From the World's Deadliest Bacteria to Cancer Therapy, Lessons from Tuberculosis and BCG

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Big Picture

How diseases inform each other?

Diseases are not isolated silos

Modern medicine categorizes disease into boxes:

- Infectious
- Cancer
- Autoimmune
- Metabolic

… and more

Diseases are not isolated silos

But biology does not recognize these categories. The immune system sees:

- Danger
- Persistence
- Tissue damage
- Adaptation

The mechanisms are shared.

Chronic threat as a biological theme

Across diseases, the immune system must decide:

- Recognize
- Eliminate
- Contain
- Tolerate
- Fail

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These decisions shape outcomes in:

- Chronic infection
- Cancer
- Autoimmunity
- Fibrosis

Where do we see these dynamics most clearly?

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Infectious diseases provide the clearest model of:

- Immune activation under sustained pressure
- Host-pathogen co-evolution
- Immune regulation and exhaustion
- Structural containment

Why study infectious diseases beyond infection?

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Infectious diseases reveal how the immune system responds under sustained biological challenge.

They reveal how the immune system:

- Detects danger
- Applies selective pressure
- Fails to eliminate threats
- Establishes equilibrium

Many foundational principles of immunology were first understood through infection.

Immunological Principle	Infectious Model / Disease	Key Scientist(s	Approx. Year	Experimental Approach	Core Discovery	Impact on Modern Immunology
Germ Theory of Disease	Anthrax, Tuberculosis	Louis Pasteur; Robert Koch	1860–1880	Microbial isolation, Koch's postulates	Specific microbes cause specific diseases	Established need for host defense mechanisms
Vaccination & Immunological Memory	Smallpox/Cowpox	Edward Jenner	1796	Cross-protection via cowpox inoculation	Protective immunity & memory	Foundation of adaptive immunity
Attenuated Vaccines	Rabies, Anthrax	Louis Pasteur	1880s	Pathogen attenuation	Artificial induction of immunity	Basis for modern vaccine development
Humoral Immunity (Antibodies)	Diphtheria, Tetanus	Emil von Behring; Shibasaburo Kitasato	1890	Serum transfer experiments	Antitoxins (antibodies) neutralize toxins	Passive immunization, antibody therapy
Cellular Immunity & Phagocytosis	Bacterial infection models	Élie Metchnikoff	1882	Microscopic observation of engulfment	Phagocytosis	Basis of innate cellular immunity
Complement System	Bacteriolysis	Jules Bordet	1890s	Heat-labile serum factor studies	Complement-mediated lysis	Key effector arm of innate immunity
Clonal Selection Theory	Antigen exposure models	Frank Macfarlane Burnet	1957	Theoretical + experimental antigen studies	Antigen-specific lymphocyte clones	Foundation of adaptive immunity theory
Delayed-Type Hypersensitivity	Tuberculosis	Karl Landsteiner (antigen specificity work)	Early 1900s	Skin test reactions	T-cell mediated immunity	Understanding of cellular immunity
Major Histocompatibility Complex (MHC Restriction)	LCMV viral infection	Rolf Zinkernagel; Peter Doherty	1974	Virus-infected mouse models	T cells recognize antigen with self-MHC	Basis of antigen presentation biology
Pattern Recognition Receptors (TLRs)	Bacterial LPS	Charles Janeway; Bruce Beutler	1989–1998	Endotoxin response studies	Toll-like receptors detect PAMPs	Molecular basis of innate sensing
Cytokine Biology	Viral & bacterial infections	Isaacs & Jean Lindenmann	1957	Interferon discovery	Antiviral cytokines	Immunoregulation and antiviral immunity

Infections as a model system for biology

Infections allow us to study:

- Host-microbe interactions
- Immune adaptation under sustained pressure
- Selection and evolution within tissues
- The balance between control and pathology

Infection provides a tractable model of chronic biological conflict.

Infection as a model system for biology

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A master of immune containment and long-term persistence

The pathogen that refuses to leave

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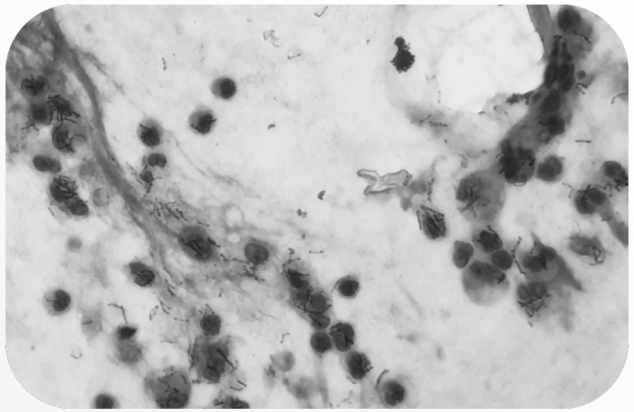
A master of immune containment and long-term persistence

Tuberculosis (TB)



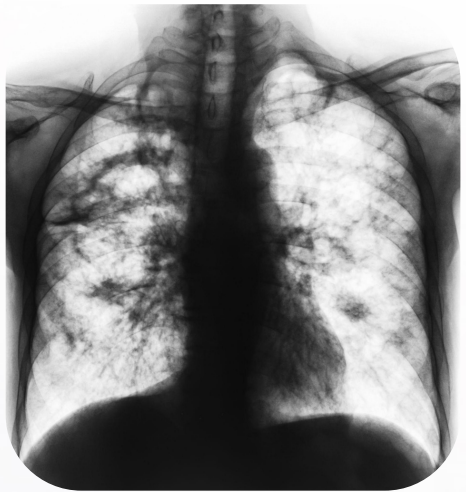


image credit: Wikimedia

What does tuberculosis have in common with cancer?

Granulomas vs tumors

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Chronic inflammation

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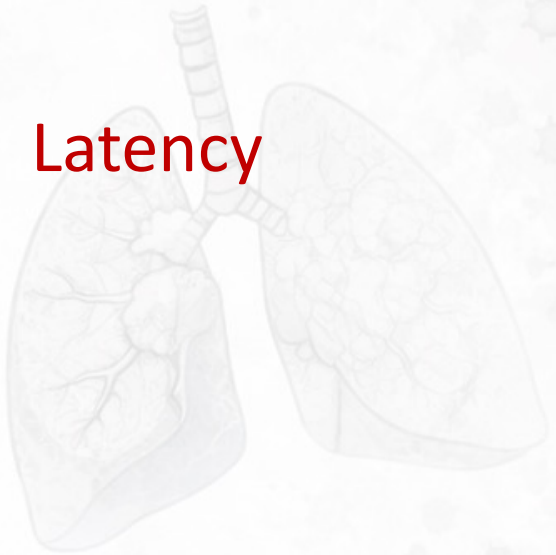
Immune evasion



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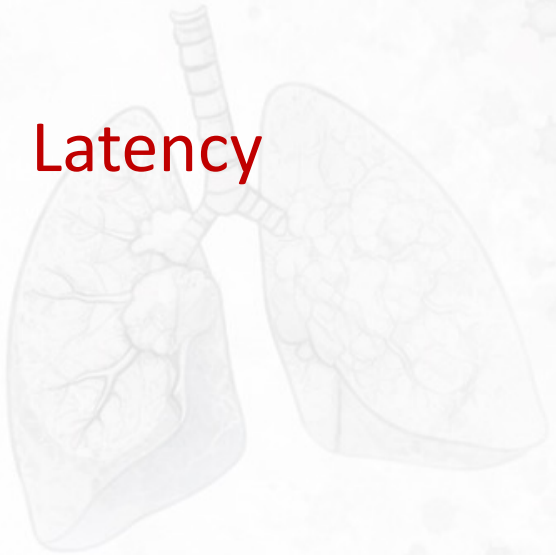
Host-pathogen arms race



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Host-pathogen arms race

What does tuberculosis have in common with cancer?

The theme: **shared immunological principles**

Why do we care about TB in the context of cancer?

In both TB and cancer:

- The immune system recognizes the threat
- The threat is not eliminated
- A structured immune niche forms
- Immune pressure selects resistant populations
- Disease persists through equilibrium

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TB illustrates how immune control and persistence can coexist.

Where does TB stand today: a historical disease or an ongoing global threat?

Sometimes the most dangerous diseases are the ones we think have already been solved, when that in fact is not the case.

10 million cases every year

1.3 million deaths a year

25% of the world latently infected

Tuberculosis is not a historical disease, it’s the highest killing infectious agent

Why is TB “invisible”?

- **It’s concentrated where power and visibility are lowest.**

Burden falls largely on low- and middle-income countries and marginalized communities everywhere.

- **It’s a slow-moving crisis**

Chronic, year-after-year deaths don’t trigger the same urgency as outbreaks.

- **Stigma + silence**

TB is tied to poverty, overcrowding, HIV, incarceration-people and systems hide it.

- **Underdiagnosis and underreporting**

Limited access to testing and care makes the true burden harder to “see.”

- **Resource mismatch**

Less political attention → less funding for R&D → fewer new tools → ongoing transmission.

Bottom line: TB persists not only because of biology, but because of inequality.

Inequality as a determinant of disease

Partners In Health

- Social and economic conditions actively shape who becomes sick and who receives care.
- Poverty, racism, political instability, and limited health infrastructure are not peripheral to disease; they influence exposure, progression, and access to treatment.

TB is not only a bacterium.
It is a mirror.

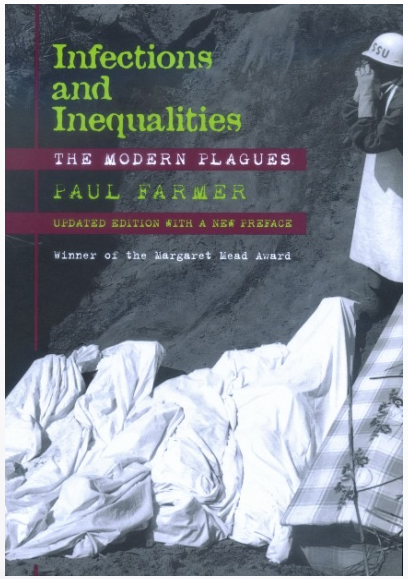

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image credit: Partners in Health

To understand why Tuberculosis persists, biologically and socially, we need to look at its history.

TB has shaped and been shaped by societies for centuries.

Tuberculosis: older than civilization

- Tuberculosis has been identified in Egyptian mummies dating back to 3000 BCE. Characteristic spinal deformities - what we now call Pott's disease appear in ancient skeletal remains across continents.
- Ancient DNA analysis confirms Mtb infection in remains from Egypt, Peru, and across Eurasia.
- The disease likely expanded alongside human settlement, animal domestication, and increasing population density.

The white plague

- By the 18th and 19th centuries, Tuberculosis caused nearly one in four deaths in parts of Europe and North America.
- It was known as “consumption,” reflecting its slow wasting of the body - chronic cough, hemoptysis, night sweats, progressive weight loss.
- Urbanization and industrial crowding accelerated transmission.
- Sanatoria promoted fresh air, rest, and sunlight as therapy.

