# Introduction

GLACIER

GREAT LAKES AIR CENTER

FOR INTEGRATED ENVIRONMENTAL RESEARCH

MICHIGAN STATE UNIVERSITY

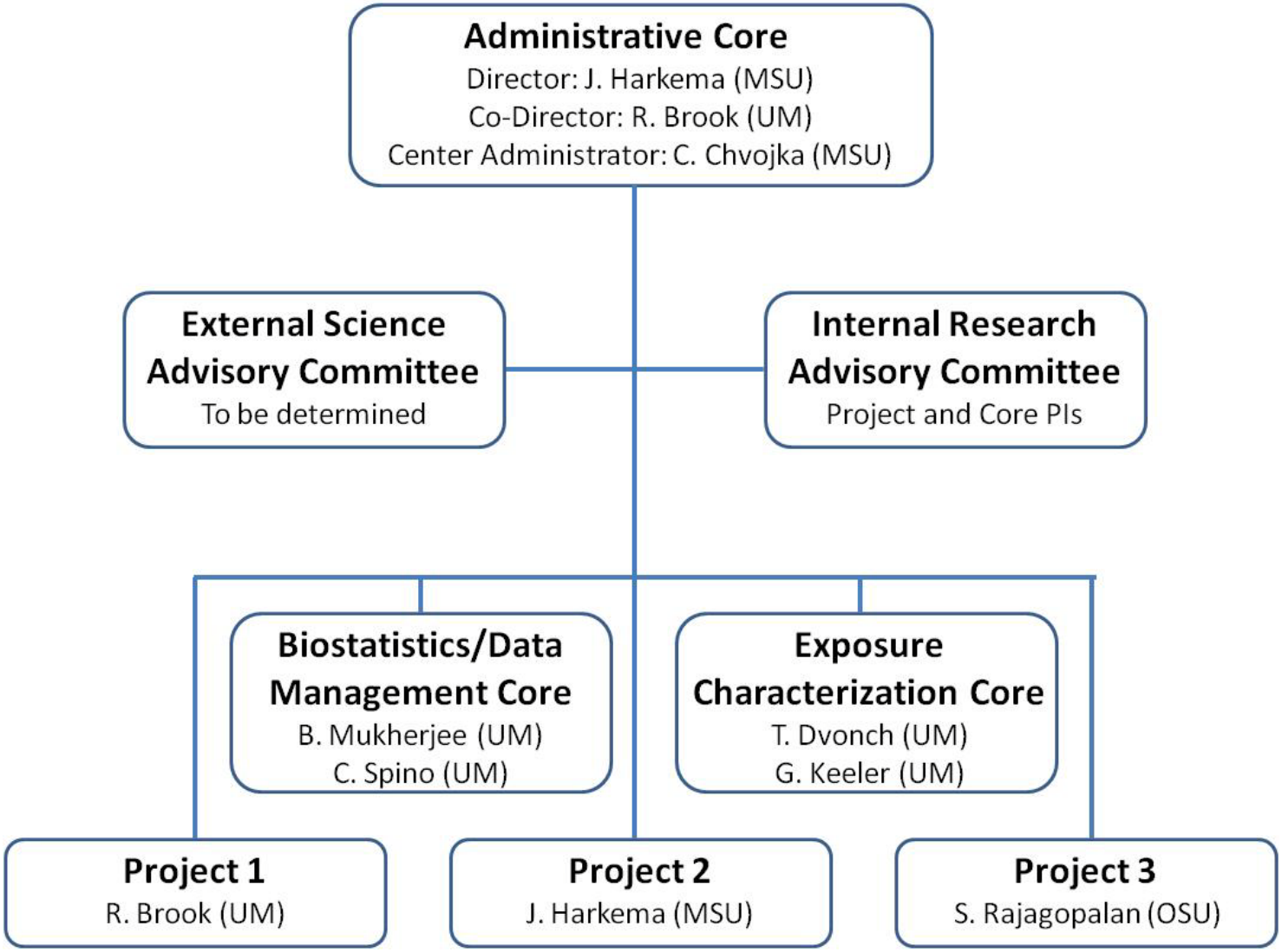
MICHIGAN

THE OHIO STATE UNIVERSITY

This research is funded by U.S. EPA - Science To Achieve Results (STAR) Program

Grant # RD83479701

# GLACIER: Structure



# Project PIs

Sanjay Rajagopalan, MD
Ohio State University

Jack Harkema, DVM, PhD
Michigan State University

Robert Brook, MD
University of Michigan

# Core PIs

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Jerry Keeler, PhD
University of Michigan

Bhramar Mukherjee, PhD
University of Michigan

Tim Dvonch, PhD
University of Michigan

Cathie Spino, PhD
University of Michigan

# Objective/Hypothesis

Explore and elucidate one of the most prevalent and important global health-environment interfaces:

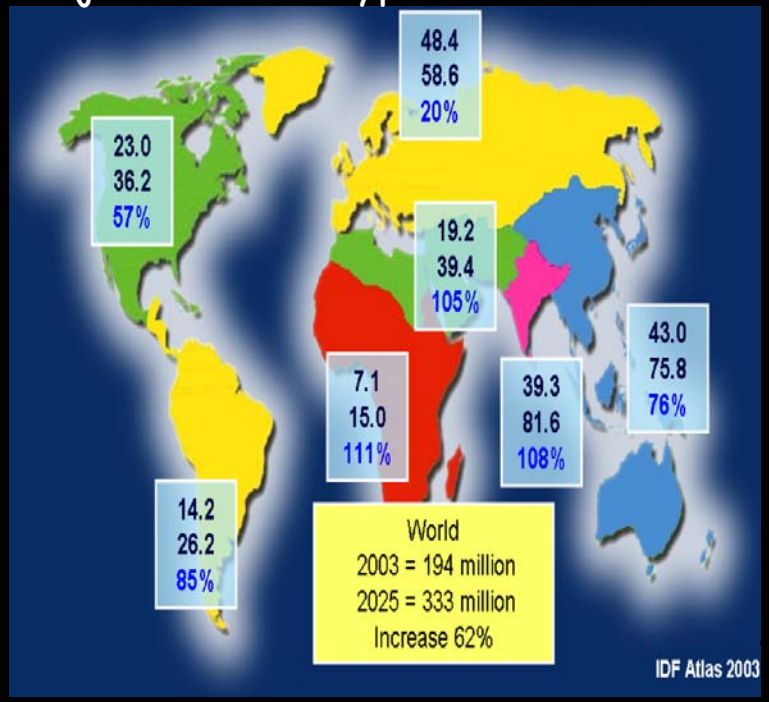
*The inter-relationships between facets of the cardiometabolic syndrome (CMS) and air pollution*

Particulate matter (PM) and ozone ($O_3$) are capable of eliciting multiple important adverse cardiometabolic health effects that are dependent on

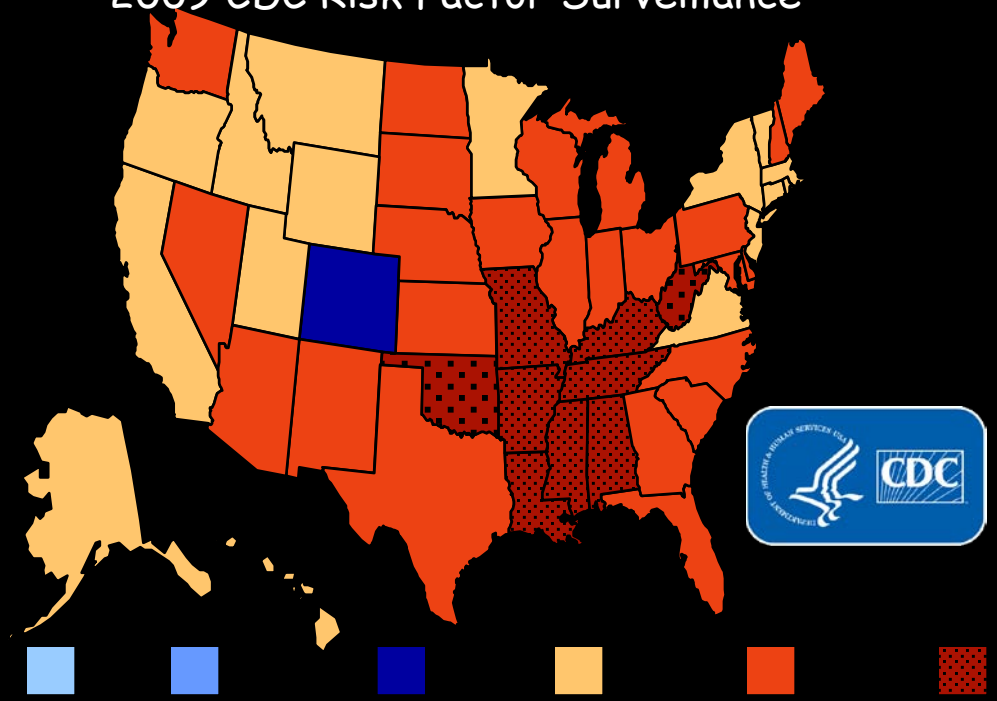
1. *the local multipollutant milieu,*
2. *an individual's pre-existing cardiovascular and metabolic condition (susceptibility),*
3. *the interactive toxicity of PM and $O_3$ coexposure*

# Cardiometabolic Disease: A Global Pandemic

Projections for Type II DM IDF




2009 CDC Risk Factor Surveillance




- Global and US projections for Type II diabetes and obesity reaching pandemic proportions[1]
- 10% and 16% of adults in China have pre-diabetes and Type 2 DM with urbanization an important factor in multivariable analysis. US data worse [1,2]

1. US Data Accessed from: http://www.cdc.gov/obesity/data/trends.html
2. Prevalence of diabetes among men and women in China. N Engl J Med. 2010; 362(1 2):1090-101

# Clinical Manifestations and Consequences of Cardiometabolic Syndrome (CMS)

**Metabolic Syndrome**

Insulin resistance

Glucotoxicity

Lipotoxicity

↓ Adiponectin

Type 2 diabetes

Dyslipidemia
- Low HDL
- Small, dense LDL
- Hypertriglyceridemia

Hypertension

inflammation

→ Atherosclerosis

- **A prior study suggests an interaction air pollution in potentiation of components of metabolic syndrome[1]**
- **Recent epidemiologic studies have confirmed this association[2-5]**
- **The mechanisms, temporal relationship and components of air pollution, and the role of multipollutants are poorly characterized**

1. Sun et al. Circulation 2009; 119: 538-46. 2. Brook RD et al. J Occup Environ Med 2008; 50: 32-38; 3. Krämer U et al SALIA cohort study. EHP 2010; 118: 1273-9; 4. Pearson JF et al. Diabetes Care 2010; 33: 2196-2201 5.Puett et al EHP 2011; 119: 384-9

