

**Limitations of the Current Pipeline:  
Lessons from Persisters and Persister Drug PZA**

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# Walsh McDermott (1909-1981) - Founding father of IOM, National Academy



Clinical evaluation of INH-  
(Lasker Award, 1955)

Cornell mouse model of TB  
Persistence

Work on pyrazinamide  
(PZA): (a) acid pH, (b)  
PZA-resistant TB lose  
PZase, (c) unique sterilizing  
activity of PZA

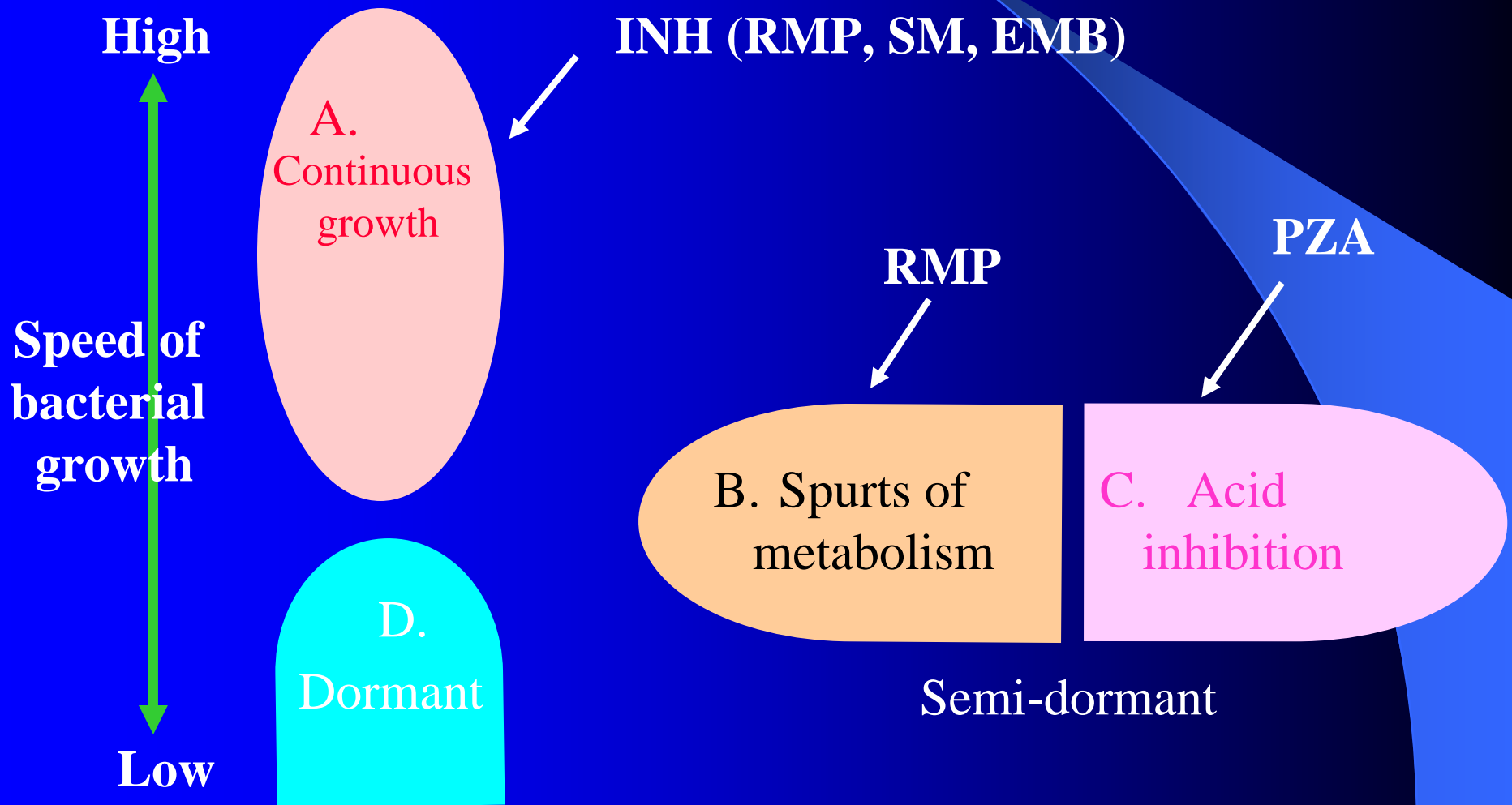
# TB Chemotherapy

- **Pre-antibiotic era:** before 1940s (e.g., cod liver oils, bed rest, fresh air)
