



**Vakzine Projekt  
Management GmbH**

eine Initiative des  
Bundesministeriums für Bildung und Forschung (BMBF)

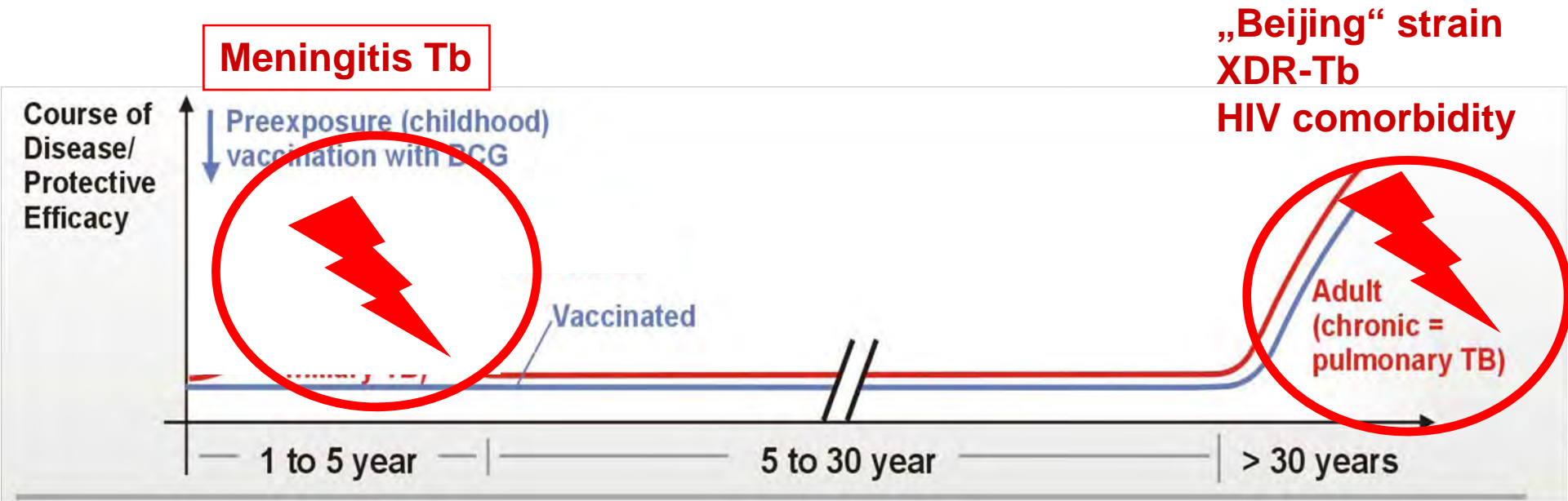
# Development of VPM1002/rBCG $\Delta$ ureC::Hly Tuberculosis vaccine

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# Dramatic Change in Tb Risk Pattern

## Tb has become a Global Emergency (WHO)



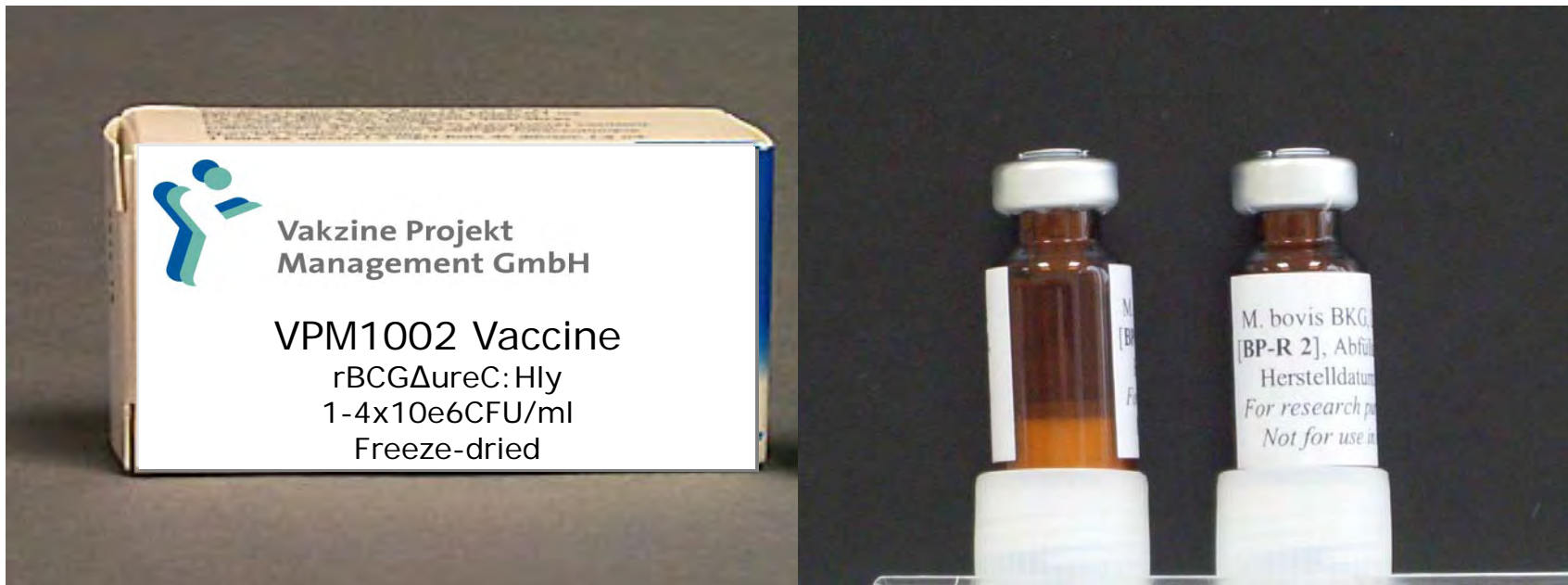
(Max-Planck Institut für Infektionsbiologie, Berlin)

# Target Product Profile of an improved vaccine against Tb



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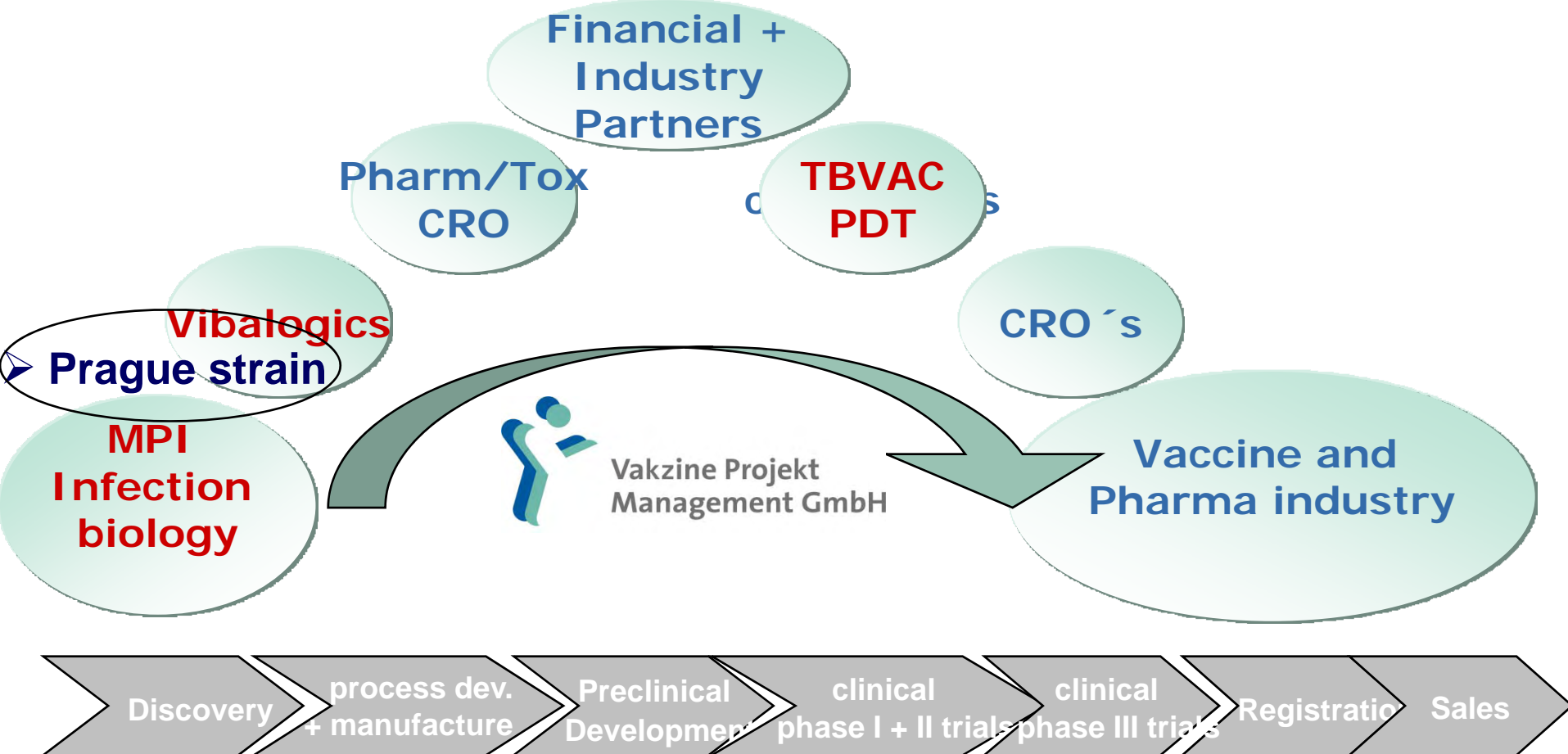
- **No interference with Tb diagnostics**
- Induction of **CD4+ AND CD8+** Immune response
- Induction of **Multifunctional T-cells** (IL-2; IFN- $\gamma$ ; TNF- $\alpha$ )
- **Safer than BCG** in immunocompromised species/vaccinees