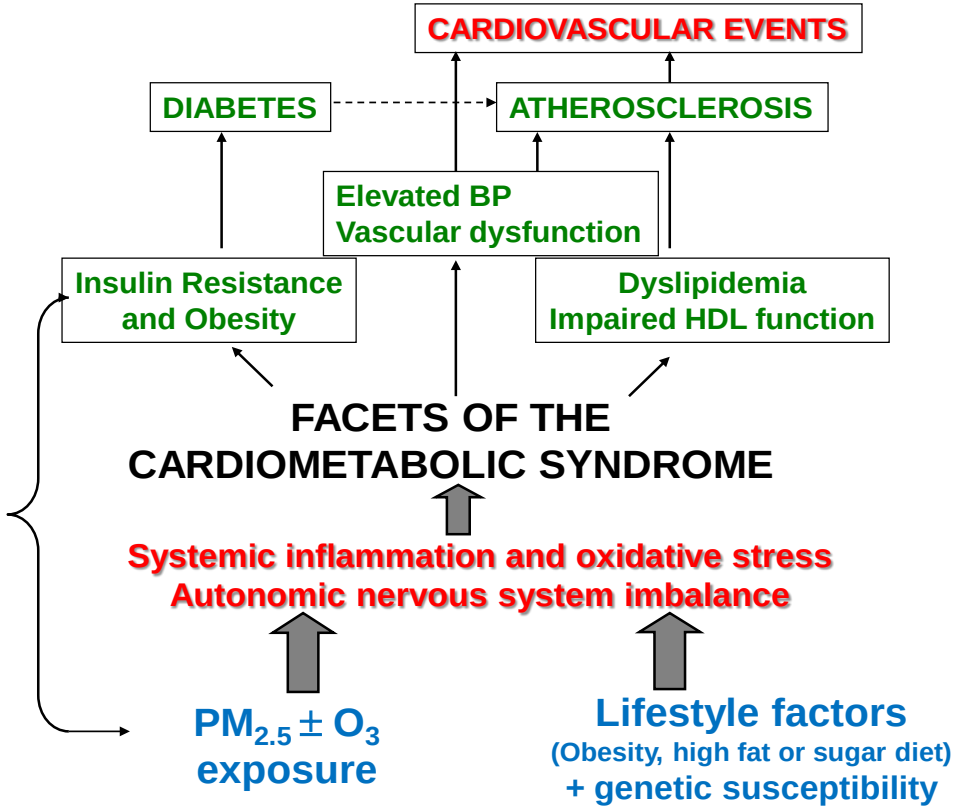
# Health Effects Questions

**What multipollutant atmospheres in the Great Lakes Region adversely affect human health?**

**Does obesity make people more susceptible to the health effects of air pollution?**

**Reciprocal relationships**

- Susceptible population
- Vulnerable population



# Projects

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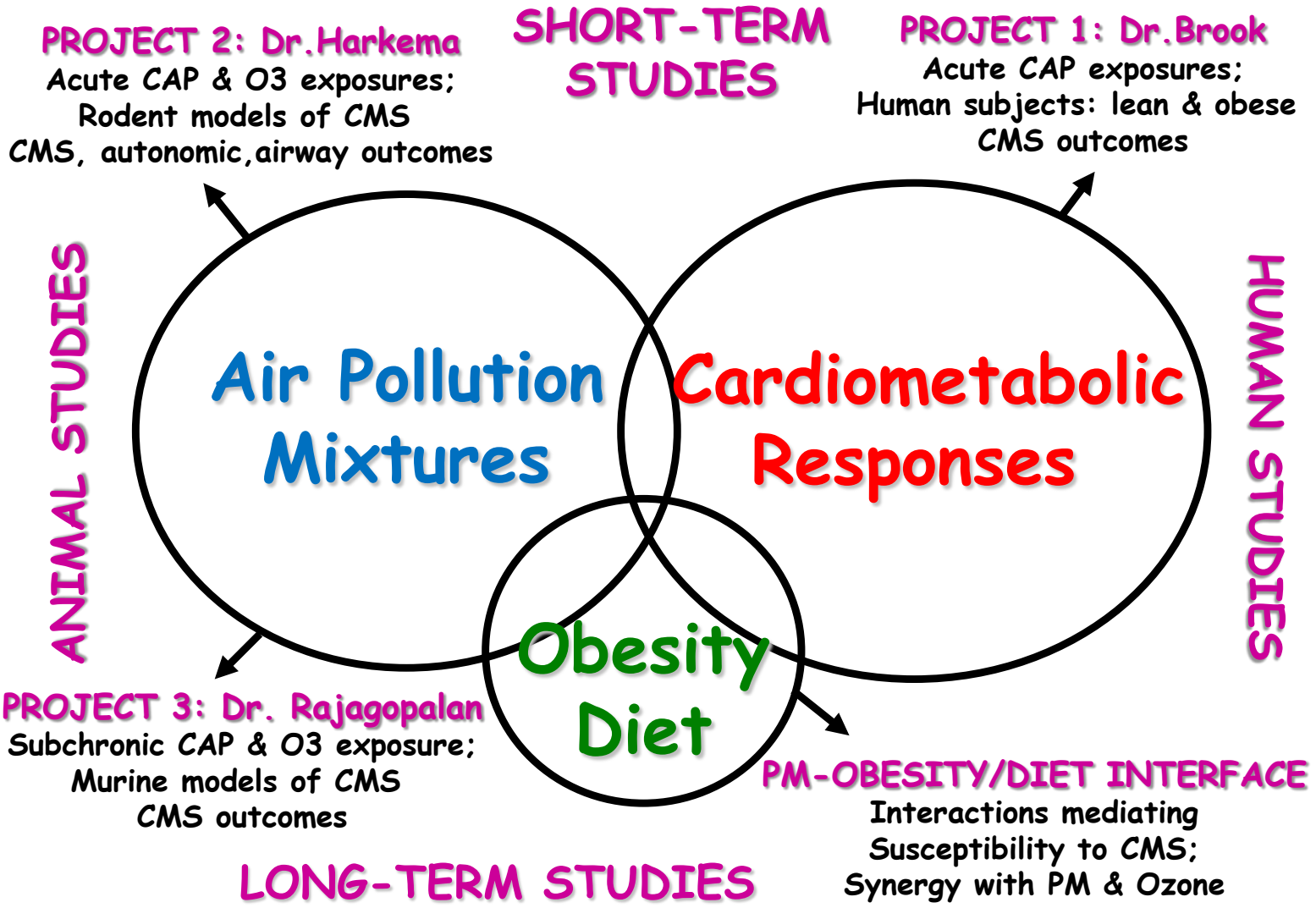

# Human and animal exposures to multipollutant atmospheres

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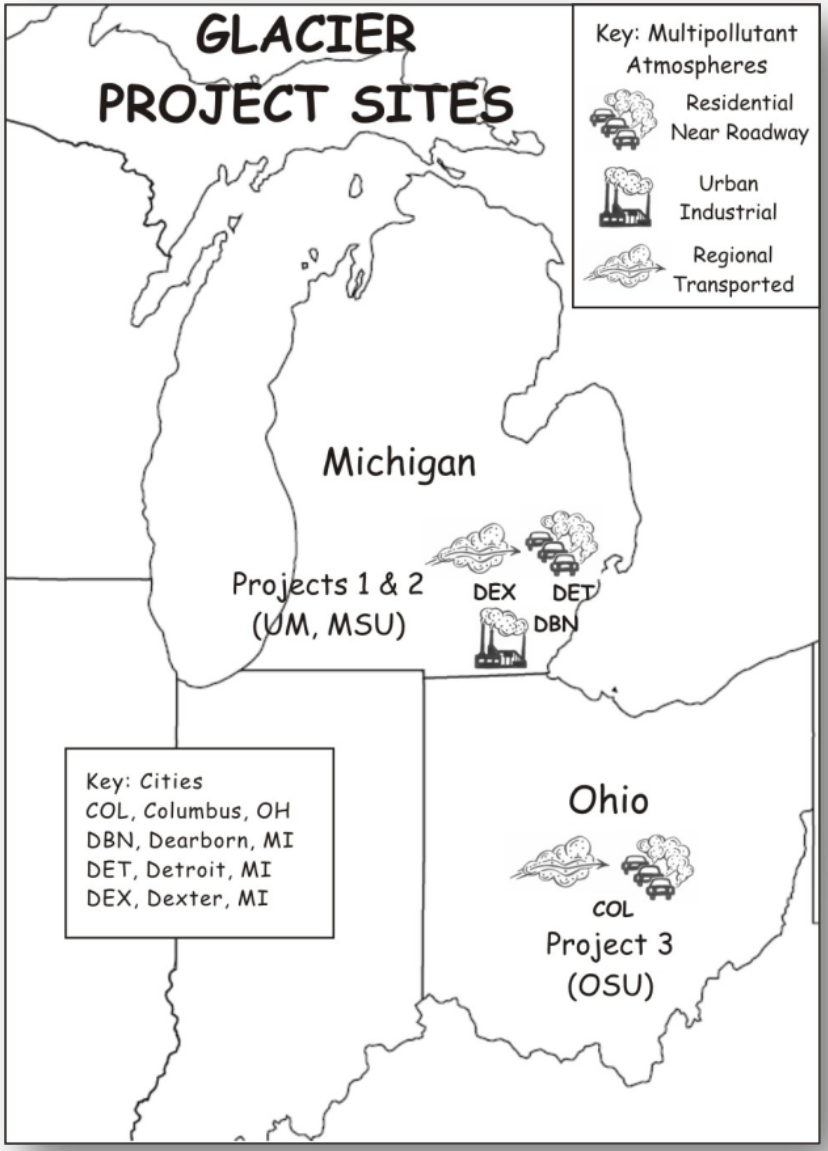


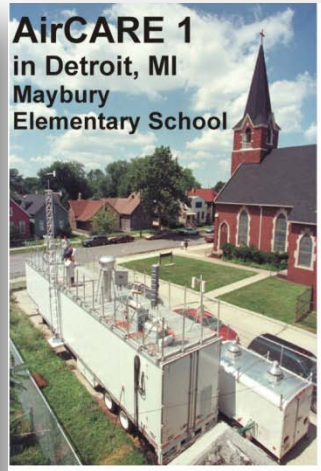




*Our results will provide critical insights into the health effects of PM, $O_3$, and their co-exposures in a multipollutant context.*

# Dearborn Exposure Site


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Medical Waste

Waste to Energy

Ambassador Bridge

Electric Utility

Steel Coating

Steel Manufacturing

Lime

Lime

Coke

Zug Island

Oil Refinery

Steel Processing

Steel

Michigan Ave

Warren Ave W

Myrtle St

Fort St W

Fort St S

Gratiot Ave

Chrysler Fwy

Inwood St

Chrysler Dr

Blvd

Miller

96

375

1

10

12

94

18

39

N

W

E

S

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© 2007 Navteq

© 2005 Google

# To understand the MI OH Football Rivalry is to Understand History…

- **MI OH nearly went to war…over Toledo!**
- **The NW Ordinance of 1787 clearly gave Toledo to MI.**
- **MI and OH gathered troops across the border in 1835**
- **Pres. Andrew Jackson interceded…Toledo was given to OH in return for the UP!**
- **As recently as 1972 the US supreme court heard arguments over Toledo…judgment favored OH…**

