WHY WE NEED A VACCINE TO CONTROL TB
and
WHAT WE IDEALLY NEED TO LEARN TO DEVELOP ONE

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If the key to controlling any infectious disease is to interrupt transmission, we are not succeeding in high burden countries.
The Implementation Problem

Cascade of Care for TB in India

Subbaraman et al, PLoS Med 2017
The MDR TB Problem

Vaccines represent a critical solution to the AMR Problem
The Quality of TB Care Problem

About 75% of Health Care in India is Private
  • Mostly Out of Pocket
Proportion of people with cough > 2w who:
  • Did not visit a health care provider = 40%
  • Did not visit a public health provider = 76%
• Number of Providers seen before TB Dx = ~3
• Number of Physicians, given TB cardinal symptoms able to Dx TB = ~ 25%
• Number of Physicians, told a case was TB, who recommended WHO standard treatment = ~ 25%

Cazabon D et al. . *Int J Infect Dis*, 2017

WE NEED EFFECTIVE VACCINES
The Spectrum of TB: Points of Vaccine Intervention

Prevent Infection or latency

eg. high risk individuals, e.g. PPD negative, TB hospital personnel

Prevent transition from latent to active disease

Treat and Cure Disease,

Prevent Recurrence

Goal: To Prevent Disease and Interrupt Transmission
What Ideally We Should Know To Develop An Effective TB Vaccine?

- Define immune mechanism(s) necessary and sufficient for protection, in animal models and humans, systemic and organ-specific.
- Define antigens required to engender protection
- Develop antigen delivery platform to generate appropriate protective immune responses in animal models, NHP.
- Confirm protective mechanisms are generated in human translational research studies
- Define a set of biomarkers of protection.
Is an Effective Vaccine Against TB Really Possible?
Mtb Infection Protects Against Reinfection

<table>
<thead>
<tr>
<th>Probationer Nurses</th>
<th>Number</th>
<th>Diseased</th>
<th>Dead</th>
<th>% Annual Morbidity</th>
<th>% Protection</th>
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<tbody>
<tr>
<td>Pirquet Positive</td>
<td>668</td>
<td>22</td>
<td>0</td>
<td>1.2</td>
<td>96%</td>
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<tr>
<td>Pirquet Negative</td>
<td>284</td>
<td>97</td>
<td>12</td>
<td>34.3</td>
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</tbody>
</table>

Nursing students in Ulleval, Norway TB Hospital, Followed for 3y

Annual Risk of Infection = 4-5%
% Primary infections developing TB = 23%
% Positives progressing to disease = 0.6%

J. Heimbeck, Brit. J. TB, 1936
Studies of Latent TB Protection Against Reinfection

Challenge: To develop a vaccine as effective as latent \textit{Mtb}

What Can We Learn from BCG?
Protection of BCG in Nurses, Ulleval, Norway

### Table IV.—Rates of Tuberculous Disease among Ulleval Nurses, 1924-1946

<table>
<thead>
<tr>
<th></th>
<th>Observation Nos.</th>
<th>Tuberculosis years</th>
<th>Disease</th>
<th>Deaths</th>
<th>Rate per 1,000 observation years</th>
<th>Morbidity</th>
<th>Mortality</th>
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<td>P+</td>
<td>668</td>
<td>1,772</td>
<td>22</td>
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<td>12.4</td>
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<tr>
<td>BCG</td>
<td>501</td>
<td>1,450</td>
<td>35</td>
<td>3</td>
<td>24.1</td>
<td>2.1</td>
<td>14.6</td>
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<td>P-</td>
<td>284</td>
<td>687</td>
<td>97</td>
<td>10</td>
<td>141.2</td>
<td>14.6</td>
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</tr>
</tbody>
</table>

BCG was half as effective as latent TB infection

*Heimbeck, J. Brit. J. Tubercul. 1948*
BCG Protection vs TB Disease in RTC

Mangtani, P et al. CID, 2014
Does BCG Protect against *Mtb* Infection?

Roy A et al. BMJ 2014
Variation in BCG Protection in Different Observational Studies

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>Population</th>
<th>Protective Efficacy %</th>
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<tr>
<td>Brazil (Sao Paulo)1</td>
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<td>India (Delhi)1</td>
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<td></td>
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<tr>
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<td>Korea (Seoul)</td>
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<td>Argentina (Buenos Aires)</td>
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<td>Cameroon (Yaounde)</td>
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<tr>
<td>Togo (Lome)2</td>
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<tr>
<td>England (Birmingham Asians)</td>
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<td>Canada (Manitoba Indians)</td>
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<td>Thailand (Bangkok)2</td>
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<td>Canada (Treaty Indians)</td>
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<td>Indonesia (Jakarta)</td>
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<td>Colombia (Cali)</td>
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<tr>
<td>Malawi (Karonga District)3</td>
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</tbody>
</table>

1=Tuberculous Meningitis  
2=Contact Study  
3=Prospective Cohort Study
The S. Indian BCG Trial
260,000 people, 15y --- No Protection vs TB Disease

- BCG may lack some critical protective antigens in *Mtb*
- Variable potency of vaccine strains
- Different genetics of human populations
- Variable persistence of live BCG
- Inadequate dosage of vaccine due to storage conditions
- Possible deleterious effect of freeze-drying
- Greater pathogenicity of infecting strains
- Interference by atypical environmental mycobacteria
  - *Eg. M. kansasii* and *M. microti*
- ???

