

# Differences in the immunobiology of *Aspergillus* colonization and ABPA

Jay K. Kolls, M.D.

Neils K. Jerne Professor of Pediatrics

Director, Division of Pediatric  
Pulmonology

Laboratory of Lung Immunology and Host  
Defense

Children's Hospital of Pittsburgh

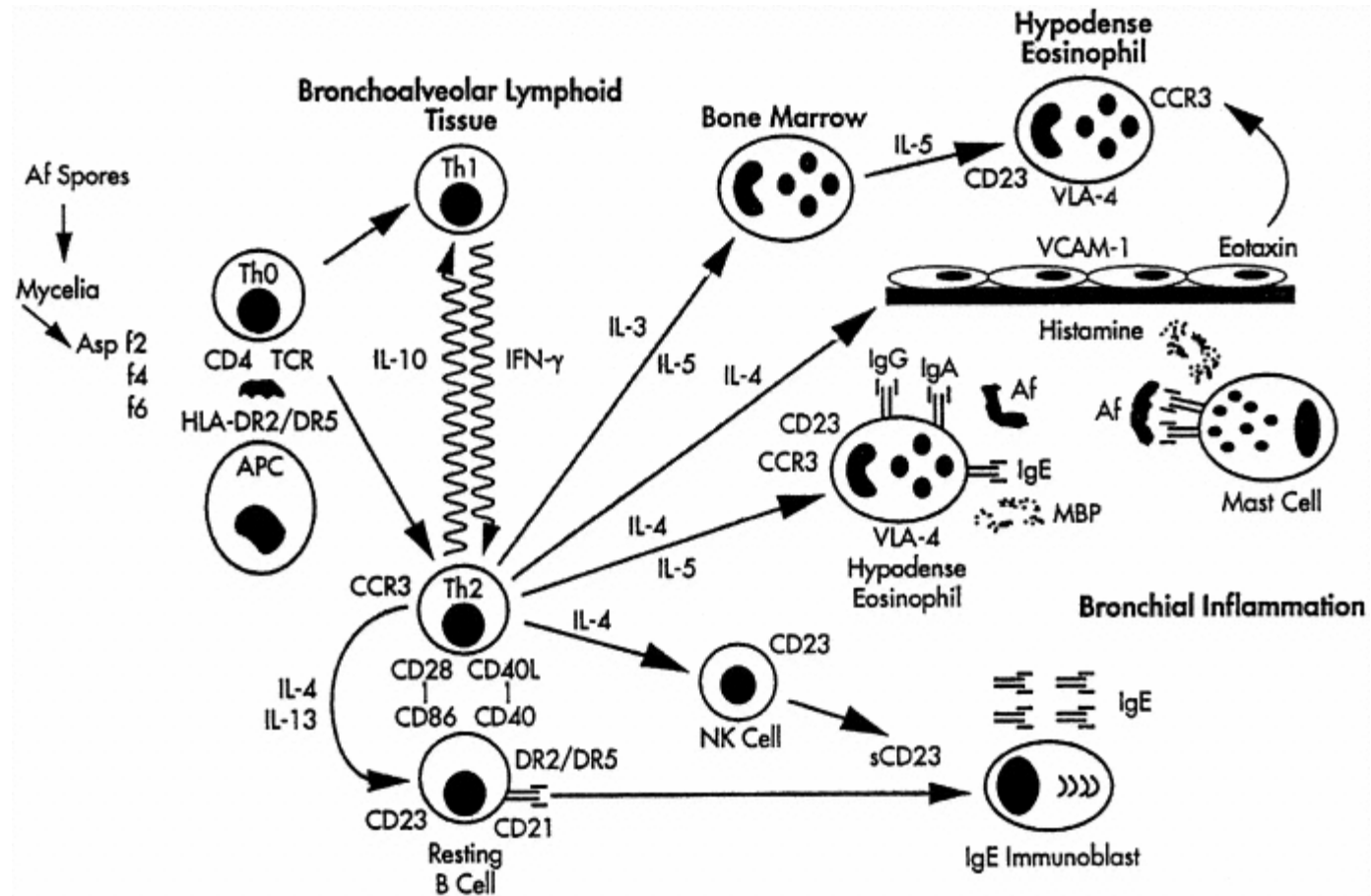
# ABPA

- Asthmatics 0.5-1%
- Cystic Fibrosis 4-15%
  - Highly associated with atopy
- In CF classic ABPA can be defined as
  - 1. Acute or subacute clinical deterioration not attributable to another etiology.
  - 2. Total serum IgE concentration of 1000 IU/mL
  - 3. Immediate cutaneous reactivity to Af or in vitro demonstration of IgE antibody to Af.
  - 4. One of the following: (a) precipitins to Af or in vitro demonstration of IgG antibody to Af; or (b) new or recent abnormalities on chest radiography (infiltrates or mucus plugging) or chest CT (bronchiectasis) that have not cleared with antibiotics and standard physiotherapy.

