Demystifying Pyrazinamide

PZA Workshop 2012

Area of Emphasis - PZA in Combination Therapy

Chairs:

Kyu Rhee (WCMC)

Khisi Mdluli (TB Alliance)

TB ALLIANCE

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT

Objectives

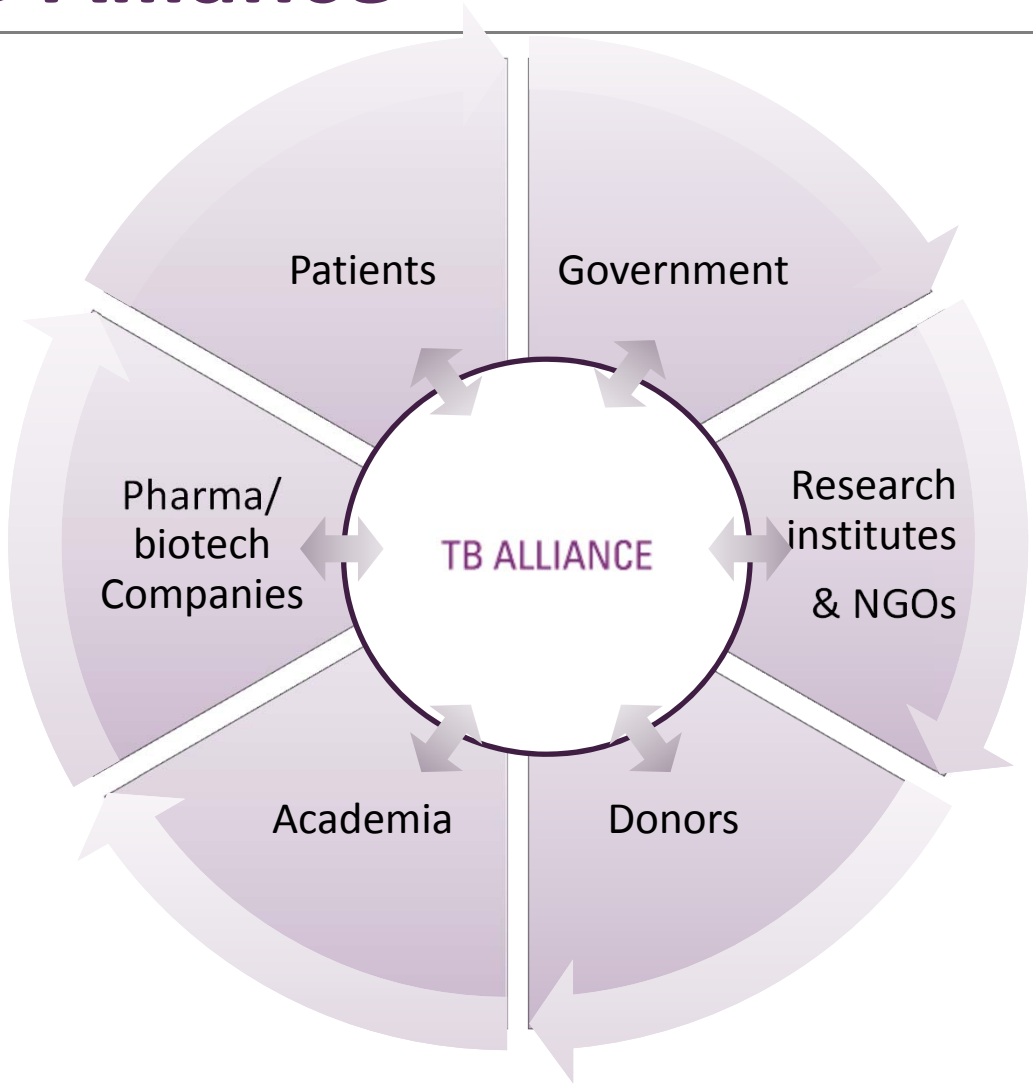
- PZA contribution to combination therapy: past, present and future
- PZA in both pre-clinical and clinical settings
- Does PZA modulate the immune system?
- The Pharmacologic principles of PZA
- *PZA synergies: magnitude, mechanisms, and meaning*
- Can PZA use be optimized?
- Can we design a better PZA?

PZA in Combination Therapy

- 8:35-9:05 **Role of PZA in Regimens to Treat TB: Past, Present, and Future -** *Eric Nuermberger*
- 9:05-9:35 **PZA: A New Look Based on RNASeq, the Hollow Fiber System, and Patient Level Data -** *Tawanda Gumbo*
- 9:35-9:50 **Break**
- 9:50-10:10 **PZA Activity vs. *M. tuberculosis* and *M. bovis* in Immunocompetent and Nude Mice -** *Nicole Ammerman*
- 10:10-10:40 **Re-Thinking the Pharmacologic Principles of PZA -** *Kyu Rhee*
- 10:40-11:45 **Discussion - *Panel Members:*** *Nicole Ammerman (K-RITH), Veronique Dartois (UMDNJ), Jan Gheuens (BMGF), Tawanda Gumbo (UT- Southwestern), Eric Nuermberger (JHU), Kyu Rhee (WCMC), Anna Upton (TB Alliance), Courtney Aldrich (U of Minn)*
- 11:45-12:30 **Lunch**

TB Alliance

- Founded in 2000
- Not-for-profit Product Development Partnership (PDP) headquartered in New York
- Entrepreneurial, virtual approach to drug discovery and development
- Largest portfolio of TB drug candidates in history



Current TB Therapy and Unmet Needs

Current Therapy

- **Drug-sensitive TB**
  4 Drugs, >6 months
- **M(X)DR-TB**
  Few available drugs; >2 years; poorly tolerated
- **TB/HIV co-infection**
  Drug-drug interactions with antiretroviral agents (ARVs)
- **Latent TB Infection**
  9 Month H

Unmet Needs

- **Shorter, simpler therapy**
- **More effective, safer regimens; shorter, simpler therapy**
- **Shorter, Co-administration with ARVs**
- **Shorter , more easily tolerated therapy**

No new drugs for TB in 40 years!

