State of California
AIR RESOURCES BOARD

RESEARCH PROPOSAL

Resolution 09-28

April 23, 2009

Agenda Item No.: 09-4-2

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 2667-264, entitled "Central Nervous System Effects of Ambient Particulate Matter: The Role of Oxidative Stress and Inflammation," has been submitted by the University of California, Irvine;

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 2667-264 entitled "Central Nervous System Effects of Ambient Particulate Matter: The Role of Oxidative Stress and Inflammation," submitted by the University of California, Irvine, for a total amount not to exceed $309,141.

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 2667-264 entitled "Central Nervous System Effects of Ambient Particulate Matter: The Role of Oxidative Stress and Inflammation," submitted by the University of California, Irvine, for a total amount not to exceed $309,141.

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 $309,141.

I hereby certify that the above is a true and correct copy of Resolution 09-28, as adopted by the Air Resources Board.

/s/

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Monica Vejar, Clerk of the Board

ATTACHMENT A

"Central Nervous System Effects of Ambient Particulate Matter: The Role of Oxidative Stress and Inflammation"

Background
Previous studies conducted by Dr. Kleinman and colleagues, examining mice exposed to fine and ultrafine particulate matter (PM) in southern California cities, showed that these exposures had significant adverse cardiovascular effects resulting in increased rates of formation of atherosclerotic-like plaques and changes in cardiac function. In addition to cardiopulmonary effects, the researchers demonstrated significant evidence of inflammation in the brains of the concentrated ambient particles (CAP)-exposed mice. The studies showed up-regulation of the transcription factors NF-κB and AP-1 and increased concentrations of the pro-inflammatory cytokines IL-1α and TNF-α. One study indicated that the inflammation persisted for up to two weeks after the CAPs exposures were ended. The extent to which induction of inflammatory parameters in the brain of PM-exposed animals may lead to potentially adverse consequences is, at present, unknown; however, there are associations between elevation of inflammatory markers in the brain and brain injury typical of degenerative neurological diseases such as Alzheimers and Parkinson's.

Objective
The objective of this study is to determine whether exposure to CAPs induces inflammation and/or oxidative stress in central nervous system (CNS) tissue of mice that are genetically modified to have impaired metabolism of lipids ($ApoE^{-/-}$ mice). The researchers will ascertain whether or not inflammation and/or oxidative stress in the brains of CAPs-exposed mice is associated with evidence of neurotoxicity and neurodegeneration and whether these changes are persistent after exposures are terminated. The study also will determine whether adverse CNS effects of CAPs are moderated by the chemical and physical characteristics of the inhaled aerosol.

Methods
Genetically modified mice ($ApoE^{-/-}$) will be exposed to CAPs or filtered air in Anaheim, California and four other US cities with PM characteristics that are distinctly different from PM in the Los Angeles area. Brains of the exposed and control mice will be harvested after exposure and analyzed for biomarkers of inflammation and oxidative stress which have been previously observed in the brains of people with degenerative neurological diseases. Histological examinations will also be performed to determine if exposures lead to CNS pathology. Extensive chemical and physical characterization of the exposure aerosols will be performed by collaborators at New York University. The *in vivo* biological responses will be correlated with physical and chemical composition of the PM and the *in vitro* potential of these particles to produce free radicals and induce cytotoxicity. These experiments will be conducted over a period of 3 years.

Expected Results
The expected results are that there will be elevations in both inflammation and oxidative stress biomarkers, but that the balance between inflammation and oxidative stress will be different among the different sites. This balance is anticipated to be moderated by

differences in PM composition, both in size distributions and in chemical components as well as differences in peak exposure concentrations and in the durations of higher exposure levels on a daily and seasonal basis. It is also expected that neurotoxicity and CNS injury will be modulated by inflammation and/or oxidative stress.

Significance to the Board
If PM induces neurological injury, and if that injury has features in common with degenerative CNS diseases, such as Alzheimer's or Parkinson's, it will be critically important to identify the PM characteristics that are related to these effects. A successful outcome of this project could provide improved understanding of the mechanisms of neurotoxicity of ambient PM, and how specific chemical constituents of the PM are causally related to health effects. This information will also aid regulators and planners in developing air quality regulations and land use guidance to better protect the health of California residents.

Contractor:
University of California, Irvine

Contract Period:
36 Months

Principal Investigator (PI):
Michael T. Kleinman

Contract Amount:
$309,141

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:
ARB is currently funding studies by Dr. Kleinman, including "Effects of Subchronic Exposures to Ambient Particulate Matter (PM) in Mice with Induced Genetic Susceptibility to Coronary Artery Disease," which is examining whether cumulative daily exposures will cause progressive changes in cardiac function in genetically modified mice, and "Effects of Inhaled Fine Particles on Lung Growth and Lung Disease," which is investigating whether cumulative daily exposures will cause permanent changes in lung growth and development during maturation of the lung using a rodent model.

Michael T. Kleinman is a Professor of Community and Environmental Medicine at the University of California, Irvine who has been studying the health effects of exposures to environmental contaminants found in ambient air for more than 30 years. He has published more than 90 articles in peer-reviewed journals dealing with the uptake and dosimetry of inhaled pollutants in humans and laboratory animals, and effects on cardiopulmonary and immunological systems after controlled exposures to ozone and other photochemical oxidants, carbon monoxide, ambient or laboratory-generated aerosols and chemically or biologically reactive metals such as lead, cadmium, iron and manganese. Dr. Kleinman's current studies focus on neurological and cardiopulmonary

effects of inhaled particles, including nano-, ultrafine, fine and coarse particles in humans and laboratory animals.

Prior Research Division Funding to University of California, Irvine:

Year	2008	2007	2006
Funding	$369,523	$1,290,054	$356,495

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

University of California, Irvine

Central Nervous System Effects of Ambient Particulate Matter: The Role of Oxidative Stress and Inflammation

DIRECT COSTS AND BENEFITS				
1.	Labor and Employee Fringe Benefits	$	193,894	
2.	Subcontractors	$	29,265	
3.	Equipment	$	0	
4.	Travel and Subsistence	$	8,857	
5.	Electronic Data Processing	$	0	
6.	Reproduction/Publication	$	1,256	
7.	Mail and Phone	$	144	
8.	Supplies	$	20,485	
9.	Analyses	$	20,000	
10.	Miscellaneous	$	7,525	
	Total Direct Costs			$281,425
INDIRECT COSTS				
1.	Overhead	$	27,716	
2.	General and Administrative Expenses	$	0	
3.	Other Indirect Costs	$	0	
4.	Fee or Profit	$	0	
	Total Indirect Costs			$27,716
TOTAL PROJECT COSTS				**$309,141**

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 (NYU)

Description of subcontractor's responsibility: Dr. Lung Chi Chen is the NYU PI. He will coordinate the activities of this project with an ongoing HEI-funded project that supports the exposures and cardiopulmonary physiology studies that will be conducted in 5 US communities with very different air pollution characteristics.

DIRECT COSTS AND BENEFITS				
1.	Labor and Employee Fringe Benefits	$	19,231	
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	$	3,281	
	Total Direct Costs			$22,512
INDIRECT COSTS				
1.	Overhead	$	6,753	
2.	General and Administrative Expenses	$	0	
3.	Other Indirect Costs	$	0	
4.	Fee or Profit	$	0	
	Total Indirect Costs			$6,753
TOTAL PROJECT COSTS				**$29,265**