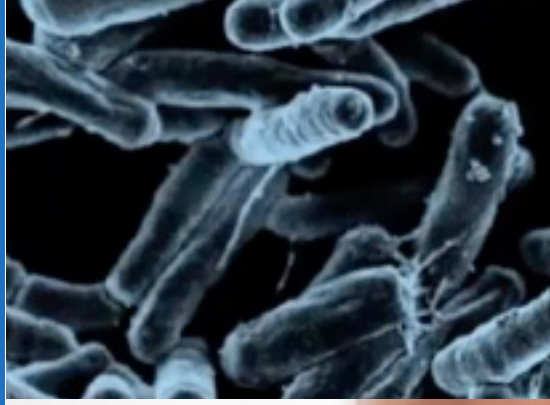
LONG-ACTING TUBERCULOSIS DRUG DEVELOPMENT WORKSHOP



Baltimore, Maryland
APRIL 15, 2024

leap

Long-Acting/Extended Release Antiretroviral Research Resource Program

ABBREVIATIONS

AE Adverse event
AI Active ingredient
API Active pharmaceutical ingredient
ART Antiretroviral therapy
ARV Antiretroviral
AUC Area under the curve
AWC Adequate and well-controlled
BA Boronic acid
BDQ Bedaquiline
BLA Biologics License Application
CAB Cabotegravir
CAT Catechol
CDC Centers for Disease Control and Prevention
CELT Centre of Excellence in Long-acting Therapeutics
CFU Colony forming unit
CHAI Clinton Health Action Initiative
CID Clinical Infectious Diseases
CMC Chemistry, Manufacturing and Controls
CS Cycloserine
DAIDS Division of AIDS
DARQ Diarylquinoline
DDI Drug-drug interaction
DEL Delaminid
DMID Division of Microbiology and Infectious Diseases
DOT Directly observed therapy
DR Drug resistant
DS Drug susceptible
DTG Dolutegravir
E Ethambutol
EGPAF Elizabeth Glaser Pediatric AIDS Foundation
EML Essential medicines list
ER Extended release
Eto Ethionamide
FACIT Functional Assessment of Chronic Illness Therapy
FDA Food and Drug Administration
FOA Funding opportunity announcement
FTC Emtricitabine
GFB Ganfeborole
GLP Good laboratory practices
GMP Good manufacturing practices
GRAS Generally recognized as safe
HBV Hepatitis B virus
HCP Healthcare provider
HCV Hepatitis C virus
HHC Household contact
HIV Human immunodeficiency virus
IM Intramuscular
IND Investigational New Drug
INH Isoniazid
IP Intellectual property
ISFI In situ forming implant
ISL Islatravir
ISR Injection site reaction
IV Intravenous
IVIVC In vitro-in vivo correlation
JHU Johns Hopkins University
Ka Absorption rate constant
Ke Elimination rate constant
LA Long acting
LAI Long-acting injectable
LaPaL Long-acting technologies Patents and Licences database
LAT Long-acting technology
LEAP Long-acting Extended-release Antiretroviral research resource Program
LEN Lenacapavir
LMIC Low-middle income country
LPAD Limited Population Pathway for Antibacterial and Antifungal Drugs
LPV Lopinavir
LTBI Latent tuberculosis infection
MAP Microneedle array patch
MDP Multidomain peptide
MDR Multi-drug resistant
MIC Minimum inhibitory concentration
MMV Medicines for Malaria Venture
MPP Medicines Patent Pool
Mtb Mycobacterium tuberculosis
MW Molecular weight
NDA New drug application
NGO Non-governmental organization
NHP Non-human primate
NI Non-inferior
NIAID National Institute of Allergy and Infectious Diseases
NIH National Institutes of Health
NOFO Notice of funding opportunity
NOSI Notice of special interest
NP Nanoparticle
NRA National regulatory authority
NTP National Treatment Program
OBR Optimized background regimen
OLI Oral lead in
PAN-TB Project to Accelerate New Treatments for Tuberculosis
PAS Para-aminosalicylic acid
PBA Phenylboronic acid
PBPK Physiology-based pharmacokinetic
PD Pharmacodynamic
PEPFAR US President's Emergency Plan for AIDS Relief
PK Pharmacokinetic
PLHIV Person living with HIV
POC Point of care
PPC Preferred product characteristics
PRO-CTCAE Patient-Reported Outcomes version of Common Terminology Criteria for Adverse Events
PZ Pangaea Zimbabwe
QD Once daily
R or RFP Rifampin
R&D Research and development
RBT or RFB Rifabutin
RFP Request for proposal
RPT Rifapentine
RIF Rifampicin
RLS Resource-limited setting
RNA Ribonucleic acid
RPV Rilpivirine
S Streptomycin
SA Short acting
SBIR Small Business Innovation Research
SC Subcutaneous
SD Single dose
SDU Southern Denmark University
SHA Salicylhydroxamic acid
SOC Standard of Care
SR Sustained release
STTR Small Business Technology Transfer
TAG Treatment Action Group
TB Tuberculosis
TBD Tuberculosis disease
TBI Tuberculosis infection
TPP Target product profile
TPT Tuberculosis prevention therapy
ULA Ultra-long acting
UNC University of North Carolina
UNMC University of Nebraska Medical Center
VDOT Video directly observed therapy
WHO World Health Organization
WHOQOL-BREF WHO Quality of Life Brief Version
Z Parazinamide
1HP One month of daily RFT and INH
3HP Three months of weekly RFT and INH
9H Nine months of daily INH

CONTENTS

Where will we LEAP next?

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On April 15, 2024 LEAP convened over 130 in-person and 50 online registrants for the inaugural workshop dedicated to the development of long-acting formulations for tuberculosis. The workshop co-chairs welcomed the impresssive group of attendees and presenters who represent the diverse perspectives of clinicians, investigators, developers, industry, regulatory authorities, community advocacy groups, and not-for-profit institutions. Opening remarks from LEAP, DAIDS, and JHU leadership were followed by three plenary sessions strategically selected to advance the LA TB field: Unmet Need and Principles; Tools, Platforms, Progress; and Path to a Commercial Product. This report summarizes the 15-minute presentations in each session.

Welcome

Eric Nuermberger
JHU

Kim Scarsi
UNMC

LEAP TB Workshop Co-chairs

"This forum is coming at a critical nexus and jumping off point - the future looks so bright for tuberculosis long-acting therapeutics."

Drs. Nuermberger and Scarsi welcomed participants to the very first long-acting TB drug development workshop. The co-chars began by recognizing LEAP and DAIDS as the workshop sponsors and the Gates Foundation for supporting the travel of several international guests. They emphasized the visionary leadership of Charles Flexner, PI of LEAP, to advance LAI therapeutics for HIV and its applications and expressed excitement that TB has now been incorporated into that vision. The co-chairs grounded the meeting in optimism about the future of LA TB therapeutics and foreshadowed a day of robust and productive discussions among the assemblage of stakeholders and presenters.

Charles Flexner Principal Investigator of LEAP

"I am hoping that years from now we willl look back on this workshop as the first shots fired in what will be a revoution in approaches to the prevention and treatment of tuberculosis"

Dr. Flexner expressed excitement, but also acknowledged tuberculosis (TB) as a difficult target for the LA field. He began by highlighting LEAP as a unique NIH resource – the only R-21 grant supporting the development of a category of drugs that is deemed high-priority to the NIH, but risky to the pharmaceutical industry. He also emphasized the program's expanding scope. Initially primarily HIV-focused, LEAP now includes TB and viral hepatitis. Despite the challenges posed by TB, Dr. Flexner expressed hope for progress similar to what we have seen in LA/ER for HIV. This inaugural LA TB workshop aims to begin the conversation and take the first steps towards understanding what it will take to bring the promise of LA and ER drug delivery to TB prevention and treatment. He recognized the efforts of key individuals: Eric Nuermberger and Kim Scarsi (TB workshop co-chairs); Julia Burnett (LEAP Coordinator); Matt Williams (Director of Communications); Marina Protopaplova (Program Officer at DAIDS); and Peter Kim (DAIDS) whose vision started this program.

Peter Kim Director, Therapeutics Research Program at DAIDS

"[millions] die every year due to lack of access to good diagnostics and good treatment. That is literally what is at stake with TB and [LA formulations]"

Dr. Kim reflected that 10 years ago, HIV was the focus of LEAP, and TB was more of a dream than a realistic possibility. Despite the substantial hurdles, he highlighted that it is now a more likely probability that we will soon have a one-shot treatment for LTBI, perhaps a two-shot treatment for active TB, and better, easier, and safer TB treatments worldwide. Although we are close, Dr. Kim cautioned that a lot of research needs to be done. He emphasized that this research must impact and change the lives of the millions we are serving. Dr. Kim affirmed DAIDS' commitment to support the development of good treatments and effective LA formulations for all who need it. Industry partners and academics at this meeting are going to make this happen, and DAIDS is a willing partner.

Amita Gupta Chair, Division of Infectious Diseases at JHU

"TB has been an epidemic for thousands of years - still 10 million cases and over a million deaths and billions infected latently - we need your energy, your science, your passion."

Dr. Gupta emphasized formulation science and the development of best methods for formulation delivery as critical to make an impact on latent and active TB. She thanked Charlie Flexner for his vision, and affirmed his incisive statement during CROI 2024, "People don't fail drugs, drugs fail people." She underscored this as the scenario we need to understand. Dr. Gupta echoed the sense of challenge and optimism around the potential of LA/ER in the TB field.

PLENARY I

Roger Ptak Chief, Drug Development and Preclinical Research Branch at NIH/NIAID/DAIDS

"NIAID perspective on LA drugs for TB "

"[The global impact of TB] is why we are all here"

NIAID Strategic Plan for Tuberculosis Research, 2024 Update

The mission is to accelerate TB elimination via:

- **Research acceleration** to better understand TB through basic, translational, and clinical research.
- **Innovation** to enhance diagnosis, prevention, and treatment through new tools and strategies.

LA TB research priorities and key objectives.

- **Improve fundamental TB knowledge.** Basic biology, transmission, and immune response.
  - ◊ Animal and non-animal models of human TB disease (Objective 1.4): Better translate and predict clinical efficacy and help streamline the pathway to advance new treatments and drug regimens to the clinic.
- **Advance TB treatment and prevention strategies.** Drug targets and clinical trials.
  - ◊ New TB drug targets and interventions (Objective 4.1): Expand the types of drugs to which LA technologies can be applied.
  - ◊ New and improved TPT interventions (Objective 4.2): Teams are already working on LA approaches.
  - ◊ Shorter and safer treatment regimens for all patients and TB forms (Objective 4.3): Better and safer treatment options is a main goal of LA.
- Other TB research priorities.
  - ◊ **Improve TB diagnosis** (POC diagnostics, biomarkers).
  - ◊ **TB vaccine development** (Correlates of protection, vaccines).

Promise of LA TB drug development.

- Address potential TB therapeutic targets.
  - ◊ Drug resistance mechanisms; Host-pathogen interactions; Virulence factors; Pathogen metabolic pathways.
- Incorporate considerations for TB treatment regimens.
  - ◊ Enable better adherence; Improve outcomes for all patients, including co-morbidities and co-infections; Reduce forward transmission.

Resources for researchers

NIAID search tool (https://www.niaid.nih.gov/research/resources).

- Filter by disease/condition and approach.
- Resources include reagents, model organisms, tissue samples, etc.

NIAID ChemDB (https://chemdb.niaid.nih.gov/).

- Chemical and biological data on >295,000 compounds active against Mtb, HIV, and opportunistic infections. Data curated from the open literature and DAIDS testing contracts, when available.

