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Increasing Mevalonate Production by Engineering the Metabolism of Escherichia coli

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Synthesis of the anti-malarial drug, artemisinin, precursor mevalonate in *Escherichia coli* branches from acetyl Co-A which is the entry point to TCA cycle. We have been using genetic and environmental manipulations to redirect carbon flux from the endogenous central metabolic pathways (CMPs) to the heterologous pathway precursors. Deletion the production pathways of acetate, which is an undesirable product of excessive glycolytic flux, result in excretion of pyruvate rather than help increase mevalonate production. Heterologous mevalonate pathway from *Enterococcus faecalis* is more effective to draw carbon flow than that of *Saccharomyces cerevisiae*. Providing limited amount of nitrogen source also efficiently cut carbon flux to biomass and redirect it to mevalonate production. We are also performing metabolic flux analysis using 13C-labeled glucose. This information will help us determine how carbon flux through native metabolic pathways is affected by the presence of heterologous pathways, allowing us to identify and correct bottlenecks in the artemisinin production pathway. Successful completion of this project will provide insights into the metabolic status of living cells under different conditions and help us build a robust bacterium capable of producing high levels of artemisinin from cheap carbon sources.

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