



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



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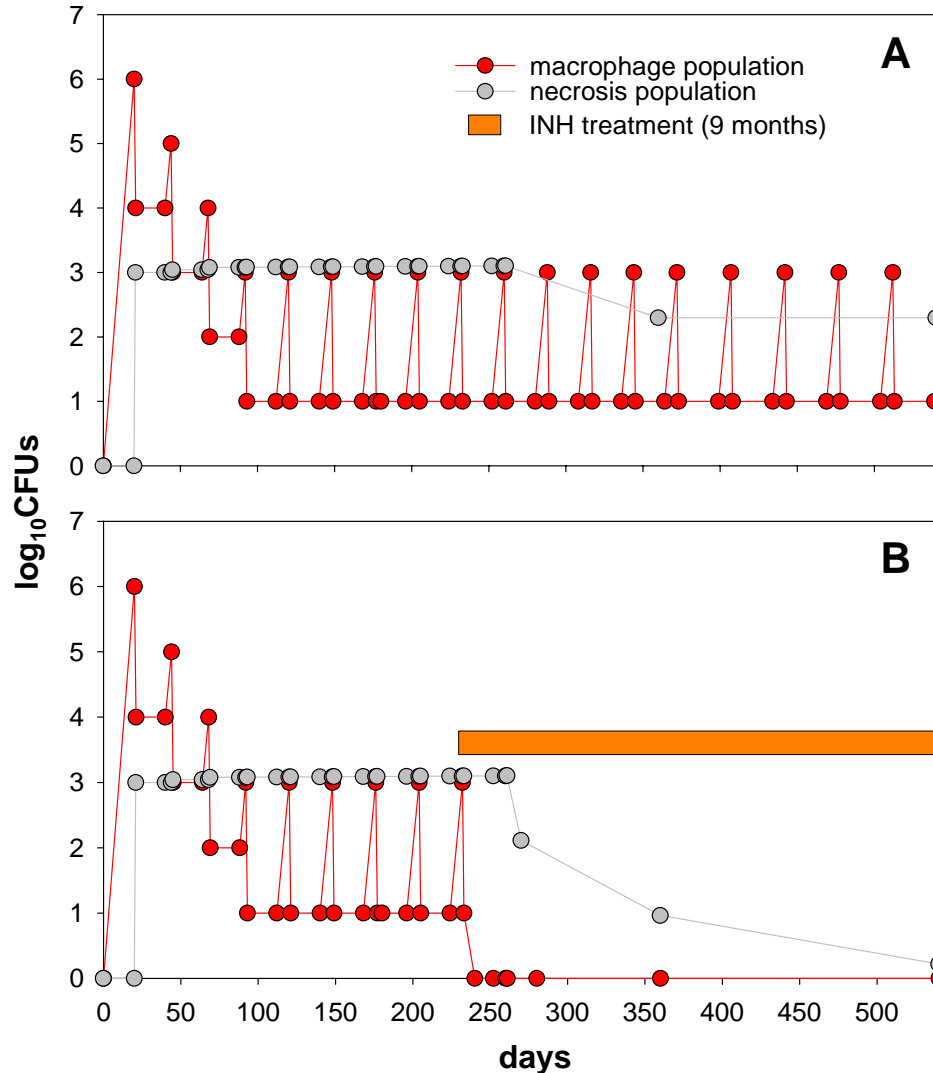


# The Rationale



# The Latent Tuberculosis Infection (LTBI).

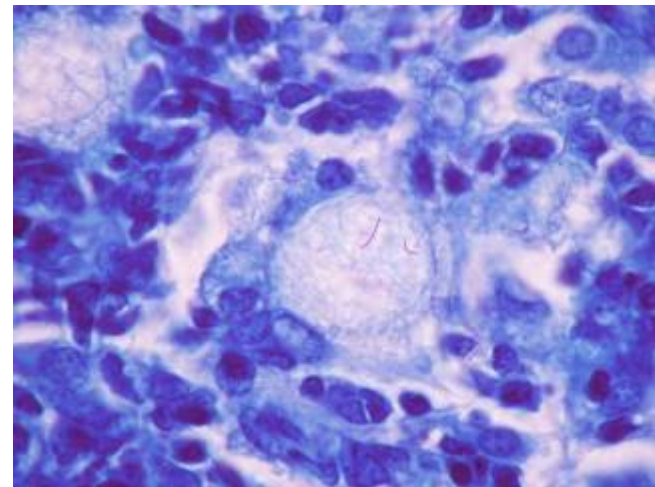
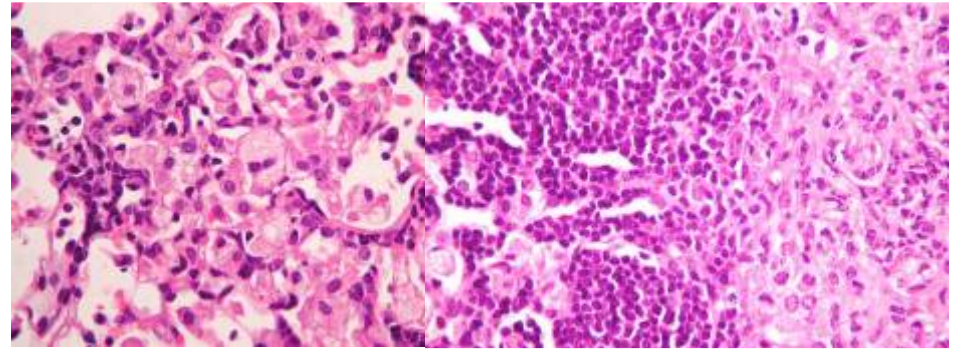
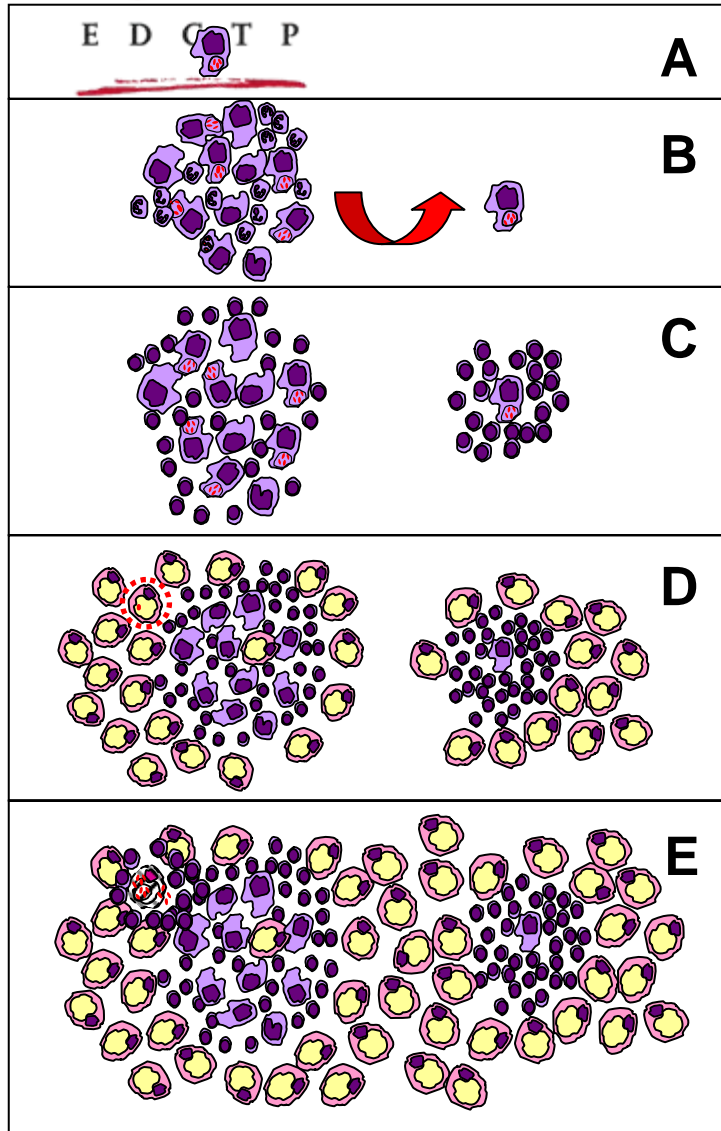
The continuous reactivation requires a prolonged chemotherapy: **9 months**



