

# The interaction between respiratory viruses and bacteria

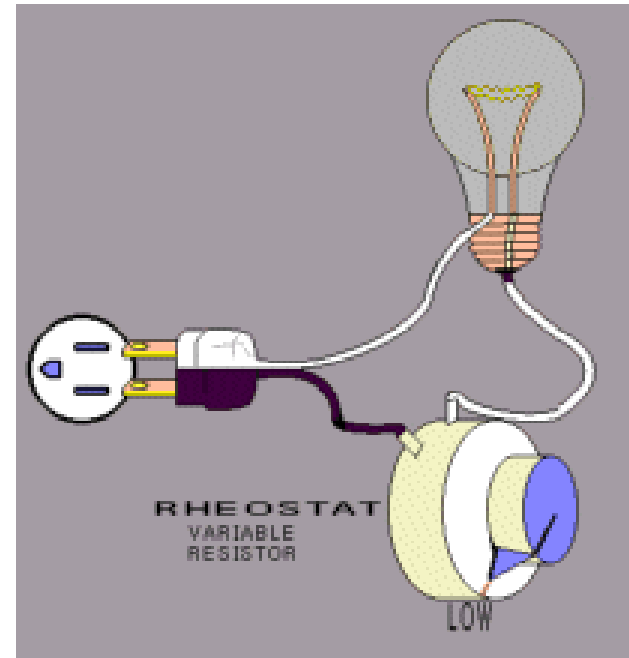
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# The Innate immune rheostat

Similar to a light controlled by a dimmer switch; innate immunity in the lung is controlled by:

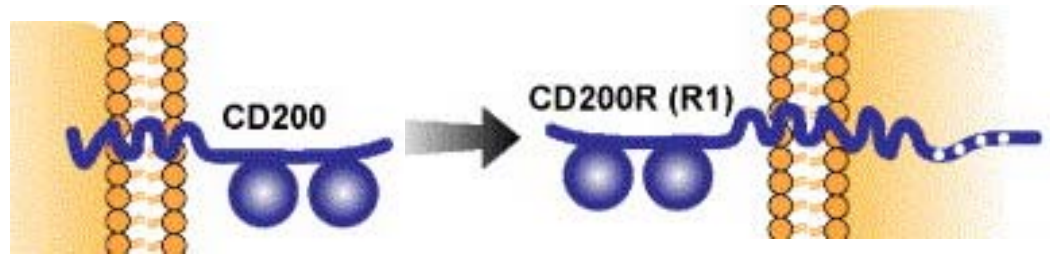
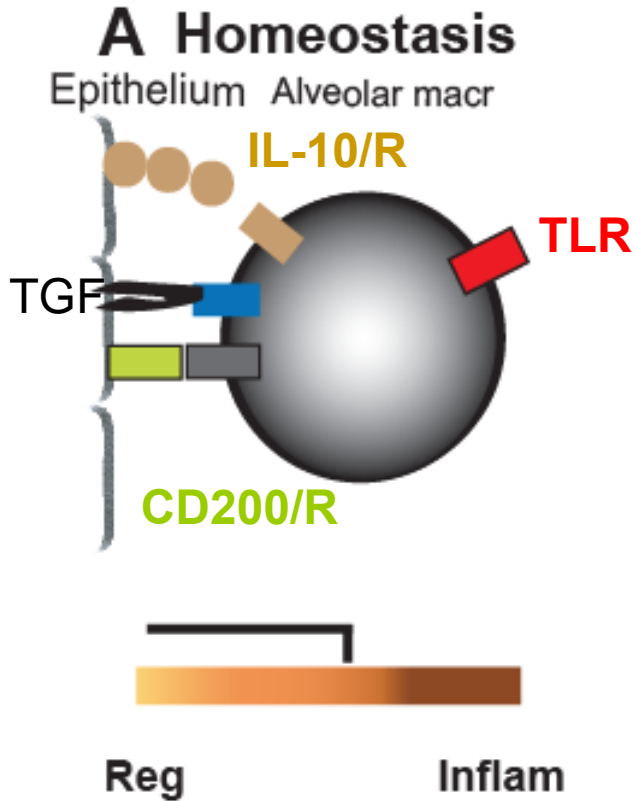
Pathways that activate (brighten) immunity: Pattern recognition receptors, CD40, OX40L

Pathways that dampen (dim) immunity: Suppressive cytokines (IL-10, TGF $\beta$ ), adenosine, CD200R



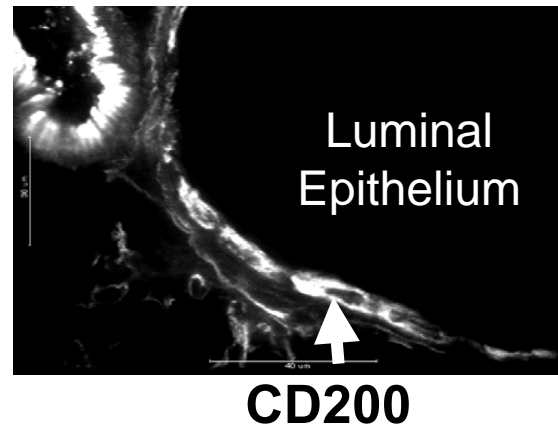
The balance of these pathways is site specific

