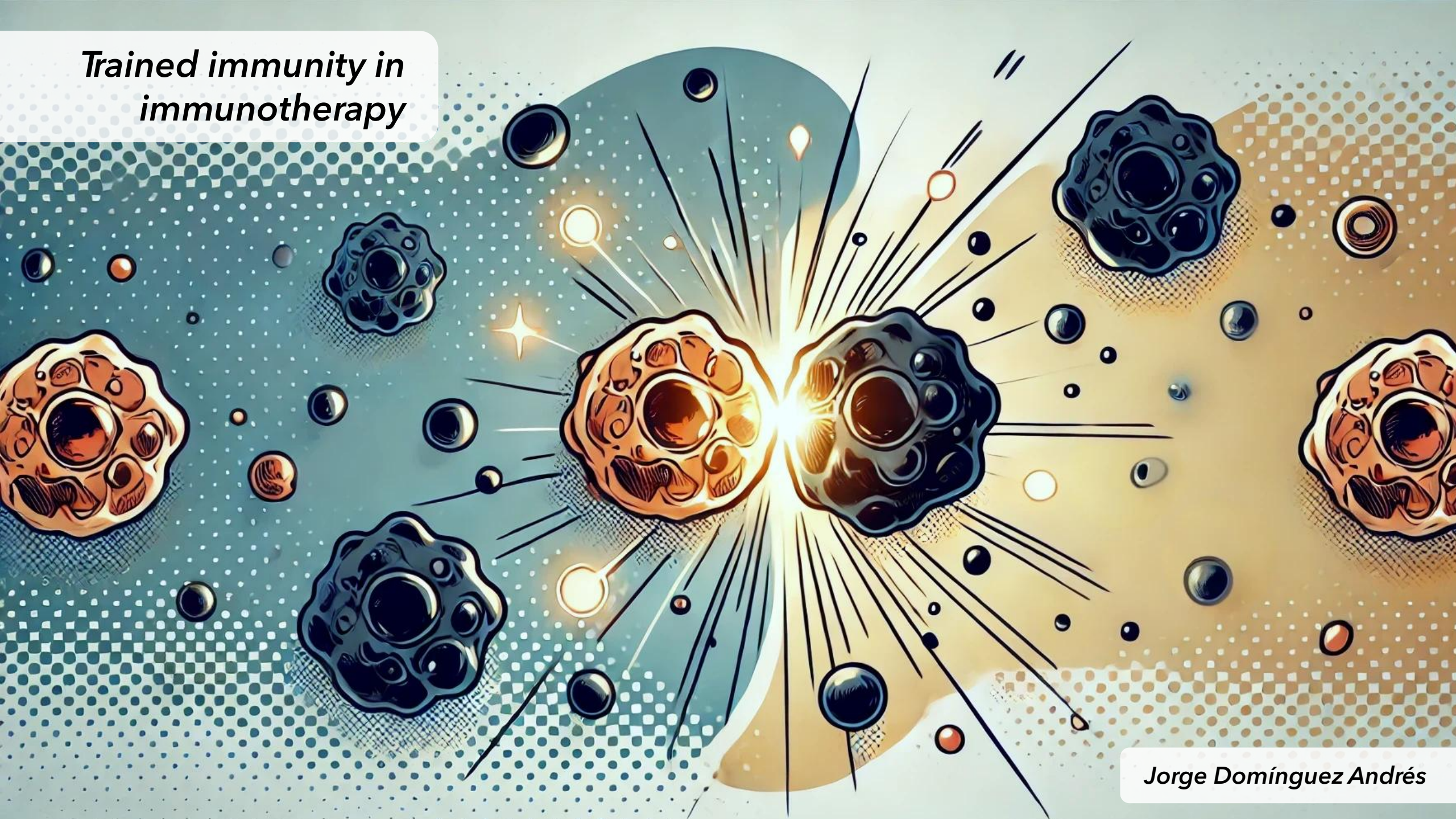
Trained immunity in immunotherapy



Jorge Domínguez Andrés

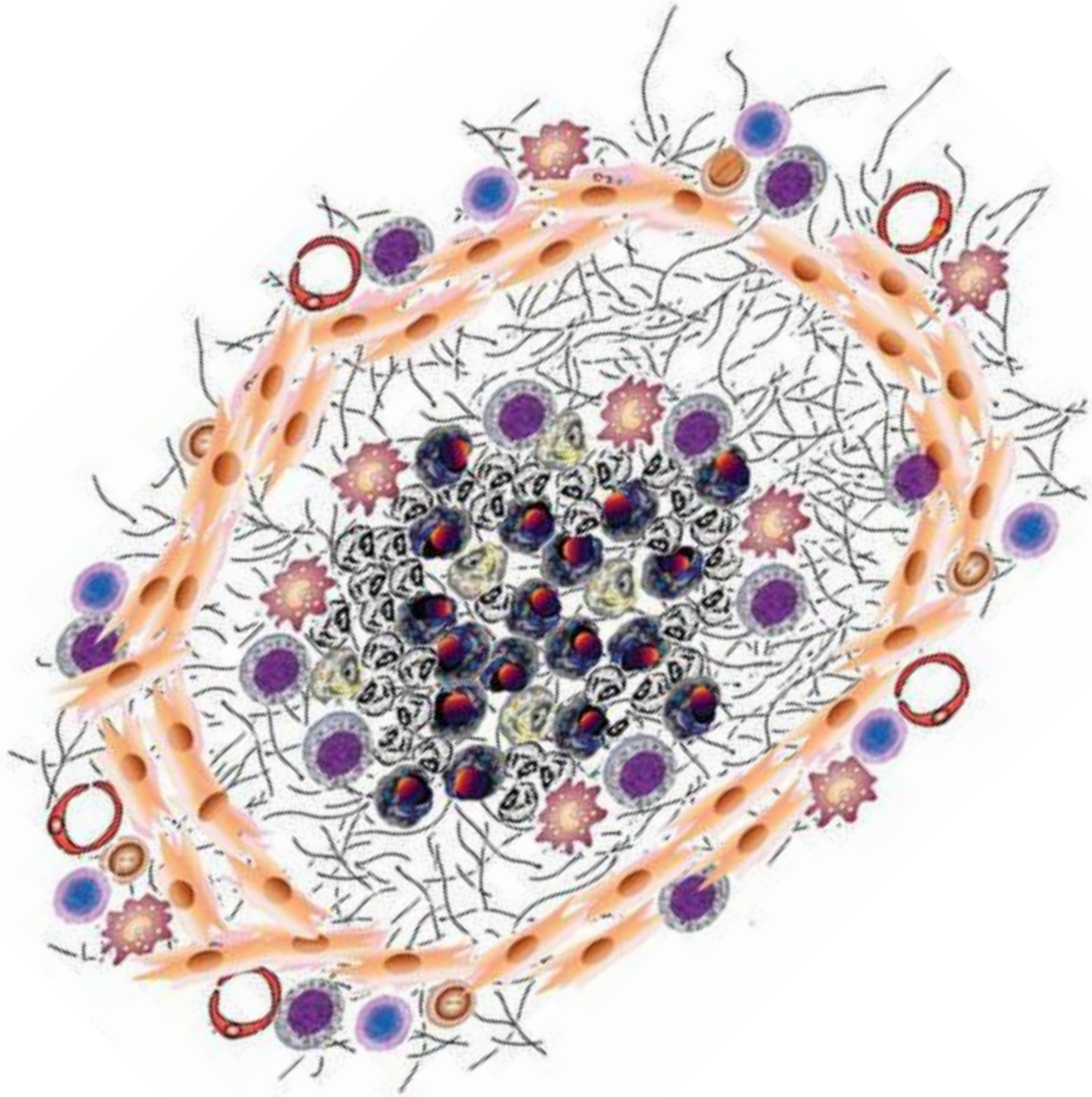
VI SIMPOSIO INTERNACIONAL EN INMUNOTERAPIA DEL CÁNCER

8 de abril 2025 | Aula Magna, Facultad de Ciencias, Universidad de Zaragoza

