Modulation of the Microtubule-Dependent Mechanotransduction as a Therapeutic Intervention in Osteoporosis

Summary

Bones become thinner and weaker as a consequence of aging. By their mid-30s most individuals have greater bone resorption (bone mass loss) compared to bone formation. Osteoporosis is the result of this loss of bone mass and subsequent changes in bone structure, contributing to skeletal fragility and increased propensity of fractures. Osteocytes within the bone are responsible for bone formation. They sense mechanical loads and respond by altering gene expression and protein bioavailability of bone formation and remodeling factors. Stimulation of bone formation has become a key therapeutic approach for the treatment of osteoporosis. UMB researchers have recently discovered that microtubule (MT)-dependent cytoskeletal stiffness (CSK) mediates how osteocytes sense and respond to mechanical cues. Specifically, this technology centers around pharmacological interventions targeting microtubule network pathways to increase the mechano-sensitivity of osteocytes, serving to improve bone quality in patients with conditions characterized by low bone mass or skeletal fragility, such as osteoporosis. It could also potentially be used to preserve bone quality in healthy individuals. MT-targeting agents, such as anti-mitotic drugs and detyrosination inhibitors, could be used alone or in combination with existing drugs used to treat osteoporosis, such as biphosphonates, anti-sclerostin antibodies, estrogen mimetic compounds, and synthetic forms of parathyroid hormone.

Key Investigator

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Field

Musculoskeletal disorder

Technology

Method of treatment for osteoporosis

Advantages

Novel indication for novel and currently-approved compounds

Approach may restore bone mass and prevent bone loss

Status

Available for licensing and sponsored research

UMB Docket Reference

JS-2017-008

Technology

The MT network is required for the influx of calcium that occurs in response to mechanical (shear) stress. This MT-dependent increase in calcium influx activates calcium/calmodulin-dependent kinase II (CamKII), which in turn downregulates the bioavailability of sclerostin in osteocytes. Sclerostin is a protein critical to the control of bone turnover, widely implicated in osteoblastogenesis and *de novo* bone formation. ***Dr. Stains has shown that following mechanical stress, Taxol (an anti-mitotic, MT-targeting agent) reduces calcium influx in response to mechanical stress, blunting the downregulation of sclerostin and increasing sclerostin protein in bone in vivo.*** This work suggests that increasing the MT density, detyrosination and/or association with MT-associated proteins can change the set point at which mechanical stress can elicit a calcium response, restoring disease-induced aberrant mechano-signaling in osteocytes, and modulating sclerostin to promote new bone formation. Either alone, or as part of a combination therapy, MT-targeting compounds may lead to increased peak bone mass and preventing bone loss.

Market

In the US, 10 million Americans have osteoporosis and another 44 million have low bone density, representing half of all adults 50 years and older. This number is expected to increase to 13.2 and 57.4 million, respectively, by 2030. There are currently two classes of FDA-approved medications for the treatment of osteoporosis: 1) antiresorptive therapies, which slow down the breakdown of bone and help prevent bone loss and, 2) anabolic therapies, which helps make new bone, increasing bone density. Current treatment guidelines (2017) recommend treatment for a duration of 5 years. Although responsible for ~2 million fractures per year, 80% of older Americans with fractures are not tested or treated for osteoporosis, suggesting a potential expanded drug market with improved screening and treatment guidelines. The average cost of a month's supply of osteoporosis medications varies greatly, ranging from $39-$1500, depending on the drug class and availability of generic drugs, with a median cost is $163/month.

Technology Status

The MT-targeting agents parthenolide and Taxol have been tested in Ocy454 cultured osteocytes.

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