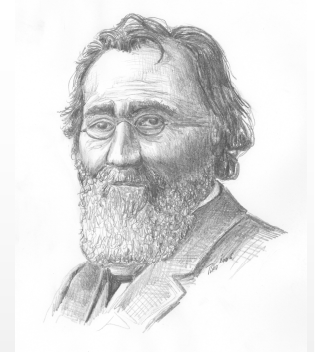




KOCH-METSCHNIKOW-FORUM МЕЧНИКОВ-КОХ-ФОРУМ



ISTC Conference
Pediatric Multidrug Resistant Tuberculosis:
Emerging Global Challenge,
November 14 and 15, 2011

TB Vaccination – Global Experience

Timo Ulrichs

Sektionsleiter und Vizepräsident,
Koch-Metschnikow-Forum;

Grundsatzfragen der europäischen und internationalen
Gesundheitspolitik,
Bundesministerium für Gesundheit



Nothing new from the TB front?

- ✓ Diagnostics: Sputum microscopy (R. Koch, 1882); cultural growth
- ✓ Therapy: Combination therapy Isoniazid, Rifampin, Ethambutol, Pyrazinamid; since Selman A. Waksman's Streptomycin (1947) developed in the 1960s
- ✓ Prevention: BCG (G. Calmette, C. Guérin, 1921)



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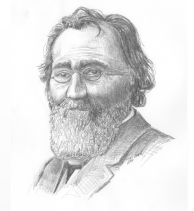
insufficient, esp. in HIV patients

- ✓ Therapy: Combination therapy Isoniazid, Rifampin, Ethambutol, Pyrazinamid; since Selman A. Waksman's Streptomycin (1947) developed in the 1960s

MDR, XDR

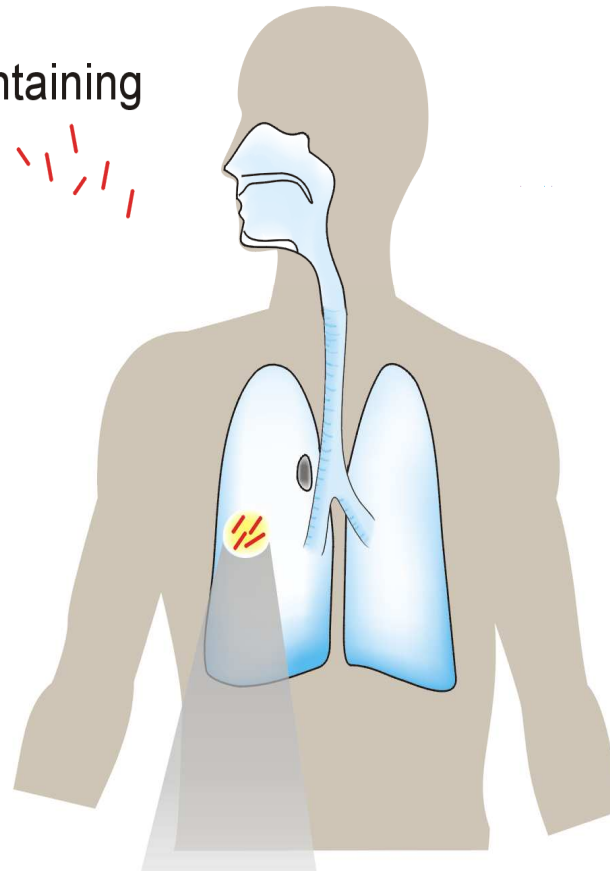
- ✓ Prevention: BCG (G. Calmette, C. Guérin, 1921)

