Decision-making in TB vaccine development: the stage-gate process

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GLOBAL FORUM TB VACCINES
NEW DELHI, 20 FEB. 2018
Definition of ‘Stage-Gate’ process

The SG Process is a Project Management tool that divides large projects into segments of activities running in parallel, the Stages, separated by check points, the Gates, where continuation of the project is decided based on Criteria.

An example:

Pre-clinical
POC in animals

Develop process lab scale
Characterize candidates
Test in animals

Process is feasible at pilot scale
Candidates characterized for potency, stability, purity.
Safe, immunogenic, effective in animal models

Clinical
Prepare Ph 1
Stage Gates for TB vaccines, 2012

Rational approach to selection and clinical development of TB vaccine candidates

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A rational process is clearly needed and can be extremely helpful for selection, assessing and advancing TB vaccine candidates from entry into preclinical and clinical development and for advancing candidates from early safety and immunogenicity clinical trials to proof-of-concept and pivotal efficacy trials. A joint effort between Aeras and the Tuberculosis Vaccine Initiative has focused on the development of objective criteria for a number of key general vaccine characteristics which can be assessed at critical stages of development. In order to maximize development efficiency, increase likelihood of success, and optimize use of scarce resources, this process includes establishment of gates for moving TB vaccine candidates through progressive development stages based on meeting the established criteria for specific vaccine candidates.
Stage Gates Criteria II project

Objectives

1. Biennial revision of the SG criteria
2. Develop target specific SG for TB vaccines
3. Support to Portfolio
4. Validate and publish

Endorsed by the GTBVP: Aeras, BMGF, EC, EDCTP, EIB, MESR (France), SA DST, SA MRC, TBVI and WHO

Funding: BMGF (2017-2021)
Stages and gates for a TB vaccine

- **Stage A:** Discovery
- **Stage B:** POC studies
- **Stage C:** Pre-clinical evaluations
- **Stage D:** Prepare FIH/Ph 1
- **Stage E:** FIH/Ph 1
- **Stage F:** Ph2
- **Stage G:** Ph 2b
- **Stage H:** Ph 3

**Legend:**
- **Stage:** (period during which one conducts the activities described in the relevant stage)
- **Gate:** (point at which one applies Gating criteria to decide whether move to next stage)
- **Critical Investment Gate**
Stage Gate, functions and their dynamic
Stage A: Perform discovery, safety, immunogenicity and efficacy evaluation in initial animal model  
Gate A: Progress to proof of concept (POC) studies in animals

<table>
<thead>
<tr>
<th>Function</th>
<th>Stage A: main activities</th>
<th>Gate A: criteria required</th>
</tr>
</thead>
<tbody>
<tr>
<td>PM/ Business</td>
<td>• Draft the Target Product Profile (TPP) with indication, target population, etc.</td>
<td>• TPP with primary indication prepared</td>
</tr>
</tbody>
</table>
| Production process              | • Select expression system at lab scale for preclinical material                         | • Suitable expression system and process that can produce target product quantity and quality selected  
|                                 |   • Select production process, at lab scale                                              | • Specific strain(s) selected                                                            |
| Product Characterization & Quality | • Screen and select antigen(s), adjuvants, other excipients and delivery system.        | • Antigens, adjuvants, other excipients, delivery system selected                        |
|                                 |   • Characterize vaccine candidate                                                      | • Characterization tests defined, including animal testing                                |
|                                 |   • In particular, demonstrate antigen expression and purity (e.g. proteins)            | • Characteristics of the vaccine candidate documented                                    |
| P-CL (Pre-Clinical) Safety      | • Identify in vitro and animal models to test for safety                                 | • Safety characteristic(s) of vaccine identified and demonstrated                       |
|                                 |   • Test preclinical safety elements relevant to candidate                               |                                                                                          |
| P-CL Immunogenicity             | • Evaluate immunogenicity                                                               | • Evidence of relevant immunogenicity to antigens in at least 1 animal species           |
|                                 |   • Compare to benchmark, if applicable                                                 | • Above baseline and/or benchmark (if applicable) responses to antigens preferred         |
| P-CL Protection, efficacy      | • Demonstrate protection in a small animal Mtb infection model                          | • Protection in a small animal Mtb infection model demonstrated                          |
|                                 |   • Compare to benchmark, as relevant                                                   | • Protection statistically better than BCG or against a relevant benchmark preferred     |
### Snapshot: Preclinical efficacy

