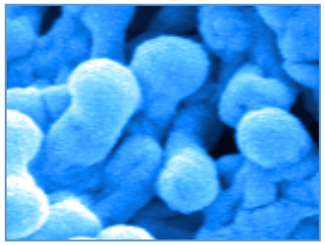
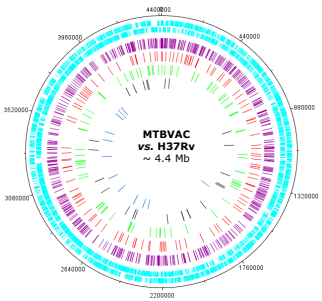
Nuevas vacunas contra la Tuberculosis

MTBVAC





Carlos Martín Montañés

26 Octubre 2013

HISTORIA NATURAL DE LA TUBERCULOSIS

95%
Cepas de MTB
De origen
Humano

ENFERMEDAD TBC

MORTALIDAD 50%

SIN TRATAMIENTO

INFECCION TBC

THE STAGES IN THE IMMUNOLOGICAL LIFE CYCLE OF TB

Modified from J. D Ernest 2012 NATURE REVIEWS IMMUNOLOGY

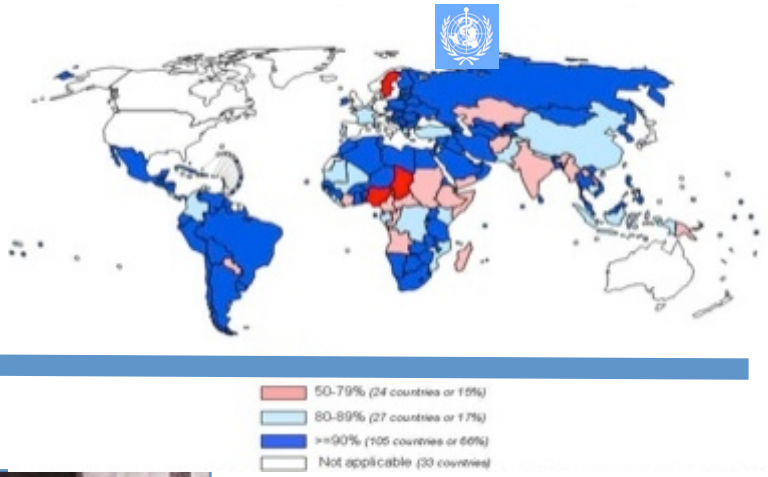
Vacuna actual contra la tuberculosis BCG

Albert Calmette (1863–1933)

Camille Guerin (1872–1961)

Nature Reviews Microbiology 2006

Pros y Contras de la vacuna BCG



GUÉRIN **CALMETTE**

BCG, initially orally administered to prevent against tuberculosis in children
Transmitted by milk from cattle

1921-1926 : 50000 vacinated children
(1.8% mortality in vaccinated vs 25% mortality unvaccinated)

Vacuna viva atenuada de *M. bovis*

Eficaz formas mortales enfermedad en niños

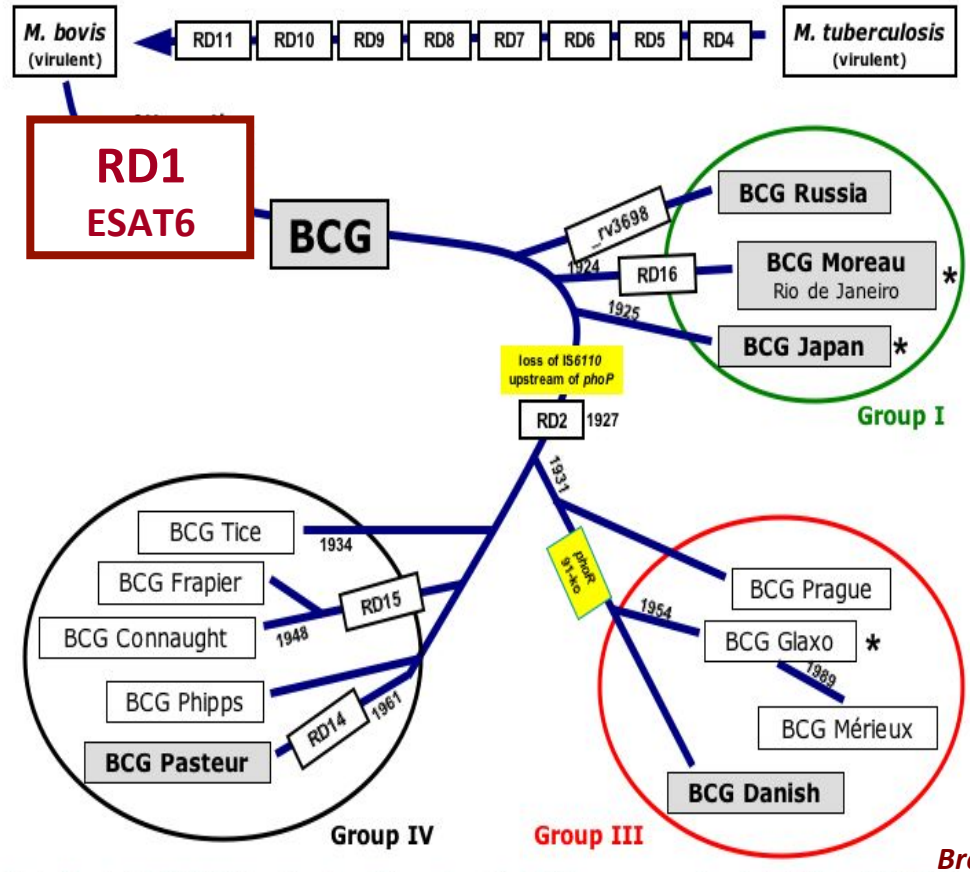
INEFICAZ EN FORMAS PULMONARES EN ADULTOS

BCG: PRESENT VACCINE AGAINST TB

M. bovis 1908-1921 230 Passages

BCG MORE THAN 100 GENES DELETED

COMPARATIVE GENOMICS: COMPLEXITY OF BCG VACCINES



DIFFERENCES IN IMMUNOGENICITY DUE TO GENOMIC DIVERSITY?

