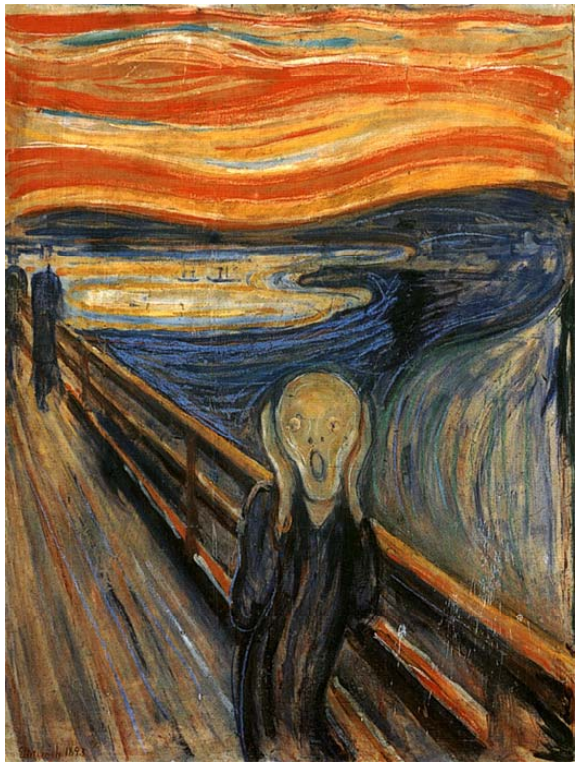
7th Scientific Meeting of the NSMM
Host – Pathogen interaction
Oslo, Norway. March 17th to 18th 2010



Edward Munch, Oslo, Norway

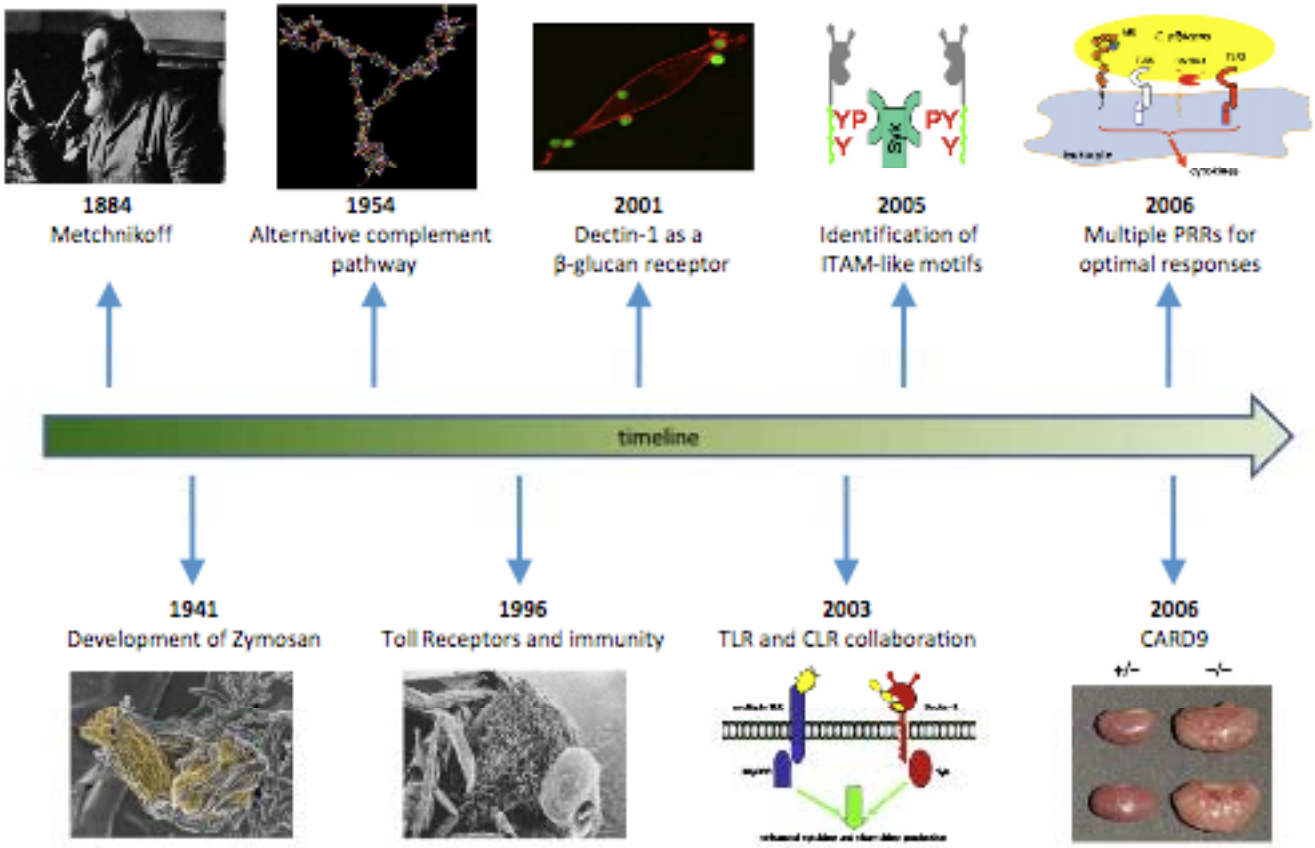
The role of the Immune system in fungal infections

Teresa Zelante,PhD
Dep. of Biochemical Science and Experimental Medicine
Microbiology section
University of Perugia, Italy

How Fungi Have Shaped Our Understanding of Mammalian Immunology

Gordon D. Brown[1,*]
[1]Aberdeen Fungal Group, Section of Immunology and Infection, Division of Applied Medicine, Institute of Medical Sciences, Foresterhill, University of Aberdeen, Aberdeen AB25 2ZD, UK
*Correspondence: gordon.brown@abdn.ac.uk
DOI 10.1016/j.chom.2009.12.005

Research into the interaction of fungi with the host has provided significant contributions to mammalian immunology. Here, I briefly review the most notable of these contributions, starting from the time of Metchnikoff, and highlight their impact on our understanding of immunity.



TIMELINE

Metchnikoff and the phagocytosis theory

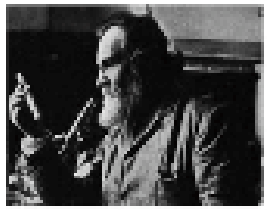
Alfred I. Tauber

Metchnikoff's phagocytosis theory was less an explanation of host defence than a proposal that might account for establishing and maintaining organismal 'harmony'. By tracing the phagocyte's various functions through phylogeny, he recognized that eating the tadpole's tail and killing bacteria was the same fundamental process: preserving the

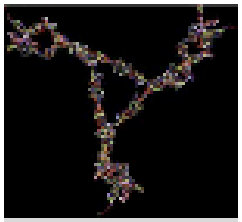
century. Indeed, the clonal selection theory and the elucidation of the molecular biology of the immune response count among the great advances in biology during our own era[1]. Metchnikoff has been assigned to the wine cellar of history, to be pulled out on occasion and celebrated as an old hero.

However, to cite Metchnikoff only as a con-

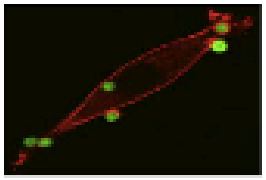
Figure 1 | **Ilya Metchnikoff, at ~45 years of age.** This figure is reproduced from REF. 14.



