New Drugs, New Regimens:
The Way Forward in TB Treatment

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Current TB Therapy - Unmet Needs

Current Therapy

- Drug-sensitive TB
  4 Drugs, 6-9 months

- M/XDR-TB
  Few available drugs; >18 months; poorly tolerated

- TB/HIV co-infection
  Drug-drug interactions with antiretroviral agents (ARVs)

- Latent TB Infection
  6-9 months of isoniazid

Unmet Needs

- Shorter, simpler therapy
- More effective, safer drugs; shorter, simpler therapy
- Co-administration with ARVs
- Shorter, better tolerated therapy

No new drugs for TB in 40 years; no market incentive
Profile of New M/XDR-TB Regimens

- Shorter duration with increased efficacy
- Fewer medicines
- No drug-drug interactions with ARVs (TB-HIV)
- Orally bioavailable; maximum of once daily dosing
- Improved safety and tolerability
- Affordable cost of goods with quality assured products
- Standardized approaches
- Less intensive monitoring
TB Alliance Vision

Success will require novel multi-drug combinations

6 – 24 months

2 – 4 months

10 days
## Global TB Drug R&D Portfolio

### DISCOVERY

- Actinomycete metabolite screening - U. Illinois Chicago, Myongji U.
- AstraZeneca Compounds
- Energy Metabolism Inhibitors - TB Alliance, U. Illinois Chicago, U. Penn
- Dipiperidines - Sequella
- Fungal metabolite screening - U. Illinois Chicago, Mycosynthetix
- GSK Focused Screening TB Alliance, GSK
- Homopiperazines and Piperazines - Sequella
- InhA inhibitors TB Alliance, GSK
- Malate Synthase Inhibitors - TB Alliance, GSK,Texas A&M
- Multifunctional Molecules - TB Alliance, U of Auckland, Colorado State U
- Mycobacterial Gyrase Inhibitors TB Alliance, GSK
- NIAID Chembridge Project - TAACF
- Persistence Target Discovery - Vertex
- Phenotypic Screening TB Alliance, U. Illinois Chicago
- Pleuromutulins TB Alliance, GSK
- Protease Inhibitors TB Alliance, IDRI
- Rimophenazines TB Alliance, IIM, BTTTRI, U. Illinois Chicago
- Screen for Synthetic Lethality in *M. tb.* Johns Hopkins U.
- Summit plc. Compounds - Lilly TB Drug Discovery Initiative
- Target discovery Vertex
- TB Protein Kinase Inhibitors - Vertex
- TL1 Inhibitors - Sequella

### PRECLINICAL DEVELOPMENT

- CPZEN-45 – Lilly TB Drug Discovery Initiative
- DC-159a – Quinolone Research Institute of Tuberculosis, JATA
- Nanodrug delivery system for anti-TB drugs – CSIR, South Africa
- Nitroimidazoles – TB Alliance, University of Auckland, Univ Illinois Chicago
- SQ73 – ethylenediamine Sequella, Inc.
- SQ609 – Dipiperidine Sequella, Inc
- SQ641 – Nucleoside-based capuramycins – Sequella, Inc.
- TB Oxazolidinone PNU-100480 – Pfizer
- TBK-613 – Quinolone TB Alliance, CROs

### CLINICAL DEVELOPMENT

- Diamine SQ-109 – Sequella
- Linezolid – (*TBTC Study 30*) CDC TBTC, Pfizer, various universities
- Pyrrole LL-3858 (Sudoterb) Lupin Pharmaceutical Inc
- Diarylquinoline TMC207 Tibotec
- Nitro-dihydro-imidazoxazole OPC-67683 – Otsuka
- Nitroimidazole-oxazine PA-824 – TB Alliance
- Rifapentine (TBTC Study 29) CDC TBTC, sanofi-aventis
- Gatifloxacin – OFLOTUB Consortium, EC, Lupin, TDR
- Latent TB Infection TBTC Study 26 – CDC TBTC, Department of Veterans Affairs
- Moxifloxacin – TB Alliance, Bayer, CDC TBTC, Johns Hopkins Univ, BMRC, UCL

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Information provided by Stop TB Partnership Working Group on New Drugs (2008)
Clinical Portfolio New TB Drugs Registration Programs

- **Oflotub, TDR**
- **Bayer, TB Alliance**
- **J&J/Tibotec**
- **Otsuka**
- **TB Alliance**
- **Sequella**
- **Lupin**

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**Phase I**

**Phase II**

**Phase III**

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**TB ALLIANCE**

GLOBAL ALLIANCE FOR TB DRUG DEVELOPMENT
Changing the Way TB Drugs are Developed

- For the first time in history, a clinical TB drug pipeline is available
- Current TB drug development approach replaces or adds one drug at a time, requiring decades to introduce meaningful change into the treatment of M/XDR-TB
- New paradigm needed for rational selection and development of new combinations and prevention of emergence of further resistance
- Optimized novel combinations of quality manufactured products are needed to address requirements for significant treatment shortening for active and resistant disease
Overcoming the Drug Development Dilemma

A new paradigm for testing regimens containing multiple novel agents for drug resistant TB

Conventional Development Paradigm

Alternative Development Paradigm

Alternative Development Paradigm

Decades

Years
Removing Barriers: Accelerating R&D

1. Increase collaboration between drug sponsors
   - Preclinical identification of novel combinations with toxicological and safety pharmacological testing; clinical evaluation of even totally novel regimens after single drug EBA trials

2. Speed clinical trials
   - Address and expand clinical trial site capacity

3. Minimize delays in operational procedures
   - Regulatory and ethical review evaluations; drug importation

4. Ensure adequate resources
   - Much greater financial support from public and private sectors
Thank You