Status report on **VPM1002** a Tuberculosis prime vaccine for the future
Reasons for failure of BCG

BCG only protects children (age 0-6) from severe forms of TB

→ BCG fails to stimulate the “right” combination of T cells
  → Therefore fails to protect properly

→ BCG only induces a poor $T_{H1}/T_{H17}$ immune response
→ BCG only weakly induces Multifunctional T-cells

BCG evokes safety issues in immune compromised individuals.

→ BCG persists for a long time in the body
→ BCG kills severe immune compromised mice (SCID model)
→ BCG negatively influences the weight gain in neonatal rabbits
Development of a **safe, well tolerated and efficacious** vaccine (rBCGΔureC:Hly/VPM1002) against tuberculosis for residents in *endemic areas* and persons at risk in *non-endemic areas*
Fast Translational Product Development

Vibalogics

AURIGON

TBVAC/PDT BioReg Cons

FOCUS CDD

Vaccine and Pharma industry

MPI Infection biology

Tb Reference Center Borstel

!!! < 4 years !!!
**Product Profile VPM1002**

**Parental Strain:**
BCG subtype Prague

**Genetic Modification:**
Listeriolysin gene inserted into bacterial genome (Urease C gene)

**Classification of Biosafety Level:**
S1 / P1 (lowest safety level)
The Challenge in Translational Research:
- Improve the Gold Standard BCG -
The Challenge in Translational Research:
- Improve the Gold Standard BCG -

VPM1002
Improved Antigen Presentation induced by VPM1002
Two Ways of Th1 Immune Response Induction

Diagram showing the process of antigen presentation and induction of Th1 immune response.
manufacturing:

VPM1002 is manufactured by submerse fermentation in minimal medium. The final product is a lyophilised cake of live bacteria. Establishment of a GMP process is completed. The process has been designed to offer full scalability.

- Modern submers 30 liter fermentation
  - Theoretically ~1 Million doses from one 30 liter batch

- Lyophilization
  - The pilot lyophilization currently gives ~3000 GMP vials which adds-up to ~60 000 doses

Each vial contains 20 human doses (~5x10e6 CFU/vial)

Stability >36 months (>2x10e6 CFU/vial)
What does safety mean in the context of BCG immunization?

- The only severe side effect in BCG vaccination is a disseminated form of BCG (BCGosis). This occurs only in immune suppressed individuals and is associated with the persistence of BCG in individuals.

- To prove the advance safety profile of VPM1002 - also for immunocompromised individuals - the following experiments were performed:

  Vaccination with VPM1002 and BCG of

  - BALB/c mice for general safety
  - SCID mice (lack of adaptive immune system)
  - IFN-γ knock-out mice (Deficiencies in IFN-γ signaling pathway)
  - Newborn Himalayan rabbits
Attenuation of BCG expressing hemolysin and urea genes - infection of SCID mice

Intravenous Innocula
BCG 4x10^8
rBCG-hly 3.5x10^7
rBCG-hly-delta urea 1.5x10^8
### Newborn Rabbit Study

<table>
<thead>
<tr>
<th>Macroscopic post-mortem findings</th>
<th>At necropsy, no test item-related changes were noted.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CFU count</td>
<td>No CFU counts were detected in liver, brain, lung, spleen or testicles/ovaries on test days 11 or 22.</td>
</tr>
<tr>
<td>Body weight</td>
<td>The body weight of the animals treated with 1-4 x 10e5 CFU BCG Vaccine was decreased up to <strong>46% for the males</strong> in week 4 and by up to <strong>27% for the females</strong> on day 22 compared saline group. After 90 days the body weight was still decreased by 11% or 5% compared to the control. <strong>No influence</strong> on body weight with 1-4 x 10e5 CFU VPM1002.</td>
</tr>
</tbody>
</table>
Preclinical Studies

