Biomarkers for the Diagnosis of Tuberculosis

Jennifer Gardiner
Program Officer, Discovery & Translational Sciences
Our strategic goal is to reduce global TB incidence

Focus of efforts

Eliminate TB

- STOP TB Partnership’s global vision of elimination by 2050
- Baseline assumption: likely requires a shift in intervention focus i.e. elimination of latent reservoir

Accelerate Reduction in global TB Incidence

- Prevention by reducing transmission and progression
- Reducing diagnostic and treatment delays
- Pulmonary TB
- Public and private sectors
- Country unit of analysis based on TBD incidence measure

Reduce TB-related Mortality

- Emphasis on general TB control (DOTS)
- Diagnosis and treatment to ensure survival without regard to transmissibility
- Pulmonary and extra-pulmonary TB
- Country focus where highest burden of TB mortality

Measure

- <1 new case/million globally
- Decrease in # of new cases per capita
- Accelerated rate of incidence decline
- Decrease in deaths due to TB

Comments

- Aspirational
- Prevention focused and achievable
- Insufficiently ambitious
# TB Strategy 2011-2016: Goal and vision of success

<table>
<thead>
<tr>
<th>Impact goal</th>
<th>Accelerate the reduction of global TB incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccines</strong></td>
<td>1 TB vaccine candidate in phase 3</td>
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<tr>
<td><strong>Drugs</strong></td>
<td>1 TB drug regimen in phase 3</td>
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<tr>
<td><strong>Diagnostics</strong></td>
<td>• 1 new TB biomarker identified</td>
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<td>• 2 new molecular diagnostics endorsed by WHO STAG</td>
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<tr>
<td><strong>Country-level Innovation in TB Control</strong></td>
<td>• Increase country TB budgets, particularly in India</td>
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<td>• Catalyze uptake of innovative TB control</td>
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<td>• New products with frugal engineering developed</td>
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<td><strong>Global Access and Market Dynamics</strong></td>
<td>• Increase quality, stabilize costs of FDC and reduce costs of second-line drugs</td>
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<td>• Accelerated uptake of innovation in target countries and globally</td>
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<tr>
<td><strong>Advocacy</strong></td>
<td>Funding secured for late-stage clinical trials</td>
</tr>
</tbody>
</table>
Our TB strategic goal is to reduce TB incidence

1. Vaccine R&D
2. Drug R&D
3. Diagnostics R&D
4. Global Access/Market Dynamics
5. Innovation in country TB control systems
6. Global resource mobilization and utilization

R&D focus
- Discover and Develop Vaccines to Prevent TB
- Discover and Develop New, More Effective, TB Drugs and Regimens
- Discover and Develop Improved TB Diagnostics

Delivery focus
- Optimizing access to affordable TB prevention and treatment
- Catalyze, evaluate and facilitate the scale up of effective interventions in our focus countries
- Increase global political and financial commitment

Global
- China
- India
- South Africa

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Diagnostic Timeline

<table>
<thead>
<tr>
<th>Year</th>
<th>Q3</th>
<th>Q4</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
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<th>Q3</th>
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- **Phase 1 (10 grants)**
  - Support Country Uptake
  - Price reductions
  - Global RFP
  - Alere - Development
  - Alere – Demo Trials
  - Alere – DST
  - China RFP
  - China Development

- **Phase 2**
  - Increase investments in mol DX
  - RFP
  - Phase 1 (10 grants)

- **Phase 3**
  - Define STAG Requirements
  - Implement STAG Process

- **Milestones**
  - Key decision point
# TB Diagnosis: *Existing solutions*

<table>
<thead>
<tr>
<th>Test</th>
<th>Sample</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liquid Culture</td>
<td>Sputum, other</td>
<td>High sensitivity</td>
<td>Requires weeks to months</td>
</tr>
<tr>
<td>Smear Microscopy (most commonly used Dx)</td>
<td>Sputum</td>
<td>Low cost 2 day turn around</td>
<td>Low sensitivity &amp; throughput Requires expertise and laboratory</td>
</tr>
<tr>
<td>Nucleic acid amplification (e.g. Gene Xpert)</td>
<td>Sputum</td>
<td>High sensitivity Same day results</td>
<td>Cost of instrument &amp; cartridge</td>
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**Needs for biomarker research:**
- High sensitivity & specificity in a low cost test that relies on either low cost or no instrument
- Test that does not rely on sputum
Program Goal and Scope

- Identify and validate biomarker(s) to enable development of a rapid (result within minutes to hours from sample collection), accurate, low cost diagnostic for active TB cases including HIV+ and, ideally, pediatric patients
- For this program, biomarker investigation is focused on blood, urine, and breath samples to enable a diagnostic that does not rely on sputum
- A triage test to refer a patient for confirmatory testing is also potentially within scope for the program pending further TPP refinement and impact modeling
- Drug resistance not explicitly included within scope for this program
New Grand Challenge in Global Health announced Feb 10, 2011

