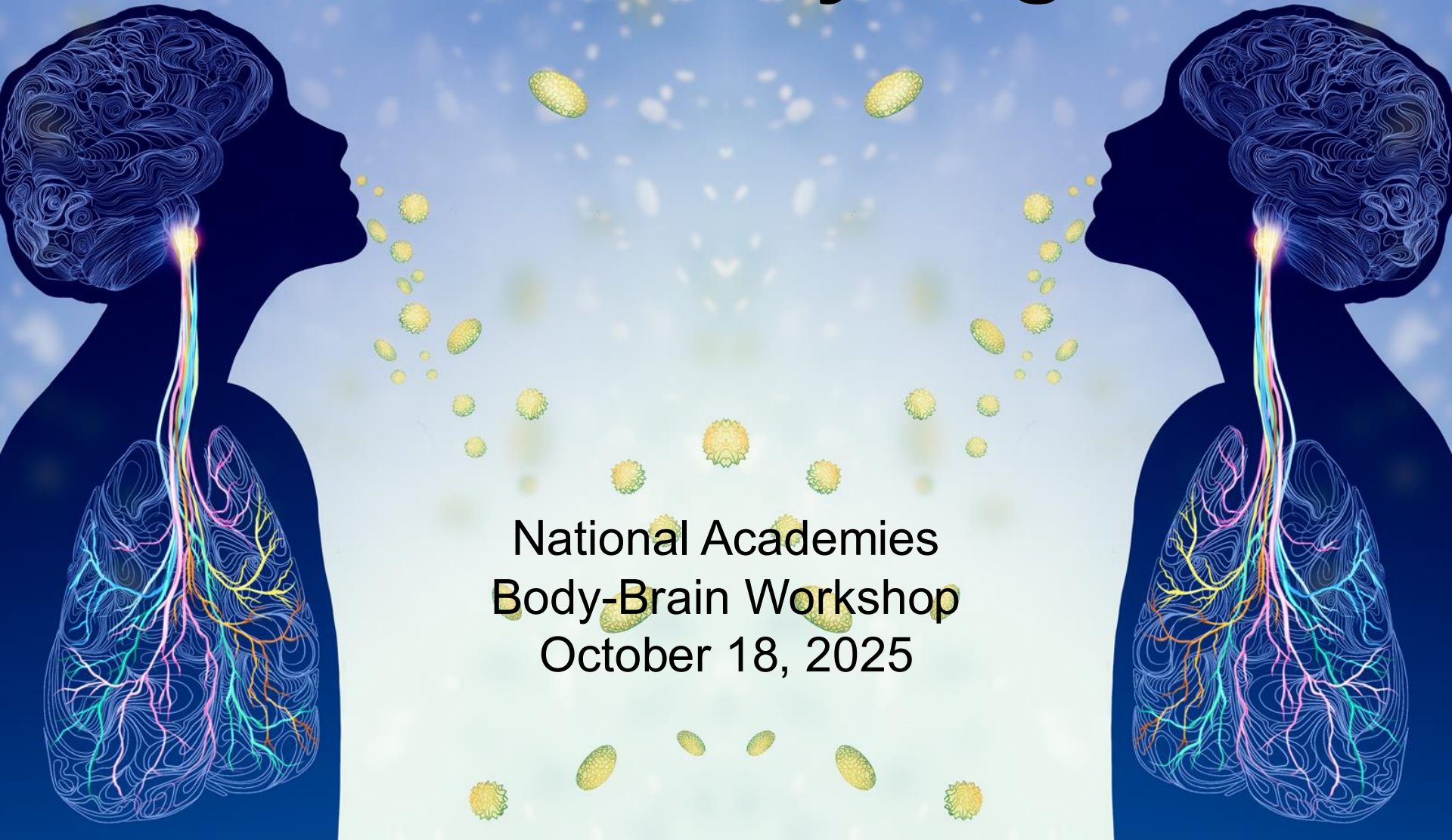
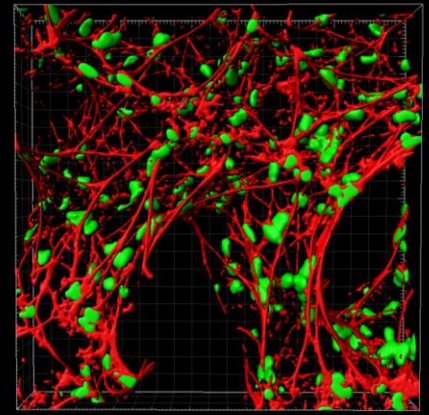
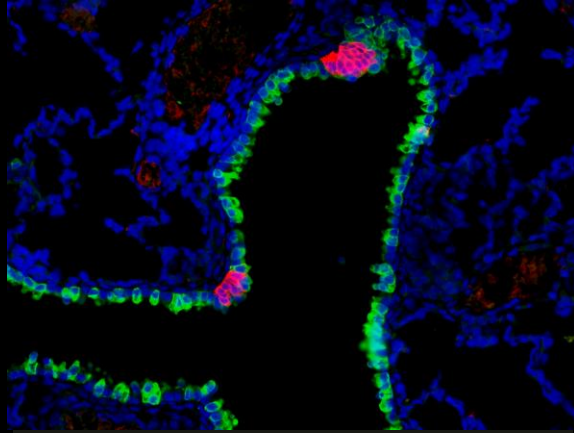
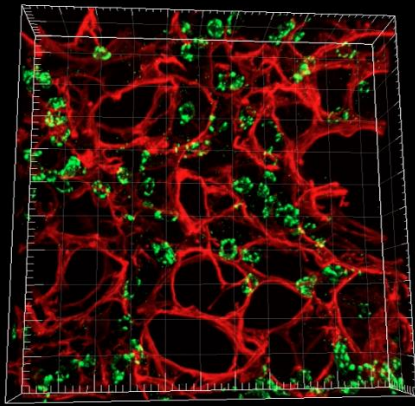


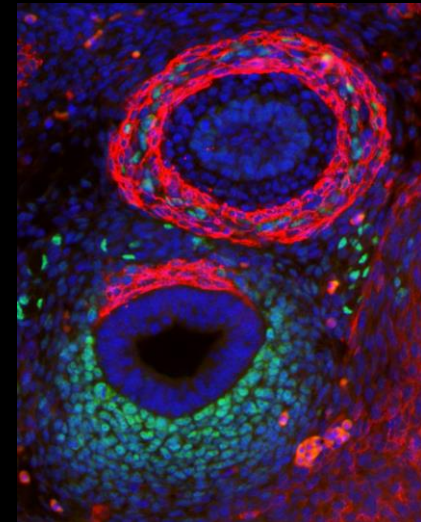
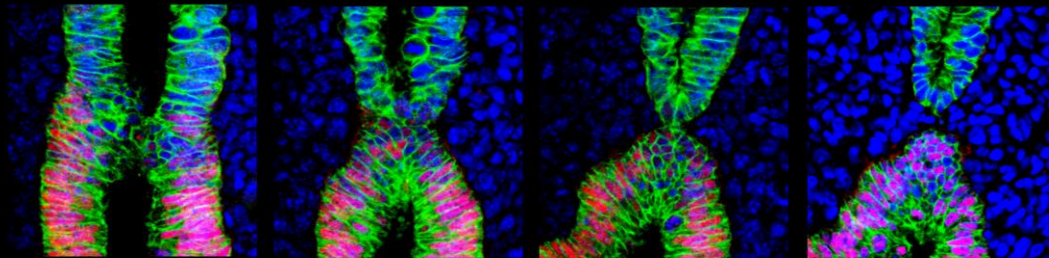
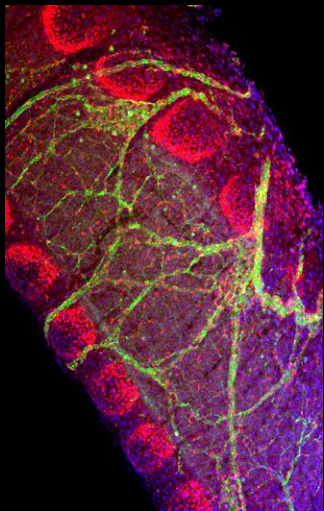
Consider the Lung as a Sensory Organ



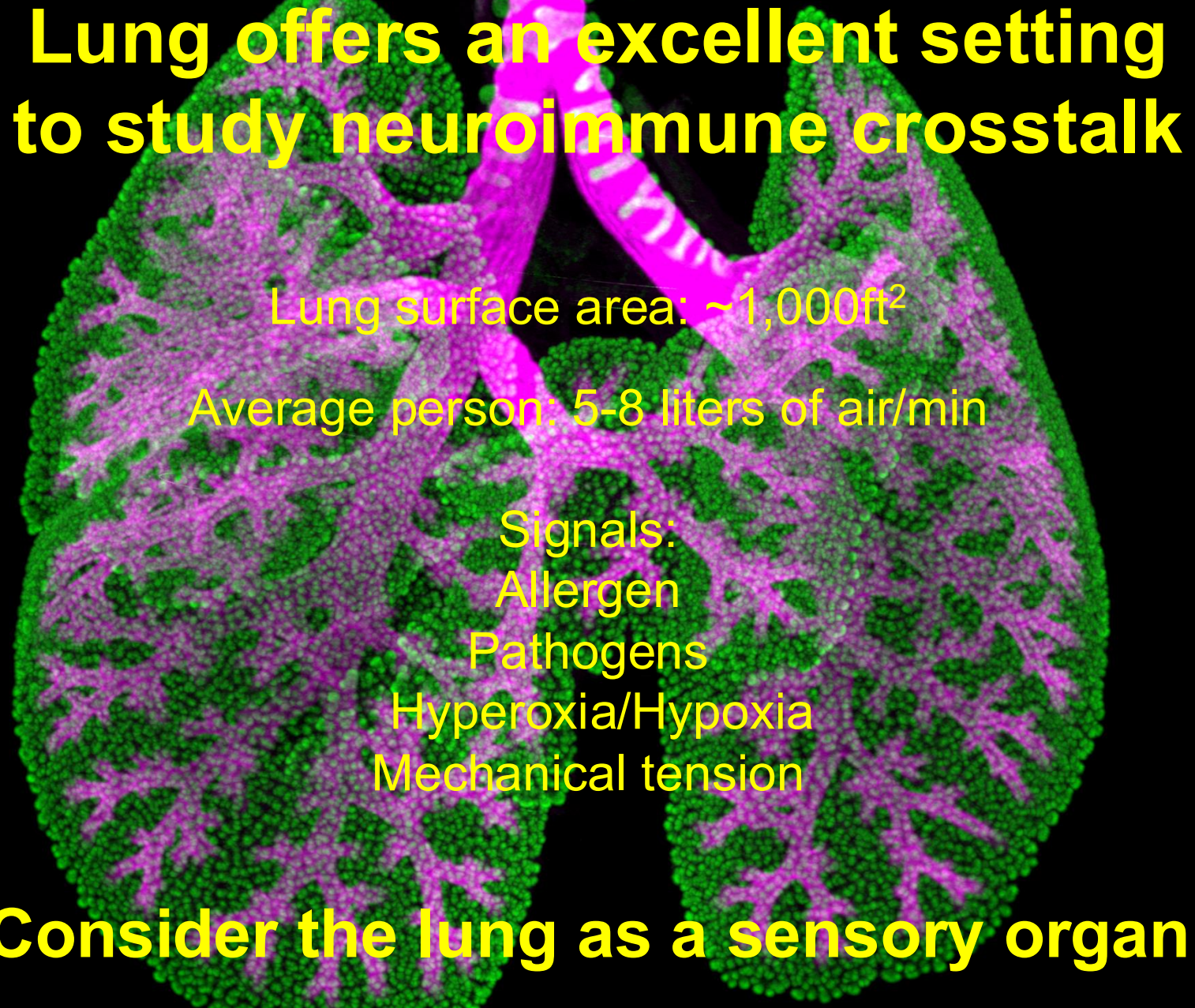
National Academies
Body-Brain Workshop
October 18, 2025



