Tuberculosis Drug Accelerator

Overview of Activities and Portfolio
“who, why, what, how, by when and where are we now”
Steve Berthel
What is the Tuberculosis Drug Accelerator?

- The TBDA is a groundbreaking partnership between:
  - 8 Pharmaceutical companies
  - 5 Major Universities
  - 2 Research Institutes
  - 1 National Institute
  - 1 non profit PDP

- With participation from:
  - Bill and Melinda Gates Foundation

- Managed through:
  - The CEO roundtable at the New Venture Fund
TBDA is a quasi-biotech

**Somewhat Biotech like**
- Discovery, preclinical and early clinical capabilities
- Multiple projects at multiple centers covering different modes of action
- Funding and portfolio management oversight

**Fairly Unique**
- Comprised of normally competitive organizations that share information and resources at an unprecedented level
- Investigating a single disease from many, many angles
- Output has global access requirements
Why have a TBDA?

- TB is one of the world’s **leading infectious killers**, disproportionately affecting developing countries:
  - 1.4 million deaths in 2015
  - 10.4 million new infections in 2015
  - 480,000 MDR TB cases in 2015
- First-line therapies for TB are **antiquated and inadequate**, taking 6 months to cure patients
- The current six month regimen contributes to **high treatment default rates** that can lead to:
  - increased transmission
  - drug resistance
  - death
- The world needs a **shorter, safer** TB drug regimen

Why have a TBDA?

- Limited investment in TB biology and drug discovery
- Lack of understanding of how to improve therapy
- Few well validated targets
- Poor assays to screen for drugs
- No new first line drugs in 50 years (safety of recent entries limit use)
- Resistance to only true sterilizing and treatment shortening agent
- Limited Candidates
What should we focus on?

- Current TB regimens drive down bacterial levels quickly, but require months of treatment to rid the body of all TB.
- The only way to overcome this persistence is through a shorter more effective regimen.
- **GOAL**—To generate multiple, mechanistically distinct TB candidates sufficient to advance a drug regimen to a **one month clinical POC by 2024**.
- Need to create a balanced portfolio:
  - Novel mechanisms
  - Sequestered sites (granulomas, cavities)
  - Tolerant sub-populations
  - Safety
  - Resistance
How will this be accomplished?

- The current research paradigm is ineffective
- No New first-line TB drug regimens in 50 years
How will this be accomplished?

- By a new approach that addresses bottlenecks in historic TB drugs development
- In this way only the best candidates advance
TBDA organization

- 17 current members
- 8 subteams
TBDA Discovery/Preclinical Development

- **Discovery**
  - Target or Cell-based Screening
  - Lead Identification
  - Lead Optimization
  - Preclinical development

- **Preclinical**
  - Clinical Phase I
  - Clinical Phase II
  - Clinical Phase III

**Timeline:**
- 2012-2013: Discovery
- 2014: Lead Identification
- 2015: Lead Optimization
- 2016: Preclinical development
- 2017: Clinical Phase I
- 2018: Clinical Phase II
- 2019: Clinical Phase III

**Key Points:**
- **2019**
  - New preclinical candidates
- **2024**
  - 1 month, 3-drug regimen proof of concept
### TBDA Discovery/Preclinical Capabilities

#### Discovery

- Target or Cell-based Screening
  - **Lead Identification**
  - **Lead Optimization**
  - **Preclinical development**

#### Preclinical

- Clinical Phase I
- Clinical Phase II
- Clinical Phase III

#### Clinical

- Libraries
  - Pharma partners (Sanofi, Merck, Bayer, AbbVie, Lilly, AstraZeneca, GSK, Pfizer)
  - Other (MMV, BioFocus)

- Target
  - ID & validation (Weill Cornell, Texas A&M)
  - Crystallography (Texas A&M)
  - Screening (IDRI, Texas A&M)

- Whole cell
  - Replicating, multiple C source (Weill Cornell, IDRI, NIH)
  - Non-replicating (Weill Cornell)
  - Low pH (Weill Cornell, IDRI, NIH)
TBDA Discovery/Preclinical Capabilities

- Medicinal Chemistry (GSK, Merck, Sanofi, Lilly, AbbVie, UCT, Dundee, CROs)
- Animal Models
  - Acute/Chronic BalbC (GSK, Sanofi, CSU)
  - Kramnik (CSU)
  - Marmoset (NIH)
- PK, Tox
  - Caseium penetration (Rutgers)
  - Metabolomics (Weill Cornell)
  - ADME, PK (Pharma, CROs)
  - In vitro/in vivo Tox (Pharma, CROs)
TBDA Discovery/Preclinical Capabilities

- **Lead(s) selected**
  - Efficacy in advanced and/or combination models (Pharma, CSU, NIH, non-TBDA collaborators)
  - In vitro tox (CROs)
  - Non-GLP tox studies (CROs)

- **Preclinical Candidate Selection** (TB Alliance, Gates Foundation, Pharma)

- **Preclinical Candidate Profiling**
  - IND enabling studies (Pharma, CROs)
  - CMC (Pharma, CROs)

- **Clinical**
  - Study design (TB Alliance, Pharma)
  - Combination study design (TB Alliance)
  - IND Preparation (TB Alliance, Pharma)
Screens
- Whole cell phenotypic screening against corporate collections complete
- Conditional screening (carbon source, pH, low O₂) continues
- Special library screening continues
- Biochemical (target-based) screening continues

Hits
- >200 compound series identified to date
- ~10 currently under triage
- ~20 currently under hit assessment
Lead Identification

- ~30 projects in hit to lead stage
- ~60% with known targets
  - MmpL3
  - QcrB
  - RNA polymerase

Pie chart showing the distribution of projects across different pathways:
- Metabolism and Respiration: 29%
- Cell Wall: 11%
- Lipid metabolism: 7%
- Information Pathways: 39%
- Unknown: 11%
- Other: 3%
Lead Optimization
- ~10 projects in Lead Optimization
- Almost all with known targets
  - DprE1
  - MmpL3
  - InhA
Preclinical Development

- 3 projects from the TB Alliance have identified candidates
  - DprE1 inhibitor TBA-7371
  - Oxazolidinone TBI-223
  - Diarylquinoline TBAJ-587
- All scheduled for P1 in next 18 m
How can the TBDA and CPTR better connect?

- Align meetings
  - Back to back if possible (TBDA meets semi-annually, 1 US based, 1 rest of world)
  - Assure no overlap- encourage co-participation when possible
- Provide clinical data on “front runners” to instruct preclinical back-up projects
- Provide clinical data to help refine, and make more predictive, TB animal models
In Conclusion

- The TBDA is a novel collaboration of 17 research organizations with the goal of discovering multiple mechanistically distinct TB candidates sufficient to advance a drug regiment to a 1 month POC by 2024
- Excellent progress has been made to date, with 3 preclinical candidates identified
- Partnerships such as the TBDA show how industry and others can work together in new ways to support global health innovation
- The TBDA model is being applied to other disease areas that lack incentives for research or require combination drug therapies
- Opportunities exist to use clinical data to inform preclinical projects