- **Drugs used to treat TB:** Streptomycin first TB drug (1944), followed by PAS (1946), isoniazid (1952), pyrazinamide (1952), rifampin (1963)
- (a) Front-line Drugs: isoniazid (INH) rifampicin (RIF), pyrazinamide (PZA), streptomycin, ethambutol
- (b) Second-line Drugs: PAS, kanamycin, cycloserine, ethionamide, thiacetazone, ciprofloxacin/ofloxacin, rifapentine, amikacin, viomycin, capreomycin
- Based on MIC type screens except PZA

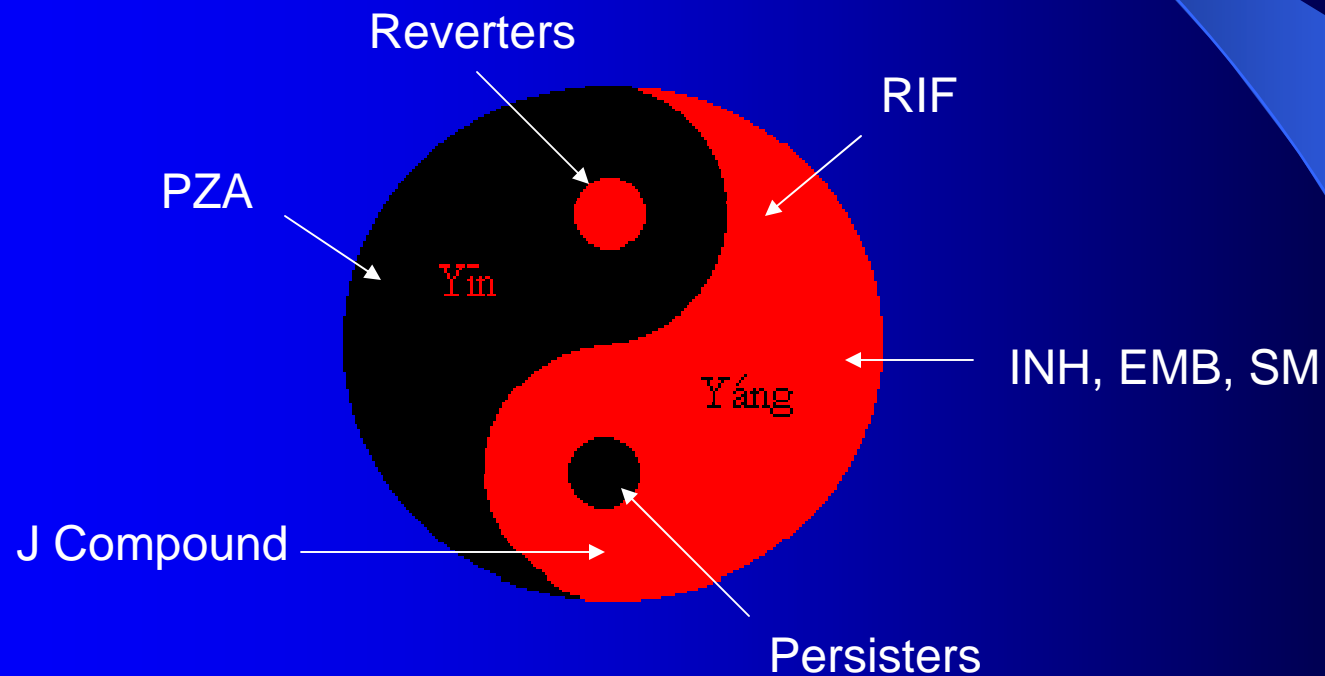
# **DOTS - The Best TB Therapy since early 1990s**

