Immunity and Immunopathogenesis of TB

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April 2, 2025 (3:25-4:10 PM)
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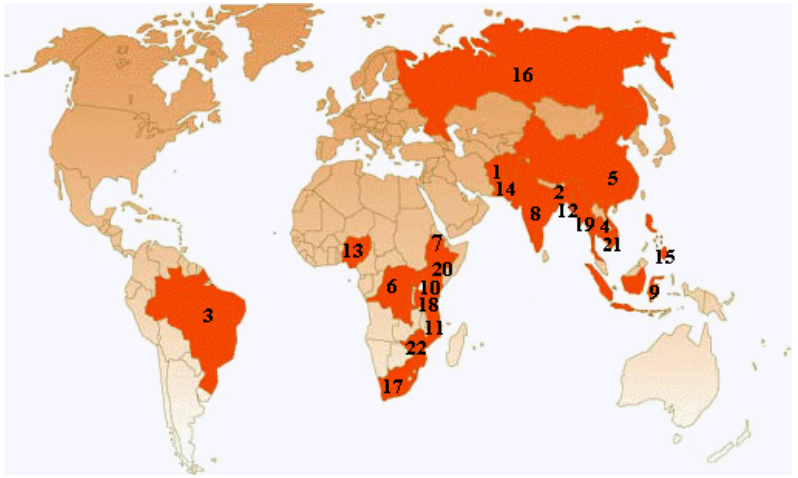
Objective: to better understand the host risk factors for TB

Denver TB Course
No conflicts of interest

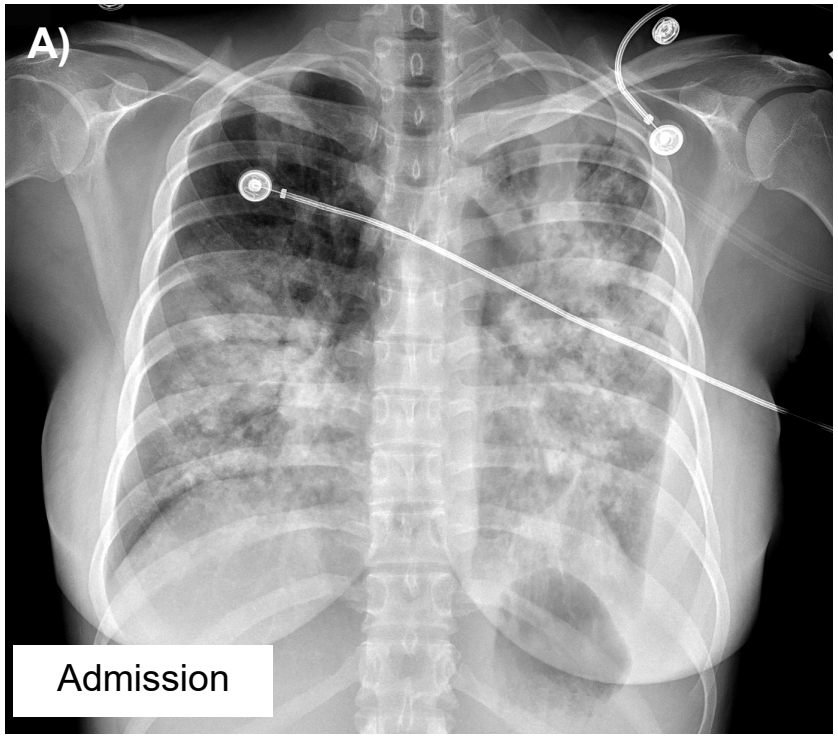
To combat TB, *"follow the middle path."*
Buddha

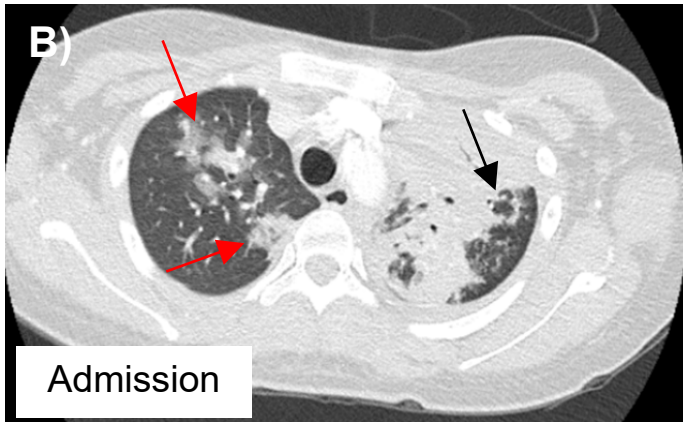
The 22 countries shown on the map accounts for 80% of the TB cases in the world

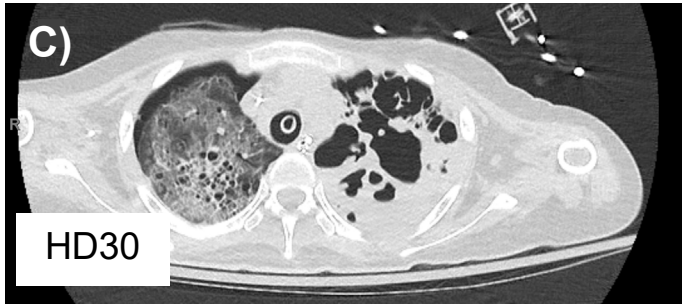


19 y.o. previously healthy woman with fulminant pulmonary TB

- Presented with 3 days of fever, cough, CP, and dyspnea
- PMH: Three weeks post-partum
- SH: emigrated from the Marshall Islands at age 8
- 101.3ºF, 121, 108/60, 42, 85% RA, BMI 20 kg/m^2







Question: Which of the following contributed to TB in this previously healthy young woman?

A. Emigrated from the Marshall Islands
B. Post-partum period
C. Thin body habitus
D. Polynesian race
E. The Compact of Free Association Act of 1985 between the U.S. and the Marshall Islands.

Answer: Yes for A, B, C, and E; maybe for D.

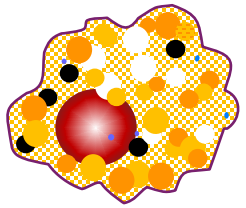
- Marshallese can travel freely to and from the U.S. as non-immigrants without visas; thus, the Marshallese do NOT require screening for active TB or LTBI.
- Between 1946 and 1958, the United States conducted > 50 nuclear tests in and around the Marshall Islands.

Two main arms of the immune system

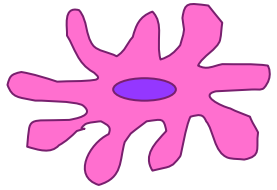
Innate immunity

"defensive line-man"

Macrophages



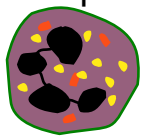
Dendritic cells



Phagocytes
Antigen-presenting cells

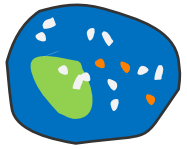
Granulocytes

Neutrophils



Eosinophils

Basophils



Innate lymphoid cells (ILC):
can kill virally-infected cells
- Natural killer (NK) cells
- ILC1/2/3

Adaptive immunity

"line-backers & secondary"

T cells

B cells

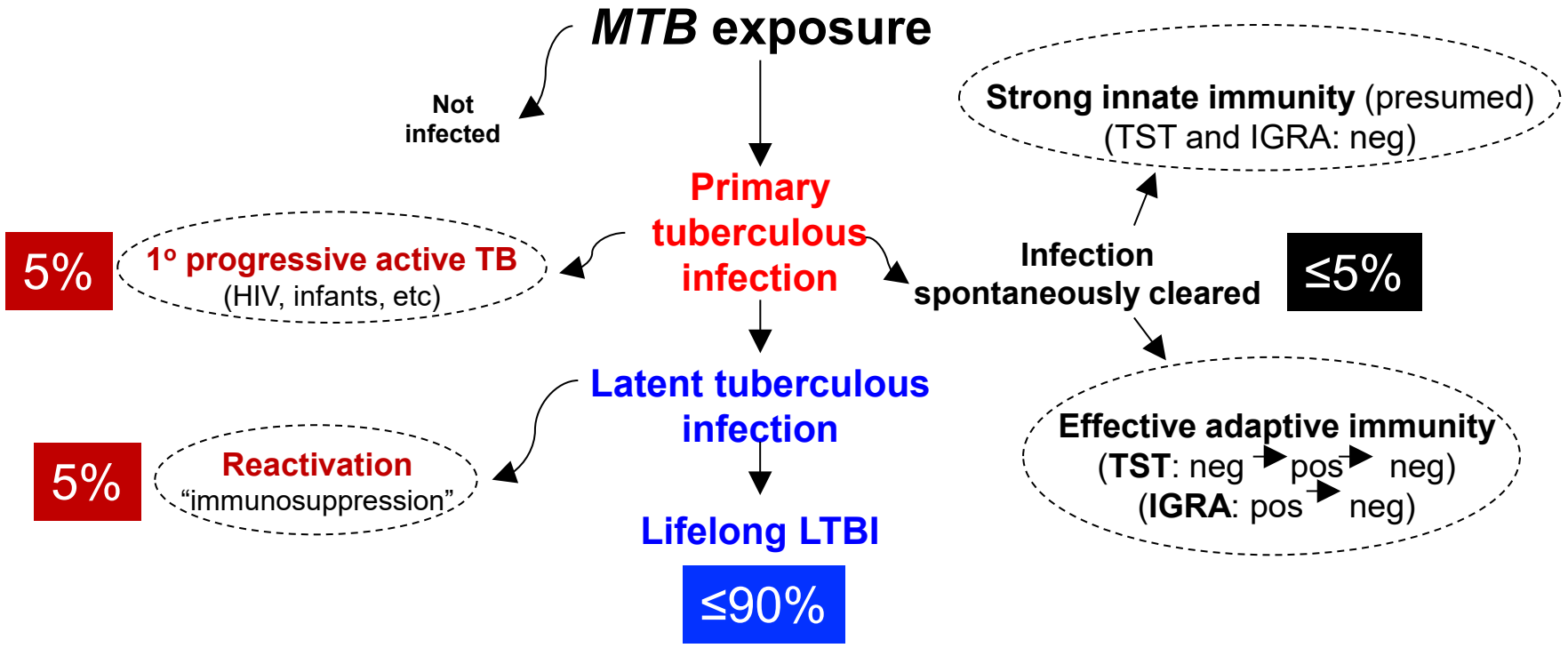
transitional, naïve, plasma,
memory, aged B cells

Mucosal immunity

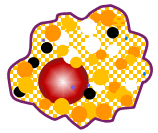
"coaching staff"