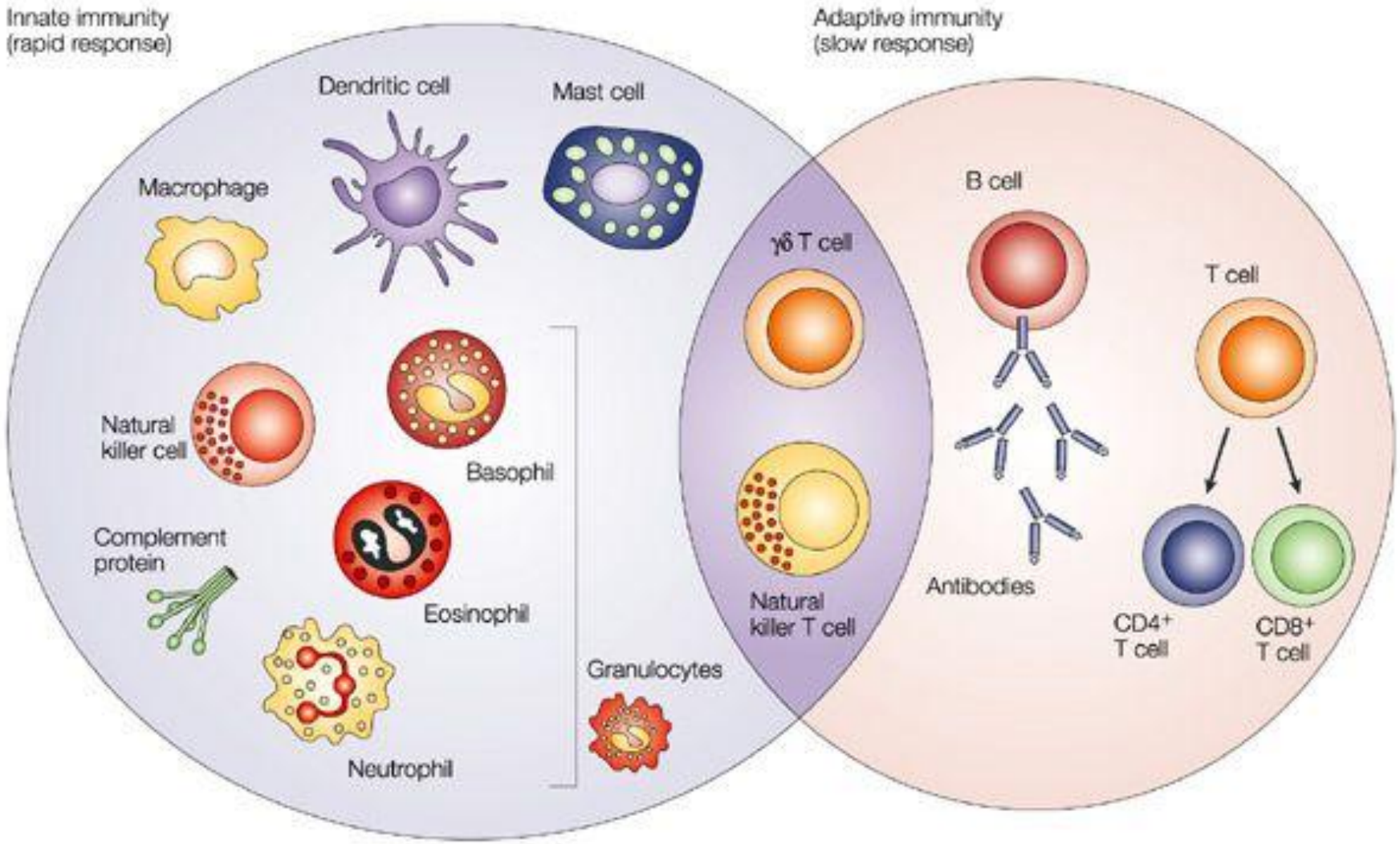
60-80%

Cancer patients do not respond to immunotherapy

Tumor microenvironment is very heterogeneous

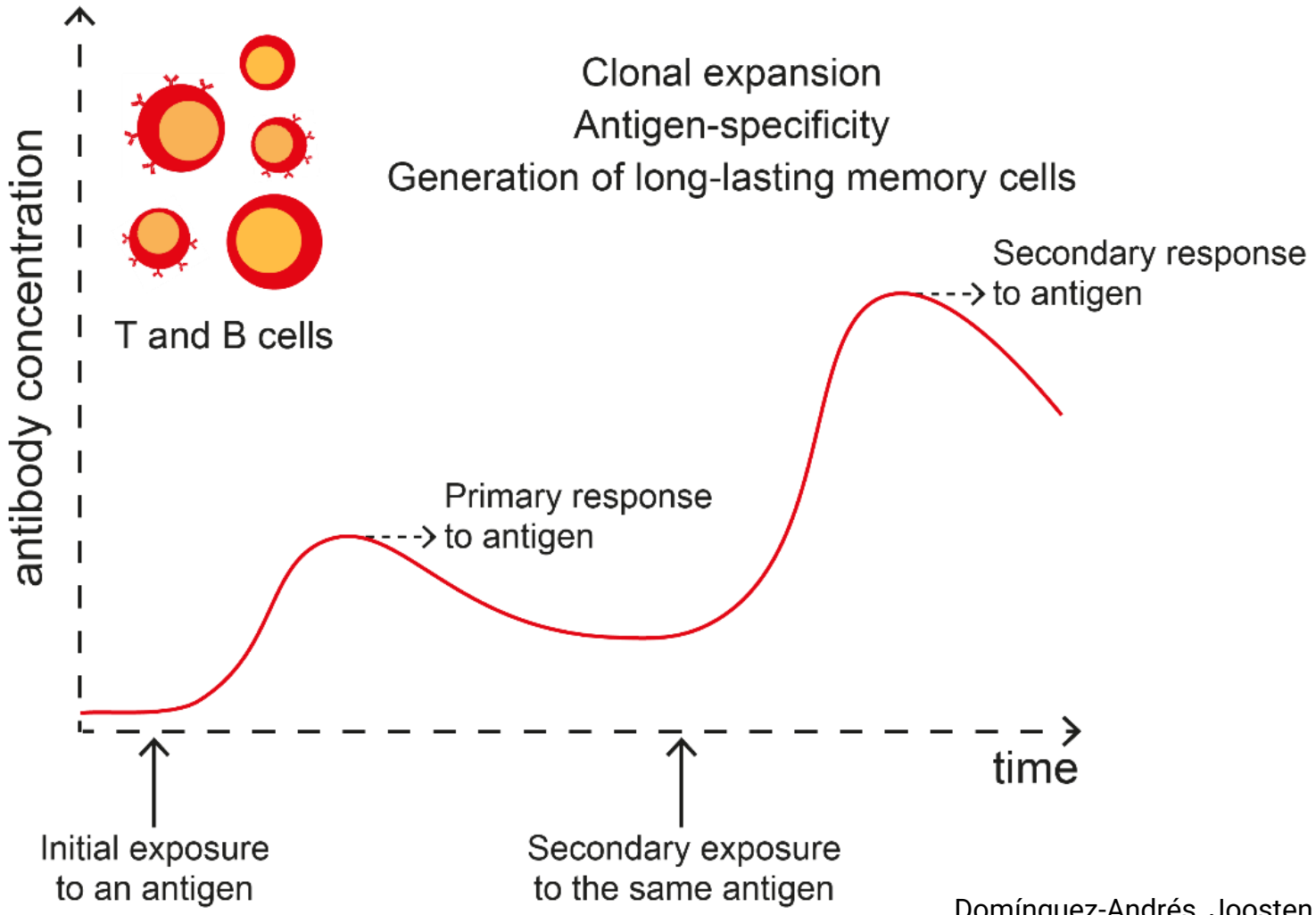


Eskiizmir and Özgür, 2018



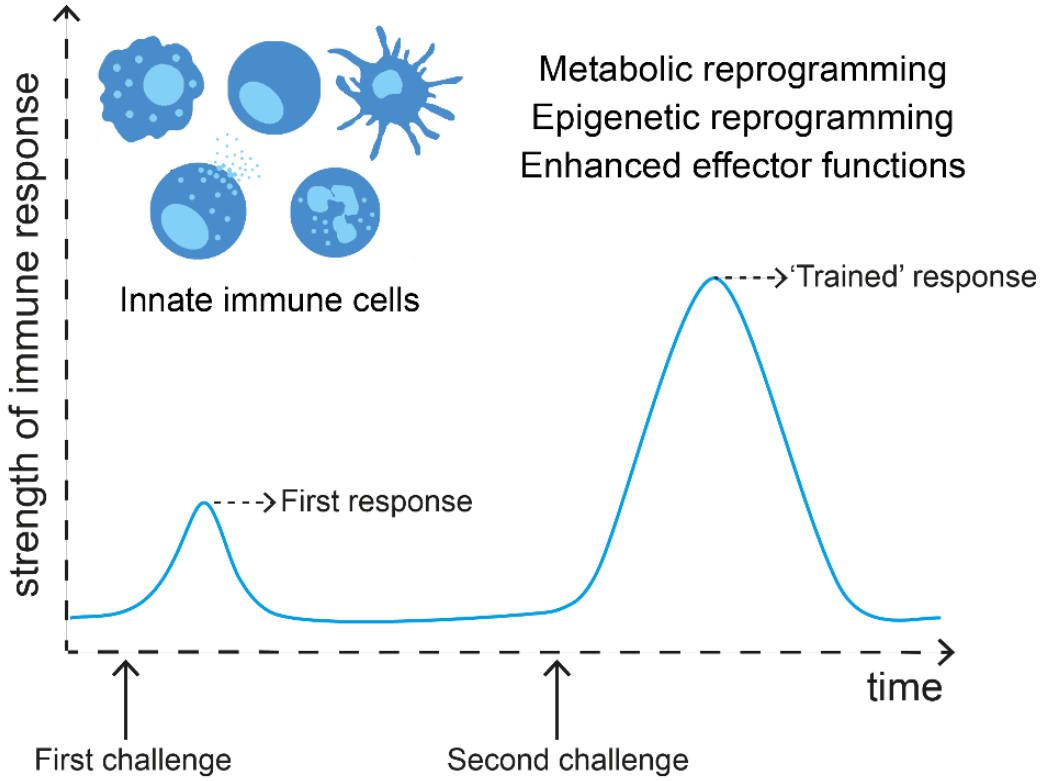
