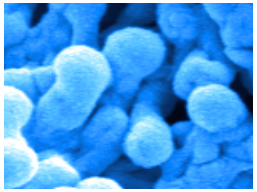
VACCINOLOGY 2017

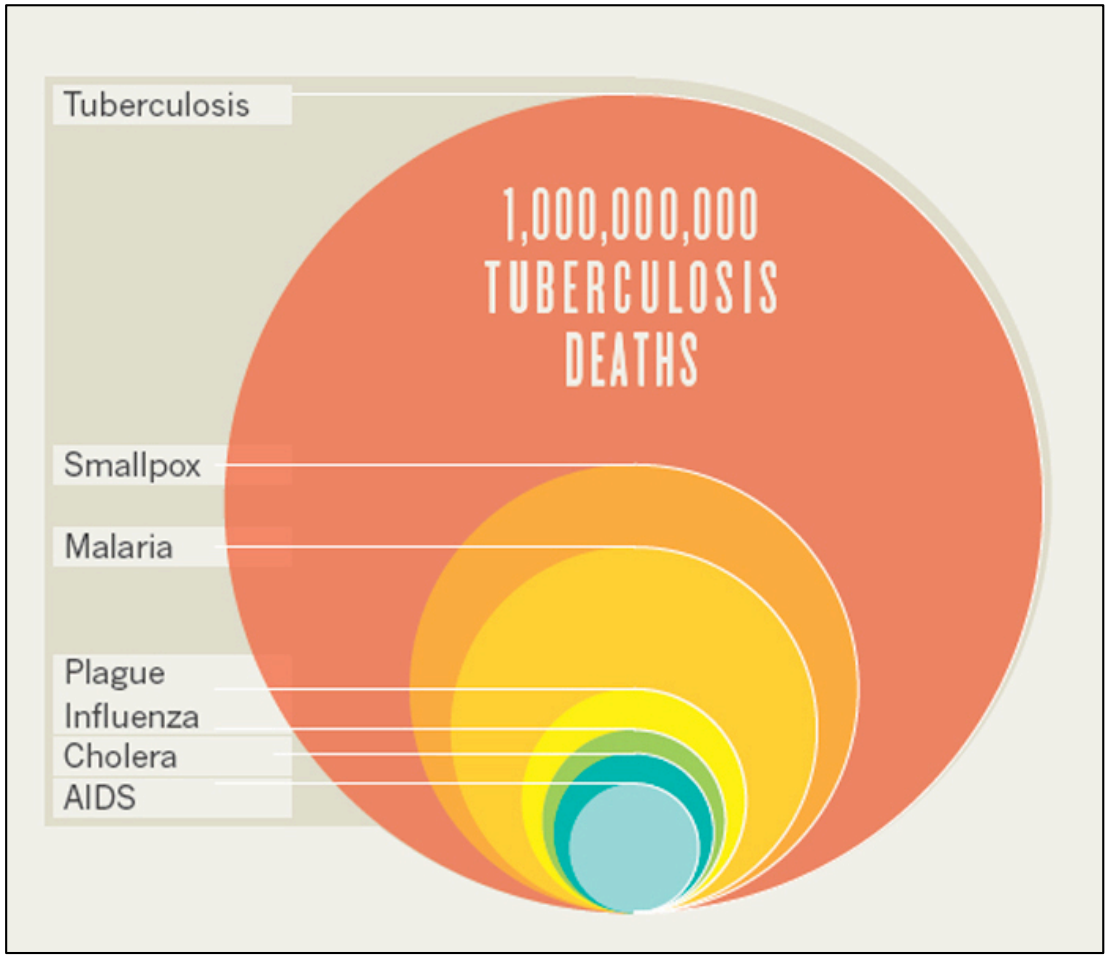
MTBVAC



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

Carlos Martín
University of Zaragoza
carlos@unizar.es

TUBERCULOSIS THE BIGGEST KILLER



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

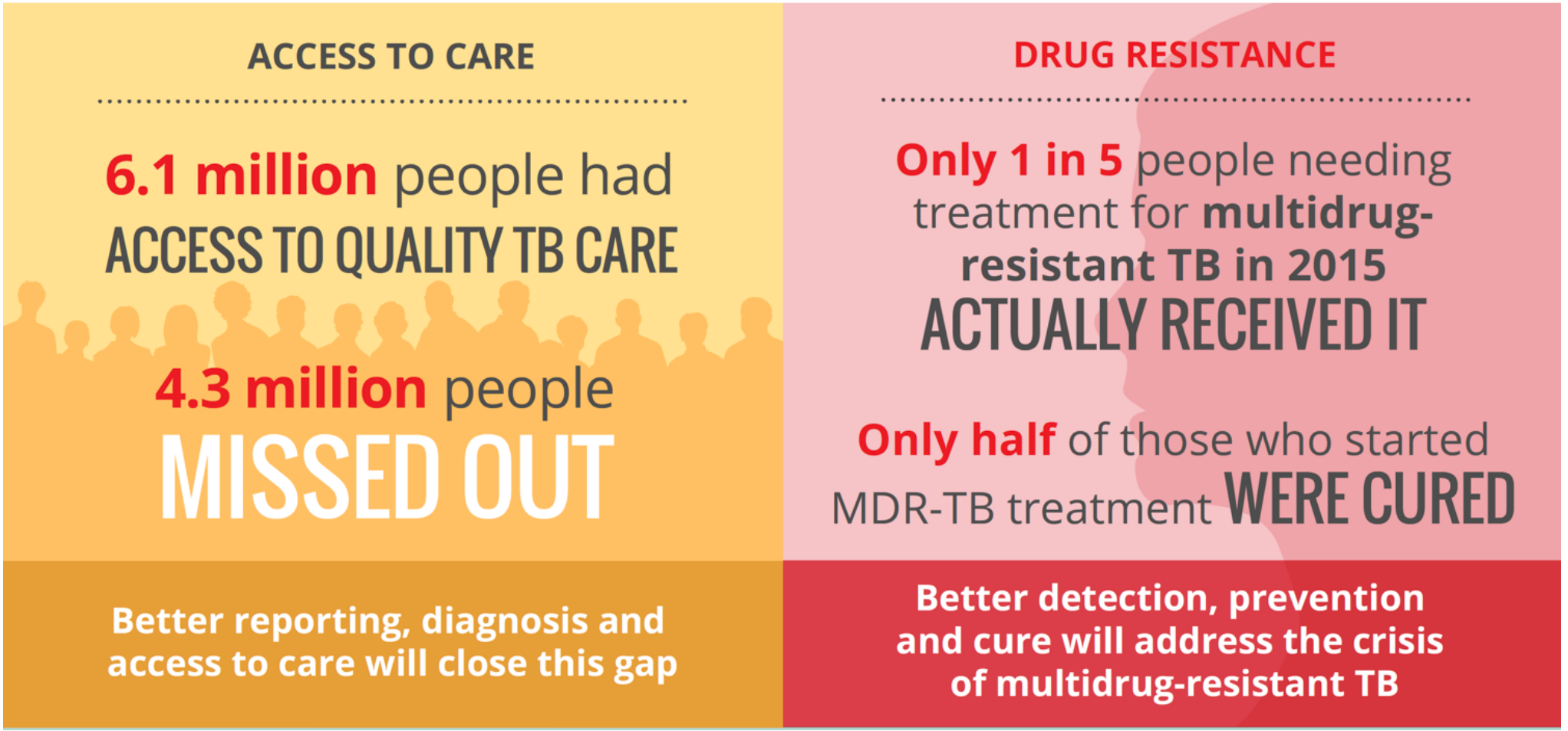
1.8 million people
DIED FROM TB
including 400,000
WITH HIV + TB

