IN THE SEARCH OF A NEW TB VACCINE: FROM THE LAB TO THE CLINICAL TRIALS IN ENDEMIC COUNTRIES

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TB has killed more than any other infectious disease in history. Over a billion lives in the past two hundred years.

Tom Paulson  Nature  2013
WHO GLOBAL TB REPORT 2016

Actions and investments to End TB fall far short

Tuberculosis among top 10 causes of death worldwide last year

Here are the statistics from 2015

10.4 million people FELL ILL FROM TB

That’s 28,500 people every day

1.8 million people DIED FROM TB

including 400,000 WITH HIV + TB

That’s over 4,900 people every day

60% of TB cases worldwide occurred in just SIX COUNTRIES

CHINA  INDIA  INDONESIA  NIGERIA  PAKISTAN  SOUTH AFRICA

More action and investment in these countries will drive down the TB burden
3 MILLION LIVES WERE SAVED BY THE GLOBAL TB RESPONSE IN 2015

ACCESS TO CARE

6.1 million people had access to quality TB care

4.3 million people missed out

Better reporting, diagnosis and access to care will close this gap

DRUG RESISTANCE

Only 1 in 5 people needing treatment for multidrug-resistant TB in 2015 actually received it

Only half of those who started MDR-TB treatment were cured

Better detection, prevention and cure will address the crisis of multidrug-resistant TB
**BCG the present vaccine against tuberculosis**

*Albert Calmette* (1863–1933)  
*Camille Guérin* (1872–1961)

**Mycobacterium bovis** 1908-1921  
230 serial passages

This isolate was subsequently distributed to several laboratories in the world and a number of strains developed:

- **BCG Russia**
- **BCG Moreau**\ Il de Janelio
- **BCG Japan**

Currently, five main strains account for more than 90% of the vaccines in use worldwide with each strain possessing different characteristics:

- BCG Russian BCG-I
- BCG Moreau RDJ
- BCG Tokyo 172-1
- BCG Pasteur 1173 P2
- BCG Danish 1331

**IGRA TEST**  
QFT +  
↑ 0.35 IU/ml

**RD1**  
ESAT6/CFP10  
PPE68

Adapted from Brosch *et al.* PNAS 2007
Intradermal administration at birth

Scar after vaccination

BCG global coverage at birth 89% worldwide

Provides variable protection against respiratory forms of TB

BENEFICIAL EFFECTS OF BCG VACCINATION:

1. BCG provides **strong protection against disseminated forms** of the disease.

2. BCG vaccination **reduces all-cause mortality** through beneficial non-specific (heterologous) effects on the immune system.

A BETTER VACCINE AGAINST RESPIRATORY FORMS TB IS NEEDED
TB vaccine research in Europe

2000 – 2004
Tuberculosis Vaccine Cluster
EU Framework Programme 5 Integrated Project

2004 – 2013
TBVAC
EU FP 6 /FP7 TBVAC/ NEWTBVAC
Integrated Projects

2007
EU R&D Commission
Supports creation of a separate entity
TuBerculosis Vaccine Initiative (TBVI)

PDT: Product Development Team
CDT: Clinical Development Team

CLINICAL TRIAL:
EDCTP (EU)
AERAS (Gates Foundation)
NORAD/ Gulbenkian

INDUSTRY: GSK, Sanofi
BIOFABRI

2015 – 2018
EU H2020 TBVAC2020

Jelle Thole
**SUBUNIT VACCINES**

**BOOSTING BCG:** VIRAL VECTOR / NEW ADJUVANTS

Ag85, ESAT6, Others Antigens (immunodominant in humans and mice…….)

<table>
<thead>
<tr>
<th>VIRAL VECTOR</th>
<th>ADJUVANTS</th>
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<tbody>
<tr>
<td>Oxford MVA85A</td>
<td>GSK M72/ AS01E</td>
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<tr>
<td>Crucell Ad 35</td>
<td>Fusion Rv1196/Rv0125</td>
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<tr>
<td>Mac Master Univ</td>
<td>SO2</td>
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<tr>
<td><strong>Modified vaccinia Ankara Expressing Ag85A</strong></td>
<td><strong>Phase 2b Efficacy</strong></td>
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<tr>
<td><strong>Adenovirus 35 Ag85A, Ag85B, TB10.4</strong></td>
<td><strong>Phase 2</strong></td>
</tr>
<tr>
<td><strong>Ad5Ag85A</strong></td>
<td><strong>Phase 1</strong></td>
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<tr>
<td></td>
<td><strong>SSI H1 + IC31</strong></td>
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<td></td>
<td><strong>Ag85B + Esat6</strong></td>
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<td></td>
<td><strong>IC31</strong></td>
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<td></td>
<td><strong>Phase 2</strong></td>
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<td></td>
<td><strong>SSI H1 + CAF01</strong></td>
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<td></td>
<td><strong>Ag85B + Esat6</strong></td>
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<td></td>
<td><strong>CAF01</strong></td>
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<td><strong>Phase 1</strong></td>
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<td><strong>SSI H4</strong></td>
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<td></td>
<td><strong>Ag85B + TB10.4</strong></td>
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<td></td>
<td><strong>IC31</strong></td>
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<td><strong>Phase 2</strong></td>
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<tr>
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<td><strong>SSI H56</strong></td>
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<td></td>
<td><strong>H1 + Rv2660c</strong></td>
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<tr>
<td></td>
<td><strong>IC31</strong></td>
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<td><strong>Phase 2</strong></td>
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<td></td>
<td><strong>ID93 IDRI</strong></td>
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<td></td>
<td><strong>Rv1813, Rv2608, Rv3619 &amp; Rv3620</strong></td>
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<td></td>
<td><strong>GLA-SE</strong></td>
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<td></td>
<td><strong>Phase 1</strong></td>
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</table>
Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial

Methods: double-blind, randomised, placebo-controlled phase 2b trial, we enrolled healthy infants (aged 4–6 months) without HIV infection who had previously received BCG vaccination. Followed up infants every 3 months for up to 37 months.

Findings: Enrolled 2797 infants (1399 allocated MVA85A and 1398 allocated placebo). 32 (2%) of 1399 MVA85A recipients meet primary efficacy point tuberculosis as did 39 (3%) of 1395 controls (BCG).

Interpretation: absence of MVA85A efficacy against tuberculosis or M. tuberculosis infection infants need exploration.
TUBERCULOSIS VACCINES IN CLINICAL TRIALS

Phase I
- ATTENUATED MTB (MTBVAC)
- Ad5Ag85A McMaster, CanSino
- ChAdO1.85A / MVA85A Oxford, Birmingham
- MVA85A / MVA85A (Aerosol) Oxford
- TB / FLU-04L RIBSP

Phase IIa
- DAR-901 Dartmouth
- RUTI Archivel Farma, S.L

Phase IIb
- RECOMBINANT BCG (VPM BCG + Hemolysin)
- H1/H5C IC31 SSI, Valneva, Aeras
- II-29 Sanofi Pasteur, SSI, Aeras
- ID93 - GLA-SE IDRI, Wellcome Trust, Aeras

Phase III
- Therapeutic
- Anhui Zhifei Longcom

- Viral Vector
- Protein/Adjuvant
- Mycobacterial - Whole Cell or Extract

THE STAGES IN THE IMMUNOLOGICAL LIFE CYCLE OF TB

95% MTB strains Human origin

"Individuals with LTBI had 79% lower risk of Progressive TB after reinfection than uninfected individual"
Andrews et al CI D 2012

Only 5-10% will develop TB disease

TB INFECTION
HUMAN RESERVOIR
Mortality 50% without treatment

Modified from J. D Ernst 2012 NATURE REVIEWS IMMUNOLOGY
RATIONALE FOR DEVELOPING MTBVAC

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

1.- ATTENUATE A PATHOGEN FROM HUMAN ORIGIN

2.- WE SELECTED A WORLDWIDE DISTRIBUTED *M. tuberculosis* CLINICAL ISOLATE

3.- WHICH GENE(S) TO INACTIVATE?

4.- AVOID LABORATORY SUBCULTURE
TWO STABLE INDEPENDENT MUTATIONS
NO ANTIBIOTIC RESISTANCE MARKERS

Vaccine
Volume 23, Issue 29, 31 May 2005, Pages 3753-3761

New live mycobacterial vaccines: the Geneva consensus on essential steps towards clinical development

Arun T. Kamath a, Uli Fruth b, Michael J. Brennan c, Roland Dobbeltaer d, Peter Hubrechts e, Mei Mei Ho f, Ronald E. Mayner g, Jelle Thole h, K. Barry Walker i, Margaret Liu j, Paul-Henri Lambert a, g, ∗

MTBVAC

phoP
fadD26
CONSEQUENCE OF \textit{fadD26} DELETION: loss of virulence factor PDIM
CONSEQUENCE OF \textit{phoP} DELETION: loss of SL, PAT, DAT; impaired ESAT6 SECRETION (\textit{espACD}) and increased secretion of MTB antigens (TAT-C regulation)

\textbf{M. tuberculosis}

\begin{itemize}
  \item Mg$^{2+}$, Cl$^-$, pH ?
  \item PhoR
  \item PhoP
  \item mcr7
  \item \textit{pks2}
  \item \textit{pks3}
  \item SL
  \item DAT
  \item PAT
  \item ESAT-6
  \item \textit{EspA}
  \item \textit{tatC} translation inhibition
  \item Ag85A and C
\end{itemize}