# The innate immune rheostat in the lung.

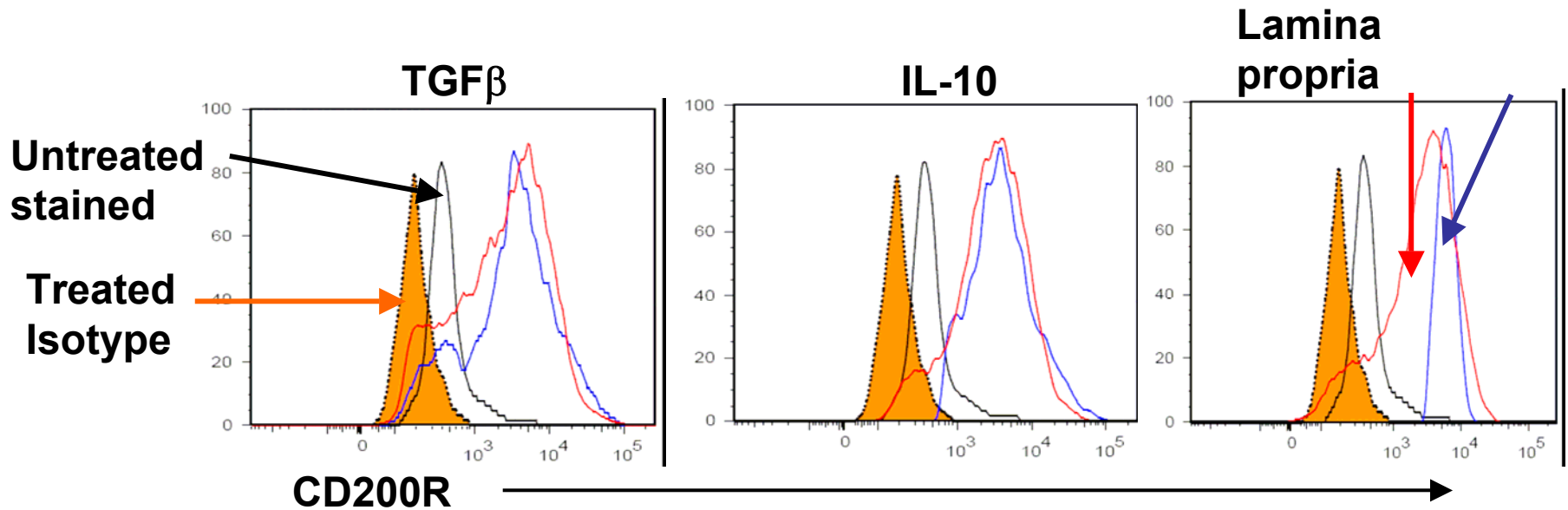
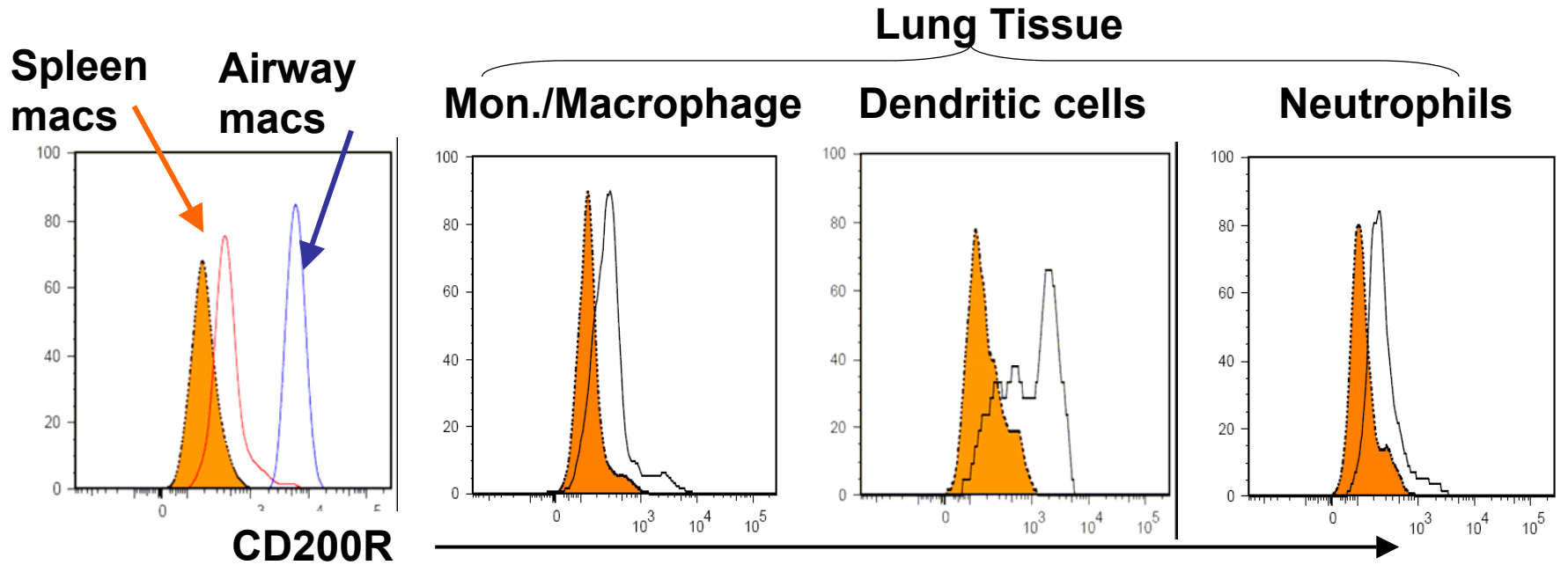


