“MTBVAC. A live attenuated *M. tuberculosis* vaccine in clinical trials”

3rd December 2015
1a. Subunit vaccines/adjuvants

1b. Subunit vaccines/viral vectors

2. Live vaccines

Source: TBVI
LIVE VACCINES:

- rBCG
- Attenuated MTB
rBCG KNOCK-IN strategy: Listeriolysin O (clinical development, phase IIa)

VPM1002 recombinant BCG (rBCG) + Listeriolysin
(L. monocytogenes) rBCGΔUreaseC : (MPIIB)
Live attenuated MTB strategy

95% of TB cases in humans are caused by *M. tuberculosis*
BCG Genome: Diminishing of T-Cell Epitopes

Compared 1.530 human T cell epitopes in BCG with MTBC

23% of the known T cell epitopes are absent in BCG (358/1530)

Copin et al Vaccine October 2014
New live mycobacterial vaccines: the Geneva consensus on essential steps towards clinical development

Arna T. Kamath, Uli Fruth, Michael J. Brennan, Roland Debbelaere, Peter Hubrechts, Mei Mei Ho, Ronald E. Mayner, Jelle Thiele, K. Barry Wallace, Margaret Liu, Paul-Henri Lambert

MTBVAC

Mycobacterium tuberculosis MT103

△phoP  △fadD26

MTBVAC

2008
PRECLINICAL STUDIES FROM 2001 to 2012

ATTENUATION, SAFETY AND BIODISTRIBUTION

2001

C57/BL6 in H37Rv

Universidad Zaragoza

Aerosol Low dose
High dose H37Rv

2012

SC 50 dose 6 Months

C57/BL6 aerosol Protection
Transgenic p25 Ag85B
Memory T cells

PROTECTION

IMMUNOGENICITY

SO2: prototype vaccine with identical phenotype as MTBVAC

MTBVAC PHASE 1 CLINICAL EVALUATION

36 HEALTHY PPD-, BCG-, HIV- (6 months follow-up)

MTBVAC 5x10^3, 5x10^4, 5x10^5
BCG: 5x10^5
(CFU in 0.1ml)

Primary Endpoints: Safety & Reactogenicity

Randomize and Allocate BCG control 3:1

Vaccination & Evaluation

Secondary Endpoint: Immunogenicity

Data Analysis and Study Conclusion
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 Retby, Katia Jaton, Laure Vallotton, Catherine Lazor-Blanchet, Juana Doce, Eugenia Puentes, Dessislava Marinova, Nacho Aguiló, Carlos Martin*
No adverse events were associated with vaccination

Spertini et al 2015 Lancet Respiratory Medicine
All volunteers were negative for ESAT-6, CFP10 at day 210, the end of active follow-up study.
SECONDARY ENDPOINT: IMMUNOGENECITY

live MTBVAC-specific response

3 CYTOKINES (IFN\text{\textgamma}, IL2, TNF \alpha) POLYFUNCTIONAL CD4+ T CELL

![Graph showing CD4 T cells expressing 3 cytokines (IFN\text{\textgamma}, IL2, TNF \alpha) over time with MTBVAC and BCG stimulation.]

MTBVAC 5.10^3, MTBVAC 5.10^4, MTBVAC 5.10^5, BCG 5.10^5

Whole Blood Assay stimulation with BCG or MTBVAC

Spertini et al 2015 Lancet Respiratory Medicine
EXPLORATORY ENDPOINTS: ONGOING

TBVAC-H2020 PROJECT

PBMCs. DIFFERENTIAL ANTIGEN-SPECIFIC IMMUNOGENECITY:

• ESAT6 (RD1)
• CFP10 (RD1)
• MTP64 (RD2)
• HBHA
• AG85A/B
• LATENCY ANTIGENS
• OTHERS
EVALUATION OF MTBVAC IN NEWBORNS (naïve population)

VACCINE EFFICACY

- Adult safety arm vaccination completed (November 2015)
EVALUATION OF MTBVAC IN ADOLESCENTS

IMPACT IN TB TRANSMISSION

http://www.ndm.ox.ac.uk/who-tb-day-2014

- BCG VACCINATED
- ENVIRONMENTAL MYCOBACTERIA
- HIGH PREVALENCE OF QFT+ INDIVIDUALS
Nacho Aguiló
José Antonio Aínsa*
Henar Alonso
Esther Broset
Carmen Arnal
Rebeca Bailo
Alberto Cebollada
Ana Belén Gómez
Jesús Gonzalo
Begoña Grácia
Daniel Ibarz Bosque
Mª José Iglesias Gozalo*
Carmen Lafoz

Carlos Lampreave
Dessi Marinova
Isabel Millan
Isabel Otal*
Ana Pico
Sara Sagasti
Sofía Samper *
Luis Solans
Santiago Uranga
Samuel Álvarez
Liliana Rodrigues

Microbiología Clínica
Mª José Revillo Pinilla
Asunción Vitoria

Dirección General de Salud Pública

Grup de Apoptosis, Inmunidad y Cancer
Alberto Anel
Julian Pardo

Centro de Encefalopatías y Enfermedades Emergentes
Marta Monzón
Juan J Badiola

* IP coordinadores de línea
Clinical Development Team

- Dr. Luc Hessel, chair
- Dr. Steven Black
- Dr. Bernard Fritzell
- Dr. Emanuèle Gerdil
- Dr. Francois Spertini, Univ. Lausanne
thank you