BEGIN WITH THE END IN MIND...OUR TARGET POPULATIONS
The world has made substantial progress in child survival since 1990

1.45 million children’s lives saved by Hib and pneumococcal vaccines since 2000

Is the end in sight for meningitis?

Polio: Closing in on zero

* WHO Children: reducing mortality, October 2017

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1.7 MILLION PEOPLE DIED FROM TUBERCULOSIS in 2016³

445,000 DEATHS DUE TO MALARIA in 2016²

525,000 CHILDREN UNDER AGE 5 KILLED BY ENTERIC AND DIARRHEAL DISEASES each year¹

2.5 MILLION CHILDREN DIE IN THE FIRST MONTH OF LIFE
1 MILLION FROM PREMATURITY⁴

¹ WHO Diarrhoeal disease fact sheet, updated May 2017
² WHO Malaria Policy and Advisory Committee Meeting Report 2018
³ WHO Global Tuberculosis Report 2017
⁴ UNICEF, 2017
TOGETHER, THESE DISEASES CAUSE TEN DEATHS EVERY MINUTE
BILL & MELINDA GATES MEDICAL RESEARCH INSTITUTE

EVERY PERSON DESERVES THE CHANCE TO LIVE A HEALTHY, PRODUCTIVE LIFE
GATES MRI MISSION

DEVELOP PRODUCTS TO ...

TUBERCULOSIS
Accelerate the end of the tuberculosis epidemic

MALARIA
Eradicate malaria

ENTERIC AND DIARRHEAL DISEASES
End diarrheal deaths in children

MATERNAL NEONATAL & CHILD HEALTH
Reduce adverse birth outcomes and mortality
**DISEASE AREA & MODALITIES**

- **Small Molecule Therapeutics**
- **Diagnostics/Biomarkers**
- **Vaccines**
- **Biologics**

---

**ENTERIC AND DIARRHEAL DISEASES**

- **Malaria**
- **Tuberculosis**
- **MNCH**

---

1. Biomarker optimization for early hand over to diagnostic companies
2. Includes mAbs and other non-small-molecule modalities, e.g., RNA, DNA, viral and cell platforms
GATES MRI AT A GLANCE

**Location**
Cambridge, MA (HQ), Seattle

**Structure**
Fully funded by a grant from the Gates Foundation

**Portfolio**
Initial focus on TB drugs, BCG booster, malaria vx with novel adjuvant, shigella vx, MNCH portfolio

**Size**
~55 as of Feb, 2019

**Quality Management System**
Quality and compliance systems implemented; first audit completed

---

**DISCOVERY/RESEARCH**
Lead optimization, working with early research partners

**TRANSLATIONAL DEVELOPMENT**
GxP studies through clinical POC in the target population, working with translational development partners

**LATE-PHASE DEVELOPMENT**
Effective handoff to late-phase development partners
RELATIONSHIP WITH THE FOUNDATION

- Wholly owned subsidiary of the Foundation
- Gates MRI is able to leverage the extensive skills and expertise of the Foundation and the long-standing relationships across academia and industry.
- We share a common belief: all lives have equal value.
- We are committed to bringing the latest industry innovations to bear in our collective work.

And many other capabilities.....
INNOVATION FOR ACCELERATED TRANSLATIONAL DEVELOPMENT

DISCOVERY PORTFOLIO: RESEARCH DECISION SUPPORT AND ACCELERATION

SYSTEMS BIOLOGY, QUANTITATIVE SCIENCES MODELING, QUANTITATIVE & SYSTEMS PHARMACOLOGY

GATES MRI

CHEMISTRY, MANUFACTURING, AND CONTROLS

INNOVATIVE CLINICAL TRIALS (DESIGN AND EXECUTION)

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OUR APPROACH TO ACCELERATING DRUG AND VACCINE DEVELOPMENT IN GLOBAL HEALTH

CASE STUDIES IN TUBERCULOSIS

BCG REVAX
WHAT IS TUBERCULOSIS?

