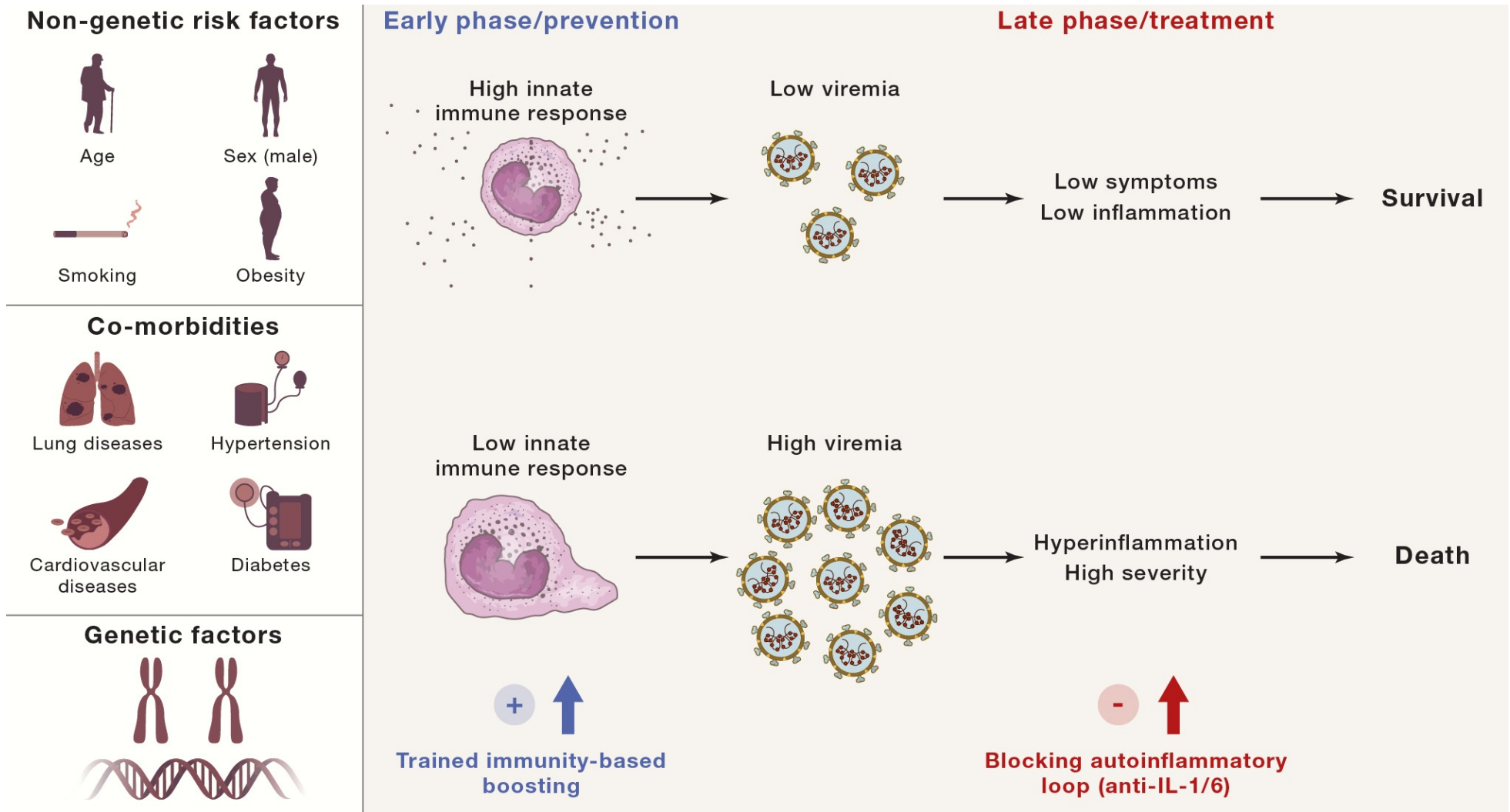


Trained immunity: role for antiviral host defense

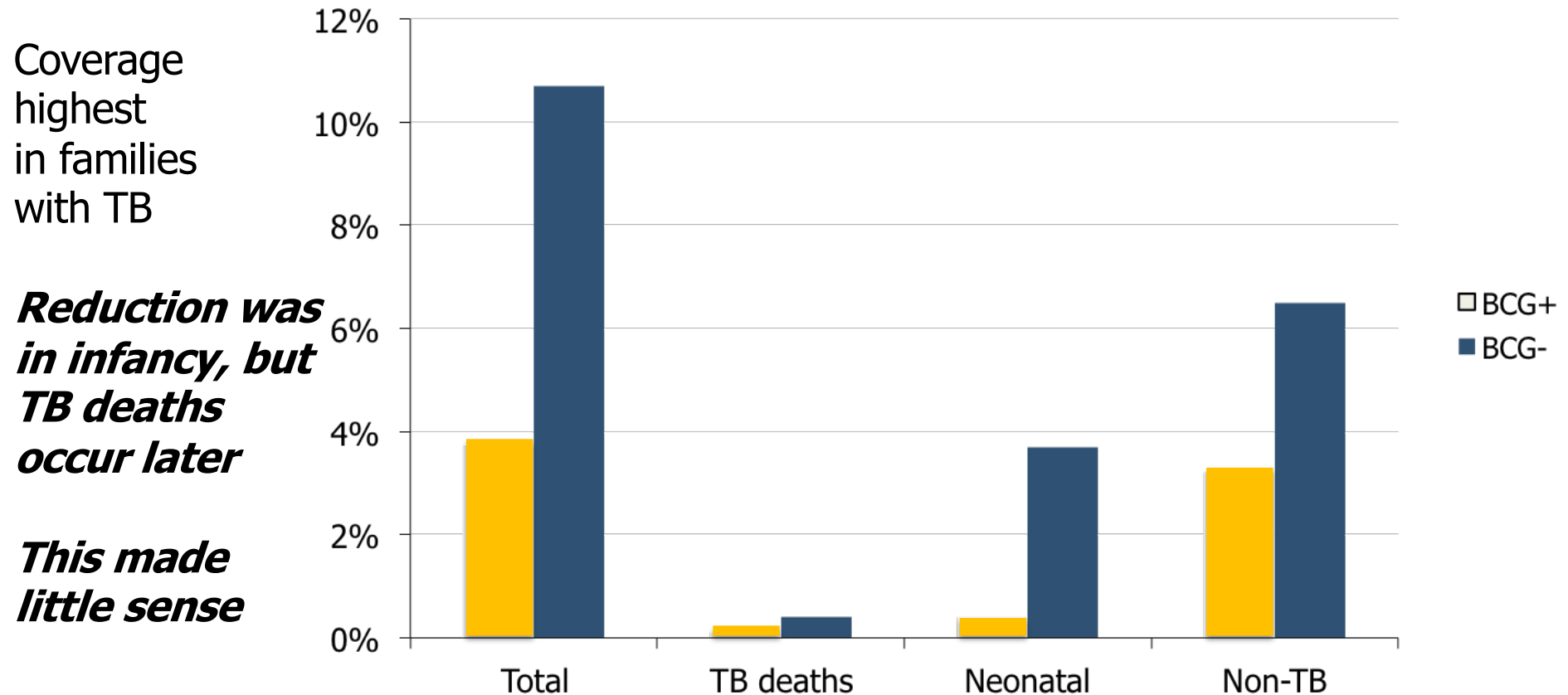
Mihai G. Netea

Radboudumc

Immune responses and severity of the infection



Introducing BCG in Norrbotten, Sweden, 1927-31



"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



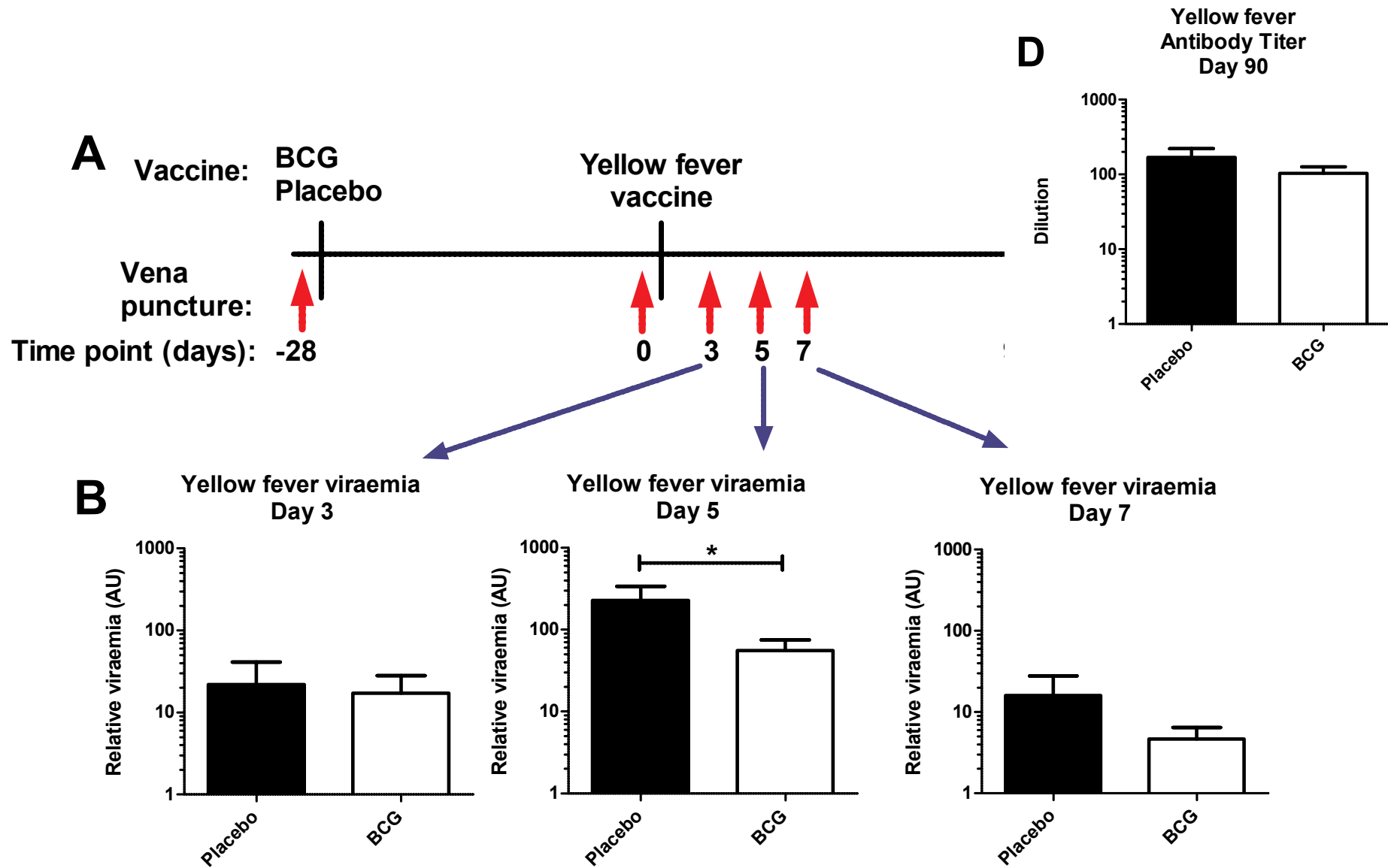
Effect of BCG Danish and oral polio vaccine on neonatal mortality in newborn babies weighing less than 2000 g in India: multicentre open label randomised controlled trial (BLOW2)

Bethou Adhisivam,¹ Chinnathambi Kamalarathnam,² B Vishnu Bhat,³ Kumutha Jayaraman,⁴ Siva P Namachivayam,⁵ Frank Shann,^{5,6} Brent McSharry,⁷ Ponrani David Raja,¹ Mangalabharathi Sundaram⁸

