University of Washington
Center for Clean Air Research (CCAR)

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Overall focus:

the cardiovascular health effects of near-roadway pollution

What is near-roadway pollution?

a complex mixture of particle, vapor and gas phase components that vary by vehicle emission source, road surface, extent of physical aging and the type and degree of atmospheric processing and photochemical reactions

a cause of cardiovascular disease

a prototypical case for developing research approaches to dealing with multi-pollutant exposure-effect relationships

Roadway proximity and left ventricular mass (LVM) in the Multi-ethnic Study of Atherosclerosis (MESA) cohort

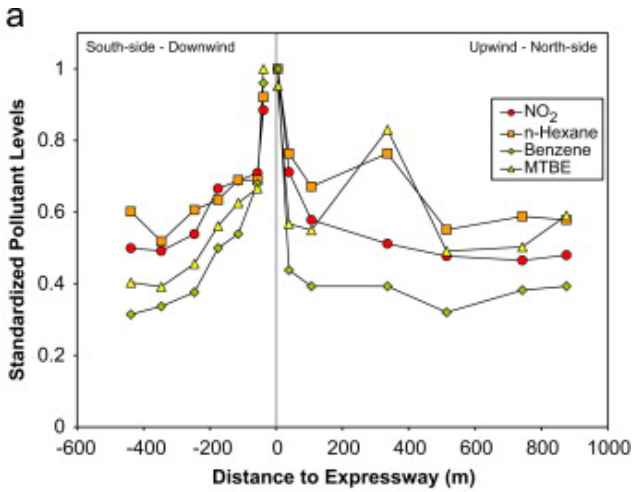
distance to road (m)	ΔLVMi (g/m^2 [95% CI])	p-value
>150	referent	
101–150	1.9 (0.6, 3.2)	0.003
50–100	1.6 (0.4, 2.9)	0.01
<50	2.3 (1.2, 3.4)	<0.001

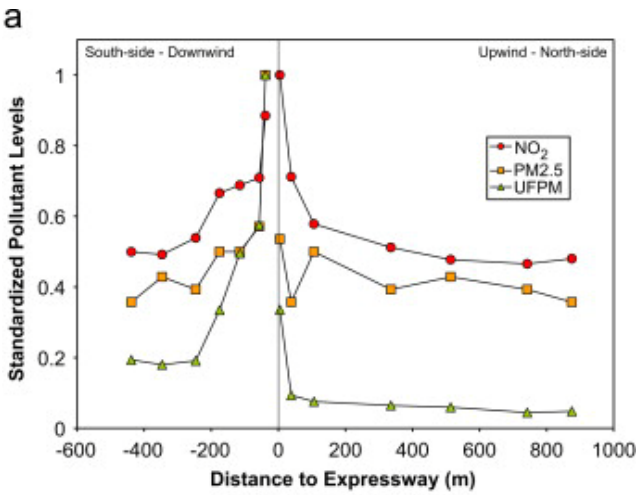
Van Hee V. Am J Respir Crit Care Med 2009;179:827-34.

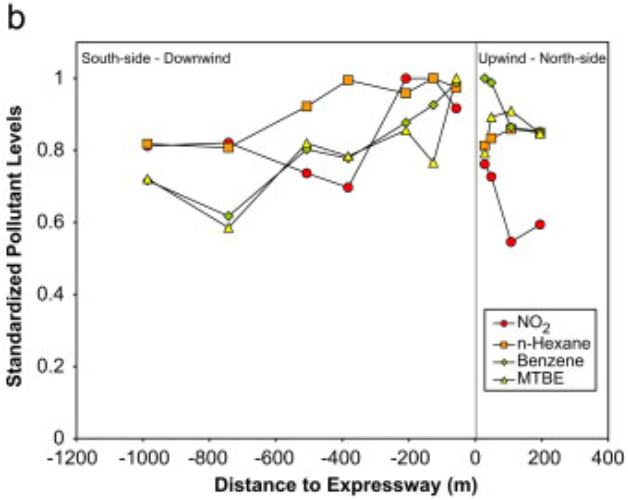
Pollutant concentrations ($PM_{2.5}$, ultrafine, NO_2, VOCs) near major roadway (Highway 401 - Toronto, Aug 5, 2004)

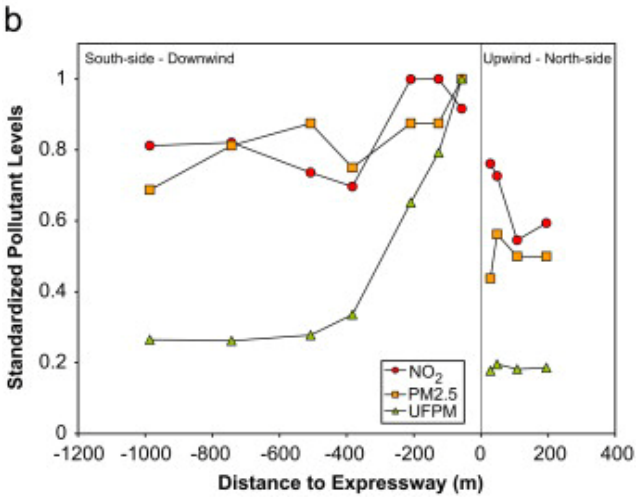
Observations:

1. distance from roadway
2. upwind vs. downwind
3. variability by site









Beckerman B, Atmos Environ 2008; 42: 275-90.

CCAR investigators

University of Washington	Sverre Vedal (director); Tim Larson (deputy director); Joel Kaufman; Lianne Sheppard; Paul Sampson; Adam Szpiro; Mike Yost; Chris Simpson; Mike Rosenfeld
Lovelace Respiratory Research Institute	Jake McDonald (deputy director); Amie Lund
University of New Mexico	Matt Campen
Washington State University	Tom Jobson; Tim VanReken

CCAR Science Advisory Committee

exposure and atmospheric science	Michael Brauer (UBC) Tom Peters (U Iowa) Barbara Turpin (Rutgers)
toxicology	Ian Gilmour (EPA) Jake Lusis (UCLA) Sanjay Rajagopalan (Ohio State)
human clinical / epidemiology	John Balmes (UCSF) Nick Mills (U Edinburgh) Arden Pope (BYU)
biostatistics	Brent Coull (Harvard)

CCAR projects

Project 1
roadway exposure characterization

M Yost (PI), T Larson, C Simpson, T Jobson, T VanReken

Project 2
exposure atmosphere generation

J McDonald (PI), T Larson

Project 3
toxicology

M Campen (PI), M Rosenfeld, A Lund, J McDonald

Project 4
human clinical studies

J Kaufman (PI)

Project 5
epidemiology cohort study

J Kaufman (PI), S Vedal

Project 6
multipollutant exposure modeling

L Sheppard (PI), A Szpiro, P Sampson

Project 1 Objectives

- Characterize spatial gradients in four MESA cities
  - Mobile monitoring in four cities over two seasons.
  - Concurrent fixed site monitoring
- Characterize near-source, downwind aging of traffic related air pollutants
  - Physical aging using mobile platform
  - Chemical aging using laboratory mixtures
- Provide detailed laboratory characterization of diluted and aged engine exhaust mixtures available for toxicology testing

Field measurements in red

Planned Measurements

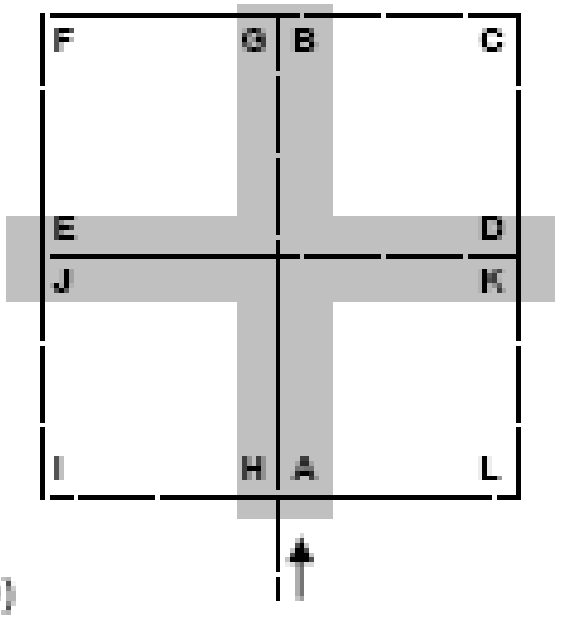
- Field Measurements
  - mobile platform
  - passive ‘snapshot’ samplers
- Laboratory Measurements
  - Mass spectroscopy (WSU)
    - VOC and iVOC information
    - particle composition
  - Field instruments moved to lab

