



Leiden University
Medical Center

TB adaptive immune evasion

May 3rd, 2016

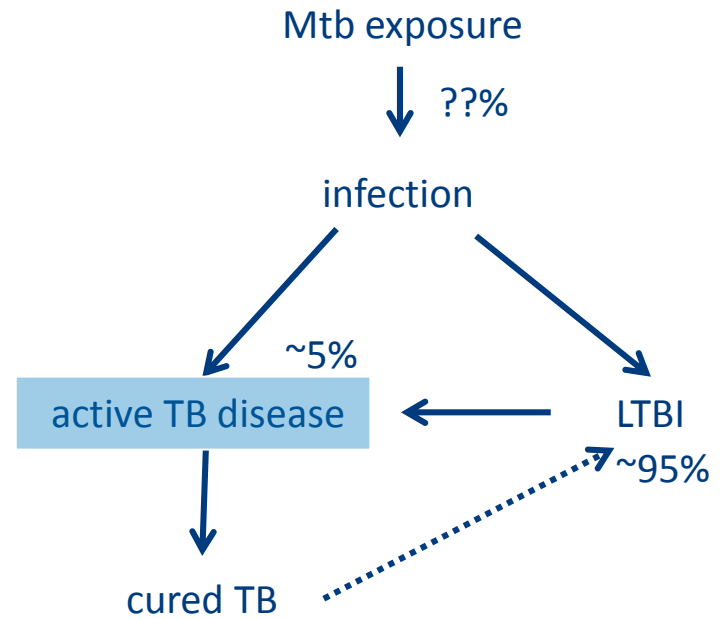
Simone A Joosten

Department of Infectious Diseases

LEIDEN UNIVERSITY MEDICAL CENTER

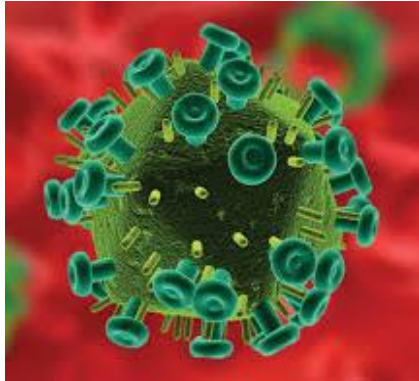


TB infection stages



BCG vaccination

Tuberculosis (TB) - interactions



HIV



helminths



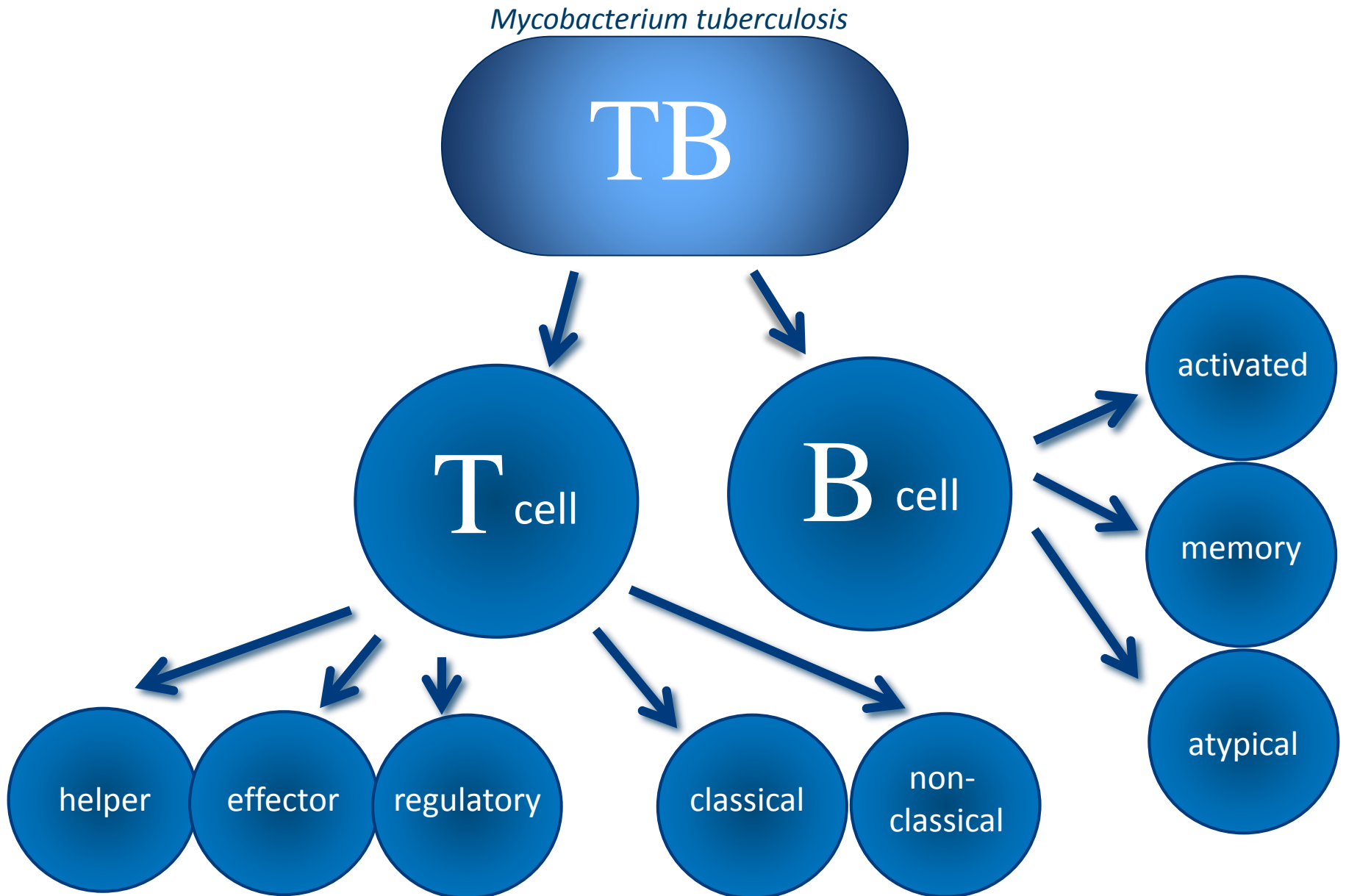
T2DM

Co-infections or co-morbidities can:

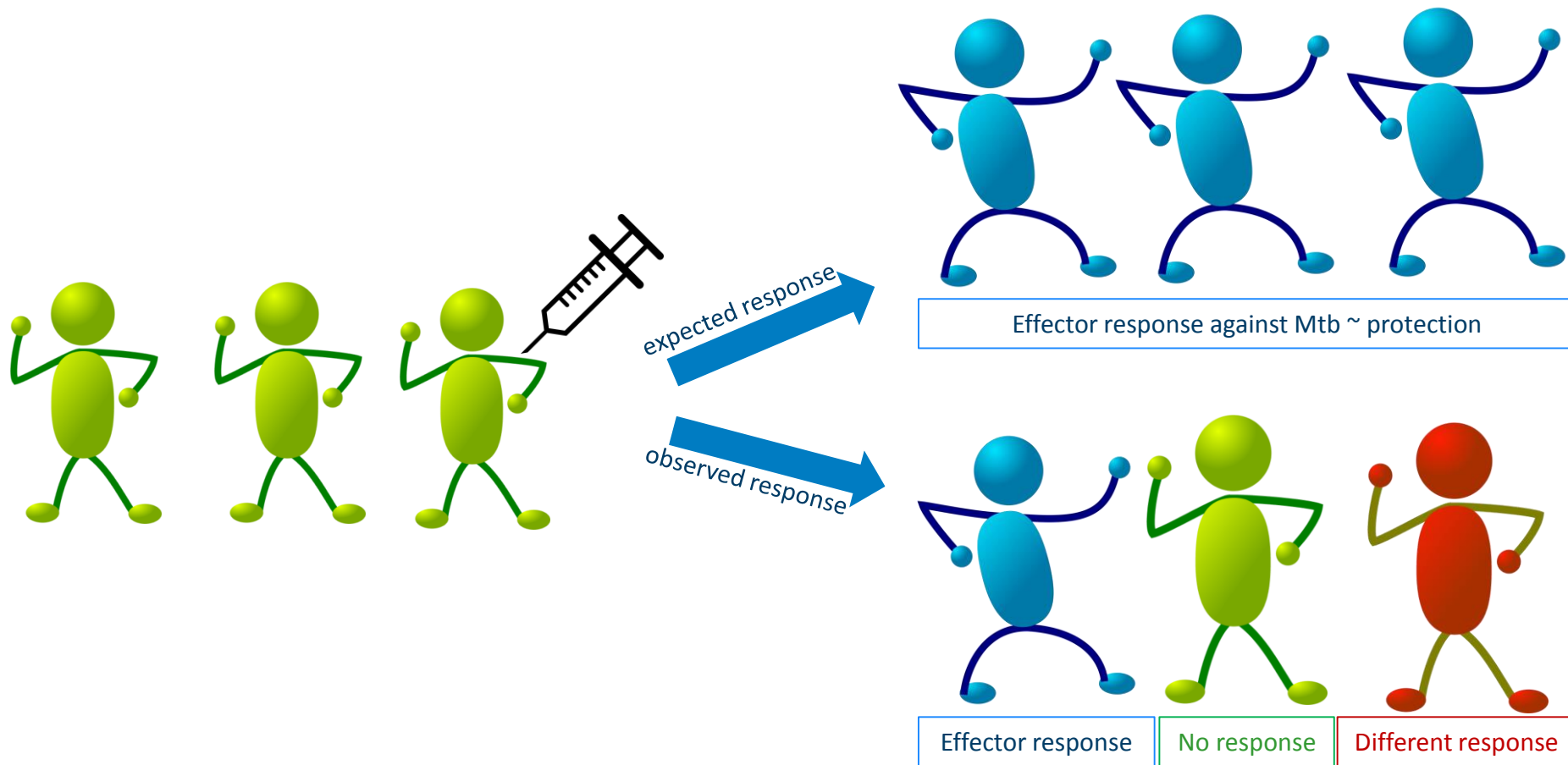
- enhance incidence of TB disease
- increase severity of TB disease
- complicate TB treatment
- prolong contagious time of TB patients and thereby disease spread
- hamper TB diagnostics
- complicate vaccination strategies

