Nucleic acid drug iSN40 shows promise for osteoporosis treatment

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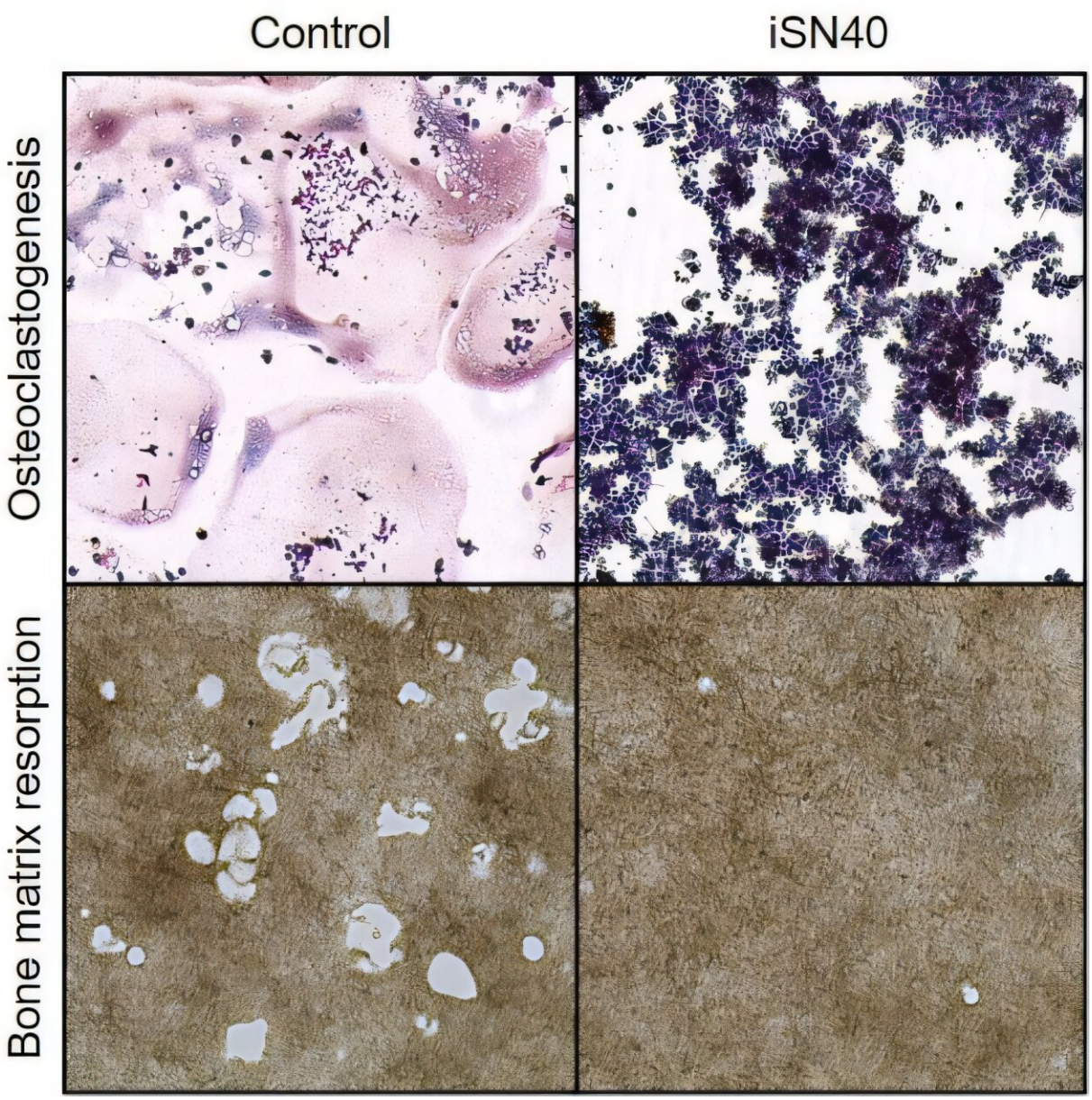

