The Effects of Particulate Matter in a Mouse Model of Allergic Airway Inflammation

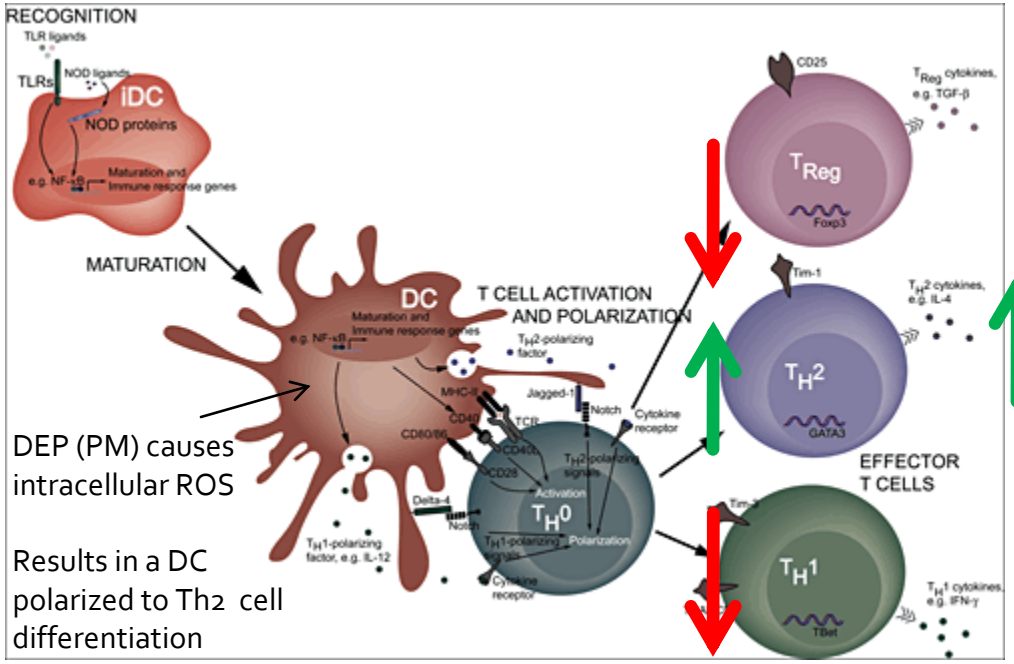
Christopher M. Carosino and Kent E. Pinkerton
Center for Health and the Environment
University of California, Davis

Particulate Pollution in the San Joaquin Valley:
Translating Science into Policy
June 9-10, 2010

Particles and Allergy

- Over 22 million Americans suffer from asthma today
- 50% of asthma cases are allergy sensitive
- Epidemiological studies have linked air pollution levels with increased asthma exacerbations, hospital admissions, and increased incidence of asthma (suggested role of PM in developing allergic asthma)
- PM studies comparing proximity to highly trafficked roadways have shown increased inflammation, cytokine production, and immunoglobulins
- Diesel exhaust particles (DEP) have been shown to exacerbate asthma conditions during allergen challenge
- Ultrafine particles (UFP) have been hypothesized to be more potent than PM2.5 or PM1.0

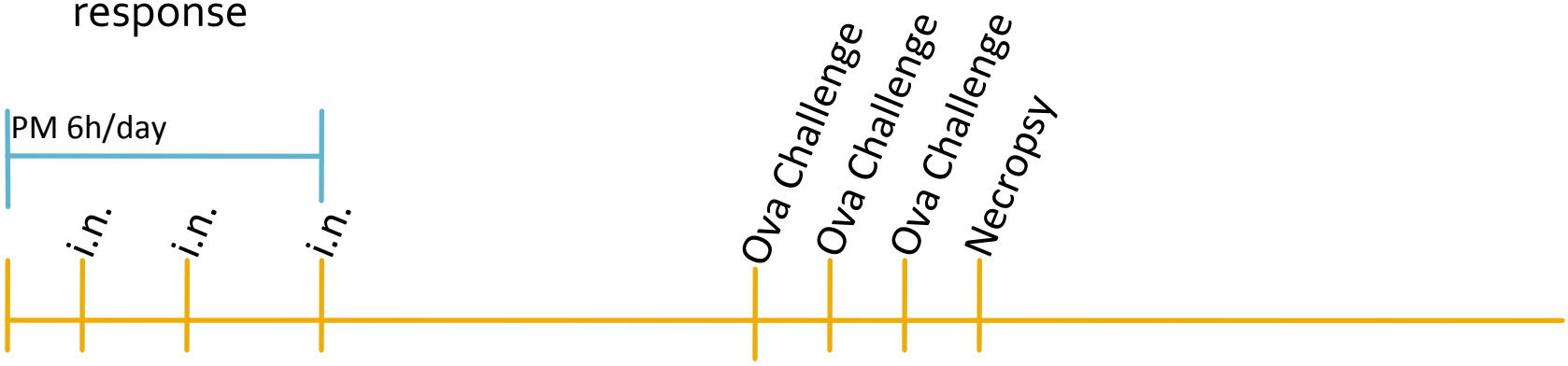
Mechanism



-Cytokines
-B-cell antibody production

The Murine Intranasal Sensitization Model of Allergic Airway Inflammation

- Balb/c mice
- Sensitization to allergen, ovalbumin (Ova)
  - 3 Intranasal instillations
    - (50µl total, 10µg Ova/instillation)
- Particle Exposure
  - Exposure by intranasal instillation or inhalation over 5-6 day period when animals are receiving allergen for sensitization
- Challenge
  - Whole animal aerosol of 1% Ova in PBS for 1 hour to elicit allergic response