DAIDs HIV preclinical services contract program (https://www.niaid.nih.gov/research/daids-services-program-accelerate-drug-development).

- FOA provides a mechanism to request gap-filling services.
- Approved applications receive services from DAIDS contractors at no cost (no funding is provided).

Program	Purpose	Appplication
Resources Access for Preclinical Integrated Drug Development (RAPIDD) (X01)	• Supports development of new drugs for HIV, TB, HCV, and HBV. • Services: Pharm/toxicity studies (GLP); Chemical synthesis of small molecules; Formulation development and manufacture of dosage forms (GMP); Preclinical efficacy studies in small animal TB models (mouse and rabbit).	• PAR-22-185 • Next due dates: Sept 1, 2024 and Jan 17, 2025
Resources to Advance Pediatrics and HIV Prevention Science (RAPPS)	• Supports nextgen prevention and treatment strategies, including age-appropriate formulations, for HIV/co-infections/co-morbidities in maternal, pediatric, and adolescent populations. • Services: Preclinical safety/tox, drug-drug interactions, and repro-tox studies (GLP); PKPD and efficacy in NHPs and small animal models; Bioanalytical method development; CMC/GMP manufacturing and product characterization; Scientific and quality/regulatory support.	• New NIAID contract. • Scientific contact: James Cummins

LEAP Resource Grant (R24 AI118397; https://longactinghiv.org).

- Charles Flexner (PI); University of Liverpool and University of Nebraska Medical Center (Collaborators).
  - ◊ **Annual workshops.** Forum to share diverse perspectives and updates and discuss challenges and future directions of LA/ER products.
  - ◊ **2022 CID Supplement.** Stand-alone issue comprising 13 articles on the development, translational and clinical science, and implementation of LA/ER drugs for HIV, TB, HCV, and HBV.
  - ◊ **2023 LA PaL.** Public, web-based platform to track IP, clinical development, and regulatory approval status of LA/ER products for HIV, TB, HCV, and HBV worldwide.

Funding opportunities

NIAID search tool (https://www.niaid.nih.gov/grants-contracts/opportunities).

- Filter by opportunity/grant type and query search terms (n=176 as of April 2024).

Notice	Purpose	Application
NOSI: Sustained release of antivirals for treatment or prevention of HIV or treatment of latent TB/HBV (SRATP)(R01)	• Develop a diverse and comprehensive portfolio of SR/LA products for HIV treatment and prevention. • 3-month minimum window of protection from a single or continuous dosing regimen. • Q1M SR/LA strategies for LTBI and HBV treatment encouraged.	• NOT-AI-22-042 • Next due date: May 7, 2024 • Scientific contact: Marina Protopopova (Treatment) James Cummins (Prevention)
NOFO: Planning for product development strategy (R34)	• Develop a comprehensive and well-defined product development strategy for nextgen treatments. • Includes treatment for HIV (comorbidities, coinfections, and complications); HIV prevention; and IND submission to FDA.	• PAR-24-029 • Next due date: Dec 4, 2024 • Scientific contact: Marina Protopopova (Treatment) James Cummins (Prevention)
NOSI for SBIR and STTR grants: Delivery technologies to allow specific tissue target homing (RNA-DASH)	• Accelerate future translation of RNA-based therapeutics to treat or prevent human disease using non-viral technologies. • DMID topic of interest: Treatment of viral, fungal, bacterial, and parasitic infections. • **DAIDS topic of interest:** Methods for specific delivery to HIV reservoir sites/sites relevant for treatment of HIV and associated infections.	• NOT-AI-24-007 • Next due date: Sept 5, 2024 • Scientific contact: Kien Nguyen (DMID/NIAID) Roger Ptak (DAIDS/NIAID)
NIH and CDC solicitation for SBIR contract proposals.	• Discovery and development of new drug classes with novel mechanisms of action for HIV, HBV, and TB.	• PHS-2025-1 (DAIDS topic) • Due date: TBD • Scientific contact: Jonathan Bryan (NIAID/DEA)

Contact information and questions.

- NIH enterprise directory (https://ned.nih.gov/search). Program Officer contact information.
- Matchmaker tool (https://reporter.nih.gov/matchmaker) Identify projects, institutes, and/or program officers.

Charles Wells Head, Therapeutics Development at Gates Medical Research Institute

"Long-acting injectable agents as tools to end TB: The future is NOW"

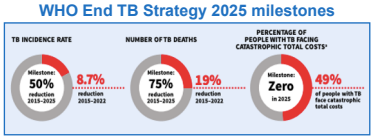
"We see this meeting as a call to action"

The unmet need

Significant progress has been made over the past 30 years, but we need to do better.

- We are still missing 3.1M of the estimated 10.6M TB cases.
- Overall treatment success has been stagnant at 85% for years.
- 60% of the estimated TB cases are successfullly treated
- The economic toll of TB on patients is devastating.

WHO End TB Strategy 2025 milestones



LAI as a complement to Gates MRI holistic TB strategy

Vaccine + LAI to prevent TB progression among the vast TBI reservoir.

- M72 vaccine is in P3 and enrolling rapidly (Q12024).
- ***50% protection over 3y (P2) leaves 50% who might not benefit.***

Simpler, safer, shorter oral TB regimens + LAI to reduce TB transmission.

- A pan-TB regimen using novel oral agents is in P2b/c treatment shortening trials (First trial launched July 2023; NCT05971602).
  - ◊ Target regimen profile: Simple "test and treat" paradigm (DS- and DR-TB); Shorter than SOC (≤3m); No baseline or ongoing safety monitoring required; All oral QD dosing; non-inferior to DS- and DR-TB SOC regimens; Affordable.
- ***Oral regimen delivery remains a struggle, even if reduced to 2-3m.***

Leveraging oral therapeutic development for LAI

The opportunity is unprecedented.

- There are many promising oral agents in the global new TB drug pipeline (2024) that could be assessed for reformulation as LAIs.
- Shelved oral agents could potentially be revisited for use as LAIs.

Collaborations for complex, resource-laden development.

- PAN-TB collaboration for a novel oral TB regimen as a model:
  - ◊ Seven organizations agreed to work together to plan, implement, execute, and govern trials.
  - ◊ Development is focused on the PAN-TB target oral regimen profile is the focus.
  - ◊ Process is collaborative and cyclical:

    Candidate selection from PAN-TB partner and Gates MRI accessible agents.

    Selection of regimen combinations and down-selection via evotec's preclinical platform (BALB/c and kramnik relapsing mouse models).

    Prioritization of regimens and clinical trials based on the PAN-TB target regimen profile.

Target LAI regimen profile

Draft target profile for pulmonary TB (priority use case).

- Ideal is a single curative injection containing ≤ 4 drugs.
  - ◊ One-time LAI (no OLI); Single SC injection <3mL containing 3-4 drugs; Coverage ≥4m.
- Minimally acceptable is OLI + maintenance LAIs x 2 with ≤ 4 drugs.
  - ◊ OLI (≤2m)+LAIs of 2-4 drugs; ≤4 separate agent IM or SC injections (<3mL) with effective PK coverage >2m; ≤2 LAI doses (e.g., at 1m and 2m).
- Additional use cases.
  - ◊ LTBI: Single curative injection containing 2 drugs.
  - ◊ Sub-clinical TB: Single curative injection containing ≤ 4 drugs.

Proactive assessment of core attributes with stakeholders and end users to hone the target profile.

- Survey among payers, providers, and patients in HBCs.
  - ◊ South Africa, India, and Phillipines.
  - ◊ Philippines was selected for pilot testing due to resource constraints (4th highest TB burden; Integrated TB services; VDOT use; High diabetes mellitus prevalence).
- Partnered with Family Health International (FHI).
  - ◊ Staff located in numerous HBCs and have translatable experience assessing the acceptability of LAIs for HIV prevention in LMICs.
- Collaborative development of survey tools.
  - ◊ FHI, MMV, UNITAID/CELT, PAN-TB partners, etc.
  - ◊ Surveys include discrete choice experiment and case scenarios.
- Enlist additional implementation partners to expand the countries.
  - ◊ USAID, SMART4TB, TAG, etc. and possibly WHO.

Technical considerations for LAI development

Candidate drug selection.

- TBD09 (MK-7762; P1) and CLB-073 (Early stage preclinical).
  - ◊ Prioritizing agents in the Gates MRI portfliio for reformulation as LAIs based on compatible solubility, clearance, and potency (as per LEAP consortium guidance).

Long-acting technology selection.

- Micronized aqueous suspensions of crystalline drug is the initial focus.
  - ◊ High drug loading and simple, low-cost manufacturing.
  - ◊ Same strategy was used to generate proof-of-concept preclinical data for LA BDQ.
- Will consider prodrug strategy or more sophisticated LATs (e.g., polymeric microspheres or ISFI) as needed to tune drug release kinetics.

We can do better to accelerate TB decline

- **LAIs have a strategic role in interrupting TB transmission & progression.** Can increase efficiency by leveraging oral therapeutics and experience from other indications (HIV, mental health, contraception, malaria).
- **LAIs are game-changer tools for patients and allow more resources for case-finding and field support.** Reduced DOT & stigma burden; Improved outcomes.
- **Harness collaboration models and community engagement** to advance and optimize LAI regimen development for maximum impact.
- **Prioritize funding and resources for LAI,** but not at the cost of prevention tools & oral therapy.

PLENARY I

Elisa H. Ignatius Johns Hopkins University School of Medicine (Presented by Eric Nuermberger)

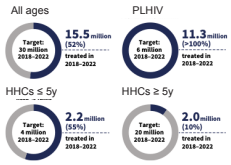
"Role of LA drugs: Where are we now, Where would we like to be?"

"We have a good bit to learn, but a lot to be inspired by"

Why we need LA TB formulations

Improve uptake and completion of lifesaving TPT.

- Global uptake and access to SOC regimens remain low.
  - ◊ 5-year WHO targets were not met, except PLHIV.
  - ◊ Duration correlates with completion rate. (Shorter is better: 1HP>3HR>4R>6H>9H).
- **A one-shot regimen at index case diagnosis could improve WHO targets.**
  - ◊ Service delivery could leverage established public health and clinical infrastructure.
  - ◊ A single injection ensures completion.



Improve completion and outcomes of TBD treatment.

- Current regimens have little forgiveness.
  - ◊ Non-adherence drives unfavorable outcomes (HR 5.7 if >10% of doses are missed).
  - ◊ ***The continuation phase carries high risk of non-adherence and discontinuation.*** The bulk of rapidly replicating bacteria have been cleared, and patients are feeling better.
- **LA formulations could improve adherence and completion rates for better individual and population health.**

Provide person-centered care.

- Understand all aspects of acceptability through research.
  - ◊ Diverse stakeholder perspectives (communities, at-risk populations, and providers).
  - ◊ Potential impact of DDIs of interest (e.g., ART, contraception, and opioid replacement).
  - ◊ Build treatment literacy around LAIs (i.e., Dissociate new LAIs from injectable aminoglycosides).
- Provide choice, as with HIV.

Considerations for initial LA targets

TPT	Continuation Phase
• One drug likely sufficient (unlikely to promote future resistance). • Pan-TB regimen is ideal (cannot reliably assess susceptibility). • Focus on sterilizing drugs for shortest possible duration. *Diarylquinolines (DARQs) and Rifamycins.* • Early inclusion of children in safety and efficacy trials. *TPT is particularlrly effective among HHC<5y.*	• Two drugs sufficient (≥3 drugs needed for induction phase). • Need for repeat dosing (goal is ≤2) • Should we focus only on the continuation phase? *Sterilizing LTBI candidates can likley be used.* • Should we advance candidates for DS and DR-TB separately or Pan-TB only?

