The only way to eliminate TB as a public health problem is
by means of coordinating scientific, political, and social efforts.

Untitled – Alexis Leiva Machado
Installation
(Variable dimensions)

'Others will say in verses, others reasons,
who knows more useful, more urgency
This didn't change its nature
Hanging between two denials,
Now, to invent art and ways
To join the chances and the certainty
Takes or not the whole life.'

Hasta la carne **(Poem) – José Saramago**

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Alexis Leiva studied at the Elementary School of Art and the National School of Art, Havana.

He has received prizes in the Municipal Salon of Visual Arts and Design (Nueva Gerona, Cuba), in the National Salon of Art Schools Professors, Provincial Center of Visual Arts and Design (Havana, Cuba), and in Biennial of Kwan-Ju, South Korea. He has also been the recipient of a scholarship from the Foundation Ludwig, Fórum Ludwig, Aachen, (Germany), and a residency at the Atelier Alexander Calder, Saché, France.

His works have been exhibited in Canada, Cuba, France, Israel, Italy, Japan, Portugal, Spain, and the United States. They are also in the collections of the National Museum of Fine Arts (Havana); the Museum of Modern Art (MOMA) (New York), the Sandretto Re Rebaudengo per l'Arte (Turín), the Museo Nacional Centro de Arte Reina Sofía (Madrid), the Gallery Gabriela Mistral (Santiago) and the Foundation Ludwig (Aachen).

CHAPTER 23

New Tuberculosis Vaccines: What is in the Pipeline?

Lewellys F Barker, Vicki Chen, Dustin Meyer, Peri K Rosenstein, and Michael J Brennan

New improved, safe, and effective TB vaccines, along with new treatments and diagnostics in combination with current interventions, are essential for controlling the TB pandemic. This pandemic, which caused over nine million new cases and almost two million deaths in 2008 (1), is being exacerbated by the emergence of MDR and XDR strains and the deadly combination of TB and HIV coinfection. Over the past few years, scientists and vaccine developers have been making great progress in the field of TB vaccine development. There are many TB vaccine candidates in preclinical development, and at least nine vaccine candidates have entered clinical development and are now advancing in clinical trials around the world.

In its Global Plan to Stop TB 2006–2015, the Stop TB Partnership has placed strong emphasis on the need for new, effective TB vaccines as an essential part of the strategic goal to eliminate TB by 2050. To assist with tracking activity and progress in TB vaccine research and development, the Task Force on Retooling—now the subgroup on Introducing New Approaches and Tools, of the Stop TB Partnership—published an inventory of new vaccines in various stages of development which is updated annually with information collected from vaccine developers. This listing of TB vaccines can be found at the home page of the Vaccines Working Group of the Stop TB Partnership website http://www.stoptb.org/wg/new_vaccines/; under Documents, see 'Vaccine Pipeline'. This chapter provides a summary of the contents of the Stop TB Partnership TB Vaccines Pipeline document.

It is anticipated that a number of new TB vaccines will be used in heterologous prime-boost regimens. This prime-boost strategy would include primary immunization with one of the existing BCGs (2–4), an improved recombinant BCG (5), or a different priming vaccine under development such as a modified, attenuated MTB vaccine, followed by a booster inoculation with any of a variety of candidates being investigated (6). The booster can be indicated for infants and young children before they are exposed to TB (pre-exposure) or to young adults, either before exposure or after exposure (postinfection) or as an adjunct to chemotherapy (immunotherapy).

TB vaccines under development are intended to achieve one or more of the following goals: (i) prevent infection; (ii) prevent progression from infection to active TB disease; (iii) prevent latent TB infection; (iv) prevent reactivation of latent TB infection to TB disease; or (v) shorten the course and improve the response to chemotherapy, that is, serve as a form of immunotherapy.

The vaccine candidates under development are placed into categories as follows:

Candidates in Clinical Trials–2009 (Section I): TB vaccine candidates that are in clinical studies as of 2009. Vaccines that have been in earlier clinical studies but are not currently being actively pursued as candidates are listed as 'Not Active'.

Candidates in Advanced Preclinical Studies and GMP– 2009 (Section II): TB vaccine candidates that are not yet in clinical trials, but as of 2009 have been manufactured under GMP for clinical use and have undergone some preclinical testing that meets regulatory standards.

Next Generation Candidates–2009 (Section III): TB vaccines candidates that are in the research and development stage with some preclinical testing performed to show that they may contain protective antigens.

Vaccine candidates are further divided into specific Vaccine Types: Recombinant Live; Viral Vectored; Recombinant Protein; or Other. A brief description is provided. The table lists vaccines intended to be used as a Prime (P) or Booster (B) vaccine, as a Postinfection vaccine (PI) or in immunotherapy (IT).

