New vaccines for Tuberculosis

Current and future perspectives

Jelle Thole
Tuberculosis in the world

According to latest WHO data, in 2006:

- 14.4 million prevalent cases of TB
- 9.2 million new cases, 0.7 million in HIV-positive people
- 1.7 million TB-related deaths, 0.2 million in HIV-positive people
- 0.5 million case of multidrug-resistant cases (MDR-TB)

- Drug resistance and TB/HIV co-infection are key barriers to progress
Estimated numbers of new cases, 2006

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries.

Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

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Worldwide Distribution of New TB Cases, 2006

New TB cases per 100,000 population in 2006

- No estimate
- 0-24
- 25-49
- 50-99
- 100-299
- 300 or more
TB/HIV Coinfection

- TB is the most common presenting illness among people living with HIV on ARV treatment worldwide.
- TB is the leading cause of death among HIV positive individuals in Africa.
- 85% of 217,000 people that died of HIV associated TB in 2006 people lived in Sub-Saharan Africa.
- At least 1/3 of the 33.2 million people living with HIV are also infected with TB and have a greater risk of developing TB disease (5-10 % annually).
Estimated HIV prevalence in new TB cases, 2006

HIV prevalence in TB cases, (%)

- No estimate
- 0–4
- 5–19
- 20–49
- 50 or more

WHO 2006. All rights reserved.
### Drug Resistance: Multidrug-resistant TB (MDR-TB)

- Drug-resistant TB is widespread and found in all 81 countries recently surveyed by WHO.
- Multidrug-resistant TB (MDR-TB) does not respond to the standard six month treatment using first line-drugs (i.e. resistant to isoniazid and rifampicin).
- MDR-TB can take up to two years to treat with drugs that are more toxic, and 100 times more expensive.
- WHO estimates 500,000 new cases and 110,000 deaths each year
- Highest rates in countries of the former Soviet Union and China
Extensively Drug-Resistant TB (XDR-TB)

- Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB plus resistance to any fluoroquinolone and any of the second-line anti-TB injectable drugs: amikacin, kanamycin or capreomycin).
- 40,000 new cases of XDR-TB each year
- 45 countries with at least one confirmed case of XDR
- The true scale of the problem remains unknown in some pockets of the world.
  - Only six countries in Africa—the region with the highest incidence of TB in the world--were able to provide drug resistance data for the latest WHO surveillance report.
  - Other countries in the region could not conduct surveys because they lack the equipment and trained personnel needed to identify drug-resistant TB.
- MDR-TB and XDR-TB are highly lethal in people living with HIV -- studies show case fatality rates of over 90%.
Countries with XDR-TB confirmed cases as of February 2008
BCG Vaccine

- Calmette & Guérin (1906-1921)
- Attenuated M. bovis
- First used in 1921
- 1928 recommended for wide spread use by League of nations
- Widespread use after 1945
- Most widely used vaccine
Variable Efficacy of BCG vs. Pulmonary TB

Vaccine Efficacy (%)

<table>
<thead>
<tr>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>British School Children</td>
</tr>
<tr>
<td>N. American Indians</td>
</tr>
<tr>
<td>USA (Chicago Infants)</td>
</tr>
<tr>
<td>Puerto Rico (Gen. Pop.)</td>
</tr>
<tr>
<td>S. India (Madanapalle)</td>
</tr>
<tr>
<td>USA (Georgia &amp; Alabama)</td>
</tr>
<tr>
<td>S. India (Chingleput)</td>
</tr>
<tr>
<td>USA (Georgia Children)</td>
</tr>
<tr>
<td>Brazil (Sao Paolo)</td>
</tr>
<tr>
<td>Argentina (Buenos Aires)</td>
</tr>
<tr>
<td>Brazil (Belo Horizonte)</td>
</tr>
<tr>
<td>Cameroon (Yaounde)</td>
</tr>
<tr>
<td>Canada (Manitoba Indians)</td>
</tr>
<tr>
<td>Indonesia (Jakarta)</td>
</tr>
<tr>
<td>Surinam (Rangoon)</td>
</tr>
<tr>
<td>Sri Lanka (Colombo)</td>
</tr>
<tr>
<td>Colombia (Cali)</td>
</tr>
<tr>
<td>Argentina (Santa Fe)</td>
</tr>
<tr>
<td>Togo (Lome)</td>
</tr>
<tr>
<td>Thailand</td>
</tr>
</tbody>
</table>
Genealogy of BCG vaccines