Group I:
MORE IMMUNOGENIC

Group III:
HIGHLY ATTENUATED

* Not produce PDIMs , PGLs
(Chen *et al* Vaccine 2007)

Brosch et al PNAS 2007 BCG Pasteur 1173 SEQUENCE

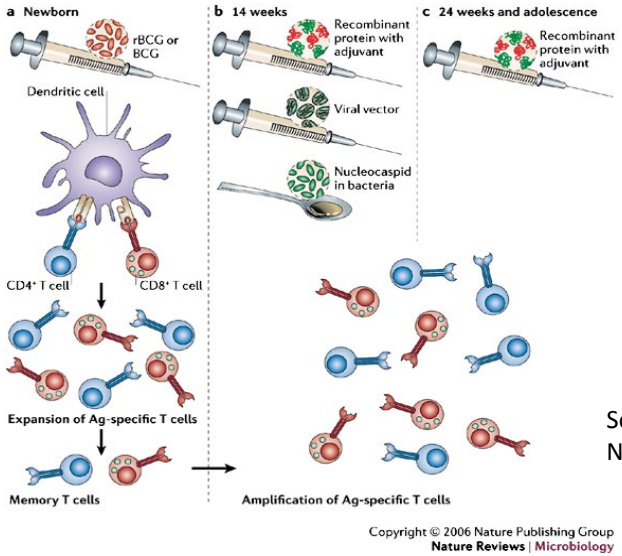
Exper Opin. Biol. Ther. (2008) 8:1-11

LIVE VACCINES ARE THE CORNERSTONE OF TB VACCINE STRATEGIES

TB VACCINE CANDIDATES:

1.- IMPROVE BCG PROTECTION: A BOOSTER VACCINE

PRIME (BCG) BOOST BOOST (Phase I, II, ……..)

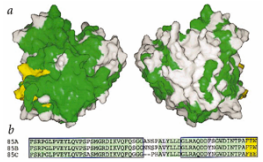


Sekeiky & Sadoff
Nat Rev Microbiol 2006

2.- REPLACE BCG VACCINE: Better protection than BCG

(Phase I, GMP next tp PhaseI or TO BE DEVELOPED ….)

Subunit Vaccines Boosting BCG

	Phase	Description	Comment
 Ag 85			
 ESAT6			
 72F GSK			
Viral-vectored booster vaccine			
Oxford MVA85A/Aeras-485[20]	2	Modified vaccinia Ankara-expressing Ag85A	Ready to undergo phase 2b efficacy trial
Crucell Ad35/Aeras-402[21]	2	Replication-deficient adenovirus 35-expressing Ag85A, Ag85B, TB10·4	Tested in infants, ready to undergo phase 2b efficacy trial
AdAg85A[22]	1	Replication-deficient adenovirus 5-expressing Ag85A	..
Fusion protein in adjuvant as booster vaccine			
Hybrid 1+IC31[23,24]	1	Fusion of Ag85B and ESAT-6 in adjuvant IC31	Contains ESAT-6, which is expressed by *M tuberculosis* but not BCG and hence could confound diagnostic tests based on ESAT-6
Hybrid 1+CAF01[24,25]	1	Fusion of Ag85B and ESAT-6 in adjuvant CAF01	See Hybrid 1, IC31
M72[26]	2	Fusion of Rv1196 and Rv0125 in adjuvant AS02	The only vaccine in clinical trials developed by big pharma (GSK)
M72[27]	2	Fusion of Rv1196 and Rv0125 in adjuvant AS01	The only vaccine in clinical trials developed by big pharma (GSK)
HyVac4/Aeras-404[23,28]	1	Fusion of Ag85B and TB10·4 in adjuvant IC31	Uses TB10·4 instead of ESAT-6 to avoid confounding of diagnostic tests

TST=tuberculin skin test, GSK=GlaxoSmithKline.

Table 1: **Most advanced vaccine candidates in clinical trials**

Tuberculosis vaccines: progress and challenges. Checkley AM, McShane H. Trends Pharmacol Sci. 2011

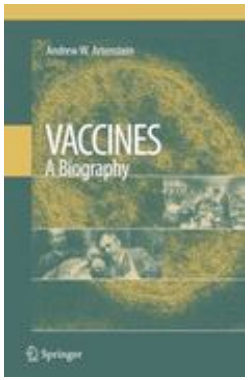
Global Clinical TB Vaccine Pipeline 2013

Phase I	Phase IIa	Phase IIb	PhaseIII
Ad5Ag85A B McMaster University, CanSino	VPM1002 P MPIIB, VPM, TBVI, SIS	MVA85A /Aeras485 B UOXF, AERAS	Mw IT DBT, Cadila (India)
Hybrid-I+CAF01 B SSI, TBVI	Hybrid-I +IC31 B SSI, TBVI, Intercell, EDCTP	Ad35/Aeras402 B Crucell, Aeras	M. vaccae IT AnHui Longcom *Pending*
ID93 + GLA-SE B IDRI, Aeras	RUTI IT Archivel Pharma	M72/ASO1E B GSK, Aeras	
MTBVAC P University Zaragoza, Biofabri, TBVI	Hyvac4/Aeras404 B SSI, SP, Aeras		
	H56 +IC31 B SSI, Intercell, Aeras		

