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Comparison of topical Nomacopan, a dual Complement and leukotriene LTB4 inhibitor, with dexamethasone in downregulating experimental immune-mediated conjunctival disease (EIC)

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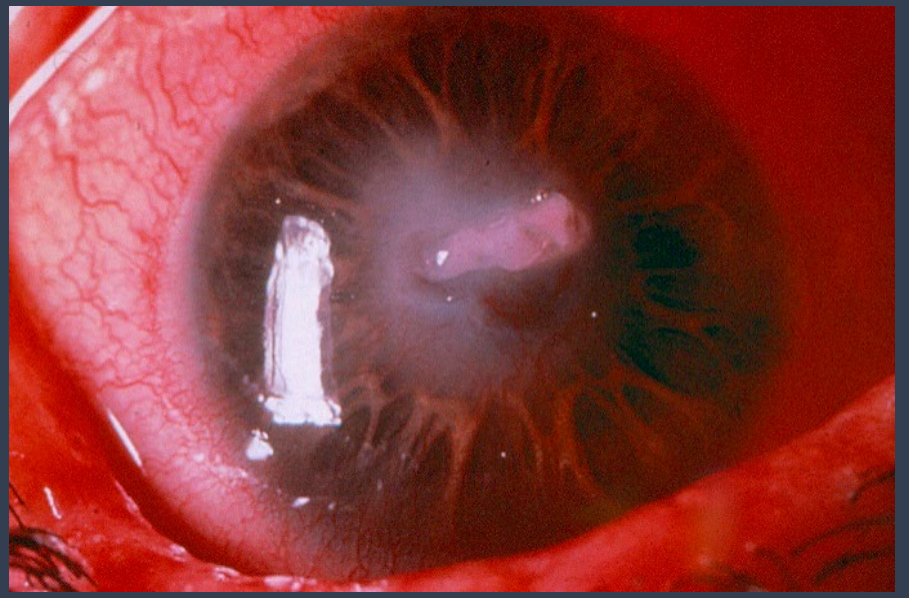
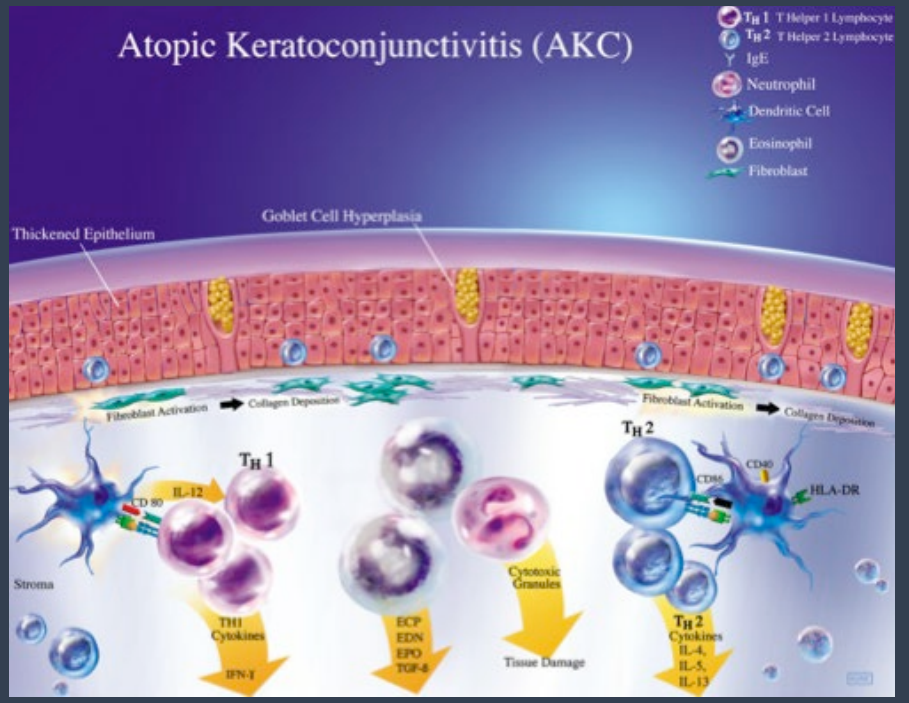
Steroid-resistant atopic keratoconjunctivitis (AKC) is difficult to treat and can lead to corneal cicatrization and vision loss. Topical or systemic dexamethasone and/or cyclosporin A (CsA) is often required.

Topical administration of Nomacopan, a therapeutic peptide, was recently shown to be effective in attenuating inflammation in a model of experimental immune-mediated conjunctivitis (EIC).

The aim of this study is to compare the anti-inflammatory effects of Nomacopan with topical dexamethasone.





Nomacopan

- a bifunctional biologic derived from blood-feeding ticks
- specifically sequesters **leukotriene B4** (LTB4) within an internal binding pocket
- prevents **complement factor 5** (C5) activation

Successful treatment of a PNH patient non-responsive to eculizumab with the novel complement C5 inhibitor coversin (nomacopan). Schols S, *et al* *Br J Haematol*. 2019 Dec 16. doi: 10.1111/bjh.16305.

Dual inhibition of complement factor 5 and leukotriene B4 synergistically suppresses murine pemphigoid disease. Sezin T, et al *JCI Insight.* 2019 Aug 8;4(15). pii: 128239. doi: 10.1172/jci.insight.128239.

