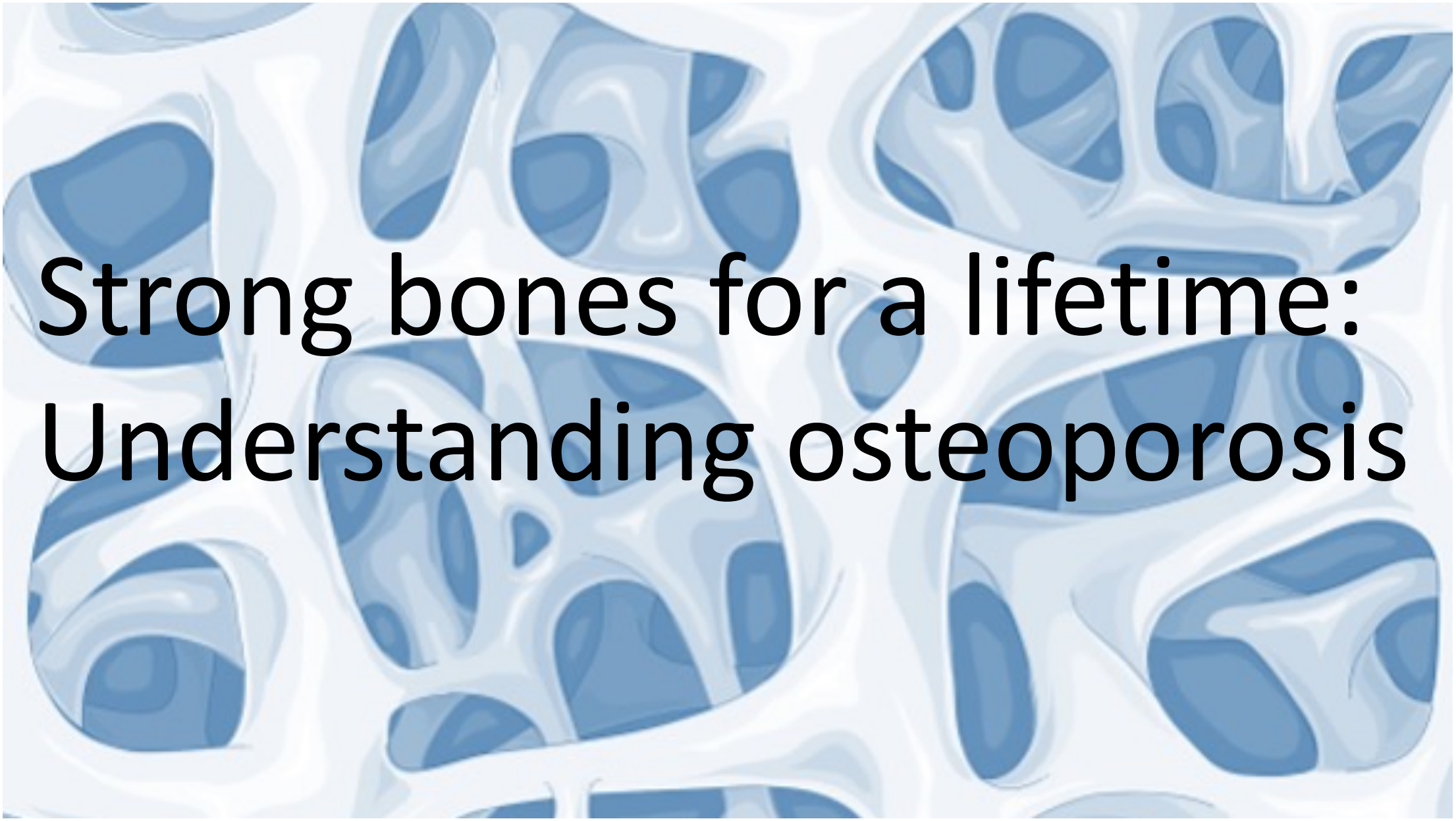
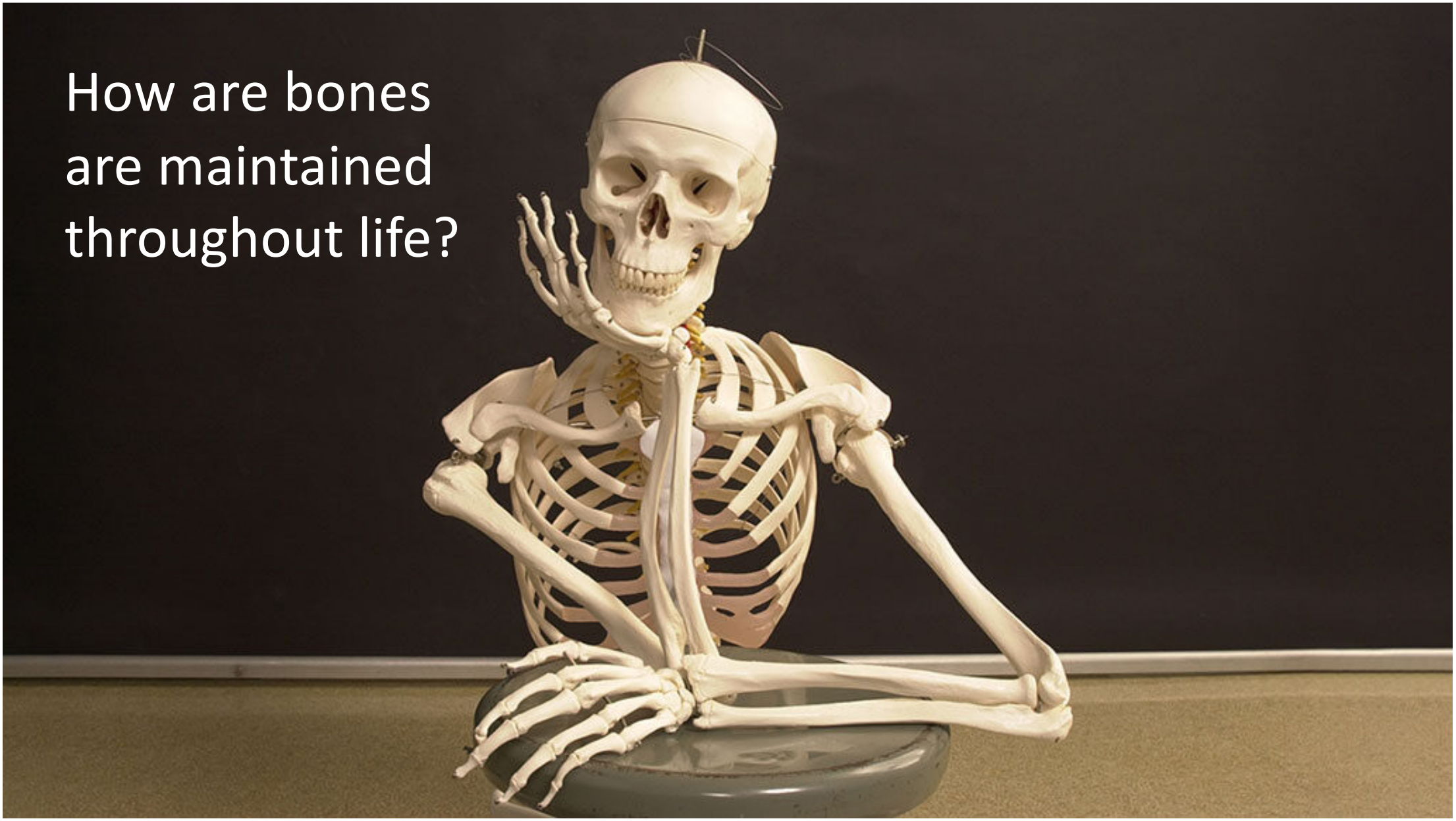

Strong bones for a lifetime:
Understanding osteoporosis


How are bones
are maintained
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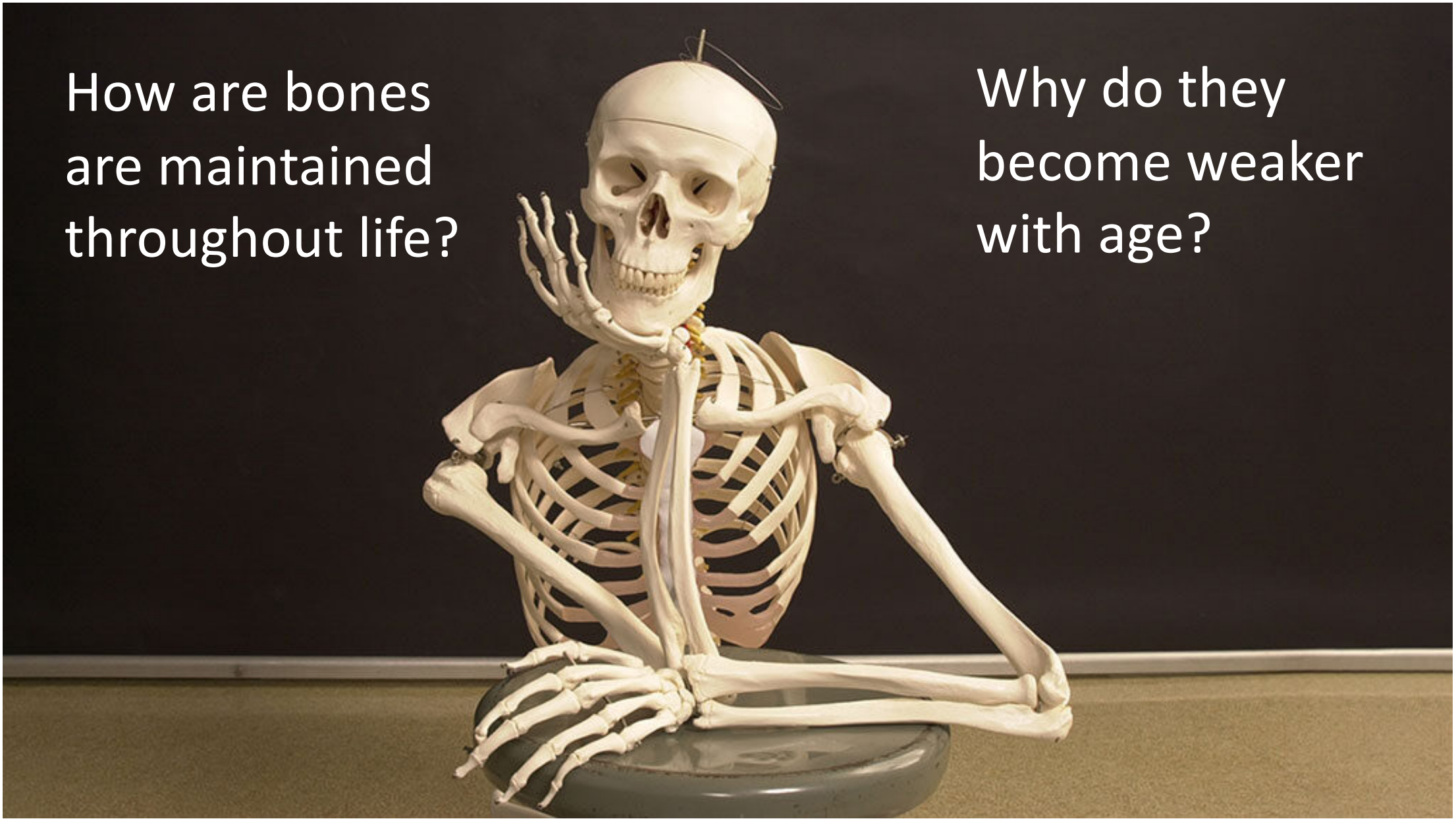
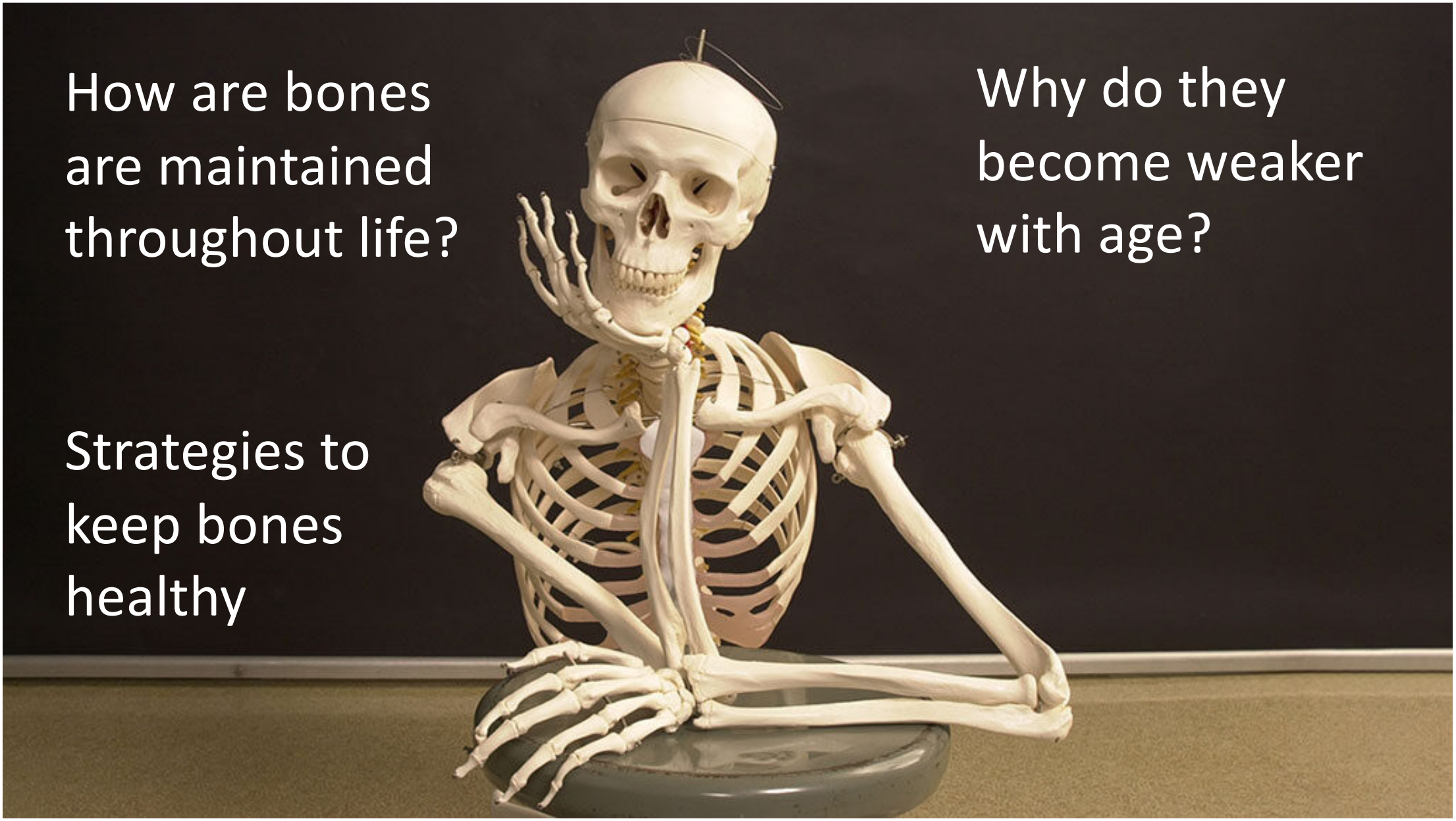

How are bones are maintained throughout life?
Why do they become weaker with age?

How are bones are maintained throughout life?

Why do they become weaker with age?

Strategies to keep bones healthy



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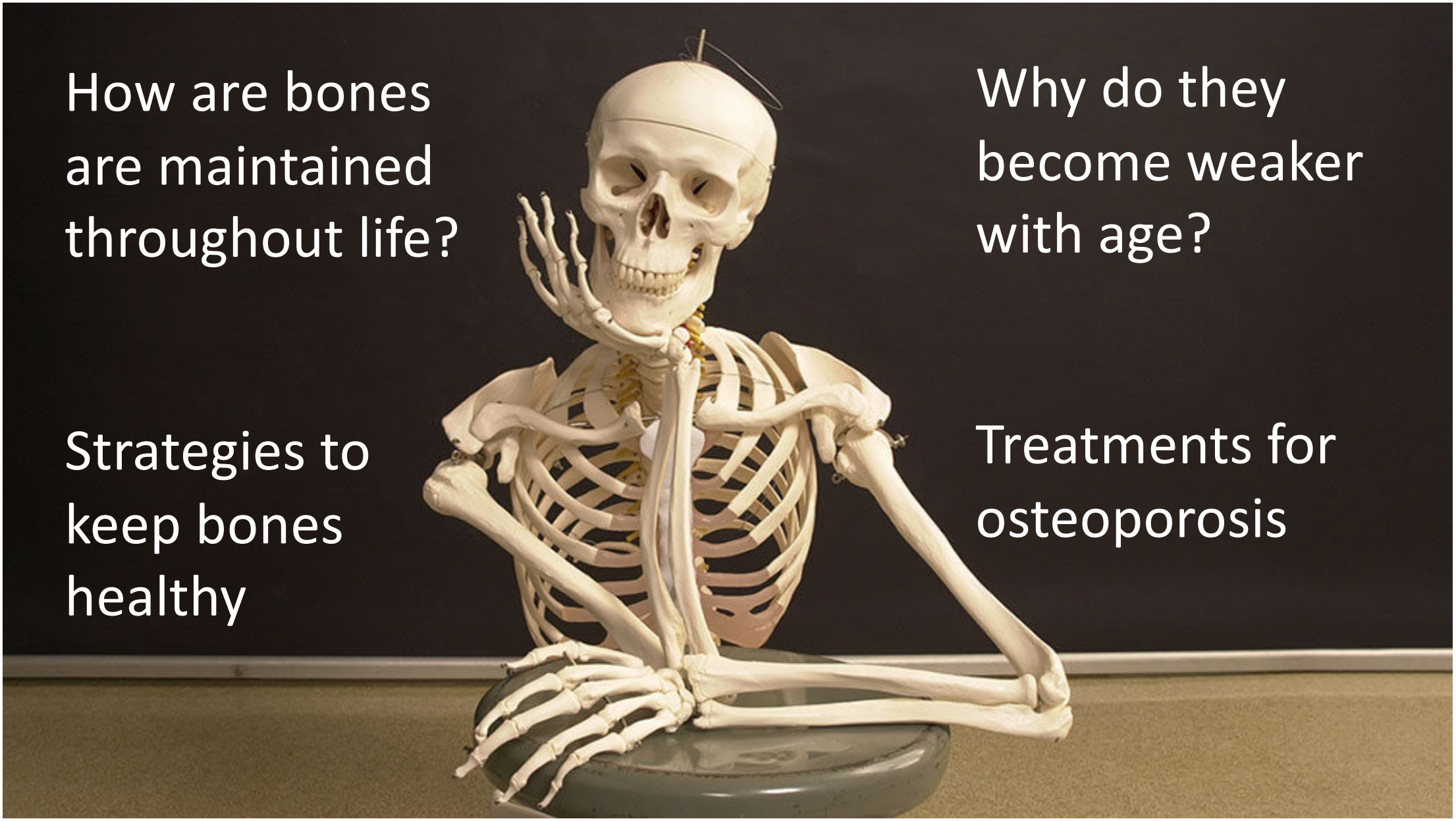
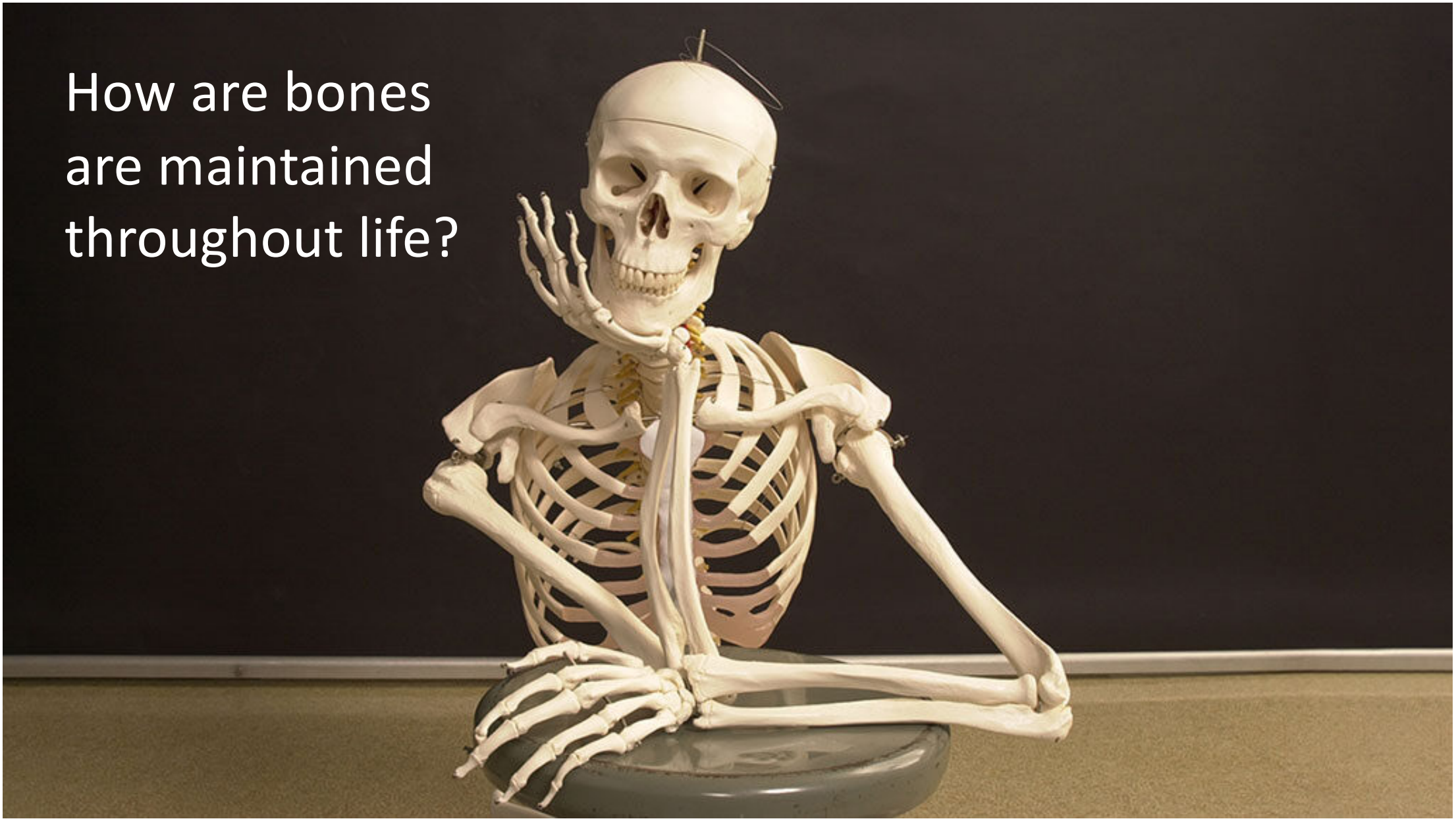


Strategies to keep bones healthy

Treatments for osteoporosis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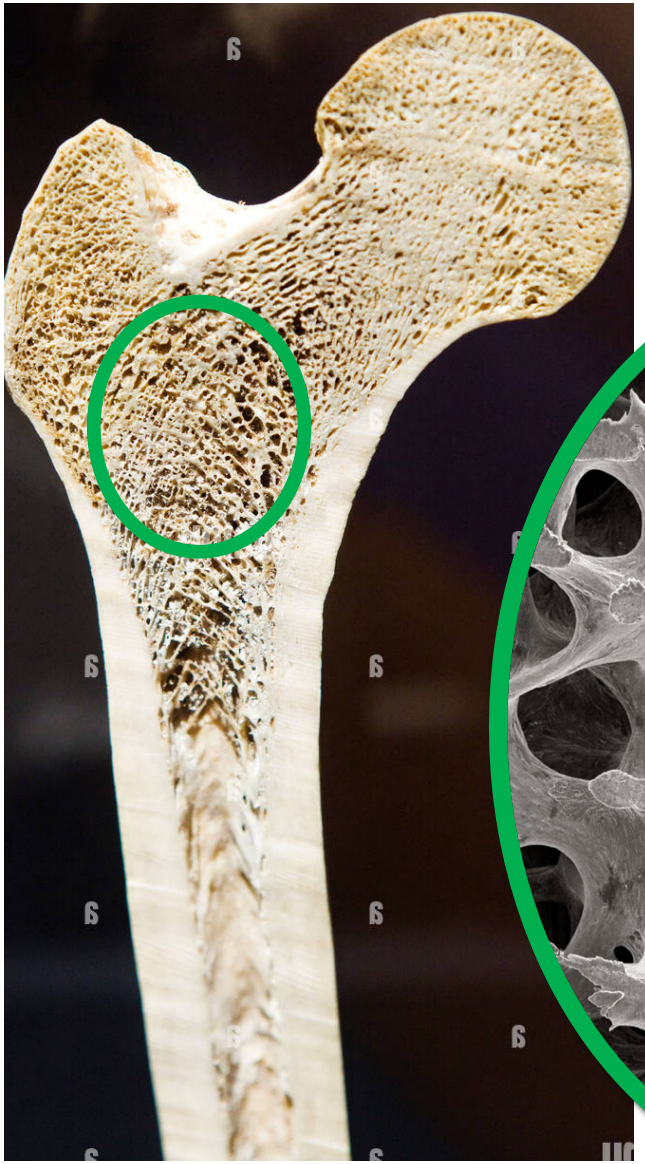
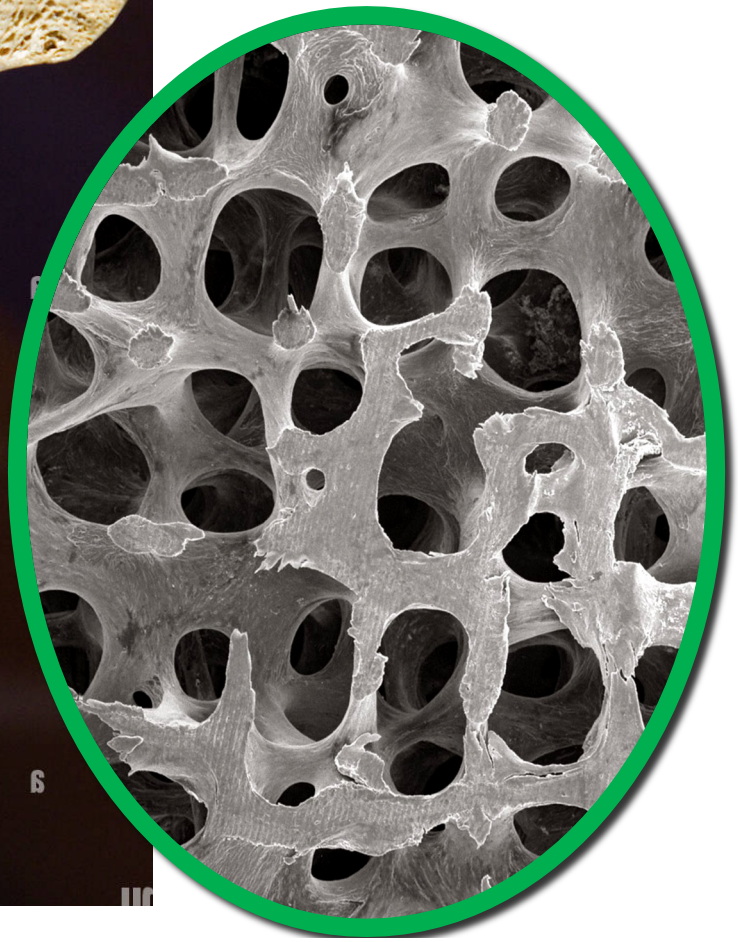
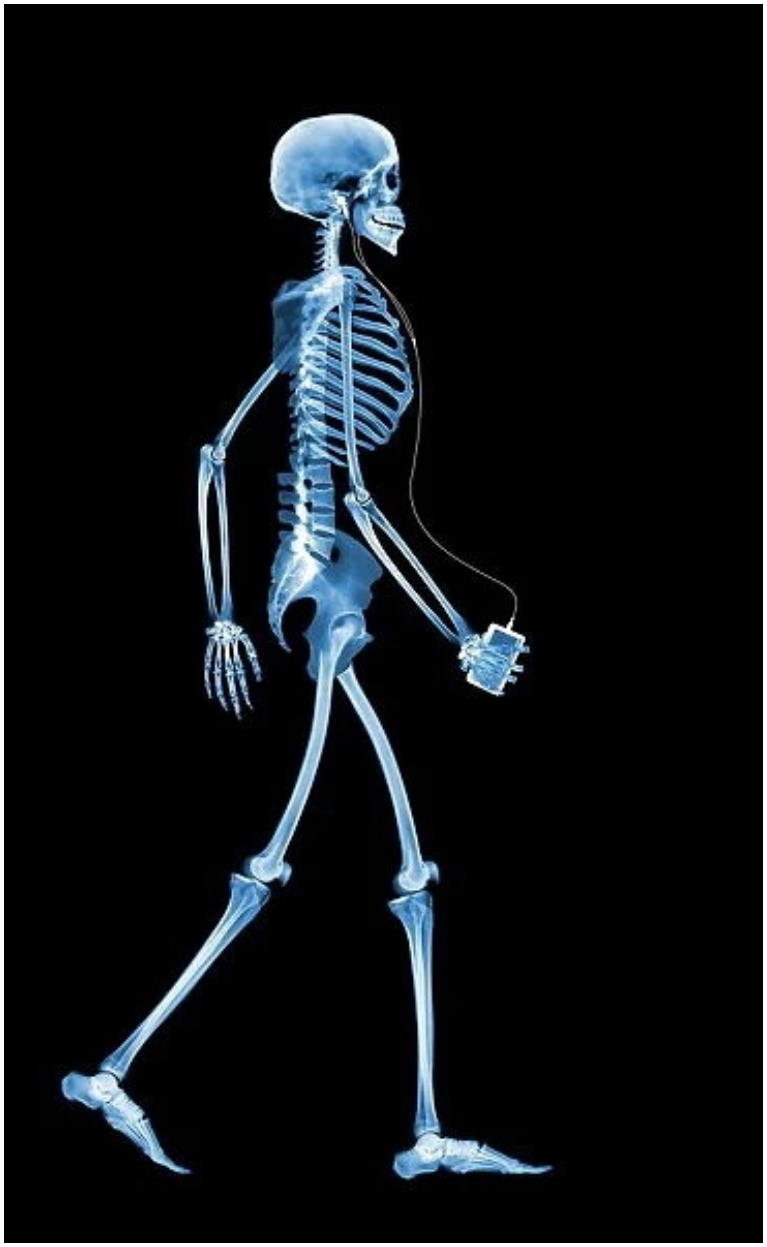
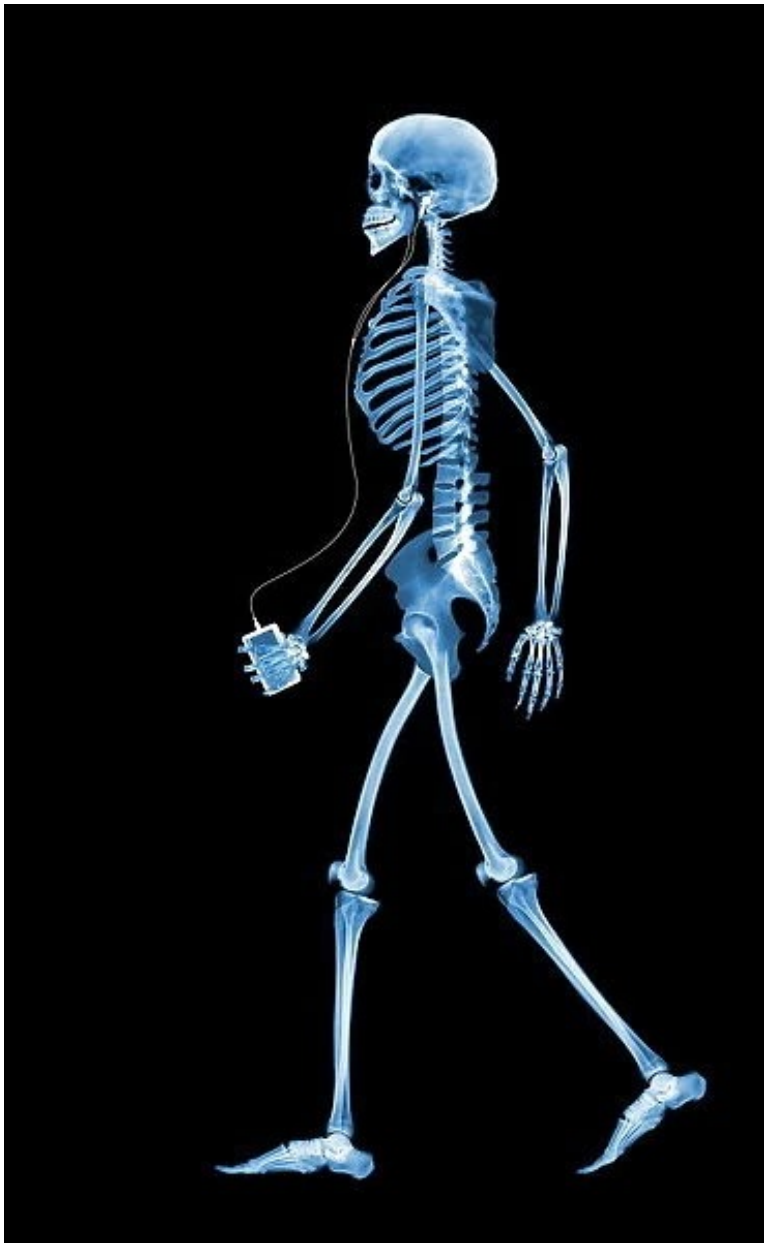