Mobile Platform

- Four MESA cities
- 30-sec averages, ~ 10 sampling days/season
- 2 seasons (heating, non-heating)
- Companion fixed site
- Measure distributional properties of “fuzzy points”

“Fuzzy Points”

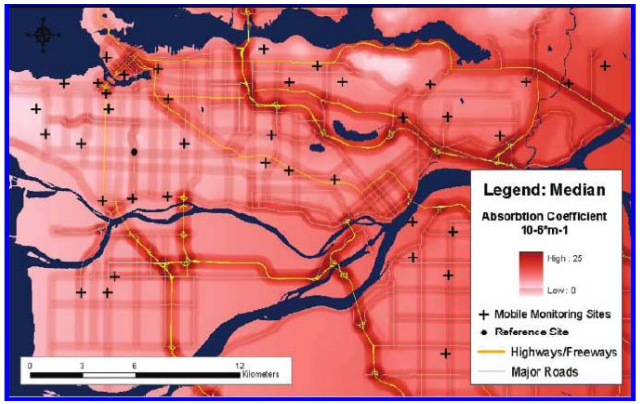
- Trace a cloverleaf at each intersection (~5-8 minutes)
- Determine the distribution properites of 30-sec adjusted readings*



LUR Model Predictions of Light Absorption Based on Fuzzy Points

Vancouver, BC

(late summer)

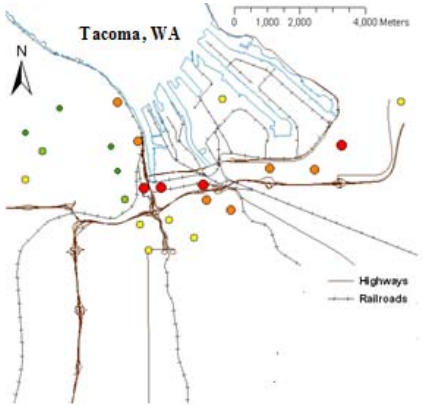


c.v. $R^2 \sim 0.7$

Larson et al (2009) *Environmental Science and Technology* 43(13), 4672-4678.

Tacoma, WA

(winter & summer)



c.v. $R^2 \sim 0.8$

Park et al (in preparation, 2011)

Extend Field Measurements to Include Multiple Pollutants

- Simultaneous measurement of a number of pollutants allows multivariate analyses
- Mobile platform (fuzzy points)
- Passive samplers (2-wk avgs, 20 sites)
- Goal is to decompose traffic-related pollution into primary vs. aged components

CCAR Field Measurements

Mobile Platform

30-sec averages*
Particle light scattering coefficient
Particle light absorption coefficient
Optical particle size distribution (300 – 32,000 nm)
Particle number concentration
Particle-bound PAHs
O_3, NO, NO2, CO, CO_2
VOCs (photo-ionization)
Mobility median diameter (25 – 100 nm)
X-Y Location

* Includes companion fixed site for temporal adjustments

Fixed Sites**

2-wk averages
Benzene Isoprene Toluene
N-Decane
Nonane
2-methylpentane
M-Xylene
Undecane
i-Pentane
N-Pentane
O-Xylene
Coarse PM

* 20 sites per season, 2 seasons

Laboratory Exposure Characterization

- Mass spectroscopy (WSU)
  - VOC and iVOC information
  - particle composition
- Photochemical aging chamber
- Simultaneous measurements with mobile platform and passive ‘snapshot’ samplers

Mass Spectroscopy

WSU Proton Transfer Reaction Mass Spectrometer

Measurement principle

$H_3O^+ + R \rightarrow RH^+ + H_2O$

- Full mass scans or multiple ion monitoring
- Quantitative.
- VOC detection limits ~ 50 pptv

Two sampling modes, alternate between

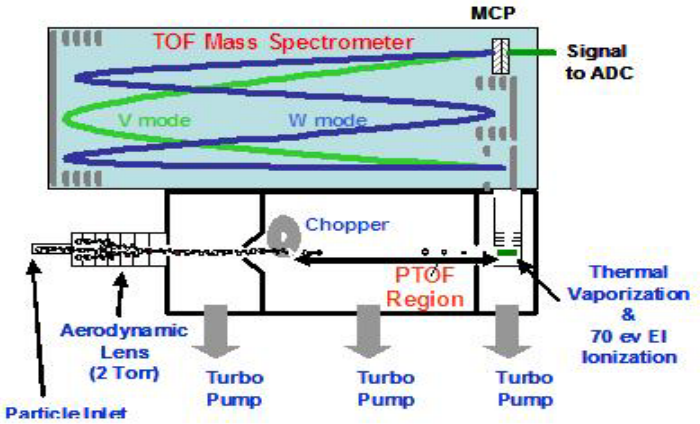
1. VOC Mode:

   Formaldehyde
   Acetaldehyde
   BTEX compounds
   Others …

2. IVOC mode:

   long chain alkanes
   monocyclic aromatics
   polycyclic aromatics

WSU High Resolution Aerosol Mass Spectrometer (AMS)

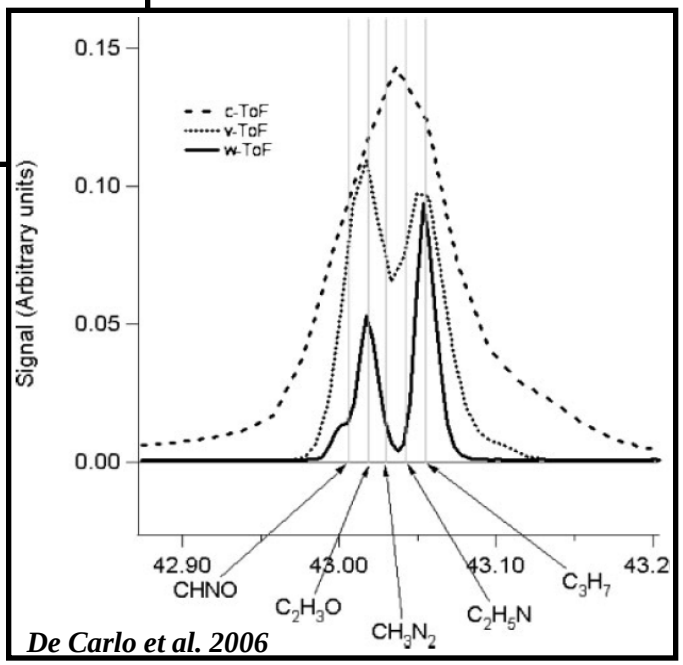


- Particles 50 < *Dp* < 1000 nm
- 'Non-refractive': Only material that volatizes below ~600 C is measured.
- Time-of-Flight Mass Spectrometer allows high resolution mass spectral data.
- Complex fragmentation patterns- chemical patterns can be identified but organic speciation is not possible.

Source Characterization with the AMS

Mohr et al. 2009

- Known sources can be characterized with a spectral ‘fingerprint’.
- This fingerprint can later be compared with ambient factors derived via PMF.
- The High Resolution AMS offers a much higher mass spectral resolution, allowing for more refined source characterization.



De Carlo et al. 2006

Proposed Sampling Schedule

Activity	Study Period	Location
Pilot Testing	June, 2011	Seattle
Field Sampling	Oct-Nov, 2011	St. Paul
Field Sampling	Jan, 2012	Los Angeles
Lab Characterization	April, 2012	Albuquerque
Field Sampling	June, 2012	Los Angeles
Field Sampling	Aug, 2012	St Paul
Lab Characterization	Oct, 2012	Seattle
Field Sampling	Jan, 2013	Winston-Salem
Field Sampling	Feb, 2013	Baltimore
Field Sampling	June, 2013	Baltimore
Field Sampling	Aug, 2013	Winston-Salem

UW Center for Clean Air Research

Project 2: Simulated Roadway Exposure Atmospheres for Laboratory Animal and Human Studies

Project 3: Cardiovascular Consequences of Immune Modification by Traffic-Related Emissions

Project 2: McDonald, Larson, Lund

Project 3: Campen, Rosenfeld, Lund, McDonald

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Objectives

- Simulate ambient exposures in the laboratory
  - Bridge these exposures to ambient measurements/modeling (Project 1)
- Compare toxicity of exposures
  - Use these results to define priorities and atmospheres for human exposures (Project 4)
- Define mechanisms of biological response

Conceptual Paradigm: Exposures

Background + **Traffic Emissions**

O_3, $(NH_4)_2SO_4$, NH_4NO_3, VOC, Ni, V

Tailpipe, Evaporative, Tire & brake, Resuspended Dust

100 m 500 m 1 km ??

