

Allergic and cardiovascular responses to concentrated ambient particle exposure

Michael T. Kleinman

University of California, Irvine

Introduction and Outline

■ Freeway Study

- Hypothesis and Description
- Progress and Results
 - Airway allergies
 - Brain inflammation

■ Cardiovascular Responses in Senescent Rats

- CAPs
- Laboratory-generated Particles

Freeway Study

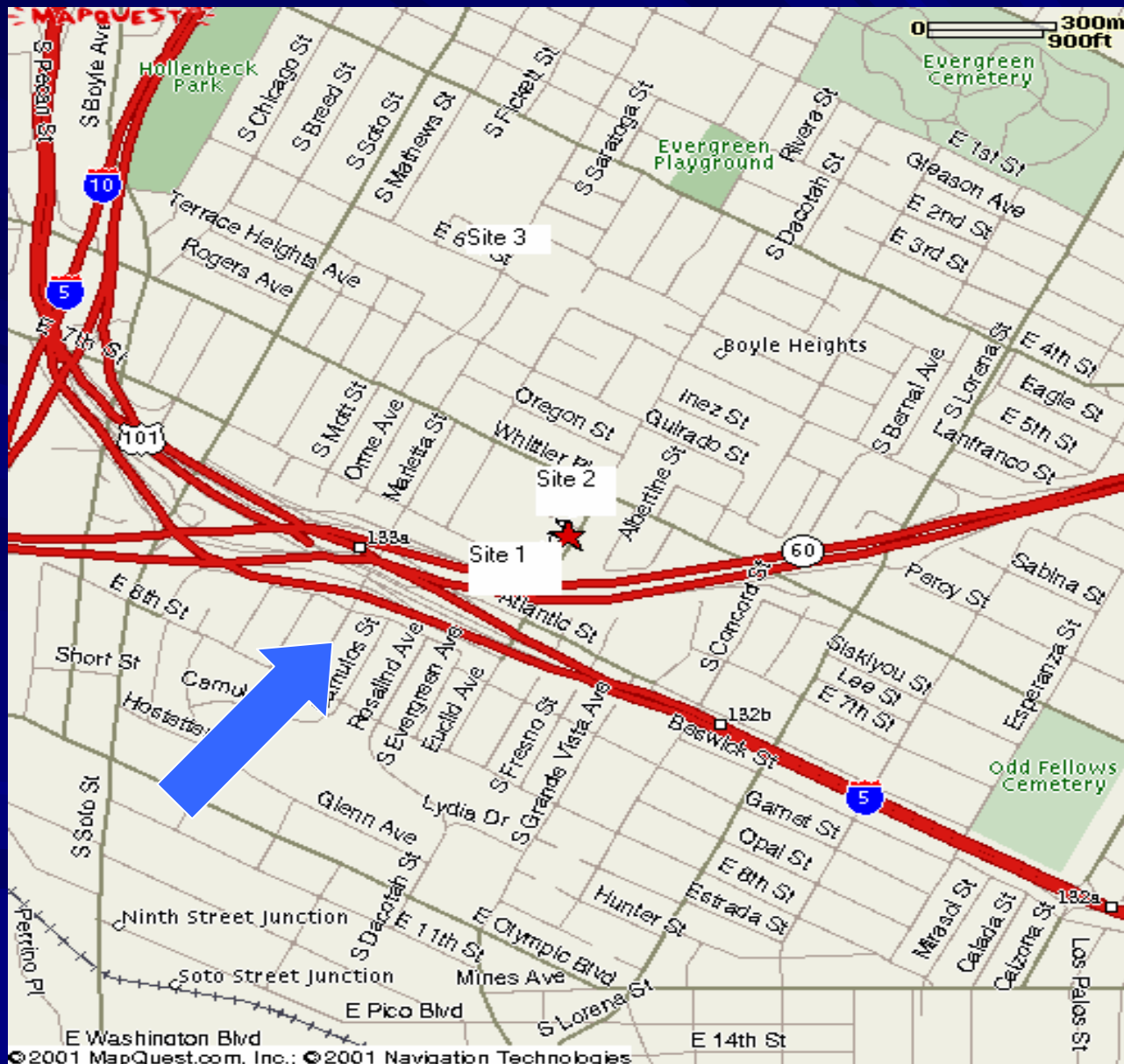
■ Hypotheses

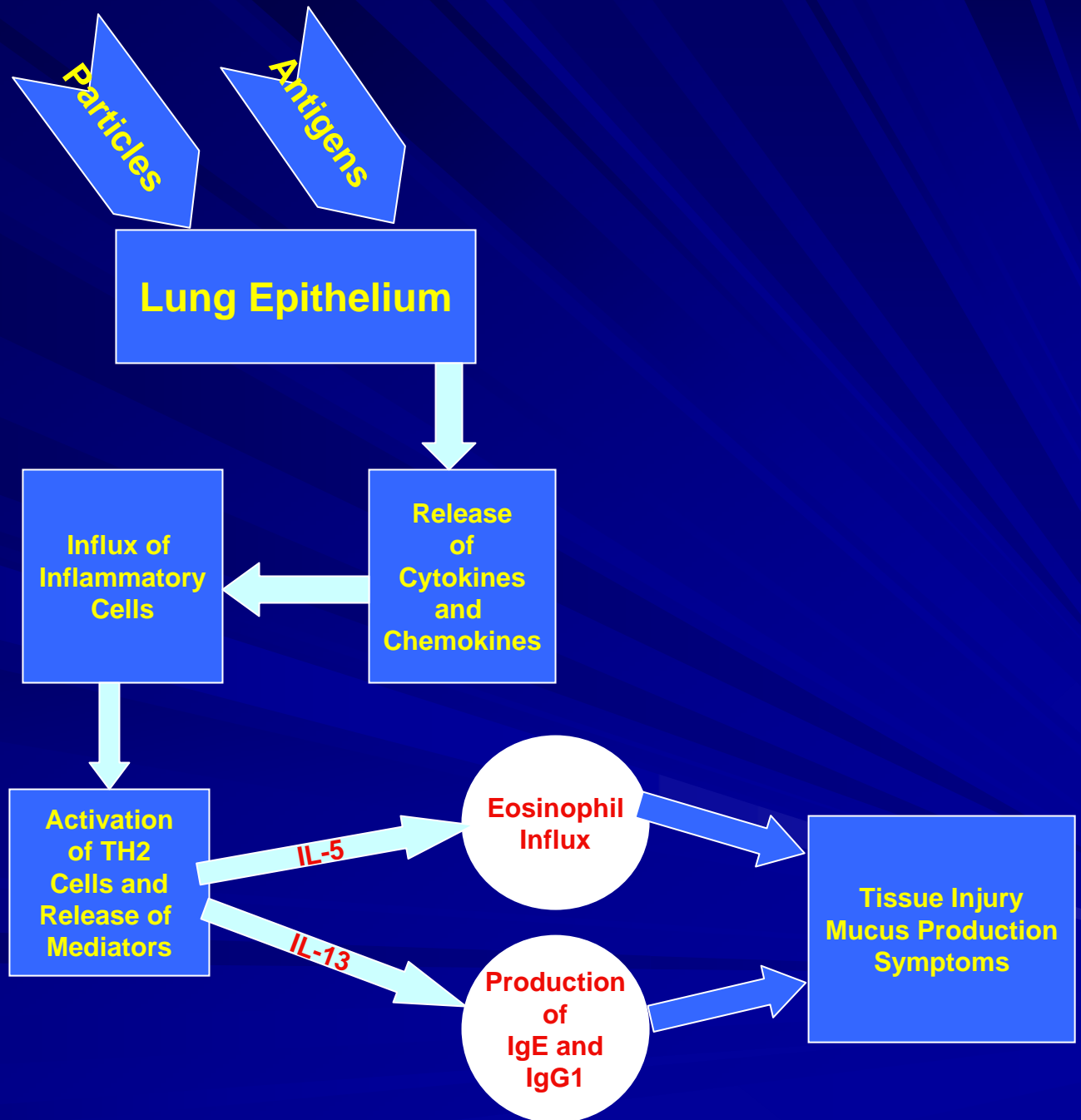
- Mobile emissions will exacerbate airway inflammation and allergic airway disease.
- The magnitude of allergic airway disease responses will be greater at sites with higher concentrations of UF particles.
- Organic and inorganic PM constituents that can generate ROS will be associated with responses.

Airway allergies

- Ovalbumin-sensitized mice are exposed to freeway-derived, concentrated ultrafine (UF) and fine+ultrafine (F+UF) particles at sites that are at progressively increasing distances downwind from a freeway.
- Particle mass concentrations are held constant ($400 \mu\text{g}/\text{m}^3$).
- Control animals are exposed to purified air.

