PENNINGTON BIOMEDICAL RESEARCH FOUNDATION LSU

Role of Inhaled Pollutants in Risk of Pathogenic Infection

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OUTLINE

Particulate matter pollution

- Hazardous PM
- Environmentally persistent free radicals (EPFRs)

Exposure to EPFRs increases severity of RTVI (infant/pediatric models)

- Epithelial injury
  - Immunosuppression
  - Failure to repair

ACKNOWLEDGEMENTS

Cormier Lab

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LSU Superfund Research Center

LSU | NC STATE UNIVERSITY | LSU Health NEW ORLEANS | The University Of Queensland AUSTRALIA | Southern University and Agricultural & Mechanical College | Dominican University of California

- NIAID: R01 AI090059-11
  - Early programing in RSV Infection in infants
- NIGMS: U54 GM104940-05S3 (Kirwan - PI)
  - TEST UP-BR:Transforming Community Engagement to Increase SARS-CoV-2 Testing in Underserved Populations in Baton Rouge
- Merck Investigators Studies Program
  - Targeting the viral and human host factors governing COVID19 disease to inform individual and population biomarkers of immunity and therapeutic development

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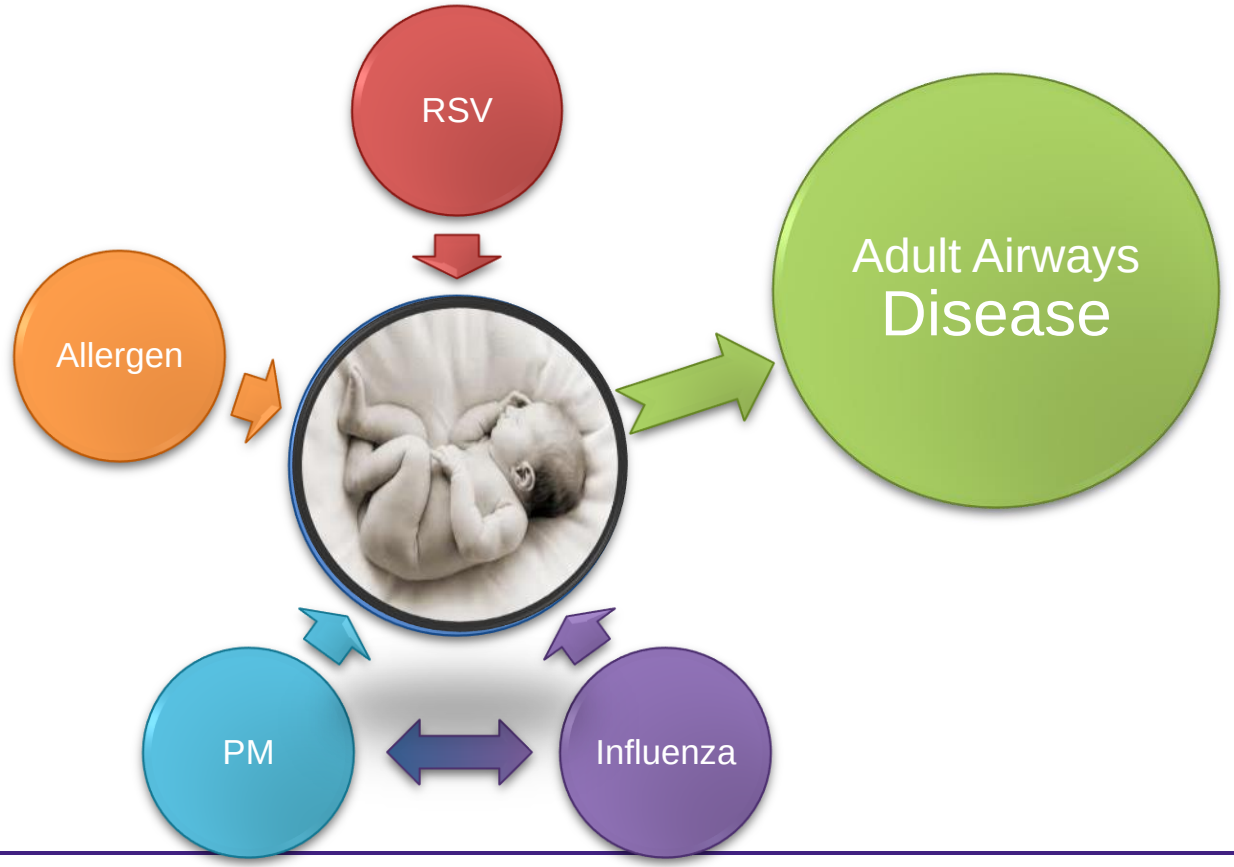
CENTRAL HYPOTHESIS

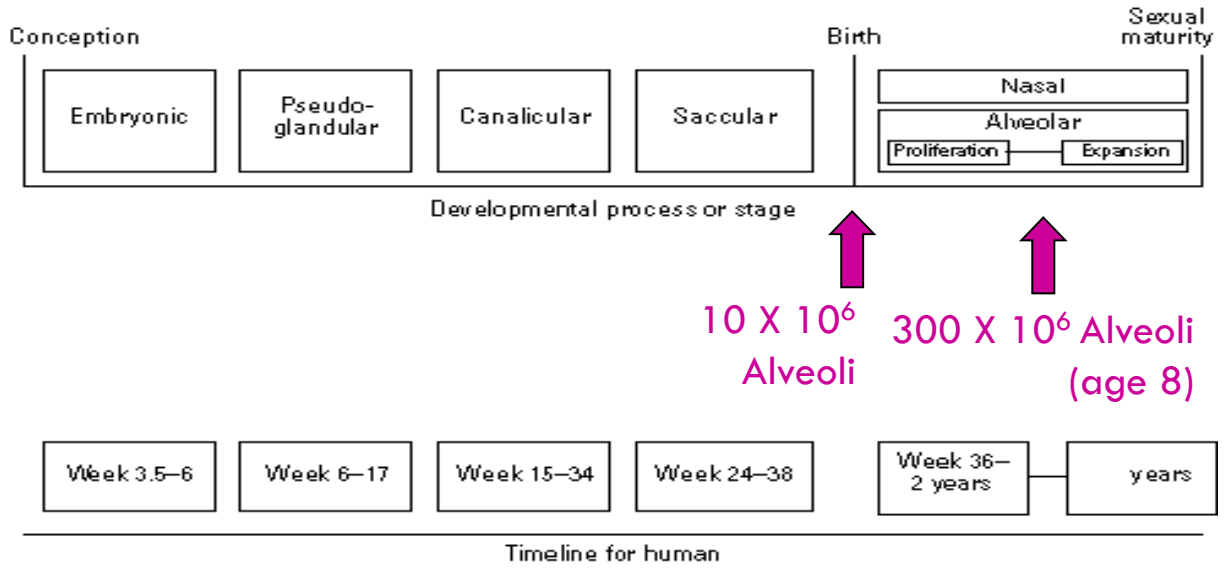
Adult respiratory diseases result, in part, from environmental insult(s) that occur during a critical phase of pulmonary immuno-maturation.

- Environment
- Viral
- Allergen



INFANTS HIGHLY VULNERABLE TO AIRBORNE EXPOSURES

Lungs & immune systems are still developing



Dieter,t 2000

High respiratory rate

Particle deposition is 35% higher compared to adolescents and adults (normalized to surface area)

THE INFANT IMMUNE SYSTEM

Infant CD4+ T cells are poised for rapid Th2 effector function

- Hypomethylation (Hyper) at Th2 (Th1) cytokine regulatory region – CNS-1 (Rose et al. JI 2007)
- Secondary allergen challenge induces Th1apoptosis (Li et al. Immunity 2004)

Infant CD8+ T responses are distinct from adults

- Neonatal CD8+ T cells are functionally immature (You et al. JI 2008)
- Require additional stimuli (McCarron et al. Hum Immunol 2010)
- Epitope dominance appears to be age-dependent (10 dpi; Ruckwardt et al. PLoS Pathogens 2011)
- Elevated Tc2 and Th2 cells elevated in infants w RSV severity (Siefker et al. 2020 AJRCCM)

Infant DCs

- Recruitment attenuated (Nelson et al. JI 1995; Upham et al. IAI 2006)
- Absolute number and subsets different (Cormier et al. JVI 2014)
- Diminished IL-12 synthesis (Lee et al. JEM 2007; Ripple et al. JI 2010)

Innate lymphoid cells

- IL33 responses are enhanced in infants (Saravia et al. PLoS Pathog 2015)
- Elevated ILC2 predicts severity (Vu et al. AJRCCM 2019)

RSV-specific IgA (Hijano et al. Scientific Reports 2018)

- Levels attenuated compared to adult
- Increased by IFNα supplementation to adult levels

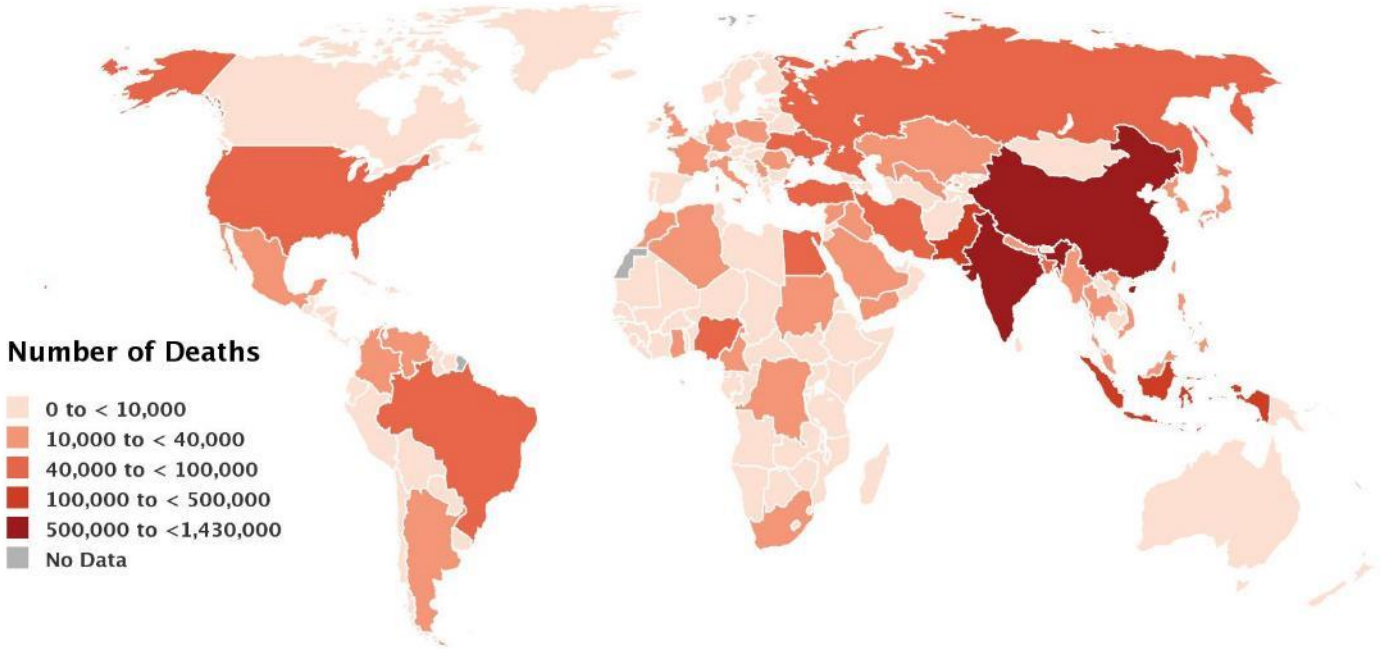
THE BURDEN OF AIR POLLUTION

- Ambient air pollution is the **5th leading cause of death** worldwide.