***Key TPP characteristics:** Infrequent administration; Superior to SOC; Similar or fewer AEs; Similar or no DDIs; Compatible with pregnancy and lactation; No cold chain requirement.

Where we are now

Diarylquinolines	
BDQ	• **TPT frontrunner.** • Single injection of BDQ-LAI (160 mg/kg) in a TPT mouse model. ◊ Bactericidal activity for 8w, then bacteriostatic for an additional 4 to 8w. • Promising regimens. ◊ BDQ/RPT(2w) + $BDQ_{LAI-160}$x1 or BDQ(4w) + $BDQ_{LAI-160}$ x2 suppressed Mtb growth at 6m.
TBAJ-876	• **More potent potential pan-TB regimen** (CROI 2024). • Dose-ranging study of a single IM injection. ◊ 62.5, 125, 250 mg/kg doses sustained target (>36ng/mL) for 4, 6, and >6w, respectively. • Single injection of 3 formulations rendered mice culture-negative for 8 to 12w. ◊ **More bactericidal than QD oral BDQ x 4w and 1HP.**

Rifamycins	
RPT	• Single injection of RPT-LAI can sustain antibacterial conc >14d. • Dose-ranging study (0.6, 2, 3.5) of single and divided-doses. ◊ $RPT_{LAI-3.5}$ has similar bactericidal activity as 1HP in a treatment model.
RBT	• Single injection of RBT-LAI has similar early bactericidal activity as 1HP. • RBT-LAI delivery via an in-situ forming implant (UNC). ◊ Increased the drug load and sustained antibacterial conc for >16w. ◊ A single injection eliminated Mtb in a pre- and post-exposure LTBI model.

Where we are going

PK challenges for LA TB formulations.

- PK targets are lower for LTBI vs TBD.
- What is the target exposure for LAIs?
  - ◊ AUC/MIC as in oral dosing; Trough concentration; 2- to 4-fold above MIC; Intermittently or consistently; Err on the side of well above the target due to resistance concerns?
  - ◊ Target exposures will be different for different agents. Validate target exposures from mouse models; Need modeling and simulation approaches.
- Is a long PK tail a concern? The paradigm (i.e., cure/eradication) is different than HIV.

Pharmaceutics considerations & types for diverse LATs.

- Potency, loading, physiochemistry, logP, Ke, prodrug approaches, volume, amphiphiles to alter solubility.
- How to best match API, technology platform, and use context?

Injectable	MAP	Implant
• Solid drug particles • Microspheres • Polymer approaches for controlled release of potent water-soluble drugs • Hyaluronidase to allow larger injection volumes.	• Minimally invasive. • More acceptable. • Patch size? • Need to push through proof of concept.	• Biodegradable, ISFI, biodurable. • Surgically implanted. • Worth it for short-duration TPT? • Need tunability for TBD treatment.

◊ Does hyaluronidase impact PK? Data suggest kinetics are affected, yet exposures are comparable.
◊ Is the cold chain issue easier to address via a solid or liquid product?

Inclusion of priority populations early in development.

- Pregnancy and postpartum. Exposure during pregnancy is inevitable given that LA formulations are detectable for weeks to months post administration.
- Adolescents. Current care models are not sufficient – LA could provide a bridge to enhance TPT and TBD treatment and help mitigate: Increased TB incidence; Higher likelihood of severe disease at presentation; Higher loss to follow; Partial adherence; and Potential long-term consequences of absenteeism from school or work.
- Need to generate pre-emptive PK and safety data. Model-based predictions are helpful, but not sufficient; Dedicated trials are often delayed, contributing to delayed access; Spinoff trials are an opportunity to test successful regimens in priority populations (sample size based on expected AE rate).

Patient-centered data collection to understand preferences and inform product development.

- Preemptive community engagement and assessment. Focus Groups and Discrete Choice Experiments.
- Prospective qualitative studies embedded in clinical trials. FACIT (TB); WHOQOL-BREF (Culturally specific); PRO-CTCAE (Cancer trials).

Where we want to be

- Widespread access to affordable & acceptable LA drugs (for TPT & DS-/DR-TB) with excellent safety & efficacy and predicatble PK, which can be administered without advanced medical training and are compatible with various life states and concomitant medications.

Andrew Owen Director, CELT at University of Liverpool

"Progress & challenges in development of LA medicines for TB treatment and prevention"

LONGEVITY is developing solid drug nanoparticles for IM injection

Overview of LAI TB drug development

Targets.

- TPT is the most plausible short-term goal. Single-dose LAIs are feasible.
  - ◊ Evidence supports shortened regimens and monotherapy: BRIEF-TB trial (1HP non-inferior to 9H) and ASTERoiD trial (Rifampicin alone).
- TB treatment is complex, but potential LA benefits are profound.
  - ◊ Long (>6m), multi-drug regimens are required, particularly for DR-TB.
  - ◊ Incomplete adherence is a major obstacle to TB elimination – Increased time to culture-negative conversion; Increased resistance; and Longer treatment.

LAT selection for TB.

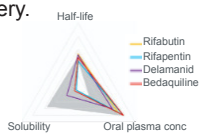
- Certain LATs may be more appropriate in certain populations. **Prenatal, perinatal, adolescent, and pediatric populations should be prioritized.**
- Key comparators:

IM Injection	SC Injection	Transdermal MAP	Subdermal Implant
• Higher dose/volume • Clinic Visit required • Example: CAB LA	• Lower dose/volume • Possible Clinic Visit • Example: LEN	• Lowest dose • No Clinic Visit • Example: None	• Lower dose • Clinic Visit required • Example: Contraception

- Unique aspects of LAI approaches, independent of route.
  - ◊ Most leverage flip-flop kinetics. When the rate of absorption is slower than rate of elimination, half-life becomes dependent on drug release (i.e., "drug release-dependent half-life extension").
  - ◊ High metabolic stability for long exposures (LEN).
  - ◊ Unprecedented potency for very long duration (ISL).

TB drug selection for LAI delivery is based on similarity to existing LAI products (Int J Tuberc Lung Dis 2018).

- Identified key API components for LAI delivery. Water solubility; Half-life; and Target concentration.
- Mapped the range for successful LAIs. Grey shaded area.
- Screened all available TB drugs. Rifamycins, delaminid, and BDQ are compatible.
- Developed a PBPK model to simulate the release rate required to achieve a LAI target (Advanced Drug Delivery Reviews 2016). Defined release rates for LAI delaminid, INH, rifabutin.



LAI solid drug particle suspensions

Characteristics of successful LAIs.

- Large API mass can be loaded into a small aqueous volume.
- Dosage form is syringeable using an appropriately sized needle.
- **Low aqueous solubility is the key to half-life extension**.
  - ◊ Low solubility rarely means no solubility: Drug particles are suspended in a saturated drug solution, which has implications for drug release.
  - ◊ Particle suspension leads to slow drug dissolution, which manifests release-dependent half-life (Ka < Ke).

Particle suspensions cannot be developed for drugs with high solubility (forms drug in solution).

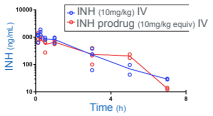
Challenges in development of LAIs

Drugs with higher aqueous solubility. Need methods to optimize LAIs based on drug particle suspensions.

- Preclinical example of prodrug derivatization to optimize LAI ARVs for HIV.
  - ◊ FTC prodrug nanoparticle suspensions achieved 20-fold half-life extension and fully protected humanized mice from HIV exposure for 14d.
  - ◊ Rapid hydrolysis is highly desirable when repositioning existing oral drugs.

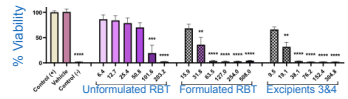
Prodrug strategy may work for INH.

- Initial studies of a novel INH prodrug (developed by JHU-CHAI under LONGEVITY) confirm rapid hydrolysis of unformulated prodrug to release INH.
  - ◊ Prodrug fully converted to INH within 10 min in rat, mouse, and rabbit plasma (*in vitro*).
  - ◊ Prodrug was undetectable in mice after IV dosing.
  - ◊ Kg-scale synthesis has been optimized (CELT); Preclinical evaluations are underway.



Inactive ingredients. Even though FDA GRAS excipients are used, LAIs require higher doses than approved products (to stabilize the large API mass needed).

- Toxicity of a novel LAI RBT formulation is attributed to an inactive ingredient.
  - ◊ Severe ISRs were observed in rats after RBT-LAI.
  - ◊ A novel primary muscle cytotoxicity assay implicates an inactive ingredient.



HuSKMC cytotoxicity assays may offer a rapid tool for excipient selection.

Reliable in vitro-in vivo correlation (IVIVC) for LATs is needed to accelerate development and reduce animal use.

- A priori predictions of *in vivo* exposure profiles for nine LA materials did not reliably match PK studies, revealing a knowledge gap (e.g., FTC).
  - ◊ IVIVC was based on convoluting *in vitro* release kinetics with IV PK disposition.
  - ◊ *IVIVC accurately predicted the ranked-release rate and PK exposure of FTC in rats; No scaling factor was identified for robust in vitro-in vivo extrapolation across LATs.*

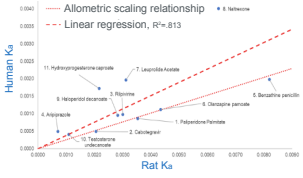
Need to further develop in vitro methods for better in vivo prediction.

Animal-to-human scaling of LAI PK is needed to better predict human dosing, guide decision-making, and accelerate P1 development.

- Half-life of IM LAIs differs across species (e.g., CAB and RPV).
  - ◊ We sourced matched rat and human data for 11 IM LAIs (from in-house studies and publications) and determined release rates from flip-flop kinetics.
  - ◊ PK half-life in mice < rats < humans.
  - ◊ Implications for paucibacillary mouse model.

Species-specific algorithms are needed for scaling preclinical PK.

- Combined dataset enabled initial investigation of two approaches:
  - ◊ Linear regression (human Ka vs rat Ka).
  - ◊ Allometric scaling of Ka by body size. (predicted human Ka = rat Ka x 0.255)
- Found reasonable concordance of human PK projections for CAB & RPV. (Assuming 50% and 100%F, respectively)
- Validation requires a priori application for a novel LAI.



Forward implementation of learnings:

LEAP Modeling and Simulation Core services.
(https://www.leapresources.org/content/use-our-services)

TEORELER web based PBPK modeling application.
(https://www.liverpool.ac.uk/centre-of-excellence-for-long-acting-therapeutics/teoreler/)

Charles Peloquin Division Head, Translational Research at University of Florida

"PKPD drug principles of TB agents"

Antimicrobial fundamentals

How antibiotics work.

- For any drug with a known mechanism of action:
  Drug enters the organism, binds a target, and produces an inhibitory or lethal effect.
- For every drug given parenterally or orally:
  The bloodstream is the only way for the drug to reach the bug.

We are playing the game of "Concentration Gradient."

- Building a strong drug concentration in blood gets drug to the bug.
  Blood concentration drives drug to interstitial fluid, which drives drug to host cells and lesions, which drives drug to the microbe.
- Drug loss occurs all along the way.
  If you administer enough drug, the drug will reach the microbe.

Mechanism of action determines the strategy.