effective only against military TB and tuberculous meningitis



Pathogenesis of tuberculosis

mycobacteria - containing
droplets



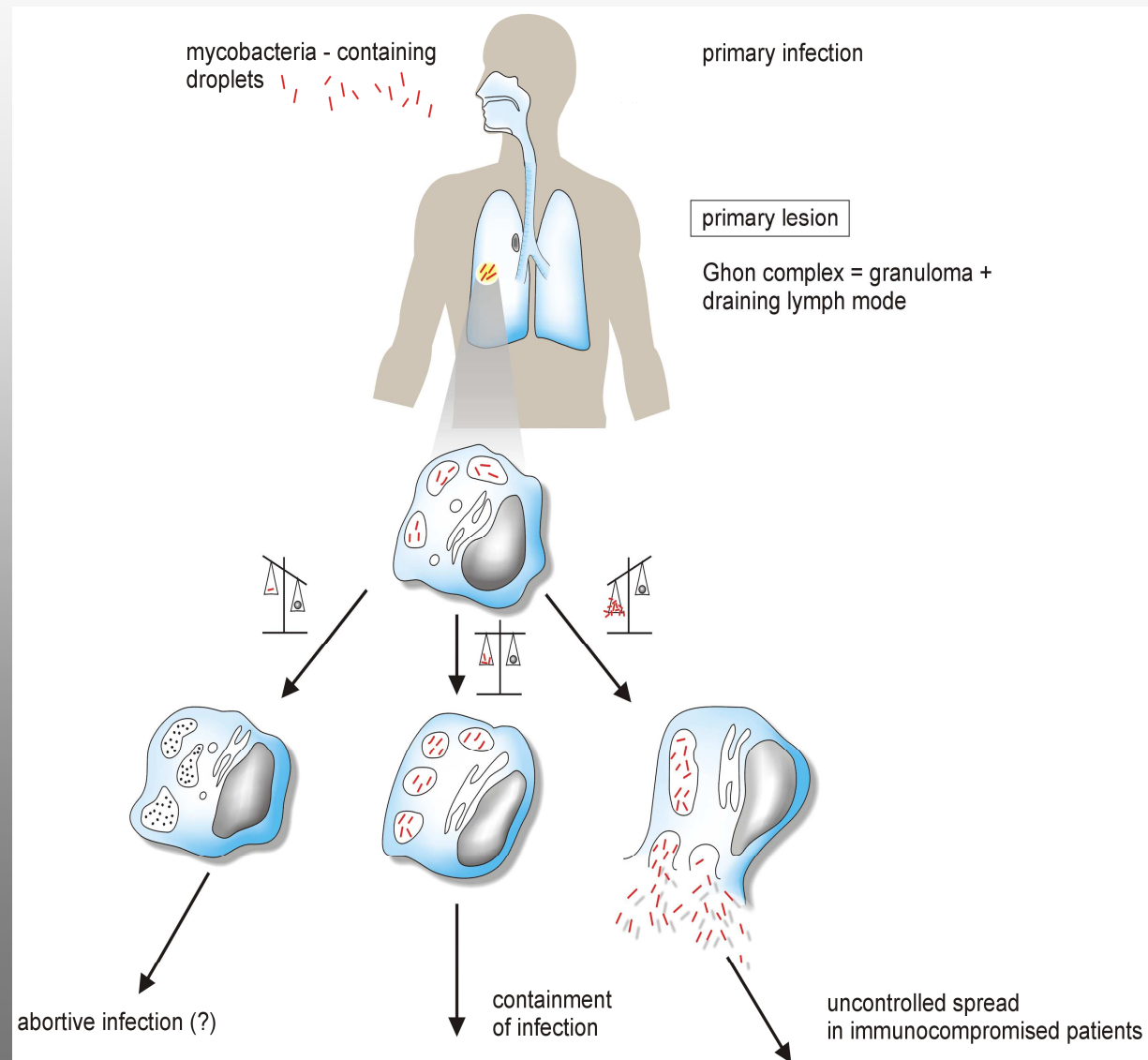
primary infection

primary lesion

Ghon complex = granuloma +
draining lymph node

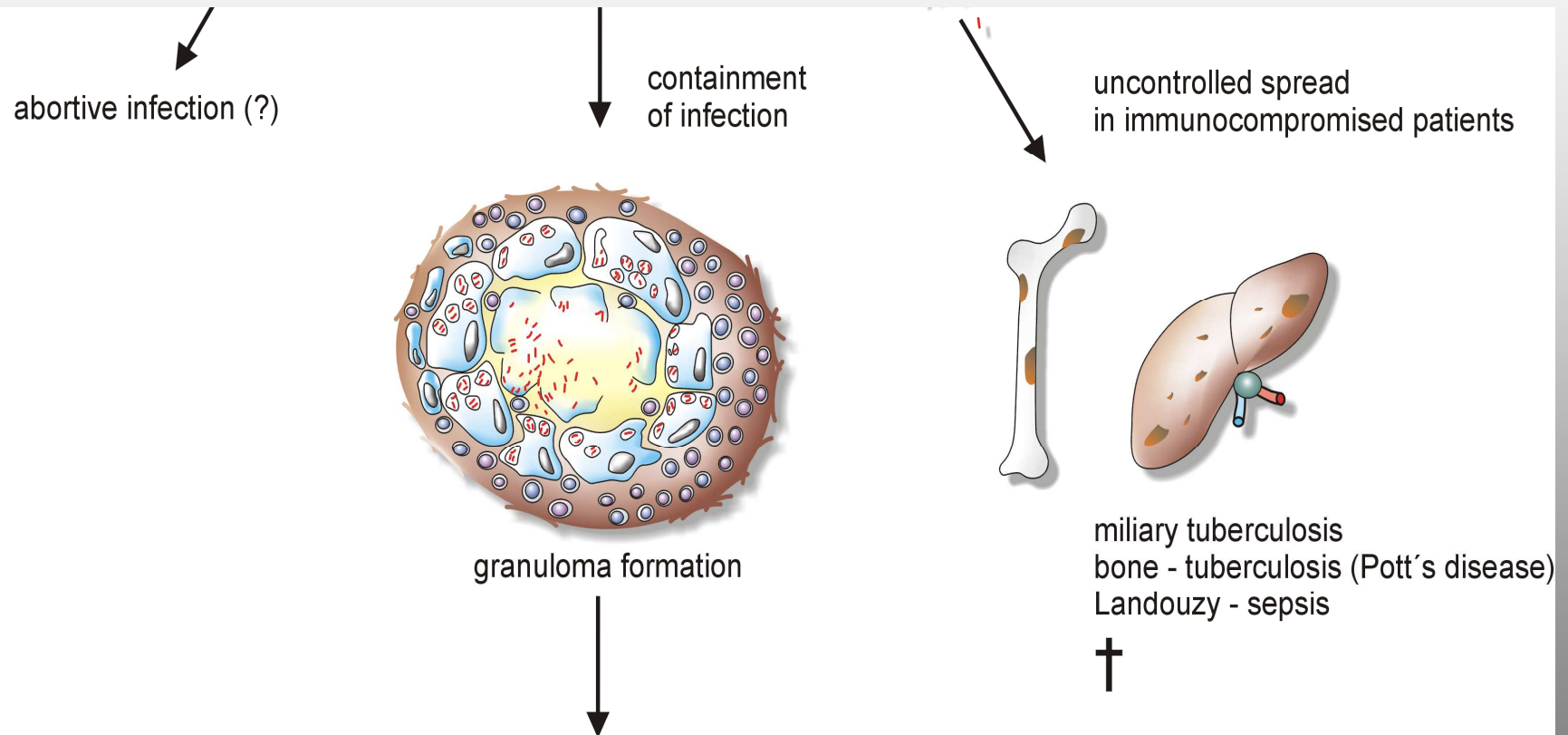


Pathogenesis of tuberculosis



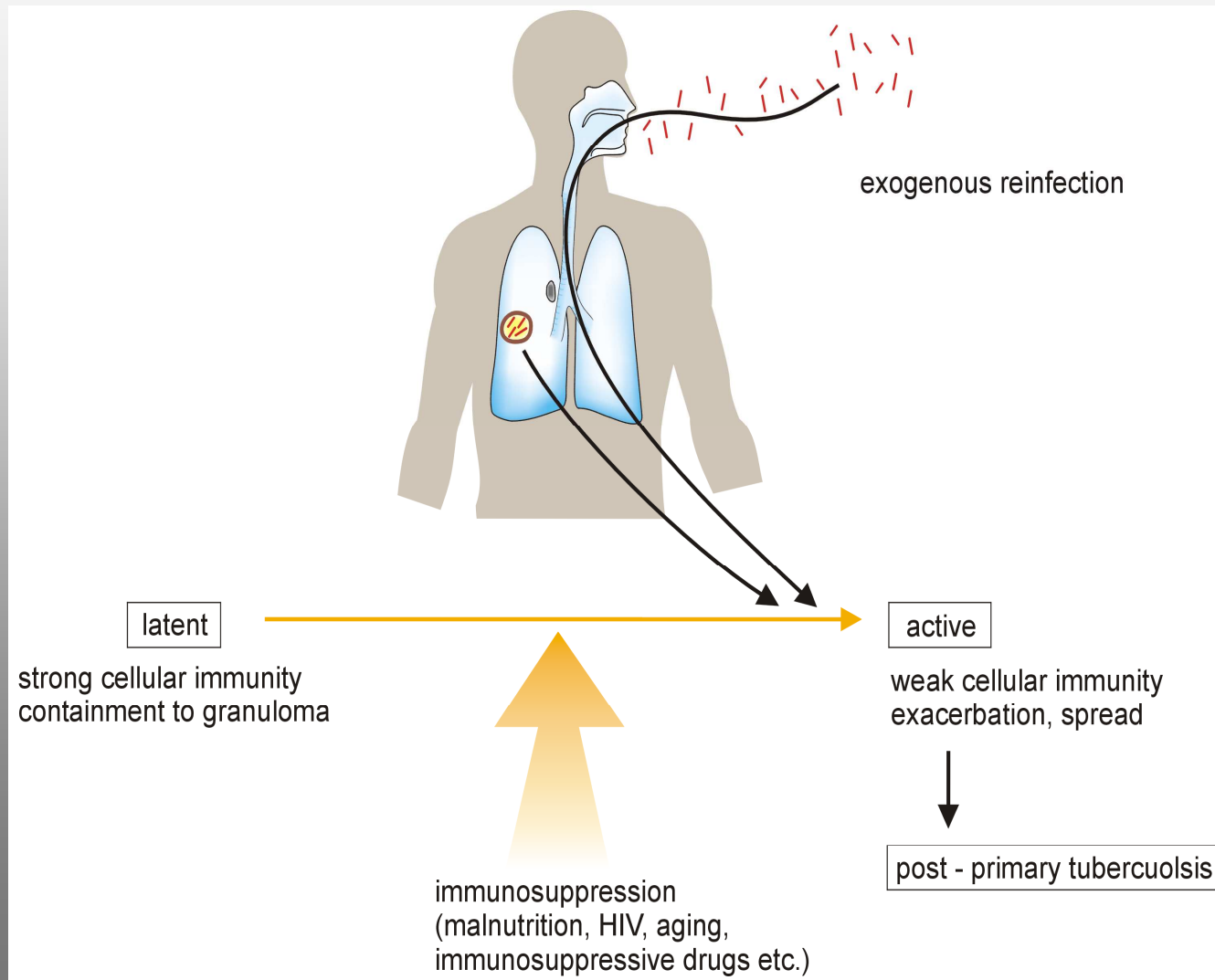


Pathogenesis of tuberculosis





Pathogenesis of tuberculosis



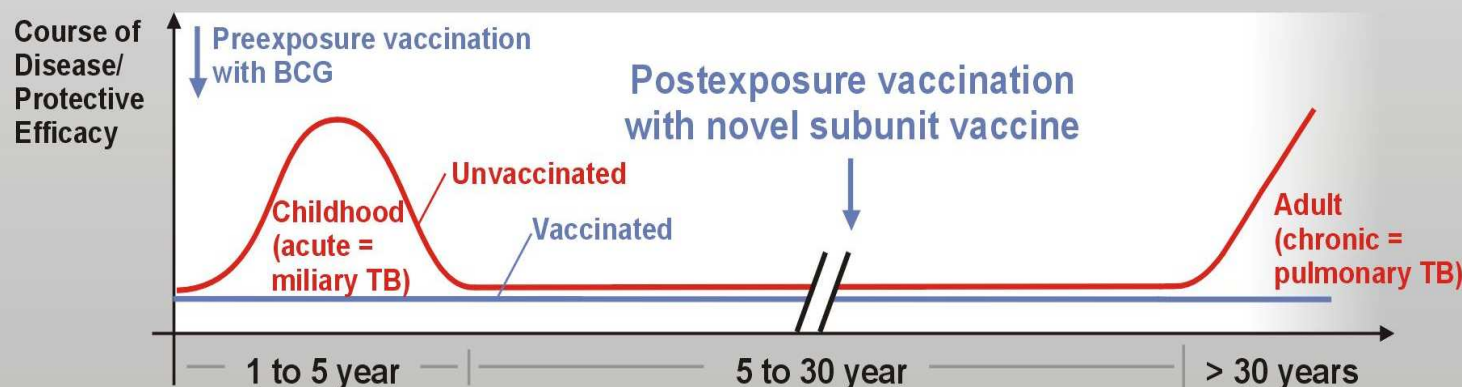
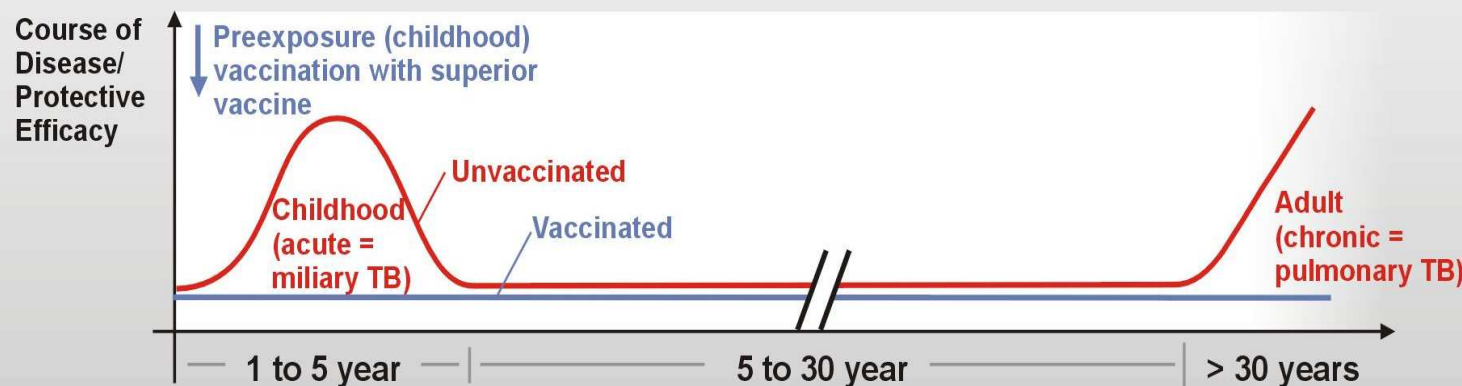
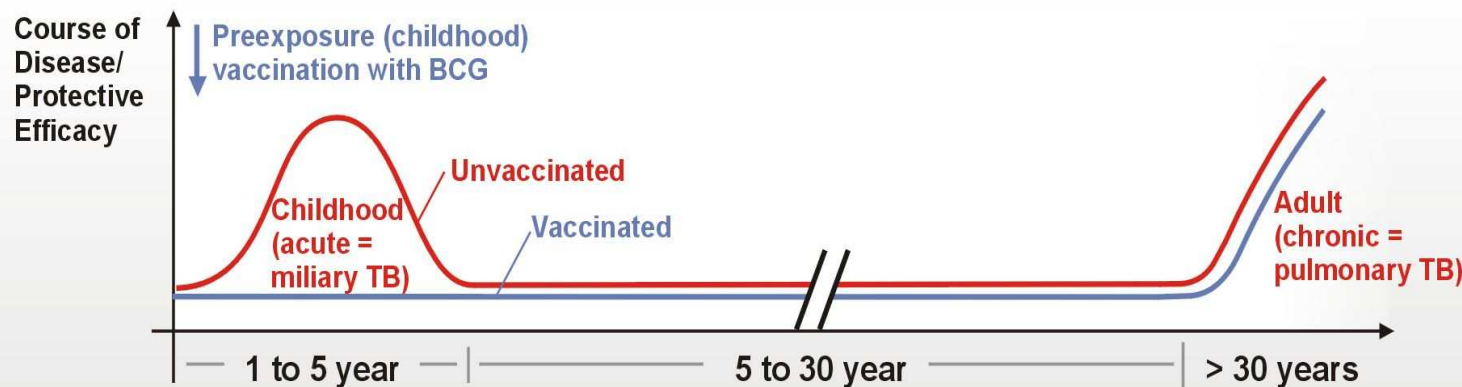


Consequences for vaccine development

- ✓ intracellular pathogen: Priming and boost of the cellular immune system;
- ✓ dormant infection: pathogen sleeps, immune system must attack anyway
- ✓ persistence over tens of years: pre- versus postexposition vaccine
- ✓ Latency and exogenous reinfection: vaccine must be more effective than natural infection



Possible scenarios





Possible strategies of vaccine development



- ✓ Live vaccine: attenuated *M. tuberculosis* or recombinant *M. bovis* BCG
- ✓ subunit vaccine: Subunits (immunodominant antigens, peptides etc.)
- ✓ DNA-vaccine
- ✓ recombinant bacteria or viruses expressing mycobacterial antigens



Vaccine candidates in the pipeline

Table 1

TB vaccine candidates in the clinic.

