



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Preclinical Selection of New Drug Combination Initiative

Open Forum 2: Key Issues in TB Drug Development
December 12-13, 2006 (London)





TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Uniqueness of TB Drug R&D

- Active TB must be treated by combination therapy, to prevent resistance and improve efficacy
- Therefore the unit for Phase II and III development should be regimen or combination, not a single compound



- A preclinical program should include two components:
 - Evaluate safety and efficacy of each new compound (NCE)
 - Identify optimal regimens in which that NCE will be developed

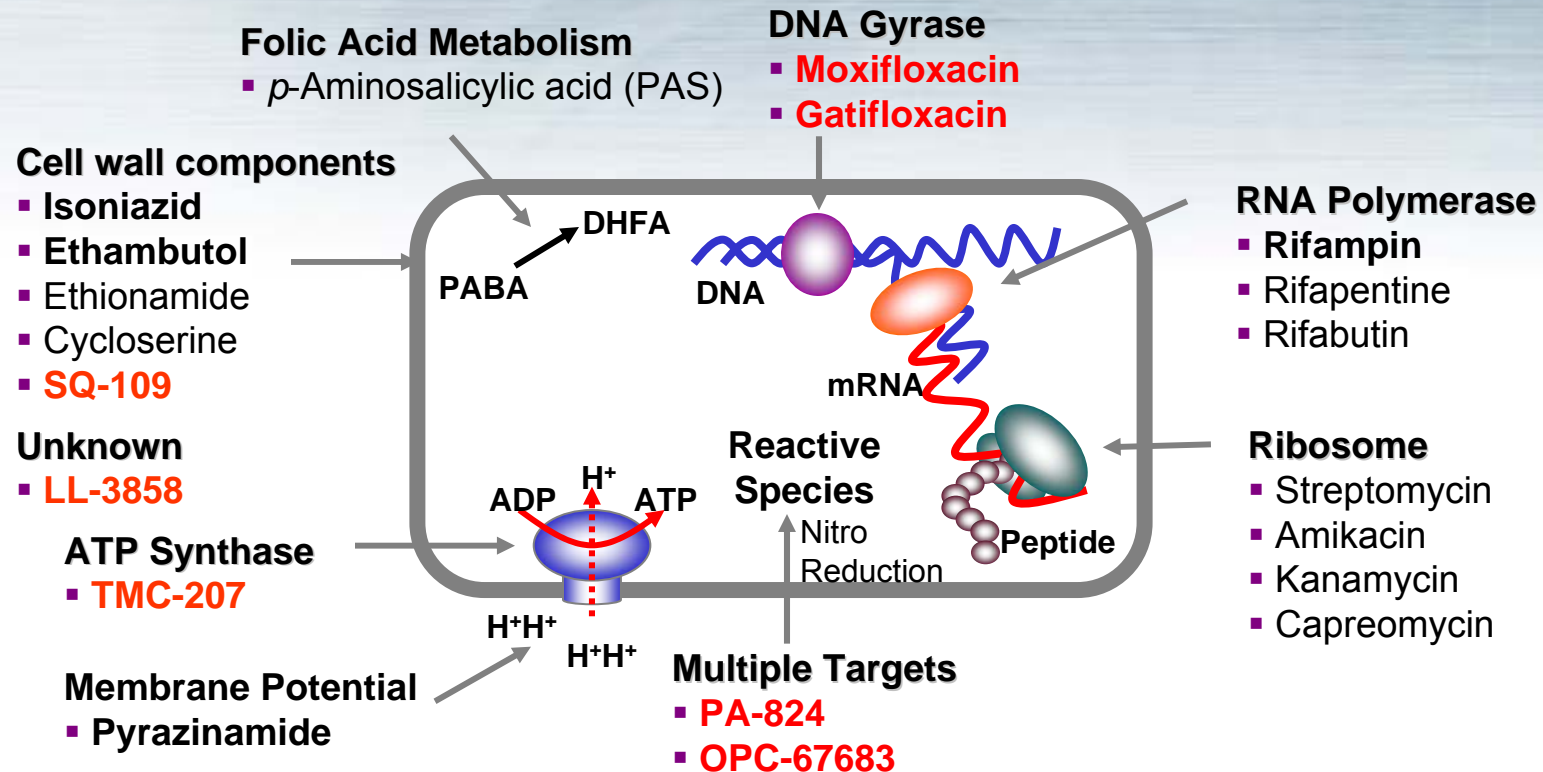
New Agents in Clinical Developments

Compound	Stage	Regimen
Gatifloxacin (G)	III	RHZ G
Moxifloxacin (M)	III and II	RHZ M and RM Z E
TMC-207 (J)	EBA	BR + J
OPC-67683 (O)	EBA	R O Z E? (Mouse model, PLoS Medicine 2006)
PA-824 (P)	I	R P Z E? (Mouse model, ICAAC 2006)
SQ-109 (S)	I	RHZ S (Yesterday's Presentation)
LL-3858 (L)	I	?
Discovery Pipeline	Discovery	?

(R: Rifampin; H: Isoniazid; Z: Pyrazinamide; E: Ethambutol)

- Current approach: Replacing one drug from standard regimen during each development cycle
- *Are we going to end up with multiple regimens, each with similar incremental improvements?*
- *Are we taking advantage what the new drugs could potentially offer?*

Drug Targets of New and Old Anti-TB Agents



- Compounds with the same target site should not be combined
- New agents provide significant target diversity and potential for better combinations