Brosch et al
PNAS, 2007,
104: 5596
Variable efficacy of BCG

- Genetic variation in BCG strains
- Genetic variation in populations
- Differences in virulence between TB strains (e.g. Beijing)
- Protection against endogenous infection but not exogenous re-infection
- Interference by non-tuberculous mycobacteria (e.g. M. avium)
- Interference by concurrent parasitic infection (Th2 induction)
Current vaccines against TB

- One vaccine, BCG, reduces risk of severe pediatric TB disease
- Variable protection against adult pulmonary TB, which accounts for most TB worldwide
- Risk of disseminated BCG in HIV positive infants
Exposure to infectious particles

- No Infection (70%)
- Infection (30%)

- Early Progression 1-2 years (5%)
- Late Progression Lifetime (5%)

Resistance

<table>
<thead>
<tr>
<th>Prevention of Reactivation</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Improved) prevention of infection and disease</td>
</tr>
<tr>
<td>Prevention of Latency</td>
</tr>
<tr>
<td>Resistance (95%)</td>
</tr>
</tbody>
</table>

Therapeutic Vaccines

ANIMAL SCIENCES GROUP WAGENINGEN UR
New TB Vaccines

- Identify “protective” immune response during infection and disease
- Identify antigens involved
- Design a vaccine capable of inducing a protective response
Immune response

No correlate of protection known

**Innate:**
- Stimulate TLR through adjuvants

**Acquired:**
- (CD4) Th1 T cells (IFN-γ, TNF-α) activate macrophage to kill Mtb
- CD8 T cells lyse and kill infected cell and Mtb
Classes of Antigens

**Stress:**
- HSP65
- HSP70
- HSP16

**Resuscitation:**
- Rv3407

**Glycolipids:**
- SGL

**Secreted:**
- Antigen85
- ESAT6
- CPF10

**Latency:**
- DosR:
  - Rv2029
  - HSP16

**RD antigens not present in BCG:**
- ESAT6
- TB10.4
Recent adjuvants in TB

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Origin</th>
<th>What</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS01B/AS02</td>
<td>GSKBio</td>
<td>MPLA from S. Minnesota plus QS21 from soap bark tree in oil or liposomes TLR4 signalling, Depot</td>
</tr>
<tr>
<td>IC31</td>
<td>Intercell</td>
<td>Antimicrobial peptide, KLK, with immunostimulatory oligonucleotide, ODN1a, TLR9 signalling, APC, Depot</td>
</tr>
<tr>
<td>DDA/TDB</td>
<td>SSI</td>
<td>dimethyldioctadecylammonium bromide (DDA), and trehalose 6,6'-dibehenate (TDB) TLR ? Depot</td>
</tr>
</tbody>
</table>

Nonclin | Phase I | Phase II | Phase III
Design of new vaccines

- **Improve BCG**
  - Adding antigens from RD regions (e.g. ESAT6)
  - Overexpression of antigens (Ag85)
  - Engineering phagosome escape (Hly, Pfo)

- **Attenuate M. tuberculosis**
  - Deleting essential genes (e.g. Phop, auxotrophic mutants)

- **(Viral) vector based**
  - MVA, Adenovirus, rBCG

- **Subunit antigens combined with adjuvants**
  - Secreted antigens (Ag85, ESAT6, TB10.4)
  - Strong immunogens (Rv1196, Rv0125)
  - Latency antigens (hsp16, DosR etc)
  - Adjuvants (IC31, AS02/1B, DDA/TDB)
TB-VAC
Design and testing of vaccine candidates against tuberculosis: identification, development, and clinical studies