LTB4 ($C_{20}H_{32}O_4$)

- potent **lipid inflammatory mediator**, derived from arachidonic acid pathway
- end product of the leukotriene biosynthetic pathway and binds via its unique receptor (**BTL1**)
- binds to G protein-coupled receptors in an autocrine or paracrine fashion to signal a cascade of kinase reactions, leading to changes in both transcriptional activity and cellular motility
- promotes infiltration of monocytes/macrophages and leukocytes into tissues and subsequent cytokine release leading to exacerbations of asthma
- mainly produced by **granulocytes, monocytes and macrophages**. LTB4 is known to induce secretion of GM-CSF, TNF- α, IL-6 and IL-1β and chemokines KC, MCP-1, CXCL1, and CXCL2

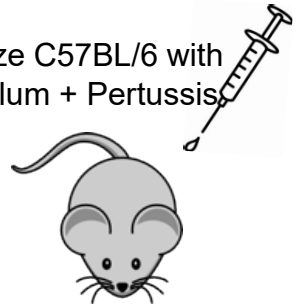
C5a

- a proteolytic breakdown product upon C5 activation, acts as a highly inflammatory peptide
- a chemotactic agent and an anaphylatoxin that is essential in innate immunity but which is also linked with adaptive immunity
- C5a receptor (C5aR1) was identified as a marker of differentiating microglial subsets in response to LPS in the inflamed eye
- C5a receptor signalling in dendritic cells controls development of Th17 immunity in experimental allergic asthma

Mouse model of experimental immune-mediated conjunctivitis (EIC)

Sensitization

Immunize C57BL/6 with OVA+ Alum + Pertussis toxin



Day 0

Rest

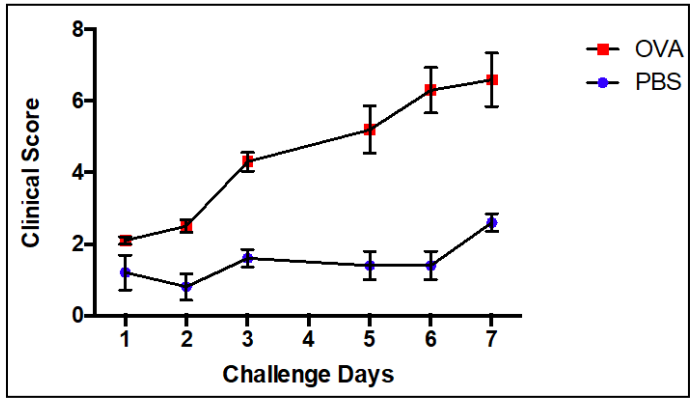
(1-3 weeks)

Elicitation

Daily OVA topical challenge

Day 22 23 24 25 26 27 28

harvest



Samples collected:

1. Whole eye: H&E and immunofluorescence staining.
2. Conjunctiva: Cells explanted from conjunctiva, re-stimulated with PMA/ionomycin and analysed by flow.
3. Cervical lymph nodes: Single cell suspension

Khandelwal *et al.,* 2013; PLOS

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Resolvin D1 Treatment on Goblet Cell Mucin and Immune Responses in the Chronic Allergic Eye Disease (AED) Model

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Increases in IL-4, IL-13, IL-17 and IFN-expressing CD4$^+$T cells were detected in dLNs.

