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Improved Network Performance via Antagonism: From Synthetic Rescues to Multi-drug Combinations

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Recent research shows that a faulty or sub-optimally operating metabolic network can often be rescued by the targeted removal of enzyme-coding genes--the exact opposite of what traditional gene therapy would suggest. Predictions go as far as to assert that certain gene knockouts can restore the growth of otherwise nonviable gene-deficient cells. Many questions follow from this discovery: What are the underlying mechanisms? How generalizable is this effect? What are the potential applications? Here, I will approach these questions from the perspective of compensatory perturbations on networks. Relations will be drawn between such synthetic rescues and naturally occurring cascades of reaction inactivation, as well as their analogues in physical and other biological networks. I will specially discuss how rescue interactions can lead to the rational design of antagonistic drug combinations that select against resistance and how they can illuminate medical research on cancer, antibiotics, and metabolic diseases.

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