Contributing to:

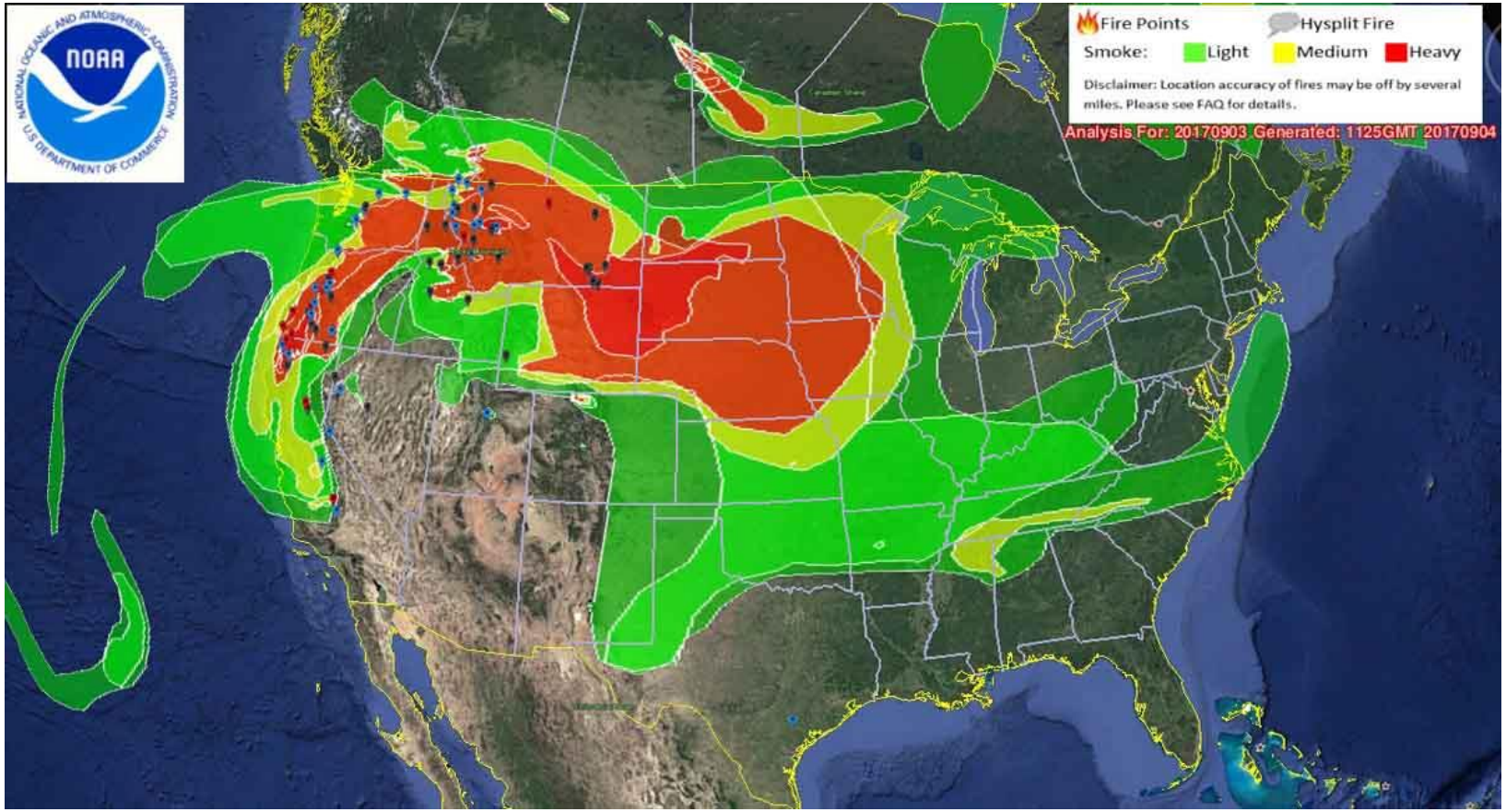
~ 4.2 million deaths worldwide

~400 000 deaths of children under five



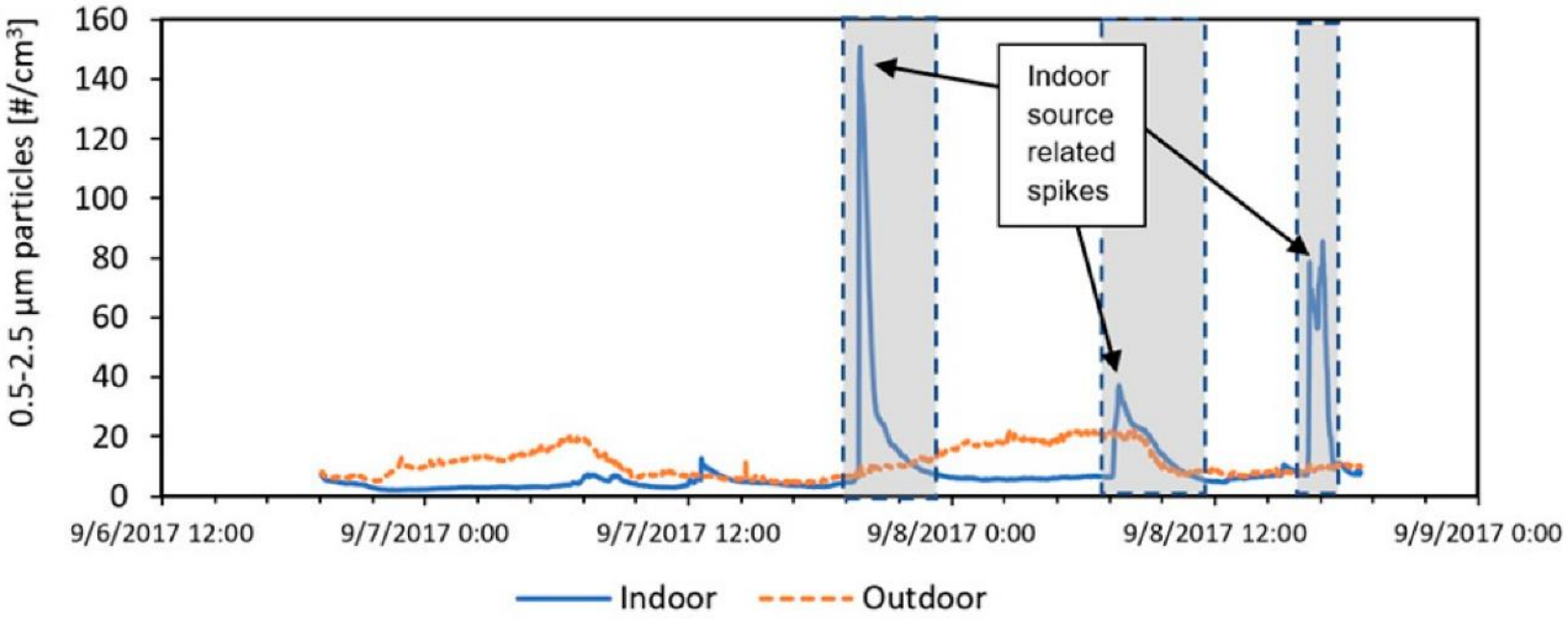
•Health Effects Institute. 2019. State of Global Air

NOT A LOCAL PROBLEM



Wildfire smoke map, 5:24 a.m. MDT September 4, 2017. The icons represent the locations of some of the large uncontained wildfires.

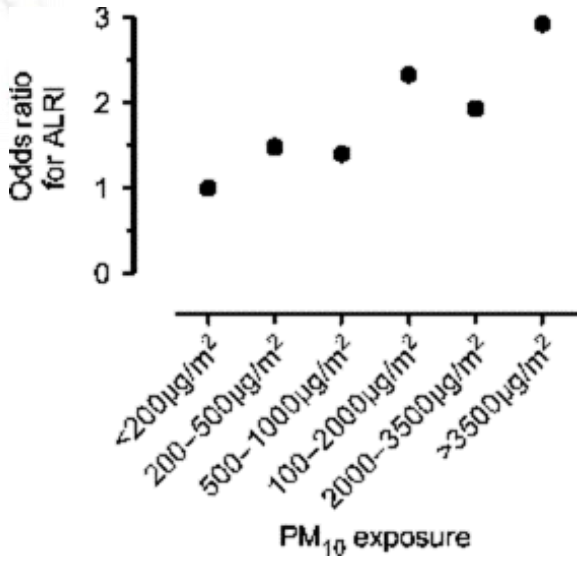
NOT JUST AN OUTDOOR CONCERN



Shresta et al. Int J Environ Res Public Health. 2019

Every year, 1.96 million people die from ARIs as a result of indoor air pollution

Source: ARIAtlas.org, World Lung Foundation 2010



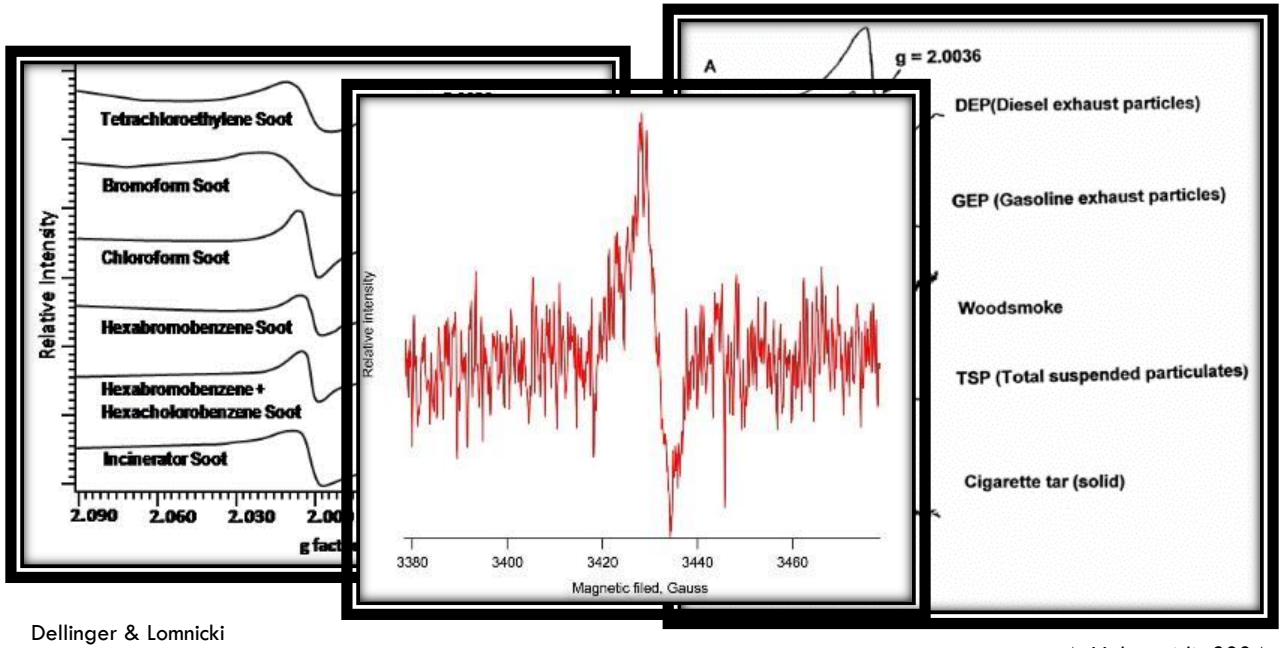
Grigg. 2011. Clinical & Experimental Allergy. 41: 1072-1075

COMBUSTION DERIVED PARTICULATE MATTER (PM)

Personal Sources
(cigarettes)

Natural Sources
(forest fires, volcanoes)

