Trained immunity and vaccination: mechanisms and new insights

Mihai G. Netea

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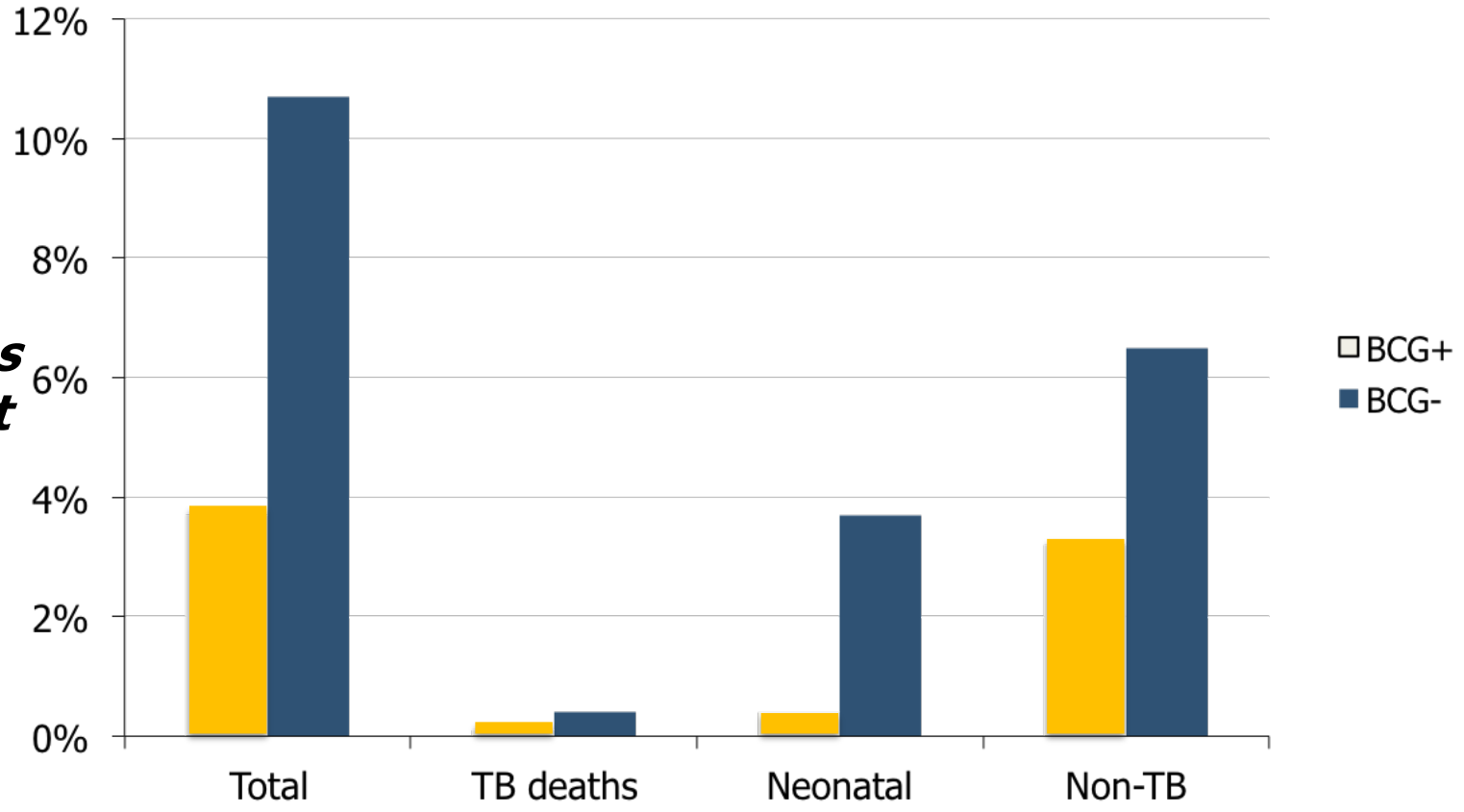
Introducing BCG in Norrbotten, Sweden, 1927-31

Coverage highest in families with TB

Reduction was in infancy, but TB deaths occur later

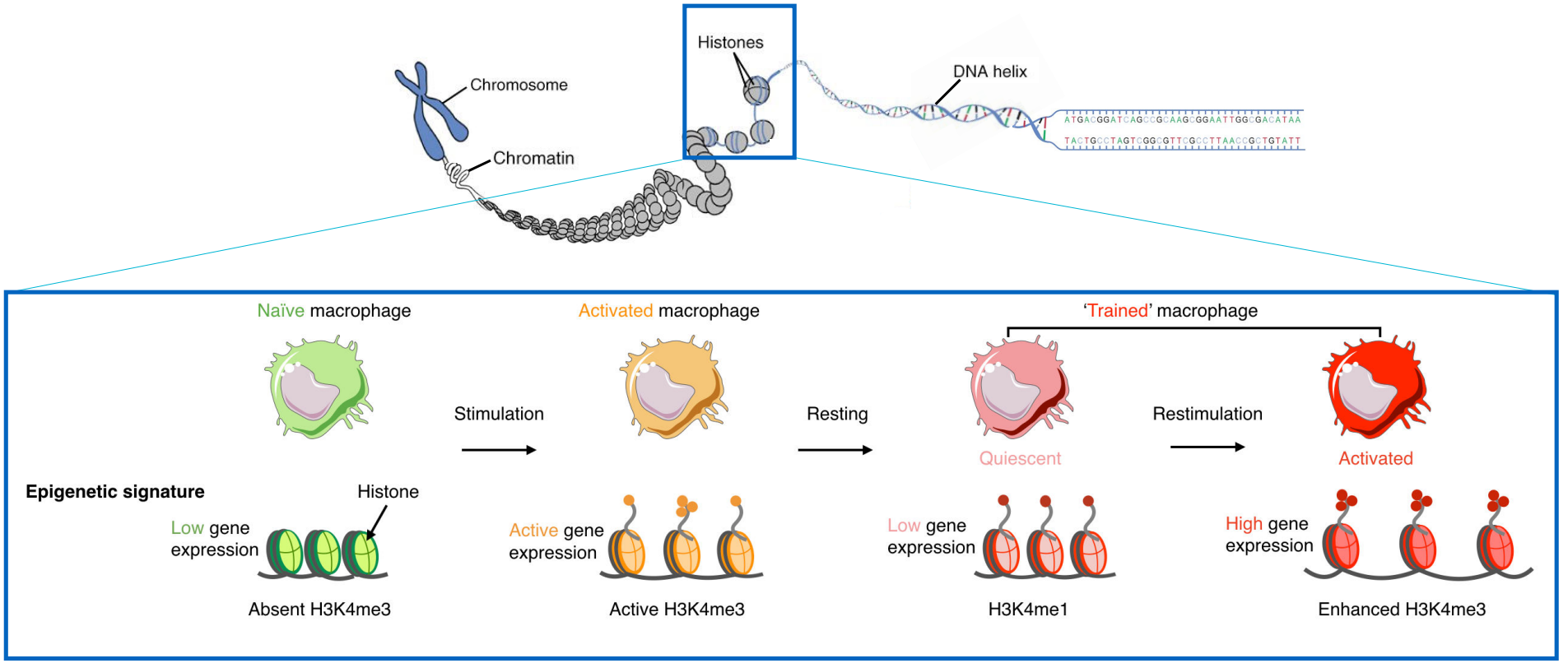
This made little sense



"One could evidently be tempted to find an explanation for this much lower mortality among vaccinated children in the idea that BCG provokes *a **non-specific immunity**...*"

