The Year in Review: Progress Towards TB Elimination

TB Alliance Stakeholders Association Annual Meeting

Mel Spigelman

Berlin, Germany

November 9, 2010

In Memoriam: Susan May Bacheller
1958-2010

TB Alliance Vision

6 – 30 months

2 – 4 months

10 days

Success will require novel multi-drug combinations

Road to Success

Effective partnerships exploiting affordable and accessible innovation

Agenda

- Research & Development
- Regulatory Progress
- Market Access
- Community Engagement

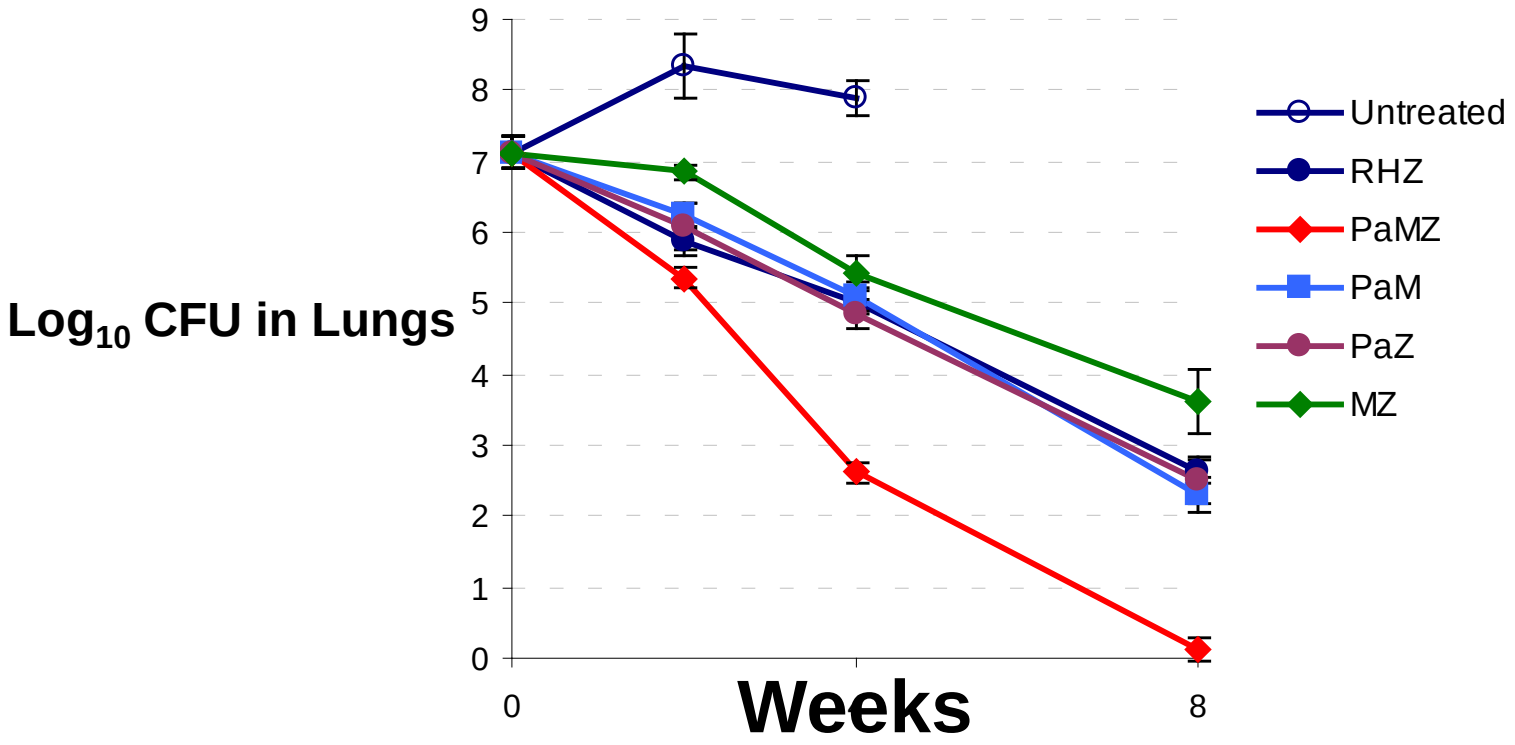
2010 Highlights

- TB Alliance/Astra Zeneca miniportfolio
- Open Forum 4
- Sharing with DNDi of nitroimidazole technologies
- First novel regimen moved into Phase II clinical development
- Critical Path to TB Drug Regimen (CPTR) initiative launched