P priming vaccine
B boosting vaccine
IT therapeutic vaccines

Marinova *et a*l in press Expert Rev of Vaccines

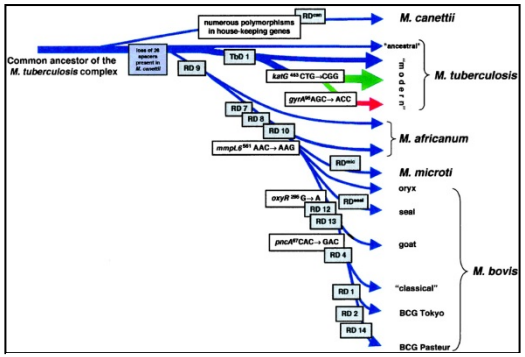
CURRENTLY UTILIZED WHOLE CELL VACCINES

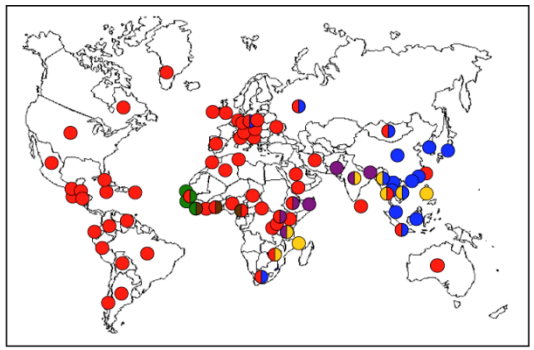


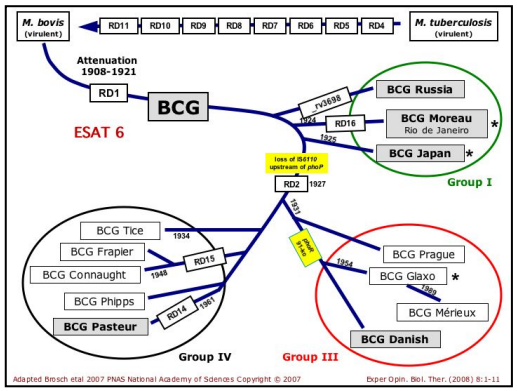
Vaccine	Organism(s) used for vaccination	Source	Vaccine type
Smallpox	Vaccinia virus	Bovine[1]	Live virus
Rabies	Rabies virus	Human	Inactivated
Typhoid	*Salmonella typhi*	Human	Inactivated, live attenuated, or purified polysaccharide
Cholera	*V. cholerae* with (live) or without (killed) deletion in toxin gene	Human	Live attenuated or inactivated + toxin subunit
Tuberculosis	BCG	Bovine	Live attenuated mycobacteria
Yellow fever	Yellow fever virus	Human	Live attenuated
Influenza	Influenza A and B	Human	Inactivated or cold-adapted live virus
Poliomyelitis	Poliovirus types 1, 2, 3	Human	Live attenuated or inactivated virus
Measles	Measles virus	Human	Live attenuated
Mumps	Mumps virus	Human	Live attenuated
Rubella	Rubella virus	Human	Live attenuated
Adenoviral acute respiratory disease	Adenovirus serotypes 4,7	Human	Live virus
Varicella	Varicella-zoster virus	Human	Live attenuated
Japanese encephalitis	JEV	Human, mosquito (live vaccine)	Inactivated or live attenuated (China)
Hepatitis A	Hepatitis A virus	Human	Inactivated
Rotavirus	Rotavirus	Bovine, human	Bovine-human reassortant

The Future of Vaccine Discovery and Development. Ian H. Frazer. VACCINES. Andrew W. Artenstein. Springer 2010

DISEÑO Y CONSTRUCCION DE UNA NUEVA VACUNA ATENUADA







1.- ATENUACION DE UN PATOGENO DE ORIGEN HUMANO

2.- CEPA DE *M. tuberculosis* DE DISTRIBUCION UNIVERSAL

3.- EVITAR SUBCULTIVOS EN EL LABORATORIO

Una cepa de *Mycobacterium bovis* CAUSO UN BROTE DE TBC MDR - XDR TB

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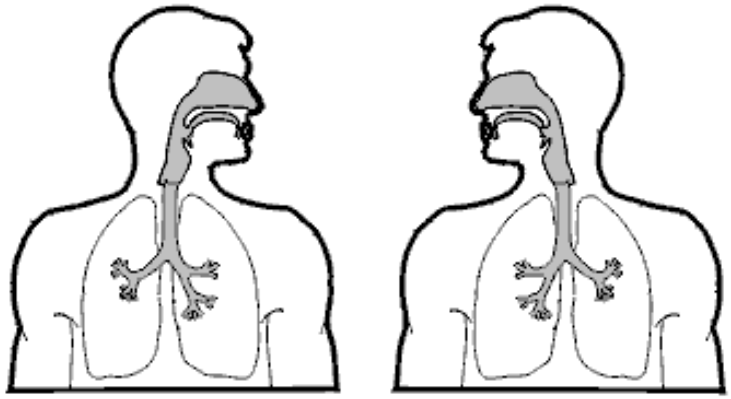
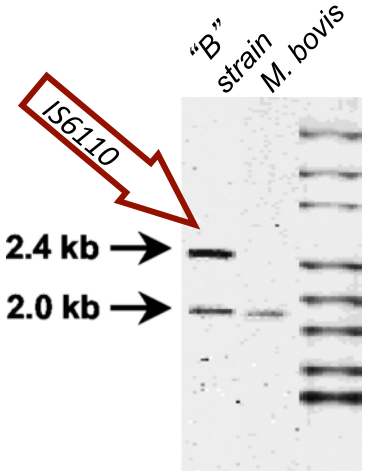
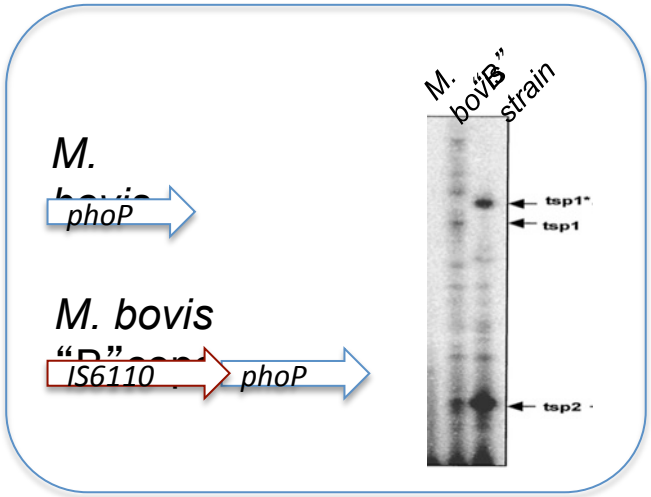
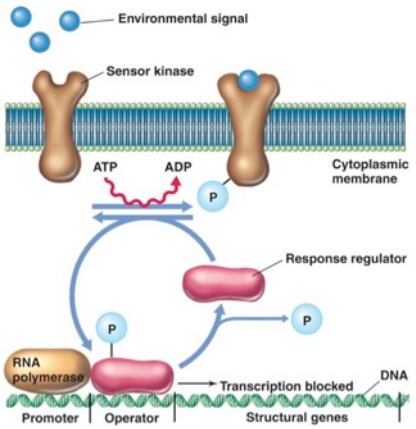
- ✓ **Primer aislamiento 1993**
- ✓ **HIV+, 114 mueren**
- ✓ **Alta transmisión respiratoria**









