MECHANISMS OF ATTENUATION AND PROTECTION OF MTBVAC:

a live attenuated TB vaccine moving to clinical efficacy trials in endemic countries
Breaking Transmission with Vaccines: The Case for Tuberculosis

**Individuals with LTBI had 79% lower risk of Progressive TB after reinfection than uninfected individual**

Andrews et al CID 2012

**TB INFECTION** only 5-10% will develop TB disease

Gonzalo et al Microbiology Spectrum 2017

**Lytic cycle** of lambda phage, similar to active TB disease

**Lysogenic cycle** of lambda phage, resembles LTBI
M. tuberculosis Vaccine Antigens, Ag85B and ESTA-6, are differentially expressed during infection.

Ag85B early expressed during infection.

ESTA-6 constantly expressed during all infection.
It is difficult to overcome the response induced by *M. tuberculosis* infection.

Clinical Trial H1 IC31: Ag85B + Esat6

H1:IC31 vaccination is safe and induces long-lived TNF-a+IL-2+CD4 T cell responses in MTB infected and uninfected adolescents.

RATIONALE FOR DEVELOPING MTBVAC

Following Pasteur’s postulates for attenuated vaccines. Learning from BCG

- ATTENUATE A PATHOGEN FROM HUMAN ORIGIN
- SELECT A WORLDWIDE DISTRIBUTED *M. tuberculosis* CLINICAL ISOLATE
- WHICH GENE(S) TO INACTIVATE?
- AVOID LABORATORY SUBCULTURE: INDUSTRIAL PARTNER
**ATTENUATION, PROTECTION & IMMUNOGENICITY**

**PRECLINICAL & PROOF-OF-CONCEPT STUDIES (2001-2012)**

*Douglas Young “road map”*

**INDUSTRIAL DEVELOPMENT FREEZE-DRIED MTBVAC (2008-2011)**

- Original lab strain MTBVAC (P0) 2008
- Master Seed Lot (MSL)
- Working Seed Lot (WSL)
- Final Lot (at least 2 clinical lots)
- Release of Final Product 2011
FIRST GENEVA CONSENSUS CRITERIA: CONSTRUCTION OF MTBVAC
NO ANTIBIOTIC RESISTANCE MARKERS
TWO STABLE INDEPENDENT MUTATIONS

MTBVAC

phoP

fadD26

SECOND GENEVA CONSENSUS: Criteria for further Clinical Development Phase 1 to 3

Esteban Rodriguez

Jelle Thole

PDT: Product Development Team TBVI

CDT: Clinical Development Team TBVI
Transcription factor PhoP plays an essential role in MTB virulence. 
~2-4% ORFS MTB genome under PhoP control (microarrays):
mainly genes implicated in virulence or immunomodulation.

PhoP

RESPIRATION
narK1, nirA, cysH, ald, nuoBCDK

STRESS PROTEINS
(hsp) groEL2

HYPOXIC RESPONSE
1. INITIAL (dosS/R)
2. ENDURING

iCl

PERSISTENCE

POLYKETIDE- DERIVED LIPIDS
Immunomodulators

LIPID METABOLISM
SL, DAT, PAT + ....lipF
MECHANISMS OF ATTENUATION AND PROTECTION OF MTBVAC:

CONSEQUENCE OF *fadD26* DELETION: loss of major virulence factor PDIM

CONSEQUENCE OF *phoP* DELETION: loss of SL, PAT, DAT; impaired ESAT6 SECRETION and increased secretion of MTB antigens

*Modified from Broset et al. mBio. 2015
Gonzalo et al. Plos One 2008*
MECHANISMS OF PROTECTION OF MTBVAC:

MTBVAC, 519 MORE EPITOPES THAN BCG

MTBVAC → 1603 epitopes

BCG → 1084 epitopes

Marinova et al. Expert Rev Vaccines 2017

Gonzalo-Asensio et al. Frontiers in Immunology 2017
Improved protection of MTBVAC as compared to BCG is associated with T-cell mediated response to CFP10/ESAT6

**Ag85B**: BCG a polymorphism unstable protein
(Copin et al. 2014)

**ESAT6/CFP10 present in RD1**

**MHC Haplotypes:**
- H-2b
- H-2d
- H-2k

**Protection in lungs (very low-dose H37Rv challenge: ≈ 20 CFU)**

Nacho Aguilo

Aguilo et al 2017 Nature Communications
ESAT6 (RD1)
A Double Edged Sword
Host immune system / *Mycobacterium tuberculosis*

