

Virus-induced immune and epithelial mechanisms in asthma development

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Outline

Why think about viral mechanisms in asthma development?

- *epidemiological data*
- *an intervention study*

Which immune mechanisms could plausibly link severe viral bronchiolitis to recurrent wheeze and asthma development?

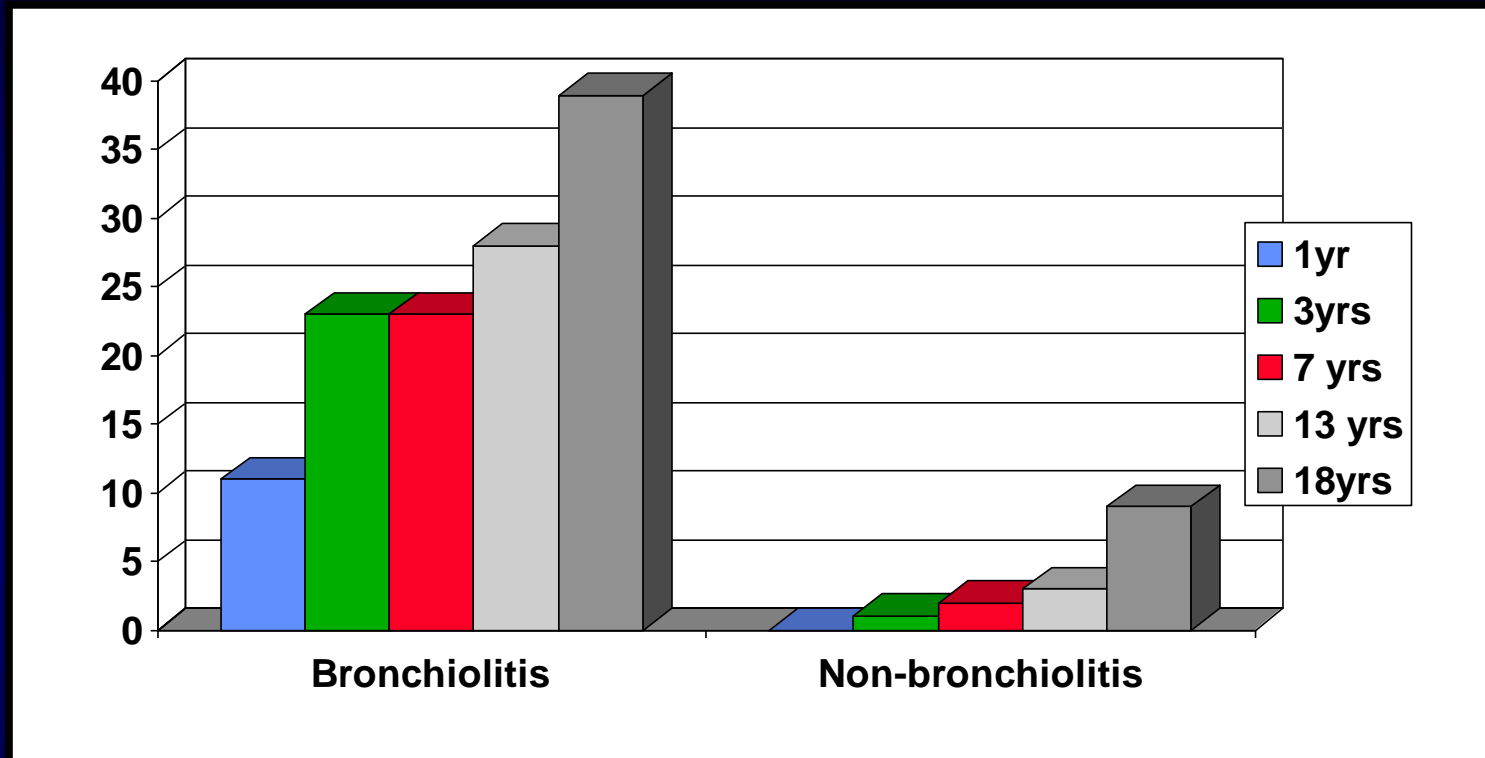
Priming of inflammation

Lung epithelial cells

Lung dendritic cells

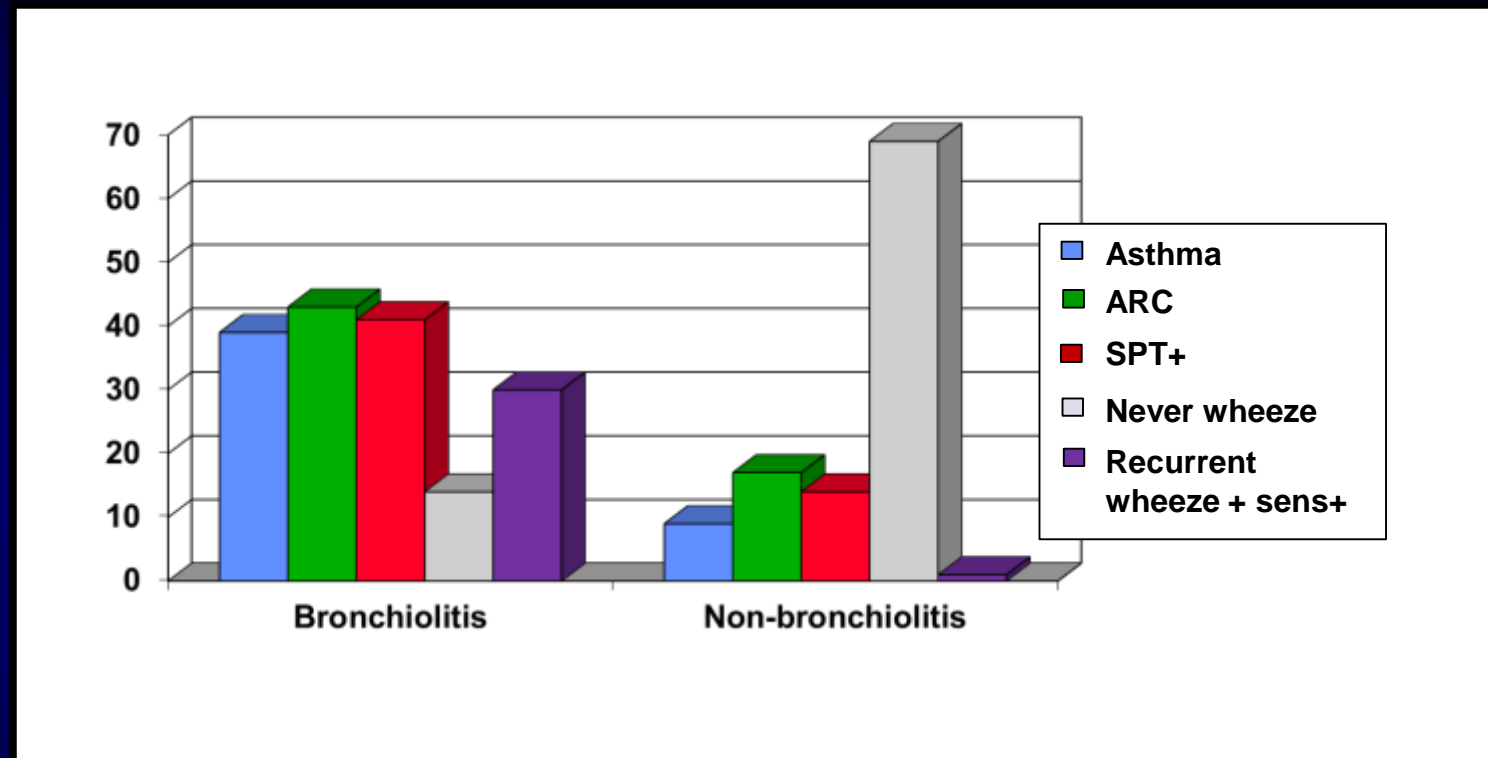


Asthma after RSV hospitalisation



