The Future of TB Diagnostic Clinical Research: *From Silos to Synergy* (& Two Challenges)

JUNE 28, 2011
2010 Workshop

Two of the major themes:

- Adaption of several new technologies
- “FTI” Collaboration - Sample Biobank for discovery and evaluation
  - Partnering with therapeutic groups/trials
Consortium for TB Biomarkers
(CTBB – aka “Frozen Trial Initiative”)

GATB, ACTG, TBTC collaborative project for standardized sample biobanking

- Funded by FDA grant, ACTG supplement (ACTG 5302)
- Form joint governance body to coordinate, develop policies/procedures, oversee operations, etc.
- Develop umbrella protocol to specify type, timing, processing, shipping of samples from selected trials
- Contract with repository vendors to establish biobank(s), QA, inventory/recovery
- Constitute advisory group to review sample use proposals

Other trial sponsors are welcome to join
Pathways to better diagnostics for tuberculosis

A blueprint for the development of TB diagnostics

By the Tuberculosis Diagnostics Group of the Stop TB Partnership

[Image of a person wearing a mask]
Objectives for TB Test Development (WHO)

- **Simplify and improve detection of TB cases**, including smear-negative, extrapulmonary, and childhood TB
  - Create and distribute simple, accurate, safe and inexpensive tests -- point-of-care, same-day results

- Enable more effective monitoring of TB treatment (latent and active)

- Rapidly identify drug resistance to both first- and second-line anti-TB medicines.

- Reliably identify latent TB infection and determine the risk of progression to active disease
Interesting Sub-objectives/Topics

- Use of new diagnostics (Xpert) for trial eligibility and trial endpoints
- Determination of infectiousness
- Detection of DR-LTBI
- Specific immune responses for risk of activation and development of DR
- Correlations with advanced imaging
- Replace Sputum!
Categories of Diagnostic Tools (WHO)

1. Optimizing TB smear microscopy
2. Rapid solid and liquid culture and phenotypic DST
3. Antigen detection tests for diagnosis of active TB
4. Antibody detection
5. T-cell-based interferon-gamma release assays
6. Nucleic acid amplification tests
7. Molecular drug resistance testing
8. Phage-based tests
9. Nose technologies!
Key Phases of TB Diagnostic Development (WHO)

- Needs assessment
- Preclinical concept and evaluations – proof of concept
- Concept definition – document providing general vision of a specific technology or product
- Feasibility determination
- Development and optimization – design lock
- Evaluation – lab studies and clinical trials
- Assessing the impact
- Assuring access
Key Barriers and Challenges (WHO)

- Absence of regulatory oversight
- Priority-setting in interests of those in need
- Knowledge sharing
- Inadequate funding
- Stimulating the market
- A broader science base
• **Cohesion is lacking** between various actors in the development of new diagnostics, and thus many initiatives work in isolation.

• The existence of so many **varying research agendas** means the most urgent medical needs don’t attract the greatest attention.

• To get the job done will take enormous resources, **coordination, collaboration** and innovative thinking.
NIH/NIAID funds are not significantly expanding
Coordination and Collaborations

Clinical Cohorts and Trials Capacity

- No one group has enough resources for any aspect of TB research for diagnostics, therapeutics, or vaccines
  - Funding -- This is not the 1990’s and this is not HIV!!
  - Site and lab capacity, capabilities, training
  - Sufficient prospective study populations and well-characterized, high quality specimens/isolates
What do we need and how to get it done?

• Enhance/adapt existing clinical research resources for TB
• Develop research strategies, agendas, and trials designs and analyses for more efficient product/device development
• Coordination and Collaborations
Plan to Combat Extensively Drug-Resistant Tuberculosis
Recommendations of the Federal Tuberculosis Task Force
Objective 54.1
Develop rapid, point-of-care diagnostics for the reliable identification of drug-sensitive and drug-resistant pulmonary and extrapulmonary TB disease and latent infection…

Action Steps

54.1.9. Establish partnerships and contribute to collaborative networks to facilitate validation of new diagnostic tests as part of clinical trials in partnership with high-burden countries.
Objective 63.1
Develop or support working groups or other mechanism to facilitate coordination of research activities among U.S. and international governmental and private agencies

Action Steps

63.1.1. Develop an effective and sustainable FORUM for coordinating TB research between U.S. and international agencies
63.1.2. Establish and articulate roles and responsibilities of each partner
Coordination and Collaborations