Samper *et al* MDR TB AIDS 1997 / Guerrero *et al* Lancet 1997 / Rivero *et al* CID 2001 / Soto *et al* JCM2004 / Samper *et al* XDR TB Extensively Drug Resistant TB EID 2007

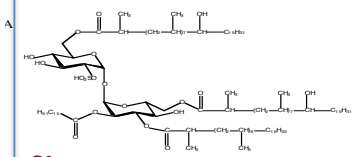
~2-4% ORFs in the *M. tuberculosis* genome under PhoP control

Universidad Zaragoza 1542

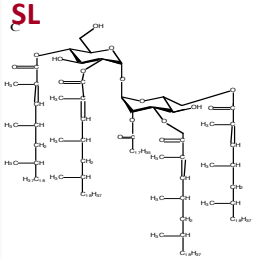
CONCEPT, CONSTRUCTION AND PROOF OF PRINCIPLE OF *phoP*-BASED VACCINE

POLYKETIDE-DERIVED LIPIDS
Immunomodulators

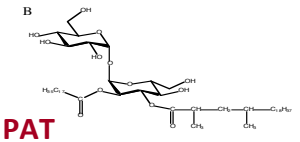
LIPID METABOLISM
SL, DAT, PAT + ... *lipF*



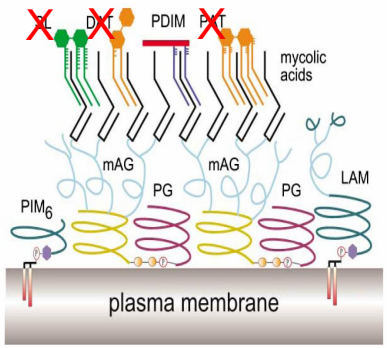
SL



PAT



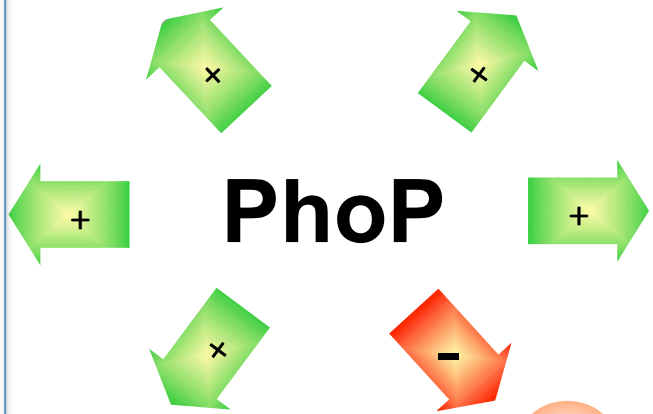
DAT



Gonzalo Asensio *et al*. JBC 2006

RESPIRATION
***narK1, nirA, cysH, ald, nuo*BCDK**

STRESS PROTEINS
(hsp) groEL2

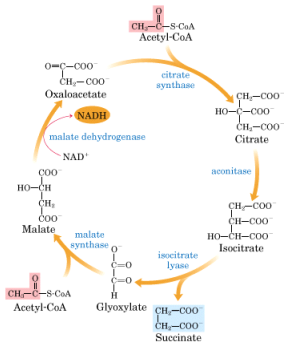


HYPOXIC RESPONSE

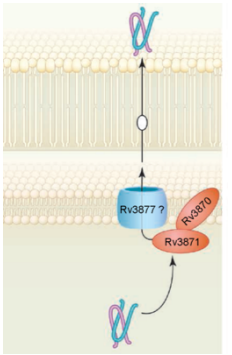
1.- INITIAL (*dosS*/R)
2.- ENDURING

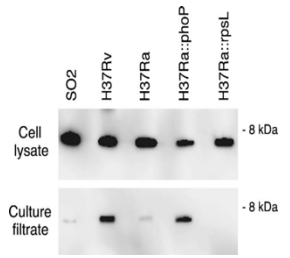
icl

PERSISTENCE



ESAT 6 SECRETION
Virulence factor





Frigui *et al*. PLoS Path 2008

Gonzalo-Asensio *et al*. PLoS ONE 2008

START POINT: INACTIVATION OF *phoP*

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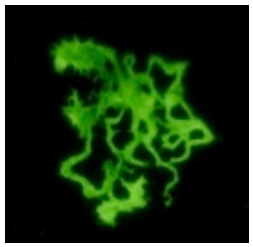
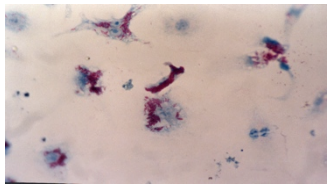
INACTIVATION OF *phoP* IN A CLINICAL ISOLATE OF *M. tuberculosis*

