“An integrated project for the design and testing of vaccine candidates against tuberculosis: identification, development, and clinical studies
Tuberculosis—a worldwide problem

- 30% of the world population infected and at risk of developing TB
- 8 million new cases each year
- 2 million deaths per year
- 1 million deaths due to HIV and TB
- Drug resistant TB
- BCG vaccine not effective against TB in young adult population
TB-VAC aims

- Discovery and optimisation of vaccine candidates
- Identification of correlates of protection and disease
- Capacity building in developing countries for clinical evaluation of phase I trials
- Evaluation of lead candidates in small clinical phase I trials
- Liaise with other consortia (MUVAPRED, Aeras)
- Liaise with EDCTP to enable further large clinical trials in African countries

- 29 European + 4 African Research Institutions
  2 major Vaccine Producers
- budget approx. 20 mE over five years (17 mE EC FP6, 1.8 SF)

NL
UK
FR
IT
ES
GE
BE
DK
CH

Senegal
Gambia
Ethiopia
South Africa
Project overview

STRATEGIC RESEARCH
Component-2
- Optimisation & delivery systems (WP1)
- Animal models (WP5)
- Preclinical evaluation
- Correlates of protection and disease in humans (WP4)
- Immunologic monitoring

DISCOVERY
Component-1
- Proteome-derived Ag
- Non-protein Ag (WP3)
- multi-component sub-unit vaccines
- Genomics & mycobacterial engineering (WP2)
- a safe « super » BCG

DOWNSTREAM DEVELOPMENT
Component-3
- FP5-derived candidate vaccines
- GMP production
- Regulatory assessment
- Phase I/IIa clinical Trials (WP6)

TB-VAC MANAGEMENT
(WP7)
WP2 Live vaccines and immunomodulatory ligands (Carlos Martin, UNIZAR, Zaragoza, ES)

- Improved BCG and attenuated TB strains as live vaccines
- Identification and effects immunomodulatory ligands (LAM, granuloma formation)

WP3 Antigen discovery (Stefan Kaufmann, MPIIB, Berlin)

- Novel antigen components with a focus on genus/strain specific and latency associated antigens
- Prime boost strategies
- Murine latency models

Strategic and downstream development
The diagram illustrates the process of phagosome and lysosome fusion. It shows the interaction of immune cells CD4 and CD8 with bacterial elements. The process includes:

1. **Early Phagosome**: Contains Listeriolysin and ΔUre rBCG-hly, both of which are marked as pH < 6.
2. **Phagolysosome**: This structure is marked as < pH 5, indicating an acidic environment.
3. **Lysosome**: This component is involved in the degradation of antigens.

The flow of the process is depicted with arrows, showing the movement from the early phagosome to the phagolysosome and the subsequent interaction with lysosomes.
Protective capacity of 
rBCGΔureC-Hly

in the murine aerosol model of tuberculosis

![Graph showing bacterial load over time after challenge with M. tuberculosis H37Rv.]

BALB/c mice were immunized with 10⁶ CFU BCG or rBCGΔureC Hly for 120 days. Bacterial load in lungs was determined post aerosol-challenge with *M. tuberculosis* H37Rv.

*Grode et al., J Clin Invest. 2005 Sep;115(9):2472-9.*
WP1 Optimisation of existing vaccine candidates (Peter Andersen, SSI, Kopenhagen, DK)

- Optimisation of delivery and composition of subunit vaccines (HYB1 Ag85B-ESAT6 fusion)
- Delivery: Liposomes, niosomes, microspheres, viral vectors
- Adjuvants, immunomodulators: mycobacterial lipids, ODN (CpG), etc.
- Posttranslational effects (E.coli vs. Mycobacterium produced)
- Effect on protection, memory/maintenance, pathology, Th1/Th2

Second generation vaccine candidates for downstream development in Phase I trials
DDA/TDB – a novel adjuvant for the efficient induction of both cell-mediated and humoral immune responses

Stable formulation based on

Cationic liposomes + Immunomodulator

CryoTEM picture of LipoVac liposomes
Long-term immune responses and protection with Ag85B-ESAT6 in DDA/TDB

*measured by ELISPOT after restimulation with vaccine (Ag85B-ESAT-6) antigen
WP5 Preclinical evaluation and selection of vaccine candidates
(Ann Rawkins, HPA-PD, UK)

- Evaluation of safety, immunogenicity, and protective efficacy in relevant animal models
  - Guinea Pigs
  - Macaques
  - Mice (SCID, worm infection, neonatal)

- Non protein antigens and adjuvants (PIM, Glycolipids, phosphoantigens)

Second generation vaccine candidates for downstream development in Phase I trials
Experiments conducted

Comparison of lead candidates ‘head-to-head’

