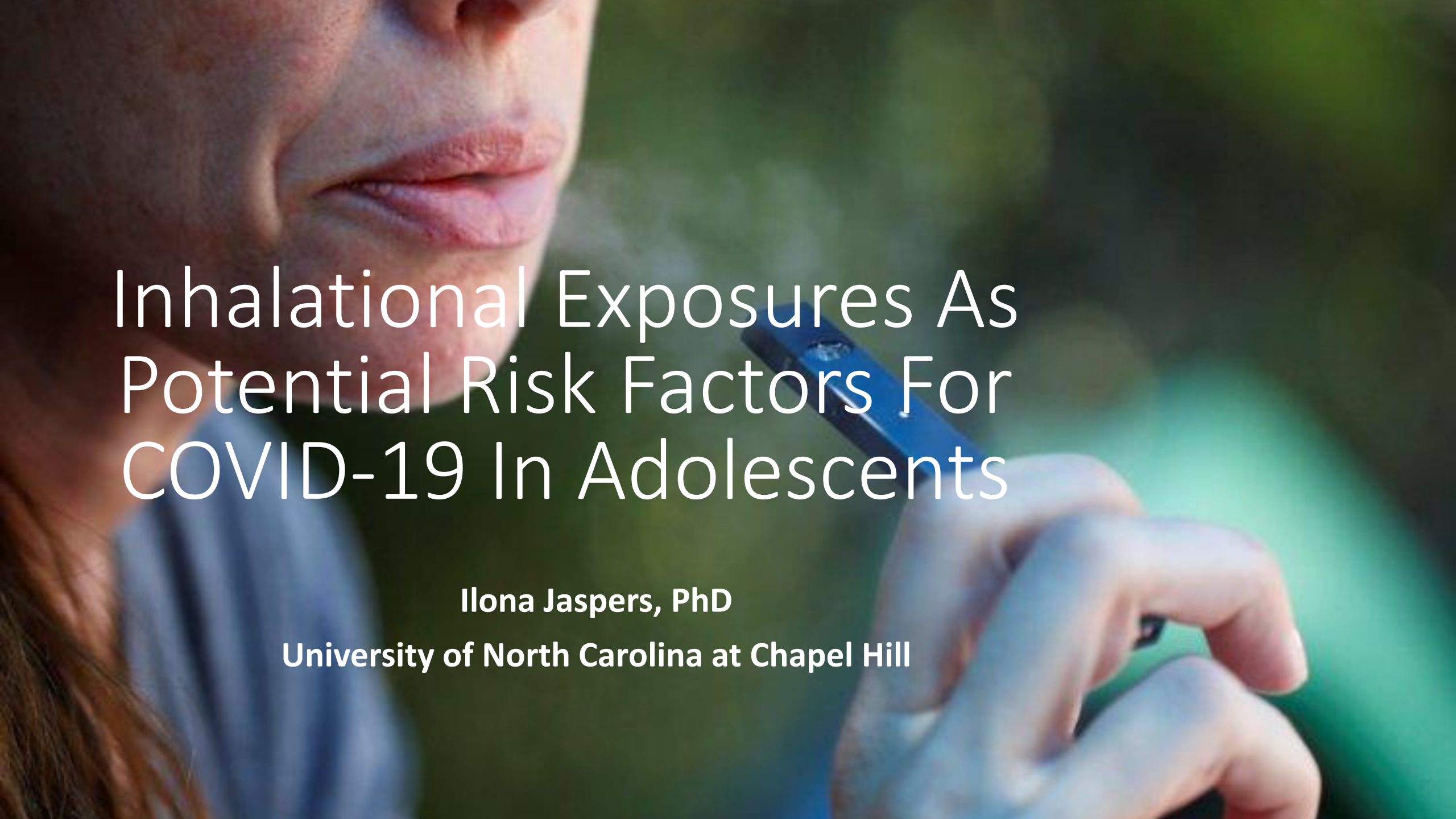
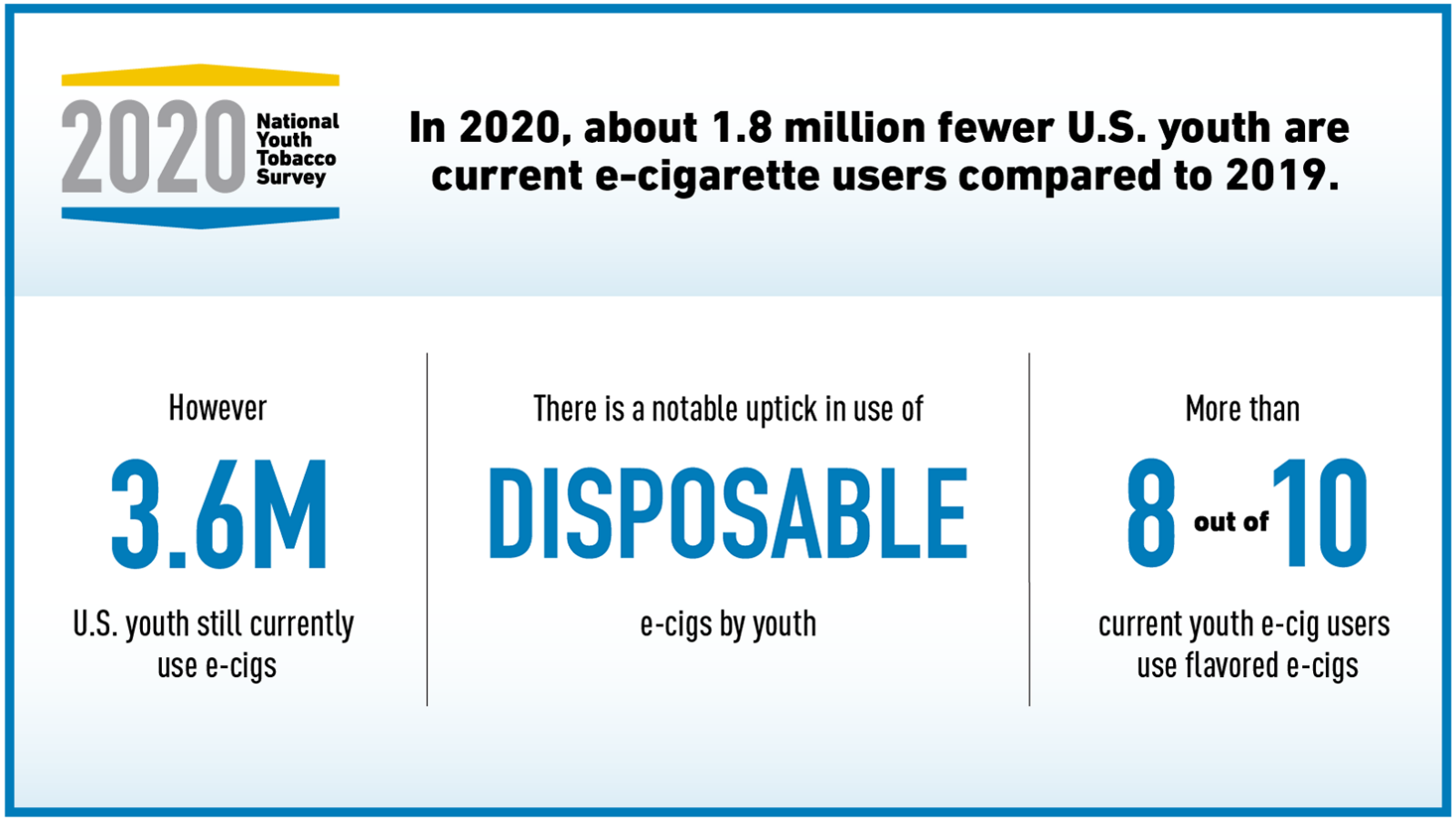