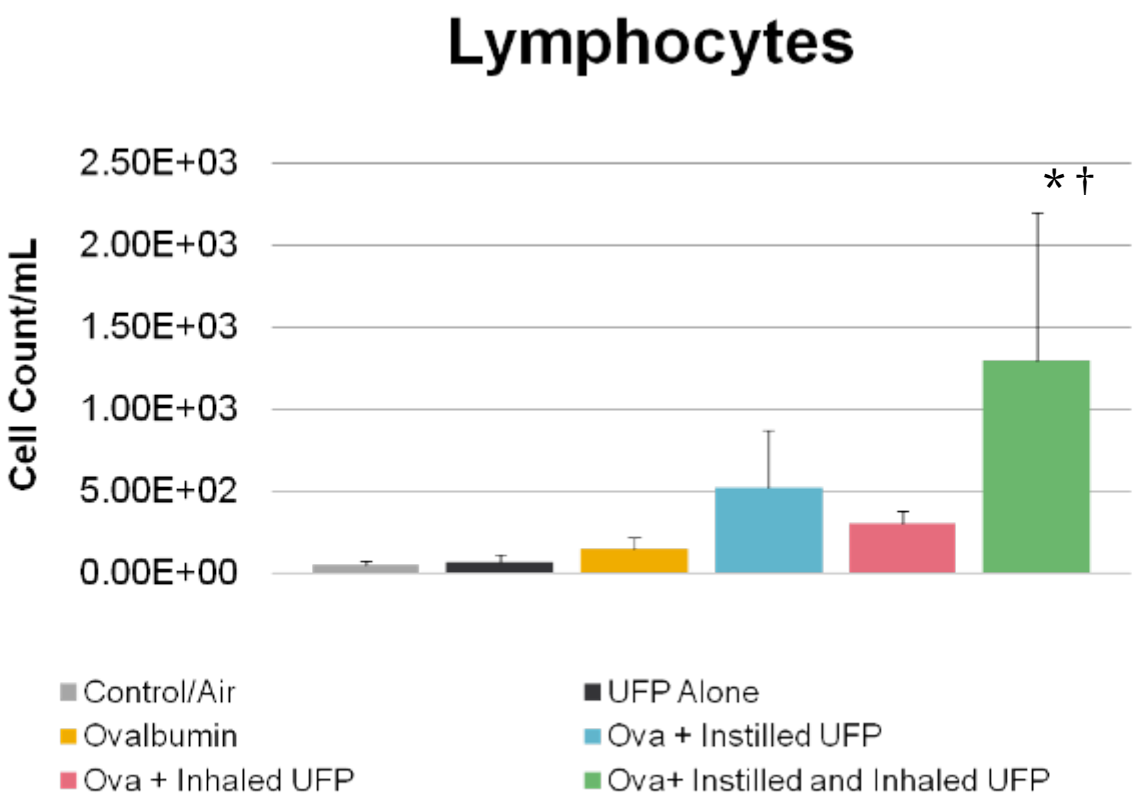


Methods

24 hours after second challenge

- BALF
  - Cell Viability
  - Cell Differentials
  - Total Protein
- Blood
  - Immunoglobulins
  - Cytokines/ Chemokines*
- Fixed Lung (PFA)
  - H&E Staining
  - AB/PAS Stain (Mucosubstances)
  - Prussian Blue (Fe Stain)
  - CEM Stain (Eosinophils/Mast cells)