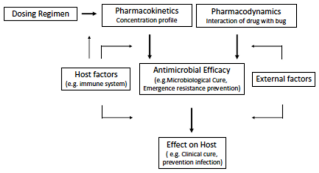
- Time-dependent agent: "Siege the castle."
  Give enough drug to maintain the target conc from dose to dose
  Cell wall active drugs (penicillins, cephalosporins, carbapenem).
- Concentration-dependent agent: "Storm the castle."
  Give as much drug as possible.
  Intracellular poisons (aminoglycosides, rifamycins, fluoroquinalones).

Recommended Resources
CH Nightingale, PG Ambrose, GL Drusano, T Murakawa, Eds. *Antimicrobial Pharmacodynamics in Theory and Clinical Practice, 2nd edition*.CRC Press; 2007.
JC Rotschafer, DR Andes, KA Rodvold, Eds. *Antibiotic Pharmacodynamics*. Humana Press; 2016.

General pharmacodynamic concepts

Multiple interrelated factors determine treatment outcome.

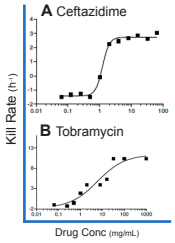
- Considerations include the bug, the drug, and the patient.



Antimicrobial killing patterns.

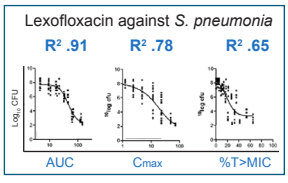
(Ceftazidime vs Tobramycin against P aeruginosa)

- Time-dependent **(A)**.
  - ◊ **More drug does not increase killing** above a certain concentration.
  - ◊ Curve resembles a step-function within the clinically useful range.
- Concentration-dependent **(B)**.
  - ◊ **More drug increases killing** across the clinically useful range.
  - ◊ Killing plateaus at very high concentrations. (all targets saturated)

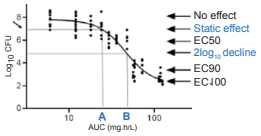


Sigmoid Emax model describes the relationship between PD parameters and efficacy.

- Best fit model describes the driver of efficacy (AUC > Cmax > %T>MIC).
  - ◊ **AUC is always a safe guess.** Usually ranks first (conc-dep) or second (time-dep), depending on the mechanism of action.
  - ◊ **PD indices are correlated** when giving a fixed dose at a fixed interval.

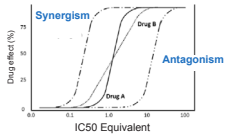


- Variable slope describes the progression from no effect to 100% Emax as drug exposure increases.
  - ◊ PD targets correspond to measures of effect. Drug concentration needed to achieve static effect **(A)** or $2log_{10}$ decline in CFU **(B)**.
  - ◊ **TB studies often use $2log_{10}$ decline in CFU.**



Two-drug interactions.

- Synergism. The drug combination produces an effect that the single drugs cannot produce (Left shift).
- Antagonism. Efficacy is lost by administering the two drugs together (Right shift).



Tuberculosis drugs

Sources of PKPD data.

- 1950s to 1970s. Gordon Ellard, Gianni Acocella, Ludo Verbist, and others generated considerable PK data.
- 1980s to 2000s. Recommended resources:

Peer-Reviewed Articles	Books
Holdiness MR. Clinical pharmacokinetics of the anti-tuberculosis drugs. Clin Pharmacokinet. 1984;9(6):511-44.	K Bartmann, ed. Antituberculosis Drugs. Springer-Verlag; 1988. **Translates several non-English papers.**
Peloquin CA. Therapeutic drug monitoring in the treatment of tuberculosis. Drugs. 2002;62(15):2169-2183. **Current opinion – updated in 2014.**	Peloquin CA. Antituberculosis Drugs: Pharmacokinetics. In: Heifets L, ed. Drug Susceptibility in the Chemotherapy of Mycobacterial Infections. CRC Press; 1991:59-88.
Nuermberger E, Grosset J. Pharmacokinetic and pharmacodynamic issues in the treatment of mycobacterial infections. Eur J Clin Mirobiol Infect Dis. 2004;23:243-55.	Global TB Alliance. Handbook of anti-tuberculosis agents. Tuberculosis. 2008;88(2):1-169. **TB drug database with a few pages on each drug.**
Budha NR, Lee RE, Meibohm B. Biopharmaceutics, pharmacokinetics and pharmacodynamics of antituberculosis drugs. Current Medicinal Chemistry. 2008;15:809-825. **Great tables with PKPD parameters.**	

Rifamycin studies indicate substantial interindividual variation and concentration-dependent killing.

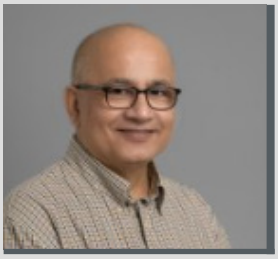
- Dose-ranging trial of rifampin (Boeree MJ et al, 2011 and 2015).
  - ◊ **High interindividual variability** in Cmax and AUC within any given dose.
  - ◊ **Concentration-dependent killing.** Highest AUC achieved largest reduction in sputum Mtb CFU.
- Daily rifapentine for treatment of pulmonary TB (Dorman SE et al, 2015).
  - ◊ **No clear trend in efficacy across study arms.** Highest % culture-negative in the RPT20 arm.
  - ◊ **Antimicrobial activity strongly associated with RPT exposures.**
  - ◊ **PKPD evaluations provide important insights.**
- High-dose rifampin.
  - ◊ PubMed search on Oct 25, 2024, yielded 631 articles (many are relevant).
  - ◊ Recommended resources:

Peer-Reviewed Articles	Books
Svensson EM et al. Potential treatment shortening with higher rifampicin doses: relating drug exposure to treatment response in patients with pulmonary tuberculosis. CID. 2018;67(1):34-41.	R Jelliffe and M Neely, eds. Individualized Drug Therapy for Patients: Basic Foundations, Relevant Software, and Clinical Applications. Academic Press; 2016.
Alkabab Y et al. Therapeutic drug monitoring and TB treatment outcomes in patients with diabetes mellitus. Int J Tuberc Lung Dis. 2023;27(2):135-139. **TDM hastened microbiological cure in a programmatic setting).**	
Alffenaar JWC, Stocker SL, Davies Forsman L, et al. Clinical standards for the dosing and management of TB. Int J Tuberc Lung Dis. 2022;26(6):483-499. **First consensus-based clinical standards.**	

Acknowledgements:
University of Florida IDPL team: TJ Zagurski; KM Kim; Y Tang; B Nelson; S Stoneberger; and N Maranchick (http://idpl.pharmacy.ufl.edu).

Eugene Sun Senior Vice President, Research and Development at TB Alliance

Rajneesh Taneja Vice President, Pharmaceutical Product Development at TB Alliance



"Long-acting injection formulations for TB drugs"

"Science is not advanced in a linear way ... this is a watershed [moment]"

Development of LAIs for TB

Represents a confluence of fortuitous circumstances.

- Formulation technology has advanced.
- Success of Cabenuva for HIV perhaps sparked competitiveness.
- Robust TB drug pipeline and high level of collaboration in the TB field.
- Multiple drugs have suitable physicochemical properties for LAI.

TB Alliance (TBA) approach.

- LTBI is the most obvious early target.
  A single LA injection would enable diagnosis and treatment on the same day/visit.
- TBD treatment requires more drugs and longer duration (≥3 drugs as LAIs).
  Oral lead-in (OLI) + single-dose (SD) LAI or LAI (3 drugs) + second injection in 2 months.
- Select TB drugs could have other applications.
  Examples include: BDQ for Leprosy and Q-203 for Buruli ulcer.

Compound and technology platform selection

Searched the TBA portfolio for compounds with suitable LAI properties.

- Compounds searched (19 in Discovery; 11 in P1 to P3; and 3 marketed products).
- Focused on TBAJ-587 (P1), TBAJ-876 (P2), Q-203 (P2), BDQ (P3), Pretomanid (Market).
- Considerations for compound selection: Crystalline; Low aqueous solubility; High potency; Long PK half-life; Low local irritation potential (Int J Tuberc Lung Dis, 2018); No pre-existing resistance.

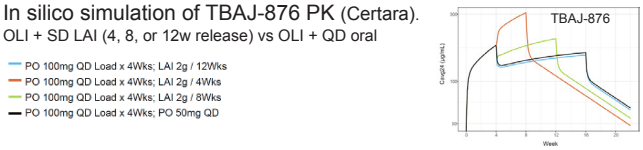
Focused on two LA technologies that are available, affordable, and adoptable.

- Nanoparticle suspension: Ready-to-use suspensions (no reconstitution); Drug release ≥ 8-12w per dose; Each dose ≤ 2 x 3mL IM injections; Administration via ≤25G needle; Stability ≥2y at room temp.
- Implant: Biodegradable, subdermal, rod-shaped device (L ≤ 40mm and OD ≤ 2mm); Reasonable COGs for formulation and insertion; Non-surgical insertion (similar to subdermal contraceptive implants); Stability ≥ 2y at room temp.
- Commercialization considerations for technology selection: Established technology with approved products; Max possible drug load and lowest drug excipient load; Simple equipment and manufacturing process; Established CMC regulatory pathways; Easy to scale up and transfer to global partners/CDMOs.

Collaborative development of LAI formulations

PK modeling informs the most desirable release profile.

- In silico simulation of TBAJ-876 PK (Certara).
  OLI + SD LAI (4, 8, or 12w release) vs OLI + QD oral



Efficacy studies of individual formulations are needed to determine target exposures.

- A standard target cannot be used across LAIs (e.g., 3xMIC or ECOFF).

Translation to humans.

- High plasma concentration and tissue penetration are promising LAI properties for translation to larger animals (Kovarova, 2022).

Collaborative programs.

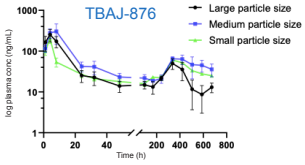
External Partner	LA Technology	Compound
Southern Denmark University (SDU) Bill & Melinda Gates Foundation (BMGF)	NP suspension	TBAJ-587 TBAJ-876 Pretomanid Q-203*
Inflammasome Therapeutics BMGF	Subdermal rod implant	TBAJ-876 Pretomanid
University of Liverpool Johns Hopkins University (JHU)	Solid drug NP	TBAJ-876
University of North Carolina NIH	In-situ forming implant	TBAJ-587 TBAJ-876

***PK analysis performed by DAIDS.**

Status of LAI diarylquinolines (TBAJ-587 and TBAJ-876)

<u>SDU/BMGF program.</u> Sustained release of three LAI TBAJ-876 formulations in vivo (PBP World Meeting 2024).

- Generated three NP suspension TBAJ-587 & TBAJ-876 formulations using established, scalable technology.
  - ◊ Small, medium, and large particle size.
- Single-dose PK in rats.
  - ◊ TBAJ-876 formulations are expected to sustain desirable Css >2m. **Dose and formulation optimization under discussion.**
  - ◊ Encouraging preliminary PK data for TBAJ-587 (week 2 and 4).

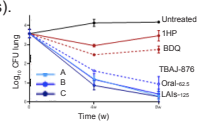


<u>Univ of Liverpool/JHU program.</u> Proof of concept for single-dose LAI TBAJ-876 IM formulation as an efficacious pan-TPT regimen (CROI 2024).

- Identified three reproducible solid drug NP TBAJ-876 formulations.
  - ◊ Formulations A, B, and C comprise 80% TBAJ-876 plus different excipients.
- PK of TBAJ-876 IM formulations in mice (A, B, C at 250, 500, and 1000 mg/kg).
  - ◊ Plasma concentration > EC50 for ≥ 8 weeks after a single dose of each formulation.
- Efficacy of TBAJ-876 IM formulations in a BALB/c TPT mouse model. (TBAJ-876 IM x1 vs QD oral 1HP, BDQ, or TBAJ-876 x 4 weeks).
  - ◊ TBAJ-876 IM Formulations A, B, and C (125 mg/kg)

    Similar bactericidal activity across TBAJ-876 IM formulations.

