Vaccine Portfolio for TB and Beyond

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EDCTP Stakeholder Meeting: Tuberculosis and mycobacterial infections

28 – 29 October 2013

Paris, France

Max-Planck-Institut für Infektionsbiologie

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Agenda

- TB and other mycobacterial diseases
- The current TB vaccine pipeline
- Different types of vaccinations
- The need for predictive biomarkers
- TB vaccine trials
  - Global portfolio management
  - Harmonization, collaboration and iteration

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Mycobacterial Diseases

Disease	Agent	Morbidity	Region	Therapy	Vaccination
Tuberculosis 	*M. tuberculosis* *M.bovis* *M. africanum*	9 million	Global (Africa, India, China) West-Africa	Yes, but MDR, XDR, TDR INH, RIF, PZA, EMB	BCG partial
Leprosy (TT-LL) 	*M. leprae*	200,000	Latin America, Africa, SE-Asia	Yes RIF, Clofazimine, Dapsone… Inflammation Superinfection	BCG partial
Buruli ulcer 	*M. ulcerans*	10,000 (50%<15 yrs)	Tropical Africa (30 countries)	Yes RIF, Streptomycin, Clarithromycin … Superinfection Inflammation	BCG partial

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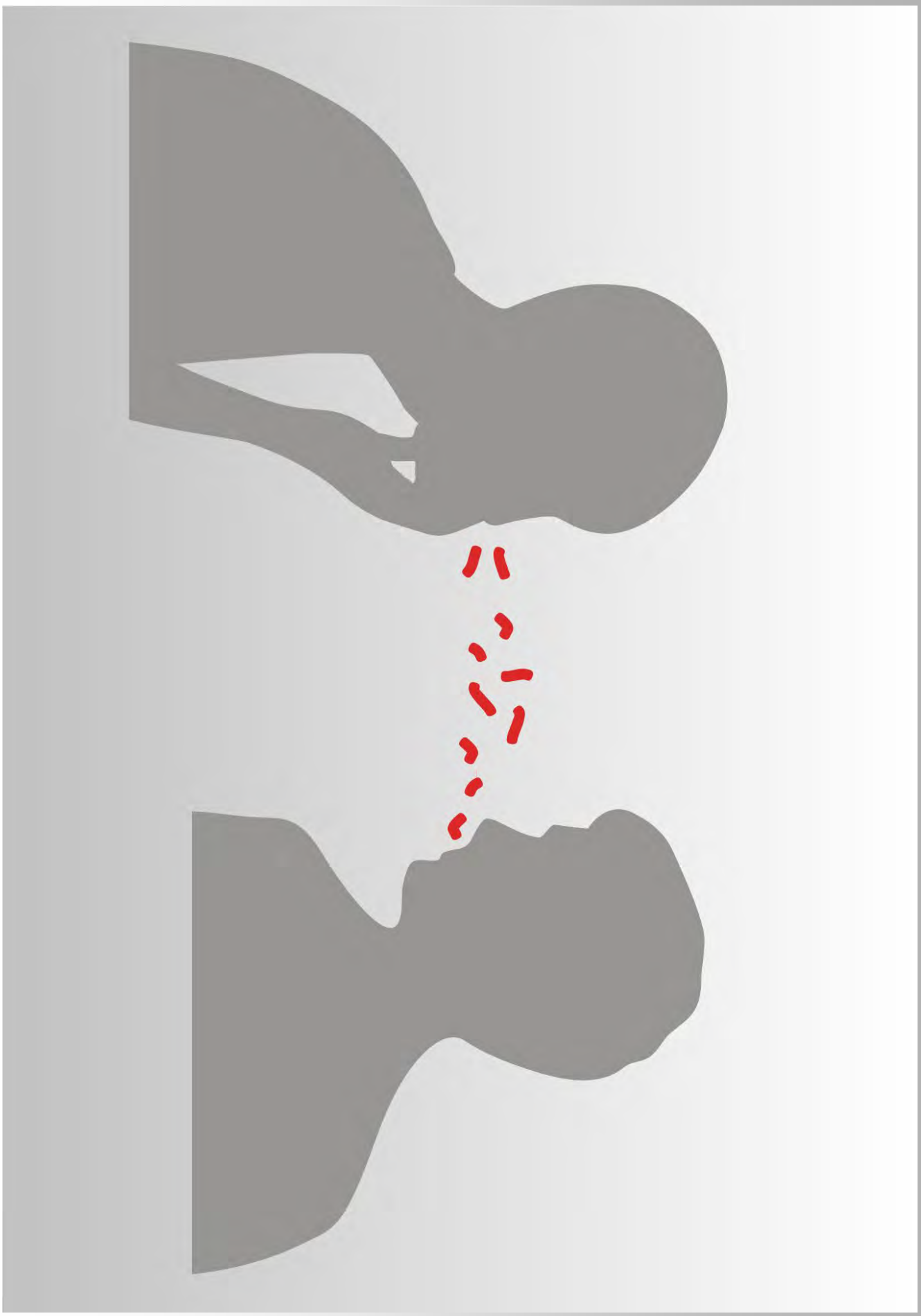

