

GGM



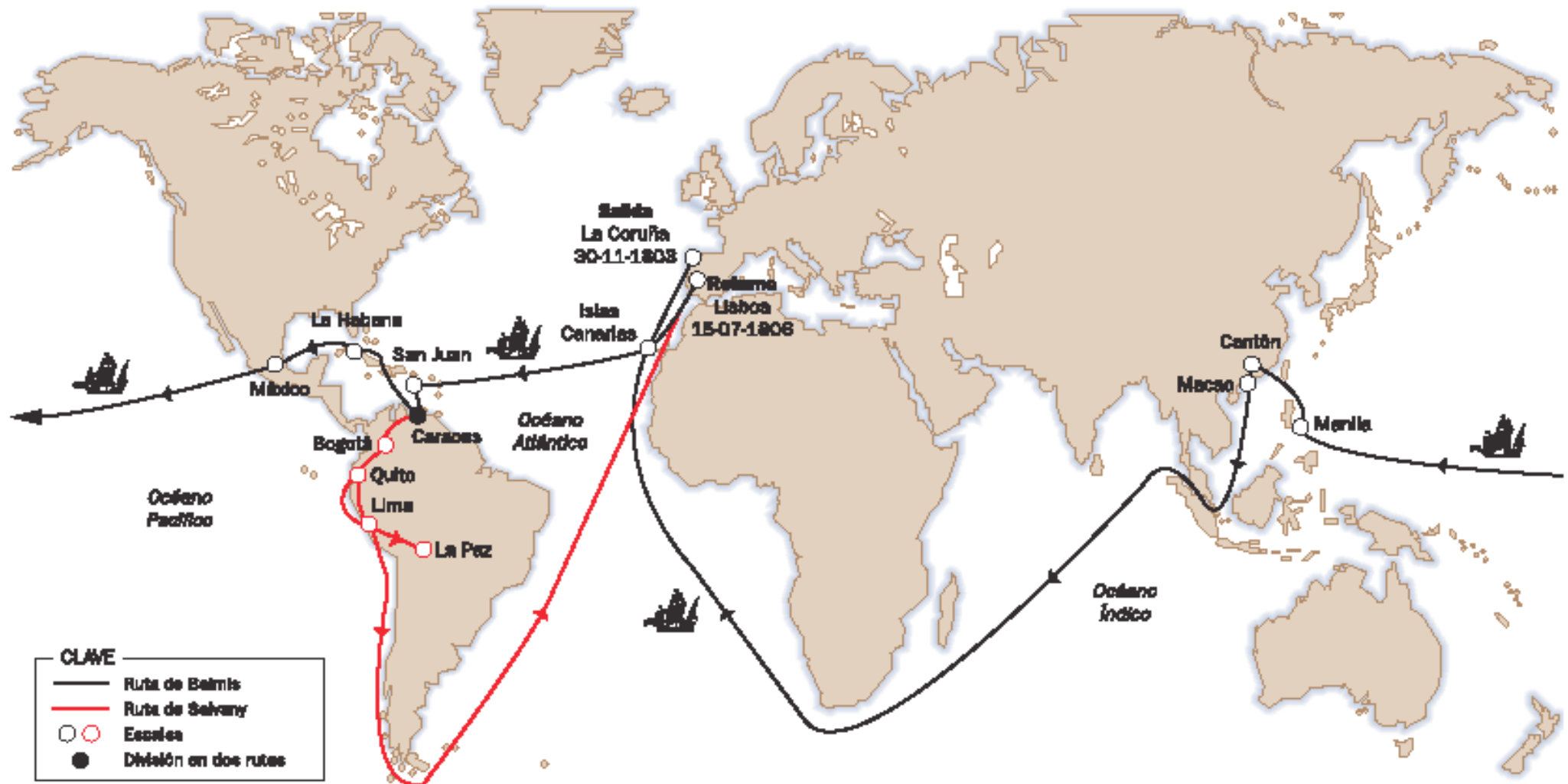
<http://genmico.unizar.es>

Investigación en Nuevas Vacunas Contra la Tuberculosis: Capaces de Reemplazar a BCG

Carlos Martín Montañés
Barcelona 14 de Marzo 2007

El itinerario de la expedición Balmis-Salvany

La corbeta María Pita partía de La Coruña en el año 1803. Al llegar a Caracas, la expedición se dividió en dos: la ruta de Balmis y la de Salvany.



Fuente: Instituto de Salud Carlos III.

