

## Unlocking new treatments for bone diseases: using PEPITEM to strengthen bones and prevent loss

Despite appearances, bones are a constantly changing organ in the body. Cells that produce new bone (named osteoblasts) and cells that break down bone (named osteoclasts) work in harmony to ensure that old bone is continuously replaced, meaning that humans have a brand new skeleton roughly every 10 years. However, imbalances in the relationship between osteoblasts and osteoclasts can lead to excessive bone loss and ultimately cause diseases such as osteoporosis. Current treatments for diseases of bone loss often cause unwanted side effects. Therefore, new treatments are needed to improve the lives of patients who are plagued with bone-loss and begin their road to recovery.

We experimented with a new “peptide” called PEPITEM, looking at its role in health and disease in bone. PEPITEM is naturally produced in the body, but the amount produced reduces as we age. Using mouse models, we showed that treatment with PEPITEM increased bone production and decreased the breakdown of bone, ultimately leading to more and stronger bones.

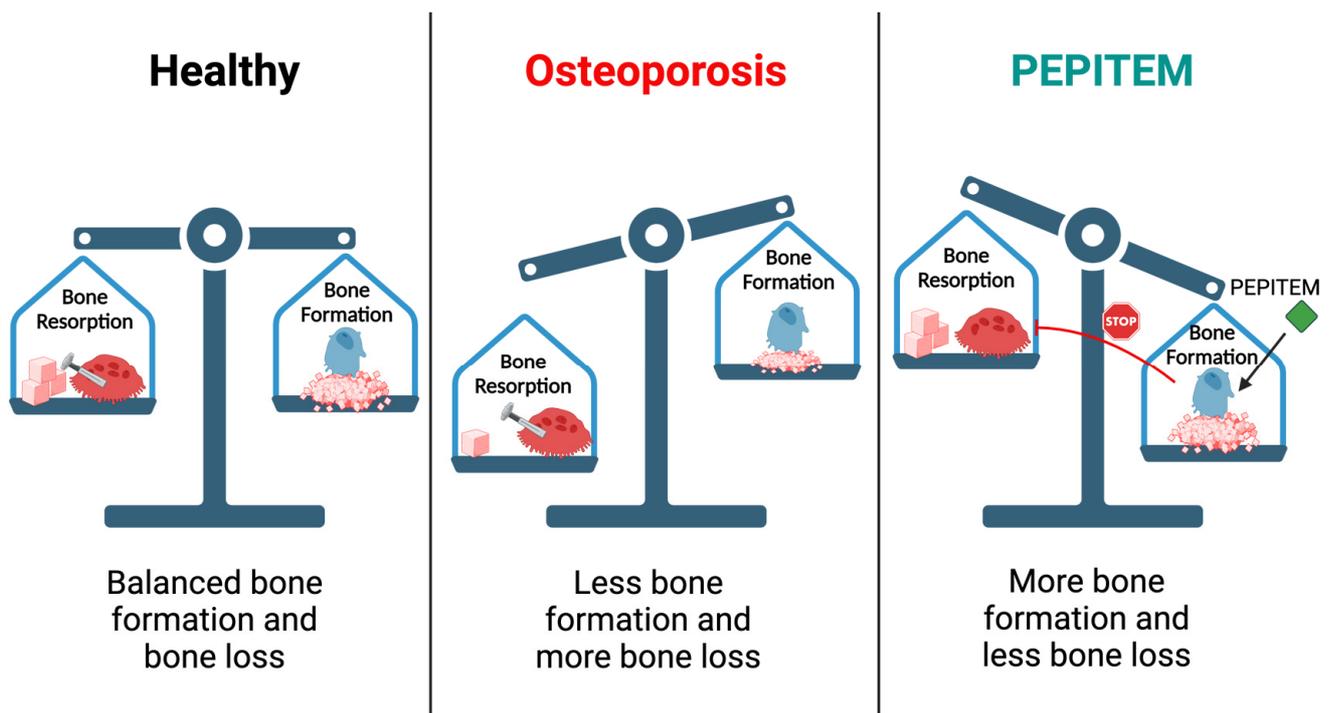


Fig. 1. In healthy bone, bone formation and bone resorption (removal) occurs at the same rate to maintain structure and function. In diseases such as osteoporosis, damaged bone is replaced at a much slower rate (i.e. less new bone is made) resulting in weaker and frailer bones. PEPITEM encourages new bone to be formed whilst limiting the removal of old or damaged bone. Development of PEPITEM as a new therapy for bone diseases could readdress the balance and allow natural bone repair to occur in patients to improve bone stability and strength.

To explore how PEPITEM caused this change in bone, we collected the osteoblasts from mouse and human bones (from patients who had undergone joint replacement surgery) and looked at how PEPITEM changed their bone production abilities. PEPITEM treatment increased the production of bone mineral by the osteoblasts, revealing how bone was increased in the mouse model. However, the way in which PEPITEM caused these changes was still unknown.

To solve this mystery, we investigated at all the proteins that PEPITEM can bind to (imagine a key fitting into a lock) and identified a protein called NCAM1 located on the surface of osteoblasts, as a key player. Inhibiting the ability of PEPITEM to bind to NCAM1 blocked the PEPITEM triggered increase in bone production, proving that this lock and key interaction was how PEPITEM works.

We also explored whether PEPITEM could influence bone destroying osteoclasts. We found that bone treated with PEPITEM had fewer osteoclasts, however those osteoclasts that remained were still able to perform their role of “eating” bone. The reason that fewer osteoclasts form following PEPITEM treatment was found to be because the osteoblasts make more of the osteoclast-inhibition protein OPG, rather than PEPITEM directing binding to osteoclasts. This is important because old bone must be removed to allow fresh healthy bone to be formed. Many of the side-effects of existing osteoporosis treatments are due to their complete prevention of osteoclast bone break-down.

Whilst improving healthy bone has its benefits, we also needed to test whether PEPITEM was beneficial the therapeutic potential of PEPITEM in diseased states. Using mouse models of age-related osteoporosis-induced bone loss and arthritis-induced bone damage, we showed that PEPITEM was able to halt the bone damage normally observed in both diseases. This offers a new type of drug for patients with bone loss diseases, which helps to halt damage as well as encouraging new bone to form – improving patient resilience to falls.

In summary, we found that PEPITEM can increase the production of bone in healthy and disease states by acting directly on osteoblasts and causing them to make more bone. This study therefore demonstrates the benefit of PEPITEM as a new therapeutic option in bone diseases.

***J.W. Lewis, K. Frost, E. Insch, A.J. Naylor, H.M. McGettrick***

*Rheumatology Research Group, Institute of Inflammation and Ageing, University of Birmingham, Edgbaston, Birmingham, B15 2TT, United Kingdom*

## **Publication**

[Therapeutic avenues in bone repair: Harnessing an anabolic osteopeptide, PEPITEM, to boost bone growth and prevent bone loss](#)

Jonathan W. Lewis, Kathryn Frost, Georgiana Neag, Mussarat Wahid, Melissa Finlay, Ellie H. Northall, Oladimeji Abudu, Edward T. Davis, Emily Powell, Charlotte Palmer, Jinsen Lu, G. Ed Rainger, Asif J. Iqbal, Myriam Chimen, Ansar Mahmood, Simon W. Jones, James R. Edwards Amy J. Naylor, Helen M. McGettrick  
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