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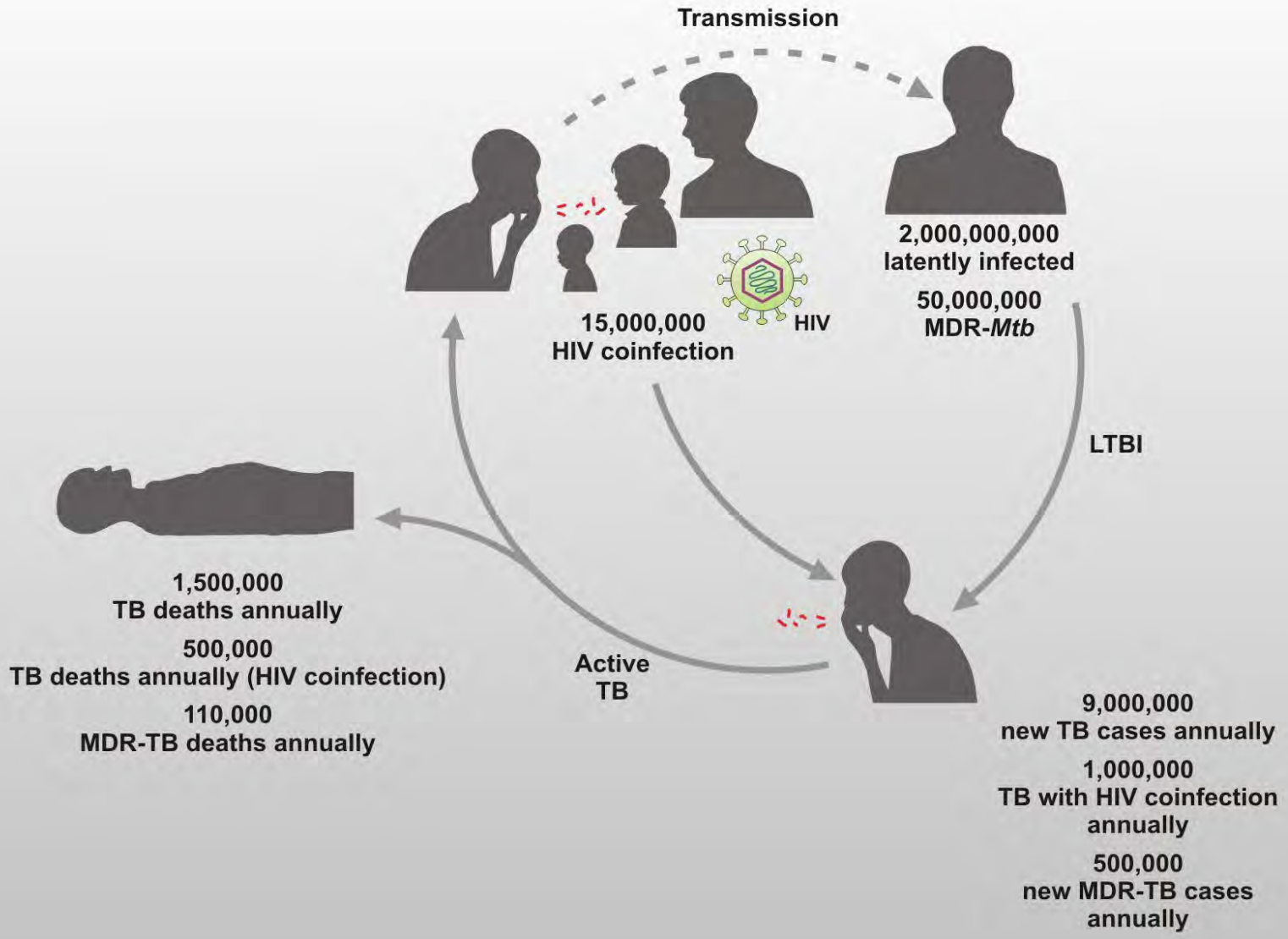
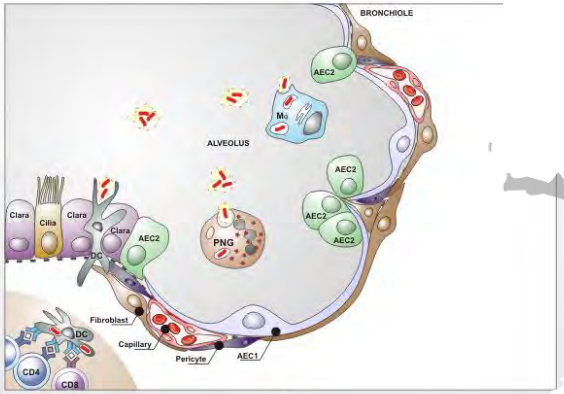
TB vaccines: an epidemiological view