The Many Curiosities of Lung



Lung offers an excellent setting to study neuroimmune crosstalk



Lung surface area: $\sim 1,000\text{ft}^2$

Average person: 5-8 liters of air/min

Signals:

Allergen

Pathogens

Hyperoxia/Hypoxia

Mechanical tension

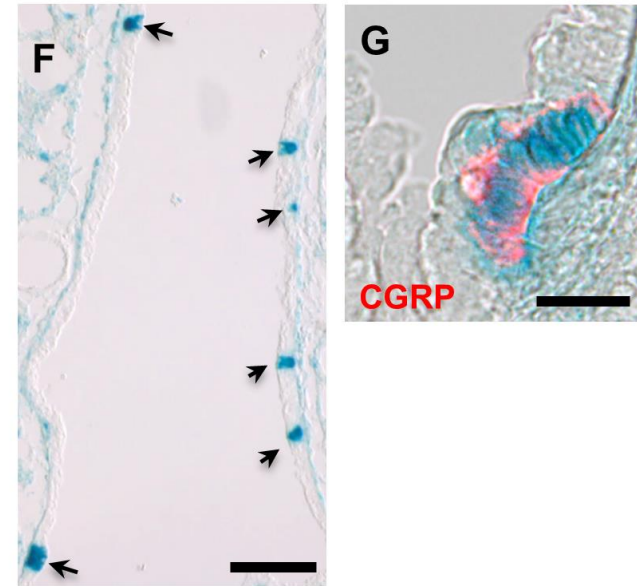
Consider the lung as a sensory organ

Pulmonary neuroendocrine cells (PNECs)

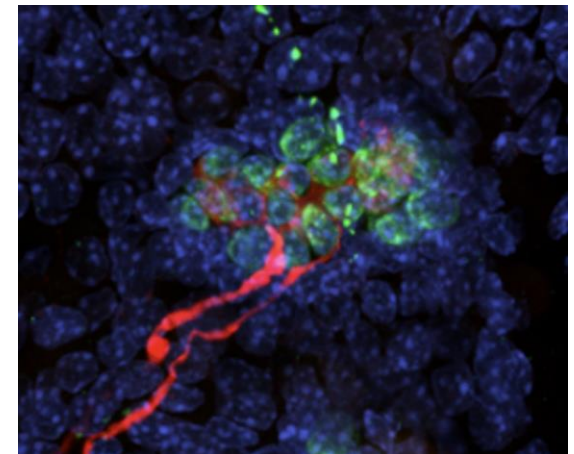
- Rare: <1% of airway epithelium.
- Senses signals and produce neuropeptides and neurotransmitters.
- Neuronally innervated.
- Changes of PNECs documented in many lung diseases: asthma, COPD, pulmonary hypertension, etc.
- Cell of origin for small cell lung cancer

Can change in a rare lung cell type impact lung function?

Robo1;2-LacZ

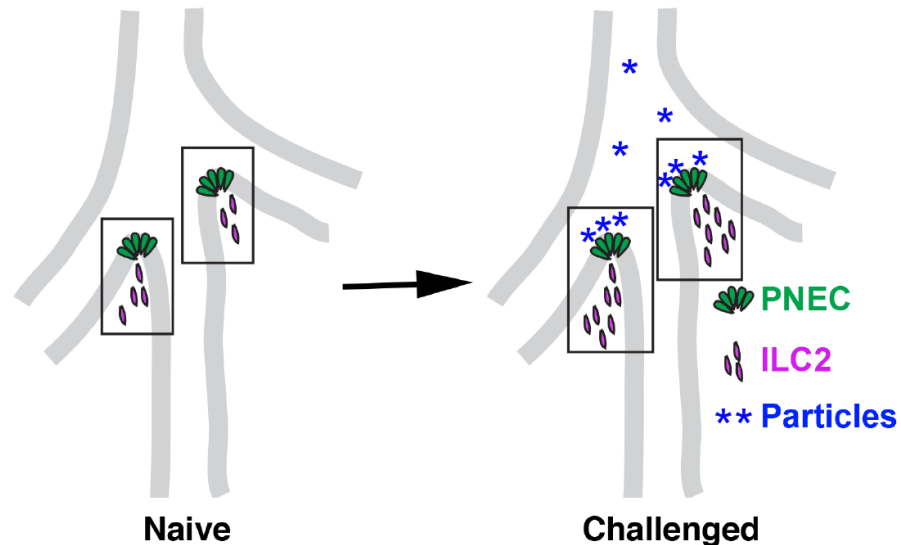
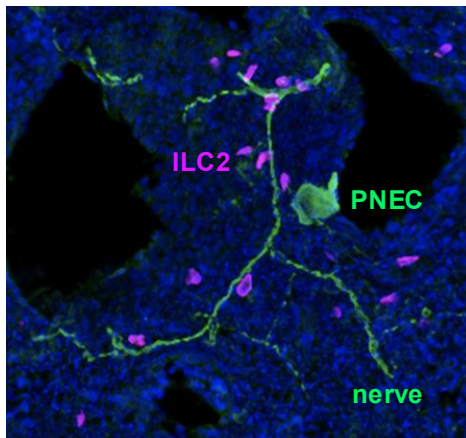
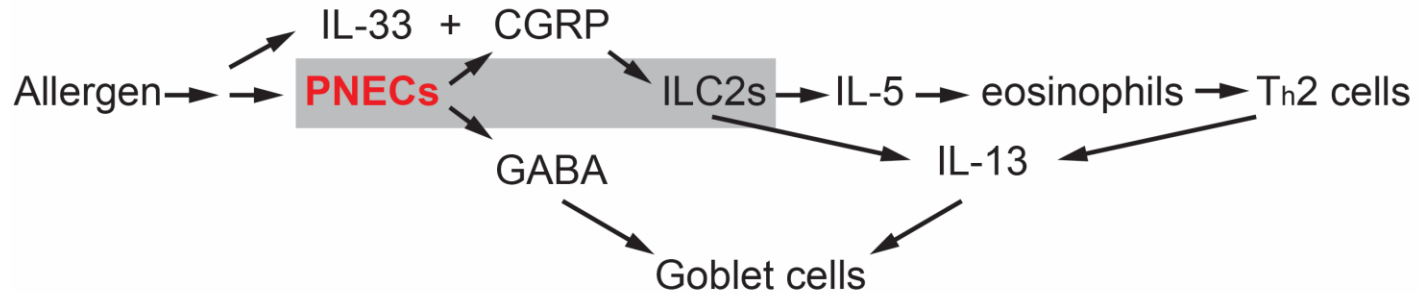


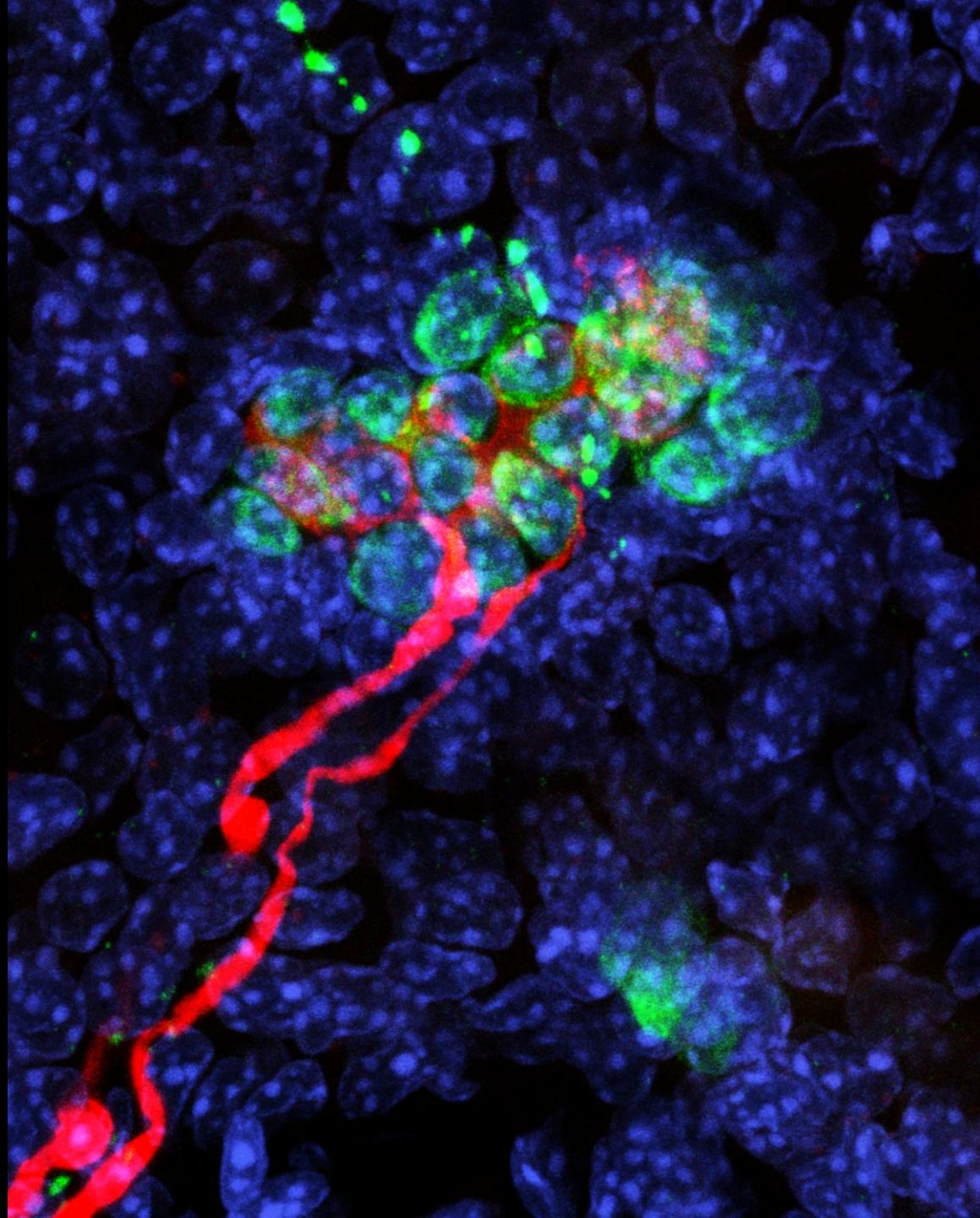
Branchfield et al. and Sun
Science, 2016.



