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POSTER ABSTRACTS – SESSION 1 (DEC. 15, 2014)

Combating Bacterial Drug Resistance by Targeting the Enzymes of Evolution

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Award: New Innovator Award

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The combination of a rising tide of bacterial drug resistance and the lack of novel therapies makes for a particularly dire situation in infectious diseases. In response to this need, we are interested in altering the paradigm for combating antibiotic resistance by targeting the very pathways that allow bacteria to mutate, adapt and evolve. Adaptation and the acquisition of drug resistance are tied to the pathway that governs stress responses, known as the SOS pathway. Activation of the SOS response is regulated by a key repressor-protease, LexA, which undergoes auto-proteolysis in the setting of stress, resulting in de-repression of adaptive SOS genes. Targeting LexA's self-cleavage therefore represents an attractive approach for slowing acquired antibiotic resistance by preventing adaptation and acquired drug resistance. Building towards this goal, we have dissected the unique active site architecture of LexA's protease domain, providing a basis for the rationale design of probes or inhibitors of the SOS pathway. This biochemical analysis demonstrated that the rate of LexA self-cleavage can be altered by mutations surrounding its scissile bond. By generating bacterial strains which span the full gamut of activation rates for LexA, our studies have also suggested that modulating the cleavage rate of LexA can tune bacterial evolution. Tunability in the SOS response overturns the notion of the SOS pathway as an on-or-off response and provides evidence for evolution is a dynamic and regulatable process in bacteria. These studies provide additional insight into bacterial evolution in response to antibiotics and further support the viability of targeting the SOS pathway as a novel approach to combating bacterial pathogens.