Epithelial cells

Most individuals infected with *MTB* do *not* develop active disease



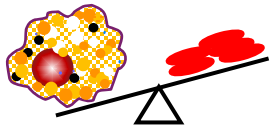
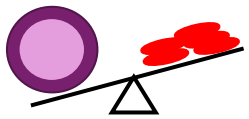
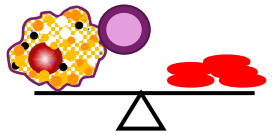
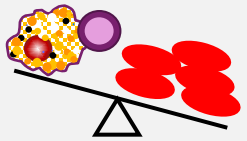
Ewer K et al. Am J Respir Dis 2006
Elkington PT and Friedland JS. Lancer Infect Dis 2015

Innate Immunity 

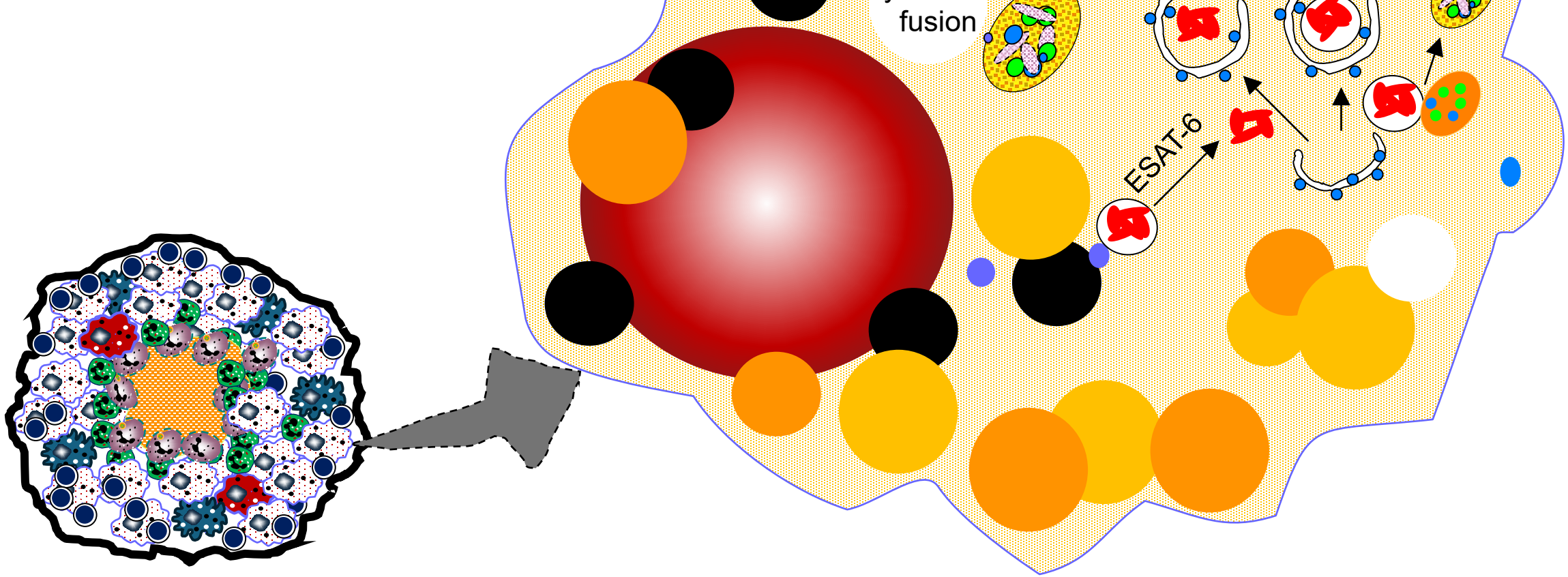
Adaptive Immunity 

Spectrum of TB infection and disease in exposed individuals

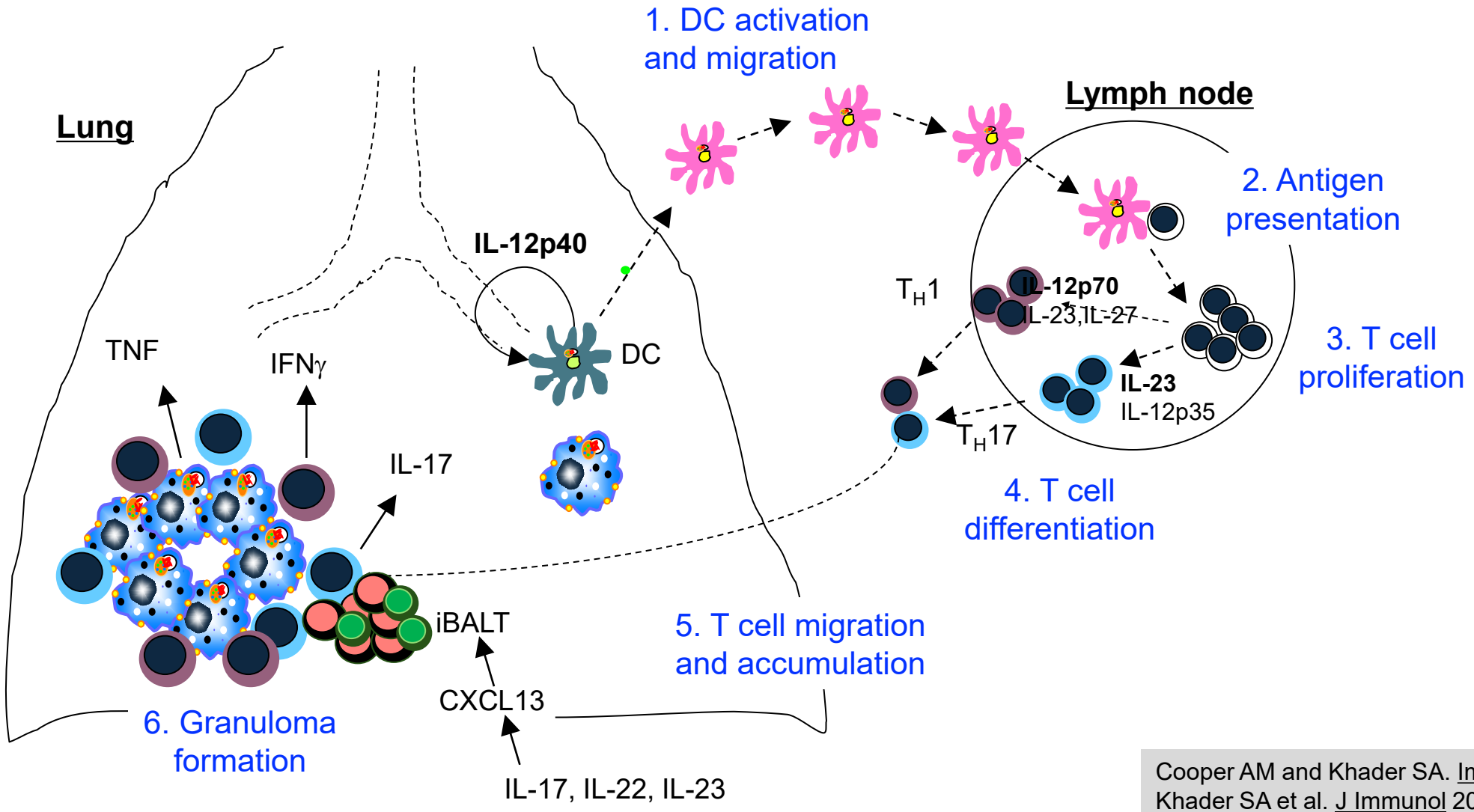
 *MTB*

Immunological or disease phenotype	Symptoms?	TST	IGRA	CXR changes?	Bacterial burden
Highly effective innate immunity 	No	Neg	Neg	None	None
Highly effective adaptive immunity 	No	Neg → Pos → Neg	Pos → Neg	None to minimal (± calcified granulomas)	None
T cell priming → LTBI 	No	Pos (or Neg)	Pos (or Neg)	None to minimal (± calcified granulomas)	+
Active TB disease 	Yes	Pos (or Neg)	Pos (or Neg)	Yes	++++

Phagosome-lysosome fusion & autophagosome-lysosome fusion are key mechanisms by which macrophages kill *MTB*



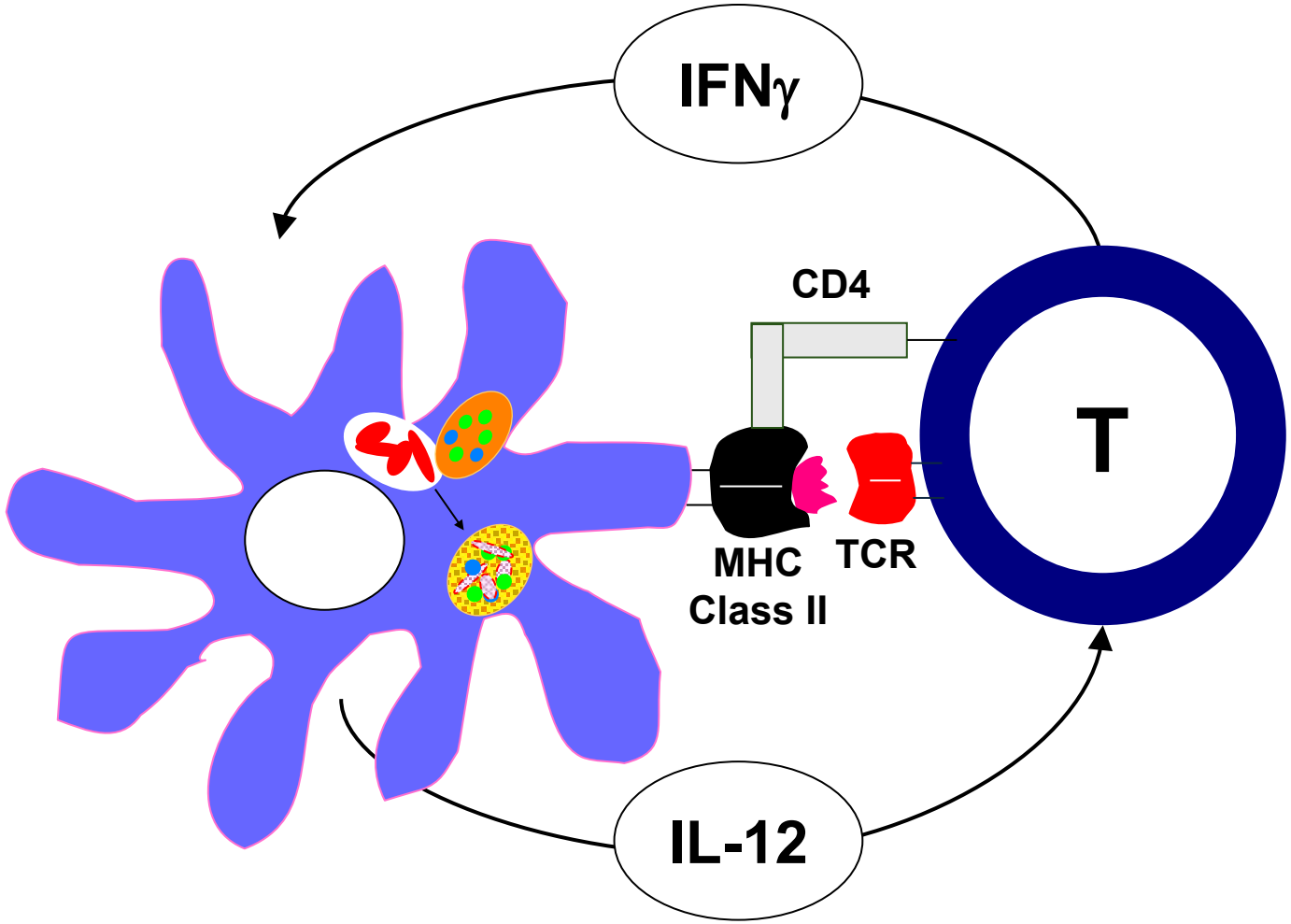
Overview of the initial innate and adaptive immune responses to *MTB* infection