But TB also complicates treatment of the co-infections or co-morbidities!

Adaptive immunity in TB disease



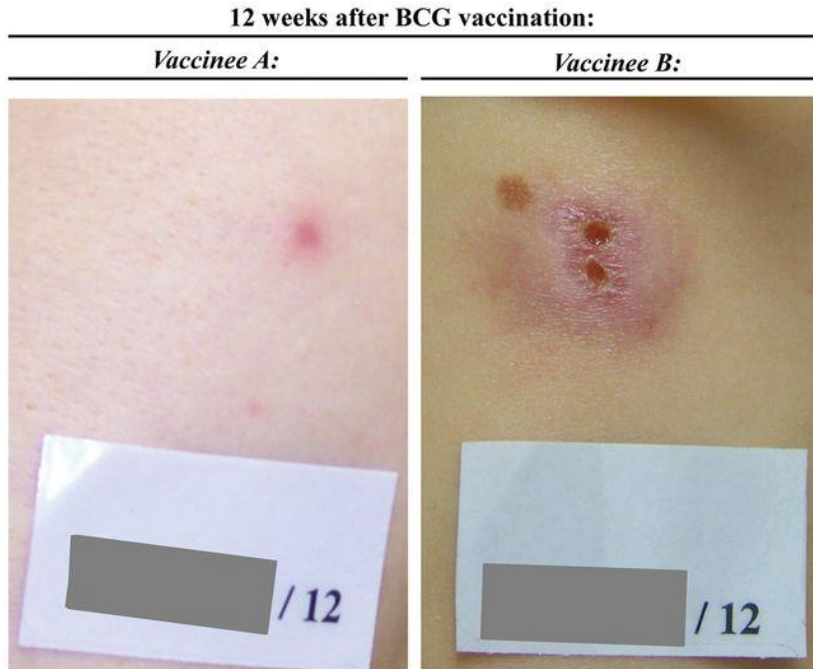
BCG vaccination



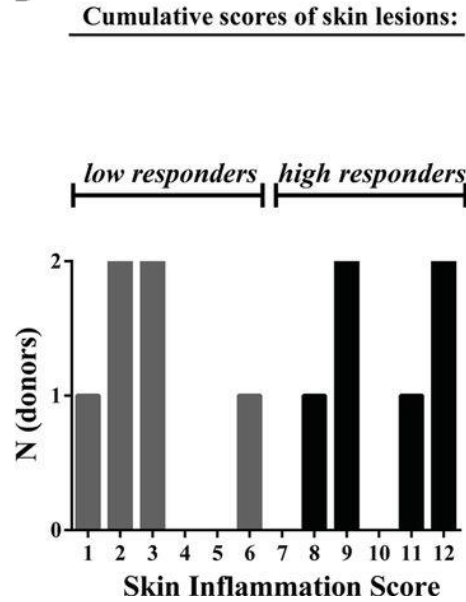
BCG vaccination study

BCG vaccination in healthy, Dutch adult volunteers

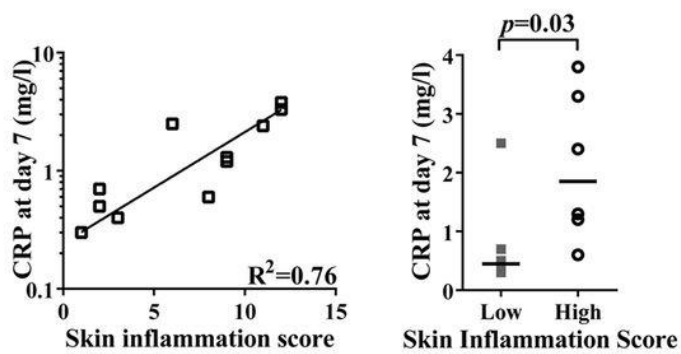
A



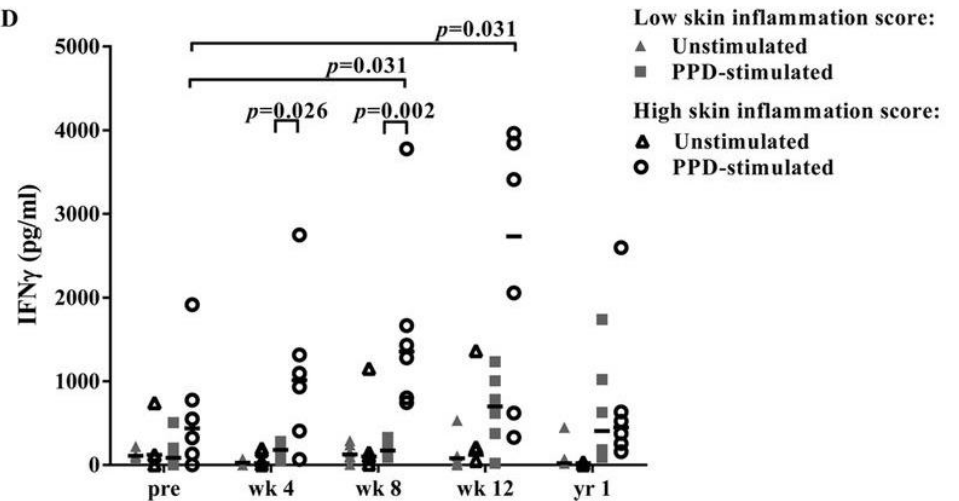
B



C

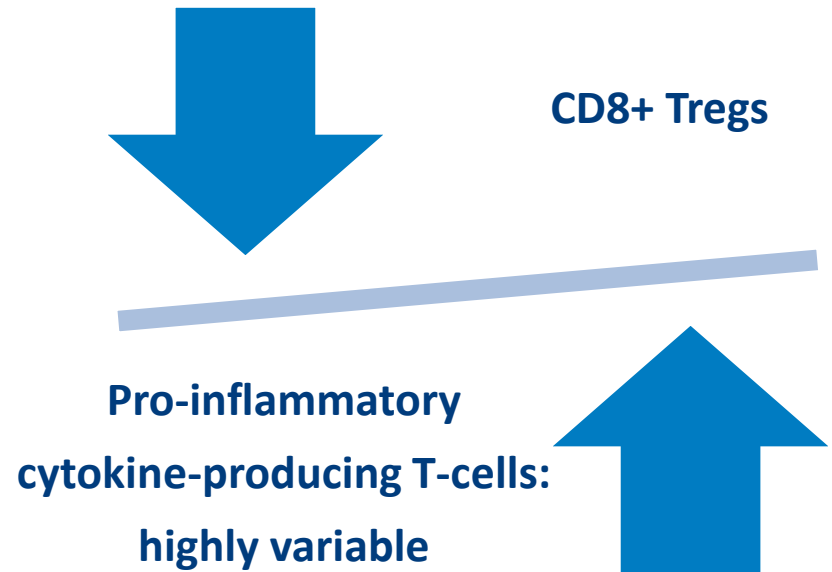
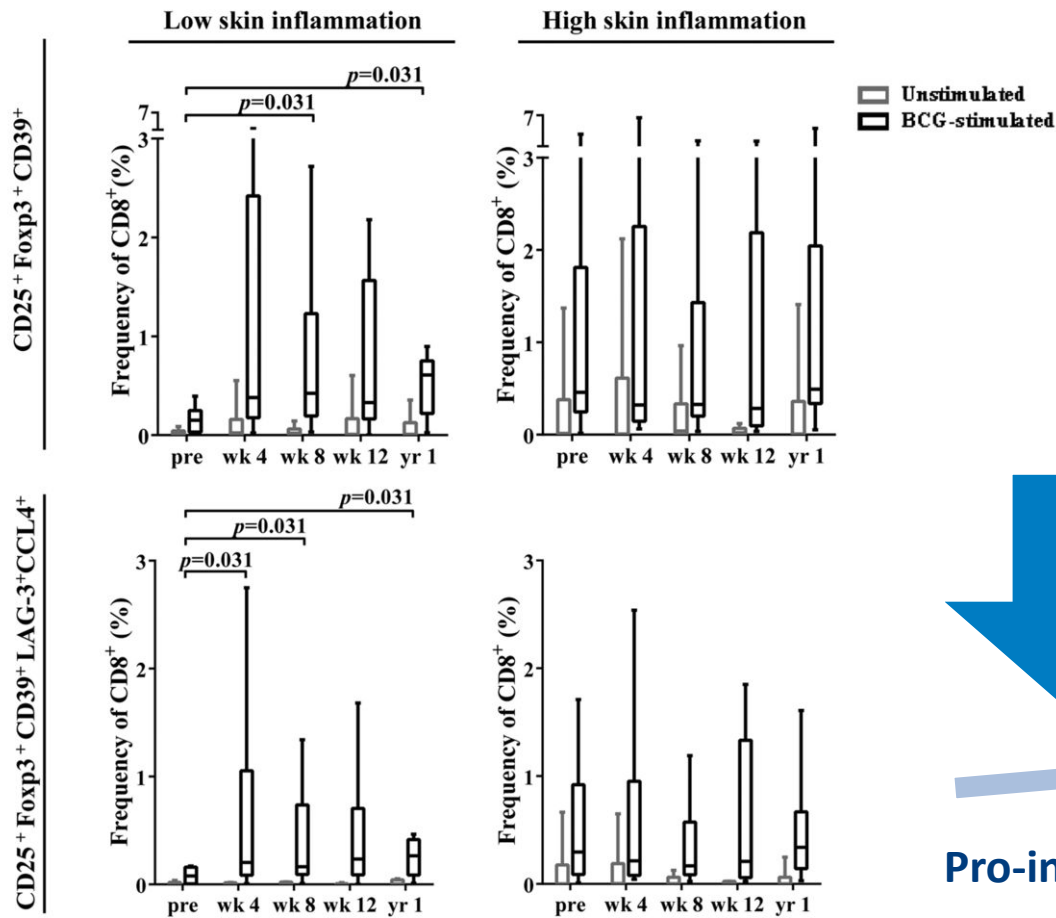


D



Immune regulation vs effector responses

B



Low skin inflammation is associated with higher level of CD8 Tregs

Regulatory T-cells

PNAS

Identification of a human CD8⁺ regulatory T cell subset that mediates suppression through the chemokine CC chemokine ligand 4

Simone A. Joosten^{*†}, Krista E. van Meijgaarden^{*†}, Nigel D. L. Savage^{*†}, Tjitske de Boer^{*†}, Frédéric Triebel[‡], Annemieke van der Wal[§], Emile de Heer[§], Michèl R. Klein^{*†}, Annemieke Geluk^{*†}, and Tom H. M. Ottenhoff^{*†¶}