1884
Metchnikoff

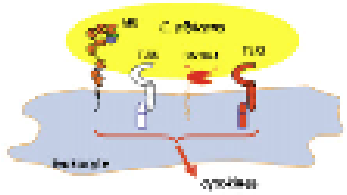


1954
Alternative complement pathway



2001
Dectin-1 as a β-glucan receptor

2005
Identification of ITAM-like motifs

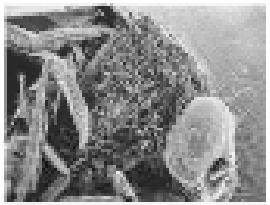


2006
Multiple PRRs for optimal responses

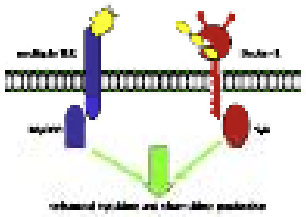
timeline

1941
Development of Zymosan

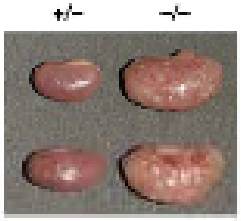
1996
Toll Receptors and immunity



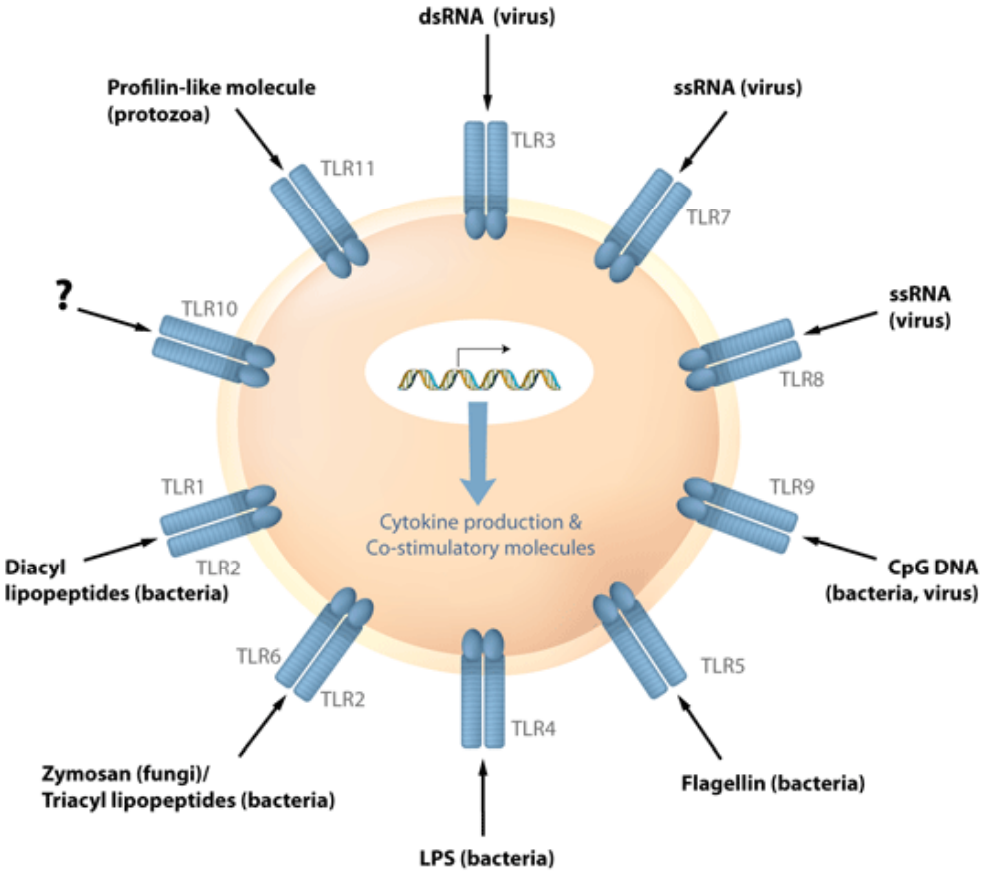
2003
TLR and CLR collaboration

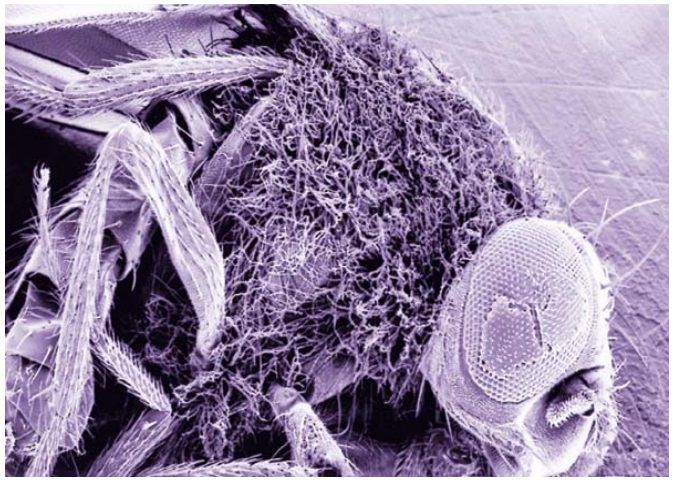


2006
CARD9



TLRs: Toll-like receptors





Cell 1996, 86:973

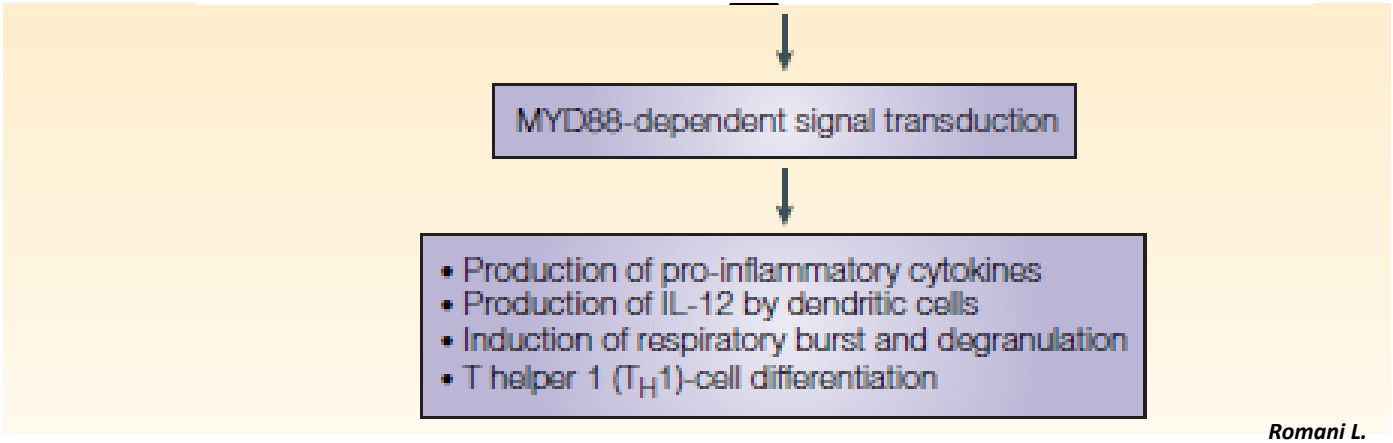
TLR2/4 C. neoformans

TLR4/MYD88 (resistance to Aspergillosis)

TLR9 (Tolerance to Aspergillus fumigatus)

TLR2 (promotes the fungicidal activity of TLR(oxidative pathway) + inflammatory cytokines

TLR4 (promotes fungicidal activity)+ anti-inflammatory cytokine



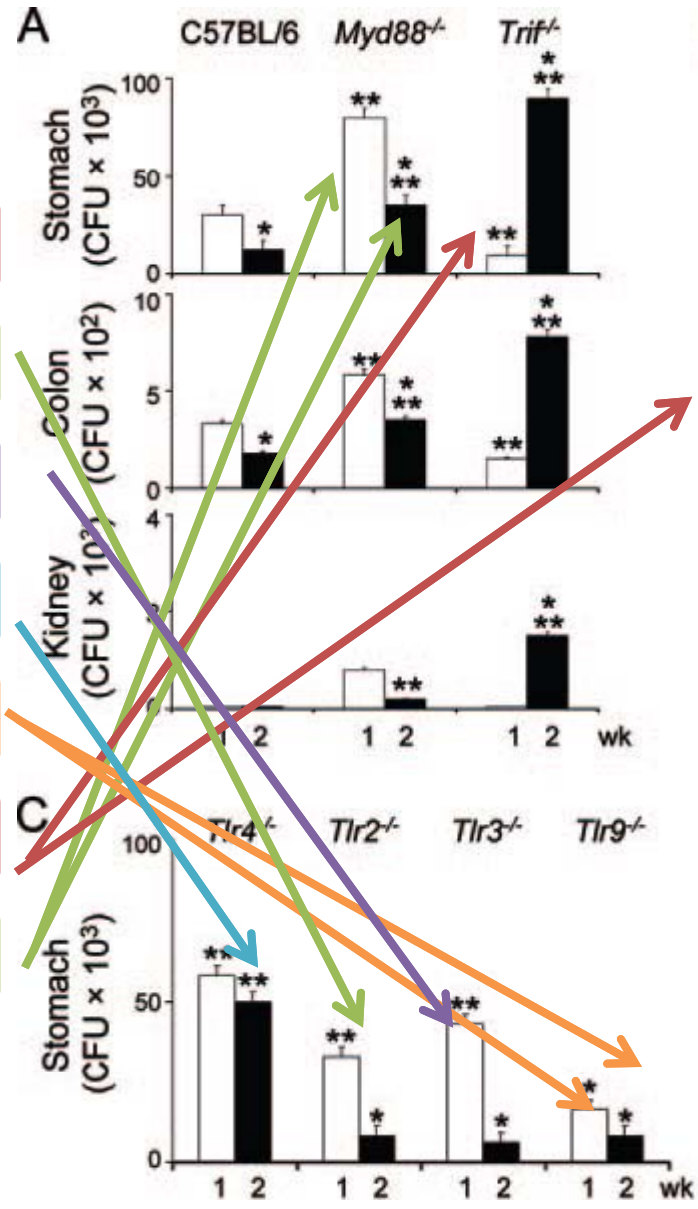
Romani L.