- **DOTS: 6 month therapy - The best therapy against TB (78%-96% cure rate)**
- **Initial phase (daily, 2 months) with 4 drugs: Isoniazid, Rifampin, Pyrazinamide, Ethambutol**
- **Continuation phase (3 times a week, 4 months) with 2 drugs: Isoniazid, Rifampin**

# Special Bacterial Populations Theory (Mitchison Hypothesis)



# Yin and Yang of Bacterial Life Cycle: Effect of Drugs



# **Pyrazinamide (PZA): A Prototype Persister Drug**

## **An unconventional and paradoxical drug**

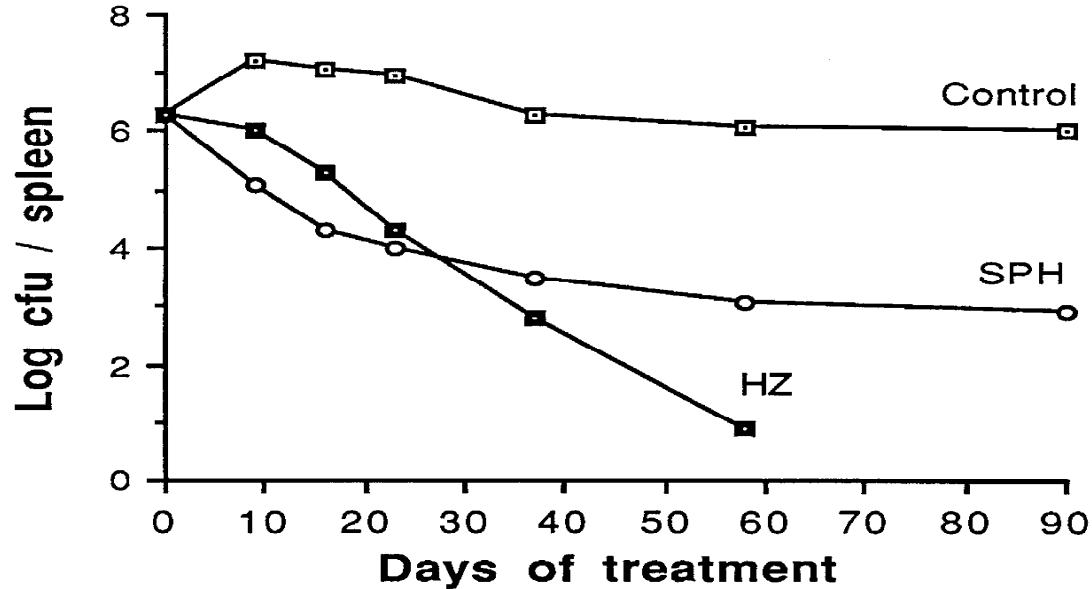
One of the most important front-line TB drug, that plays a key role in shortening the therapy, because PZA kills persister TB bacilli that are not killed by other TB drugs

Despite its powerful in vivo activity in shortening the therapy, curiously, PZA has no activity against TB bacilli in vitro in normal culture medium.

# Paradoxical Features of PZA

- PZA is active at acidic pH (pH 5.5) (McDermott 1954)
- MIC is high = 50-100 ug/ml at acid pH 5.5-6.0, and kills MTB slowly
- PZA kills old, dormant bacilli more effectively than actively growing bacilli (Zhang et al., 2002)
- PZA kills non-replicating TB bacilli more effectively under hypoxic/anaerobic conditions (Wade and Zhang, 2004)
- In vivo (mice or humans), it has impressive sterilizing activity against persister bacilli and can shorten therapy
- EBA studies in humans: INH has high EBA in first 2 days, PZA has poor or no EBA in first 2 weeks

# PZA achieves high sterilizing activity with INH - Basis for SCC



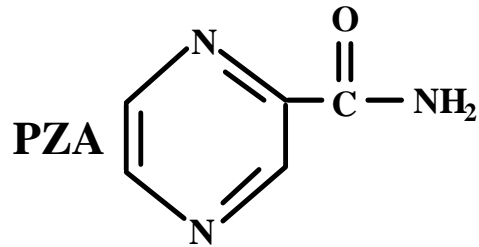
From McCune R M, Tompsett R, McDermott W  
J Exp Med 1956; 104: 763-802.



