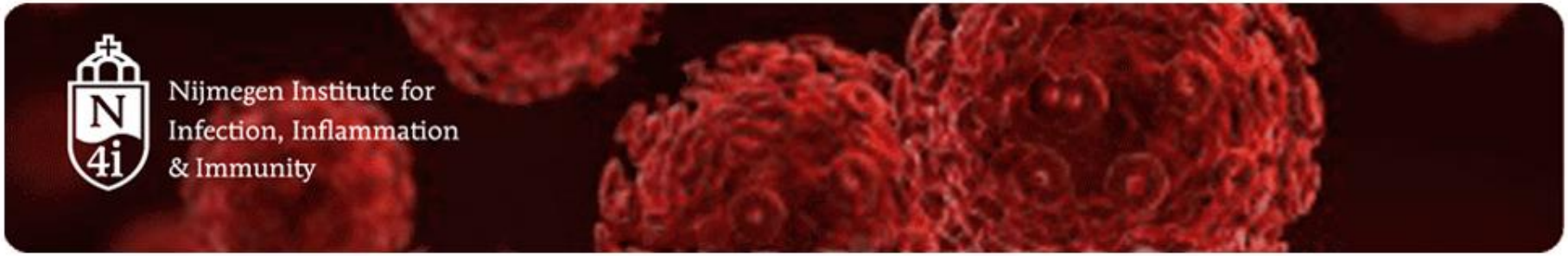

Trained immunity: impact for non-specific effects of vaccination

Mihai G. Netea

UMC St Radboud

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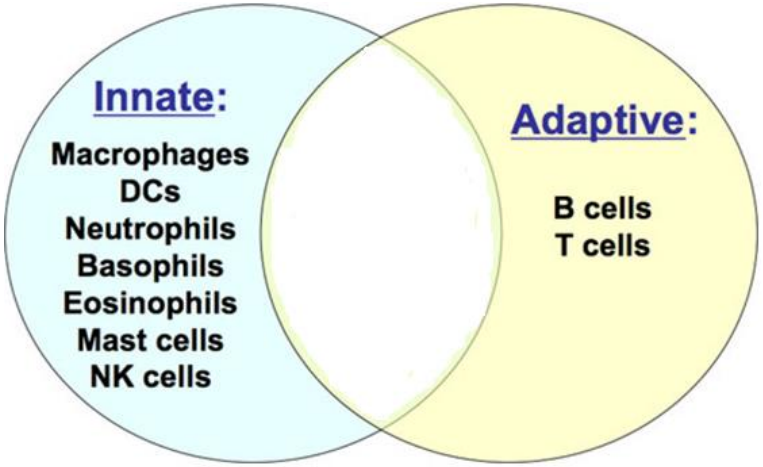
Innate versus specific immunity



Innate immunity:

- rapid
- effective
- not-specific, indiscriminate
- lacks immunological memory

Adaptive immunity:

- needs 10-14 days
- a specific activation against a particular microorganism, enhancing the effectivity of the response
- builds immunological memory

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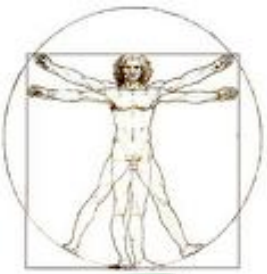
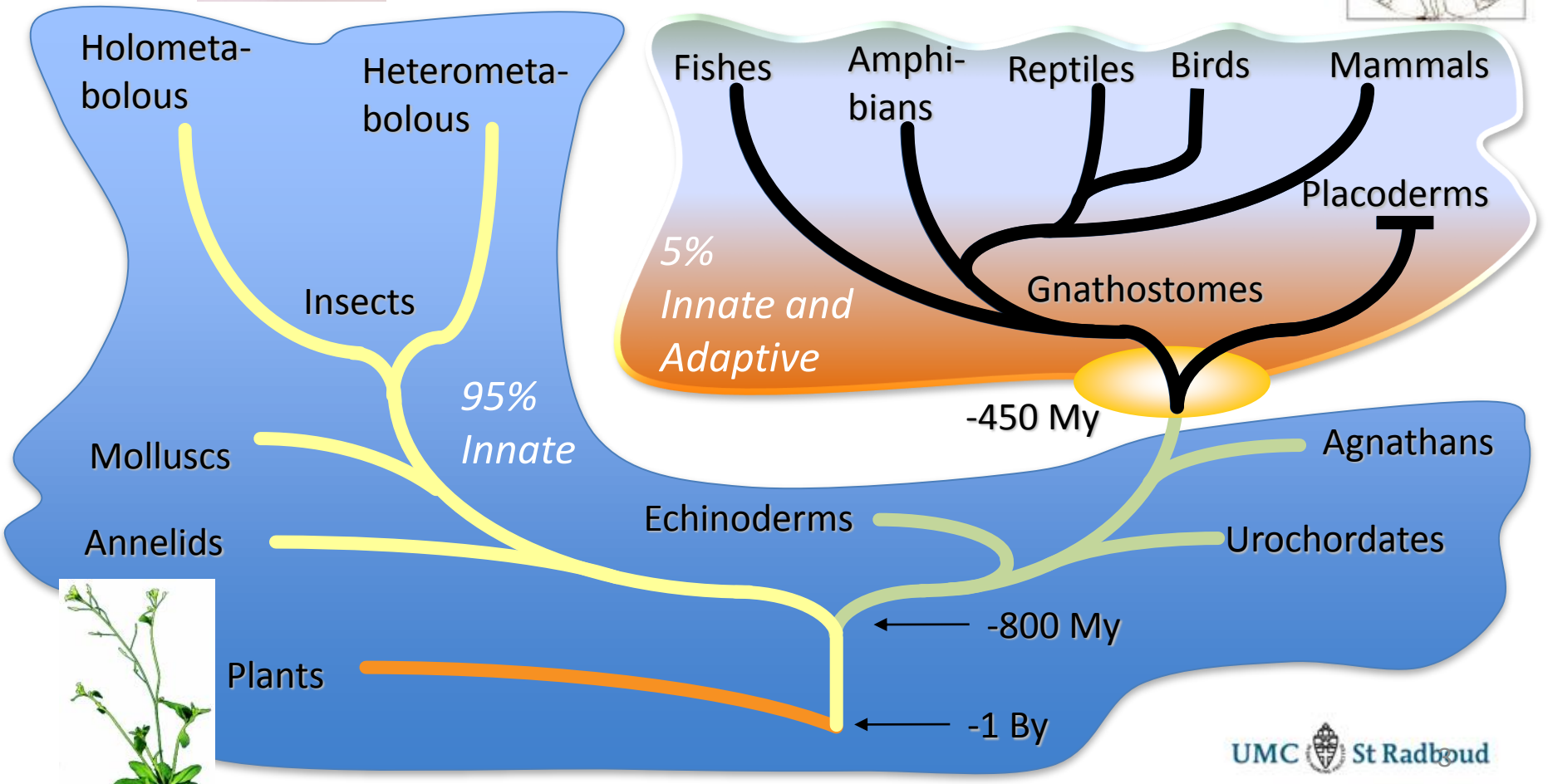
"Memory: the ability of a system to store and recall information on previously encountered characteristics"





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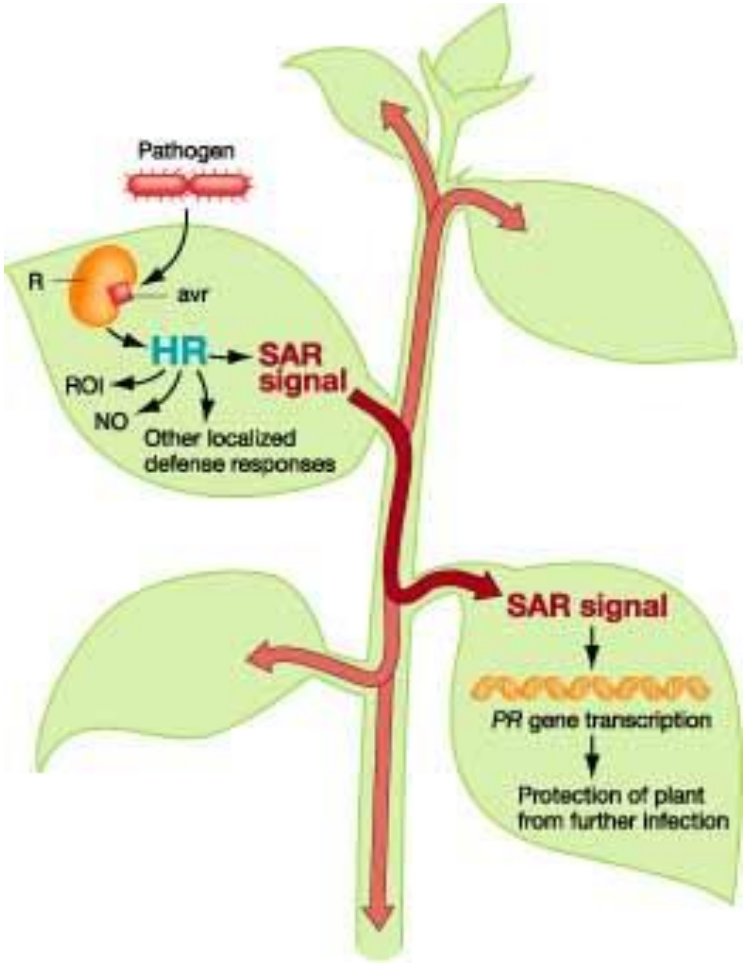
Systemic acquired resistance



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Do insects have immunological memory?

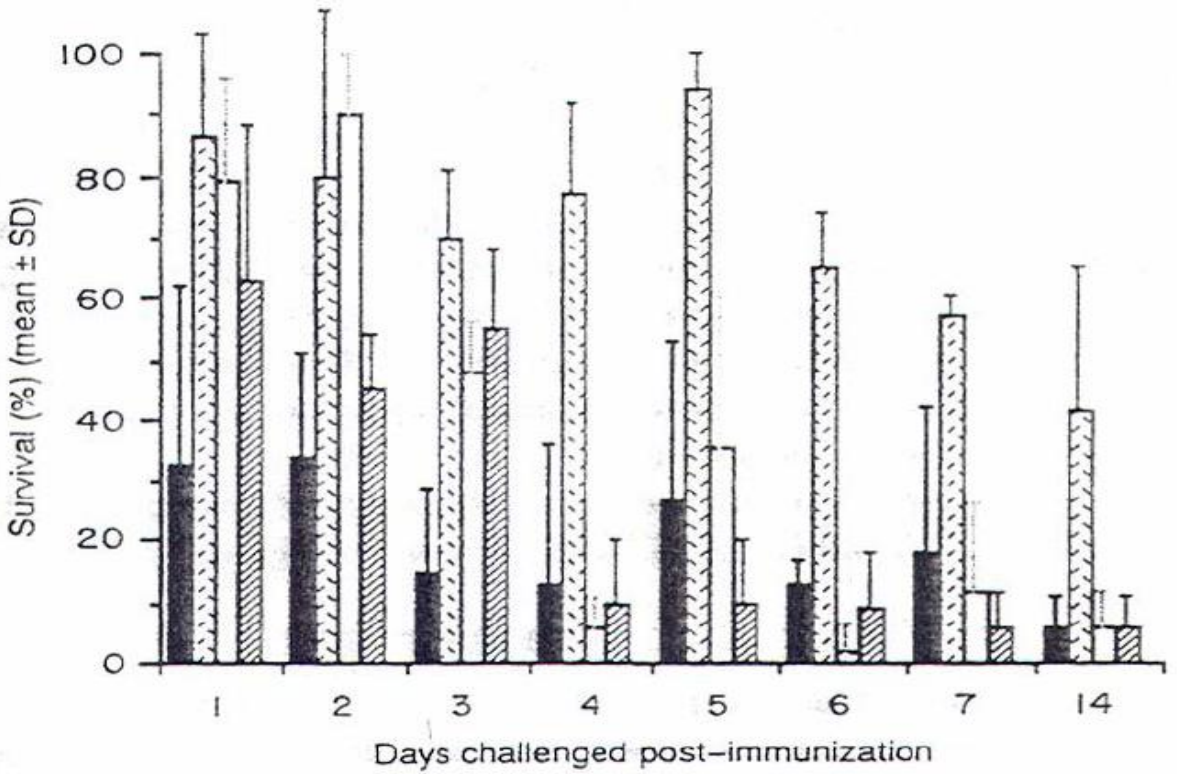

Figure 2. Specificity of the antibacterial response as determined by immunizing with Gram-positive bacteria. Adult male cockroaches were immunized with either fixed *Pseudomonas aeruginosa* (⊠), *Micrococcus lysodeikticus* (□), *Streptococcus lactis* (▨) or injected with BTS (■). Individual groups were challenged with viable *P. aeruginosa* at the times indicated post-immunization. Survival was scored 48 hr post-challenge. There were at least three trials per time-point.

Faulhaber, Karp (1992) Immunology, 75(2):378-381.

