

DRAFT

**Draft Strategic Plan
of the
Stop TB Partnership Working Group on TB Vaccine Development**

2nd Global Plan to Stop TB 2005-2015 (GPII)

Status: 28 April 2005

Background

The current BCG vaccine, an attenuated variant of *Mycobacterium bovis*, is a core component of the EPI. Delivered at or near birth, it has been shown to protect against severe childhood forms of disease, including the often fatal tuberculous meningitis. It also confers protection against leprosy. However, it has failed to protect against adult pulmonary tuberculosis in endemic countries. The reasons for the failure of BCG have been widely debated, and remain the topic of active research. Natural exposure to environmental mycobacteria is thought to exert an important influence on the immune response, and this may negate the effect of BCG vaccination in tropical countries. It is important to note that, in contrast to a classical vaccine-preventable disease like smallpox, recovery from initial TB infection does not guarantee resistance to a second infection. A truly effective TB vaccine may, therefore, have to elicit an immune response that is superior to that induced by natural infection. This represents a challenge beyond that met by current infectious disease vaccines.

TB research over the last decade has been driven by the genomics revolution. Major advances in our understanding of mycobacterial pathogenesis have been achieved through the sequencing of the genome of *Mycobacterium tuberculosis*, and the development of tools for gene deletion and for exchange of genes between mycobacteria. In parallel, gene knockout technology has generated important fundamental insights into the mechanisms of host immunity. These advances have had direct impact on the prospects for new TB vaccines. The primary target of TB vaccines is to establish memory pools of type 1 (IFN γ -producing) CD4⁺ and CD8⁺ T cells. These can be induced using live attenuated mycobacteria, or by appropriate delivery of selected mycobacterial genes or gene products.

DRAFT

The search for a vaccine capable of making an impact on the global control of tuberculosis has taken on a new momentum with the recent progression from laboratory-based studies to clinical trials of new candidates. Important factors in this are the recent contributions by donor agencies such as the European Commission and the US-National Institutes of Health and most significantly, the award of \$83m from the Bill & Melinda Gates Foundation to support the work of the not-for-profit Aeras Global TB Vaccine Foundation. However, the path to a new TB vaccine is neither simple nor guaranteed. In parallel with clinical trials of the best available candidates, there is a need to strengthen scientific understanding of immunological mechanisms underlying successful vaccination against this disease, and to translate this knowledge into a further round of new improved candidates. The complexity of this challenge is such that it is unlikely to be met by one single organisation. More than ever, there is a need for dialogue and coordination between the many stakeholders involved in TB vaccine development, from the laboratory scientists and vaccine developers, to the regulatory agencies and public health bodies responsible for trials and ultimate implementation.

This coordinating function is currently exercised by the Vaccine Working Group within the Stop TB Partnership (TBVAC). Stop TB is a global movement to accelerate social and political action to stop the spread of tuberculosis around the world and includes representation from the groups involved in TB control, research and funding. TBVAC was formed by building on previous structures within the WHO Initiative for Vaccine Research (WHO/IVR), and includes a broad representation from the TB vaccine community. TBVAC has an annual plenary meeting which serves as a forum for discussion of roadblocks to TB vaccine development which are then addressed by a series of specific targeted Task Forces.

DRAFT

Achievements against the first Global Plan to Stop TB (2000 – 2005)

Extensive collaborative networks have been fundamental to progress in preclinical screening. Centralised vaccine testing facilities have been made available through NIH support in the US, and head-to-head comparisons of multiple candidates have been a central component of TB vaccine research within the European Community TB vaccine research programme. The Preclinical Task Force of the Stop TB Working Group has provided an important forum for coordination of these activities, including standardisation of protocols and exchange of reagents. The more successful candidates identified in these experimental models are now ready for clinical testing (see table 1).

The overall objective of the TB Vaccine Working Group within the context of the first Global Plan was to stimulate research and promote the transition of at least five candidate vaccines from preclinical research into phase clinical trials. This goal is most likely to be achieved with 5-6 candidates in phase I safety evaluation by the end of 2005. Details on progress are as follows:

- A vaccinia virus-vectored subunit vaccine based on a secreted antigen (Ag85A) of *Mycobacterium tuberculosis*, developed at Oxford University has completed initial phase I clinical evaluation in the UK in 2004. Safety and immunogenicity of that vaccine were reported to be excellent, in particular when used as "booster" dose, on top of BCG vaccination, even when the BCG had been given decades ago.
- Two more vaccine candidates have entered phase I clinical trials, one adjuvanted fusion protein that is being developed by GSK and a BCG recombinant for Ag85A, co-developed by University of California, Los Angeles, and the Aeras Global TB Vaccine Foundation.
- Three more vaccine candidates, one adenovirus construct, another recombinant BCG and a second adjuvanted fusion protein are planned to enter phase I trials in 2005.

