Use of collateral sensitivity networks to design drug cycling protocols that avoid resistance development.

New drug deployment strategies are imperative to address the problem of drug resistance, which is limiting the management of infectious diseases and cancers. We evolved resistance in Escherichia coli toward 23 drugs used clinically for treating bacterial infections and mapped the resulting collateral sensitivity and resistance profiles, revealing a complex collateral sensitivity network. On the basis of these data, we propose a new treatment framework—collateral sensitivity cycling—in which drugs with compatible collateral sensitivity profiles are used sequentially to treat infection and select against drug resistance development. We identified hundreds of such drug sets and demonstrated that the antibiotics gentamicin and cefuroxime can be deployed cyclically such that the treatment regimen selected against resistance to either drug. We then validated our findings with related bacterial pathogens. These results provide proof of principle for collateral sensitivity cycling as a sustainable treatment paradigm that may be generally applicable to infectious diseases and cancer.