Vaccines in Tuberculosis

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Global Epidemiology

In 2015:
- 10.4m new cases of TB
  - 1.2m in HIV+
  - ~480,000 MDR-TB
- 1.8m deaths
  - 0.4m in HIV+
- Rate of decline of incidence only 1.5%
  - Needs to be 4-5% by 2020
Global Plan to End TB: 2016 - 2020

• UN Sustainable Development Goals
  – Goal 3: Ending the TB epidemic by 2030

• 5 year investment plan

• US$65b needed

• US$9b to fund new tools
  – New drugs
  – New diagnostics
  – New vaccines
Target populations for an effective TB vaccine

• Infants
  – High burden of disease, particularly in SSA

• Adolescents / young adults
  – Greatest economic impact
  – Main population responsible for transmission

• HIV-infected adults
  – Still at increased risk despite ART
Indications for an effective TB vaccine

• Prophylactic
  – Infants
  – *M. tb* uninfected adolescents / young adults
  – Prevention of disease and/or prevention of infection

• Post-exposure
  – *M. tb* infected

• Therapeutic
  – As adjunct to chemotherapy
  – MDR/XDR
Challenges in TB vaccine development

- Uncertain predictive value of animal models
- Lack of immunological correlate
- Disease incidence
- Site infrastructure
BCG

- Live attenuated *M. bovis*
- First used in 1921 (per os)
- Efficacy:
  - Good
    - Disseminated TB and TB meningitis
    - Leprosy
  - Bad
    - Lung disease
    - Boosting *(Rodrigues et al, Lancet 2005)*
Design of an improved vaccine against TB

• Include BCG in new regime

• Needs to induce cellular immune response
  – Importance of humoral immunity unclear

• 2 potential strategies:
  – Boost BCG with a subunit vaccine
    • Protein + adjuvant
    • Viral vector
  – Replace BCG with improved BCG / attenuated *M. tb*
Global Clinical Portfolio

Phase 1
- DAR-901
  Dartmouth, Aeras
- MTBVAC
  Biofabri, TBVI, Zaragoza
- Ad5 Ag85A
  McMaster, CanSino
- ChAdOx1.85A / MVA85A
  Oxford, Birmingham
- MVA85A / MVA85A (ID, Aerosol)
  Oxford
- TB / FLU-04L
  RIBSP

Phase 2a
- RUTI
  Archivel Farma, S.L
- H1/H56: IC31
  SSI, Valneva, Aeras
- H4: IC31
  Sanofi Pasteur, SSI, Aeras
- ID93 + GLA-SE
  IDRI, Wellcome Trust, Aeras

Phase 2b
- VPM 1002
  SIU, Max Planck, VPM, TBVI
- M72 + AS01E
  GSK, Aeras

Phase 3
- Vaccæ™
  Anhui Zhifei Longcom

Please note: Information is self-reported by vaccine sponsors.

Revised on December 17, 2015
Increased vaccine efficacy against tuberculosis of recombinant *Mycobacterium bovis* bacille Calmette-Guérin mutants that secrete listeriolyisin

Leander Grode,1 Peter Seiler,1 Sven Baumann,1 Jürgen Hess,1 Volker Brinkmann,1 Ali Nasser Eddine,1 Peggy Mann,1 Christian Goosmann,1 Silke Bandermann,1 Debbie Smith,2 Gregory J. Bancroft,2 Jean-Marc Reyrat,3 Dick van Soolingen,4 Bärbel Raupach,1 and Stefan H.E. Kaufmann1

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The Journal of Clinical Investigation  http://www.jci.org  Volume 115  Number 9  September 2005

Safety and Immunogenicity of the Recombinant *Mycobacterium bovis* BCG Vaccine VPM1002 in HIV-Unexposed Newborn Infants in South Africa

