Persistent Immune Effects of Wildfire PM Exposure During Childhood Development

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UCDAVIS
CALIFORNIA NATIONAL
PRIMATE RESEARCH CENTER

OVERVIEW

- California National Primate Center program
- Nonhuman primates as a model for early childhood development
- Rationale for investigation of wildfire smoke PM
- Effects of wildfire smoke PM on immunity
- Effects of wildfire smoke PM on lung function

NPRC Organization

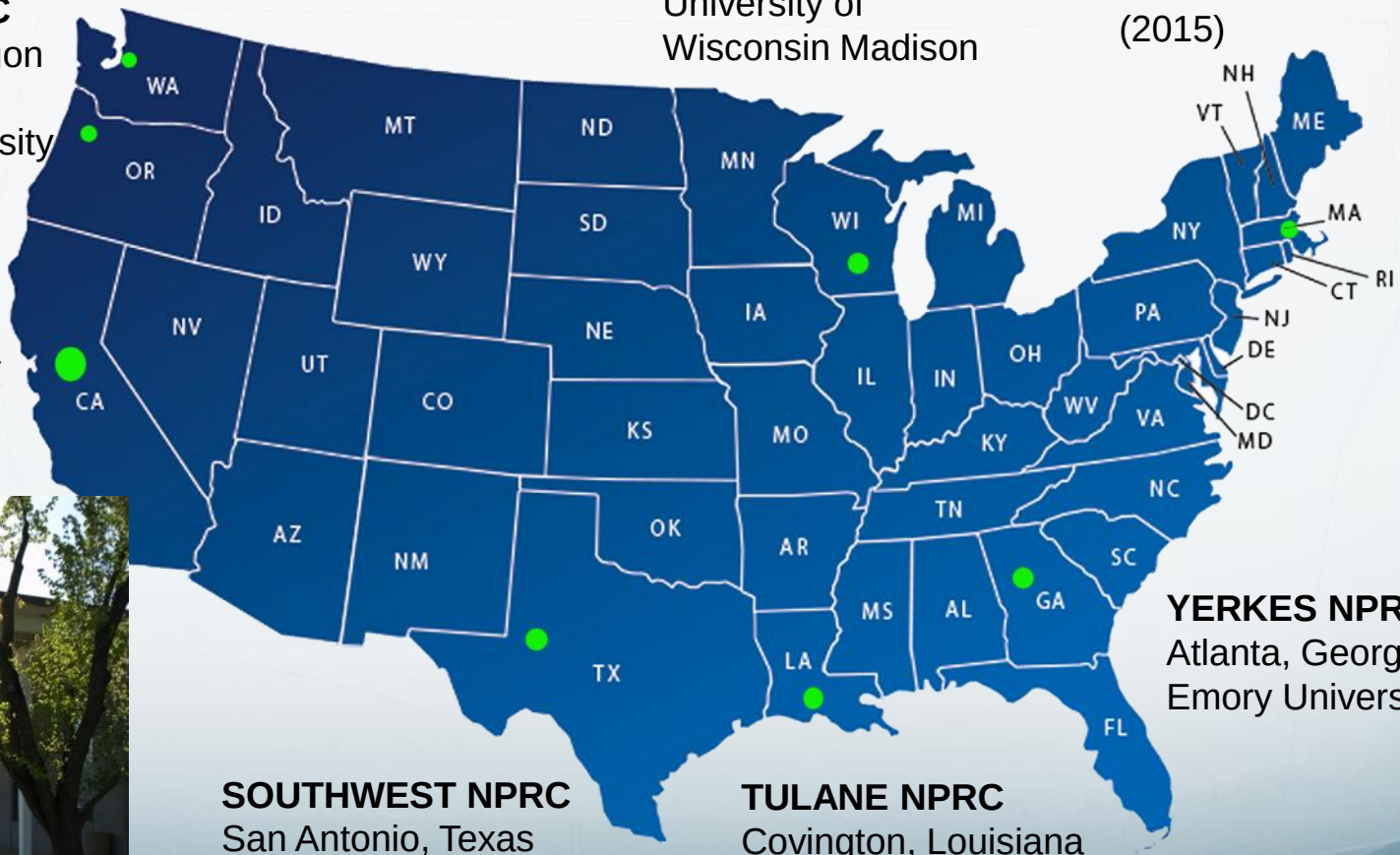
WASHINGTON NPRC
Seattle, Washington
University of Washington Seattle

NEW ENGLAND NPRC
Southborough, Massachusetts
Harvard University
(2015)

WISCONSIN NPRC
Madison, Wisconsin
University of Wisconsin Madison

OREGON NPRC
Beaverton, Oregon
Oregon Health Sciences University

CALIFORNIA NPRC
Davis, California
University of California Davis



SOUTHWEST NPRC
San Antonio, Texas
University of Texas Health Science Center

TULANE NPRC
Covington, Louisiana
Tulane University

YERKES NPRC
Atlanta, Georgia
Emory University

CNPRC Vital Statistics

- 300 acre site, occupy 85 acres
- 20 core scientists, ~70 affiliate scientists
- ~400 employees
- ~40 graduate students and postdoctoral fellows
- ~60 undergraduate students
- ~5,000 monkeys
- Current NIH P51 base operating grant = $11 M total cost
  - Administration of P51 Core Grant Activities
  - Breeding Colony and Unassigned Animals
  - Support for Core Scientists and Research Units
  - Pilot Research Program
  - Consortium Activities

CNPRC Nonhuman Primates: Rhesus Macaque and Titi Monkey

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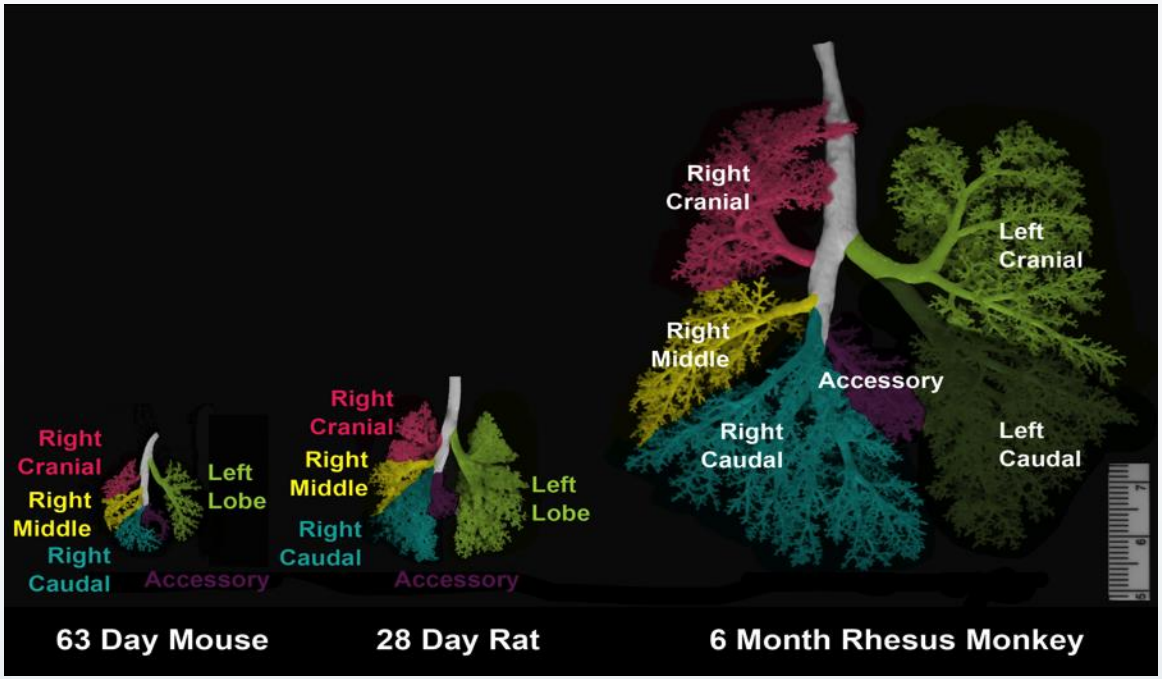
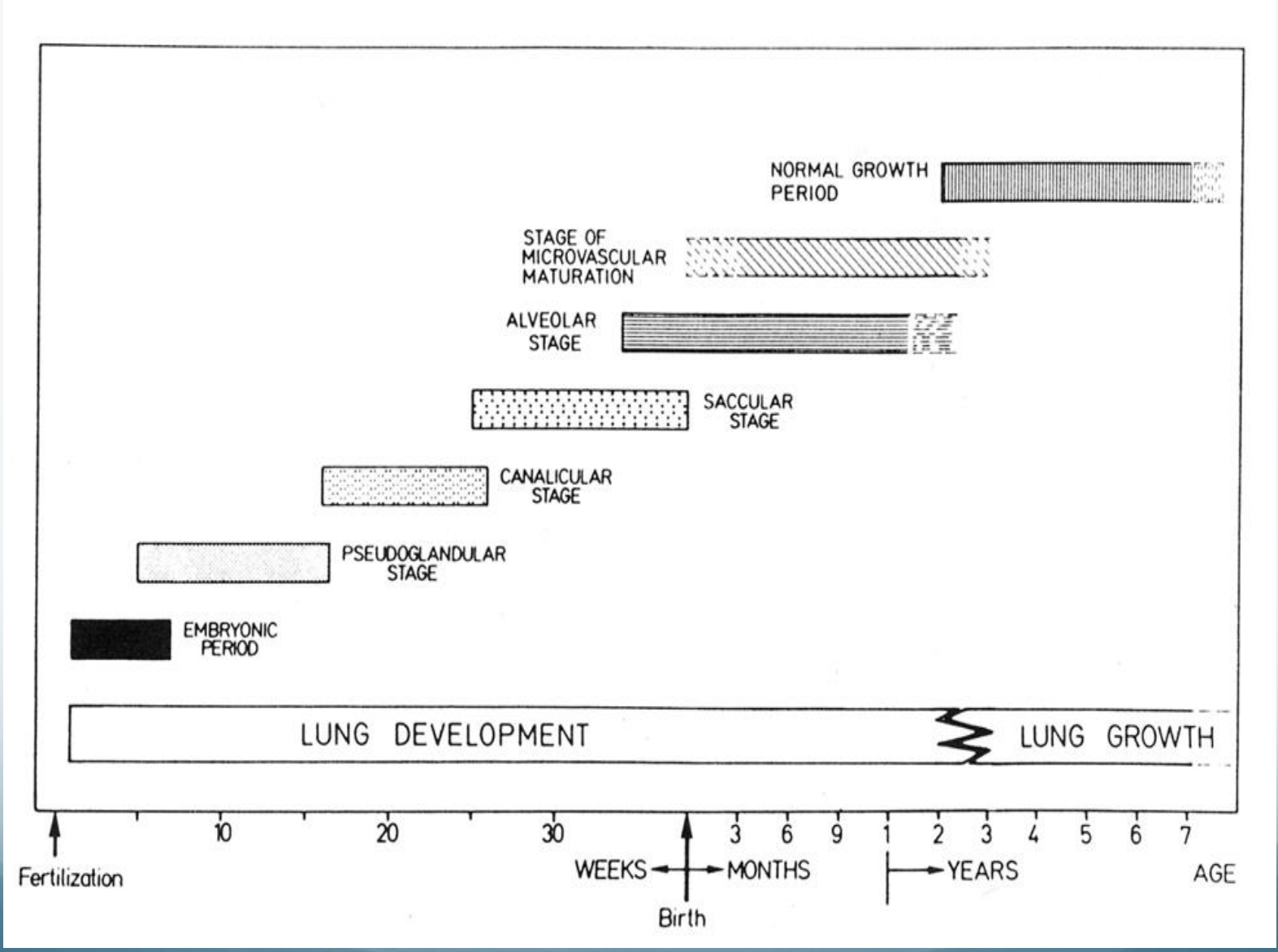
Nonhuman Primate Models of Lung Disease