That's over 4,900 people every day

60% of TB cases worldwide occurred in just SIX COUNTRIES

More action and investment in these countries will drive down the TB burden

World Health Organization



World Health Organization

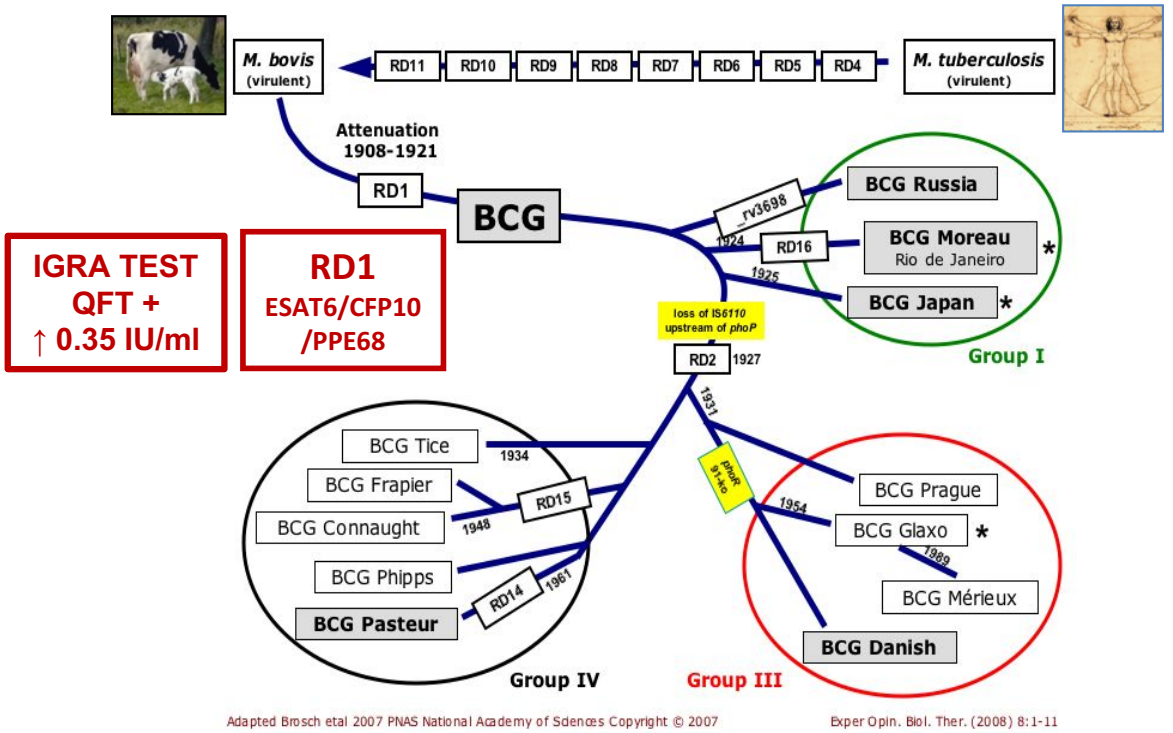
BCG the present vaccine against tuberculosis

Albert Calmette (1863–1933)

Camille Guérin (1872–1961)

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

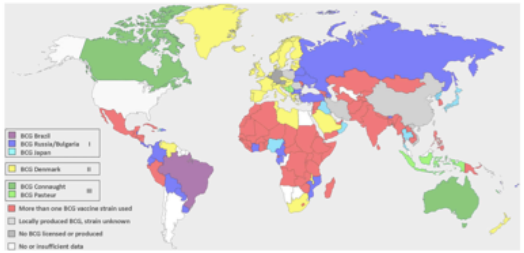
This isolate was subsequently distributed to several laboratories in the world and a number of strains developed



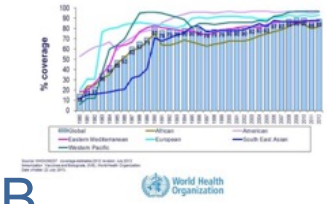
Adapted from Brosch *et al* PNAS 2007

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**

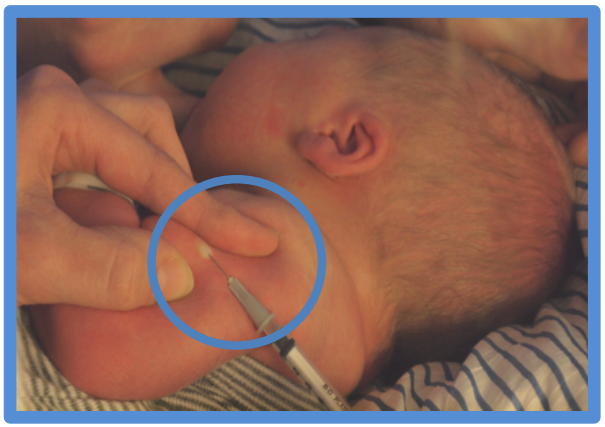


BCG global coverage at birth 89% worldwide

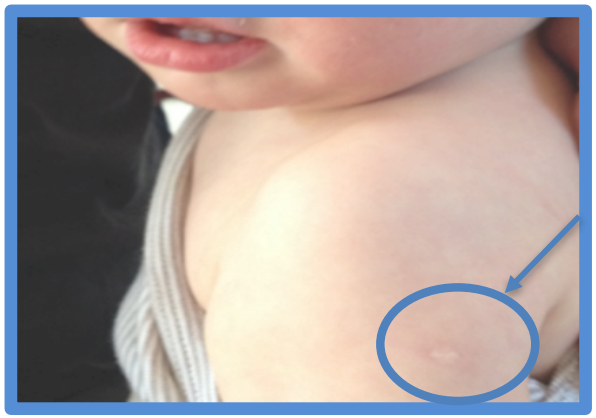


Provides variable protection against respiratory forms of TB

Intradermal administration at birth



Scar after vaccination



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 RESPITATORY 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

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

INDUSTRY: GSK, Sanofi
BIOFABRI

2015 – 2018
EU H2020 TBVAC2020

2000 → **Present**

TBVI
TuBerculosis Vaccine Initiative

2007EU R&D Commission
Supports creation of a separate entity

TuBerculosis Vaccine Initiative (TBVI)

PDT: Product Development Team
CDT: Clinical Development Team

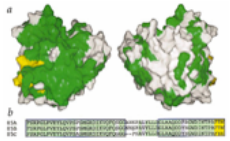
Jelle Thole

SUBUNIT VACCINES → BOOSTING BCG:

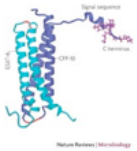
VIRAL VECTOR / NEW ADJUVANTS

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

Ag 85 A/B/C

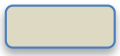


ESAT6



72F GSK

Ag85B + Esat6
TB10.4



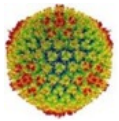
H1 / H4

H1 + Rv2660c

H56

VIRAL VECTOR

Oxford MVA85A		**Modified vaccinia Ankara Expressing Ag85A**	**Phase 2b Efficacy**
Crucell Ad 35		**Adenovirus 35 Ag85A, Ag85B, TB10.4**	**Phase 2**
Mac Master Univ		**Ad5Ag85A**	**Phase 1**



ADJUVANTS

GSK M72/ AS01E	**Fusion Rv1196/Rv0125**	**SO2**	**Phase 2**
SSI H1 + IC31	**Ag85B + Esat6**	**IC31**	**Phase 2**
SSI H1 + CAF01	**Ag85B + Esat6**	**CAF01**	**Phase 1**
SSI H4	**Ag85B + TB10.4**	**IC31**	**Phase 2**
SSI H56	**H1 + Rv2660c**	**IC31**	**Phase 2**
ID93 IDRI	**Rv1813, Rv2608, Rv3619 & Rv3620**	**GLA-SE**	**Phase 1**

Lancet. 2013 Mar 23;381(9871):1021-8.

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 Mahomed†, Helen McShane†, and the MVA85A 020 Trial Study Team

UNIVERSITY OF OXFORD

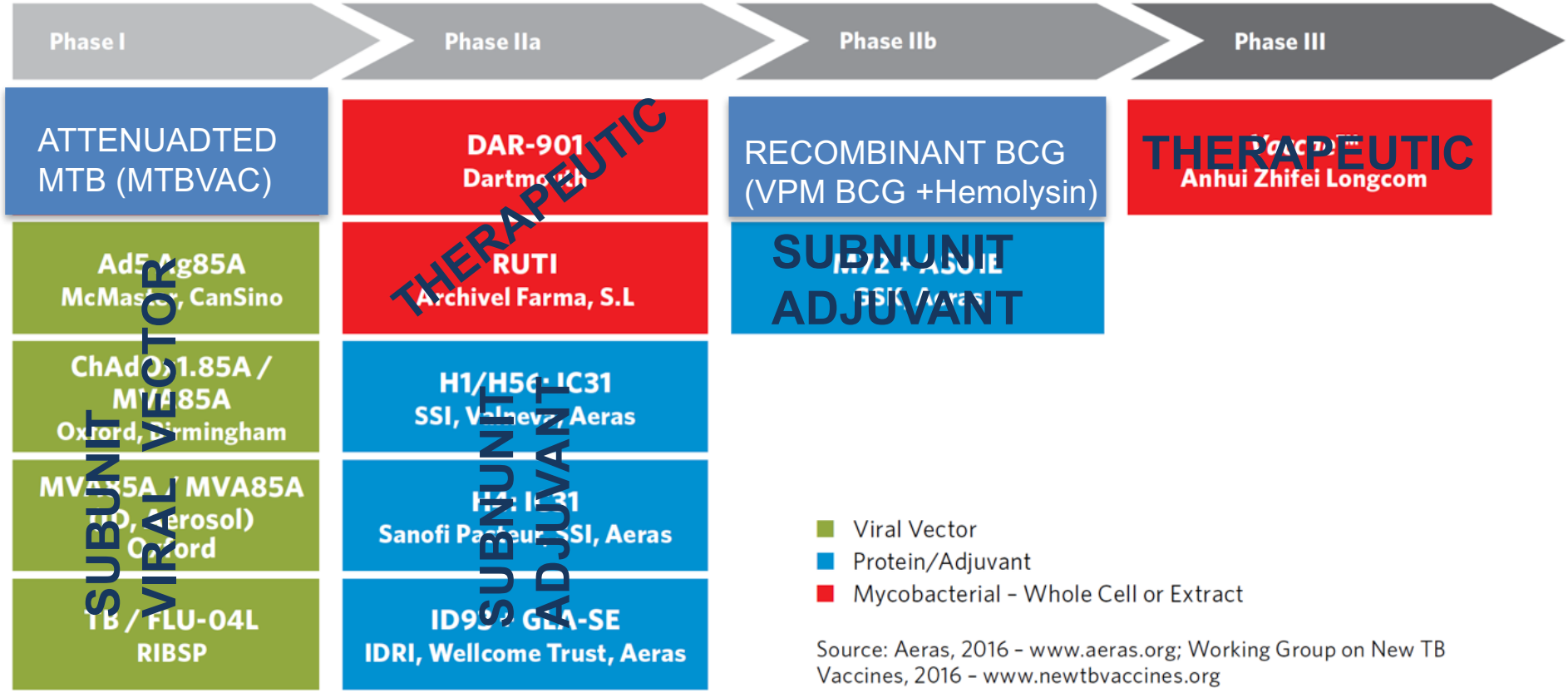
satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

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



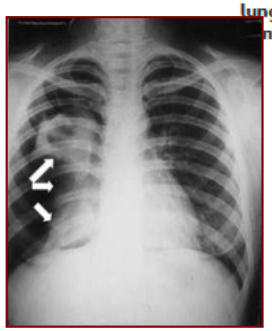
Source: Aeras, 2016 – www.aeras.org; Working Group on New TB Vaccines, 2016 – www.newtbvaccines.org

TBVI
TuBerculosis Vaccine Initiative

AERAS
GLOBAL TB VACCINE FOUNDATION

NATURAL HISTORY OF TUBERCULOSIS

95%
MTB strains
Human
origin



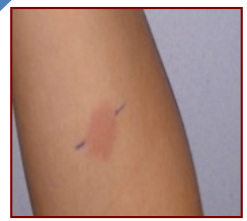
TB DISEASE

HUMAN RESERVOIR

MORTALITY 50%
WITHOUT TREATMENT

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

Andrews *et al* CI D 2012



TB INFECTION

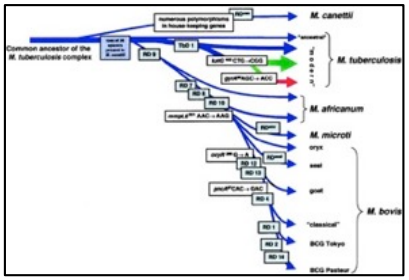
only 5-10%
will develop
TB disease

THE STAGES IN THE IMMUNOLOGICAL LIFE CYCLE OF TB

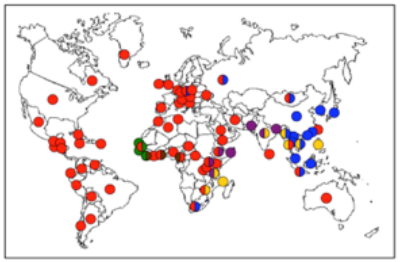
Modified from J. D Ernst 2012 NATURE REVIEWS IMMUNOLOGY

RATIONALE FOR DEVELOPING MTBVAC

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

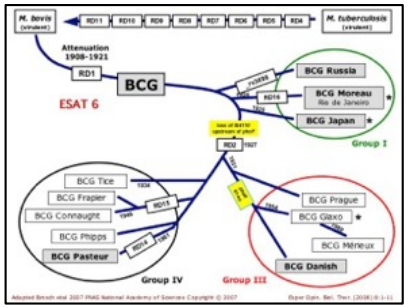


1.- ATTENUATE A PATHOGEN FROM HUMAN ORIGIN



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

3.- WHICH GENE(S) TO INACTIVATE?