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

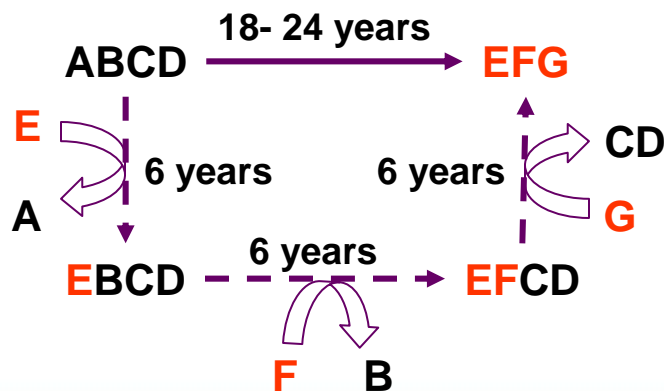
Need for Novel Therapy

- Major issues in TB chemotherapy:
 - Long treatment duration
 - MDR- and XDR-TB
 - TB/HIV co-infection
- A drug combination that simultaneously addresses these problems would have the greatest impact
- To do so, replacing almost all the current drugs from the standard RHZE regimen would be optimal
 - Rifampin: MDR and P450 induction
 - Isoniazid: MDR and lack of sterilizing activity
 - Ethambutol: no significant contribution to efficacy

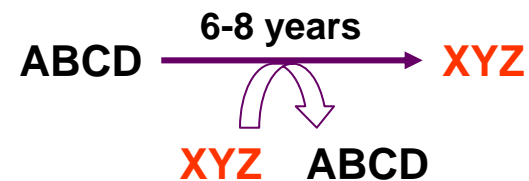
Need for New Approach

- Conventional approach would need 18-24 years to develop a combination that contains ≥ 3 new drugs
- A new paradigm is needed for rational selection of new combinations from ALL agents that meet the baseline requirements (efficacy, safety and PK)

Conventional Approach:



New Approach:





Importance of Preclinical Selection

- Unpractical (unnecessary) to study all potential combinations in man

Number of drugs in each combination	Total potential combinations	
	N = 8 (drug pool)	N = 10 (drug pool)
2-drug combination	28	45
3-drug combination	56	120
4-drug combination	70	210

- Current animal models are not perfect but good enough for narrowing down possibilities



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Request for Proposals (RFP) Preclinical Selection of New Drug Combinations

Thanks to many SAC members and scientific consultants of the TB Alliance for their inputs!