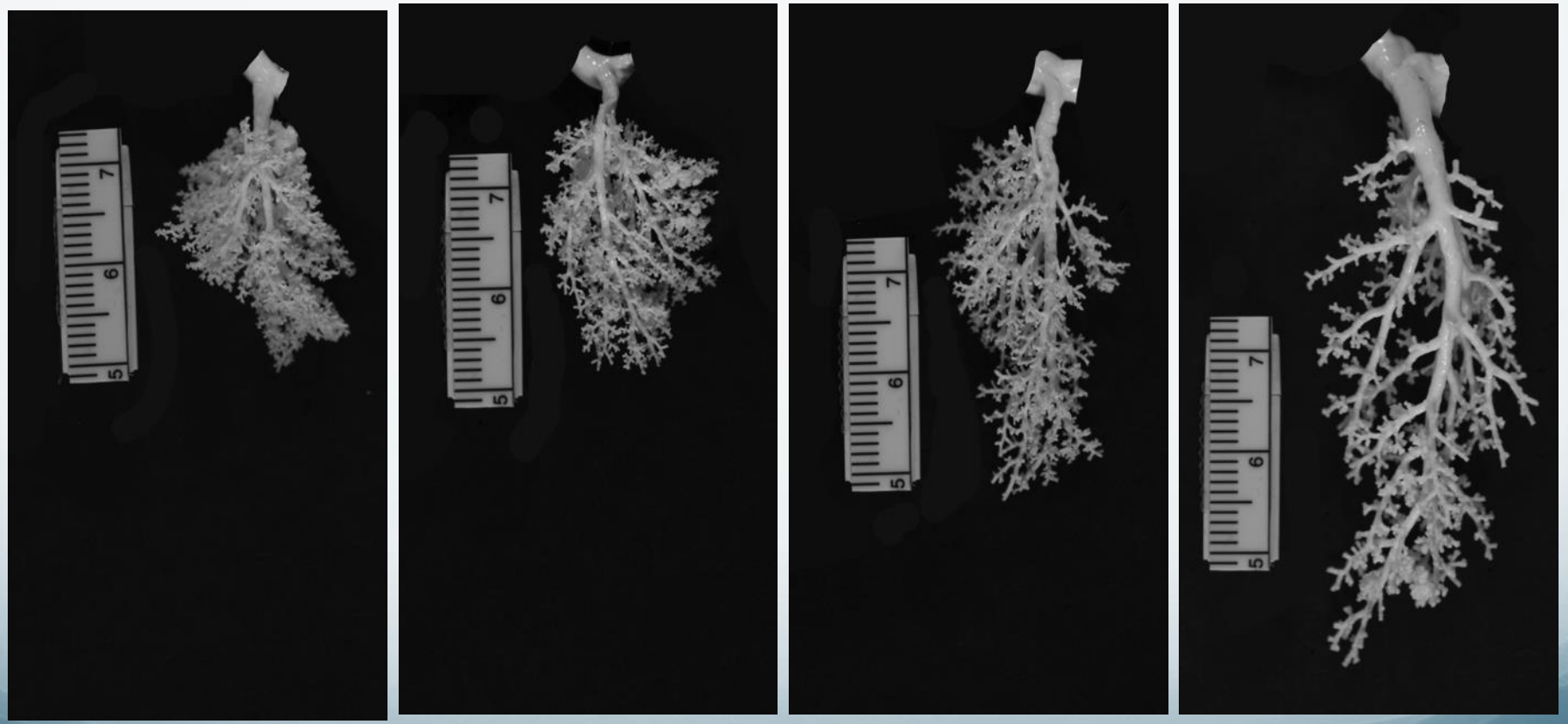
Overall lung architecture of nonhuman primates is most similar to human (monopodial vs. dichotomous growth)

Stages of Human Lung Development



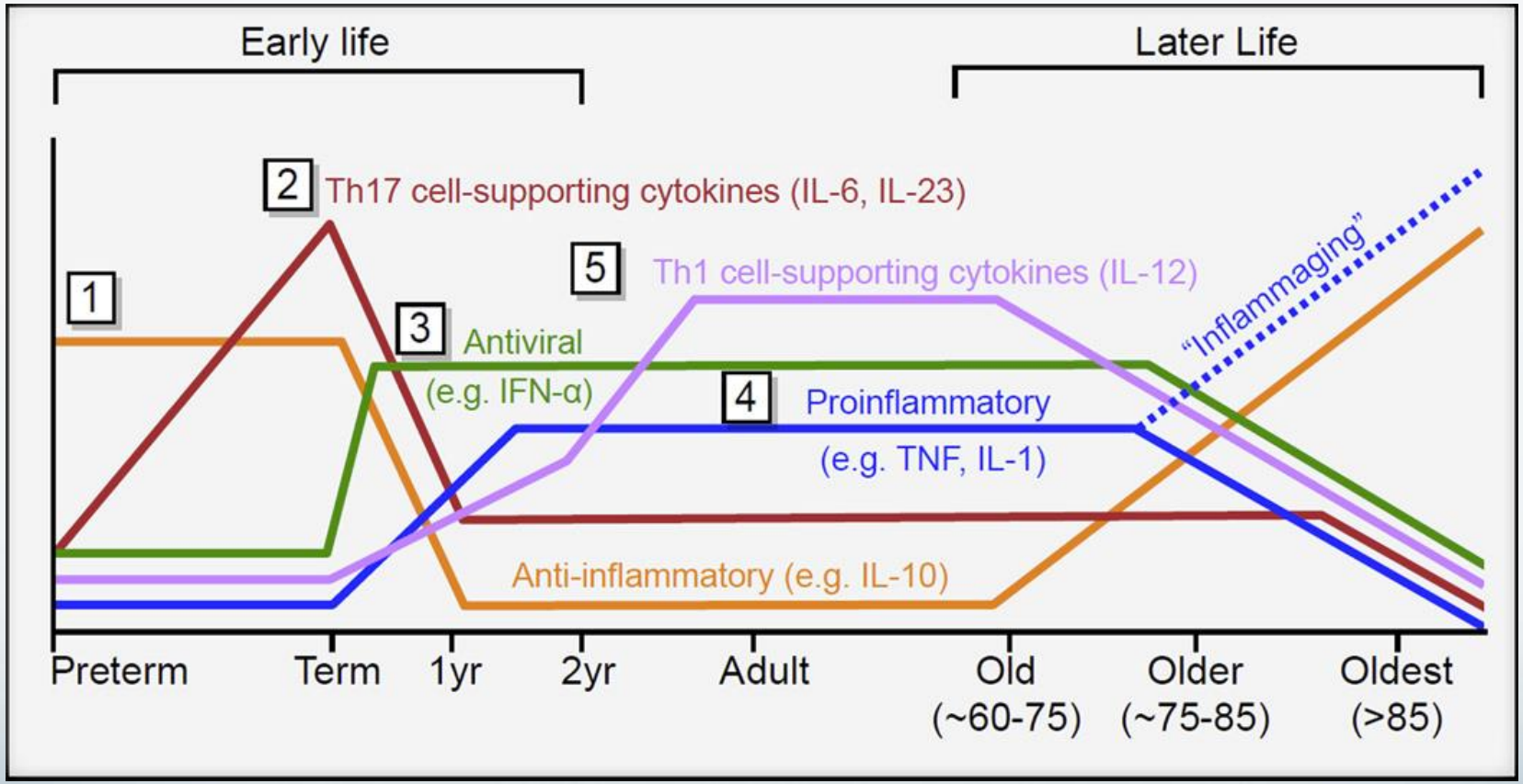
Comparative Lung Anatomy in the Rhesus Macaque

