DAR-901: inactivated *Mycobacterium obuense*

A whole cell non-tuberculous mycobacterial vaccine booster

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Correcting the record on BCG before we license new vaccines against tuberculosis

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1. BCG as a prime is >70% effective in mycobacteria-naïve infants

2. BCG as a prime is highly effective for 20 years, with lower levels of efficacy demonstrable for 50 years.

3. BCG as a prime is effective against pulmonary tuberculosis

4. There are no data to support a geographical differences in the efficacy of a BCG prime in mycobacteria-naïve infants

5. Multiple live and inactivated whole cell vaccines have been shown effective in the prevention of tuberculosis in humans

6. Data on heterologous immunity supports the development of vaccines based on any species within the genus *Mycobacteria*
M. obuense SRL172 (agar)
A multiple dose booster vaccine

Heat-inactivated, whole-cell preparation derived from rough variant of an environmental non-tuberculous mycobacterium (NTM)

Background
- Originally developed by J. Stanford & G. Rook
  - Goal was a *therapeutic* vaccine for treatment of active TB
  - Designated *M. vaccae* based on phenotypic methods
  - 16s rRNA now indicates 99.92% homology with *M. obuense*

Animal studies
- Immunogenic and effective in *preventing* TB
  (Skinner, Hernandez-Pando, Abou-Zeid)

GMP product manufactured by SR Pharma (*agar-based method*)
- 0.1 mL intradermal dose contained estimated $10^9$ CFU
- Demonstrated safe and well-tolerated in humans
SRL172 – Dartmouth Phase 1, 2 and 3 Trials

- Dartmouth group conducted an entirely independent SRL-172 development program, including safety, immunogenicity, and efficacy studies.
- All studies investigator-initiated (funding: NIH, EGPAF, Sigrid Juselius Foundation)
- All results presented in peer-reviewed publications
SRL172 Phase 3 booster vaccine study 2001-2008 (DarDar Trial)

- Placebo-controlled, randomized (1:1), double-blind, GCP
- **Eligibility**: BCG scar, HIV positive, CD4≥200
- **Location**: Dar es Salaam, Tanzania
- **Funding**: US National Institutes of Health
- **Intervention**: 5 intradermal doses of SRL 172 or placebo
- **Endpoints**
  - Primary: TB bacteremia (disseminated)
  - Secondary: All culture positive TB

2013 subjects randomize (1:1) to SRL-172 (0, 2, 4, 6, 12 mo) or Placebo.
SRL-172 Phase 3 Results

At year 7, DSMB recommended the trial be stopped based on efficacy in preventing definite TB. The only new TB vaccine in development to have shown efficacy in humans.

Table 3. Study endpoints and protection against tuberculosis.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Intention-to-treat (n = 2013)</th>
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<tbody>
<tr>
<td></td>
<td>No. of endpoints</td>
</tr>
<tr>
<td></td>
<td>MV</td>
</tr>
<tr>
<td>Disseminated tuberculosis</td>
<td>7</td>
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<tr>
<td>Definite tuberculosis</td>
<td>33</td>
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<tr>
<td>Probable tuberculosis</td>
<td>48</td>
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Median follow-up = 3.3 years
**M. obuense** DAR-901 (broth)  
A multiple dose booster vaccine

Target product profile
- BCG booster for adolescents and adults

Broth-grown manufacturing process developed
- Robust, scalable, high yield fermentation process
- Cost $1.5-2 per dose

Pre-clinical studies completed
- Animal toxicology studies
- IFN\(\gamma\) and antibody dose response in 2 murine species
- TB challenge study in BCG-primed mice
  - 1 mg DAR-901 boost x2 confers greater protection against TB challenge than BCG boost*

IND filed with US FDA

*Lahey et al. PLoS One, 2016*
59 adult subjects in US with prior BCG: IGRA neg, IGRA pos, HIV neg, HIV pos

Dose escalation cohorts 0.1, 0.3, 1 mg → 1 mg best response

Three-injection series 1 mg DAR-901 was safe, well tolerated, and immunogenic
- Injection site reaction (ISR) at 7 days, median 6-10 mm erythema
- Cellular and humoral immune responses, no IGRA conversions

Support: Dartmouth, Aeras, Byrne Foundation
DAR-901: Injection site 7 days after intradermal injection
IFN-γ Responses to Vaccine Sonicate

SRL172 x 5 (agar)  
Phase 3, N = >400

DAR-901 x 3 (broth)  
Phase 1, N = 10

Graph showing IFN-γ response to MVS, pg/ml.
Antibody to LAM

SRL172 x 5 (agar)
Phase 3, N = >400

DAR-901 x 3 (broth)
Phase 1, N = 10
DAR-901 Phase 2b prevention of infection trial in adolescents in Tanzania (DAR-PIAT)

Goal: Prevent new TB infection (defined by neg IGRA → pos IGRA)
Sample size: 650 adolescents age 13-15
Eligibility: BCG scar, negative IGRA at baseline and 2 months
Design: Randomized (1:1) to DAR-901 or placebo at 0,2,4 mos
Follow-up: repeat IGRA at 2, 12, and 24 months
Status: Apr 2016 – Start
Feb 2017 – 632 complete 3 doses; safe, well-tolerated
Dec 2018 – Last subject, last visit (scheduled)
## DAR-PIAT: Baseline T-spot IGRA results

<table>
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<tr>
<th>Baseline IGRA</th>
<th>n (%) (N=931)</th>
<th>Baseline TB Status*</th>
<th>Trial Eligibility</th>
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<tbody>
<tr>
<td>Positive</td>
<td>152 (16%)</td>
<td>Infected</td>
<td>Ineligible</td>
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<tr>
<td>Negative</td>
<td>757 (81%)</td>
<td>Uninfected</td>
<td>Eligible</td>
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</table>

*Remaining 3% ”borderline” or invalid

* Based on interpretation of T spot IGRA
# DAR-901 Development Plan

<table>
<thead>
<tr>
<th>Year</th>
<th>Task Description</th>
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<tr>
<td>Q4 2018</td>
<td>Complete Phase 2b Prevention of Infection (POI) trial in Tanzania</td>
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<tr>
<td>Q1 2020</td>
<td>Establish design &amp; venue for Phase 3 Prevention of Disease (POD) trial</td>
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<tr>
<td>Q1 2025</td>
<td>Complete Phase 3 POD trial</td>
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## Acknowledgements

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