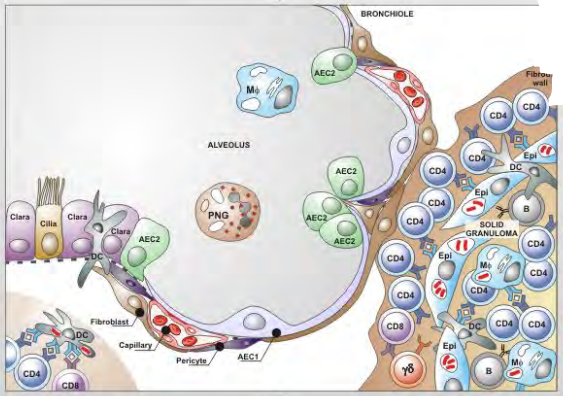


TB vaccines: an immunopathological view

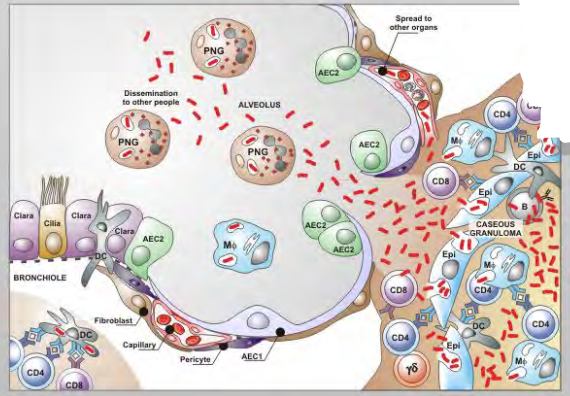
Infection



LTBI



Active TB



Transmission

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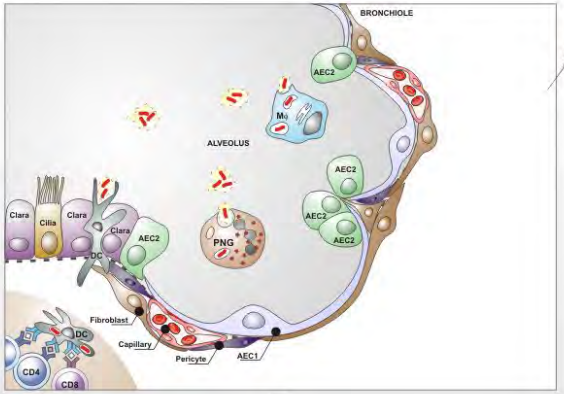
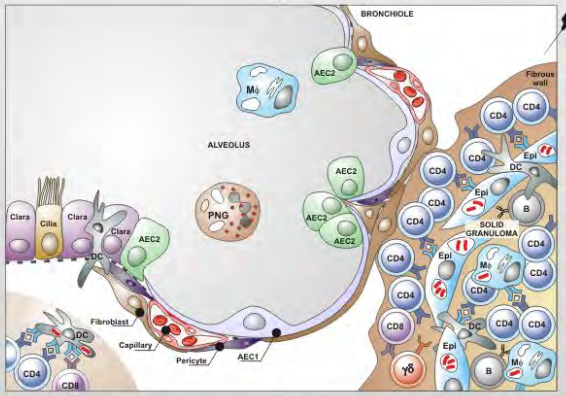
TB vaccines: an immunopathological view