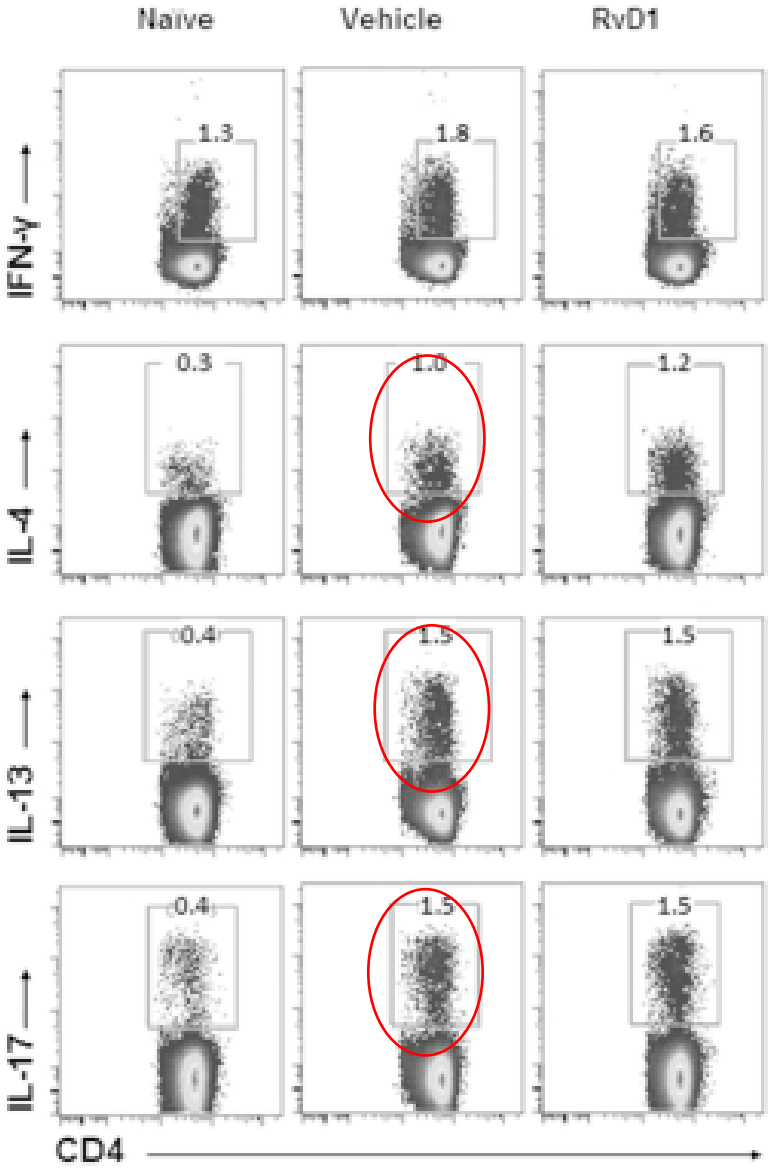
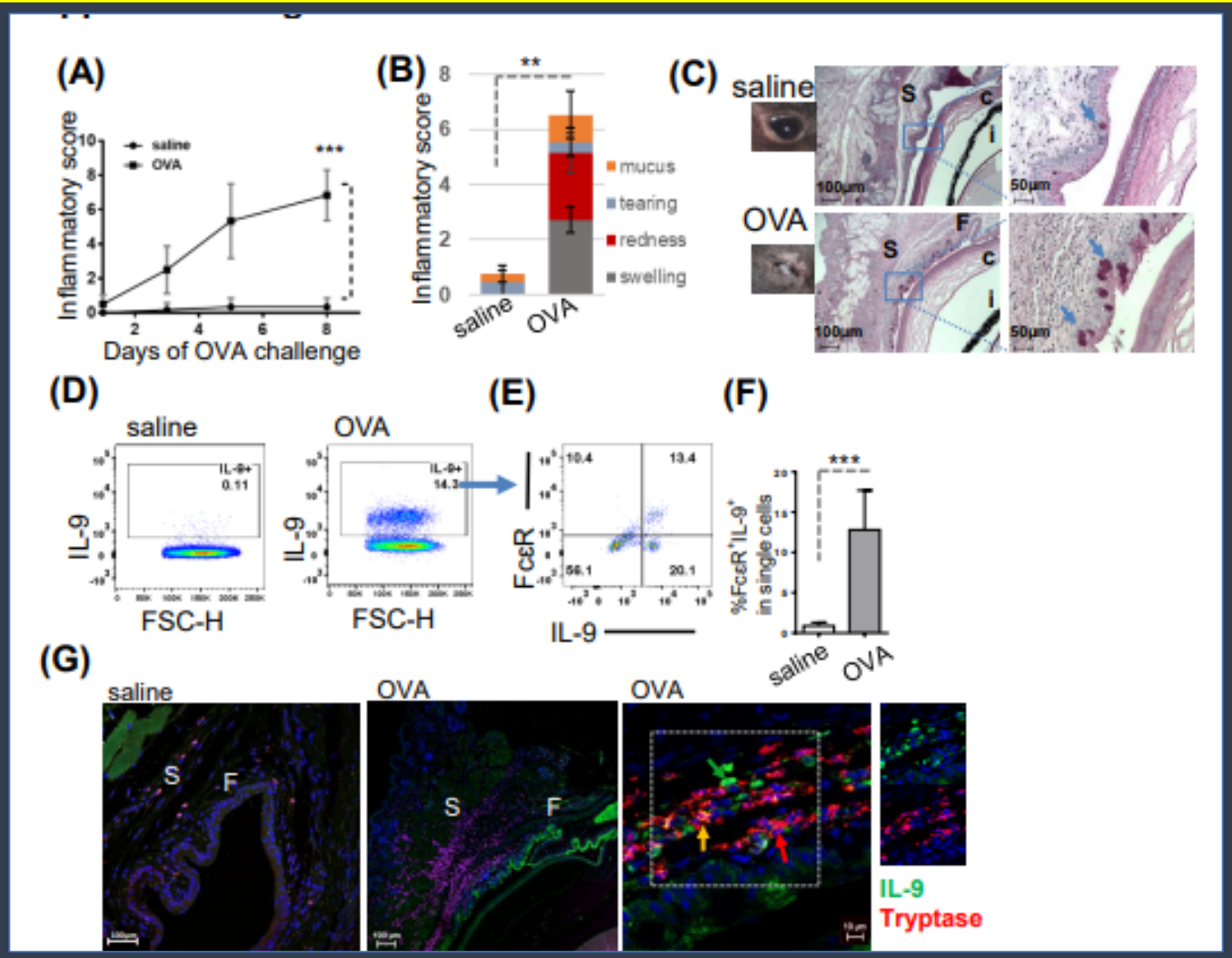
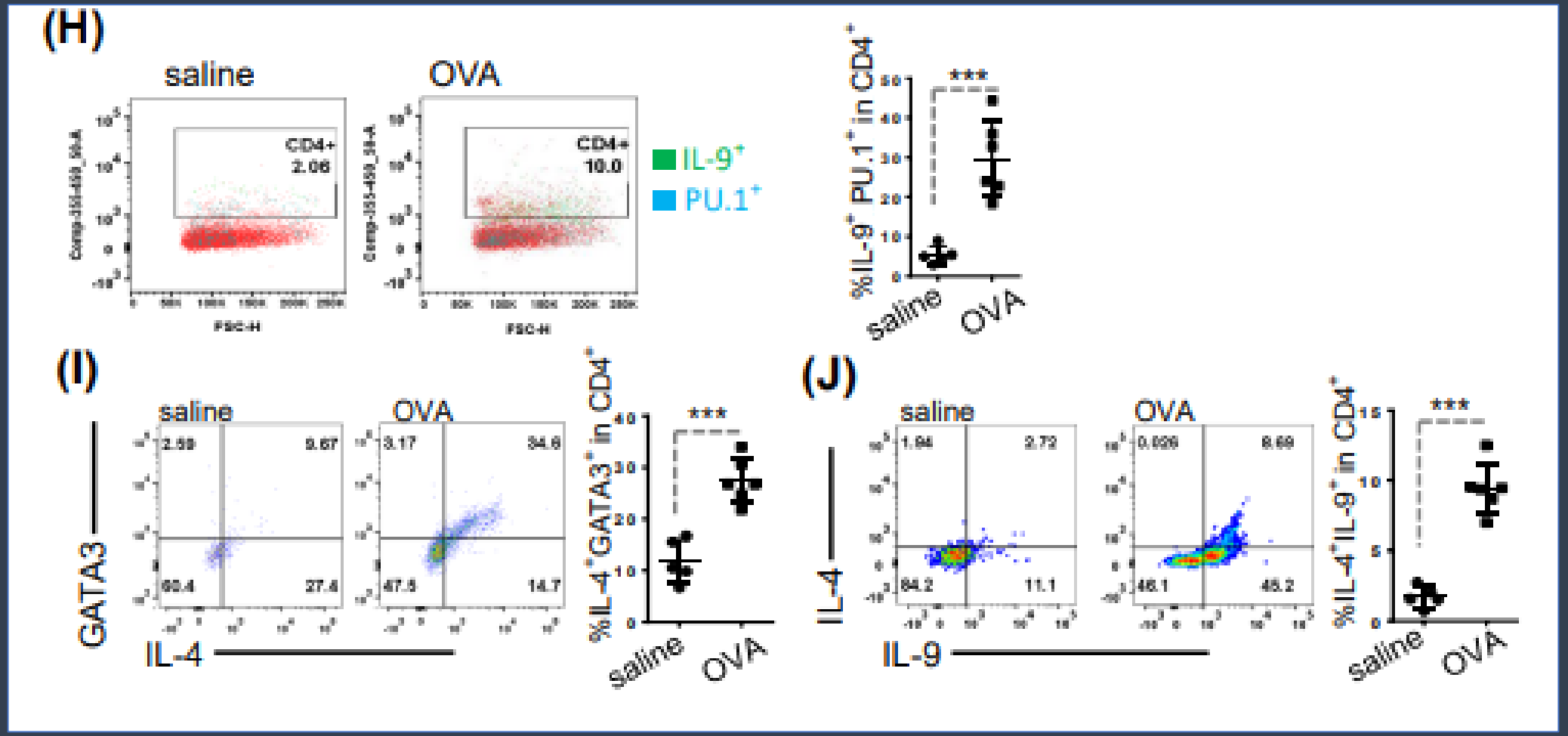


