

# Interleukin-4 directly activates olfactory neurons and induces loss of smell in mice

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## BACKGROUND

- Loss of smell is a cardinal symptom in patients with chronic rhinosinusitis with nasal polyps (CRSwNP)<sup>1</sup>
- Dupilumab, a human interleukin (IL)-4 receptor alpha (IL-4Rα) monoclonal antibody that binds to IL-4Rα and blocks both IL-4 and IL-13 signaling, rapidly improves sense of smell in patients with CRSwNP, with improvements observed as early as 3 days in randomized clinical trials<sup>2-4</sup>
  - The mechanism(s) underlying this rapid improvement in sense of smell are not understood
- Recently, IL-4 and IL-13 were reported to directly activate sensory neurons to mediate itch sensation,<sup>5,6</sup> however effects on smell function are unknown

## OBJECTIVE

To investigate the effects of IL-4 and IL-13 on smell function in mice

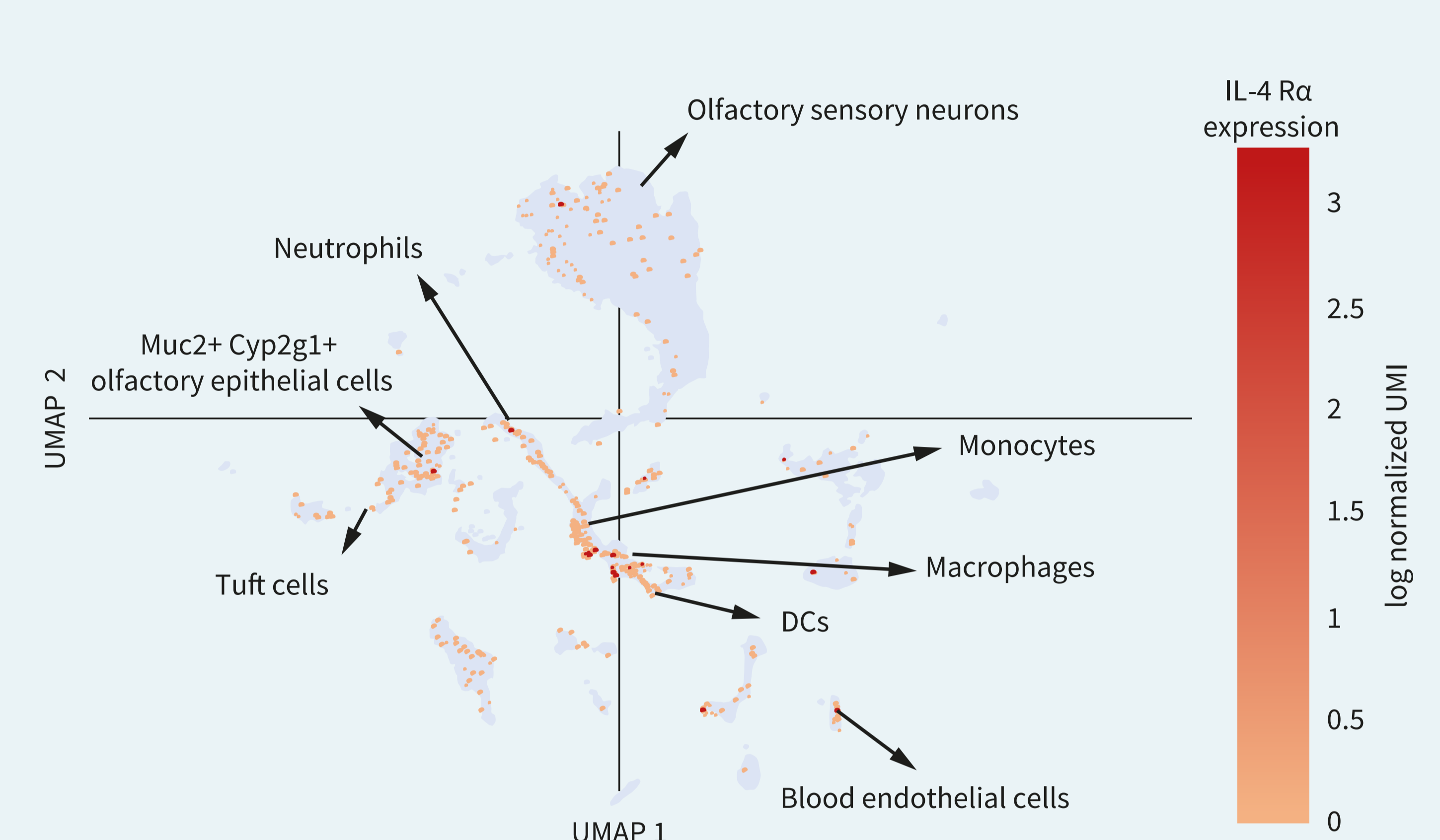
## METHODS

- Olfactory sensory neurons (OSN) were isolated from the olfactory epithelium of 8-week-old mice
- Calcium uptake in primary OSN was measured using dyes Fura-red and Fluo-4
- Sense of smell in mice was assessed by time to discover hidden food at baseline and after 5 consecutive days of intranasal administration of IL-4 and/or IL-13

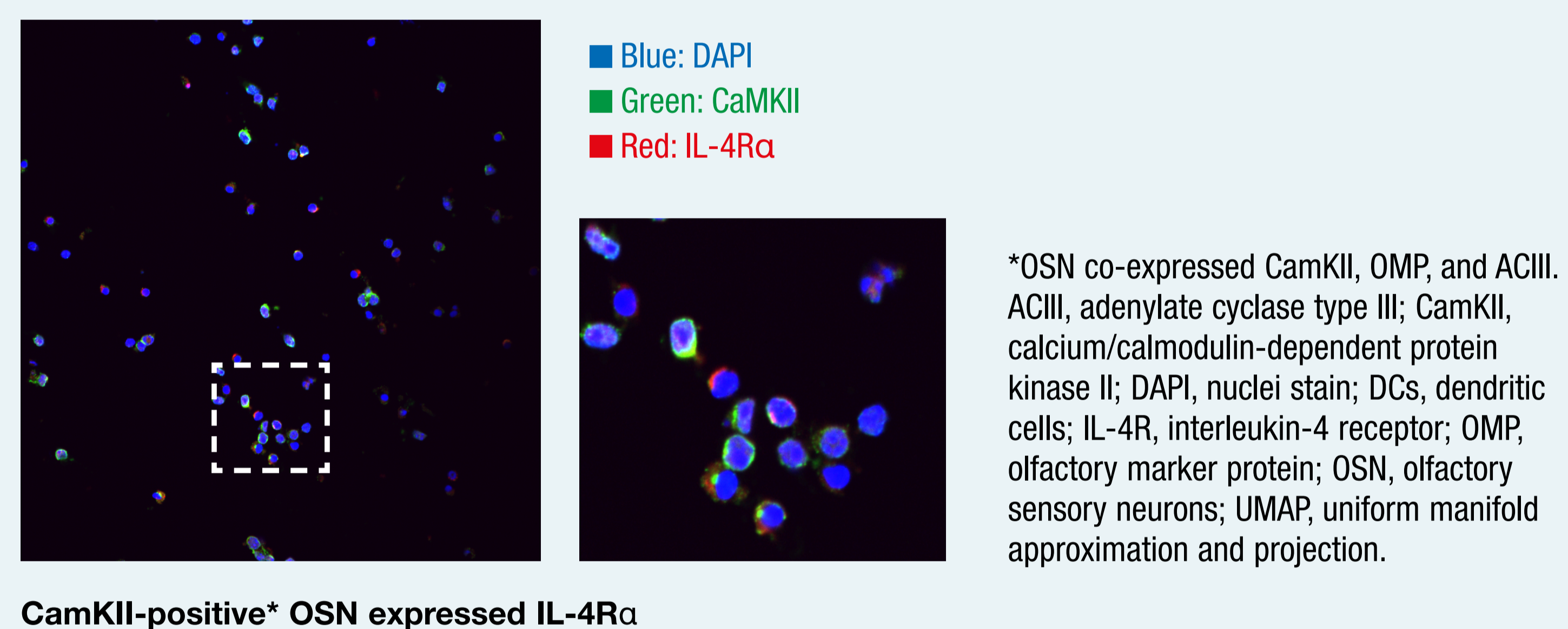
## RESULTS

**Figure 1. IL-4Rα, shared receptor for both IL-4 and IL-13, is widely expressed in murine olfactory epithelium, including immature and mature OSN**

