Challenges and prospects for new tuberculosis vaccines

David JM Lewis MD

Imperial College Healthcare NHS Trust
Learning Objectives

• Epidemiology
  • Burden, trends

• Pathogen
  • Physical composition, “life cycle”, antigens

• Host-Pathogen interaction
  • Nature of infection<→>disease, immunopathology<→>protection

• Pre-clinical models and Predictive Markers
  • Which one? Do they mean anything?
  • Surrogate markers: infection – disease – immunity – protection

• Vaccine design & development
  • What is “BCG”? Does it work? Is it safe? Can/will it be replaced?
  • Choice of antigen(s) / delivery system
  • Multiplicity of approaches, down-selection <→> competition
Epidemiology
TB Epidemiology – in 2014

- 9.6 million people developed TB
  - African Region 28%, India 23%, China 10%, Indonesia 10%
  - 56% male adults, 34% adult women, 10% children
  - 12% HIV infected (3/4 are in in African Region)
  - 1.5 million died – 73% HIV-negative

- TB incidence declining
  - ↓ 1.5% each year since 2000
  - TB mortality ↓ 47% since 1990

- Multi-Drug Resistant TB (MDRTB)
  - Worldwide: 3.3% new cases 20% of relapses
  - ~10% of MDRTB is XDRTB or untreatable
  - MDRTB is a driver for vaccine development
Pathogen
M. *tb*: structure & function

- Complex antigens
  - Proteins
    - In cell wall, and internal
    - Many are secreted at different stages of infection
  - Mycolipids, lipids, sugars, glycoproteins
    - Non-classical antigen presentation of lipids
    - No lipid vaccines to guide us – Koch removed lipids from “PPD”

- Complex “life cycle”
  - Logarithmic growth
    - Multiple secreted antigens $\rightarrow$ immunodominant
  - Ability to become latent / dormant *in vivo*
    - Latency genes, Latency antigens
    - Immunosilent, antibiotic resistant, may relapse to active disease
Host–Pathogen Interactions
M. *tb* and *Homo sapiens*: 73,000 years of co-evolution

Geographical distribution of current “lineages” of *M. tb*, time since divergence (10k years), mapped onto hypothesized human migration from African origin.

Published online 1 September 2013; doi:10.1038/ng.2744
“Classical” story of TB immunity: granulomas

**Innate Immunity**
- Phagocytes
  - Ingest & kill mycobacteria

**CMI Cell Mediated Immunity**
- CD4+ T cells
  - Secrete Cytokines
  - Activate phagocytes
  - Phagocytes kill bacilli

**DTH Delayed Type Hypersensitivity**
- CD8+ T cells
  - “Last defence” - failing phagocytes
  - T cells kill phagocytes
  - Necrosis - tissue destruction
  - Highly infectious

Infection

- Macrophage infection
- Fused infected macrophages
- Granulomas - high bacterial load
- Granulomas - low bacterial load
- Necrotic granulomas - very high bacterial load

Spread

LEGEND
- CD4+ T Cell
- CD8+ T Cell
- NK T Cell
- γδ T Cell
- Macrophage
- Langhans Giant Cell
- Fibroblast
- Tubercle Bacilli

Log (MtB load)

Time (weeks)

3

6

9
Primary Disease: non-immune people

- Bacilli inhaled
- Infect lung via airways

M. *tb* immunity (CMI & DTH) is now present in lung tissues

Meningitis Miliary TB

Innate & CMI overwhelmed DTH ineffective

- Bacilli inhaled
- Infect lung via airways

95% Recovery

M. *tb* Escapes

Blood

No M. *tb* immunity in lung tissue

Innate-CMI in balance DTH low

Innate-CMI in balance DTH low
Post Primary Disease: “immune” people

- Inhalation of a new infection
- Reactivation of latent infection

M. tb CMI & DTH is already present in tissues

Innate & CMI – exhausted
DTH – harmful
- necrosis & fibrosis
- cavities, bacteria, infectious!

Transport of bacilli in blood

Infectious lung disease

Necrotic destructive disease – cavities with multiple bacilli
Multiple TB vaccines?

- Inhale *M. tb.*
  - Immediate Killing (90%)
  - Primary Infection (10%)
  - Localised Disease
  - Recovery DTH+
  - Latency
  - Re-infection
  - Latency Antigens
  - Re-activation

- Disseminated Disease
- Post Primary Disease

Types of vaccines:
- Prophylactic
- Therapeutic
- Booster
TB : 4 *different* vaccines needed?

- **Primary disease (non-immune)**
  - Enhanced innate immunity? Avoid DTH?
  - Prevent extra-pulmonary spread (meningitis..) – replace BCG?
  - Neonatal use (maturity of immune system, EPI vaccines, effect of HIV...)

- **Post-primary disease (immune – hypersensitive)**
  - Prevent pulmonary (infectious) disease: block transmission
  - Work in the context of DTH / pre-immunity / Boost BCG+?
  - Must reach teenagers & Adults. Effect of established HIV... ?