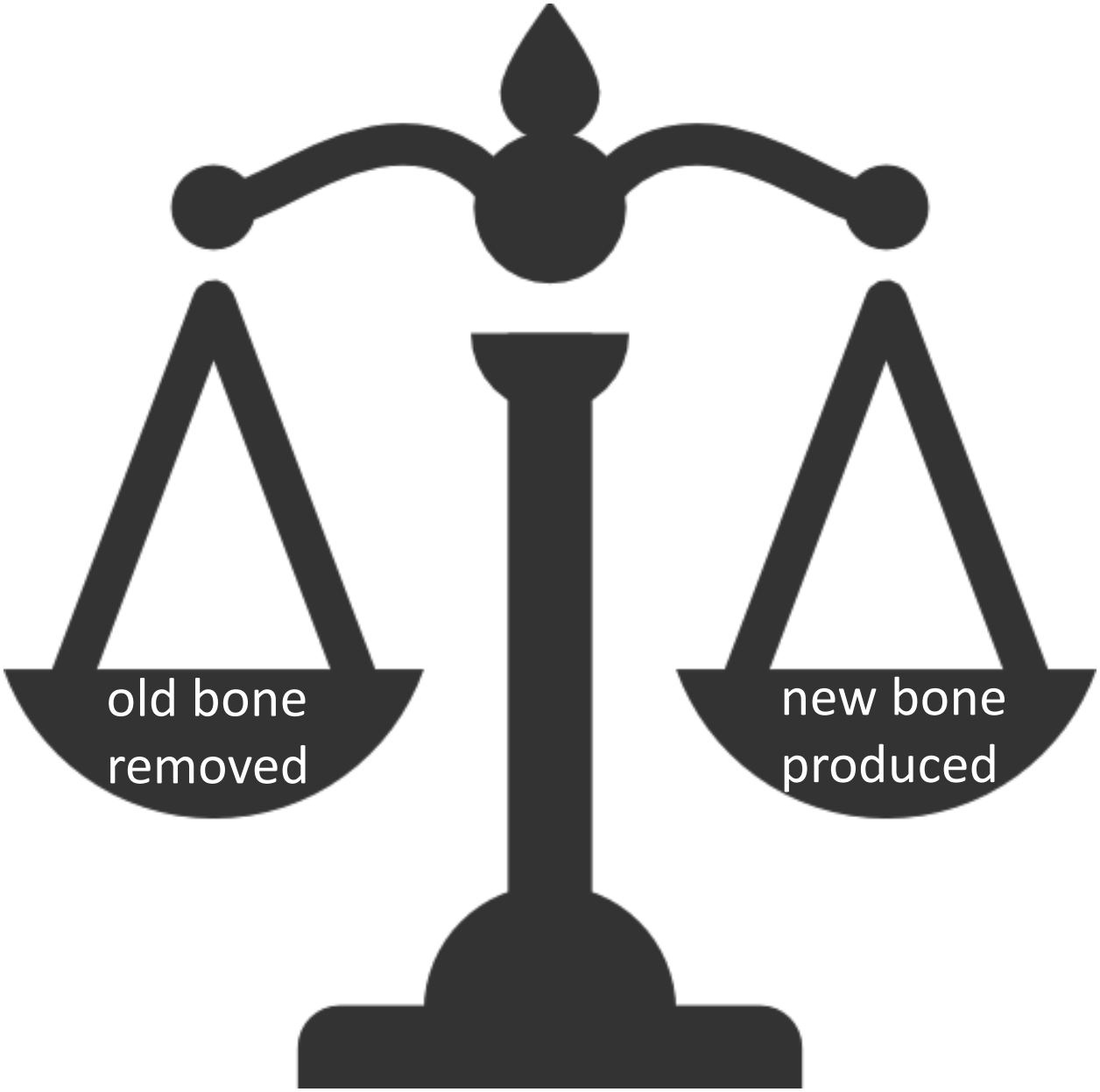




Entire skeleton
is replaced
every 10 years




old bone
removed


old bone
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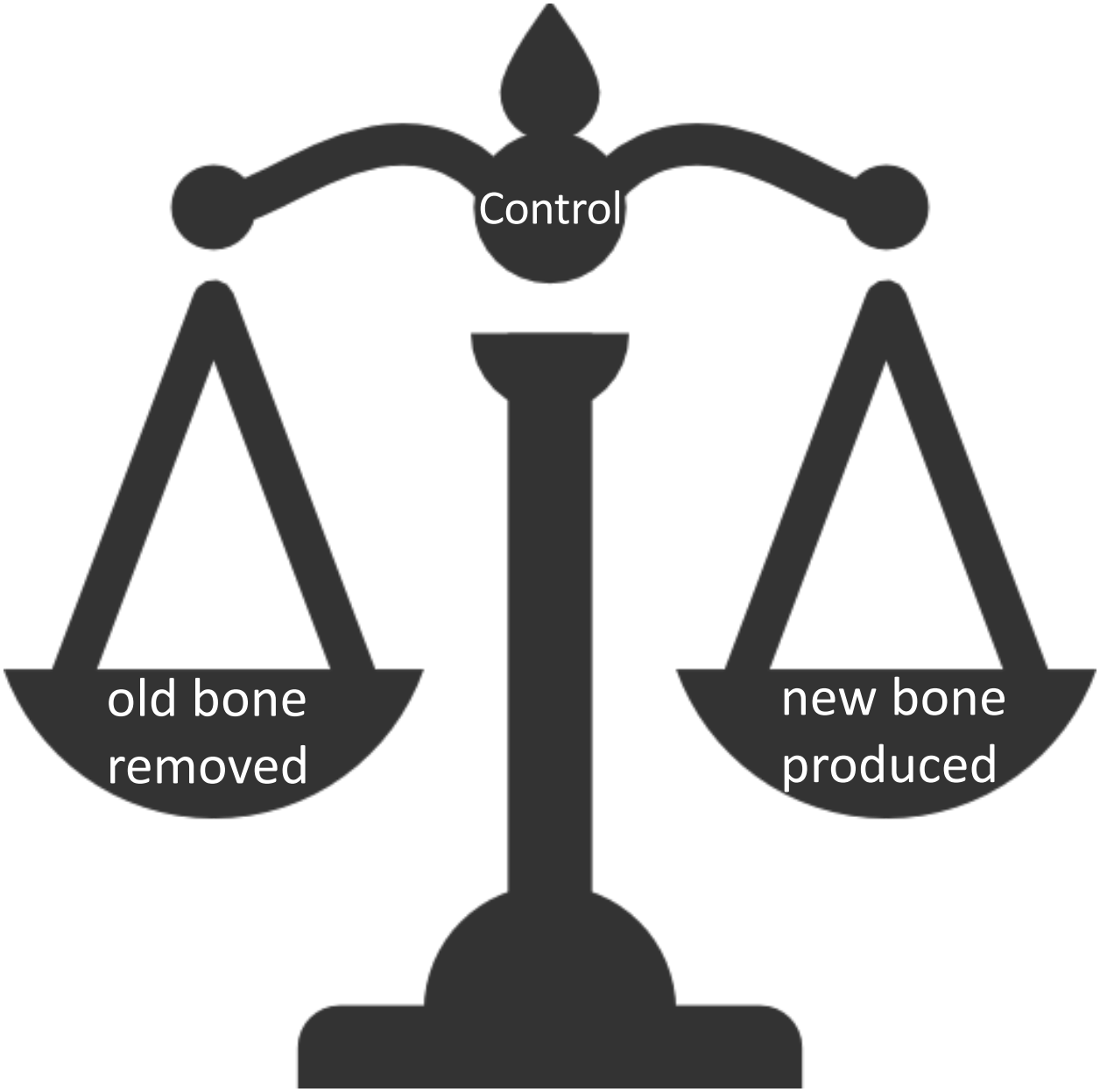
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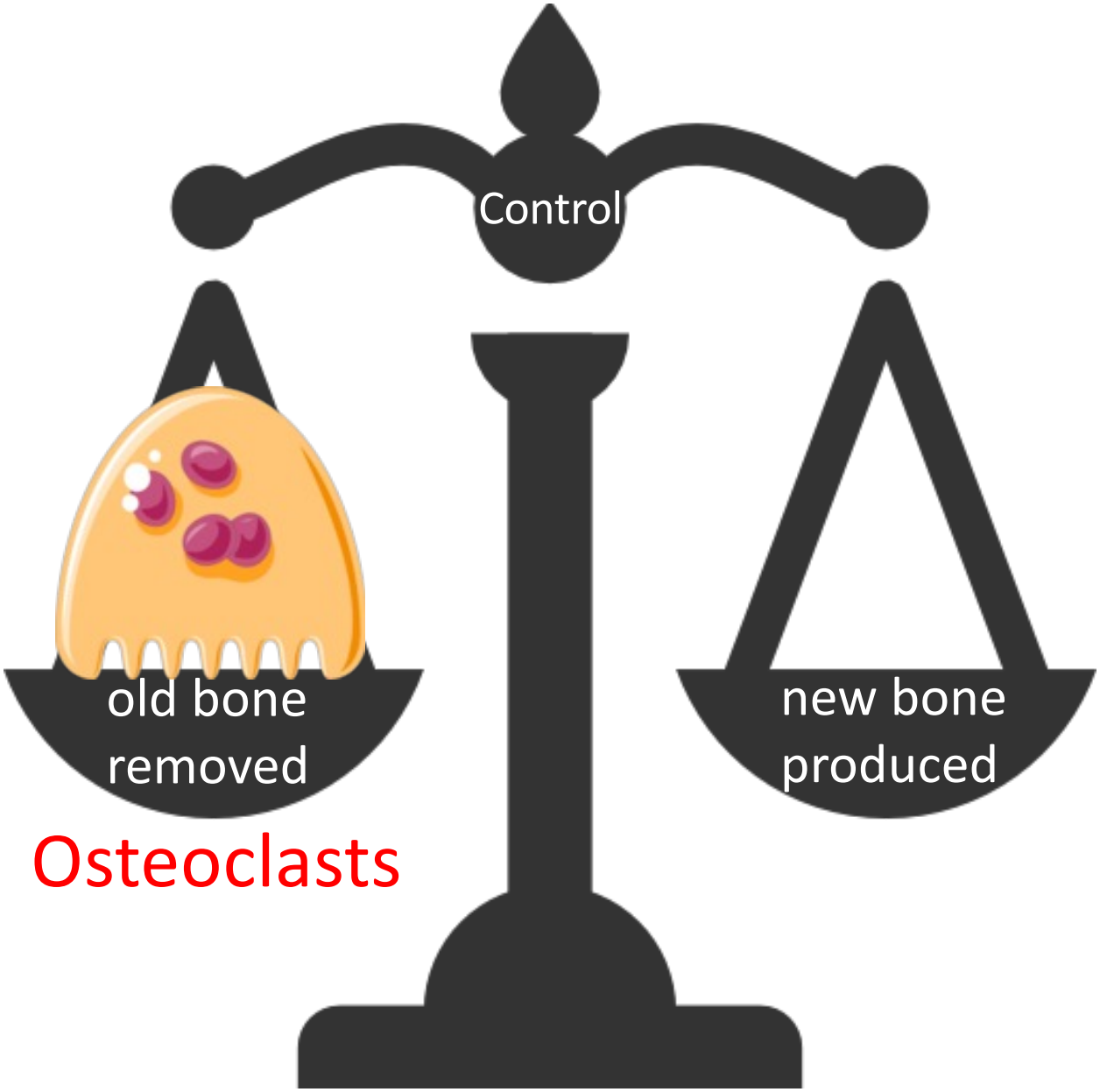
Control
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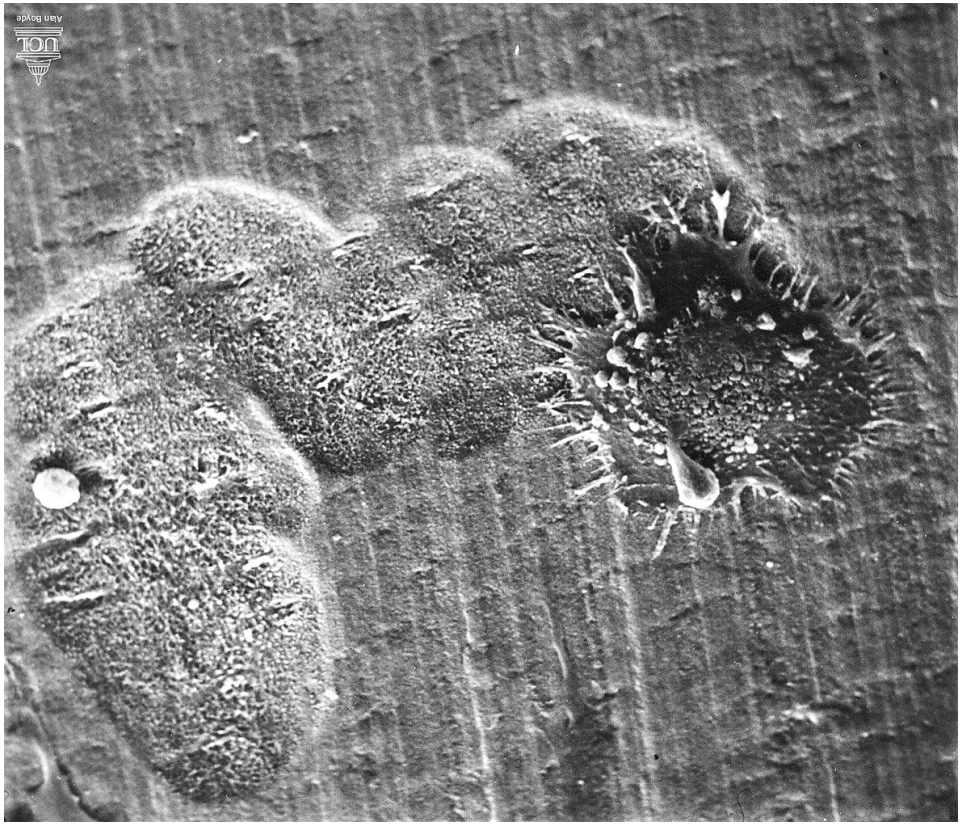
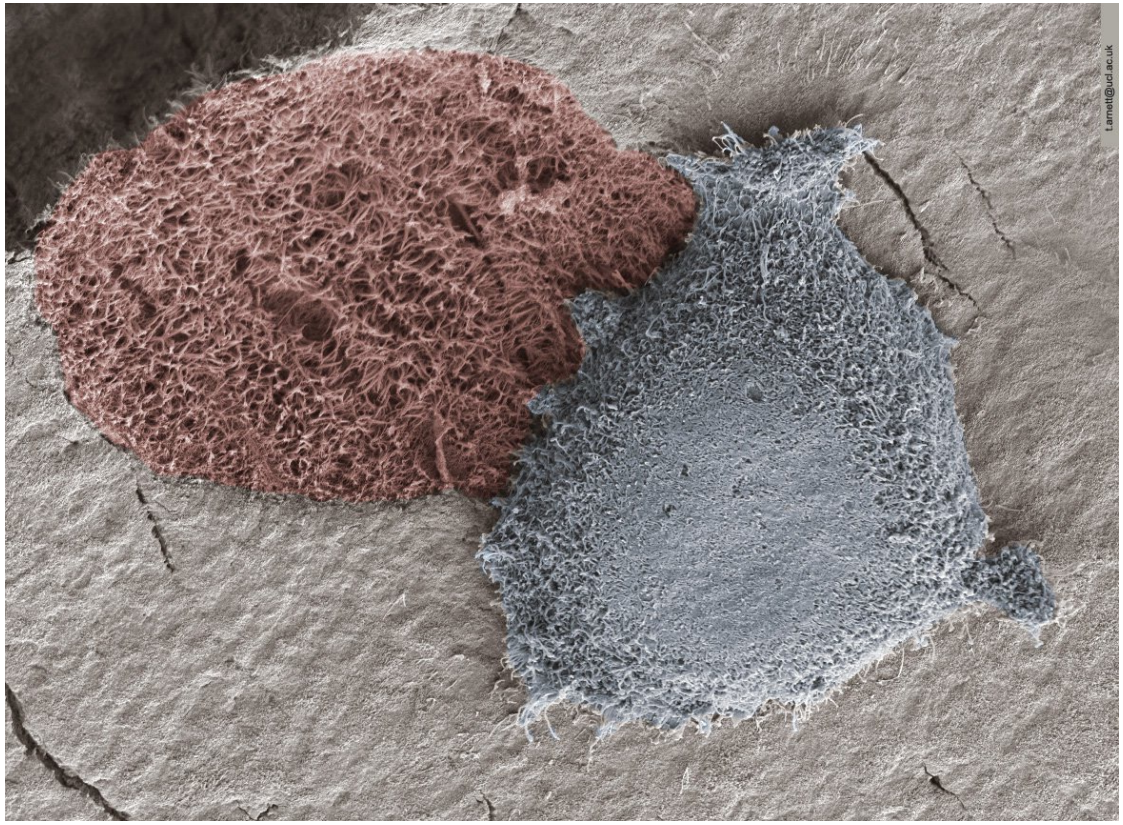
removed
new bone
produced
Osteoclasts

# ‘Osteoclast’ – from Ancient Greek: Osteon = bone
Clastos = broken

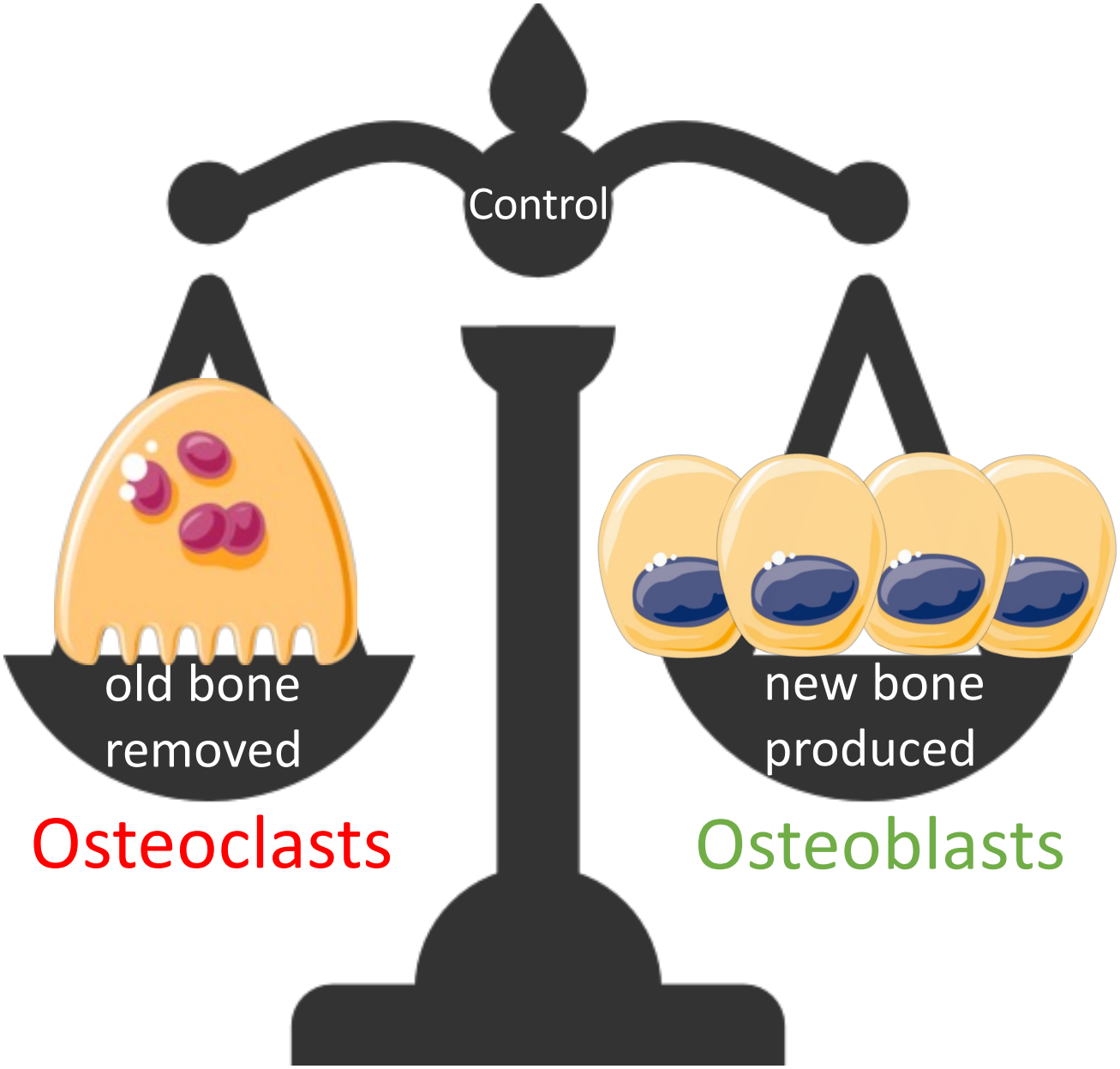
The bone eating cell



With kind permission from Prof. Alan Boyde



With kind permission from Prof. Tim Arnett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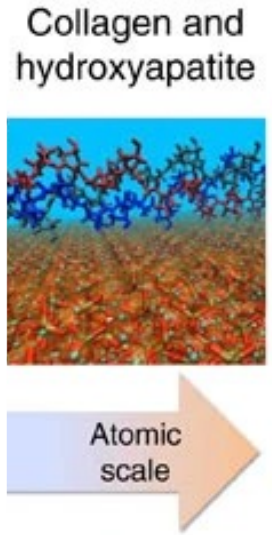
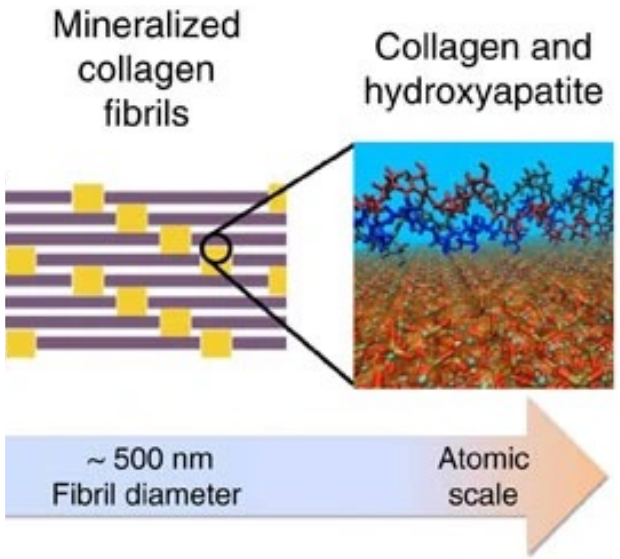
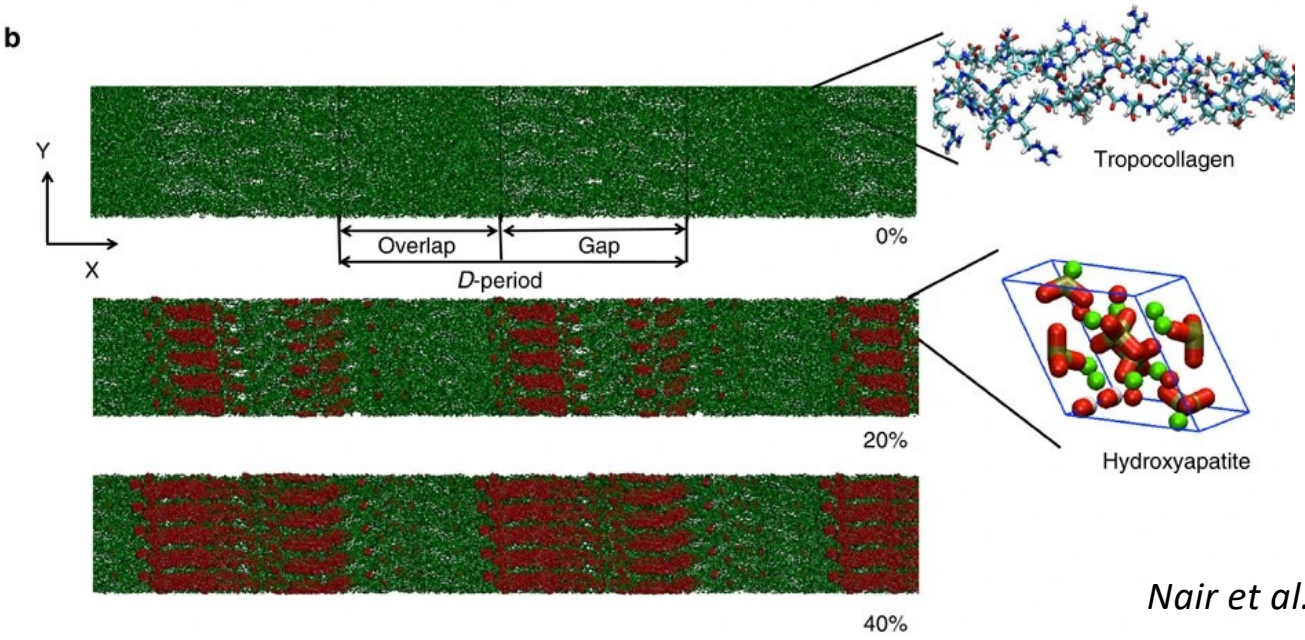


Nair et al. 2013. Nature Comms





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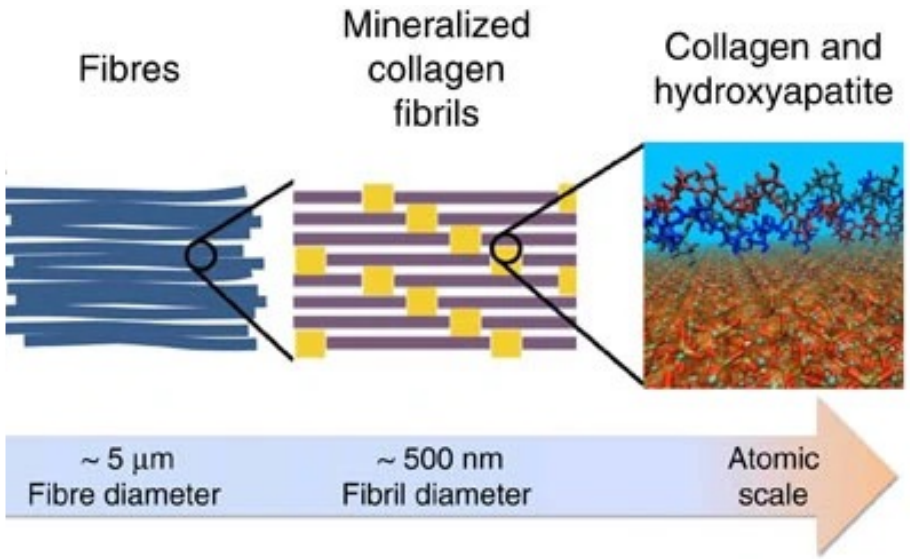

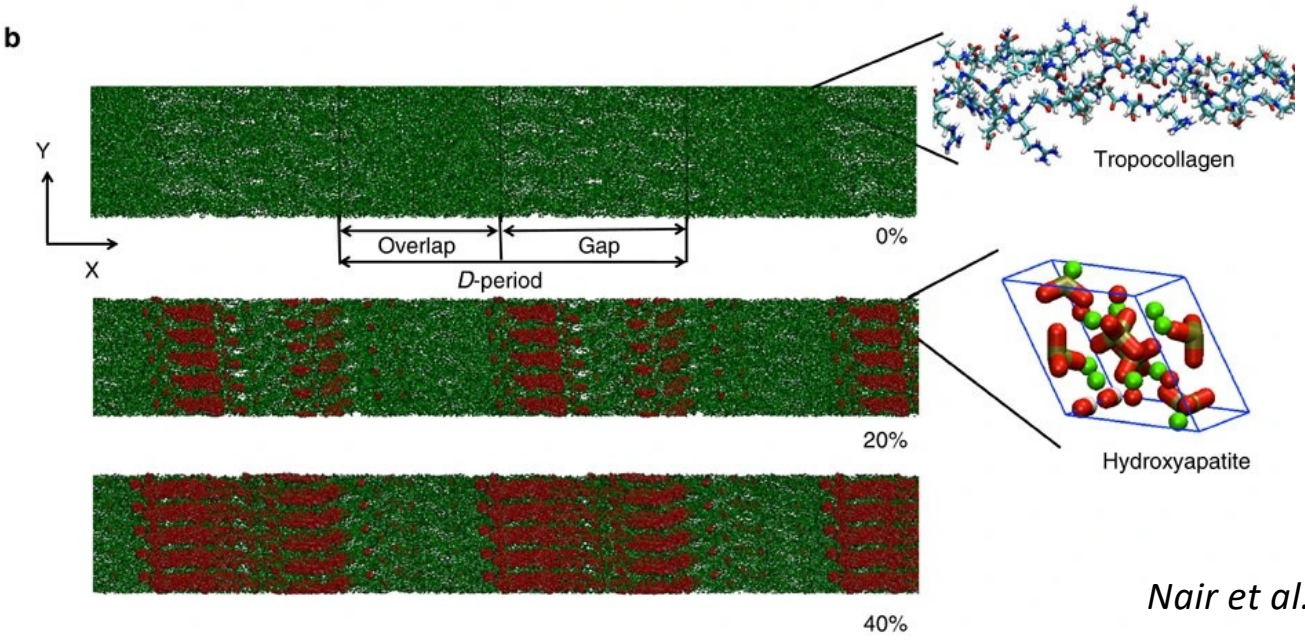

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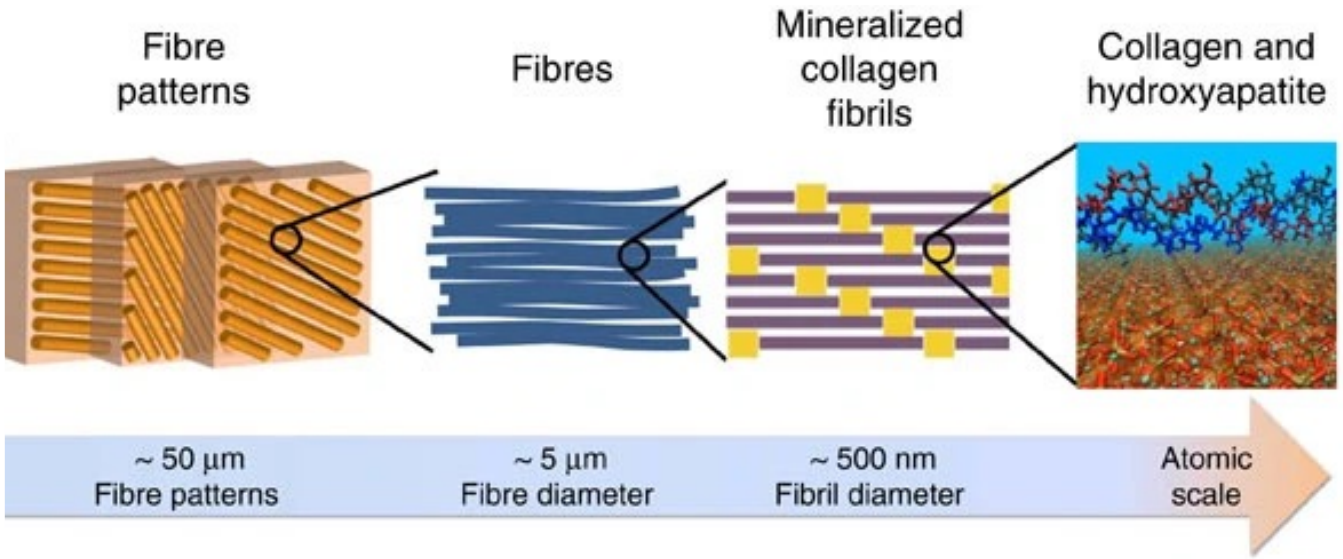