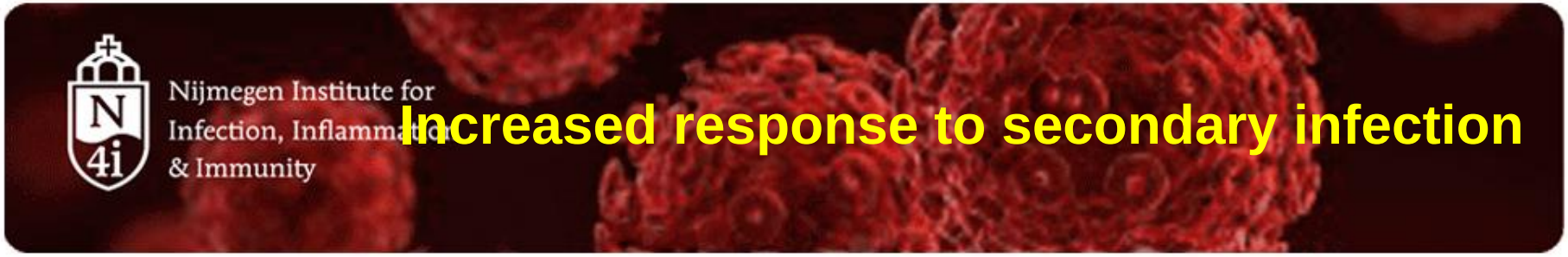

Table 1. Selected Experimental Models in which Biological Activity Compatible with the Concept of Trained Innate Immunity Has Been Reported

Organism	Experimental Model	Biological Effect	Specificity	References
Plants—Systemic Acquired Resistance				
Large variety of plants	Viruses, bacteria, fungi	Protection against reinfection	Variable	Durrant and Dong, 2004; Sticher et al., 1997
Nonvertebrates				
Mealworm beetle	LPS, or bacterial prechallenge	Protection against secondary infection	No	Moret and Siva-Jothy, 2003
Drosophila	*S. pneumoniae* prechallenge	Protection against *S. pneumoniae*	Uncertain	Pham et al., 2007
Anopheles gambiae	*Plasmodium* prechallenge	Protection against *Plasmodium*	No	Rodrigues et al., 2010
Sponges	Transplantation	Rejection	Yes	Hildemann et al., 1979
Corals	Transplantation	Rejection	Yes	Hildemann et al., 1977
Vertebrates				
Mice	BCG	Protection against candidiasis	No	Van 't Wout et al., 1992
Mice	*Candida* vaccination	T/B cell-independent protection	No	Bistoni et al., 1986, 1988
Mice	Murine CMV infection	NK-dependent protection	No	Sun et al., 2009
Humans	BCG	Nonspecific protection to secondary infections	No	Garly et al., 2003

Netea et al: Cell Host and Microbe 2011

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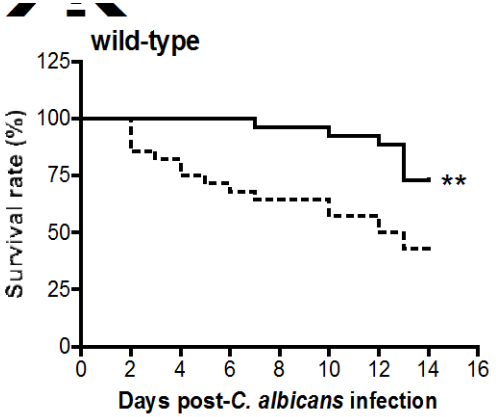
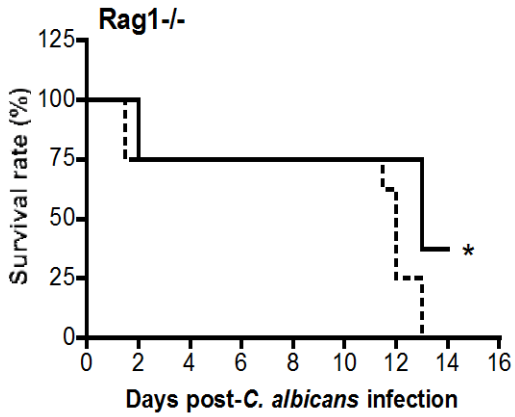
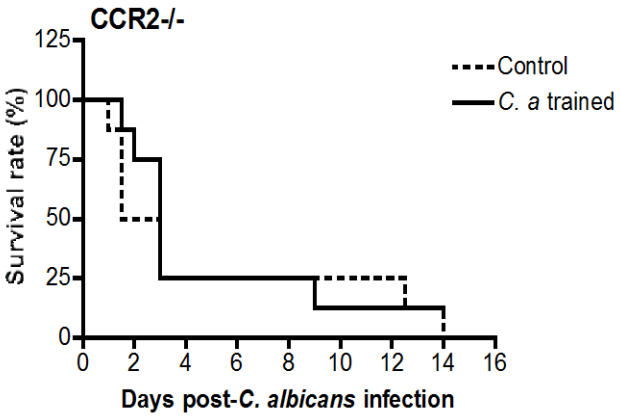
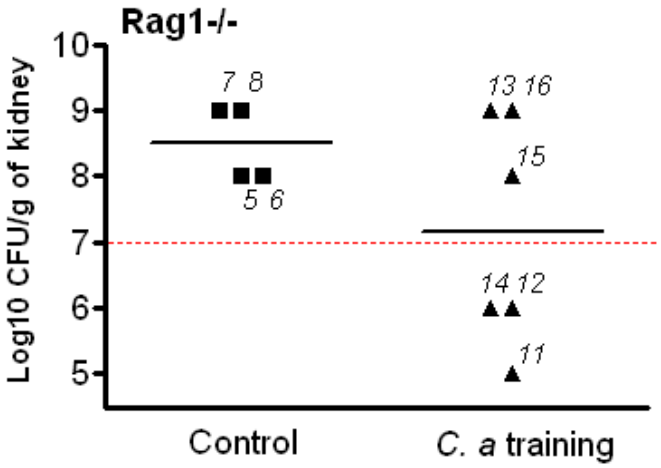
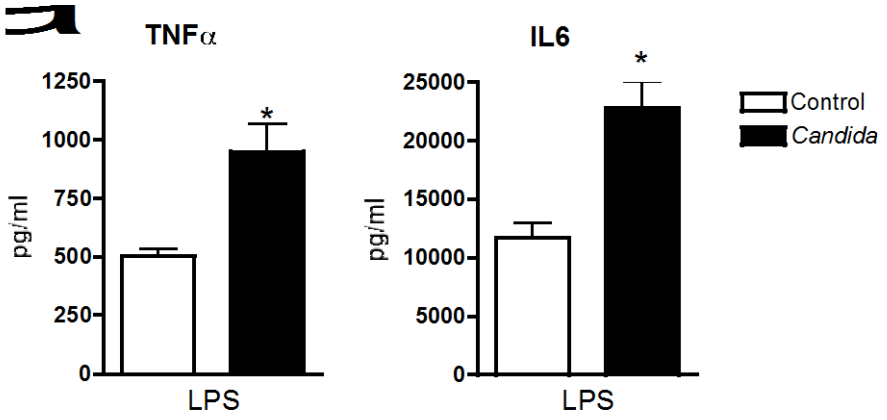
Innate immunity-dependent protection in mice











Quintin et al, Cell H&M, 2012

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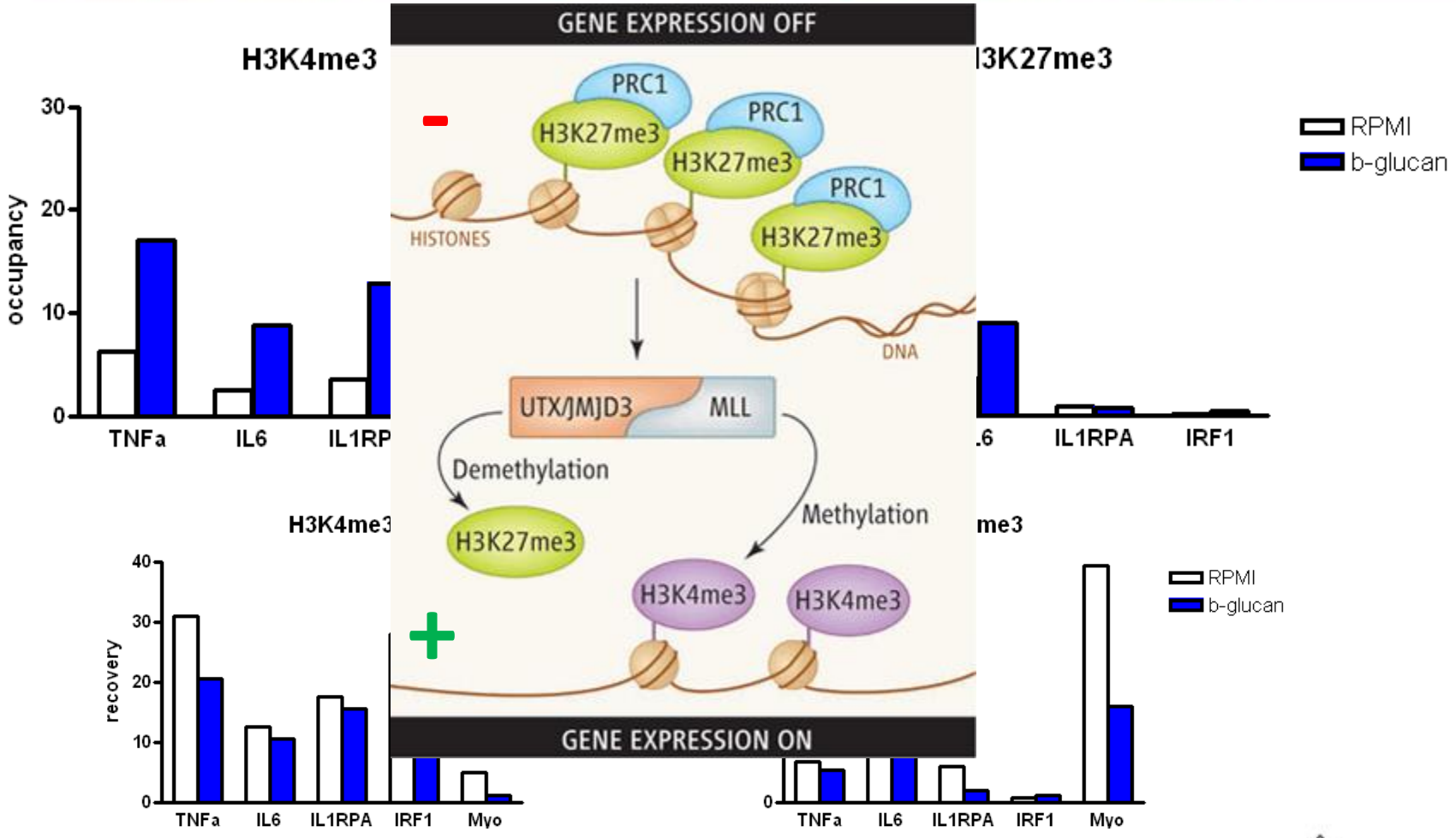
Methylation status of H3



Quintin et al, Cell H&M, 2012

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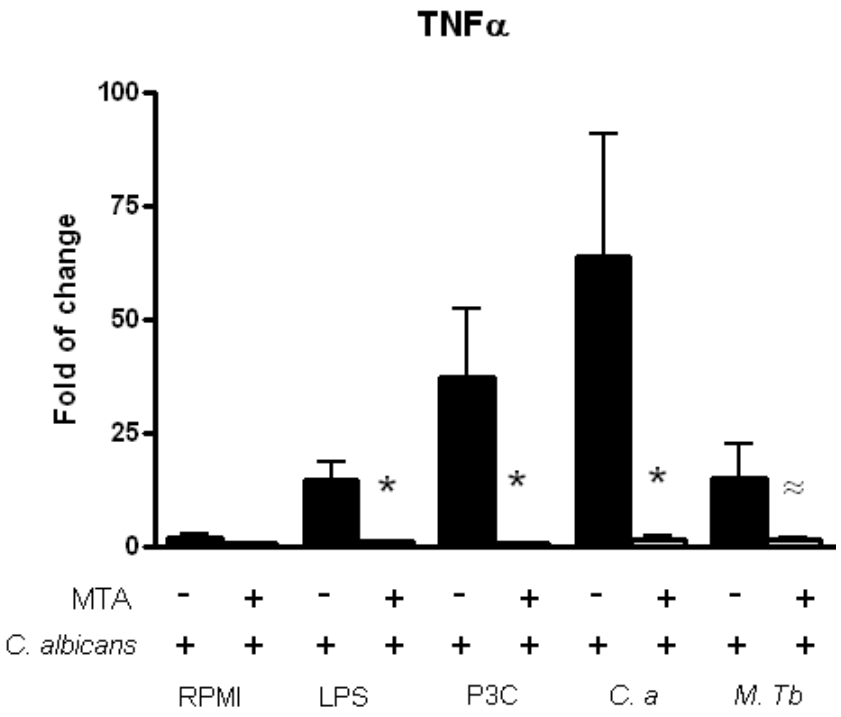
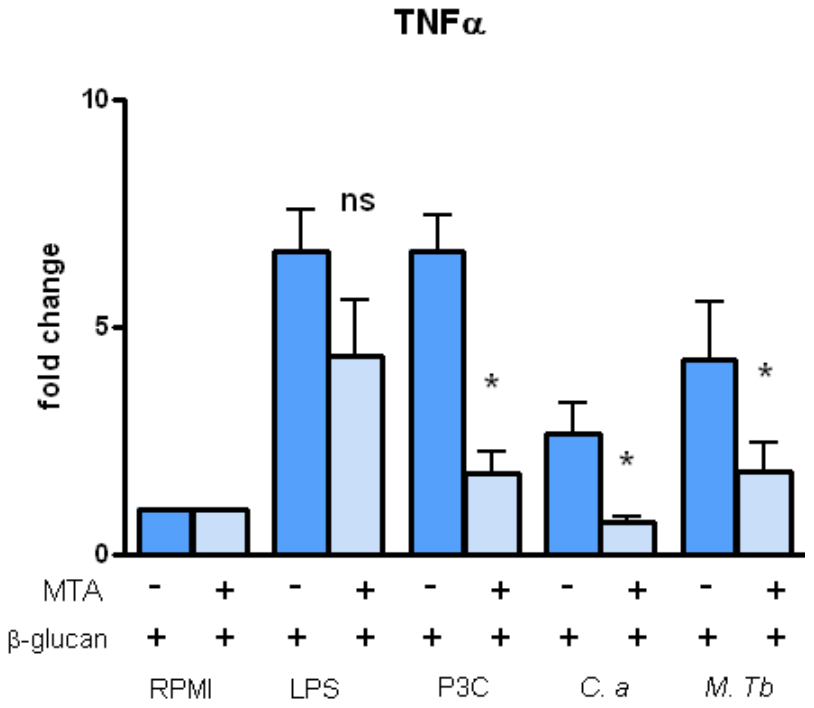
MTA: Histone methyltransferase inhibitor