TB Alliance Vision

Current Treatment

6-30
Months

New Treatments in Development

2-4
Months

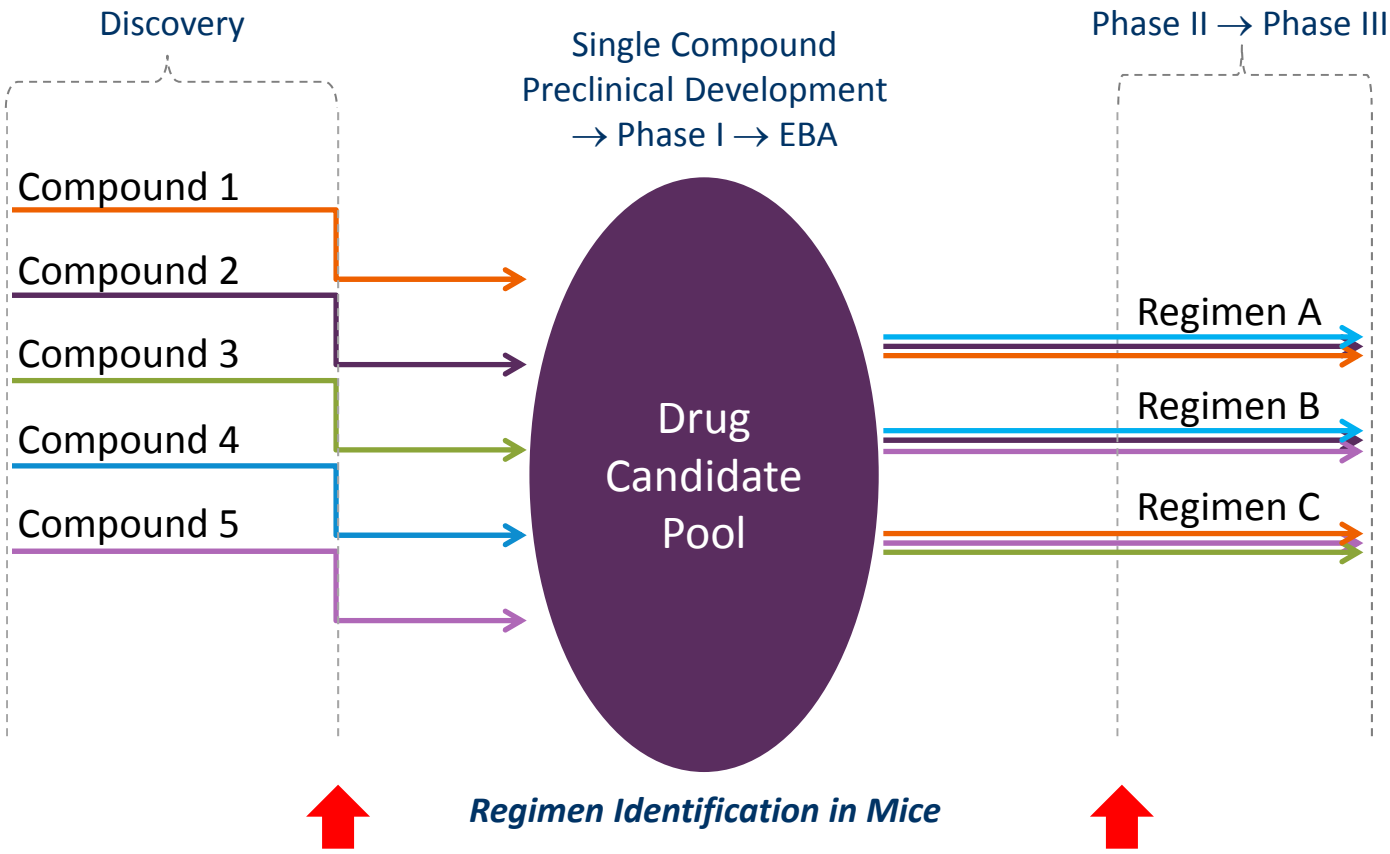
Our Vision

7-10
Days

Success will require novel drug combinations

TB Drug/Regimen

Discovery and Development Process



Questions for Panel of Discussants

- What is the mechanism for PZA synergy?
- Is the PZA synergy with other drugs occurring at some or all phases of treatment (initial or continuation)?
- Which proposed PZA mode of action hypothesis best explains the observed synergistic behaviors and activity against persisters?
- Is there an i*n vitro* condition where synergy between PZA and other drugs is observed similarly to how it is observed *in vivo* or is synergy an *in vivo* only phenomenon?
- How can PZA use be optimized in the clinic – change of dose? Change of dosing schedule? Change of partner drugs?
- A new PZA should synergize the companion drugs, and shortens the duration of therapy – how can we screen for such compounds?
  - (a) using a diverse compound library?
  - (b) using a targeted library of PZA analogs?
- Do we need a “better” PZA?