# Bone-Targeted Local Activation of a Cathepsin K Inhibitor Enhances Efficacy in Osteoporosis: Preserving Skeletal Readiness in the Female Warfighter

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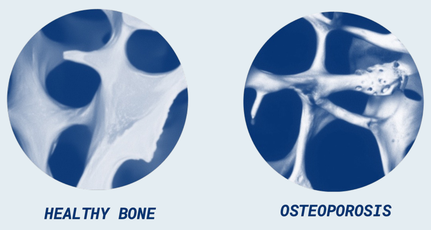
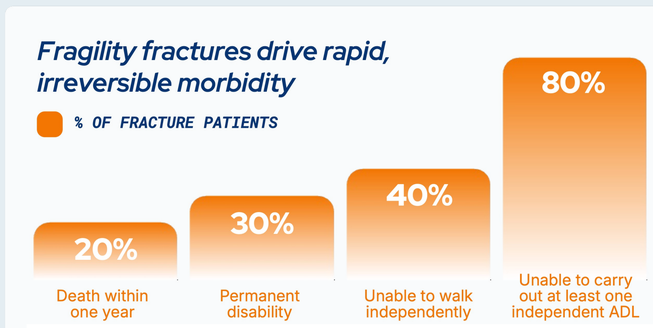
## Bone health is a readiness problem for the female warfighter

*Early risk factors – menstrual irregularity, rapid weight change – go unevaluated until skeletal decline is advanced.*



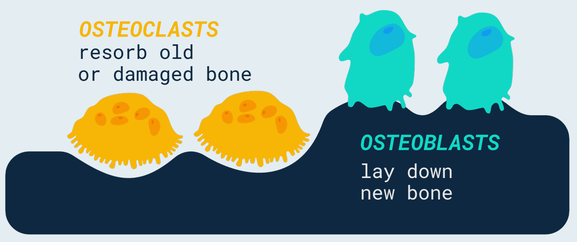

**> 1B** people affected worldwide

**65%** of medically nondeployable Soldiers – musculoskeletal injury

**20%** of female trainees sustain a stress fracture

*Of people over fifty* — *ONE IN 2 WOMEN* — *ONE IN 4 MEN* — *have osteoporosis*

## Osteoporosis results from dysregulated bone turnover, not simply bone loss

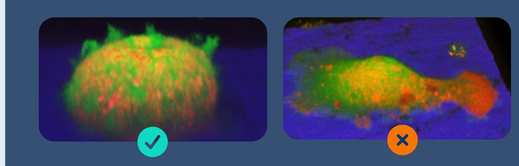



Indiscriminate killing of osteoclasts leads to reduced bone formation and increased fragility

Compensatory increases in bone formation exacerbates bone resorption, does not address the etiology of disease

**NOT ALL OSTEOCLASTS ARE THE SAME:**

Patterns of physiologic bone resorption are *unique* from inflammatory resorption.



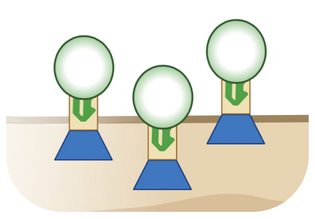

## OASIS Platform

OASIS: Osteoclast-Activated Skeletal Intervention System

- **Lead program:** SKE001, a bone-targeted cathepsin K inhibitor for postmenopausal osteoporosis
- **Enabling architecture:** OASIS localizes and activates payloads at sites of bone disease

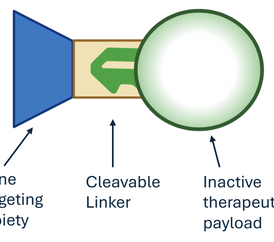
### Physical targeting

Affinity targeting enables accumulation at the bone surface.



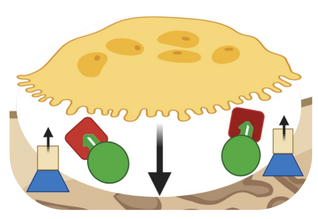
### Prodrug chemistry

Accommodates a diversity of payloads with masked activity.

