TB Pathogenesis and Drug Targets

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TRTC TUBERCULOSIS RESEARCH & TRAINING CENTER
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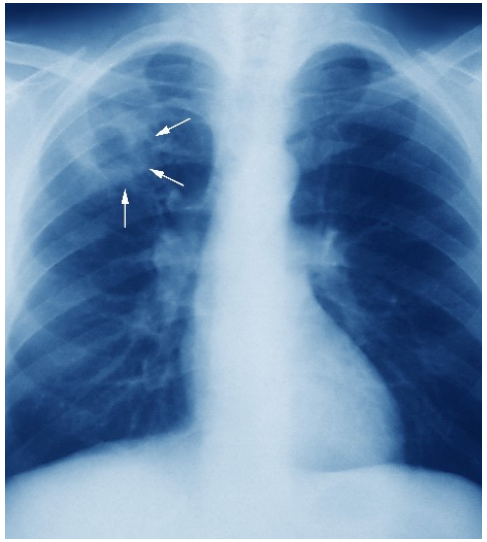
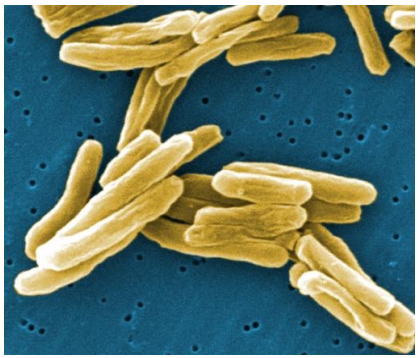
What is Tuberculosis?

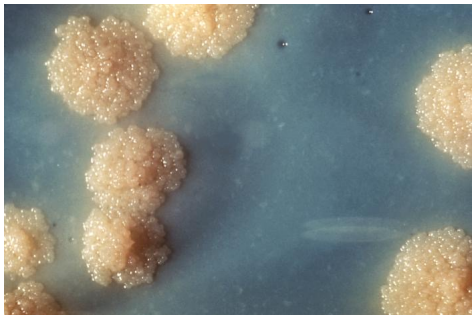


- The clinical picture of a tuberculosis patient:
  - Thin, febrile, coughing (often blood)

What is *Mycobacterium tuberculosis*?



- Aerobic, non-spore-forming, nonmotile bacilli
- Very slow growing
  - Generation time ~20 hours
  - 3 weeks to form a visible colony
  - Other mycobacteria range from 2 hr generation time to unculturable
- Waxy coat, rich in high molecular weight mycolic acid
- Lack "classical" virulence factors such as flagella and toxins

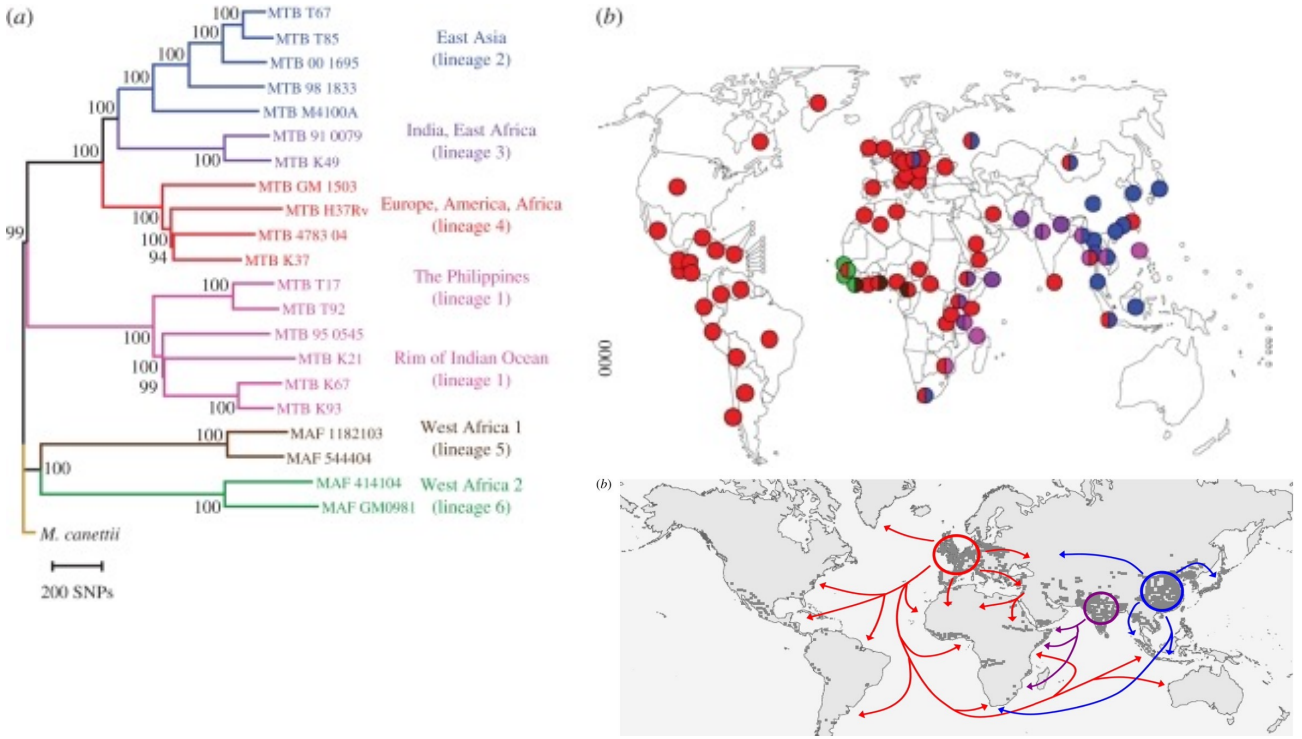


Where did MTB come from?

