Clinical development of ID93 + GLA-SE as a prophylactic or therapeutic vaccine for tuberculosis

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Strategies for TB Vaccine Development

Prophylactic
  Pre-infection
    - prevent infection and/or disease
    - either initial or sustained infection
  Post-infection
    - prevent disease
    - prevent reactivation from latency

Immunotherapy
  - shorten the course of chemotherapy for active TB
  - decrease relapse or reinfection rates
What Type of Immune Response Should be Elicited by an “ideal” TB Vaccine

Prophylactic
- Elicit a protective response from a naïve-like baseline
- Pulmonary tissue resident T-cell memory
- Functional antibodies patrolling lung spaces
  - Orchestrate Mtb killing
  - Attract and activate innate cells
  - Antibody-dependent cellular phagocytosis
  - Antibody-dependent cellular cytotoxicity
- Rapid recall response that traffics to lung
- Long-lasting memory response

Therapeutic
- Elicit an immediate effector response through boosting and redirect existing response
- T cells trafficking to lung and inside lesions
  - Lethal effector functions within inflamed environment and amidst moderate antigen load
  - Avoid exacerbating disease and inducing harmful pathology
- Functional antibodies reach lesion interior
- Durable memory to protect from re-infection
# Current TB Vaccine Landscape

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Candidate</th>
<th>Stage</th>
<th>Potential Advantages / Disadvantages</th>
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</thead>
<tbody>
<tr>
<td><strong>Protein Subunit</strong></td>
<td>M72/AS01E</td>
<td>Phase 2b</td>
<td><strong>Safety</strong> - safety/reacto varies</td>
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<tr>
<td></td>
<td>H56:IC31</td>
<td>Phase 2a</td>
<td><strong>Immunology</strong> - offers multivalency, both T cell and Ab response</td>
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<tr>
<td></td>
<td>H4:IC31</td>
<td>Phase 2a</td>
<td><strong>Manufacture</strong> – easy, locally produced, cost varies by adjuvant</td>
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<tr>
<td></td>
<td>ID93 + GLA-SE</td>
<td>Phase 2a</td>
<td></td>
</tr>
<tr>
<td><strong>Viral Vector</strong></td>
<td>Ad5 Ag85A</td>
<td>Phase 1</td>
<td><strong>Safety</strong> - safety/reacto varies</td>
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<tr>
<td></td>
<td>ChAdOx185A/MVA 85A</td>
<td>Phase 1</td>
<td><strong>Immunology</strong> – few antigens, strong T cell response, low antibody response</td>
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<tr>
<td></td>
<td>TB/FLU-04L</td>
<td>Phase 2a</td>
<td><strong>Manufacture</strong> – ease? cost?</td>
</tr>
<tr>
<td><strong>Killed / Inactivated / Extract</strong></td>
<td>Vacciae</td>
<td>Phase 3</td>
<td><strong>Safety</strong> - safety/reacto could vary?</td>
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<tr>
<td></td>
<td>DAR-901</td>
<td>Phase 2b</td>
<td><strong>Immunology</strong> – many antigens but individual variability?</td>
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<tr>
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<td>RUTI</td>
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<td><strong>Manufacture</strong> – ease? consistency? in country? cost?</td>
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<tr>
<td><strong>Live / Attenuated</strong></td>
<td>VPM 1002</td>
<td>Phase 3</td>
<td><strong>Safety</strong> - safety/reacto could be an issue</td>
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<td>MTBVAC</td>
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ID93 + GLA-SE

- **ID93** is a fusion of 4 Mtb antigens with diverse roles, recognized in exposed individuals, protection in mouse models, and no human sequence homology
  - *Rv1813* - Up-regulated under hypoxic conditions
  - *Rv2608* - PPE protein, outer-membrane associated
  - *Rv3619* - EsX protein family of secreted virulence factors
  - *Rv3620* - EsX protein family of secreted virulence factors

- **GLA-SE** is a synthetic TLR-4 agonist adjuvant formulated in a squalene oil in water nano-emulsion
  - *Demonstrated safety thus far*— another TLR4 ligand adjuvant has been approved for licensure
  - *Induces Th1-biasing response* (even in existing strong Th2 environment)
  - Readily *scalable* for *local production* at *low cost*

