

W0218

**Structures of HMG-CoA Synthase Complexes Reveal Mechanistic Details.** Michael J. Theisen<sup>1</sup>, Ila Misra<sup>2</sup>, Dana Saadat<sup>2</sup>, Henry M. Miziorko<sup>2</sup>, David H.T. Harrison<sup>1</sup>, <sup>1</sup>Rosalind Franklin Univ. of Medicine & Science, North Chicago, IL 60064, <sup>2</sup>Medical College of Wisconsin, Milwaukee, WI 53226.

HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) is a precursor molecule necessary for isoprenoid biosynthesis including cholesterol. The gene has been shown to be essential for many gram-positive bacteria. HMG-CoA synthase (HMGS) condenses acetoacetyl-CoA (AcAc-CoA) with an acetyl group from acetyl-CoA to yield HMG-CoA. The structures of 1) *Staphylococcus aureus* acetyl-S-enzyme intermediate complexed with AcAc-CoA, and 2) the product complex of enzyme with HMG-CoA have been determined in the space groups P2<sub>1</sub> and P1 at a resolution of 2.0 Å. Overall, the fold is homologous to the β-ketoacyl-acyl carrier protein synthases (KAS) with distinct differences in the active site. These complexes constitute structures on the catalytic pathway and confirm a key mechanistic role for Cys111. Further, the structures strongly implicate the functions of Glu79 and His233 in the condensation step as the catalytic base and acid, respectively. Interestingly, solution studies show enhanced cleavage of HMG-CoA in the presence of the enzyme and the ability to form a covalent adduct with HMG-CoA with mutated avian enzyme. These findings suggest that the two complexes have nearly the same free energy.