COMBUSTION-GENERATED PM CONTAINS RADICALS



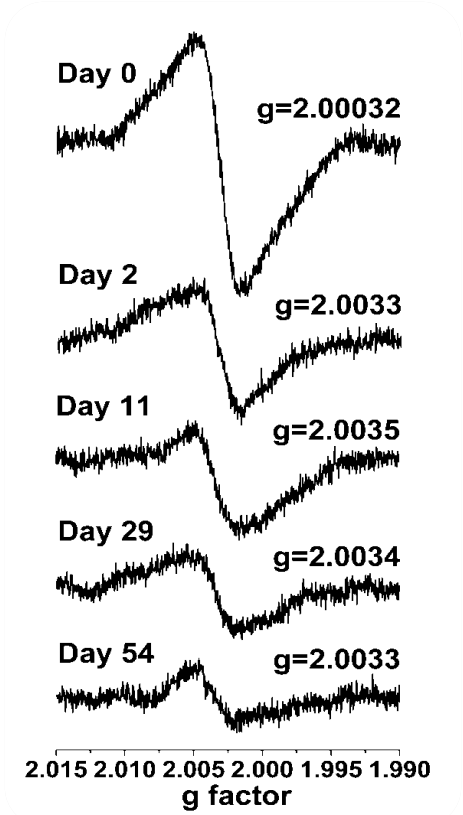
Dellinger & Lomnicki

T.E. Sussan et al 2015

A. Valavanidis 2004

CS tar: 1e16 radicals/g
E-cig TPM: 2.6e15 radicals/g *T.E. Sussan et al PLOS One 2015*
$PM_{2.5}$:1e16 - 1e17 radicals/g (BR); 1e17 – 1e19 radicals/g (Memphis) *Oyana TJ et al. ES&T. 2017*

ENVIRONMENTALLY PERSISTENT FREE RADICALS (EPFRS)



Baton Rouge $PM_{2.5}$

$T_{1/2}$ = 21d

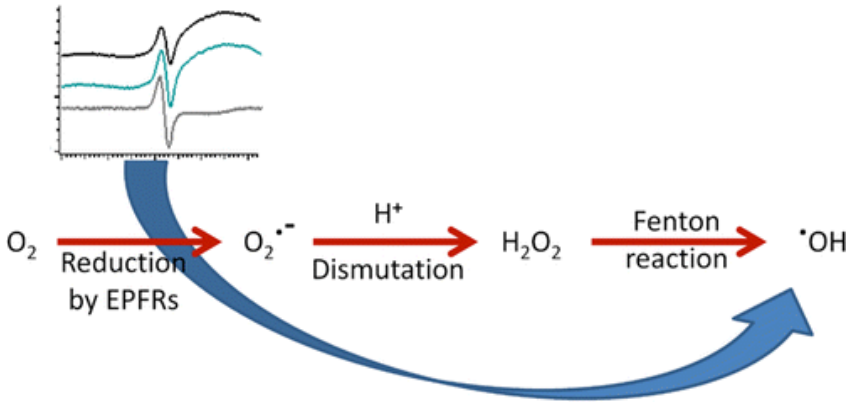
CS tar: 1e16 radicals/g
E-cig TPM: 2.6e15 radicals/g
$PM_{2.5}$:1e16 - 1e17 radicals/g (BR); 1e17 – 1e19 radicals/g (Memphis)

Gehling et al. 2013

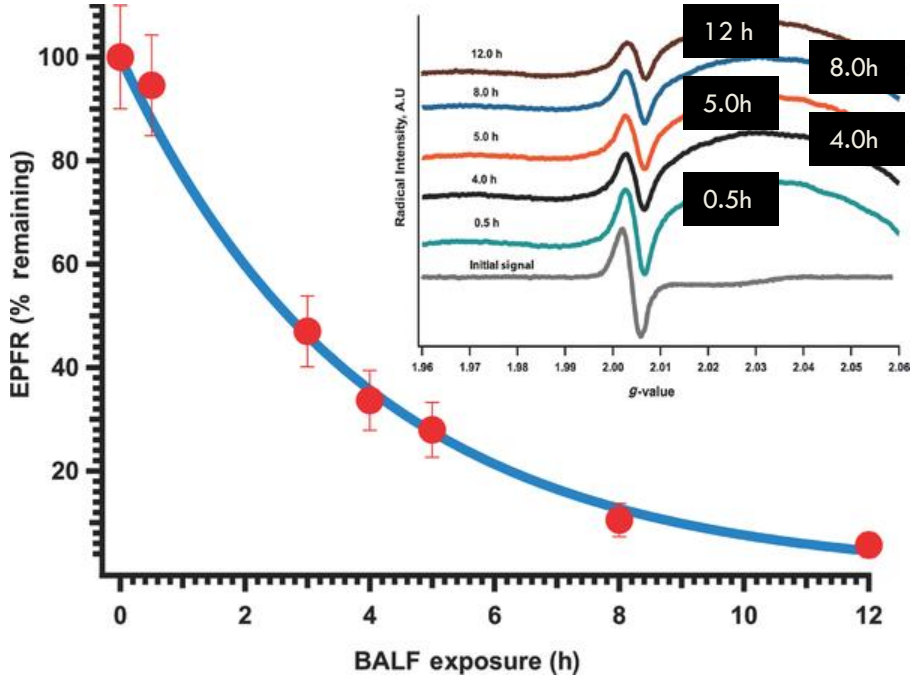
T.E. Sussan et al PLOS One 2015

Oyana TJ et al. ES&T. 2017

PERSISTENCE OF EPFRS IN BIOLOGICAL SOLUTIONS



Kelley et al., Chem Res Toxicol, 2013

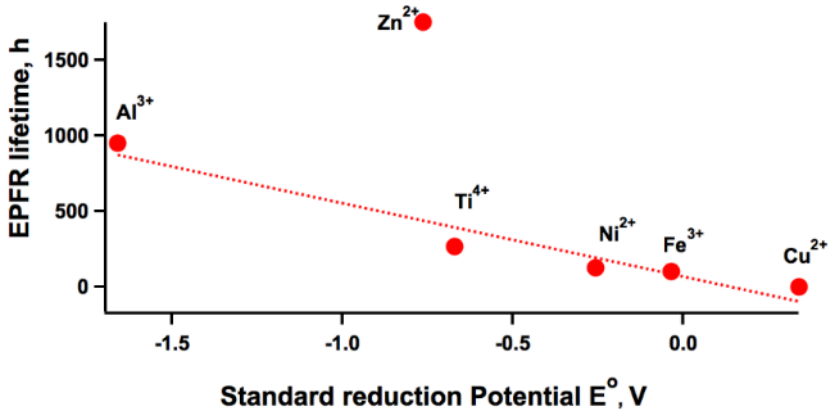


Saravia *et al.*, 2012

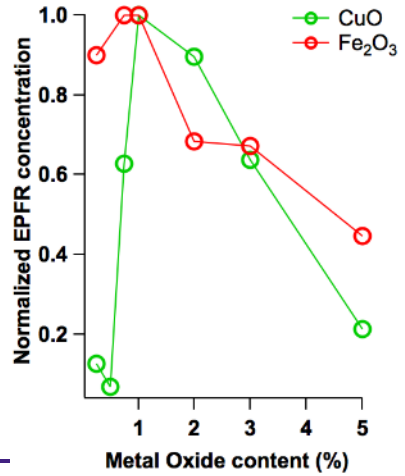
Dugas

Cormier

METAL OXIDE CONTENT AFFECTS LIFETIME OF EPFRS AND PCDD/F YIELDS

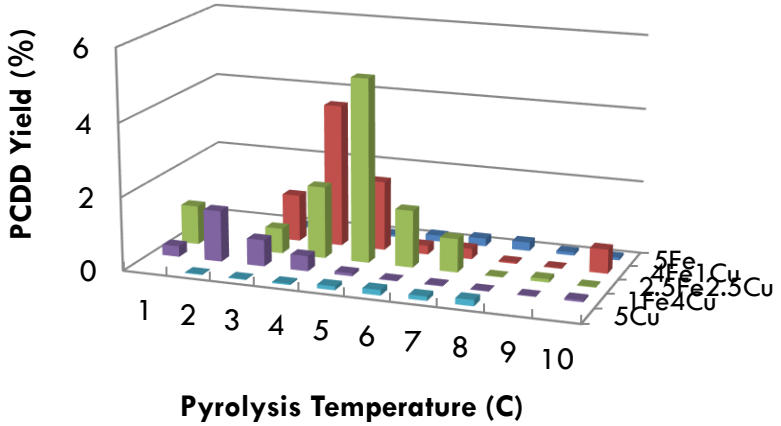


Metals affect EPFR lifetime and yield



Sprunger

Co-presence of metals affects both redox potential (not shown) and PCDD/F yields



Lomnicki

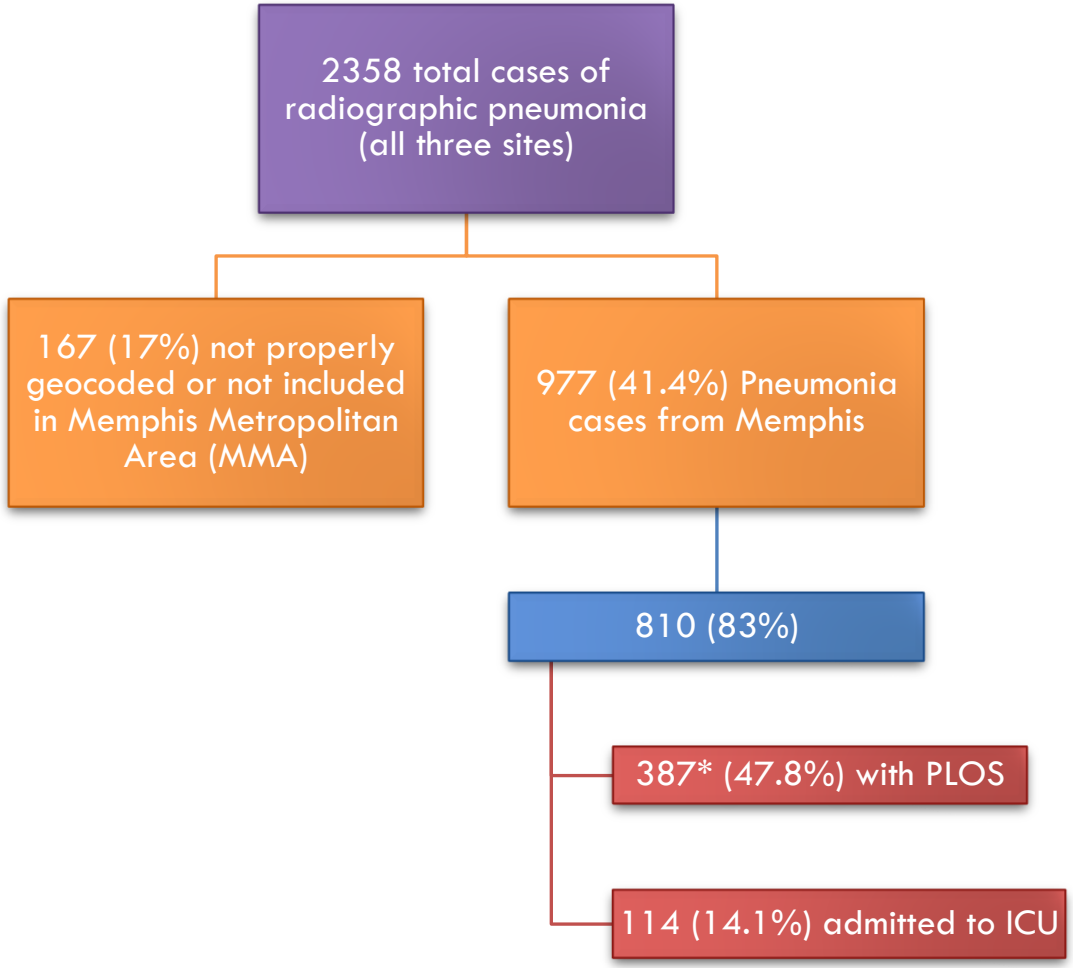
EXPOSURE TO EPFRs INCREASES SEVERITY OF RTVI