- Wide Communication/Information Sharing
- Focused Coordination/Harmonization
- Selective Collaborative studies
• ACTG 5274 ("REMEMBER")
• PanACEA "PROMPT"
  ○ Both are very similar trials that will begin accrual this Summer

• “STATIS” (SYSTEMATIC EMPIRIC TB TREATMENT IN AIDS PATIENTS TO IMPROVE SURVIVAL)
  ○ In development until aborted in 12/10 when the European proposers became aware of these other two trials
Coordination of Phase II Combo Trials

NIAID – ACTG, TBRU
CDC – TBTC

WHO, NGOs, etc.

GATB

Coordinate Phase II Combination Work

PHARMAs

EDCTP – PANACEA
UKMRC

FDA/EMA, etc.
CPTTR Initiative
BMGF—in association with the TB Alliance and C-Path—will work to accelerate the development of new TB drug regimens

1. CPTTR Tools Consortium
   “Regulatory Science”
   - Data standards/integration
   - Qualified biomarkers
   - Disease progression models

2. CPTTR Drug Coalition
   “Drug Development”
   - New clinical trial designs
   - Drug combination testing and development

3. CPTTR Infrastructure
   “Key Success Factors”
   - Clinical trial capacity
   - Regulatory harmonization
   - Funding

Focus

Participants
- Pharma companies
- TB Alliance
- TB experts
- Regulators
- Patient representatives
- Others

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- Reagan-Udall Foundation
- NIH
- CDC
- BMGF
- Other funders
Coordination and Collaborations

Many and varied – NO ONE SIZE TO FIT ALL

Broad Coalitions

CPTR – for combination drug development

More Focused, multilateral coalitions

“CTBB/Frozen Trials Initiative” GATB, ACTG, TBTC with FDA grant support for biomarker development sample collection

Bilateral coordination/collaborations – of all sorts

ACTG/TBTC - Rifapentine trials for treatment and prevention
Coordination and Collaborations

Issues/Choices with coordination partnerships

• Scope of agenda
  • Focus on which aspect of development?

• Priority setting/decisions on strategies, priorities, and what to coordinate (or collaborate)

• Information/data sharing

• Membership
  o Sponsors - Public/NGOs/private/industry – which ones?
  o International – which countries or regions?
  o National Agencies/Regulators?
  o Pre-clinical – clinical
  o Individuals/small-medium groups/Networks
Coordinating and Collaborations

Proposal for discussion:

TB Diagnostics Research Forum

The purpose of the Diagnostics Forum is to initiate and sustain discussion and information sharing among participating organizations to coordinate clinical assessments and trials of new TB diagnostics.

- Avoid redundancy and strive for synergy
Challenges - THE CRITICAL GAP

KEY ASPECT FOR IMPROVING TB THERAPY

More Rapid Elimination:
Persisting / Non-replicating / “Dormant” / Inactive / Fat-and-Lazy Bugs*

*Need to standardize terminology
Detection/measurement of PERSISTERS (true surrogate for sterilizing activity) is crucial for advancing TB therapy and drug/combo discovery and development

- Detect markers for dormant state or gene activity/products or metabolites involved with transition to or maintenance of dormant state
- Stimulate dormant bugs to become active and growing
And now, we enter into the realm of the **UNDEAD**
Where nothing is as it seemed before...

Confused?
Dangerous Dormancy

NO MICs here!

Who cares about EBA?

YES HE IS A PERSISTER!

The UNDEAD
Hell no, we won’t grow!

Maybe come back again in 10 years or so?
INH, RMP- cidal?? Are you kidding me?

I am SO scared!
Dude, I’m Fat and Lazy...