# ABPA- additional risk factors

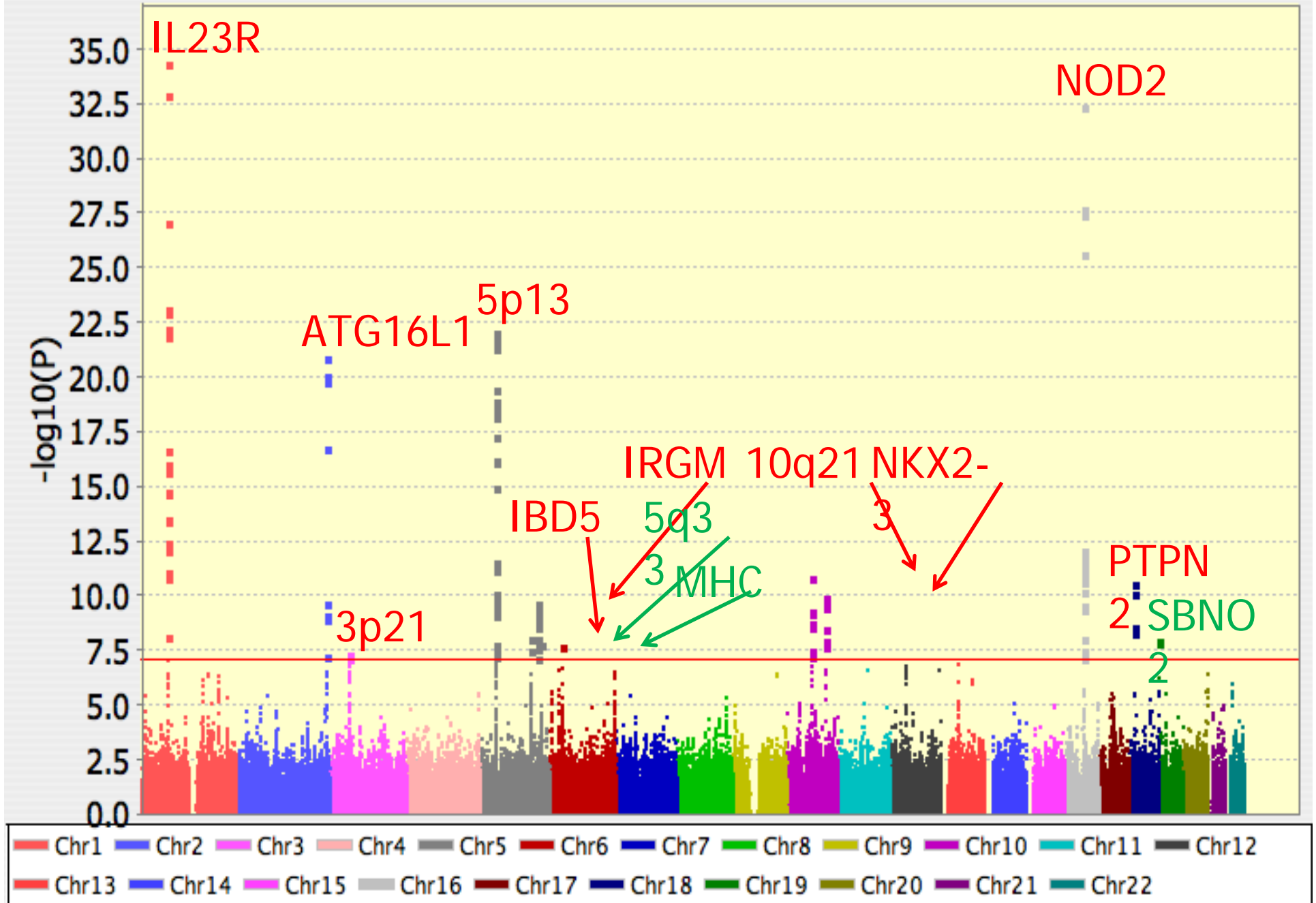
- HLA DR- DR2 and DR5; DQ2 is protective
- CFTR mutations

# ABPA - a TH2 Disease?

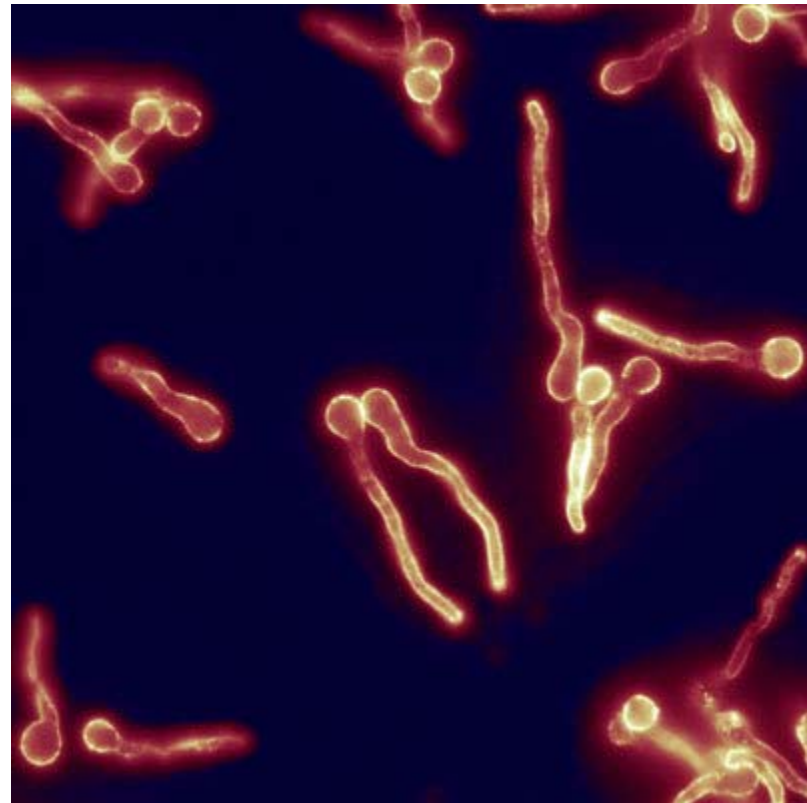
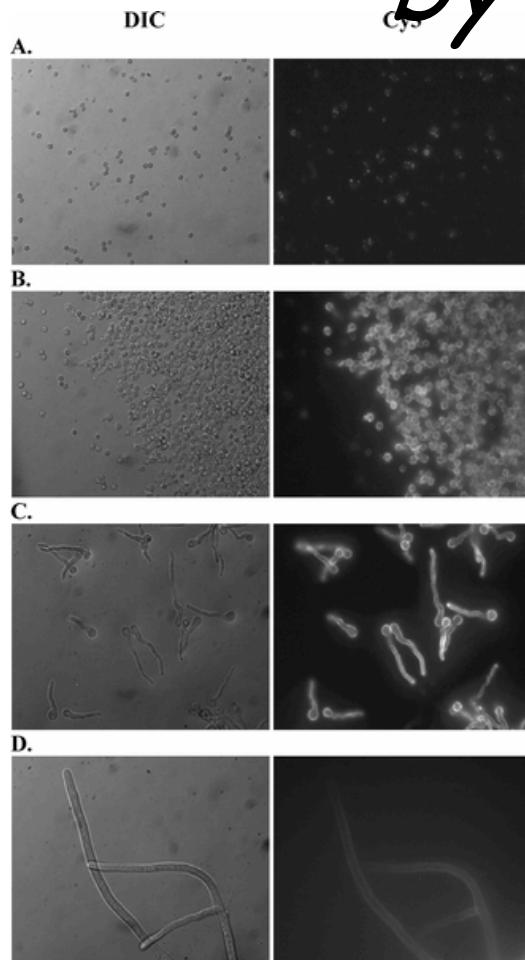


Clin Infect Dis. 2003 Oct 1;37 Suppl 3:S225-64.