Carl Naeslund 1932

Long-term epigenetic reprogramming in myeloid cells



Resting | **Infection** | **Resting** | **Re-infection**

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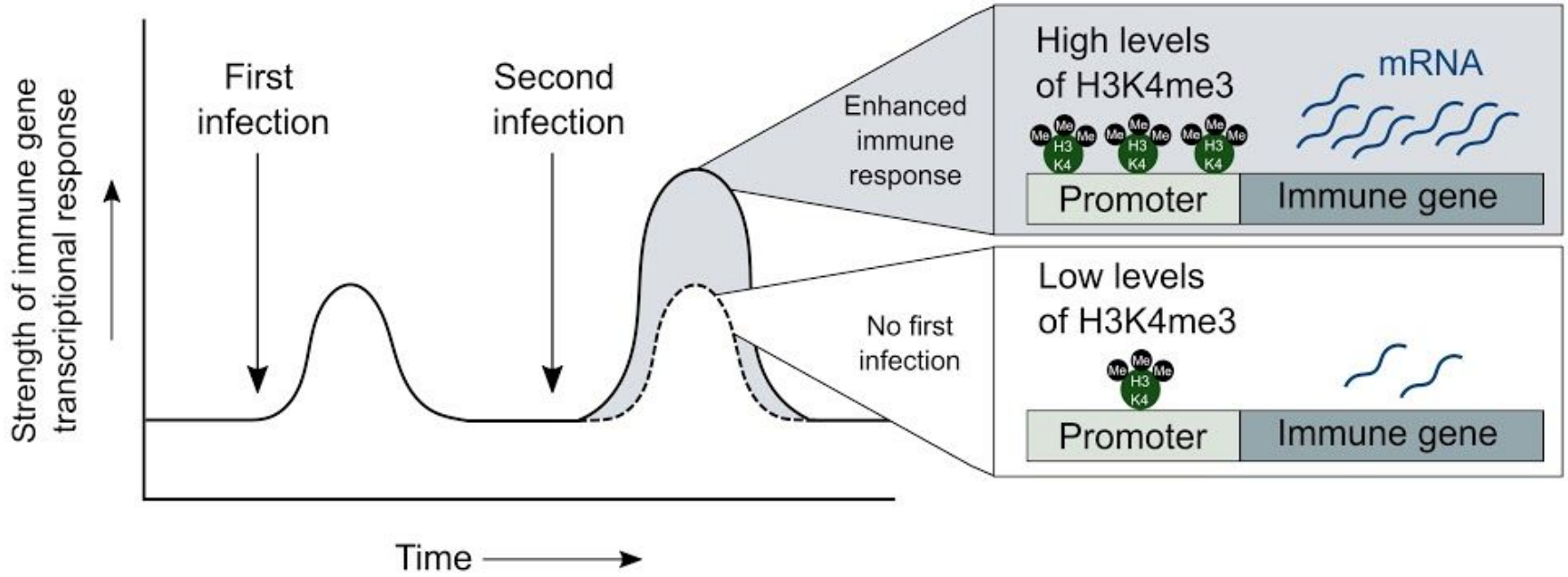
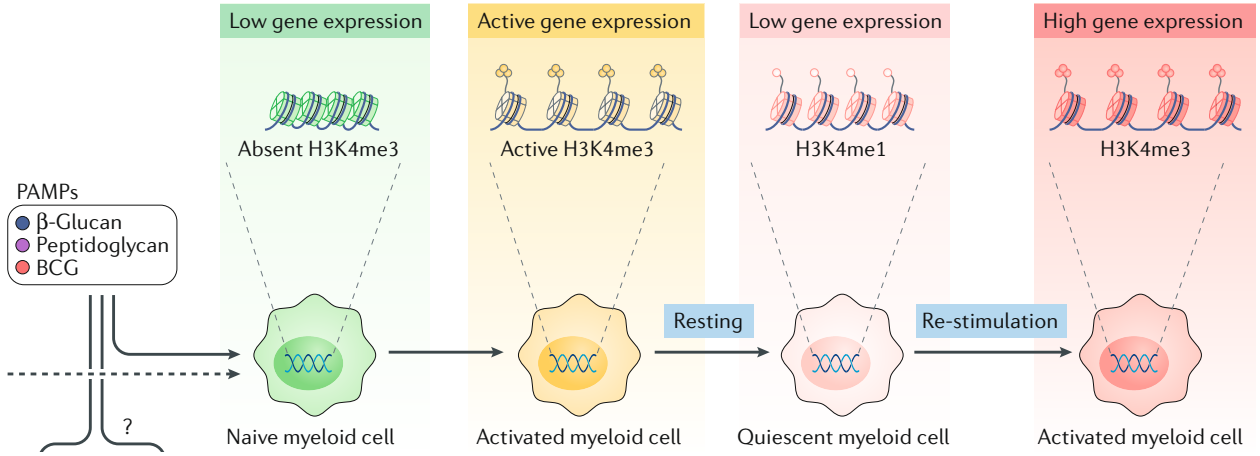
Long-term epigenetic reprogramming in myeloid cells





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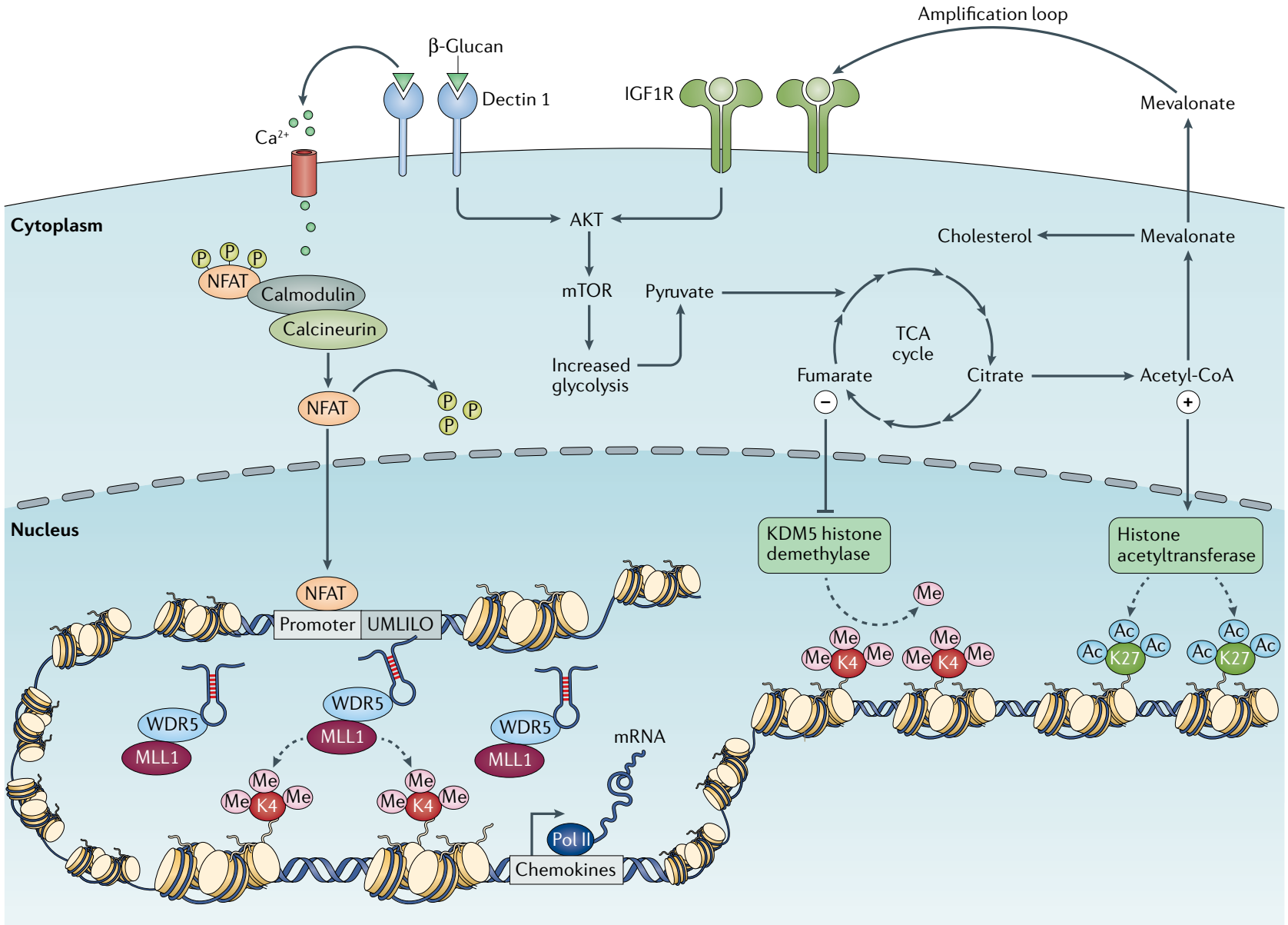
Trained immunity: mechanisms