Freeway Study Sites

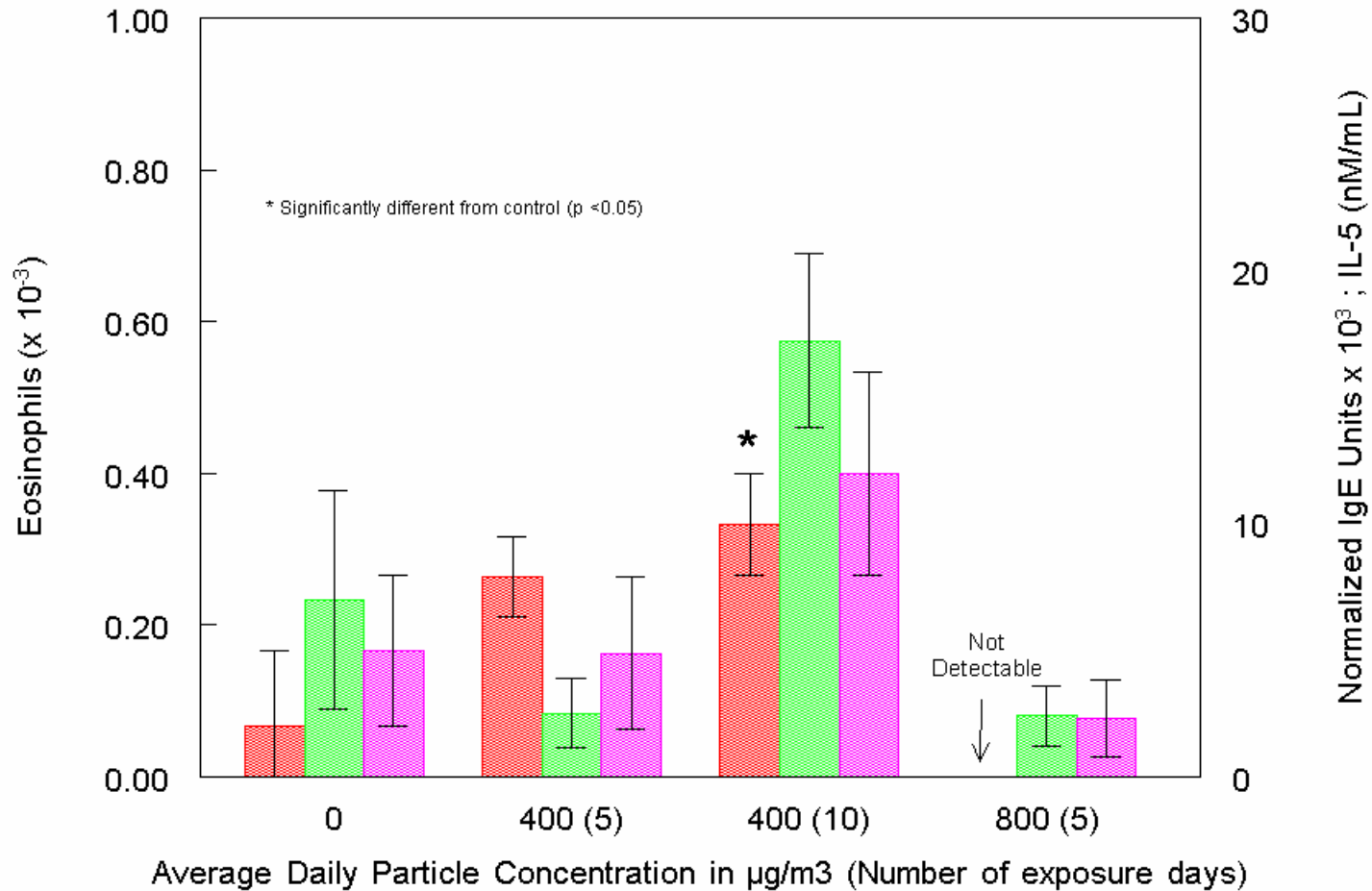




Responses of Mice Exposed ~50 Downwind of Freeway to CAPs and OVA

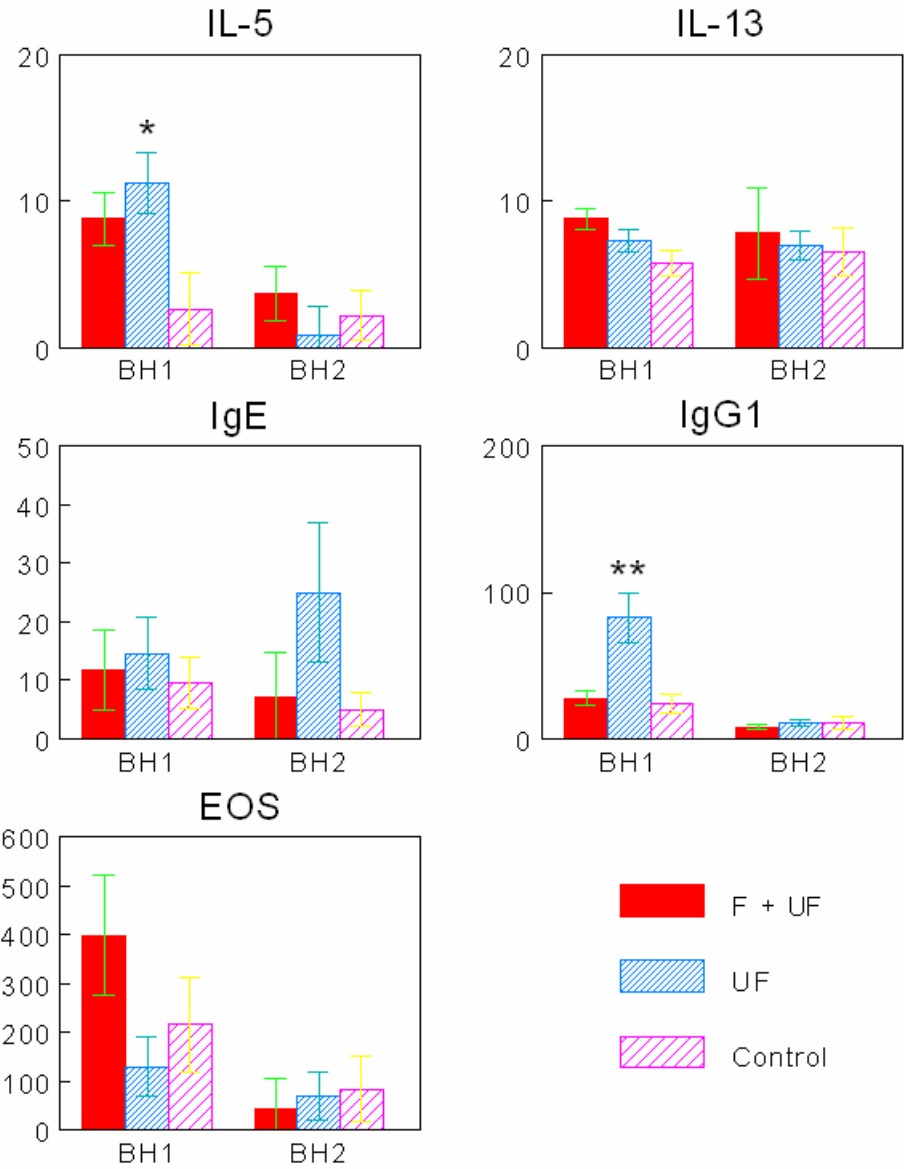
Group Sizes = 9 Bars Represent Mean \pm SE

IL-5 Eosinophils OVA-IgE



