TBVI Symposium TB Vaccines and Immunity

MTBVCAC, an update

Eugenia Puentes, Biofabri

Annual TBVAC 2020 Meeting, 1st – 5th February 2016, Les Diablerets
MTBVAC, a live attenuated freeze dried vaccine against TB

Construction of MTBVAC

Derived from a clinical isolate of M. tuberculosis (Euro-American lineage)

MTBVAC, a live attenuated freeze dried vaccine against TB

SCHEMATIC REPRESENTATION OF THE PHENOTYPIC DIFFERENCES BETWEEN

MTBVAC AND WILD-TYPE M. TUBERCULOSIS

MTBVAC, a live attenuated freeze dried vaccine against TB

Preclinical studies from SO2 to MTBVAC
Based on “Douglas Young Roadmap”: 2001 – 2012

Attenuation

- BalbC/IT
- SCID Aerosol / IV
- Universidad Zaragoza
- SC 50 dose 6 Months
- Universidad Zaragoza
- NHP IT Erdman
- C57/BL6 aerosol Protection Transgenic p25 Ag85B Memory T cells

Protection

- C57/BL6 in H37Rv
- Aerosol Low dose High dose H37Rv

Immunogenicity

MTBVAC, a live attenuated freeze dried vaccine against TB

**INDUSTRIAL AND CLINICAL DEVELOPMENT STATUS**

- **2008**
  - Preclinical Studies

- **2009**
  - Phase Ia (adults)

- **2010**
  - Phase Ib (adults and newborns)
  - Stability data

- **2011**
  - MTBVA transferred to BIOFABRI 23 JUL’08
  - GMO and IMP Authorization
  - Process development

- **2012**
  - cGMP of MTVAC Characterization & QC release of final product

- **2013**
  - Manufacturing facility Design, Construction & Validation

- **2014**

- **2015**

- **2016**

- **2017**

*Universidad Zaragoza*
MTBVC, a live attenuated freeze dried vaccine against TB

Industrial Development (2008-2015)

Consistent Production process with satisfactory yields

(> 20 pilot batches, 3000 vials)

Stability data from GMP batches to support a shelf life > 24 months stored at +2-+8°C

Product ready to scale up
MTBVAC, a live attenuated freeze dried vaccine against TB

INDUSTRIAL DEVELOPMENT: NEW MANUFACTURING FACILITY 2014-2015

AEMPS GMP Authorisation (Jan. 2016)

Final Product Full Process and QC Validation
MTBVAC, a live attenuated freeze dried vaccine against TB

PHASE I DOUBLE BLIND, RANDOMIZED CONTROLLED, DOSE-ESCALATION STUDY TO EVALUATE THE SAFETY AND IMMUNOGENICITY OF MTBVAC IN COMPARISON WITH BCG IN ELISPOT TB (ESAT-6, CFP10, PPD) AND HIV-NEGATIVE VOLUNTEERS NCT02013245

Trial Center: Centre Hospitalier Universitaire Vaudois (CHUV)
Principal Investigator: Francois Spertini
Sponsor: BIOFABRI, S.L.
TBVI Call: TBVI010-02 MTBVAC

Safety of human immunisation with a live-attenuated Mycobacterium tuberculosis vaccine: a randomised, double-blind, controlled phase I trial

François Spertini*, Régine Audran, Reza Chakour, Olfa Karoui, Viviane Steiner-Monard, Anne-Christine Thierry, Carole E Mayor, Nils Rettby, Katia Jaton, Laure Vallotton, Catherine Lazor-Blanchet, Juana Doce, Eugenia Puentes, Dessislava Marinova, Nacho Aguilo, Carlos Martin*
MTBVAC, a live attenuated freeze dried vaccine against TB

PHASE I IN LAUSANNE VACCINATION AND SAFETY FOLLOW-UP

**Cohort 1**
MTBVAC $5\times10^3/0.1\text{ml}$ n= 9  
BCG SSI $5\times10^5/0.1\text{ml}$ n= 3  
First vaccination 23 Jan’13
ID inj. 23 Jan’13 – 1 Apr’13

**Cohort 2**
MTBVAC $5\times10^4$ n=9  
BCG SSI $5\times10^5$ n= 3  
DSMB 10 Apr’13
ID inj. 15 Apr’13 – 12 Jun’13

**Cohort 3**
MTBVAC $5\times10^5$ n=9  
BCG SSI $5\times10^5$ n= 3  
DSMB 15 Jul’13
ID inj. 24 Jul’13 – 6 Nov’13

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TBVI  BMGF TBVI010-02

Centre hospitalier universitaire vaudois

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First vaccination 23 Jan’13  
End of active follow-up 6 Jun 2014  
End of passive follow-up 5 Nov 2014  
Final data report Q2, 2015

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ID inj.  
23 Jan’13 – 1 Apr’13  
15 Apr’13 – 12 Jun’13  
24 Jul’13 – 6 Nov’13
MTBVAC, a live attenuated freeze dried vaccine against TB
PHASE I IN LAUSANNE

PRIMARY ENDPOINT: SAFETY

• Acceptable safety profile, with similar reactogenicity to BCG

SECONDARY ENDPOINTS: IMMUNOGENICITY

ELISPOT

• Negative IGRA tests 7 months after MTBVAC immunization
(A transient increase in CFP-10 specific IFN-g response over the limit of positivity in two subjects from MTBVAC 5x10^4 and in one subject of MTBVAC 5x10^5 at day 28)
   – key element for progressing MTBVAC to efficacy and prevention of sustained infection trials.

