

Tracking influenza in its first battleground: The nose

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Credit: Unsplash/CC0 Public Domain

The answer to curbing influenza could be right under our noses—or, more accurately, inside them. New research maps happenings in the nose during the course of influenza in exquisite detail, and could potentially

lead to new targets and more effective nasal flu vaccines.

The nose is often the gateway to respiratory infections, where viruses first set up shop and start replicating. But strangely, the [immune response](#) in the nose has been relatively unexplored.

"The National Heart, Lung, and Blood Institute has traditionally covered the lung through the trachea, and another NIH institute funds research for craniofacial and dental disorders," says Boston Children's Hospital researcher José Ordovás-Montañés, Ph.D. "Where does the nose fit?"

Ordovás-Montañés first took on this underfunded body part during the COVID-19 pandemic. His lab showed that people who developed severe COVID-19 had weak antiviral responses in the nose and throat. In new work led by Samuel Kazer, Ph.D., the team analyzed what happened in the noses of mice during flu [infection](#).

Unlike the COVID study, which analyzed patients' nasal swabs at a single point in time, the new study tracked events throughout the nose, including parts not reachable with a nasal swab, throughout a flu episode.

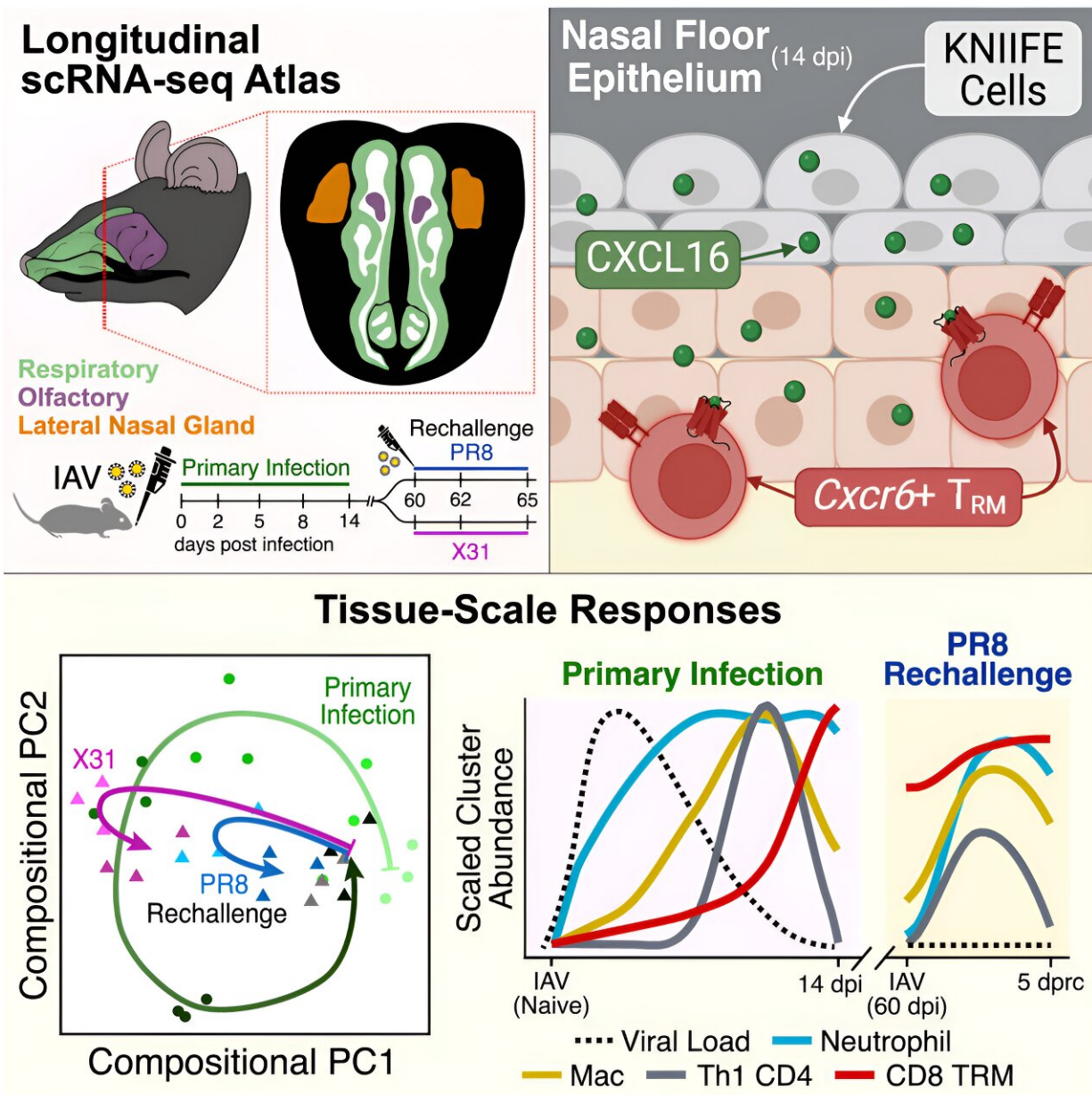
To better understand [immune memory](#), the researchers resampled the mice after a second influenza infection. [They published](#) their findings in the journal *Immunity*.