#92 A. Haynesworth

URP!
Dealing with Persisters

- The best targets are NOT necessarily the most “vulnerable” or microbe-specific
- Membrane integrity or membrane-function
- More difficult to discover or design agents
- Some potentially sterilizing agents with low activity against active bugs are ignored
- Diagnostics/biomarkers – the TB markers probably differ with changes in subpopulations and disease stage
- Markers for dormant bacilli may be scant to nil at times and change unpredictably as the bugs adapt
- Background NOISE
Switching to DST
And now a few words about:

PZA
• Improving MDR therapeutic development –

The DST Platform needed for RIF-resistant TB

○ Practical PZA DST testing improved phenotypic testing, and clinical correlations

○ Sequencing of wide collection of resistant isolates*

○ Rapid DST for quinolones, injectables, and INH (high/low) – and again collect isolates

○ If susceptible, these drugs + clofazimine may be a very reasonable regimen even without a new agent (STREAM trial)

*ACTION ITEM
PZA – Critical Drug

PZA/TB Sterilization Workshop Next Year

- Best sterilizer and synergizer and we know very little about how it works or how to optimize its use!
- Rapid, accurate, affordable DST is critical
A new era of technological innovation - HOPE

- Despite the barriers and challenges, recent developments in diagnostics **offer HOPE**
- Convergence of **multiple disciplines** is revolutionizing research and shifting development from the biological to molecular level.
- Advances in biological **test platforms** continue to hold enormous promise for improving TB diagnostics on many levels

Based on The WHO NDWG *Pathways to Better Diagnostics for Tuberculosis: a Blueprint for Development of TB Diagnostics*
Progress...

- CS, PAS
- ETH
- SPUTUM
- DOGMA
- EMPIRIC
- OBT
- DR-TB

#92 A. Haynesworth
THANK YOU
Even the DC Metro cannot stop them!

ALL ABOARD to the Zombie capital of Metro DC:
Objective 55.1
Develop serologic, immunologic, and microbiologic tests to assess response to treatment. Evaluate technologically advanced tests...for measuring drug efficacy in clinical trials of new therapeutics

Action Steps

55.1.6. Establish partnerships and contribute to collaborative networks to facilitate validation of tests to determine response to therapy as part of clinical trials in partnership with high-burden countries.
Objective 59.1
Optimize integration, coordination, and **synergy** between U.S. government agencies, international organizations, and national TB/HIV programs to achieve reduction in disease rates through...nonduplicative allocation of funding, staff, and resources.

**Action Steps**

**59.1.1. Develop programs or working groups to maximize cooperation between international organizations and align resources for an efficient, resource sparing response in high-burden countries.**
Operational/Implementation of New Advances

Ensuring widespread utilization of new developments from clinical trials --

• Initial assessment for eventual applicability
• Cost-effectiveness assessments
• Impact evaluations – on communities/regions
• Operational/implementation research

--- Partnerships with USAID/PEPFAR and beyond
Coordination and Collaborations

Spectrum of **Partnerships** outside of NIAID

*NOT EXHAUSTIVE!*

- NIH – NICHD, NHLBI, FIC
- USG – CDC/TBTC PETTS, USAID/PEPFAR, US Military*
- NGOs – GATB, Gates, WHO/STOP TB and TDR
- International – EDCTP (PanACEA), UKMRC, ANRS, other European-based clinical research networks
- Industry – Many pharma/biotech, device companies
SPUTUM
Coordination and Collaborations

Multiple disciplines –
• Physics, (micro)engineering, nanotechnology, nanobiotechnology, molecular biophysics, biochemistry, molecular biology, immunology, genomics/transcriptomics/proteomics/metabolomics, microbiology, and biomedical sciences……
• Therapeutics and vaccine investigators
Coordination and Collaborations

Standardization/harmonization or coordinated performance needed for efficient collaboration

- **Data elements**, standards, endpoint definitions, AEs
- **Lab procedures** for diagnostics/**endpoints**, DST, QA
  - Central reference labs
- **Site/lab** surveys, qualifications/standards, training, and monitoring
- **Stored sample** collection specifications and procedures

Will require Information sharing and administrative support
Innovation for development of new clinical diagnostics and therapeutics

- Accelerated overall development strategies
- Carefully designed evaluation plans and trial designs
- Quantitative response measurements and later, robust biomarkers → surrogate efficacy endpoints
- Modeling/optimal analyses of quantitative treatment responses including sterilization potency
- New platforms and multiplexing
- ‘OMICS, ‘OMICS, ‘OMICS and discovery biology
Biomarker Development Collaborations

Prognostic biomarkers
• Do not have to be POC or highly specific

Applications:
• Treatment efficacy/risk of relapse - impact on sample size
• Possibly shorter/individualized treatment duration
• Risk of /early detection resistance development
• Risk of IRIS
• Risk of LTBI progression to active TB
• Immunologic correlates of protection
• Early detection of toxicities