

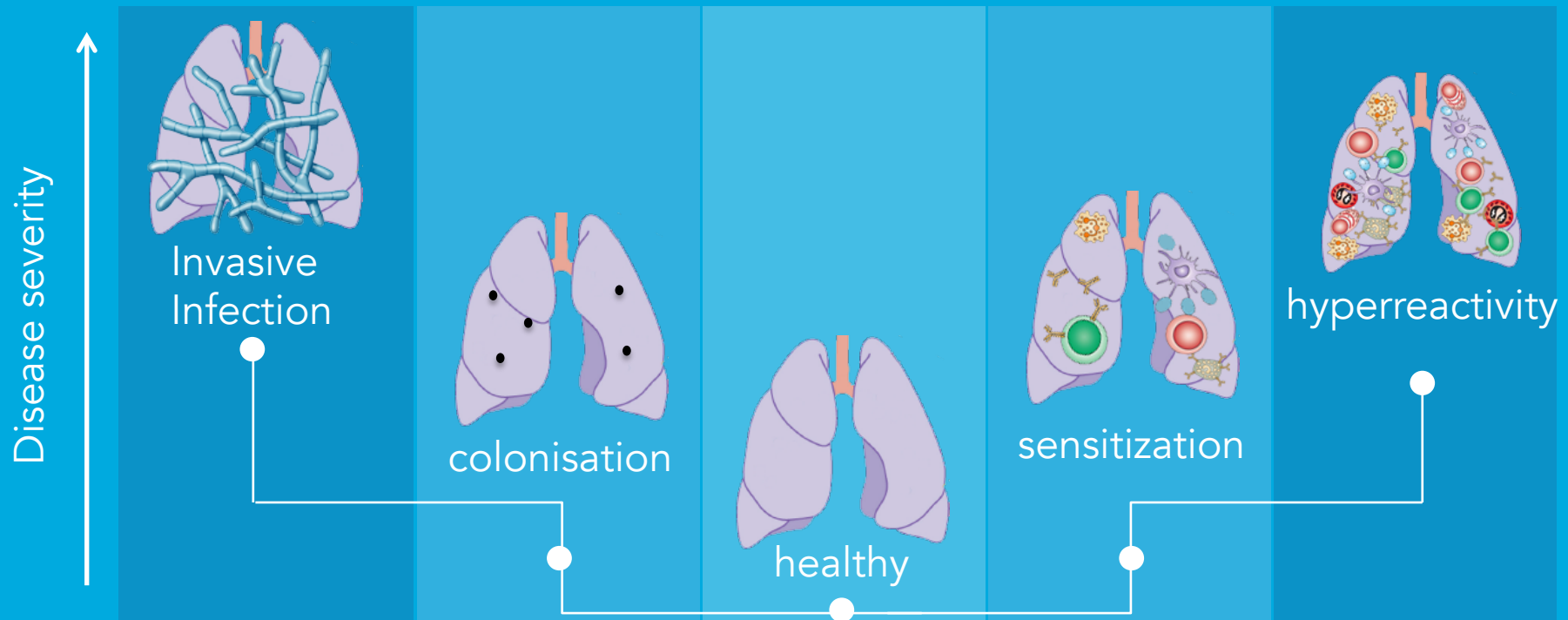
Fungus-specific CD4 T Cells as Specific Sensors for Pulmonary Fungal Infections & Sensitization

Alexander Scheffold, Ph.D.

Charité-Universitätsmedizin Berlin

Berlin, Germany

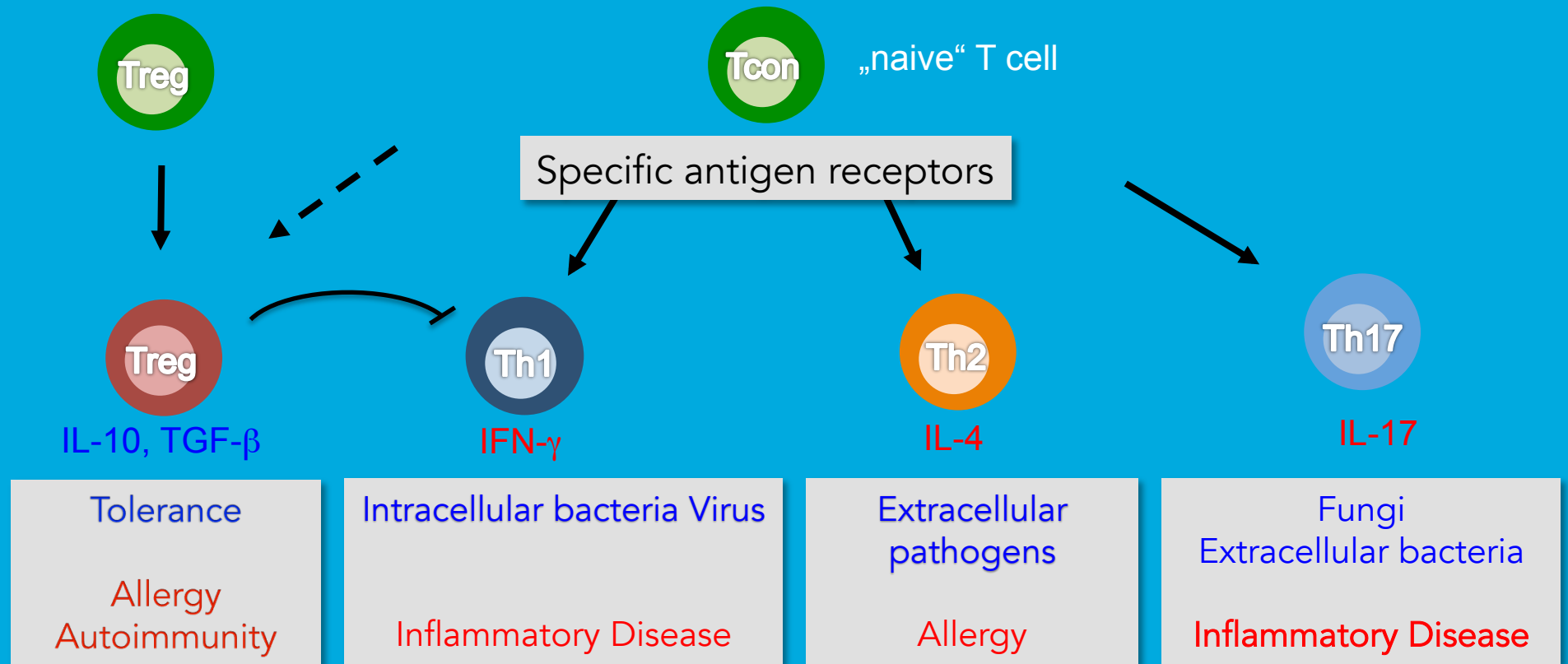
Complex patterns of host-fungus interaction status