Tuberculosis in the cultural imagination

- The pale, thin appearance of TB patients became aestheticized during the Romantic era associated with sensitivity and artistic genius.
- Writers such as John Keats and composers like Chopin died of Tuberculosis.
- Before germ theory, TB's tendency to affect multiple family members led to superstition and "vampire panics."

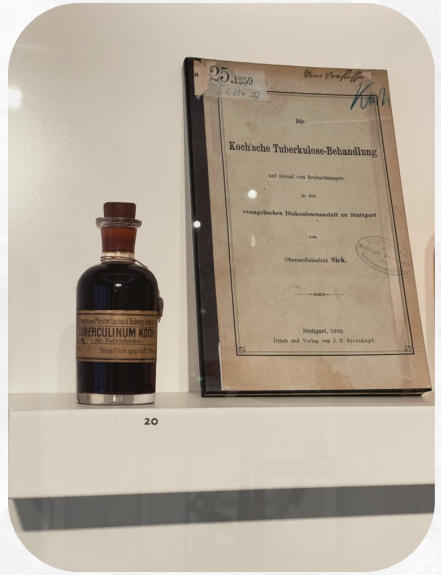
image credit: ASM

The discovery of the tubercle bacillus

- On March 24, 1882, Robert Koch announced the discovery of *Mycobacterium tuberculosis*.
- This discovery helped establish bacteriology and Koch's postulates.

image credit: Wikimedia

The discovery of the tubercle bacillus



- On March 24, 1882, Robert Koch announced the discovery of *Mycobacterium tuberculosis*.
- This discovery helped establish bacteriology and Koch's postulates.
- Koch later introduced "tuberculin" as a therapeutic breakthrough.
- It failed as a cure but became the basis for diagnostic testing.
- Scientific clarity did not mean immediate control.

Image credit:imdb

ACT II

TB Biology and vulnerabilities

Meet *Mycobacterium tuberculosis*

- Aerobic, slow-growing bacillus
- Airborne transmission
- Intracellular pathogen of macrophages
- Lipid-rich cell wall
- Doubling time ~24 hours

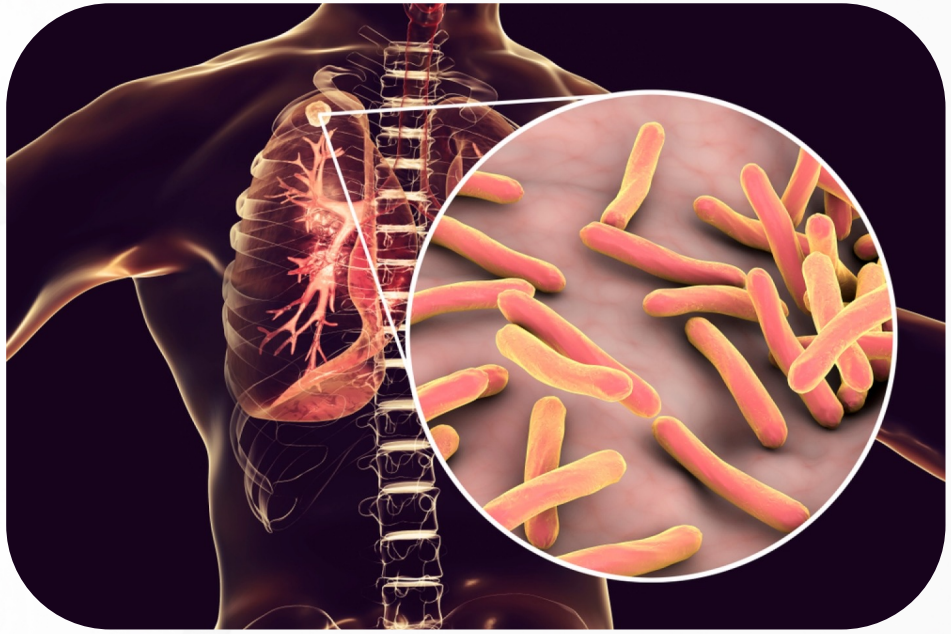


image credit: Weill Cornell Medicine

Entry and early infection

- Inhaled into the alveoli
- Phagocytosed by macrophages
- Inhibits phagosome-lysosome fusion
- Survives intracellularly

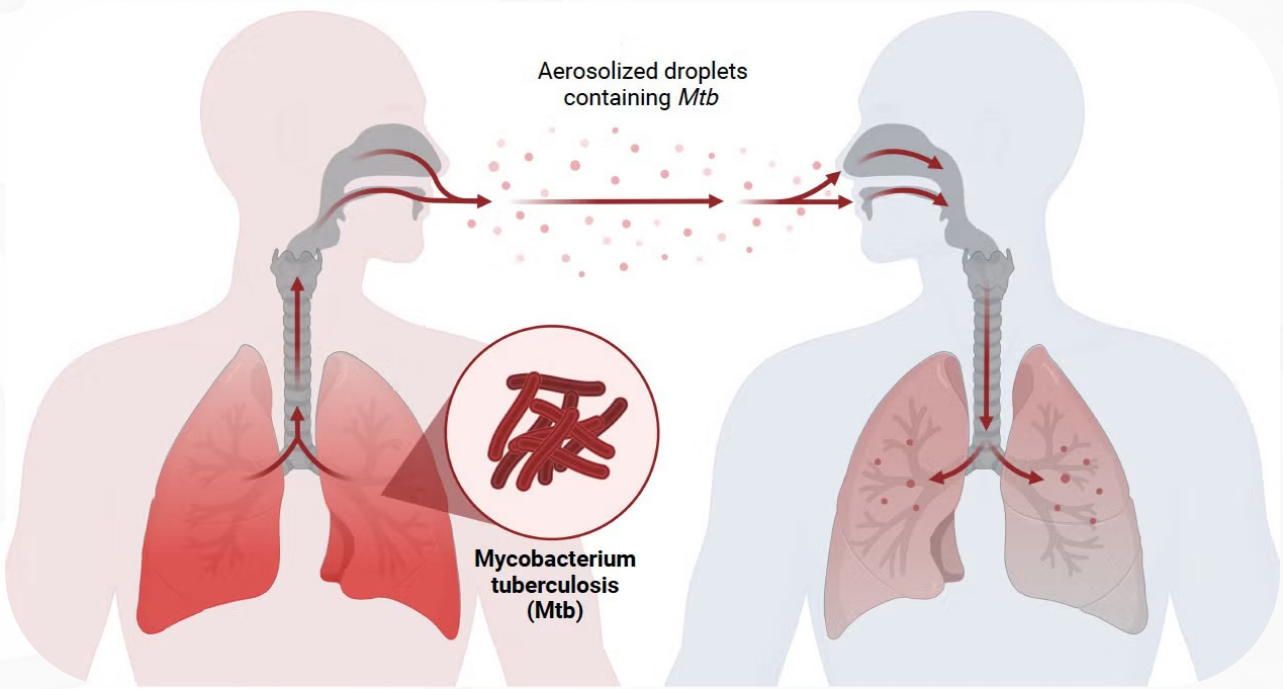


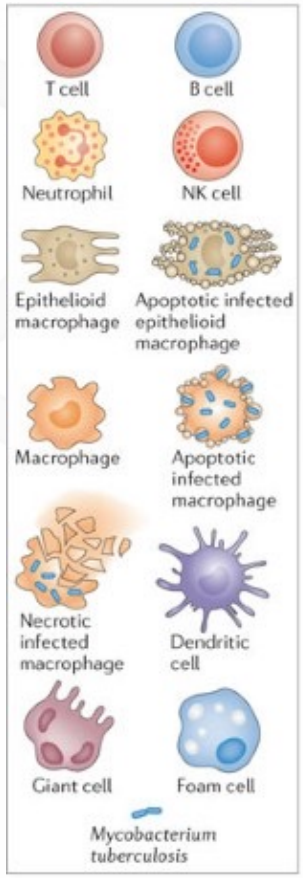
image credit: Carpenter lab

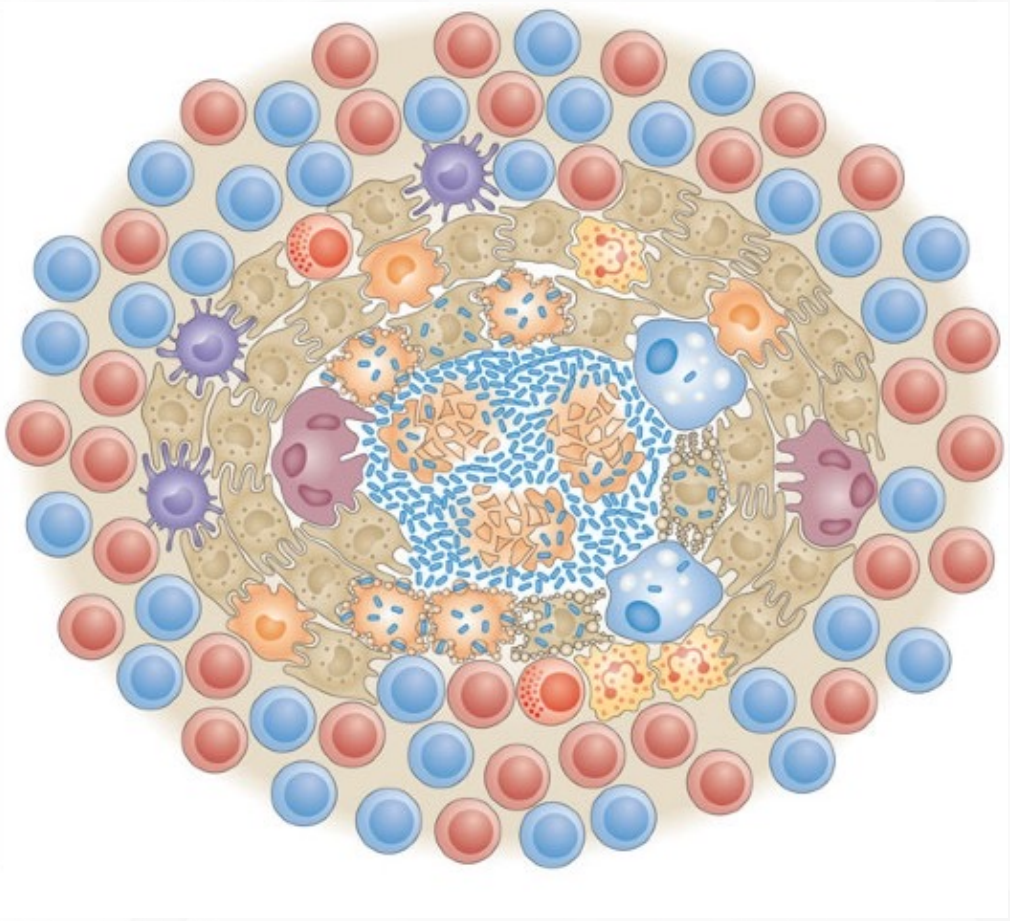
Immunity to Mtb

- **Alveolar macrophages are the first defenders**, phagocytosing the bacteria and initiating antimicrobial responses.
- **Activated macrophages produce ROS/RNS** that contribute to early bacterial control
- **Dendritic cells present Mtb antigens to T cells** and migrate to draining lymph nodes to prime adaptive immunity.
- **$CD4^+$ T cells differentiate primarily into Th1 cells**, producing IFN-γ and TNF that activate macrophages and enhance intracellular killing.
- **$CD8^+$ T cells and other T subsets contribute to immune control** by cytokine production and cytotoxic activity.
- **Granuloma formation** reflects organized immune containment that limits bacterial spread but often does not achieve sterilization.