- There is an indication that UF particles are more potent than F

- The exposures closest to the roadway produced significant increases in some biomarkers

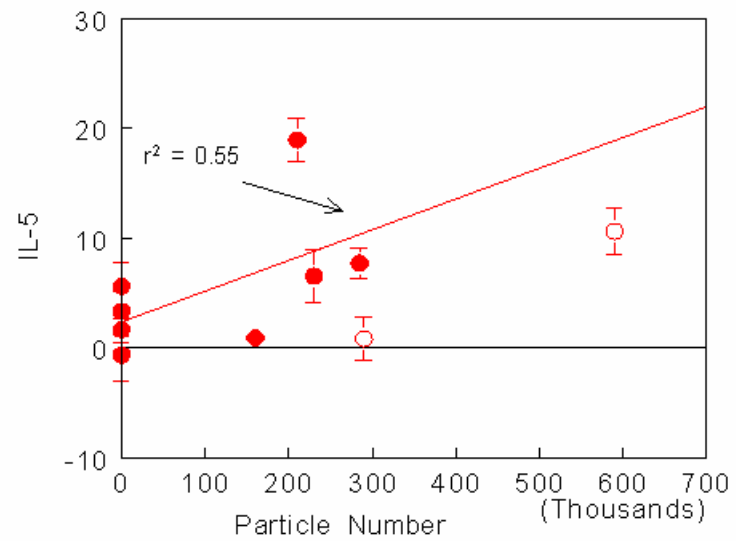


Markers of Airway Allergy in OVA-Sensitized Mice Exposed at 50 and 150 m Downwind of a Freeway

