

OS23-3 **The Creation of New Functional Molecules by Rational Design at Protein-Protein Interface of Fatty Acid Synthase and Polyketide Synthase**

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Polyketides, non-ribosomal peptides, and fatty acids are complex molecules biosynthesized by large enzyme complexes called polyketide synthase (PKS), non-ribosomal peptide synthetase (NRPS), and fatty acid synthase (FAS), respectively. These large enzyme complexes consists of 10 – 100+ enzyme domains and biosynthesized a specific product by a highly choreographed transportation of building blocks among the enzyme domains. How protein-protein interactions in PKS, NRPS and FAS help convey product specificity remains largely a mystery, and the lack of such knowledge has hampered rational design of complex molecules via mega-synthase engineering. Presented herein is our recent progress in the structural and functional studies of a trans-acyltransferase PKS-NRPS and FAS that focus on the engineering of protein-protein interface to promote new complex molecule formation. Data of X-ray crystallographic structures, protein NMR, molecular dynamic simulation, *in vitro* and *in vivo* assay results are presented to provide a high resolution and dynamic picture of mega-synthases in action.