Dranoff, *NRC*, 2004

Adaptive immune memory

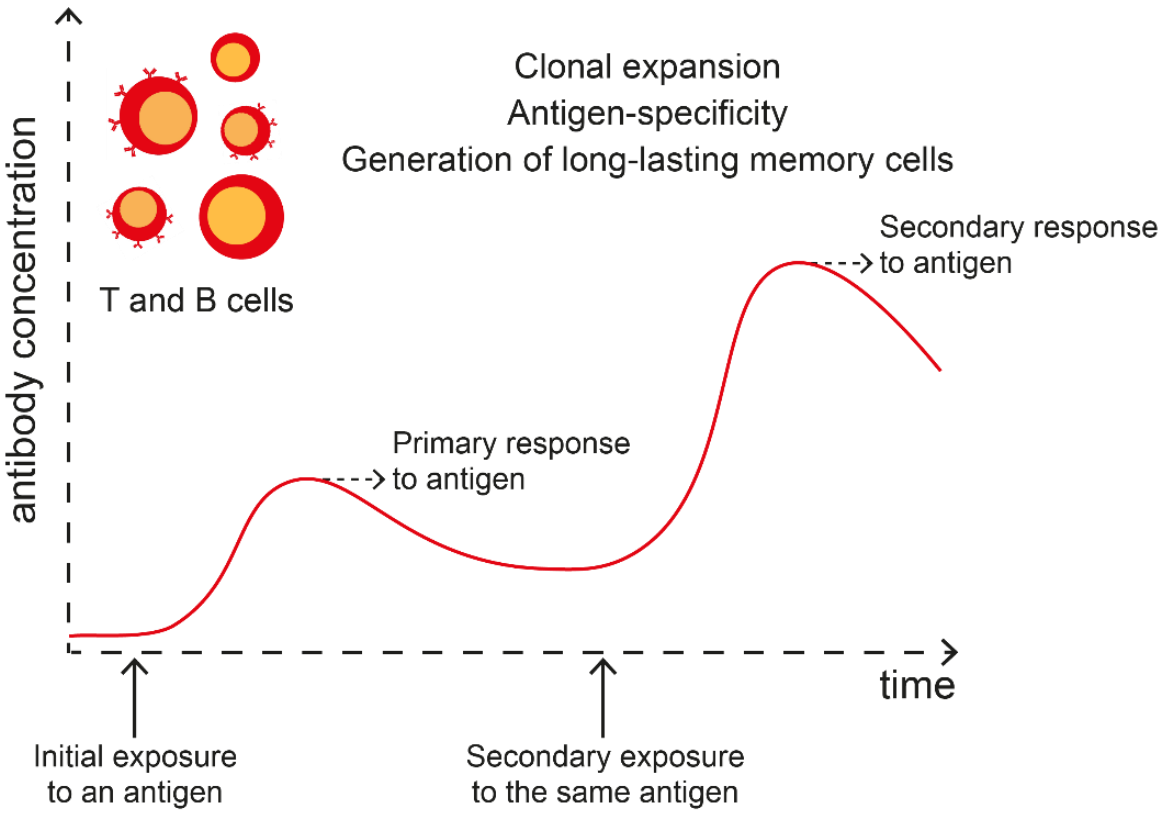


Domínguez-Andrés, Joosten, Netea. *Curr Opin Immunol*, 2019

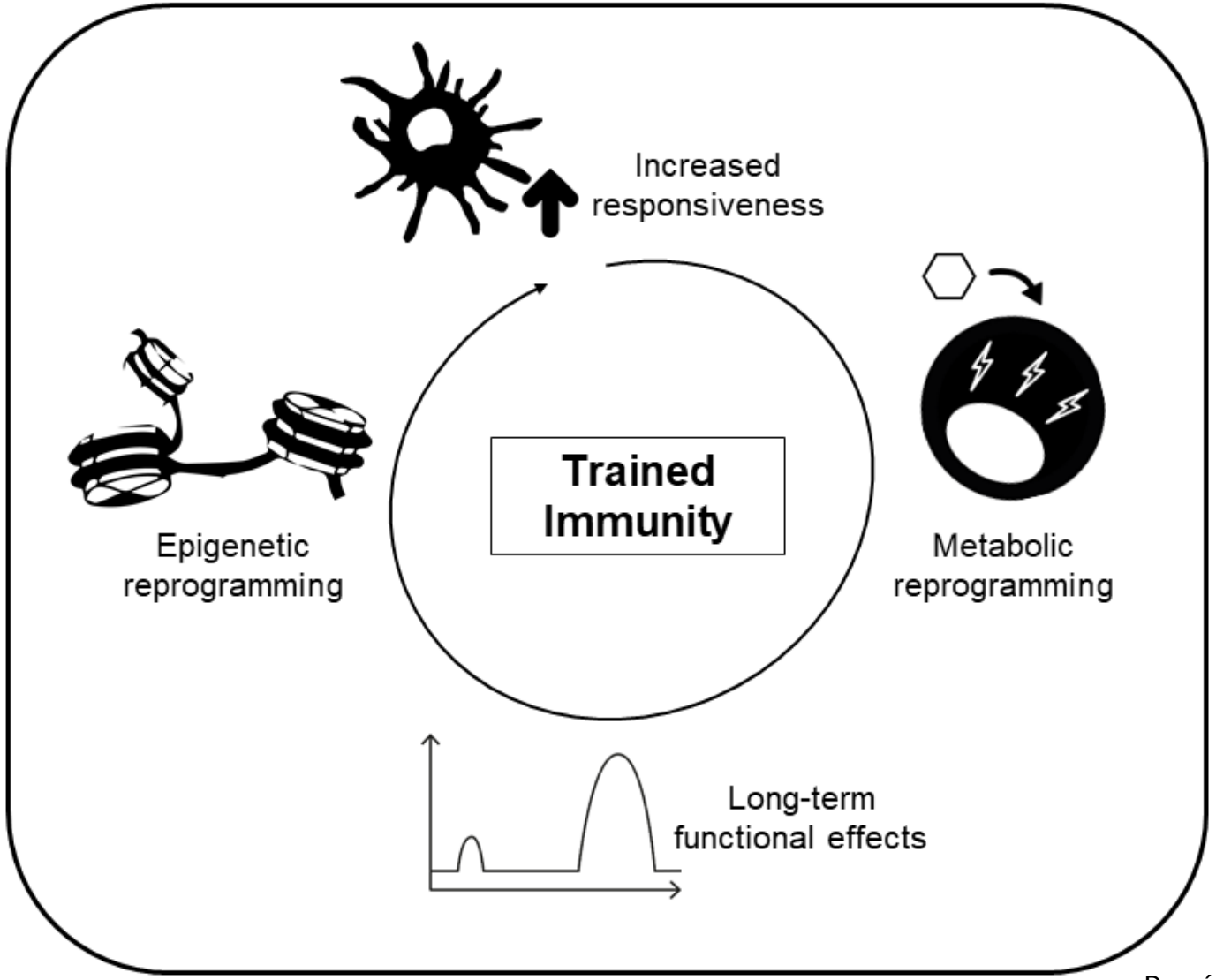
Innate immune memory



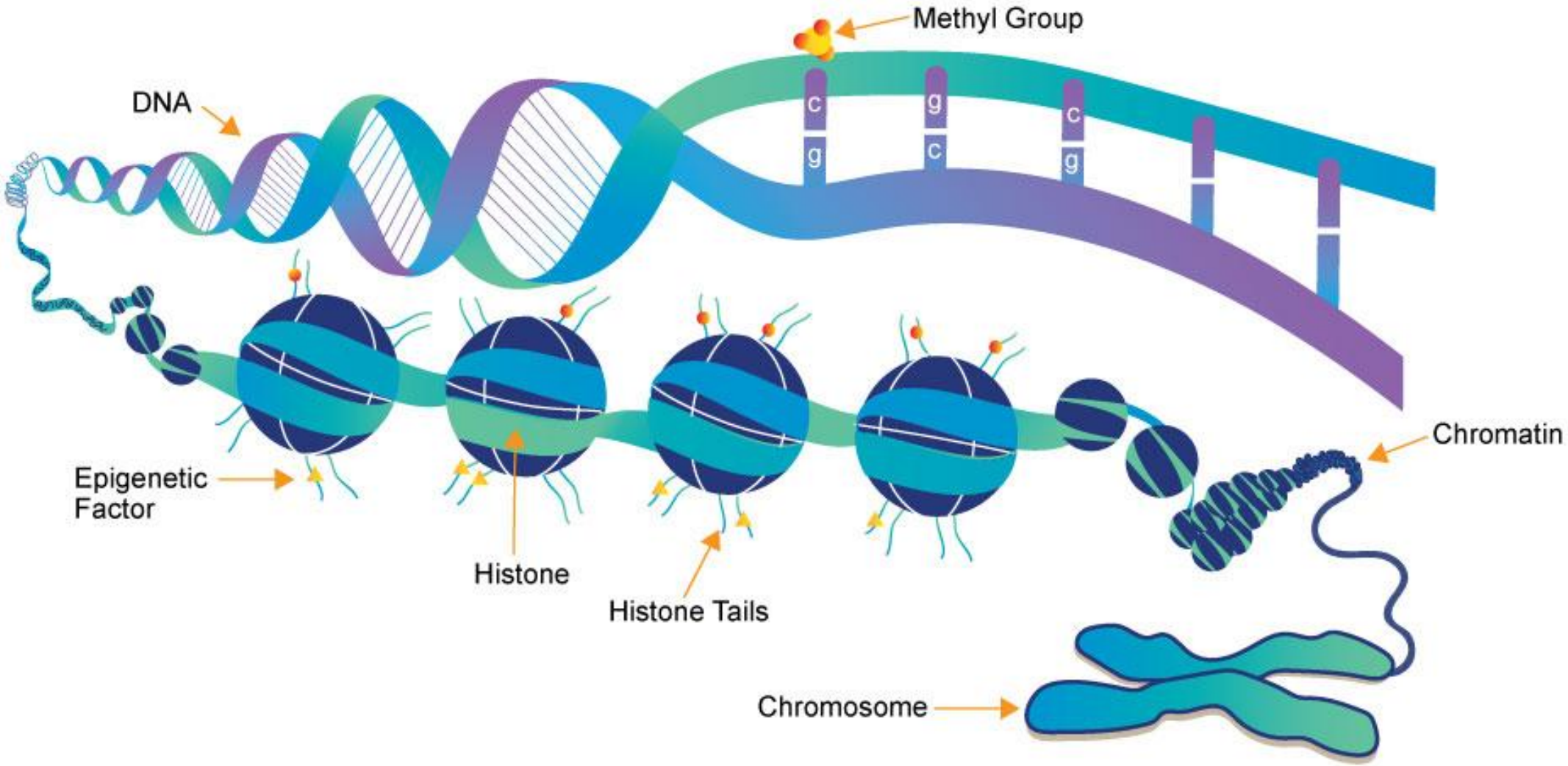