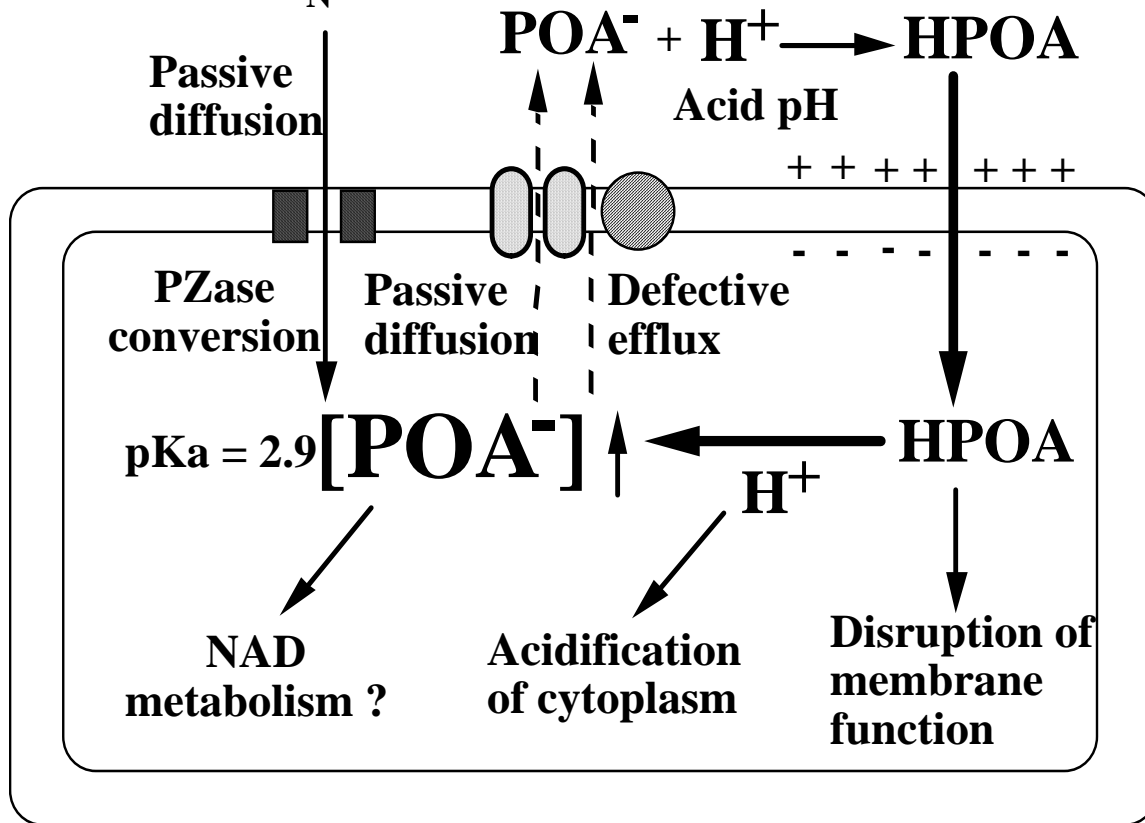
# History of PZA

- Unconventional discovery: In 1944, Chornie found nicotinamide (niacinamide), a vitamin B3 derivative (structure Fig.) had antimycobacterial activity in animal models-> in 1948, Lederle Lab made analogs of nicotinamide -> PZA
- Used in clinical treatment in 1952 (same year as INH), mainly used as a second-line drug for drug-resistant cases or relapse because of liver toxicity due to high dose and long term use
- In late 1970s and early 80s, through clinical trials by British MRC, PZA was found to shorten the therapy from previously 9-12 months to 6 months -> now used as first-line drug -> Basis for modern short-course TB therapy