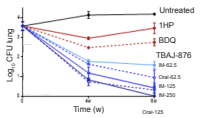
    TBAJ-876 LAIs > oral 1HP (p<0.0001) and BDQ (p<0.0001), and at least similar to the equivalent total oral TBAJ-876 dose given over 4 weeks.



  - ◊ TBAJ-876 IM Formulation B (62.5, 125, and 250 mg/kg).

    Dose-dependent bactericidal activity of Formulation B.

    Further pre-clinical development is warranted:
    Cross-species PK for human dose projections, safety and tolerability, and assessment of CMC procedures.



PLENARY II

Vivian Cox Clinical Lead, TB and Global Public Health R&D at Johnson & Johnson

"Long-acting Bedaquiline (BDQ)"

Considerations for LA TB drug formulations

Possible indication for LTBI and TBD treatment.

- Once-off or intermittent TPT.
- Opportunity to "shorten" TBD treatment by incorporating LA formulation(s) into the continuation phase.
- Role as a companion drug for either indication.

Need to understand acceptability of IM and SC injections.

- Important to consider patient preference studies and patient reported outcomes.

Potential to improve adherence and easy to integrate into established ART service delivery.

BDQ as a LA formulation for TPT

Favorable CMC properties for LA.

- Low aqueous solubility (0.0002 mg/mL).
- Low plasma clearance (0.04 L/h/kg).
- Efficacy at low drug exposures (MIC for *Mtb* = 0.03 mcg/mL).

Could lead to a pan-TB indication as monotherapy.

- Active against DS and DR forms of TB.
- A single IM injection would ensure TPT completion.
- Could further shorten TPT – a single injection at a single visit vs SOC (3HP or 1HP).

Oral formulation has a favorable side effect profile.

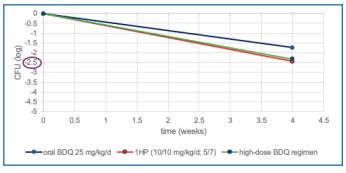
- Years of data are reassuring regarding QTc prolongation.

Target formulation would have ambient storage conditions.

Existing data on LA BDQ in a TPT mouse model

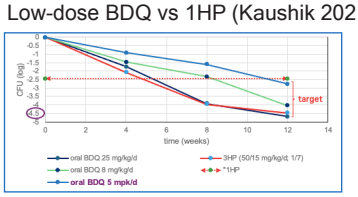
Bactericidal effect is similar to oral SOC (1HP).

- High-exposure BDQ vs 1HP (Kaushik 2019):



Similar CFU decline at 4 weeks (-2.5 $\log_{10}$CFU)

- Low-dose BDQ vs 1HP (Kaushik 2021):



CFU decline matched 1HP at 12 weeks (-2.5 $\log_{10}$CFU)

Estimated target exposure: 0.3 mcg/mL over 3 months

Uncertainties in preclinical data limit translation to humans

Pharmacokinetic uncertainties.

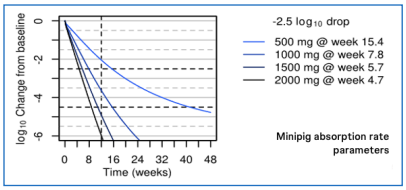
- Preclinical target exposure (0.3 mcg/mL) is based on oral BDQ AUC x 2 (correction for M2 metabolite).
  - ◊ Translational PKPD modeling of 1HP suggests that change in concentration over time also drives CFU decline, not AUC alone (Radtke et al 2021).
  - ◊ LAI and oral formulations may have different effects despite similar average concentration due to different PK profiles and M2 contribution.

Pharmacodynamic uncertainties.

- What is the contribution of the M2 metabolite?
- Does short-term CFU decline translate to long-term sterilization?
- What is the contribution of exposure beyond 3 months?
  This is a unique consideration given the long half-life of BDQ.

Ongoing translational PKPD modeling is needed.

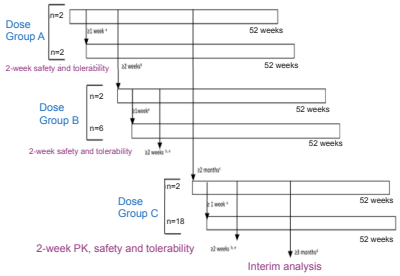
Refine the target PD endpoint and target dose based on that endpoint.



LAI BDQ will soon be in P1

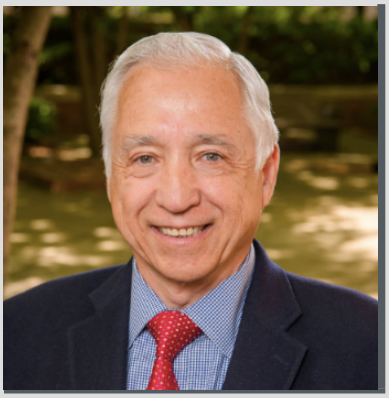
Single ascending-dose study design:

- PK, safety, & tolerability of IM dosing in 32 healthy volunteers.
- Lower-dose PK assessed before proceeding with the ascending dosing strategy.
- Planned interim analysis at Group C enrollment to inform next steps.



Considerations for future use of LAI BDQ for prevention and treatment

- **Improve the reliability of PD models**, our assumptions, and the translatability of preclinical models to humans.
- **Consider new chemical entities** in our pipeline for early development of LA/ER formulations.
- **Pursue collaborations** to develop two LAI drugs for TBD treatment (as has been done for HIV).
- **Engage TB stakeholders** to understand patient, provider, and National TB Program views on the role of LAI for prevention and treatment indications.



J. Victor Garcia Chair, Department of Microbiology at University of Alabama Birmingham

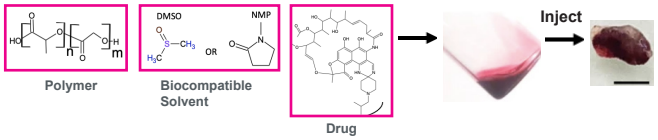
"Long-acting formulations based on ISFIs for TB"

"LA Rifabutin was our first foray into the TB field"

In situ forming implant (ISFI) technology

Process is simple and scalable:

- Prepare a liquid suspension comprising three key components (pink).
- The suspension forms a solid after injection into the body.



Many clinical examples of long, efficacious drug release.

- Successful delivery of single, double, and triple drug combinations for HIV has inspired development for TB.

Multiple parameters are easily modified for any given drug to generate a formulation with desired drug delivery.

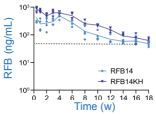
- Polymer molecular weight (MW). Higher MW increases or decreases the initial burst release of hydrophilic or hydrophobic drugs, respectively.
- Polymer concentration. Lower concentration increases the initial burst release.
- Drug load. Higher load increases initial burst release.
- Polymer composition, polymer end group, solvent type, and additives. Affect the release profile of any formulation.

Previous work on LA RFB formulations

Preclinical studies of initial formulations (RFB14 and RFB14KH).

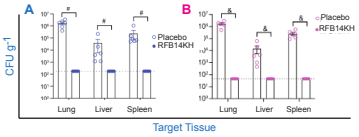
- Long duration *in vivo* drug release.

  Both formulations release RFB and maintain plasma concentrations above the MIC for Mtb ≥16 weeks.



- Efficacy of RFB14KH for *Mtb* prevention and treatment in mice.

  Pre- **(A)** and post-exposure **(B)** dosing demonstrate significant bactericidal activity in Mtb tissue targets at day 28 vs placebo.



RFB14KH modification generates new formulations with improved PK (RK400, RK400OA150).

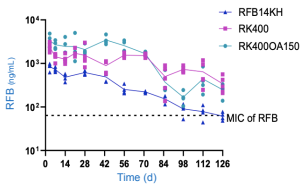
- Increased drug delivery enables translation of preclinical PK from NHPs to humans.

  RK400OA150 > RK400 > RFB14KH.

  $AUC_{RK400OA150}$ > $AUC_{RFB14KH}$ (5.2-fold; p<0.0001)

  AUC_{RK400} > $AUC_{RFB14KH}$ (3.5-fold; p<0.0001)

  $AUC_{RK400OA150}$ > AUC_{RK400} (1.5 fold; p=0.0003)



LA Delamanid formulations

Rationale for delaminid (DEL).

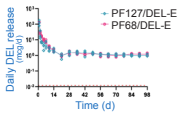
- Effective anti-TB agent developed for MDR-TB (FDA approval in Aug 2017). Inhibits synthesis of mycobacterial cell wall components.
- Low MIC for *Mtb* (12.5 ng/mL).
- PK studied in three species (mouse, rat, and dog).

Prepared several DEL formulations.

- Liquid suspensions are transportable and all form solid implants.

Favorable in vitro drug release (PF127/DEL-E and PF68/DEL-E).

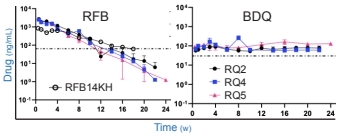
- Both formulations release delaminid and sustain conc >100-fold above the MIC for *Mtb* for ≥ 98d.



LA multi-drug delivery systems

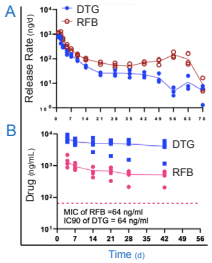
Two-in-one drug formulation for TPT and TB treatment.

- Considerations for pairing RFB and BDQ.
  - ◊ Different mechanisms of action.
    RFB inhibits bacterial RNA synthesis; BDQ inhibits mycobacterial ATP synthase.
  - ◊ Different MIC, half-life, logP, and solubility.
    DMSO is the best solvent for RFB; NMP is the best solvent for BDQ.
- Prepared several RFB/BDQ co-formulations (RQ1, RQ2, RQ3, RQ4, RQ5).
  - ◊ Liquid suspensions form solid implants.
- **Individual drug release (*in vivo*).**
  - ◊ RFB was released. PK was similar to the single-drug formulation (RFB14KH).
  - ◊ **BDQ was not released. Failed drug release drug was observed with initial delaminid formulations and is fixable.**
  - ◊ **Further formulation work is needed to modify drug release properties.**



Two-in-one drug formulation for TB and HIV prevention.

- Considerations for pairing RFB and Dolutegravir (DTG).
  - ◊ DTG is a second generation INSTI with a lot of clinical experience and is expected to come out of patent in a couple of years.
  - ◊ There is a theoretical concern that RFB could interfere with DTG concentrations.
- DTG/RFB co-formulation (DTG/RFB-A).
  - ◊ Liquid suspension is injectable with a 19G needle and forms a solid implant.
- Individual drug release.
  - ◊ ***In vitro* (A).**
    - *** Both drugs are released from the polymer.**
    - *** RBT and DTG have similar release kinetics.**
  - ◊ ***In vivo* (B).**
    - *** DTG and RFB remained >64 ng/mL ≥42 days.**
    - *** RFB did not impact DTG concentration.**
    - *** Individual drug release from the co-formulation matched published PK data for the single-drug formulations (RFB14KH and ULA-DT).**



Acknowledgements:
Manse Kim engineered all formulations; UNC shared the technology; CSU is the partner institution.

