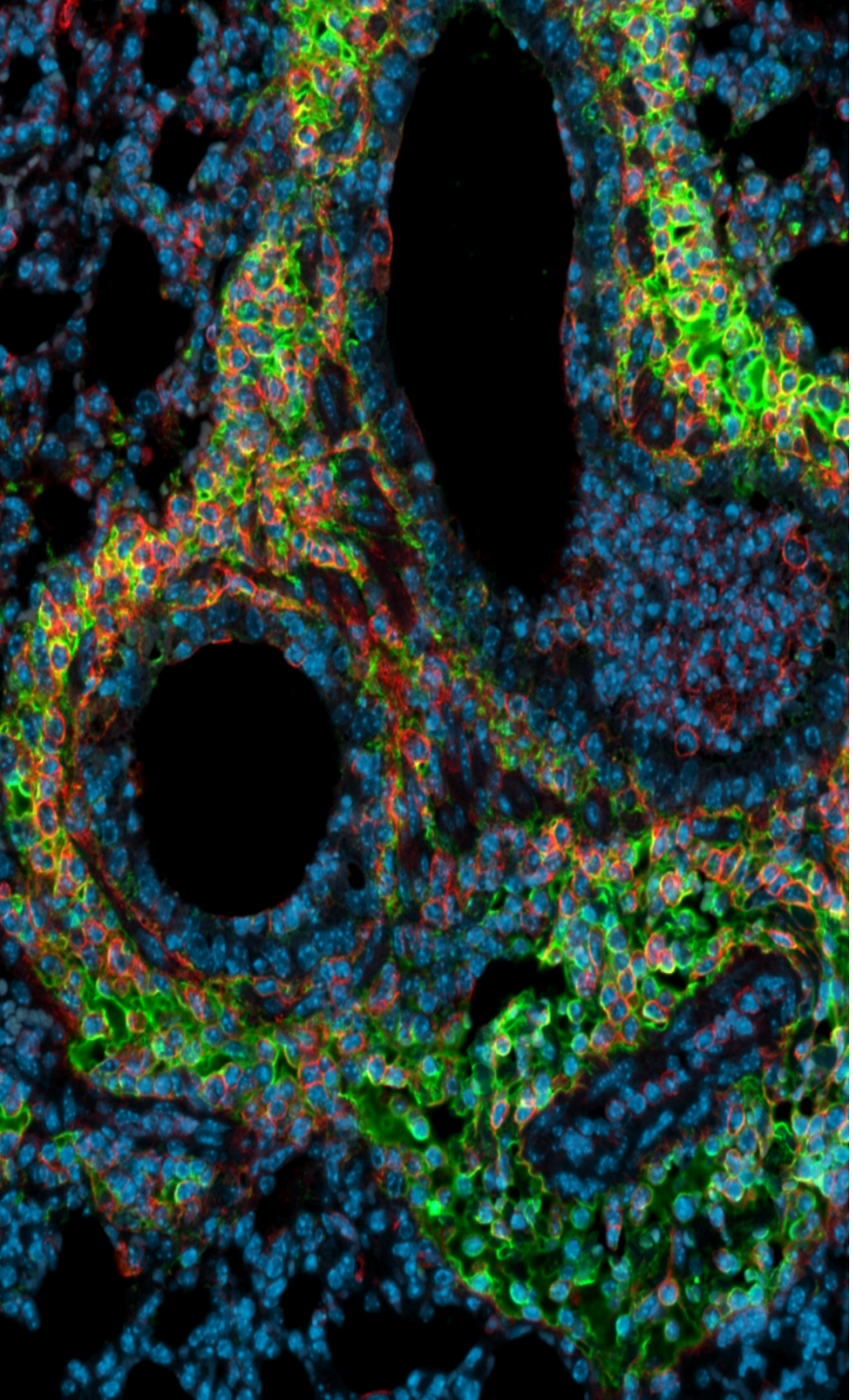

Decision making in lung immunity

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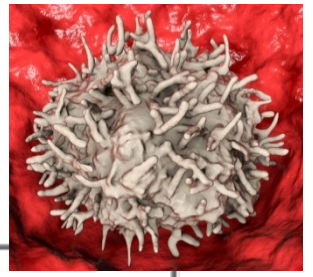
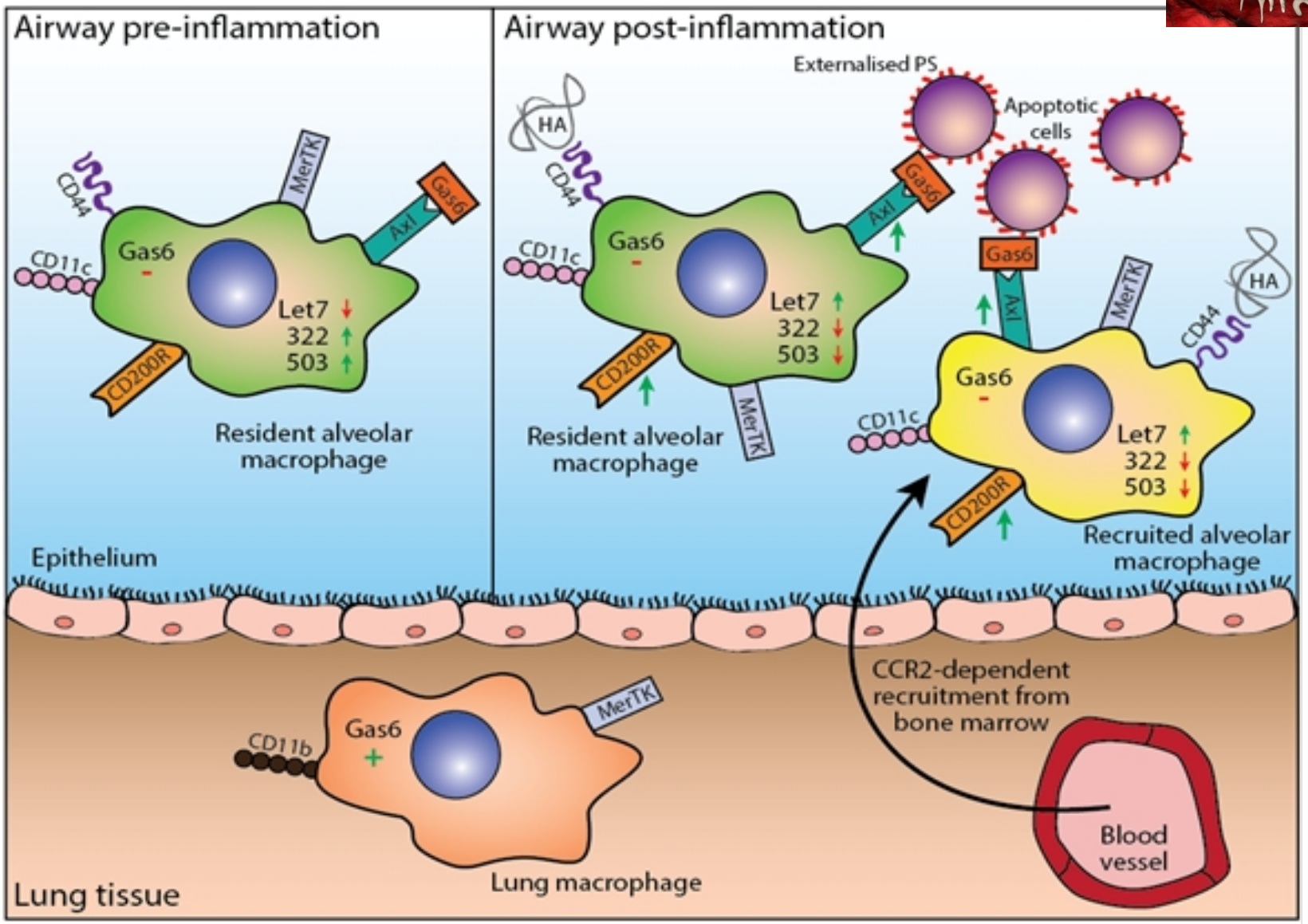
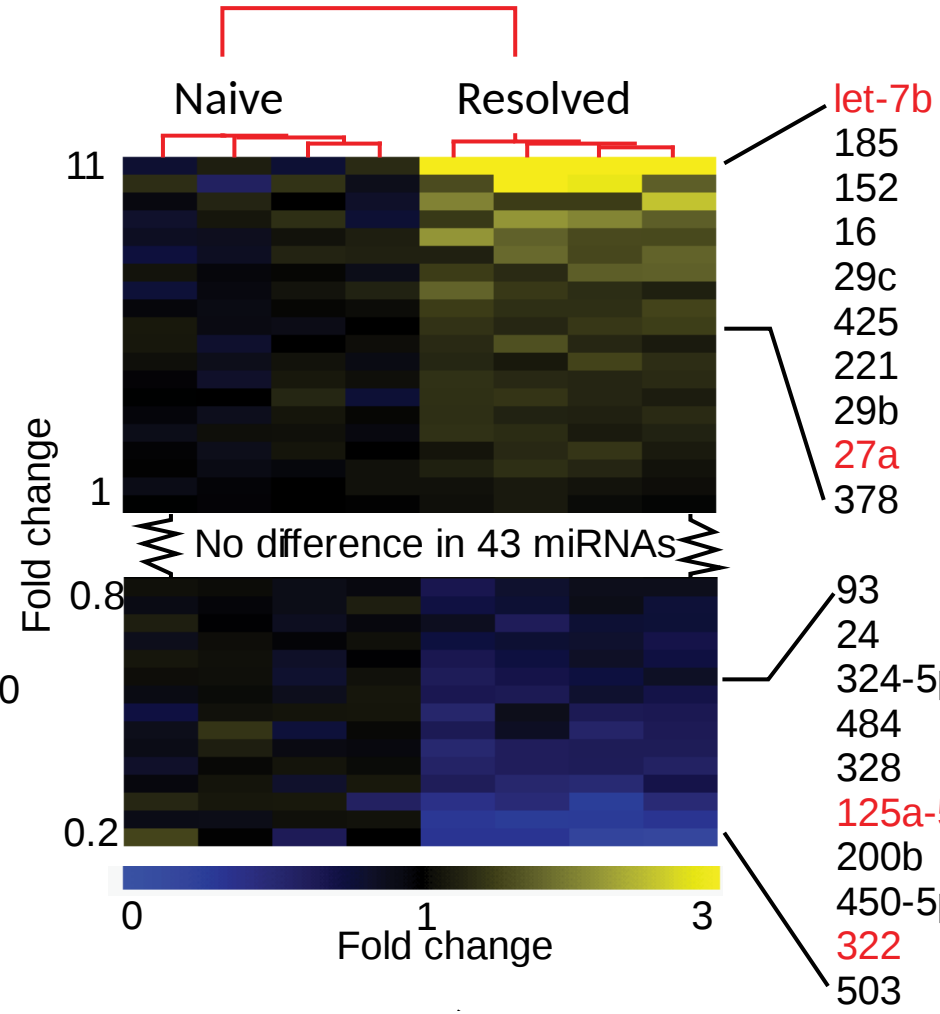
- Tissue complexity
- Homeostasis
- Normal processes that do not stop

