Systemic vascular effects caused by inhaled toxicants, especially particulate matter

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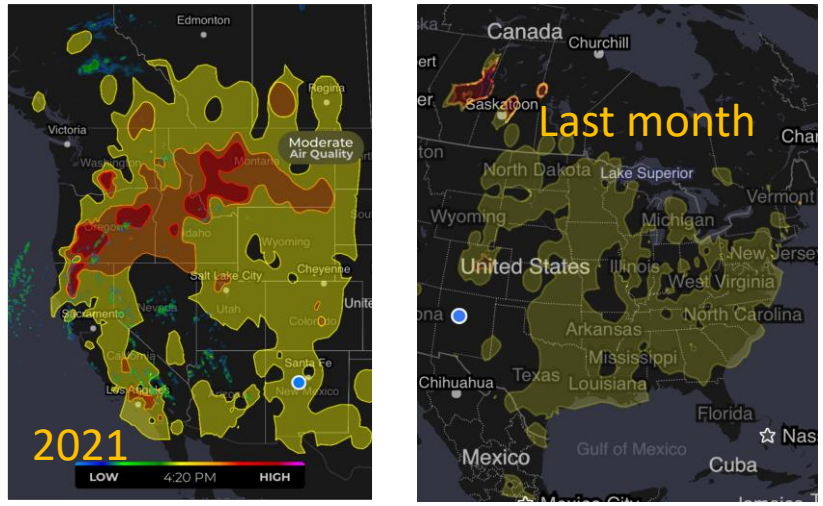
COLLEGE OF PHARMACY

Many Health Consequences of Air Pollution Exposure Occur Beyond the Lungs

- **Air pollution exposure has been associated with:**
  - Pulmonary Disease (NEJM 2015; 372:905-913)
  - Metabolic Disease (Circulation. 2009;119:538-546)
  - Maternal-fetal health effects (NTP, 2019)
  - **Cardiovascular Disease (JACC 2018, 72:2054-2070)**
  - **Neurological Disease (EHP 2016, 124:23–29)**
    - **Neurodegenerative and developmental**



MyRadar App

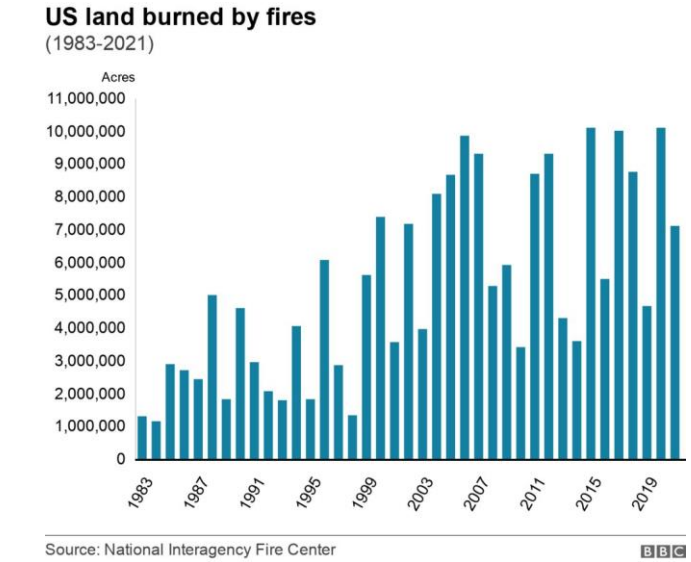
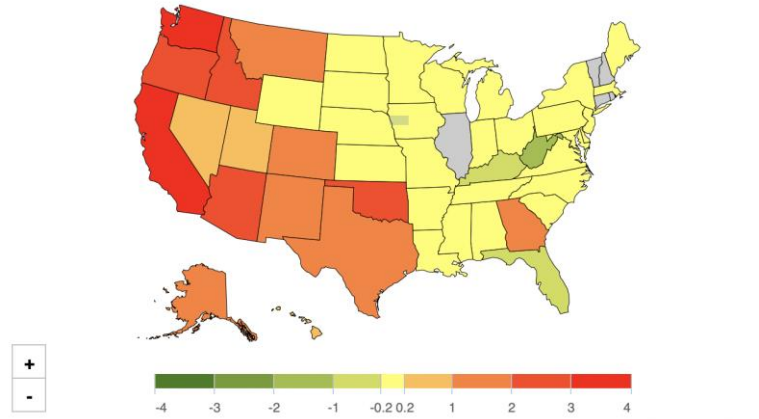
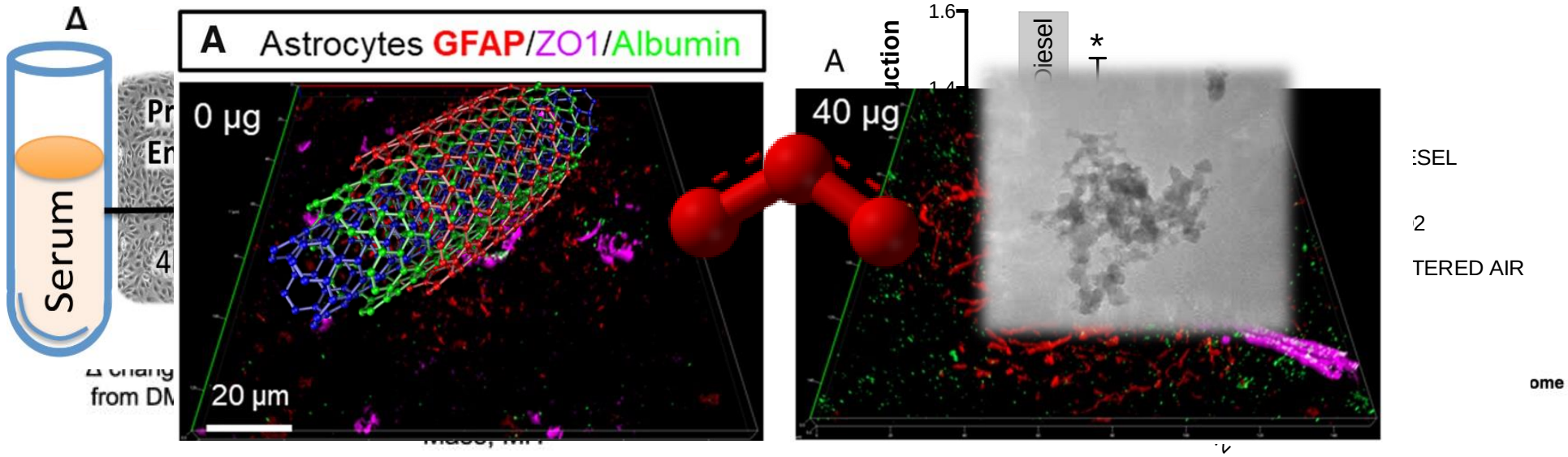


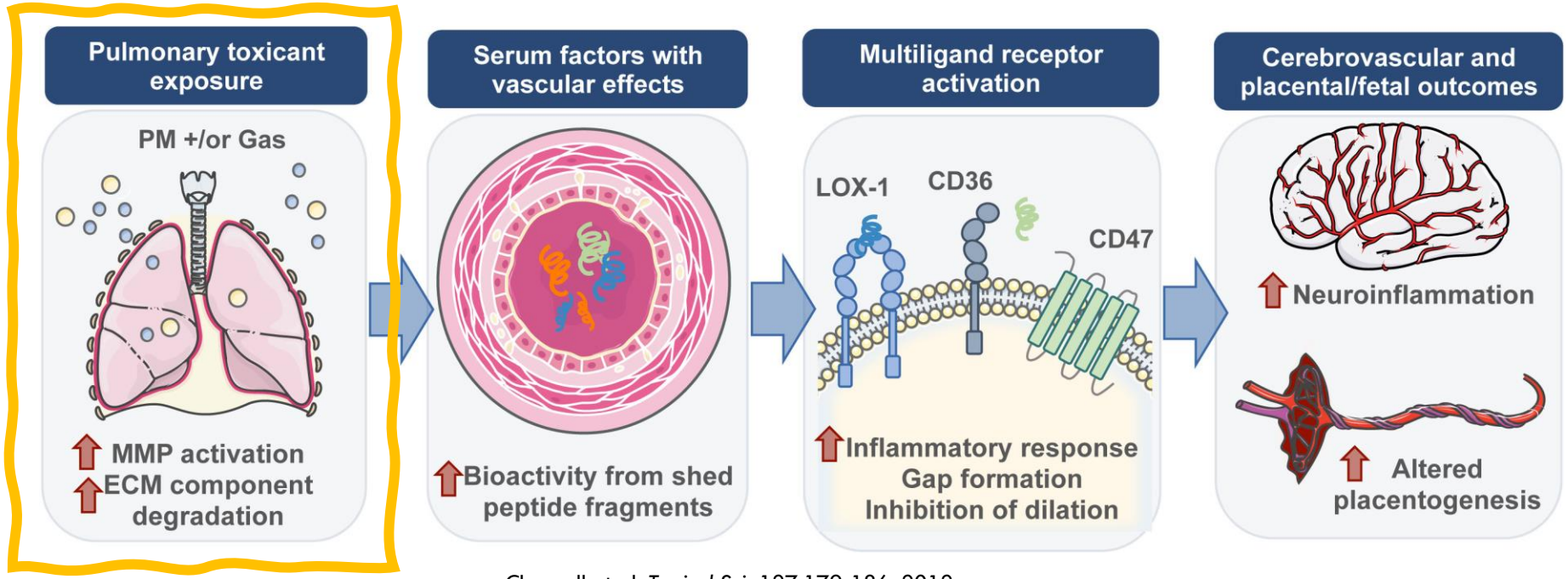
Figure 5. Change in Annual Burned Acreage by State Between 1984-2001 and 2002-2020