# Partnering with experts along the value chain of development

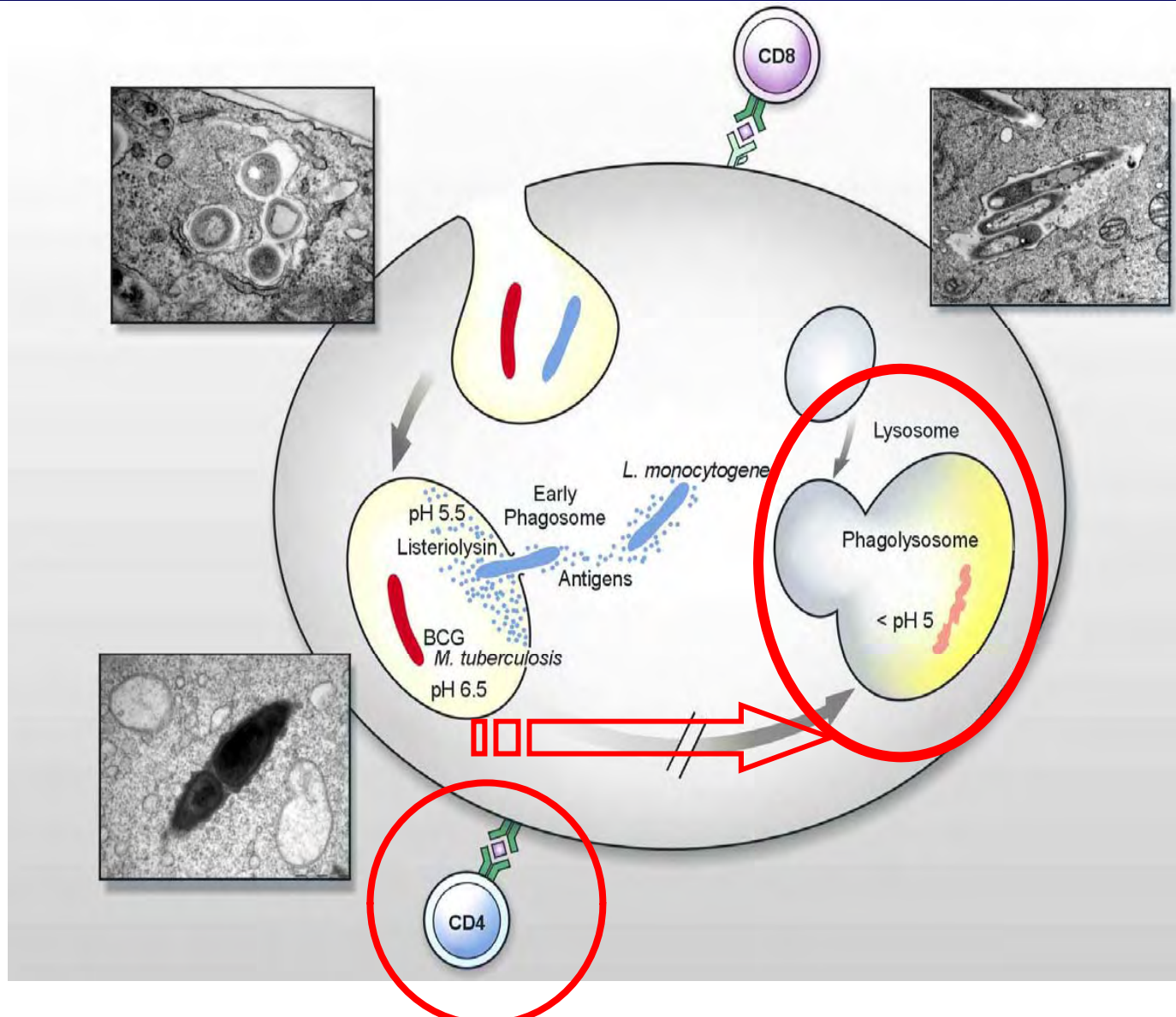


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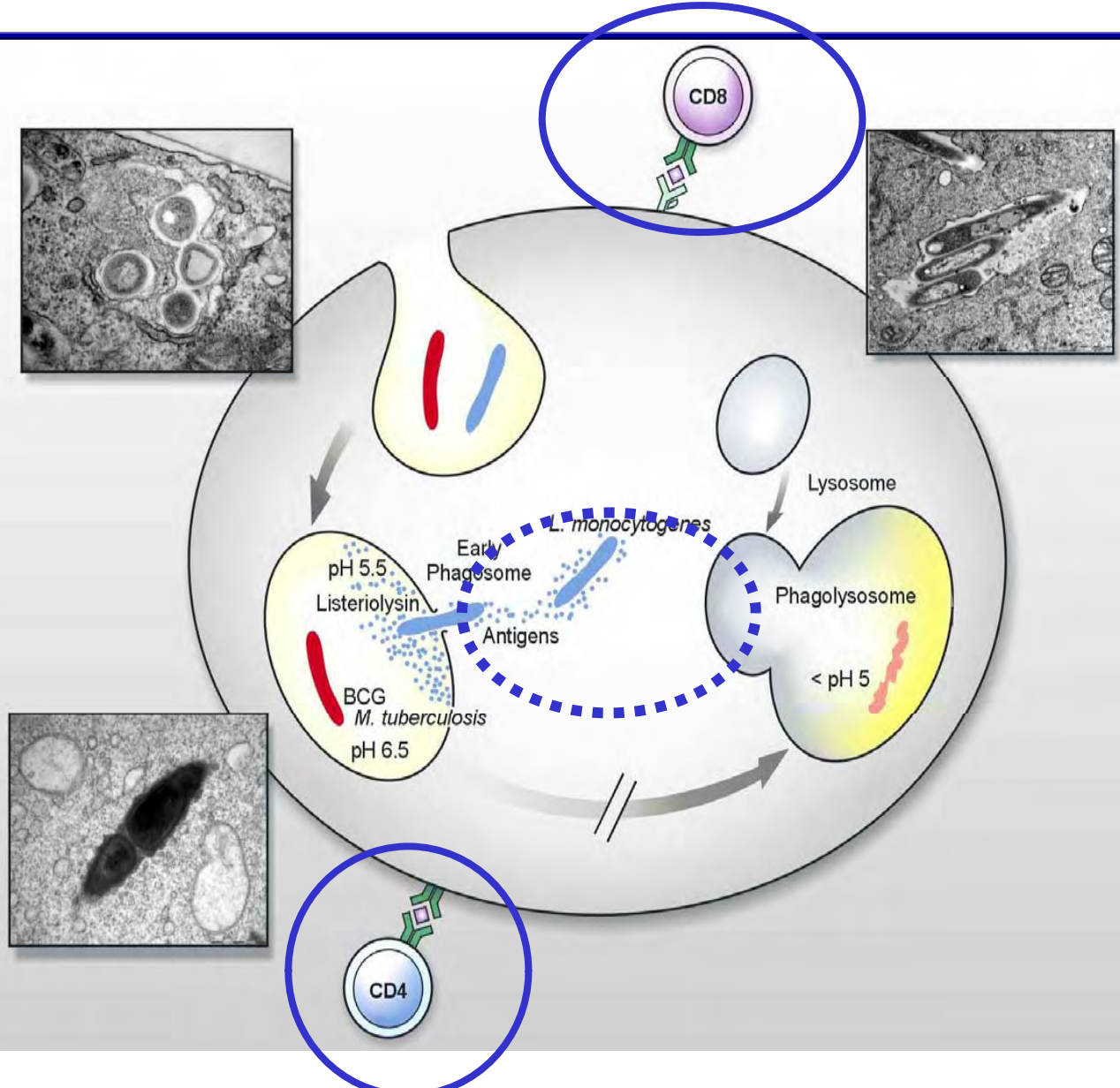
# The Challenge in Translational Research: - Improve the Gold Standard BCG -