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Communicated by Johannes van Rood, Europedonor Foundation, Leiden, The Netherlands, March 21, 2007 (received for review November 14, 2006)

European Journal of
Immunology

CD39 is involved in mediating suppression by *Mycobacterium bovis* BCG-activated human CD8⁺CD39⁺ regulatory T cells

Mardi C. Boer¹, Krista E. van Meijgaarden¹, Jérémy Bastid², Tom H.M. Ottenhoff^{*1} and Simone A. Joosten^{*1}

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PLOS ONE

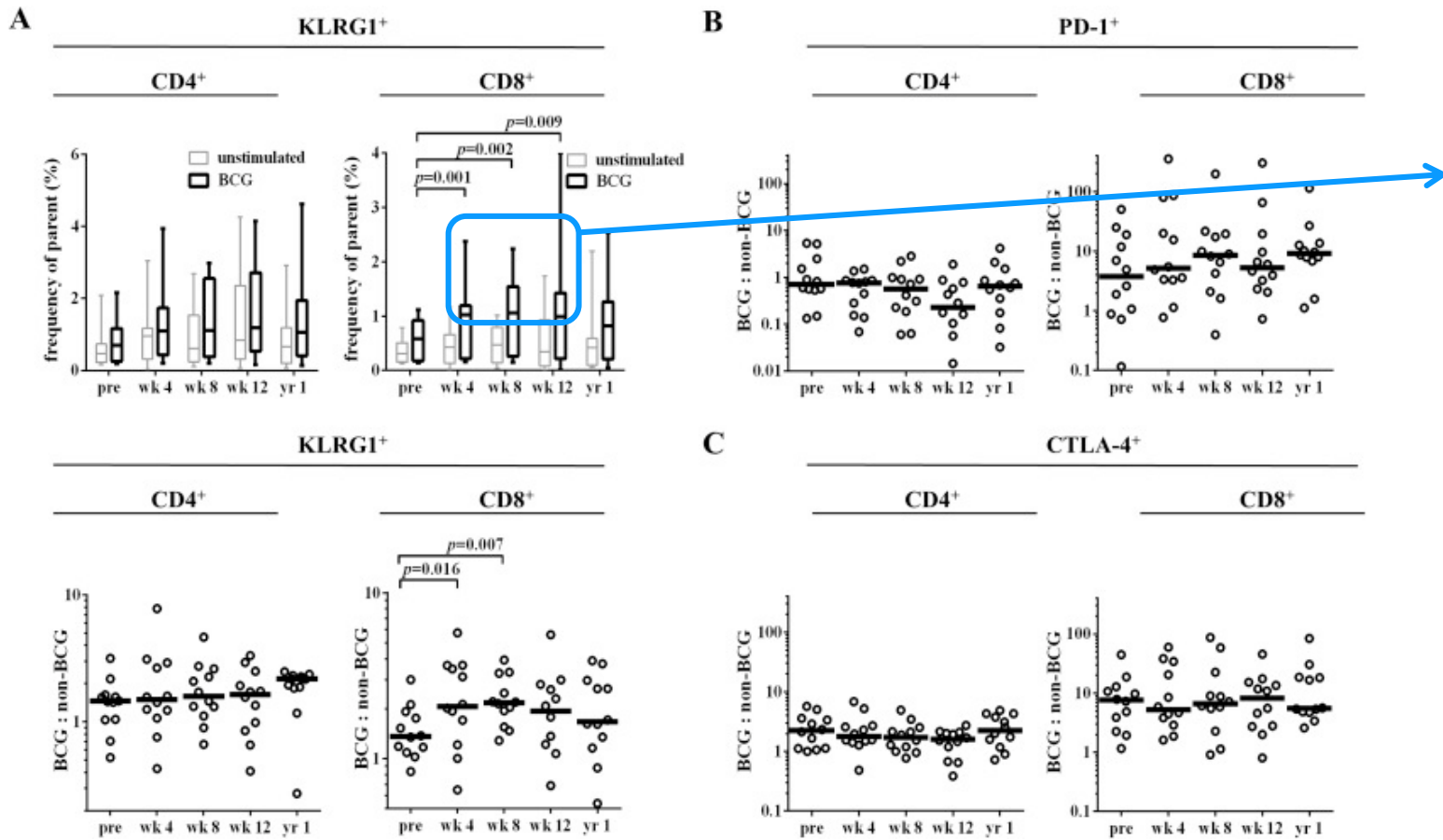
CD8⁺ Regulatory T Cells, and Not CD4⁺ T Cells, Dominate Suppressive Phenotype and Function after *In Vitro* Live *Mycobacterium bovis*-BCG Activation of Human Cells

Mardi C. Boer, Krista E. van Meijgaarden, Simone A. Joosten[¶], Tom H. M. Ottenhoff^{*¶}

Department of Infectious Diseases, Leiden University Medical Center, Leiden, The Netherlands

Immune regulation
may not be only
inhibitory response
induced by BCG.....