In a new study, researchers from Japan reveal that iSN40 suppresses osteoclast differentiation and bone matrix resorption, offering a potential therapeutic approach for osteoporosis by restoring the balance between bone formation and resorption. Credit: Dr. Tomohide Takaya, Shinshu University, Japan

Osteoporosis, characterized by an imbalance in bone remodeling, is a growing health concern worldwide. Previous research has highlighted the role of osteogenic CpG oligodeoxynucleotide (iSN40) in promoting osteoblast differentiation and supporting bone formation. A new study reveals that iSN40 also inhibits osteoclastogenesis, reducing bone resorption. By modulating both bone formation and resorption, iSN40 offers a potential new approach for the treatment of osteoporosis.

Osteoporosis leads to reduced bone density and an increased risk of fractures, particularly in aging populations. The imbalance occurs between osteoblasts, responsible for bone formation, and osteoclasts, which break down bone tissue. This disrupted process results in weakened bones and increased susceptibility to fractures.

In light of these challenges, there is an urgent need for effective and affordable treatments for osteoporosis. While current treatment options, including antibody-based drugs, offer some relief, they can be costly and not universally accessible. Alternative approaches, such as nucleic acid-based treatments, are being explored to address this growing concern.

Osteogenic CpG oligodeoxynucleotide (iSN40) has emerged as a promising candidate in this search for better solutions. In previous studies, iSN40 has been shown to stimulate osteoblast differentiation, promoting bone formation by enhancing mineralization. This process has been associated with increased bone strength and density, providing a potential pathway to improve bone health in those with osteoporosis.

A research team led by Associate Professor Tomohide Takaya along with Ms. Rena Ikeda, Chihaya Kimura, Dr. Yuma Nihashi, Dr. Koji Umezawa, and Dr. Takeshi Shimosato from the Faculty of Agriculture, Shinshu University, Japan, investigated the effects of iSN40 on osteoclast differentiation, an essential process in bone resorption. Their findings were published in the journal *Life* on November 30, 2024.

Osteoclasts play a crucial role in bone remodeling by breaking down bone tissue. Excessive osteoclast activity can lead to increased bone resorption, which contributes to osteoporosis. The findings revealed that iSN40 completely inhibits the differentiation of osteoclast precursor cells into mature osteoclasts, effectively reducing bone resorption.

"We were pleased to see that iSN40 not only promoted bone formation by osteoblasts but also inhibited osteoclast differentiation, which could have a major impact on preventing bone loss in osteoporosis," said Dr. Takaya. "By targeting both sides of the bone remodeling process, iSN40 has the potential to provide a balanced and effective treatment approach."

In laboratory experiments, iSN40 was shown to interfere with the signaling pathways involved in osteoclastogenesis, particularly through the toll-like receptor 9 (TLR9) in pre-osteoclasts. This inhibition resulted in a significant reduction in the expression of genes essential for osteoclast differentiation, thus suppressing the activity of these bone-resorbing cells.

"By targeting the TLR9 pathway, iSN40 effectively blocks the formation of osteoclasts, which play a critical role in osteoporosis development," says Dr. Takaya.

Further experiments in a co-culture system with osteoblasts and osteoclasts confirmed iSN40's dual action. The results indicated that

while promoting osteoblast activity and bone formation, iSN40 simultaneously inhibited osteoclast differentiation and suppressed bone resorption. This balanced effect makes iSN40 a promising candidate for osteoporosis treatment.

The study also highlighted that iSN40's effects were dose-dependent, allowing for careful adjustment of treatment to maximize therapeutic benefits.

Overall, the study paves the way for more affordable and effective treatments for osteoporosis, especially in light of the current burden on health care systems worldwide.

"With the potential to be used as a nucleic acid-based therapeutic, iSN40 could become an essential tool in addressing the growing osteoporosis epidemic, providing an alternative to costly antibody-based treatments," concludes Dr. Takaya.

More information: Rena Ikeda et al, Osteogenic CpG Oligodeoxynucleotide, iSN40, Inhibits Osteoclastogenesis in a TLR9-Dependent Manner, *Life* (2024). DOI: 10.3390/life14121572

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