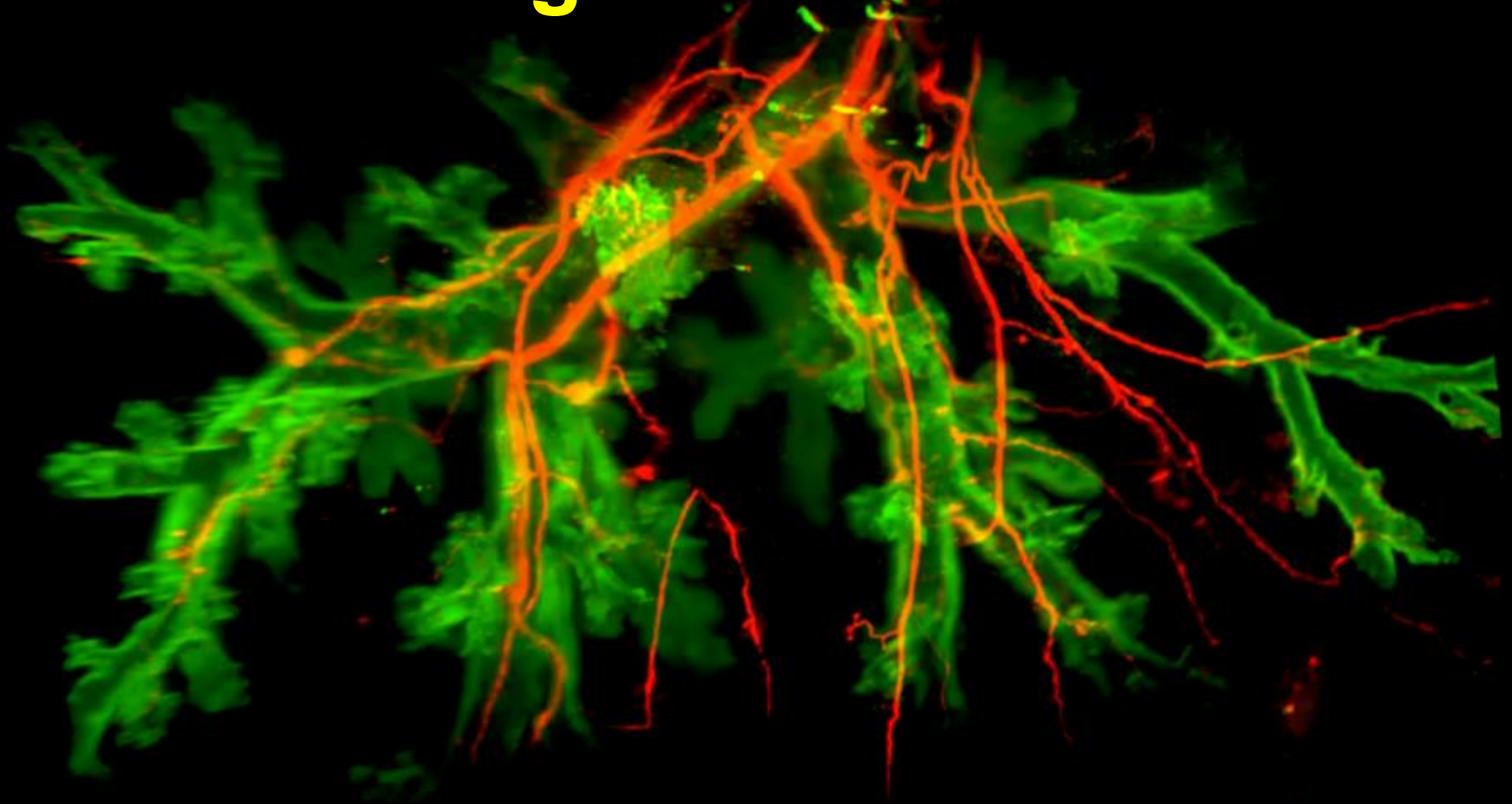
Su, Barr, Sun et al., AJP 2022

PNECs are essential for allergen-induced asthmatic response





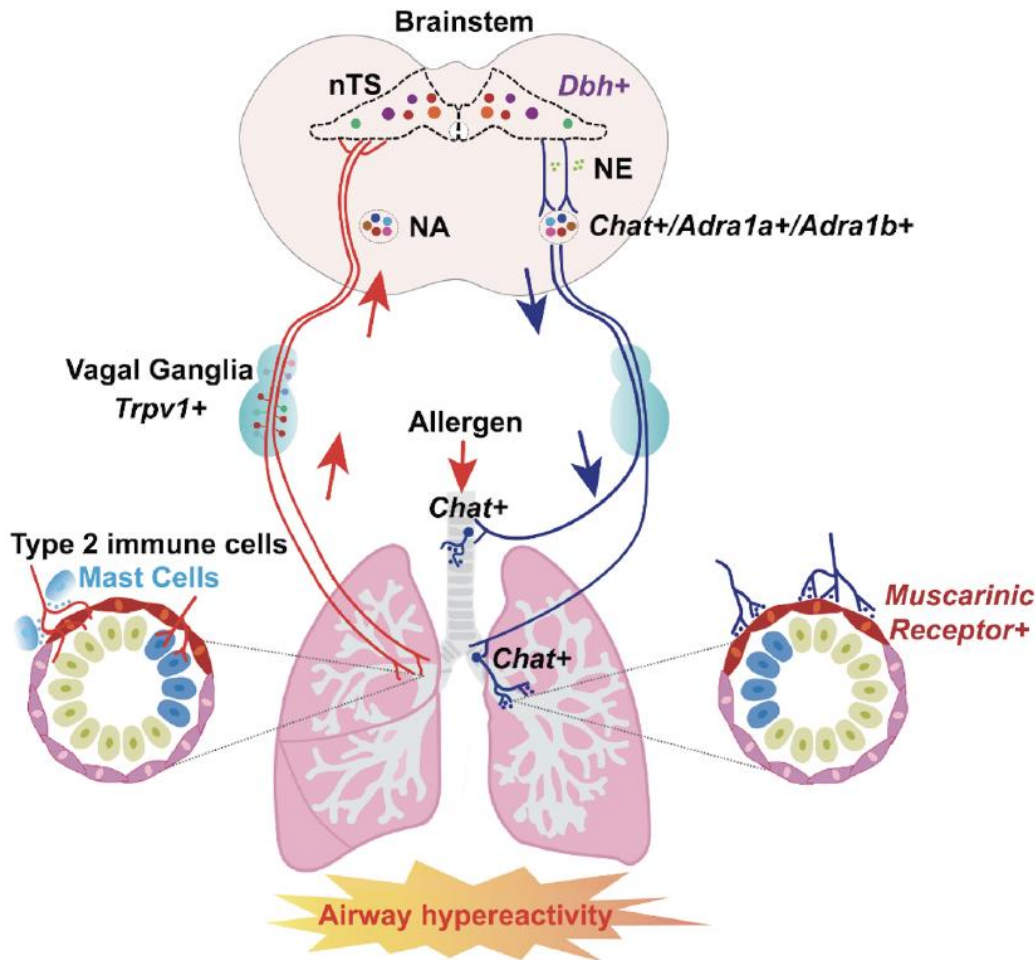
Lung Innervation



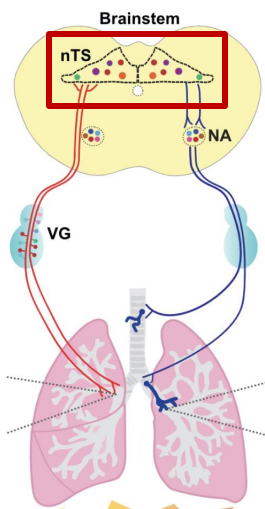
Nkx2.1^{GFP} *Vglut2-cre; tdTom*

Su and Barr et al. and Sun, *AJP*, 2022

An Allergen Circuit



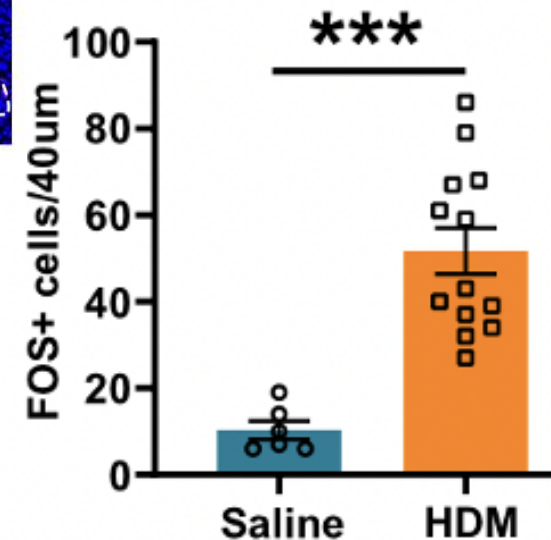
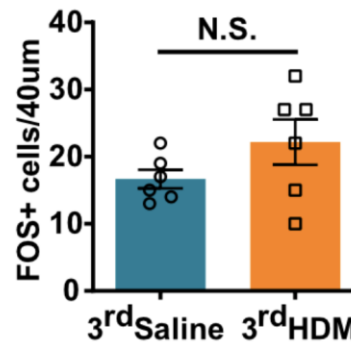
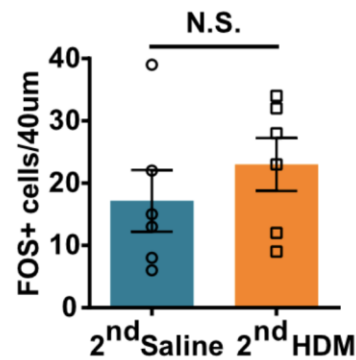
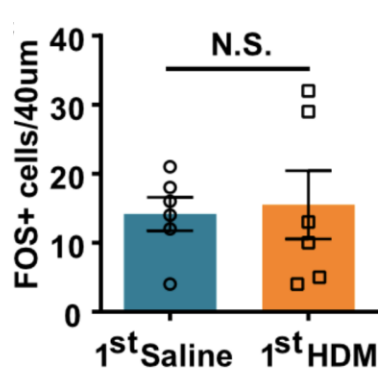
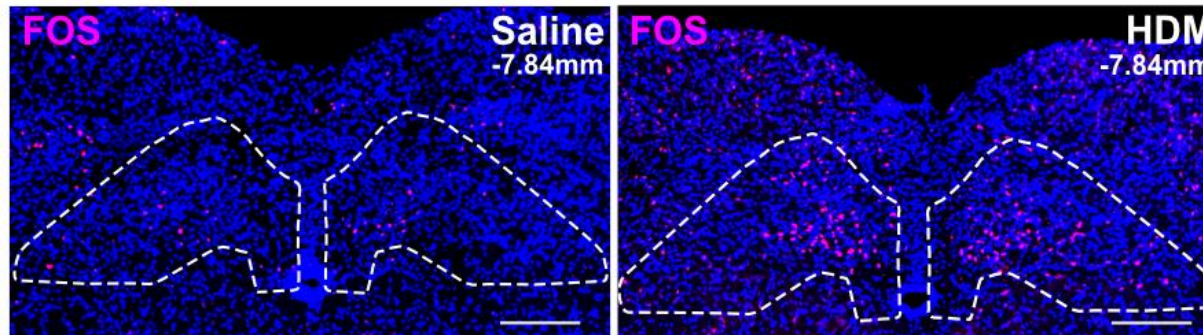
- Rich foundational knowledge
- Chronic response
- Disease (asthma) relevant
- From lung to brain and back to lung