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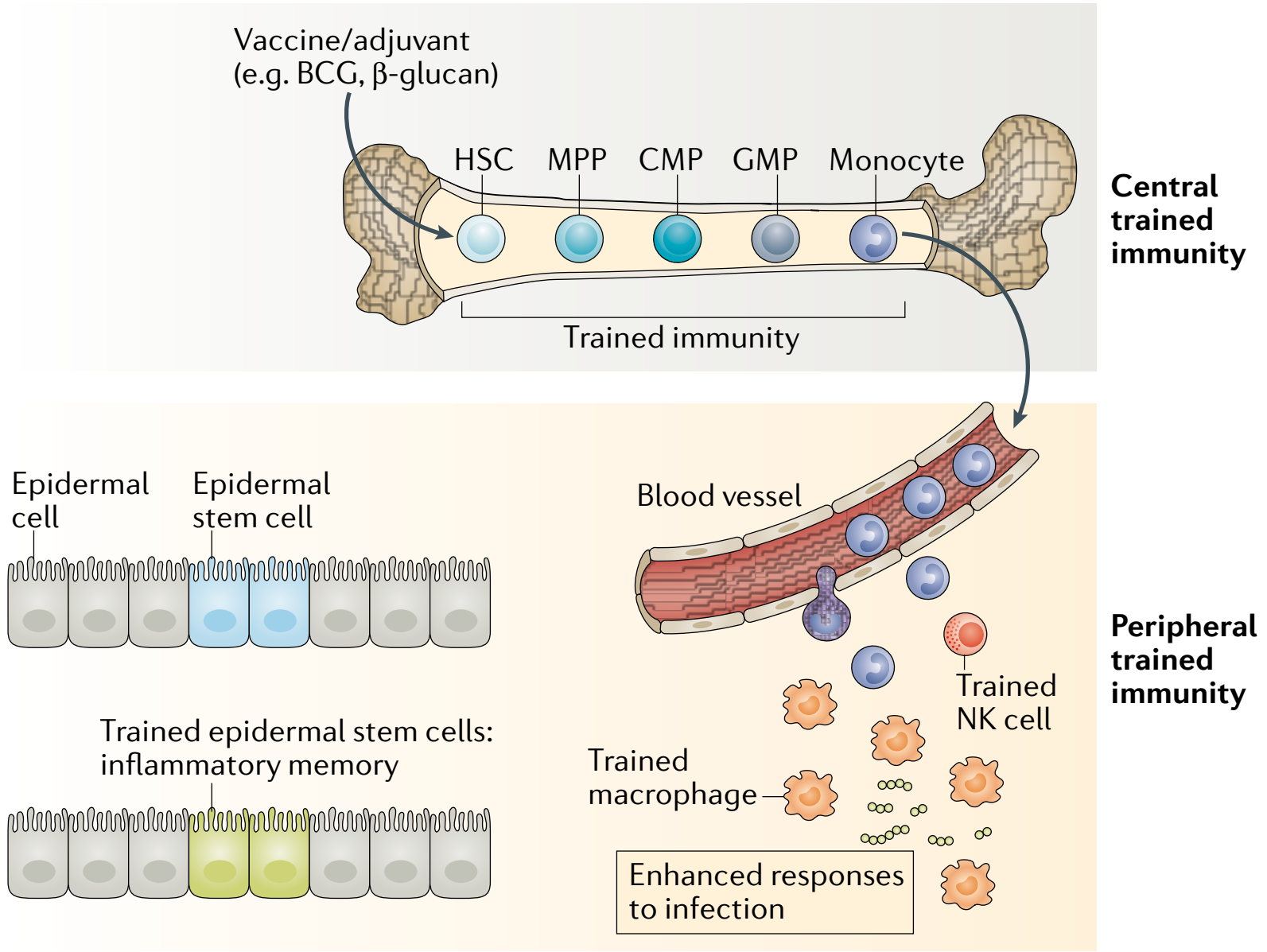
Netea et al, Nature Rev Immunol 2020

Trained immunity: from bone marrow to local defenses



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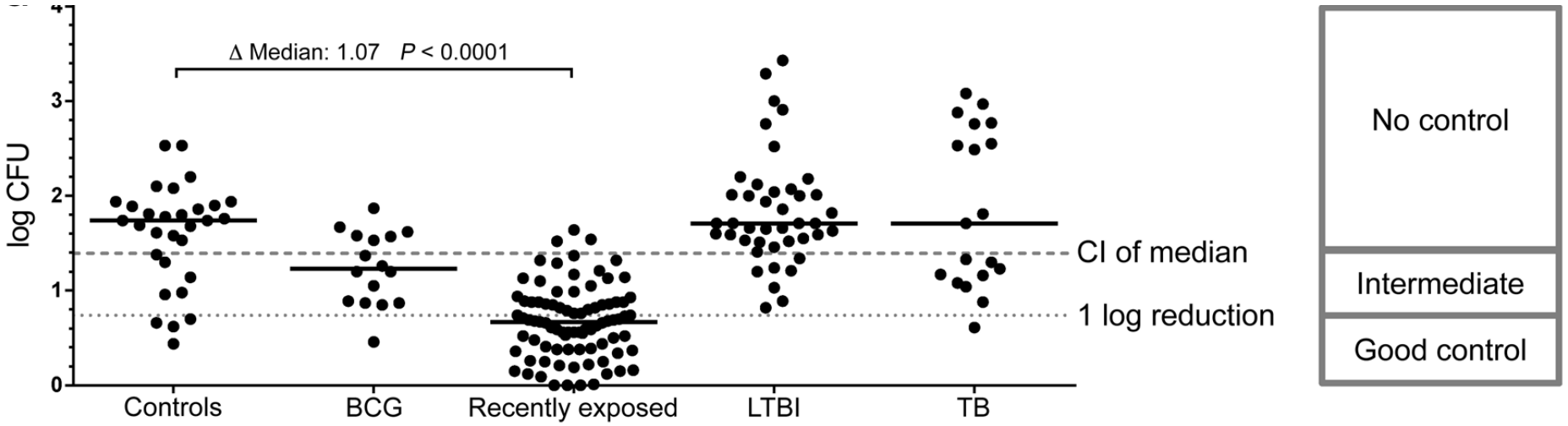
Netea et al, Nature Rev Immunol 2020

