Biocatalytic deuterium incorporation into amino acid substrates by PLP-dependent enzyme GntC

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The substitution of hydrogen atoms with their slightly heavier isotope deuterium (D) is a conservative chemical change that can have a dramatic impact on a compound's bioactivity. Select addition of D atoms can improve the pharmacokinetics of existing drugs by reducing their oxidative metabolism, leading to an increase in their *in vivo* circulation and physiological effects. This strategy has been previously employed to enhance the lifespan of pharmaceutical agents like deutetrabenazine (Huntington's disease treatment), RT001 (neurodegenerative diseases), and notably, the modified amino acid *d3*-L-DOPA (Parkinson's disease). While chemical strategies exist to incorporate D atoms into drug-like molecules, biocatalytic approaches using pyridoxal-5'-phosphate (PLP)-dependent enzymes have become increasingly popular due to their environmentally-friendly conditions and use of deuterium oxide (D2O) as a D source.

Recently, our lab collaboratively elucidated the biosynthetic pathway of guanitoxin, a potent cyanobacterial neurotoxin. The second biosynthetic step uses the PLP-dependent enzyme GntC to catalyze an intramolecular cyclization on a modified arginine substrate. *In vitro* D2O protein assays and liquid chromatography-mass spectrometry analyses have identified that GntC incorporates up to three D atoms in both its product and substrate. Subsequent investigation into GntC has identified that it efficiently deuterates polar and positively charged amino acids, deviating from the substrate scope of previously established PLP-dependent biocatalysts. We are continuing to investigate the applicability of GntC to produce scalable quantities of deuterated amino acid-like molecules. We intend to use this biocatalytic tool to produce deuterated substrates for use as late-stage intermediates in biomedical research.

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