Less Methylation





Quintin et al, Cell H&M, 2012

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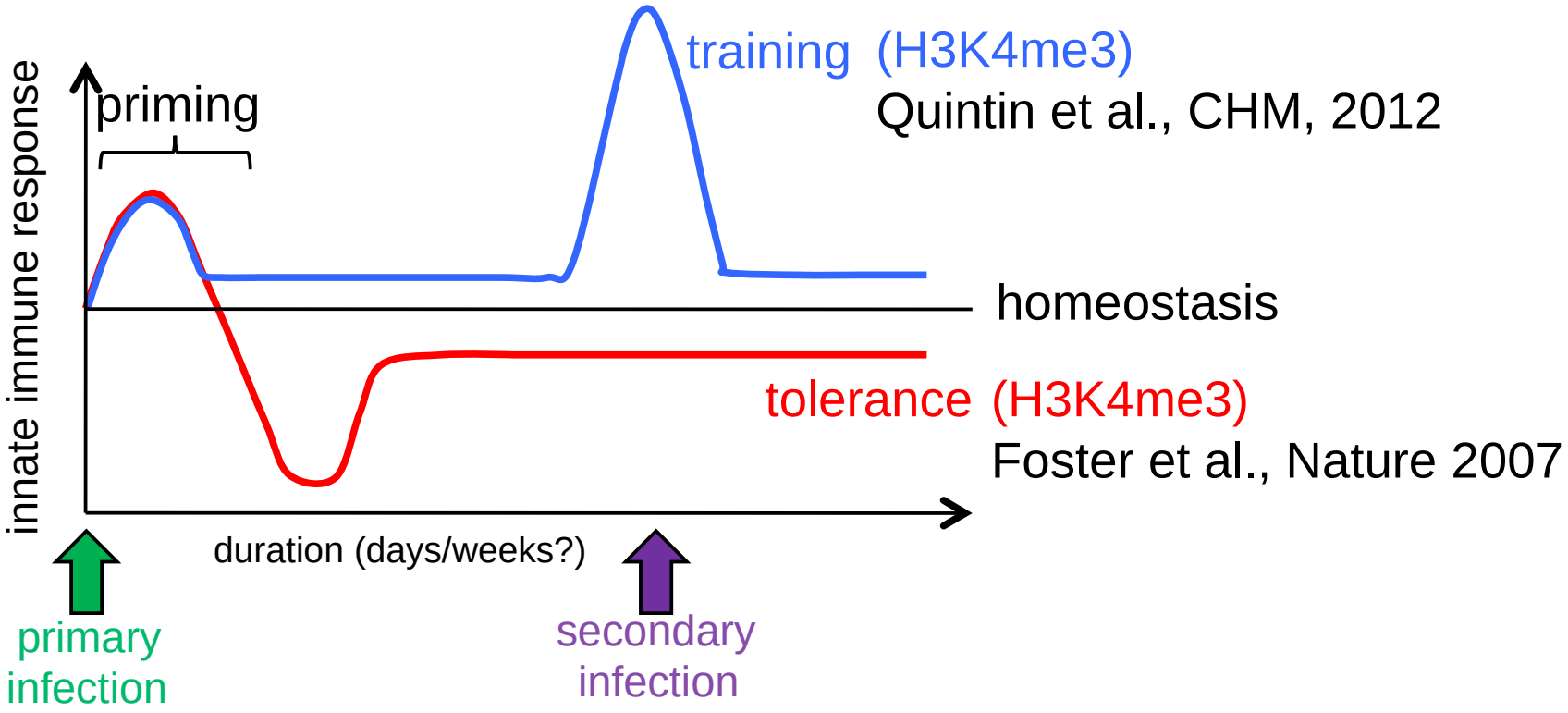
Trained immunity versus tolerance



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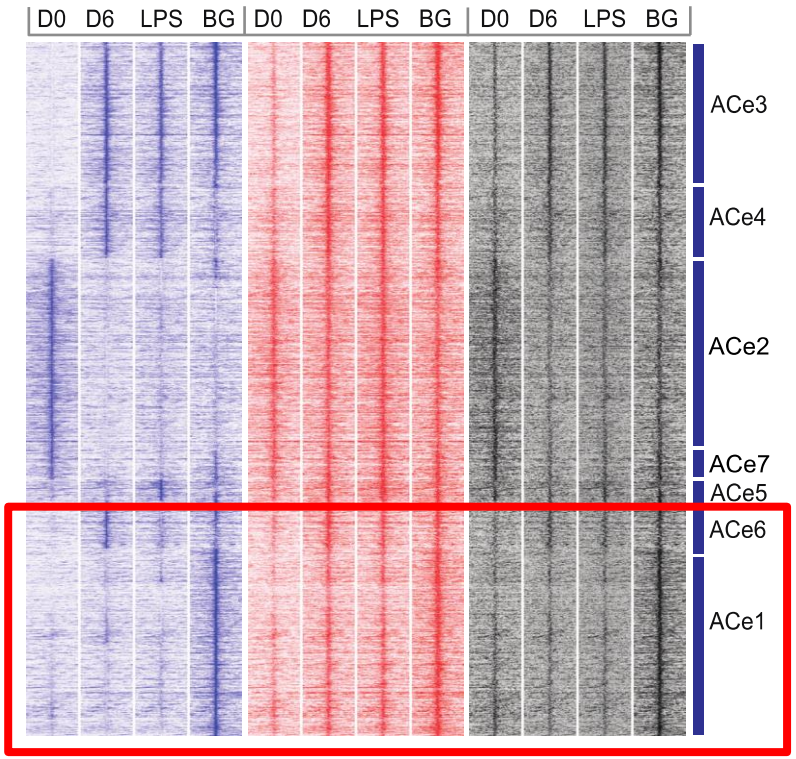
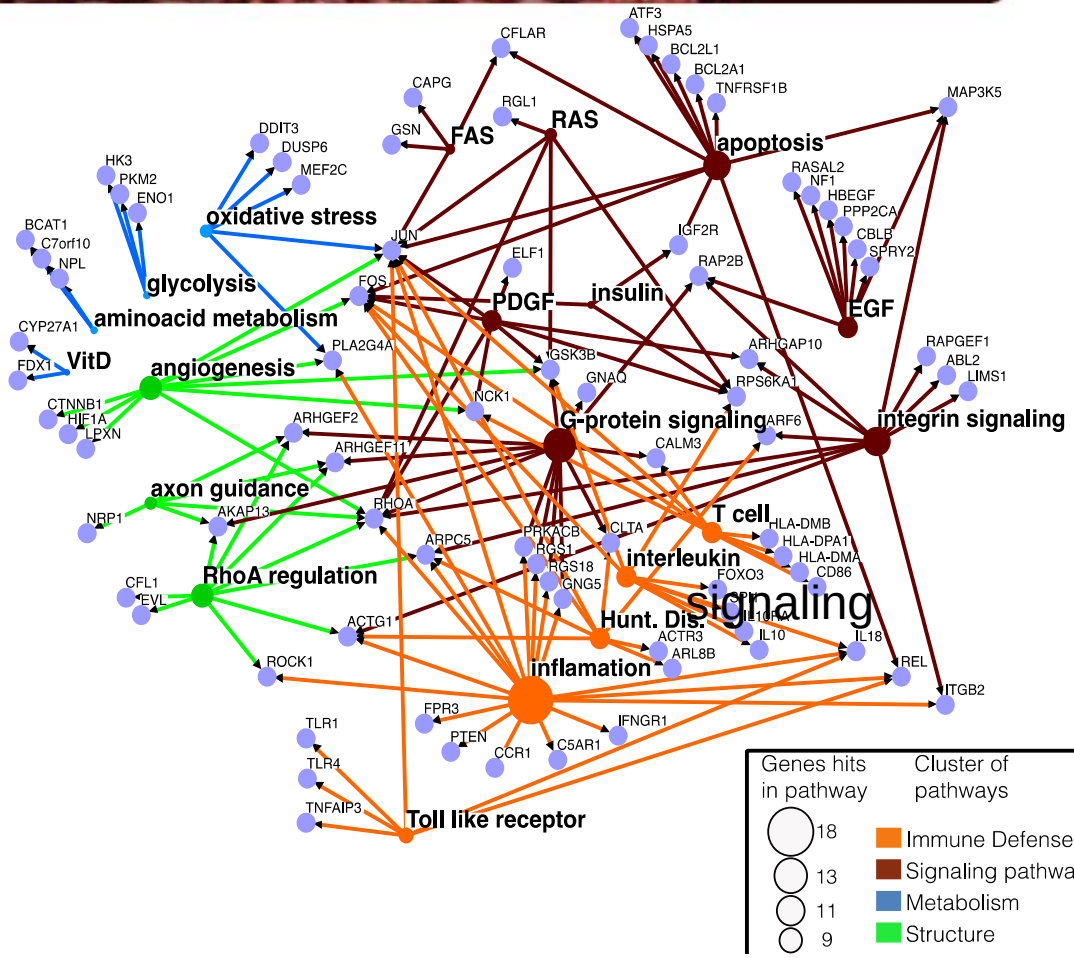
What are the pathways distinguishing Training vs Tolerance ?





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Saeed, Quintin et al, Science, 2014

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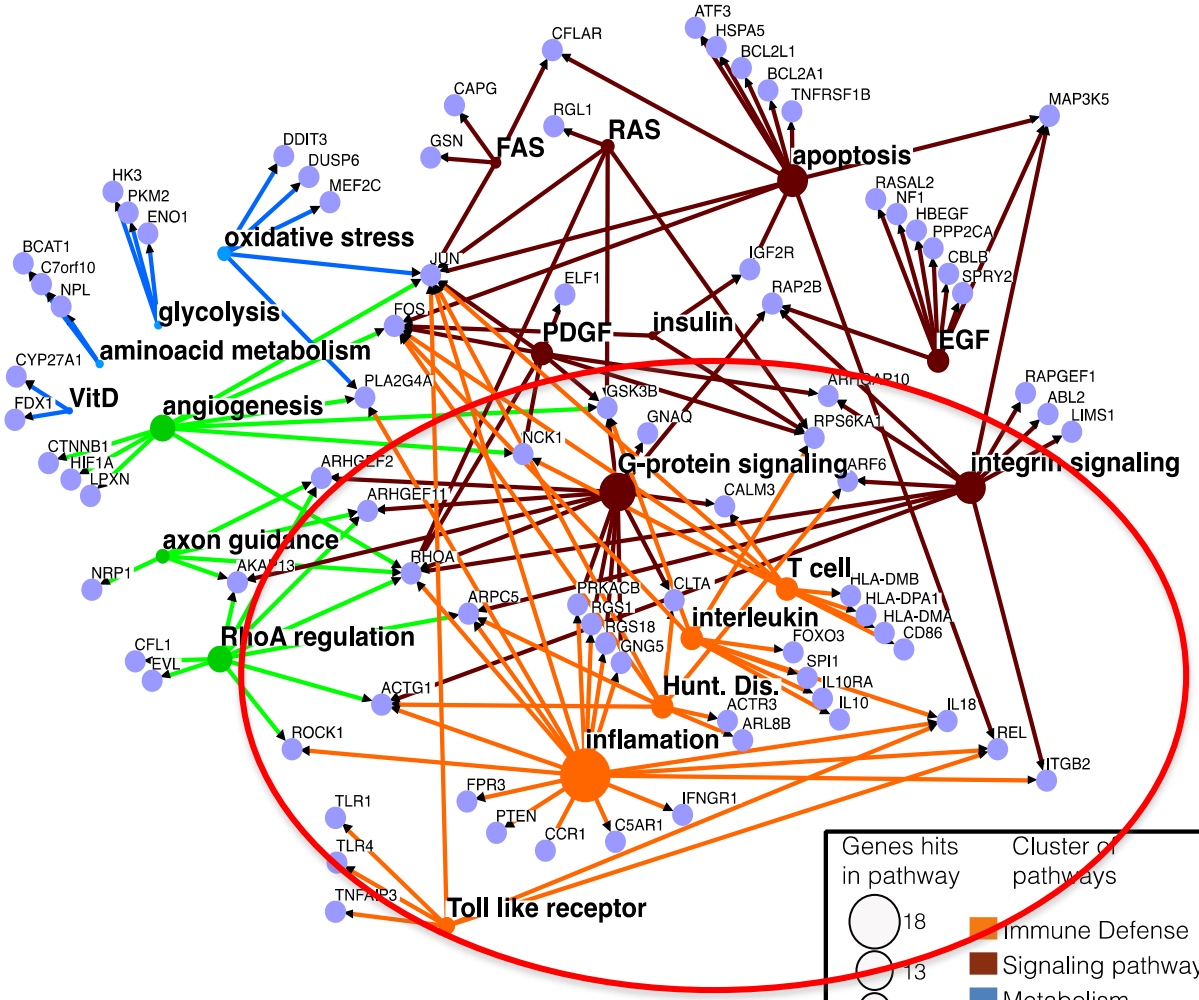
What are the pathways distinguishing Training vs Tolerance ?

