

**World  
Aspergillosis  
Day**  
Feb 1st 2018

**AAA Aspergillosis 2018  
Lisbon 1-3 February 2018**



# *Aspergillus* Immunology *and* Inflammation

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Pathology Section  
Perugia



# PERUGIA

città universitaria

The University of Perugia was founded in 1308. Today, research, education and consulting activities in the various disciplines are organized in 16 Departments, with about 23,500 students, 1,100 professors and researchers and 1,000 staff members. The University offers study programs also in two other Umbrian towns: Assisi and Terni.

Piazza IV novembre





**Department of Experimental Medicine  
Pathology Section  
Perugia**

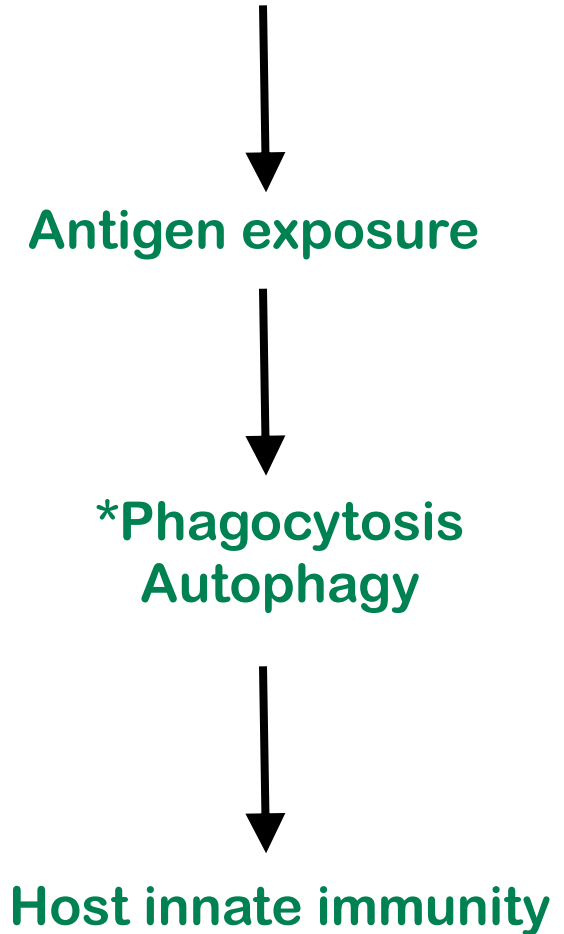
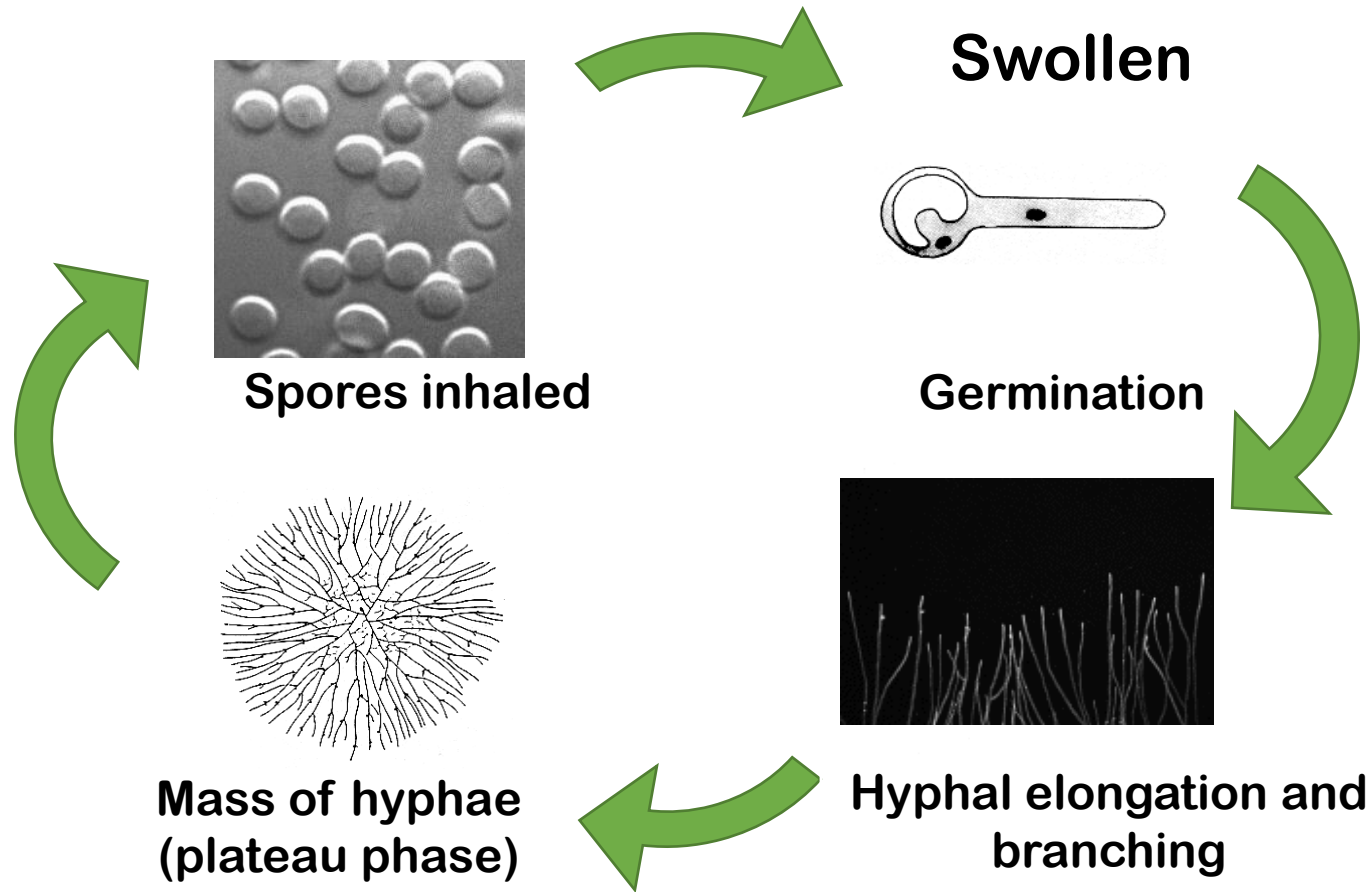


## Besides Immunology:

- ✓ The life cycle of *Aspergillus*
- ✓ *Aspergillus* diseases
- ✓ The antifungal resistance
- ✓ *Aspergillus* metabolism and fungal adaptation
- ✓ The interaction between the fungus and the microbiome

# The life cycle of *Aspergillus*

Pathogen associated molecular pattern



\*152 Canonical versus noncanonical autophagy in the fight against *Aspergillus fumigatus* infection  
V Oikonomou



# Aspergillus diseases

## Superficial mycoses

- Affect the skin, hair and nails

## Subcutaneous mycoses (tropical)

- Affect the muscle and connective tissue immediately below the skin

## Systemic (invasive) mycoses

- Involve the internal organs
- Primary vs. opportunistic

## Allergic mycoses

- Affect lungs or sinuses
- Patients may have chronic asthma, cystic fibrosis or sinusitis

Adaptive cell priming



Th polarization



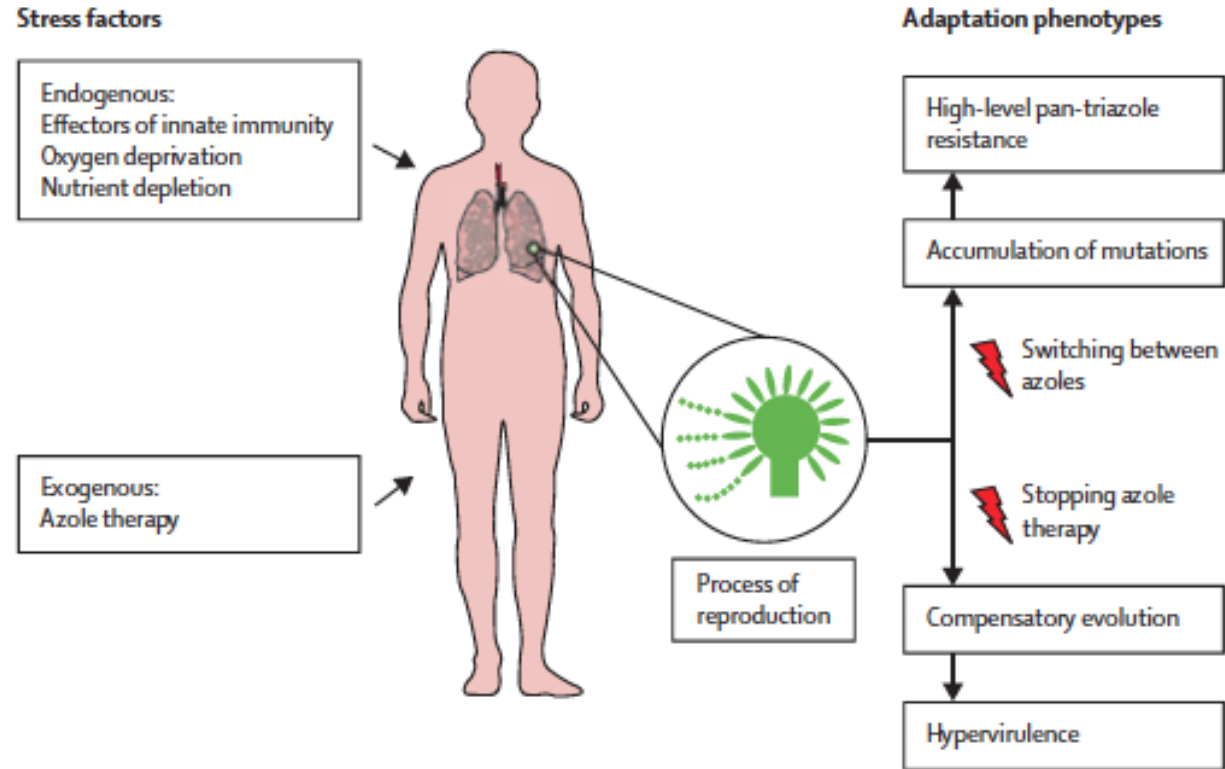
Tolerance/resistance



T cell memory/  
Chronic inflammation



# The azole resistance



Immune dysfunction



Fungal persistence



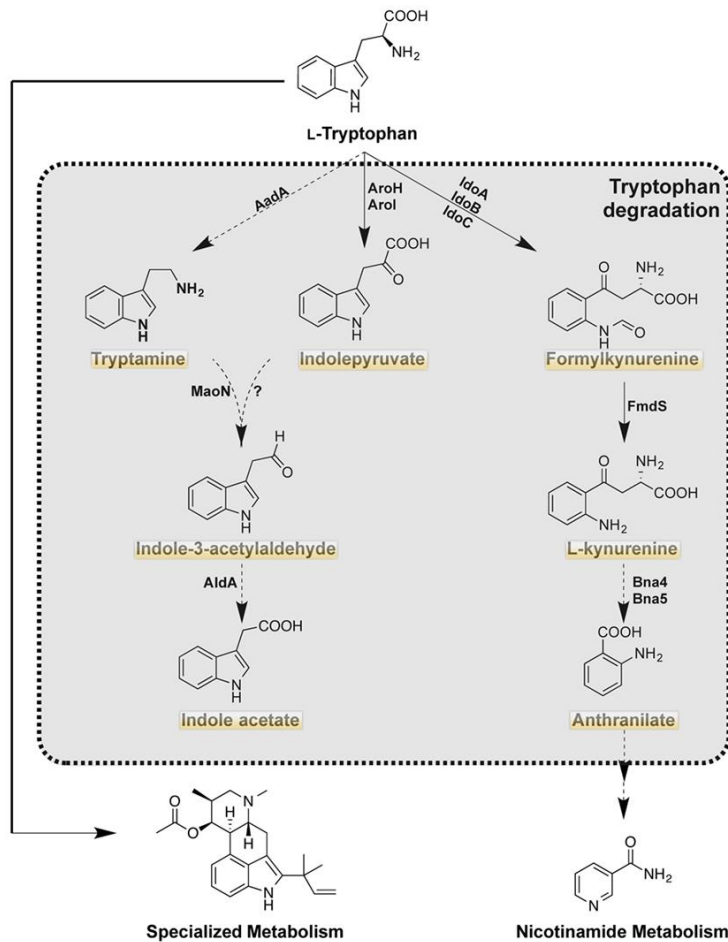
Genetic adaptation



Impaired host resistance



# Aspergillus metabolism



Immune hyperactivity



Metabolic switch



\*Fungal metabolic alterations



Impaired host tolerance

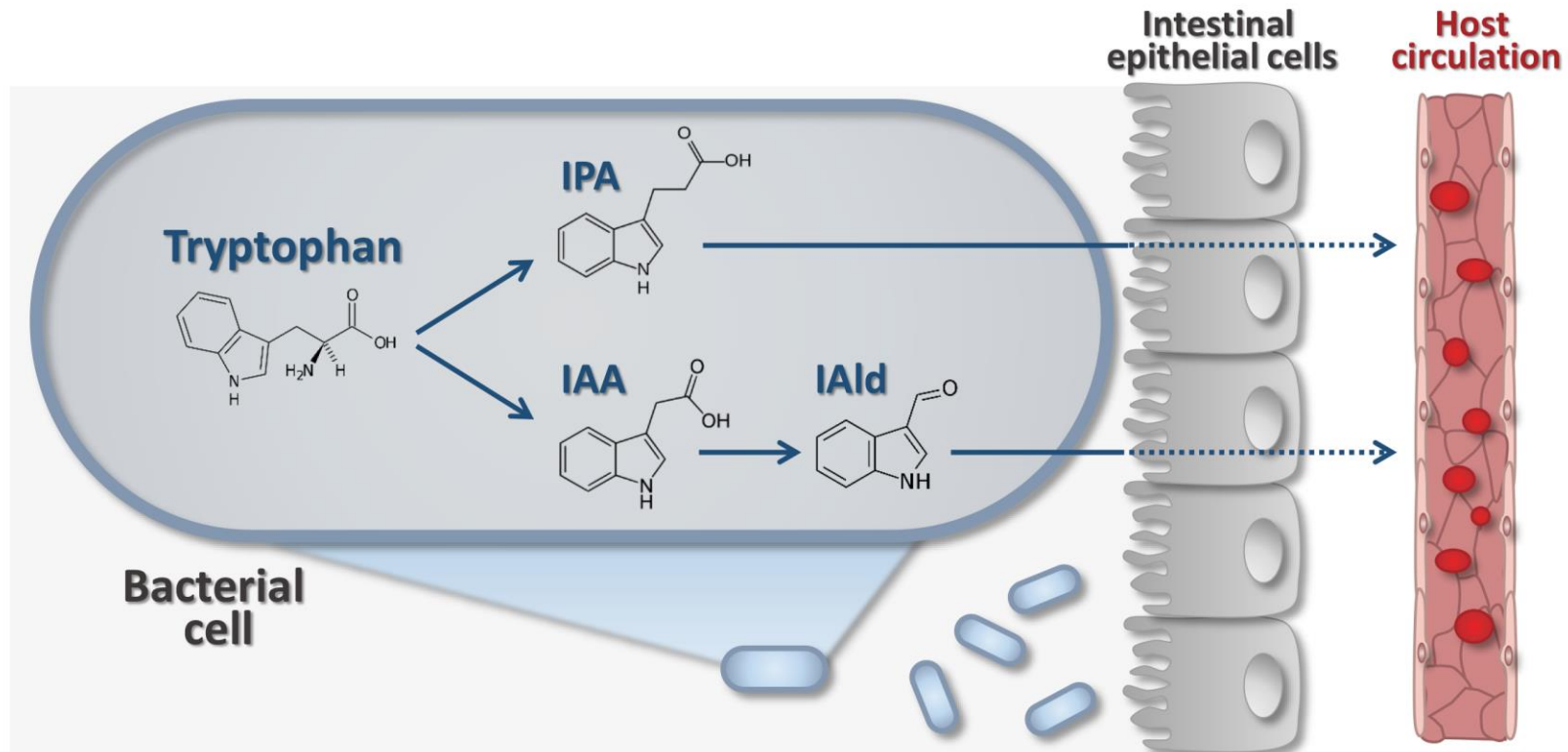
*\*125 Growth substrate of Aspergillus fumigatus alters spore toxin profile ensuing virulence in a murine model of invasive aspergillosis*

