

# Strategic Plan of the Stop TB Partnership Working Group on New TB Vaccines 2006-2015

## Strategic Vision

Development of new vaccines to protect against tuberculosis is gaining substantial momentum. Encouraging and consistent scientific results from the laboratory and from early field trials indicate that introduction of new effective TB vaccines will be an essential component of any strategy to eliminate tuberculosis by 2050. New TB vaccines to prevent childhood and adult forms of tuberculosis, to reduce tuberculosis in persons co-infected with HIV and to shorten drug treatment regimens will fundamentally alter our approach to TB control.

The aim of the Stop TB Partnership's Working Group on New TB Vaccines Development is to foster and coordinate collaborative efforts to develop novel vaccination approaches that are effective in reducing TB disease. It is probable that the next generation of vaccines will work by complementing the immune response induced by the current BCG vaccine. New vaccines could be delivered together with BCG at an early age before exposure to *M. tuberculosis* has occurred, as a separate booster to young adults or as an adjunct to chemotherapy. The Working Group is promoting research and development of several approaches to the development of new candidate vaccines and new delivery strategies. The timetable for vaccine development is driven by the availability of suitable candidates and preclinical requirements for human trials, and it is anticipated that a new vaccine will be available by 2015. It is difficult to predict the exact contributions to TB control that such a new vaccine will have. However, the impact of new vaccines can be simulated by introducing vaccine-related parameters into existing epidemiological models of the TB pandemic. Such a simulation suggests that introducing a new vaccine between 2014 and 2018 that can be given to everybody could reduce TB incidence in Africa and South East Asia by over 20% during the first 10 years of use and up to 40% by 2050<sup>1</sup>. The strategic vision of the Working Group is that improved vaccines and vaccination strategies will make a crucial contribution to achieving the Stop TB Partnership's target for 2050 of reducing the global incidence of TB disease to less than 1 case per million population.

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

In 2000, the Working Group took note of the historic opportunities for development of new TB vaccines that resulted from the availability of techniques for the genetic manipulation of mycobacteria, and completion of the genome sequence of *M. tuberculosis*. These advances facilitated production of new vaccine candidates in the form of live recombinant mycobacteria or mycobacterial genes expressed in a variety of immunogenic forms. In parallel, advances were being made in our understanding of the cellular and molecular mechanisms underlying protective immunity, in humans as well as in experimental laboratory animals. The Working Group concluded that the priority for TB vaccine development was to advance promising vaccine candidates into clinical studies in humans. This was formulated as an objective **to have five candidates in phase I trials by the end of 2005**. With 4 candidates in phase I trials in 2005 and three more lined up to follow during the first few months of 2006, this goal can largely be considered as achieved.

- A vaccinia virus-vectored subunit vaccine based on a secreted antigen (Ag85A) of *Mycobacterium tuberculosis*, developed at Oxford University, completed initial phase I clinical evaluation in the United Kingdom in 2004. Safety and immunogenicity of the 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. Further phase I safety and immunogenicity trials have now been completed in

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<sup>1</sup> assumptions: 5 years needed to reach 80% final coverage, 80% efficacy in immunocompetent individuals and 40% efficacy in HIV positive individuals, 10 years duration of immunity, MDR and HIV prevalence stable at current values

The Gambia. Phase II studies in latently infected subjects are underway in The Gambia and South Africa.

- A fusion protein (Mtb72f) developed by Corixa in Seattle, Washington, and delivered with an adjuvant formulation developed by GlaxoSmithKline, has completed a phase I clinical trials in the United States, a Phase I/II trial in Europe and has initiated a Phase II safety and immunogenicity study in healthy PPD+/TB-infected adults in 2005.
- A recombinant BCG vaccine over-expressing Ag85A developed at UCLA is has completed phase I trials in the United States.
- An adjuvanted fusion protein (Ag85B-ESAT6) developed at the Statens Serum Institut in Copenhagen, the first clinical trial of which started in October 2005. It tests the vaccine in a conventional parenteral vaccination strategy, using a mixture of oligodeoxynucleotides and polycationic amino acids as the adjuvant (IC31). A second trial will test the same antigen by the nasal route, using LTK63 from Chiron, a modified, heat-labile enterotoxin from *E. coli* as an adjuvant
- A BCG vaccine, carrying the listeriolysin gene as well as an urease deletion is being developed at the Max-Planck-Institute for Infection Biology in Berlin. The development of another recombinant BCG candidate as well as an adenovirus-vectored vaccine, both including antigens from the Ag85 family, is being spearheaded by the Aeras Global TB Vaccine Foundation, a not-for-profit organisation dedicated to TB vaccine development. These three vaccine candidates will enter phase I trials in late 2005 or early 2006.