Candidates selected based on pre-set criteria such as evidence of efficacy in other models, safety and clinical relevance
Survival of guinea pigs up to 26 weeks post high-dose (500CFU) aerosol challenge
STRATEGIC: Optimisation of existing vaccine candidates towards Phase I trials

**Strategic research**

**WP4 (WPL Tom Ottenhoff, LUMC, Leiden)**

Identify and develop correlates of protection

Identify and develop markers of TB disease and TB immunopathology

- Classically restricted CD4 and CD8 T cells specific for *M. tuberculosis*
- Unconventional T cells specific for *M. tuberculosis*
- Surrogate markers, new assays and gene expression profiling of *in vivo* host immunity

Impact on the time and resources for evaluation of vaccine candidates in future clinical trials and early identification of the most effective vaccines
Heparin-binding haemagglutinin adhesin required for extrapulmonary dissemination

native HBHA induces IFN\(_\gamma\) production in PBMC of latently infected individuals

Mascart et al.
WP6 Optimisation of existing vaccine candidates towards Phase I trials (WPL, Paul-Henry Lambert, Geneva)

- GMP production
- Regulatory aspects of vaccine development (ao. pre-clinical files)
- Phase I clinical trials, in TB endemic and non-endemic areas

Selection of candidates for further trials (involvement of EDCTP)
WP6

Discovery/strategic:
- Live mycobacteria
- Dormant antigens
- HBHA, non-proteic antigen

FP5
MVA-85A, Ag85B-ESAT6, Mtb72f

DOWNSTREAM DEVELOPMENT

2005-8 Clinical Trials
<table>
<thead>
<tr>
<th>Candidate - vaccines</th>
<th>Developer</th>
<th>Initial cGMP Production</th>
<th>Regulatory Assessm.</th>
<th>Phase I Clinical Trials</th>
<th>Clinical Trials in PPD+</th>
<th>Clinical Trials in PPD+ &amp; HIV+</th>
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<tbody>
<tr>
<td>MVA-Ag85A, (VV, Pr-b)</td>
<td>UOXF</td>
<td>Done (lot1)</td>
<td>Done (lot1)</td>
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<td>rBCG-UreC-Hly</td>
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<td>Pre-PDT exploratory meetings</td>
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First Payment – 80% M0-18
Second Payment – 20% M1-12 + 80% M19-30
Third Payment – 20% M13-24 + 80% M31-42

m1-12 report
m13-24 report
m25-36 report

Implem. plan M1-18
Implem. plan M13-30
Implem. plan M25-42

Review EC, EAC

etc
## Two review teams

### External Advisory Committee
- Juhani Eskola, Finnish National Public Health Institute KTL, Helsinki, Finland
- Uli Fruth, Initiative for Vaccine Research, WHO, Geneva, Switzerland
- Greg Hussey, University of Cape Town, South-Africa
- Peter Small, Bill & Melinda Gates Foundation, Seattle WA, USA
- Hans Wolf, Universität Regensburg, Regensburg, Germany

### EC mid term review team
- Bernard Fourie, South African Medical Research Council, Pretoria, SA
- Douglas Young, Imperial College, London, UK
Review process

• Technical Annex (January 2005)
• Second annual meeting, Les Diablerets (February 2005)
• First Periodic report (April 2005)
• M18 summary report (August 2005)
• Steering Committee meeting with both review teams (September 2005)
• Reports and recommendations available (November 2006)
• SC meetings: New plan and budget (November/December 2005)
• Proposed in assembly: Budget (26/31) and New partners (31/31) approved (January 2006)
  • Redistribution of budget according to new plans after M30 (30%)
  • Two new partners
• Submitted to EC April 2006
Consortium management

Legal issues
- Amendments to CA
- Drafting of subcontracting conditions
- Formalities on election of additional Steering Committee members
- Drafting legal document for collaboration with third parties
- End on participation of a partner
- Introduction of and formalities regarding new partners
- Publication formalities
- Drafting of necessary secrecy agreements/statements
## Consortium management

<table>
<thead>
<tr>
<th>Ethical Issues (B. Gicquel)</th>
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<tbody>
<tr>
<td>- GMO</td>
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<td>- Animal experiments</td>
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<tr>
<td>- Human samples</td>
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<tr>
<td>- Approval for phase I trials</td>
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</table>
Consortium management

- **Internal Communication**
  - Reporting tool via website
  - Activities and expenditure
  - Summaries of SC meetings (tel conf; face to face 10/year)
  - WP meetings (2/year)
  - Annual assembly (1/year), Advisory committee

- **External communication**
  - 12 month report plus new implementation plan to EC
  - Specific meetings (with other projects and on specific subjects)
  - Press conferences
  - Publications
  - Web-site (www.tb-vac.org)
## Progress budgets and realizations

