The Development of Anti-Tuberculosis Drugs

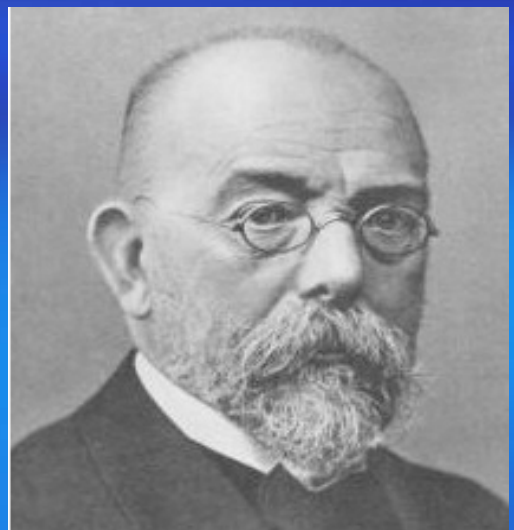
YANG Junwei

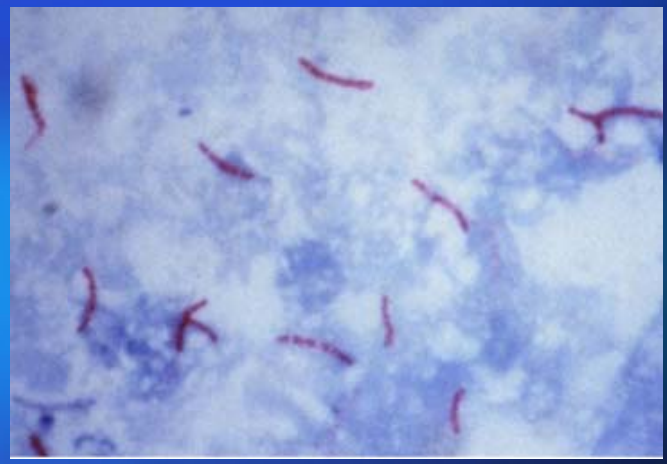
Supervisor: Prof. ZHAO Guoping

11/12/2009

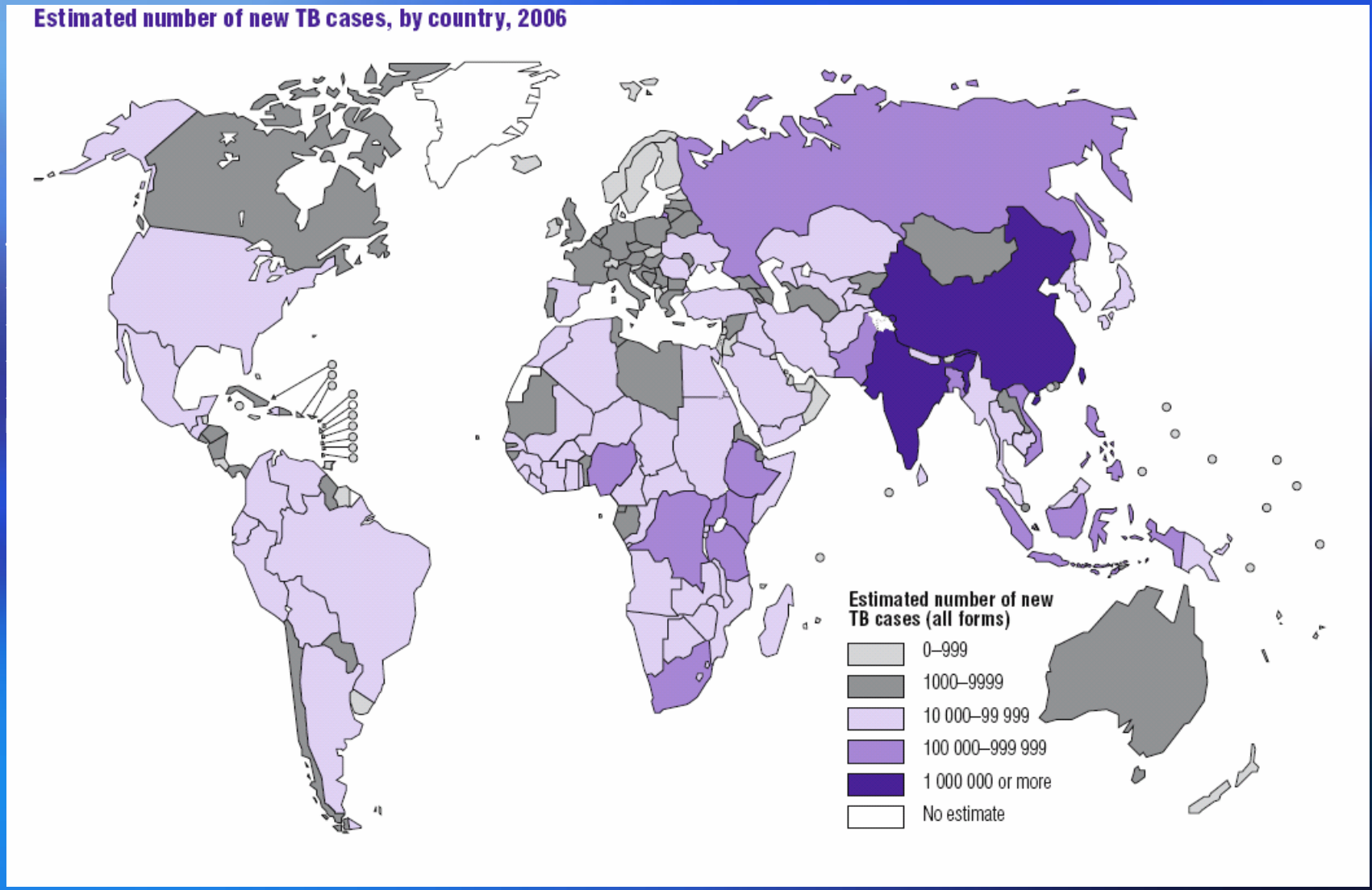
What is tuberculosis (TB)?