An 'atlas' of cell responses to flu

Over the course of infection, the researchers sequenced the RNA of thousands of individual cells in the nasal mucosa (the tissue lining the nasal cavity)—in all, more than 150,000 readouts over two weeks. This created a dynamic "atlas," cataloging what kinds of cells were there and how each was responding.

The team identified 127 cell types and subtypes, including the [epithelial cells](#) that line the mucosa, multiple types of immune cells, cells making up connective tissue, and even neurons that facilitate smell.

"We saw lots of interesting cellular diversity within this micro-anatomy," says Ordovás-Montañés. "When we sample people with swabs, we just scrape the surface. Sam was able to look at the full tissue."



Graphical abstract. Credit: *Immunity* (2024). DOI: 10.1016/j.immuni.2024.06.005

Different cells came and went during influenza infection. For example, neutrophils (first-responder immune cells) appeared almost immediately, but left once the virus was cleared. Tissue-resident memory T cells (TRM cells), which maintain memory of an infection in the tissue, showed up around day 14.

They remained in the nose thereafter, right through the second bout of flu, as did plasmablasts, which matured into antibody-producing plasma cells.

Maintaining a memory of influenza

One previously undescribed group of cells took stage one to two weeks after the start of infection. Dubbed Krt13+ nasal immune-interacting floor epithelial cells (KNIIFE cells), they run along the bottom of the [nasal cavity](#), just above the palate of the mouth. Kazer's expertise at the intersection of biology and computational science made their discovery possible, says Ordovás-Montañés.

"We almost threw those cells out because they looked so weird," he adds.

These cells may be key to the more rapid, coordinated immune responses the team saw during the second influenza infection.

"KNIIFE cells express many genes associated with immune function that we're not used to seeing in epithelial cells," Kazer elaborates. "They

expand after the virus is cleared, in the same anatomical location as the TRM cells. We think they may help maintain the memory of an infection."

Nosing around to create a vaccine

The team is now further exploring the role of KNIIFE cells and plans to correlate the findings from mice with nasal-swab data from people with influenza and from children seen at Boston Children's Hospital with other viral infections. Kazer hopes their work will one day lead to a long-lasting nasal vaccine that could limit the spread of disease beyond the nose by helping the nose "remember" the flu virus.

"Memory can take place in many types of cells," he says. "Understanding how memory looks in a barrier tissue like the [nasal mucosa](#) is some basic biology we're trying to get at."

More information: Samuel W. Kazer et al, Primary nasal influenza infection rewires tissue-scale memory response dynamics, *Immunity* (2024). [DOI: 10.1016/j.immuni.2024.06.005](https://doi.org/10.1016/j.immuni.2024.06.005)

Provided by Children's Hospital Boston

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