*Cardona PJ 2006*

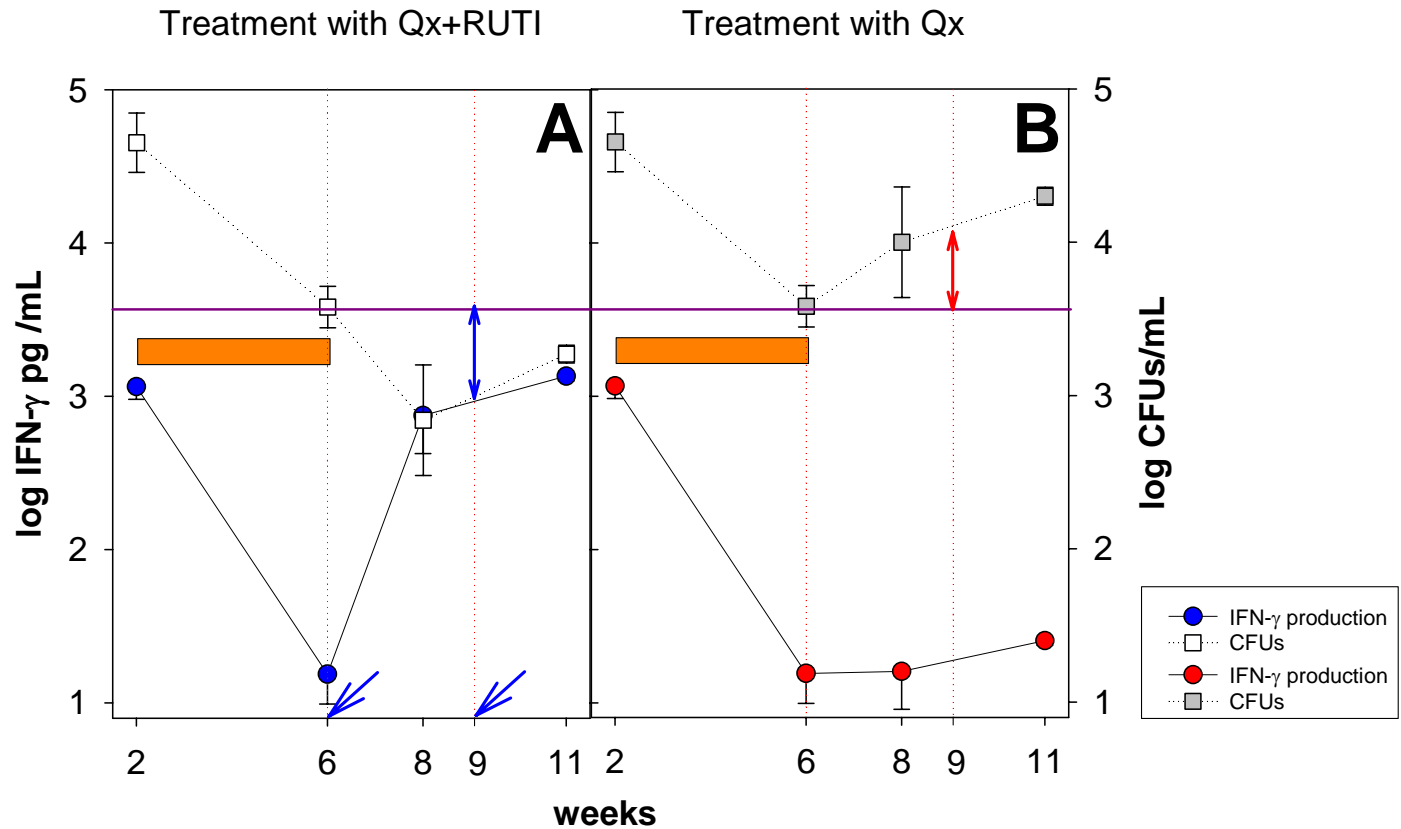


# The LTBI. *Cardona et al 2000, 2003, 2004*



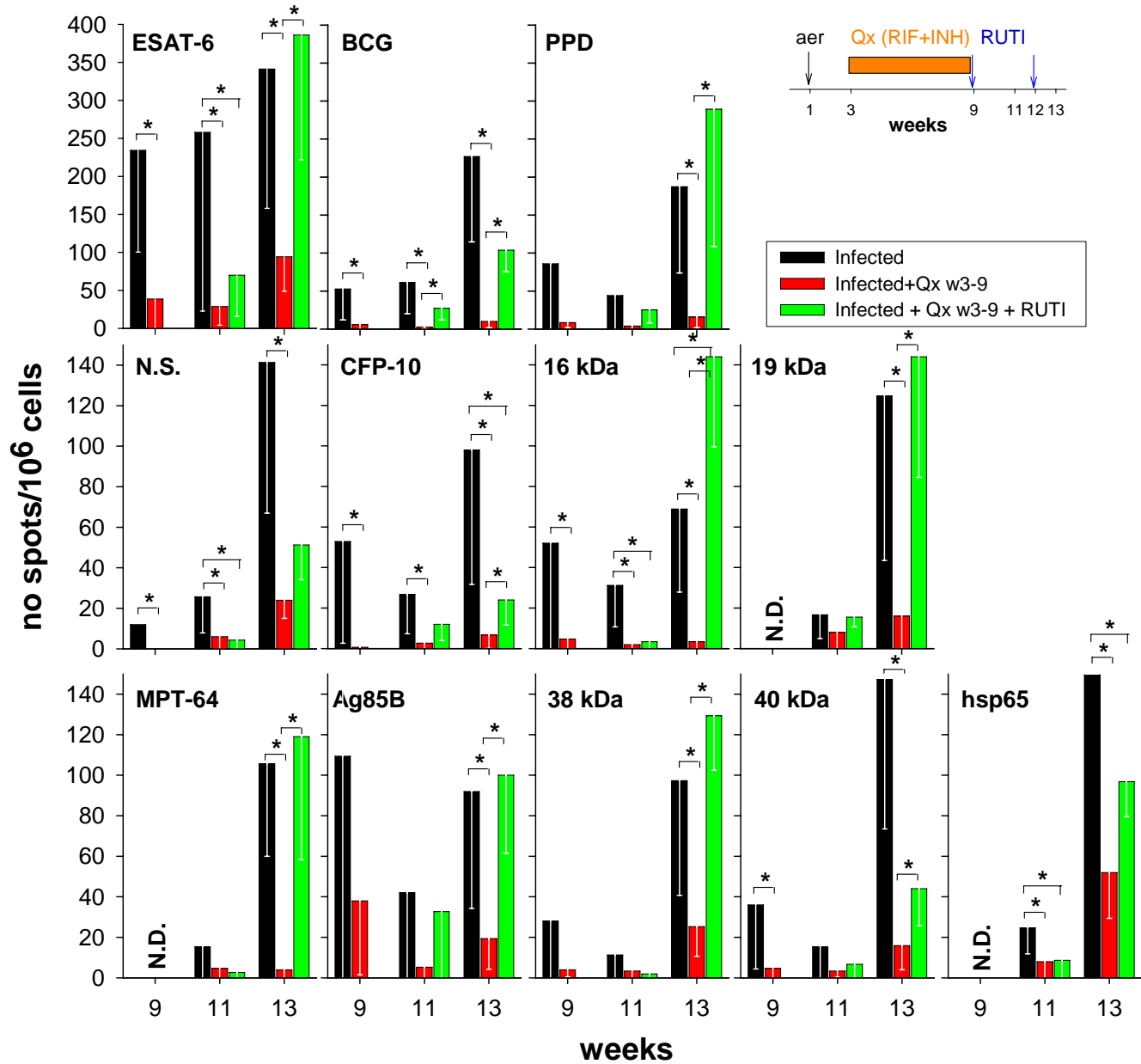


**RUTI restimulates the immune response after the short-term chemotherapy, against