The granuloma

- Organized immune structure
- Macrophages, T cells, myeloid cells
- Limits spread but enables persistence





The granuloma as a dynamic immune microenvironment.

image credit: Ramakrishnan et al. 2012

Latent vs active TB

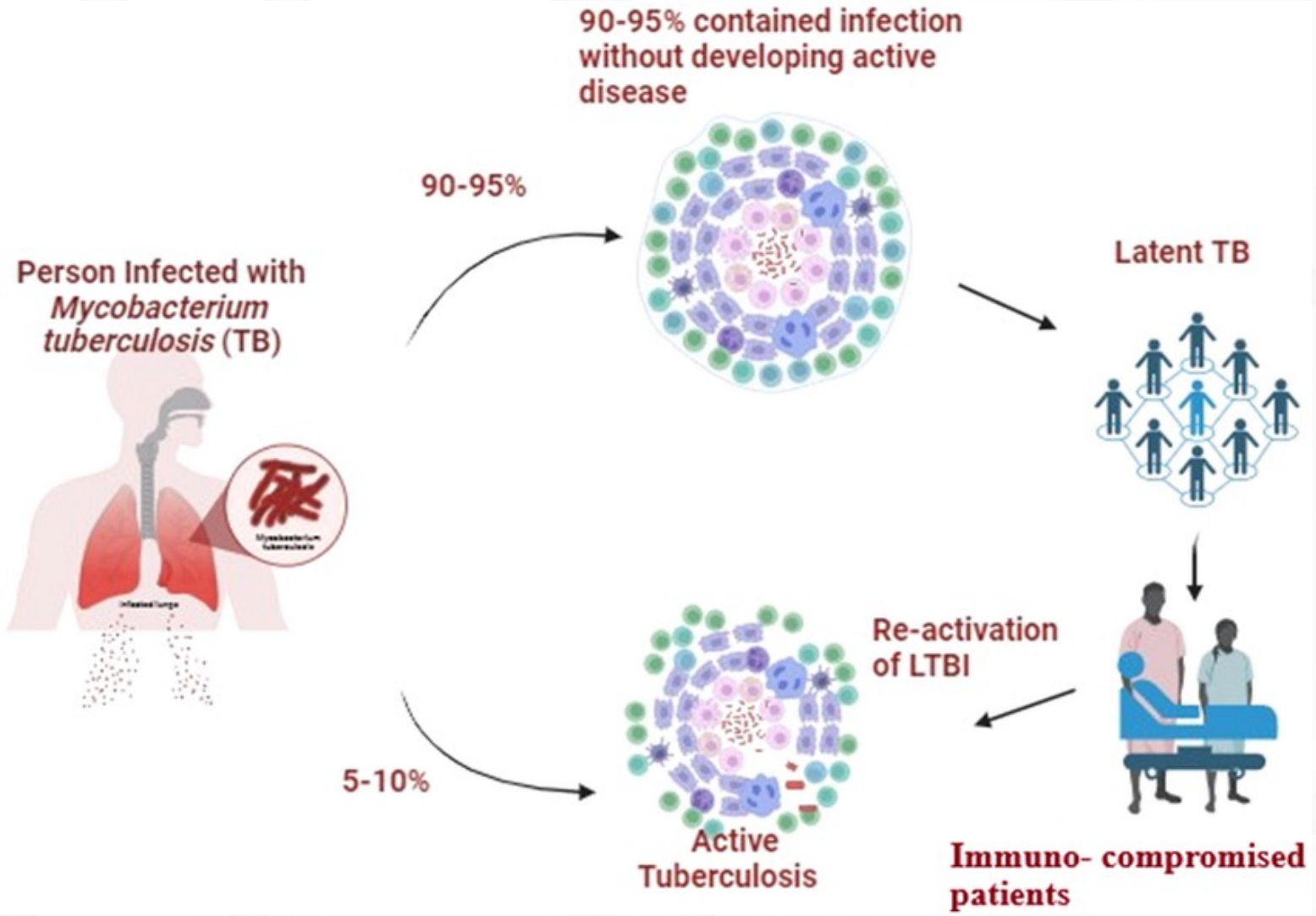


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image credit: Palaniev et al. 2023

Treatment for TB

Treatment for drug **susceptible** strains

Standard 6-month regimen:

Intensive phase (2 months):

- Isoniazid
- Rifampin
- Pyrazinamide
- Ethambutol

Continuation phase (4 months):

- Isoniazid
- Rifampin

Treatment for drug **resistant** strains

- Bedaquiline
- Pretomanid
- Linezolid

Treatment: 18-24 months

More toxic, less effective

Drug-resistant TB accounts for about

1 in 3

deaths from antimicrobial resistance

image credit: TB Alliance

Any mechanisms that we can target to kill drug resistant strains?

- Respiration is essential for Mtb survival in vivo
- Disrupting respiration collapses bacterial energy homeostasis.
- Targeting metabolism has become a cornerstone of TB therapy.

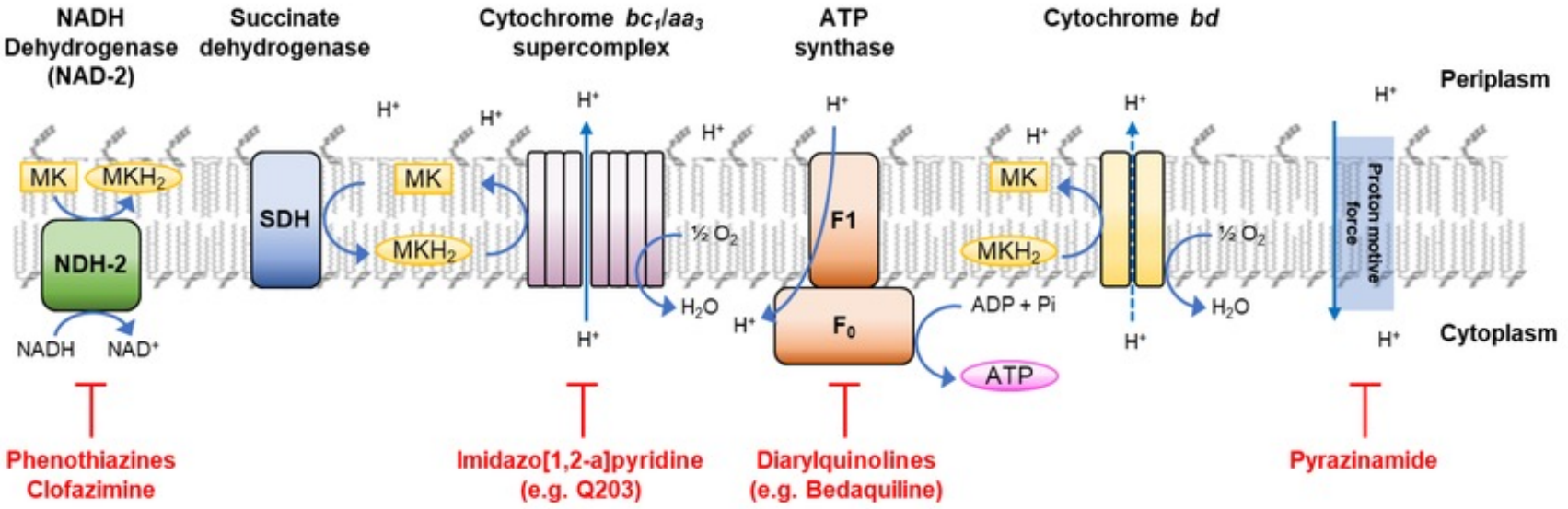

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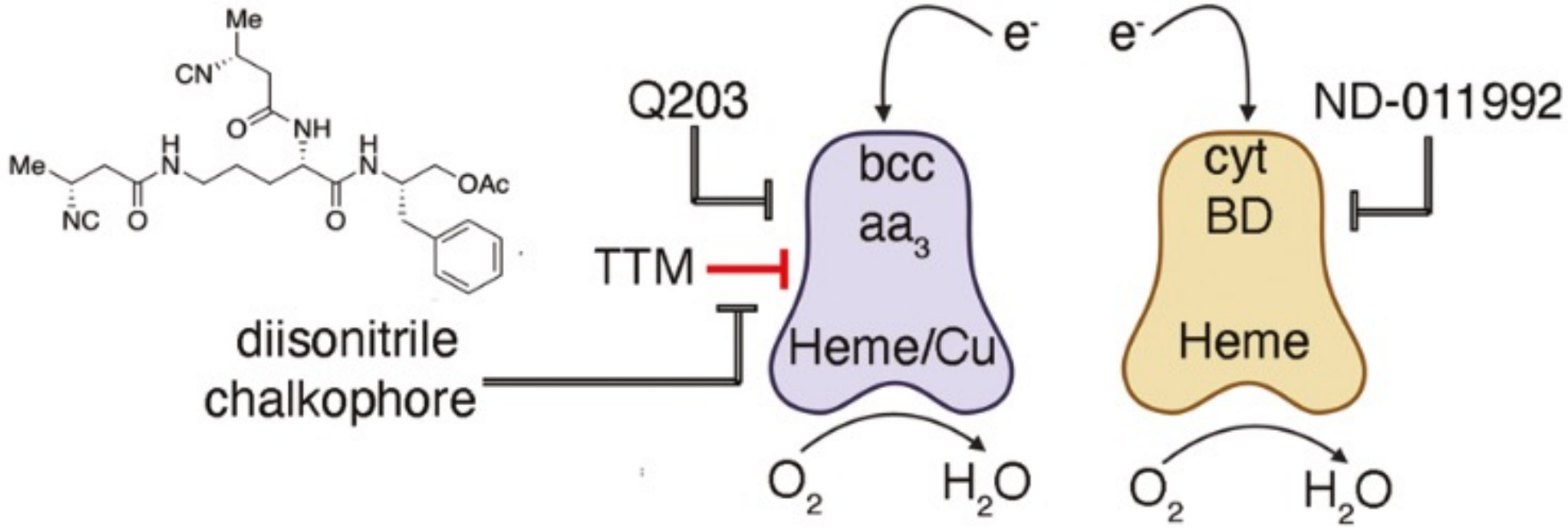
image credit: Brown et al. 2020

