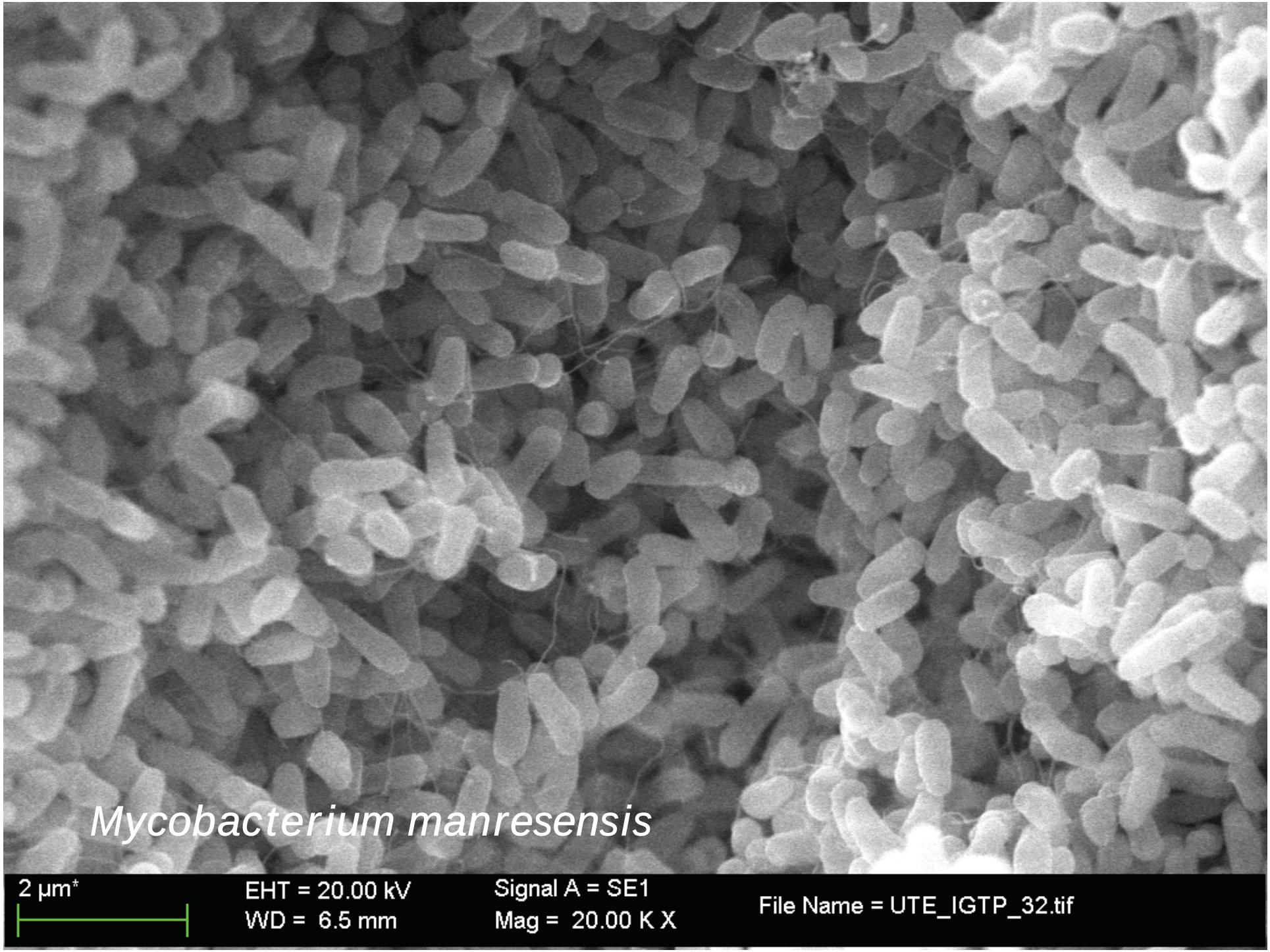
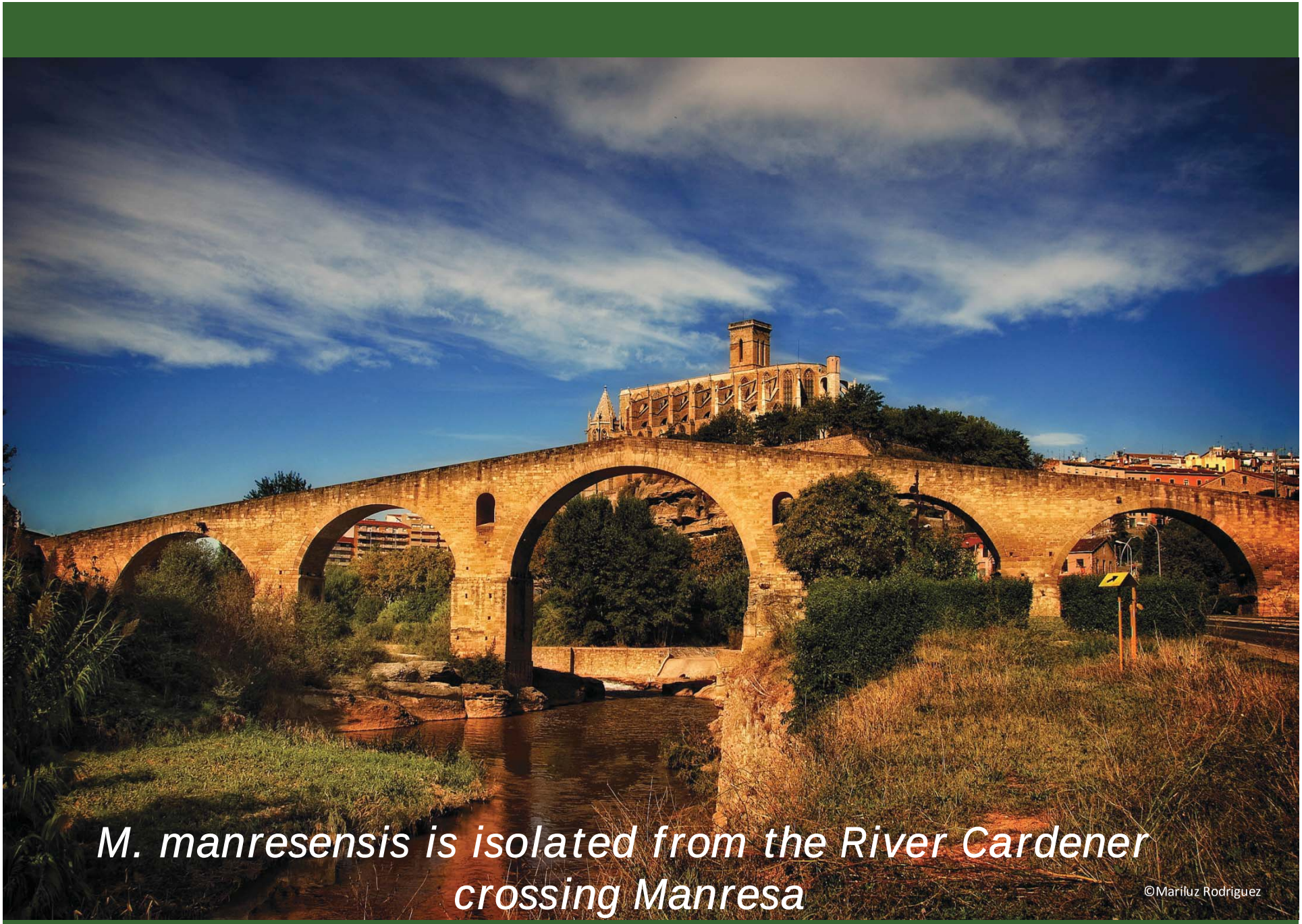

Nutraceuticals are part of the future? The case of Nyaditum resae®

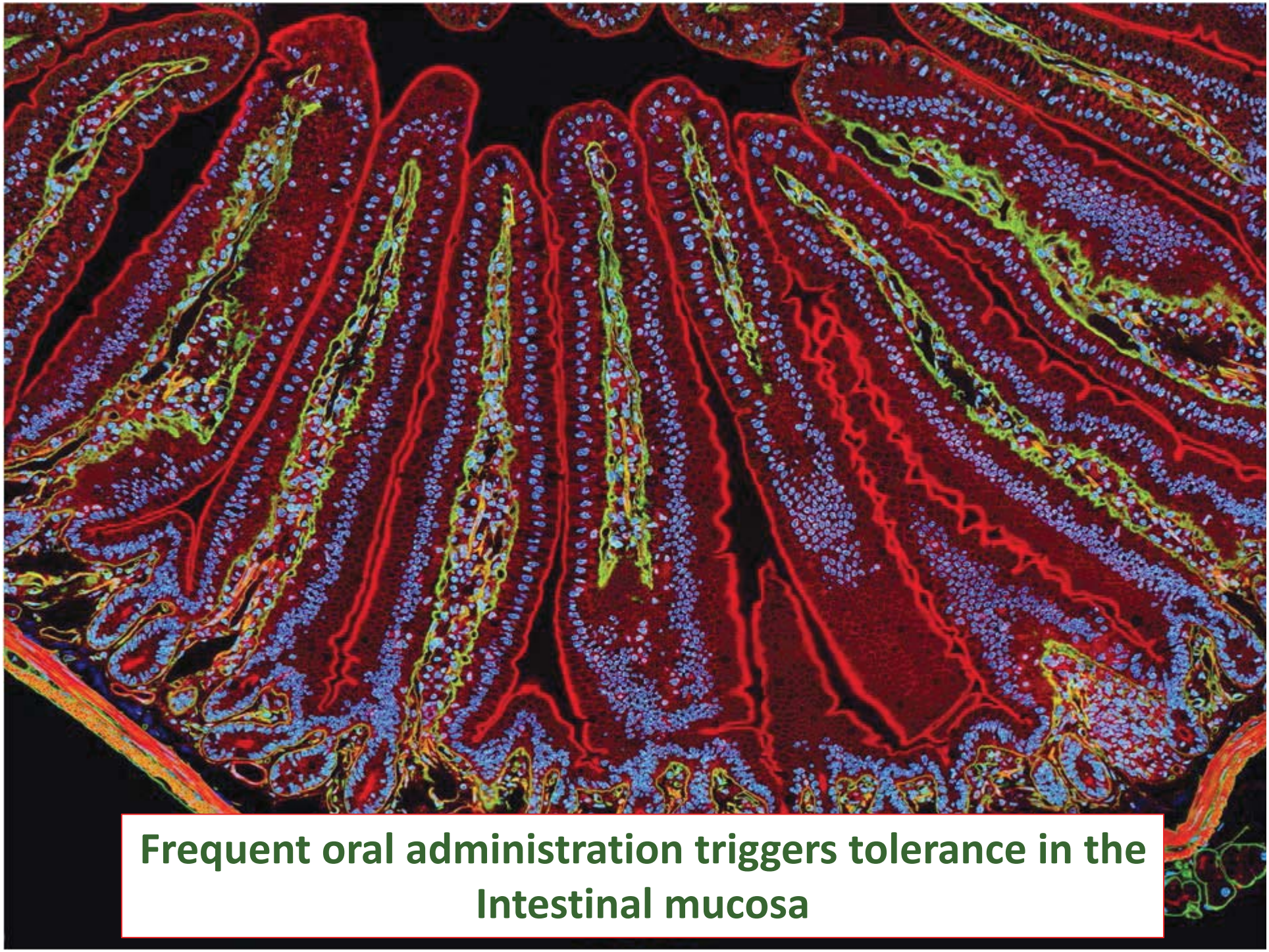

Mycobacterium manresensis
2 µm*
EHT = 20.00 kV
WD = 6.5 mm
Signal A = SE1
Mag = 20.00 K X
File Name = UTE_IGTP_32.tif