BCG

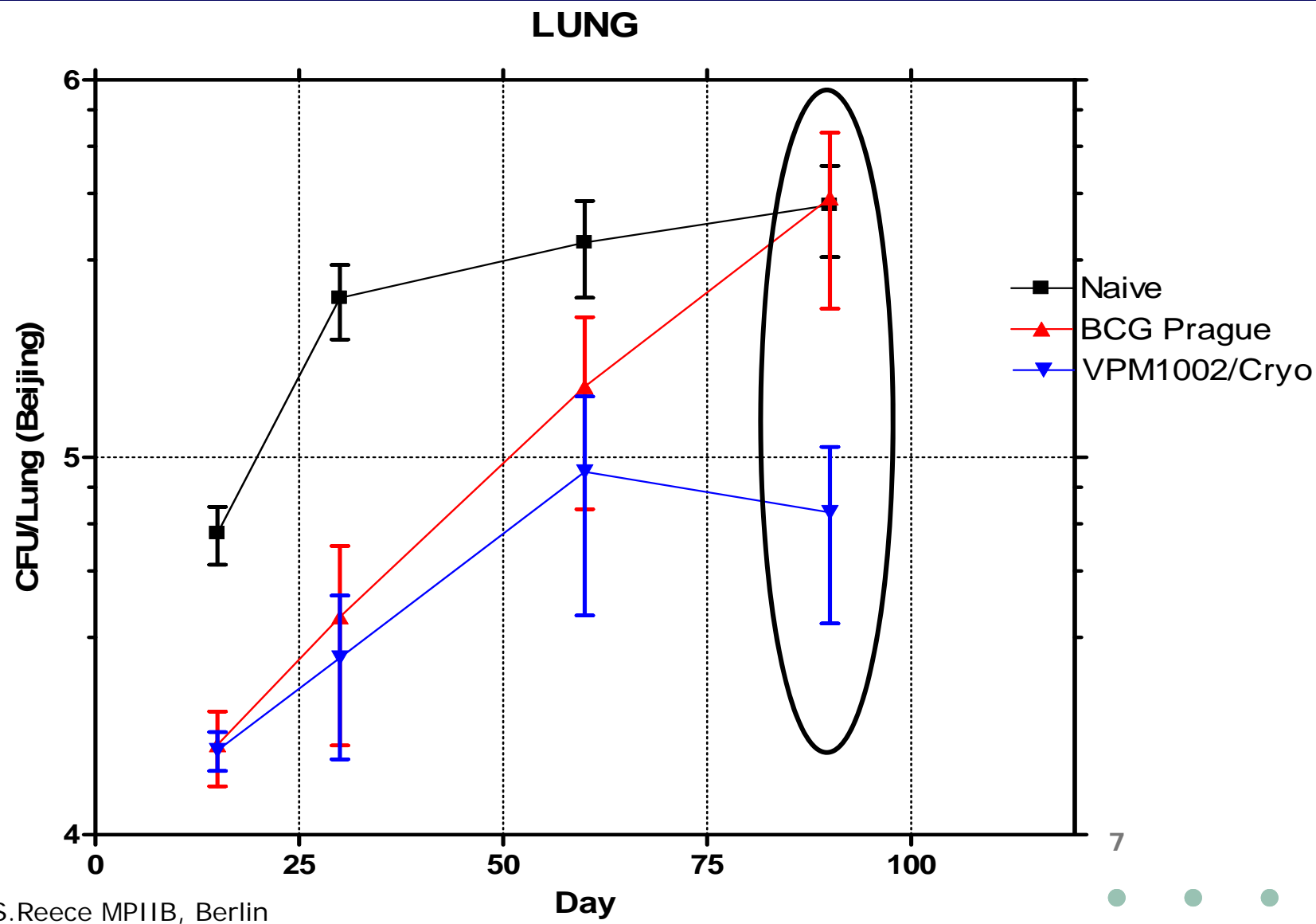


# The Challenge in Translational Research: - Improve the Gold Standard BCG -

VPM1002

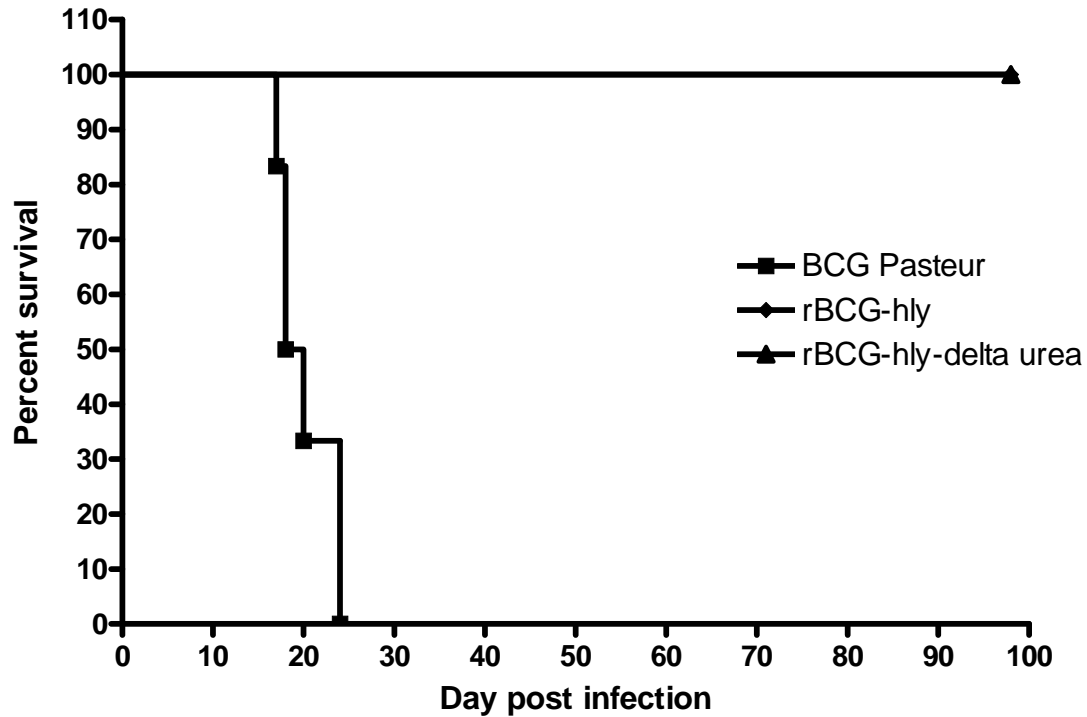


# Challenge mouse model VPM1002 cryo



# VPM1002: General Safety

Attenuation of BCG expressing hemolysin and urea genes  
- infection of SCID mice



Intravenous Inocula  
BCG  $4 \times 10^8$   
rBCG-hly  $3.5 \times 10^7$   
rBCG-hly-delta urea  $1.5 \times 10^8$