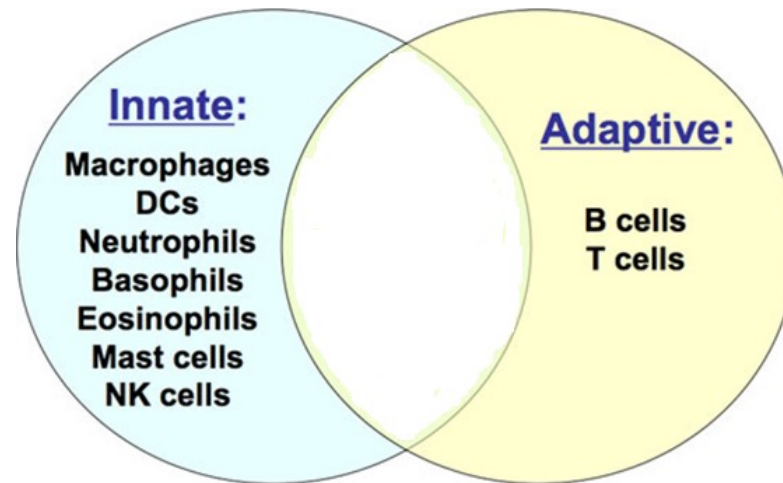
Table 2 | Outcome data in newborn babies weighing <2000 g assigned to receive BCG Danish and OPV within 48 hours of admission (intervention) or delayed at least to discharge (control)

	Mortality rate (deaths/total person years); No		Adjusted hazard ratio (95% CI)	P value*
	Early BCG-OPV	Control		
Deaths ≤28 days (primary outcome)	1.29 (238/184); 2714	1.50 (273/182); 2706	0.83 (0.69 to 0.98)	0.03
Deaths from infection	0.40 (73/184); 2707	0.73 (133/182); 2702	0.53 (0.40 to 0.70)	<0.001†
Deaths from non-infectious cause	0.89 (164/184); 2707	0.77 (139/182); 2702	1.10 (0.88 to 1.39)	0.41†
Deaths in hospital	2.33 (237/102); 2714	2.69 (269/100); 2706	0.83 (0.70 to 0.99)	0.04†
Deaths ≤28 days; controls censored when BCG-OPV given ≤28 days (original primary outcome)	1.29 (238/184); 2714	2.25 (273/121); 2706	0.78 (0.65 to 0.93)	0.006‡
Per protocol analysis	1.28 (236/184); 2702	2.26 (275/122); 2709	0.77 (0.65 to 0.92)	0.004§
Time of death after enrolment (days):				
0-2	2.53 (56/22.1); 2714	3.41 (75/22.0); 2706	0.72 (0.51 to 1.03)	0.07¶
3-6	3.48 (99/28.4); 2658	4.13 (116/28.1); 2631	0.84 (0.64 to 1.10)	0.21¶
7-27	0.62 (83/134); 2553	0.62 (82/132); 2512	0.91 (0.67 to 1.24)	0.55¶

BCG vaccination in vivo & yellow fever vaccine



Innate versus specific immunity



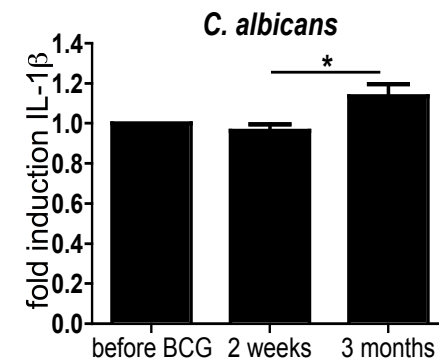
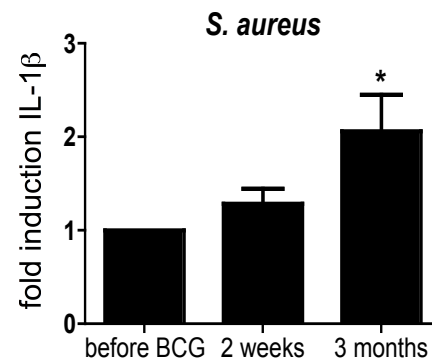
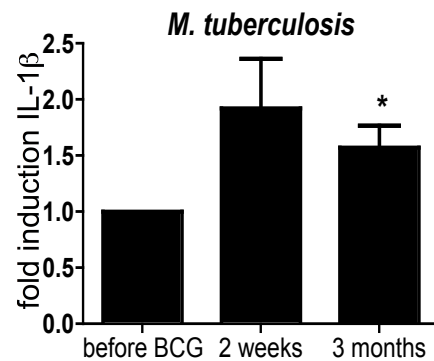
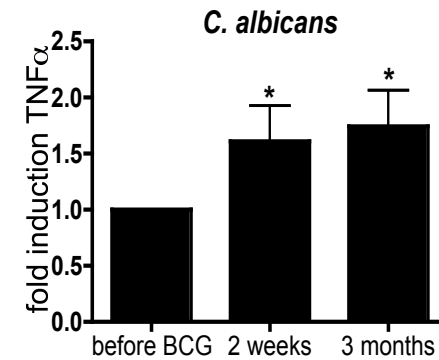
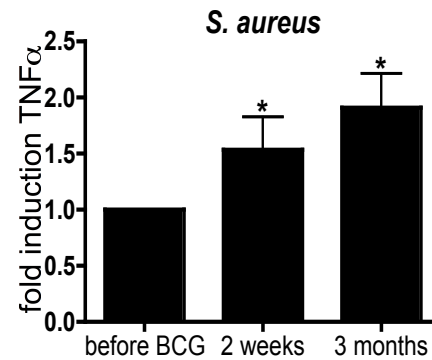
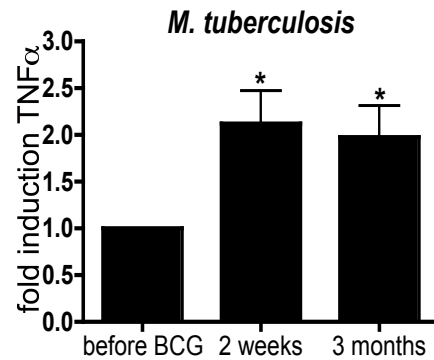
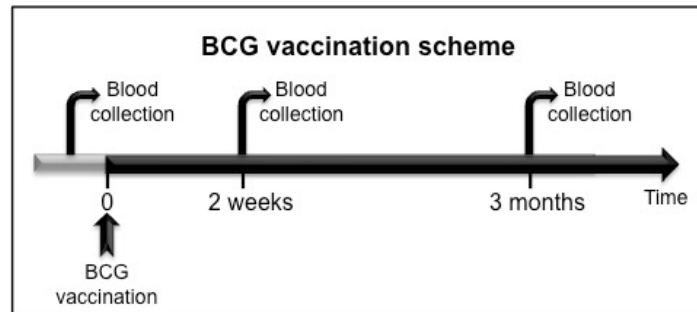
Innate immunity:

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

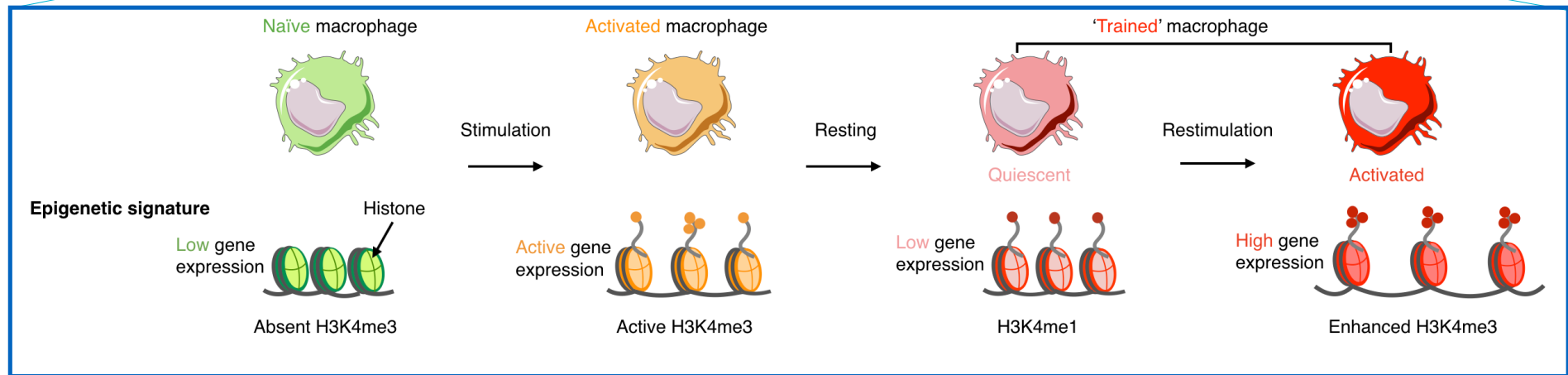
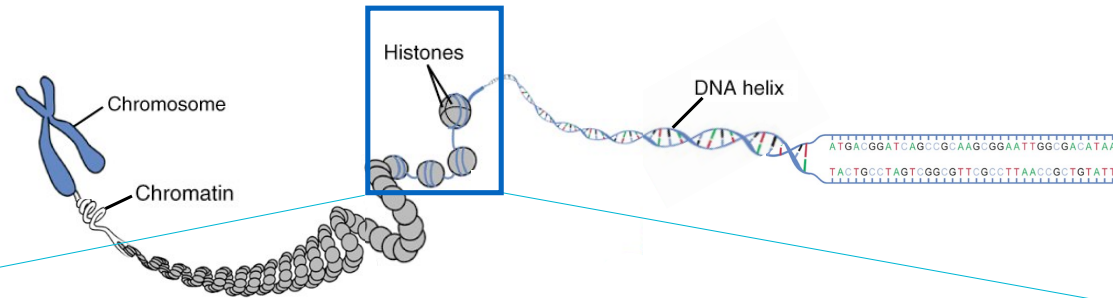
Adaptive immunity:

