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9-Aminoacridine inhibits ribosome biogenesis and synergizes with cytotoxic drugs to induce selective killing of p53-deficient cells.

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Common cancer treatments target rapidly dividing cells and do not discriminate between cancer and normal host cells. One approach to mitigating negative side-effects of cancer treatment is to temporarily arrest cell cycle progression and thus protect normal cells during cytotoxic treatments, a concept called cyclotherapy. We recently proposed that transient inhibition of post-transcriptional steps of ribosome biogenesis (RBG) can be used to selectively arrest p53-positive host cells and not p53-null cancer cells. In this study, we investigated whether cytoprotective RBG inhibition can be achieved through small

molecule treatment. We report that treatment of cells with 9-aminoacridine (9-AA) inhibits pre-rRNA processing as well as RNA Polymerase I (Pol I) transcription, in a dose-dependent manner. We propose a mechanism for 9-AA inhibition of RBG by disruption of binding between pre-ribosomes and small nucleolar RNAs (snoRNAs) required for rRNA maturation. Our data also indicate that the mechanism of Pol I inhibition by 9-AA is distinct from that of actinomycin D (Act D), an established Pol I inhibitor. We demonstrate in a model 3T3 cell system that low doses of 9-AA that reversibly inhibit RBG can be protective for p53-positive cells and used in synergy with anti-cancer agents camptothecin and methotrexate to selectively kill p53-negative cells. The ability of 9-AA to cause RBG inhibition, as well as the decoupling of the inhibition of Pol I transcription and pre-rRNA processing, positions acridines as a new tool for RBG and cyclotherapy research.