

W0409

Human Carboxylesterase 1: Structural Insights into a Multifunctional Bioscavenger. C.D. Fleming¹, S. Bencharit¹, C.L. Morton², E.L. Howard-Williams¹, P.M. Potter², and M.R. Redinbo¹, ¹Univ. of North Carolina at Chapel Hill. ²St. Jude Children's Research Hospital.

Human Carboxylesterase 1 (hCE1) is a broad-spectrum bioscavenger with roles in drug and narcotic metabolism, including the metabolism of heroin and cocaine. We present three crystal structures of hCE1 in complexes with cholesterol lowering drug mevastatin at 3.0 Å resolution, a fatty acyl ethyl ester (FAEE) analogue ethylacetate at 3.0 Å resolution, and the breast cancer drug tamoxifen at 3.1 Å resolution. These structures outline three ways hCE1 functions as a bioscavenger in the body. First, the enzyme hydrolyzes small ester linkages in xenobiotics, which leads to the activation of drugs like mevastatin, or the clearance of cocaine. Second, hCE1 can transesterify short and long aliphatic chains with ethanol to create ethylacetate or FAEE's, toxic metabolites that arise from alcohol abuse. Third, hCE1 can bind to clinical drugs such as tamoxifen and traffic them to other detoxifying enzymes like cytochrome P450s. The structures presented here may enhance the use of hCE1 in prodrug therapies, the treatment of narcotic abuse, or the prophylactic protection from nerve agents.