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

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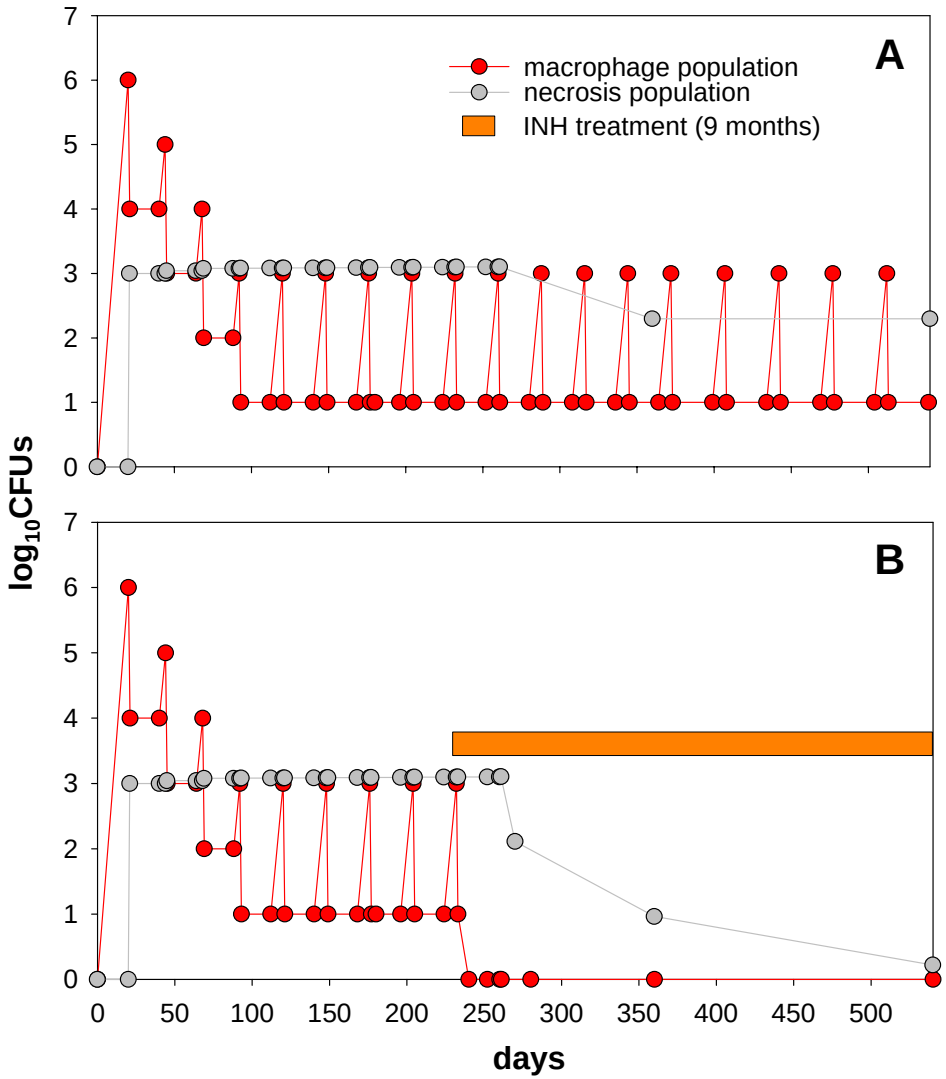
The Rationale

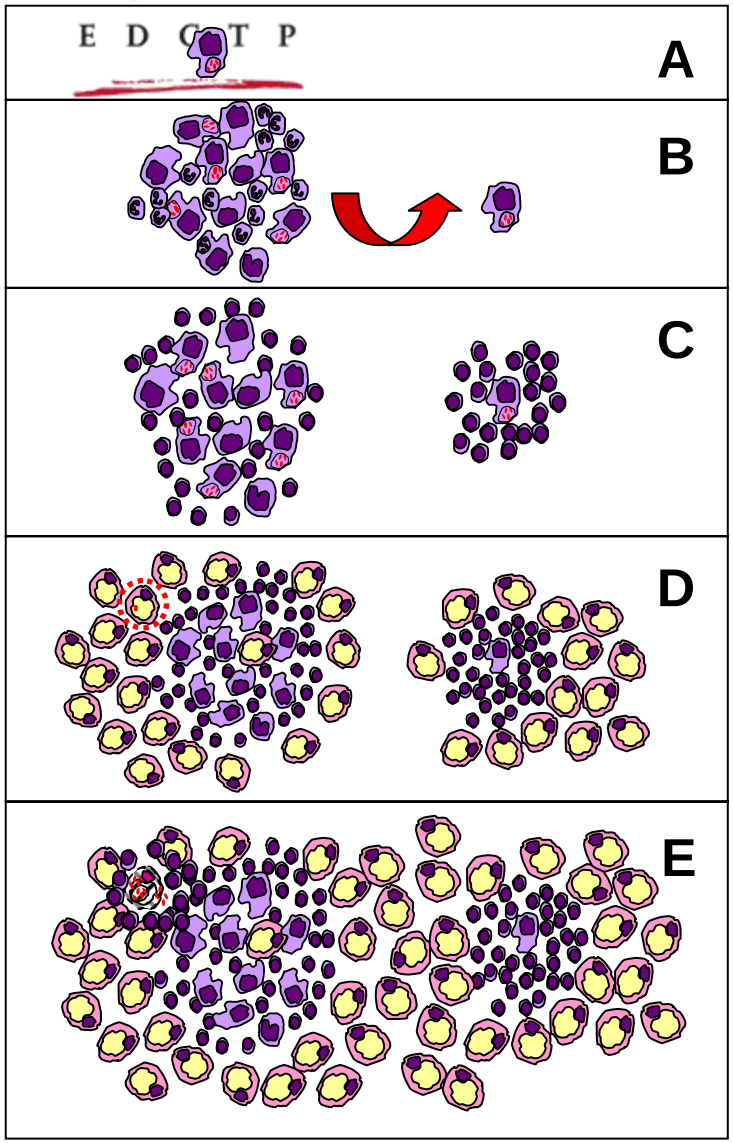
The Latent Tuberculosis Infection (LTBI).

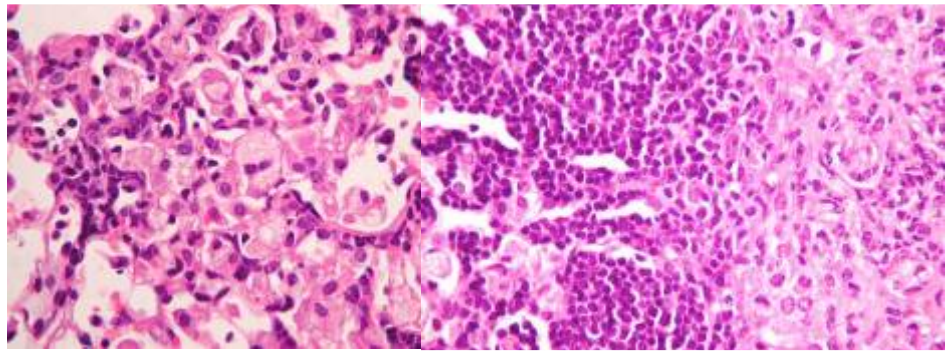
The continuous reactivation requires a prolonged chemotherapy: **9 months**