Sigurs N et al. *Pediatr* 1995; *AJRCCM* 2000 ; *AJRCCM* 2005 ; *Thorax* 2010.

AR and allergic sensitisation after RSV hospitalisation



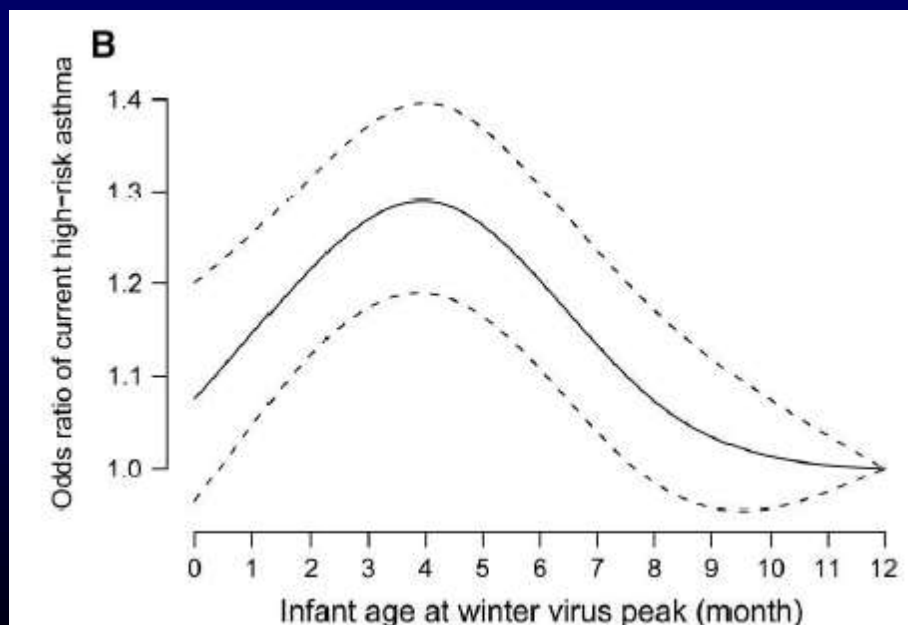
Bronchiolitis during RSV season increases risk of childhood asthma.

TennCare and KPNC cohorts (James K, JACI 2013)

**Routine data, ~260,000 infants \geq 32 wks GA variable:
bronchiolitis in RSV season in 1. year**

outcome: childhood asthma by 4.5 – 6 years

- **adj. OR for asthma 1.94 /1.87**



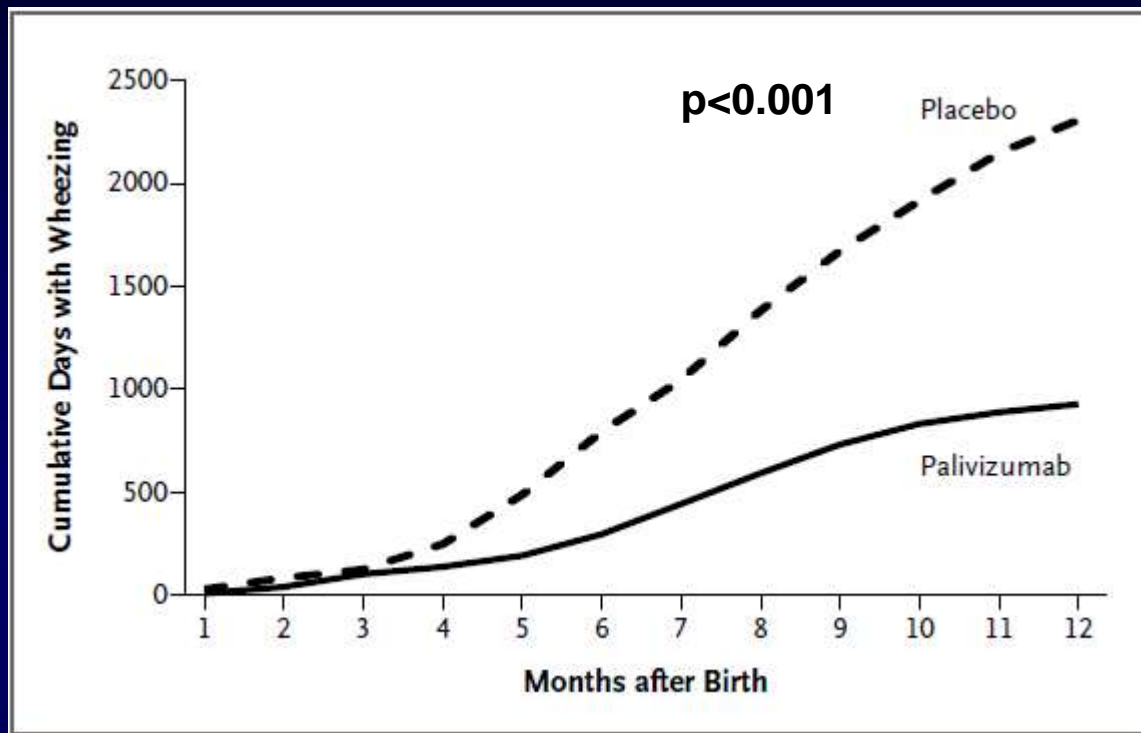
TennCare cohort (Wu P, AJRCCM 2008)