M. tuberculosis



Cording

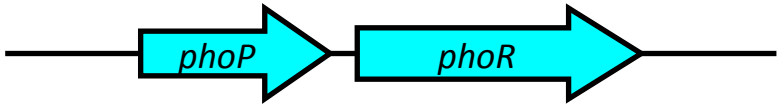


Macrophages multiplication

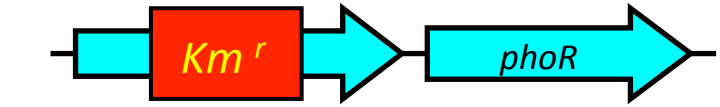
CFUs in lung, liver & spleen

SO2 *phoP* PROTOTYPE VACCINE

M. tuberculosis

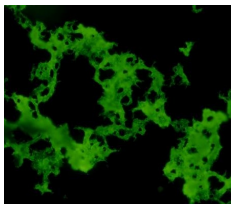


SO2 M. tuberculosis phoP-

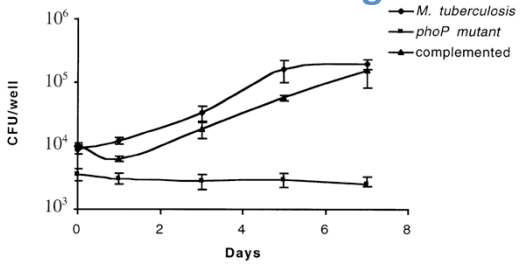


Pérez *et al.* Mol Micro 2001

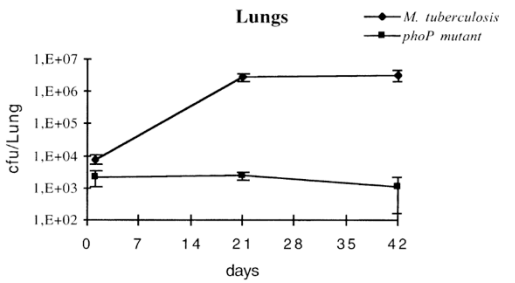
SO2 M. tuberculosis phoP-



Lost of cording



Attenuation *in vitro*



Attenuation *in vivo*

ESTUDIOS PRECLINICOS SO2 **2001 → 2012**

STEP-BY-STEP PRECLINICAL TESTING STRATEGY

BASED ON Douglas Young "*Road Map*"

1	2				3		
	Safety				**Immunogenicity Protection**		
	Cell	**Animal Model**			**Animal Model**		
Construction Live Vaccine Candidate	Macrophages (1) →	Mice (1,2) →	SCID Mice (3) →	Guinea pigs (5) →	Mice (3,4,7) →	Guinea pigs (2,3) →	Primate (6)
							

(1) Perez *et al* Mol Micro 2001 (2) Williams *et al* Tuberculosis 2005 (3) Martín *et al* Vaccine 2006 (4) Aguilar *et al* 2007 CEI (5) Cardona *et al* Vaccine 2009 (6) Verreck *et al* PLOs ONE 2009 (7) Nambiare *et al* Eur J Immunology 2012

GENEVA CONSENSUS CRITERIA: CONSTRUCTION OF MTBVAC01

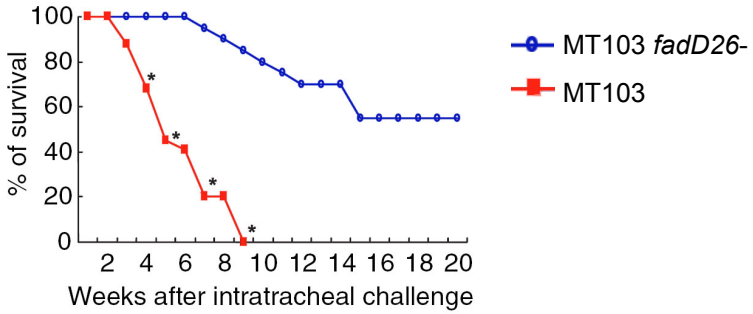
TWO STABLE INDEPENDENT MUTATIONS RECOMMENDED FOR LIVE VACCINES

Available online at www.sciencedirect.com
SCIENCE DIRECT®
Vaccine 23 (2005) 3753–3761
Vaccine
www.elsevier.com/locate/vaccine

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

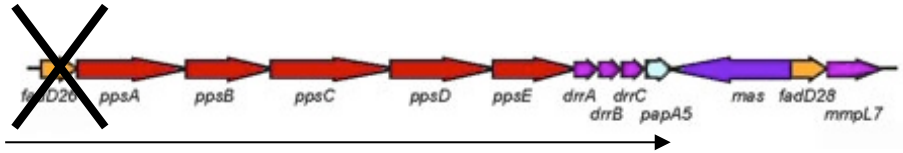
Arun T. Kamath[a], Uli Fruth[b], Michael J. Brennan[c], Roland Dobbelaer[d], Peter Hubrechts[e], Mei Mei Ho[f], Ronald E. Mayner[g], Jelle Thole[h], K. Barry Walker[i], Margaret Liu[j], Paul-Henri Lambert[a,*]