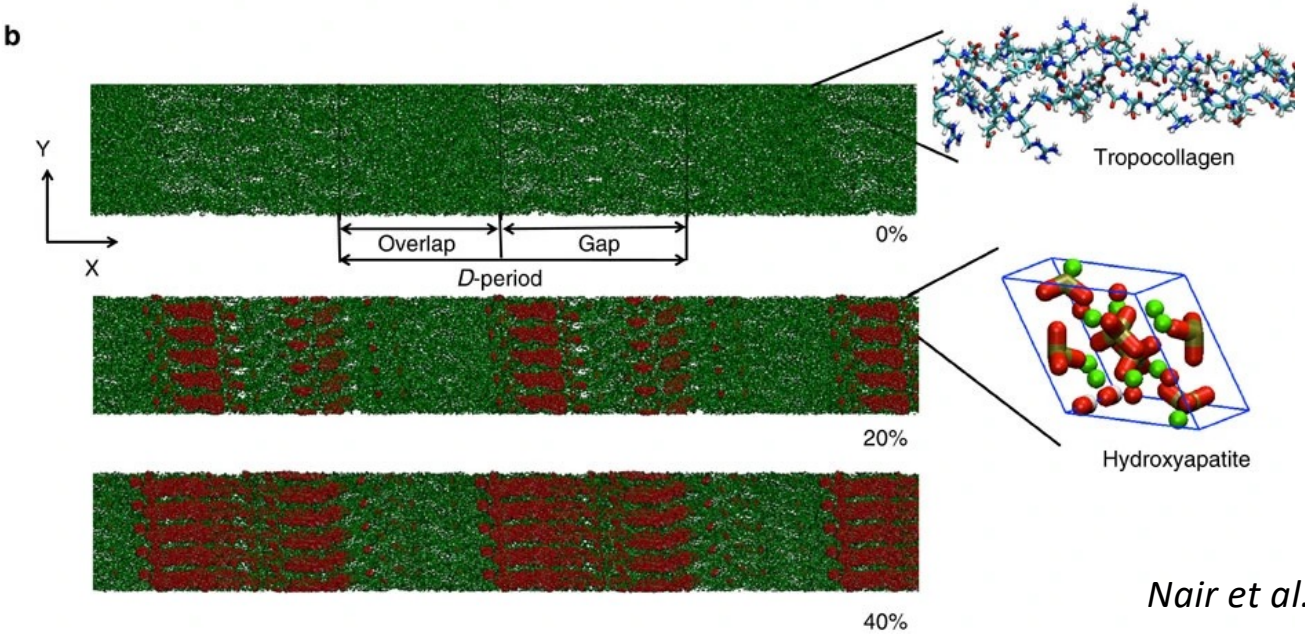

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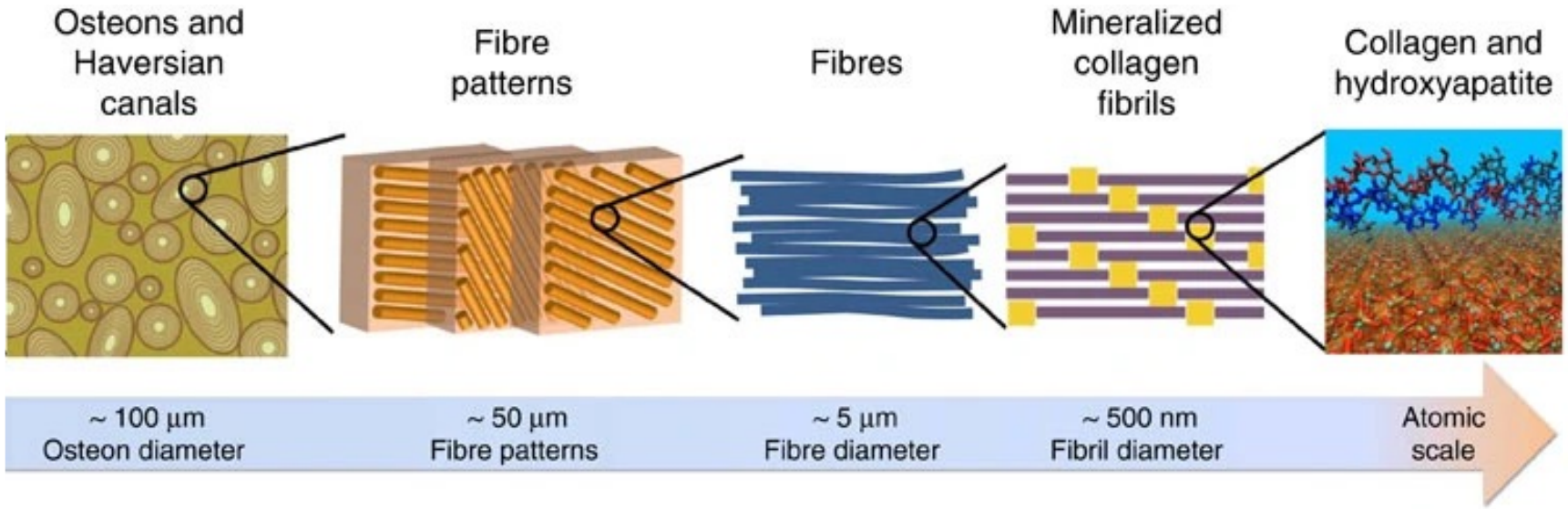

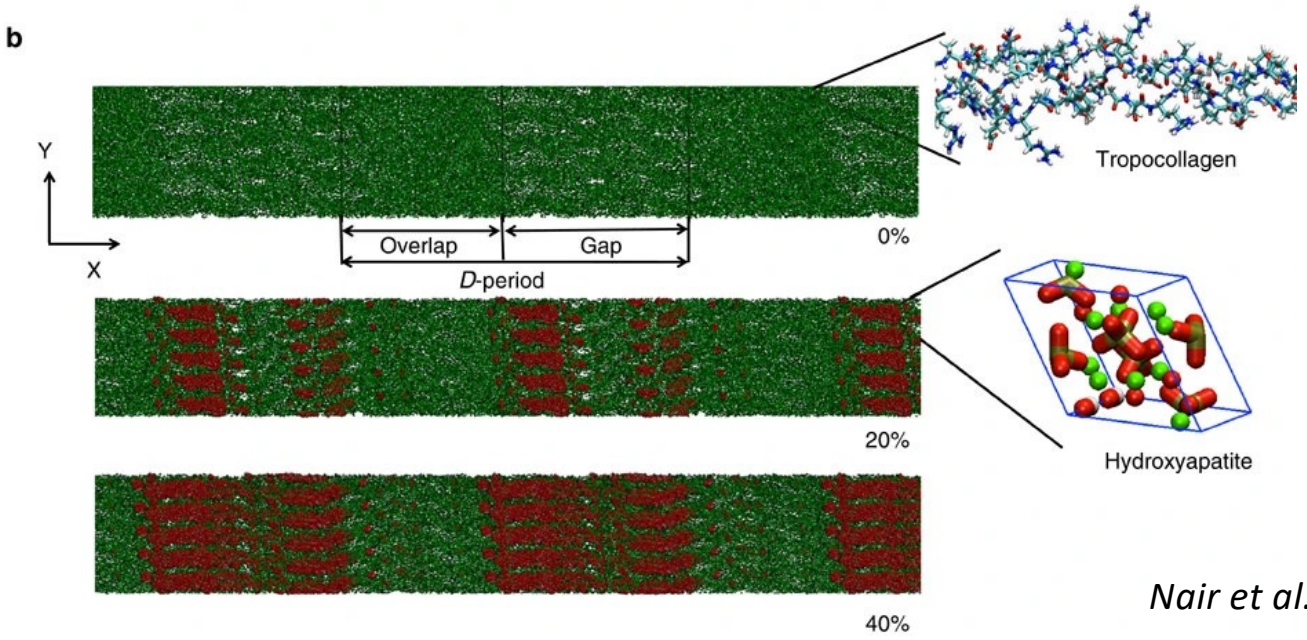

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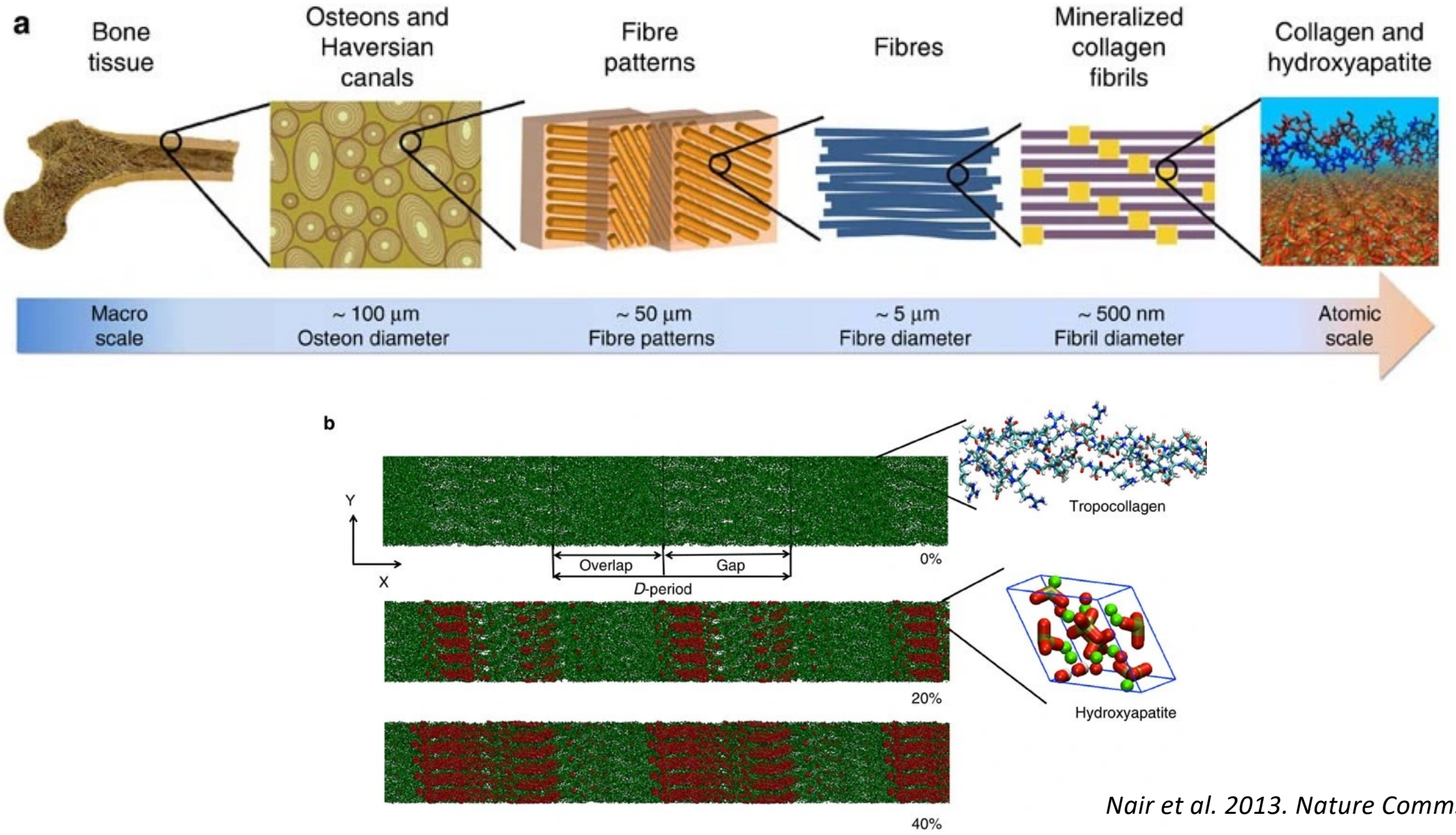

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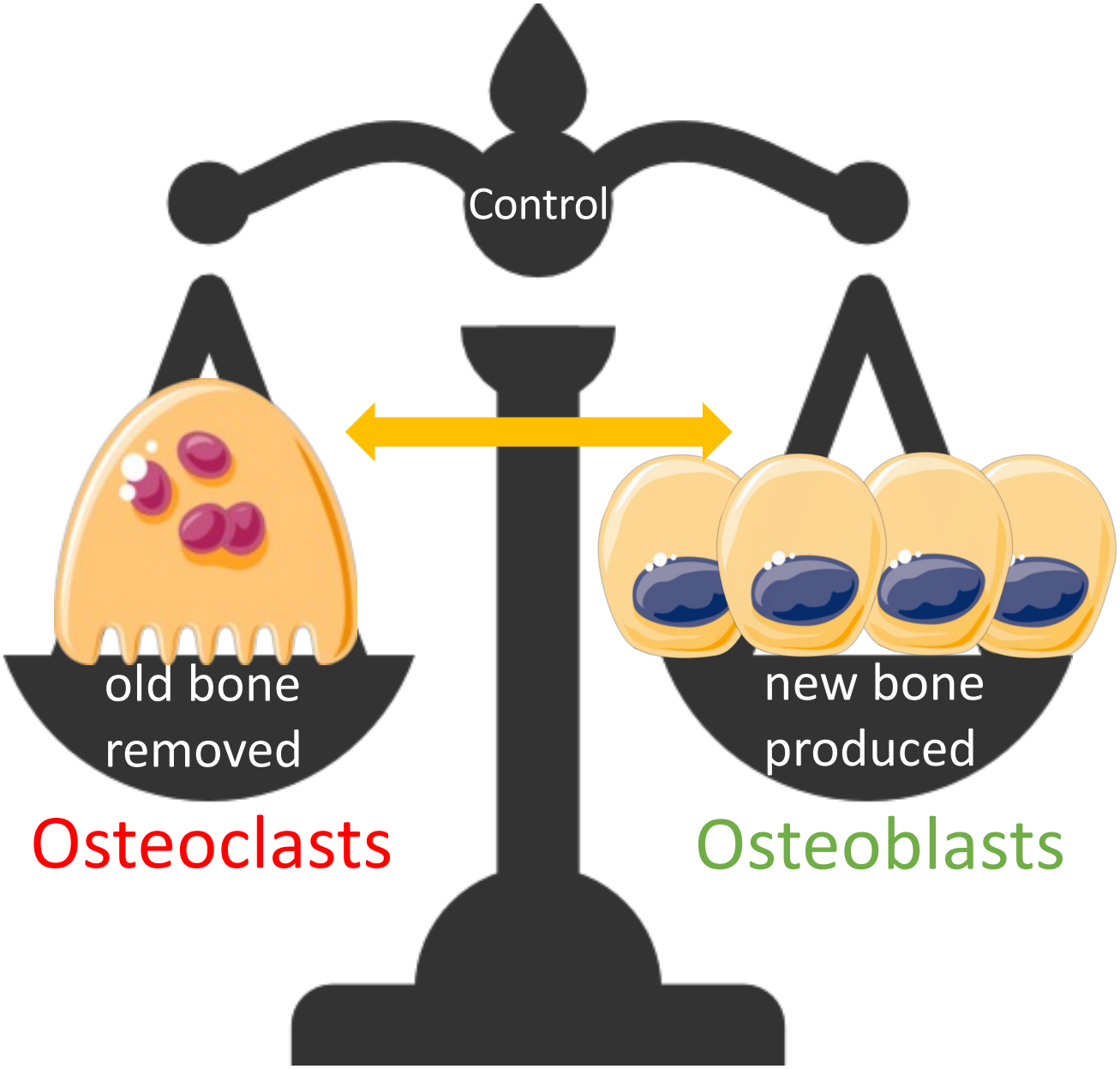
Control
old bone
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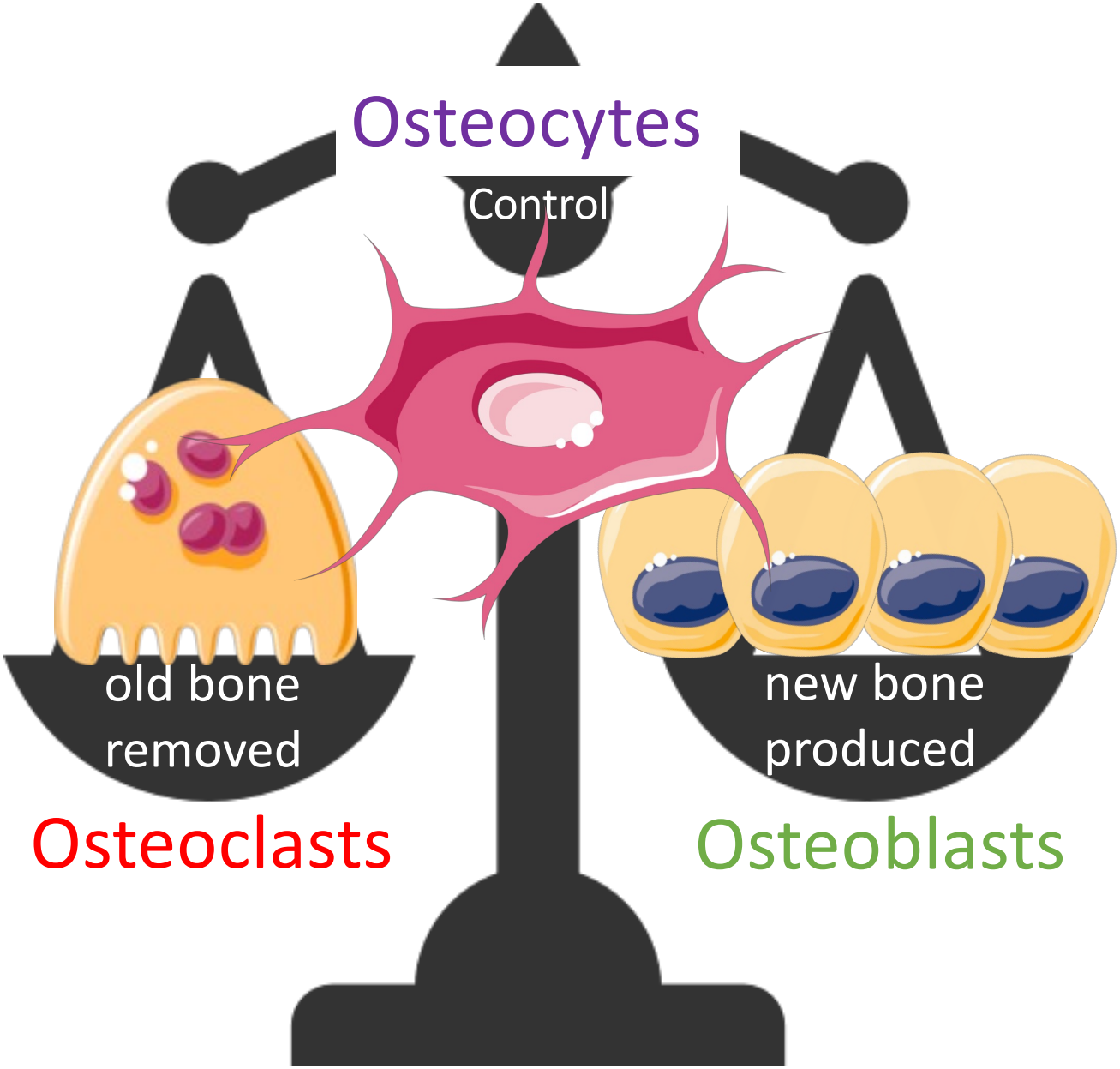
new bone
produced
Osteoclasts
Osteoblasts


Osteocytes
Control
old bone
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new bone
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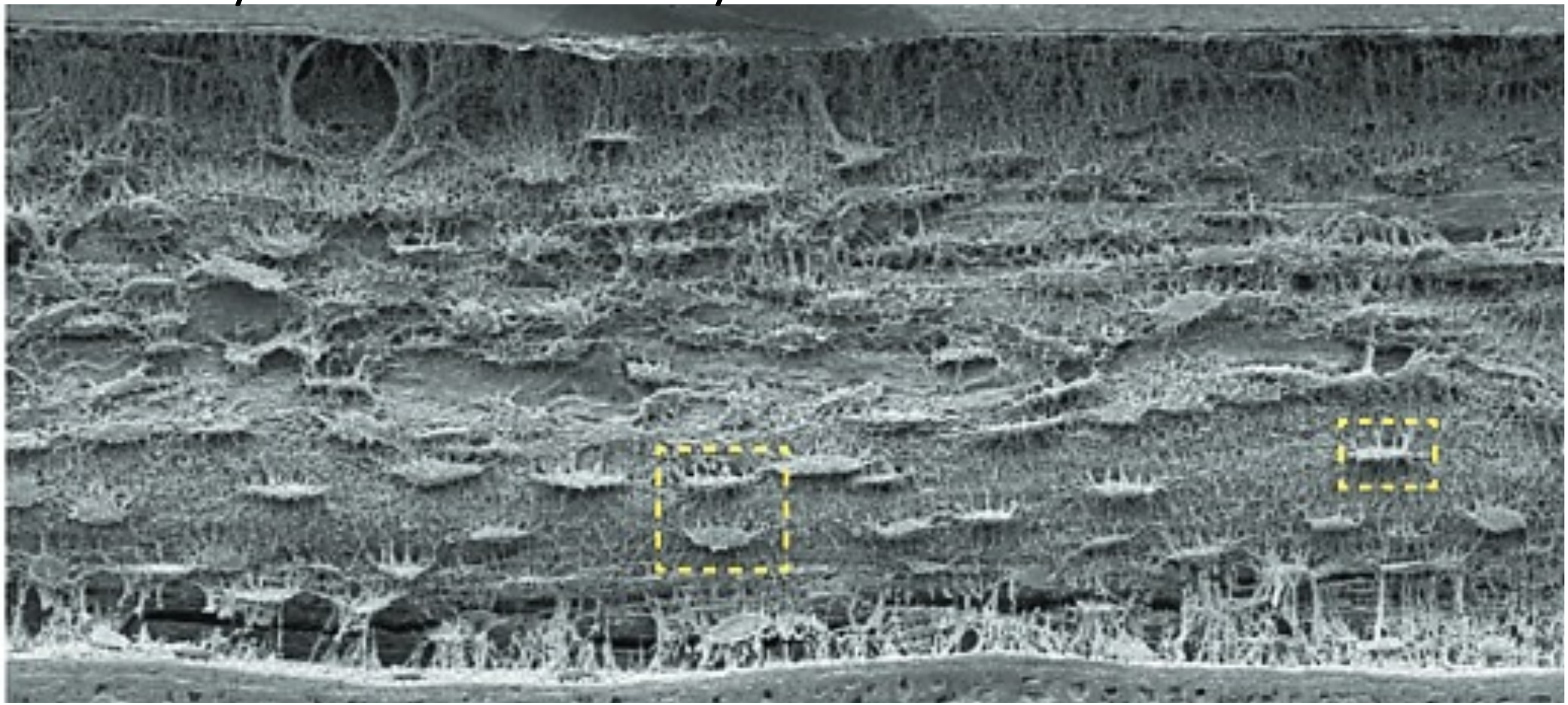
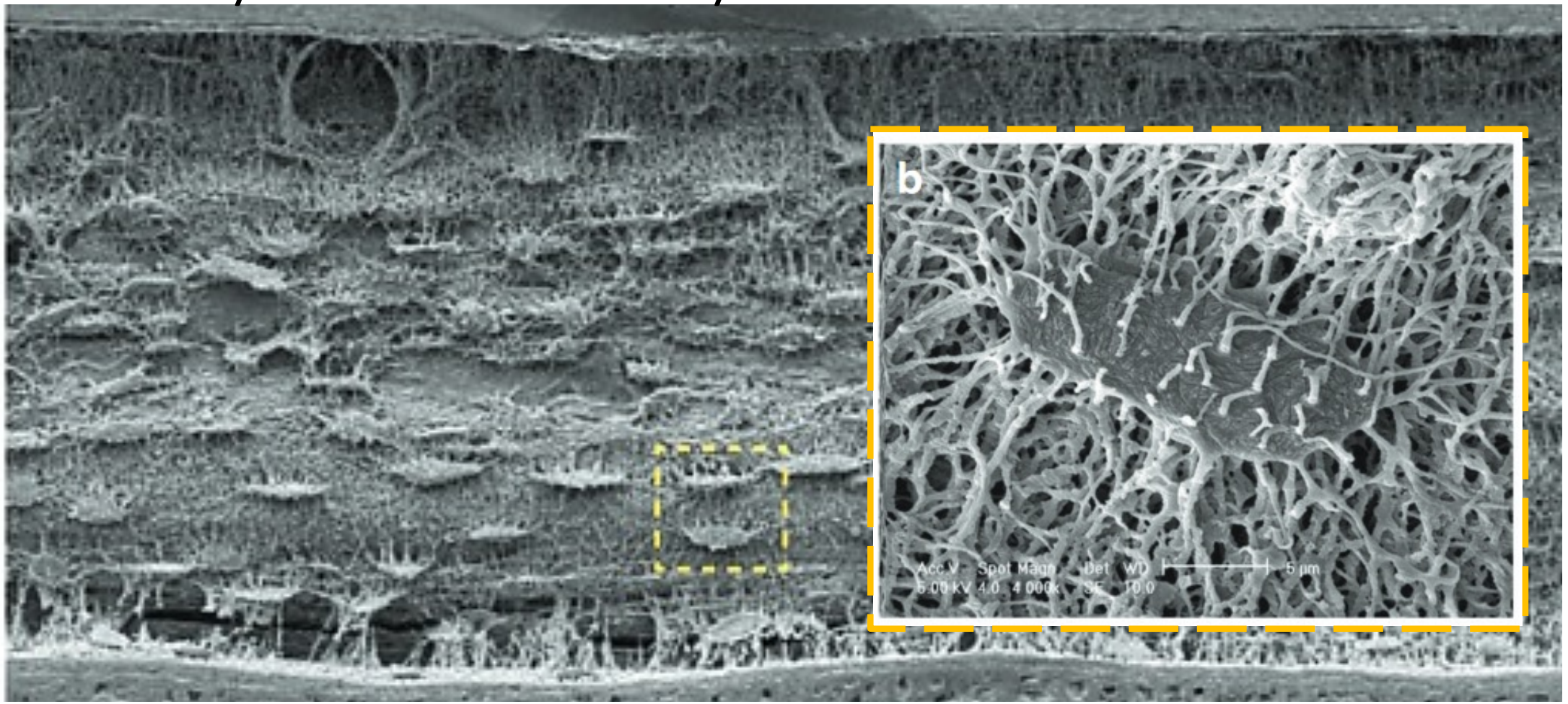
Osteocyte Connectivity



Bonewald et al. 2013

Osteocyte Connectivity



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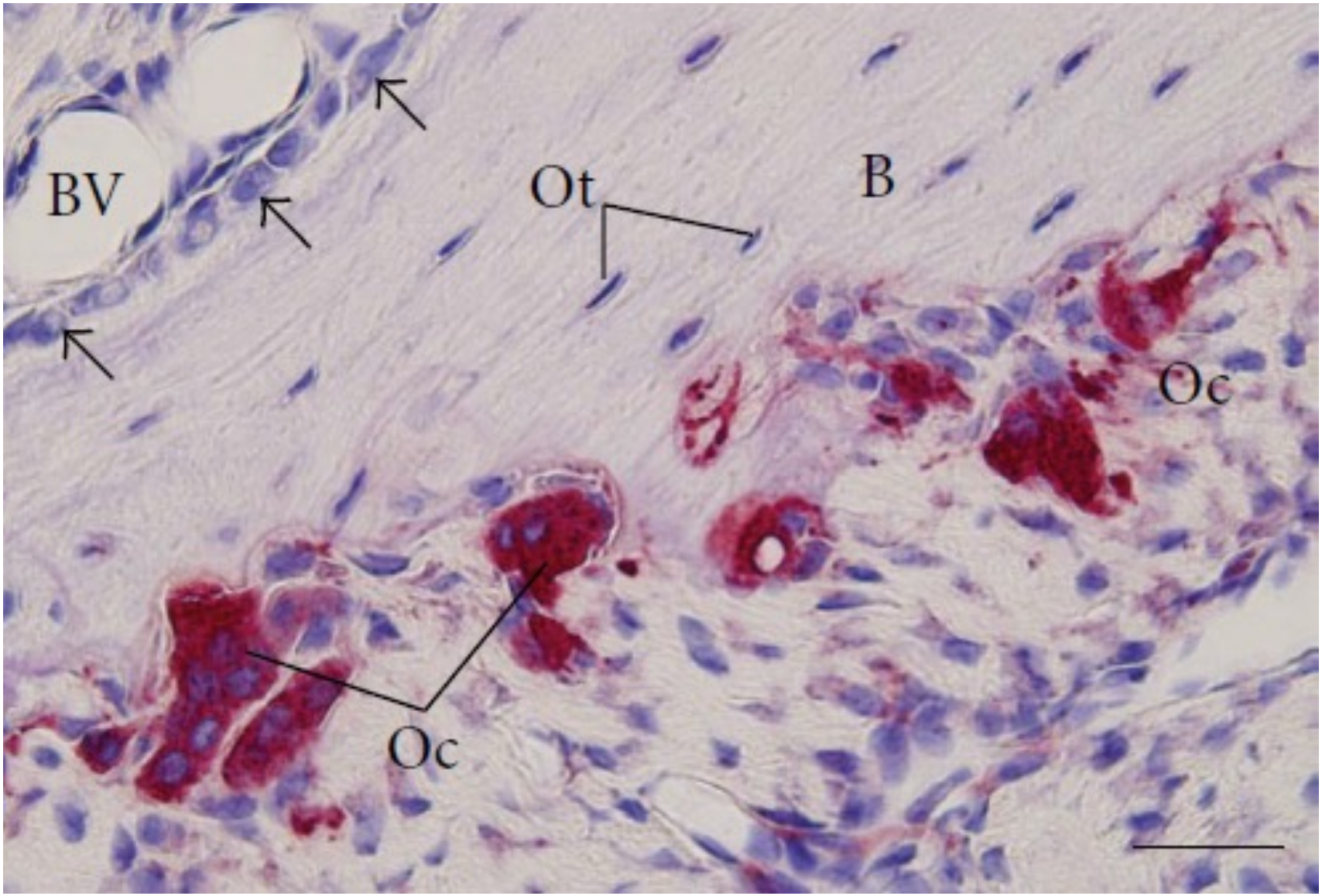
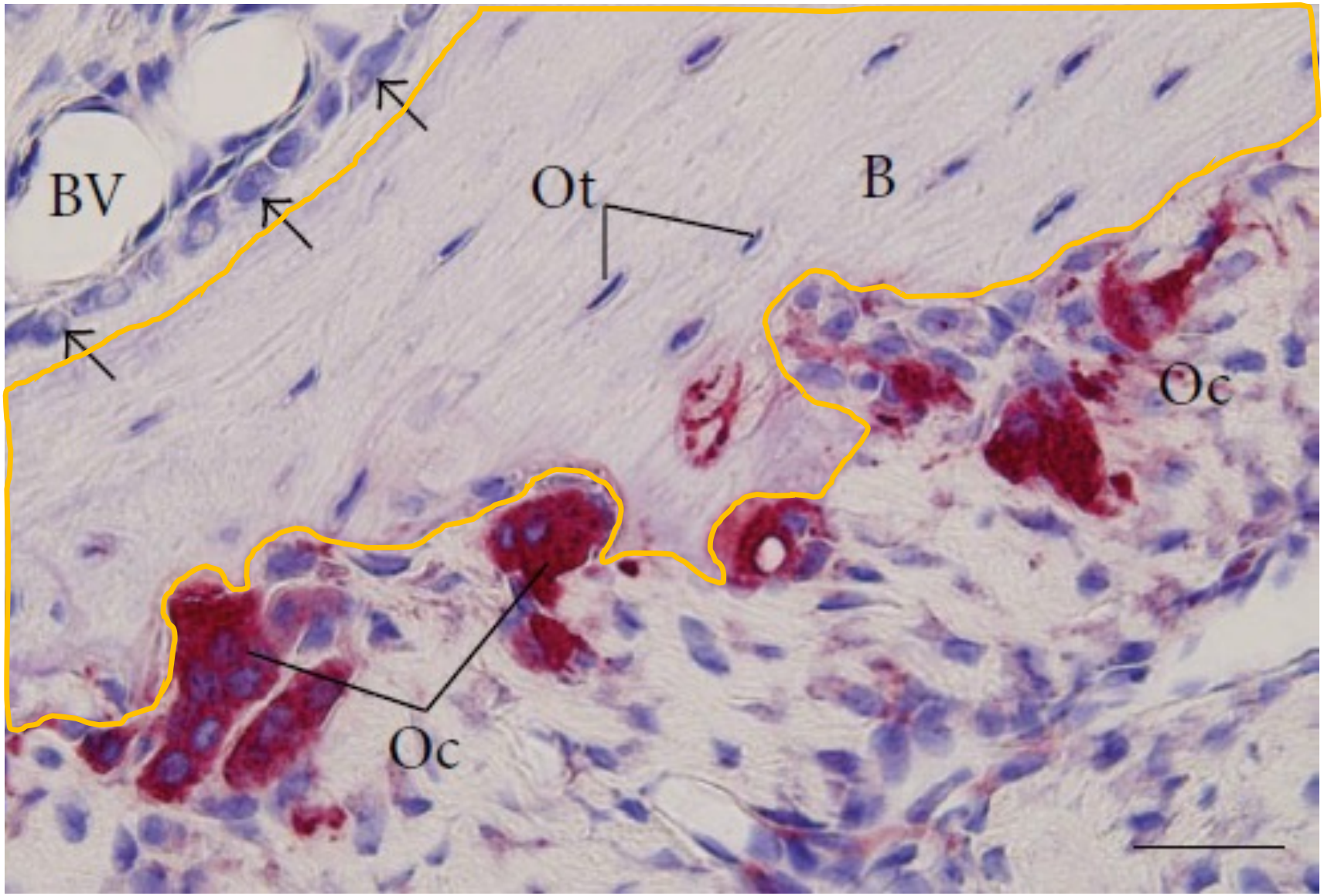


