“DE AQUÍ A LA ETERNIDAD,

¿QUÉ NOS ESPERA EN VACUNAS?”

“TUBERCULOSIS,
EL PRINCIPIO DEL FIN”

Carlos Martín
15 Abril 2021
carlos@unizar.es
COVID-19

2020 ≈ 1.8 M Deaths
≈ 100 M Cases

TB COVERAGE ≥90%

TUBERCULOSIS

2020 ≈ 1.4 M Deaths
≈ 10 M TB cases
≈ 100 M TB Infected

(Estimated that an average of 5 M deaths per year in the last 200 years) Paulson Nature 2013
**BCG PROVIDES VARIABLE PROTECTION AGAINST RESPIRATORY FORMS OF TB**

(Needs for improvement: Protection pulmonary forms of TB  long term Protection in adolescents)

**Intradermal administration at birth**

**Scar after vaccination**

**BCG** 0.05 ml
20 doses

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**BENEFICIAL EFFECTS OF BCG VACCINATION:**

1. **BCG provides STRONG PROTECTION AGAINST DISSEMINATED FORMS OF TB** (meningitis, miliary TB). It is estimated that BCG saves 70,000 deaths per year.

2. BCG vaccination REDUCES ALL-CAUSE MORTALITY not related to MtB and adding reduction in respiratory infections and sepsis also unrelated through beneficial effects: “Off-target”, “Non-specific”, “Heterologous” on the immune system.
The Non-Specific Effects of Vaccines have been studied in randomized controlled clinical trials:

- **Vaccine scarring** has been associated with reductions of more than 40% in overall mortality among adults.
- **The measles vaccine** is associated with more survival benefits than expected.
- **BCG** at birth nearly halves neonatal mortality.

**CAN THE INNATE IMMUNE SYSTEM LEARN?**

The models used to study the adaptive programs in innate immunity, including trained immunity.

Behavior of innate immune responses during adaptive programs induced in innate immune cells.

BCG Trained Immunity: Innate Immune Memory

MIHAI NETEA

EPIGENETIC MODIFICATION

TRI-METHYLATION AT THE 4TH LYSINE RESIDUE OF THE HISTONE H3

- IL-1β
- IL-6
- TNFα
PROSPECTIVE STUDIES OF NON SPECIFIC EFFECT OF BCG:

- NON SPECIFIC EFFECT OF LIVE ATTENUATED VACCINE BCG

- RATE OF UPPER RESPIRATORY TRACT INFECTIONS WAS:
  LOWER IN THE BCG REVACCINATED GROUP (2.1%) P<0.001
  9.4% in subunit vaccine H4:IC31 group or
  7.9% in Placebo group

BCG HAD A PROTECTIVE EFFECT AGAINST, NON-TUBERCULOUS
INFECTIONS IN INFANTS WITH A BIRTH WEIGHT OF 2.500 grames or less

ADULTS ADOLESCENTS UPPER RESPIRATORY TRACT INFECTIONS:

PREVENTION OF M. TUBERCULOSIS INFECTION WITH H4:IC31 VACCINE OR BCG REVACCINATION

BCG-INDUCED NON-SPECIFIC EFFECTS ON HETERLOGOUS INFECTIOUS DISEASE IN UGANDAN NEONATES: AN INVESTIGATOR-BLIND RANDOMISED CONTROLLED TRIAL

NEONATES ON ALL-CAUSE INFECTION DISEASE MORBIDITY
### DIVERSITY OF THE PIPELINE OF TB VACCINE CANDIDATES IN CLINICAL TRIALS

<table>
<thead>
<tr>
<th>ORIGIN</th>
<th>ADJUVANT/ VIRAL VECTOR</th>
<th>CONTENT IN M. tuberculosis T-CELL ANTIGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>Ad Ag85A</td>
<td>Phase 1</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>Chimpanzee Adenovirus +MVA</td>
<td>Phase 1</td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>Influenza virus</td>
<td>Phase 2A</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORIGIN</th>
<th>SOURCE</th>
<th>METHOD FOR ATTENUATION/ INACTIVATION</th>
<th>CONTENT IN M. tuberculosis T-CELL ANTIGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. vaccae</td>
<td>Phase 3</td>
<td>Non-Tuberculous Mycobacteria</td>
<td>Heat</td>
</tr>
<tr>
<td>M. indicus pranii</td>
<td>Phase 3</td>
<td>Non-Tuberculous Mycobacteria</td>
<td>Heat</td>
</tr>
<tr>
<td>M. vaccae</td>
<td>M. bovense</td>
<td>Phase 2B</td>
<td>Detoxified fragments of M. tuberculosis in a liposomal formulation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>ORIGIN</th>
<th>BCG RECOMMENDATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. bovis</td>
<td>Loss of &gt;100 genes within RD deletions</td>
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</table>