PLENARY II

Eric Nuermberger Division of Infectious Diseases at Johns Hopkins School of Medicine

"Long-acting rifapentine is efficacious in a mouse model of TB prevention "

Rationale of LAI RPT for TPT

RPT is the basis for the shortest oral TPT regimens.

- WHO-recommended 1HP (1-month QD INH + RPT).
- RPT as monotherapy (6-week QD RPT) is being evaluated in the ASTERoiD trial.

RPT physicochemical properties are suitable for a LAI.

- High potency (Low MIC for *Mtb*: 0.06 mcg/mL); Low solubility (0.02 mg/mL); and Low clearance (0.03 L/h/kg).

Review of data from a paucibacillary TPT model in BALB/c mice

The model represents a stable, low-level Mtb lung infection.

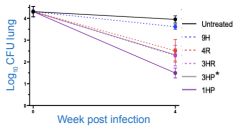
- Model generation.
  - ◊ Immunization via aerosol infection with *M. bovis* (rBCG30), followed by challenge via aerosol infection with *Mtb* (H37Rv) at 6 weeks.
  - ◊ rBCG30 immunization helps mice contain the subsequent low-dose aerosol infection with virulent *Mtb*.
- Treatment regimen is initiated at 6 weeks post *Mtb* infection.

Untreated mice inform the course of LTBI in humans.
(i.e., stalemate between bacteria & human host with likely reactivation in 1 to 2 years)

- Mice maintain a stable, low bacterial burden for months.
  - ◊ Bacteria exist in compact granulomas inside foamy macrophages from 6 weeks to 5.5 months post Mtb challenge.
- As mice age, some reactivate and develop more progressive disease.
  - ◊ Larger lesions with more chronic and diffuse inflammation at 7.5 months post Mtb challenge.

Treated mice inform clinical translation.

- Ranked WHO-recommended TPT regimens by bactericidal effect.
  - ◊ Informed the order of WHO recommendation: 1HP>3HP>3HR>4R>9H.
  - ◊ Provided the preclinical rationale for the BRIEF TB trial (1HP vs 9H; Swendels et al, 2019), which supports TPT shortening (1HP non-inferior to 9H).



- PKPD modeling of daily TPT regimens.
  - ◊ 1HP vs 6wP indicates INH has minimal impact on the RPT exposure-response curve.
  - ◊ Provided further rationale for the ASTERoiD trial of RPT as monotherapy (6wP).

Understanding PKPD relationships of potential LAI RPT formulations

PK modeling without an available LAI formulation.

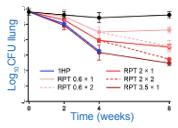
- Leveraged dynamic oral RPT dosing to simulate multiple LAI exposure profiles over 4 or 8 weeks.
  - ◊ Used de-escalating 7/7 oral dosing (7 days a week, twice per day) to simulate a LAI.
  - ◊ Modeled several dose levels administered as a SD or two doses given 28 days apart.
- Selected high, middle, and low concentration targets:

Target (day 28 and 56)	Rationale
3.5 mcg/mL	C_{avg} in humans receiving 1HP.
2.0 mcg/mL	In between high and low targets.
0.6 mcg/mL	Predicted day 28 conc for simulated SD RPT (750mg) IM.

- Compared predicted (RPT LAI) vs observed (1HP) exposure profiles.
  - ◊ The model overpredicted exposures somewhat and underestimated the degree of autoinduction with oral dosing.
  - ◊ SC or parenteral route might be better than oral.

Simulated the efficacy of LAI RPT exposure profiles in a TPT mouse model.

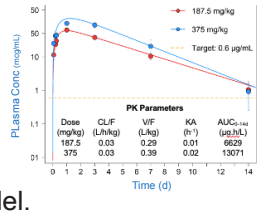
- Bacterial burden at 4 and 8 weeks (simulated LAI RPT vs 1HP).
- Identified RPT exposure profiles that may be efficacious as TPT:
  - ◊ **Two highest RPT dose levels** had similar bactericidal activity as 1HP.
  - ◊ **Two-dose schedule** sustained longer duration bactericidal activity than single dose (8w vs 4 w).



Preclinical studies of a novel RPT solid drug NP formulation

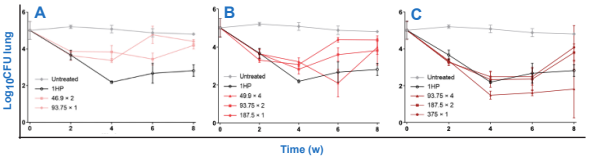
PK of single-dose RPT IM in rodents.

- Longer plasma exposure duration in rats vs mice (≥ 21 vs 14 d). **Expect slower clearance in humans vs rats.**
- Dose-linear PK (187.5 and 375 mg/kg) and terminal release-dependent, flip-flop kinetics in mice (see Figure).



Efficacy studies in a TPT mouse model.

- Dose-escalation and fractionation study design (LAI RPT vs 1HP or 1P).
  - ◊ Selected three total dose levels bracketing the median cAUC for 1HP (7000 mg*h/L): **(A)** 93.75 mg/kg; **(B)** 187.5 mg/kg, and **(C)** 375 mg/kg.
  - ◊ Each total dose was divided into one, two, and four doses over 4 weeks.
  - ◊ Bi-weekly lung CFU counts through week 8 and in-life/terminal plasma PK sampling.



- Key findings:
  - ◊ **Dose-dependent bactericidal activity.**
  - ◊ **Trend towards superior efficacy with divided dosing** (Weekly > Bi-weekly > SD).
  - ◊ **Several regimens achieved an E_{max} similar to 1HP in humans.** Weekly LAI RPT (187.5 mg/kg); Single-dose LAI RPT (375 mg/kg); and Bi-weekly LAI RPT (375 mg/kg).
  - ◊ **Repeat, weekly doses had lower exposures than expected** (based on initial simulations). Repeated injections into the mouse thigh may disrupt tissue architecture and affect drug release. PK study was repeated and PKPD modeling is underway.

Conclusions and next steps

- **Provided proof of concept** for a LAI RPT formulation to achieve efficacy comparable to 1HP in a validated TPT mouse model.
- **Preliminary scaling data** suggest the feasibility of achieving effective RPT exposures in humans for ≥28 days after a single dose of LAI RPT.
- **Work is underway** to further characterize the PK for repeat dosing in mice and enable PKPD modeling and human dose projections.
- **GLP toxicology studies** are planned to support first-in-human studies.

Kevin McHugh Department of Bioengineering at Rice University

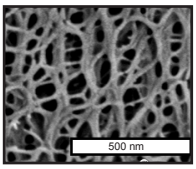
"Leveraging dynamic covalent bonding to create a LA Ganfeborole formulation: PK and efficacy for TB"

"We see [dynamic covalent bonding] as a flexible tool"

Overview of hydrogels

Hydrogel composition and nanostructure.

- Up to 99% water and 1% material of interest
- Natural (peptides) or synthetic (polymers) materials can be used.
- Fibrous nanostructure enables the potential to retain bioactive agents.
  (hydrogel encapsulates the drug of interest).



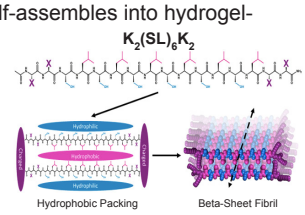
Application for TB treatment.

- We are using interesting chemistry to develop a LA hydrogel formulation of a TB drug candidate (Ganfeborole [GFB]) that requires daily oral dosing for >8w.

Engineering peptide hydrogels

Multidomain peptide (MDP) primary structure.

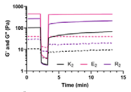
- The "right" amino acid sequence self-assembles into hydrogel-forming nanofibers that can load and release small-molecule drugs.
- General MDP design.
  Core: Alternating hydrophilic and hydrophobic residues drive Beta-sheet formation.
  Termini: A pair of charged residues enables non-covalent cross-linking of nanofibers.



- Key MDP characteristics.

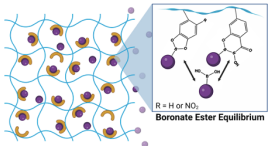
Valuable characteristics	Limitation
• Biocompatible • Biodegradable (enzymatic degradation to aa). • Injectable (via 25G needle or smaller) • Mild preparation conditions (aq. salt solution) • Easy and inexpensive to produce	Small-molecule drugs are rapidly released over hours via diffusion or weak electrostatic forces.

MDPs are injectable due to shear thinning and recovery.
The thixotropic material "liquifies" under shear stress (i.e., while passing through a small-bore needle) and "re-gels" on the other side (i.e., once the shear stress is removed).



Drug-nanofiber interactions can tailor drug release.

- Various mechanisms bond the drug to the hydrogel (e.g., covalent linkage, electrostatic interaction, and hydrophobic association).
- **Dynamic covalent bonding is a "traceless" mechanism with potential for long-lasting release of bioactive drug.**
  - ◊ Specific chemistry forms a reversible, slightly energetically favored covalent bond between the drug and hydrogel (drug is unmodified).
  - ◊ The equilibrium between bound and soluble drug is shifted towards the bound state.
  - ◊ Only the smaller proportion of soluble drug is free to diffuse out, extending the release.



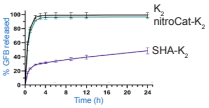
Leveraging dynamic covalent bonding for LA/ER formulations

MDP modification with boronate esters - catechol (Cat-K_2), nitrocatechol (nitroCat-K_2), or salicylhydroxamic acid (SHA-K_2).

- Functionalized MDPs retain key MDP functions: Self-assembly; Beta-sheet formation; Hydrogel integrity; and Shear recovery.
- Boronate ester groups form dynamic covalent bonds with boronic acid in BA-containing drugs (i.e., GFB), which could extend drug release.

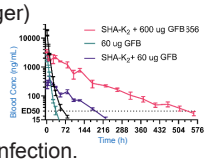
Catechol	nitroCat and SHA
Weak dynamic covalent bonder; More drug in the soluble state; **More rapid drug release.**	**Stronger dynamic covalent bonders** (oxidation resistant); More drug in the bound state; **Extended release**.

- *in vitro* studies confirm delayed release of small-molecule BA drugs mixed with modified (Cat-, nitroCat-, SHA-K_2) vs unmodifed MDPs (K_2).
  - ◊ SHA modification significantly delayed the release of all four drugs (Ixazomib, Bortezomib, Tavaborole, and GFB).
  - ◊ Only SHA-K_2 significantly delayed GFB release and was advanced to *in vivo* studies.

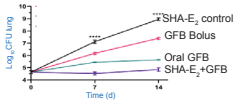


PK and efficacy of GFB+hydrogel SC in BALB/c mice.
(TB test case in collaboration with Eric Nuermberger)

- Single-dose PK in uninfected mice.
  (SHA-K_2+GFB SC vs GFB SC)
  - ◊ SHA-K_2 extended the release of GFB.
  - ◊ SHA-K_2+GFB(600mcg) sustained conc above ED50 for ≥3w; AUC increased 2.8 fold.



- Single-dose efficacy in mice with acute Mtb infection.
  (SHA-E_2+GFB SC vs GFB SC x1 vs QD oral GFB x2w)
  - ◊ SHA-E_2 outperformed the equivalent daily oral dose and single soluble injection.
  - ◊ SHA-E_2+GFB suppressed Mtb growth for 2w; Growth observed at 3w was due to depot depletion.



Expanding drug flexibility

Drug modification with phenylboronic acid (PBA).

- Enables dynamic covalent bonding between functionalized MDPs and drugs that do not contain BA (Only five BA-containing drugs are FDA-approved).
- Modified hydrogels extend the release of PBA-modified small molecules and biologics; bioactivity is not significantly altered.