- Bacterial infection
- Caused by *Mycobacterium tuberculosis*
- Damages a person's lung or other parts of the body
- Fatal if not treated properly





2 million death annually
1/3 world population infection
>1/3 in populous India and China



Tools for better TB control

- Diagnostics
- Isolation
- Vaccine (BCG)
- Drugs

Current drugs for TB

- **First Line:**
  - Isoniazid, Rifampin, Streptomycin, Ethambutol, Pyrazinamide
- **Second Line:**
  - Amikacin, Kanamycin, Capreomycin, Cycloserine

Disadvantages of current drugs

- Long duration and complex treatment caused adverse effects and non-adherence to drugs
- Drug resistance
- Drug interactions between the anti-HIV and anti-TB drugs
- Not effective for latent TB infection

Goals for new drug development

- Shorten and simplify the treatment of active, drug-sensitive TB
- Effective for drug-resistant disease
- Develop drugs for TB patients co-infected with HIV
- Shorten therapy of latent TB infection

Strategy for developing anti-TB drugs

- **Existing TB drugs optimized:** Rifapentine
- **New chemicals addressing known targets: Gatifloxacin (GAT) and moxifloxacin (MXF)**
-
- **New chemicals addressing novel targets: Malate synthase inhibitors**

Rifapentine: long-acting

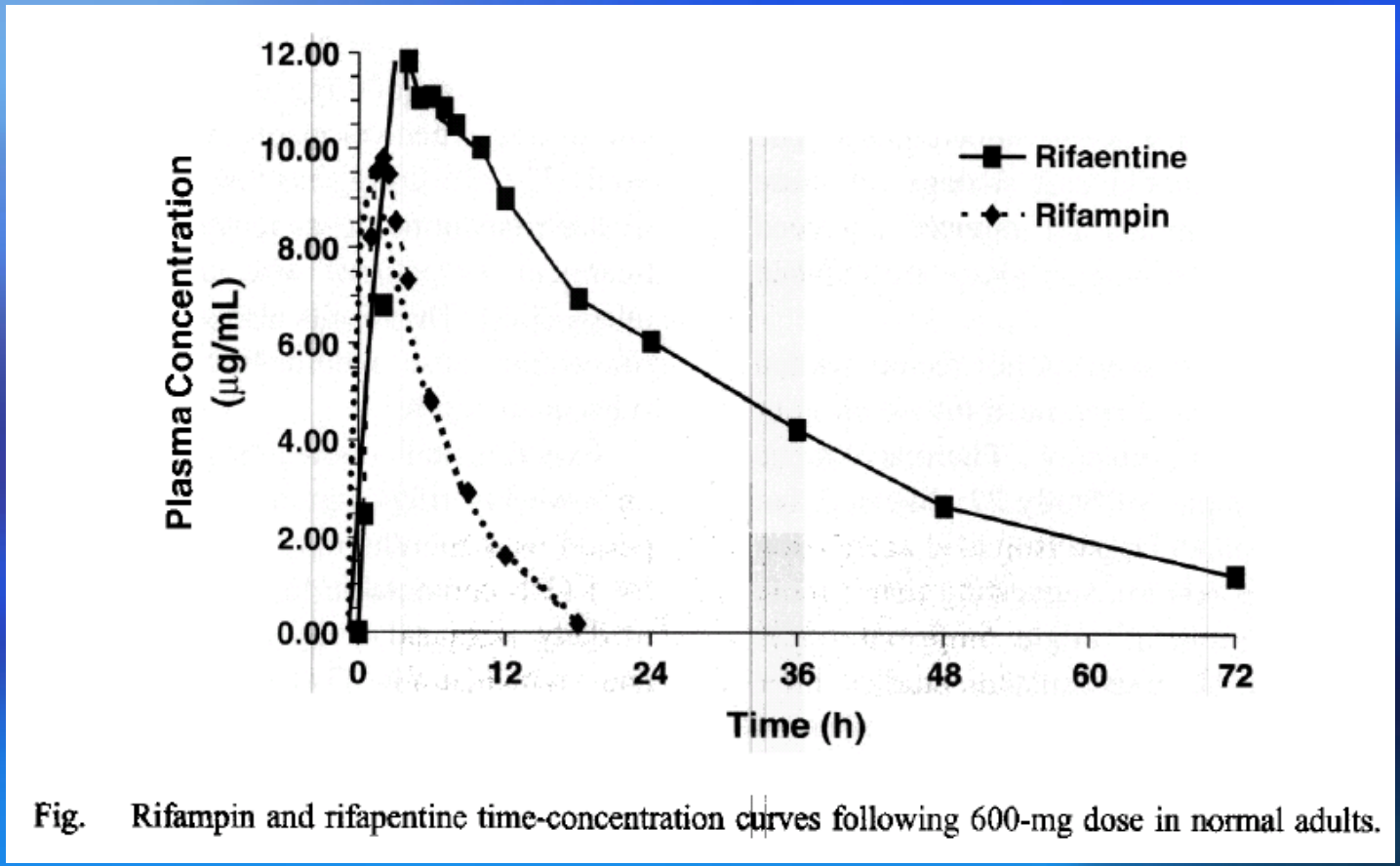


Fig. Rifampin and rifapentine time-concentration curves following 600-mg dose in normal adults.

O'Brien RJ, Spigelman M. Clin Chest Med. 2005 Jun;26(2):327-40.

Strategy for developing anti-TB drugs

- **Existing TB drugs optimized:** Rifapentine
- **New chemicals addressing known targets: Gatifloxacin (GAT) and moxifloxacin (MXF)**
- **New chemicals addressing novel targets: Malate synthase inhibitors**

GAT and MXF: potential candidates for shortening TB treatment thorough inhibiting DNA gyrase

TABLE 1. MICs of GAT, MXF, and LVX against 23 *M. tuberculosis* isolates[a]

Antimicrobial agent	MIC (μg/ml)		
	50%	90%	Range
GAT	0.031	0.031	0.007–0.12
MXF	0.062	0.125	0.031–0.12
LVX	0.5	1	0.12–1

Alvirez-Freites EJ, Carter JL, Cynamon MH. Antimicrob Agents Chemother. 2002 Apr;46(4):1022-5.

Strategy for developing anti-TB drugs

- **Existing TB drugs optimized:** Rifapentine
- **New chemicals addressing known targets: Gatifloxacin (GAT) and moxifloxacin (MXF)**
-
- **New chemicals addressing novel targets: Malate synthase inhibitors**

Malate synthase inhibitors: potentially shorten TB treatment through potent killing of **persistent bacteria**

