Poster Presentation

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Developing an antibiotic effective against multi-drug resistant bacteria.

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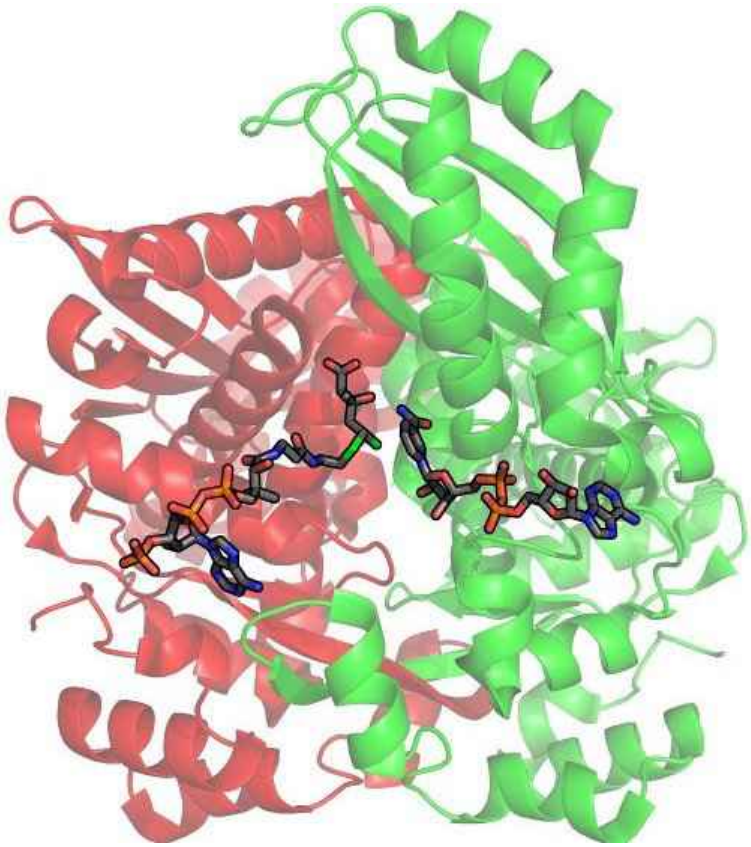
The emergence of multi-drug resistant pathogenic bacteria is one of the great challenges to modern medicine. The gram positive cocci Methicillin Resistant Staphylococcus aureus (MRSA) and Vancomycin Resistant Enterococcus faecalis (VRE) are two particularly virulent examples. In vivo studies have shown that the eukaryotic like 'mevalonate' isoprenoid pathway used by these pathogenic cocci is essential to their growth and virulence [1]. Our structures of HMG-CoA reductase (HMGR) from P. mevalonii demonstrated that the bacterial enzymes are structurally distinct from the human enzymes allowing for specific antibacterial activity [2]. High throughput in vitro screening against bacterial HMGR at the Southern Research Center, Birmingham, AL uncovered a lead compound with an IC50 of 80 µM with a competitive mode of action. Our x-ray crystal structures of HMGR from E. faecalis complexed with the lead compound and its variations have informed the synthesis of new inhibitors that have improved the IC50 to 5 µM [3]. Studies of this compound show it to be active against both MRSA and VRE in culture, effective against these bacteria in biofilms, and efficacious in a model system of eukaryotic infection. Structures and kinetics of these compounds will be presented and future directions discussed.

[1] *Wilding et al, J Bacteriol. 2000 Sep;182(18):5147-52.,* ***[2]*** *Steussy et al, Biochemistry. 2013 Aug 6;52(31):5195-205,* ***[3]*** *Steussy et al, Manuscript in preparation*



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