- Caused by a bacterium, *Mycobacterium tuberculosis* (Mtb)
- 25% of the world’s population is infected with Mtb
- 90% of those infected are asymptomatic for life
- 10% will develop pulmonary disease
- In normal, healthy individuals, we can’t predict who will get pulmonary disease (correlates of risk)
- We also don’t understand immune mechanisms of protection (correlates of protection)
- Current treatment: 4 drugs for 6 to 9 months
- Current vaccine: BCG for neonates/infants
  / Will soon have its 100th birthday
TB CAUSES 1.7 MILLION DEATHS/YEAR
NEARLY ALL ARE IN LOW INCOME COUNTRIES

WHO Global TB Report 2018
TB IS A DISEASE OF OLDER ADOLESCENTS AND YOUNG ADULTS IN LICS

Cape Town, South Africa

<table>
<thead>
<tr>
<th>Group</th>
<th>Infection Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infants</td>
<td>7%</td>
</tr>
<tr>
<td>Kids (5-10 yr)</td>
<td>28%</td>
</tr>
<tr>
<td>Adolescents (12-18 yr)</td>
<td>50%</td>
</tr>
<tr>
<td>Adults (25 yr)</td>
<td>75% (plateau)</td>
</tr>
<tr>
<td>Adults (31-35 yr)</td>
<td>88% (peak)</td>
</tr>
</tbody>
</table>

*M. tb* infection rates increase rapidly between age 10-25 years

Not feasible to implement pre-vaccination IGRA testing

New TB vaccine strategy may use age to target *M. tb*-infected/-uninfected populations
NEW INTERVENTIONS ARE NEEDED TO HELP END THE TB EPIDEMIC

2018: A HISTORIC YEAR FOR TB VACCINES

Phase 2b Controlled Trial of M72/AS01 E Vaccine to Prevent Tuberculosis


October 25, 2018
DOI: 10.1056/NEJMoal803484

Prevention of M. tuberculosis Infection with H4:IC31 Vaccine or BCG Revaccination


July 12, 2018
DOI: 10.1056/NEJMoal714021
Chinese Translation 中文翻译
**Bacillus Calmette-Guerin (BCG) Vaccine**

- Live, attenuated bovine tuberculosis strain (*Mycobacterium bovis*) that does not cause disease in humans but induces protective immunity
- Most widely used human vaccine
- First used in humans in 1921; more widely utilized after WWII
- Currently recommended for neonates and infants born in countries with high prevalence of TB
  - Prevents disseminated TB, TB meningitis
  - Efficacy ~50%
- There are six vaccines prequalified by the World Health Organization (WHO)
EFFICACY OF BCG IN ADOLESCENTS AND ADULTS APPEARS HIGHLY VARIABLE

- Efficacy ranges from 0 to 80% and is lowest in areas with highest TB incidence
- Factors associated with low efficacy in adults are unclear
  - Study designs
  - Force of infection
  - Latitude – those closer to the equator are exposed to other mycobacteria that may interfere with BCG immunity
  - Other?
H4:IC31 TB VACCINE PHASE II PREVENTION OF INFECTION STUDY

• Proof of Concept
  / Safety and Prevention of (established) Infection

• Population
  / QuantiFERON-negative, uninfected adolescents (aged 12-17 years)
  / Received BCG at birth
  / Western Cape, South Africa (SATVI)
  / High risk of infection (~10% per year)

• Sample size=990 subjects

• 3 Study Arms:
  / H4:IC31 vaccine (n=331)
  / BCG revaccination (n=330)
  / Placebo (saline) (n=329)

• Primary Efficacy Endpoint:
  / QuantiFERON conversion from negative to positive Day >84
BCG REVACCINATION OF ADOLESCENTS APPEARS TO PROVIDE PROTECTION AGAINST SUSTAINED *Mtb* INFECTION (POSI)

- **Primary endpoint not met**: No efficacy of BCG or H4:IC31 for the prevention of primary QFT conversion (>Day 84)

- **Secondary endpoint met**: 45% efficacy for BCG and 30% efficacy for H4 at preventing sustained (>6 mos) QFT conversion

- **Exploratory endpoint met**: Both vaccines showed efficacy against primary conversion to >4.0 IU/mL
WHERE TO FROM HERE?
**GATES MRI – OUR APPROACH TO BCG REVAX**

**H4iC31: PHASE II SAFETY AND EFFICACY RESULTS**

- **Safety**
  - Both vaccines safe and immunogenic
  - No vaccine-related serious adverse events
  - Most common vaccine-related adverse event was injection site swelling in BCG revaccinated participants

- **Primary Efficacy Endpoint: Initial QFT Conversion**
  - No statistically significant efficacy

- **Secondary Efficacy Endpoint: Sustained QFT Conversion**
  - 45% Efficacy for BCG
  - Efficacy statistically significant at nominal p-value of 0.05