Vaccine	Source	Stage	Description
<i>Priming vaccines</i>			
BCG30	UCLA/Aeras	Phase 1 US	rBCG with plasmid overexpressing Ag85A
VPM-X	Max Plank/VPM/TBVI	Phase 1 Europe	rBCG with chromosomal expression of listeriolysin
AERAS-rBCG	Aeras	Phase I (2009) US	rBCG with chromosomal expression of perfringolysin and Ag85A, Ag86B, Rv3427, rpfA, rpfB, rpfC, and Dos R regulated proteins
<i>Viral vectored booster vaccines</i>			
MVA85A/AERAS-485	Oxford/Isis/Aeras/Emergent	Phase IIb Europe, Africa	Recombinant modified vaccinia vectored vaccine expressing Ag85A
AERAS-402/ Crucell Ad35	Crucell/Aeras	Phase I and IIa US	Recombinant adenovirus 35 expressing antigens Ag 85A, Ag 85B, and Mtb10.4
<i>Protein booster vaccines</i>			
GSK M72	GSK/Aeras	Phase I and IIa Europe, Africa	Fusion molecule comprised a protein from the PPE family Rv1196 and an inactive serine protease Rv0125 with AS01 adjuvant
Hybrid I	SSI/Intercell/TBVI	Phase I and IIa Europe, Africa	Fusion molecule comprised Ag85B and AgESAT-6 with adjuvant IC31
HyVac 4/AERAS-404	Sanofi Pasteur/SSI/Intercell/Aeras	Phase I Europe, Africa	Fusion molecule comprised Ag85B and Mtb10.4 with adjuvant IC31



Vaccine candidates in the pipeline



Type of Vaccine	Products	Product description	Sponsor	Indication	Status as of 2009
Recombinant Live	VPM 1002	<i>rBCG Prague strain expressing listeriolysin and carries a urease deletion mutation</i>	Max Planck, Vakzine Projekt Management GmbH, TBVI		Phase I
	rBCG30	<i>rBCG Tice strain expressing 30 kDa Mtb antigen 85B; phase I completed in U.S.</i>	UCLA, NIH, NIAID, Aeras		Phase I [not active]
Viral Vectored	Oxford MVA85A / AERAS-485	<i>Modified vaccinia Ankara vector expressing Mtb antigen 85A</i>	OETC, Aeras		Phase IIb
	Crucell Ad35/ AERAS-402	<i>Replication-deficient adenovirus 35 vector expressing Mtb antigens 85A, 85B, TB10.4</i>	Crucell, Aeras		Phase II
	AdAg85A	<i>Replication-deficient adenovirus 5 vector expressing Mtb antigen 85A</i>	McMaster University		Phase I
Recombinant Protein	Hybrid-I+IC-31	<i>Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6</i>	SSI, TBVI, Intercell		Phase IIa
	Hybrid-I+CAF01	<i>Adjuvanted recombinant protein composed of Mtb antigens 85B and ESAT-6</i>	SSI		Phase I
	M72	<i>Recombinant protein composed of a fusion of Mtb antigens Rv1196 and Rv0125 & adjuvant</i>	GSK, Aeras		Phase II
	HyVac 4/AERAS-404	<i>Adjuvanted recombinant protein composed of a fusion of Mtb antigens 85B and TB10.4</i>	SSI, Sanofi-Pasteur, Aeras, Intercell		Phase I
Other	RUTI	<i>Fragmented Mtb cells</i>	Archivel Farma, S.I.; Badalona, Spain		Phase I
	<i>M. vaccae</i>	<i>Inactivated whole cell non-TB mycobacterium; phase III in BCG-primed HIV+ population completed; reformulation pending</i>	NIH, Aeras, Immodulon		Phase III
	<i>M. smegmatis</i> *	<i>Whole cell extract; phase I completed in China</i>	*communicated by the Wuhan Inst. of Biol.Products		Phase I [not active]

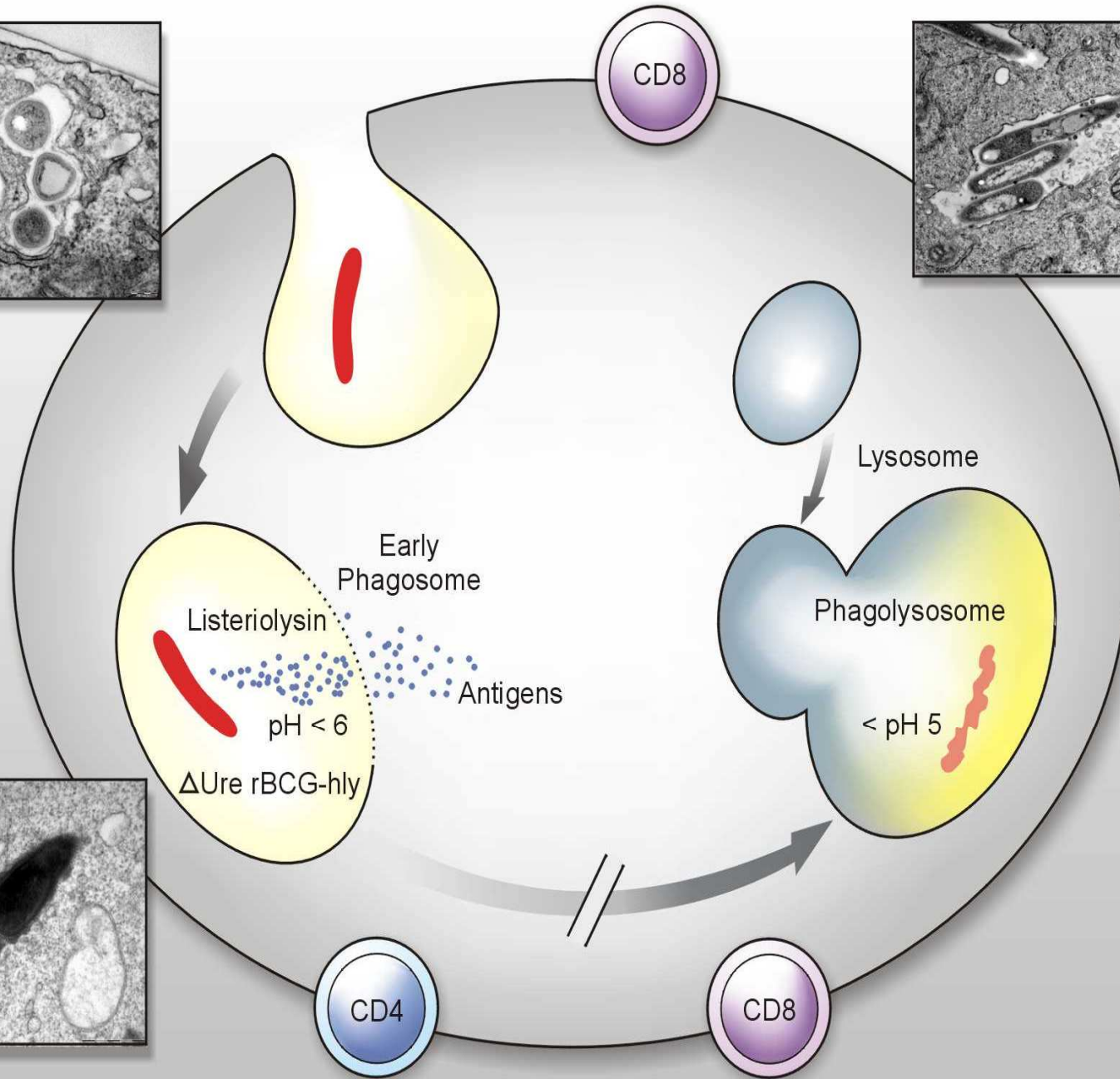
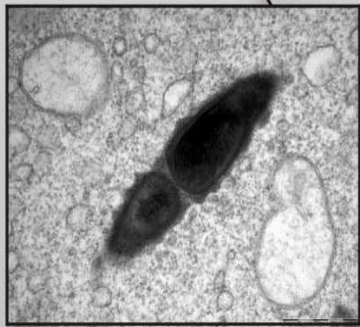