KLRG1 and PD1 following BCG vaccination



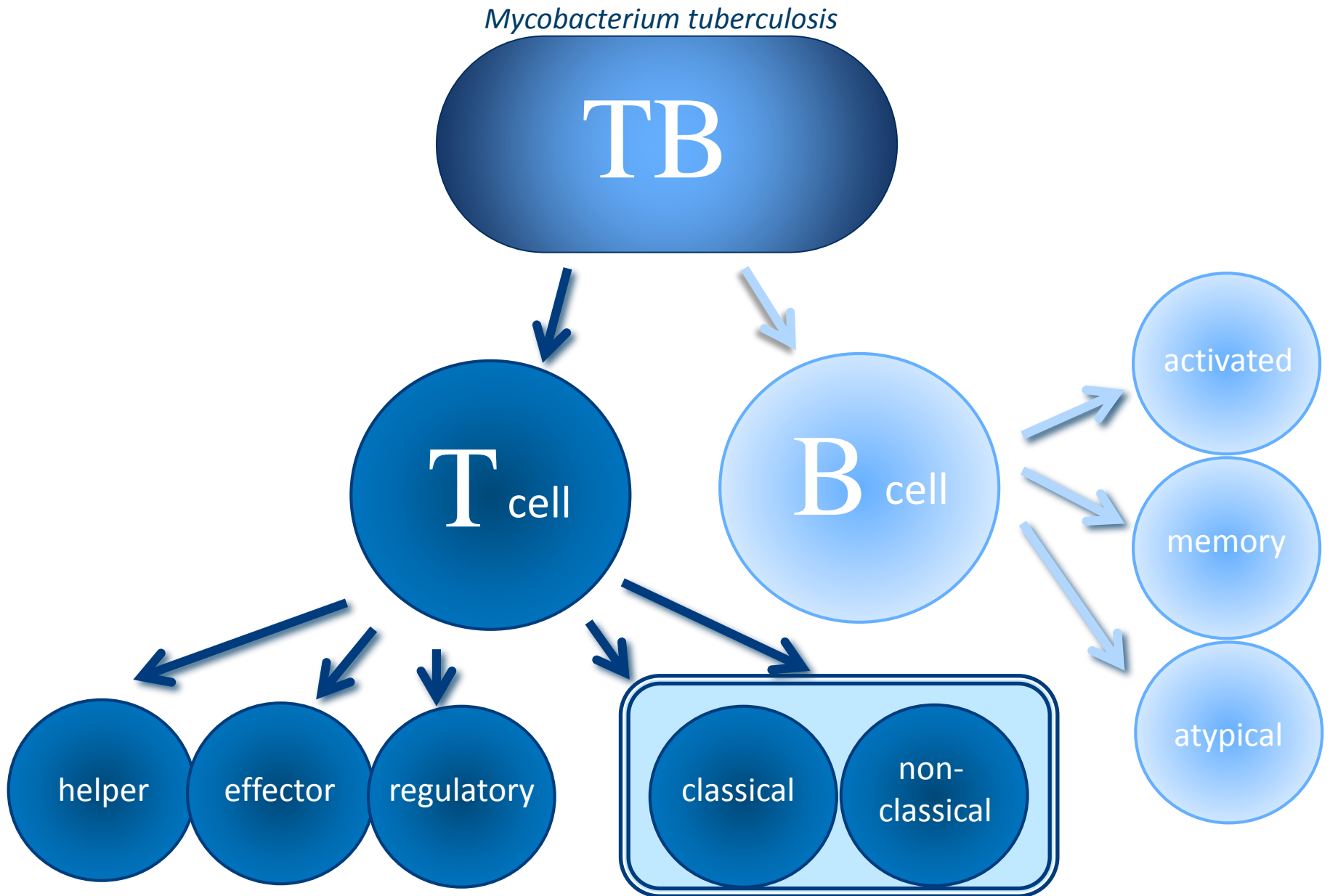
Poorly proliferating population

TB patients:

PD1 and KLRG1 on CD4⁺ T-cells, not on CD8⁺ T-cells

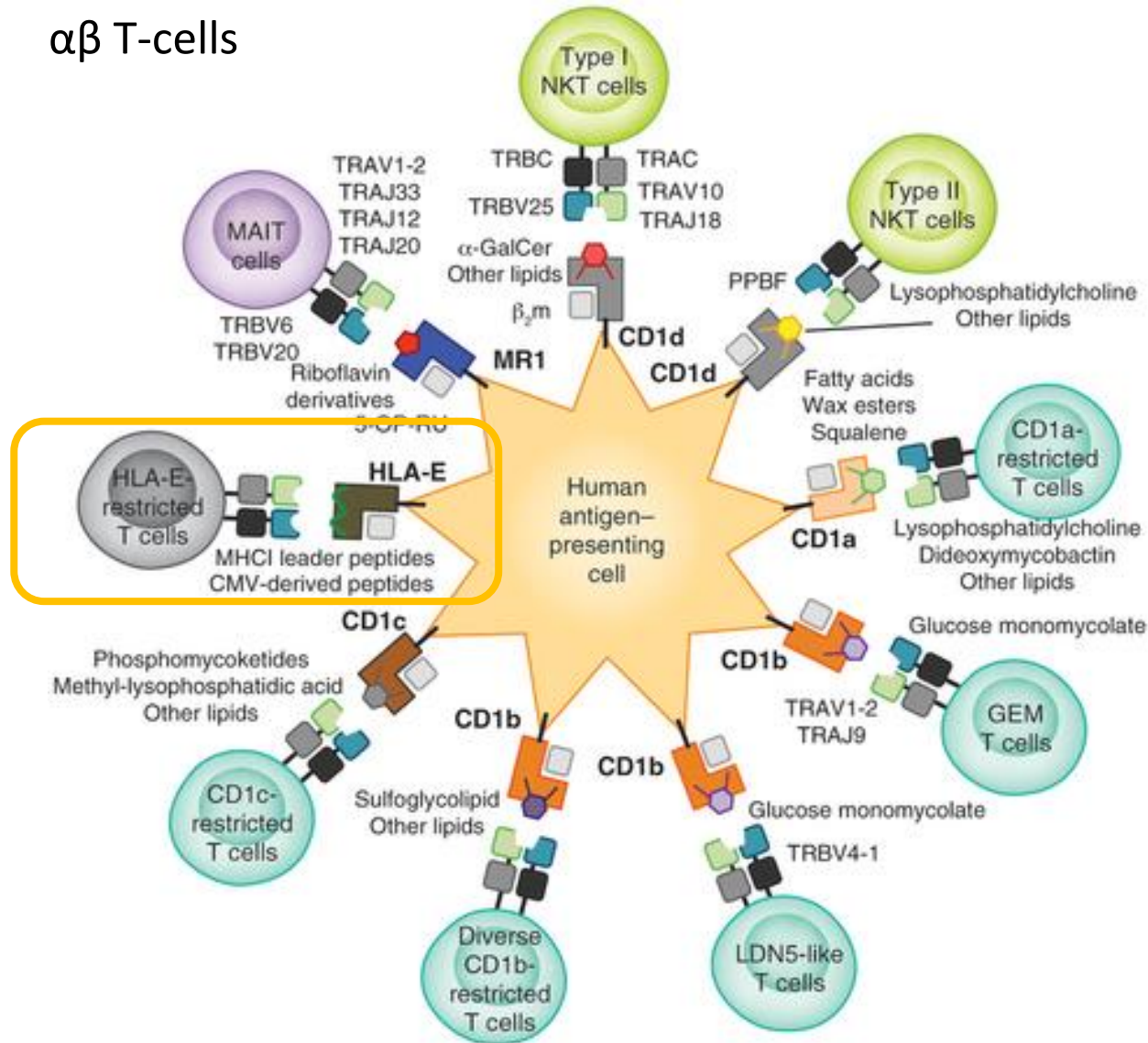
Increased frequency in active TB patients, highest in cured TB patients

Adaptive immunity in TB disease



Unconventional immunity – donor unrestricted T-cells

$\alpha\beta$ T-cells



HLA-E

3 alleles,

2 functional proteins,

single amino acid difference:

HLA-E*0101: position 107= arginine > E^R

HLA-E*0103: position 107= glycine > E^G

E^R and E^G frequencies in population are about equal

No significant differences in crystal structure

E^G has slightly increased cell surface expression

E^G has stronger peptide affinity

E^G has increased thermal stability

Functional significance?