BCG vaccination, macrophage activation and TB control



Joosten et al, JCI 2018

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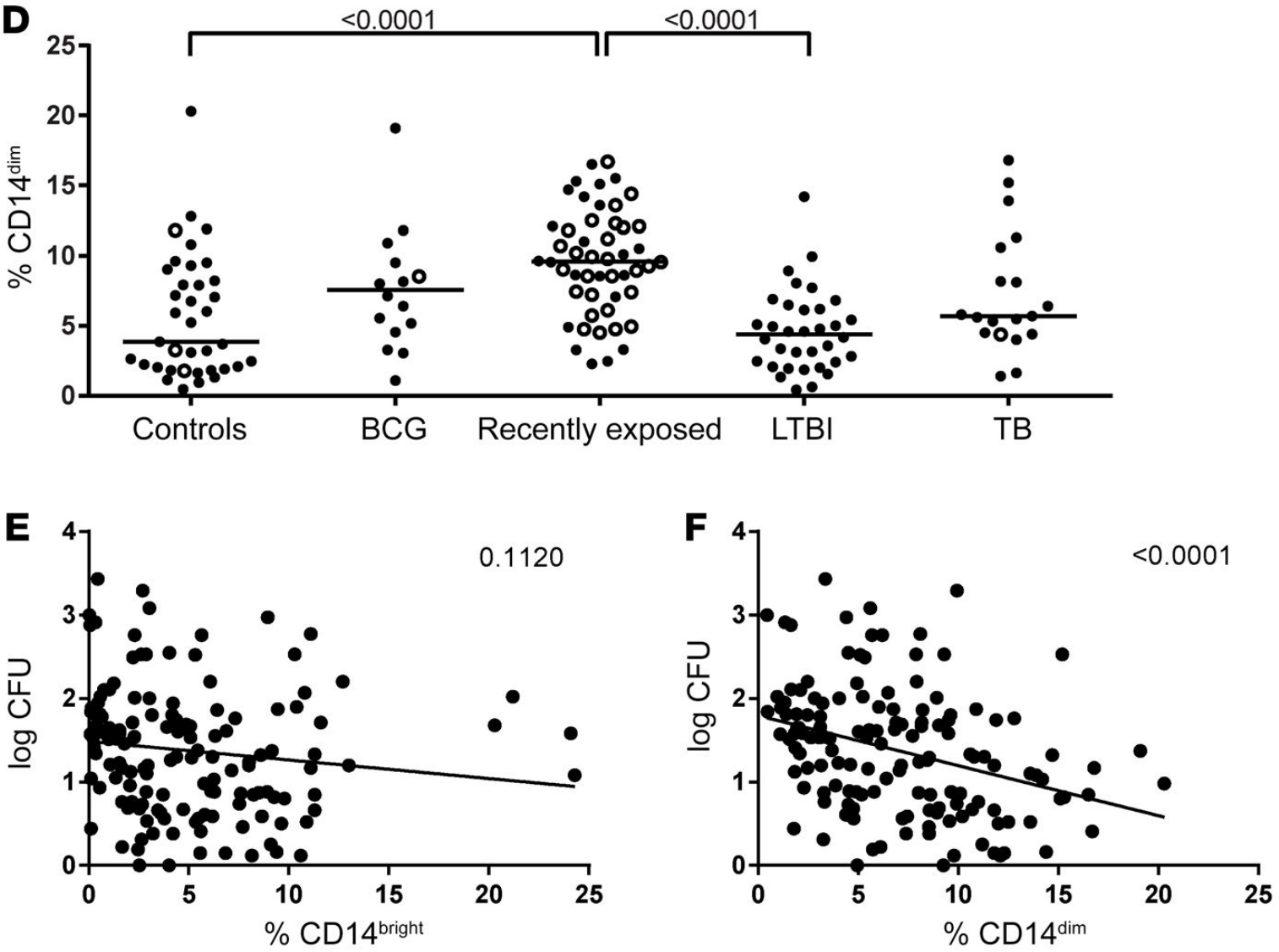
BCG vaccination, macrophage activation and TB control