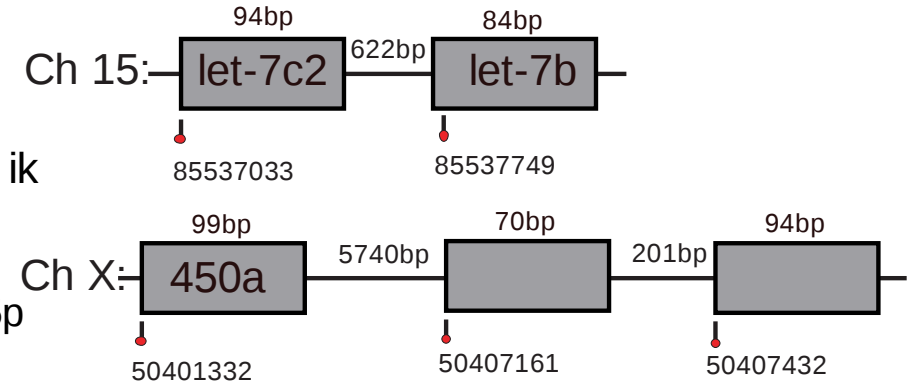
Multiple factors affecting macrophage inflammatory tone



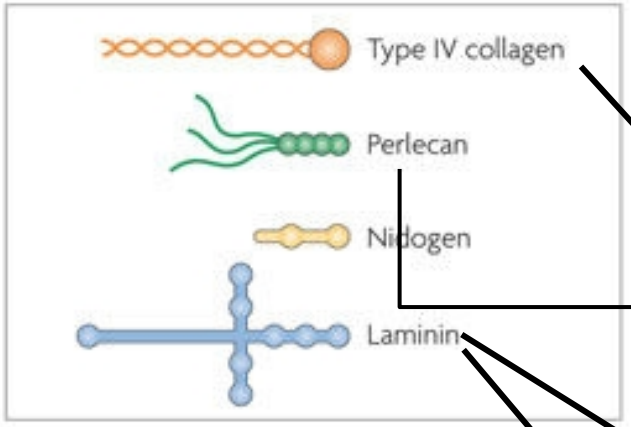


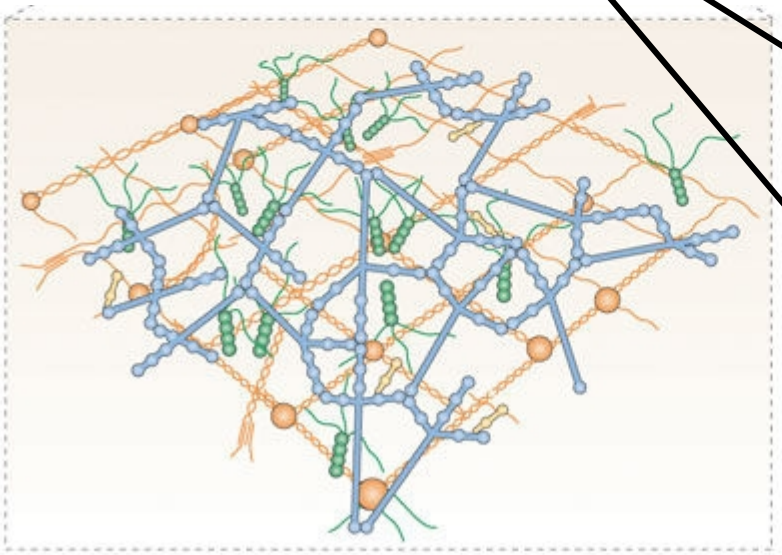
Blind folding airway macrophages: miRNA modifications





