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Treatment of Lowe Syndrome

A novel therapeutic strategy uses allosteric activators and high-throughput screening to restore enzymatic function for the treatment of Lowe Syndrome and Dent-2, with potential for oral pharmaceutical compositions.

Lowe Syndrome (LS) and Dent-2 (D2) are incurable genetic diseases with treatment options focusing on symptoms and having limited effectiveness. The symptoms of these diseases are severe and include ocular, neurological, and renal abnormalities, with culmination in early death. The diseases arise from mutations in the OCRL1 (oculo-cerebro-renal syndrome of Lowe) gene, leading to dysfunctions in the inositol 5-phosphatase Ocrl1 enzyme. Allosteric activators, through their ability to stabilize the enzymatically active conformer of the Ocrl1 enzyme, have emerged as a potential component in developing therapies for these diseases.

Purdue Researchers have utilized allosteric activators to develop a therapeutic strategy that leverages the changes in Ocrl1 enzyme that do not directly impact the enzyme's catalytic site but lead to phosphatase domain inactivation. Researchers have developed a variety of allosteric activators that can be combined into effective pharmaceutical compositions that show promise when administered in therapeutic quantities. These compositions, which include carriers, excipients, and other common pharmaceutical additives like lactose, mannitol, glucose, hydroxypropylcellulose, and microcrystalline cellulose, can be administered via various routes. Researchers have also developed various formulations suitable for oral administration, some of which are tablets, powders, syrups, and others, with options for sugar or gastric/enteric coating for tablets and pills as needed. This approach shows potential for providing a first-of-a-kind treatment for LS or D2 disease and could also be adapted to tackle other similar genetic diseases.

Technology Validation:

- Suppression of the Golgi/OCRL1 fragmentation phenotype in specific cell lines (HK2 OCRL KO cells stably expressing OCRL10451G) was shown

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Category
Pharmaceuticals/Drug Discovery & Development
Pharmaceuticals/Small Molecule Therapeutics
Pharmaceuticals/Drug Delivery & Formulations
Pharmaceuticals/Research Tools & Assays

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- Restoration of enzymatic function was seen when 4-PBA (4-Phenyl Butyric Acid) was used as well as suppression of the phenotypes of other OCRL1 mutated variants (D451G, V508D or I393F)

- High-throughput screening process involving three compound libraries (LOPAC1280, the ChemBridge 30Klibrary, and the 7.2Kfragmented library) was used to assess the impact on the enzymatic activity of the OCRL10451G variant

Advantages:

- Targeted application towards restoration of enzymatic activity of proteins

- High-throughput screening for screening of large number of compounds

- Personalized treatment for LS or DS through identification of different mutated variants of a protein.

Applications:

- Treatment of LS or DS

- Drug discovery for related diseases

- Personalized medicine

TRL: 3

Intellectual Property:

Provisional-Gov. Funding, 2022-11-08, United States | PCT-Gov. Funding, 2023-11-07, WO | NATL-Patent, 2025-05-08, United States

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