Distance From Roadway

Exposures

Chemical Transformation

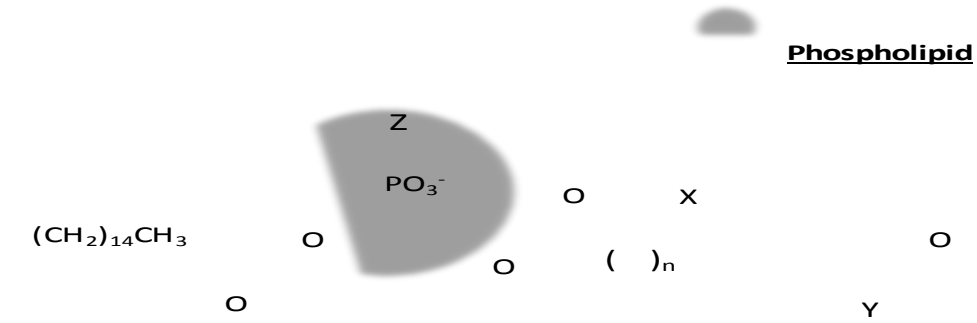
OH^-, Sunlight

Aging

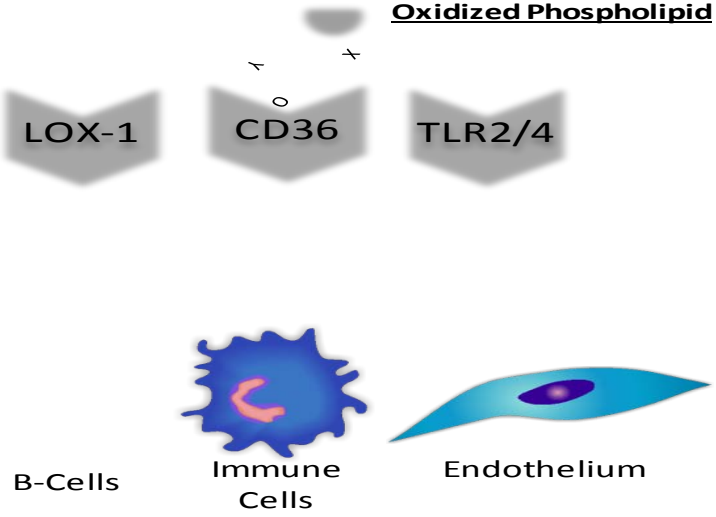
Nucleation, Agglomeration

Conceptual Paradigm: Toxicology Mechanisms

Exogenous Toxicants



X = -H, -OH
Y = - O, -OH
Z = choline, inosital, -H, etc



Comparative Exposure/Toxicology

Hypothesis:

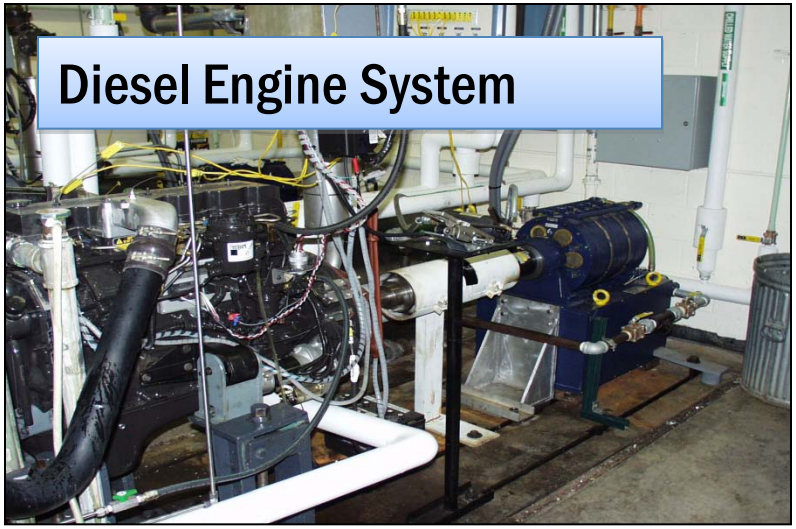
1. Motor vehicle emissions toxicity decreases when transformed in the atmosphere.

2. Background air and non-exhaust roadway emissions (road surface dust, tire and brake wear material, inorganic ions, metals, and ozone) do not contribute significantly to roadway-associated cardiovascular morbidity

Methodology

- Laboratory generated simulated atmospheres
  - Gasoline + Diesel
    - Physical and/or Chemical Transformation
  - Urban air simulated mixture (O_3, Inorganic Ions, Road dust)
  - Paved Road Dust (non-motor vehicle roadway emission)
- Detailed Characterization (complements Project 1 Ambient Measurements)
  - Particle size, number, mass, composition
  - Gas composition