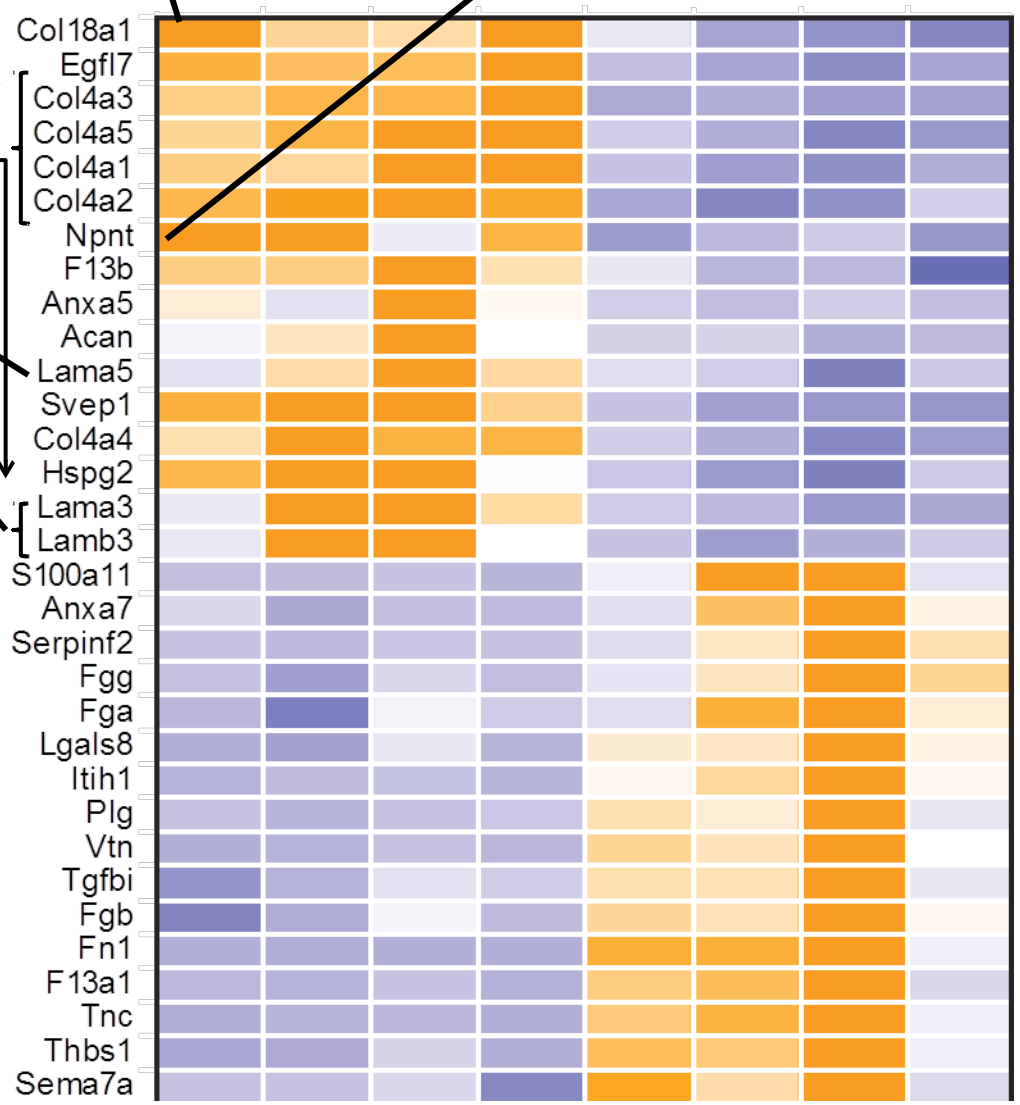
Dr Alexander Godlee



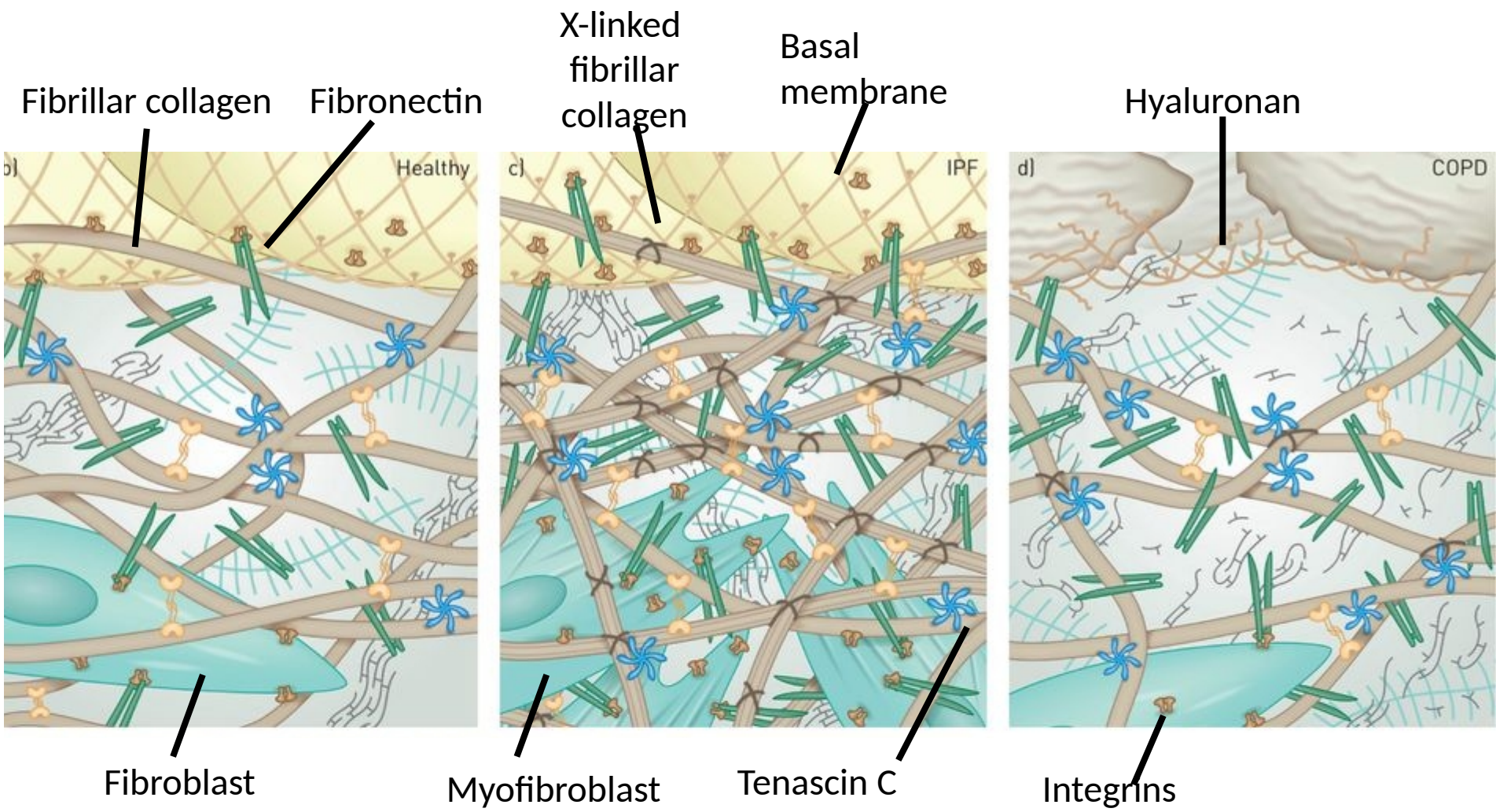


collagen type XVIII alpha 1 chain

Nephronectin: binds integrin $\alpha 8\beta 1$

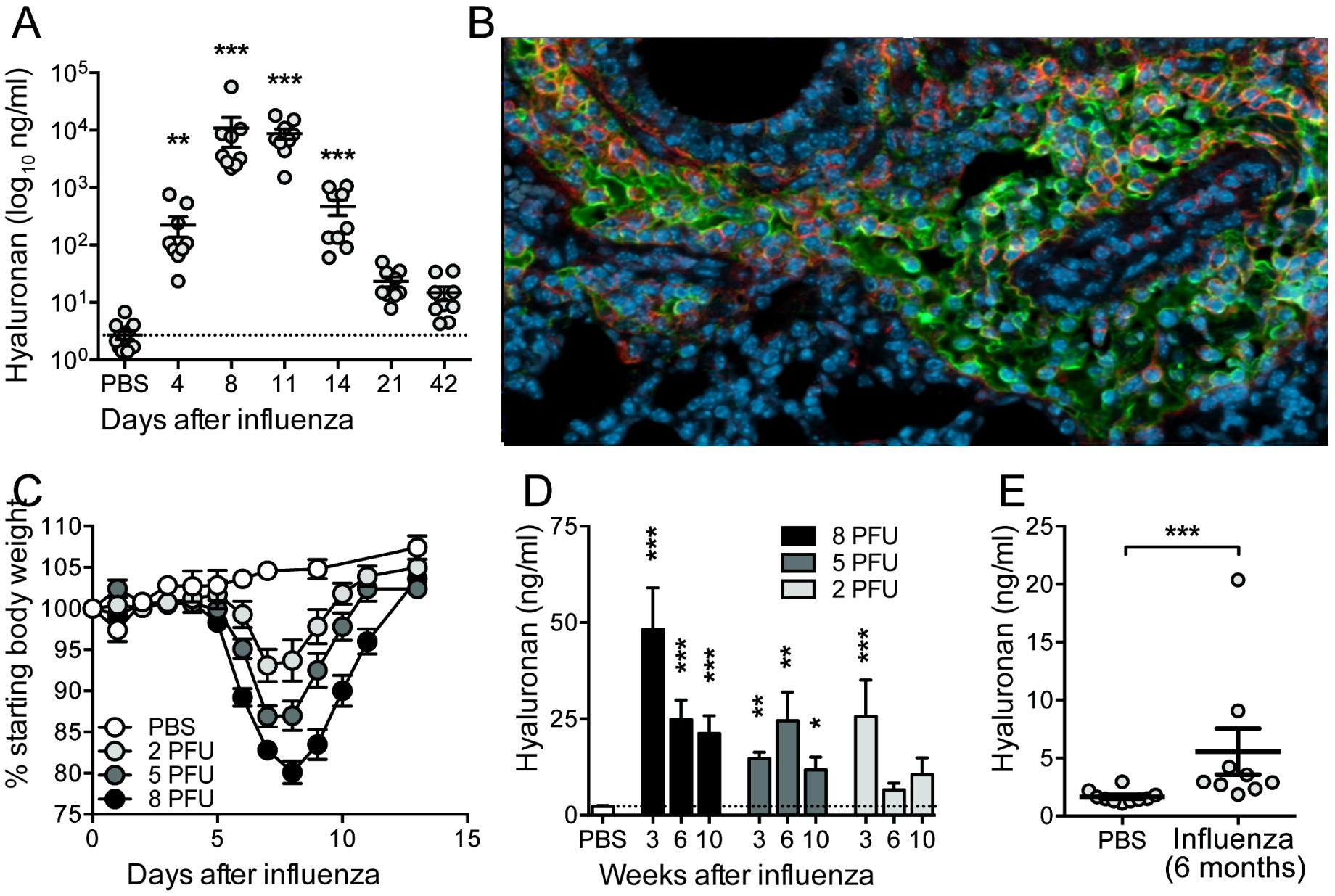


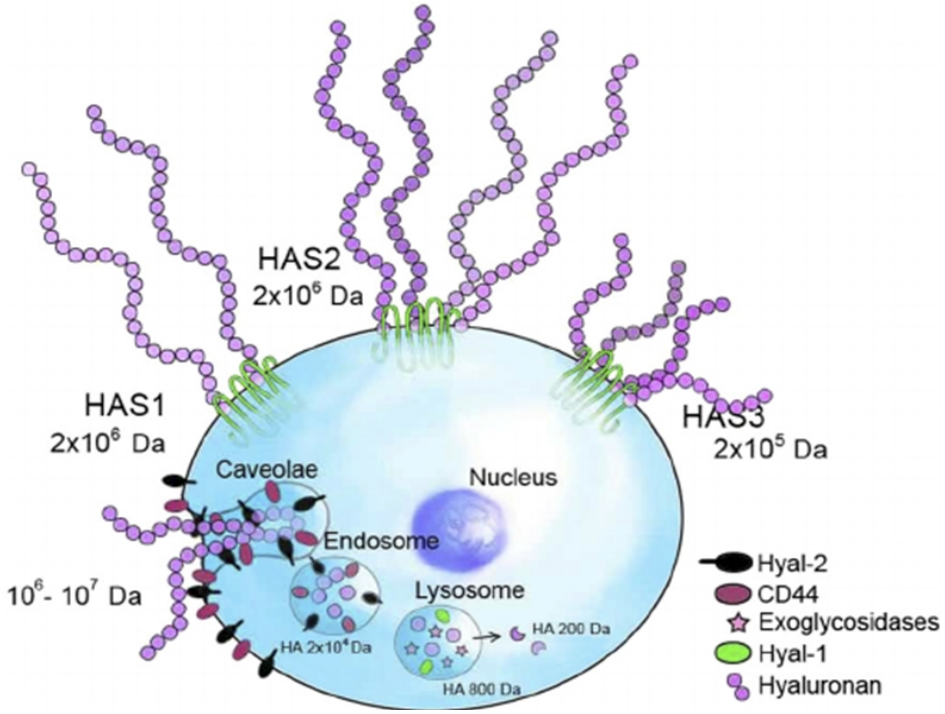
The impact of the extracellular matrix on inflammation. Lydia Sorokin Nature Reviews Immunology volume 10, pages 712–723 (2010)000



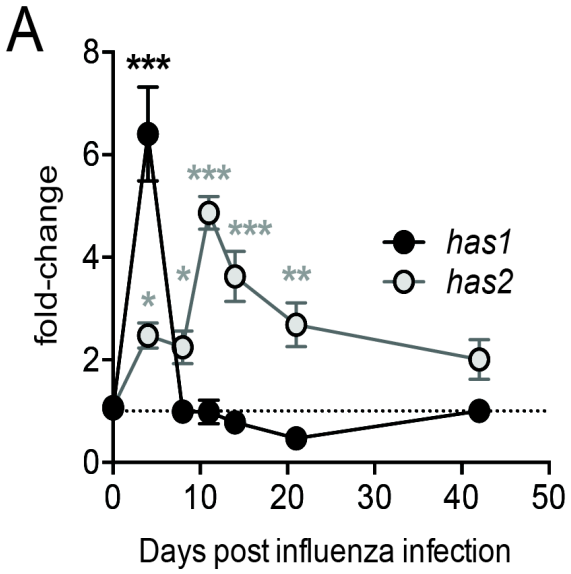
The instructive extracellular matrix of the lung: basic composition and alterations in chronic lung disease
Gerald Burgstaller, Bettina Oehrle, Michael Gerckens, Eric S. White, Herbert B. Schiller, Oliver Eickelberg.
European Respiratory Journal 2017, 50: 1601805; DOI: 10.1183/13993003.01805-2016

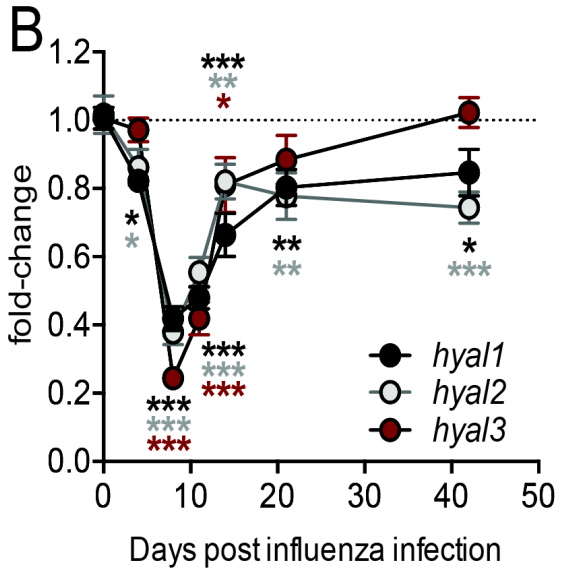
Hyaluronan is a major constituent of the inflamed lung

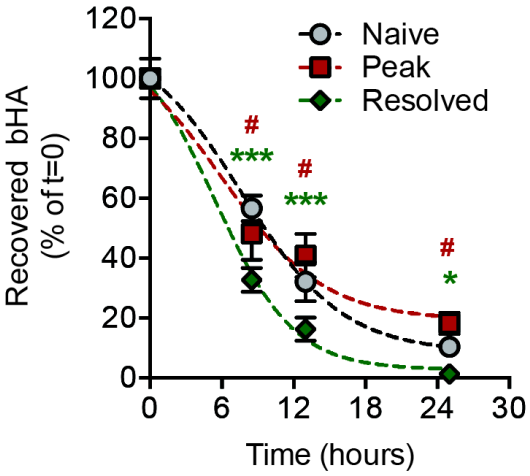




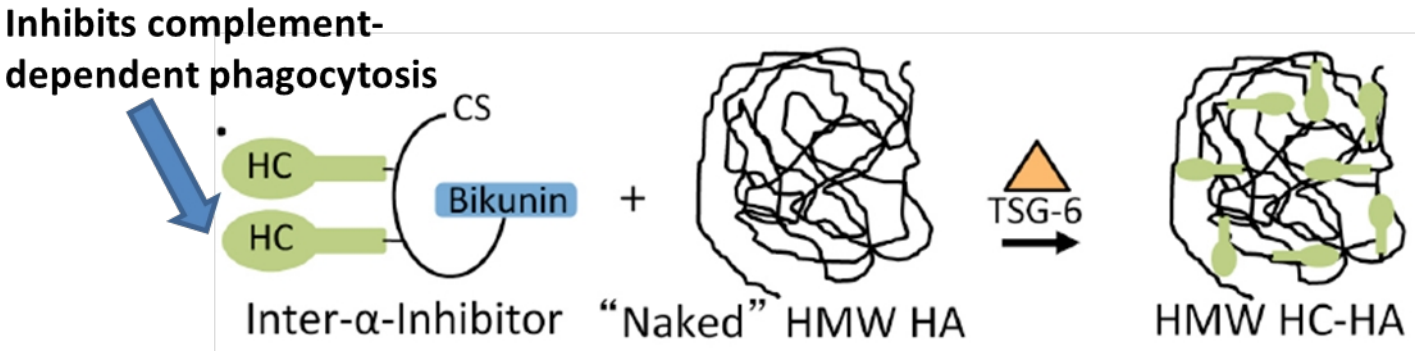
Why does matrix persist? Production versus degradation

