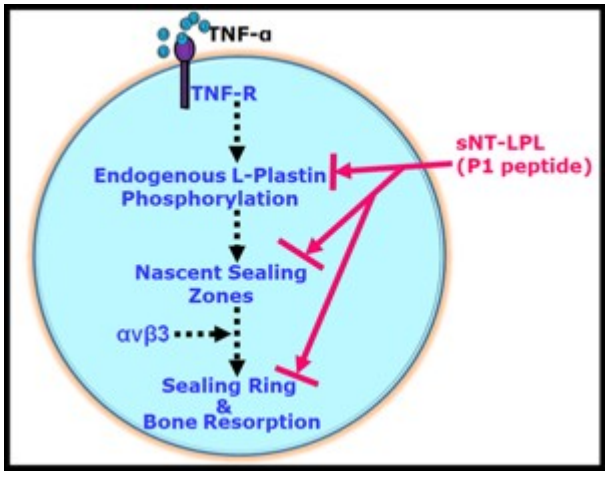
TECHNOLOGY

Inhibition of L-Plastin Activity in Osteoclasts to Reduce Bone Loss

OVERVIEW

Osteoclasts (OCs) are specialized cell types that develop a focused microenvironment where bone matrix degradation can occur for the process of bone resorption or bone breakdown. Bone breakdown by osteoclasts requires the formation of tight sealing zone or ring in order for efficient focal bone breakdown to occur. L-plastin (LPL) is a cytoskeletal-associated protein, regulates the formation of nascent sealing zones (NSZs) at the early phase of sealing ring inception. The formation of this tight sealing ring is necessary for efficient bone breakdown by OCs. The ability to inhibit the bone breakdown process is an attractive mechanism to potentially address bone-loss, a disease called osteoporosis. Osteoporosis is a common and incurable bone disease that weakens the bones and affects an estimated 10 million people in the US. This technology is a LPL peptidomimetic that has the potential to enter into OCs, suppress the phosphorylation of cellular LPL competitively and hence NSZs/sealing ring formation and bone resorption by OCs (schematic diagram below). Studies *in vitro* in osteoclast cultures and *in vivo* with mice identified LPL as a potential novel therapeutic target for osteoclast-mediated bone resorption.

Using a TAT-fused, amino-terminal small molecular weight LPL peptide (sNT-LPL) containing serine 5 and 7 aa residues, it was demonstrated that bone resorption can be reduced *in vitro* in OC cultures by significantly reducing NSZ and sealing ring formation, ultimately suppressing OC resorption activity. *In vivo,* studies using aging (40 wks) C57/BL6 female mice with a 15 week treatment course with sNT-LPL showed improved bone quality and reduced bone resorption. Interestingly, the peptidomimetic LPL inhibitors do not affect bone formation activity by osteoblasts. LPL peptidomimetic therapy will be a feasible intervention to control OC-driven aging and post-menopausal-associated bone loss.



APPLICATIONS

Osteoporosis remains a major public health concern worldwide. Decreasing levels of estrogen hormone in women affect normal skeletal bone remodeling resulting in postmenopausal osteoporosis. It is estimated that up to 20% bone mass is lost within 5 to 7 years after menopause. This type of osteoporosis occurs mainly in women 50 to 65 years of age. Bone loss is also a part of the natural aging process in men or women over the age of 75 years, resulting in hip fractures. By 2025, the cost of osteoporosis-related fractures in the U.S. is expected to exceed $25 billion each year to treat more than three million predicted fractures. Currently, the drugs approved for the treatment of osteoporosis are bisphosphonate antiresorptive and anabolic therapies. Although targeted therapies are currently available to treat and/or prevent osteoporosis by blocking OC activity, evidence shows that long-term treatments cause a reduction in osteoblast-mediated bone formation, resulting in atypical skeletal fractures. Therefore, novel and improved therapies are critically needed to more efficiently target osteoclast-mediated bone loss resulting in osteoporosis.

ADVANTAGES

Novel target for the treatment of bone resorption and potentially osteoporosis

STAGE OF DEVELOPMENT

Ongoing *in vivo* testing

Targeted delivery formulation testing

(RB- 3/11/19)

LICENSING POTENTIAL

Available for licensing

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Additional Information

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PATENT STATUS

U.S. Patent # 11,485,762 (issued 2022)

LICENSE STATUS

Available for licensing

CATEGORIES

- Therapeutics
- Biologics

INVESTIGATOR(S)

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ATTACHMENTS

- Download MC-2015-066 Marketing Summary Final.pdf

EXTERNAL RESOURCES

- Peptidomimetic inhibitors of L-plastin reduce the resorptive activity of OC but not the bone forming activity of OB in vitro

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