- RFP released in September 2006
- Currently in proposal solicitation and review process
- Project will initiate in first part of 2007

See www.tballiance.org for RFP



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Objectives

To identify novel 3-drug combinations that have potential to:

- Shorten treatment to 2 months
- Be co-administered with ARVs
- Be effective against MDR- and XDR-TB

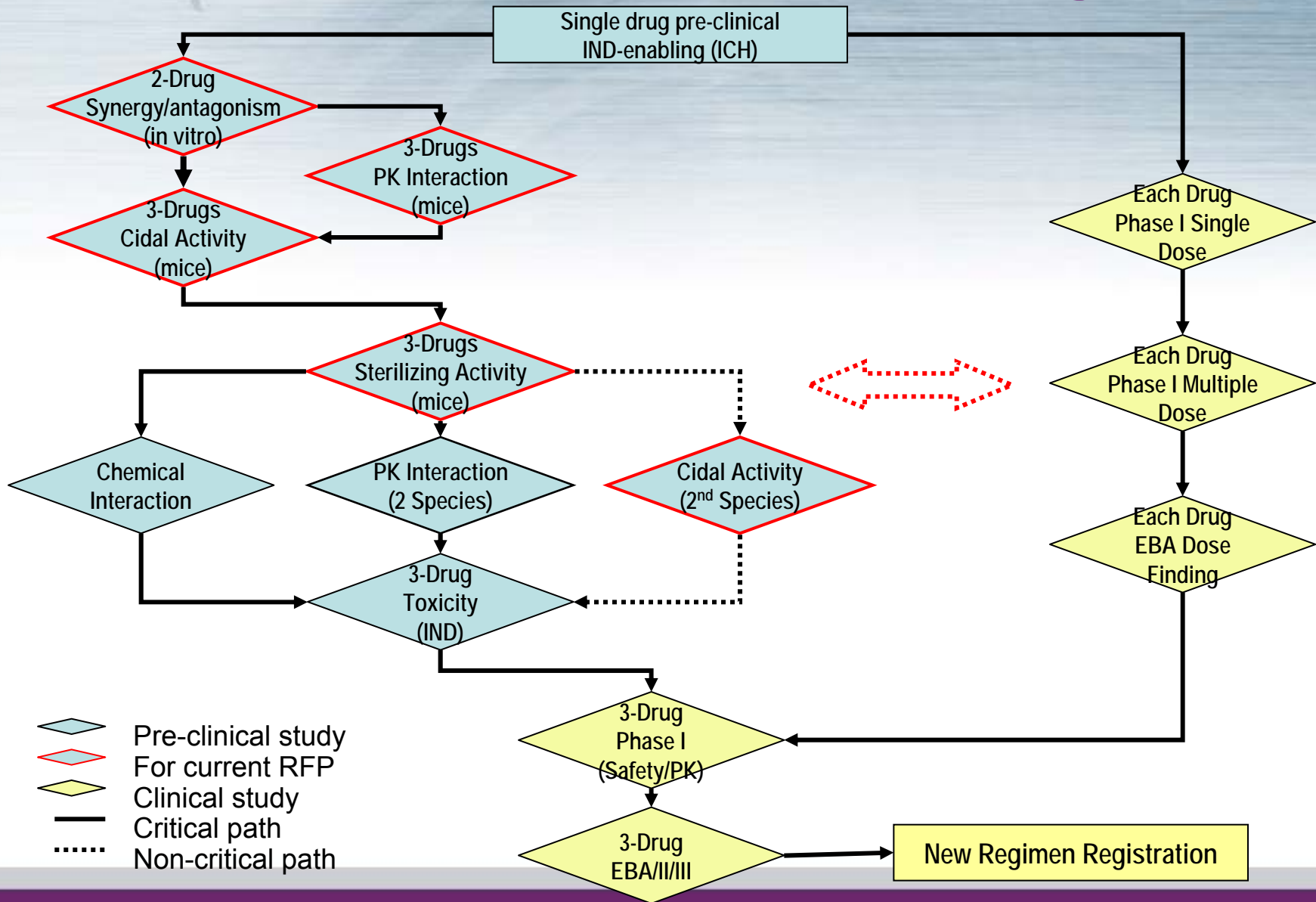


TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Major Challenges

- **Technical:**
 - Predictability of the current animal models
- **Regulatory:**
 - Guidelines for developing novel combinations
- **Sponsor:**
 - Cooperation amongst sponsors