Vaccine candidates in the pipeline

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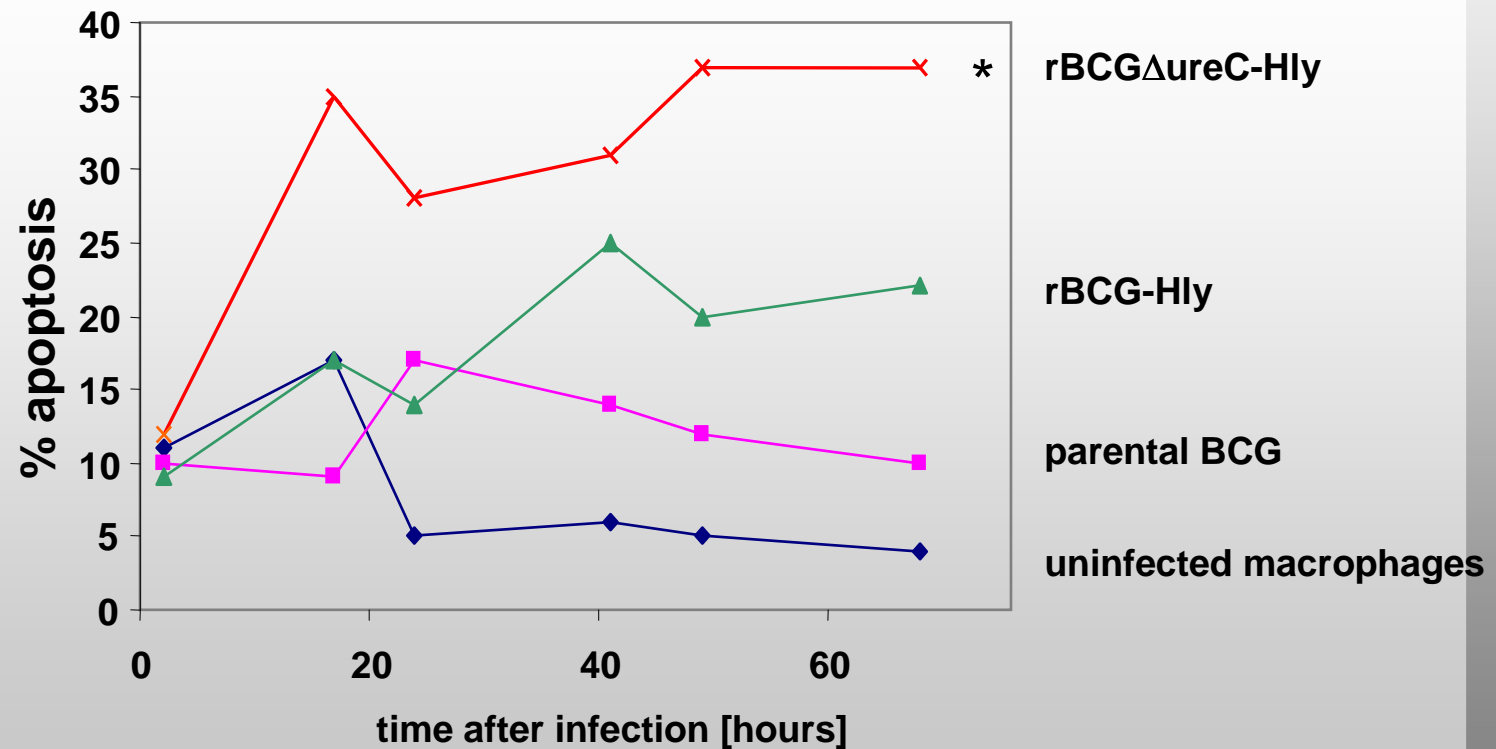
TB vaccine candidates in the clinic.