Adaptive immune memory

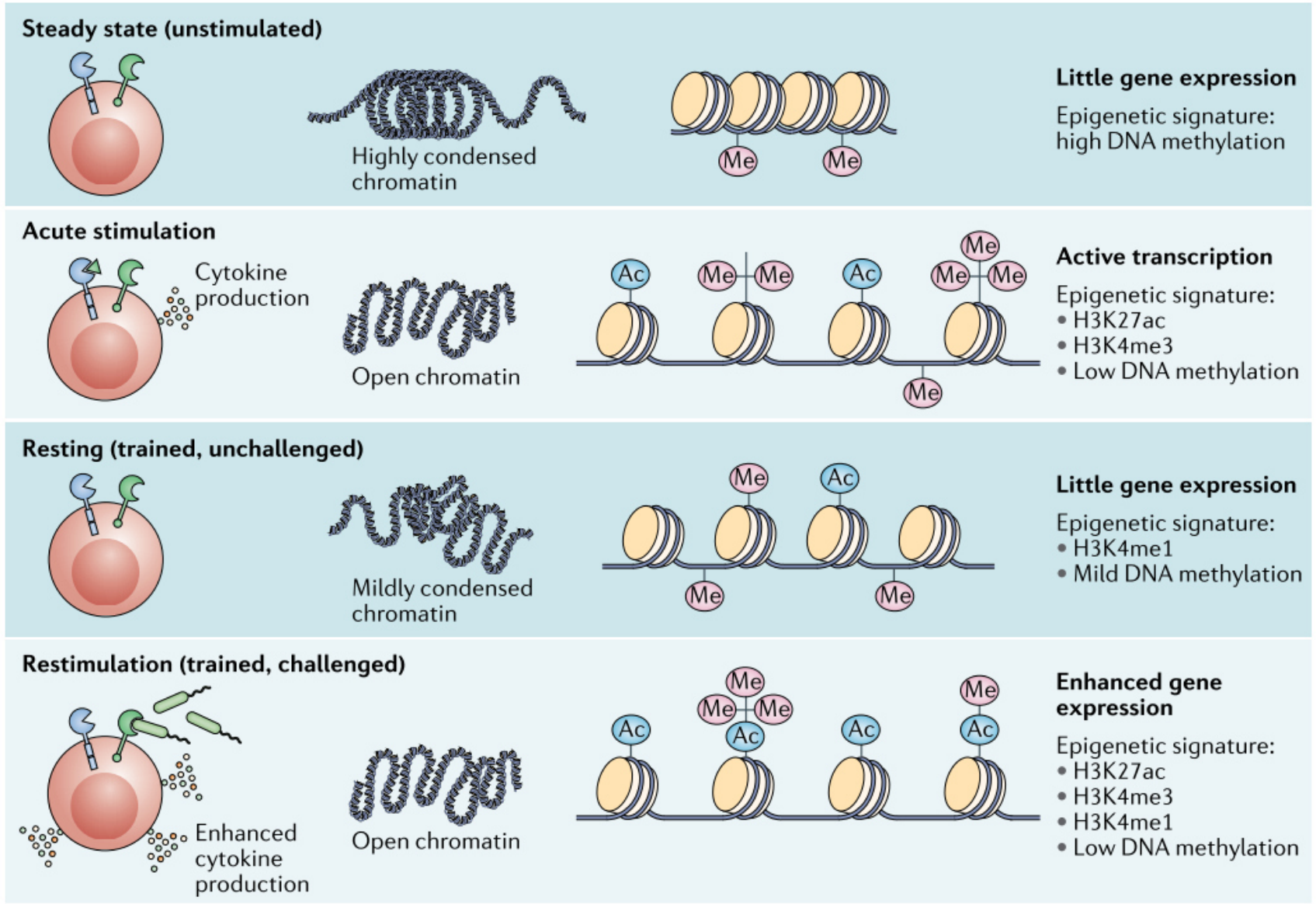


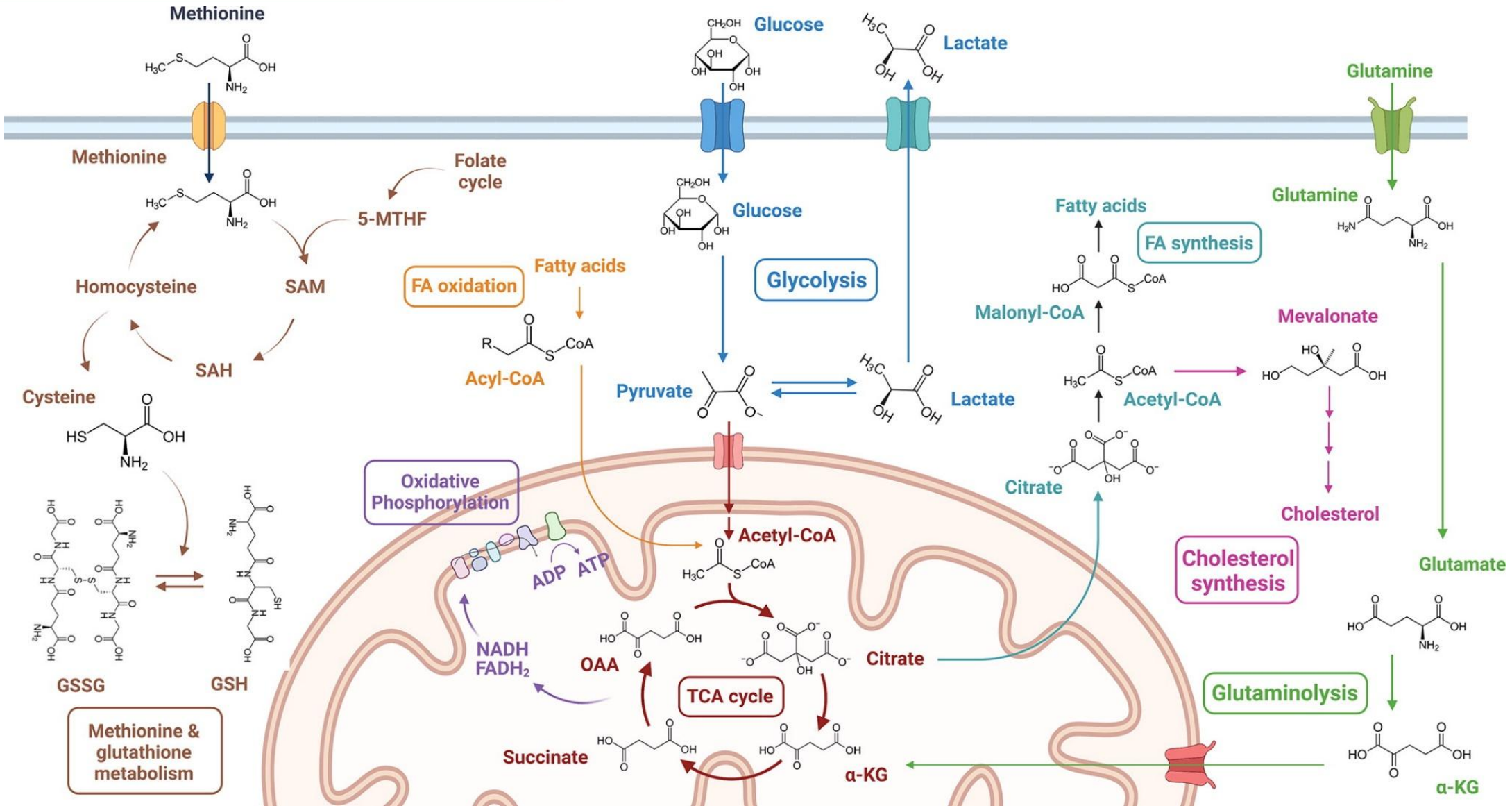
Domínguez-Andrés, Joosten, Netea. *Curr Opin Immunol*, 2019



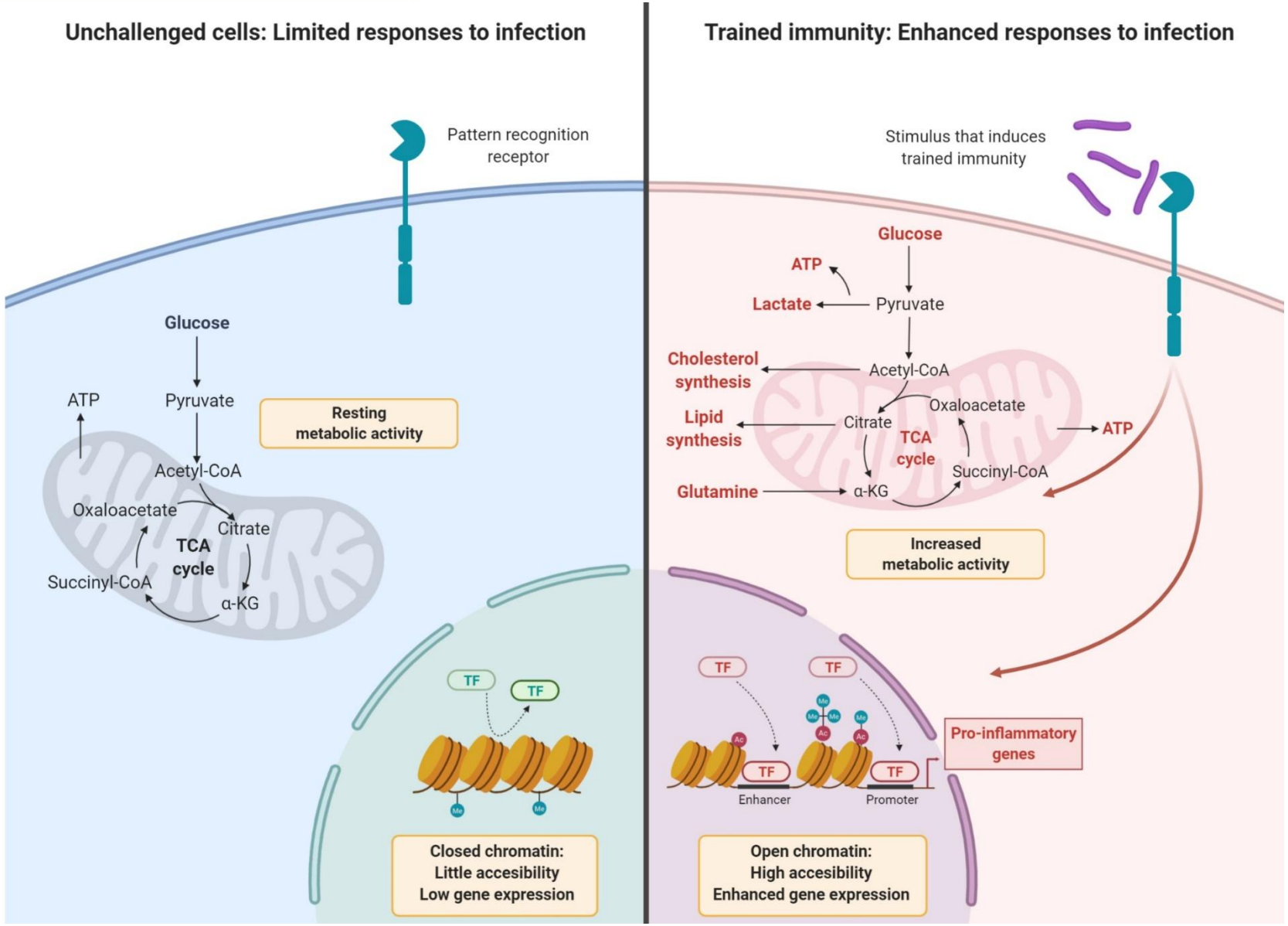
Domínguez-Andrés *et al*, *J Leukoc Biol* , 2018