metabolism



signaling

Saeed, Quintin et al, Science, 2014

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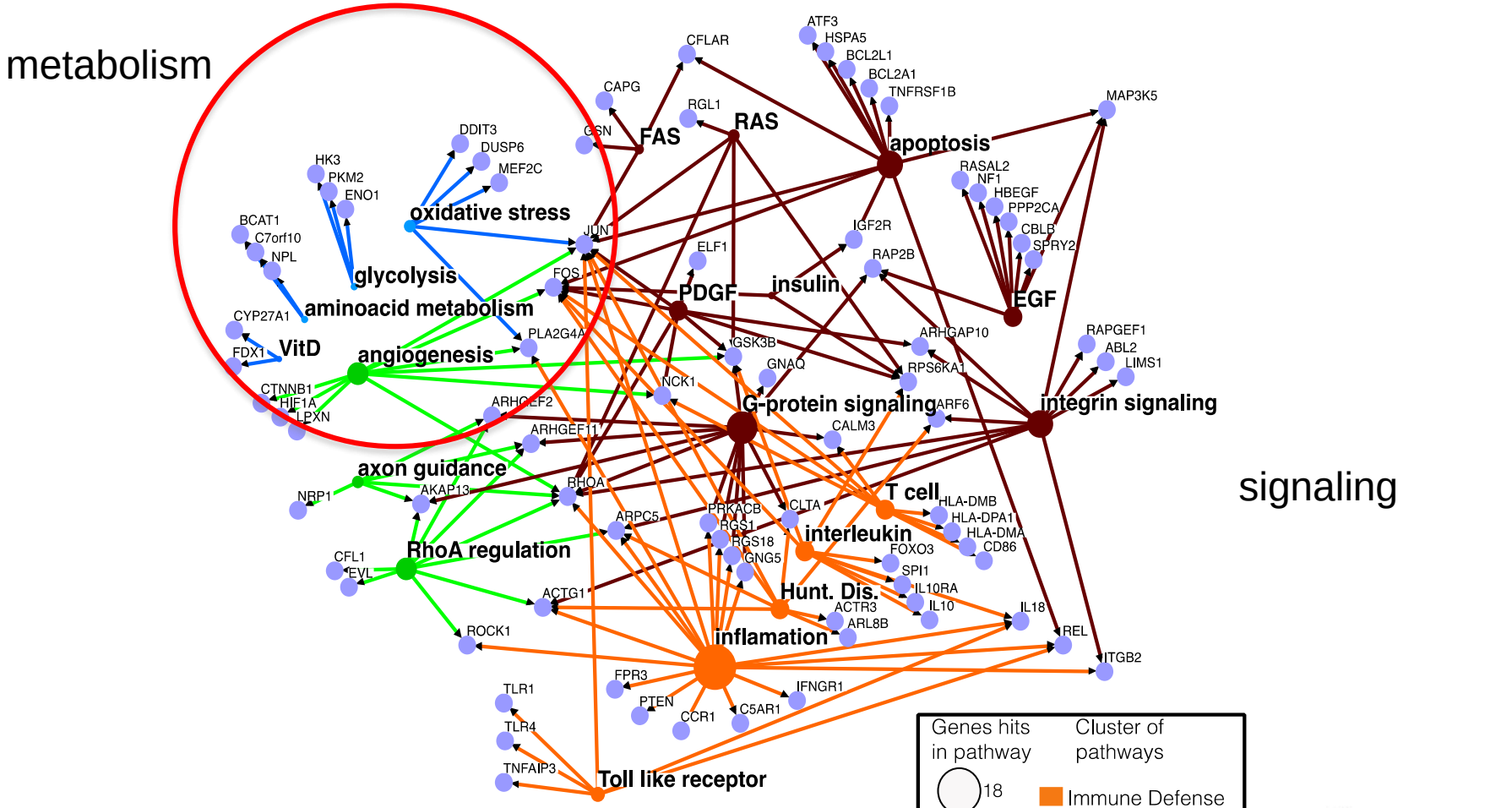
What are the pathways distinguishing Training vs Tolerance ?



Saeed, Quintin et al, Science, 2014

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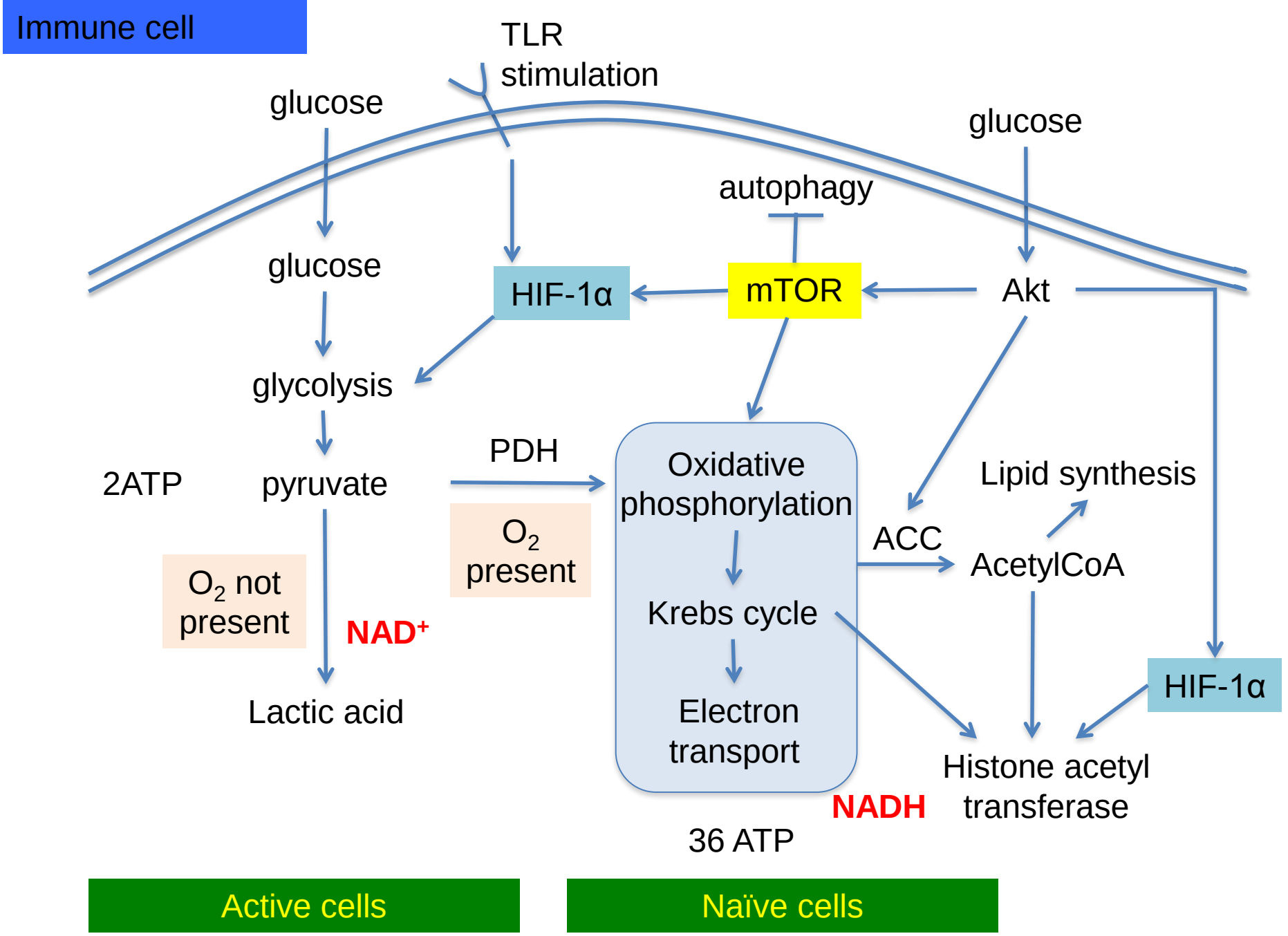
Immune cell
TLR stimulation
glucose
glucose
glucose
autophagy
HIF-1α
mTOR
Akt
glycolysis
2ATP
pyruvate
PDH
Oxidative phosphorylation
Lipid synthesis
ACC
AcetylCoA
O2 not present
NAD+
O2 present
Krebs cycle
Electron transport
HIF-1α
Lactic acid
Histone acetyl transferase
NADH
36 ATP
Active cells
Naïve cells

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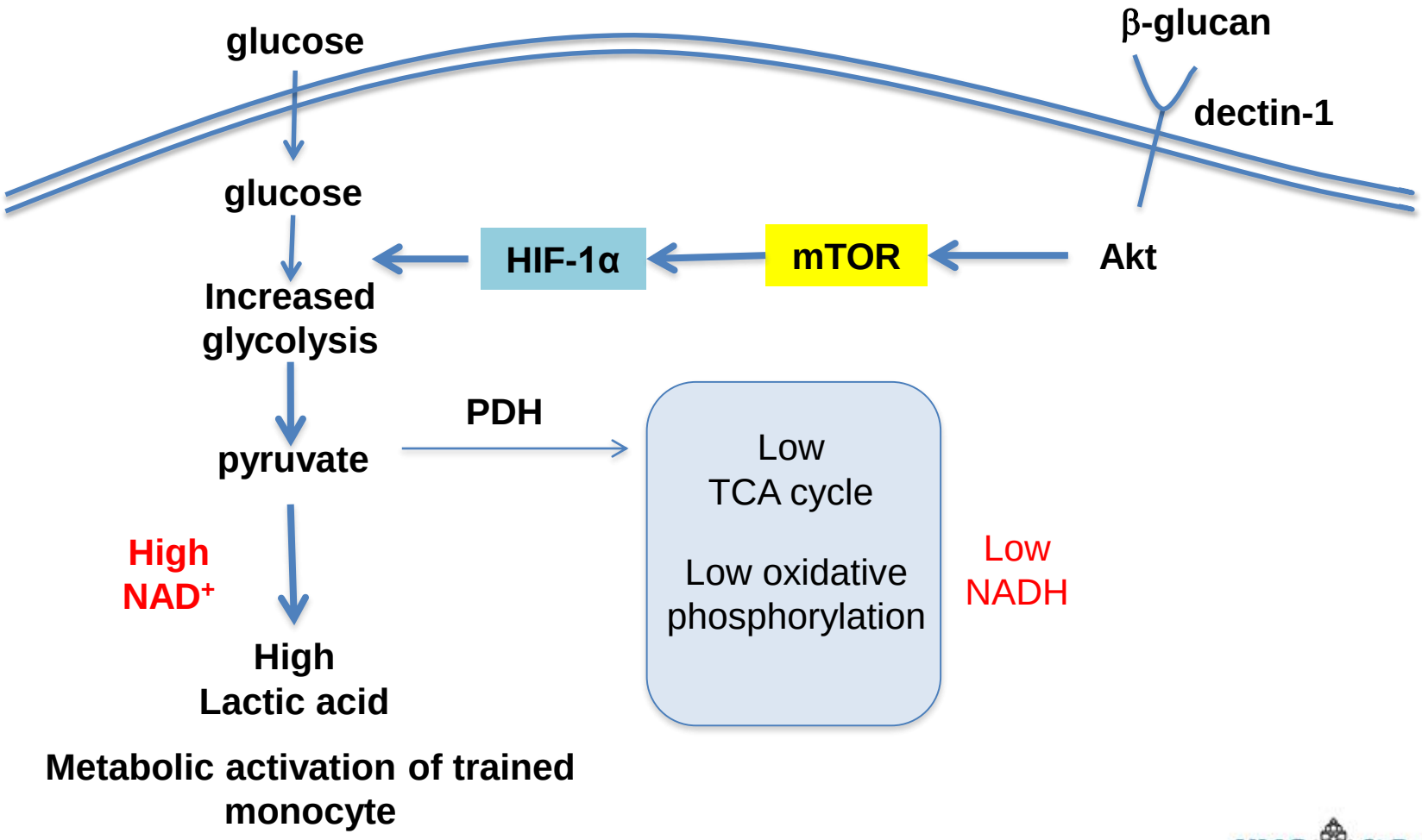
Model of metabolic activation of trained monocytes