Florencio-Silva et al. 2015



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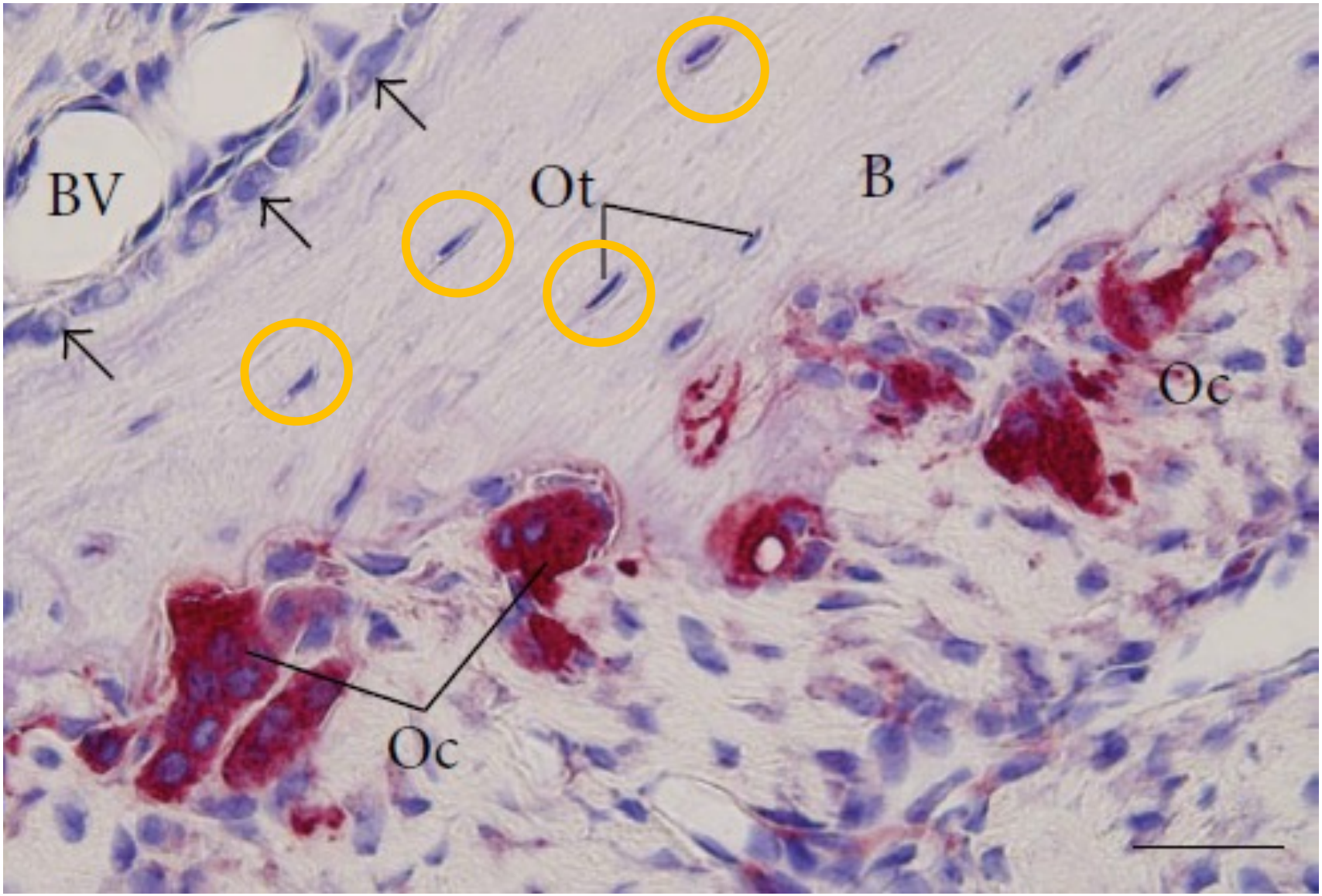

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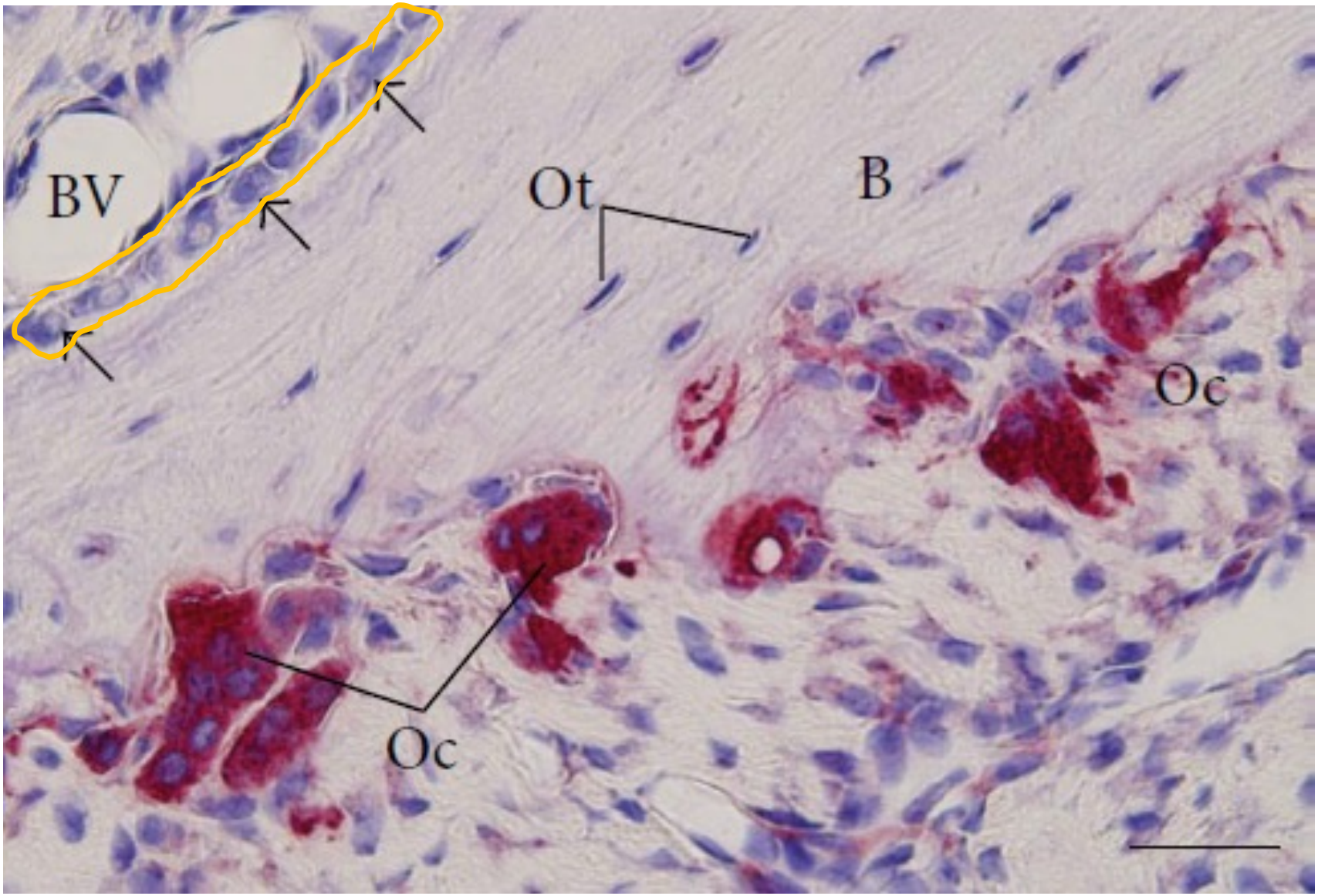

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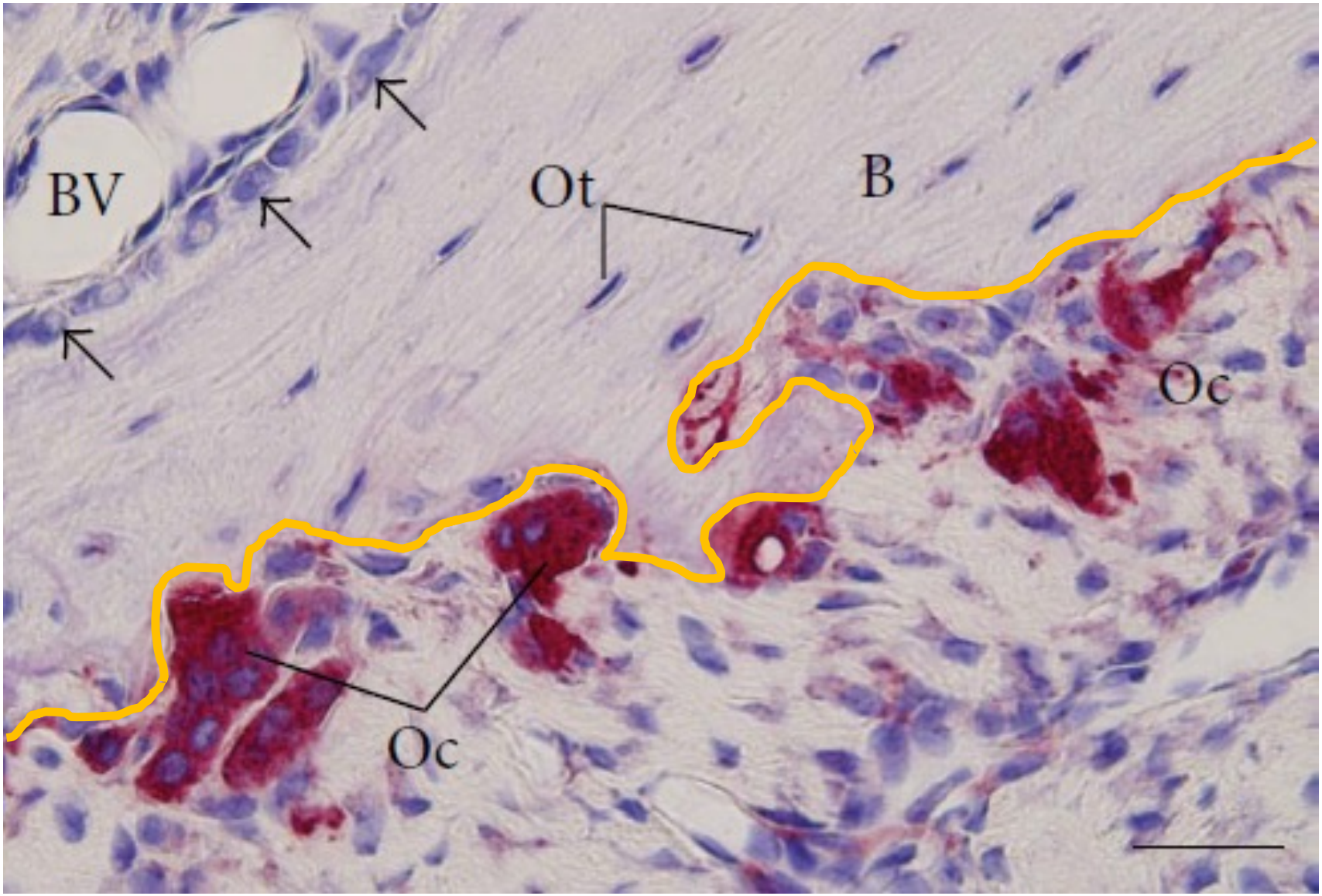

Florencio-Silva et al. 2015

Osteoporosis

Low bone mass/mineral density (measured by DEXA scan).

Increased risk of fracture from low impact falls/trauma

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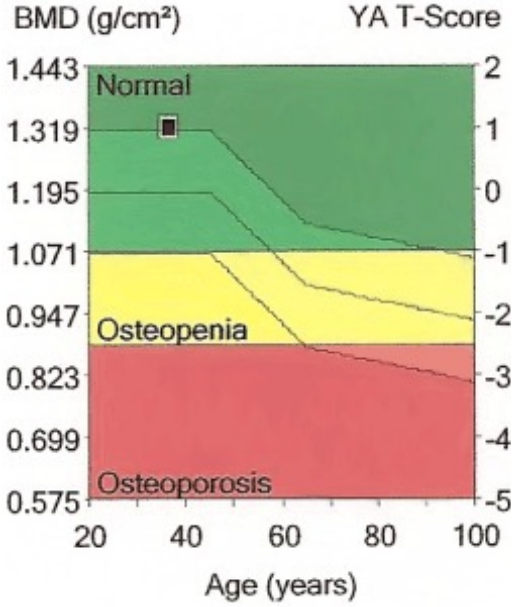
Low bone mass/mineral density (measured by DEXA scan).

Increased risk of fracture from low impact falls/trauma

T score > -1.0 S.D	Normal bone mineral density
T score between -1.0 and -2.5 SD	Osteopenia
T score ≤ - 2.5 SD	Osteoporosis
T score ≤ - 2.5 SD with 1 or more fragility fractures	Severe osteoporosis

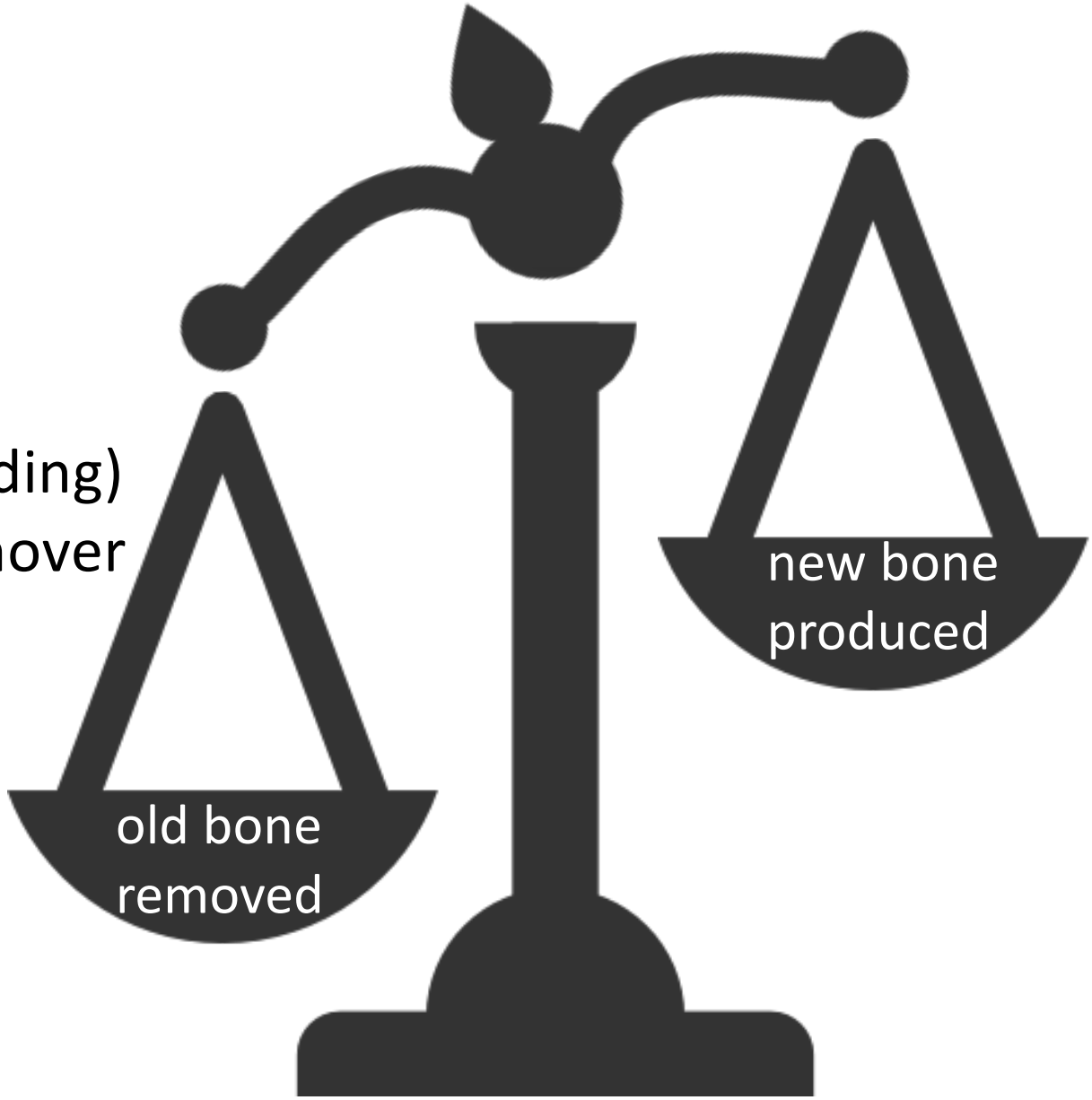


- DEXA T-Score
  - T score is the number of standard deviations away from a young healthy adult

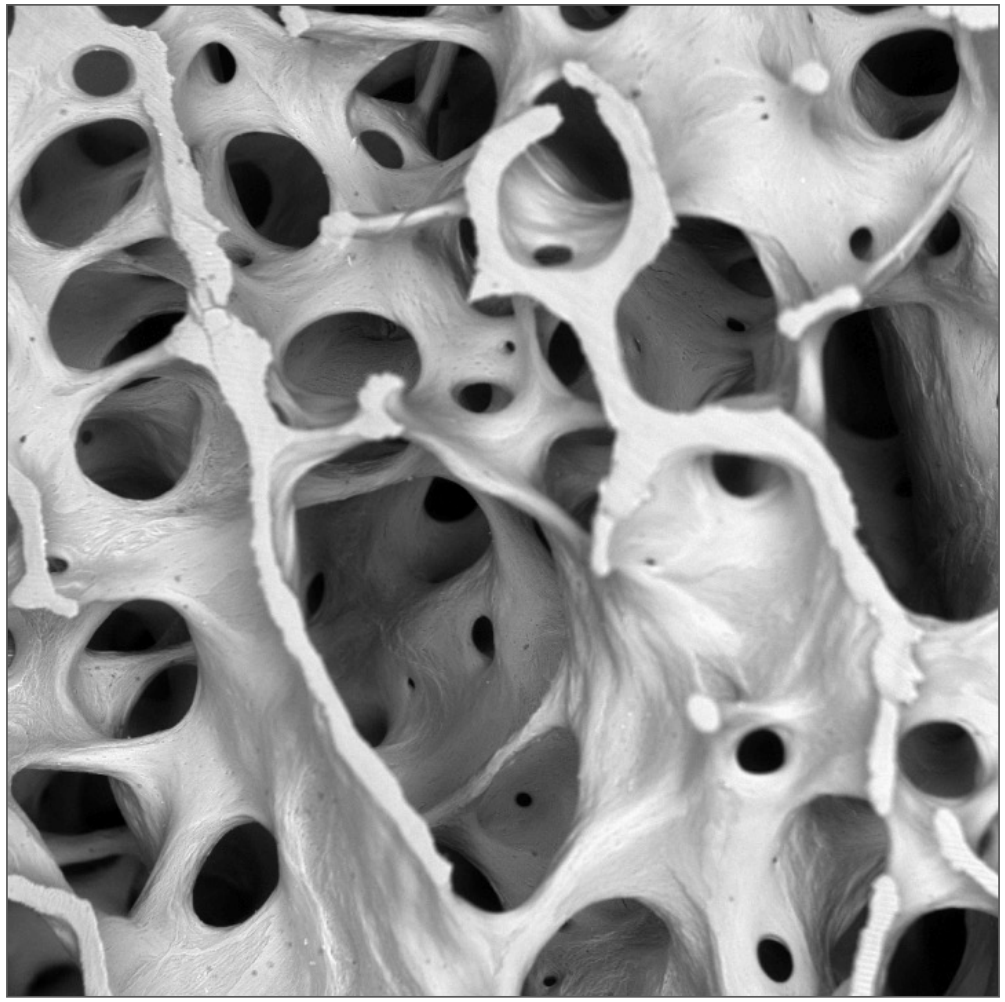
Osteoporosis

Caused by:

- Hormonal changes
- Reduced physical activity (loading)
- Errant regulation of bone turnover



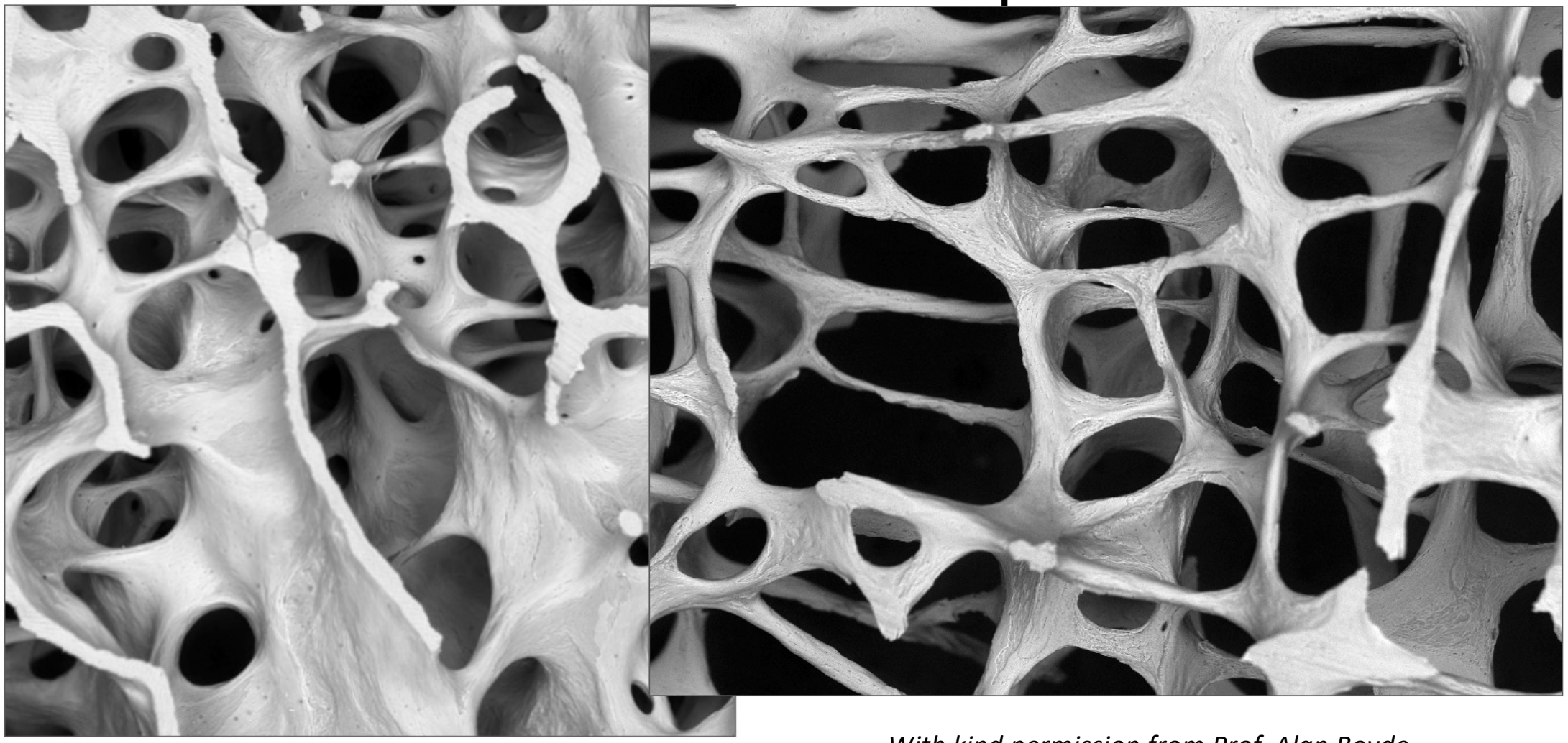
Normal bone



With kind permission from Prof. Alan Boyde

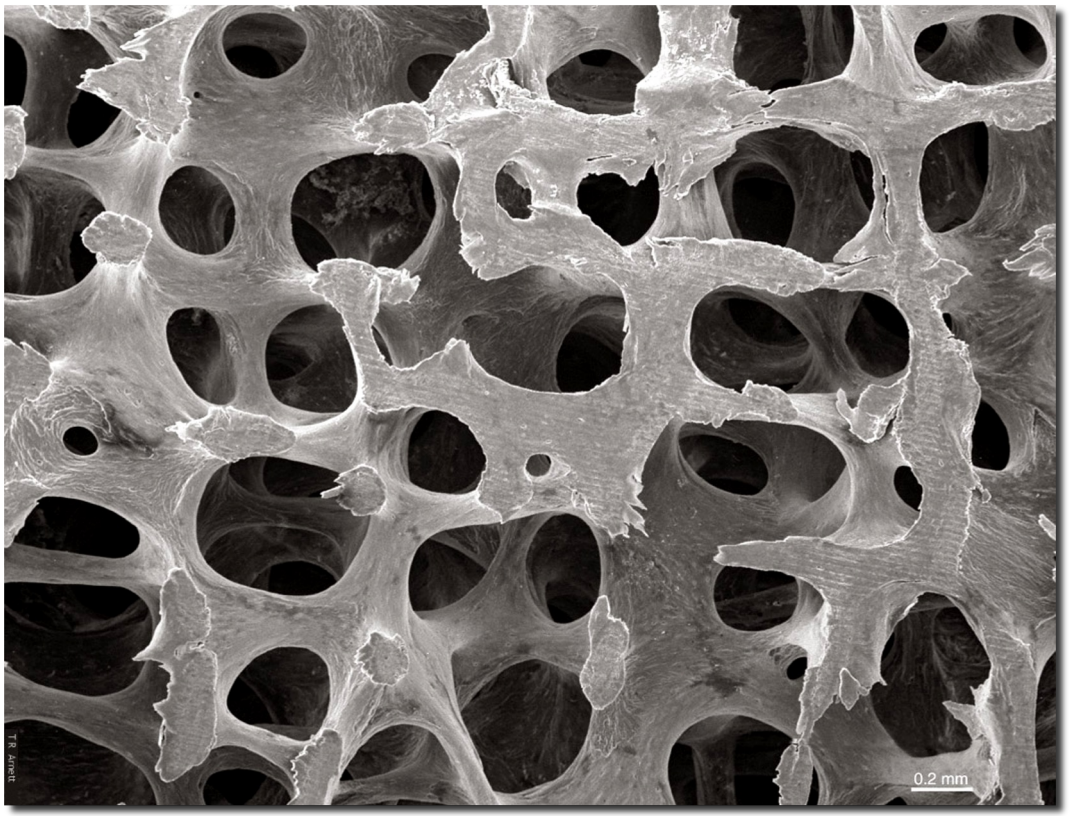
Normal bone

Osteoporotic bone

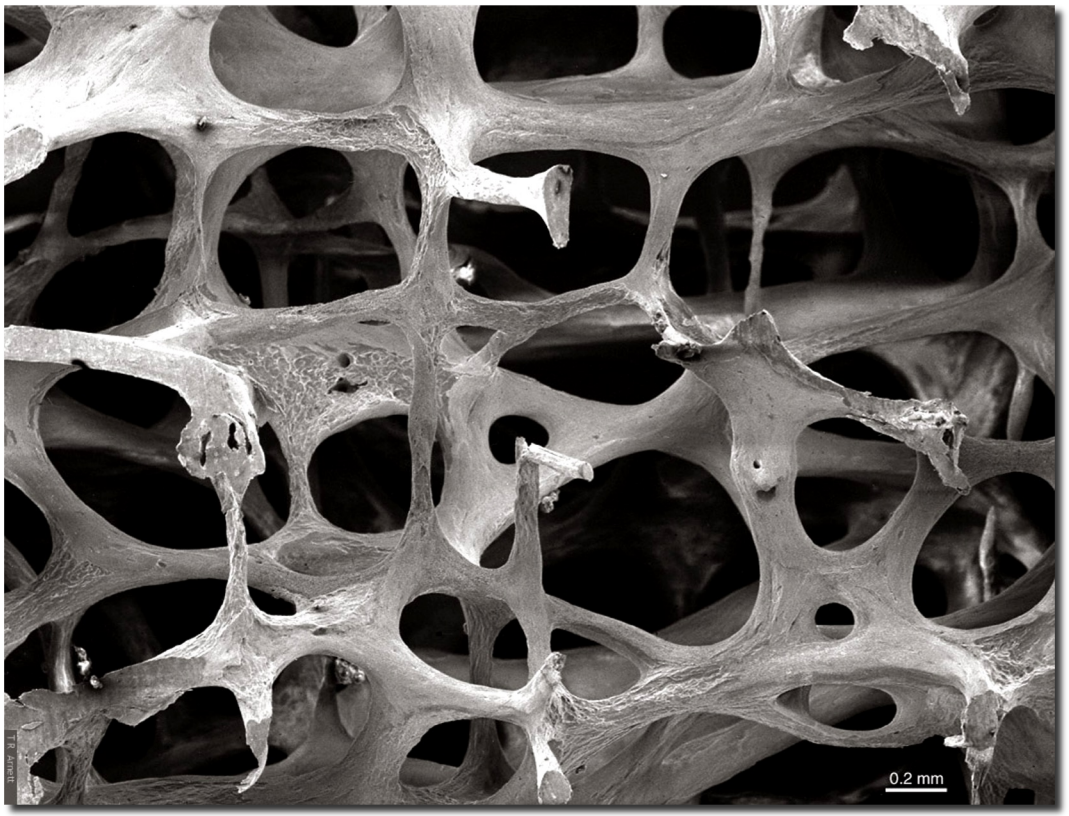


With kind permission from Prof. Alan Boyde

Normal bone



Osteoporotic bone



With kind permission from Prof. Tim Arnett

Osteoporosis most commonly affects:

- Postmenopausal women
- Men over 50
- Patients taking long term corticosteroids

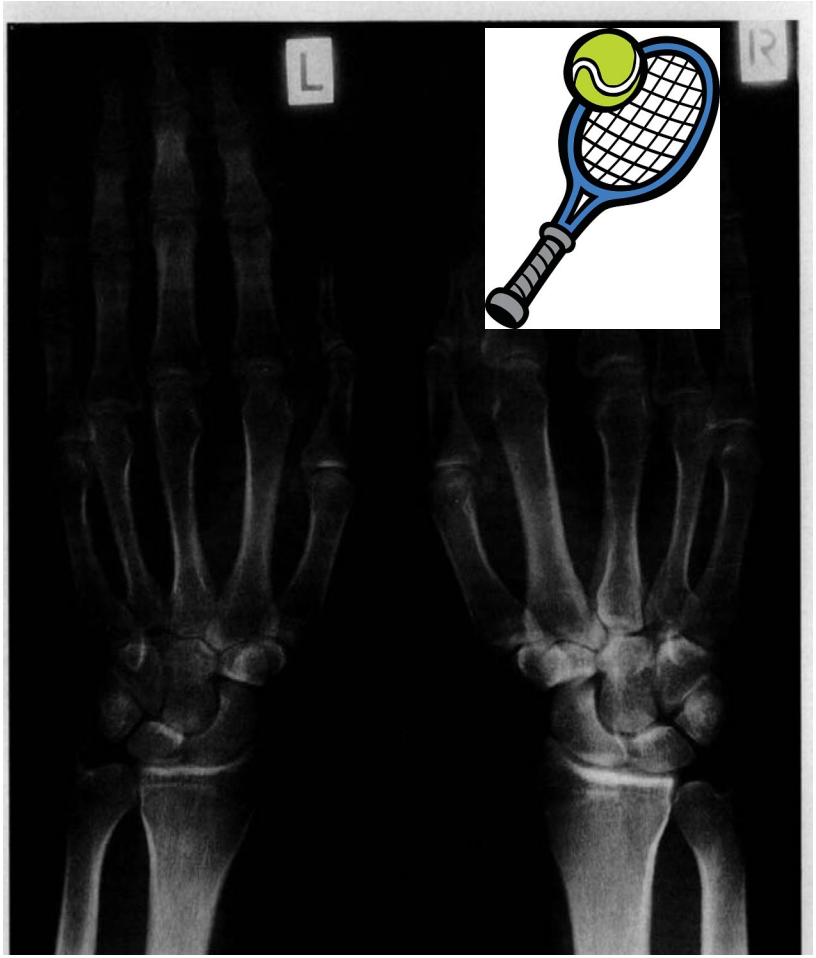
Other risk factors include:

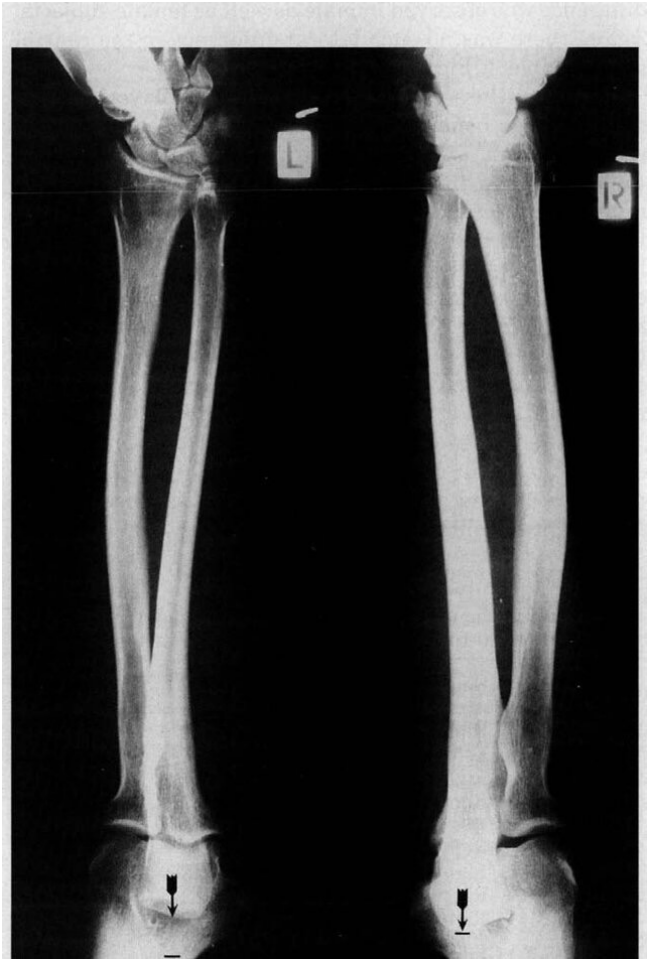
- Smoking and/or excess alcohol intake
- Vitamin D or calcium deficiency
- Rheumatoid arthritis, diabetes, anorexia