Unique Resources

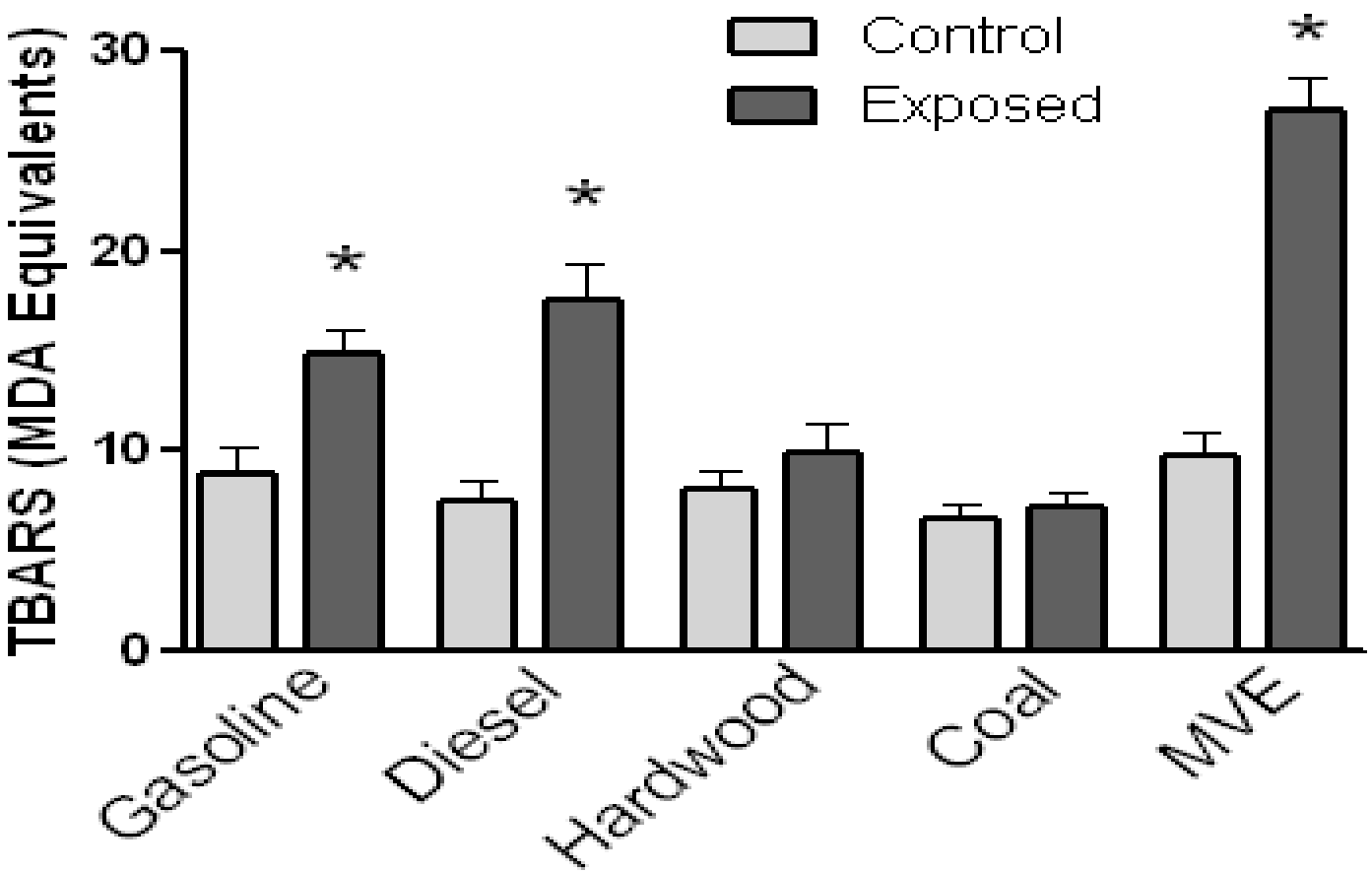


Biological Mechanisms

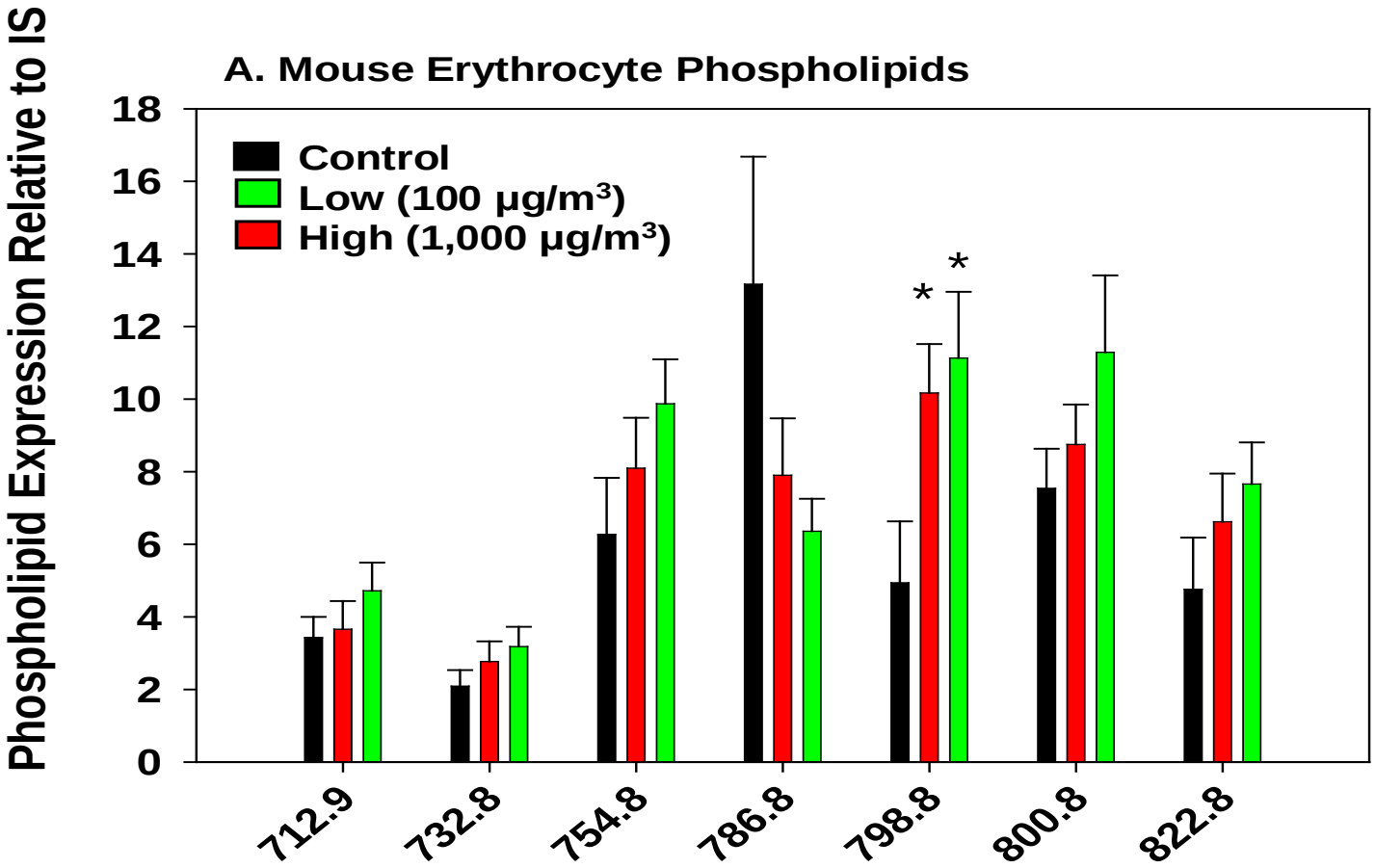
Hypothesis:

Emissions-induced oxidation of certain endogenous phospholipids, presumably in the pulmonary surfactant, can stimulate the activity of immune cells and in turn promote the monocytic invasion of existing vascular lesions.

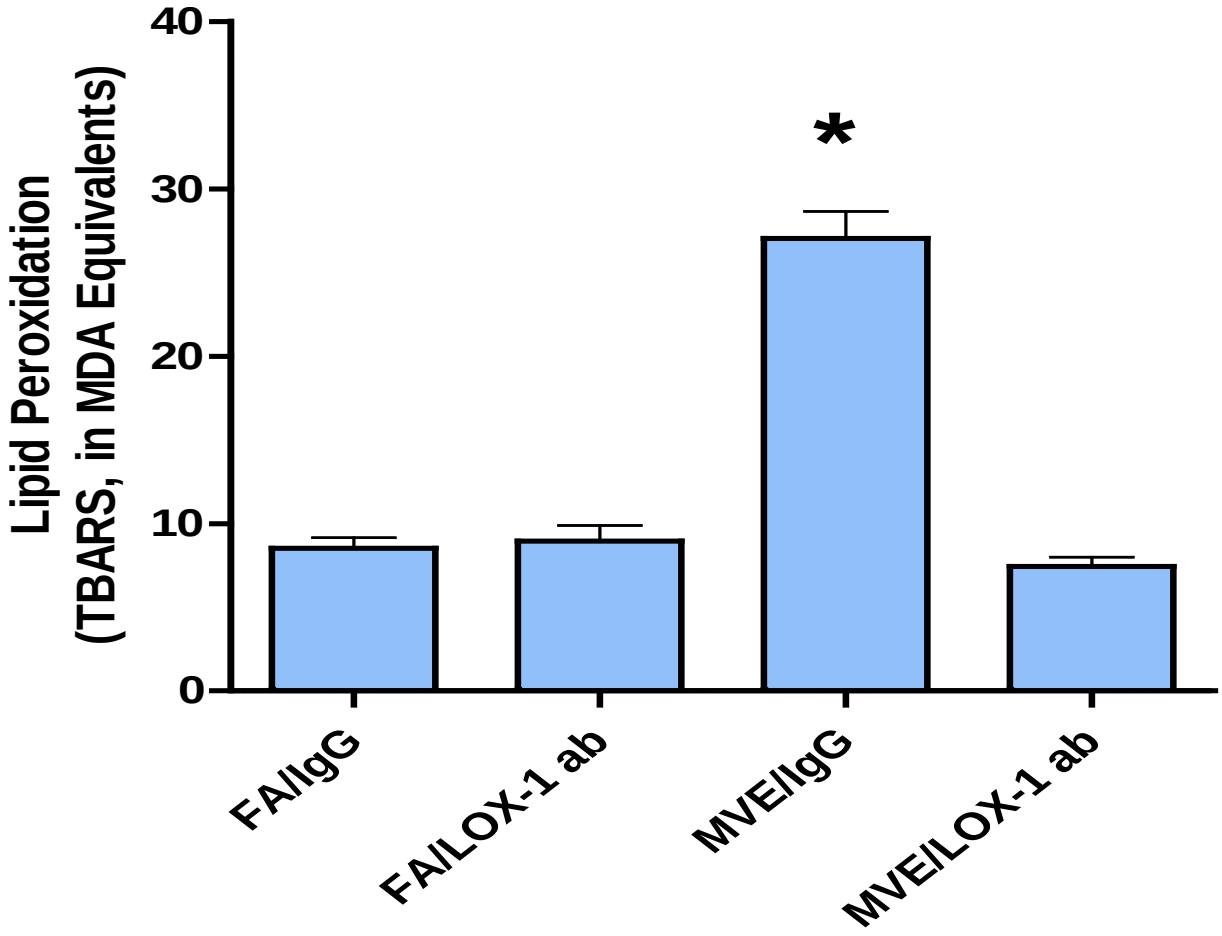
Motivation: MVE Shows Most Prominent Response of Lipid Oxidation