Right Middle Lobe



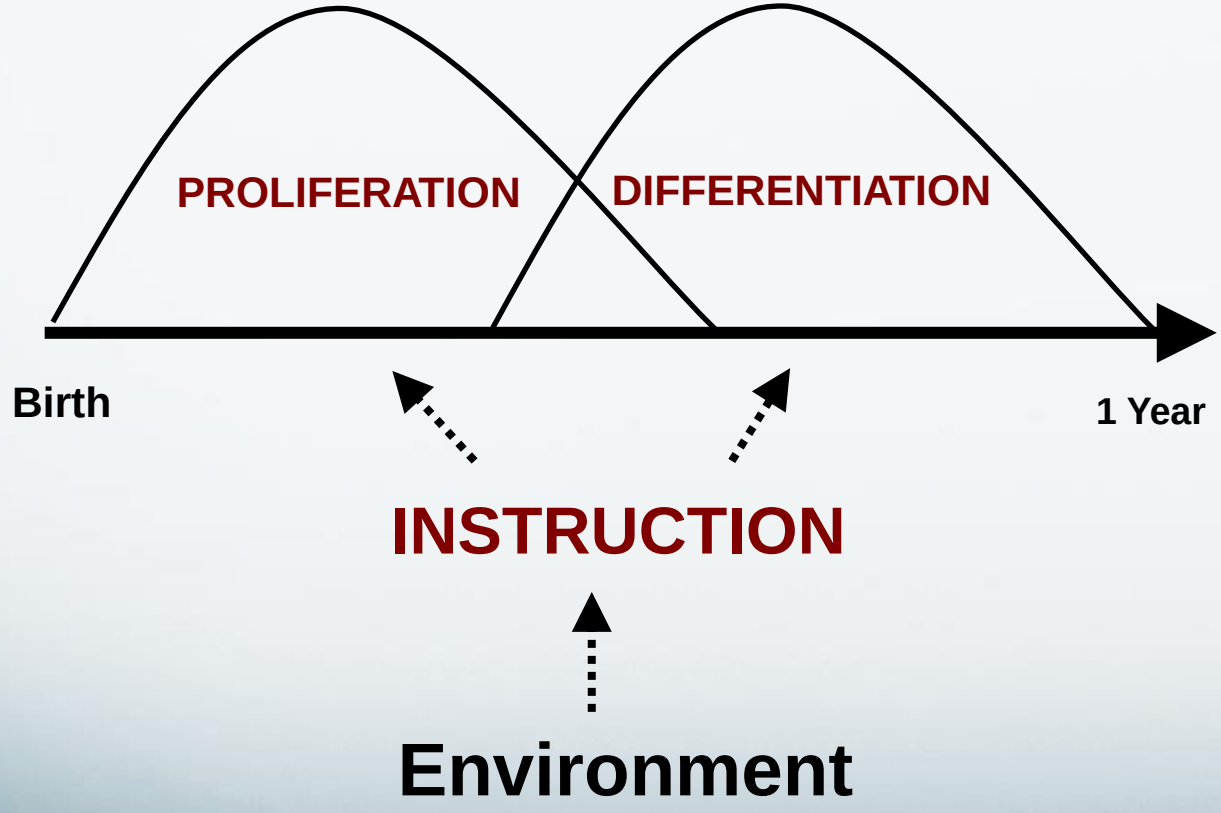
32 days | 90 days | 6 months | Adult

Age-Dependent Changes in Innate Immune Function



Kollman, et. al. Immunity 2012

Postnatal Lung and Immune Systems Develop in a Synchronized Fashion



Innate Immunity
Adaptive Immunity
Lung Function

The Monkey as a Model for Early Childhood Development

- Similar postnatal maturation of lung development
- Similar postnatal maturation of immune cell development

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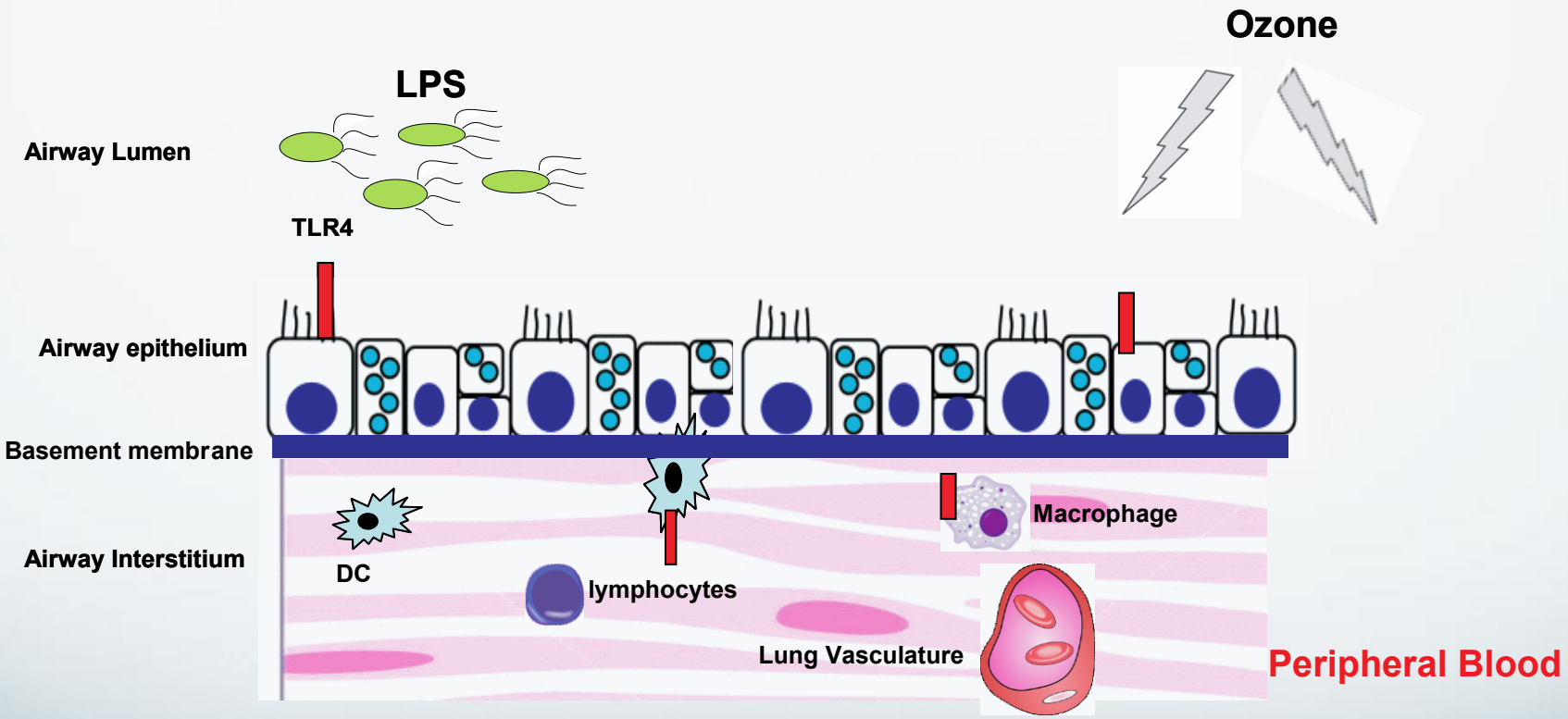
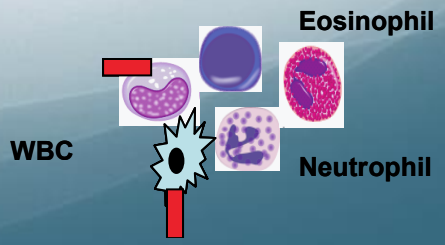
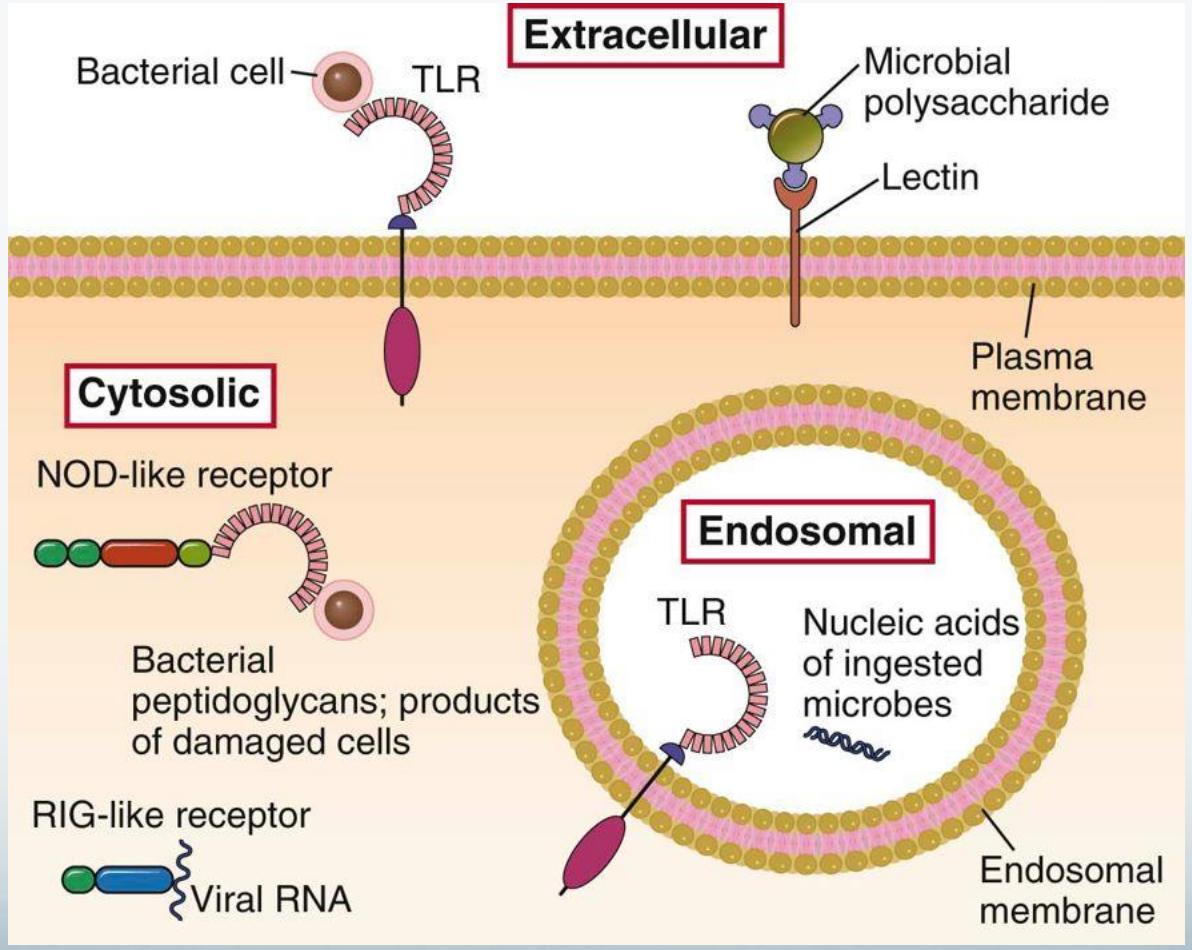
Persistent Effects of Ozone Exposure During Lung Development: Impact on Innate Immunity





