Persistent Immune Effects of Wildfire PM Exposure During Childhood Development

Lisa A. Miller, Ph.D.
Associate Professor, UC Davis School of Veterinary Medicine
Associate Director of Research, CNPRC
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
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
- 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
Overall lung architecture of nonhuman primates is most similar to human (monopodial vs. dichotomous growth)
Stages of Human Lung Development

- Embryonic Stage
- Pseudoglandular Stage
- Canalicular Stage
- Alveolar Stage
- Stage of Microvascular Maturation
- Normal Growth Period

Time:
- Weeks
- Months
- Years

Development Stages:
- Lung Development
- LUNG GROWTH
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

INSTRUCTION

Environment

Birth

1 Year

- Proliferation
- Differentiation
The Monkey as a Model for Early Childhood Development

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

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/m³ 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**
- 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
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 $\Rightarrow$ 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

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?