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

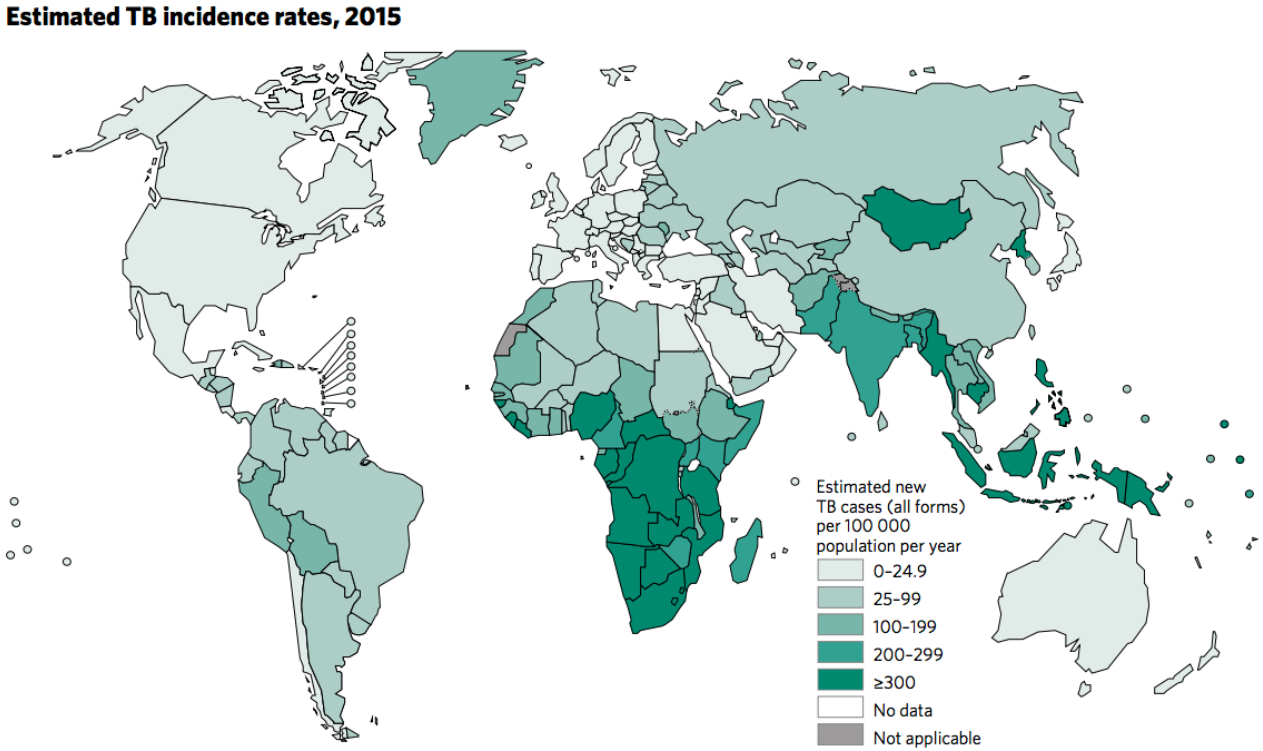
- Discovery, preclinical and early clinical capabilities
- Multiple projects at multiple centers covering different modes of action
- Funding and portfolio management oversight

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

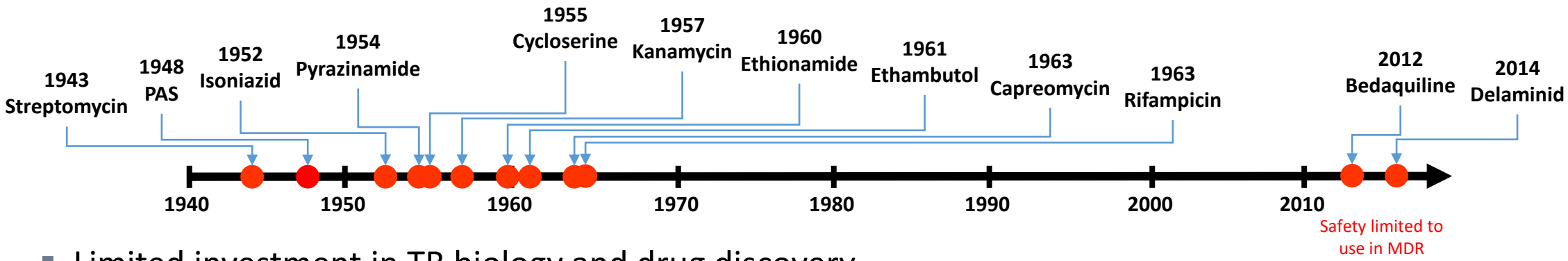
Why have a TBDA?