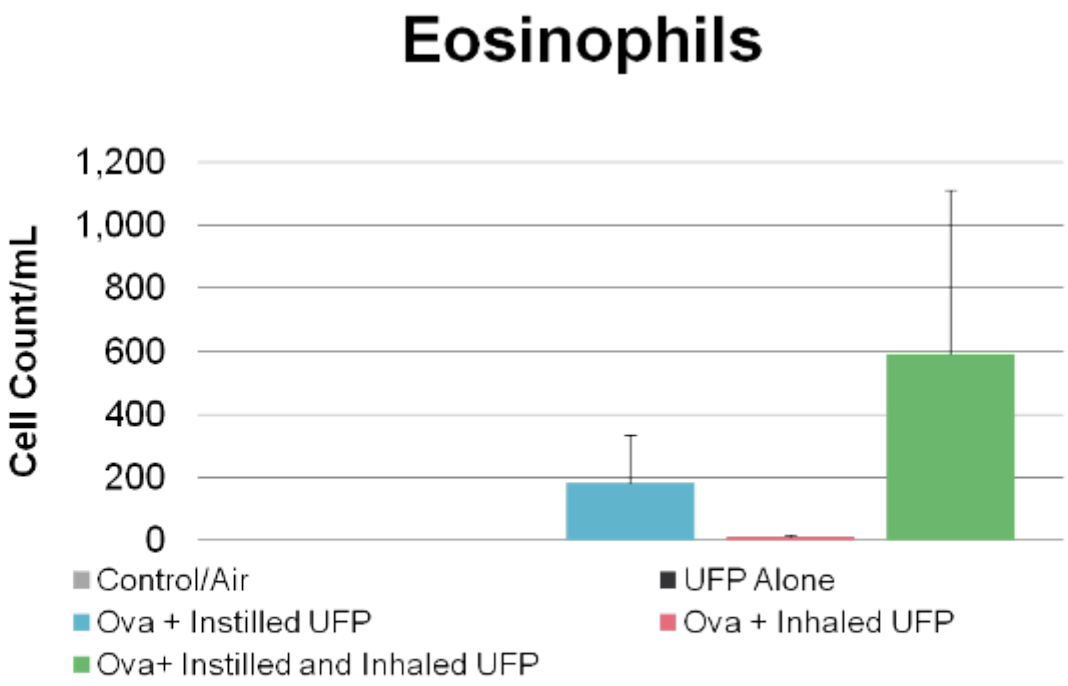
Inflammatory Profile



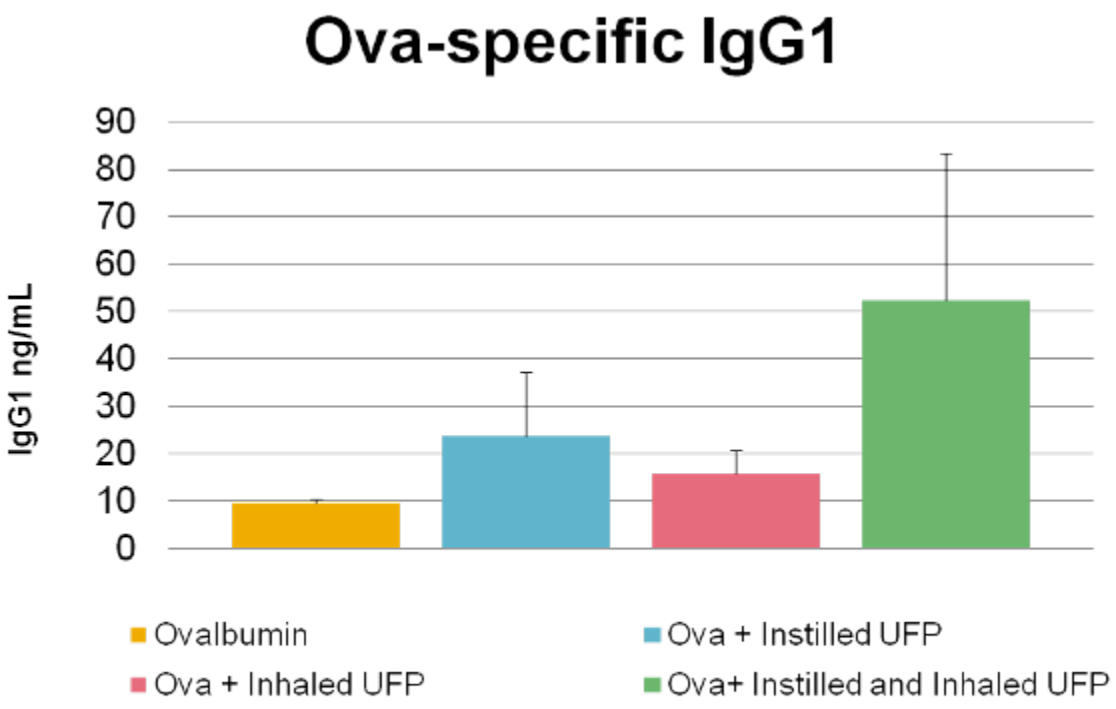
**P<0.05 versus Control/Air*

† P<0.05 versus UFP Alone

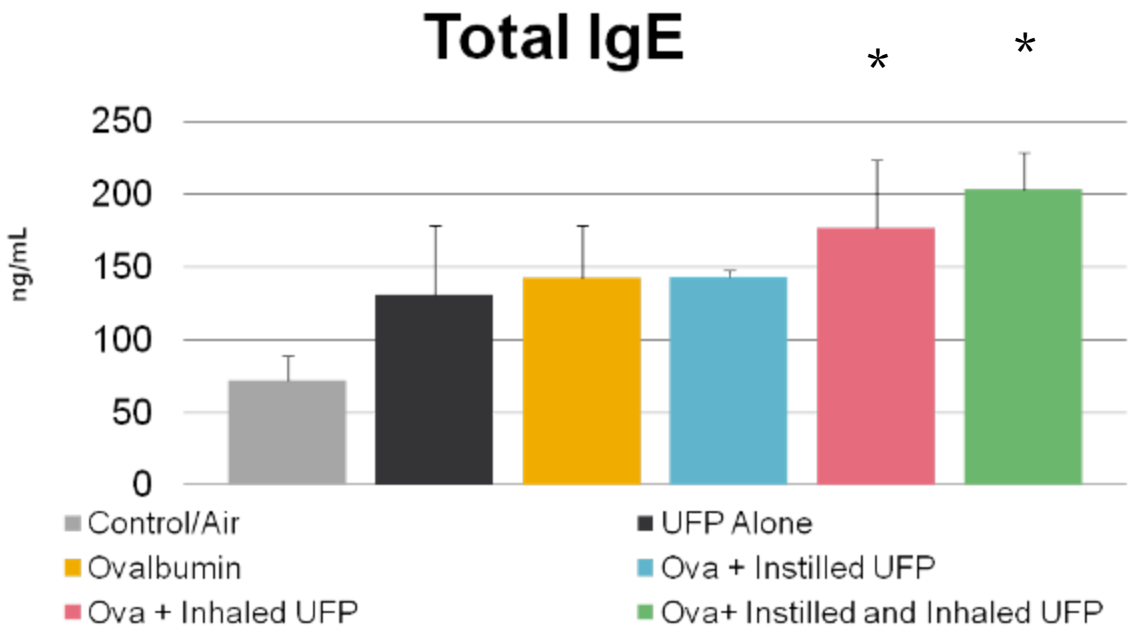
Inflammatory Profile



Circulating Antibodies

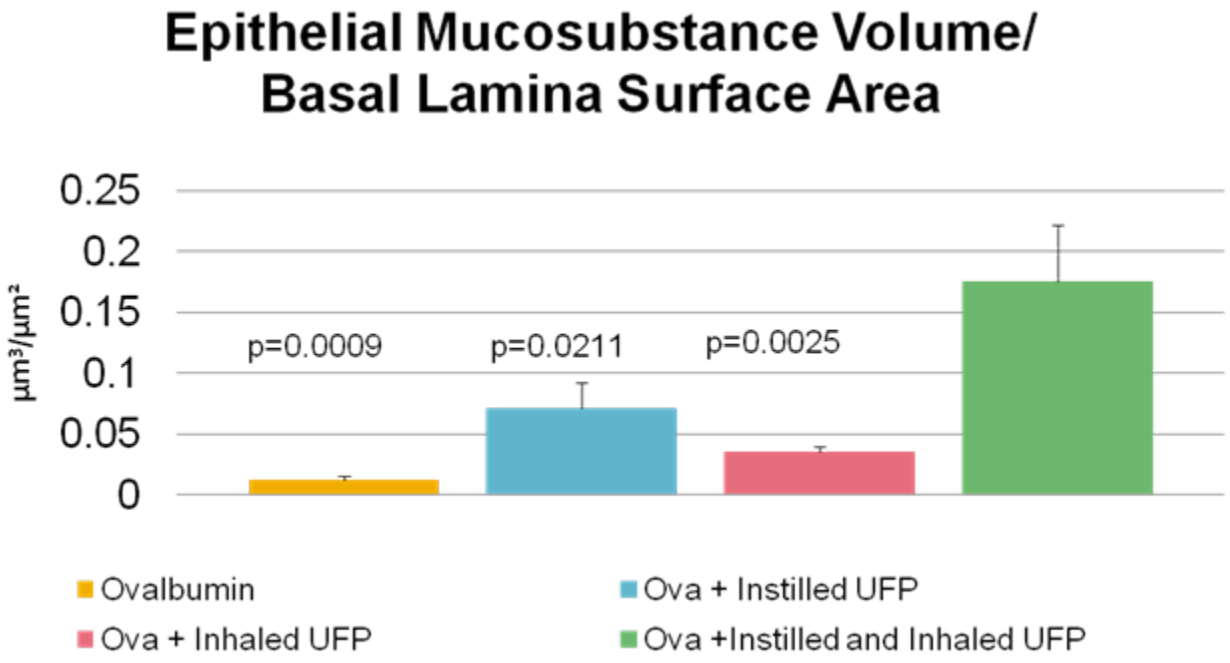


Circulating Antibodies



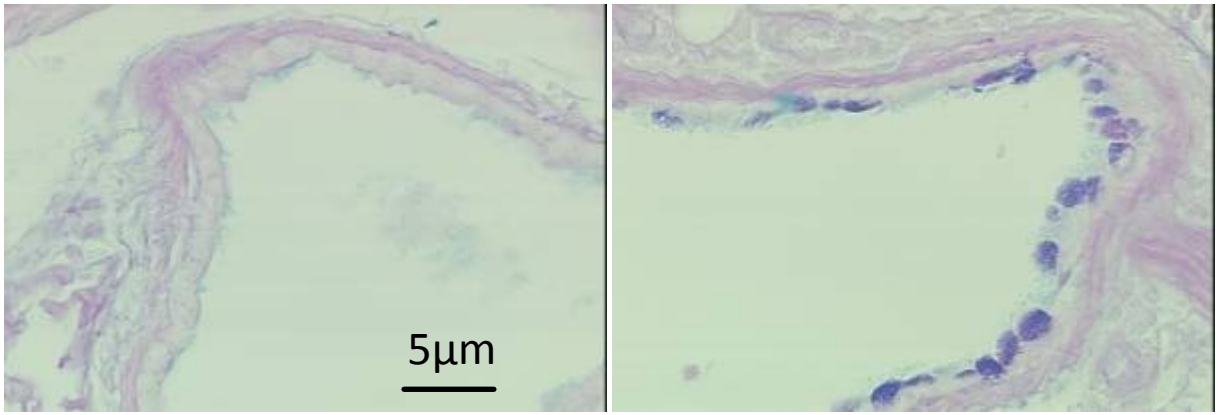
*P<0.05 versus Control/Air

Results – Lung Histology



Lung Histology

Alcian Blue/Periodic Acid Schiff Stain for Mucosubstances in the axial pathway of the proximal lung.



