State of California
AIR RESOURCES BOARD

RESEARCH PROPOSAL

Resolution 04-36

November 18, 2004

Agenda Item No.: 04-10-2

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 2557-245, entitled “The Role of Inhaled Particles in the Pathophysiology of Cardiovascular Disease”, has been submitted by the University of California, Irvine;

WHEREAS, the staff of the Air Resources Board has reviewed and recommended this proposal for approval; and

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

> Proposal Number 2557-245 entitled “The Role of Inhaled Particles in the Pathophysiology of Cardiovascular Disease” submitted by the University of California, Irvine, for a total amount not to exceed $446,357.

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 2557-245 entitled “The Role of Inhaled Particles in the Pathophysiology of Cardiovascular Disease” submitted by the University of California, Irvine, for a total amount not to exceed $446,357.
>
> 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 $446,357.

I hereby certify that the above is a true and correct copy of Resolution 04-36 as adopted by the Air Resources Board.

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Lori Andreoni, Clerk of the Board

ATTACHMENT A

"The Role of Inhaled Particles in the Pathophysiology of Cardiovascular Disease"

Background

Exposure to levels of particulate matter (PM) found in California has been linked to an increased risk of heart disease, but the mechanisms are not well understood. However, an important factor in cardiovascular disease is the development of atherosclerosis, and many researchers believe that inflammation and oxidative stress may be important factors in the acceleration of atherosclerosis. Previous research results by the UC, Irvine investigator support the hypothesis that inflammatory events induced in the lung by inhaled PM can alter cardiac function. Recently, New York University (NYU) conducted experiments using genetically altered mice that tend to develop atherosclerotic lesions in the coronary arteries that are similar to human coronary artery disease. NYU found that higher PM exposure resulted in faster development of atherosclerosis and in premature mortality.

The investigator hypothesizes that PM exposure abnormally activates endothelial cells and induces vascular inflammation that leads to increased expression of adhesion molecules, increased peroxidation of lipids and lipoproteins, increased levels of oxidative stress biomarkers, and increased formation of fatty streaks or atherosclerotic lesions. To test this hypothesis, the investigator proposes to use the same genetically altered mice that NYU used, to examine the link between PM-induced inflammation and the development of atherosclerosis in normal and atherosclerosis-prone mice.

Objective

The objective of this study is to examine the effects of both fine and ultrafine PM exposures on markers of vascular cell inflammation in normal and atherosclerotic-prone mice. Different exposure periods will be used to determine acute, subchronic, and chronic effects.

Methods

The investigator will examine the link between particle-induced inflammation and the development of atherosclerosis in normal and atherosclerosis-prone mice, using both fine and ultrafine PM exposures. The investigator will also examine signaling pathways for oxidative stress and inflammation-associated tissue damage to determine the relative importance of these mechanisms in the development or exacerbation of heart disease.

Expected Results

The results should help improve our understanding of the roles of oxidative stress and inflammation-associated tissue damage from PM exposure as mechanisms that lead to heart disease.

Significance to the Board
The results of the project could lead to cost-effective ways to prevent or treat heart diseases caused by air pollution.

Contractor:
University of California, Irvine

Contract Period:
36 months

Principal Investigator (PI):
Michael T. Kleinman, Ph.D.

Contract Amount:
$446,357

Co-Funding:
Although no money will be provided, this study will be coordinated with a similar study in New York City, conducted by PI Morton Lippmann at New York University (NYU). Both teams intend to use the same exposure techniques, parameters, concentrators, and chamber design. The PIs intend for UCI perform all cytokine analyses, and for NYU to conduct all morphometry. Both teams will benefit from technology transfer regarding mouse breeding and electrocardigram analyses. In addition, NYU intends to lend UCI some of the animal implants to help UCI get started on this aspect of the study.

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:
Professor Michael T. Kleinman has successfully completed several research contracts for the Air Resources Board. The most recent project was titled "Mechanisms of Particulate Toxicology: Systemic Effects in Sensitive Animal Models and Susceptible Humans".

Prior Research Division Funding to UCI:

Year	2003	2002	2001
Funding	$676,814	$0	$0

B U D G E T S U M M A R Y

University of California, Irvine

The Role of Inhaled Particles in the Pathophysiology of Cardiovascular Disease

DIRECT COSTS AND BENEFITS

1.	Labor and Employee Fringe Benefits	$303,734	
2.	Subcontractor	$ 18,000	
3.	Equipment	$ 0	
4.	Travel and Subsistence	$ 11,892	
5.	Electronic Data Processing	$ 0	
6.	Reproduction/Publication	$ 300	
7.	Mail and Phone	$ 750	
8.	Supplies	$ 45,105*	
9.	Analyses	$ 3,000	
10.	Miscellaneous	$ 25,887	
	Total Direct Costs		$408,668

INDIRECT COSTS

1.	Overhead	$ 37,689	
2.	General and Administrative Expenses	$ 0	
3.	Other Indirect Costs	$ 0	
4.	Fee or Profit	$ 0	
	Total Indirect Costs		$ 37,689

TOTAL PROJECT COSTS $446,357

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*Supplies:

reagents, antibodies, and stains	$12,450
telemetry implants	$15,705
gene expression assays	$16,200
filters and analytical supplies	$ 750

Attachment 1

S U B C O N T R A C T O R S' B U D G E T S U M M A R Y

Subcontractor: New York University

New York University will perform histological assessments of blood vessels and X-ray fluorescence for trace metals on filters.

DIRECT COSTS AND BENEFITS			
1.	Labor and Employee Fringe Benefits	$ 0	
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	$ 18,000	
10.	Miscellaneous	$ 0	
	Total Direct Costs		$ 18,000
INDIRECT COSTS			
1.	Overhead	$ 0	
2.	General and Administrative Expenses	$ 0	
3.	Other Indirect Costs	$ 0	
4.	Fee or Profit	$ 0	
	Total Indirect Costs		$ 0
TOTAL PROJECT COSTS			**$ 18,000**

The costs for these analyses represent time and materials required to perform the assays. The rate is discounted by 50% because this study is performed in collaboration with ongoing studies at NYU.