New advances in TB vaccination

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Overview

- BCG is current gold standard tuberculosis (TB) vaccine
- Variable efficacy of BCG demands new approaches
- New TB vaccine approaches aim to boost or replace BCG

TB: Challenges

HIV Infection and Multidrug-Resistant Tuberculosis—The Perfect Storm

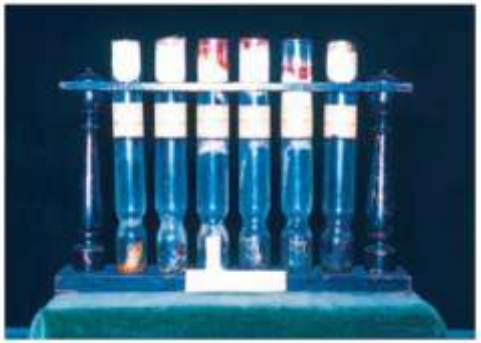
Charles D. Wells,[1] J. Peter Cegielski,[1] Lisa J. Nelson,[2] Kayla F. Laserson,[3] Timothy H. Holtz,[1] Alyssa Finlay,[1] Kenneth G. Castro,[1] and Karin Weyer[4]

The Journal of Infectious Diseases 2007; 196:S86–107

History of BCG

***Mycobacterium bovis* BCG (Bacille Calmette et Guérin)**

Albert Calmette
1863-1933

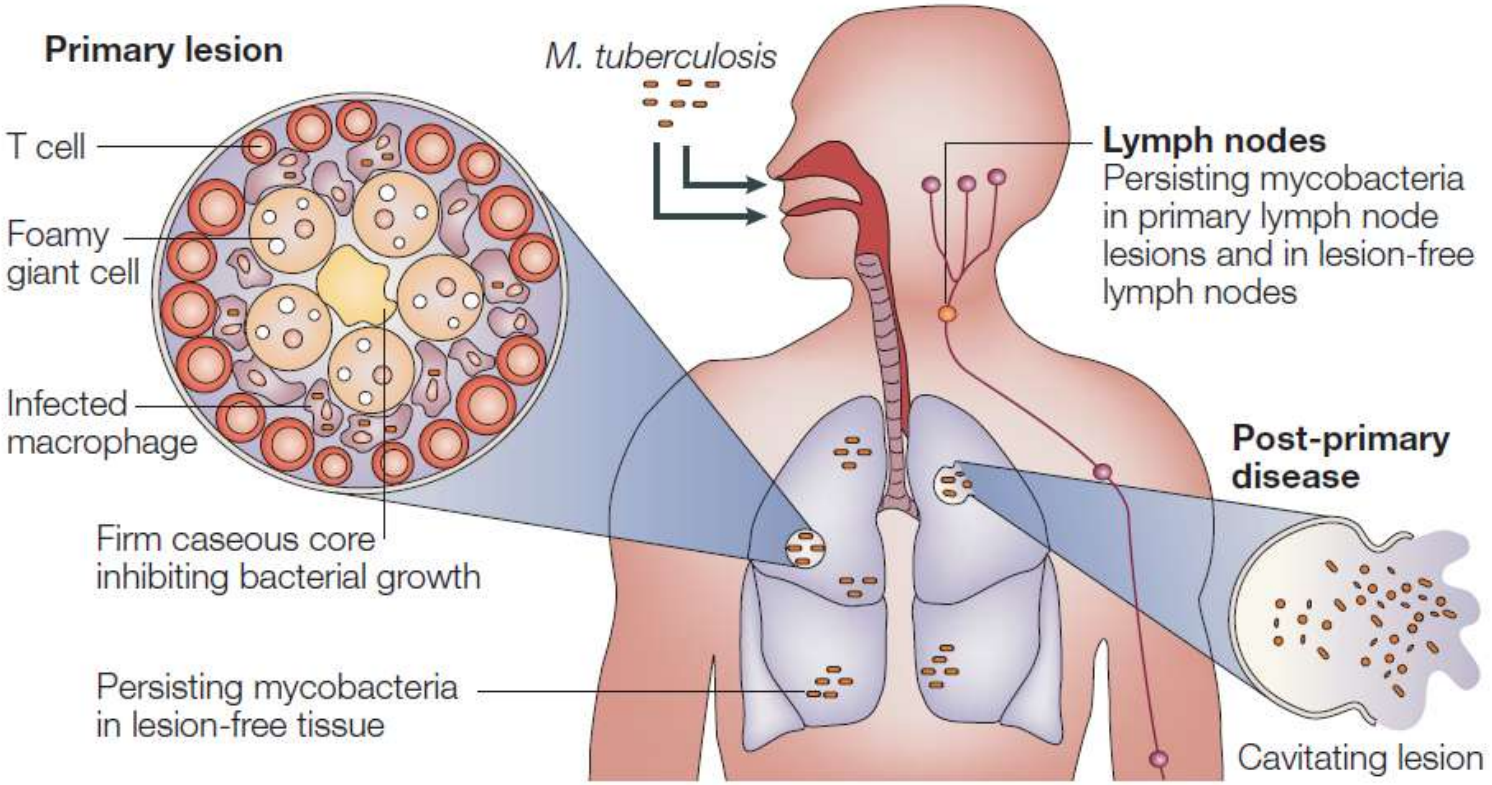


Camille Guérin
1872-1961

BCG: The basics

- BCG (Bacille Calmette et Guérin): Attenuated form of *Mycobacterium bovis*
- First human use in 1921
- Most widely used vaccine in the world

TB: Infection Cycle



Stewart *et al*. (2003) Nature Reviews 97-105

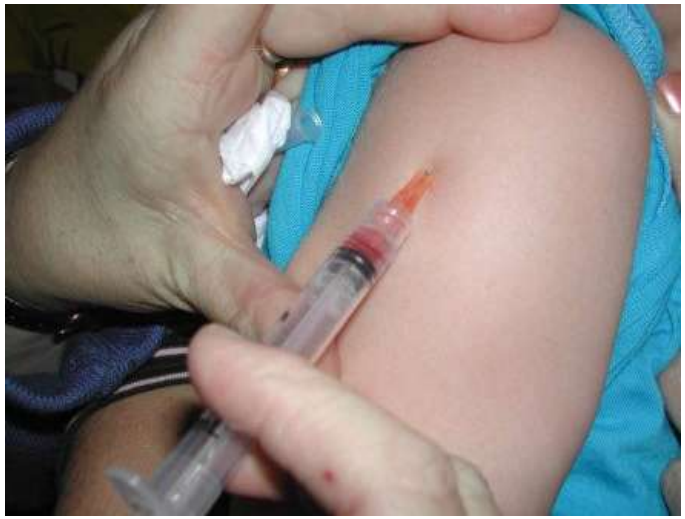
BCG: The basics

- BCG vaccination induces cell- and antibody-mediated immunity
- Protection against subsequent challenge with virulent mycobacterial strains

BCG: Pros and cons

BCG: The benefits

- Excellent safety record
- Protects against childhood tuberculosis meningitis (TBM) and other forms of disseminated disease
- Protection against and treatment of other diseases (eg leprosy, bladder cancer)



BCG: The problems

- Injectable
- Limited duration of immunity
- Variable efficacy
- Limited antigenic repertoire
- Interference with diagnosis
- Safety concerns in immune-compromised individuals

International study suggests benefits of TB vaccine have been underestimated

The BCG vaccine used to prevent tuberculosis has a bigger role in protecting children than previously thought, according to a new study.