4.- AVOID LABORATORY SUBCULTURE

GENEVA CONSENSUS CRITERIA: CONSTRUCTION OF MTBVAC

TWO STABLE INDEPENDENT MUTATIONS
NO ANTIBIOTIC RESISTANCE MARKERS

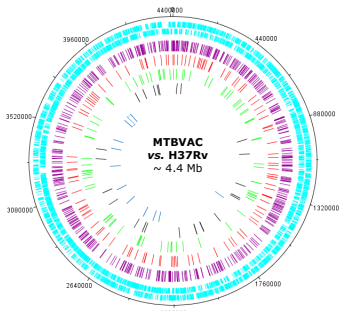
ELSEVIER

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 Dobbelaer [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]



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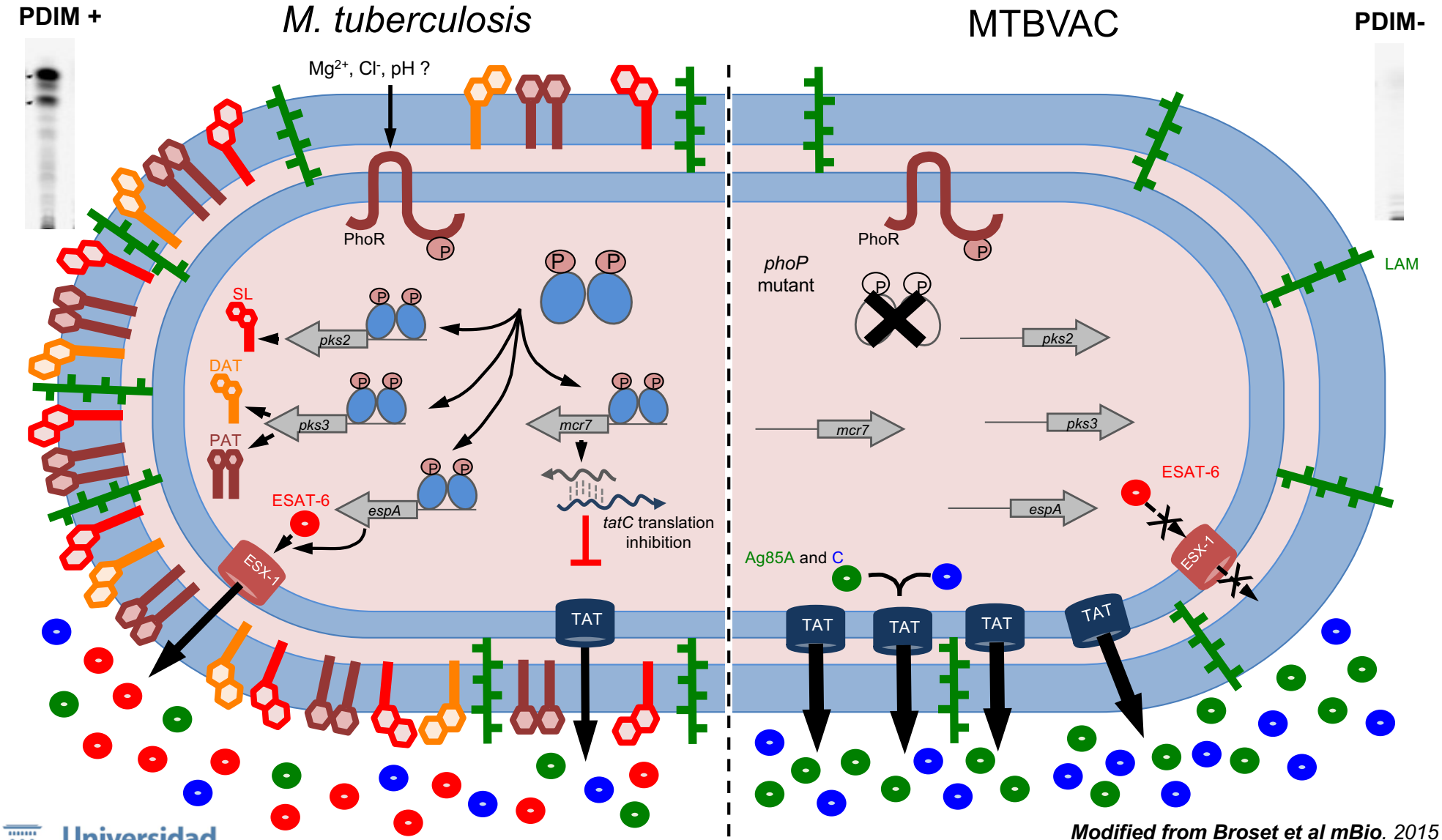
MTBVAC