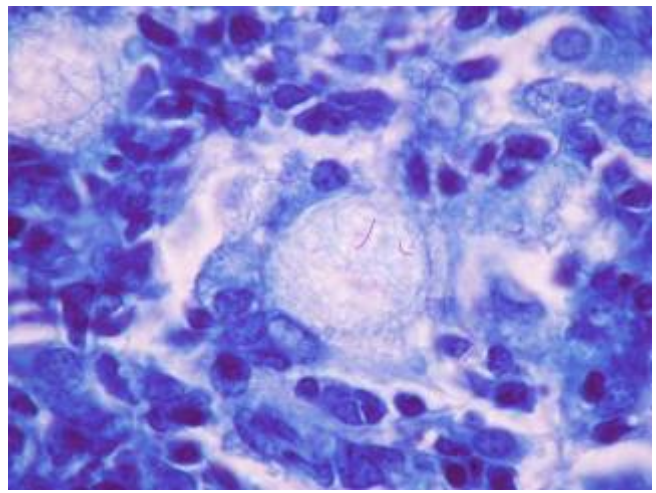


Cardona PJ 2006

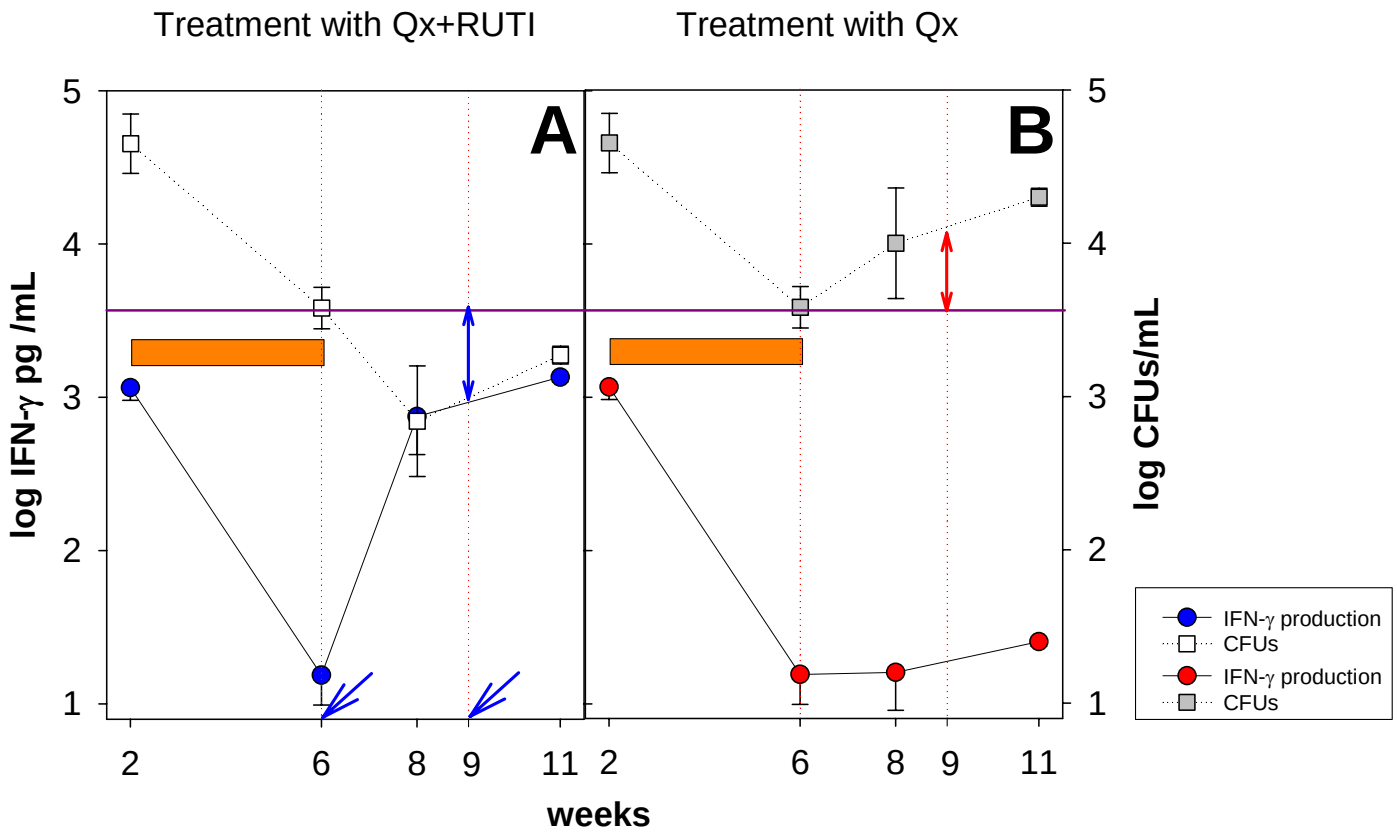
The LTBI. *Cardona et al 2000, 2003, 2004*



