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Characterization of a Novel Oral Small Molecule PTH1R Agonist: Proof of Concept for an Alternative to Injectable Peptide-based Therapy for Hypoparathyroidism

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Abstract

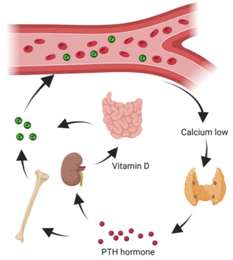
Hypoparathyroidism (HP), a rare endocrine disorder characterized by insufficient levels of parathyroid hormone (PTH), leads to hypocalcemia and hyperphosphatemia. Most HP cases arise due to damage of the parathyroid glands during thyroid or neck surgery. HP symptoms include severe muscle cramps, tingling, burning and numbness, memory loss, and headaches, all leading to a decreased quality of life. Calcium and vitamin D supplementation do not fully ameliorate the disease and may contribute to renal disease. Chronic HP increases the risk of major complications, such as calcium depositions in the brain, eye, and kidneys. Similarly, it can lead to low bone turnover and increased bone mineral density with associated increased bone mineralization. In comparison to standard of care and traditional injectable PTH1R agonist peptide-based therapies, oral small molecules may have multiple advantages clinically. However, there are no oral small molecules currently in development.

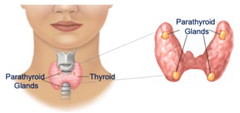
Here we describe the characterization of novel, potent, and selective oral small molecules, and show that they act on PTH1R as agonists and elicit similar downstream effects to PTH peptides. To assess PTH1R engagement in the major targeted organs, kidney and bone, expression of PTH1R target genes were accessed in both tissues. In kidney, CYP27B1 and CYP24A1, two key enzymes involved in Vitamin D conversion and activation, were reciprocally regulated in the kidney by both PTH and small molecule treatment. In bone, the expression of coupling genes that bridge anabolic / catabolic activities (RANKL and OPG) were both similarly upregulated by PTH and small molecule treatments. Importantly, oral administration of a single dose of SP-1805 in a rat surgical thyroparathyroidectomy (TPTx) model resulted in significant upregulation of serum calcium levels for a period of 24 hours in a dose dependent manner at 3, 10 and 30 mg/kg. Repeat treatment of SP-1353 in TPTx animals for 28 days demonstrated sustained serum calcium upregulation at 3 and 5 mg/kg. The observed degree of serum calcium regulation is comparable to injectable PTH peptides currently in development to treat hypoparathyroidism.

These data suggest that oral small molecule PTH1R agonists engage PTH pathways similar to native PTH and have the potential to replace injectable PTH peptides to treat PTH-related disorders, including hypoparathyroidism.

Background

PTH functions through activation of the parathyroid hormone 1 receptor (PTH1R), a class B G protein-coupled receptor. The main target tissues for PTH1R activation include bone and kidney. In the kidney, PTH stimulates reabsorption of calcium and at the same time inhibits tubular phosphate reabsorption, promoting phosphate excretion into the urine. In bone, PTH binds to PTH1R on osteoblasts that are responsible for bone formation and stimulates release of calcium by indirectly activating osteoclasts which are responsible for bone resorption. In addition, PTH indirectly acts on the intestine by inducing renal 1-alpha hydroxylation of calcidiol to become calcitriol (also known as 1,25-dihydroxyvitamin D3, or active vitamin D). Calcitriol acts on the intestine to increase calcium and phosphate absorption.





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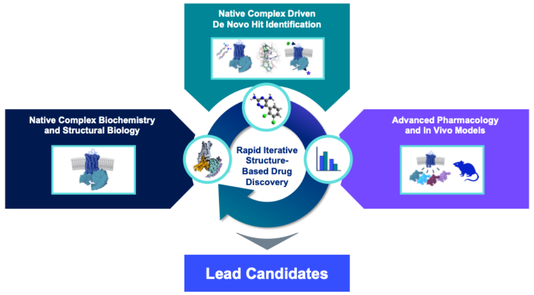
Septerna's Native Complex Platform™

- ✓ Novel technology for isolating and purifying wild-type G protein-coupled receptors (GPCRs) and reconstituting them with transducers (e.g., G proteins) and ligands (endogenous and synthetic)
- ✓ Leverages a modern discovery toolbox that includes structural biology and screening technologies such as DNA-encoded libraries and virtual screening to unlock difficult-to-drug GPCR targets

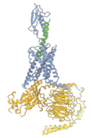


Novel Hit Discovery Technologies and Rapid Structure-Based Drug Design

- ✓ Discovery of novel small molecule ligands with a diverse range of activities including agonists, antagonists, and positive and negative allosteric modulators
- ✓ Rapid and iterative structure-based drug design:
  - Enables novel insights into compound mechanisms
  - Establishment of structure-activity relationships to drive rapid compound optimization
  - Discovery of novel ligand binding sites for molecular docking, molecular dynamics simulations and virtual screening
  - Optimizing selectivity between related GPCRs and across species
- ✓ Allows translation into and from functionally relevant cell-based & in vivo disease models

Discovery of PTH1R Agonists

- ✓ The Native Complex Platform™ was applied to PTH1R, a historically difficult-to-drug small molecule target and yielded multiple tractable chemical series.
- ✓ A novel orthosteric agonist series was discovered with high potency and selectivity and promising pharmaceutical properties including high oral bioavailability and pharmacokinetic properties compatible with daily dosing.