phoP *fadD26*

BIOFABRI

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



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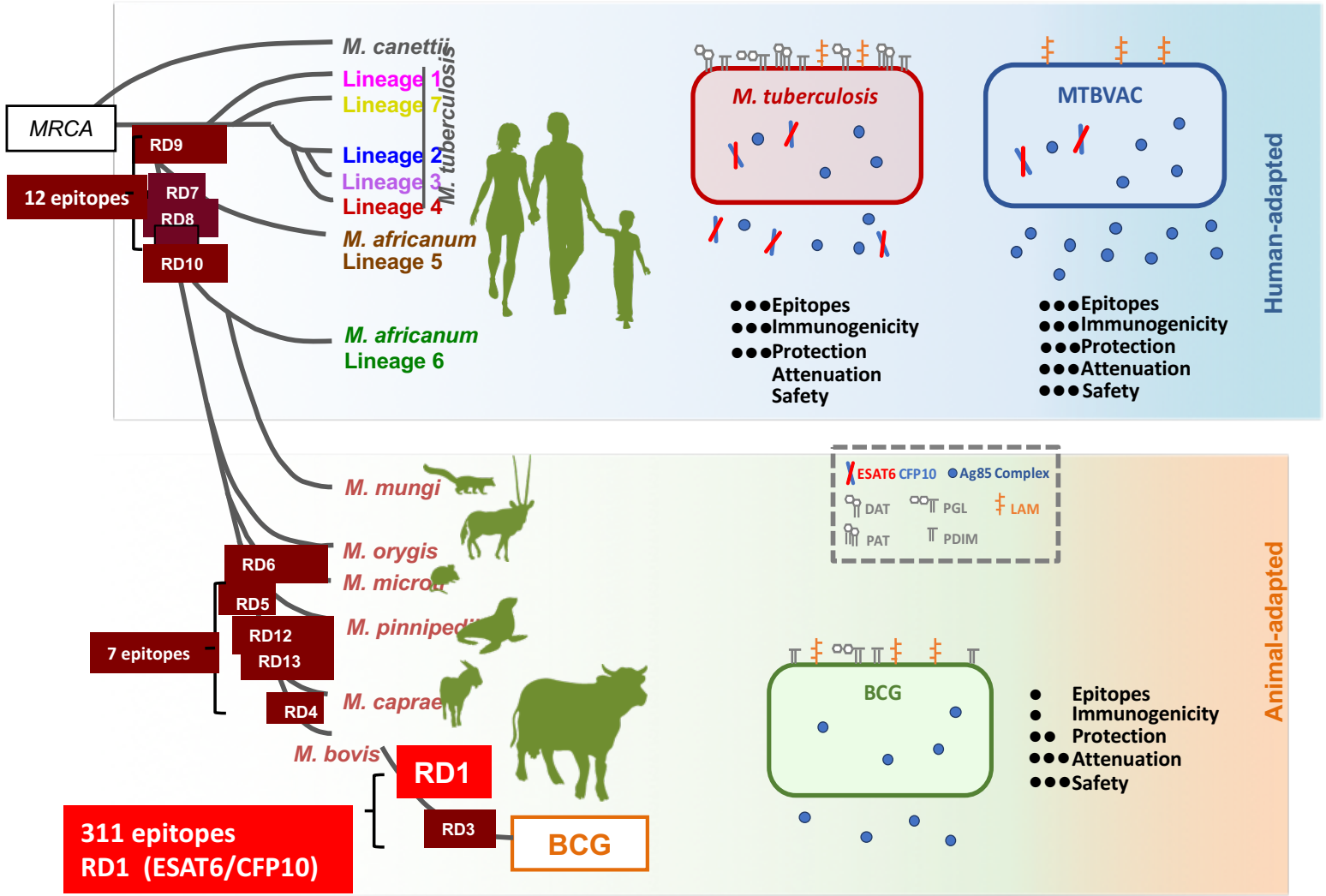
***Modified from Broset et al mBio**. 2015*
Solans et al. PLoS Pathogen 2014
Gonzalo et al Plos One 2008

MTBVAC, 519 MORE EPITOPES THAN BCG WHICH REPRESENTS AN INCREASE OF 48%



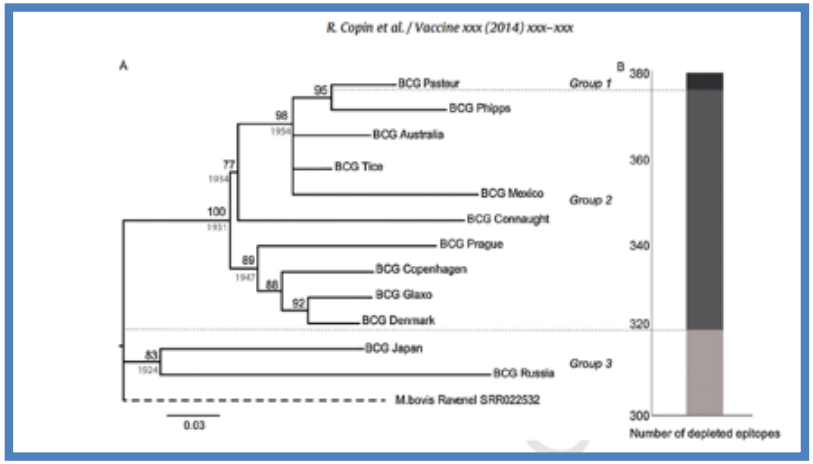
MTBVAC →
1603 epitopes

BCG →
1084 epitopes

Adapted from Marinova *et al* Expert Rev Vaccines 2017

***Gonzalo-Asensio et al unpublished* Oct 2017**

BCG Genome: Diminishing of human T-Cell epitopes, which are conserved in MTBVAC



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.

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

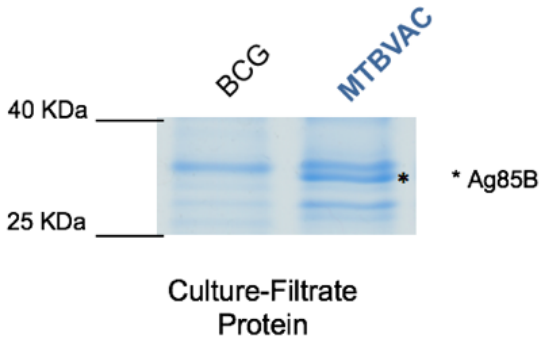
Rv1985c	rv1985c	Probable transcriptional regulatory protein	Regulatory proteins	RD2	23
Rv3878	espJ	Hypothetical protein	Cell wall and Cell processes	RD1	17
Rv2653c	rv2653c	phiRv2 prophage protein	Insertion seqs and phages	RD11	12
Rv2654c	rv2654c	phiRv2 prophage protein	Insertion seqs and phages	RD11	6
Rv1979c	rv1979c	Possible conserved permease	Cell wall and Cell processes	RD2	6
Rv1769	rv1769	Hypothetical protein	Conserved hypotheticals	RD14	4

Copin et al Vaccine October 2014

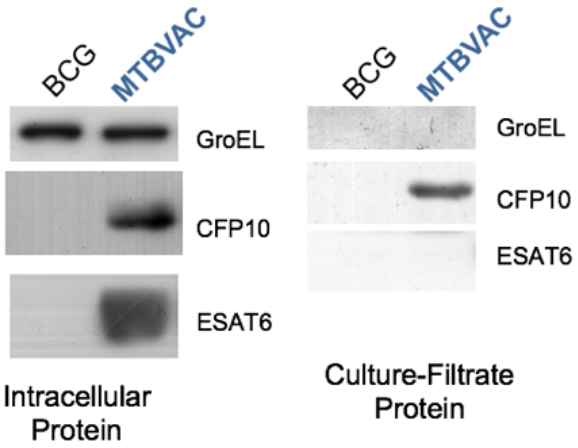
Improved protection of MTBVAC as compared to BCG is associated with T-cell mediated response to CFP10/ESAT6