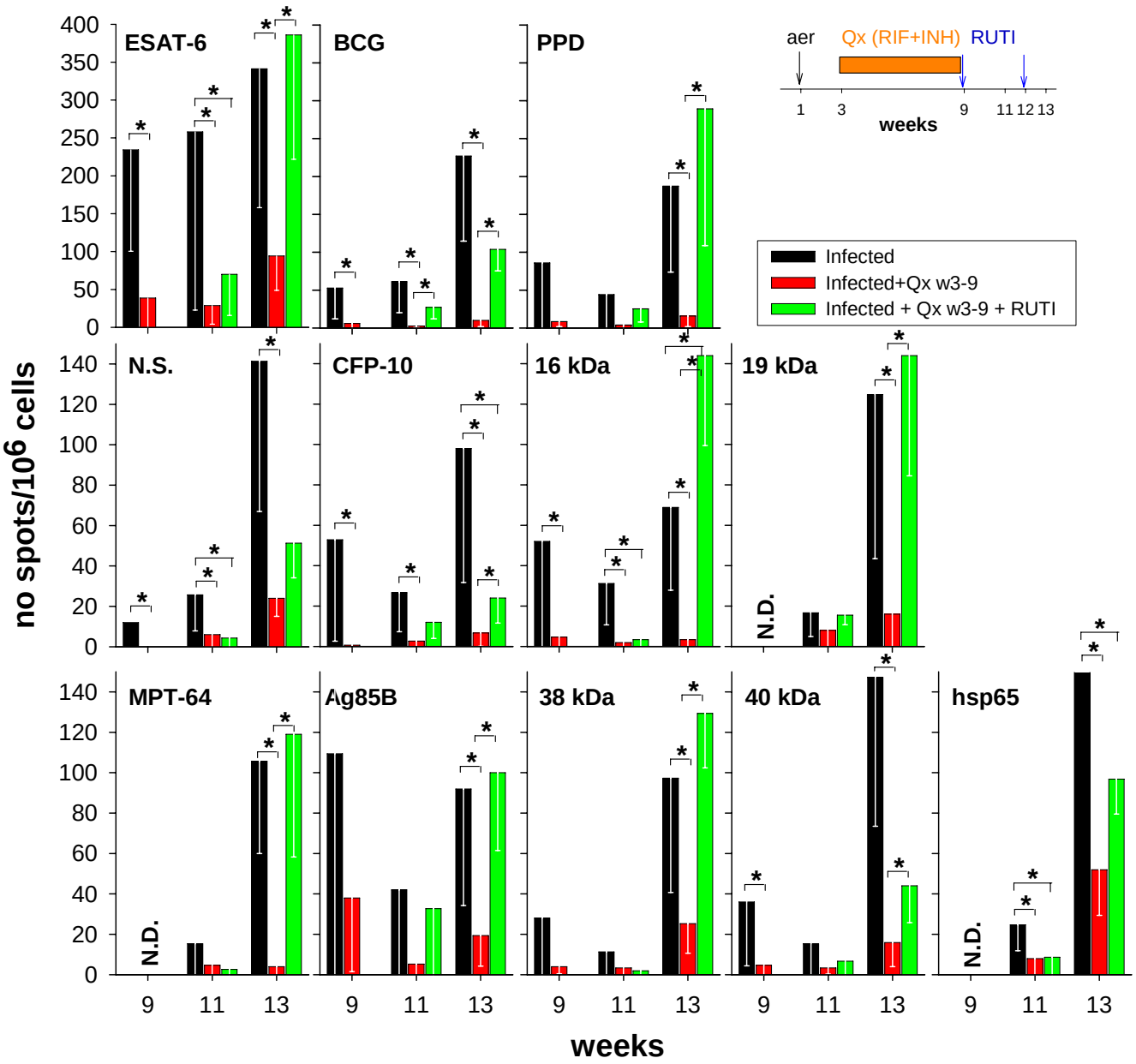




RUTI restimulates the immune response after the short-term chemotherapy, against a high number of *M. tuberculosis* antigens, not only against the growing bacilli.

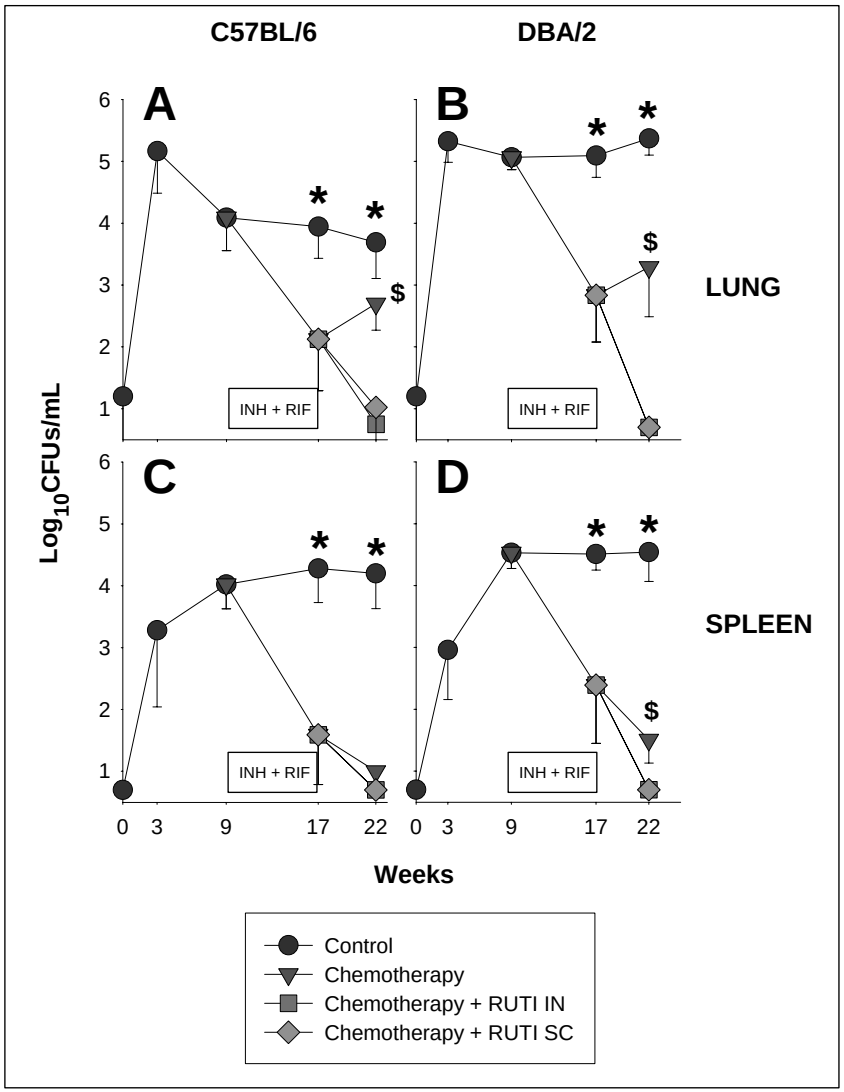


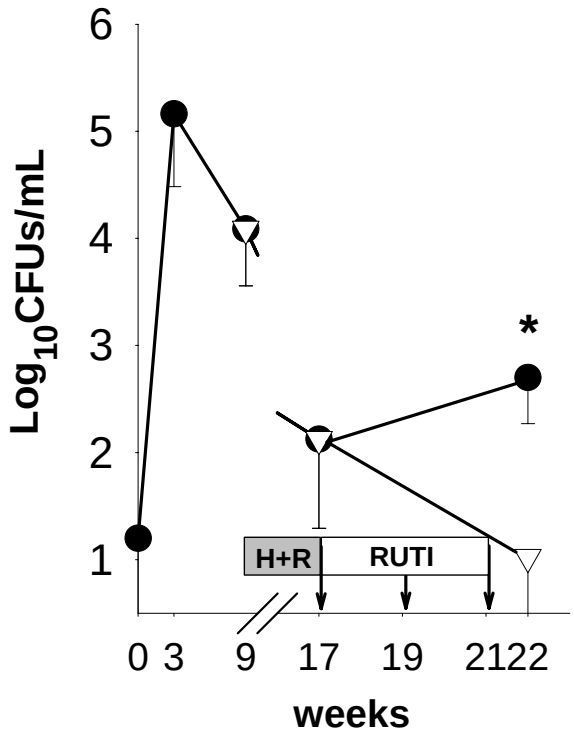
The poliantigenic Response against Growing/ resting bacilli



Efficacy of RUTI in the murine model

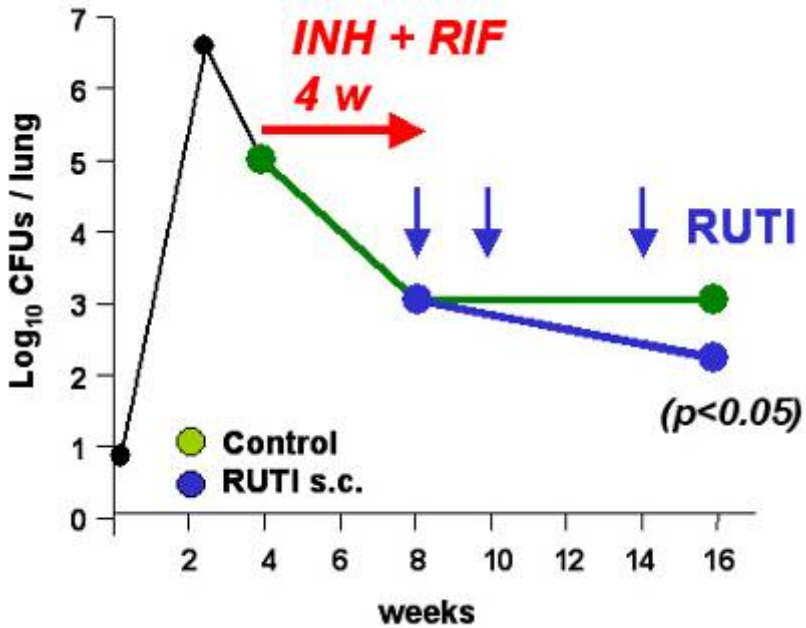
(Cardona et al Vaccine 2005)