Important factors contributing to the successful completion of the major objective of the for TB vaccine development set in the Stop TB Partnership's first Global Plan 2001-2005 included major strategic investments by the European Community and the U.S. National Institutes of Health. These donors established consortia of vaccine researchers and centralized facilities for preclinical evaluation, that have allowed comparative testing and selection of optimal candidates for progression to clinical trials. In addition, progress towards clinical trials has been promoted by major awards from the Bill & Melinda Gates Foundation to support the Aeras Global TB Vaccine Foundation and its predecessor, Sequella Global TB Foundation.

## Objectives

The overall objective of the Working Group for 2006-2015 is to have **a safe, effective, licensed vaccine available at reasonable cost by 2015.**

### Objective 1. Maintain and improve BCG vaccination programmes

It is anticipated that BCG will remain the cornerstone of TB vaccination programmes over the period covered by the 2006-2015 Global Plan, with the next generation of new vaccines introduced as an addition to BCG vaccines commonly given at birth in many countries. Important issues include sustaining BCG production by a diminishing number of international suppliers, analysis of possible variations in vaccine efficacy as a result of genetic changes in BCG substrains, and establishment of a rational system for deciding when and how different substrains should be used.

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

There is a need to expand discovery and translational research on vaccines. The success of the current clinical candidates does not signal an end of discovery research, but rather provides novel opportunities to link fundamental research to human studies. It is likely that experience gained as current candidates move through clinical trials will contribute to development of new sets of candidates in an iterative process of refinement. In parallel, there is a well-recognized need for further research in immunology to support development of evaluation criteria for vaccines in Phase II/IIb trials and for the identification of correlates of immunity in phase III trials. The Working Group anticipates that scientists from high-burden countries will make a growing contribution in this area, particularly in the areas of epidemiology and human immune assay development.

### **Objective 3. Facilitate preclinical development**

There is a need to identify and assist in the development of facilities for production of pilot lots of vaccine candidates suitable for human trials, and to ensure that these candidates are subject to appropriate tests to confirm biological potency and lack of toxicity in experimental systems.

### **Objective 4. Build capacity at vaccine trial sites**

Carrying out vaccine trials requires the availability of local expertise as well as baseline data in the populations who will participate in these trials. Prerequisites include baseline epidemiological information, development of community interaction programmes, development of protocols that comply with legal and ethical requirements, coordination with national regulatory authorities, local proficiency in immunological assays and optimized diagnostic procedures, and infrastructure through which the developmental vaccine will be delivered. These activities provide important opportunities for training and capacity strengthening, and require interactions with other Working Groups in the Stop TB Partnership.

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

The potential to scale up production of experimental vaccines to a level suitable for widespread distribution in multi-center, multinational studies is an essential factor in the selection of candidates for clinical trials. Also, it is anticipated that a new licensed vaccine would be made available at a cost that is affordable for resource-poor countries. It is likely that these demands will exceed the capacity of existing vaccine production facilities and will necessitate investment in one or more dedicated GMP-quality production facilities. This activity will require the development of innovative partnerships with manufacturers in developing and developed countries.

### **Objective 6. Perform clinical trials**

Evaluation of vaccine candidates requires transition through a series of clinical trials of increasing size, complexity and cost to progressively evaluate their safety, immunogenicity and finally efficacy. Assuring commitment of investments by collaborators in developed and developing nations is a major challenge for the Partnership at this juncture.

- Phase I trials include initial assessment of safety, typically in groups of about 30 healthy adults.
- Phase II trials require expanded safety studies with larger group sizes, testing different vaccine doses and delivery protocols, and including specific target populations (previously exposed to *M. tuberculosis*, co-infected with HIV, adolescents, children and infants, etc). Immunogenicity measurements in phase II trials provide key criteria in deciding future development plans.
- Phase IIB trials necessitate a further expansion of phase II, testing whether the candidate meets performance criteria set for entry into full scale phase III efficacy trials.
- Phase III trials, which are substantially larger and require extensive resources, test the efficacy of the vaccine. Decision criteria for moving into phase III trials include: the availability of a suitable clinical site to access target populations, a facility to perform “scaled-up” manufacturing of reproducible vaccine lots, a clinical development plan that assures data for licensure will be created if trials are successful, potential to develop correlates of immunity (or surrogates) from the trial, a country willing to license the vaccine, regulatory process to license the vaccine, and discussion with local TB care programmes to facilitate integration with TB drugs and diagnostics for trials. In order to assure the availability of sufficient numbers of trial participants and geographically representative trial results, multiple phase III trials sites in different parts of the world will be needed.
- Phase IV trials are post-licensure studies, using in-country infrastructure to monitor safety and determine effectiveness of the vaccine through epidemiological studies.

