Allegheny-Singer Research Institute

Annual Progress Report: 2012 Formula Grant

Reporting Period

July 1, 2014 – December 31, 2014

Formula Grant Overview

The Allegheny-Singer Research Institute received $79,614 in formula funds for the grant award period January 1, 2013 through December 31, 2014. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Outdoor Air Pollution, Airway Inflammation and Acute Exacerbations of Asthma – The specific aim of this project is to characterize the relationship between levels of indoor and outdoor air pollution (OAP) and lower airway inflammation in patients with acute asthma exacerbations.

Duration of Project

1/1/2013 – 12/31/2014

Project Overview

The specific aim of this project is to characterize the relationship between levels of indoor and outdoor air pollution (OAP) and lower airway inflammation in patients with acute asthma exacerbations. The project will consist of a single visit. One hundred six total subjects will be recruited as follows for enrollment into one of three groups:

Acute asthma exacerbation group (n=40): Subjects will be recruited from the pool of patients seeking acute treatment for an asthma exacerbation at an emergency department associated with West Penn Allegheny Health System (WPAHS).

Stable asthma group (n=33): Subjects will be recruited from the pool of patients presenting to an outpatient asthma/allergy clinic associated with WPAHS for routine follow-up for their asthma.

Environmental control group (n=33): Subjects will be recruited at an emergency department associated with WPAHS. Subjects will be either 1) a family member of an acute asthma subject who is with the acute asthma subject in the emergency department on the date of presentation, or 2) they will be another individual presenting the same day as the subject with acute asthma at the same emergency department.

Note: This project is funded, in part, under a grant with the Pennsylvania Department of Health. The Department specifically disclaims responsibility for any analyses, interpretations or conclusions.

Eligible subjects will complete a demographic survey, respiratory survey, measurement of fractional exhaled nitric oxide (FeNO), and spot urine collection for measurement of urinary cotinine levels. In addition, in the acute asthma group, a clinical assessment of severity of exacerbation will be performed. These data will be combined with local OAP and weather data (temperature) over the preceding 7 days to construct a model for the relationship between airway inflammation, airborne pollution and acute exacerbation, controlling for the above potentially confounding variables.

Principal Investigator

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Other Participating Researchers

Arvind Venkat, MD – employed by Allegheny-Singer Research Institute
Albert Presto, PhD – employed by Carnegie Mellon University
Gajanan G. Hegde, PhD; Jennifer Shang, PhD– employed by University of Pittsburgh

Expected Research Outcomes and Benefits

The results of the project are expected to show an association between levels of outdoor air pollution and lower airway inflammation in patients with acute asthma exacerbations. It is anticipated that these results will be used as preliminary data in a future NIH application to evaluate the impact of different interventions on these outcomes. The long term goal of this research is to prevent or attenuate acute respiratory exacerbations in patients exposed to outdoor air pollution.

Summary of Research Completed

During the current reporting period, we have concentrated our efforts on enrollment of subjects into our study. We are pleased to report that we have completed enrollment of subjects in each of our three groups, enrolling a total of 106 subjects per the research plan included in our proposal. Specifically, in the acute asthma exacerbation group, in which subjects are recruited from the pool of patients seeking acute treatment of an asthma exacerbation at an emergency department associated with the Allegheny Health Network (AHN), we enrolled 40 patients. In the stable asthma group, in which subjects are recruited from the pool of patients presenting to an outpatient asthma/allergy clinic associated with AHN for routine follow-up care for their asthma, we enrolled 33 patients. In the environmental control group, in which subjects are recruited at an emergency department associated with AHN and are either 1) a family member of an acute

asthma subject who is with the acute asthma subject in the emergency department on the date of presentation, or 2) another individual presenting the same day as the subject with acute asthma at the same emergency department, we enrolled 33 patients. See **Table 1** below.

Since subjects in the current study are enrolled by multiple research groups at multiple locations, we have held a series of regular "check-in" meetings among investigators and research staff in the emergency department and the outpatient asthma/allergy clinics which are participating in this study. These meetings were instrumental in allowing us to complete our enrollment goals during the current reporting period and in ensuring that study visits continued to be conducted appropriately per the research protocol and that all data collected were valid and reliable.

Per the research protocol submitted to the Department of Health, all subjects enrolled into the study have completed a demographic survey, respiratory survey, and measurement of fractional exhaled nitric oxide (FeNO), and have a provided a spot urine sample for measurement of urinary cotinine levels. Buccal and nasal swabs have been collected from all subjects and are being stored for potential future analyses of the effects of genetic polymorphisms and identification of respiratory viruses; separate funding will be sought in the future to complete these analyses. Additionally, subjects in the acute asthma group have undergone an assessment of severity of asthma exacerbation. All subjects enrolled in the study, regardless of study group, have completed all assessments per the study protocol.