Cheng et al, Science, 2014

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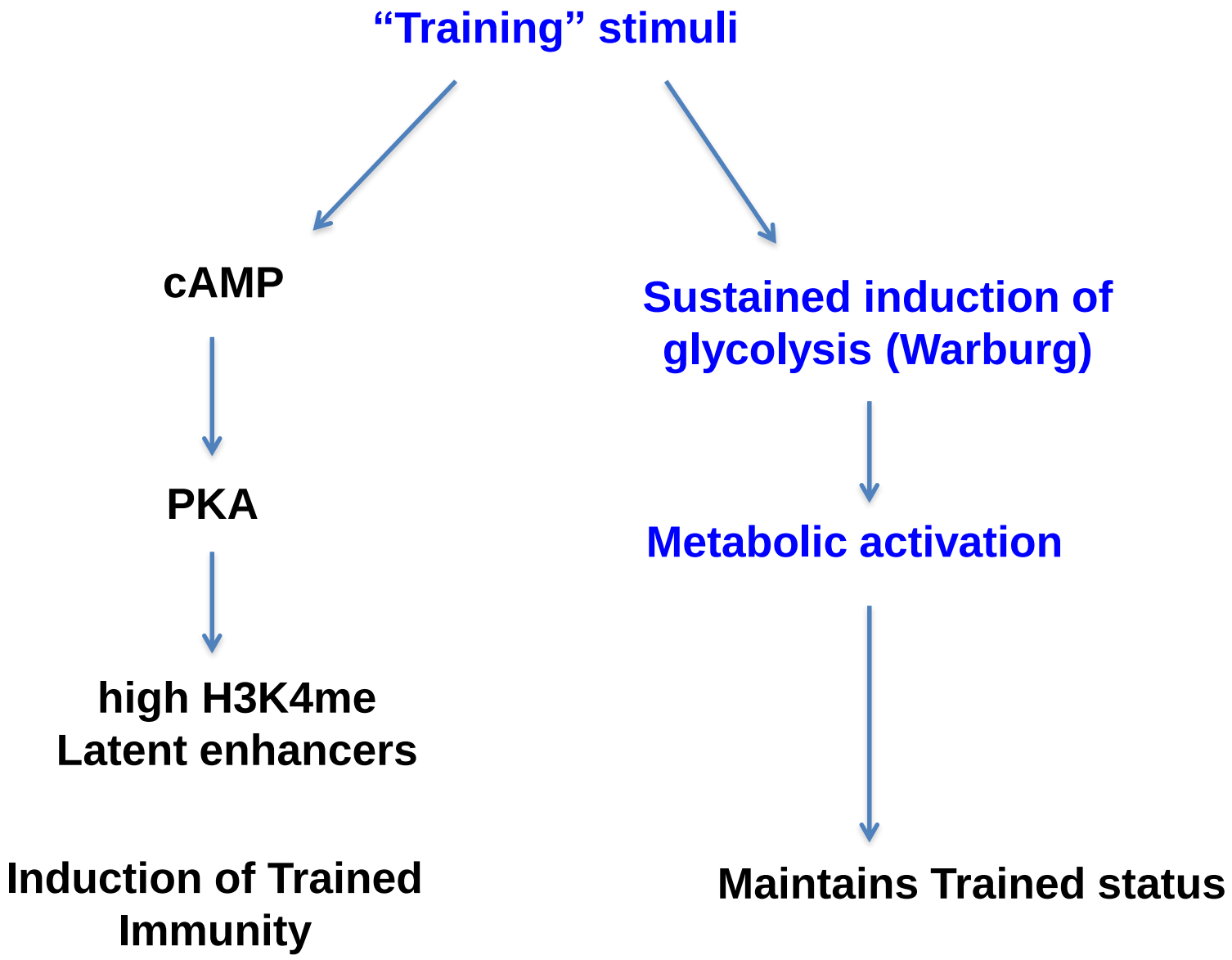
Metabolic status and epigenetic programming decides the long-term activation fate of the monocyte



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Trained immunity in humans

Pediatr Allergy Immunol 2008: 19: 455–468
DOI: 10.1111/j.1399-3038.2007.00668.x

PEDIATRIC ALLERGY AND IMMUNOLOGY

Potential health effects from non-specific stimulation of the immune function in early age: The example of BCG vaccination

New Scientist
Aug. 2013

Small shot, big impact

Some vaccines seem to provide us with a host of extra benefits. Michael Brooks sees the cornerstone of modern medicine in a new light

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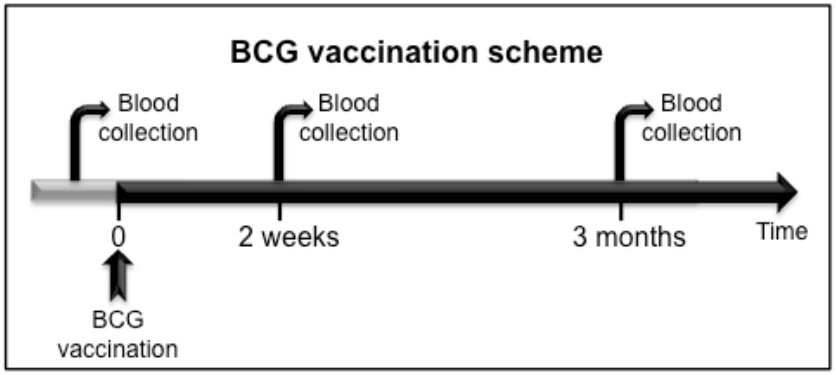
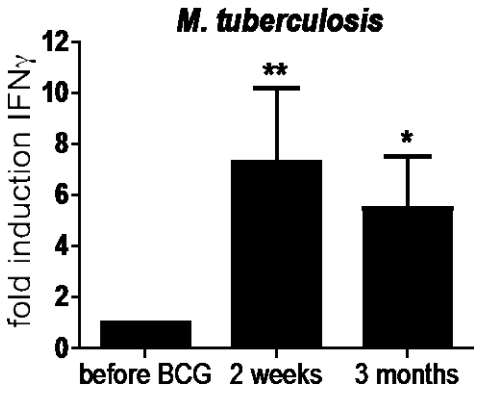
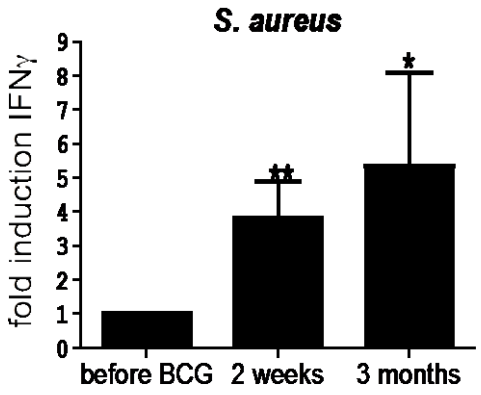
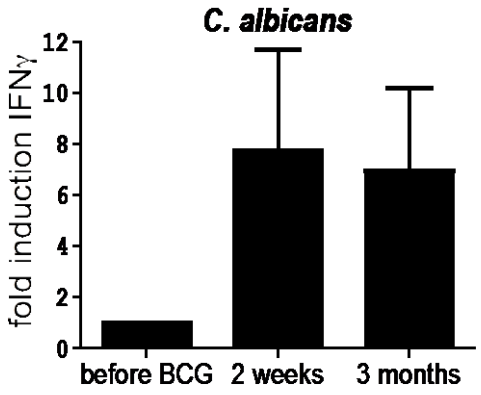
Does this happen in vivo in humans?









Kleinnijenhuis et al, PNAS, 2012

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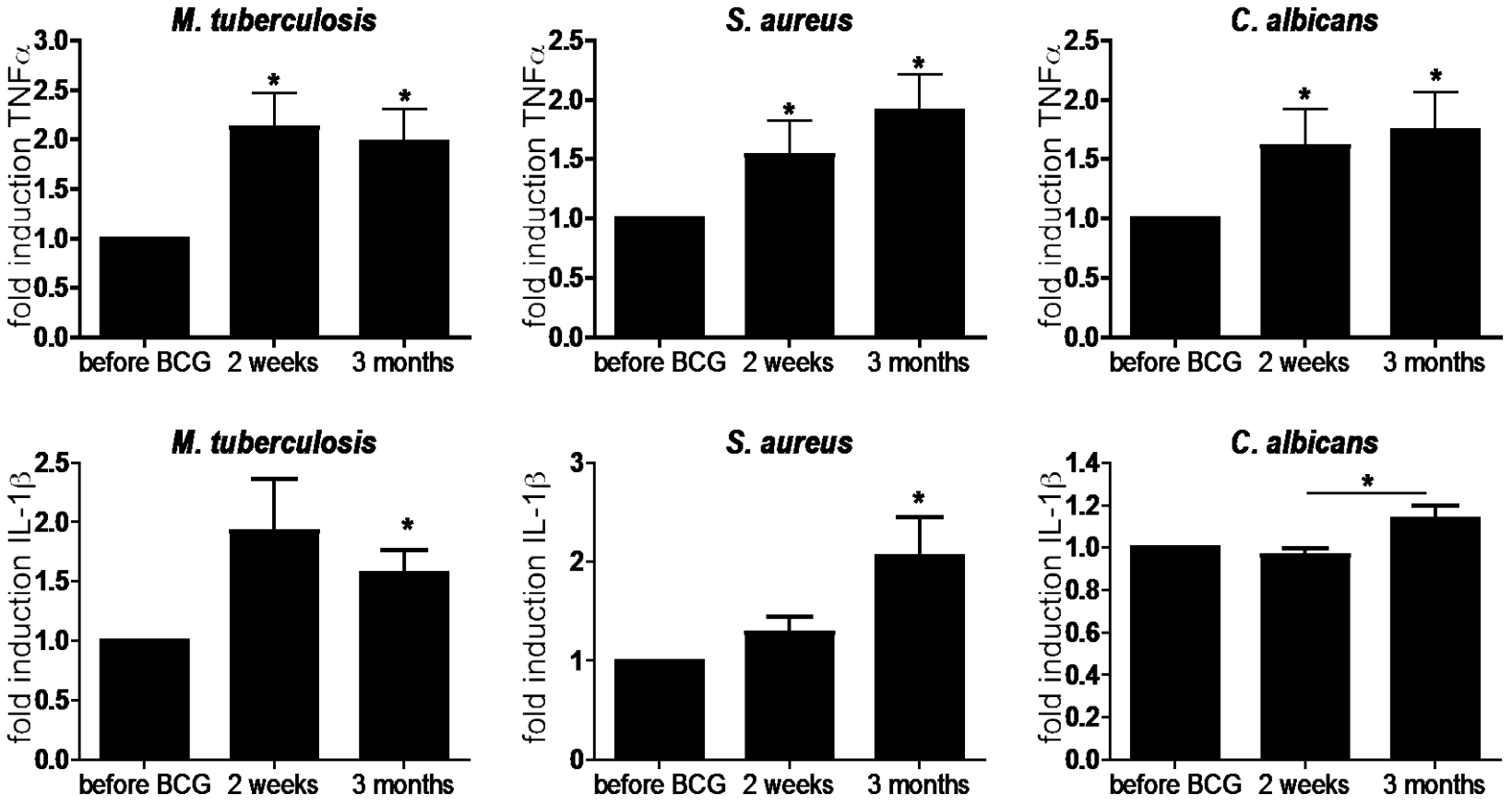
BCG enhances monocyte-derived cytokines



Kleinnijenhuis et al, PNAS, 2012

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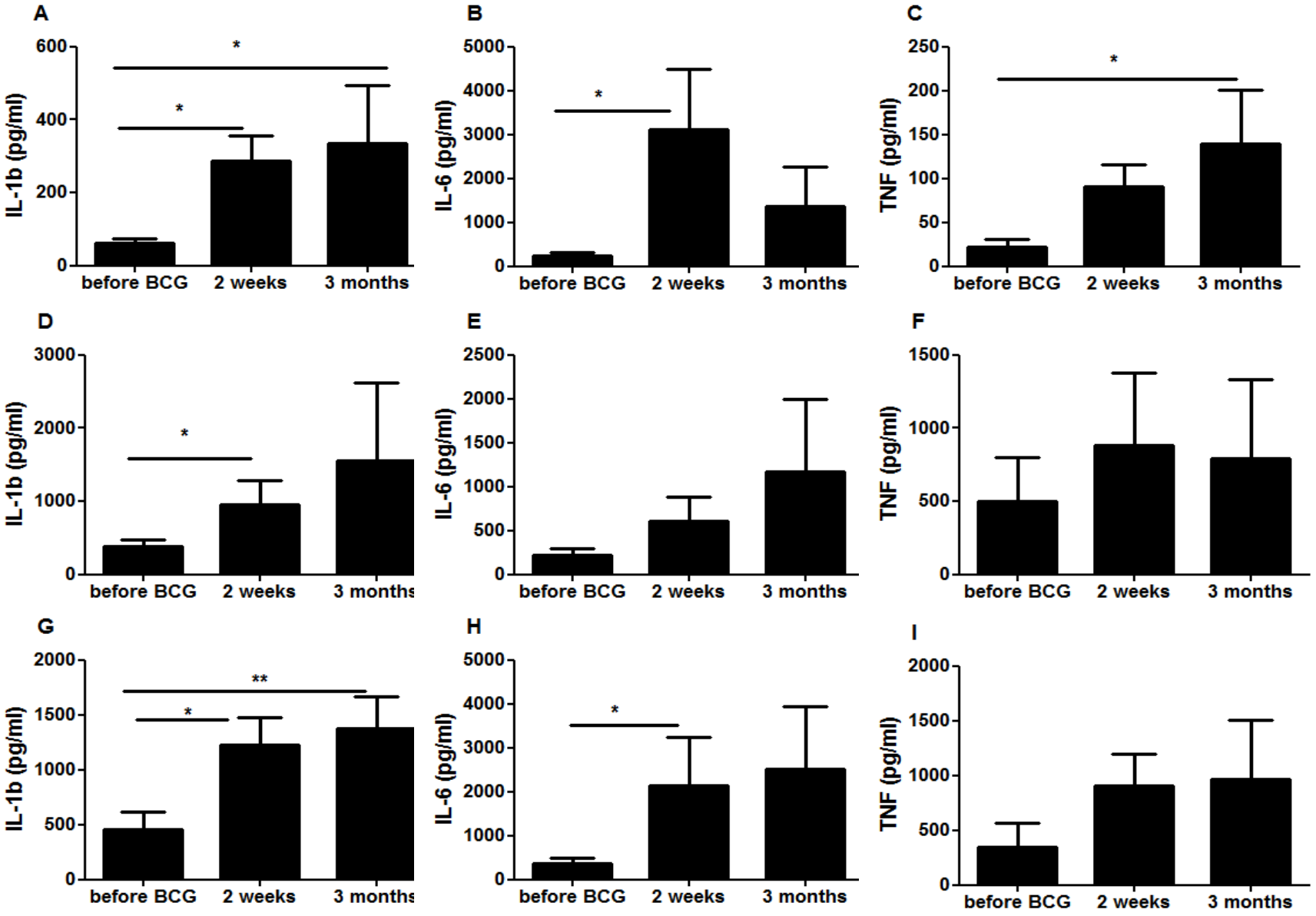
BCG increases NK cell function