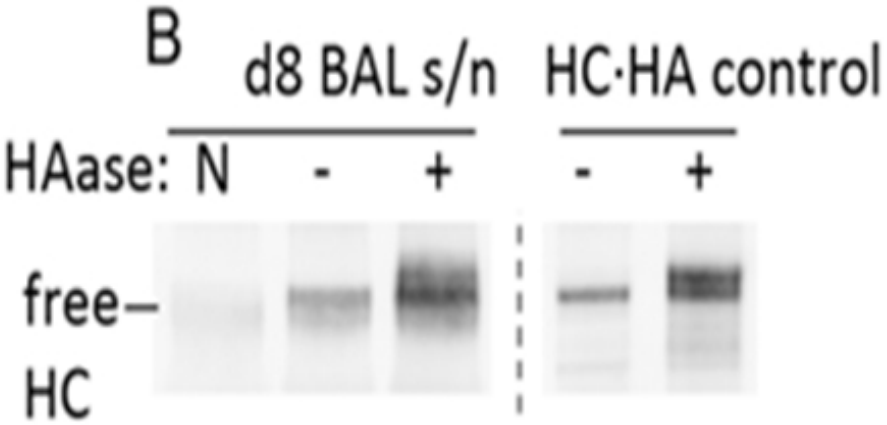




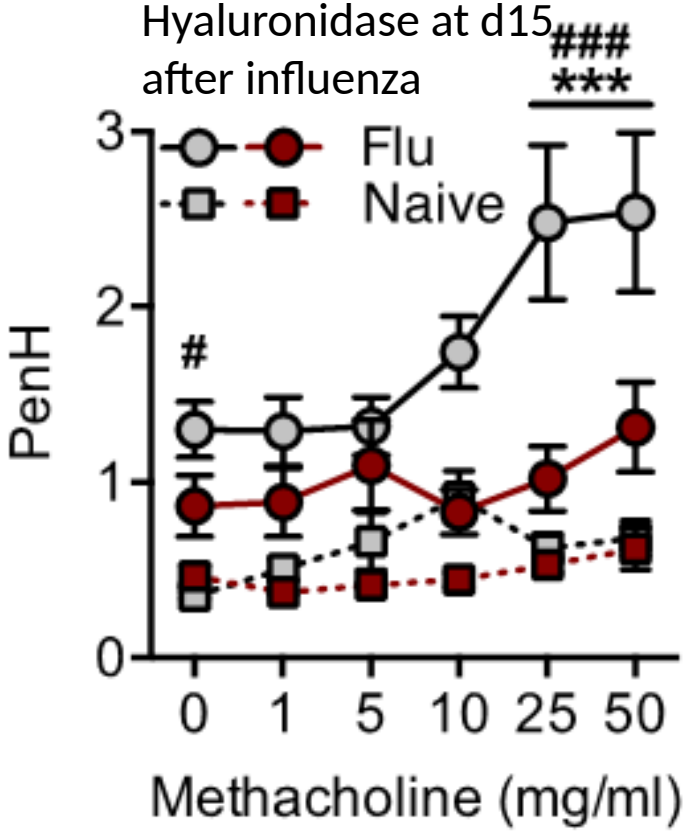


Digestion of HA restores lung function





Hyaluronidase at d15 after influenza

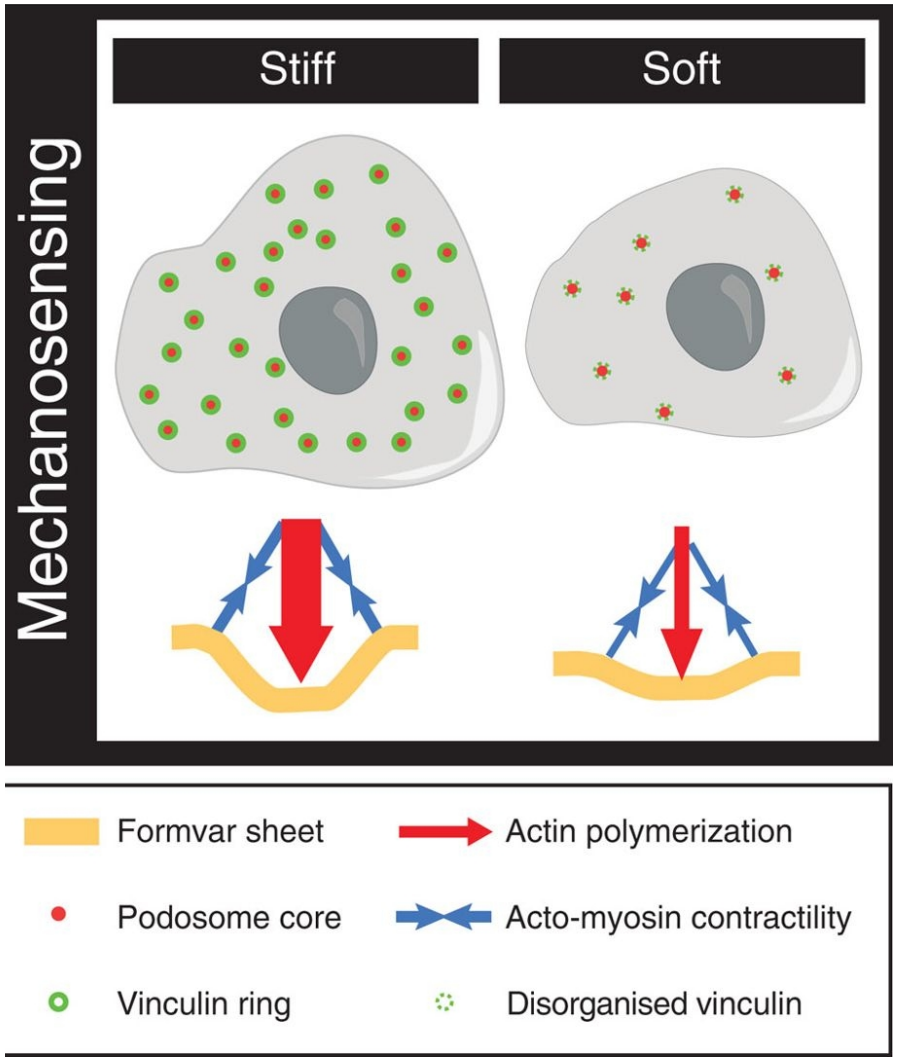


Mechanosensing podosomes exert a protrusive force that senses environment stiffness

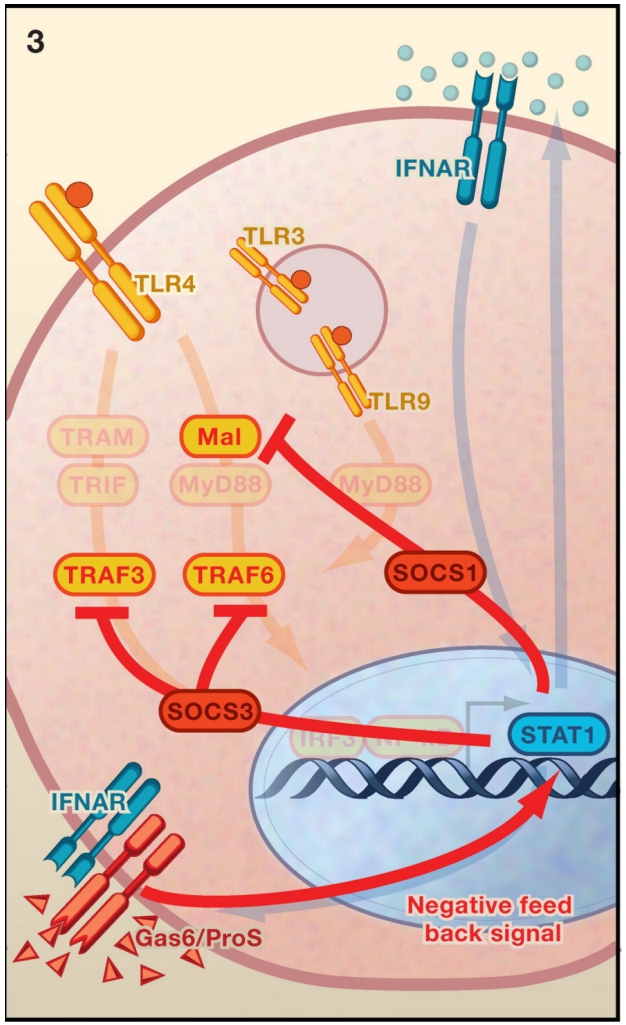
F-actin-rich cone-shaped structures ~600 nm height and submicron diameter,

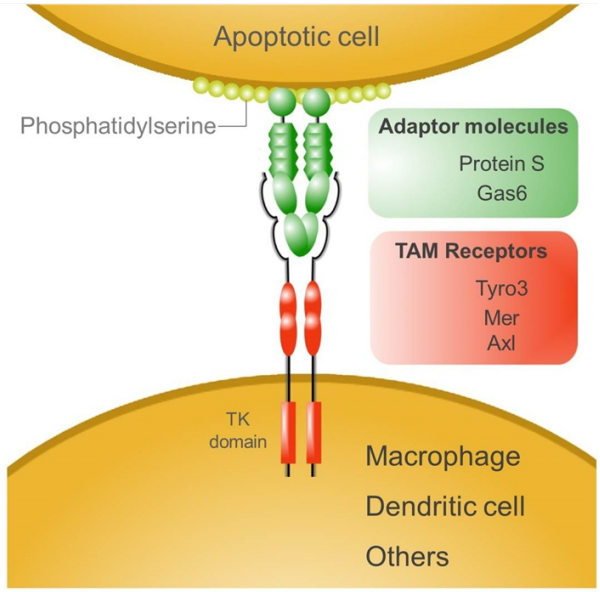
Located at the basal face of cells, perpendicular to, and in contact with, the substratum via integrins at the podosome ring

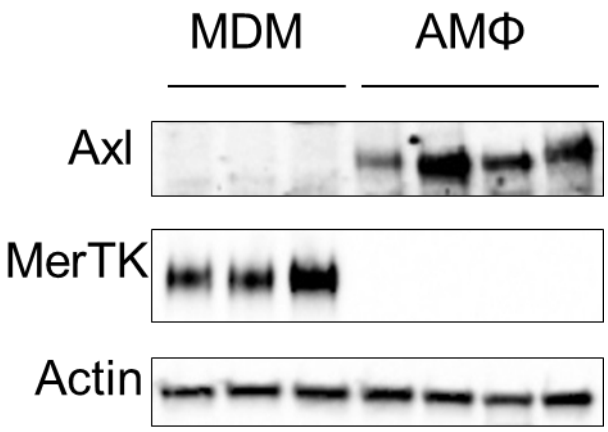
Typical lifespan of 10 min, with an actin turnover of ~30 s



