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Harnessing Genomic Recombination to Improve Microbial Metabolic Phenotypes

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The microbial production of energy, pharmaceutical, and industrial compounds is a growing alternative to traditional, often costly, production processes. Many naturally occurring metabolic pathways of *Escherichia coli* and *Saccharomyces cerevisiae* have been enhanced for increased production of desired compounds. However, despite numerous advances, optimization of metabolic phenotypes faces many challenges as pathway improvement often requires both the redirection of intermediates and reestablishment of gene regulation – frequently requiring the modulation of many genes simultaneously. Furthermore, predicting the complement of genes that function cohesively for an organism to achieve a chosen metabolic phenotype may be exceedingly difficult, particularly if those gene products act at a distance from the pathway enzymes themselves. Genome shuffling (GS), a recently introduced strain improvement strategy, addresses these challenges through the use of genomic recombination to increase the genetic diversity of a population. When coupled with phenotypic screening and genome sequencing, GS holds the potential to discover genetic alterations that improve a phenotype as well as establish connections between gene products that may not otherwise be intuited from our current understanding of gene function or metabolic networks. Here, we present our recent efforts to develop protocols for protoplast fusion and genome shuffling in the industrial organisms *E. coli* and *S. cerevisiae.* We also discuss our current shuffling-based screens and selections that test the feasibility and effectiveness of GS in a directed application, namely increased production of the carotenoid 4,4′-diapolycopene, a product of the isoprenoid pathway. Through deep sequencing and comparative genomics, we will assess the new genotypes of strains that arise from this approach. As all isoprenoids share common metabolic precursors, the strains and genomic knowledge generated through this research may be applicable to the biosynthesis of a wide number of valuable industrial, pharmaceutical, and energy-related compounds. The results of this study will deepen our understanding of metabolic networks and will increase our knowledge of the diverse genomic landscapes that may converge on a select phenotype.