Kleinnijenhuis et al, Clin Immunol 2014

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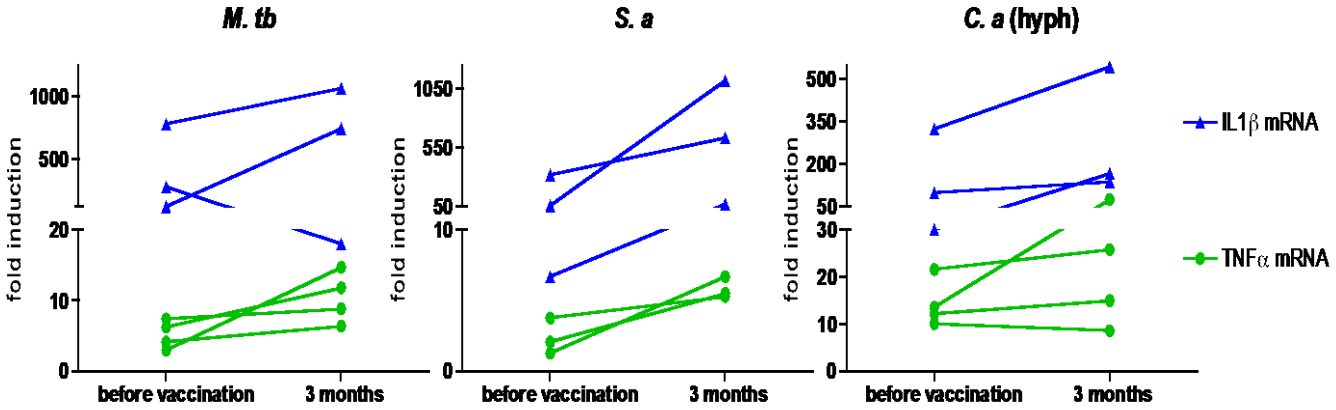
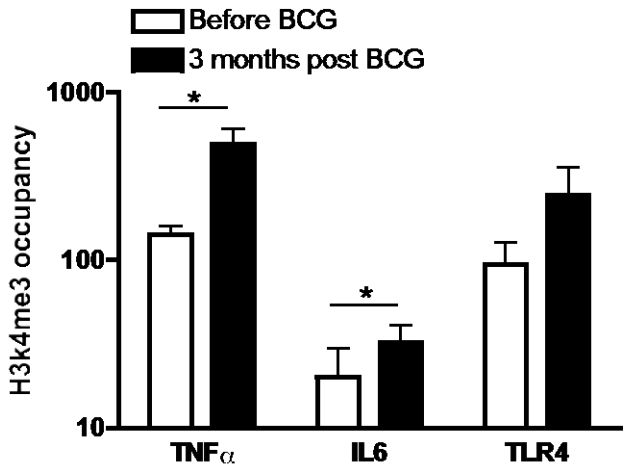
BCG effects on epigenetics and transcription





Kleinnijenhuis et al, PNAS, 2012

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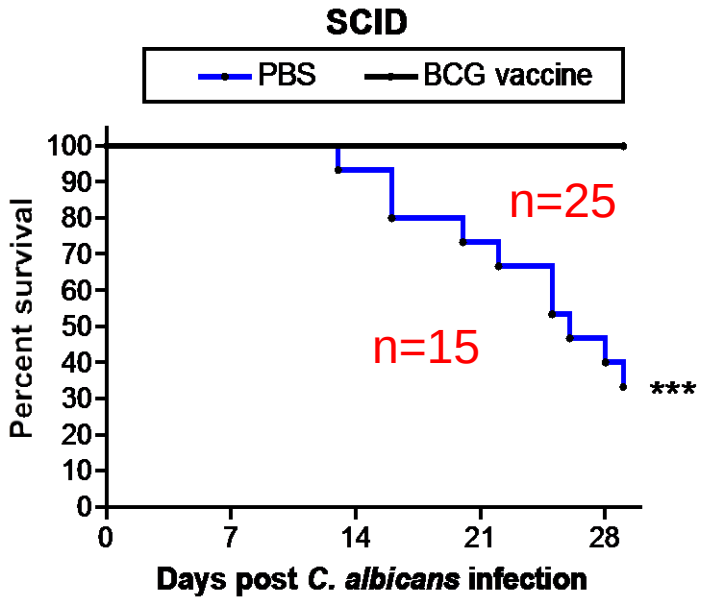
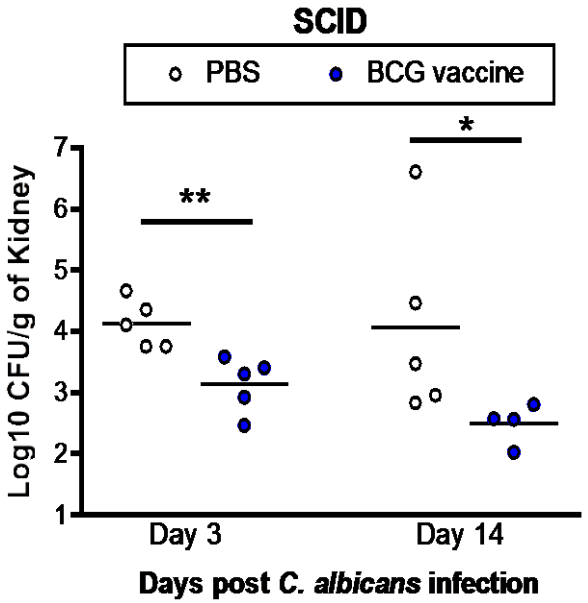
BCG protects against candidiasis in a T/B-independent fasion





Kleinnijenhuis et al, PNAS, 2012

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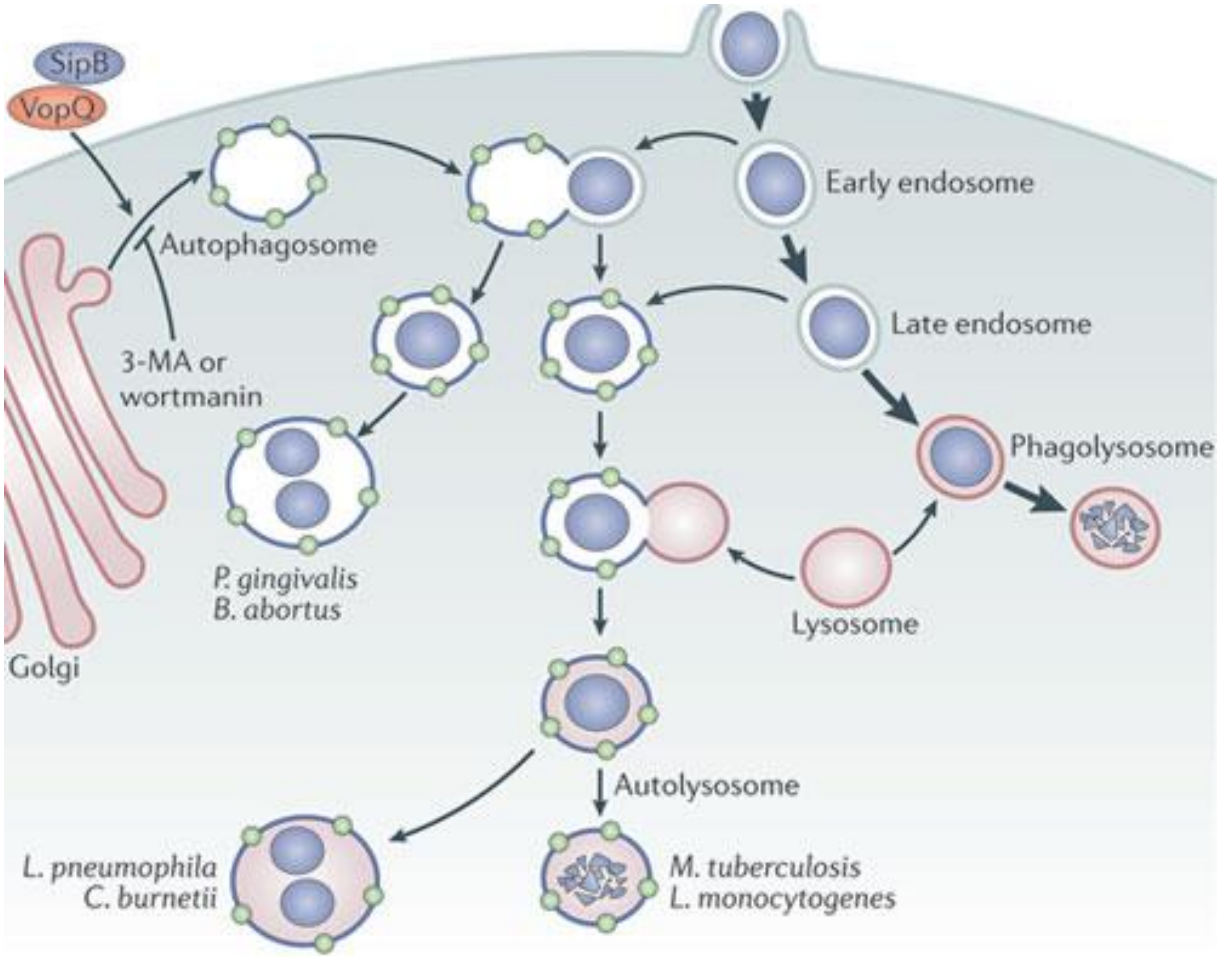
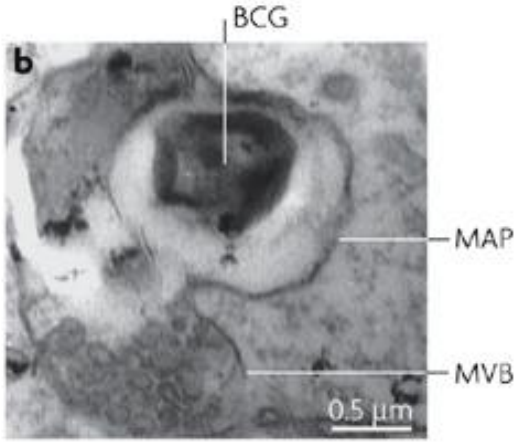
Is autophagy involved in Trained Immunity induced by BCG ?



Nature Reviews | Microbiology



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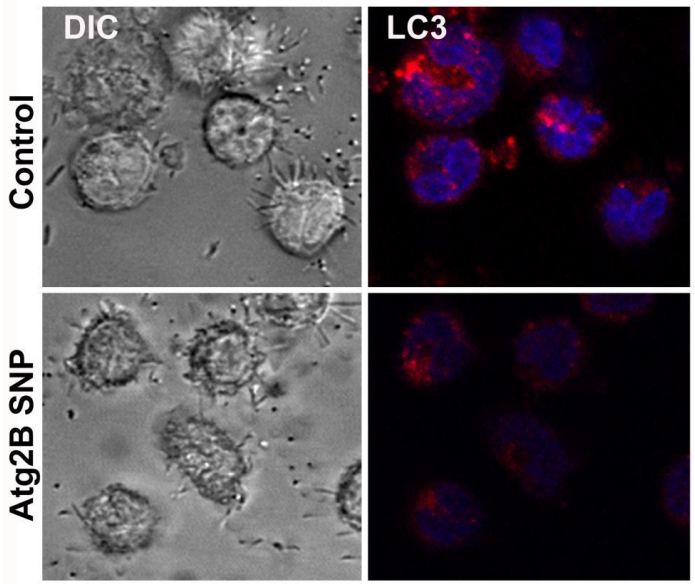
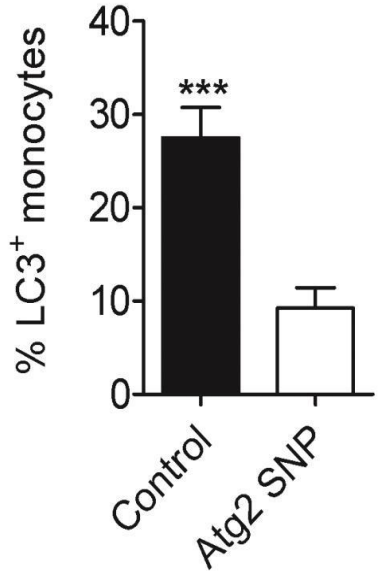
SNP in ATG2B (rs3759601)