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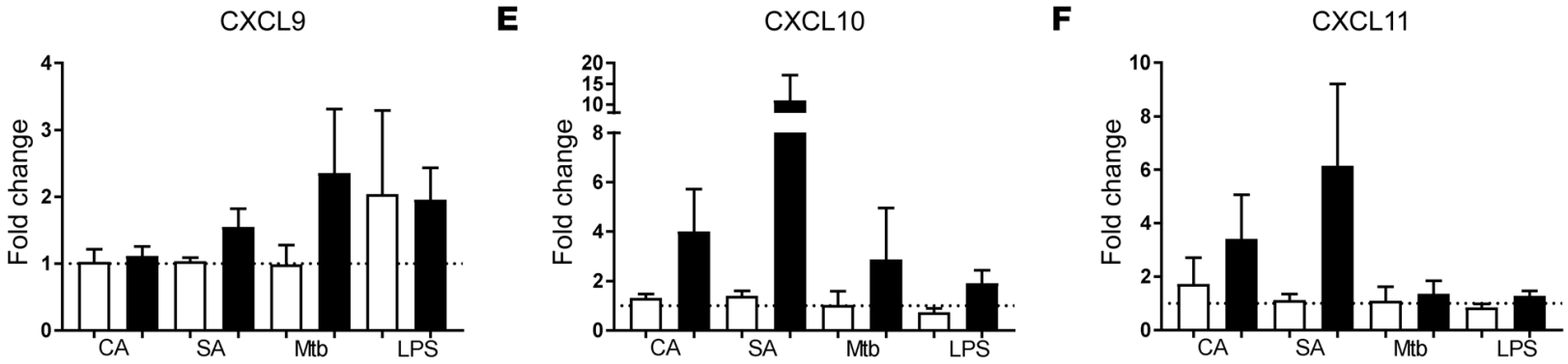
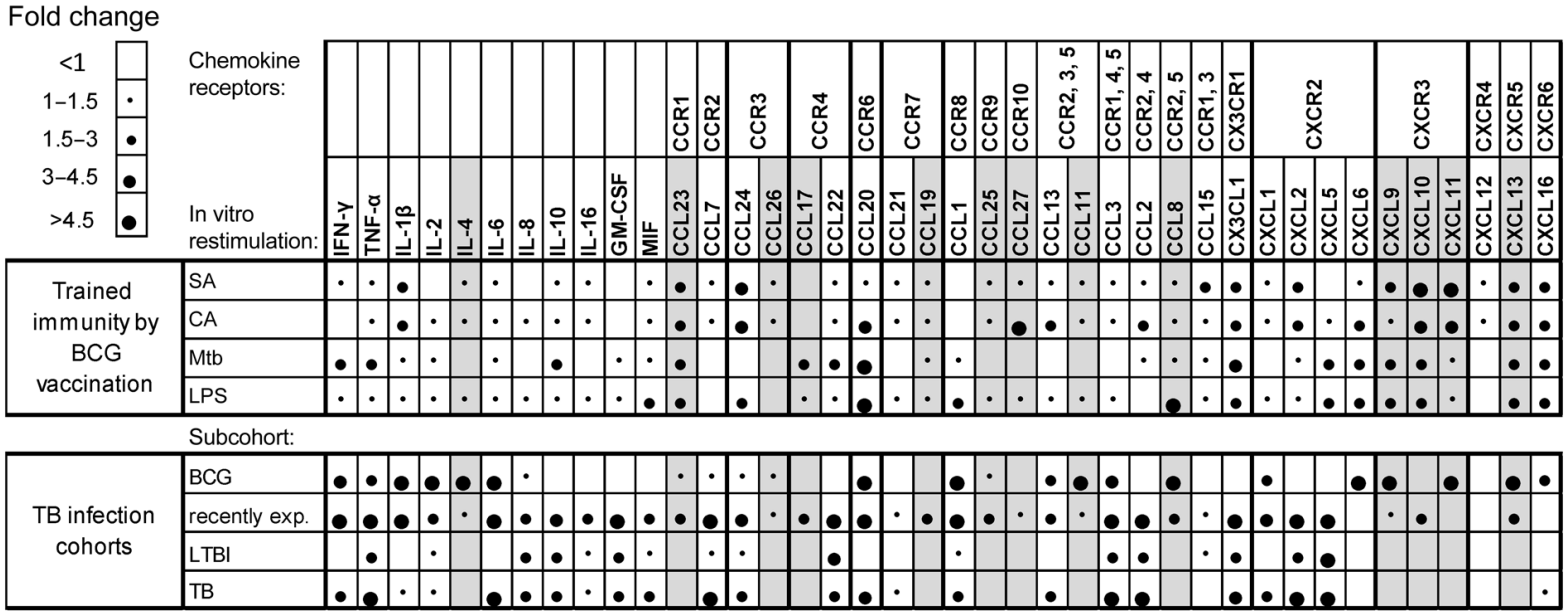
Joosten et al, JCI 2018

BCG vaccination, TB infection and cytokine production





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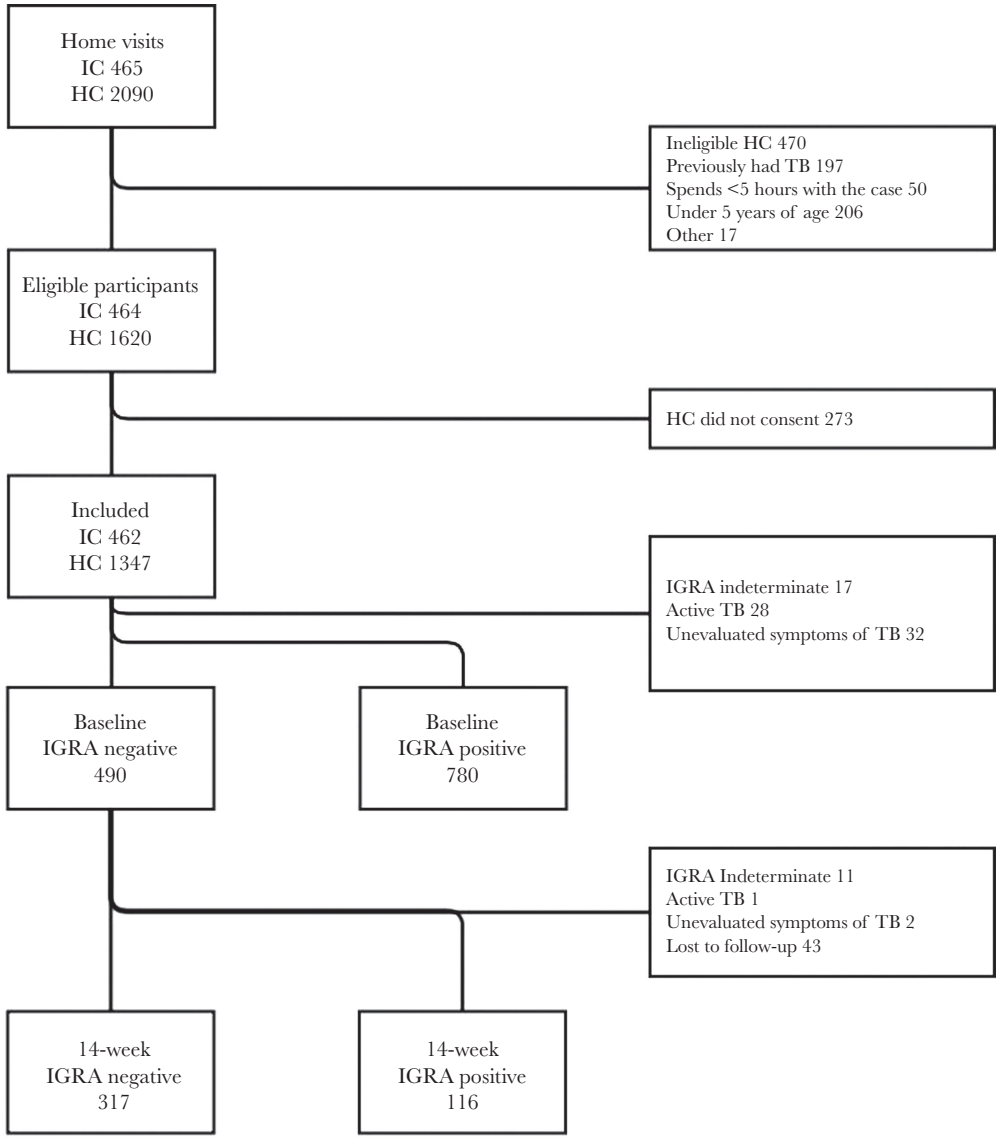
Joosten et al, JCI 2018

BCG vaccination and protection against TB infection



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Verrall et al, JID 2020

BCG vaccination and protection against TB infection

Table 5. Assessment of Risk Factors for Interferon-γ Release Assay Conversion in Household Contacts Who Were IGRA Negative at Baseline (n = 432)