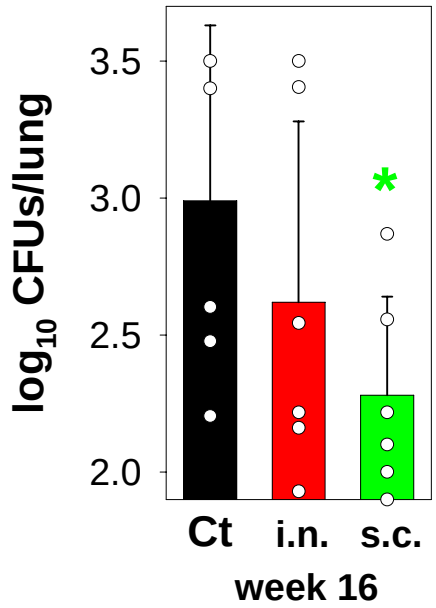


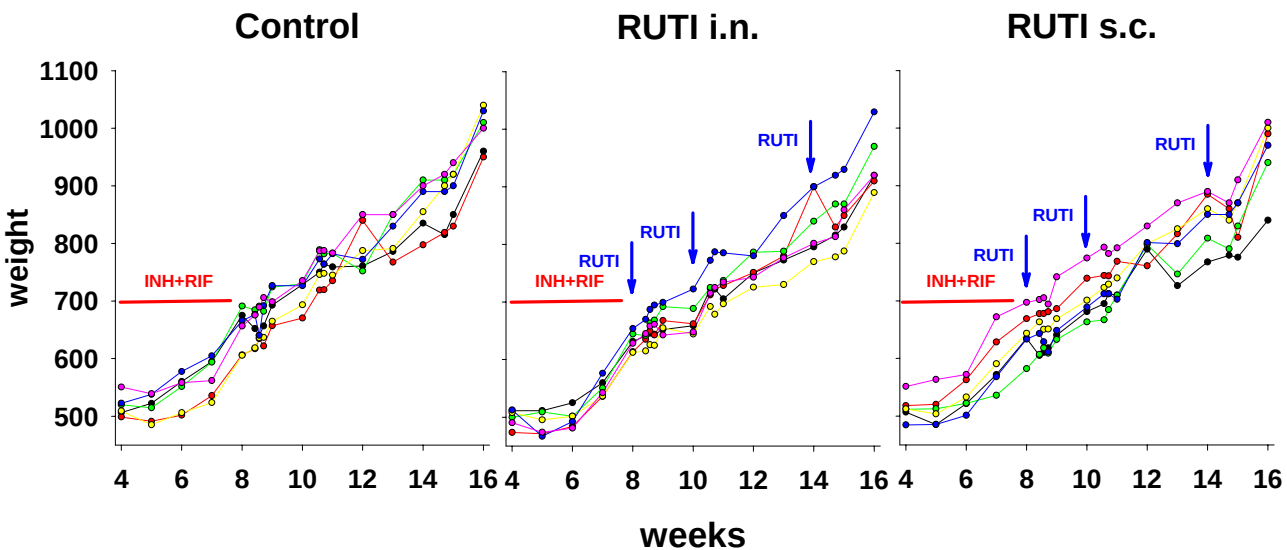


Efficacy of RUTI in the guinea pig model

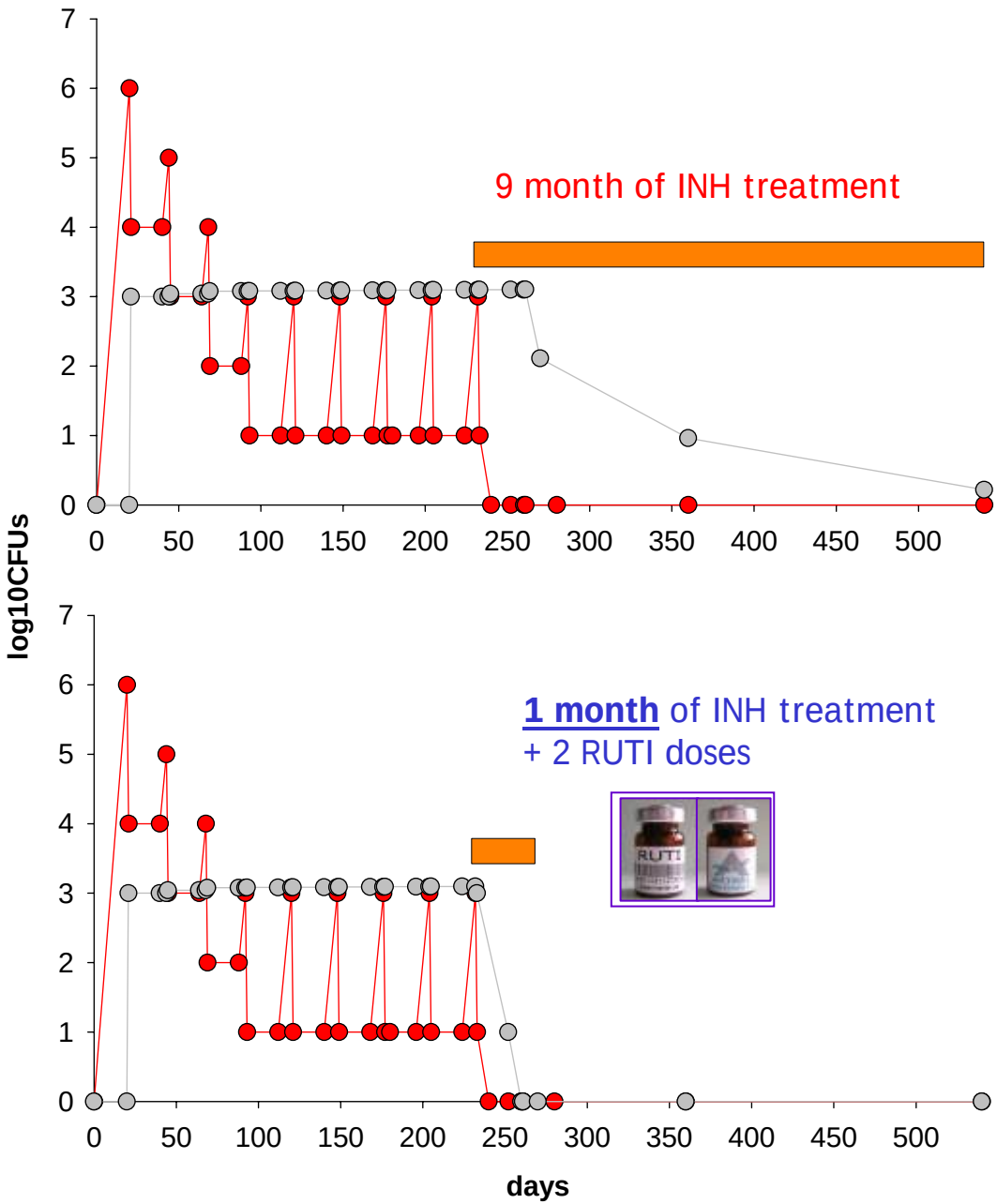
(Guirado et al 2005)



