BCG: THE CURRENT VACCINE FOR TUBERCULOSIS & THE CHALLENGES FOR DEVELOPING NEW TB VACCINES

Thipchuta Bharnthong
Chief of Vaccine Production Department
Queen Saovabha Memorial Institute

THAI RED CROSS
The heroes of tuberculosis research
Robert Koch, Albert Calmette, Calmille Guérin
HISTORY OF BCG

BCG was derived from *Mycobacterium bovis*

- Calmette and Guérin studied on a strain isolated from a cow with tuberculous mastitis
- 13 years of subculture
- Demonstration of attenuation
  - unable to cause tuberculosis disease in research animals.
  - confer protection against TB in cattle
- They transferred the BCG strain to Pasteur Institute
- Live attenuated BCG vaccine was first given orally to infants in Paris
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1902</td>
<td>First isolation of <em>Mycobacterium bovis</em></td>
</tr>
<tr>
<td>1908-21</td>
<td>BCG development from serial passage of <em>Nocardia</em> strain</td>
</tr>
<tr>
<td>1921</td>
<td>First human BCG vaccination</td>
</tr>
<tr>
<td>1928</td>
<td>BCG was adopted as standard vaccine</td>
</tr>
<tr>
<td>1929-30</td>
<td>Lubeck disaster</td>
</tr>
<tr>
<td>1939</td>
<td>Multiple puncture technique</td>
</tr>
<tr>
<td>1948</td>
<td>First International BCG congress concluded that BCG is effective,</td>
</tr>
<tr>
<td>1948-74</td>
<td>WHO and UNICEF campaigns; 1.5 billion vaccinations carried out</td>
</tr>
<tr>
<td>1948-97</td>
<td>Yearly increase of BCG vaccination</td>
</tr>
</tbody>
</table>
The ‘Bacille Calmette Guérin’ (BCG)

- live attenuated vaccine
- very old vaccine
- has been used throughout most parts of the world
- have a protective effect in children
- doubts about its effectiveness in adult
- varies in efficacy in different population
- more concern in the era of HIV/AIDS
Failure of BCG

- Protective efficacy of BCG against adult pulmonary TB has varied widely in different geographic areas.

- Infection with environmental mycobacteria interferes with the induction of protection by BCG.
**Major Cause of Failure**

- Environmental mycobacteria interfere with BCG

  BCG is blocked before multiplication

  (due to the recognition by the immune system of antigens shared between environmental mycobacteria and BCG)

- BCG fails to prime T cells
Interaction between environmental mycobacteria and BCG

(A) Regions of higher latitude

BCG vaccination

T cell

T cell

IFN-γ

TB infection

T cell

T cell

T cell

T cell

T cell

IFN-γ

(TB complex specific antigens)

(Shared antigens)

(B) Tropical regions

Presensitisation

BCG vaccination

IFN-γ

TB infection

T cell

T cell

T cell

T cell

T cell

IFN-γ

(TB complex specific antigens)

(Shared antigens)
Problems with BCG Vaccination:

- It is a live vaccine and the property itself raises a question about its safety
- The tuberculin reaction cannot distinguish tuberculosis patients from BCG-vaccinated population

Solutions:

Mycobacterial protective antigen against TB should be isolated and non-living vaccine be constructed to replace BCG
Attempts to develop new TB vaccine have been limited

- Treatment is sufficient for global control
- General agreement exists that BCG can protect at least severe forms of tuberculosis in children
- Difficulties of research on a slow-growing bacteria
- Requiring biosafety containment
- Requiring multi-collaborations
Vaccines based on *M. tuberculosis*

- DNA vaccine (using genes encoding immunodominant mycobacterial antigens)
- Subunit vaccine (using specific proteins)
- Recombinant vaccine (using protection genes transferred into suitable vectors)
- Attenuated strain of *M. tuberculosis*
Vaccines based on BCG

• **Recombinant BCG** (Recombinant vaccine expressing of specific Ag)