https://www.epa.gov/climate-indicators/climate-change-indicators-wildfires

General Concept for Pulmonary-Derived, Pathologic circulating factors



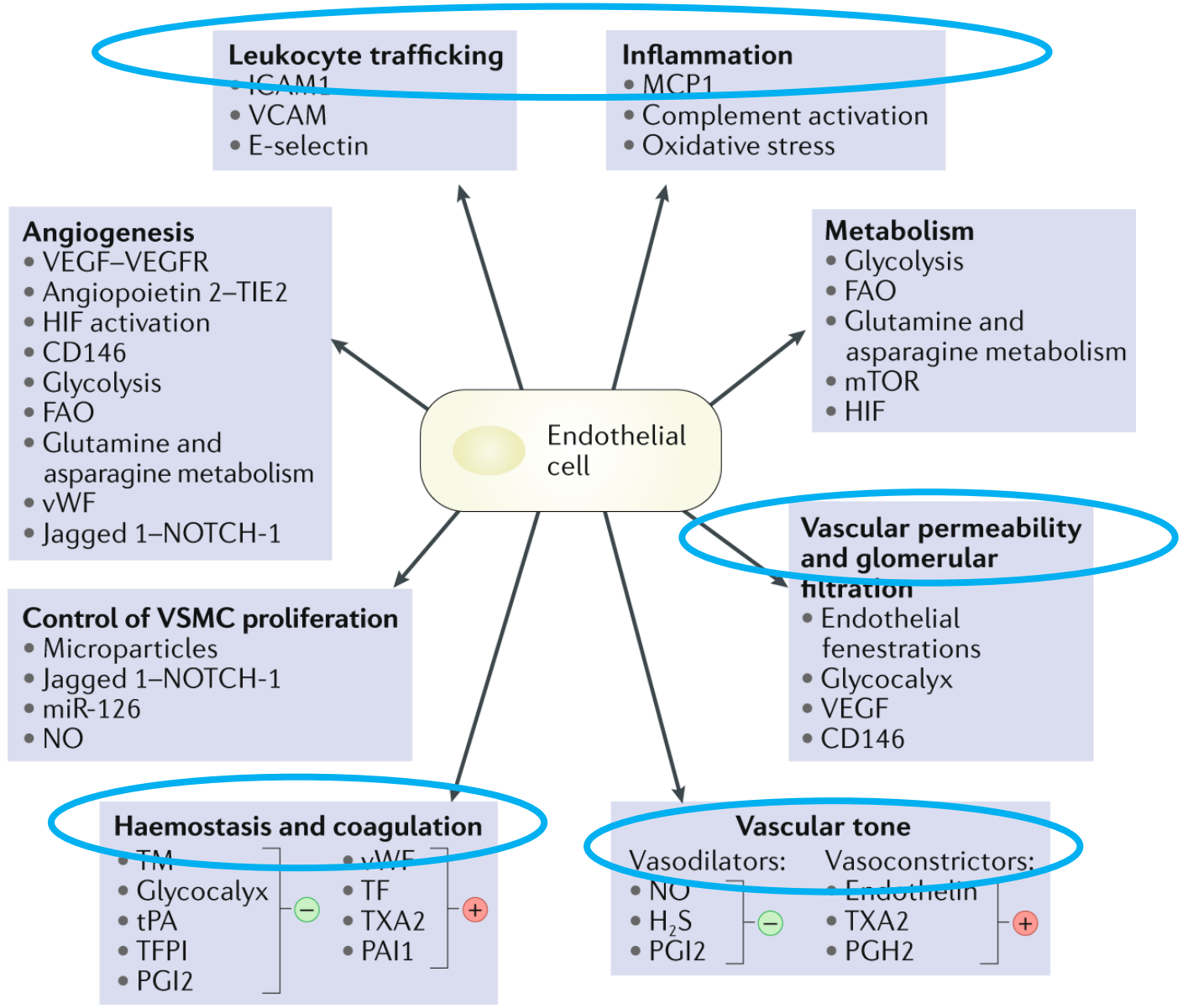


Channell et al. *Toxicol Sci*, 127:179-186, 2012.
Schisler et al. Inhal Toxicol, 27:272-280, 2015.

Mostovenko *et al.*, *ToxSci*, 182:107-119, 2021

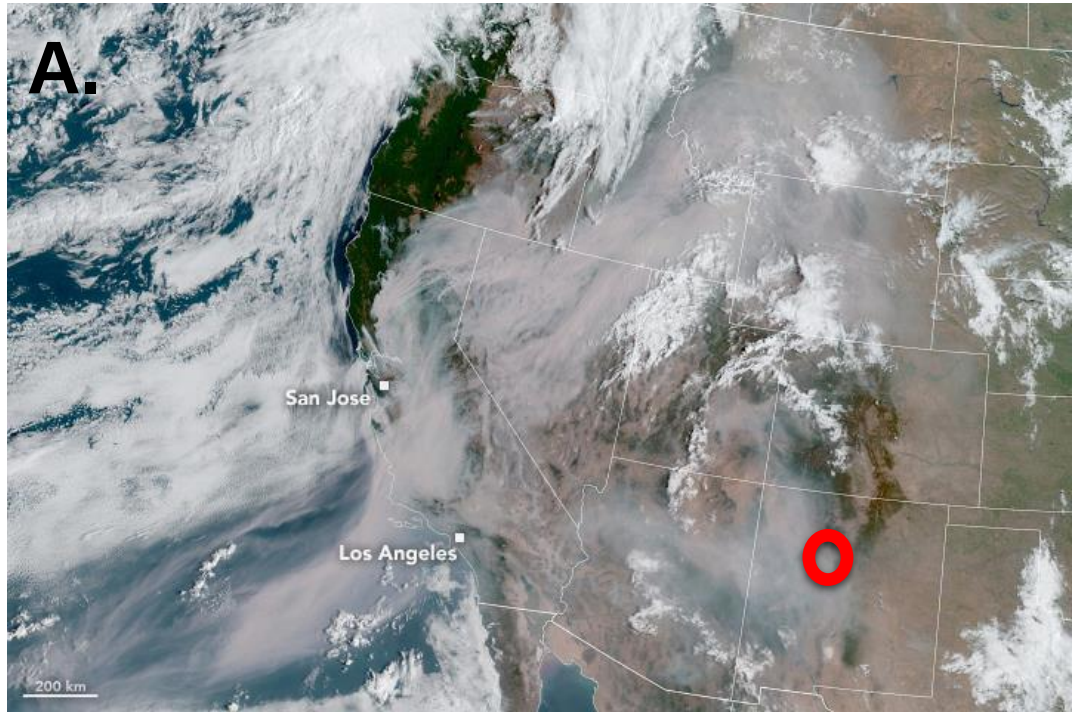
Implications of a "bioactive" circulation

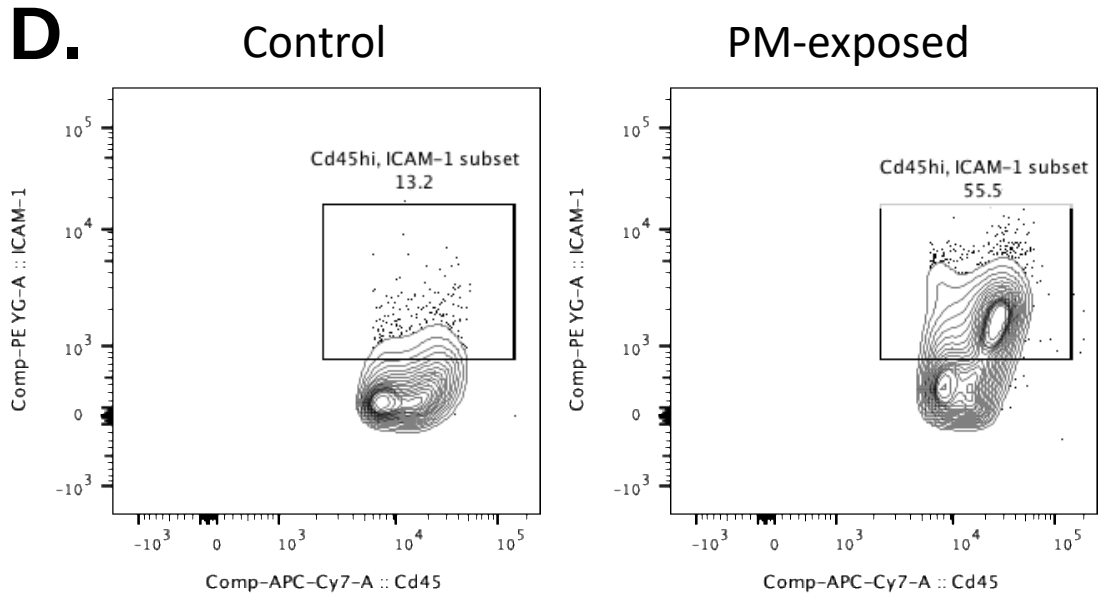
- The serum/plasma comes in contact with endothelial cells throughout the body
- Endothelial cells have a major homeostatic role for all organ systems
- Thus, endothelial cells are often involved in any disease pathogenesis