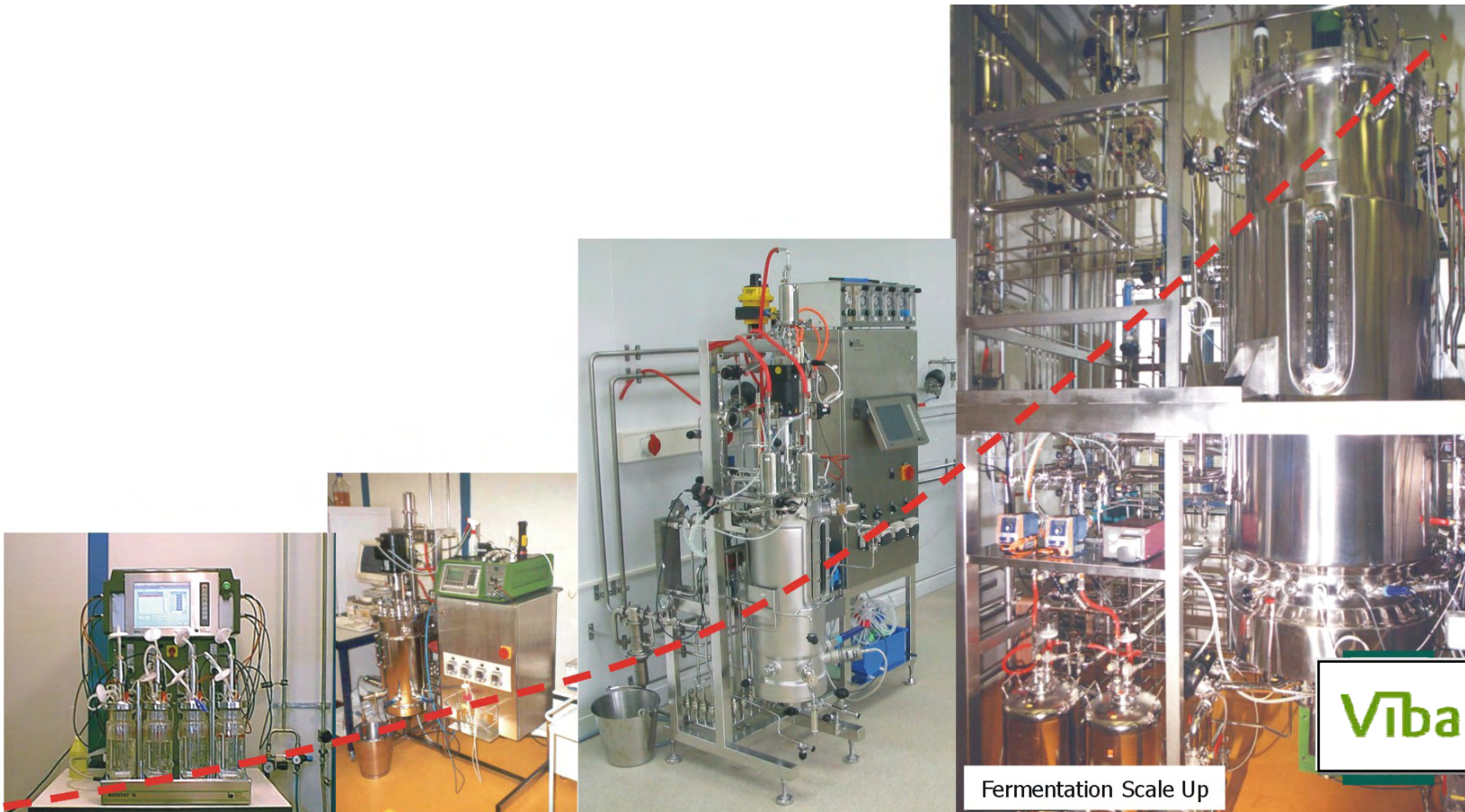
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# Scale-up for Fermentation at Vibalogics



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Fermentation Scale Up

Vibalogics



## → Parental Strain:

→ Danish, subtype Prague

## → Genetic Modification:

→ Listeriolysine gene inserted into chromosome  
(Urease C gene)

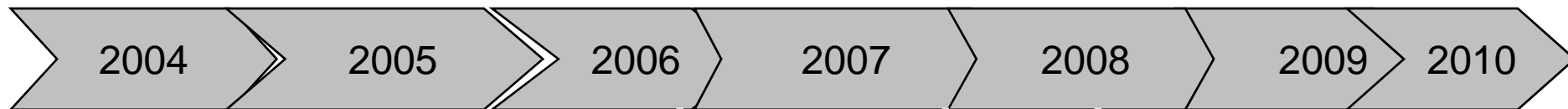
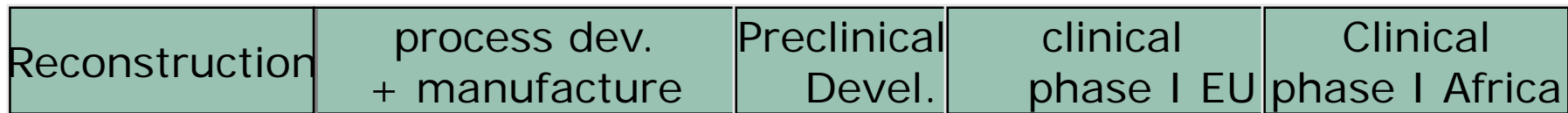
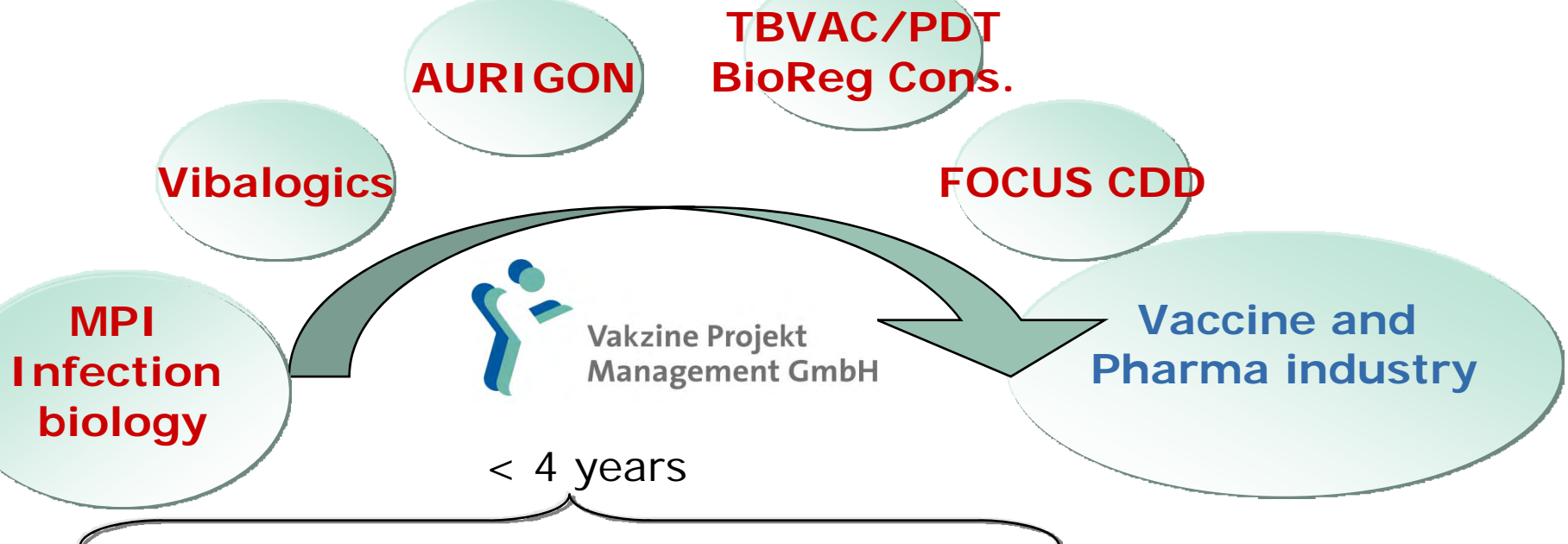
→ Resistance to Hygromycin (to be removed)

## → Classification: S1 / P1

# Preclinical Studies

- 6 months toxicology study in **guinea-pigs** including one PPD skin test; **Successfully completed**, no adverse events, normal weight gain
- 42 days safety studies (highest dose  $1-4 \times 10^7$  CFU/animal) in **guinea-pigs**; in-life phase **successfully completed** without adverse events, normal weight gain; gross necropsy and histology findings similar to control groups
- **Rabbit** toxicology study (**successfully completed**)
- **Safety studies in immune deficient mice**
  - 105 days SCID mouse studies four doses ranging from  $1-4 \times 10^5$  to  $1-3 \times 10^8$  CFU/animal; in-life phase **successfully completed** even the highest dose below LD50
  - 105 days IFN-gamma k.o. mouse study; two dose  $1-4 \times 10^5$  and  $1-4 \times 10^6$  CFU/animal; **successfully completed** 100% survival
- Protection / Challenge in a **murine model** (**successfully completed**)

