

**W0408**

**Human Carboxylesterase 1 in Cholesteryl Ester Hydrolysis and Atherosclerosis.** S. Bencharit<sup>1</sup>, C.L. Morton<sup>2</sup>, E.L. Howard-Williams<sup>1</sup>, P. Kuhn<sup>3</sup>, P.M. Potter<sup>2</sup>, M.R. Redinbo<sup>1</sup>, <sup>1</sup>Univ. of North Carolina at Chapel Hill, <sup>2</sup>St. Jude Children's Research Hospital. <sup>3</sup>The Scripps Research Institute.

Human Carboxylesterase 1 (hCE1) acts as a neutral cholesterol ester hydrolase controlling the level of cholesterol in macrophages. Accumulation of cholesteryl esters leads to macrophage foam cell transformation, the first step in creating an atherosclerotic plaque. Overexpression of hCE1 in macrophages inhibits this transformation. We have reported the first structures of hCE1, which have elucidated hCE1's promiscuous and specific roles in narcotic and xenobiotic metabolism. No structural information exists on the roles of hCE1 in cholesterol and fatty acid metabolism. Here we present the crystal structures of hCE1 in complexes with coenzyme A, homatropine-palmitate-coenzyme A, cholate-palmitate, and taurocholate. These structures show that hCE1 utilizes its "side door" secondary product exit pore in the hydrolysis of fatty acyl coenzyme A substrates and cholesteryl esters. We conclude that hCE1 acts as an enzymatic bioscavenger in macrophages and requires its side door to process large and small endogenous compounds. These structures provide insights into hCE1's role in preventing atherosclerosis and heart disease.