Jourde-Chiche et al. *Nature Reviews Nephrology* **15**:87–108, 2019

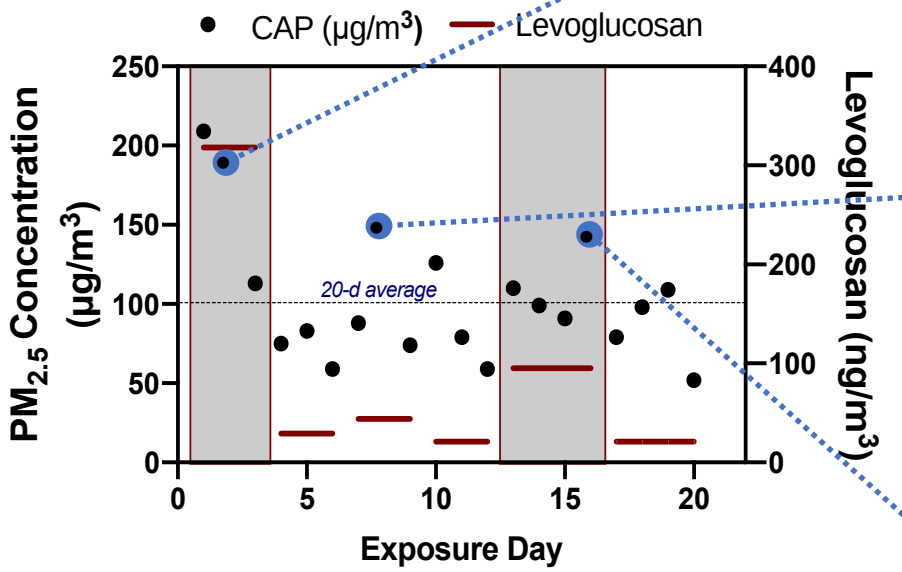
Study 1
CALIFORNIA FIRES, 2020

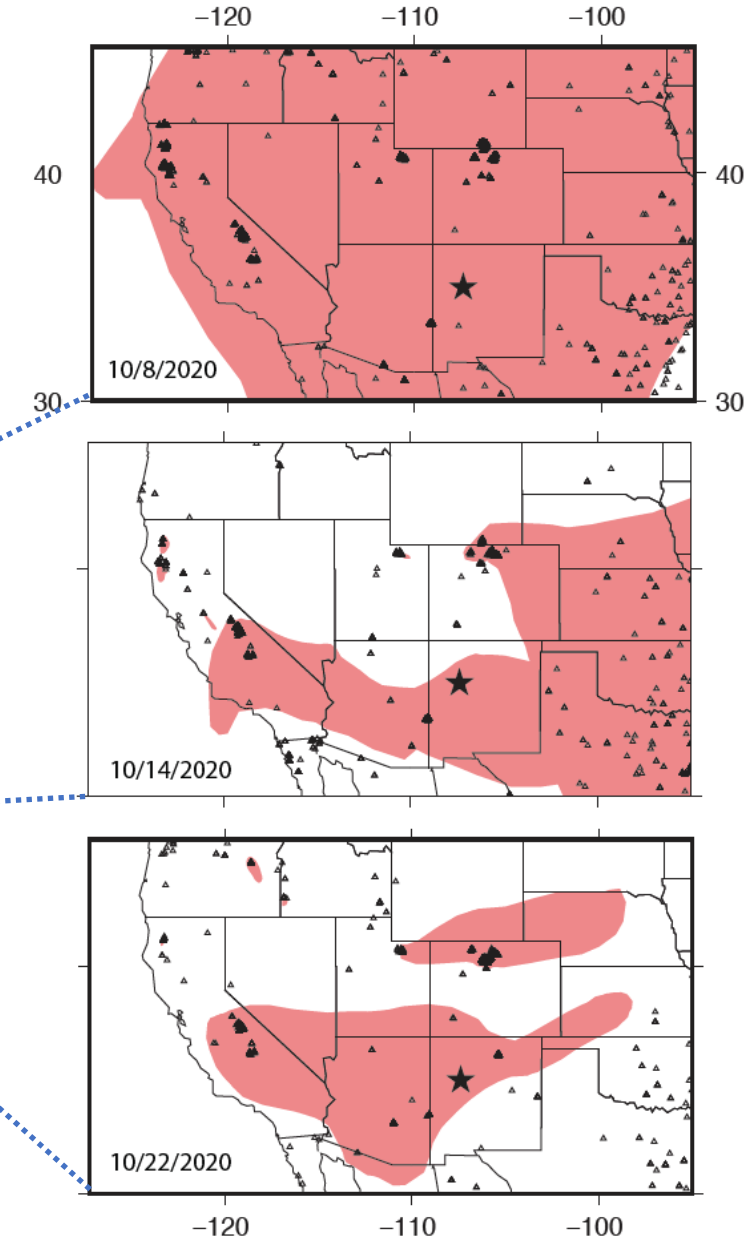




Real-World Exposure

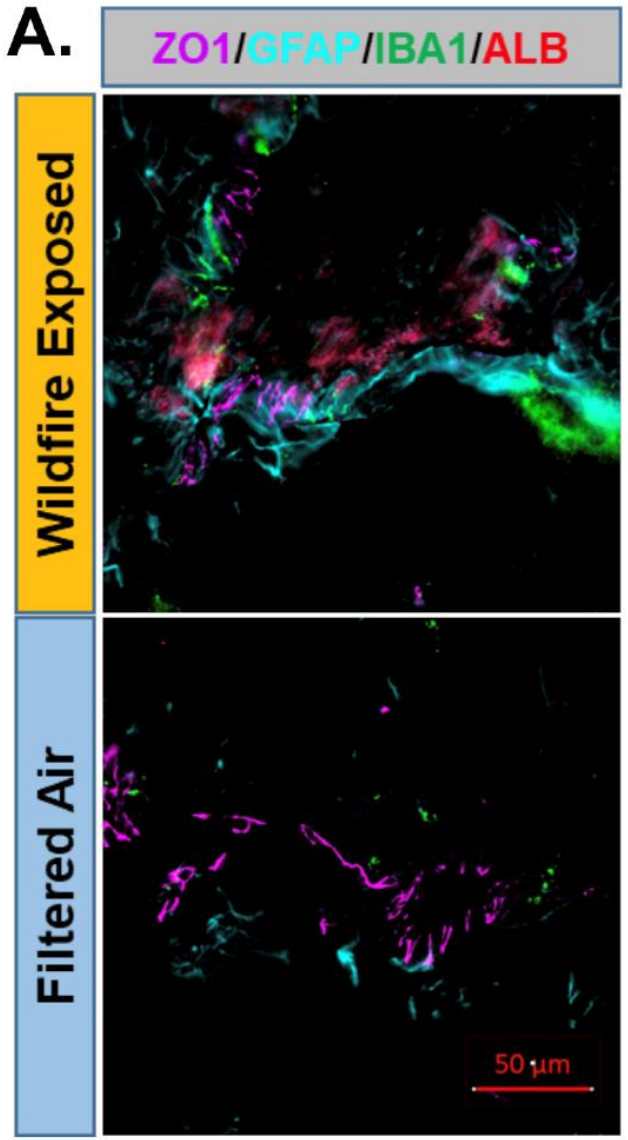
- Mobile laboratory located on the Pueblo of Laguna, NM (AirCARE1, on loan from Michigan State)
- 20 days, 4h/d
- C57BL/6 mice, male 8 wks
- Average for all 4h periods was **104 µg/m3**
- Meteorological conditions varied, but at least 5 days included a high component of wildfire smoke, assessed by levoglucosan and climate modeling