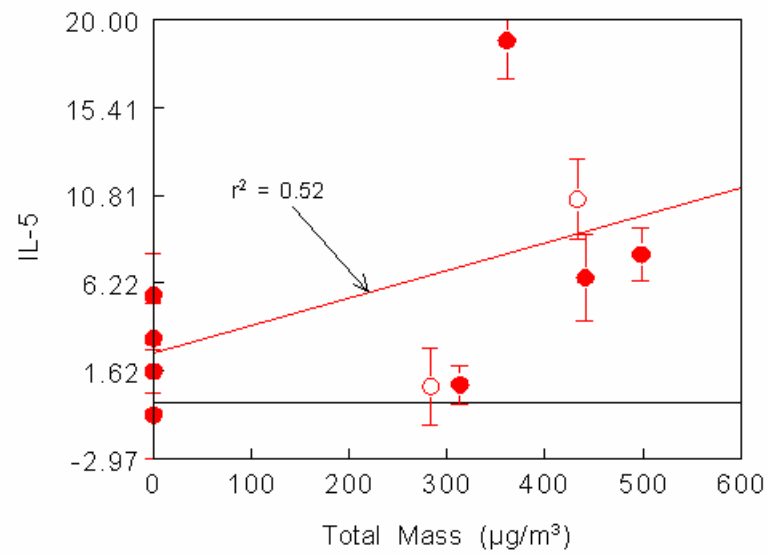
Do the data fit our hypothesis?

- If UF are the key driving force for responses than we should see a stronger relationship between response and particle number than with mass.
- We don't have enough data yet to really test the hypothesis but we can look at two examples to see how things are developing.

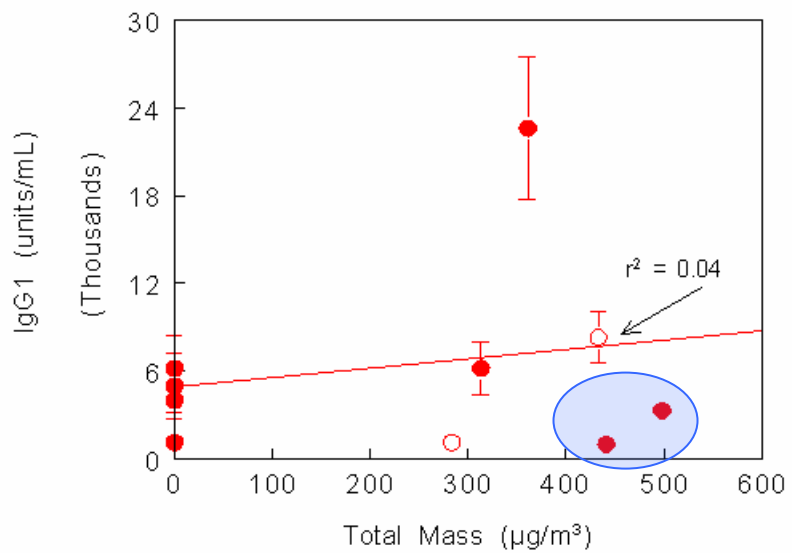
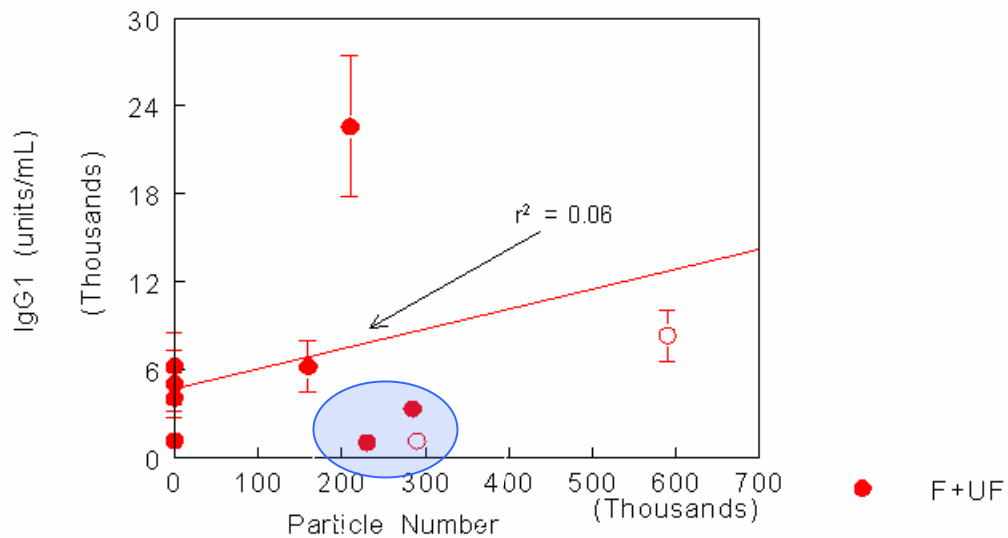
IL-5 vs. Particle Number and Mass



