Introducing the Tuberculosis Vaccine Initiative (TBVI)

ASEAN-EU STI Days
Bangkok, Thailand – 21-23 Jan 2014

René Coppens,
Director Resource Mobilisation

Facilitating European efforts towards the development of new TB vaccines

www.tbvi.eu
TuBerculosis Vaccine Initiative

• **TBVI**: Consortium of (mainly European) TB Vaccine Research Organizations that have joined forces to speed up development programs by means of looking for synergies between various programs and information sharing.

• **TBVI**: Non-profit foundation with an operational office to ‘service’ the TBVI consortium (financial and technical support).
TBVI History

2000 – 2004
Tuberculosis Vaccine Cluster
EU Framework Programme 5 Integrated Project

2004 – 2009
TBVAC (17 million €)
EU FP 6 Integrated Project

As of 2008:
• Total of 6 new EU FP7 projects
• New support:
  • Bill & Melinda Gates Foundation
  • Calouste Gulbenkian Foundation
  • Institut Mérieux
  • GSK Biologicals
  • FIT Biotech
  • Biofabri
  • EDCTP
  • Norwegian Government

2007
EU R&D Commission
Supports creation of a separate entity

2010-2014
NEWTBVAC (12 million €)
EU FP 7 Integrated Project

05-03-2008: TBVI foundation established
TBVI research community
## Research partners funded through TBVI (2013)

### Argentinia
- INTA Institute of Biotechnology

### Belgium
- Université Libre de Bruxelles
- Scientific Institute of Public Health
- GSK-Biologicals

### Denmark
- Statens Serum Institute

### Ethiopia
- Armauer Hansen Research Institute

### Finland
- FIT Biotech

### France
- Centre National de la Recherche Scientifique
- Institut National de la Santé et de la Recherche Médicale
- Institut Pasteur
- Institut Pasteur de Lille
- Institut Mérieux
- PX’ therapeutics

### Germany
- University of Lübeck
- Technical University of Munich
- Max-Planck Institute for Infection Biology
- University of Tübingen
- University of Ulm
- University of Erlangen-Nürnberg
- Vakzine Projekt Management

### Italy
- National Institute for Infectious Diseases “Lazzaro Spallanzani”
- University of Palermo
- Istituto Superiore Di Sanita
- University of Padua

### Netherlands
- Central Veterinary Institute of Wageningen UR
- Biomedical Primate Research Centre
- Leiden University Medical Centre
- Free University Medical Centre Amsterdam
- Intravacc

### Portugal
- University of Porto

### Republic of Korea
- Institut Pasteur Korea
- Educational Foundation Yonsei University
- International Vaccine Institute

### Senegal
- Es esper Pour La Santé (EPLS)
- Centre Hospitalier Universitaire (CHU) Le Dantec

### South Africa
- University of Cape Town
- Stellenbosch University

### Spain
- Universidad de Zaragoza Facultad de Medicina
- Fundacio Institut De Investigado de Ciencies De La Salut Germans Trias I Pujol
- CZ Veterinaria/BIOFABRI

### Switzerland
- Institute for Research in Biomedicine
- University of Geneva
- University Hospital of Basel
- University of Zürich
- Centre Hospitalier Universitaire Vaudois

### Uganda
- The Infectious Diseases Institute (IDI) at Makerere University

### United Kingdom
- Public Health England, Porton Down
- University of Birmingham
- Aston University
- Manchester University Medical School
- Imperial College of Science Technology and Medicine
- National Institute for Biological Standards - MHRA
- University of Oxford
- London School of Hygiene and Tropical Medicine
- Veterinary Laboratory Agencies
Our research partners
About TBVI Foundation

• European non-profit foundation
  – Supported by governmental organizations, foundations and private industry
  – Network of >50 universities, research institutes and industries working on vaccine development

• Dedicated to the principle that new TB vaccines must be accessible and affordable for the developing world

• Product oriented TB vaccine pipeline
  – Individual partners have responsibility and ownership for each candidate TB vaccine
Mission and vision

Our vision: Safe and effective tuberculosis vaccines for all people

Our mission: TBVI supports, integrates, translates and prioritises R&D efforts to discover and develop new TB vaccines that are accessible and affordable to all people
TBVI Foundation - Governance

- Governance Board
- Steering Committee
- Operational Office
- Council of Trustees
TBVI Foundation - Operational Office

