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Inhibitors that reduce the acquisition of antibiotic resistance

The rapid emergence of antibiotic resistance is a worldwide crisis, endangering the efficacy of antibiotic treatment. A recent article in Scientific America (December 16, 2014) highlights the importance of developing strategies for reducing antibiotic resistance and prolonging the life of current antibiotics, where they state that "The true cost of antimicrobial resistance (AMR) will be 300 million premature deaths and up to $100 trillion (£64 trillion) lost to the global economy by 2050". The rise in antibiotic resistance has become a particular concern with the emergence of antibiotic resistant "superbugs" in the clinic, which stresses the need for strategies that prolong the lifetime of antibiotics, as the pipeline of new antibiotics is not keeping pace with the development of resistance

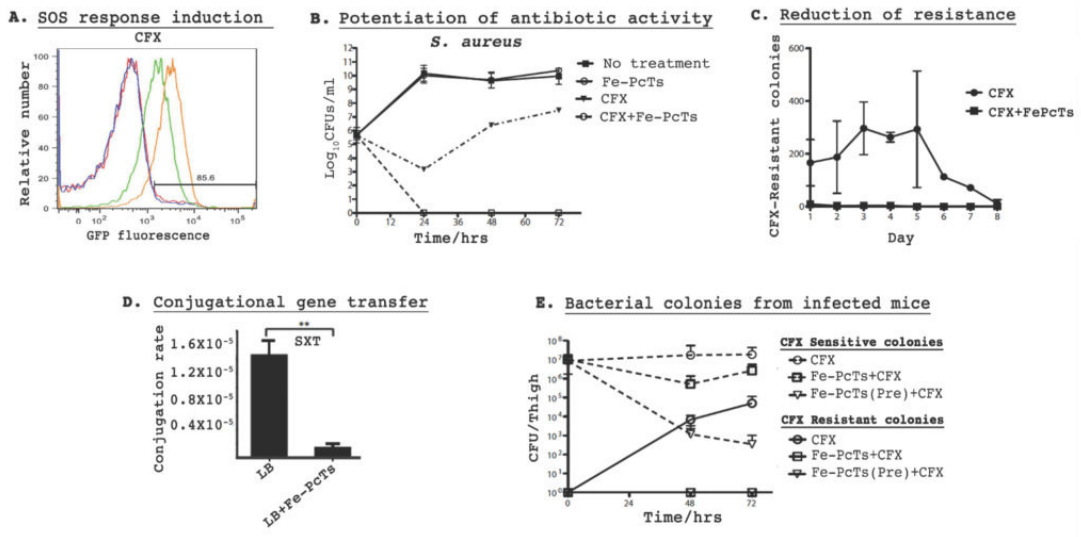

Fig. 1. RecA inhibitor, Fe-PcTs (iron(III) phthalocyanine-4, 4', 4'', 4'''-tetrasulfonic acid) inhibits bacterial SOS response, potentiates antibiotic activity, inhibits horizontal gene transfer, and reduces the acquisition of antibiotic resistance. A. SOS response induction in *E. coli* treated with Fe-PcTs and ciprofloxacin (CFX). SOS response was monitored using an *E. coli* strain (SS996) engineered to express GFP under the control of the LexA-regulated sulAp promoter. GFP expression was measured using flow cytometry three hours after addition of CFX (2.5 μM) in the presence or absence of Fe-PcTs (25 μM). B. Potentiation of CFX activity by Fe-PcTs in S. aureus ATCC2913 (Gram-positive). Cells were untreated (No treatment), treated with Fe-PcTs (25 μM), treated with CFX (6.5 μM), or treated with CFX (6.5 μM) and Fe-PcTs (25 μM). CFUs/ml was determined at indicated time points. Errors bars represent the SD from three independent experiments. C. Fe-PcTs reduces the acquisition of CFX resistance. *E. coli* (ATTC29522) cells were cultured on LB plates containing CFX (40 nM) with or without Fe-PcTs (25 μM). CFX-resistant ATTC29522 CFUs obtained in the presence and absence of Fe-PcTs per day. Error bars represent the SD from three independent experiments. D. Inhibition of conjugational gene transfer of mobile genetic elements (SXT) between donor (VB82) and recipient (VB38) strains by Fe-PcTs. Conjugation experiments were carried out on LB agar plates containing 10 g/l NaCl with or without 50 μM Fe-PcTs. Conjugation rate was calculated as conjugants observed per recipient cell. Error bars represent the SD from three independent experiments where *$p < 0.05$ and ** $p < 0.01$. E. In vivo analysis of Fe-PcTs activity in neutrapenic mouse bacterial infection model. Mice were infected with ATCC25922 cells and treated with CFX or CFX and Fe-PcTs. Fe-PcTs was either administered 24 hours before CFX treatment (pre-) or co-administered with CFX. Mice were sacrificed at 48 and 72 hours and ATCC25922 cells from mice thighs were cultured on LB plates with or without CFX (40 nM) to determine the number of CFX-sensitive (dashed lines) and CFX resistant (solid lines) cells. Error bars represent SD from five independent experiments.

In our recent publication in the journal *Cell Chemical Biology,* we outlined a strategy to block the development of resistance and prolong the life of antibiotics. This paper describes the development and characterization of a new class of phthalocyanine-based RecA inhibitors. RecA is a recombinase that is activated during bactericidal antibiotic treatment. Activated RecA turns on the SOS response by inactivating the SOS response repressor protein LexA.

Treatment of bacteria with our RecA inhibitor reduced the ability of bactericidal antibiotics to turn on SOS response pathway (Fig. 1a). This makes bacteria more sensitive to antibiotic treatment (Fig. 1b), as well as reducing their ability to acquire antibiotic resistance mutations (Fig. 1c) and genes (Fig. 1d). RecA inhibitors are effective in Gram positive and Gram negative bacteria including two multi-drug resistance bacteria: *Pseudomonas aeruginosa* and *Staphylococcus aureus*. RecA inibitors also potentiated the activity of ciprofloxacin and reduced the development of ciprofloxacin in a neutrapenic mouse bacterial infection model (Fig. 1e).

Our study highlights the advantage of including RecA inhibitors in antibiotic therapies by demonstrating their ability to potentiate the activity of antibiotics and to block the development of antibiotic resistance, both of which will ultimately prolong antibiotic shelf life.

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Publication

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