

PROJECT SUMMARY

Penn Medicine contributes substantially to the local economy. In 2008, Penn Medicine employed 37,000 faculty and staff and created \$5.4 billion in regional economic activity, with the area's highly trained workforce producing more than 24,600 applications for just 840 open Penn staff research positions. The current proposal will create or preserve 3 jobs.

This is an application for an Administrative Supplement to **1R01-ES015087: Pathways of PAH Activation in Human Lung cells** (Project end date: 03/31/10). PAH (polycyclic aromatic hydrocarbons) are ubiquitous environmental pollutants and tobacco carcinogens. They may be causative agents in lung cancer in smokers, never smokers exposed to environmental tobacco smoke, and never smokers living in urban areas. Metabolic activation of PAH is a pre-requisite for these compounds to exert their deleterious effects; and one pathway involves their metabolic activation by aldo-keto reductases (AKRs) to form electrophilic and redox-active PAH *ortho*-quinones. Recently, we have published exciting data to show that the AKR pathway is intact in human lung adenocarcinoma (A549) cells; and using an exquisitely sensitive immunoaffinity column stable isotope dilution liquid chromatography/mass spectrometry (LC/MS) assay shown that this pathway results in increased amounts of the mutagenic lesion 8-oxo-dGuo in these cells. Others have shown that AKRs may well be tobacco smoke exposure and response genes in normal bronchial epithelial cells (NHBE). Aim#3, of the original application was to phenotype the expression of competing pathways of PAH-metabolism in immortalized NHBE cells and use stable-isotope dilution LC/MS methodologies to measure benzo[a]pyrene metabolism. In light of the advances described, we now propose to expand this aim and translate our studies to human subjects. Specifically, we will conduct a confirmatory Affymetrix microarray analysis of gene expression in NHBE cells from bronchial brushes obtained by bronchoscopy from 20 patients who are smokers with lung cancer and 10 patients who are never smokers that do not have lung cancer. The NHBE cells obtained from the never smokers will be expanded in cell culture and exposed to cigarette smoke which will be titrated by measuring nicotine levels in the media or will be untreated. A portion of the two sets of cultured cells will be re-examined for their expression profile while another portion will be used to study benzo[a]pyrene metabolism using both radiotracers and stable-isotope dilution LC/MS. These studies will help validate whether AKRs are upregulated in response to tobacco smoke exposure and importantly whether a metabolic consequence of this over expression is enhanced benzo[a]pyrene activation.

RELEVANCE : These studies will determine whether aldo-keto reductases acting as tobacco smoke exposure and response genes leads to benzo[a]pyrene activation.

Project/Performance Site Primary Location

Organizational Name: University of Pennsylvania, School of Medicine

DUNS: 042250712

Street 1: 3620 Hamilton Walk

Street 2: 130C John Morgan Bldg.

City: Philadelphia

County: Philadelphia

State: PA

Province:

Country: USA

Zip/Postal Code: 19104

Project/Performance Site Congressional Districts: PA-002

Additional Project/Performance Site Location

Organizational Name:

DUNS:

Street 1:

Street 2:

City:

County:

State:

Province:

Country:

Zip/Postal Code:

Project/Performance Site Congressional Districts:

Program Director/Principal Investigator (Last, First, Middle): **Penning, Trevor M.**

SENIOR/KEY PERSONNEL. See instructions. *Use continuation pages as needed* to provide the required information in the format shown below. Start with Program Director(s)/Principal Investigator(s). List all other senior/key personnel in alphabetical order, last name first.

Name	eRA Commons User Name	Organization	Role on Project
Penning, Trevor M	PENNING	UPenn	Principal Investigator

OTHER SIGNIFICANT CONTRIBUTORS

Name	Organization	Role on Project
Hass, Andrew	UPenn	Pulmonologist

Human Embryonic Stem Cells No Yes

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: <http://stemcells.nih.gov/research/registry/>. *Use continuation pages as needed.*

If a specific line cannot be referenced at this time, include a statement that one from the Registry will be used.

Cell Line