Cell death: A double edged sword in lung repair

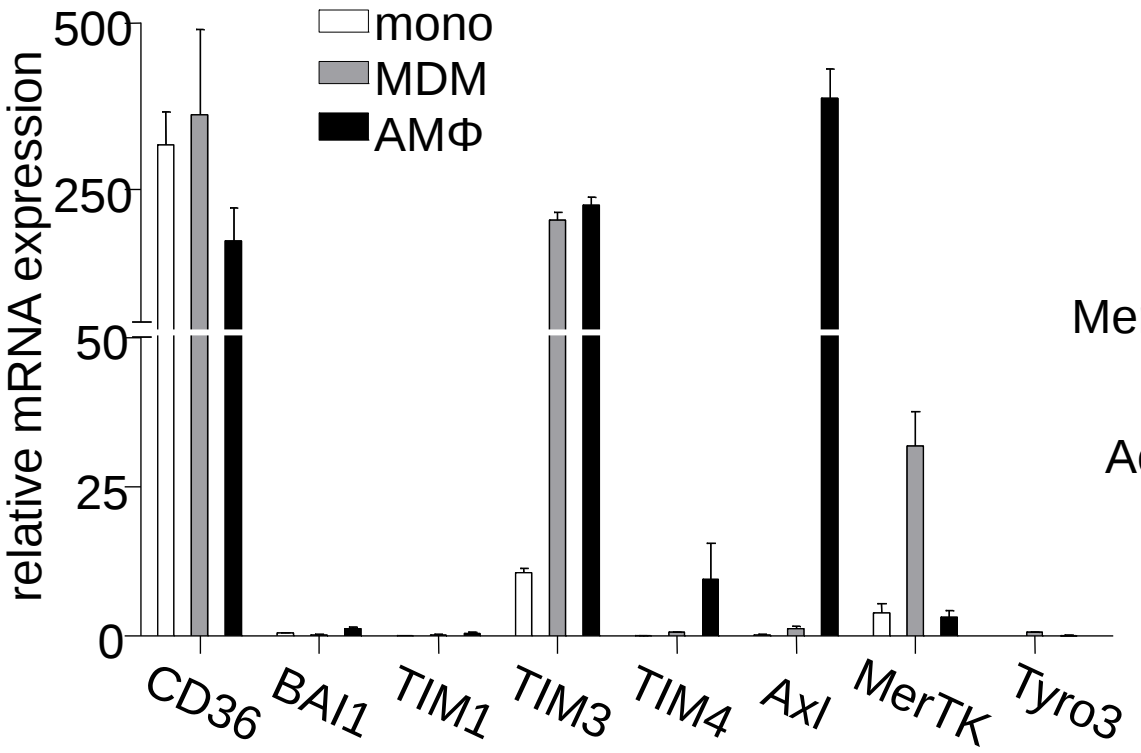


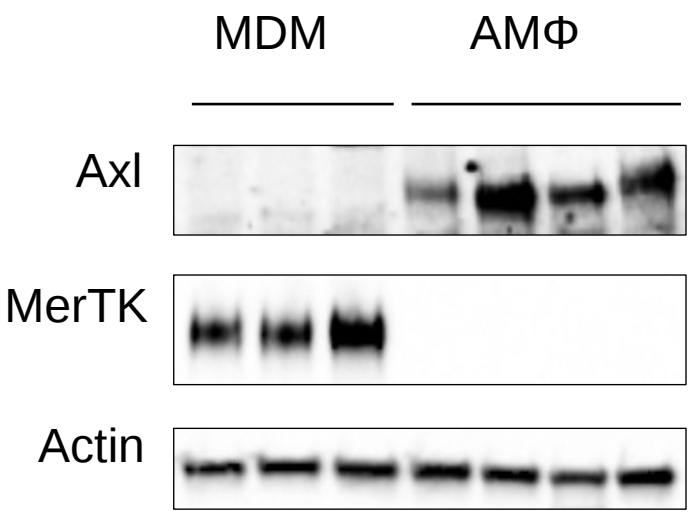




Fujimori T, Grabiec AM, Kaur M, Bell TJ, Fujino N, Cook PC, Svedberg FR, MacDonald AS, Maciewicz RA, Singh D, Hussell T. Mucosal Immunol. 2015;8(5):1021-30.

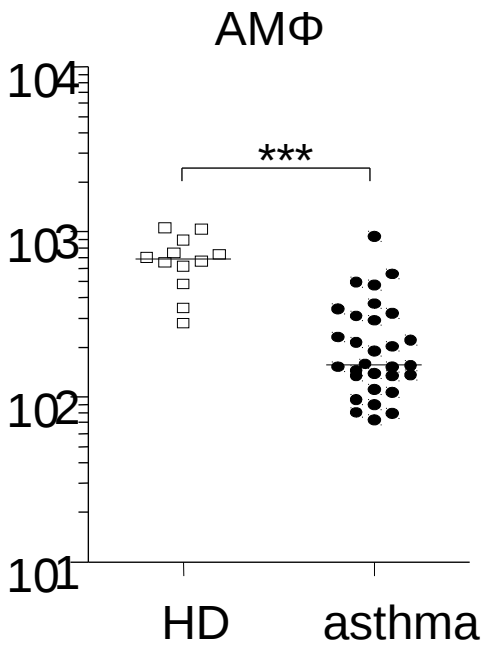
Differential expression of TAM receptors on human macrophage subsets

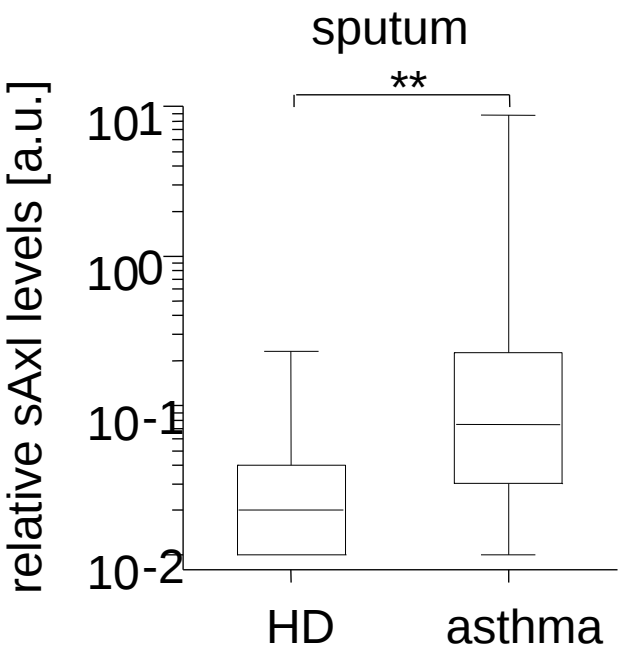


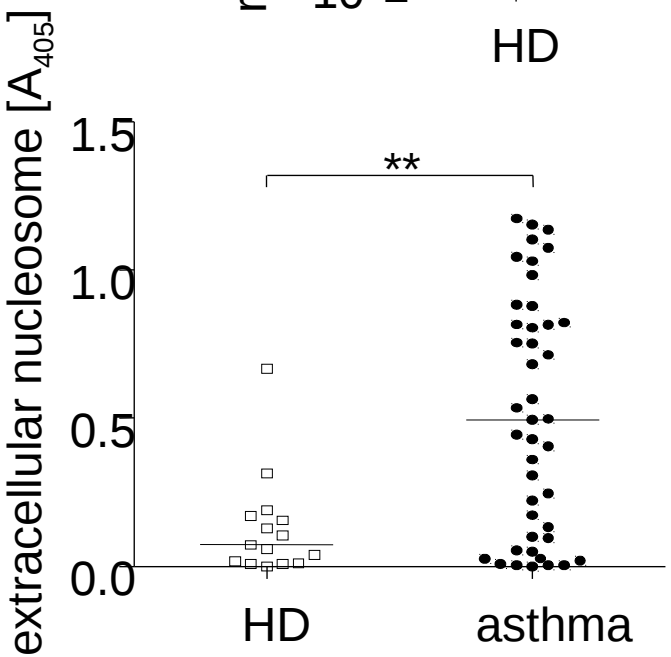


Grabiec AM, Denny N, Doherty JA, ……Fowler SJ, Simpson A, Hussell T.
Diminished airway macrophage expression of the Axl receptor tyrosine kinase is associated with defective efferocytosis in asthma.
J Allergy Clin Immunol. 2017 Apr 12. (17)30585-7.

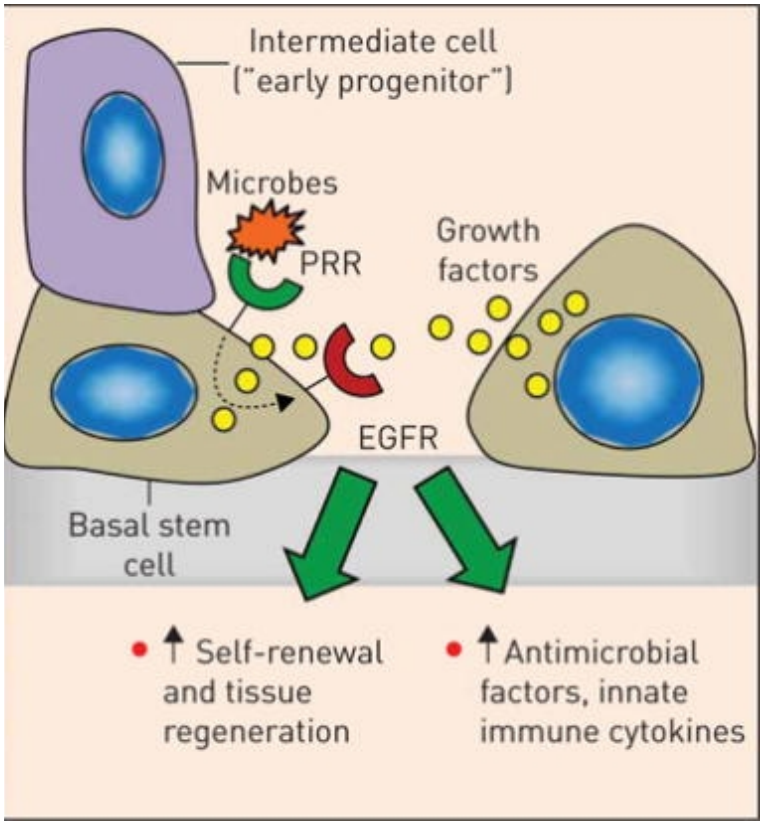
Cell death: A double edged sword in lung repair