Allergen challenge activated brainstem nTS neurons in a dose-dependent manner

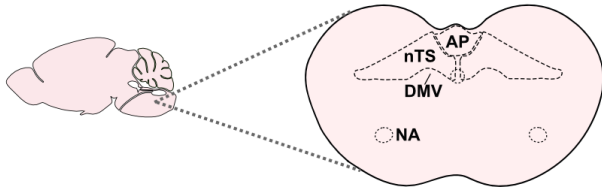


HDM
House dust mites

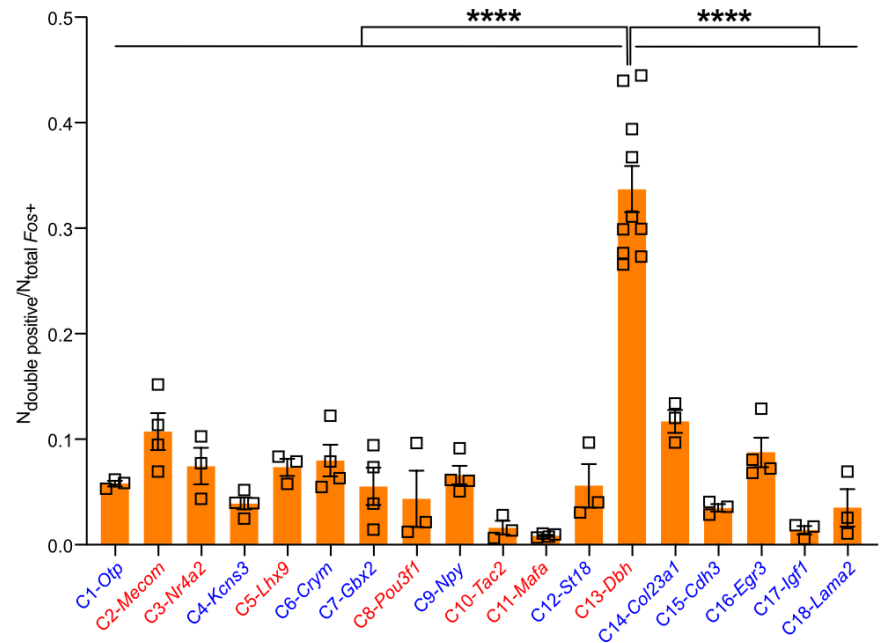
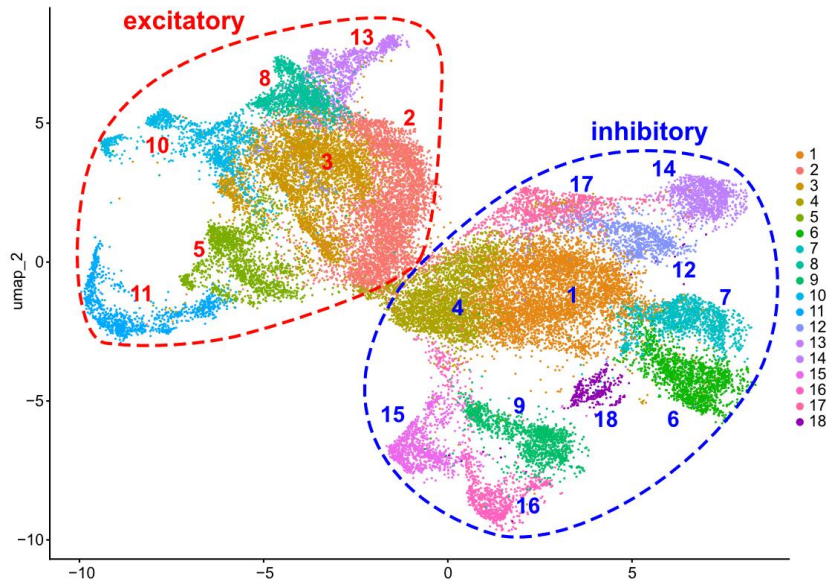


Dbh+ nTS neurons are preferentially activated

Enriched activation of Dbh+ nTS neurons



n=6 biological replicates, n=12 mice
32,880 nTS neurons

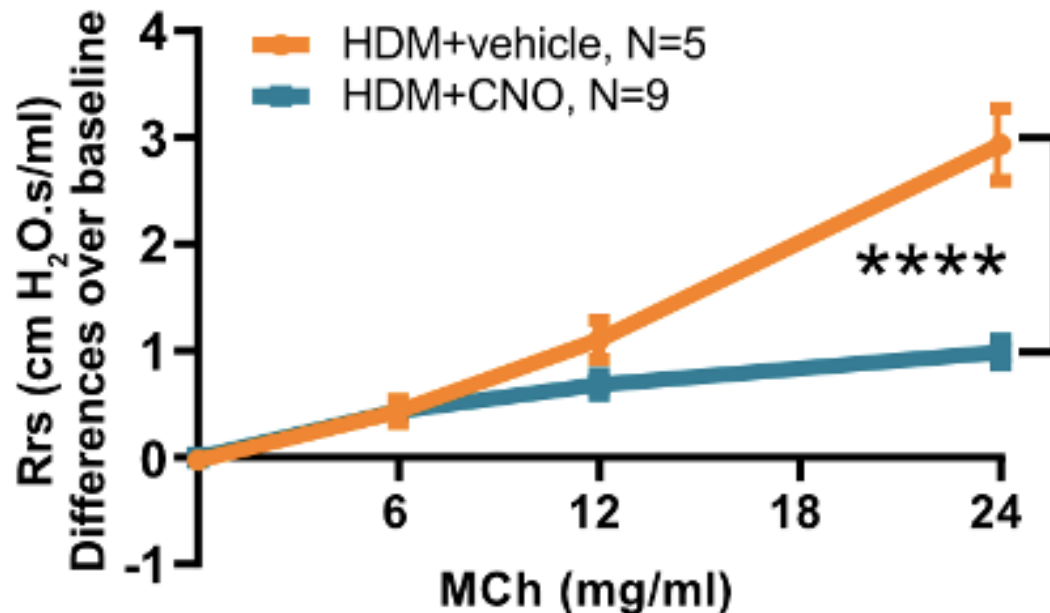
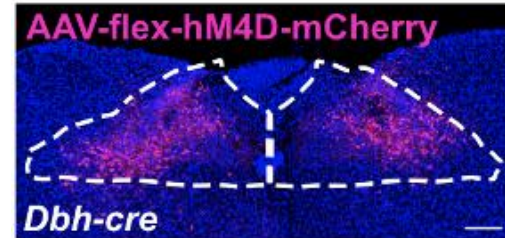


nTS DBH+ neurons are necessary for allergen-induced airway hyperreactivity

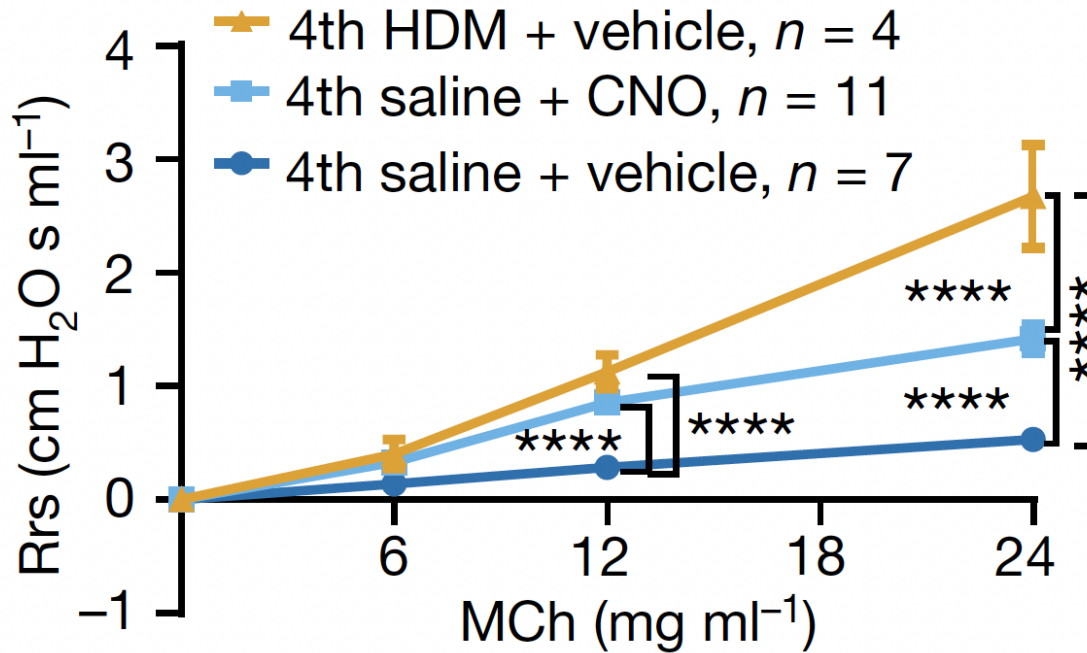
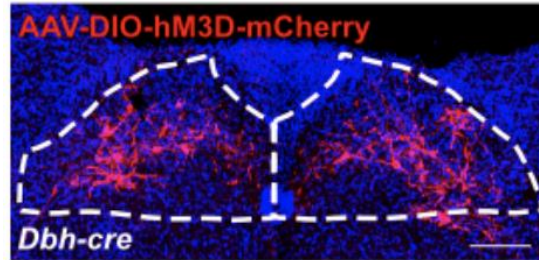
Toxin: DBH-saponin