WBA

• MTBVAC demonstrated promising immunological properties with dose-response dependent induction of polyfunctional CD4 T-cells expressing at least one cytokine (IFNg⁺, TNFa⁺, IL-2⁺).

• Compared to BCG, MTBVAC 5x10^5 group induced greater magnitude response in terms of IFNg⁺, IL-2⁺, and 3 cytokines⁺ polyfunctional T-cell. A higher number of responders were observed after MTBVAC vaccination with a peak at D28.
MTBVC, a live attenuated freeze dried vaccine against TB

Target population as prime in newborns

**Phase Ia and 1b**
Safety / Immunogenicity in Adults
Safety / Immunogenicity in neonates in endemic areas

**Phase II a**
Safety / Immunogenicity
Dose selection

**Phase II b POC Trial**
IMPROVED EFFICACY OVER BCG
MTBVAC, a live attenuated freeze dried vaccine against TB

MTBVAC PHASE IB (ENDEMIC COUNTRY)

A randomized, double blind, dose-escalation clinical trial of the safety, reactogenicity and immunogenicity of three doses of MTBVAC compared to BCG Vaccine SSI, in newborns (HIV-negative mothers and with no household contacts of TB) living in a tuberculosis endemic region with a safety arm in adults

**Trial Center:** South African Tuberculosis Vaccine Initiative (SATVI)
University of Cape Town

**Principal Investigator:** Michelle Tameris

**Sponsor:** BIOFABRI, S.L.

**TBVI Call:** TBVI 012-01 NORAD Grant

**SATVI-AERAS-DFI Grant**
MTBVAC Phase Ib (endemic country)
Double blind, controlled, randomized, dose-escalation study in neonates born to HIV negative mothers with a initial safety arm in adults

Global injection schedule and safety and immunogenicity follow up

0                                3                 5                      7                    9                     12                     14                        21

First vaccination Oct’15
MTBVAC  5x10^5 n=9
BCG x10^5 n=9

ID inj.
Adults arm

MTBVAC 2,5x10^3 n=9
BCG x10^5 n=3

ID inj.
Neonates Cohort 1

MTBVAC 2,5x10^4 n=9
BCG x10^5 n=3

ID inj.
Neonates Cohort 2

MTBVAC 2,5x10^5 n=9
BCG x10^5 n=3

ID inj.
Neonates Cohort 3

End of study

BCG dose rescue

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NORAD
satvi

MTBVAC Phase Ib (endemic country)
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MTBVAC 2,5x10^4 n=9
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ID inj.
Neonates Cohort 2

MTBVAC 2,5x10^5 n=9
BCG x10^5 n=3

ID inj.
Neonates Cohort 3

End of study

BCG dose rescue

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MTBVAC, a live attenuated freeze dried vaccine against TB

**PHASE Ib IN SOUTH AFRICA: SAFETY ARM IN ADULTS**

Adults stage - Detailed injection schedule and safety follow up

- Days: D0, D7, D14, D28, D56, D90, D180
- MTBVAC 5x10^5/0.1ml; n=9
- BCG 5x10^5/0.1ml; n=9

↑ Vac. Inj

Safety follow up

D28-D56 SAFETY AND REACTOGENICITY IN HEALTHY BCG VACCINATED, HIV -ve, QFT -ve, ADULTS

Acceptable safety profile
MTBVCAC, a live attenuated freeze dried vaccine against TB

Target population as booster in BCG vaccinated adolescents and Young adults

Phase Ia /Ib
Safety /Immunogenicity in Adults
Safety in Adults in endemic areas

Phase II a
Dose finding study in both QTF + and QTF – individuals from endemic areas. Safety /Immunogenicity

Phase II b POC Trial
Prevention of sustained infection
Grupo de Genética de Micobacterias

Prof. Carlos Martín
Dr. Ainhoa Arbués
Dr. Jesús Gonzalo Asensio
Dr. Juan Ignacio Aguiló
Dr. Dessi Marinova
Ana Belén Gómez
Santiago Uranga
Carmen Arnal
Luis Solans Bernad

Dr. Jelle Thole

TBVI PDT
Dr. Georges Thiry
Dr. Micha Roumiantzeff
Dr. Barry Walker
Dr. Mei Mei Ho
Dr. Eddy Rommel
Dr. Brijesh Patel

TBVI CDT
Prof. Juhani Eskola
Dr. François Spertini
Dr. Roland Dobbelraer
Dr. Luc Hessel
Dr. Bernard Fritzell
Dr. Emmanuèlle Gerdil

Dr. François Spertini
Dr. Reza Chakour
Dr. Olfa Karoui
Dr. Régine Audran
Dr. Laure Valloton
Prof. J.D. Aubert

DSMB Phase Ia and Ib
Prof. Paul-Henri Lambert
Dr. Hassan Mahomed
Dr. Jaap Van Dissel
Dr. D.J. Lewis
Dr. Francois Spertini
Dr. Brial Eley

Dr. Mark Hatherill
Dr. Michelle Tameris
Prof. Tom Scriba
Dr. Helen Mearns