Inhalational Exposures As Potential Risk Factors For COVID-19 In Adolescents

Ilona Jaspers, PhD

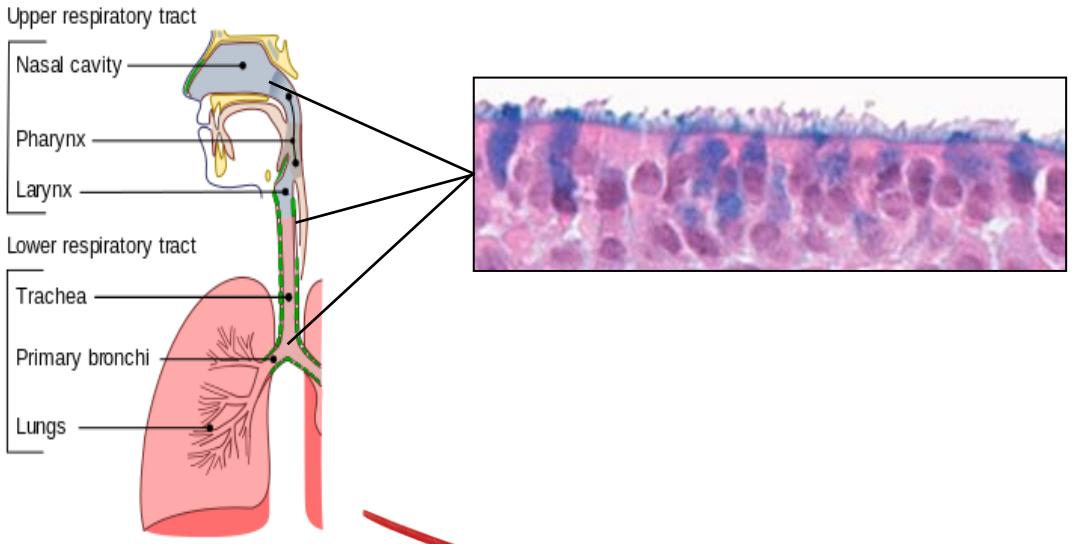
University of North Carolina at Chapel Hill

E-cig Use –
A Significant Risk Factor For COVID-19 in Adolescents?



Innate Defense Mechanisms of the Respiratory Tract

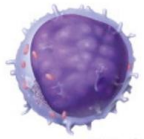
- We inhale 11,000 liters of air per day (volume of a concrete mixer truck)
- There are approximately 5,400,000 bacteria in 11,000 liters of air[1]
- Approximately 5,170,000 virus particles[1]



White Blood Cells

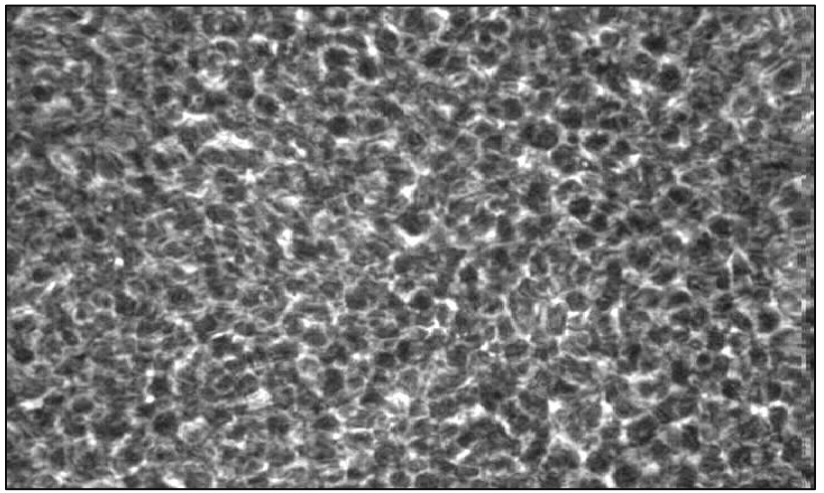
Macrophages

Neutrophils



Natural Killer (NK) Cells

Epithelial Cells

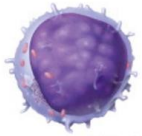


[1]Prussin 2nd, A. J., E. B. Garcia, and L. C. Marr. "Total Virus and Bacteria Concentrations in Indoor and Outdoor Air." Environmental science & technology letters 2.4 (2014): 84-88.

Do *flavored e-liquids* Impact the Respiratory Tract?
Example - Cinnamaldehyde

Macrophages

Neutrophils



Natural Killer Cells

+

Flavored E-liquids

➡

?

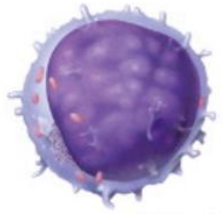
Cinnamaldehyde Inhibits Immune Cell Functions