EXPANDING TO COMMUNITY HEALTH

Le Bonheur Children's Hospital

EPIC

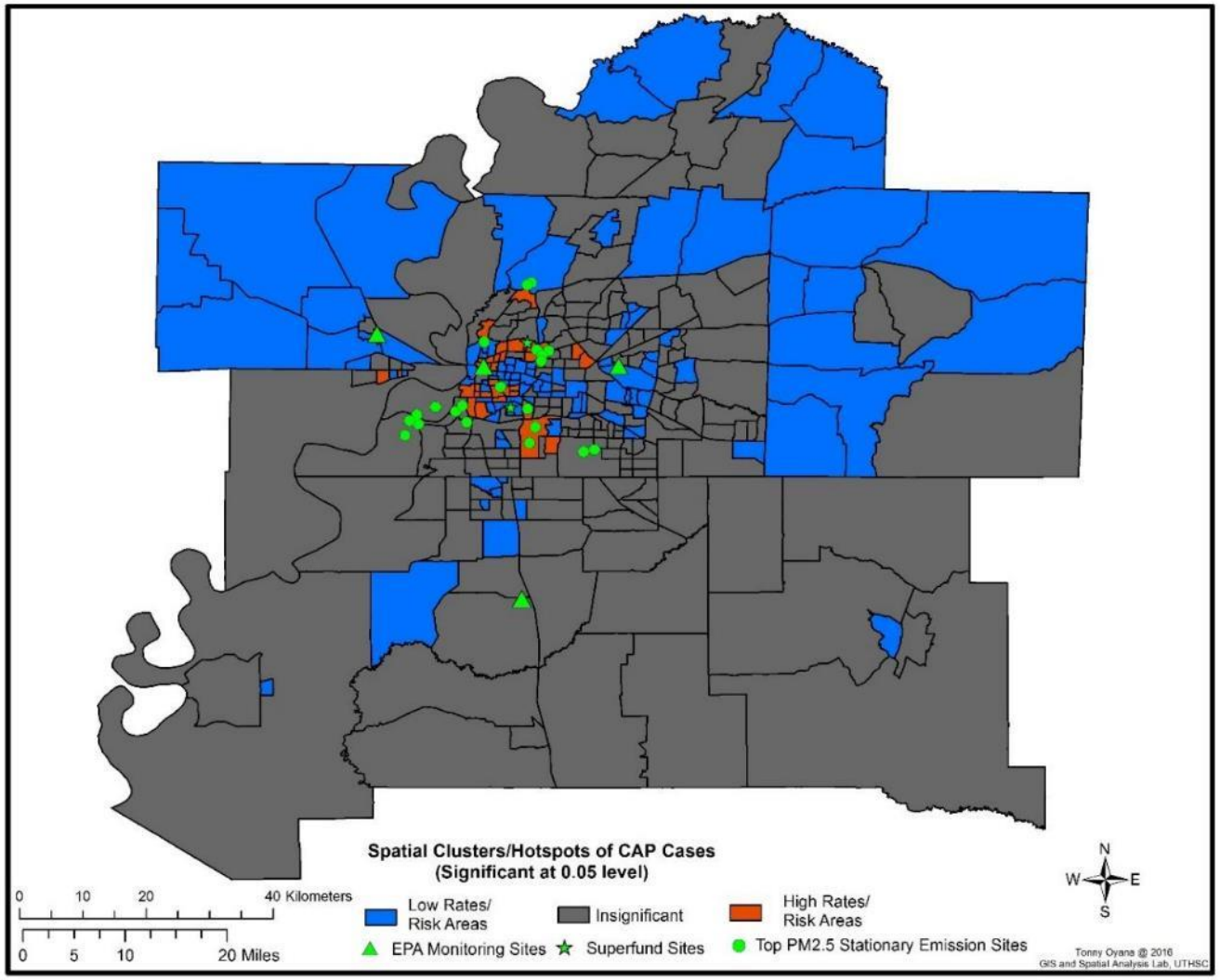
POPULATION BASED PNEUMONIA STUDY



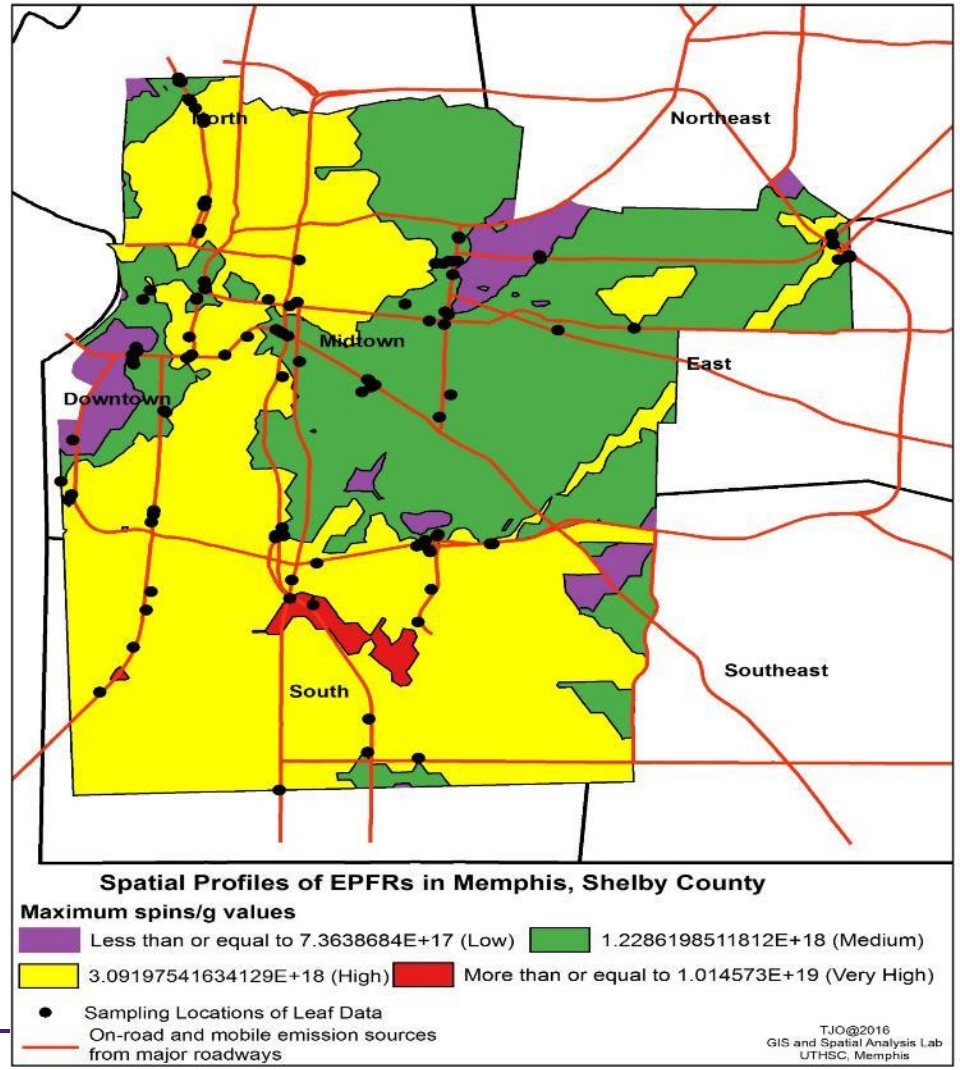
CDC EPIC Cohort

Oyana et al., EBM 2021

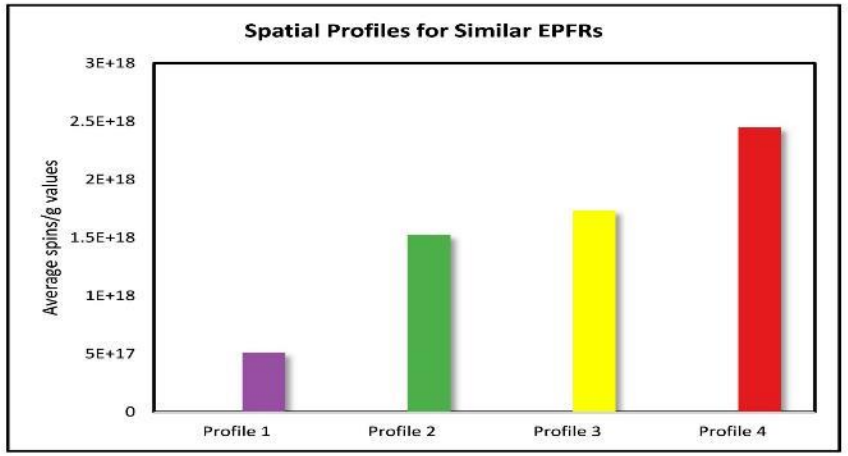
COMMUNITY ACQUIRED PNEUMONIA (CAP) "HOTSPOTS"



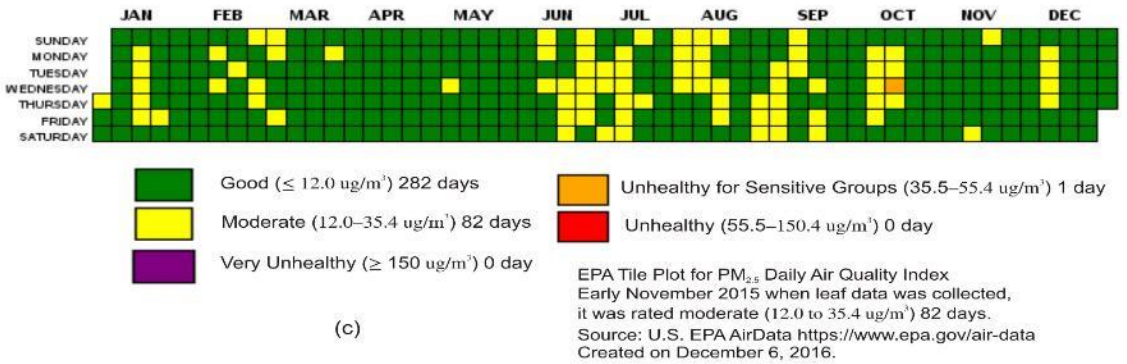
SPATIAL PROFILES OF EPFRS IN MEMPHIS, TN



(a)



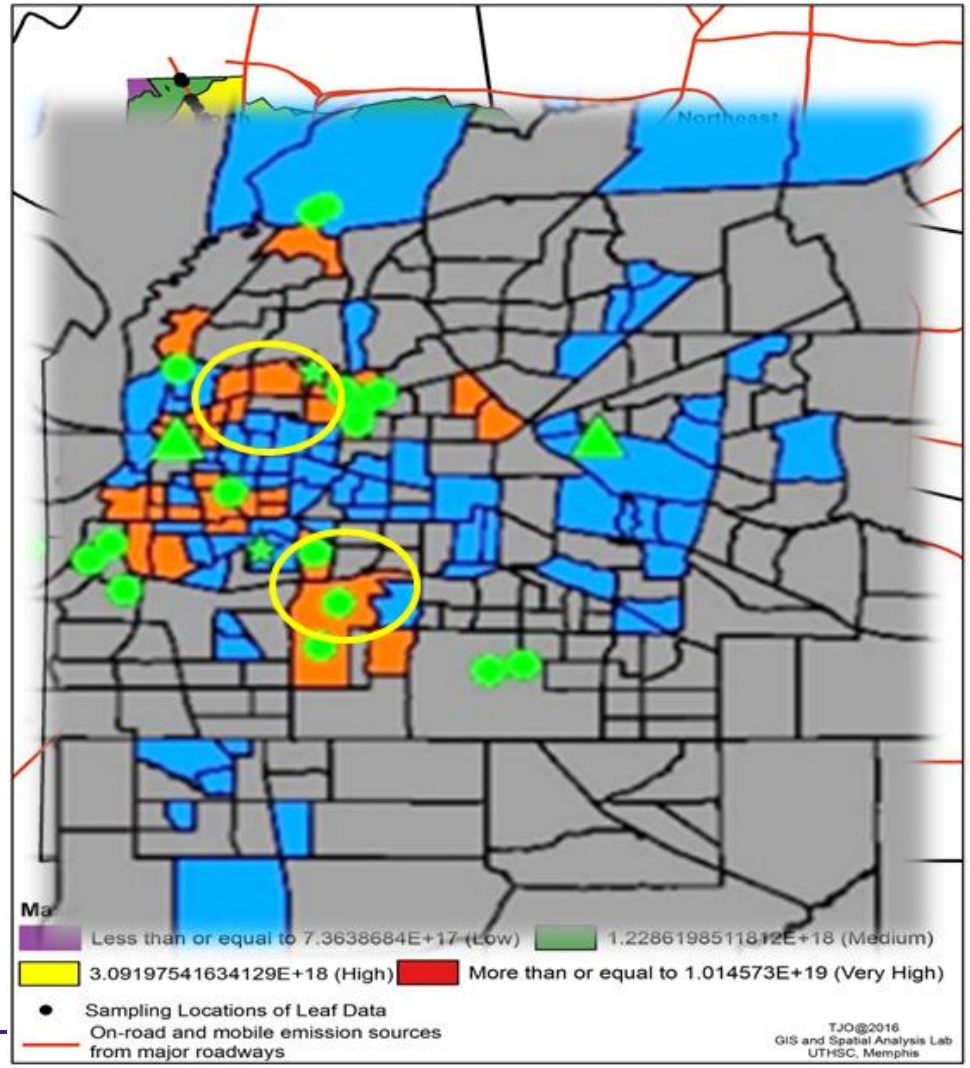
(b)