a high number of *M. tuberculosis* antigens, not only against the growing bacilli.**





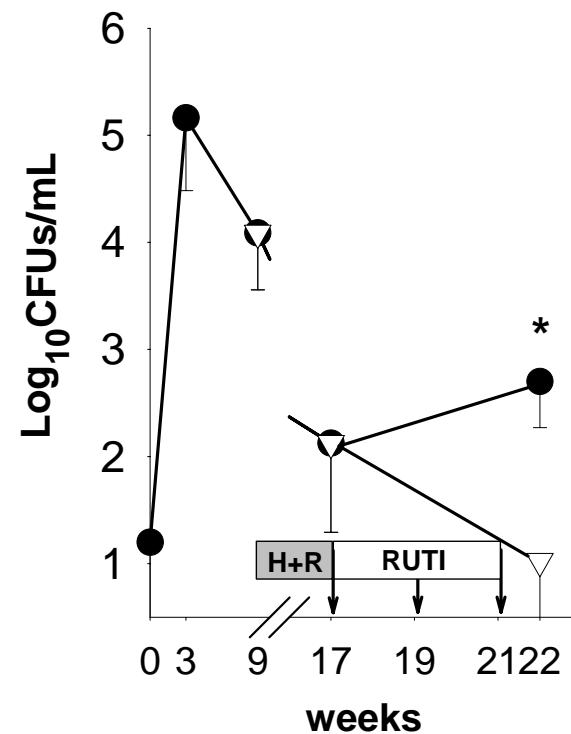
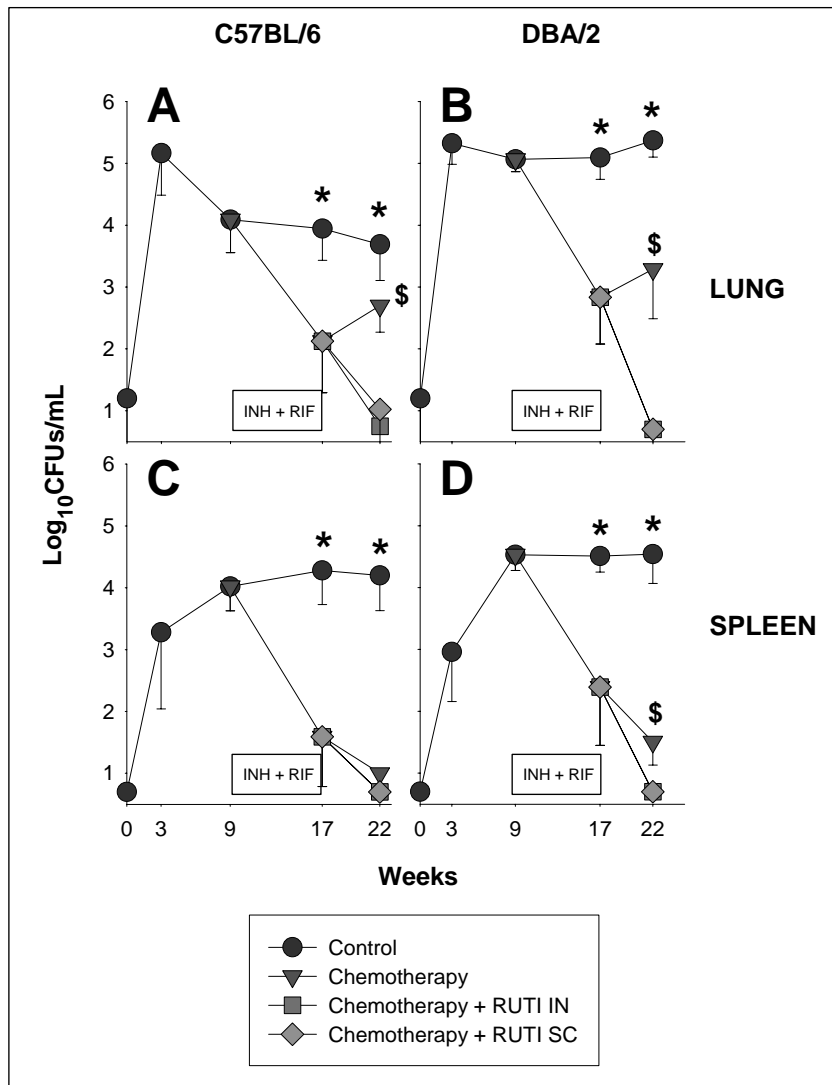
The poliantigenic Response against Growing/ resting bacilli