# Project 1: Short-term Human Studies

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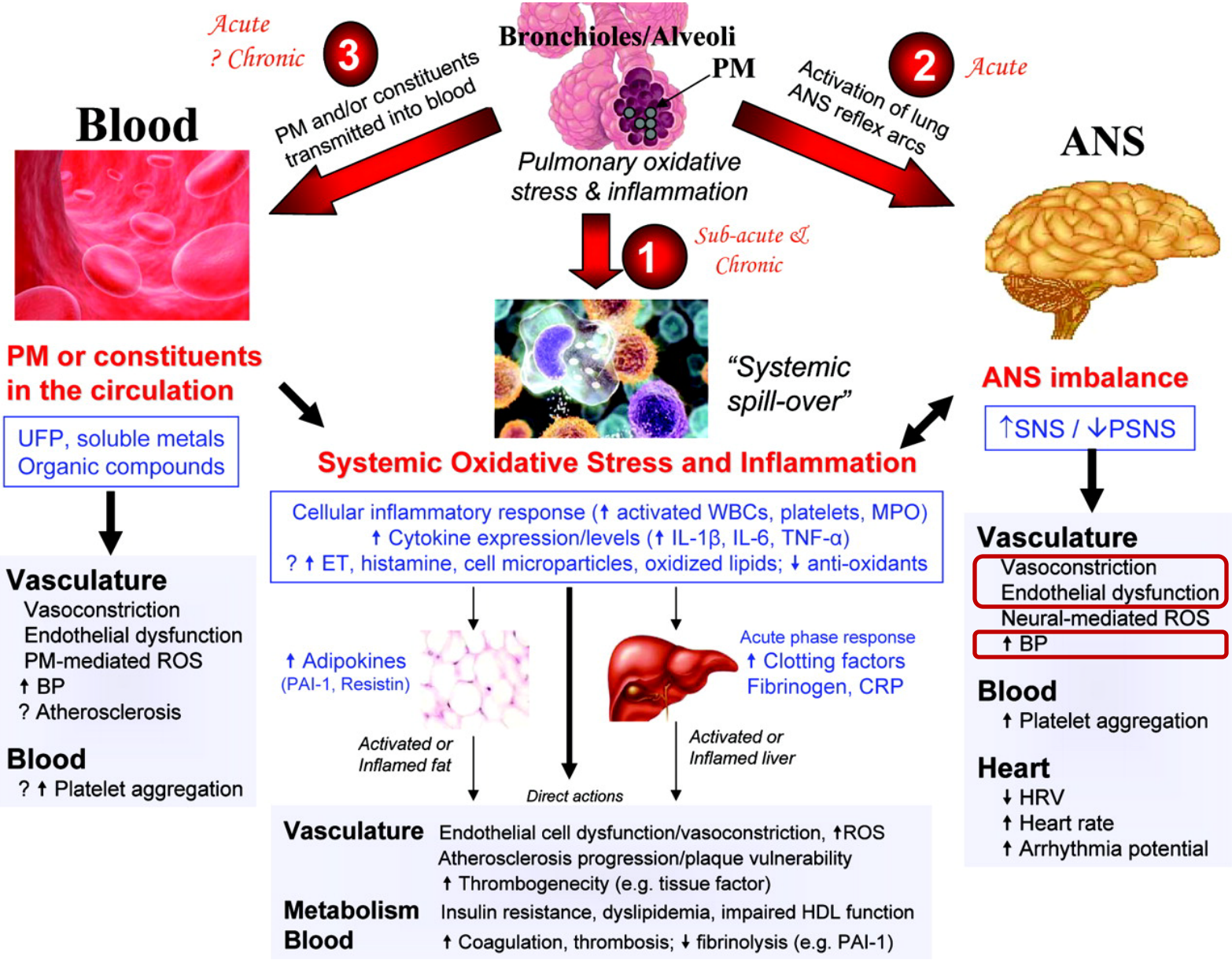
## Cardio-metabolic Effects of Exposure to Differing Mixtures and Concentrations of Coarse and Fine CAP in Obese and Lean Adults


Robert Brook MD†, Elif Oral MD†
Marianna Kaplan MD† and Jesus Araujo MD*

† *The University of Michigan; Ann Arbor, MI*
**University of California Los Angeles; CA*

# Biological Pathways Linking AP and CMS




SHOWN BY OUR FINE CAP STUDIES

*Brook RD et al. Circulation 2010;121:2331-2378*

# HUMAN STUDIES TIMELINE

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| YEAR | EXPOSURE/LOCATION | Human Study |
|---|---|---|
| 1 | Regional/Rural Coarse CAP | 1 |
| 2 | Urban/Industrial Coarse CAP | |
| | | |
| 3 | Urban/Industrial Fine CAP | 2 |
| 4 | Urban/Industrial Fine CAP | |
| 5 | Urban/Industrial Fine CAP | |
| *6* | *Near Roadway Fine CAP* | *3* |

# Human Study #1 (Coarse CAP)

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**HYPOTHESIS 1:**

***Regional/rural & urban/industrial* coarse CAP mixtures both elicit metabolic insulin resistance (IR) in addition to elevating diastolic BP and impairing vascular endothelial function (VEF) *(as shown with fine CAP).***

- *Specific Aim 1.0: To demonstrate that coarse CAP mixtures elevate diastolic BP during particle inhalation and impair VEF 20 hours post-exposures.*

- *Specific Aim 1.1: To demonstrate that coarse CAP exposures also elicit metabolic IR 20-hours later (frequently sampled intravenous glucose tolerance test)*

- *Specific Aim 1.2: To evaluate if other biologically-linked adverse cardio-metabolic changes are also elicited:*

  - *HDL dysfunction*
  - *↑ Pro-inflammatory monocyte sub-sets*
  - *↓ Endothelial progenitor cell levels/function*
  - *↓ Adipocytokines (adiponectin levels)*
  - *Δ HRV/autonomic balance*

# Human Study #1 (Coarse CAP)

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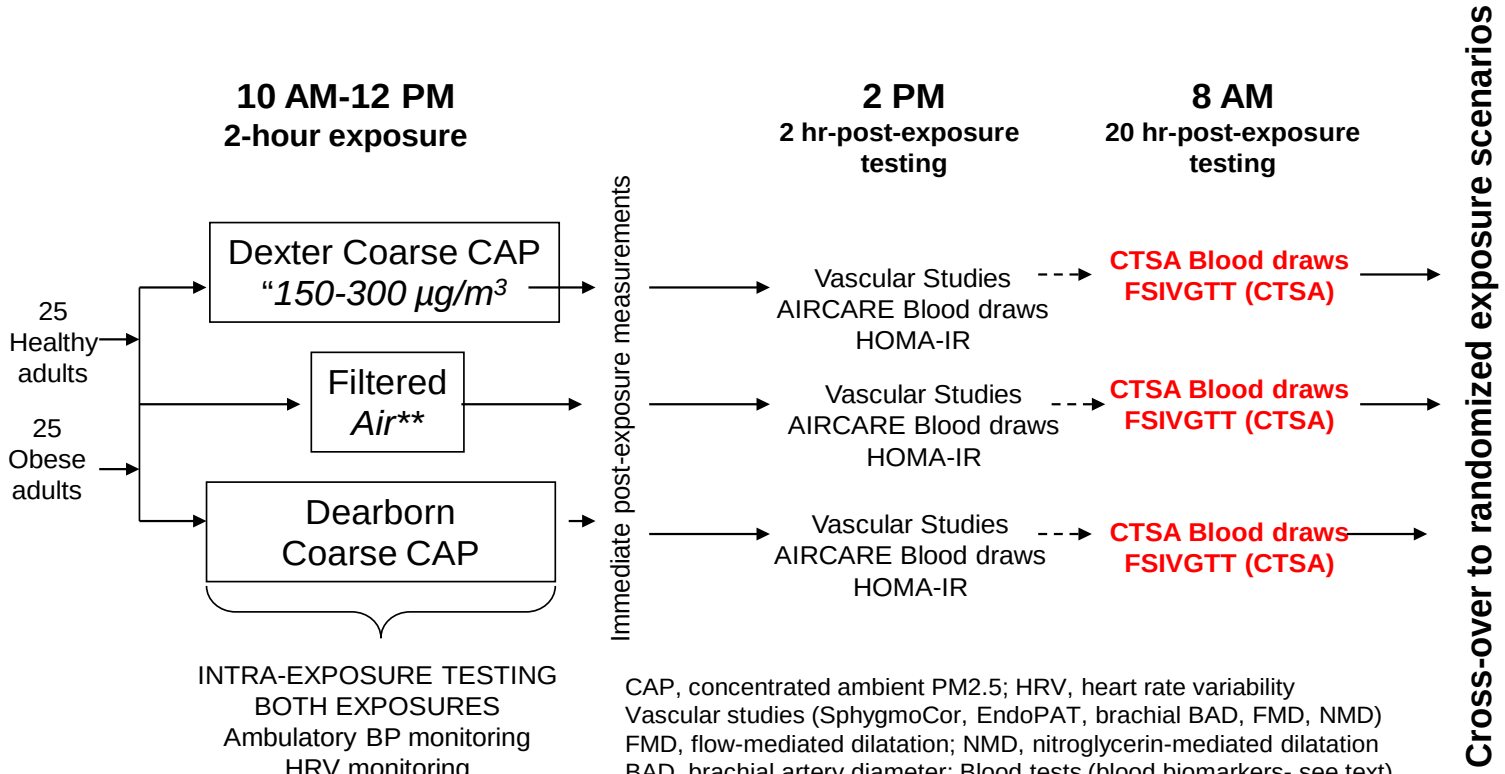
## HYPOTHESIS 2:

**Obese individuals are more susceptible than lean adults to the adverse CMS responses induced by both coarse CAP mixtures.**

*Specific Aim 2.0: To demonstrate that exposures to similar concentrations of coarse CAP induce greater adverse cardio-metabolic responses in subjects with a body mass index (BMI) > 30 kg/m$^2$ than those with a BMI < 27 kg/m$^2$.*

*Specific Aim 2.1: To evaluate if BMI (and/or pre-exiting CMS abnormalities) are linearly associated with the extent of adverse CAP-induced CMS changes*

# Human Study #1
# STUDY DESIGN




CAP, concentrated ambient PM2.5; HRV, heart rate variability
Vascular studies (SphygmoCor, EndoPAT, brachial BAD, FMD, NMD)
FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation
BAD, brachial artery diameter; Blood tests (blood biomarkers- see text)
HOMA-IR, homeostasis model assessment of insulin resistance
FSIVGTT, frequently sampled intravenous glucose tolerance test

**FA will be done only once per subject. This will be done in all patients in Dexter. If subjects do not follow-up and get a 3rd Dearborn exposure in year 2, they will then receive 2 exposures (FA and coarse CAP) in Dearborn. If they got a FA in Dexter and are participating in Dearborn in year 2, they will get only 1 coarse exposure and they will not get a second FA exposure

Bold and red endpoints at 20 hour post are performed in the CTSA

# Human Study #2 (Fine CAP)

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## HYPOTHESIS 3:

## Urban Fine CAP exposures also elicit metabolic insulin resistance.

*Specific Aim 3.1: To demonstrate that fine CAP exposures also elicit metabolic IR 20-hours later as determined (frequently sampled intravenous glucose tolerance test)*

*Specific Aim 3.2: To evaluate if other biologically-linked adverse cardio-metabolic changes are also elicited:*

- *HDL dysfunction*
- *↓ Adipocytokines (adiponectin levels)*
- *↑ Pro-inflammatory monocyte sub-sets*
- *Δ HRV/autonomic balance*
- *↓ Endothelial progenitor cell levels/function*

# Human Study #2 (Fine CAP)

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## HYPOTHESIS 4:

**ANS imbalance triggers the acute elevation in diastolic BP, while pro-inflammatory mediators elicit the slower impairment in VEF by fine CAP.**

*Specific Aim 4.0: To demonstrate that sympathetic nervous system (**SNS**) blockade (α+β adrenergic antagonism) obviates fine CAP-induced elevations in diastolic BP/ vasoconstriction that occurs during (BP) and immediately after (BAD).*

*Specific Aim 4.1: To evaluate the associations between CAP-induced changes in VEF with alterations in pro-inflammatory mediators known to affect VEF: (a) adipocytokines,(b) endothelial progenitor cell (**EPC**) function, (c) dysfunctional high density lipoprotein (**HDL**)*

*Specific Aim 4.2: To evaluate the associations between CAP-induced metabolic IR with changes in adipocytokines known to affect insulin sensitivity.*