Chalkophores are required to maintain the function of respiratory chain in Mtb



Buglino and Ozakman *et al.*, Elife 2025

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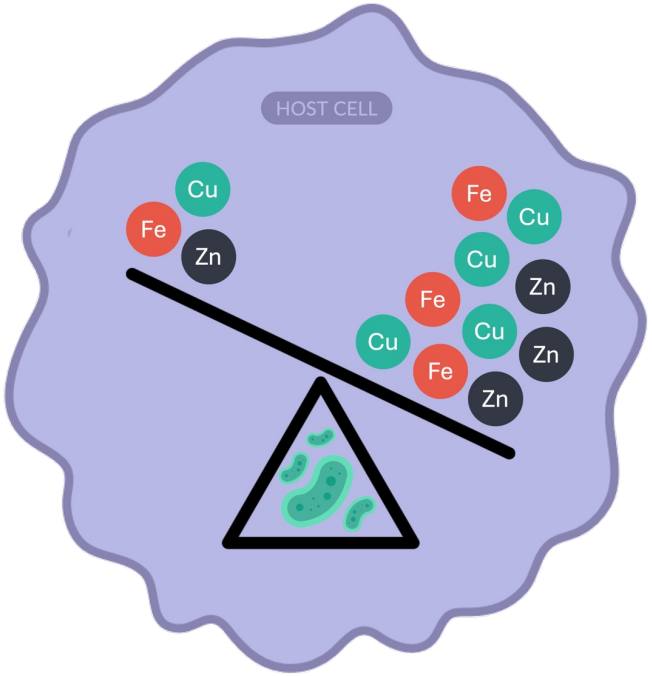

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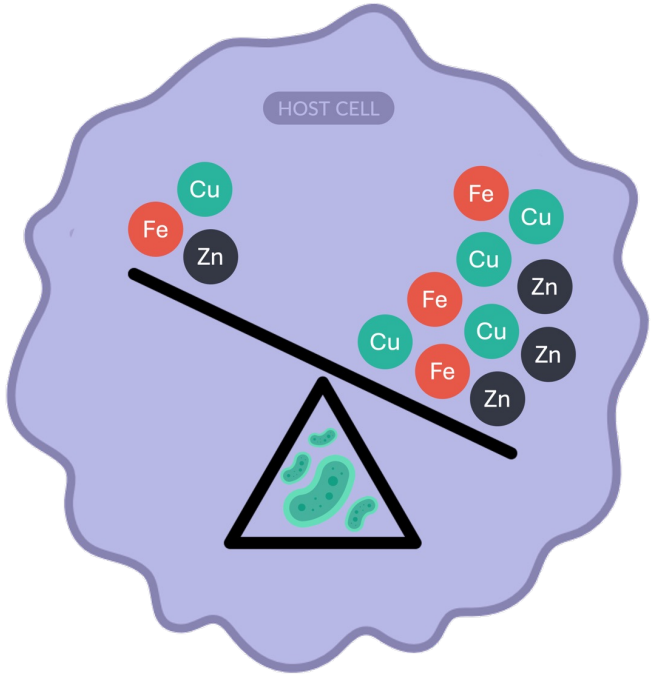

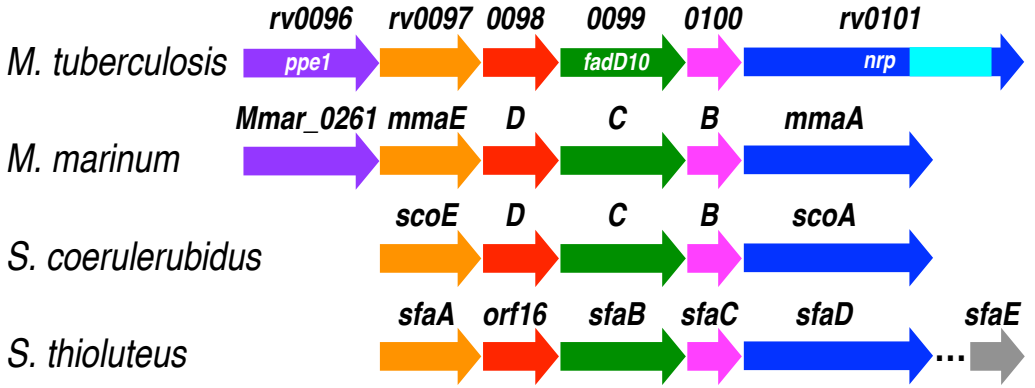

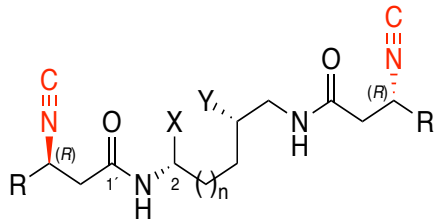

	R	n	X	Y
1 (SF2768)	Me	1	CH(OH)–*Y*	*X*–O
2 (*S. coeruleorubidus*)	Me	1	CH_2OAc	H
3 (*S. coeruleorubidus*)	Me	1	CH_2OH	H
4 (*M. marinum*)	$(CH_2)_6Me$	1	COOH	H
5 (*M. marinum*)	$(CH_2)_8Me$	1	COOH	H
6 (SF2369)	Me	0	CH_2OH	H
7 (*M. tuberculosis*)	$(CH_2)_{10\text{-}16}Me$	0	Phe-CH_2OH	H

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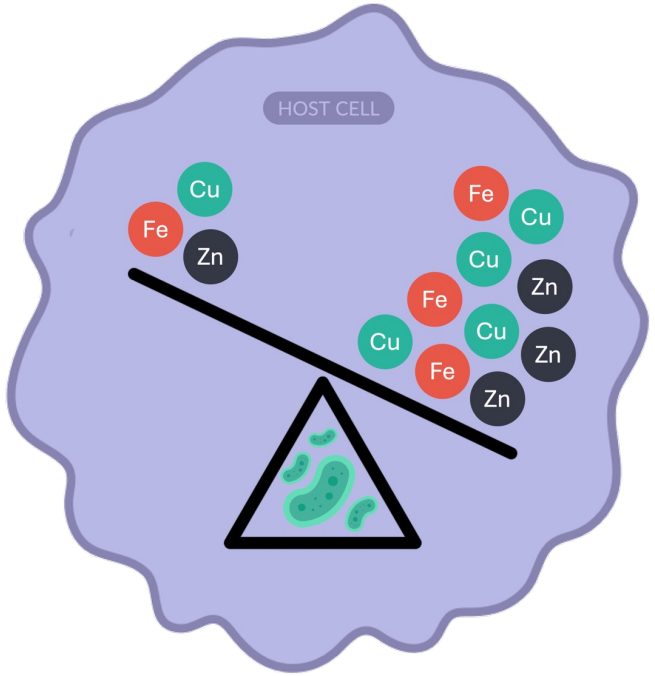

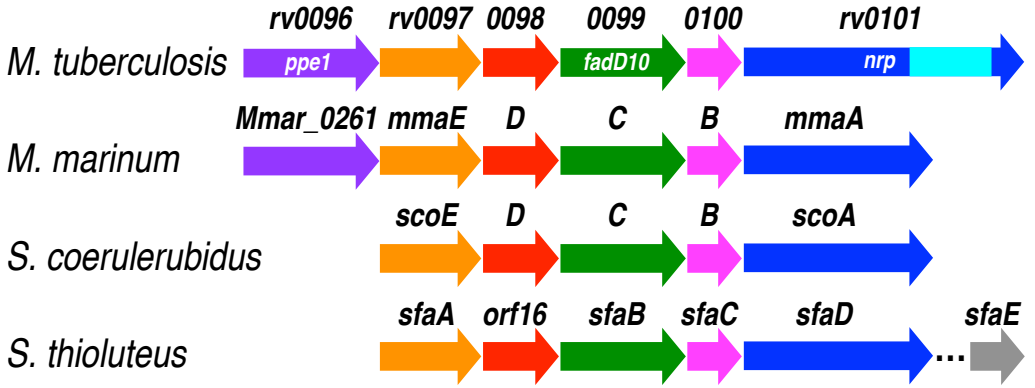

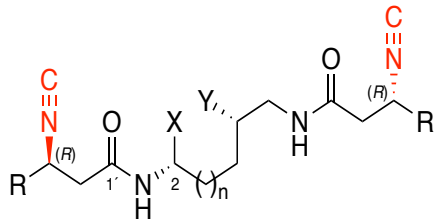

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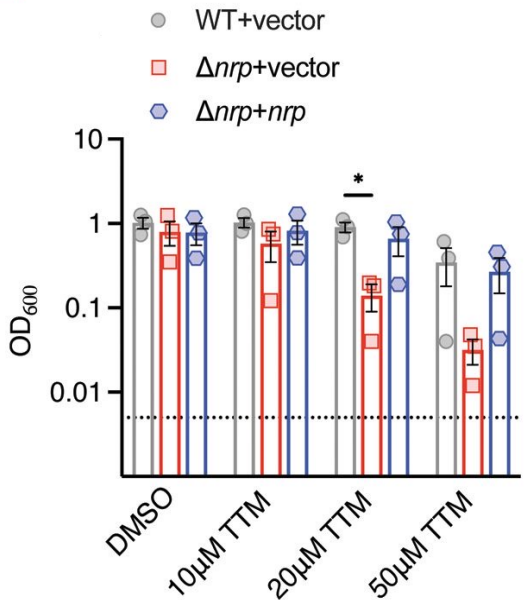

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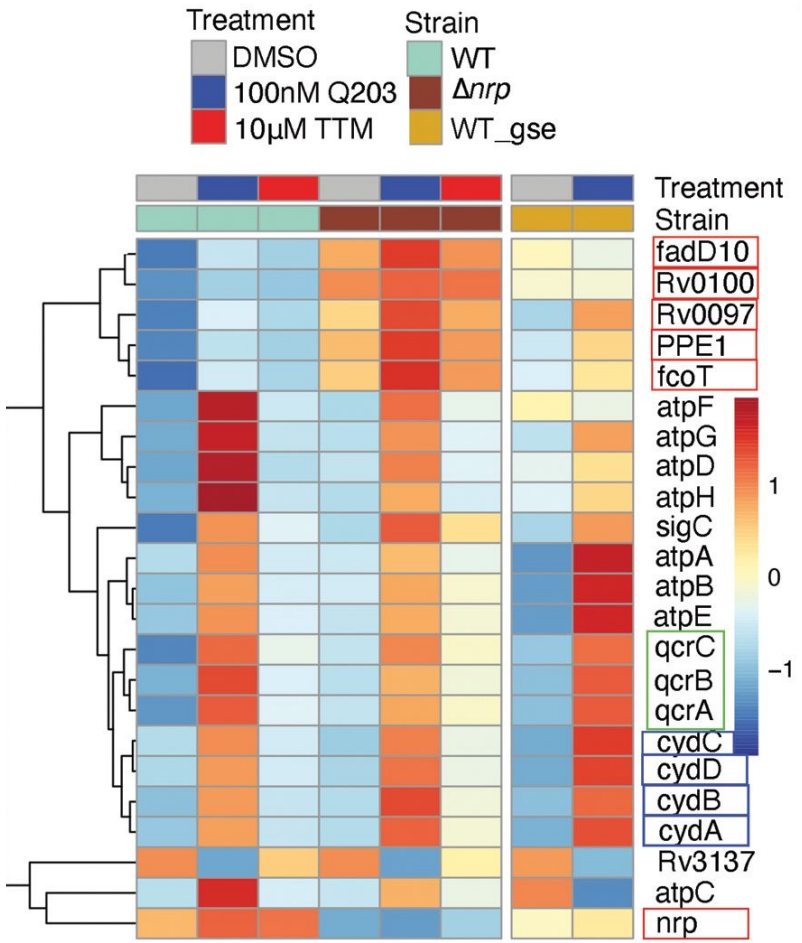