### Partner - Year - Projectpart - Activity

| ID-Lelystad - 3 - 3.1 - RTD |

### Budgets and realizations

<table>
<thead>
<tr>
<th>Category</th>
<th>Budget '18 M</th>
<th>After 6 months</th>
<th>After 12 Months</th>
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Period 6 months: 01-01-06 - 30-06-06.
Period 12 months: 01-01-06 - 31-12-06.
### Partner - Year - Project part - Deliverable

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<th>Partner-Year-Projectpart</th>
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### Progress deliverables

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<tr>
<th>Annex</th>
<th>After 6 months</th>
<th>After 12 months</th>
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<td>12/31/2006</td>
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</table>

**Summary explanation of major deviations**

Analysis of cellular proteins of two independent grown cultures of H37Rv WT with Beijing 1237 WT revealed the presence of 55 differentially expressed spots. 26 spots were only detectable in the Beijing strain, whereas 22 spots were only detectable in H37Rv. In
New live mycobacterial vaccines: the Geneva consensus on essential steps towards clinical development

Arun T. Kamath, Uli Fruth, Michael J. Brennan, Roland Dobbelaer, Peter Hubrechts, Mei Mei Ho, Ronald E. Mayner, Jelle Thole, K. Barry Walker, Margaret Liu, Paul-Henri Lambert

a Department of Pathology and Immunology, Center for Vaccinology and Neonatal Immunology, University of Geneva, 1 rue Michel Servet, 1211 Geneva, Switzerland
b Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland
c Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA
d Health, Food Chain Security and Environment, Scientific Institute of Public Health, Brussels, Belgium
e Quality Control Department, Statens Serum Institut, Copenhagen, Denmark
f Division of Bacteriology, National Institute for Biological Standards and Control, South Mimms, Potters Bar, UK
Greas Global TB Vaccine Foundation, Bethesda, MD, USA
h Division of Infectious Diseases, Animal Sciences Group, Lelystad, The Netherlands

Received 4 March 2005; accepted 9 March 2005
Available online 24 March 2005
Press conference

Press release

Joint Forces against Tuberculosis

In these days bird flu predominate newspaper headlines. Yet HIV, malaria and TB continue to ravage as major killers amongst plagues with dramatic economic consequences, notably in low-income countries. European scientists have joined forces and formed two major scientific networks supported by the EU frame work program 6 with 30 million Euro. TBVAC and MUVAPRED attempt to rationally develop vaccines against these poverty related diseases with emphasis on tuberculosis. A hundred years after the Nobel Prize for the discovery of the etiologic agent of tuberculosis to Robert Koch, who worked in Berlin, members of the two EU networks meet in Berlin to plan their future strategies. TBVAC aims at the rational development of novel vaccines to prevent pulmonary tuberculosis in young adults. Of particular interest is a vaccine for HIV-infected individuals who are particularly susceptible to tuberculosis. Several promising vaccine candidates are currently optimized in preclinical models. A phase I trail with one of the vaccine candidates, developed in TBVAC, has just been initiated. MUVAPRED aims at a vaccine that directly acts at the local site of TB manifestation – the mucosa. Vaccines will be developed which are easily administered in low-income countries where TB rampages most. Both networks complement each other in an ideal way and hence develop their strategies jointly to gain highest possible synergies.

Representatives of MUVAPRED and TBVAC will discuss this on Monday, 28. November at 12h in the Robert Koch auditorium of the Institute for Microbiology Charité, Berlin.
Protective Capacity rBCG $\Delta$ureC-Hly Challenge “Beijing“ (200 CFU 120 d post vaccination)

$\Delta \log = 2.3$

* $\Delta \log = 2.1$

<table>
<thead>
<tr>
<th>Vaccines tested / in progress</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guinea Pigs</strong></td>
</tr>
<tr>
<td><strong>Macaques</strong></td>
</tr>
<tr>
<td><strong>Mice</strong></td>
</tr>
<tr>
<td>- SCID, worm infection, neonatal</td>
</tr>
<tr>
<td><strong>Macaques, guinea pigs, mice</strong></td>
</tr>
</tbody>
</table>

- **Hybrid 1** - various adjuvant formulations, with and without BCG prime
- MVA / FP9 / Ad expressing Ag85A with or without BCG prime
- Heparin Binding Haemagglutinin Antigen (HBHA) in adjuvant
- *M. tuberculosis* (MT103) phoP mutant and H37Rv phoPR mutant
- Rv3407 DNA with BCG prime
- BCG-RD1 modification
- BCG – Hly

- Antigens = Ac2SGL, PIM4 and other lipids
- Adjuvant with Hyb1, picostim
WP7 Project management

Organisation of TB-VAC
  Roles

Project Process
  12/18 month rolling over project cycle
  Evaluation and new implementation plans
  Legal issues

Communication
  Internally
  Externally