- 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



World Health Organization Global Tuberculosis Report 2016

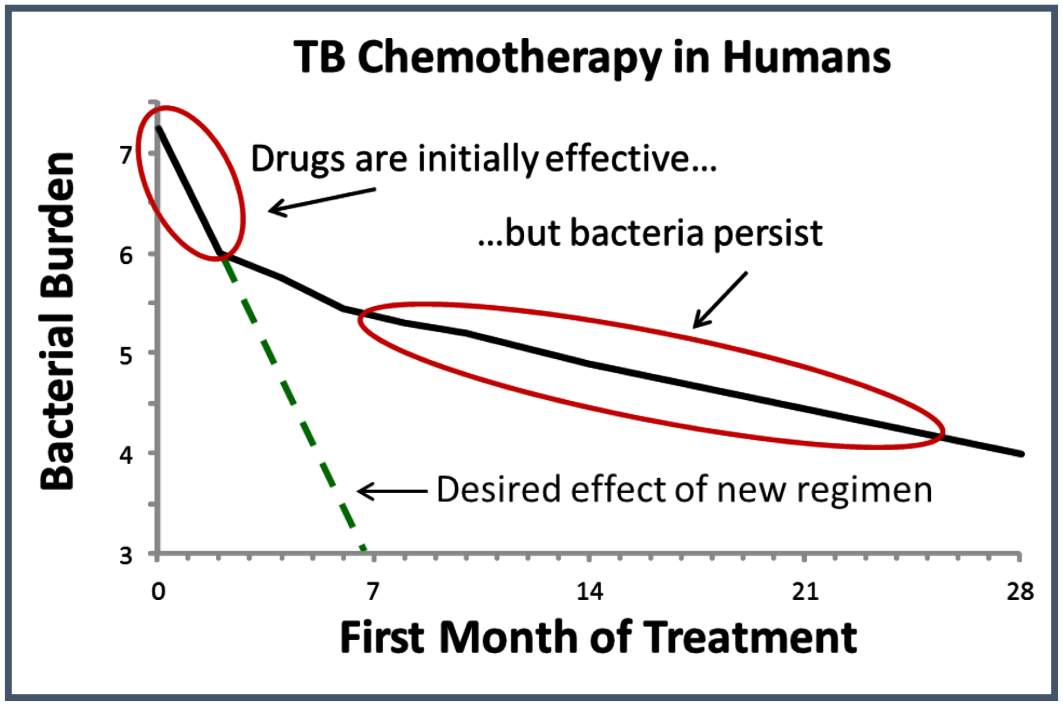
Why have a TBDA?



- 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

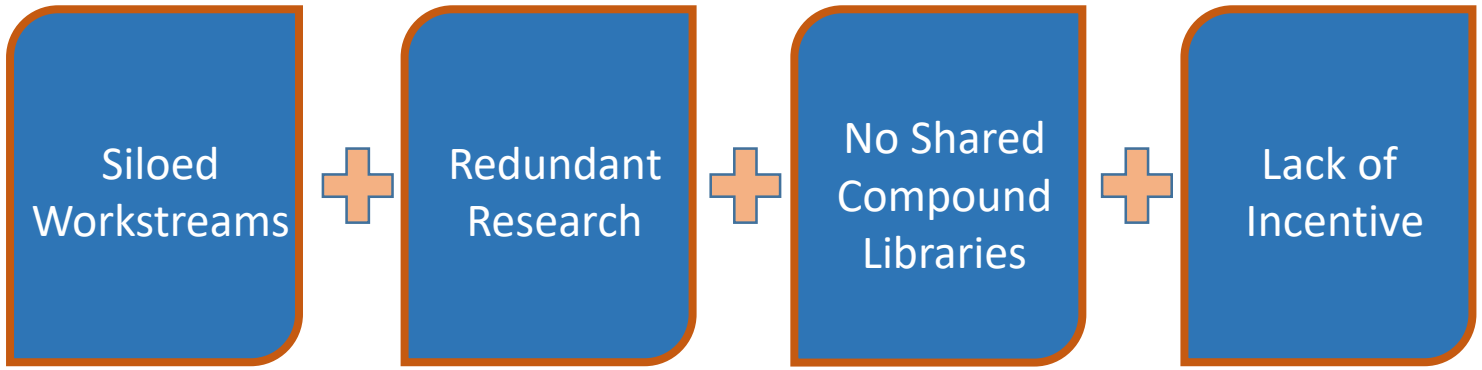
What should we focus on?