# Timeline along the value chain of development



GMP-Material

CTA

FIM



**First Vaccinee** enrolled on Sep 08, 2008



**Last Vaccinee** enrolled on June 2, 2009

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# VPM1002-GE-1.01TB: N=80

Dosage Group	Pre-Disposition (BCG-vaccination and PPD status)	N per group	N for intensive safety monitoring	Start week
BCG	No (neither vaccinated nor PPD-pos.)	10	3	1
1	No (neither vaccinated nor PPD-pos.)	10	3	1
2	No (neither vaccinated nor PPD-pos.)	10	3	3
3	No (neither vaccinated nor PPD-pos.)	10	3	5
BCG	Yes (vaccinated or PPD-pos.)	10	3	7
1	Yes (vaccinated or PPD-pos.)	10	3	7
2	Yes (vaccinated or PPD-pos.)	10	3	9
3	Yes (vaccinated or PPD-pos.)	10	3	11
Total		80	24	

Group 1: 5 x 10<sup>3</sup> CFU VPM1002  
 Group 2: 5 x 10<sup>4</sup> CFU VPM1002  
 Group 3: 5 x 10<sup>5</sup> CFU VPM1002  
 BCG: 5 x 10<sup>5</sup> CFU BCG

1-2-3-4 exposition

Stratification regarding the status of pre-disposition:  
 No = lack of BCG-vaccination in the personal vaccination documents and no BCG-scar and PPD-Skin-Test negative (< 1 mm)  
 Yes = documented BCG-vaccination in the personal vaccination documents or BCG-scar or PPD-Skin-Test positive (at least 1 mm but less than 10 mm)



## Primary parameters:

### → **Tolerability**

According to the study protocol 56 days and 6 months after vaccination the subjects were asked.

Till know:

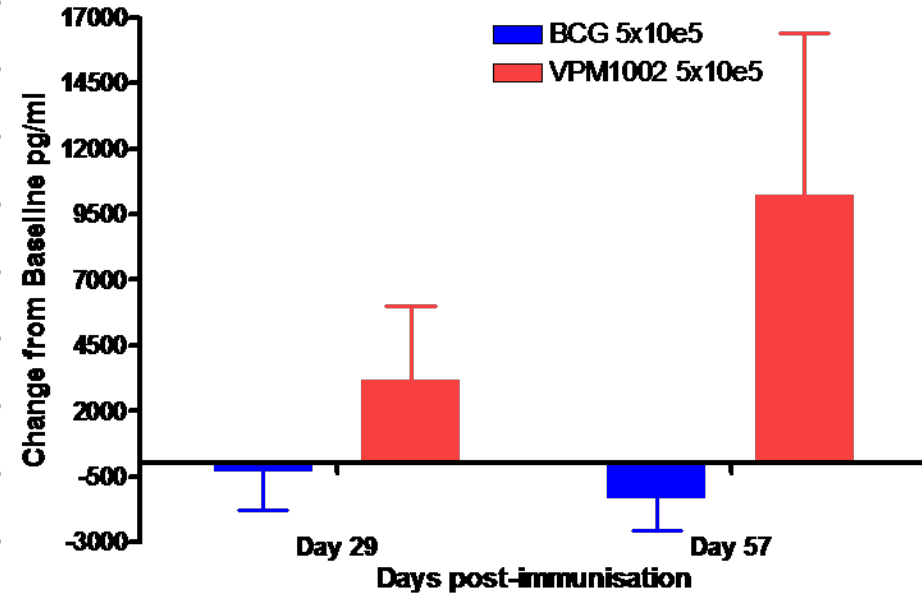
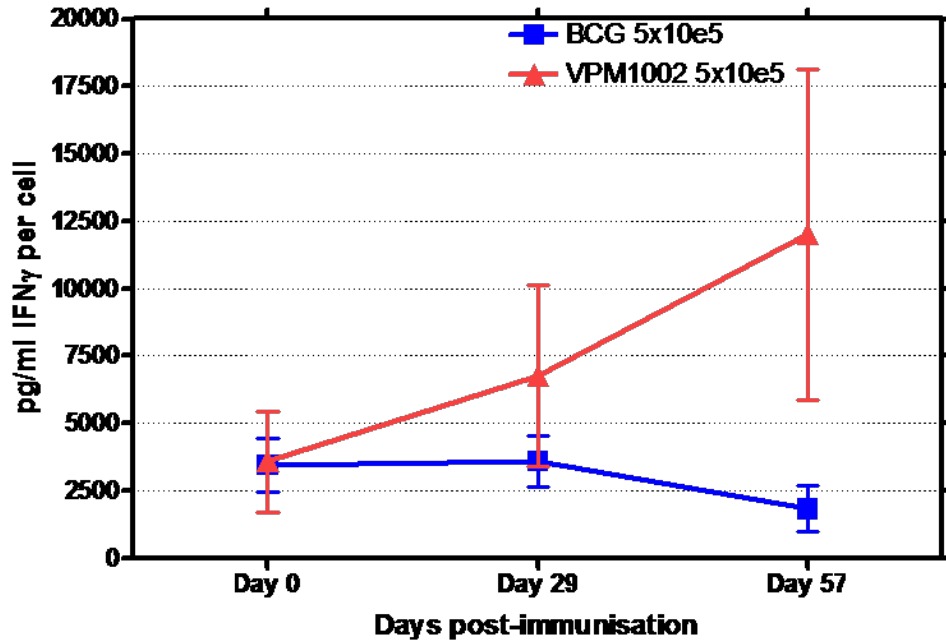
- 57% stated the tolerability as **very good**
- 40% good
- 3% bad (only in the BCG group)

### → **Safety**

- **No Serious Averse Events**
- Some Adverse drug Reactions, mostly (63%) induration, erythema and swelling at the injection side

# Immunogenicity

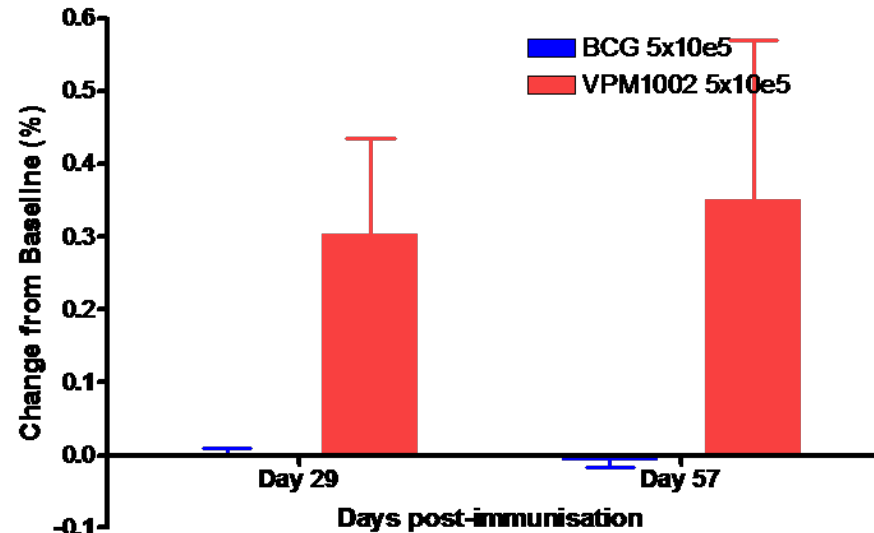
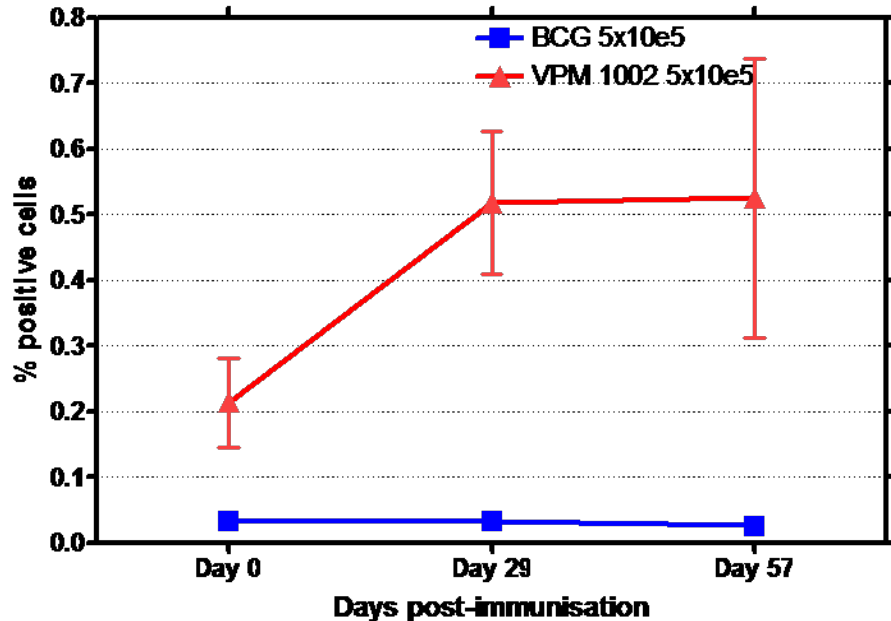
## IFN- $\gamma$ levels increased



VPM1002 increases the IFN- $\gamma$  levels in PBMC from adults.  
The cells were stimulated with Ag85B (2 $\mu$ g/ml).