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

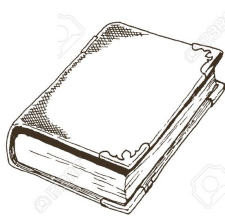
BCG enhances monocyte-derived cytokines



Long-term epigenetic reprogramming in myeloid cells



Resting



Infection



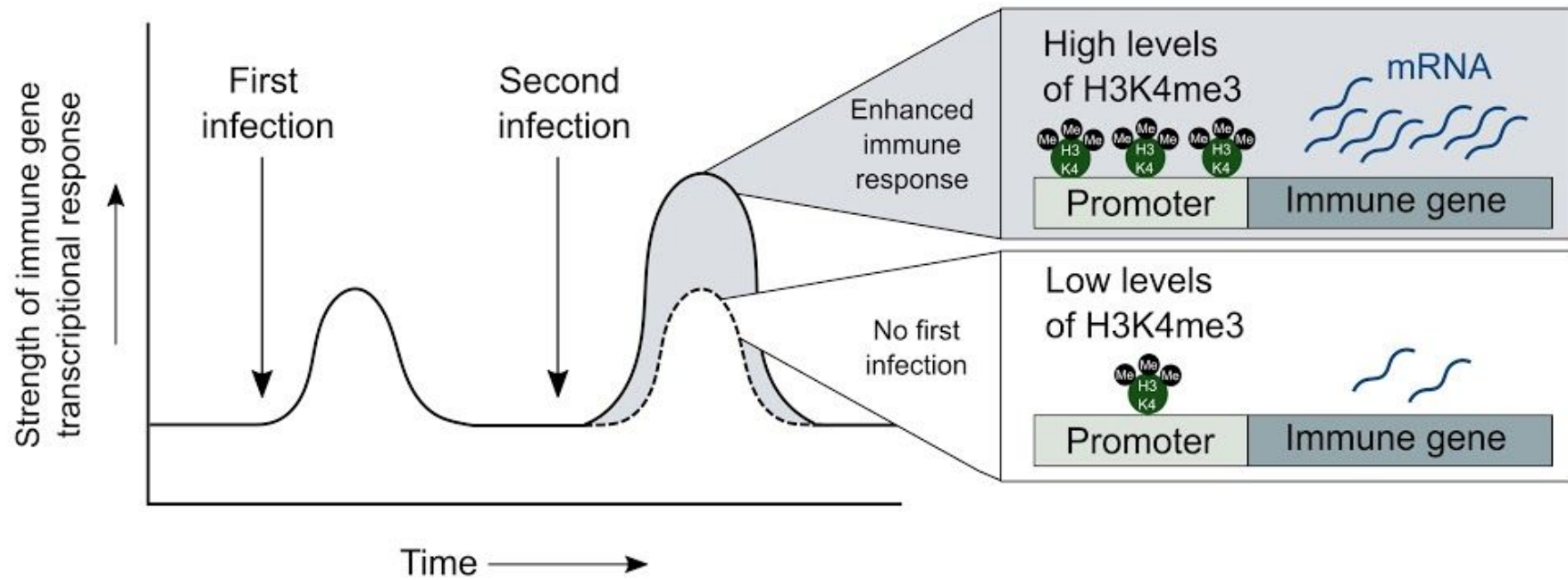
Resting



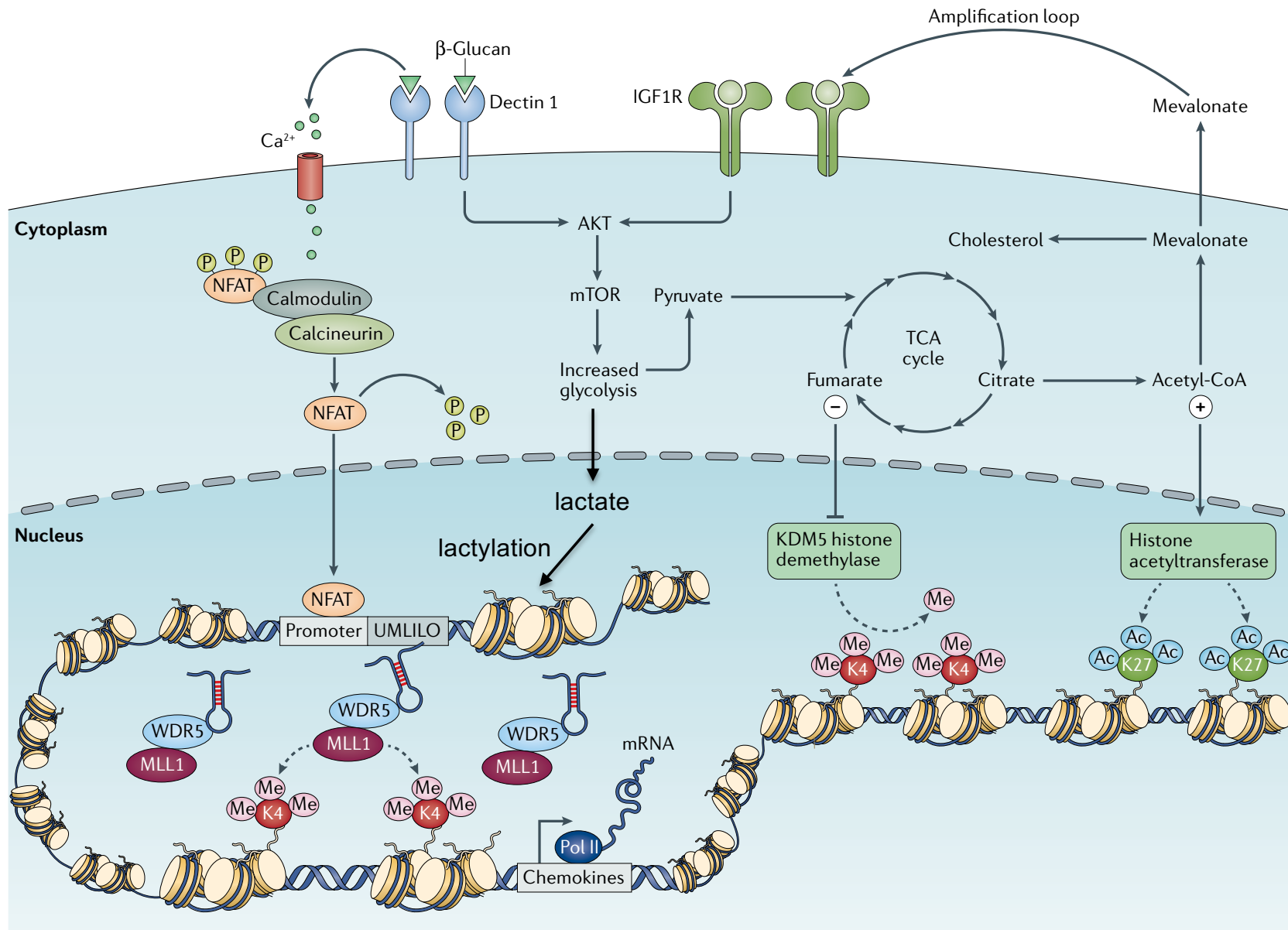
**Re-
infection**



Long-term epigenetic reprogramming in myeloid cells

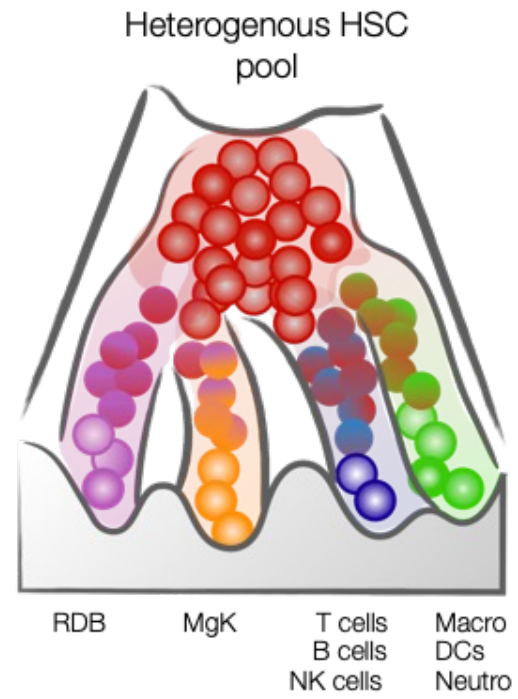
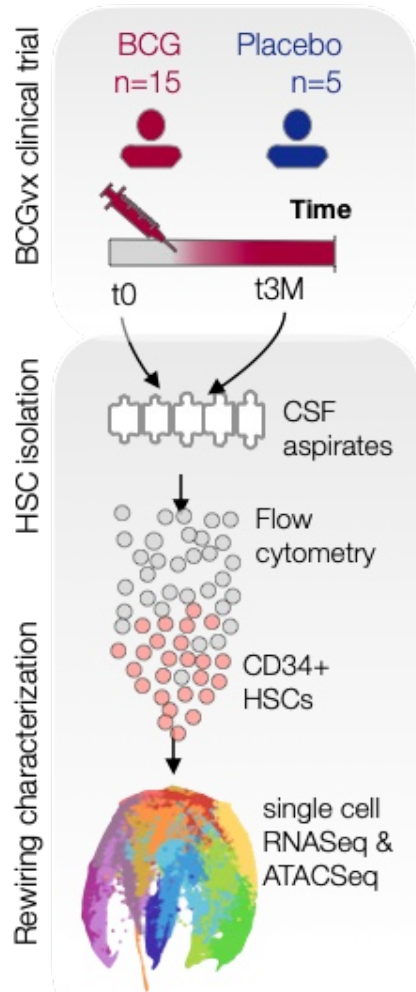