EXPEDICIÓN FILANTRÓPICA VACUNA

Balmis-Salvany 1803



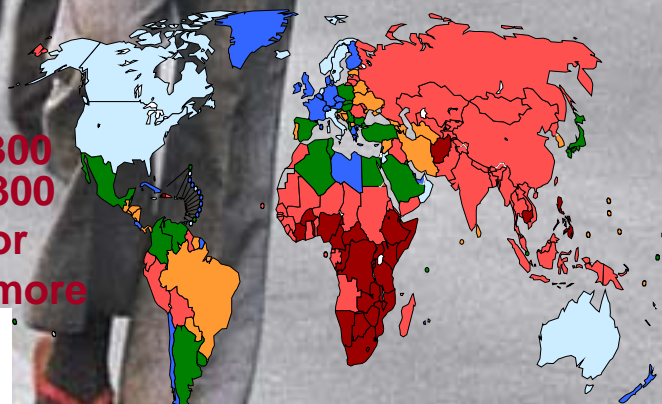
TUBERCULOSIS Vaccines:

LIVE VACCINES

Protection Pulmonary TB

➤ **Replace BCG**

TB cases per
100 000



*Global Tuberculosis
Control WHO Report*

DESDE 1921 BCG VACUNA CONTRA TB VACUNA VIVA



Albert CALMETTE



Camile GUÉRIN

BCG: Bacille Calmette / Guérin

1908-1921, après 230 passages sur milieu bilié

Protección contra TB Pulmonar muy variable distintos estudios

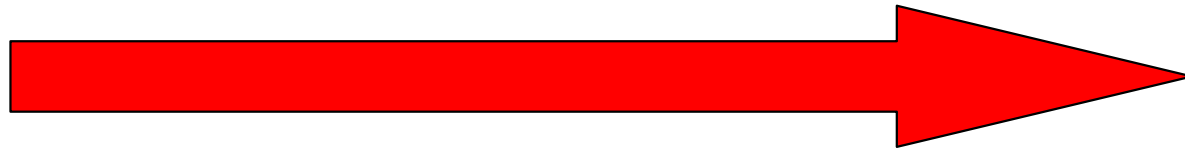
- MRC (UK) 50-60 70%
- Sur de India 70 No Protección

EFICAZ CONTRA LAS FORMAS GRAVES DE TB EN NIÑOS

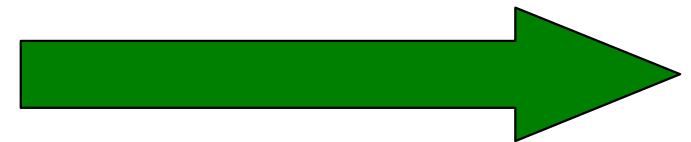
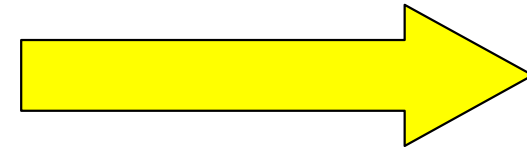
BCG VACUNA MAS USADA DEL MUNDO