Director
• Dr. Jelle Thole

Staff
• Danielle Roordink, Project Manager
• Erna Balk, Director Advocacy & Communications
• Anne Meinema, Director Finance and Administration
• Koen de Lange, General Legal Counsel
• Cora Agterdenbosch, Management Assistant
• René Coppens, Director Resource Mobilisation

Product Development Team
• Dr. Georges Thiry, chair
• Dr. Mei Mei Ho
• Dr. Brijesh Patel
• Dr. Micha Roumiantzeff
• Dr. Eddy Rommel

Clinical Development Team
• Dr. Luc Hessel, chair
• Dr. Steven Black
• Dr. Bernard Fritzell
• Dr. Emauèle Gerdil
• Dr. Francois Spertini
Operational Office:

• Project initiation and submission
• Project management
• Assist GB, CoT and SC
• Coordinating and connecting
• Resource Mobilisation
• Advocacy and Communication
• PDT/CDT technical support activities
Activities

• TBVI provides support through acquisition, management, coordination, and financing of TB vaccine and biomarker projects

• TBVI brings together efforts of globally leading universities, research institutes, biotech and vaccine companies

• TBVI stimulates translation from discovery to product development and early clinical development via expert guidance

• TBVI manages the portfolio of vaccines and biomarkers by selection of the most promising candidates
Tuberculosis Vaccines: A Strategic Blueprint for the Next Decade

- A unified global strategy
- Renewed, intensified and well integrated international effort
- Outlining major scientific challenges, critical activities and crucial questions
TBVI strategy follows Blueprint: 5 priority areas

- Creativity in research and discovery
- Correlates of Immunity and Biomarkers for TB Vaccines
- Clinical Trials – Harmonisation and Cooperation
- Rational Selection of TB Vaccine Candidates
- Building Support through Advocacy, Communications and Resource Mobilisation
Priority R&D areas TBVI

- Mechanisms of protection
- Improve antigenic vaccine repertoire and introduce new vaccine mechanisms
- Development of new priming and boosting vaccines
- Comparative preclinical animal models that mimic TB disease
- Explore novel approaches to identify correlates of protection
- Design of clinical trials with appropriate endpoints for determining acceptable efficacy of TB vaccines in different target populations
- Rational selection of TB vaccine candidates; gating criteria and portfolio management
Results of main TBVI projects (I):

• 4 vaccine candidates from discovery ->preclinical
• 4 vaccine candidates moving into and tested in clinical PhI to PhII trials
• Identification of 15 candidate biomarkers
• Development of 3 adjuvant molecules
• Centralised preclinical animal models with calls to select candidates
• Capacity building 2 clinical trial sites
• >90 publications, >10 IP
Results of main TBVI projects (II):

NEWTBVC (2010-2013):

• 40 TB vaccine approaches supported
• 22 vaccine candidates from research -> discovery
• 6 vaccine candidates from discovery -> preclinical
• 4 vaccine candidates -> clinical Phase I
• 17 candidate biomarkers further characterized and validated
• Identification of 18 candidate biomarkers
• Currently approx. 90 publications, more to follow
Results of main TBVI projects (III):

Other projects:

• Scientific symposia, workshops, networking
• Creating awareness, advocacy activities
• Down selection of portfolio from 43 -> 29

In collaboration with Aeras:

• Blueprint for TB vaccine development
• Development of Stage Gating Criteria
• Development TB vaccine business case for innovative funding
Key success factors

• No ownership of IP -> Freedom to operate
• Product Development Team and Clinical Development Team -> vaccines progress more efficiently through the pipeline
• Very open exchange of information during meetings and workshops -> accelerating innovation and new partnerships
Management of Portfolio

• Investigators are owners;
• Candidates are compared head-to-head in animals models;
• Refer to ‘gates’ and ‘criteria’ for progression and up-selection of candidates;
• Expertise in product & clinical development;
• Formal portfolio management processes
Product Development Team and Clinical Development Team

- PDT and CDT fill the gap between research and development
- Neutral and confidential expert groups, composed of international experts in vaccine development
- Objectives: support the product or clinical development phase of the candidate vaccines
- Refinement of regulatory policies and requirements
- Selection of CRO

In brief:
- A light and effective structure that brings necessary expertise to scientists to accelerate development, and bring quality and methodology (since 2004)
- Allow TBVI to monitor progress of portfolio
Fill the gap - translation

Research

PDT - CDT

Development

Entry criteria:
• Select candidate(s)
• Feasibility
• Proof of concept in animals