Trained immunity: mechanisms

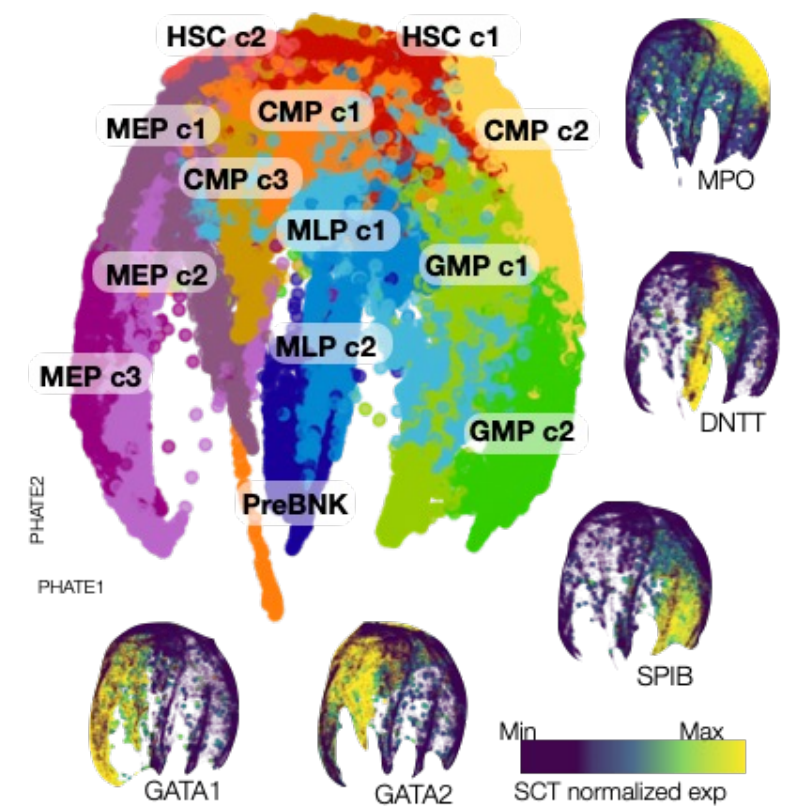


Netea et al, Nat Rev Immunol 2020
 Ziogas et al, Cell 2025

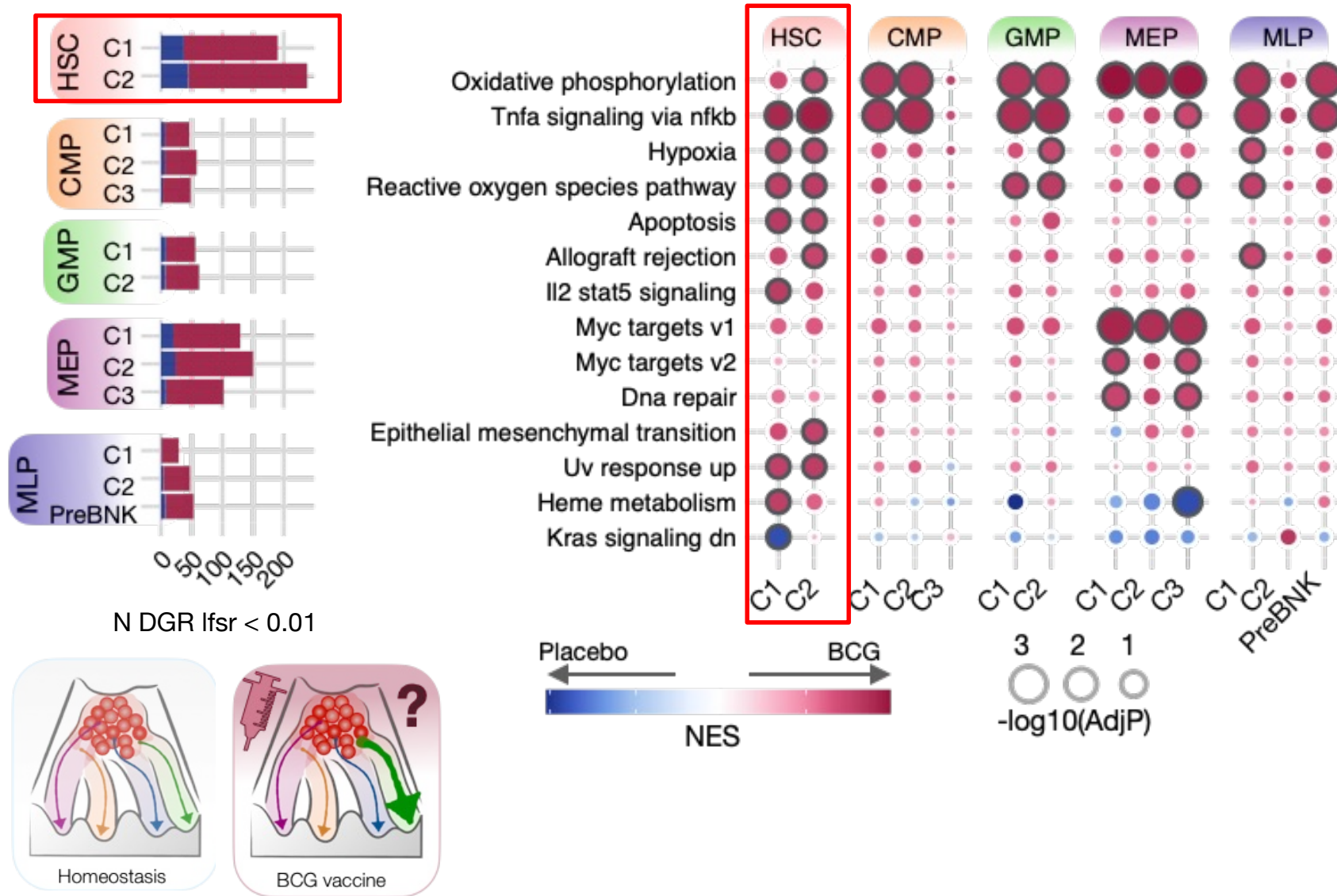
BCG vaccination impact on human bone marrow at single cell level



92K CD34+ hematopoietic stem cells

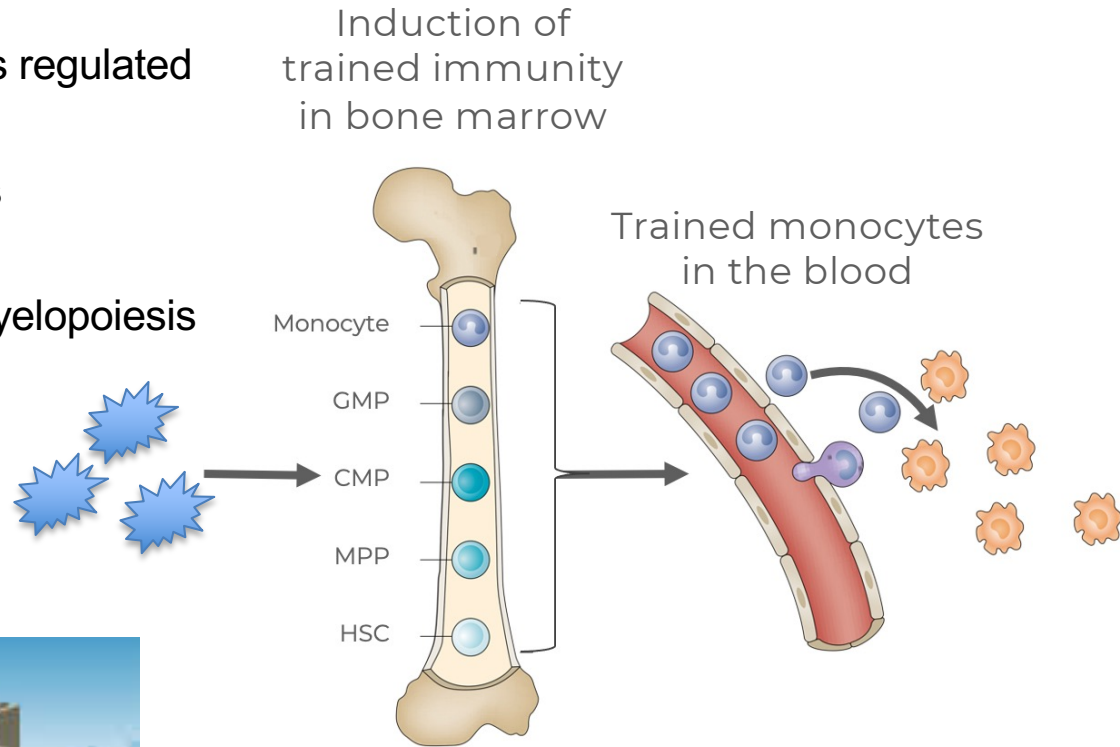


BCG vaccination has impact on human bone marrow



Trained immunity regulates myelopoiesis

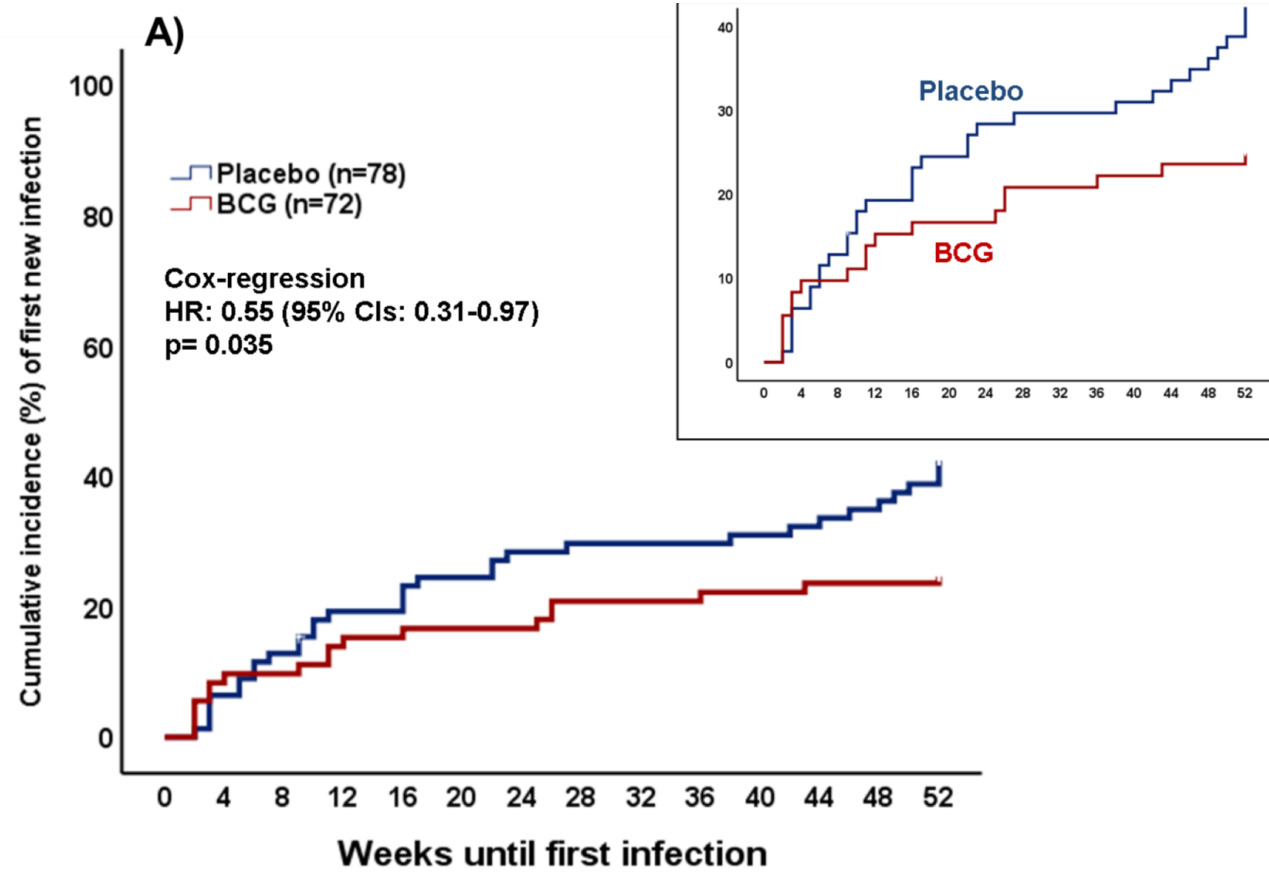
- Systemically, trained immunity is regulated by bone marrow progenitor cells
- Its induction leads to 'trained' myelopoiesis



GMP= Granulocyte Monocyte Progenitor
CMP= Common Myeloid Progenitor
MPP= Multipotent Progenitor
HSC= Hematopoietic Stem Cells