Which fungus ?

Which type of host-pathogen interaction status ?
Immune defense *versus* immune pathology ?

Antigen-specific CD4 T helper cells organize immune protection *versus* pathology

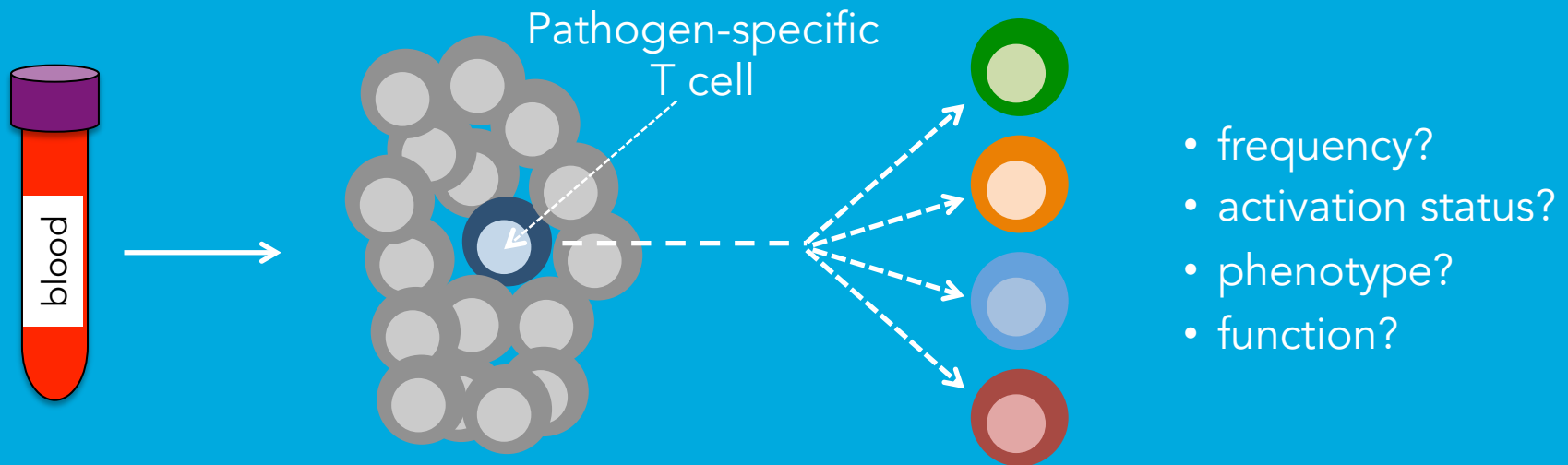


Antigen-specific T cells as diagnostic sensors

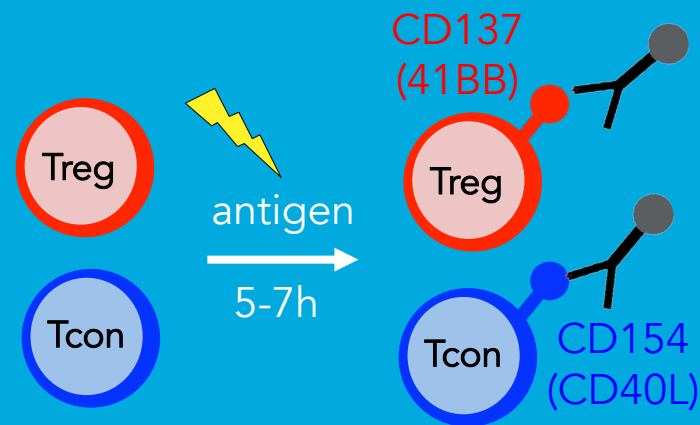
Working Hypotheses

Status of the antigen-specific T cell = host-antigen-interaction status

Antigen-specific T cell-based diagnostics & therapeutics

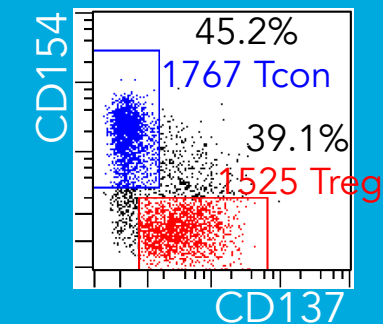