In addition to enrolling subjects and completing study visits, during the current reporting period we successfully completed collection of outdoor air pollution (OAP) data for all zip codes represented by study subjects. Dr. Albert Presto's group (Dr. Presto is a consultant on the current project) used a proprietary mobile atmospheric sampling unit as well as a stationary reference site to collect OAP levels for the zip codes in which subjects in the current study reside. OAP parameters collected include black carbon, particulate matter, particle bound polycyclic aromatic hydrocarbons, nitrogen oxides, ozone, and the air toxins benzene and toluene. Upon completion of all study visits and entry into the data analysis phase of the project, OAP data from each subject's zip code over the seven days preceding the subject's visit was utilized to construct a model for the relationship between airway inflammation, airborne pollution, and acute asthma exacerbations. Dr. Presto's team has collected OAP data for the majority of Allegheny County, including complete coverage of all zip codes represented by subjects enrolled in the study. Dr. Presto worked closely with the research team at AHN and the study's statistical consultants to analyze the resulting OAP data, specifically contributing to analyses of the relationship between OAP and acute asthma exacerbations in each of our three experimental groups.

As subjects were enrolled and study visits were completed, we continued to enter data in real time into the study's secure database, completing data analysis for all subjects enrolled throughout the duration of the project. Clinical, demographic, and laboratory data have been entered into our database by study staff using appropriate data entry procedures. Access to the study database remained restricted only to authorized study personnel.

Having achieved our enrollment goals, effort during the current reporting period was focused heavily on data analysis. An ANOVA was utilized to compare FeNO levels among the three

groups. Correlation among potential confounders (asthma controller medications, smoking history) was assessed using the Spearman's Correlation test. We then implemented hierarchical regression to evaluate whether a significant association existed between outdoor air pollution and FeNO levels.

As demonstrated below in **Table 2**, patients presenting with an acute asthma exacerbation showed significantly higher FeNO levels ($F=35.4$, $P<0.001$). Our results also demonstrated that use of inhaled corticosteroids alone correlated with measured FeNO levels (correlation co-efficient=0.36, $P=0.02$ in acute asthma subjects). In addition, we determined that outdoor air pollution was not significantly associated with elevated FeNO levels ($P>0.05$ in hierarchical regression inclusive of inhaled corticosteroid use for acute asthma and stable asthma subjects with mean annual, mean presentation day, mean presentation day to day minus two and mean presentation day to day minus seven BC and PAH levels). FeNO is significantly elevated among patients with acute asthma exacerbations presenting to the ED in comparison to environmental and stable asthma controls. FeNO is an independent marker of asthma control that does not appear to be associated with outdoor air pollution exposure based on the results of this study.

Throughout the performance period, we used our experience with the current study as a springboard to development of future research directions and "next steps." We anticipate that the results of the current study will serve as the basis of future grant applications to the NIH and asthma foundations.

In summary, during the current reporting period we have 1) achieved our overall enrollment goal of 106 subjects; 2) completed all remaining study visits; 3) completed collection of OAP data for all zip codes represented by subjects enrolled in our study; 4) completed data analysis; 5) determined that FeNO, and independent marker of asthma control, is significantly higher in acute asthma patients compared to stable asthma patients and environmental control subjects; and 6) begun to develop and refine plans for continuation of the line of research being pursued with the current project, including development of plans to seek future research funding.

Table 1. Enrollment summary.

Group	Enrollment	Enrollment goal
Acute asthma exacerbation	40	40
Stable asthma	33	33
Environmental control	33	33

Table 2. Study results for acute asthma patients, environmental control subjects, and stable asthma patients.

Independent Variable	Acute Asthma (N=40)	Environmental Control (N=33)	Stable Asthma (N=33)
Age (Mean, SD)	26.68 (9.18)	38.51 (13.45)	24.82 (10.29)
Sex (% Female)	57.5	66.7	66.7
Race (% Black)	75	50	18.2
Residential Zip Codes Sampled (#)	21	22	19
Work Zip Codes Sampled	15	8	12

(#)			
Urine Cotinine 0.5 or less – Non-Smoker and Unexposed to Passive Smoke (%)	32.5	27.3	72.7
Urine Cotinine 1-125 – Exposed to Passive Smoke (%)	27.5	27.3	15.2
Urine Cotinine >125 – Smoker (%)	37.5	45.4	12.1
Urine Cotinine Missing (%)	2.5	0.0	0.0
Annual BC Exposure Work Zip Code – Mean, SD (mcg/mL)	1.24, .18	1.20, .07	1.25, .18
Annual BC Exposure Residential Zip Code – Mean, SD (mcg/mL)	1.18, .17	1.17, .14	1.23, .15
Daily BC Exposure in Seven Days Prior to Presentation Work Zip Code – Median, IQR (mcg/mL)	1.18, 1	1.18, 1	0.97, 1
Daily BC Exposure in Seven Days Prior to Presentation Residential Zip Code – Median, IQR (mcg/mL)	1.14, 1	1.17, 1	0.97, 0
Annual PAH Exposure Work Zip Code – Mean, SD (ng/mL)	17.29, 3.29	16.31, 1.42	16.39, 3.73
Annual PAH Exposure Residential Zip Code – Mean, SD (ng/mL)	15.67, 3.81	14.94, 3.09	15.04, 1.94
Daily PAH Exposure in Seven Days Prior to Presentation Work Zip Code – Median, IQR (ng/mL)	16.06, 15.0	16.07, 17.0	15.55, 11.0
Daily PAH Exposure in Seven Days Prior to Presentation Residential Zip Code – Median, IQR (ng/mL)	14.30, 12.0	15.76, 13.0	14.12, 12.0
FeNO Level – Mean, 95% CI	87.9, 73.6-102.2	19, 16.3-21.7	44.2, 30.1-58.3