

## **DESIGN AND EVOLUTION OF ENZYMES WITH NON-CANONICAL CATALYTIC MECHANISMS**

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Enzyme design and evolution strategies rely exclusively on Nature's standard amino acid alphabet of twenty canonical residues which contain limited functionality. Here we demonstrate that incorporation of non-canonical amino acids into enzyme active sites provides a fruitful avenue to probe complex biological mechanisms and can lead to the creation of designed enzymes with wholly new catalytic functions. Significantly, optimization of enzyme activity can be achieved using directed evolution workflows adapted to an expanded genetic code. We are optimistic that this integration of enzyme design, genetic code expansion and laboratory evolution can provide a versatile strategy for creating enzymes with catalytic functions not accessible to Nature.