- NL
- UK
- FR
- IT
- ES
- GE
- BE
- DK
- CH

- Consortium of 29 European + 4 African Partners
- 1-1-2004 - 31-12-2008
- 17 mE EC FP6, and 1.8 mSF OFES

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
- New approaches
- New antigens

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)
Discover and Preclinical Development

- 5 new vaccine candidates (live and subunit)
- 15 candidate surrogate markers
- 3 candidate adjuvant molecules
- Preclinical animal models
  - Vaccine efficacy
  - Immunogenicity
  - Safety
  - Post-exposure

- >50 publications; >10 IP
BCG::RD1

- BCG::RD1 gives better protection
- Overcomes inhibition of protection to BCG after pre-exposure to M. avium
- BCG::RD1 more virulent than BCG in SCID
Listeriolysin
\(\Delta_{\text{Ure}}\) rBCG-hly

\(\text{pH} < 6\)

Early Phagosome

Antigens

Lysosome

Phagolysosome

\(< \text{pH} 5\)
Protective Capacity rBCG ΔureC-Hly Challenge “Beijing“ (200 CFU 120 d post vaccination)

* Δ log = 2.3
* Δ log = 2.1

M. tuberculosis::PhoP

Attenuation by deletion of PhoP gene

Signal Transduction Systems enable bacteria to detect environmental stimuli and respond to them

Sensor Protein

Transcription Factor

11 TCSs in *M. tuberculosis*

limited number of TCS when compared with other bacteria
Survival of guinea pigs up to 26 weeks post high-dose (500CFU) aerosol challenge.
New live mycobacterial vaccines: the Geneva consensus on essential steps towards clinical development

Arun T. Kamath\textsuperscript{a}, Uli Fruth\textsuperscript{b}, Michael J. Brennan\textsuperscript{c}, Roland Dobbeltaer\textsuperscript{d}, Peter Hubrechts\textsuperscript{e}, Mei Mei Ho\textsuperscript{f}, Ronald E. Mayner\textsuperscript{g}, Jelle Thole\textsuperscript{h}, K. Barry Walker\textsuperscript{i}, Margaret Lin\textsuperscript{j}, Paul-Henri Lambert\textsuperscript{a,*}

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\textsuperscript{c} Initiative for Vaccine Research, World Health Organization, Geneva, Switzerland
\textsuperscript{d} Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, MD, USA
\textsuperscript{e} Health, Food Chain Security and Environment, Scientific Institute of Public Health, Brussels, Belgium
\textsuperscript{f} Quality Control Department, Statens Serum Institut, Copenhagen, Denmark
\textsuperscript{g} Division of Bacteriology, National Institute for Biological Standards and Control, South Mimms, Potters Bar, UK
\textsuperscript{h} Aeras Global TB Vaccine Foundation, Bethesda, MD, USA
\textsuperscript{i} Division of Infectious Diseases, Animal Sciences Group, Lelystad, The Netherlands
\textsuperscript{j} Division of Immunobiology, National Institute for Biological Standards and Control, South Mimms, Potters Bar, UK

\textsuperscript{a,*} Transgene S.A., Strasbourg, France

Received 4 March 2005; accepted 9 March 2005
Available online 24 March 2005
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-ESAT6) antigen

Log10 CFU in lungs

- Naive
- BCG
- DDA/TDB

*measured by ELISpot after restimulation with vaccine (Ag85B-ESAT6) antigen
Downstream development

- Product development teams for 6 vaccines
- GMP production of 2 vaccines
- 3 vaccines in phase I/IIa trials
- 3 new vaccines entering downstream development
- One adjuvant entering clinical trials (DDA/TDB)
- Capacity in 2 new African clinical trial sites (AHRI, Ethiopia; Ledantec, Senegal)
<table>
<thead>
<tr>
<th>Discovery</th>
<th>Pre-clinical efficacy</th>
<th>GMP-Production</th>
<th>Non-clinical safety</th>
<th>IND file</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Effective protection (mice, g-pigs, N-hu Prim)</td>
<td>Lot consistency-Formulation</td>
<td>Incl. neonatal.</td>
<td>TOX studies</td>
</tr>
</tbody>
</table>