- 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



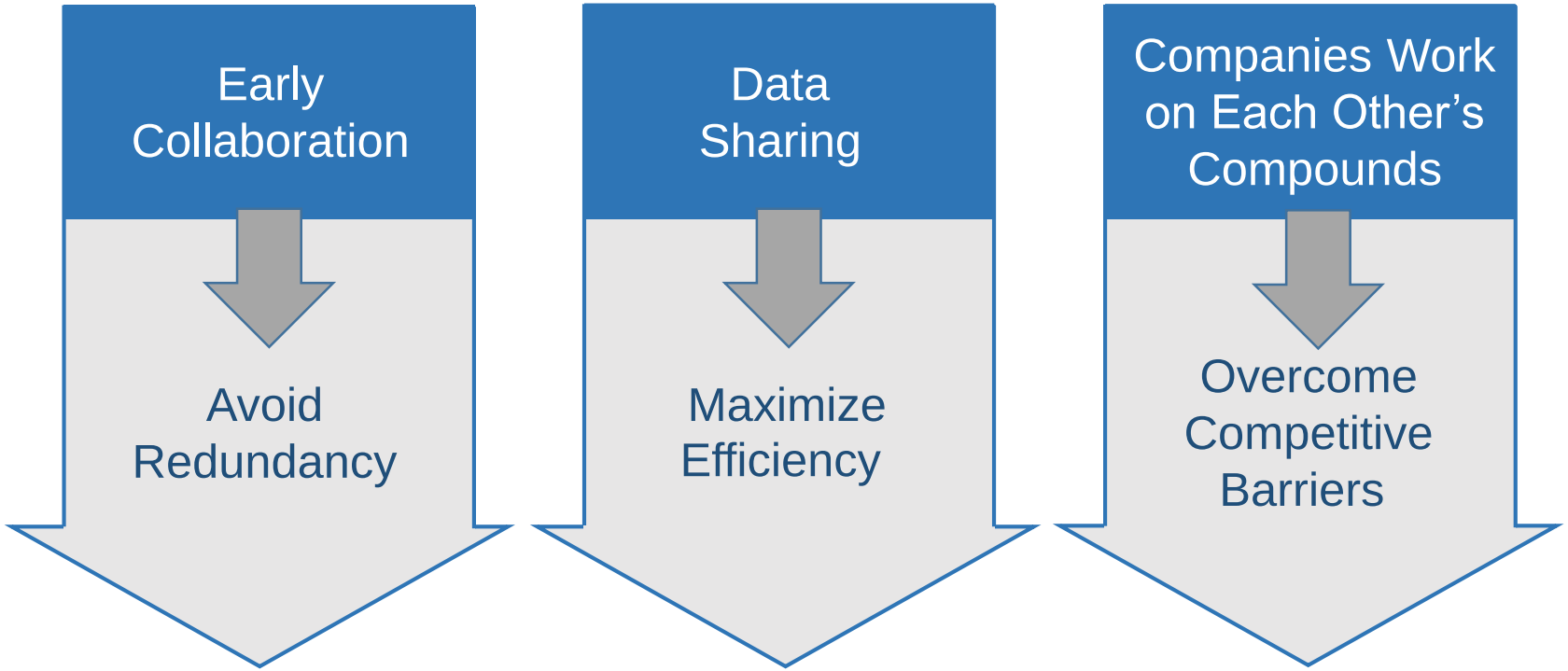
How will this be accomplished?