- 6 months toxicology study in **guinea-pigs** including one PPD skin test; **Successfully completed**, no adverse events, normal weight gain
- 42 days safety studies (highest dose 1-4x10e7 CFU/animal) in **guinea-pigs**; in-life phase **successfully completed** without adverse events, normal weight gain; gross necropsy and histology findings similar to control groups
- **Rabbit** toxicology study (**successfully completed**)
- **Neonatal Rabbit** toxicology study (**successfully completed**)
- **Safety studies in immune deficient mice**
  - 105 days **SCID mouse** studies four doses ranging from 1-4x10e5 to 1-3x10e8 CFU/animal; in-life phase **successfully completed** even the highest dose below LD50
  - 105 days **IFN-gamma k.o.** mouse study: two dose 1-4x10e5 and 1-4x10e6 CFU/animal; **successfully completed** 100% survival
- Protection / Challenge in a **murine model** (**successfully completed**)
- Safety in **macaques** (**successfully completed**)
VPM1002: Clinical Data
VPM1002-GE-1.01TB
Phase I: 80 volunteers in Germany

First Vaccinee enrolled on Sep 08, 2008

Last Vaccinee enrolled on June 2, 2009
<table>
<thead>
<tr>
<th>Dosage Group</th>
<th>Pre-Disposition (BCG-vaccination and PPD status)</th>
<th>N per group</th>
<th>N for interim safety monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG</td>
<td>No (neither vaccinated nor PPD-pos.)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>No (neither vaccinated nor PPD-pos.)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>No (neither vaccinated nor PPD-pos.)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>No (neither vaccinated nor PPD-pos.)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>BCG</td>
<td>Yes (vaccinated or PPD-pos.)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>1</td>
<td>Yes (vaccinated or PPD-pos.)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>Yes (vaccinated or PPD-pos.)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>Yes (vaccinated or PPD-pos.)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>80</td>
<td>24</td>
</tr>
</tbody>
</table>

- **Group 1**: $5 \times 10^{-3}$ CFU VPM1002
- **Group 2**: $5 \times 10^{-4}$ CFU VPM1002
- **Group 3**: $5 \times 10^{-5}$ CFU VPM1002
- **BCG**: $5 \times 10^{-5}$ CFU BCG

- **Stratification regarding the status of pre-disposition:**
  - No = lack of BCG-vaccination in the personal vaccination documents and no BCG-scar and PPD-Skin-Test negative (< 1 mm)
  - Yes = documented BCG-vaccination in the personal vaccination documents or BCG-scar or PPD-Skin-Test positive (at least 1 mm but less than 10 mm)

- **1-2-3-4 exposition**
Primary Objective

The primary objective of this study was to investigate the safety of single doses of VPM1002.

Tolerability
According to the study protocol 56 days and 6 months after vaccination the subjects were asked.

- 57% stated the tolerability as very good
- 40% good
- 3% bad (only in the BCG group)

Safety

- No Serious Averse Events
- (Expected!) Adverse drug Reactions, mostly induration, erythema and swelling at the injection side
IFN-γ Secretion after Ag85B Resti.
Naive Volunteers

PBMC ELISA

ELISpot

Whole Blood ELISA
Phase Ib in South Africa

24 volunteers

Phase Ib Open Label, Randomized, Controlled, Dose-Escalation Study to Evaluate Safety and Immunogenicity of VPM1002 in Comparison with BCG in Healthy Volunteers in South Africa
VPM1002-ZA-1.10TB
Phase Ib in South Africa: 24 volunteers

First Vaccinee enrolled on April, 2010

Last Vaccinee enrolled on July, 2010
Whole-Blood IFN-γ ELISA

Line plot for median values of IFN-gamma (pg/ml) per time point and treatment group

- BCG
- VPM1002 (10e3)
- VPM1002 (10e4)
- VPM1002 (10e5)
Clinical Development Phase Ia-II

- **Phase Ia:** Evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in healthy adult Caucasians compared to reference control (BCG)

- **Phase Ib:** Evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in healthy adult Africans compared to reference control (BCG)

- **Phase II:** Open label, randomized, BCG controlled Phase II study with VPM1002 vaccination for evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in neonates.
Phase II Open Label, Randomized, Controlled Study to Evaluate Safety and Immunogenicity of VPM1002 in Comparison with BCG in HIV-unexposed, BCG naive newborn infants in South Africa
Timelines for S.Africa