# Immunogenicity

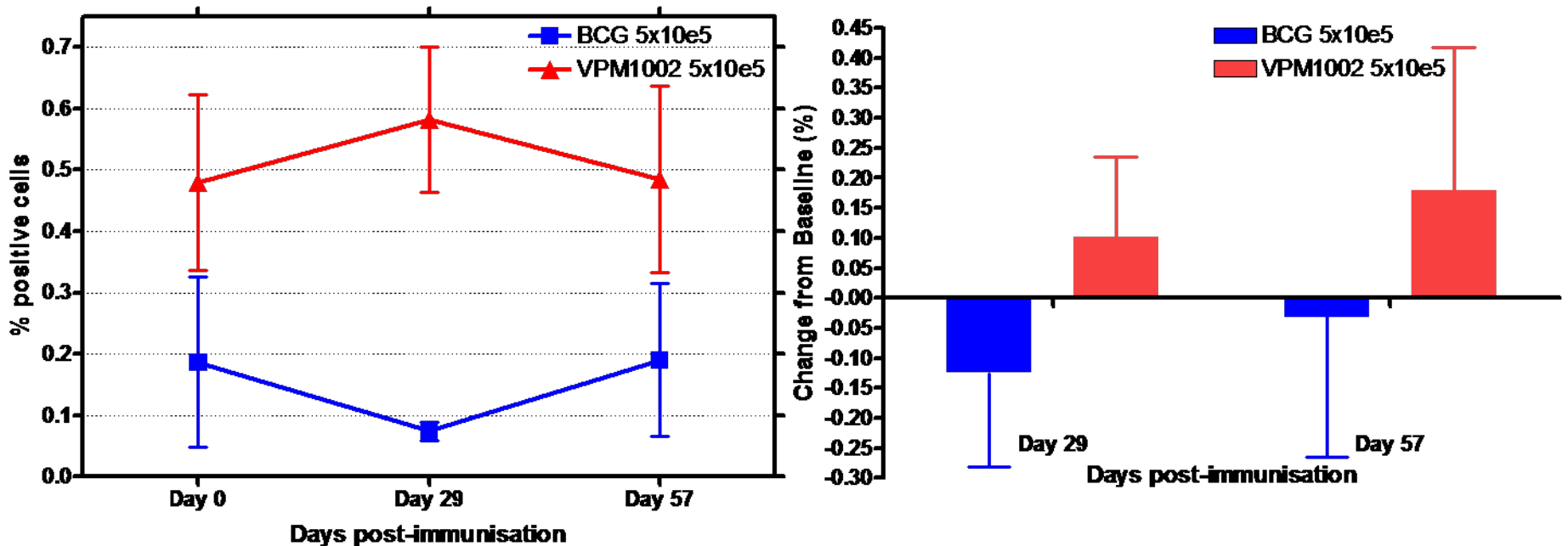
## Multifunctional CD4 T cells



**VPM1002 increases the frequency of multifunctional CD4+ T cells in adults.** Multifunctional CD4+ T cells (expression of IFN- $\gamma$ , IL-2 and TNF- $\alpha$ )  
The cells were stimulated with Ag85B (2 $\mu$ g/ml).

# Immunogenicity

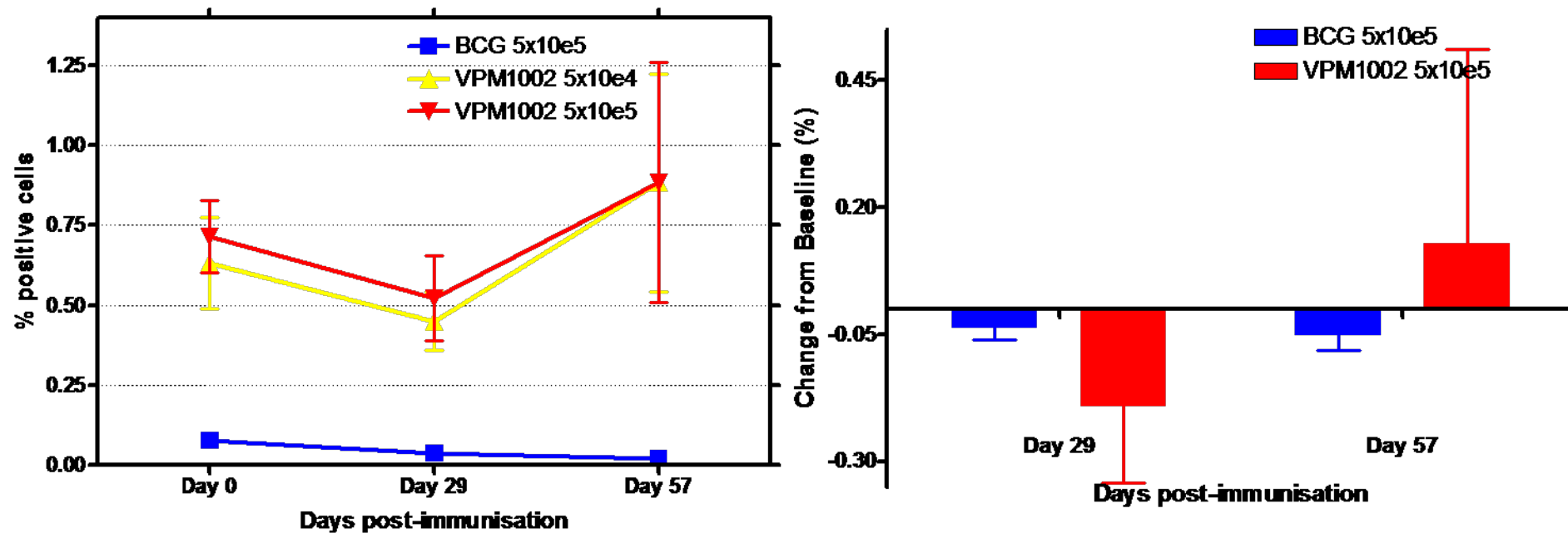
## Multifunctional CD4 T cells



**VPM1002 increases the frequency of multifunctional CD4+ T cells in adults.** Multifunctional CD4+ T cells (expression of IFN- $\gamma$ , IL-2 and TNF- $\alpha$ )  
The cells were stimulated with PPD (10 $\mu$ g/ml).