DRAFT

Table 1 Vaccine candidate portfolio

VACCINE	COMPOSITION/MODIFICATION	DEVELOPMENT STAGE/Transition date	RESEARCHERS/ Funders
Research Candidate for next Generation - fundamental work to identify most promising candidates			
Mtb peptides	5 Mtb peptides (synthetic)	(abandoned?)	Intercell
Hsp65	DNA vaccine/ purified protein	?	Lowrie, Silva/ Immunobiologics
LAM-TT conjugate	Lipoarabinomannan-tetanus toxiod conjugate vaccine	?	Svensson, Pawlow Karolinska Institute
Preclinical Development candidate vax being studied to meet regulatory requirements (e.g. IND enabling studies)			
85B/10.4	Fusion protein	Preclinical studies	SSI/Aeras
AF112	rBCG with perf and Ag85A,B,Y	Preclinical studies	MAeras
BCG::RD1	RD-1 locus of <i>M. tuberculosis</i> introduced into BCG Pasteur	Continuing pre-clinical studies/?	Cole, Institut Pasteur/Eurovac
<i>M. tuberculosis</i> PhoP	A virulence-associated gene, PhoP is deleted from <i>M. tuberculosis</i> genome	Continuing pre-clinical studies and GLP product production	Martin, Gicquel Eurovac
<i>M. tuberculosis</i> mc ² 6020	LysA and panCD deleted from <i>M. tuberculosis</i> genome (non-replic.)	Production of GMP product and application to FDA	Jacobs, Albert Einstein CoM
<i>M. tuberculosis</i> mc ² 6030	panCD and RD-1 locus deleted from <i>M. tuberculosis</i> genome (replicating)	Production of GMP product and application to FDA	Jacobs, Albert Einstein CoM
rBCGAUreCHly	Listeriolysin of <i>L. monocytogenes</i> ino BCG Pasteur, urease gene is deleted	Phase 1 planned for Q3 of 2005	Kaufmann, MPI / VPM
<i>AdVac85A,B,Y</i>	Adenovirus vectored Ag85A	Phase 1 planned for early 2006	Crucell/Aeras
Ag85B/ESAT-6	Fusion protein	Phase 1 planned for mid-2005	P. Andersen, SSI
Phase I			
M72f	Fusion protein	Phase 1 trial in USA nearing completion, Europe started	Corixa, GSKBio
rBCG30	Over expression of Ag85B, encoded by a plasmid in BCG Tice	Results of Phase I trial (in USA) being analysed	Horwitz, UCLA
<i>MVA-85A</i>	Vaccinia-vectored Ag 85A	Phase 1 in UK completed, phase 1 in The Gambia ongoing	Hill/McShane, Oxford University
To Be Classified			
<i>M. vaccae</i>	Heat killed	Phase III underway in Tanzania	Von Reyn/NIH

DRAFT

Strategic Vision 2005 – 2015

The vision of the Stop TB Vaccine Working Group is to promote synergies in order to accelerate development and licensure of at least one safe, effective and affordable vaccine for use in the TB high burden by the year 2015. Once such a vaccine becomes available, every effort must be made to ensure its rapid introduction in populations most in need without the often decade -long transition periods characteristic of current new vaccine introduction schemes along a socio-economic gradient.

A new TB vaccine is likely to have no or little impact by 2015. However, benefits beyond the MDG deadline are likely to be considerable. Two general delivery strategies/product profiles for TB vaccines are being discussed. The first is based on vaccines that, like BCG, would be delivered prior to exposure to mycobacterial infection. The intention is to prime an immune response that would either completely eliminate any infecting organisms, or at least contain the infection at a subclinical level throughout the life of the individual. The second approach is to enhance immunity in individuals with a pre-existing immune response to mycobacteria induced by infection with *M. tuberculosis* or by prior BCG vaccination. An attraction of this post-exposure approach is that it could be applied to the two billion people already infected with *M. tuberculosis* and would therefore have a more immediate impact on the incidence of disease.

The Stop TB Vaccine Working Group perceives a need for both types of vaccine and therefore promotes their development in a parallel track mode. However, it is envisaged that both pathways will come together some time around 2015, with either the same antigens being useful for both pre- and post-exposure vaccination or through combination vaccines composed of pre-and post-exposure antigens.

DRAFT

Objectives and Key Activities:

Objective 1 Maintain and Improve BCG Programmes

- It is highly likely that BCG remains the cornerstone of TB vaccination programmes for the foreseeable future. It is therefore important to ensure good functioning of the BCG programmes and BCG supply. Furthermore, shortcomings such as the poor characterization of currently used BCG strains be overcome

Objective 2 Discovery and translation research ("keeping the pipeline filled")

- need more researchers focused on TB vaccine basic research – estimate ~20 devoted labs currently-need 50
- need programs that stimulate translational research, epi research, clinical research, regulatory science
- animal modeling for safety, efficacy, and that mimic human immunization regimens
- a focus on developing country scientists and programs for TB vaccines

Objective 3 Perform preclinical development

- development of GMP-like tests for assuring vaccine is sterile, pure, non-toxic, potent, efficacious in animal models
- find/develop pilot facilities
- find partners to develop and perform tests