**CONCLUSIONS:**
- Never design a clinical trial with only one hypothesis or endpoint
- NTM exposure may interfere with vaccine protection in areas with high environmental mycobacteria exposure
Specificity of Protection: BCG vs *M. microti*
20y Follow-up

MRC Trial - 54,000 tuberculin negative UK adolescents in 1950-2 randomized into vaccinated and control.

- BCG and *M. microti* vaccines were used.
- Delivered transdermally by 40 needles with 2mm tine device

- The protective efficacy of both *M. microti* and BCG during the first 5 years were equivalent = 84%
- Protection gradually decreased to ~77% for each over 20y.

*D’Arcy Hart and Sutherland. BMJ 1977*

- BCG’s derived after 1931 lack ESAT-6, CFP-10, MPT64, MPT70, or MPB8 but still protected

Vaccines need to contain multiple antigens, but which?
Intravenous BCG Protects of Rhesus Macaques from Aerosol Mtb Challenge

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Animal no.</th>
<th>Lung involvement</th>
<th>Lymphadenopathy</th>
<th>Hematogenous spread</th>
<th>Total</th>
<th>Mean</th>
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<tr>
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<td></td>
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<td>20</td>
<td>70</td>
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</tr>
</tbody>
</table>

Barclay, WR et al. I & I, 1970  

Is it important to have systemic immunization?
MHC Class I T-cells in Mice are Necessary for Protection vs TB, but not vs BCG

Flynn, J et al. PNAS 1992
CD 8+ Cells are Critical for Protection in NHP

We Need More Human Studies:
Human Immune Responses Differ in Important Aspects from Common Animal Models

- Different Mechanisms of Killing of *Mtb* by macrophages
- Vitamin D dependence of macrophage killing and autophagy; *Not in mice.*
- CD1a, 1b, 1c present Ag to T cells; *no mouse homolog*
- CD8 CTL release antimicrobial peptides; *Granulysin is absent in mice.*
- IL-32 activates human macrophages to kill and cross-present Ags to CD8 T-cells. *No mouse homolog.*
- IL-26 induces antimicrobial responses: *No mouse homolog*
- Latency. *Not in mice or rhesus macaques.*
Reports of Nonspecific Protection against Disease by BCG

- Leprosy 76% for multibacillary (lepromatous) forms
  62% for paucibacillary (tuberculoid) forms.

- All-Cause Mortality in Children (~50% in 5 LIC)
- Acute Lower Respiratory Disease (26% in infants)
- Superficial (NMIBC) Bladder Cancer (~70%) protective
- Type I Diabetes?
- Multiple sclerosis? (~50 reduction in demyelinating lesions)
Potential Importance of Bone Marrow and Innate Immunity

BCG in BM increases innate immunity and epigenetic changes
What are Possible Immunologic Differences Generated by *Mtb* and not BCG and other Candidates?

*Mtb* protects against TB better than BCG in humans and NHP.

Possible Mechanisms:
- *Mtb* has many antigens not present in BCG, e.g. RD1, ESX
- *Mtb* requires CTL for protection, BCG does not.
- *Mtb* can secrete antigens into cytoplasm that generate ‘antimicrobial CTL’
- Perforin+ - lyses infected MΦ
- Granzyme+, Granulysin + - Kill intracellular *Mtb*
- *Mtb* may generate protective antibody isotypes
- *Mtb* persists in bone marrow in latent TB and generates innate immunity and epigenetic changes.
- ???

...
Cost-Effectiveness of a TB Vaccine
Cost Estimates from BCG

• Per DALY $40 - $170
• Per Case Averted $5,000-$8,000
• Per Life Saved $8,000 - $11,000

• BCG Vaccination is Highly Cost-Effective
  Dye, C and Floyd, K. Tuberculosis Chapt. in DCP2, 2006

• But human trials are expensive
  ~$1m to produce one GLP/GMP candidate for clinical study
  ~$5 million for exploratory human studies
  ~$100 million for an efficacy trial.

Vaccine trials can fail. Research studies do not fail.
Bottom Line
What is Needed.

- Translational Studies in humans (Pre-Ph I, Ph I, Ph 2) to learn:
  - Immune responses generated by different vaccine candidates
    Systemic and organ-specific
  - What immune responses correlate with protection against infection, disease, and reactivation
  - Correlates of protection by measuring every possible relevant parameter
  - Learn best route, age and dose that is safe and protective.
  - Develop a safe live *Mtb* challenge strain
- Preliminary and Parallel studies in Non-Human Primates
- More field sites associated with good labs for trials and analysis
- Biorepositories for enabling later analysis of immune responses with new assays to identify correlates of protection
- A larger pipeline of candidates
- Greater financial resources

*The only vaccine studies that fail are those from which we fail to learn.*
Where We are Now

From Marcel Tanner