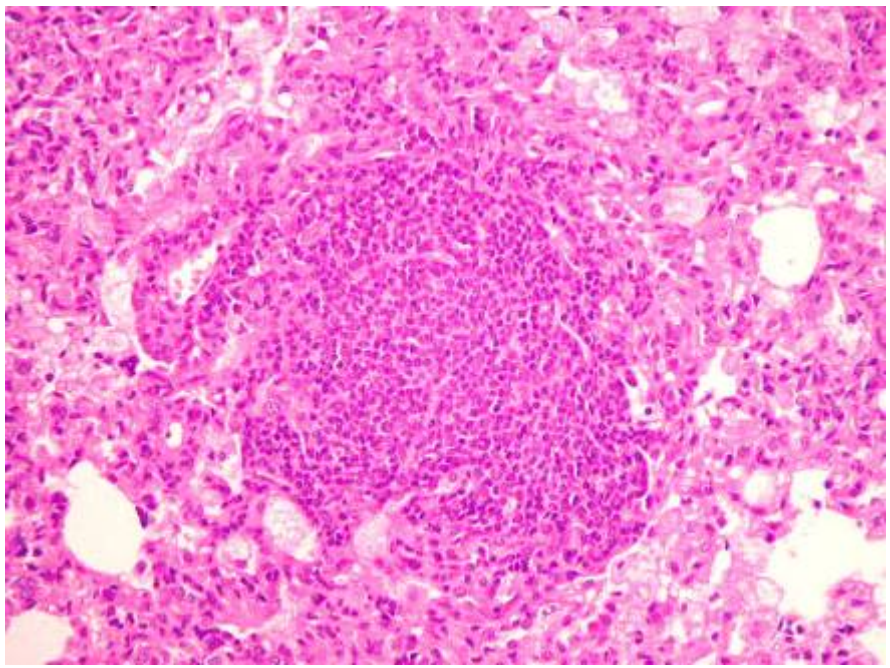


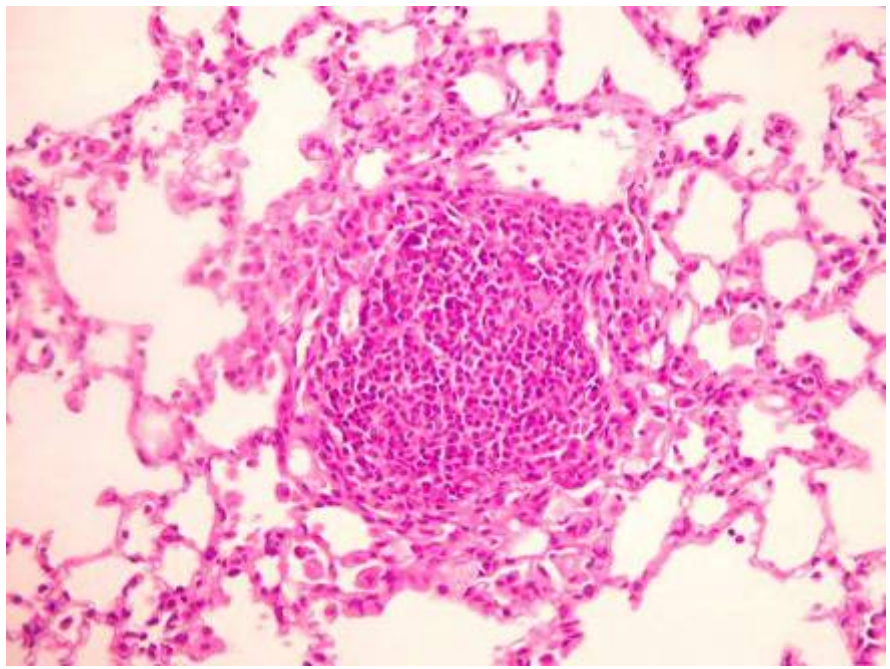


RUTI will reduce the LTBI treatment period

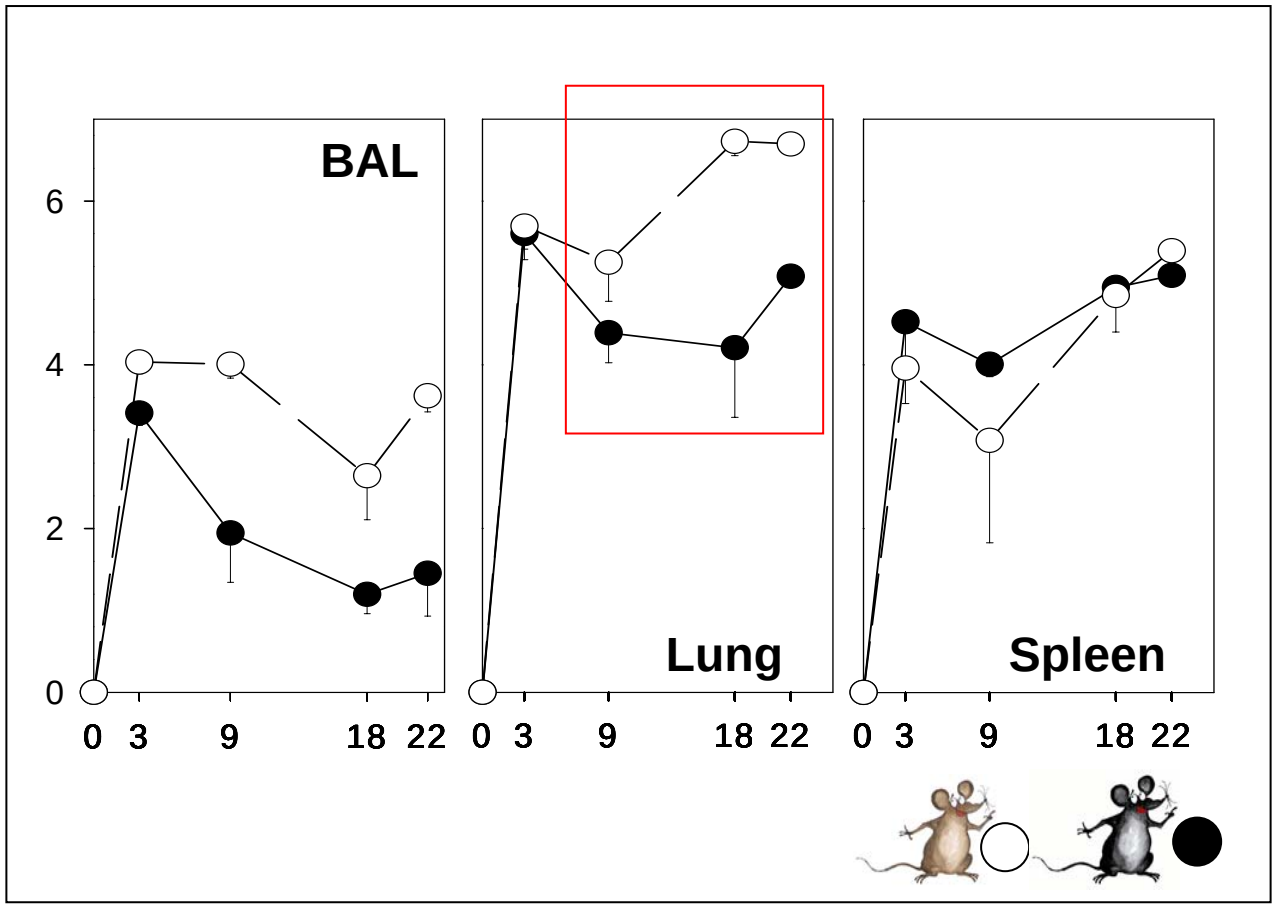


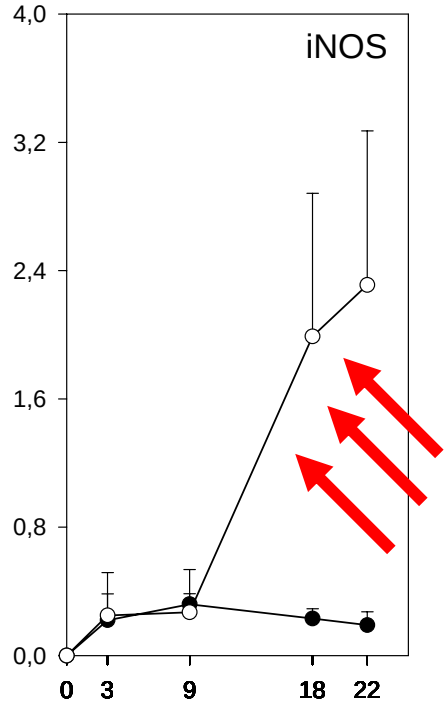
Short-term chemotherapy removes foamy macrophages





