Abstract: The UCLA-Boston University Lung Cancer Biomarker Development Laboratory
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This competitive revised U01 application, in response to PAR-12-011, will support an expansion of the scope of our existing U01 funding from the NCI's Early Detection Research Network (EDRN) to study airway gene expression as a non-invasive biomarker for smoking-related lung cancer. This revised application will extend the work in our parent grant by studying the airway gene-expression response to other tobacco-related products, specifically electronic cigarettes (ECIGS), and establishing rapid and quantifiable approaches for evaluating the potential carcinogenic effects of airway epithelium exposures to these types of products. Our current proposal leverages both the biological premise and scientific approach of the parent grant as it relates to the airway "field of injury", as well as leveraging the extensive infrastructure that has been built within the parent EDRN Biomarker Discovery Laboratory between BU and UCLA.

Our current proposal leverages the same airway "field of injury" paradigm underlying the U01 grant from the EDRN. Our group has pioneered the concept that inhaled toxins such as tobacco smoke alter gene expression in airway cells that line the entire respiratory tract and that measuring these gene-expression alterations in readily accessible airway cells provides a strategy to gain comprehensive insights into the physiological impact of that exposure within an individual. Using this biological premise, our group has previously shown that the tobacco-related field of airway injury is different in patients with lung cancer and that bronchial airway gene-expression can serve as a clinically-relevant biomarker for the early detection of lung cancer. In the EDRN parent grant, we are extending our work characterizing the gene-expression profiles of cancer in bronchial epithelium to gene-expression profiles of cancer in nasal epithelium in order to develop less invasive diagnostic biomarkers for lung cancer. The same "field of injury" paradigm and scientific approach underlies the aims of our current proposal where bronchial airway gene-expression will initially be studied in order to gain insights into the physiological response to tobacco-product exposures and these gene-expression signatures will then be extended to nasal epithelium. The transition from bronchial epithelium to nasal epithelium in the setting of lung cancer biomarkers is motivated by a need for biomarkers that can be assessed in minimally invasively collected tissues in broader cohorts of smokers who are at risk for lung cancer development. The transition from bronchial epithelium to nasal epithelium in the setting of tobacco-product exposure assessment is motivated by a need to enable the rapid evaluation of the physiological impacts of tobacco-product exposures using readily collected samples in potentially large-scale population studies. This revision also seeks to identify molecular signatures of the potential carcinogenicity of tobacco and tobacco related products. These new signatures developed in this proposal will then be evaluated as potential biomarkers of cancer risk in the lung cancer cohorts being studied in the parent grant.

Importantly, this revised application will use the clinical, scientific, computational and administrative infrastructure that has been developed over the past 2 years within the parent U01 grant. In order to accomplish the aims of our EDRN Biomarker Discovery Lab, BU and UCLA have created uniform clinical protocols at both sites for recruitment of human subjects, collection of clinical data, collection of airway and blood samples and sharing these biological samples between sites for molecular profiling. Biological samples from more than 120 subjects collected at UCLA have already been shipped and molecularly profiled at BU within the parent grant. Further, BU and UCLA have jointly developed computational pipelines and warehouses for storage, sharing and analysis of clinical and molecular data from these studies, as well as sharing statistical and computational approaches for analysis of molecular data. We

will also leverage the administrative infrastructure established within our parent grant including monthly teleconference calls, twice yearly face-to-face meetings and governance regarding publication and intellectual property-related issues that will arise.

This infrastructure from our productive ongoing collaboration is a critical prerequisite for the successful completion of the detailed molecular assessment of new tobacco product exposures that we propose.