# Efficacy of RUTI in the murine model

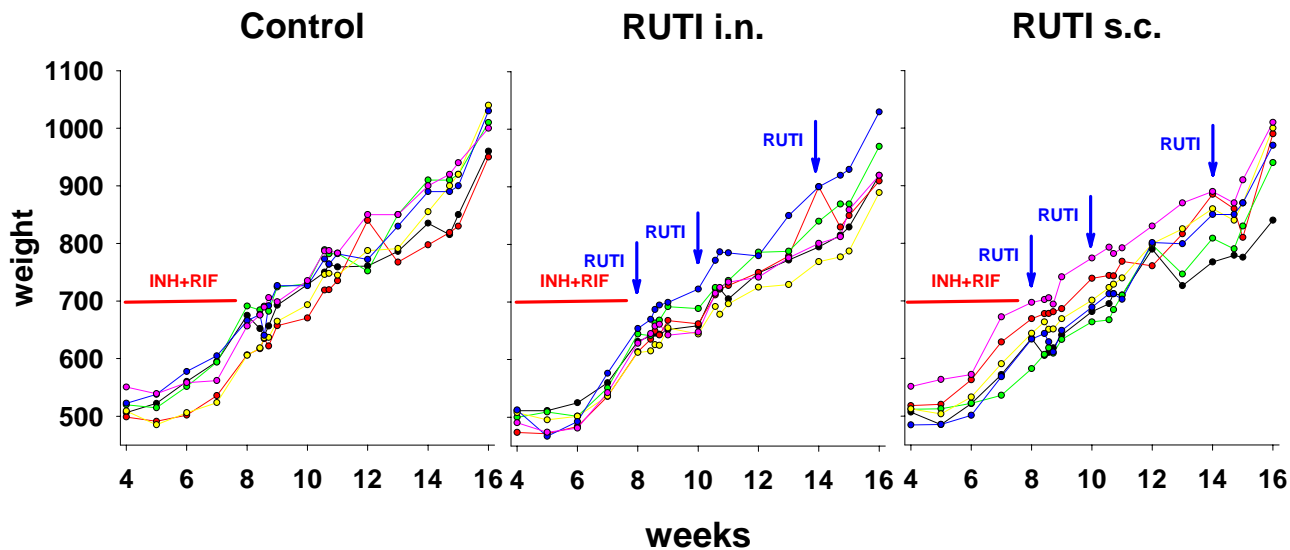
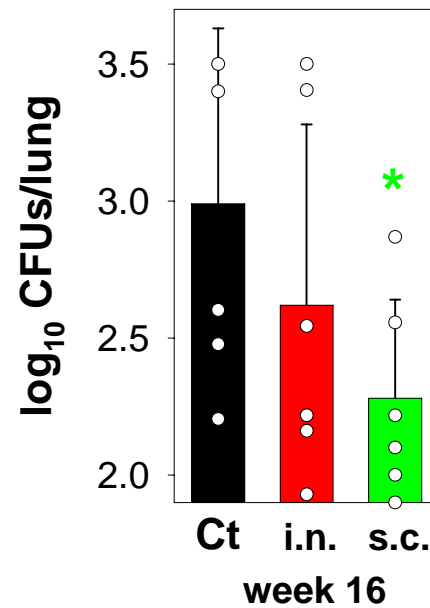
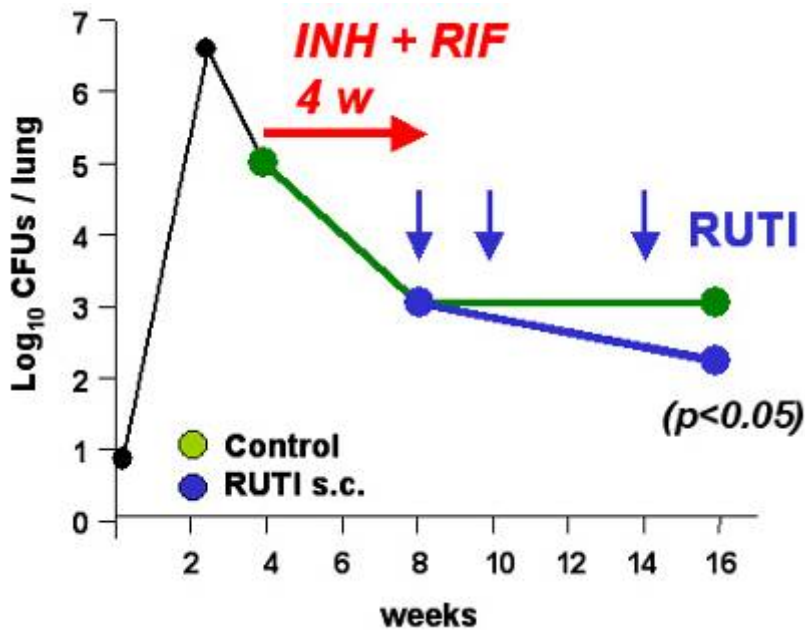
(Cardona et al Vaccine 2005)





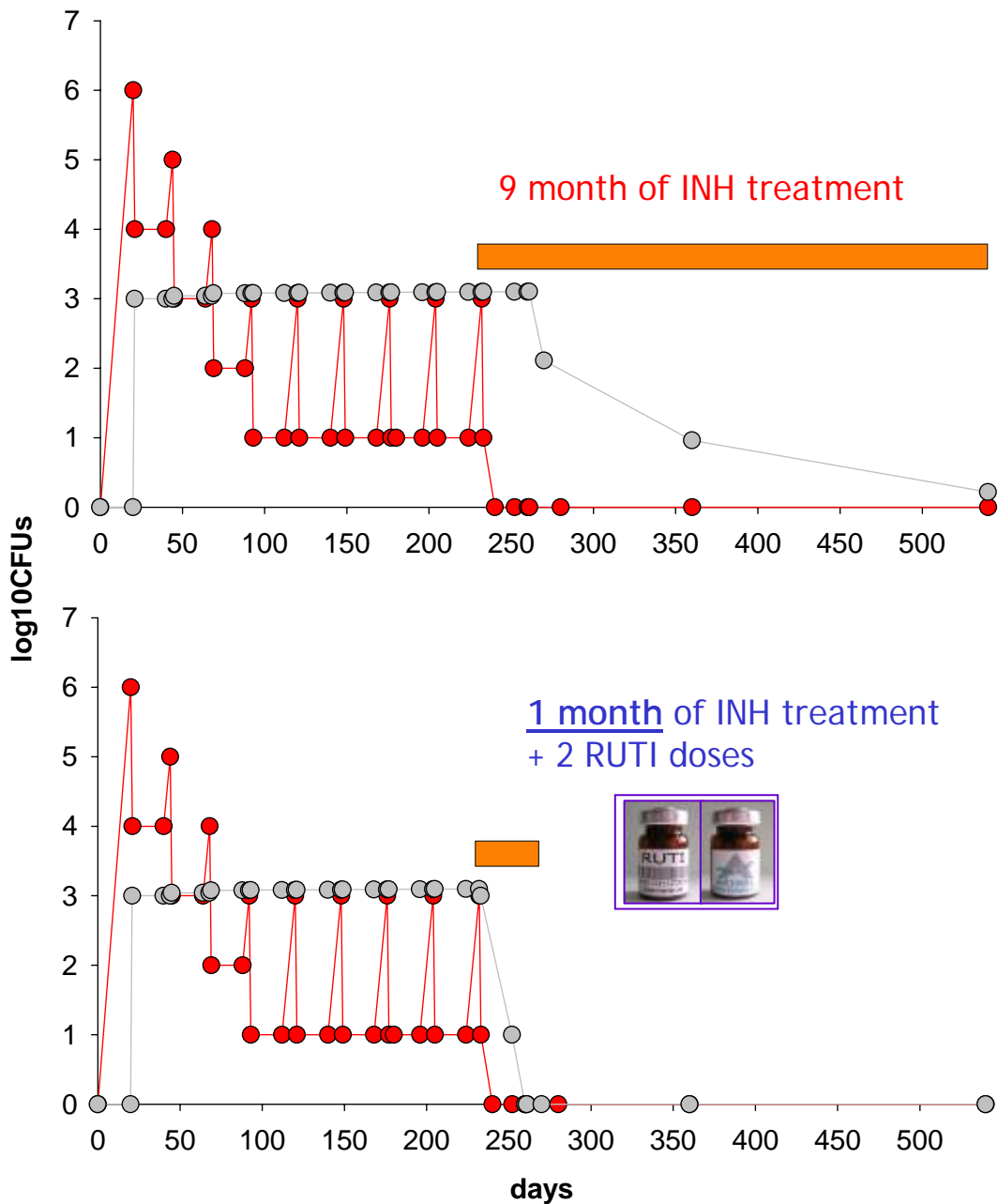
# Efficacy of RUTI in the guinea pig model