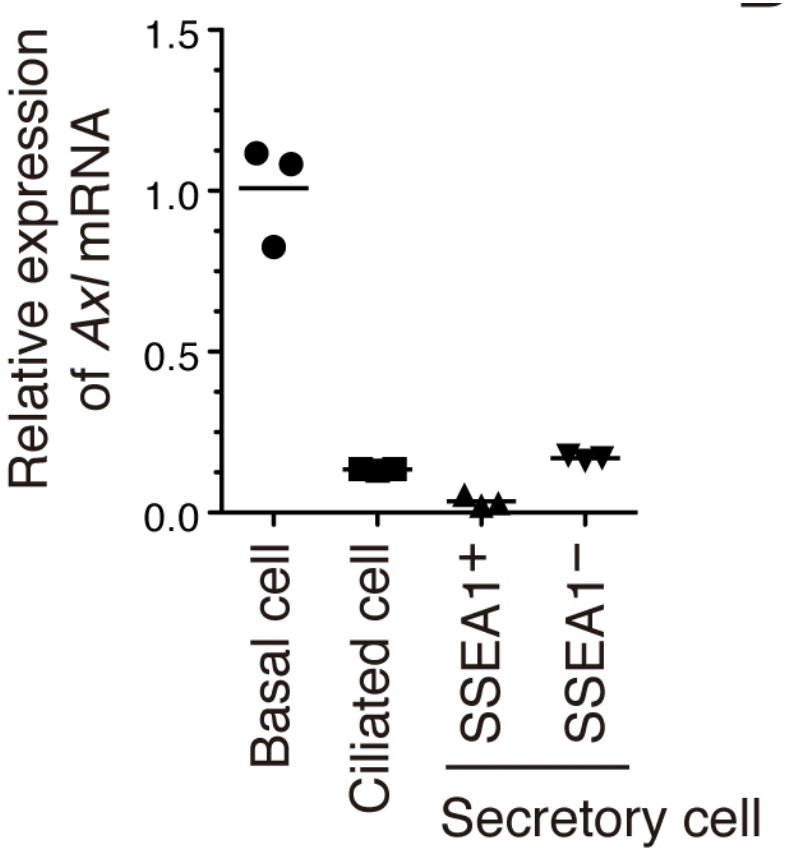




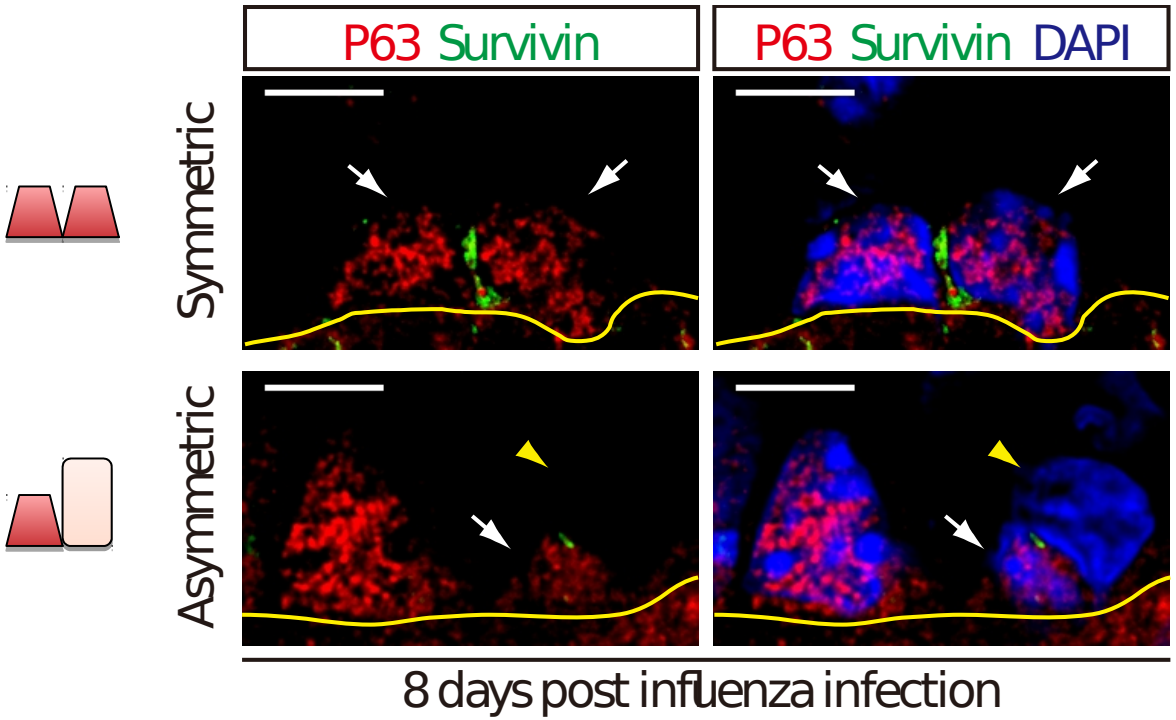


Apoptotic sensing by lung basal cells

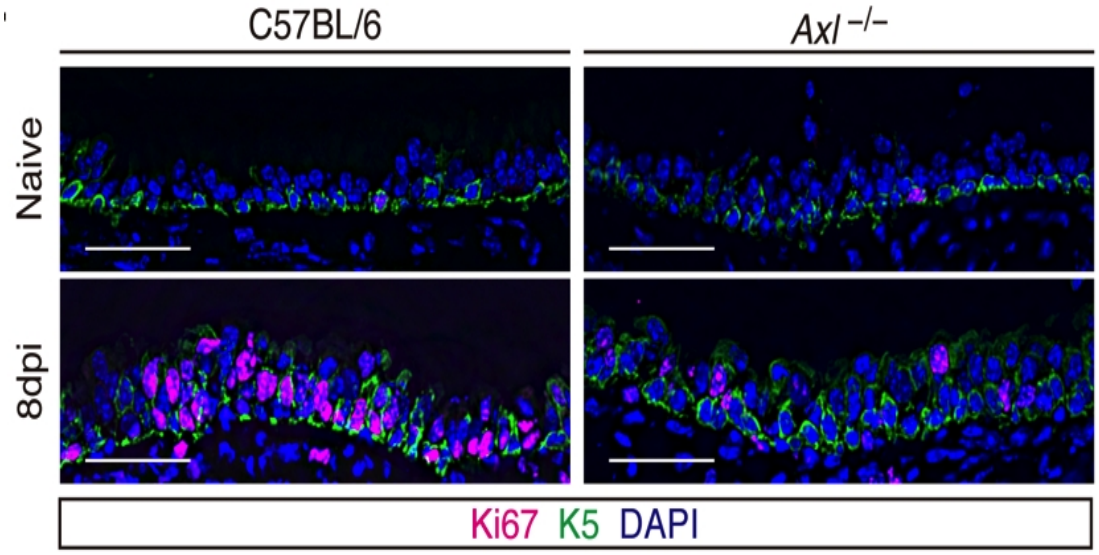




Multitasking basal cells: combining stem cell and innate immune duties.
Shaykhiev R. Eur Respir J. 2015 Oct;46(4):894-7

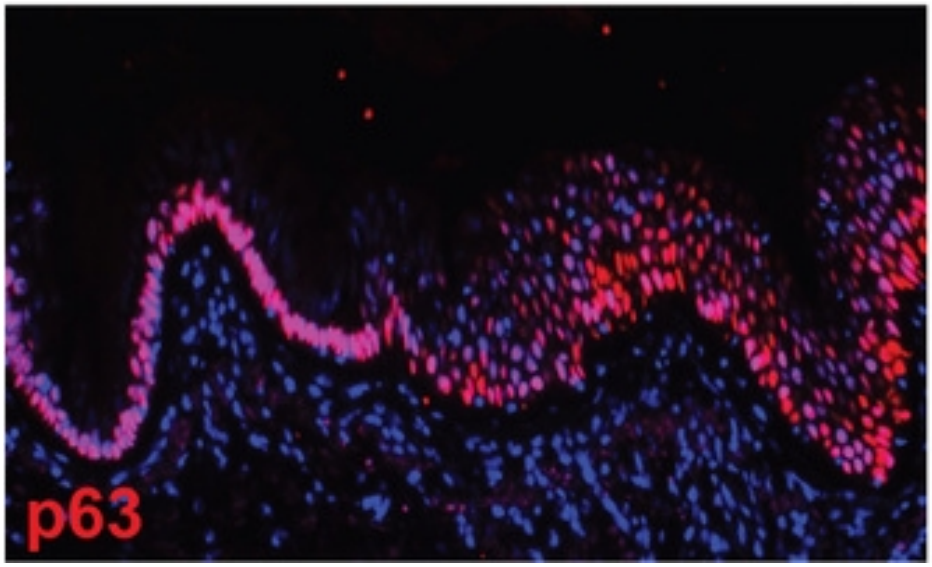


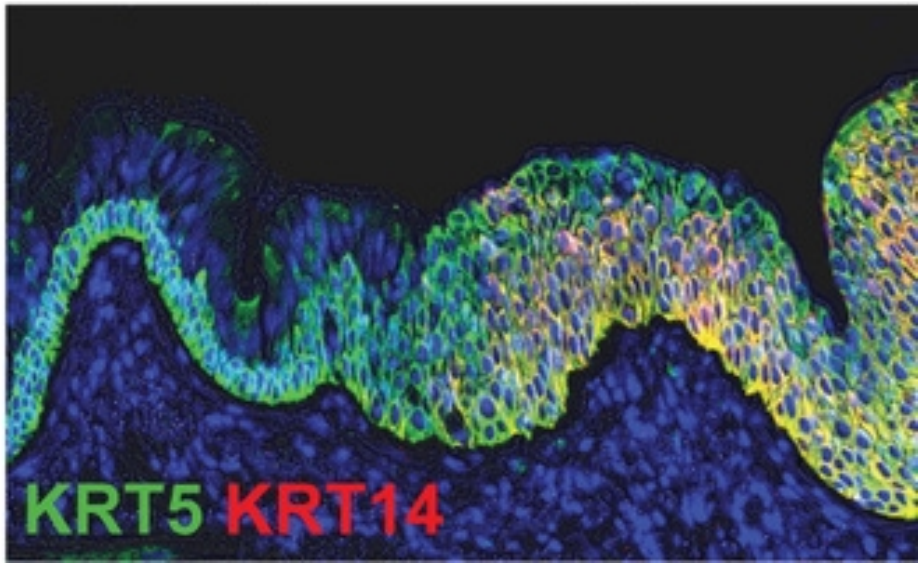
Basal cells respond to local cues: apoptotic cells