Macrophages

↓ Ability to Ingest Bacteria

Neutrophils

↓ Ability to Ingest Bacteria



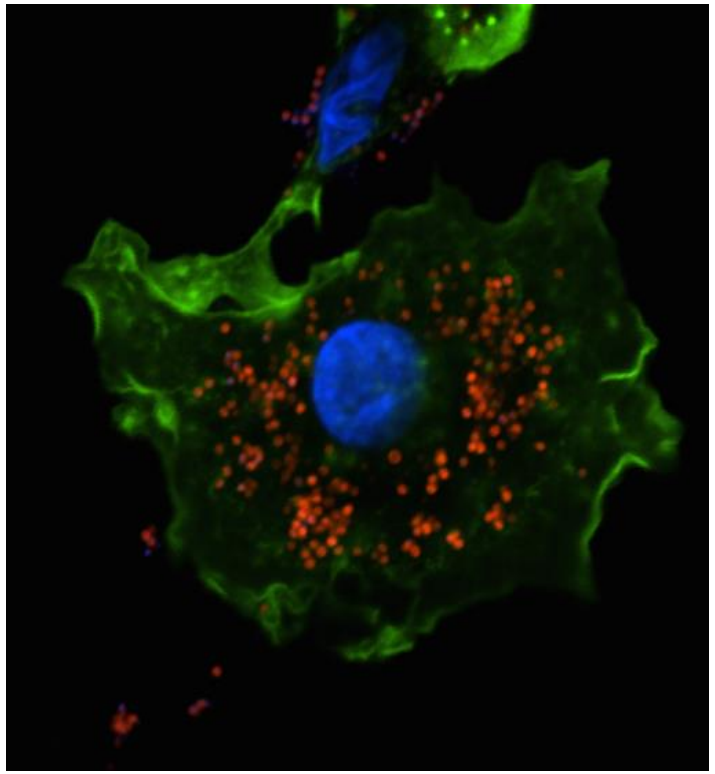
Natural Killer Cells

↓ Ability Kill Tumor/Virus-infected Cell

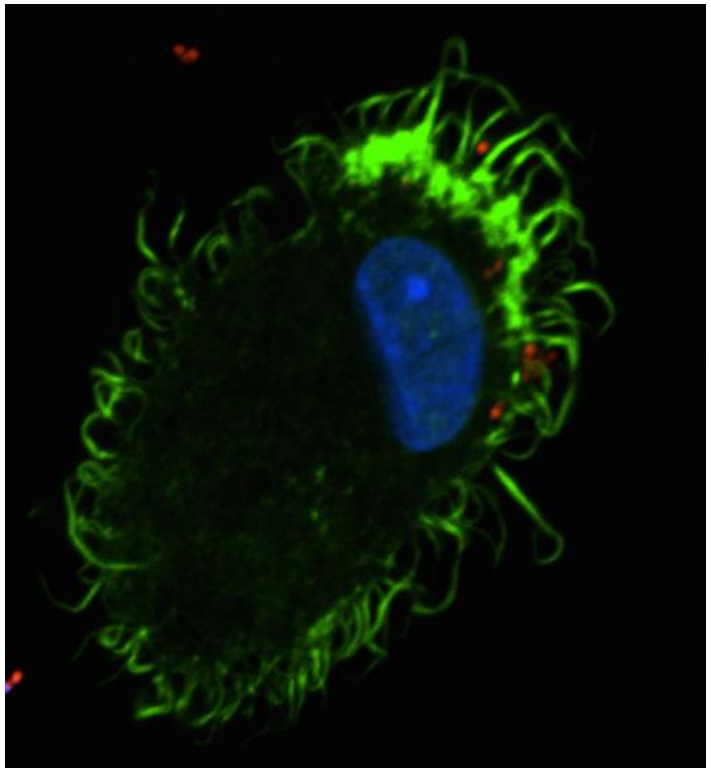
Clapp et al., 2017

Sini-cide Alters Macrophages

PG/VG



0.25% Sini-cide



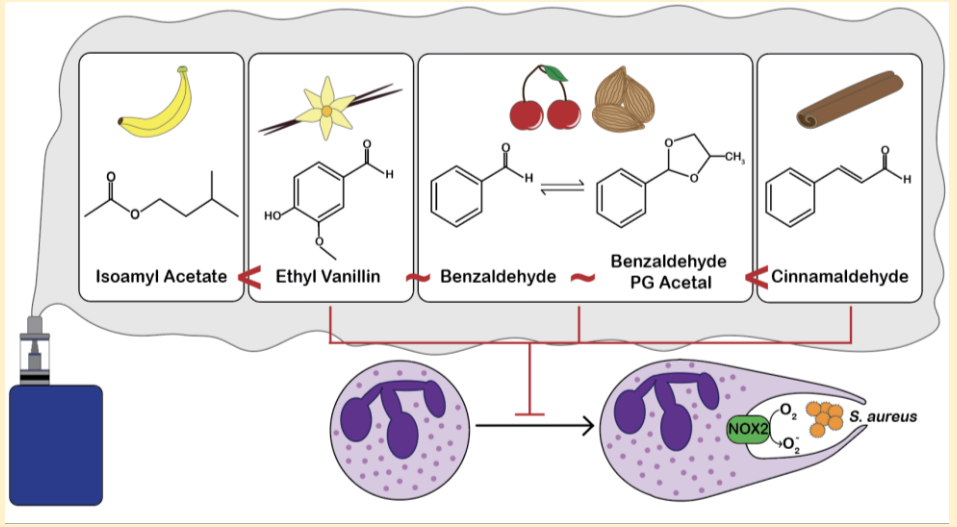
E-cig Flavorings Significantly Affect Neutrophil Function

- E-liquid flavorings can impair neutrophil functions at concentrations that do not produce cytotoxicity.
- Not all flavoring chemicals are created equal. Chemical classes can influence effects.
- Vaping **aromatic aldehyde-containing e-liquids** could result in impaired innate immune system response to airway infection.

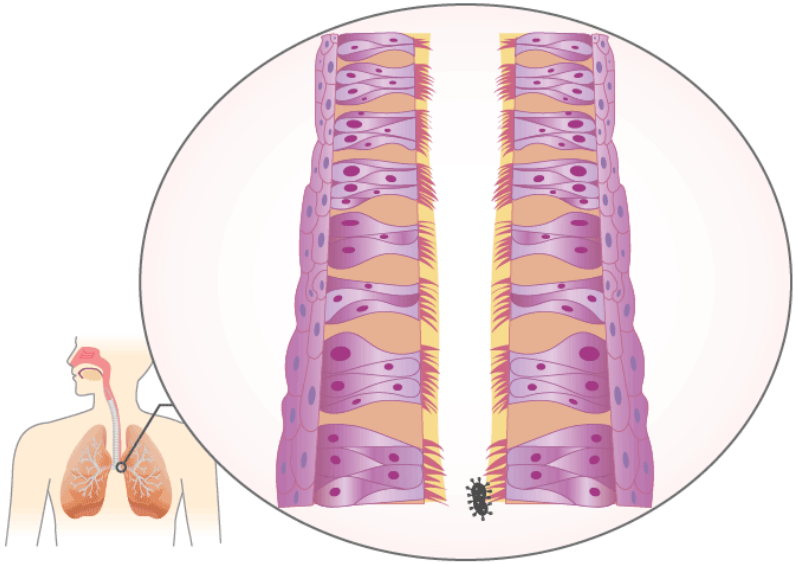
Common E-Cigarette Flavoring Chemicals Impair Neutrophil Phagocytosis and Oxidative Burst

Hickman, Herrera, Jaspers

Chemical Research in Toxicology, May 2019

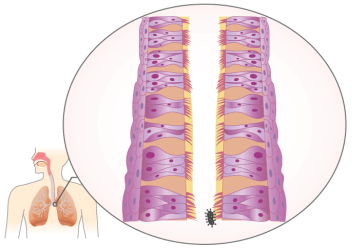


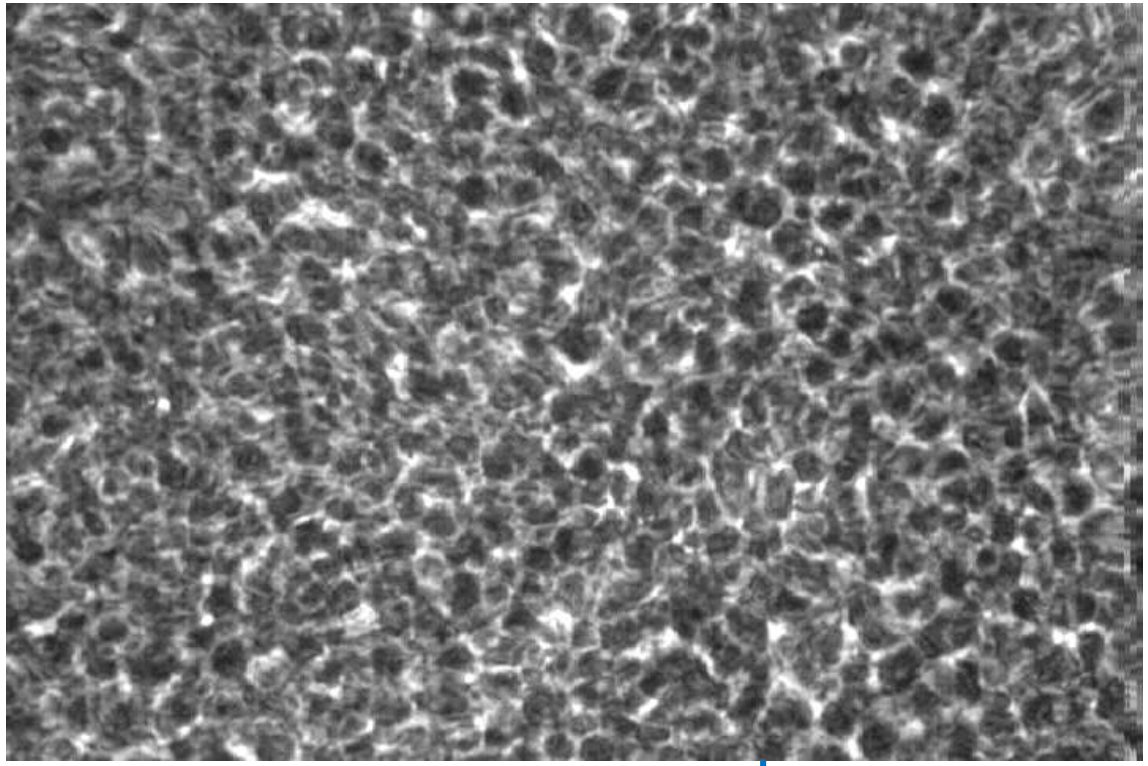
Do *flavored e-liquids* Impact the Respiratory Tract?
Example - Cinnamaldehyde