CD200:  
 T + B cells  
 Epithelial/endothelial cells  
 Central/peripheral nerves  
 Trophoblasts, retinal cells

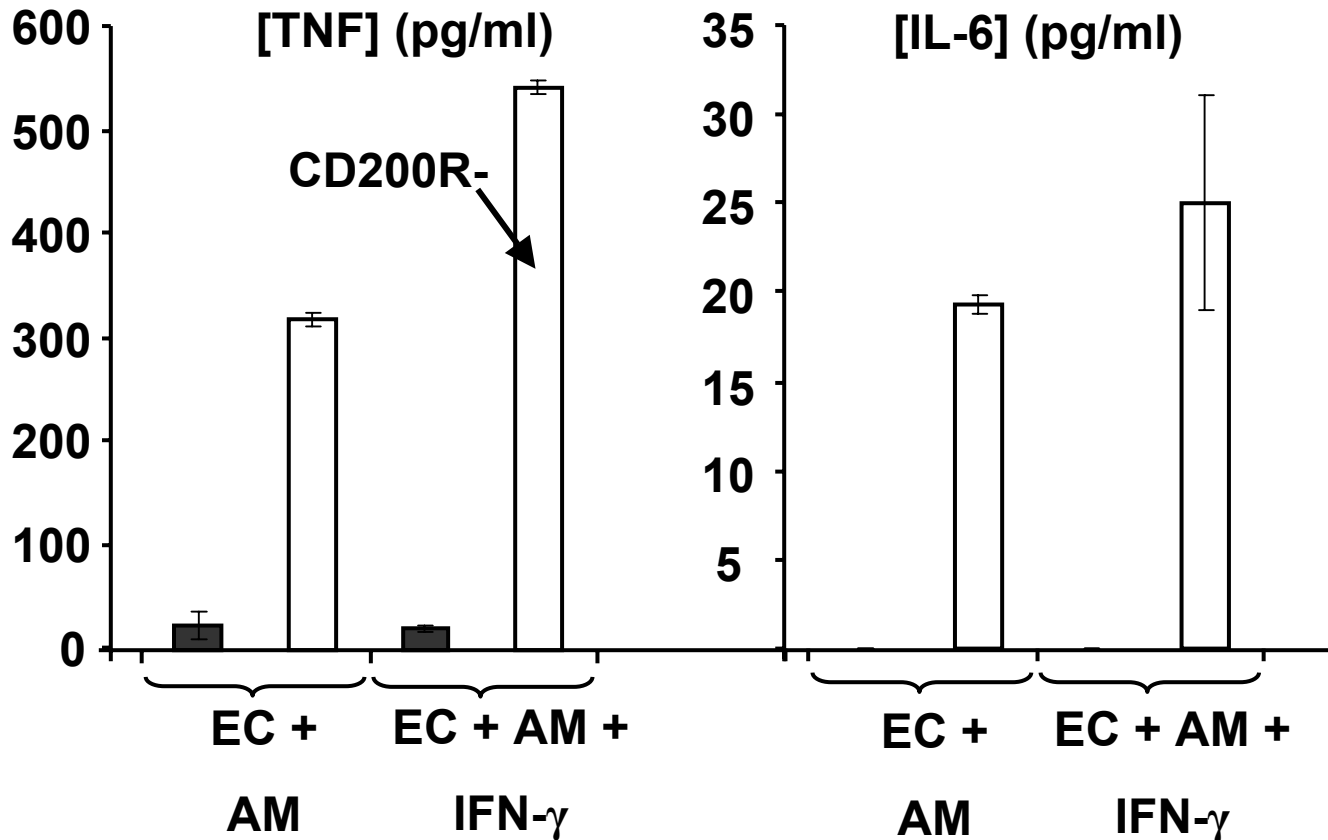
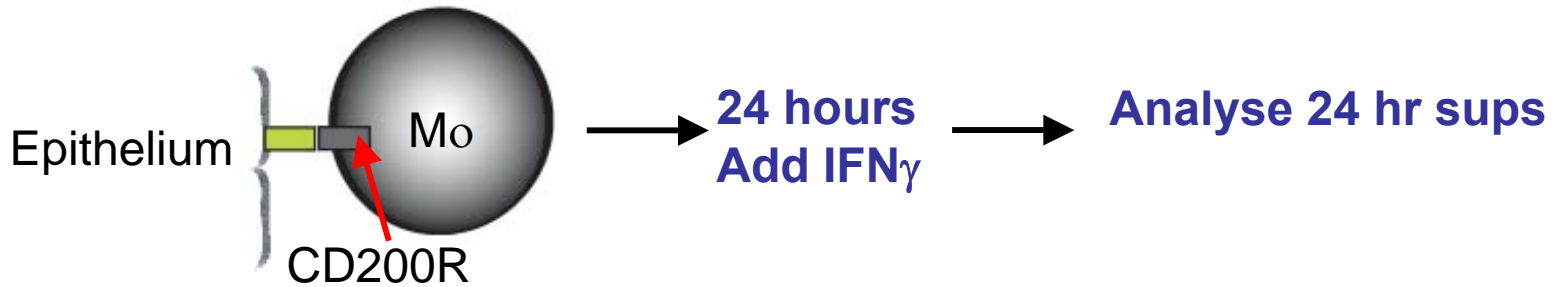
CD200R:  
 Macrophages,  
 neutrophils  
 Basophils, some DCs  
 and  $\gamma/\delta$  T cells