Cooper AM and Khader SA. Immunol Rev 2008
Khader SA et al. J Immunol 2011

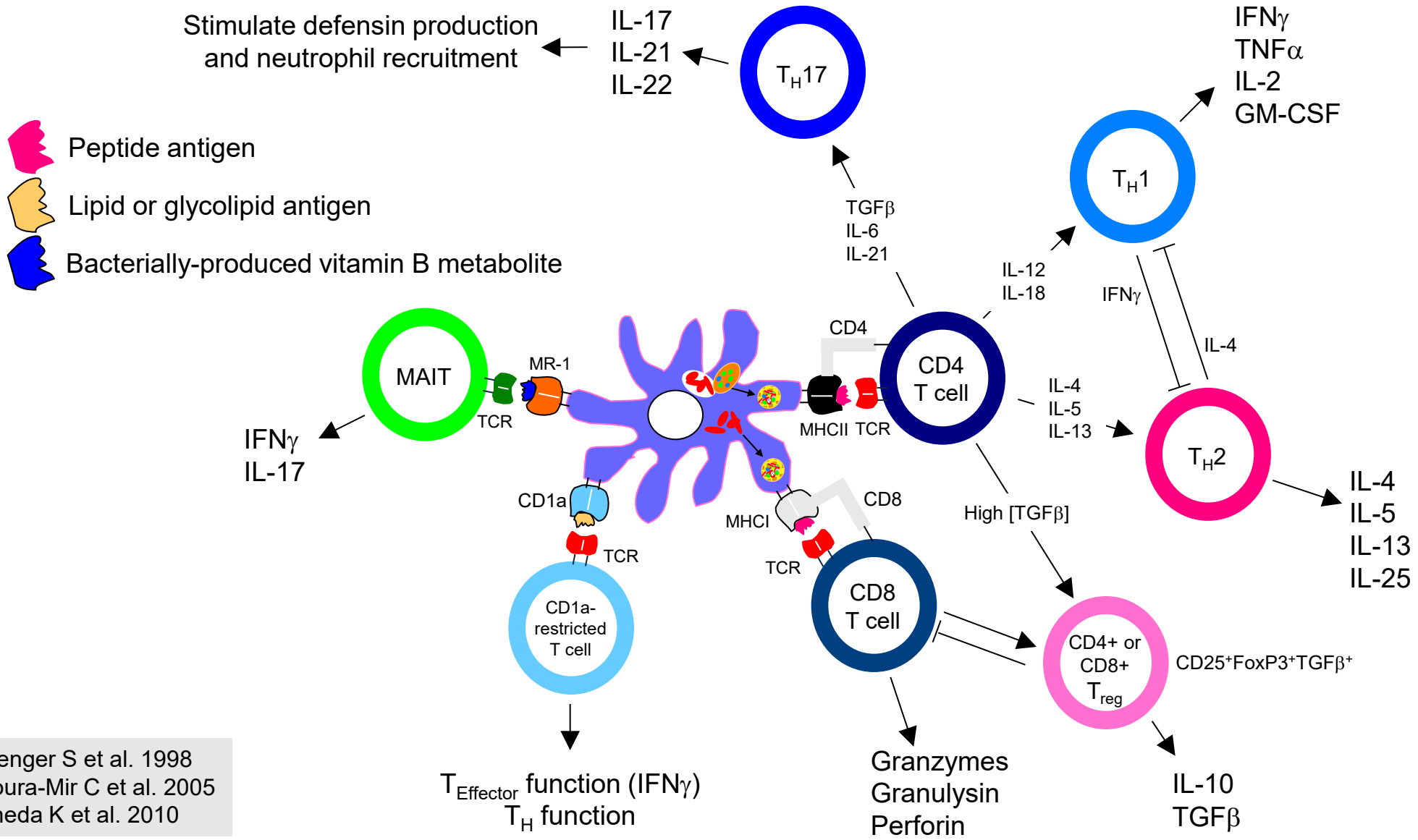
A central component in the defense against *MTB*

Antigen-presenting cell
(innate immunity)



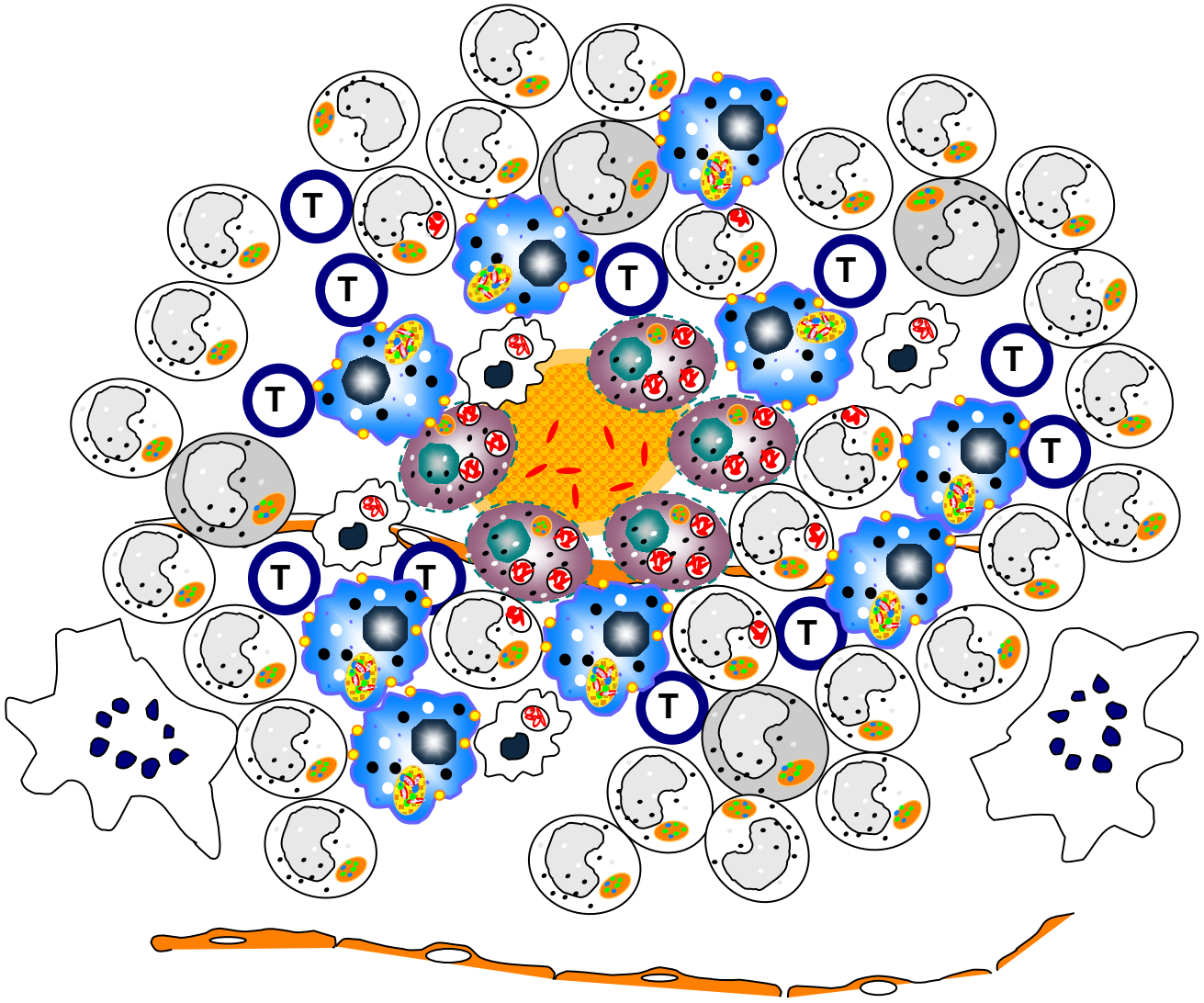
T cell
(adaptive immunity)

Innate-adaptive immune interactions are more complicated



Stenger S et al. 1998
Roura-Mir C et al. 2005
Dheda K et al. 2010

Granuloma: Chronic latent TB infection



Solid caseous center remains intact

↓

Any bug that escapes the caseous edge are ingested by highly activated macrophages