The information on the vaccine candidates was provided for the Pipeline document by the vaccine development organizations and/or individual scientists unless otherwise noted by an asterisk. Details about many of the candidates can be found in the listed references and elsewhere in the published literature.

Table 23.1 Tuberculosis Vaccine Candidates – 2009

SECTION I: Candidates in Clinical Trials – 2009

Type of Vaccine	Products	Product Description	Sponsor	Indication	Status as of 2009	Citations
Recombinant Live	VPM 1002	*rBCG Prague strain expressing listeriolysin and carries a urease deletion mutation*	Max Planck, Vakzine Projekt Management GmbH, TBVI	P	Phase I	(6–8)
	rBCG30	*rBCG Tice strain expressing 30 kDa MTB antigen 85B; phase I completed in US*	UCLA, NIH, NIAID, Aeras	P	Phase I (not active)	(9–13)
Viral Vectored	Oxford MVA85A / AERAS-485	*Modified Vaccinia Ankara vector expressing MTB antigen 85A*	OETC, Aeras	B PI IT	Phase IIb	(14–18)
	AERAS-402/ Crucell Ad35	*Replication-deficient adenovirus 35 vector expressing MTB antigens 85A, 85B, TB10.4*	Crucell, Aeras	B	Phase II	(19–22)
	AdAg85A	*Replication-deficient adenovirus 5 vector expressing MTB antigen 85A*	McMaster University	P B	Phase I	(23–27)
Recombinant Protein	Hybrid-I+IC-31	*Adjuvanted recombinant protein composed of MTB antigens 85B and ESAT-6*	SSI, TBVI, Intercell	P B IT	Phase IIa	(28–31)
	Hybrid-I+CAF01	*Adjuvanted recombinant protein composed of MTB antigens 85B and ESAT-6*	SSI	P B PI	Phase I	–
	M72	*Recombinant protein composed of a fusion of MTB antigens Rv1196 and Rv0125 & adjuvant*	GSK, Aeras	B PI	Phase II	(32–34)
	HyVac 4/AERAS-404, +IC-31	*Adjuvanted recombinant protein composed of a fusion of MTB antigens 85B and TB10.4*	SSI, Sanofi-Pasteur, Aeras, Intercell	B	Phase I	(35–37)
Other	RUTI	*Fragmented MTB cells*	Archivel Farma, S.I.; Badalona, Spain	B PI IT	Phase I	(38–42)

(*continued*)

Table 23.1 (*continued*)

Type of Vaccine	Products	Product Description	Sponsor	Indication	Status as of 2009	Citations
	M. vaccae	*Inactivated whole cell non-TB mycobacterium; phase III in BCG-primed HIV+ population completed; reformulation pending*	NIH, Aeras, Immodulon	Ⓑ PI IT	Phase III	(43–47)
	M. smegmatis *	*Whole cell extract; phase I completed in China*	communicated by the Wuhan Inst. of Biol. Products	Ⓑ PI IT	Phase I (not active)	–

SECTION II: Candidates in Preclinical Studies and GMP– 2009

Type of Vaccine	Products	Product Description	Sponsor	Indication	Citations
Recombinant Live	AERAS-rBCG	*rBCG Danish 1331 strain expressing perfringolysin and at least three MTB antigens or with ΔsecA2-DNIsodA modification (dominant-negative interfering SodA mutant)*	Aeras	Ⓟ	(19, 21, 48)
	MTB (Δ*lysA* Δ*panCD* Δ*secA2*)	*Non-replicating, MTB strain auxotrophic for lysine and pantothenate; attenuated for secA2*	Albert Einstein College of Medicine	Ⓟ	(49, 50)
	MTBVAC01 (Δ*phoP*, Δ*fad D26*)	*Live vaccine based on attenuation of MTB by inactivation of phoP and fad D26 genes*	University of Zaragoza, Institute Pasteur, TBVI	Ⓟ	(51–55)
Recombinant Protein	HBHA	*Naturally methylated 21-kDa purified protein from M.bovis BCG*	Institute Pasteur of Lille, INSERM, TBVI	Ⓟ Ⓑ PI IT	(56–60)
	Hybrid 56	*Adjuvanted recombinant protein composed of MTB antigens 85B, ESAT-6, and Rv2660*	SSI, Aeras, Intercell	Ⓟ Ⓑ PI	–
Other	HG85 A/B	*Chimeric DNA vaccines—Ag85A/Ag85B*	Shanghai H&G Biotech	Ⓑ IT	(61–65)