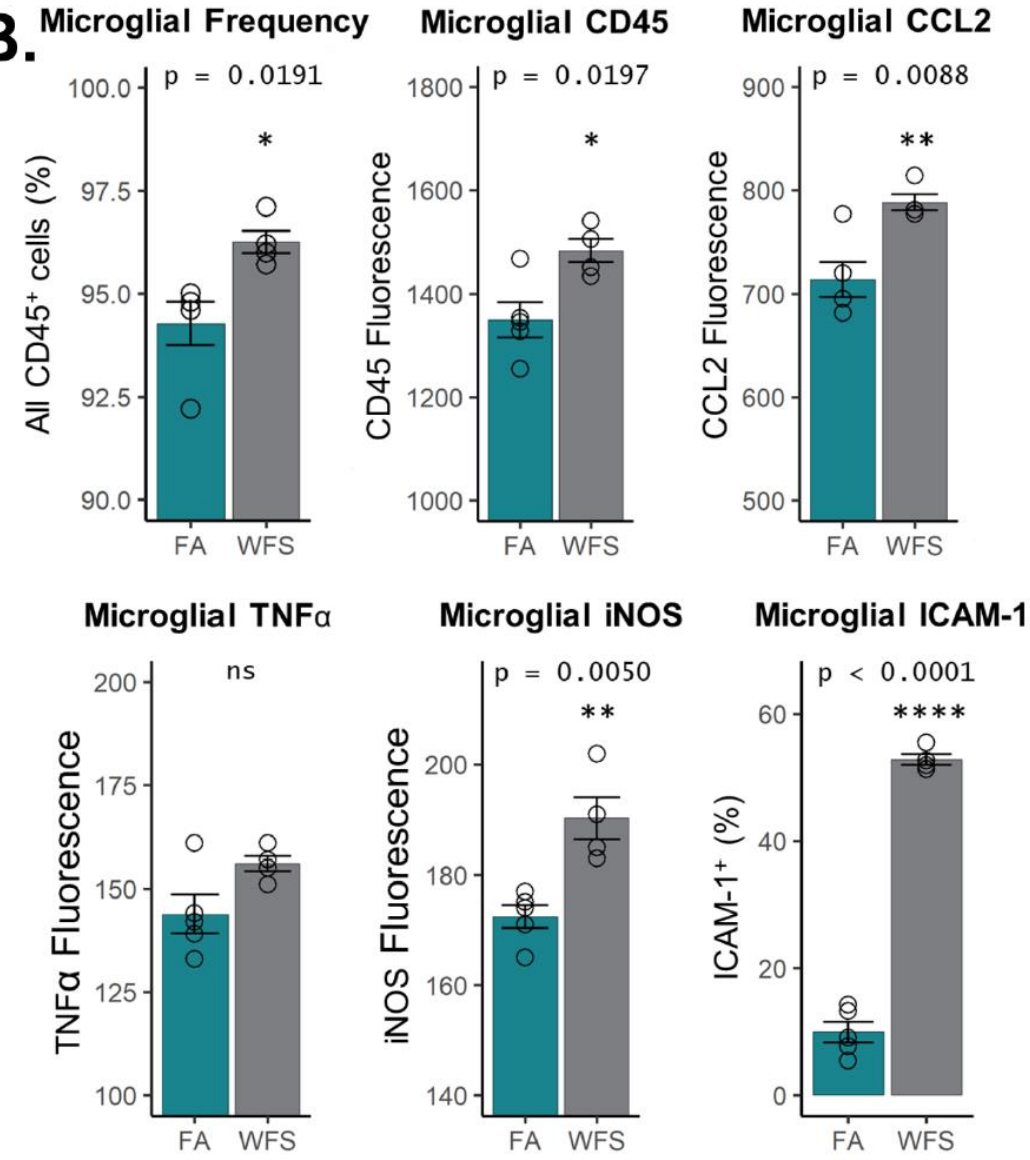




Scieszka et al., Toxicol Sci, 2020

Microglial Activation



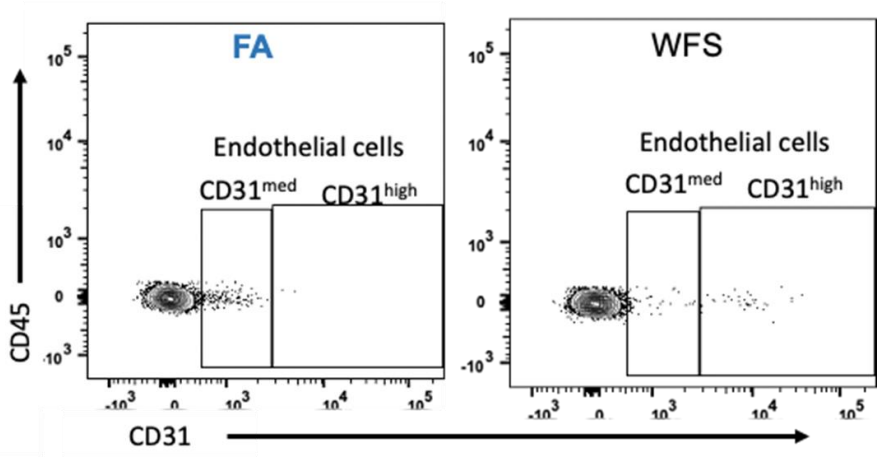


Dr. Shahani Noor

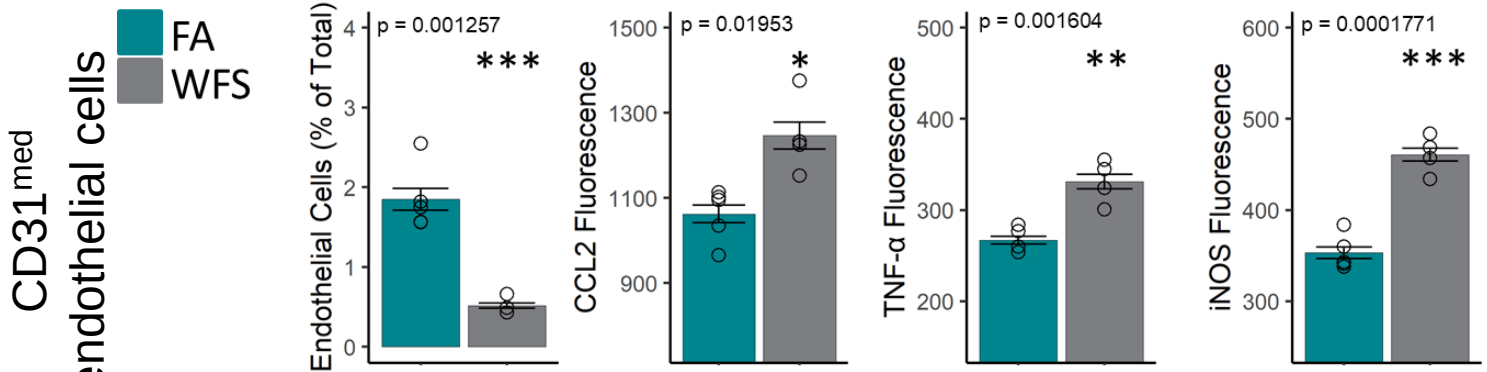
David Scieszka

Scieszka et al., Toxicol Sci, 2020

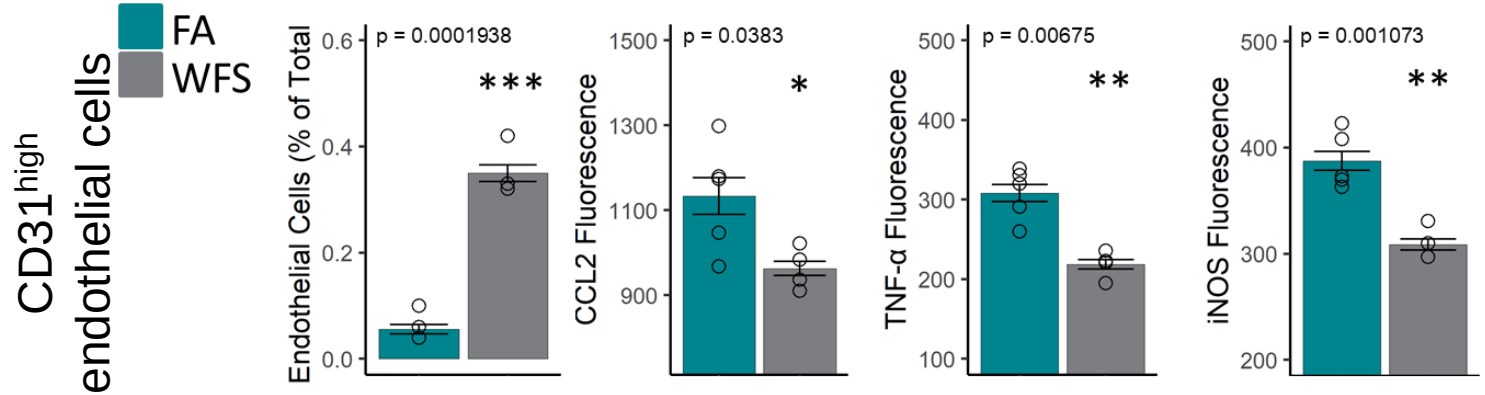
More anti-inflammatory endothelial cells after 20d woodsmoke exposure