# High homeostatic CD200R levels in mucosal tissues

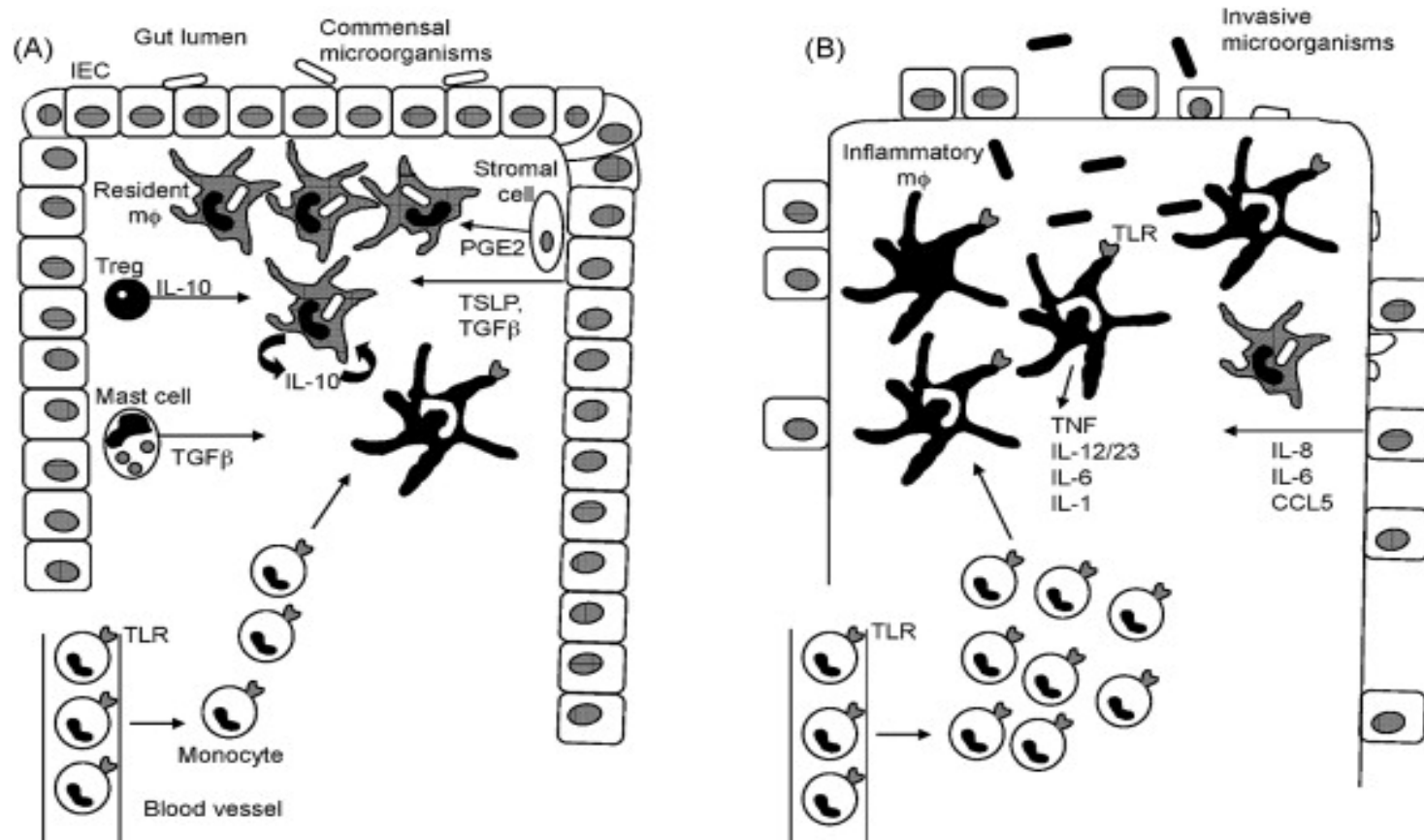


# Control of airway macrophages by epithelial cells



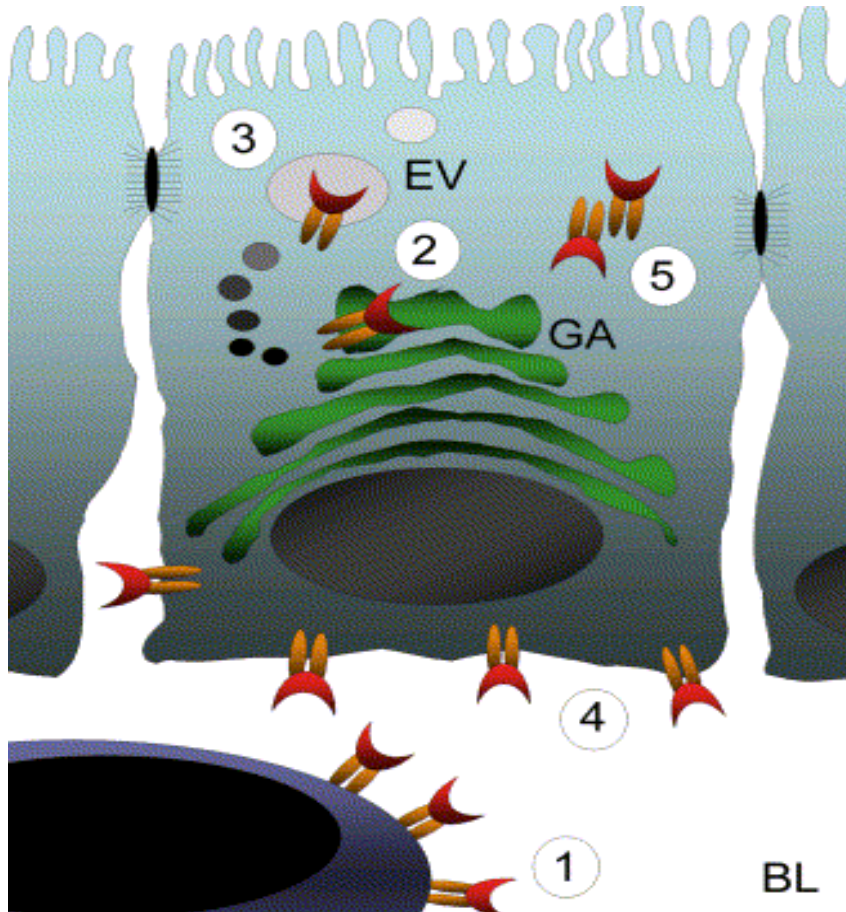
RJ Snelgrove, J Goulding ....T Hussell. A critical function for CD200 in lung immune homeostasis and the severity of influenza infection. Nature Immunol. 2008.

# The innate immune rheostat in the gut



Andrew M. Platta and Allan Mcl. Mowat [Immunology Letters](#)  
[Volume 119, Issues 1-2](#), 15 August 2008, Pages 22-31