Methyl Group
DNA
c
g
g
c
c
g
Chromatin
Epigenetic Factor
Histone
Histone Tails
Chromosome

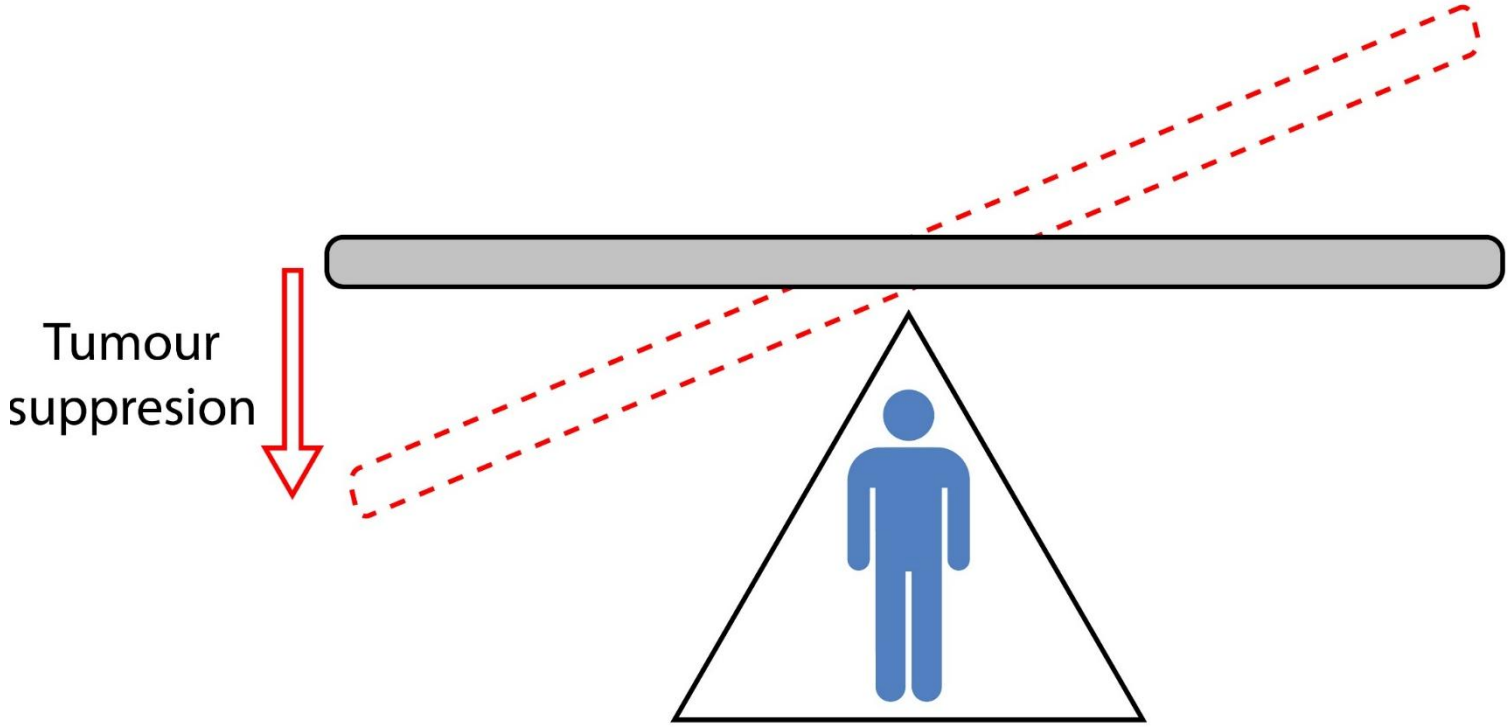

Steady state (unstimulated)
Highly condensed chromatin
Me
Me
Little gene expression
Epigenetic signature:
high DNA methylation
Acute stimulation
Cytokine production
Open chromatin
Ac
Me
Me
Ac
Me
Me
Me
Active transcription
Epigenetic signature:
• H3K27ac
• H3K4me3
• Low DNA methylation
Resting (trained, unchallenged)
Mildly condensed chromatin
Me
Ac
Me
Me
Little gene expression
Epigenetic signature:
• H3K4me1
• Mild DNA methylation
Restimulation (trained, challenged)
Enhanced cytokine production
Open chromatin
Me
Me
Me
Ac
Ac
Ac
Me
Ac
Enhanced gene expression
Epigenetic signature:
• H3K27ac
• H3K4me3
• H3K4me1
• Low DNA methylation



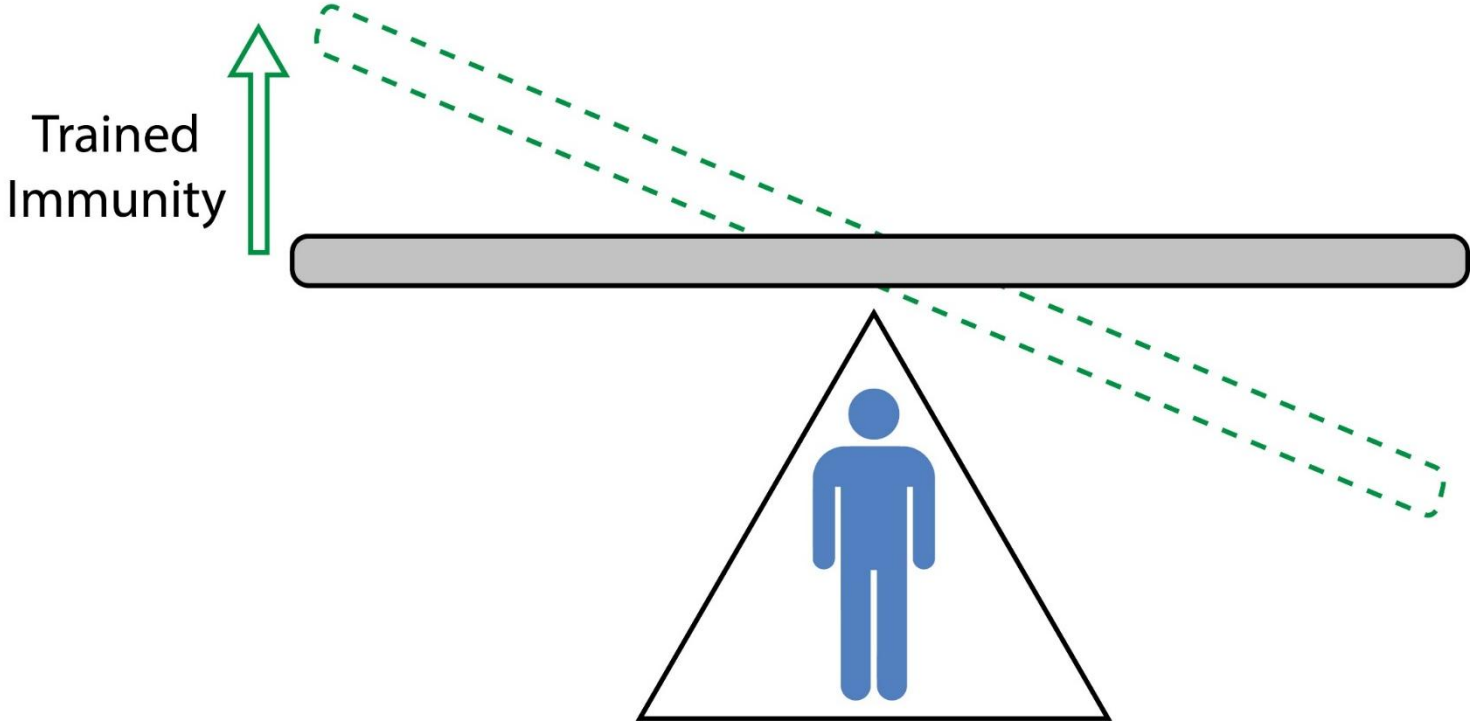
Domínguez-Andrés, Dos Santos, Bekkering *et al. 2023*


Unchallenged cells: Limited responses to infection
Trained immunity: Enhanced responses to infection
Pattern recognition receptor
Stimulus that induces trained immunity
Glucose
ATP
Pyruvate
Lactate
Acetyl-CoA
Cholesterol synthesis
Lipid synthesis
Oxaloacetate
Citrate
TCA cycle
Succinyl-CoA
α-KG
Glutamine
Resting metabolic activity
Increased metabolic activity
TF
Me
Ac
Enhancer
Promoter
Pro-inflammatory genes
Closed chromatin: Little accesibility Low gene expression
Open chromatin: High accesibility Enhanced gene expression

Immunosuppression



Trained immunity



Surgical Section.

July 13, 1909.

Mr. J. Warrington Haward, President of the Section, in the Chair.

The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus).

By William B. Coley, M.D. (New York.)[1]

New York Times - July 29, 1908

ERYSIPELAS GERMS AS CURE FOR CANCER

Dr. Coley's Remedy of Mixed Toxins Makes One Disease Cast Out the Other.