Infection



Prevent disease
(Prevent infection)

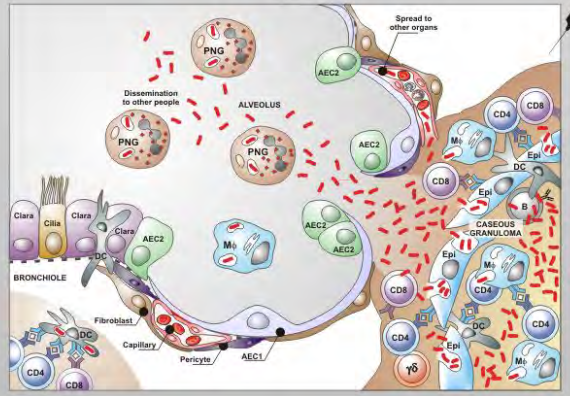
LTBI



Prevent disease
(Eradicate infection)

Transmission

Active TB



Cure disease

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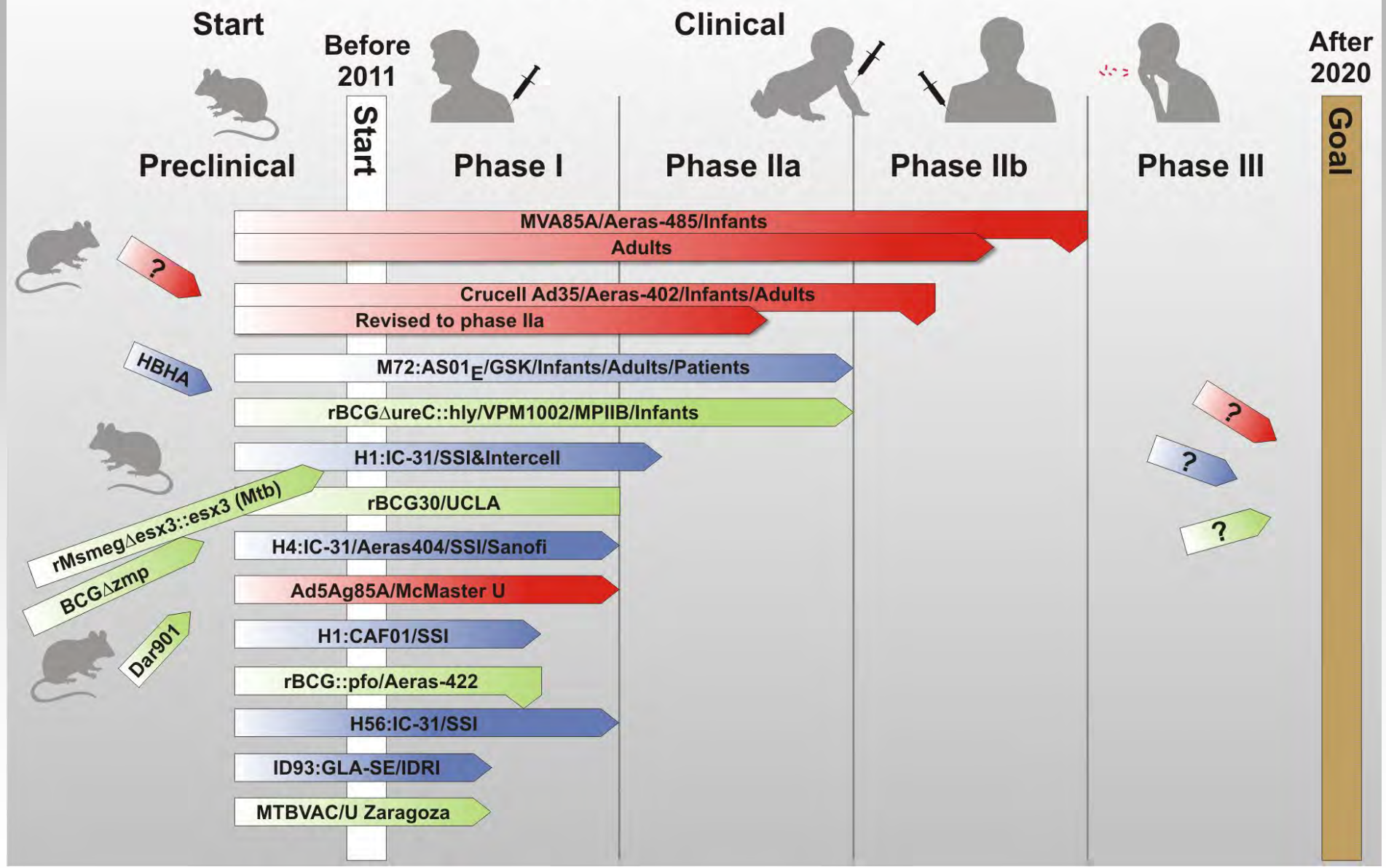
Preventive TB vaccines