# Location, location, location

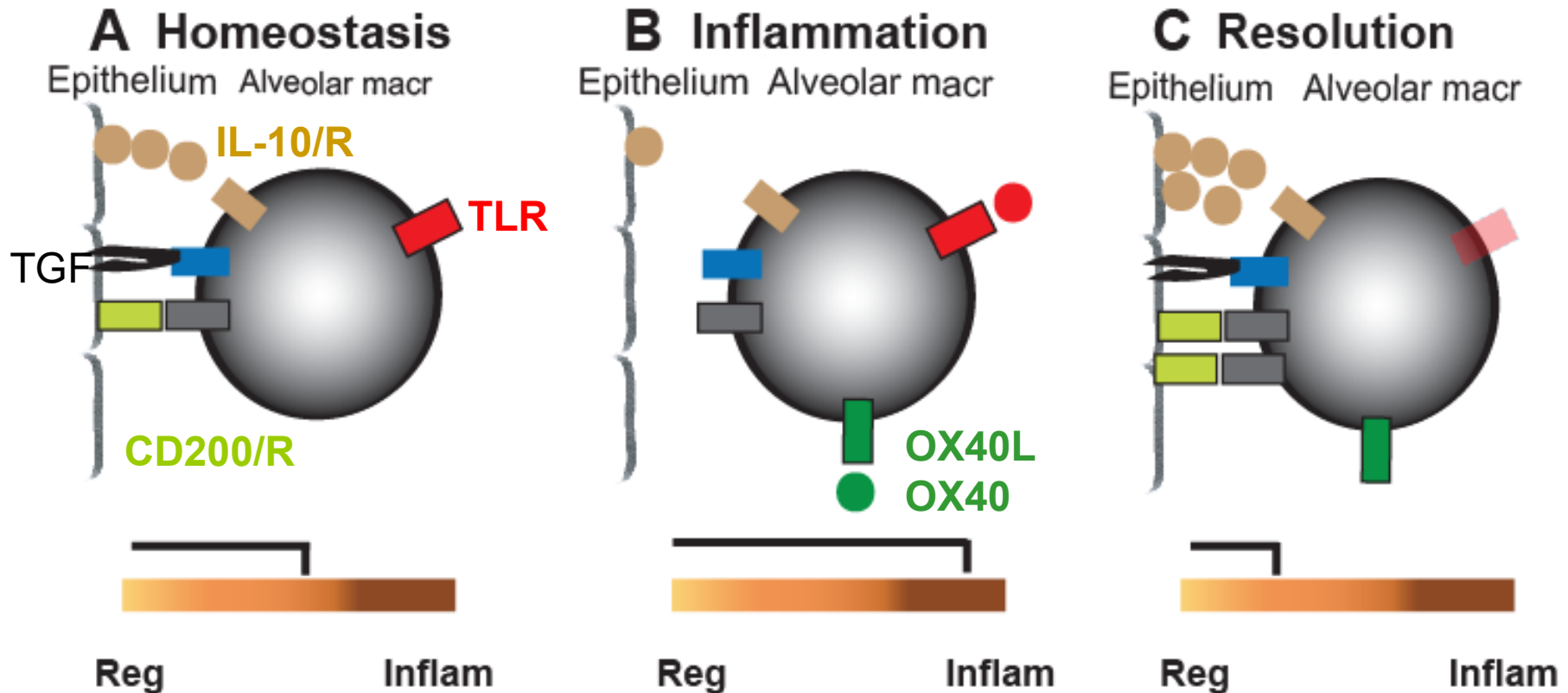


- 1 = TLR4 expr on Macs
- 2 = TLR4 in golgi
- 3 = “damage”  
redistributes TLR4 to  
the luminal aspect
- 4. TLR5 restricted to  
basolateral side
- 5. Cytoplasmic NOD  
proteins control PAMPs  
in cytosol

Fredrik Bäckhed and Mathias Hornef. Toll-like receptor 4-mediated signaling by epithelial surfaces: necessity or threat? [Microbes and Infection Volume 5](#), 2003, P: 951-959

C.F. Ortega-Cava, et al Strategic compartmentalization of TLR 4 in the mouse gut. *J. Immunol.* **170** (2003), pp. 3977–3985

# The innate immune rheostat.



# Predominant Role of Bacterial Pneumonia as a Cause of Death in Pandemic Influenza: Implications for Pandemic Influenza Preparedness

David M. Morens, Jeffery K. Taubenberger, and Anthony S. Fauci

*National Institute of Allergy and Infectious Diseases, National Institutes of Health, The Journal of Infectious Diseases 2008;198*

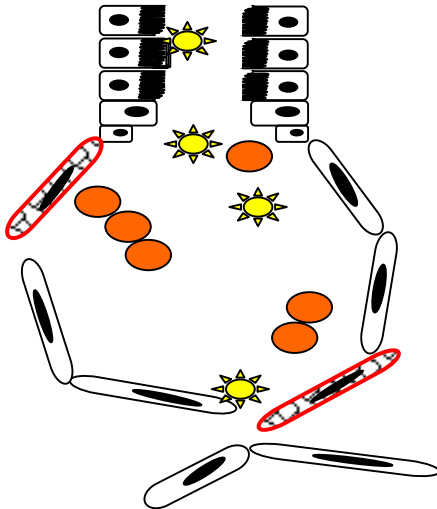
**Table 1. Bacterial culture results in autopsy series involving 96 postmortem cultures of lung tissue from victims of the 1918–1919 influenza pandemic.**

Type of autopsy series	No. of results	No. (%) of cultures from which organism was recovered, by organism							