Age at winter virus peak

→ definable risk of childhood asthma

→ causal factor

Clinical intervention study; Palivizumab – prospective wheezing in 1st year



Preterm infants,
GA 33-35 weeks
 ≤ 6 months at start of
RSV season, $n=429$
1:1 randomised to
palivizumab or
placebo over winter
season, median of 4
doses
Follow up to 1 yr,
median 10 months

- Outside RSV season 73% reduction in wheezing days ($p < 0.001$)
- Reduced recurrent wheeze: 11.2 vs 20.9% ($p < 0.005$)

Clinical intervention study; Palivizumab – follow up at 6 years of age

395 children followed up, 342 lung function tests

Parent reported current asthma (wheeze/asthma meds in last 12 months): Control Group: 24%

RSV-prevention group: 14.1%, ARR 9.9% (CI 2.2-17.6)

Current asthma in children with infant wheeze:

Control Group: 31%

RSV-prevention group: 18%, ARR 13.1% (CI 0.1-26.2)

No difference in lung function, FeNo, sIgE, doctor diagnosed asthma.

→ “RSV prophylaxis: no major effect on current asthma or lung function at age 6 years”

Plausible mechanisms at the innate / adaptive immune interface

Prolonged pro-inflammatory epithelial cell responses?

Prolonged inability of epithelial cells to suppress immune responses (DCs / T cells) ?

Prolonged immune stimulatory capacity of lung DCs?

Amplification of Th-2 memory?

Lung epithelial cells (LEC)

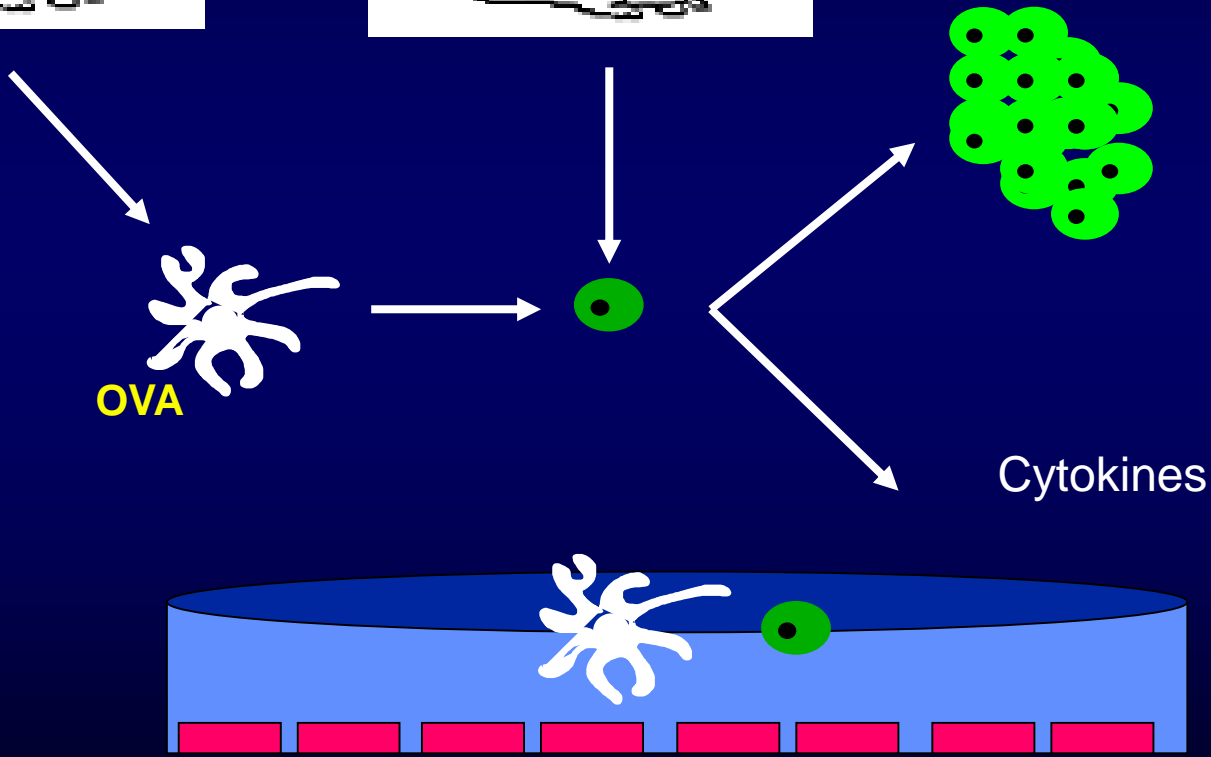
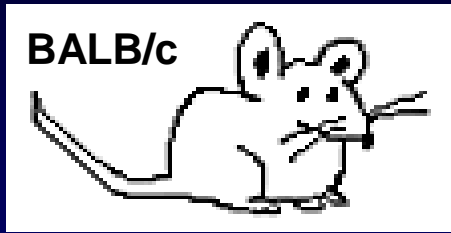
Primary target of RSV, early anti-viral response.

Produce pro-inflammatory mediators upon infection, including alarmins.

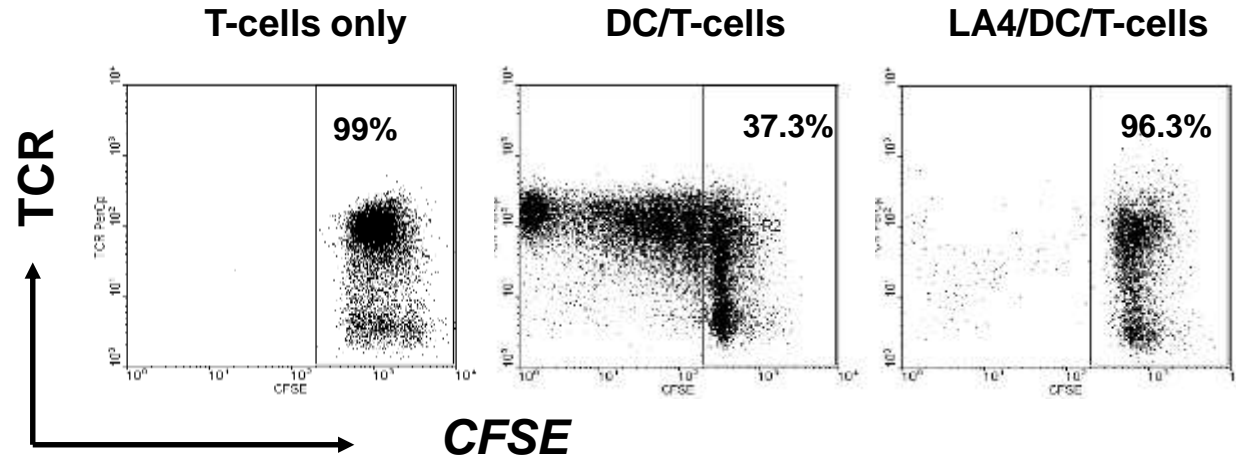
Do 'healthy' LEC have immune regulatory effects?