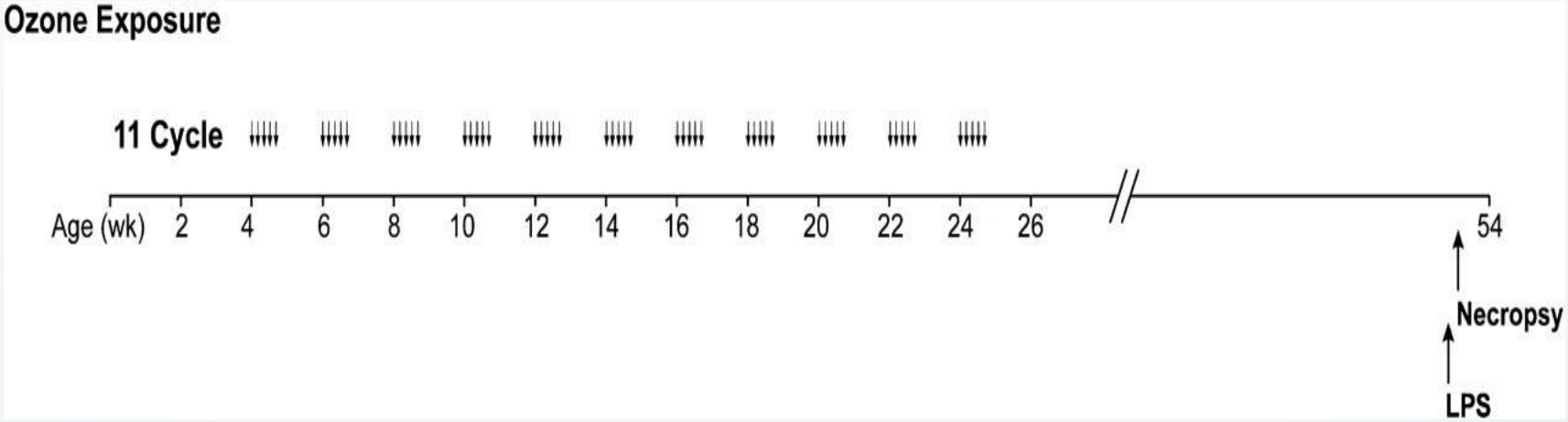
Persistent Effects of Ozone Exposure During Lung Development: Impact on Innate Immunity



Receptors on cells of the innate immune system recognize PAMPS

PAMPS=Pathogen associated molecular patterns

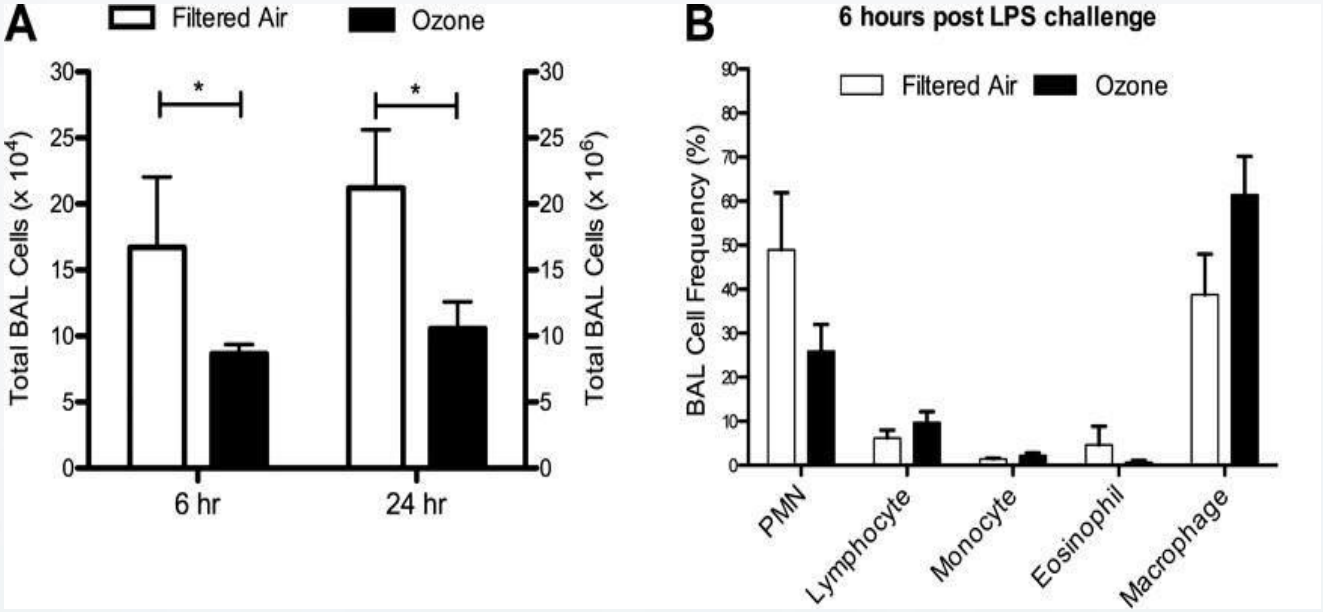
Persistent Effects of Ozone Exposure During Lung Development: Impact on Innate Immunity



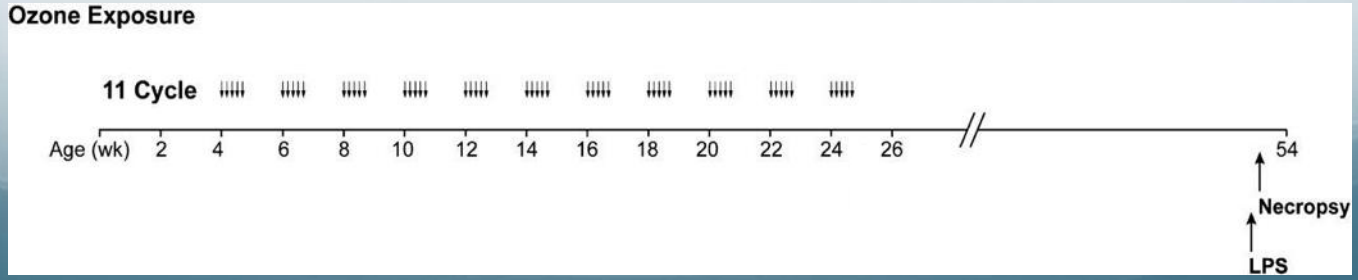
- Monkeys exposed to 0.5 ppm/8 hr/day ozone until 6 months of age
- Exposed animals remain in filtered air until 12 months of age
- Animals challenged with a single dose of endotoxin (LPS) at 12 months of age

Maniar-Hew, et. al. Am J Physiol Lung Cell Mol Physiol 2011

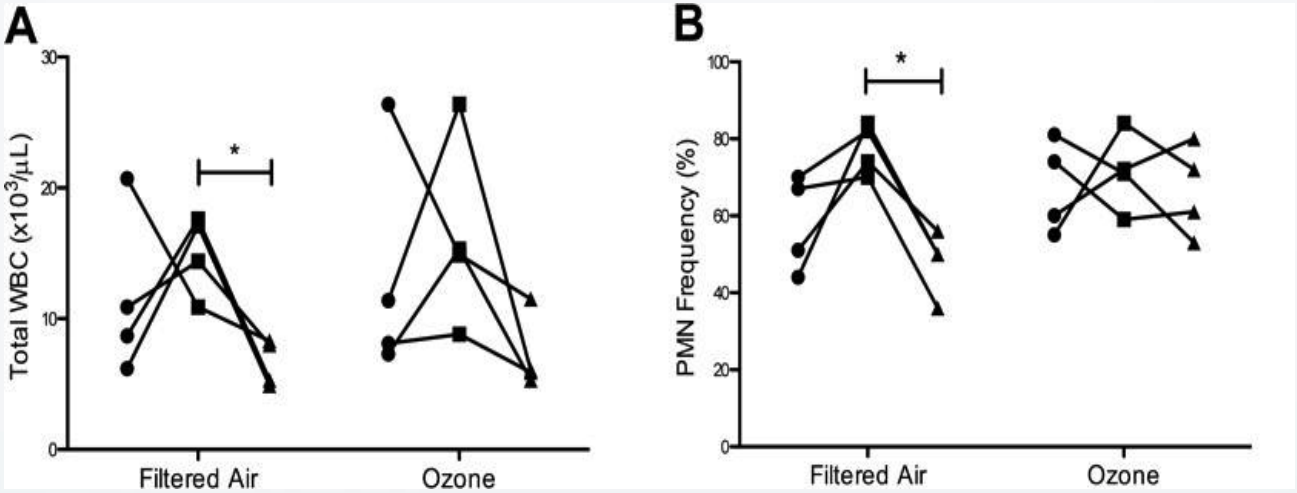
Persistent Effect of Ozone: Lung (In Vivo LPS)