André G. Loxton,1 Julia K. Knaul,1 Leander Grode,1 Andrea Gutschmidt,1 Christiane Meller,1 Bernd Eisele,1 Hilary Johnstone,1 Gian van der Spuy,2 Jeroen Maertzdorf,2 Stefan H. E. Kaufmann,2 Anneke C. Hesseling,2 Gerhard Walzl,3 Mark F. Cotton,1 the VPM Study Group

A

B

C

\[ \text{log CFU/lung (H37Rv)} \]

Days after challenge

**ESC MID eLibrary**

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MVA.85A Boosting of BCG and an Attenuated, phoP Deficient M. tuberculosis Vaccine Both Show Protective Efficacy Against Tuberculosis in Rhesus Macaques

Frank A. W. Verreck¹,², Richard A. W. Vervenne³, Ivanela Kondova², Klaas W. van Kralingen³, Edmond J. Remarque¹, Gerco Braskamp⁵, Nicole M. van der Werff¹, Ariena Kersbergen¹, Tom H. M. Ottenhoff³, Peter J. Heidt³, Sarah C. Gilbert³, Brigitte Gicquel⁶, Adrian V. S. Hill⁷, Carlos Martin⁷, Helen McShane⁵, Alan W. Thomas⁵

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First Human Immunization with A Live-Attenuated Mycobacterium tuberculosis: a randomized, double-blind, controlled phase I trial

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PPD

SFU / million PBMC

MTBVAC 5x10³

MTBVAC 5x10⁴

MTBVAC 5x10⁵

BCG 5x10⁵
Safety and immunogenicity of candidate vaccine M72/AS01E in adolescents in a TB endemic setting

Adam Penn-Nicholson a, b, *, Hennie Geldenhuys a, b, Vivine Burny b, Robbert van der Most b, Cheryl L. Day a, c, d, Erik Jongert b, Philippe Moris b, Mark Hatherill a, Opokua Ofori-Anyinam b, 2, Willem Hanekom a, 2, the Vaccine Study Team,

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c Department of Global Health, Rollins School of Public Health, Atlanta, GA, USA
d Emory Vaccine Center, Emory University, Atlanta, GA, USA
The multistage vaccine H56 boosts the effects of BCG to protect cynomolgus macaques against active tuberculosis and reactivation of latent *Mycobacterium tuberculosis* infection

Philana Ling Lin,1 Jes Dietrich,2 Esterlina Tan,3 Rodolfo M. Abalos,2 Jasmin Burgos,3 Carolyn Bigbee,4 Matthew Bigbee,4 Leslie Milk,4 Hannah P. Gideon,4 Mark Rodgers,4 Catherine Cochran,4 Kristi M. Guinn,5 David R. Sherman,5 Edwin Klein,6 Christopher Janssen,6 JoAnne L. Flynn,4,7 and Peter Andersen2

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Modified vaccinia Ankara (MVA)
- Poxvirus
- No replication in mammalian tissues
- Good T cell boosting vector
- Excellent safety record

*M.tbc* antigen 85A
- Mycolyl transferase
- Major target antigen
- Protective in small animals
- In all environmental mycobacteria
- Doesn’t interfere with new diagnostic tests

BCG - MVA85A regimen
Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Michele D Tameris*, Mark Hatherill*, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, J Bruce McClain, Gregory D Hussey, Willem A Hanekom, Hassan Mahomedt, Helen McShane†, and the MVA85A 020 Trial Study Team

- Birth 16-24 weeks
- BCG MVA85A or placebo
- 1-3 years

ADAPTIVE IMMUNITY
PBMC stored from ~2700 infants
Before immunisation and +28 days

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Assays for immune correlates of risk analysis

- **Transcriptional analysis**
  - Illumina HT12 arrays

- **Functional Assays**
  - Mycobacterial growth inhibition assays

- **Immune Assays**
  - IFN-γ ELISPOT assays (UNS, PHA, BCG, 85A)
  - Antibodies on serum samples
  - Luminex on supernatants from above assays*

- **Cellular phenotyping**
  - Cell surface flow cytometry for lymphoid and myeloid cells
  - Markers of activation, exhaustion, T cell regulation*

- *Secondary assays to be performed on stored supernatant, RNA, frozen/fixed cells
T-cell activation and BCG IFN-γ ELISPOT are immune correlates in BCG-vaccinated infants

Measured in healthy infants up to 3 years before disease develops

Fletcher HA et al Nature Communications, 2016
Antibodies correlate with reduced risk of TB disease

Are they directly involved in protection or correlating with another immune parameter?