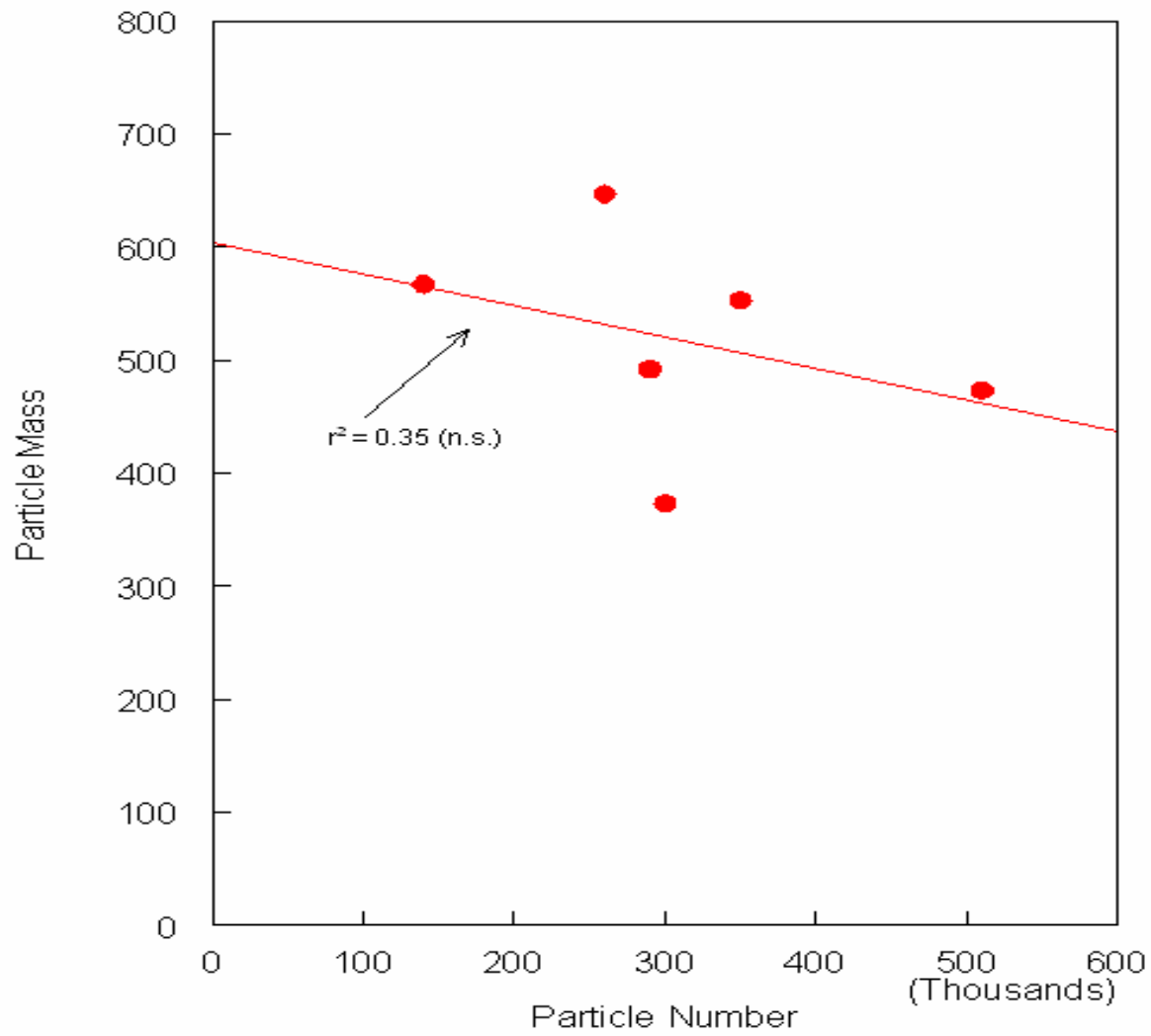
- F+UF
- UF



IgG1 vs. Particle Number and Mass



There is a slight but not significant mass-number relationship



Statistical Analyses

- 2-way ANOVA
 - Site vs. Exposure
- IL-5 Significant increase 50 m CAPs exposed vs. other exposed or controls.
- IgG1 Significant increase 50 m CAPs exposed vs. other exposed or controls.
- EOS Significant increase 50 m CAPs exposed vs. other exposed.

Inflammatory Mediators in the Brain

- There have been speculations that non-familial neurodegenerative diseases are:
 - related to exposures to environmental toxins
 - at least, in part, due to oxidant-related mechanisms
- Dogs exposed to air pollution in Mexico City exhibit lesions in brain tissue.
- Brain tissues from mice exposed at BH2 were analyzed for expression of IL-1, TNF and NFkB.

Data From Brain Tissue Analyses

Brain Inflammation Markers			
Tissue from Mice Exposed at BH2 2002			
	Control	UF	F+UF
TNF α (ng/mL)	2.0 \pm 0.1	2.2 \pm 0.1	2.5 \pm 0.2
IL-1 α (ng/mL)	1.6 \pm 0.2	2.7 \pm 0.3*	2.0 \pm 0.4*
NF κ B (units x 10 ³)	8.5 \pm 4.4	11.0 \pm 1.6**	10.7 \pm 3.0**

Note:

*p < 0.05

**p < 0.01

Cardiopulmonary Responses

- Previous studies had shown that the 'geriatric' rat was sensitive to particle-induced inflammation and hemodynamic effects.
- The geriatric rat is a reasonable model for particle effects in a sensitive human population.

Approach

- Rats aged 24-26 months were exposed to the highest achievable F+UF concentration at the site 50 m downwind of a freeway.
- Exposures were 4 hours per day for 3 consecutive days. There were 8 controls (filtered air) and 8 exposed rats.
- Rats were implanted with blood pressure and EKG transponders.

