TUBERCULOSIS VACCINE CANDIDATES – 2011

Stop TB Partnership Working Group on New TB Vaccines

According to the Global Plan to Stop TB, 2011-2015, "There is an urgent need for modern, safe and effective vaccines that prevent all forms of TB, in all age groups and among people with HIV. … According to recent modeling studies, the introduction of new effective TB vaccines and vaccination strategies will make a crucial contribution to achieving the Partnership's goal to reduce the global incidence of TB disease to less than one case per million population by 2050, and development of new vaccines to protect against TB is gaining substantial momentum."

A number of the new generation of TB vaccines may work best using a heterologous prime-boost strategy to complement the immune response induced by the current BCG. This "prime-boost" strategy could include administration of BCG or a new recombinant live replacement vaccine as the "prime", followed by a "booster" inoculation with a different vaccine to infants and young children before they are exposed to TB (pre-exposure), as a separate booster to young adults, either before they are exposed or who may have already been exposed to TB (post-infection) or as an adjunct to chemotherapy (immunotherapy).

TB vaccines under development could work in several ways:

- Prevent infection
- Prevent primary disease
- Prevent latent infection
- Prevent reactivation of latent infection
- Shorten the course and improve the response to chemotherapy

In the following table**,** tuberculosis vaccine candidates are presented in three categories:

***Candidates Tested in Clinical Trials (Section I)*:** TB vaccine candidates that were in clinical studies in 2011. Certain candidates that had been in clinical studies in the past but were not in clinical trials in 2011 are listed as *'completed.'*

Candidates in Preclinical Studies & GMP-2011 (Section II): TB vaccine candidates that as of December 2011 were not yet in clinical trials but had been manufactured under good manufacturing practice (GMP) for clinical use and had undergone some preclinical testing that met regulatory standards.

Next Generation Candidates-2011 (Section III): TB vaccine candidates that are in the research and development stage with some preclinical testing performed to show that they may confer protection.

Vaccine candidates are further divided into specific Vaccine Types: Recombinant Live; Viral Vectored; Recombinant Protein or Other and a brief description is provided. The Table lists vaccines intended to be used as a Prime (P) or Booster (B) vaccine, as a Post-infection vaccine (PI) or in immunotherapy (IT). *Please note that post-infection vaccines are those that are intended to prevent TB in those who have been exposed and/or infected with M.tb. Immunotherapy vaccines are those vaccine candidates that are intended to be used as an adjunct to chemotherapy to enhance and/or shorten the treatment of active disease.*

The information contained here was provided and updated by the vaccine developers. If vaccine developers were contacted but did not provide a response, any respective preclinical and next generation candidates were removed for lack of update, even if listed in the 2010 pipeline. This document contains information on the candidates of which the Working Group on New Vaccines is aware, but it may not be an exhaustive list.

Questions regarding the 2011 TB Vaccine Pipeline, updates for consideration, or additional candidates for inclusion in the 2012 TB Vaccine Pipeline may be directed to Jennifer Woolley at jwoolley@aeras.org.

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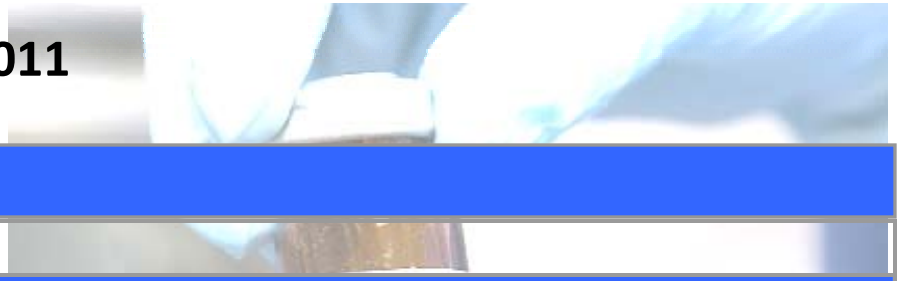

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SECTION I: Candidates Tested in Clinical Trials