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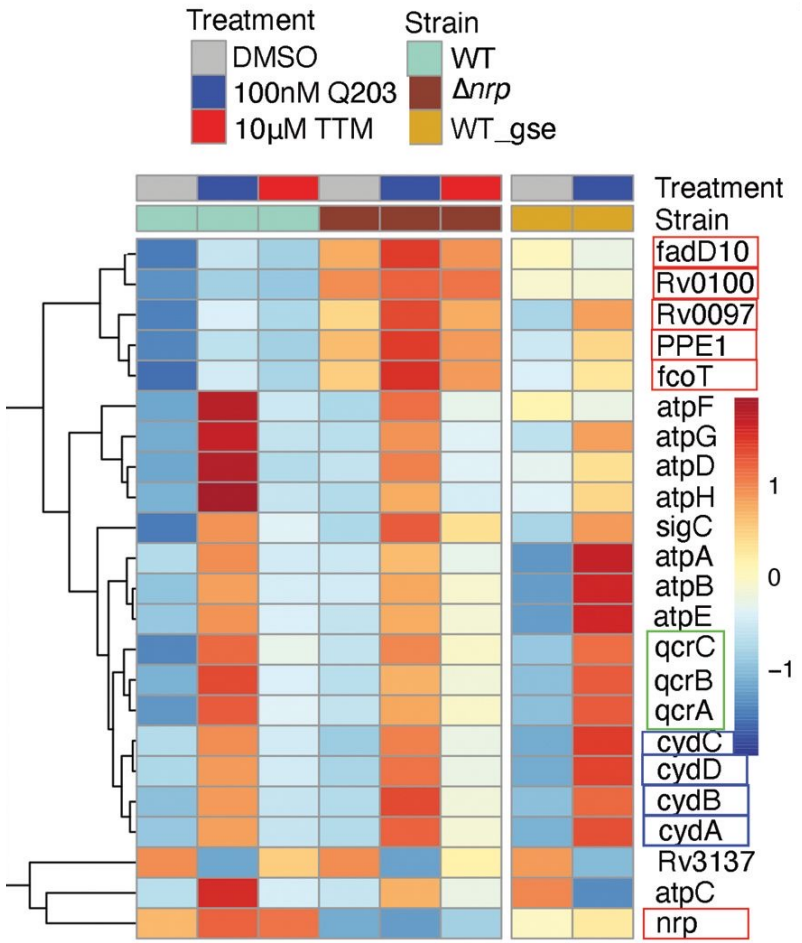

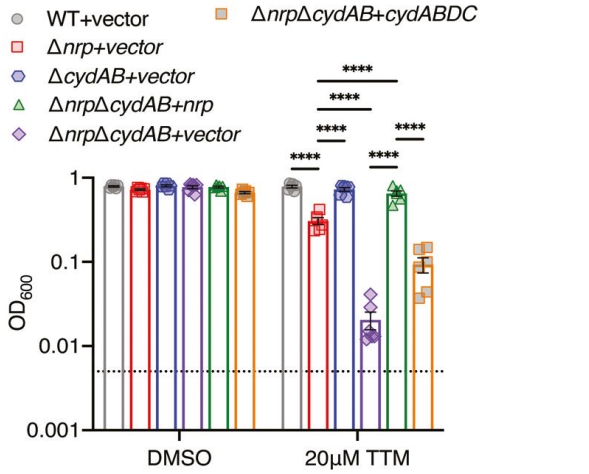

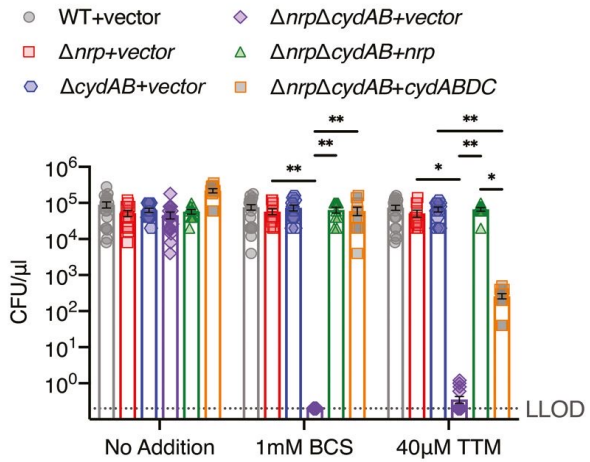

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Diisonitriles maintain oxidative phosphorylation under Cu starvation

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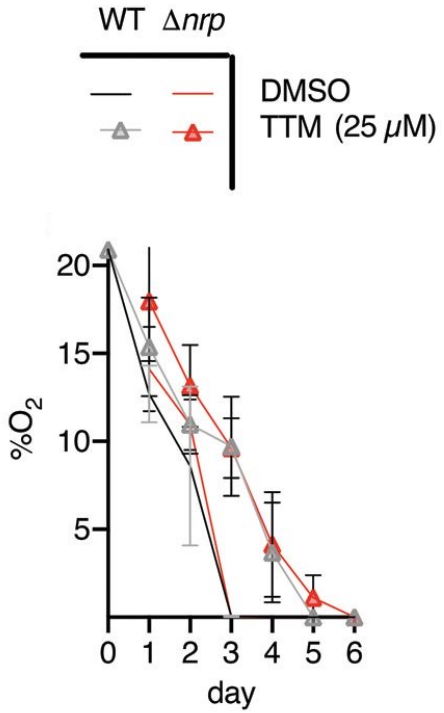

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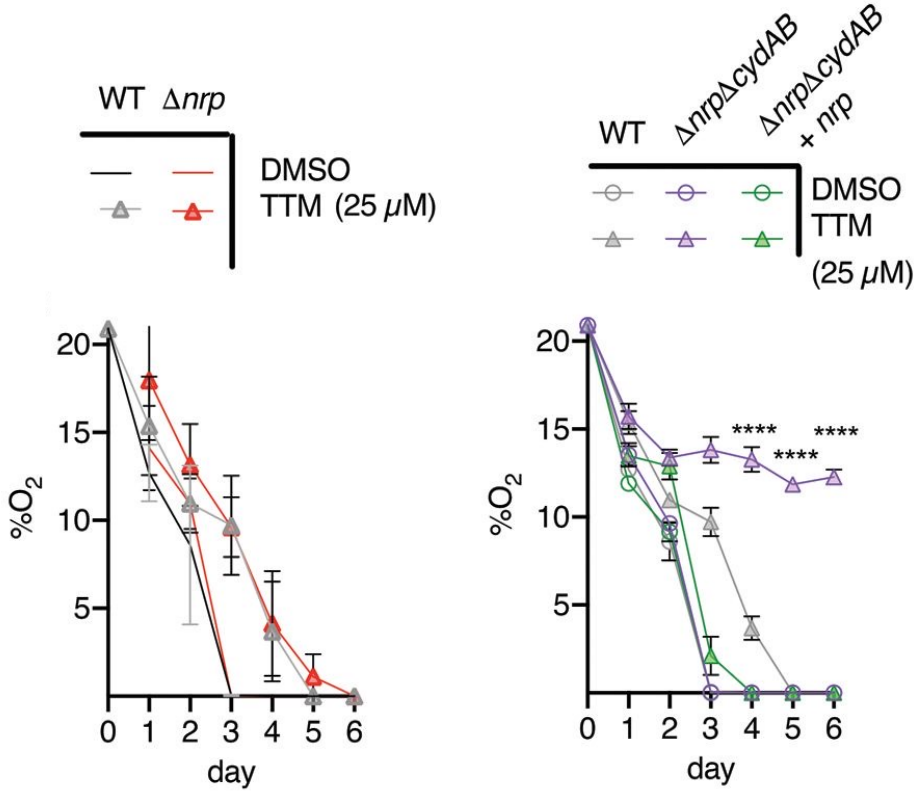

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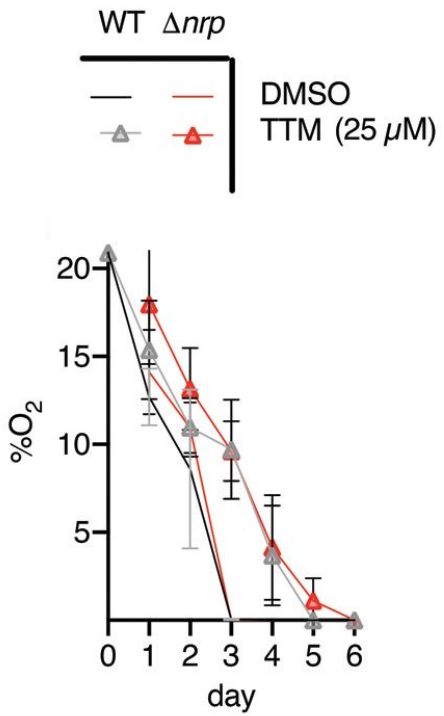