# Human Study #2 (Fine CAP)

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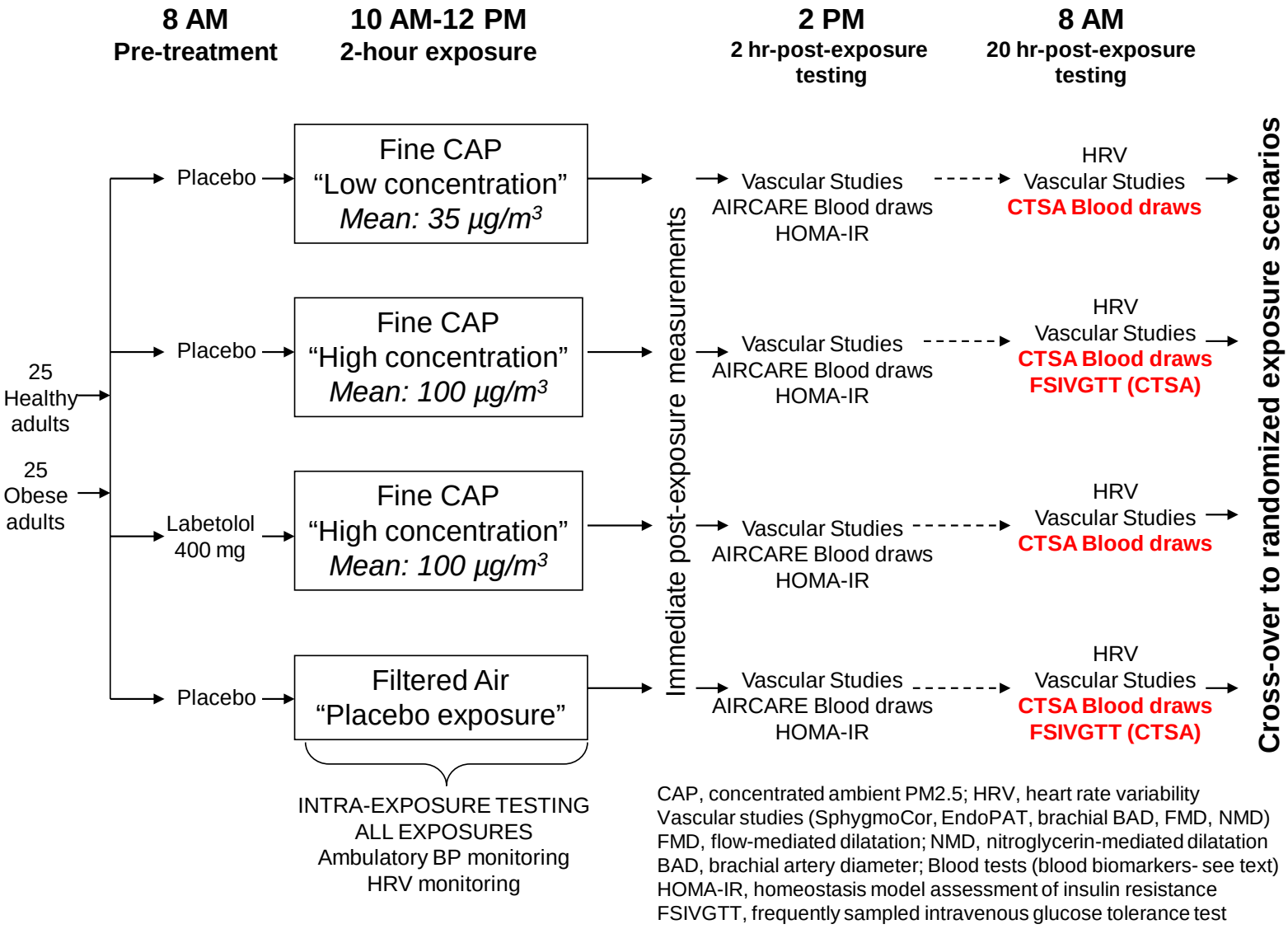
**HYPOTHESIS 5**

**The CMS changes induced by fine CAP occur in a concentration-response manner and extend to $PM_{2.5}$ levels < 35-100 $\mu g/m^3$.**

*Specific Aim 4.0: To demonstrate that higher levels of exposure to fine CAP (~100 $\mu g/m^3$) elicit greater adverse CMS changes than lower concentrations (~35 $\mu g/m^3$), while both CAP exposures trigger adverse responses compared to filtered air.*

*Specific Aim 4.1: To evaluate the nature of the concentration-response relationship between CMS responses and fine CAP exposure levels ranging from below 35 to above 100 $\mu g/m^3$ and to investigate if a threshold concentration exists (lower doses not eliciting adverse responses).*

# Human Study #2
# STUDY DESIGN




CAP, concentrated ambient PM2.5; HRV, heart rate variability
Vascular studies (SphygmoCor, EndoPAT, brachial BAD, FMD, NMD)
FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation
BAD, brachial artery diameter; Blood tests (blood biomarkers- see text)
HOMA-IR, homeostasis model assessment of insulin resistance
FSIVGTT, frequently sampled intravenous glucose tolerance test

Bold and red endpoints at 20 hour post are performed in the CTSA after vascular testing done prior in AIRCARE

# Project 2: Short-term Animal Studies

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## Cardiometabolic, Autonomic, and Airway Toxicity of Acute Exposures to $PM_{2.5}$ from Multipollutant Atmospheres in the Great Lakes Region

Jack Harkema, DVM, PhD, Greg Fink, PhD
and James Wagner, PhD

*Michigan State University*
*East Lansing, MI*

# Project 2: Overall Objective

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To determine the cardiovascular (CV), autonomic nervous system (ANS), and airway toxicity in rodents acutely exposed to concentrated ambient PM (CAP) from distinct multi-pollutant atmospheres commonly found in the Great Lakes Region of the United States

# PROJECT 2: Approach

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- Extends and complements the human studies
- Lean and obese rats with and without diet-induced facets of the cardiometabolic syndrome
- Rats acutely exposed to CAPs (with and without O3) from distinct GL locations dominated by industrial/urban or transported/regional emissions
- Use mobile air research facility for real-time CAP exposures in multipollutant airsheds
- Blood pressure, heart rate, heart rate variability and direct measurements of autonomic nerve activity (continuous radiotelemetry)
- Overlaps and integrates with long-term animal studies in Project 3

# PROJECT 2: Design

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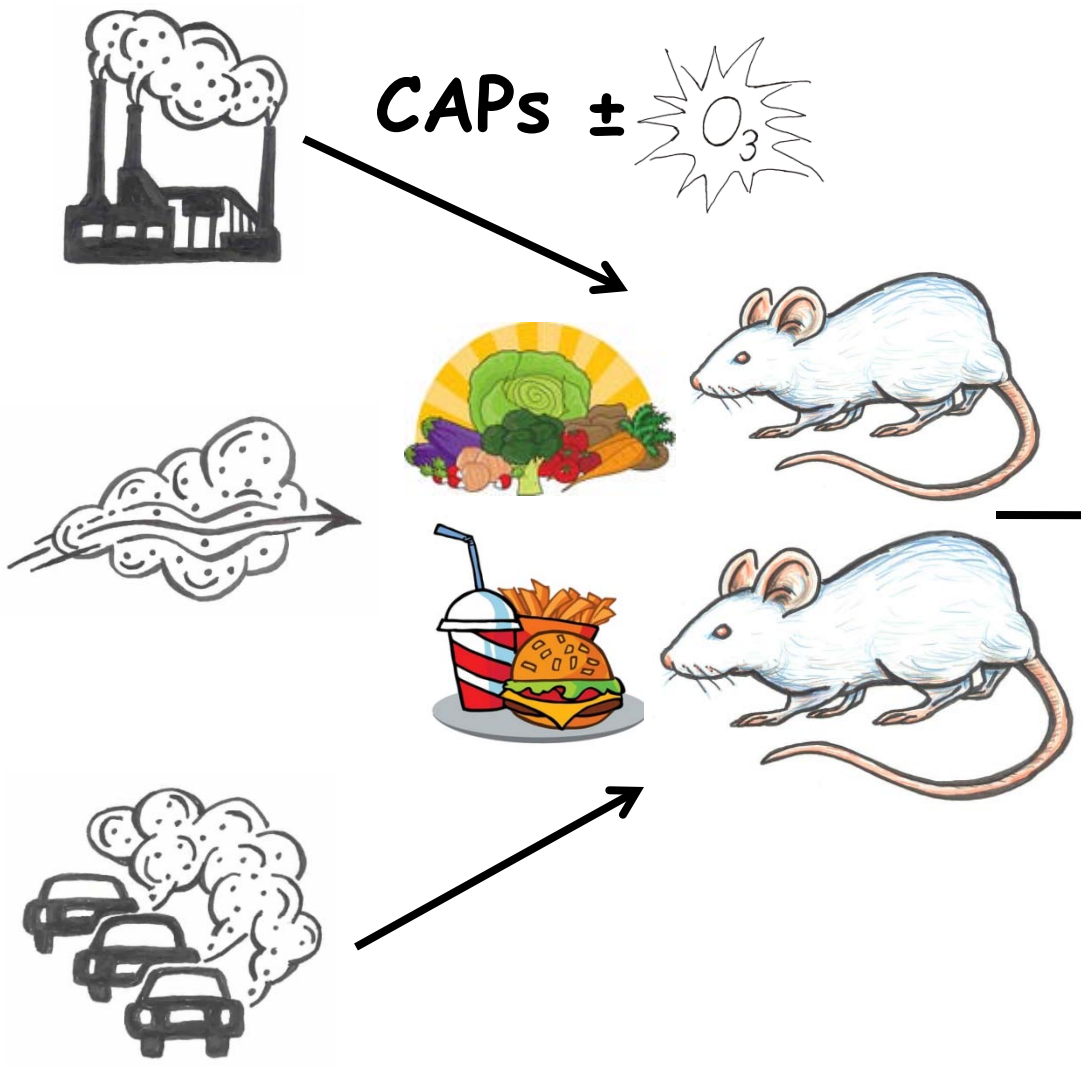


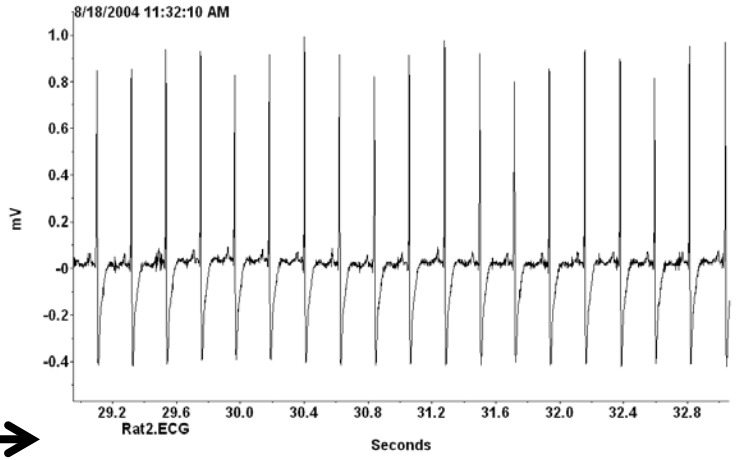


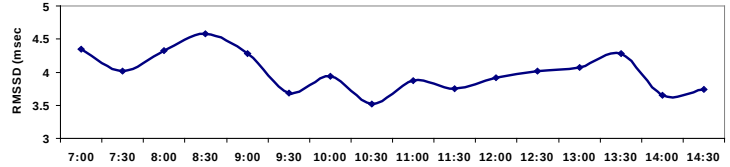


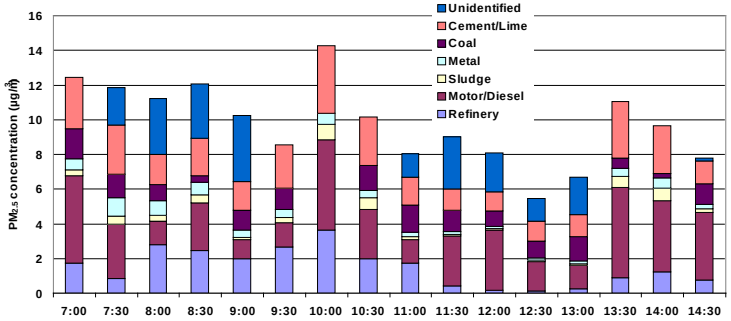

# PROJECT 2: Approach

| Year | Site | Inhalation Chamber Exposure | | | |
|---|---|---|---|---|---|
| | | AIR | **CAP | *O3 | **CAP/*O3 |
| 1 | DBN | 8ND/8HFD | 8ND/8HFD (fine PM) | 8ND/8HFD | 8ND/8HFD |
| 2 | DBN | 8ND/8HFD | 8ND/8HFD (fine PM) | 8ND/8HFD | 8ND/8HFD |
| 3 | DEX | 8ND/8HFD | 8ND/8HFD (fine PM) | 8ND/8HFD | 8ND/8HFD |
| 4 | DEX | 8ND/8HFD | 8ND/8HFD (coarse PM) | 8ND/8HFD | 8ND/8HFD |
| 5 | DEX | 8ND/8HFD | 8ND/8HFD (coarse PM) | 8ND/8HFD | 8ND/8HFD |

**CAP, fine (PM2.5) or coarse (PM2.5-10); *O3, 0.5 or 0.25 ppm; DEX, Dexter, MI; DBN, Dearborn; ND, Rats on normal diet; HFD, Rats on high-fructose diet (insulin resistant animals).