Status	Products	Product Description [Citations]	Sponsors	Indication	Type of Vaccine	Target Populations
Phase III	*Mw* [*M. indicus pranii* (MIP)]	*Whole cell saprophytic non-TB mycobacterium* [1-3]	Department of Biotechonology (Ministry of Science & Technology, Government of India), M/s. Cadila Pharmaceuticals Ltd.	IT	Whole cell, Inactivated or Disrupted	–
Phase IIb	MVA85A/AERAS-485	*Modified vaccinia Ankara vector expressing Mtb antigen 85A* [4-8]	Oxford-Emergent Tuberculosis Consortium (OETC), Aeras	B PI IT	Viral Vectored	BCG-vaccinated infants and adolescents; HIV-infected adults
	AERAS-402/Crucell Ad35	*Replication-deficient adenovirus 35 vector expressing Mtb antigens 85A, 85B, TB10.4* [9-13]	Crucell, Aeras	B	Viral Vectored	BCG-vaccinated infants, children and adults
Phase II	M72 + AS01	*Recombinant protein composed of a fusion of Mtb antigens Rv1196 and Rv0125 & adjuvant AS01* [14-17]	GSK, Aeras	B PI	Recombinant Protein	Adolescents/adults, infants
	Hybrid-I+IC31	*Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6* [18-22]	Statens Serum Institute (SSI), TBVI, EDCTP, Intercell	P B PI	Recombinant Protein	Adolescents; adults
	VPM 1002	*rBCG Prague strain expressing listeriolysin and carries a urease deletion mutation* [23-27]	Max Planck, Vakzine Projekt Management GmbH, TBVI	P B	Recombinant Live	–
	RUTI	*Fragmented Mtb cells* [28-32]	Archivel Farma, S.L..	B PI IT	Whole cell, Inactivated or Disrupted	HIV+ adults, LTBI diagnosed
Phase I	AdAg85A	*Replication-deficient adenovirus 5 vector expressing Mtb antigen 85A* [33-37]	McMaster University	P B PI	Viral Vectored	Infants; adolescents; HIV+
	Hybrid-I+CAF01	*Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6* [19-20, 38-40]	SSI, TBVI	P B IT	Recombinant Protein	Adolescents, adults
	Hybrid 56 + IC31	*Adjuvanted recombinant protein composed of Mtb antigens 85B, ESAT-6 and Rv2660* [41-42]	SSI, Aeras, Intercell	P B PI	Recombinant Protein	Adolescents, adults
	HyVac 4/AERAS-404, + IC31	*Adjuvanted recombinant protein composed of a fusion of Mtb antigens 85B and TB10.4* [43-46]	SSI, sanofi-pasteur, Aeras, Intercell	B	Recombinant Protein	Infants
	AERAS-422	*Recombinant BCG expressing mutated PfoA and overexpressing antigens 85A, 85B, and Rv3407* [9-10, 52]	Aeras	P	Recombinant Live	Infants

P Prime, B Boost, PI Post-infection, IT Immunotherapy

Phase III *[completed]*	*M. vaccae*	*Inactivated whole cell non-TB mycobacterium; phase III in BCG-primed HIV+ population completed; reformulation pending* [47-51]	NIH, Immodulon	Ⓑ PI IT	Whole cell, Inactivated or Disrupted	BCG-vaccinated HIV+ adults
Phase I *[completed]*	rBCG30	*rBCG Tice strain expressing 30 kDa Mtb antigen 85B* [53-57]	UCLA, NIH, NIAID, Aeras	Ⓑ PI	Recombinant Live	Newborns, adolescents, and adults
	M. smegmatis	*Whole cell extract*	–	Ⓑ PI IT	Whole cell, Inactivated or Disrupted	–

SECTION II: Candidates in Preclinical Studies & GMP – 2011

Type of Vaccine	Products	Product Description [Citations]	Sponsor	Indication
Recombinant Live	BCG Danish ΔpanCD ΔmmaA4	*Non-replicating, Mtb strain auxotrophic for lysine and pantothenate; attenuated for secA2* [58-59]	Albert Einstein College of Medicine	Ⓟ
	MTBVAC [*ΔphoP, ΔfadD26*]	*Live vaccine based on attenuation of Mtb by stable inactivation by deletion of phoP and fadD26 genes without antibiotic resistance markers in compliance with 2005 and 2010 Geneva consensus safety requirements* [60-64]	University of Zaragoza, Institute Pasteur, BIOFABRI, TBVI	Ⓟ
Protein	HBHA	*Naturally methylated 21-kDa purified protein from M.bovis BCG* [65-69]	Institute Pasteur of Lille, INSERM, TBVI, Aeras	Ⓟ Ⓑ PI IT
DNA	HG85A	*DNA vaccines—Ag85A* [70-74]	Shanghai H&G Biotech	Ⓑ IT
	Hsp DNA vaccine	*Codon-optimized heat shock protein from M. leprae, a CpG island* [75-77]	Sequella, Shanghai Public Health Clinical Center	Ⓑ PI IT