Approach to Novel Regimen Development

- Use animal model(s) to identify most promising regimens
- Conduct full preclinical, Phase I and Phase II EBA evaluations of each individual drug
- Explore drug-drug interactions and, as necessary, preclinical toxicology of combinations
- Take combinations/regimens into clinical development (Phase II, III)

Preclinical Data on First Novel Regimen (PaMZ) in Phase II Trial



R= rifampin

H= isoniazid

Z= pyrazinamide

Pa= PA-824

M= moxifloxacin

PaMZ Regimen Potential

- Treatment shortening to 4 months or less
- Equally effective against drug sensitive and drug resistant TB
- No need to test for either isoniazid or rifampin resistance
- Lower cost of goods of MDR TB treatment to as little as 10% of present costs

TB Alliance Portfolio

Discovery

TARGET OR CELL-BASED SCREENING

- **Natural Products** IMCAS
- **Protease Inhibitors** IDRI
- **TB Drug Discovery Portfolio** NITD
- **Topoisomerase I Inhibitors** AZ/NYMC

LEAD IDENTIFICATION

- **Whole-Cell Hit to Lead Program** GSK
- **Malate Synthase Inhibitors** GSK/TAMU
- **Gyrase B Inhibitors** AZ
- **Folate Biosynthesis Inhibitors** AZ
- **Whole-Cell Hit to Lead Program** AZ
- **RNA Polymerase Inhibitors** AZ/Rutgers
- **Energy Metabolism Inhibitors** AZ/U. Penn
- **Phenotypic Hit to Lead Program** U. Ill Chicago
- **Menaquinone Biosynthesis Inhibitors** CSU

LEAD OPTIMIZATION

- **Mycobacterial Gyrase Inhibitors** GSK
- **InhA Inhibitors** GSK
- **Diarylquinolines** Tibotec/U. of Auckland
- **Riminophenazines** IMM/BTTTRI
- **Pyrazinamide Analogs** Yonsei

Preclinical Development

- **Nitroimidazoles** U. of Auckland/ U. Ill Chicago
- **Preclinical TB Regimen Development** JHU/U. Ill Chicago

Clinical Development

CLINICAL PHASE I

CLINICAL PHASE II

- **PA-824** Novartis
- **TMC207** Tibotec
- **PA-824/Pyrazinamide**
- **TMC207/Pyrazinamide**
- **PA-824/ Moxifloxacin/ Pyrazinamide**

CLINICAL PHASE III

- **Moxifloxacin (+ H, R, Z)** Bayer
- **Moxifloxacin (+ R, Z, E)** Bayer

Novel TB regimen development

Current first-line TB treatment consists of Isoniazid (H) + rifampicin (R) + pyrazinamide (Z) + ethambutol (E)

OUR R&D PARTNERS

- AstraZeneca (AZ)
- Bayer Healthcare AG (Bayer)
- Beijing Tuberculosis and Thoracic Tumor Research Institute (BTTTRI)
- Colorado State University (CSU)
- GlaxoSmithKline (GSK)
- Infectious Disease Research Institute (IDRI)
- Institute of Materia Medica (IMM)
- Institute of Microbiology, Chinese Academy of Sciences (IMCAS)
- Johns Hopkins University (JHU)
- Johnson & Johnson / Tibotec (Tibotec)
- New York Medical College (NYMC)
- Novartis Institute for Tropical Diseases (NITD)
- Novartis Pharmaceutical (Novartis)
- Rutgers: The State University of New Jersey (Rutgers)
- Texas A&M University (TAMU)
- University of Auckland (U. of Auckland)
- University of Illinois at Chicago (U. Ill Chicago)
- University of Pennsylvania School of Medicine (U. Penn)
- Yonsei University (Yonsei)

Launch of Critical Path to TB Drug Regimens (CPTR)

THE WALL STREET JOURNAL.

A8 Thursday, March 18, 2010 THE WALL STREET JOURNAL.

U.S. NEWS

FDA Is Easing Way for Drug Cocktails

Agency Draws Up Guidelines for Approving Two or More New Drugs Together to Fight Deadly Diseases Such as TB, AIDS

By Mark Schoofs

The Food and Drug Administration is devising guidelines that could accelerate testing and approval of multidrug regimens for some of the world's most deadly diseases.