- The current research paradigm in ineffective
- No New first-line TB drug regimens in 50 years



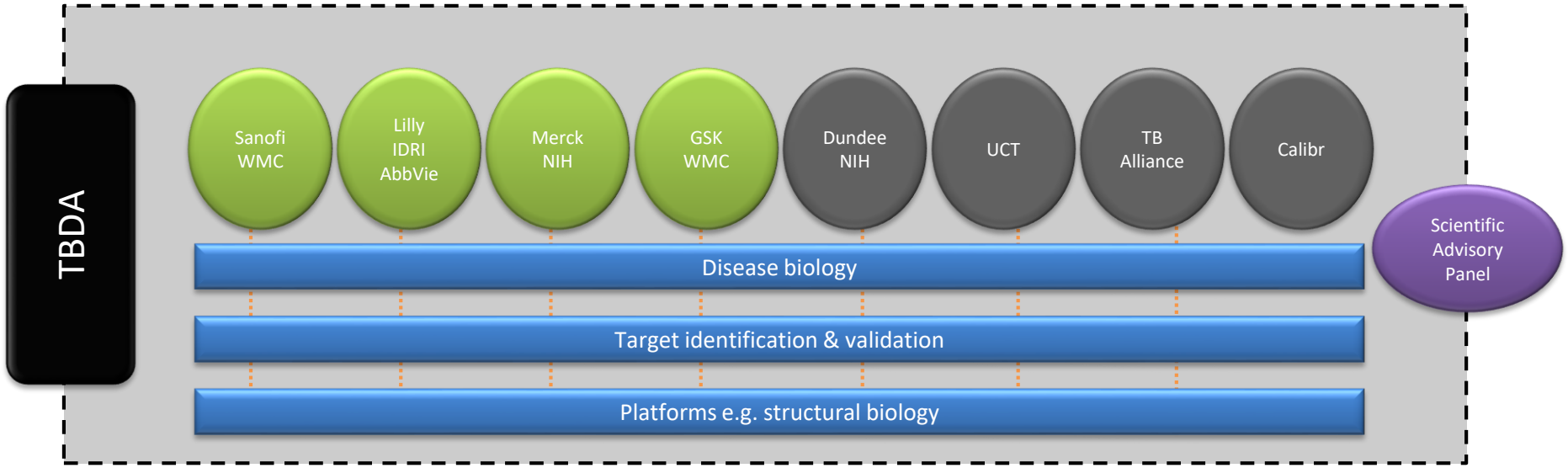
How will this be accomplished?