Motivation: Phospholipid Expression is Enhanced in Mice



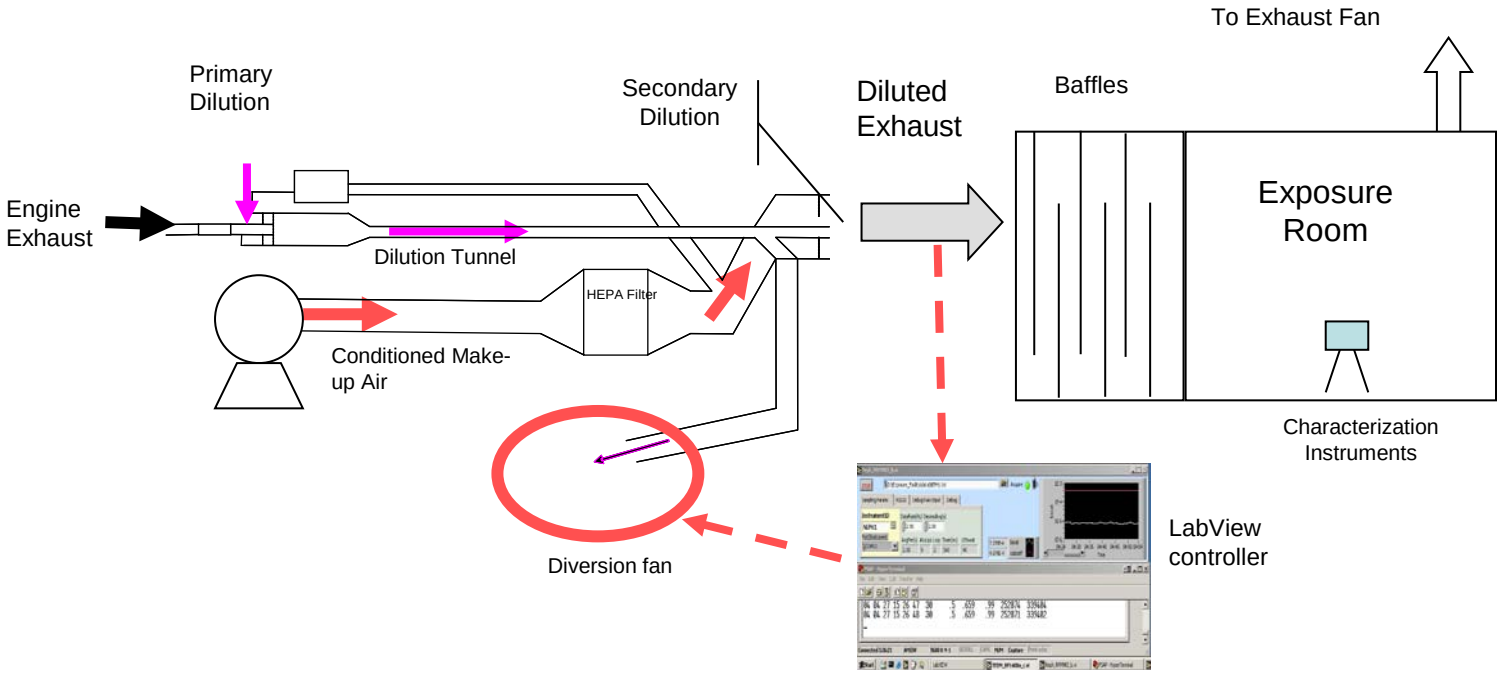
Motivation: Lipid Peroxidation is Blunted with LOX-1 Antibody Treatment



Project 4
PI: Kaufman

Vascular Response to Traffic-Derived Exhaust in Humans

UW Controlled Exposure Facility



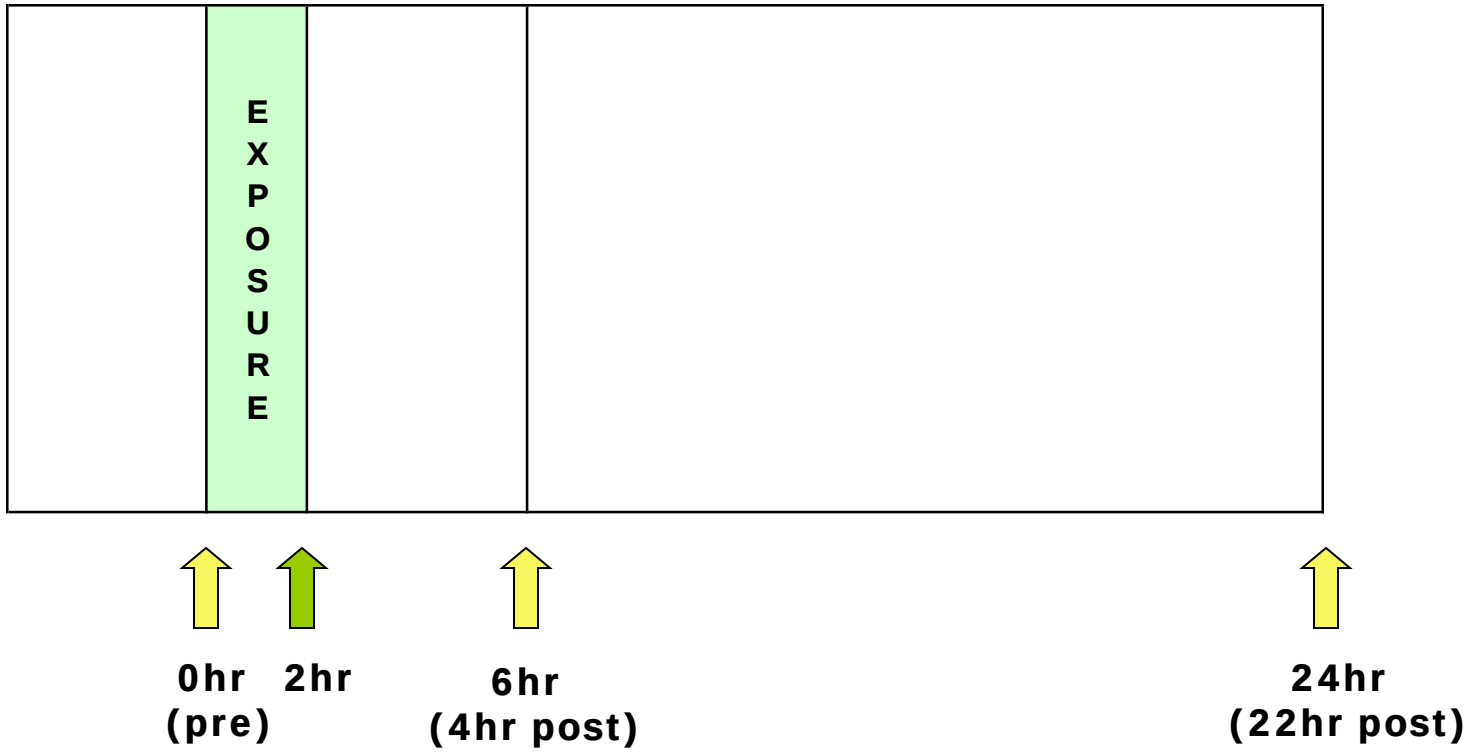
Human Controlled Exposure Study

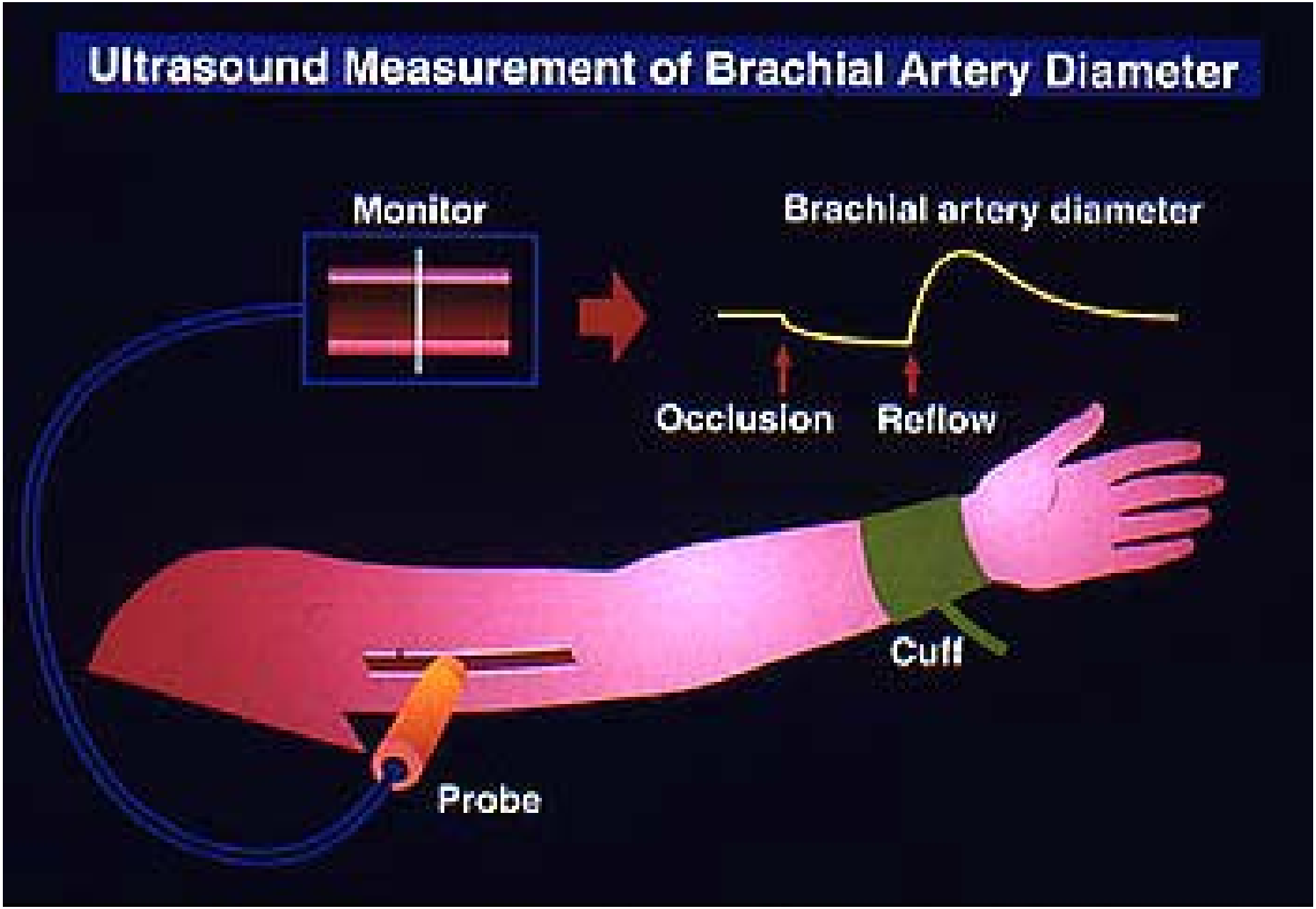
- Crossover Design (target n = 24)
- Years 3-5 of Center
- Exposures Chosen Based on Project 3 results
- Project 2 Provides Exposure Generation and Characterization Leadership
- Randomized Latin-Square
  - FA / Placebo
  - FA / Pharmacologic Agent
  - Traffic Pollution Low Toxicity/ Placebo
  - Traffic Pollution High Toxicity / Placebo
  - Traffic Pollution High Toxicity / Pharmacologic Agent
- Genotype-Stratified Trial

