Chemical Biology Approaches for Uncovering Interindividual Variability in Drug Metabolism

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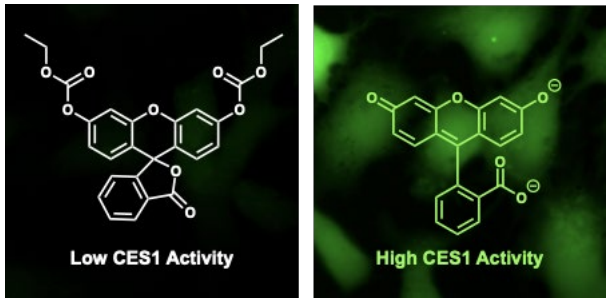

Abstract
Much of life is dictated by the spatial organization of (bio)chemical reactions. One area this plays a role in human health is the localization of drug metabolizing enzymes in the digestive tract and liver. Variability in the activity of these enzymes can cause person to person differences in the efficacy and safety of orally administered small molecule therapeutics. This has been studied in context several key enzymes involved in drug metabolism, however, the factors that influence carboxylesterase (CES) activity have been relatively understudied despite their established role in the hydrolysis of many xenobiotic esters. We believe that this lack of knowledge is due to the scarcity and limitations of currently available techniques to investigate CES activity in live samples. To address the need for new approaches to study CESs, we have developed new fluorogenic chemical tools that can specifically report on CES activity in live cells. Subsequently, we demonstrate our tools can identify potential CES-mediated drug-drug interactions and use these tools to create an assay that can identify CES sequence-dependent activity variations in live cells. Overall, the chemical tools and approaches we generated can help uncover factors that result in variability in response to treatment with CES-substrate drugs.

Biosketch
Professor Beck received his B.S. in Chemistry with a Biochemistry concentration and ACS certification from Tennessee Technological University in 2011. During his undergraduate studies, he conducted research with Professor Edward C. Lisic, synthesizing metal-thiosemicarbazone complexes and examining their antimicrobial effects. He then earned his Ph.D. in Chemistry from the University of Michigan in 2015, working with Professor Mi Hee Lim and spending the final year of his graduate studies as a visiting research scholar at the Ulsan National Institute of Science and Technology in South Korea. His graduate work focused on creating small molecule chemical tools to investigate metal-protein interactions in neurodegenerative diseases. Afterwards, he worked as a postdoctoral scholar with Professor Bryan Dickinson at the University of Chicago, where he developed fluorogenic chemical tools to study covalent cysteine post-translational modifications. Professor Beck joined the faculty at Eastern Illinois University in the Department of Chemistry and Biochemistry in Fall 2019 and leads a research group that focuses on providing students with the opportunity to gain experience and learn the skills they need to succeed in the next stage of their scientific training or career. To achieve this, his group uses common techniques and approaches to pursue cutting-edge research at the interface of chemistry and biology. Current projects in his research group focus on designing and using small molecule chemical tools in live systems to understand spatially organized (bio)chemical processes that impact human health.