Salt-Inducible Kinase Activators to Treat Bone and Mineral Diseases

An innovative and efficacious oral treatment for bone and mineral diseases.

Technology

The Partridge Lab has demonstrated the utility of small molecule Salt-Inducible Kinase (SIK) activators to reverse severe bone and mineral abnormalities. In a bespoke mouse model, the Partridge Lab recapitulated the etiological hyperactive parathyroid hormone (PTH) signaling in osteoblasts common among numerous bone diseases. These animals exhibited enhanced expression of the major osteoclastogenic cytokine *RANKL*, resulting in the characteristic high bone turnover and severe bone abnormalities. As integral regulators of both PTH-mediated bone resorption and bone formation, SIKs represent unique therapeutic targets for treating both parathyroid-related bone and mineral diseases. In proof of concept studies, the Partridge Lab showed that knockdown of SIK2 and SIK3 in calvarial osteoblasts results in enhanced PTH-mediated CRTC2 nuclear translocation and subsequently enhanced *RANKL* expression. Conversely, the Partridge Lab has successfully utilized commercially-available small molecule activators of SIKs to reduce PTH-mediated *RANKL* expression, demonstrating the utility of these compounds in restoring bone and mineral homeostasis and resolving associated abnormalities.

Background

Multiple bone diseases are caused by hyperactive PTH signaling, including hyperparathyroidism, Jansen's metaphyseal chondrodysplasia (JMC) or Fibrous Dysplasia/McCune-Albright Syndrome (FD/MAS), as well as mineral disorders such as hyperphosphatemia and hypercalcemia. These bone diseases cause major developmental and disabling lifelong effects on the skeleton. JMC and FD/MAS are rare genetic bone diseases, resulting from the gain-of-function mutations in either the receptor for PTH, PTHR1, or the downstream signaling molecule Gsα. Current treatment of these diseases is limited to invasive surgery and palliative pharmaceutical injections. Moreover, numerous mineral disorders are also caused by aberrant PTH, such as hypercalcemia which is the leading metabolic disorder associated with cancer, affecting an estimated 2-30% of all cancer patients. The innovation described here offers a rational oral drug design strategy, as an alternative to surgery or injections for the treatment of patients suffering from these debilitating bone and mineral diseases.

Applications

Several bone and mineral diseases characterized by hyperactive parathyroid hormone signaling, including:

Technology ID

PAR07-01

Category

Life Sciences/Biochemicals & Small Molecules
Life Sciences/Therapeutics/Dental
Life Sciences/Therapeutics/Kidney Disease
Doug Brawley

Authors

Nicola Partridge, PhD

Learn more

- Hyperparathyroidism, primary and secondary
- Jansen's metaphyseal chondrodysplasia (JMC)
- Fibrous Dysplasia-McCune-Albright's Syndrome (FD/MAS)
- Hypercalcemia, of malignancy and others
- Hypophosphatemia
- Chronic kidney disease-metabolic bone disease

Advantages

- **Oral delivery:** Offers rational design of oral therapeutics
- **Eliminates surgery:** Eliminates standard-of-care surgery for bone diseases
- **Clear patient population:** Clear genetic link between hyperactive parathyroid hormone signaling and numerous bone and mineral diseases

Intellectual Property

NYU has filed a U.S. provisional patent application covering the method of using SIK activators (commercially-available and potentially proprietary compositions) for treating bone and mineral diseases.