At least two pharmaceutical consortia are poised to take advantage of the forthcoming policy: a group of 10 drug companies and several nonprofit organizations convened by the Bill and Melinda Gates Foundation to develop medicines to fight tuberculosis; and pharmaceutical giants **Merck** & Co. and **AstraZeneca** PLC, which are jointly testing two anticancer agents.

Many diseases, such as AIDS, tuberculosis and cancer, require multidrug combinations. Such drug cocktails can prevent the development of drug resistance, because the microbe or cancer cell needs to undergo more mutations to escape several drugs than to escape just one. By attacking the disease in different ways, drug combinations pace with the use of products in combination.

Now the FDA is drafting guidelines on how testing and what research would be required in the test tube, animals and humans to determine side effects, proper dosage and each drug's contribution to any cause certain side effects. "Society wouldn't tolerate this degree of uncertainty" except for drugs to treat dire illnesses, she said.

Multidrug-resistant cases—exceeding half a million annually—take two years to treat with drugs that often cause severe side effects but only executives of 14 drug companies. A representative of **Sanofi-Aventis** SA said the meeting helped catalyze that company's participation in the current tuberculosis collaboration. On Thursday in Washington, D.C., the foundation is expected to unveil the collaboration, in which all partners agree to share data and test new drugs in combination treatments early in the development process.

For companies, sharing the cost of clinical trials and bringing proven combinations to market more quickly might save money. But if a regimen fails, it could give every drug in it a bad reputation, which could be costly to overcome, even for drugs that ultimately prove safe and effective. And there are thorny questions on how competing companies would share data, decide which drugs to combine into regimens, and market their drugs.

The Gates collaboration, known as the Critical Path to TB Regimens, includes drug giants **Pfizer** Inc.,

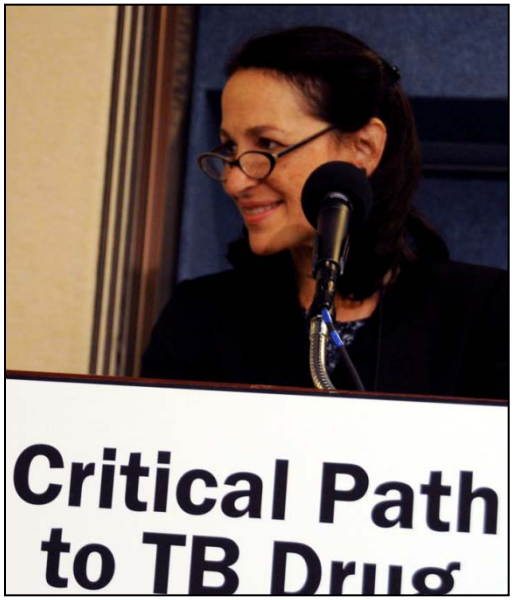
In the Pipeline | Tuberculosis compounds currently in development

Developer	Experimental drug	Class	How it kills the TB bacteria
Tibotec Johnson & Johnson subsidiary; **Global Alliance for TB Drug Development**	TMC-207	Diarylquinolone	**Disrupts cellular energy production**
Otsuka Pharmaceutical	OPC-67683	Nitroimidazole	**Disrupts synthesis of lipids and proteins**
Global Alliance for TB Drug Development	PA-824	Nitroimidazole	
Lupin	LL 3858	Pyrrole derivative	**Not well understood**
Sequella	SQ-109	Ethylenediamines	**Affects cell wall, may have other mechanisms**

Development of TB drugs and cocktails

- **1952:** First combination therapy using three drugs
- **1960s:** One drug in cocktail replaced
- **1970s:** Fourth drug added to cocktail
- **1980s:** One drug in combination replaced

Sources: Global Alliance for TB Drug Development; Stop TB Partnership's Working Group on New TB Drugs; WSJ reporting; Zhenkun Ma and Christian Lienhardt, article in Clinics in Chest Medicine