Human Controlled Exposure Study

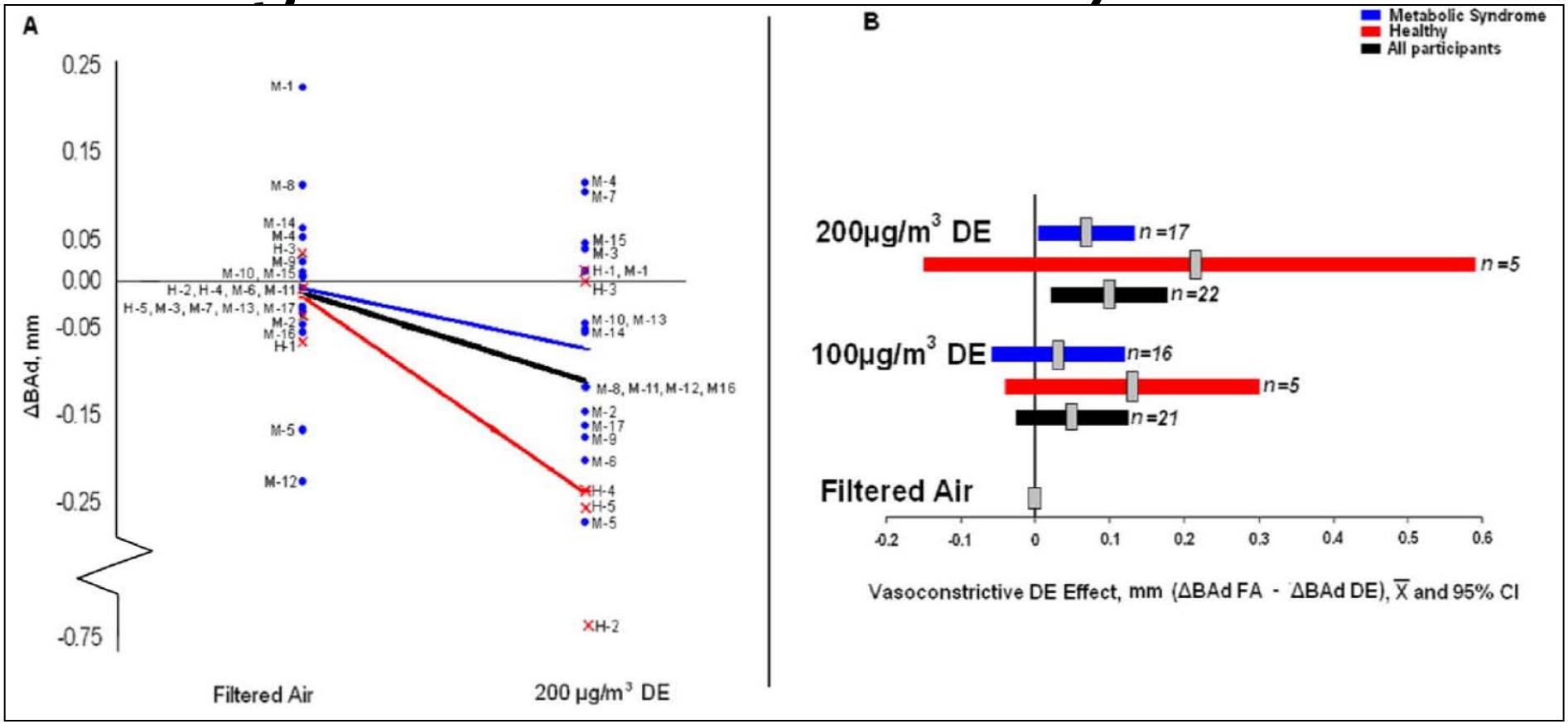
- 2 hr at 200 mcg/m^3 simulated traffic exposure or filtered air
- Monitor blood pressure
- Serial cytokine measurements
- Mononuclear cell gene expression
- Brachial artery dimensions and flow mediated dilation
- DNA methylation
- Evaluate effects of genotypic difference
- Evaluate effects of pharmacologic intervention

Timeline of exposure day




Ultrasound Measurement of Brachial Artery Diameter
Monitor
Brachial artery diameter
Occlusion
Reflow
Cuff
Probe