Pro-inflammatory or arterial

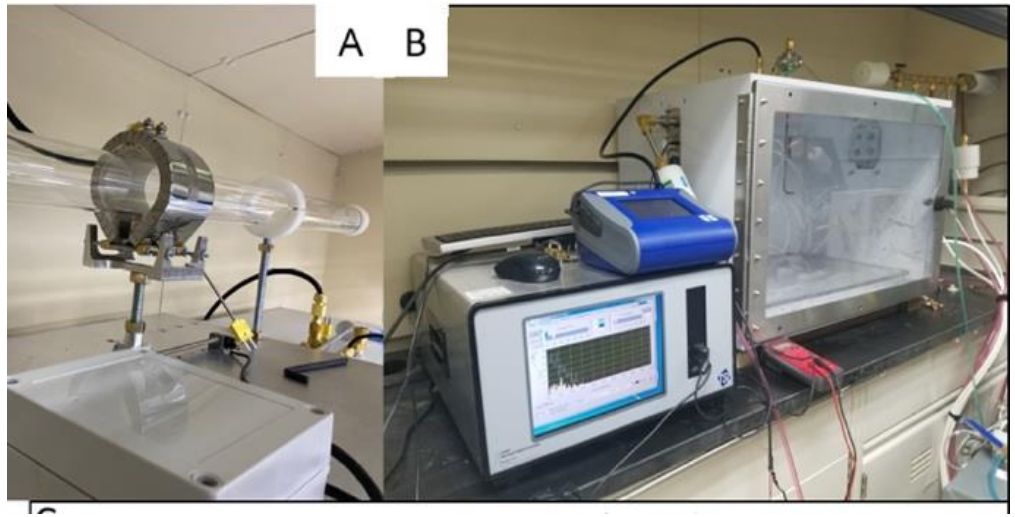


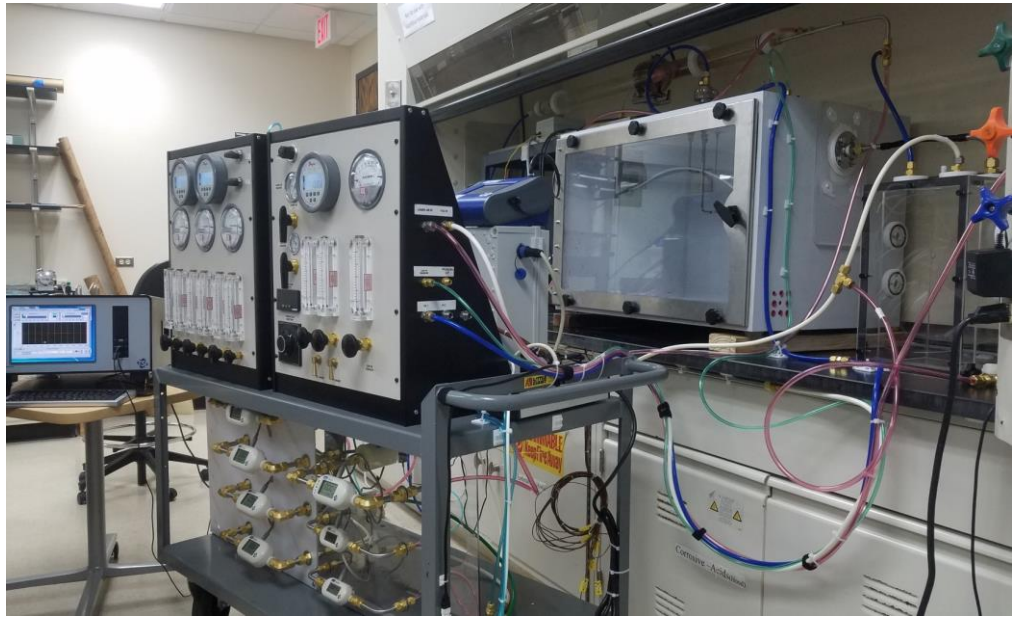
Anti-inflammatory or capillary/venous

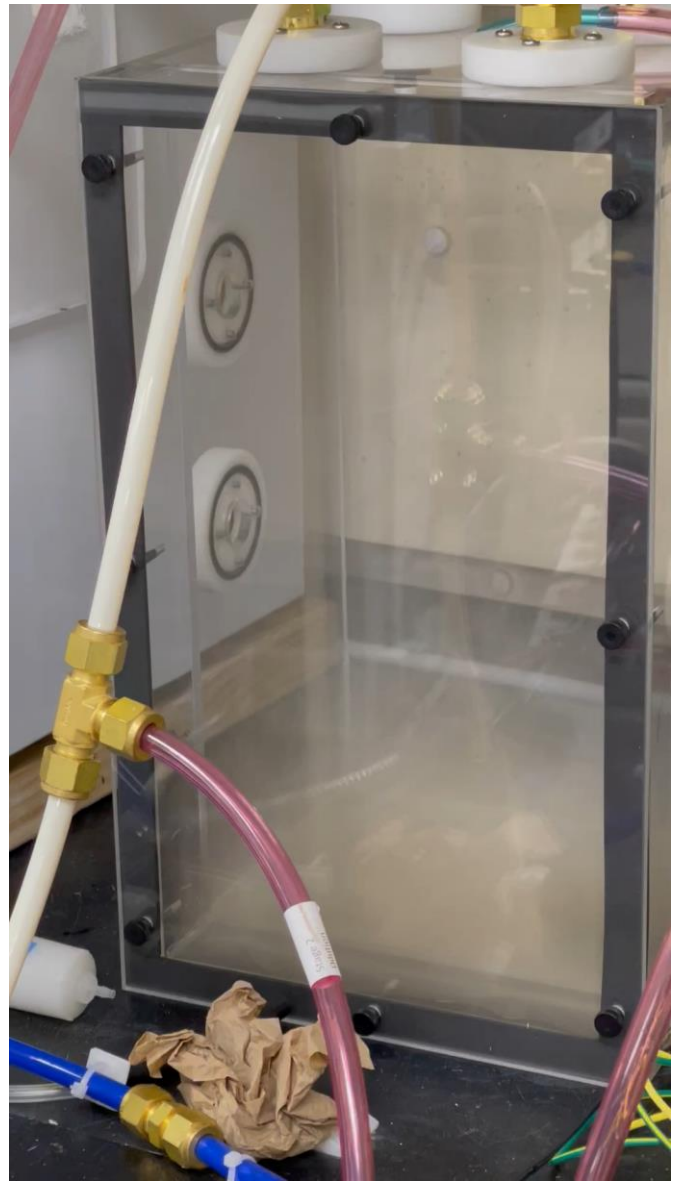


Scieszka et al., Toxicol Sci, 2020

Lab-Based Woodsmoke Mouse Exposure Chamber

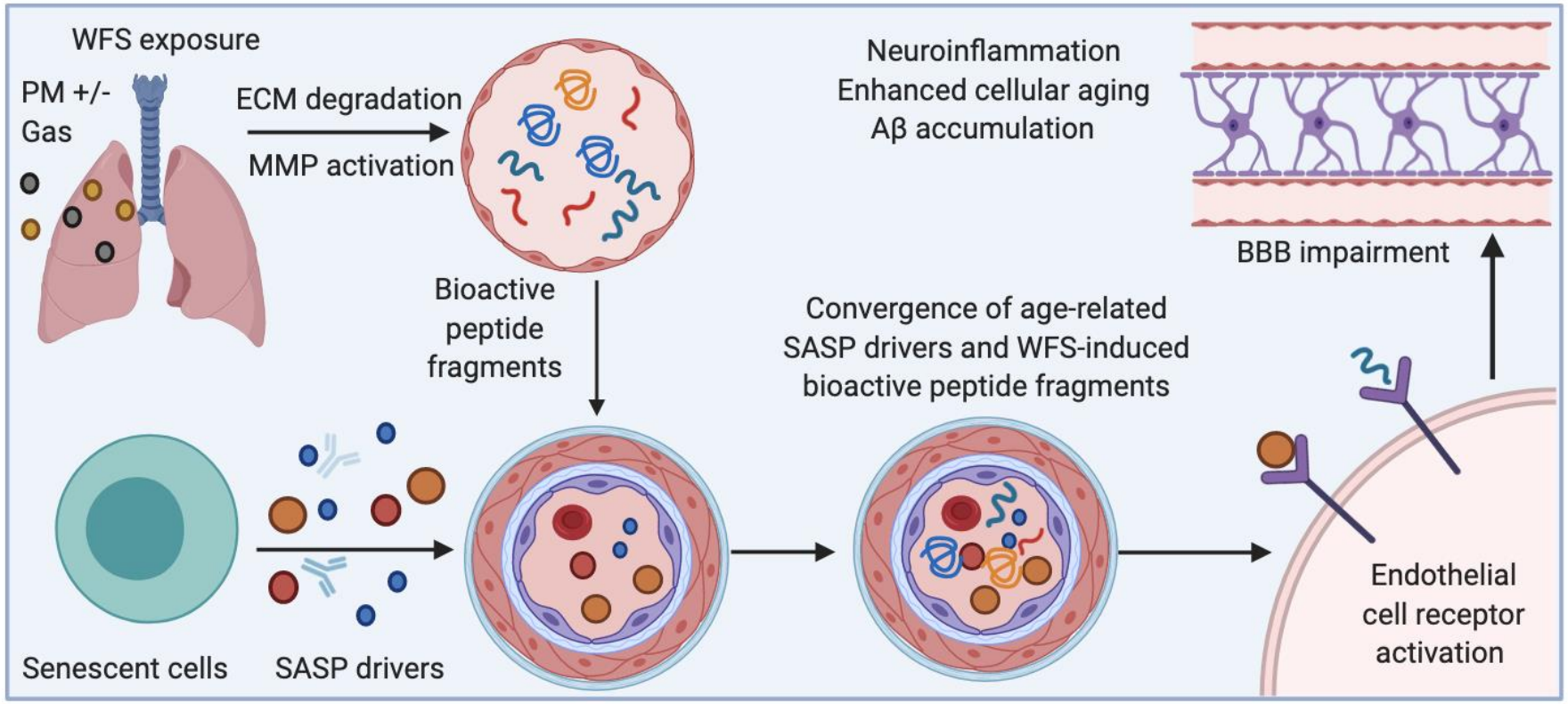