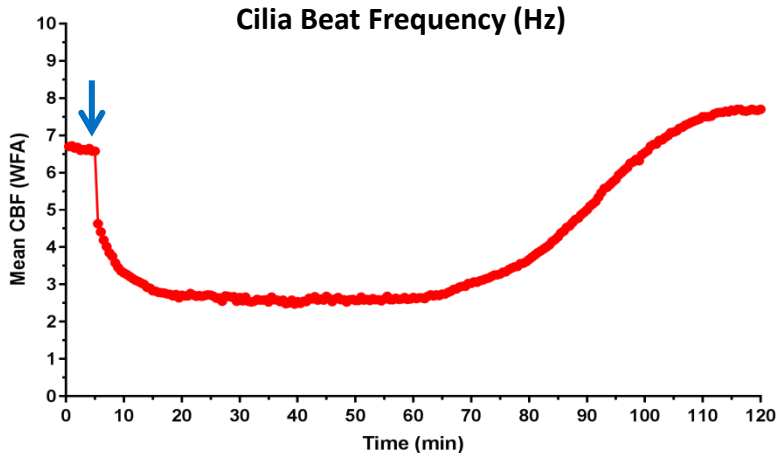


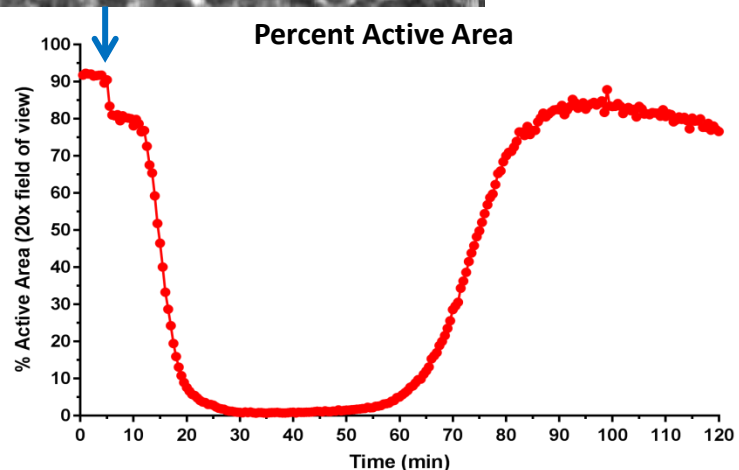
+ **Flavored E-liquids** → ?

1% Sinicide E-liquid on HBECs









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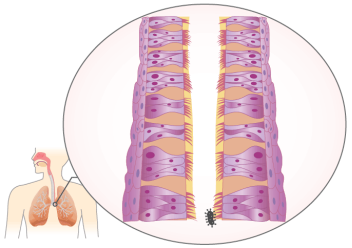
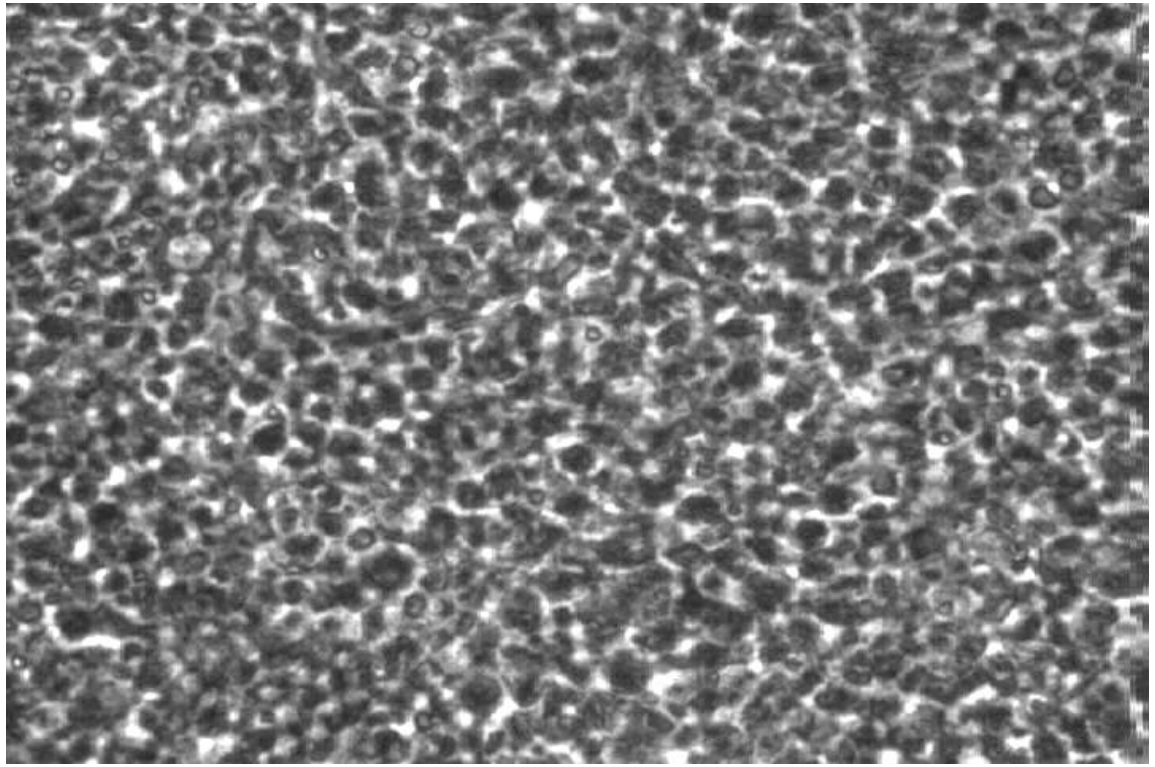
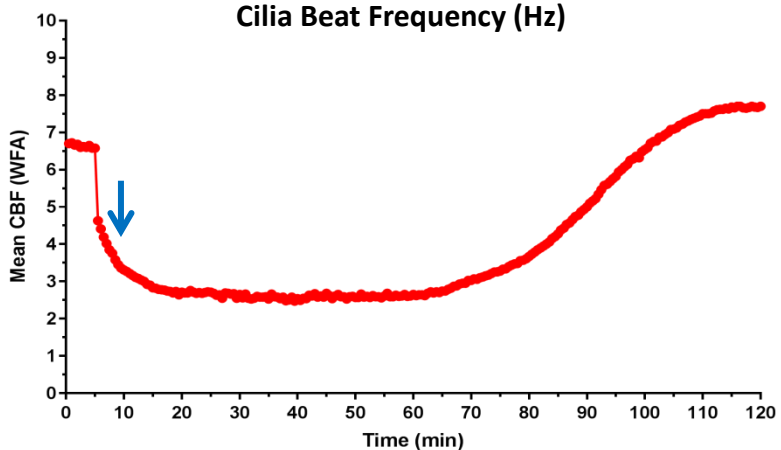
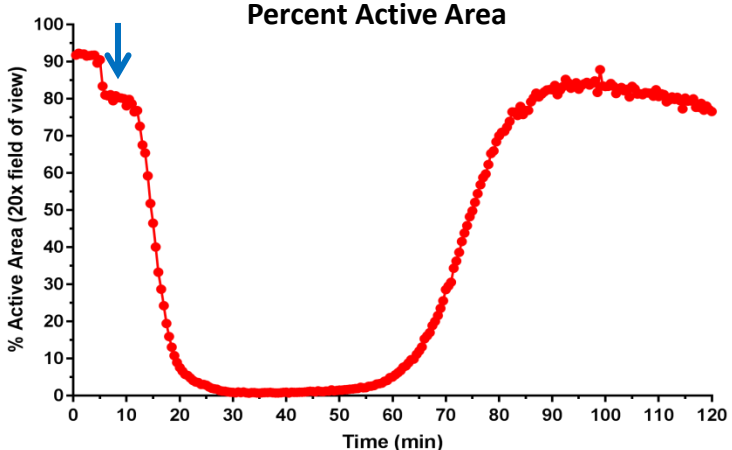




Cilia Beat Frequency (Hz)