# Crohn's disease GWA meta-analysis



# Specific morphologies of *Aspergillus fumigatus* recognized by dectin-1



Steele et al. PLoS Pathog. 2005  
Dec;1(4):e42.

# ABPA

- Is Dectin or glucan signaling critical for the development of Af specific Th2 cells in patients with ABPA
- Are there differences in Dectin expression or signaling in CF patients that develop ABPA compared to those that do not?
- Do CF patients without ABPA but are colonized with *A. fumigatus* develop anergy or regulatory T-cells to Af?

# Enrollment criteria

## Inclusion

1. diagnosis of CF
2. age  $\geq$  6 years
3. presence of *A. fumigatus* in culture of airway flora, or the presence of one or more of the diagnostic criteria for ABPA

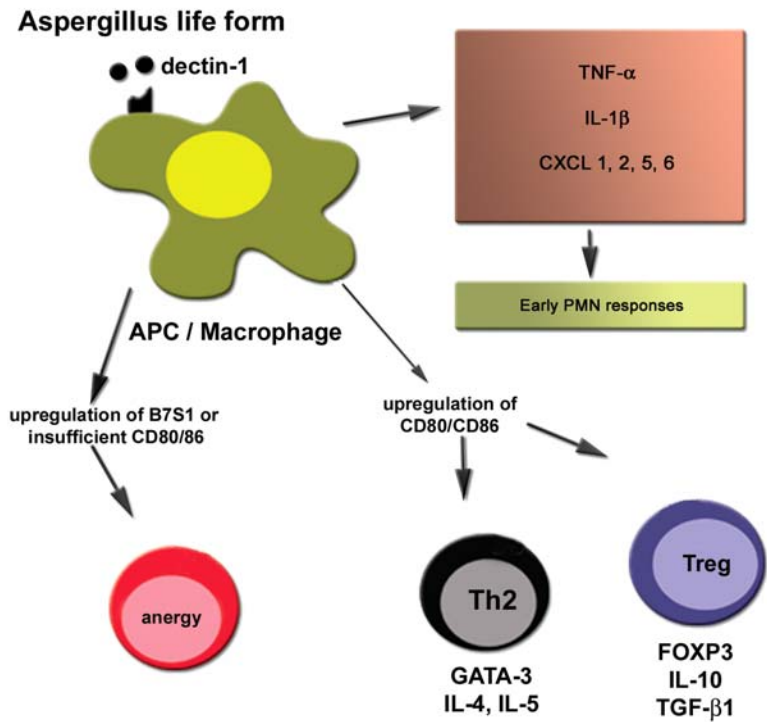
## Exclusion

1. uncontrolled CF-related diabetes mellitus (HgbA1C  $>$  7.0% within the six months)
2. use of oral steroids at a dose  $\geq$  0.5 mg/kg/day
3. history of lung transplantation
4. pulmonary exacerbation as defined by requirement for use of intravenous antibiotics or need for hospitalization within the preceding 14 days
5. a diagnosis of HIV and a CD4+ T-cell count below 500 cells/ml