- Pathogenic mycobacteria evolved from soil-dwelling bacteria (bogs)

- Over 120 species

MTB: Seven global lineages

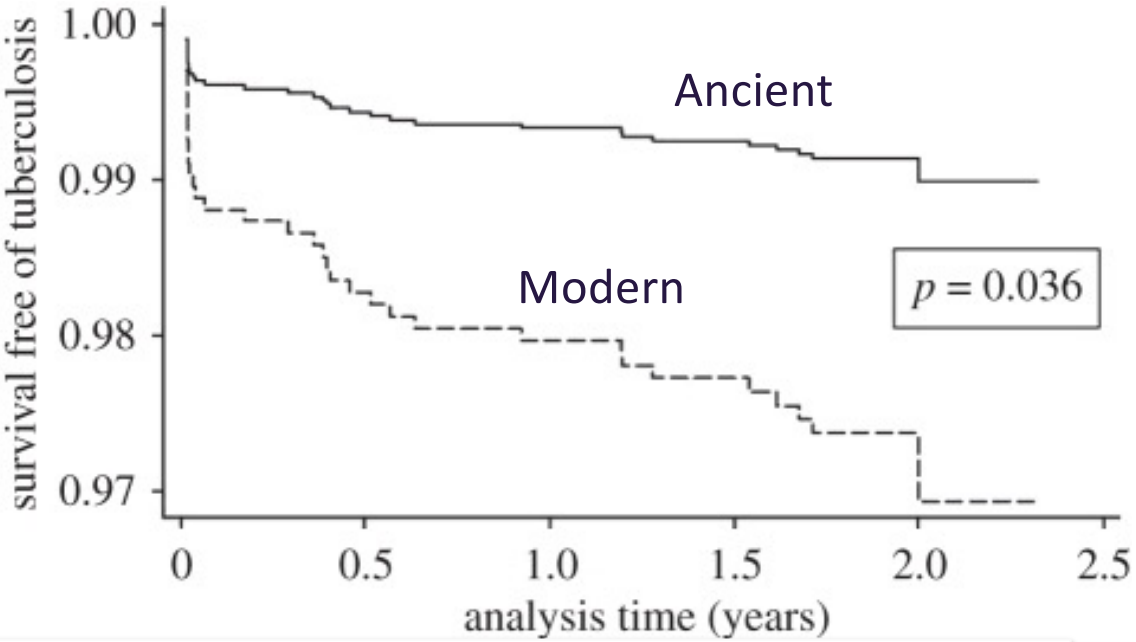


Gagneaux, Philos Trans R Soc Lond B Biol Sci. 2012; 367: 850–859

Comas I., et al, 2010. Nat. Genet. 42, 498–503

Comas I., et al, 2013. Nat. Genet. 45, 1176–82

Differences between modern and ancient MTB lineages



Strain-specific differences: an important current research topic

Gagneaux, Philos Trans R Soc Lond B Biol Sci. 2012; 367: 850–859

TB disease progression

Transmission

5%

ACTIVE infection
10 M / Yr

DEATH
1.8 M / Yr

95%

LATENT infection
2 B globally

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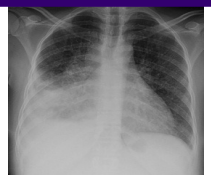
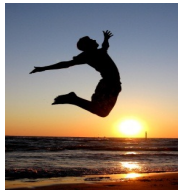
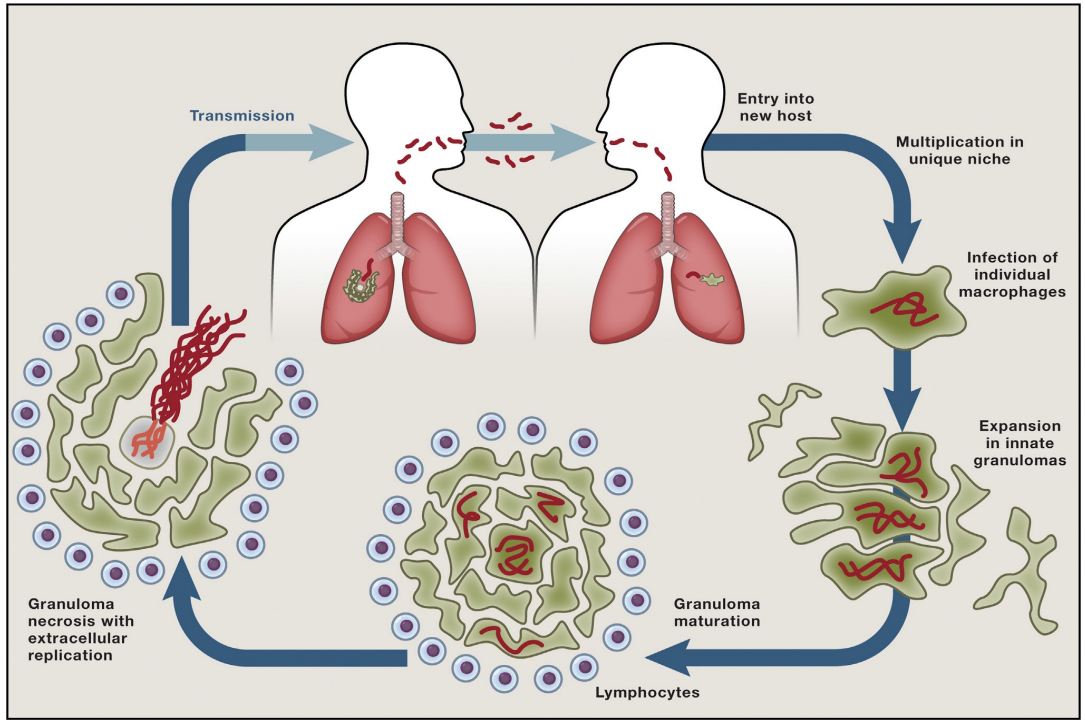