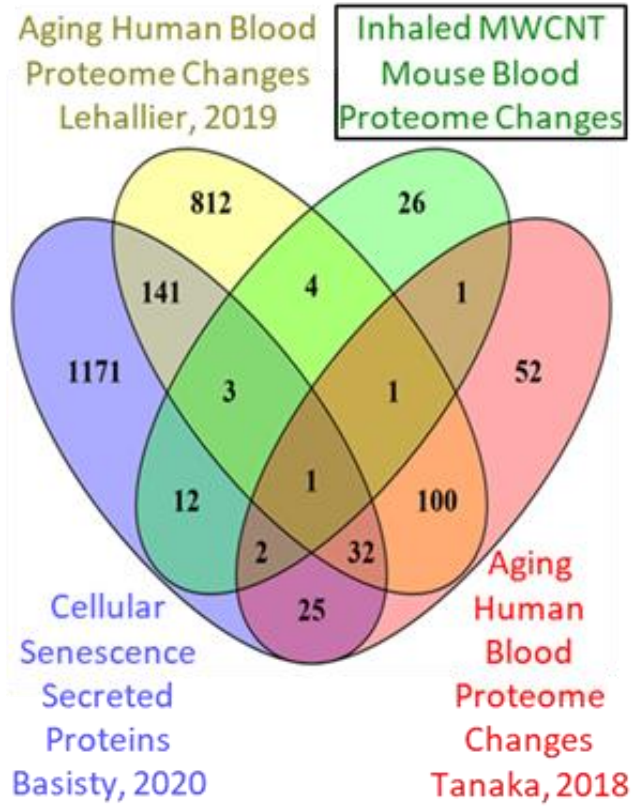




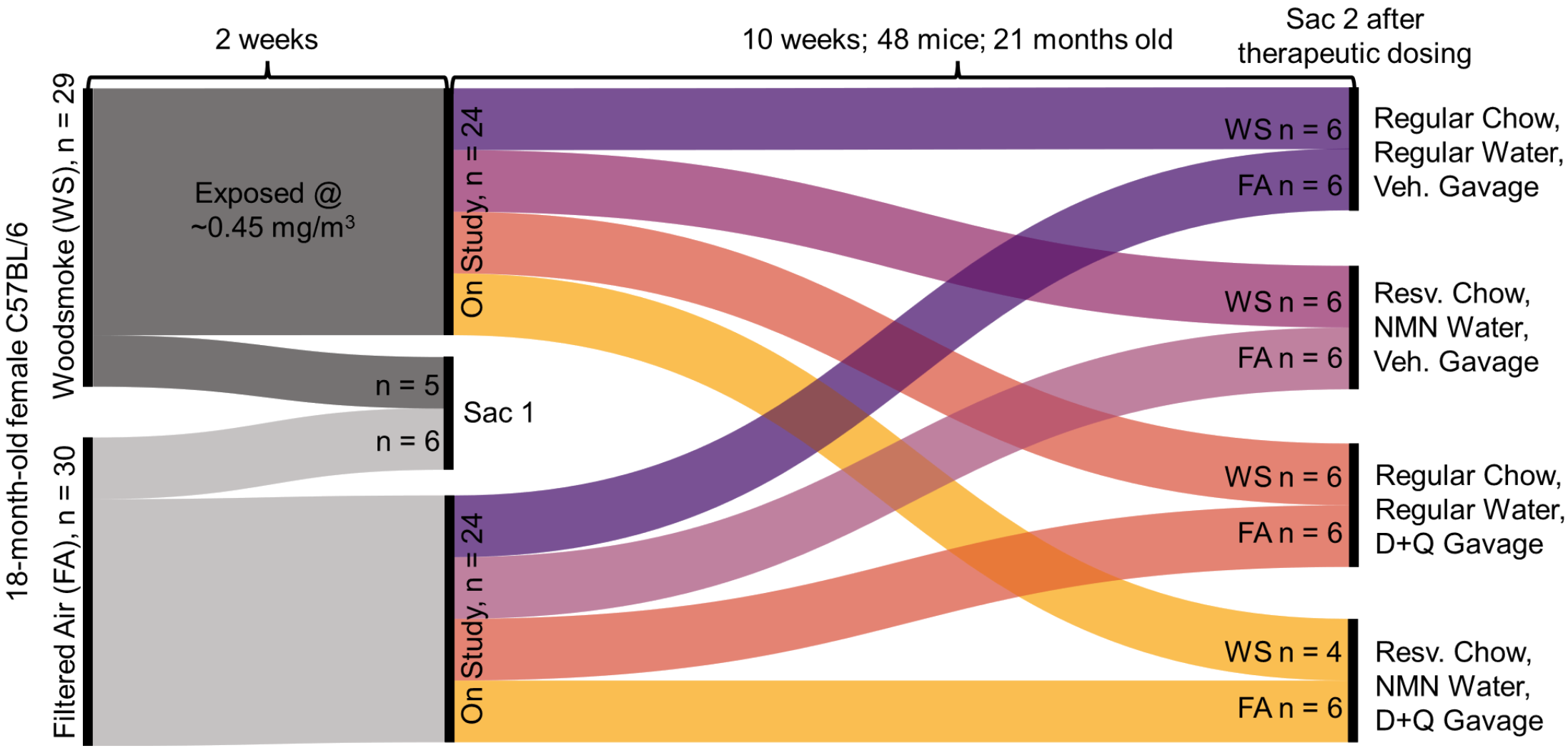
Ed Barr

Is Advanced Age a Risk Factor? Interactions between lung spillover and senescence-associated secretory proteins





Study 2
Metabolites & Aging



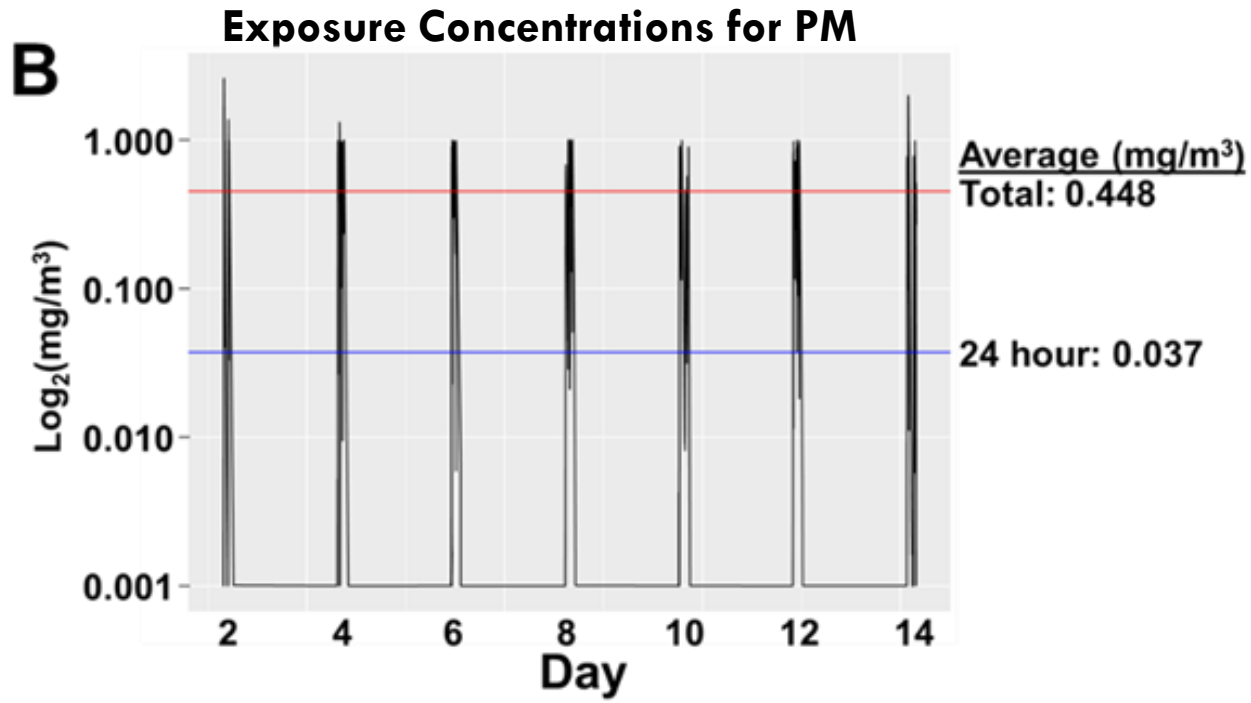
Drug groups:

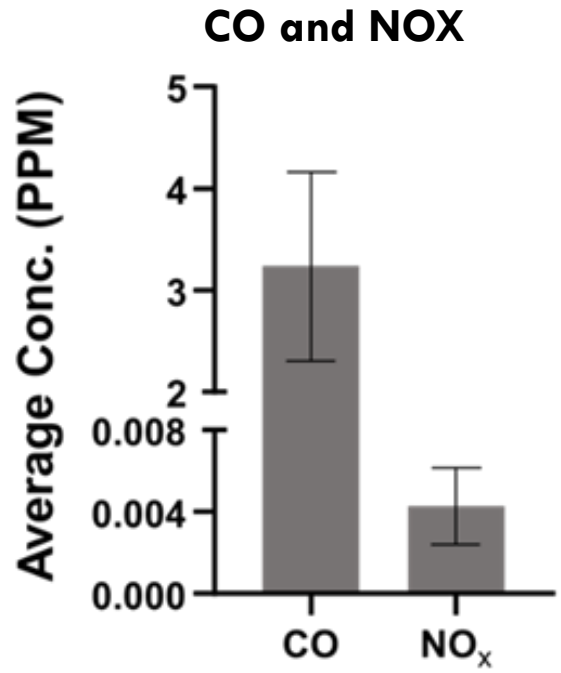
Veh = Vehicle

Resv + NMN = resveratrol + nicotinamide mononucleotide

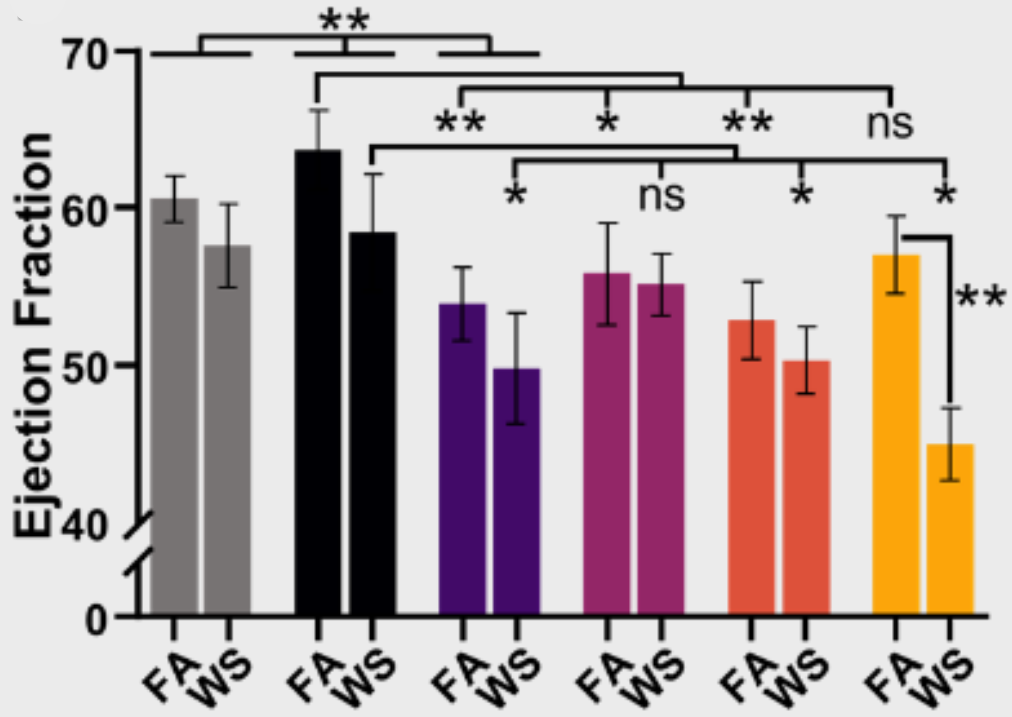
D+Q = senolytics (Dasatinib + Quercetin)

Exposure Concentrations: $PM_{2.5}$ and Gases



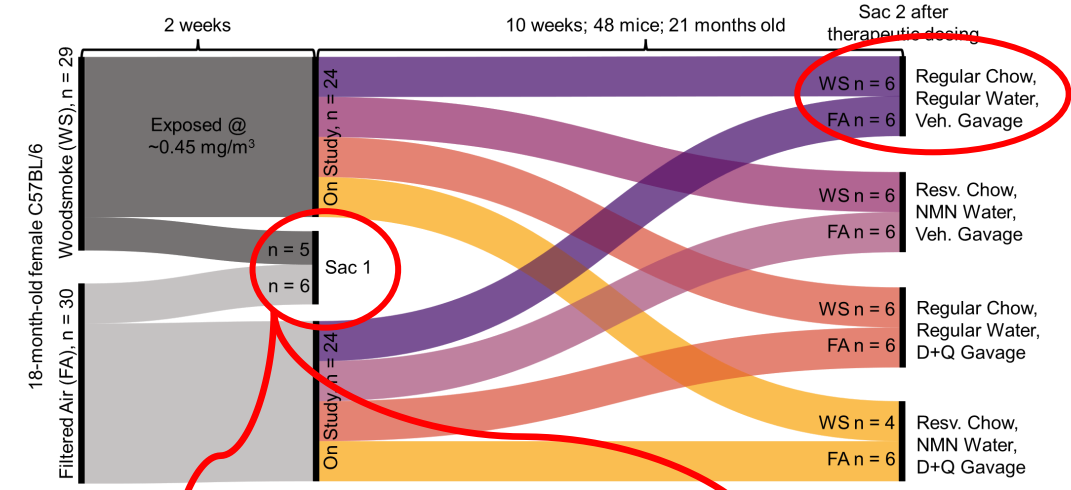


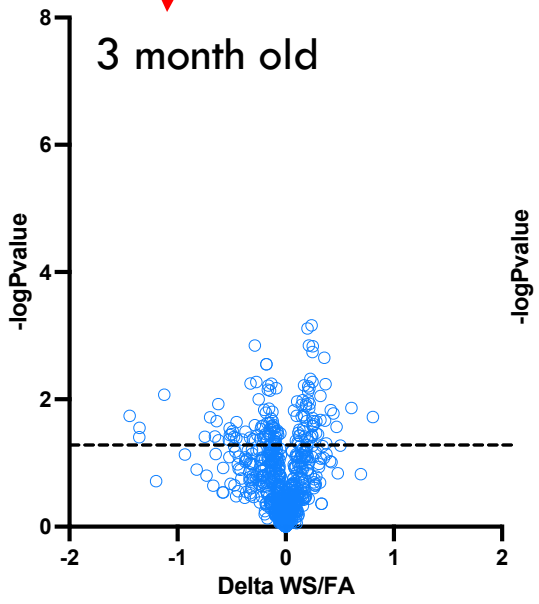
3 mo
18 mo
21 mo Veh
21 mo R+NMN
21 mo D+Q
21 mo RNDQ

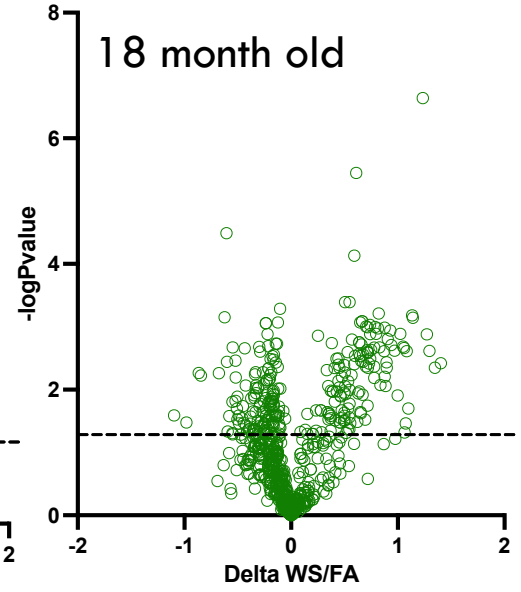


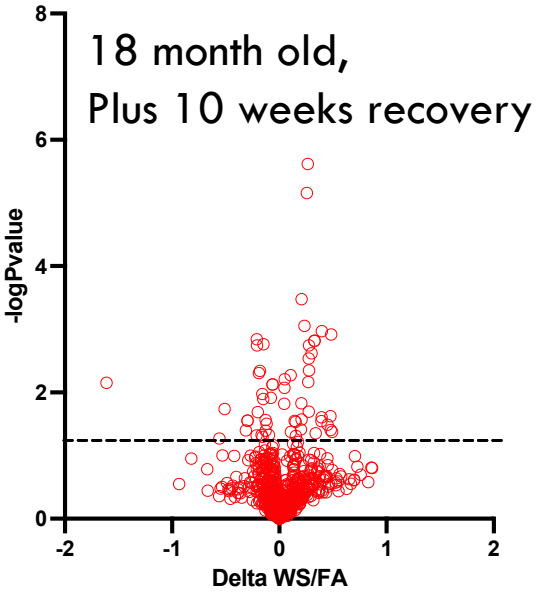
Cardiac Function is impacted by Woodsmoke and Aging

- Cardiac Metabolomic Response to woodsmoke is greater in older mice
- Sustained effect > 10 weeks after exposure