sanofi aventis — Because health matters

Sequella Incorporated

Novartis

AstraZeneca

gsk GlaxoSmithKline

Bayer

TAG Treatment Action Group

Johnson & Johnson

Anacor Pharmaceuticals

Pfizer

Otsuka

EDCTP

Vertex

Critical Path Institute — Improving the Path for Innovative Therapies

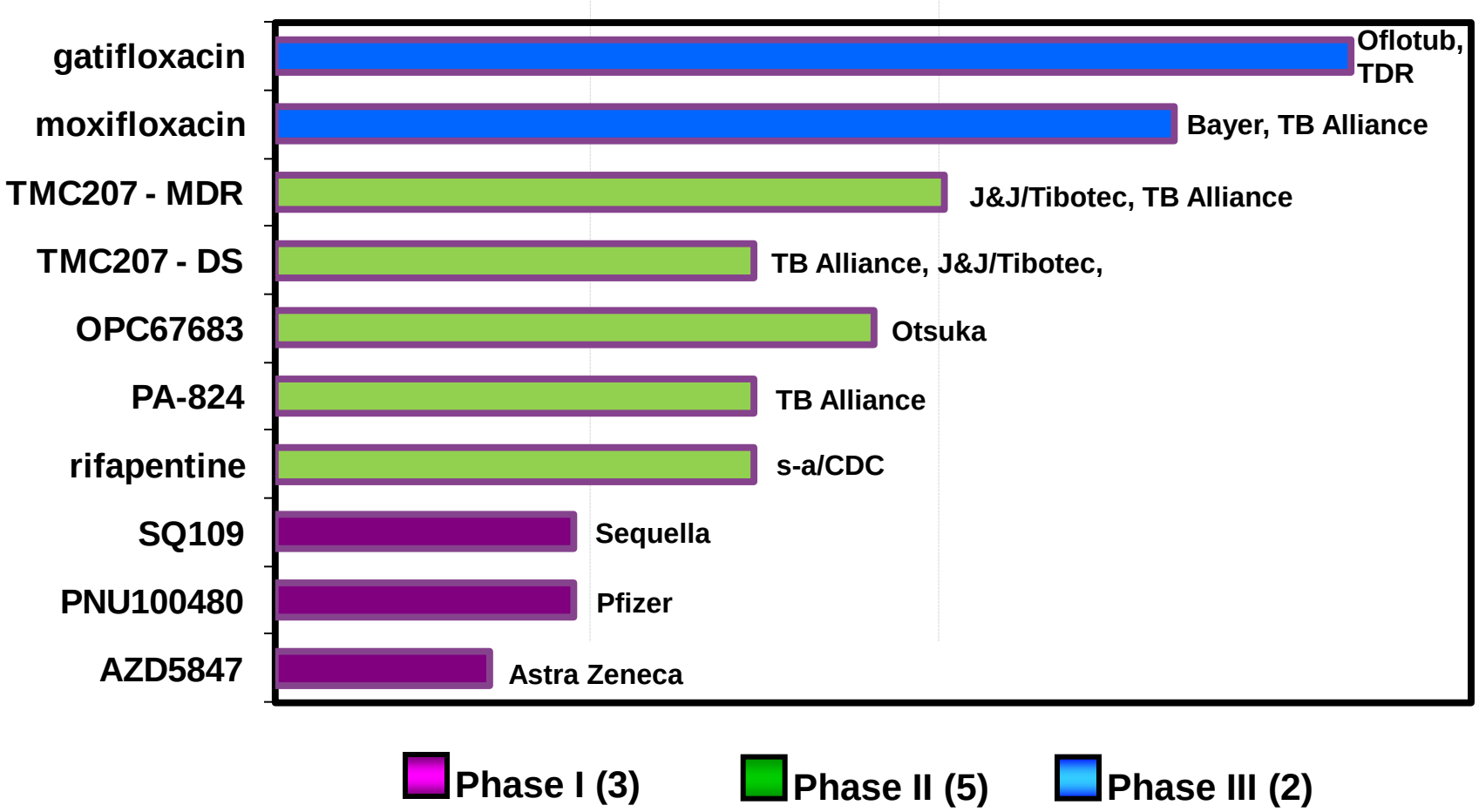
TB Alliance — Global Alliance for TB Drug Development

Bill & Melinda Gates foundation

Please visit CPTRinitiative.org for more information

TB Drugs in Clinical Development

Global Portfolio



TB Alliance Donors through the Decade

Bill & Melinda Gates Foundation

Irish Aid

United States Food and Drug Administration

The Netherlands Ministry of Foreign Affairs

United Kingdom Department for International Development

United States Agency for International Development

The Rockefeller Foundation

European Union

Opportunity and Challenge

Significantly improve TB therapy (drug sensitive and resistant TB)

Mobilize necessary resources to execute against the present plan

Thank you !

Critical Path to TB Drug Regimens

Focus

- Data standards & integration
- Biomarkers and endpoints as disease response assays
- Animal models
- Pharmacology
- Disease progression models

- Drug combination testing and development

- Clinical trials infrastructure
- Resource mobilization
- Regulatory harmonization
- Access and appropriate use