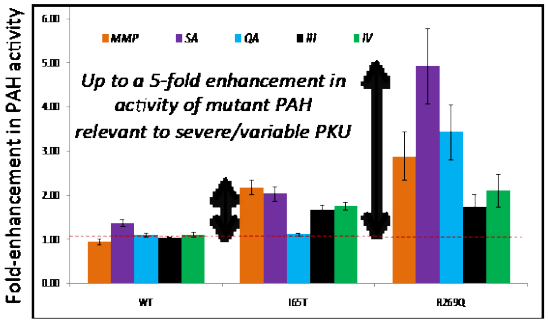
Plant-derived Pharmacological Chaperones for Treatment of Phenylketonuria (PKU)



Stabilization effect of 3 PCs (orange, purple, blue) and two reference compounds (black, green) on WT and two PKU-mutants (I65T and R261Q) of PAH

Abstract

Pharmacological chaperones (PCs) are a promising strategy for the treatment of genetic disorders based on enzyme enhancement therapy, such as phenylketonuria (PKU). PKU is a common in-born error of amino acid metabolism that is related to more than 500 disease-causing mutations of phenylalanine hydroxylase (PAH) or by a defect in the synthesis or re-generation of tetrahydrobiopterin (BH4). To date, lifelong dietary Phe-restriction and BH4 supplementation are the only accepted treatment options for PKU patients. However, special low-protein diets can lead to malnutrition, psychosocial or neurocognitive complications due to *poor compliance*, while BH4 therapy is costly and *only* 20-30% of PKU patients are responsive.

Using a novel screening strategy to identify small molecules from a chemical library with chaperone activity, McMaster researchers have identified plant-derived natural products (and synthetic analogs) that enhance the activity of denatured/inactive *wild-type* PAH and two clinically relevant PKU *mutant enzymes*. These plant-derived natural products are present in variable amounts in the human diet and thus offer a safe yet effective therapeutic treatment of PKU via nutritional supplementation, notably for patients with *severe phenotypes*.

Applications and Advantages

- Enzyme replacement therapy has recently been shown to reduce plasma Phe levels by 40% in mouse models of PKU. However recombinant enzyme therapy is costly and requires careful monitoring to avoid toxicity and immunogenicity.
- Only a handful of studies have identified putative PCs to correct the folding of PKU mutants and most of these have had only *modest* efficacy in enhancing mutant PAH activity.
- The current PCs can be administered orally and are safe natural products already present in the human diet. They offer a simple way to *rescue mutant PAH from cellular degradation in vivo* thus enabling rapid clinical translation. An unprecedented <u>*5-fold*</u> enhancement in mutant PAH activity has been demonstrated with lead PC candidates.

Tech ID

15-066

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Patent Status

US Provisional

Stage of Research

Proof of Principle data available.

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