# Immunogenicity

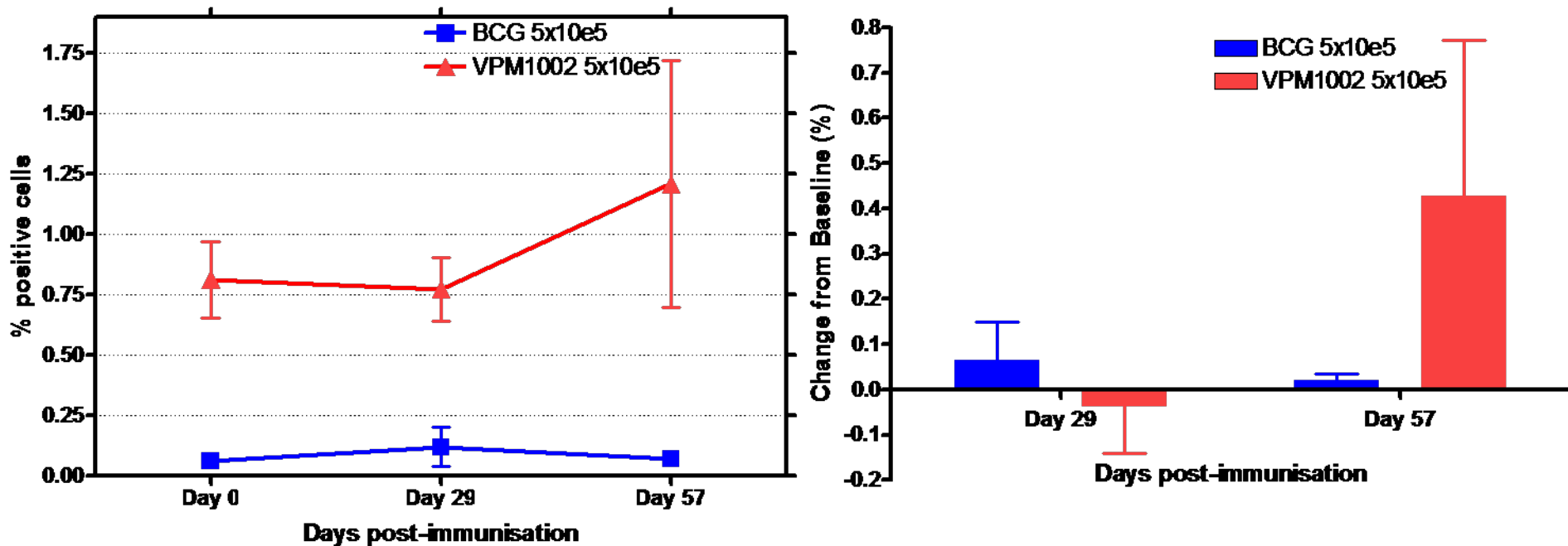
## Multifunctional CD8 T cells



**VPM1002 increases the frequency of multifunctional CD8+ T cells in adults.** Multifunctional CD8+ T cells (expression of IFN- $\gamma$ , IL-2 and TNF- $\alpha$ )  
The cells were stimulated with Ag85B (2 $\mu$ g/ml).

# Immunogenicity

## Multifunctional CD8 T cells

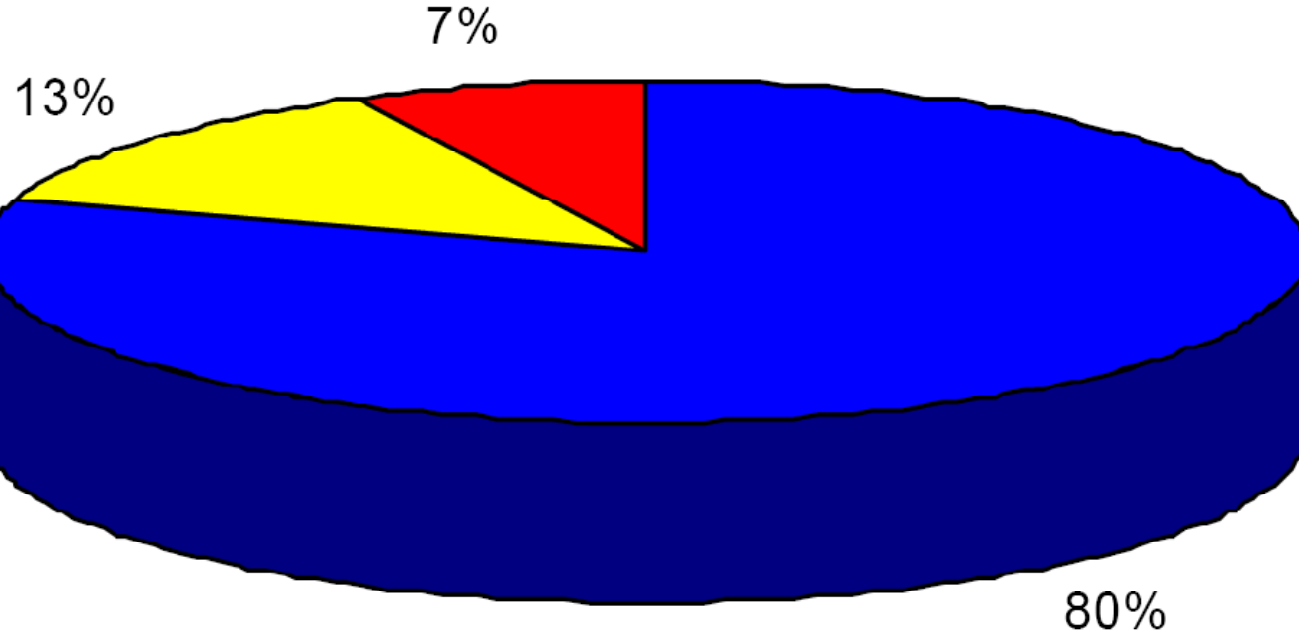


**VPM1002 increases the frequency of multifunctional CD8+ T cells in adults.** Multifunctional CD8+ T cells (expression of IFN- $\gamma$ , IL-2 and TNF- $\alpha$ ) The cells were stimulated with PPD (10 $\mu$ g/ml).

# Multifunctional T-cells

(IFN- $\gamma$ , TNF- $\alpha$ , IL-2)

**A) BCG day 57 post immunization (CD8+ PPD)**

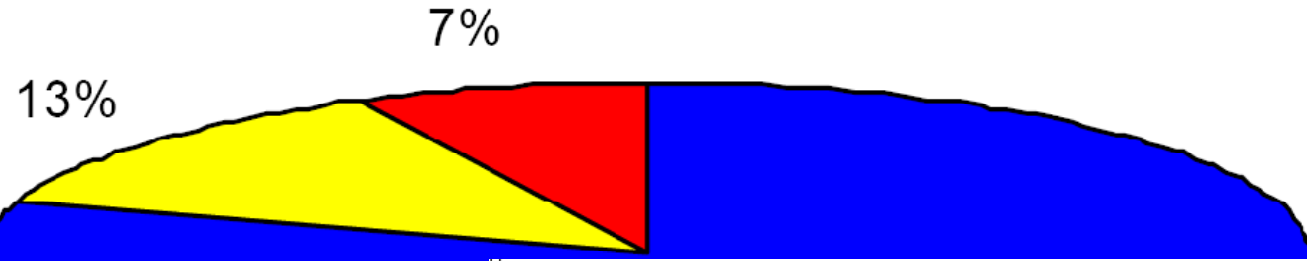


# Multifunctional T-cells

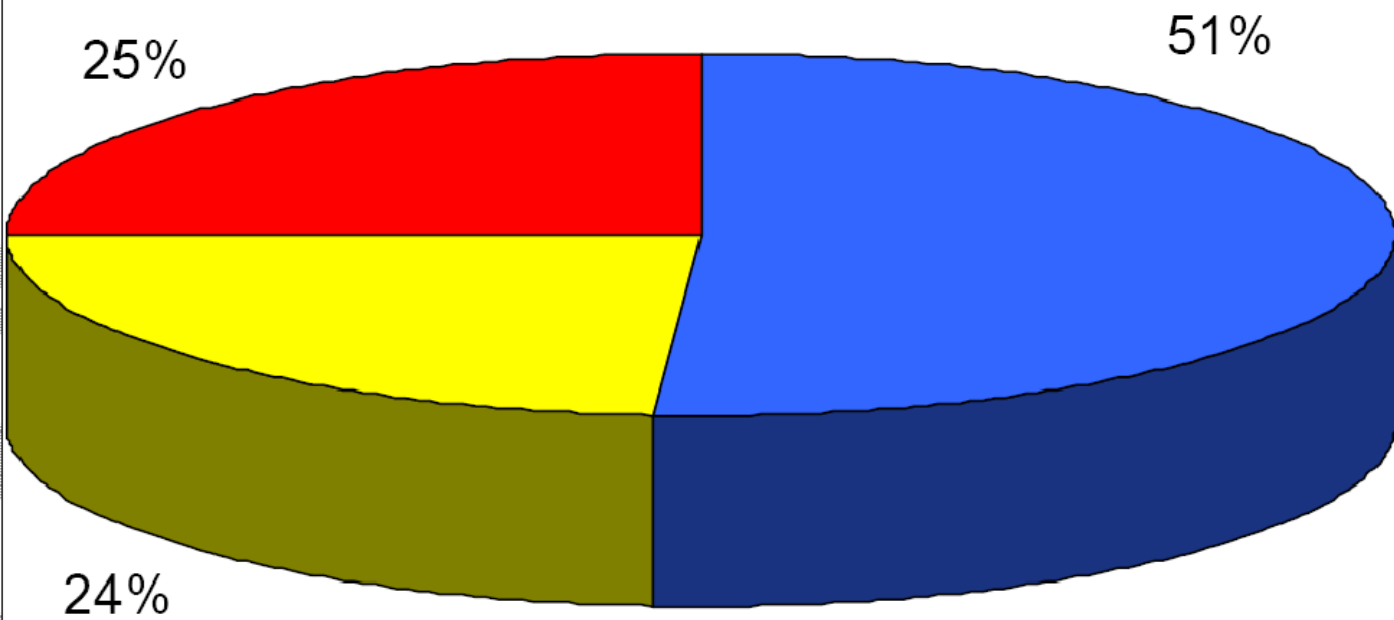
--- marked Increase with VPM1002 ---



A) BCG day 57 post immunization (CD8+ PPD)



