THE H1/H56 TB SUBUNIT VACCINE - AN UPDATE

Peter Andersen
Statens Serum Institut
Denmark
H1/H56 FUSION PROTEINS AND ADJUVANTS

**Cationic particles (IC31)**
- **Vehicle**: Cationic peptide (KLK)
- **PAMP**: ODN1a (TLR 9)
- **Profile**: Th1 - Memory

**Cationic liposomes (CAF01)**
- **Vehicle**: Cationic Surfactant (DDA)
- **PAMP**: TDB (Mincle)
- **Profile**: Th1/Th17 - Memory
H56 VACCINATION PROMOTES LESS DIFFERENTIATED TCM LIKE T CELLS

CXCR3 (IP10 receptor)

H56

Naïve → Naive

TNF-α → IL-2 → IL-2/TNF-α → IFN-γ

Central memory

Effector memory

EBL infection

KLRG1+ (exhaustion marker)

Woodworth et al., Mucosal Imm. 2016
H56 SPECIFIC T CELLS FROM THE LUNG VASCULATURE EFFICIENTLY TRAFFIC INTO THE LUNG

Control or H56-vacc.
C57BL/6 (CD45.2)

IV label
Harvest lungs

Transplant IV+CD4+ cells

Infect Mtb

IV stain

Ctrl
H56

KLRG1

IV stain

Blood vessel
Airway (BAL)
Lung Parenchyma

CD45-FITC

Input (IV+ESAT6+)

Recipient (ESAT6+)

IV stain

Woodworth et al., Mucosal Imm. 2016
H56/CAF01 promotes a population of less differentiated/Tcm like KLRG1- CXCR3+ recirculating IL2 +T cells that efficiently home into the lung parenchyma.
H56/IC31 BOOST BCG IN NHP’S

Experiment 1

- None
- BCG
- BCG+H56/IC31

Surviving animals (%)

0 20 40 60 80

0 20 40 60 80 100

Survival

Experiment 2

- None
- BCG
- BCG+H56/IC31

Surviving animals (%)

0 20 40 60 80

0 20 40 60 80 100

Experiment 3

- None
- BCG
- BCG+H56/IC31

Surviving animals (%)

0 20 40 60 80

Unvaccinated group

N=10

weeks 0

BCG

H56/CAF01

H56/CAF01

Mtb (10 CFU)

Mtb (10 CFU)

necropsy

18F-FDG PET/CT

Lin et al. JCI 2012
Phase I – Safety (low endemic, NL)
Adjuvant dose escalation study
Healthy adults, N=36

Phase I - Safety (high endemic, ET)
M.tb. naive / BCG vacc / LTBI
Adults, N=48

Phase Ila - Target population
Antigen dose / schedule study
In depth immunogenicity
240 adolescents, SATVI, ZA

Phase Ila - HIV infected
Adults, N=48
Aurum inst, ZA, Bagamoyo TZ
Phase I - “First In Man”
Safety / Antigen dose-escalation study
Relevant target pop. (Healthy / LTBI)
N=25, SATVI, ZA

Phase IIa – Dose / Schedule study
Relevant target pop. (Adults +/- LTBI)
N=98, SATVI, ZA, dose recently unblinded

Phase IIa - Safety in TB patients
Safety and dose finding
H1/H56 OVERALL PICTURE FROM CLINICAL TRIALS

• Safe – well-tolerated with minimal reactogenecity at site of injection

• Longlived CD4 response

• A T cell response dominated by IFNγ+/IL2+/TNF+ and IL2+/TNF+ with a TCM/TEM phenotype
**H56:IC31 PREVENTION OF INFECTION TRIAL**

**EPI pilot**
- 4% conversion confirmed at Mwanza

**Vaccine**

**ESAT-6 free IGRA conversion**

**Q3 2017**

<table>
<thead>
<tr>
<th>Sites</th>
<th>Mwanza, Tanzania</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aurum, South Africa</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>AERAS</td>
</tr>
<tr>
<td><strong>Trial duration</strong></td>
<td>24 months</td>
</tr>
<tr>
<td><strong>Vaccine efficacy</strong></td>
<td>50%</td>
</tr>
<tr>
<td><strong>Incidence</strong></td>
<td>4% IGRA conversion / yr</td>
</tr>
<tr>
<td><strong>Loss to follow up</strong></td>
<td>15%</td>
</tr>
<tr>
<td><strong>Power</strong></td>
<td>80%</td>
</tr>
<tr>
<td><strong>Significance level</strong></td>
<td>0.05</td>
</tr>
<tr>
<td><strong>Sample size/arm</strong></td>
<td>700</td>
</tr>
<tr>
<td><strong>Expected prim. endpoints</strong></td>
<td>44</td>
</tr>
</tbody>
</table>
ACKNOWLEDGEMENTS

TB Vaccine
Rasmus S. Mortensen
Claus Aagaard
Rolf Billeskov
Niels Peter Knudsen
Joshua Woodworth
Thomas Lindenstrøm
Helena Clemmesen

TB Vaccine Developm.
Ingrid Kromann

Adjuvant Research
Dennis Christensen
Jes Dietrich
Gabriel K. Petersen
Signe T. Schmidt

Human Immunol.
Morten Ruhwald
Thomas Blauenfeldt
Line L. Holm

Collaborators/partners
Flynn, Lin and DiFazio; Pittsburg Uhrdahl; Seattle BioMed
Scriba, Hateril and Nemes; SATVI Churchyard; Aurum Institute
Grevall; Bergen Universiy Ginsberg, Tait, Lempicki; AERAS Kidola, Changalucha, Mwanza,Tanzania SATVI; Tom Scriba
Dyrhol-Riise; Oslo Copenhagen University
Friis,Faurholt-Jepsen,Bengaard; Copenh. Ottenhoff; LUMC

wellcome
trust

European Commission

ADITEC

EDCTP

AERAS

The Research Council of Norway

TBVAC 2020

TBVI

GLOBAL TB VACCINE FOUNDATION

valneva