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





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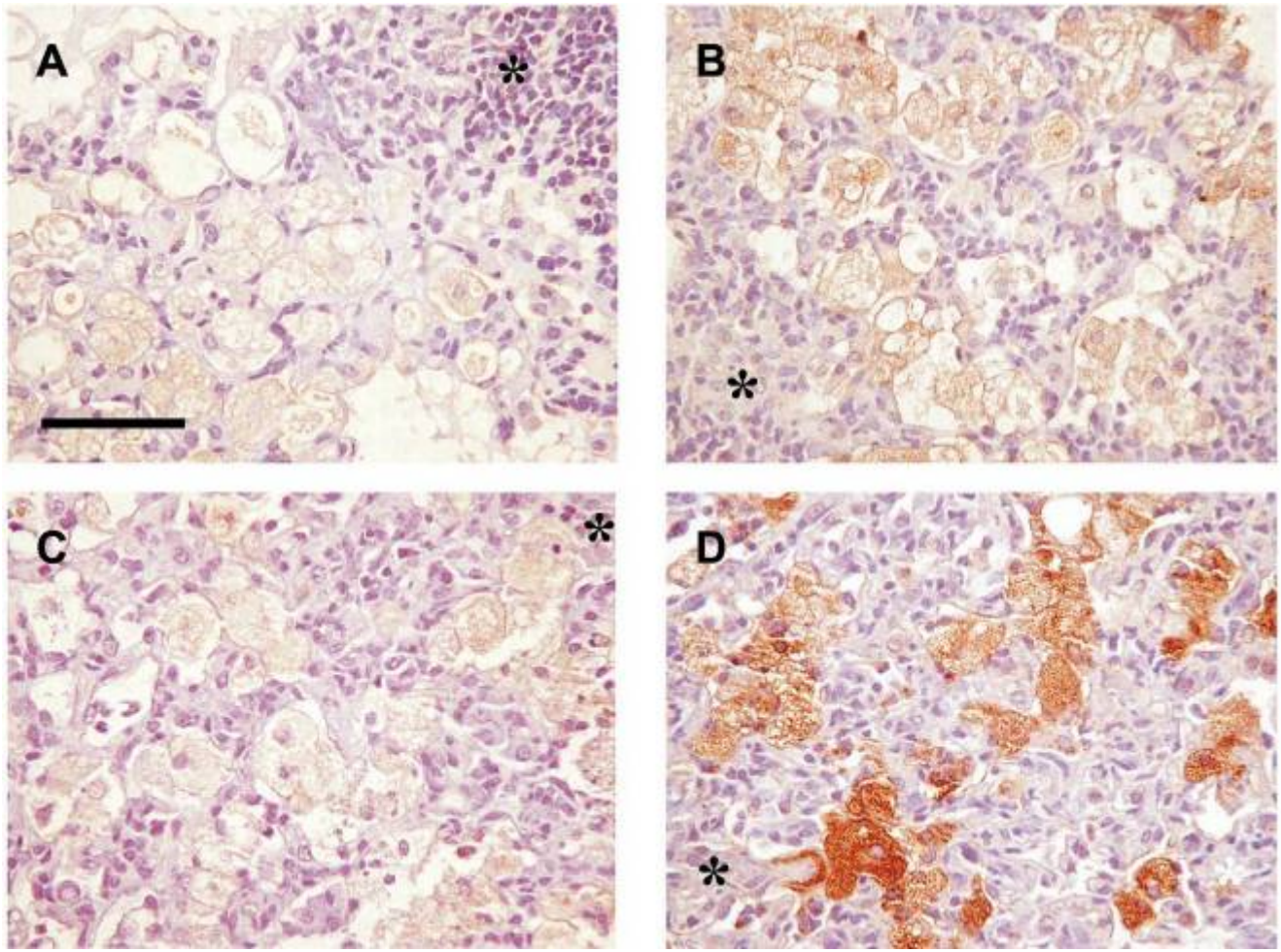