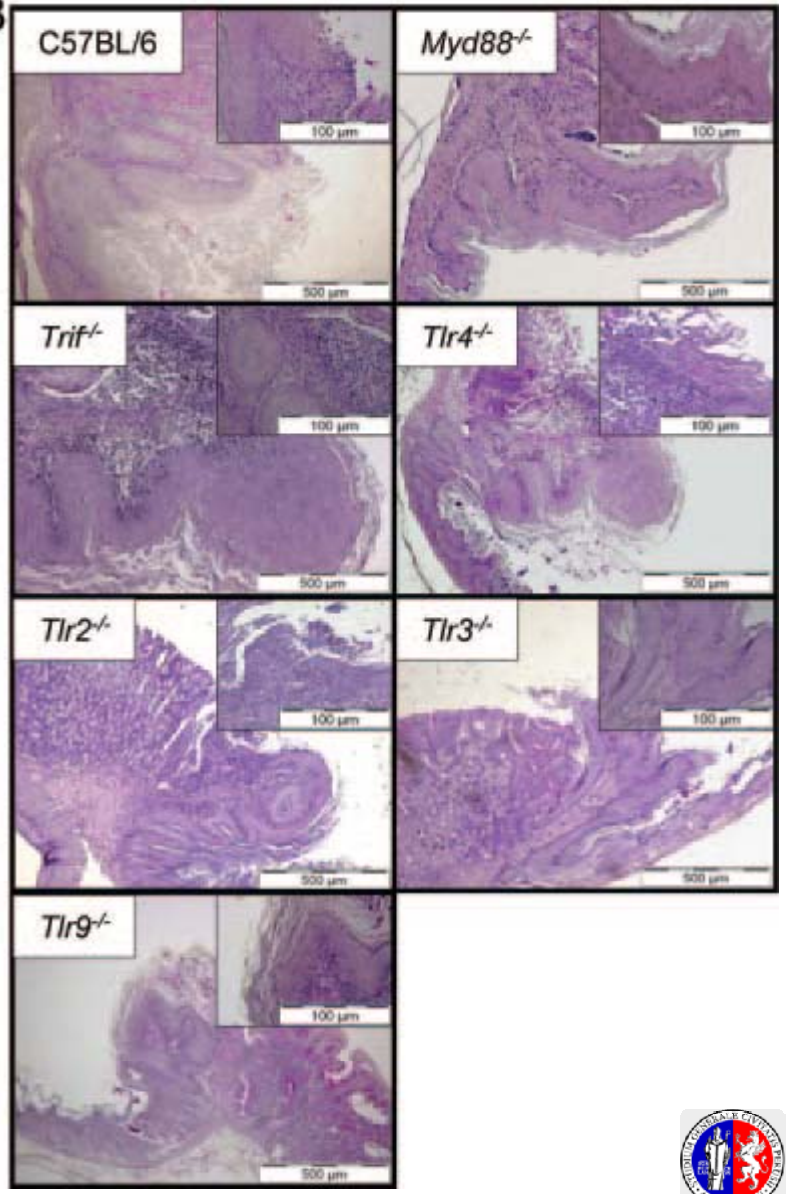
JANUARY 2004 | VOLUME 4

Experimental animal models of TLRs deficiency

Deficiency of

- TLR2
- TLR3
- TLR4
- TLR9
- TRIF
- MYD88





A. De Luca, The Journal of Immunology, 2007

ELSEVIER

Experimental Hematology

Experimental Hematology 2009;37:1022–1029

Polymorphisms in Toll-like receptor genes and susceptibility to infections in allogeneic stem cell transplantation

Agostinho Carvalho[a], Cristina Cunha[a], Alessandra Carotti[b], Teresa Aloisi[b], Ornella Guarrera[a], Mauro Di Ianni[b], Franca Falzetti[b], Francesco Bistoni[a], Franco Aversa[b], Lucia Pitzurra[a], Fernando Rodrigues[c], and Luigina Romani[a]

[a]*Microbiology, Department of Experimental Medicine and Biochemical Sciences, University of Perugia, Perugia, Italy;* [b]*Division of Hematology and Clinical Immunology, Department of Clinical and Experimental Medicine, University of Perugia, Perugia, Italy;* [c]*Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal*

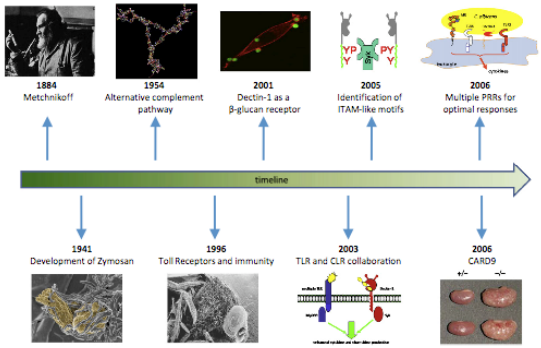
(Received 5 May 2008; revised 29 April 2009; accepted 9 June 2009)

Objective. **Discovery of genetic variations in the genes encoding for Toll-like receptors (TLRs) has highlighted a potential link between genomic variation of the host and susceptibility to infections.**

Materials and Methods. **We investigated the association between polymorphisms in the *TLR2*, *TLR4*, and *TLR9* genes in recipients of allogeneic hematopoietic stem cell transplant and susceptibility to infections caused by cytomegalovirus and filamentous fungi.**

Results. **A significant association was observed between the presence of the T-1237C polymorphism (*TLR9*) and susceptibility to viral pneumonia ($p = 0.04$; odds ratio [OR]: 1.73). For fungi, a significant association was observed between the presence of the cosegregating Asp299Gly/Thr399Ile polymorphisms (*TLR4*) and fungal colonization ($p = 0.003$; OR: 10.6). However, susceptibility to fungal infections, predominantly fungal pneumonia, was instead significantly decreased in the presence of the same polymorphisms ($p = 0.03$; OR: 0.23).**

Conclusion. **Thus, fungal colonization may not predict susceptibility to infection in the presence of these single nucleotide polymorphisms. The finding that defective viral but not fungal sensing may predict susceptibility to infection highlights the divergent function of TLRs in the pathogenesis of opportunistic infections.**



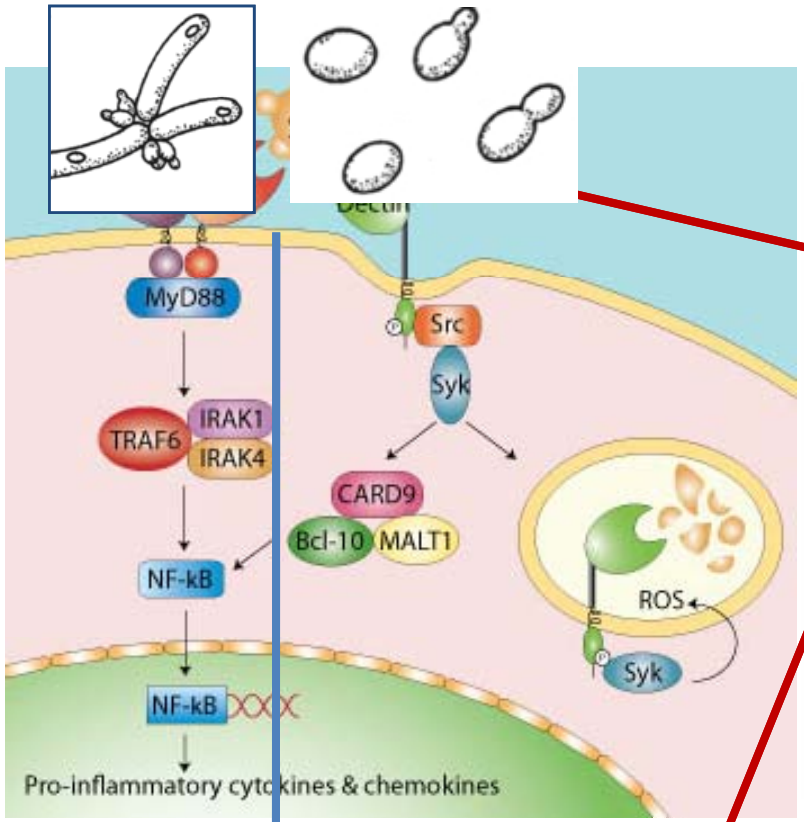
Innate Immunity: host PRRS and fungal PAMPs

PAMPs: pathogen-associated molecular patterns

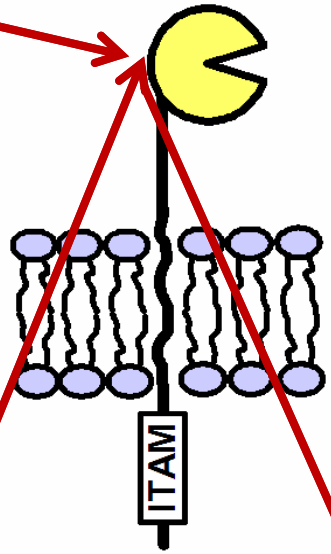
PRRs: pattern recognition receptors

- **TLRs: Toll-like receptors**
- **NLRs: NOD-like receptors**
- **CLRs: C-type-lectin receptors**
- **(RLHs) retinoic acid-inducible gene I (RIG-I)-like helicases**