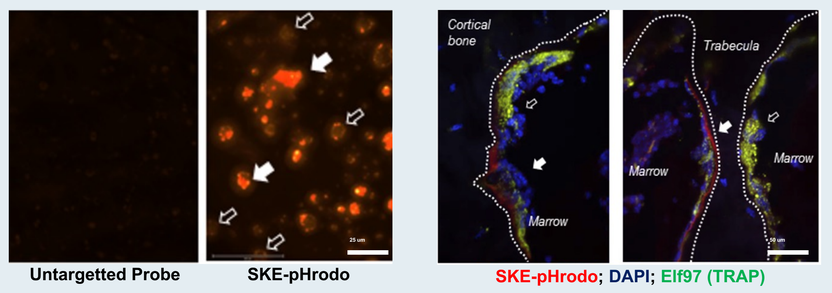



### Local activation

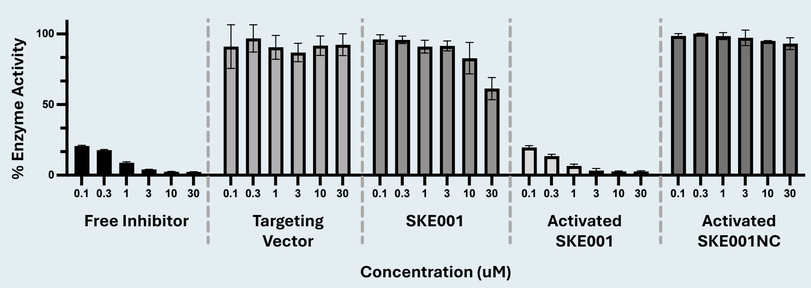
Limits drug activity to actively resorbing OC.



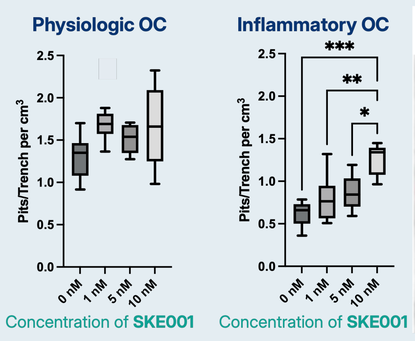
**OASIS** efficiently localizes to sites of bone turnover with single-OC specificity.




**Prodrug approach** limits target engagement to sites of resorption.

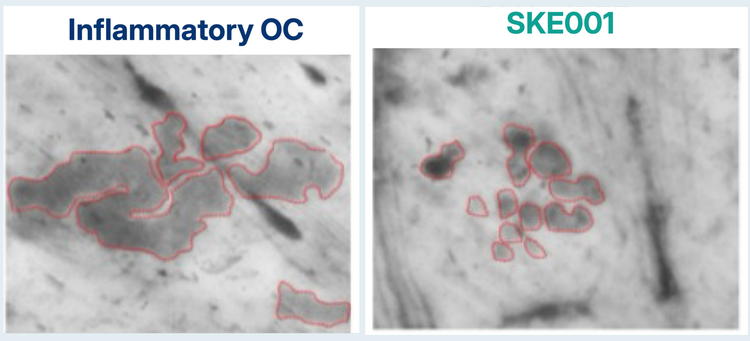



## SKE001 selectively suppresses disease-associated resorption



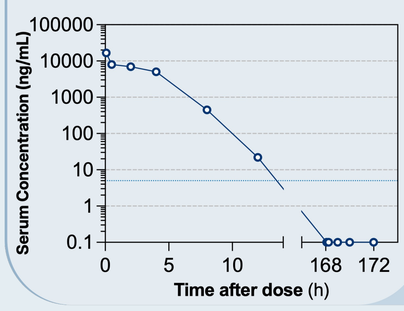




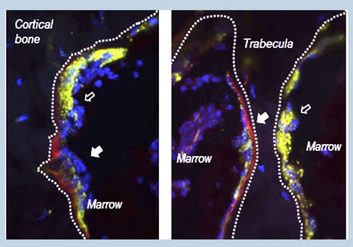



## Uncoupled PK/PD supports local bone activity rather than prolonged systemic exposure.

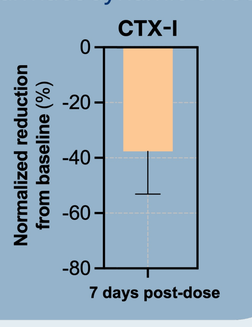
Rapid circulation and clearance of prodrug