		<i>Streptococcus pneumoniae</i>	<i>Streptococcus hemolyticus</i>	<i>Staphylococcus aureus</i>	<i>Diplococcus intracellulare meningitidis</i>	Mixed pneumopathogens	<i>Bacillus influenzae</i>	Other bacteria	No growth
All military ( <i>n</i> = 60)	3515	<b>855 (24.3)</b>	615 (17.5)	263 (7.5)	40 (1.1)	707 (20.1)	387 (11.0)	484 (13.8)	164 (4.7)
All civilian ( <i>n</i> = 36)	1751	380 (21.7)	281 (16.0)	164 (9.4)	1 (<0.1)	<b>398 (22.7)</b>	132 (7.5)	339 (19.4)	56 (3.2)
All military and civilian ( <i>n</i> = 96)	5266	<b>1235 (23.5)</b>	896 (17.0)	427 (8.1)	41 (0.8)	1105 (21.0)	519 (9.9)	823 (15.6)	220 (4.2)
All higher- quality military and civilian <sup>a</sup> ( <i>n</i> = 68)	3074	712 (23.2)	553 (18.0)	238 (7.7)	21 (0.7)	<b>828 (26.9)</b>	144 (4.7)	353 (11.5)	225 (7.3)
Predominance of pneumopathogens not confirmed ( <i>n</i> = 14)	1115	209 (18.7)	132 (11.8)	52 (4.7)	0 (0.0)	24 (2.2)	210 (18.8)	<b>402 (36.1)</b>	86 (7.7)

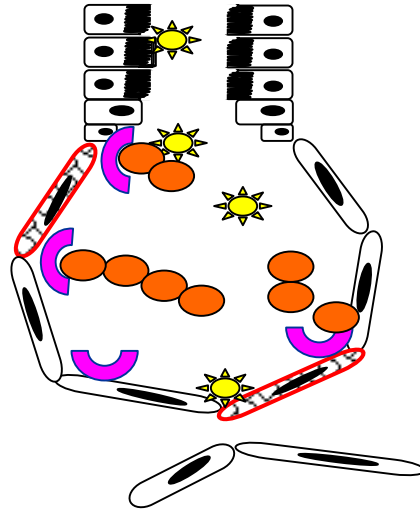
# Why do secondary bacterial infections occur?