Go Human

• Develop plan and strategy
• Review process & characteristics
• Select manufacturer
• Review animal data; prepare tox & pre-clinical studies; select CRO
• Prepare clinical trial approval form
• Prepare protocol Ph 1; select PI
• Project management & IP
## Prioritisation -
### Stages of development of new vaccines and gates

<table>
<thead>
<tr>
<th>Gate</th>
<th>From</th>
<th>To</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Discovery</td>
<td>Preclinical</td>
</tr>
<tr>
<td>2</td>
<td>Preclinical (Process/Tox2.1; CTA application 2.2)</td>
<td>Phase 1 – 1st in man</td>
</tr>
<tr>
<td>3</td>
<td>Phase 1 (3.1) + Phase 2a (3.2)</td>
<td>Phase 2b</td>
</tr>
<tr>
<td>4</td>
<td>Phase 2b</td>
<td>Phase 3</td>
</tr>
<tr>
<td>5</td>
<td>Phase 3</td>
<td>Market authorization</td>
</tr>
<tr>
<td>6</td>
<td>MA</td>
<td>Introduction</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Gate 1</td>
<td>Gate 2</td>
</tr>
<tr>
<td>------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Production process</td>
<td>Process developed at lab stage</td>
<td>cGMP process defined</td>
</tr>
<tr>
<td>Product Characterization &amp; Quality</td>
<td>Genetic stability shown, R gene removed</td>
<td>cGMP process defined</td>
</tr>
<tr>
<td>Safety</td>
<td>Relevant safety elements identified</td>
<td>Safer than BCG</td>
</tr>
<tr>
<td>Immunogenicity</td>
<td>Relevant immunogenicity shown</td>
<td>Specific vaccine relevant immune responses characterised, clinical assays identified</td>
</tr>
<tr>
<td>Protection / efficacy</td>
<td>Protection against M. Tb challenge demonstrated</td>
<td>Protection vs. Mtb challenge is statistically better than BCG in 2 animal models. (eg mice &amp; gps) as demonstrated by a read-out with high statistical power for the group size, typically 0.5 log statistically significant decrease in CFU.</td>
</tr>
<tr>
<td>Clinical</td>
<td>TPP and general plan considered</td>
<td>CDP drafted, trial sites considered, partners identified</td>
</tr>
<tr>
<td>Regulatory</td>
<td>No major blocks identified</td>
<td>Clear review of regulatory factors</td>
</tr>
<tr>
<td>Business</td>
<td>IP and MTA, freedom to act clear</td>
<td>IP finalised, partners recruited, finances identified.</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Gate 3</td>
<td>Gate 4</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Production process</strong></td>
<td>Process developed under GMPs and ready to be scaled-up</td>
<td>Final process consistently scaled-up to commercial level</td>
</tr>
<tr>
<td><strong>Product Characterization &amp; Quality</strong></td>
<td>Test product passes final product QC and released assays required for licensure</td>
<td>Consistency lots pass QC, batch and final product release tests</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>Safety profile acceptable to move to target population at selected dose</td>
<td>Safety profile satisfactory in the target population</td>
</tr>
<tr>
<td><strong>Immunogenicity</strong></td>
<td>Immune responses above baseline and supportive of a given dose regimen in the target population</td>
<td>Immune responses satisfactory in the final target population</td>
</tr>
<tr>
<td><strong>Protection / efficacy</strong></td>
<td>Immunological endpoints validated</td>
<td>Phase 2B results supports vaccine efficacy (clinical PoC)</td>
</tr>
<tr>
<td><strong>Clinical</strong></td>
<td>CDP established, study sites identified and GCP monitoring processes established</td>
<td>CDP and Phase 3 study protocol validated and TPP updated</td>
</tr>
<tr>
<td><strong>Regulatory</strong></td>
<td>Regulatory strategy established, including scientific advice</td>
<td>Regulatory pathway validated up to review process (inc. prequalification)</td>
</tr>
<tr>
<td><strong>Business</strong></td>
<td>IP status satisfactory Partnership and budget established</td>
<td>Strong industrial partnership established and supportive market environment</td>
</tr>
</tbody>
</table>
Four types of tpp’s in new tb vaccines

Prime, infants
• Protect at earliest stage of infection
• Prevent invasive disease & induce enduring protection against pulmonary TB
• Safe including in immuno-compromized
• No interference with EPI vaccines
• Prime for sub-unit vaccines

Boost, adolescents and adults
• Prevent infection & TB in naive adolescents and young adults
• Boost / complement prior immunity
• Prevent reactivation in LTBI
• Safe including in immuno-compromized
• Safe in Mtb infected
• No immuno-pathology