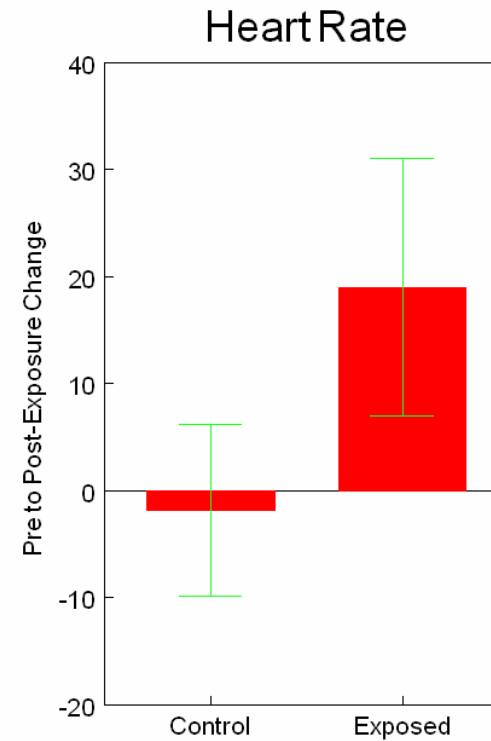
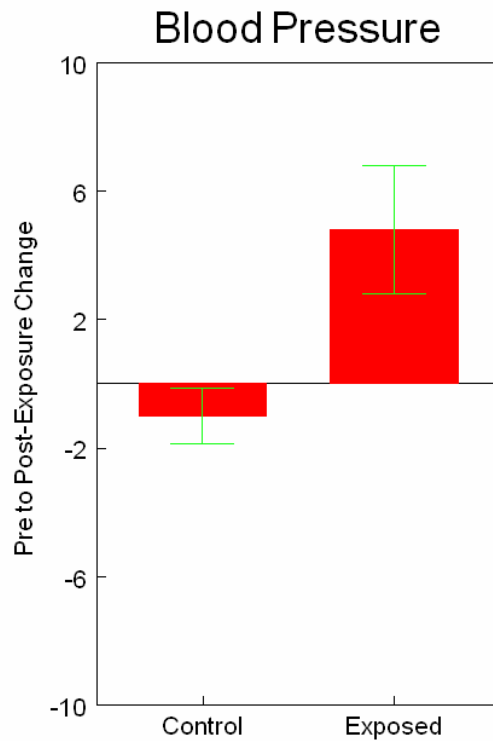
Endpoints

- Animals were killed 24 hours after the last exposure. Lungs were lavaged. BAL was analyzed for cytokines.
- Macrophages were isolated and functional assays were run.
 - Free Radical (superoxide) production
 - Phagocytic activity.

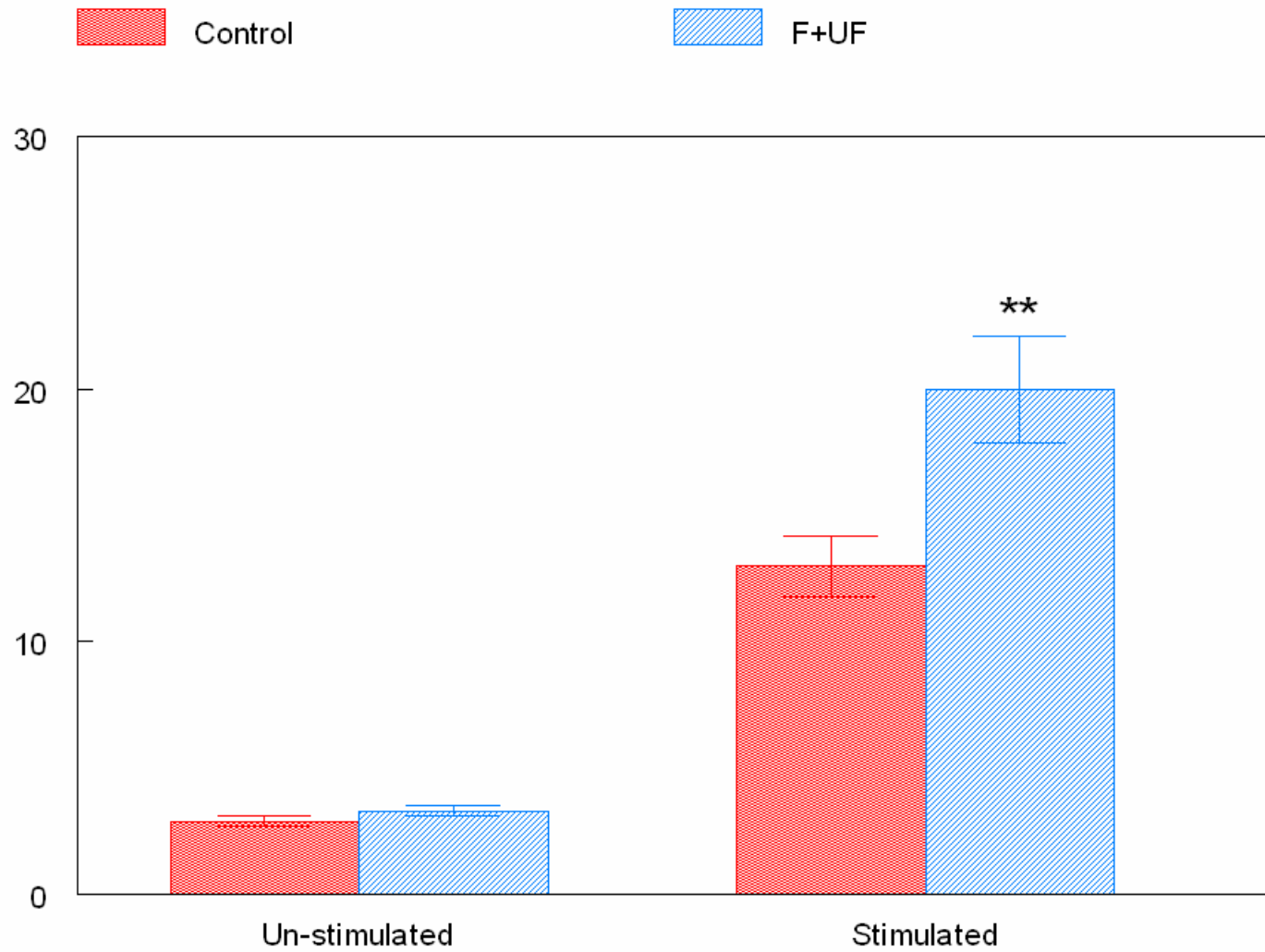
Results

- Exposures were low - $140 \mu\text{g}/\text{m}^3$
- Average heart rate and blood pressure data were measured before and after control and CAPs exposures.
- Cytokines were assayed using Bio-Plex Cytokine Array Processor.
- Free radical production was measured using chemiluminescence.
- ECG data were analyzed