	IGRA Persistently Negative	IGRA Converter						
Contact Characteristic	(n = 317)	(n = 115)[a]	RR	(95% CI)	*P* Value	ARR[b]	(95% CI)	*P* Value
Age[c] scaled	27.9 (12.1–39.8)	22.8 (14.6–35.7)	0.99	(.90–1.08)	.8	0.97	(.88–1.07)	.6
Sex								
Female	170 (54)	59 (51)	1.00	ref		1.00	ref	
Male	147 (46)	57 (49)	1.08	(.79–1.50)	.6	0.88	(.57–1.36)	.6
BCG vaccination[d]								
No	41 (13)	30 (26)	1.00	ref		1.00	ref	
Yes	276 (87)	86 (74)	0.56	(.40–.79)	.001	0.56	(.40–.77)	< .001
Smoking history								
Nonsmoker	241 (76)	78 (68)	1.00	ref		1.00	ref	
Current smoker	76 (24)	37 (32)	1.34	(.97–1.85)	.07	1.47	(.96–2.26)	.08
Diabetes[e]								
No diabetes	292 (92)	103 (89)	1.00	ref		…	…	
Prediabetes	14 (4)	7 (6)	1.28	(.67–2.42)	.5	…	…	
Diabetes	11 (3)	6 (5)	1.35	(.69–2.65)	.4	…	…	
Hemoglobin[f] (g/dL)	13.8 (1.6)	14.2 (1.6)	1.11	(1.01–1.21)	.04	1.14	(1.01–1.30)	.04
Hematocrit[f] (%)	41.2 (4.2)	42.0 (4.8)	1.03	(.99–1.08)	.1	…	…	
Neutrophils[f] (1000/μL)	4.3 (1.6)	4.3 (1.6)	1.00	(.90–1.10)	.9	…	…	
Lymphocytes[f] (1000/μL)	2.6 (0.7)	2.6 (0.8)	1.02	(.82–1.26)	.9	…	…	
Monocytes[f] (1000/μL)	0.4 (0.2)	0.4 (0.2)	0.75	(.30–1.91)	.6	…	…	

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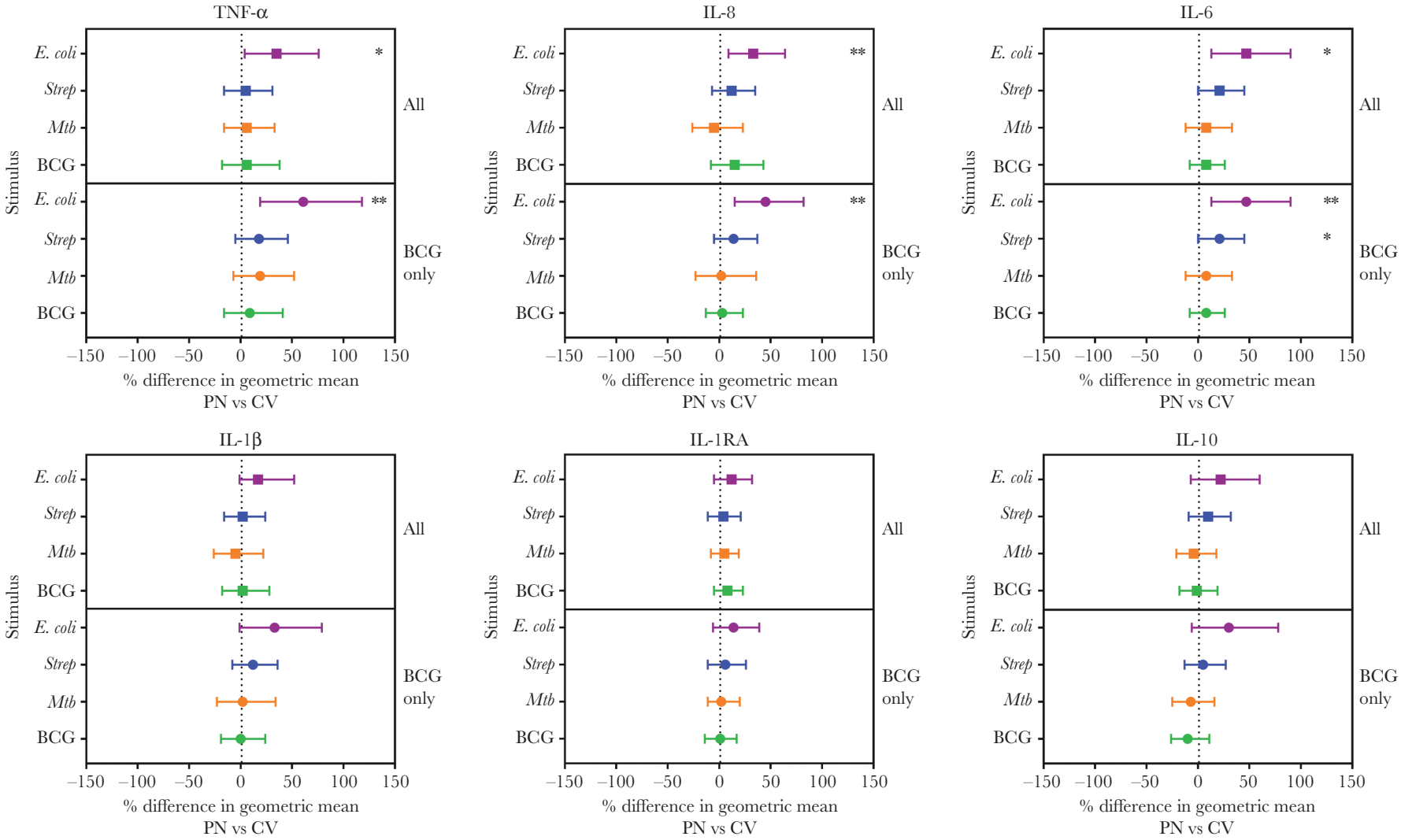
Early clearance and innate cytokine production



Verrall et al, JID 2020

frontiers in Immunology

TLR Agonists as Mediators of Trained Immunity: Mechanistic Insight and Immunotherapeutic Potential to Combat Infection

*Allison M. Owen[1], Jessica B. Fults[1,2], Naeem K. Patil[1], Antonio Hernandez[1] and Julia K. Bohannon[1,3]**

MPLA	*i.p.*	*P. aeruginosa* (topical inoculation of burn wound or *i.p.*)	↑ Bacterial clearance ↑ Leukocyte recruitment	Romero et al. (65)
		Polymicrobial abdominal sepsis (CLP surgical model)	↓ Pro-inflammatory cytokines (plasma)	
	i.p.	*P. aeruginosa (topical inoculation of burn wound)*	↑ Neutrophil mobilization & recruitment to site of infection	Bohannon et al. (67)
	i.p.	*P. aeruginosa (i.p.)*	↑ Neutrophil & macrophage recruitment ↓ Pro-inflammatory cytokines (plasma)	Fensterheim et al. (76)
	i.v.	*S. aureus* (*i.v.*) *C. albicans (i.v.)*	↑ Bacterial clearance ↓ Pro-inflammatory cytokines (plasma) ↓ Organ injury (kidney)	Fensterheim et al. (63)