INVESTIGACIÓN
Nuevas Vacunas contra TB

NUEVOS CANDIDATOS



PRECLÍNICA

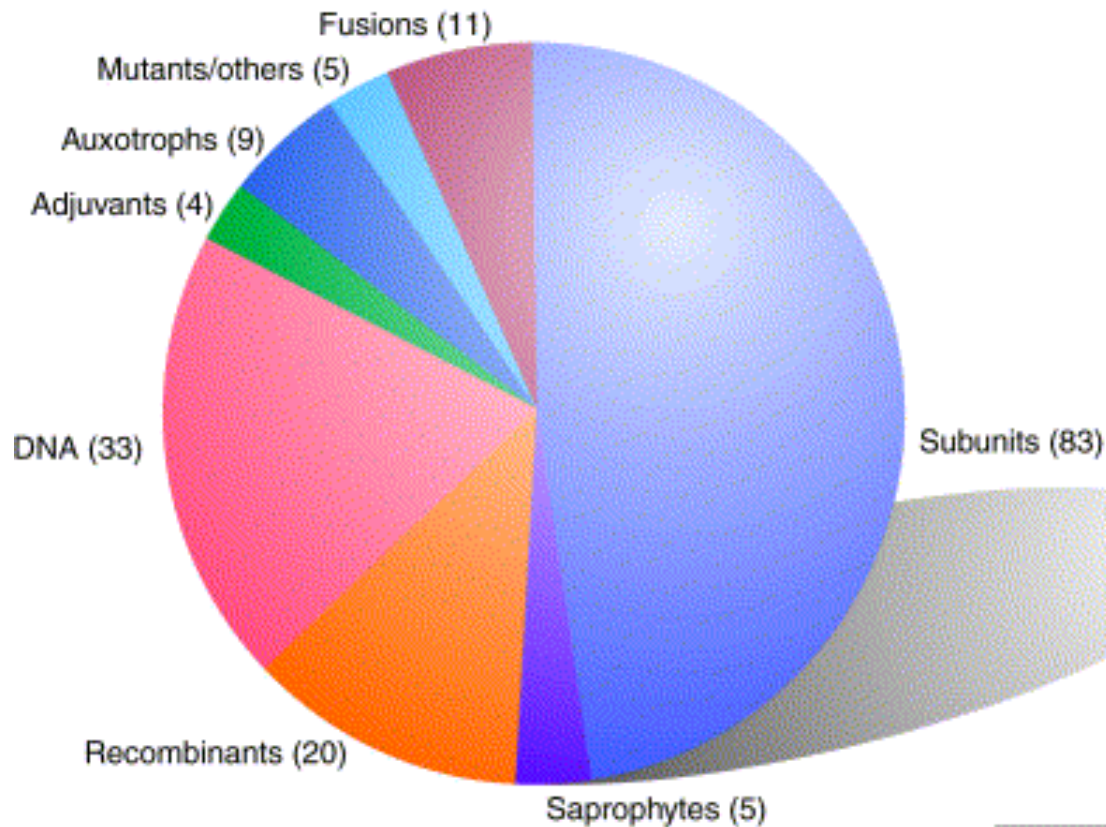


CLÍNICA
FASES 1, 2, 3....

TB Research Materials and Vaccine Testing Contract

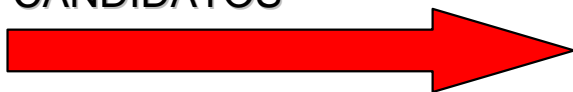
NIH, NIAID NO1 AI-75320

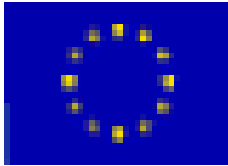
Colorado State University



TRENDS in Microbiology

INVESTIGACIÓN NUEVOS CANDIDATOS





CLUSTER TUBERCULOSIS VACCINE QLK2-1999-01093 (2000-2004)

CANDIDATOS SUBUNIDADES

150: identificados, producidos y probados

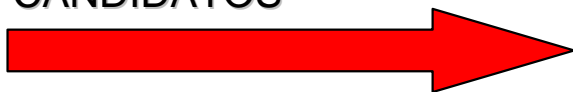
VACUNAS VIVAS

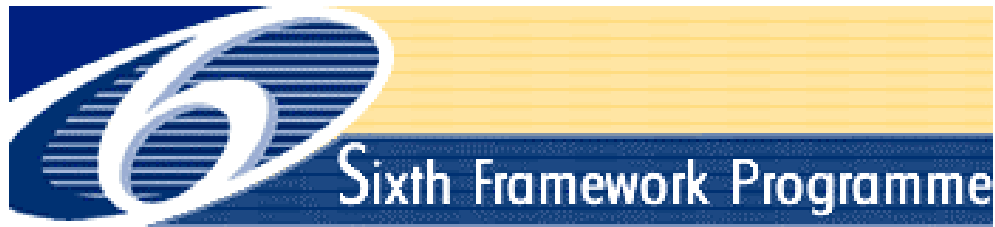
rBCG

M. tuberculosis atenuadas

M. tuberculosis phoP

INVESTIGACIÓN NUEVOS
CANDIDATOS





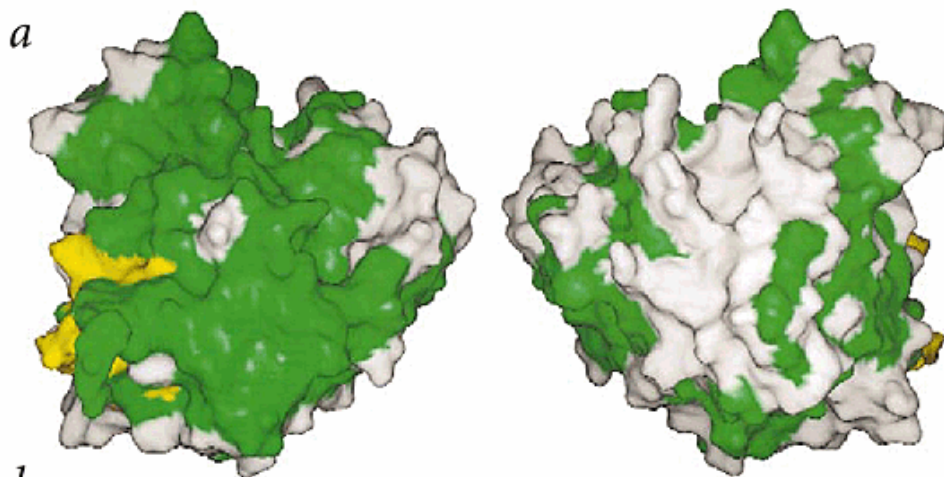
TB VAC

VACUNAS SUBUNIDADES:

¡ ALTA PRIORIDAD!