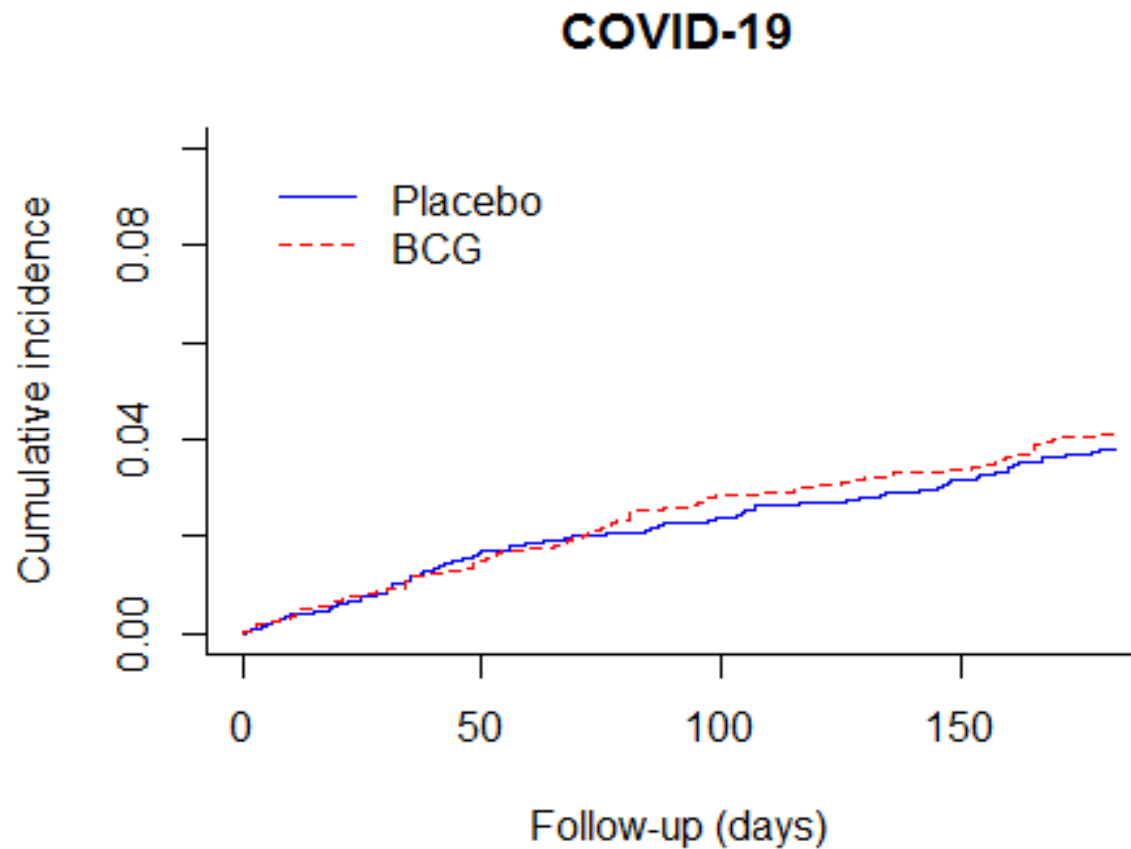


ACTIVATE study: BCG in elderly

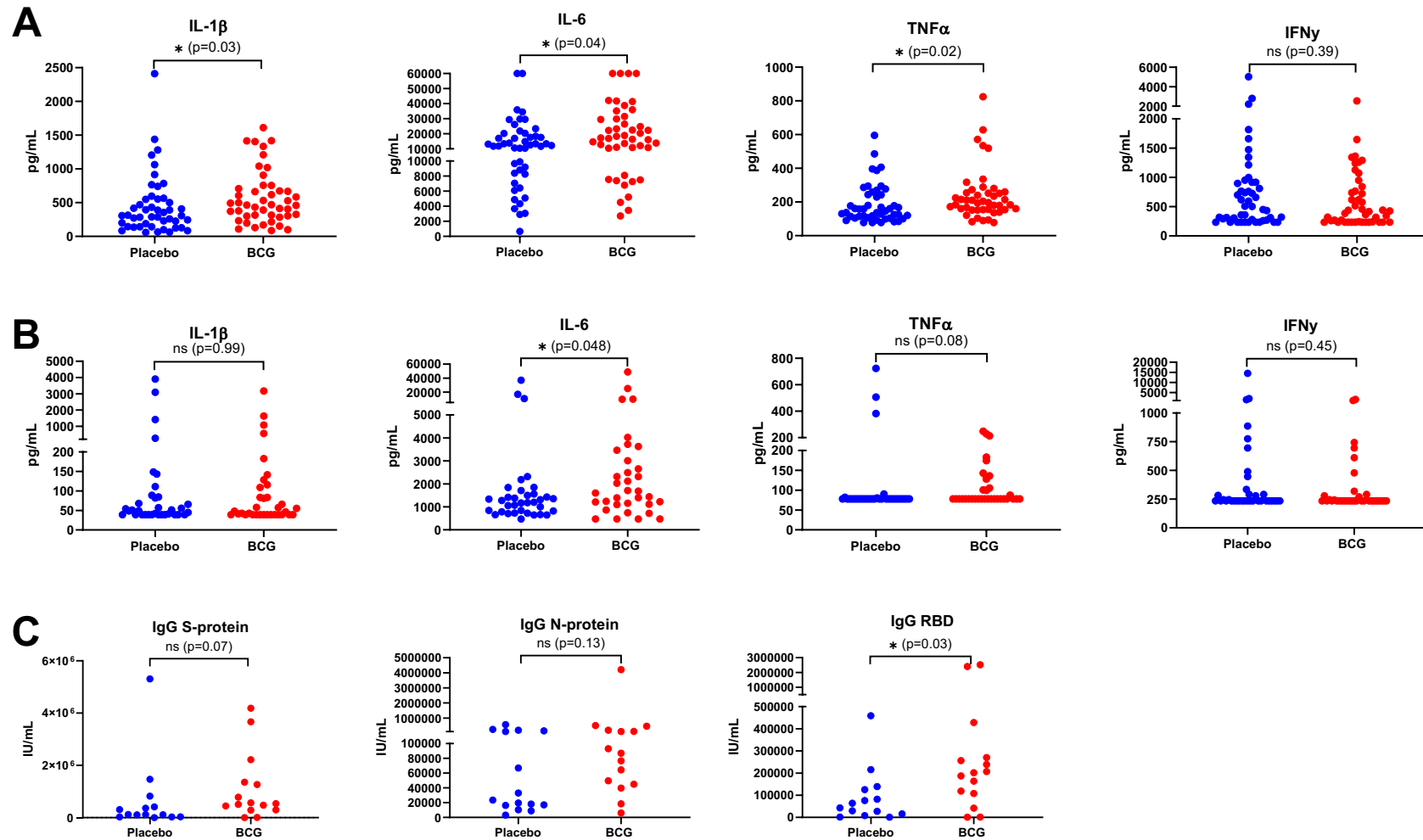


No of pts at risk	0	4	8	12	16	20	24	28	32	36	40	44	48	52
Placebo	78	73	68	62	59	58	55	54	54	54	53	51	49	45
BCG	72	65	65	61	60	60	60	57	57	56	56	55	55	54

BCG-Prime study in the Netherlands (n=3000+3000)

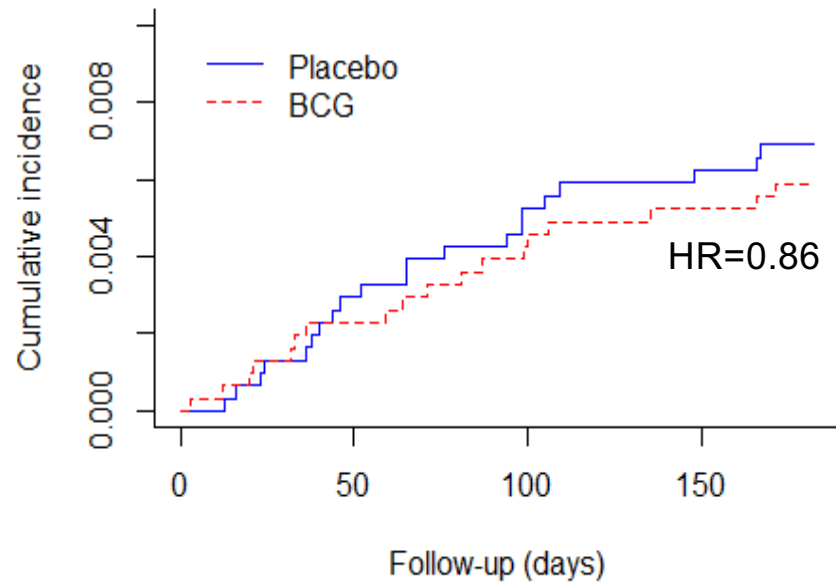


BCG-Elderly study in the Netherlands

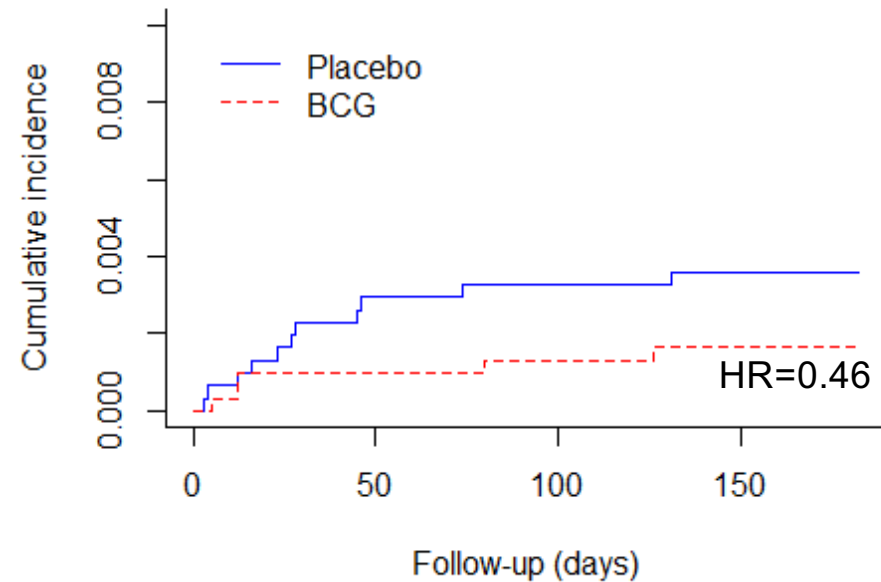


BCG-Prime study in the Netherlands (n=3000+3000)

COVID-19 related admissions



Influenza infection



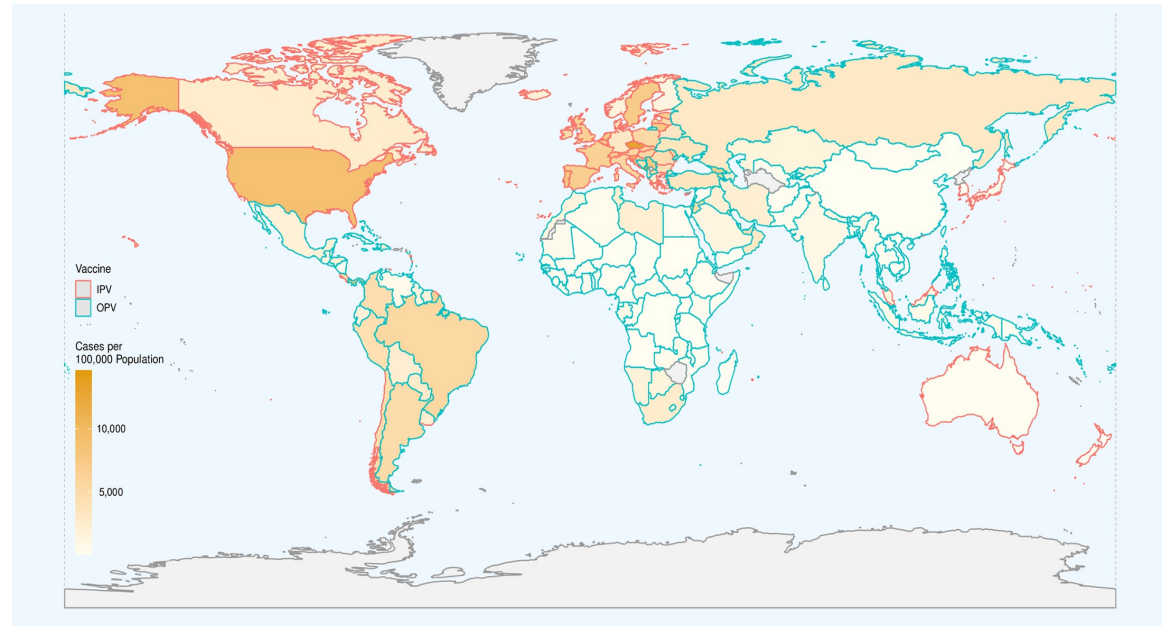
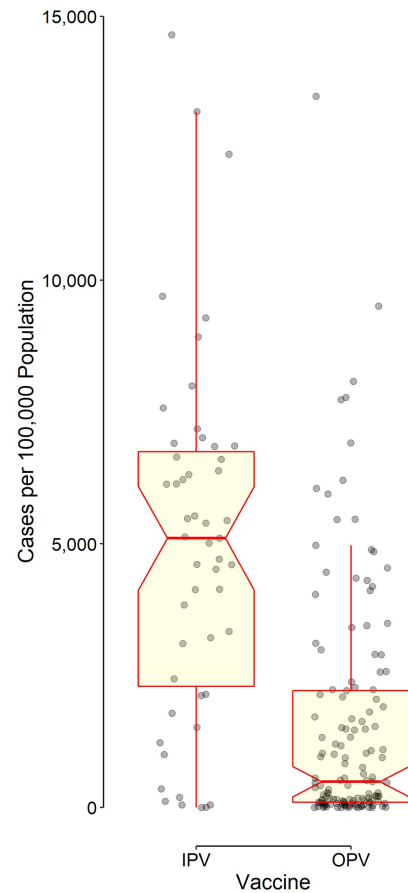
BCG effect on all-cause mortality in COVID19 RCTs