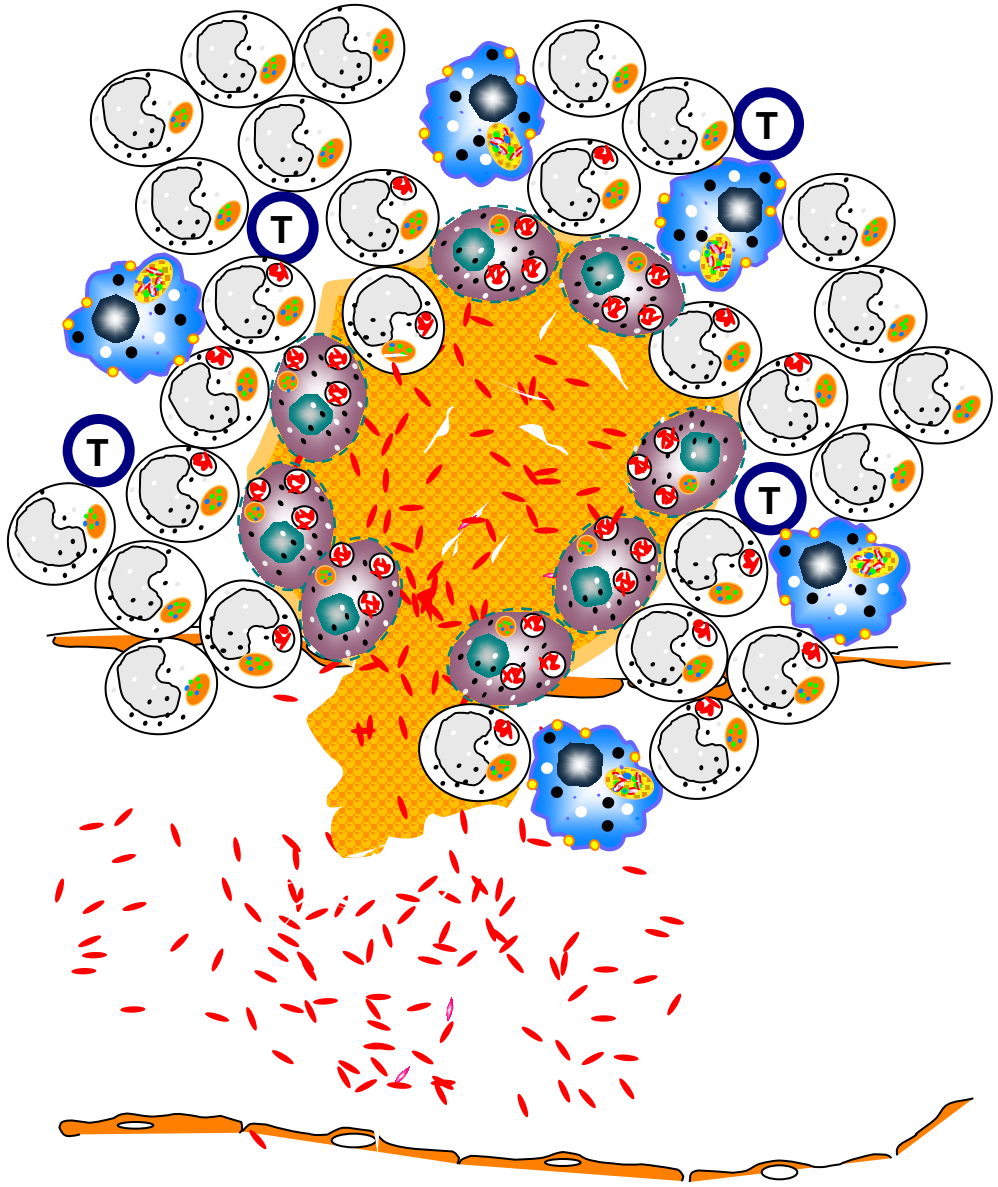
↓

Giant cells form
(a syncytium of epithelioid macrophages)

↓

If the caseation remains solid and does not liquify, **a chronic latent infection is established**

Granuloma: Decline in immunity



<u>Immunosuppression</u>
AIDS, cancer, anti-TNF,
age, malnutrition

↓

Loss of integrity of granuloma

↓

Liquifaction of the caseous material (“caseous necrosis”) provides a favorable medium for tremendous multiplication of *M. tb*.

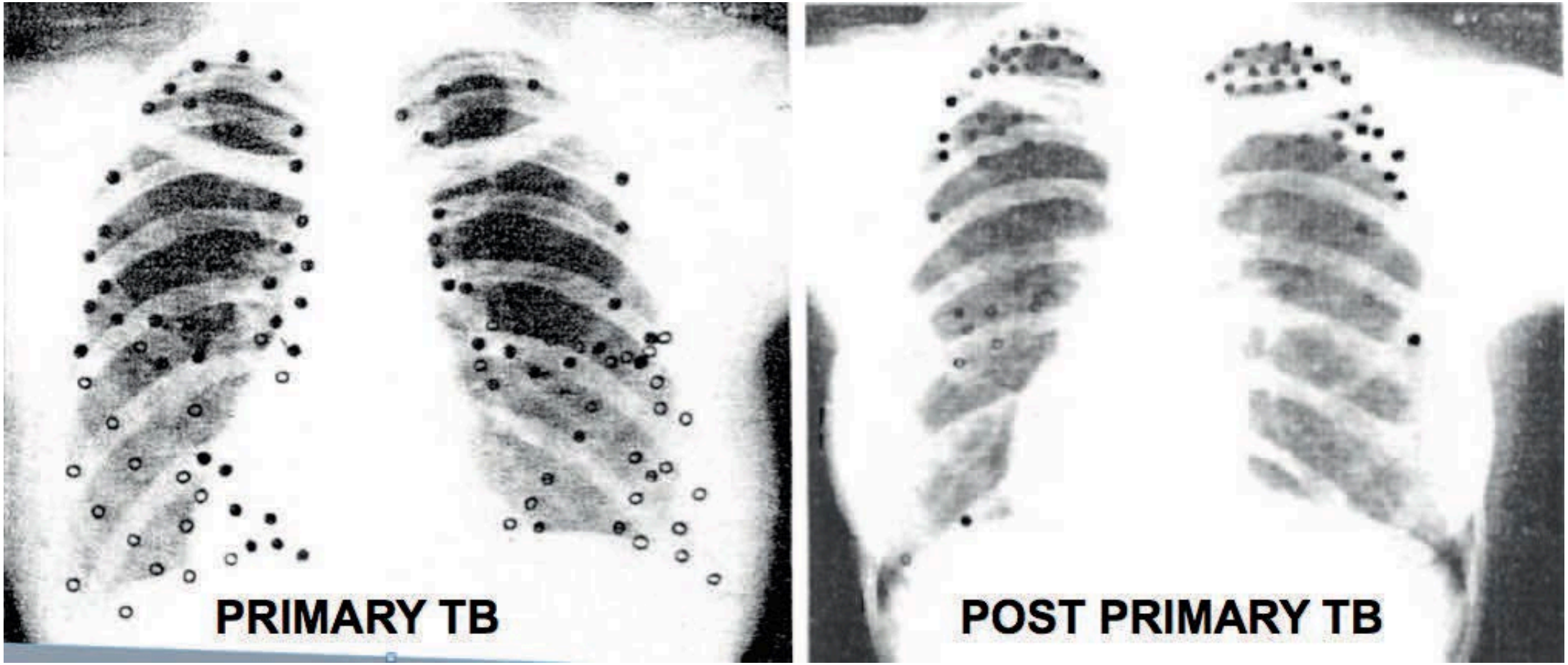
↓

Cavity formation

↓

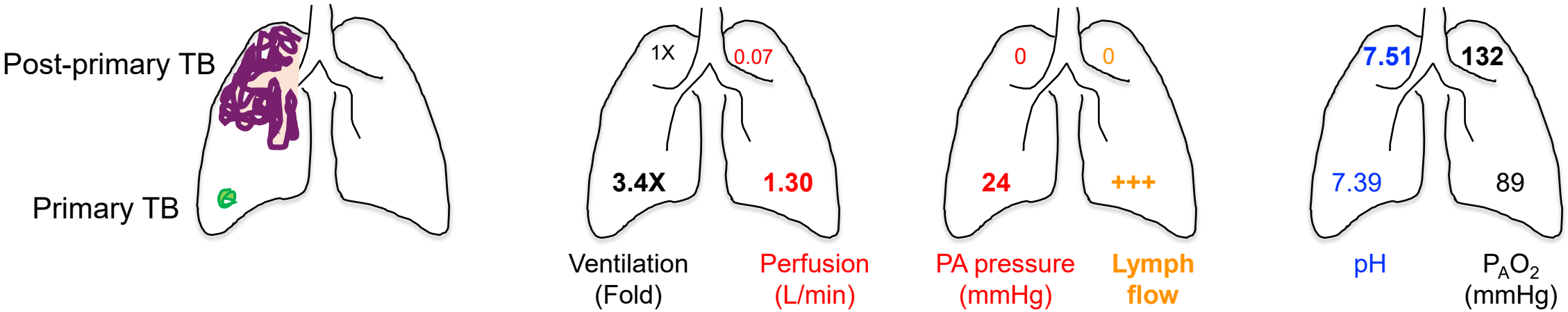
Rupture and spread to other parts of the lungs and to other individuals

Why is post-primary TB located mostly in the upper lung zones whereas primary TB (latent) mostly in the lower lung zones?



Medlar EM. *Am Rev Tuberc* 1948; 58: 583-611

Hypothesis: dormant *MTB* residing in the upper lobes are more likely to reactivate due to…



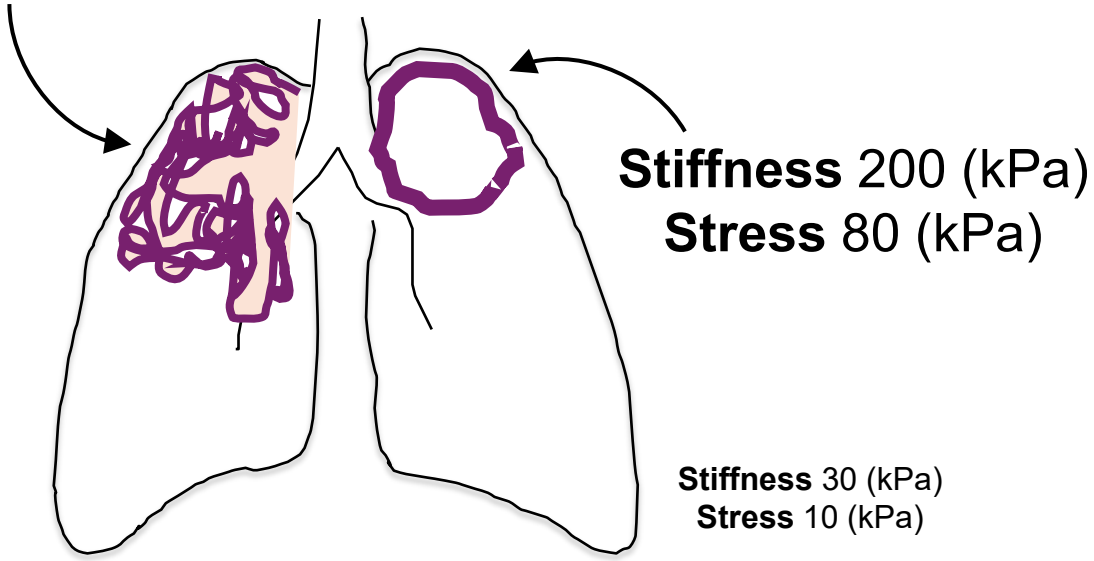
- Decreased blood perfusion → decreased influx of immune cells.
- Decreased lymph formation→ accumulation of mycobacteria & their antigens → increased DTH inflammation.
- Increased pH → increased aerobic glycolysis → attenuate autophagy.
- Increased alveolar O_2 due to decreased deoxygenated blood flow → increased growth of *MTB*.

Dock W. Arch Intern Med 1954
Dock W. Am Rev Tuberc 1946

West JB & Dollery CT. J Appl Physiol 1960
Murray JF. Am J Respir Crit Care Med 2003

Why do most cavities that form in post-primary TB occur in the upper lobes?