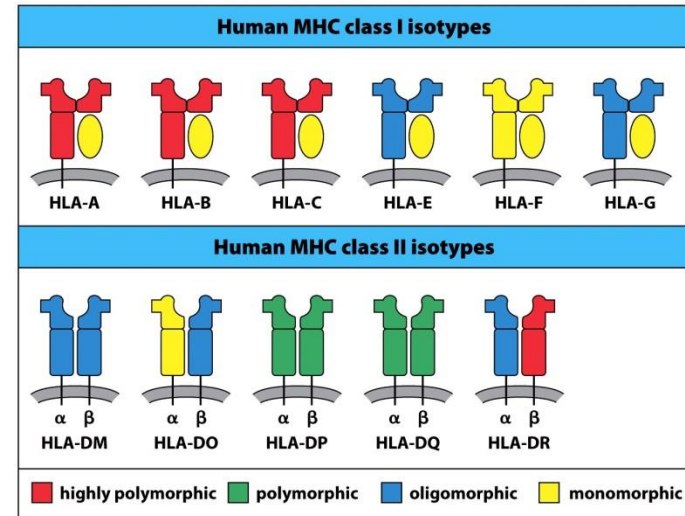
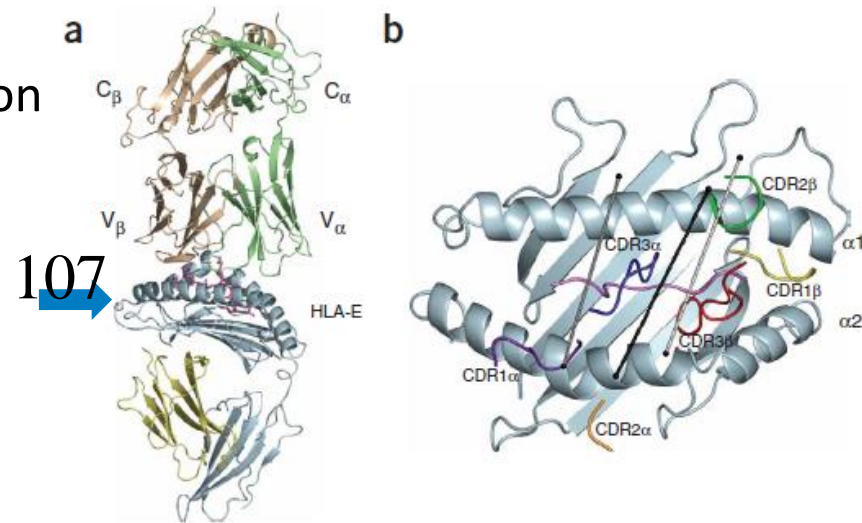


Figure 5.24 The Immune System, 3ed. (© Garland Science 2009)



HLA-E in tuberculosis

Only 2 variants described in humans: single peptides can be presented by most (all) individuals → potentially interesting vaccine target

HLA-E is not down-regulated by HIV-nef, potentially interesting to use HLA-E peptides for post-exposure vaccination against Mtb in HIV⁺ setting

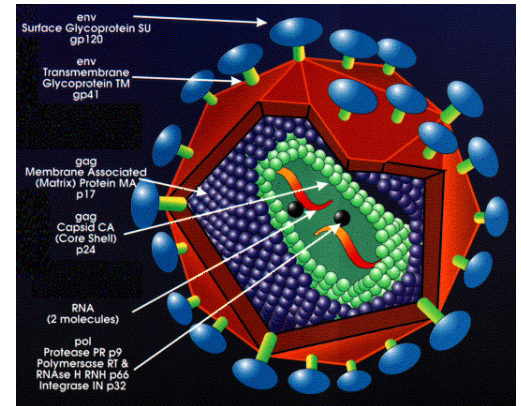
Cohen et al, Immunity, 1999, 10, 661

HIV p24 may stabilize HLA-E molecules and thereby even enhance HLA-E surface expression

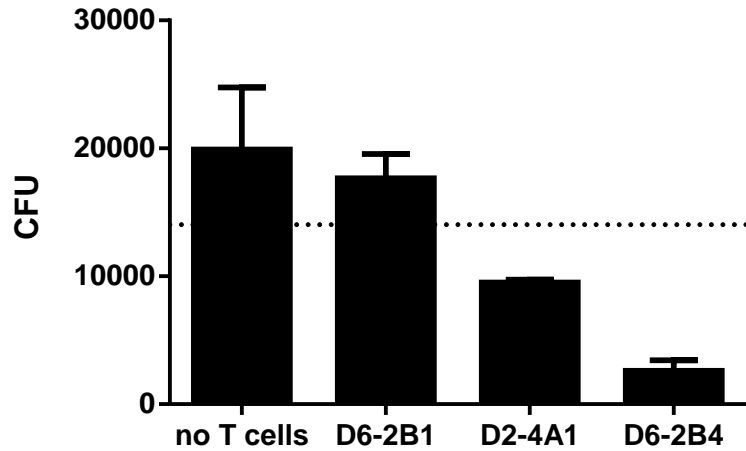
Nattermann et al, Antivir Ther, 2005, 10: 95

HLA-E is enriched within Mtb phagosome compared to HLA-A2, HLA-E may preferentially present phagosomal antigens

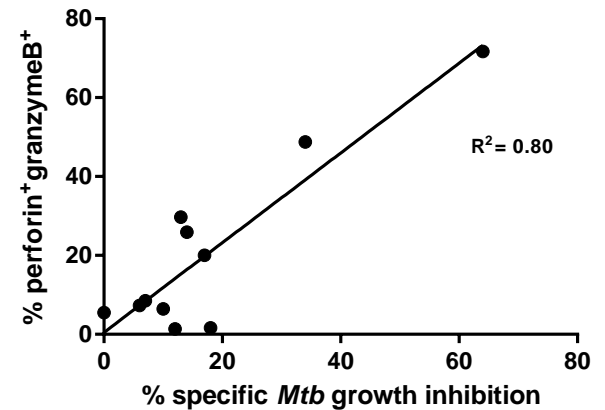
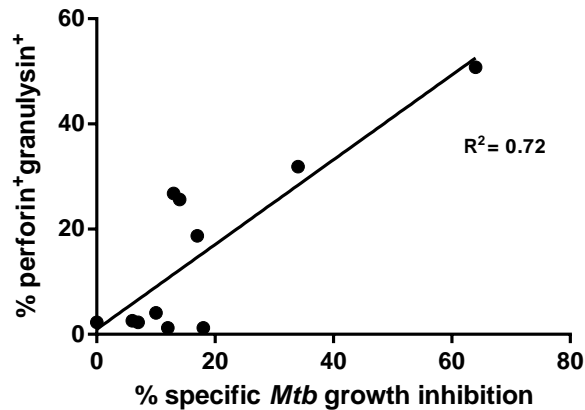
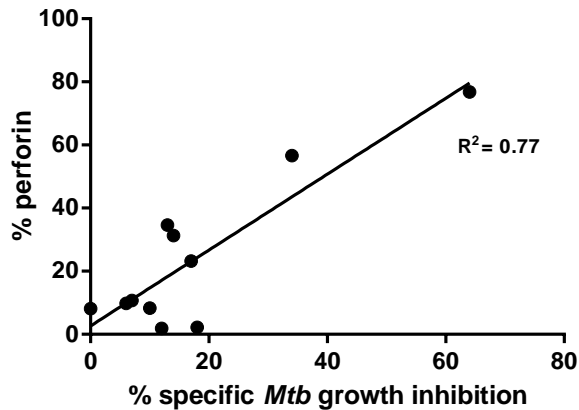
Grotzke, Lewinsohn et al Plos Pathogens, 2009, 5(4): e1000374