Country; reference	Vaccine used; population; test for COVID-19	Age groups	Mortality (deaths/N)		Mortality risk ratio (BCG/placebo) (95% CI)
			BCG	Placebo	
Greece (1)	BCG vs placebo at hospital discharge; 12 months follow-up, interim analysis	Mean age 80 years	5/72	8/78	0.68 (0.23-1.97)
Greece (2)	BCG vs placebo; 6 months follow-up	301 elderly, 50+ years with co-morbidity	0/148	3/152	0 (undefined)
The Netherlands (BCG PRIME)(3)#	BCG vs placebo; 12 months follow-up	65+ years	13/3058	18/3054	0.72 (0.35-1.479)
The Netherlands (CORONA-Elderly)(4)#	BCG vs placebo; 6 months follow-up	65+ years	2/1008	3/1006	0.67 (0.11-3.97)
South Africa (submitted) (5)	BCG vs Placebo; 6 months follow-up	HCWs	0/500	4/500	0 (undefined)
Combined analysis			20/4786	36/4790	0.57 (0.33-0.97) P=0.04

Notes: # unpublished but presented at BCG conference, Pasteur Institute, Lille, November, 2021

Use of oral polio vaccine and the incidence of COVID-19 in the world

Farrokh Habibzadeh^{1,2}, Konstantin Chumakov³, Mohammad M. Sajadi^{4,5}, Mahboobeh Yadollahie⁶, Kristen Stafford^{4,5}, Ashraf Simi², Shyamasundaran Kottilil^{4,5}, Iman Hafizi-Rastani², Robert C. Gallo^{4,5*}

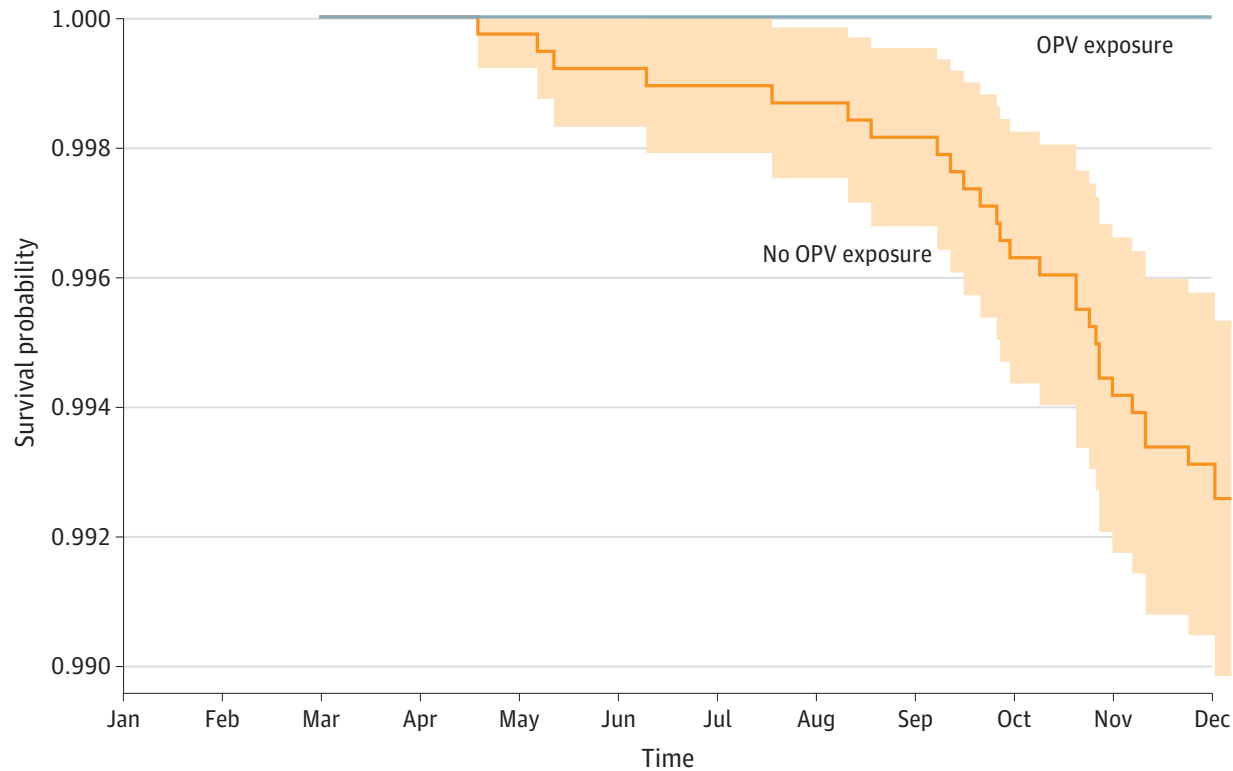




Original Investigation | Infectious Diseases

COVID-19 Infection Among Women in Iran Exposed vs Unexposed to Children Who Received Attenuated Poliovirus Used in Oral Polio Vaccine

Farrokh Habibzadeh, MD; Mohammad M. Sajadi, MD; Konstantin Chumakov, PhD; Mahboobeh Yadollahie, MD; Shyamasundaran Kottlil, MD, PhD; Ashraf Simi, BScN; Kristen Stafford, PhD; Saeid Saeidimehr, MD; Mohammad Rafiei, MD; Robert C. Gallo, MD

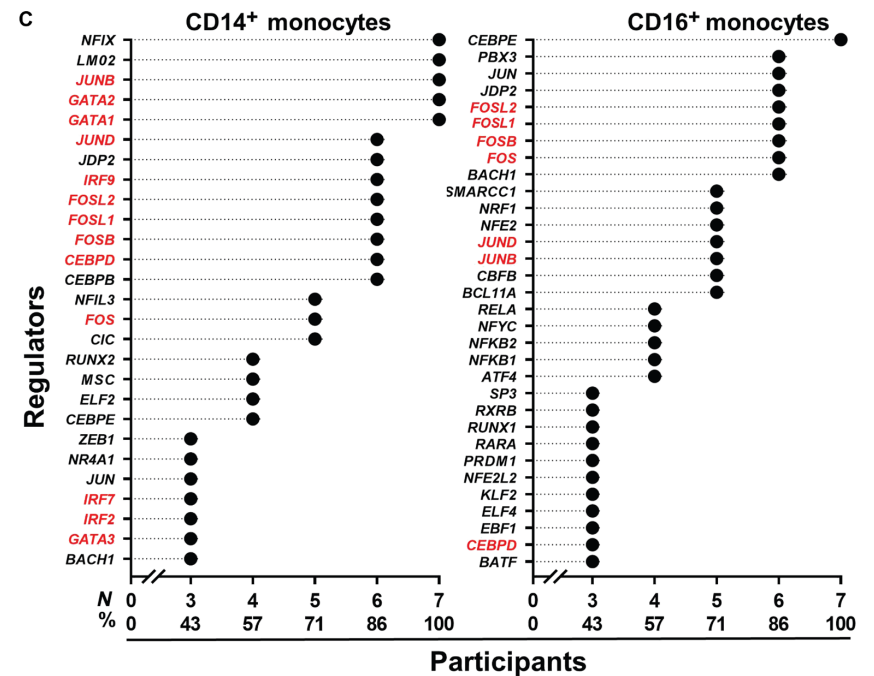
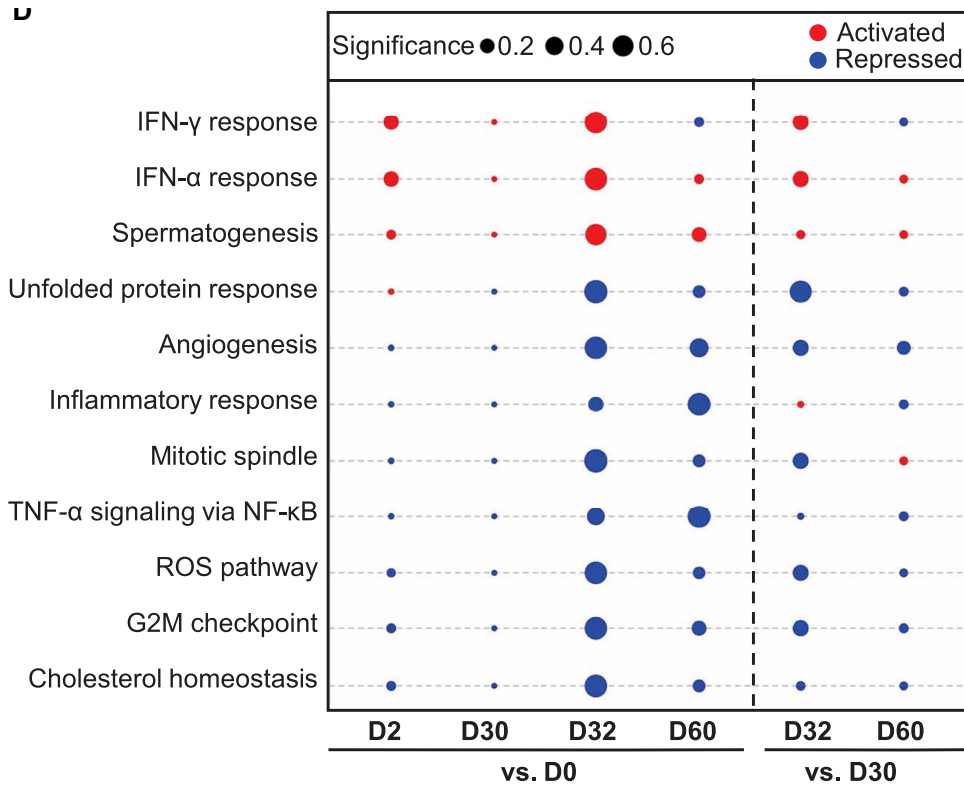


No. at risk		Jan	Feb	Mar	Apr	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec
Not exposed	3771	3771	3771	3770	3768	3767	3766	3764	3757	3750	3745		
Exposed	419	386	358	319	269	192	136	67	28	2			

ADJUVANTS

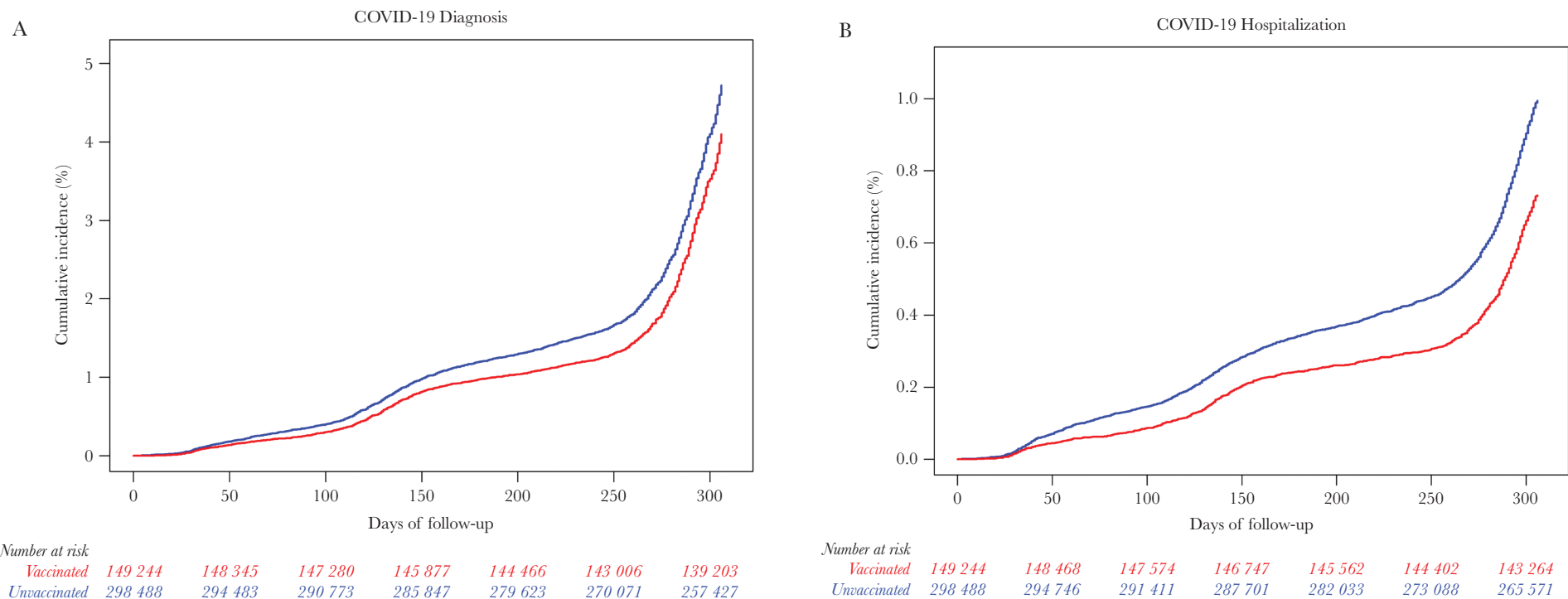
Functional and epigenetic changes in monocytes from adults immunized with an AS01-adjuvanted vaccine