Figure 2. T helper cell frequencies in the draining lymph node of AED mice are not affected by topical RvD1 treatment

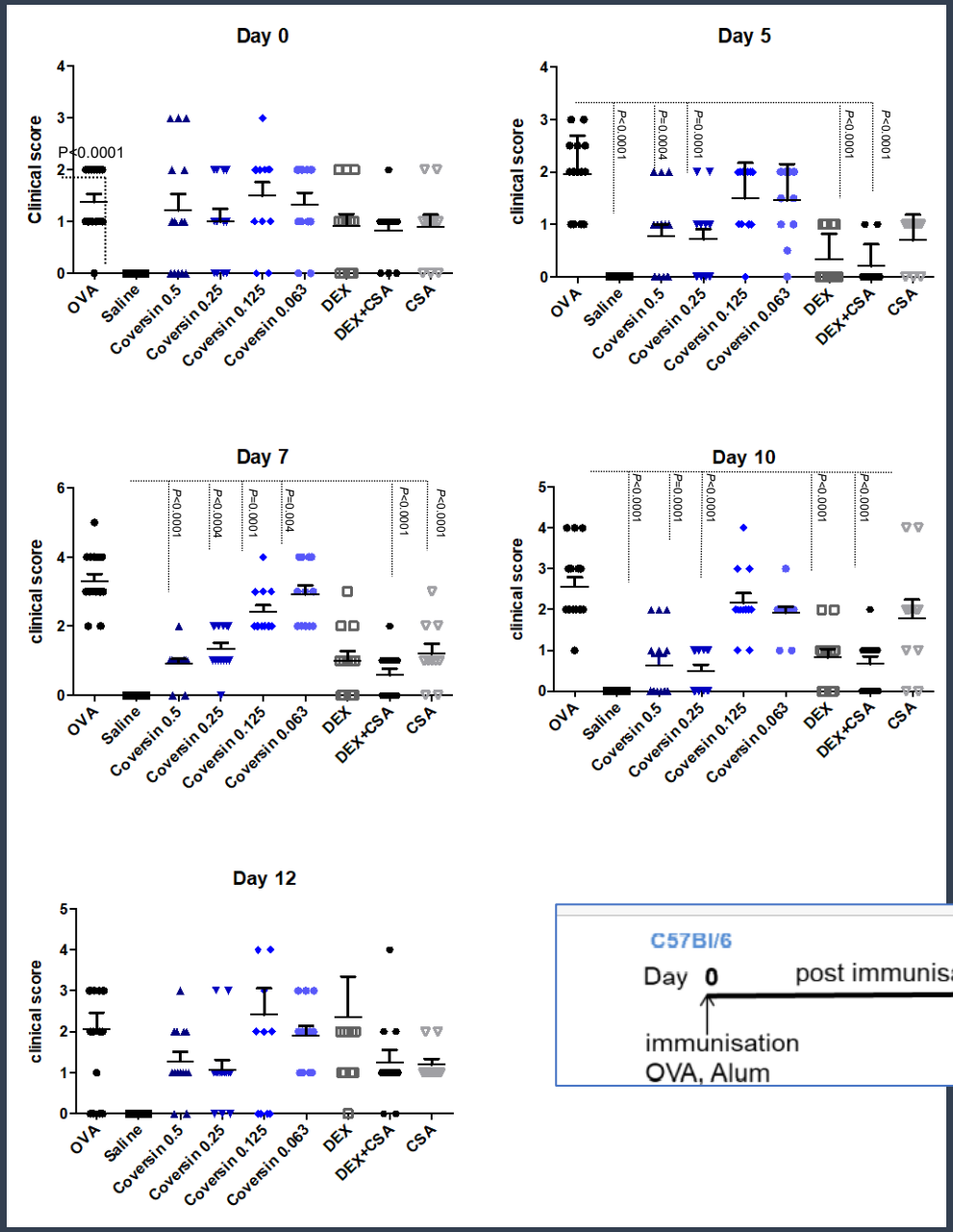
Conjunctival inflammation is associated with increased conjunctival cellular infiltration, increased IL-9 expressing cells (Mast Cells).

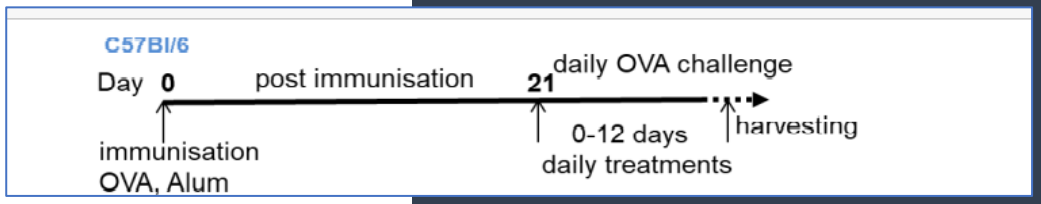


Conjunctival Th2 and Th9 ($PU.1^{+}IL\text{-}9^{+}CD4^{+}$) cells were increased in response to OVA challenge



Topical Nomacopan, dexamethasone and CsA downregulated conjunctival inflammatory scores on Days 5-10 of challenge





Topical Nomacopan, dexamethasone and CsA downregulated conjunctival inflammatory scores, Th2 cells