Dectin-1 signalling: pro-inflammatory and anti-inflammatory signals



Dectin-1

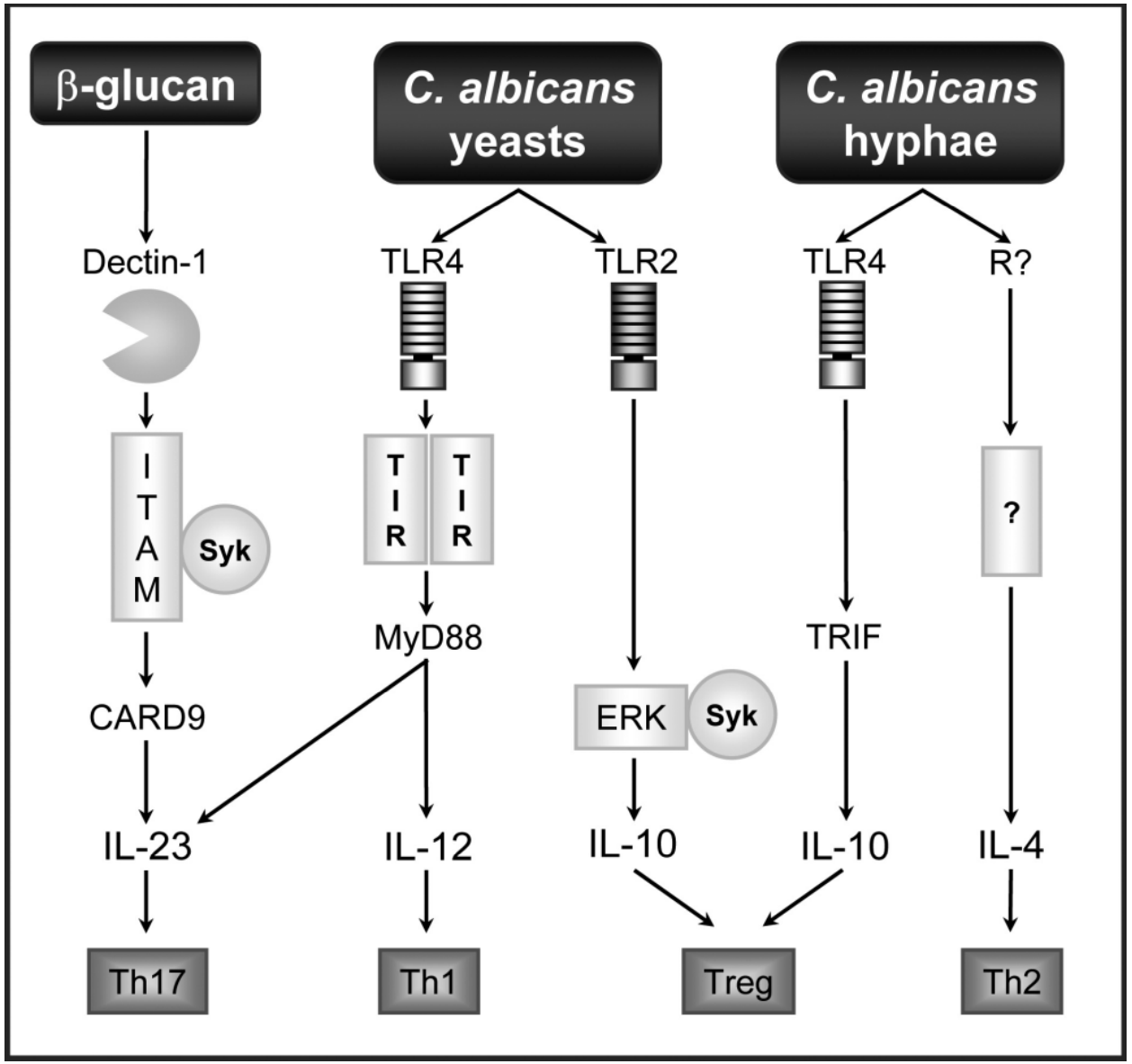


Curdlan

IL-10 → Treg

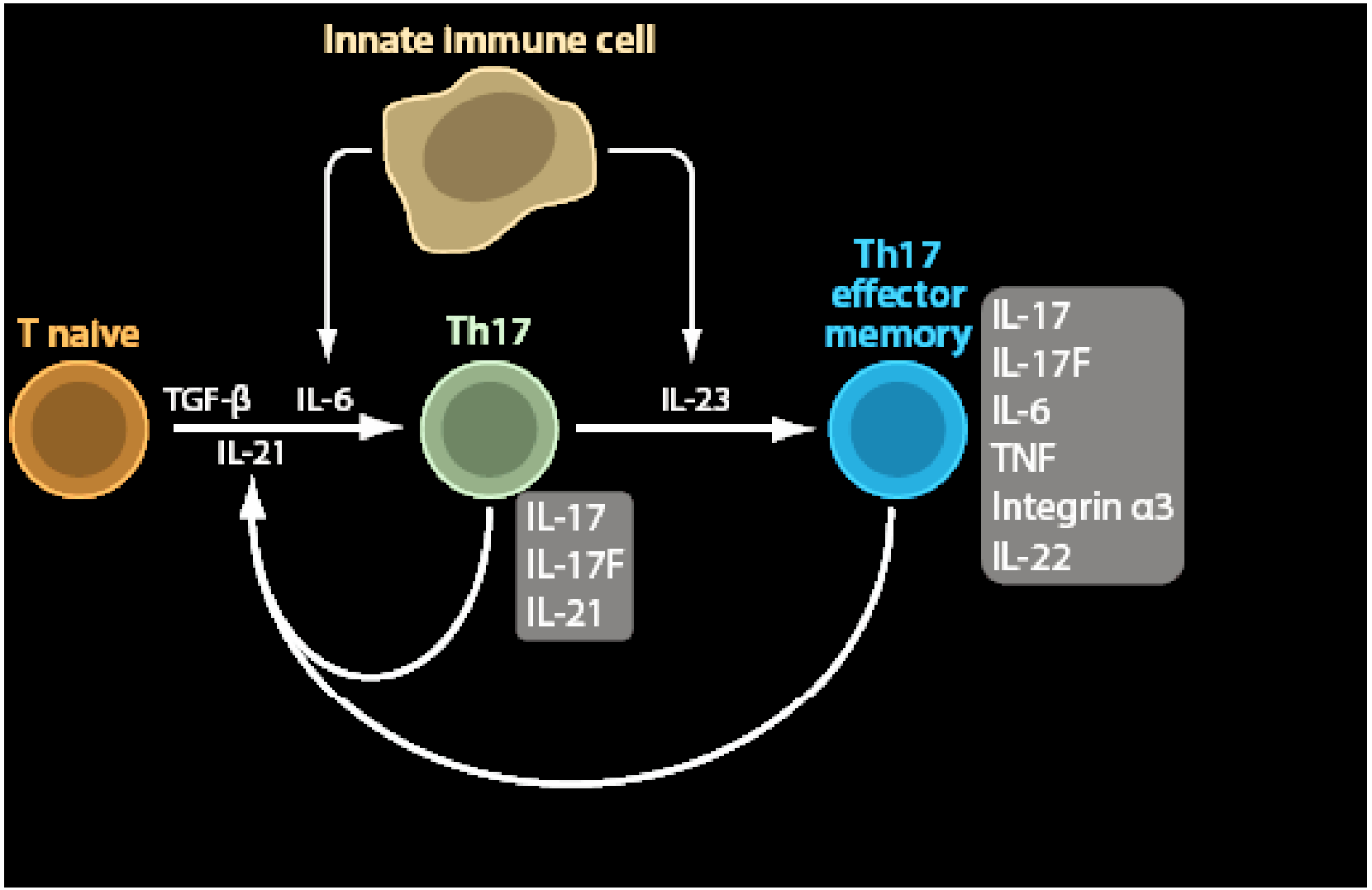
IL-23, IL-6, TGF-β → Th17

Th17 in *Candida albicans* infection



Medical Mycology September 2008, 46, 515529

The Th17 lineage

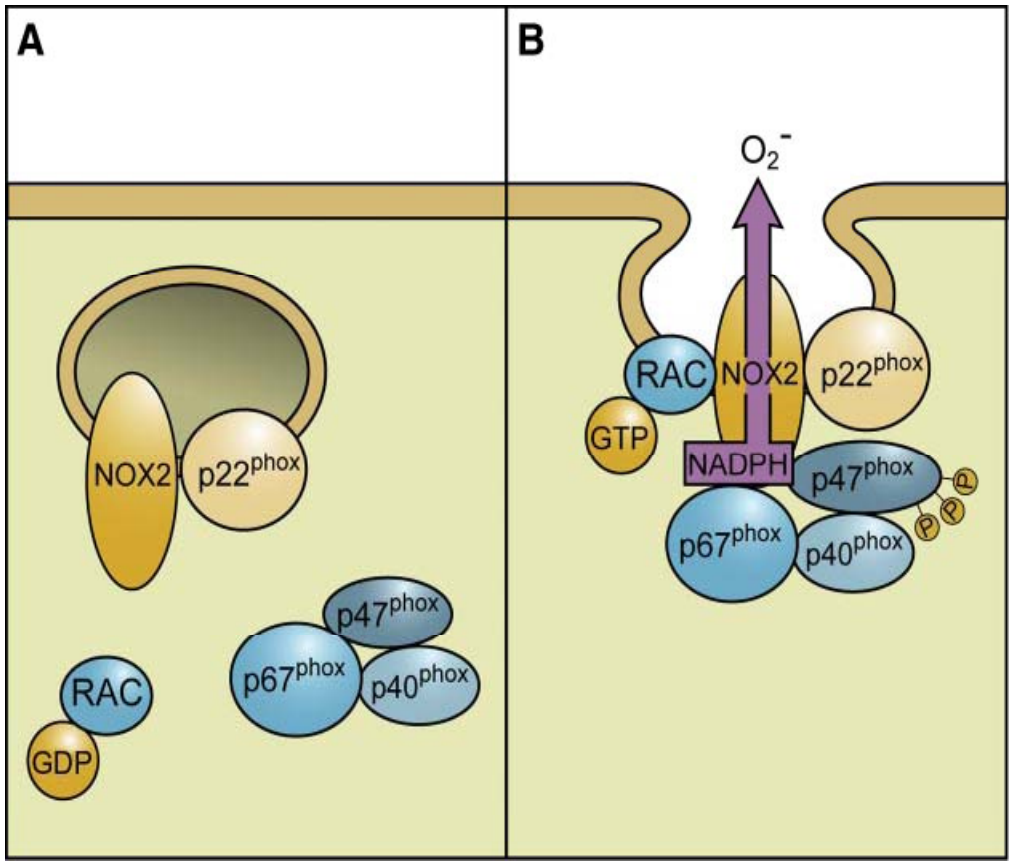


Pathogenic Th17 in fungal infections

Genotype	Infection	Clinical Features
IL-12 p35 deficiency	Candidiasis Aspergillosis	Defective Clearance Inflammation
TRIF deficiency	Candidiasis	Defective Clearance Inflammation
TIR8/SIGIRR deficiency	Candidiasis Aspergillosis	Defective Clearance Inflammation
NADPH oxidase deficiency	Aspergillosis	Defective Clearance Inflammation