Change in Brachial Artery Diameter

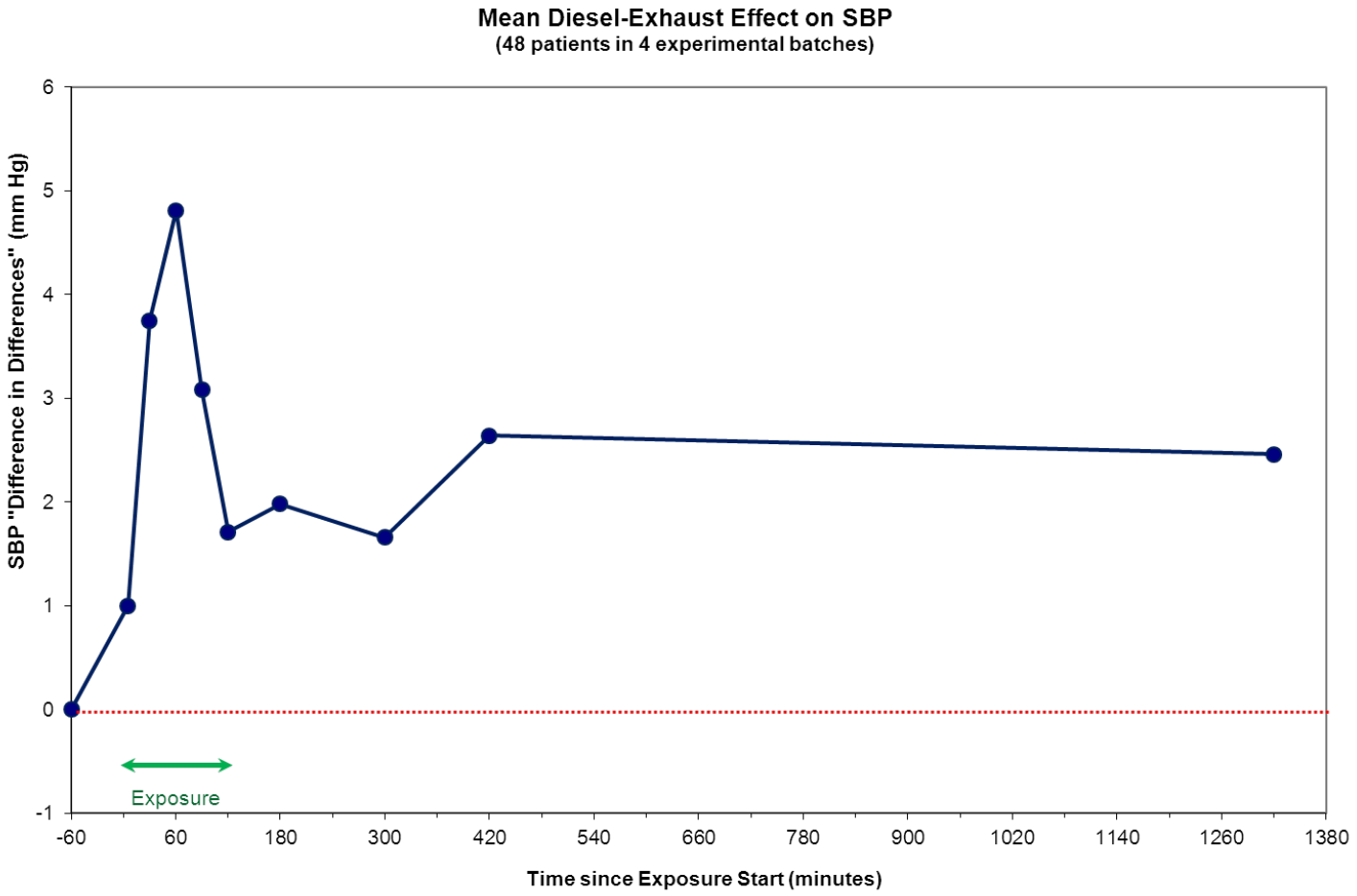


Vasoconstriction with Diesel Exhaust Inhalation

A. Changes in brachial artery diameter (BAd) following exposures to 200µg/m^3 DE or FA; lines represent mean Δ BAd (pre-to-post) at each exposure level.

B. Dose-response relationship of diesel exhaust effect on brachial artery diameter. Bars show mean and 95% confidence interval for vasoconstrictive effect for two study sub-populations and overall group. Wide confidence intervals for healthy group reflect small sample size and not higher variance.

DE Impact on Blood Pressure



Project 5
PI: Kaufman

Effects of long-term exposure to TRAP on subclinical measures of CVD in the Multi-Ethnic Study of Atherosclerosis

Background: The Multi-Ethnic Study of Air Pollution (MESA Air)

- To prospectively examine the relation between an individual assessment of long-term air pollution exposures and the progression of subclinical CVD
- To assess individual-level exposure to specific particulate and gaseous ambient-derived air pollutants
- To assess the relation between individual assessments of long-term air pollution exposures and incidence of CVD events, including MI and CVD mortality

Our Approach in MESA Air

- Pair state-of-the-art cardiovascular epidemiology with state-of-the-art exposure estimation
  - Unusual dedication of resources
- Encourage extensive collaborations and promote opportunities for ancillary studies
  - MESA Air as research platform

Adjudicated clinical events

- Myocardial Infarction
- Stroke/TIA
- Congestive Heart Failure
- Coronary Revascularization
  - PTCA
  - CABG
- Angina
- Peripheral Vascular Disease
- Cardiovascular Death

Extensive interviews

- Medical History
- Medications
- Personal History
- Family History
- Health and Life
- Physical Activity
- Diet
- Neighborhood Characteristics
- Residential History
- Sleep History
- Cognitive Assessment

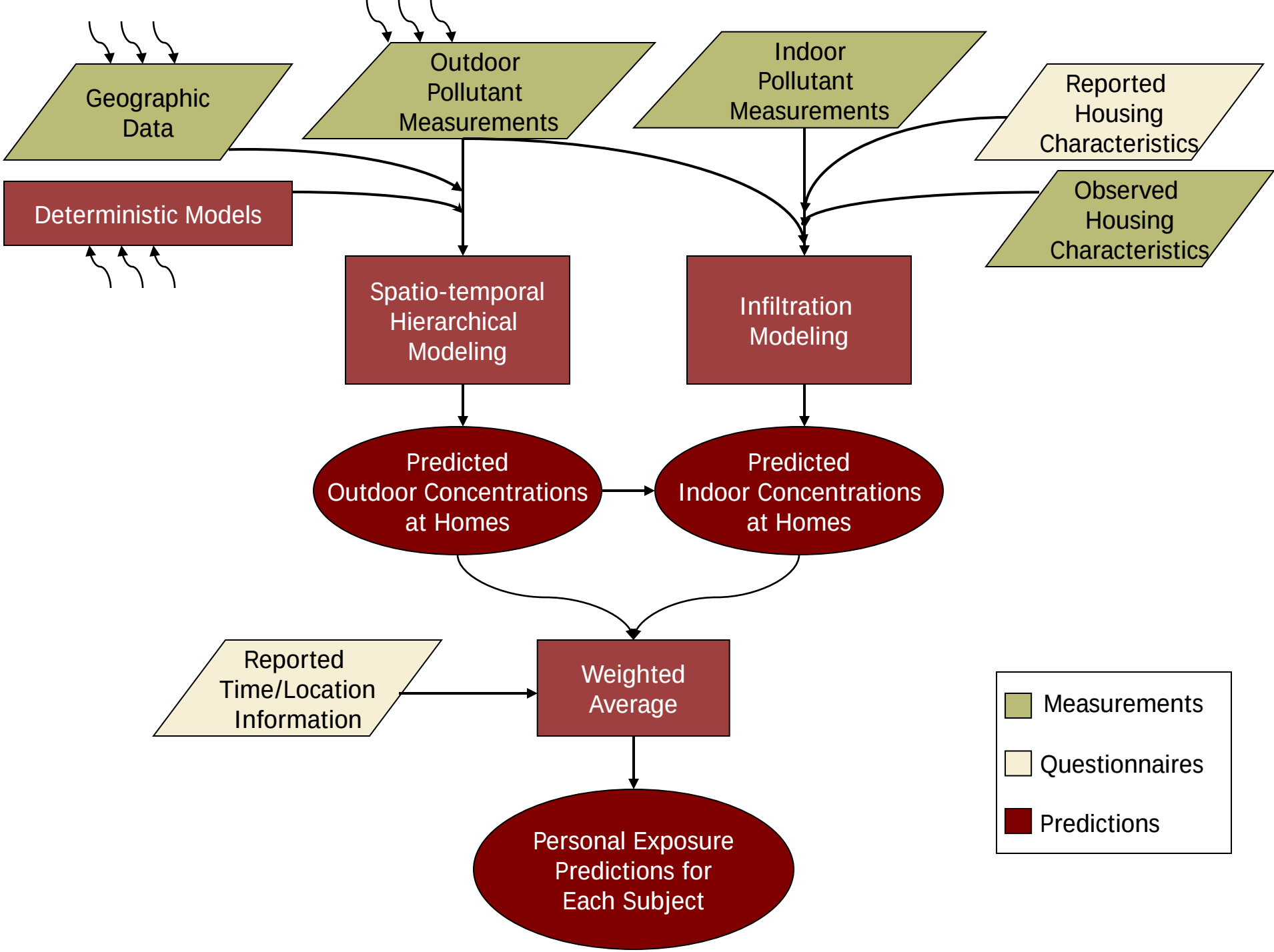
Other Measures and Specimens

- Anthropometry
- Resting Blood Pressure
- Ankle/Brachial Blood Pressure Index
- ECG
- Spirometry (MESA Lung)

- Cardiac MRI
- Retinal Photography (MESA Eye)
- Quantitative Lung CTs (MESA Lung)

- Urine Collection
- Blood Collection

- Genomics/Epigenomics
  - MESA Family
  - Candidate Genes
  - CARe
  - SHARe
  - DNA methylation
  - Gene Expression


Geographic Data
Outdoor Pollutant Measurements
Indoor Pollutant Measurements
Reported Housing Characteristics
Deterministic Models
Observed Housing Characteristics
Spatio-temporal Hierarchical Modeling
Infiltration Modeling
Predicted Outdoor Concentrations at Homes
Predicted Indoor Concentrations at Homes
Reported Time/Location Information
Weighted Average
Personal Exposure Predictions for Each Subject
Measurements
Questionnaires
Predictions

CCAR Project 5

- Aim 1: To build a multi-pollutant exposure model for traffic-derived air pollutants for use in epidemiological analysis
- Aim 2: To develop and validate individual-level exposure estimates for traffic-derived air pollutants, including a determination of the effect of time in transit
- Aim 3: To estimate the effect of individual-level exposure to traffic-derived air pollution on subclinical cardiovascular disease in MESA Air