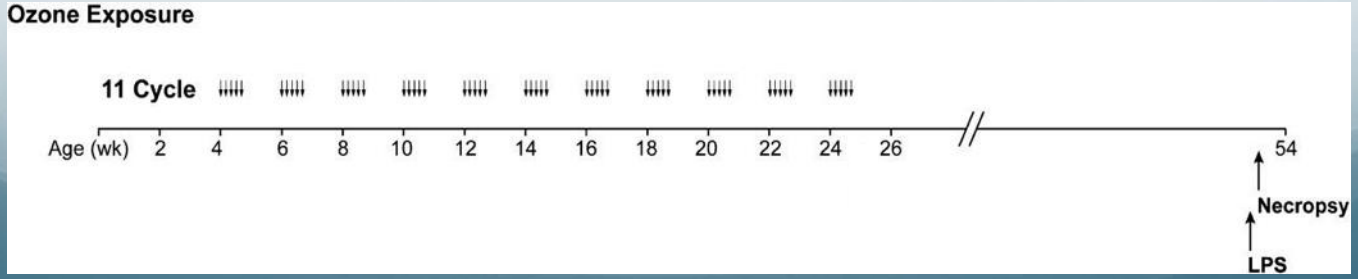
- LPS challenge = ↑BAL cells, ↑PMN
- LPS challenge in animals with prior ozone = ↓BAL cells, ↓PMN



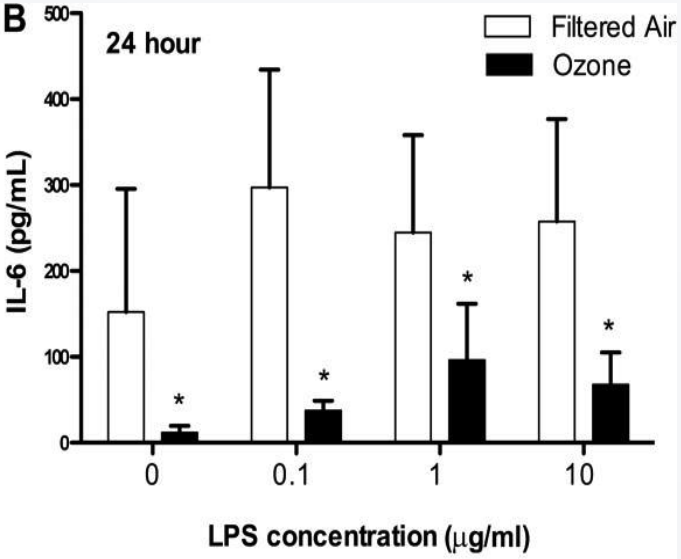
Persistent Effect of Ozone: Peripheral Blood (In Vivo LPS)

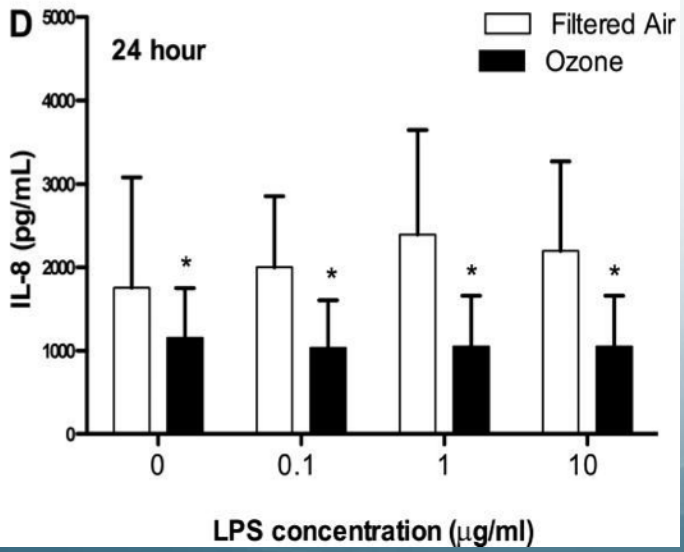


- LPS challenge = ↑ WBC ↑PMN
- LPS challenge in animals with prior ozone= Variable



Persistent Effect of Ozone: Peripheral Blood (In Vitro LPS)





Peripheral Blood from Ozone Exposed Animals : LPS Challenge *In Vitro*

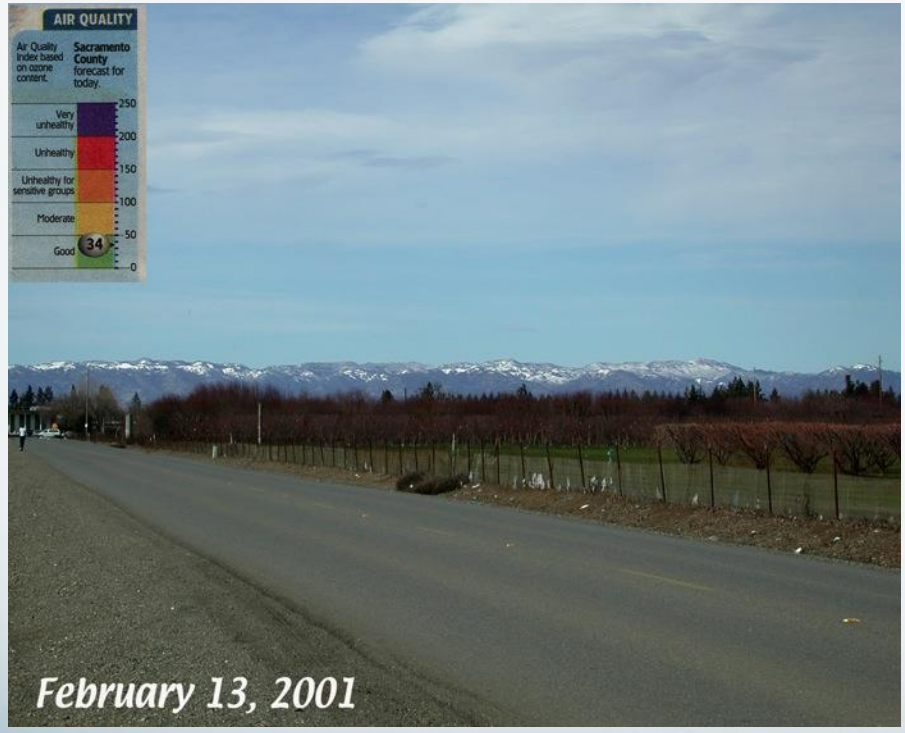
Filtered air = ↑ IL-6 ↑IL-8

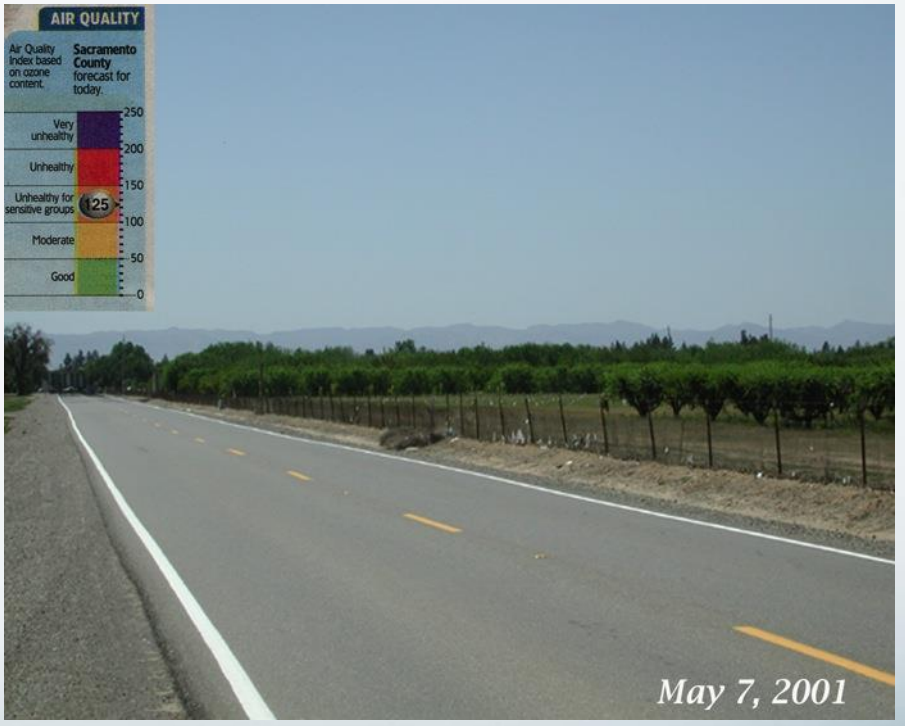
Ozone = ↓IL-6 ↓IL-8

Summary

- Postnatal ozone exposure results in a persistent attenuation of the inflammatory response to LPS
- Both lung and systemic (peripheral blood) compartments are affected by prior exposure to ozone
- TLR4 signaling pathway is likely to be an important target for environmental persistence, but may have some overlap with other TLR pathways

CNPRC Monkey Model of Ambient Air Pollutant Exposure





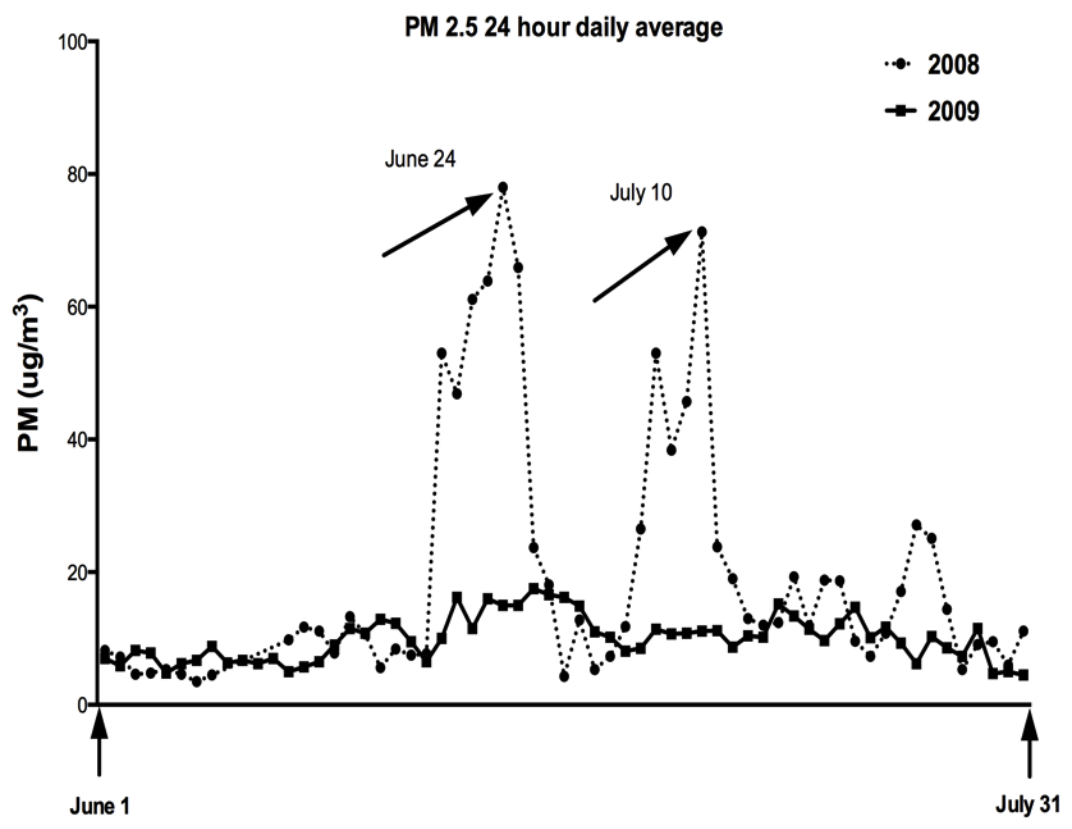
A short bike ride to the Primate Center…