T Choera\*, A Vang, P Wiemann, NP Keller



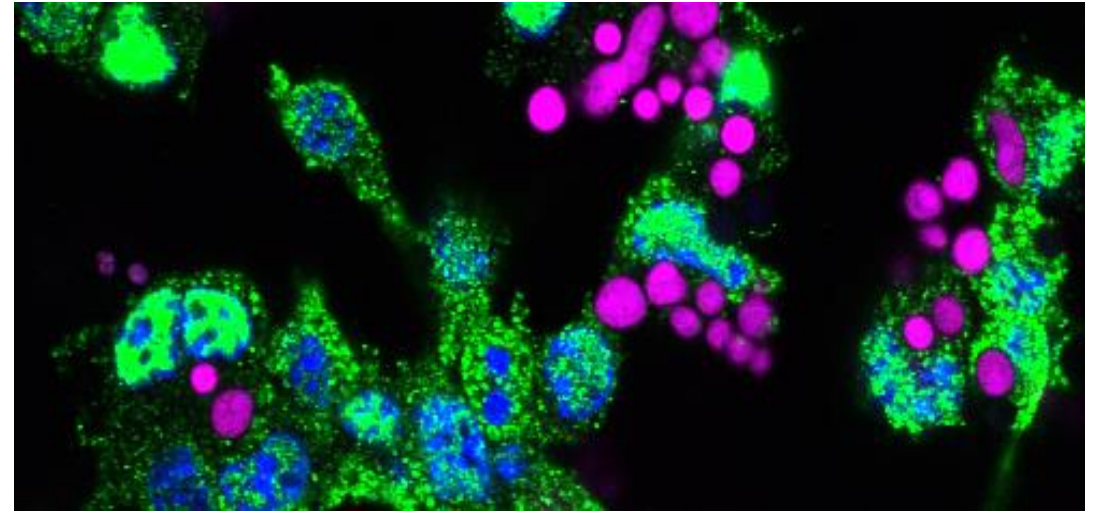


# Aspergillus – microbiome/postbiotic interaction

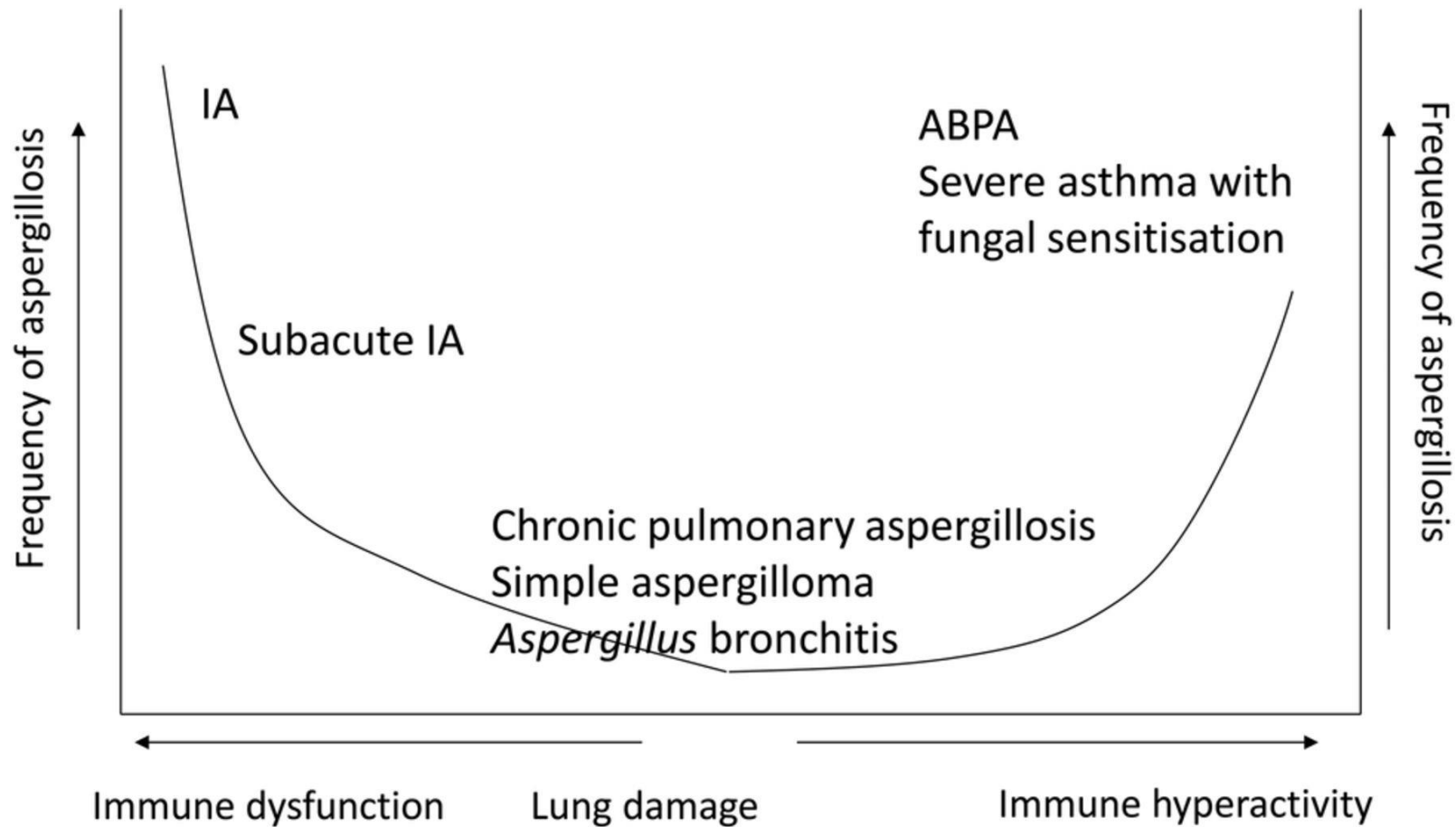


# Immunology

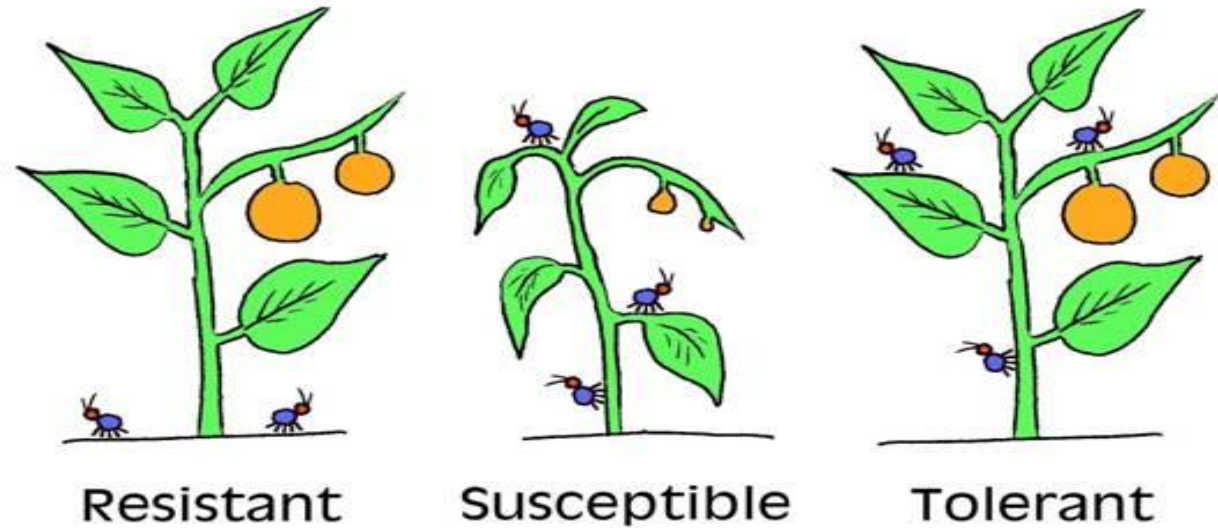
This biochemical versatility of *A. fumigatus* contributes to its role as the predominant fungal pathogen of immunocompromised patients.



# Immunology: dysfunction and hyperactivity

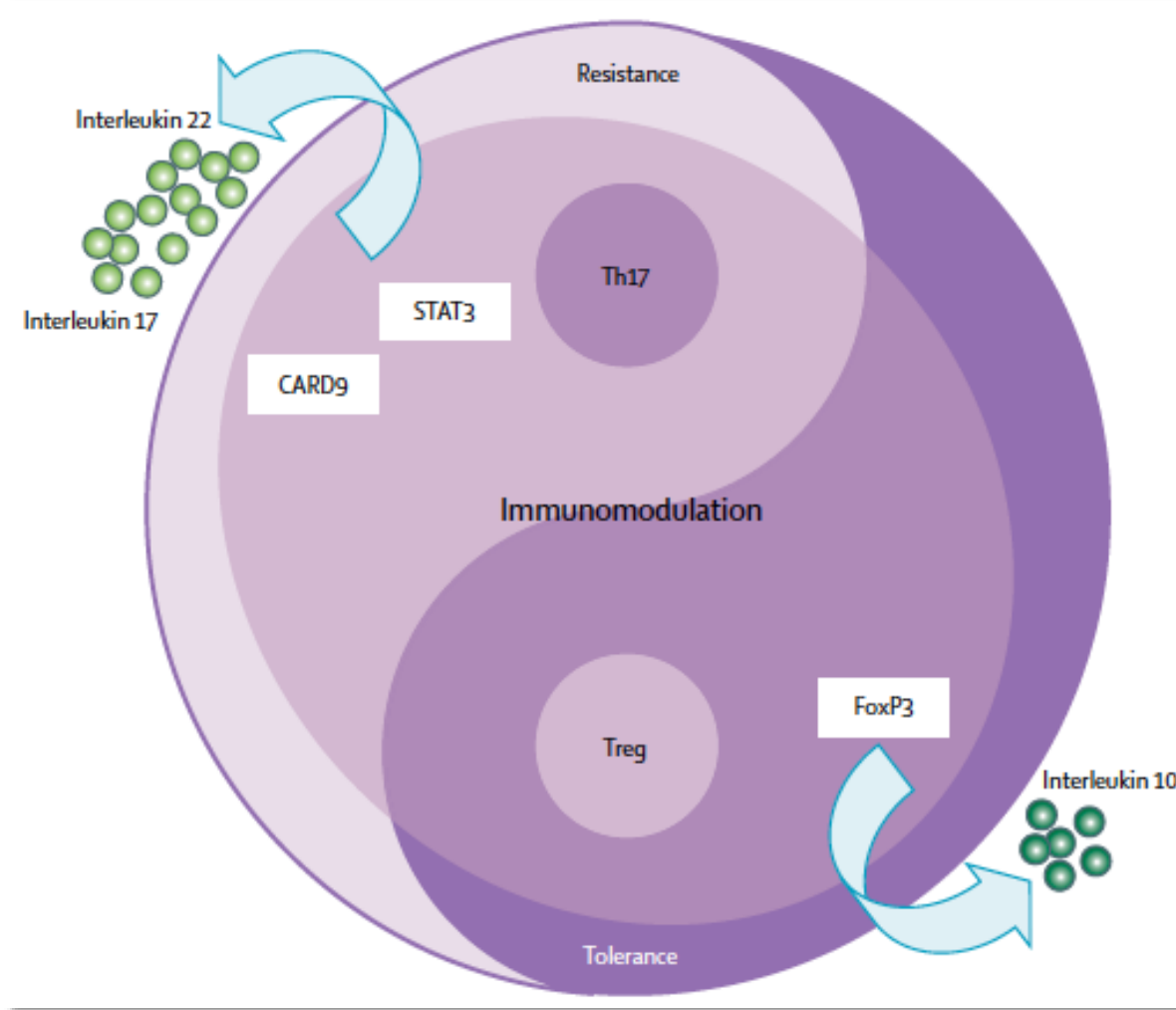


# The *victim* phenotype



- **Resistance** is a way of minimizing the **number** of successful **enemy attacks**
- **Tolerance** is a way of minimizing the **fitness impact** of these attacks.

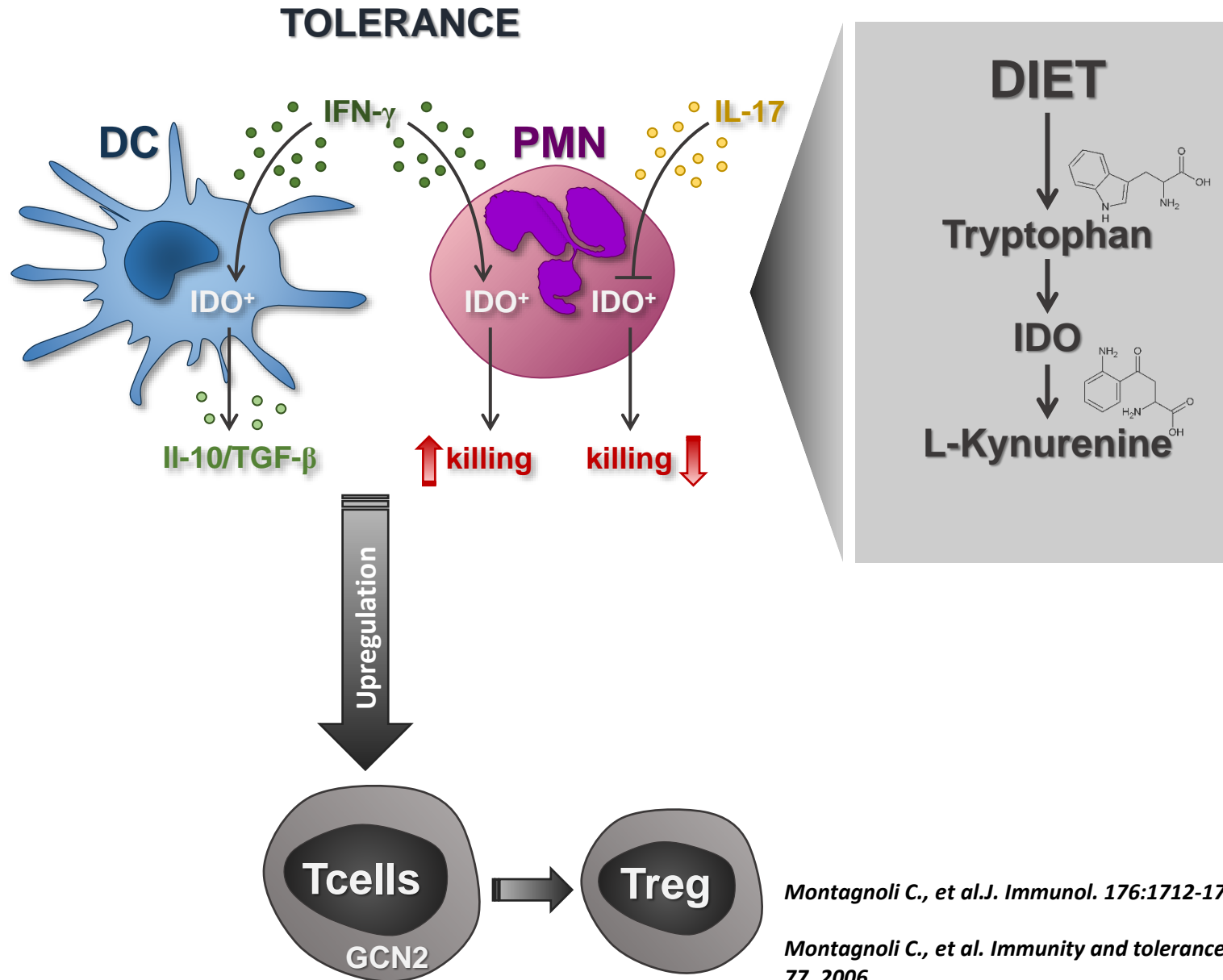
# Anti-*Aspergillus* Defensive Strategies : the ying and yang



Science 29 June 2007



# Anti-*Aspergillus* Defensive Strategies : the ying and yang

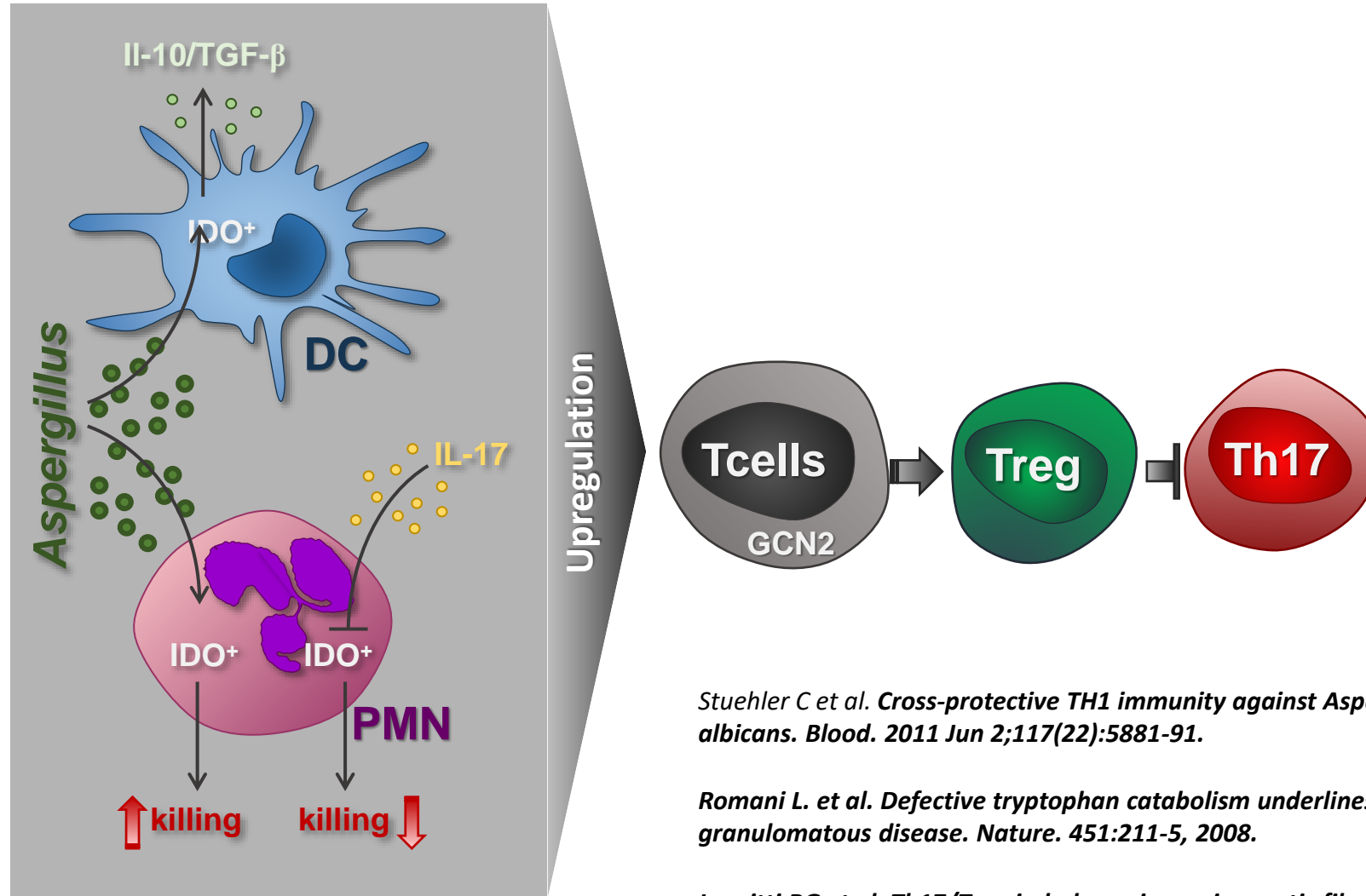


Montagnoli C., et al. *J. Immunol.* 176:1712-1723, 2006.