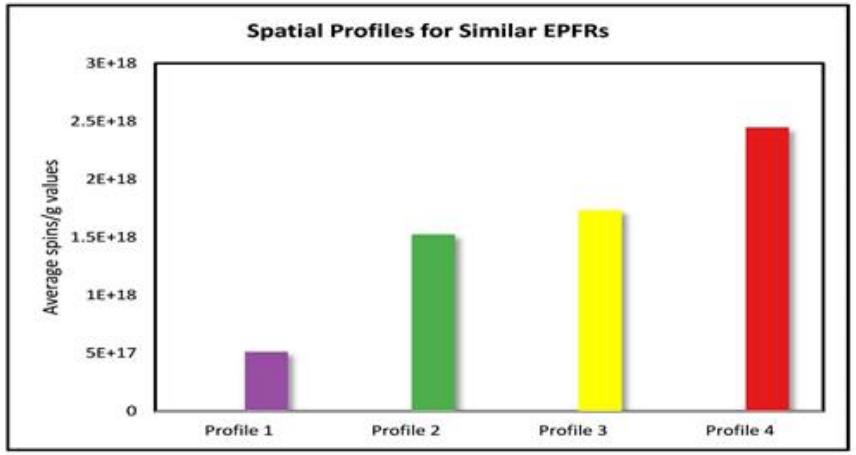
(c)

Oyana et al. 2017, **EST**

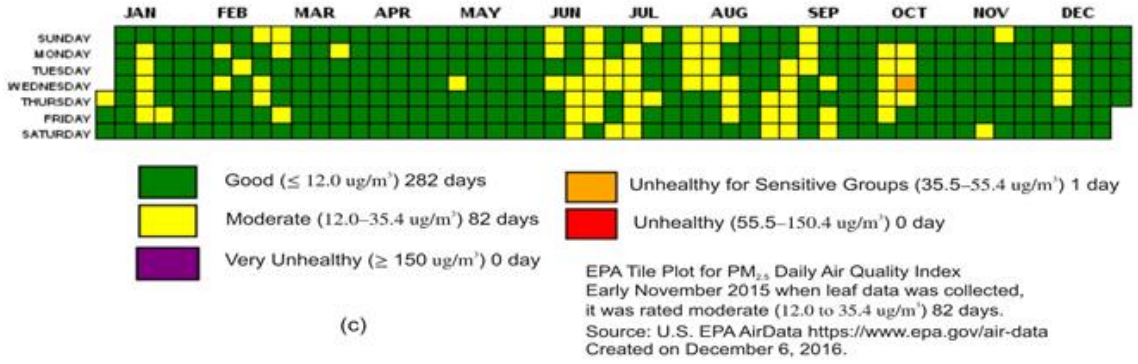
SPATIAL PROFILES OF EPFRS IN MEMPHIS, TN



(a)



(b)



(c)

EPA Tile Plot for $PM_{2.5}$ Daily Air Quality Index
Early November 2015 when leaf data was collected,
it was rated moderate (12.0 to 35.4 ug/m³) 82 days.
Source: U.S. EPA AirData https://www.epa.gov/air-data
Created on December 6, 2016.

PROXIMITY TO $PM_{2.5}$ SOURCES PREDICTS PNEUMONIA SEVERITY IN CHILDREN

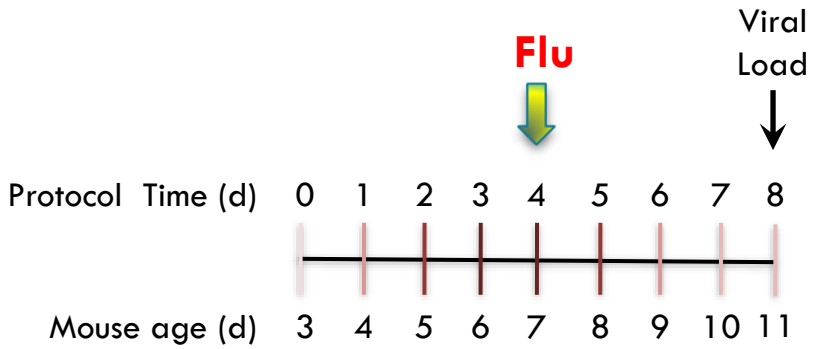
- CAP has a non-homogenous geospatial distribution
- Higher than the mean $PM_{2.5}$ was associated with living in a high-risk area for CAP [adjusted odds ratio (aOR) 2.47, 95% confidence interval (CI) 1.31–4.66]
  - Mean $PM_{2.5}$ (10.75 µg/m^3)
- Increased risk for CAP associated with
  - Viral vs bacterial infection
- 1st to show possible $PM_{2.5}$ effects at exposure levels lower than the current EPA limit
  - Recent reduction in WHO PM2.5 annual 5 µg/m3 and 24h mean 15 µg/m3
- Spatial overlap with high environmental EPFR concentration *Oyana et al. 2017, EST*