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

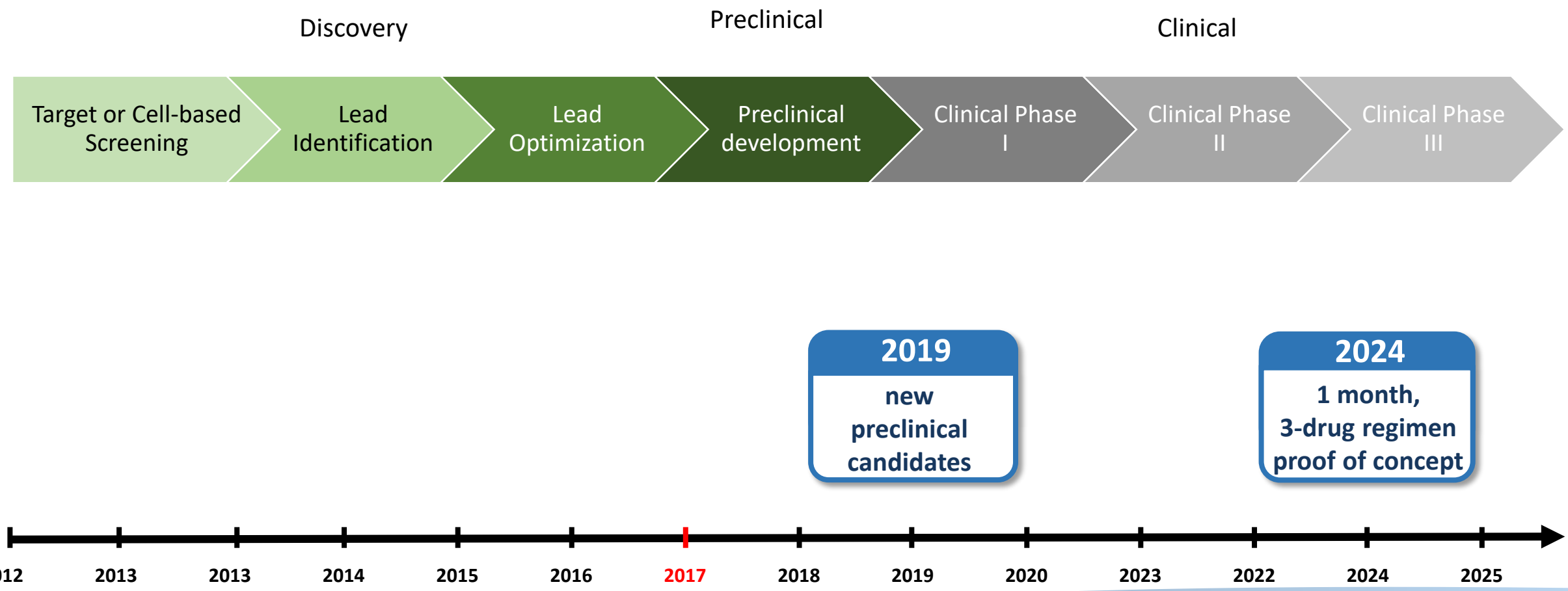


TBDA organization

- 17 current members
- 8 subteams



TBDA Discovery/Preclinical Development



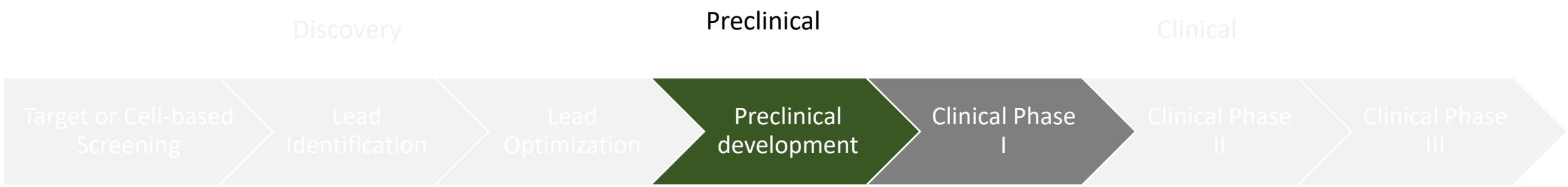
TBDA Discovery/Preclinical Capabilities

- 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)

TBDA Discovery/Preclinical Portfolio

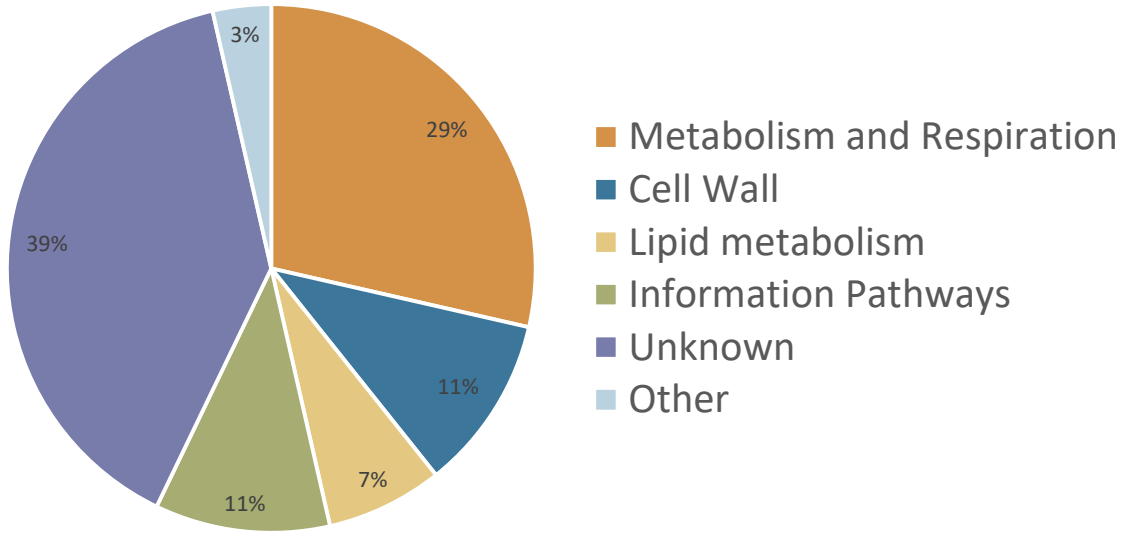
- Screens
  - Whole cell phenotypic screening against corporate collections complete
  - Conditional screening (carbon source, pH, low O_2) continues
  - Special library screening continues
  - Biochemical (target-based) screening continues
- Hits
  - >200 compound series identified to date
  - ~10 currently under triage
  - ~20 currently under hit assessment