Montagnoli C., et al. *Immunity and tolerance to Aspergillus fumigatus.* Novartis Foundation Symposium 277, 2006.



# Anti-*Aspergillus* Defensive Strategies : the ying and yang



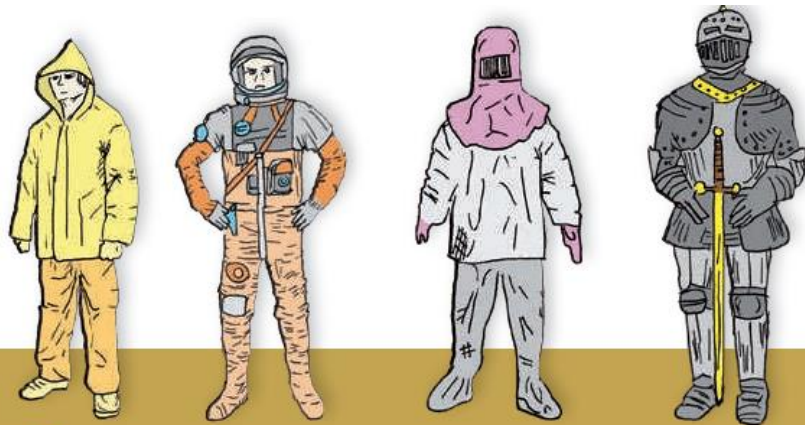
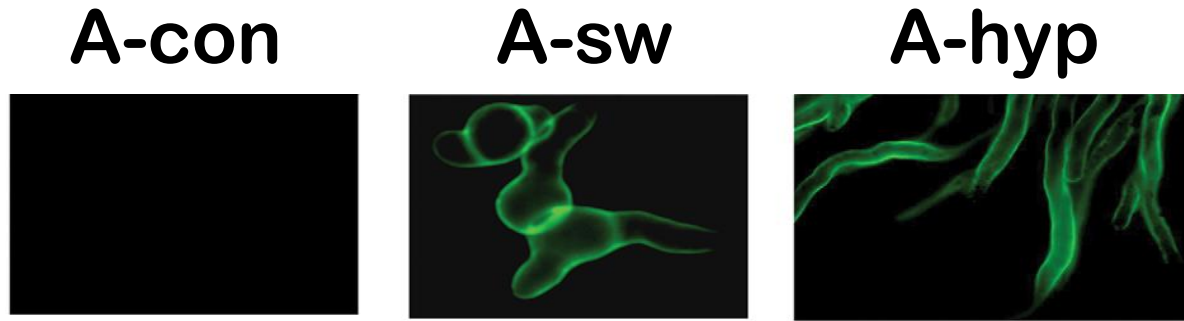
Stuehler C et al. Cross-protective TH1 immunity against *Aspergillus fumigatus* and *Candida albicans*. *Blood*. 2011 Jun 2;117(22):5881-91.

Romani L. et al. Defective tryptophan catabolism underlines inflammation in mouse chronic granulomatous disease. *Nature*. 451:211-5, 2008.

Iannitti RG et al. Th17/Treg imbalance in murine cystic fibrosis is linked to indoleamine 2,3-dioxygenase deficiency but corrected by kynurenines. *Am J Respir Crit Care Med*. 2013 Mar 15;187(6):609-20.



# The importance of being a 'particulate'



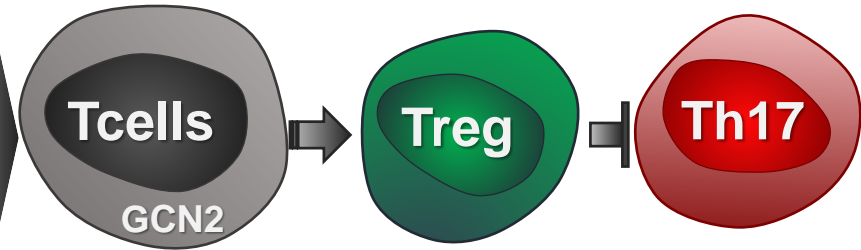
INNATE IMMUNITY

A protective fungal spore coat

*Nature Reviews Microbiology* 7, 690 (October 2009)

- Commensal and environmental fungi are rich in  $\beta$  glucan on their cell wall
- *Aspergillus fumigatus* has the ability to display the  $\beta$  glucan cell wall layer while internalized in the lung

Upregulation

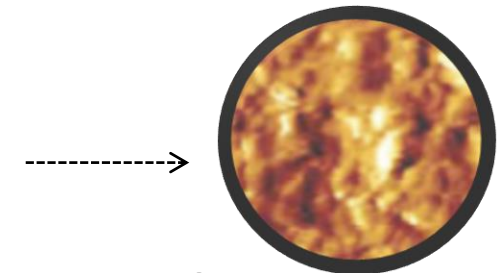


1uM

3uM



CON

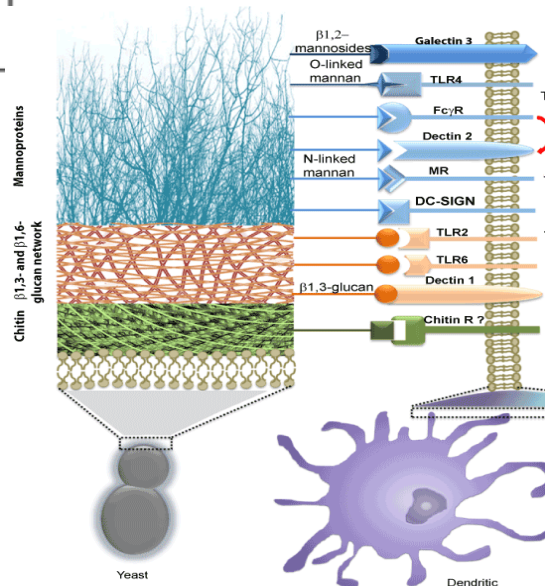
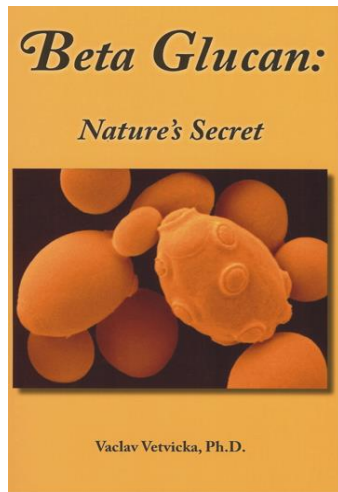
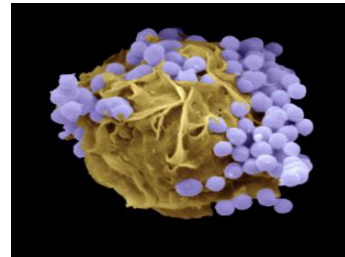
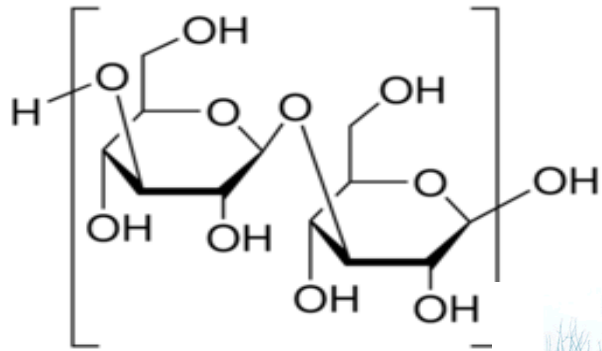


SW



# The importance of being a 'particulate'

WGP

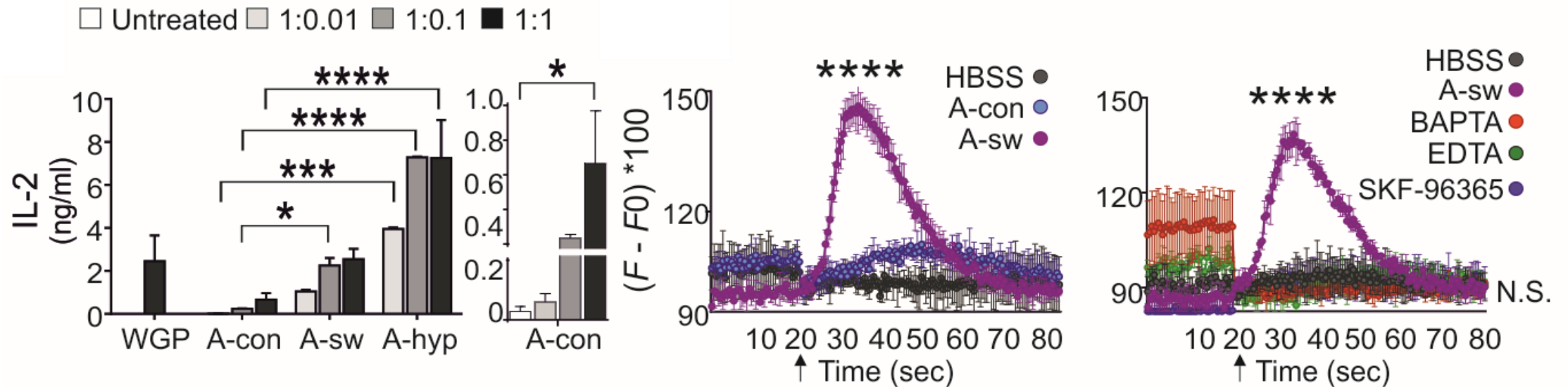


$\beta$ -glucans

|         |             | kDa | $\mu$ m |
|---------|-------------|-----|---------|
| Zymosan | Particulate | –   | 3       |
| Curdlan | Aggregate   | –   | 3       |
| PGG     | Soluble     | –   | -       |
| WGP     | Particulate | –   | 3       |

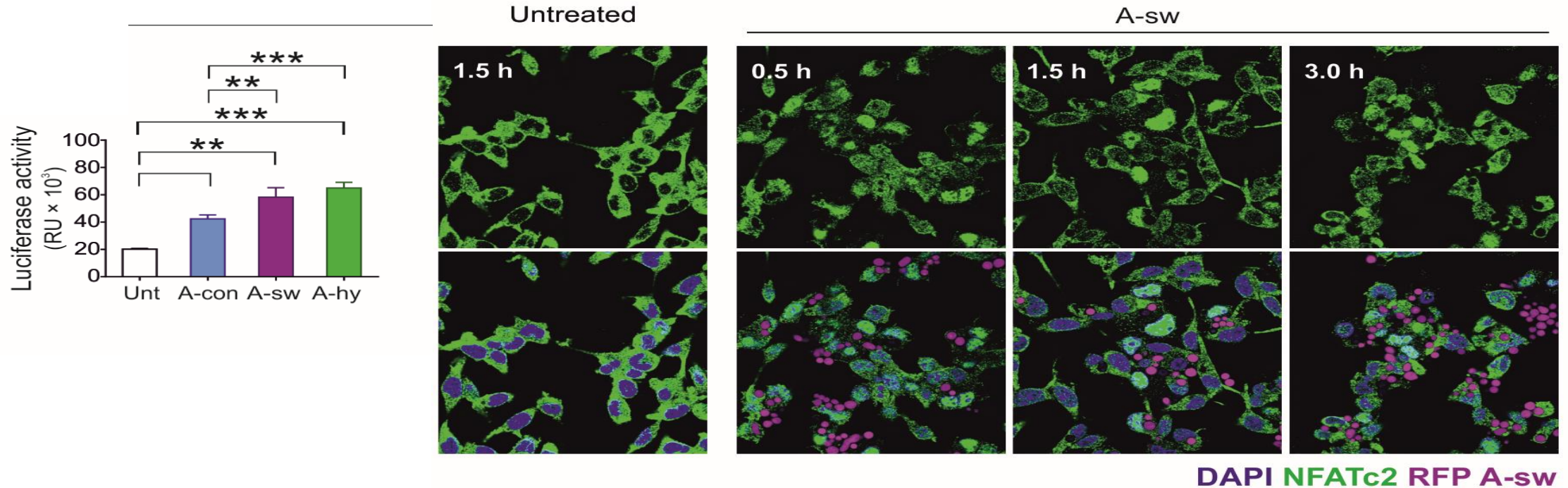
Rogers, N. C., Slack, E. C., 2005. *Immunity*, 22, 507-17.  
 Sancho, D. & Reis E Sousa, C. 2012. *Annu Rev Immunol*, 30, 491-529.

# $\beta$ glucan particles and *Aspergillus* triggers IL2 production in DCs through the $-Ca^{2+}$ -Calcineurin-NFAT Signaling Pathway



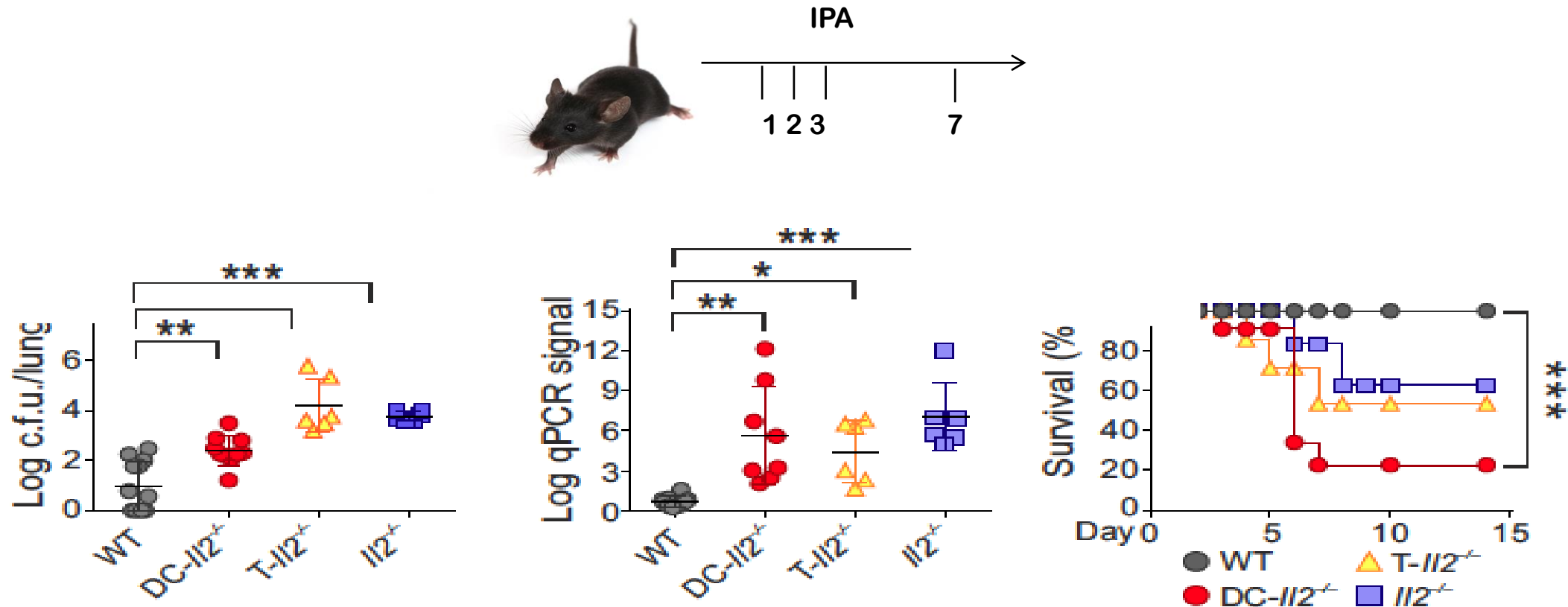
Zelante T, Wong AY, Ping TJ, Chen J, Sumatoh HR, Viganò E, Hong Bing Y, Lee B, Zolezzi F, Fric J, Newell EW, Mortellaro A, Poidinger M, Puccetti P, Ricciardi-Castagnoli P. CD103(+) Dendritic Cells Control Th17 Cell Function in the Lung. *Cell Rep.* 2015 Sep 22;12(11):1789-801.

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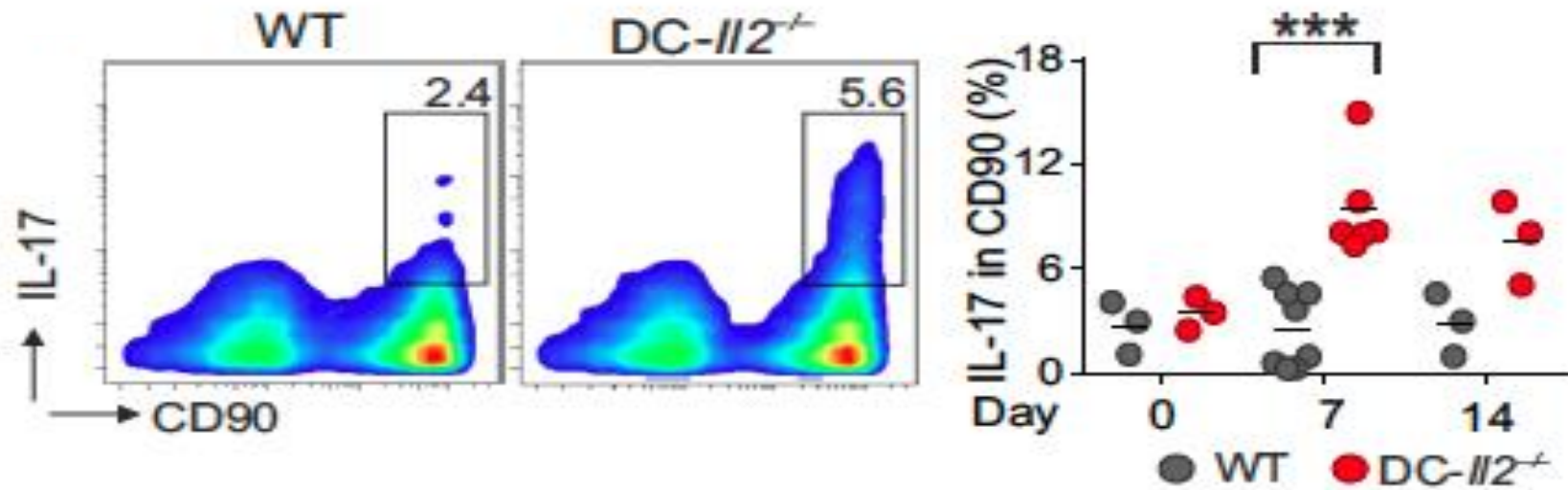
Zelante T, Wong AY, Ping TJ, Chen J, Sumatoh HR, Viganò E, Hong Bing Y, Lee B, Zolezzi F, Fric J, Newell EW, Mortellaro A, Poidinger M, Puccetti P, Ricciardi-Castagnoli P. CD103(+) Dendritic Cells Control Th17 Cell Function in the Lung. *Cell Rep.* 2015 Sep 22;12(11):1789-801.