**CLINICAL TRIAL SIMULATIONS**

- Define virtual population characteristics that mimic what we expect to encounter in the revaccination study (demographics, TB burden disease comorbidities (e.g., HIV co-infection), assay performance / correlation with outcomes)

- Avatars capture patient-level, target population in line with the enrollment criteria

- Create a sampling distribution algorithm to assign response attributes in line with predefined functional relationships and the protocol event schedule

- Construct treatment-response algorithms for all responses of interest
  - Mtb infection / hT (RT, TB burden, comorbidities, age, biomarker baseline)
  - AEs: hT (RT, TB burden, comorbidities, age, biomarker baseline)
  - Therapeutic Window Composite metrics = TTD

- Define covariate relationships that may alter response(s) and be considered as simulation scenarios
  - Assay threshold windows and variability
  - TB burden
  - Inclusion / exclusion criteria
  - Stratification
  - Sample size

**INNOVATION FOR TB VACCINES**

- Apply human biology to overcome roadblocks

  - **Antigen discovery**
  - **Immune correlates**
  - **Clinical biomarkers**
  - **Model validation**

- **Discovery**
  - Small animal models
  - Non-human primates
  - Phase 1/1b

- **Phase 2a/2b**
  - Phase 3

- **Molecular epidemiology**
  - Most-directed therapy clinical trials
  - Vaccine clinical trials

**ROADBLOCKS**

- Antigenic determinants of protection unknown
- Key immune cell subsets not well correlated with protection
- Small animal and non-human primate models not always predictive of clinical outcome
- No human challenge model
- Lack of standardization for immune correlates
- Surrogate endpoints for prevention of infection need refinement
- 10K+ subjects needed for prevention of disease studies

**INNOVATIONS TO IMPROVE INTERROGATION OF VACCINE-ELICITED IMMUNITY AND PROTECTION**

- Can be applied broadly across the entire study (3000+ participants)
  - Blood transcriptomics
  - Blood flow cytometry
  - Urine LAM

- Can be applied in an experimental medicine sub-study
  - PET/CT Imaging
  - Pulmonary immunity (BAL)
  - Blood CyTOF and single-cell transcriptomics

**KEY QUESTIONS FOR A REPEAT ADOLESCENT BCG PREVENTION OF INFECTION TRIAL:**

- Can we repeat the initial observation in the same population, with statistical rigor?
- How generalizable are the findings? Is the prevention of infection effective specific to the studied population, or can it be seen in other populations?
- Differences in force of infection, exposure to environmental mycobacteria, other variables
- What is the durability of the prevention of infection effect?
- What are the immune correlates of protection?
- How can biological observations made in this study impact the broader TB vaccine development effort?
• Key questions identified i.e., factors most likely to confound study
  / Study population, force-of-infection, latitude (exposure to other mycobacteria)

• Confirming the initial findings of POSI in a “high force-of-infection” country
  / Randomized (1:1), placebo controlled, observer-blind Phase 2b study in ~1800 subjects in South Africa

• Biomarkers and quantitative sciences
  / Further validate the QuantiFERON biomarker assay
  / Deep immuno-profiling for correlates of risk and correlates of protection

• CMC
  / Reviewed lineages of different vaccine strains from 1921 to present day
  / Utilizing additional assays to better characterize vaccine potency for clinical trial
What data are needed for a policy recommendation for a booster dose of BCG?

Will prevention of sustained infection translate to prevention of pulmonary disease?

90% of those with naturally occurring infection never develop symptoms

A meta-analysis of studies conducted in children shows that BCG prevents infection AND disease, in a pattern similar to other vaccines

How can we show the same is true for adolescents/adults?

Source: BMJ 2014;349:g4643
OUR APPROACH TO ACCELERATING DRUG AND VACCINE DEVELOPMENT IN GLOBAL HEALTH

CASE STUDIES IN TUBERCULOSIS

NEW TB DRUG REGIMENS
BEGIN WITH THE END IN MIND...
1943 - streptomycin (S)
1952 - Isoniazid (H)
1954 - Pyrazinamide (Z)
1955 - Cycloserine
1960 - Ethionamide
1961 - Ethambutol (E)
1963 - Capreomycin
1963 - Rifampicin (R)
1946 - First randomized trial: S
Monotherapy led to S resistance
1952 - First regimen: S/PAS/H
24 months of therapy
1960s - PAS replaced by E: S/H/E
18 months of therapy
1970s - Addition of R: S/H/R/E
9-12 months of therapy
1980s - S replaced by Z: H/R/Z/E
6-8 months, oral therapy
2014 - Delaminid
2012 - Bedaquiline
STANDARD OF CARE (SOC)