Viviane Bechtold^{1*†}, Kinga K. Smolen^{1,2†‡}, Wivine Burny¹, Simone P. de Angelis¹, Simon Delandre¹, Ahmed Essaghir¹, Arnaud Marchant², Cheikh Ndour³, Martin Taton², Robbert van der Most^{1§}, Fabienne Willems^{2¶}, Arnaud M. Didierlaurent^{1*¶¶}



Recombinant Adjuvanted Zoster Vaccine and Reduced Risk of Coronavirus Disease 2019 Diagnosis and Hospitalization in Older Adults

Katia J. Bruxvoort,^{1,2,a} Bradley Ackerson,^{1,a} Lina S. Sy,¹ Amit Bhavsar,³ Hung Fu Tseng,^{1,4} Ana Florea,¹ Yi Luo,¹ Yun Tian,¹ Zendi Solano,¹ Robyn Widenmaier,⁵ Meng Shi,⁵ Robbert Van Der Most,⁶ Johannes Eberhard Schmidt,⁷ Jasur Danier,^{5,©} Thomas Breuer,³ and Lei Qian¹



Systems vaccinology of the BNT162b2 mRNA vaccine in humans

<https://doi.org/10.1038/s41586-021-03791-x>

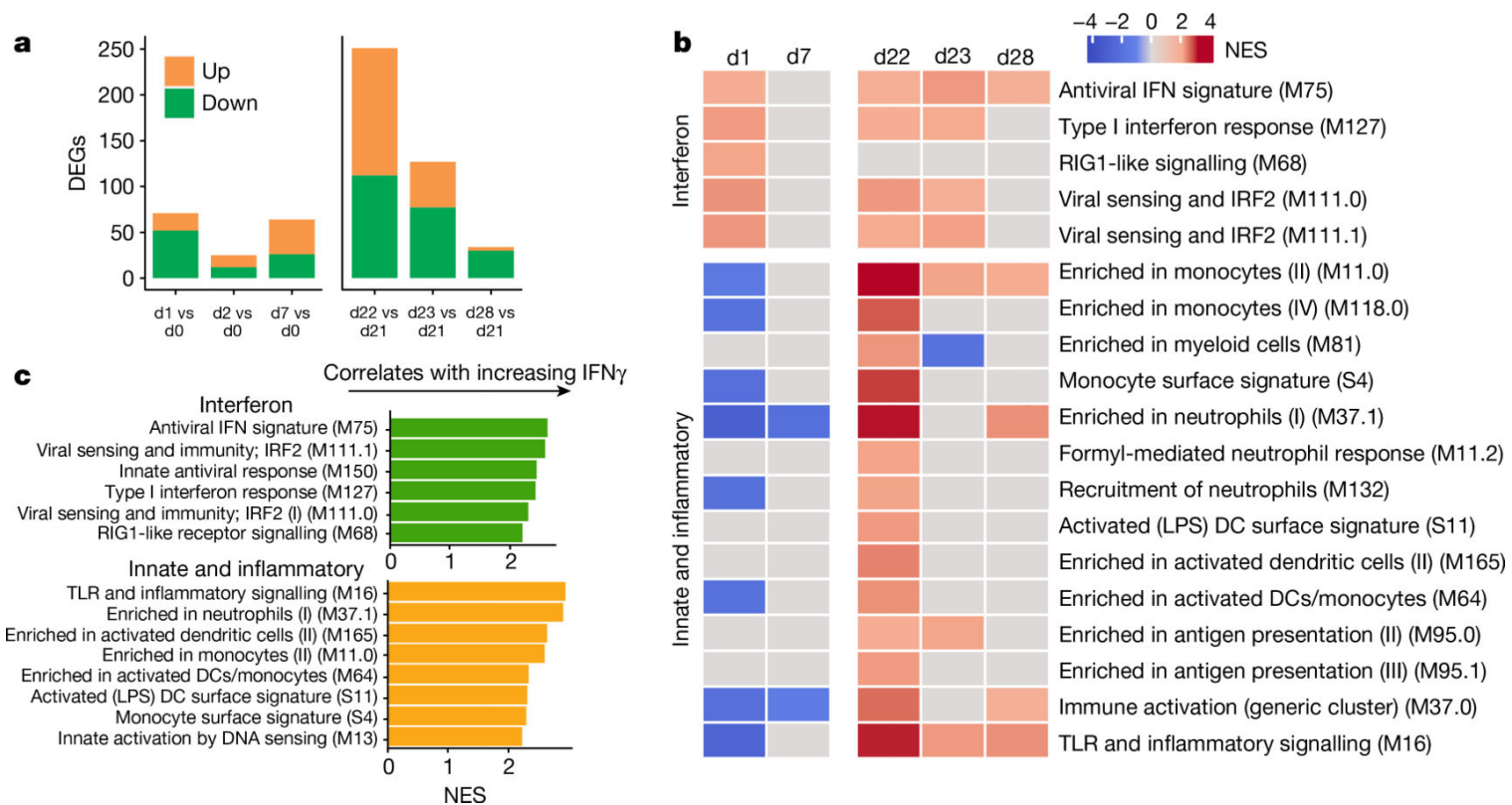
Received: 19 April 2021

Accepted: 1 July 2021

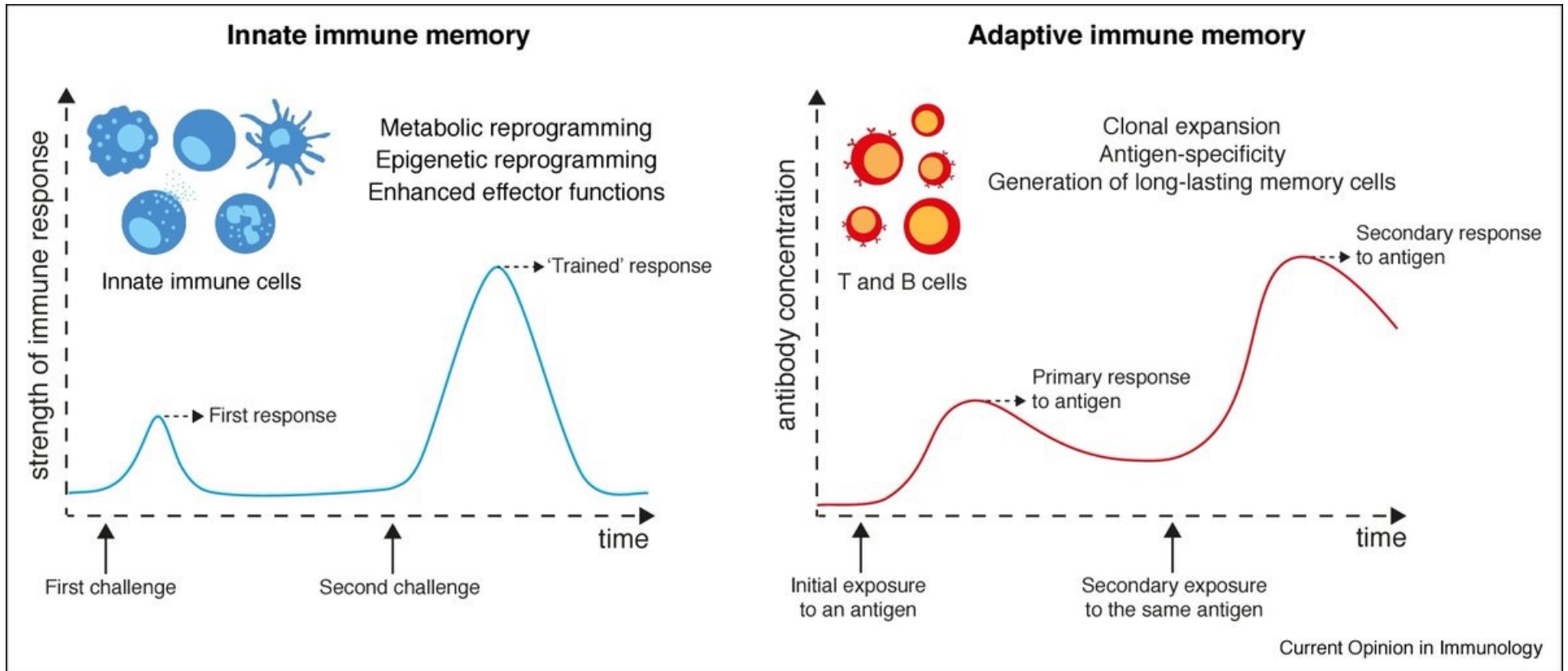
Published online: 12 July 2021

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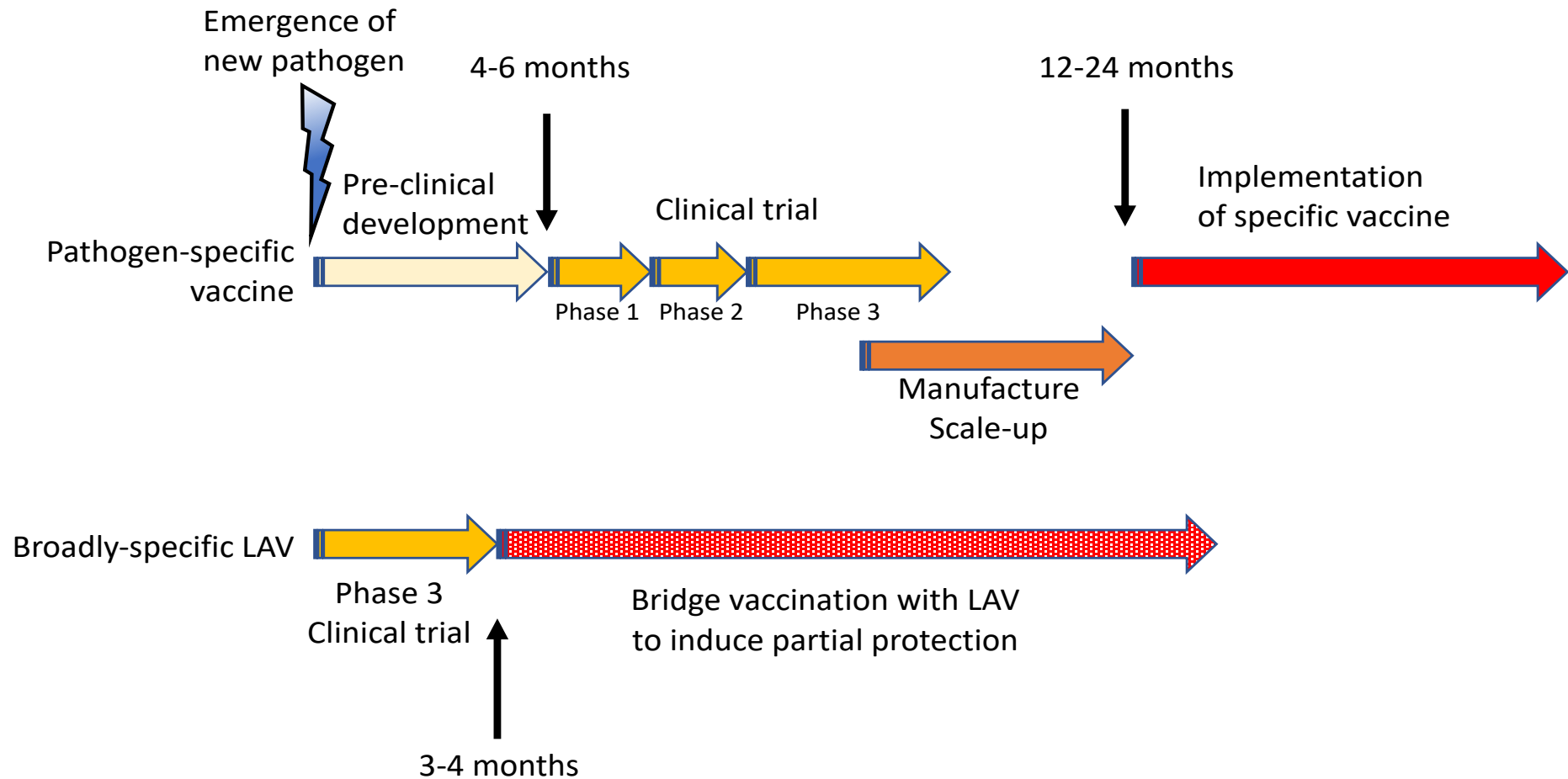
Prabhu S. Arunachalam^{1,14}, Madeleine K. D. Scott^{1,2,14}, Thomas Hagan^{3,4,14}, Chunfeng Li¹, Yupeng Feng¹, Florian Wimmers¹, Lilit Grigoryan¹, Meera Trisal¹, Venkata Viswanadh Edara⁵, Lilin Lai⁵, Sarah Esther Chang^{1,6}, Allan Feng^{1,6}, Shaurya Dhingra^{1,6}, Mihir Shah⁷, Alexandra S. Lee⁷, Sharon Chinthrajah⁷, Sayantani B. Sindher⁷, Vamsee Mallajosyula¹, Fei Gao¹, Natalia Sigal¹, Sangeeta Kowli¹, Sheena Gupta¹, Kathryn Pellegrini⁵, Gregory Tharp⁵, Sofia Maysel-Auslender¹, Sydney Hamilton⁵, Hadj Aoued⁵, Kevin Hrusovsky⁸, Mark Roskey⁸, Steven E. Bosinger^{8,9}, Holden T. Maecker¹, Scott D. Boyd^{7,10}, Mark M. Davis^{1,10,11}, Paul J. Utz^{1,6}, Mehul S. Suthar⁵, Purvesh Khatri^{1,2,13}, Kari C. Nadeau^{7,12,13} & Bali Pulendran^{1,10,11}✉



