“Tuberculosis Vaccination: toward new regimens”

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Remembering heroes of tuberculosis vaccine research

BCG vaccine: success and failure story

- *M. bovis* BCG – the only vaccine licensed for human use.
- BCG vaccine – administered by the intradermal route.
- Large percentage of world’s total population is vaccinated with BCG.
- Effective against childhood meningitis and extra-pulmonary tuberculosis.
- Ineffective against adult pulmonary tuberculosis.
- Protective efficacy - blocked/masked by exposure to environmental mycobacteria.
- Protective immunity - difficult to improve by subsequent booster doses.
- BCG failure - an impetus for search of new vaccines.
Hiding inside: cell mediated immunity is the key

Envisioning future vaccination strategies using new generation vaccines

Different types and combination of second generation vaccines would require:
- Pre-infection priming vaccines
- Post-exposure booster vaccines
- Therapeutic vaccines

Scenario 1: BCG vaccinated adult
Scenario 2: BCG non-vaccinated adult

Scenario 3: newborn child

The most advanced TB vaccine candidates in clinical trials and their status

- Subunit vaccines:
  - ESAT-6 and Ag85B fusion protein (Hybrid-1) + IC31 – Andersen, SSI, Denmark
  - TB 10.4 and Ag85B fusion protein (Hybrid-2) + IC31/DDA-TDB - SSI, Denmark
  - Recombinant MVA expressing Ag85A – Hill and McShane, Oxford University, UK

- Recombinant BCG vaccines:
  - rBCG expressing Ag85B (rBCG30) – Horwitz, UCLA, US
  - rBCG expressing listeriolysin (ΔlureC Hly rBCG) – Kaufmann, Max Plank, Germany
The new entrants in the clinical arena

- AERAS TB vaccines:
  - AERAS 401/AFRO-1: Endosomal BCG escape
  - AERAS 402: Ad35 expressing Ag 85 A, Ag 85 B, TB 10.4
  - AERAS 403: Reactivation-TB10.4, Ag85 Rv3407, Rv2660C
  - AERAS 404: Hyvac4
  - AERAS 405: Oral vaccine
  - AERAS 406: Anti-Latency
  - AERAS 407: Multistage-BCG which over-expresses Ag 85A, 85B, 10.4, Rv3407, 40 DosR
  - AERAS 408: Pro-apoptotic

- Attenuated TB vaccines: - PhoP+FadD mutant

- DNA vaccine: - HVJ-liposome/ HSP-65DNA+IL12 DNA

- Other subunit vaccines: - Mtb glycolipids, HBHA

- Other rBCG vaccines: - rBCG-RD1

Post-exposure and therapeutic vaccines

- Staten Serum Institute post-exposure vaccines:
  - Hybrid56 (Ag85B-ESAT6-Rv2660c) + DDA-MPL/ODA-TDB
  - Hybrid32 (Ag85B-ESAT6-Rv2631c) + DDA-MPL/ODA-TDB
  - HyVac21 (Ag85A-TB10.4-Rv2660c) + DDA-MPL/ODA-TDB
  - HyVac28 (Ag85B-TB10.4-Rv2660c) + DDA-MPL/ODA-TDB
  - Rv2659c + DDA-MPL/ODA-TDB

- AERAS post-exposure vaccines:
  - Resuscitation factors (Rv6A/Rv987c; Rv1884c; RvD/Rv2388c) + Dormancy associated (Rv3133-DosR)
  - RUTI (M. tuberculosis cell wall)

- CSU post-exposure vaccine: - Rv1411-ESAT-6 fusion protein

Therapeutic vaccine: - Killed M. vaccae

Prime-boost strategies

AERAS Global TB Vaccine Foundation Approach - Dr. Jerald Sadoff
**Mucosal Vaccines**

- Current TB vaccine strategies are aimed at breakdown of disease or reactivation rather than preventing infection
- Tuberculosis - a pulmonary disease
- Intranasal immunization - effective against respiratory diseases
- Nasal vaccines:
  - Nasal subunit – Alanine proline rich antigen + DDA/MPL
  - Intradermal BCG prime – Nasal subunit boost (Arabinomannan covalently linked to Ag85B + L3 adjuvant)

Intranasal BCG immunization induces significantly high specific Th1 response in the lungs

![Diagram showing immune responses](image)

*A representative of immune responses studied at 12 weeks p.i.m. is depicted*

**Frequency of antigen specific IFN-γ secreting cells in the lungs of i.n. BCG immunized mice**

![Diagram showing immune responses](image)
**Frequency of antigen specific IFN-γ and IL-2 secreting cells in the lungs of i.n. subunit cocktail immunized mice**

*Immune response was evaluated at 2 weeks p.i. *

**Immunogen specific antibody isotype levels in nasal lavage of i.n. subunit cocktail immunized mice**

**Our observations**

- Intranasal BCG immunization induces superior Th1 response in the lungs as compared to s.c. immunization.
- Intranasal BCG or subunit immunization induces widespread immunity in mucosal and systemic compartments.
- *M. tuberculosis* Apa was highly immunodominant among all vaccine candidates evaluated following i.n. BCG and subunit cocktail-DDA-MPL immunization.
- Apa appears to be a promising candidate for a future mucosal subunit vaccine against TB.
Progress and advances: Entry of new players

- Bill and Melinda Gates Foundation
- AERAS Global TB Vaccine Foundation
- TB-VAC Consortium
- WHO and TB Vaccine Task Force
- Industry partners – GlaxoSmithKline, Intercell, Crucell etc

Challenges and concerns

- Funding - $
- Regulatory issues
- Correlates of protective immunity
- Surrogate markers of protection
- Training, manufacturing, IP concerns
- Animal models

Tuberculosis Vaccination: past, present and future

Kaufmann SHE – Max Planck Institute, Berlin, Germany

If it's tough to make predictions, especially about the future. – Yogi Berra
Summary

- Increasing consensus to replace or improve BCG.
- Entry of second generation vaccines in clinics.
- Prime-boost approach might be the key for success.
- > $1.5 billion needed.
- CDC – a major role to play.

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