Percent Active Area



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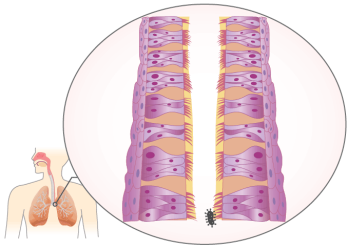
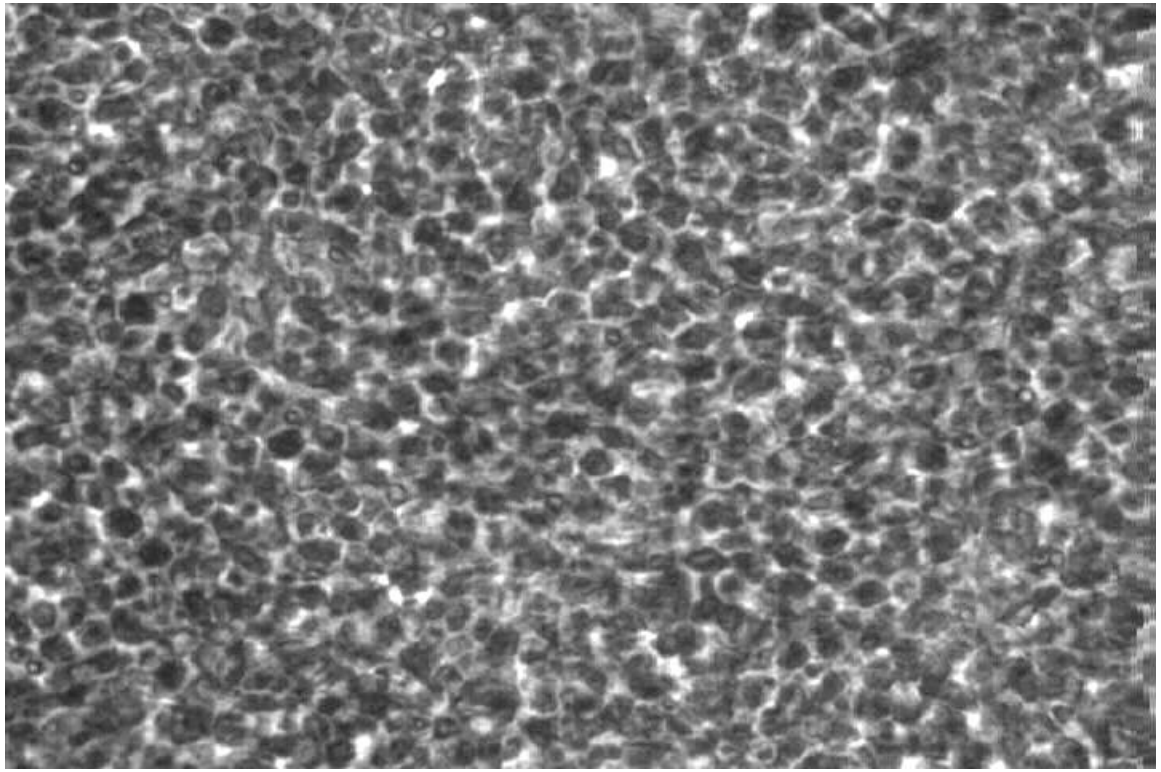
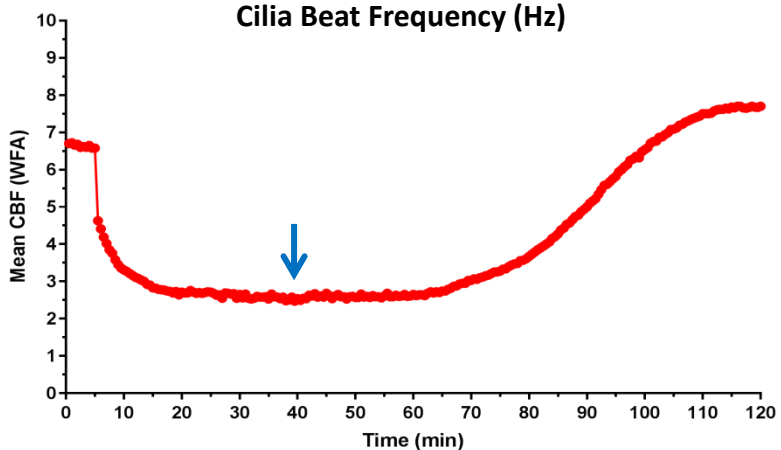
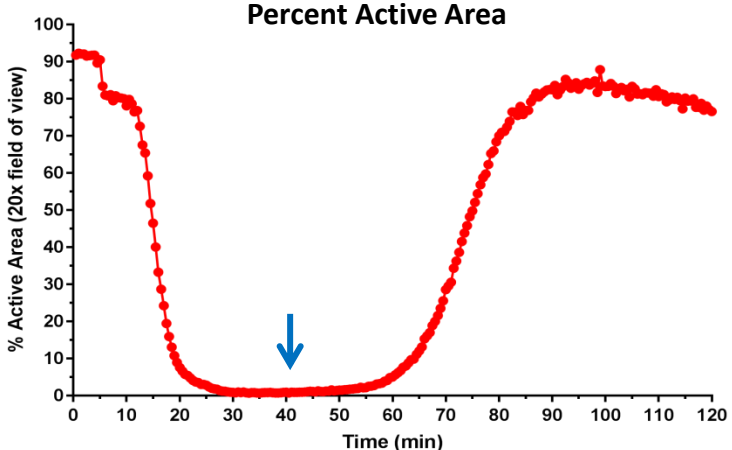




Cilia Beat Frequency (Hz)



Percent Active Area



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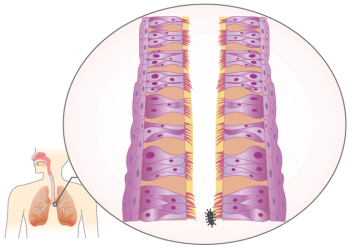
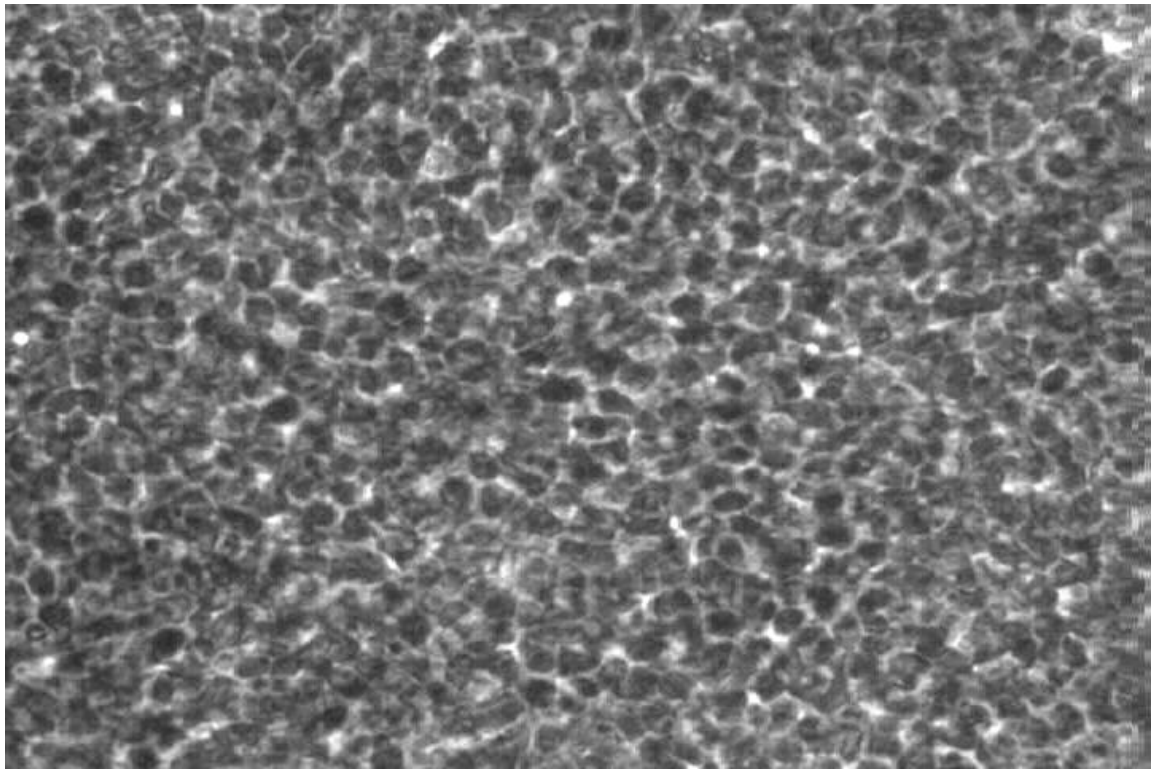
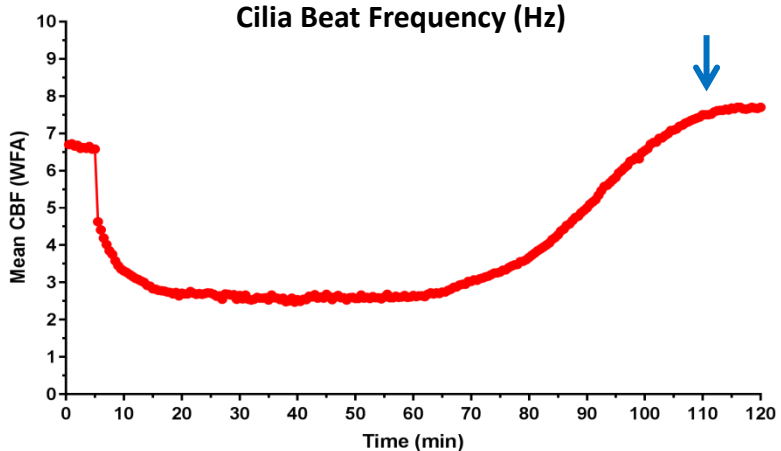
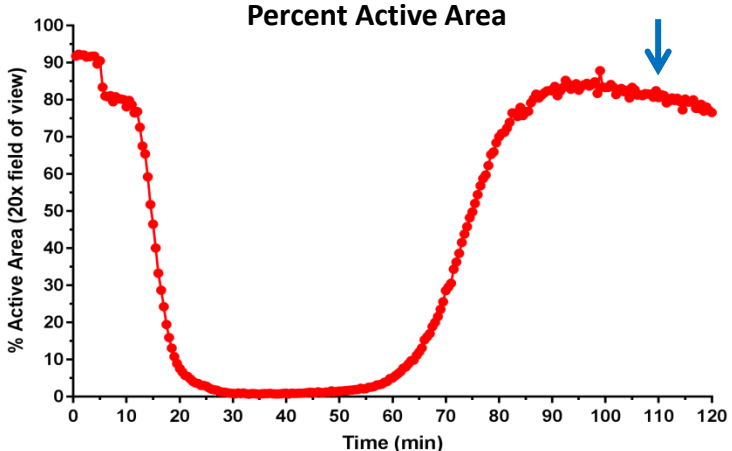








