BCG for Prime Vaccination: TB and Beyond TB

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NIAID/WHO Workshop:
Heterologous Prime-Boost Vaccine Strategies for HIV, Malaria and TB

17 – 18 April 2012
Fishers Lane Conference Center, Rockville
A short history of BCG

**Discoverers:** Albert Calmette and Camille Guérin

**Name:** Bacille Bilié Calmette Guérin

(continues passage on potato slices soaked with ox gall)

Later shortened to Bacille Calmette Guérin

1906: Start of **serial passage** of 14-day cultures

1908: 30th passage proved to be **safe and protective**

1919: 230th passage ready for **large-scale experiments** with: (i) cattle, (ii) experimental animals (guinea pigs, rabbits, non-human primates)

Albert Calmette 1863 - 1933

Camille Guérin 1872 - 1961
Agenda

- The complexity of current BCG
- r-BCG vaccine candidates for TB
- Further improvement of r-BCG
- r-BCG & homologous antigens
- r-BCG & heterologous antigens
A short history of BCG

**1921:** First vaccination of human newborn (household with one tuberculosis patient)

**1921-1924:** Mass vaccination of babies (households with at least one tuberculosis patient)

**1927:** Evaluation of 20,300 vaccinees:
- death of 25% of non-vaccinated newborns
- less than 1% death of tuberculosis amongst vaccinated newborns
- less than 5% of all death cases of vaccinated newborns
BCG Today

Protection:
• Against tuberculous meningitis and miliary TB in infants
  NB: protects against leprosy (PEM Fine)
But: No reliable protection against adult TB / transmission
  (variable efficacies)

Coverage:
• High (> 80%); part of the expanded program on immunization (EPI)
• Ca. 100 million children BCG-vaccinated per year
  Ca. 4 billion vaccinations thus far

Safety:
• Safe but adverse reactions possible
• Risk for HIV+ newborn

Immunology:
• CD4 Th1, Ab, some CD4Th17, few CD8

Prime-Boost:
Prime basis of current TB booster vaccine candidates
Figure 1. Summary of estimates of the efficacy of BCG (bacille Calmette-Guérin) vaccines against tuberculosis, as derived in randomized controlled trials, case-control studies, and household-contact studies. Note that vaccine efficacy (percentage reduction in risk attributable to vaccination) is expressed on a logarithmic scale. Bars indicate 95% confidence intervals. Dotted lines reflect interim analyses of unpublished studies. The two case-control studies carried out in Brazil (indicated by asterisks) were of tuberculous meningitis. See [2, 5] for primary sources.
Possible reasons for variations in BCG efficacy against pulmonary TB in adults (after PEM Fine with my own ideas)

<table>
<thead>
<tr>
<th>Reason</th>
<th>Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure to environmental mycobacteria</td>
<td>Likely; exposure can mask or inhibit protection due to: (low level) protection which cannot be increased by BCG or due to premature elimination of BCG by pre-existing immunity</td>
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<tr>
<td>BCG strains</td>
<td>Perhaps</td>
</tr>
<tr>
<td>Genetics of populations</td>
<td>Unclear</td>
</tr>
<tr>
<td><em>M. tuberculosis</em> genotypes</td>
<td>Likely; in animal models no or low BCG-induced protection against Beijing family members</td>
</tr>
<tr>
<td>Risk of infection</td>
<td>Probable</td>
</tr>
<tr>
<td>Age at vaccination</td>
<td>Probable; best protection against primary TB</td>
</tr>
<tr>
<td>Time since vaccination</td>
<td>Probable</td>
</tr>
<tr>
<td>Route and dose of BCG administration</td>
<td>Questionable</td>
</tr>
<tr>
<td>Nutrition</td>
<td>Questionable</td>
</tr>
<tr>
<td>Coinfections with helminths</td>
<td>Probable (Th2 vs. Th1)</td>
</tr>
<tr>
<td>Name</td>
<td>Synonym</td>
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<tr>
<td>Russia</td>
<td>Moscow</td>
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<td>Moreau</td>
<td>Brazil</td>
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<td>Sweden</td>
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<td>Danish</td>
<td>Copenhagen</td>
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<td>Prague</td>
<td>Czechoslovakian</td>
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<td>Glaxo</td>
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<td>Tice</td>
<td>Chicago</td>
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<td>Frappier</td>
<td>Montreal</td>
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<tr>
<td>Connaught</td>
<td>Toronto</td>
</tr>
<tr>
<td>Pasteur</td>
<td></td>
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</tbody>
</table>
Refined genealogy of BCG vaccines

From Brosch R et al. PNAS 2007
## General Use of Multiple BCG Vaccinations
*(Zwerling et al., PLoS Med 2011)*