Blood Pressure and Heart Rate Were Increased After CAPs Exposures

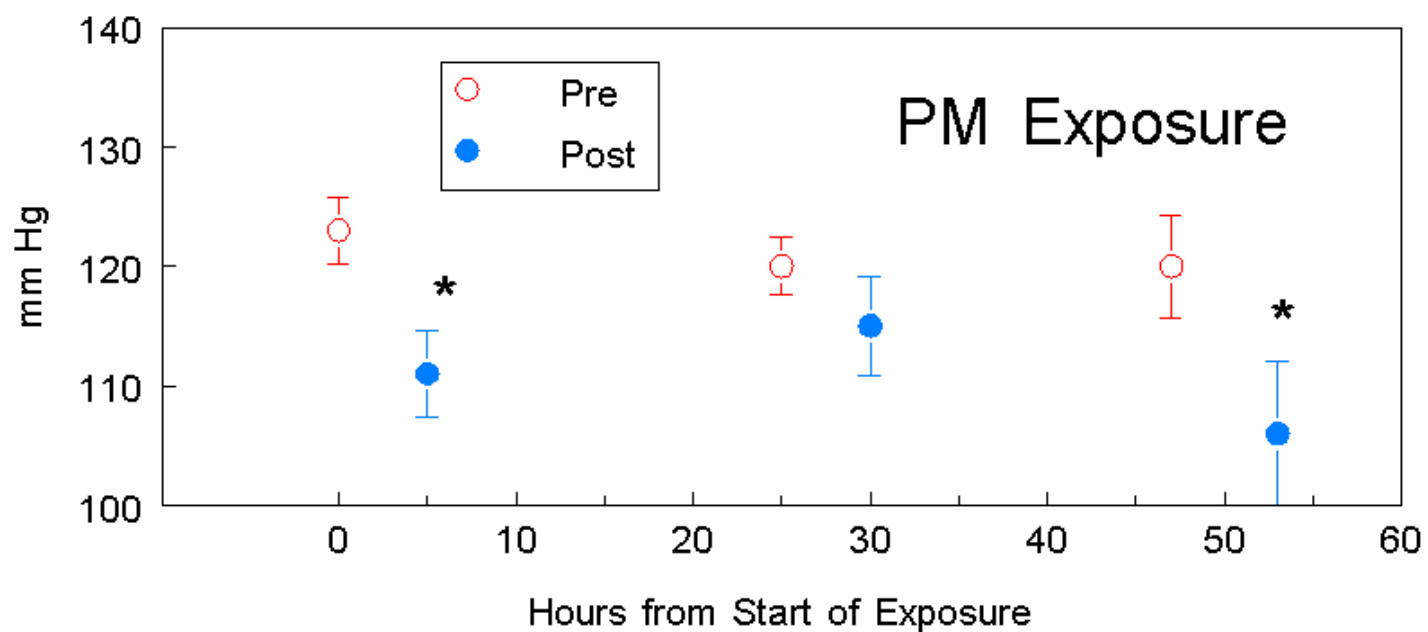
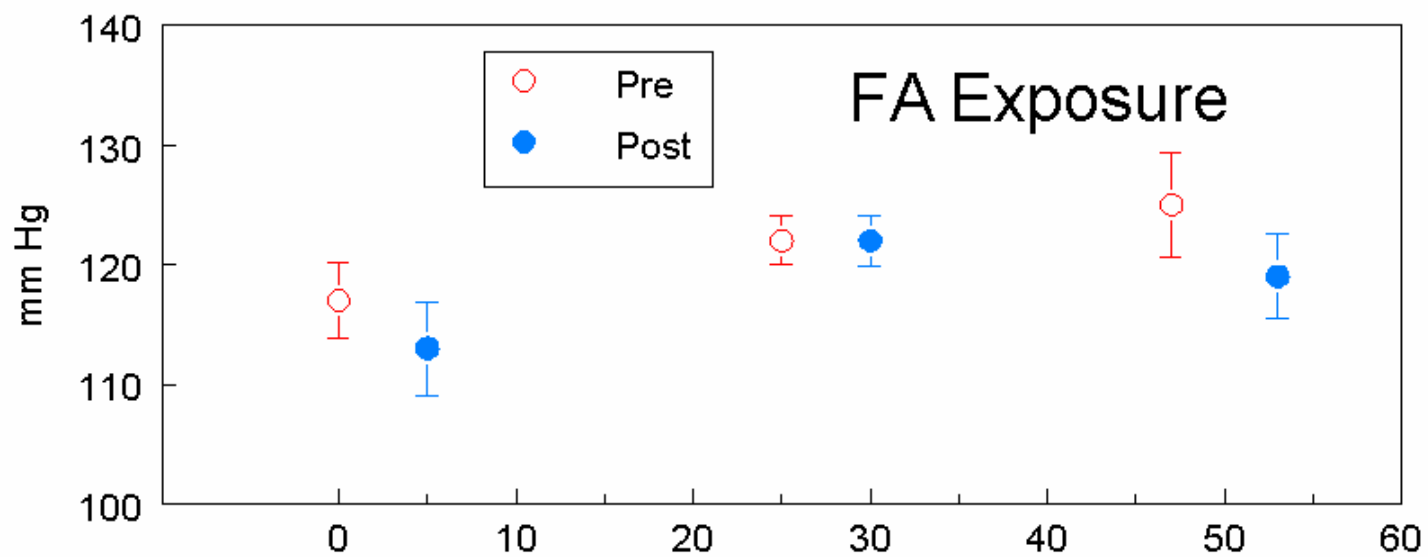