**Product Development Team (PDTs)**

- **Ph1-Safety / immunogenicity adults (high endemicity area)**
  - PPD neg & BCG primed
  - LTBI

- **Ph1 Trials Safety / immunogenicity adults (in area of production)**
  - PPD neg
  - BCG primed
  - LTBI or treated TB
  - HIV infected

- **Ph2a- Safety / immunogenicity ados. + infants**
  - Adults/Ados
  - Infants
  - [Formulation. Bridg.]
  - Interference studies
  - HIV pos ados/infants 2009-10

**Phase IIb**
- Adults/ados
- infant

**Phase III**
- Adults/ados
- infants
<table>
<thead>
<tr>
<th>Pre-clinical efficacy</th>
<th>GMP-Production</th>
<th>TOX studies</th>
<th>IND file</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective protection (mice, g-p, N-hu P)</td>
<td>Done</td>
<td>OK</td>
<td>OK (UK)</td>
</tr>
</tbody>
</table>

**Safety / immunogenicity**

- EU-adults
- PPD neg
- BCG primed

### JAN 2004

**MVA-Ag85A**

- U-OXF + IDT
- UK + DE

**Immunogenicity:**

- excellent primary + secondary responses

**Safety:** low reactogenicity

![Graph](image)

**Response to:** Ag85A

![Map](image)
<table>
<thead>
<tr>
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<th>GMP-Production</th>
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<td>OK</td>
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</tbody>
</table>

**Safety / immunogenicity** *(EU- adults)*

<table>
<thead>
<tr>
<th>PPD neg</th>
<th>BCG primed</th>
<th>LTBI or treated TB</th>
<th>HIV infected</th>
</tr>
</thead>
</table>

**MVA-Ag85A**
U-OXF + IDT
UK + DE

**Ph1** - Safety / immunogenicity *(AFR- adults)*

<table>
<thead>
<tr>
<th>PPD neg &amp; BCG primed</th>
<th>LTBI</th>
<th>HIV infected</th>
</tr>
</thead>
</table>

**Ph2a** - Safety / immunogenicity *ados. + infants* *(AFR)*

<table>
<thead>
<tr>
<th>Ados/ Infants</th>
<th>Age de-escalation</th>
<th>Dose escalation</th>
<th>Interference studies</th>
<th>HIV infected ados/infants</th>
</tr>
</thead>
</table>

**MVA live vector expressing Ag85A**

**Phase 2b AFR**

<table>
<thead>
<tr>
<th>Ados</th>
<th>Infants 2008-12</th>
</tr>
</thead>
</table>

**Phase 3 AFR**

<table>
<thead>
<tr>
<th>Ados 2009</th>
<th>Adults 2009-12</th>
</tr>
</thead>
</table>
### Overview

**Ag85B-ESAT6 + IC31 (H1)**  
SSI + Intercell

<table>
<thead>
<tr>
<th>Pre-clinical efficacy</th>
<th>GMP-Production</th>
<th>Pre-clinical safety</th>
<th>IND file</th>
</tr>
</thead>
<tbody>
<tr>
<td>(mice, g-p, N-hu P)</td>
<td>Done- DK (several lots)</td>
<td>neonatal mice OK</td>
<td>OK (NL, UK)</td>
</tr>
<tr>
<td>Effective protection ++</td>
<td></td>
<td>TOX studies OK</td>
<td></td>
</tr>
</tbody>
</table>