Is LEC immune regulation lost after RSV infection?

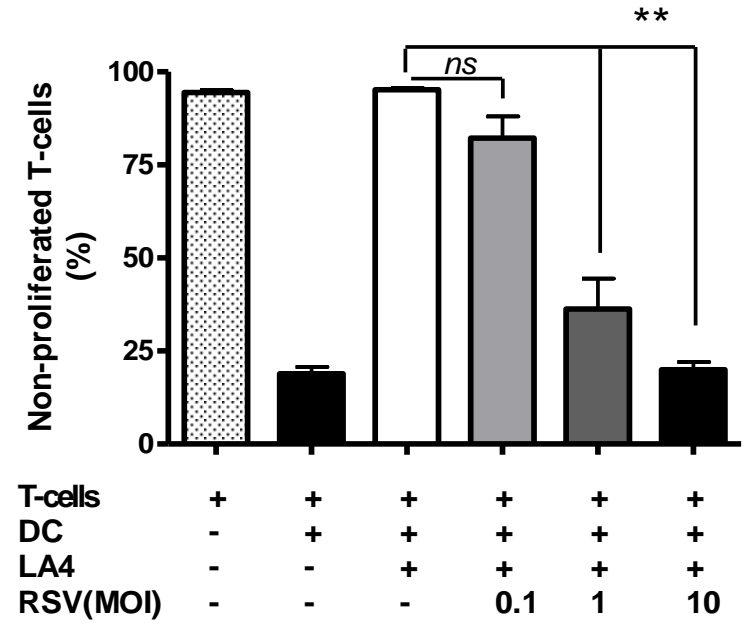
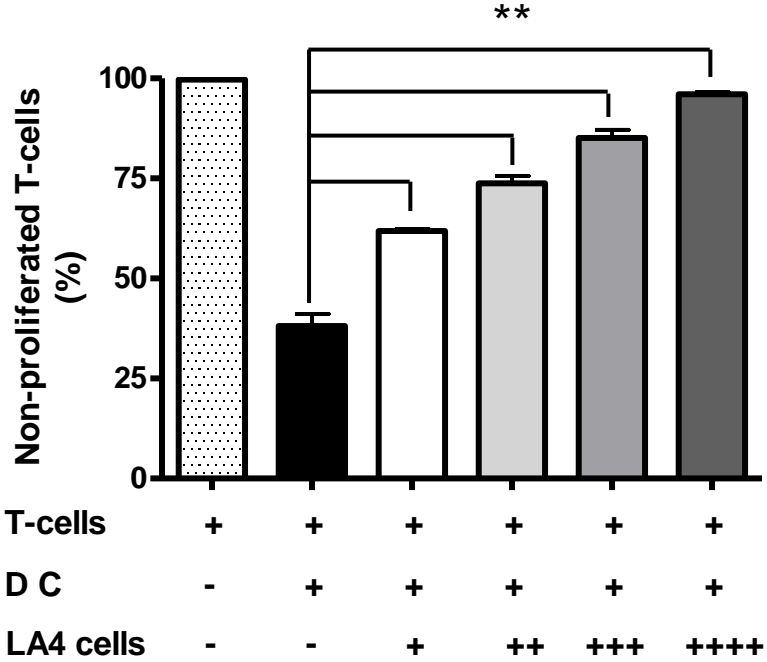