Acquisition and Analysis of Samples from the Nasal Mucosa

Nasal Scrape Biopsy

Obtain Nasal Biopsy from Healthy Volunteers

Analysis of Immune Gene Expression

Comparison of Non-Smokers, Smokers, and E-cigarette Users

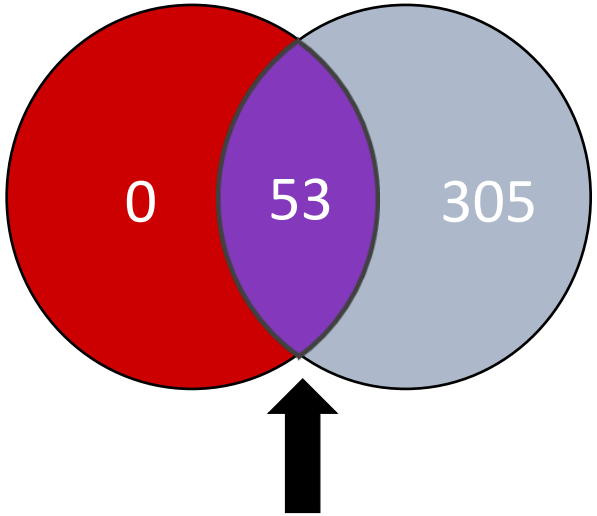
Indication of Changes in Respiratory Immune Status of Smokers and E-cigarette Users

Subjects were classified based on self-recorded smoking/vaping status and 3-week smoking/vaping behavior diary.

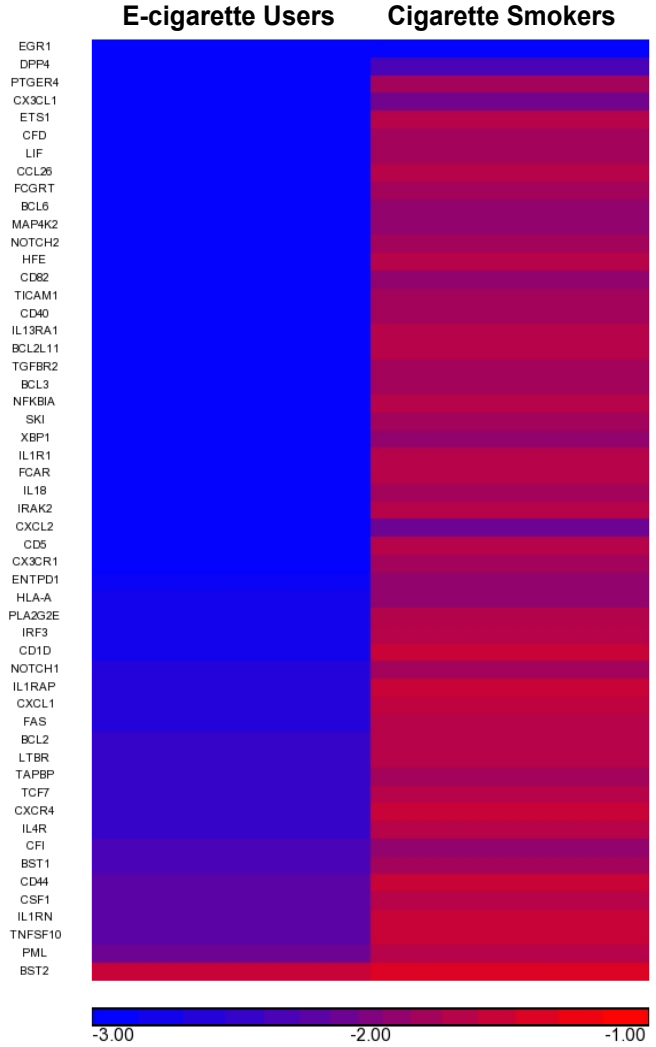
Individuals identified as mixed users based on the smoking diaries were excluded from the analyses

Martin et al., 2016

E-cig Usage Induces Greater Changes Than Cigarettes



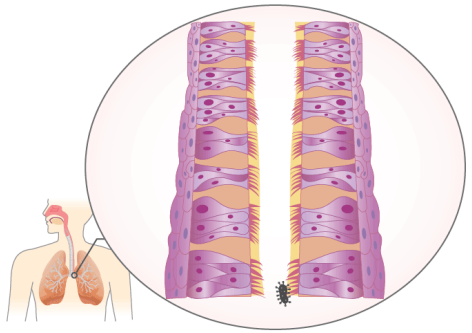
All changes in immune gene expression was **down-regulation**!

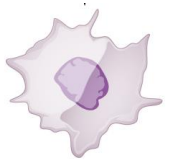


Martin et al., 2016

Our Lab's Research

Respiratory Host Defense





Macrophages

Neutrophils

E-cigarette cause an overall suppression of key host defense functions and immune dysfunction in the respiratory tract!

E-Cigarettes and Respiratory Host Defense

- E-cigarette aerosols, e-liquids, and their components can alter the function of airway cells and respiratory immune cells in multiple model systems and with a wide variety of exposure paradigms.
- Impairs antiviral pulmonary immune defenses in a mouse model. *(Sussan et al 2015, Madison et al 2019)*
- E-cigarette exposure can change virulence, bacterial persistence, and development of biofilm (*Gilpin et al 2019*)
- E-cigarettes increase antibiotic resistance *(Hwang et al 2016*)
    - E-cigarettes increase Staphylococcal virulence, causes resistance to antimicrobial peptides, and increases biofilm formation.

