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Narrowing the search for suicide genes. A few genes have been shown to protect animal cells against the lethal action of suicidal agents like mitomycin C. We tested whether the gene coding for mouse dihydrofolate reductase (DHFR) can protect human HeLa cells against apoptosis-inducing ligands. Treatment with methotrexate (MTX) protected the cells from apoptosis induced by TGF-beta, actinomycin D or etoposide but not by staurosporine or UV-irradiation, as expected from previous results. Remarkably, MTX also protected the cells against staurosporine-induced apoptosis in the presence of human but not mouse dihydrofolate reductase. Human dihydrofolate reductase was expressed at the mRNA and protein levels in

staurosporine-treated cells and in staurosporine-resistant clones. In addition, our results indicate that the targeted inactivation of a single gene, like DHFR, may be more powerful than the use of gene-activated suicide systems like the herpes simplex virus thymidine kinase-ganciclovir combination.

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