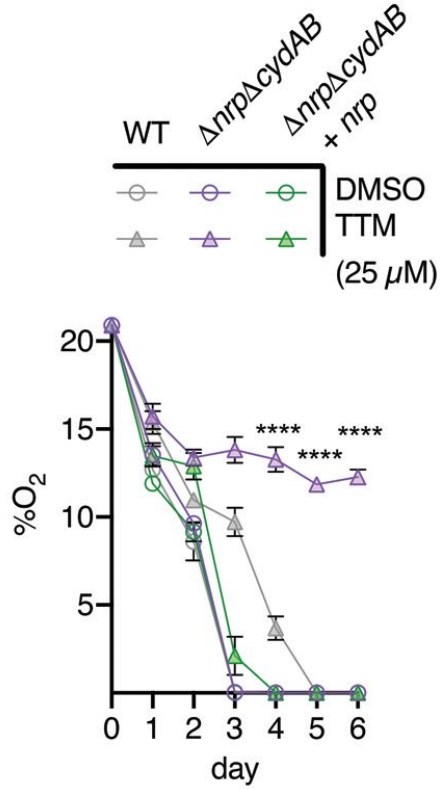

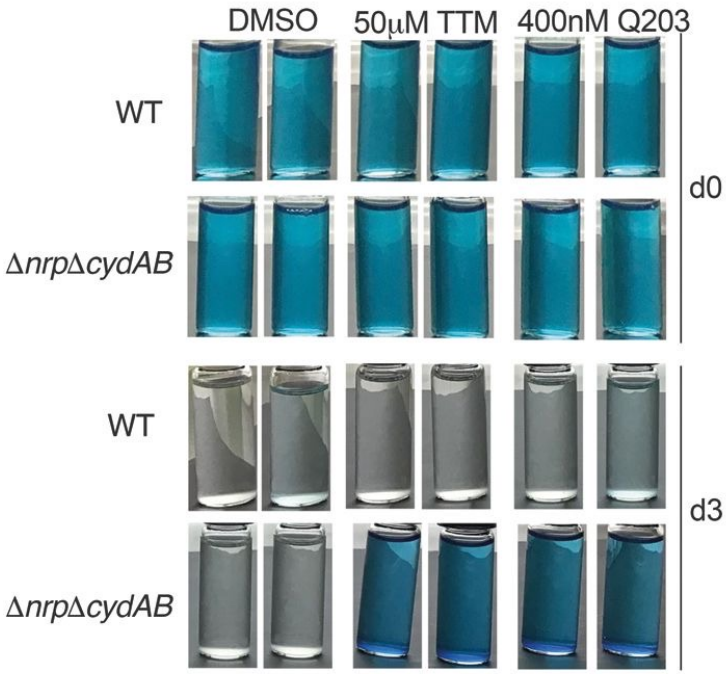

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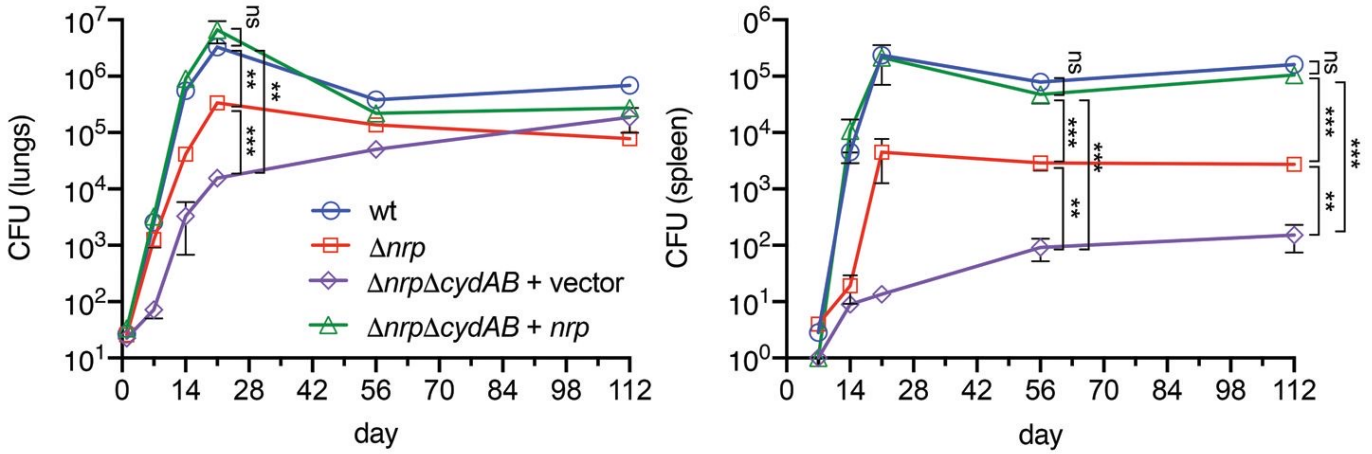
Respiratory chain flexibility is critical for Mtb virulence



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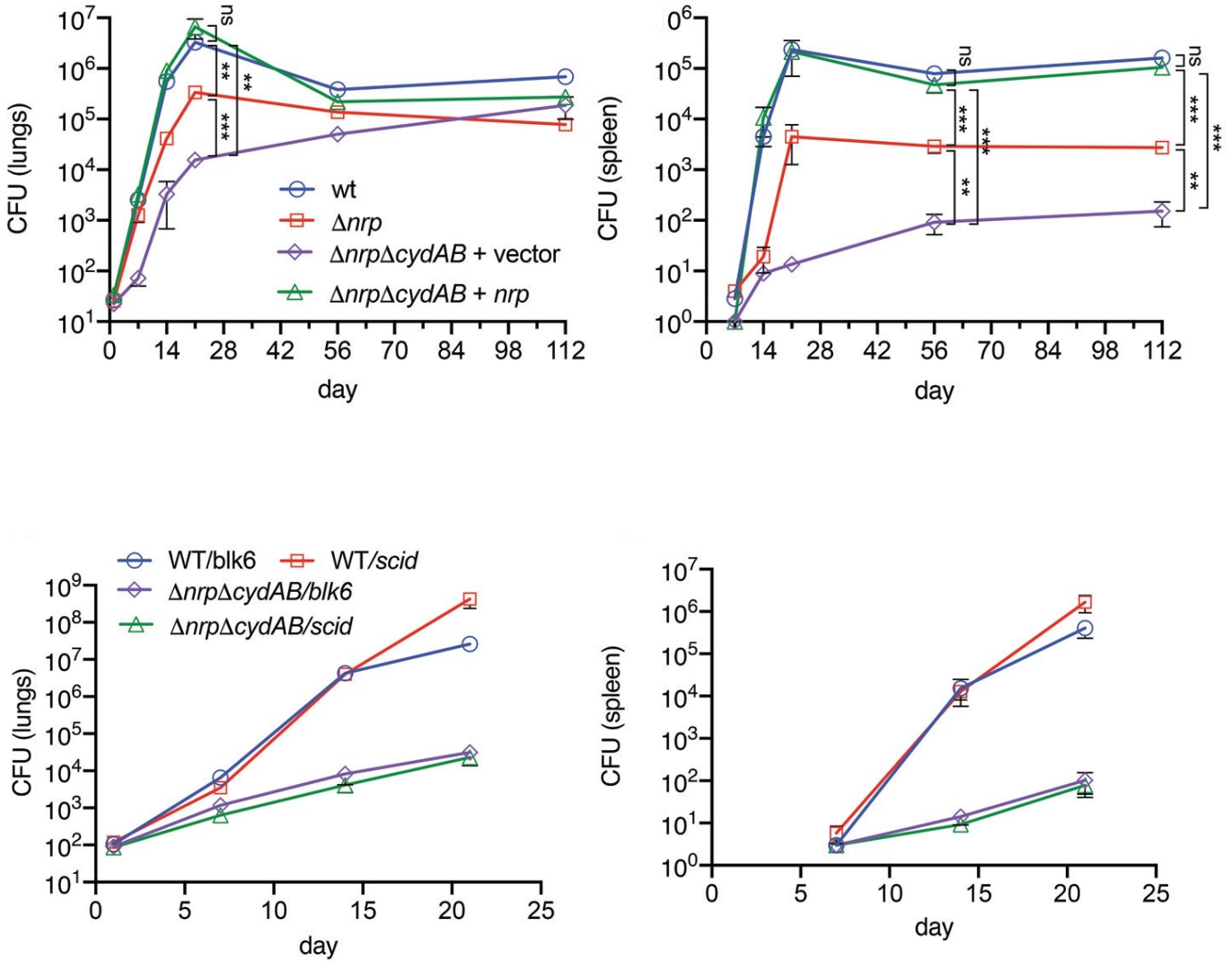

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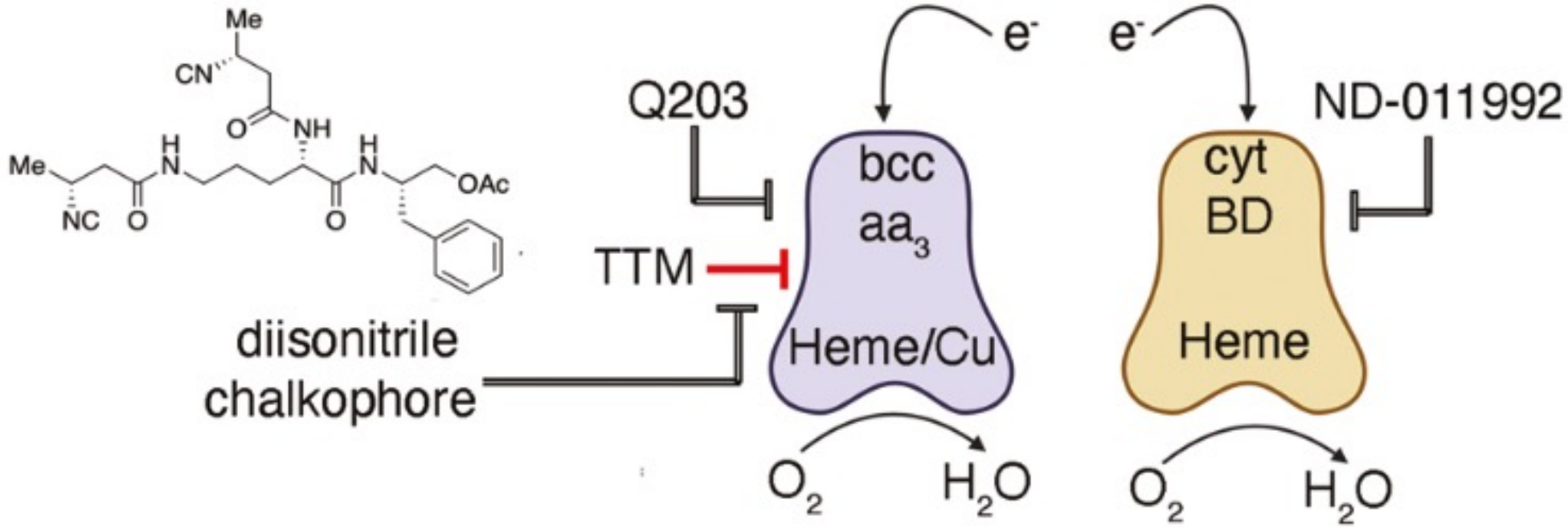

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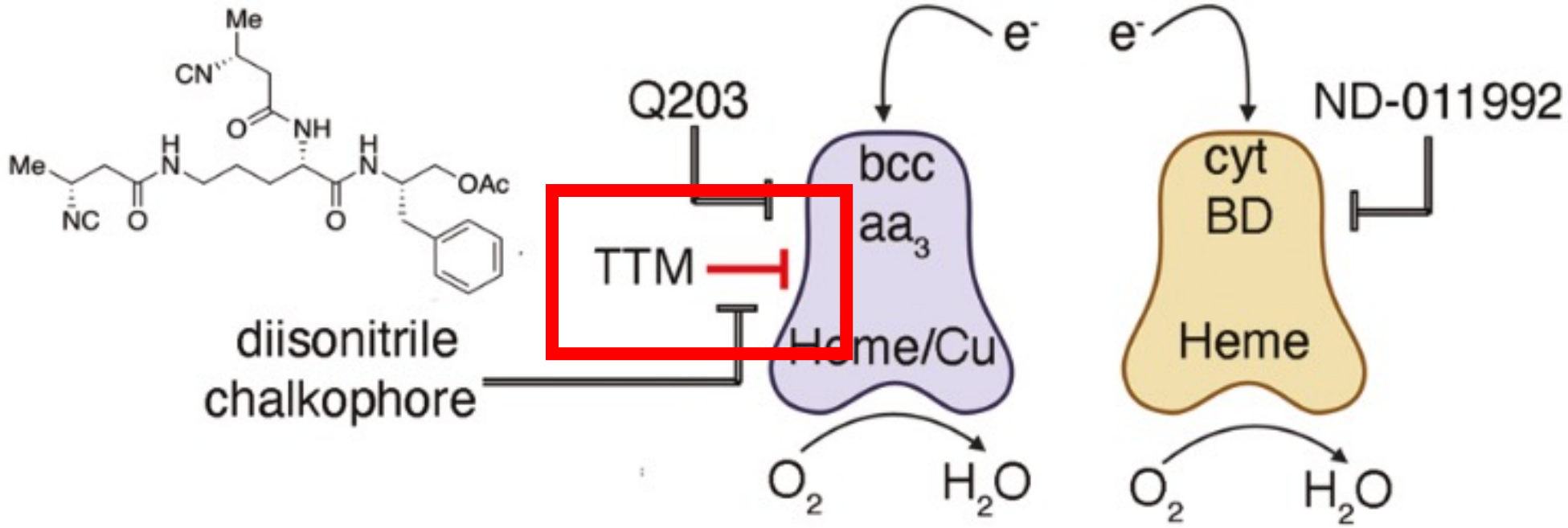
Buglino and Ozakman *et al.*, Elife 2025

