Inactivated *Mycobacterium obuense*

A whole cell non-tuberculous mycobacterial vaccine booster

SRL172 (agar)
DAR-901 (broth)

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Keiko Nakamura, MD, PhD - Tokyo Medical and Dental University
Robert D. Arbeit, MD - Tufts University School of Medicine
Greetings from Dartmouth, New Hampshire, USA

- Dartmouth College, founded 1769, 9th oldest in the US
- Dartmouth Medical School, founded 1784, 4th oldest in the US
Global TB elimination by 2035
(World Health Organization)

Current global trend: -2% / year

Optimize current tools, pursue universal health coverage & social protection -10% / year

Introduce new vaccine, new prophylaxis -> -17% / year
Objective and Goals

1. To develop DAR-901 as the first new TB vaccine to meet Preferred Product Characteristics (PPCs) developed by the World Health Organization (WHO) in October 2017:
   - Booster for BCG in adolescents/adults
   - Efficacy ≥50% against TB disease
   - Safe, including in HIV

2. To establish a pharmaceutical partnership to complete the final stages of development

3. To license DAR-901 by 2025, the WHO target date for introduction of a new TB vaccine.
New TB vaccines in clinical trials

- Preclinical
- Phase I
- Phase IIa
- Phase IIb
- Phase III

Vacciae/Anhui
M72:AS01E/GSK/Aeras
DAR-901/Dartmouth/Aeras
rBCG\ureC::hly/VM1002/MPIIB/VM/SII
RUTI/Archivel
H1:IC-31/SSI/Valneva
H56:IC-31/SSI/Valneva/Aeras
H4:IC-31/Aeras404/SSI/Sanofi
ID93:GLA-SE/IDRI/Aeras
Ad5Ag85A/McMaster U
MTBVAC/U Zaragoza/Biofabri/TBVI
MVA85A-MVA85A/UOXF
Ad35+MVA85A/Aeras
TB-FLU-04L/RIBSP
SRL 172 - A multiple dose boosting vaccine

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

The organism
- *Mycobacterium obuense* (first described from Obu, Japan)
- Vaccine strain was isolated from soil in Uganda by Stanford and Rook (UK)

GMP vaccine manufactured by SR Pharma (*agar-based method*)
- 0.1 mL intradermal dose administered in multiple dose series
- Demonstrated safe and well-tolerated in humans
### SRL 172 - Dartmouth Phase 1, 2 and 3 Trials

(multiple dose)

<table>
<thead>
<tr>
<th>Phase</th>
<th>Site</th>
<th>SRL172 (N)</th>
<th>Control (N)</th>
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<tbody>
<tr>
<td>1</td>
<td>US HIV -</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>US HIV+</td>
<td>23</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>US HIV+</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Zambia</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>Tanzania</td>
<td>~1000</td>
<td>~1000</td>
</tr>
</tbody>
</table>

- 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
- **Intervention**: 5 intradermal doses of SRL 172 (or placebo)
- **Endpoints**
  - Primary: TB bacteremia (disseminated)
  - Secondary: All culture positive TB

2000 subjects randomize (1:1) SRL-172 (0, 2, 4, 6, 12 mo) Placebo
SRL-172 Phase 3 Results

At year 7, DSMB recommended the trial be stopped based on efficacy in preventing definite TB.

DAR-901 is the only new TB vaccine in development to have shown efficacy in humans.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Intention-to-treat (n = 2013)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of endpoints</td>
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<tr>
<td></td>
<td>MV</td>
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<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
DAR-901

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
- IFNγ and antibody dose response in 2 murine species
- TB challenge study in BCG-primed mice
  - Boost with 1 mg DAR-901 x3 confers greater protection against TB challenge than boost with BCG *

IND filed with US FDA

DAR-901 Phase 1 dose escalation

- 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 comparable to 5 doses of SRL-172
- Partnership support: Dartmouth, Aeras, Byrne Foundation

P = phlebotomy: P1, P2, P3 obtained prior to respective doses
ISR = injection site reaction examination 7 days after each dose
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

Interferon gamma response to DAR-901 (pg/ml)

Placebo
MV
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 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 IGRA results

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

Risk factors for IGRA positive vs IGRA negative
(multivariable analysis)

- Encounters with traditional alcohol beverage drinkers.
- House with one living room
- Limited sunlight in living room or bedroom
- Residing close to health facility
- Contact with TB patient at school