1. Lung epithelial barrier breakdown
2. Up-regulation of bacterial adhesion molecules
3. Subversion of anti-bacterial immunity

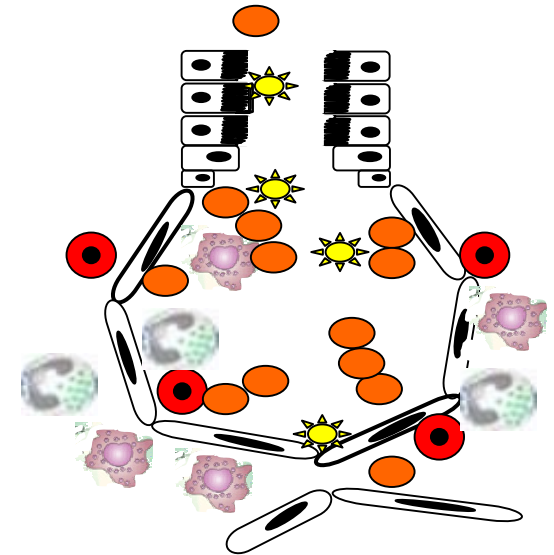
Barrier breakdown



Bacterial adhesion



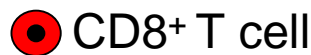
Skewed immunity



Flu



Bacteria



CD8+ T cell



Macrophage

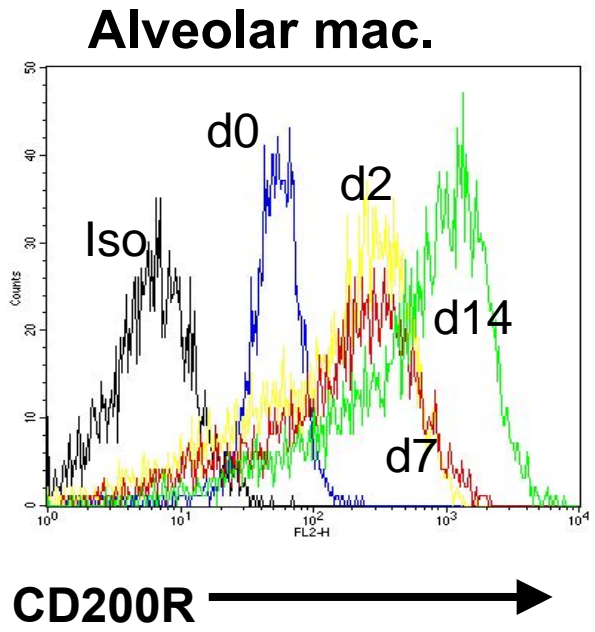


Neutrophil



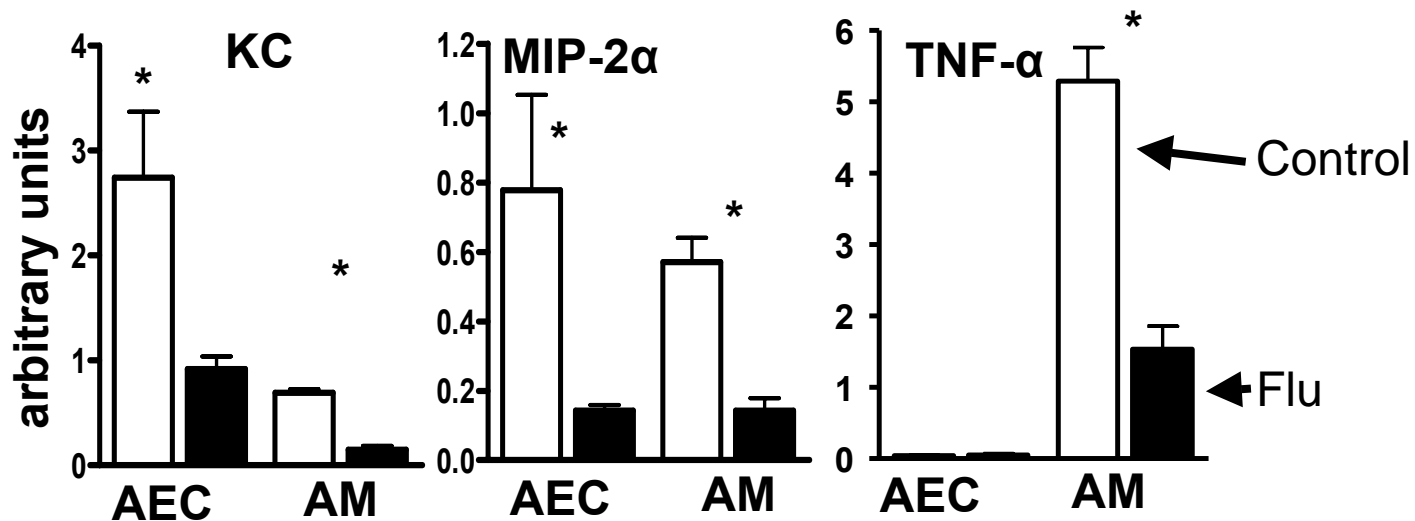
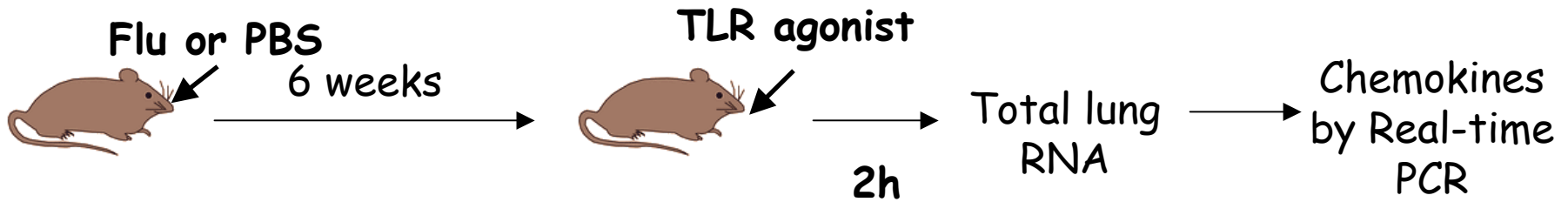
Bacteria adhesins