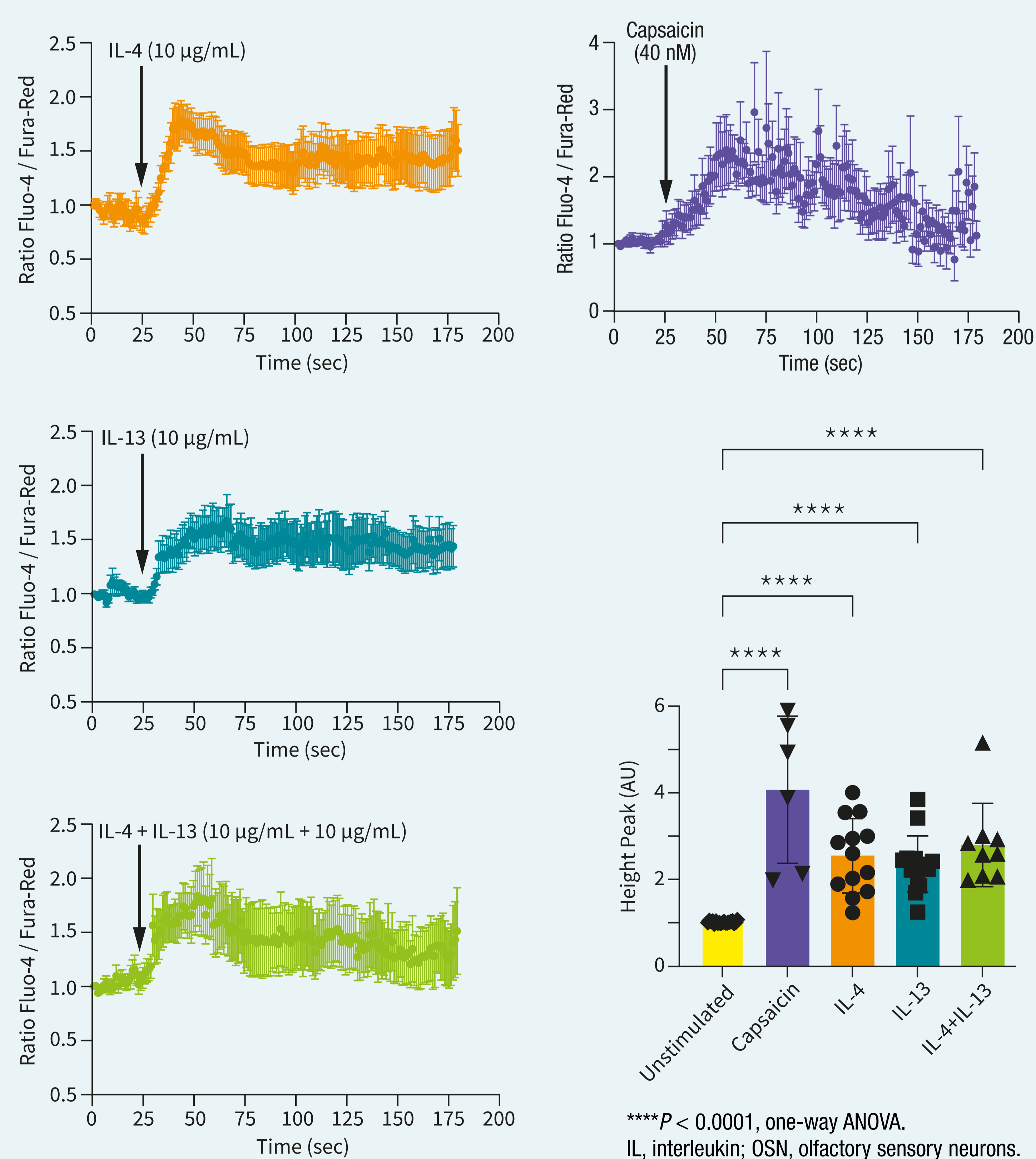
**(A) Single-cell RNA sequencing in mouse nasal epithelium<sup>7</sup>**



