

Preclinical Portfolio

Zhenkun Ma, Ph.D.
Global Alliance for TB Drug Development
October 24, 2011
Lille, France

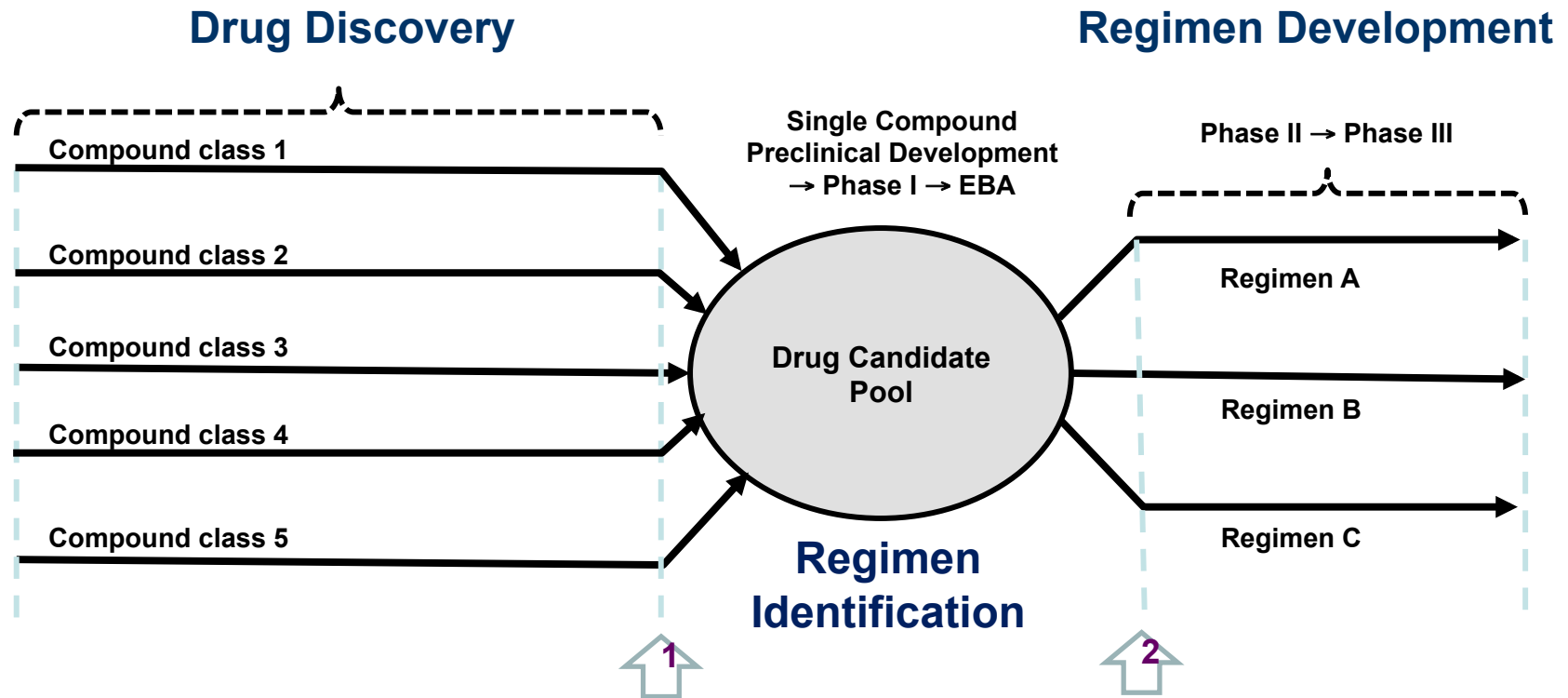


TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2011/10/24 SHA Meeting

Objectives of Preclinical Programs



2011 TB Alliance Portfolio

Discovery			Preclinical Development	Clinical Development		
TARGET OR CELL-BASED SCREENING	LEAD IDENTIFICATION	LEAD OPTIMIZATION		CLINICAL PHASE I	CLINICAL PHASE II	CLINICAL PHASE III
Natural Products IMCAS	Whole-Cell Hit to Lead Program GSK	Mycobacterial Gyrase Inhibitors GSK	TBA-354 U. of Auckland/ U. Ill Chicago		PA-824 Novartis	Moxifloxacin (+ H, R, Z) Bayer
TB Drug Discovery Portfolio NITD		THPP Series GSK	Preclinical TB Regimen Development JHU/U. Ill Chicago		TMC207 Tibotec	Moxifloxacin (+ R, Z, E) Bayer
Topoisomerase I Inhibitors AZ/NYMC	Gyrase B Inhibitors AZ	Pyrazinamide Analogs Yonsei			PA-824/Pyrazinamide	
	Folate Biosynthesis Inhibitors AZ	Diarylquinolines Tibotec/U. of Auckland			TMC207/Pyrazinamide	
	Whole-Cell Hit to Lead Program AZ	Riminophenazines IMM/BTTTRI			PA-824/TMC207	
	RNA Polymerase Inhibitors AZ				PA-824/ Moxifloxacin/ Pyrazinamide	
	Energy Metabolism Inhibitors AZ/U. Penn					