CURE

The TB Lifecycle



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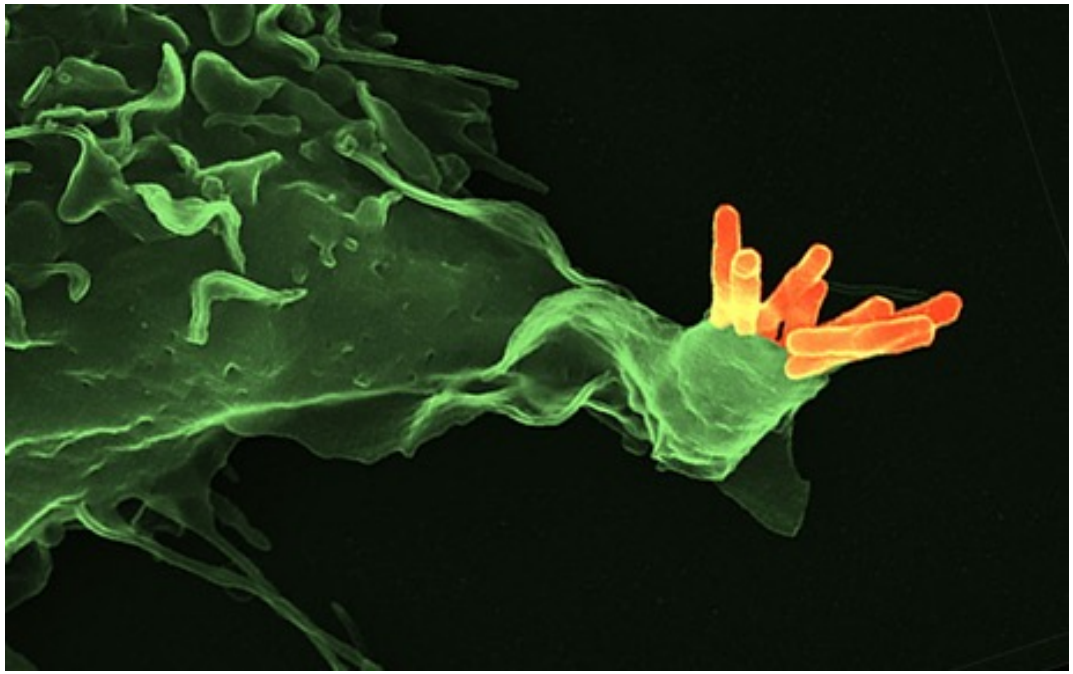
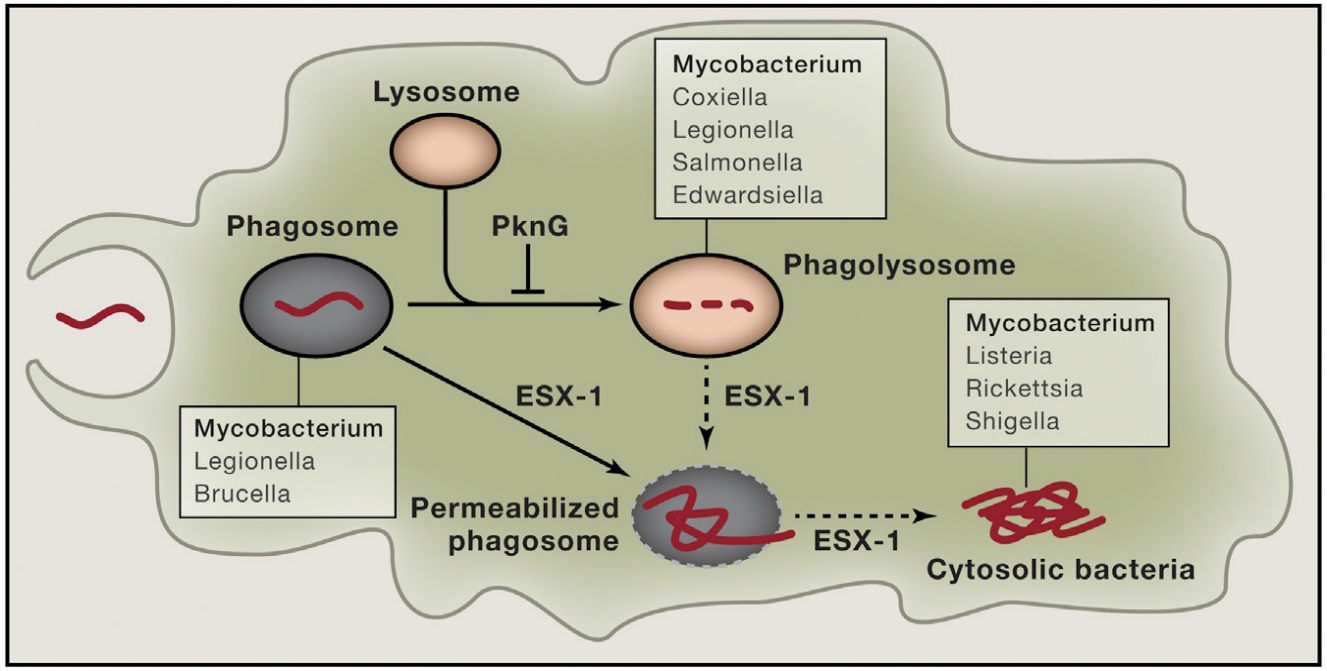
Cambier et al. 2014 Cell