Boost, infants
• Same
• Boost & complement responses from priming mycobacteria

Therapeutic
• Shorten treatment of (MDR) TB
• Safe including in immunocompromized
• No immuno-pathology
# TBVI vaccine portfolio (as per dec 2013)

<table>
<thead>
<tr>
<th>Discovery and Pre-clinical</th>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
</tr>
</thead>
<tbody>
<tr>
<td>rBCG (n)</td>
<td>P</td>
<td></td>
<td>rBCG VPM1002 P</td>
</tr>
<tr>
<td>Bilthoven, Zurich, Berlin</td>
<td></td>
<td></td>
<td>Berlin, SII</td>
</tr>
<tr>
<td><strong>attMtb</strong> Rv1503c</td>
<td>P</td>
<td>att MTBVAC</td>
<td></td>
</tr>
<tr>
<td>Toulouse</td>
<td></td>
<td>P</td>
<td></td>
</tr>
<tr>
<td><strong>attMtb SigE::Fad26</strong></td>
<td>P</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Padua</td>
<td></td>
<td>Zaragoza, Biofabri</td>
<td></td>
</tr>
<tr>
<td>Native and rHBHA</td>
<td>B</td>
<td>SAV/Ag85a</td>
<td>Hybrid I + IC31 B</td>
</tr>
<tr>
<td>IP Lille, Aeras</td>
<td></td>
<td>Oxford</td>
<td>SSI, Intercell, EDCTP</td>
</tr>
<tr>
<td>LCMV Vector</td>
<td>B</td>
<td></td>
<td>MVA85A B</td>
</tr>
<tr>
<td>Geneva</td>
<td></td>
<td></td>
<td>Oxford, AERAS</td>
</tr>
<tr>
<td>SAV / rec</td>
<td>B</td>
<td>Inactivated MTBVAC</td>
<td>H56 + IC31 B</td>
</tr>
<tr>
<td>Oxford</td>
<td></td>
<td>B</td>
<td>SSI, Intercell, Aeras</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Zaragoza</td>
<td>M72/AS01E B</td>
</tr>
<tr>
<td>rBCG::Ac2SGL (isoforms)</td>
<td>B</td>
<td></td>
<td>GSK, Aeras</td>
</tr>
<tr>
<td>Toulouse</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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*Note: P indicates phase.*

*Source: [TBVImune](https://www.tbvimmune.com/)*
TB: a huge cost to humanity

- World Bank: The global burden of tuberculosis is estimated at hundreds of billions of dollars every year.
- World Bank: The annual economic loss is 0.52 per cent of the world’s gross national income
- Recent study University of Kiel, Germany: TB costs EU €537 mln/yr (direct costs)
- Development of new TB vaccine costs about €600 mln (recent calculation of TBVI and Aeras)
Projected acceleration of TB incidence decline to target levels (WHO)

- Current global trend: -2%/year
  - Average: -10%/year
- Optimize current tools, pursue universal health coverage and social protection
- Introduce new vaccine, new prophylaxis
  - Average: -17%/year
  - -5%/year
Global TB vaccine Partnership (I)

• Portfolio of >30 vaccine candidates in discovery/preclinical/clinical development
• Approx. €600 mln needed to develop vaccines for the market (from discovery -> Phase III)
• Conditions:
  – Global portfolio approach
  – Rigorous stage gating criteria
  – Innovative trial designs
  – Combined and increased funding
Global TB vaccine Partnership (II)

- Plan initiated by TBVI
- Support of European Parliament via resolution
- Working group (EIB, EC, BMGF, EDCTP, TBVI, Aeras) chaired by EIB to further develop the plan
- Funding synergies for all phases (discovery up until and including phase III/IV) through various instruments and funders
- Aiming for a Heads of agreement to support a Global TB vaccine partnership in Q1 2014
Global progress in TB vaccine development

- 15 candidates are currently being evaluated in clinical trials
- Robust pipeline of >25 candidates in discovery / preclinical development
- Capacity and infrastructure developed or being developed at several sites, including South Africa, Kenya, Uganda, Mozambique, Ethiopia, Senegal and the Gambia
- Manufacturing capacity being developed and manufacturing agreements are being explored with particular emphasis on emerging economies
- Regulatory pathways and market and economic impact research being conducted now to lay the groundwork to accelerate adoption and uptake of new TB vaccines
### Global Clinical TB Vaccine Pipeline