Objective 4 Build capacity at vaccine trial sites

Objective 5 Ensure availability of vaccine production capacity/scale-up

Objective 6 Perform clinical trial

Phase I

- safety, immunogenicity, pilot lot manufacturing, development of lot release tests for vaccine, esp: potency, toxicology

DRAFT

Phase II

- safety in specific target groups, age de-escalation studies, vaccine dose and regimen studies, immunogenicity including development of human assays
- phase IIB for specific target groups = post-infection, pediatric, HIV co-infection, therapeutic vaccines
- important decisions to move forward into phase III
- can manufacturing be “scaled up”

Phase III

- Decision making process to move into large efficacy trials includes:
- Clinical site to test target population;
- Facility to perform “scaled-up” manufacturing and perform 3 consistency lots of vaccine;
- Evidence that vaccine will be available for licensure if trials are successful
- Potential to develop correlate of immunity (or surrogates) from trial;
- Country willing to license vaccine
- Regulatory process to license vaccine
- Need to integrate with TB drugs and diagnostics for trials

Phase IV

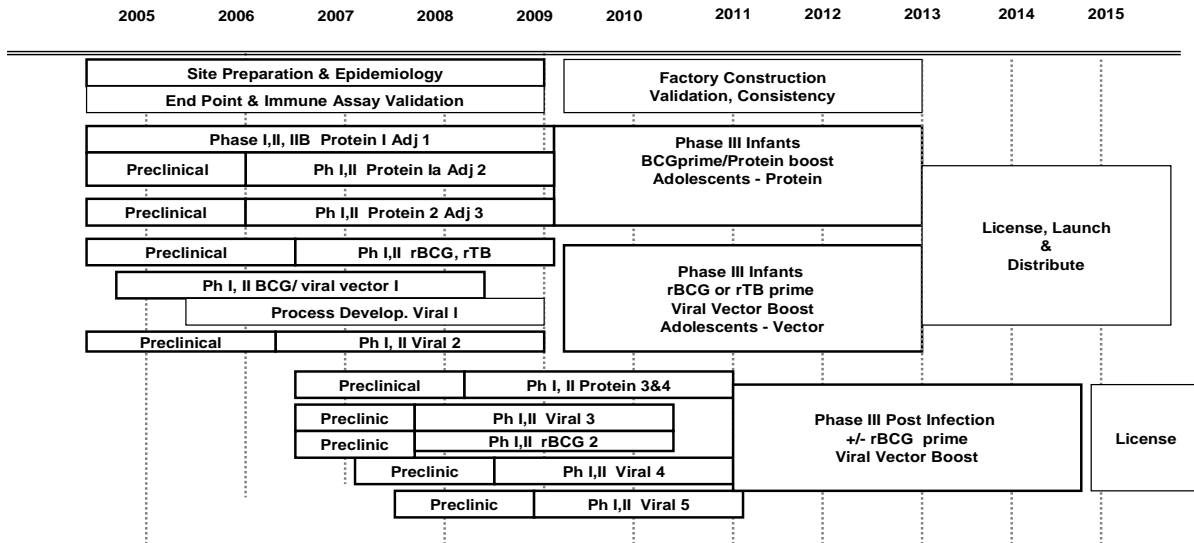
- in-country infrastructure to assure quality of vaccine and perform epi studies

Objective 7 Providing an Enabling Infrastructure

- prepare Scientific Blueprint
- elaborate Economic Analysis
- facilitate International Regulatory Harmonization
- provide Preclinical and Clinical Standards
- ensure timely vaccine production/availability
- prepare accelerated access in countries

DRAFT

Timelines for TB vaccine development 2005 - 2015



Monitoring and Evaluation

An important function of the TB Vaccine Working Group will be to annually map progress among the partners and other entities that may enter drug development for TB. A small database of projects, compounds, and clinical trials will be established to survey the current status worldwide. The development of international monitoring standards and increased global monitoring ability are needed to assure that promising agents are not impeded in their progress towards registration and utilization to curtail the global TB epidemic.

Key Risk Factors

- Scientific Imponderabilities
- Sustainability

DRAFT

- Political Will
- Lack of Global Coordination Efforts

- **Activities, budget, funding and financial gap**

WORKING GROUP: TB Vaccine Development 2006 - 2015			
Activities	Financial needs		
	Budget*	Funding*	Financial gap*
Objective 1 Maintain and Improve BCG Programmes	1300	1300	0
Objective 2 Discovery and translation research ("keeping the pipeline filled")	1200	710	490
Objective 3 Perform preclinical development	15	0	15
Objective 4 Build capacity at vaccine trial sites	15	12	3
Objective 5 Ensure availability of vaccine production capacity/scale-up	192	5	187
Objective 6 Perform clinical trials	387	46	341
Objective 7 Prepare access to new vaccines	1	1	0
Objective 8 Providing an Enabling Infrastructure	6	1	5
Total programmatic needs (Objective 1)	1300	1300	0
Total research needs (Objectives 2-7)	1810	764	1036
Total Working Group running costs (Objective 8)	6	1	5
TOTAL 2006 - 2015	3116	2065	1041

*in million US\$