# Mode of Action of PZA

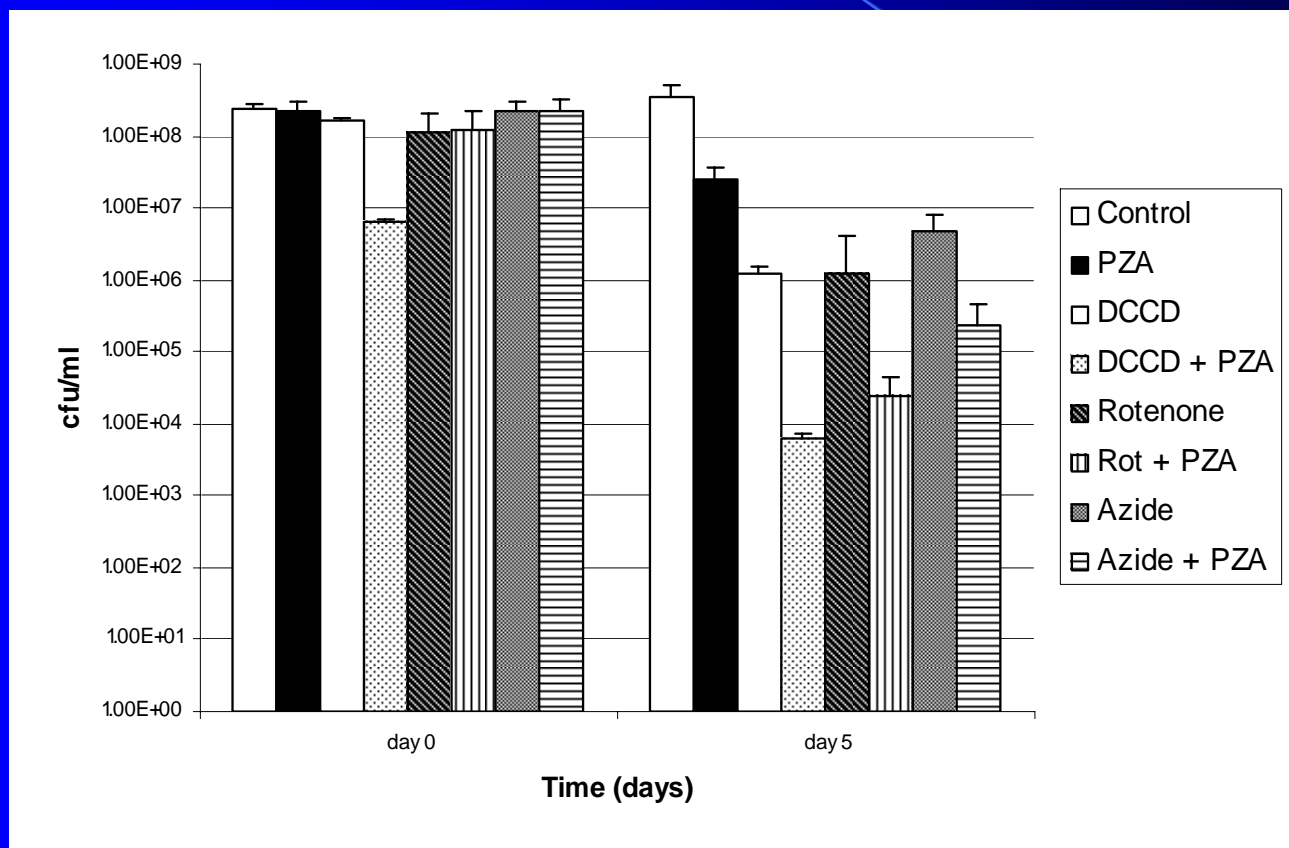


Model can explain unusual properties of PZA:  
 Acid pH, preferential activity for non-replicating  
 persisters, hypoxic conditions