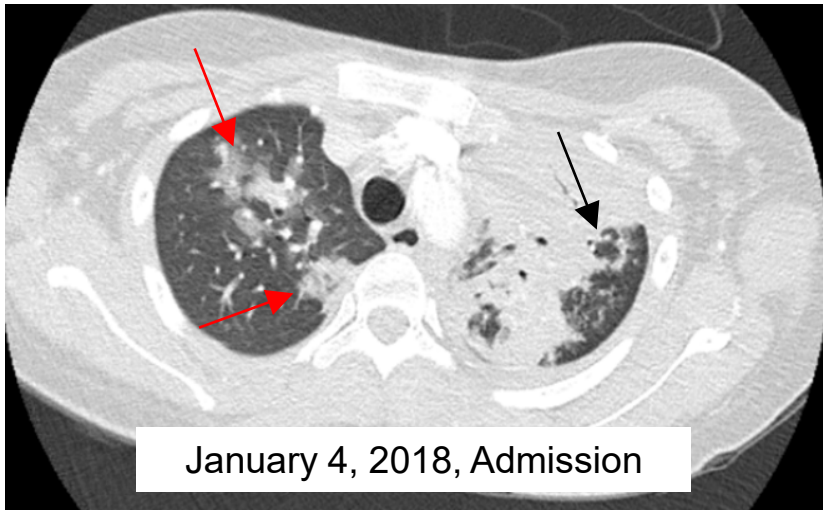
Decreased blood perfusion
Decreased lymph formation
Increased pH
Increased P_AO_2

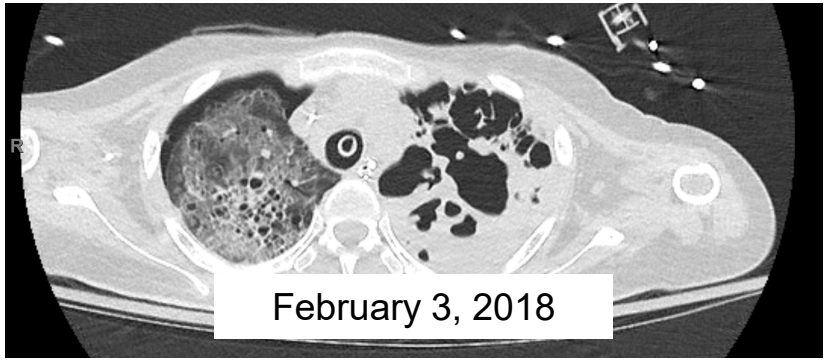


Stiffness 200 (kPa)
Stress 80 (kPa)

Stiffness 30 (kPa)
Stress 10 (kPa)

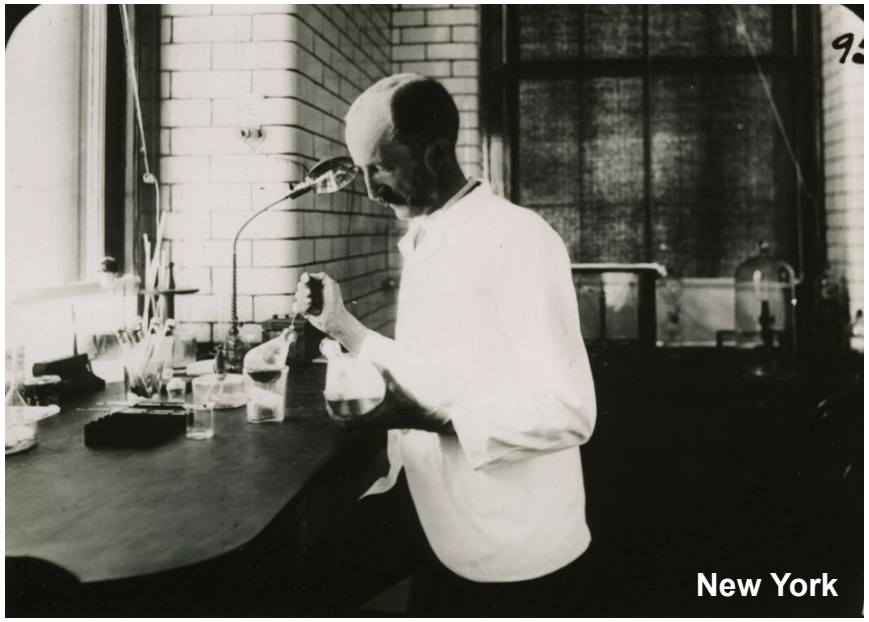
19-y.o. Marshallese woman post-partum

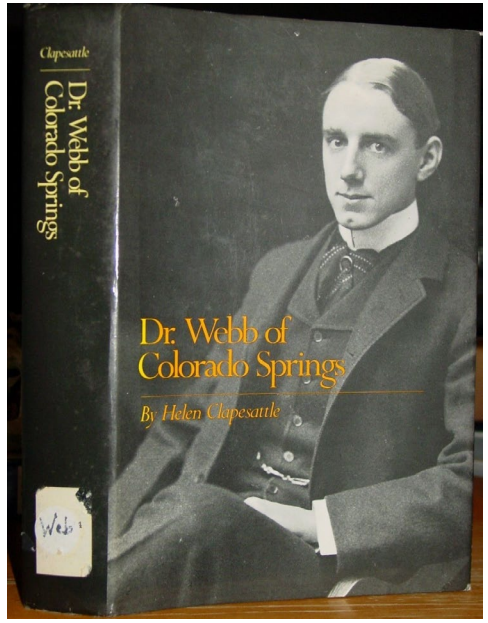




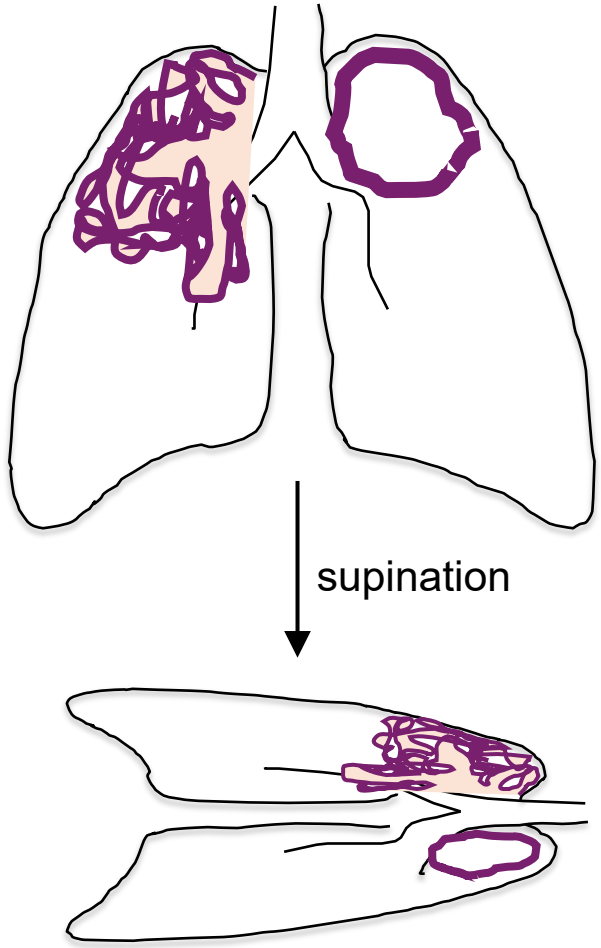
In the pre-antibiotic era, clinical observations showed that bedrest had therapeutic effects

- I know I have hurt nobody by rest, but I am quite sure I often have by allowing them to exercise (Edward Livingston Trudeau, MD).
- A good rule is the following: Never stand when you can sit, never sit when you can lie down (Webb GB & Ryder CT. Overcoming TB: An Almanac of Recovery, 3rd edition).





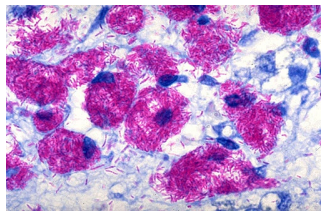
Is there rationale for bedrest in those with post-primary (upper lobe) TB?



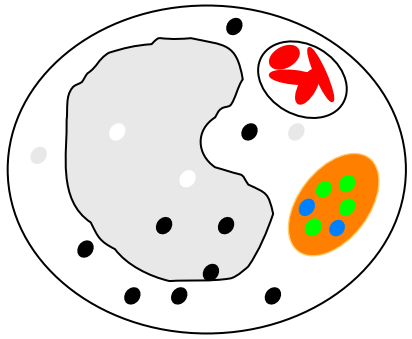
Yes, it reverses all those physiologic variables that are deleterious to the host in the upright position!

- **Increased blood perfusion** → increased influx of immune cells.
- **Increased lymph formation and flow** → Increased efflux of *MTB* and antigens.
- **Decreased pH** → decreased aerobic glycolysis → increase autophagy.
- **Increased deoxygenated blood flow** → increased oxygen extraction by the blood → decreased P_AO2 → reduced growth of *MTB*.
- **Decreased expansion of chest** → decreased mechanical stress and alveolar size → decreased risk for cavitation or attenuation of cavity size.