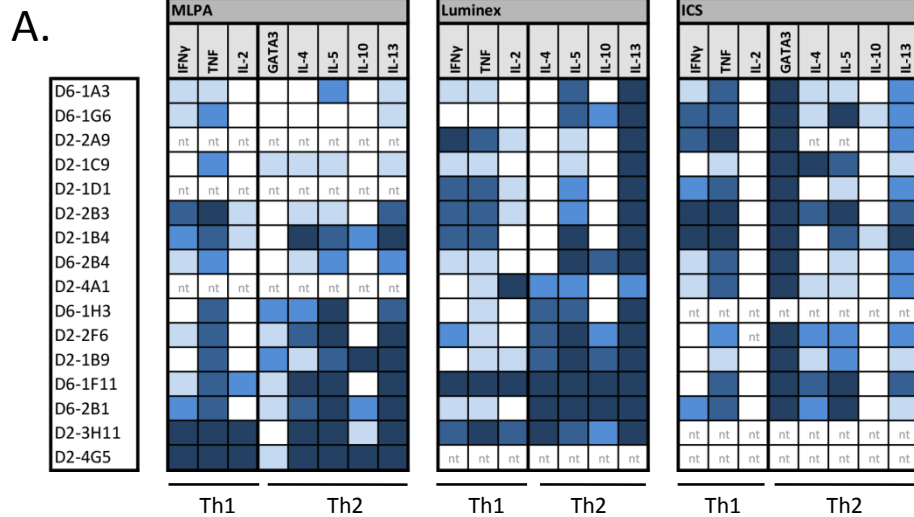
HLA-E restricted T-cell clones can inhibit intracellular growth of Mtb



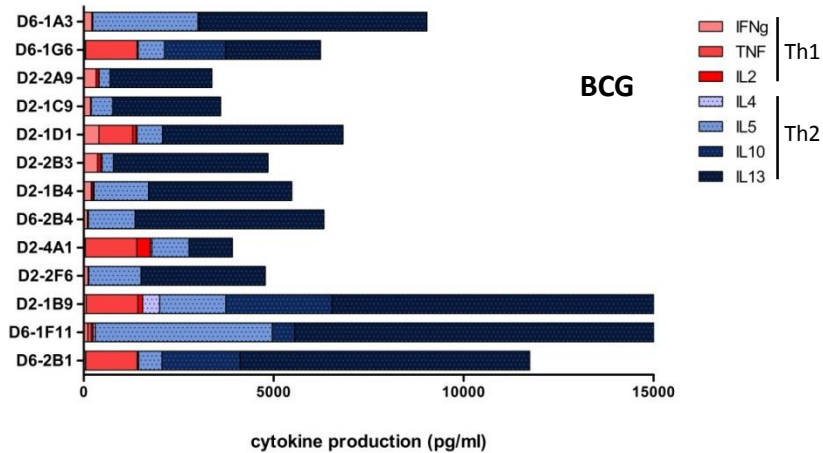
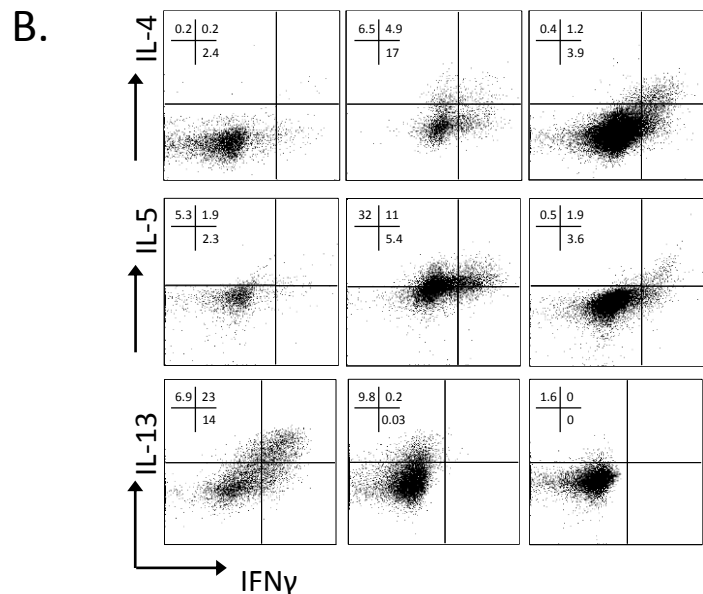
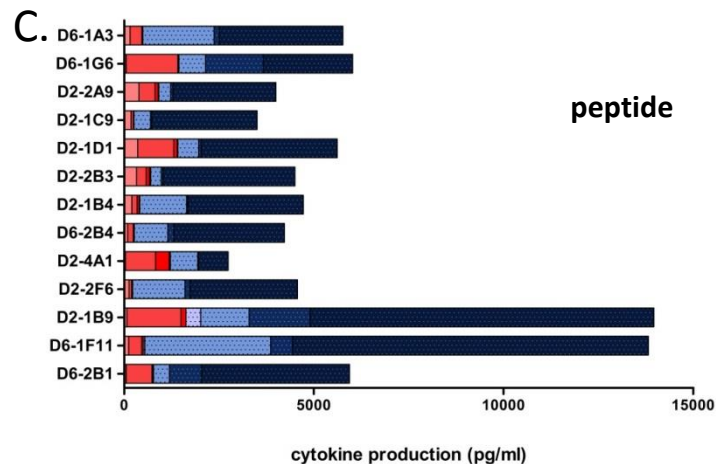
HLA-A2 negative macrophages were infected with live H37Rv and HLA-E restricted CD8+ T cell clones were added (5:1 ratio) for 24 hours. Subsequently cells were lysed and plated to determine the number of colony forming units



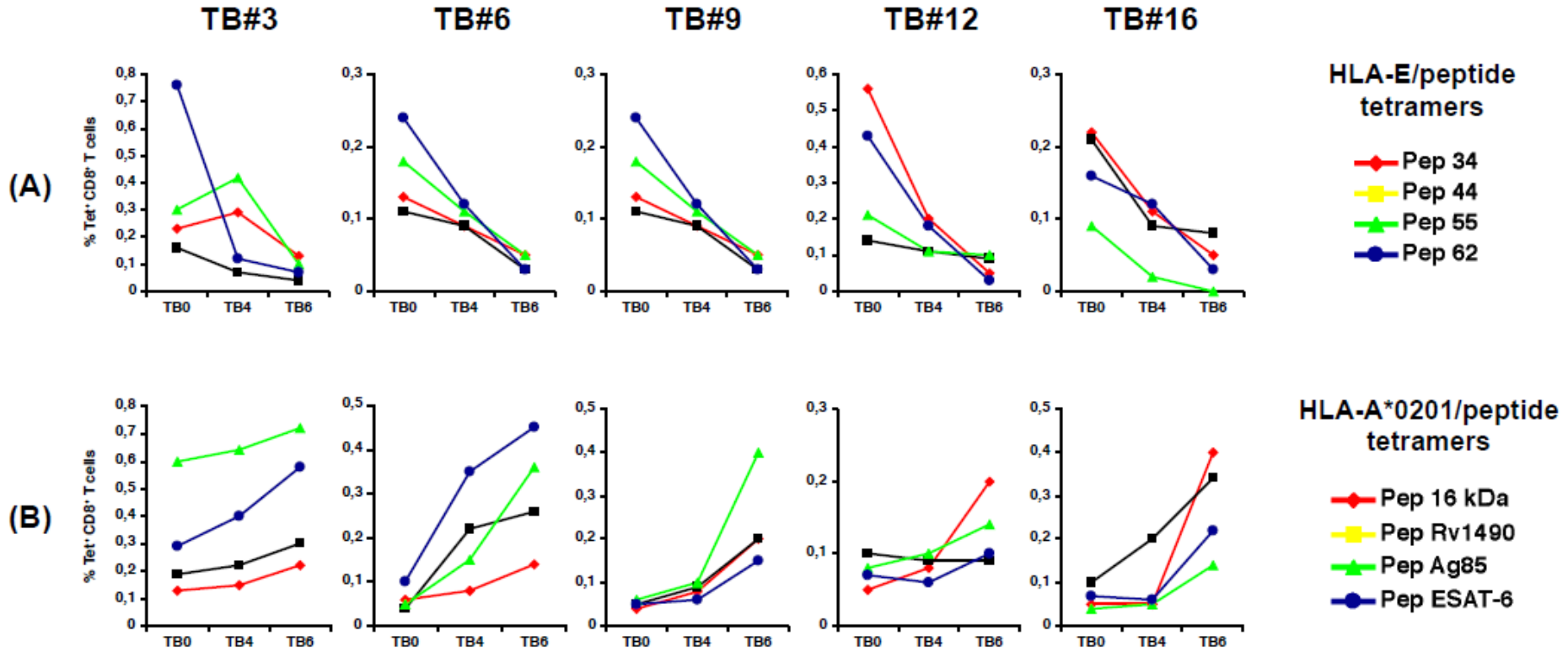
Mtb specific HLA-E restricted T-cell clones produce Th2 cytokines



