Tau Kinase Inhibitor for Preventing or Treating Glucocorticoid-Induced Osteoporosis

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Life Sciences/Biochemicals & Small Molecules

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Unmet Need

There is an increasing need for novel therapeutic approaches limiting the deleterious skeletal actions associated with the high dosage and long-term usage of glucocorticoids (GCs), while maintaining its beneficial anti-inflammatory effects.

Technology

The inventors have discovered that tau protein is a low-affinity receptor of glucocorticoids (GCs) and an essential player in high-dose GC-induced bone loss. Tau, also known by its role in the pathophysiology of Alzheimer's Disease (AD) and other tauopathies, is phosphorylated on Ser422 by the kinase TTBK1 upon GC binding. This leads to a downstream signaling cascade involving NFkB that eventually enhances osteoclastogenesis and causes glucocorticoid-induced osteoporosis (GIO). The inventors have shown in several rodent models of osteoporosis, that the TTBK1 inhibitor TRx0237, currently in phase III clinical trials for the treatment of mild AD, is both therapeutic and prophylactic against GIO through inhibition of tau phosphorylation in Ser422.

Background

Glucocorticoids (GCs) are immunosuppressive and anti-inflammatory drugs widely used in several autoimmune and inflammatory diseases, including rheumatoid arthritis, lupus, psoriatic arthritis, inflammatory bowel disease, and others. They modulate the immune system by interacting with GC receptors, thereby blocking pro-inflammatory cytokine production. Despite being the most widely prescribed drugs worldwide, with approximately 2.5 million people in the US taking GCs, high GC dosage and long-term use can lead to side effects such as hyperglycemia, disorders of lipid metabolism, myopathy, and secondary osteoporosis. Glucocorticoid-induced osteoporosis (GIO) is in fact the most common drug-induced cause of secondary osteoporosis, and around 50% of the individuals on long-term GC therapy will eventually develop GIO. The resulting fractures entail a high socio-economic burden in US and worldwide.

Applications

Use in combination with glucocorticoids (GCs) to treat inflammatory and autoimmune diseases (e.g. lupus, rheumatoid arthritis, inflammatory bowel disease), while preventing glucocorticoid-induced osteoporosis (GIO).

Advantages

Novel therapeutic option to both prevent and treat skeletal adverse effects of high-dose, long-term GC treatment

Strong safety profile as shown during the phase I-III clinical trials of TRx0237 for Alzheimer's Disease

Non-invasive, convenient, and safe administration route

- Orally administered

Well-characterized, disease-implicated signaling pathway

- NFkB cascade blocked by TRx0237 has been extensively studied in osteoporosis and suppression of bone resorption from the blockage is broadly established

IP Status

Provisional patent application pending