# A pathogenic Aspergillosis is developed under deficiency of IL-2 in DCs



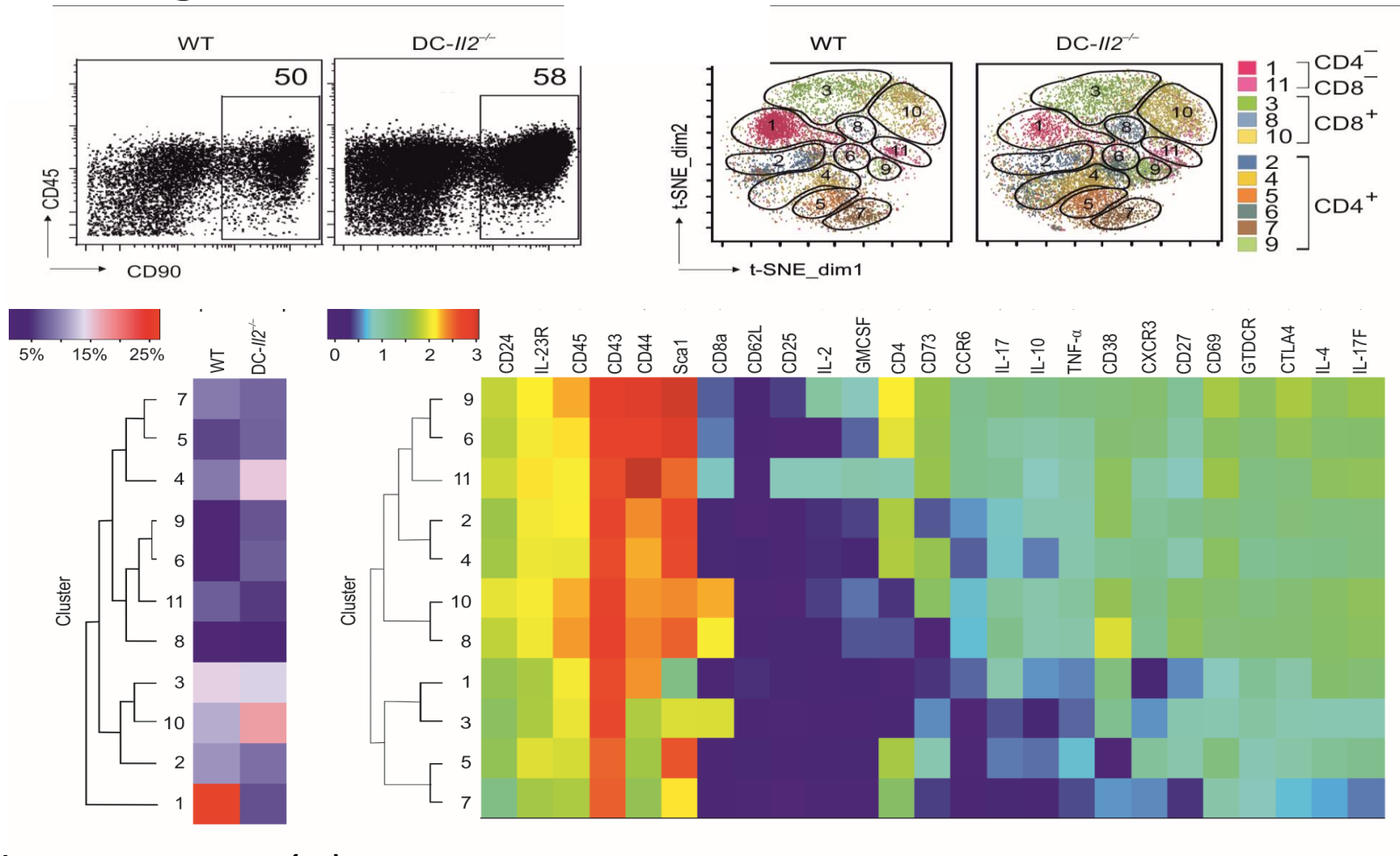
Zelante T, Cell Rep. 2015 Sep 22;12(11):1789-801.

# A pathogenic Th17 is developed under deficiency of IL2 in DC



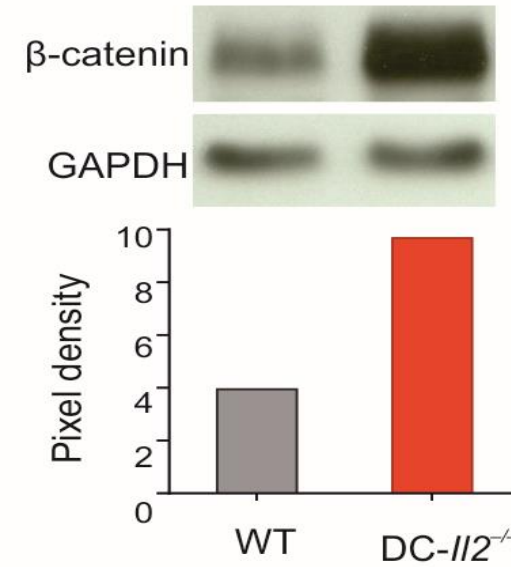
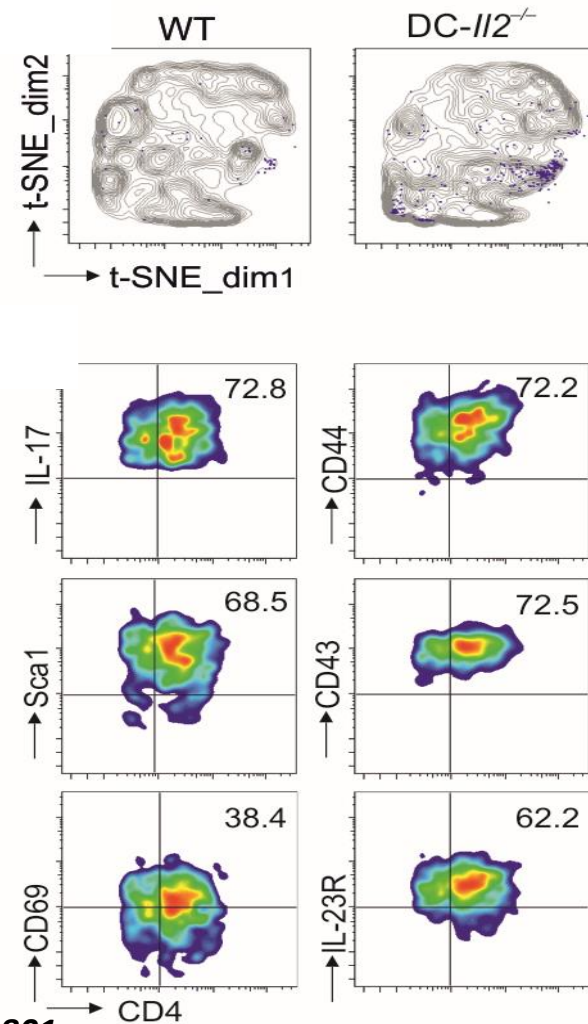
Zelante T, Cell Rep. 2015 Sep 22;12(11):1789-801.

# A pathogenic Th17 is developed under deficiency of IL2 in DC

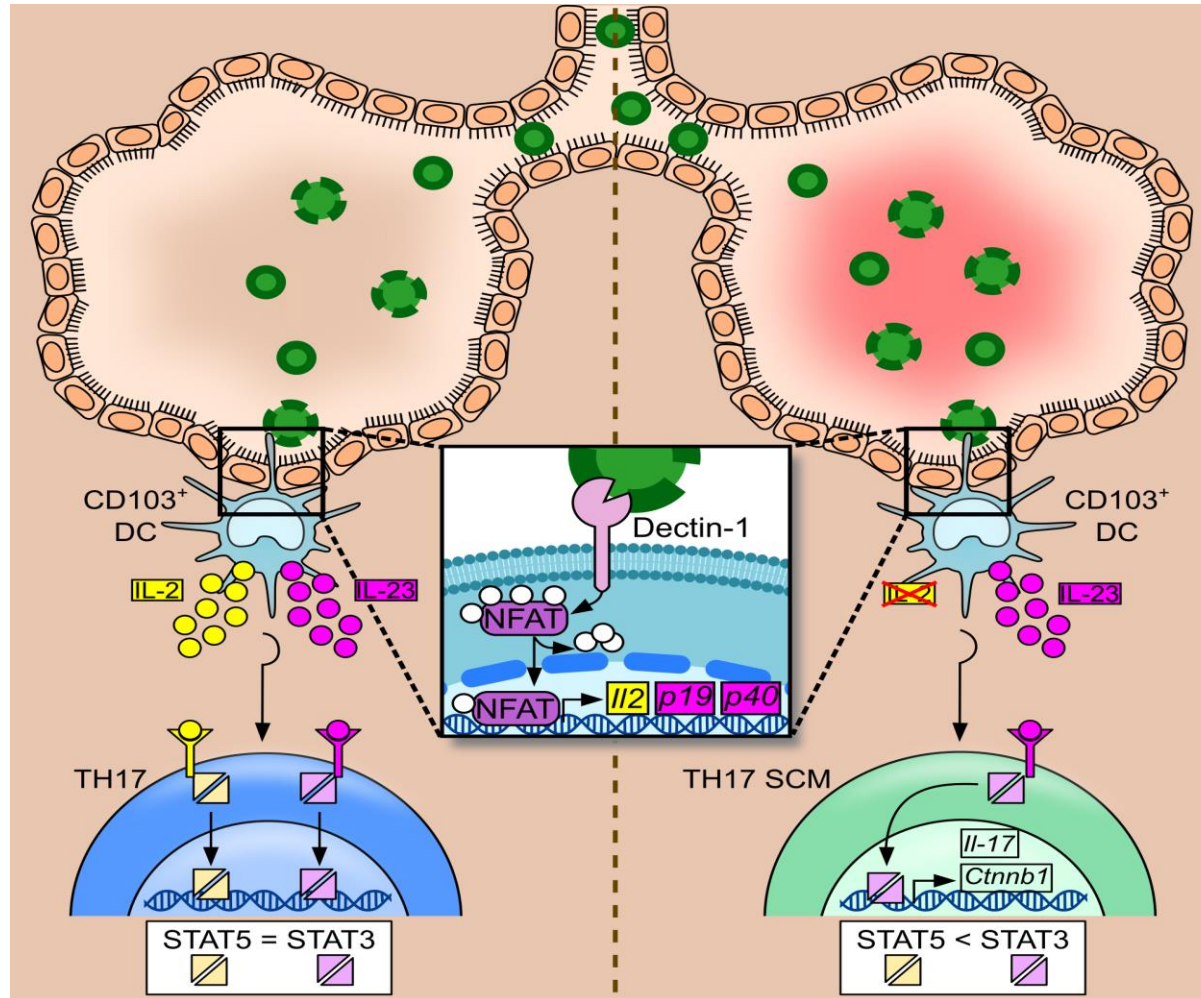


Zelante T, Cell Rep. 2015 Sep 22;12(11):1789-801.

# Th17 stemness regulation by IL-2 was defined by using CyTOF

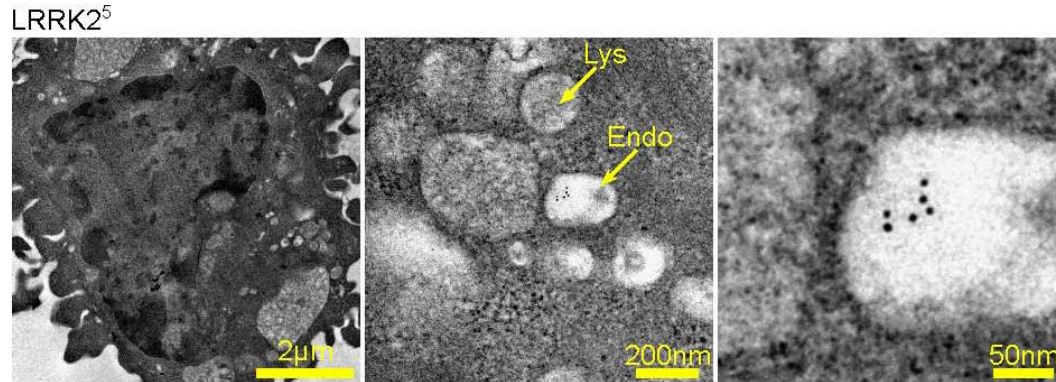
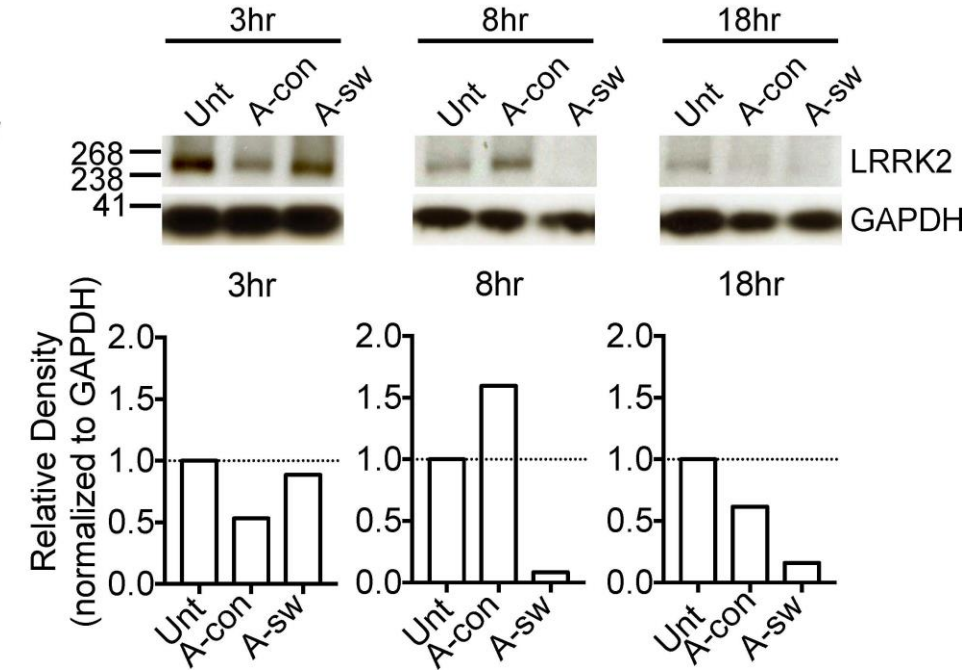
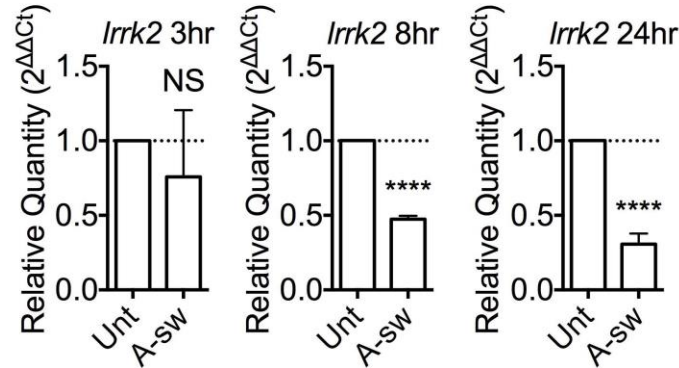
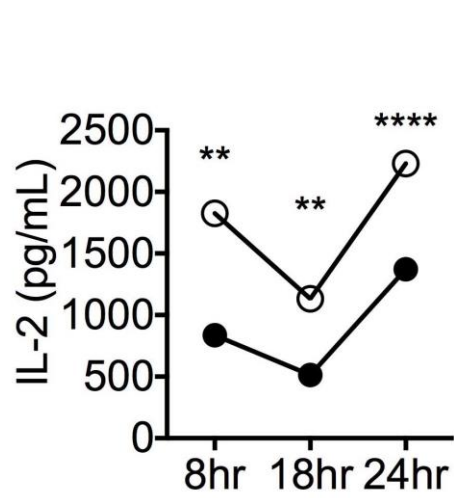