Zelante et. al., J Immunol. 2008 Apr 15;180(8):5157-62

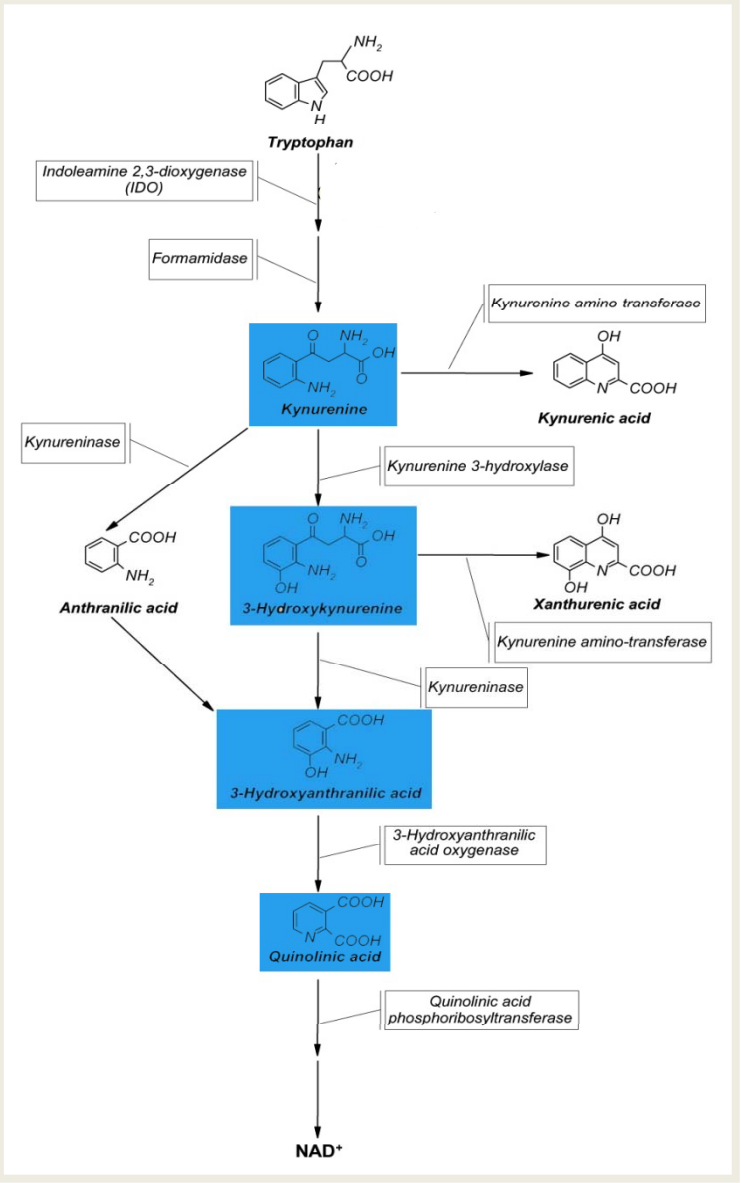
IL-17A in Inherited Primary Immunodeficiency Syndrome: The Chronic Granulomatous Disease



CGD gene	Genetic Transmission	Frequency (%)
gp91 phox (CYBB)	X-linked	65
p47 phox (NCFI)	Autosomal recessive	25
p67 phox (NCF2)	Autosomal recessive	5
p22 phox (CYBA)	Autosomal recessive	5

Physiol Rev 87: 245–313, 2007;

Who's who



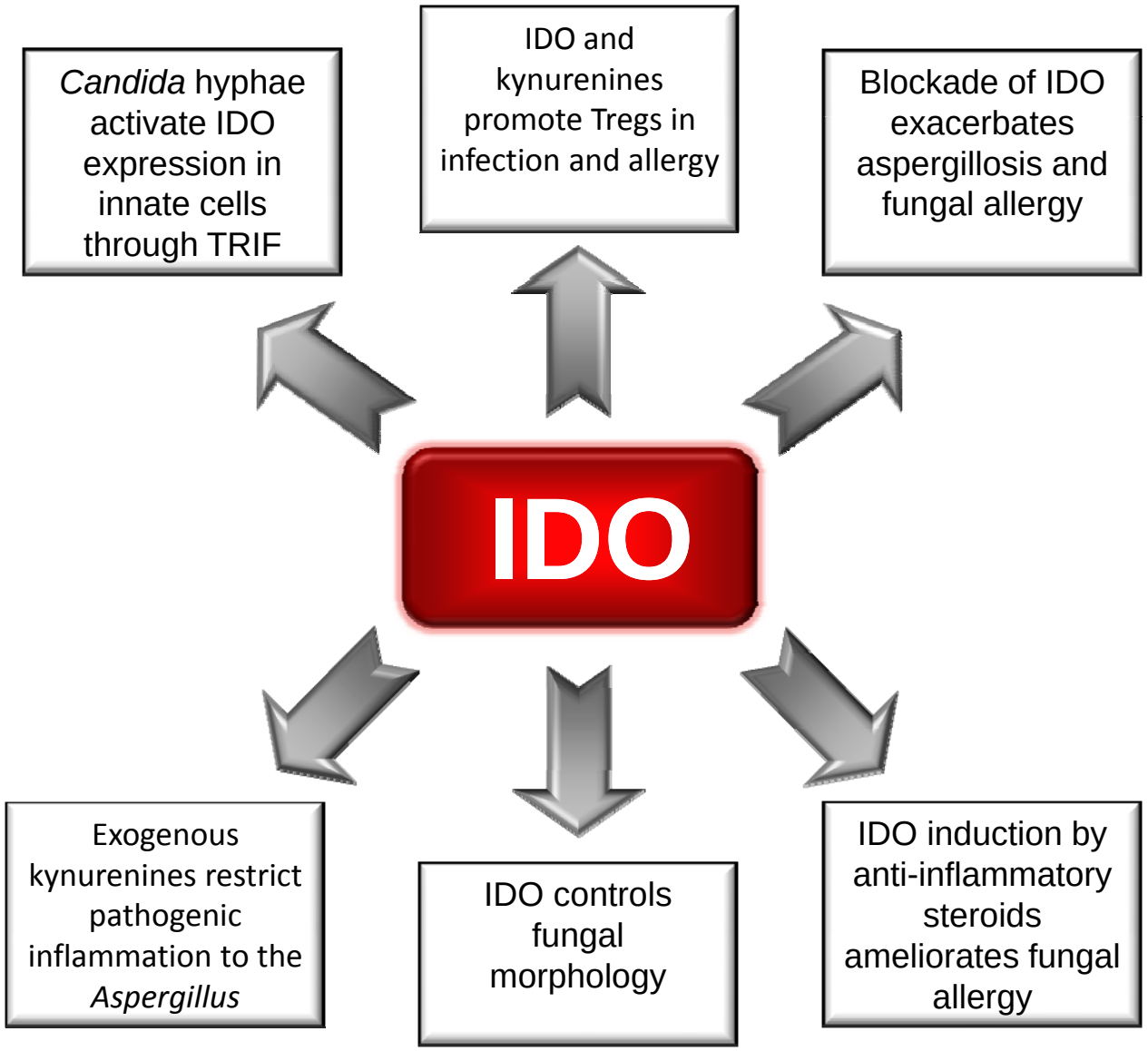
IDO

(indoleamine 2,3-dioxygenase)

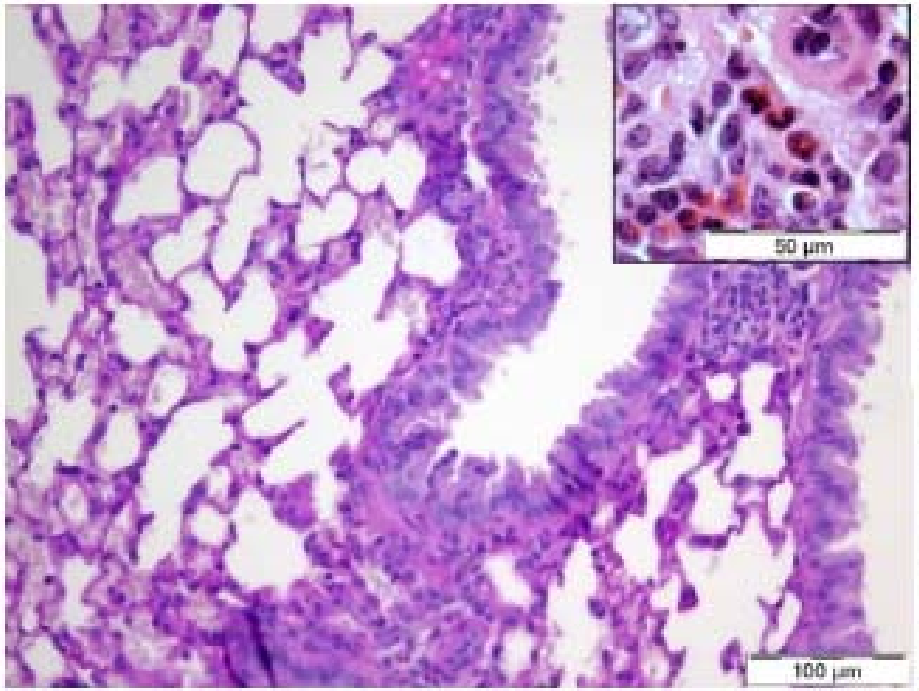
◆***Intracellular heme-containing enzyme that catalyzes the initial rate-limiting step in tryptophan degradation along the kynurenine pathway.***