• **BCG + boosting** its protective efficacy against adult forms of tuberculosis (Prime/Boost regimen)
# New TB Vaccine

## Five candidates in clinical trials

<table>
<thead>
<tr>
<th>Candidate</th>
<th>Description</th>
<th>Institution</th>
<th>Year</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA-85A</td>
<td>Mtb gene in vaccinia</td>
<td>Oxford</td>
<td>2014</td>
<td>(Boost)</td>
</tr>
<tr>
<td>M72f</td>
<td>protein in adjuvant</td>
<td>GSK</td>
<td>2014</td>
<td>(Boost)</td>
</tr>
<tr>
<td>rBCG30</td>
<td>recombinant BCG</td>
<td>UCLA</td>
<td>2015</td>
<td>(Prime)</td>
</tr>
<tr>
<td>Ag85B/ESAT-6</td>
<td>protein in adjuvant</td>
<td>SSI</td>
<td>2015</td>
<td>(Boost)</td>
</tr>
<tr>
<td>rBCGΔureC:Hly</td>
<td>recombinant BCG</td>
<td>Max Planck</td>
<td>2015</td>
<td>(Prime)</td>
</tr>
</tbody>
</table>

Completion of phase 3
Challenges of New TB Vaccine Development

- using BCG in novel ways
- modify BCG to make it more uniformly effective

Type of New TB vaccine:
1) BCG Prime, rBCG * Boost
2) BCG Prime, Sub-unit vaccine* Boost

*M.tuberculosis* gene / protein
(MPT64, ESAT-6 may be used as key Ag)
The new generation of TB vaccines will likely work best via a strategy called "prime-boosting."

An initial vaccine would be administered; this "prime" inoculation would be followed by a "booster" shot of a different vaccine. Researchers believe this "prime-boost" strategy will not only enhance protection, but also extend protection over a longer period of time.

An improved and modern recombinant BCG vaccine (rBCG) would be the "prime" given to newborns to teach their body to recognize and respond to TB.

This would be followed by a "booster" inoculation with a recombinant protein, to be given at time intervals to be determined in clinical trials. This "booster" shot would be designed to stimulate the body's memory immune cells. "Prime-boost" regimens of this sort have proved to be powerful inducers of cellular immune responses in humans.

www.aeras.org
- QSMI has the experiences in mass-cultivation of BCG
- QSMI has know-how in live vaccine manufacturing
- QSMI has a production plant designed with biosafety containment facilities
- QSMI has the potential of BCG vaccine production in compliance with GMP
ความสำคัญของ BCG

• เป็นวัคซีนที่ได้รับพระราชทานจากพระบาทสมเด็จพระเจ้าอยู่หัวให้สร้างโรงงานผลิตขึ้นภายในประเทศ
• เป็นวัคซีนที่ผลิตได้เองตั้งแต่เชื้อเริ่มต้นมี Know-how อยู่แล้ว
• รูปแบบของวัคซีนที่พัฒนามาถึงปัจจุบันเป็นที่ยอมรับว่าทัดเทียมกับวัคซีนต่างประเทศ
• เชื้อ BCG สายพันธุ์ที่มีอยู่มีคุณค่ามากสำหรับการวิจัยและพัฒนาเป็นรูปแบบของ Recombinant vaccine
Advantages of BCG

- Non pathogenic organism
- Very low incidence of complication
- Can induce CMI and long-lasting
- BCG is a potent adjuvant: enhanced immunization with rabies vaccine (Arch virol 1981; 69: 167-76)
- Its remarkable immunostimulating properties have been used for immunotherapy
- Protective effects on the immune responses to heterologous antigens
A favourable development in TB control

new vaccine will add something to BCG

New BCG is a challenge
Critical Success Factors

- Community advocacy for new TB vaccine
- Increase knowledge about the value of new vaccine
- Basic science development capacity
- Promising vaccine candidates
- Clinical trial Field Site infrastructure
- Demonstrated efficacy
- Manufacturing infrastructure
Thank you