(Guirado et al 2005)



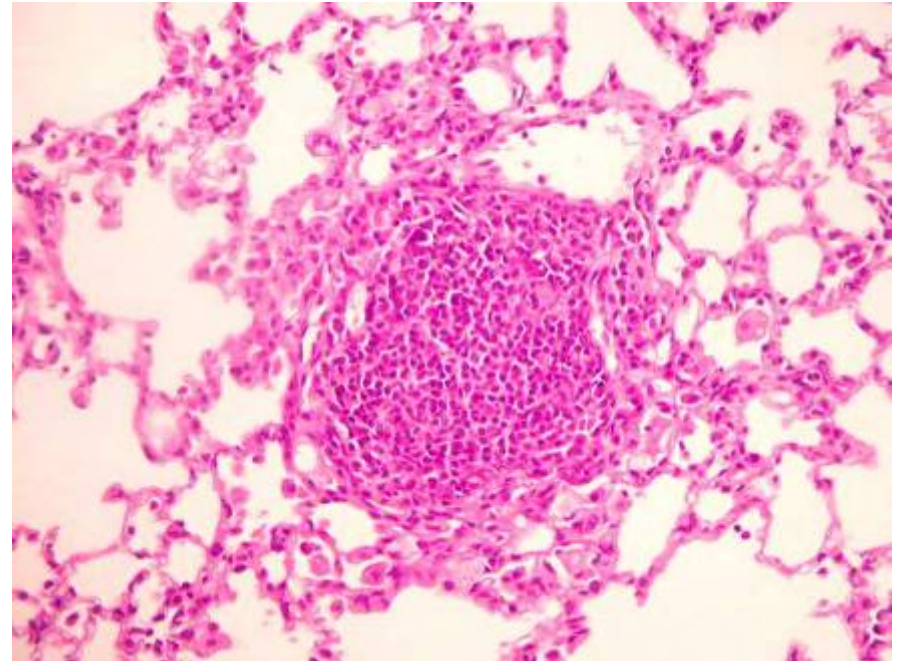
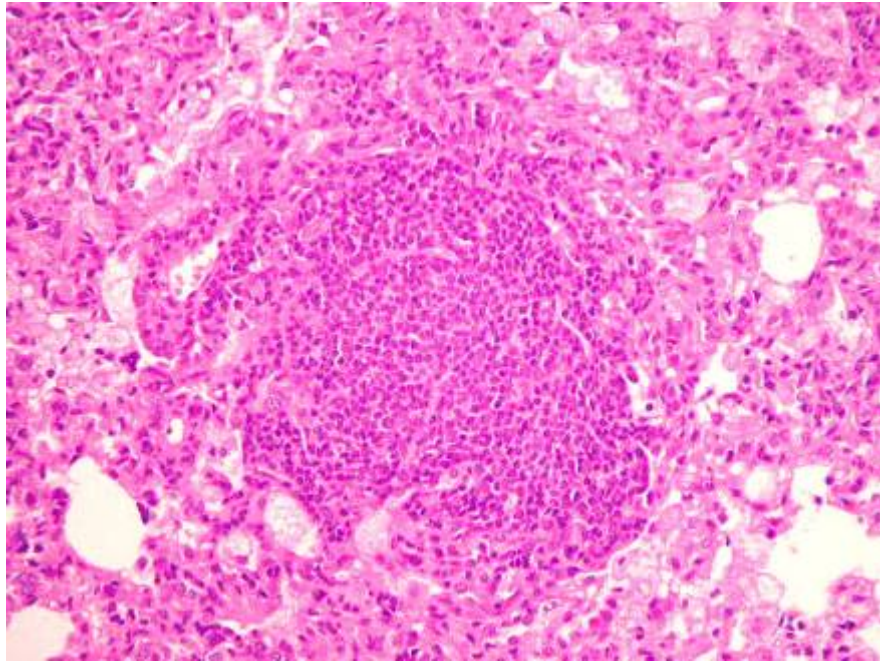