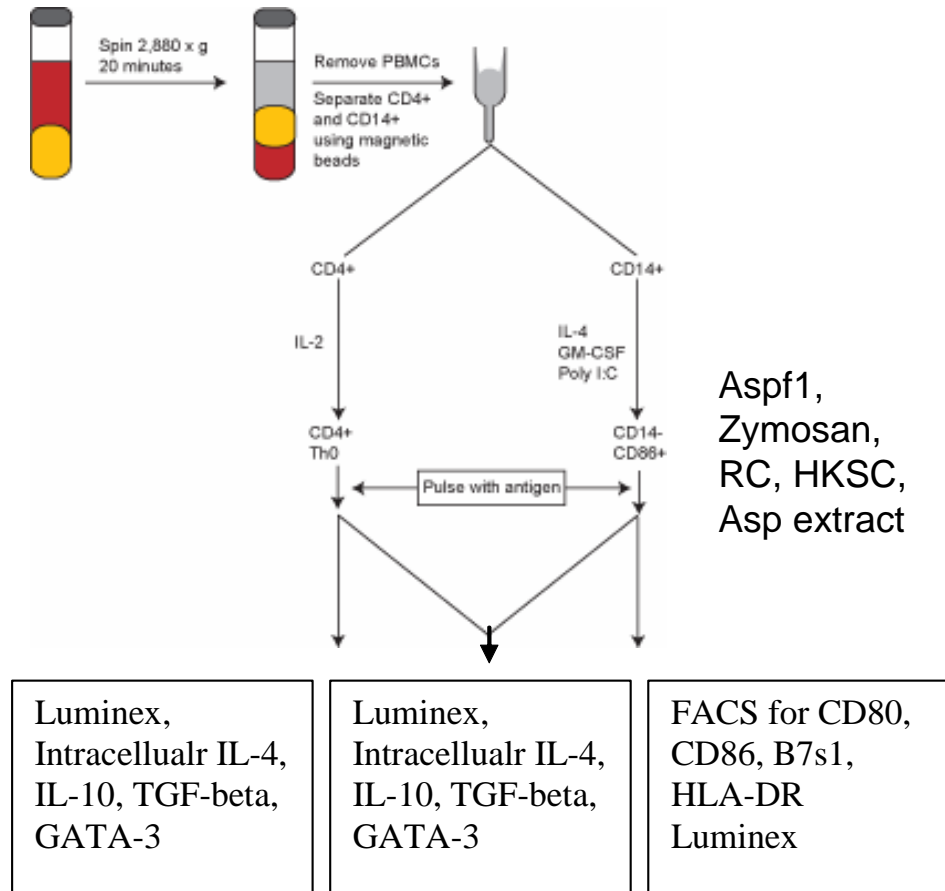


# Characteristics

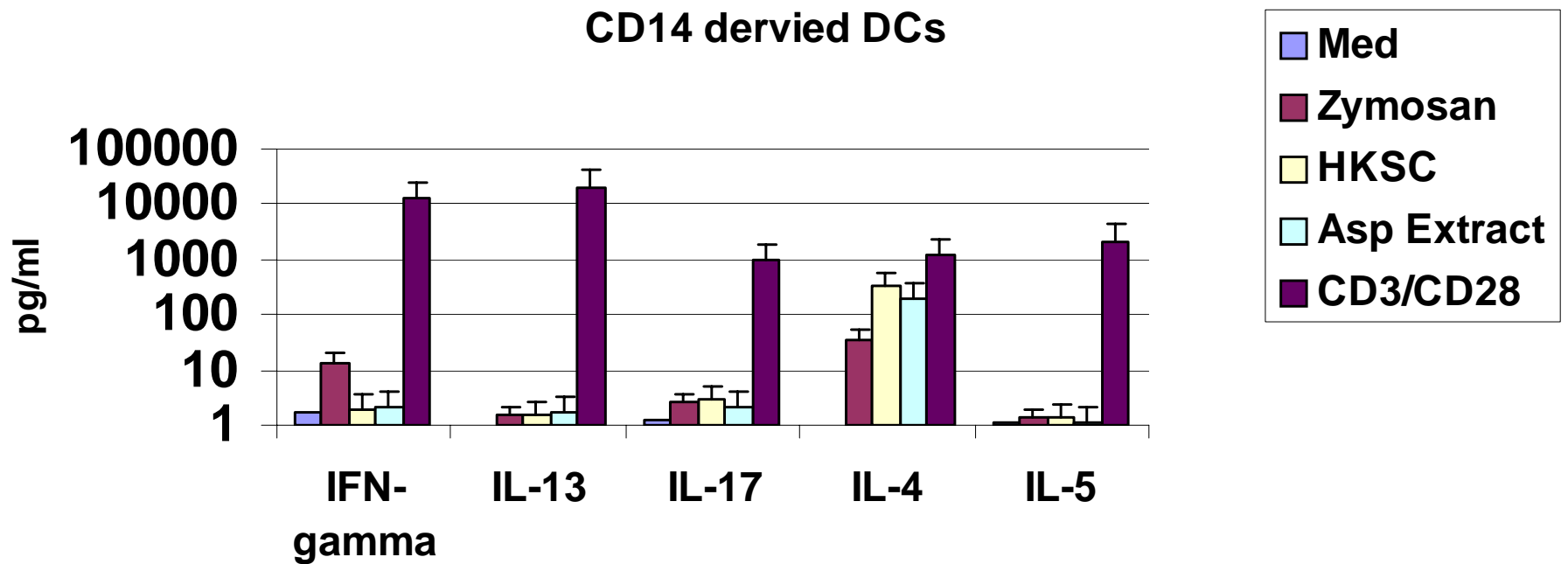
Variable	ABPA	
	Aspergillus + (N = 17)	Aspergillus + (N = 13)
Age (range in years)	23 (14-44)	35 (17-59)
Sex (number of male/female)	9/8	8/5
FEV <sub>1</sub> (% predicted)	65 (25-120)	62 (22-112)



