Summary/Abstract
The proposed project will forge a collaboration between two EHSCC Centers, each of which has a long but independent history addressing the need for novel functional biomarkers for early detection of exposure to environmental toxicants. NIEHS-supported basic research projects that were inspired by community engagement activities at our respective Centers (Center for Environmental Health Sciences (CEHS) at MIT and the Center of Excellence in Environmental Toxicology (CEET) at UPenn) have established two research projects that will be bonded together in this study. At MIT, we specialize in DNA adducts as risks to informational integrity and we have developed an early-onset pattern of mutations that predicts later-life cancers in livers of animals and humans known or suspected to have been exposed to aflatoxin B_1. The technology can detect a carcinogen-specific pattern as early as 10 weeks after a single exposure to the carcinogen. This novel technology, through recently funded grants, is being expanded to determine if a similarly distinctive pattern of mutations occurs with other liver carcinogens, notably N-nitrosodimethylamine (NDMA), which contaminates a local Superfund site, and alcohol, another agent well known to accelerate the onset of hepatocellular carcinoma. A unique animal model and mutation risk assessment technology was developed for this project, and it will be used in the proposed collaboration that will bring our genetic studies to the proteomic level. At UPenn, in work once again stimulated by community engagement, we have developed a mass spectrometric assay that enables the mapping of N-acetyl posttranslational modifications of the alarmin, HMGB1. HMGB1 is a small protein with many functions, the foremost of which is to signal cellular stress via the NLRP3 inflammasome to the innate immune system. The toxicant studied by the UPenn group is asbestos, which is the etiologic agent leading to mesothelioma and related lung diseases. The unifying technology underlying the joint proposal stems from recent work at UPenn showing that a SILAC-based mass spectrometry method can sensitively detect acetylation patterns spanning 29 HMGB1 lysine residues in human plasma and serum. While serum presents certain drawbacks, plasma or whole blood are excellent and validated media for the proposed study. This analytical tool is now ready for analysis of the HMGB1 posttranslational modification patterns in plasma from toxicant-exposed humans, animals, and cells in culture. Critically, alkylating agents from the NDMA class and alcohol, as well as asbestos, have been shown to activate HMGB1, but the details of that activation, which likely involves post-translational modification of the parent protein, have not been established. Such details are important for two reasons. First, they will help us probe the underlying mechanism of inflammasome-mediated establishment of the inflammatory state known to drive development of cancer and other diseases. Second, at a very practical level, these details will allow us to pressure-test the potential of post-translationally modified HMGB1 as a biomarker of disease in humans (e.g., mesothelioma, liver cancer, and steatohepatitis). More broadly, the inflammation-provoking property of HMGB1 is thought to be involved in the etiologies of other cancers, autoimmune diseases, cardiovascular diseases, neurodegenerative diseases and Type I and II diabetes. Hence, the project could nucleate many collaborations across the EHSCC network.