Date: 15 Aug 2012

Category: Health,Science,
Type: News

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The BCG vaccine used to prevent tuberculosis (TB) has a bigger role in protecting children than previously thought, according to an international study led by investigators at Imperial College London and published in the *American Journal of Respiratory and Critical Care Medicine*. BCG was understood to prevent severe illness from tuberculosis, but not to prevent infection with TB bacteria. Now data collected from five countries in Europe suggest that the vaccine is also effective at preventing infection.

The BCG vaccine is made from a weakened form of bacteria closely related to human TB. The vaccine is 70-80 per cent effective against the most severe forms of TB, such as TB meningitis in children. In the UK, it is not given as part of the routine childhood vaccination schedule unless a baby is thought to have an increased risk of coming into contact with TB.

BCG: Variable efficacy

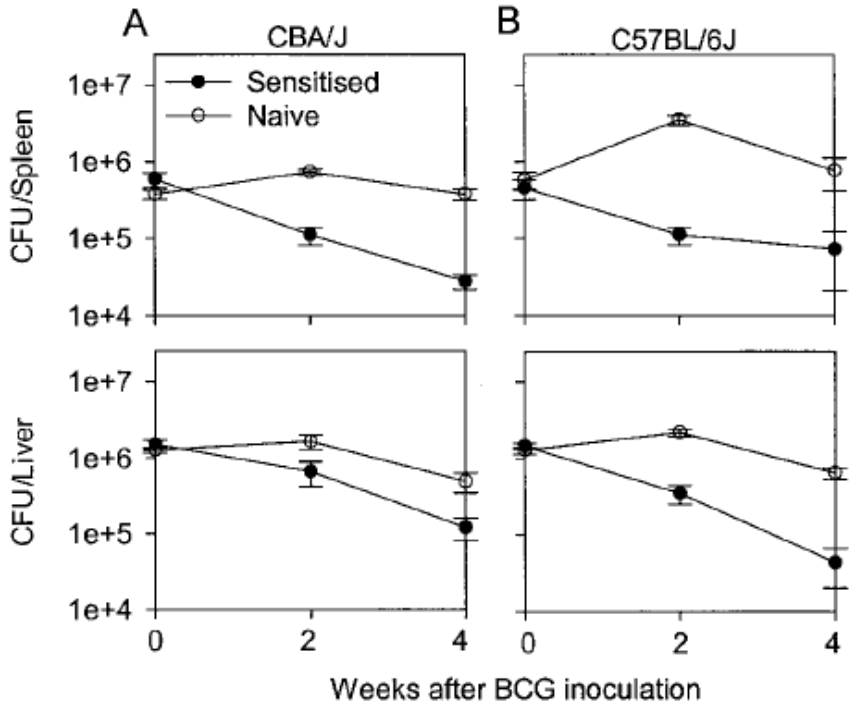
- 0-80% efficacy against pulmonary tuberculosis
- Possible explanations:
  - BCG strain variation
  - Environmental mycobacteria
  - Masking effects of endemic TB
  - Population genetics
  - Nutrition (eg. Vitamin D)
  - Other infections (eg. helminths)

BCG: strain variation

- Seed lots established in 1956
- Genome era has revealed numerous sequence differences in commonly used strains
- Differences in immune responses, not necessarily in protective efficacy

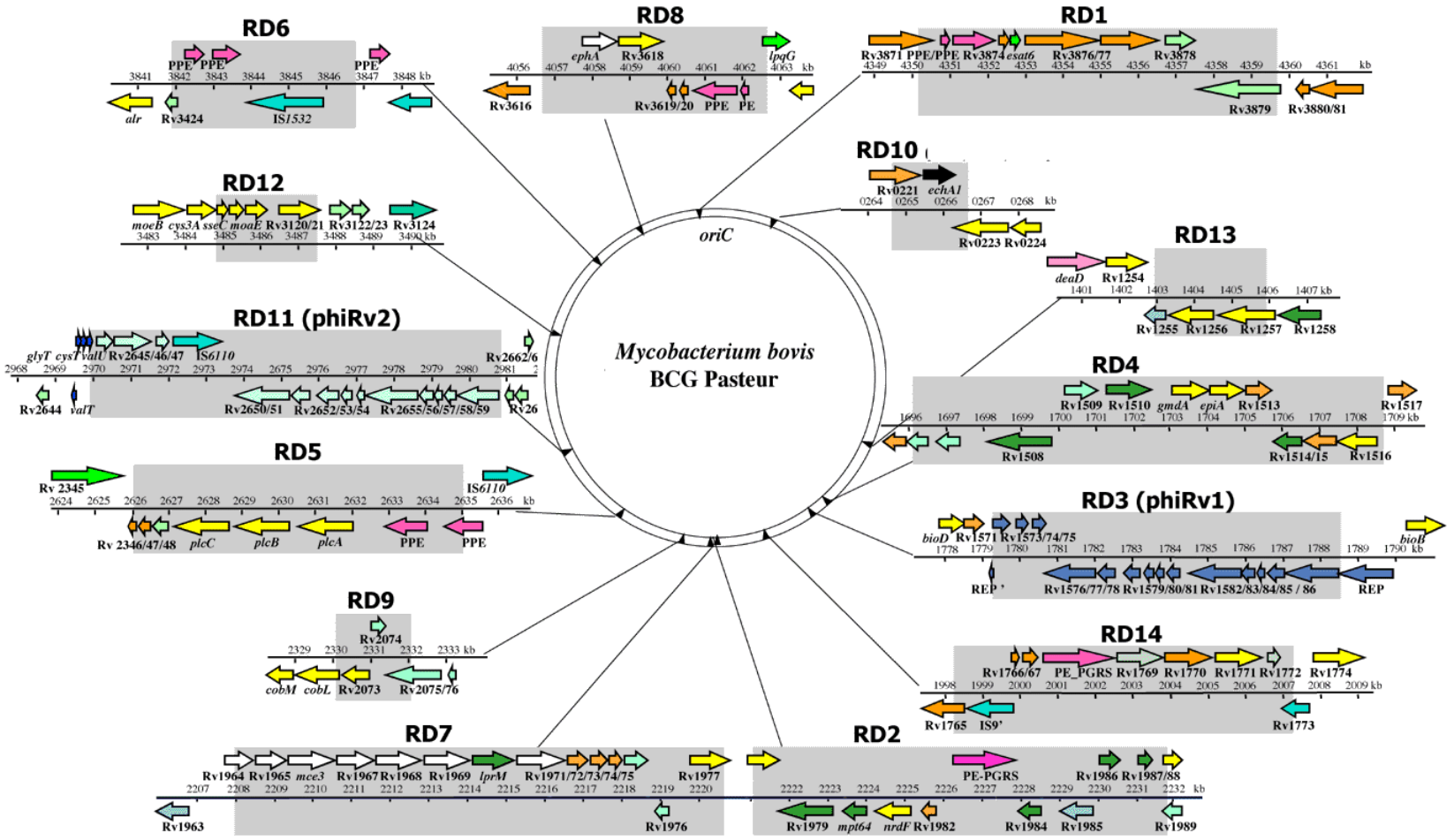
BCG: influence of environmental mycobacteria