Ag85B: BCG a polymorphism unstable protein

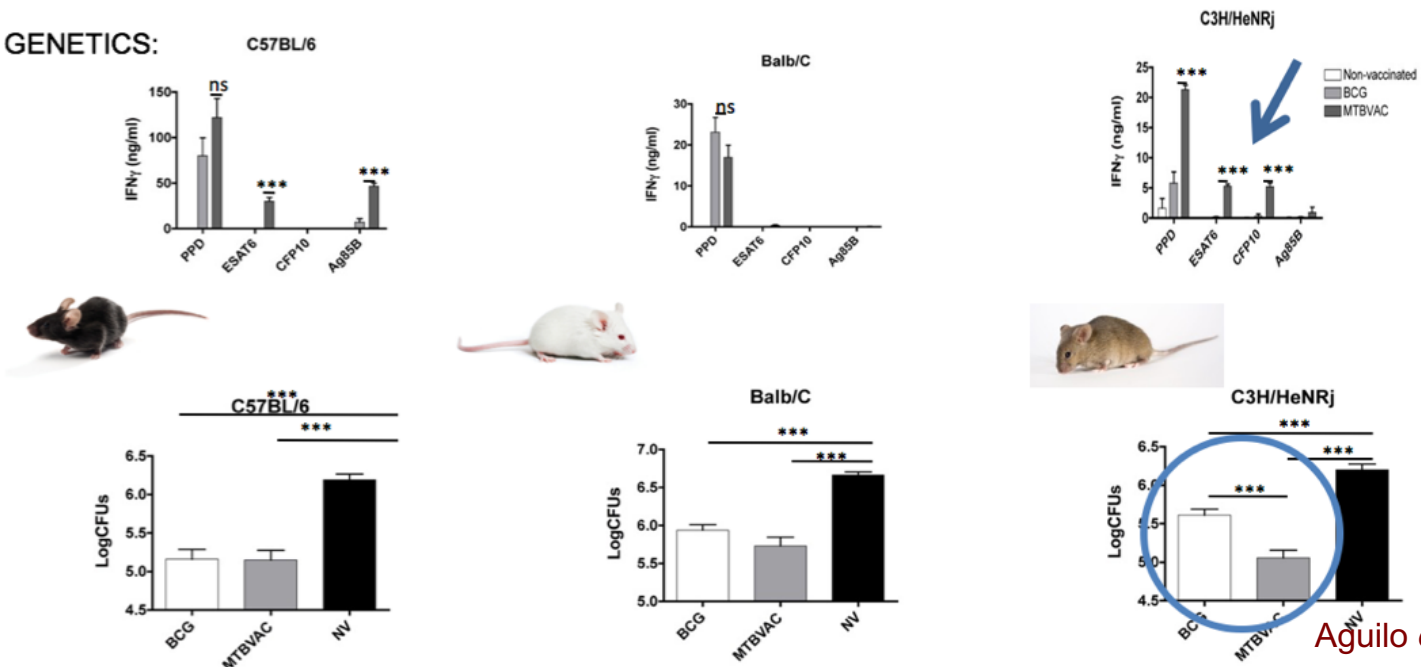
(Copin *et al.* 2014)



ESAT6/CFP10 present in RD1



HOST GENETICS:



Aguilo *et al July 2017 Nat Comm*

Universidad Zaragoza

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Sixth Framework Programme

SEVENTH FRAMEWORK PROGRAMME

TBVI

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

1992-2000
EU FP3/FP4

INSTITUT PASTEUR

ATTENUATION, PROTECTION & IMMUNOGENICITY




U†E

THE UNIVERSITY OF SYDNEY

Health Protection Agency

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

BIOFABRI

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**)

Regulatory requirements for live TB vaccines to enter Phase I trials, in particular those based on attenuated *M. tuberculosis*

ELSEVIER

Vaccine

Volume 28, Issue 11, 8 March 2010, Pages 2259-2270

Conference report

The second Geneva Consensus: Recommendations for novel live TB vaccines ☆

K.B. Walker, M.J. Brennan, M.M. Ho, J. Eskola, G. Thiry, J. Sadoff, R. Dobbelaer, L. Grode, M.A. Liu [a, b], U. Fruth, P.H. Lambert

Criteria for further clinical development from Phase I through to Phase III

CLINICAL DEVELOPMENT MTBVAC

2010 2011 2012 2013 2014 2015 2016 2017

MTBVAC
final lot
May 2011

Long-term, real time stability studies

Non-clinical studies to support clinical evaluation
25 Aug'10 – 20 Dec'11

Phase I CTA Preparation
Oct'11 – April '12

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

CTA Evaluation

Centre Hospitalier Universitaire Vaudois

PHASE Ia HEALTHY ADULTS in CHUV Switzerland
PPD⁻, BCG⁻, HIV⁻
(18-45 yrs)

Last visit V10
End of study
6 Jun 2014

Approval
3 Oct 2012

Vaccination phase:
23 Jan - 6 Nov 2013

Unblinded data
March 2015

ClinicalTrials.gov: NCT02013245

Published Dec 2015
The Lancet Respi Medi

CTA Evaluation
11 May 2015

Approval
13 May 2015
HREC+ DAFF
5 Agust 2015

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

New born vaccination phase
16 feb - 21 Sep 2016

ClinicalTrials.gov NCT02729571

PDT: Product Development Team **TBVI**

CDT: Clinical Development Team **TBVI**

MTBVAC PHASE 1a ADULTS:
TRIAL CONCLUSIONS

Phase 1a

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$^+$).

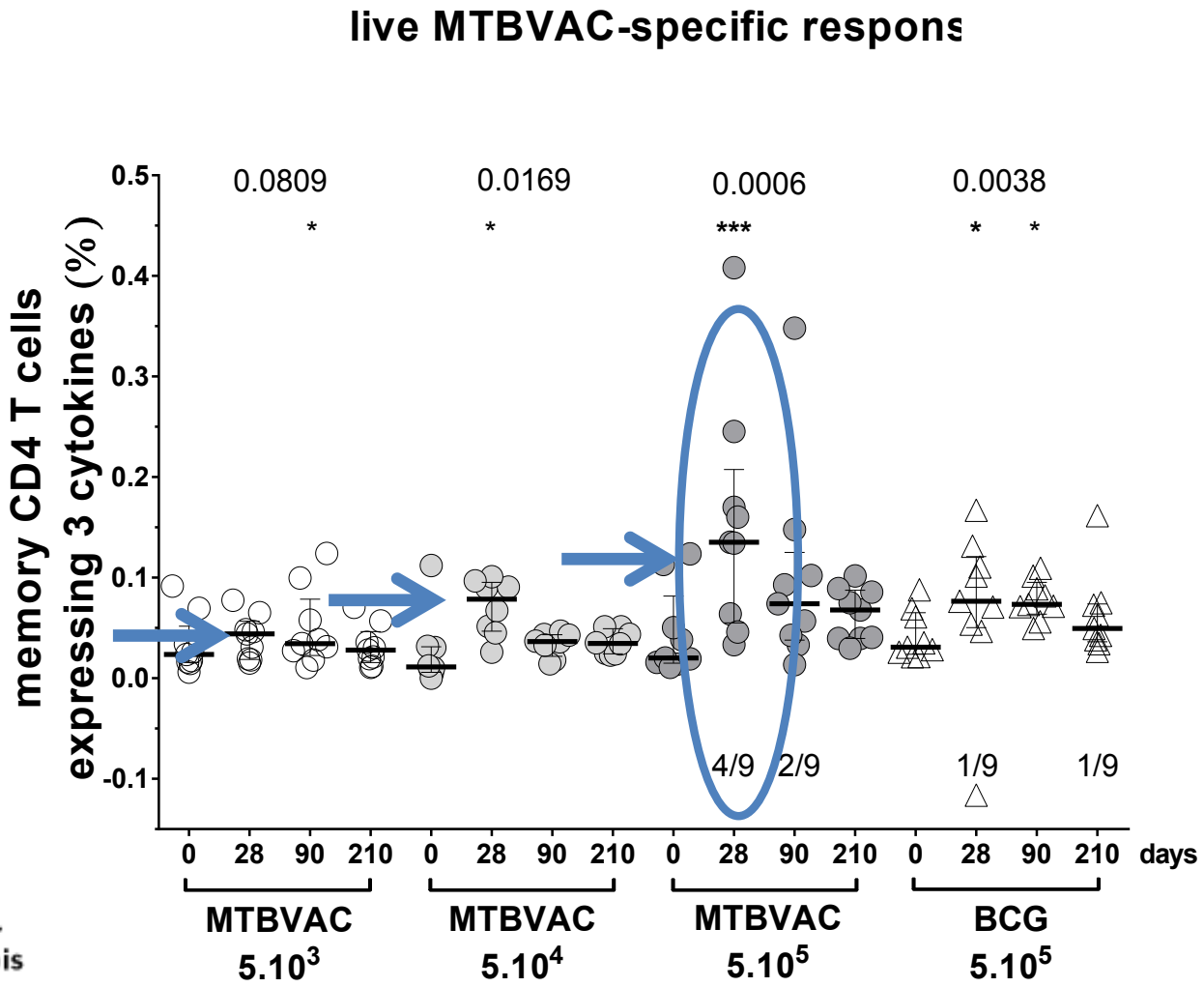
Comparing MTBVAC 5x10^5 group and BCG, a **greater induction of 3 cytokines+** and higher number of responders were observed after MTBVAC vaccination with a **peak at D28.**