Disuse loses bone

Loss of 2% bone mass every month in space or with bed rest

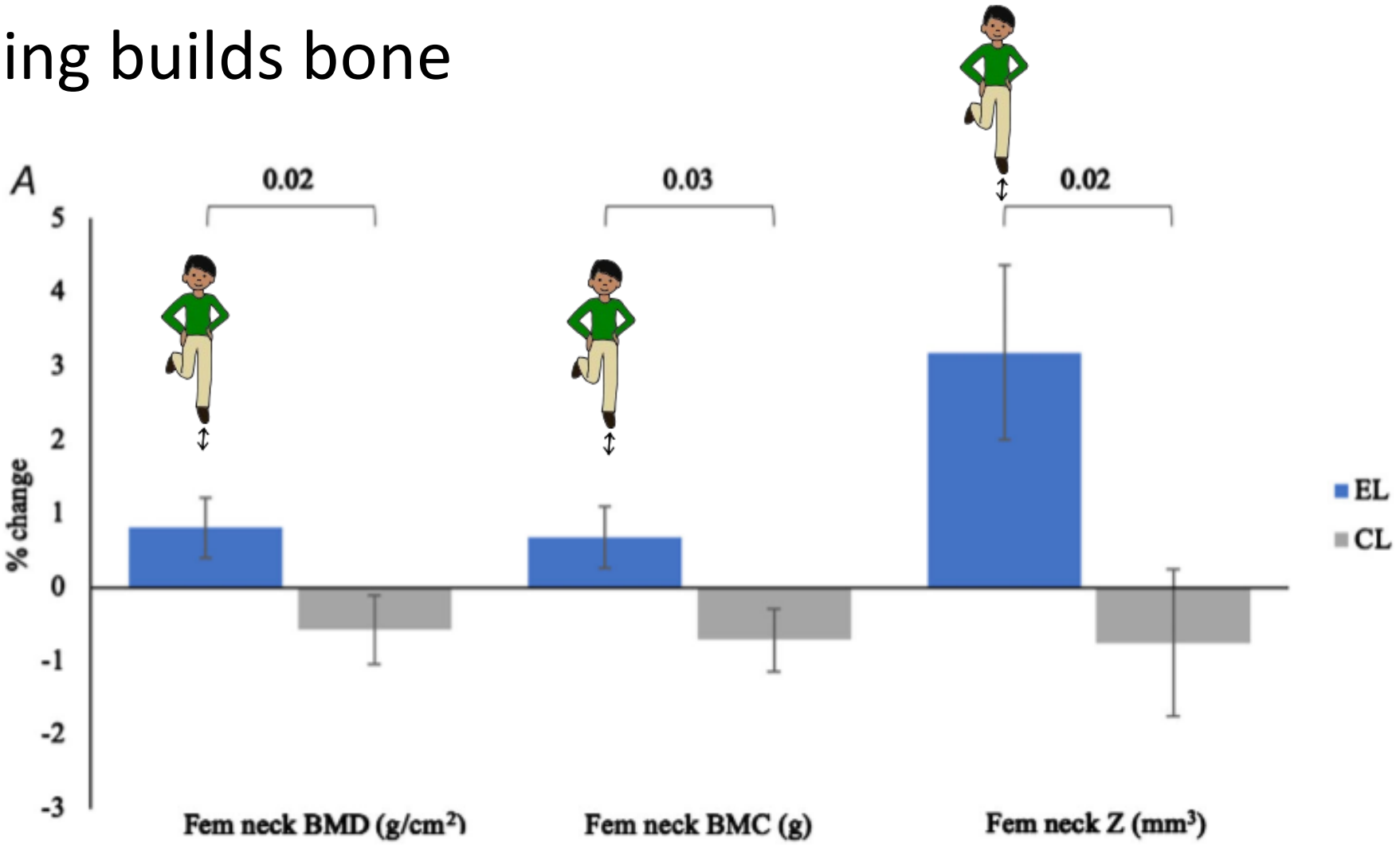
Loading builds bone





Krahl et al. 1994. American Journal of Sports Medicine

Loading builds bone



Hartley et al. 2019. JMBR

Hopping (50 hops daily on one leg) for 6 months. Postmenopausal women

Tips to reduce the risk of osteoporosis

1. Weight bearing exercise

Tips to reduce the risk of osteoporosis

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2. Weight bearing exercise

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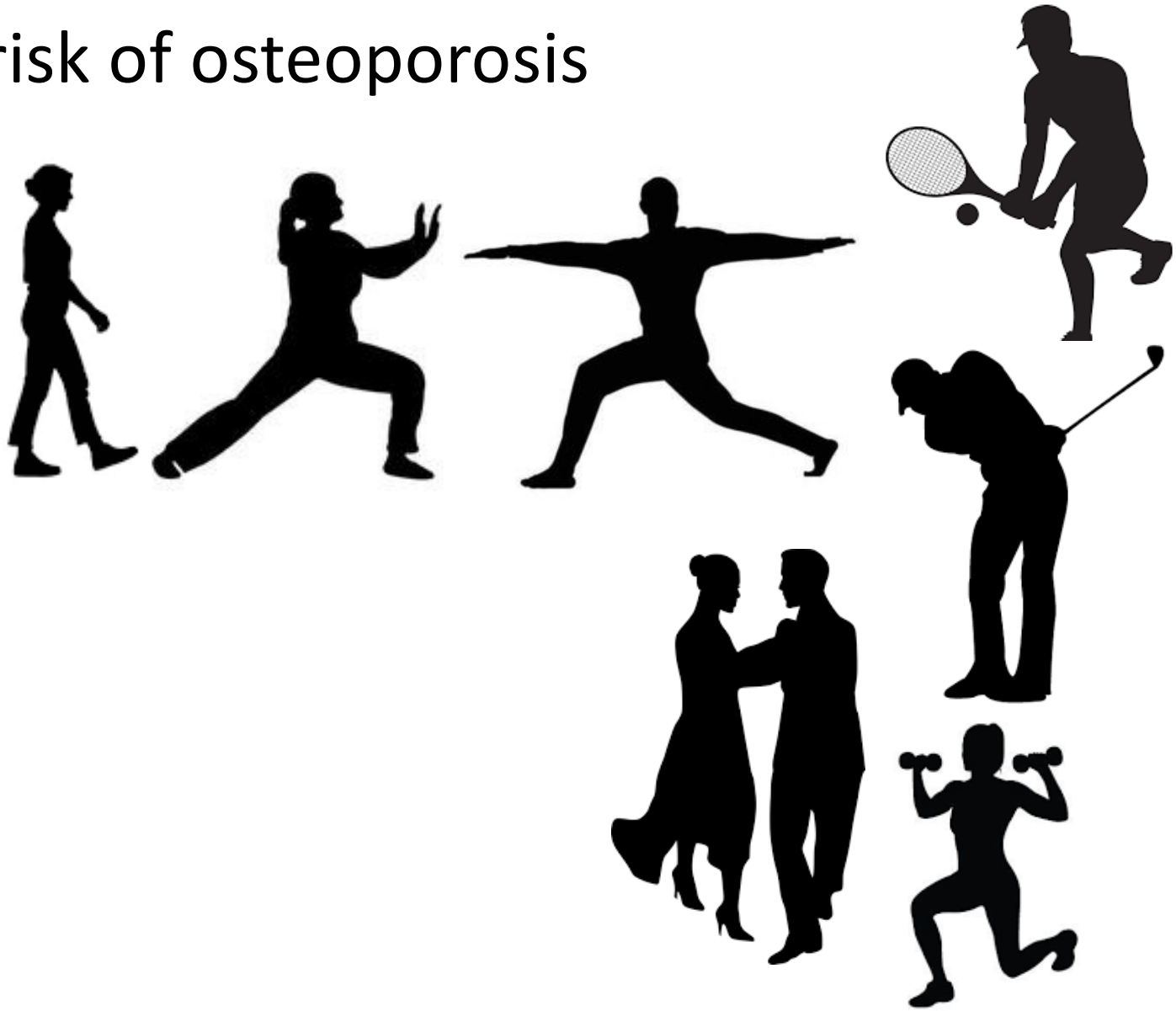

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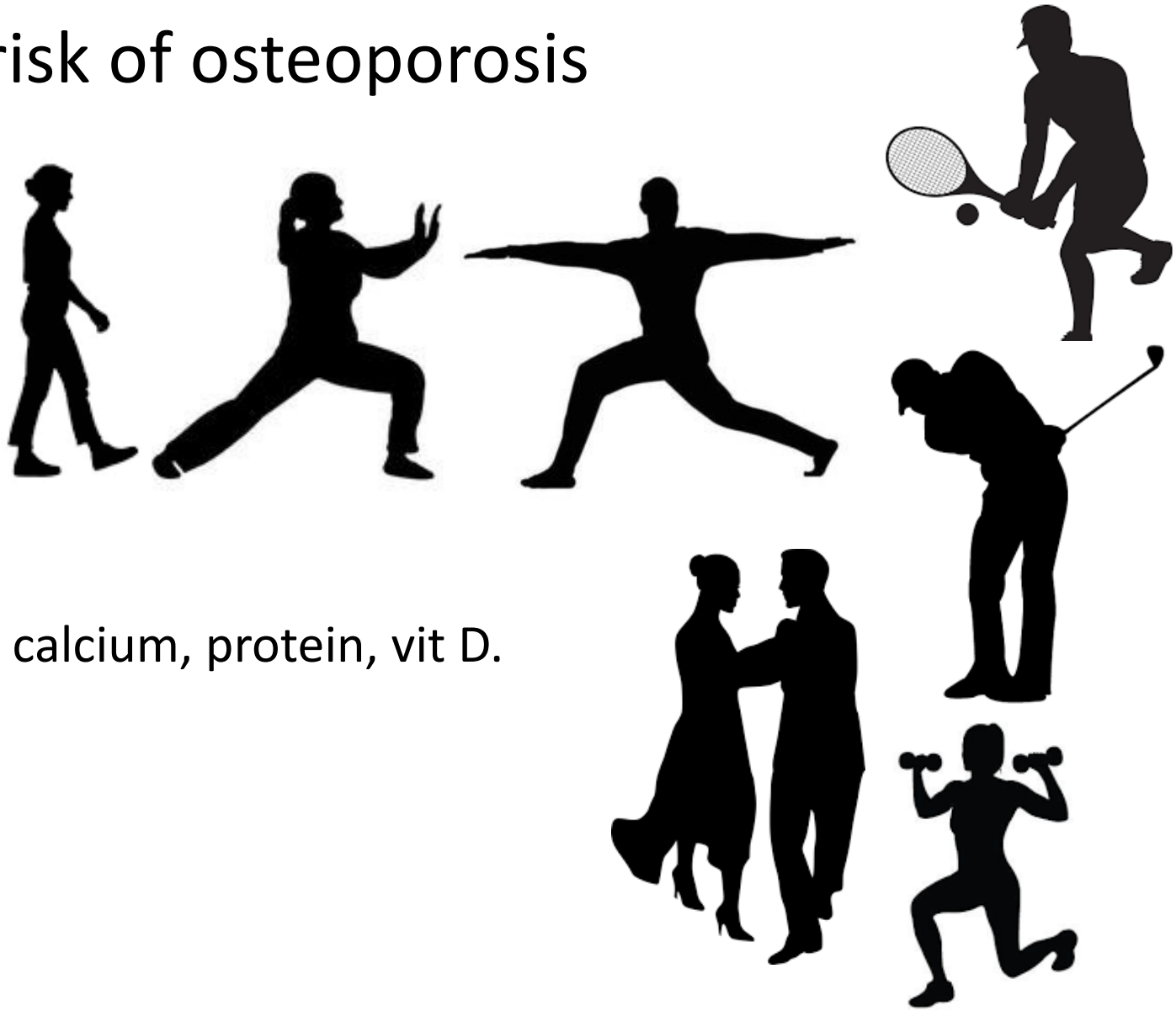

Also important:

1. Adequate nutrition e.g., calcium, protein, vit D.

Tips to reduce the risk of osteoporosis

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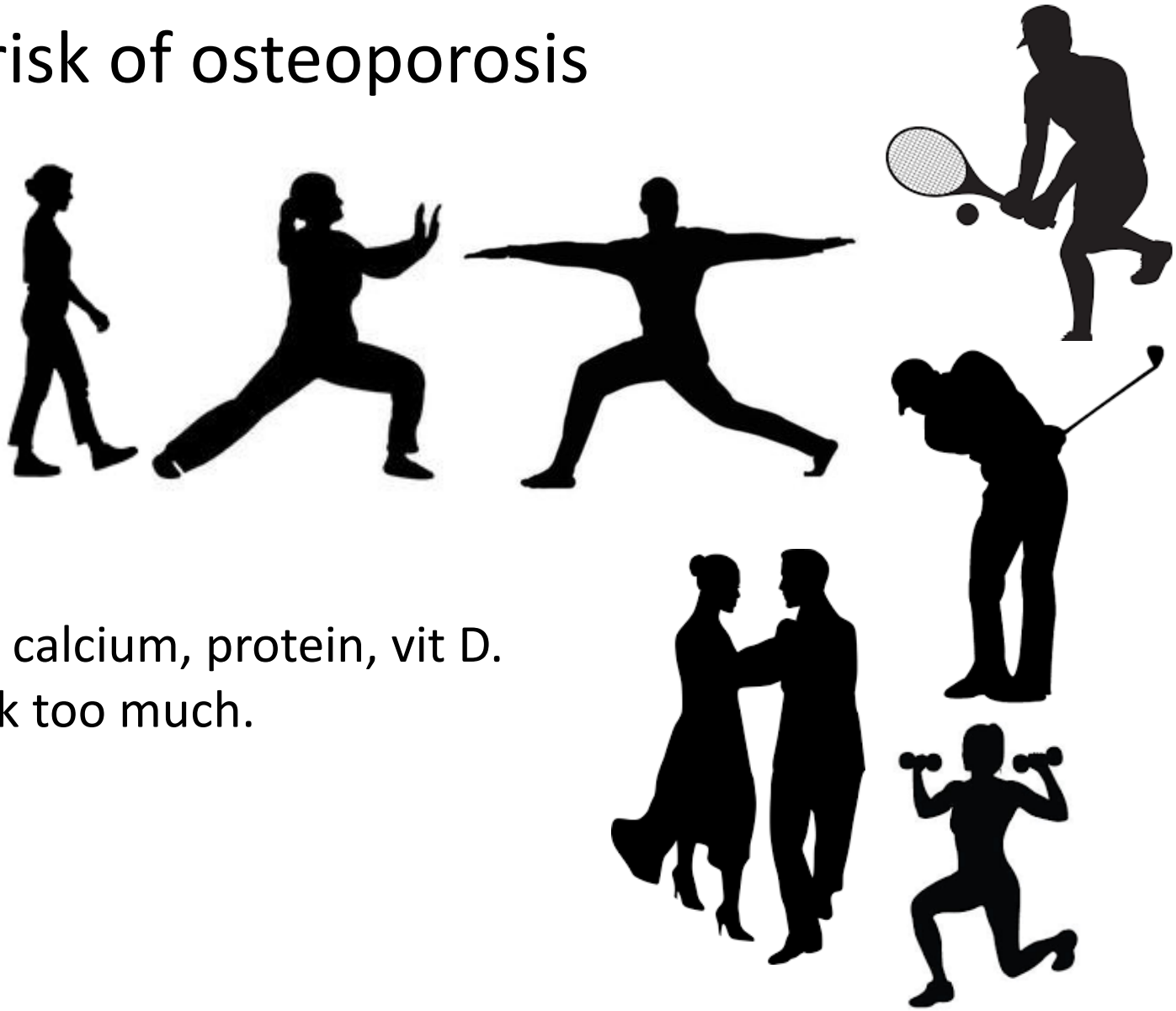

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Tips to reduce the risk of osteoporosis

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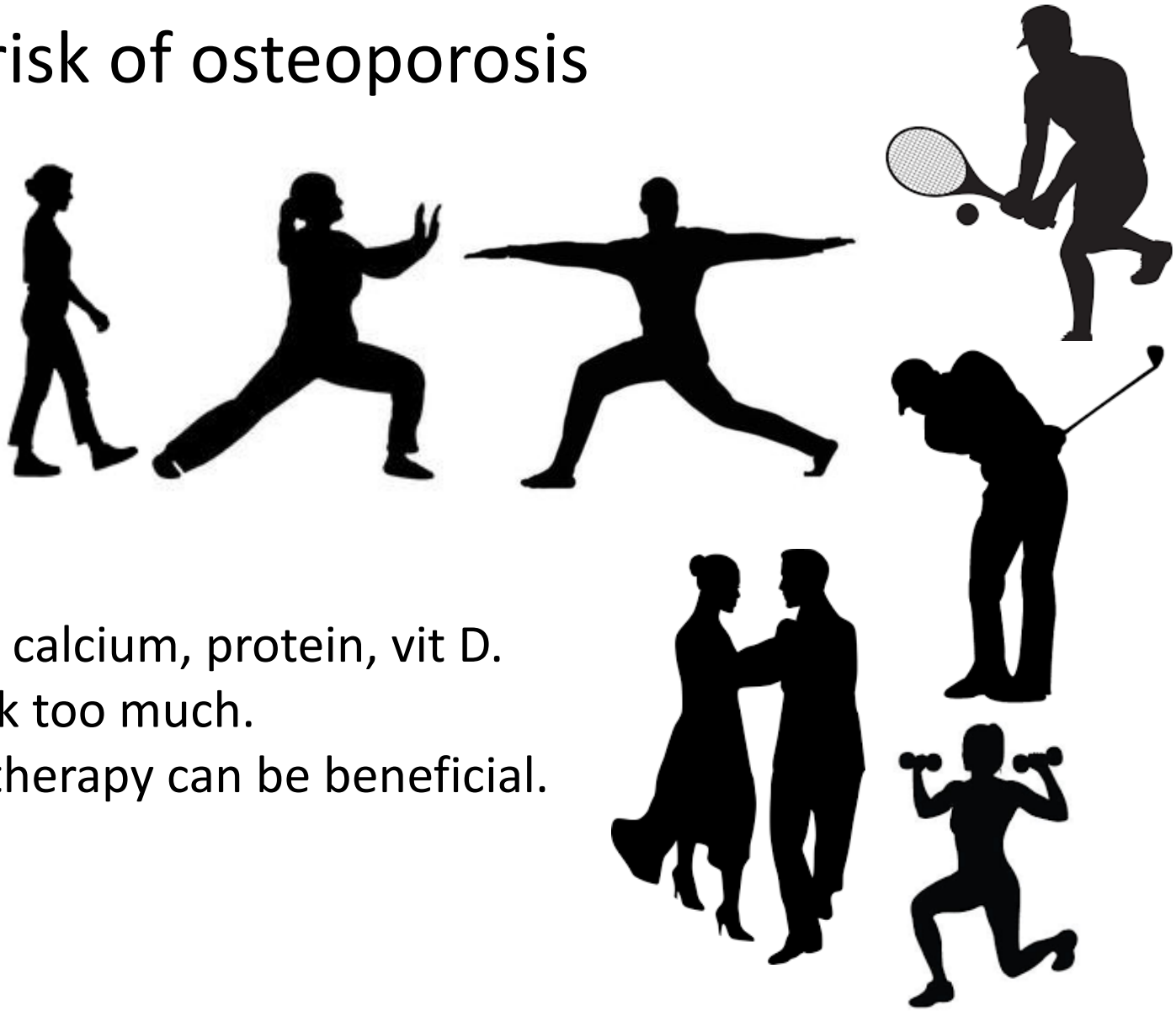
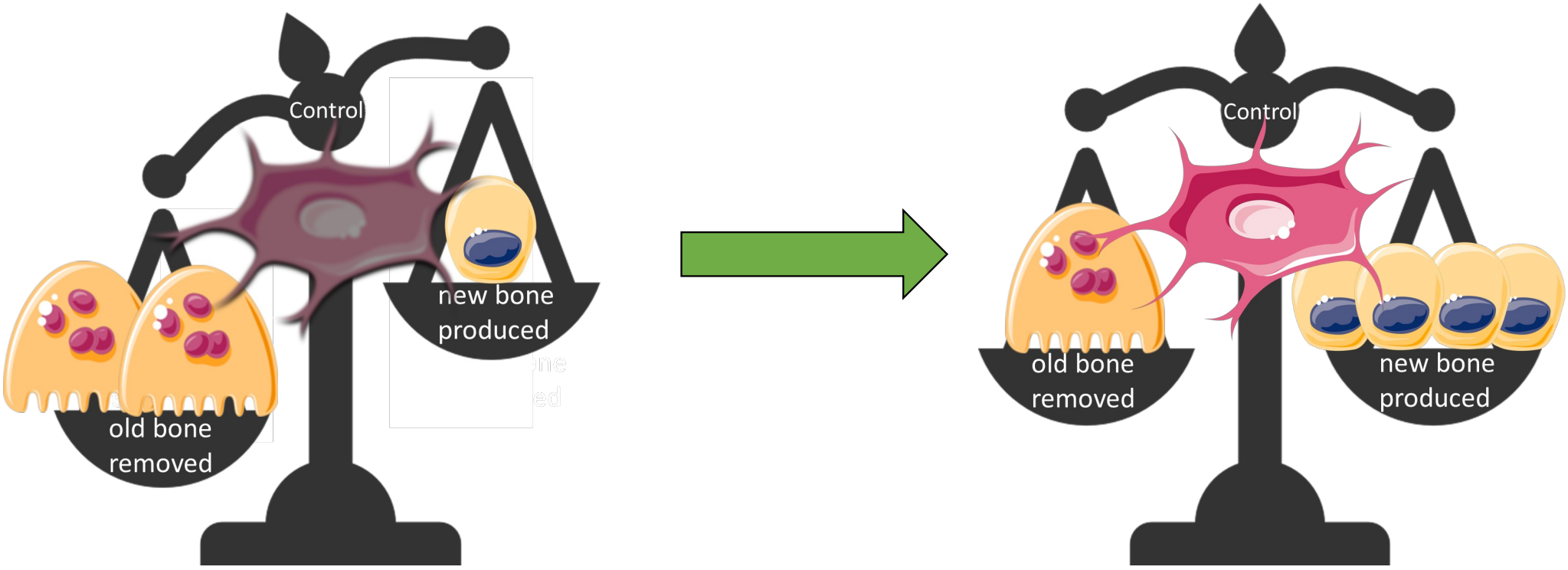


Also important:

1. Adequate nutrition e.g., calcium, protein, vit D.
2. Don’t smoke, don’t drink too much.
3. Hormone replacement therapy can be beneficial.

Medications to treat osteoporosis



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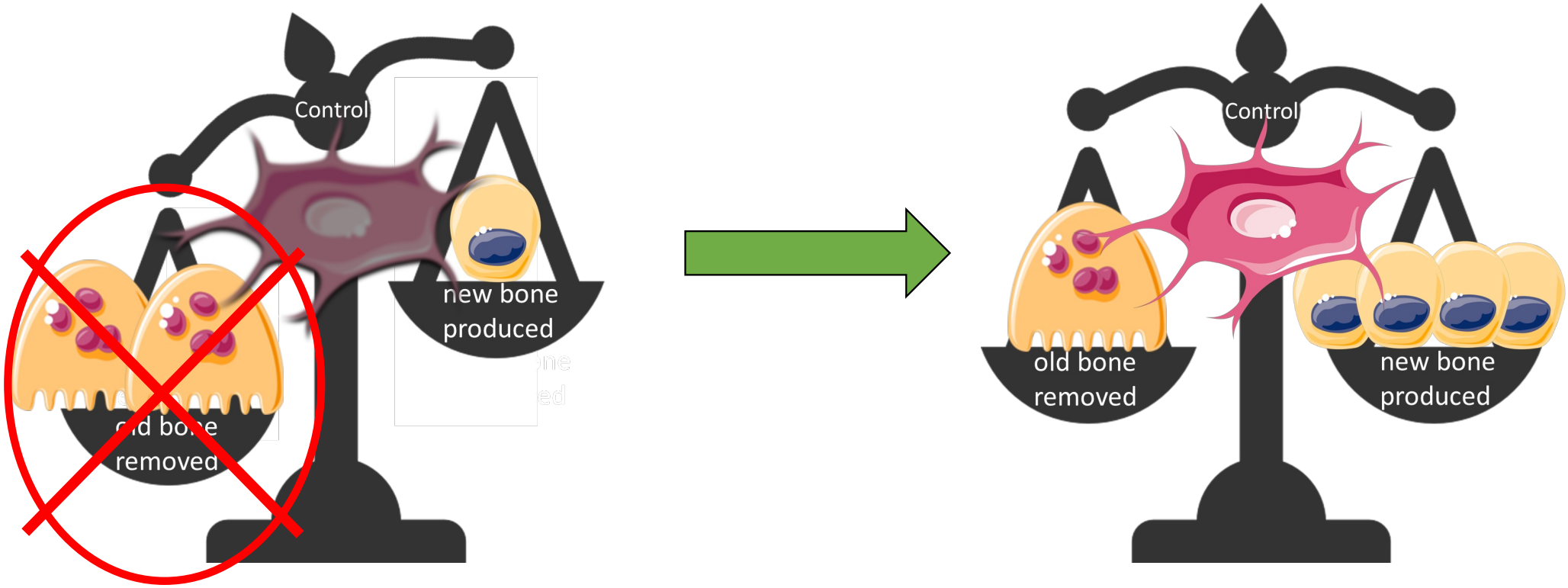
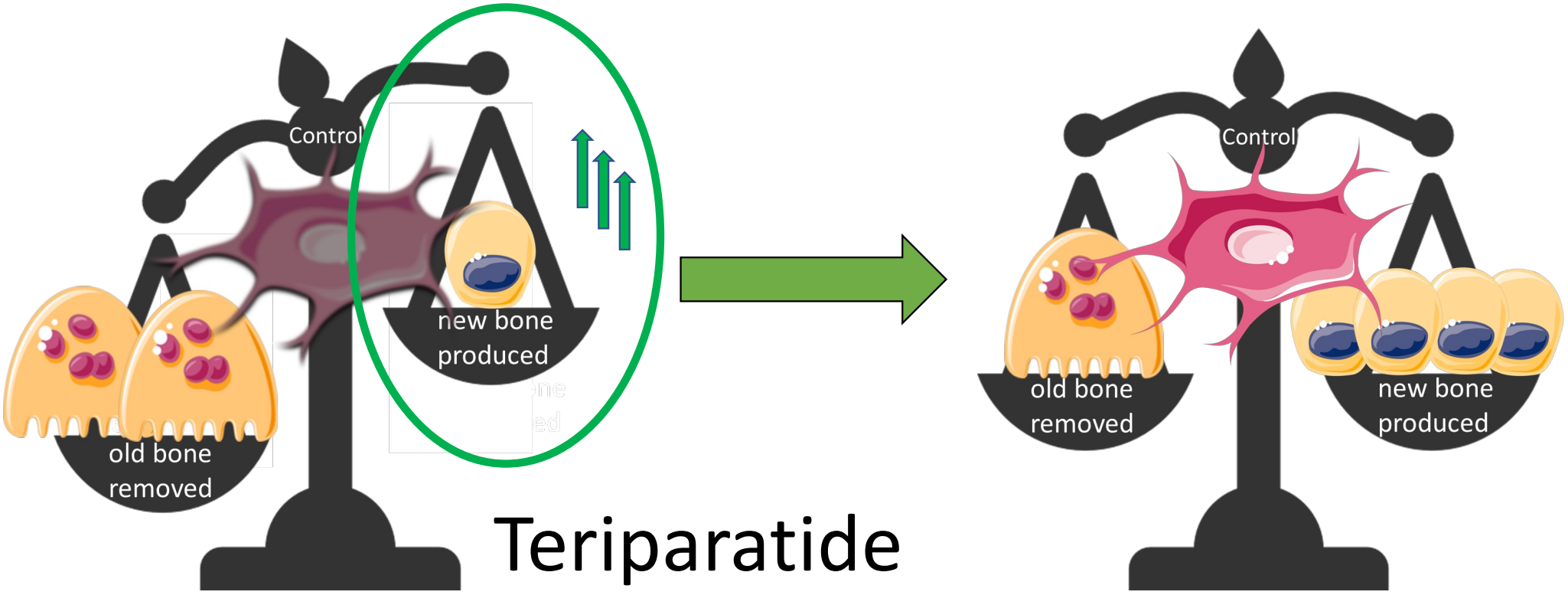


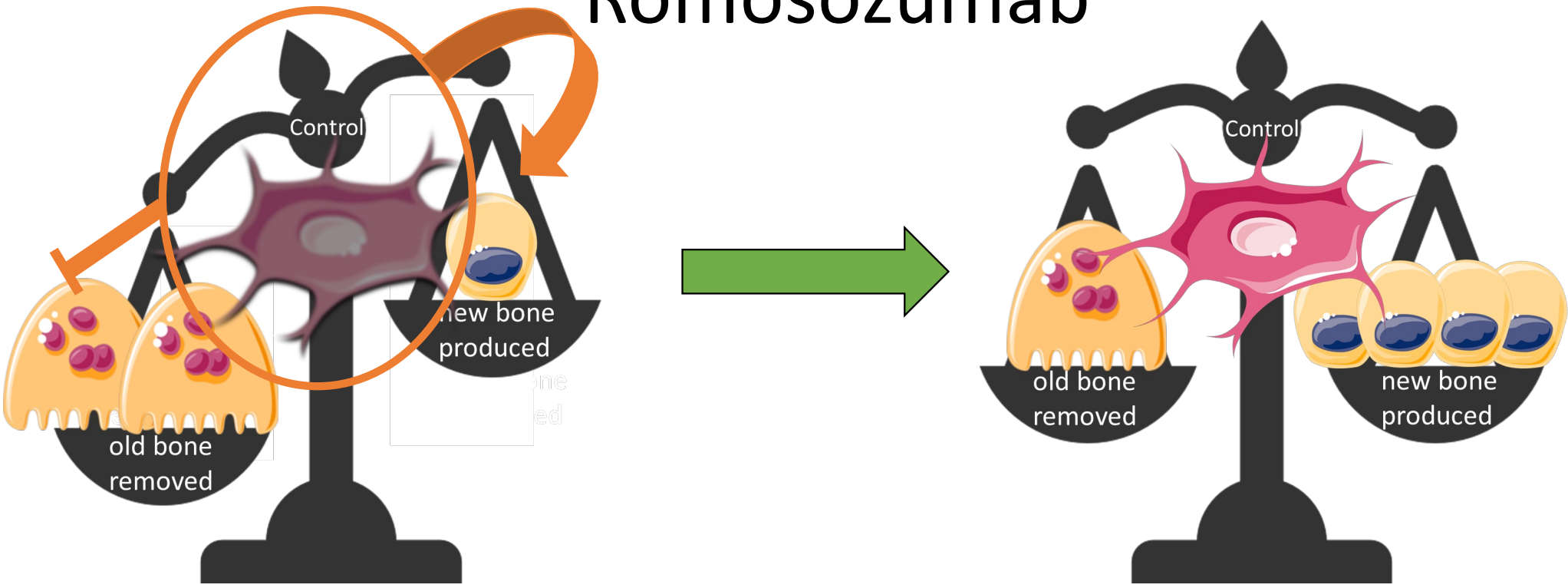
Bisphosphonates or Denosumab

Medications to treat osteoporosis

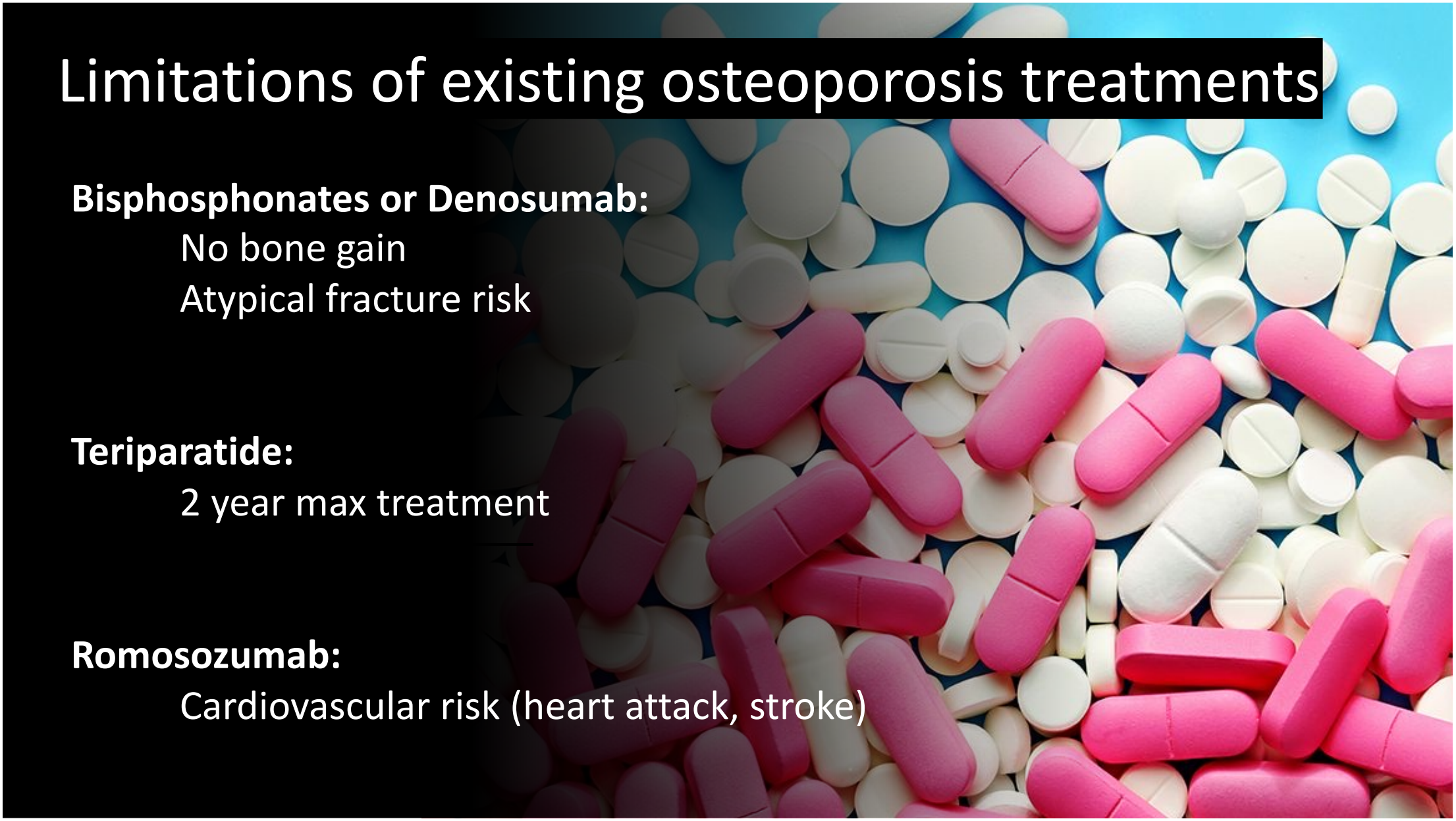


Medications to treat osteoporosis

Romosozumab



Limitations of existing osteoporosis treatments



Bisphosphonates or Denosumab:

No bone gain

Atypical fracture risk

Teriparatide:

2 year max treatment

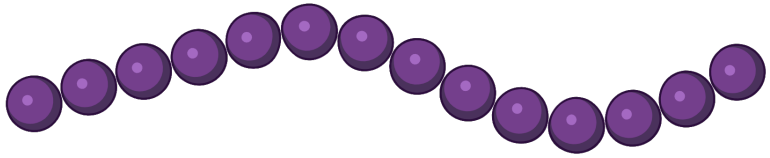
Romosozumab:

Cardiovascular risk (heart attack, stroke)

HOW IS BIRMINGHAM RESEARCHING TO IMPROVE THE TREATMENT OF OSTEOPOROSIS?