# Th17 stemness regulation by fungal particulates





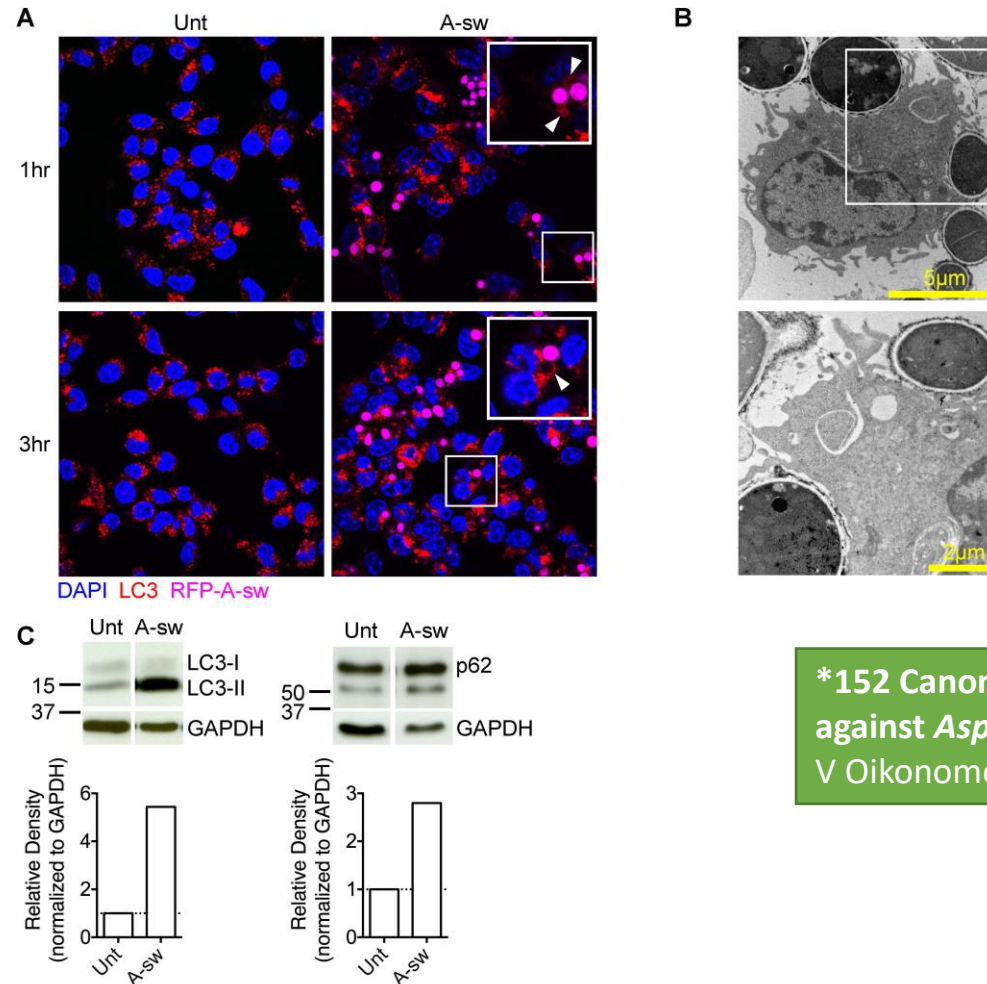
# LRRK2 controls the Ca<sup>2+</sup>/NFAT/IL-2 pathway in DCs during *Aspergillus* non-canonical



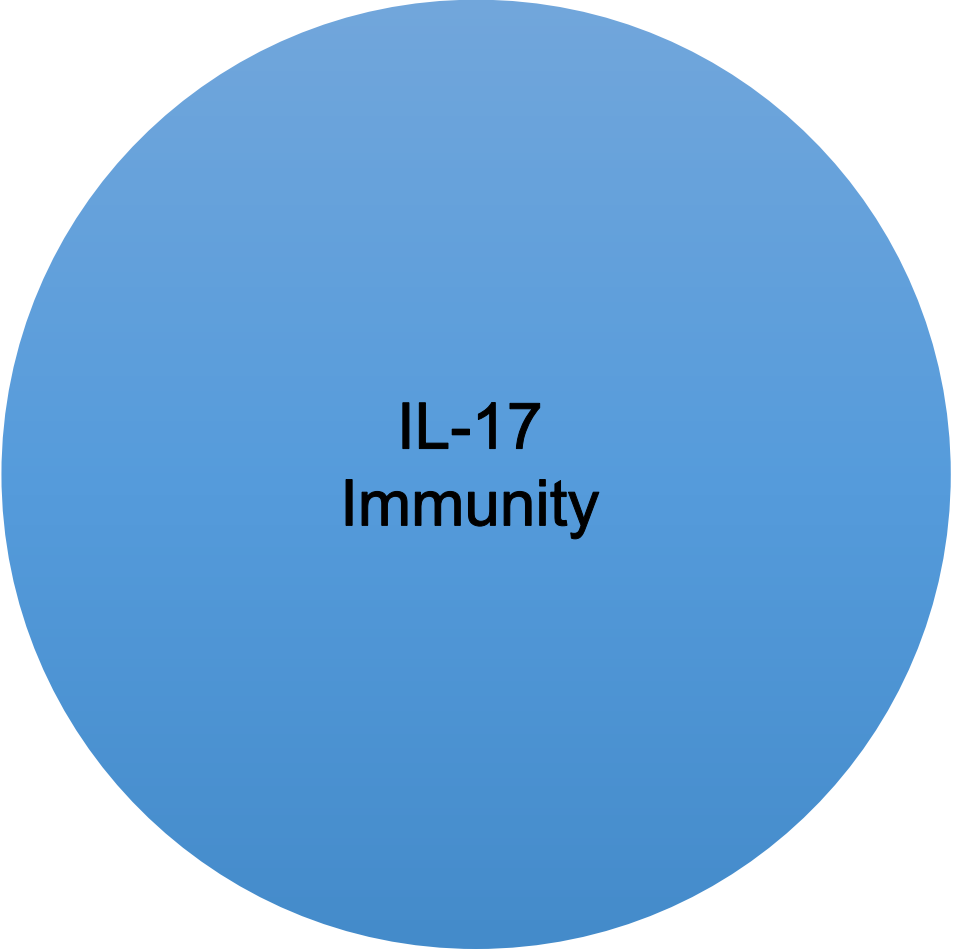
SiGN



# LRRK2 controls the Ca<sup>2+</sup>/NFAT/IL-2 pathway in DCs during *Aspergillus* non-canonical

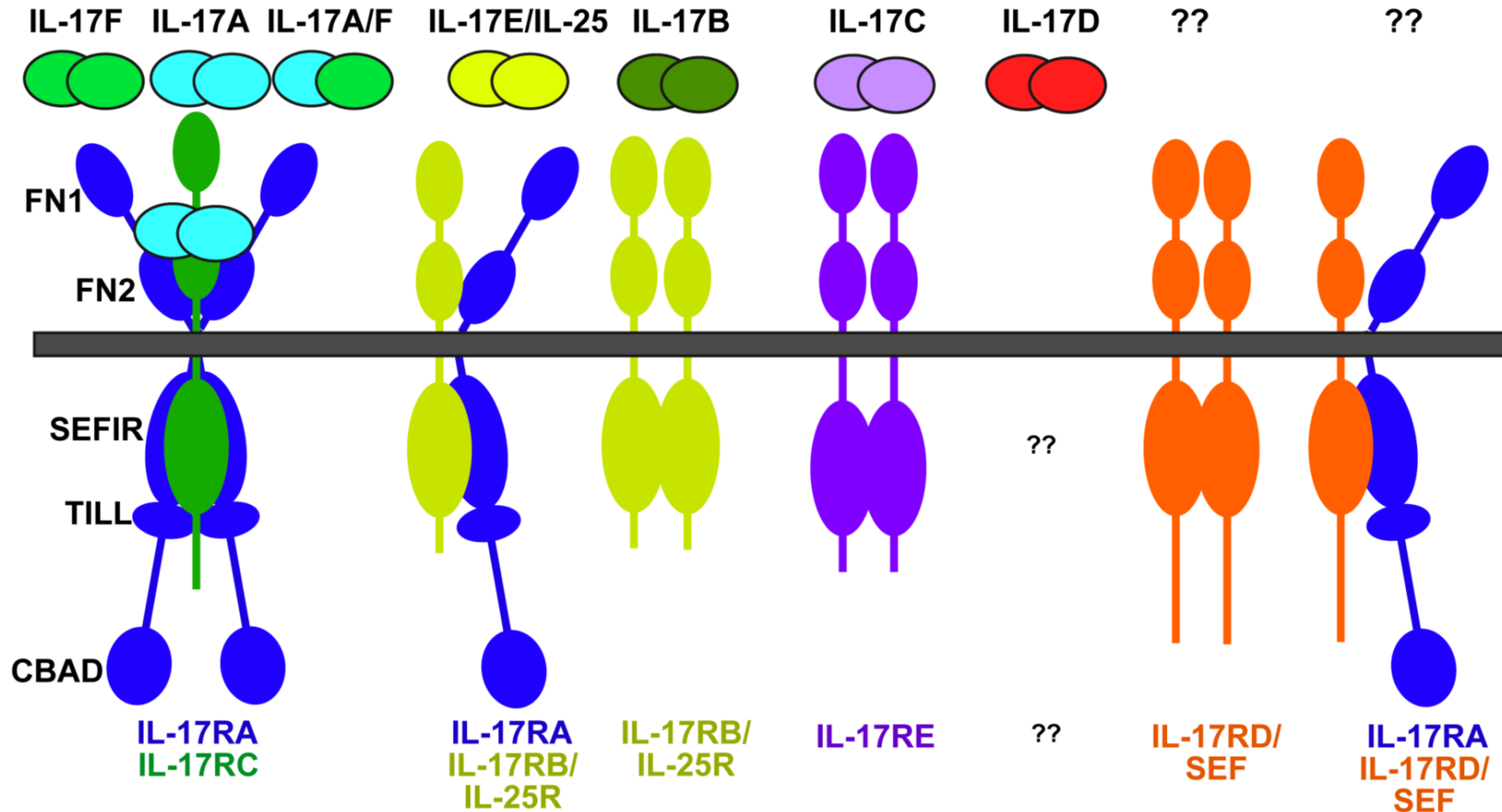


**\*152 Canonical versus noncanonical autophagy in the fight against *Aspergillus fumigatus* infection**  
V Oikonomou



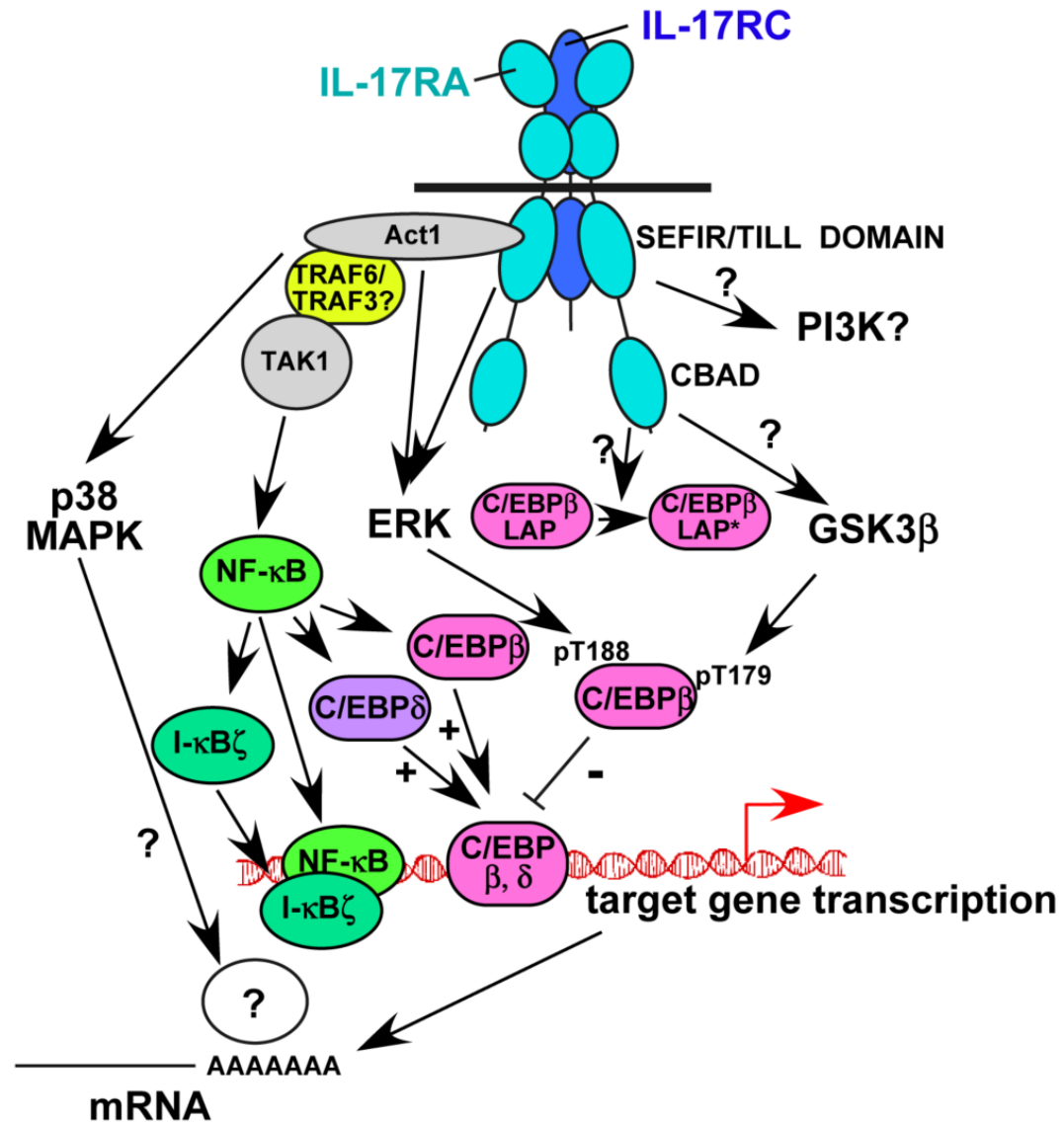
**IL-17  
Immunity**

# IL-17R family members



Structure and signalling in the IL-17 receptor family

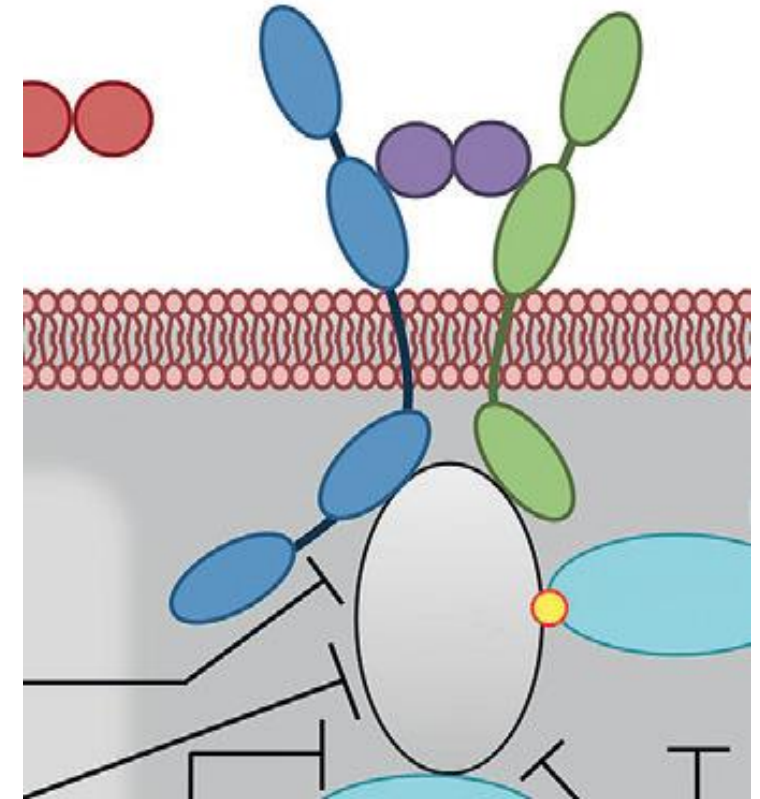
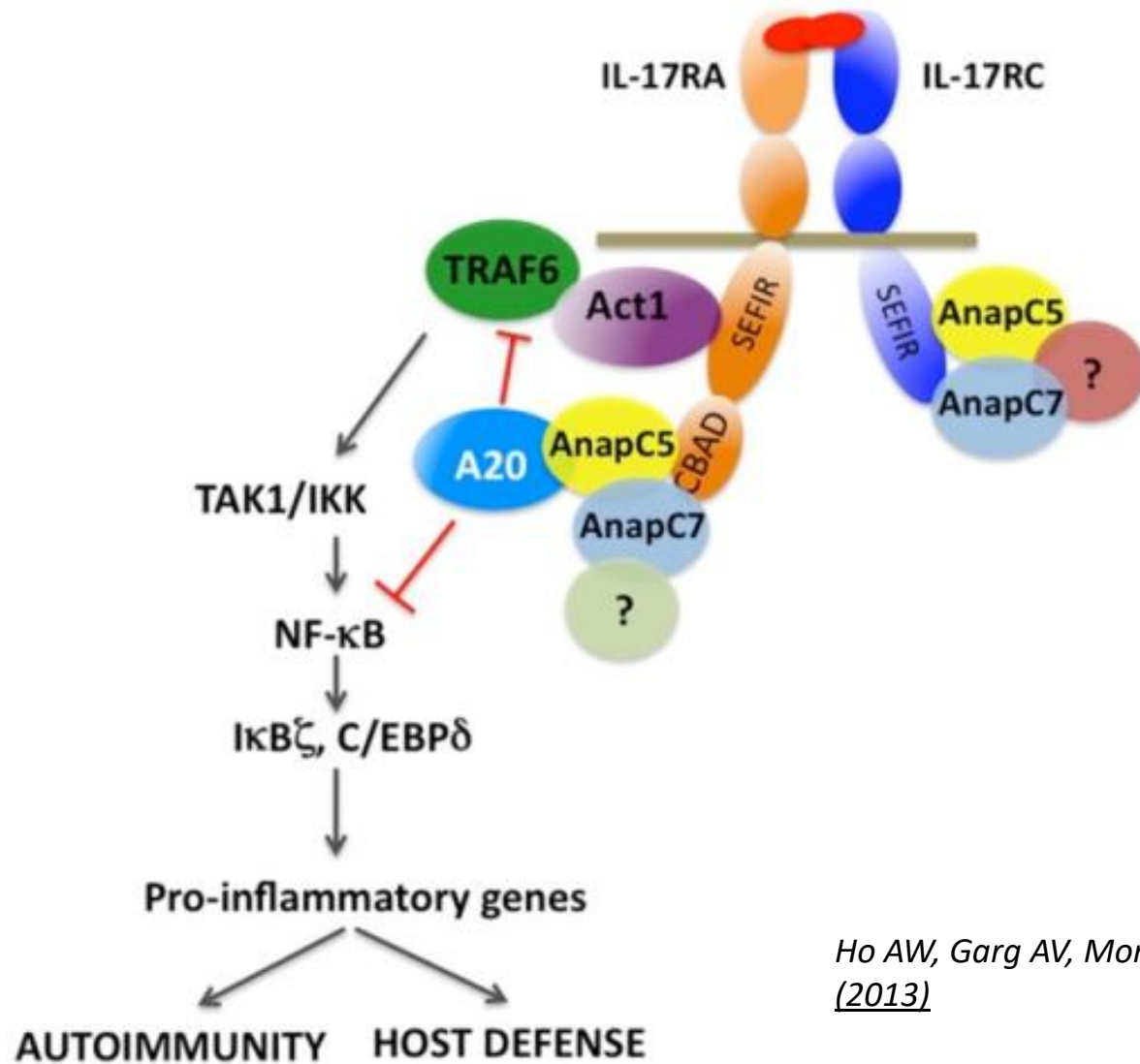
Article · Literature Review · September 2009 DOI: 10.1038/nri2586 ·