<table>
<thead>
<tr>
<th>Development Phase</th>
<th>Stage: main activities</th>
<th>Gate: criteria required</th>
</tr>
</thead>
</table>
| **A: Discovery** | **Stage A: Perform discovery, safety, immunogenicity and efficacy evaluation in initial animal model**  
• Demonstrate protection in a small animal Mtb infection model  
• Compare to benchmark, as relevant | **Gate A: Progress to proof of concept (POC) studies in animals**  
• Protection in a small animal Mtb infection model demonstrated  
• Protection statistically better than BCG or against a relevant benchmark preferred |
| **B: POC studies** | **Stage B: Perform POC studies in animals**  
• Confirm robust protection in a small animal Mtb infection model  
• Prepare read-outs to evaluate protection in NHP (or other model) study | **Gate B: Progress to Pre-Clinical activities**  
• Protection in a small animal Mtb infection model confirmed  
• Protection statistically better than BCG or against a relevant benchmark reproduced independently in same species or in a second animal model confirmed  
• These data support proposed mode of protection, and support the NHP (or another advanced model) study design  
• Read-outs for NHP (or other model) ready |
| **C: Pre-clinical evaluations** | **Stage C: Perform Pre-Clinical evaluations**  
• Confirm protection or PoC  
Note: the animal models for evaluation should be justified based on candidate’s proposed mechanism of action | **Gate C: Progress to preparation for Ph 1, First-In-Human (FIH)**  
• Protection vs Mtb challenge statistically better than BCG and/or relevant benchmark using primary endpoint in 2 animal models, as demonstrated by a read-out with high statistical power for the group size:  
• Protection vs Mtb challenge in a small animal model confirmed  
• Protection vs Mtb challenge in a NHP or justified, human-relevant, advanced animal model confirmed |
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Populations & Indications

Vaccination

Prevent disease

Neonatal
Populations & Indications

- Neonatal
  - Prevent disease

- TB negative
  - Prevent disease

- Ados, adults
  - Latency
  - Prevent reactivation

- Vaccination
Populations & Indications

- **Neonatal TB negative**: Prevent disease
- **Ados, adults latent**: Prevent disease, Prevent reactivation
- **Treated with drugs cured**: Increase cure rate, Decrease recurrence rate

- **Infection Disease**
- **Latency**
- **Vaccination**
## Specific Stage Gates Criteria

<table>
<thead>
<tr>
<th>STAGE</th>
<th>Indication</th>
<th>Replace BCG</th>
<th>Prevent disease</th>
<th>Shorten therapeutic treatment, increase cure rate in DR-TB and/or DS-TB</th>
<th>Prevent recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>A: Discovery</td>
<td>Protection statistically better than BCG or against a relevant benchmark reproduced independently in same species or in a second animal model confirmed)</td>
<td>Prevent TB diseases: pulmonary TB, severe disseminated TB and TB meningitidis</td>
<td>Consider a plus to have evidence of protection and or immune response in neonatal model</td>
<td>Demonstrate treatment shortening and/or decreased relapse rate or bacterial load following drug treatment and immunogenicity, in relevant animal species</td>
<td>Under preparation</td>
</tr>
<tr>
<td>B: POC</td>
<td>P-Cl</td>
<td>Neonates</td>
<td>Adolescents and adults</td>
<td>Adjunct immunotherapy for treatment of disease.</td>
<td>Adolescents, adults at completion of TB treatment for DS or DR TB.</td>
</tr>
</tbody>
</table>

**Population**
- Neonates
- Adolescents and adults

**DR-TB and/or DS-TB**
- Adolescents, adults at completion of TB treatment for DS or DR TB.
Stage Gates Criteria II Project

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## Technological platforms

<table>
<thead>
<tr>
<th>Platform</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live</td>
<td>Live mycobacteria, recombinant BCG</td>
</tr>
<tr>
<td>WC</td>
<td>Whole cell bacteria, extracts</td>
</tr>
<tr>
<td>SU</td>
<td>Sub unit, as proteins or lipids, adjuvanted</td>
</tr>
<tr>
<td>Vector</td>
<td>Vectored, viral vector</td>
</tr>
<tr>
<td>NA</td>
<td>Nucleic Acid, DNA, RNA</td>
</tr>
</tbody>
</table>
Portfolio vaccines by populations, SG and platforms (partial list, under preparation)

- **Neonatal**
  - MBTVAC
  - H4:IC31
  - M72/ASO1
  - DAR-901

- **Ados Adults**
  - MTBVAC
  - H56:IC31
  - MVA85 Aero
  - TB/Flu04L

- **Treated Cured**
  - Ad5 Ag85
  - ChAd5/MVA
  - MVA85 Aero
  - TB/Flu04L

- **Live**
- **WC**
- **SU**
- **Vector**
- **NA**

**Portfolio vaccines by populations, SG and platforms (partial list, under preparation)**

- **A Discov**
  - HBHA
  - rBCGdAIS
  - BCG-ZMP1

- **B POC**
  - MTBVAC+
  - H64:CAF01
  - CysVac2/Ad

- **C Pr-Cl**
  - MTBVAC
  - MVA-TG

- **D PrefIh**
  - Ad5 Ag85
  - MVA-TG

- **E FIH**
  - Ad5-ChAd5
  - RUTI

- **F Ph2a**
  - H56:IC31
  - ID93/GLASE

- **F Ph2b**
  - H56:IC31
  - ID93/GLASE

- **G Ph3**
  - MTBVAC
  - TB/Flu04L

- **H Ph3**
  - M.Vaccae
Stage Gates Criteria II Project

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Stages and gates for a TB vaccine
Webtool: navigate through Stages Gates
Navigate within Stages

**STAGE A**

**Discovery**
Perform discovery, safety, immunogenicity and efficacy evaluation in initial animal model.

**MAIN ACTIVITIES**

- STAGE A PREPARATION - PM/BUSINESS
  - Draft the Target Product Profile (TPP) with indication, target population, etc.