# RUTI will reduce the LTBI treatment period

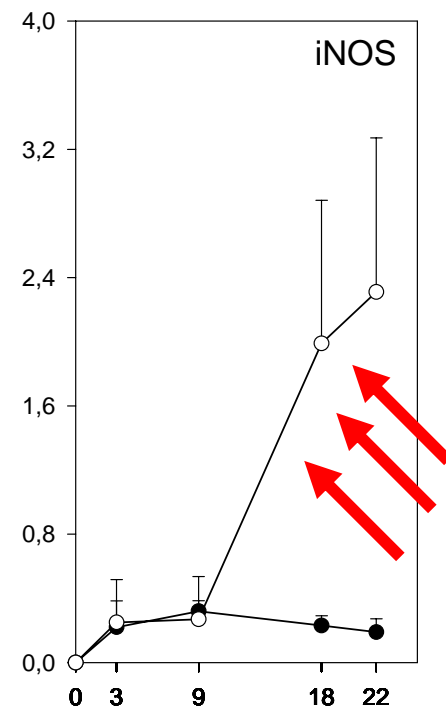
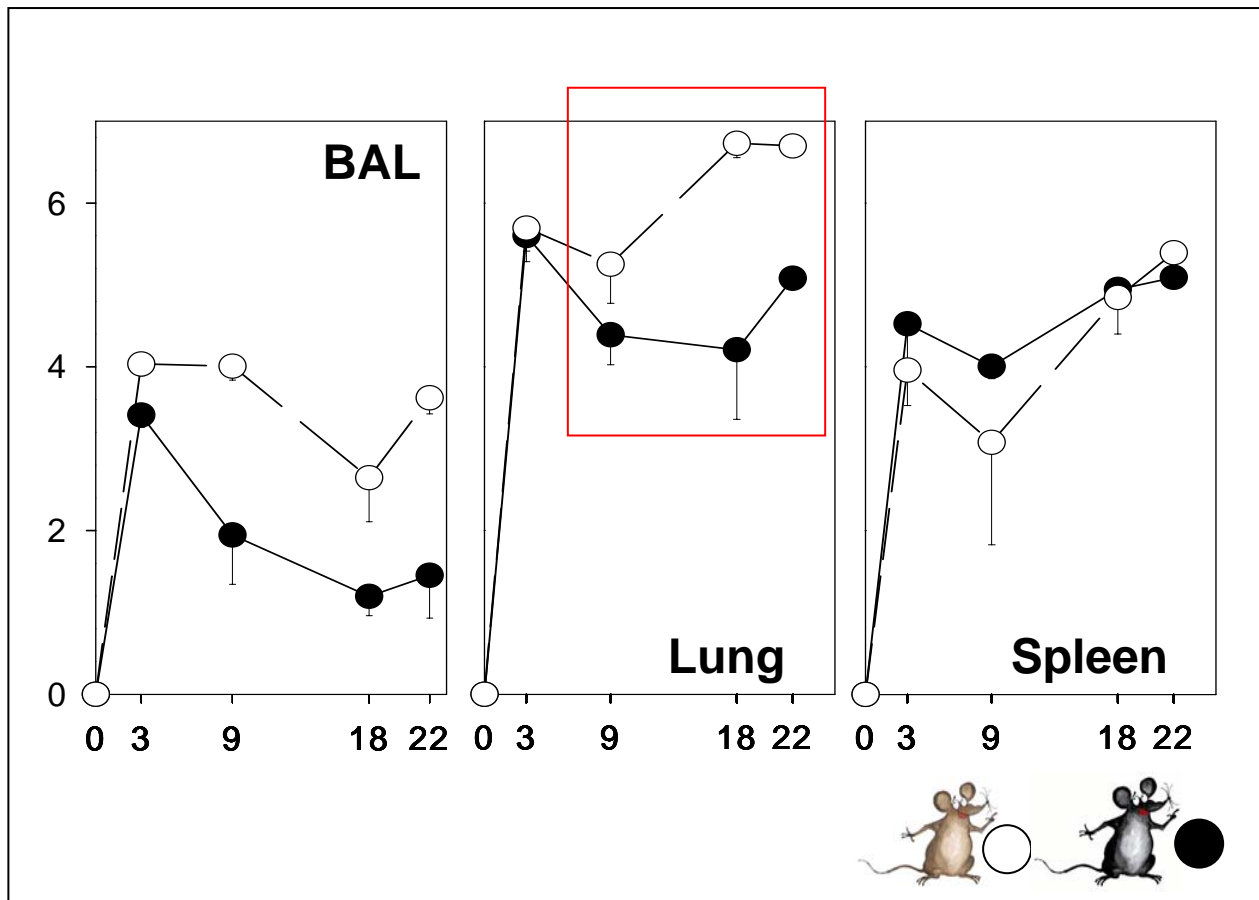




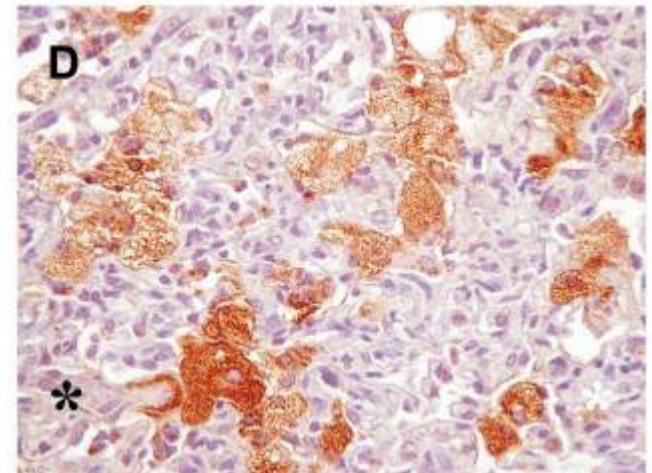
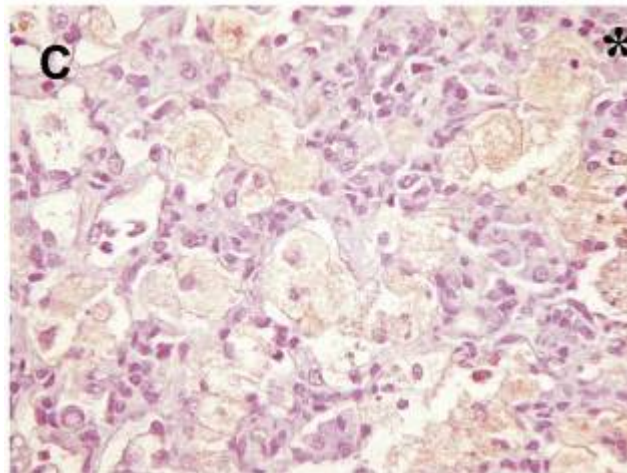
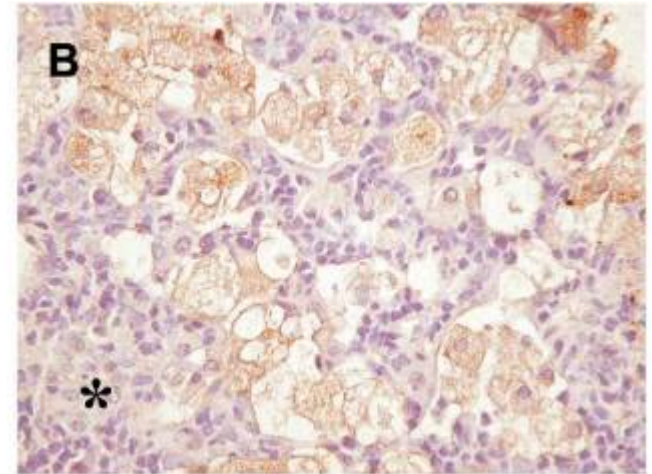
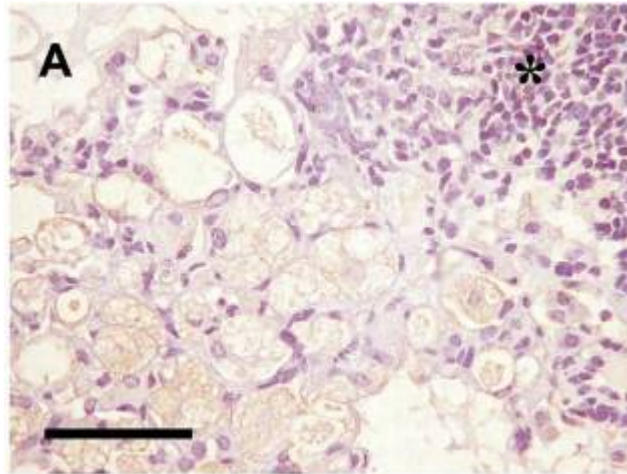
## Short-term chemotherapy removes foamy macrophages