Genetic ablation: *Dbh-cre*;DTR

DREADD: designer drug inactivation



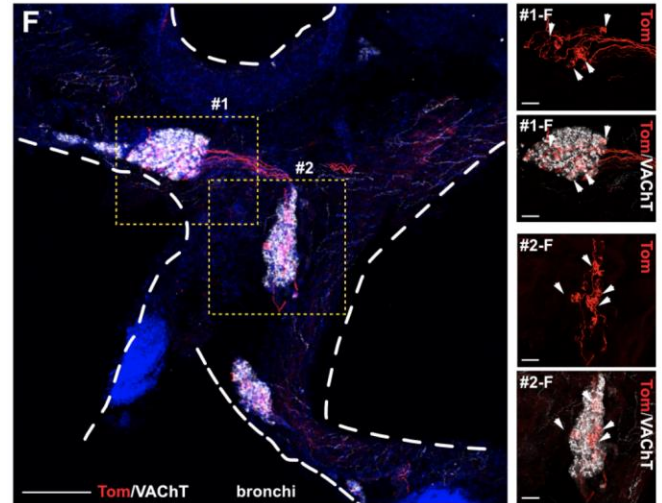
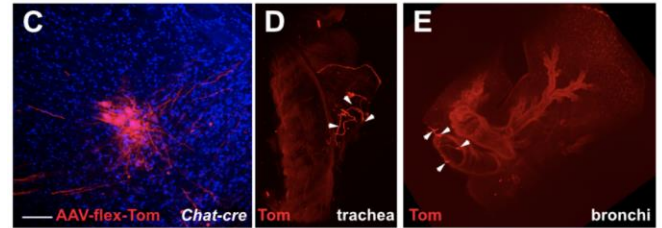
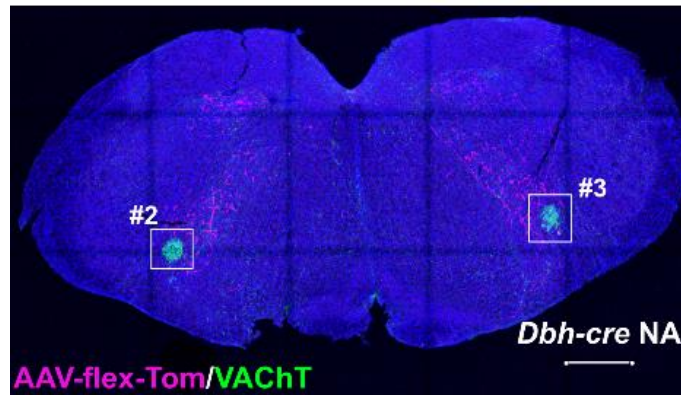
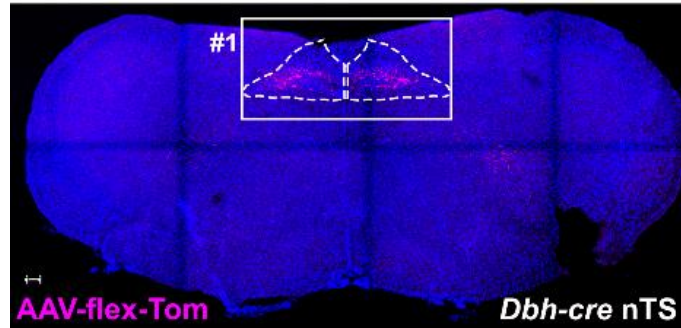
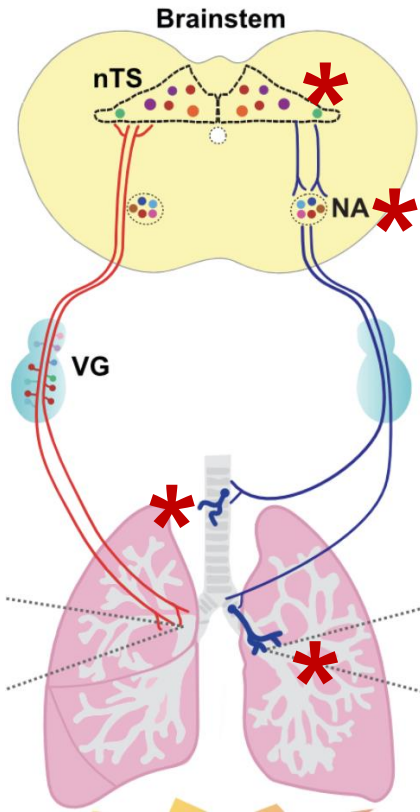
nTS DBH+ neurons are partially sufficient for allergen-induced airway hyperreactivity



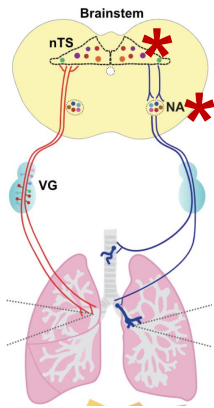
Efferent pathway?

The path back:

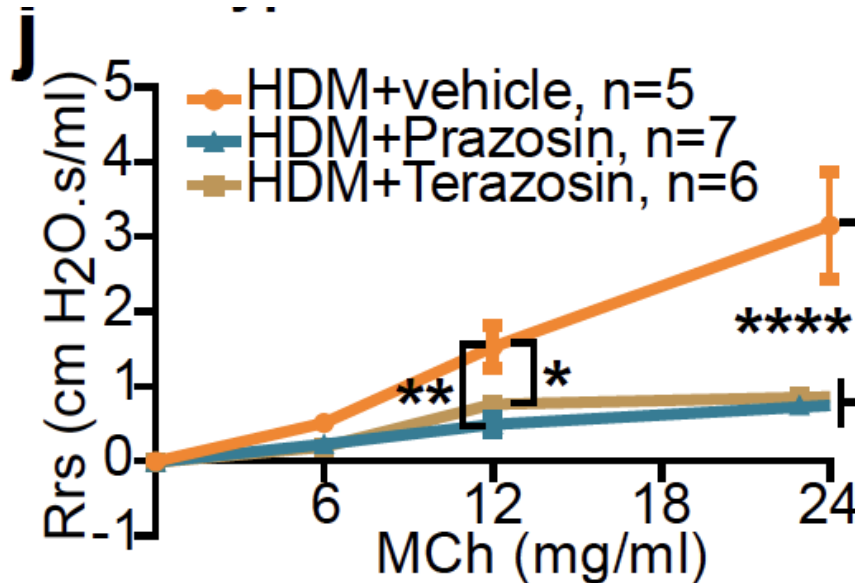
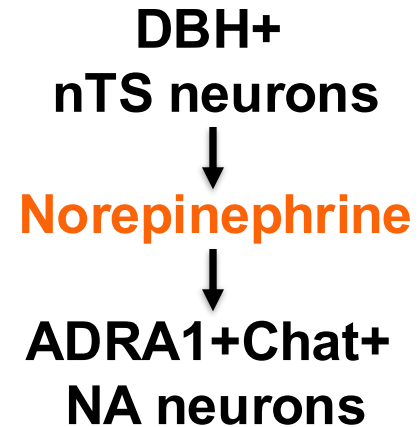
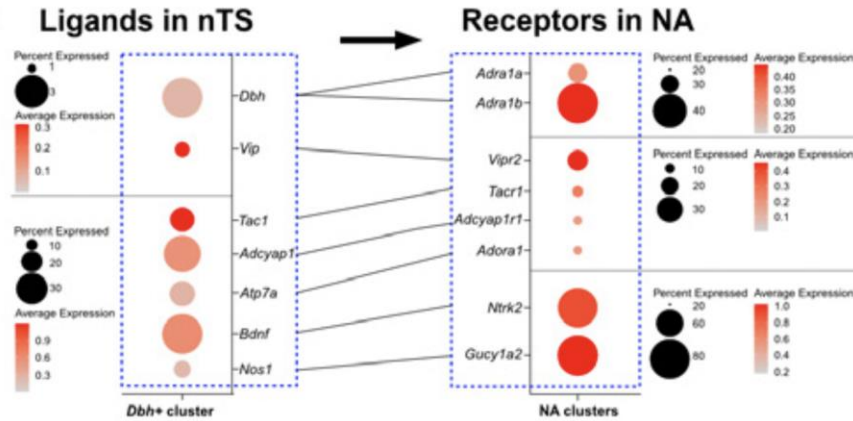
nTS > NA > postganglionic > airway smooth muscles



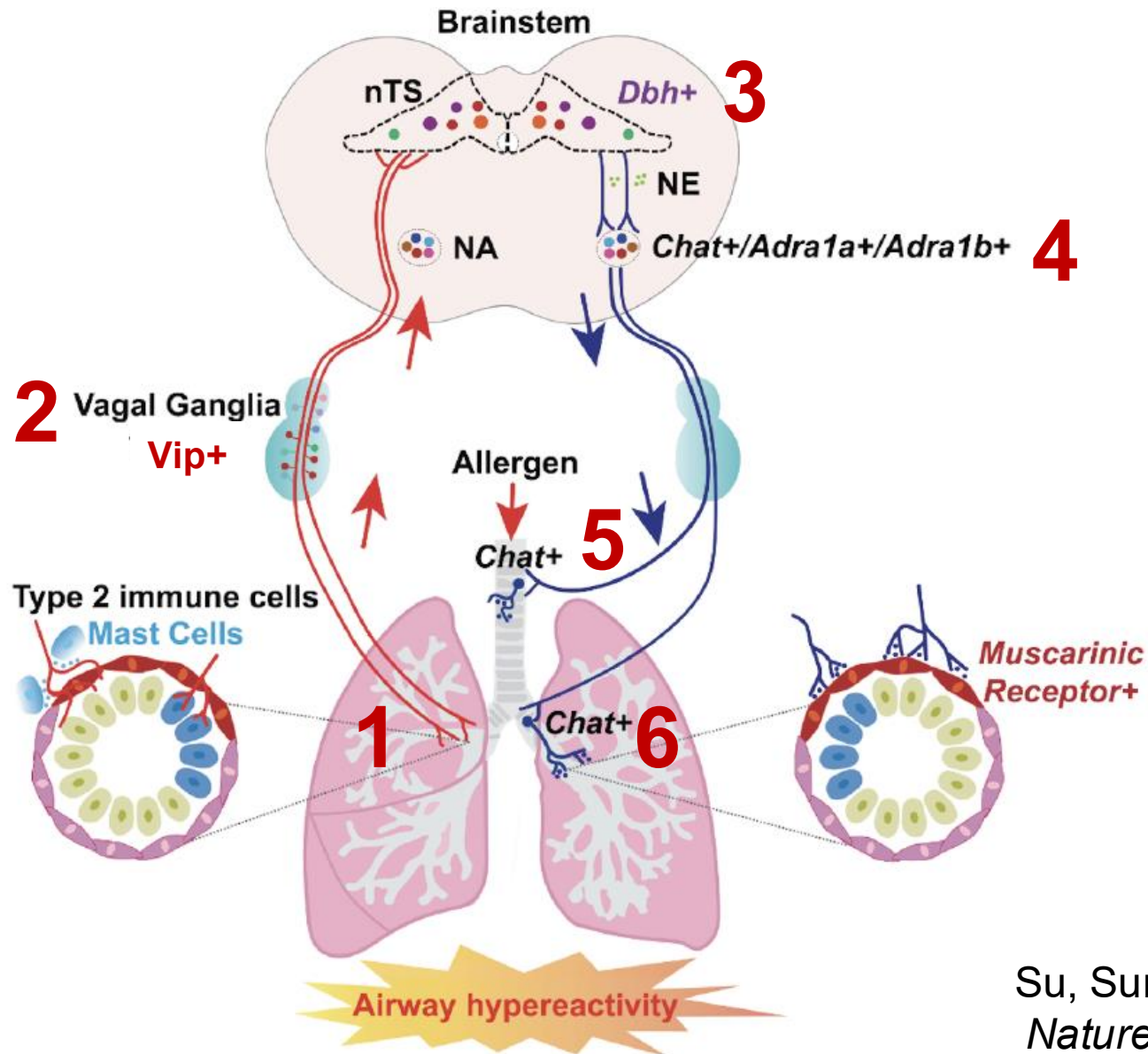
Molecule?