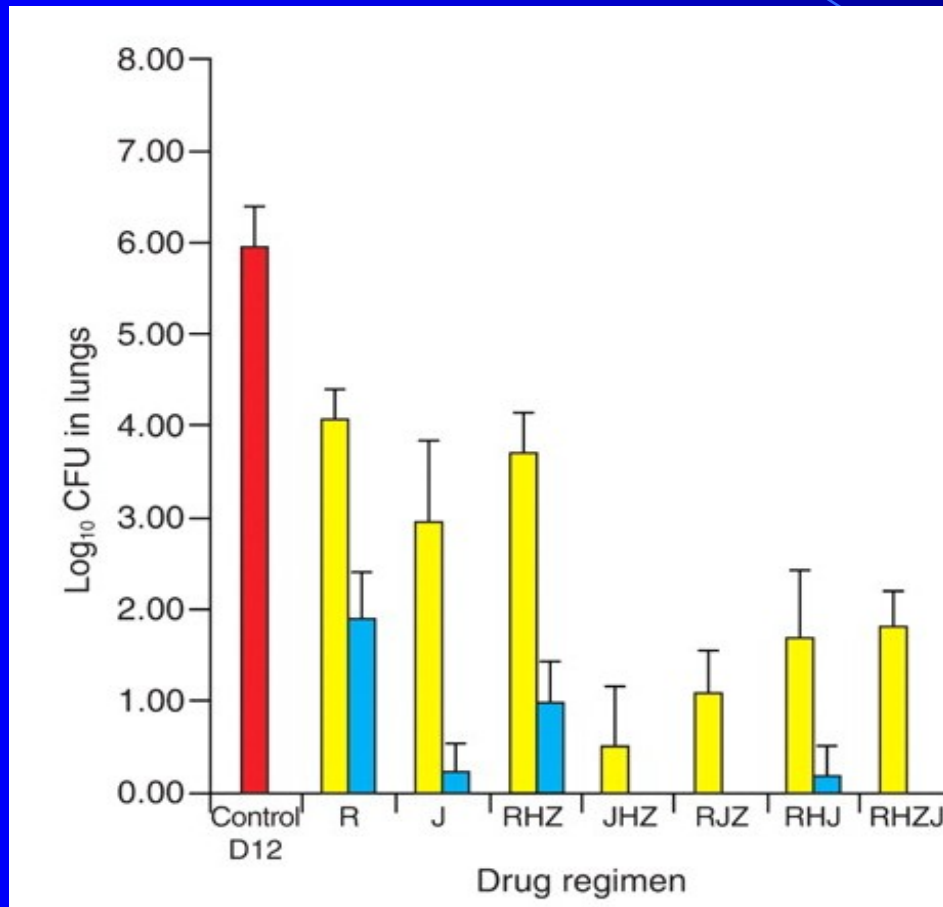
# Enhanced PZA activity by energy inhibitors