Macrophage taking up MTB

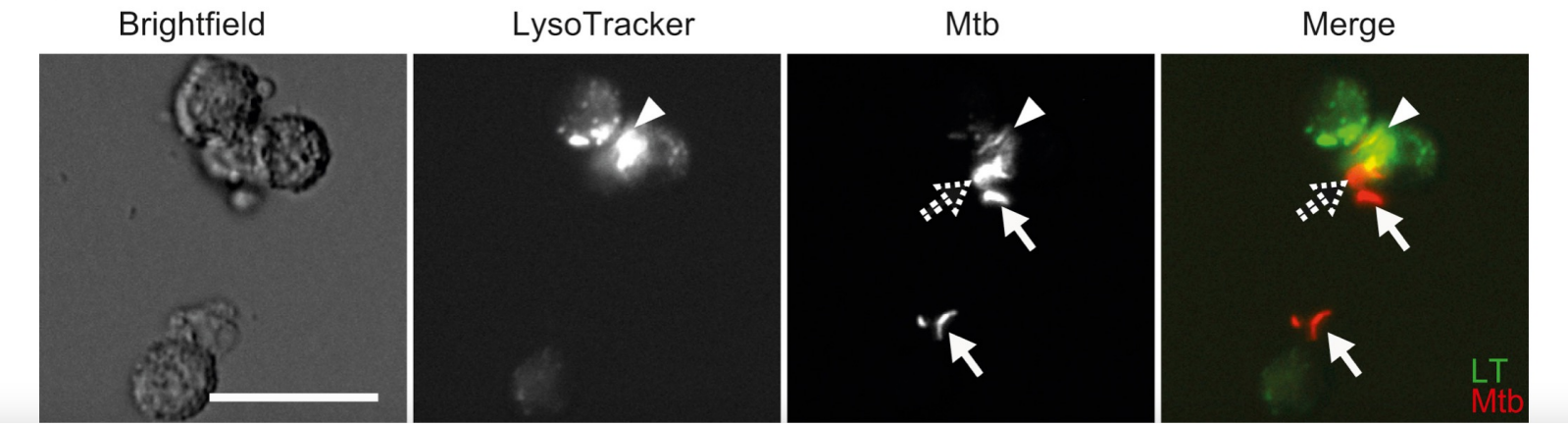


The fate of (myco)bacteria in the macrophage



Cambier et al. 2014 Cell

MTB inside macrophages

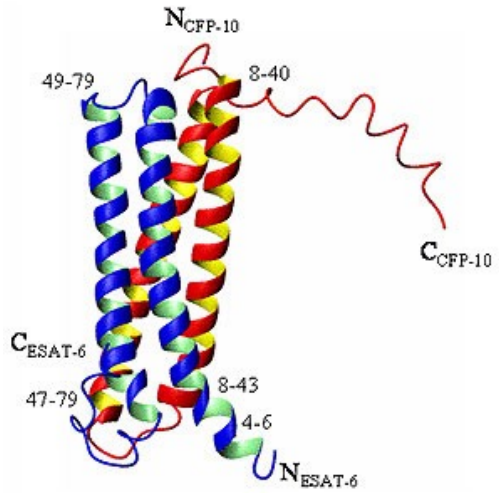


Levitte et al. Cell Host and Microbe 2016

Type VII secretion and MTB Virulence

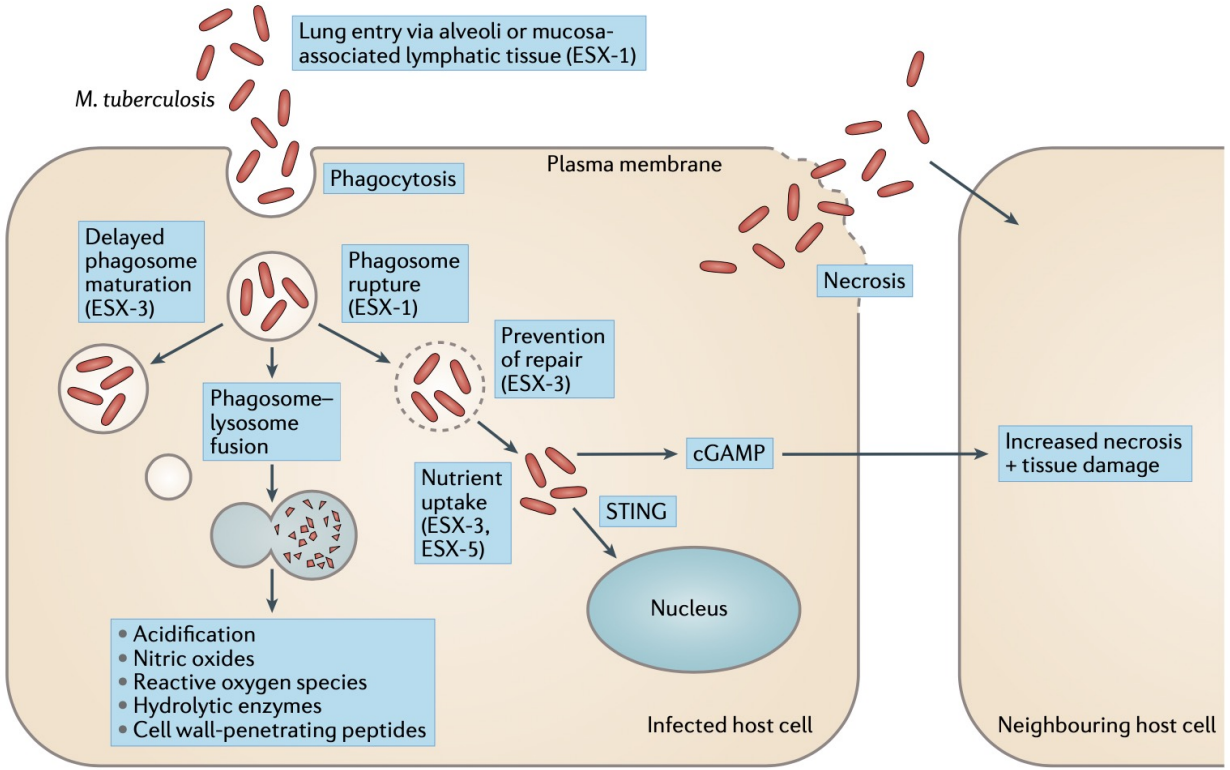
- Five different mycobacterial type VII secretion systems named ESX-1 to ESX-5
- Dedicated protein transport machines
  - Play crucial roles in the life cycle of pathogenic mycobacteria including metabolite uptake and immune evasion
- These systems are prime candidates for targeted drug discovery