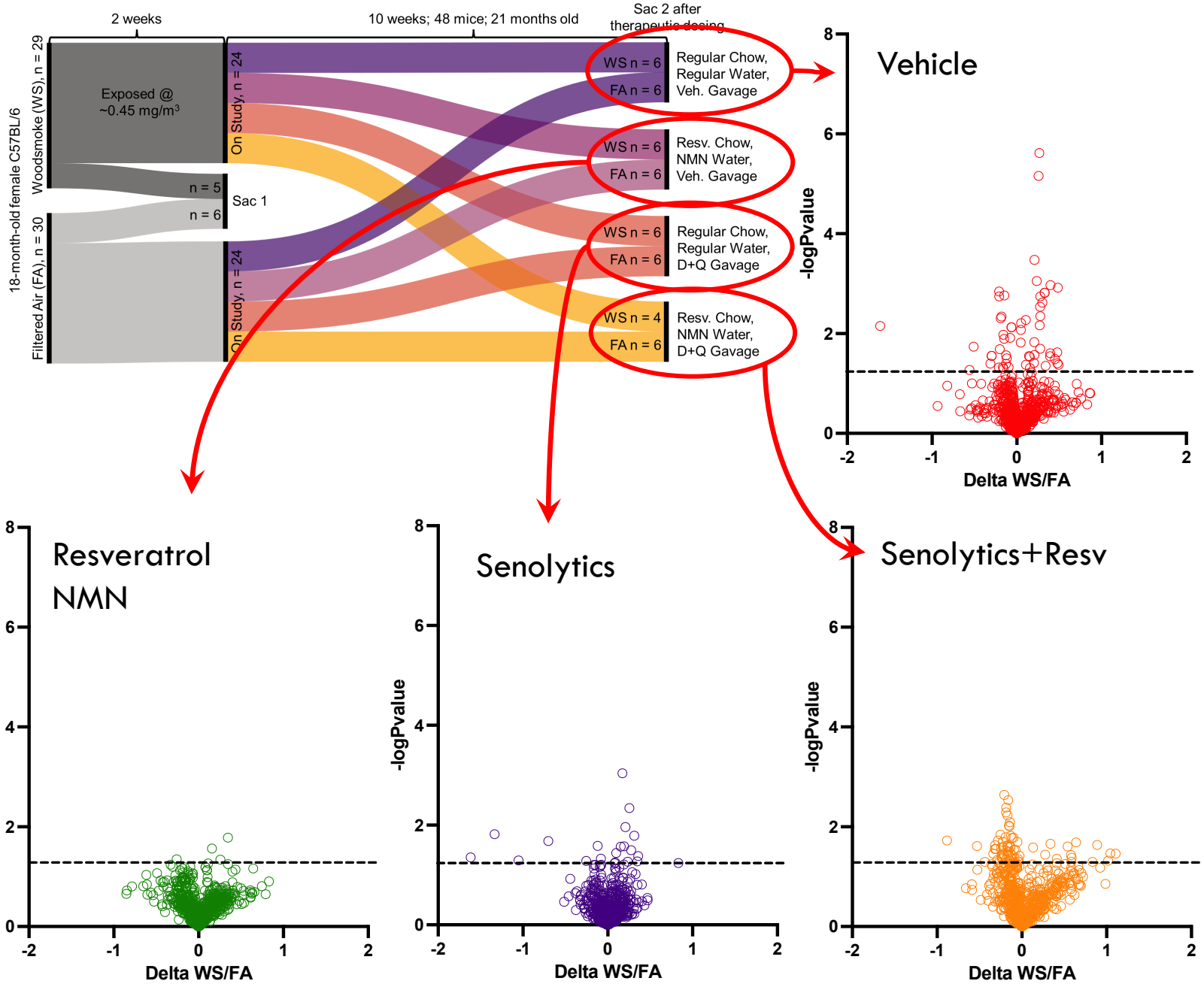






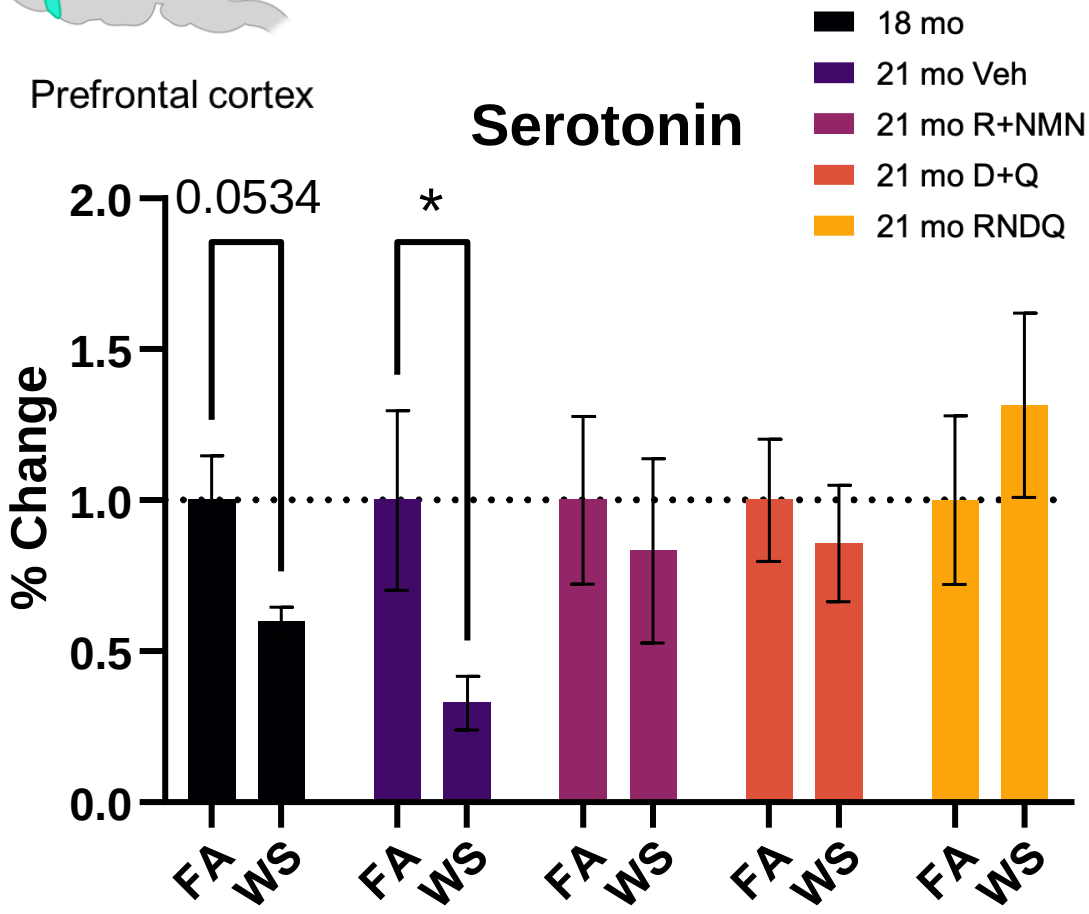


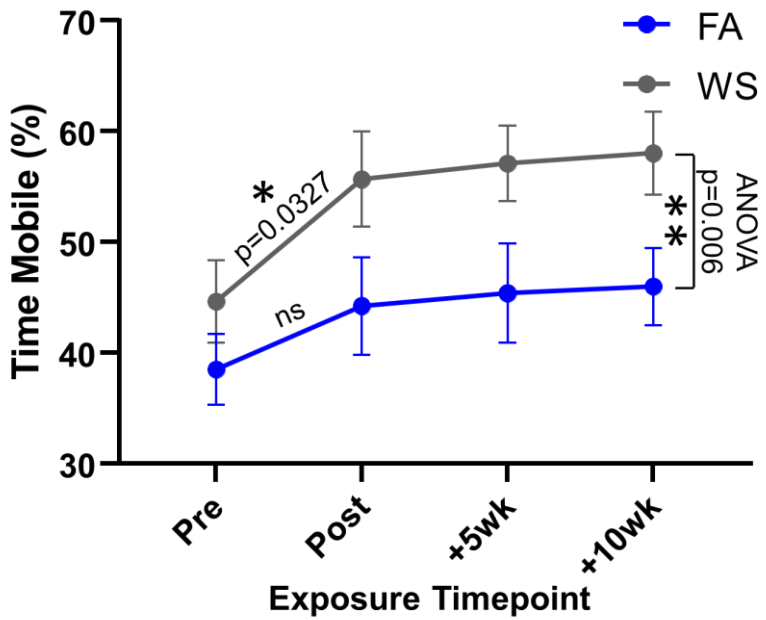
- Sustained cardiac metabolomic response appears reduced by interventions
- Resveratrol + Nicotinamide Mononucleotide is the best overall recovery

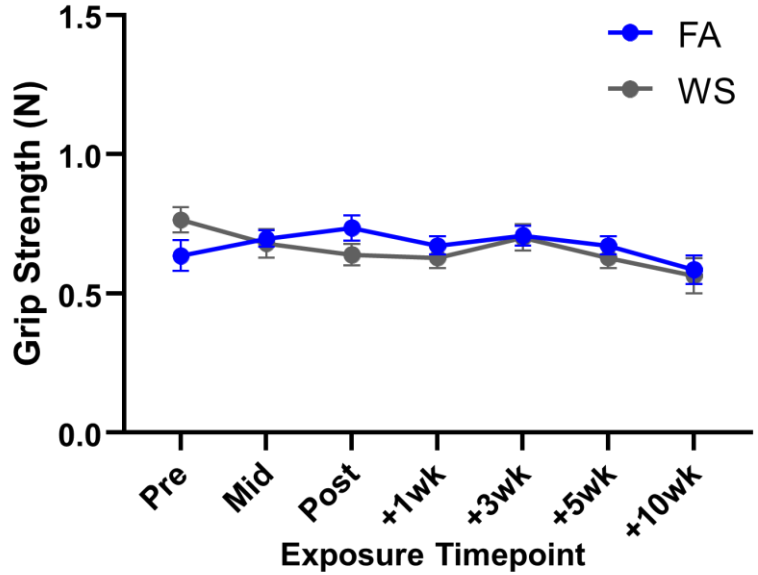


WS exposure reduces Serotonin, which is rescued by each drug intervention

Prefrontal cortex







Conclusions

- Wildfire smoke has the potential to impact health beyond the lungs
  - Study 1 – naturally occurring PM from wildfires 1000km away induced neuroinflammation, altered brain metabolites, and serum peptides
    - Not shown, neuroinflammation evolved and resolved over a 28-day period
  - Study 2 – In older mice, sustained impacts on cardiac metabolites, largely resolved by several interventions
    - Persistent neurometabolic concerns exist as well
- Our data raises concerns about cardiac and neurological issues that may be long-lasting beyond the end of exposure
- Epidemiological studies on the relationship between wildland fire smoke exposure and depression should be undertaken to assess whether firefighters or impacted communities may be at risk

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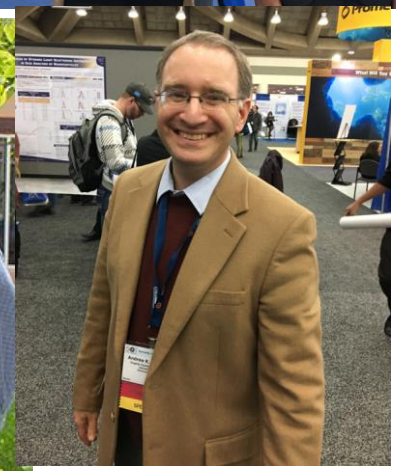

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Questions?