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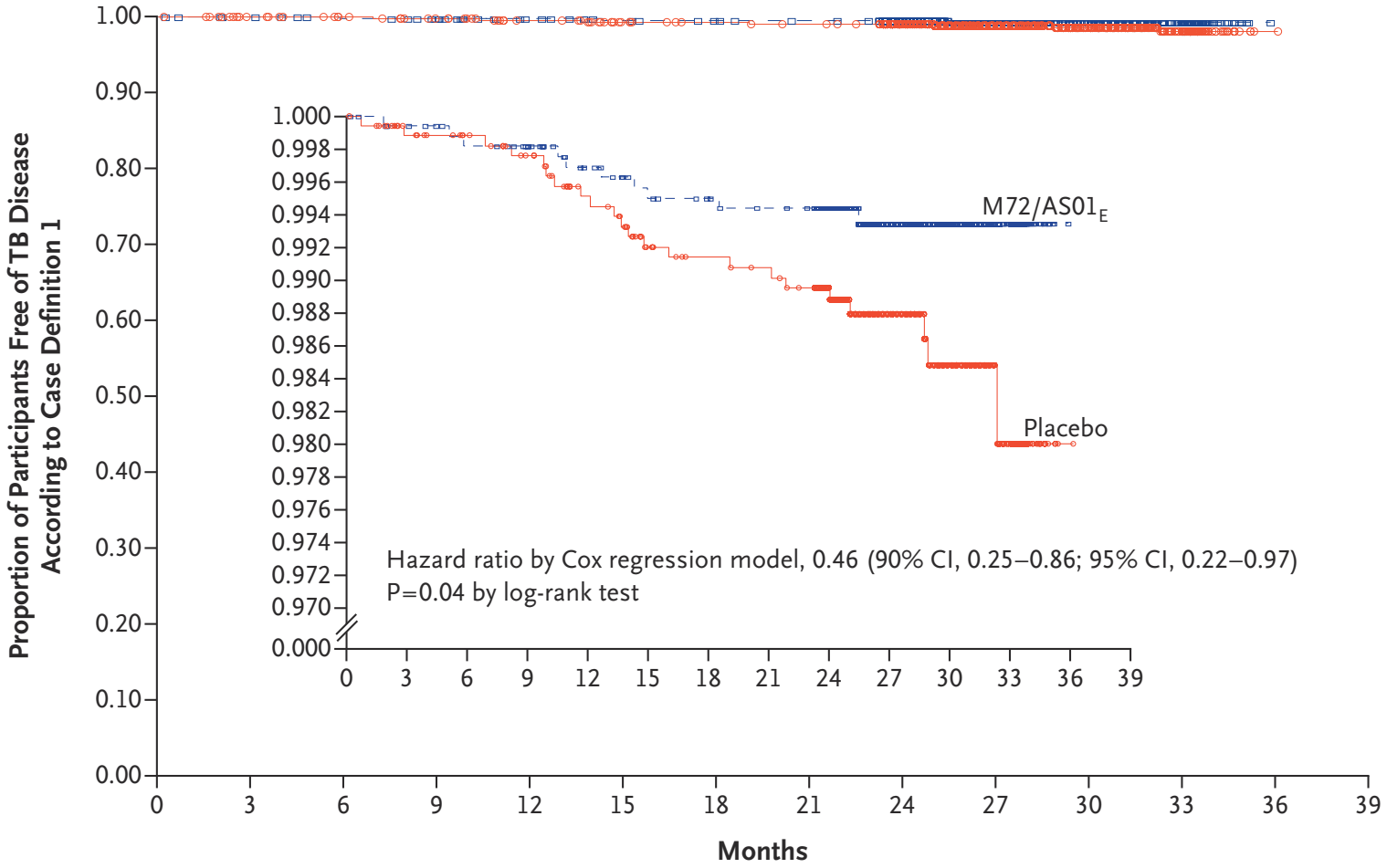
M72/ASO1 and TB protection



No. at Risk

M72/AS01$_E$	1623	1618	1612	1607	1593	1584	1580	1576	1354	847	500	166	0
Placebo	1660	1648	1640	1630	1613	1594	1587	1584	1347	849	509	170	1

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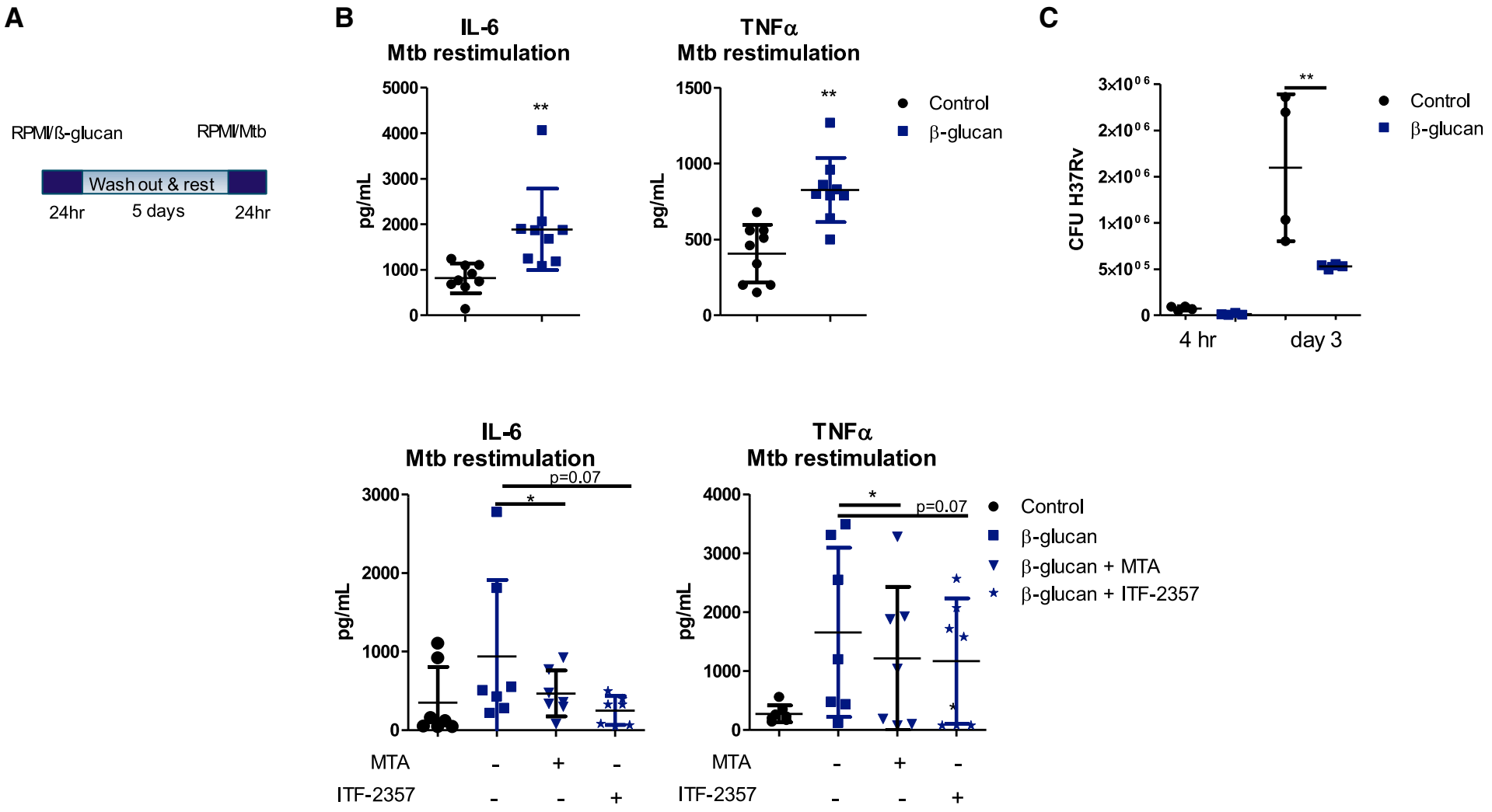
Van der Meeren et al, NEJM 2018