**Safety / immunogenicity (EU- adults)**
- PPD neg
- BCG primed
- LTBI

**Safety / immunogenicity (AFR- adults)**
- PPD neg
- BCG primed
- LTBI

**Ph1-Safety / immunogenicity**  
(AFR- adults)
- PPD neg & BCG primed
- LTBI

**JAN 2008**

**Immunogenicity:** good primary response  
**Safety:** low reactogenicity

**IFNγ ELISPOT**

**Resp. to:** Ag85B, ESAT6, H1

**Diablerets Feb 08**
### Completed & on-going trials – USA + Europe

<table>
<thead>
<tr>
<th>Trials</th>
<th>Status</th>
<th>Funding source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 – trial(s) in PPD neg</td>
<td>Done 04-05 - USA/BE</td>
<td>GSK</td>
</tr>
<tr>
<td>Phase 1 - trial(s) in PPD pos (BCG or latent TB)</td>
<td>Done 05-06 - CH</td>
<td>TB-VAC &amp; GSK</td>
</tr>
<tr>
<td>Phase 1 – trial(s) in HIV pos</td>
<td>Planned 08 - CH</td>
<td>GSK &amp; TB-VAC</td>
</tr>
</tbody>
</table>

- **Pre-clinical efficacy**: M, GP, NHP
- **GMP-Production**: ++
- **TOX studies**: Done several lots
- **IND**: OK

**Mtb72F + AS-02**

**M72+AS02 or M72+AS01**

**GSK**

**BE**

**Ra12**

**TbH9**

39 kDa

**Ra35**

**JAN 2008**
Mtb72F + AS-02
M72+AS02 or M72+AS01
GSK
BE

**JAN 2008**

- Highly immunogenic in BCG-primed and Mtb-exposed individuals (boosting)
- Vaccine shown to be safe with acceptable local reactogenicity in BCG-primed individuals

**Pre-clinical efficacy**
M, GP, NHP

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<td>Planned 08 - CH</td>
<td>GSK &amp; TB-VAC</td>
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**Mtb72F** + AS-02

**GMP-Production**

**TOX studies**

**IND**

- ++
- Done several lots
- OK
- OK

**Completed & on-going trials – USA + Europe**

- Mtb72F + AS-02
- M72+AS02 or M72+AS01
- GSK
- BE

**Ra12**
- TbH9 39 kDa
- Ra35

**M72-AS01**
<table>
<thead>
<tr>
<th>Candidate - vaccines</th>
<th>Developer</th>
<th>Initial cGMP Production</th>
<th>Regulatory Assessm.</th>
<th>Phase I PPD-</th>
<th>Phase I/II In PPD+</th>
<th>Clinical Trials in PPD+ and HIV exposed</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA-Ag85A, (VV, Pr-b)</td>
<td>UOXF</td>
<td>Done (lot1)</td>
<td>Done (lot1)</td>
<td>On-going</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2003-4 UOXF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mtb72f hybrid recAg + AS02</td>
<td>GSKbio</td>
<td>Done (lot1)</td>
<td>Done (lot1)</td>
<td>Initiated</td>
<td>USA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Feb 2004</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>USA</td>
<td></td>
<td></td>
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<tr>
<td>Ag85B-ESAT6 recAg + IC31</td>
<td>SSI</td>
<td>planned</td>
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Diablerets Feb 08
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<td>Done (lot1)</td>
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<td>On-going 2003-4 UOXF</td>
<td>2004-5 UOXF</td>
<td>2005 UOXF</td>
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<td>Done (lot1)</td>
<td>Initiated Feb 2004 USA</td>
<td>09-2005 Lausanne</td>
<td>2007 Lausanne</td>
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<tr>
<td>Ag85B-ESAT6 recAg + IC31</td>
<td>SSI</td>
<td>Done 2004</td>
<td>Done (lot1)</td>
<td>09/ 2005 Leiden</td>
<td>2007 Leiden</td>
<td>2007 Ethiopia</td>
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<tr>
<td>rBCG-UreC-Hly</td>
<td>MP-VPM/BPR</td>
<td>Done 2007</td>
<td>Done 2007</td>
<td>Planned 2007</td>
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<tr>
<td>Mtb- PhoP HBHA</td>
<td>INSERM/ULB</td>
<td>Pre-PDT exploratory meetings</td>
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</table>
A cluster for tuberculosis vaccine developments

The TB-VAC project aims to develop improved vaccines, particularly for the young adult population. Vaccine candidates and strategies will be optimised for evaluation in Phase 1 clinical trials.
TuBerculosis Vaccine Initiative (TBVI)

