PROPOSED

State of California
AIR RESOURCES BOARD

RESEARCH PROPOSAL

Resolution 11-7

February 24, 2011

Agenda Item No.: 11-1-1

WHEREAS, the Air Resources Board (ARB or 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 2706-269, entitled "Location Specific Systemic Health Effects of Ambient Particulate Matter," has been submitted by the University of California, Davis;

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 2706-269 entitled "Location Specific Systemic Health Effects of Ambient Particulate Matter," submitted by the University of California, Davis, for a total amount not to exceed $285,866.

NOW, THEREFORE, BE IT RESOLVED that ARB, 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 2706-269 entitled "Location Specific Systemic Health Effects of Ambient Particulate Matter," submitted by the University of California, Davis, for a total amount not to exceed $285,866.

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 $285,866.

ATTACHMENT A

"Location Specific Systemic Health Effects of Ambient Particulate Matter"

Background
The investigators have previously demonstrated that (1) mice exposed for two weeks to concentrated ambient particles (CAPs) have altered levels of serum inflammatory mediators, and platelets are activated to a more pro-coagulant state; (2) there is upregulation of genes associated with polycyclic aromatic hydrocarbon (PAH) metabolism, inflammation, and reactive oxygen species generation in the lungs; (3) the magnitude of platelet and inflammatory mediator responses and upregulation of genes in the lung appears to be season and location specific; (4) cultured human monocytes have different responses to summer and winter PM2.5; and (5) urban and rural PM2.5 contain different amounts of PAH and endotoxin. Parallel studies of mice exposed to equal doses of PM2.5 by inhalation of CAPs and by intratracheal instillation have demonstrated comparable responses to the two methods of exposure.

Objective
The hypothesis of the study is that regional and seasonal differences in composition of environmental particulate matter from the San Joaquin Valley influence the nature and extent of systemic pro-inflammatory and pro-coagulant responses. The specific objectives are to compare the influence of location and season specific ambient particle composition on pro-inflammatory mediator release and platelet activation in mice exposed by intratracheal instillation to PM2.5 collected during summer and winter at an urban and a rural site near Fresno, California. The second objective is to determine the relative contributions of transition metal-related reactive oxygen species generation, PAH compounds and endotoxin on generation of systemic pro-coagulant and inflammatory responses in mice exposed as noted above.

Methods
The project will investigate the effect of inhibition of specific biologically active PM2.5 components on systemic and pulmonary pro-inflammatory and pro-coagulant responses in BALBc mice intratracheally instilled with an aerosolized mist of previously characterized PM2.5 collected during the summers of 2007 and 2008 at rural and urban sites near Fresno. The study will focus on summer PM2.5 because previous studies in the investigator's lab have found that summer PM2.5 from both urban and rural sampling locations elicits a more robust inflammatory response than winter PM2.5. In some experiments, the particles will be pre-treated to neutralize endotoxin or to chelate soluble metals to investigate the relative contributions of these PM sub-species to lung and systemic inflammatory and pro-coagulant responses in different groups of mice. Twenty-four hours after instillation, the mice will be euthanized and blood will be collected for serum preparation and platelet isolation, and the lung tissue will be prepared for inflammatory gene expression and histopathology analyses using standard methods. Histopathology will be performed using standard techniques, with the slides evaluated by a board certified Veterinary Pathologist. Thirty-two cytokines will be assayed in serum samples using a commercially available assay kit. Platelet and

monocyte activation assays will be done on whole blood or on platelets collected at euthanasia using standard platelet activation assays, as will evaluation of interactions between platelets and monocytes, and platelets and other leukocytes. Microdissected sections of lung tissue will be used for analyses of gene expression for proteins involved in PAH metabolism, reactive oxygen species responses, production of tissue specific inflammatory cytokines, and systemic activation of platelets and monocytes.

Expected Results
The investigators expect to see different correlations between biological endpoints and summer/winter and urban/rural PM2.5. They also anticipate that pro-inflammatory and pro-coagulant responses to the particulate challenges will vary with the amount of PAH, soluble metal, and endotoxin in the particles to which the mice are exposed.

Significance to the Board
The project addresses the topic of whether or not there are significant differences in responses to PM of differing chemical composition, and will support the question as to whether it would be more health protective to reduce one type of PM as opposed to the ambient mixture as a whole.

Contractor:
University of California, Davis

Contract Period:
24 months

Principal Investigator (PI):
Dennis W. Wilson, DVM, Ph.D., and Fern Tablin VMD, Ph.D.

Contract Amount:
$285,866

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:
This is the third project ARB has funded with these investigators. Their past work has been of high quality, has been produced in a timely fashion, and has resulted in peer reviewed publications. Both Drs. Wilson and Tablin are well regarded among the scientific community.

Prior Research Division Funding to the University of California, Davis:

Year	2009	2008	2007
Funding	$1,588,387	$1,419,135	$ 773,346

BUDGET SUMMARY

Contractor: University of California, Davis

"Location Specific Systemic Health Effects of Ambient Particulate Matter"

DIRECT COSTS AND BENEFITS			
1.	Labor and Employee Fringe Benefits	$ 236,762	
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	$ 17,418	
9.	Analyses	$ 0	
10.	Miscellaneous	$ 6,268	
	Total Direct Costs		$260,448
INDIRECT COSTS			
1.	Overhead	$ 25,418	
2.	General and Administrative Expenses	$ 0	
3.	Other Indirect Costs	$ 0	
4.	Fee or Profit	$ 0	
	Total Indirect Costs		$25,418
TOTAL PROJECT COSTS			**$285,866**