<table>
<thead>
<tr>
<th>Total people</th>
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<tbody>
<tr>
<td>ID93 + GLA-SE &gt; 200</td>
</tr>
<tr>
<td>GLA-SE &gt; 1000</td>
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</tbody>
</table>
Pre-Clinical Data: Proof of principle in mice, guinea pigs, and non-human primates

Prophylactic

Therapeutic
TBVPX-113: Phase 1a Study in the US

- **Design**: first in human, phase 1, randomized, double-blind, dose-escalation
- **Population**: 60 BCG-, QFT-, healthy adults
- **Safety**: good
- **Immunogenicity results**:
  - GLA-SE increases T cell magnitude and polyfunctionality
  - GLA-SE increases antibody response; IgG1 and IgG3 but not IgG2 or IgG4
  - *Multi-functional* antibodies post ID93+GLA-SE vaccination

Poster by Day et al.
GLA-SE increases antibody functionality

A

IFNγ

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<tr>
<th>Day0</th>
<th>Day84</th>
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</thead>
<tbody>
<tr>
<td>ID93</td>
<td>ID93+GLA</td>
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MIP1β

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CD107a

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ADCP

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B

ID93

- IgG1
- IgG2
- IgG3
- IgG4
- IgM
- IgA1
- IgA2

C

Polyfunctionality

Data Courtesy of Lennette Lu and Galit Alter, Ragon Institute
TBVPX-114: Phase 1b in South Africa

- **Design:** randomized, double-blind, dose-escalation
- **Population:** 66 BCG+, QFT+/-, adults
- **Safety:** good
- **Immunogenicity:**
  - More robust CD4 responses in QFT+ adults suggests boosting from natural infection
  - QFT+ express more IFN-γ
  - Multivalent vaccine increases complexity of T-cell response
  - Tem (immediate effect) + Tcm (long lasting)
Multivalency lends complexity for CD4 T cell responses

**Rv2608**
Whole blood assay data from Adam Penn-Nicolson and team, SATVI

**Rv3620**

Vaccination on Day 0, Day 28, Day 112

A spectrum of T cell phenotypes are induced by individual antigens: potentially with diverse functionalities
TBVPX-203: Phase 2a in South Africa

- **Design**: randomized, double-blind, placebo-controlled
- **Population**: 60 HIV-, BCG+, treated TB patients
- **Safety**: good
- **Interim immunogenicity data** on 1st cohort
  A. CD4 T cells boosted similarly to QFT+ individuals
  B. Antibody responses appear higher than in QFT+ individuals

Preliminary conclusion: Post TB treatment patients are not immunosuppressed in ways that impair T-cell or antibody responses to ID93 + GLA-SE
Clinical Trials with ID93 + GLA-SE

Completed Trials

Phase 1
TBVPX-113
N=60
- BCG- QFT-

Phase 1b
TBVPX-114
N=66
- BCG+ QFT-
- BCG+ QFT+

Phase 2a
TBVPX-203
N=60
- BCG+ QFT+
- TB patients

PoR
Phase 2b
TBVPX-204
N=840
- BCG+ QFT+
- TB patients

Planned Trials

Phase 1
DMID 12-0109
Liposomal
N=70
- BCG- QFT-

Phase 1
TBVPX-120
Lyophilized
N=48
- BCG- QFT-

Pol
Phase 2
N=180
Quratis
- BCG- QFT-
- Healthcare workers

Therapeutic
Phase 1/2

Therapeutic
Phase 1/2

BCG+ QFT+
BCG+ DS TB patients
BCG+ MDR patients

BCG+ MDR patients
Conclusion:

- **ID93 antigens are unique and diverse**: Rv2608, Rv3619, Rv3620, Rv1813
  - PE/PPE family, ESX-family, hypoxia-related
- **GLA-SE adjuvant appears safe and is amenable to low cost local manufacture**
  - TLR4-agonist target
  - Synthetic
    - readily scalable, low cost
    - is being manufactured in endemic countries
  - Dose sparing
- **Immune response profile – Th1 with strong functional antibody responses**
  - Spectrum of CD4 T cell differentiation and memory profiles
  - Most functional IgG subclasses against all 4 antigens
- **Acceptable safety profile** in Mtb-naïve, Mtb-infected, and TB patients at end of treatment
- **Poised for**
  - Phase 2b proof of concept testing for prevention of recurrence in treated TB patients, prevention of infection/disease
  - Safety testing in TB patients during treatment (DS and MDR)
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