SECTION III: Next Generation Candidates – 2009

Type of Vaccine	Products	Product Description	Sponsor	Indication	Citations
Recombinant Live	HG856-BCG	*rBCG overexpressing chimeric ESAT-6/Ag85A DNA fusion protein*	Shanghai Public Health Clinical Center	Ⓑ PI IT	(61–63, 66, 67)
	paBCG	*BCG with reduced activity of anti-apoptotic microbial enzymes including SodA, GlnA1, thioredoxin, and thioredoxin reductase*	Vanderbilt University with exclusive license to Aeras	Ⓟ	(68)
	rBCG(*mbtB*)30	*rBCG with limited replication overexpressing the 30 kDa MTB Antigen 85B*	UCLA, NIH, NIAID	Ⓟ	(69)
	rBCG T+B rM. smegmatis T+B	*rBCG and rM. smegmatis expressing multiple T and B epitopes of MTB*	Finlay Institute, Universiti Sains Malaysia	Ⓟ Ⓑ PI	(70–72)
	Streptomyces live vector	*Recombinant streptomyces expressing multiple T and B epitopes from Mtb*	Finlay Institute, Institute of Pharmacy and Food, Cuba	Ⓟ Ⓑ PI IT	(71–74)
Recombinant Protein	Ac_2SGL Diacylated Sulfoglycolipid *	*Mycobacterial lipids with Ac_2SGL, a novel glycolipid antigen*	Institut de Pharmacologie et Biologie Structurale du CNRS	Ⓟ Ⓑ PI IT	(75)
	HspC TB	*Heat shock HspC protein antigen complexes*	ImmunoBiology Ltd	Ⓑ	(76, 77)
	ID83 and ID93 in GLA-SE adjuvant	*Subunit fusion protein composed of 3 MTB antigens (ID83) or 4 MTB antigens (ID93)*	Infectious Disease Research Institute	Ⓑ PI IT	(78, 79)

(*continued*)

Table 23.1 (*continued*)

Type of Vaccine	Products	Product Description	Sponsor	Indication	Citations
	r30	*30kDa MTB Ag85B protein purified from rM. smegmatis*	UCLA, NIH, NIAID	Ⓑ PI	(80–84)
	R32Kda (recombinant 85A)	*Purified recombinant 85A protein from BCG*	Bhagawan Mahavir Medical Research Center, LEPRA Society-Blue Peter Research Centre	Ⓑ	(85–87)
Other	AERAS-Capsid	*Shigella-delivered recombinant double-stranded RNA nucleocapsid*	Aeras	Ⓑ PI	(21)
	HG856A	*Chimeric DNA vaccines—ESAT-6/Ag85A; Ag85A/Ag85B*	Shanghai H&G Biotech	Ⓑ IT	(88)
	HG856-SeV	*Recombinant Sendai virus overexpressing chimeric ESAT-6/Ag85A protein*	Shanghai H&G Biotech	Ⓑ	–
	Hsp DNA vaccine	*Codon-optimized heat shock protein from M. leprae, a CpG island*	Cardiff University, Sequella	Ⓑ	(89–92)
	HVJ-Envelope/HSP65 DNA+IL-12 DNA	*Combination of DNA vaccines expressing mycobacterial heat-shock protein 65 & IL-12*	Osaka University	Ⓑ PI IT	(93–97)
	Liporale-BCG	*Live attenuated BCG Danish Strain in a novel lipid adjuvant and delivery system for an oral vaccine*	Immune Solutions Ltd.	Ⓟ Ⓑ	(98–102)
	NasL3/AM85B conjugate	*Nasal vaccine with man-capped Arabinomannan oligosaccharide conjugated to Ag85B in Eurocine L3™ adjuvant*	Karolinska Institute	Ⓑ	(103–107)

Type of Vaccine	Products	Product Description	Sponsor	Indication	Citations
	NasL3/HtkBCG (BCG adjuvant)	*Intranasal heat-killed whole BCG Copenhagen strain in Eurocine L3™ adjuvant*	Karolinska Institute	P B PI	(108–110)
	TBVax	*T cell epitope-based DNA-prime/peptide boost vaccine*	EpiVax , Inc.	P B	(111–113)
	PS- conjugate *	*Subunit MTB polysaccharide protein conjugate*	Albert Einstein College of Medicine	B	–
	Mycobacterial liposomes and proteoliposomes	*Liposomes from M. smegmatis and proteo-liposomes from BCG and M. smegmatis*	Finlay Institute, Universiti Sains Malaysia	P B PI IT	–

Key:

P Prime

B Boost

PI Candidate is indicated postinfection

IT Candidate is indicated for immunotherapy

IL – Interleukin
GSK – GlaxoSmithKline Biologicals
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

* No new information received from vaccine sponsor in 2009.

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