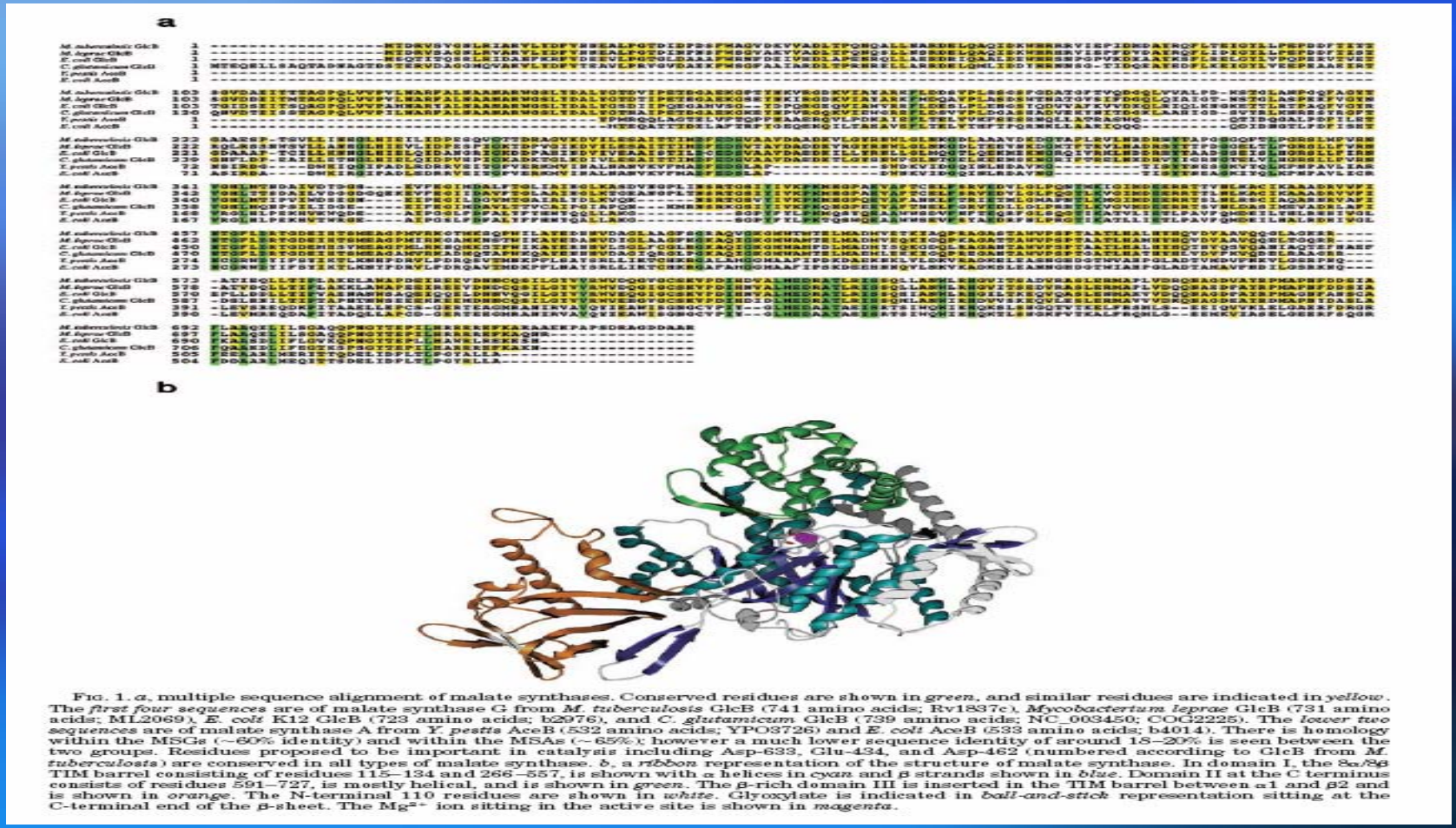


FIG. 1. *a*, multiple sequence alignment of malate synthases. Conserved residues are shown in *green*, and similar residues are indicated in *yellow*. The *first four sequences* are of malate synthase G from *M. tuberculosis* GlcB (741 amino acids; Rv1837c), *Mycobacterium leprae* GlcB (731 amino acids; ML2069), *E. coli* K12 GlcB (723 amino acids; b2976), and *C. glutamicum* GlcB (739 amino acids; NC_003450; COG2225). The *lower two sequences* are of malate synthase A from *Y. pestis* AceB (532 amino acids; YPO3726) and *E. coli* AceB (533 amino acids; b4014). There is homology within the MSGs (~60% identity) and within the MSAs (~65%); however a much lower sequence identity of around 18–20% is seen between the two groups. Residues proposed to be important in catalysis including Asp-633, Glu-434, and Asp-462 (numbered according to GlcB from *M. tuberculosis*) are conserved in all types of malate synthase. *b*, a *ribbon* representation of the structure of malate synthase. In domain I, the $8\alpha/8\beta$ TIM barrel consisting of residues 115–134 and 266–557, is shown with α helices in *cyan* and β strands shown in *blue*. Domain II at the C terminus consists of residues 591–727, is mostly helical, and is shown in *green*. The β-rich domain III is inserted in the TIM barrel between $\alpha 1$ and $\beta 2$ and is shown in *orange*. The N-terminal 110 residues are shown in *white*. Glyoxylate is indicated in *ball-and-stick* representation sitting at the C-terminal end of the β-sheet. The Mg^{2+} ion sitting in the active site is shown in *magenta*.

Smith CV, Huang CC, Miczak A, Russell DG, Sacchettini JC, Höner zu Bentrup K. **J Biol Chem. 2003 Jan 17;278(3):1735-43. Epub 2002 Oct 21.**

TB drug candidates in clinical development

Compound	Development stage	Sponsor or coordinator
Gatifloxacin	Phase 3	OFLOTUB Consortium; European Commission; WHO TDR; Lupin Ltd.
Moxifloxacin	Phase 2, 3	Bayer; TB Alliance; CDC; University College of London; Johns Hopkins University
TMC207	Phase 2	Tibotec
OPC-67683	EBA	Otsuka Pharmaceutical Co., Ltd.
PA-824	Phase 1	TB Alliance
LL-3858	Phase 1	Lupin Ltd.
SQ-109	Phase 1	Sequella, Inc.

WHO TDR, World Health Organization Tropical Disease Research; CDC, US Centers for Disease Control and Prevention.

Ginsberg AM, Spigelman M. Nat Med. 2007 Mar;13(3):290-4.

Thanks!!!