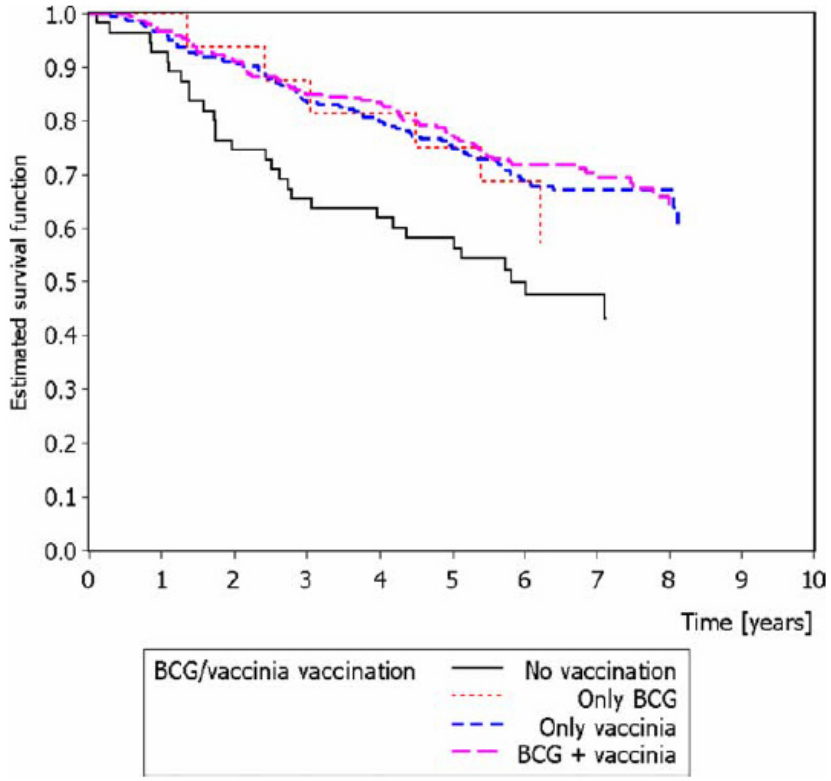
MANY CASES CURED HERE

Physician Has Used the Cure for 15 Years and Treated 430 Cases— Probably 150 Sure Cures.

Following news from St. Louis that two men have been cured of cancer in the City Hospital there by the use of a fluid discovered by Dr. William B. Coley of New York, it came out yester-

Prior immunisation of patients with malignant melanoma with vaccinia or BCG is associated with better survival. An European Organization for Research and Treatment of Cancer cohort study on 542 patients

K.F. Kölmel [a,*], J.M. Grange [b], B. Krone [c], G. Mastrangelo [d], C.R. Rossi [e], B.M. Henz [f], C. Seebacher [g], I.N. Botev [h], M. Niin [i], D. Lambert [j], R. Shafir [k], E.-M. Kokoschka [l], U.R. Kleeberg [m], O. Gefeller [n], A. Pfahlberg [n]

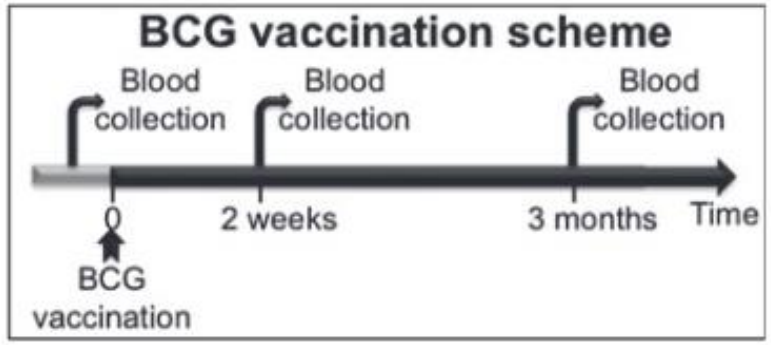


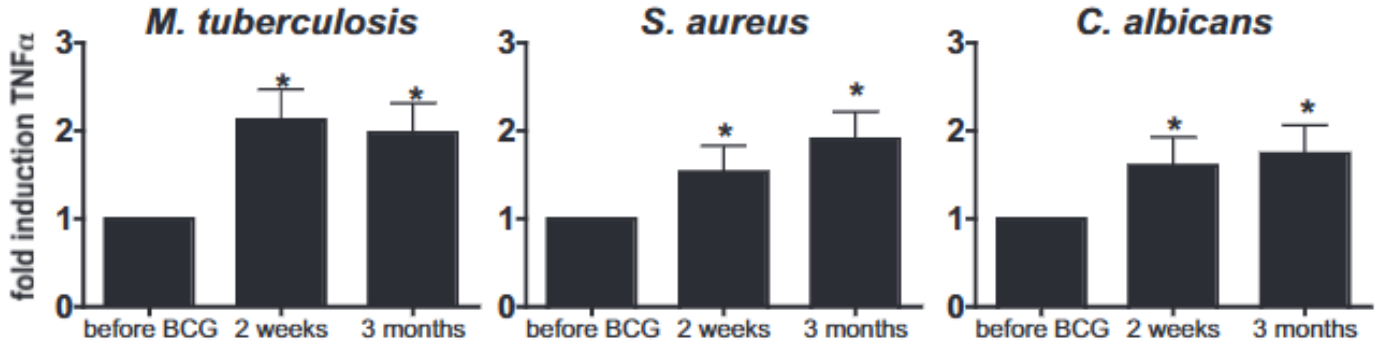
Kölmel et al., *Eur J Cancer*, 2005

Bacille Calmette-Guérin induces NOD2-dependent nonspecific protection from reinfection via epigenetic reprogramming of monocytes

Johanneke Kleinnijenhuis[a,b,1], Jessica Quintin[a,b,1], Frank Preijers[c], Leo A. B. Joosten[a,b], Daniela C. Ifrim[a,b], Sadia Saeed[d], Cor Jacobs[a,b], Joke van Loenhout[e], Dirk de Jong[f], Hendrik G. Stunnenberg[d], Ramnik J. Xavier[g,h], Jos W. M. van der Meer[a,b], Reinout van Crevel[a,b], and Mihai G. Netea[a,b,2]

PNAS





Open access Original research

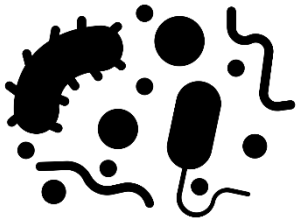
Journal for ImmunoTherapy of Cancer

Intravesical BCG in patients with non-muscle invasive bladder cancer induces trained immunity and decreases respiratory infections

Jelmer H van Puffelen ,[1,2] Boris Novakovic,[3] Liesbeth van Emst,[1] Denise Kooper,[4] Tahlita C M Zuiverloon,[4] Ursula T H Oldenhof,[2] J Alfred Witjes ,[5] Tessel E Galesloot,[2] Alina Vrieling,[2] Katja K H Aben,[2,6] Lambertus A L M Kiemeney,[2] Egbert Oosterwijk,[5] Mihai G Netea,[1,7] Joost L Boormans,[4] Antoine G van der Heijden,[5] Leo A B Joosten,[1,8] Sita H Vermeulen[2]

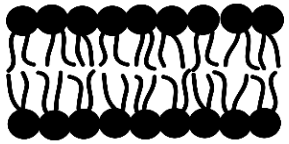
Microbial agents

β-glucans
Lipopolysaccharides (LPS)
Peptidoglicans and muramyl dipeptides (MDP)
Bacillus Calmette-Guérin (BCG)
Candida albicans
Listeria monocytogenes
Shigella



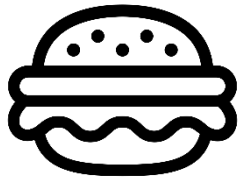
Lipids and metabolites

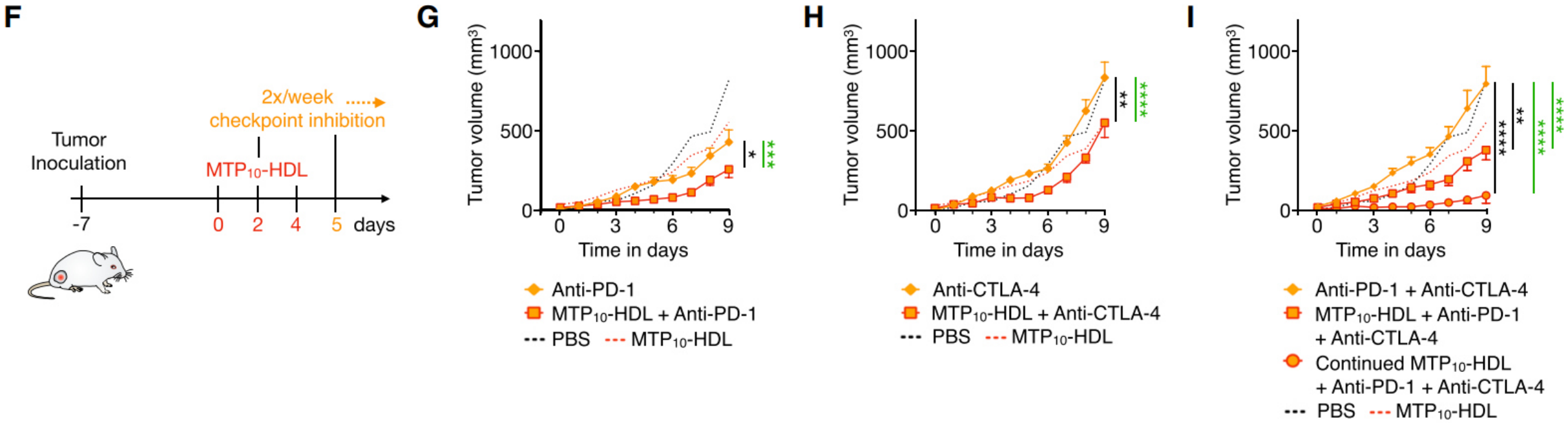
Mevalonate
Escualene
Free fatty acids
Derivatives of itaconate and fumarate
oxLDL