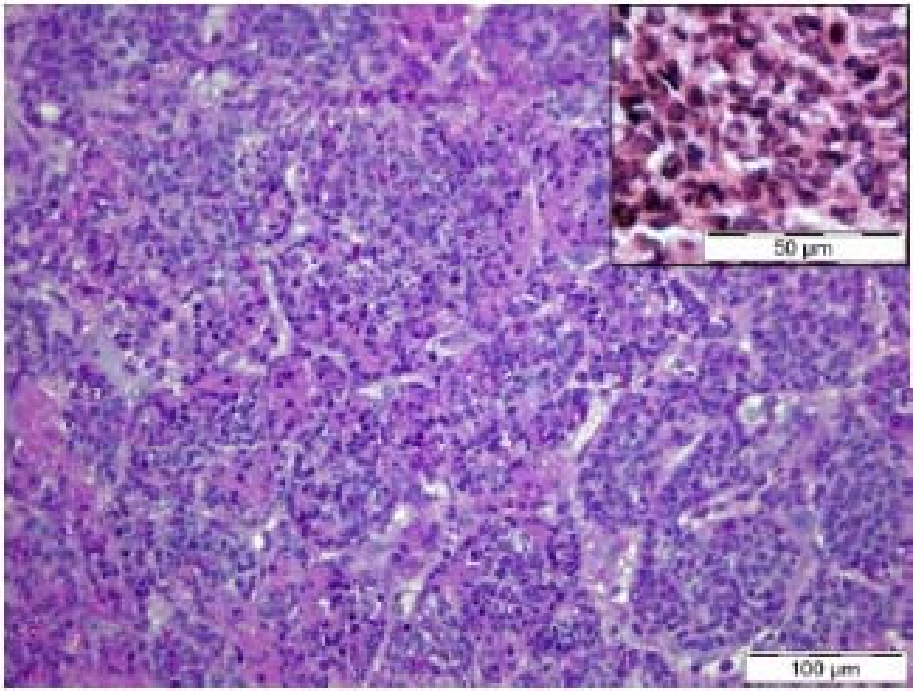
◆***Expressed in brain, lung, gut, placenta, spleen, lymph nodes, and thymus.***