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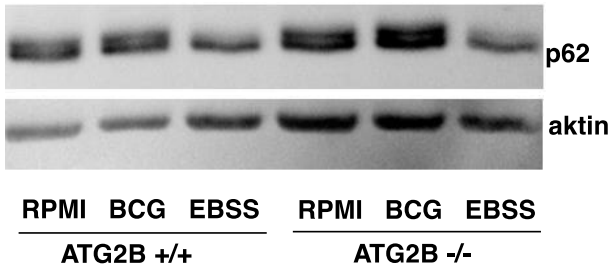

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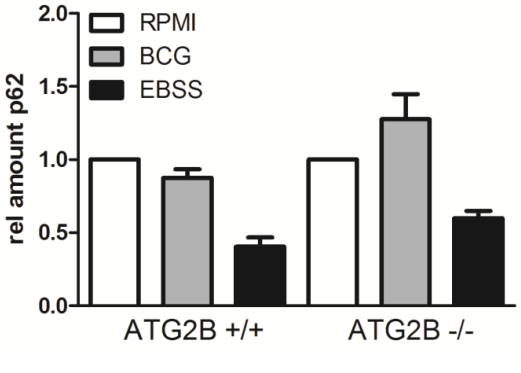

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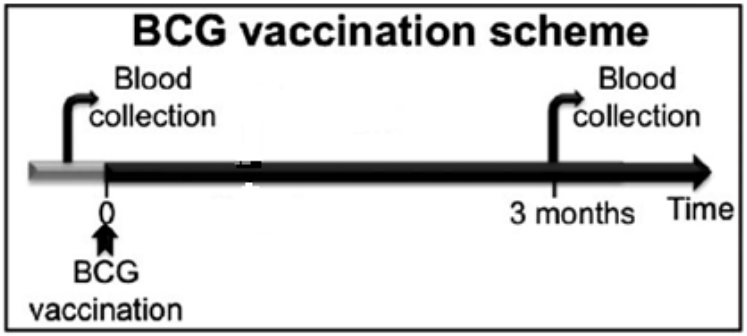
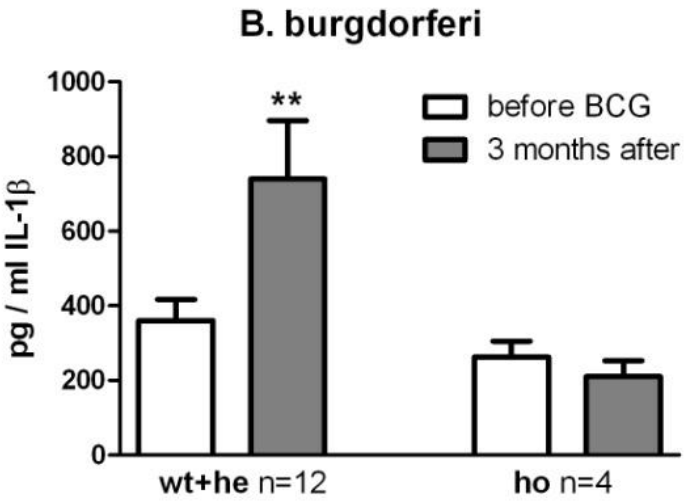
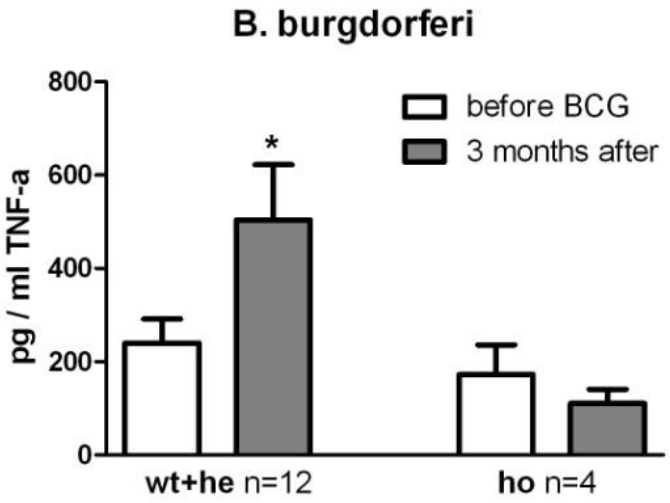
Buffen et al, PLoS Pathogens, in press

BCG study – in vivo





ATG2B
(rs3759601)



ATG2B
(rs3759601)

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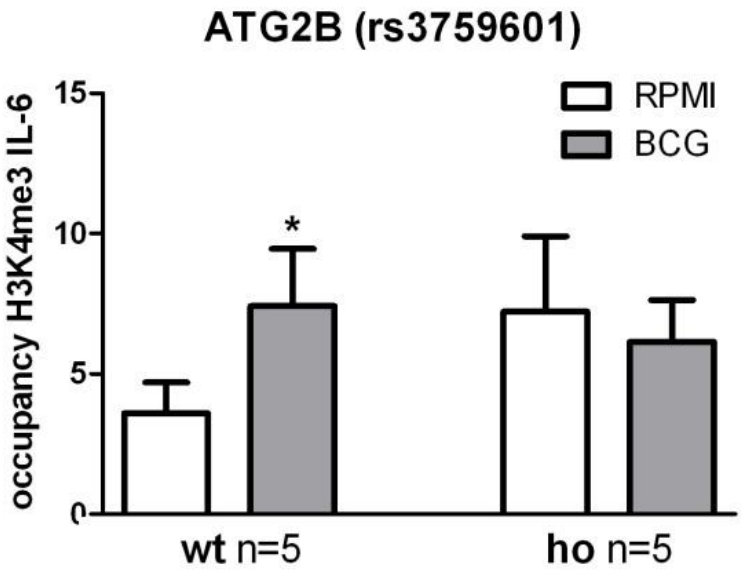
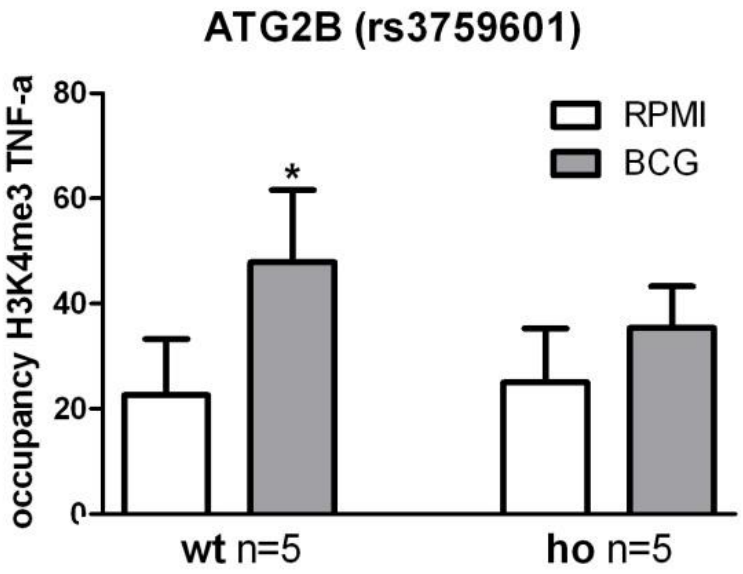
Buffen et al, PLoS Pathogens, in press