- **Latent disease**
  - What is “latent TB” – how do we detect infection and not just immunity?
  - Different “latency” antigens ? What immunity – prophylactic or therapeutic?

- **Therapeutic / adjuvant therapy**
  - MDRTB – increasing need? Reduce infectivity quicker?
  - Which antigens?
  - Exacerbate disease (Koch phenomenon, HIV immune reconstitution)?
The Challenge Of An Existing Vaccine

Baccille Calmette–Guérin: BCG
What is Bacille Calmette Guérin: BCG?
The first (and only) TB vaccine – 1930s

BCG is not *A* vaccine but a *family* of vaccines!

**RD1** is a key deletion to attenuate BCG from virulent *M. bovis*

ESAT antigens, CFP10 antigen deleted
Ag85 cell wall antigen retained

Adapted from Vaccine 28 (2010) 2259–2270 and doi:10.1038/nrmicro1472
BCG controversies: does it work?

- **BCG prevents primary disease**
  - UK trial **80% effective**: miliary and TB meningitis in children
  - US First Nation: 50%+ protection (pulmonary) lasting >50 years

- **Geographical / genetics effect on efficacy**
  - Madras / Chennai trial in India – **0% effective** against any disease
  - Environmental mycobacteria – skewed immunity? Inhibit BCG?

- **BCG Sub-Strain differences?**
  - Phenotype, immunology, **reactogenicity**, but not **efficacy**?

- **19th Century manufacturing techniques – not cGMP**
  - Different immunity seen after slow and fast growth
  - Moving a factory 200 miles – no growth, ineffective, withdrawn
  - Frequent shortages when manufacturing fails (cancer therapy)

- **Does BCG prime correctly?**
  - M. tb antigens missing. “Chronic” infection – immune response? Skew?
    Interfere with vaccines?
  - **But The Whole World Is BCG primed … !**
BCG controversies: is it safe?

• Most number of doses of any vaccine delivered
  • Local lymphadenitis <1 in 100, resolves
  • Suppurating lymphadenitis, bone, disseminated disease < 1:1000 (immunodeficient)
  • Marked sub-strain differences in reactogenicity

• Increased disseminated disease in HIV+ neonates
  • WHO guidelines against use in known HIV+
    • But high HIV+ is where TB prevalence high too …

• Can it be used to prime infants?
**BCG?**

BCG ✗ (even where it works)

BCG ❌ (even where it works)

**BCG**

- Infants
  - Meningitis
  - Miliary TB

- Adults, Adolescents
  - Pulmonary spreaders
  - Extra pulmonary
  - HIV related

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"I suppose I’ll be the one to mention the elephant in the room."
Models of Infection & Protection

http://stm.sciencemag.org/content/6/265/265ra167.abstract
Animal models – predictive or misleading?

- **Mouse**
  - Do not form **granuloma**
    - Primary TB only
    - Mouse strain differences
  - **Reductions** in bacterial load
- **Guinea Pig**
  - Mimic human lung disease.
    - Limited reagents
    - **Mortality** measure only
    - Very hard to **improve** on BCG
- **Non-Human Primates**
  - Mimic **human disease**
    - Acute Phase Proteins, pathology ⋯
    - Costs, availability, NHP issues ⋯
Human Challenge Models?

- Inject BCG into skin, do biopsy
  - Measure bacterial load: culture / PCR
  - BCG loads in BCG+ < BCG −
  - Inverse correlation immunity and PCR after MVA85A
  - BCG − not *M. tb* − predictive of ⋯?

- Blood functional assays
  - Mix whole blood / separated blood cells with BCG or *M. tb* & measure bacterial killing
  - Humans can be studied, cytokines, field use
  - Blood is not the tissue that fights TB

- Aerosol challenge with attenuated TB, BCG
  - Human models? May better predict TB?
  - Still not *M. tb* − with all virulence genes & antigens

http://dx.doi.org/10.1080/21645515.2015.1134407
Predictive Markers of Protection
Making better vaccines than BCG
Surrogate markers: “immunity” ≠ “efficacy”

- Most “traditional” vaccines have antibody titre as surrogate - easy to standardise

- Classical evaluation of CD4 T cell-based TB vaccines:
  - Interferon gamma secretion (PBMCs) in response to ex vivo antigen stimulation

- Problem: increasing evidence that in humans IFNg responses do not correlate with protection
Measuring *Effector* T cells: polyfunctionality – better at predicting effectiveness?

Challenge:
- Use complex datasets in a *quantitative* way?
- How to *standardise* labs / developers?
- Will they *correlate* with protection in humans – still T cell readouts…?