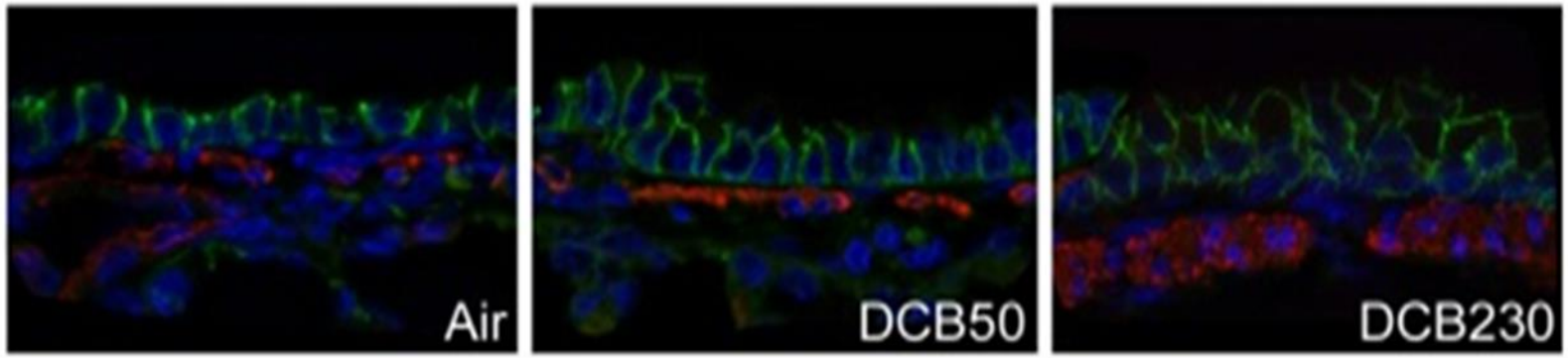
Oyana et al. 2021, **EBM**

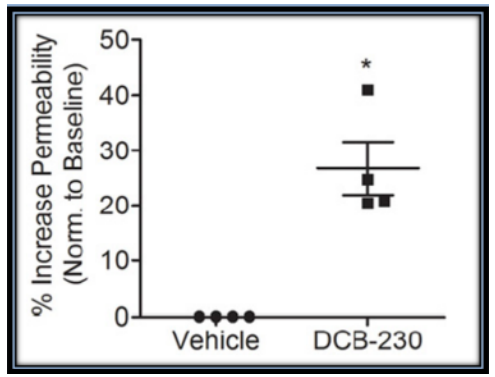
pb

EXPOSURE TO EPFRs INCREASES SEVERITY OF RTVI

EXPOSURE AND INFECTION PROTOCOL

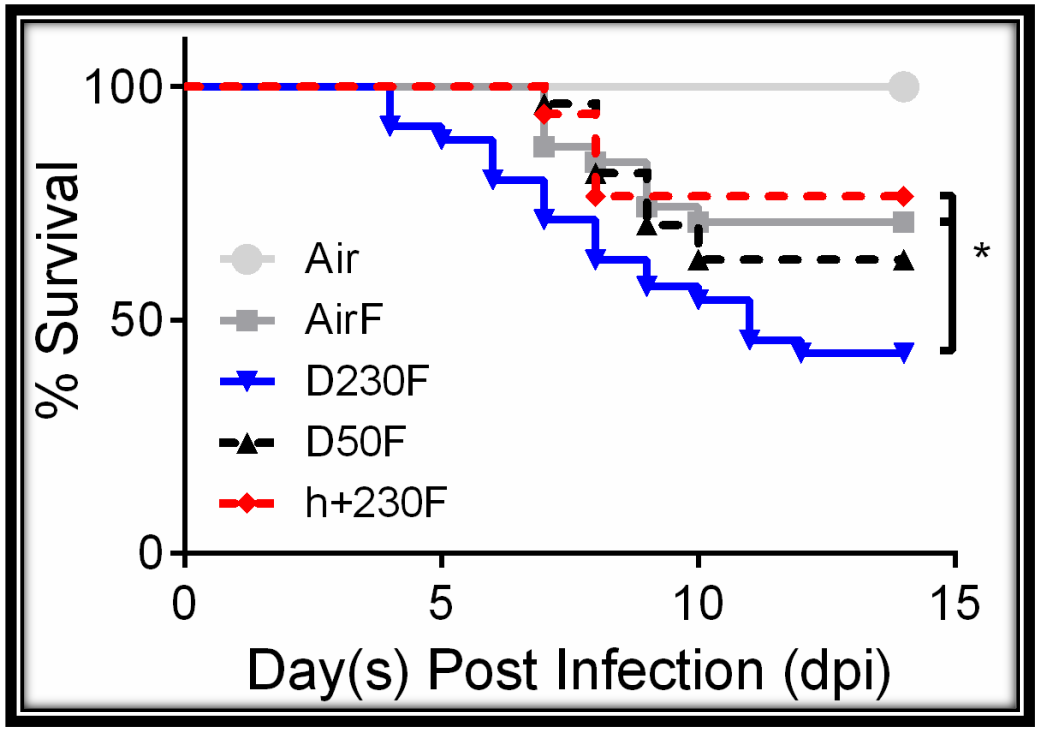






Lee, et al. PFT. 2014

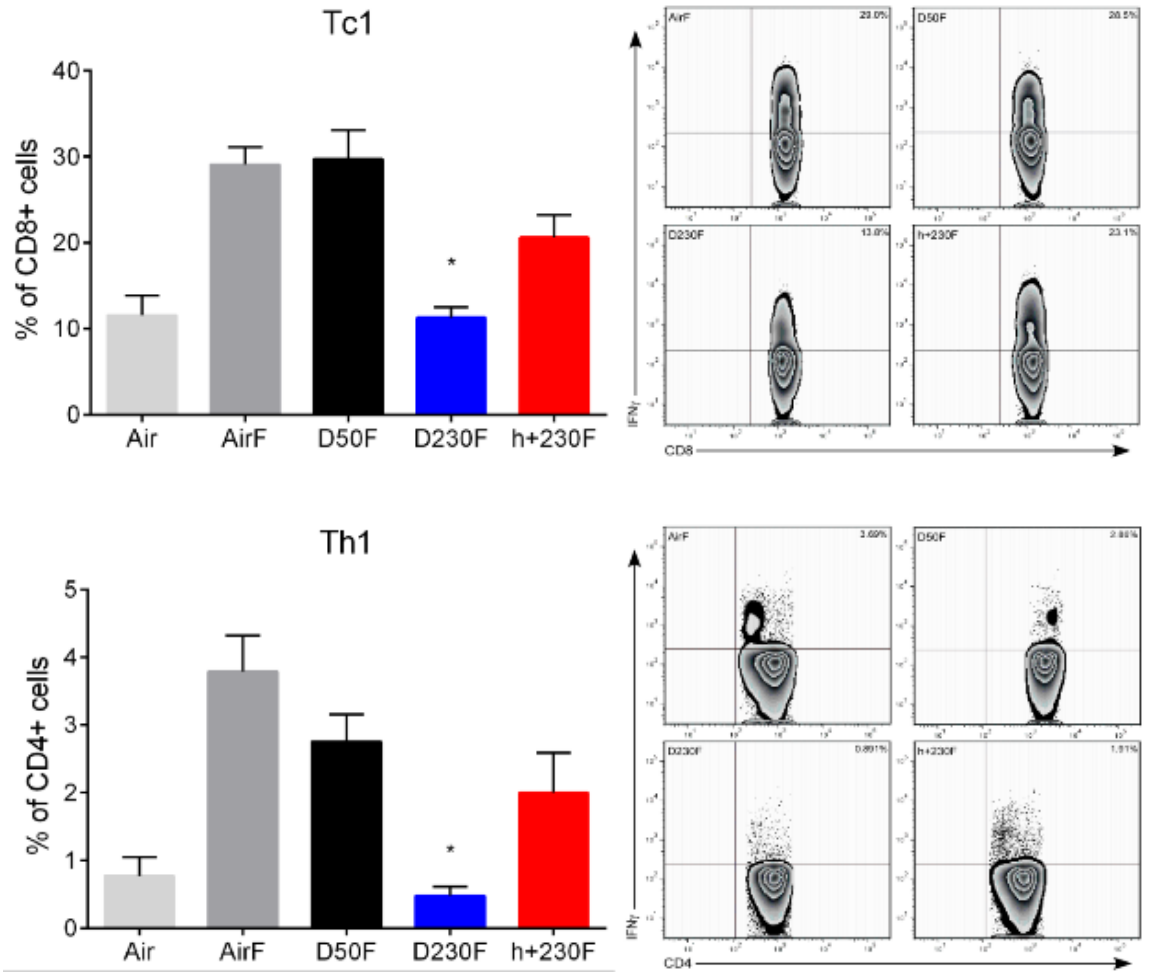
EPFR EXPOSURE ENHANCES INFLUENZA MORTALITY



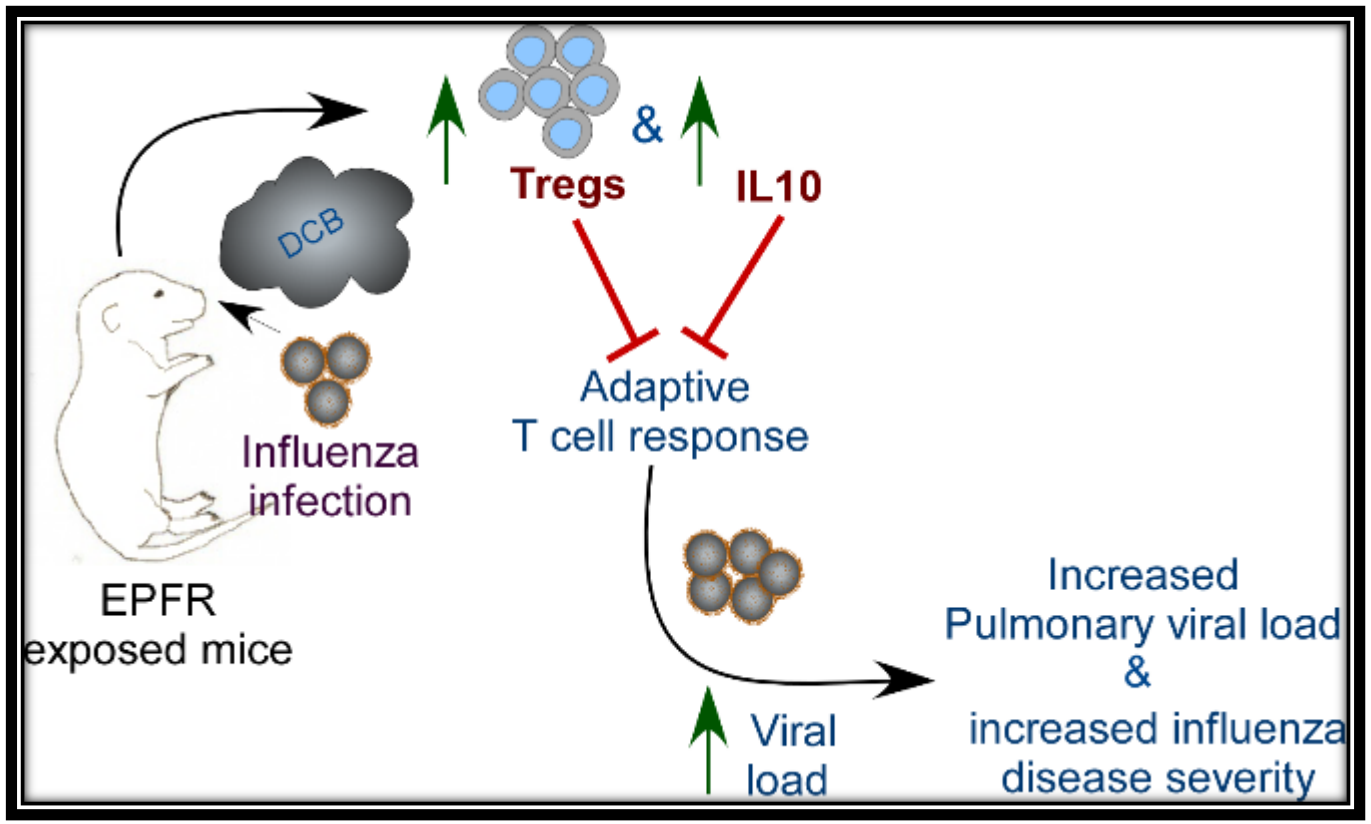
AirF	air	Flu
D50F	non-EPFR PM	Flu
D230F	EPFR PM	Flu
H+230F	hSOD2 + EPFR PM	Flu

n = 16-35

EXPOSURE TO EPFRS SUPPRESSES PROTECTIVE IMMUNE RESPONSES



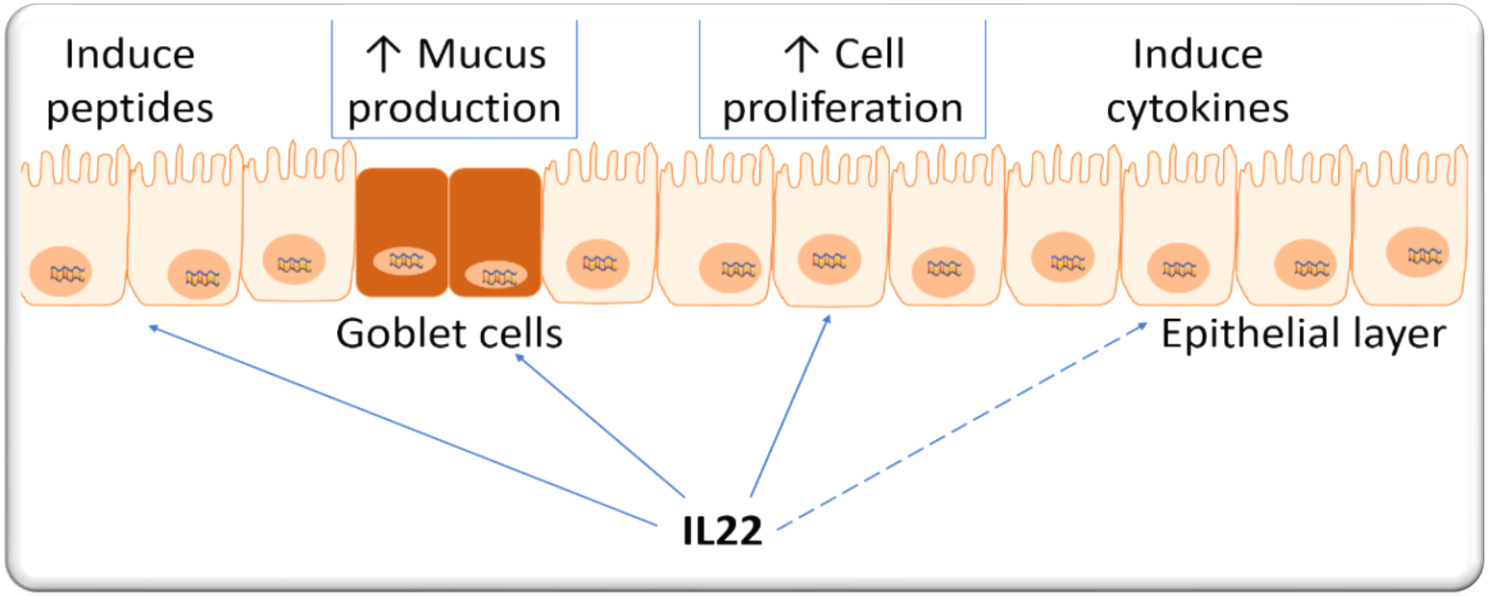
SUMMARY



- Depletion of Tregs/IL10 in PM exposed mice increases protective T cell responses and reduces influenza morbidity & mortality
- IL10 alone recapitulates PM enhanced influenza morbidity

Jaligama et al. RR 2017

ROLE FOR IL22?