TBDA Discovery/Preclinical Portfolio

Discovery | Preclinical | Clinical

Target or Cell-based Screening → **Lead Identification** → Lead Optimization → Preclinical development → Clinical Phase I → Clinical Phase II → Clinical Phase III

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

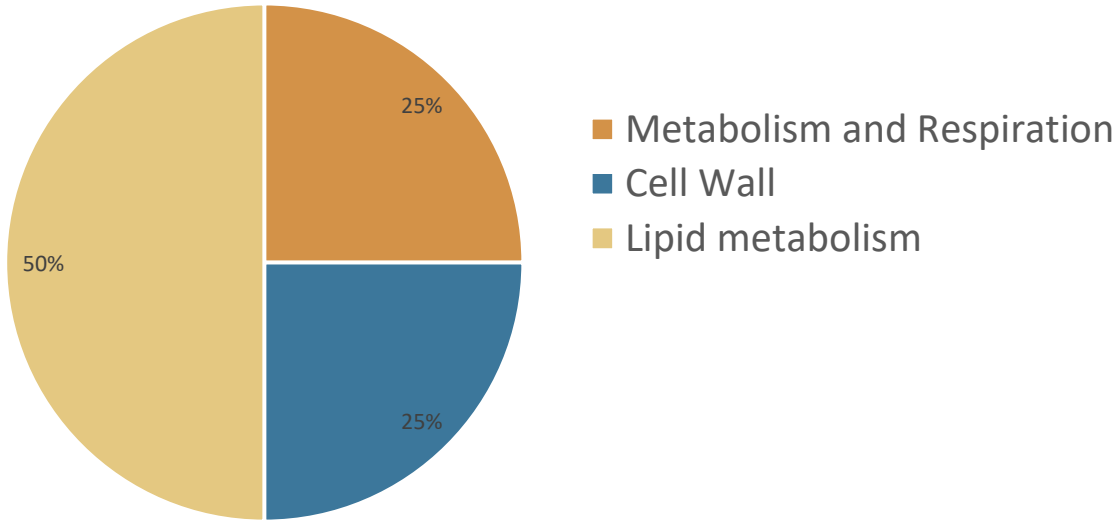


TBDA Discovery/Preclinical Portfolio

Discovery | Preclinical | Clinical

Target or Cell-based Screening → Lead Identification → **Lead Optimization** → Preclinical development → Clinical Phase I → Clinical Phase II → Clinical Phase III

- Lead Optimization
  - ~10 projects in Lead Optimization
  - Almost all with known targets
    - DprE1
    - MmpL3
    - InhA

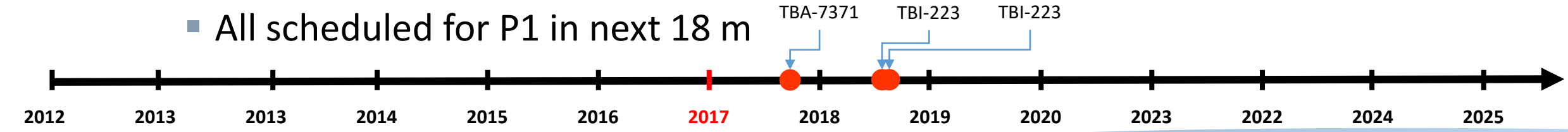


TBDA Discovery/Preclinical Portfolio

Discovery | Preclinical | Clinical

Target or Cell-based Screening → Lead Identification → Lead Optimization → **Preclinical development** → Clinical Phase I → Clinical Phase II → Clinical Phase III

- 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