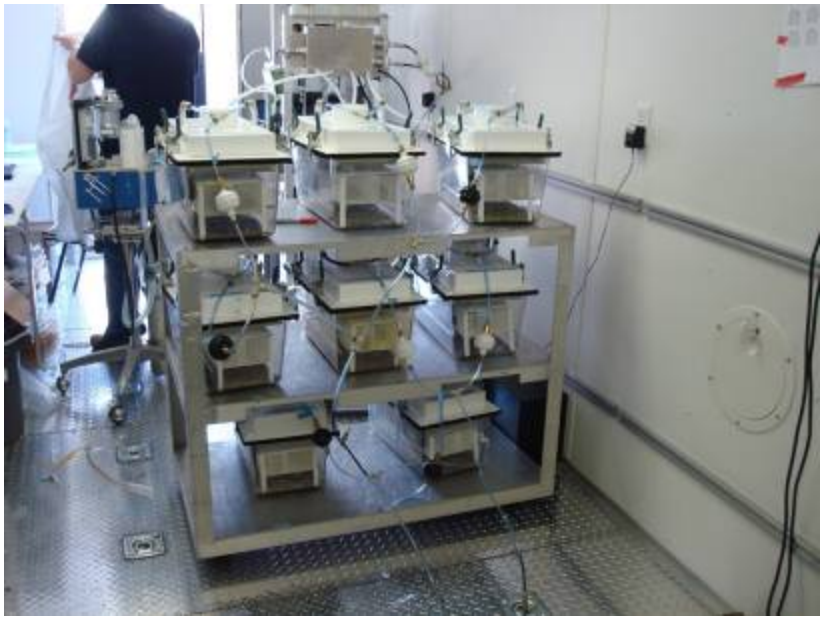
Left: Ovalbumin proximal lung airway
Right: Ova and Instilled/Inhaled proximal lung airway

Aims

To test if *inhalation* of San Joaquin Valley concentrated ambient particles differentially increases allergic airway inflammation.

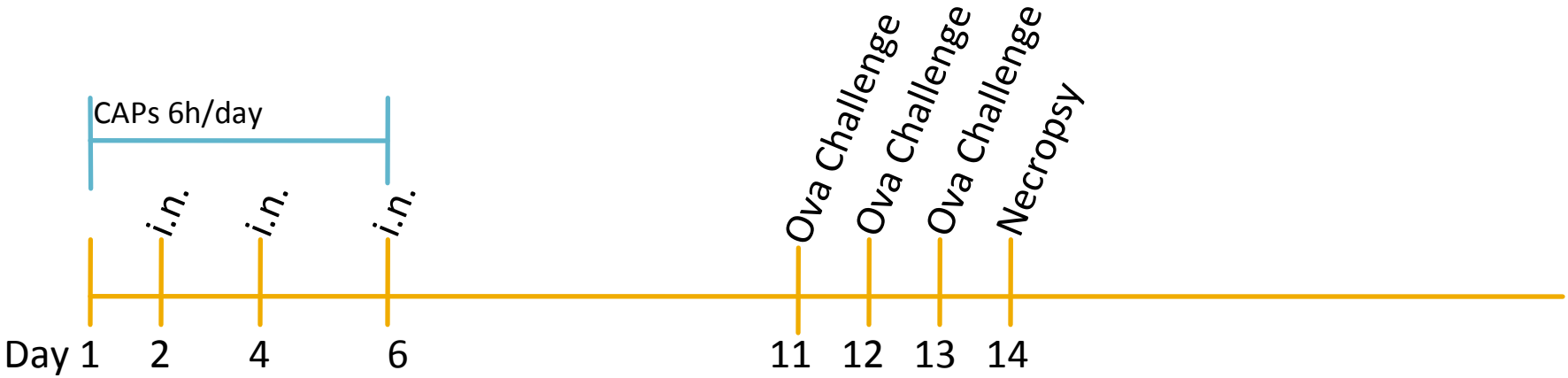
Concentrated Ambient Particles

- CAPs by Versatile Aerosol Concentration Enhancement System (VACES)
- Fresno, CA – non-attainment for $PM_{2.5}$, PM_{10}, O_3
- Highest incidence of asthma in the state