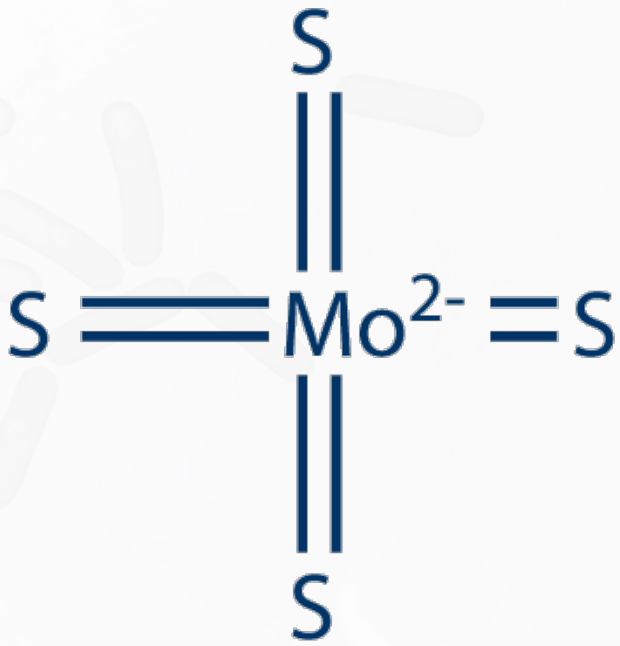
Respiratory chain flexibility is critical for Mtb virulence



Buglino and Ozakman *et al.*, Elife 2025

How do we model host copper limitation?

- We use tetrathiomolybdate (TTM) to chelate copper.
- TTM binds copper with high affinity.
- This creates a controlled copper-starved environment.
- It allows us to isolate the metabolic consequences.



TTM was developed for other diseases

- TTM has been used to treat Wilson disease (copper overload).
- Copper chelation has been explored in cancer to limit angiogenesis.
- A therapeutic tool from one disease enabled mechanistic discovery in another.
- Cross-disease knowledge accelerates research.

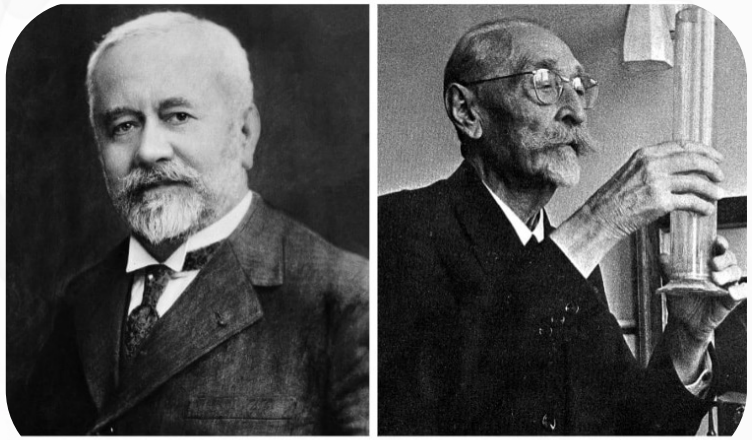
Maiti *et al.*, 2021

ACT III

BCG and what does it teach us?

BCG: A vaccine that became immunotherapy

- Attenuated strain of *Mycobacterium bovis*
- Developed 1908-1921
- Albert Calmette & Camille Guérin at Institut Pasteur
- Live attenuated vaccine
- Only licensed vaccine for TB and is part of routine newborn immunization in over 180 countries.



Albert Calmette

Camille Guérin

Memorial Sloan Kettering Cancer Center

Image source: Wikimedia, Scientific American

BCG is not the cure for TB

BCG is highly effective (≈70–90%) at preventing severe childhood TB, including:

- TB meningitis
- Disseminated (miliary) TB

Protection against pulmonary TB (PTB) is highly variable, ranging from:

- ~80% efficacy in some populations
- 0% protection in others

Despite variability, BCG remains the most widely administered vaccine worldwide.

Why BCG is not the cure for TB?

Why BCG is not the cure for TB?

Reasons for variable efficacy include:

- Human genetic diversity
- Mycobacterial strain differences
- Exposure to environmental mycobacteria
- Coinfections (viral or parasitic)
- Geographic and socioeconomic factors

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Image source: New Scientist

Immunity to BCG

Innate activation

- Recognition by macrophages & dendritic cells
- ROS and RNS production
- Cytokine and chemokine release
- Neutrophil recruitment

Adaptive priming

- Dendritic cell migration to lymph nodes
- Activation of $CD4^+$ and $CD8^+$ T cells
- Differentiation into Th1, Th17, Th2 subsets
- Activation of B cells
- Cytotoxic responses

Memory

- Formation of memory $CD4^+$ and $CD8^+$ T cells
- Memory B cells
- Tissue-resident immune populations
- Enhanced responsiveness upon re-exposure

Why BCG is protective for babies but not adults?

Infant Immune System

- Immunologically naïve
- Strong Th1 priming after BCG

Adult Immune System

- Prior environmental mycobacterial exposure
- Pre-existing immune imprinting
- Heterogeneous memory responses
- Reduced incremental benefit

Context Matters!

- Microbiome differences
- Baseline inflammation
- Geographic variation

image credit: Wikipedia

Can we still learn from BCG?

BCG and bladder cancer

- Intravesical BCG therapy (1976)
- Standard of care for non-muscle invasive bladder cancer
- Reduces recurrence and progression
- Still used today!

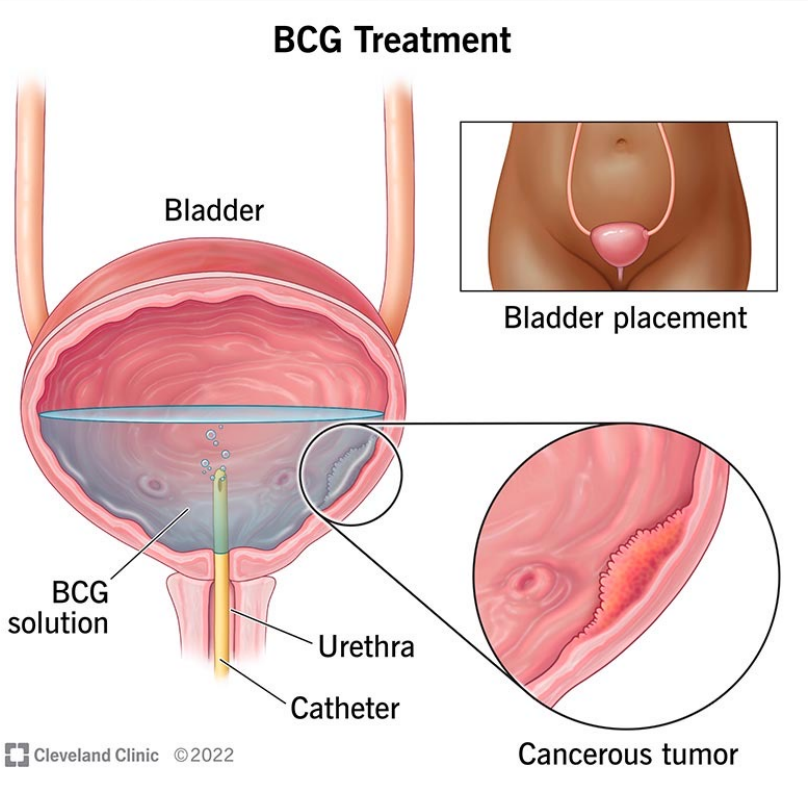

image credit: Cleveland Clinic

BCG and bladder cancer

1950s–1960s

Observations of antitumor immune effects

Experimental studies show that mycobacterial stimulation can enhance immune responses against tumors.

1976

Dr. Alvaro Morales pioneers intravesical BCG therapy

BCG is instilled directly into the bladder to treat non-muscle-invasive bladder cancer, demonstrating reduced tumor recurrence.

1980s

FDA approval of BCG for bladder cancer

BCG becomes the first approved cancer immunotherapy.

Research institutions, including centers including **MSK**, help establish its clinical effectiveness.

Further reading

Volume 43, Issue 8, 11 August 2025, Pages 1442-1459.e10

Article

Microbial cancer immunotherapy reprograms hematopoiesis to enhance myeloid-driven anti-tumor immunity

Andrew W. Daman [1 2 12], Anthony C. Antonelli [1 3 12], Gil Redelman-Sidi [4 12], Lucinda Paddock [2 5 6 13], Shireen Khayat [7 13], Mythili Ketavarapu [2], Jin Gyu Cheong [1], Leonardo F. Jurado [8], Anna Benjamin [3], Song Jiang [9], Dughan Ahimovic [1 2], Victoria R. Lawless [1 2], Michael J. Bale [1 2], Oleg Loutochin [8], Victor A. McPherson [10], Maziar Divangahi [8], Rachel E. Niec [1 11], Dana Pe'er [5 6], Eugene Pietzak [9], Steven Z. Josefowicz [1 2 14 15 *] ✉ ...Michael S. Glickman [1 3 4 14 **] ✉

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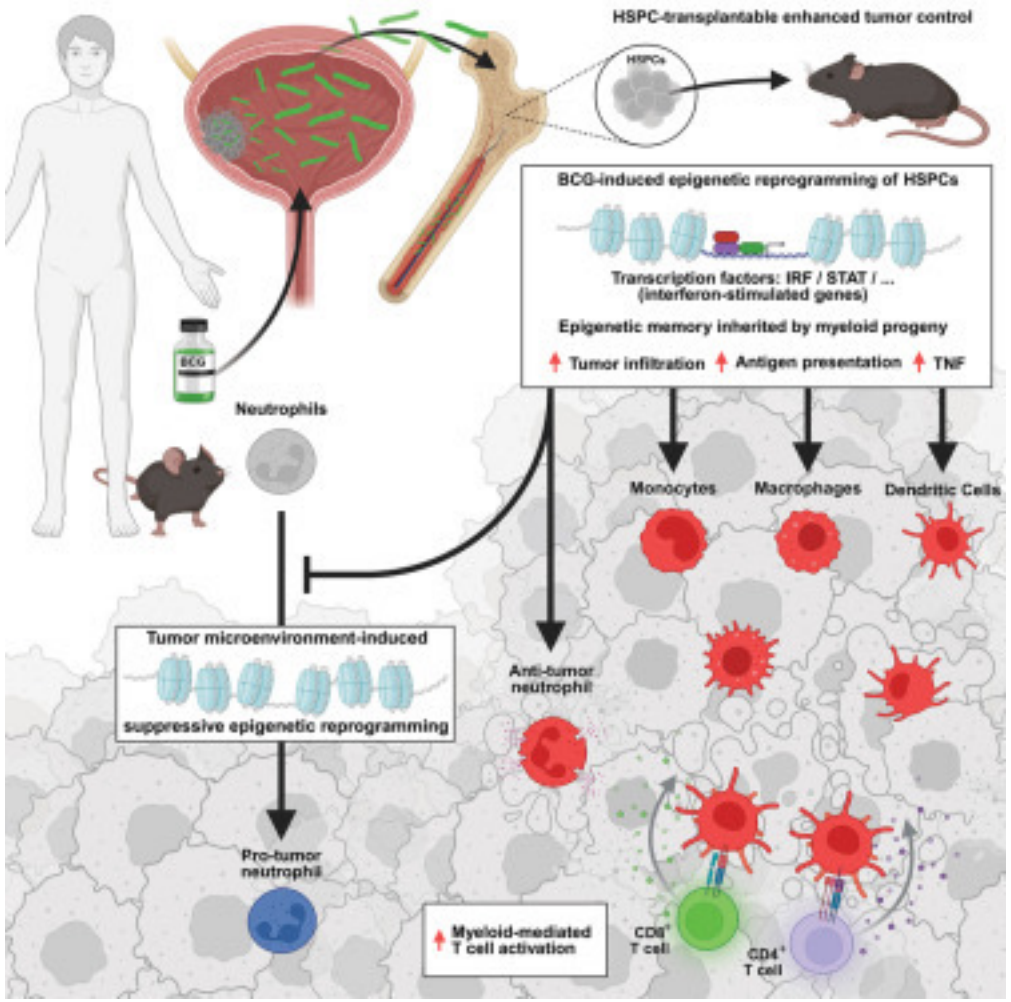