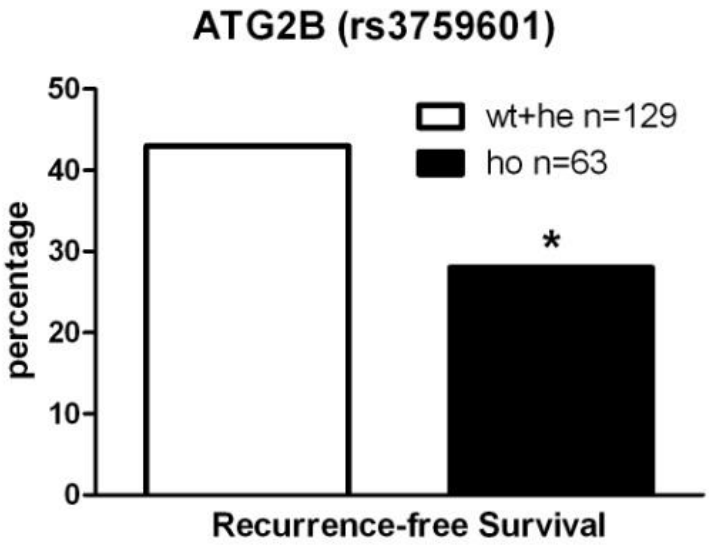
Effect on epigenetic level

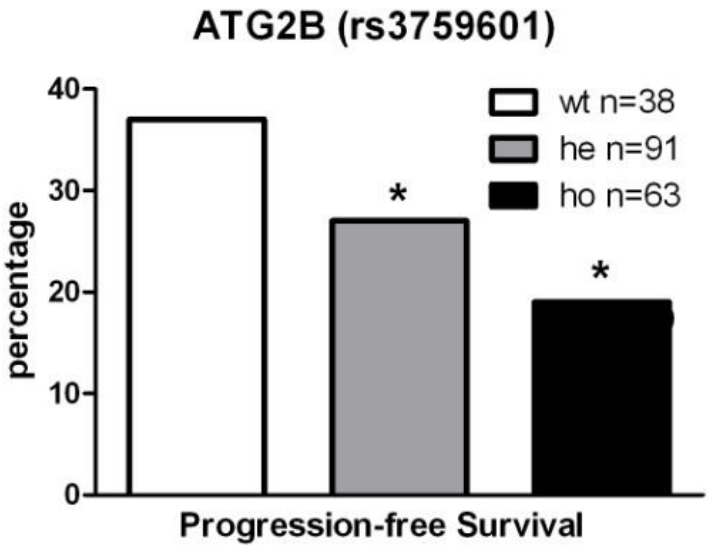




Buffen et al, PLoS Pathogens, in press

Bladder cancer study





Buffen et al, PLoS Pathogens, in press

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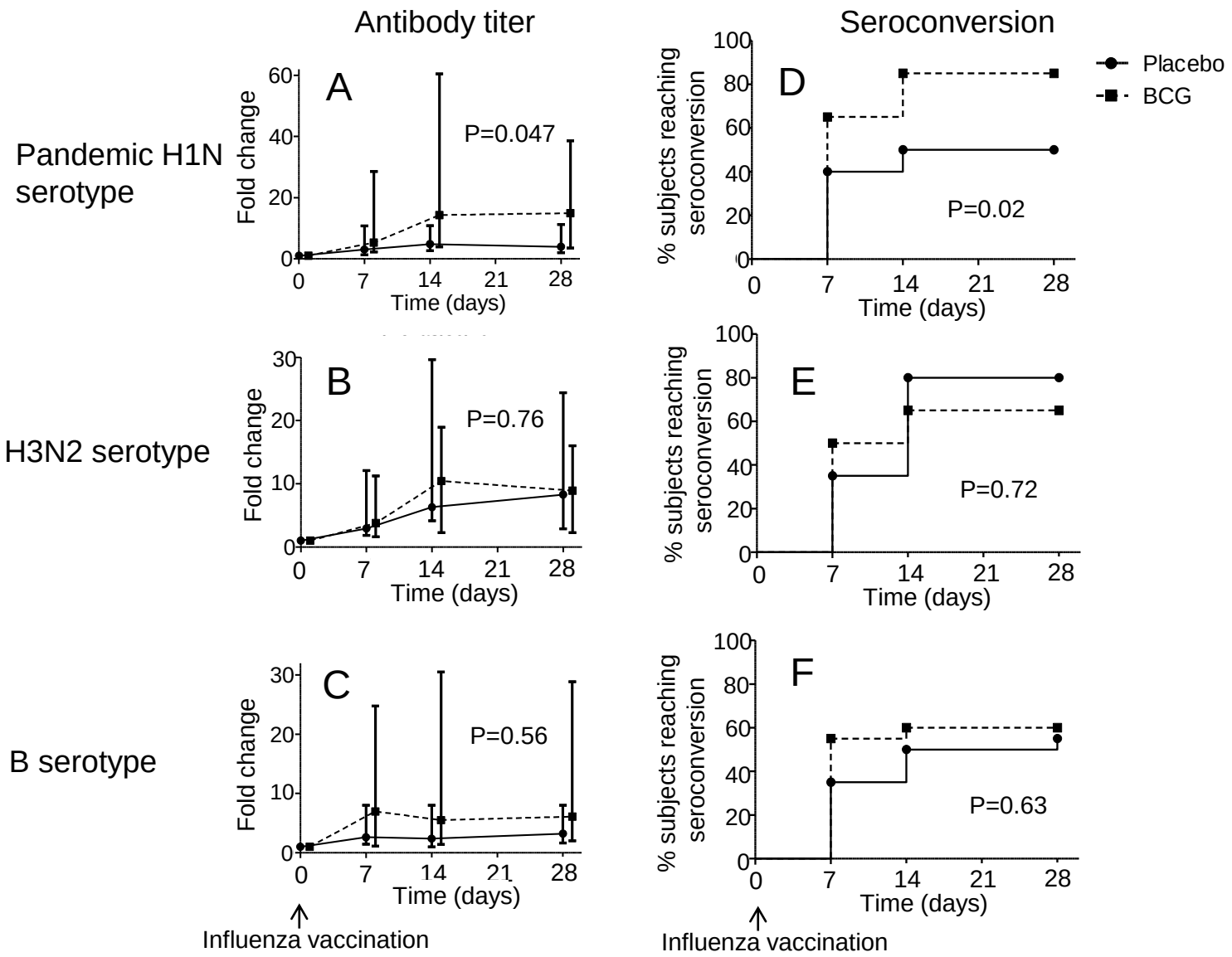
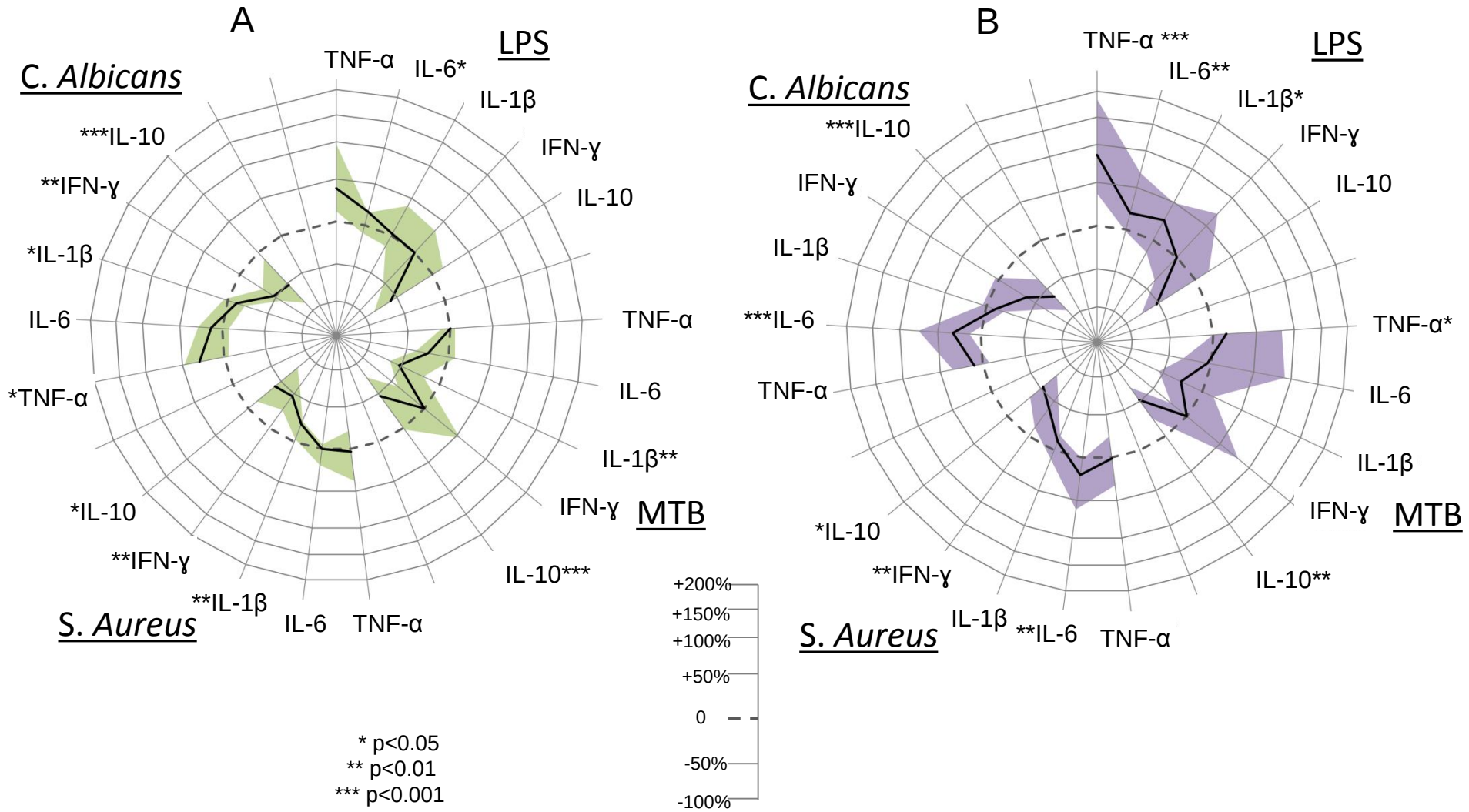
BCG increases immunogenicity of influenza vaccine



Leentjens et al, submitted

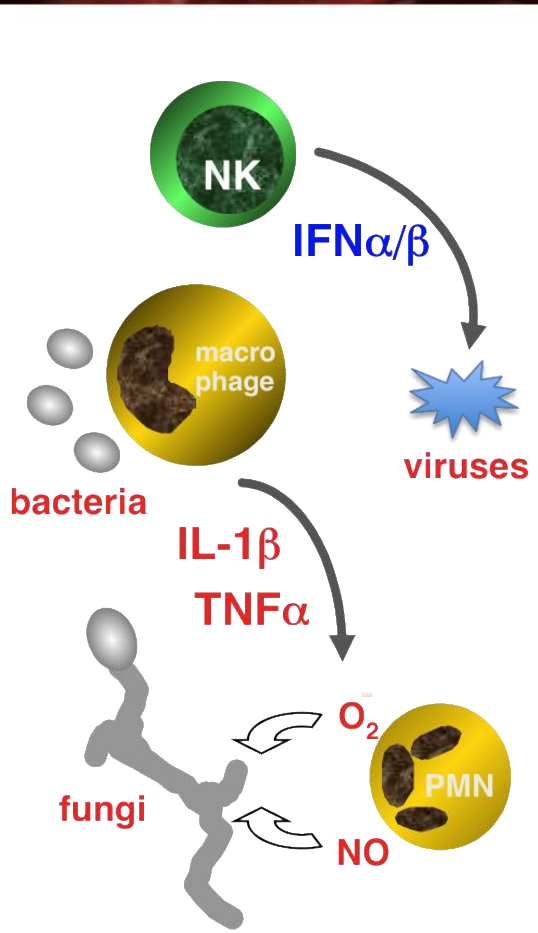
BCG increases immunogenicity of influenza vaccine

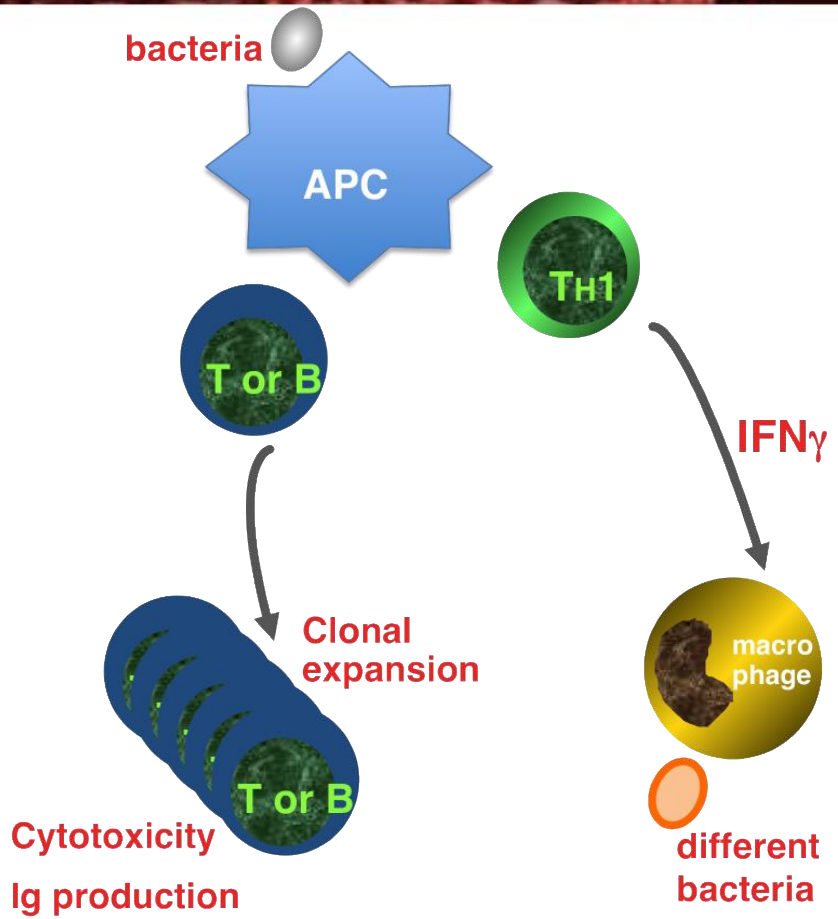


Leentjens et al, submitted

Nijmegen Institute for Infection, Inflammation & Immunity

Classical view





Innate immunity

Rapid, non-specific, no memory

Adaptive immunity

Slow, specific, builds memory

T-cell/IFNγ dependent cross-protection

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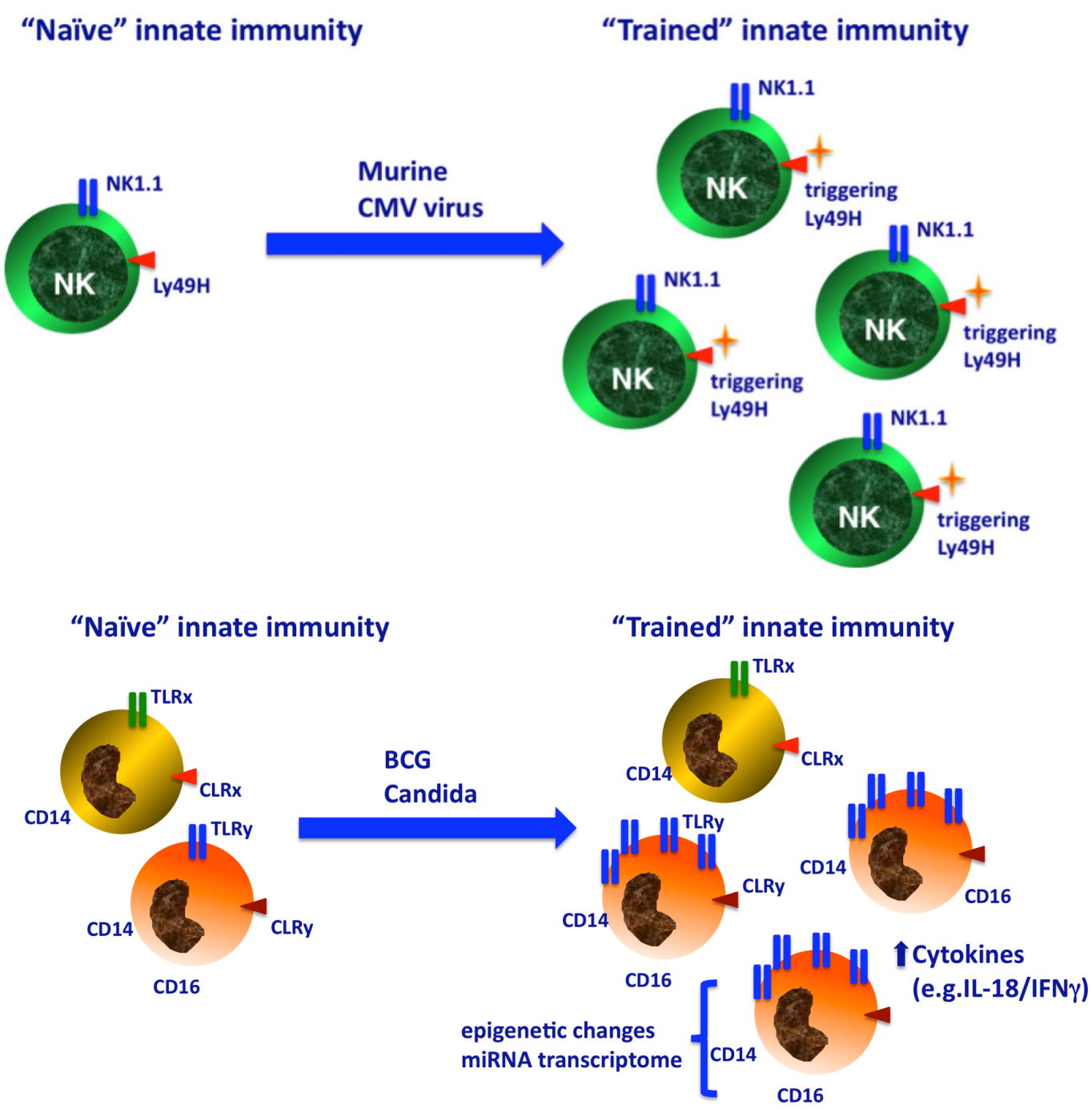
"Naïve" innate immunity
"Trained" innate immunity
NK1.1
NK
Ly49H
Murine
CMV virus
triggering
Ly49H
"Naïve" innate immunity
"Trained" innate immunity
TLRx
CLRx
CD14
TLRy
CLRy
CD16
BCG
Candida
Cytokines
(e.g.IL-18/IFNγ)
epigenetic changes
miRNA transcriptome
St Radboud

Our lab

Jessica Quintin
James Cheng
Siroon Bekkering
Johanneke Kleinnijenhuis
Jos W.M. van der Meer
Leo Joosten
Reinout van Crevel

Dept. Molecular Biology - Radboud

Sadia Saeed
Joost Martens
Colin Logie
Henk Stunnenberg

Dept. Intensive Care - Radboud

Matthijs Kox
Peter Pickkers

AMC - Amsterdam

Brendon Scicluna
Tom van der Poll

Harvard University

Aylwin Ng
Ramnik Xavier

Trinity College

Luke O'Neill

Athens University

Evangelos Giamarellos

East Tennessee State University

David Williams

UMC St Radboud