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase IIa</th>
<th>Phase IIb</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ad5 Ag85A</td>
<td>B</td>
<td>Ad35/Aeras402</td>
<td>MVA85A /Aeras485</td>
</tr>
<tr>
<td>McMaster University, Canada Sino</td>
<td>B</td>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>ID93 + GLA-SE</td>
<td>B</td>
<td>VPM1002</td>
<td>M72/ASO1E</td>
</tr>
<tr>
<td>IDRI, Aeras</td>
<td>P</td>
<td>MPIIB, VPM, TBVI, SII</td>
<td>B</td>
</tr>
<tr>
<td>MTBVAC</td>
<td>P</td>
<td>RUTI</td>
<td>M. indicus pranii</td>
</tr>
<tr>
<td>UniZaragoza, Biofabri, TBVI</td>
<td></td>
<td>Archivel Pharma</td>
<td>IT Dpt of Biotechn (Govt of India), Cadila</td>
</tr>
<tr>
<td>Dar-901</td>
<td>B</td>
<td>Hybrid I + IC31</td>
<td>M. vaccae</td>
</tr>
<tr>
<td>Dartmouth University (pending)</td>
<td></td>
<td>B</td>
<td>IT An Hui Longcom (pending)</td>
</tr>
<tr>
<td>SAV/Ag85a</td>
<td>B</td>
<td>H56 + IC31</td>
<td>P priming vaccine</td>
</tr>
<tr>
<td>UOXF, TBVI, Wellcome Trust</td>
<td></td>
<td>B</td>
<td>B boosting vaccine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hyvac4/Aeras404</td>
<td>IT therapeutic vaccines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>B</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>SSI, SP, Aeras</td>
<td></td>
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<td>MVA85A /Aeras485 B</td>
<td>M. Indicus pranii IT</td>
</tr>
<tr>
<td>McMaster University, Can Sino</td>
<td>McMaster (then Aeras)</td>
<td>UOXF, AERAS</td>
<td>Dpt of Biotechn (Gvt of India), Cadila</td>
</tr>
<tr>
<td>ID93 + GLA-SE</td>
<td>VPM1002 B</td>
<td>M72/ASO1E B</td>
<td>M. vaccae IT</td>
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<td>IDRI, Aeras</td>
<td>MPIIB, VPM, TBVI, SII</td>
<td>GSK, Aeras</td>
<td>An Hui Longcom (pending)</td>
</tr>
<tr>
<td>MTBVAC P</td>
<td>RUTI IT</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UniZaragoza, Biofabri, TBVI</td>
<td>Archivel Pharma</td>
<td></td>
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<tr>
<td>Dar-901 B</td>
<td>Hybrid I + IC31 B</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dartmouth University (pending)</td>
<td>SSI, TBVI, Intercell, EDCTP</td>
<td></td>
<td></td>
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<tr>
<td>SAV/Ag85a</td>
<td>H56 + IC31 B</td>
<td></td>
<td>P priming vaccine IT</td>
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<tr>
<td>UOXF, TBVI, Wellcome Trust</td>
<td>SSI, Intercell, Aeras</td>
<td></td>
<td>boosting vaccine</td>
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<tr>
<td></td>
<td>Hyvac4/Aeras404 B</td>
<td></td>
<td>IT therapeutic vaccines</td>
</tr>
<tr>
<td></td>
<td>SSI, SP, Aeras</td>
<td></td>
<td>Current/former TBVI</td>
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<tr>
<td></td>
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<td></td>
<td>involvement</td>
</tr>
</tbody>
</table>
Discovery & Pre-clinical Pipeline

- Robust pipeline of >25 candidates in discovery / preclinical development
- Need for continuous investment in discovery and pre-clinical to generate new candidates for clinic
- In discovery aim to avoid duplication in efforts and support new and innovative approaches that add value to the portfolio
- GTBVP to liaise with various ongoing and new r&d programs focused on new candidate generation to link to clinical development funding instruments (uptake in clinical pipeline via portfolio management)
Connection TBVI – Southeast Asian and other International Partners

- Network open and accessible to new partners
- Interest in new partners with new tb vaccine approaches complementary to portfolio (discovery, pre-clinical as well as clinical)
- Link to European research community on new TB vaccine development
- Link to European Union funding mechanisms – joint call applications proposal writing and project management
- Link to GTBVP
- Continuous strengthening of consortium (new research approaches, collaboration, information sharing) to reach final goal of new vaccines against TB.
Foundation to facilitate European efforts towards the global development of new TB vaccines

www.tbvi.eu

Thank you for your attention!