# Foamy macrophages are a source of immunodepression *(Cardona et al 2003)*



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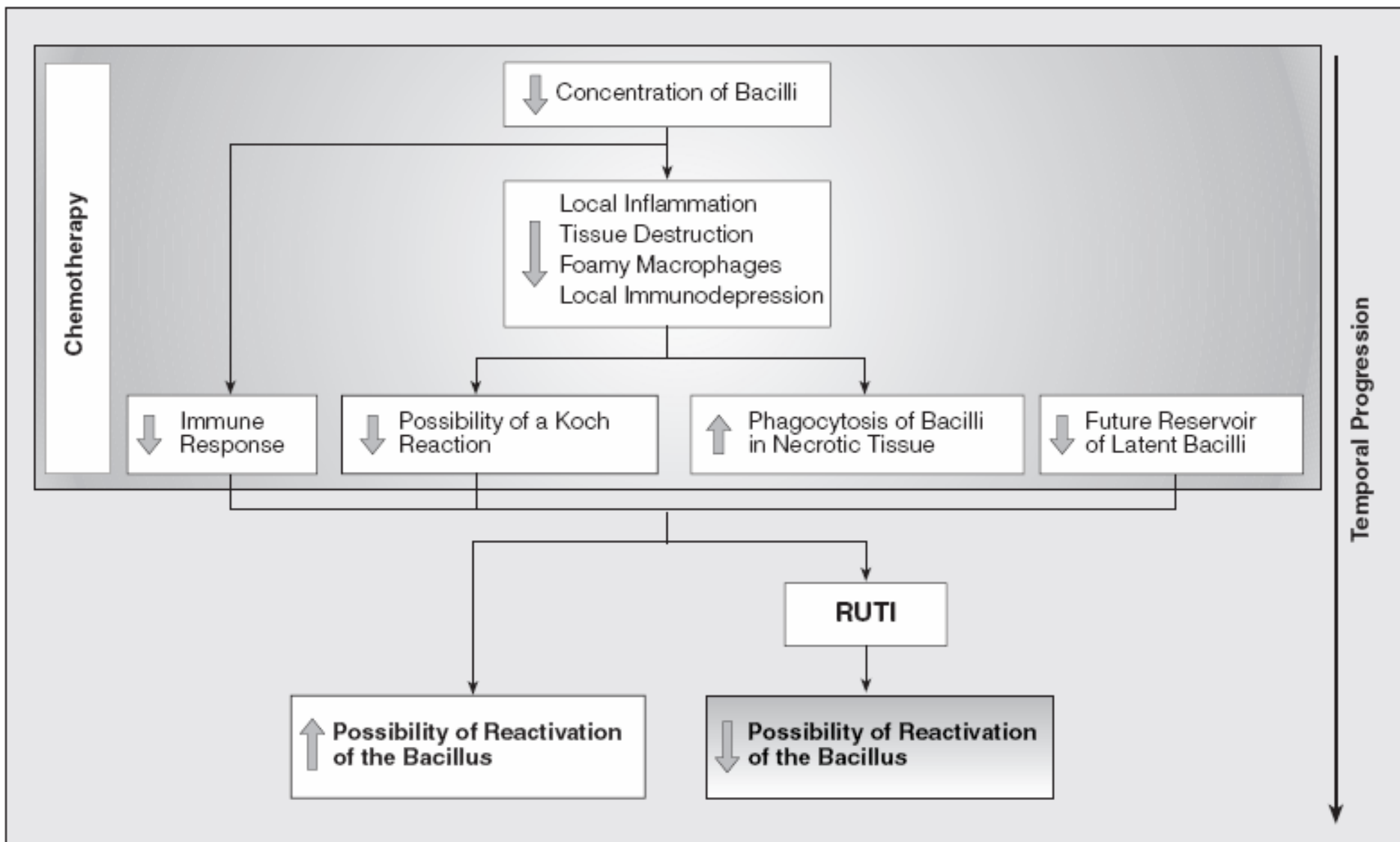


Figure. Temporal strategy for the use of RUTI, indicating the effects of short-course chemotherapy and the requirement for subsequent immunotherapy.



# 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  $\mu\text{g}$ ) 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



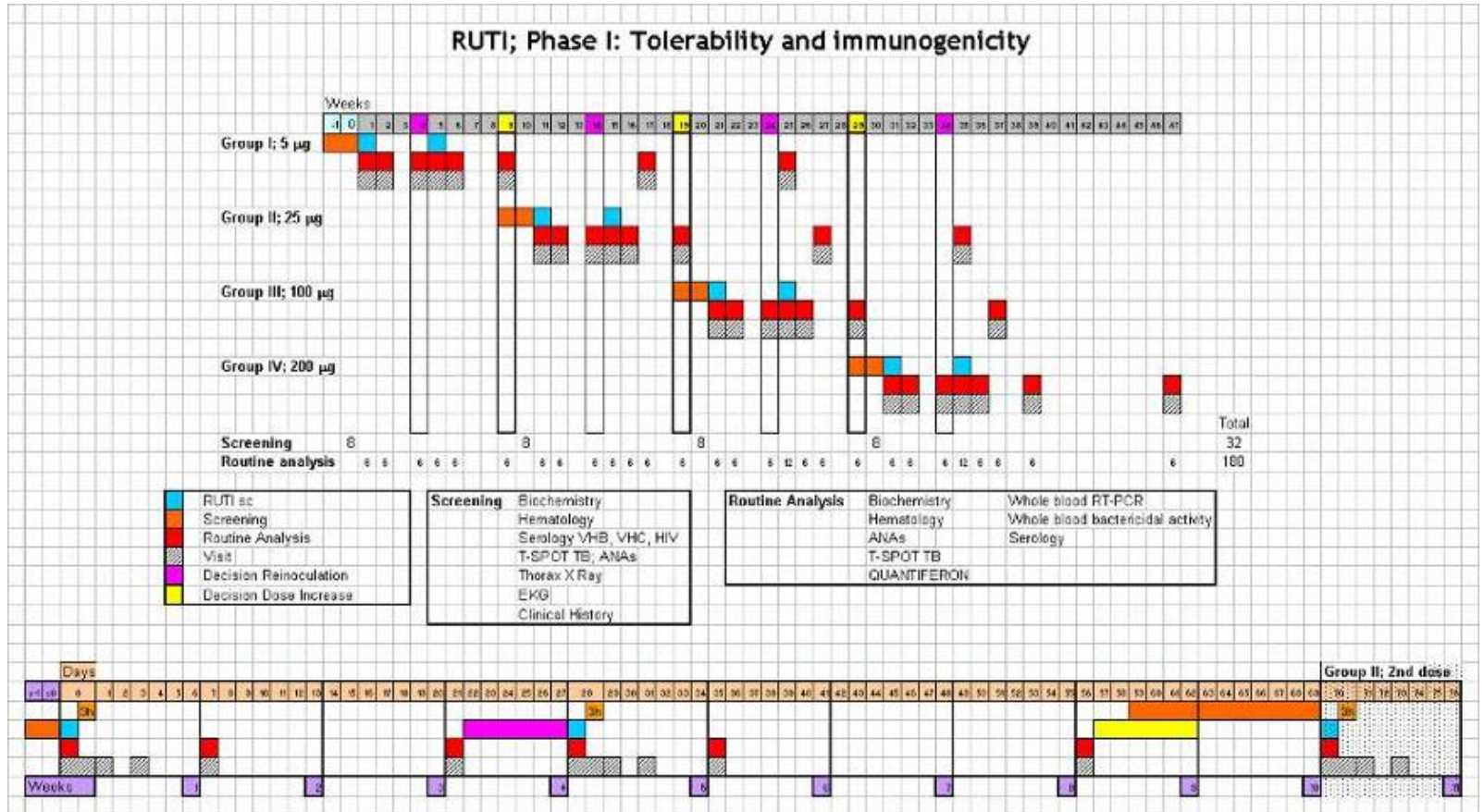
# Methods (2)