Zhang et al. J. Antimicrob. Chemother. 2003



Young H37Ra cell; PZA=100  $\mu$ g/ml; 5 day incubation at pH5.5

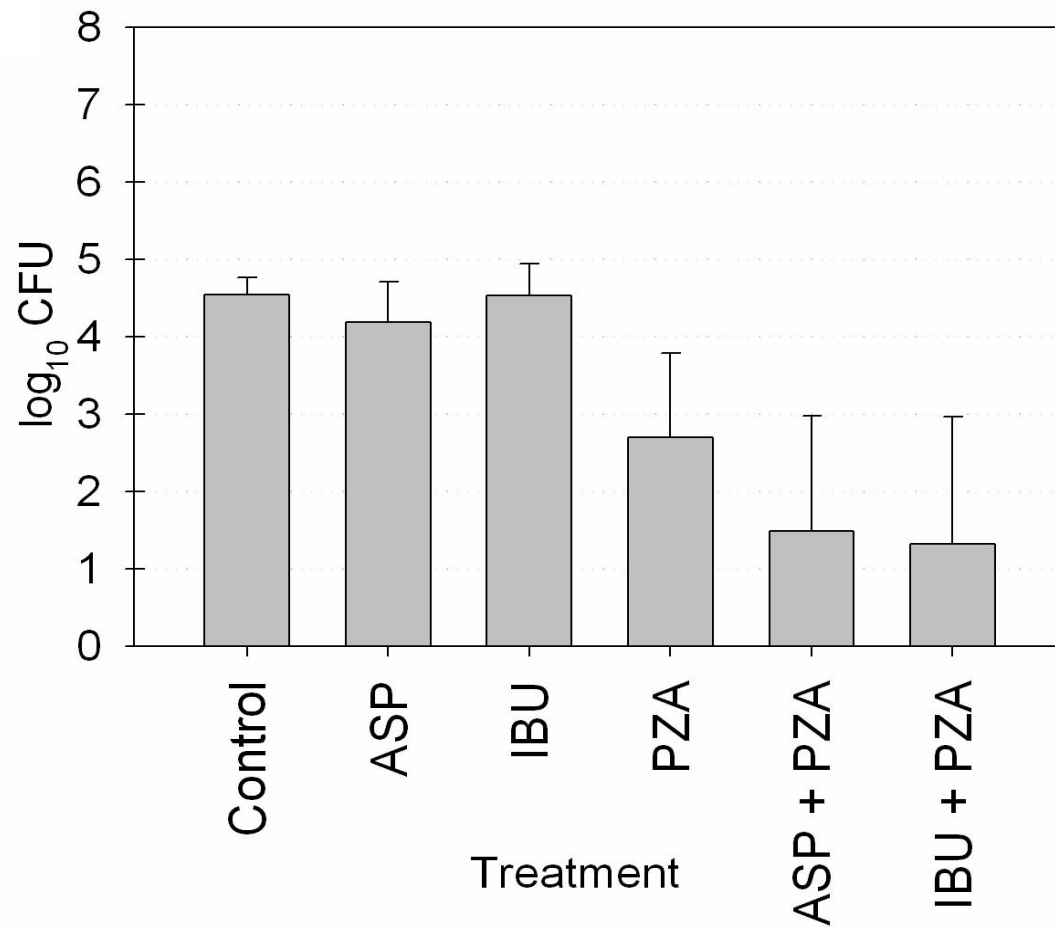
# Synergy Between Diarylquinoline (J) and PZA (Andries et al., 2005, Science, 307: 223-7)



Like DCCD, J compound  
Inhibits F1F0 H-ATPase

# Aspirin and Iburpofen Enhance PZA Activity in Mice

(Byrne, Denkin, Zhang, JAC, Dec 21, 2006)



# New Drug Development

## FDA approved drugs:

-New rifamycin: rifapentine in 1998, first TB drug in 40 years

## Under clinical development:

-New quinolones (Bayer): moxifloxacin, gatifloxacin, Phase II trials

-Ethambutol analog, SQ-109 (Sequella), Phase I trial

-Nitroimidazoles: nitroimidazolepyran-PA-824 (Chiron), activity in mice ->human Phase I trial (GATB)

-OPC-67683 (Otsuka), a nitro-dihydro-imidazooxazole derivative, OPC+RIF+PZA shorten therapy to 2 months in mice

-Diarylquinoline drugs (Johnson & Johnson): diarylquinoline showing good activity in mice and shorten treatment with INH+PZA to 2 month-> human Phase I, II trial

NIH Pre-clinical development: Southern Research Inst (in vitro)-> Colorado State U (mouse)

Global Alliance for TB Drug Development (GATB)

Gates Foundation

# Different Drug Screens

- Whole cell screens:
  - MIC-based screens: actively growing bacilli
  - Persister screens: non-growing bacilli
    - \*anaerobic conditions
    - \*acid pH
    - \*RIF-tolerant persisters
- Target based screens:

## Why is TB therapy this long (6 months)?

(a) Dormant or persistent tubercle bacilli (as in Cornell model).

(b) The current TB drugs are not good enough!!!

