

State of California
AIR RESOURCES BOARD

RESEARCH PROPOSAL

Resolution 07-30

June 21, 2007

Agenda Item No.: 07-7-2

WHEREAS, the Air Resources Board has been directed to carry out an effective research program in conjunction with its efforts to combat air pollution, pursuant to Health and Safety Code sections 39700 through 39705;

WHEREAS, a research proposal, number 2630-256, entitled "Effect of GSTM1 Genotype on Ozone-induced Allergic Airway Inflammation," has been submitted by the University of California, San Francisco to augment contract number 03-315;

WHEREAS, the Research Division staff has reviewed and recommended this proposal for approval; and

WHEREAS, the Research Screening Committee has reviewed and recommends for funding:

Proposal Number 2630-256 entitled "Effect of GSTM1 Genotype on Ozone-induced Allergic Airway Inflammation," has been submitted by the University of California, San Francisco to augment contract number 03-315, for a total amount not to exceed \$249,999.

NOW, THEREFORE BE IT RESOLVED, that the Air Resources Board, pursuant to the authority granted by Health and Safety Code section 39703, hereby accepts the recommendation of the Research Screening Committee and approves the following:

Proposal Number 2630-256 entitled "Effect of GSTM1 Genotype on Ozone-induced Allergic Airway Inflammation," has been submitted by the University of California, San Francisco to augment contract number 03-315, for a total amount not to exceed \$249,999.

BE IT FURTHER RESOLVED, that the Executive Officer is hereby authorized to initiate administrative procedures and execute all necessary documents and contracts for the research effort proposed herein, and as described in Attachment A, in an amount not to exceed \$249,999.

I hereby certify that the above is a true and correct copy of Resolution 07-30, as adopted by the Air Resources Board.

Lori Andreoni, Clerk of the Board

ATTACHMENT A

“Augmentation to Effect of GSTM1 Genotype on Ozone-induced Allergic Airway Inflammation”

Background

Epidemiological data suggest that asthmatics may be more sensitive to ozone (O₃) than nonasthmatics. Animal studies provide evidence that O₃ can enhance allergic inflammatory responses in the lungs. Controlled studies of the airway inflammatory responses of allergic asthmatics to O₃ suggest that O₃ enhances responses to inhaled allergen in some, but not all, allergic asthmatics. Data also indicate that genetic variability between individuals may explain the wide range of responsiveness to O₃ exposure, in both healthy and asthmatic people. One particular gene, GSTM1, which codes for the antioxidant enzyme glutathione S-transferase, has been implicated as a candidate gene possibly influencing responsiveness to O₃.

Contract 03-315 with the University of California, San Francisco (UCSF), was approved in September 2004. The project, as funded, included one experiment designed to investigate three objectives: (1) whether ozone exposure enhances specific lower airway inflammatory responses of asthmatic subjects during late-phase reactions to inhaled allergen, (2) to determine whether the GSTM1 null genotype is an important predictor of susceptibility of asthmatic subjects to develop enhanced late-phase reactions to allergen challenge presented after ozone exposure, and (3) to determine whether pre-exposure to allergen enhances the subsequent inflammatory responses to ozone exposure.

The UCSF human subjects committee refused to approve the protocol as originally designed because of the number of bronchoscopies per subject. Staff proposed to address this issue by splitting the project into two independent experiments, each with a different group of subjects, and augmenting the monies of the original contract to maintain the original intent of the project, which was strongly supported by the Board, and enable the investigators to address all three objectives.

Objective

This augmentation will provide the additional monies required to address objective 3 of the original project: To determine whether the GSTM1 null genotype is an important predictor of the susceptibility of asthmatic subjects to develop enhanced late-phase reactions to allergen challenge after O₃ exposure.