LEC inhibition of cDC-induced T cell proliferation is prevented by RSV infection

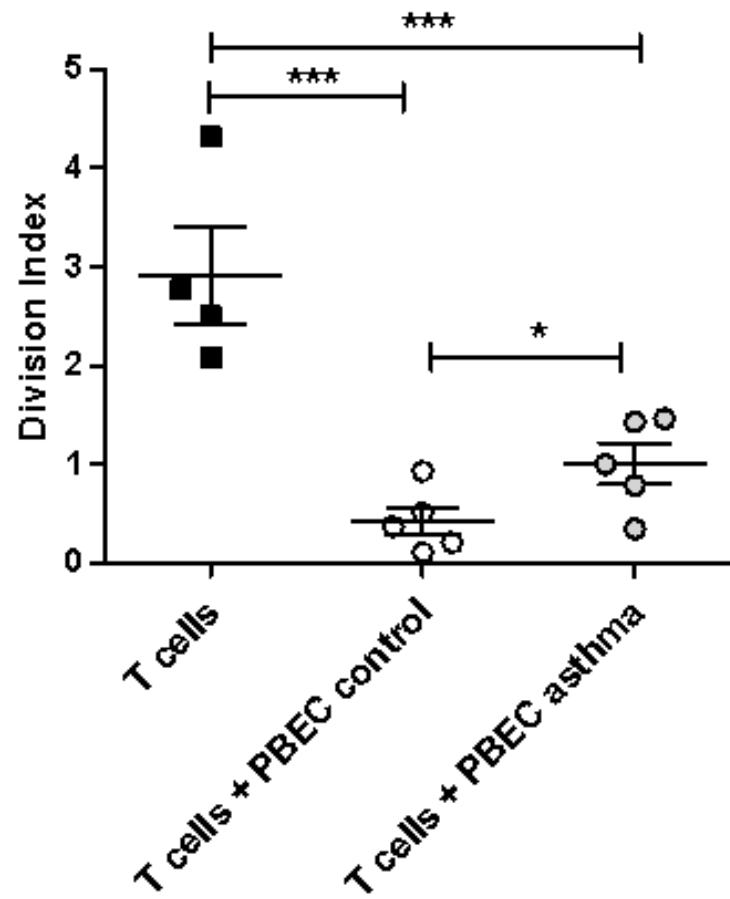
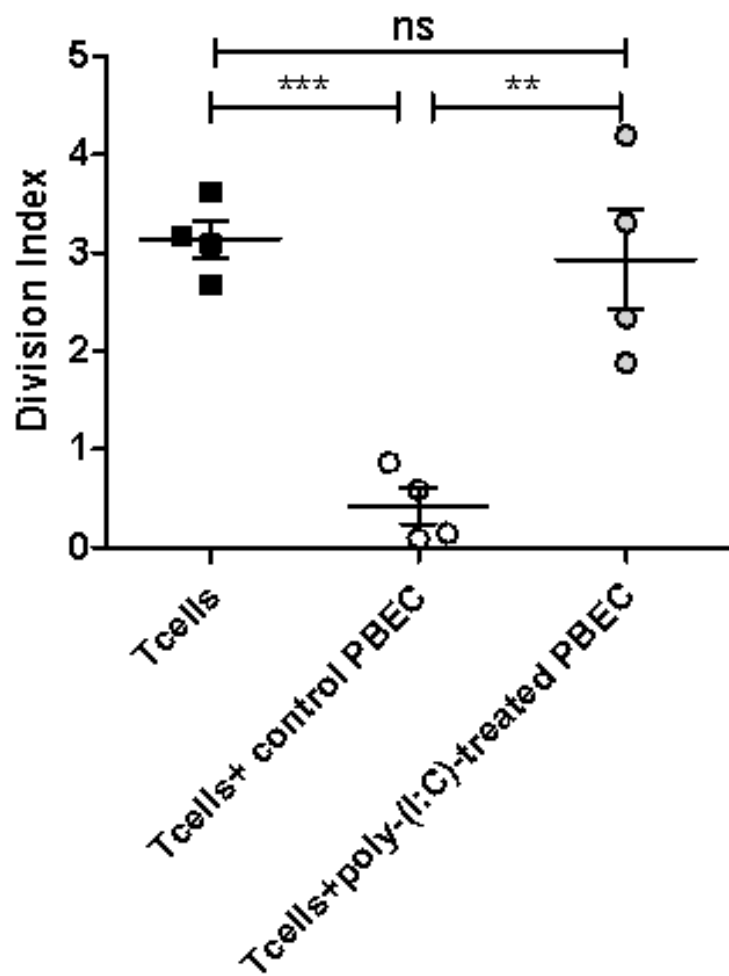


Wang et al., 2009
Thorax, 64:283-90



The viral mimic poly(I:C) reduces T cell inhibition by human PBECs.

B



Schwarze et al.,
ERJ 2016

Summary: Lung Epithelial Cells

LEC are potent inhibitors of immune activation of T cells (and DCs)

LEC may be important in maintaining the quiescent, tolerogenic immune environment in the healthy lung.

RSV infection/ poly(I:C) treatment of LEC abrogates their T-cell inhibitory capacity, which is also reduced in asthma.

Loss of immune regulation by LEC in RSV infection may contribute to excessive immune and inflammatory responses in respiratory viral infection and in asthma.

Lung dendritic cells in RSV infection

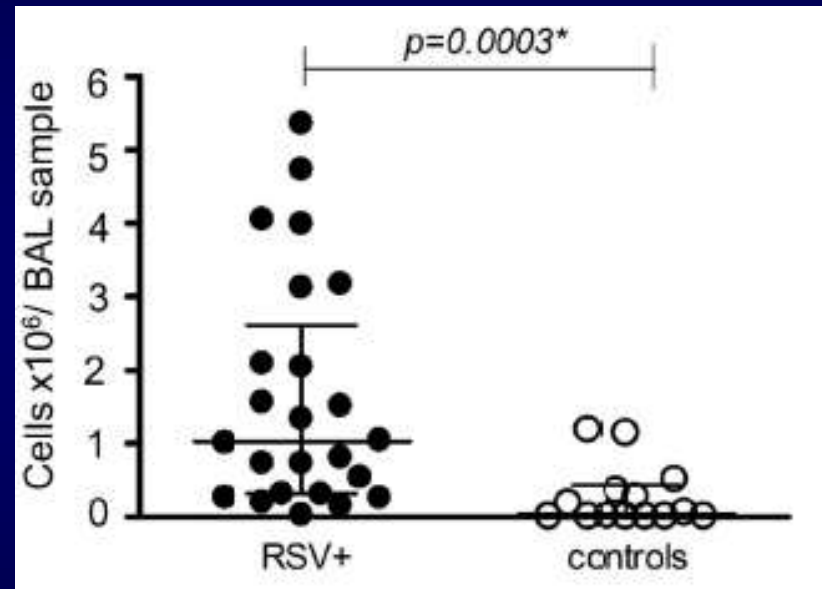
RSV mouse model:

- Increases in CD8 and CD4 T cell numbers in the lung during RSV inflammation. Depletion of T cell abrogates RSV disease.*
- Increases in conventional activated lung DCs with strong T cell stimulating ability.*
- Plasmacytoid DCs are required for the antiviral response*
- Hypothesis: Inflammatory lung cDC are important in the development of RSV inflammation and disease*



DCs in severe RSV bronchiolitis of infants

- Infants intubated & ventilated with RSV bronchiolitis or for elective surgery (controls)
- Non-bronchoscopic broncho-alveolar lavage (BAL)