Blocking norepinephrine receptors in NA blunted airway hyperreactivity

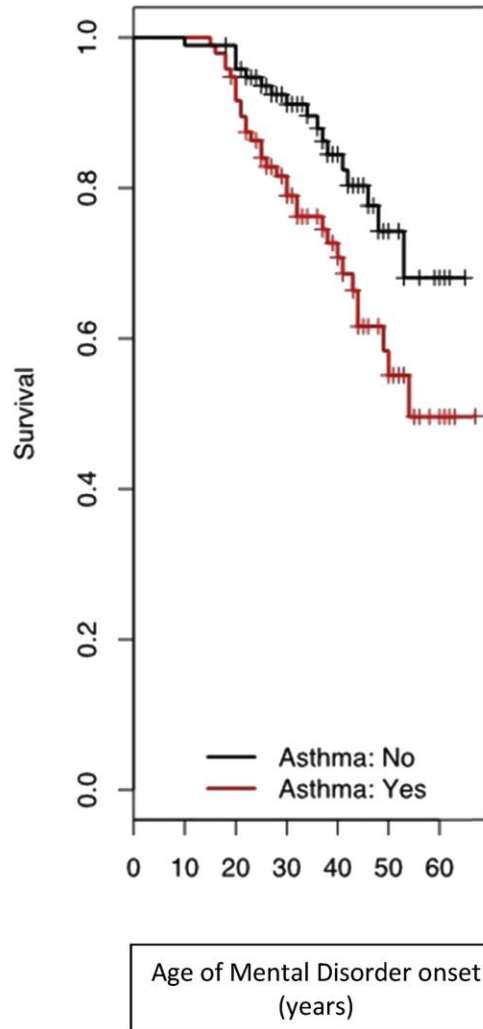


An Allergen Circuit

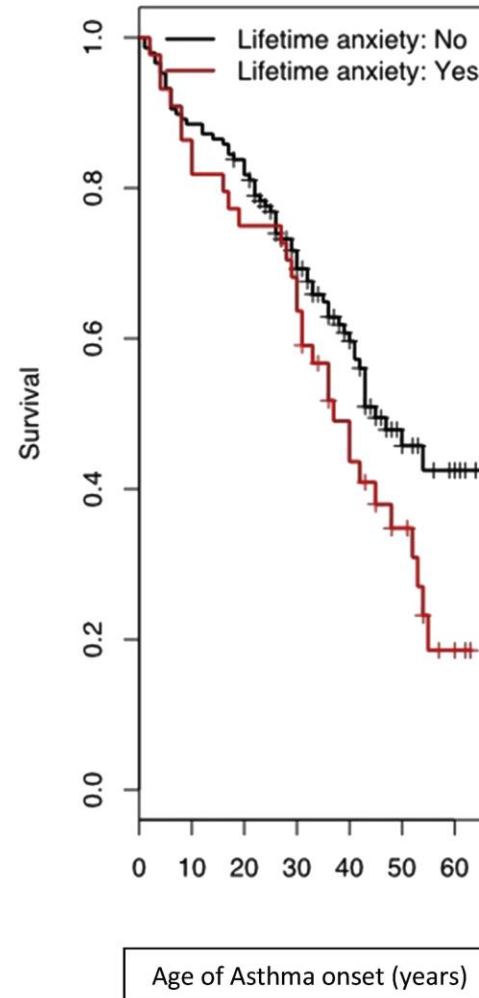


Su, Sun et al.,
Nature, 2024.

Asthma ↔ Stress

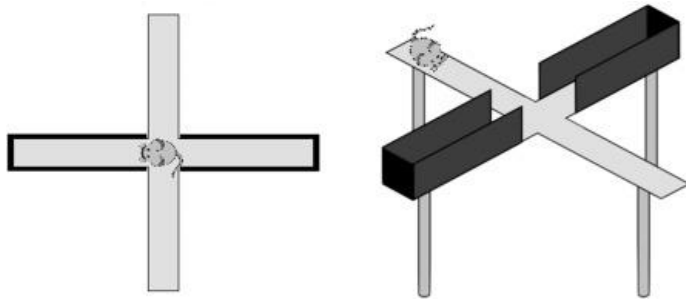


Del Giacco et al., 2016, PMID: 27817815
Abuaish S et al., 2023, PMID: 37887495
Litt JS et al., 2020, PMID: 32445826
Griffiths D et al., 2021, PMID: 33058494

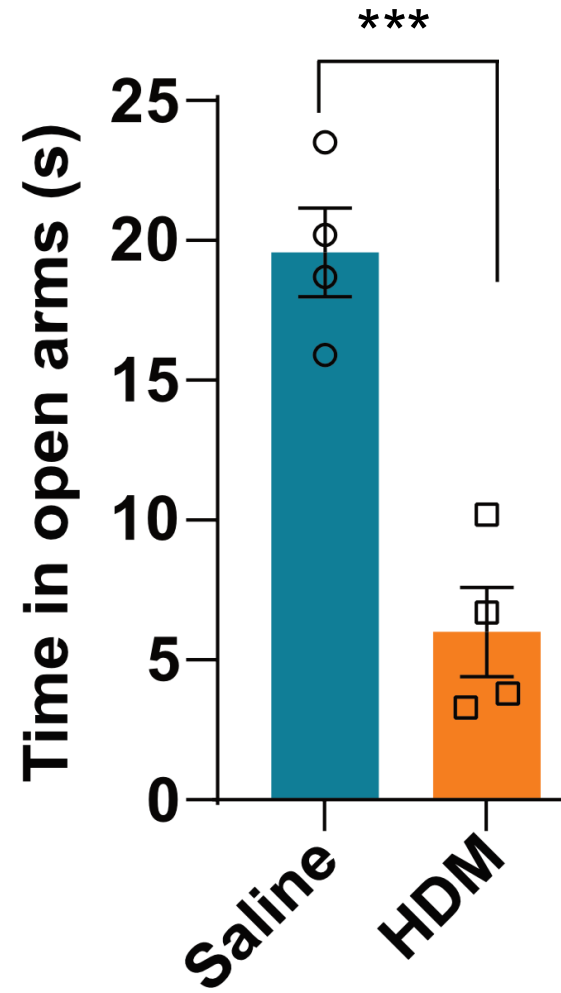


Goodwin RD et al., 2003, PMID: 14609888
Scott KM et al., 2008, PMID: 18941133
Richardson LP et al., 2006, PMID: 16950996

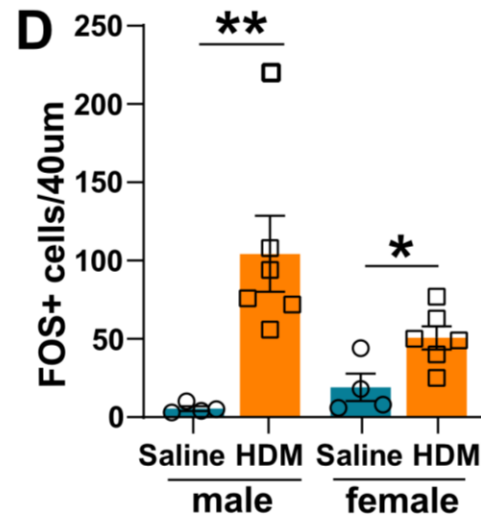
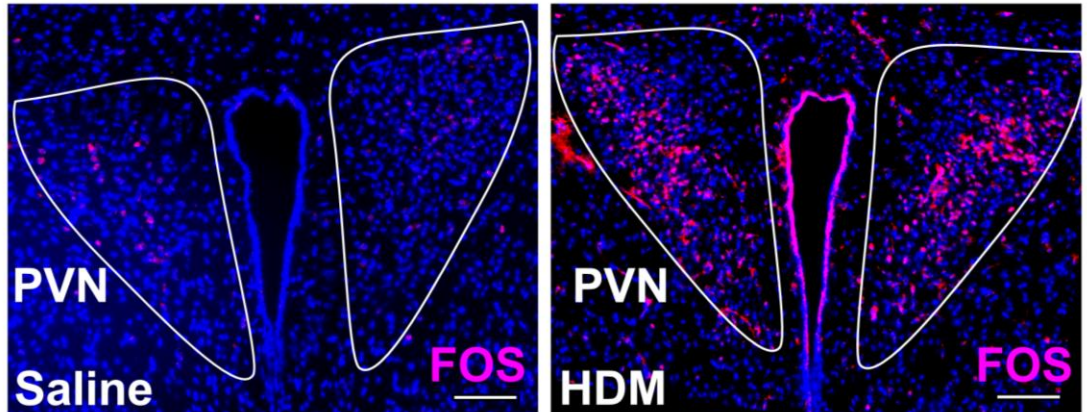
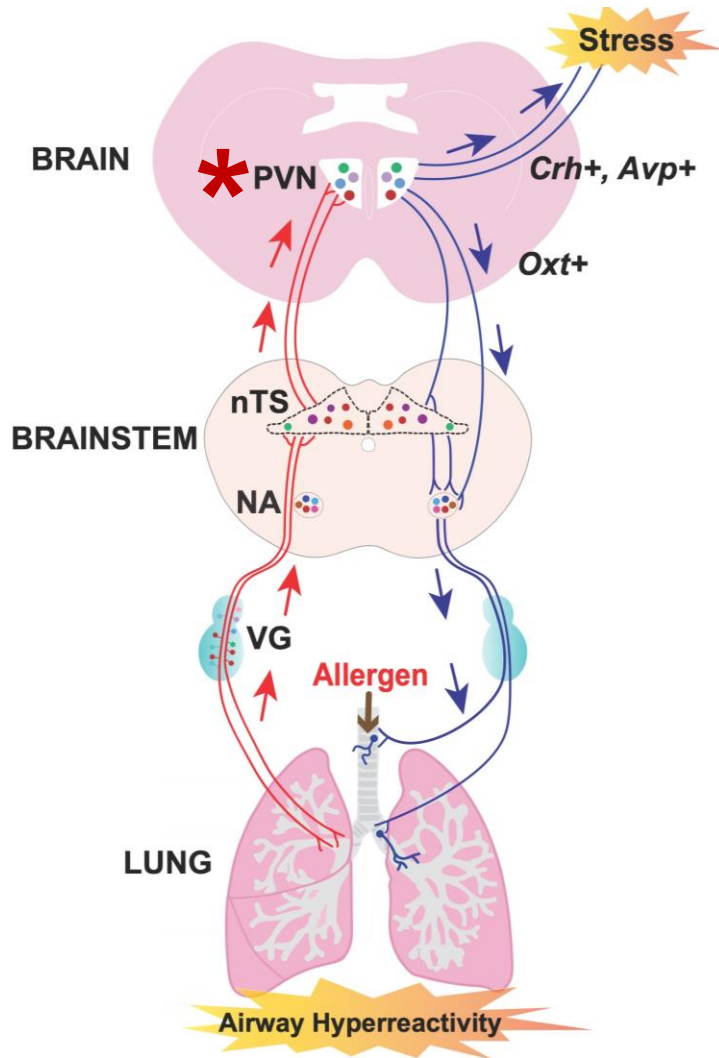
Allergen challenge induced stress behavior



