

Defining HPHCs toxicity thresholds by the esophageal 3D organoids system

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Abstract

Tobacco products contain nearly 80 chemical carcinogens that are listed by FDA as harmful and potentially harmful constituents (HPHCs) and implicated in the pathogenesis of esophageal squamous cell carcinoma (ESCC). Many HPHCs (e.g. acetaldehyde) cause oxidative stress and DNA damage, promoting DNA mutations, genomic instability and malignant transformation. The overall objective is to build a novel platform that allows standardized and high-throughput assessment of the toxicity thresholds for each HPHC in physiologically relevant contexts. Our central hypothesis is that toxicity thresholds for HPHCs may be defined as the minimal dose of HPHCs inducing DNA damage and that are influenced by cellular capability of detoxifying HPHCs. For example, accumulation of acetaldehyde is exacerbated by deficiency of ALDH2, an enzyme detoxifying acetaldehyde. This hypothesis will be pursued in interrelated Specific Aims: (i) To define toxicity thresholds for HPHCs in human and mouse 3D esophageal organoids; and (ii) To determine the toxicity threshold of acetaldehyde in mouse 3D esophageal organoids with or without *ALDH2* mutation. We will evaluate highly innovative esophageal 3D organoids, a single-cell derived miniature organ-like structure grown *ex vivo* to delineate the influence of *ALDH2* mutation upon acetaldehyde-induced toxicity thresholds. These studies will fundamentally advance the fields of regulatory science, building a novel and robust platform for standardized and high-throughput testing for the toxicity thresholds for each HPHC and that may open new avenues of translational applications for prevention and therapy of ESCC and other tobacco products-related diseases and conditions. Using PENN CEET Translational Biomarker Core, the proposed studies will address one of the NIH-FDA Tobacco Regulatory Science Program research priorities: "toxicity thresholds for each of the 20 HPHCs identified in the March 2012 guidance for industry". Finally, this project will help the applicant to prepare for a future NIH grant submission for further study in this field.