The importance of BCG strain differences in determining bladder cancer efficacy
Global Burden

• In 2019,
  – 10 million new cases of Tb
  – 1.2 million TB deaths among HIV neg
  – 0.2 million TB deaths among HIV-pos
• Bacille Calmette-Guérin (BCG) – only available vaccine
  – Protects (>80% efficacy) against severe Tb (meningitis and miliary) in children
  – Adolescents and Adults: variable efficacy
BCG vaccination practices by country

Global Burden

• Historically,
  – BCG strains considered to possess ‘equivalent’ vaccine properties
  – Only one BCG strain usually selected for vaccine studies

• Advances in genomics and understanding of virulence mechanisms of M. tb - re-evaluate assumptions about strain differences
Conclusions

- BCG strains differ genetically
- Are their strain differences?
- Do strains have differences in efficacy?
BCG: History
History of BCG vaccine

• Timeline
  – “Lait de Nocard” – *M. bovis* isolated from cow with Tb mastitis
  – 1908-Pasteur Institute (Calmette and Guerin)
  – 1915-Cows then guinea pigs
  – **1921- First** administered to baby
  – 1921-1924- 217 Paris children
  – 1924 – Mass production began
In vitro evolution of BCG

• Despite efforts to standardize the growth and preparation of the vaccine, different passaging conditions were used in different production laboratories.

• Dozens of distinct daughter strains emerged:
  – BCG-Pasteur
  – BCG-Japan (Tokyo-172)
  – BCG-Danish (Copenhagen-1331)
  – BCG-Glaxo
Genealogy of BCG strains

BCG strains in TB Efficacy

- 5-10% of infected individuals develop active TB disease
- Correlates of protection not available
- Head-to-head trials not been done
Platinum Priority – Bladder Cancer

Editorial by XXX on pp. x–y of this issue

Bacillus Calmette-Guérin Strain Differences Have an Impact on Clinical Outcome in Bladder Cancer Immunotherapy

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Abstract

Background: Whether the commonly used bacillus Calmette-Guérin (BCG) strains Connaught and Tice confer different treatment responses in non–muscle-invasive bladder cancer (NMIBC) is unknown.

Objectives: To compare clinical efficacy, immunogenicity, and genetics of BCG Connaught and Tice.

Design, setting, and participants: A prospective randomized single-institution trial with treatment of 142 high-risk NMIBC patients with BCG Connaught or Tice.

Intervention: Patients were randomized to receive six instillations of BCG Connaught or Tice. For experimental studies, BCG strains were compared in C57Bl/6 mice. Bladders and lymphoid tissues were analyzed by cytometry and the latter cultivated to detect live BCG. BCG genomic DNA was sequenced and compared with reference genomes.

Comparison and outcomes: After 1 year, no differences were found in clinical outcomes. Immunogenicity and BCG virulence were higher with Connaught than Tice, whereas Tice induced more BCG-specific T-cell responses in vivo and in vitro. BCG strains differed in virulence-related genes, whereas Mycobacterium bovis BCG con003 was found to be homologous with BCG Connaught and BCG Tice.

Conclusion: BCG strain differences may impact clinical outcomes in the treatment of NMIBC. Furthermore, BCG strain-related differences in immunogenicity and virulence are likely related to different virulence-related genes.
Intravesical BCG instillations

Analysis of adaptive immune response

(b) PBS Tice Conn aught

(c) Mtb32309-318 Tetramers

(d) CFUs / DLN
Are some BCG strains better than others?

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<tr>
<th>Survival Probability at 5 yr</th>
<th>95% CI</th>
<th>p</th>
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<tbody>
<tr>
<td>Connaught</td>
<td>74%</td>
<td>62.8-87.2%</td>
</tr>
<tr>
<td>Tice</td>
<td>48%</td>
<td>35.5-65.1%</td>
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A Prospective Comparative Study of Intravesical Bacillus Calmette-Guérin Therapy with the Tokyo or Connaught Strain for Nonmuscle Invasive Bladder Cancer
Atsushi Sengiku, Masaaki Ito, Yu Miyazaki, Harutake Sawazaki, Takeshi Takahashi, Keiji Ogura
S1602 Trial Schema

Randomize

CIS, HG TA, or HG T1 bladder cancer

Intravesical BCG
- TICE (50 mg/dose)

Intravesical BCG
- (Tokyo strain 80 mg/dose)

Prime: intradermal BCG
- (Tokyo strain 100 µl at 0.5 mg/ml)
- Intravesical BCG
  - (Tokyo strain 80 mg/dose)