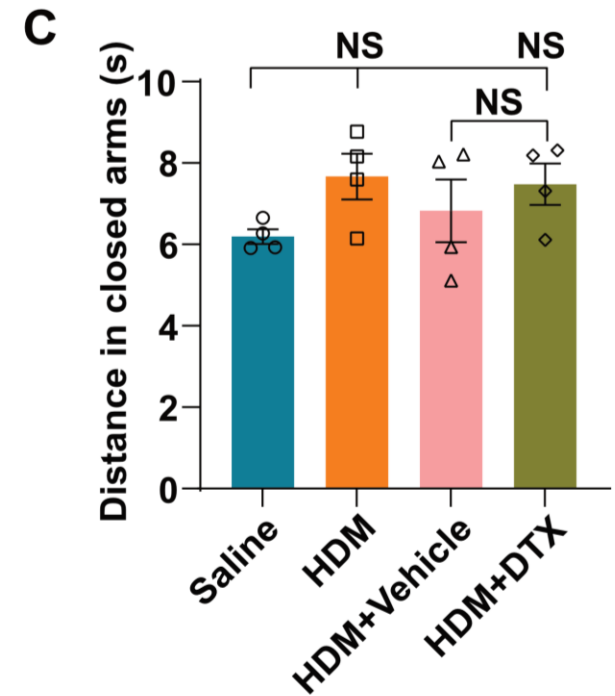
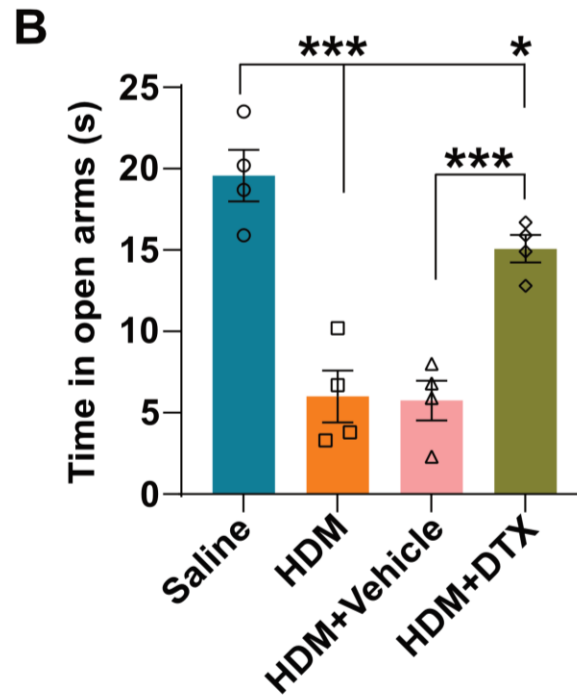
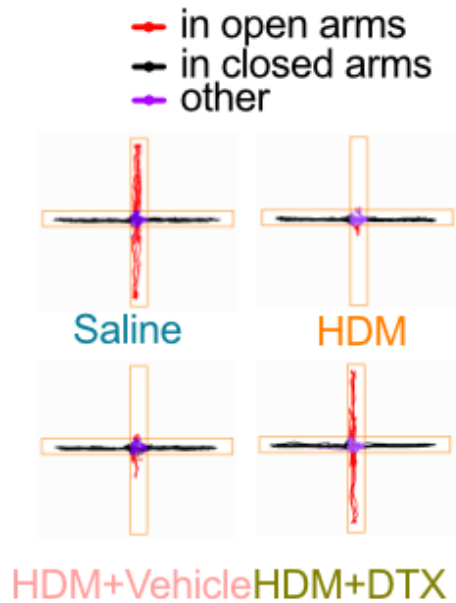
Elevated plus maze tests (EPM)



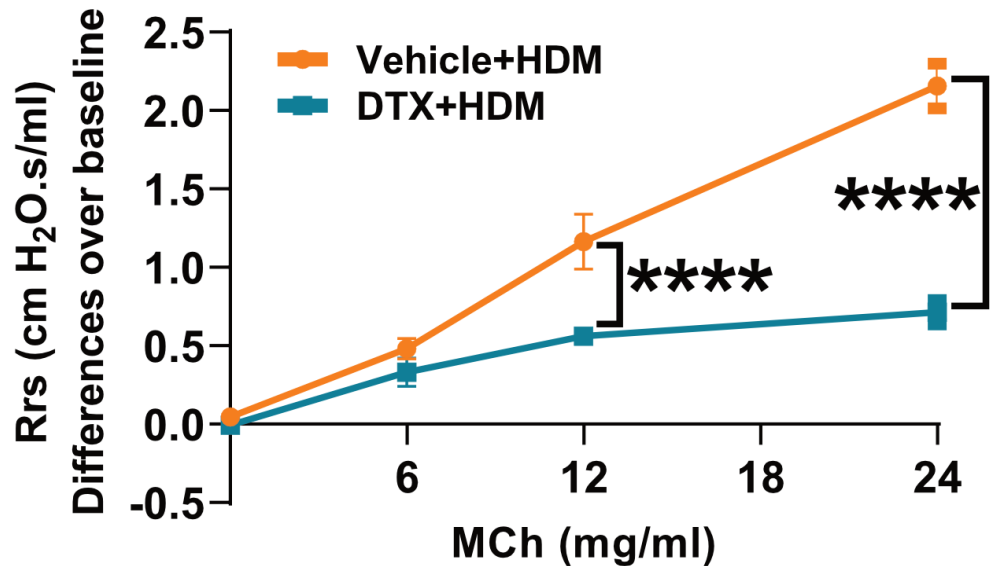
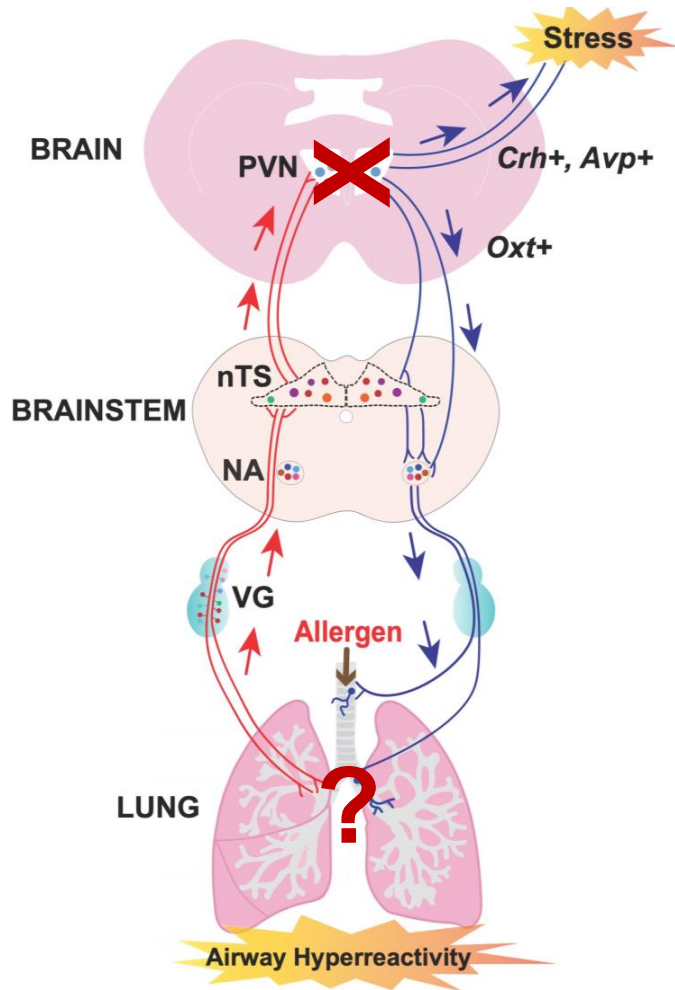
Allergen challenge to lung activates PVN neurons



Ablation of allergen-activated PVN neurons relieved allergen-induced stress behavior



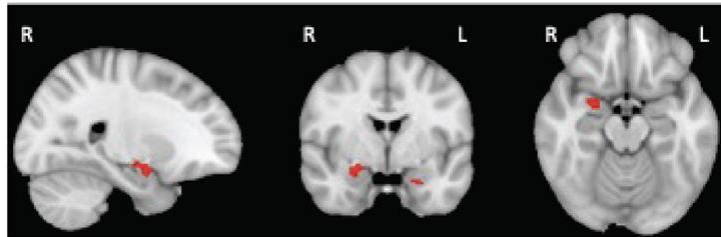
Ablation of allergen-activated ($Fos^{creERT2}$) PVN neurons blunted allergen-induced airway hyperreactivity



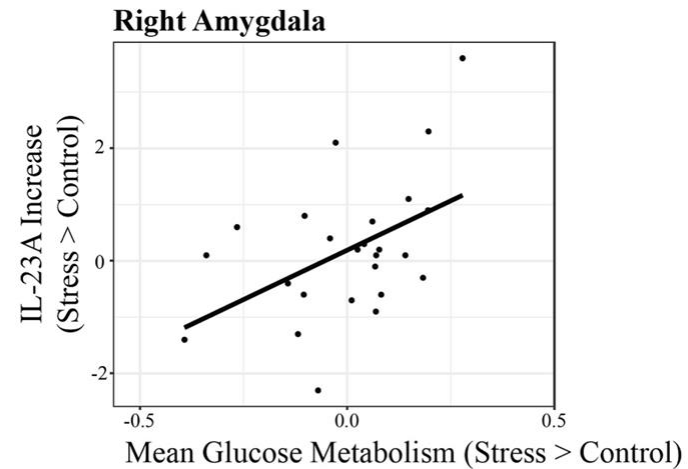
Specificity?