**Figure 5**

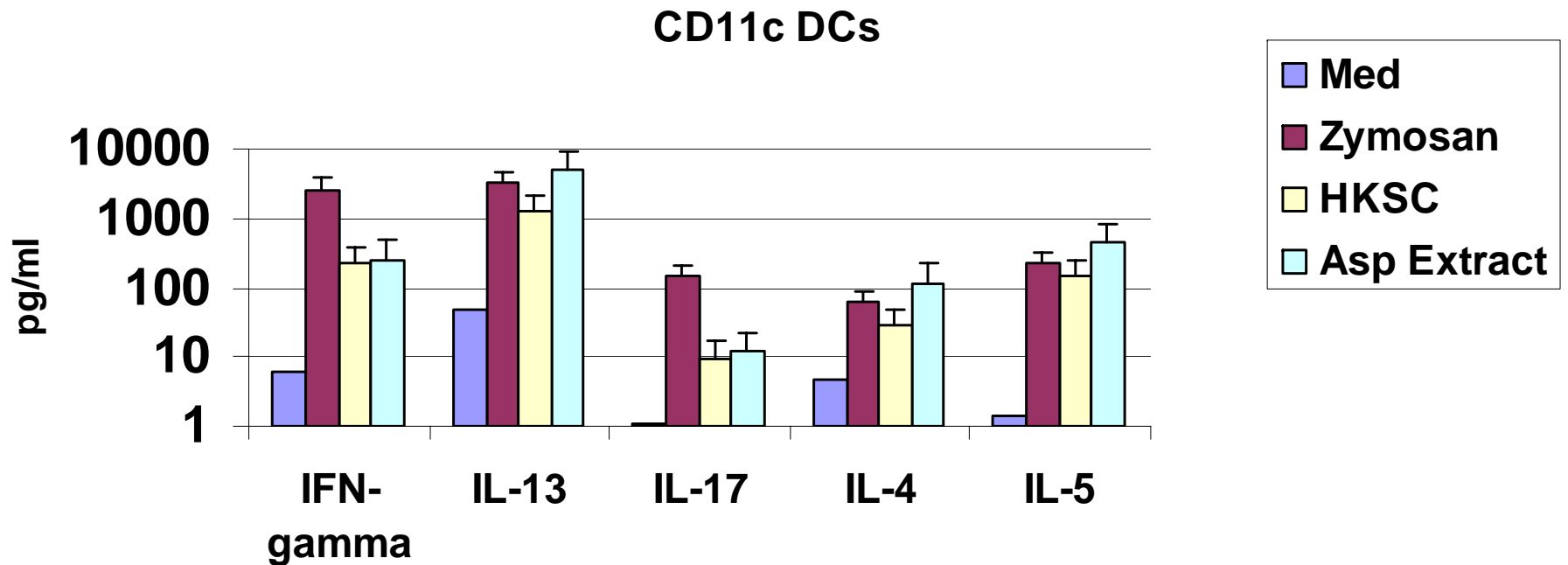


# CD14+ derived DCs are poor detectors of Th2 cells in patients with ABPA



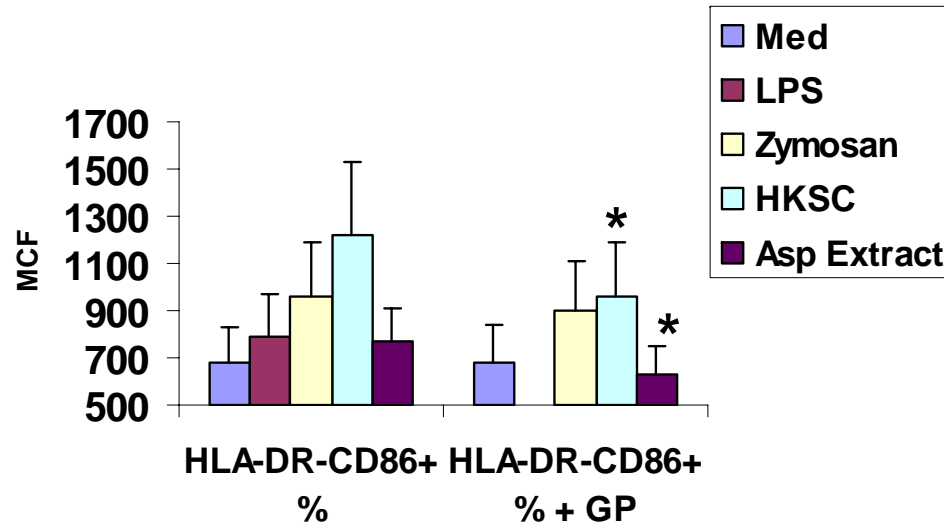
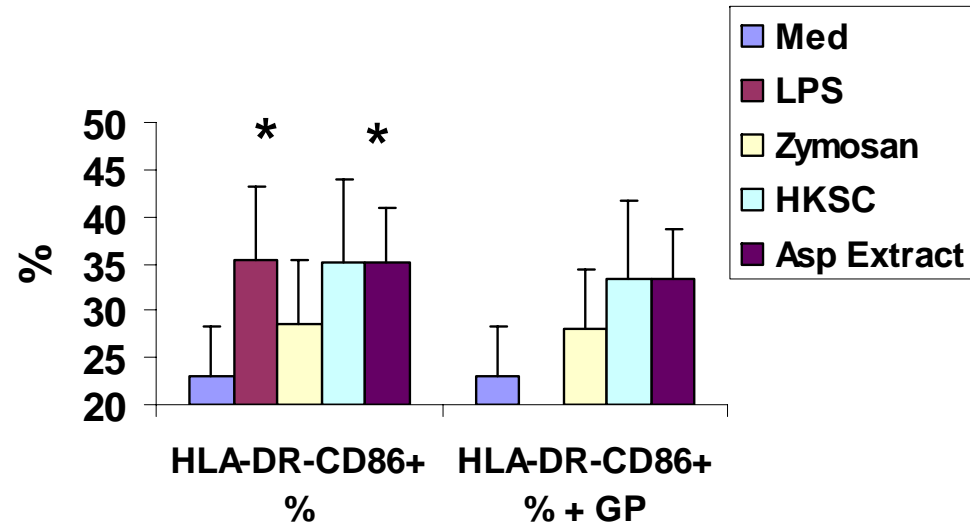
N=9

# Enhanced detection of Af Th2 and IL-17 producing T cells by CD11c DCs

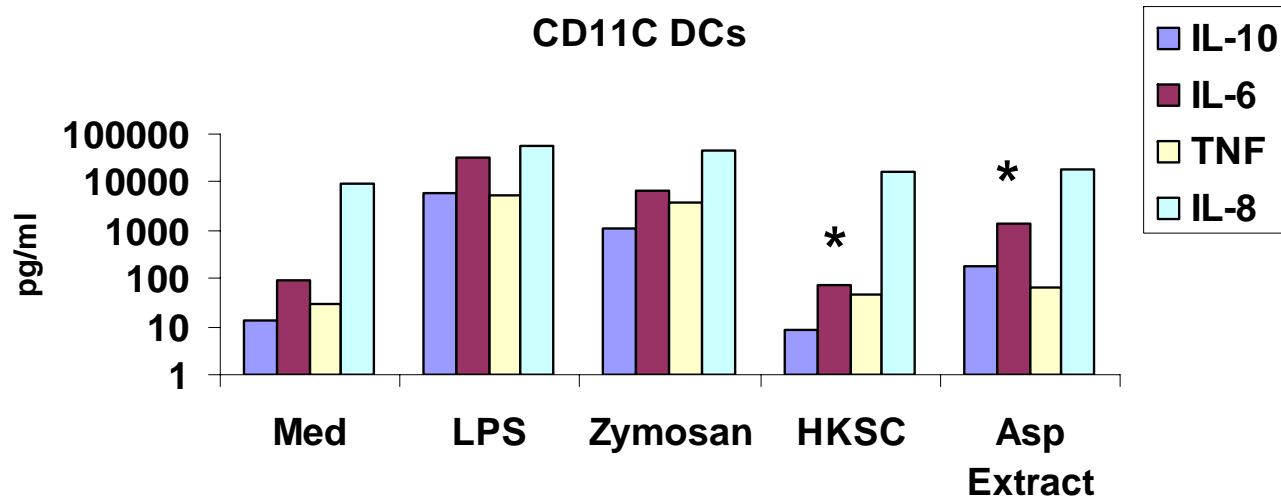
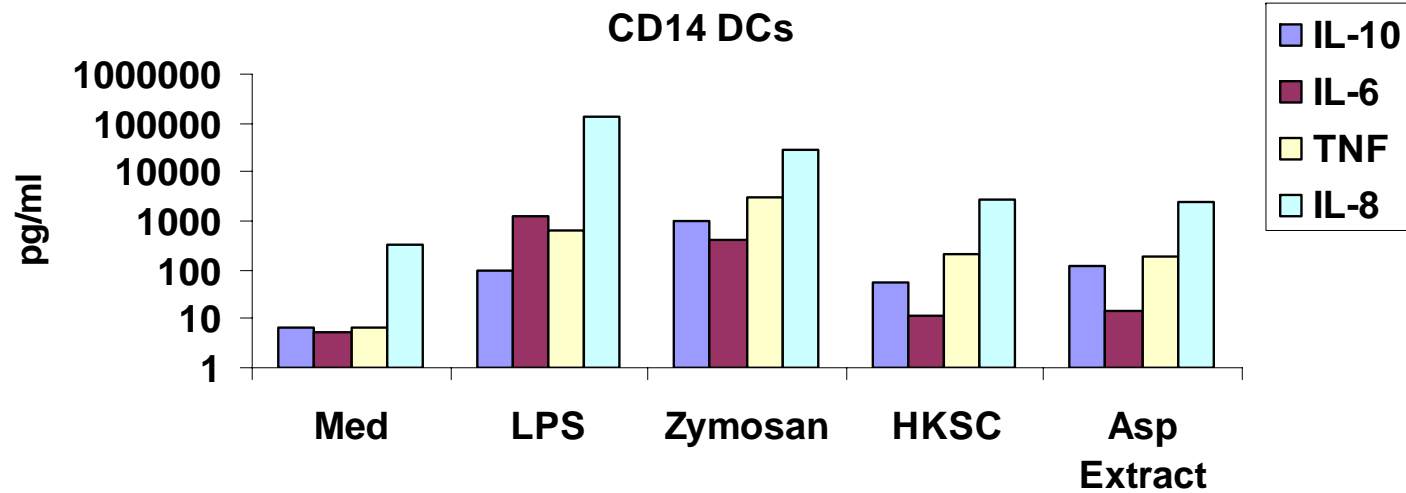