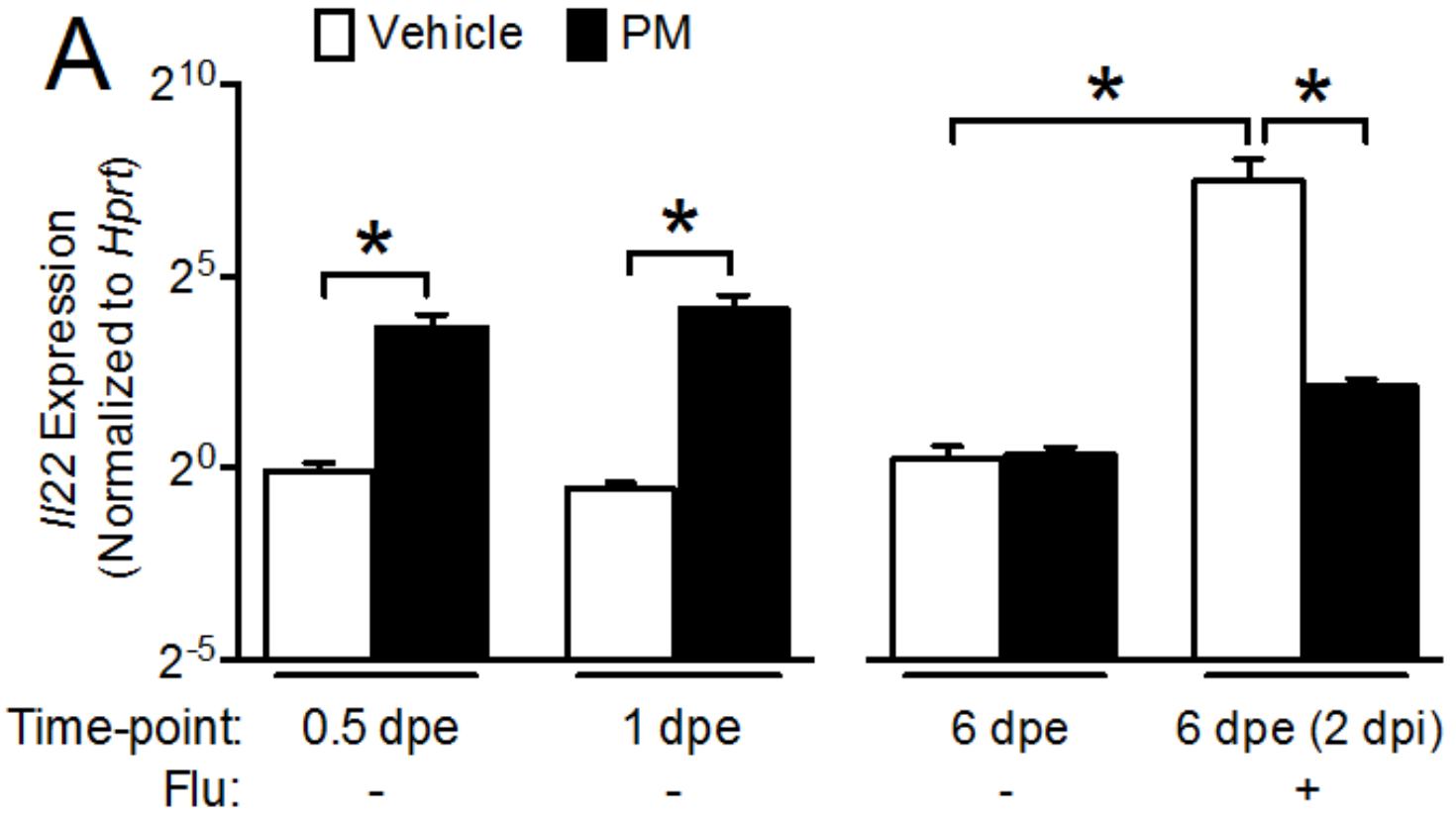


Essential for damage repair after Flu infection

- Increase trans-epithelial resistance
- Epithelial cell proliferation
- Prevent secondary infection

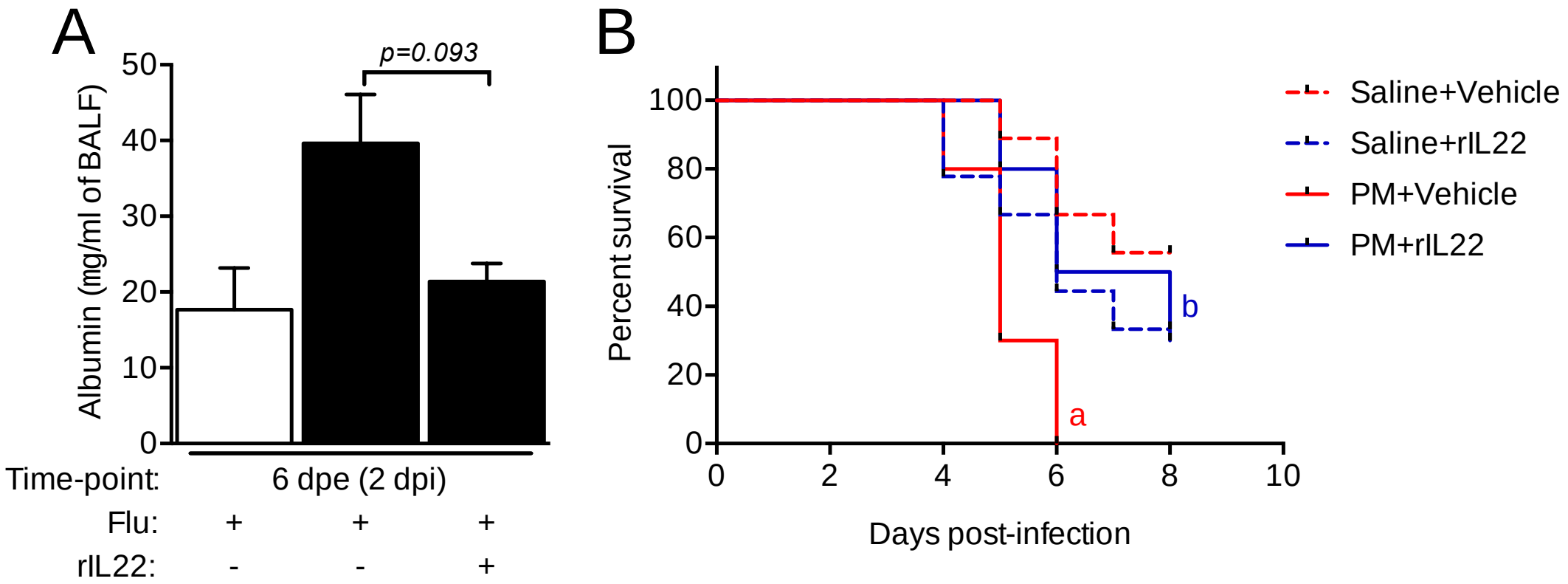
Pociask D, et al. Am J Pathol 2013, 182: 1286-1296
Kumar P, et al. Mucosal Immunol. 2013 Jan; 6(1):69-82
Guo H and Topham DJ, J Virol. 2010 Aug; 84(15):7750-9
Ivanov S, et al. J Virol. 2013 Jun; 87(12):6911-24

CONTINUOUS EPFR EXPOSURE RESULTS IN A FAILURE TO INDUCE *Il22* EXPRESSION IN RESPONSE TO FLU



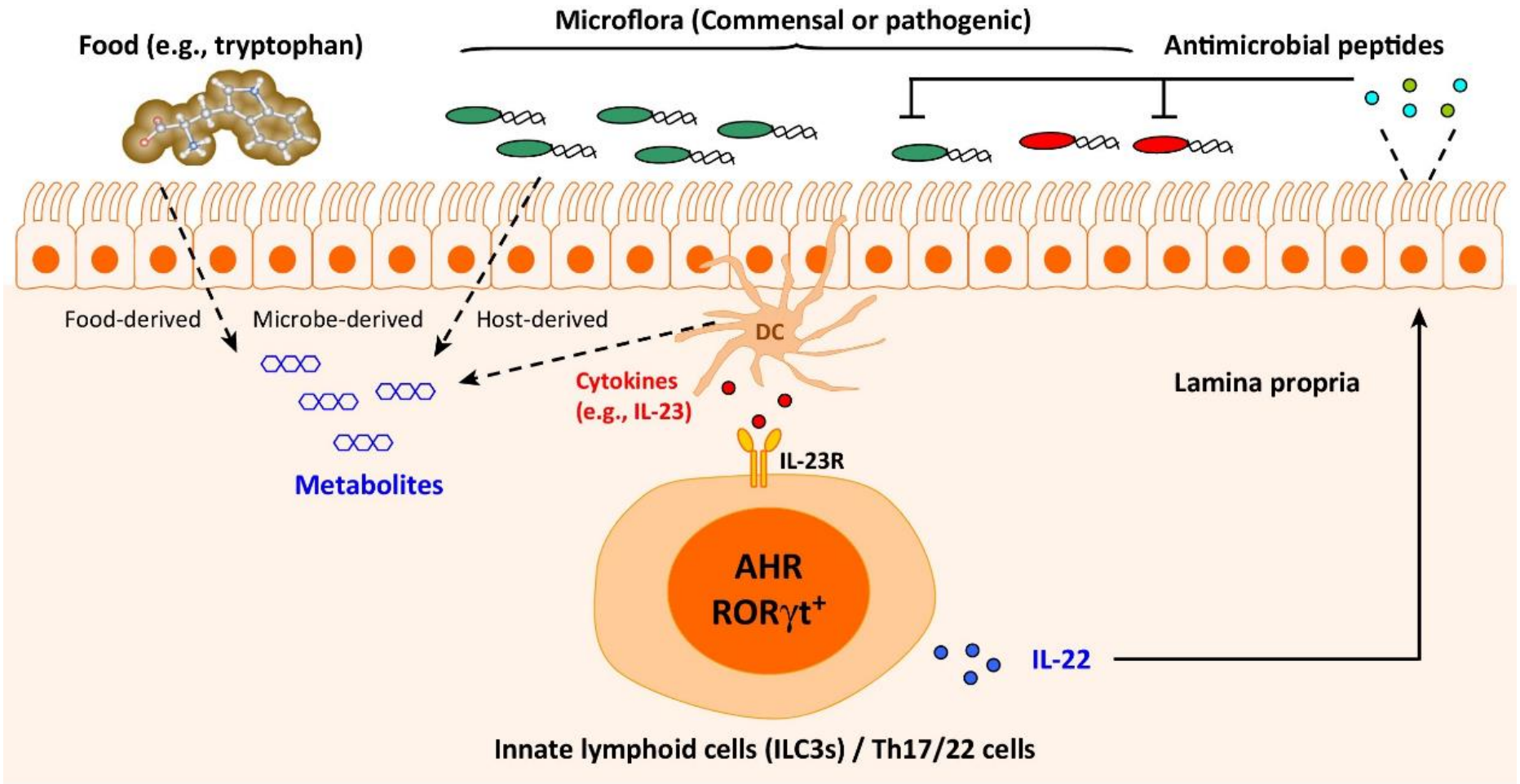
Kumar et al., PFT, 2021 In Press

RIL22 PROTECTS AGAINST PM INDUCED LUNG INJURY AND IMPROVES SURVIVAL IN FLU-INFECTED MICE



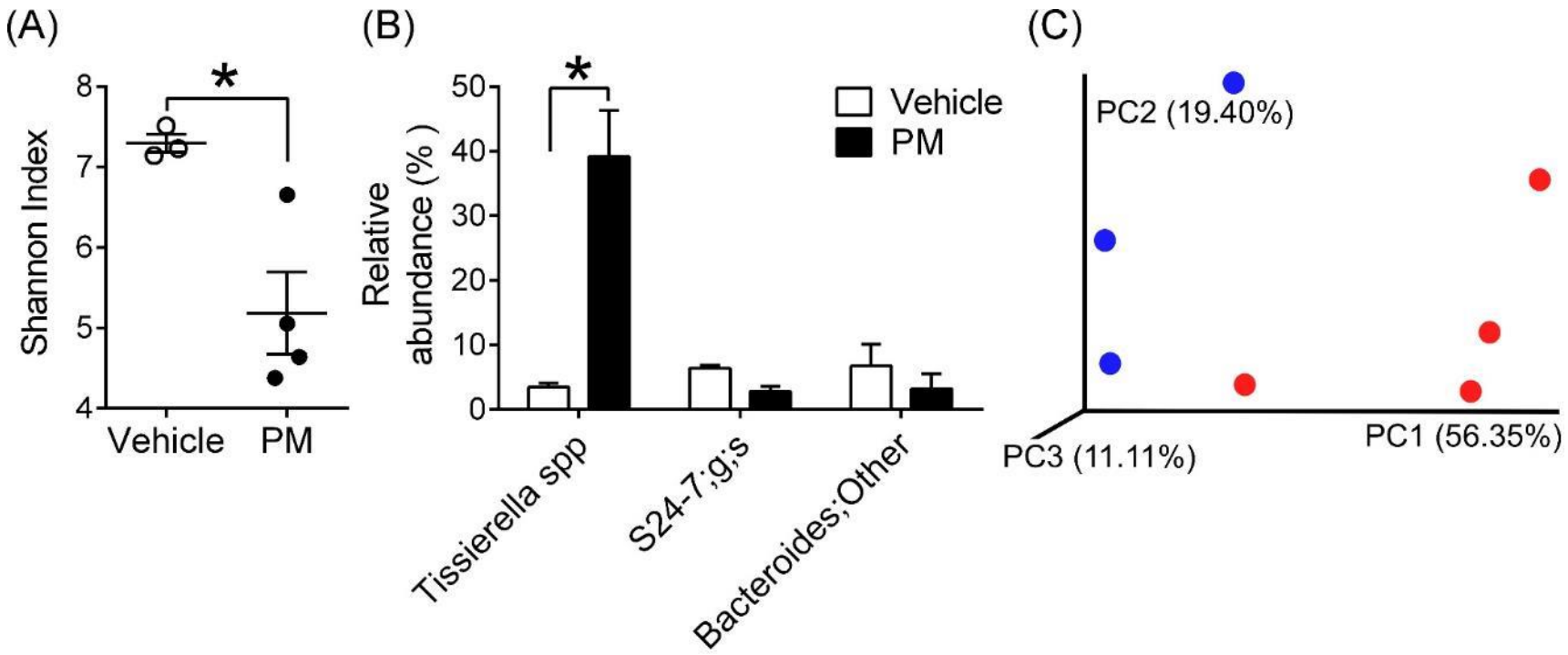
rIL22 (5 ng/g body weight) 1dpe-2dpi

WHY DOES CONTINUOUS EPFR EXPOSURE RESULT IN A FAILURE TO INDUCE IL22 EXPRESSION IN RESPONSE TO FLU?