Allergy
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Allergic eye disease: Blocking LTB4/C5 in vivo suppressed disease and Th2 & Th9 cells

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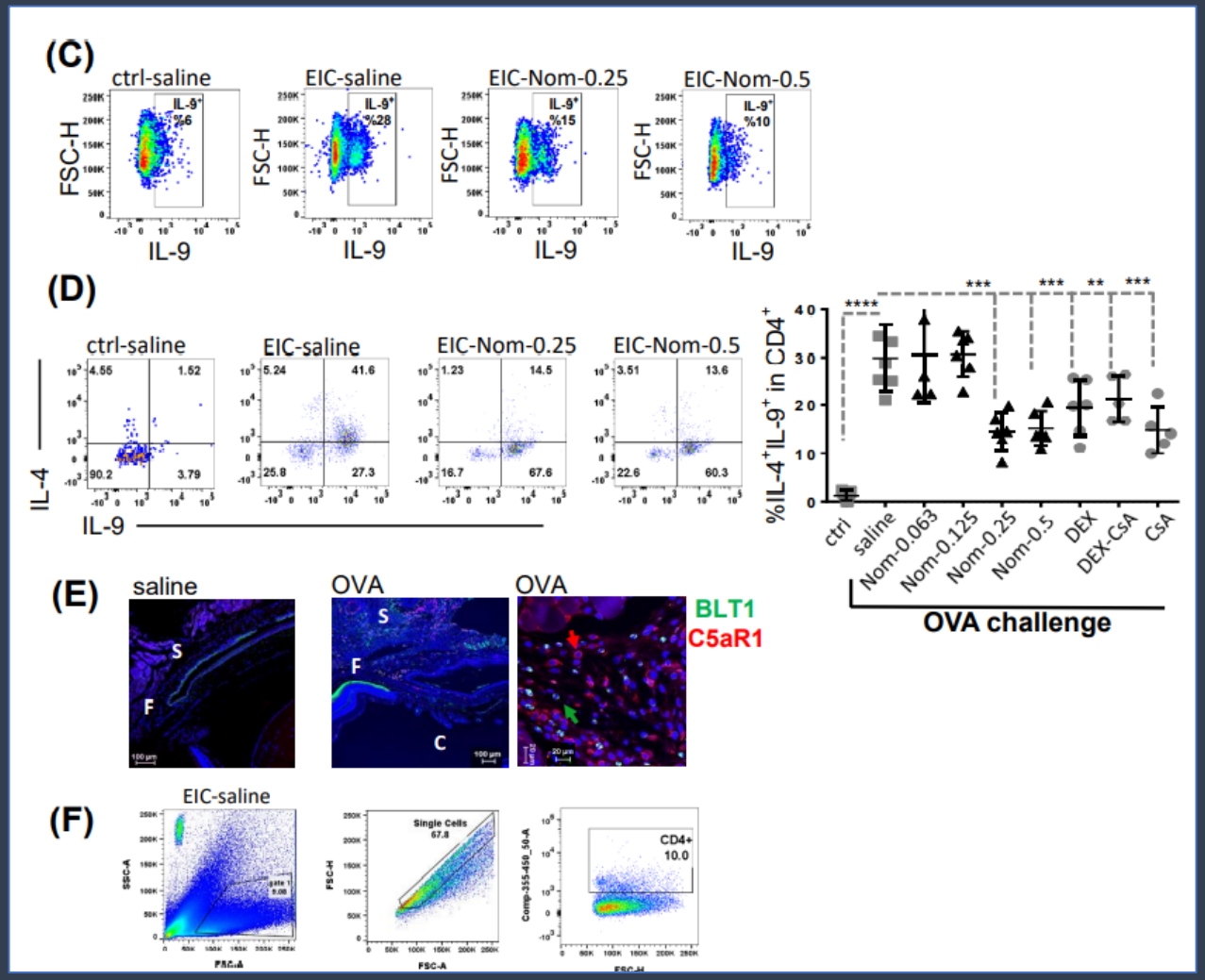
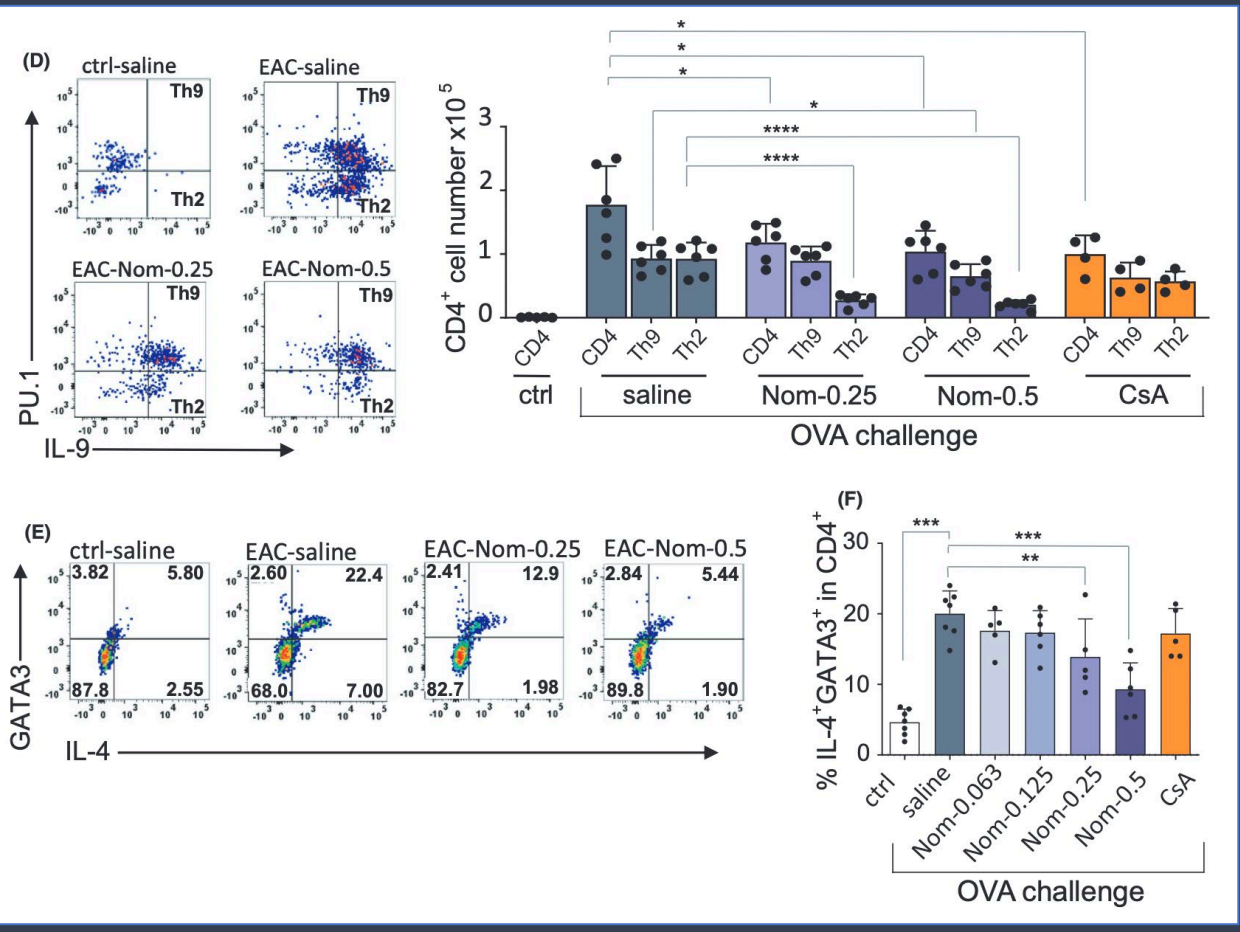
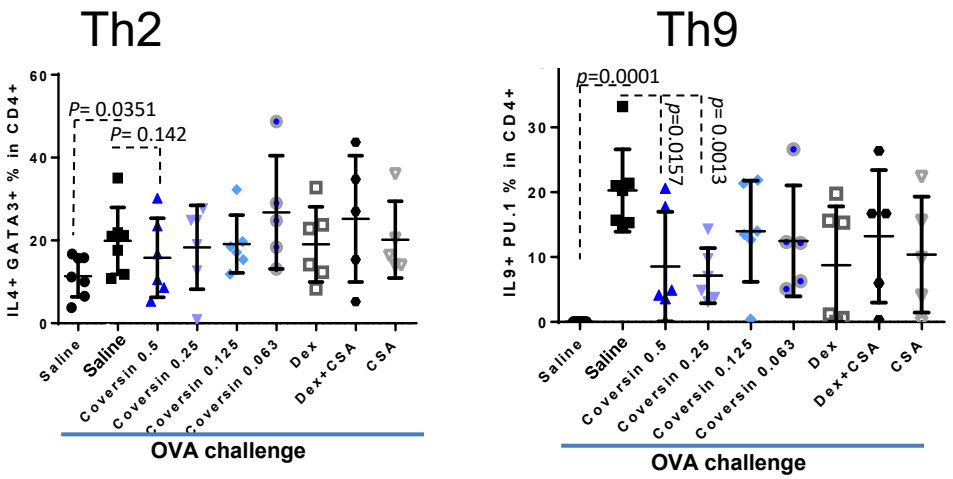