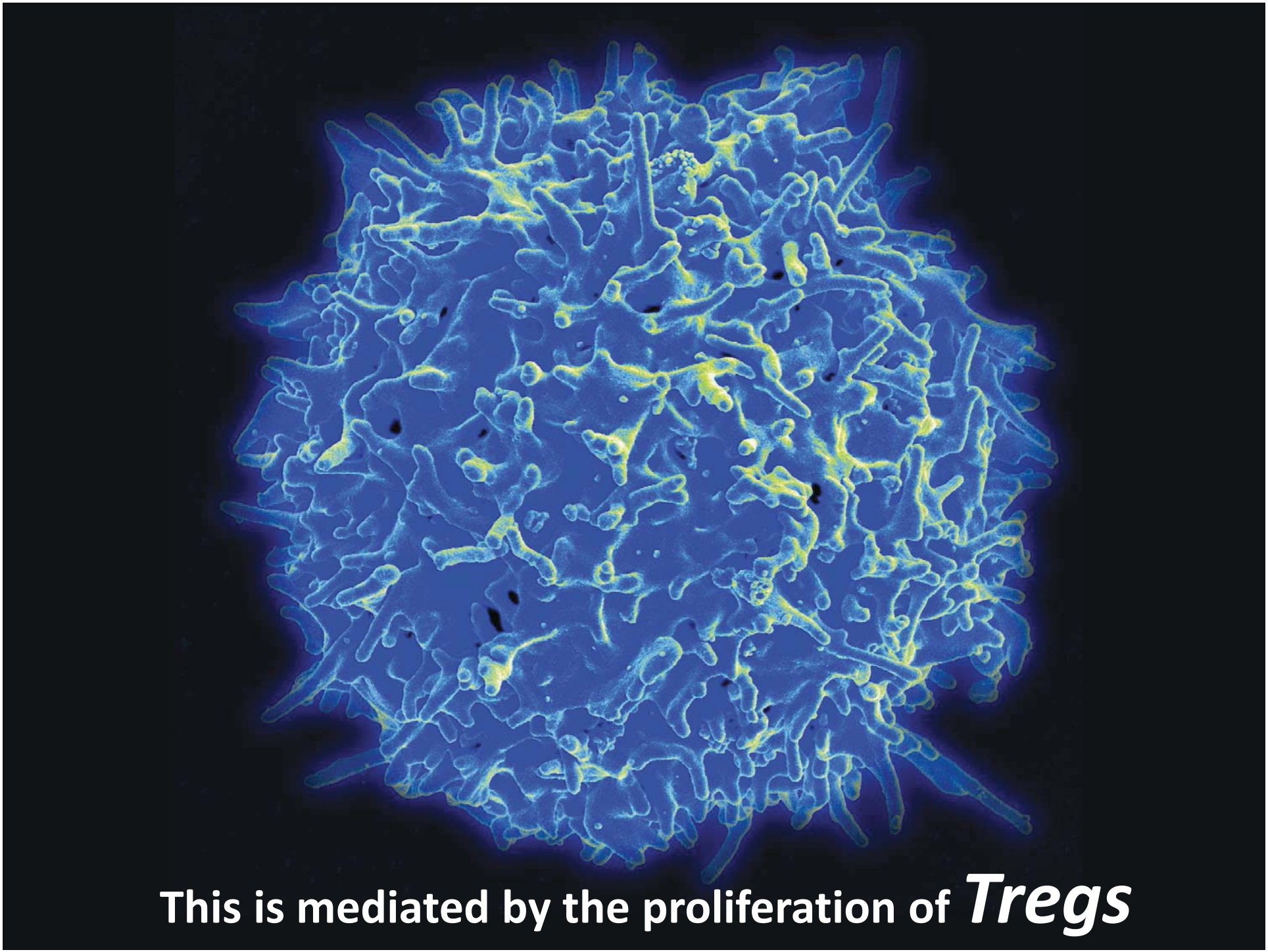
M. manresensis is isolated from the River Cardener crossing Manresa

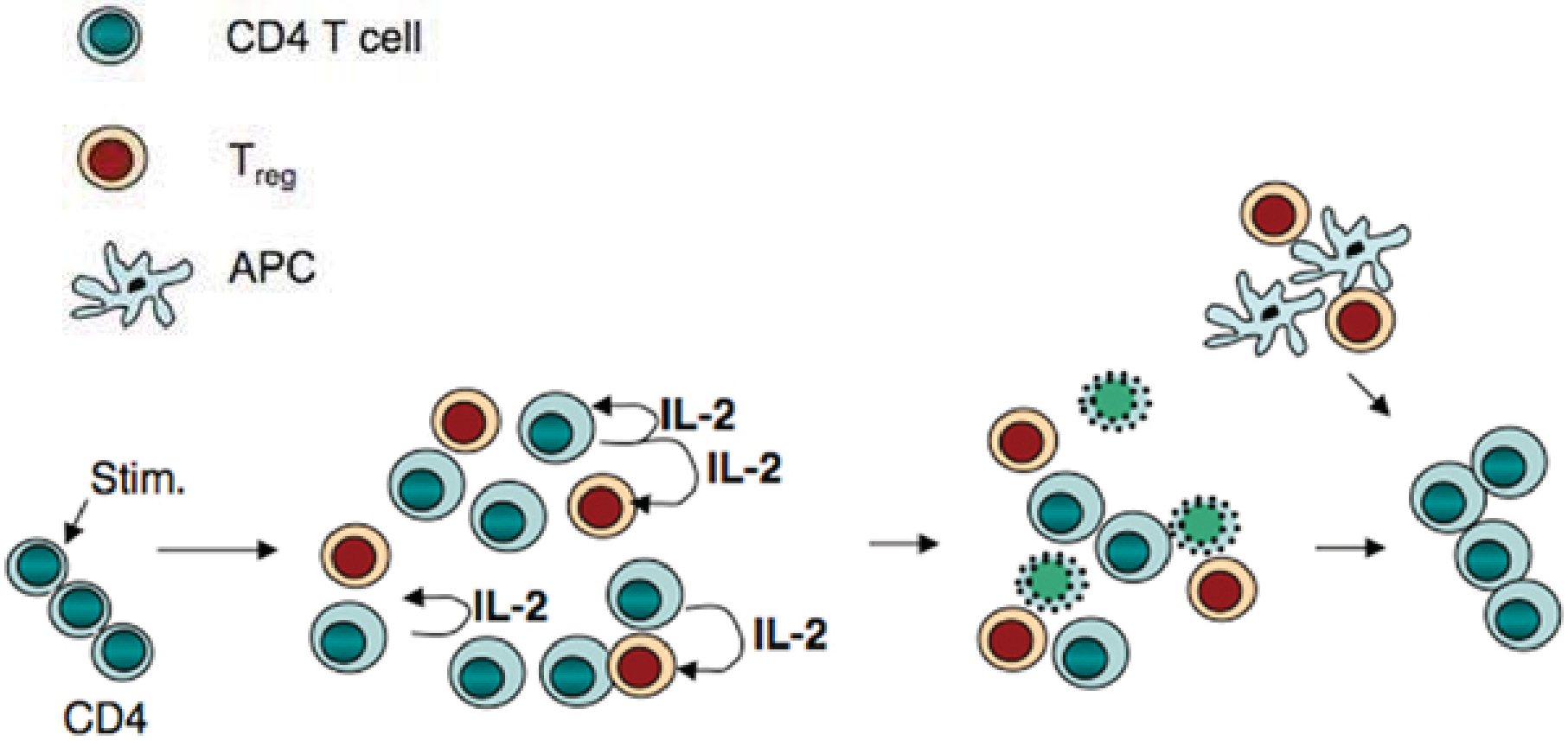
Mycobacterium manresensis **is in the potable water**

Why is that interesting?