Young people who ever used **e-cigarettes**

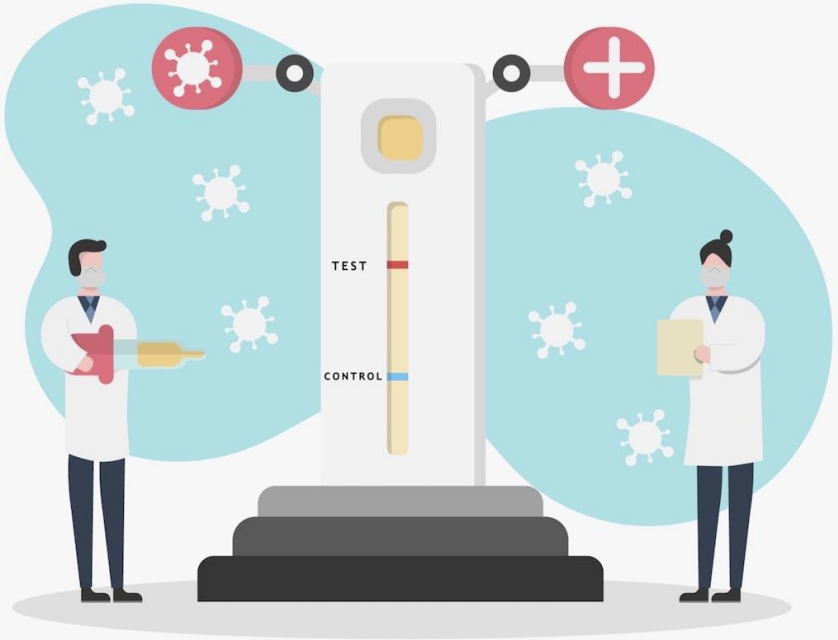
5x

more likely to be **diagnosed with COVID-19**

Young people who ever used **e-cigarettes plus conventional cigarettes**

7x

more likely to be **diagnosed with COVID-19**



ELSEVIER

JOURNAL OF ADOLESCENT HEALTH

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Original article

Association Between Youth Smoking, Electronic Cigarette Use, and Coronavirus Disease 2019

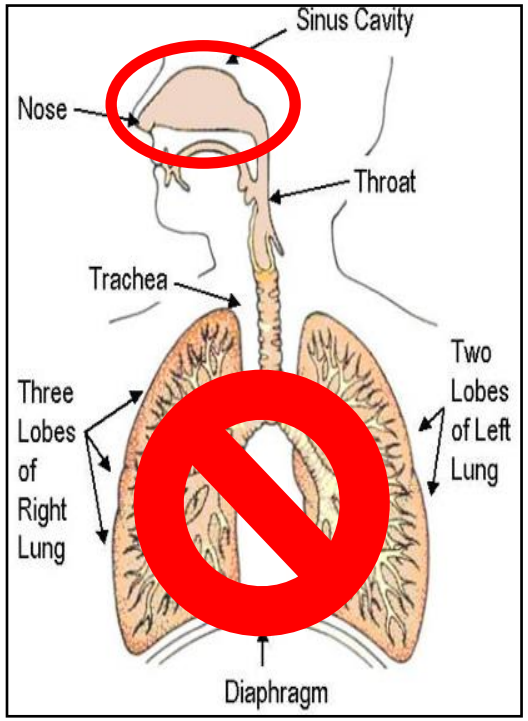
Shivani Mathur Gaiha, Ph.D. [a], Jing Cheng, Ph.D. [b], and Bonnie Halpern-Felsher, Ph.D. [a,*]

[a] *Division of Adolescent Medicine, Department of Pediatrics, Stanford University, Palo Alto, California*
[b] *Division of Oral Epidemiology and Dental Public Health, University of California, San Francisco, San Francisco, California*

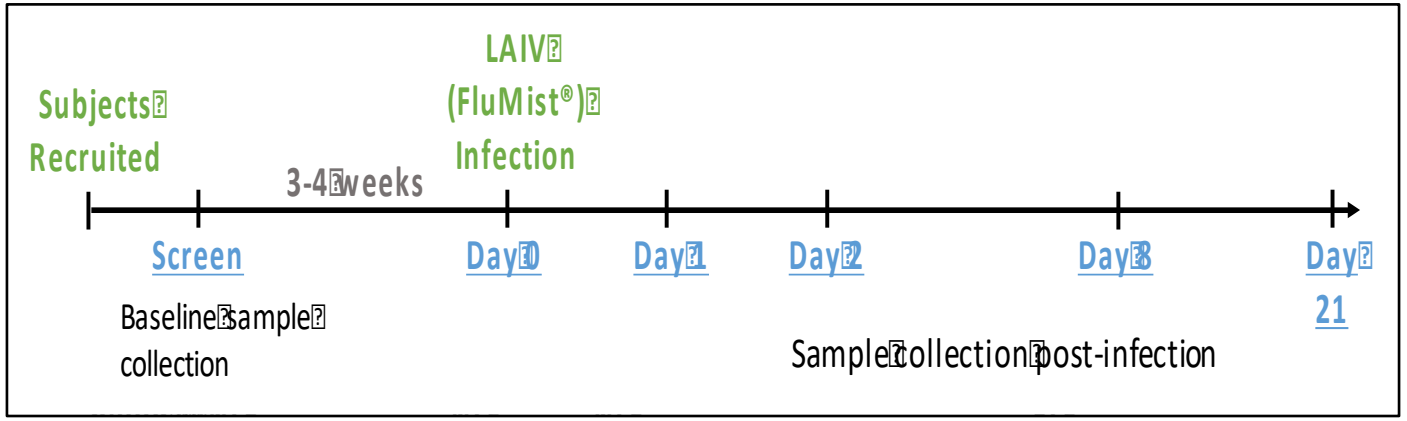
Human *in vivo* studies of Influenza Infections

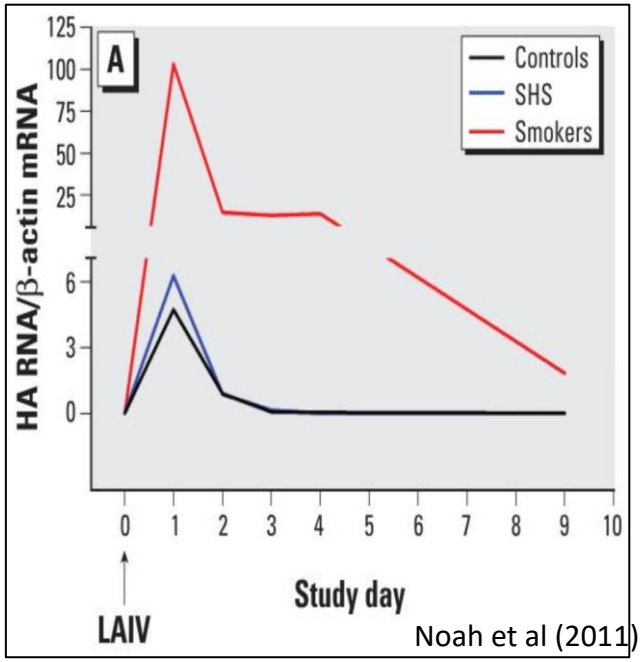
fluMist
Influenza Virus Vaccine
Live, Intranasal

- **FluMist™ is a cold-adapted Live Attenuated Influenza Virus (LAIV) vaccine**
- **"cold-adapted", thus replication limited to nasal cavity (32°C)**
- **It generates a replicative but self limited viral infection with innate and immune host defense responses**
- **Provides a safe tool to study influenza virus infections *in vivo***

