Immunoassays in Phase I/II Trials of New TB Vaccines

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Immunogenicity, Efficacy & Effectiveness

- BCG is highly immunogenic
- BCG can be highly efficacious
- BCG has not been highly effective
- New TB vaccines must do all 3
  -in Phase I/II immunogenicity only
- No certain immunological correlates
  -in Phase I/II trials study carefully

Selection of Phase I Candidates

- Animal data demonstrating safety
- Induction of Type 1 immunity in animals
- Animal data demonstrating efficacy ≥ BCG
- Ideally lack PPD cross-reactivity
- Mucosal & systemic vaccine candidates
- Long-term industrial support

Immunoassay Target Population Issues

- Initial Target Population:
  - Healthy, young adults
  - PPD negative, HIV negative
  - Avoid highest TB exposure risks
- Later Target Populations:
  - PPD+ without active disease
  - Likely need larger sample sizes

Immunoassay Trial Design Issues

- Sample size (initially identify large effects)
- Vaccination routes & schedules
- Kinetic immunity (peak/memory)
- Controls (pre-vaccine/concurrent placebo)
- Comparisons with BCG immunogenicity
- Randomized and double-blinded evaluations

Basic Immune Considerations

- Type 1 immunity (Th1/CTL)
- Th1 memory precursors vs effectors
  -IFN-γ vs IL-12R vs Tbet
- CTL IFN-γ/perforin/proliferation
- Inhibition of mycobacterial growth

Immunologic End Points for TB Vaccines

- Ag specific cellular immunity
- Live mycobacteria stimulation
- Purified mycobacterial antigen
- Type 1 immunity (Th1/CTL)
- Mycobacterial growth inhibition
- Effects on PPD-specific DTH

Specific Immunoassays

- Ag-specific lymphoproliferation
- Ag-specific IFN-γ responses
  -Whole blood vs PBMC secretion
  -Cytokine ELISPOT assays
  -Intracellular cytokine stimulation
- Ag-specific inhibitory T cells
  -Whole blood inhibition
  -Primary lymphocyte inhibition
  -Secondary lymphocyte inhibition

Pros/Cons of Proliferation Assays

- Easy with fresh whole blood/PBMC
- Measures functional expansion capacity
- Validated in BCG vaccine trials
- Not specific for Type 1 immunity
- Not highly correlated with inhibition
- Less useful with frozen samples (esp. with small samples sizes)

Pros/Cons of IFN-γ Secretion Assays

- Easy with fresh whole blood/PBMC
- Measures Type 1 immunity
- Validated in BCG vaccine trials
- Uncertain immune subset origin
- Not highly correlated with inhibition
- Less useful with frozen samples (esp. with small samples sizes)

Pros/Cons of IFN-γ ELISPOT Assays

- Minimally labor intensive/expensive
- Can enumerate Th1 vs Tc1 cells
- Enhanced sensitivity/specificity?
- Identifies peak effector responses
- Does not measure proliferative capacity
- Uncertain correlation with inhibition
- Not yet validated in BCG vaccine trials
- Less useful with frozen cells
  (esp. with small sample size)

Pros/Cons of Intracellular IFN-γ Detection Assays

- Fresh stimulation/frozen transport
- Can enumerate Th1 vs Tc1 cells
- Enhanced sensitivity/specificity?
- Identifies peak effector responses?
- Does not measure proliferative capacity
- Expensive due to Flow Cytometry
- Uncertain correlation with inhibition
- Not yet validated in BCG vaccine trials

Pros/Cons of Mycobacterial Growth Inhibition Assays

- Measure most relevant immune function
- Validation in BCG vaccine trials
- Whole blood simpler/unclear mechanism
- 1° lymph assays detect intracellular effects
- 2° lymph assays detect intracellular effects
- LAs labor intensive, therefore expensive
- Better prediction of in vivo protection?
- Most successful with fresh samples

Intradermal BCG Challenge Model

- Could measure in vivo protection
- Efficacy estimates in small sample sizes
- Validation of immune correlates
- Intradermal infection not usual natural route
- Unknown variability of measureable endpoints

Advancing Beyond Phase I Trials

- No initial safety concerns
- Immunogenicity > BCG or enhanced safety
- Induction of inhibitory T cells
- Repeat phase I in PPD+ population
- Dose/Schedule/Route optimization trials
- Phase I/II studies in high risk populations