- STAGE 1 SELECTION - PRODUCTION PROCESS
  - Select expression system at lab scale for pre-clinical material
  - Select production process at lab scale

- STAGE 2 SELECTION - PRODUCT CHARACTERIZATION & QUALITY
  - Screen and select antigens, adjuvants, other excipients and delivery system

**GATE A**

**Progress to POC**
Progress to proof of concept (POC) studies in animals

**CRITERIA REQUIRED**

- STAGE 1 SELECTION - PM/BUSINESS
  - TPP with primary indication prepared

- STAGE 2 SELECTION - PRODUCTION PROCESS
  - Suitable expression system and process that can produce target product quantity and quality selected
  - Specific strain(s) selected

- STAGE 2 SELECTION - PRODUCT CHARACTERIZATION & QUALITY
  - Antigens, adjuvants, other excipients, delivery system selected
Navigate through Functions
Example: PM & Business

**Stage A: Perform discovery, safety, immunogenicity and efficacy evaluation in initial animal model**

- **Gate A: Progress to proof of concept (POC) studies in animals**

<table>
<thead>
<tr>
<th>Main Activities</th>
<th>Criteria Required</th>
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<tbody>
<tr>
<td>Draft the Target Product Profile (TPP) with indication, target population, etc.</td>
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</table>

**Stage B: Perform POC studies in animals**

- **Gate B: Progress to Pre-Clinical**

<table>
<thead>
<tr>
<th>Main Activities</th>
<th>Criteria Required</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update TPP and draft Product Development Plan (PDP)</td>
<td>TPP revised; PDP drafted</td>
</tr>
<tr>
<td>Describe Intellectual Property (IP) status</td>
<td>No major IP obstacles or strategy for resolution in place</td>
</tr>
<tr>
<td>If necessary, identify potential partners to support development</td>
<td>As necessary, viable partners identified; MTA and other agreements established</td>
</tr>
</tbody>
</table>

**Stage C: Perform Pre-Clinical evaluations**
## Next steps

<table>
<thead>
<tr>
<th>Activities</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Review SG criteria</td>
<td>November 2017</td>
</tr>
<tr>
<td>Consult stakeholders and TB community</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Document specific SG for 3 targets</td>
<td>2q 2018</td>
</tr>
<tr>
<td>- Infants</td>
<td></td>
</tr>
<tr>
<td>- Adults &amp; Adolescents</td>
<td></td>
</tr>
<tr>
<td>- Therapeutic</td>
<td></td>
</tr>
<tr>
<td>Publish in journal</td>
<td>2-3q 2018</td>
</tr>
<tr>
<td>Write a Guidance Document and develop the Webtool</td>
<td></td>
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</table>
Conclusions

SG is a project management tool applied to TB vaccine development to assist developers, managers, funders and other decision-makers.

Engage stakeholders for validation, and community for use.

Combine with Portfolio Management.
# TBVI - AERAS Working Group

<table>
<thead>
<tr>
<th>TBVI</th>
<th>Aeras</th>
<th>Role</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georges Thiry</td>
<td>Maria Lempicki *</td>
<td>Lead</td>
</tr>
<tr>
<td>Leo van der Pol</td>
<td>Maria Lempicki</td>
<td>Production process, Product Characterization &amp; Quality</td>
</tr>
<tr>
<td>Ann Rawkins</td>
<td>Dominick Laddy</td>
<td>Preclinical Safety, Immunogenicity, Protection and Efficacy</td>
</tr>
<tr>
<td>Bernard Fritzell</td>
<td>Ann Ginsberg, Derek Tait</td>
<td>Clinical Safety, Immunogenicity, Protection and Efficacy</td>
</tr>
<tr>
<td>Emmanuelle Gerdil</td>
<td>Maria Lempicki</td>
<td>Regulatory</td>
</tr>
<tr>
<td>Anne Marie Graffin</td>
<td></td>
<td>Market access</td>
</tr>
<tr>
<td>Gerald Voss, Jelle Thole</td>
<td></td>
<td>Business</td>
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<tr>
<td>Danielle Roordink, Ilona van den Brink</td>
<td>Maria Lempicki</td>
<td>PM</td>
</tr>
</tbody>
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* Barry Walker, 2012 - 2016  
  Danilo Casimiro, 2017
Thank you!