- Biomarkers for the diagnosis of TB
  - $12M initiative, 2 phase program
  - 371 applications, 21 full proposals invited
  - Phase 1: 10 individual grants for up to $750k each, up to 24 mos.
  - Phase 2: expect 3-6 projects, ~$3-4M, follow on funding for further validation of promising biomarkers

grandchallenges.org/biomarkers
Standardized Samples: TB Cases & Controls

- Case & control definitions and procurement of samples will be key to the success of biomarker discovery/validation projects.
- Working with FIND to provide access to well characterized banked samples and new collections, as needed, for all projects funded under this program.
- Enable analysis of data across projects to identify potential promising combinations for Phase 2 testing.
Biomarkers for the Diagnosis of TB Investments

Confidence in Biomarker

Ease of translating onto a point of care platform

Sputum
- Metabolites
- Oligomeric Sugars
- Mtb Enzymes
- Mtb Proteins
- Whole Bug
- Nucleic Acid
- Mycolic Acid

Blood
- Antibodies
- Mtb Proteins
- Mtb Enzymes
- Non-Ab Host
- Nucleic Acid
- Mycolic Acid

Urine
- Metabolites
- Mtb Proteins
- Mtb Enzymes
- Oligomeric Sugars
- Nucleic Acid
- microRNA
- Mycolic Acid

Breath
- VOCs - specific
- VOCs - pattern
<table>
<thead>
<tr>
<th>Project Description</th>
<th>Location/Method</th>
</tr>
</thead>
<tbody>
<tr>
<td>500 SRM Assays for Mtb proteins</td>
<td>Plasma, Urine, Sputum Inst Sys Bio, Moritz</td>
</tr>
<tr>
<td>Exosomes, Mtb proteins by SRM</td>
<td>Serum, Urine, CSU, Dobos</td>
</tr>
<tr>
<td>Mtb cell surface by Ab magnetic beads</td>
<td>Serum, Urine, Sputum</td>
</tr>
<tr>
<td>Novel Ab class to Mtb prot, by elisa</td>
<td>Serum</td>
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<tr>
<td>LAM &amp; Mtb prot by aptamers</td>
<td>Serum, Urine</td>
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<tr>
<td>Mycolic acids &amp; metabolites, MS</td>
<td>Serum, Urine, Sputum CSU, Belisle</td>
</tr>
<tr>
<td>Mtb proteins by Ab, Simoa assay</td>
<td>Urine</td>
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<tr>
<td>Ab to Mtb lipids, synthetic arrays</td>
<td>Serum</td>
</tr>
</tbody>
</table>

Breath
Louisville, Graham
CSU, Belisle
Serum, Urine, Sputum
CSU, Dobos
Serum
Somalogic, Ochsner
Mycolic acids & metabolites, MS
CSU, Belisle
Mtb proteins by Ab, Simoa assay
Urine
Forsyth, Campos
Ab to Mtb lipids, synthetic arrays
Serum
Alberta, Lowary
Pathogen

- 500 SRM Assays for Mtb proteins
  - Plasma, Urine, Sputum
  - Inst Sys Bio, Moritz

- Exosomes, Mtb proteins by SRM
  - Serum, Urine
  - CSU, Dobos

- Mtb cell surface by Ab magnetic beads
  - Sputum
  - Rutgers, Alland

- LAM & Mtb prot by aptamers
  - Serum, Urine
  - CU, Feldheim

- Mtb proteins by Ab, Simoa assay
  - Urine
  - Forsyth, Campos

Pathogen + Host

- 16 Mtb and 1200 host proteins, aptamers
  - Serum
  - Somalogic, Ochsner

- Mycolic acids & metabolites, MS
  - Serum, Urine, Sputum
  - CSU, Belisle

Host

- Novel Ab class to Mtb prot, by elisa
  - Serum
  - Burnet, Anderson

- Ab to Mtb lipids, synthetic arrays
  - Serum
  - Alberta, Lowary

- Volatiles in breath by Mass Spec
  - Breath
  - Louisville, Graham
Protein

- Mtb proteins by Ab, Simoa assay
  - Urine
  - Forsyth, Campos

- 16 Mtb and 1200 host proteins, aptamers
  - Serum
  - Somalogic, Ochsner

- 500 SRM Assays for Mtb proteins
  - Plasma, Urine, Sputum
  - Inst Sys Bio, Moritz

- Exosomes, Mtb proteins by SRM
  - Serum, Urine
  - CSU, Dobos

- Ab to Mtb lipids, synthetic arrays
  - Serum
  - Alberta, Lowary

- Novel Ab class to Mtb prot, by elisa
  - Serum
  - Burnet, Anderson

- Protein + lipid

- Mtb cell surface by Ab magnetic beads
  - Sputum
  - Rutgers, Alland

- Lipid + metabolite

- Mycolic acids & metabolites, MS
  - Serum, Urine, Sputum
  - CSU, Belisle

- Protein + sugar

- LAM & Mtb prot by aptamers
  - Serum, Urine
  - CU, Feldheim

- Volatile organic cmpd

- Volatiles in breath by Mass Spec
  - Breath
  - Louisville, Graham
Summary

- 10 projects funded to investigate a wide spectrum of potential biomarkers for diagnosing TB

Focus of the program:
- Blood and urine as potential samples
- Protein biomarkers
- Pathogen biomarkers
- Variety of detection technologies

Moving to Phase 2 of the program in Q1 2014 to further validate promising biomarkers and refine/optimize detection