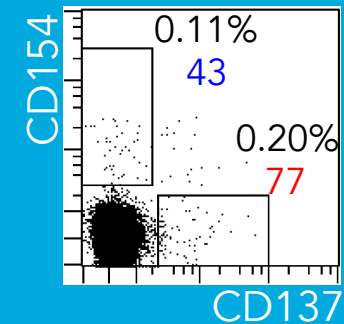
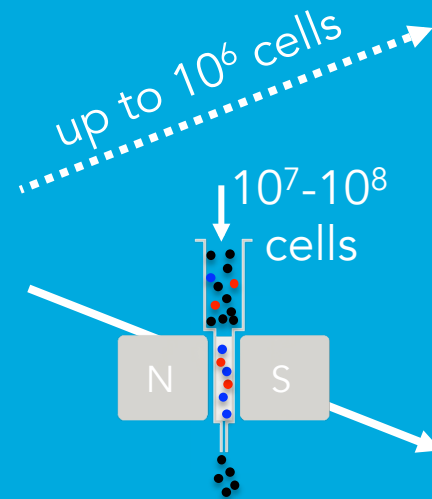


Antigen-Reactive T cell Enrichment (ARTE)



CD137 & CD154 identify
Ag-activated Tcon & Foxp3⁺ Treg

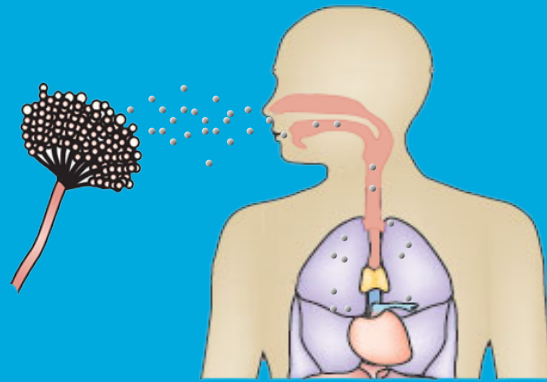
Frentsch et al & Thiel Nat Med 2005
Schönbrunn et al. & Thiel J Immunol 2012



CD154⁺/CD137⁺ Enrichment (ARTE)

Bacher et al Cell 2016
Bacher et al. J Immunol 2013
Bacher et al. Mucosal Immunol 2014

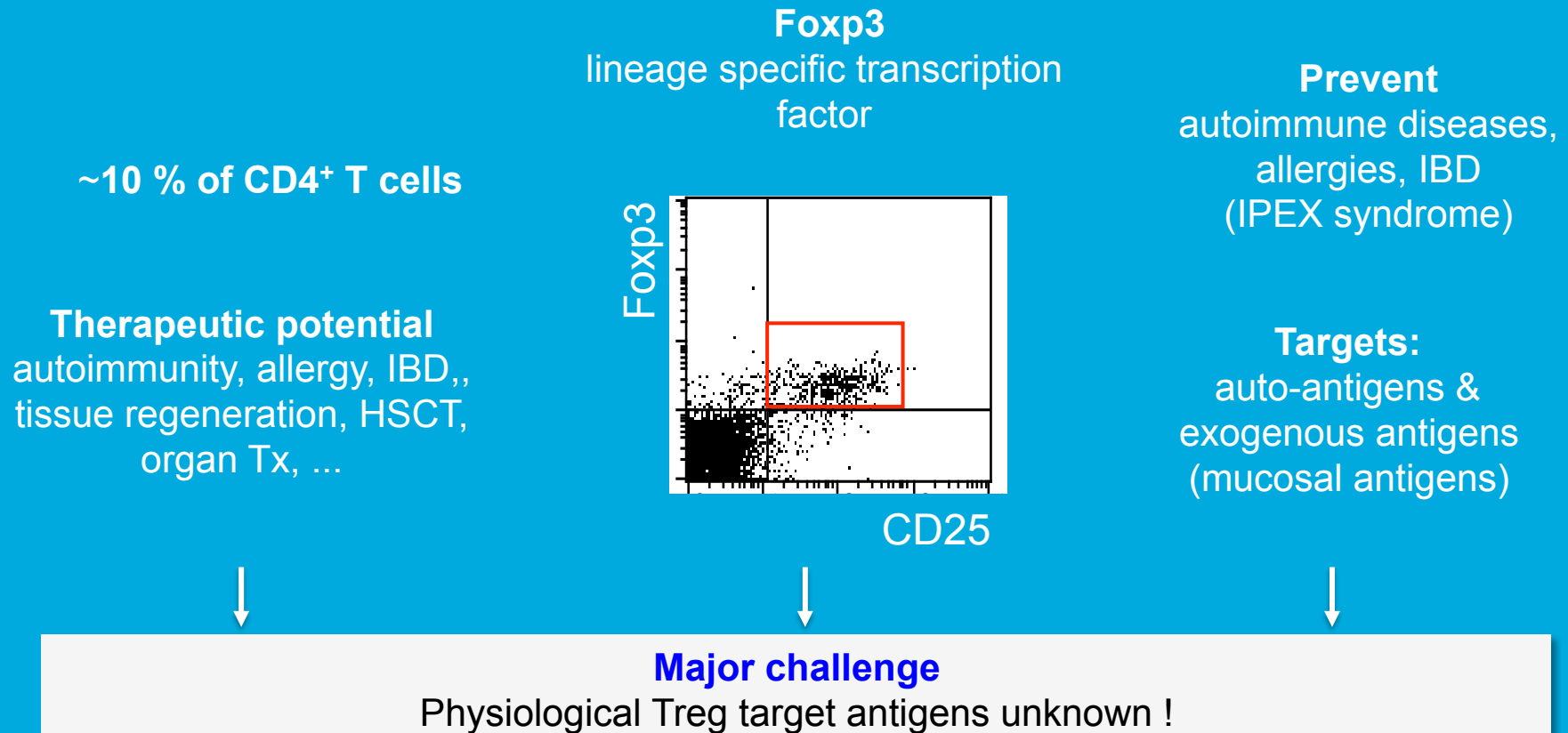
Fungal pathogens are chronically encountered environmental antigen