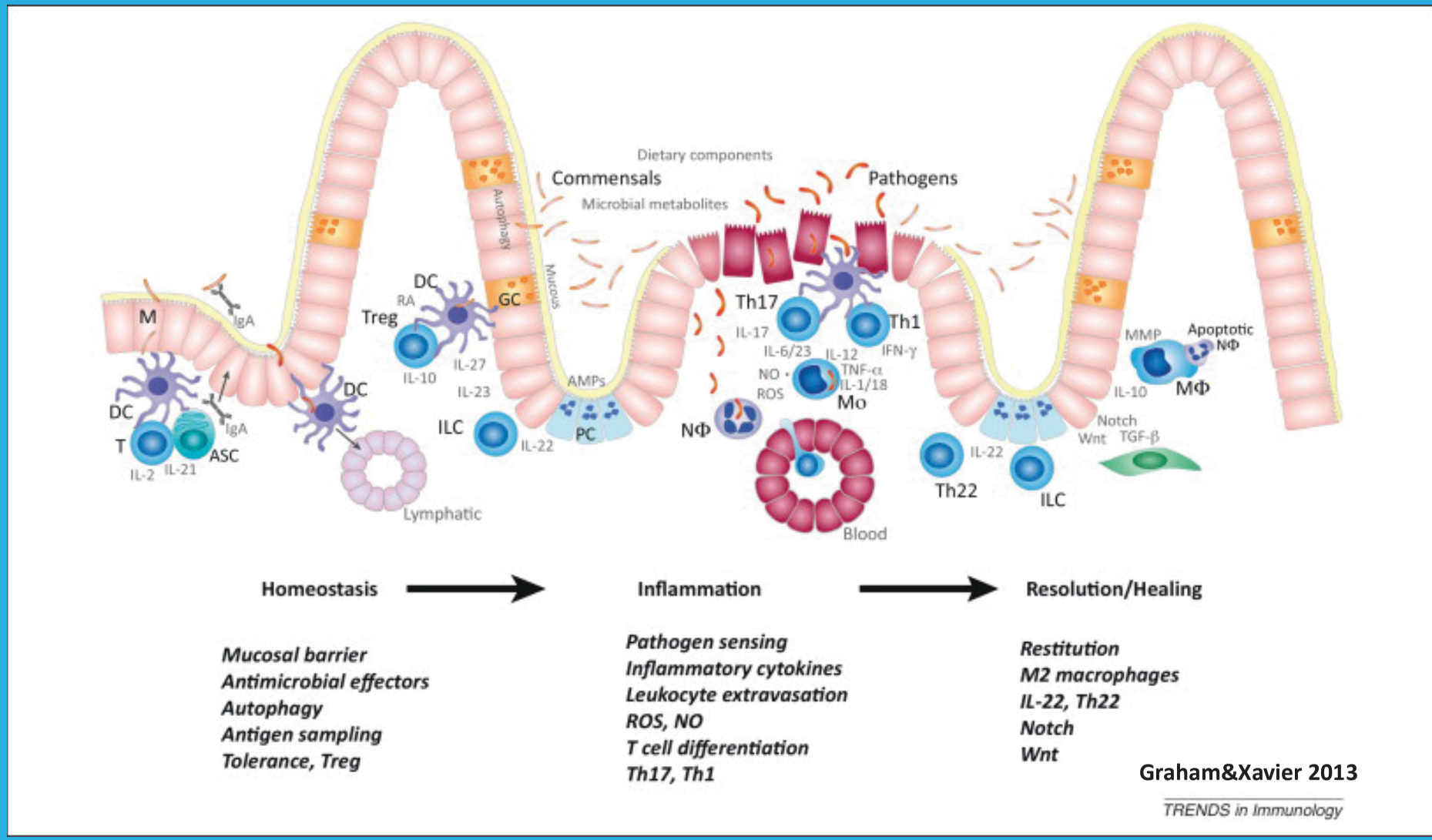


Frequent oral administration triggers tolerance in the Intestinal mucosa


This is mediated by the proliferation of *Tregs*

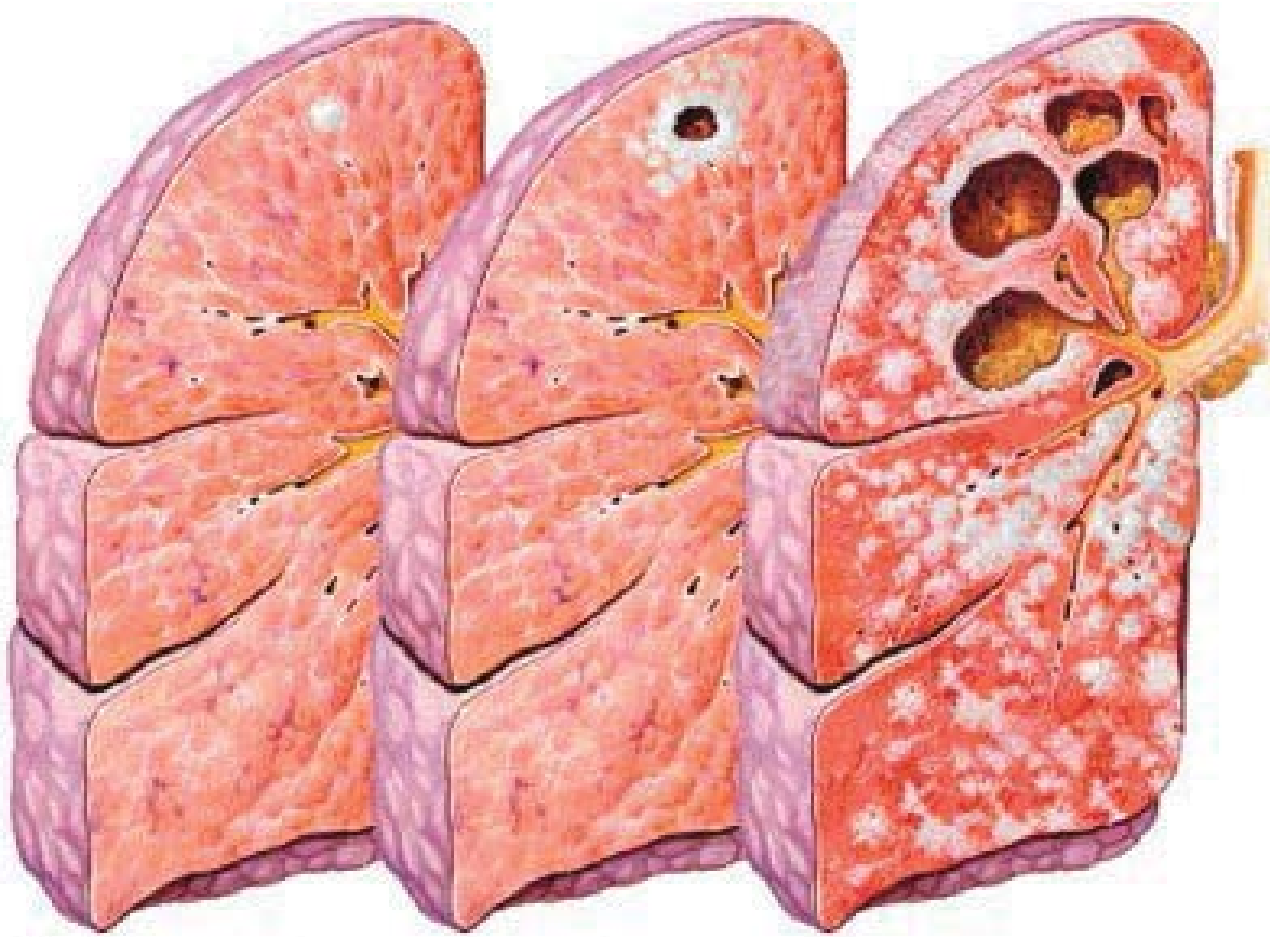


Tregs modulate exaggerated immune responses



Tregs modulate exaggerated immune responses:
This is well known in intestinal inflammatory disease

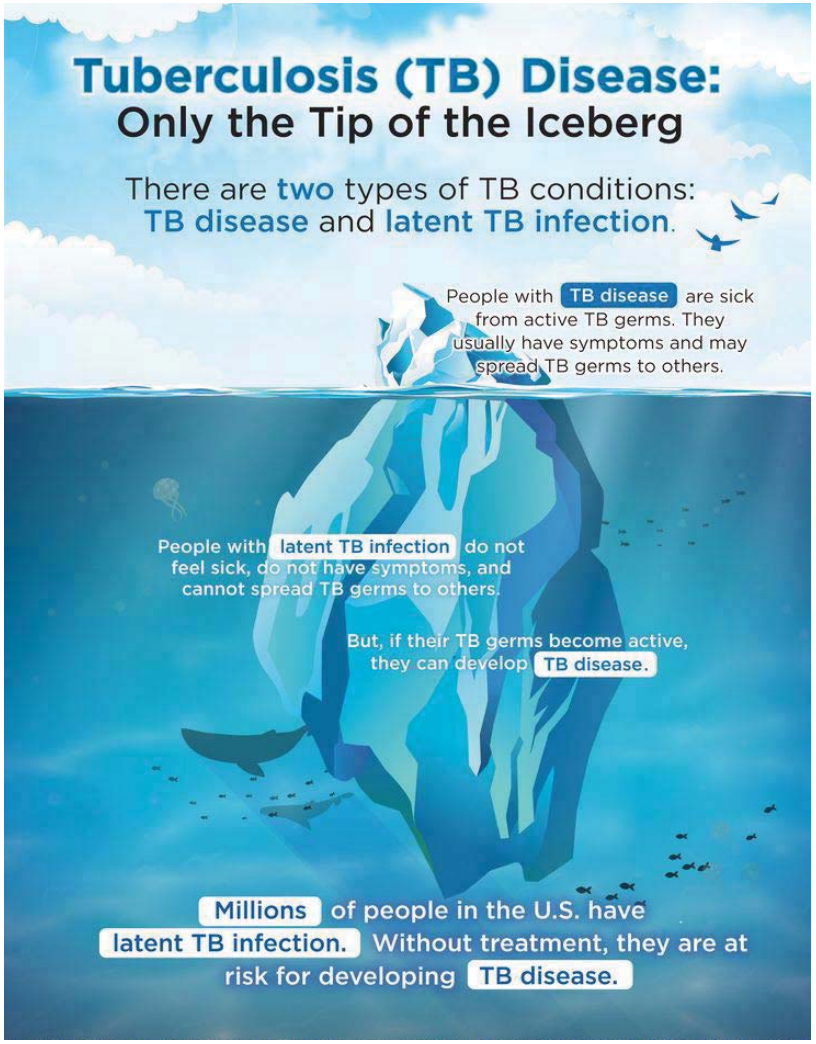
What's the relation of Tregs induction and Tuberculosis risk reduction?



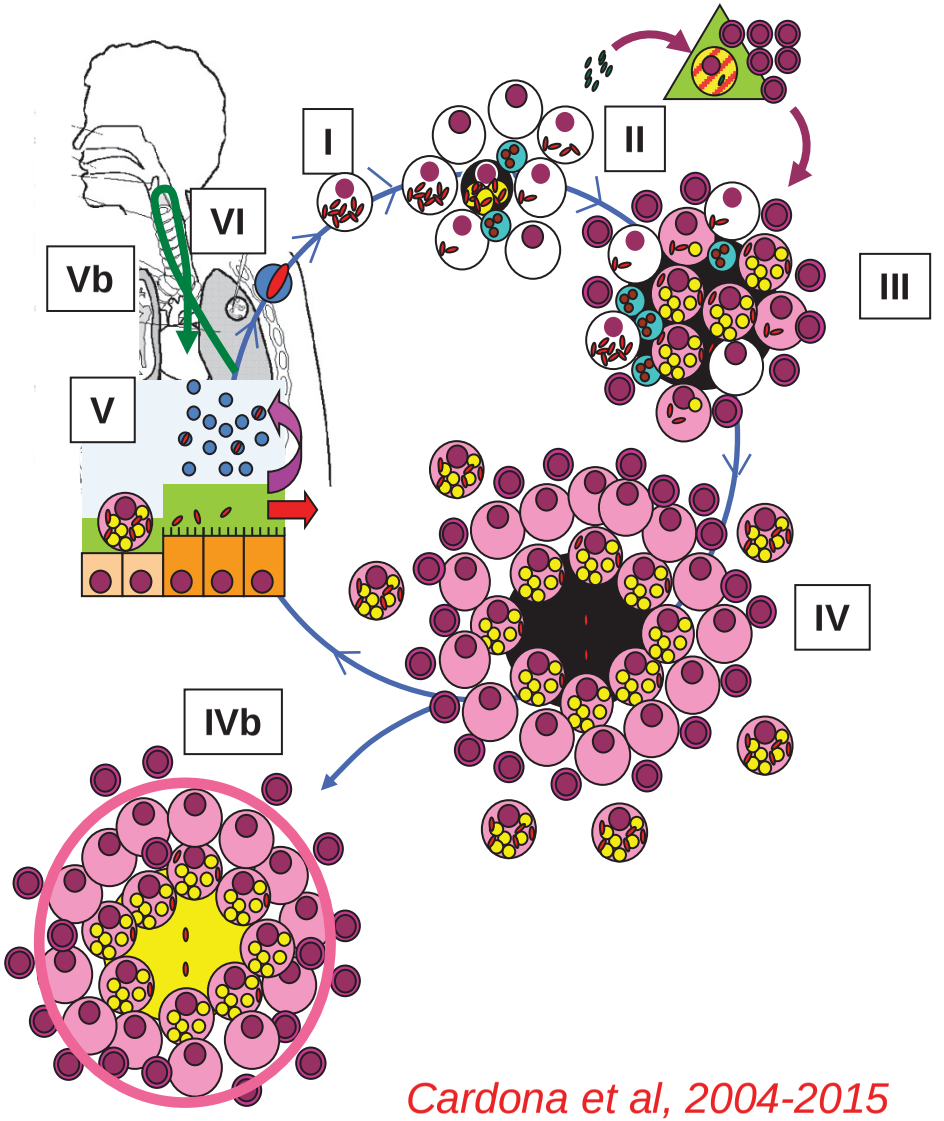
Tuberculosis is characterized by a massive destruction of The lung after a period of latent infection