• Drug Susceptible: 6 to 9mos (Isoniazid, Rifampin, Pyrazinamide, Ethambutol or HRZE)
  / HRZE for 2mos then HR for 4mos
  / 92% cure rate in trial setting; ~55–85% in field*
  / ~20% Grade 3 to 4 AEs
  / ~20-25% with AE of hepatotoxicity
  / Rifampin – prototype CYP inducer, DDI liability
  / Inexpensive - ~$50/course

• Multi-drug Resistant: 9 to 24mos
  / Newer Short Course Regimen: 7 drugs for 9 to 12mos (Kanamycin; Moxifloxacin; Prothionamide; Clofazimine; Pyrazinamide; Isoniazid; Ethambutol)
  / 80% cure rate in trial setting; Older SoC 20-24mos ~50% in field**
  / Middle income countries, treatment and medical costs ~$6,000***

** http://guadalajara.worldlunghealth.org/media/conference-news-updates/stream-clinical-trial-results-provide-vital-insight-into-nine-month-treatment-regimen-for-multidrug-resistant-tuberculosis
***Laurence et al. Pharmacoeconomics, May 2015
A SHORTER, SAFER, SIMPLER TB DRUG REGIMEN IS NEEDED

<table>
<thead>
<tr>
<th>Current Standard of Care</th>
<th>Desired: Universal/Pan TB Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug Sensitive</strong></td>
<td></td>
</tr>
<tr>
<td>• 4 drugs for 2 mos; 2 drugs for 4 mos</td>
<td>• 3 or 4 drugs regardless of resistance</td>
</tr>
<tr>
<td>• 92% cure rate in trials; 55-85% in field*</td>
<td>• Shorter - &lt;2 months</td>
</tr>
<tr>
<td>• ~20% Grade 3-4 adverse events including hepatotoxicity</td>
<td>• Safer - No safety lab or ECG monitoring</td>
</tr>
<tr>
<td>• Inexpensive ~$50/course</td>
<td>• Simpler</td>
</tr>
<tr>
<td><strong>Multi-Drug Resistant:</strong></td>
<td>/ No sensitivity testing</td>
</tr>
<tr>
<td>• Short Course Regimen: 7 drugs 9-12mos</td>
<td>/ All oral; fixed dose combination</td>
</tr>
<tr>
<td>• 80% cure rate in trials; ~50% in field**</td>
<td>/ No interactions with other drugs; no need to modify dosing with anti-retrovirals</td>
</tr>
<tr>
<td>• Middle income countries, treatment and medical costs ~$6,000***</td>
<td>• Affordable</td>
</tr>
</tbody>
</table>
HISTORY OF TB DRUGS

1943 streptomycin (S)
1948 PAS
1952 Isoniazid (H)
1954 Pyrazinamide (Z)
1955 Cycloserine
1957 Kanamycin
1960 Ethionamide
1961 Ethambutol (E)
1963 Capreomycin
1963 Rifampicin (R)
1965 – PAS replaced by E: S/H/E 18 months of therapy
1969 – First regimen: S/PAS/H 24 months if therapy
1980s – S replaced by Z: H/R/Z/E 6-8 months, oral therapy
1990 – 2000 – PAS replaced by E: S/H/E 18 months of therapy
2000 – 2010 – PAS replaced by E: S/H/E 18 months of therapy
2010 – 2014 – Delaminid

1946 – First randomized trial: S Monotherapy led to S resistance
1970s – Addition of R: S/H/R/E 9-12 months of therapy

TB Alliance founded
TB Drug Accelerator
Bill & Melinda Gates Foundation founded
2012 Bedaquiline
2014 Delaminid
Multiple Candidates, Advance Regimen to Proof of Concept

Hit Generation

Target Identification

Company Compound Libraries

Collaborative Discovery Research

Lead Optimization

PHARMACEUTICAL COMPANIES:

RESEARCH INSTITUTIONS:

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CHALLENGES IN GLOBAL HEALTH TB DRUG REGIMEN DEVELOPMENT

- Individual drugs in the regimen will originate from different partners; Robust governance needed
- Mouse models are time- and resource-intensive
- Predicting the long term outcome of short regimens requires novel biomarkers
- Adaptive trials needed for efficient development; introduce regulatory complexity
- 20 drug candidates would present ~5000 possible 4-drug combinations
- Quantitative science models are not yet integrated with experimental tools to aid in regimen prioritization
- Drug supply logistics from multiple partners are complex
PRECLINICAL: INTEGRATED EXPERIMENTAL QS APPROACH TO REGIMEN PRIORITIZATION

**Challenges**

- Mouse models are time- and resource-intensive
- Recent clinical failures have cast doubt on the translatability of mouse-derived regimens
- 20 drug candidates would present about 5000 possible 4-drug combinations

**Opportunities**

- Use *ex vivo* experiments and *in silico* tools to explore a wider range of potential combinations
- Perform mechanistic and predictive modelling to refine understanding of combination synergy
- Industrialize throughput and speed of physiologic *in vivo* models for final down-selection and prioritization of regimens

**Ongoing Activities**

- **Map existing data and execute gap-filling experiments**
- **Adapt the relapsing mouse model to regimens**
- **Evaluate novel endpoints (TB RNA, fluorescent biomarkers, imaging)**
- **Operationalize predictive and mechanistic models from academic partners**
BIOMARKERS: OPTIMIZING DECISION-MAKING

Challenge

Current sputum mycobacterial biomarkers are not validated to predict cure from short term regimens; readouts are delayed

Opportunities

Gates MRI biomarker, statistics and QS experts are contributing to an experimental framework for the assessment and validation of novel TB drug biomarkers, while building the underlying operational capabilities and infrastructure needed.

Validated Clinical Biomarkers

- Formal biomarker validation including assessment of preanalytical, analytical and biomarker variability
- Iterative hypothesis testing and refinement to clinically validate biomarkers

Regulated Bioanalysis

- Establishing a network of bioanalytical labs using the innovator’s method and bioanalytical CRO where possible

Biorepository & Sample Tracking

- Working with a well established clinical biorepository; implementing 2Q2019
- Implementing a cloud-based SAS solution for sample tracking and management
1. Assign patients to control or experimental arm
2. Assess serum sputum culture conversion (SSCC) and novel biomarkers
3. Predict/assess relapse free cure rates at 12 months based on short-course regimens
4. Define and evolve quantitative go/no-go criteria for failure vs success based on ongoing data collection
5. If graduated or futile, introduce new combination therapy and update randomization
QUANTITATIVE SCIENCE IS INTEGRAL TO EVERYTHING WE DO

Pick the Best Combinations
Response surface modeling (RSM) and other predictive models coupled with patient-level TB data (AI/ML approach) and mechanistic QSP modeling

Pick the Right Doses
PK, PK/PD, Population PK/PD modeling, DDI simulation

Pick the Right Biomarkers
Computational/statistical framework for biomarker ID and validation

Inform Adaptive Trial Design and Execution
Clinical trial simulations, Bayesian statistics, decision rules, response-adaptive randomization

Support Downstream Registrations
Coordination of modeling deliverables with regulators (e.g. FDA)
FROM PATIENT TO MOLECULE...
BEGINNING WITH THE END IN MIND
OUR ONLY BOTTOM LINE:
LIVES SAVED
/ BEGIN WITH THE END IN MIND...
BEGIN WITH THE END IN MIND...

Top 10 global causes of deaths, 2016

<table>
<thead>
<tr>
<th>Cause Group</th>
<th>Cause</th>
<th>Deaths (millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Communicable, maternal, neonatal and nutritional conditions</td>
<td>Ischaemic heart disease</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Stroke</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Chronic obstructive pulmonary disease</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Lower respiratory infection</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Alzheimer disease and other dementias</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Trachea, bronchi, lung cancers</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Road injury</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Diarrhoeal disease</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Tuberculosis</td>
<td>1</td>
</tr>
</tbody>
</table>

GLOBAL IMPACT

Reduction in Diarrheal Hospitalizations Associated with Rotavirus Vaccines

South & Central America

- El Salvador* 79-86%
- Bolivia* 70%
- Mexico** 60-70%

Africa

- Rwanda* 61-70%
- Ghana* 49%
- South Africa* 54-58%

*Rotavirus hospitalizations
**All-cause diarrhea hospitalizations

Richardson V, Pichardo JH, Solares MQ et al. NEJM; 2010: 362: 358-360