■ Novel TB regimen development

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



Portfolio Approach: Balancing Impact/Risk

- 1. Optimize known compound classes:** to fully capitalize on the success of compounds already in development; develop best-in-class
 - TMC207 – a novel class for both DS/DR-TB
 - PA-824 – a novel class for both DS/DR-TB
 - Pyrazinamide – an important agent for future regimens
 - Clofazimine – known class for leprosy, potential for both DS/DR-TB
- 2. Develop novel classes based on known targets:** to capitalize on validated drug targets, discover novel classes to address resistance
 - RNA polymerase inhibitors – target of rifamycins
 - DNA gyrase inhibitors – target of fluoroquinolones
- 3. Develop novel classes based on novel targets:** to discover new drug classes with novel mode of action
 - Topoisomerase I inhibitors
 - FoIB inhibitors
 - Chemical genomic approach - whole-cell screening



TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2011/10/24 SHA Meeting

2011 Major Advancements

- Multiple novel drug regimens identified with potential to shorten duration of therapy to < 2 months (JHU)
- TBA-354, a new generation nitroimidazole, advanced into preclinical development (ACSRC/UIC)
- THPP, a novel compound class with a novel mode of action, advanced into lead optimization (GSK)
- Pyrazinamide (PZA) analog program initiated to identify a next generation PZA, ideally to overcome PZA resistance (BioDuro/Yonsei)



TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2011/10/24 SHA Meeting

2011 Discontinued Projects

- Protease inhibitors – strategic change to focus on later stage programs
- Menaquinone A inhibitors – selectivity, did not meet *in vivo* milestones
- InhA inhibitors – did not meet *in vivo* milestones, DDI issues
- Malate synthase inhibitors – did not meet *in vivo* milestones



New Partners

- Sanofi portfolio
- Abbott portfolio
- Scripps Research Institute



Potential Compounds for Regimens

(Current orally active compounds in clinical trials)

- Rifampin/Rifapentine
- Isoniazid
- Pyrazinamide
- Ethambutol
- Clofazimine
- Moxifloxacin/Gatifloxacin
- Linezolid/PNU-100480/AZD5847
- TMC207
- PA-824/OPC-67683
- SQ109