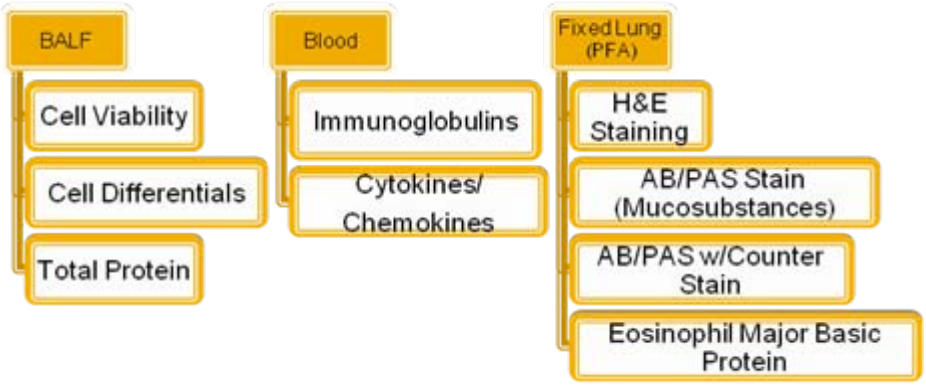


CAPs Urban Fresno- Summer 2009

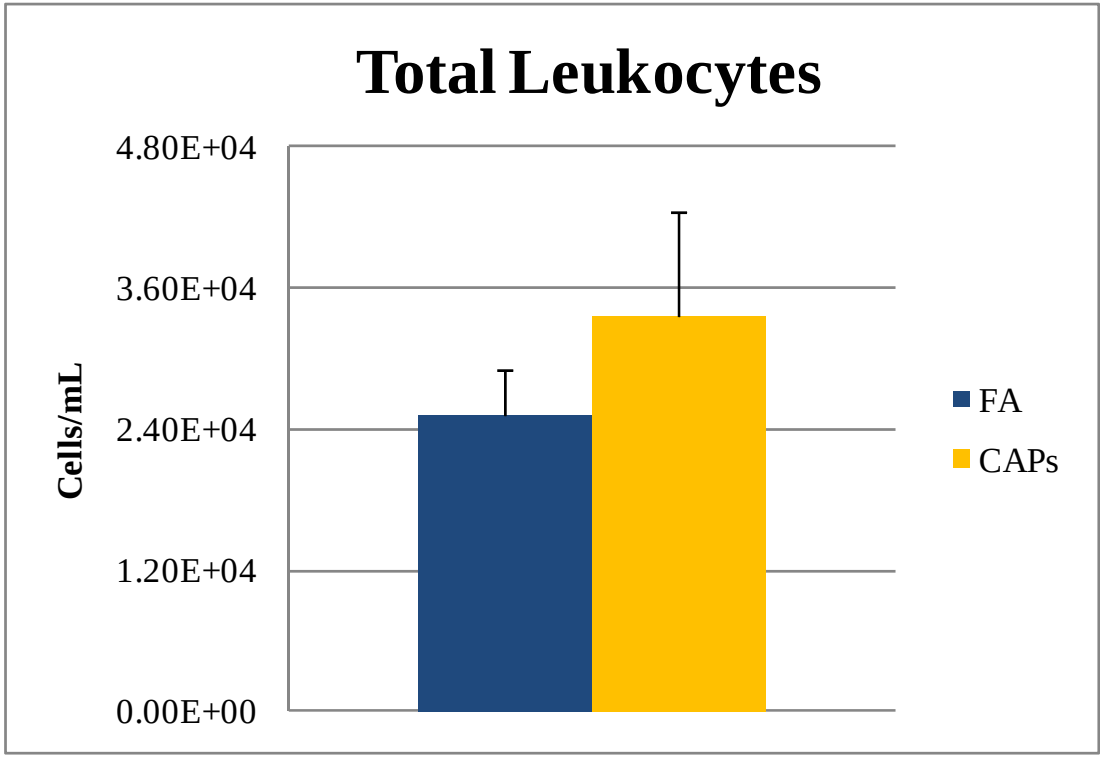
- Mice exposed for 6 days to 125 µg/m^3 CAPs



