# TB Vaccine Development: Challenges & Opportunities

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# In my talk I plan to address

- What makes prevention of TB so special?
- Where do we need to dig deeper?
- Is there light at the end of the tunnel?

# The TB "enigma"

- About 90% of immunocompetent individuals infected with *M. tuberculosis* do not develop active disease during their entire lifespan, whereas untreated HIV-infected individuals or individuals suffering from congenital cytokine/receptor deficiencies (IFNg, IL-12) have a hugely increased susceptibility

  - *Conclusion: the human immune system can mount a protective (CD4$^+$ T cell only?) immune response against TB and it should be possible to increase this capacity using a vaccine*

  - *Question: since there is something immunologically, genetically, environmentally "special" about the remaining 10% - will we ever be able to reach them (all) using a vaccine ?*

# The BCG "enigma"

- BCG protects (a) children against non-pulmonary TB, (b) against leprosy and (c) in certain populations – mostly outside tropical regions – reasonably well and potentially for a very long time against pulmonary TB

- In order to protect, BCG must be alive and be given early in life. Immunity against TB cannot be boosted by a subsequent BCG shot.
  - Question 1: the above phenomena are often explained by the action of differing densities of "environmental/non-tuberculous" mycobacteria: is that true and what is the consequence for 2nd generation TB vaccines?
  - Question 2: Wherever BCG protects reasonably well against pulmonary TB, protective efficacy peaks around 60% : is that a ceiling for any vaccine or a sign of the insufficient protective quality of BCG?

# Where to dig deeper: (a) Mode of prevention

- Primary  focus currently: prevention of primary disease and/or reactivation
- Broaden that focus:
  - Sterilizing immunity, ie kill the bug at entry
  - Transmission-blocking
  - Prevent reinfection/relapse
  - Therapeutic vaccination
  - (passive vaccination?)

# Where to dig deeper: (b) Pre- & nonclinical

- Aim to do "better than nature", i.e. rethink the focus on immunodominant T cells antigens
  - subdominant AGs, AGs from different stages of the "lifecycle", role of Abs/non-protein AGs
- Pick up promising approaches from other fields at an early stage , e.g. replicating vectors
- More relevant animal models, .e.g. transmission models
- More relevant bioassays, e.g. "functional assays", translate progress in systems biology into field tools

# Where to dig deeper: (c) Clinical

- Speed up pre-licensure evaluation by more efficient and earlier candidate up-selection and more efficient Test-of-Concept trials
- Experimental medicine trials, including "human challenge" models
- Develop trial sites in different regions with different epidemiological criteria
- Participate in the identification of new regulatory approaches to clinical trial approval and vaccine licensure

# Where to dig deeper:
# (d) Community & Stakeholders

- Strengthen decision making in high-endemicity countries on selection of vaccine type, clinical trial performance, etc, e.g. through building regulatory capacity
- Involve high endemicity countries in all steps of the vaccine development continuum, i.e. research, development and manufacture
- Facilitate participation of communities at a higher level, e.g. "Global Community Advisory Board"
- Synergize the work of the vaccine development community more efficiently, e.g. through an "Global TBVI" or "CAVD-equivalent", global portfolio management , etc

# The silver lining: Indicators of Feasibility

- 90% of imunocompetent individuals infected with *M. tuberculosis* do not develop disease during their entire lifespan
- Human immunology – Humans with IL-12 and INF γ pathway defects highly susceptible to TB
- BCG has been shown to be long-term protective against pulmonary TB in certain populations
- Infectious challenge models of protection against TB in animals have demonstrated superiority of some new vaccines over BCG (alone)

# Thank you for your attention

& the following colleagues & friends for useful discussions in preparation of this talk:

Gilla Kaplan, Christine Sizemore, Mike Brennan & Willem Hanekom and many more


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