Ⓟ Prime, Ⓑ Boost, PI Post-infection, IT Immunotherapy

SECTION III: Next Generation Candidates – 2011

Type of Vaccine	Products	Product description [Citations]	Sponsor	Indication
Recombinant Live	HG856-BCG	*rBCG overexpressing chimeric ESAT-6/Ag85A DNA fusion protein* [78]	Shanghai Public Health Clinical Center	Ⓑ PI
	IKEPLUS *M. smegmatis* with ESX-3 deletion/ complementation	*Live M. smegmatis with deletion of ESX-3 encoding locus and complementation with Mtb locus*	Albert Einstein College of Medicine, Aeras	Ⓑ
	paBCG	*BCG with reduced activity of anti-apoptotic microbial enzymes including SodA, GlnA1, thioredoxin, and thioredoxin reductase* [79]	Vanderbilt University	Ⓟ
	Proapoptotic rBCG	*Recombinant BCG expressing mutated PfoA and including mutations shown at AECOM to induce macrophage apoptosis*	Aeras, by utilizing a pro-apoptotic vaccine approach developed at Vanderbilt University, with contributions by Albert Einstein College of Medicine	Ⓟ
	rBCG(*mbtB*)30	*rBCG with limited replication overexpressing the 30 kDa Mtb Antigen 85B* [80]	UCLA, NIH, NIAID	Ⓟ
	rBCG T+B rM. smegmatis T+B	*rBCG and rM. smegmatis expressing multiple T and B epitopes of Mtb* [81-83]	Finlay Institute, Universiti Sains Malaysia	Ⓟ Ⓑ PI
	Streptomyces live vector	*Recombinant streptomyces expressing multiple T and B epitopes from M.tb* [81-82,84]	Finlay Institute; Institute of Pharmacy and Food, Cuba	Ⓟ Ⓑ PI IT
	rBCG38	*rBCG Tice strain overexpressing the 38 kDa protein* [85-88]	Universidad Nacional Autónoma de México	Ⓟ Ⓑ Ⓟ Ⓑ
	rBCGMex38	*rBCG Mexico strain overexpressing the 38 kDa protein* [87, 89-91]	Universidad Nacional Autónoma de Mexico	Ⓟ Ⓑ
	rM.microti30 rM.microti38	*rM.microti strain overexpressing the 30 or 38kDa protein* [56, 92-93]	Universidad Nacional Autónoma de Mexico	Ⓟ
	rBCG85C	*rBCG overexpressing antigen 85C of M. tuberculosis* [94]	University of Delhi South Campus and Department of Biotechnology, Government of India	Ⓟ
	Disruption of the SapM locus	*Recombinant M. bovis BCG in which the SapM locus has been disrupted* [95]	FWO-Ghent University-VIB	Ⓟ
	BCG zmp 1	*BCG zmp 1 deletion mutant* [96-98]	University of Zurich, TBVI	Ⓟ

