



Colloquium

Studying and engineering metalloenzymes through genetic code expansion

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Studying enzyme function or engineering enzymes often relies on mutagenesis that enables only coarse-grain modifications that radically change the target amino acid. Using genetic code expansion to introduce non-canonical amino acids (ncAAs) can enable atomistic control of mutagenesis. However, histidine remains challenging to systematically target with this method. Histidine has the highest catalytic propensity among canonical amino acids, enabled by its ability to play versatile roles in catalysis, including as an acid, a base, a nucleophile, and a coordinating ligand to a catalytic metal. Herein, we describe a toolkit consisting of nine new aminoacyl-tRNA synthetase/tRNA pairs for the site-specific genetic encoding of an expanded set of 12 new histidine-like ncAAs. The 12 ncAAs feature broadly tuned nitrogen pKaH, alternative heterocycles, and varying substitution patterns. Herein, we present the rationale for ncAA selection, the evolution of the toolkit, and applications of the tool kit to study metalloenzymes.

Thursday, November 5, 2026 10:30am - 12:00pm

Office Bldg West / Ground floor / Heinzl Seminar Room (I21.EG.101)



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