The multifaceted activity of IDO in fungal infections



Pathogenic Th17 in fungal infections in NADPH deficiency



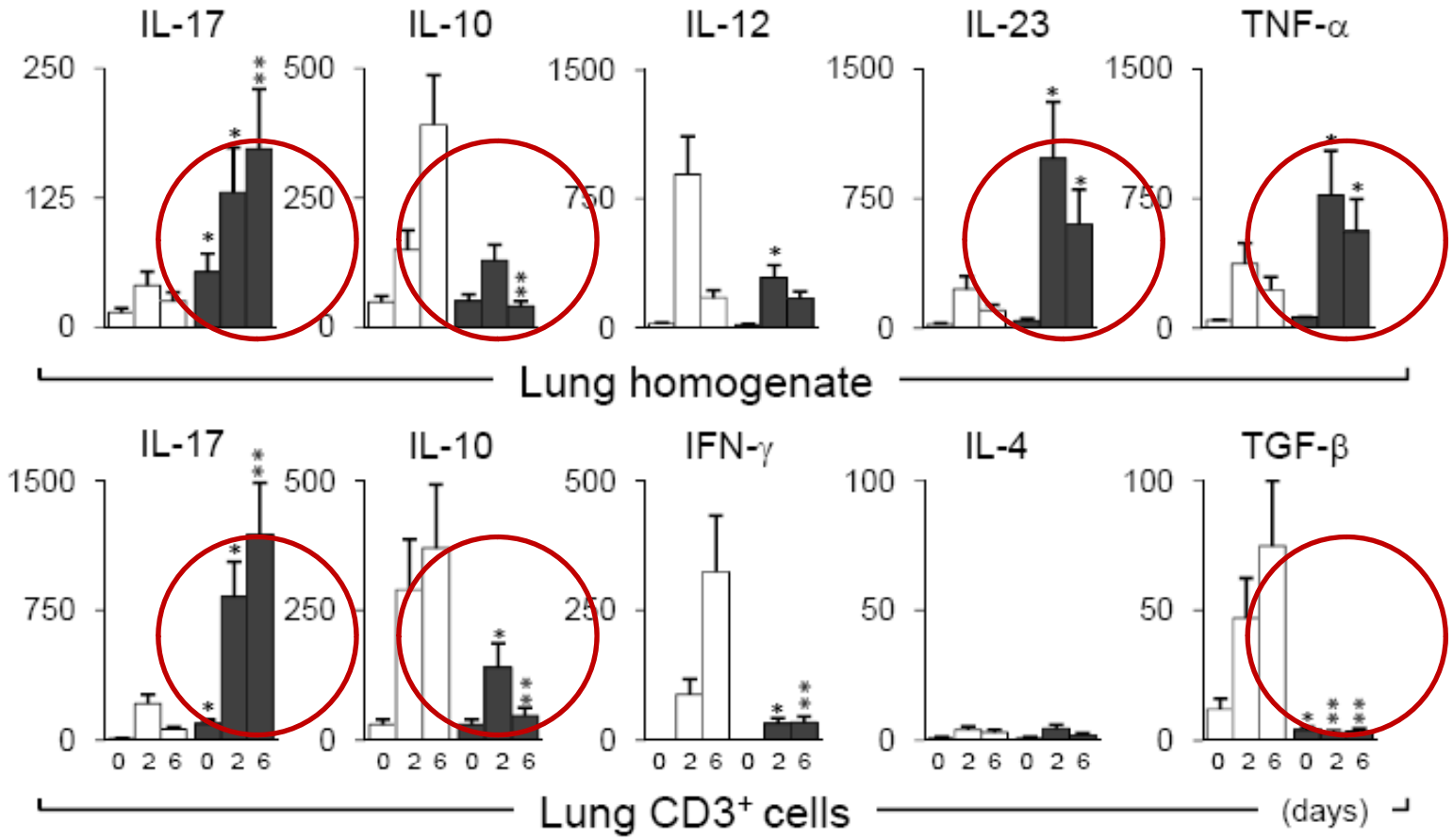


WT

p47$^{-/-}$

Romani et al. Nature. 2008 Jan 10;451(7175):211-5

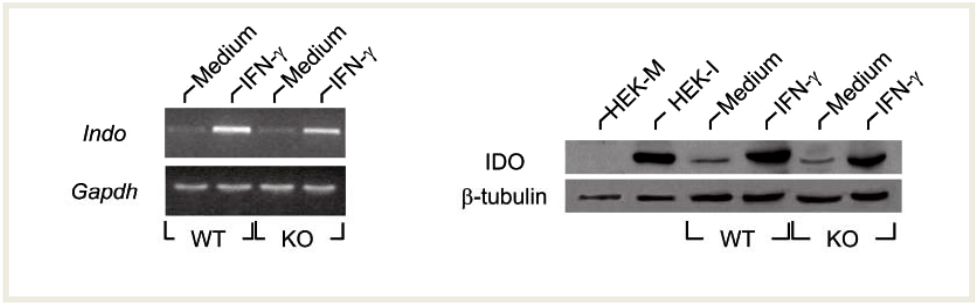
IL-17 levels correlate with pathology

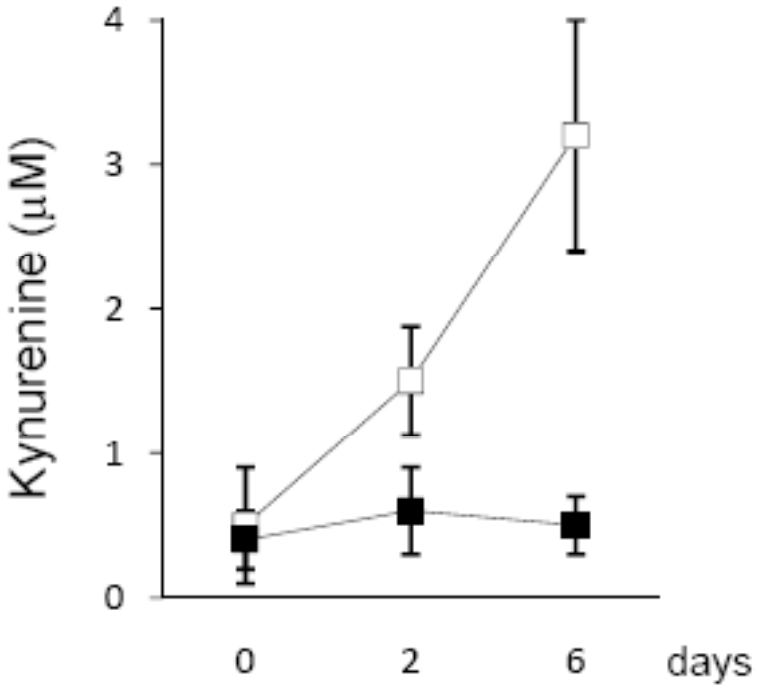


WT *p47*$^{-/-}$

Romani et al. Nature. 2008 Jan 10;451(7175):211-5

IDO defective activity was found in CGD mice

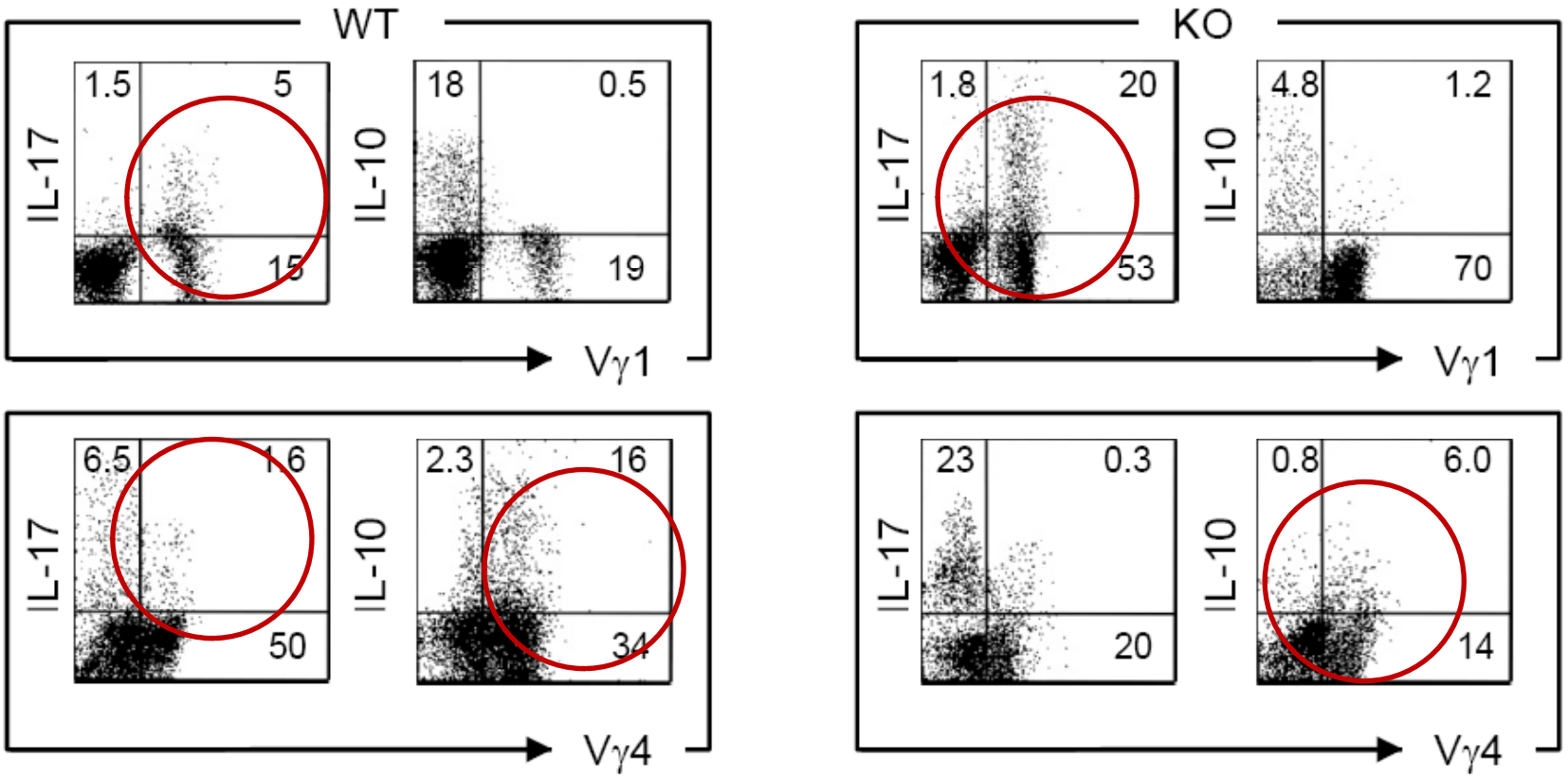




□ **WT** ■ ***p47-/-***

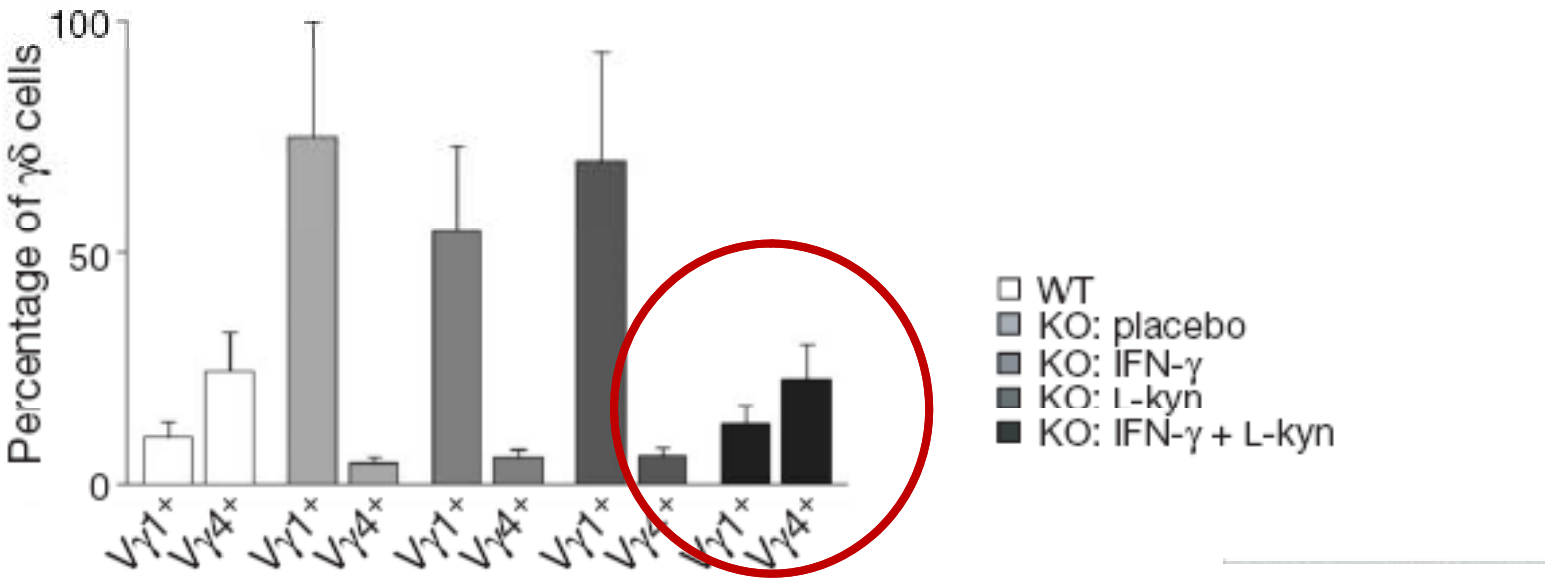
Romani et al. Nature. 2008 Jan 10;451(7175):211-5