# PROJECT 2: Approach

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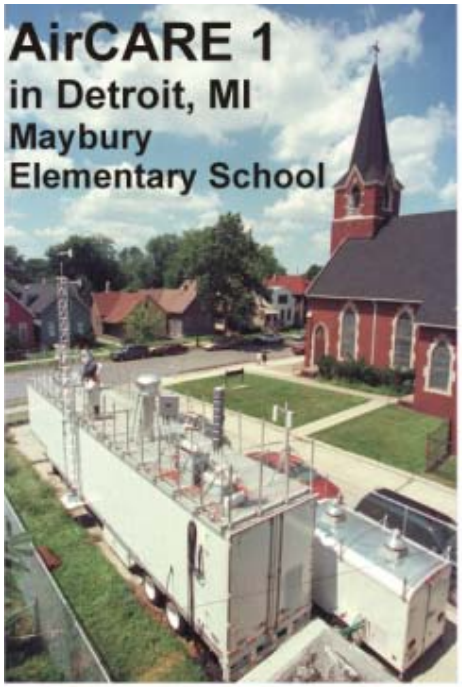



# PROJECT 2: Approach

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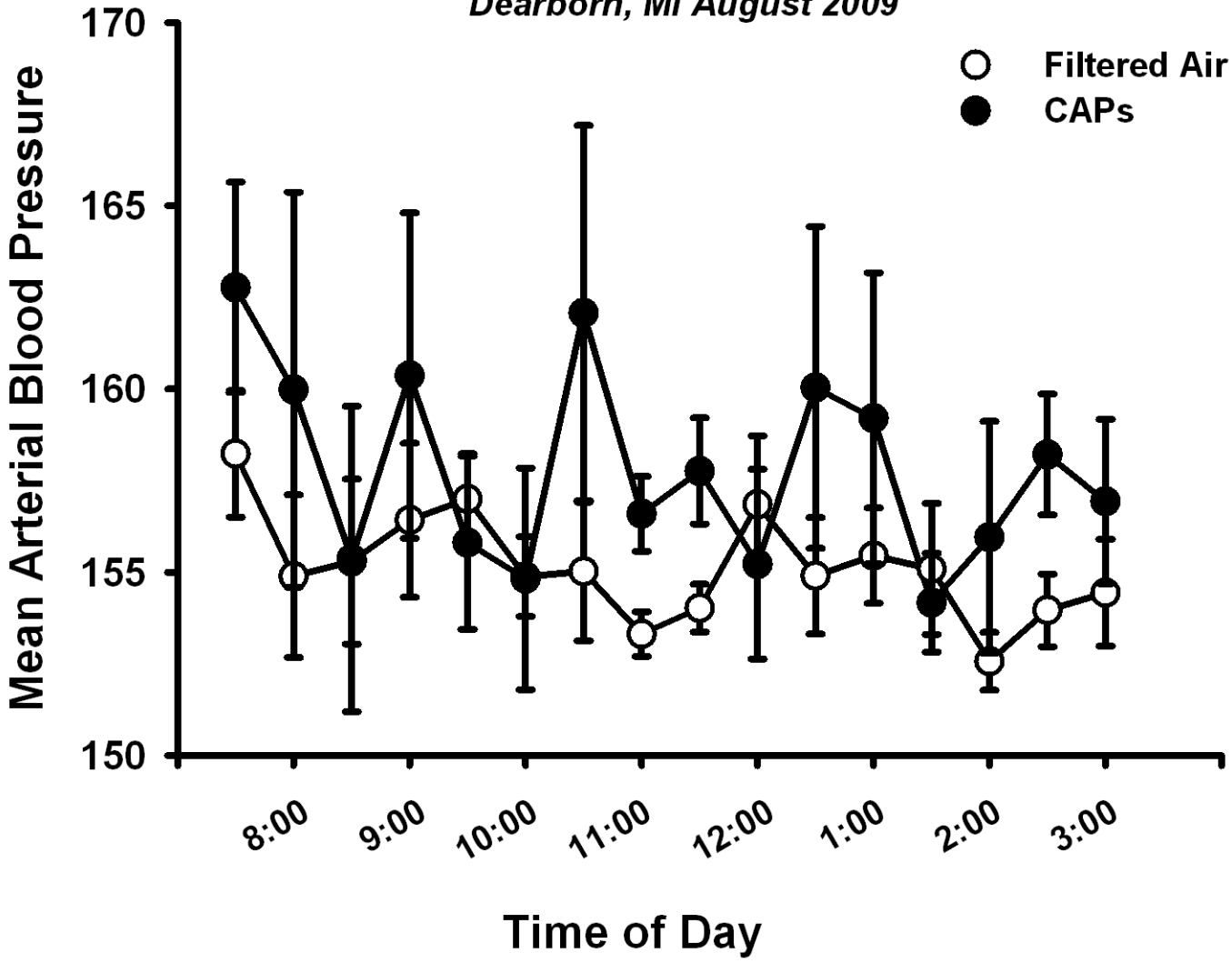
*Fig. 3* Effect of CAPs Inhalation on Blood Pressure in Spontaneously Hypertensive Rats

*Dearborn, MI August 2009*



# Exposure Characterization Core

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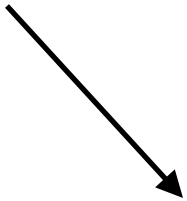
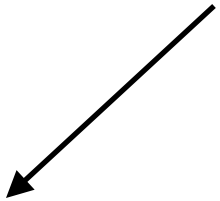
Tim Dvonch, Jerry Keeler, Masako Morishita

Characterize the chemical components of air pollution exposures

Identify emission sources contributing to air pollution exposures





Assess impacts of air pollution components and emission sources on cardiometabolic responses observed for each of Projects 1-3

# Exposure Characterization Core

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## *Chemical Characterization:*

- PM gravimetric mass by TEOM and teflon filters.
- Particle number: APS and SMPS.
- Inductively coupled plasma-mass spectrometry (ICP-MS): trace elements (e.g., Fe, Ni, Zn, Cu)
- Ion chromatography: sulfate, nitrate, chloride, potassium, sodium, ammonium.
- Thermal-optical-transmission analysis: total organic and elemental carbon.
- SEAS Sampler (semi-continuous trace elements).

## *Source Apportionment:*

- PM quantified and categorized based on chemical composition.
- HYSPLIT air mass back-trajectories.
- Multivariate receptor modeling methods, Positive Matrix Factorization (PMF).
- Associations between health outcomes and individual pollutants and CAP components as well as their likely emission sources.

Dr. Morishita and SEAS

# Semi-continuous HRV and Sources (30min)

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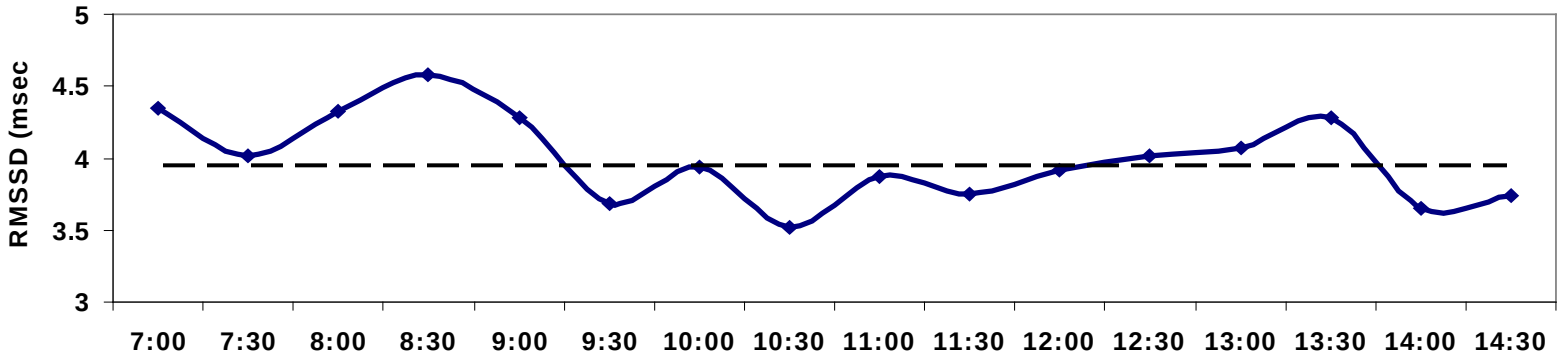