UTE

M. tuberculosis **causes a latent infection that last for years thanks to a constant reinfection.**



CDC USA. 2015



Cardona et al, 2004-2015

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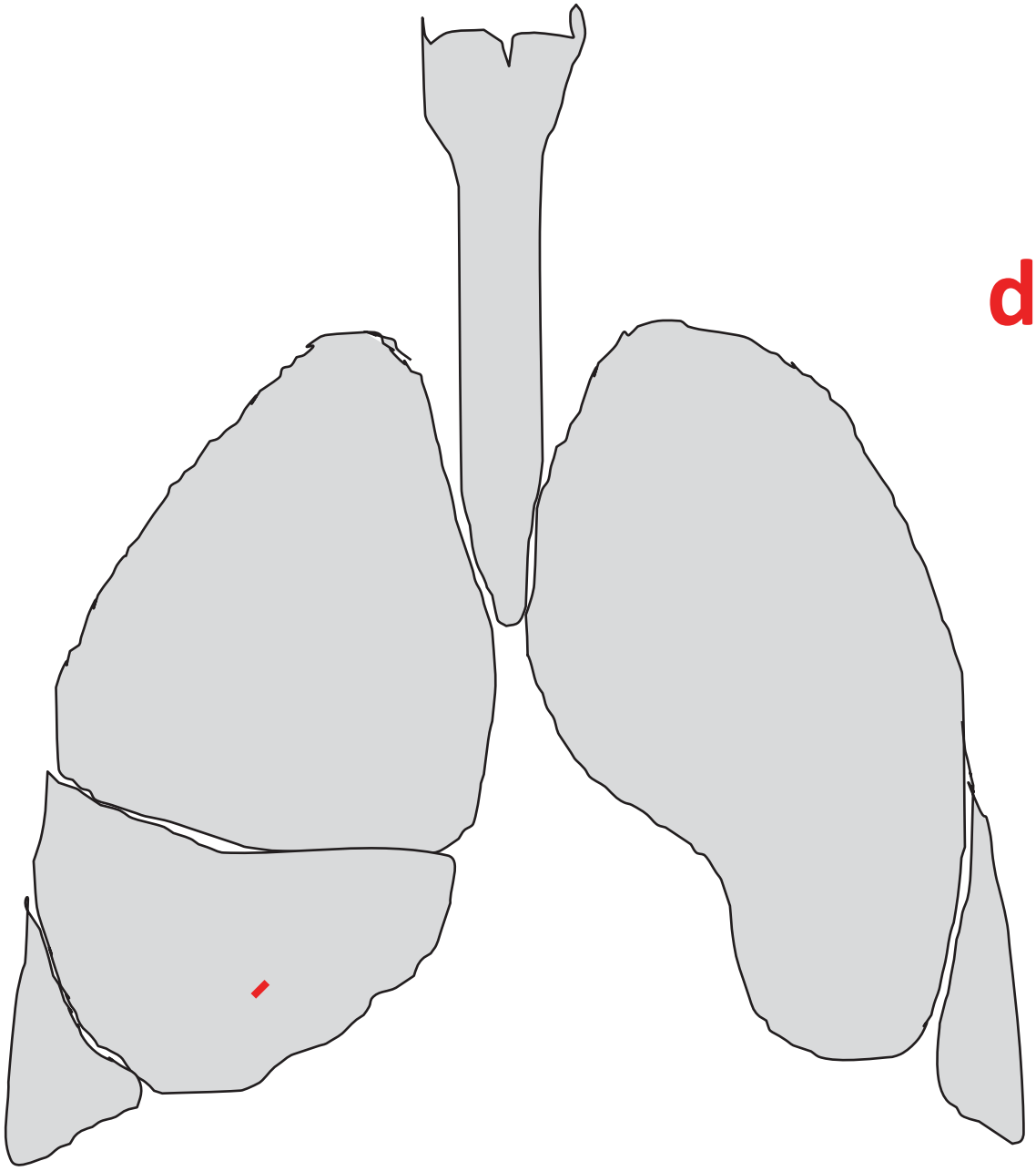
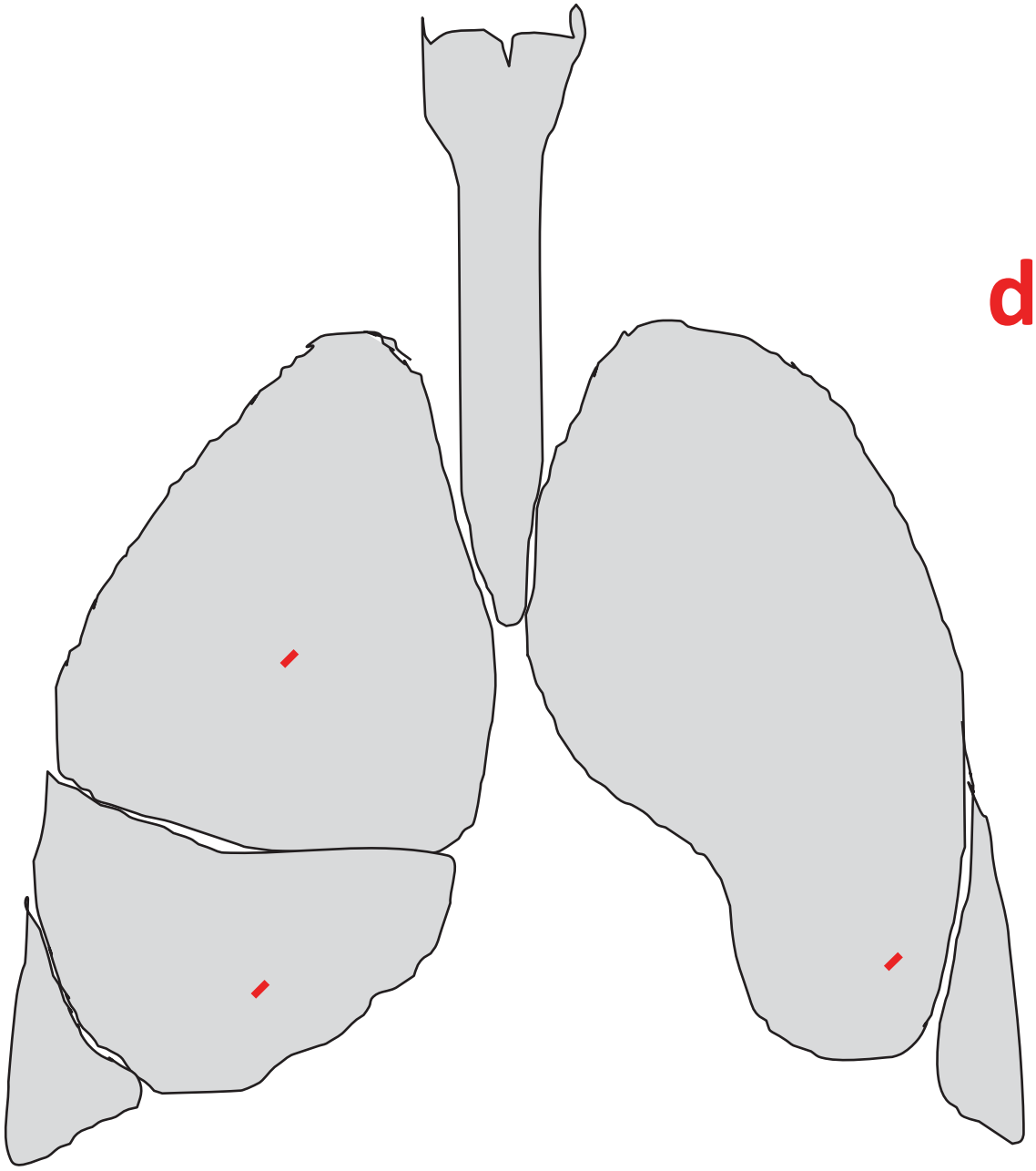