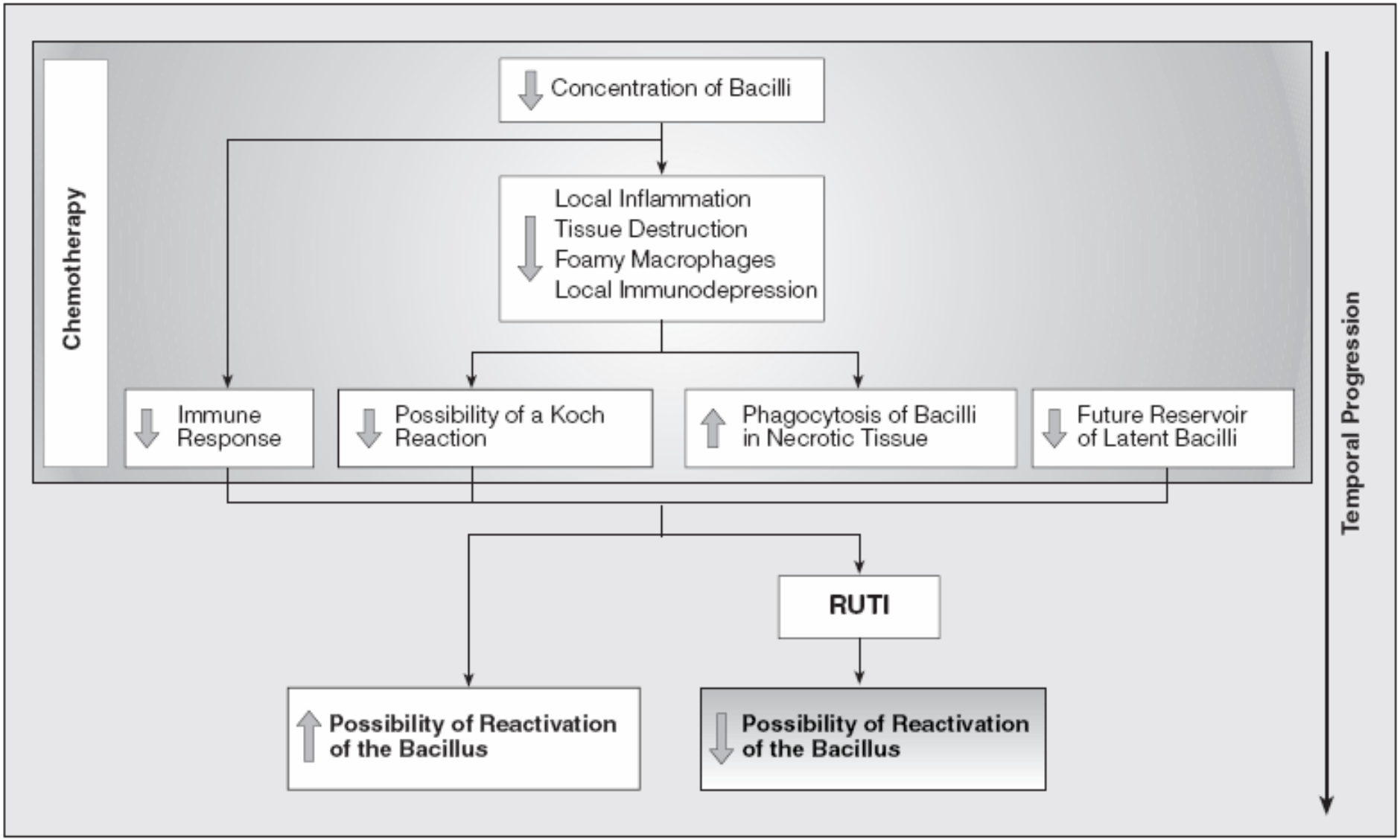


Figure. Temporal strategy for the use of RUTI, indicating the effects of short-course chemotherapy and the requirement for subsequent immunotherapy.

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)

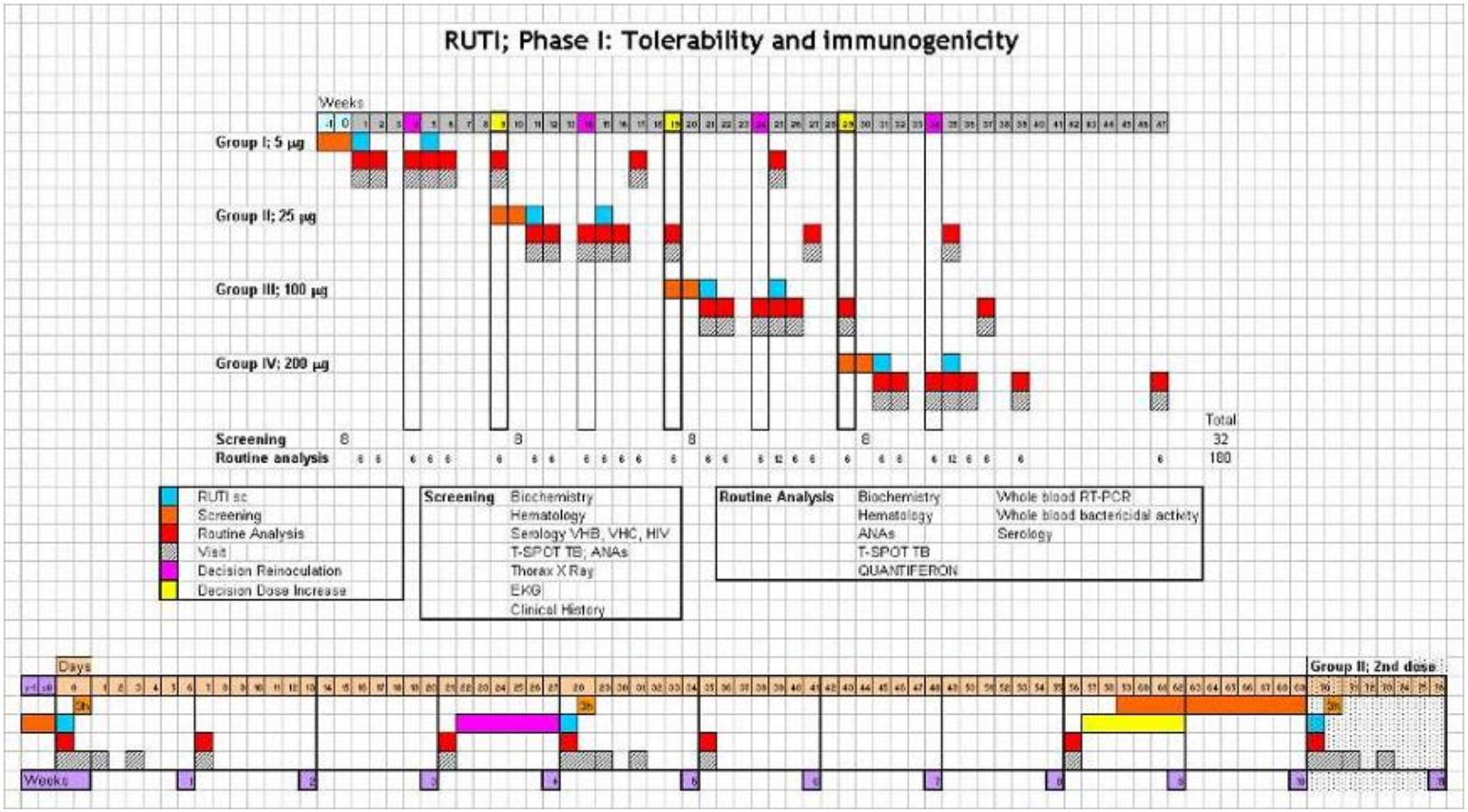
- Healthy volunteers have been recruited (HIV-, Hepatitis B and C -, and absence of latent tuberculosis infection (LTBI) through T-SPOT assay
- They are included in a random double blind assay controlled with placebo.
- Increasing doses of RUTI are administered (5, 25, 100 and 250 μg) in 4 groups of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

Methods (2)

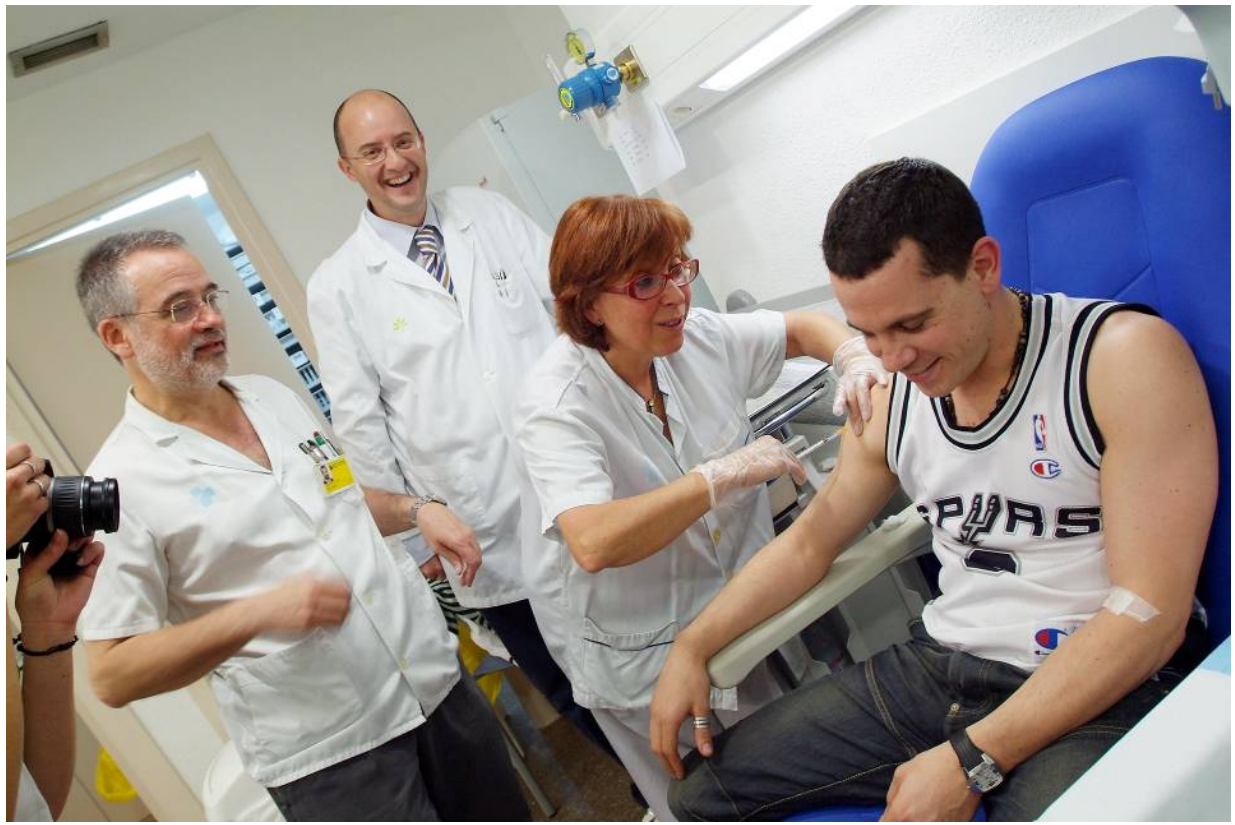
- Toxicity is monitored for 168 days through regular clinical examinations (0, 1, 3, 7, 21, 28, 29, 31, 35, 56, 112 and 168 days post first inoculation); and haematological and biochemical determinations in peripheral blood samples (at 0, 7, 21, 28, 35, 56, 112 and 168 day post first inoculation)