In RSV: ↑↑ of total BAL cells,
neutrophils,
macrophages/monocytes

BAL CD8/CD4 T cell ratio and cDC numbers increase in severe RSV bronchiolitis

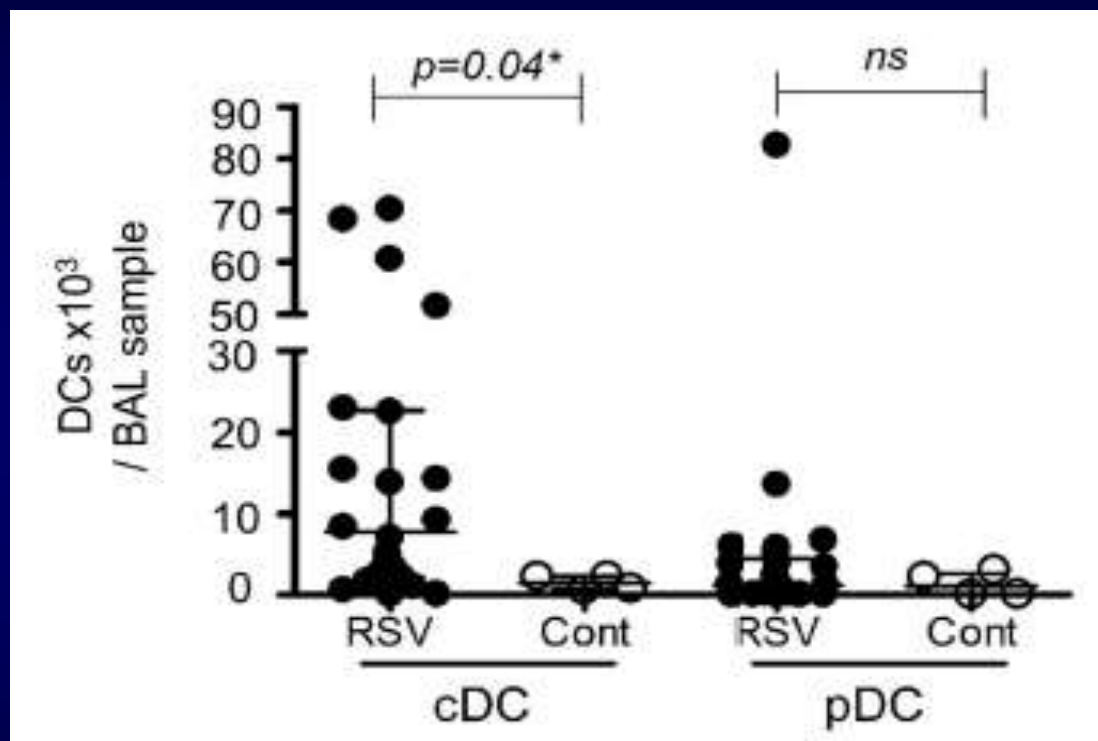
CD8/CD4 ratio:

Control 0.3 (1.8)

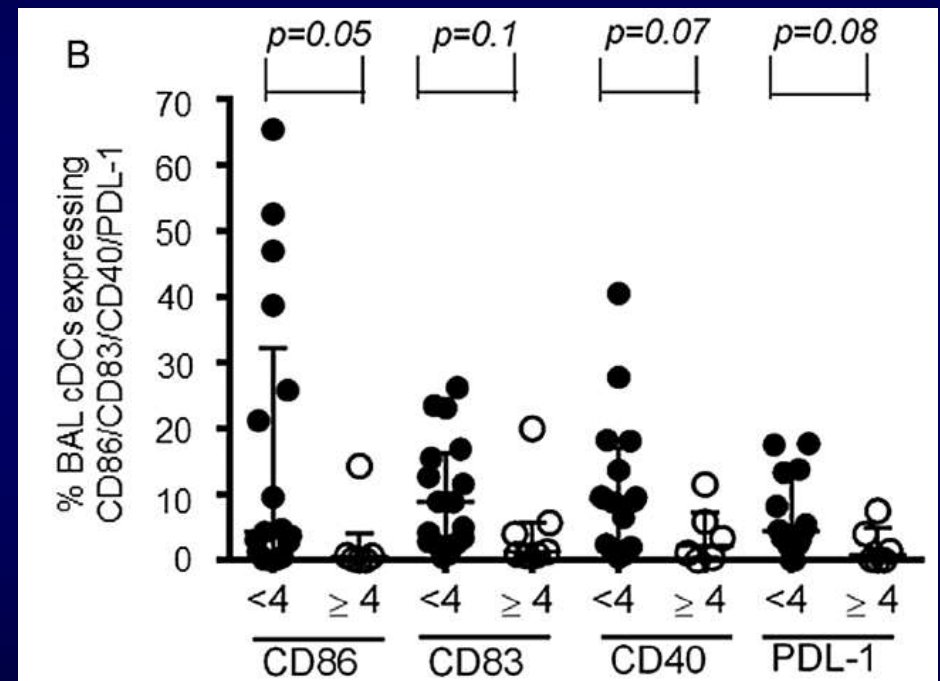
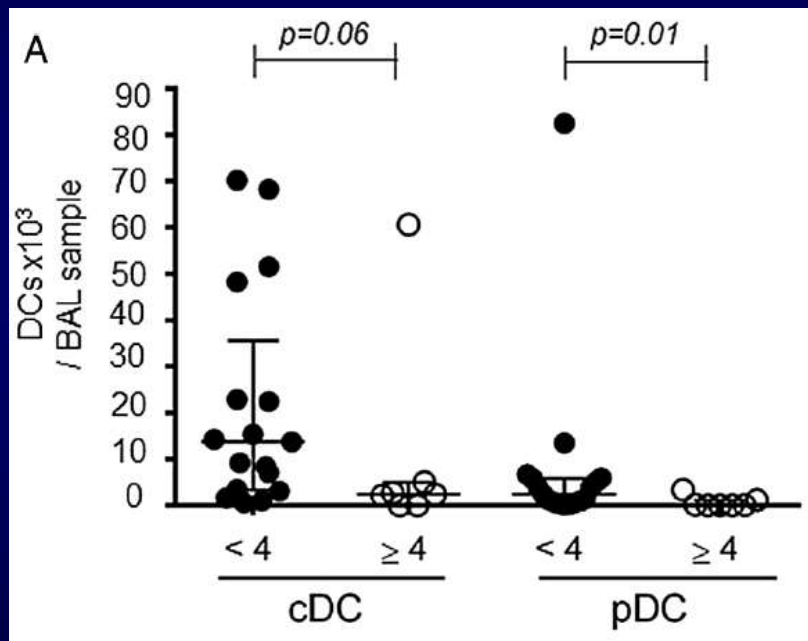
RSV 3.1 (5.4)

$P = 0.08$

BAL



Older infants (≥ 4 m) have lower BAL pDC numbers, whereas younger infants appear to have higher cDC numbers and activation



Summary: BAL Dendritic Cells (Infants)

***Hypothesis:
Airway DC responses reveal distinct endotypes of RSV
bronchiolitis;***

- 1) heightened inflammatory response
(activated cDCs)***
- 2) poor anti-viral response
(low pDCs).***