d0

Cardona PJ 2015

UTE



d2

Cardona PJ 2015

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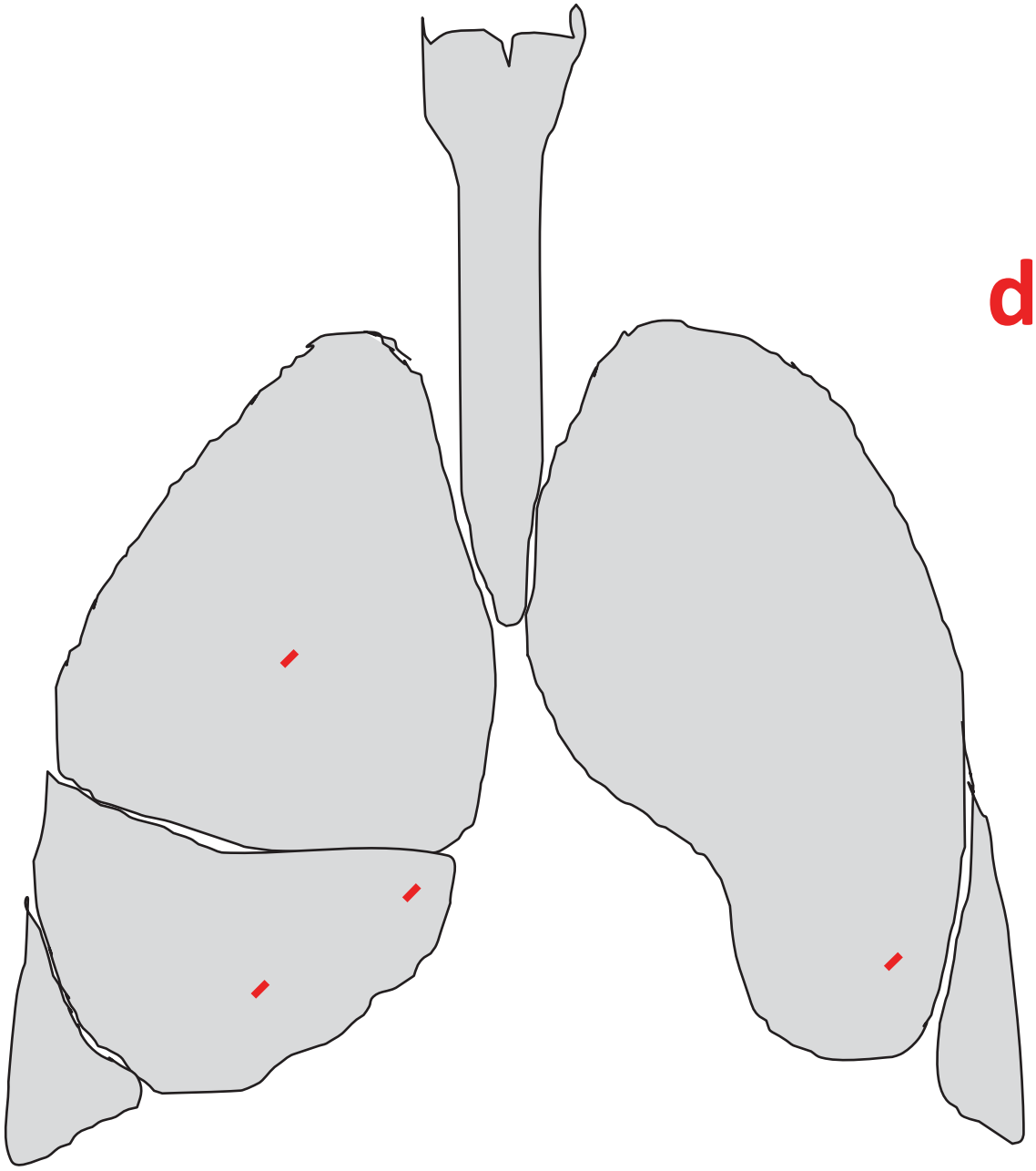

d3

Cardona PJ 2015

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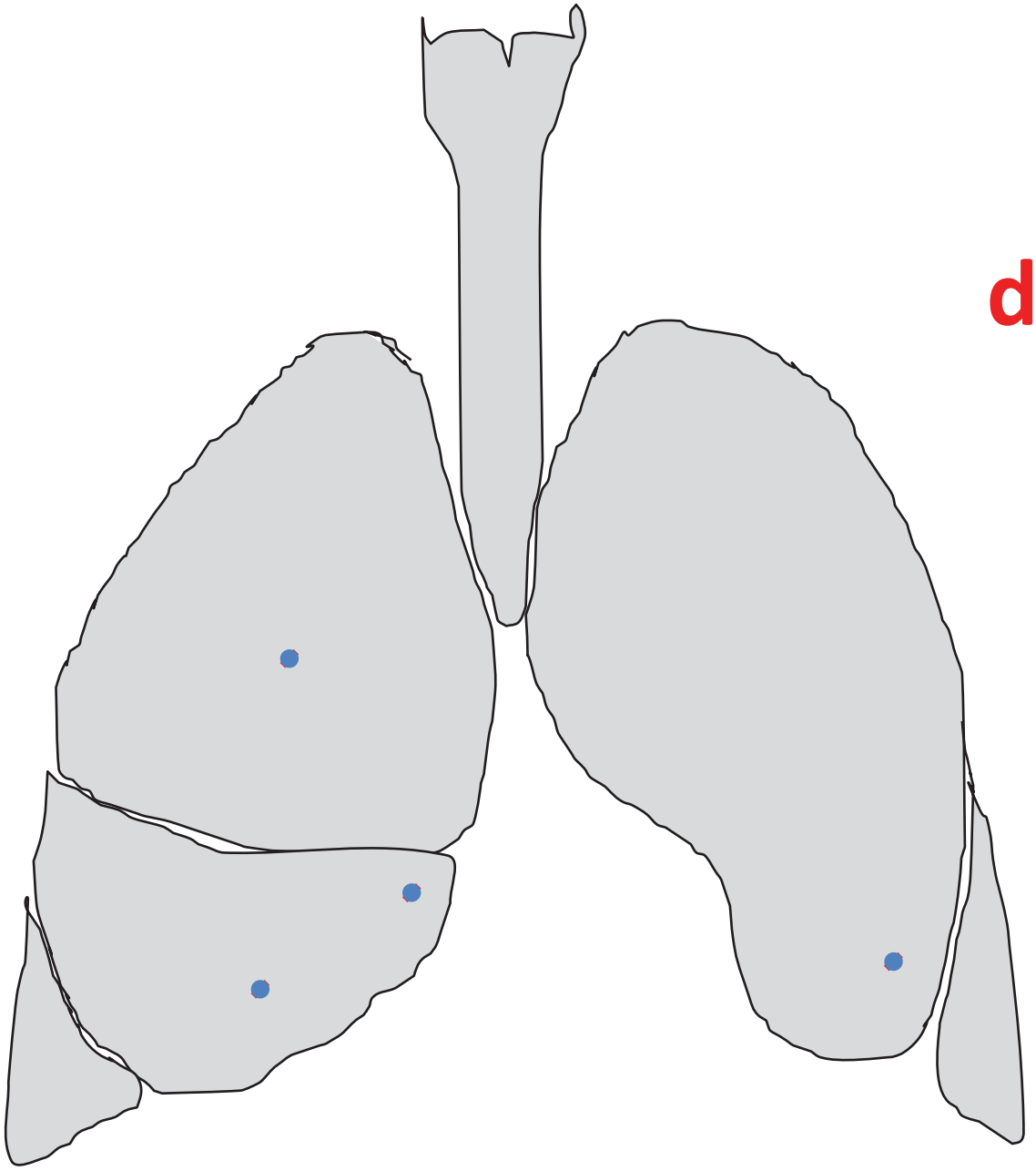

d15

Cardona PJ 2015

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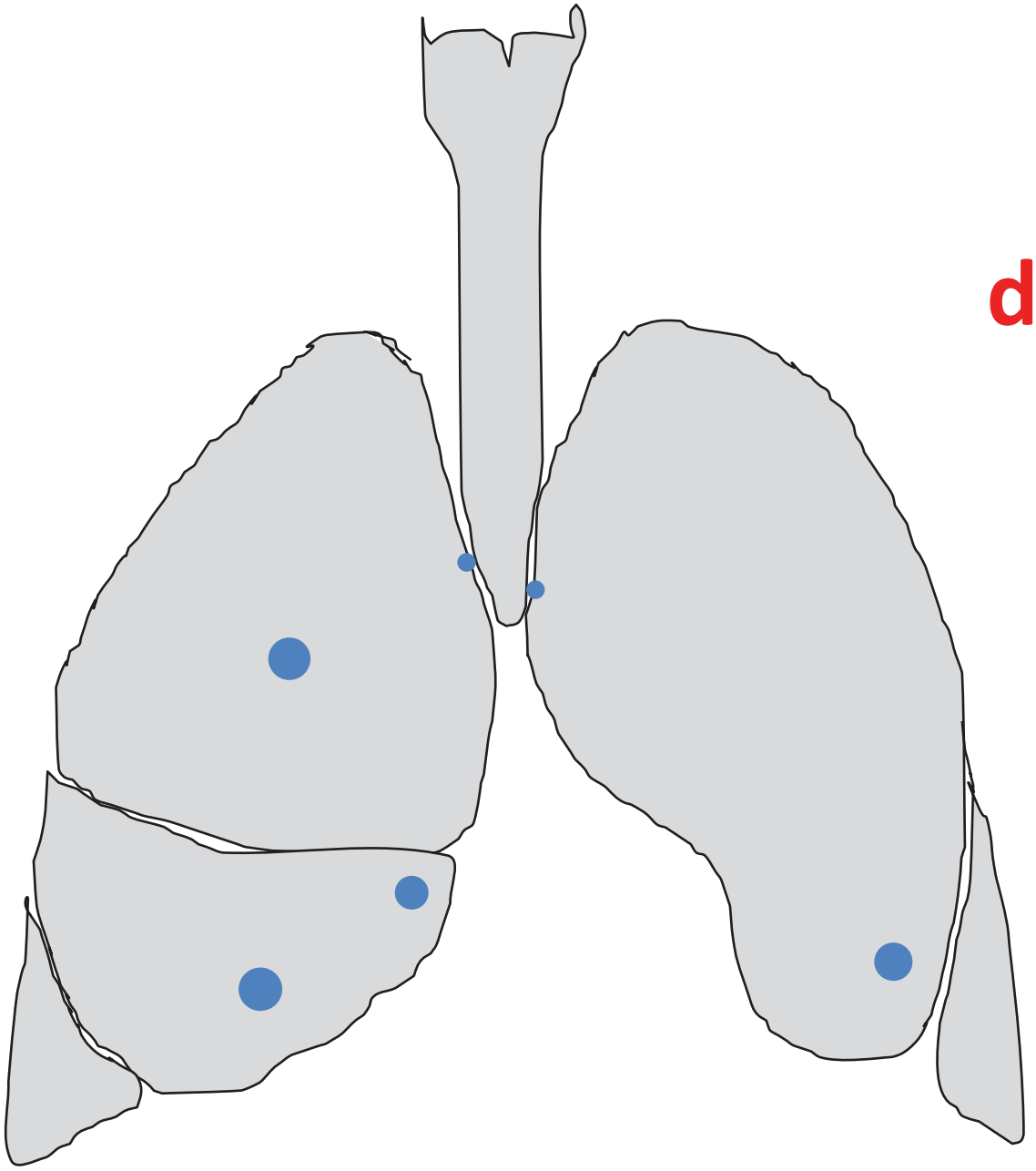
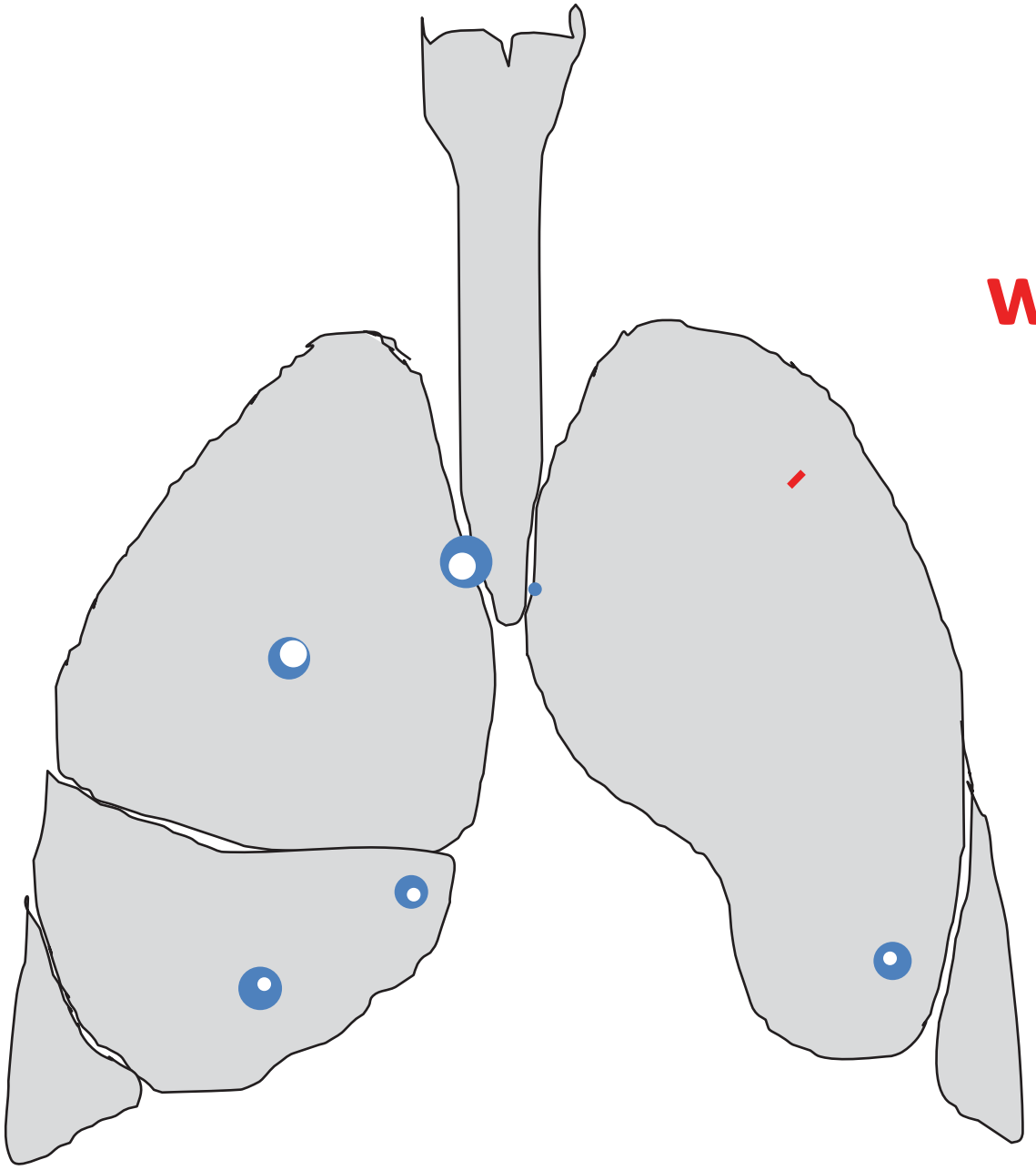