- Sensitization with environmental mycobacteria can influence BCG replication and protective efficacy



Brandt *et al* (2002) Failure of the Mycobacterium bovis BCG vaccine: some species of environmental mycobacteria block multiplication of BCG and induction of protective immunity to tuberculosis. *Infect Immun* 70(2):672-8

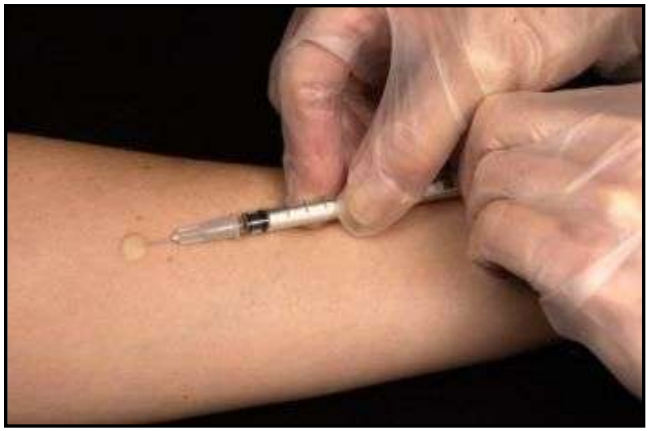
BCG: Antigenic repertoire

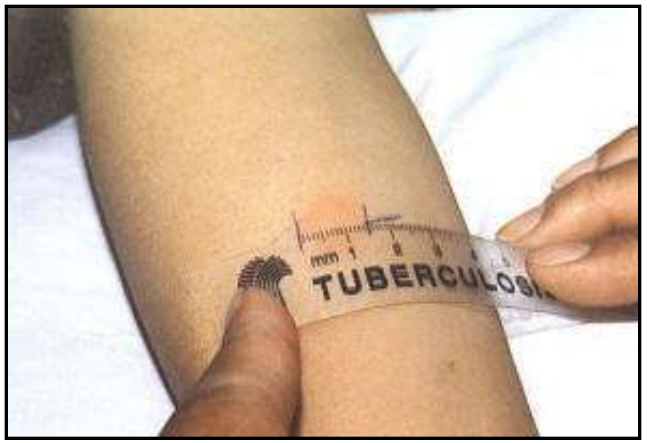


http://www.pasteur.fr/recherche/unites/Lgmb/Deletion.html

BCG and TB diagnosis

- Mantoux tuberculin skin test used routinely to identify TB infection
- Intradermal injection of PPD (purified protein derivative) causes DTH response in sensitized individuals
- BCG vaccination can cause <u>false-positive tuberculin skin test</u>





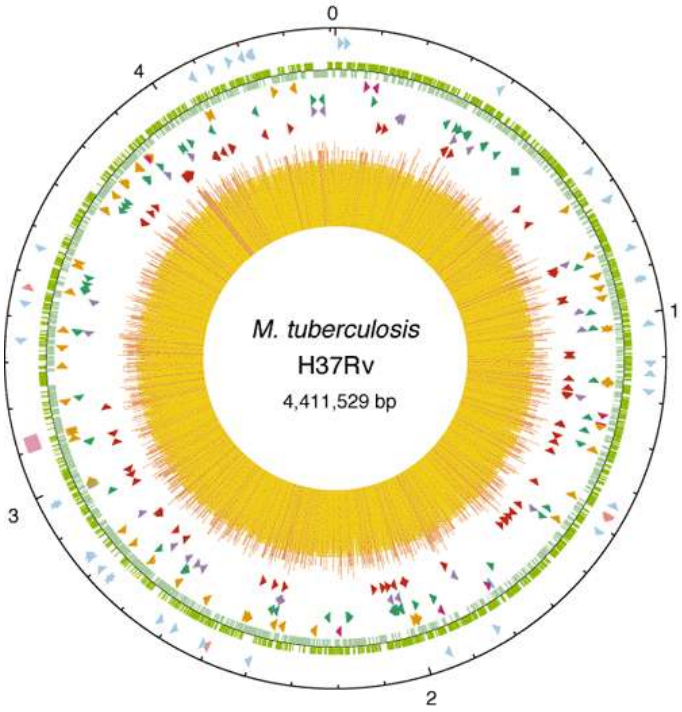
BCG: Safety concerns

- WHO/GACVS: “The reported risk associated with vaccinating HIV-infected children may outweigh the benefits of preventing severe tuberculosis, especially since the protective effect of BCG against tuberculosis in HIV-infected children is not known.”
- Hesseling *et al*. (2009) Bull World Health Organ. Disseminated bacille Calmette-Guérin disease in HIV-infected South African infants.