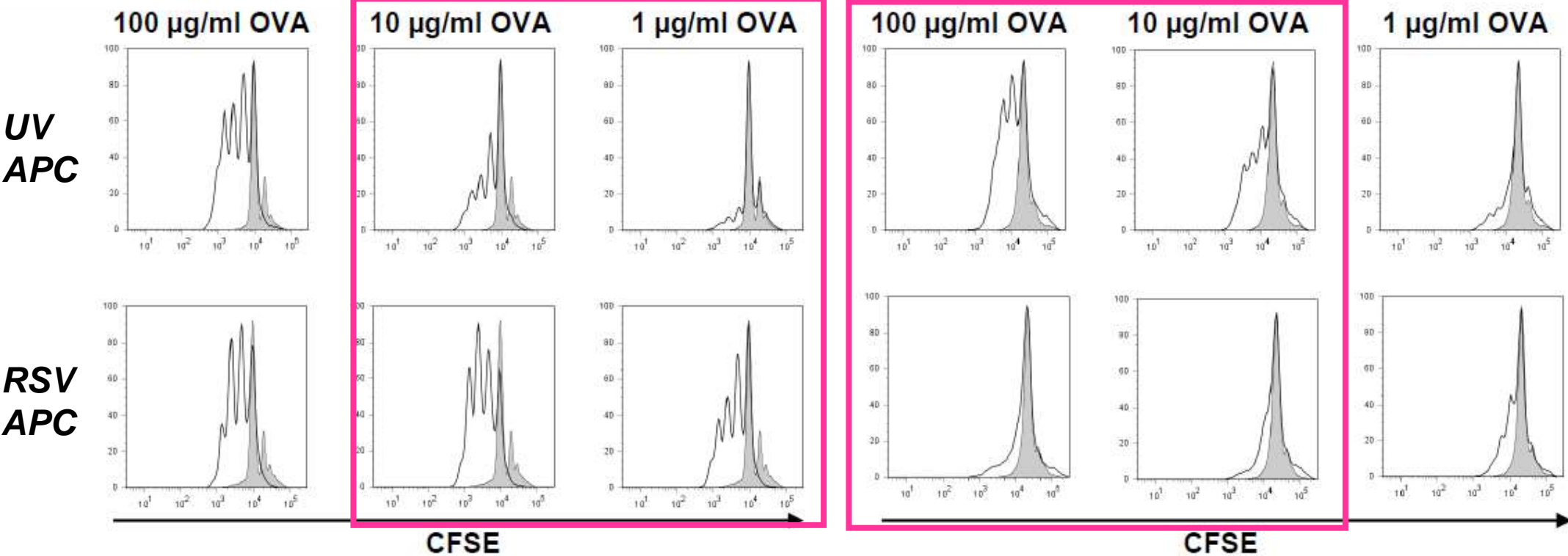
**What do cDCs do during resolution of RSV-
infection?**

**Can they restimulate allergen reactive
CD4⁺T cells?**

Increased restimulation of Th2 memory/effector T-cells by lung mDC during RSV resolution