ESX-1 and MTB Virulence



- 12 protein, Type VII secretion system
- Essential for virulence
  - Deleted from BCG
- Also referred to as RD1
- Substrates include ESAT-6 (EsxA) and CFP-10 (EsxB)

Roles of MTB type VII secretion systems



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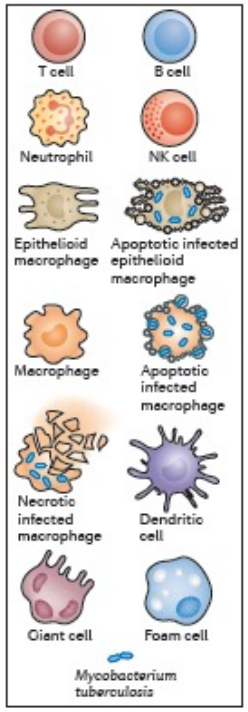
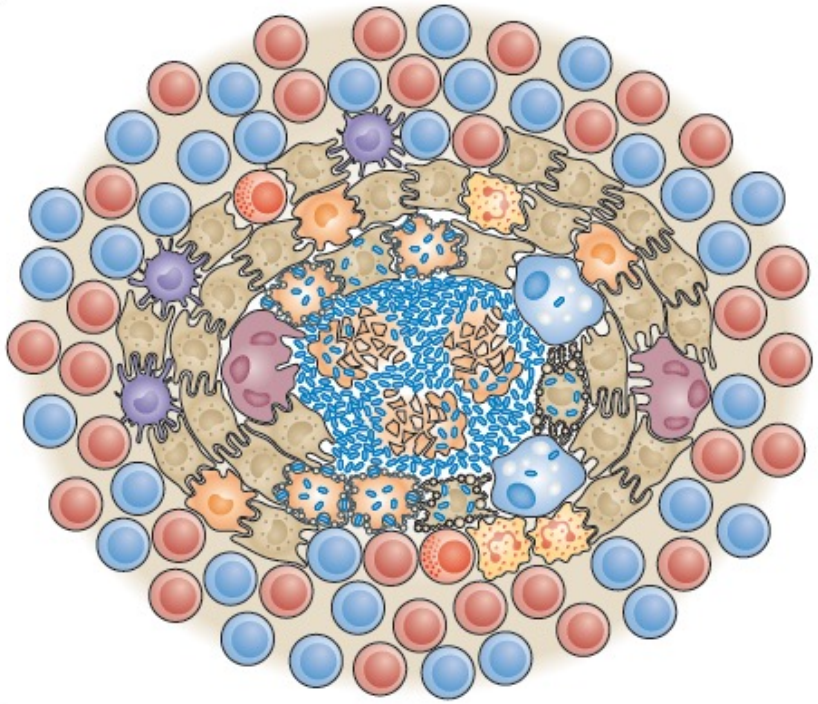
Rivera-Calzada et al. 2021 Nature Reviews Microbiology

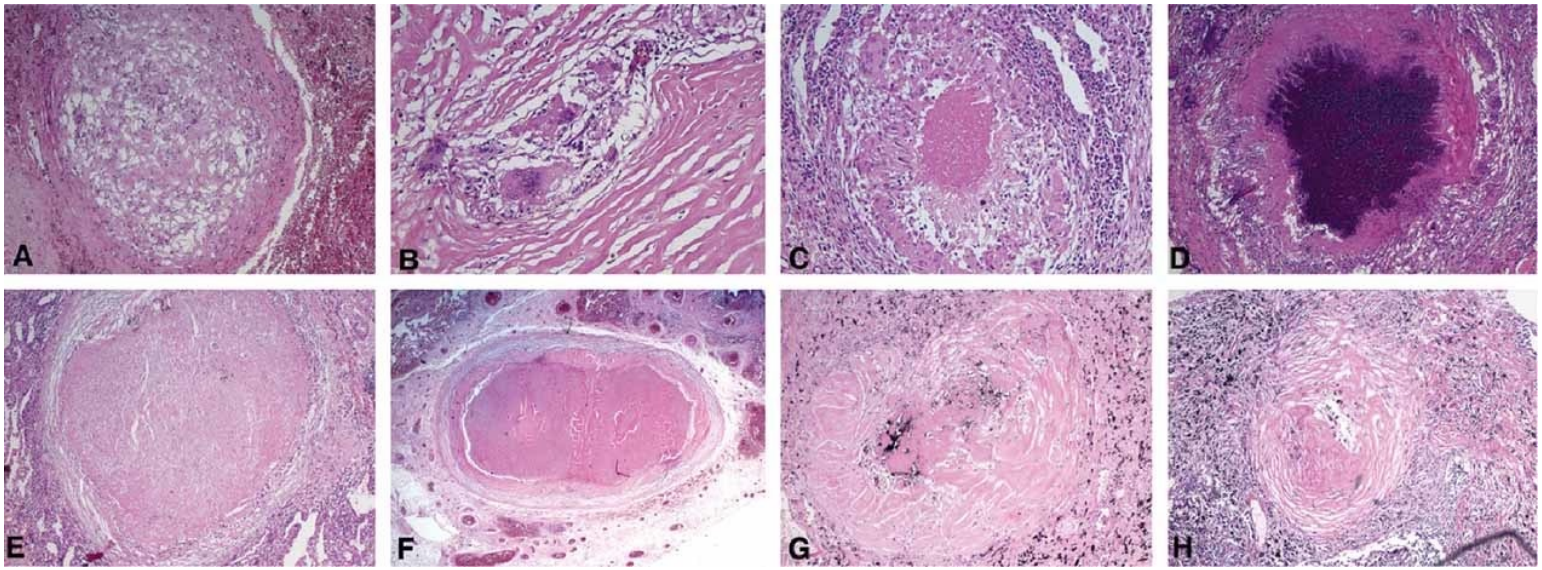
The Granuloma





Ramakrishnan, Nature Rev Immunology 2012

Different Types of Granulomas



Kim et al. EMBO Mol Med 2010

The Granuloma: containing infection

Immunology 1999 **98** 324–328

Granuloma formation is required to contain bacillus growth and delay mortality in mice chronically infected with *Mycobacterium tuberculosis*