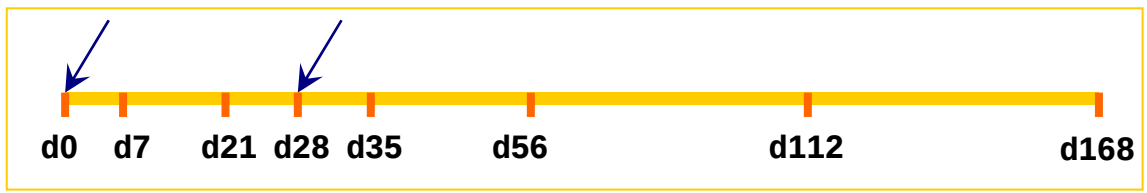
- Immunological monitoring will be done from peripheral blood samples. Cellular immunity will be followed looking at IFN-γ production through an ELISPOT assay and whole blood assay against antigens ESAT-6, CFP-10, 16 kDa, MPT-64, Ag85B, 38 kDa, hsp 65, PPD and BCG; CD4+ CD25 high regulatory T cells; and $\gamma\delta$ 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 μg) has been already inoculated without showing any toxic effects and an increasing immunological response with dose.

Phase I trial

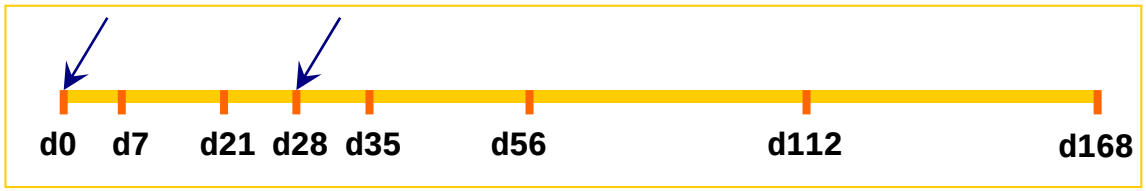
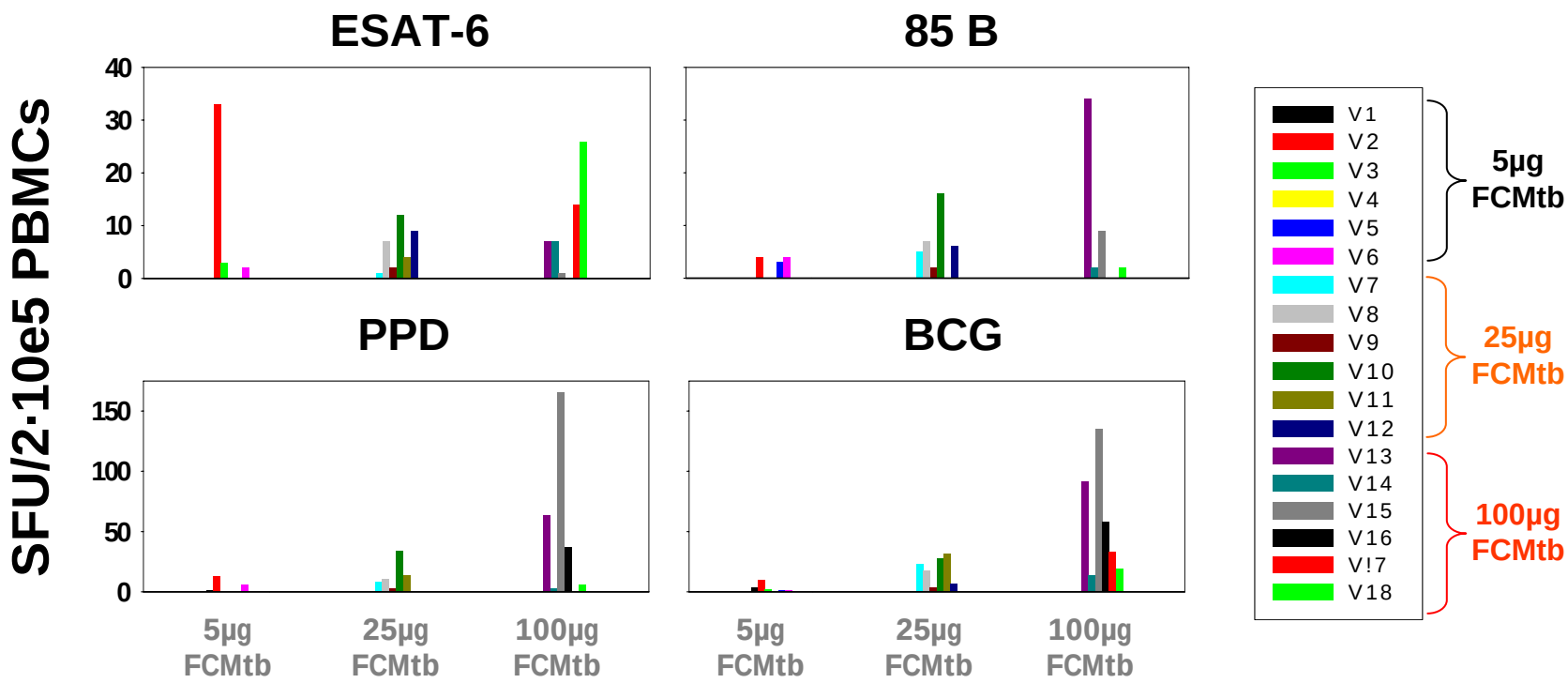


Table 1. Recorded Adverse Events (possibly or probably related to the vaccination)

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

ELISPOT IFN-γ 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 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

Years	8		2009				2010				2011				2012				13	
Quarters	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2
Capacity building																				
Trial approvals																				
Phase IIa trial																				
Phase IIa Analysis/Report																				
Phase IIb trial																				
Recruitment																				
Trial																				
Phase IIa Analysis/Report																				

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