B) VPM1002 day 57 post immunization

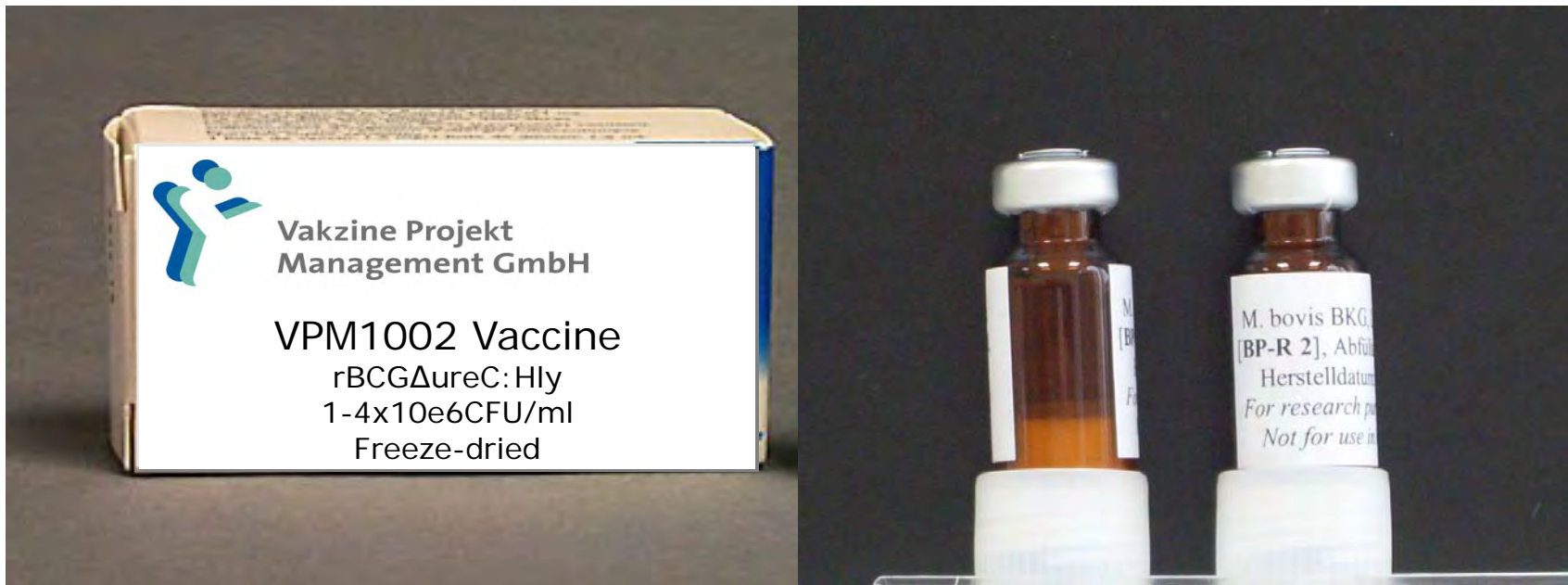


# Product Profile of VPM1002



Vakzine Projekt  
Management GmbH

- **No interference with Tb diagnostics**
- Induction of **CD4+ AND CD8+** Immune response
- Induction of **Multifunctional T-cells** (IL-2; IFN- $\gamma$ ; TNF- $\alpha$ )
- **Safer than BCG** in immunocompromised species

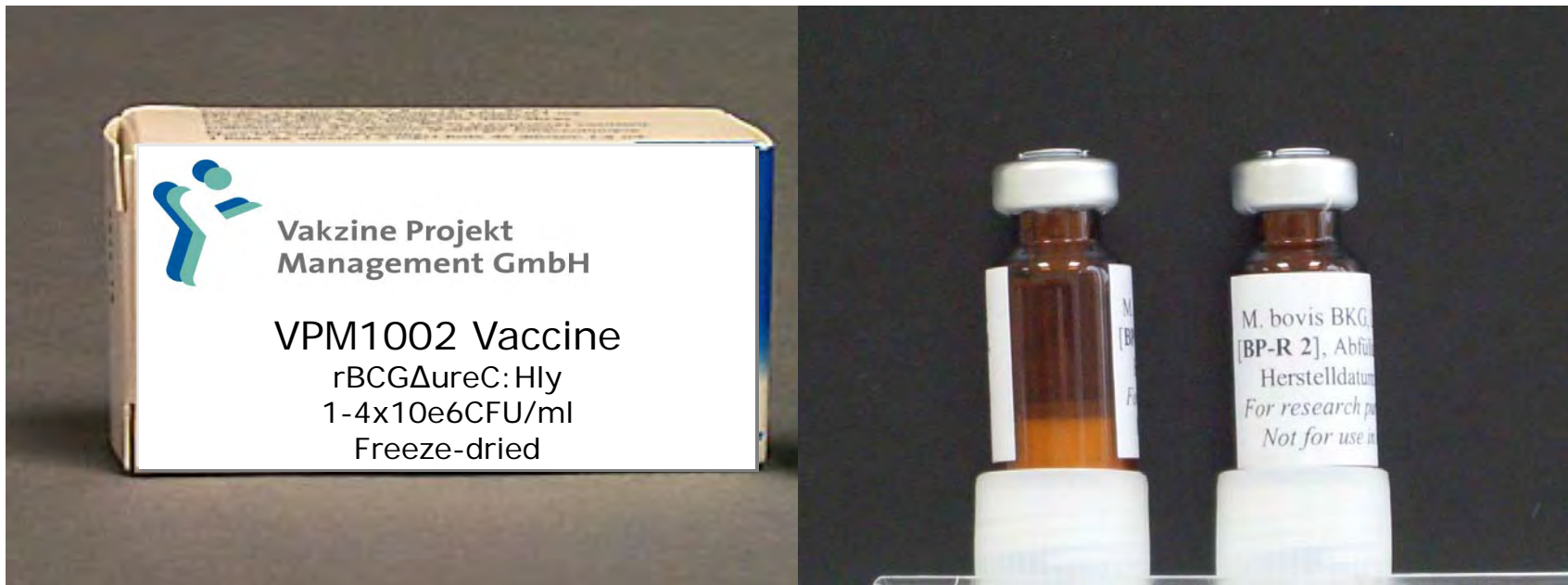


# Product Promise of VPM1002



Vakzine Projekt  
Management GmbH

- **No interference with Tb diagnostics** (→ **unproblematic use**)
- Induction of **CD4+ AND CD8+** Immune response (→ **improved protection**)
- Induction of **Multifunctional T-cells** (IL-2; IFN- $\gamma$ ; TNF- $\alpha$ ) (→ **in children AND adults**)
- **Safer than BCG** in immunocompromised species (→ **usable in high-risk babies**)



# Clinical Program Phase Ia-II

(currently under discussion with Authorities)

- **Phase Ia:** Evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in healthy **adult Caucasians** compared to reference control (BCG)
- **Phase Ib:** Evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in healthy **adult Africans** compared to reference control (BCG)
- **Phase II:** Double-blind, randomized, BCG controlled Phase II study with VPM1002 vaccination for evaluation of safety, local and systemic tolerability and immunogenicity of VPM1002 in **neonates**.

# Acknowledgement

VPM is funded by



# Acknowledgement 2

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