B. M. SAUNDERS,*‡ A. A. FRANK† & I. M. ORME* **Mycobacteria Research Laboratories, Department of Microbiology, and †Department of Pathology, Colorado State University, Fort Collins, CO, USA*

Immunology and Cell Biology (2000) **78**, 334–341

Special Feature

Restraining mycobacteria: Role of granulomas in mycobacterial infections

BERNADETTE M SAUNDERS[1] and ANDREA M COOPER[2]

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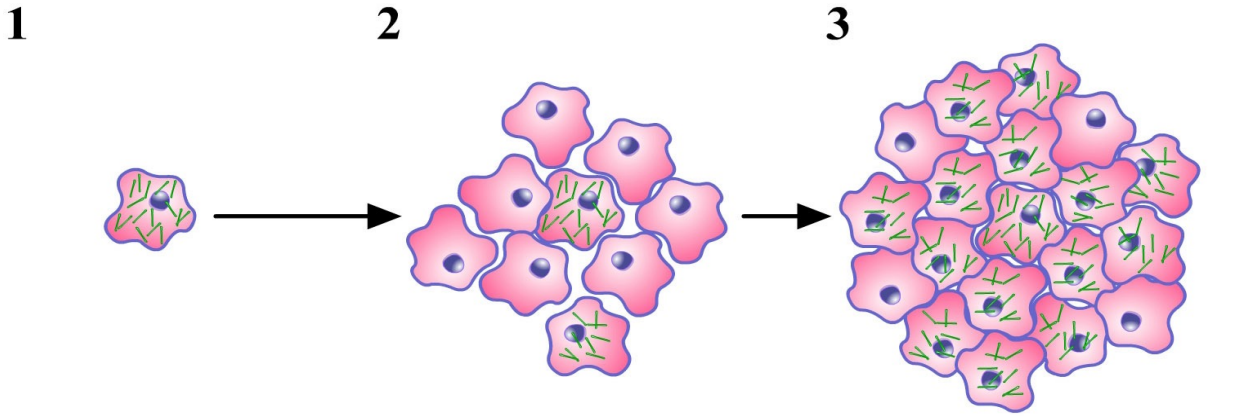
The Granuloma: Promoting MTB expansion



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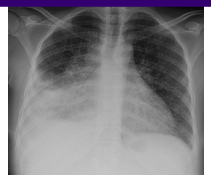

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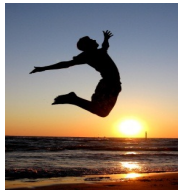
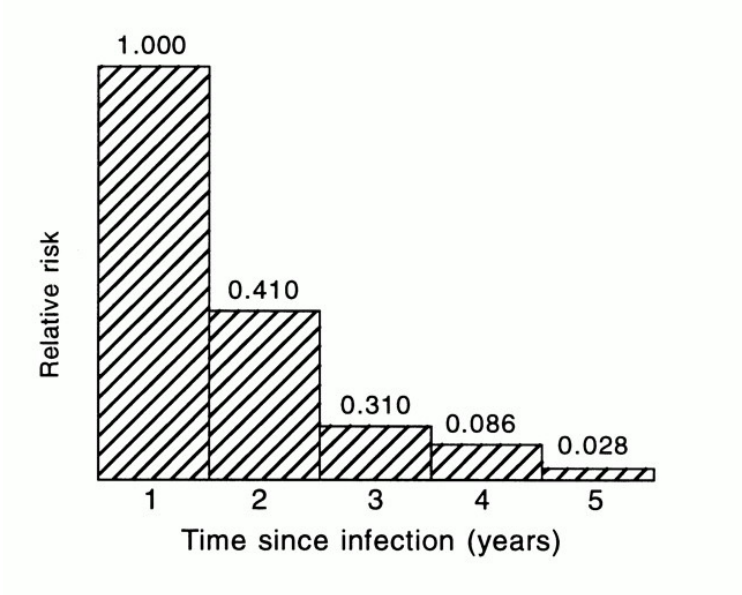


CURE

TB latency

- Clinically defined: evidence of MTB infection with no evidence of disease
- ~1.8 billion people
- Host immune factors?
  - ~10% lifetime chance of reactivation
  - HIV coinfection increases risk of reactivation 10% per year
- Physiology of the bacteria?

Risk of TB disease following infection



Depends on:

Age at infection

Current age

Geography (host factors?)

Strain?