DIM locus was found as **a virulence gene cluster** of *M. tuberculosis* by **signature-tagged transposon mutagenesis** Camacho *et al. Mol Microbiol* 1999; Cox *et al. Nature* 1999



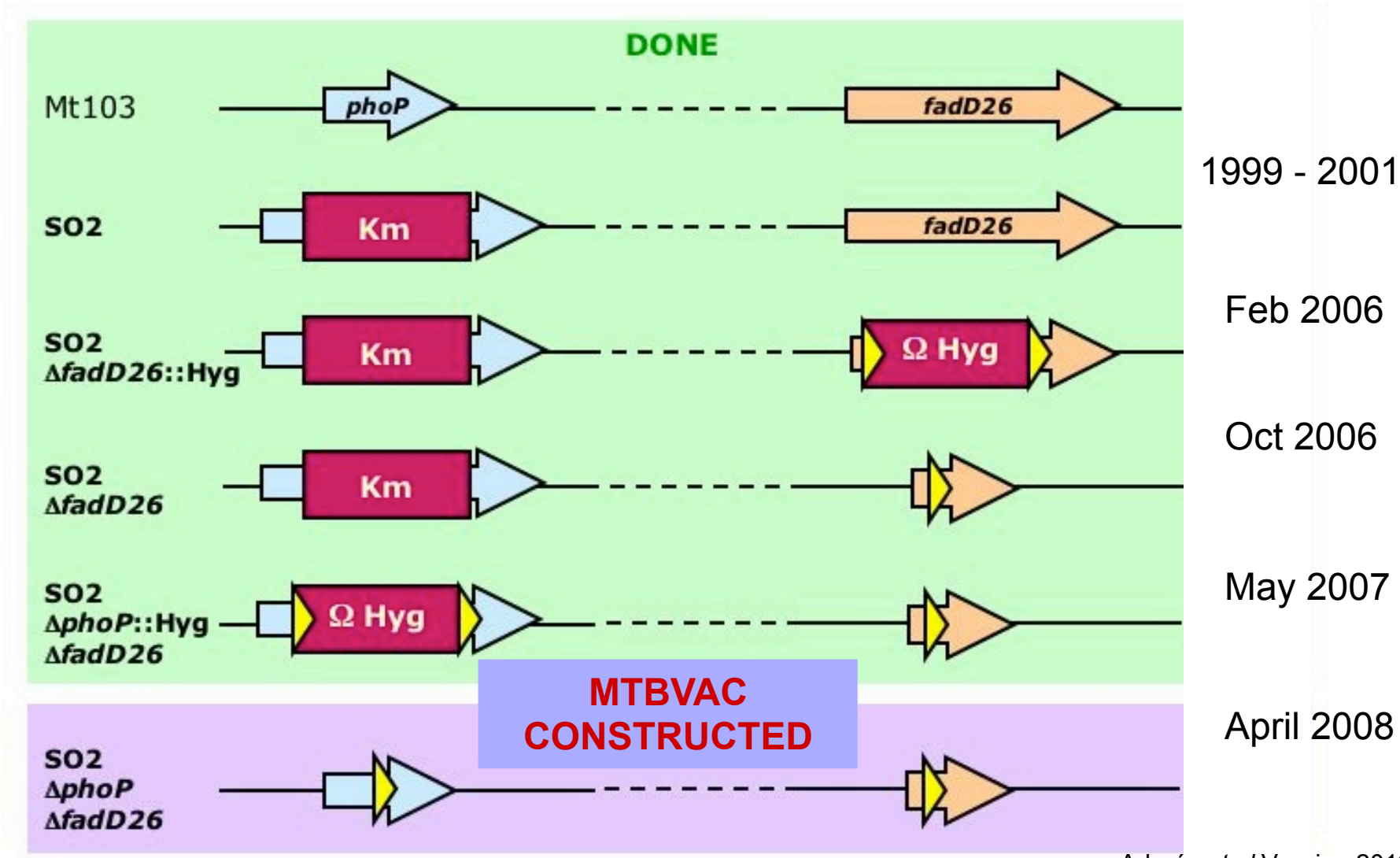
ATTENUATION and protection of *M. tuberculosis fadD26* mutant. Infante *et al.* Clin Exp Immunol 2005