- MCC approval – 27 July 2011
- Stellenbosch IRB approval – 12 July 2011
- Department of Agriculture (GMO import) approval – 10 August 2011
This study is the first application of VPM1002 in HIV-unexposed, BCG-naive newborn infants as tuberculosis candidate vaccine.
To investigate the safety and tolerability of a single dose of the recombinant BCG vaccine, VPM1002, in HIV-unexposed, BCG naive newborn infants in a region with a high burden of tuberculosis.
To investigate the immunogenicity of a single dose of the recombinant BCG vaccine, VPM1002, in HIV-unexposed, BCG naive newborn infants in a region with a high burden of tuberculosis.
## Overview of Vaccine Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Intradermal vaccination within 8 days after birth</th>
<th>N per group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Routine BCG</td>
<td>BCG Danish Strain, SSI (1-4 x 10e5 CFU)</td>
<td>12</td>
</tr>
<tr>
<td>VPM1002</td>
<td>VPM1002 (1-4 x 10e5 CFU)</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>48</td>
</tr>
</tbody>
</table>
## TB Vaccine Pipeline

### Candidates in Clinical Trials

<table>
<thead>
<tr>
<th>Type of Vaccine</th>
<th>Products</th>
<th>Product description</th>
<th>Sponsor</th>
<th>Status as of 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant Live „Prime“</td>
<td>VPM 1002</td>
<td>rBCG Prague strain expressing listeriolysin and carries a urease deletion mutation</td>
<td>Max Planck, Vakzine Projekt Management GmbH, TBVI</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>rBCG30</td>
<td>Development stopped</td>
<td>UCLA, NIH, NIAID, Aeras</td>
<td>Phase I [completed]</td>
</tr>
<tr>
<td>Viral Vectored</td>
<td>Oxford MVA85A / AERAS-485</td>
<td>Modified vaccinia Ankara vector expressing Mtb antigen 85A</td>
<td>OETC, Aeras</td>
<td>Phase IIIb</td>
</tr>
<tr>
<td></td>
<td>AERAS-402/ Crucell Ad35</td>
<td>Replication-deficient adenovirus 35 vector expressing Mtb antigens 85A, 85B, TB10.4</td>
<td>Crucell, Aeras</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>AdAg85A</td>
<td>Replication-deficient adenovirus 5 vector expressing Mtb antigen 85A</td>
<td>McMaster University</td>
<td>Phase I</td>
</tr>
<tr>
<td>Recombinant Protein</td>
<td>Hybrid-I+C-31</td>
<td>Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6</td>
<td>SSI, TBVI, Intercell</td>
<td>Phase IIa</td>
</tr>
<tr>
<td></td>
<td>Hybrid-I+CAF01</td>
<td>Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6</td>
<td>SSI</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>M72 + AS01</td>
<td>Recombinant protein composed of a fusion of Mtb antigens Rv1196 and Rv0125 &amp; adjuvant AS01</td>
<td>GSK, Aeras</td>
<td>Phase II</td>
</tr>
<tr>
<td></td>
<td>HyVac 4/AERAS-404, +IC-31</td>
<td>Adjuvanted recombinant protein composed of a fusion of Mtb antigens 85B and TB10.4</td>
<td>SSI, Sanofi-Pasteur, Aeras, Intercell</td>
<td>Phase I</td>
</tr>
<tr>
<td>Other</td>
<td>RUTI</td>
<td>Fragmented Mtb cells</td>
<td>Archivel Farma, S.l.; Badalona, Spain</td>
<td>Phase I</td>
</tr>
<tr>
<td></td>
<td>M. vaccae</td>
<td>Inactivated whole cell non-TB mycobacterium; phase III in BCG-primed HIV+ population completed; reformulation pending</td>
<td>NIH, Aeras, Immodulon</td>
<td>Phase III [completed]</td>
</tr>
<tr>
<td></td>
<td>M. smegmatis *</td>
<td>Whole cell extract; phase I completed in China</td>
<td>communicated by the Wuhan Inst. of Biol. Products</td>
<td>Phase I [completed]</td>
</tr>
</tbody>
</table>

Source: WHO 2010; www.STOPTB.org
Properties of VPM1002
Superior protection

- Immunisation with VPM1002 induces a superior mixed $T_\text{H}1/T_\text{H}17$ response compared to BCG
- VPM1002 induces multifunctional T cells
- VPM1002 accelerate recruitment of antigen-specific T cells to the lung compared to BCG
- VPM1002 induces an accelerated T cell recruitment = earlier infection containment = lower CFU than BCG
Properties of VPM1002
Advanced safety profile

- VPM1002 persists only for a limited time in the recipient
- VPM1002 has no negative effect on immune compromised species (e.g.) SCID
- VPM1002 has no negative effect on weight gain in neonatal rabbits