Spring is Peak Birthing Season at the CNPRC

Summer 2008 California Wildfires

On June 21-22 2008, a dry low pressure system produced dry lightning which ignited approximately 2000 forest fires across Northern California (Humboldt County)

Summer 2008 California Wildfires: PM 2.5

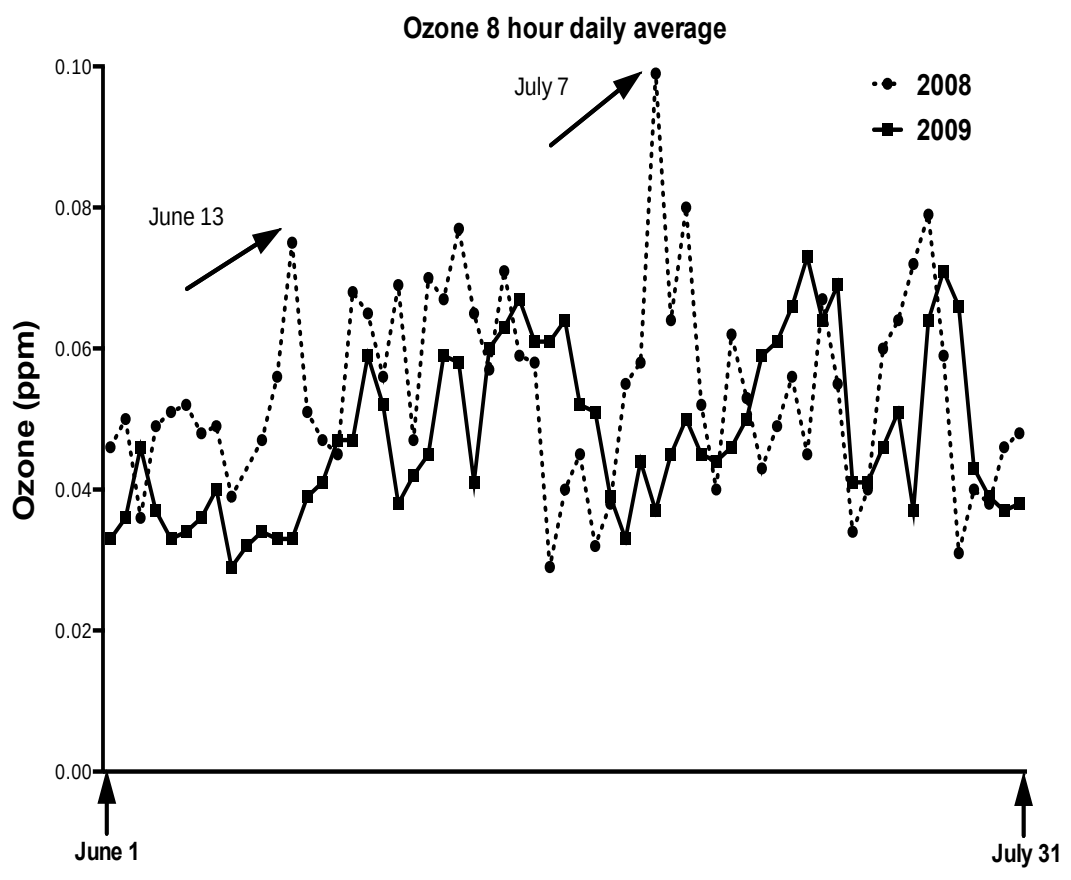


- From June 21-27 much of Northern California was covered in a thick blanket of smoke
- Air quality in the Sacramento valley improved after June 28 due to onshore winds and Delta breeze
- With calm winds, hazy conditions returned on July 7

Daily 24 hour average concentration of PM 2.5 from June 1-July 31 on UC Davis campus

NAAQS standard 35 ug/m^3 per 24 hour period

Summer 2008 California Wildfires: Ozone



Daily 8 hour average concentration of ozone from June 1-July 31 on UC Davis campus

June 13 and July 7 exceed the current NAAQS standard of 0.075 ppm/8 hours

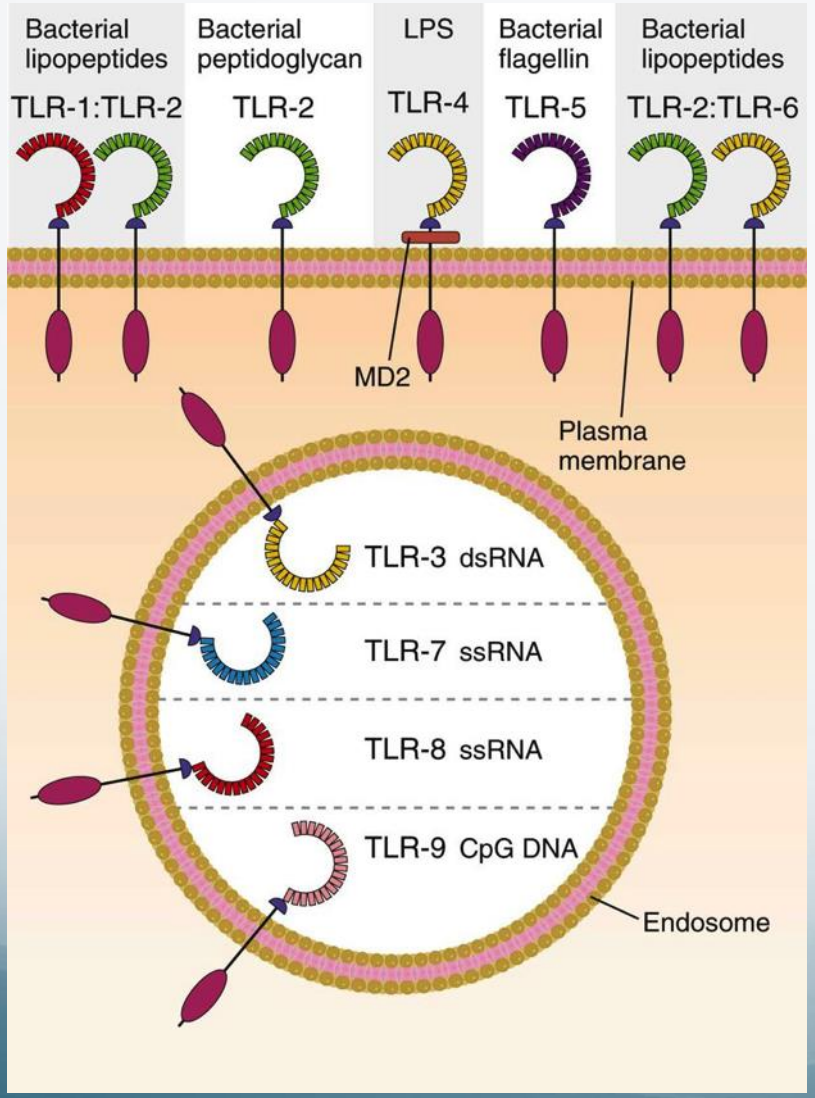
Summer 2008 California Wildfires: Persistent Effects of Wildfire Smoke Exposures

- Can we detect persistent immune effects under ambient exposure conditions in animals that were housed outdoors as infants?
- Can we detect persistent lung function effects under ambient exposure conditions in animals that were housed outdoors as infants?