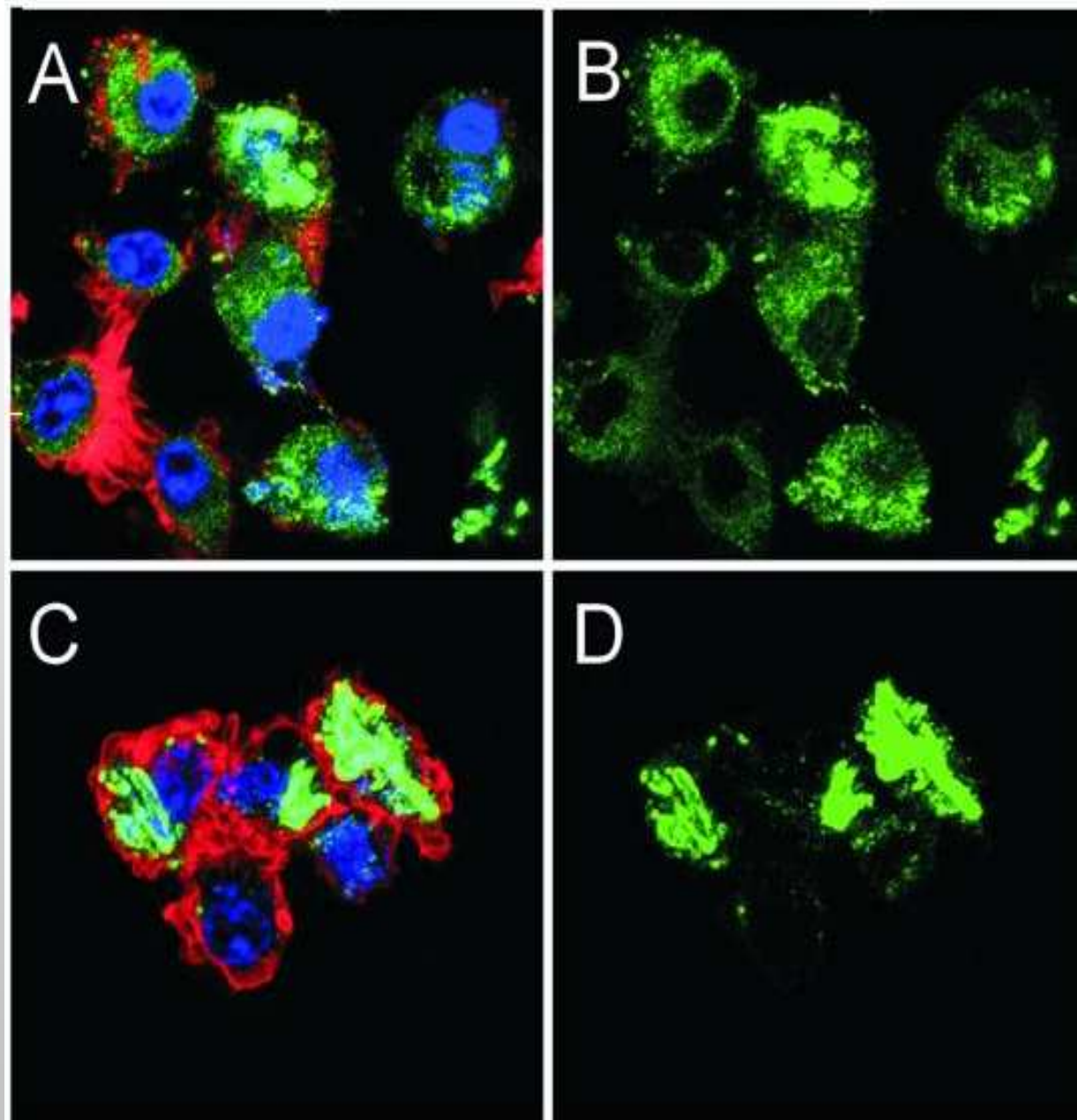
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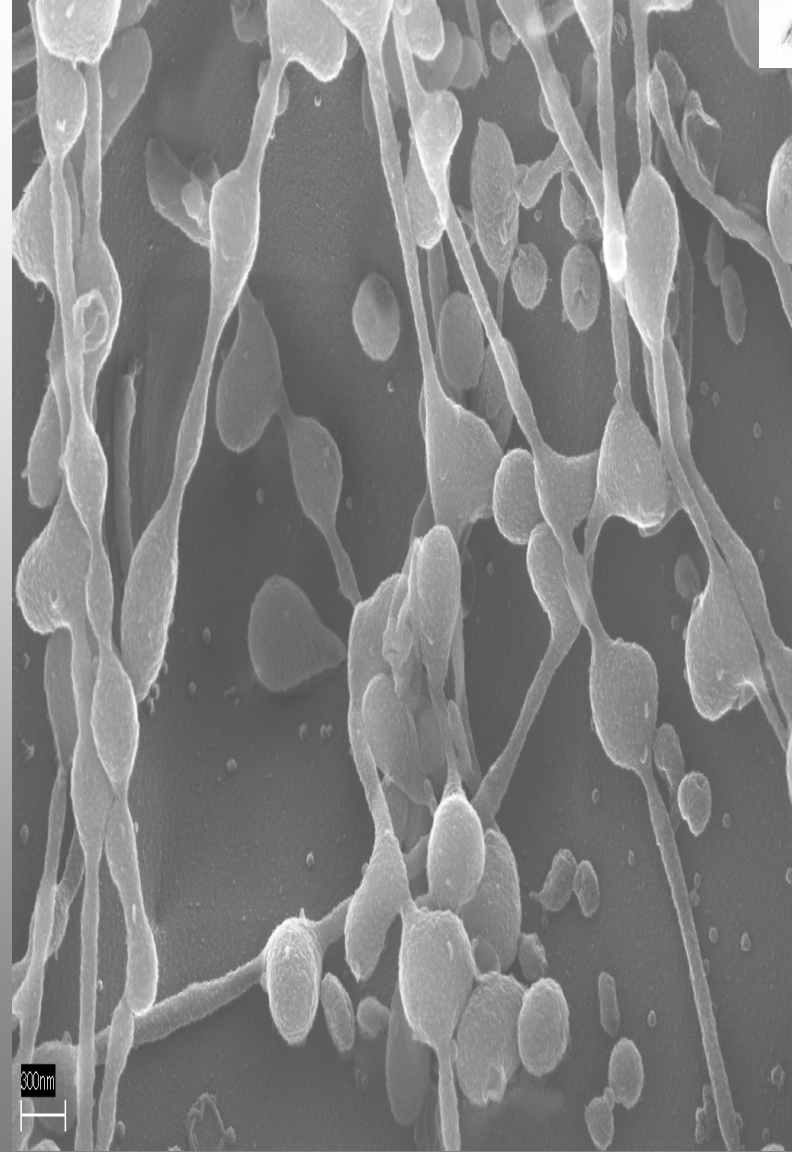
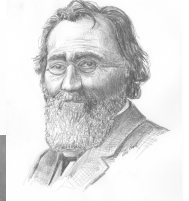
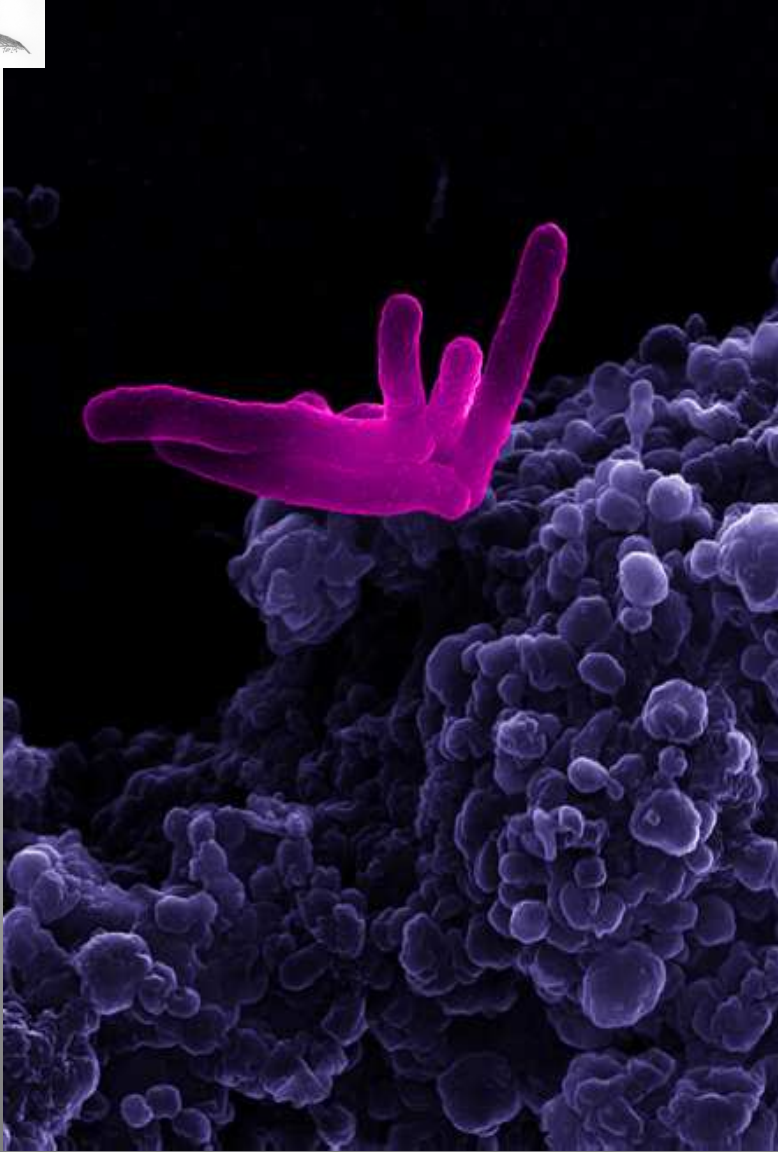