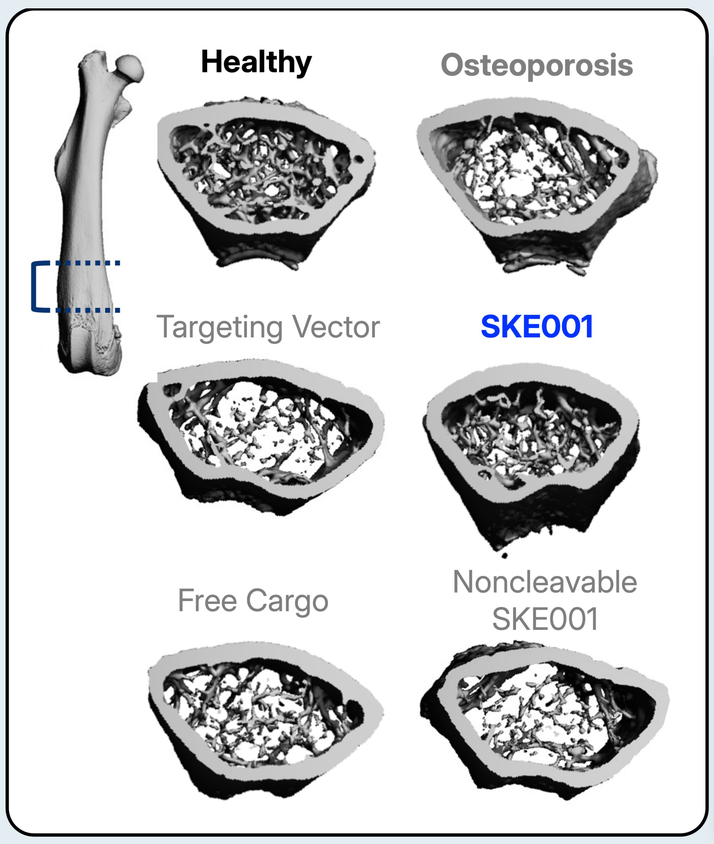

Redistribution selective to bone surfaces

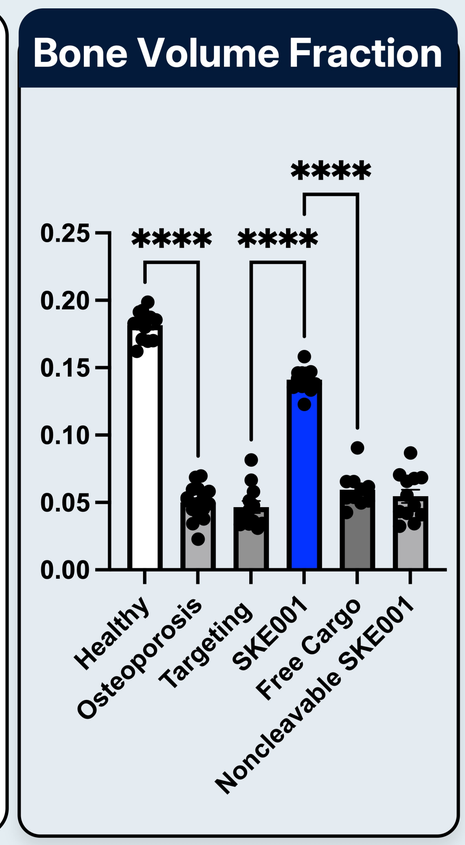



Durable pharmacodynamic effect




## SKE001 inhibits a validated pathway, restoring bone mass in a translational model of estrogen-deficiency bone loss




- **Skeletalis** has developed a small-molecule delivery platform uniquely capable of inhibiting inflammatory bone resorption and decreasing fracture risk without inhibiting bone formation.
- **SKE001** is a targeted medicine with tissue and cell specificity, enabling more specific intervention in disease progression.
- **Military relevance:** OASIS supports a shift from late-stage fracture repair to scalable prevention of skeletal decline in the female warfighter, preserving combat readiness.

**Disclosures:** The University of Michigan holds patent protection for the intellectual property disclosed in this work; Skeletalis has an exclusive, worldwide license to use it. Swanson, Weivoda, and Greineder are inventors and shareholders in Skeletalis.
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