### **Objective 7. Providing an enabling infrastructure**

The Working Group will serve as a focal point for discussion of vaccine development issues, to serve as an honest and impartial broker among different stakeholder communities, and to facilitate the development of consensus protocols and vaccine assessment criteria. Specific initiatives include

preparation of a Scientific Blueprint, assessment of the economic impact of vaccines with different performance characteristics, facilitation of international regulatory harmonization for TB vaccines, identification of standard reagents and protocols to produce comparable preclinical and clinical data, identification of facilities for timely vaccine production, and preparation for accelerated access to licensed vaccines for high-burden countries. The Working Group also serves as a centralized mechanism for integrating these activities with the development of vaccines for other diseases

## **Targets and indicators**

In the overall workplan for 2006 – 2015, the **first target** is that at least 20 vaccine candidates will have entered phase I clinical trials by 2015. It is anticipated that multiple candidates will progress through clinical trials in a parallel manner and that unsuccessful candidates will have to be replaced continually by new entrants.

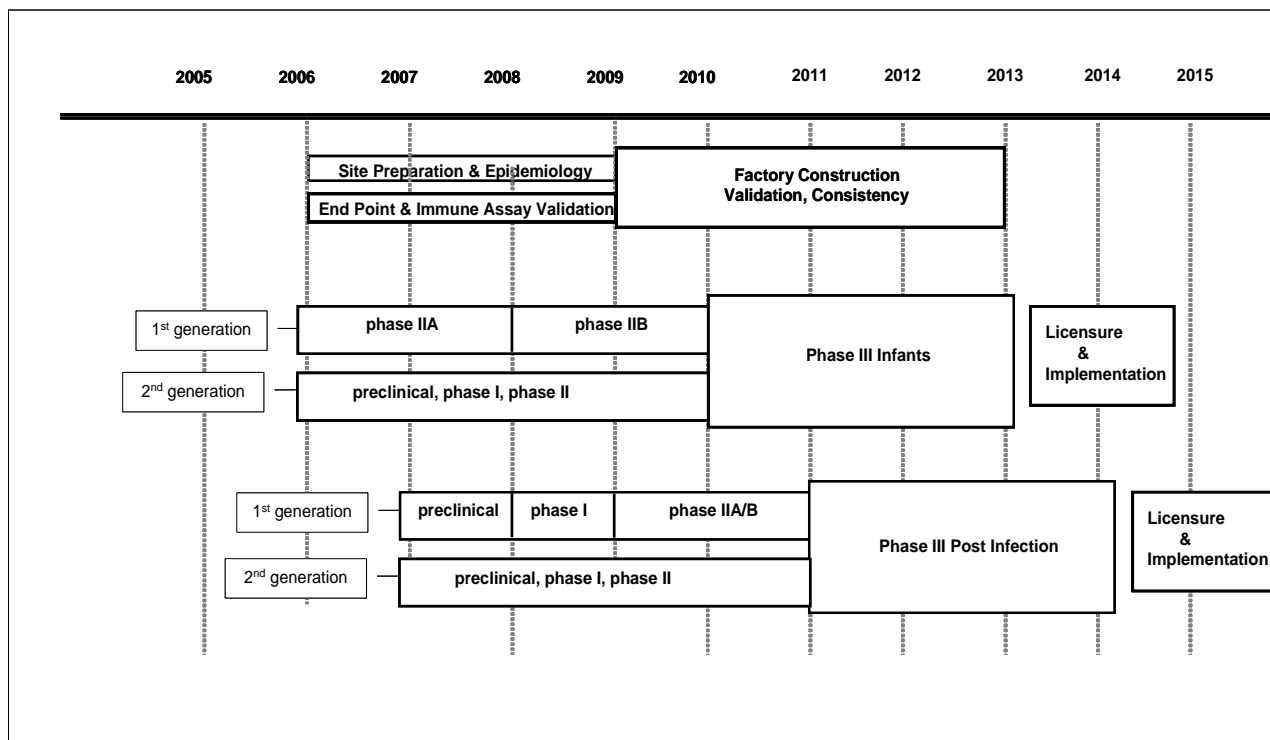
It is anticipated that phase II trials of the first candidates will be well underway in 2006. Initial phase II trials will take approximately 3 years, with an expected reduction to 2 years following development and refinement of trial protocols and immunological assays. **The second target** is that 9 candidates will be evaluated in phase II trials. Furthermore, by 2008 there will be at least two vaccines in phase IIb or 'Proof of Concept' (PoC) trials which will provide some early indication of efficacy and therefore significantly reduce the risk of failure in phase III.