d21

Cardona PJ 2015

UTE



w6

Cardona PJ 2015

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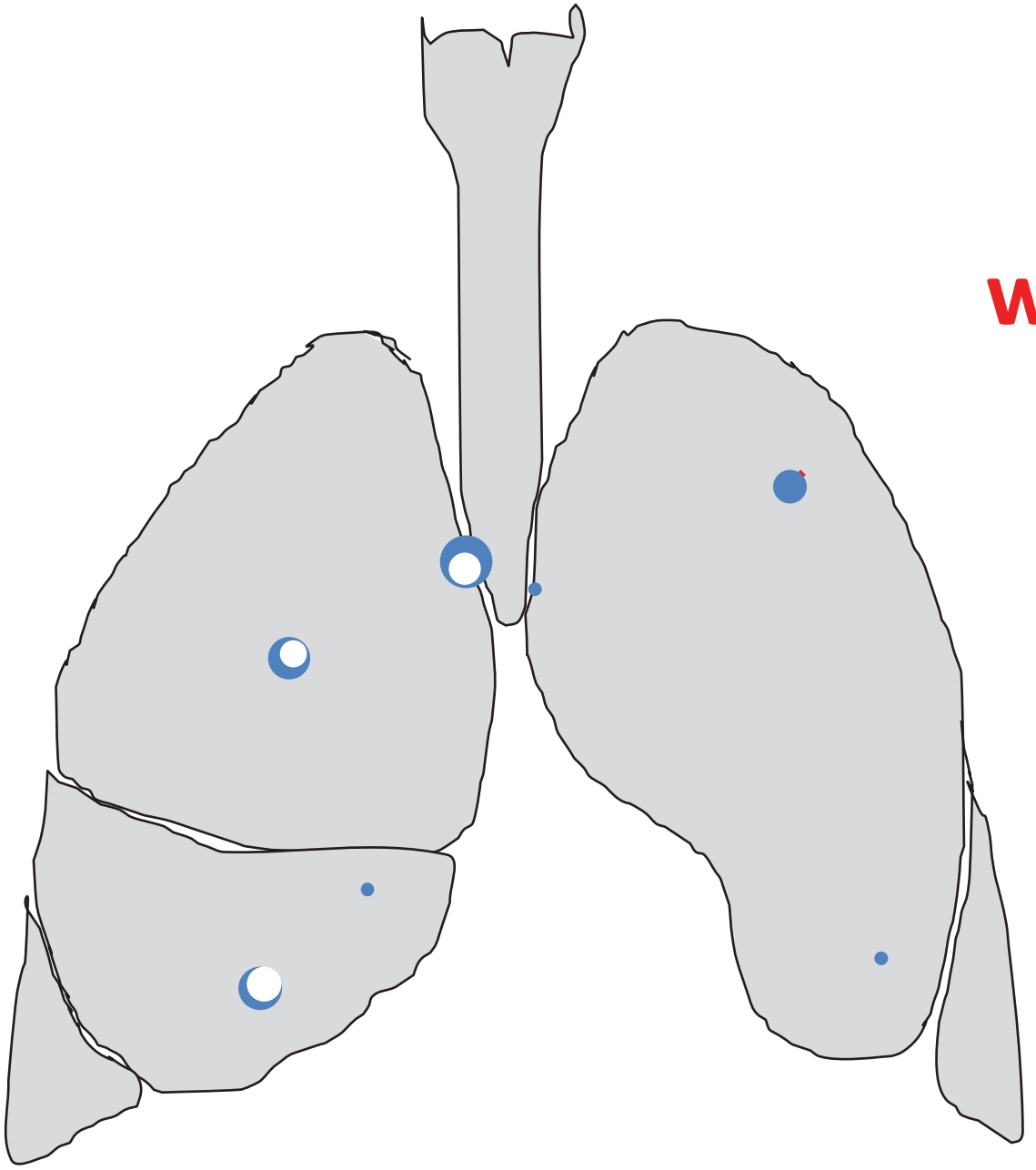

w8

Cardona PJ 2015

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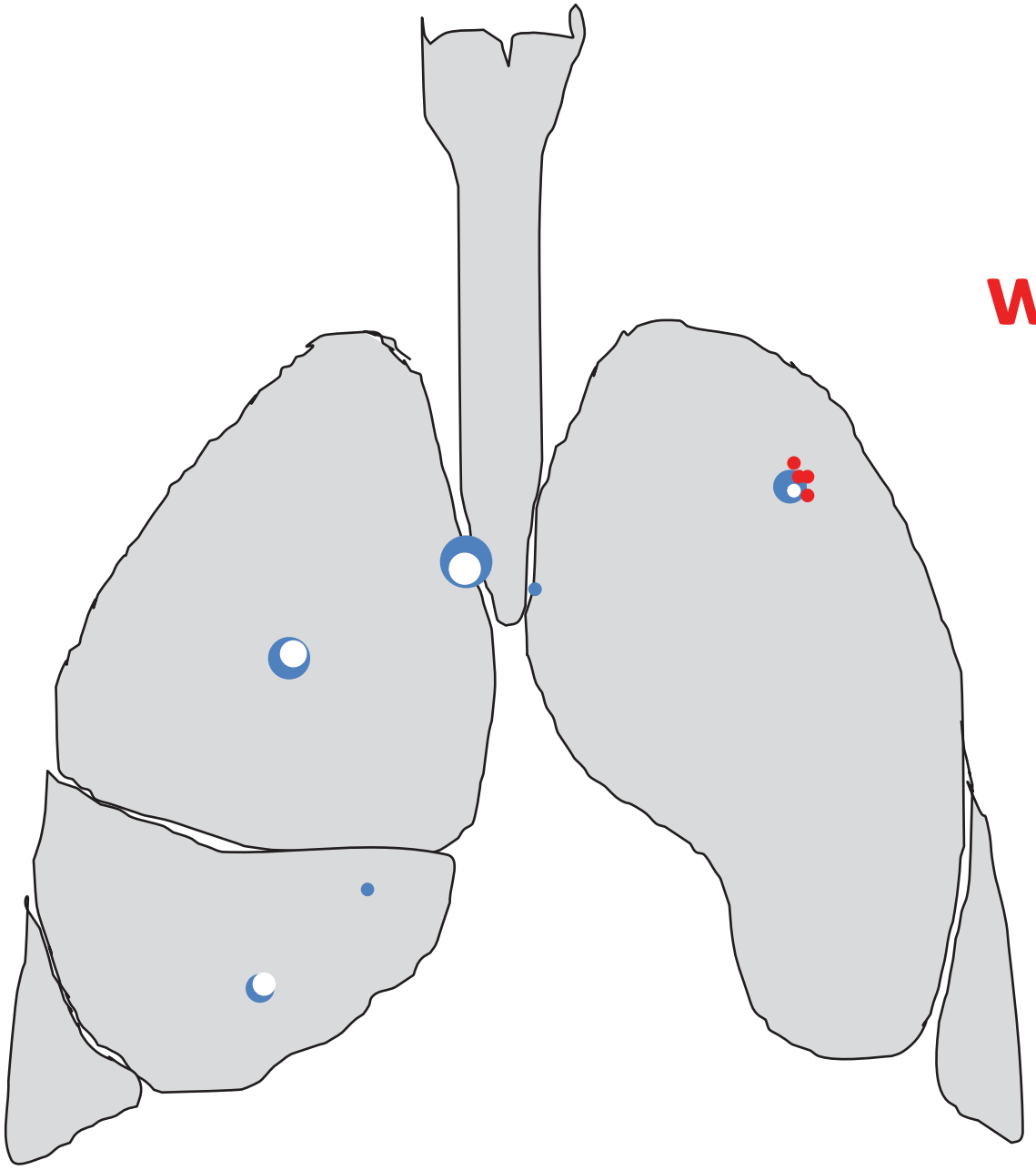