New approaches

Our new arsenal

- Genome sequence(s)
- Genetic tools
- Improved understanding of TB immunology
- Novel funding approaches
- Infrastructure
- New vaccine candidates

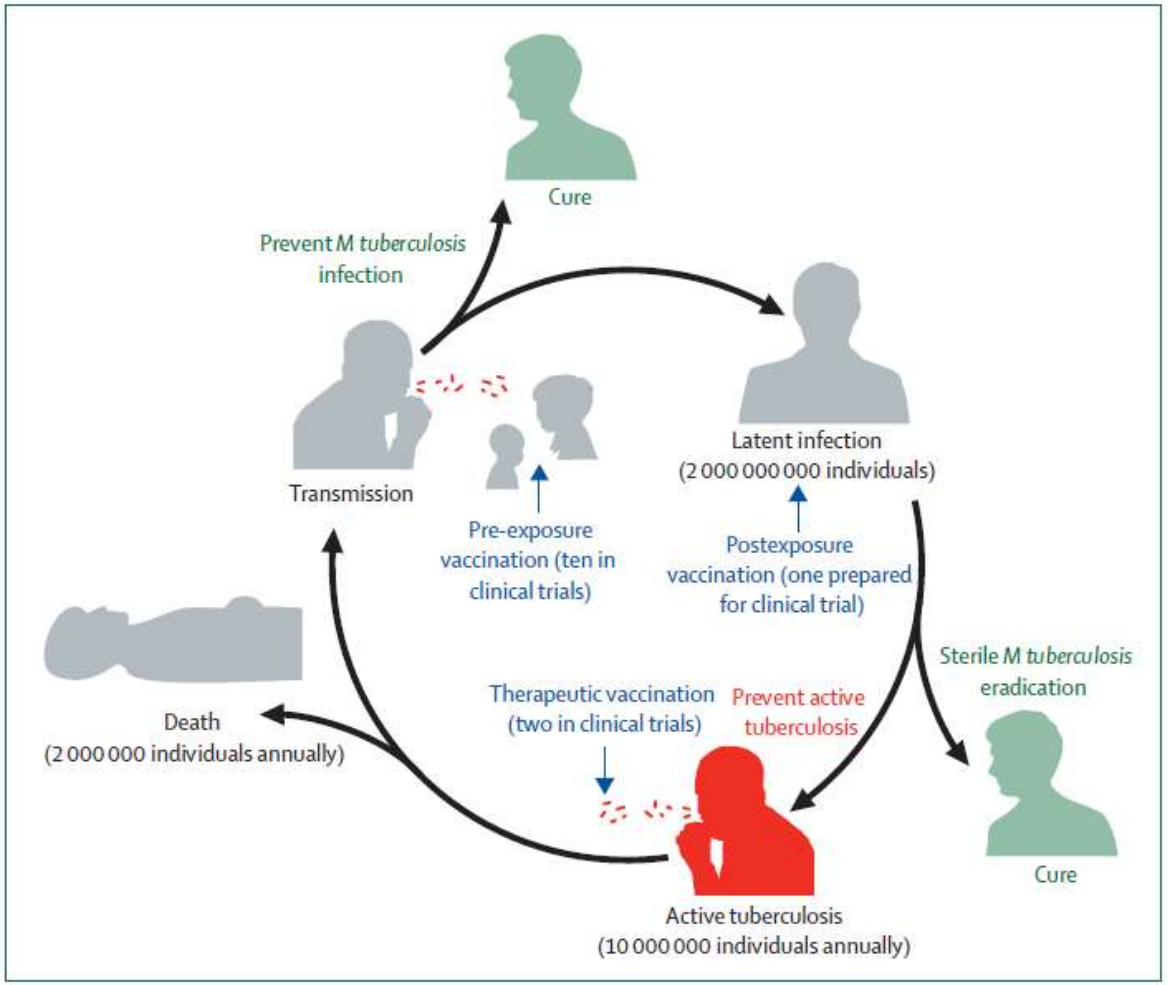


Cole *et al*. (1998) *Nature,* 393:537-44

The ideal

- Affordable
- Easily administered soon after birth
- Safe
- Immunogenic
- Effective at all ages, in all populations
- Effective in preventing primary TB, reinfection and reactivation as well as extrapulmonary disease