**Potential 3- and 4-drug combinations:
330 (without even varying dose)**



**The need for
prioritization using
preclinical models**

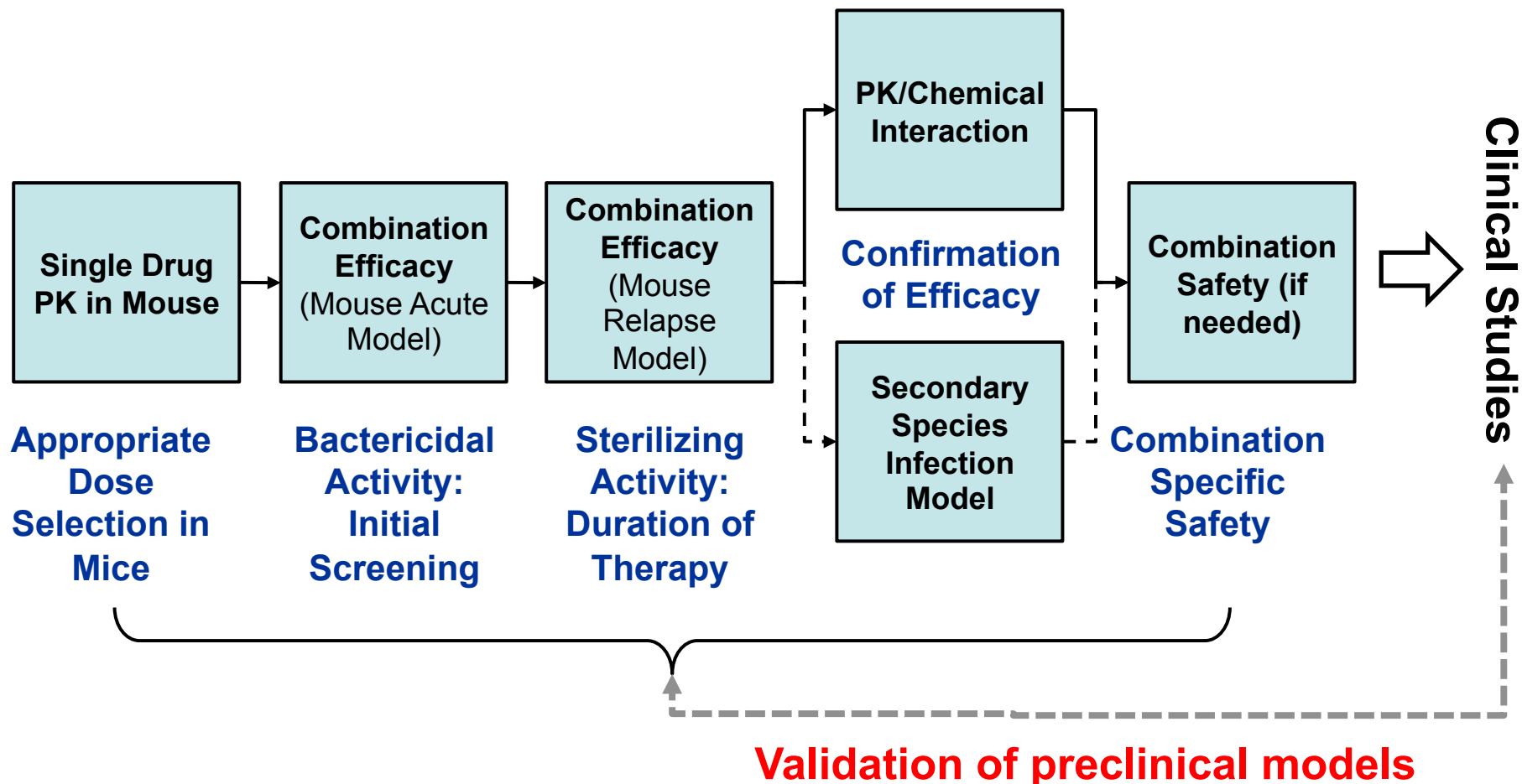


TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Process for Novel Regimen Discovery

An unbiased, data-driven approach:



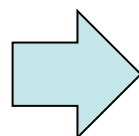
TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

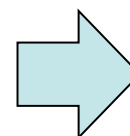
Novel Regimens Identified to Date

Compound Classes in Combo Study:

Rifampin (R)
Isoniazid (H)
Pyrazinamide (Z)
Ethambutol (E)
Moxifloxacin (M)
Linezolid (L)
Clofazimine (C)
PA-824 (Pa)
TMC207 (J)



**189 potential
3- and 4-drug
combinations**



Promising Regimens Identified (Duration in months)

PaMZ (4)
JPaZ (4)
JMZ (4)
JLZ (3)
JPZ (2)
JCZ (2)
JCMZ (2)

.....

Key criteria for selecting regimens for further development:

- Duration of therapy (4 months for DS and 6 months for MDR)
- Drug resistance (MDR and XDR-TB)
- Safety/tolerability including Phase I
- Co-administration with ARV
- Compliance issues (PK, once daily or less frequent dosing)
- Cost of goods

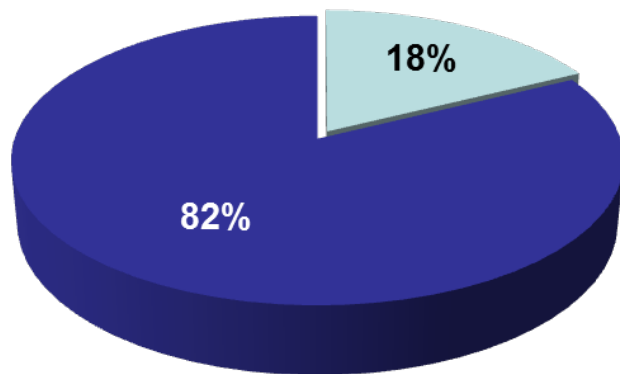


TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2011 Partner Contribution

Discovery Resources



- TB Alliance
- Partner Contribution

Current discovery portfolio partners:

- AstraZeneca
- Auckland Cancer Society Research Center
- Beijing Tuberculosis and Thoracic Tumor Research Institute
- BioDuro/PPD
- Colorado State University
- GlaxoSmithKline
- Institute of Microbiology, Chinese Academy of Sciences
- Institute of Materia Medica, Chinese Academy of Medical Sciences
- Johns Hopkins University
- NIH/NIAID
- Novartis Institute of Tropical Diseases
- New York Medical College
- Research Triangle Institute
- Tibotec/J&J
- University of Illinois at Chicago
- University of Pennsylvania
- Yonsei University



TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

2011/10/24 SHA Meeting

Thanks to...

- Funders/Stakeholders
- Partners
- TB Alliance staff