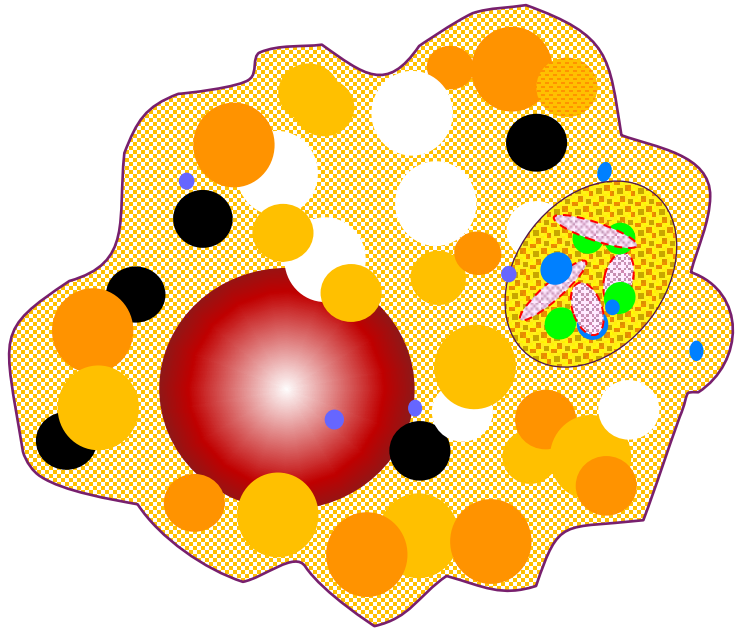
Three molecules that can activate macrophages



Unactivated macrophage



IFNγ
TNF
Vitamin D

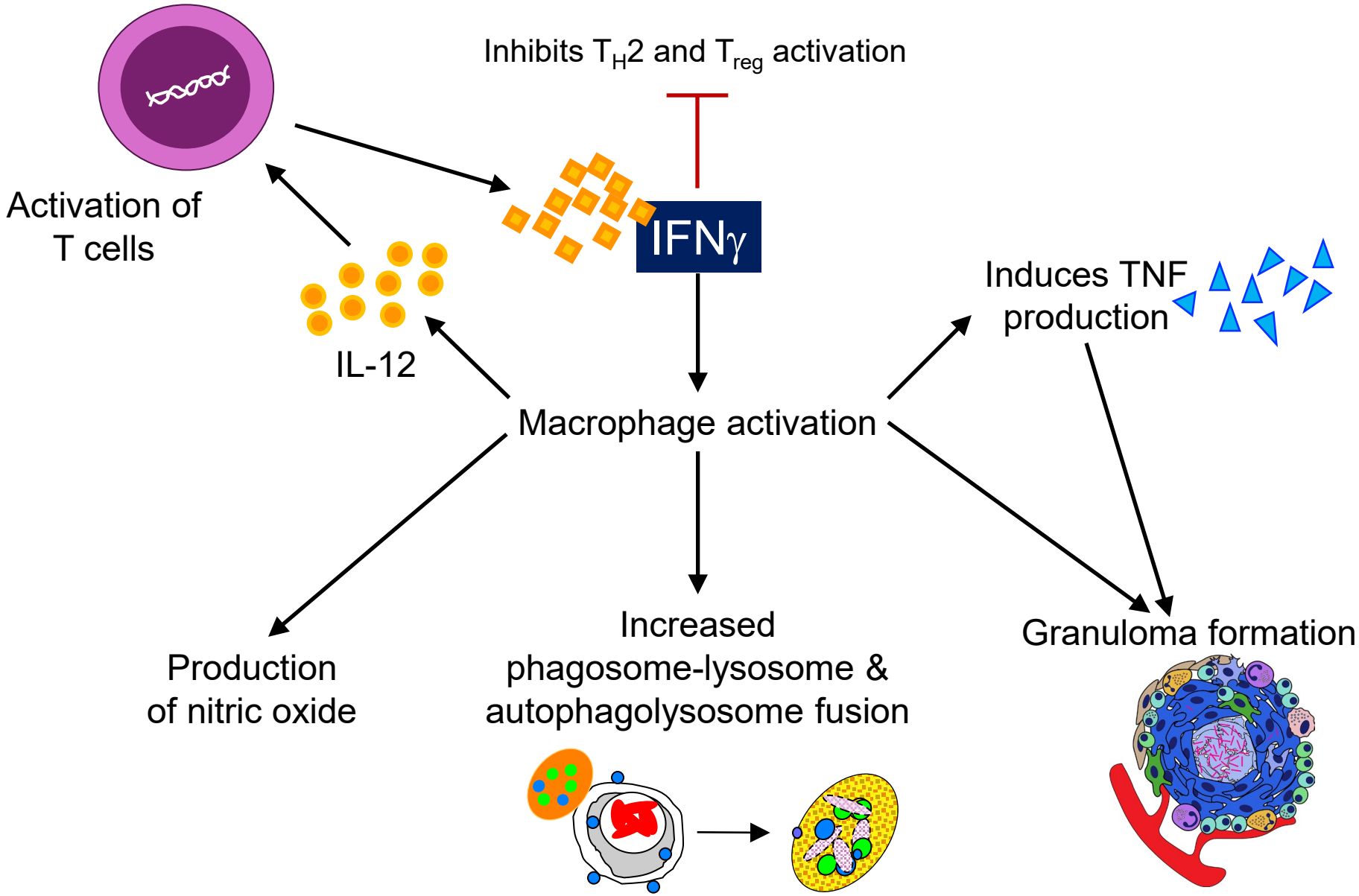


Fully-activated macrophage

Summary of vitamin D & TB

- Circumstantial evidence (epidemiological / experimental) that vitamin D combats against TB.
- Studies are mixed on whether vitamin D supplementation helps resolve TB in humans.
- Just keep vitamin D at good (not toxic) level (30-50 ng/mL of 25-OH vitamin D).

How IFNγ is protective against TB



TNF and TB

- **Responsible for many clinical manifestations of TB:** fever, night sweats, weight loss, and tissue necrosis.
- **Responsible for host-defense functions against TB**
  - **TNF is critical for granuloma formation and TB control** by increasing the expression of adhesion molecules, NO, chemokines, and chemokine receptors.
  - **TNF helps mediate macrophage apoptosis**, an important feature of granulomas.
- **Mice with genetic disruption for TNF receptor** have increased morbidity and mortality from TB.
- ***Is there a more compelling evidence that TNF is important in controlling TB in man …?***

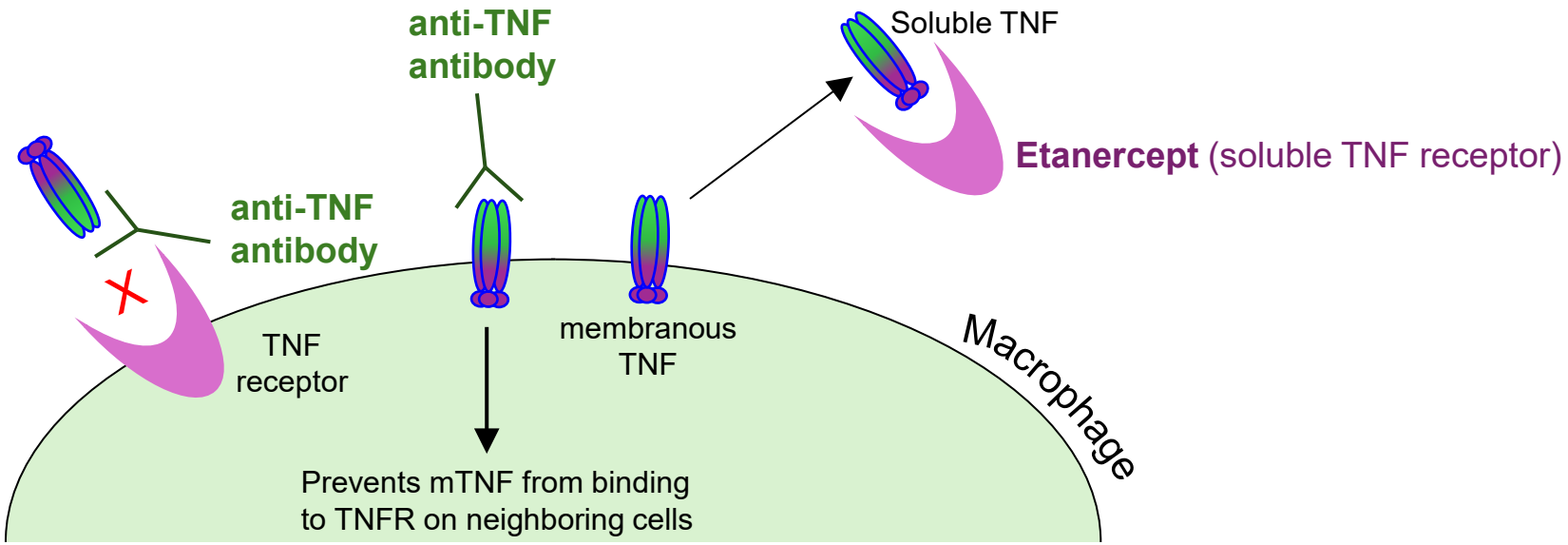
NEJM 2001; 345:1098

TUBERCULOSIS ASSOCIATED WITH INFLIXIMAB, A TUMOR NECROSIS FACTOR α–NEUTRALIZING AGENT

JOSEPH KEANE, M.D., SHARON GERSHON, PHARM.D., ROBERT P. WISE, M.D., M.P.H., ELIZABETH MIRABILE-LEVENS, M.D., JOHN KASZNICA, M.D., WILLIAM D. SCHWIETERMAN, M.D., JEFFREY N. SIEGEL, M.D., AND M. MILES BRAUN, M.D., M.P.H.

- **Infliximab: a monoclonal antibody that neutralizes TNF**.
- **Method:** all reported cases of TB following infliximab therapy were examined: **70 patients**.
- **Strong circumstantial evidence** that inhibition of TNF increases the risk of reactivation TB:
  - TB was diagnosed a median of **3 months** *after* beginning infliximab.
  - In 48 patients, TB developed after **3 or fewer infusions**.
  - **56% had extra-pulmonary TB** (vs **~18%** for non-HIV individuals)
  - **24% had disseminated disease** (vs **< 2%** for non-HIV individuals).
  - Rate of **infliximab-associated TB** is ~4X **backgound rate** for RA.

How do anti-TNF agents increase susceptibility to TB?



Anti-TNF inhibits *MTB*-induced IFNγ production (effect greater with anti-TNF antibody than etanercept)

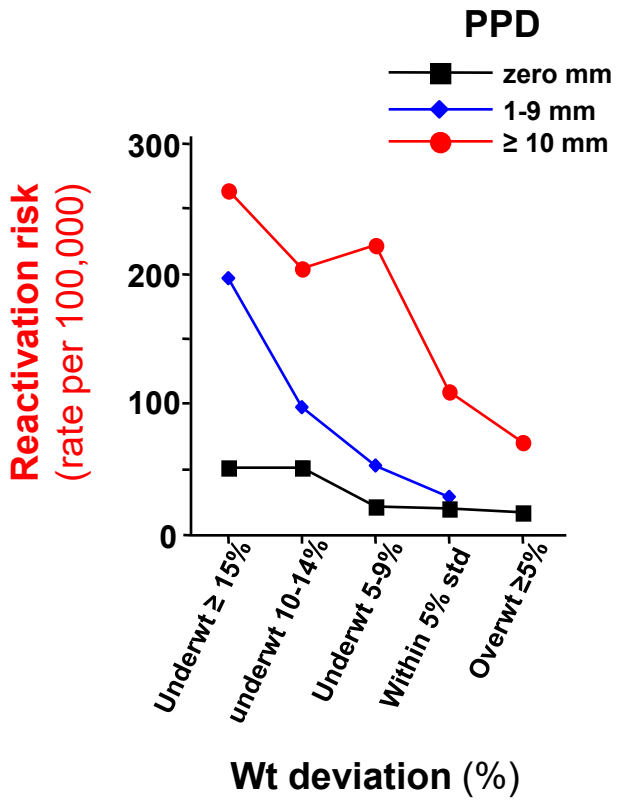
Anti-TNF inhibits apoptosis of macrophages (inhibiting a known killing mechanism of intracellular MTB)