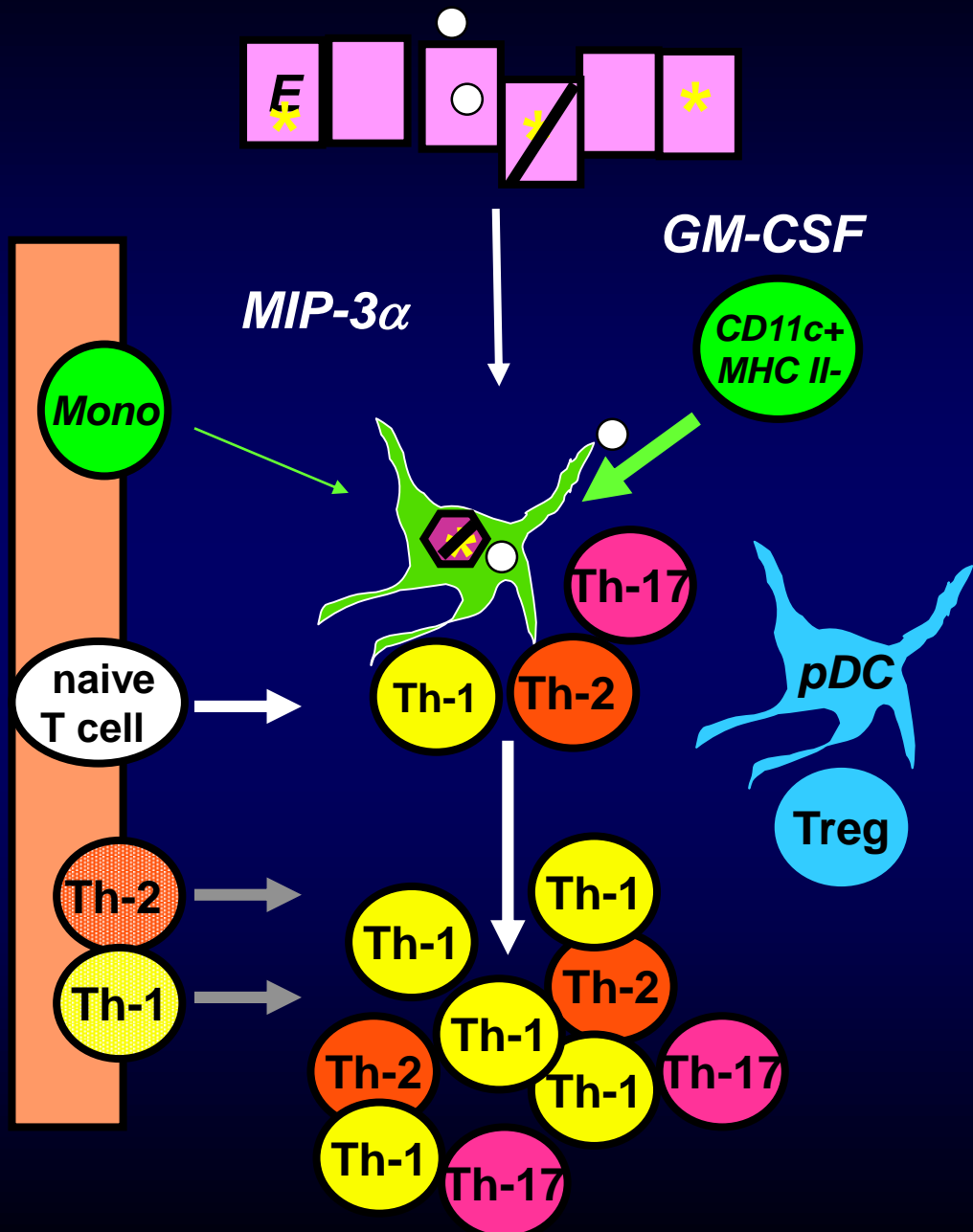
Th2

Th1

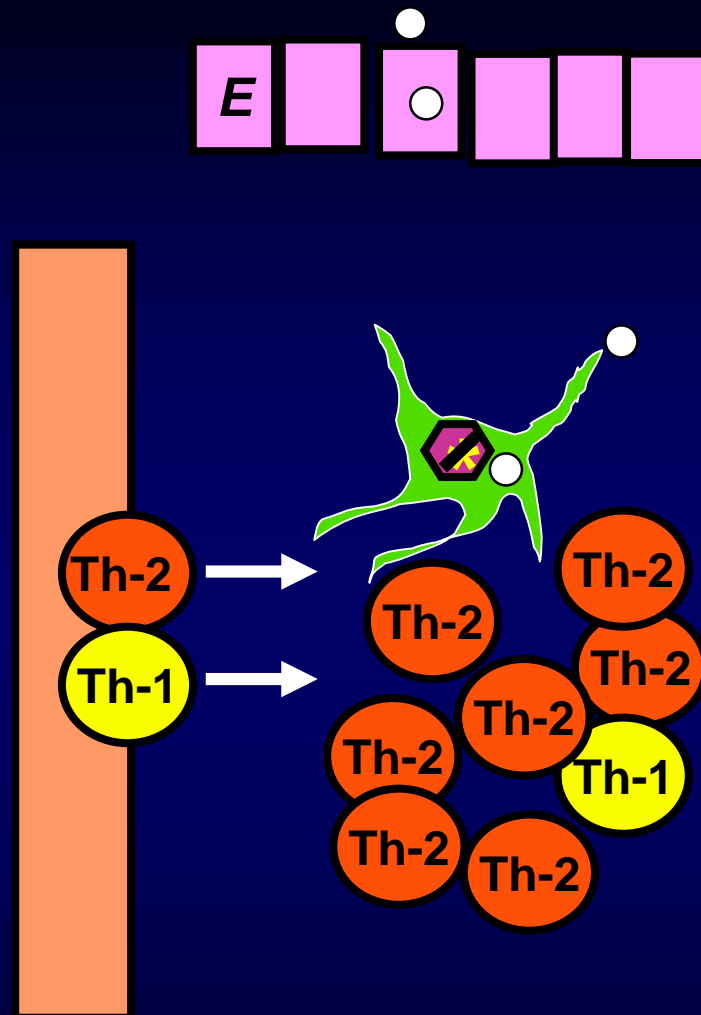


*Ilchmann,
Schwarze
unpublished*

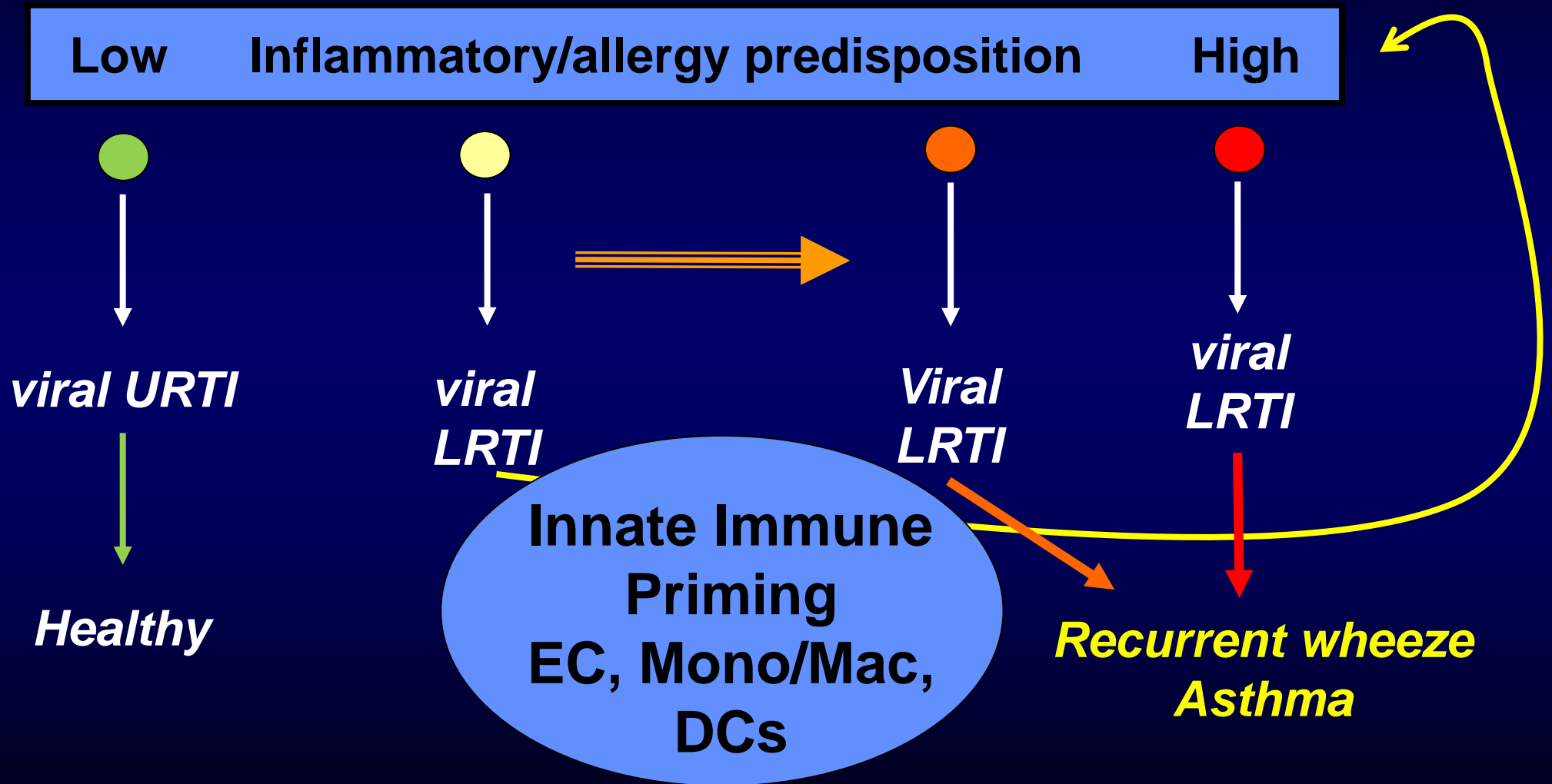
Acute Viral Inflammation



Resolution of Viral Inflammation



Interactions between viral LRTI and asthma development



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Thank you !



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Gating for BAL dendritic cells

