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New weapons against antimicrobial resistance: Targeting SOS response to recover bactericidal activity of antibiotics

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Drug Resistant Bacteria represent a global emergency, limiting the effective treatment of bacterial infections.The development of novel strategies fighting bacterial infections is strongly desirable. The SOS pathway has been recently validated as a key target for combating the evolution of antibiotic resistance. In bacteria the SOS response is orchestrated by two proteins: RecA, the sensor protein, and LexA, the regulator one. As a consequence of damage to the DNA, RecA monomers can form large nucleoprotein filaments on single stranded damaged DNA and promote self-cleavage of LexA, a repressor binding a palindromic sequence of 16 base pairs (lexA binding Box), thus inducing the expression of more than 40 genes involved in DNA repair and mutagenesis.
In an effort to identify new LexA inhibitors, starting form the available LexA crystal structures, a structure based virtual screening of a database of available chemicals was conducted, searching for potential inhibitors able to block proteolytic activity of LexA C-terminal domain. In parallel, a full gene-to-crystal structure pipeline of a sequence coding for recombinant LexA C-terminal domain have been optimized in order to characterize and screen the most promising hits. In parallel, new approaches for high-throughput *in vitro* screening of small compounds libraries have been developing in our laboratory. Such an approach has the potential to open up new strategies for reversing drug resistance by targeting the SOS response.