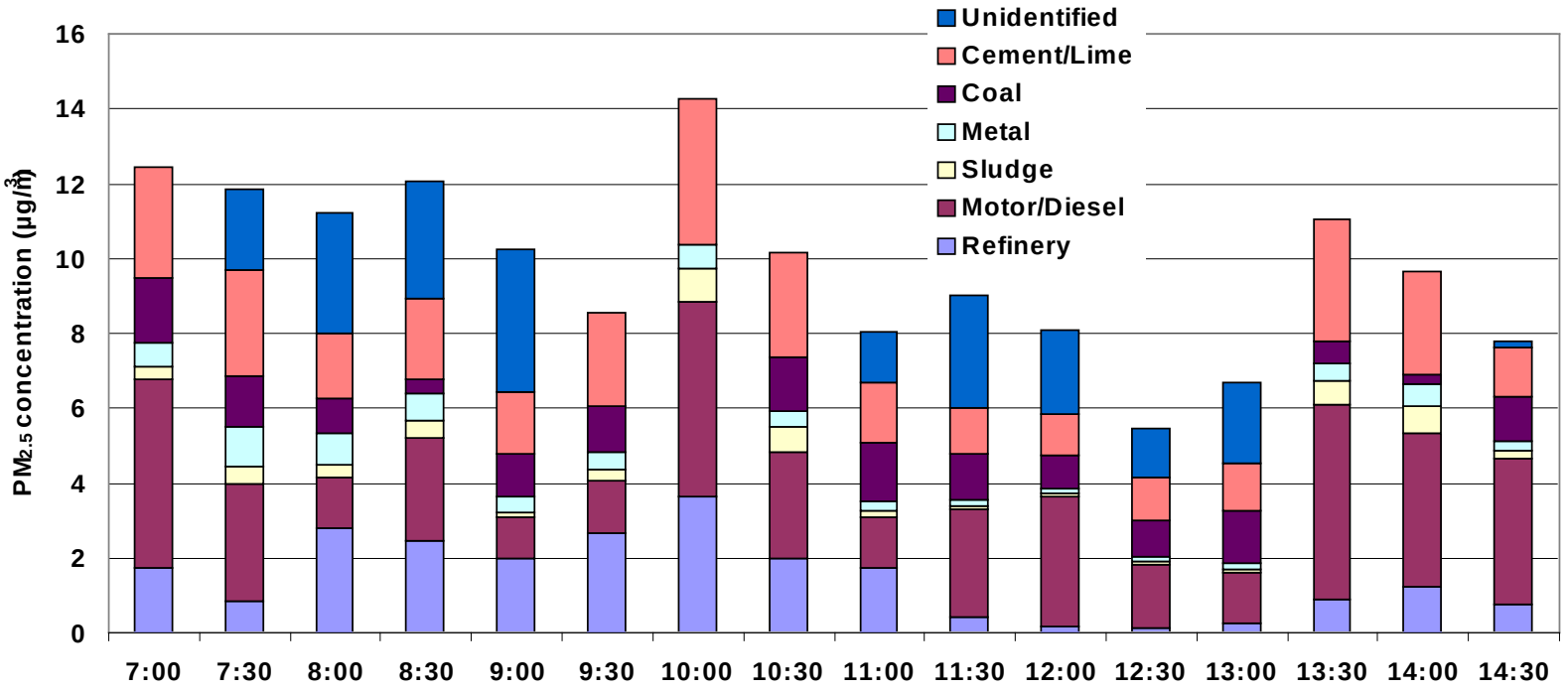

# PROJECT 2: Approach

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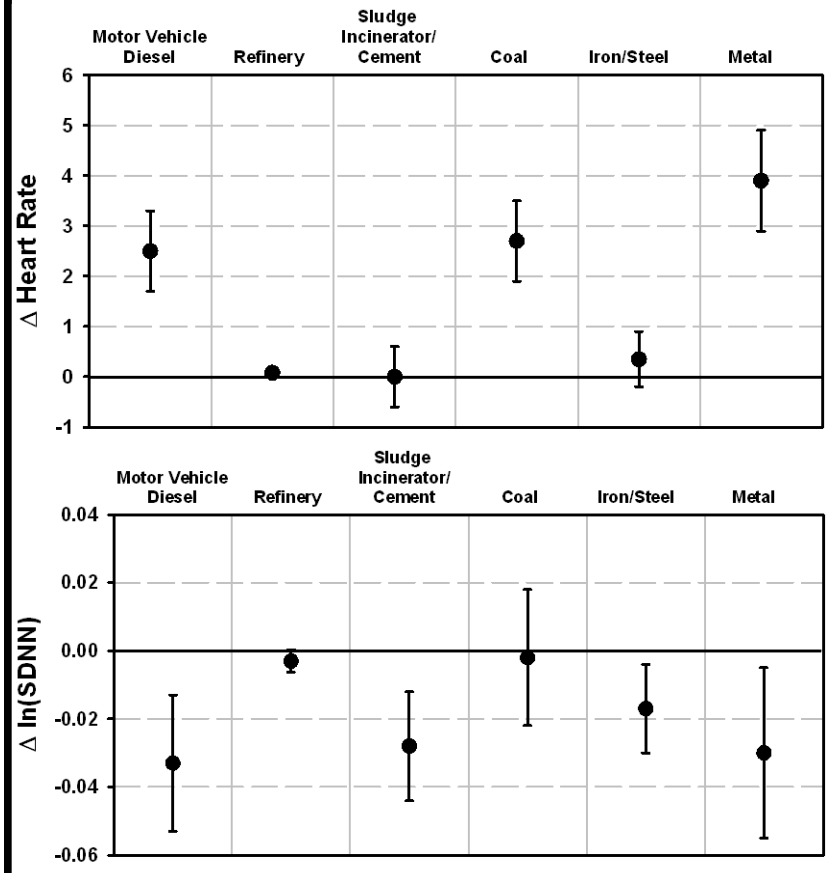
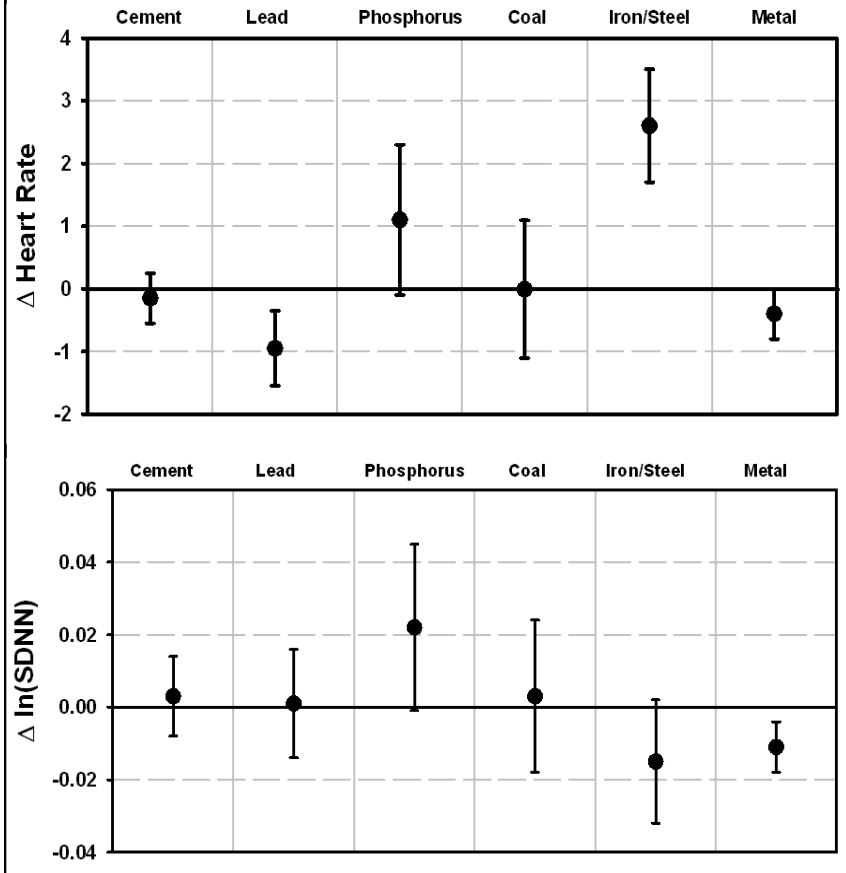
## *Figure 2: PM2.5 Emission Source Factors Associated with Altered Cardiac Function*

**Detroit:** Impact of PM Sources on Alterations in Cardiac Function




**Steubenville:** Impact of Sources on Alterations in Cardiac Function



# PROJECT 2: Expected Results

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- Susceptibility of rats with diet-induced CMS to multipollutant atmospheric exposures

- Concentration/response relationships for PM, $O_3$ and PM/$O_3$

- Atmospheric mixtures of PM, and their constituents, responsible for health effects

- Mechanisms underlying the CV responses

- Novel health effects of PM/$O_3$ coexposures

# Project 3: Long-term Animal Studies

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## Long-term Metabolic Consequences of Exposures to Multipollutant Atmospheres in the Great Lakes Region

Sanjay Rajagopalan, MD and Qinghua Sun MD, PhD
*The Ohio State University*
*Columbus, OH*

# Project 3: Chronic Effects of Multi-pollutant mixtures

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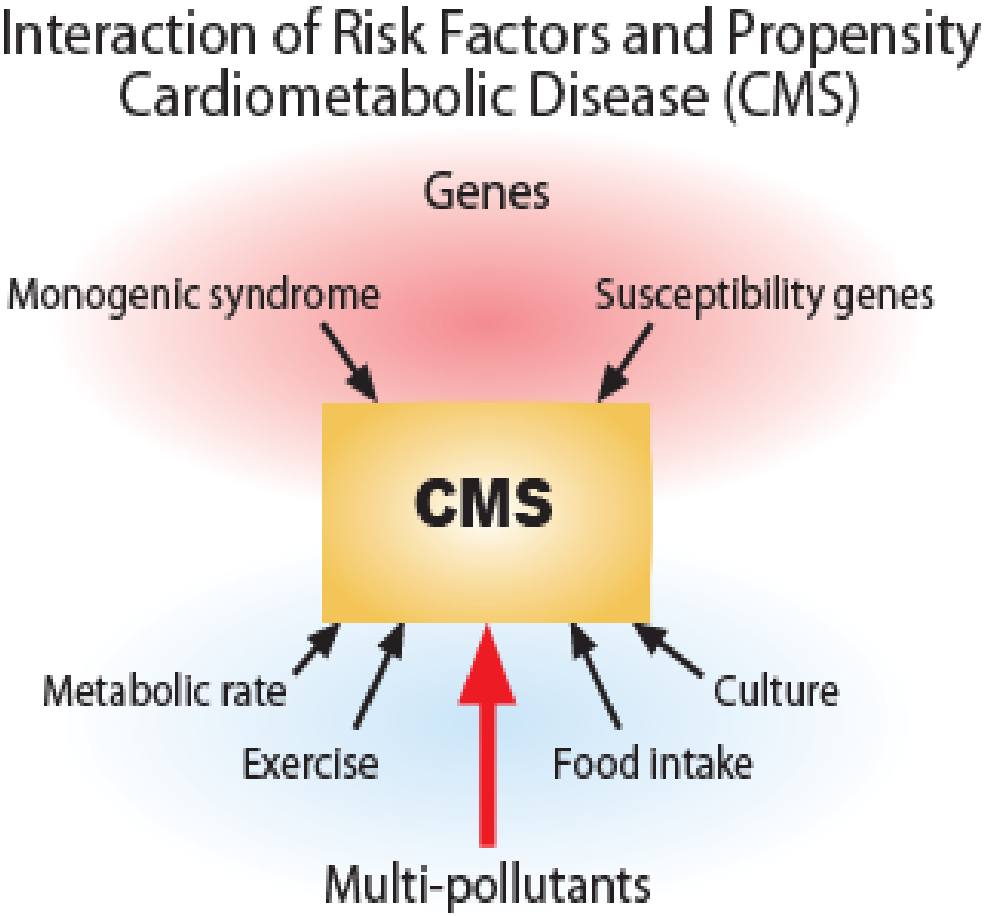
## Overall Hypothesis