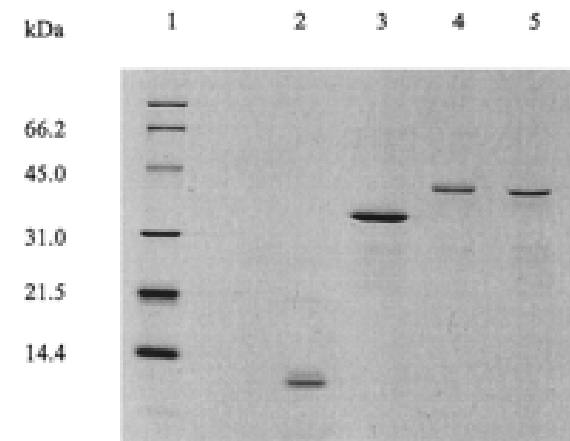
VACUNA SUBUNIDAD
Antígeno 85B y ESAT-6
Peter Andersen
Staten Serum Institut

Protective Effect of a Tuberculosis Subunit Vaccine Based on a Fusion of Antigen. Olsen et al. *Infect. Immun.*2004



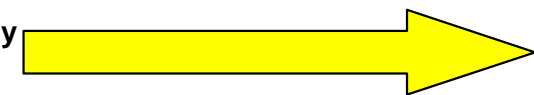
b

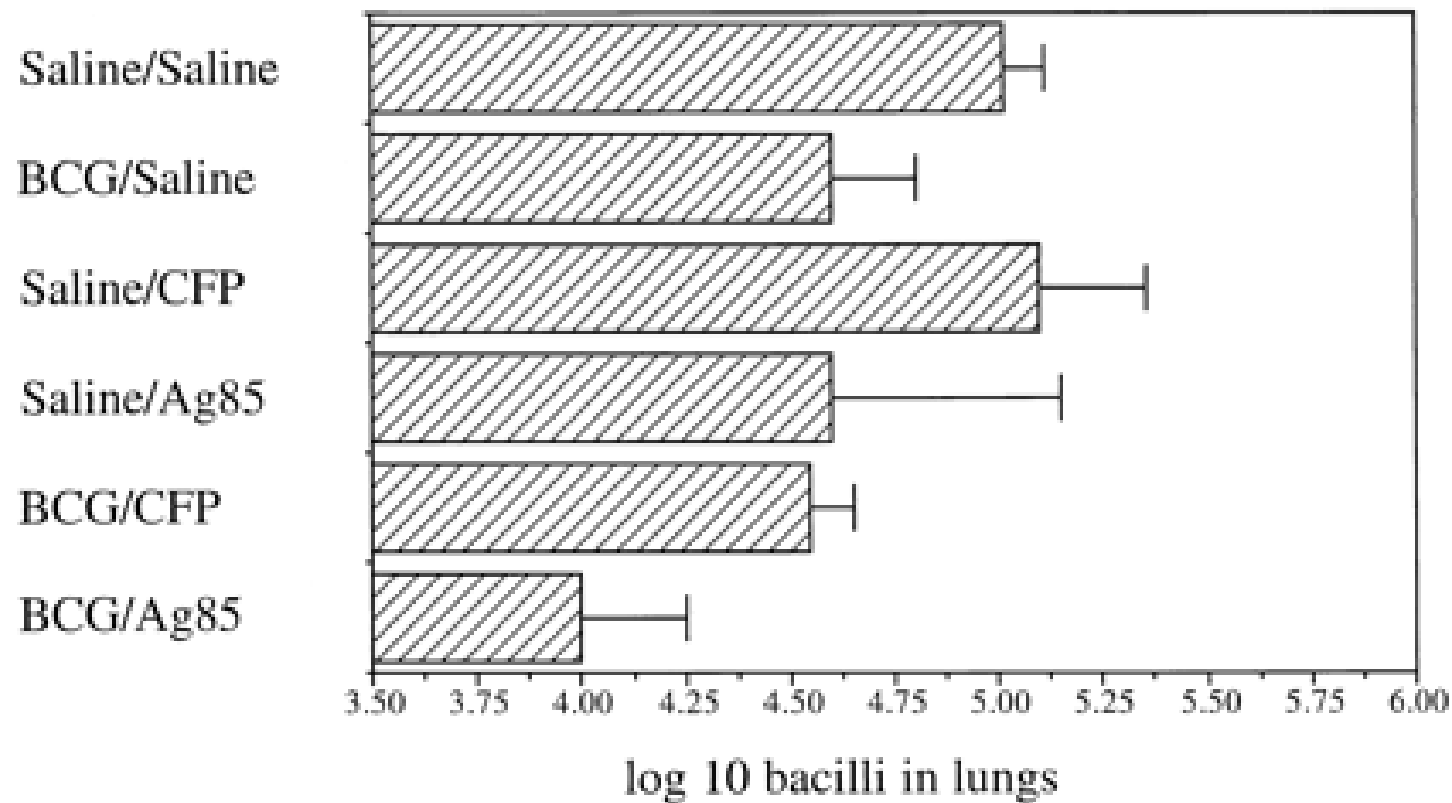
85A	FSRPGLPVEYLQVPSMGRDIKVFQSGGANS	PALYLLDGLRAQDDFSGWDINTPAFEW
85B	FSRPGLPVEYLQVPSMGRDIKVFQSGGNNS	PAVYLLDGLRAQDDYNGWDINTPAFEW
85C	FSRPGLPVEYLQVPSASMGRDIKVFQGGG	--PHAVYLLDGLRAQDDYNGWDINTPAFEE