AXL drives basal cell proliferation

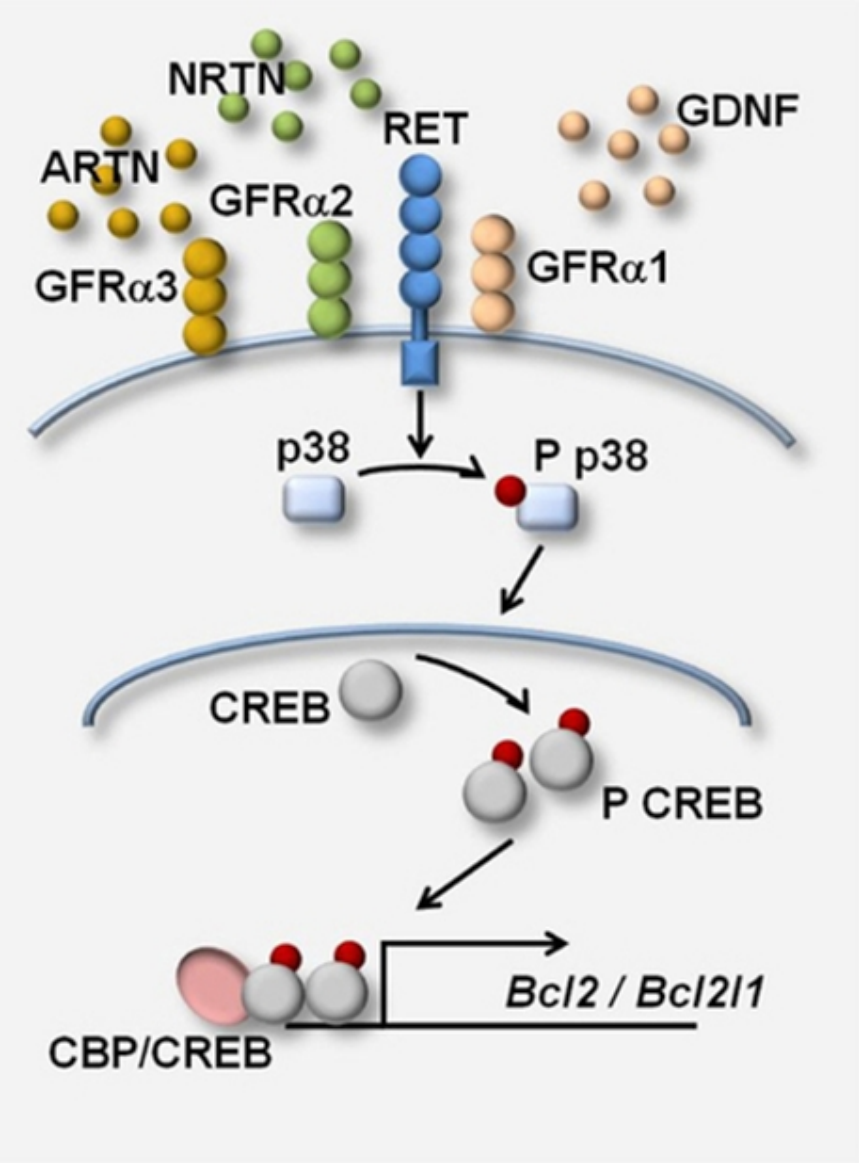
Basal cell hyperplasia





Rock JR, Randell SH, Hogan BL. Dis Model Mech. 2010 Sep-Oct;3(9-10):545-56.
Airway basal stem cells: a perspective on their roles in epithelial homeostasis and remodelling.

Epithelial macrophage cross-talk via the Glial cell line-derived neurotrophic factor family

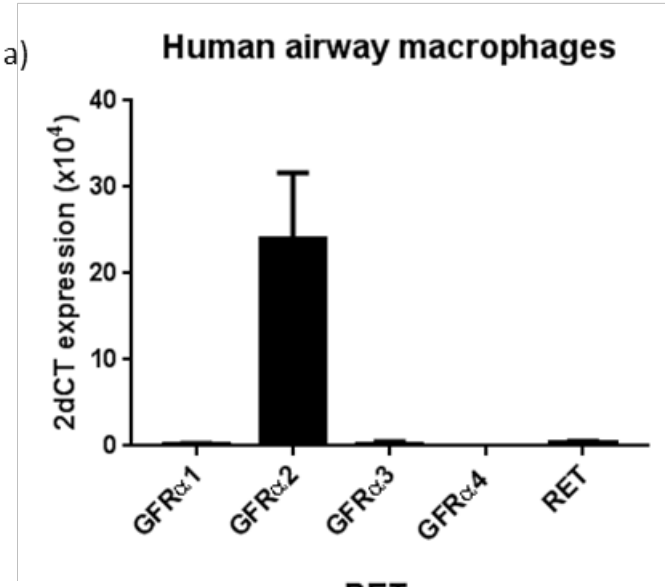


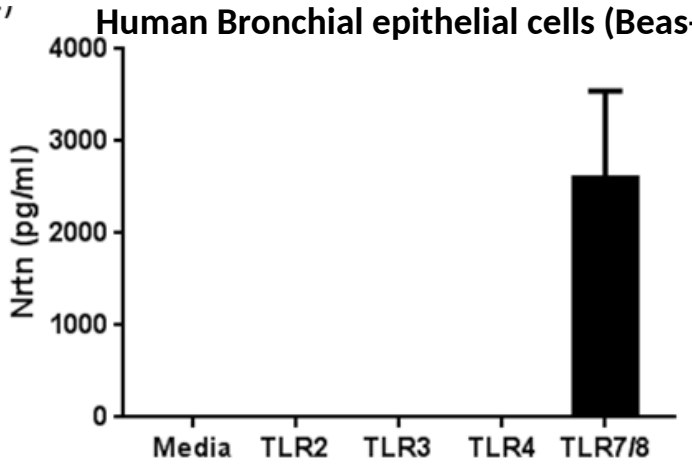
Key roles in the control of neuron survival and differentiation.

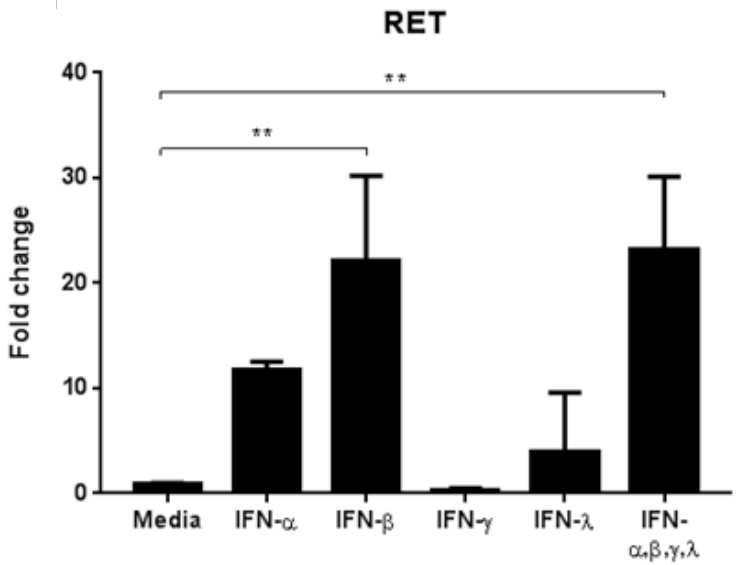
Distant members of the TGF-β superfamily

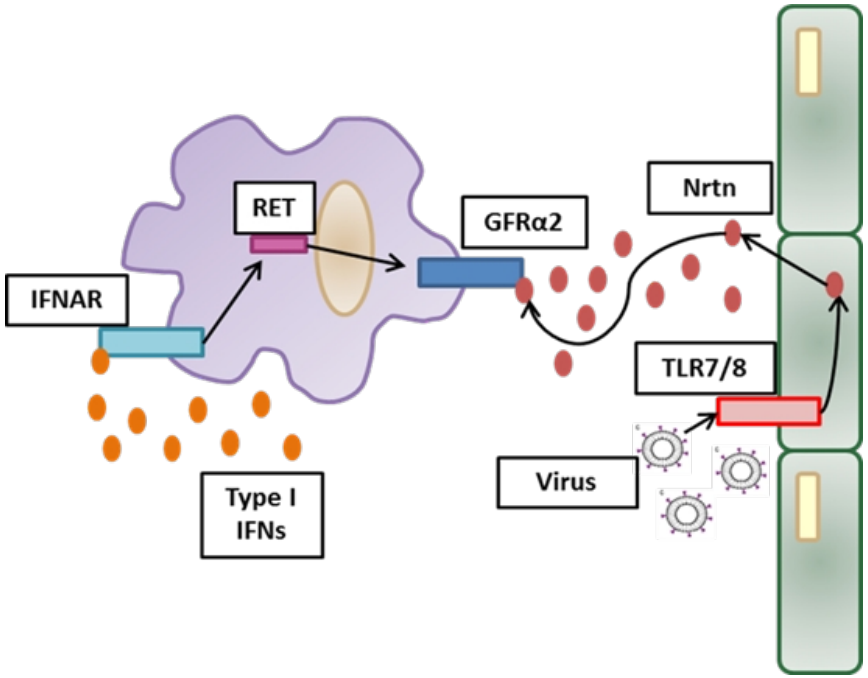
Neurturin influences inflammatory responses and airway remodeling in different mouse asthma models.
Mauffray M, Domingues O, Hentges F, Zimmer J, Hanau D, Michel T. J Immunol. 2015;194(4):1423-33.