<table>
<thead>
<tr>
<th>Country</th>
<th>Age of first BCG</th>
<th>Age of second BCG (years)</th>
<th>Age of third BCG (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Armenia</td>
<td>Birth</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Belarus</td>
<td>Birth</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Croatia</td>
<td>Birth</td>
<td>14</td>
<td>–</td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Birth</td>
<td>11</td>
<td>–</td>
</tr>
<tr>
<td>Kazakhstan</td>
<td>Birth</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>Norway</td>
<td>Birth</td>
<td>13–15</td>
<td>–</td>
</tr>
<tr>
<td>Russian Federation</td>
<td>Birth</td>
<td>7–14</td>
<td>–</td>
</tr>
<tr>
<td>Turkmenistan</td>
<td>Birth</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Ukraine</td>
<td>Birth</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Uzbekistan</td>
<td>Birth</td>
<td>7</td>
<td>14</td>
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</table>
Current status r-BCG and other mycobacterial carriers

<table>
<thead>
<tr>
<th>Preclinical</th>
<th>Clinical</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BCG Δzmp1</strong></td>
<td><strong>I</strong></td>
<td><strong>Antigen Presenting Cell</strong></td>
</tr>
<tr>
<td><strong>BCG RD1⁺</strong></td>
<td><strong>II</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mtb ΔphoP ΔfadD26</strong></td>
<td><strong>III</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Mtb ΔRD1 ΔpanCD</strong></td>
<td></td>
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<tr>
<td><strong>M. smeg Δesx-3::esx-3 (Mtb)</strong></td>
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**Antigen Presenting Cell**

- Phagosome
- Nucleus

**Mechanism of Action**

- MHC I
- MHC II

**Clinical**

- **VPM1002**
- **rBCG30**
- **AERAS-422**

**Kaufmann & Gengenbacher, Curr Opin Biotech, 2012**
F. Winau et al, Immunity 2006
U. Schaible et al, Nat Med 2003
C. Desel et al., JID 2011; unpublished
Status r-BCGΔure:Hly

- Highly efficient and safe in preclinical models (both lab strain & clinical isolate)
- Worldwide license to Vakzine Projekt Management (VPM).
- P1-level approved (GMO, genetically modified organism).
- Large-scale GMP production: achieved.
- Safety/toxicity achieved (VPM/BioProtect).
- Hygromycin resistance removed.
- Phase I trial: successfully completed (safety and immunogenicity) in Germany & South Africa (Sponsor VPM)
- Phase IIa trial in newborn: ongoing in South Africa Q4 2011 (Sponsor VPM).
Improvement of wild type and recombinant BCG vaccine

Construction of pro-apoptotic, pro-autophagic mutant (to enhance CD8 & Th17 T cell responses)
• Deletion of secA2 and nuoG from rBCG ΔureC-hly^+

Construction of safer rBCG (suitable for immuno-compromised newborns)
• Construction of auxotrophic strain (deletion of pdxH to make rBCG auxotrophic to vitamin B6)

Construction of r-BCG expressing additional antigens (for pre- & post-exposure and prime-boost)
• Starvation, dormancy, resuscitation antigens
Construction of new strains based on rBCG::ΔureC::hly backbone

- pMPIIB01
  - Plasmid-based expression of latency-associated antigens

Reece et al. Vaccine 2011
Immunogenicity of rBCG::ΔureC::hly(pMPIIB01)

IFN-γ measured after 72hr culture of splenocytes

Reece et al. Vaccine 2011
Improved protection by rBCG::ΔureC::hly(pMPIIB01) at day 200 p.i. After Beijing/W aerosol infection

Reece et al. Vaccine 2011
BCG as carrier for heterologous antigens

**Measles:** Fennelly et al., *JID* 172, 1995

**Papilloma virus:** Govan et al., *Vaccine*, 2006

**Pneumococcal pneumonia:** Langermann et al., *J Exp Med*, 1994

**Lyme disease:** Stover et al., *J Exp Med*, 1993; Edelman et al., *Vaccine*, 1999

**Pertussis:** Nascimento et al., *Microbes Infect.*, 2008

**Leishmaniasis:** Streit et al., *Exp. Parasitol.*, 2000

**Listeriosis:** Grode et al., *J. Immunol.*, 2002

**HIV:** Im et al., *J. Virol*, 2007; Rosario et al., *J. Virol*, 2010; Hopkins et al., *EJI*, 2011

**Malaria:** Matsumoto et al., *J Exp Med*, 1998; Arama et al., *Vaccine*, 2011; Arama et al., *Vaccine*, 2012