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Biocatalytic Redesign for Phenylketonuria: Engineered Pah Variants with Clinically Relevant Improvements in Stability, Activity, and Immunogenicity

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Human phenylalanine hydroxylase (hPAH) catalyzes the hydroxylation of L-phenylalanine (L-Phe) to L-tyrosine, initiating a catabolic pathway that subsequently feeds into neurotransmitter synthesis. Phenylketonuria (PKU) arises from an hPAH deficiency, resulting in toxic levels of L-Phe and a reduction in neurotransmitter precursors within the central nervous system, which together cause cognitive disabilities and neurological damage. While therapeutics such as Kuvan and Pegvaliase have significantly advanced PKU treatment, current pharmaceutical interventions face limitations in pan-specificity, age restrictions, and immunogenicity. Enzyme replacement therapy (ERT) is among the most discussed approaches in this area, with hPAH being a favorable candidate due to its low immunogenicity. In this work, we present the development of engineered hPAH with improved thermostability and enzymatic activity, offering potential for ERT in PKU patients.