Study Design

- Select animals from outdoor colony born in spring of 2008 (1-3 months of age, males n=25, females n=25)
- Select animals from outdoor colony born in spring of 2009 (1-3 months of age, males n=24, females n=25)
- Collect peripheral blood and measure pulmonary physiology

Study Methods



- LPS ➔TLR4 ➔ IL-6, IL-8
- Flagellin ➔TLR5➔ IL-6, IL-8
- Compare measures of innate immunity ligand stimulation in peripheral blood samples with pulmonary function measures

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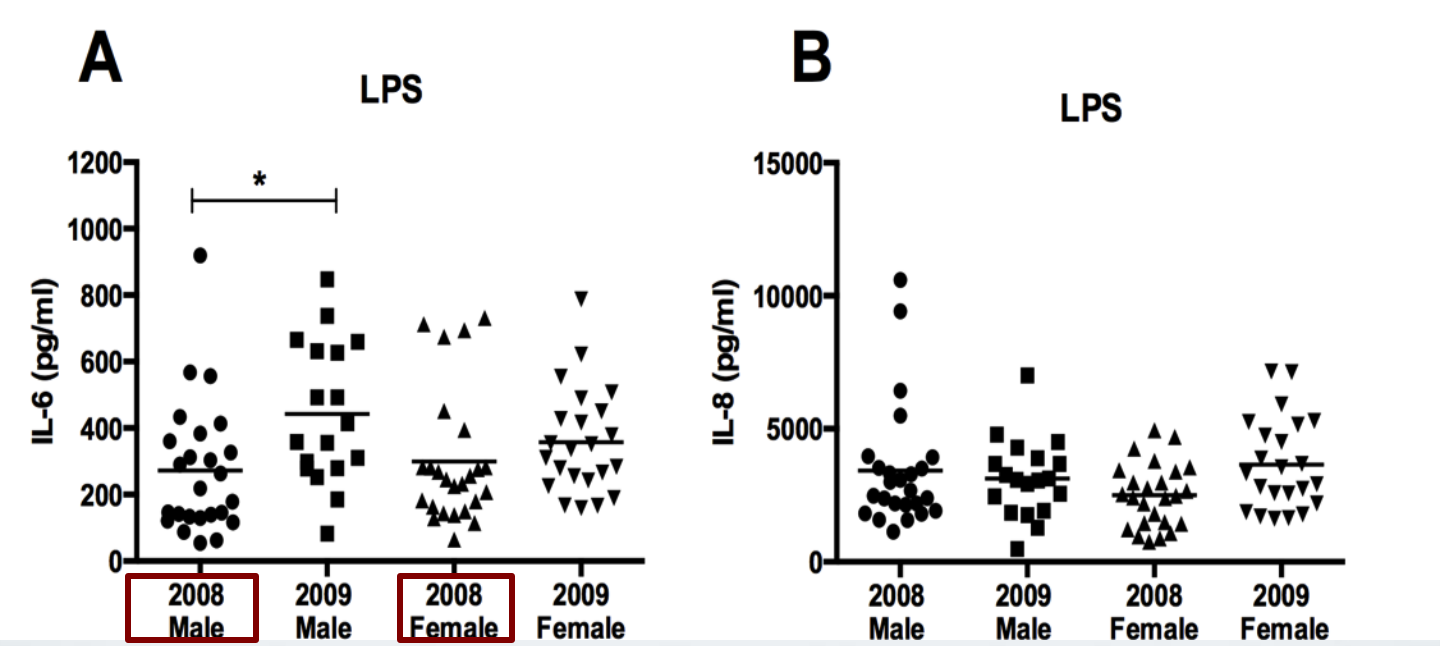
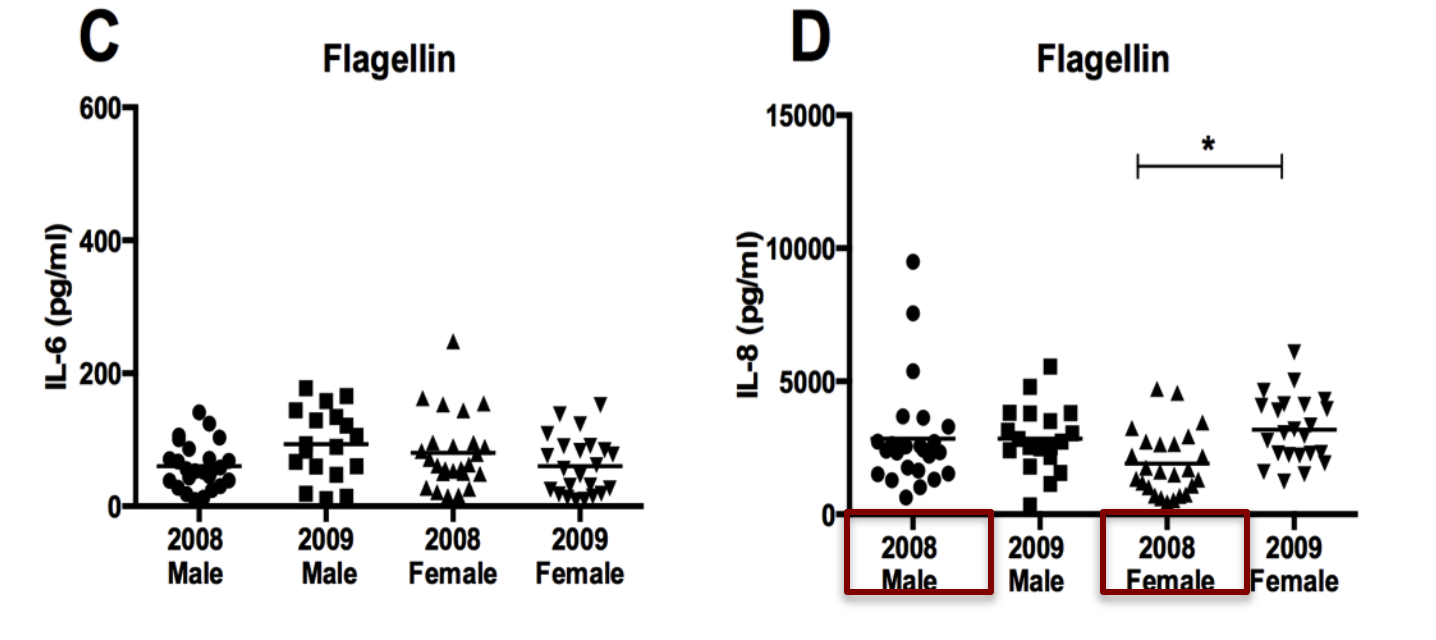
Persistent Effects of Wildfire Smoke Exposures: LPS Stimulation of Peripheral Blood Cells from 3 Year Old Animals



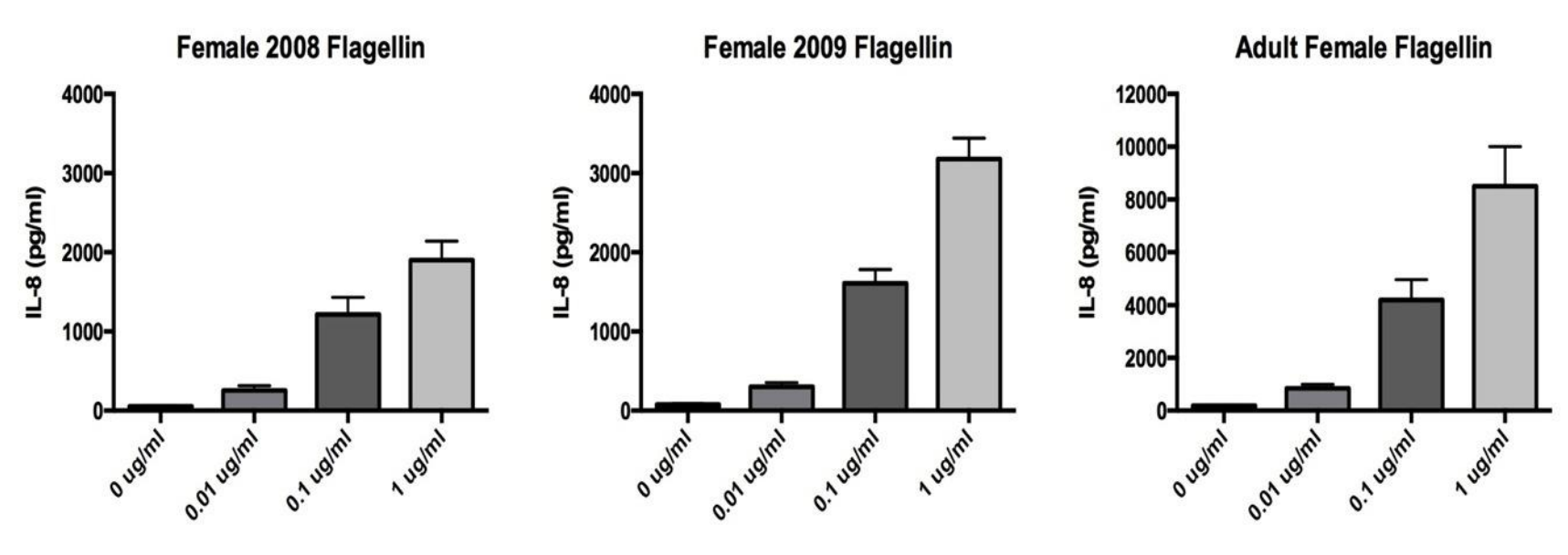
Wildfire Smoke = ↓ IL-6

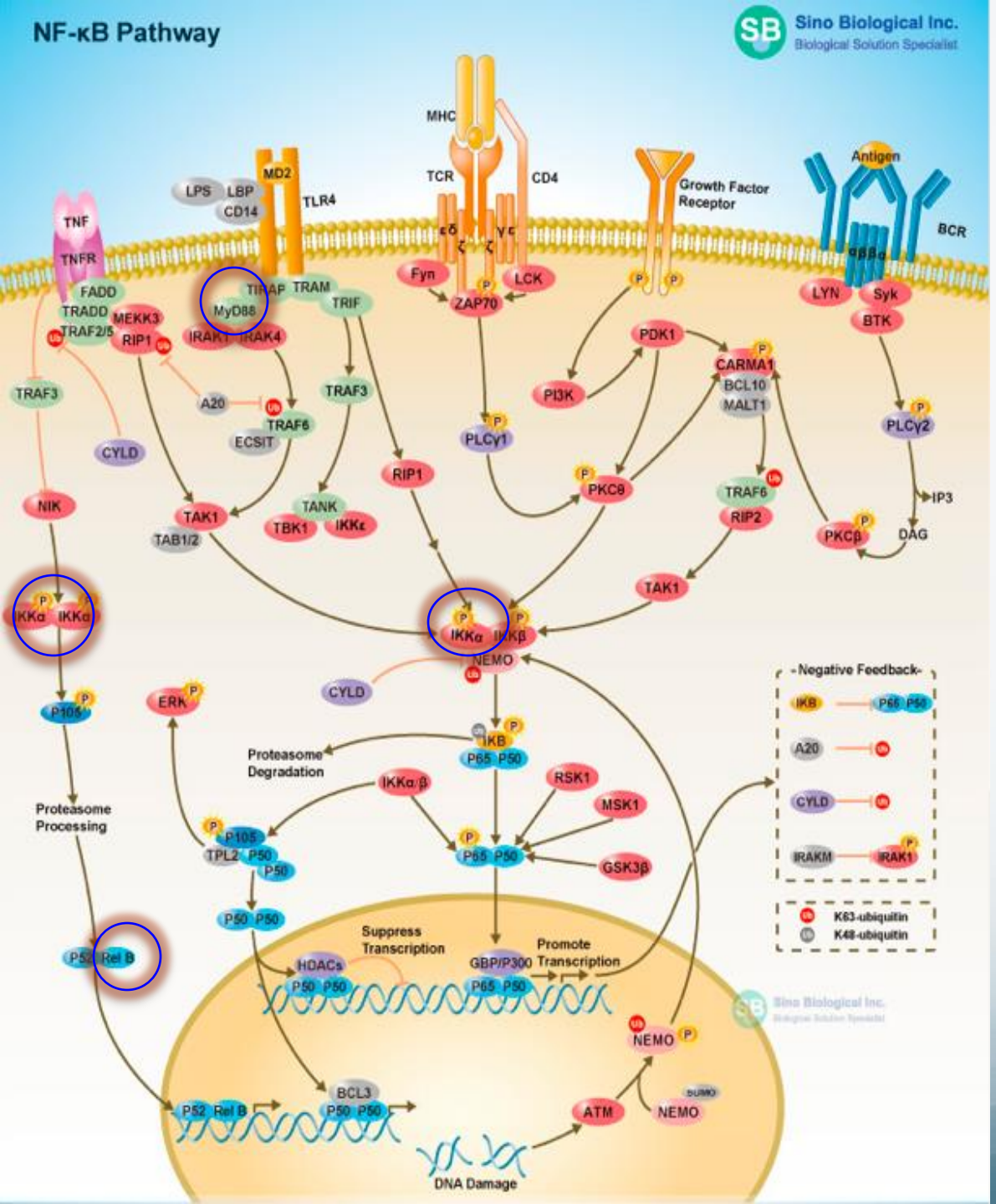
Persistent Effects of Wildfire Smoke Exposures: Flagellin Stimulation of Peripheral Blood Cells from 3 Year Old Animals