w10

Cardona PJ 2015

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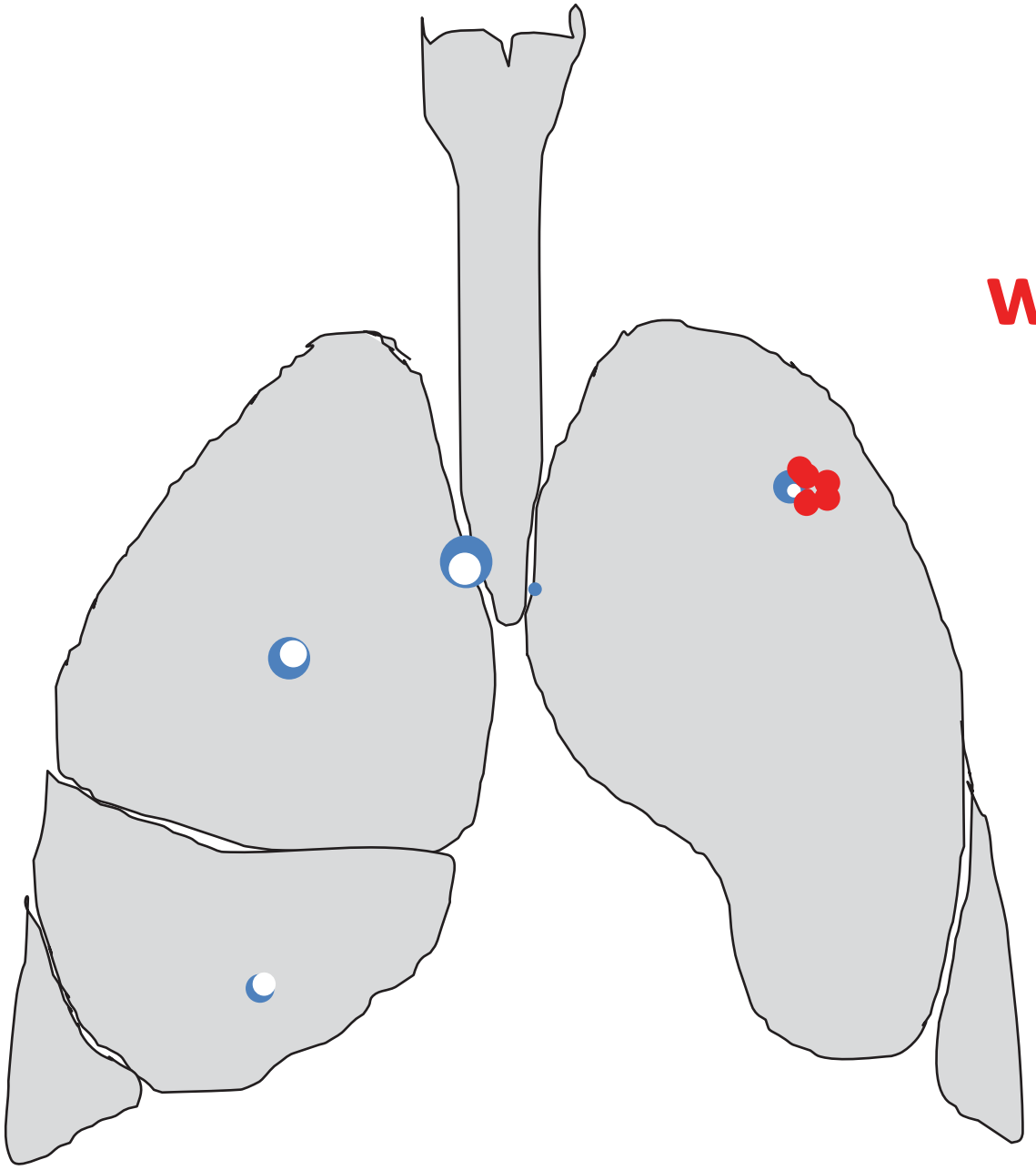
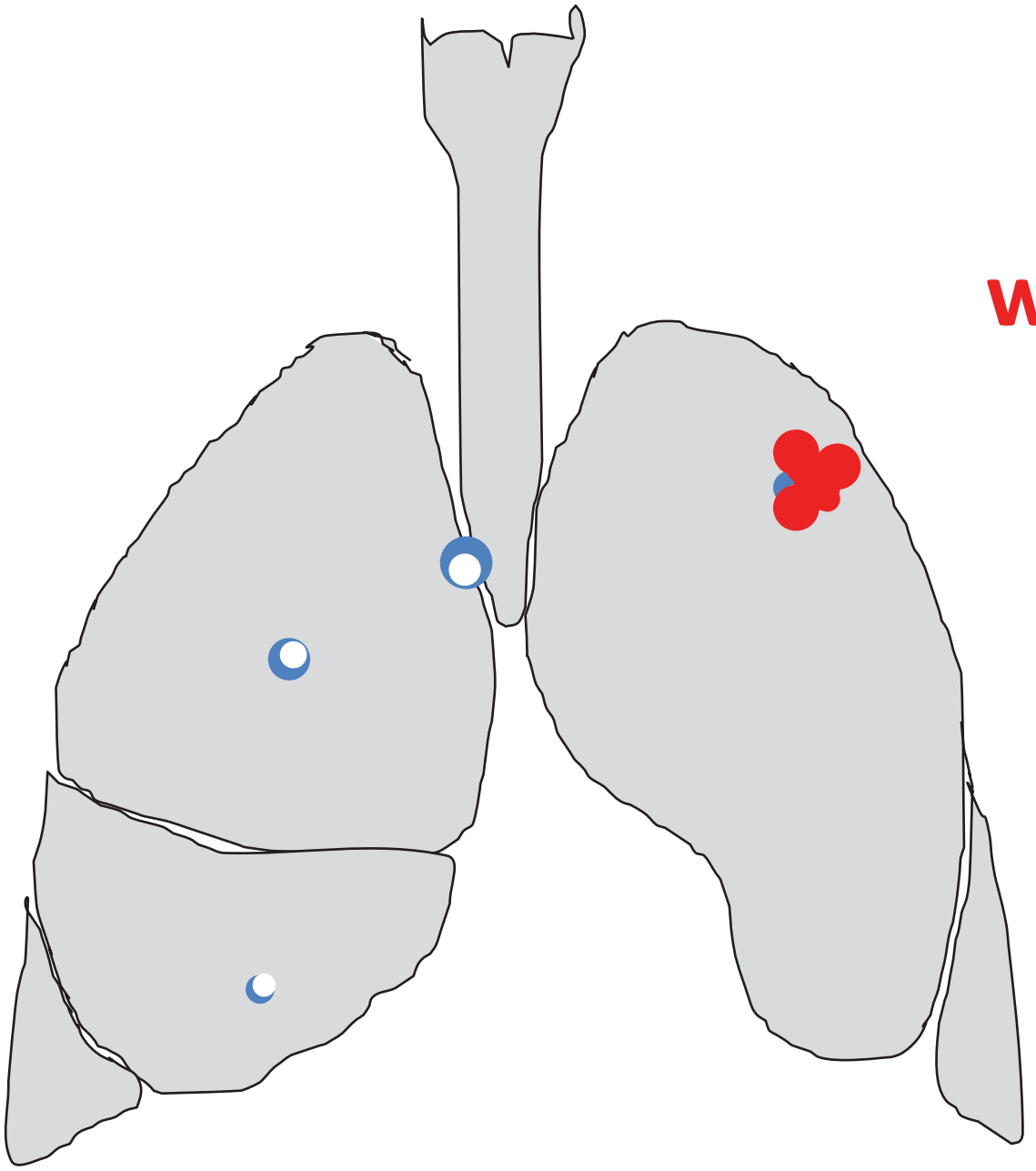


w11

Cardona PJ 2015

UTE



w12

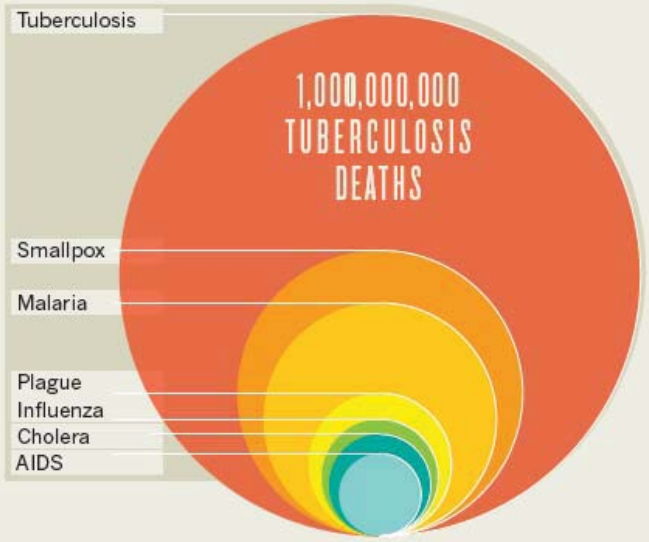
Cardona PJ 2015

A MORTAL FOE

Tuberculosis is one of the world's most lethal infectious diseases. Further progress in consigning it to the past is a massive challenge. By **Tom Paulson.**

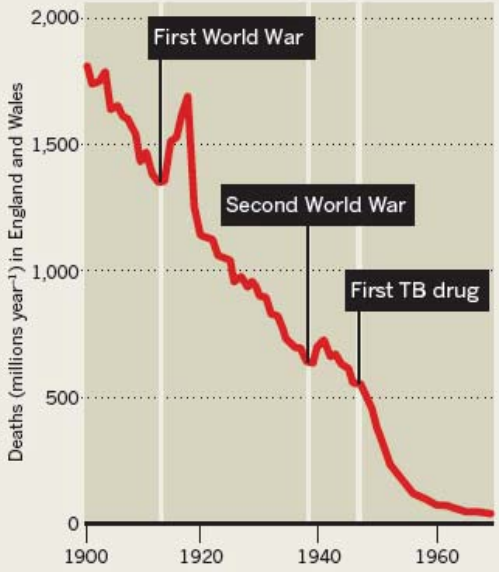
THE BIGGEST KILLER

Tuberculosis has killed more than any other infectious disease in history. Over a billion lives in the past two hundred years.



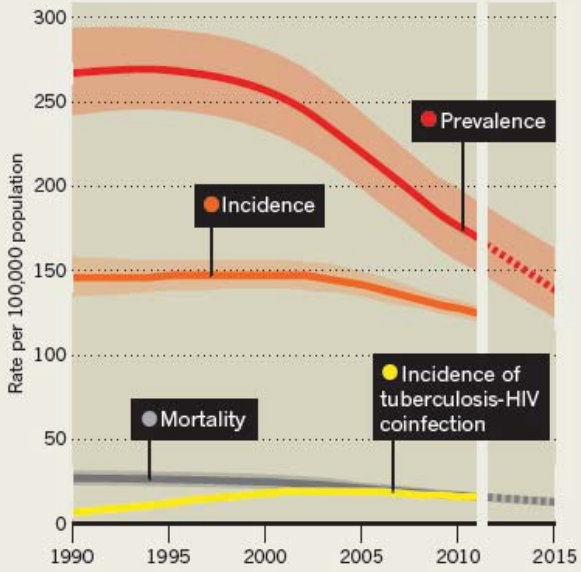
THE 100 YEARS BATTLE

Rising living standards in industrialized nations, interupted by two World wars, and new antibiotics had tuberculosis in decline.