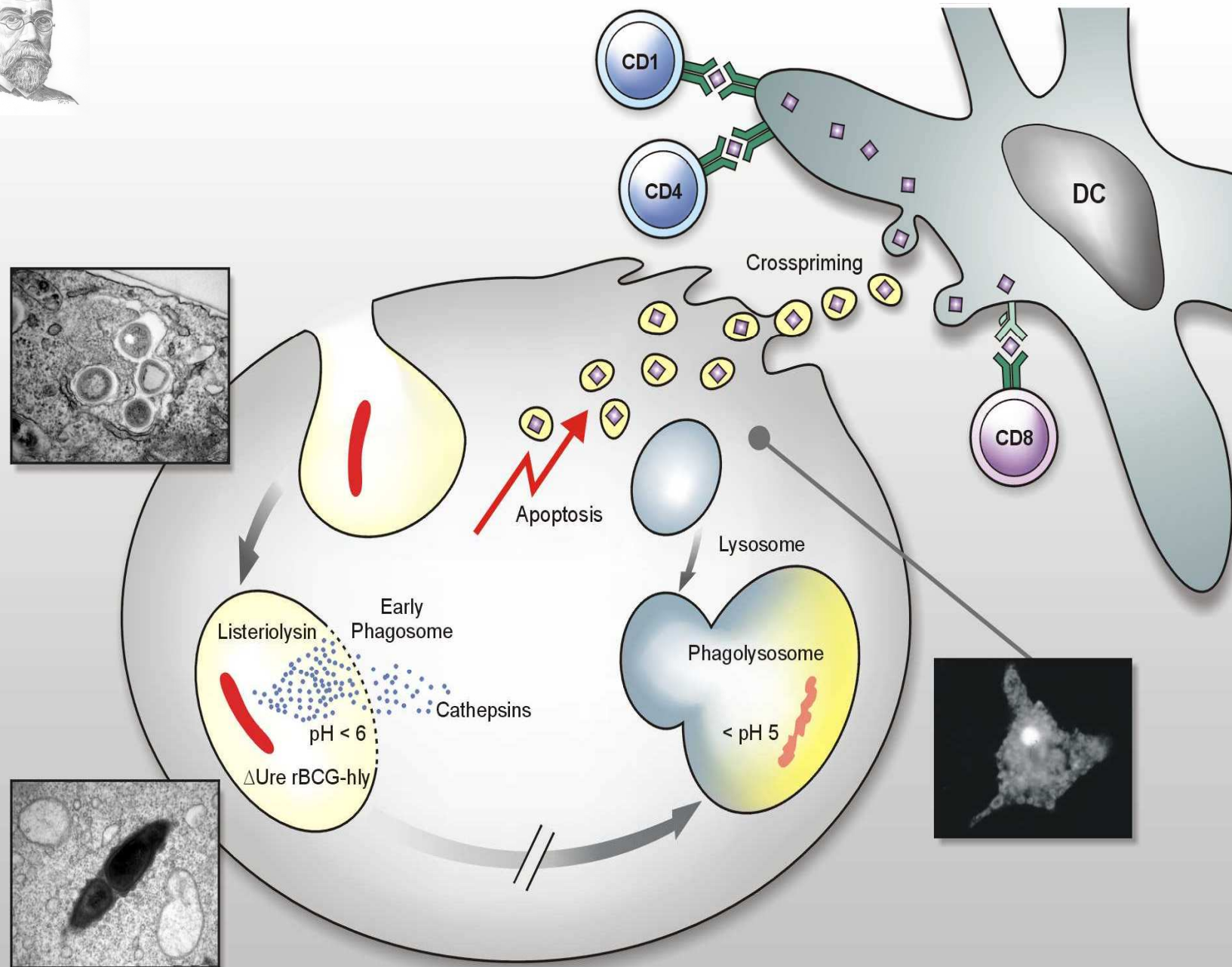


Induced apoptosis of macrophages by rBCGDureC:Hly-listeriolysin









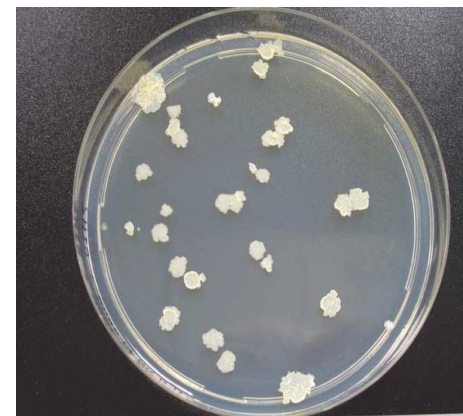
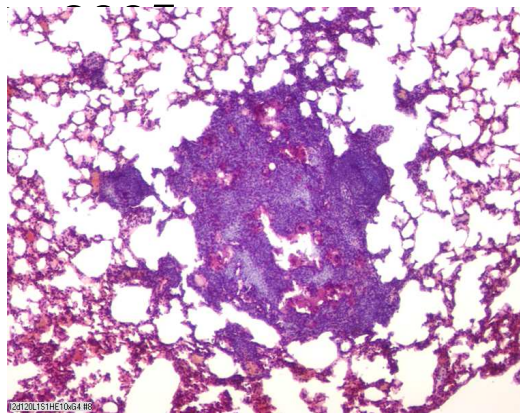


Vaccine Efficacy against TB



Pathogen	Vaccine	
	BCG	r-BCG Δ ureC:Hly
Lab strain (H37Rv)	13-fold reduction	130-fold reduction
Clinical isolate (Beijing family)	3-fold reduction	200-fold reduction*

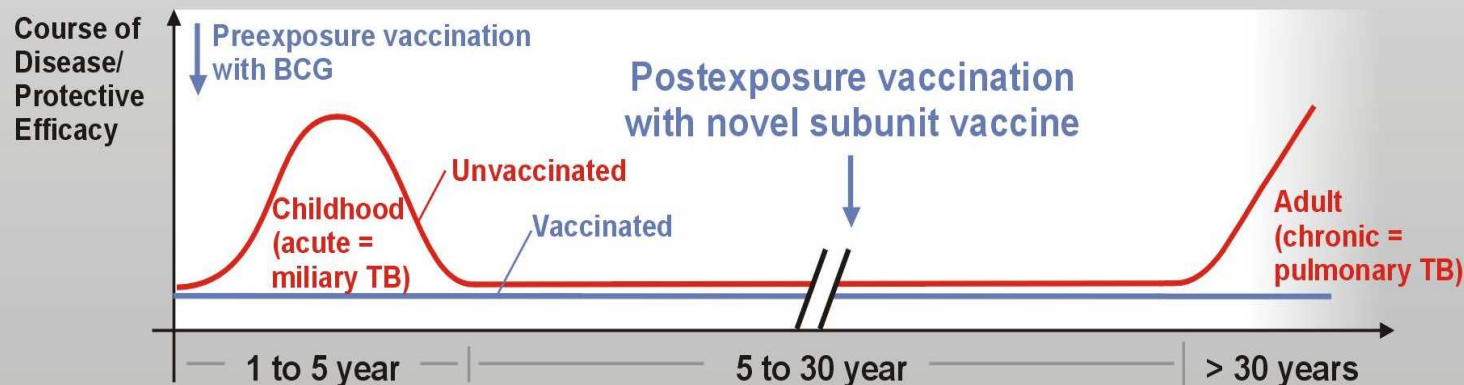
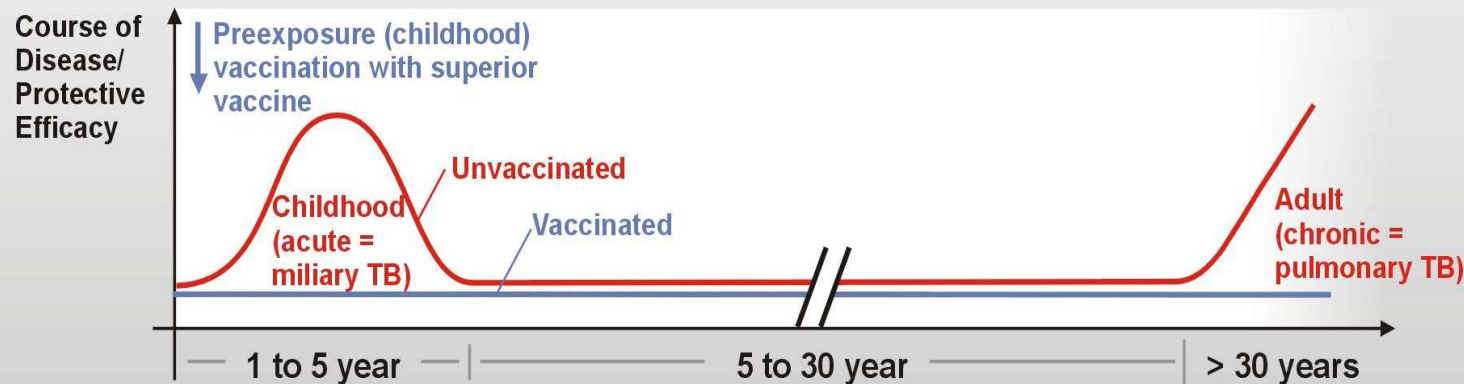
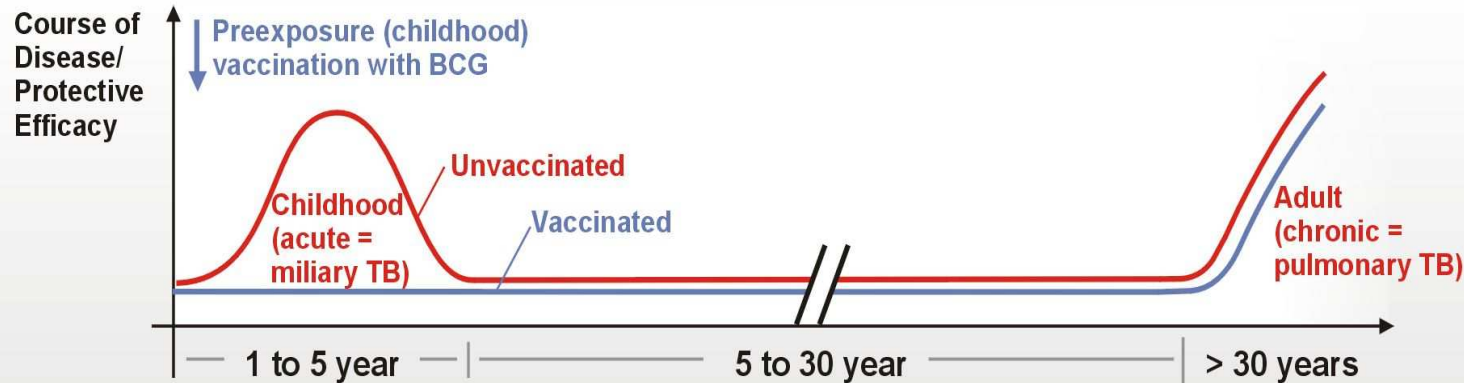
* From 1,000,000 auf 5,000 organisms in the lung
(99.5% growth inhibition) Grode et al., J. Clin. Invest.,