Wildfire Smoke = ↓ IL-8

Persistent Effects of Wildfire Smoke Exposures: Comparison of 3 Year Old Animals with Adult Animals





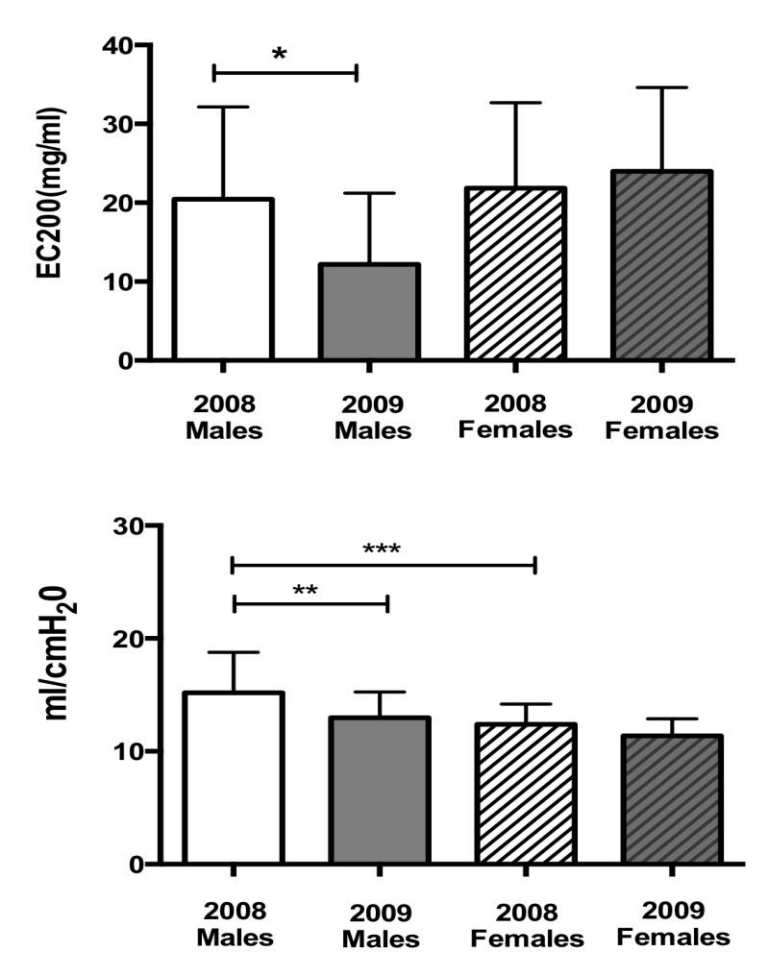
Persistent Effects of Wildfire Smoke Exposures:

Changes in Toll-like Receptor Pathway Gene Expression

Blood samples from female monkeys born in 2008 show:

- ↑ c-Rel, Rel B
- ↑ MyD88 (LPS)
- ↑ IKK alpha (Flagellin)

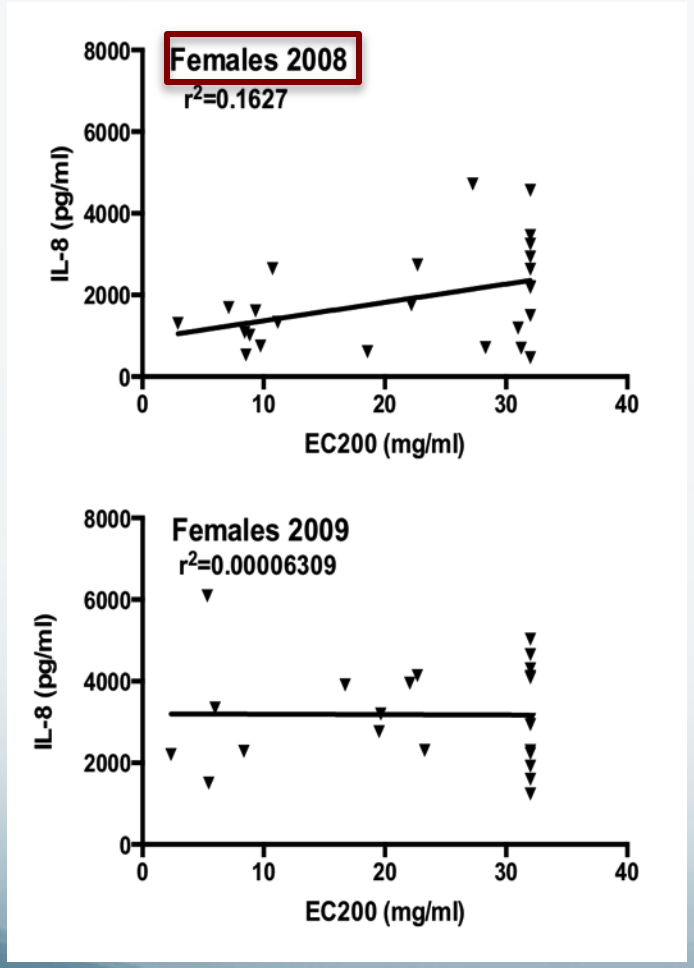
Persistent Effects of Wildfire Smoke Exposures: Airways Responsiveness and Compliance in 3 Year Old Animals



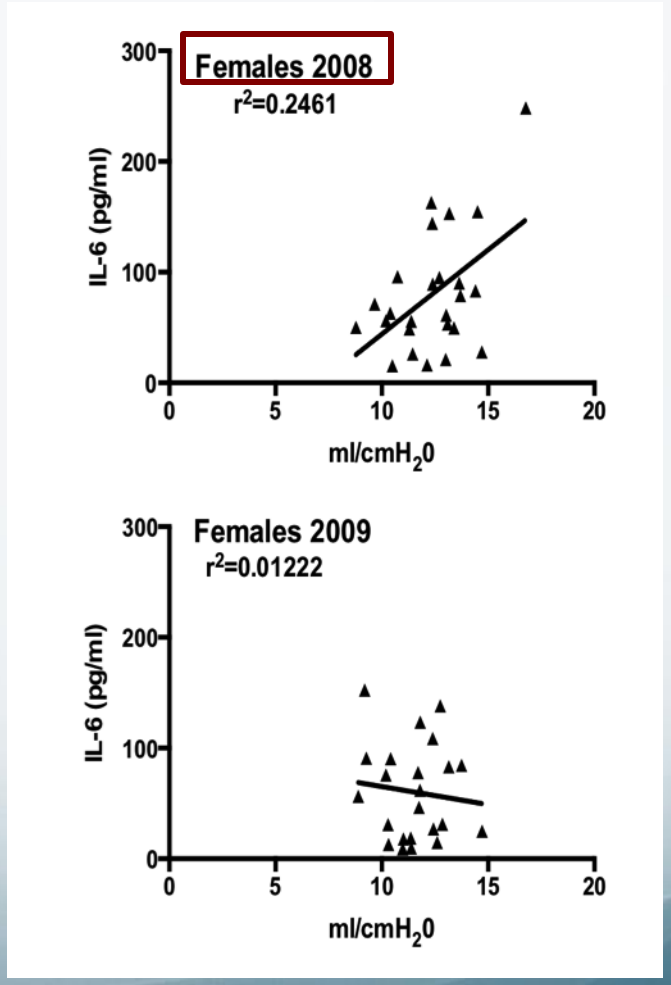
Airways Responsiveness

Compliance

Correlation of Flagellin Induced Cytokine Synthesis with Lung Function



Airways Responsiveness



Compliance

Summary

CNPRC monkeys exposed to ambient wildfire smoke at infancy:

- exhibit persistent down regulation of LPS and flagellin-induced cytokine responses in peripheral blood cell cultures
- show gender dependent effects of exposure on parameters of innate immunity and lung function
- demonstrate a persistent change in molecular programming of peripheral blood cells

Conclusions

Development

Environment

Effect of Early Life Exposures on Innate Immunity and Lung Function

Respiratory Disease Center

- Opening February 27, 2014
- 19,000 sq ft
- Inhalation exposure facility
- Pulmonary function laboratory
- Open bay laboratory space
- Office/conference space

QUESTIONS?