Ⓟ Prime, Ⓑ Boost, PI Post-infection, IT Immunotherapy

Recombinant Protein	ID93 in GLA-SE adjuvant	*Subunit fusion protein composed of 4 Mtb antigens* [99-100]	Infectious Disease Research Institute	Ⓑ PI IT
	Latency fusion proteins	*recombinant fusion proteins composed of antigens 85A-85B-Rv3407, Rv3407-Rv1733c-Rv2626c, Rv0867c-Rv-1884-Rv2389c*	Aeras	Ⓑ
	r30	*30kDa Mtb Ag85B protein purified from rM. Smegmatis* [53-57]	UCLA, NIH, NIAID	Ⓑ PI
	R32Kda (recombinant 85A)	*Purified recombinant 85A protein from BCG* [101-105]	Bhagawan Mahavir Medical Research Center, LEPRA Society- Blue Peter Research Centre	Ⓑ PI IT
Viral Vectored	Recombinant LCMV	*Recombinant lymphocytic choriomeningitis virus expressing Ag85A, Ag85B, or Ag85B-ESAT6* [106-107]	University of Geneva, TBVI	Ⓟ Ⓑ PI IT
	rhPIV2-Ag85B	*Replication-deficient human parainfluenza type 2 virus expressing Ag85B* [108-110]	National Institute of Biomedical Innovation, Japan; Japan BCG Laboratory	Ⓟ Ⓑ
DNA	HVJ-Envelope/HSP65 DNA+IL-12 DNA	*Combination of DNA vaccines expressing mycobacterial heat-shock protein 65 & IL-12* [111-115]	Osaka University	Ⓑ PI IT
	pUMVC6/7 DNA	*DNA vaccine plasmid vectors pUMVC6 or pUMVC7 expressing Rv3872, Rv3873, Rv3874, Rv3875 or Rv3619c* [116-117]	Kuwait University	Ⓟ
	DNAacr	*DNA* vaccine expressing α-crystallin, a key latency associated antigen of *M. tuberculosis* [118]	University of Delhi South Campus and Department of Biotechnology, Government of India	Ⓑ
	rBCGacr/DNAacr	rBCG and DNA vaccines expressing α-crystallin of M. tuberculosis in a heterologous prime boost approach [119]	University of Delhi South Campus and Department of Biotechnology, Government of India	Ⓟ Ⓑ
	HG85 A/B	*Chimeric DNA vaccines—Ag85A/B* [70-74]	Shanghai H&G Biotech	Ⓑ IT
	HG856A	*Chimeric DNA vaccines—ESAT-6/Ag85A; Ag85A/Ag85B* [78]	Shanghai H&G Biotech	Ⓑ IT
Other	HG856-SeV	*Recombinant Sendai virus overexpressing chimeric Ag85A/B protein*	Shanghai H&G Biotech; Shanghai Public Health Clinical Center; DNAVEC Corporation, Japan	Ⓑ (IT)
	LIP1 Ac_2SGL sulfoglycolipid	*Ac_2SGL/PIM2 in DDA/TDB* [120-122]	Centre National de la Recherche Scientifique (CNRS), TBVI	Ⓟ Ⓑ PI IT
	LIP2 SL37 (synthetic) sulfoglycolipid	*SL37/PIM2 in DDA/TDB* [123-124]	CNRS, TBVI	Ⓟ Ⓑ PI IT

	EspC	*Recombinant protein and/or viral-vectored* [125]	Imperial College London	P B PI IT
	Liporale™ TB	*Live attenuated BCG Danish Strain in a novel stable lipid matrix for oral vaccination* [126-130]	Immune Solutions Ltd.	P B
	Mycobacterial liposomes and proteoliposomes	*Liposomes from M. smegmatis and proteo-liposomes from BCG and M. smegmatis* [131]	Finlay Institute Universiti Sains Malaysia	P B PI IT
	PS- conjugate	*Subunit Mtb polysaccharide protein conjugate*	Albert Einstein College of Medicine	B
	T-BioVax	*Heat shock HspC protein antigen complexes* [132-133]	ImmunoBiology Ltd.	P B IT
	TBVax	*T cell epitope-based DNA-prime/peptide boost vaccine* [134-136]	EpiVax , Inc.	B PI

Key:

- (P) Prime
- (B) Boost
- [PI] Candidate is indicated post-infection
- [IT] Candidate is indicated for immunotherapy

BCG – Bacille Calmette-Guérin
IL – Interleukin
GMP – Good Manufacturing Practices Manufacturing
GSK – GlaxoSmithKline Biologicals
M. bovis – *Mycobacterium bovis*
Mtb – *Mycobacterium tuberculosis*
NIAID– National Institute of Allergy and Infectious Diseases
NIH – National Institutes of Health
OETC – Oxford-Emergent Tuberculosis Consortium, Ltd.
SSI – Statum Serum Institute
TBVI – Tuberculosis Vaccine Initiative
UCLA – University of California Los Angeles

The aim of the ***Stop TB Working Group on New Vaccines*** is to bring together the wide range of international groups with an interest in TB vaccine development, acting as a "broker" to promote synergy and to accelerate identification and introduction of the most effective vaccination strategy. This is achieved by representation of national and international public health organisms, major funding organizations, TB endemic countries, commercial and non-profit institutions involved in TB vaccine development, as well as experts in regulatory issues associated with vaccine development.

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