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

Centre Hospitalier Universitaire Vaudois

Spertini *et al Dec* 2015 Lancet Respiratory Medicine

WBA 3 CYTOKINES (IFNY, IL2, TNFα) POLYFUNCTIONAL CD4+ T CELL



Higher number of responders peak at D28 in MTBVAC $5x10^5$ group

Centre Hospitalier Universitaire Vaudois

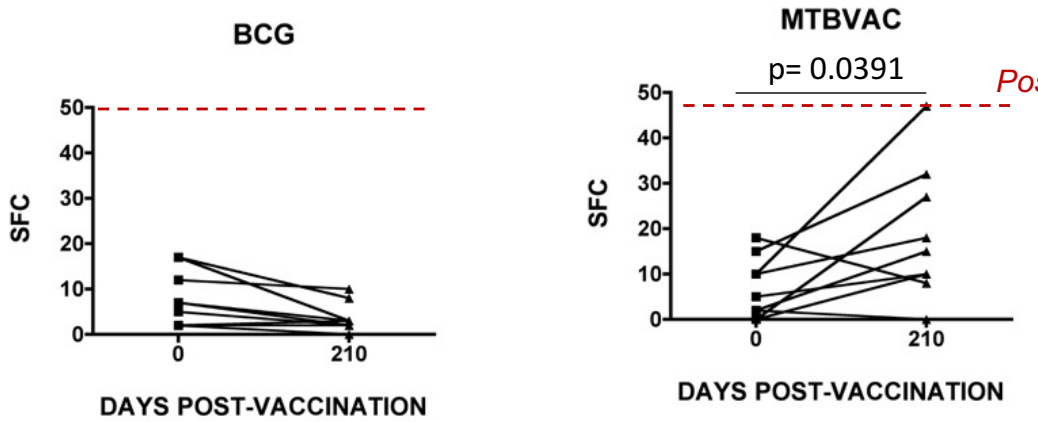
Dose-response induction of polyfunctional CD4 T-cells expressing at least one cytokine ($IFNY^+$, $TNF\alpha^+$, $IL\text{-}2^+$).

Spertini *et al* 2015 Lancet Respiratory Medicine

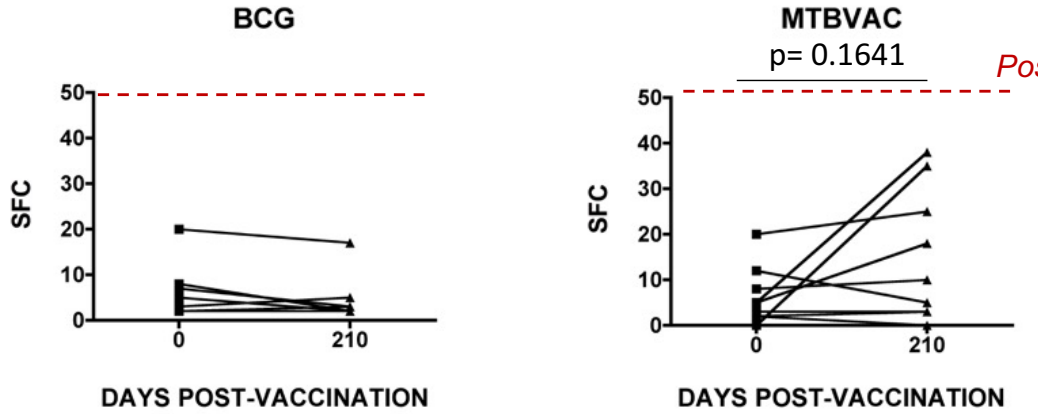
CFP10 and ESAT6 -specific responses in MTBVAC-vaccinated humans

MTBVAC Phase 1a Clinical Trial

CFP10 Elispot



ESAT6 Elispot



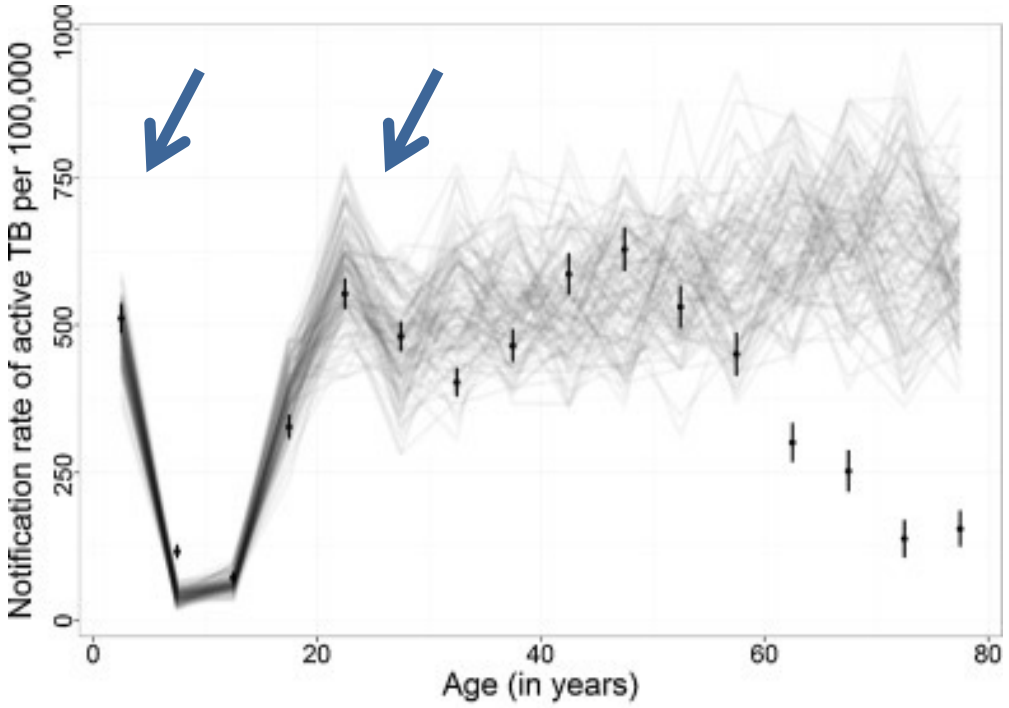
Vaccination with MTBVAC induces a CFP10-specific immune response in humans