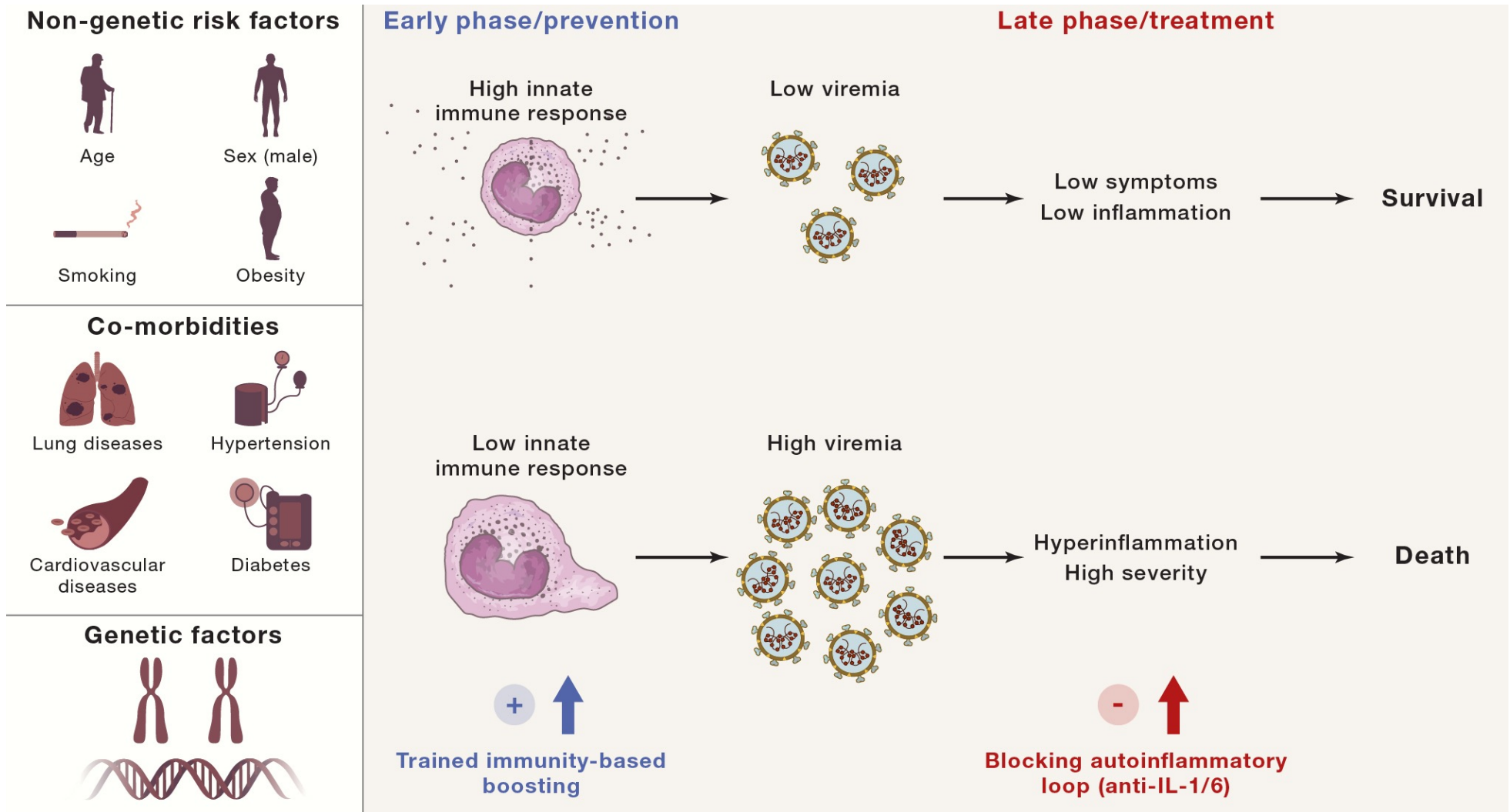
Vaccines combining trained immunity and adaptive memory

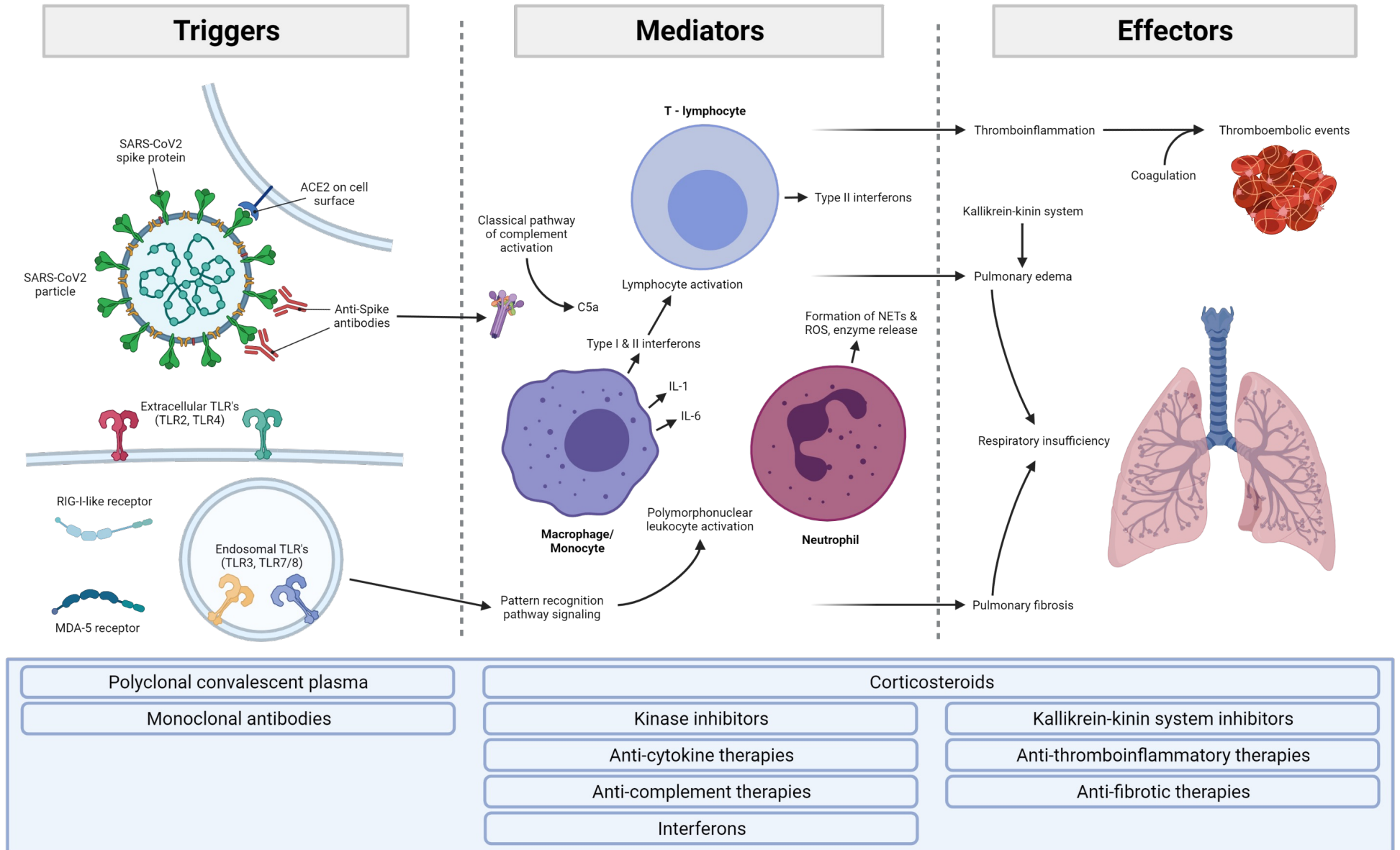


Trained immunity-inducing vaccines as a tool



Trained immunity-inducing vaccines as a tool





Host-Directed Therapy in Pandemic Preparedness

Mihai G. Netea, MD, PhD; Frank L. van de Veerdonk, MD, PhD; Evangelos J. Giamarellos-Bourboulis, MD, PhD

The importance to add insuring immunomodulatory therapy for pandemic preparedness:

- *Mortality in many (if not most) patients with severe influenza or coronavirus infections is due to immune dysregulation*
- *Immune dysregulation is antigen- and virus-agnostic*
- *More people were saved by steroids/anti-IL6/anti-IL-1 therapy than antivirals during the COVID-19 pandemic*
- *Production capacity is limited*
- *We do not know which immunotherapy would be effective in influenza*

Thank you !

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7th International Conference on Innate Immune Memory

September 23-25, 2026

Research Institute of the McGill University Health Centre
Drs. Sylvia & Richard Cruess Amphitheatre & Elspeth McConnell Atrium

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George Hajishengallis | *USA*
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Katherine King | *USA*
Shabaana Khader | *USA*
Kamal Khanna | *USA*
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