Model-driven discovery of synergistic inhibitors against E. coli and S. enterica serovar Typhimurium targeting a novel synthetic lethal pair, aldA and prpC - DTU Orbit (25/12/2018)

Mathematical models of biochemical networks form a cornerstone of bacterial systems biology. Inconsistencies between simulation output and experimental data point to gaps in knowledge about the fundamental biology of the organism. One such inconsistency centers on the gene aldA in Escherichia coli: it is essential in a computational model of E. coli metabolism, but experimentally it is not. Here, we reconcile this disparity by providing evidence that aldA and prpC form a synthetic lethal pair, as the double knockout could only be created through complementation with a plasmid-borne copy of aldA. Moreover, virtual and biological screening against the two proteins led to a set of compounds that inhibited the growth of E. coli and Salmonella enterica serovar Typhimurium synergistically at 100-200 μM individual concentrations. These results highlight the power of metabolic models to drive basic biological discovery and their potential use to discover new combination antibiotics.
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