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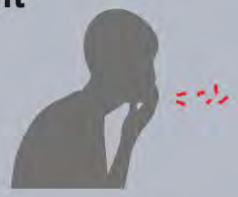
Target populations	Infection/Disease	Vaccine type	Advanced Candidates
Infant 	Uninfected	Preexposure/Preventive BCG replacement	rBCG: VPM1002 r-Mtb: NEWTBVAC
 Infant	Uninfected BCG	Preexposure/Preventive Prime-boost	Viral vectored: MVA85A/Aeras-485 Protein/adjuvant: H4:IC-31
Adolescent/ Adult 	LTBI/BCG (TST^+)	Postexposure/Preventive Prime-boost	Viral vectored: MVA85A/Aeras-485 Protein/adjuvant: M72:AS01$_E$ H56:IC-31 ID93:GLA-SE
Adolescent/ Adult 	Active TB	Therapeutic	Killed mycobacteria: *M. indicus pranii* *M. vaccae* RUTI

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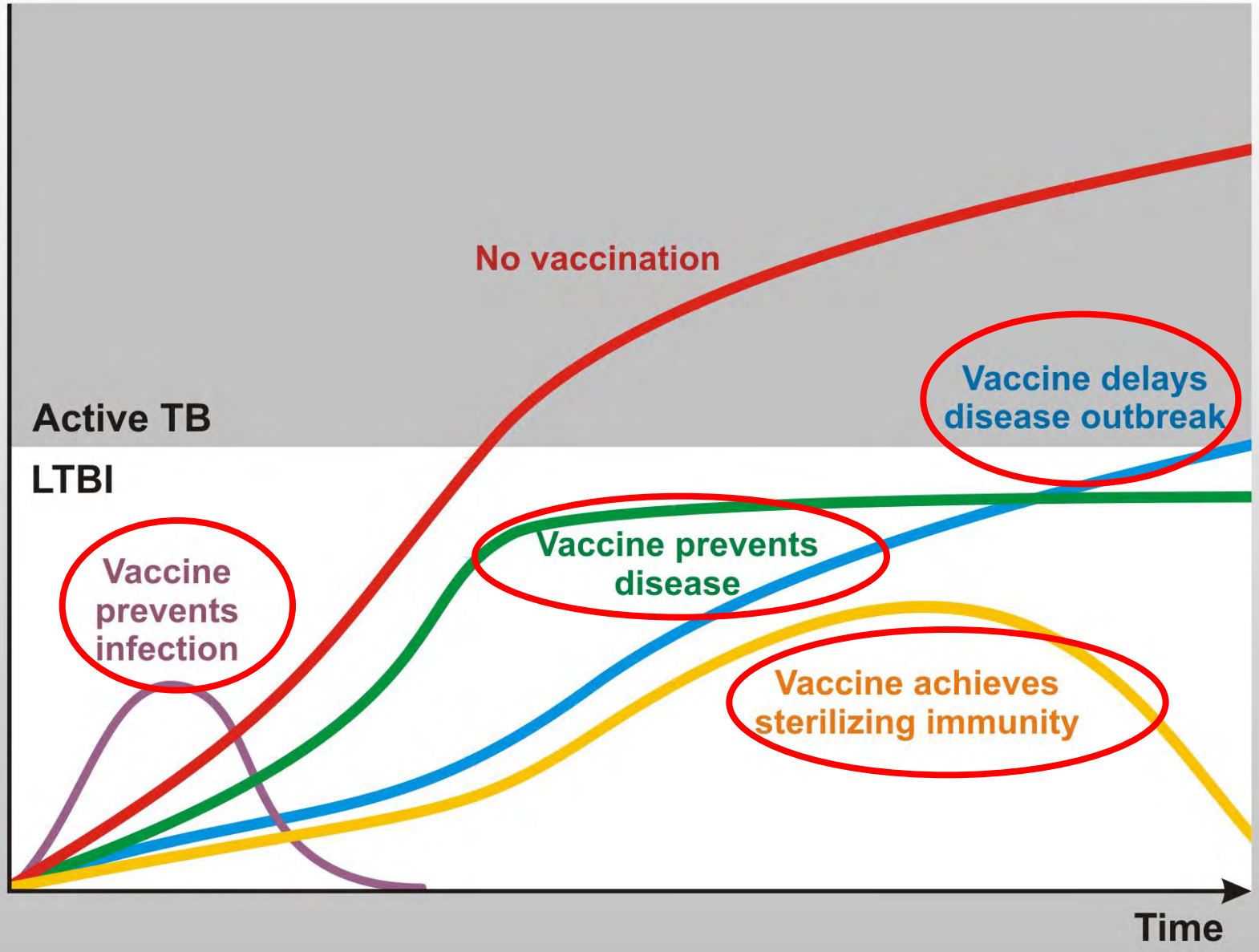
Target populations	Infection/Disease	Vaccine type	Advanced Candidates