\textbf{MTBVCAC}

\begin{itemize}
  \item \textit{phoP} mutant
  \item \textit{pks2}
  \item \textit{pks3}
  \item \textit{mcR7}
\end{itemize}

\textbf{CONSEQUENCE OF \textit{fadD26} DELETION: loss of virulence factor PDIM}

PDIM +

PDIM -

\textbf{Modified from Broset et al mBio. 2015}
\textbf{Solans et al. PLoS Pathogen 2014}
\textbf{Gonzalo et al Plos One 2008}
MTBVC, 519 more epitopes than BCG which represents an increase of 48%
BCG Genome: Diminishing of human T-Cell epitopes, which are conserved in MTBVC

Compared 1.530 human T cell epitopes in BCG with MTBC

23% OF THE KNOWN T CELL EPITOPES ARE ABSENT IN BCG (358/1530)

Table 1
Classification and characteristics of M. tuberculosis T cell antigens absent from BCG strains.

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Description</th>
<th>Strain(s) Absent</th>
<th>RD1 Region</th>
</tr>
</thead>
<tbody>
<tr>
<td>RV1985c</td>
<td>Probable transcriptional regulatory protein</td>
<td>RD2</td>
<td>24</td>
</tr>
<tr>
<td>RV3878</td>
<td>Hypothetical protein</td>
<td>RD1</td>
<td>17</td>
</tr>
<tr>
<td>RV2653c</td>
<td>phiRv2 prophage protein</td>
<td>RD11</td>
<td>12</td>
</tr>
<tr>
<td>RV2654c</td>
<td>phiRv2 prophage protein</td>
<td>RD2</td>
<td>6</td>
</tr>
<tr>
<td>RV1979c</td>
<td>Possible conserved permease</td>
<td>RD14</td>
<td>4</td>
</tr>
<tr>
<td>RV1769</td>
<td>Hypothetical protein</td>
<td>Conserved hypotheticals</td>
<td>4</td>
</tr>
</tbody>
</table>

RD1 region contains most of the epitopes (307/1603 close to the 20%): ESAT6 (98), CFP10 (86) & PPE68 (65)
present in MTBVC and absent in BCG

Gonzalo et al unpublished

Copin et al Vaccine October 2014
Improved protection of MTBVC 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

HOST GENETICS:

Aguilo et al July 2017 Nat Comm
**ATTENUATION, PROTECTION & IMMUNOGENICITY**

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

**GMP DEVELOPMENT OF 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

**PDT:** Product Development Team (TBVI)

*M. tuberculosis* Genetic tools (col Brigitte Gicquel)

1992-2000 EU FP3/FP4

**INSTITUT PASTEUR**
Criteria for further clinical development from Phase I through to Phase III
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
CTA Evaluation
Approval
3 Oct 2012

2016

2017

PHASE Ia HEALTHY ADULTS
in CHUV Switzerland
PPD-, BCG-, HIV-
(18-45 yrs)
Vaccination phase:
23 Jan - 6 Nov 2013

PHASE Ib in NEWBORNS
With a safety arm in adults (BCG+, PPD-, HIV-)
Sept 2015 - Jan 2016

Approval
11 May 2015

ClinicalTrials.gov
v: NCT02013245

Unblinded data
March 2015

Approval
13 May 2015

HREC+ DAFF
5 Aug 2015

Published Dec 2015
The Lancet Respi Medi

New born vaccination phase
16 Feb - 21 Sep 2016

PDT: Product Development Team TBVI
CDT: Clinical Development Team TBVI

ClinicalTrials.gov
NCT02729571
MTBVAC PHASE 1a ADULTS:
TRIAL CONCLUSIONS

PRIMARY ENDPOINT: SAFETY
ROBUST SAFETY & REACTOGENICITY PROFILE SIMILAR TO BCG

SECONDARY ENDPOINTS: IMMUNOGENICITY

Whole Blood Assay: MTBVAC/ BCG stimulation
MTBVAC demonstrated promising immunogenic properties with dose-response dependent induction of polyfunctional CD4 T-cells expressing at least one cytokine (IFNγ+, TNFα+, IL-2+).

Comparing MTBVAC 5x10^5 group and BCG, a greater induction of 3 cytokines+ and higher number of responders were observed after MTBVAC vaccination with a peak at D28.

ELISPOT ASSAY ESAT-6/CFP-10 Negative 7 months after MTBVAC immunization.

Spertini et al Dec 2015 Lancet Respiratory Medicine

Centre Hospitalier Universitaire Vaudois
WBA 3 CYTOKINES (IFNY, IL2, TNFα) POLYFUNCTIONAL CD4+ T CELL

Dose-response induction of polyfunctional CD4 T-cells expressing at least one cytokine (IFNY+, TNFα+, IL-2+).

Higher number of responders peak at D28 in MTBVAC 5x10⁵ group.