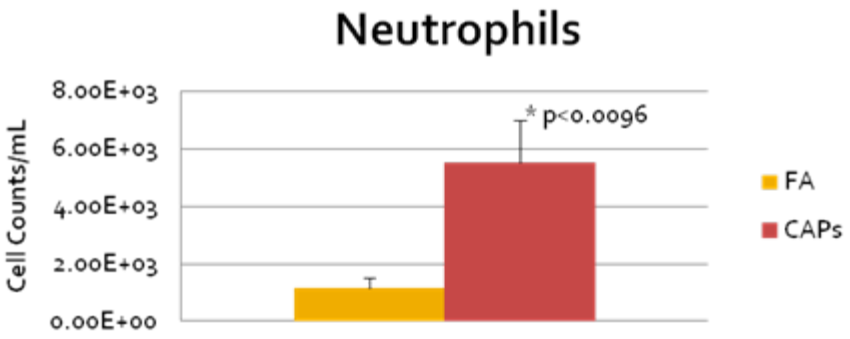
24 hours after third challenge

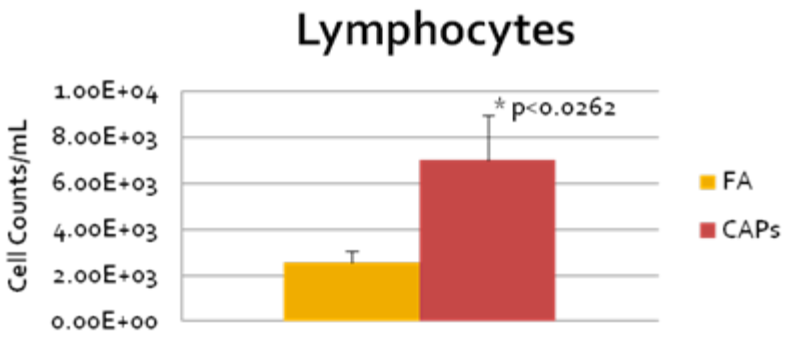


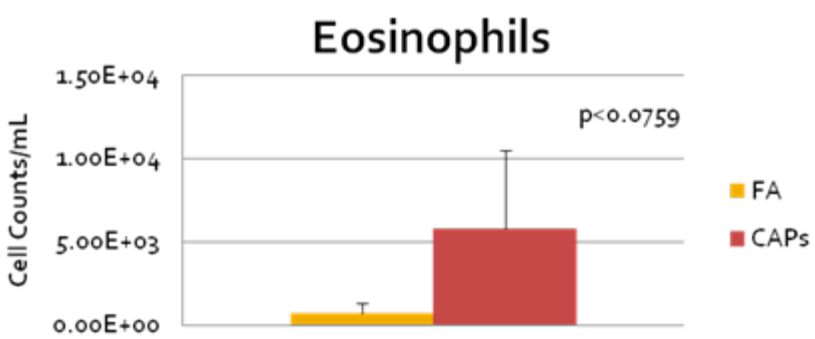
Inflammatory Profile

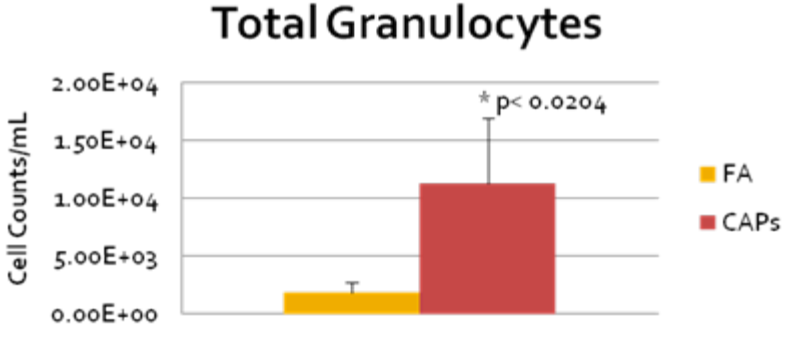


Inflammatory Profile

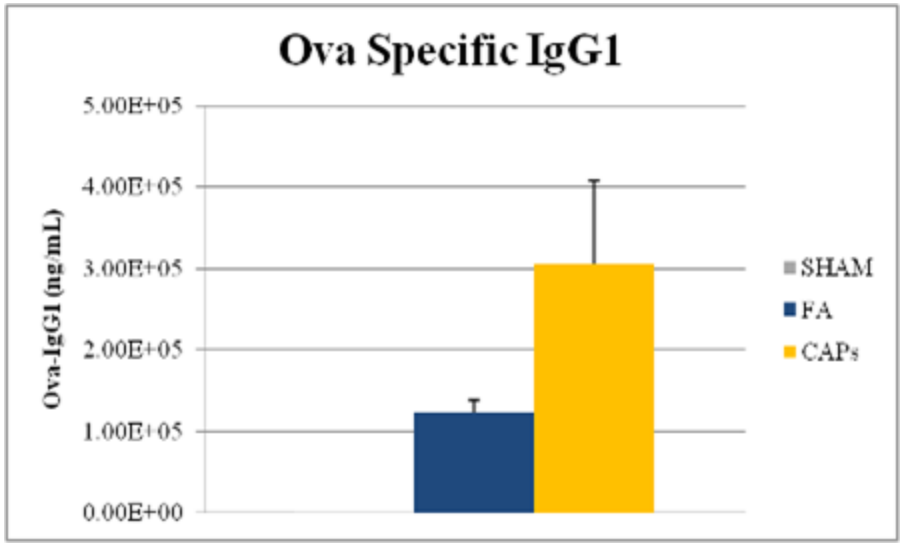


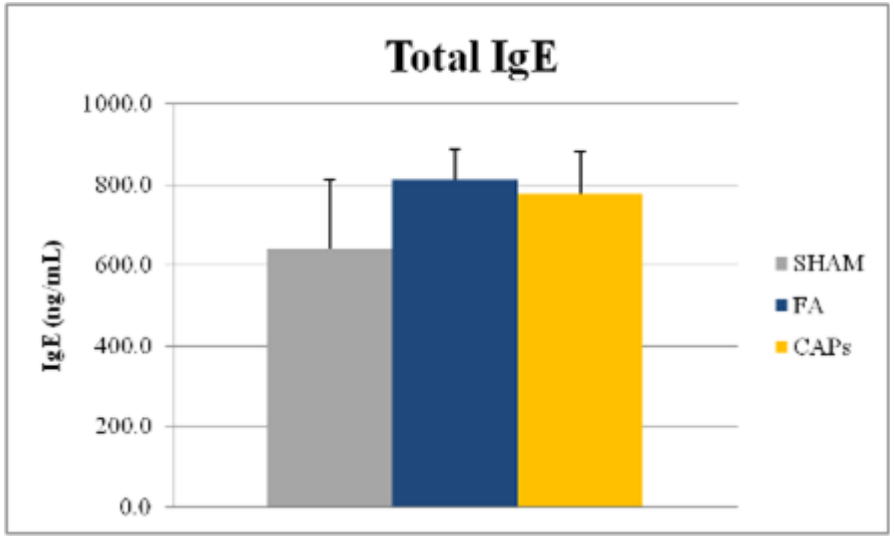






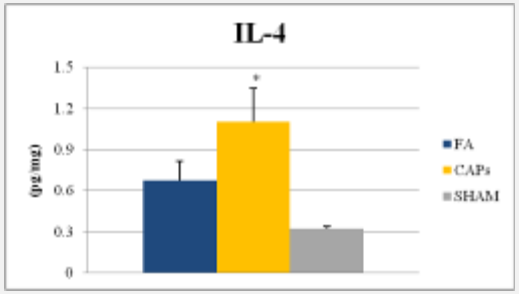
Circulating Antibodies

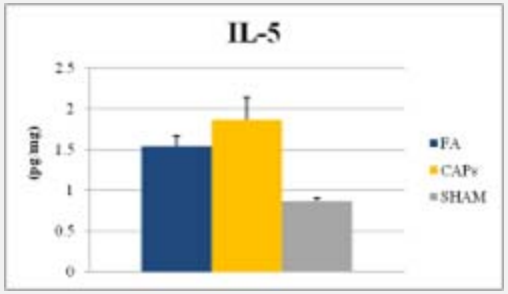


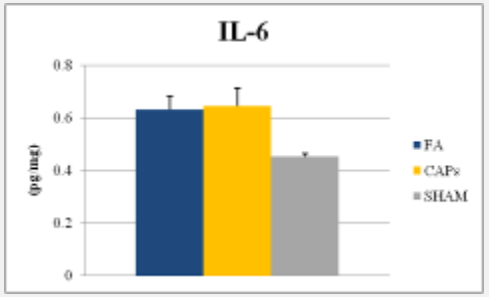


Pulmonary Cytokine Responses

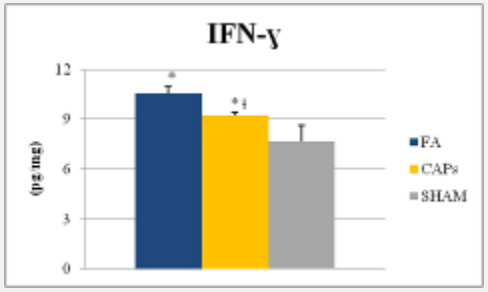
Th2

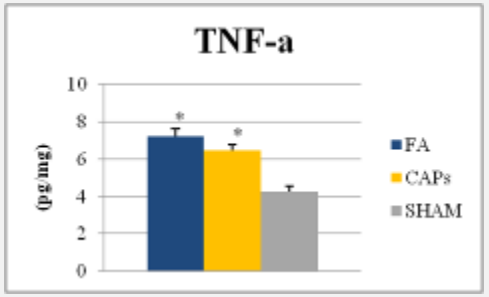






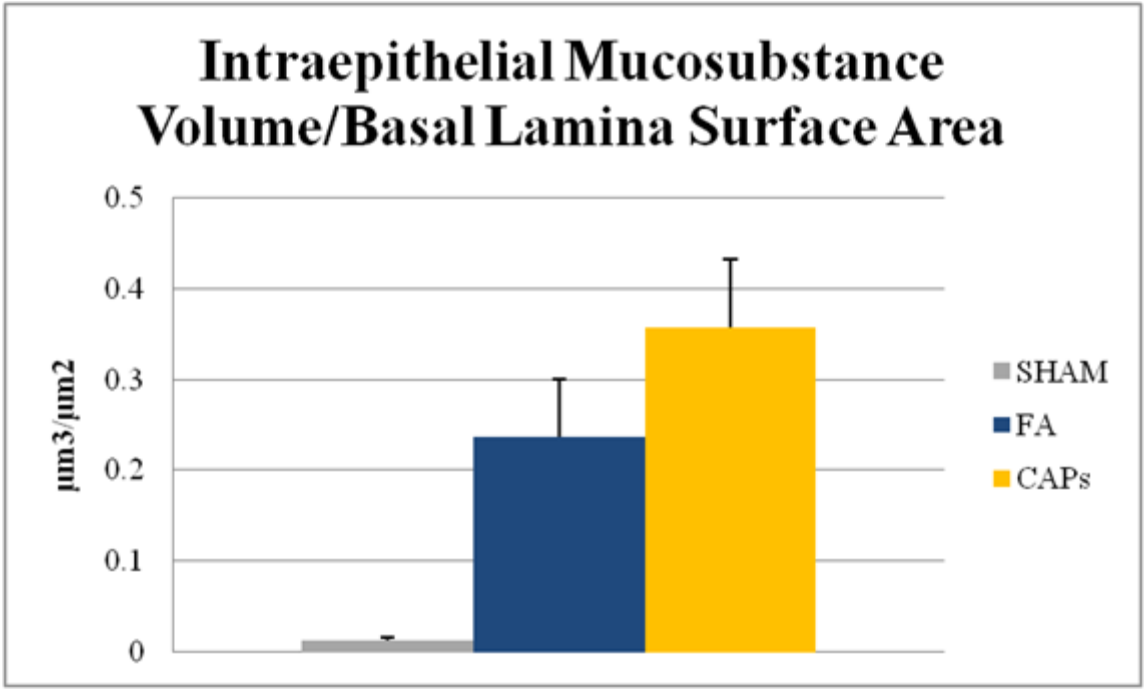
Th1





Th2 and Th1 associated cytokine levels per mg of protein from homogenized lung tissue. (Mean ± SE) Significance noted when $p<0.05$ from null (*) and FA (†) groups.

Lung Histology



Conclusions

- Exposure to low concentration Fresno CAPs yields
  - Increased inflammatory cell recruitment
    - Neutrophils, Lymphocytes and Total Granulocytes
  - Trend towards increased IgG1
  - No change in Total-IgE
    - Ova-IgE in progress*
  - Trend towards increased intraepithelial mucosubstances
- Further Research in Progress
  - Eosinophil Major Basic Protein Immunohistochemistry
  - Cytokine analysis
  - Chemical speciation
- Source-Oriented Particles

Acknowledgements

- Pinkerton Laboratory
  - Dale Uyeminami
  - Imelda Espiritu
  - Janice Peake
  - Dr. Lei Wang
  - Laurel Plummer
  - Kyrsten Bulliet
- Dr. Jerrold Last
- Dr. Nicholas Kenyon
- Dr. Valerie Mitchell
- Collaborators
  - Dr. Anthony Wexler
  - Dr. Michael Kleeman
  - Dr. Keith Bein
  - Dr. Chris Ruehl
  - Dr. Yongjing Zhao
  - Dr. Jack Harkema (MSU)
- Atmospheric Aerosols and Health
- NIEHS Training Grant