Vaccination strategies

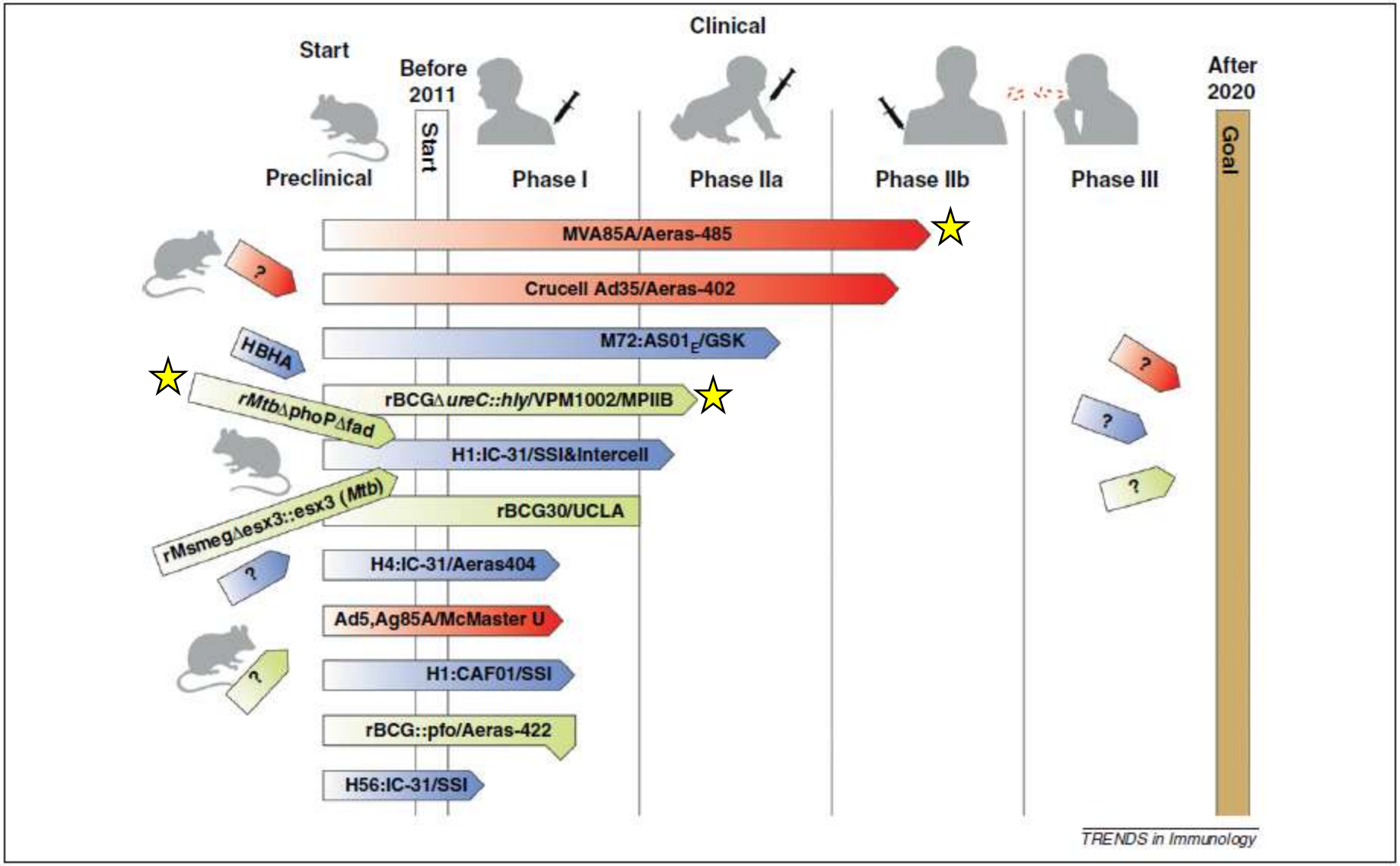


Kaufmann (2011) *Lancet Infect. Dis.*

Viral vectored

Adjuvanted protein booster

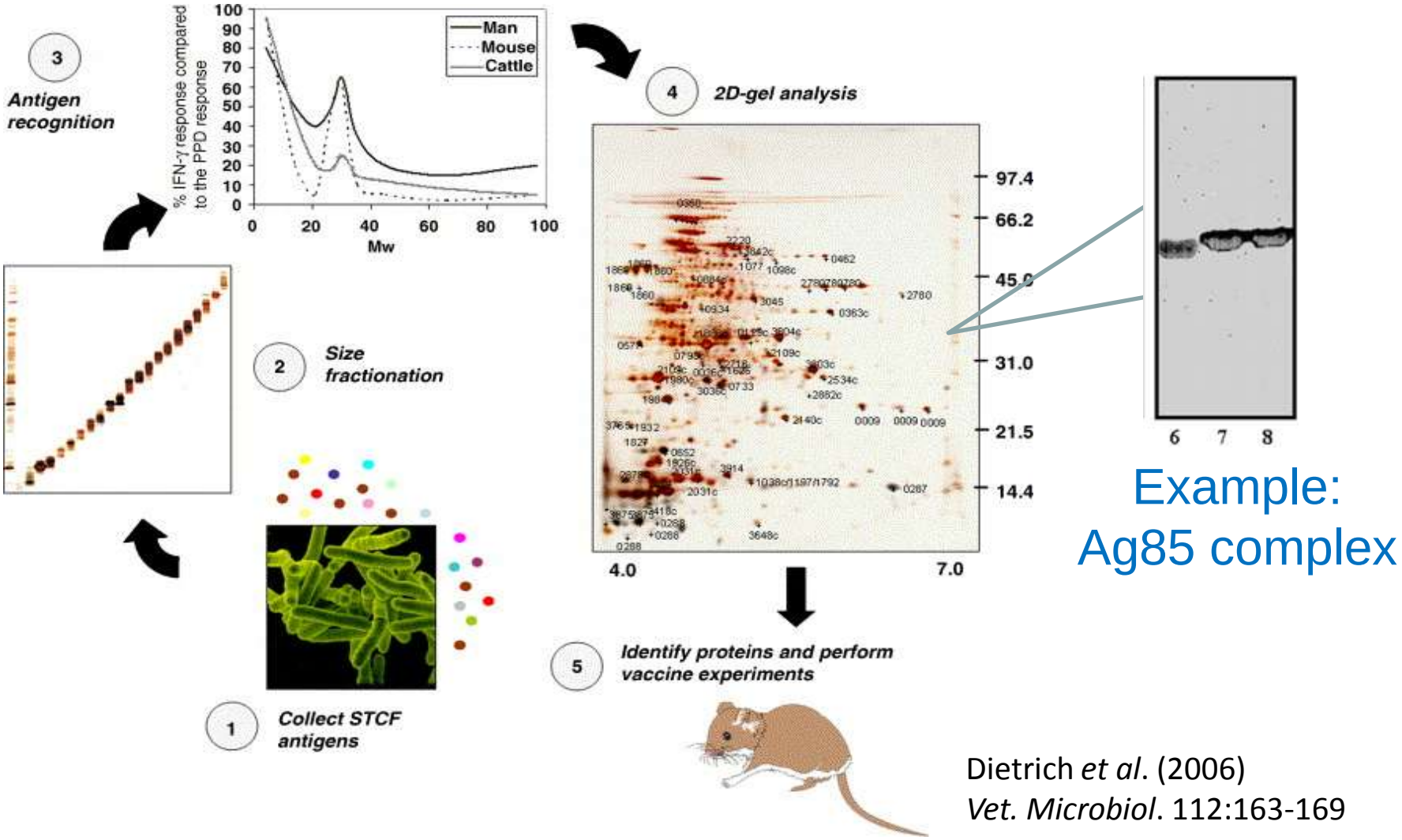
Recombinant mycobacterial prime



Kaufmann (2012) *Trends in Immunology*

New candidates: 3 examples

Pre-clinical: antigen mining



Example:
Ag85 complex

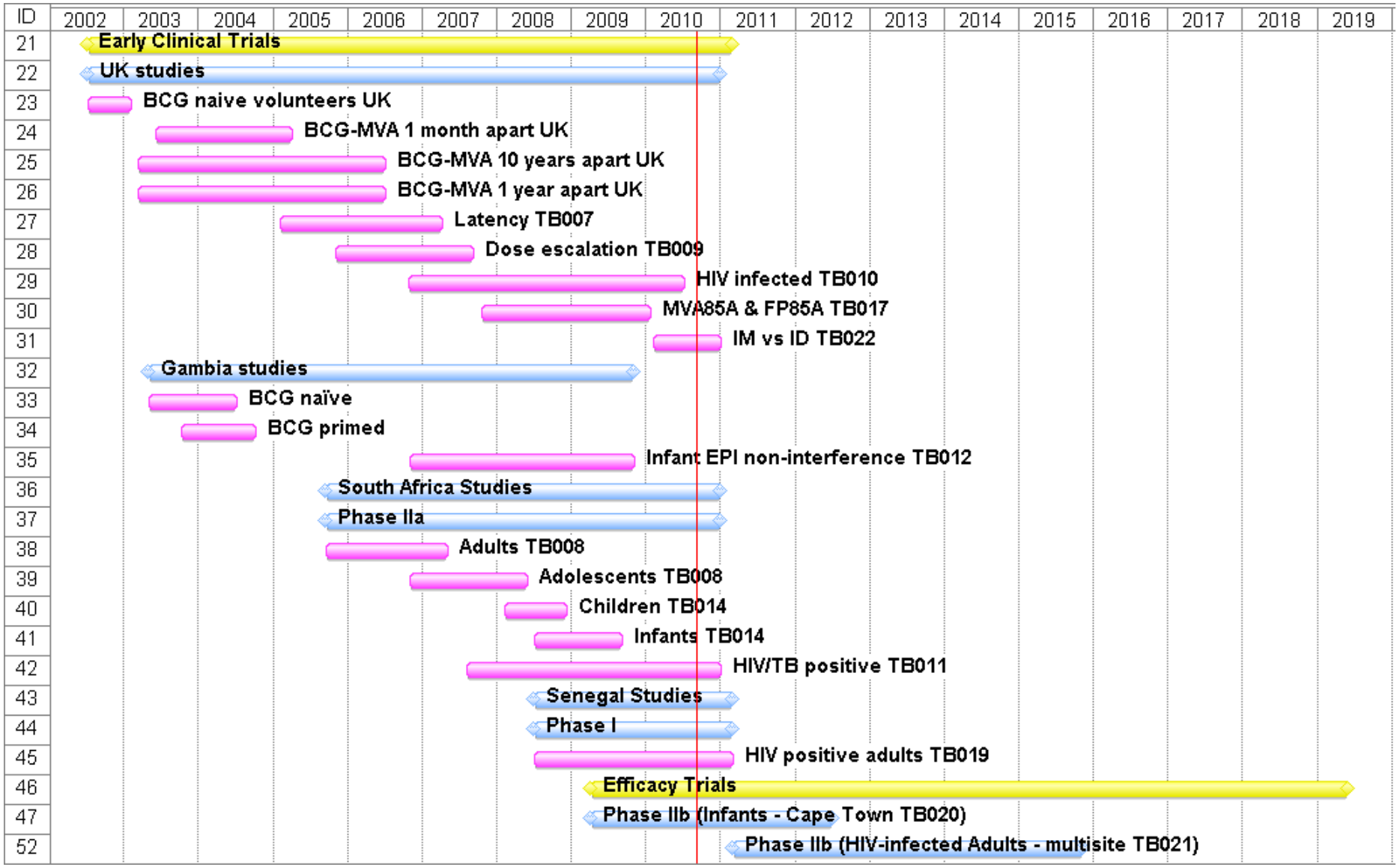
Dietrich *et al*. (2006)
Vet. Microbiol. 112:163-169