The first phase III trials could begin as early as 2010. They will test vaccine candidates' ability to act as pre-exposure vaccines and will take 4 years to complete. Post-infection trial protocols will be available from 2011 and are expected to take 3 years for completion. **The third target** for the Global Plan is to carry out a total of four phase III efficacy trials.

Approximately two years will be required to complete licensing procedures and to begin to distribute a successful vaccine. The final target is to have a safe, effective, licensed vaccine available at reasonable cost by 2015.

Targets and timelines are illustrated in the attached figure.

## **Timelines for TB vaccine development 2006 - 2015**



## Summary text on resource needs

**Objective 1. BCG vaccination.** The costs of maintaining the BCG vaccine programme from 2006–2015 are based on an estimate of 10 cents per dose with an annual production of 400 million doses per year. Distribution costs are estimated at 90 cents per dose for an annual cohort of 100 million children (the higher production numbers represent non-vaccine uses of BCG such as the treatment of bladder cancer and wastage due to multiple dose vials).

**Objective 2. Supporting research.** The estimate for current funding is based on an assumption that one third of the total NIH expenditure on TB research (about \$100 million per year) is relevant to vaccines, and that this budget represents approximately half of the total global investment in vaccine discovery and development. It is assumed that there is an equivalent contribution by European consortia. The financial gap represents the need to expand translational research while maintaining discovery research.

**Objective 3. Preclinical development.** Preclinical development (including toxicology, safety, regulatory, IP) is estimated at \$725K per candidate (20 candidates).

**Objective 4. Site development.** Estimated as 10% of total trial costs for phase I and II trials.

**Objective 5. Vaccine production.** Phase I lots (\$15 million); phase II/III lots (\$76.5 million); manufacturing facility (\$100 million).

**Objective 6. Clinical trials.** Phase I: 20 candidates/6 permutations/30 subjects—\$45 million. Phase II: 9 candidates/6 permutations/300 subjects—\$100 million. Phase III: 4 trials/40,000 subjects - \$240 million.

**Objective 7. Enabling infrastructure.** Critical items include staff and communications (\$225K/year); economic analysis and blueprint (\$850K), meetings (\$100K/year), consultancy (\$45K/year), scientific outreach activities (\$50K/year).

## Monitoring and evaluation

Progress towards the overall goal of producing an effective vaccine by 2015 will be reviewed against the targets and timelines set out above at annual meetings of the Working Group. Dedicated secretarial staff will monitor progress on a continuous basis and highlight bottlenecks and problems at the annual meeting of the full Working Group, or to appropriate individuals or sub-groups. 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.

## Risks and challenges

**Scientific challenges:** The major factor that could preclude achievement of the 2015 target relates to the scientific uncertainty about protective immunity to TB and our current lack of experience with new TB vaccines in human populations. In spite of recent advances in our understanding of host responses to *M. tuberculosis* infection and TB disease, we may nevertheless be unable to identify vaccine candidates that provide consistent protection against TB. The dual strategy of maintaining support for relevant activities in vaccine discovery research while maximizing the number of candidates introduced into clinical trials, provides the optimal means of increasing our chances for developing an effective vaccine. Additionally, we may be able to identify a promising preclinical candidate that confers enhanced immune responses, but displays unacceptable adverse events, for example, exacerbating other underlying disease symptoms. We may be able to develop a vaccine that is effective in immune competent individuals, but that fails at a population level in areas with high rates of HIV co-infection. It is conceivable that a successful vaccine could select strains of *M. tuberculosis* with altered pathogenicity that allows them to escape from vaccine control.

**Financial uncertainties:** Vaccine development is expensive. Despite impressive commitments by the public sector and philanthropy, a funding gap remains of at least 60% of the total R& D fund required to achieve the objectives of the TB vaccine development plan in time.

The problem largely lies in insufficient commercial investment in TB vaccine development. As with the development of many new vaccines and drugs against diseases of poverty, this is due to the small current size of the market for these innovative, but expensive, products. Diverse mechanisms have been put in place or are being considered to overcome this, including direct research funding, provision of disease burden information and others. However, experts agree that such "push" initiatives, valuable as they are, are not enough and that "pull" efforts are needed to create a market for developing country pharmaceuticals in order to achieve the same level of involvement of the pharmaceutical industry that is typically observed for diseases prevalent in affluent countries. Mechanisms that assure market take-up of new products are also essential and advanced purchasing agreements may be advantageous in this regard. However, such advance market commitments will not materialize for TB vaccine alone, but only as part of a comprehensive package to provide new tools against a whole range of major communicable disease including HIV and malaria. Therefore it must be a prime objective for the TB community to actively advocate and ensure that TB tool development is part of any initiative to create an enlarged market for innovative new pharmaceuticals for developing countries.

## Activities, budget, funding and financial gap

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

\*in million US\$