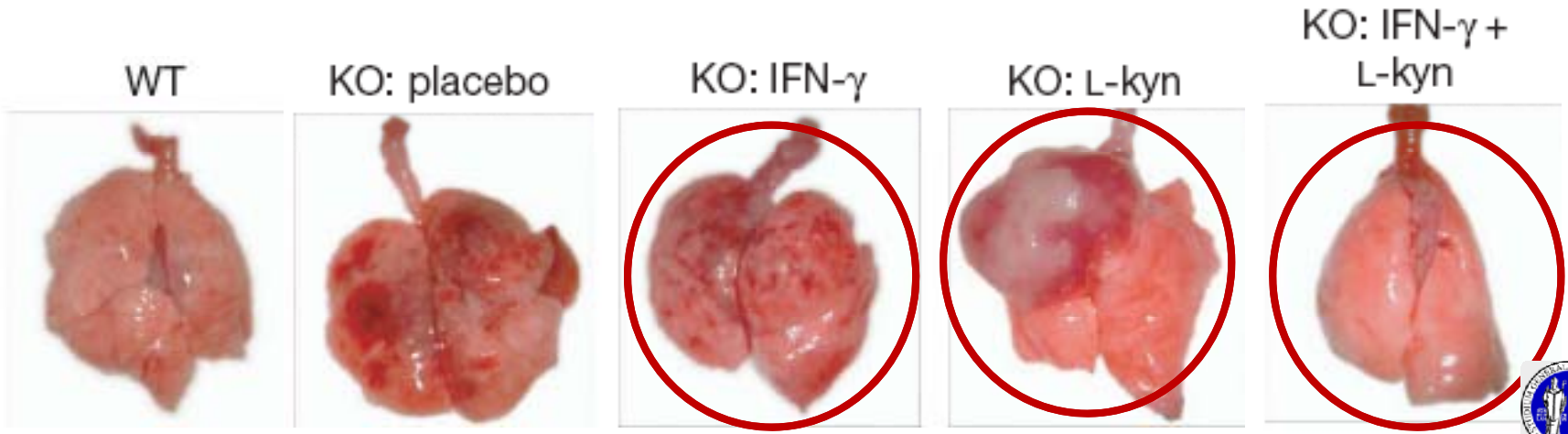
Vγ1+/Vγ4+ balance



Romani et al. Nature. 2008 Jan 10;451(7175):211-5

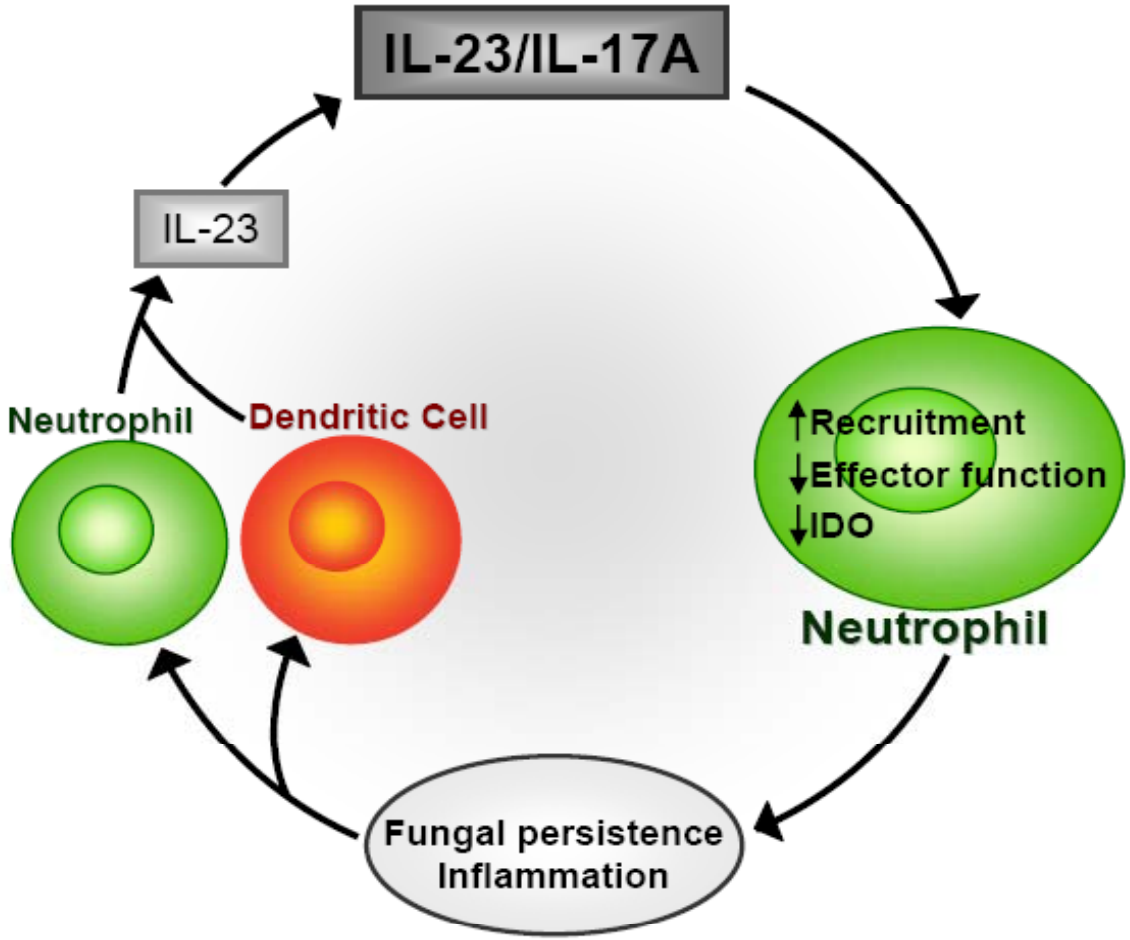
The Kynurenines therapy



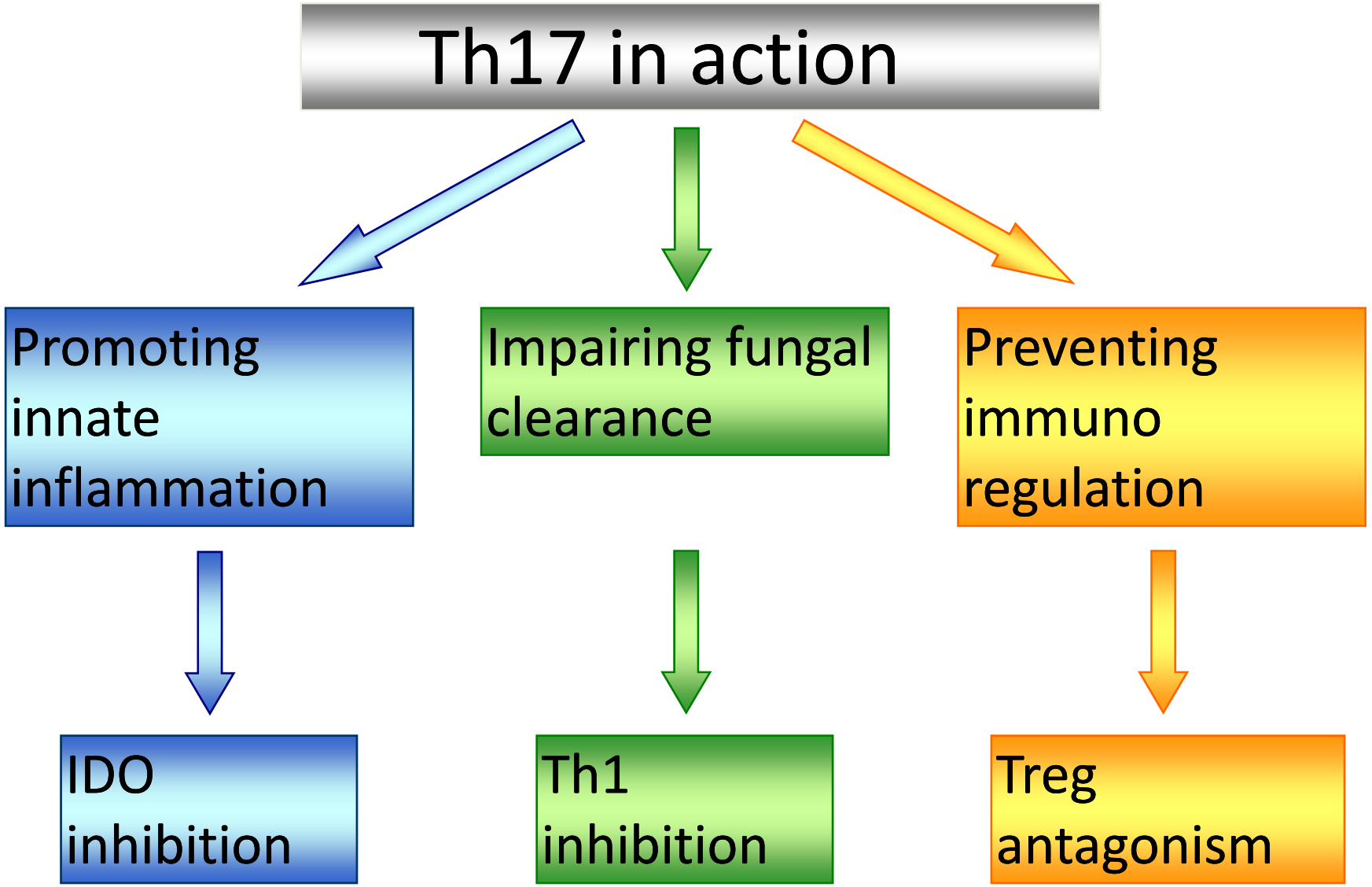


Romani et al. Nature. 2008 Jan 10;451(7175):211-5

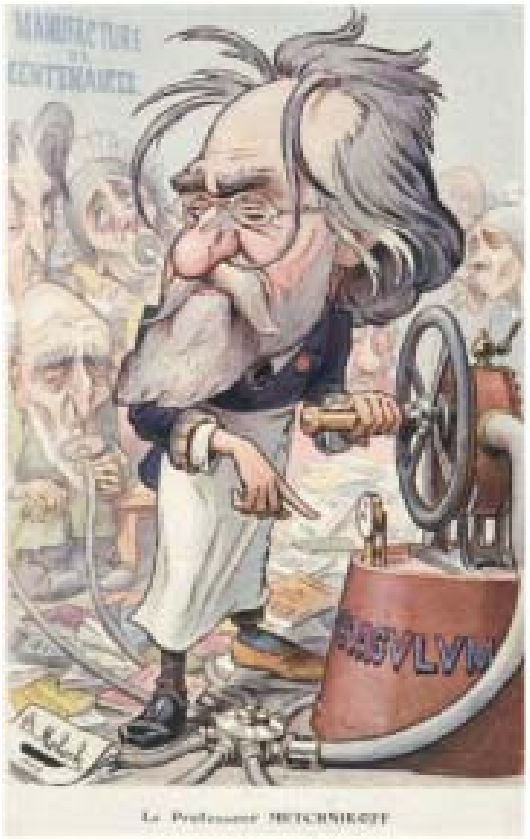
Pathogenic Th17 in fungal infections in NADPH deficiency : the Kynurenine therapy



Zelante et al. J Immunol. 2008 Apr 15;180(8):5157-62.


Th17 in action
Promoting innate inflammation
Impairing fungal clearance
Preventing immuno regulation
IDO inhibition
Th1 inhibition
Treg antagonism

Tolerance as an old strategies to preserve Fungal benefits



Eur. J. Immunol. 2008. 38: 3257–3264

University of Perugia

Microbiology

Francesco Bistoni

Silvia Bozza

Carmen D'Angelo

Antonella De Luca

Gloria Giovannini

Silvia Moretti

Lucia Pitzurra

Rossana Iannitti

Silvia Zagarella

Pierluigi Bonifazi

Agostinho Carvalho

Cristina Cunha

Luigina Romani

Pharmacology

Francesca Fallarino

Carmine Vacca

Paolo Puccetti