Structure and signalling in the IL-17 receptor family

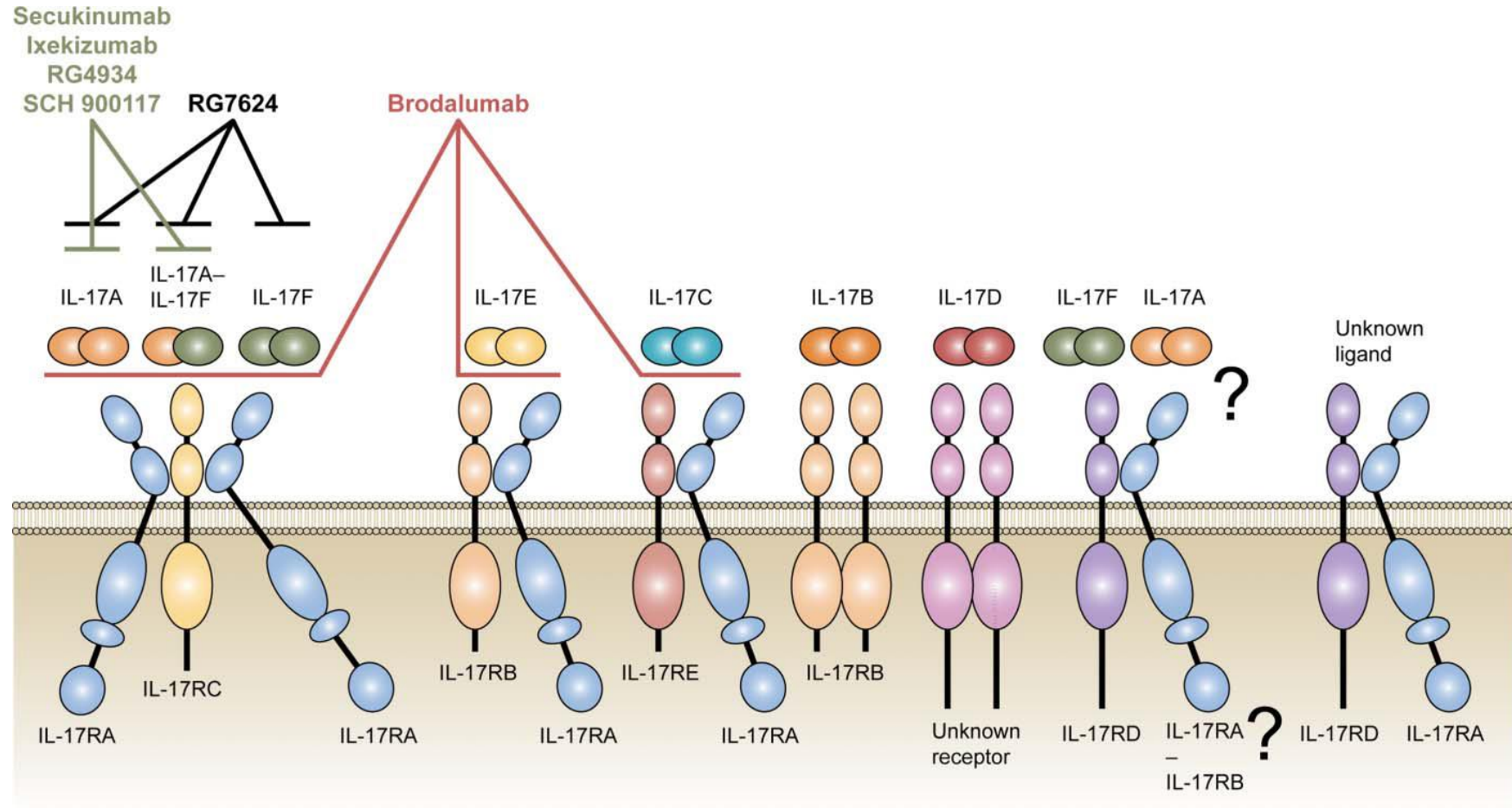
Article · Literature Review · September 2009 DOI: 10.1038/nri2586 ·

# IL-17R PROXIMAL AND DISTAL SIGNALING



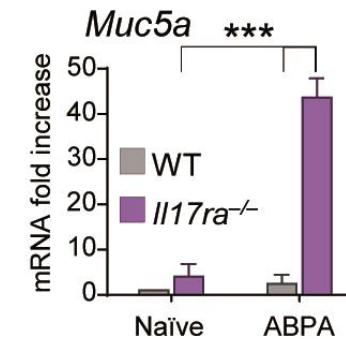
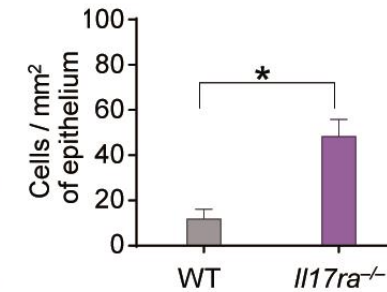
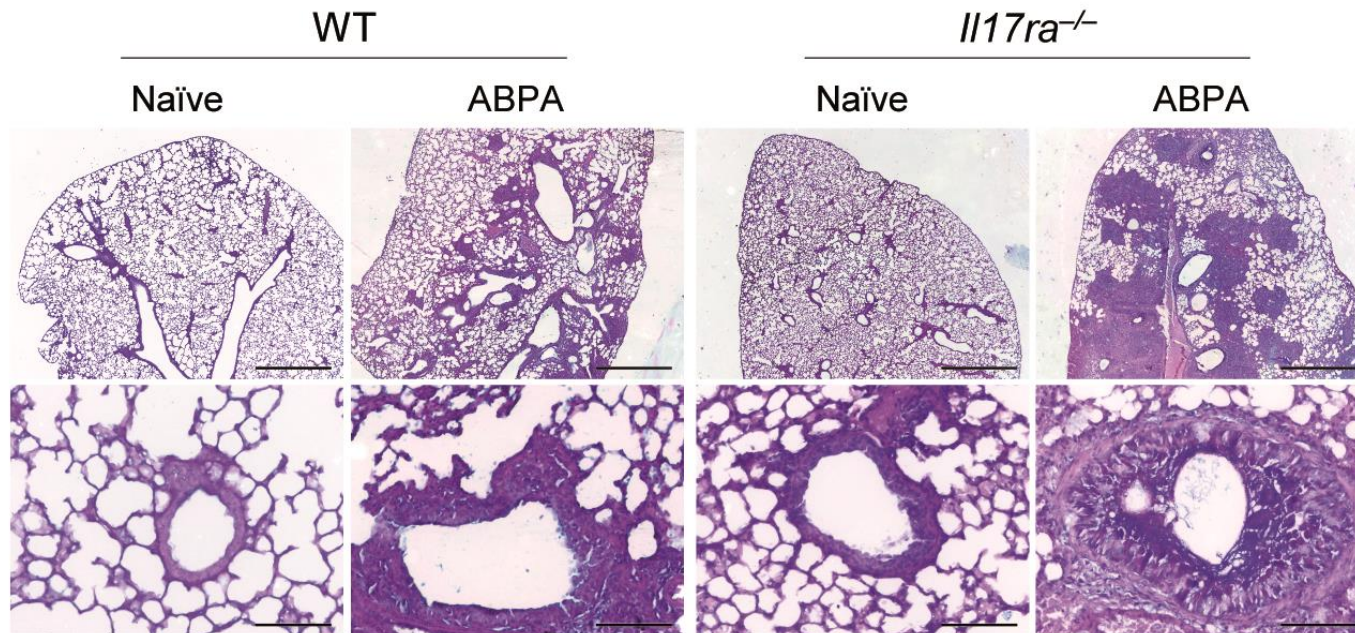
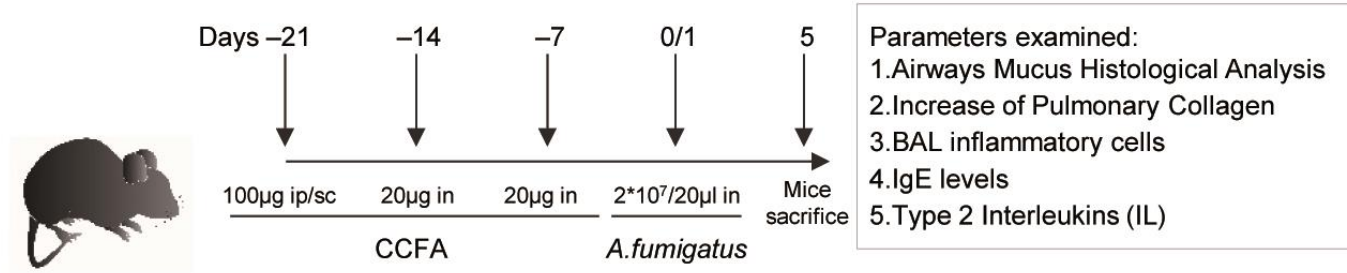
Ho AW, Garg AV, Monin L, Simpson-Abelson MR, Kinner L, Gaffen SL - *PLoS ONE* (2013)

# IL-17R based therapy in autoinflammation



Patel DD, Lee DM, Kolbinger F, Antoni C. *Ann Rheum Dis.* 2013 Apr;72 Suppl 2:ii116-23. doi: 10.1136/annrheumdis-2012-202371. Epub 2012

# Mice lacking IL-17RA are more susceptible to allergic inflammation

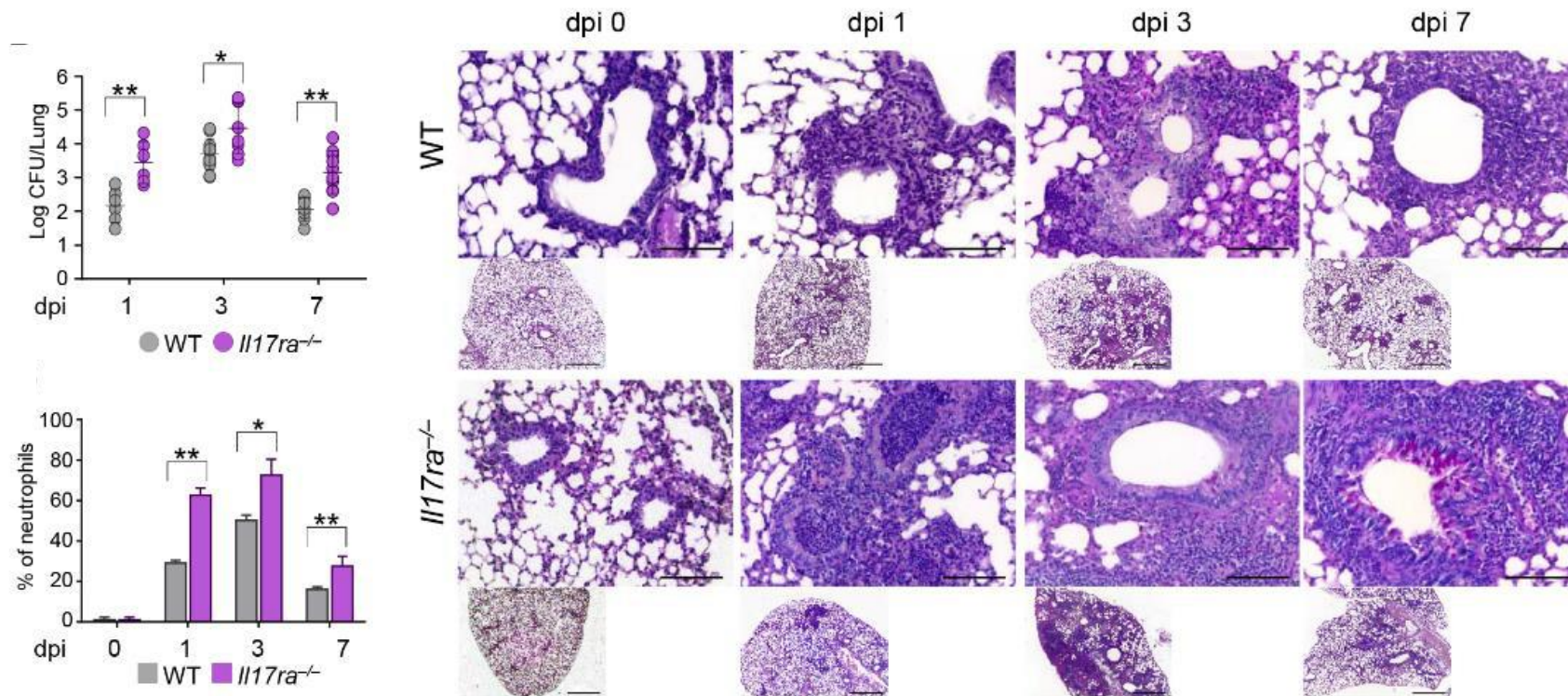
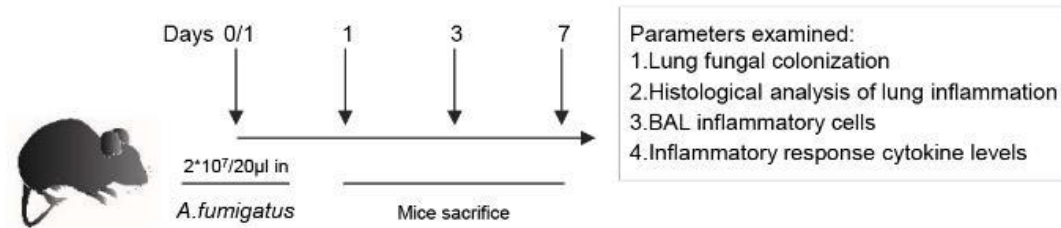


[De Luca A, et al. Cell Rep. 2017 Aug 15;20\(7\):1667-1680](#)





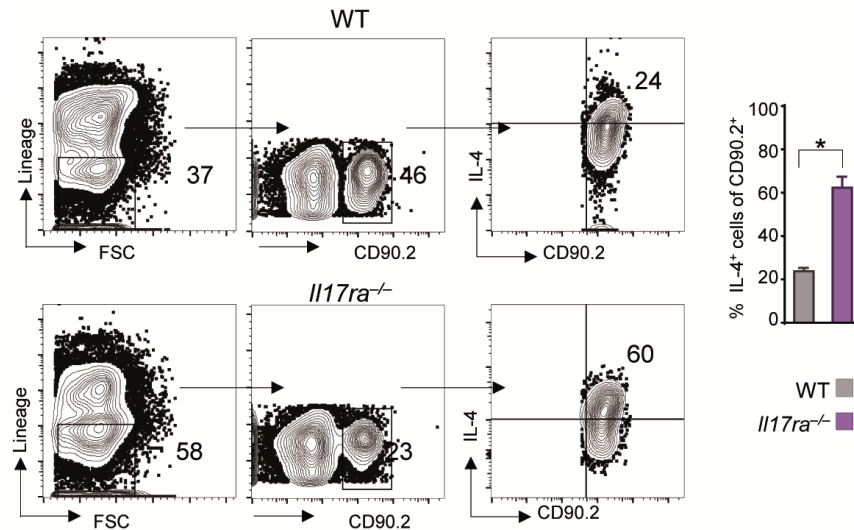
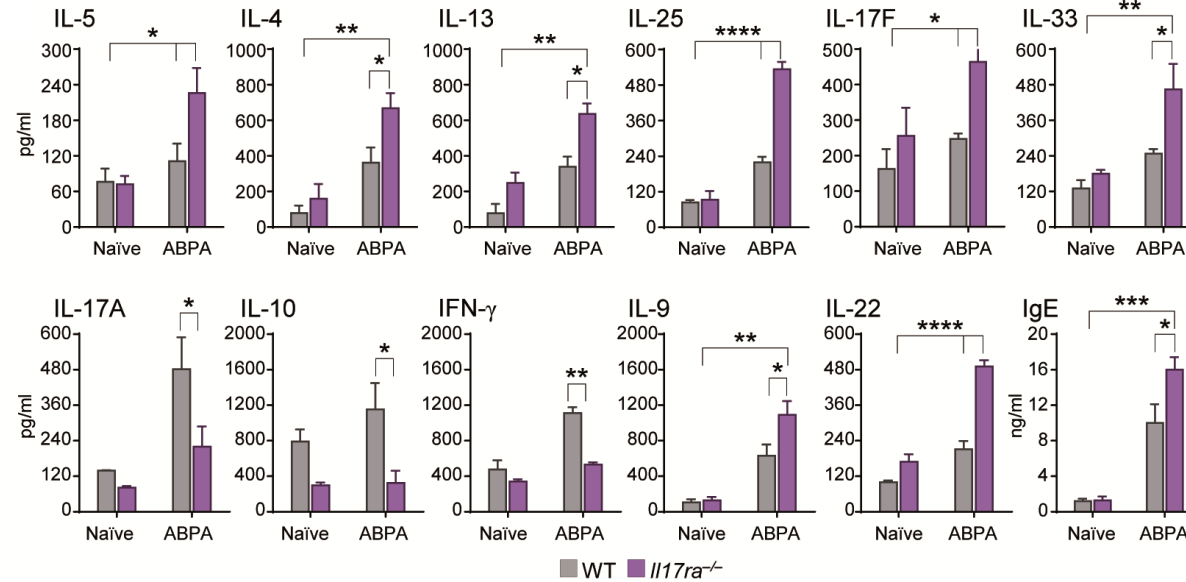
# Mice lacking IL-17RA are more susceptible to infection