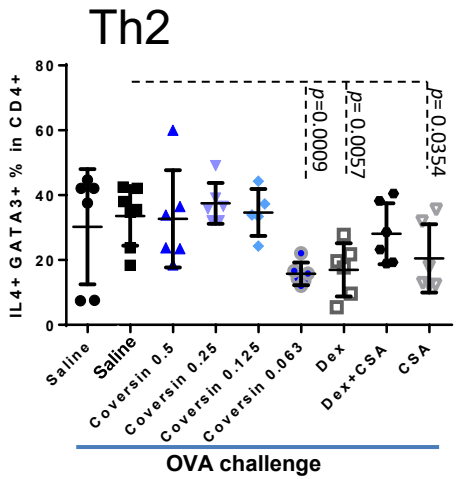


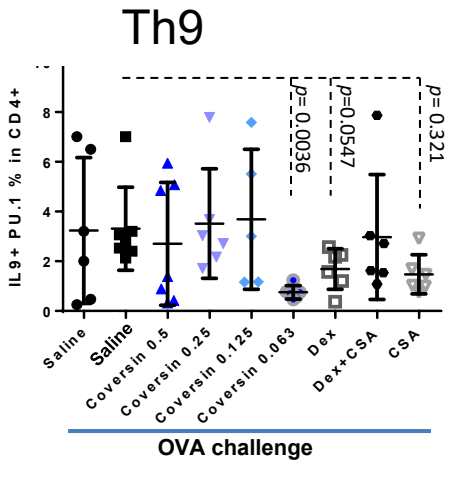
Th2 & Th9 levels in conjunctiva were downregulated by Nomacopan (Coversin). Th2 & Th9 in dLNs were downregulated by all treatments