SECOND MUTATION IN DIM LOCUS: DELETION IN *fadD26* GENE

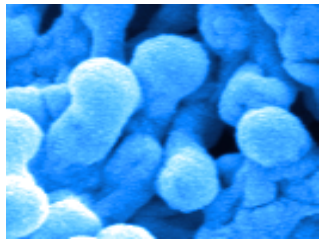


FROM SO2 TO MTBVAC

DOUBLE MUTANT GENEVA 1 VACCINE CONSTRUCTION STEPS



Arbués *et al* Vaccine 2013



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MTBVAC

TBVI
TuBerculosis Vaccine Initiative

Vaccine 31 (2013) 4867–4873

Contents lists available at ScienceDirect

Vaccine

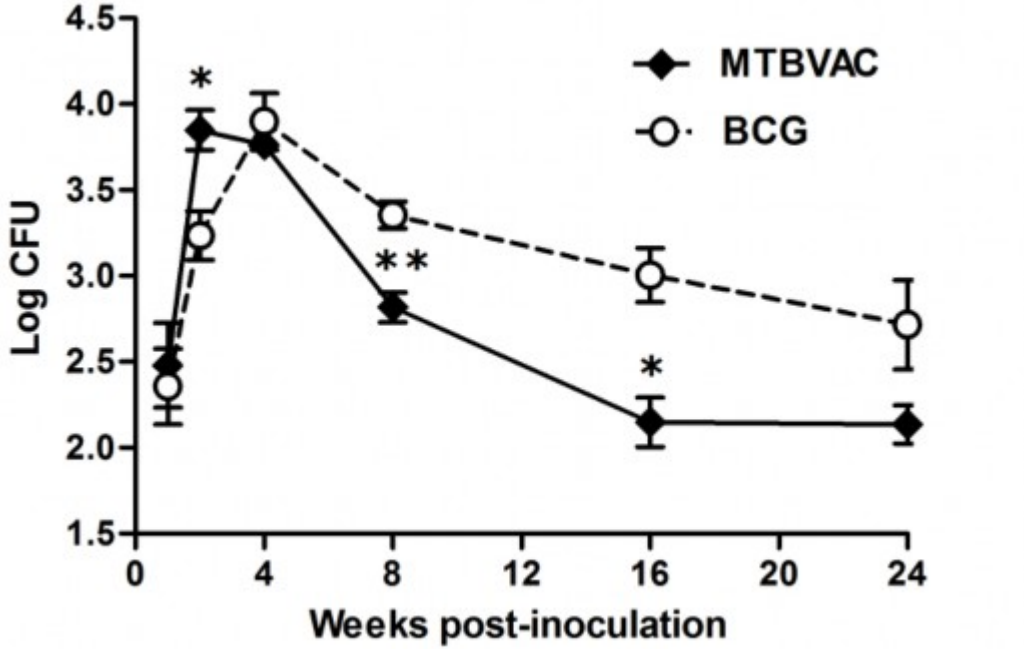
journal homepage: www.elsevier.com/locate/vaccine

Construction, characterization and preclinical evaluation of MTBVAC, the first live-attenuated *M. tuberculosis*-based vaccine to enter clinical trials

Ainhoa Arbues[a,b,1], Juan I. Aguilo[a,b], Jesus Gonzalo-Asensio[a,b,c], Dessislava Marinova[a,b], Santiago Uranga[a,b], Eugenia Puentes[d], Conchita Fernandez[d], Alberto Parra[d], Pere Joan Cardona[b,e], Cristina Vilaplana[b,e], Vicente Ausina[b,f], Ann Williams[g], Simon Clark[g], Wladimir Malaga[h,i], Christophe Guilhot[h,i], Brigitte Gicquel[j], Carlos Martin[a,b,c,*]

October 2013

MTBVAC biodistribution profile in Balb/c mice



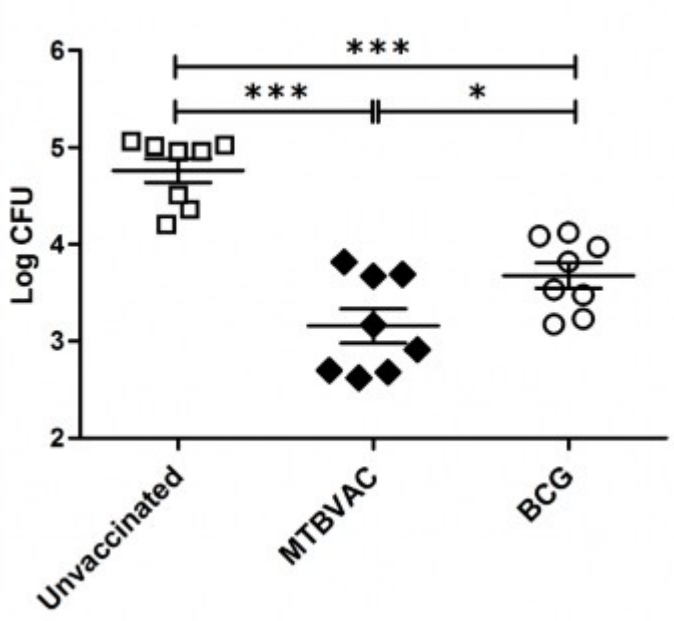
Lymph nodes

Comparable biodistribution profile of MTBVAC and BCG Danish 1331

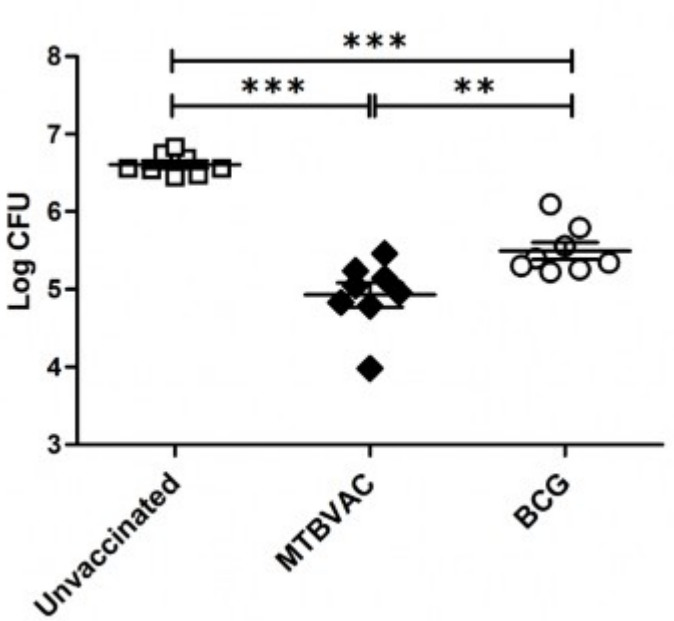
Arbues *et al* Vaccine 2013

Protective efficacy of MTBVAC in C57BL/6 mice

Lungs



Spleens



MTBVAC induces improved protection in mice compared with BCG

Arbues *et al* Vaccine 2013

LIVE ATTENUATED VACCINES FROM BCG TO MTBVAC

TBVI
TuBerculosis Vaccine Initiative

BCG

M. bovis
1908 / 1921
230 Passages

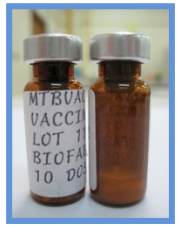
1921-1926 — **BCG Clinical Trial**

1997 — **DEVELOPMENT GENETIC TOOLS**

2005 — **GENEVA CONSENSUS I**

2010 — **GENEVA CONSENSUS II**

2013 — **MTBVAC First in humas**



MTBVAC

Phase I

BIOFABRI

MTBVAC PHASE 1 CLINICAL EVALUATION

Centre Hospitalier Universitaire Vaudois

36 HEALTHY PPD-, BCG-, HIV-

MTBVAC $5x10^3$, $5x10^4$, $5x10^5$
BCG: $5x10^5$

(CFU in 0.1ml)