INVESTIGACIÓN PRECLÍNICA

Nature Structural Biology
Roening et al (2000)

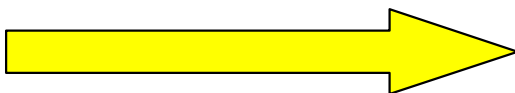




Boosting Vaccine for Tuberculosis

Bellisle and Orme 2001 Infection and Immunity,

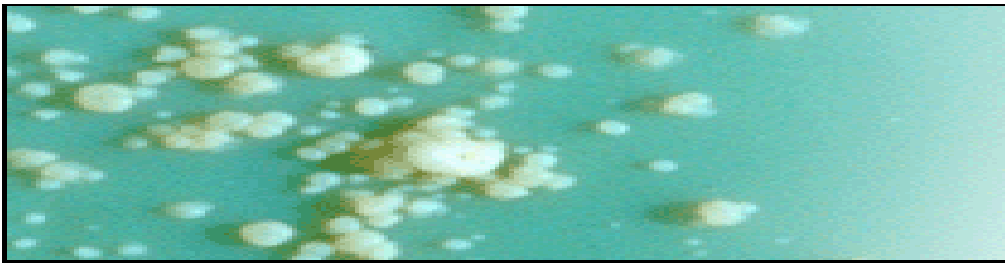
INVESTIGACIÓN PRECLÍNICA



BCG + SUBUNIDADES

CLINICAL TESTING TB VACCINE

TB VACCINE TYPE	DEFINITION	STAGE OF DEVELOPMENT	Pharmaceutical company or Research Group
SUBUNIT			
72f	Selected antigens identified from human response	Phase I trial, ready for phase II BCG Boosting strategy	GSK / (EU TB VAC AERAS)
85B-ESAT6	Recombinant major antigens	Phase I trial BCG Boosting strategy	SSI (EUTBVAC)
VIRAL VECTOR			
MVA-85A	Recombinant modified vaccinia virus Ankara Ag85A	Phase I trial BCG Boosting strategy	OXFORD UNIVERSITY (EU TBVAC)
LIVE VACCINES			
rBCG30	Recombinant BCG: Over expression of Ag85B	Phase I trial	(UCLA/INH/ AERAS)



WP2.1 IMPROVING LIVE VACCINES

WP2.1.1 rBCG Δ ureC Hly

Team 14 MPIIB

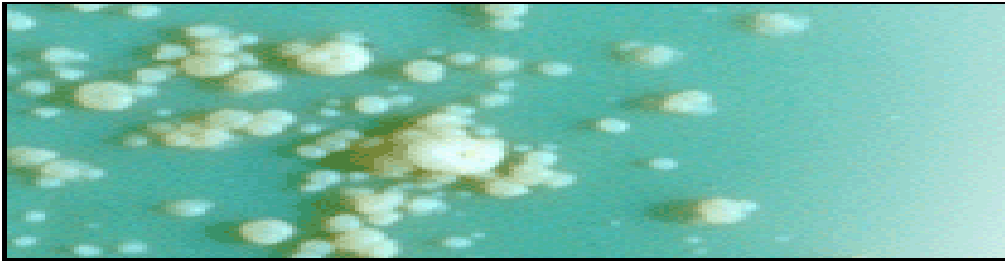
WP2.1.2 rBCG::RD1

Team 27 I Pasteur

WP2.1.3 Attenuated *M. tuberculosis phoP*

Team 21 UNIZAR

LIVE VACCINE CANDIDATES FOR PHASE I



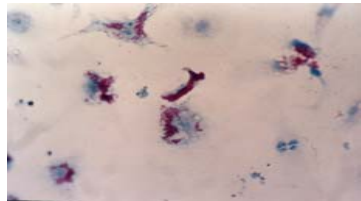
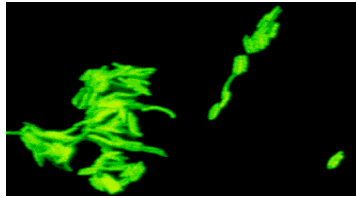
WP2.1 IMPROVING LIVE VACCINES

WP2.1.3 Attenuated *M. tuberculosis phoP* Team 21 UNIZAR

LIVE VACCINE CANDIDATES FOR PHASE I

Inactivation *phoP*: Essential role of *phoP* in the virulence of *M. tuberculosis*

