RUTI: a new therapeutic vaccine to shorten the latent tuberculosis infection treatment

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The Rationale
The Latent Tuberculosis Infection (LTBI).
The continuous reactivation requires a prolonged chemotherapy: 9 months

Cardona PJ 2006
The LTBI. Cardona et al 2000, 2003, 2004
RUTI restimulates the immune response after the short-term chemotherapy, against a high number of *M. tuberculosis* antigens, not only against the growing bacilli.
The poliantigenic Response against Growing/resting bacilli
Efficacy of RUTI in the murine model
(Cardona et al Vaccine 2005)

[Diagram showing the efficacy of RUTI in murine models with C57BL/6 and DBA/2 strains, comparing control, chemotherapy, chemotherapy + RUTI IN, and chemotherapy + RUTI SC treatments, with Log10CFUs/mL over weeks 0, 3, 9, 17, and 22 for lung and spleen tissues.]
Efficacy of RUTI in the guinea pig model

(Guirado et al 2005)

Log$_{10}$ CFUs/lung

Ct i.n. s.c.

Control

RUTI i.n.

RUTI s.c.

INH + RIF

(p<0.05)

INH + RIF

4 w

RUTI

INH + RIF

INH + RIF

INH + RIF

Control

RUTI

RUTI

RUTI

weeks

weight

weeks
RUTI will reduce the LTBI treatment period

9 month of INH treatment

1 month of INH treatment
+ 2 RUTI doses
Short-term chemotherapy removes foamy macrophages
Foamy macrophages are a source of immunodepression (Cardona et al 2003)
Foamy macrophages are a source of immunodepression (Cardona et al 2003)
Figure. Temporal strategy for the use of RUTI, indicating the effects of short-course chemotherapy and the requirement for subsequent immunotherapy.
Objectives

• To demonstrate the lack of toxicity of RUTI in healthy volunteers (Phase I trial).

• To follow up the immunological response induced after the inoculation of RUTI
Methods (1)

- Healthy volunteers have been recruited (HIV-, Hepatitis B and C -, and absence of latent tuberculosis infection (LTBI) through T-SPOT assay
- They are included in a random double blind assay controlled with placebo.
- Increasing doses of RUTI are administered (5, 25, 100 and 250 μg) in 4 groups of 6 volunteers. Two of them will be inoculated with placebo and 4 with the real vaccine.
- 2 inoculations of RUTI are administered 4 weeks apart in each case, once lack of toxicity is certified after the first inoculation
Methods (2)

• Toxicity is monitored for 168 days through regular clinical examinations (0, 1, 3, 7, 21, 28, 29, 31, 35, 56, 112 and 168 days post first inoculation); and haematological and biochemical determinations in peripheral blood samples (at 0, 7, 21, 28, 35, 56, 112 and 168 day post first inoculation)

• Immunological monitoring will be done from peripheral blood samples. Cellular immunity will be followed looking at IFN-γ production through an ELISPOT assay and whole blood assay against antigens ESAT-6, CFP-10, 16 kDa, MPT-64, Ag85B, 38 kDa, hsp 65, PPD and BCG; CD4+ CD25 high regulatory T cells; and γδ T cells proliferation. Whole blood bactericidal activity will be also followed, as well as humoral response.
Phase I trial

![Diagram showing Phase I Tolerability and Immunogenicity study with various screening and routine analysis procedures over different weeks and groups.](image-url)
Phase I trial
Results

• So far, the second inoculation of the third RUTI dose (100 μg) has been already inoculated without showing any toxic effects and an increasing immunological response with dose.
Table 1. Recorded Adverse Events (possibly or probably related to the vaccination)

<table>
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<tr>
<th>AE</th>
<th>Number of subjects (n=12)</th>
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<tr>
<td>Local</td>
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<td>Twiching</td>
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<td>Pain</td>
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<td>Vesiculated lesions</td>
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<td>Systemic</td>
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<tr>
<td>Fever</td>
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ELISPOT IFN-γ AT D7:

ONE WEEK AFTER THE FIRST RUTI INOCULATION

ESAT-6

85 B

PPD

BCG

SFU/2·10e5 PBMCs

5µg FCMtb

25µg FCMtb

100µg FCMtb

5µg FCMtb

25µg FCMtb

100µg FCMtb

V1
V2
V3
V4
V5
V6
V7
V8
V9
V10
V11
V12
V13
V14
V15
V16
V17
V18
Future perspectives

• **Phase IIa trials** are planned for the end of 2008 in HIV- and HIV+ people in *Europe*.

• A **Phase IIa** trial in HIV- and HIV+ people will be started at the second half of 2009 in *Africa*.

• A **Phase IIb** trial in coinfected HIV+ people in *Europe* and *Africa* will start at 2010 to demonstrate the efficacy of the 1 month INH treatment plus 2 inoculations of RUTI vs 6 month INH treatment.
Future perspectives

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