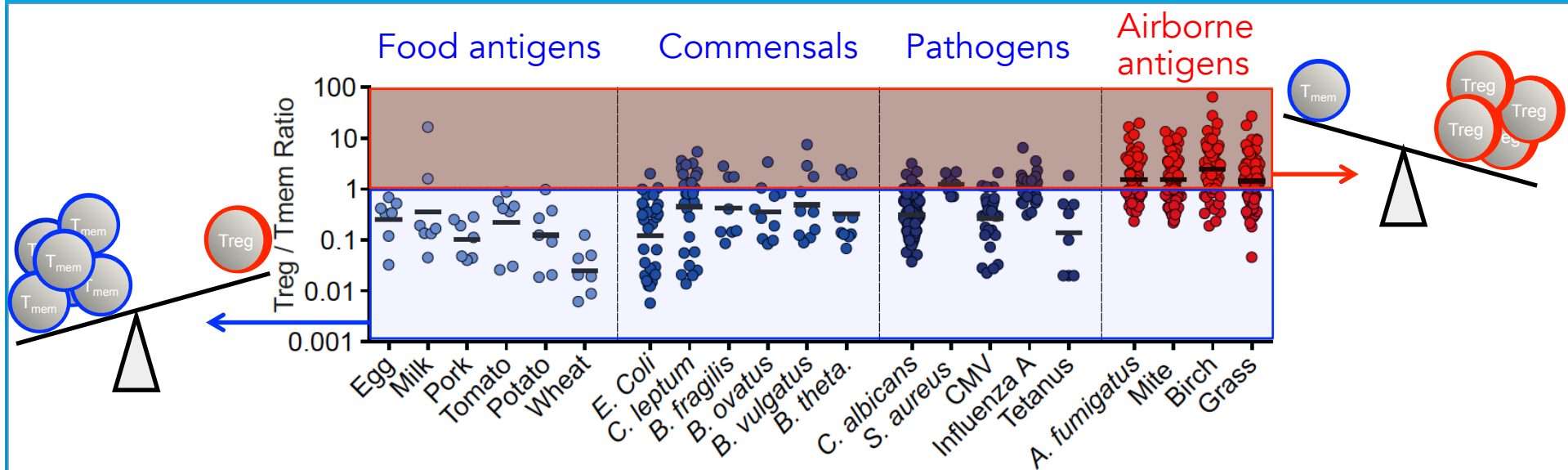
Immune Control ?
Active or passive
tolerance ?

Healthy

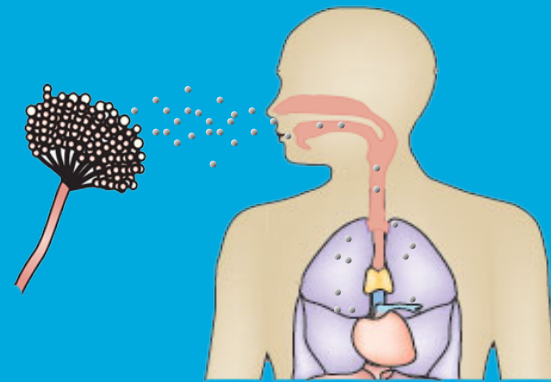
Foxp3+ regulatory CD4 T cells (Tregs): Guardians of immunological tolerance



Treg-dominated „tolerogenic“ response against airborne antigens in healthy donors



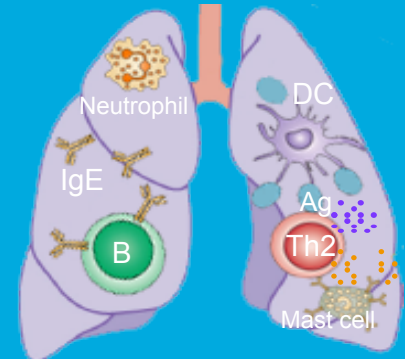
Fungal pathogens are chronically encountered environmental antigen