M. tuberculosis

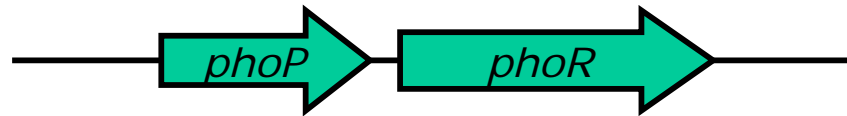


Macrophages multiplication

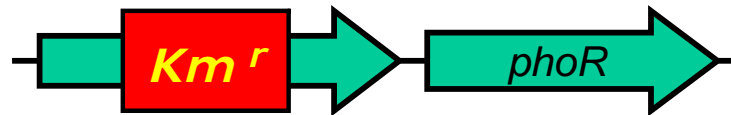


cfus in lung, liver & spleen

M. tuberculosis

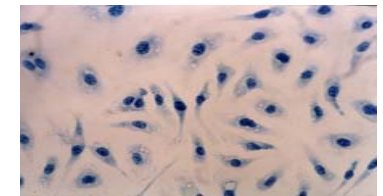
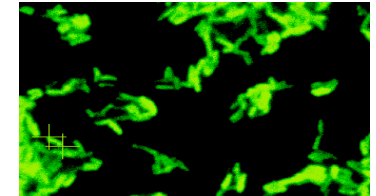