MLPA	Luminex (pg/ml)		ICS (%)
(norm. peak area)	IFNγ/IL-4/IL-5 IL-10/IL-13	TNF/IL-2	
200-1000	10-500	10-100	<1
1000-2500	500-1000	100-500	1-5
2500-5000	1000-2000	500-1000	5-10
5000-10000	2000-5000	1000-2000	10-20
>10000	5000-10000	2000-3500	>20

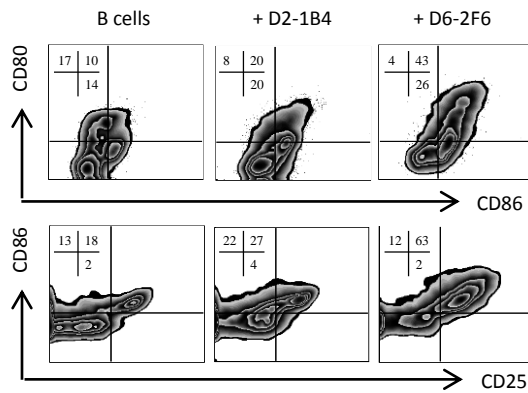


TB patients recognize HLA-E TM strongest before therapy, in contrast HLA-A2 TM are increasingly recognized during treatment

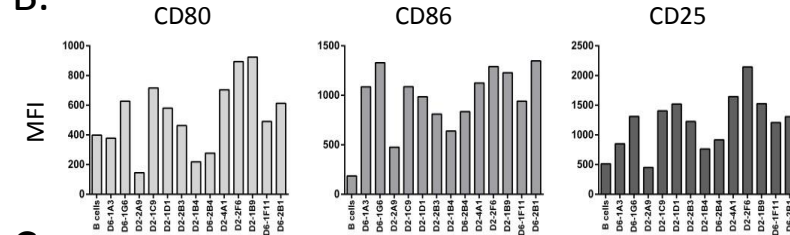


HLA-E restricted Mtb specific T-cell clones utilize IL-4 to provide B-cell help

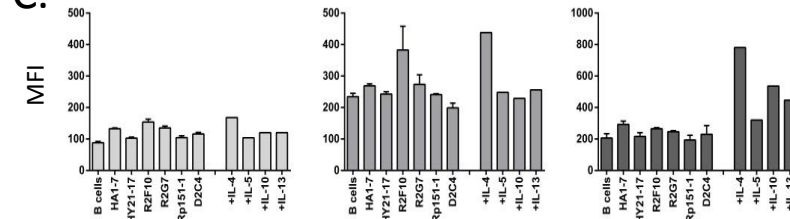
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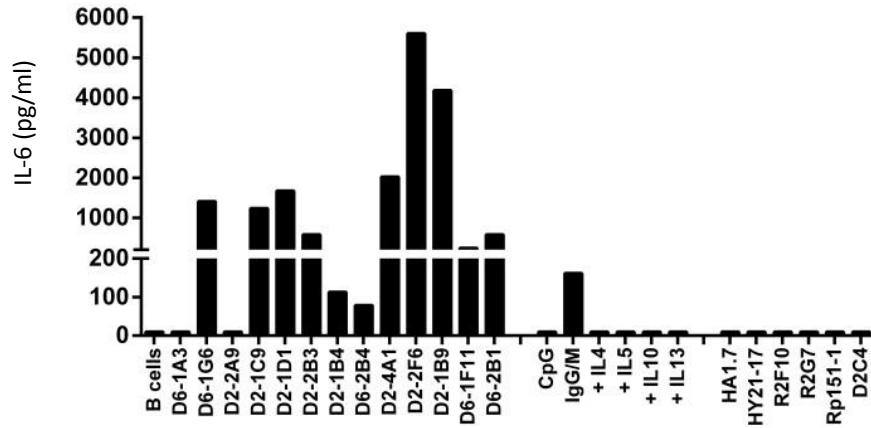
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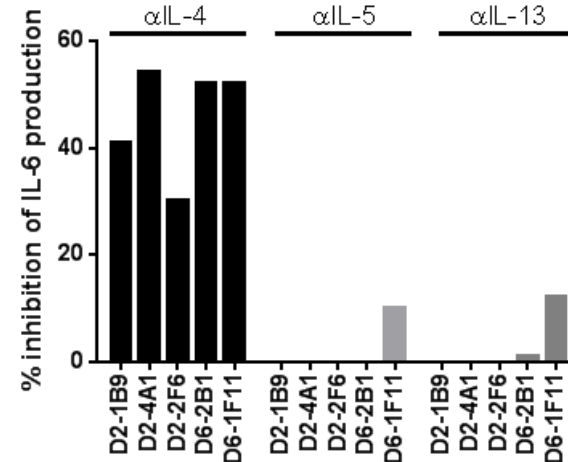
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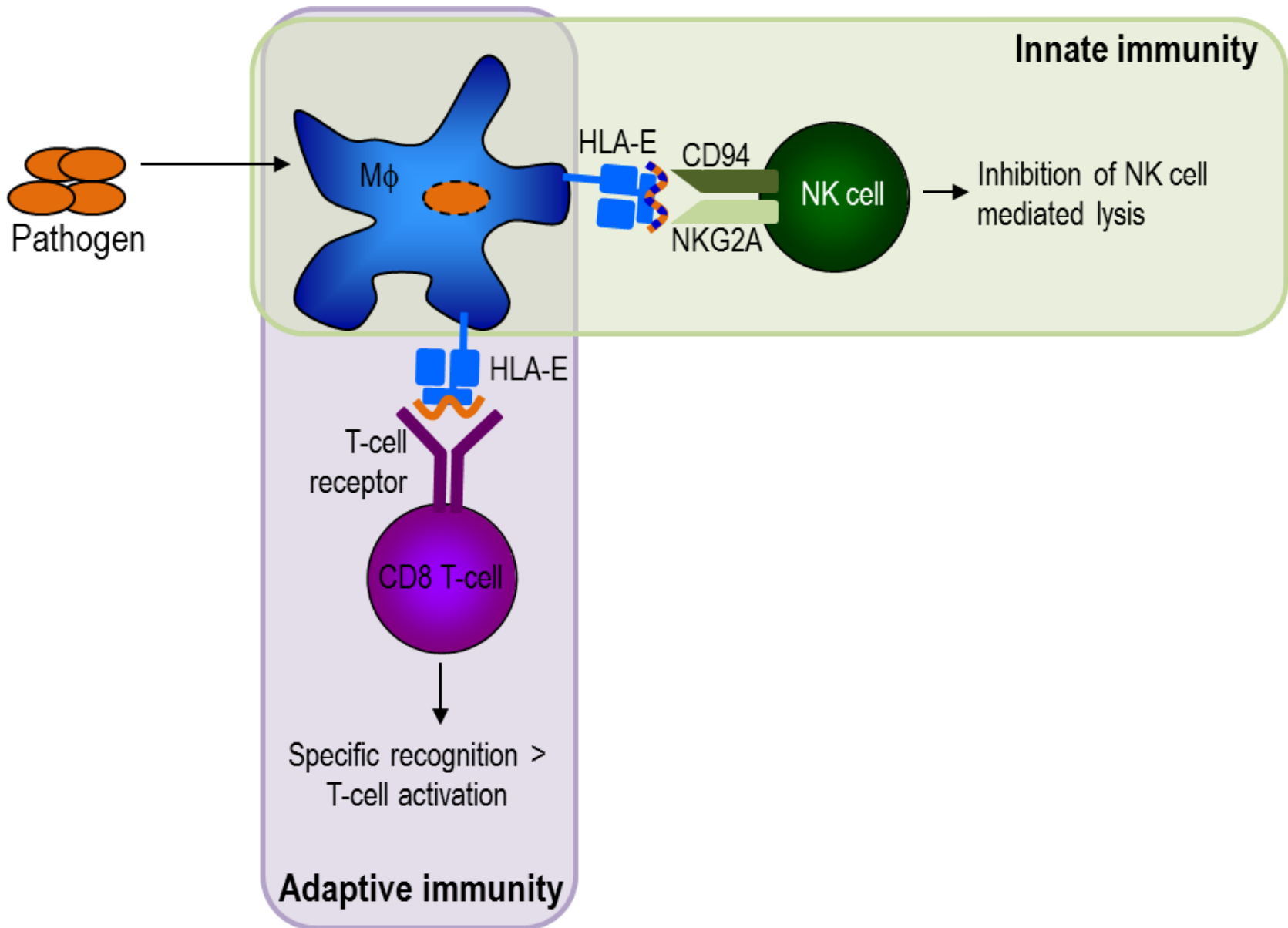


D.