Kathryn Frost - PhD student

Introducing PEPITEM

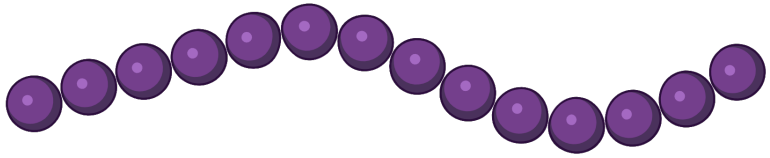


Name: **PEPITEM**

Seq: **SVTEQGAELSNEER**

PEPITEM is a small protein produced naturally by the body

Introducing PEPITEM



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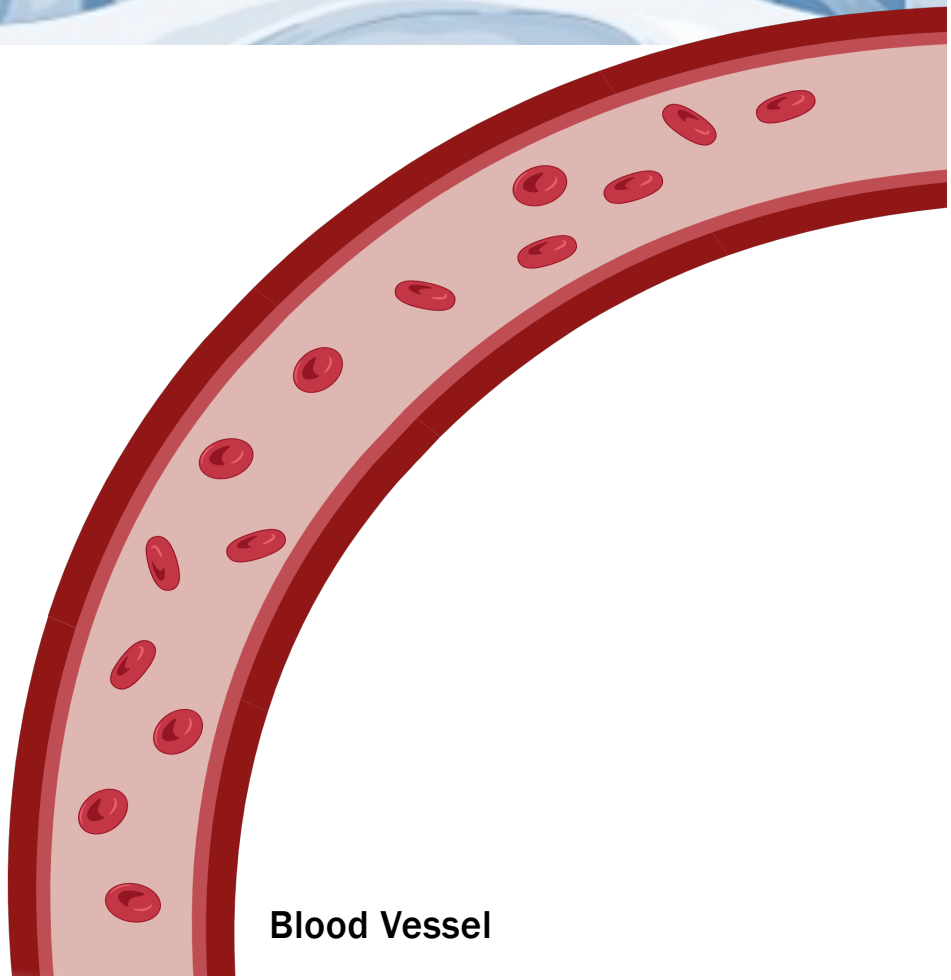
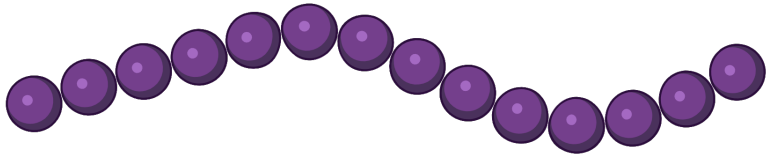


Blood Vessel

Introducing PEPITEM



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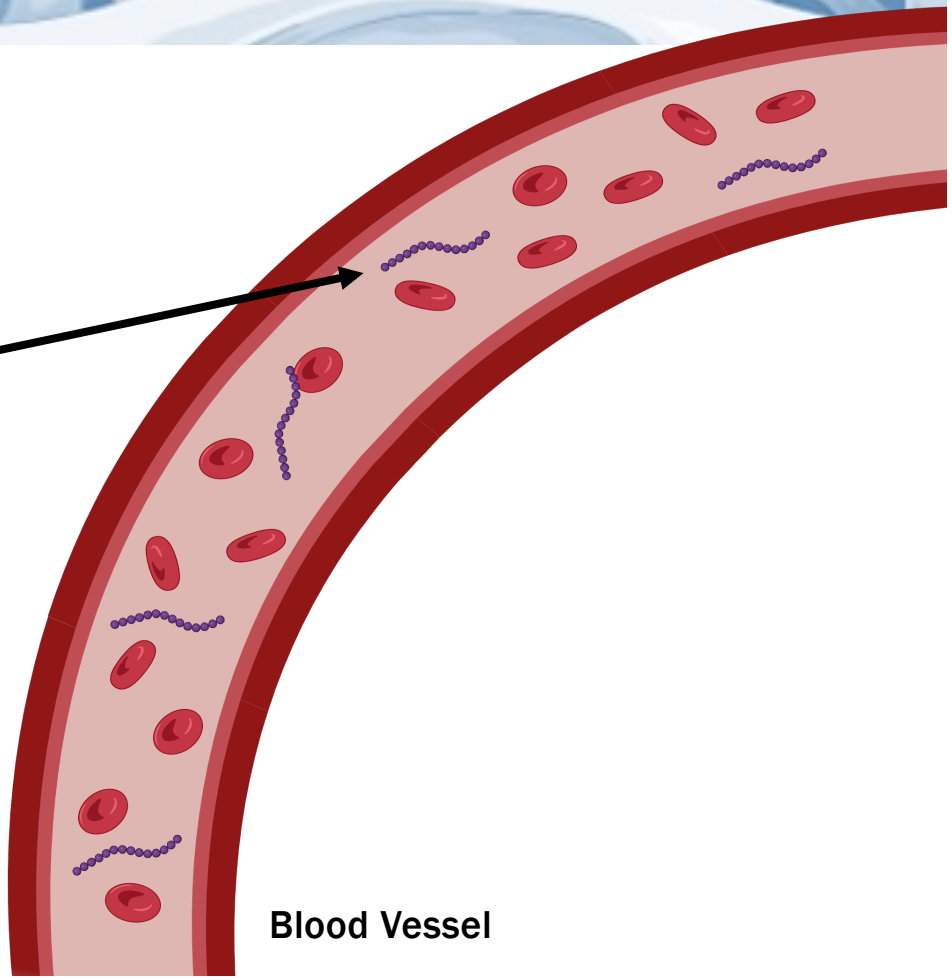
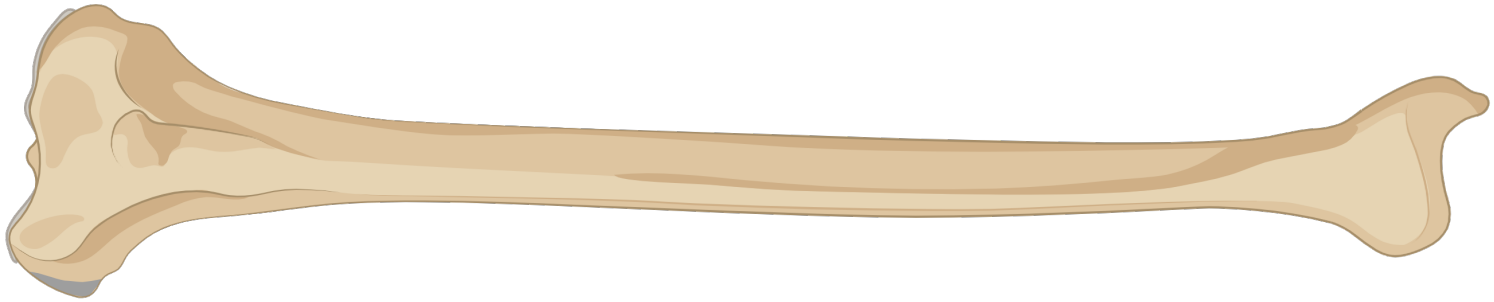


PEPITEM is a small protein produced naturally by the body

Blood Vessel

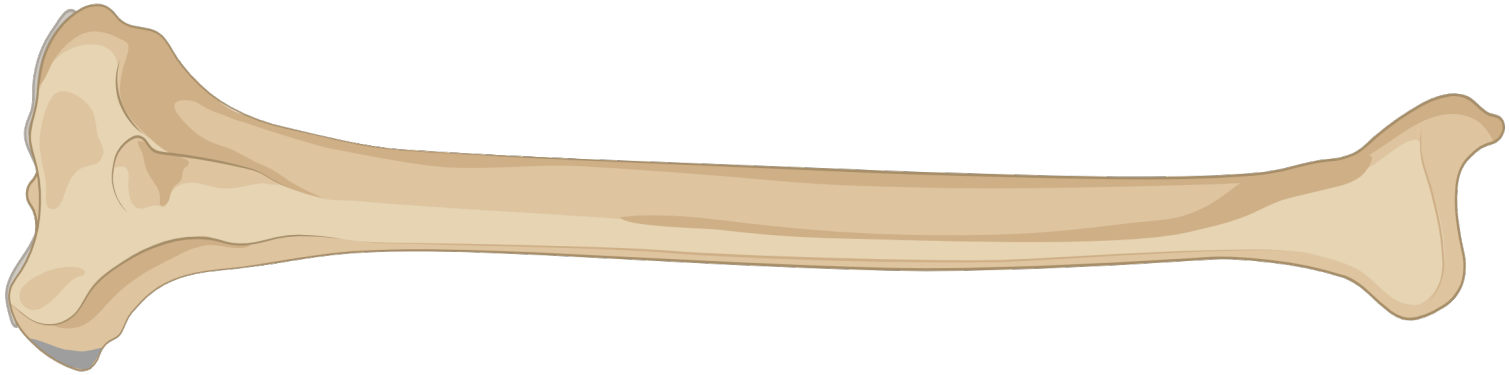
PEPITEM increases bone volume



PEPITEM has been shown to increase bone volume/mass.

PEPITEM increases bone volume

PEPITEM



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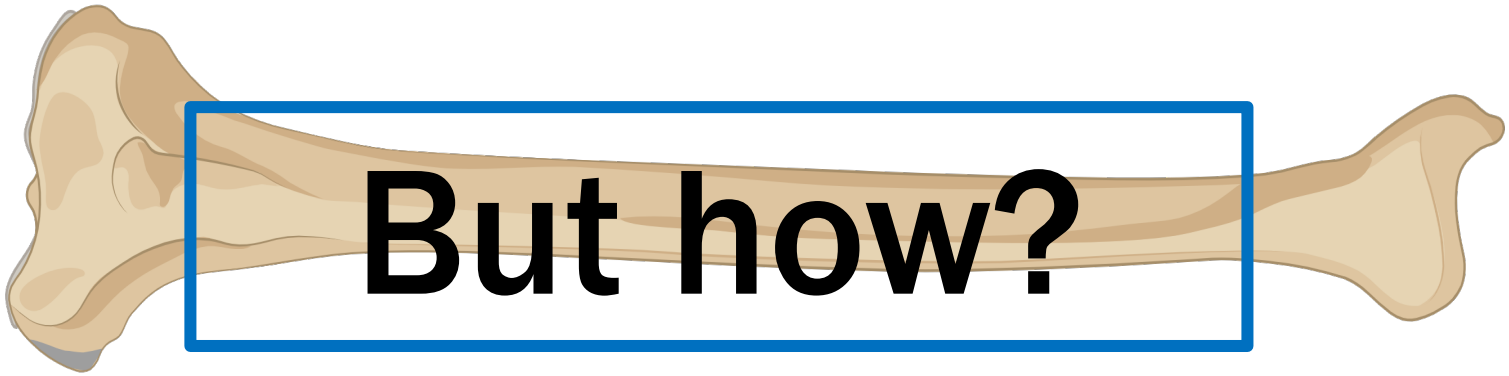
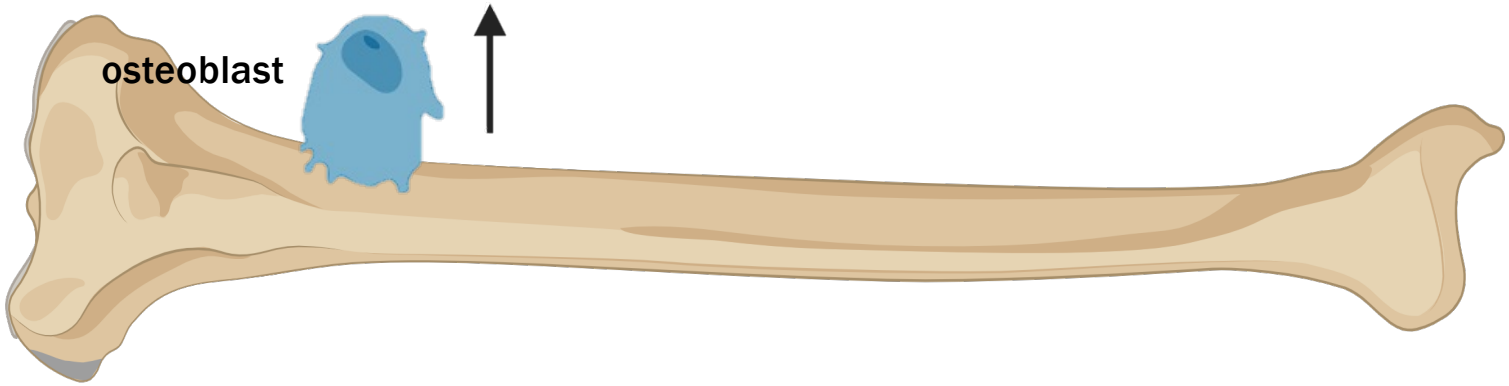


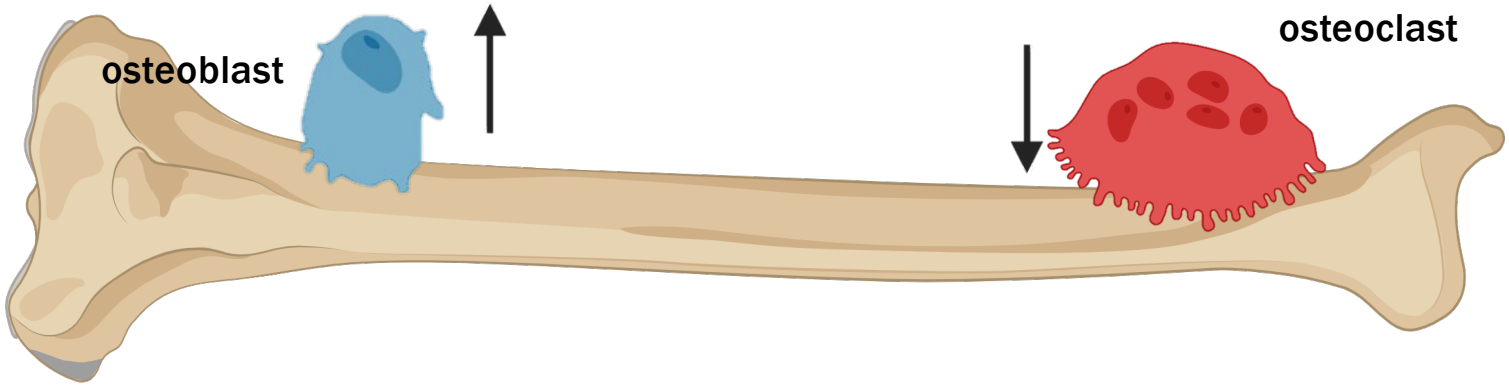
PEPITEM has been shown to increase bone volume/mass.

PEPITEM increases bone volume



Is it through the increased action of osteoblasts, the bone building cells?

PEPITEM increases bone volume



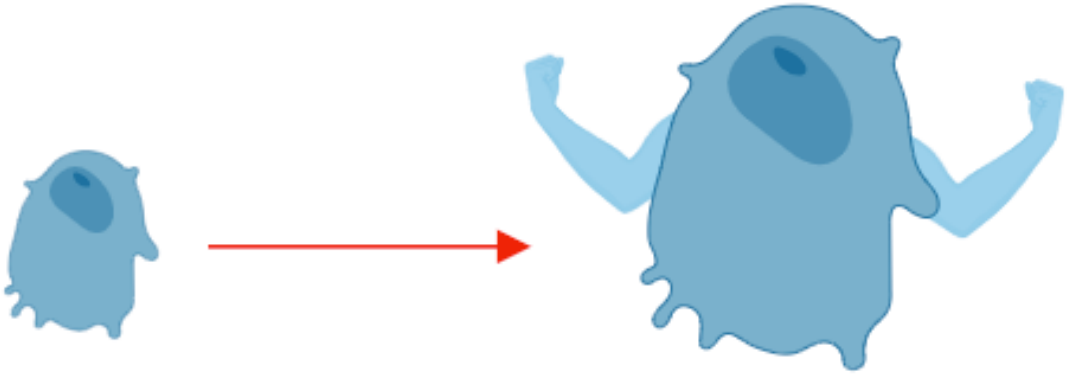
Or through the reduced action of osteoclasts, the bone breaking cells?

How does PEPITEM affect bone building?

PEPITEM increases bone building

Osteoblasts grow up (in a sense) and mature, these mature cells are more active and are better builders

PEPITEM increases bone building



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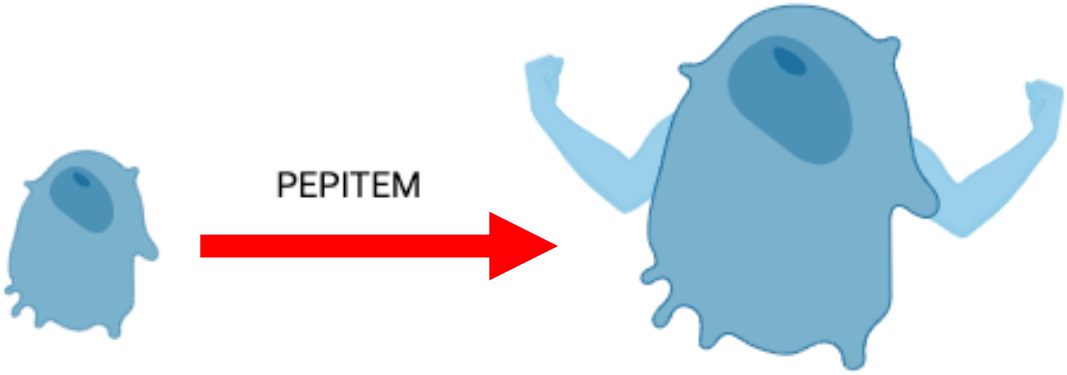
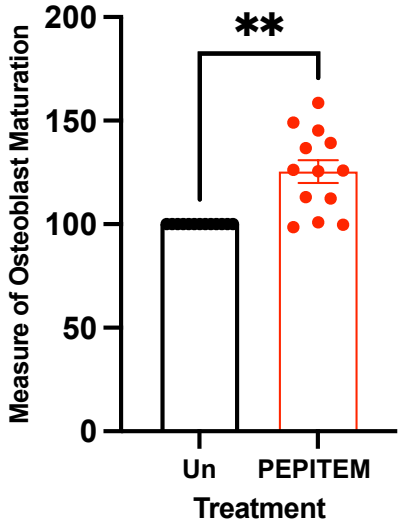


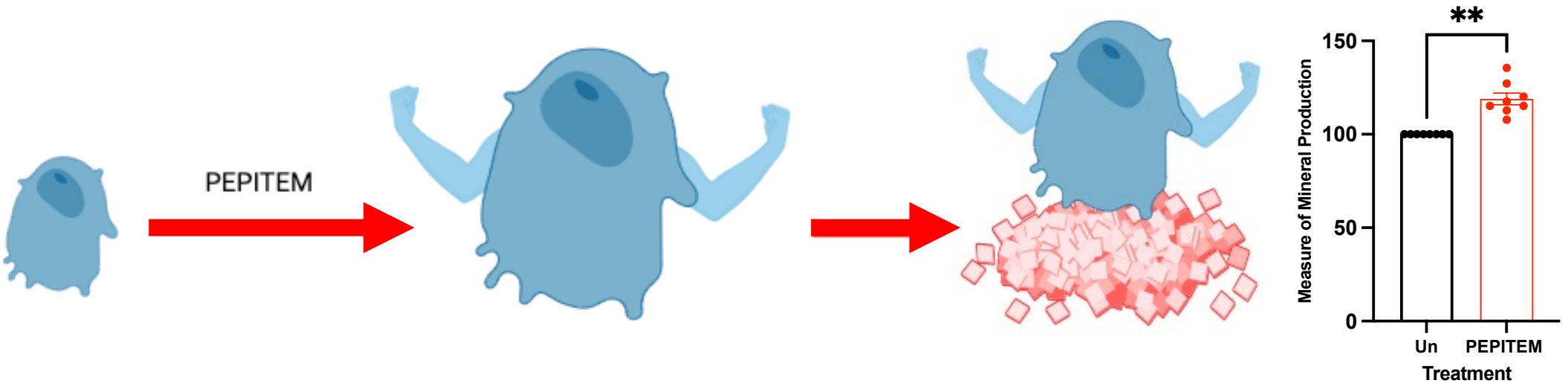


Osteoblasts grow up (in a sense) and mature, these mature cells are more active and are better builders

PEPITEM increases bone building

Mature osteoblasts produce mineral (the building blocks of bone): PEPITEM increases mineral production.

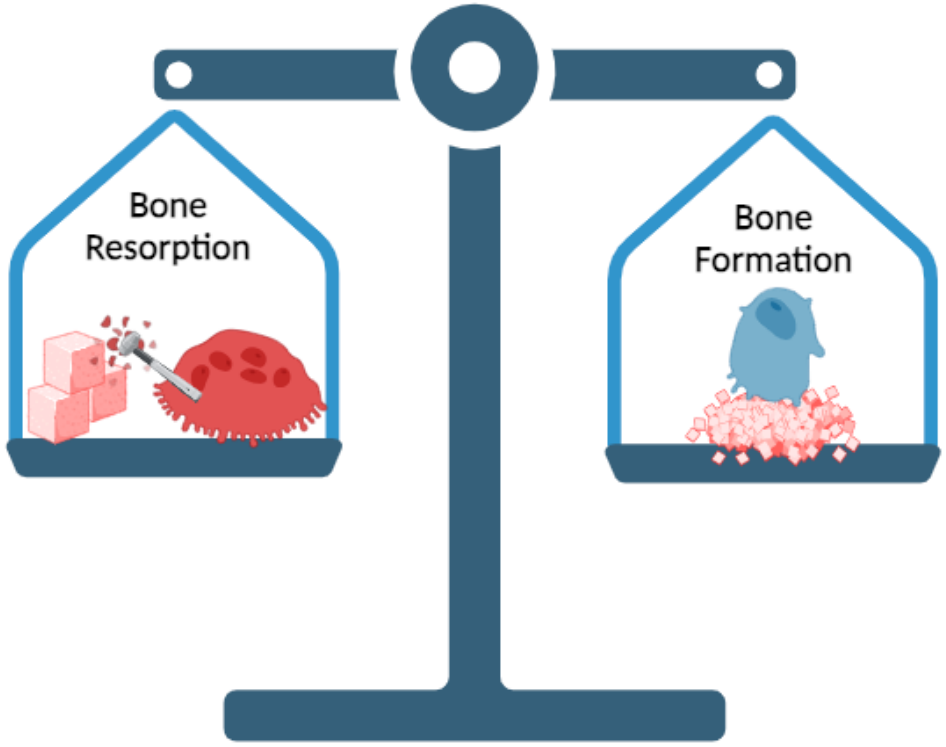
PEPITEM increases bone building



Mature osteoblasts produce mineral (the building blocks of bone): PEPITEM increases mineral production.

PEPITEM decreases bone building

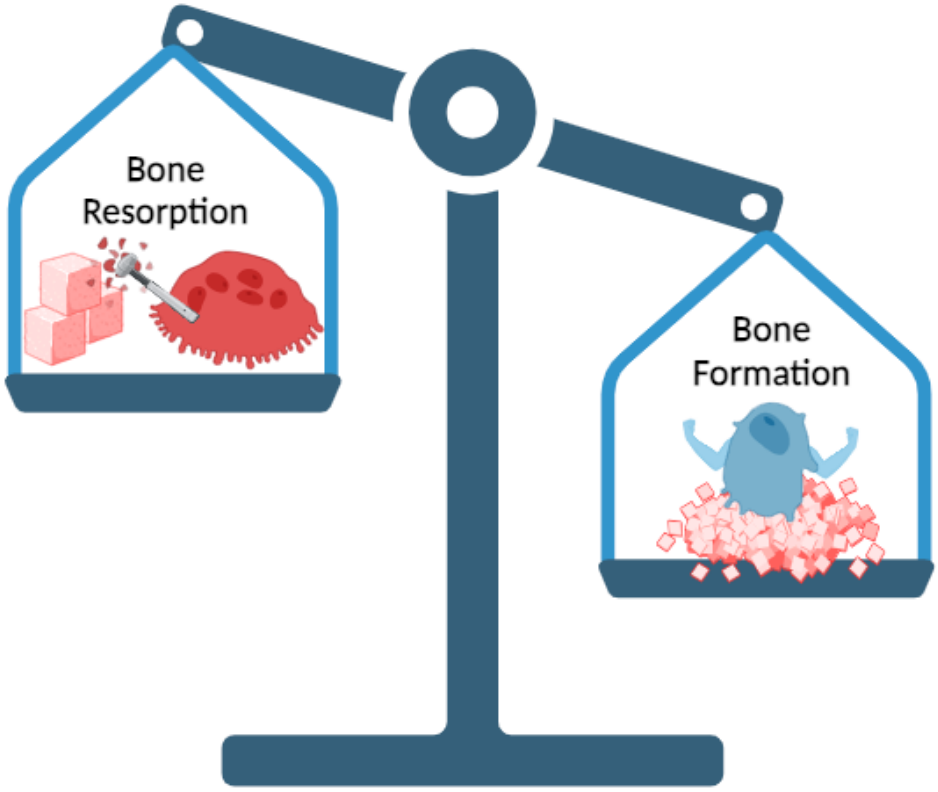
Normal Bone Remodeling



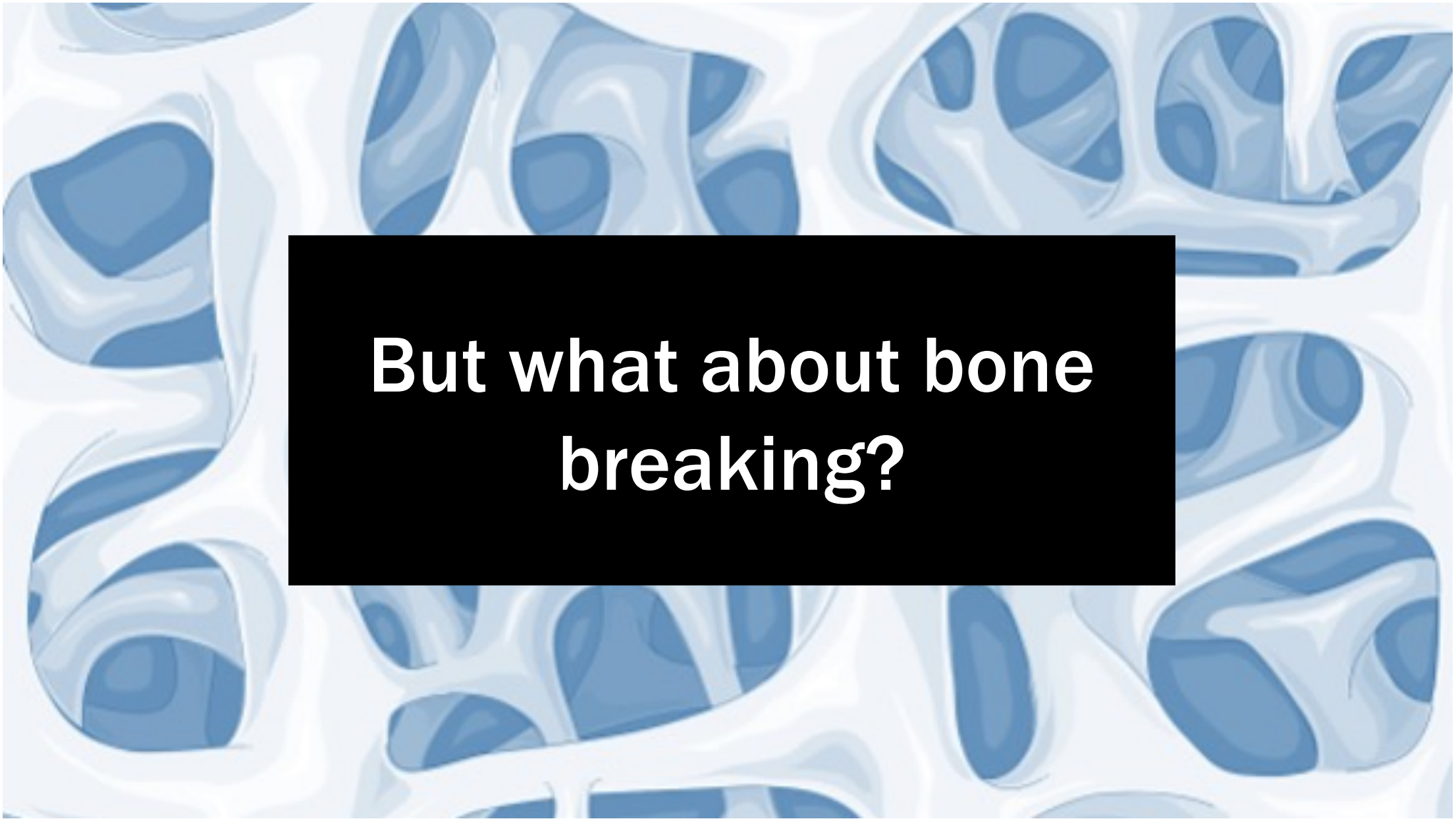
During normal bone remodeling, breaking and building are equal.