Epitopes in RD regions absent

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<tr>
<th>ORIGIN</th>
<th>BCG RECOMMENDATION</th>
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<tbody>
<tr>
<td>M. bovis</td>
<td>Same than BCG with urease C deletion and lysteriolysin insertion</td>
</tr>
</tbody>
</table>

Epitopes in RD regions absent

Double deletion of phoP-fadD26 virulence genes

ALL present

### ADJUVANTED

<table>
<thead>
<tr>
<th>SUBUNITS</th>
<th>ORIGIN</th>
<th>METHOD FOR ATTENUATION/ INACTIVATION</th>
<th>CONTENT IN M. tuberculosis T-CELL ANTIGENS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>MT2/AS01E</td>
<td>AS01E Liposomal formulation of MPL and saponin QS-21</td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>IC319</td>
<td>antibacterial peptide and a synthetic oligonucleotide</td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>DEAE-dextran core and CpG oligonucleotide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>M. tuberculosis</td>
<td>GLA-SE Glucopyranosyl Lipid A (GLA), in oil-in-water emulsion (SE)</td>
<td></td>
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</table>

### LIVE ATTENUATED

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<tr>
<td>M. tuberculosis</td>
<td>Phase 2B</td>
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Epitopes in RD regions present

Update on TB Vaccine Pipeline. Martín et al, Applied Sciences 2020
BCG *Mycobacterium bovis* isolated from cows attenuation RD1 deletion

**MTBVAC**, 519 MORE EPITOPES THAN BCG WHICH REPRESENTS AN INCREASE OF 48%
A WORLD WITHOUT TB

Distance) from) Cape) Town
ca.) 110km

Worcester (Field Site
University (and (laboratories

SAFETY AND IMMUNOGENICITY IN NEWBORNS
DOSE-ESCALATION SAFETY AND IMMUNOGENICITY STUDY TO COMPARE MTBVAC TO BCG IN NEWBORNS WITH A SAFETY ARM IN ADULTS

Michele Tameris

ClinicalTrials.gov
NCT02729571

Phase 1b

XII Jornada de Vacunas AEP 15 Abril 2021 Carlos Martin
KINETICS OF TOTAL CD4⁺ T-CELL RESPONSES INDUCED BY VACCINATION

Longitudinal kinetics of antigen-specific CD4 T cells expressing the indicated cytokine responses in participants after vaccination and measured by whole blood intracellular cytokine staining assay.

CD4 T cells indicate a significant difference between the groups: Any Cytokine +, Th1+, Th1 + polyfunctional
ANTIGEN SPECIFIC T CELL RESPONSES: IGRA QFT

Day 180 and day 360 interferon-γ values, as measured by QuantiFERON-TB-Gold assay, in each trial group, each line represents data for one participant. The pink shaded area represents the manufacturer’s threshold for test positivity (0.35 IU per millilitre).

DOSE RELATED QFT CONVERSION MTBVAC
Up to 0.35 IU per millilitre at day 180:

- 0 of 8 BCG (0%)
- 3 of 8 low-dose ($10^3$) (37.5%)
- 6 of 8 medium-dose ($10^4$) (75.0%)
- 7 of 9 high-dose ($10^5$) (77.8%)
A clear dose-dependent increase in MTBVAC immunogenicity was observed.

The highest MTBVAC dose of $2.5 \times 10^5$ CFU induced a response of greater magnitude than the same dose of BCG.

The induced CD4 T cell immune response was predominantly polyfunctional and comprised a range of different IFN-γ, TNF-α and/or IL-2-expressing subsets highest than in BCG vaccinated.

DATA SUPPORT ADVANCED CLINICAL DEVELOPMENT OF MTBVAC
Objectives:

- To study the protective efficacy conferred by a single intradermal vaccine with MTBVAC or BCG against exposure to low doses of aerosol with *M. tuberculosis* in rhesus macaques.