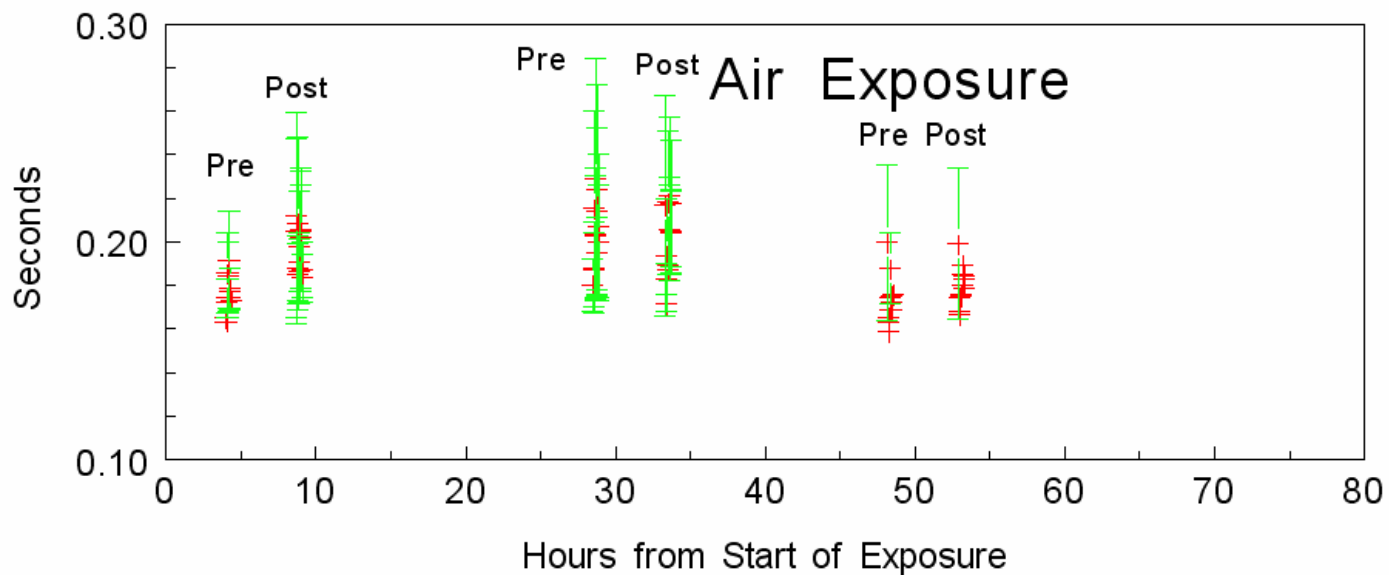
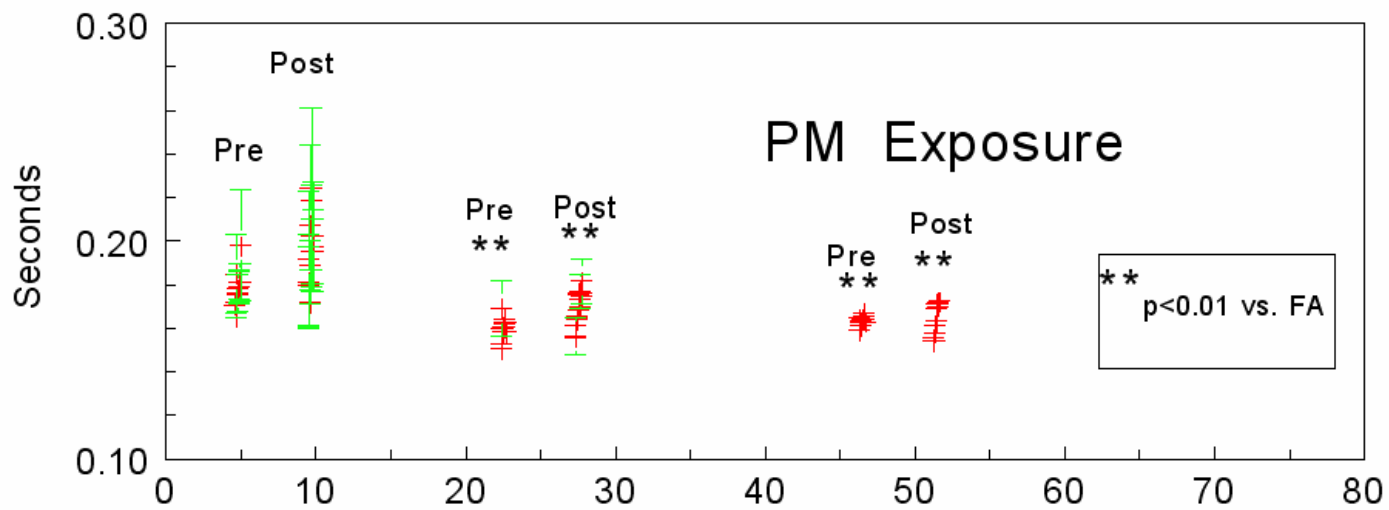
Superoxide production was increased in macrophages after CAPs exposure in Aged Rats



Follow on Experiment

- Rats were exposed to laboratory-generated particles (EC + AMN) at 250 $\mu\text{g}/\text{m}^3$ 4 hr per day for 3 days.
- BP, HR and HRV were evaluated





Conclusions

- Some allergic biomarkers were elevated in mice exposed at the site 50 m from the freeway.
- Responses at the site 150 m downwind were not significantly different from controls.
- Responses appear to be a function of the number of particles to which the mice were exposed but a relationship to mass can't be ruled out at this time.

Conclusions

- The geriatric rat model showed changes in HR, BP and macrophage responses .
 - Exposures were at lower levels than planned
- Technical issues for the cardiac implants will need to be better addressed
 - Start with somewhat younger animals and let them age before exposure.
- The finding that significant inflammatory responses are observed in brain tissue 2 weeks after the CAPs exposures were completed are possibly of relevance to the role of environmental agents in neurological diseases such as Parkinson's.

Conclusion

- Additional statistical analyses are needed to determine the significance of particle number, particle composition and particle mass interactions.
- In addition to dose response studies, time-response studies are needed because the cytokine and other signals are interrelated in a complex way with initiators and suppressors each having their own temporal patterns.