PEPITEM decreases bone building

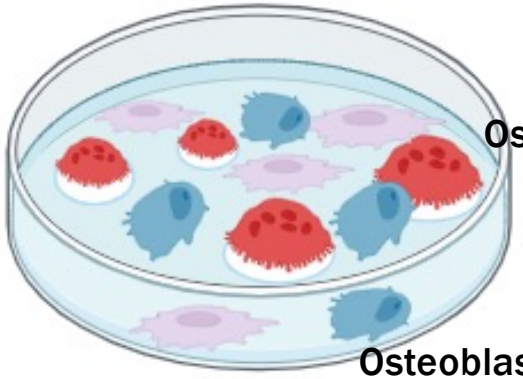
PEPITEM



PEPITEM can shift this balance to a higher level of bone building

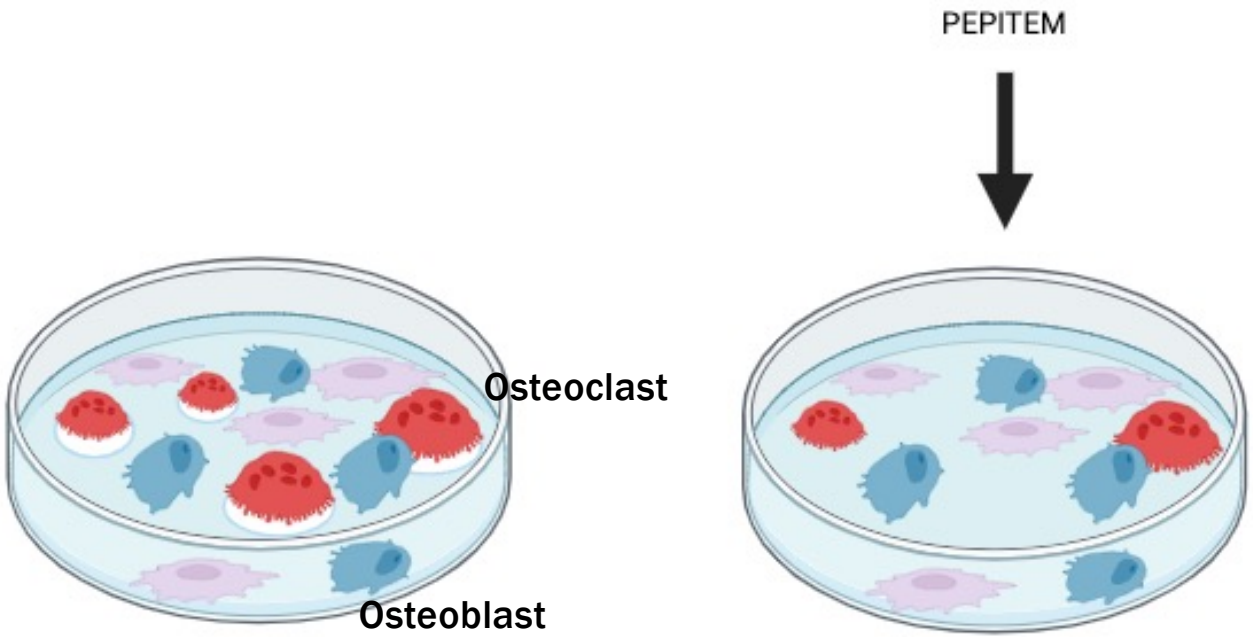

But what about bone breaking?

PEPITEM decreases bone breaking



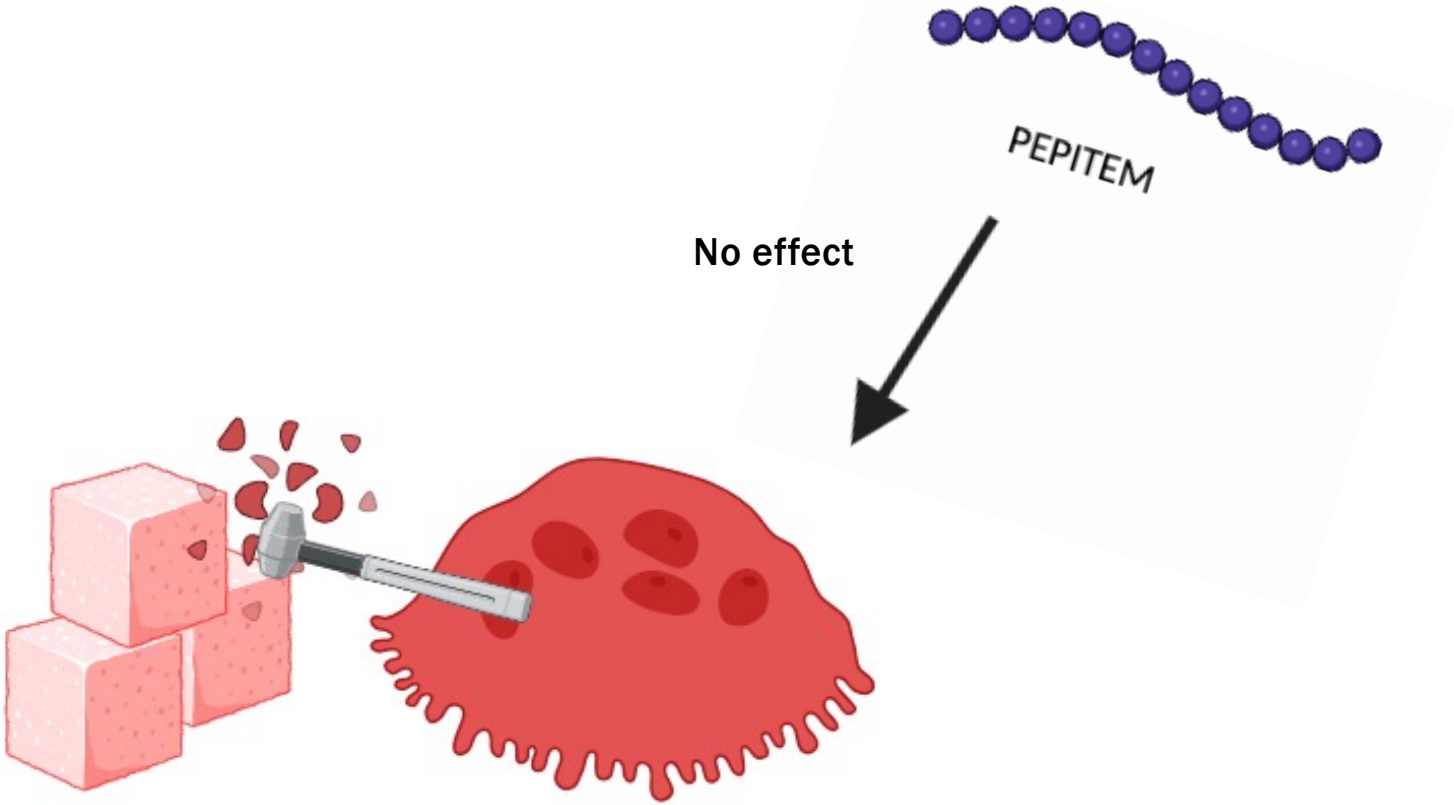
Culturing multiple bone cells together allows us to understand how these cells ‘talk’ to each other

PEPITEM decreases bone breaking



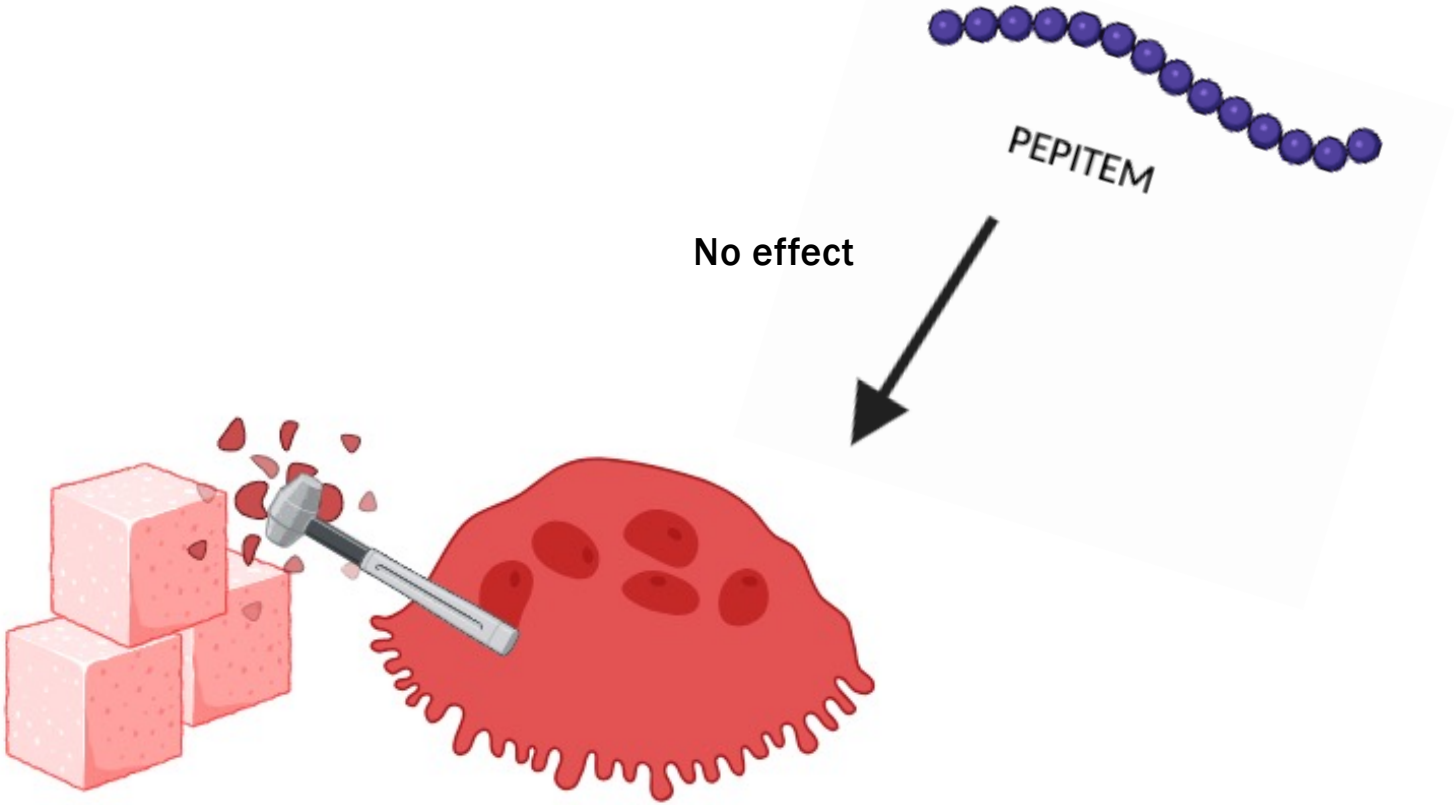
PEPITEM in these cultures reduces the activity of osteoclasts, reducing bone breaking

PEPITEM decreases bone breaking



PEPITEM does not act on osteoclasts directly to affect bone resorption

PEPITEM decreases bone breaking



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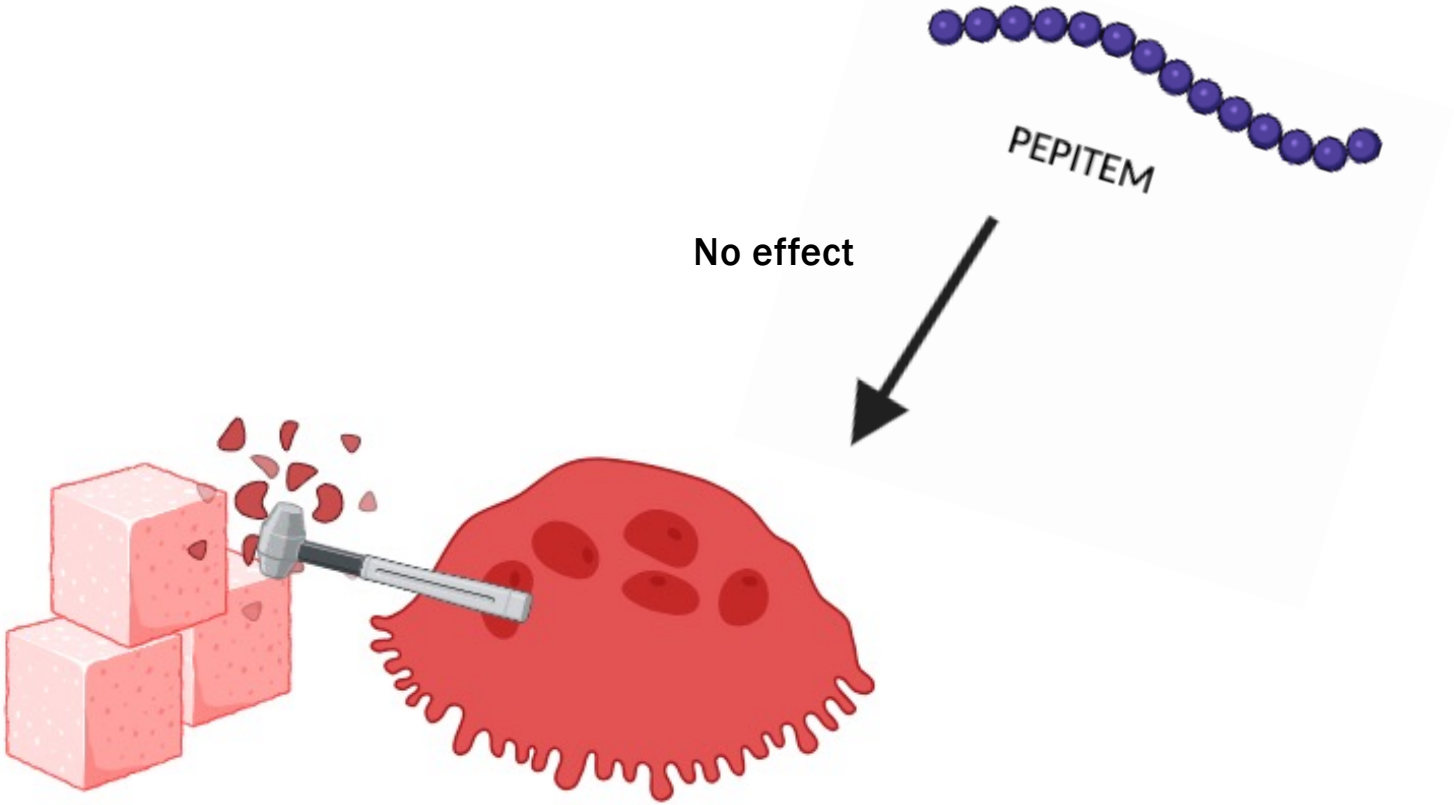

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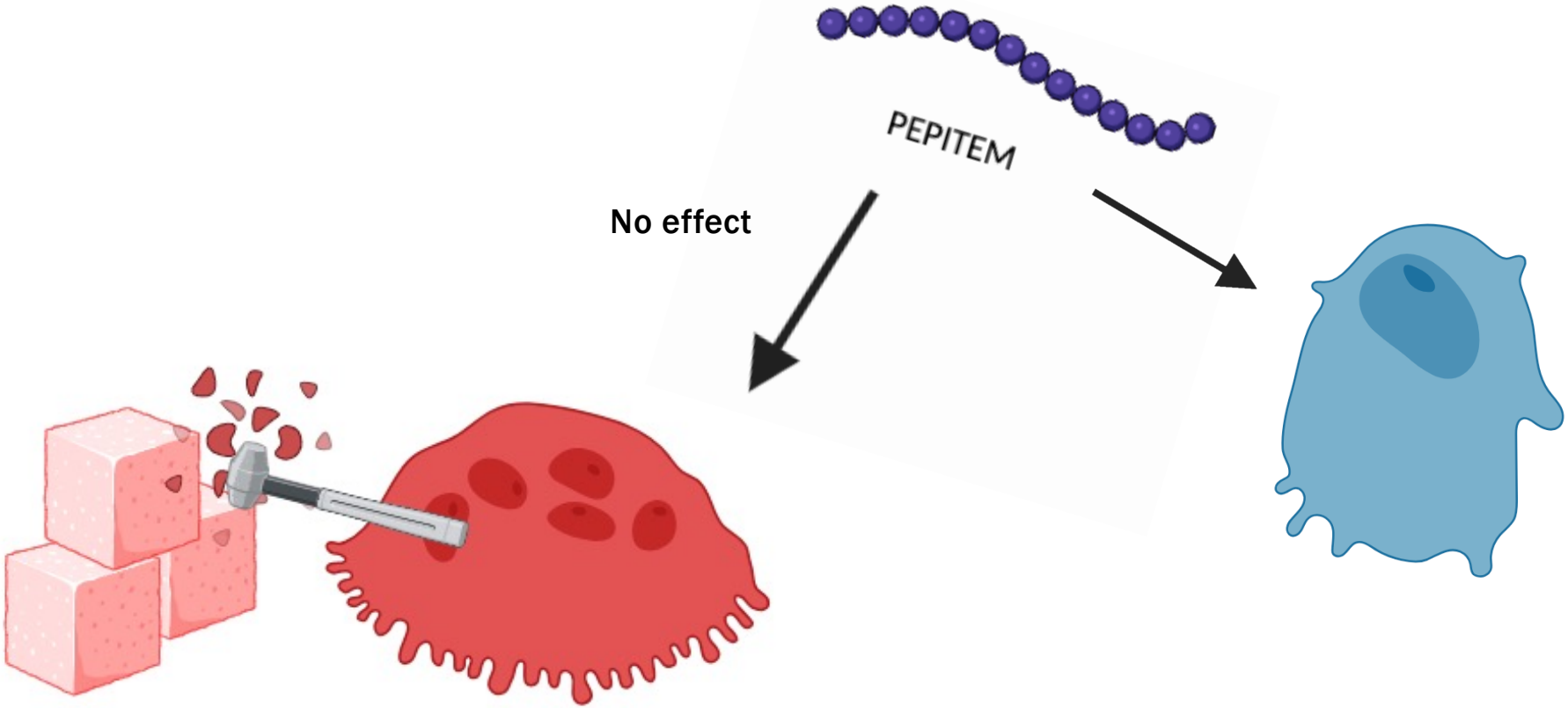
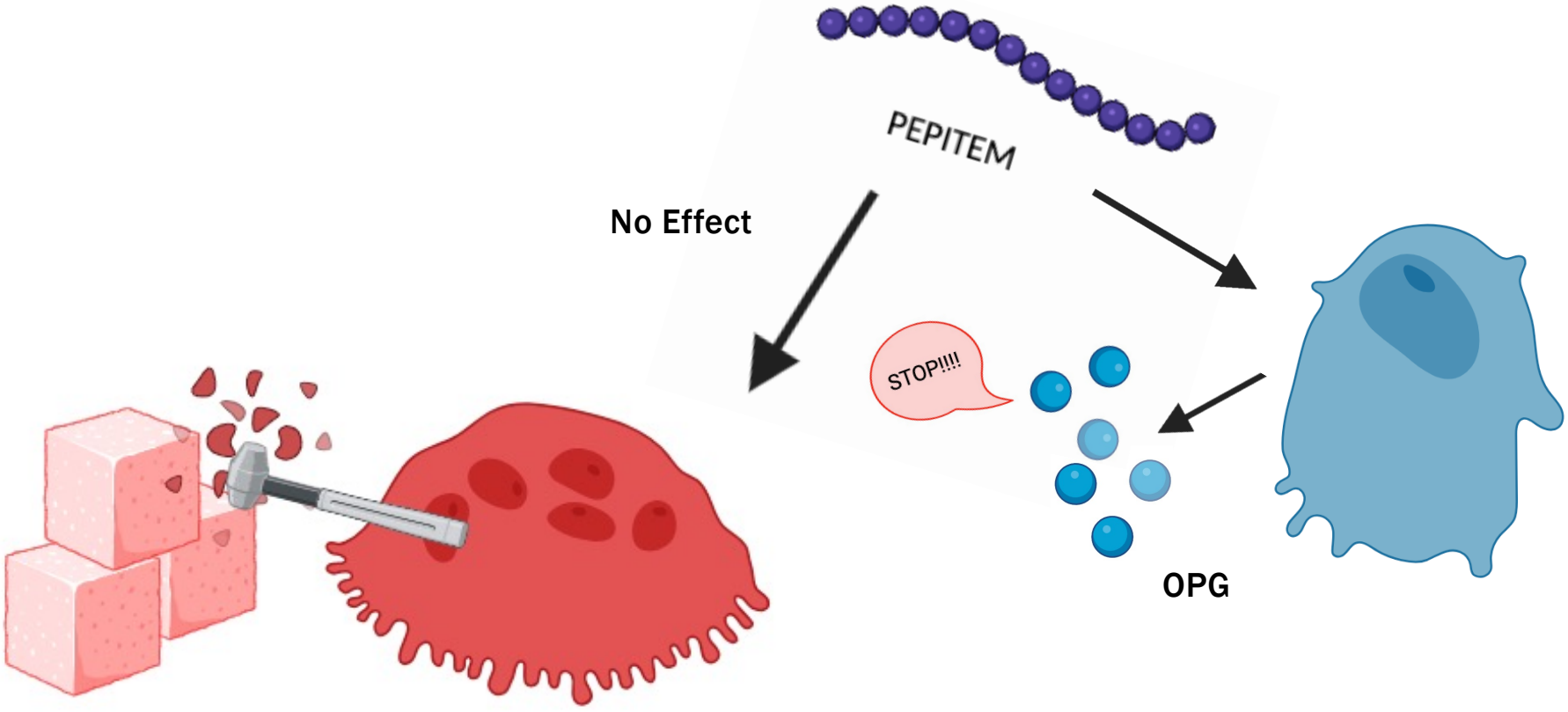


PEPITEM can disrupt the conversation between osteoblasts and osteoclasts

PEPITEM decreases bone breaking



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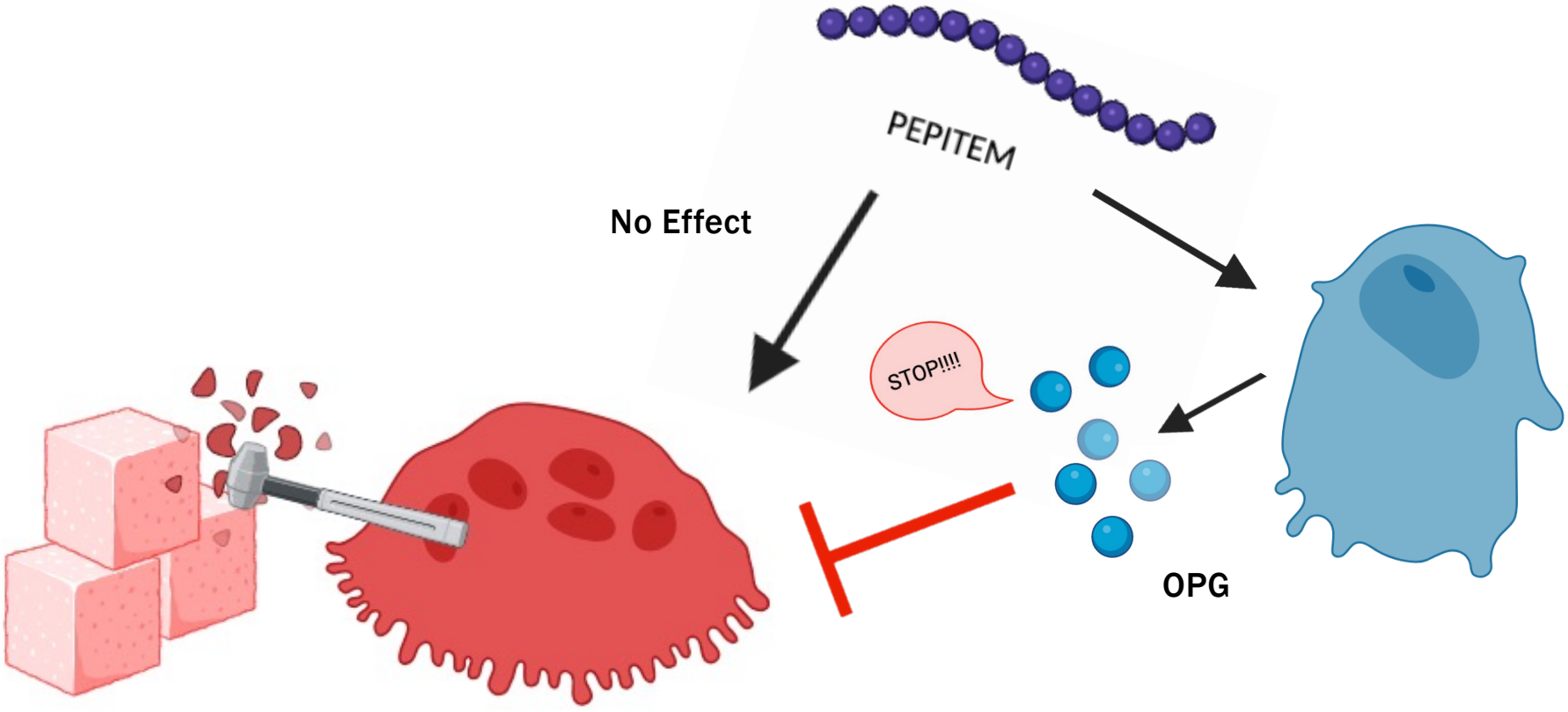

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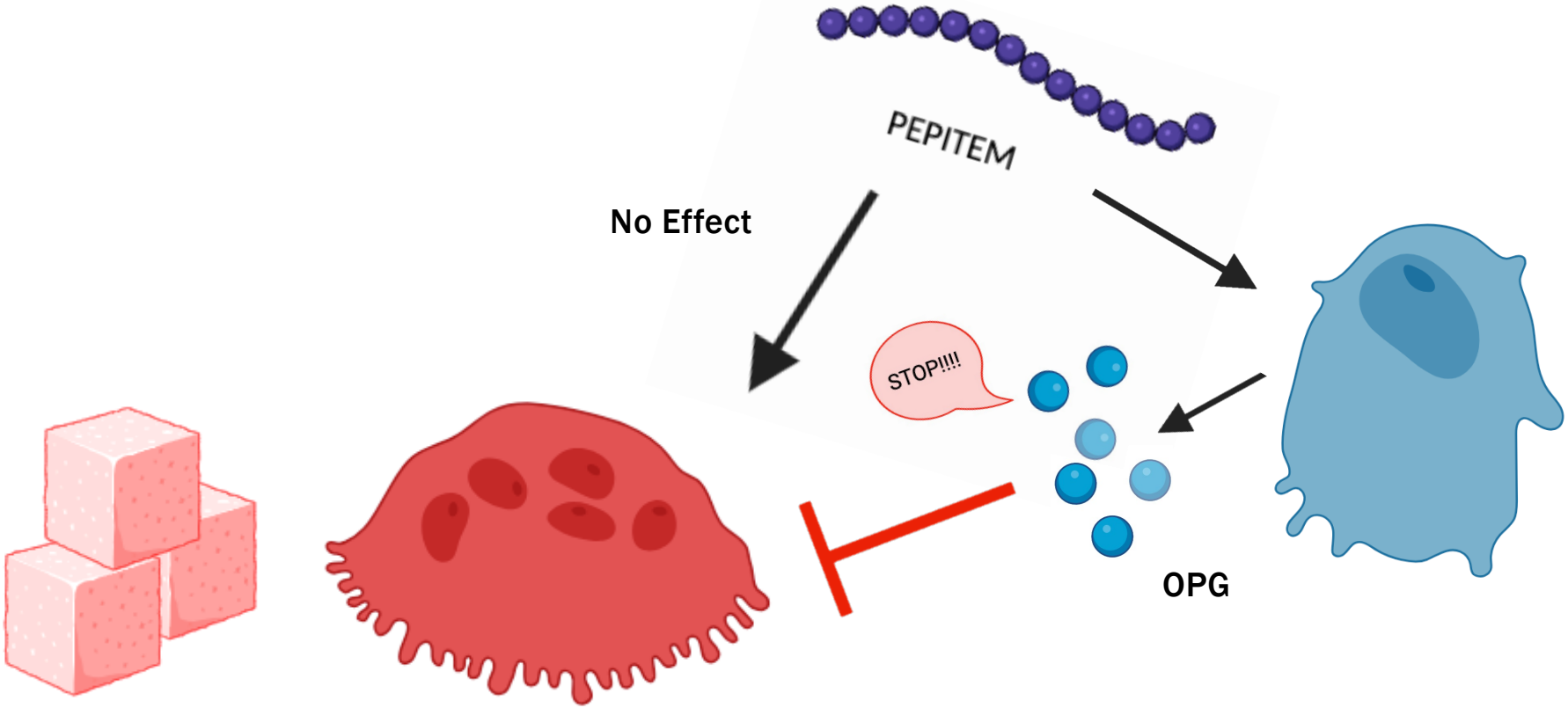
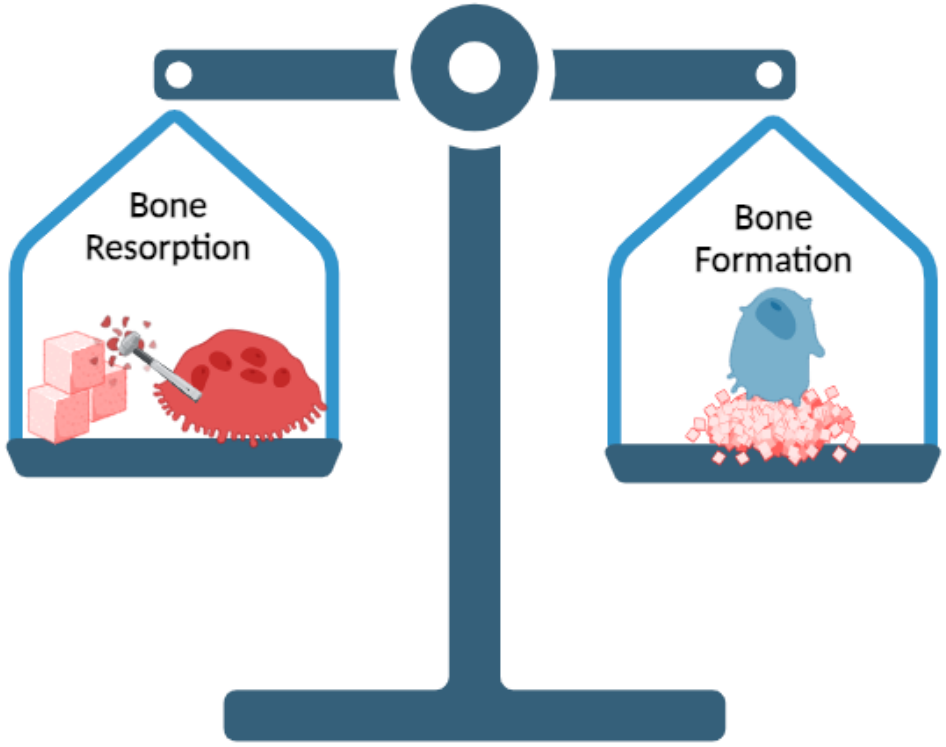


Reducing the number of active osteoclasts, reducing bone breaking

PEPITEM increases bone building and decreases bone breaking

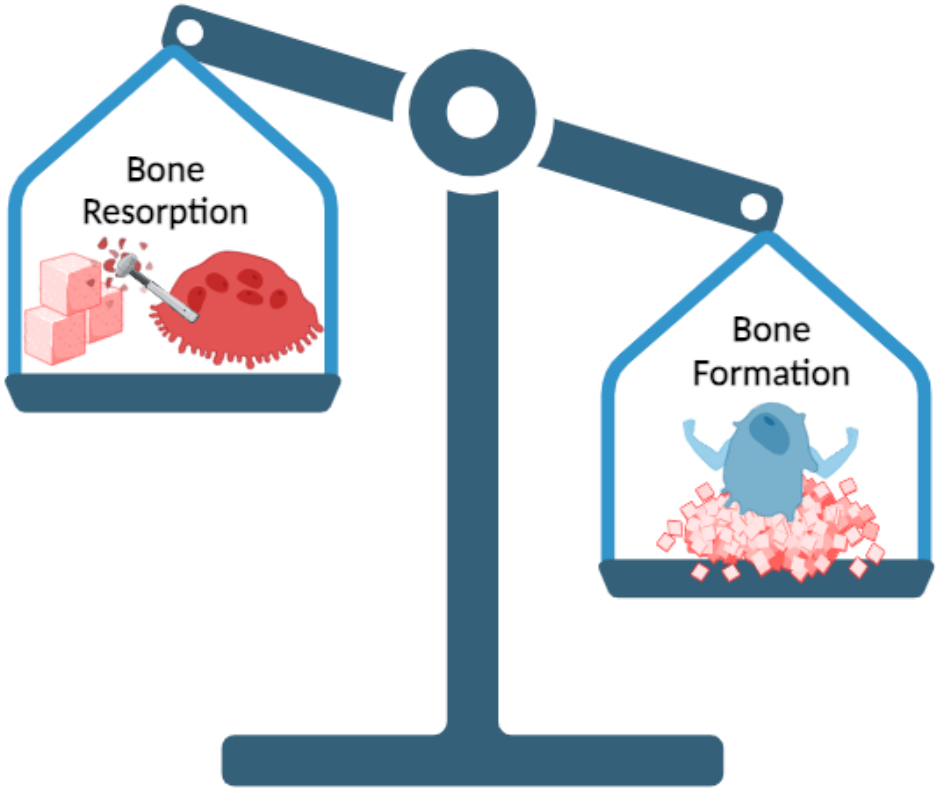
Normal Bone Remodeling



During normal bone remodeling, breaking and building are equal.