**(B) Immunofluorescence staining**

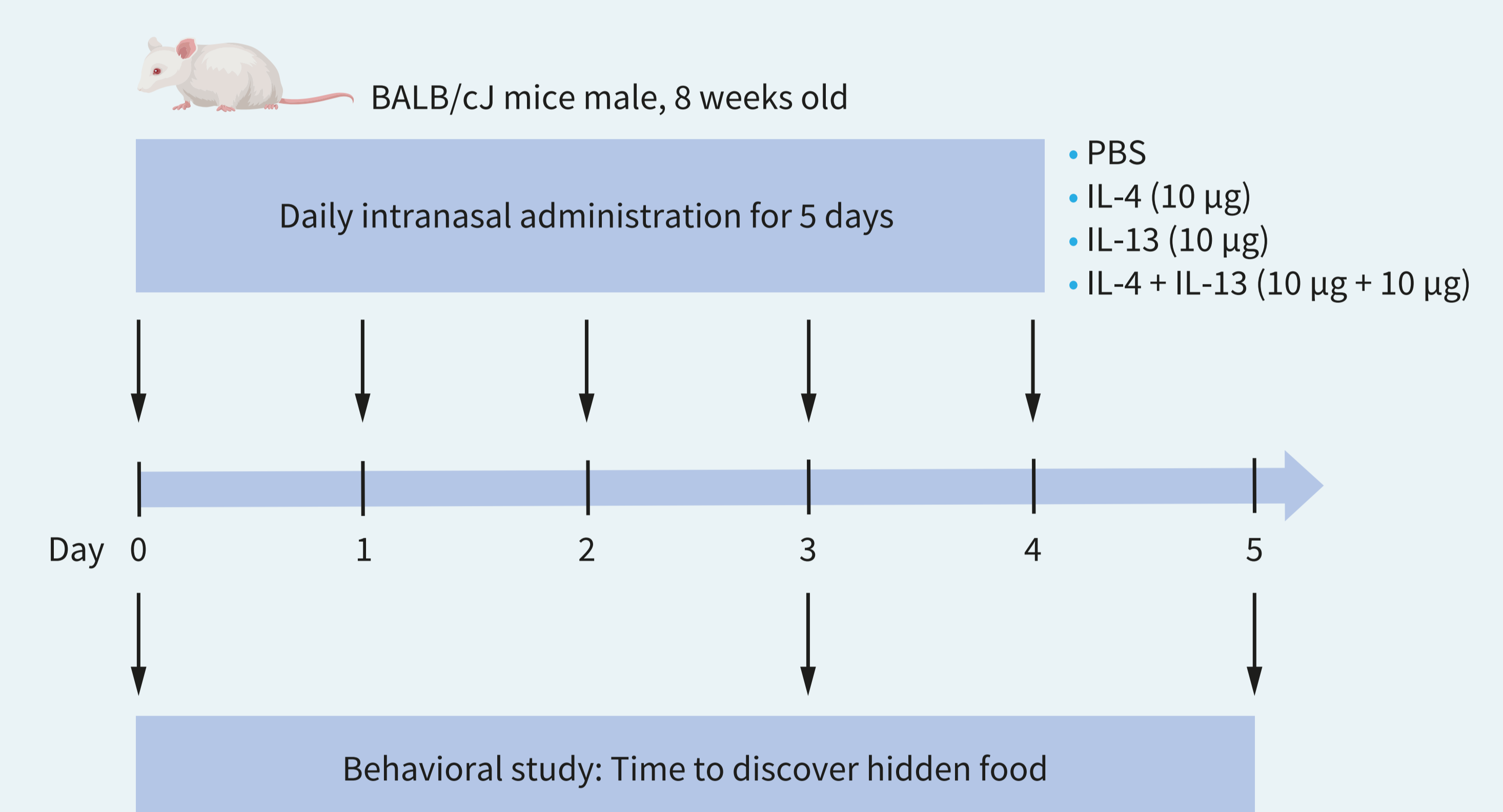


**Figure 2. IL-4 and IL-13 each significantly increased calcium uptake in murine OSN**

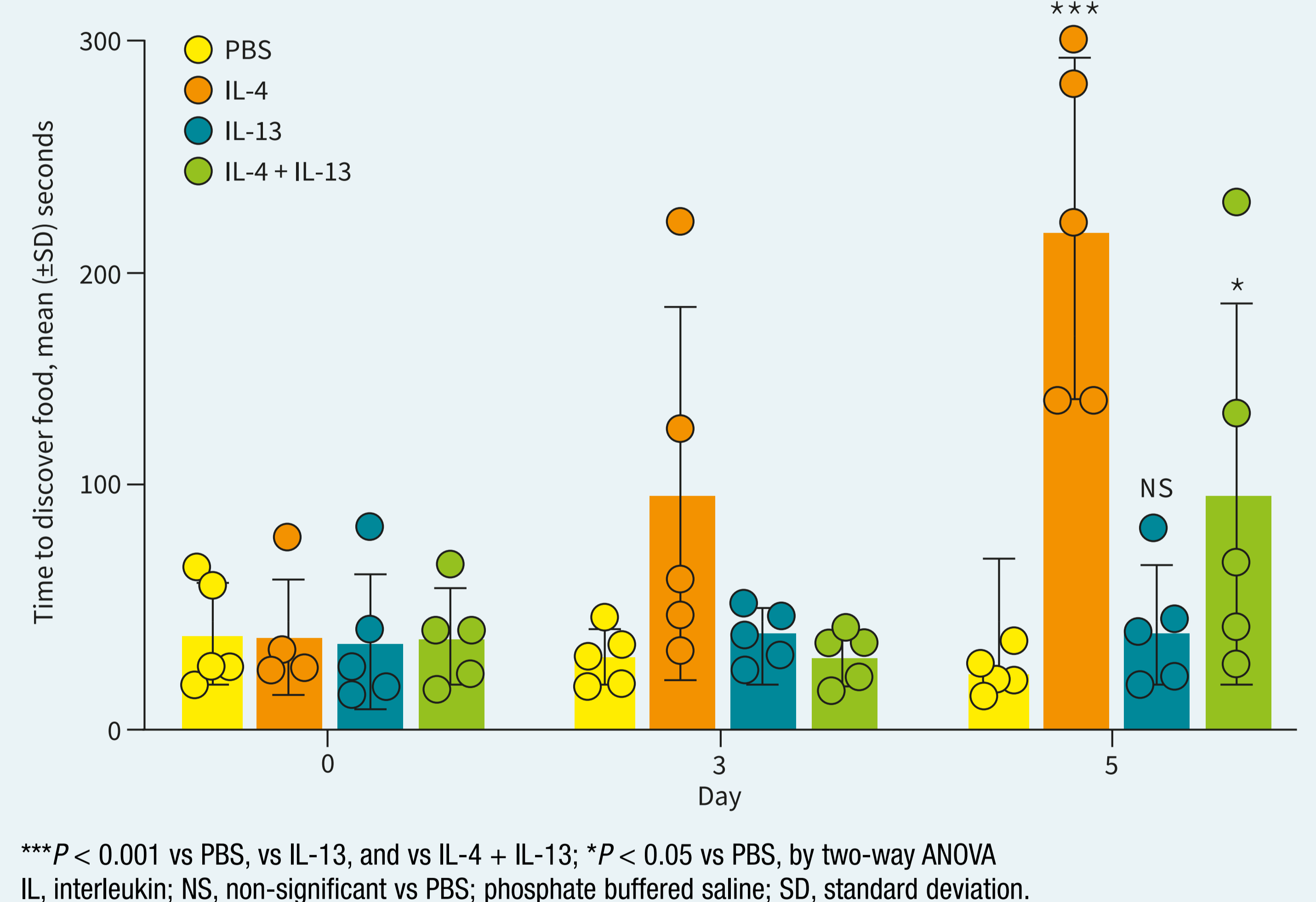


**Figure 3. IL-4, but not IL-13, induced anosmia in mice**

**(A) Experimental setup**



**(B) Time to discover hidden food**



## CONCLUSIONS

- IL-4Rα is widely expressed in murine olfactory epithelium, including in immature and mature OSN
- IL-4 and IL-13 each activate calcium uptake in murine OSN *in vitro*
- Intranasal administration of IL-4, but not IL-13, induces rapid loss of smell in mice, demonstrating non-redundant functions of these cytokines in early loss of smell
- IL-4 signaling effects may play a dominant role in the therapeutic effects of dupilumab in restoring smell function in CRSwNP
  - Direct effects on OSN activity may contribute to this mechanism
- Studies are ongoing to further investigate the role of IL-4 signaling in smell loss