Anti-TNF disrupts granuloma (as TNF is required for granuloma integrity)

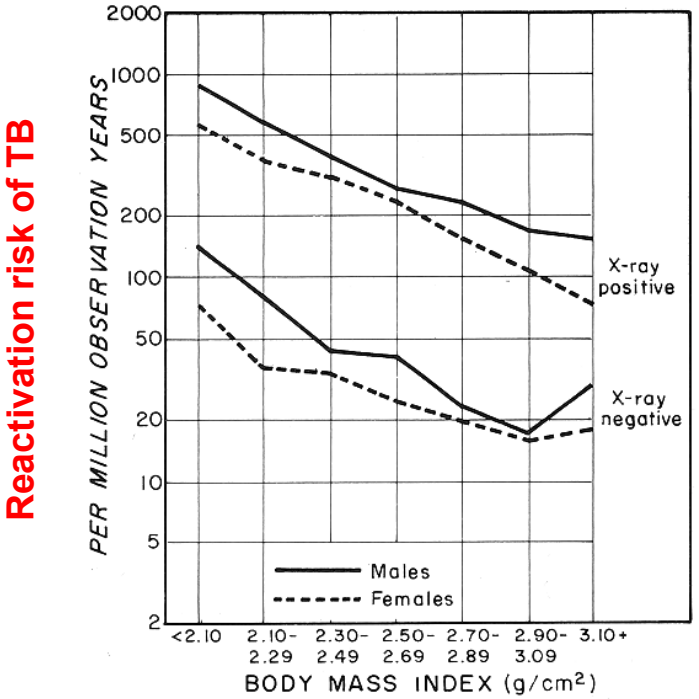
Anti-TNF reduces the number of $CD8^+CD45RA^+$ effector memory T cells (Bruns H et al. J Clin Invest 2009).

Is being thin a risk factor for TB?

68,754 U.S. Navy Recruits (1949-1951)
Palmer CE et al. *Am Rev Tuberc* 1957

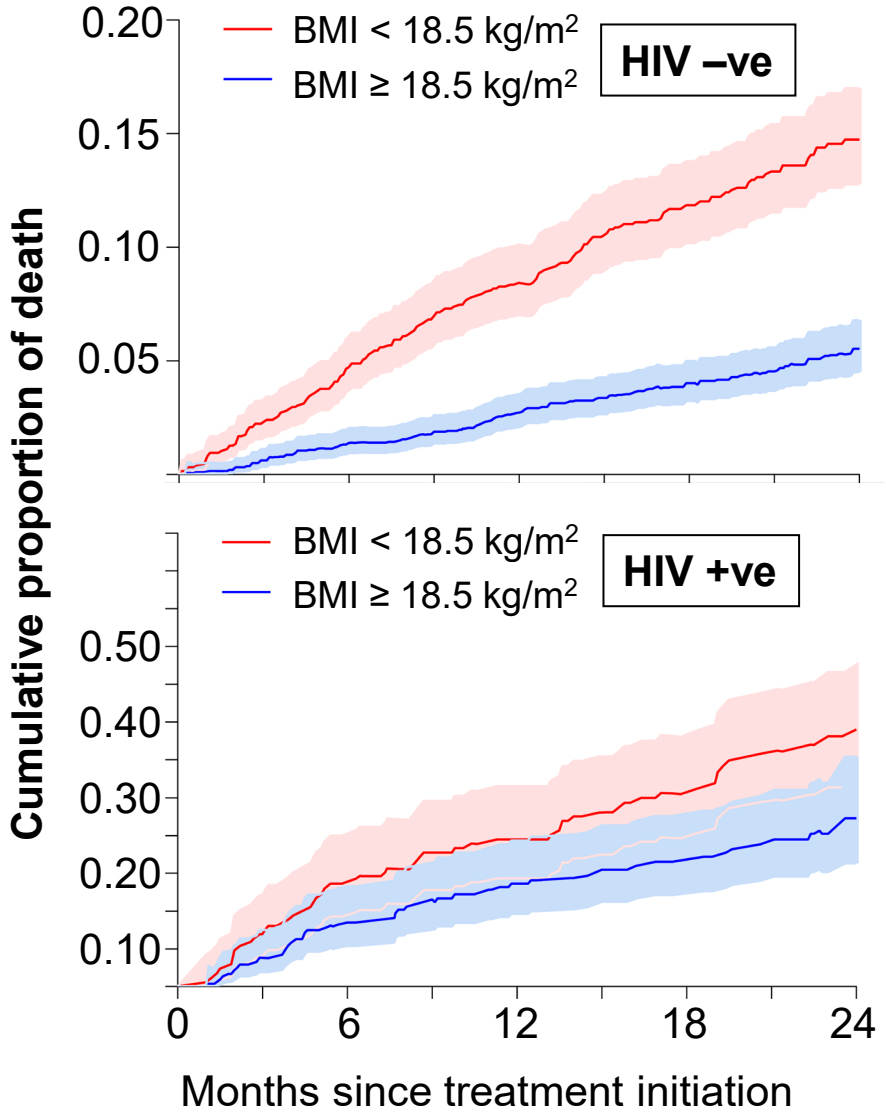


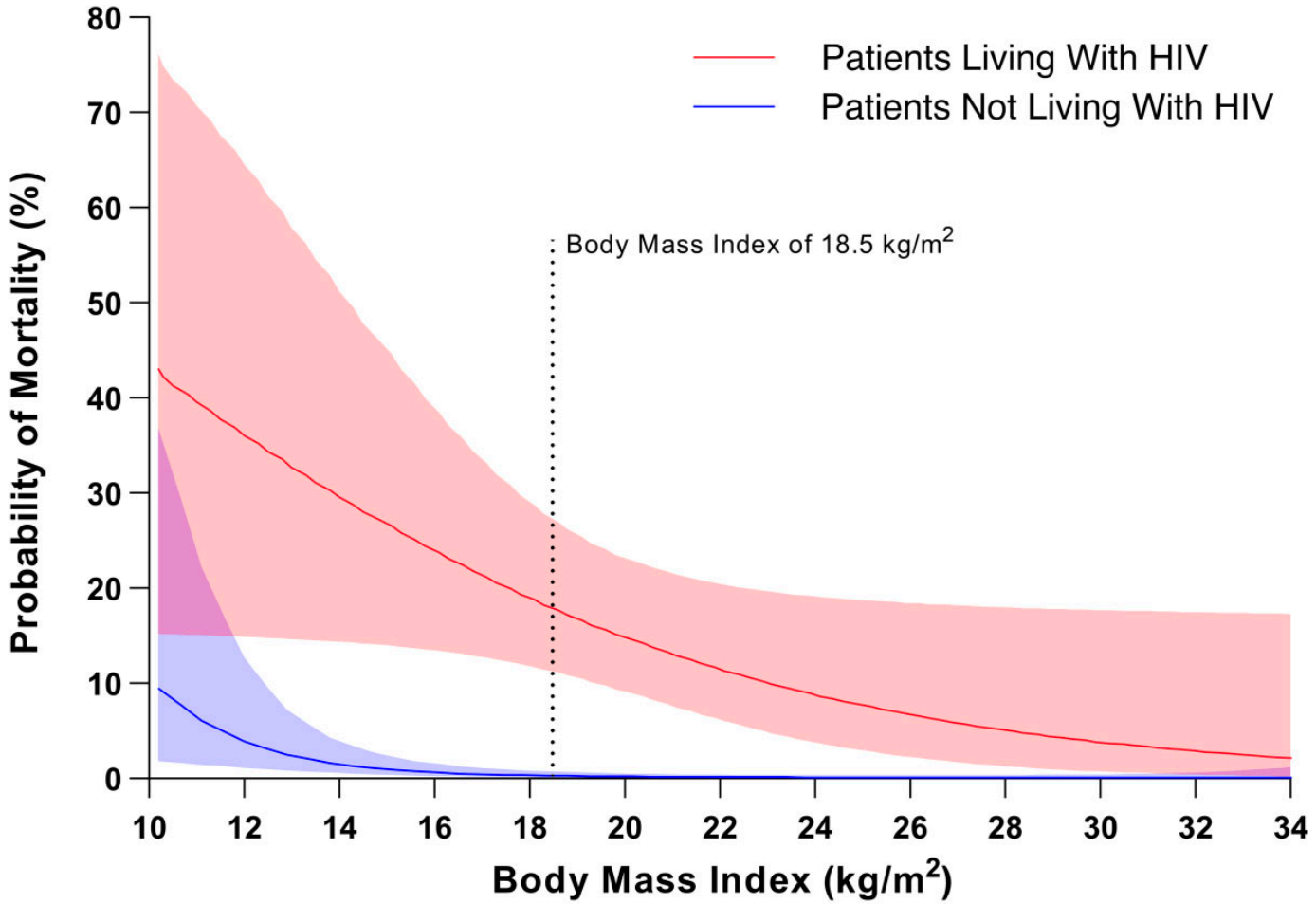
1,717,655 Norwegiens with compulsory miniature X-rays (1963-1975)
Tverdal A. *Eur J Respir Dis* 1986



Individual patient data-meta-analysis of RR/MDR-TB of low BMI (1993-2016: 5,148 patients from multiple countries)

Adjusted odds ratio of BMI<18.5 kg/m²:
- unfavorable outcome: 1.7
- death: 3.1





Campbell JR et al. Clin Infect Dis 2022

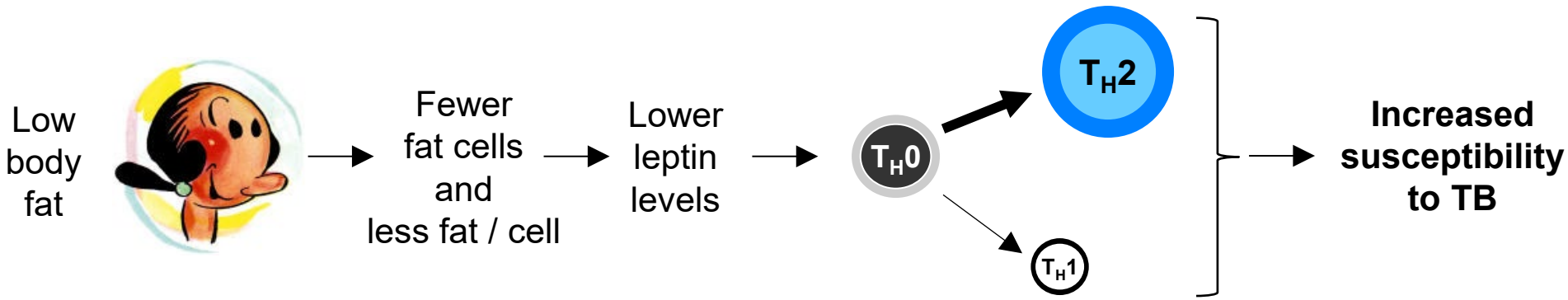
Q: Why are thin individuals more susceptible?