Avg. time to symptoms = 1.4 yrs

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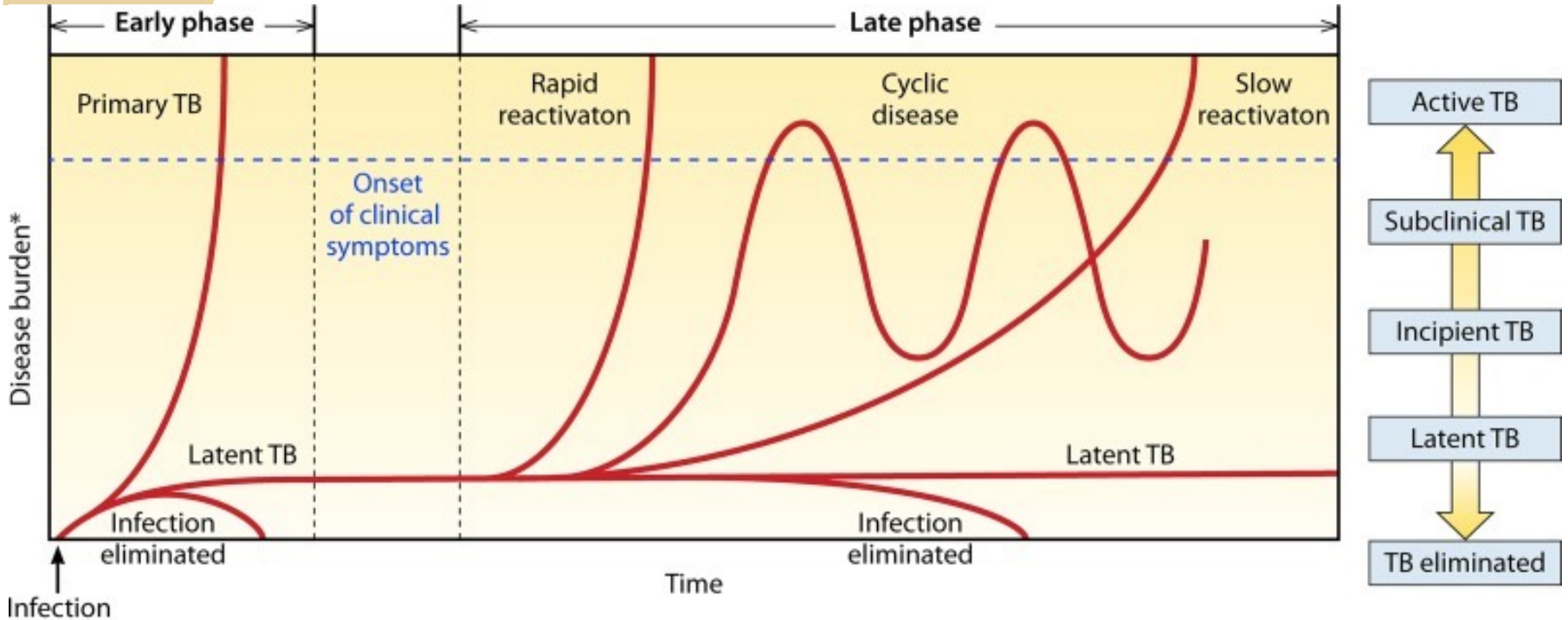
American Journal of Epidemiology
Vol. 152, No. 3
Printed in U.S.A.

Lifetime Risks, Incubation Period, and Serial Interval of Tuberculosis

Latent TB…sub-clinical TB…active TB



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Drain, Clin. Microbiol Rev, 2018

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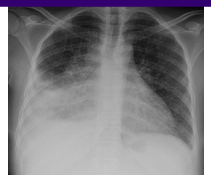
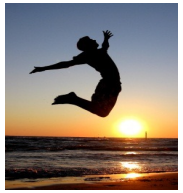
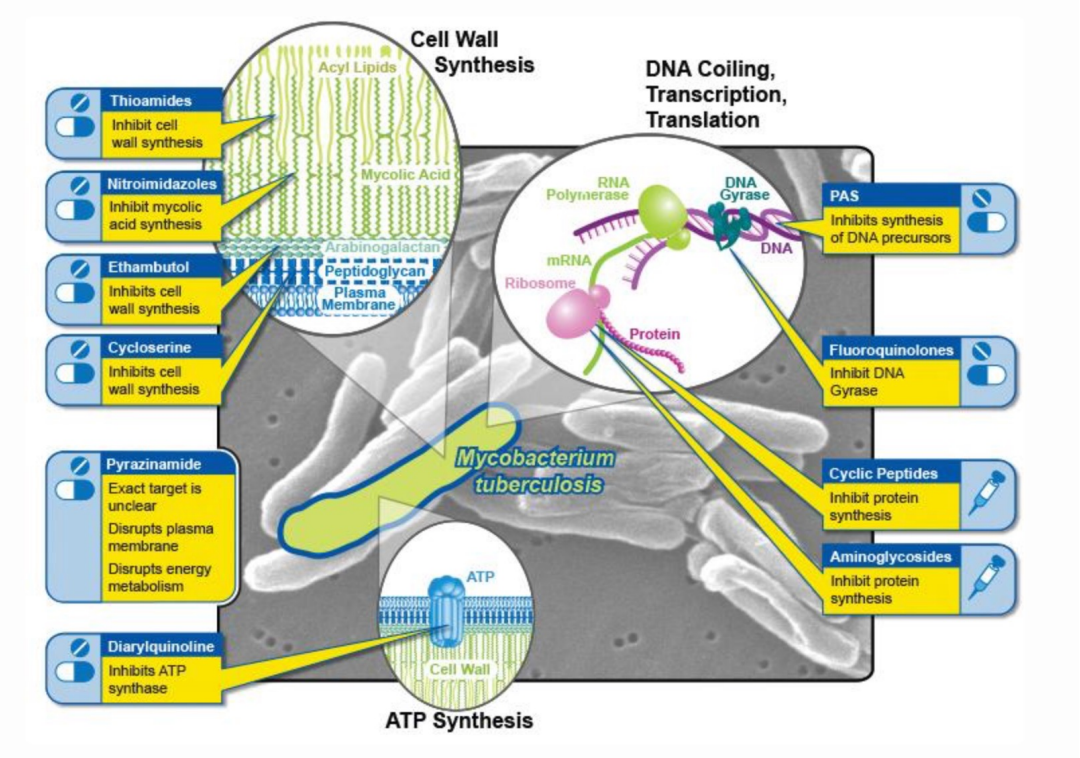