New candidates: Example 1

MVA85A

- MVA85A: Modified vaccinia virus Ankara + Ag85A
- BCG prime/MVA85A boost strategy
- Immunogenicity and protective efficacy demonstrated in various animal models
- 1st subunit vaccine in clinical trials
- Extensive preclinical and clinical data supporting immunogenicity and safety

MVA85A: Summary of clinical trials



McShane *et al*

New candidates: Example 1

But...

Immunogenicity of the Tuberculosis Vaccine MVA85A Is Reduced by Coadministration with EPI Vaccines in a Randomized Controlled Trial in Gambian Infants
Martin O. C. Ota *et al.*
Sci Transl Med **3**, 88ra56 (2011);

New candidates: Example 2

MTBVAC01

- *M. tuberculosis* Δ*phoP* Δ*fad26*
- Two attenuating mutations:
  - PhoP: part of 2-component regulator
  - FadD26: PDIM synthesis
- Confers protection in animal models
- More attenuated than BCG

New candidates: Example 2

Info / News

TB vaccine one step closer as a result of effective EU research and development

by TBEC Coordinator on Oct 17, 2012 • 1:40 pm No Comments

European scientists are one step closer to delivering a new, safe and more effective vaccine against tuberculosis developed through EU research funding, according to a press release from the European Commission published yesterday.

The live vaccine, MTBCAC, is the first to be based on Mycobacterium tuberculosis; a strongly weakened version of the bacterium that causes TB. It should stimulate the human immune system to recognise and eventually prevent TB infection. The TuBerculosis Vaccine Initiative (TBVI), who took part in the pre-clinical development of the vaccine, explain the trial as a big win for scientists all over Europe as the first candidate of its kind ever to be tested in humans.

Significantly, the press release symbolises how the vaccine pipeline for TB is better then it ever has been. Along with MTBVAC, MVA85A – the most advanced TB vaccine – is currently in phase 2b trials with results due later this year. Both of these, whether or not they go any further in the clinical trial stage, undoubtedly serve to advance TB vaccine research even further.

If MTBVAC does manage to pass tests and shows good immune responses, it will be able to move to the next phase of evaluation that involves larger and younger groups of volunteers.

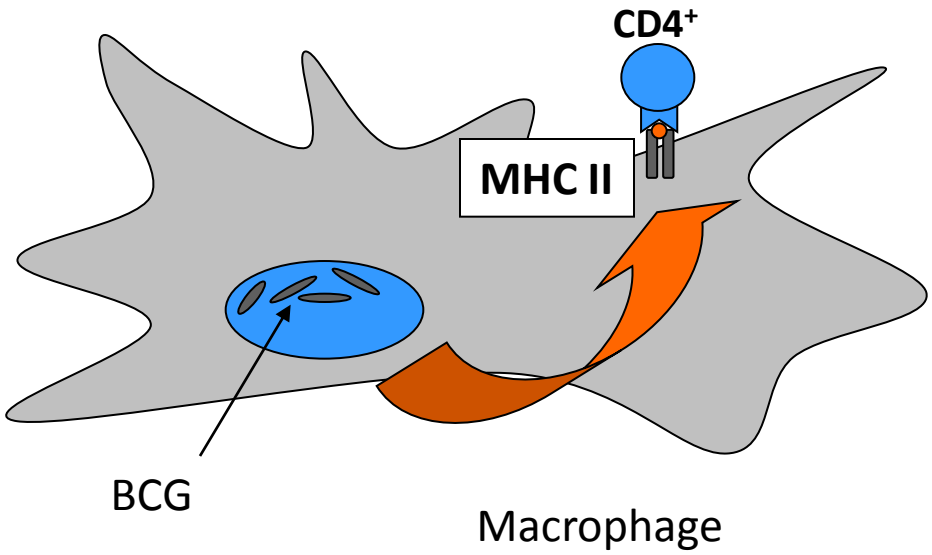
Crucially, it must be recognised that the vaccine is still in the early phases of clinical trials and it may not necessarily lead to anything. However, what is important is that it highlights how critical ongoing

New candidates: Example 3

VPM1002 (rBCG Δ*ure::hly*)

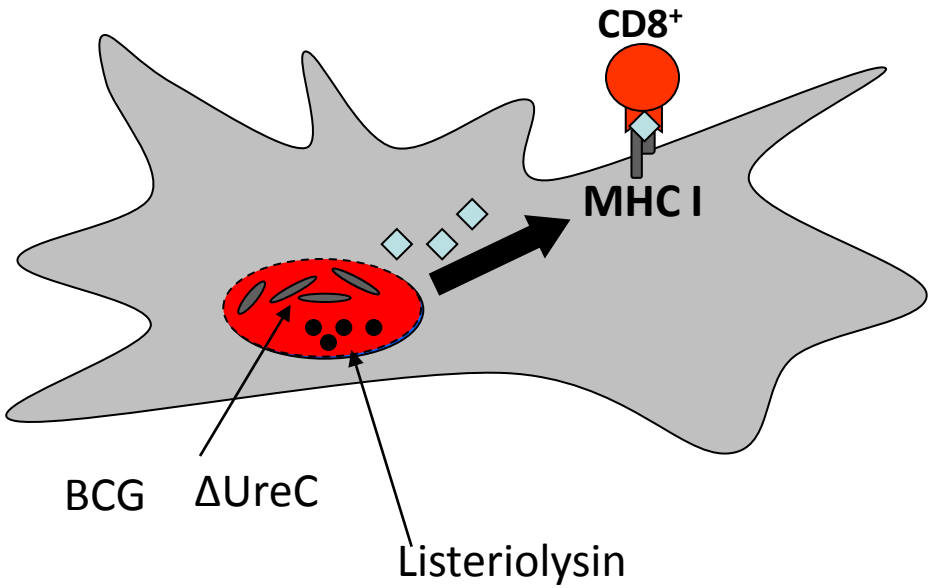
- Recombinant BCG lacking urease C gene, expressing listeriolysin
- Promotes antigen translocation to cytoplasm and enhanced apoptosis and antigen cross-presentation
- Superior protection in animal models
- Clinical Phase I in 2007