Beta-glucan-induced trained immunity and TB



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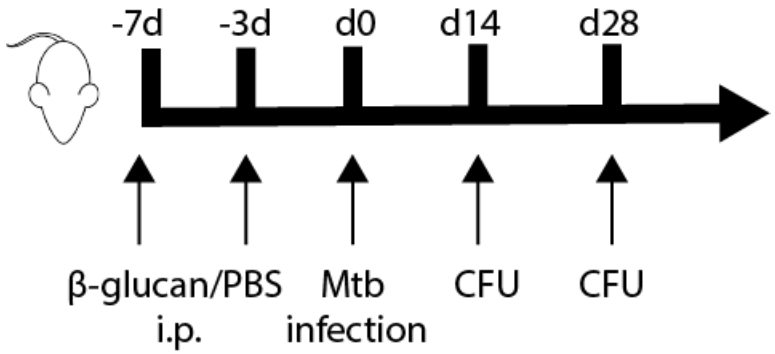
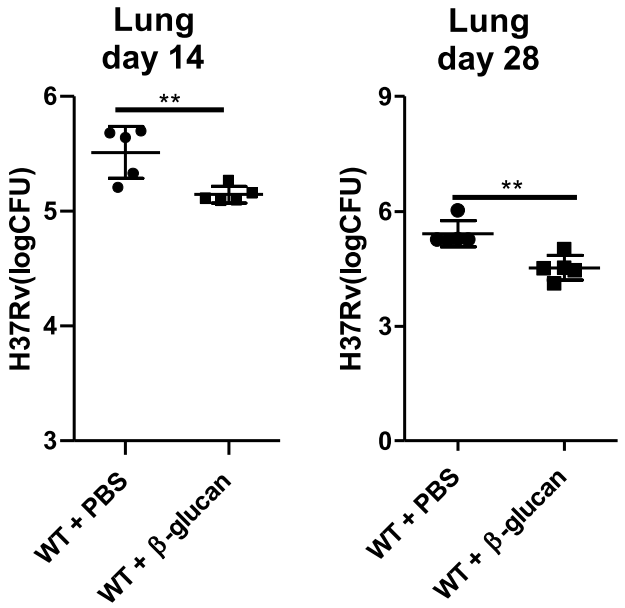
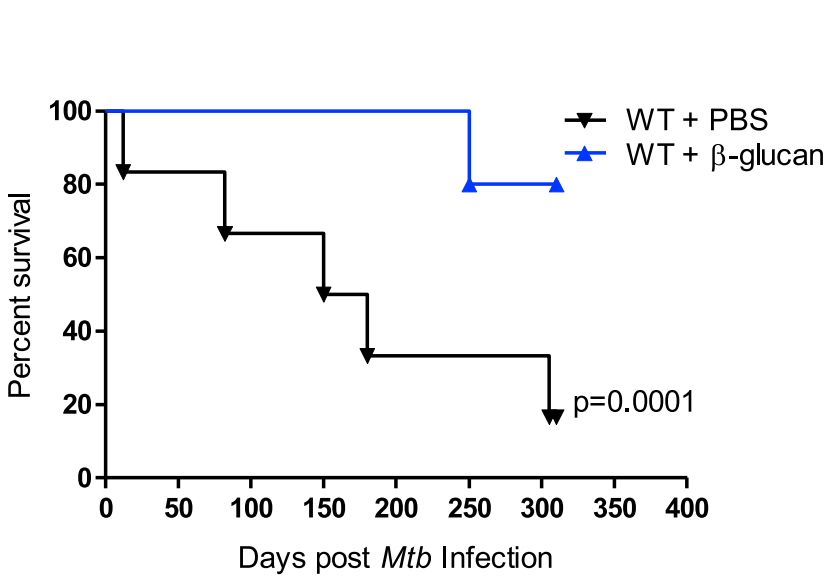
Moorlag et al, Cell Reports 2020

Beta-glucan-induced trained immunity and TB







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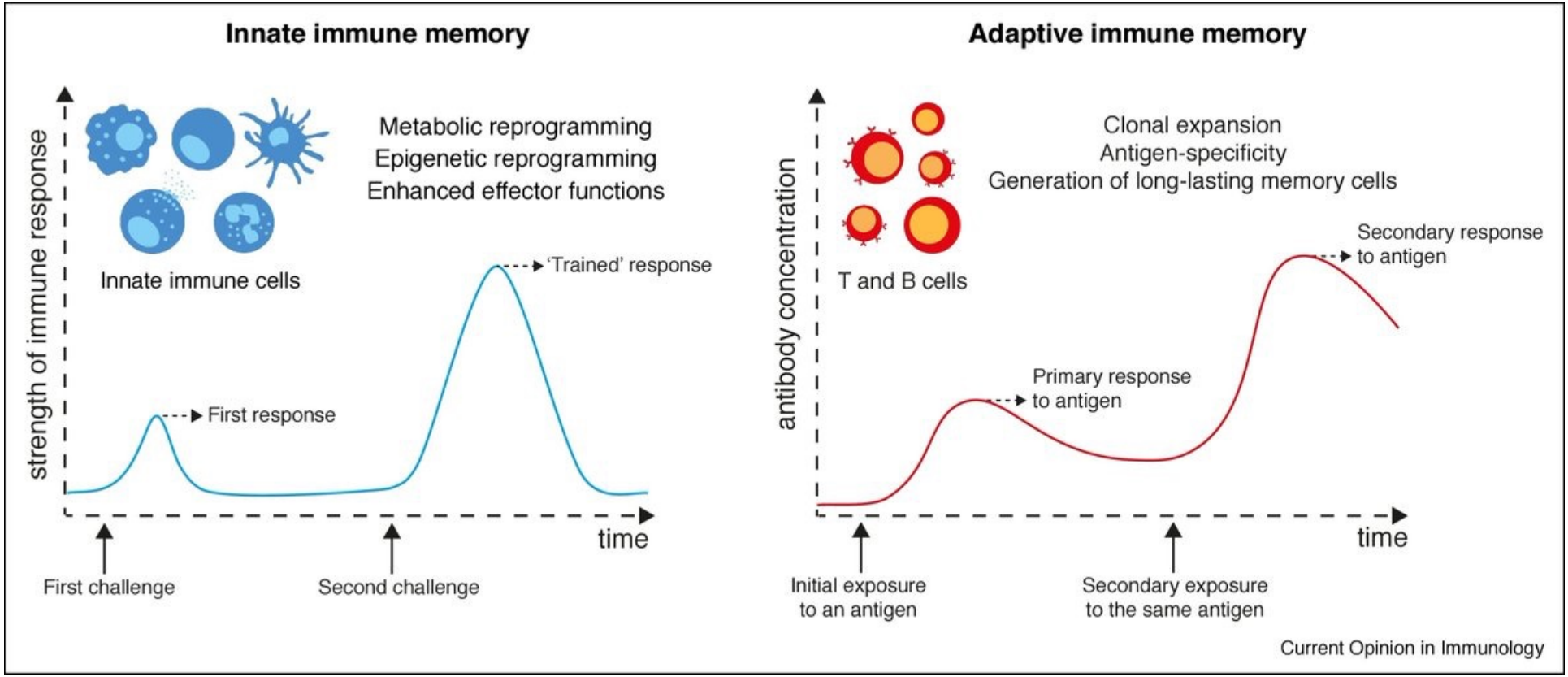
Moorlag et al, Cell Reports 2020

Future vaccine could combine induction of trained immunity and adaptive memory



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Thank you !

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