**Multipollutant ($PM/O_3$) exposure interacts with diet and genetic factors to promote development of CMS.**



# Project 3 Basis: Chronic $PM_{2.5}$ Exposure (20 wk) Potentiates Inflammation and IR

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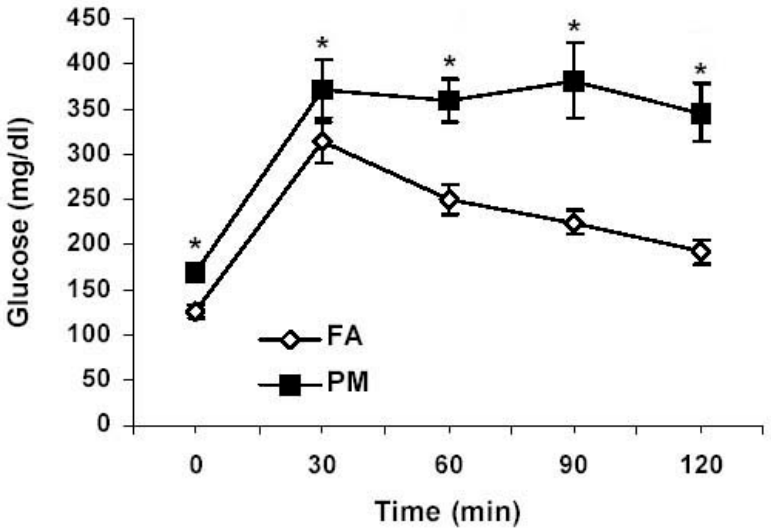
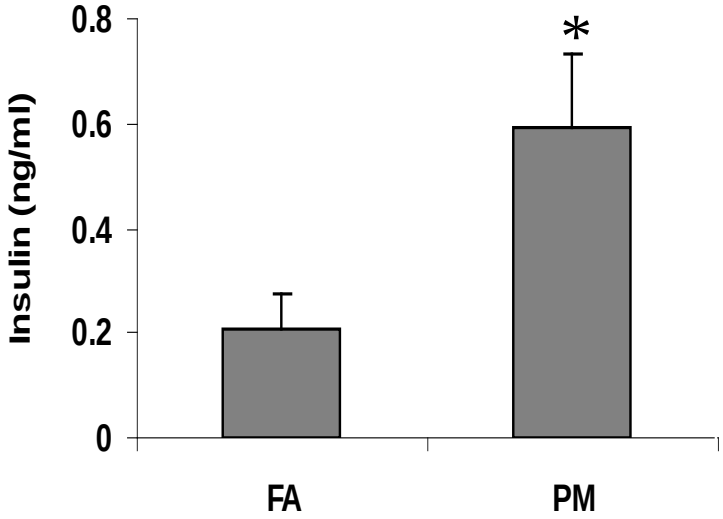
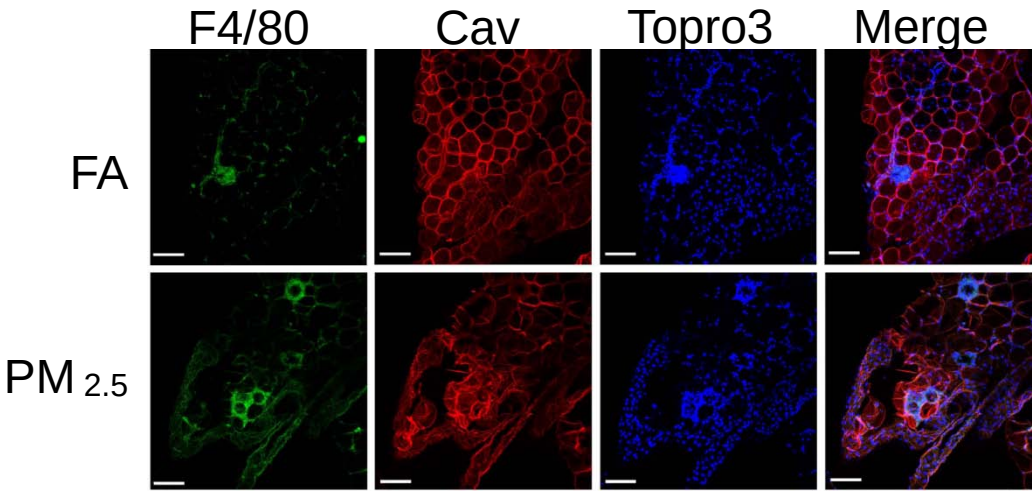
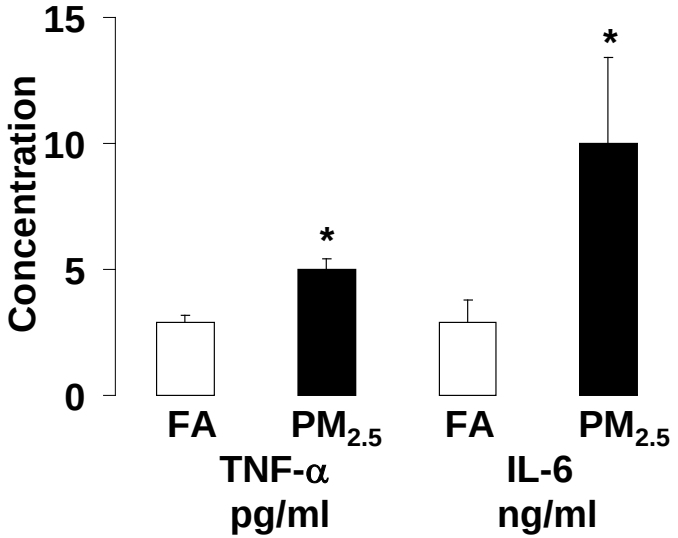


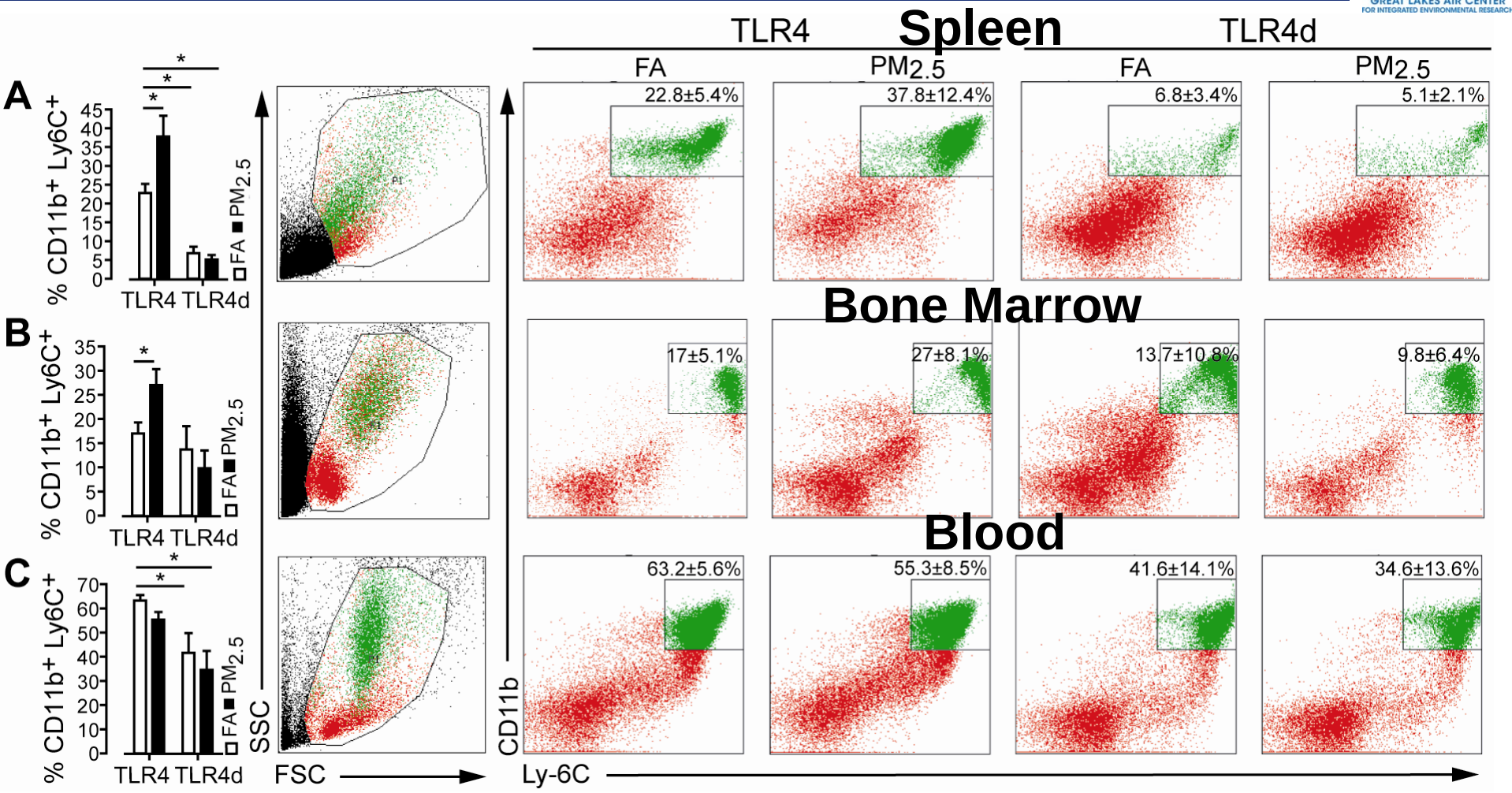




*Sun Q, Yue et al. Circulation 2009; 119(4):538-46.*

# Project 3 Basis: Inflammatory Monocyte Efflux in Response to $PM_{2.5}$




20 week CAPS exposure; Mean concentrations in chamber 85 mcg/m3; Ambient Concentration: 10 mcg/m3; OASIS -1 VACES System in OSU

*Kampfrath et al Circ Res 2011*

# Project 3 Basis: Inflammatory Phospholipids with Chronic PM2.5 Exposure

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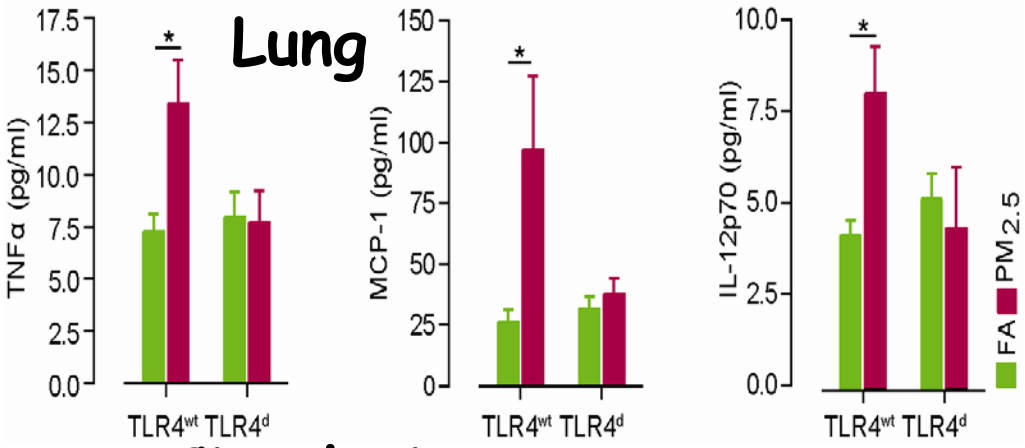
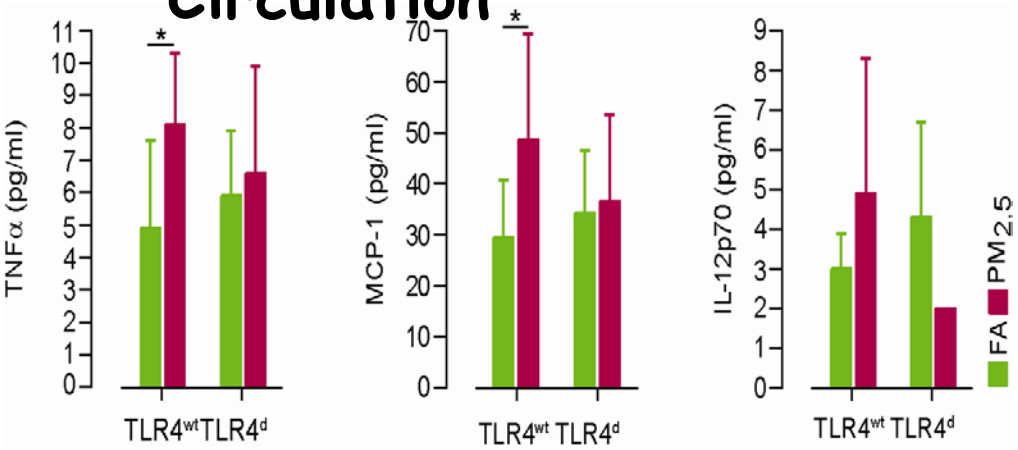
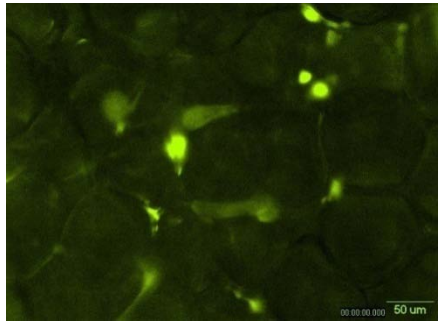
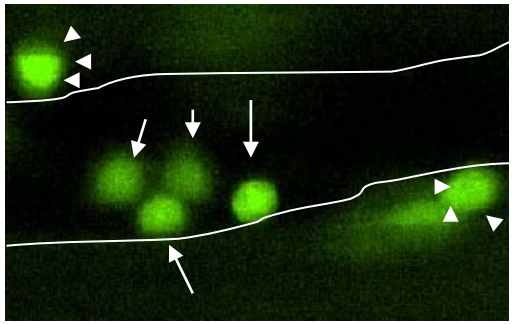
## Lung