Zhou et al. 2015. Trends in Immunology 37:17-31

PM EXPOSURE INDUCES DYSBIOSIS OF LUNG (BALF) MICROBIOTA

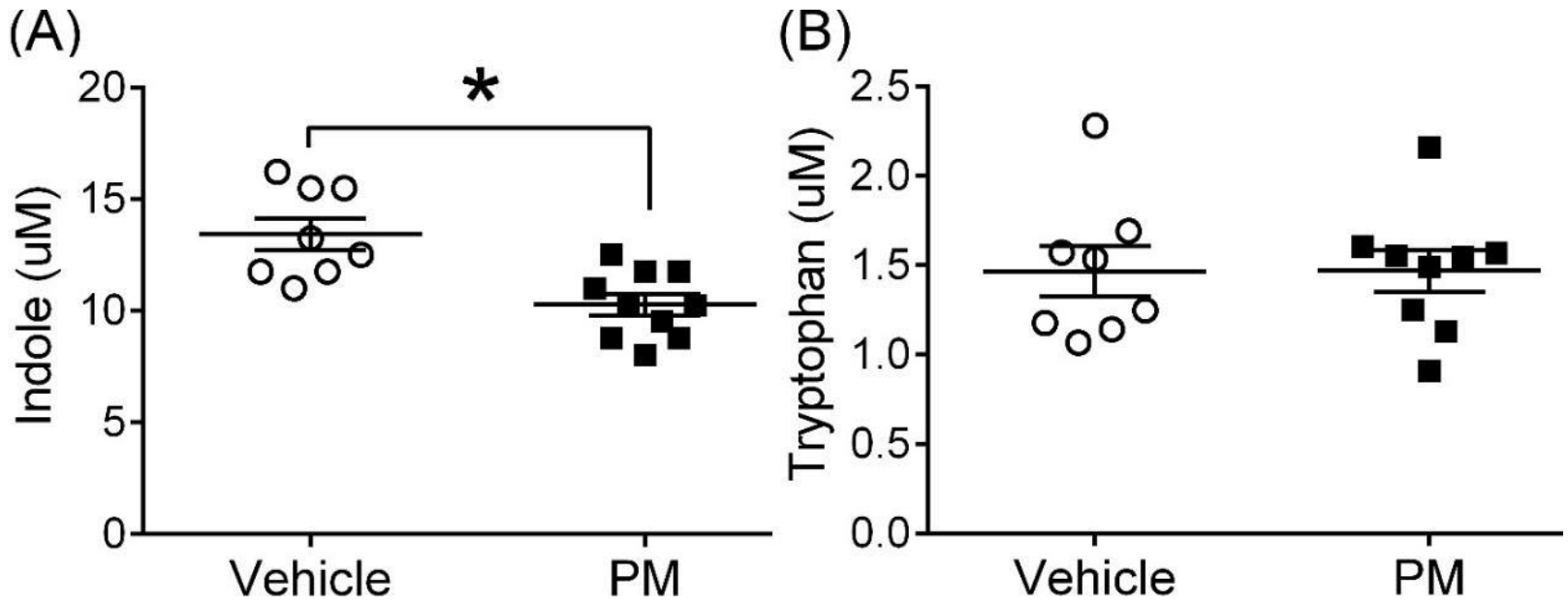


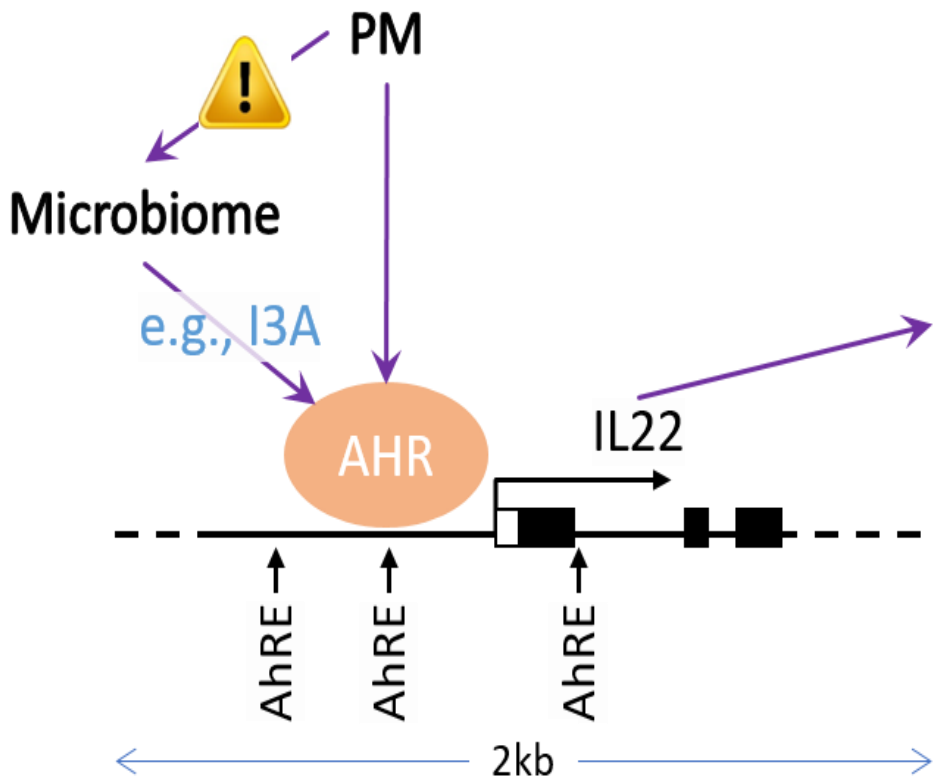
Alpha diversity
(# of species in sample)

Beta diversity
(dissimilarity between sample pairs)

4 dpe, BALF

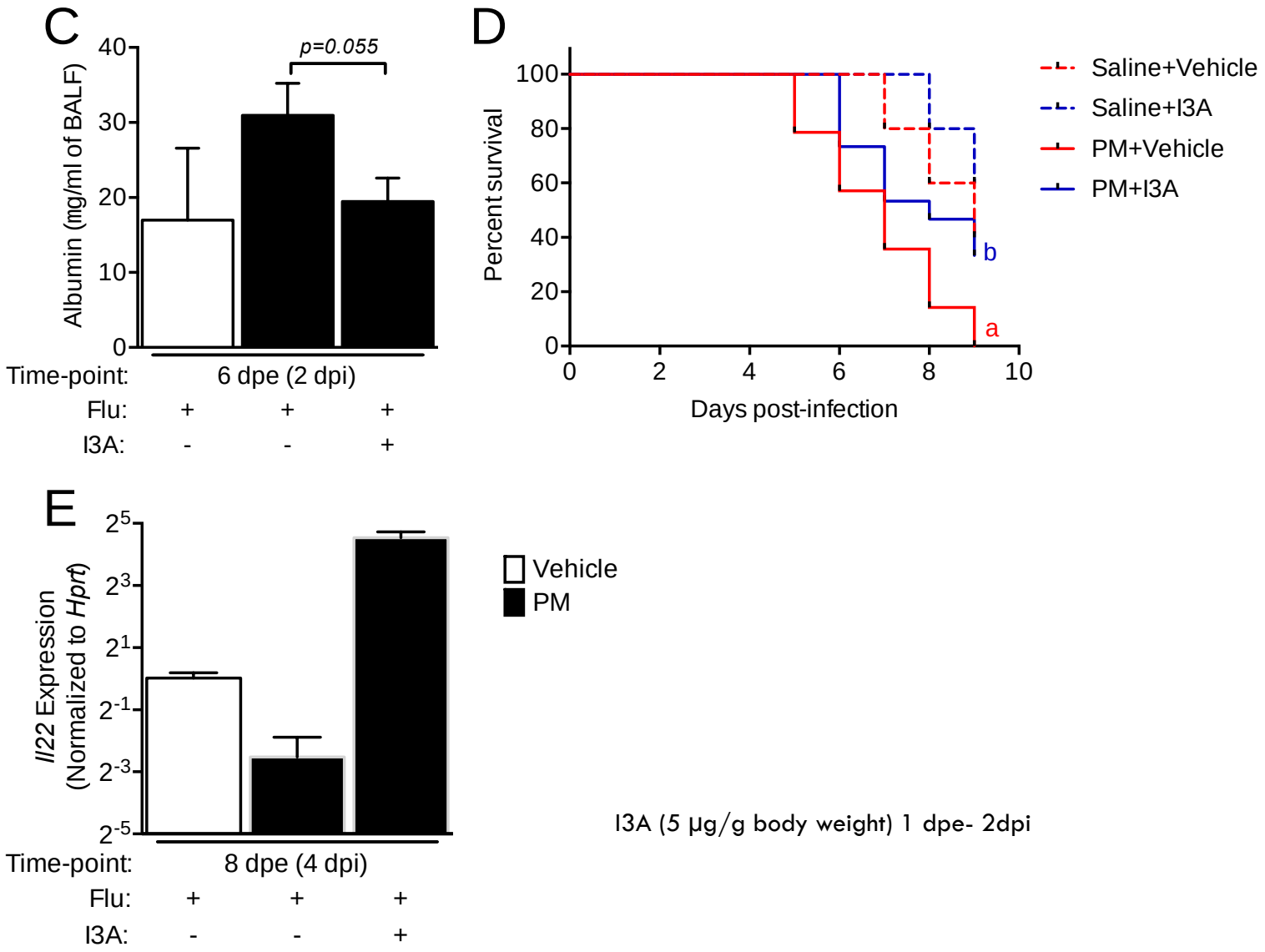
PM EXPOSURE DECREASES MICROBIAL-DERIVED INDOLE





Flu
- Epithelial repair
- Protective adaptive immune responses

I3A PROTECTS AGAINST PM EXACERBATED LUNG INJURY AND FLU INDUCED MORTALITY



I3A (5 µg/g body weight) 1 dpe- 2dpi

KEY RESULTS

Exposure to EPFR containing PM

- Increased morbidity and mortality from influenza virus infection
  - Oxidative stress required
  - Supplementation with antioxidants reduced lung injury and improved survival
- Correlates with
  - Enhanced pneumonia risk in a pediatric population
  - Increased incidence respiratory tract infections in exposed communities
- Increased morbidity and mortality from influenza virus infection
  - Reduced IL22 following influenza infection
  - Supplementation with IL22 reduced lung injury
- Microbiome important in production of AHR ligands required for survival and maintenance of IL22
  - EPFR containing PM alter lung microbiome
  - I3A supplementation can protect against EPFR induced lung injury and Flu Induced Mortality

Thevenot P, et al. AJRCMB. 2013. 48:188-97
Balakrishna S, et al. PFT. 2011;8:11
Wang P, et al. AJRCMB. 2011. 45: 977-983
Oyana, et al. EST. 2017
Oyana, et al EBM. 2021
Kumar et al., PFT, 2021 In Press

IMPACT

Global Environmental Health

- Role of inhalation exposures in the exacerbation of respiratory tract infections
- Mechanisms by which PM exacerbates disease
- Potential therapeutic targets for attenuating PM-induced RTVI morbidity and mortality

Environmental Policy

- Enhance monitoring practices to include EPFRs
- Development of air quality standards for exposure to EPFR containing PM

QUESTIONS?

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