New candidates: Example 3



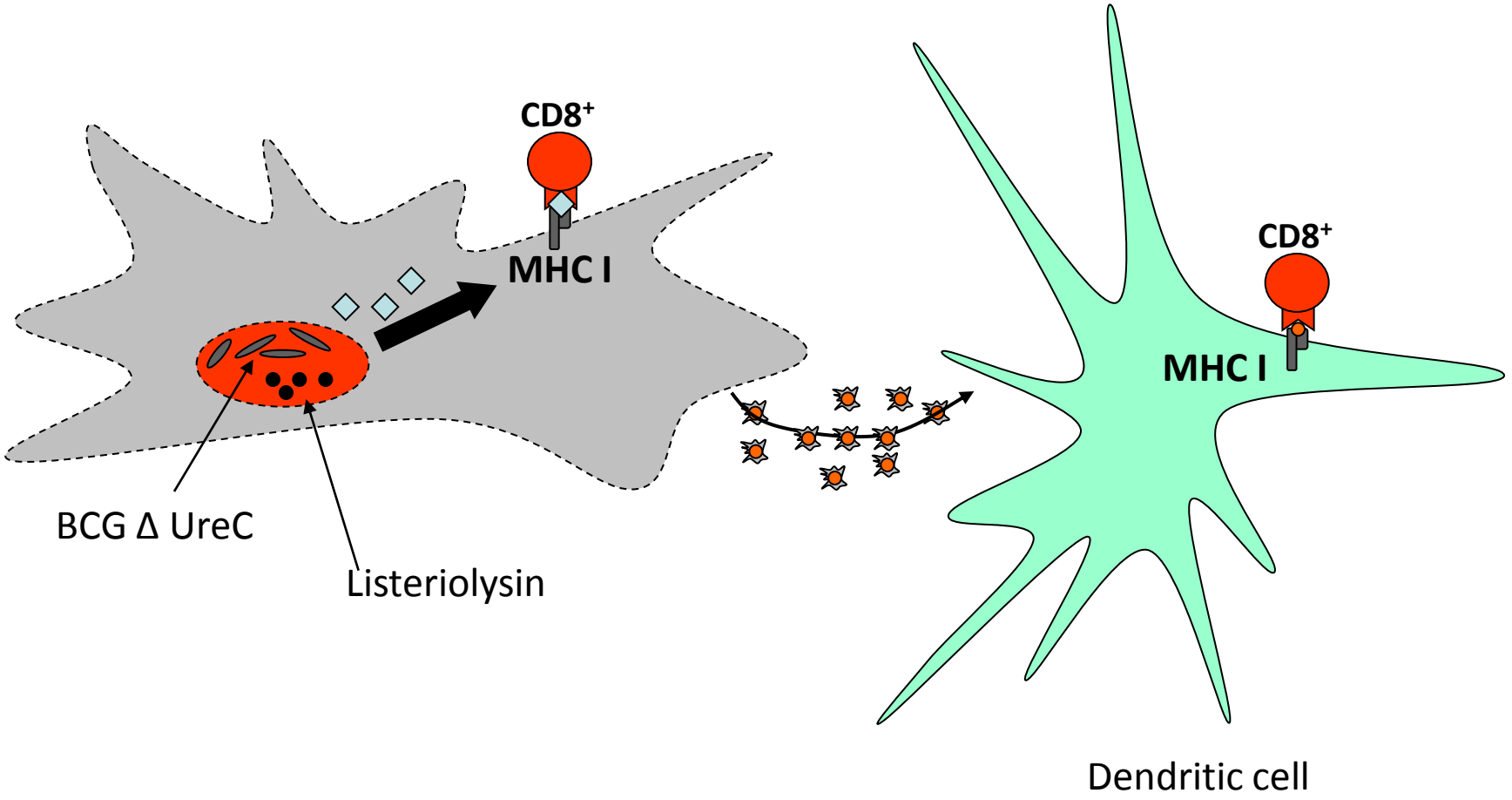
New candidates: Example 3

rBCG Δ*ure::hly*



New candidates: example 3

rBCG Δ*ure::hly*

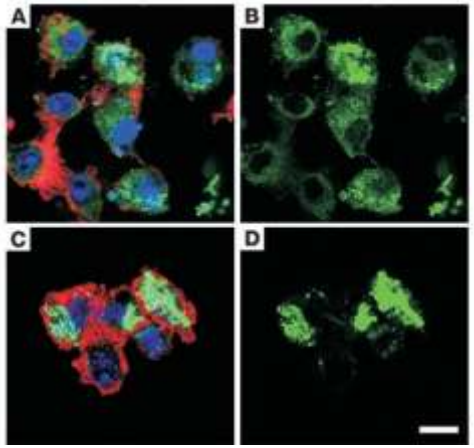


New candidates: rBCG Δ*ure::hly*$^{+}$

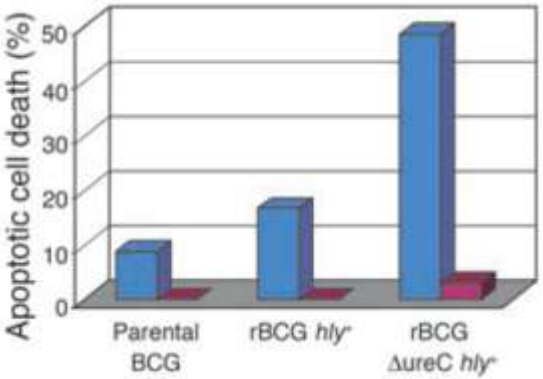
Promotes antigen translocation to cytoplasm