M. tuberculosis phoP⁻



Mol Micro Pérez *et al* 2001

M. tuberculosis phoP⁻



Attenuation *in vitro*



Attenuation *in vivo*

- More attenuated than BCG survival in SCID mice infected

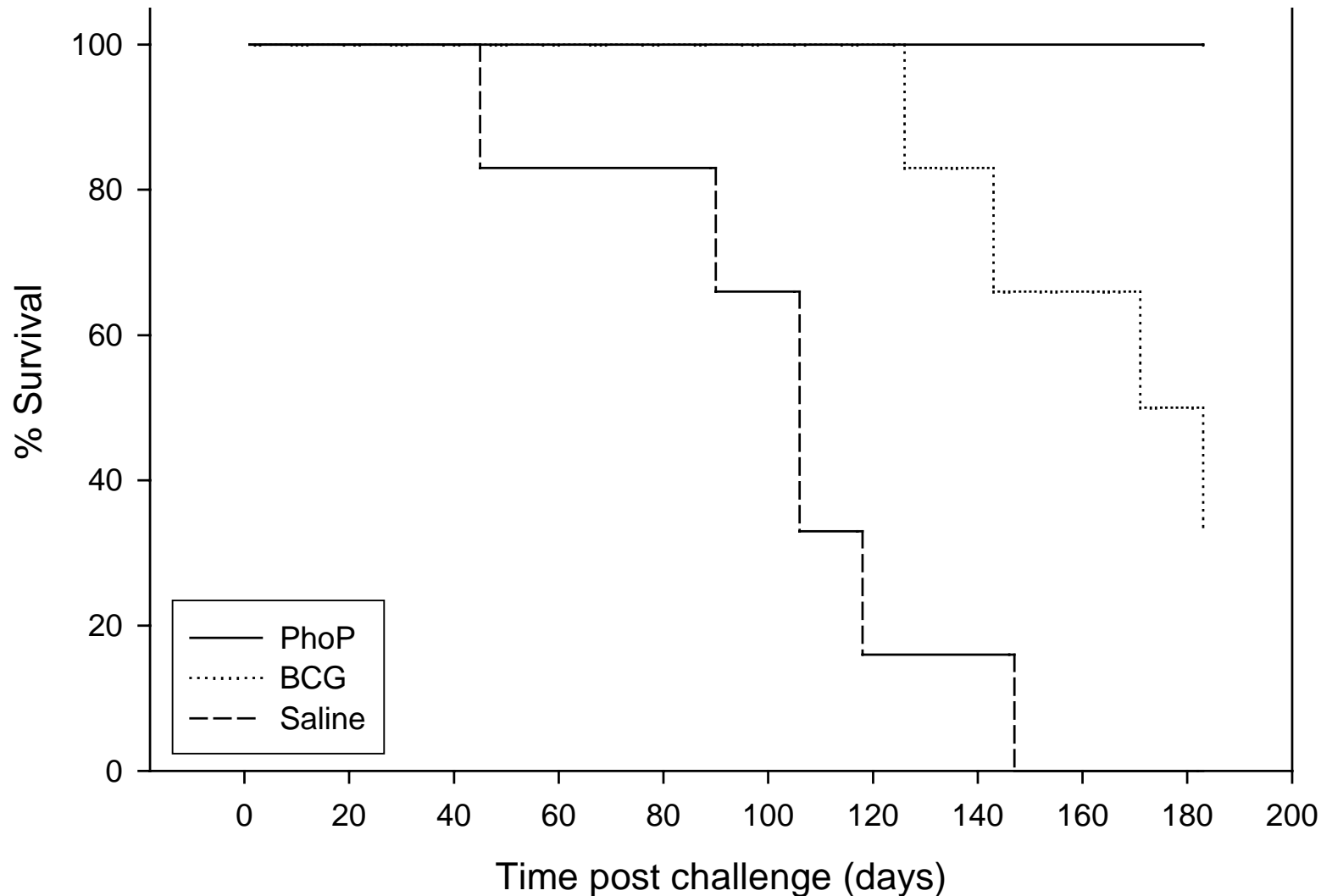
Vaccine Martín *et al* 2006

- Full attenuated compared with MT103 wild type survival Balbc mice

CEI Aguilar *et al* 2007

24 Vaccine Candidates tested (EU FP5) GP protection against aerosol of *M. tuberculosis* H37Rv

Tuberculosis 2005 Willians *et al*



FP5



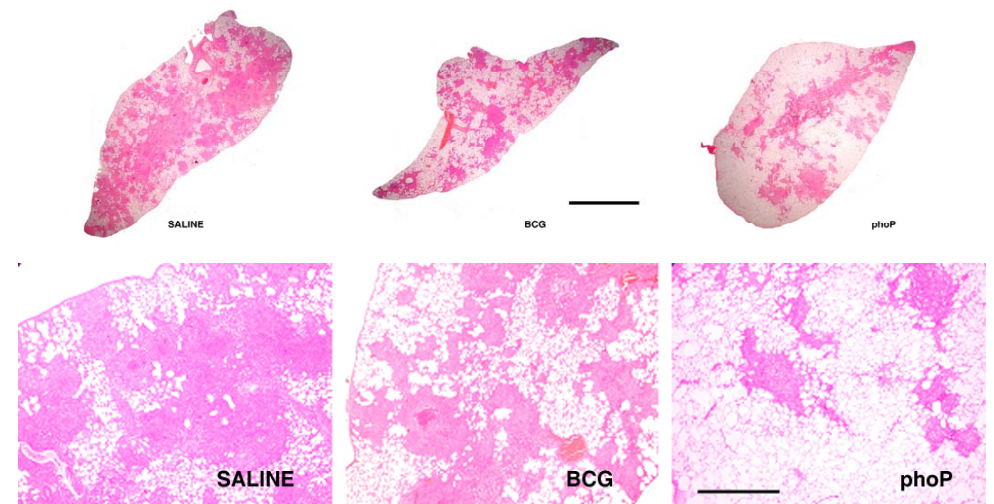
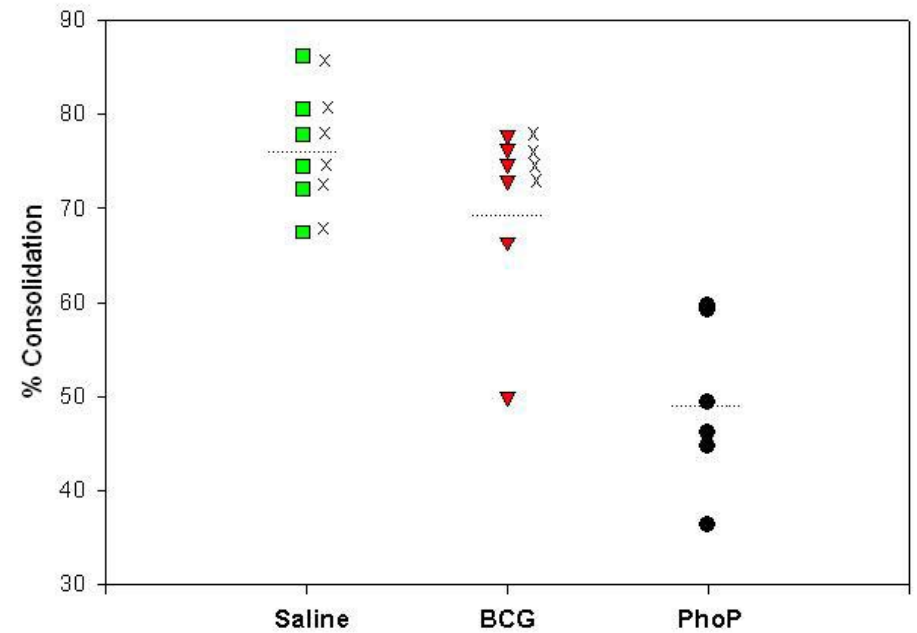
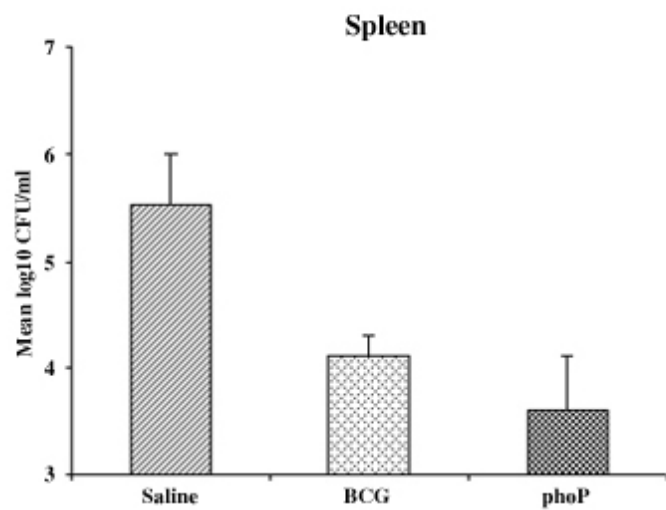
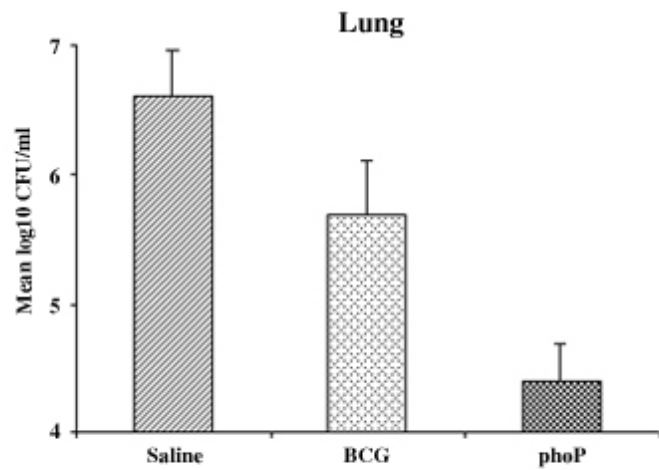
Two vaccine strategies better than BCG : I.- BCG prime /boost MVA Ag85A / Ag85 II.- Single dose vaccine phoP Vaccine 2006 Martin *et al*