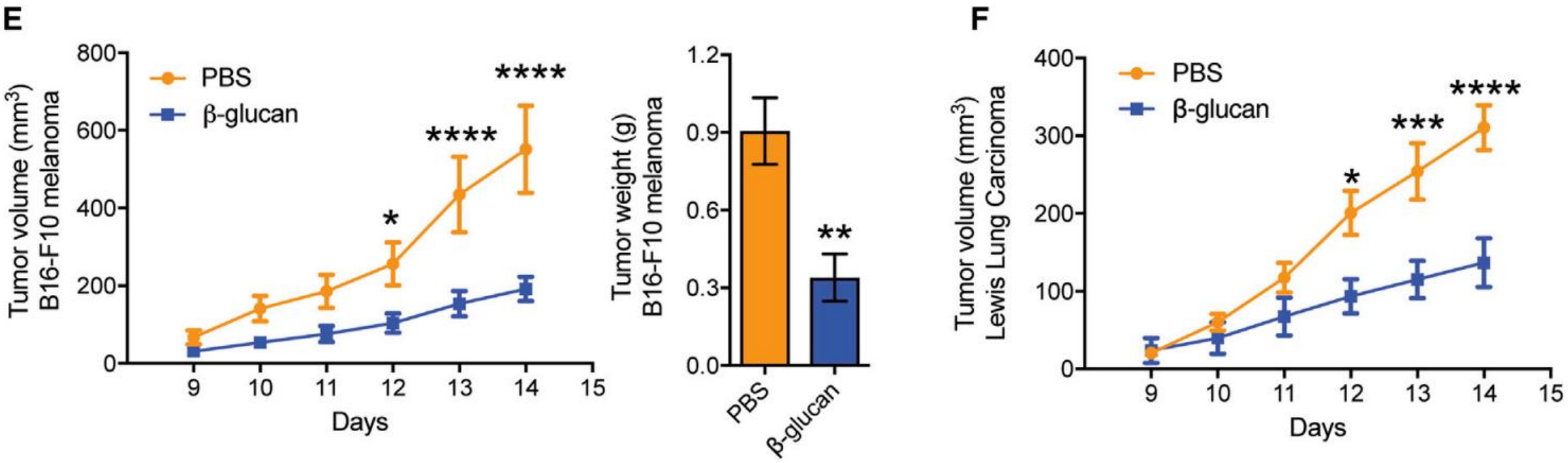
Environmental stimuli

High fat and sugar diet
Resveratrol
Pollutants





Priem et al., *Cell*, 2020



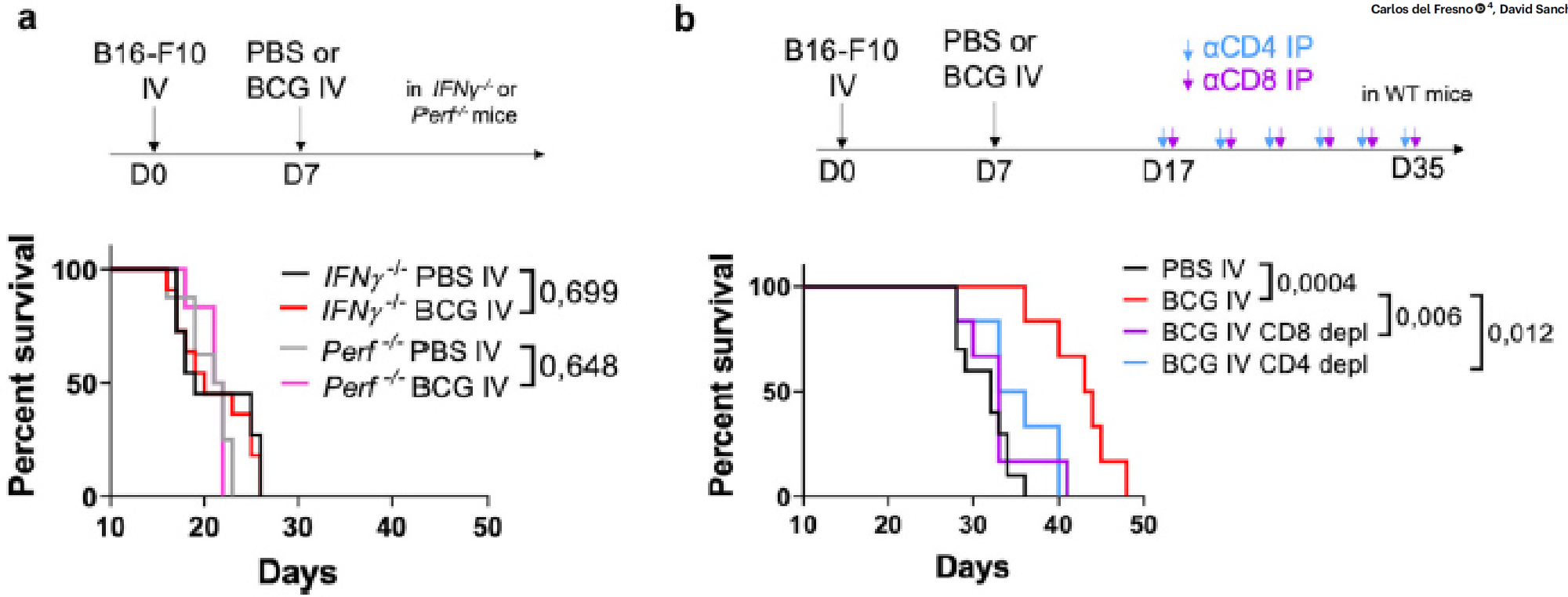
Kalafati et al., *Cell*, 2020

Article

https://doi.org/10.1038/s41467-023-41768-8

Intravenous administration of BCG in mice promotes natural killer and T cell-mediated antitumor immunity in the lung

Eduardo Moreo[1,2], Aitor Jarit-Cabanillas[3], Iñaki Robles-Vera[3], Santiago Uranga[1,2], Claudia Guerrero[1,2], Ana Belén Gómez[1,2], Pablo Mata-Martínez[4], Luna Minute[4], Miguel Araujo-Voces[1,2,5], María José Felgueres[6], Gloria Esteso[6], Iratxe Uranga-Murillo[7,8], Maykel Arias[7,8], Julián Pardo[7,8], Carlos Martín[1,2], Mar Valés-Gómez[6], Carlos del Fresno[4], David Sancho[3] & Nacho Aguiló[1,2]

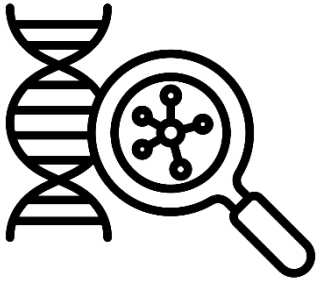


Moreo et al., *Nat Communications*, 2023

Research Type	Tumor Type	β-Glucan Form	Main Effects	Reference
SACT Phase I/II	Mixed advanced	Soluble/P.O.	Relatively increased blood cell counts	Ab, 2008
RCT	Mixed	NS/P.O.	Increased energy intake	Milla et al., 2024
SACT Phase I/II	High-risk chronic lymphocytic leukemia	Soluble/I.V.	A high complete response rate	Cs et al., 2015
RCT	ASCUS/LSIL	Soluble/T.O.P.	Increased disease clearance rates	Laccetta et al., 2015
RCT Phase II	High-risk relapsed metastatic neuroblastoma	NS/P.O.	Enhanced seroconversion of anti-ganglioside IgG1	Cheung et al., 2023
SACT Phase II	Stage IV KRAS-mutant colorectal cancer	Soluble/I.V.	Compelling clinical activity	Segal et al., 2016

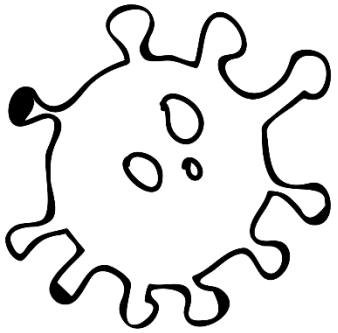
Research Type	Tumor Type	β-Glucan Form	Main Effects	Reference
CCT	Esophageal carcinoma	Soluble/I.V.	Increased chemotherapy efficacy, pro-inflammatory ILs, decreased anti-inflammatory ILs	Ji et al., 2012
SACT	Pancreatic cancer	Superfine dispersed/P.O.	Increased quality-of-life scores	Shimizu et al., 2009
RCT	Breast cancer	Soluble/P.O.	Decreased IL-4	Ostadhimi et al., 2024
SACT	Gastric cancer	Soluble/I.V.	Increased quality-of-life scores	H et al., 2009
RCT Phase II	Advanced NSCLC	Soluble/I.V.	Increased ORR	Thomas et al., 2017

Research Type	Tumor Type	β-Glucan Form	Main Effects	Reference
SACT	Advanced breast cancer	Soluble/P.O.	Increased peripheral monocyte count	Demir et al., 2007
RCT	Breast cancer	Soluble/P.O.	Decreased IL-4; increased IL-12; enhanced energy intake	Ostadhimi et al., 2014
RCT	Breast cancer	Soluble/P.O.	Decreased IL-4; increased IL-12; enhanced energy intake	Ostadhimi et al., 2014
SACT	NSCLC	Particulate/P.O.	Decreased MDSC	Albeituni et al., 2016
RCT	Advanced NSCLC	Soluble/I.V.	Relatively increased ORR	Engel-Riedel et al., 2018



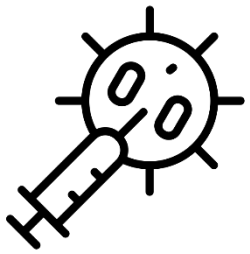
Biomarker identification: We need specific signals that can predict which patients will respond best to these treatments.

Effect duration: We must optimize the persistence of immune reprogramming without adverse effects.



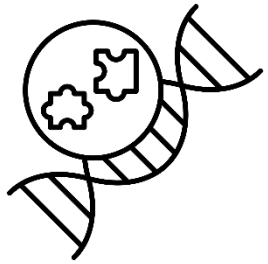
Interaction with the adaptive system: It is essential to understand how to coordinate innate and adaptive responses to maximize the therapeutic benefit.