1. Hypothesis: due to a relative deficiency of leptin

2. Leptin is a satiety hormone produced by fat cells: the more fat one has → the more leptin is produced.

3. Leptin biases the immune response toward the T_H1 (IFNγ-producing) phenotype.

4. Thus, thin individuals → less leptin → less IFNγ-producing T_H1 cells.



5. Leptin-deficient mice are more susceptible to *MTB* and *M. abscessus*.

Wieland CW et al. Int Immunol 2005
Ordway D et al. J Leuk Biol 2008

Host risk factors for active TB

Acquired

- Originated from TB endemic country
- Extremes of age / post-partum status
- Thin body habitus / malnutrition
- AIDS & other acquired immunosuppression; e.g., cancer, organ transplant
- Immunosuppressives including GC and anti-TNF agent
- Tobacco smoke exposure
- Diabetes mellitus / ESRD
- Silicosis
- Vitamin D deficiency?

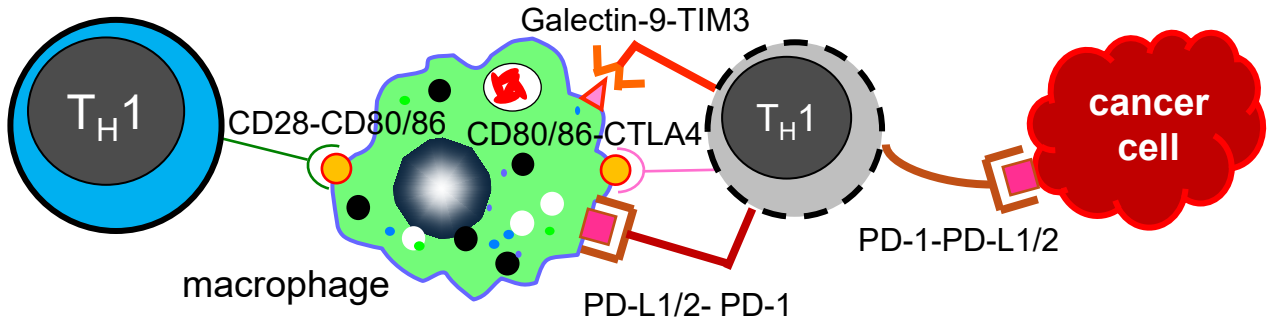
Hereditary

- Defects in the interferon-gamma-IL-12 axis
- Certain race or ethnicity? (controversial)
- Individuals with polymorphism of the vitamin D receptor, various cytokines, and polymorphism.

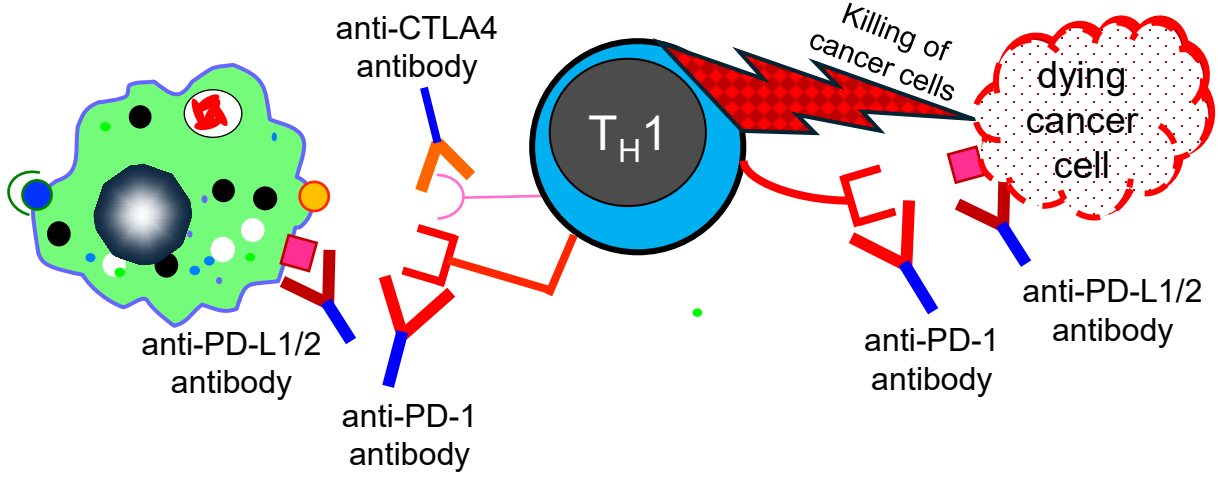
Poverty – underlying factor for malnutrition, crowded living conditions, and *MTB* exposure and infection.

Whether immune checkpoint inhibitors (ICIs) predispose to active TB is controversial

A) Immune checkpoints deactivate T_H1 cells



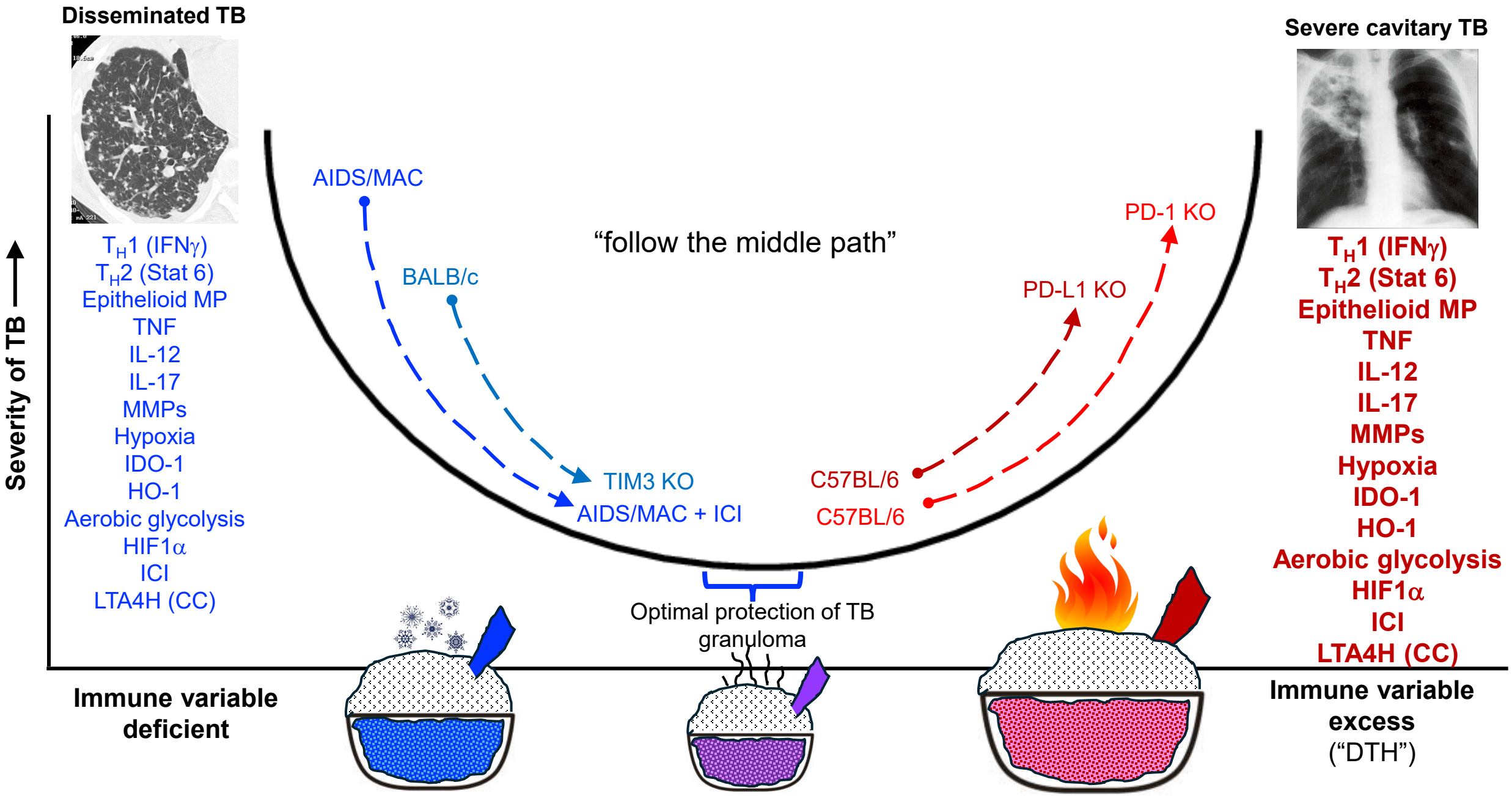
B) **Immune checkpoint inhibitors** activate T_H1 cells to kill cancer cells



Q: Since ICIs (*e.g.*, anti-PD1 antibody) augment $IFN\gamma^+T_H1$ cell activity, would you predict mice *knocked out* for PD-1 (which would increase $IFN\gamma^+T_H1$ cell activity) be more protective against *MTB*?

A: Yes, I would also predict that mice *knocked out* for PD-1 (which would increase $IFN\gamma^+T_H1$ cell activity) be more protective.

But in reality, PD-1 KO mice were actually **more susceptible** to TB, with increased *MTB* burden and reduced survival.


Disseminated TB
Severe cavitary TB
Severity of TB
T_H1 (IFNγ)
T_H2 (Stat 6)
Epithelioid MP
TNF
IL-12
IL-17
MMPs
Hypoxia
IDO-1
HO-1
Aerobic glycolysis
HIF1α
ICI
LTA4H (CC)
AIDS/MAC
BALB/c
TIM3 KO
AIDS/MAC + ICI
"follow the middle path"
PD-1 KO
PD-L1 KO
C57BL/6
C57BL/6
Optimal protection of TB granuloma
Immune variable deficient
Immune variable excess ("DTH")

Three test questions

Which statement is true about leptin?

A. It skews T cells toward the T_H1 (IFNγ-producing) phenotype.
B. It causes increase appetite and weight gain.
C. Its levels are high in thin individuals.

Which statement is false regarding vit D and TB?

A. Deficiency of sunlight can result in vit D deficiency and theoretically increase the risk for TB.
B. Since it is a water soluble vitamin, it is safe to take vit D in "large" doses.
C. Vit D can induce the production of a protein that can directly kill intracellular *MTB*.
D. Vit D enters the cell nucleus and directly turns on certain genes.

Which statement is true about AIDS and TB?

A. TB in patients with advanced HIV+ve is associated with well-formed granulomas.
B. It illustrates the importance of $CD4^+$ T-cells in the defense against TB.
C. It is associated with increased levels of IFNγ.