Methods

This controlled human exposure study will investigate the effect of variants in a gene (GSTM1) in allergic asthmatics. This gene has been identified as involved in responses to ozone, and in mediating airway inflammation. Fifteen well-characterized allergic asthmatic subjects will participate in exposures to filtered air (FA) and 0.16 ppm O₃. The subjects will undergo allergen challenge before the two exposures. Bronchoscopy with bronchoalveolar lavage will follow each of the exposures to assess airway inflammation.

The subjects will be genotyped for GSTM1. Exploratory genetic screening will also be done for several other genes that have been identified as candidates for involvement in mediating injury and repair processes in the airway tissues. The fluid recovered after bronchoalveolar lavage will be analyzed for inflammatory cells, and inflammatory proteins. Lung function will be monitored throughout the experimental periods.

Expected Results

This study will address gaps in the knowledge base on air pollution and human health, namely, what are the biological bases for the inconsistent responses reported among individual allergic asthmatics exposed to O₃. The study will also contribute to resolution of questions regarding the influence of genetic variants on responses to O₃.

Significance to the Board

The results of the study are critical to development of ambient air quality standards that are protective of allergic asthmatics. The results will fill in critical data gaps on the responses of asthmatics to O₃.

Contractor:

University of California, San Francisco

Contract Period:

24 months

Principal Investigator (PI):

Dr. John Balmes, MD

Contract Amount:

\$250,000

Basis for Indirect Cost Rate:

The State and the UC system have agreed to a ten percent indirect cost rate.

Past Experience with this Principal Investigator:

Dr. Balmes has performed several previous studies for ARB. His work is consistently of the highest quality. The results of his research have contributed significantly to development of ambient air quality standards by addressing critical gaps in the scientific knowledge base on the health effects of ambient air pollutants.

Prior Research Division Funding to the University of California, San Francisco:

Year	2006	2005	2004
Funding	\$	\$	\$399,393

BUDGET SUMMARY

Contractor: University of California, San Francisco

“Augmentation to Effect of GSTM1 Genotype on Ozone-induced Allergic Airway Inflammation”

DIRECT COSTS AND BENEFITS

1.	Labor and Employee Fringe Benefits	\$	171,700
2.	Subcontractors	\$	10,000
3.	Equipment	\$	0
4.	Travel and Subsistence	\$	2,000
5.	Electronic Data Processing	\$	0
6.	Reproduction/Publication	\$	0
7.	Mail and Phone	\$	0
8.	Supplies	\$	17,930
9.	Analyses	\$	0
10.	Miscellaneous	\$	<u>25,642¹</u>
	Total Direct Costs		\$227,272

INDIRECT COSTS

1.	Overhead	\$	22,727
2.	General and Administrative Expenses	\$	0
3.	Other Indirect Costs	\$	0
4.	Fee or Profit	\$	<u>0</u>
	Total Indirect Costs		<u>\$22,727</u>

TOTAL PROJECT COSTS

\$249,999

¹ Computer and general lab supplies, including toner, paper, software, lab glass- and plastic-ware, compressed gases, chemicals.

Attachment 1

SUBCONTRACTORS' BUDGET SUMMARY

Subcontractor: Karron Power, MD

Description of subcontractor's responsibility: Dr. Power's roles in the project will involve clinical oversight, subject screenings, and assistance with bronchoscopies.

DIRECT COSTS AND BENEFITS

1.	Labor and Employee Fringe Benefits	\$	10,000
2.	Subcontractors	\$	0
3.	Equipment	\$	0
4.	Travel and Subsistence	\$	0
5.	Electronic Data Processing	\$	0
6.	Reproduction/Publication	\$	0
7.	Mail and Phone	\$	0
8.	Supplies	\$	0
9.	Analyses	\$	0
10.	Miscellaneous	\$	<u>0</u>
	Total Direct Costs		\$10,000

INDIRECT COSTS

1.	Overhead	\$	0
2.	General and Administrative Expenses	\$	0
3.	Other Indirect Costs	\$	0
4.	Fee or Profit	\$	<u>0</u>
	Total Indirect Costs		<u>\$0</u>

TOTAL PROJECT COSTS

\$10,000