Aim 1: Generate individual-level predictions of outdoor pollutant levels

- Predictions of long-term average multi-pollutant concentration fields achieved by combining the predictions from two seasonal co-kriging models in each city: Baltimore, Winston-Salem, Chicago, Los Angeles
- Predictions of the impact of traffic patterns and roadway class on pollutant concentrations

Aim 2: Understand in-vehicle exposures

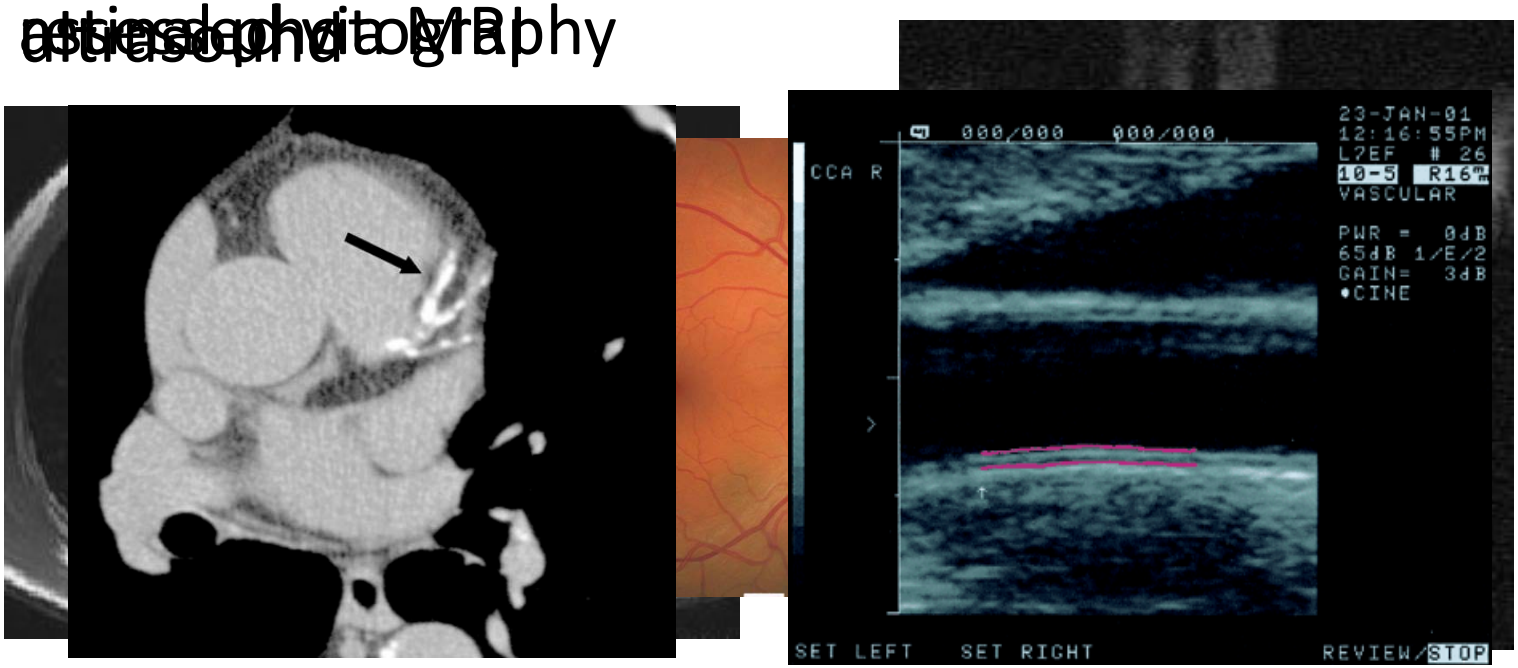
- Recruit 144 participants from Winston-Salem and LA to participate in 2 two-week sampling events
  - Indoor, outdoor, personal, and in-vehicle monitoring
  - NO_X, NO, NO_2, SO_2, O_3, and a suite of up to 11 VOCs

  - GPS data-logging devices to track location

- Information learned from the in-vehicle monitoring study will be applied to all participants, including VOC infiltration efficiency and the relationships between:
  - total personal exposure and in-vehicle exposure
  - reported time-in-transit and measured time-in-transit

Aim 3: Epidemiologic Analysis in the MESA cohort

- To understand the relation between exposure to traffic-derived air pollutants and change in
  - carotid IMT over 10 years, assessed via US and
  - atherosclerotic MRI



Project “6”: exposure modeling in a multipollutant context

Goal

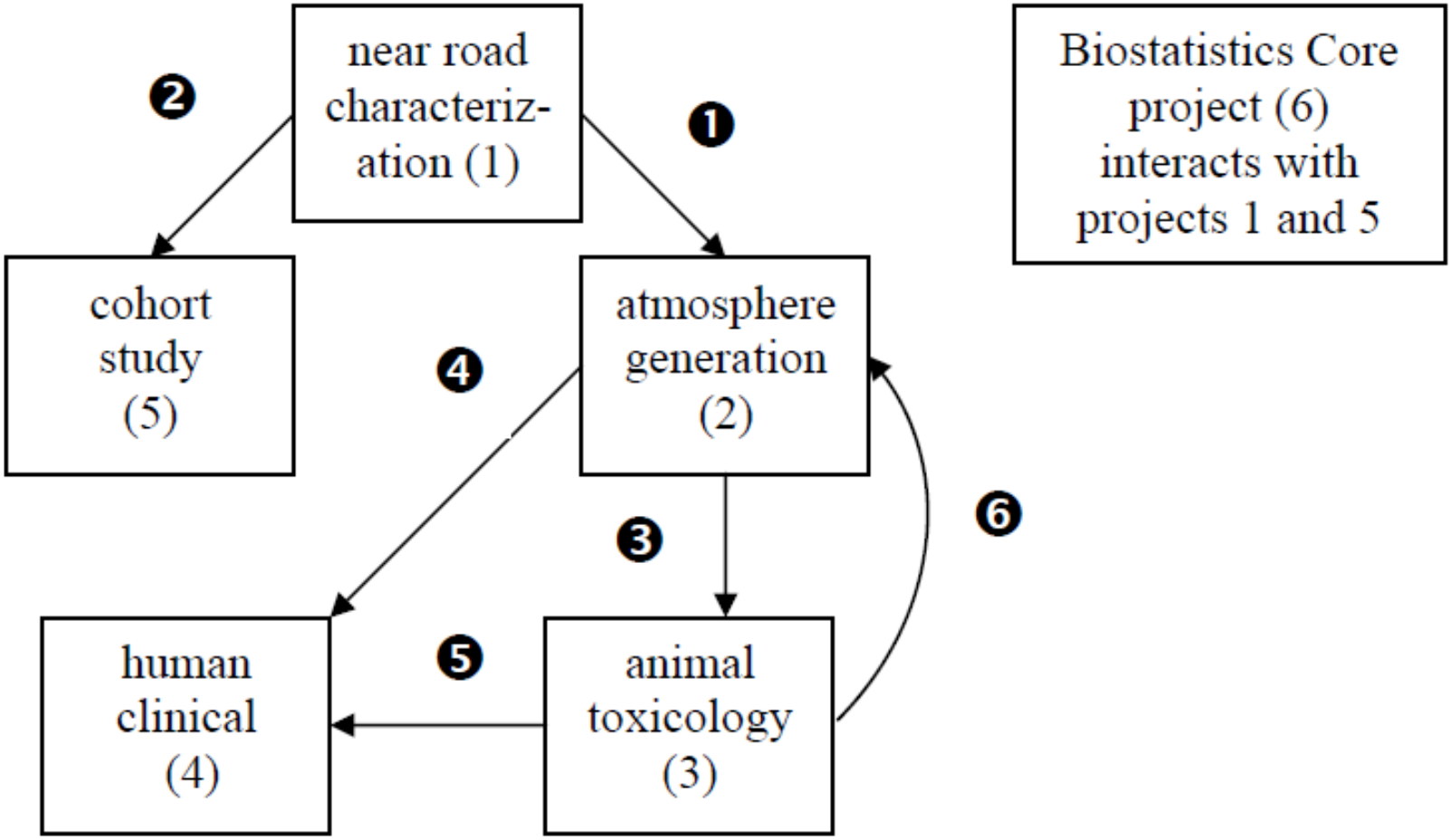
Develop set of tools to:

- specify baseline multipollutant mixtures
- calculate RRs for alternative mixtures

Details

Integrated methodology to:

- construct multivariate exposure model
- account for correlations in space and time between mixture components
- reduce mixture exposure dimensions
- correct for measurement error using bootstrap methods



A “sum is greater than its parts” approach to investigating the health effects of a multipollutant air pollution exposure