N=9

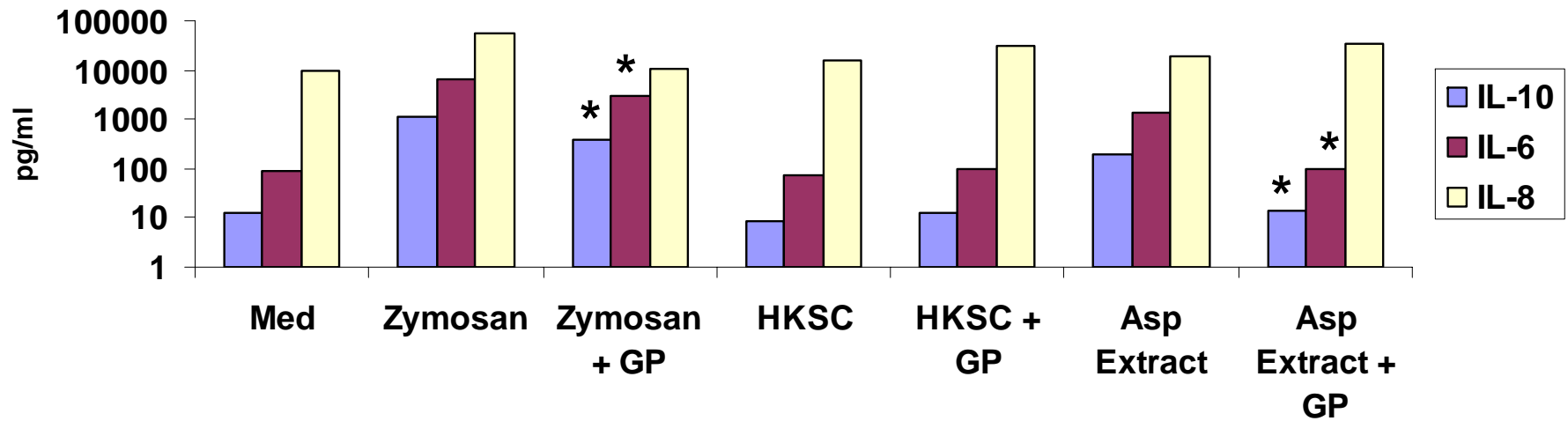
# $\beta$ -glucan dependent increases in CD86 expression on human DCs