Fueling the fire in the lung-brain axis: The salience network connects allergen-provoked TH17 responses to psychological stress in asthma

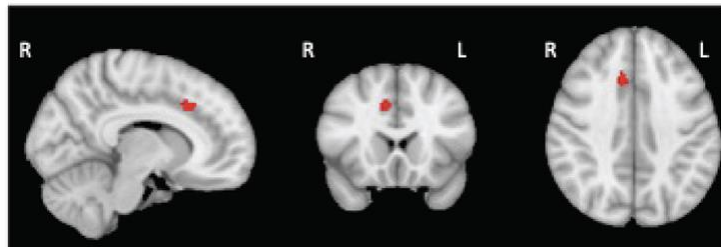
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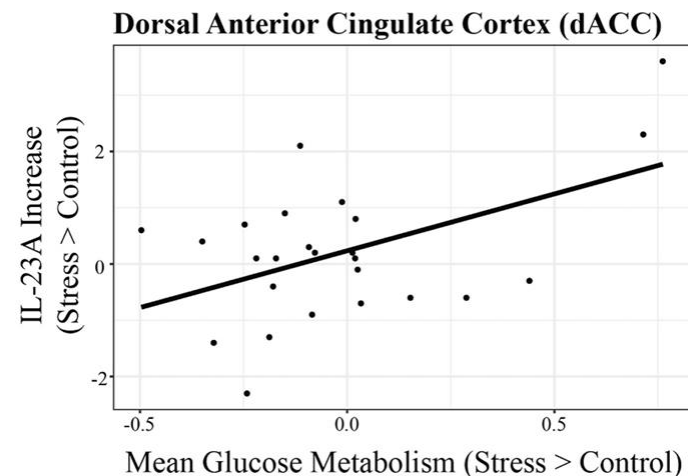
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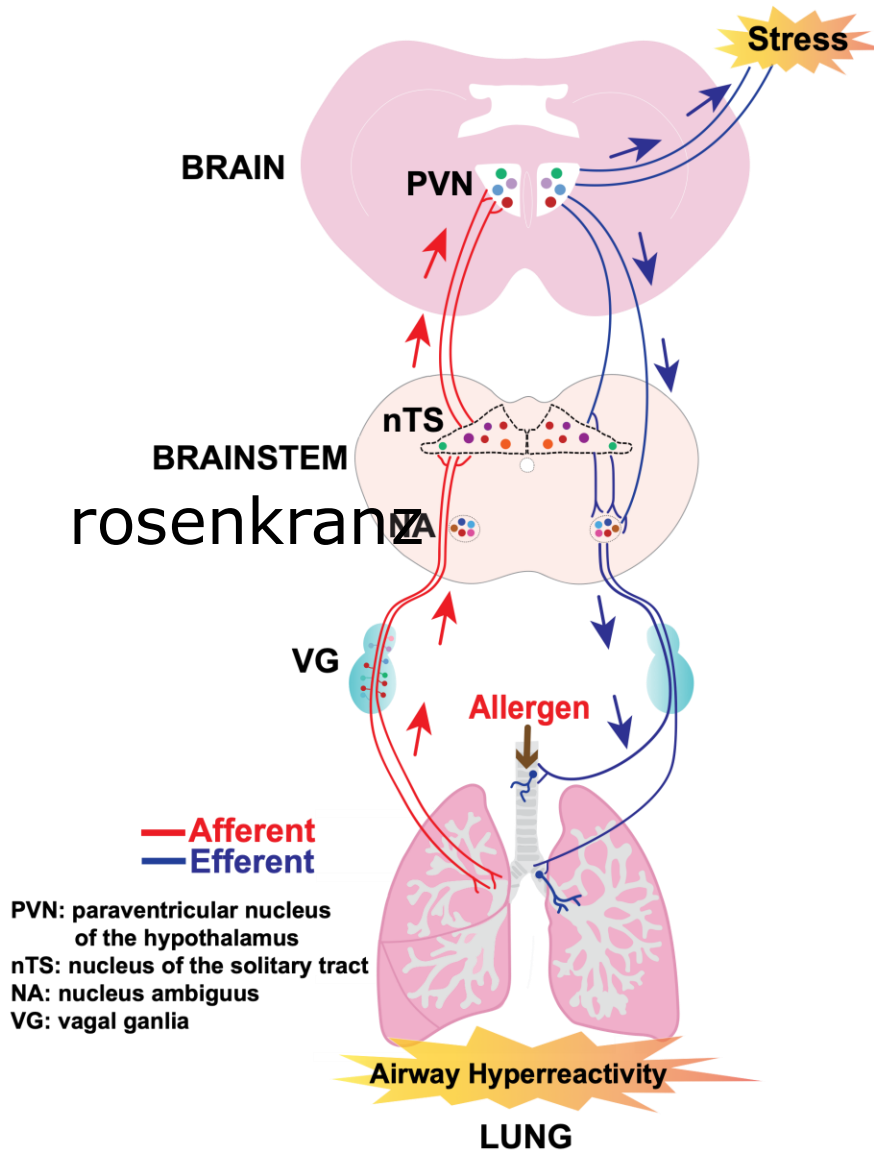
C



D



Disease-Relevant Lung-Brain Circuits



Acknowledgements

Sun lab:

Yujuan Su

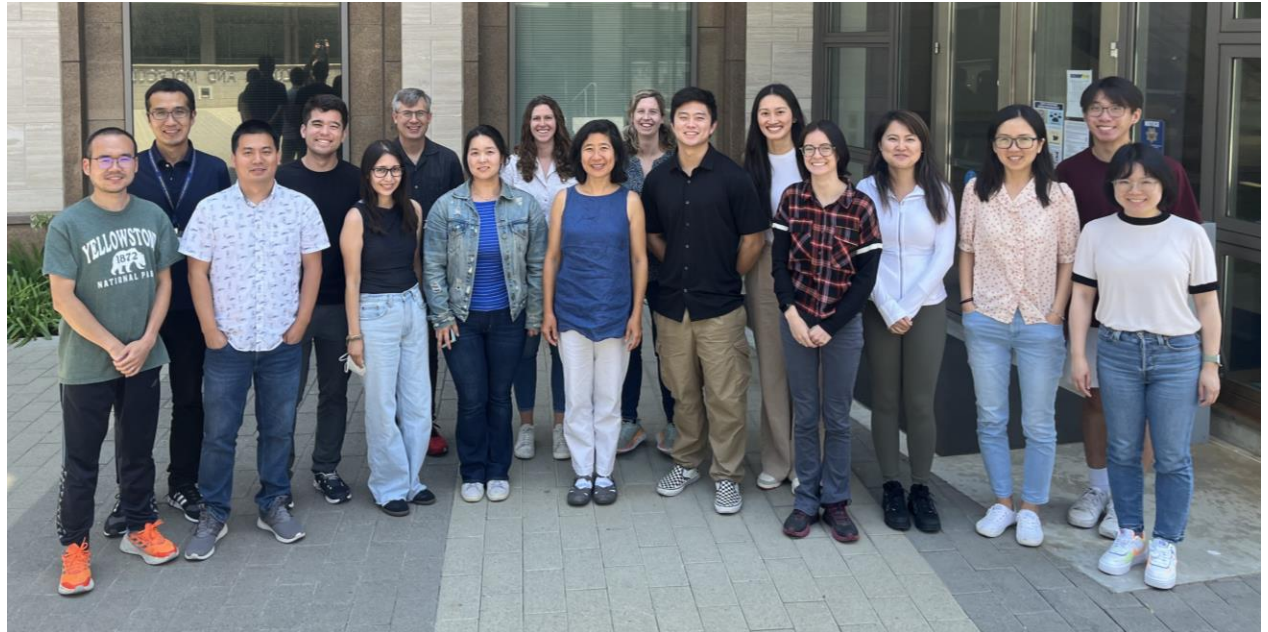
Jamie Barr
Elizabeth Duong
Annika Jorgensen
Rongbo Li
Changcheng Li
Gidsela Luna
Rebecca Salamon
Jamie Verheyden
Ruijia Wang
Brian Wells
Le Xu
Bingpeng Yao
Ziai Zhu

Collaborators:

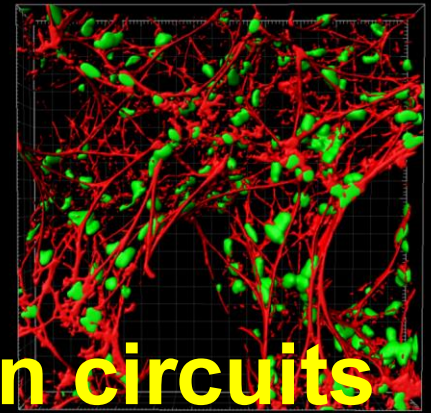
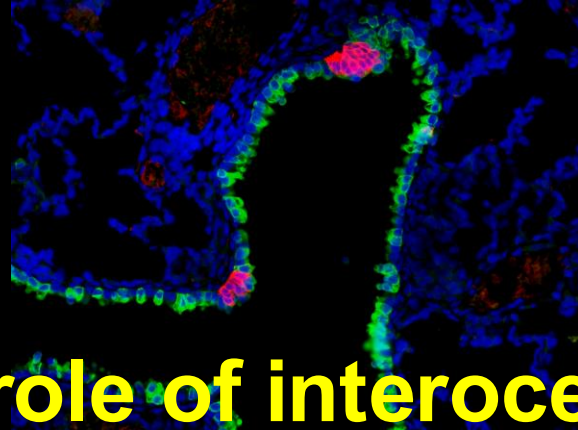
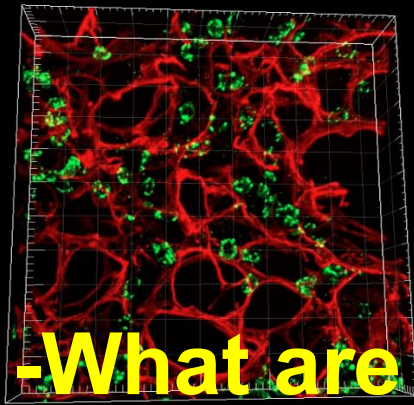
Dr. Axel Nimmerjahn
Dr. Li Ye
Dr. Takaki Komiyama
Dr. Byungkook Lim

Funding:

NCCIH
NHLBI



xinsunlab.org



-What are the role of interoception circuits in coordinated body-brain development, inflammation, stress and aging?

-How do the interoception circuits evolve and remodel in disease and aging, and what controls their plasticity and memory?