Aims

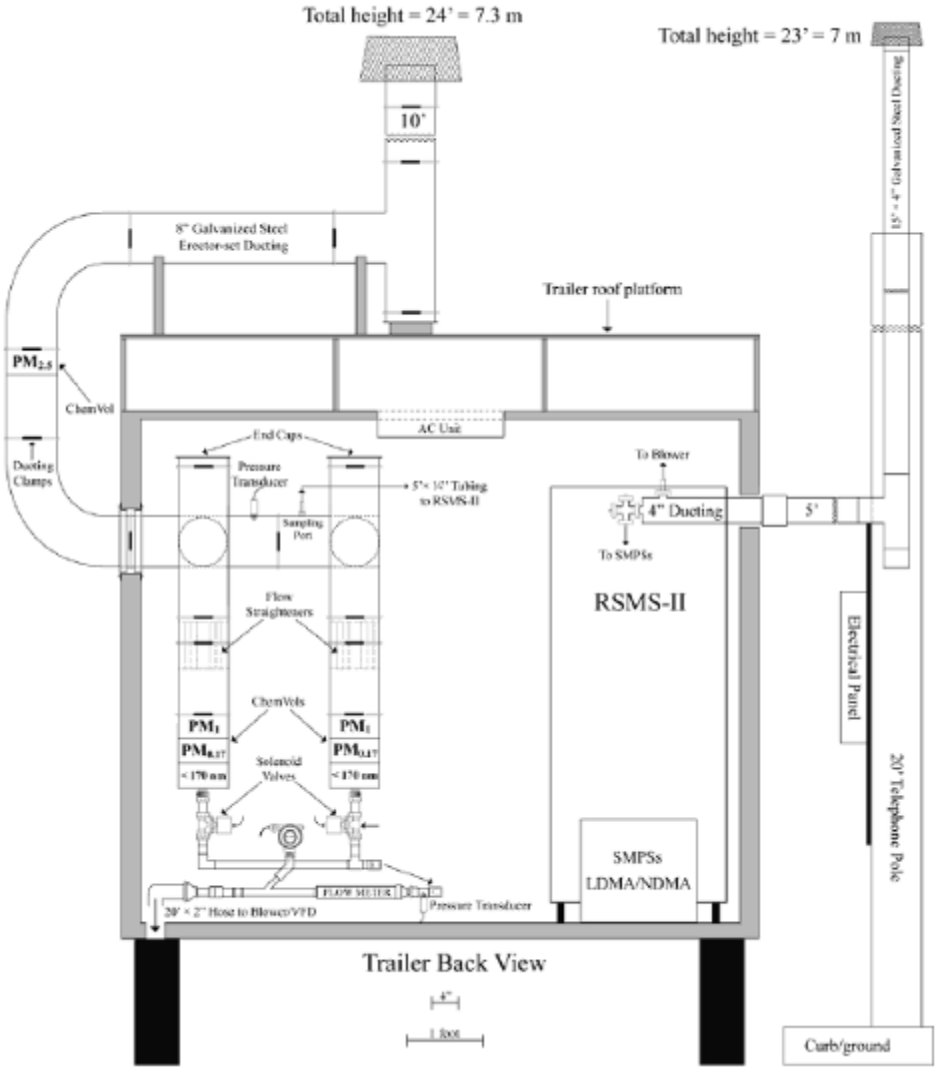
Test if *inhalation* of seasonal San Joaquin Valley concentrated ambient particles differentially increase allergic airway inflammation

Utilize source-oriented fractions of ultrafine and submicron fine ambient particles and evaluate their differential effects on allergic airway inflammation.

Source-Oriented Particles

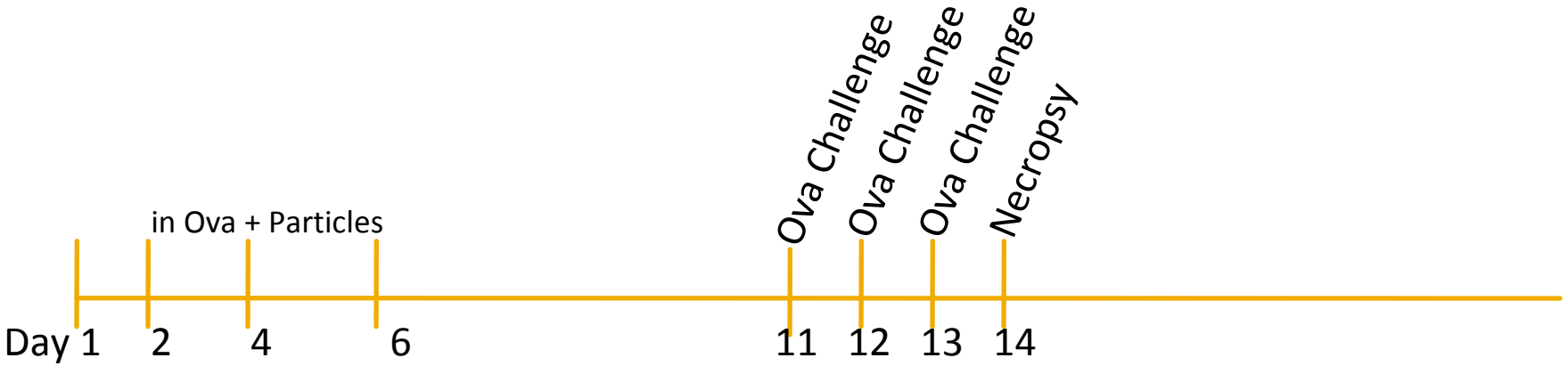
- RSMS-II, single particle MS
- ChemVol Sampling Train
- Computer Controlled w/Learning Algorithm
- Particles sorted in high time resolved manner
- Particles that occur together will be collected together, "particle class"
- Generally maximum 2-3 different sources per "particle class"
- Source(s) determined by source attribution

- Novel research looking at atmospherically processed particles by source



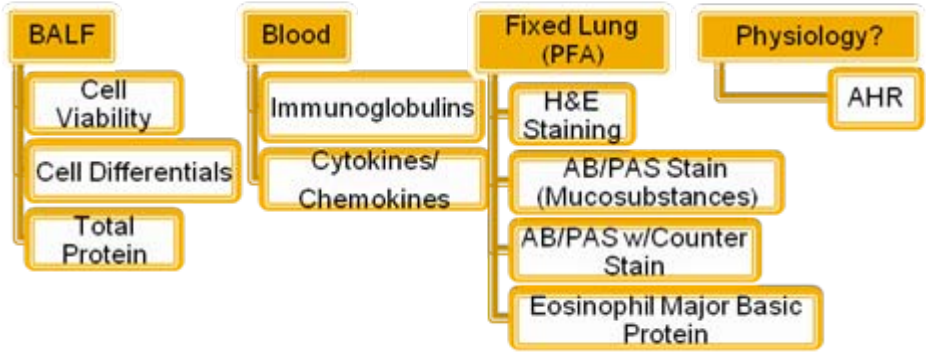
Source-Oriented Particles

- Mice exposed 3x by intranasal instillation



24 hours after

third challenge



Inflammatory Profile