1V209-PBA + SHA-K_2 or nitroCat-K_2	*in vitro* release over days vs hours.
IgG-PBA + SHA-K_2	*in vivo* release over months vs days.
Insulin-PBA + SHA-K_2	Corrected blood glucose over days vs hrs

Summary

- **Developing a library of functionalized hydrogels** capable of dynamic covalent bonding with BAs for extended release.
- **Demonstrated extended release** of BA-containing drugs and PBA-modified drugs and proteins.
- **Demonstrated preclinical efficacy** of LAI GFB for TB treatment.
- **Future directions:** Chronic infection studies; Optimize SHA-modified hydrogel; Model PK in humans; Combination therapy with new small-molecule drugs and protein therapeutics.

PLENARY 3

Ramya Gopinath Associate Director for Therapeuic Review, Division of Anti-infectives at FDA

"Developing TB drugs: A regulatory perspective"

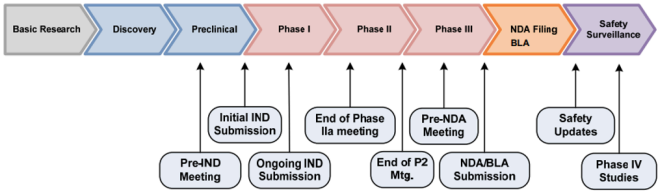
Regulatory considerations applied from LA ARV development

Publications to facilitate development of LA ARVs for HIV treatment and prevention.

- Novel challenges due to unique PK properties of ARVs (2015).
  - ◊ Determining the appropriate dosing regimen; need for OLI; and leveraging existing data from an approved oral agent.
- Key considerations for LAIs, implants, and MAPs (2020).
  - ◊ In particular, the impact of residual drug exposures following discontinuation of the LAI product and use of LA formulations in specific populations (i.e., children and pregnancy).

General drug development and specific considerations for the TB indication

Overview of the drug development pathway.



*** Early FDA consultation is encouraged**

Potential scenarios for LA TB drug development.

- Novel LA TB drug or LA formulation of an approved TB drug.
  Other scenarios exist, but will not be discussed here (e.g., prodrug).
- Two adequate and well-controlled (AWC) trials are optimal.
  Demonstrating clinically meaningful and robust statistical therapeutic effect for PTB.
- One AWC may suffice, supported by confirmatory studies.
  - ◊ Nonclinical and *in vitro* studies that evaluate drug activity. Early bactericidal activity (EBA) studies that quantify viable bacteria on solid or liquid media and/or P2 trials with early microbiological outcomes.
  - ◊ Goals are to inform: **Bactericidal effect** of the candidate drug; **Dose selection; Preliminary safety and tolerability**; and **Contribution of each drug to the overall treatment effect**.

General features of TB treatment trials apply to long-acting and short-acting (SA) formulations.

- Noninferiority (NI) or superiority design.
  - ◊ NI trial evaluates whether the performance of an investigative regimen falls within a pre-specified margin of the standard regimen (e.g., treatment-shortening regimen or investigational drug replaces one drug in the regimen).
  - ◊ Superiority trial often evaluates the investigative drug + OBR vs placebo + OBR.
- Considerations for inclusion of study participants.
  - ◊ Adults and adolescents; Early pediatric development is encouraged; Pulmonary vs extra-pulmonary disease, HIV infection, and DS- or DR-TB based on trial objectives.
- Clinical endpoint.
  - ◊ Directly meaures the therapeutic effect of a single drug or regimen. Accounts for survival, *Mtb* growth on serial sputum culture examinations, and a follow-up period after treatment completion.
  - ◊ Clinical success: Alive; Serial *Mtb* culture negative; No relapse or recurrence during follow-up.
  - ◊ Clinical failure: Death; *Mtb* growth on sputum culture; Disease progression on treatment; Switch in therapy due to intolerance or clinical progression; Signs/symptoms of TB during follow-up.
- Safety considerations.
  - ◊ Size of the safety database (Discussed with the sponsor during clinical trial formulation).
  - ◊ Management of AEs (Hypersensitivity, QT prolongation, hepatotoxicity).
  - ◊ Robust safety monitoring (Informed by safety profile, if there is an approved oral formulation).
  - ◊ Risk management strategies (Strict inclusion criteria; Initial dosing in 1-2 sentinel participants; Stringent stopping rules; Safety review committee).
- Surrogate endpoint.
  - ◊ Marker that is not a direct measure of clinical benefit.
  - ◊ Validated endpoint known to predict clinical benefit could support traditional approval. (e.g., HIV viral load in HIV treatment trials).
  - ◊ Endpoint reasonably likely to predict clinical benefit could support accelerated approval. (e.g., Positive to negative sputum culture conversion during TB treatment using time-to-conversion analysis or a fixed timepoint).
- Clinical pharmacology considerations for LA TB drug formulations.
  - ◊ Dosage form is key (Injectable vs MAP vs implant).
  - ◊ Identification of an appropriate dosing regimen (e.g., Injection volume, location, and number).
  - ◊ Impact of missed doses (Forgiveness of the regimen; Role of existing oral agent?) and residual systemic exposure after treatment completion (Resistance and potential AEs).

Drug applications for a LA formulation of an approved TB drug

Application type should be discussed with the FDA early in development - the distinction is not always clear.

- A broad distinction is the source of data for safety and effectiveness.
  - ◊ 505(b)(1): Safety and efficacy studies are conducted by or for the drug sponsor.
  - ◊ 505(b)(2): At least some of the evidence comes from studies not conducted by the applicant, and the applicant has not obtained a right of reference or use.
- Potential 505(b)(2) scenarios include changes in:
  - ◊ **Dosage form** (e.g., Solid oral to transdermal MAP).
  - ◊ **Formulation** (e.g., Different quantity or quality of excipients than approved drug).
  - ◊ **Combination product** (e.g., New combination of previously, individually approved AIs).
  - ◊ Strength; Route of administration; Substitution of a different AI (Approved or unapproved); Dosing regimen; Active ingredient; or Indication.

Additional development considerations.

- Leverage exposure-response relationships from SA formulations.
- Role of the SA formulation as an oral lead-in (Quickly achieve steady state or evaluate safety) or supplement given in concert (Cover potential missed doses).

Regulatory pathways and designations to facilitate LA TB drug development

Accelerated approval.

- Approval is based on a surrogate endpoint or clinical endpoint that can be measured earlier than morbidity or mortality (Traditional approval is based on a clinical endpoint or validated surrogate endpoint).
- ***Trial to confirm clinical benefit must be ongoing at the time of approval.***

Expedited programs.

- Designed to address unmet medical need in the treatment of serious or life-threatening conditions, such as TB.
- Fast Track designation; Breakthrough Therapy designation; Priority Review.
- Qualified infectious disease product designation; Limited population pathway for antibacterial and antifungal drugs (LPAD).

Lindsay McKenna TB Project Co-Director at Treatment Action Group (TAG)

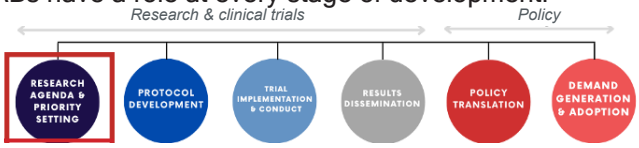
"Engaging communities in the development and introduction of long-acting TB technologies"

Community engagement in R&D of long-acting TB technologies

Rationale is inherent and instrumental.

- Participation in research as more than a trial participant is a human right.
- Community engagement ensures social value, a pre-requisite for ethical research.
- Communities can inform product development, helping to ensure that new LA technologies (LATs) address the priorities and needs of those affected by TB.

CABs have a role at every stage of development.



- Questions community engagement can help answer at the current stage of LATs for TB (Red box):
  - Do new technologies address the priorities and needs of those affected by TB?
  - What is the role of LATs in TB prevention and treatment?
  - What challenges in TB would LATs ideally solve?
  - What is the acceptability of LAI formulations?

The TB community has opinions

Global TBCAB position papers (Public Health Action 2023).

- Five papers responding to the scientist- and funder-driven TB research agenda without considering community input.
  - Presented as a symposium at The Union Conference 2023: *Flipping the Script: Communities Sharing Perspectives on TB Treatment and Vaccines Research.*
- Two papers are particularly relevant to the development of new TB treatment regimens and the research agenda for LA TB treatment.
  - **Paper 1: Balancing toxicity and duration.** Response to the perceived outsized focus on duration without considering other aspects that affect treatment completion, outcomes, & QoL. (e.g., Pill burden, safety, tolerability, side effects, and healthcare system engagement).
  - **Paper 3: Choices for TB prevention and treatment.** Response to the push for one-size-fits-all TB treatment.
- Key points (Paper 1).
  - Even mild/moderate AEs and side effects matter.
    The experience of AEs is at least as important as treatment duration in determining treatment completion. **Need to optimize safety and tolerability alongside efficacy and duration.**
  - Acceptable trade-offs depend on perspective.
    Researchers & stakeholders may accept similar side effects for shorter duration, whereas affected communities may not. **Meaningful community consultation is needed to understand perspectives.**
  - Treatment duration has been narrowly defined by clinical researchers.
    Focusing on treatment duration overlooks time spent engaging in all aspects of care (Feeling unwell, waiting for test results, monitoring visits, out-of-pocket expenses).
    Measures of time spent in the clinic could be co-primary endpoints.
    (e.g., Home Time: number of days without in-person healthcare interactions).
- Proposals and conclusions (Paper 1).
  - Person-centered endpoints and deeper examination of treatment non-completion.
  - Co-primary and secondary endpoints for future TB trials. Cure with no significant AEs; Amount of time spent feeling unwell; Required toxicity monitoring schedule (HCP visits, waiting time for results); Relative impact of any grade AE on QoL; Out-of-pocket expenses.
  - There is a real concern about toxicity. Shorter therapeutic duration is not always better, especially if individual drugs have increased toxicity or require more intensive monitoring for toxicity.

Other CABs are promoting TB community perspectives.

- Growing interest in documenting patient and community needs and priorities regarding TB treatment to inform TB trial design.
  - Unite4TB community survey aims to develop and prioritize a list of core outcomes.
- Growing realization that understanding community perspectives is essential for translation to policy.
  - Informs discussions of values, preferences, and equity in development of national and global guidelines.
- Growing urgency to think beyond non-inferiority to SOC.
  - Novel person-centered outcomes that articulate the benefits of other aspects of treatment regimens and are increasingly important as new regimens perform better and make gains in safety and efficacy.

Community acceptability is critical for development of LAIs for TB

Change the narrative around injectables.

- Difficult side effects (e.g., pain & permanent disability) led to a years-long campaign to remove injectable agents from global SOC TB regimens.
- New LAI agents are not the same, but negative associations may carry over and need to be overcome.

Begin a robust community engagement program now, not when the final LAI product is available.

- Forum to address myths and misinformation and build trust.
- Qualitative research to understand values and preferences.
  - **Structured community consultations** to inform TPP and PPC documents.
  - **Patient preference surveys** to inform product design (dosing interval, route, privacy/stigma).
  - **Normalize the inclusion of qualitative acceptability work in clinical trials and the application of high evidentiary standards for patient preference and acceptability:** UNMC/LONGEVITY patient & provider acceptability surveys for specific products. ATLAS & FLAIR trials included acceptability studies of LAIs for HIV.

Cautionary advice

Avoid LAT take over - the research agenda needs to maintain a diverse portfolio.

- Because there are few funders of TB R&D, a shift in the priorities or focus of one donor would impact the entire field.
- Determine the role of LATs (define issues that LAT would address), but also acknowledge oral options are needed & may be preferred by some.