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 enviromental mycobacteria**

  Avoid potential “masking” and/or “blocking” effects on vaccine-induced protection or vaccine take

  (Mangtani *et al* CID 2013, Barreto *el 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 Respitatory 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

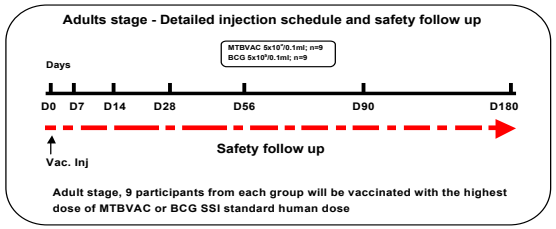
Phase 1b Dose-escalation Safety and Immunogenicity Study to Compare MTBVAC to BCG in Newborns in a TB endemic region

Phase 1b

BIOFABRI

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

Sept 2015

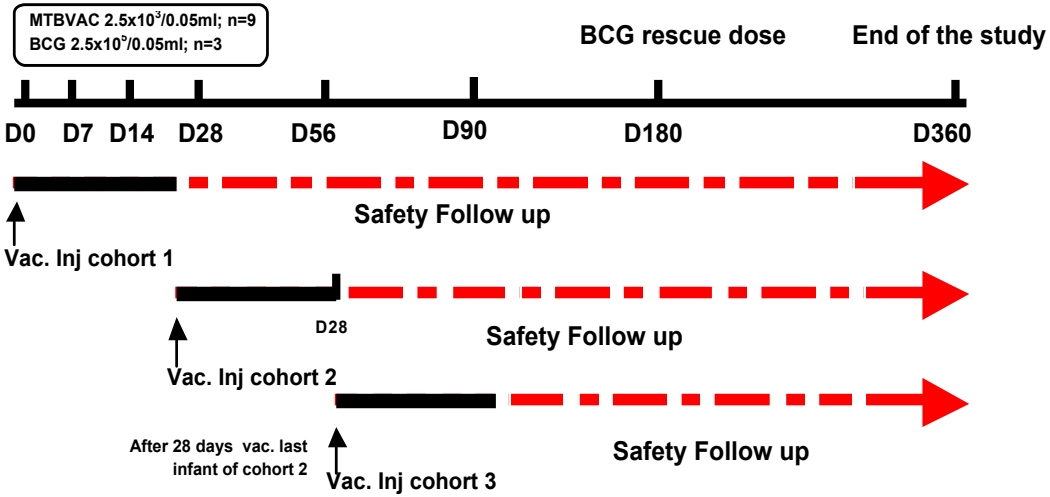


satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

PI Dr. Michele Tameris

ClinicalTrials.gov Identifier: NCT02729571

Infant stage - Global injection schedule and safety follow up



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

Newborn vaccination phase
16 feb - 21 Sep 2016-
ONE YEAR FOLLOW SEPT 2017

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, Univ ersity Cape Town , SA

TBVI -- NORAD

Medical Adviser : Dr. Federico Martinon

MTBVAC Dose-Defining Safety and Immunogenicity Study in Newborns in a TB endemic region

Phase 2a

EDCTP 2017

BIOFABRI

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

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University of Cape Town

TBVI TuBerculosis Vaccine Initiative

PARTICIPANTS

Biofabri / Spain / Coordinator Ingrid Murillo

TuBerculosis 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

Universidad Zaragoza

EPLS Centre de Recherche Biomédicale Espoir Pour La Sai

Institut Pasteur de Madagascar

MTBVAC Adolescents / Adults

Phase 2a

CDMRP
2017

AERAS

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.**

ClinicalTrials.gov Identifier: NCT02933281

Coordinator Ann Ginsberg

AERAS

PI Mark Hatherill

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

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University of CapeTown (UCT)
Universidad de Zaragoza

BIOFABRI

TBVI TuBerculosis Vaccine Initiative

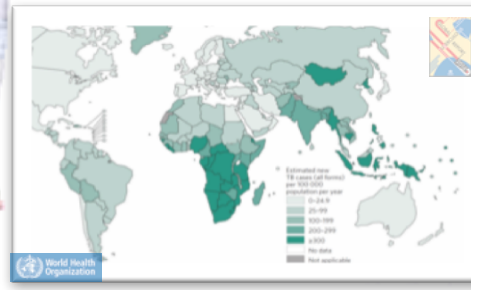
Universidad Zaragoza 1542

A New TUBERCULOSIS VACCINE:

LIVE VACCINES

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

**Safer / Better
than BCG**



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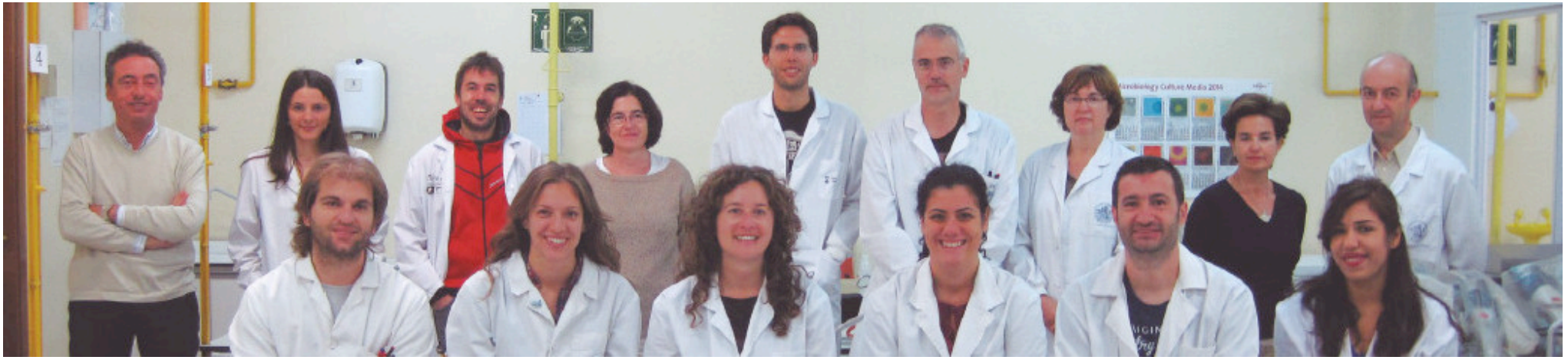

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FECYT
FUNDACIÓN ESPAÑOLA PARA LA CIENCIA Y LA TECNOLOGÍA

ciberes
Centro de Investigación Biomédica en Red
Enfermedades Respiratorias

H2020

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