TB subunit vaccines adjuvanted with the cationic adjuvants CAF01 and IC31

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SSI TB-vaccine fusion proteins

**H4**
- Ag85B
- TB10.4

Boost an existing BCG-induced immunity
- Infants – children
- BCG vaccinated

**H1**
- Ag85B
- ESAT-6

Prevent acute TB disease as well as reactivation of existing latent infection
- Adolescents
- With or without latent infection

**H56**
- Ag85B
- ESAT-6
- Rv2660
Adjuvants for the TB subunit vaccines

**Cationic liposomes (CAF01)**
- **The vehicle**
  - DDA (Dimethyldioctadecyl ammonium bromide) (Cationic surfactant)
  - Depot formation/slow release
- **The immunostimulant**
  - TDB (Mycobact. cordfactor) (Mincle)
- **The immune response**
  - Th1/Th17/Humoral
  - Longlived memory

**Cationic particles (IC31)**
- **The vehicle**
  - Poly leucine/lycine peptide (Cationic peptide)
  - Depot formation/slow release
- **The immunostimulant**
  - ODN1a (TLR 9)
- **The immune response**
  - Th1/(humoral)
  - Longlived memory
## SSI TB-vaccines in clinical trials

### H1:IC

- **Ag85B**
- **ESAT-6**

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<tr>
<th>Phase I trials</th>
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<td>2 Phase II trials</td>
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<tr>
<td>- THYB-01: Safety in Naive/Adjuvant dose</td>
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<td>- THYB-02: Safety in BCG/TBI</td>
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<td>- THYB-03: Safety in Naïve/BCG/LTBI</td>
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<td>- THYB-04: Ag-Dose/Schedule</td>
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<td>- THYB-05: HIV infected</td>
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### H56:IC

- **Ag85B**
- **ESAT-6**
- **Rv2660**

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<td>- C-032: Safety in Naïve/LTBI</td>
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<td>- C-035: Dose in Naïve/LTBI</td>
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<tr>
<td>- C-037: Safety in TB patients</td>
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### H4:IC (SANOFI)

- **Ag85B**
- **TB10.4**

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<td>- C-006: Safety / Antigen dose</td>
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<td>- C-011: Safety / Antigen dose</td>
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<td>- C-013: Safety in recent BCG vac.</td>
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### H1:CAF01

- **Ag85B**
- **ESAT-6**

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**Preliminary data**
CAF01 – stable liposomes

Synthetic two-component cationic adjuvant

Delivery
Dimethyldioctadecyl ammonium (DDA)

Immunomodulator
Trehalose-dibehenate (TDB)

Th$_1$/Th$_{17}$/humoral

150 - 300 nm
CAF01 maintains longlived T cell memory – for the lifespan of the mice

Lindenstrøm et al, JI 2009
H56 in IC31 or CAF01 - NHP immunogenicity data

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<th>W-22</th>
<th>W-9</th>
<th>W-6</th>
<th>W-0</th>
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<tbody>
<tr>
<td>BCG</td>
<td>Boost 1</td>
<td>Boost 2</td>
<td>Mtb</td>
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**BCG - H56 (IC31)**

Spots/10^6 PBMCs (Minus background)

**BCG - H56 (CAF01)**

Spots/10^6 PBMCs (Minus background)
Survival and Pathology - NHP

Lin et al, JCI. 2012

Red : surviving animals
H56 prevents reactivation of latent infection

BCG
BCG/H56

MtB low dose challenge

Active

Latent

Anti-TNF Ab

To reactivate 50%

Control monkeys (Lin, et al 2010)

Bacterial burden: reactivation

Lin, Diedrich et al, JCI, 2012
Clinical trials at LUMC in Leiden

In collaboration with Jaap Van Dissel and Tom Ottenhoff

SAFETY

• No vaccine related serious adverse events
• Mild injection site reactions (a few moderate but no severe)

Both IC31 and CAF01 has an acceptable safety profile
• i.m. administration at 0 and 2 months, follow-up 32/78 wks
• three groups, with 12 subjects each

Group I (n=12)
50 μg antigen
0 and 2 months

Group II (n=12)
50 μg antigen + 100 nmol KLK + 4 nmol ODN1a
0 and 2 months

Group III (n=12) – follow-up 78 wks
50 μg antigen + 500 nmol KLK + 20 nmol ODN1a
0 and 2 months
H1/IC31 – Priming responses in naive individuals

IFN-γ ELISPOT

IFN-γ ELISA

Dissel, Vaccine 2010
H1:IC31 – long term TH1 memory

Dissel, Vaccine 2010
H1/IC31 – boosting in primed individuals

**IFN-γ ELISPOT**

400-700 spots

Weeks post vaccination

Dissel, Vaccine 2011
Leiden University Medical Centre (LUMC)
A total of 37 Healthy adult volunteers 18 to 55 years of age
Not BCG vaccinated and no TB infection (TST and QFT negative)

Fixed dose H1 (50 ug) + CAF01 (DDA / TDB) dose escalation:

Group I: No CAF01
N=7

Group II: Low dose (125/ 25 ug)
N=10

Group III: Intermediate dose (313/ 63 ug)
N=10

Group IV: High dose (625/ 125 ug)
N=10

Weeks

-4 0 1 6 8 9 14 32 52

QuantiFERON and TST

QuantiFERON

TST
Major points from clinical trials

IC31 and CAF01:

- Primes a TH1 response in the range from 400-1000 IFN-γ spots/million – this level is the same as in NHP efficiently protected by H56

- Very stable immunological CMI memory - up to 2.5 years post vaccination

- Boost responses (BCG/LTBI) are accelerated but the stable plateau obtained after boost does not seem to be markedly higher than after two primary vaccinations in naive individuals (more like an addition of 500 spots on top of 100)

- The immune signature includes several cytokines (INF-g, IL-2, TNF-a, IL17, IL13, GM-CSF and MIG), but we don’t know yet if the two adjuvants promote different signatures in man.

- The dose of antigen seems important. Low dose of antigen (5 and 15 ug) drives a higher T cell response and more polyfunctional T cells - and protects better in animal models
Adjuvant research
Dennis Christensen
Karen Korsholm
Thomas Lindenstrøm
Jes Dietrich

TB vaccine discovery
Else Marie Agger
Claus Aagaard
Rolf Billeskov
Truc Thanh Hoang
Ida Rosenkrands
Joshua Woodworth
Søren Hoff

Vaccine development
Ingrid Kromann
Lars. V. Andreasen
Grith Krøyer Wood
Peter Bang
Birgit Thierry-Carstensen

Collaborators:
Dissel, Ottenhoff, Josten, LUMC
Hanekom/Mahomed – SATVI
G. Pantaleo - Lausanne University Hospital
Joanne Flynn, Pittsburg
Bob Ryall and colleagues – Sanofi Aventis
Alex Von Gabain - Intercell

Acknowledgements