomechanical analysis of Elastic energy and Stiffness, is reverted by combined PG1180/Alendronate treatment

PG1180 combined with Alendronate dramatically reduces weight gain in ovariectomized mice

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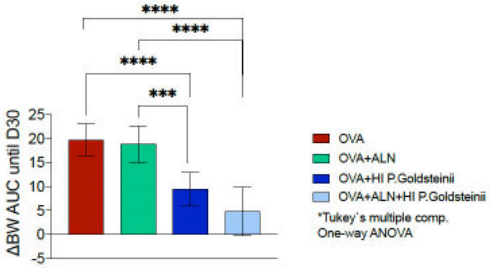
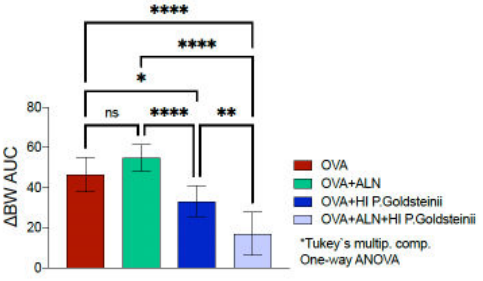
Body weight gain of ovariectomized female mice starting 2 months after the surgery to address the curative effects of the treatment.

Mice were administered with the respective treatment starting at day 0, which is 2 months flowing ovariectomy.

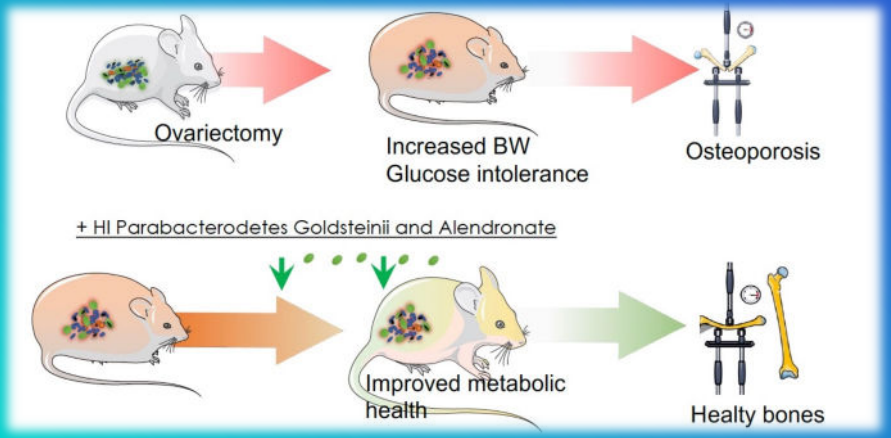


Cumulative Body weight gain until day 29 after starting the treatment.



Cumulative body weight gain until day 60 after starting the treatment

PG1180 prevents and postmenopausal osteoporosis and metabolic disfunction and treats in combination with bisphosphonates



Publications and Intellectual Property

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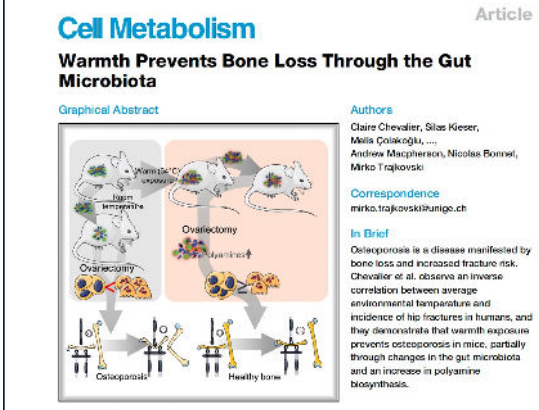

Article

Cell Metabolism

Warmth Prevents Bone Loss Through the Gut Microbiota

Graphical Abstract

Authors

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In Brief

Osteoporosis is a disease manifested by bone loss and increased fracture risk. Chevalier et al. observe an inverse correlation between average environmental temperature and incidence of hip fractures in humans, and they demonstrate that warmth exposure prevents osteoporosis in mice, partially through changes in the gut microbiota and an increase in polyamine biosynthesis.

Highlights

CLFR:481 METHODS AND PROBIOTIC COMPOSITIONS FOR THE TREATMENT OF BONE DISORDERS

- Granted: US
- Pending: EP, CA, AU, US

CLFR:486 METHODS AND PROBIOTIC COMPOSITIONS FOR THE TREATMENT OF METABOLIC DISEASES AND DISORDERS

- Granted: US
- Pending: US, EP, JP, CN, CA, AU

CLFR:539 COMBINATION THERAPY FOR THE TREATMENT OF METABOLIC DISEASES AND DISORDERS

- Provisional filed in 2023. Converted to regular US and PCT in 2024

Target Product Profile

- **Product:** lyophilized heat inactivated *P. goldsteinii* (PG1180 probiotic)
- **Standalone, or combined with Standard of care (bisphosphonates):** synergistic effect that enhances activity of and reduces required dosage of bisphosphonates, thereby reducing side effects associated with bisphosphonates, and provides metabolic benefits such as reduction of weight gain.
- **Primary indication:** Prevention and treatment of osteoporosis
- **Patient population:** Post-menopausal women
- **Treatment duration:** chronic
- **Delivery mode:** oral capsule
- **Mode of Action:** Thorough understanding of the cellular and molecular mechanisms
- **Side effects:** None detected, nor expected – product based on a bacterial strain that naturally inhabits healthy gut flora
- **Indication expansion:** Prevention and treatment of osteoporosis and prevention of weight gain and onset of diabetes in post-menopausal women and the general population

Next Steps

- ✓ Address the dynamics of the PG1180 at various time points post-ovariectomy
- ✓ **Seeking a biotech/ pharma partner to:**
  - ➢ Industrialize the manufacturing process
  - ➢ Product development

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PG1180

Prevention and treatment of post-menopausal osteoporosis and obesity.

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