Proposed Algorithm

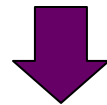




TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Five Specific RFP Activities

1. Study in vitro synergistic/antagonistic effects
2. Study potential PK interactions
3. Screen cidal activity of combinations in mice
4. Evaluate sterilizing activity of combinations in mice
5. Confirm efficacy in a secondary animal species



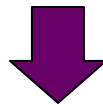
3-5 Combinations for further preclinical and clinical development



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Development of TB Drug Database

- **Compound Selection:** all TB drugs in use and drug candidates in development
 - First-line drugs
 - Second-line drugs
 - Drugs used anecdotally (linezolid, clofazimine, etc)
 - New compounds in clinical and perhaps preclinical development
- **Data Collection:** all relevant information for new combination development
 - Physicochemical properties
 - Potency/efficacy information
 - PK/PD information
 - Safety/tolerability information



Select 8-10 best agents for combination studies

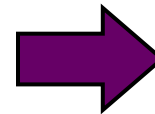


Activity 1: In Vitro Synergy/Antagonism

- Test possible 2-drug combinations in checker board format
 - Under both replicating and non-replicating conditions
 - Compounds with the same binding site will not be studied

Example: 8 drugs → 28 2-drug combinations

	R	I	Z	E	M	P	O	J
R		RI	RZ	RE	RM	RP	RO	RJ
I			IZ	IE	IM	IP	IO	IJ
Z				ZE	ZM	ZP	ZO	ZJ
E					EM	EP	EO	EJ
M						MP	MO	MJ
P							PO	PJ
O								OJ
J								



Each 2-drug combinations

X MIC	1/4	1/2	1	2	4	8
1/4						
1/2						
1						
2						
4						
8						



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Activity 2: PK Interactions

- All potential 3-drug combinations will first be triaged: combinations that contain any pair of the following will be excluded:
 - known antagonism
 - identical mode of action
 - known chemical interaction
 - unmatched PK
 - same metabolic pathway
 - same toxicity/target organs
- The remaining 3-drug combinations will be administered orally in combination and as single drug to study the PK interactions

Example:

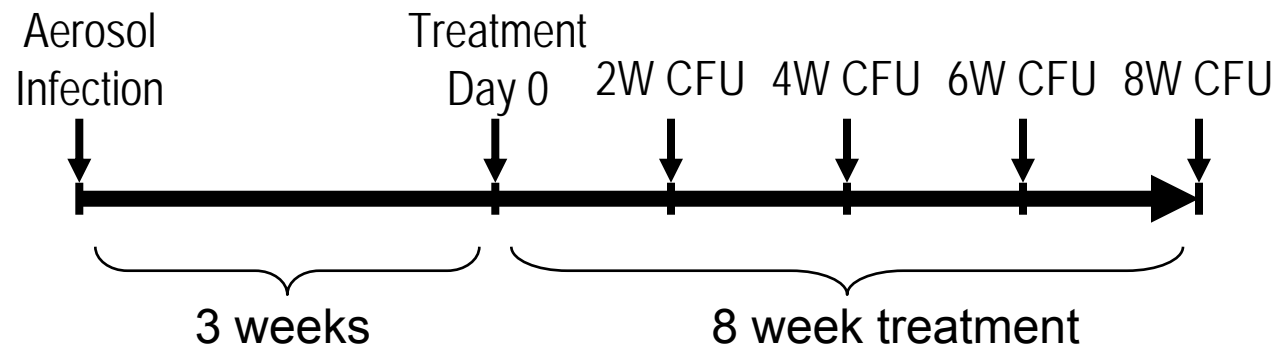
8 drug pool → 56 3-drug combinations ^{Triage} → ~28 3-drug combinations