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

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
<th>Partners</th>
</tr>
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<tbody>
<tr>
<td>Q4 2018</td>
<td>Complete Phase 2b Prevention of Infection (POI) trial in Tanzania</td>
<td>GHIT partnership</td>
</tr>
<tr>
<td>Q1 2020</td>
<td>Establish design &amp; venue for Phase 3 Prevention of Disease (POD) trial</td>
<td>GHIT partnership</td>
</tr>
<tr>
<td>Q1 2025</td>
<td>Complete Phase 3 POD trial</td>
<td>Pharmaceutical partner &amp; GHIT</td>
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</table>
DAR-901 Summary

Advantages for a pharmaceutical partner

• De-risked product in advanced stage of development
• Extensive safety data, including in HIV
• Efficacy demonstrated in fully powered Ph3 RCT
• Robust, economical manufacturing method
• License available from (non-profit) Dartmouth College, USA
• Development support from GHIT
• Meets WHO PPC and is on target for 2025 registration
• US FDA registration would provide Priority Review Voucher
• Global market: Billions of adolescents and adults
• Unique opportunity to make a high-profile contribution to global health
• Market entry for non-communicable diseases in low income countries
• Potential for vaccine-based prevention of pNTM in developed countries
ありがとうございます

Thank you for your attention

And our thanks to GHIT for critical support in the development of DAR-901
End here
Options for Phase 3 POD Trial Design*

*Both options assume the following:
- Randomized (1:1) Vaccine : Placebo
- Endpoint: Xpert, culture, or smear positive TB
- Vaccine efficacy 50%, power = 0.8

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<tr>
<th>Characteristic</th>
<th>Trial A</th>
<th>Trial B</th>
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<tr>
<td>Population</td>
<td>Healthy household contacts</td>
<td>HIV patients</td>
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<tr>
<td>No. per arm</td>
<td>8000</td>
<td>2000</td>
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<tr>
<td>Duration – enroll</td>
<td>1 yr</td>
<td>2 yr</td>
</tr>
<tr>
<td>Duration – follow-up</td>
<td>3 yr</td>
<td>3 yr</td>
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<tr>
<td>Location</td>
<td>India</td>
<td>Tanzania</td>
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<tr>
<td>No. of sites</td>
<td>10</td>
<td>2</td>
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DAR-901 boost superior to BCG boost

Mice primed with BCG, boosted with BCG or DAR-901, then challenged with live MTB

Key Findings

Dose response with increasing DAR-901 dose

1 mg DAR-901 boost superior to BCG boost ($P = 0.036$ lungs $P = 0.028$ spleen)
BCG booster will have a greater effect on TB rates than new BCG prime

- Study using low income countries with endemic Tb and modeling reduction in TB cases with a new vaccine at different levels and durations of efficacy.
- A new effective booster vaccine gives greater reduction in TB cases in first 10 years.

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Efficacy over 10 yrs</th>
<th>Reduction in TB cases</th>
<th>Cost effective vaccine price</th>
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<tr>
<td>New BCG prime (infant)</td>
<td>80%</td>
<td>2%</td>
<td>$\leq1.36$</td>
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<tr>
<td>Booster for BCG (adult)</td>
<td>40%</td>
<td>40%</td>
<td>$\leq6.44$</td>
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Booster vaccine efficacy of 20% would be cost-effective at $1.19
## Acknowledgements

<table>
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<tr>
<td>Dartmouth</td>
<td>Richard Waddell</td>
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<td>Timothy Lahey*</td>
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<td>Juhani Eskola, Matti Ristola</td>
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<td>Ajit Lalvani*</td>
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<tr>
<td>Other</td>
<td>John Modlin (Seattle)</td>
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<td>Karim Manji (Dar)</td>
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<td>Dan Hoft (St. Louis)</td>
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Antibody to LAM

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

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

Antibody response to lipoarabinomannan (OD)

- Placebo
- MV

Visit 1, Pre-dose 2, Post-dose 3 Day 7, Post-dose 3 Day 28, Post-dose 3 Day 56, Post-dose 3 Day 180
The current vaccine: BCG

Live, attenuated *Mycobacterium bovis* bacille Calmette Guerin (BCG) — is the *most widely used vaccine* in the world.

In endemic countries, immunization at birth is routine

Efficacy of BCG in infancy (“prime”)

— 50-80% protection through childhood
— After age 15-20, protection wanes

Efficacy of second BCG (“boost”)

— 0%

New TB vaccines in development

- BCG prime for infants
- BCG booster for adolescents/adults