Personalised vaccines



Combine agents that induce adaptive and innate memory

Epigenetic inhibitors

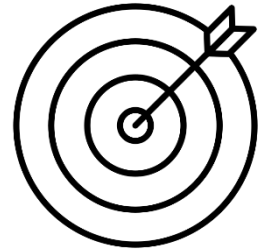


DNA methylation and acetylation modulators

Combined therapies

Integrate trained immunity with existing therapies

Targeted administration



Tumor site/bone marrow: e.g., nanoparticles

Acknowledgements

Radboudumc
Mihai Netea
Leo Joosten
Ilayda Baydemir
Özlem Bulut
Anaísa Valido
Gizem Kilic
Evelien Floor
Marisol Baez

Jena University Hospital
Sebastian Weis
Karen Dlubatz
Dania Martinez
Franziska Roestel
Gianna Hirth

MCRI Melbourne
Boris Novakovic

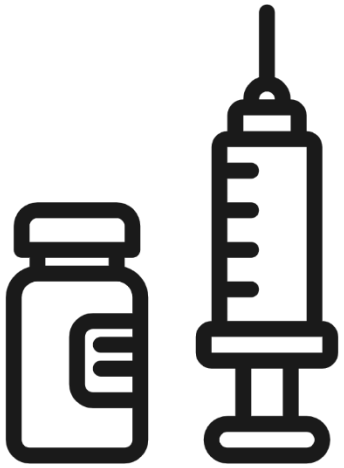
UK Münster
Yahya Sohrabi

Helmholtz Hannover
Yang Li

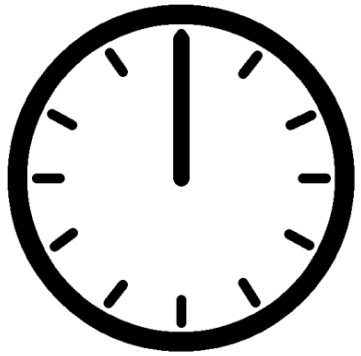
University of Athens
Victoria Spanou
Theano Andriopoulou
Evangelos Giamarellos Bourboulis

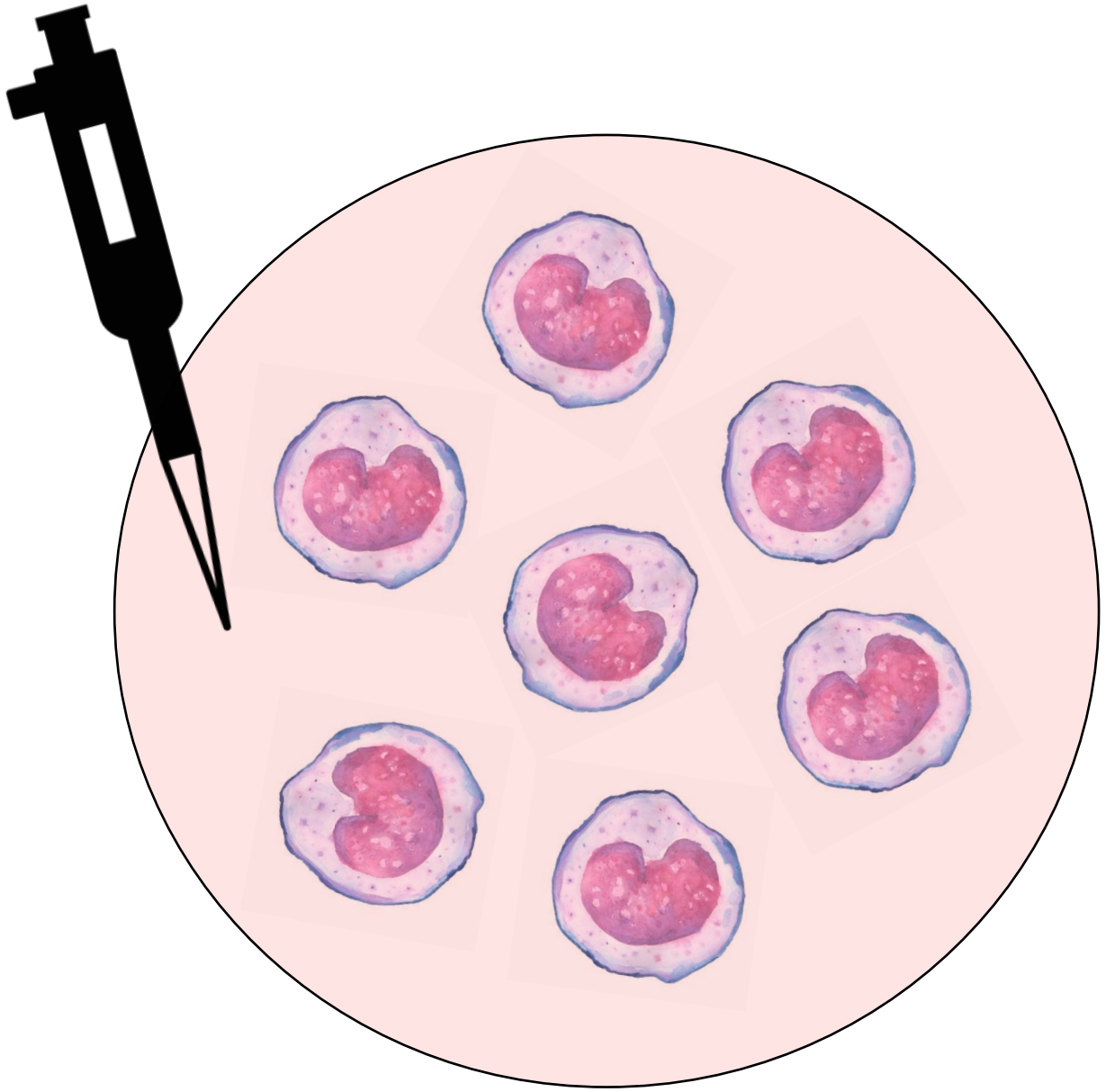
TU Braunschweig
Karsten Hiller
Fabian Nikolka

Cáncer de pulmón	Influenza A	Wang et al. 2023
Cáncer de pulmón y melanoma	β-glucano	Kalafati et al., 2020; Ding et al. 2023
Cáncer de páncreas	β-glucano	Geller et al., 2022; Woeste et al., 2023
Melanoma	β-glucano, CTB, MTP10-HDL	Vuscan et al., 2024; Tepale et al., 2024; Priem et al., 2020
Carcinoma hepatocelular	BCG	Vaziri et al., 2024
Cáncer de vejiga	BCG	Buffen et al., 2014



Stimulus



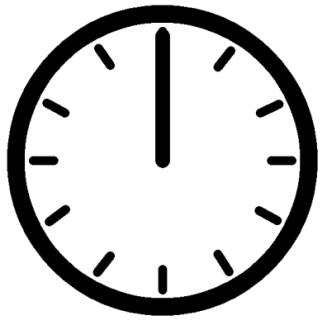


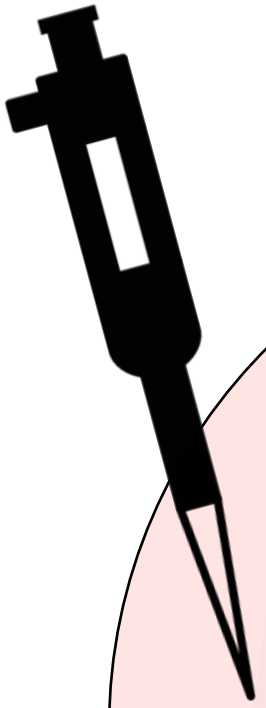
Modulator

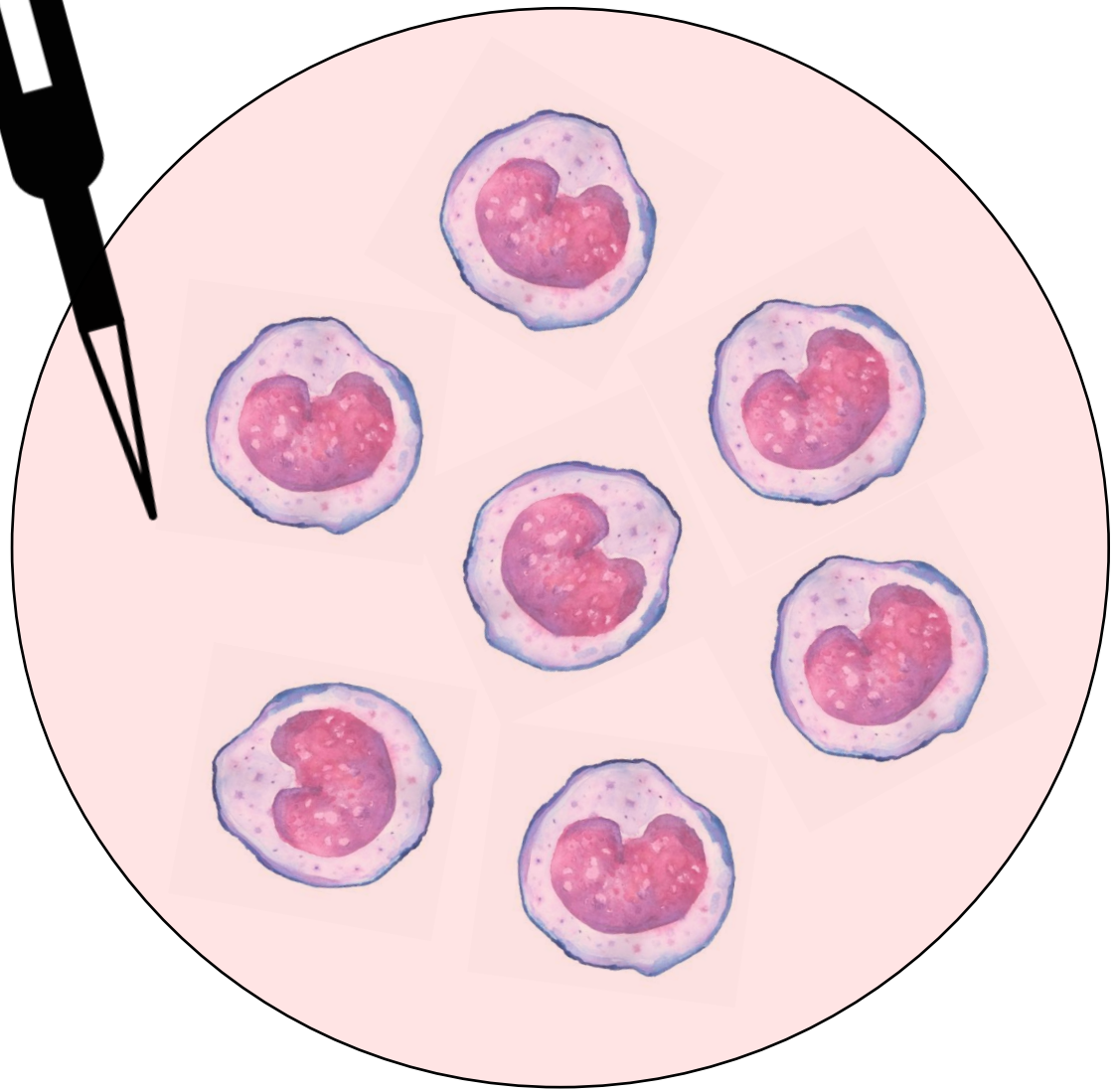
Metabolic reprogramming

Epigenetic reprogramming

Increased responsiveness







LPS