Activity 3: In Vivo Cidal Screening

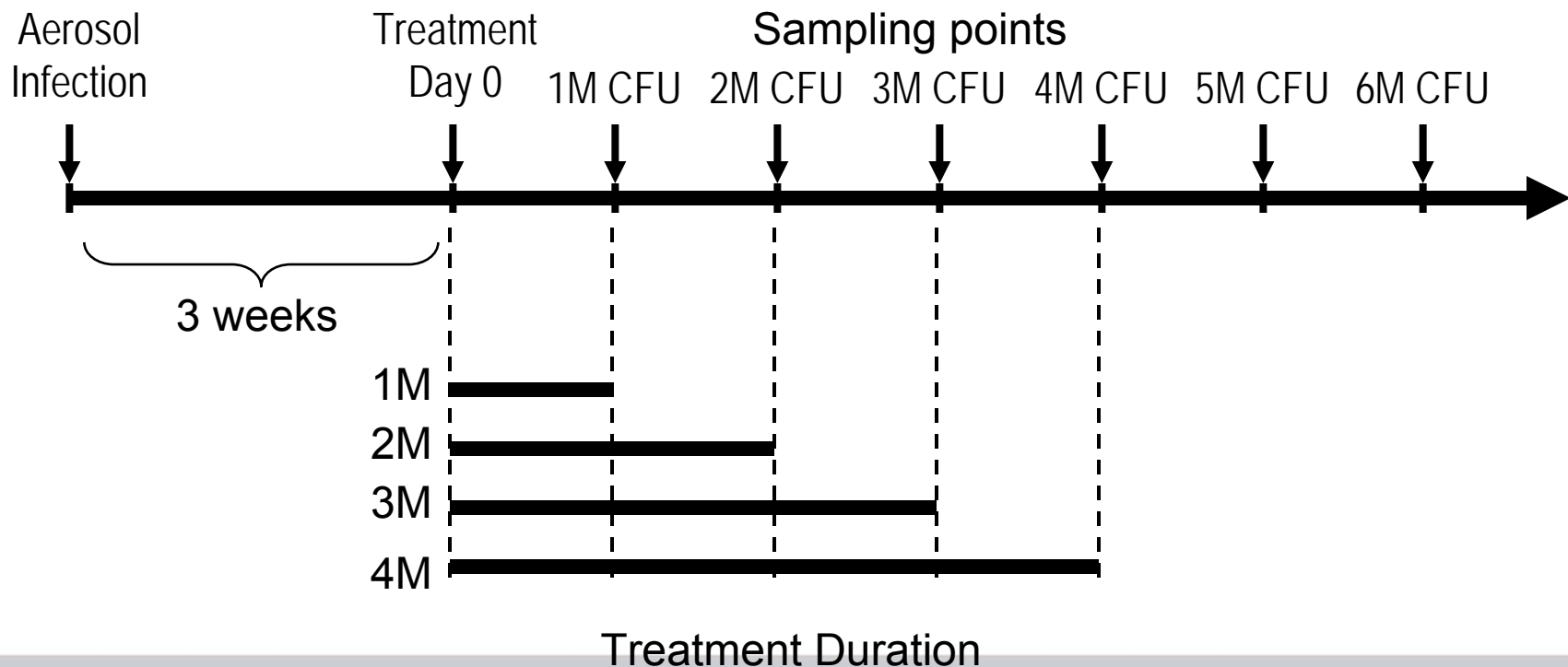
- The remaining 3-drug combos will be tested in a short-term screening mouse model
- Dose selection: human equivalent dose or mouse bactericidal doses
- Identify 5-10 combos based on level and speed of CFU reduction

Example screening model (all 3-drug combinations + control groups):



Activity 4: In Vivo Sterilizing Activity

- The 5-10 most promising combos will be tested in the long-term mouse model for relapse to study duration
- Identify 3-5 combos that give the most rapid cure without relapse (2RHZE/4RH as control)





TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Activity 5: Confirmation Model

- The 3-5 combinations will be evaluated in a secondary animal model for cidal or sterilizing activity
- Model selection should be based on both predictability and feasibility
- Results will be used to prioritize the combinations for further advancement



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Further Preclinical Studies for the Final 3-Drug Combination

- Chemical stability and interactions
- PK interactions in other species
- Toxicology and safety pharmacology studies



TB ALLIANCE
GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Thank You