Vaccination against mycobacterial diseases (TB, leprosy, Buruli ulcer)

- Follow the lead of the TB vaccine pipeline
- Likely candidates for leprosy / Buruli ulcer:
  recombinant viable vaccines (r-BCG, r-Mtb),
  killed vaccines (RUTI, *M.vaccae, M. indicus pranii)*
- **Subunit vaccines**: shared antigens required

TB vaccines: ambitious view of a scientist



Three phases of clinical trials for TB vaccines

Phase I:

Safety/immunogenicity, small study groups (≥ 10 participants/group). First in region of vaccine development; repeated in high endemic area.
>12 candidates in/through Phase I.

Phase II:

Optimal dose and route; immune parameters for efficacy (reliable biosignature not available);
large groups (≥ 100 (IIa) / > 2,000 (IIb) participants/group)
5 candidates in/through Phase II.

Phase III:

Efficacy and safety in high endemic area (≥ 25,000 participants/group; ≥ 50,000 participants per trial over several years in different regions; total: ≥ 200,000 participants).

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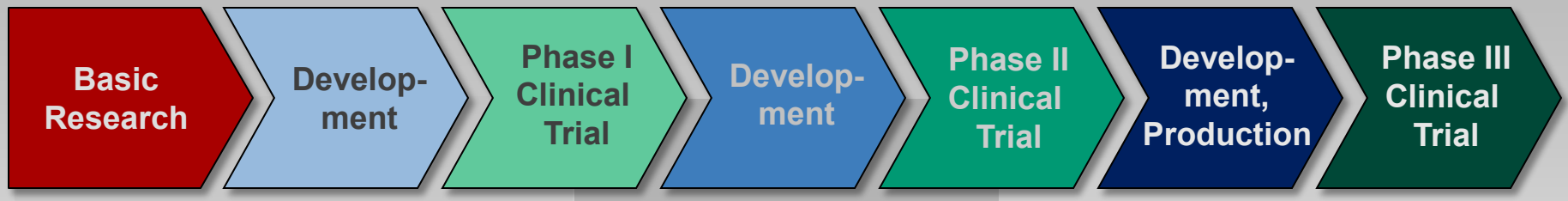
From Bench to Bed to Bush



Cost:

10^6 US$ range

10^6-10^7 US$ range

10^7-10^8 US$ range

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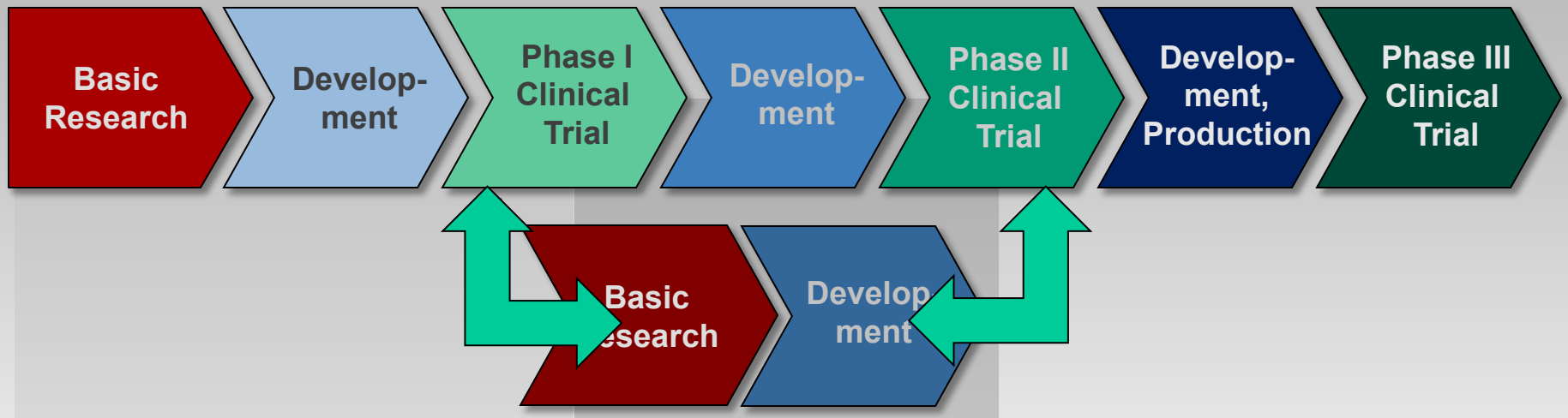
From Bench to Bed to Bush & Back to the Bench



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From Bench to Bed to Bush & Back to the Bench

To accelerate development of novel vaccines (and drugs and diagnostics) we need reliable biomarkers

Cost:			
	10^6 US$ range	10^6-10^7 US$ range	10^7-10^8 US$ range

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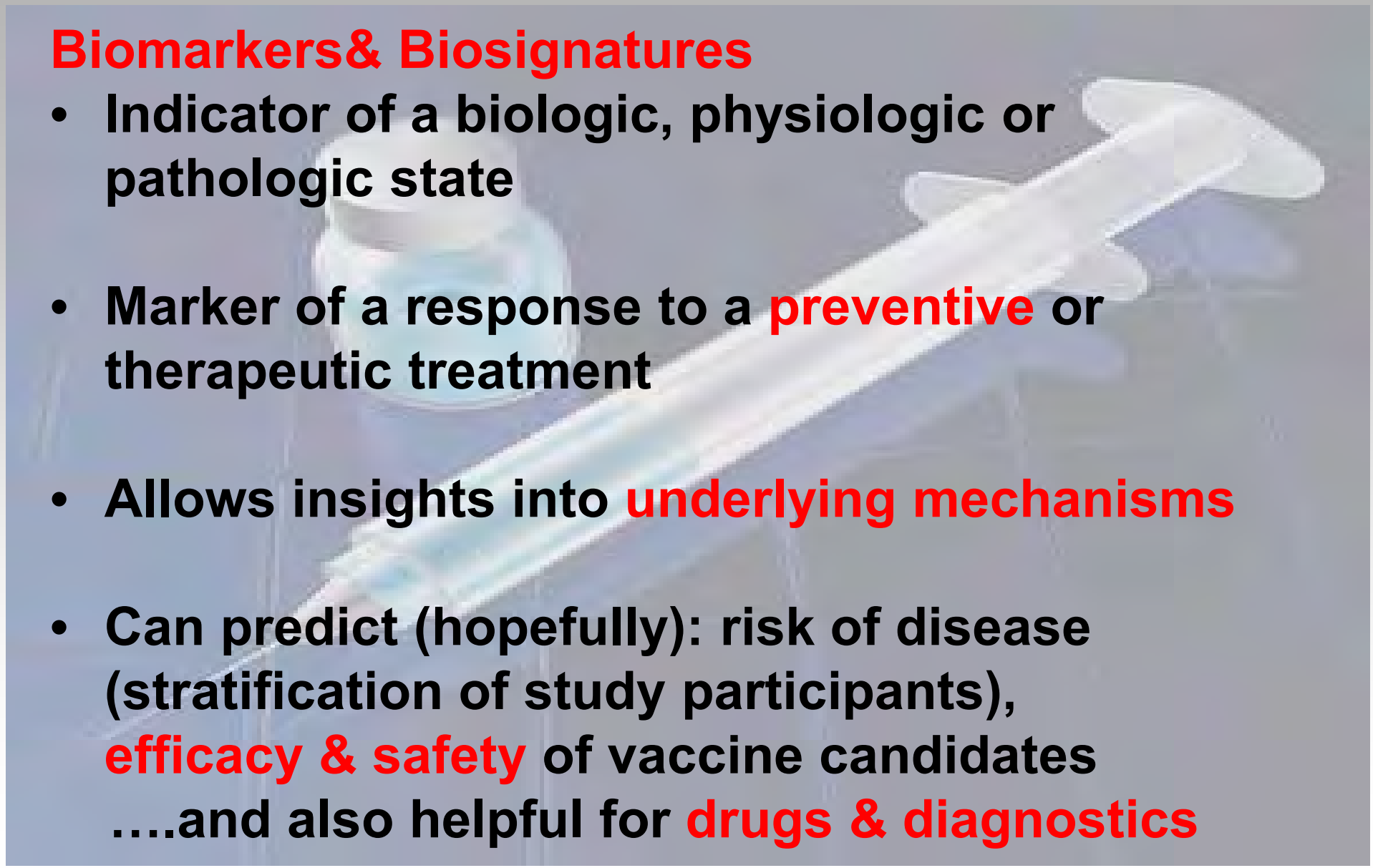
Biomarkers and biosignatures