rBCG

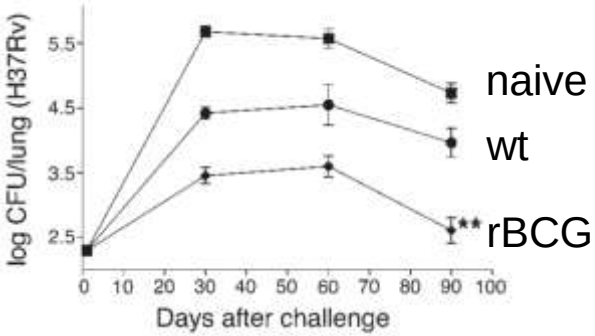
wt



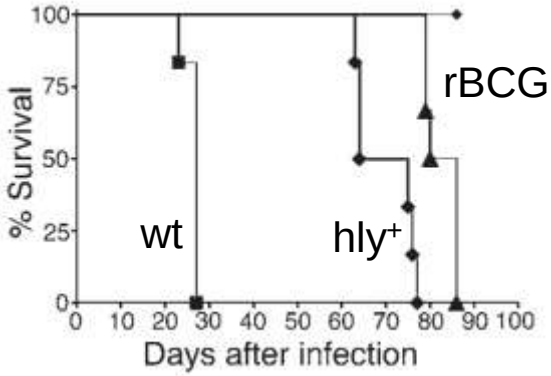
Enhances apoptosis (and cross-presentation)



Protection



Safety



Grode *et al*, (2005) J Clin Invest

Additional considerations

- Biomarkers
- Regulatory concerns
- Ethical issues
- Economic considerations
- Trial site infrastructure
- Route
- Timing/Application
  - Pre-infection
  - Booster
  - Post-infection
  - Adjunct to therapy

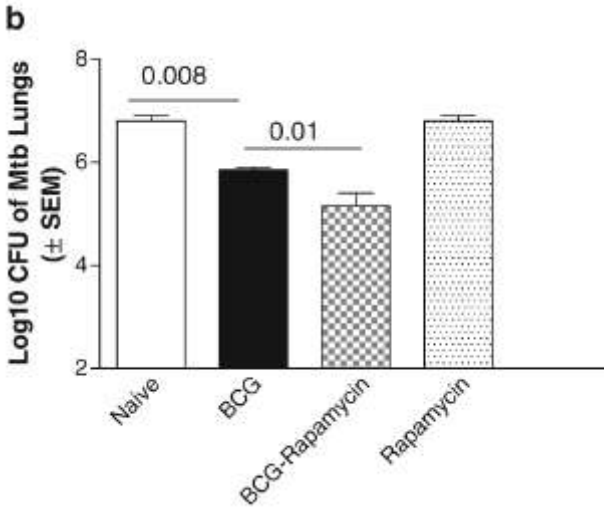
Novel Approaches?

- Immunomodulation

Methods Mol Biol. 2012 ; 821: 295–303. doi:10.1007/978-1-61779-430-8_18.

Rapamycin-Induced Enhancement of Vaccine Efficacy in Mice

Chinnaswamy Jagannath and **Pearl Bakhru**



Novel Approaches?

Drying a tuberculosis vaccine without freezing

Yun-Ling Wong*, Samantha Sampson†, Willem Andreas Germishuizen*, Sunali Goonesekera†. Giovanni Caponetti‡, Jerry Sadoff§, Barry R. Bloom†¶, and David Edwards*‖

PNAS | February 20, 2007

Oral Vaccination with Lipid-Formulated BCG Induces a Long-lived, Multifunctional CD4^{+} T Cell Memory Immune Response

Lindsay R. Ancelet[1], Frank E. Aldwell[2], Fenella J. Rich[1], Joanna R. Kirman[3]*

PLOS ONE September 2012 | Volume 7 | Issue 9 | e45888

New candidates: summary

Example	Some advantages
MTBVAC01	• safe • ease of production • wider antigenic repertoire
VPM1002 (rBCG Δure Hly+)	• “safe” • regulatory benefits • ease of production • superior immune response
MVA85A/Aeras-485	• safe • diagnostic benefits • ease of production • regulatory benefits

Summary

- BCG is current gold standard tuberculosis (TB) vaccine
- Variable efficacy of BCG demands new approaches
- New TB vaccine approaches to replace or boost BCG
    - Live (……)
    - Subunit (……)
    - Immune modulation (……)
    - Delivery systems (……)

Learning outcomes

- Outline the strengths and limitations of the current form of the TB vaccine, BCG
- Discuss how new TB vaccine candidates aim to overcome some of the limitations of BCG

References

1) Kaufmann (2011) Fact and Fiction in tuberculosis vaccine research: 10 years later. *Lancet Infect Dis.* 11:633-40 (Good general overview of TB vaccine development)
2) Brosch (2007) Genome Plasticity of BCG and Impact on vaccine efficacy. *PNAS*. 104:5596-5601 (Detail on history and genetic diversity of BCG strains)
3) Dockrell HM. (2008) Real vaccines in the real world: tuberculosis vaccines move south. *Expert Rev Vaccines*.7(6):703-7 (Comments on practical issues facing new TB vaccine development)
4) Tseng *et al* (2011) Cost-effectiveness of novel vaccines for tuberculosis control: a decision analysis study. *BMC Public Health*. 11:55 (Modelling analysis of cost-benefit of an improved TB vaccine)
5) Hesseling *et al.* (2009) Disseminated bacille Calmette-Guérin disease in HIV-infected South African infants. *Bull World Health Organ*. 87(7):505-11. (Underlines significant risk associated with BCG immunization of HIV-positive children)
6) Abu-Raddad *et al*. (2009) Epidemiological benefits of more-effective tuberculosis vaccines, drugs, and diagnostics. *Proc Natl Acad Sci USA*. 2009 106(33):13980-5 Use (Use of mathematical models to predict impact of various TB interventions)
7) Sander *et al*. (2009) Safety and immunogenicity of a new tuberculosis vaccine, MVA85A, in Mycobacterium tuberculosis-infected individuals. *Am J Respir Crit Care Med*. 179(8):724-33 (Details of Example 1)
8) Reed *et al* (2009) Defined tuberculosis vaccine, Mtb72F/AS02A, evidence of protection in cynomolgus monkeys. *Proc Natl Acad Sci U S A*. 106(7):2301-6 (Details of Example 2)
9) Grode *et al* (2005) Increased vaccine efficacy against tuberculosis of recombinant Mycobacterium bovis bacille Calmette-Guérin mutants that secrete listeriolysin. *J Clin Invest.* 115(9):2472-9 (Details of Example 3)
10) Tchilian *et al*. (2009) Immunogenicity and protective efficacy of prime-boost regimens with recombinant (delta)ureC hly+ Mycobacterium bovis BCG and modified vaccinia virus Ankara expressing M. tuberculosis antigen 85A against murine tuberculosis. *Infect Immun*. 77(2):622-31 (Details of Example 1 & 3)