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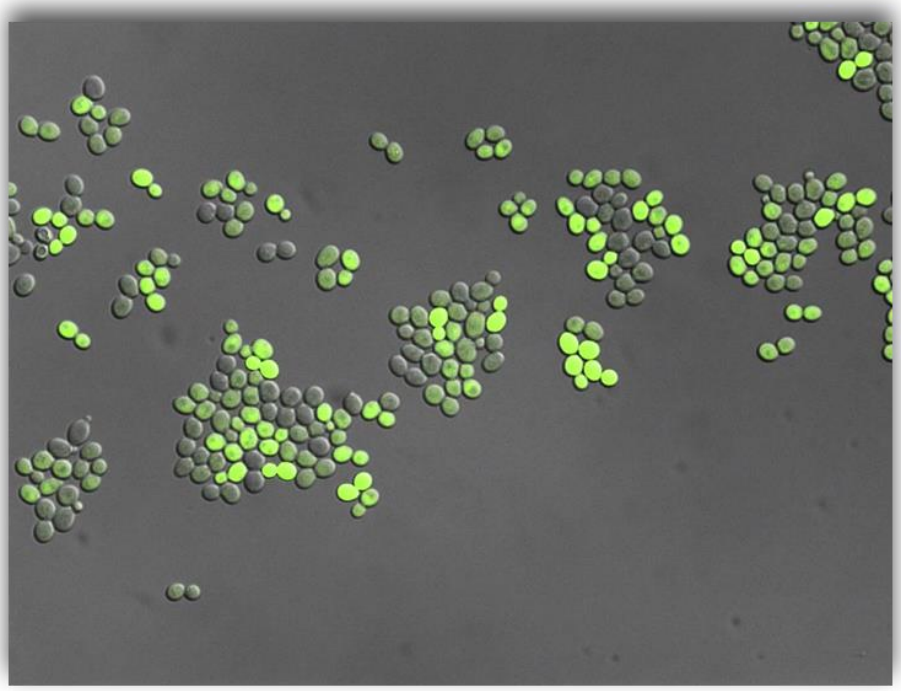
Spontaneous Development of Drug Resistance in a Synthetic Gene Network



The development of drug resistance is a serious problem that reduces therapeutic susceptibility and complicates the treatment of infectious disease and cancer. To explore non-genetic causes of spontaneous drug resistance in rapidly proliferating cell populations, we constructed a set of synthetic transcriptional regulatory networks in yeast Saccharomyces cerevisiae to control the expression of the pleiotropic drug resistance gene PDR5. This gene is a conserved homologue of a human multidrug resistance gene (MDR1) that protects cells from many first line chemotherapies and implicated in the development of drug resistant cancers. For this reason, we hypothesized that transcriptional regulation may contribute to drug resistance and examined how certain transcriptional regulatory network features, or motifs, contribute to cell survival in the presence of a cytotoxic drug. Our results reveal that the coherent feedforward motif can enhance cell survival in the presence of the drug by allowing rapid and prolonged activation of gene expression, and that combining coherent feedforward and positive feedback motifs leads to increased drug resistance. These observations provide direct evidence that certain gene network motifs cause reduced susceptibility to drug treatment and underscore the importance of regulatory network interactions in the development of non-genetic drug resistance.