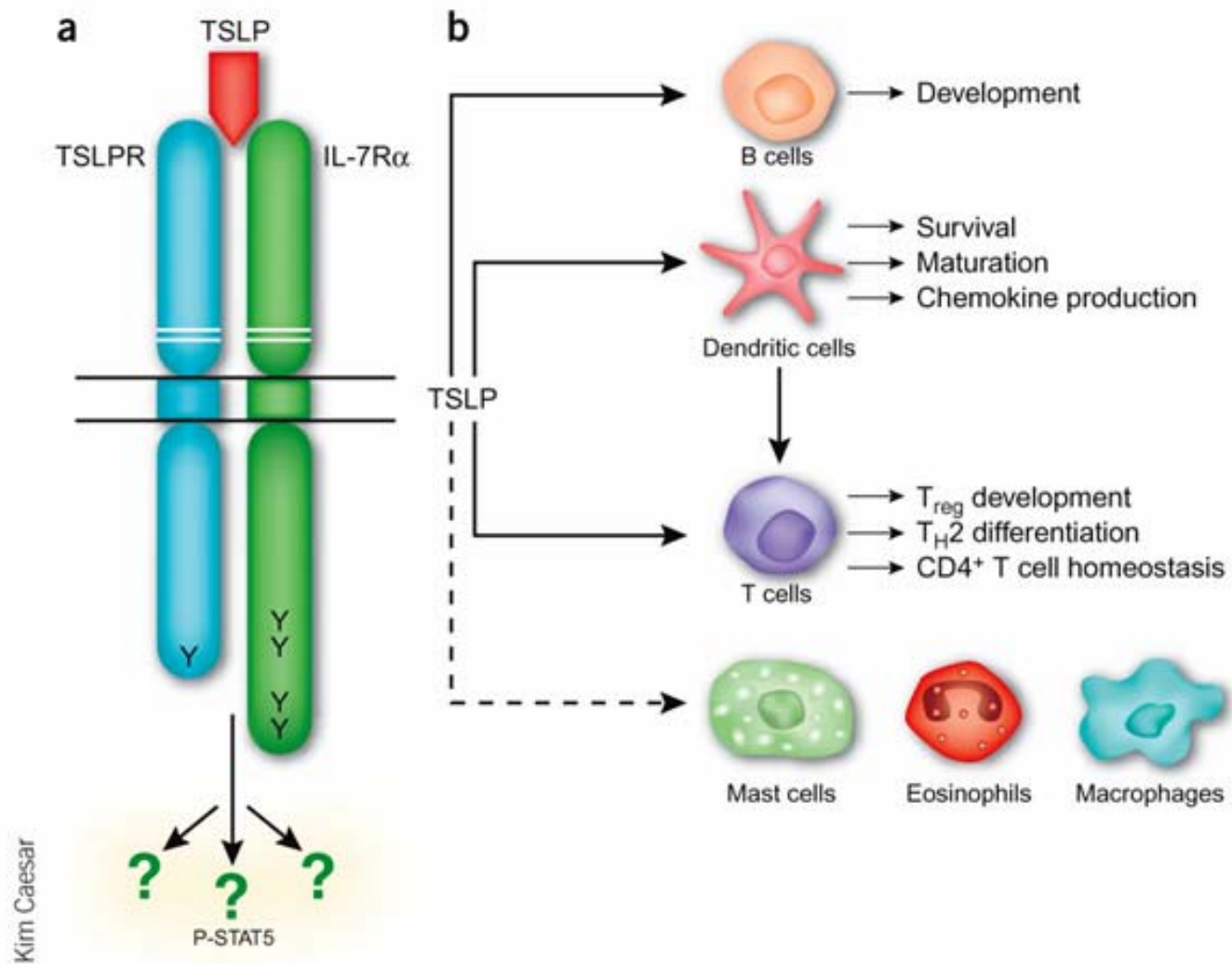
# CD11c DCs produce more IL-6 to Af antigens



# $\beta$ -glucan dependency of IL-6 and IL-10 in DCs



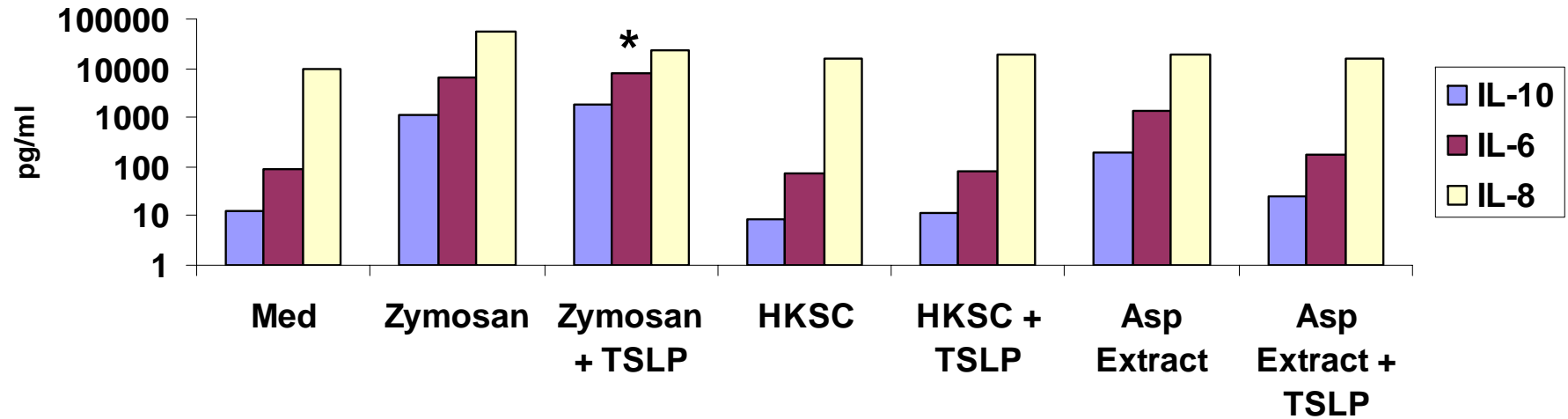
N=9, CD11c DCs



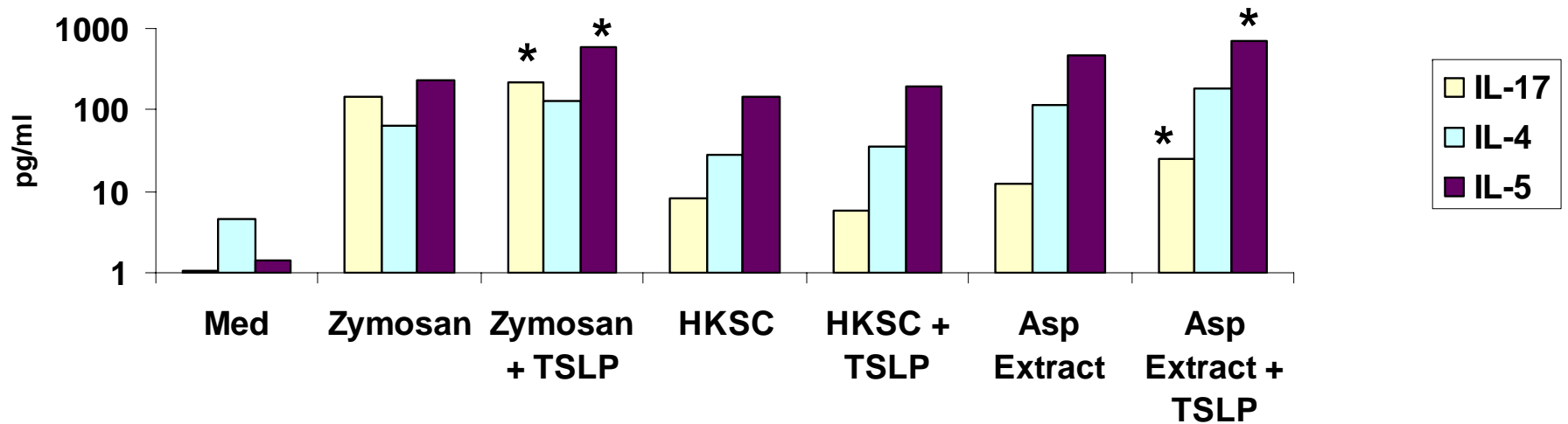
Ziegler SF, Liu YJ. Nat Immunol. 2006 Jul;7(7):709-14.