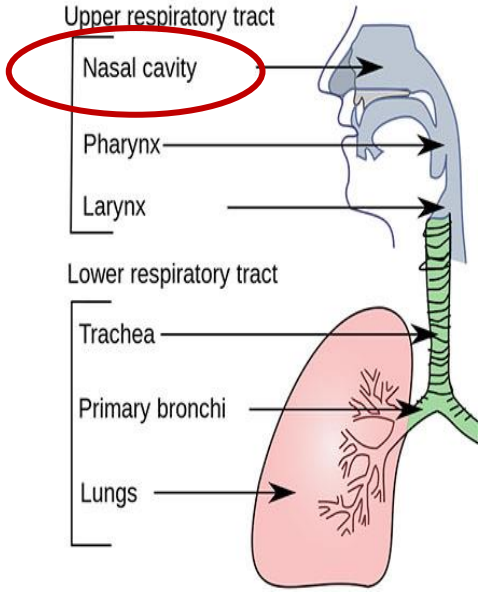


Study Timeline





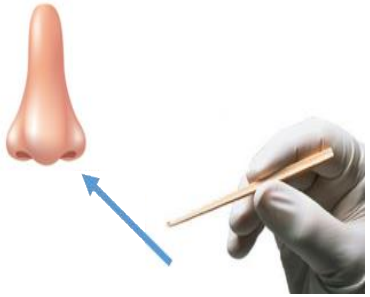
Noah et al (2011) EHP



- ELF
- NLF
- Nasal biopsy

Analysis Methods

Nasal Scrape Biopsy



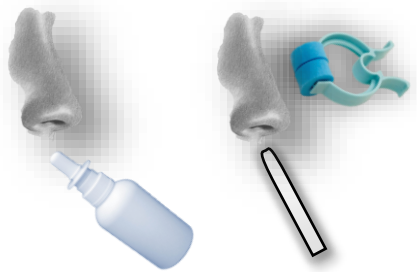
RNA extraction

Analysis of Immune Gene Expression

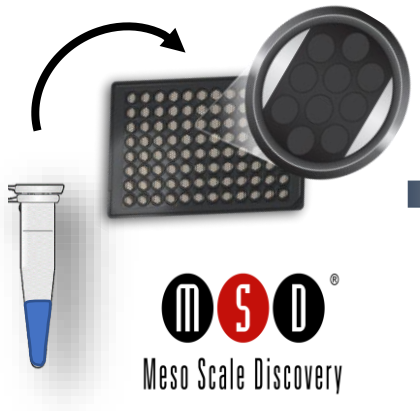
nanoString

Comparison of Non-Smokers, Smokers, and E-cigarette Users

ELF and NLF



ELF extraction and NLF processing



MSD

Meso Scale Discovery

IgA ELISA and multiplexed ELISA

Comparison of Non-Smokers, Smokers, and E-cigarette Users

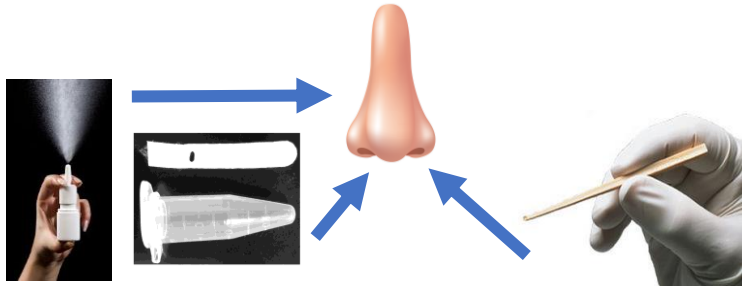
Evidence That E-cigs Affect Viral Infections

FluMist Quadrivalent
Influenza Vaccine Live, Intranasal

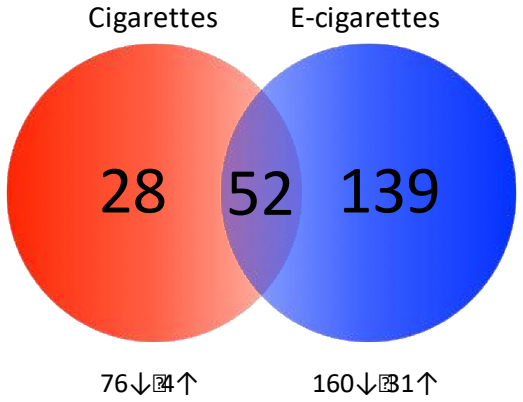
Live-attenuated influenza virus (LAIV)

- Live – it replicates like normal flu
- Attenuated – milder and limited to nose

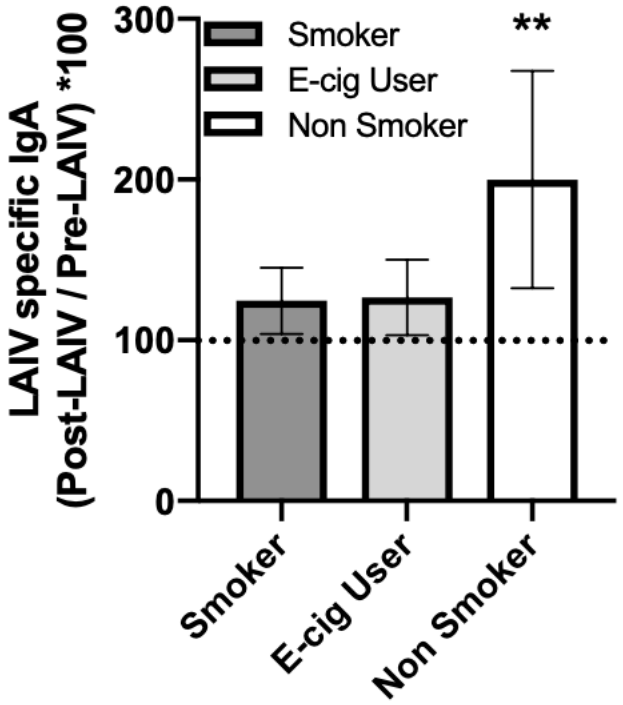
Recruited 1) Non-smokers, 2) Smokers, and 3) E-cig Users



Decreased Expression of Immune Genes



Decreased Levels of LAIV-specific Antibodies



Rebuli et al., 2020

Summary

- **The gene expression changes induced in the nasal mucosa of smokers and e-cigarette users are consistent with an immunosuppressive phenotype.**

- **Gene expression changes induced in the nasal mucosa of e-cigarette users overlap with those induced in cigarette smoker, but were greater (in # and magnitude) in e-cigarette users**

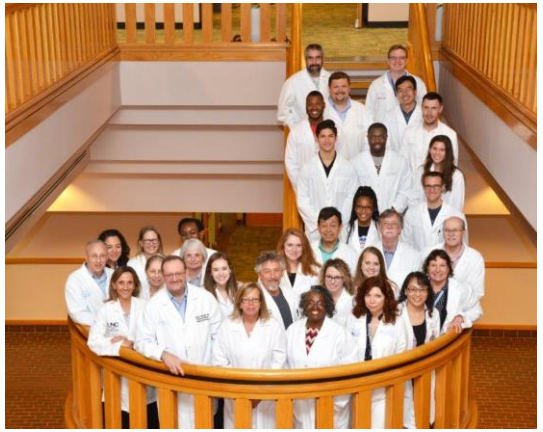
- **Antiviral host defense responses are compromised in smokers and e-cig users; nasal mucosal antibody levels are reduced**

What does this mean for vaping adolescents?

- **Even though their COVID-19 morbidity is usually mild, does vaping modify the disease?**

- **How does vaping affect nasal mucosal/systemic anti-SARS-CoV-2 antibodies? Magnitude? Persistence?**

Acknowledgements



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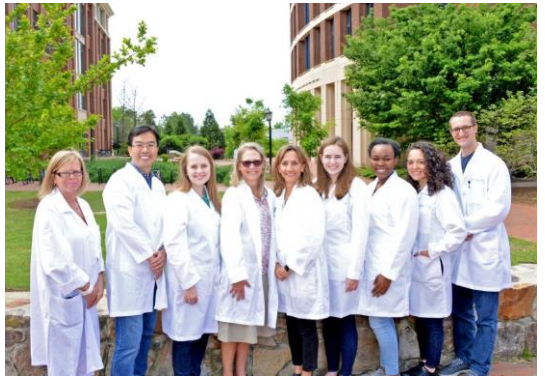

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Questions?

Summary of Previous Findings in Cigarette Smokers

Experimental virus infections (using the live attenuated influenza virus vaccine) resulted in blunted immune responses and enhanced markers of viral replication in the nose. (Noah et al., 2011, 2012)

These effects included reduced recruitment and activation of immune cells as well as decreased levels of key soluble mediators known to orchestrate host defense responses (Horvath et al.,2011, 2012)

General Immunosuppressive phenotype in Cigarette Smokers