Conj

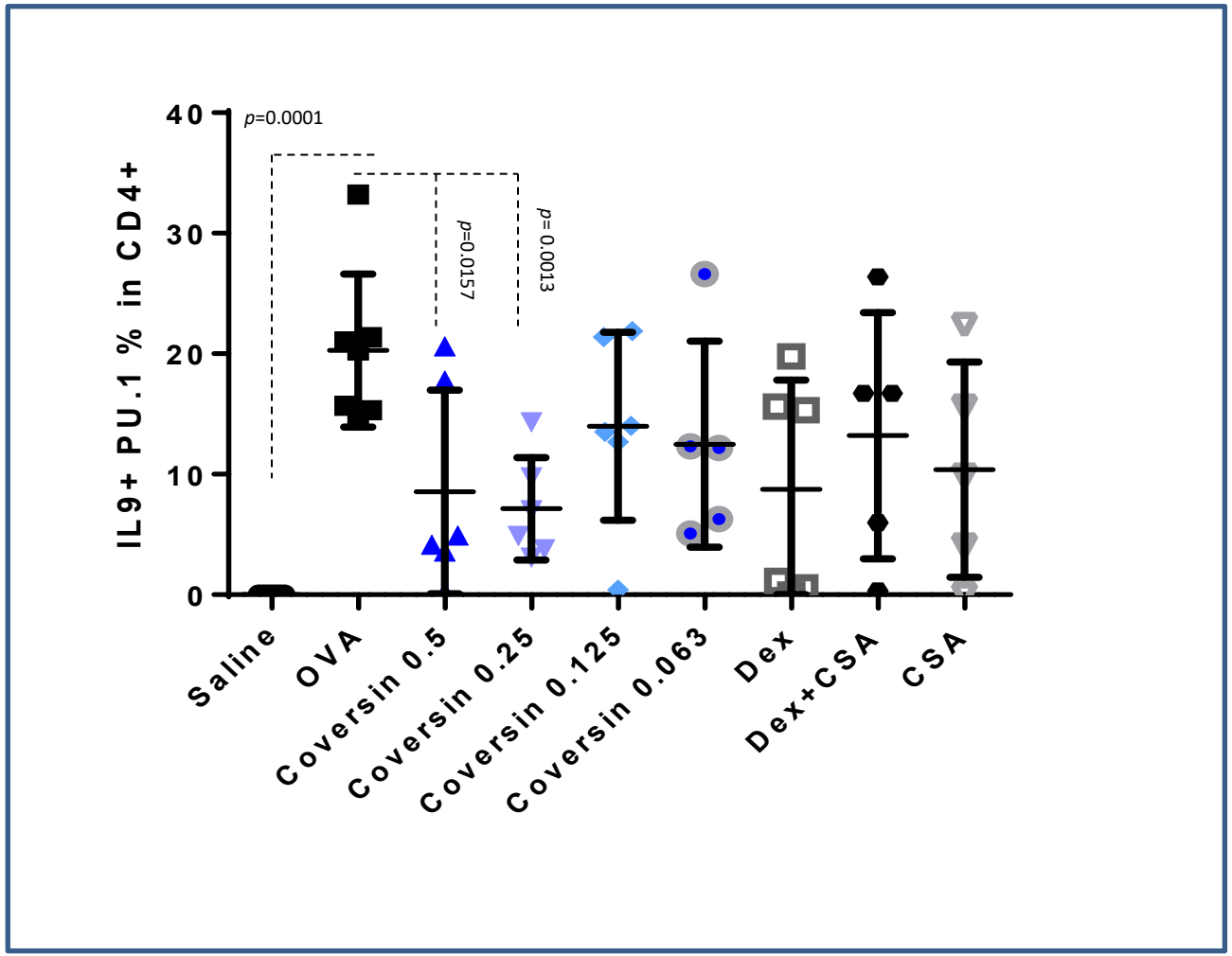


dLNs

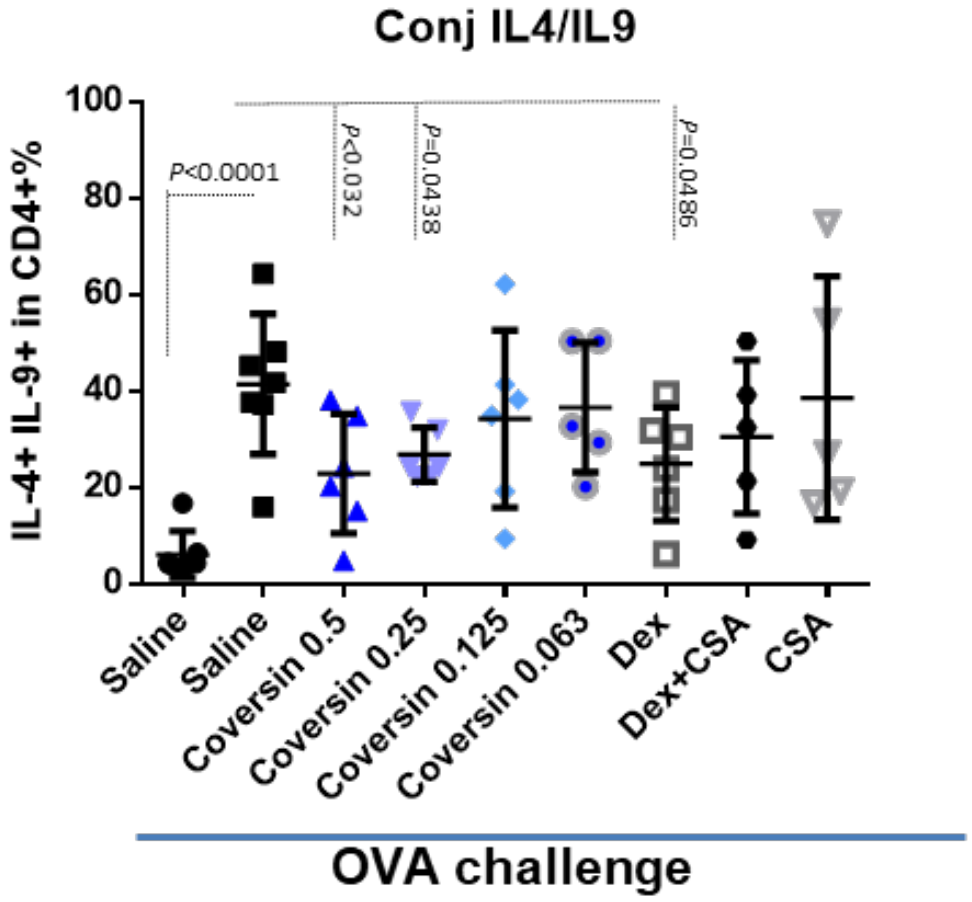




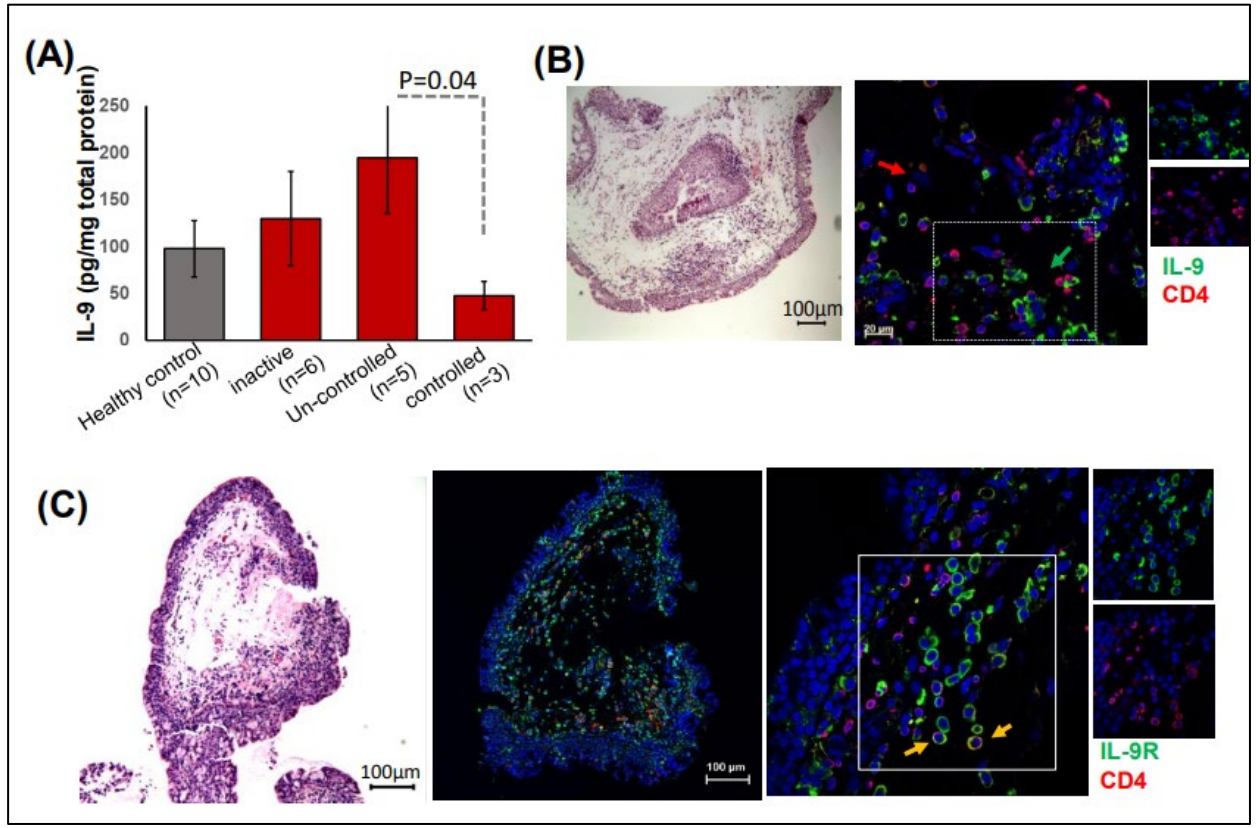
Conjunctival Th9 cells were significantly decreased by Nomacopan

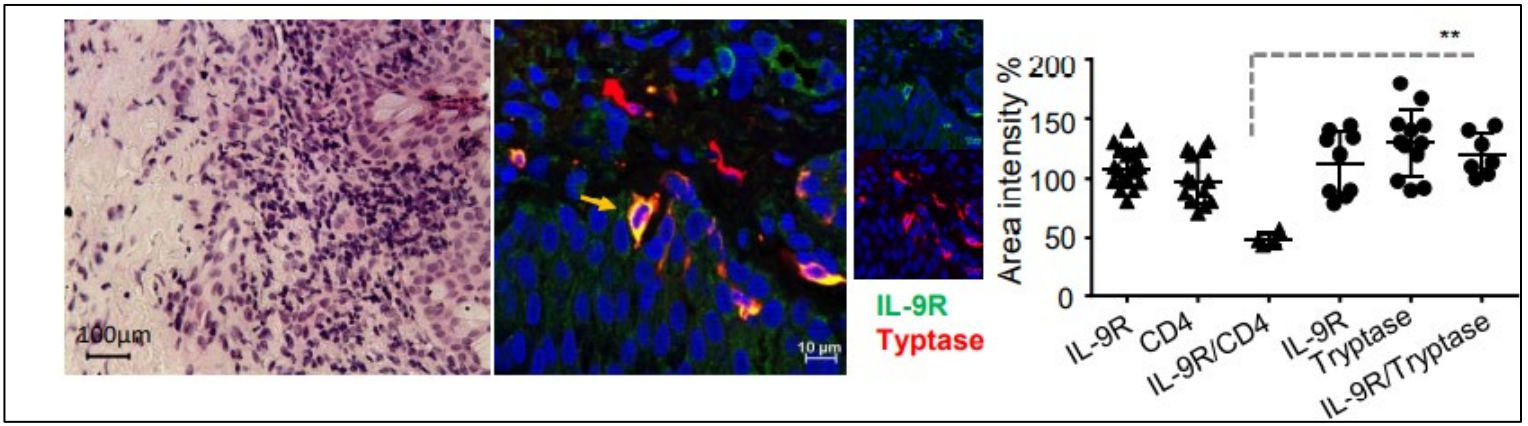


Conjunctival IL-4/IL-9 co-expressing CD4^{+}T cells were downregulated by Nomacopan (Coversin) and Dex



Detecting IL-9 in Tear Fluids (A) & IL-9-expressing CD4^{+}T cells (B) in VKC Conjunctival Tissues





IL-9-receptor expression by conjunctival mast cells & CD4^{+}T cells in VKC

Conclusion

- IL-9-expressing mast cells and $CD4^{+}$T cells are upregulated during OVA-induced EIC
- Nomacopan preferentially downregulated conjunctival Th2 and Th9 cells
- Nomacopan, dexamethasone and CsA effectively decreased Th2 and Th9 cells in dLNs

	Nomacopan	Dexamethasone	CsA
Conj Th2	↓	—	—
Conj Th9	↓	—	—
dLN Th2	↓	↓	↓
dLN Th9	↓	↓	↓

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Thank you for your attention!

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