Treg-mediated tolerance

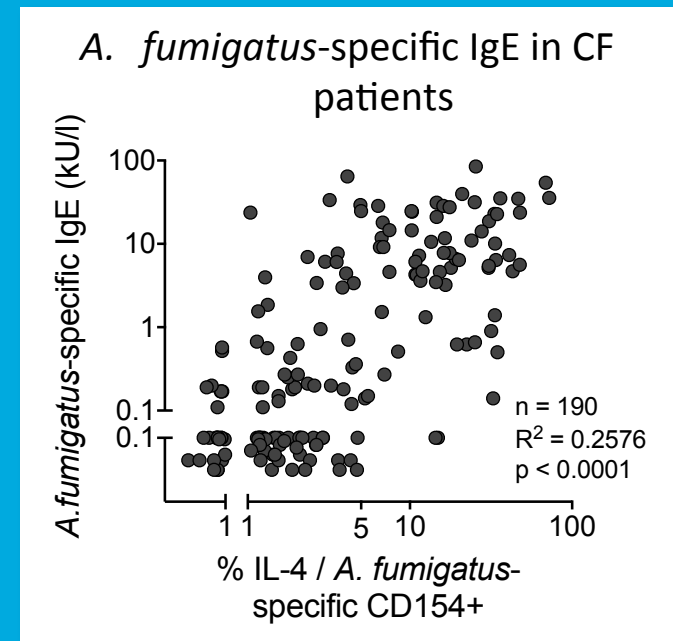
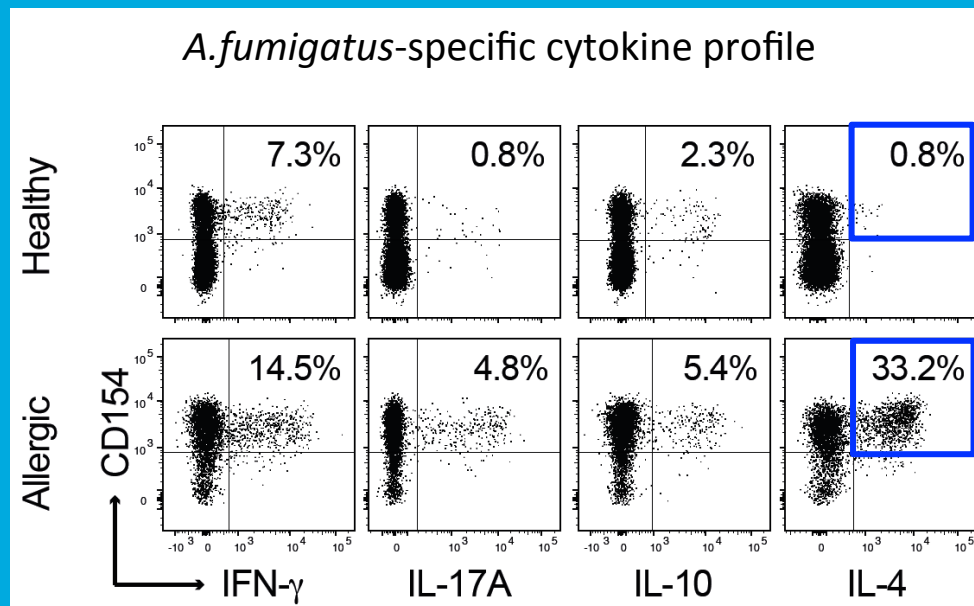
Healthy

Hypersensitivity

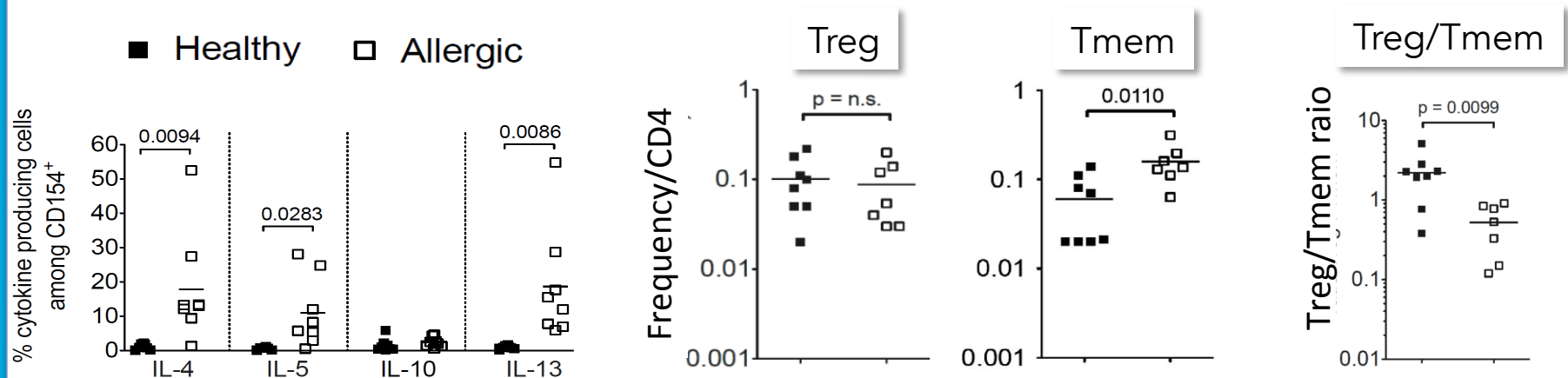


Defective Treg ?

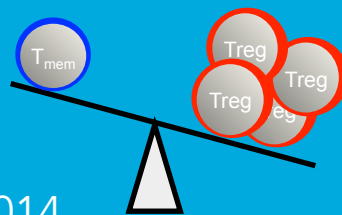
Strong Th2 responses in patients with CF allergic to *A. fumigatus*



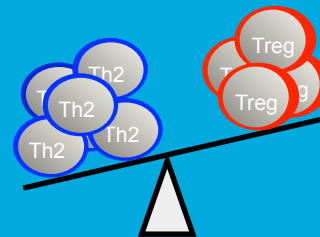
Patients with CF allergic to *A. fumigatus* have strong Th2 but normal Treg responses