**Latent TB Infected (LTBI)**

90% LTBI
GRANULOMA = CONTENTION

1/3 POPULATION

The acquired cellular response, by CD4 T cells, provides protective immunity

- TST +
- QFT +

**TB LUNG DISEASE**

5-10% LTBI INFECTED

CD4 T cells, also promoting the development
CASEOUS NECROSIS REQUIRED FOR TRANSMISSION

**RD1**
31FP10) 1 epitopes (PPE68/ESAT6/C

**RD1**
(ESAT6/CFP10)
AFTER 100 YEARS OF BCG FIRST EFFICACY TRIAL OF A TB VACCINE

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

Tameris et al Lancet. 2013

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 Mahomed†, Helen McShane†, and the MVA85A O20 Trial Study Team

TODAY STILL LEARNING FROM THIS CLINICAL TRIAL

Serial QuantiFERON testing and tuberculosis disease risk among young children: an observational cohort study

Andrews et al Lancet Respiratory Medicine 2017

Jason R Andrews, Elisa Nemes, Michele Tameris, Bernard S Landry, Hassan Mahomed, J Bruce McClain, Helen A Fletcher, Willem A Hanekom, Robin Wood, Helen McShane, Thomas J Scriba, Mark Hatherill

INVESTIGATE THE RELATION BETWEEN QFT CONVERSION INF-γ VALUES AND RISK OF TB
QFT conversion at interferon-γ values between 0.35–4.00 IU/ml did not have significantly increased risk of TB disease.

QFT <0.35 IU/ml
QFT 0.35 – 4.00 IU/ml
QFT >4.00 IU/ml

Percentage TB–free survival from day 336 study visit, stratified by quantitative QFT.

QFT + >4.00 IU/ml associated with substantially increased disease incidence

QFT - <0.35 IU/ml, QFT + 0.35–4.00 IU/ml NO INCREASED RISK OF DISEASE

Andrews et al Lancet Respir Med 2017
CLINICAL DEVELOPMENT MTBVAC

- **2010**
  - MTBVAC final lot
  - May 2011

- **2011**
  - Non-clinical studies to support clinical evaluation
  - 25 Aug’10 – 20 Dec’11

- **2012**
  - Phase I CTA Preparation
  - Oct’11 – April’12

- **2013**
  - Long-term, real time stability studies

- **2014**
  - First ever live attenuated *M. tuberculosis* vaccine to enter clinical trial

- **2015**
  - PHASE Ia HEALTHY ADULTS in CHUV Switzerland
    - PPD, BCG, HIV (18-45 yrs)
  - Approval
    - Oct 2012

- **2016**
  - PHASE Ib in NEWBORNS
    - With a safety arm in adults (BCG+, PPD-, HIV-)
  - New born vaccination phase
    - 16 Feb - 21 Sep 2016

- **2017**

François Spertini
Spertini et al Lancet Respiratory Medicine 2015
MTBVAC Phase 1a ADULTS Clinical Trial

Vaccination with MTBVAC induces a CFP10-specific immune response in humans

Aguilo et al. 2017 Nat Comm
PHASE 1B DOSE-ESCALATION SAFETY AND IMMUNOGENICITY OF MTBVAC IN NEWBORNS (with a Safety Arm in Adults (MTBVAC-Ph1b))

Michele Tameris

Tom Scriba

Mark Hatherill

Helen Mearns

ClinicalTrials.gov
NCT02729571
Efficacy Evaluation of a New TB Vaccine:

In Newborns: A pre-exposure vaccines could allow for reliable efficacy determination.

In Adults/Adolescents: More impact, but previous sensitization to BCG, MTB or NTM could have potential masking/blocking effects.

Role of Adults/Adolescents in the Transmission of TB and TB Vaccine Strategies.
VACCINATION AT BIRTH (NEONATES): PHASE 2A
Dose-Defining Safety and Immunogenicity Study and Capacity Building to Support Vaccine Efficacy Trials in TB-Endemic Regions of Sub-Saharan Africa.

PI. DR. MICHELE TAMERIS (SATVI)

Expected trial initiation date: / 3rd Quarter 2018
RE-VACCINATION IN ADOLESCENTS / ADULTS: PHASE 2A
Randomized, Double-blind, Active-controlled, Safety, Immunogenicity, and Dose-escalation Study in Adults with and without Latent Tuberculosis Infection in South Africa.

PI ANGELIQUE KANY KANY LUABEYA (SATVI)

Expected trial initiation date: 2nd Quarter 2018
A New TUBERCULOSIS VACCINE:

LIVE VACCINES
(Huge experience in the production, distribution and use of BCG)

Safer / Better than BCG