- Characterize the immune response induced after vaccination and compare the immune responses in macaques with the responses in humans immunized with BCG and MTBVAC.
Concordance between immune profiles measured in clinical trials and a preclinical study of macaques demonstrating a significantly improved outcome after exposure to *M. tuberculosis* as evidence to support the continued development of MTBVAC as an effective prophylactic vaccine for vaccination against TB.
Phase 1a Adults (NCT02013245)

Elispot ESAT6/CFP10 (CHUV)

**ELISPOT**

**CFP10 Elispot**

- **BCG**
  - Positive cut-off for TB infection
  - **MTBVC**
  - Positive cut-off for TB infection

- **p = 0.0391**

- **ESAT6 Elispot**

- **BCG**
  - ESAT-6 and CFP-10 as positive if the number of SFUs was at least 55 SFU per 10⁶ cells

- **MTBVC**

- **p = 0.1641**

- **Agullo et al 2017 Nat Comm**

- **Spertini et al Lancet Resp Medicine 2015**

**ELISPOT CFP10 and ESAT6-specific responses in MTBVAC-vaccinated adults**

**CFP10 signficative higer but, Negative for the 3 doses of MTBVAC and the end of the study (7M)**
### NON SPECIFIC EFFECTS TB LIVE ATTENUATED VACCINES

<table>
<thead>
<tr>
<th>BCG</th>
<th>MTBVAC</th>
</tr>
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<tr>
<td>• Trained immunity in human cells. <em>Kleinnijenhuis et al</em> 2012 <em>Proc Natl Acad Sci USA.</em></td>
<td>• Trained immunity in human cells (epigenetic and metabolic reprogramming of the cells from the innate immune system). <em>Tarancon et al</em> 2020 <em>Plos Pathogens.</em></td>
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<td>• Therapeutic efficacy against established asthma. <em>Tarancon et al</em> 2021 <em>Ebiomedicine.</em></td>
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New live attenuated tuberculosis vaccine
MTBVAC induces trained immunity and confers protection against experimental lethal pneumonia

Raquel Tarancón, Jorge Domínguez-Andrés, Santiago Uranga, Anaísa V. Ferreira, Laszlo A. Groh, Miriam Domenech, Fernando González-Camacho, Niets P. Riksen, Nacho Aguilo, José Yuste, Carlos Martín, Mihai G. Netea

MTBVAC induces epigenetic reprogramming in human PBMCs
Induction of glycolysis and glutaminolysis and the accumulation of histone methylation marks at the promoters of proinflammatory Genes: TNFα, IL6

MTBVAC protect in vivo in mice against S. pneumoniae infection
Heterologous protection against a lethal challenge with S. pneumoniae in an experimental murine model of pneumonia.
THERAPEUTIC EFFICACY MTBVAC AGAINST ESTABLISHED ASTHMA

BCG and MTBVAC intranasal revert established allergic airway responsiveness in an OVA-driven chronic model.

BCG and MTBVAC intranasal vaccination reverts established allergic airway responsiveness induced by the relevant house dust mite allergen HDM.
Immunization with DTaP alone failed to trigger a Th1 response, as measured by the production of IFN-γ. Both BCG and MTBVAC when administered before DTaP, triggered Th1 immune responses against diphtheria, tetanus, and pertussis in mice.

**BENEFICIAL IMPACT ON IMMUNIZATION WITH DTaP VACCINE (DIPHTHERIA, TETANUS, AND ACELLULAR PERTUSSIS)**

**HUMORAL RESPONSES AGAINST DTaP ANTIGENS WERE ALSO ENHANCED BY PREVIOUS IMMUNIZATION WITH BCG OR MTBVAC**
HUMAN EPIDEMIOLOGICAL DATA SHOWED THAT PERTUSSIS INCIDENCE WAS 10-FOLD LOWER IN COUNTRIES THAT USE DTaP and BCG COMPARED TO COUNTRIES THAT USE ONLY DTaP.
TUBERCULOSIS Vaccines:

LIVE VACCINES

Protection Pulmonary TB
Better than BCG + same nonspecific effects
Years of effort and billions of dollars have driven polio to just a few impoverished corners of the world. The campaign is intensifying, but the virus is tenaciously resisting.

**Polio: The Final Assault?**
Puente de Piedra (Zaragoza) Puente de Rande (Vigo)

MUCHAS GRACIAS

Hospital CHUV (Lausana) Universidad de Ciudad del Cabo Pórtico de la Gloria (Santiago)