Foundation to facilitate European efforts towards the development of new TB vaccines

5 March 2008
TBVI Activities

- Facilitate Discovery, Preclinical and Early clinical TB vaccine development
- Responsibility and Ownership of candidate vaccine with individual project partners
- Guide and Advice on development by tailor made product development teams (PDT)
- Stimulate late clinical development through product development partnerships
<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Who</th>
<th>PDT</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA85A</td>
<td>UOXF</td>
<td>+</td>
</tr>
<tr>
<td>M72-AS01B</td>
<td>GSKBIO</td>
<td>+</td>
</tr>
<tr>
<td>85B-ESAT6-IC31</td>
<td>SSI</td>
<td>+</td>
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<tr>
<td>BCG-ΔureA-Hly</td>
<td>MPIIB/VPM</td>
<td>+</td>
</tr>
<tr>
<td>Mtb-PhoP</td>
<td>UNIZAR</td>
<td>+</td>
</tr>
<tr>
<td>HBHA</td>
<td>IPL</td>
<td>+</td>
</tr>
<tr>
<td>GL</td>
<td>CNRS</td>
<td>+</td>
</tr>
<tr>
<td>BCG-RD1</td>
<td>IPAS</td>
<td>TBD</td>
</tr>
</tbody>
</table>

**TBVAC Vaccine Pipeline**

- **Discovery**
- **Nonclin**
- **Phase I**
- **Phase II**
- **Phase III**
Global pre and non clinical development pipeline

As of March 2008:

- 10 Priming, Pre-exposure candidates
- 17 Boosting, Pre-exposure candidates
- 12 Post-exposure – immunotherapy candidates

Nine additional candidates scheduled for clinical trials in 2008 according to sponsors
### TB vaccines in clinical trials

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Origin</th>
<th>What</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
</tr>
</thead>
<tbody>
<tr>
<td>MVA85A</td>
<td>UOXF</td>
<td>Recombinant vaccinia expressing Ag85A, to boost BCG</td>
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<tr>
<td>M72 in AS01B</td>
<td>GSKBio</td>
<td>Subunit fusion protein of Rv1196 and Rv0125 in ASO1B adjuvant, to boost BCG</td>
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<tr>
<td>85B-ESAT6 in IC31 (Hyb1)</td>
<td>SSI</td>
<td>Subunit fusion protein of Ag85B and ESAT6 in IC31 adjuvant, to boost BCG</td>
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<tr>
<td>rAd35-Ag85A, 85B, TB10.4</td>
<td>Crucell</td>
<td>Recombinant adenovirus35 expressing Ag 85A, 85B, 10.4 to boost (recombinant)BCG</td>
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<tr>
<td>85B-TB10.4 in IC31 (HyVAC4)</td>
<td>SSI</td>
<td>Subunit fusion protein of Ag85B and TB10.4 in IC31 adjuvant, to boost BCG</td>
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<tr>
<td>rBCG-Ag30</td>
<td>UCLA</td>
<td>Recombinant BCG overexpressing Ag85B, to replace BCG</td>
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<tr>
<td>RUTI</td>
<td>Archivel Pharma</td>
<td>Detoxified Fragmented MTB, to treat latently infected individuals</td>
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</tbody>
</table>
Future TB vaccines

Boost MVA85A 72M H1 HyVac4 Ad35/Ag85A B,TB10.4
Improved BCG rBCG-Hly rBCG-PFO Mtb-PhoP Latency DosR Rv3409

STOP-TB/MDG: less than 1 case/million in 2050
Summary and Future challenges

- More TB vaccine candidates than ever before, and prospect of new vaccine between 2015-2020
- Keep pipeline filled with second and third generation vaccines
  - Vaccines (latent bacteria, improved protection)
  - Delivery (systems/adjuvants, applications (needless) and routes eg. ID, mucosal)
  - Preclinical models to select for clinical development
- Biomarkers and correlates of protection
- (Global) clinical site development