CURE

Mechanisms of Action of Current TB Drugs



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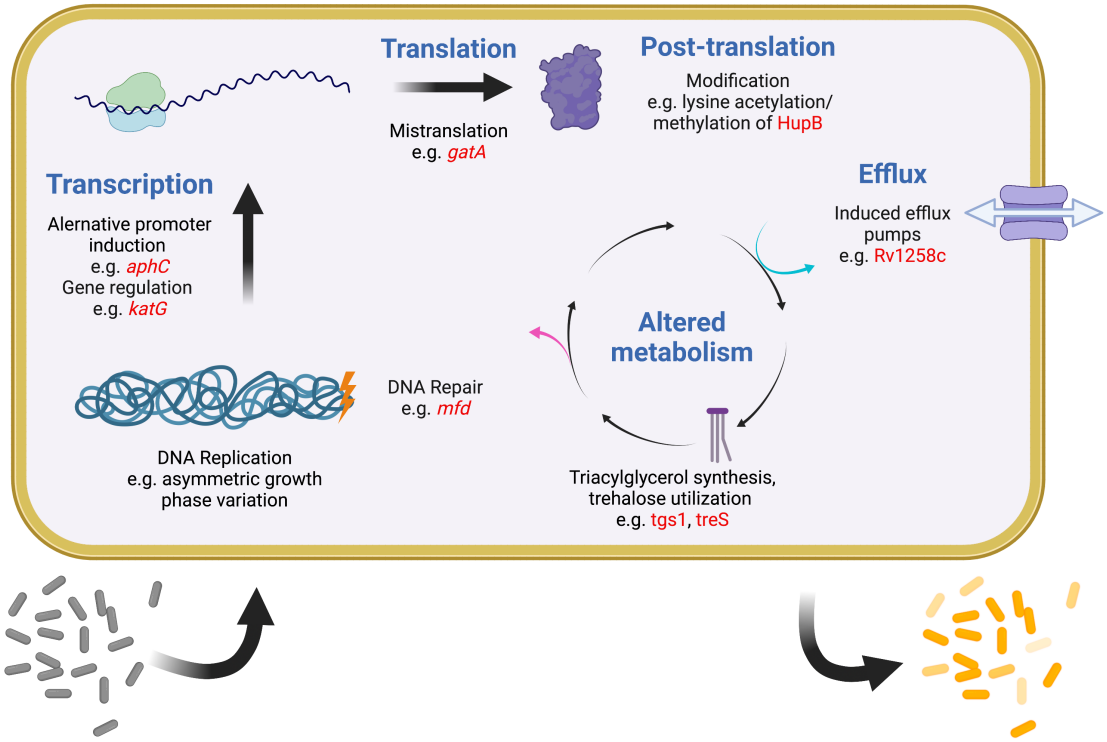
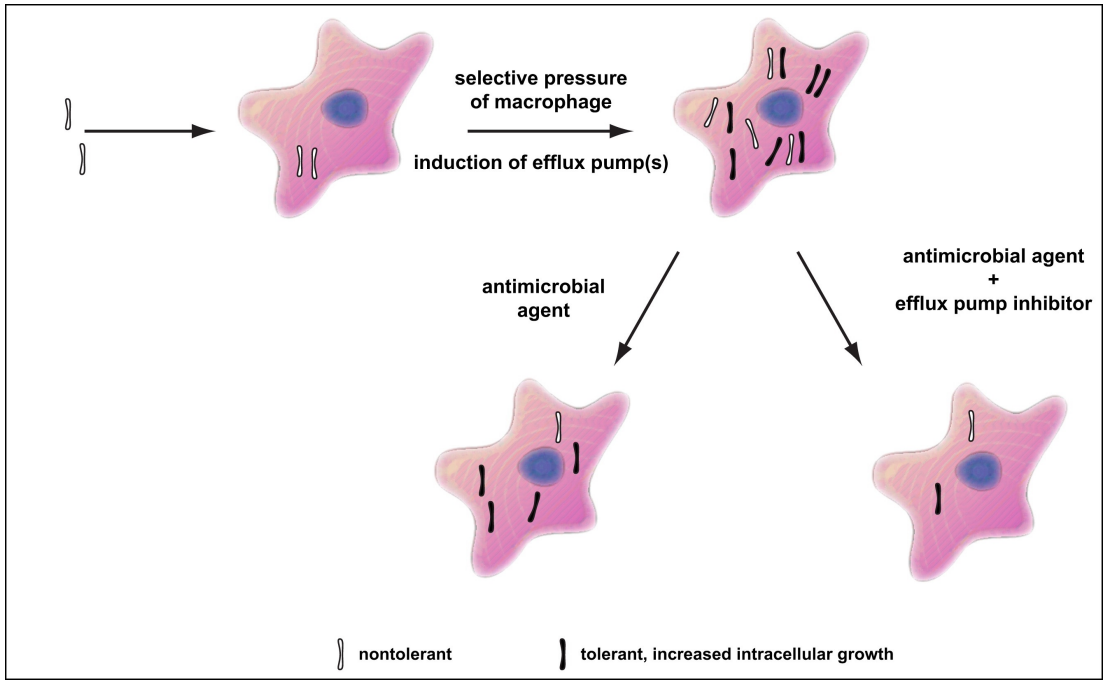
Credit: NIAID

Many paths to drug tolerance



MTB efflux pumps important for intracellular survival and drug tolerance



Adams et al. Cell 2011

Summary

- **TB: global scourge**
  - **Seven lineages**
  - **Modern strains are more successful**
- **Intracellular TB can subvert macrophages**
  - **Esx-1/RD1**
- **TB latency- very common**
  - **Sub-clinical disease**
- **Virulence and drug tolerance**