

UCSD NANO & CHEMICAL ENGINEERING  
**SPECIAL SEMINAR**

March 6th 2023

Seminar Presentation: 9:30am – 10:30am

**SME Room 248**



*“Evolving enzymes for biocatalysis and gene editing”*

**Monica Neugebauer, PhD**

*NRSA Post-doctoral Fellow*

*MIT and Harvard*

**Abstract:** Enzymes catalyze chemical transformations with exquisite selectivity. Through directed evolution, we can reprogram enzymes for applications in biocatalysis and medicine. In the first part, I will discuss my work to discover, characterize, and engineer Fell/ $\alpha$ -ketoglutarate-dependent enzymes that halogenate unactivated Csp3—H bonds. I solved the anaerobic crystal structure of a novel lysine halogenase (BesD), discovered homologs that enable the formation of nine new chlorinated amino acids, and developed enzymatic cascades to produce chlorinated heterocycles, diamines, keto-acids, and peptides. Through structural studies and high-throughput screening, I investigated the mechanistic basis for regioselectivity and catalytic selectivity within this enzyme family and used the resulting insights to engineer hydroxylases to perform halogenation with activity and selectivity comparable to that of native halogenases. In a second story, I developed novel cytosine base editors (CBEs) through directed evolution. Base editors consist of a programmable DNA binding protein, such as catalytically impaired Cas9, fused to a deaminase enzyme, and enable precise nucleotide changes within a target site in the genome. CBEs, which convert C•G base pairs into T•A, are typically larger and have more undesired off-target editing than their adenine base editor (ABE) counterparts. To develop a new class of CBEs that retain the favorable properties of ABEs, I used continuous protein evolution to evolve ABEs to instead perform highly efficient cytosine base editing within therapeutically relevant sites and cell types. These newly evolved base editors overcome several limitations of existing CBEs and demonstrate the power of protein evolution for addressing challenges in biotechnology.

**Educational Development and Training:** The projects described in this talk encompass a broad range of interdisciplinary techniques and benefitted from the contributions of trainees across various career stages, including those at the undergraduate level.

**Biosketch:** Monica obtained her B.Sc. in Chemical and Biological Engineering from MIT, where she conducted research in the laboratory of Prof. Alice Ting. She then earned her Ph.D. in Chemical and Biomolecular Engineering from UC Berkeley in the group of Prof. Michelle Chang. During her Ph.D., she discovered novel biosynthetic pathways and engineered enzymes for biocatalysis. As a post-doctoral fellow in the laboratory of Prof. David Liu at the Broad Institute of MIT and Harvard, she used directed evolution to develop novel gene editing tools with enhanced therapeutic properties. Her research uses protein evolution to develop useful tools and to gain basic mechanistic insights into enzymatic catalysis including the Nature Nano Award.