Combinations of cytokines measured on the same cell at the same time by multi-colour flow cytometry.
BIOMARKERS: what can predict protection and disease in humans?
The Challenge Of Too Many Vaccine Candidates
<table>
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<th>Discovery</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase Ila</th>
<th>Phase IIb</th>
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<tr>
<td>Approximately 20 novel TB vaccine</td>
<td>Combination vaccines prime-</td>
<td>MVA85A (ID, Aerosol) University of Oxford,</td>
<td>VPM1002 VPM, SII, TBVI</td>
<td>M72 + AS01E GSK, Aeras</td>
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<td>strategies in development, several</td>
<td>boost</td>
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<td>Native and RHBHA</td>
<td>H64 + CAF01 SSI, TBVI</td>
<td>MTBVAC University of Zaragoza, TBVI</td>
<td>H1/H56 : IC31® SSI, Valneva,</td>
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<td>LCMV based candidates</td>
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<td>Aeras</td>
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<td>ChAV based candidates</td>
<td>rBCGΔais1/zmp1</td>
<td>ChAdOx1.85A MVA85A University of Oxford,</td>
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<td>Latency antigens</td>
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<td>Resuscitation and subdominant</td>
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<td>Peptidome antigens</td>
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<td>Glycolipid antigens</td>
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<td>Therapeutic vaccine - MVA platform</td>
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<td>Adjuvanted / Subunit</td>
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<td>recombinant BCG or M. tb</td>
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<td>other mycobacterial species</td>
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Pipeline - March 2016
www.tbvi.eu
www.aeras.org
ESATs: latency antigens

- ESATs play role in *M. tb* modulation of host immunity
  - Deleted from BCG (RD1)
  - Included in vaccines (& diagnostic tests)

- Relevant in reactivation of latent infection
  - *M. tb*. encounters a distinct immunological milieu in latently infected persons
  - Environmental ‘trigger’ changes *M. tb*. gene expression
  - **H56 subunit** & IC31 / CAF01 adjuvants
    - fusion-protein: Ag85B, ESAT-6 and **Rv2660c** (latency)
    - H56 vaccine effective in Cornell model of mycobacterial persistence after anti-TB drug treatment

http://doi:10.1038/nm.2285
http://dx.doi.org/10.1016/j.vaccine.2012.05.035
**MVA–Ag85A**

- **S Africa Phase 2b trial**
  - Replicating vector $\rightarrow$ CMI
  - Ag85A (BCG & *M. tb*) $\rightarrow$ boost BCG at birth
  - 1 dose – 4–6 month infants
  - TB infection endpoint

- **Safe, No protection**
  - No correlate of immunity
  - Did BCG fail to prime?
  - Infants unable to respond?
  - Wrong TB disease type?

- **2b HIV+ adults: no efficacy**
AERAS402

• Replication-deficient human adenovirus 35
  • TB antigens Ag85A, Ag85B and TB10.4 (ESAT family)
  • Safe, immunogenic in Ph 1
  • Reduced *M. tb* in mice

• Dose-finding, multicentre Phase 2 trial
  • Healthy, HIV-uninfected infants
  • BCG-vaccinated → “BCG+” strategy
  • 3 IM doses on days 0 and 28, 6m
  • Response << BCG vaccinated adults
  • T cells not increased by a third dose

dx.doi.org/10.1016/j.vaccine.2015.03.070
MTBVACC doi: 10.1016/S2213-2600(15)00435-X

• Live, recombinant M. tuberculosis
  • Attenuated by two gene deletions:
    • phoP: transcription factor, virulence
    • fadD26, synthesis of lipid virulence factors
  • Superior protection in animal studies
  • Safe and immunogenic in Phase I trial
  • Phase Ib testing South African field site
• Is it safe to give live rM. Tuberculosis?
  • HIV infected / mothers / infants of HIV+?
• Will injected live attenuated M. tb
  • Give better type of immunity than BCG?
  • Longer duration (adults)?
  • Be boostable?
• **Subunit latency vaccines**
  * fusion protein of
    * Ag85B – BCG & TB
    * ESAT-6 – TB secreted (deleted BCG)
    * Rv2660c – TB latency
  * Adjuvant IC31®
    * Repeating oligonucleotides I–C – CMI

• **South African Tuberculosis Vaccine Initiative**
  * Phase 1/ 1a
    * HIV-negative adults
    * BCG primed in infancy
    * With and without latent TB infection
  * Phase 1
    * Adults recently treated for pulmonary TB

doi:10.1016/j.vaccine.2013.07.05
Challenge for trials: down-selection, commercial competition & funding

• Geographic diversity in risk of TB infection and disease
• Clinical endpoints?
  • Disease? Infection? Latency? Cure?
• What level of efficacy will be acceptable?
• Duration of trials
  • decades to detect post-primary disease?
• Trial sites
  • overload, is the population globally representative?
• How to integrate with BCG or replace BCG
  • BCG at birth will skew immunity? Huge BCG+ birth cohort already.
• Impact of HIV in endemic areas / co-epidemiology.
• Can “gateways” prioritise candidates
  • if correlates & animal models absent or non-predictive … ?
Blueprint for TB vaccine success

doi: 10.1016/S1472-9792(12)70005-7

1. **Creativity** in research and discovery
2. **Correlates** of immunity and biomarkers for TB vaccines
3. **Cooperation**: Clinical trials, harmonization etc.
4. **Rational selection** of TB vaccine candidates
5. **Advocacy**: community acceptance and funding of vaccines within overall public health strategies
Thank You

David JM Lewis MD