WNY Center for Research on Flavored Tobacco Products (CRoFT)
Institution: Roswell Park Comprehensive Cancer Center
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Research Project 1: In vitro and in vivo assessment of flavorant toxicity
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Project 1 Abstract:
This project addresses the Center for Tobacco Products (CTP) research priorities under **Toxicity** scientific domain as defined in RFA-OD-17-006, and the **overarching integrative scientific theme** of this TCORS coalesce for **testing the effects of flavorings in tobacco products and characterize the pulmonary toxicity.** Emerging tobacco products (Electronic Nicotine Delivery Systems ENDS/e-cigarettes, cigarillos, waterpipe tobacco), often sold in flavored varieties, represent a significant and increasing proportion of tobacco consumption in the United States. Flavoring chemicals are commonly used in ENDS products, cigarillos and waterpipe tobacco. **Commonly marketed flavors** include tobacco, mint/menthol, fruits/candy (grapes, mango, melon, pineapple, apple, peach, banana), coffee/tea, chocolate, berries (strawberry and blueberry), crème/butter, clove/cinnamon, and alcoholic beverages. Underlying these flavors are chemical flavorings, some of which have known respiratory toxicity (e.g., diacetyl, cinnamaldehyde). The development of comparative toxicity data -- based on oxidative stress, DNA damage, and inflammation resulting from exposure to aerosol/smoke with different flavorings in tobacco products- is urgently needed. We **hypothesize** that different chemical flavorings used in emerging flavored tobacco products (e-cigarettes/ ENDS, cigarillos, and waterpipe) differentially influence toxicity in terms of oxidative, DNA damage, epithelial barrier dysfunction, and inflammatory responses, and influence toxicity *in vitro* and *in vivo* (lungs) with varying intensity and duration of exposure. Our **goal** is to determine and compare the effects of various flavorings in emerging tobacco products (e-cigarettes, cigarillos, and waterpipe) on toxicological and immune-inflammatory responses. Specifically, we will: **Aim 1)** Determine comparative *in vitro* toxicity of selected tobacco product flavorings using the aerosol exposure system for cell-free reactive oxygen species reactivity, and exposure to human lung epithelial cells by air-liquid interface system, and in a 3D culture system, **Aim 2)** Determine comparative oxidative, DNA damage and immune-inflammatory responses to tobacco product flavorings in commonly used mouse strains C57BL/6J (Th1 response) and Balb/c (Th2 response), and using the state-of-the-art reporter models (NF- B luciferase and DNA repair/NHEJ reporter mouse) to determine the predictive nature of flavoring toxicity for adverse respiratory health outcomes of flavorings, and **Aim 3)** Determine comparative epigenomics (DNA methylation and transcriptomics)-epigenetic biomarkers in response to tobacco product flavorings. This will determine the biological effects on respiratory health by flavoring tobacco products in terms of toxicity, biomarkers, and hazard ranking of flavorings. **Outcomes for Regulatory Science:** Assessment of toxicity of the same class of flavorings across the different types of tobacco products in *in vitro* and *in vivo* studies will provide crucial information related to toxicity/hazard ranking (higher to lower) and adverse health outcomes associated with specific flavorings, which would directly support the FDA's regulatory efforts.