Consider access earlier in development.

- New formulations can come with new IP protections, even drugs with expired primary patents.
- Leverage public and philanthropic funding and resources to:
  - Ensure availability, accessibility, acceptability, & quality (AAAQ).
  - Improve transparency of R&D costs, commercialization, voluntary license terms, etc.

Community engagement resources:

LAT CAB	• Cross-disease CAB sponsored by TAG and AfroCAB. • **Assists with all stages of R&D, demand creation, and access expansion.**
TAG Publications	• **Communities as actors in the R&D process** (https://www.treatmentactiongroup.org/publication/communities-as-actors-in-the-research-and-development-process/). • **Developing acceptable LA formulations for TB amidst a push for all-oral treatment** (https://www.treatmentactiongroup.org/resources/tagline/tagline-october-2021/injectables-redux-developing-acceptable-long-acting-formulations-for-tb-prevention-amidst-a-push-for-all-oral-treament/). • **TBCAB community position papers** (Public Health Action 2023).

PLENARY 3

Imelda Mahaka Executive Director, Pangaea Zimbabwe

"Perspectives from the community and advocates"

Strong coalition with civil society & communities is essential for access to LA TB formulations

Access to LA products is critical for the End TB Strategy

LA TB formulations have potential to address key issues.

- Adherence; Treatment completion; Costs of TB treatment; and Emergence of DR-TB.
- Building strong coalition with civil society and communities is key to optimize access. Second principle of the End TB pillars and principles.

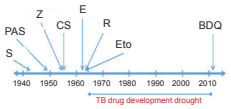
Community guiding principles are linked to the End TB Strategy principles.

- Lead with equity; Center the community and user; Accelerate scale and speed; Deliver impact; Work with what we know while continually adding to the evidence base.
- Need to think beyond the drugs.
  - **Social Justice** is equally important. Need to address social injustices and social determinants of TB.
  - **Equitable and timely access**.

Community recommendations for improved access to LA TB drugs

Accelerate the process from research, development, and regulatory pathway to programmatic scale.

- Discovery, development, and rapid uptake are part of the End TB strategy.
- Need more investments in R&D, particularly LA agents.
  - No new TB drugs were introduced for >40y.
  - There has been progress with new drugs in the pipeline. Hopefully it will not take decades to access new options, *especially with introducing LA into the system*.



- Need a regulatory strategy that is expansive.
  - We advocate for simultaneous dossier submissions, not FDA first, then other countries.
  - We believe this will speed up the regulatory pathway and accelerate access to new formulations.

Licensing and Pricing to accelerate early launch and rollout.

- Need volunteer licensing agreements & manufacturing equity shortly after proof of efficacy, not after first approval.
  - This includes: Distributive manufacturing; Plans for voluntary licensing (MPP collaboration); Engagement with generic suppliers, and Plans for technology transfer.
- Need not-for profit pricing.
  - Cost-effective, affordable, and transparent pricing of all LA TB products. 49% of TB patients face catastrophic costs (2023 Global TB Report).
  - A set public sector price for all LMICs based on Public Health imperatives, not World Bank classification or geographic location (i.e., For all public sector procurement by individual governments, public sector donors, and UN agencies).

Optimize implementation & impact & promote innovations.

- Need an implementation science agenda that takes a parallel approach to product introduction, not sequential.
  - Need to design, fund, and implement ongoing research, implementation science, and scale programs in parallel to accelerate access while gathering more information.
  - There has been movement in this direction: PEPFAR introduced LA CAB in a few countries at the same time as implementation science.
- Need innovative service delivery models that are efficient, effective and equitable.
  - Advocate borrowing from HIV DR-TB programming.
  - Strongly advocate for community-led monitoring for TB to allow survivors to monitor quality of services and provide data and feedback to policy makers.
- Need to understand the market size for different options.
  - TB treatment is not one-size-fits-all.
  - Choice matters: Options are needed for short- and long-acting TB treatment in response to user needs.
- Need innovative demand creation strategies.
  - Advocate for inclusion of a process to test, iterate, and share across projects.

Health and community systems preparedness to move at speed when LA products are available.

- Country preparedness for accelerated and sustained access. Introduction and transition to LA formulations takes time and investments.
  - Update national guidelines and EMLs to include new LA formulations, including development of policies, investments, capacities and accurate forecast data.
  - Urgently need to build and expand supply chain systems for new formulations.
- Healthcare worker training is critical for adoption and buy-in and should be well-timed with transition plans.
  - Develop or adapt materials and tools on new formulations for clinicians.
  - May need more intensive patient reminder systems to minimize missed clinic visits.
- Strengthened engagement with civil society, communities and patient groups to accelerate access to new formulations.
  - Advocacy and information gathering/sharing can help increase prevention and treatment literacy and promote demand.
  - Community engagement helps ensure that demand creation and delivery strategies are person-centered and community led.
  - Need to incorporate many lessons learned from DR-TB for comprehensive, patient-centered care along with LA. Decentralized treatment monitoring; Differentiated models; Post-treatment counseling and support; TB stigma; and Social protection.

"Everyone with TB should have access to the innovative tools and services they need for rapid diagnosis, treatment and care. This is a matter of social justice, fundamental to our goal of universal health coverage. Given the prevalence of drug-resistant tuberculosis, ensuring high-quality and complete care will also benefit global health security. I call for intensified global solidarity and action to ensure the success of this transformative End TB Strategy."

Margaret Chan
Former Director General
World Health Organization

Paul Domanico Senior director, Global Health Sciences at Clinton Health Access Initiative (CHAI)

"Perspective from the Clinton Health Access Initiative"

Collaborative, future-focused development is critical for sustainable product access in LMICs

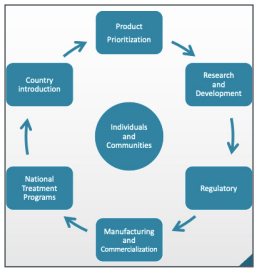
CHAI is committed to delivering access to care in LMICs

Broad-acting mission.

- Save lives and reduce the burden of disease in LMICs.
- Sustainably strengthen government and private health systems in the countries where we work.

Product access requires collaboration across the continuum of care.

- Complex technical, logistical, cultural, and financial processes are inherent in the discovery, development, and introduction lifecycle.
- Well-designed product access programs can unlock the potential of emerging markets, meet public health goals, and become commercially viable.
- Success requires:
  - ◊ Assembling the talent, passion and commitment of diverse individuals.
  - ◊ Maintaining coordination and alignment for years.
  - ◊ Being proactive, purposeful, transparent, and respectful.



- ***CHAI is active, engaged, and willing to partner with like-minded groups.***

Key considerations for product access

The goal is to minimize or eliminate barriers at each stage.

Research & Development → Normative & Regulatory → Manufacture & Commercialization → Procurement & Supply Management → Introduction & Scale

**** Often by planning ahead and collaborating with groups that have the skill and knowledge.***

Research and development.

- Barriers: No consensus on **TPP**; Lack of optimally designed product for **relevant patient populations**; Weak **IP** estate management; **Insufficient evidence** for approval & adoption.
- Interventions: Issue a **TPP**; New product development; **Global approach** to IP management; **Clinical studies** (with the right patients and volunteers); **Implementation research**.
- Partners: Academia; Donors, Industry, Ministries, NGOs, NTP, Patients, SRAs, WHO.

Normative and regulatory.

- Barriers: Lack of a **clear regulatory pathway** for product class; Lack of WHO pre-qualification for target product; Lack of **NRA** approval or waiver for target product; Product not included or recommended in **WHO guidelines** or essential medicines list or in focal **countries' EML or clinical guidelines**.
- Interventions: **Development of regulatory strategy**; Simplified registration; Dossier submission; Guidelines submission.
- Partners: Academia, Donors, Industry, Ministries, NGOs, NTP, Patients, SRAs, WHO.
- We must leverage accelerated regulatory pathways.
  - ◊ Planning ahead and working with the FDA on novel approaches, CHAI was able to shorten the time to pediatric approval (<2y vs average adult approval of 8-10y).

Manufacture and commercialization.

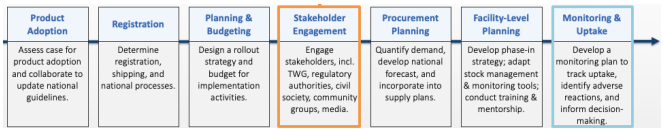
- Barriers: Manufacturing/sales restricted by **IP** provisions; Limited supplier **footprint or interest** in serving key markets; Limited production **capacity** or long lead times; Price too high to be considered cost-effective or adopted in guidelines; Lack of clarity on **target price** for the relevant market.
- Interventions: **Demand forecasting**; Licensing agreements; Strategic sourcing; New supplier entry; Manufacturing optimization; **Commercialization partnerships**; Price analysis and negotiation.
- Partners: Donors, Industry, Ministries, NGOs, NTP, Patients, SRAs, WHO.
- Need to ensure common ground across many parties (TPP established).
  - ◊ What is the accessible market? What is the value to the nation, patient, and business? ***To be sustainable, someone needs to make it, someone needs to make money on it, patients need to take it, and patients need to be monitored.***

Procurement and supply management.

- Barriers: Insufficient or unsustainable **financing** for procurement; Fragmented or irregular procurement; Limited visibility into **demand**; Insufficient supply chain and **distribution** network; Supplier does not satisfy conditions to participate in the **tender or RFP**.
- Interventions: **Demand visibility**; **Coordinated supply planning**; Pooled procurement; variant optimization; All-inclusive procurement; Product bundling; Tender optimization; Supply chain optimization.
- Partners: Donors, Industry, Ministries, NGOs, NTP, Patients.
- Need to facilitate common ground across agendas (Ministries of Health, Budget, and Finance; NRAs; and different countries).
  - ◊ Finding common ground ensures political will to roll out a new product and necessary care, including diagnostics, training, and public awareness.
  - ◊ Coordination is very country-specific, even for things like packaging.

Introduction and scale.

- Barriers: Lack of **awareness** or willingness to use product or service; Insufficient or unsustainable **financing for introduction activities**; Limited interest or **political will**; **Complementary** products or **services** not available; **Healthcare workforce** lacks necessary mandate, training, or capacity; Required **infrastructure** is insufficient; Limited delivery channels/access points; High out of pocket **costs** to end-user.
- Interventions: **Forecasting and quantification**; Stock monitoring options; **Infrastructure strengthening**; **Workforce capacity strengthening**; Resource mobilization; End-user awareness campaigns.
- Need to begin activities years before generic dossier submission.
  - ◊ Secure funding and work with ministries, patient advocates, and groups that issue guidelines.
  - ◊ Build a business case to convince ministries that the transition is worth the effort. This includes a lot of in-country work to ensure demand (Market-shaping, enhancing infrastructure).
- Example: pDTG for children living with HIV.



- ◊ **Global and national partnerships** accelerated adoption and introduction of a product that transformed care in a relatively small population of children.

  WHO, PEPFAR, EGPAF, the Global Fund, Unitaid, and CHAI published a joint statement in December 2022.
- ◊ **Work with local agencies** ensured operational research (implemented by local staff) was customized to the patient population they are serving:

  Nigeria, Benin, and Uganda: CHAI-supported research initiatives focused on patient/caregiver satisfaction, side effects, VL, adherence, and other indicators.

  Kenya, Zimbabwe, and Malawi: Demonstrated enhanced monitoring can be done within existing data and pharmacovigilance systems.

Long-Acting/Extended Release
Antiretroviral Research Resource Program