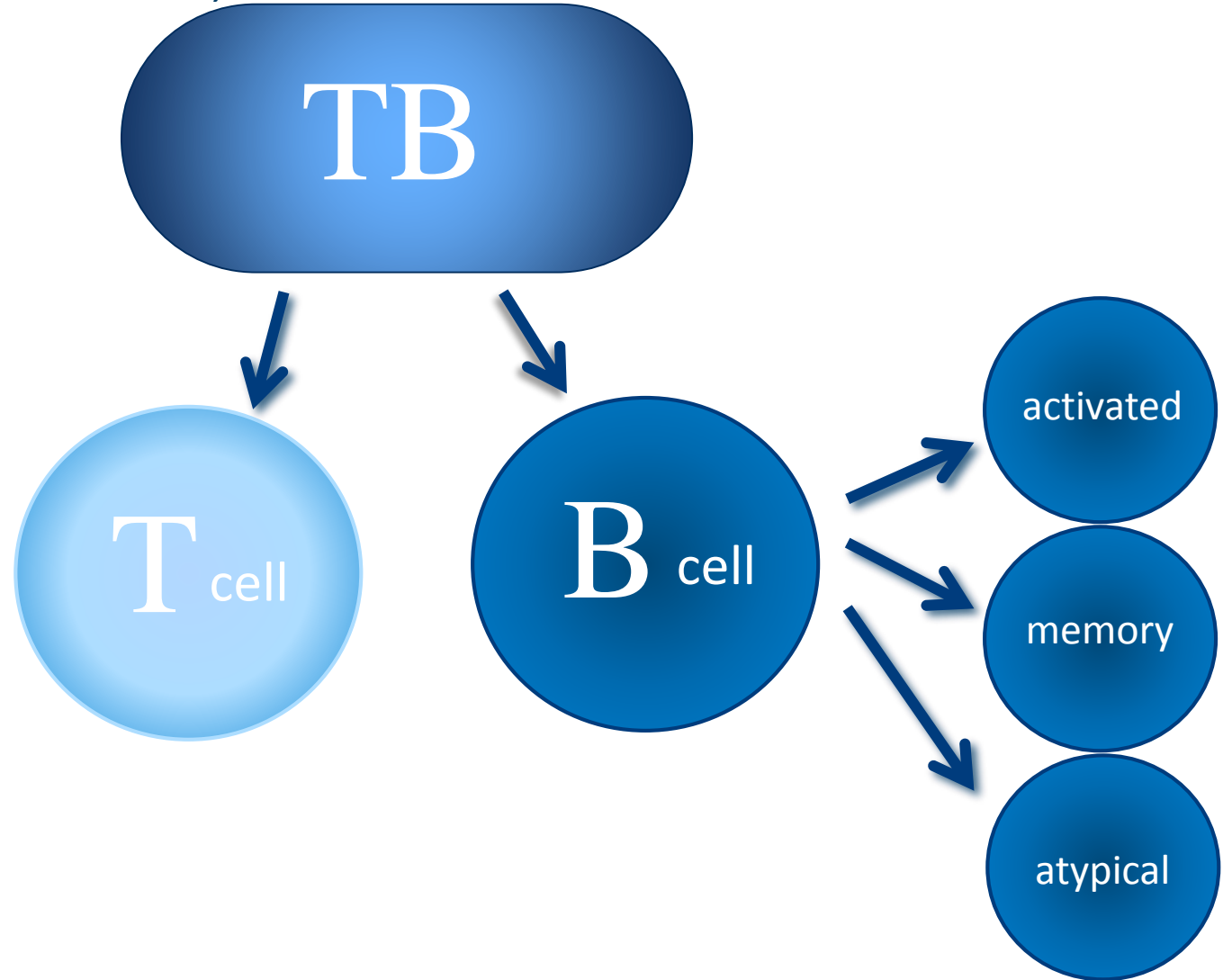
E.



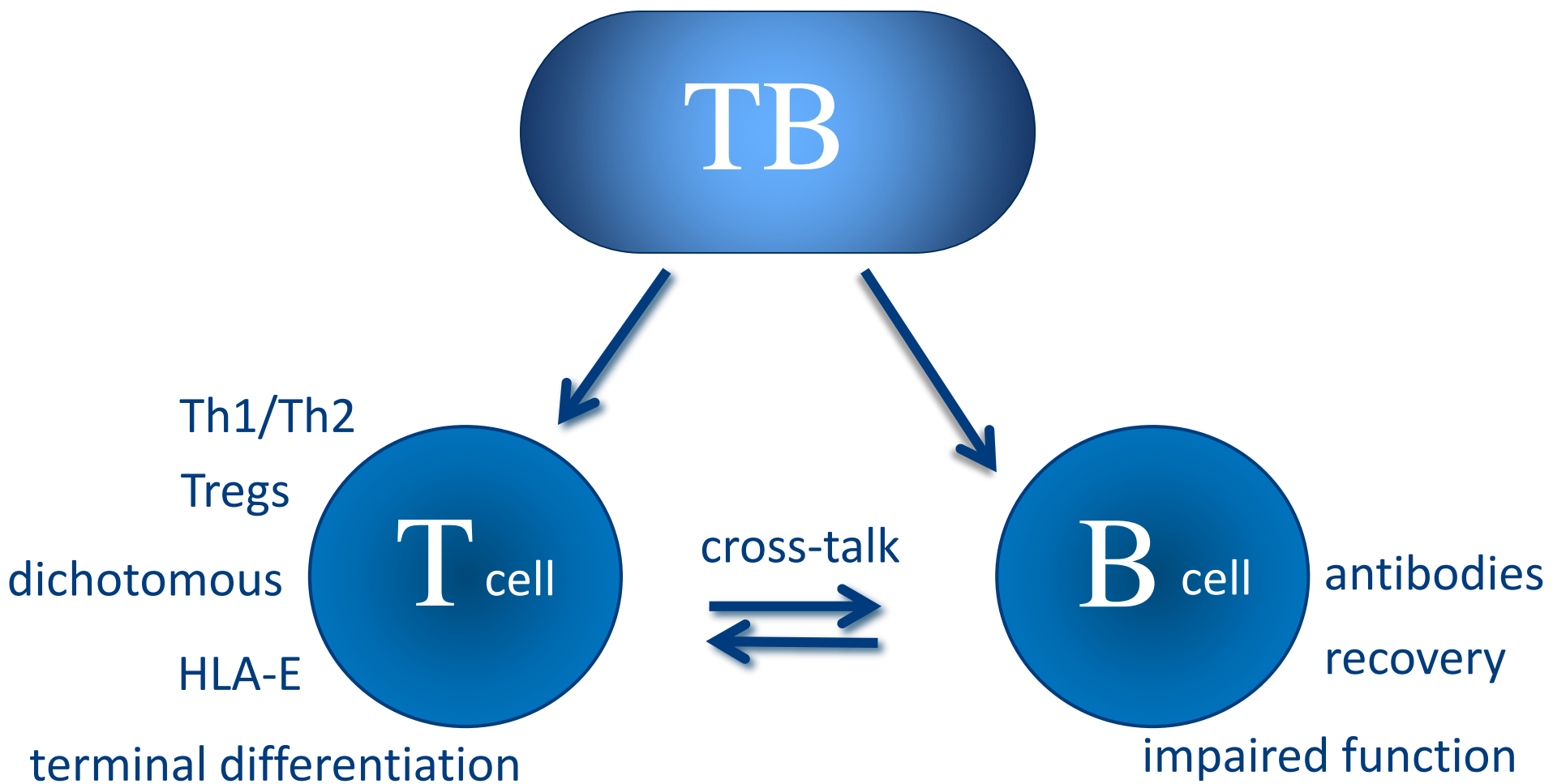


Adaptive immunity in TB disease

Mycobacterium tuberculosis



summary



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2020