Neuturin and its receptor in the lung



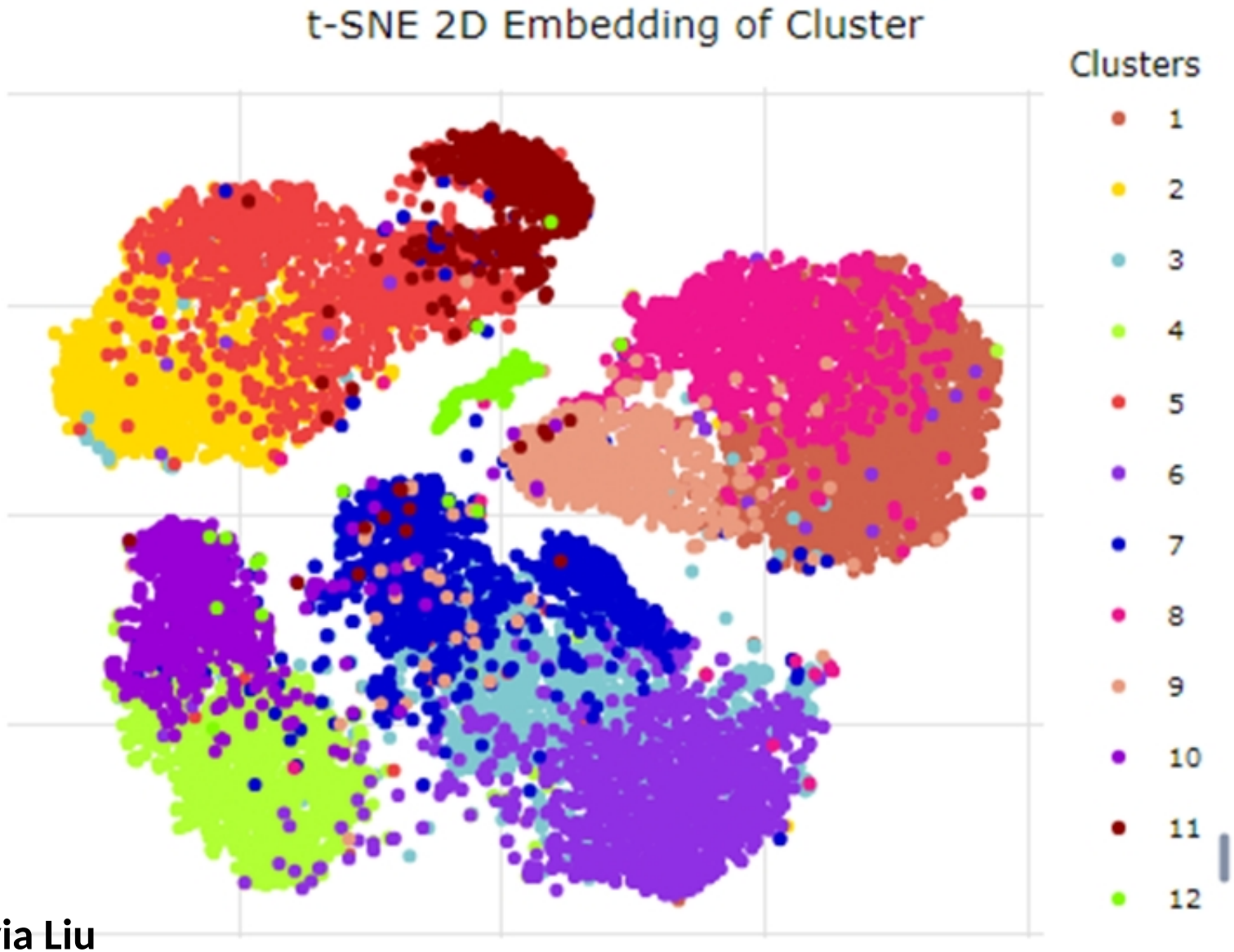






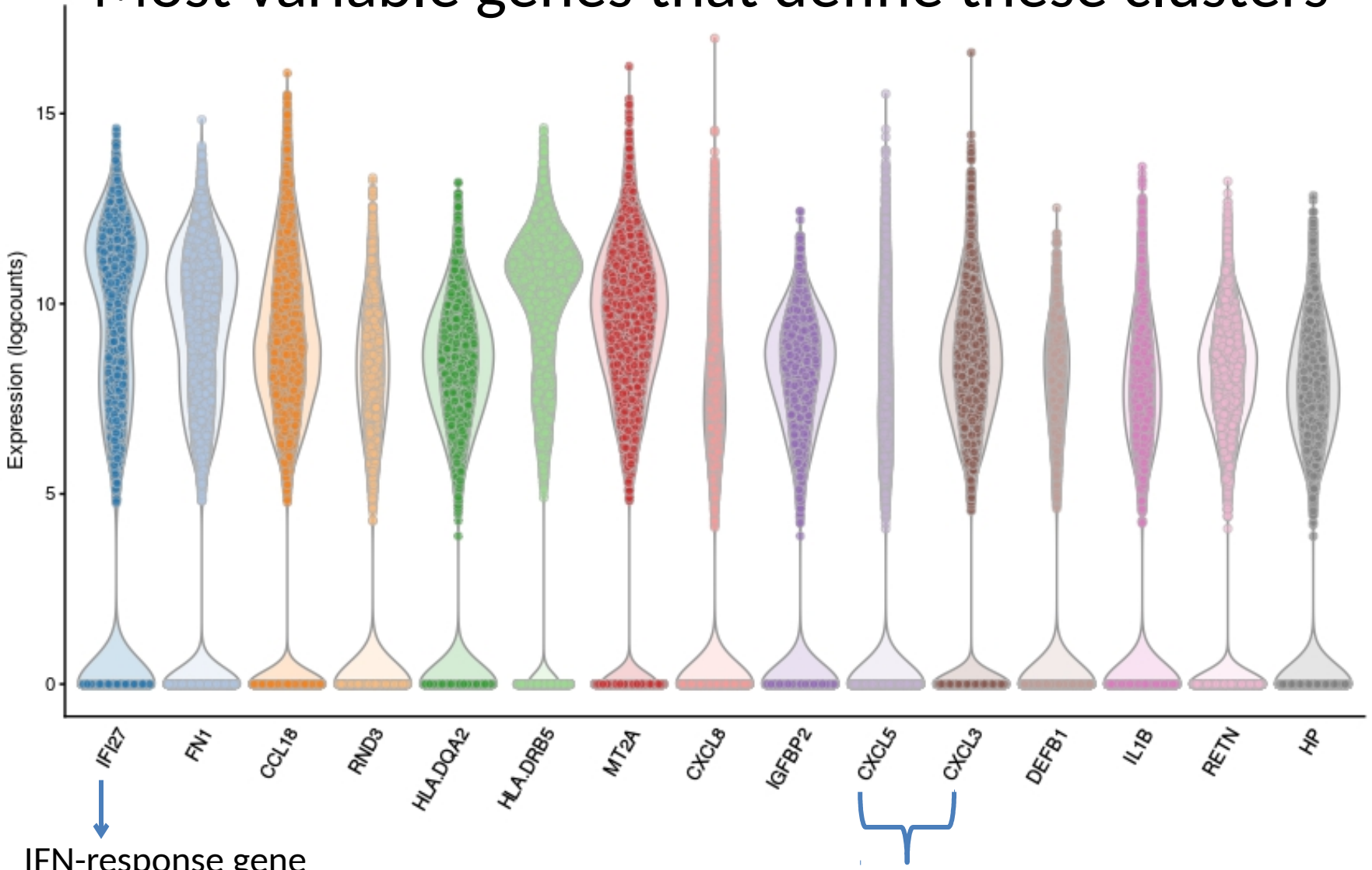
Emma Connolly

Not all cells are affected equally



Dr Sylvia Liu

Most variable genes that define these clusters



IFN-response gene
Induces apoptosis
In same group as IFITM3/M2

Bind CXCR2
Recruits Mono and neuts

Where are the opportunities?

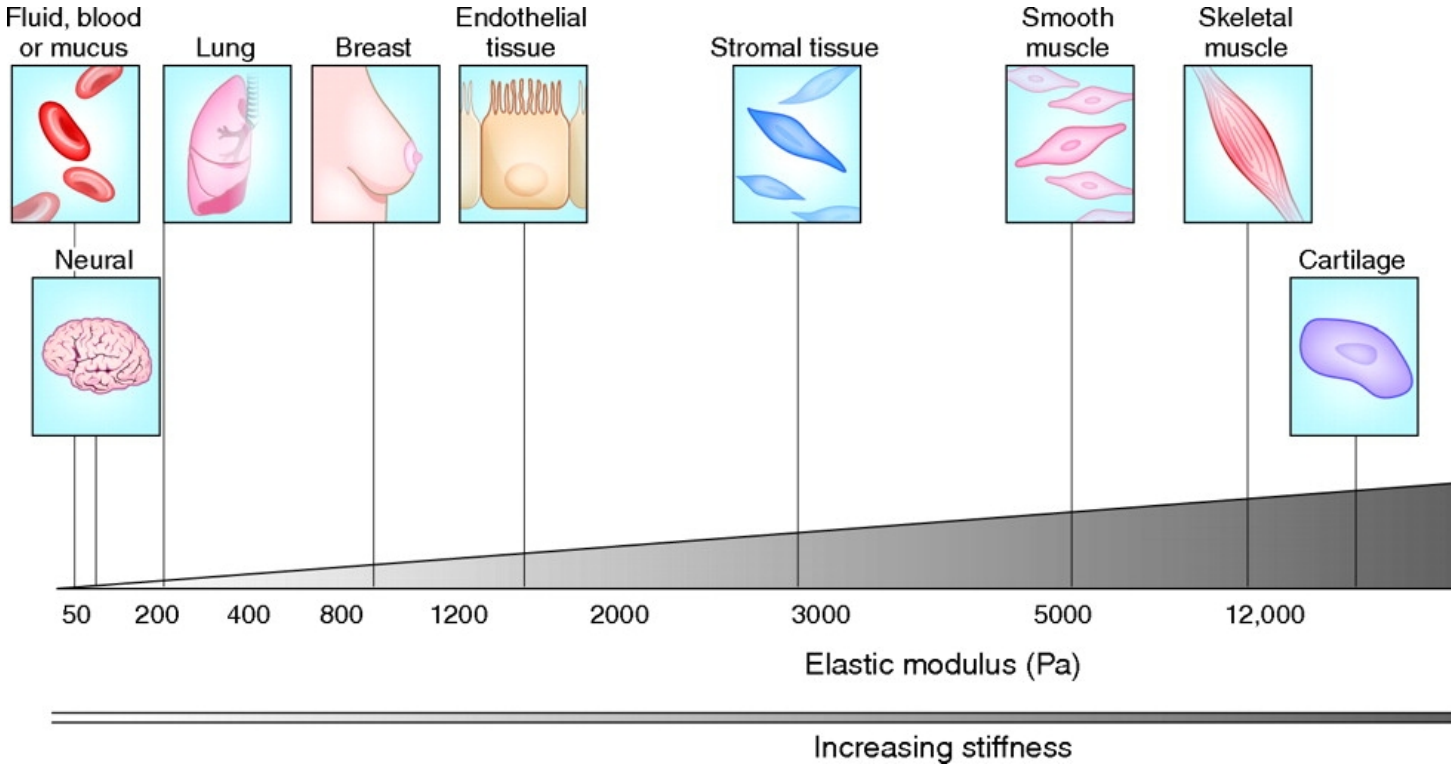
Health at different life stages
What drives change?

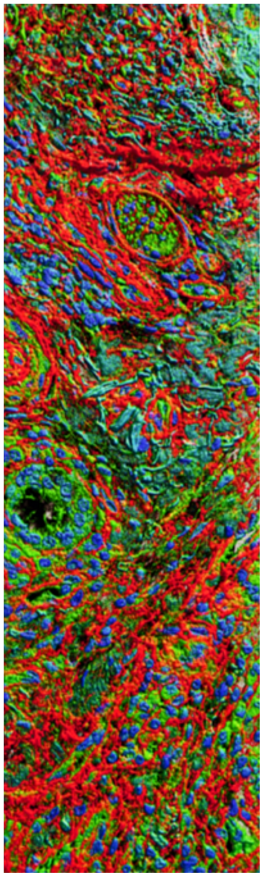
Do the same pathways explain immune deficits in infants?

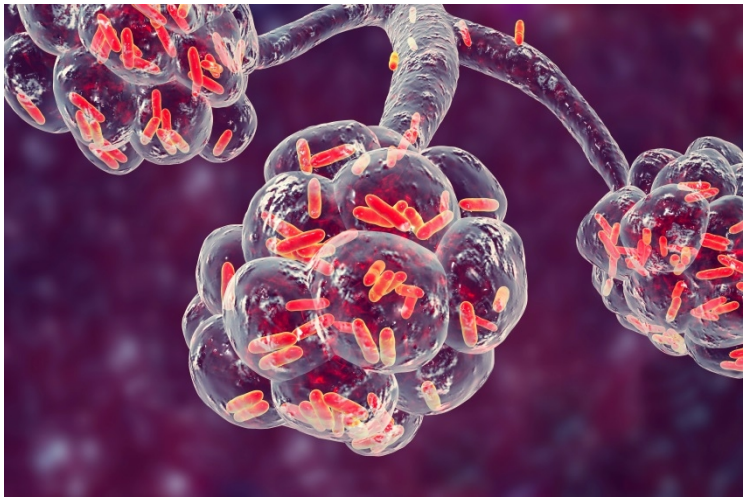
Matched for sex and ethnicity All healthy diagnosis	**Infants** (n=20)	**Adults** (n=20)
Age, median(range)	11 months (6-23)	59 years (36-78)
BAL fluid instilled (mL), median	15 (5-20)	50 (40-100)
BAL fluid retrieval (%), median	20 (5-40)	40 (20-66)
AMϕ yield (cells x 10^5), median	2.9 (1.8-18)	2.35 (1.2-13)

Dr Anu Goenka
Prof Peter Arkwright

Restoring tissue physiology to limit “inflammatory” disease







Inflamed tissues or trapped inflammatory cells?

Do our lungs become more stromal as we age

Is there a good and bad placental environment – training pre-birth.

Thanks to:

Past members:

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Dr Naoya Fujino
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Dr Mark Fife
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Dr Alexandra Godlee
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Dr Christine Chew
Dr Oliver Bland
Mirium Franklin
Sarah Warbach

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Professor Stephen Fowler
Professor Rob Niven
Professor Jurgen Vestbo