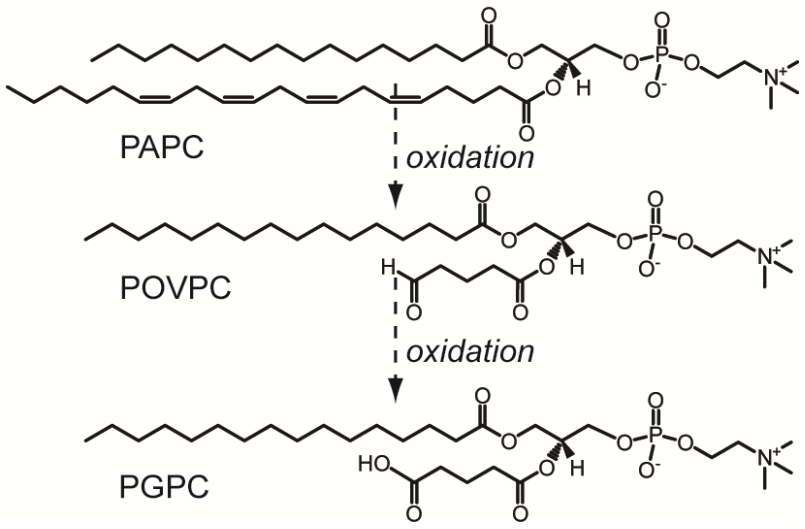


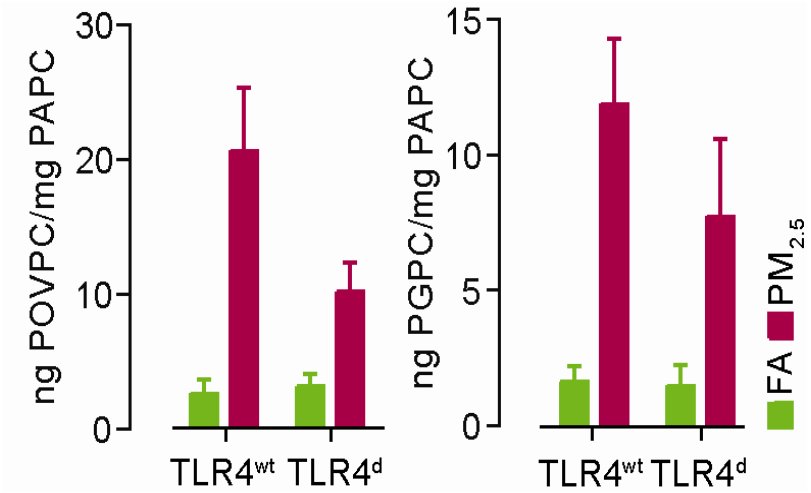

## Circulation






*Kampfrath et al Circ Res March 2011*

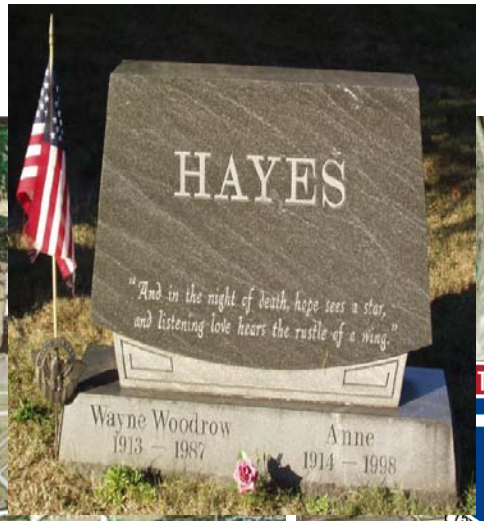
# Project 3: Goals

- Hypothesis 1: Near-roadway CAP exposure promotes the development of obesity and insulin resistance.
- Hypothesis 2: Co-exposure of near-roadway CAP and ozone influences the development of insulin resistance and adipose/vascular inflammation.
- Hypothesis 3: Ozone modulates multi-pollutant exposure induced inflammatory responses

## TIME LINES

| Project Year | Project 3 OSU Exposure Site(Dominant Emissions) |
|---|---|
| Year 1 | Columbus, OH (Regional fine PM2.5 vs. Near Roadway PM2.5) |
| Year 2 | Columbus, OH (Near roadway±O3) |
| Year 3 | Columbus, OH (Near roadway±O3 |
| Year 4 | Columbus, OH (Near roadway± O3) |
| Year 5 | Dearborn, MI (Industrial) AND Columbus OH (Near roadway± O3) |

# OASIS 1






# OASIS 2


# Project 3: Aim 1

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**Hypothesis: Near-roadway CAP exposure promotes development of obesity and insulin resistance.**

**Design: C57Bl/6 model fed normal chow or high-fat chow starting at 6 weeks and exposed to FA/CAP for 12 or 18 weeks. KKAy mice exposed to CAP over 8-10 weeks.**

- A. To assess effects of multi-pollutant CAP (near-roadway vs. regional) on glucose/insulin homeostasis, inflammation and insulin signaling pathways.
- B. To identify differential induction of inflammatory/chemokine mediators. Systematic analysis of oxidized phospholipids and chemokine mediators in BAL/plasma/lung from Aim 1A.
- C. To investigate temporal response of multipollutant CAP and CM effects. By performing experiments on the most potent multipollutant CAP in Aim 1A in a model of genetic T2DM (KKAy).

# Project 3: Aim 2

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**Hypothesis:** Co-exposure of near-roadway CAP and ozone influences temporal development of IR and inflammation.

**Design:** Genetic KKAy model exposed to CAP, FA or CAP+$O_3$ for 8-9 weeks beginning at 3-4 weeks.

- A. To assess interactive effect of $O_3$ + near-roadway CAP on temporal development of IR. IPGTT/ITT weekly while other measures at week 12.
- B. To assess the interactive effect of ozone with near-roadway CAPs on inflammatory/cellular mediators in the lung/systemic.
- C. To assess the effects in potentiating inflammatory monocyte activation. Monocyte sub-fractions ($Ly6C^+$) in lung and systemic circulation will be isolated and assessed for various end-points.

# Project 3: Aim 3

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**Hypothesis:** Ozone modulates multi-pollutant exposure induced inflammatory responses

**Design:** C57Bl/6 model fed normal chow starting at 6 weeks and exposed to CAP+O3, CAP or FA for 12-18 weeks

- A. To assess effects of $O_3$ in modulating adaptive and innate immune response in the lung/systemic circulation. Innate and adaptive immune change in lung, mediastinal LNs, spleen and vasculature will be assessed. Appropriate transgenic/KO models will be used based on Aims 1/2.
- B. To compare effects of most potent multipollutant CAP ± $O_3$ in Columbus OH with that of Dearborn, MI. Whole body insulin sensitivity, adipokines, insulin signaling and inflammatory pathways will be evaluated.

# Biostatistics and Data Management Core

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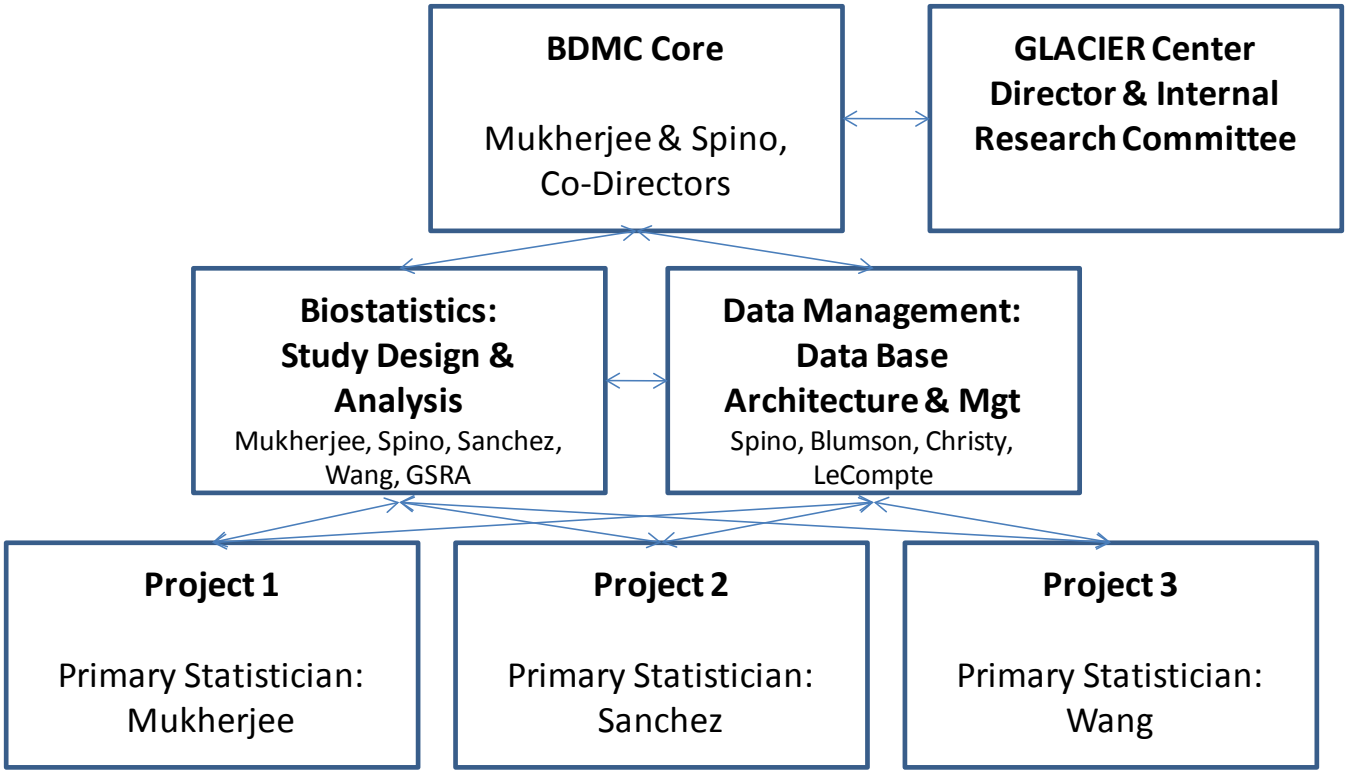
## Biostatistics & Data Management Core Structure



# Biostatistics and Data Management Core

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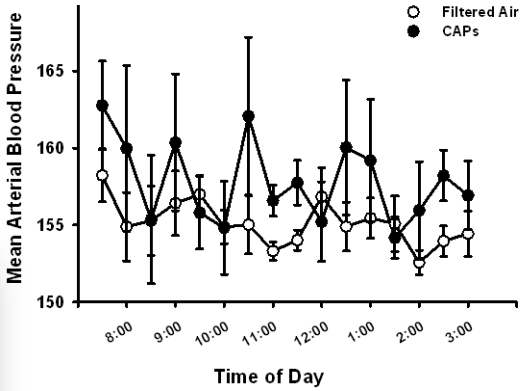
- **Aim 1:** To assist GLACIER investigators with statistical and data aspects of their research by providing expertise in the design, conduct and analysis of studies conducted by the GLACIER.

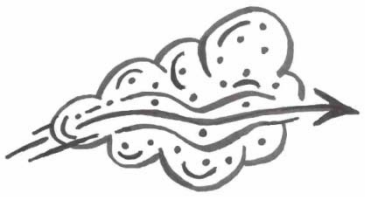
- **Aim 2:** To establish a database for each project conducted by the GLACIER on a secure computerized server. Ensure data harmonization across study sites.

- **Aim 3:** To implement a website to allow data import and export in a secured, controlled environment with a user-friendly interface.

- **Aim 4:** To develop new methodology for modeling complex exposure and outcome data for example: Functional modeling of high density repeated measures outcome, interaction and mixture of pollutant, threshold models, latent variable models.

# Questions?



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