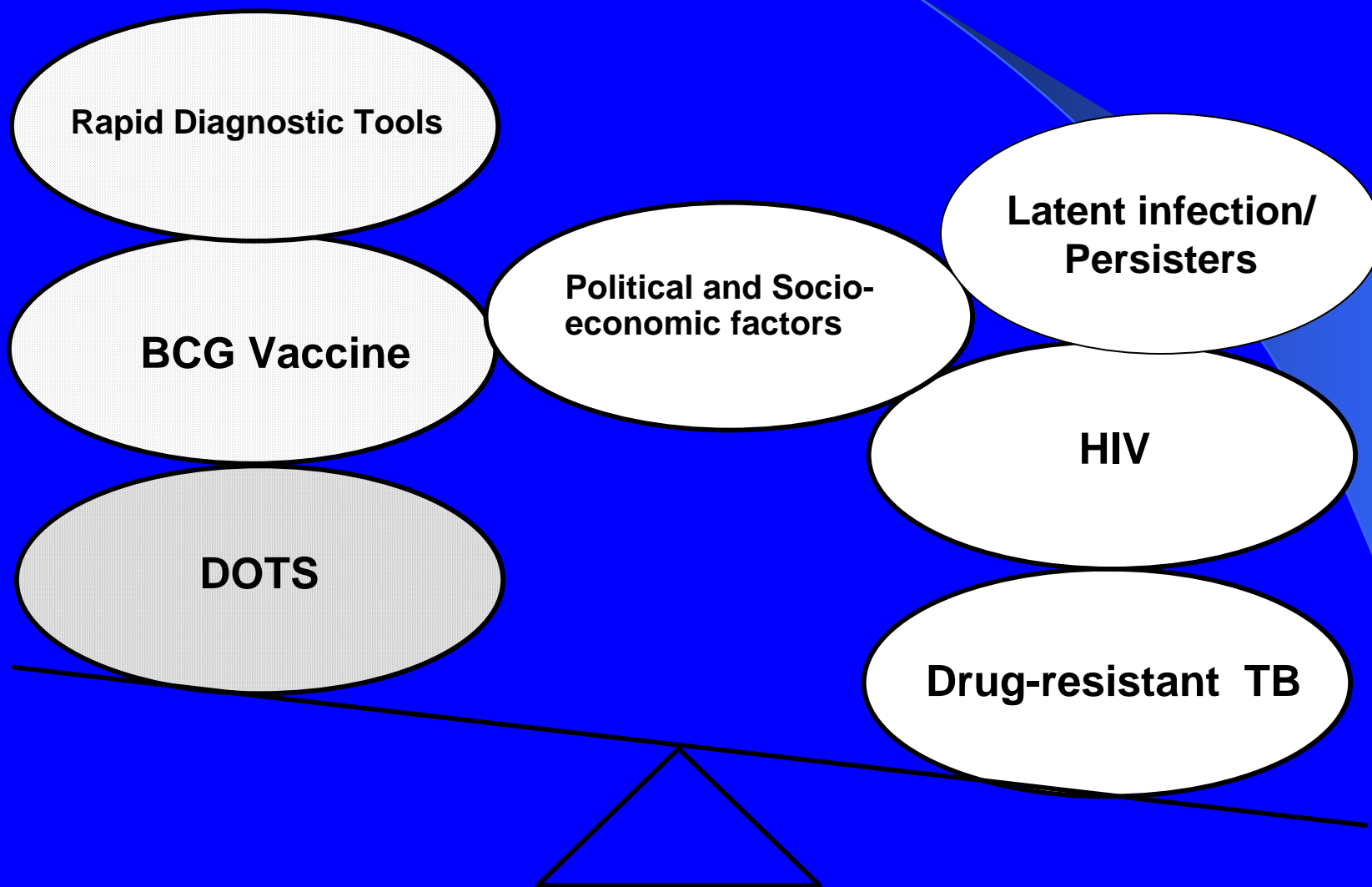
All the TB drugs are only active against actively growing bacilli, except PZA and RIF, thus they cannot kill persisters/dormant bacilli. Drugs that can kill persisters/dormant bacilli could shorten the therapy.

Not just new drugs active against drug-resistant TB, more importantly, drugs that are active against dormant/persistent bacilli and shorten the therapy.

New challenge: Develop more effective drugs that can shorten the therapy from 6 months to a few weeks.

TB Control Strategy

Factors that make TB worse



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