[De Luca A, et al. Cell Rep. 2017 Aug 15;20\(7\):1667-1680](#)



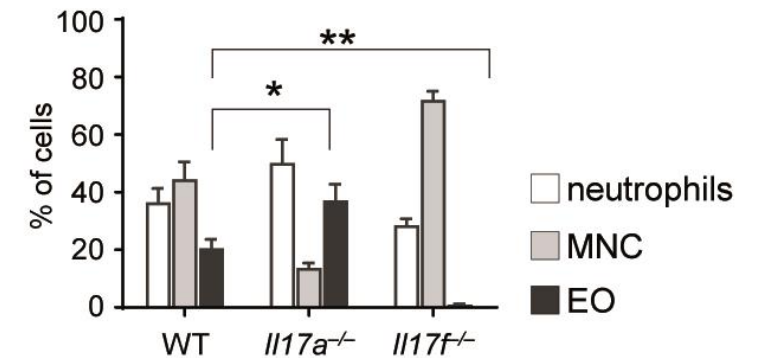
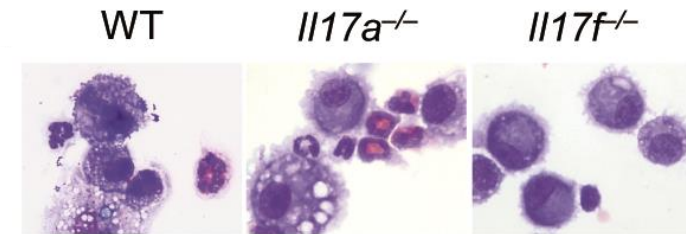
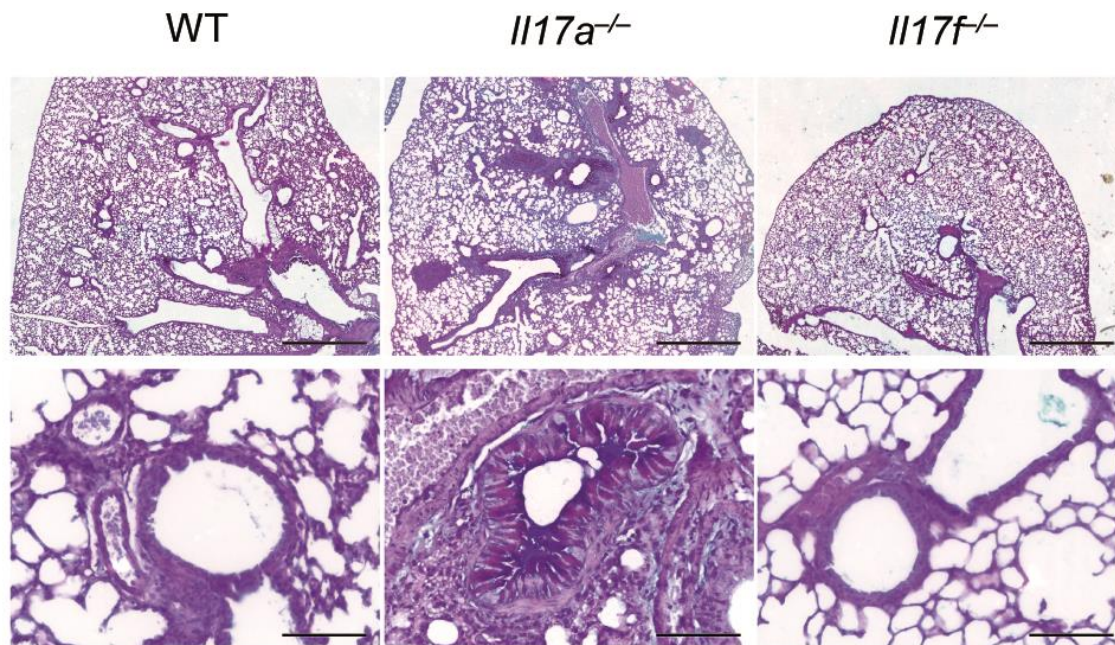
# Mice lacking IL-17RA display type 2 inflammation



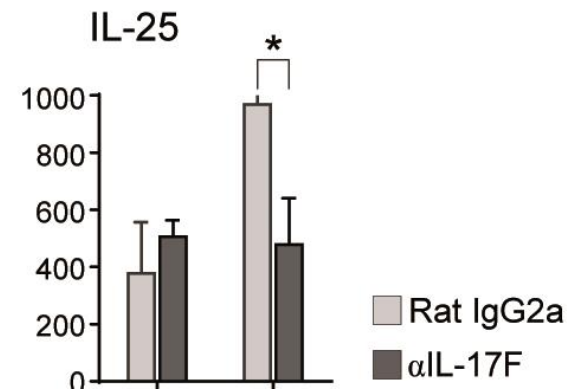
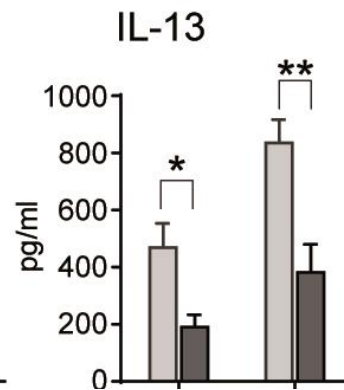
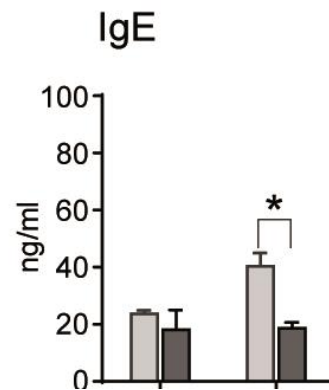
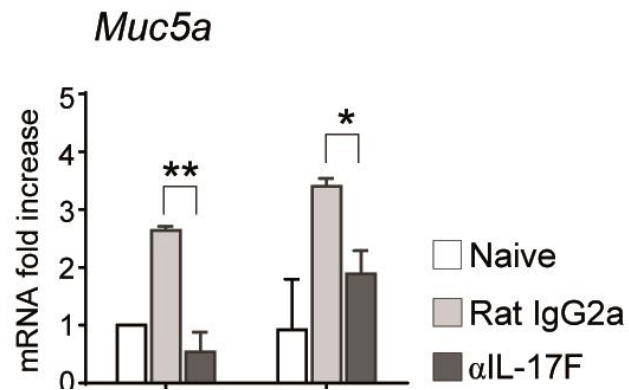
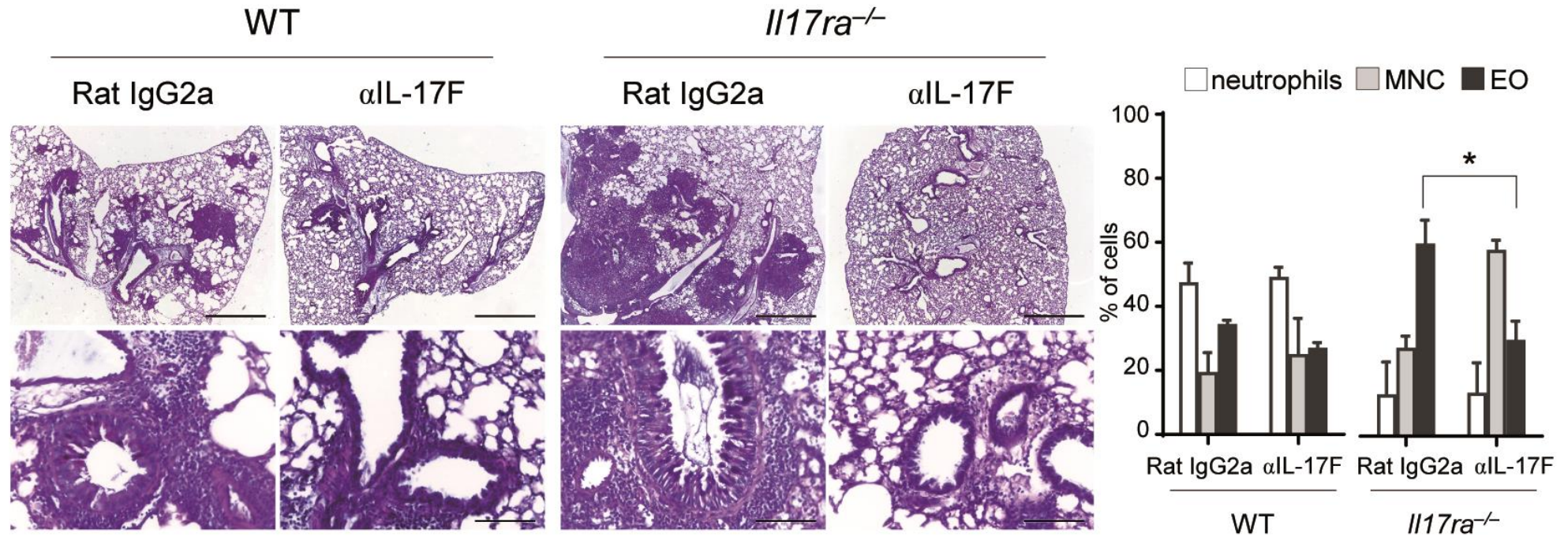
[De Luca A, et al. Cell Rep. 2017 Aug 15;20\(7\):1667-1680](https://doi.org/10.1016/j.celrep.2017.07.038)



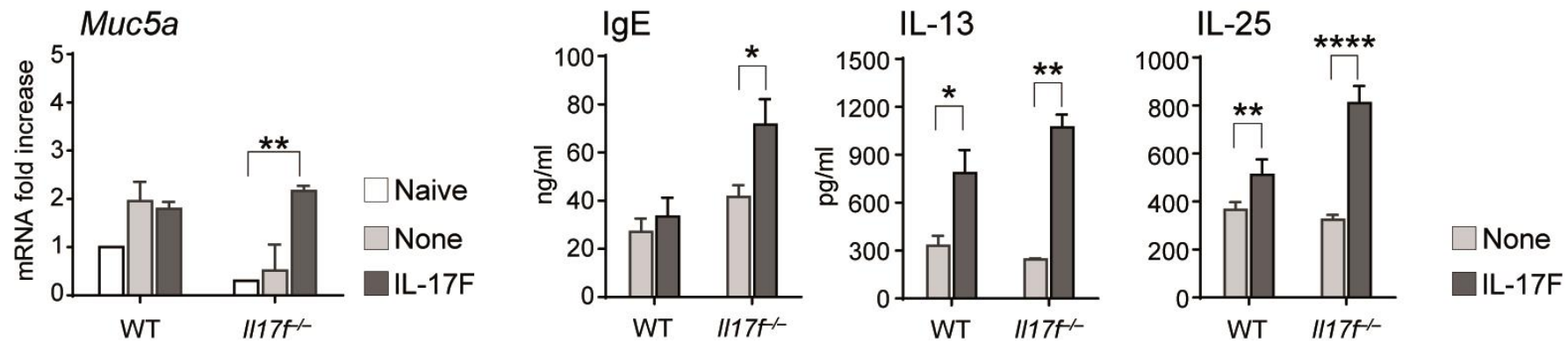
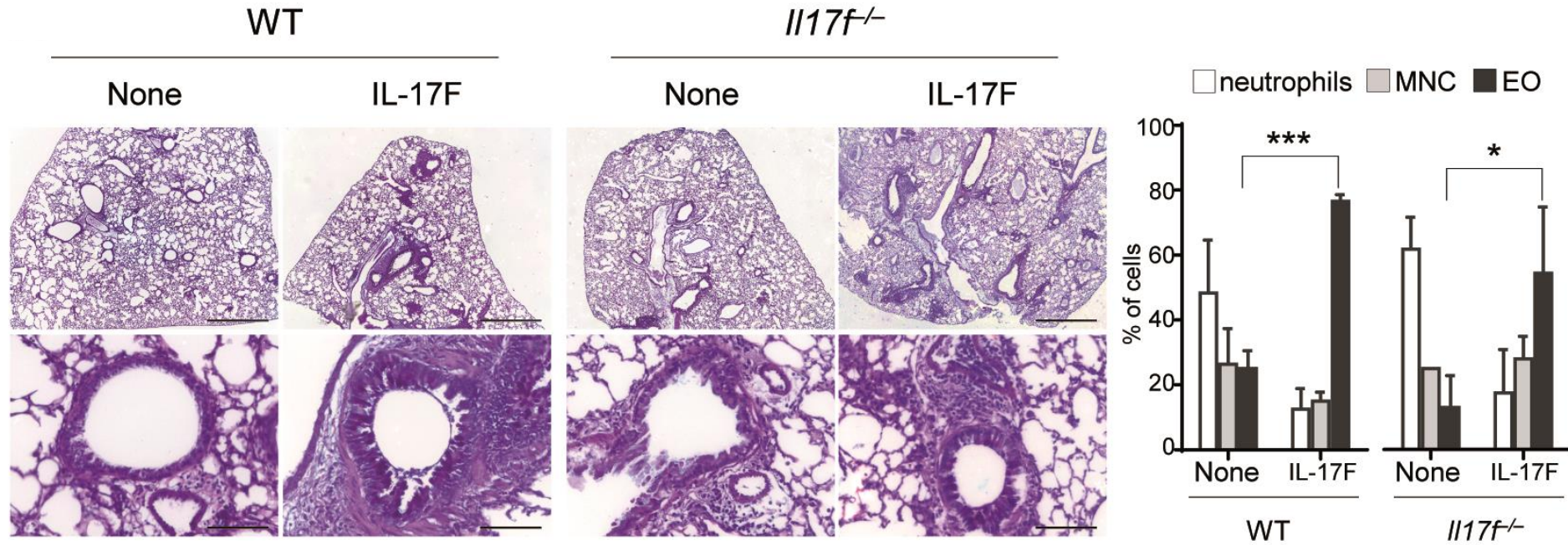
# Mice lacking IL-17A display type 2 inflammation



# Mice lacking IL-17RA treated with $\alpha$ IL-17F become resistant to ABPA

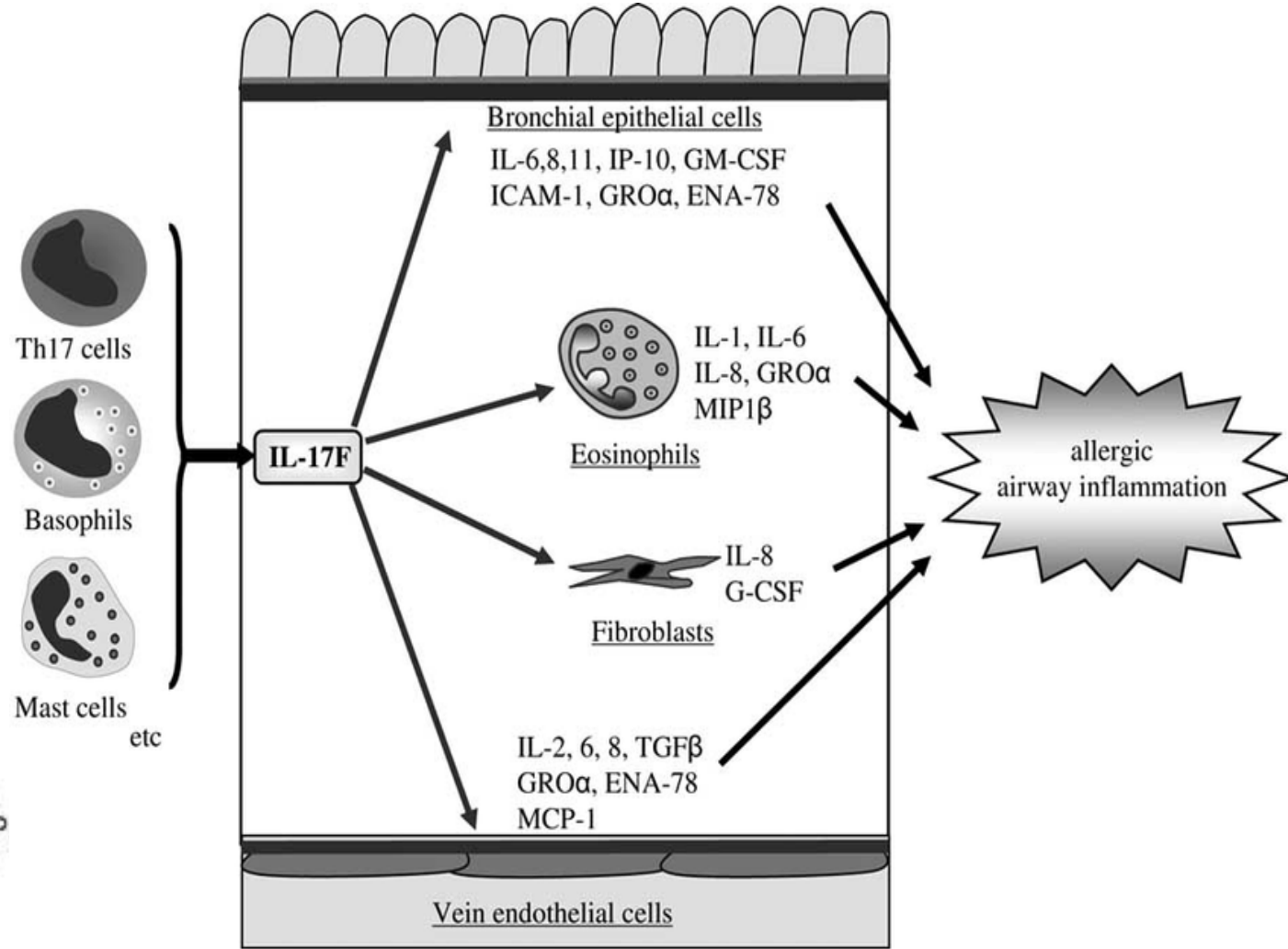
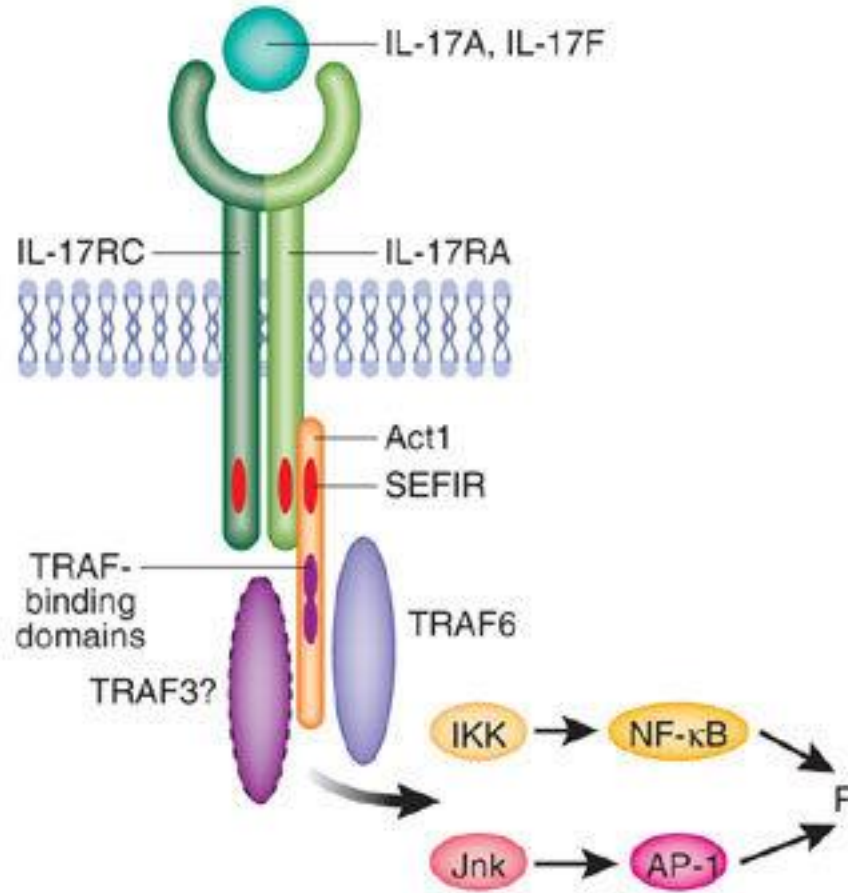