Biomarkers& Biosignatures

- Indicator of a biologic, physiologic or pathologic state
- Marker of a response to a preventive or therapeutic treatment
- Allows insights into underlying mechanisms
- Can predict (hopefully): risk of disease (stratification of study participants), efficacy & safety of vaccine candidates ….and also helpful for drugs & diagnostics

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- Some food for thought

TB vaccine Trials – an altruistic view:

More than assessment of a single vaccine

Also a guide for future vaccines (drugs, diagnostics)

- **Specimens / biobanks**
- **State-of-the-art assays & analysis (incl. bioinformatics)**
- **Transparency**
- **Readiness to share**

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- **Iteration between clinical trial & clinical/targeted/basic research**

Translation

Targeted Research

Product Development

Clinical Studies

Basic Research

Clinical Trials

Iterative Approach

- Accelerated Generation of Knowledge
- Accelerated Product Development

Targeted Research

Product Development

Clinical Studies

Basic Research

Hypothesis Generation

Clinical Trials

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From Clinical Trial to Experimental Medicine Studies

Understanding general principles of protection to generic vaccine types (vs. “natural” protection to infection)

- **Plus/minus HIV**
- **BCG**
- **Recombinant live vaccines**
- **Viral vector vaccines**
- **Subunit / adjuvant vaccines**
- **Killed bacterial vaccines**
- **Pre-exposure vaccination**
- **Post-exposure vaccination**
- **Therapeutic vaccination**

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Include computational biology

Bringing forward TB vaccines

- **Global portfolio management**
- **Selection by rational and generally approved gating strategies at each stage**
- **Harmonization between different clinical sites**
- **Harmonized trials with more than one candidate (head-to-head)**
- **Harmonization with other trials (TB drugs, diagnostics, HIV/AIDS)**
- **Stratification of high risk individuals**
- **Monitoring to predict clinical outcome**

Bringing forward TB vaccines

Global Portfolio Management

- G
- *Involve all stakeholders:*
  - *EDCTP*
  - *TBVI*
  - *Horizon 2020*
  - *WHO*
  - *AERAS*
  - *European Investment Bank*
  - *BMGF*
  - *Industry, Academia ….*
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Bringing forward TB vaccines

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Bringing forward TB vaccines

- Gl
- s *Head-to-Head*

  Ideal scenario

- ***Step 1:***
- ***Compare different prime vaccines (r-BCG, r-Mtb)***
- ***Compare different boost vaccines (viral vectored, portein/adjuvants)***
- ***Step 2:***

  Compare different combinations of heterologous prime/boost

- S
- **Monitoring to predict clinical outcome**

Bringing forward TB vaccines

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Many thanks to Jelle Thole, Tom Evans Willem Hanekom and many others.

Thank you so much for your attention, …and for listening to my sometimes naive views (by purpose)
…and for your interest in, and your efforts to solve, such a devastating health issue.

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Disclaimer

Stefan H.E. Kaufmann is co-inventor of the VPM1002 vaccine (r-BCGΔureC::Hly)

Cooperation with Quiagen on the development of a host mRNA based biomarker TB test (to complement IGRA)