Spertini et al 2015 Lancet Respiratory Medicine
Vaccination with MTBVAC induces a CFP10-specific immune response in humans

Aguilo et al July 2017 Nat Comm
TB notification rates by age in the HIV-negative in Cape Town

Worcester, 2-3 % TB cases in infants BCG vaccinated (Tameris et al Lancet 2013)

Infants/ Adolescents / Adults

Tuberculosis in Cape Town: An age-structured transmission model
Blaser et al Epidemics, 2016, 14: 54–61
Rationale for developing MTBVAC in neonates as priming immunisation against TB

• **TB incidence remains highest among young children from endemic regions**
  > 1% in BCG vaccinated children younger than 2-3 years.

• **Neonates represent the only naive age group unsensitized to BCG, MTB or environmental mycobacteria**
  Avoid potential “masking” and/or “blocking” effects on vaccine-induced protection or vaccine take
  (Mangtani et al CID 2013, Barreto et al Vaccine 2014).

• **MTBVAC, a live-attenuated MTB vaccine with the closest antigenic profile to MTB and as safe as BCG in line with the WHO consensus on live attenuated TB vaccines**

Spertini et al Lancet Respiratory Medicine 2015
R&D MTBVAC

Primary objective: Develop MTBVAC as a vaccine for newborns as BCG replacement

Secondary objective: Explore MTBVAC as vaccine in adolescents and adults have received previous BCG vaccination, with and without LTBI
Phase 1b Dose-escalation Safety and Immunogenicity Study to Compare MTBVAC to BCG in Newborns in a TB endemic region

SAFETY ARM IN ADULTS WITH HIGHEST DOSE MTBVAC PREVIOUSLY VACCINATED WITH BCG

Sept 2015

Infant stage - Global injection schedule and safety follow up

MTBVAC $2.5 \times 10^7/0.05$ml; n=9
BCG $2.5 \times 10^7/0.05$ml; n=3

Data Safety Monitoring Board (DSMB).
Prof. Paul-Henri Lambert, UNIGE, CH (Chair)
Dr. Hassan Mahomed, Cape Town, SA
Dr. François Spertini, U Lausanne, CH
Dr. Brian Eley, University Cape Town, SA

Medical Adviser: Dr. Federico Martinon

ClinicalTrials.gov Identifier: NCT02729571

DSMB GO/NO
GO TO NEWBORNS
Sept 2015 - January 2016

Newborn vaccination phase
16 Feb - 21 Sep 2016 - ONE YEAR FOLLOW SEPT 2017
VACCINATION AT BIRTH (NEONATES):

Dose-Defining Safety and Immunogenicity Study and Capacity Building to Support Vaccine Efficacy Trials in TB-Endemic Regions of Sub-Saharan Africa.

PI Michel Tameris

DOSE SELECTION Safety, Reactogenicity and Immunogenicity

PARTICIPANTS

Biofabri / Spain / Coordinator Ingrid Murillo
TuBerculosís Vaccine Initiative (TBVI) / Netherlands
Universidad de Zaragoza / Spain
University of Cape Town (UCT) / South Africa
Center de Recherche Biomedical e Espoir Pour La Santé (BRC-EPLS)/ Senegal
Institut Pasteur de Madagascar (IPM)/ Madagascar
MTBVC Adolescents / Adults

Phase 2a

Re-VACCINATION IN ADOLESCENTS / ADULTS
Randomized, Double-blind, Active-controlled, Safety, Immunogenicity, and Dose-escalation Study in Adults with and without Latent Tuberculosis Infection in South Africa.

Coordinator Ann Ginsberg

ClinicalTrials.gov Identifier: NCT02933281

PI Mark Hatherill

PARTICIPANTS:
Biofabri / Spain
TuBerculosis Vaccine Initiative (TBVI)
University of CapeTown (UCT)
Universidad de Zaragoza
A New TUBERCULOSIS VACCINE: LIVE VACCINES
(Huge experience in the production, distribution and use of BCG)

Safer / Better than BCG
Clara Aguilar
Ignacio Aguilo
José Antonio Aínsa*
Esther Broset
Carmen Arnal
Alberto Cebollada
Ana Belén Gómez
Jesús Gonzalo
Begoña Gracia
Daniel Ibarz Bosque
Mª José Iglesias Gozalo*
Carmen Lafoz
Carlos Lampreave
Ainhoa Lucia
Elena Mata
Dessi Marinova
Isabel Ojal*
Irene Pérez
Ana Pico
Sofía Samper*
Luis Solans
Santiago Uranga
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Dr. Roland Dobbelaer
Dr. Micha Roumiantzeff
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Esteban Rodriguez
Oswaldo Alvarez
Dr. Conchita Fernandez
Dr. Eugenia Puentes
Dr. Alberto Parra
Dr. Juana Doce
Dr. Ingrid Murillo