# Mice treated with IL-17F become susceptible to ABPA

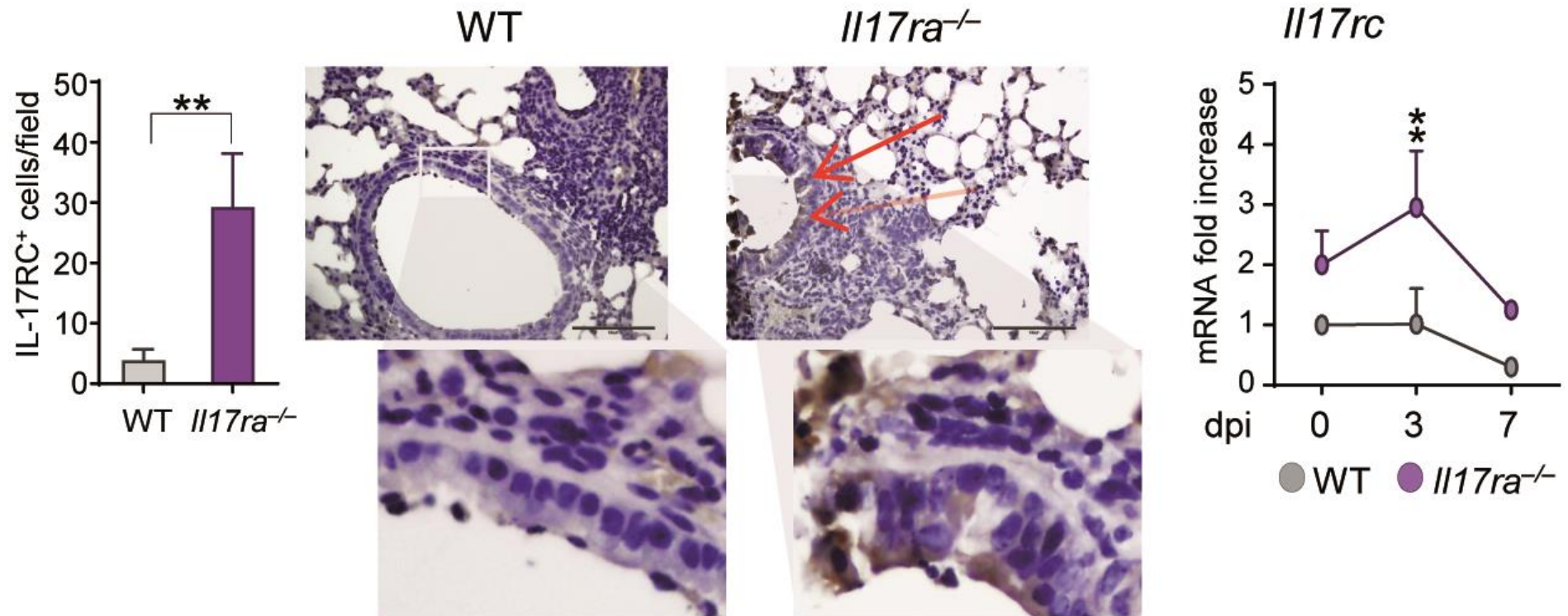


# IL-17F: new insights

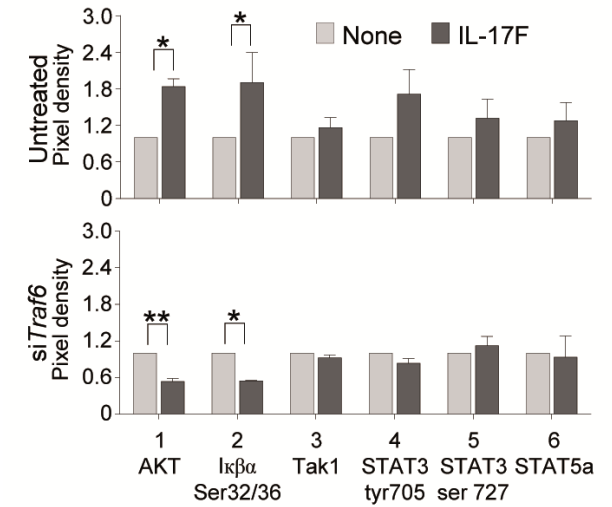
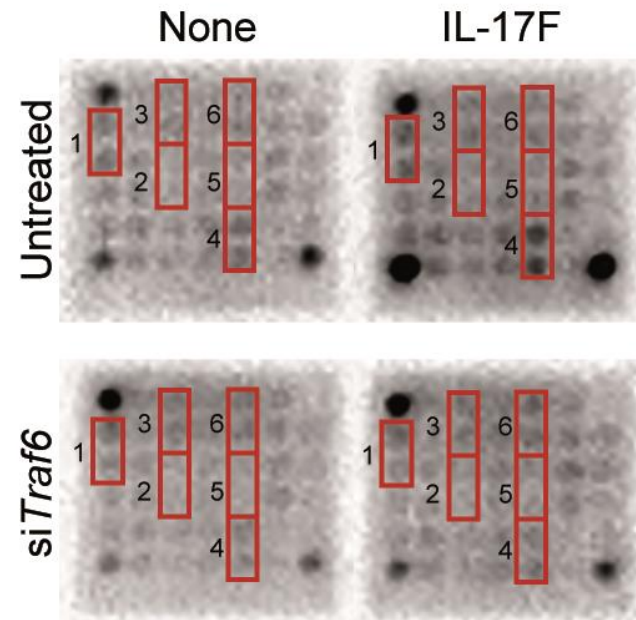
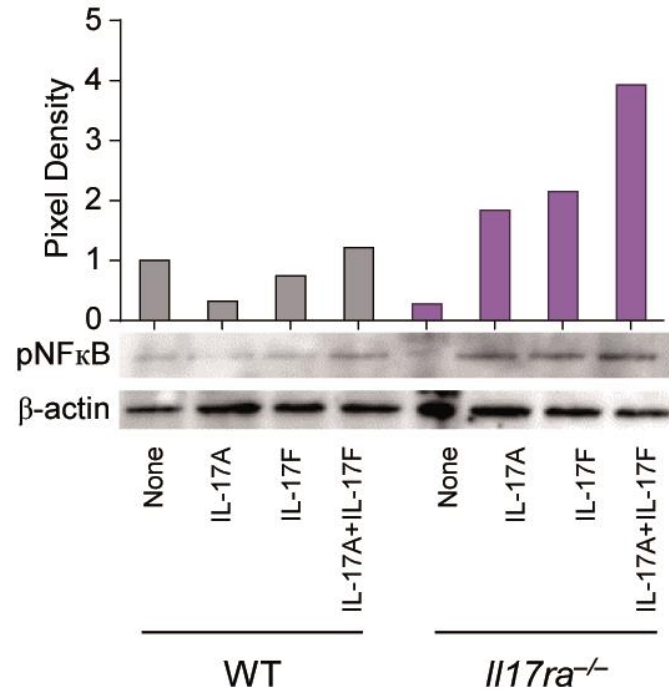
Epithelial cells and astrocytes



# IL-17RC is highly expressed in IL-17RA KO mice



# IL-17RC is functional in IL-17RA KO mice

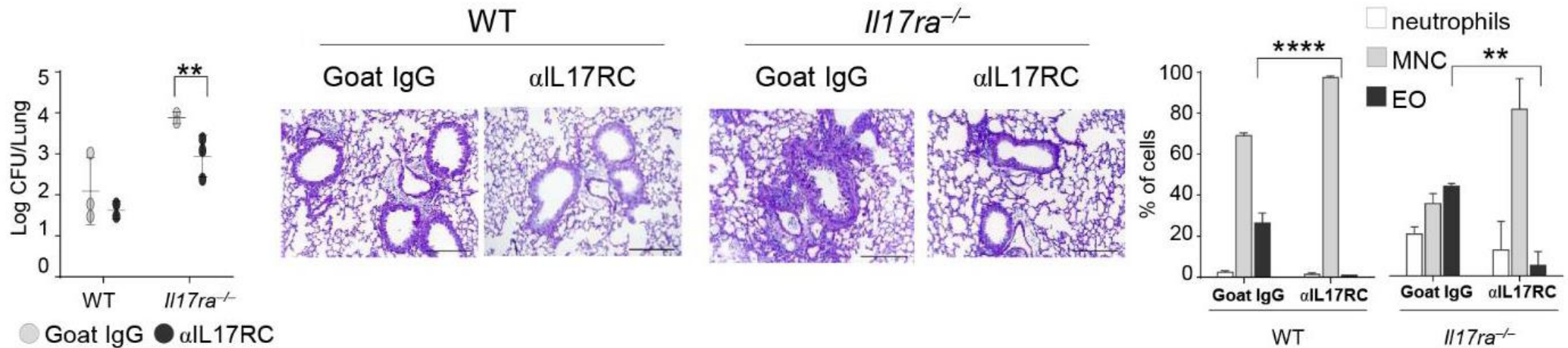


[De Luca A, et al. Cell Rep. 2017 Aug 15;20\(7\):1667-1680](#)



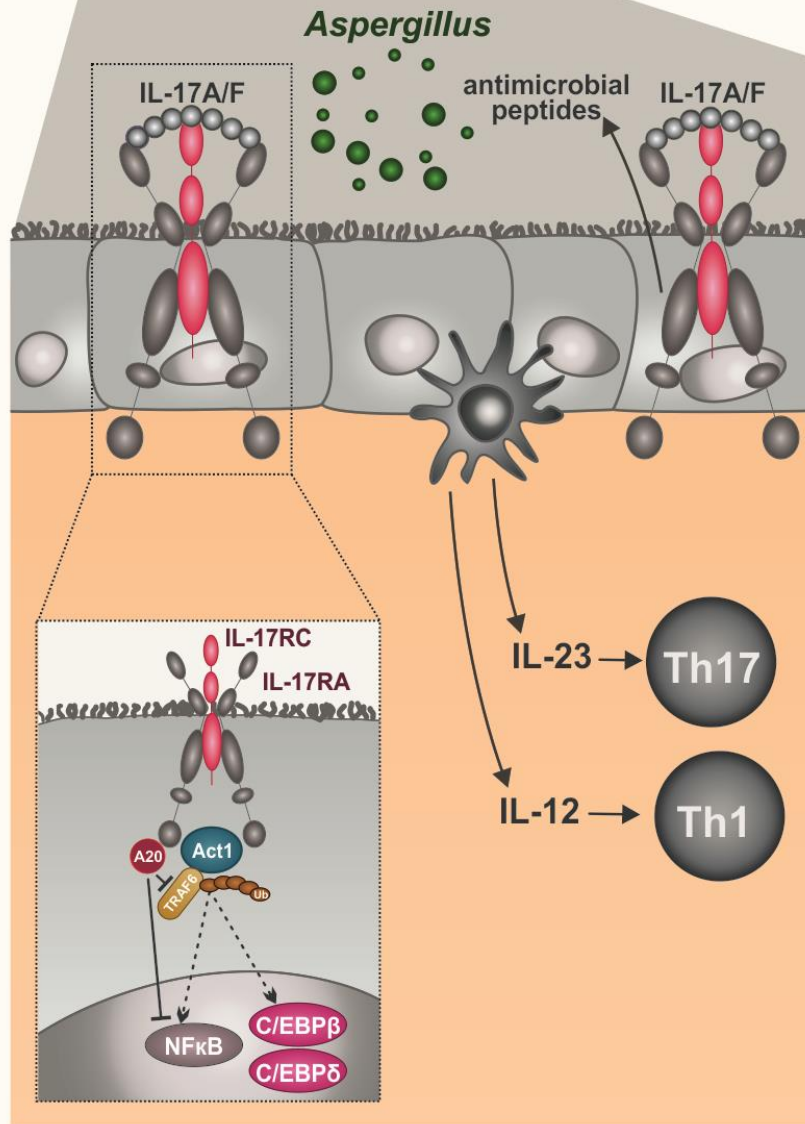


# IL-17RC blockade reduces IL-17RA pathology



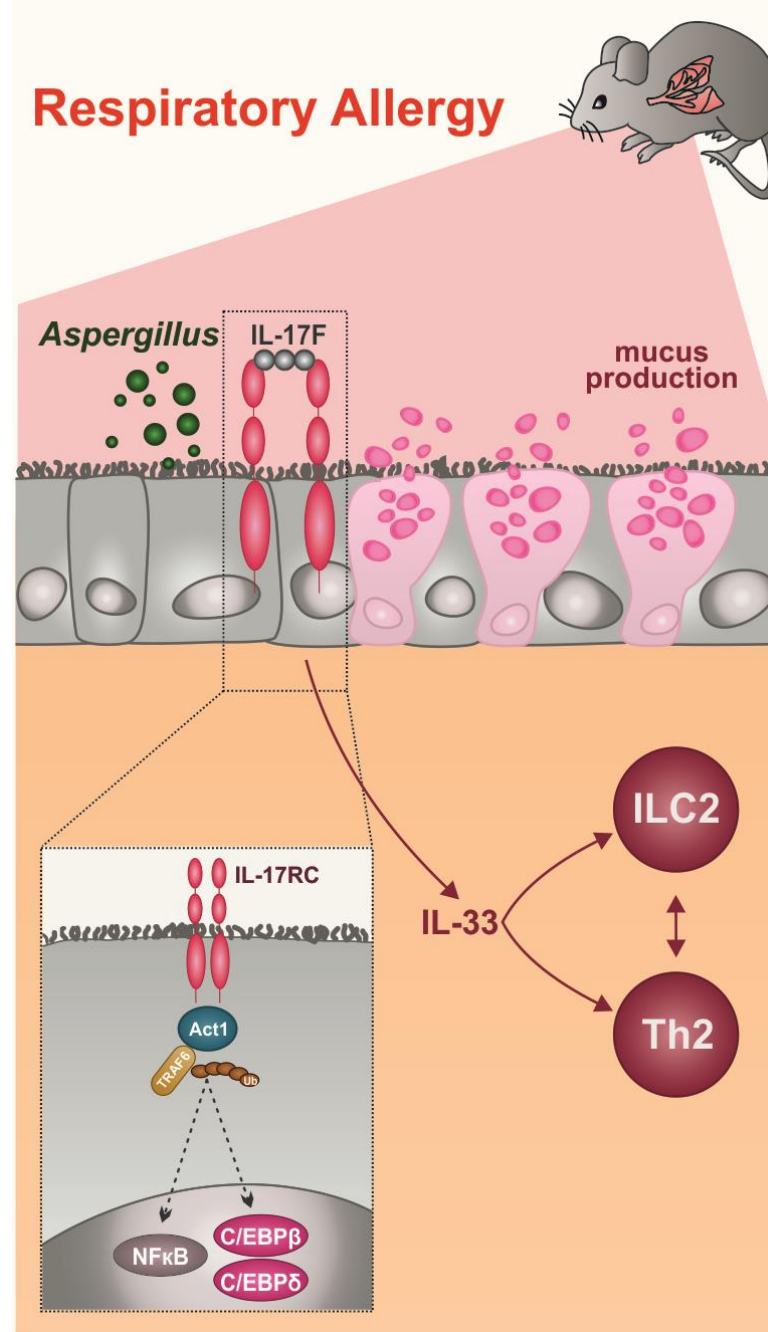


# Homeostasis



# Conclusion 1

## Conclusion 2



# Conclusions

## Immunology and Inflammation in Aspergillosis

- ✓ The importance of regulation in phagocytosis/autophagy
- ✓ The T cell priming stemness and Th17 pathogenicity
- ✓ The regulation of Type 2 immunity and avoidance of allergy



Sign

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Paola Castagnoli

Alicia Wong

YU Hong Bing

Jan Fric

Tang Jing Ping

Lim Tong Seng

Andrea Mencarelli

Radoslav Sobota

Tay Hock Soon

Sabrina Nabti

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