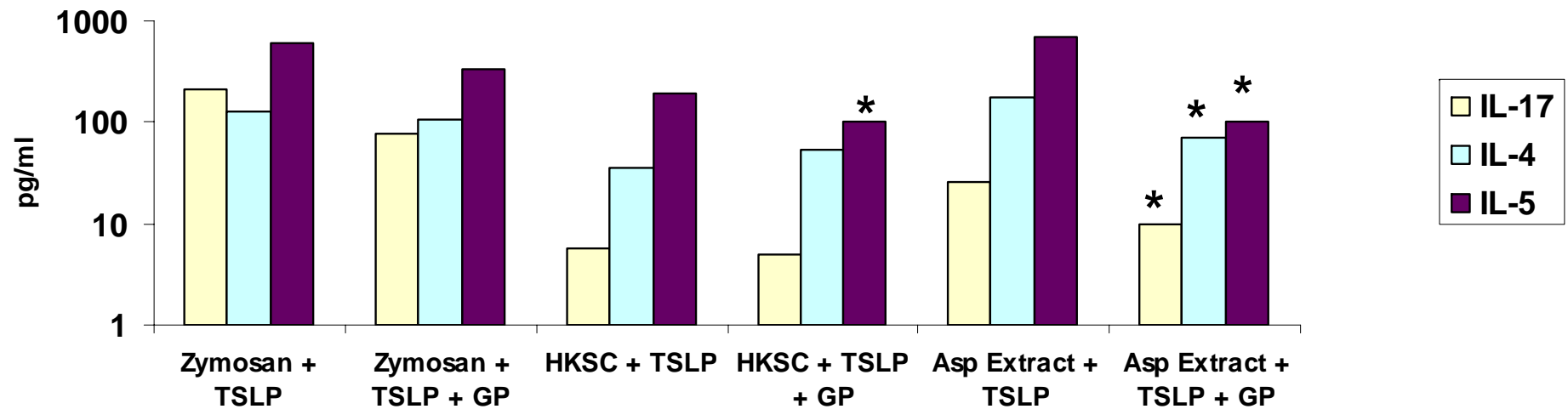
# TSLP increases Zymosan induced IL-6 production by CD11c cells



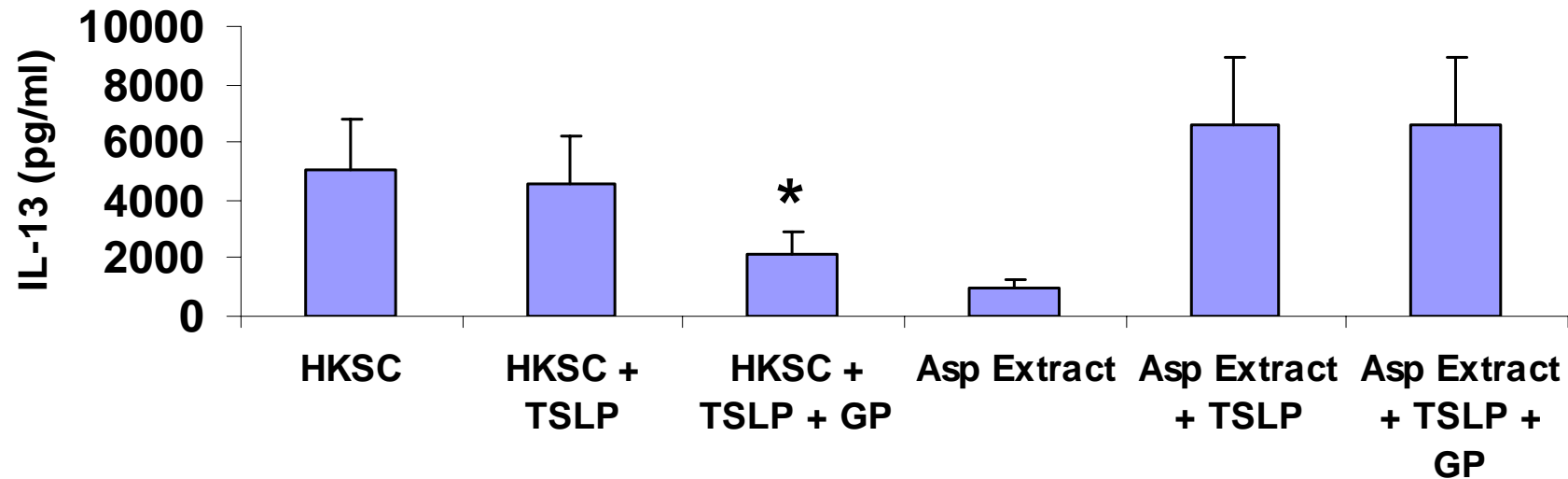
# TSLP-DCs elicit greater Th2 and Th17 responses in ABPA subjects



# $\beta$ -glucan dependence of T-cell responses to Af antigens elicited by TSLP DCs



# $\beta$ -glucan dependence of T-cell responses to Af antigens elicited by TSLP DCs



# Conclusions

- CD11c+ DCs elicit both Th2 and Th17 cytokine production in patients with ABPA
- Both TSLP and glucan signaling augment detection of Th2 and Th17 cells in patients with ABPA and represent new targets for therapy

# Acknowledgments

## University of Pittsburgh

Peter Finelli

Jill Granger

Alison Logar

Amy Magill

Anuradha Ray

Todd Dodick

Joe Pilewski

Patricia Dubin

Shean Aujla

Yvonne R. Chan

Ray Frizzell

## CHOP

Jim Kreindler

## UAB

Chad Steele

## NIH

P30-DK072506

P50-HL084932

R01-HL079142