rBC



Possible scenarios





The Future

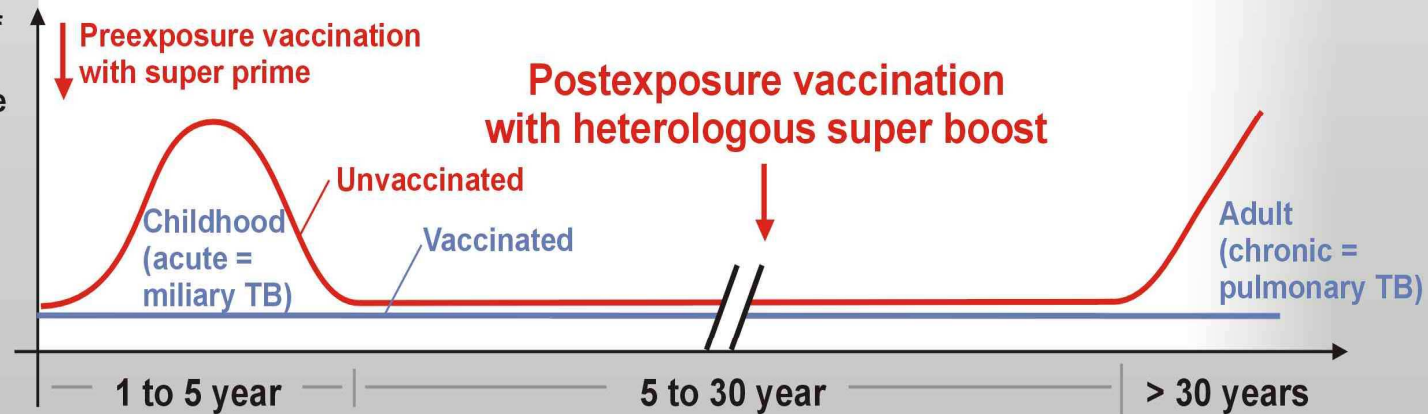


Compete



Take the best of both:
Combine heterologous prime / boost

Course of
Disease/
Protective
Efficacy



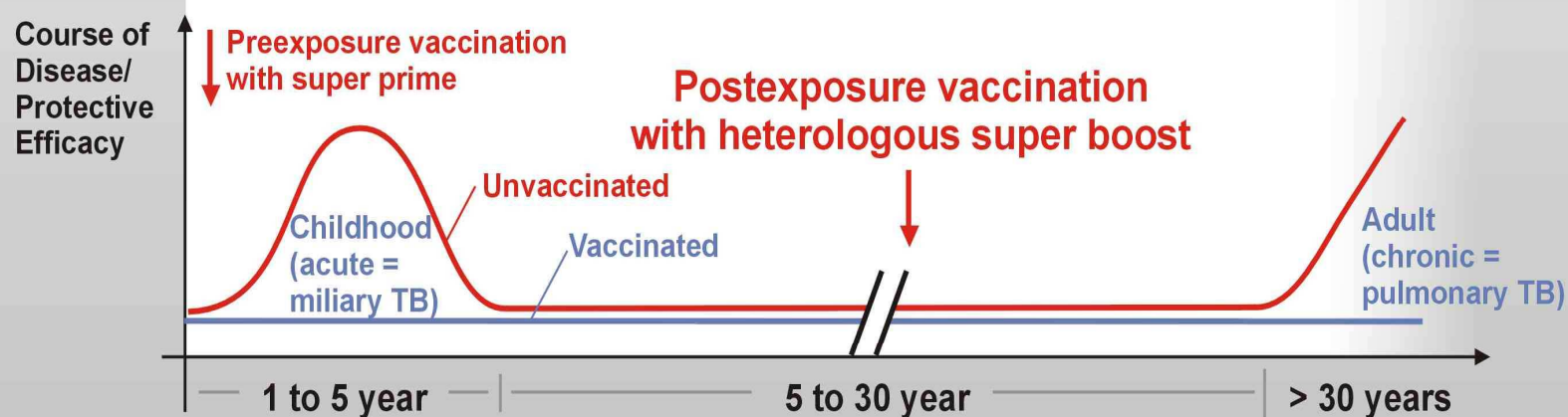


The Future

Box 1 Prime-boost strategies for preventing different forms of TB disease

Immunization strategy	BCG replacement/prime	Boost	Latency vaccine/immunotherapy
Prevention of clinical pathology	Meningeal/miliary TB	Pulmonary TB	Reactivation TB (pulmonary TB)
TB vaccine candidates	Live rBCG expressing <i>Mtb</i> antigens	Viral vectored, for example, vaccinia, adenovirus-35	Live or acellular vaccines containing latent stage antigens, for example, Rv3427, DosR regulated antigens, HBHA
	Live rBCG with endosome perturbation properties	Proteins with adjuvant, for example, 85A/ESAT-6 IC31, 85A/10.4 IC31, 72f AS01	
	Live attenuated <i>Mtb</i>		

rBCG—recombinant BCG; HBHA—heparin-binding hemagglutinin.





Next steps



- ✓ Further improvement of rBCG vaccine candidates
- ✓ Introduction of latency antigens
- ✓ Introduction of cytokine genes
- ✓ Deletion of anti-apoptotic genes
- ✓ metabolically active, non-replicating *M. tuberculosis*
- ✓ Enhancement of the immune response



Koch-Metschnikov-Forum



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