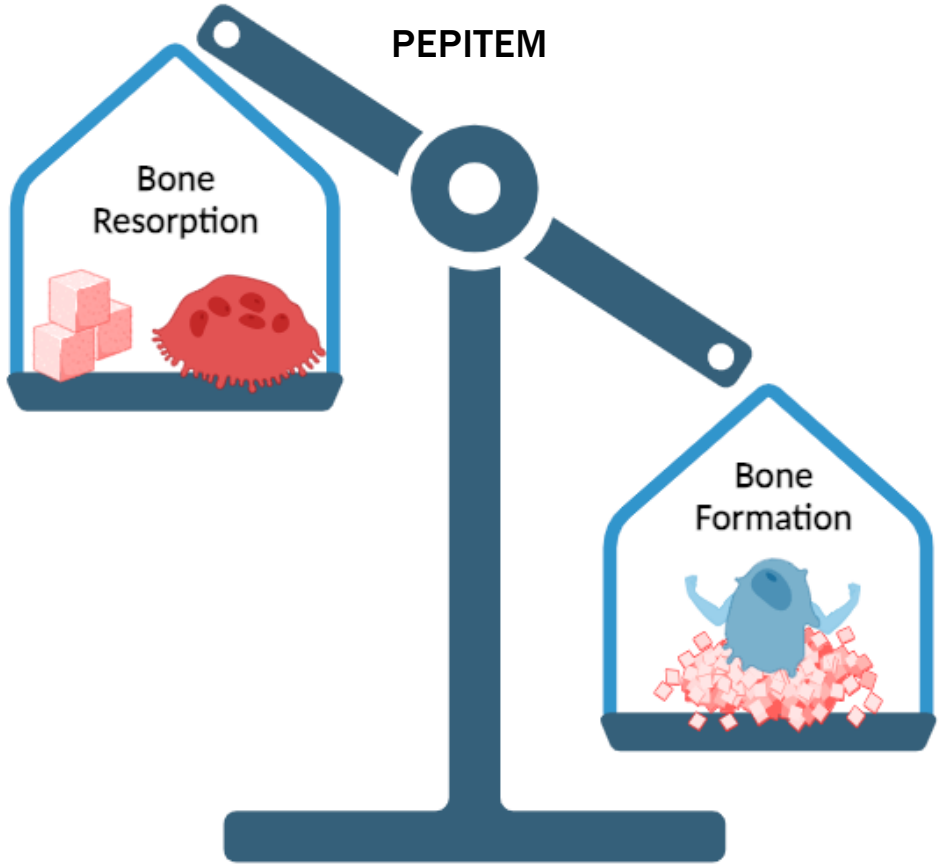
PEPITEM increases bone building and decreases bone breaking

PEPITEM



PEPITEM can shift this balance to a higher level of bone building

PEPITEM increases bone building and decreases bone breaking

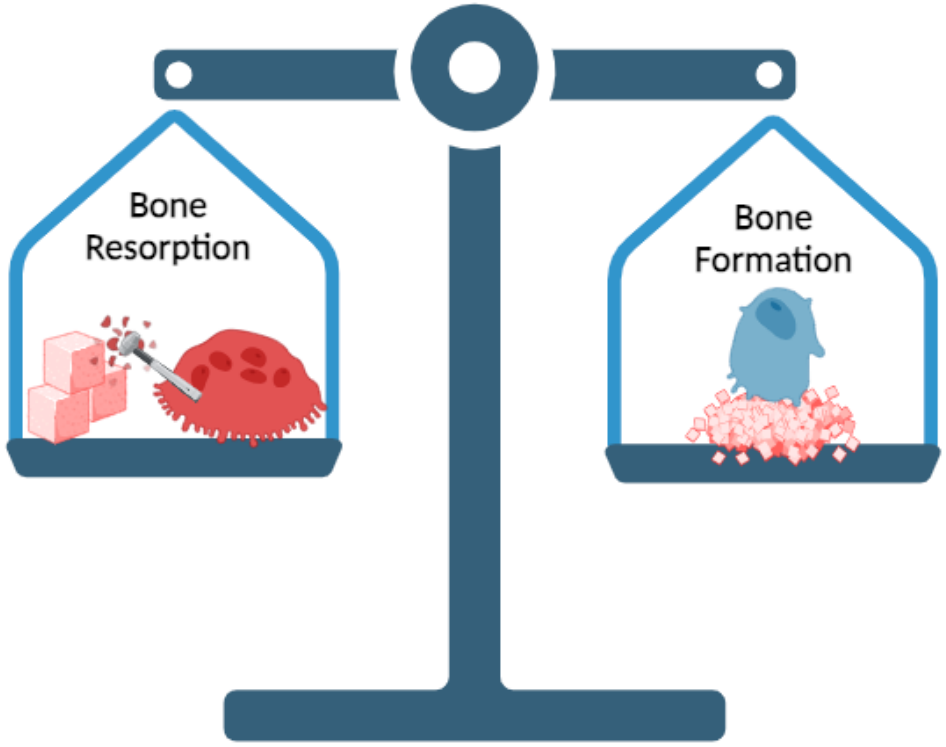


PEPITEM can shift this balance further to a higher level of bone building by also reducing bone breaking

What does this mean for Osteoporosis?

PEPITEM in Osteoporosis

Normal Bone Remodeling



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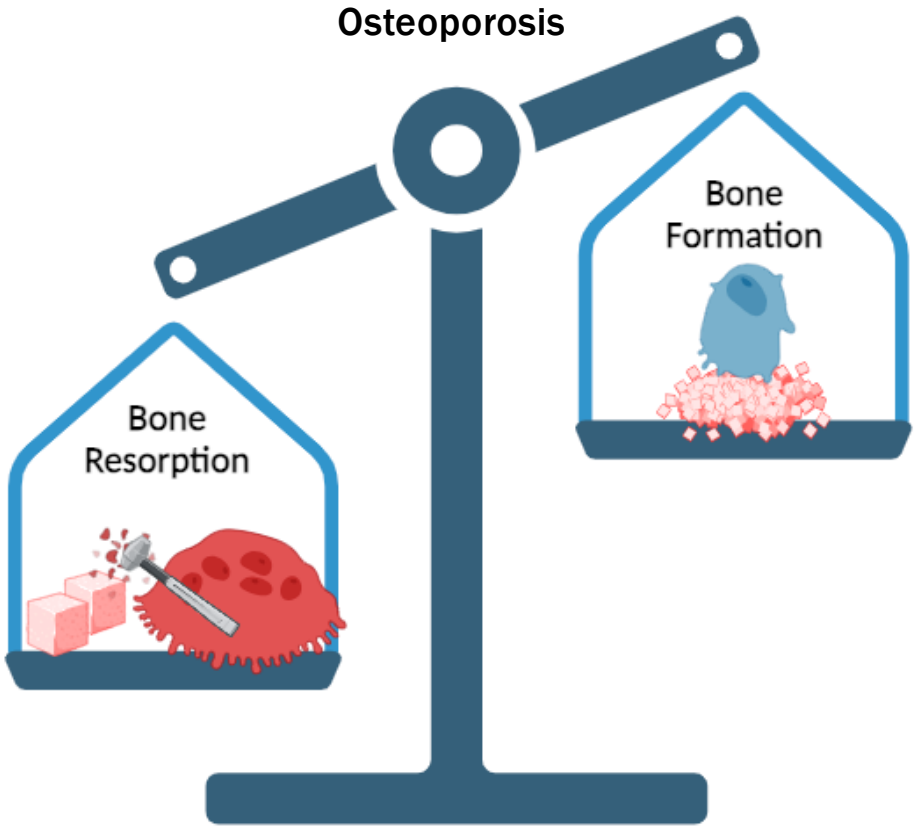
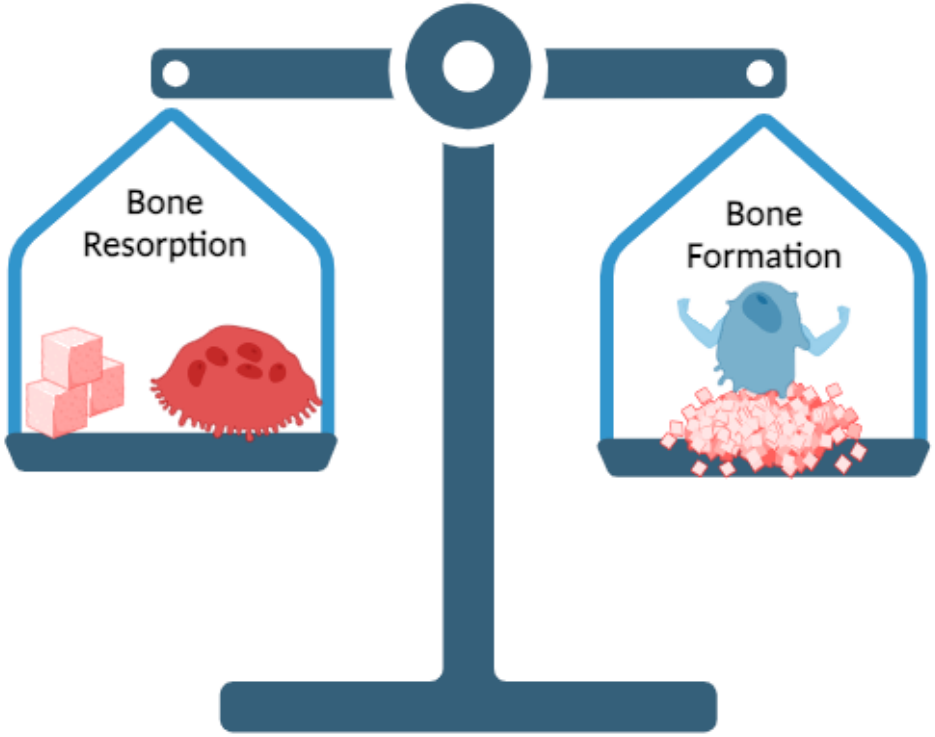
PEPITEM in Osteoporosis



In osteoporosis this balance is skewed, resulting in increased bone breaking.

PEPITEM in Osteoporosis

PEPITEM in Osteoporosis



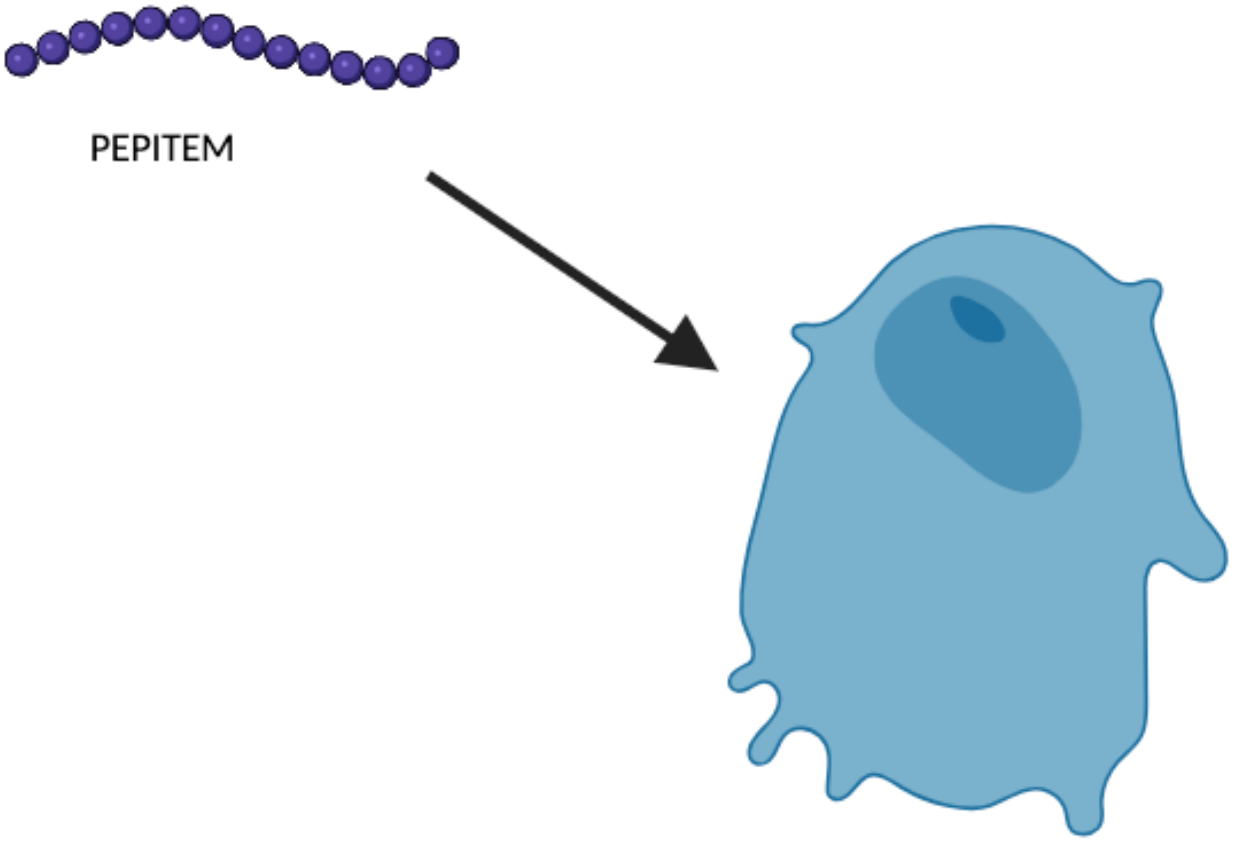
PEPITEM can equalize this though powering osteoblasts and reducing osteoclasts.

How does PEPITEM work?

How does PEPITEM work?

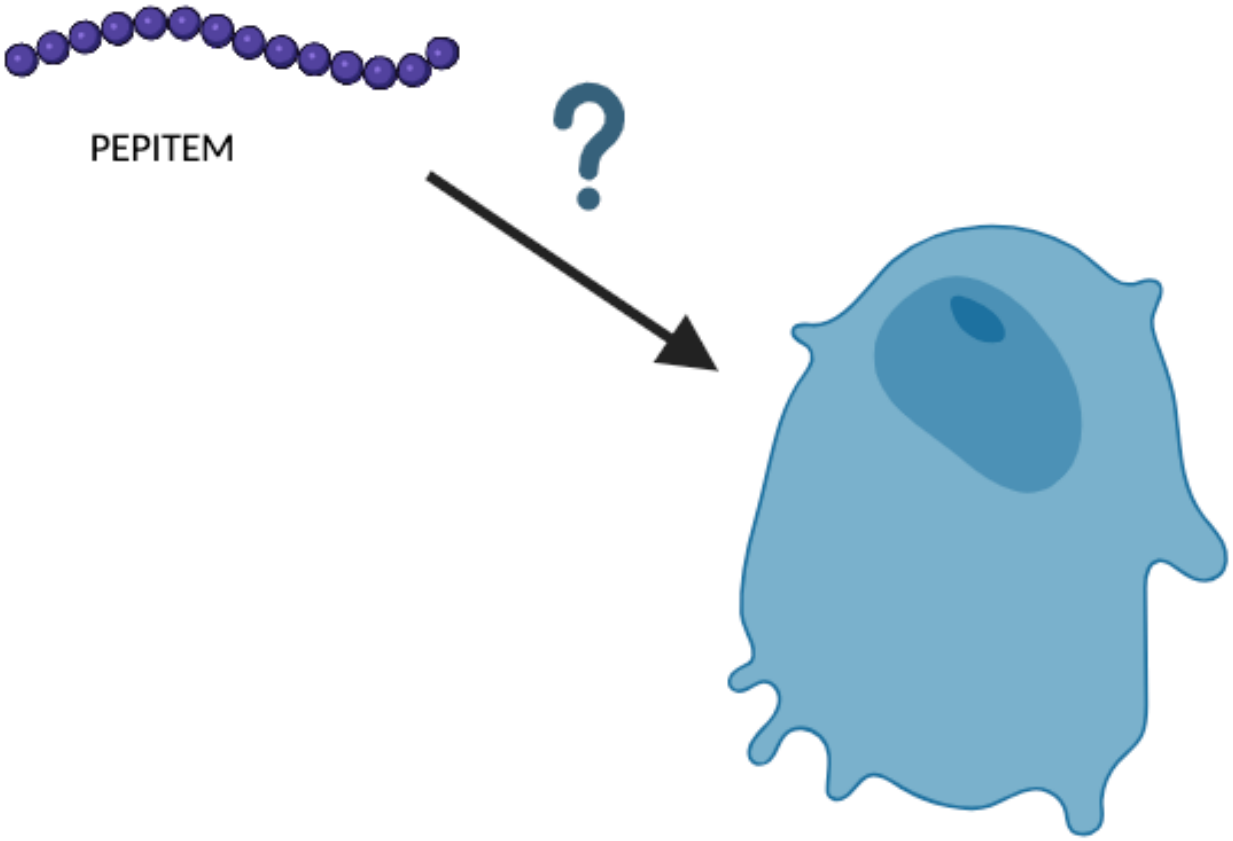
That’s what I’m working on

Understanding how PEPITEM works can lead to new targets



Currently we know PEPITEM acts on osteoblasts, but we are still figuring out how

Understanding how PEPITEM works can lead to new targets



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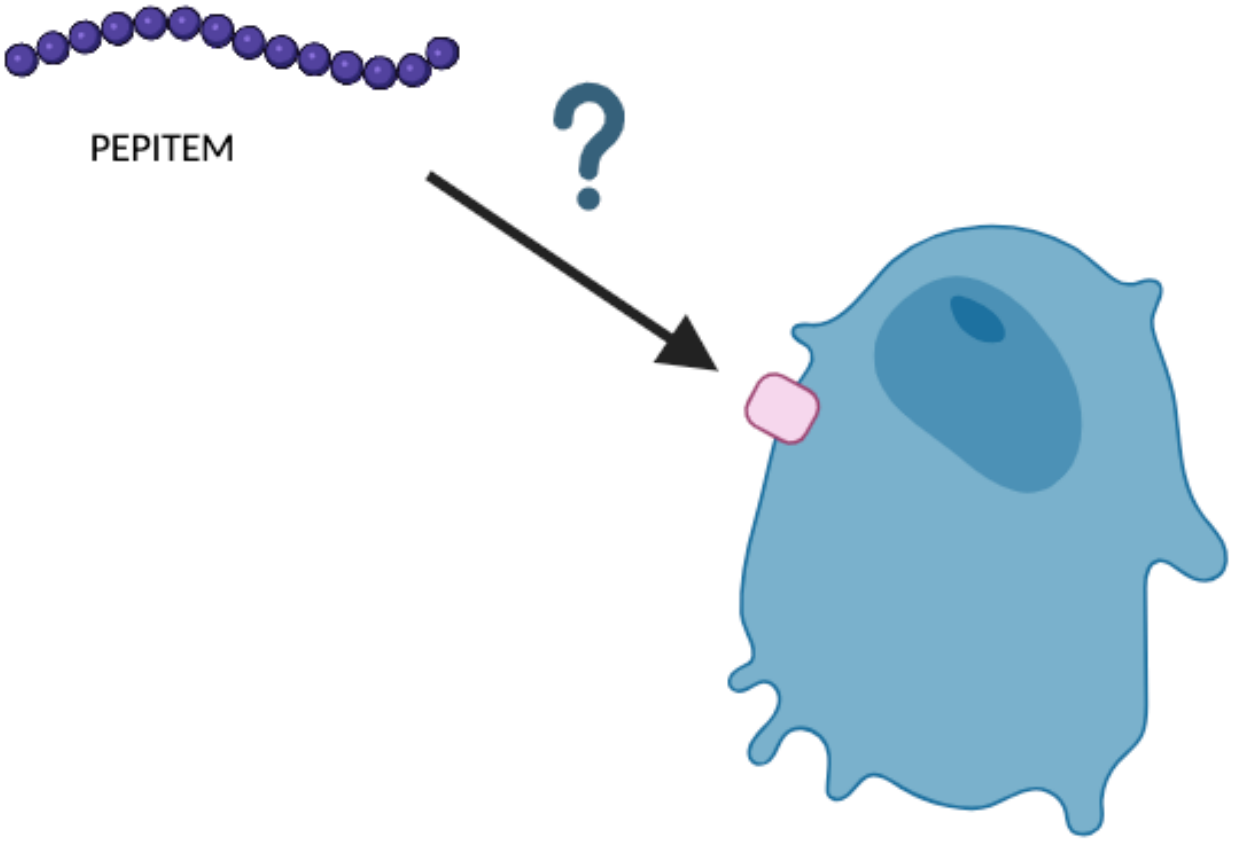
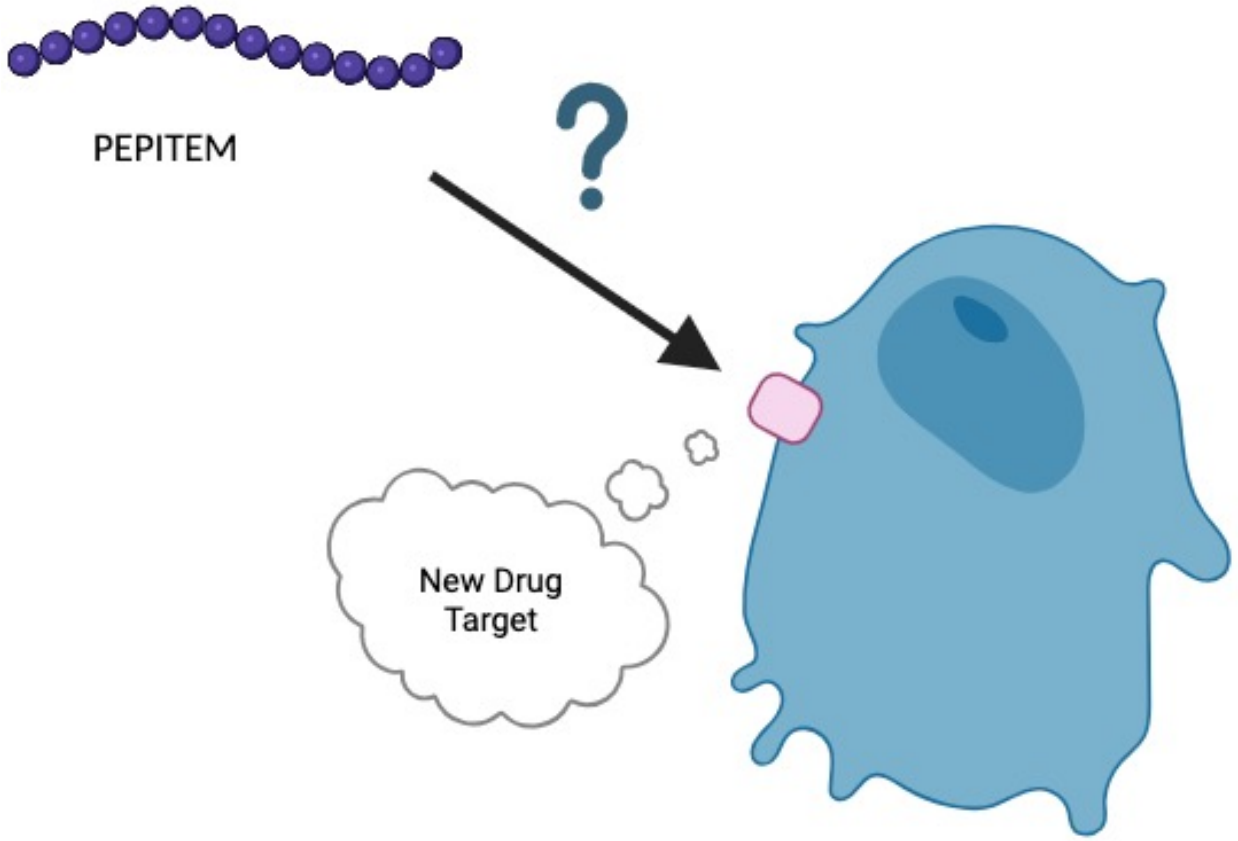
Understanding how PEPITEM works can lead to new targets



We are looking at the receptor (on switch) of PEPITEM

Understanding how PEPITEM works can lead to new targets



Finding out how PEPITEM acts and whether this is altered with age or disease will help identify more medicines.

Can I buy PEPITEM?

Can I buy PEPITEM?

I’m afraid not ☹

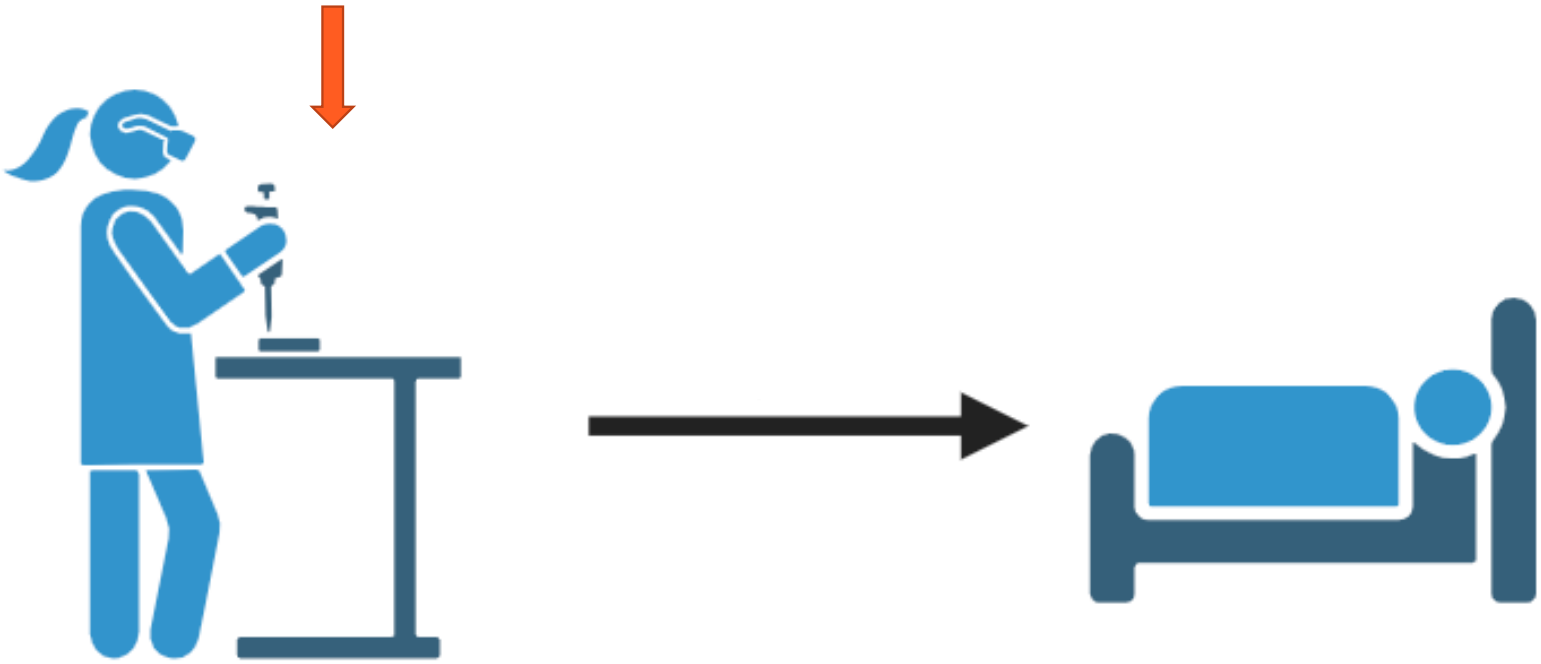
Moving from Bench to Bedside

We are here

PEPITEM is still in it's infancy and currently only for lab use

Moving from Bench to Bedside

We are here



We hope to one day get PEPITEM to clinics

Moving from Bench to Bedside

We are here

To Do List:

- ☐
- ☐
- ☐
- ☐

But there is a lot to do first

Moving from Bench to Bedside

We are here

To Do List:

- ☐ Show PEPITEM increases Bone volume
- ☐
- ☐
- ☐

We have shown that PEPITEM increases bone volume

Moving from Bench to Bedside

We are here

To Do List:

- [x] Show PEPITEM increases Bone volume
- [ ]
- [ ]
- [ ]

We have shown that PEPITEM increases bone volume

Moving from Bench to Bedside

We are here

To Do List:

- [x] Show PEPITEM increases Bone volume
- [ ] Find out how PEPITEM works
- [ ]
- [ ]

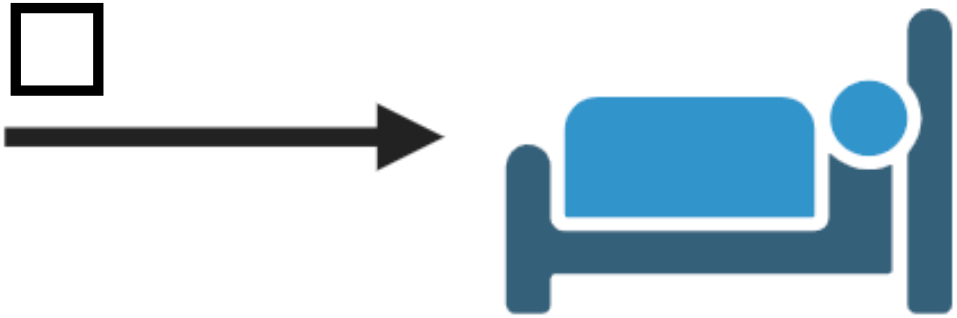
We've started to understand how PEPITEM works

Moving from Bench to Bedside

We are here

To Do List:

- [x] Show PEPITEM increases Bone volume
- [ ] Find out how PEPITEM works
- [ ] Make PEPITEM into a better medicine
- [ ]



Currently PEPITEM is so small it's quickly broken down in the body.
We need find ways to make it more stable or target the new pathway.

Moving from Bench to Bedside

We are here

To Do List:

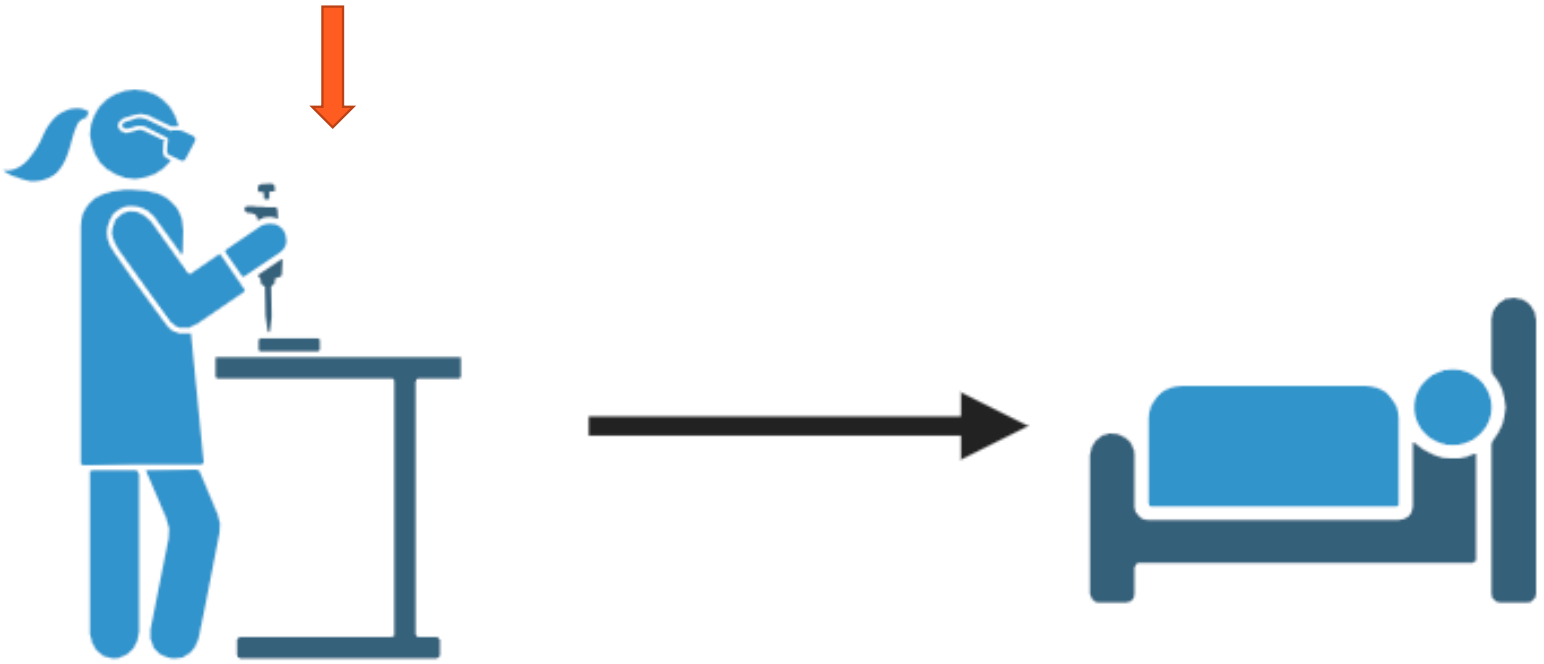
- [x] Show PEPITEM increases Bone volume
- [ ] Find out how PEPITEM works
- [ ] Make PEPITEM more Druggable
- [ ] Safety check

We also need to check PEPITEM's safety.
It is a natural protein but higher concentrations could still be harmful

Moving from Bench to Bedside

We are here

There is a way to go!



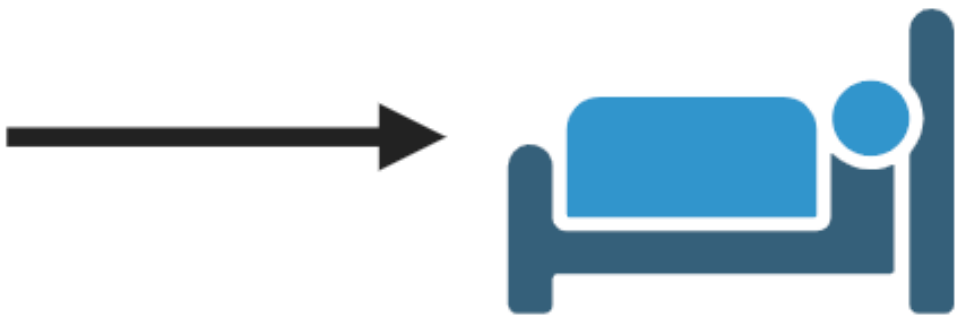
Moving from Bench to Bedside

We are here

There is a way to go!

BUT

It's a start and talking to YOU
can help us get there




Thank you for listening!