PTH1R

PTH1R small molecule agonists with high potency and optimized drug properties

Results

Figure 1. Agonist effects of PTH peptide, SP-1462 and SP-1805 on kidney and bone suggests similar PTH1R pathway and tissue engagement. To assess PTH1R-mediated effects in key target organs (kidney and bone), Sprague Dawley rats were treated with PTH, SP-1462 and SP-1805 for 2 or 6 hours and RNA was isolated from the cortex of the kidney and the tibia. Gene expression analysis showed PTH1R-regulated genes were similarly impacted by both PTH peptide and small molecule agonists.

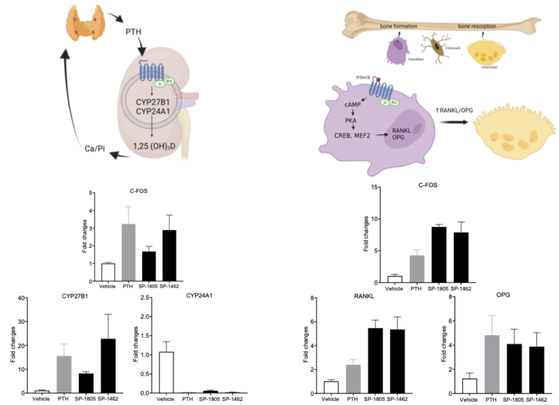
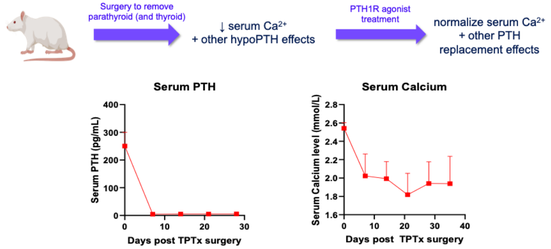


Figure 2. TPTx is a translatable preclinical model with sustained decrease of endogenous PTH and serum calcium. TPTx model mirroring surgical loss of parathyroid glands was developed in Sprague Dawley rats. One week post surgery, the animals showed sustained low serum PTH and significant decrease of serum calcium levels, similar to what is observed in HP patients. To determine treatment efficacy, PTH1R agonists were administrated after the serum calcium was stabilized.



Results

Figure 3. A single dose of SP-1805 restored serum calcium and phosphorus levels to the normal range in a TPTx rat model similar to PTH peptide. TPTx animals were randomized by body weights, serum calcium, and phosphorus. Administration of a single dose of SP-1805 showed a dose-dependent upregulation of serum calcium and downregulation of serum phosphorus similar to a long acting PTH peptide.

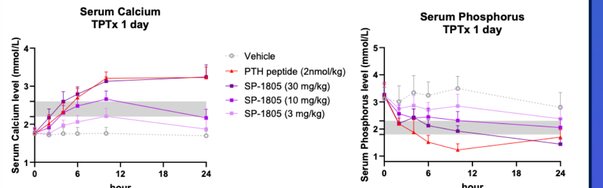
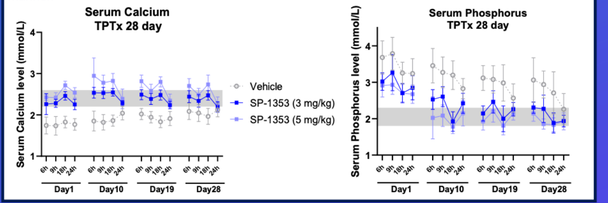


Figure 4. Daily dosing of SP-1353 restored serum calcium and phosphorus levels to the normal range in TPTx rats. Daily oral administration (BID) of SP-1353 at 3 and 5 mg/kg for 28 days was associated with sustained regulation of serum calcium and phosphorus levels in a dose-dependent manner.



Summary

- Septerna's Native Complex Platform™ drove the rapid discovery of multiple potent oral PTH1R agonists with promising drug-like properties.
- Similar to PTH, Septerna compounds activate PTH1R and elicit downstream effects on bone and kidney by regulating key genes important for calcium homeostasis.
- In the TPTx rat model, Septerna compounds show sustained control of serum calcium and phosphorus levels over 28 days with daily oral administration.
- Together, these data suggest an effective oral small molecule alternative to PTH peptides for the treatment of PTH-related disorders, including hypoparathyroidism.

Acknowledgements and Disclosures

- At the time the work was conducted, all authors were employees and shareholders of Septerna, Inc..
- All in vivo studies were conducted under supervision of an Institutional Animal Care and Use Committee.
- The authors wish to acknowledge the contributions of all Septerna employees who strive to accelerate the discovery and development of meaningful therapies for patients.