# The innate immune rheostat is qualitatively different after influenza infection



Note high basal level of CD200R on alveolar macrophages

# Post-viral desensitisation to TLR ligands

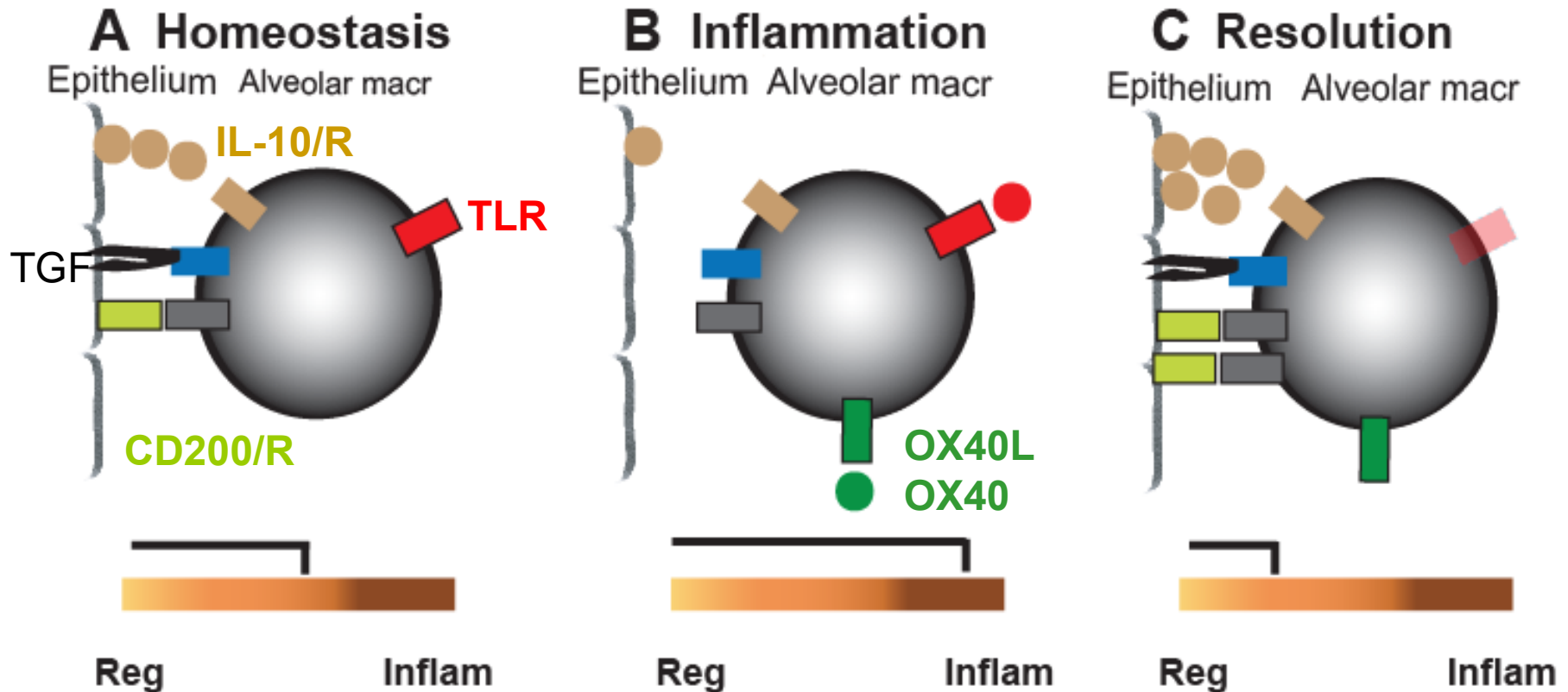


## The innate imprinting hypothesis

[Didierlaurent A .....Hussell T.](#) J Exp Med. 205 (2008):323-9

[Walzl, G.....Hussell, T.,](#) J. Exp. Med. 192<sub>1</sub> (2000),1317-1326

# The innate immune rheostat.



# Thanks to:

## Current Lab members:

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Michel Nussenzweig (CD11c-YFP)

Bart Lambrecht (DC networks)

Mick Croft/Carl Ware (OX40)

Neil Barclay (CD200R)

Jonathon Sedgewick (CD200R null mice)

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