Fletcher HA et al Nature Communications, 2016
Why didn’t MVA85A protect?

• Immunogenicity ‘modest’
  – Immunogenicity 10-fold lower than in UK adults
  – Single vector not potent enough?

• Wrong route?

• Single antigen?

• Wrong population?
  – Immunogenicity lowest in infants
Future efficacy trials

• Focus on adolescents/adults
  – Responsible for most transmission
  – Candidate vaccines less immunogenic in infants

• Prevention of infection
  – Faster (therefore cheaper) trial as many more endpoints
  – BUT
  – Will a vaccine that prevents disease necessarily prevent infection?
An inhaled TB vaccine

• Route of immunisation = route of infection
• BCG does not reliably protect against pulmonary TB
• Mucosal immunisation can generate potent durable immune responses
• Specialised lymphoid tissue
• Inhalation is a common route of drug delivery
• Feasible
• Needle free
• Pain free
• Not a new idea!
Assessing the inhaled route in a human clinical trial

• Phase I trial
  – 22 BCG vaccinated adults randomised to $1 \times 10^7$ pfu MVA85A inhaled or ID
  – Randomised single blinded paired placebo design
  – Bronchoscopy day 7 BAL

• Primary and secondary outcome
  – Safety: local & systemic AEs, $S_aO_2$, spirometry, bronchoscopy
  – Systemic and mucosal cellular immunogenicity: blood and BAL
BAL Ag85A specific CD4+ T cell responses stronger after aerosol than i.d administration

\[ P = 0.033 \]

\[ P = 0.05 \]

\[ P = 0.04 \]

\[ P = 0.0151 \]

A: Aerosol
ID: Intradermal

Satti et al, Lancet Infect Dis 2014
Whole blood Ag85A CD4+ T cell responses at least as strong after aerosol than i.d administration

Satti et al, Lancet Infect Dis 2014
New *in-vitro* and *in vivo* models
Principles of the MGIT Assay

- 37°C + convection currents
- Oxygen-quenched fluorochrome → UV light
- Intensity of fluorescence ∝ mycobacterial growth
- Read-out = time taken to detection (TTD) in hours (converted to Net Growth using std curve and ctrl)
MGIA detects BCG vaccine effect in UK adults

Fletcher H et al. CVI 2013
MGIA detects BCG vaccine effect in mouse splenocytes

In vitro MGIT

In vivo M.tb Challenge

Marsay et al, Tuberculosis 2013
MGIA correlates with protection from *M. tb* challenge

Tanner R et al, unpublished
Human mycobacterial challenge models

• An effective vaccine against BCG should also protect against *M. tuberculosis*

• Does intradermal BCG ‘challenge’ provide a good model for aerosol *M. tuberculosis* challenge?
  – Validation in preclinical animal models
Pilot BCG challenge study

- BCG (SSI), $2 \times 10^5$ cfu/ 100 ul
- Route i.d
- Sampling: 4mm punch biopsy
- Biopsy at 1, 2, or 4 weeks post BCG

Minassian A et al, JID 2012
Aerosol BCG delivery

1. A more effective route of vaccination

2. A human mycobacterial challenge model:
   – For vaccine evaluation
   – To determine early innate events in the airway
Summary

- Progress in clinical testing of TB vaccine candidates
- Correlate samples from efficacy trials can yield important information
- Aerosol immunisation appears safe and highly immunogenic
- Evaluation in the target population is critical
- A MGIA and a human mycobacterial challenge model may be of utility in vaccine selection
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