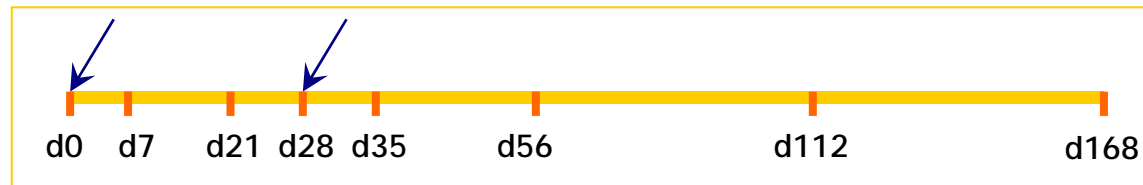
- Toxicity is monitored for 168 days through regular clinical examinations (0, 1, 3, 7, 21, 28, 29, 31, 35, 56, 112 and 168 days post first inoculation); and haematological and biochemical determinations in peripheral blood samples (at 0, 7, 21, 28, 35, 56, 112 and 168 day post first inoculation)
- Immunological monitoring will be done from peripheral blood samples. Cellular immunity will be followed looking at IFN- $\gamma$  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  $\gamma\delta$  T cells proliferation. Whole blood bactericidal activity will be also followed, as well as humoral response .



# Phase I trial



# Phase I trial





# Results



- So far, the second inoculation of the third RUTI dose (100  $\mu\text{g}$ ) has been already inoculated without showing any toxic effects and an increasing immunological response with dose.



# Phase I trial

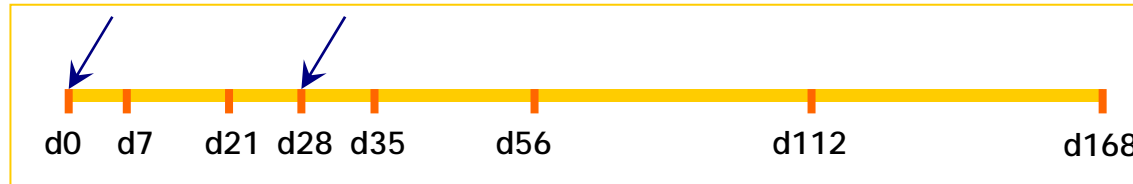
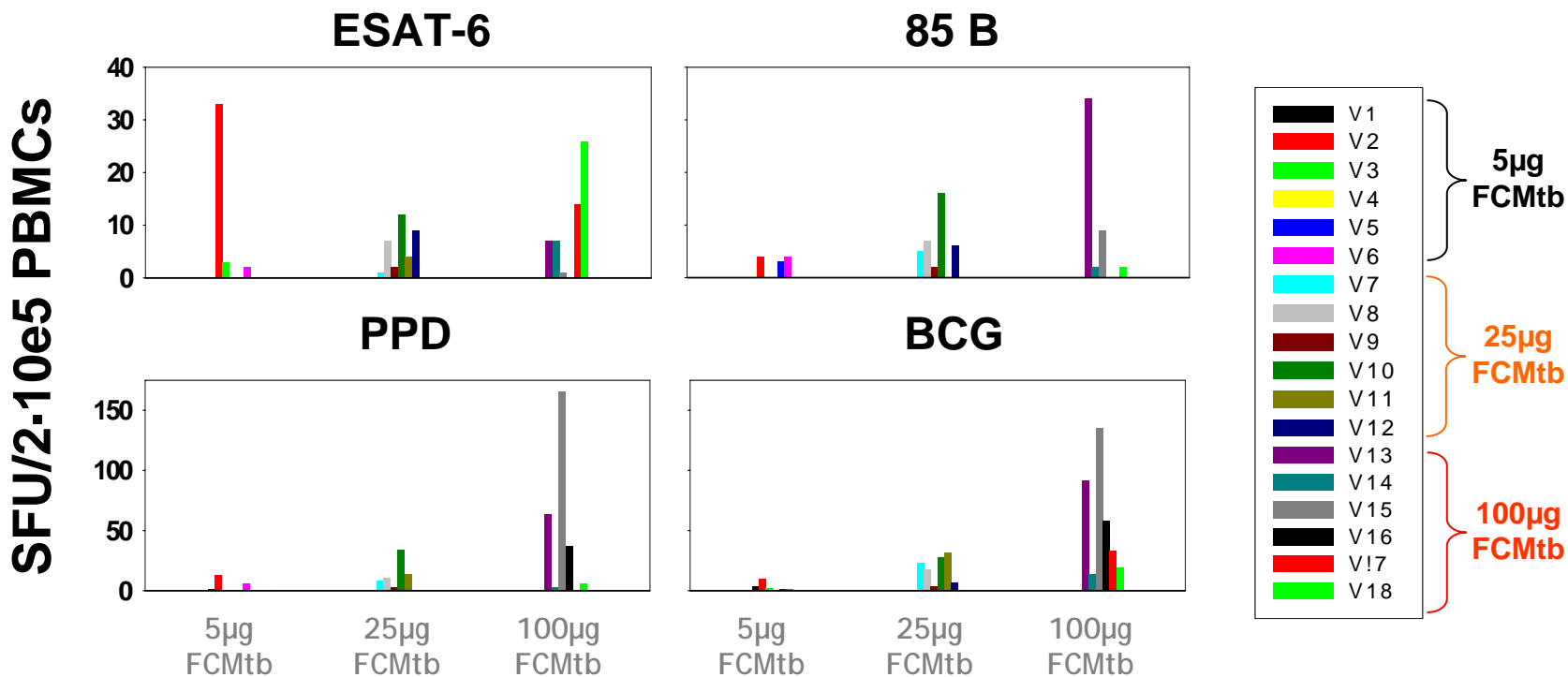


Table 1. Recorded Adverse Events (possibly or probably related to the vaccination)

	AE	Number of subjects (n=12)
Local	Twiching	2
	Pain	1
	Vesiculated lesions	1
Systemic	Fever	1

# ELISPOT IFN- $\gamma$ AT D7:

## ONE WEEK AFTER THE FIRST RUTI INOCULATION





# 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 coinfecting 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**.





# RUTI will reduce the LTBI treatment period

