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Strategies to Improve Resistance and Production Phenotypes of *E. coli*

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Many of the microbial phenotypes of interest to metabolic engineers are complex in that multiple genes, pathways, and regulatory networks are involved in generating the targeted behavior. *A priori* prediction of additional changes that will further improve phenotypes can therefore prove difficult due to our incomplete understanding of the functions and connectivity of gene products far removed from the pathway of interest. One complement to rational approaches is to exploit the strength of mutation and selection or screening to obtain strains capable of improved resistance to pretreatment growth improved production titers in the case of production phenotypes. Towards these goals, we are employing and refining methods that rely on natural or augmented mutation rates or on directed protein evolution to improve *E. coli* phenotypes. Our three major avenues of investigation include selection for inhibitor resistance by continuous culture in chemostats, development of inducible and temperature sensitive mutator plasmids, and generation and screening plasmid libraries of mutated gene regulators for enhanced phenotypic behavior. We are interested in both the genetic and regulatory alterations that underlie phenotypic improvements.

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