Tolerance



Allergy

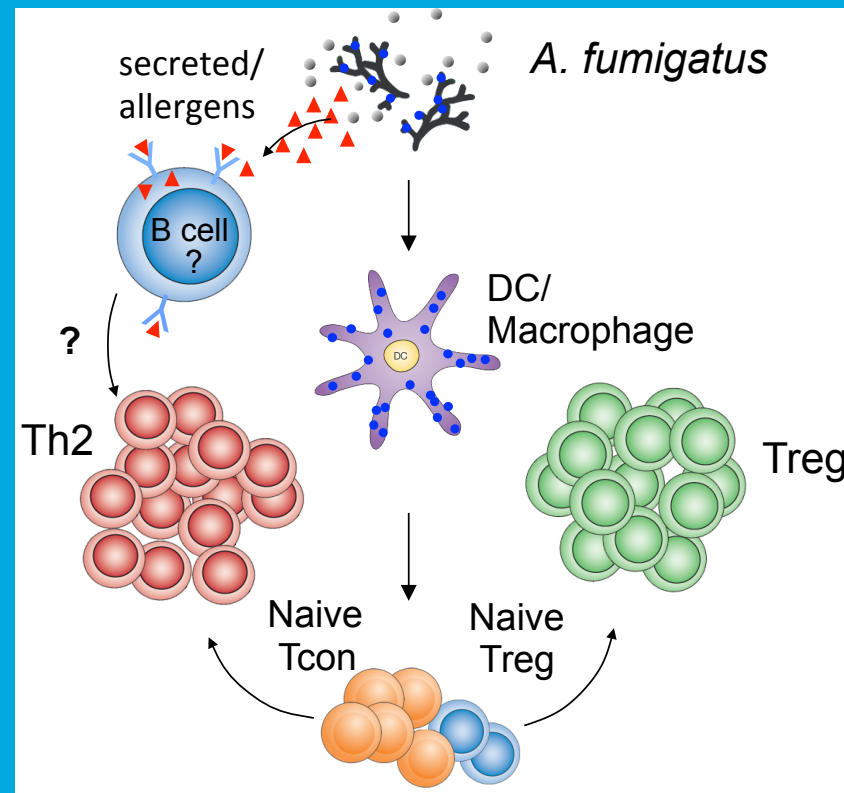


How do Th2 escape Treg tolerance?

Th2 cells react against secreted proteins enabling antigen-specific escape from Treg-mediated tolerance

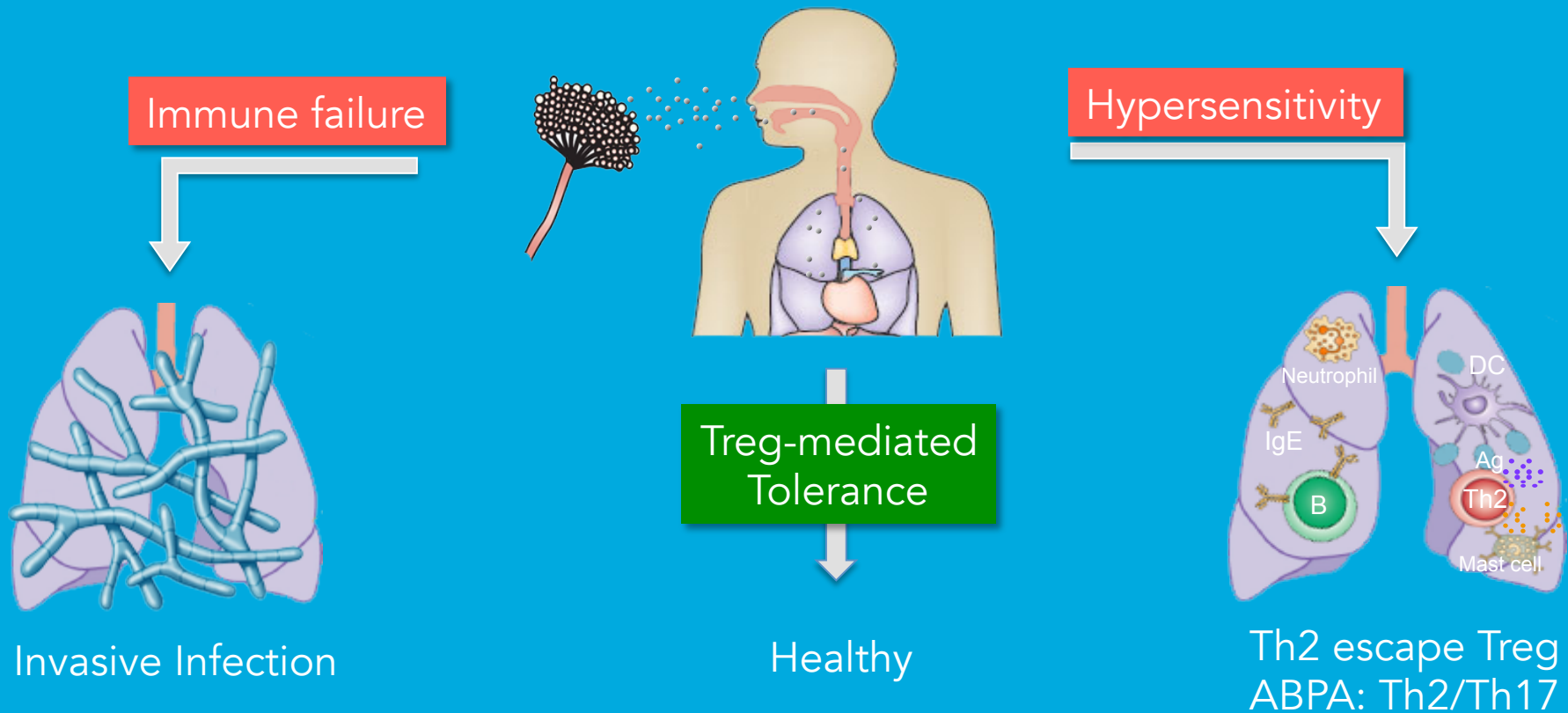
Th2 sensitization:

- Allergy
- ABPA



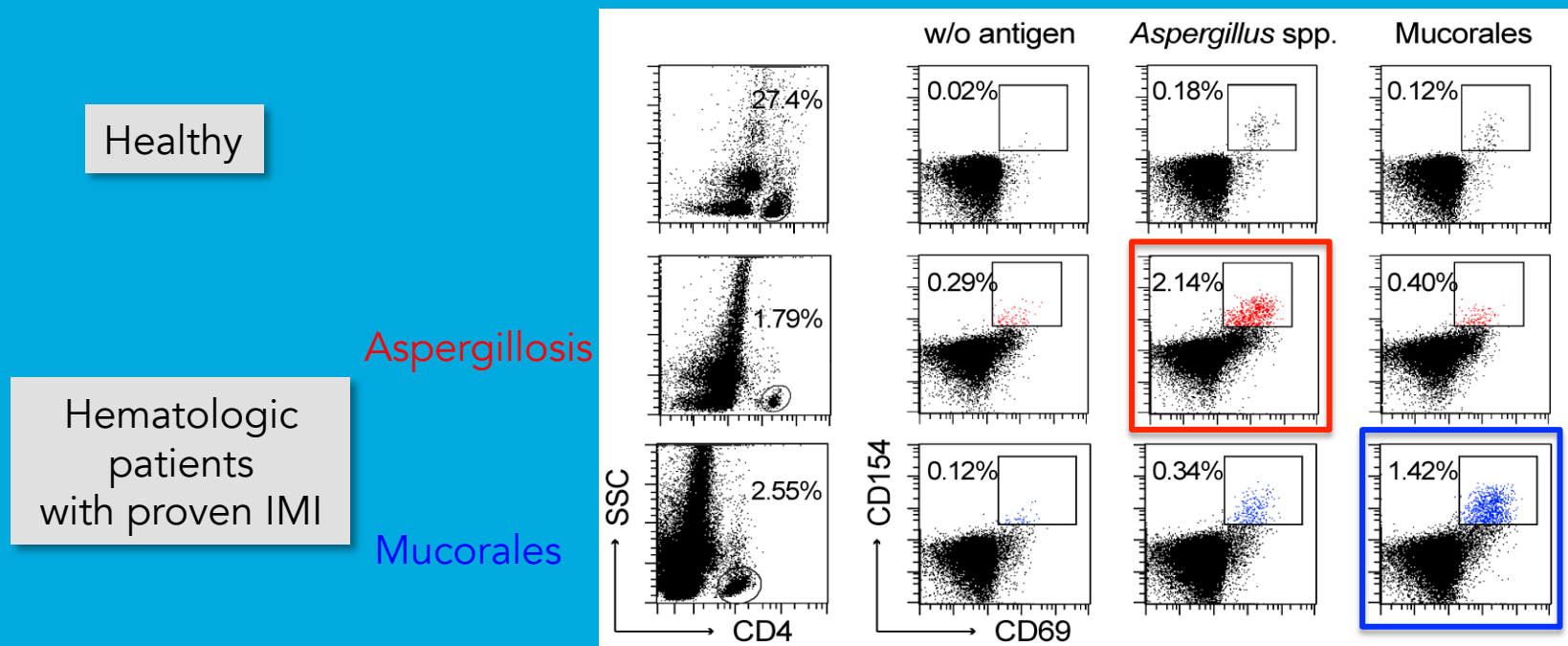
Tolerance in healthy individuals

Fungal pathogens are chronically encountered environmental antigen

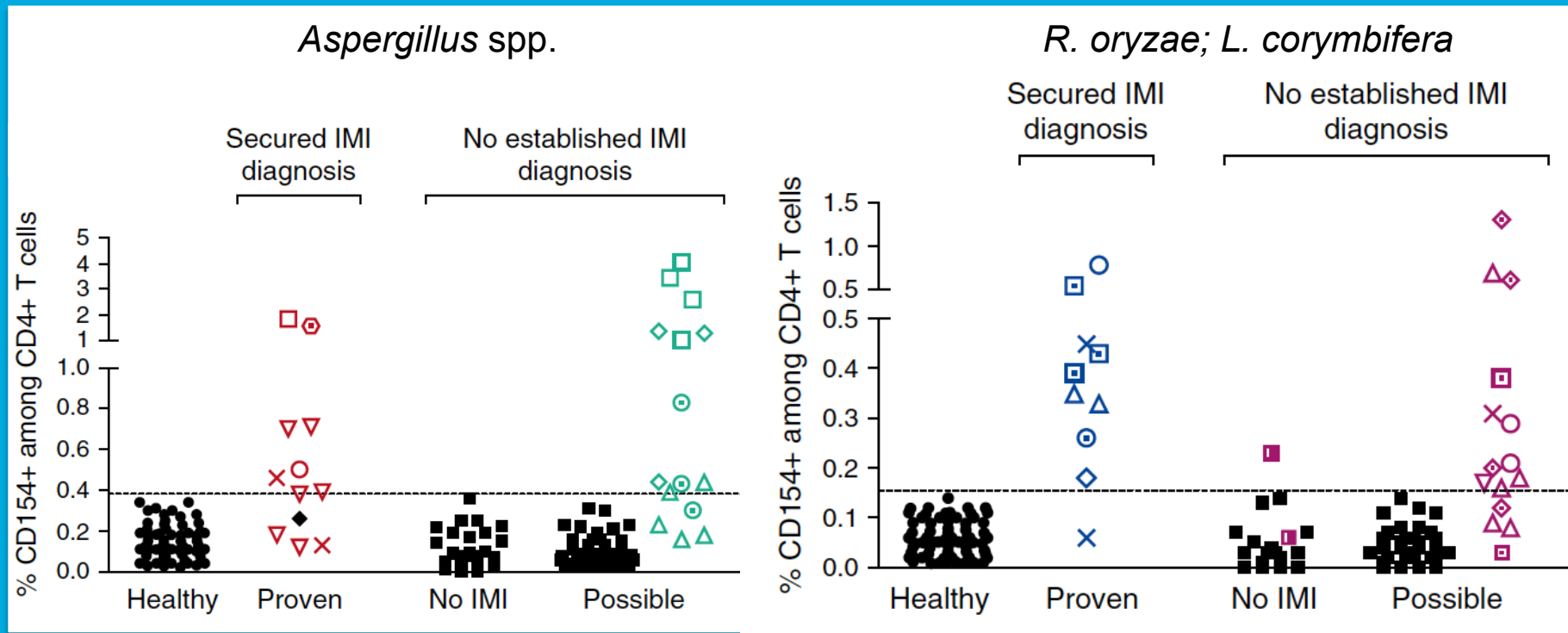


Fungus-specific T cells for diagnosis of Invasive Mycosis (IMI)

- Hematologic patients at risk for Invasive Mycoses (IMI) n= 59
- 10 proven, 29 possible IMI, 20 no signs of IMI

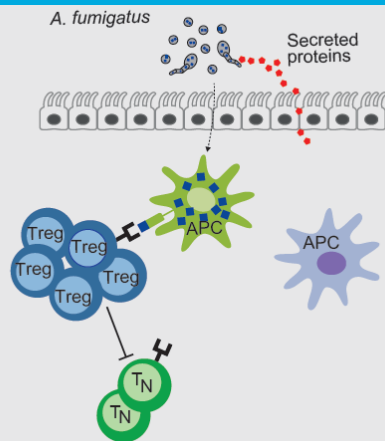


Fungus-specific T cells for diagnosis of Invasive Mycosis (IMI)



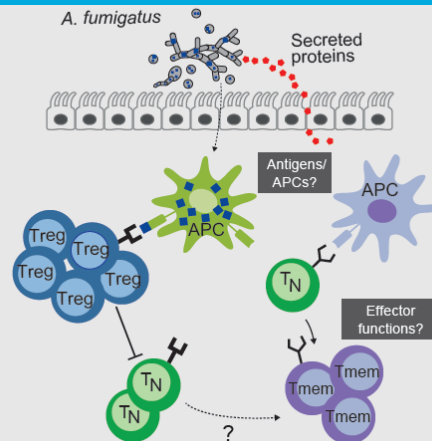
T cells identify the interaction status of fungal pathogens with its human host

Healthy



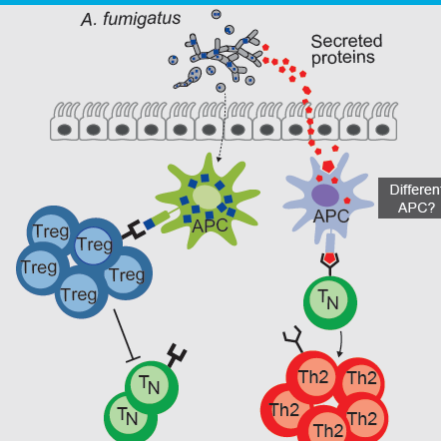
Treg-mediated tolerance

Colonization/ Sensitization



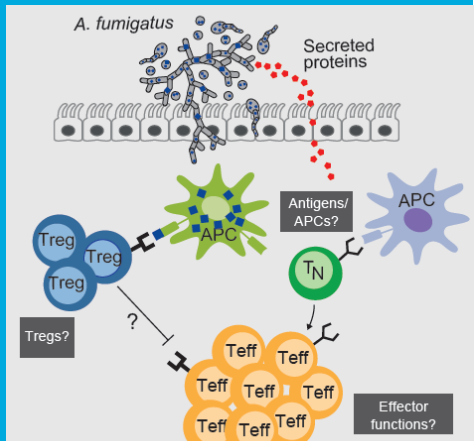
Fungus-specific Tcon responses: Th1, Th2, Th17, ?

Allergy/ABPA



Fungus-specific Th2 (Th17) during allergy/ABPA

Invasive Infection



Elevated fungus-specific T cells (Ki67+ ?)

Summary

- *A. fumigatus*-specific Treg provide tolerance in healthy and allergic individuals
- No strong protective T cell response in healthy humans
- Th2 cells escape Treg mediated tolerance by selective targeting secreted antigens
- Diagnosis via fungus-specific T cell phenotype or frequency
 - Identifies invasive mycoses (increased frequencies)
 - Allergy (Th2), ABPA (Th2/Th17)
 - Other types of fungal sensitization/hypersensitivity reactions
- Ongoing: T cell responses against relevant pathogens (*A. fumigatus*, *C. albicans*, *S. apiospermum*, *F. solani*, *P. aeruginosa*, *S. aureus*) in a large cohort of patients with CF, COPD & asthma & correlation with microbiology & clinical data

Thanks to

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