Randomize and Allocate BCG control 3:1

IP: **Francois Spertini**

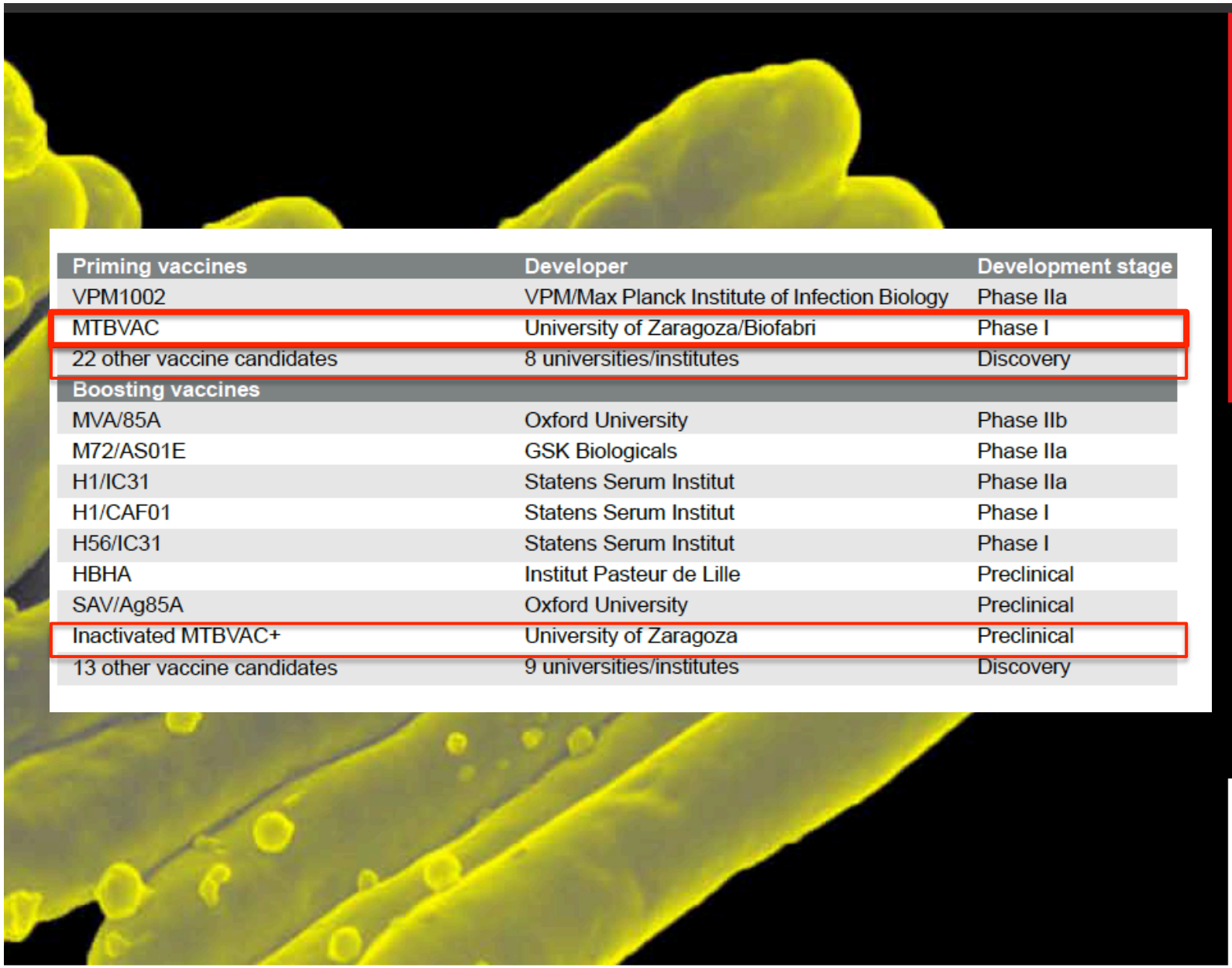
Vaccination & Evaluation

Primary Endpoints: **Safety** & **Reactogenicity**

Secondary Endpoint: **Immunogenicity**

Data Analysis and Study Conclusion

TBVI
TuBerculosis Vaccine Initiative



Priming vaccines	Developer	Development stage
VPM1002	VPM/Max Planck Institute of Infection Biology	Phase IIa
MTBVAC	University of Zaragoza/Biofabri	Phase I
22 other vaccine candidates	8 universities/institutes	Discovery
Boosting vaccines		
MVA/85A	Oxford University	Phase IIb
M72/AS01E	GSK Biologicals	Phase IIa
H1/IC31	Statens Serum Institut	Phase IIa
H1/CAF01	Statens Serum Institut	Phase I
H56/IC31	Statens Serum Institut	Phase I
HBHA	Institut Pasteur de Lille	Preclinical
SAV/Ag85A	Oxford University	Preclinical
Inactivated MTBVAC+	University of Zaragoza	Preclinical
13 other vaccine candidates	9 universities/institutes	Discovery

Annual Report 2012

Tameris *et al* "Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised, placebo-controlled phase 2b trial." **Lancet. 2013** Mar 23;381(9871):1021-8.

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