Vaccine protection in Guinea Pigs :

Prolonged survival of vaccinated guinea pigs following aerosol infection with *M. tuberculosis*

Reduced cfus in Lungs and spleens

Histology Consolidation in lung



PRE-CLINICAL TESTING

LIVE TB VACCINES	DEFINITION	Research Group
rBCG::RD1	Recombinant BCG RD-1 of <i>M. tuberculosis</i> introduced	Institute Pasteur Paris (EU-TBVAC)
rBCG-Δure-hly	Recombinant BCG with BCG urease gen deleted and Listeriolysin of <i>Listeria monocytogenes</i> introduced	Max Planck Institute Berlin (EU-TBVAC)
<i>M. tuberculosis</i> <i>phoP</i> mutant	Rational attenuated <i>M. tuberculosis</i> clinical isolated by <i>phoP</i> regulated virulence gene inactivated	Zaragoza University (EU-TB VAC)
<i>M. tuberculosis</i> Auxotrophic mutant	Rational attenuated <i>M. tuberculosis H37Rv</i> by <i>lysA</i> and <i>panCD</i> deletion	Albert Institute C. Medicine NY (INH)

VACUNA FRENTE A TUBERCULOSIOS

¿Mejorar inmunidad de BCG?

¿REEMPLAZAR A BCG?



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Ainhoa Arbués

Alberto Cebollada

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Ana Belén Gómez

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Health Protection Agency (UK)

Ann Rawkins

Graham Hatc

Simon Clark

Philipp Marsh



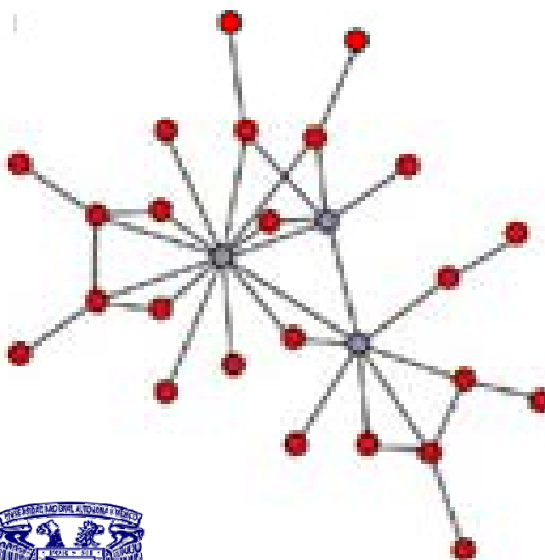
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Biomedical Primate Research Center (NL)

Frank Verreck

Alan Thomas





Artículo 130 de los Estatutos de la Universidad de Zaragoza

8. La Universidad velará para que sus invenciones y contratos de investigación se utilicen para fomentar la paz y el desarme y para contribuir a la desaparición de las desigualdades sociales y económicas entre las personas y entre los pueblos