BCG and chronic metabolic diseases

Evidence under investigation:

- Long-term follow-up suggests reduced risk of type 1 diabetes in some BCG-vaccinated cohorts
- Trials exploring BCG as immune-modulating therapy in autoimmune disease

Proposed mechanisms:

- Immune tolerance recalibration
- Metabolic reprogramming of immune cells
- Shifts in inflammatory set point
- Epigenetic changes in innate immunity

BCG and Alzheimer's disease

Observational findings:

- Bladder cancer patients treated with intravesical BCG show lower rates of Alzheimer's disease in retrospective analyses
- Some studies suggest delayed onset of neurodegenerative symptoms

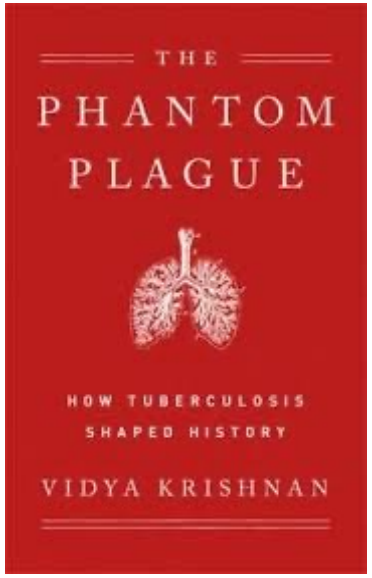
Proposed biological links:

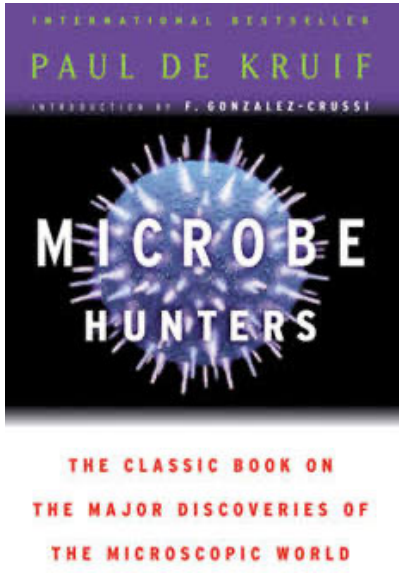
- Modulation of systemic inflammation
- Rebalancing of innate immune tone
- Possible effects on microglial activation
- Long-term immune reprogramming (trained immunity)

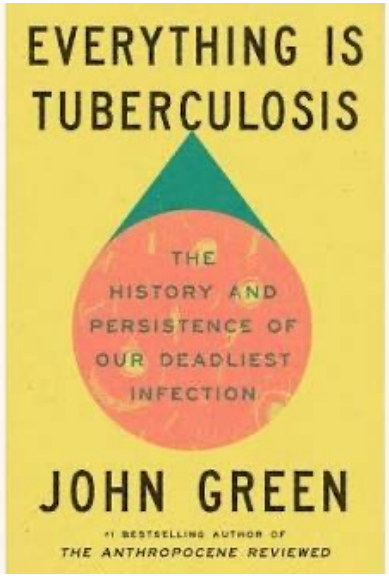
To summarize…

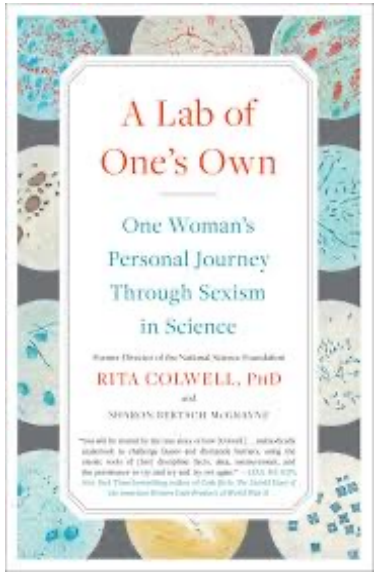
- Tuberculosis illustrates the tension between immune control and immune evasion.
- The immune system shapes pathogen metabolism but does not always achieve eradication.
- Studying these pressures reveals therapeutic vulnerabilities.
- BCG demonstrates that immune responses can be intentionally reprogrammed.
- Discoveries in infectious disease biology can inform therapies across diseases.

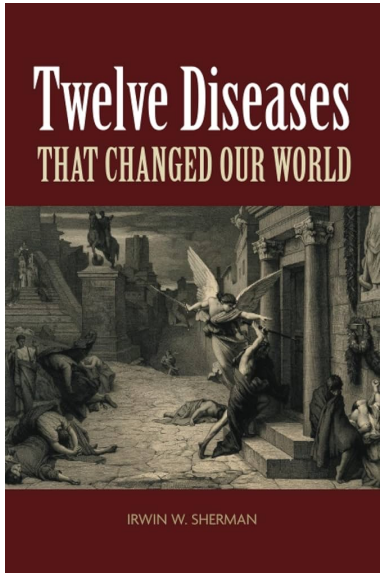
Further reading

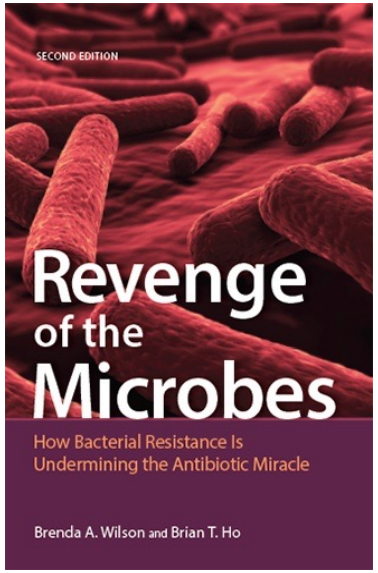


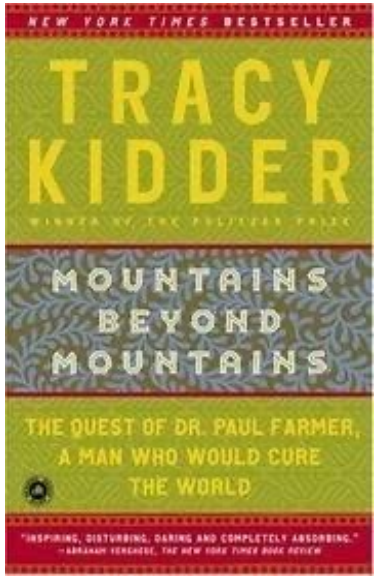


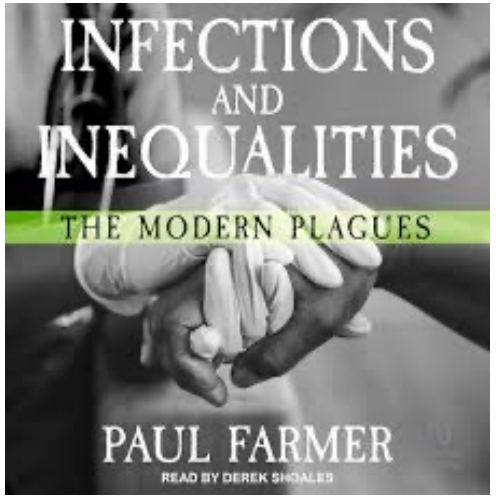


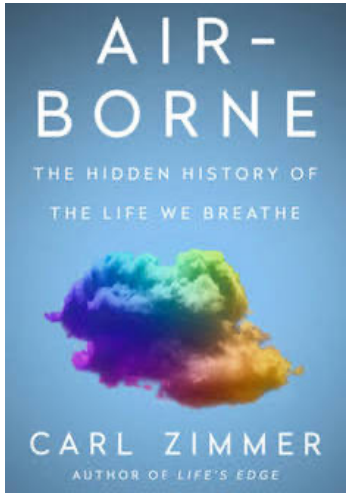


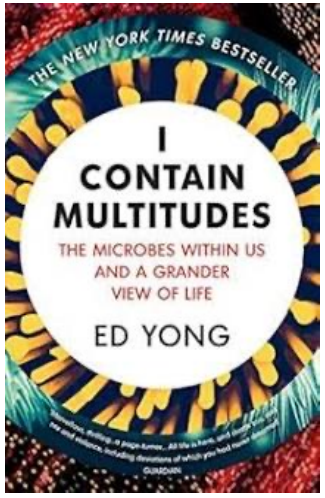












ACT IV

Your work

Borrowing biology across diseases

We’ve seen that TB, cancer, and other chronic diseases share recurring biological principles.

Scientific progress often happens when a concept escapes its original disease.

Your task: identify and transfer one.

If you studied only one disease…

Each group is assigned a disease:

- Tuberculosis
- Cancer
- HIV
- Influenza
- Autoimmune disease
- Sepsis
- Antibiotic-resistant infection

or something else of your choosing

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or something else of your choosing

1. Identify one major biological insight this disease revealed. (Think principle, not fact.)
2. Choose a completely different disease field that should borrow this insight.
3. Explain why the transfer makes biological sense.
4. Propose one research question.
5. Suggest one therapeutic implication.

If you studied only one disease…

What Counts as a “Biological Insight”?

Not:

- A specific cytokine
- A detailed pathway
- A fact from a textbook

Think bigger:

- Selection under pressure
- Chronic inflammation
- Immune evasion
- Containment vs elimination
- Loss of tolerance
- Evolution under therapy
- Dynamic immune states
- Focus on transferable logic

If you studied only one disease…

Each group should present:

- Disease assigned
- Core biological insight
- Borrowed disease field
- Why the transfer works
- One research question
- One therapeutic implication

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Each group should present:

- Disease assigned
- Core biological insight
- Borrowed disease field
- Why the transfer works
- One research question
- One therapeutic implication

You are not expected to be experts in every disease. You are expected to think mechanistically and comparatively.