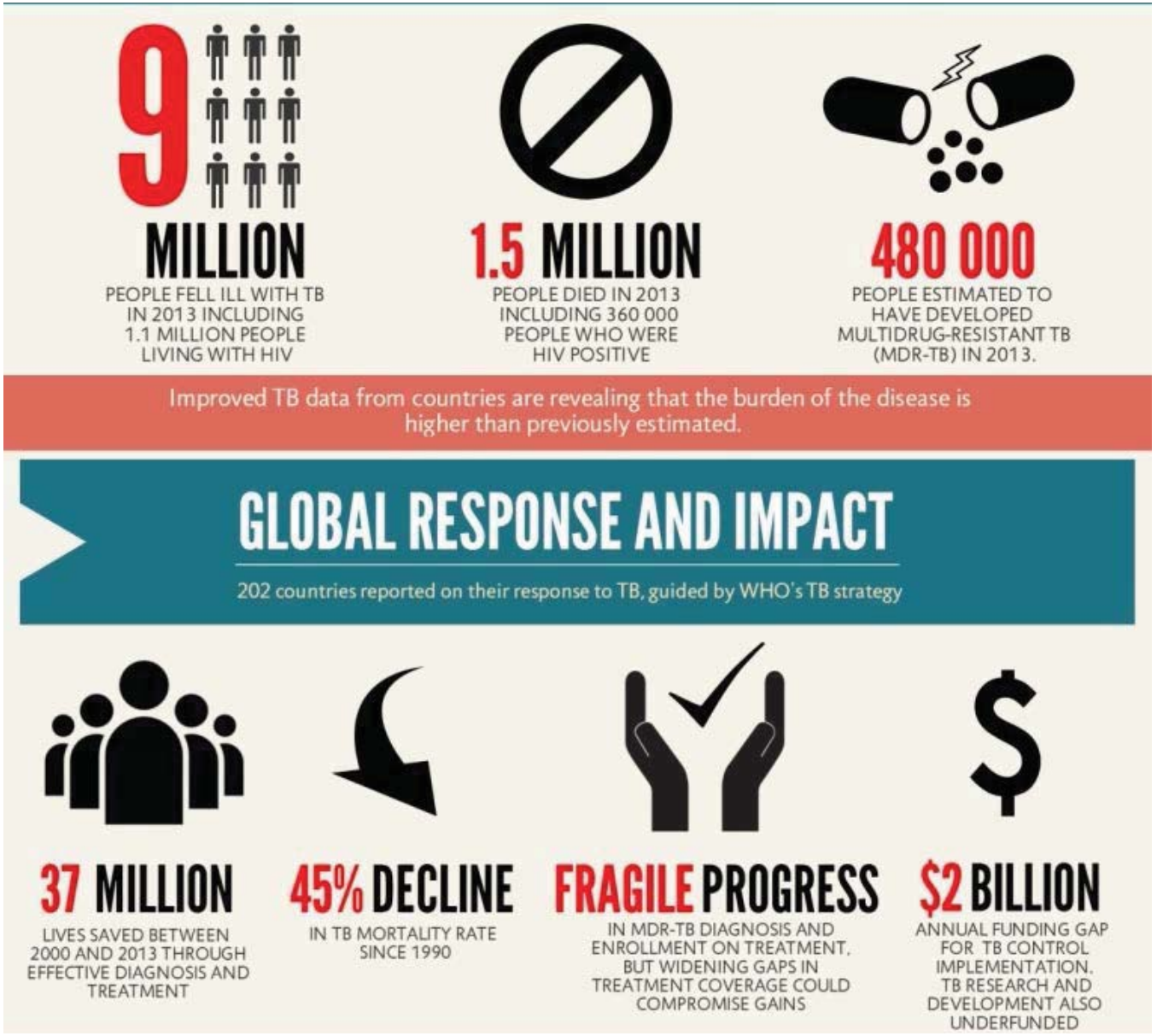


SLOW PROGRESS

Over the past fifteen years, an invigorated anti-TB effort has begun to reduce the global burden of disease worsened by HIV.



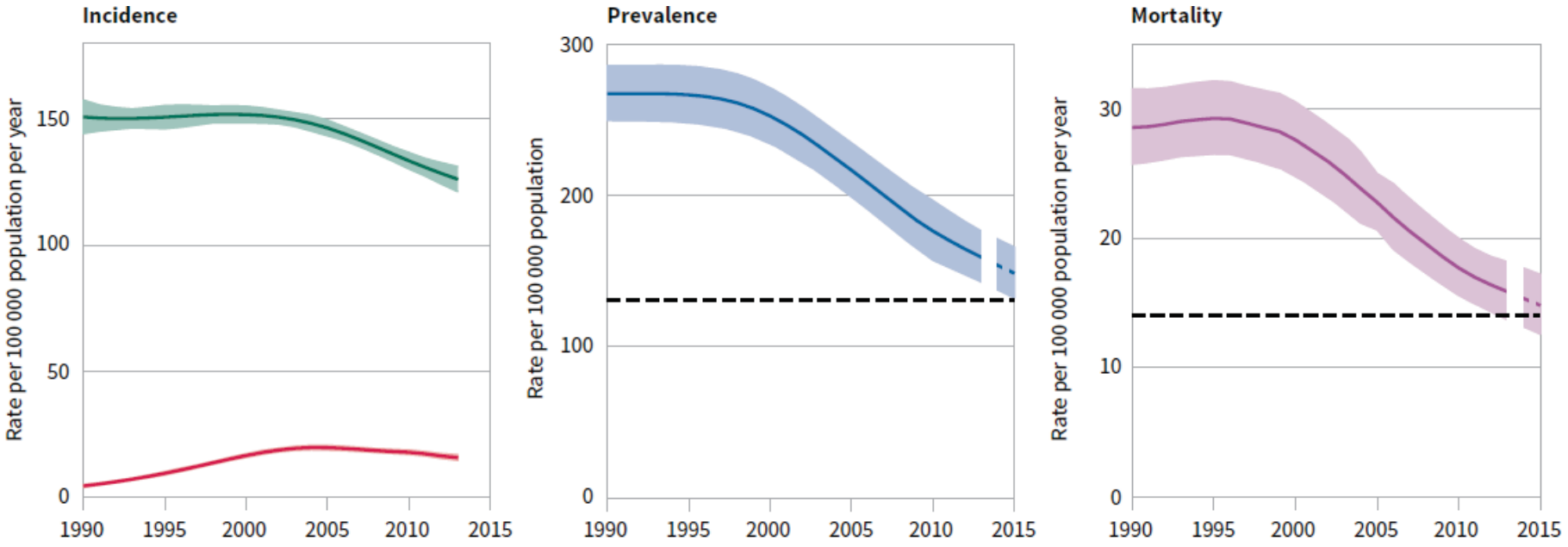
Tuberculosis is still a humankind threat



World Health Organization

WHO Report 2014

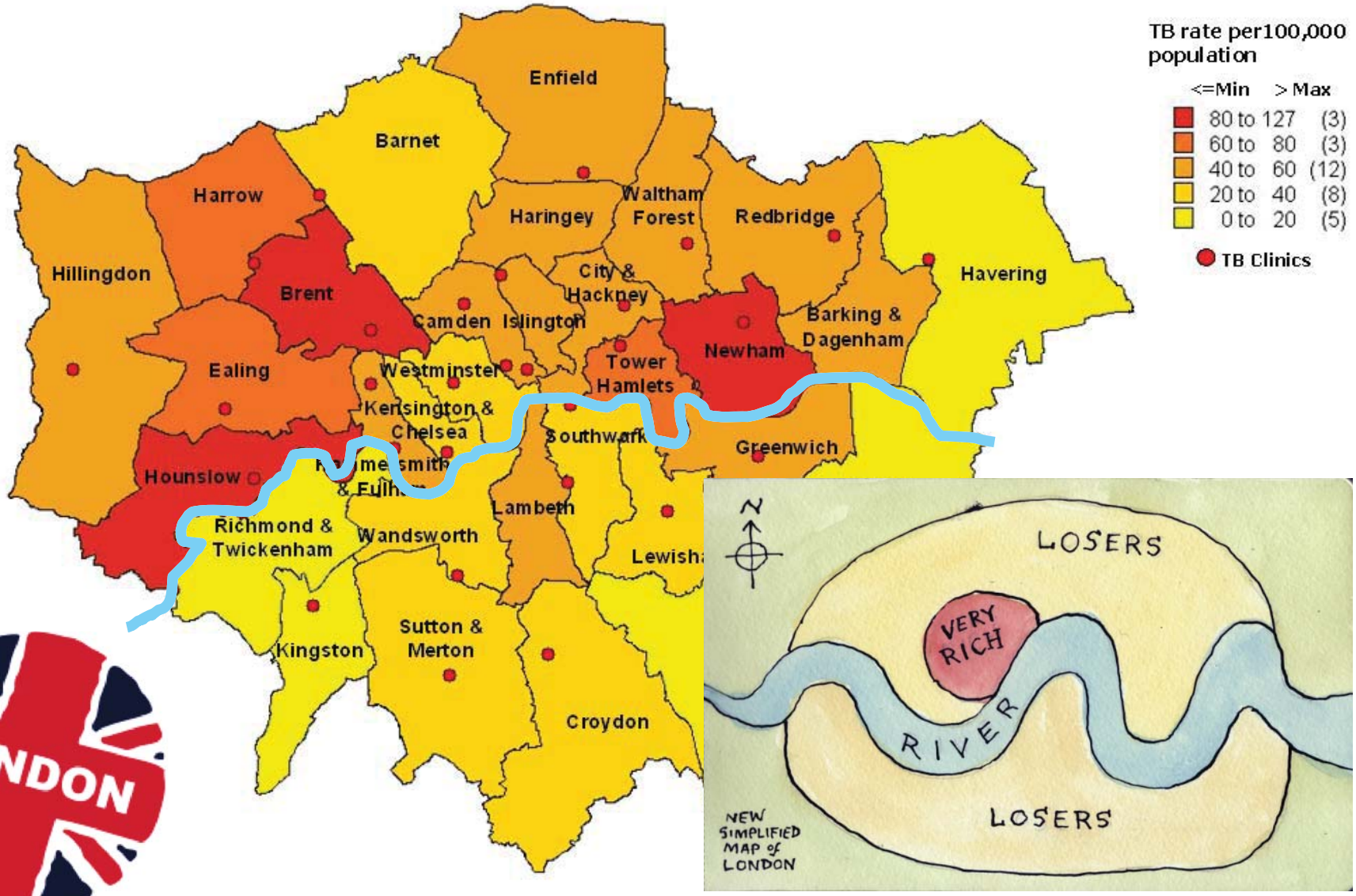
Tuberculosis is still a humankind threat



WHO Report 2014

22 countries have the 85% incidence

TB rate per 100,000 population, by PCT of residence, 2009



Tuberculosis Investigation Unit of Barcelona

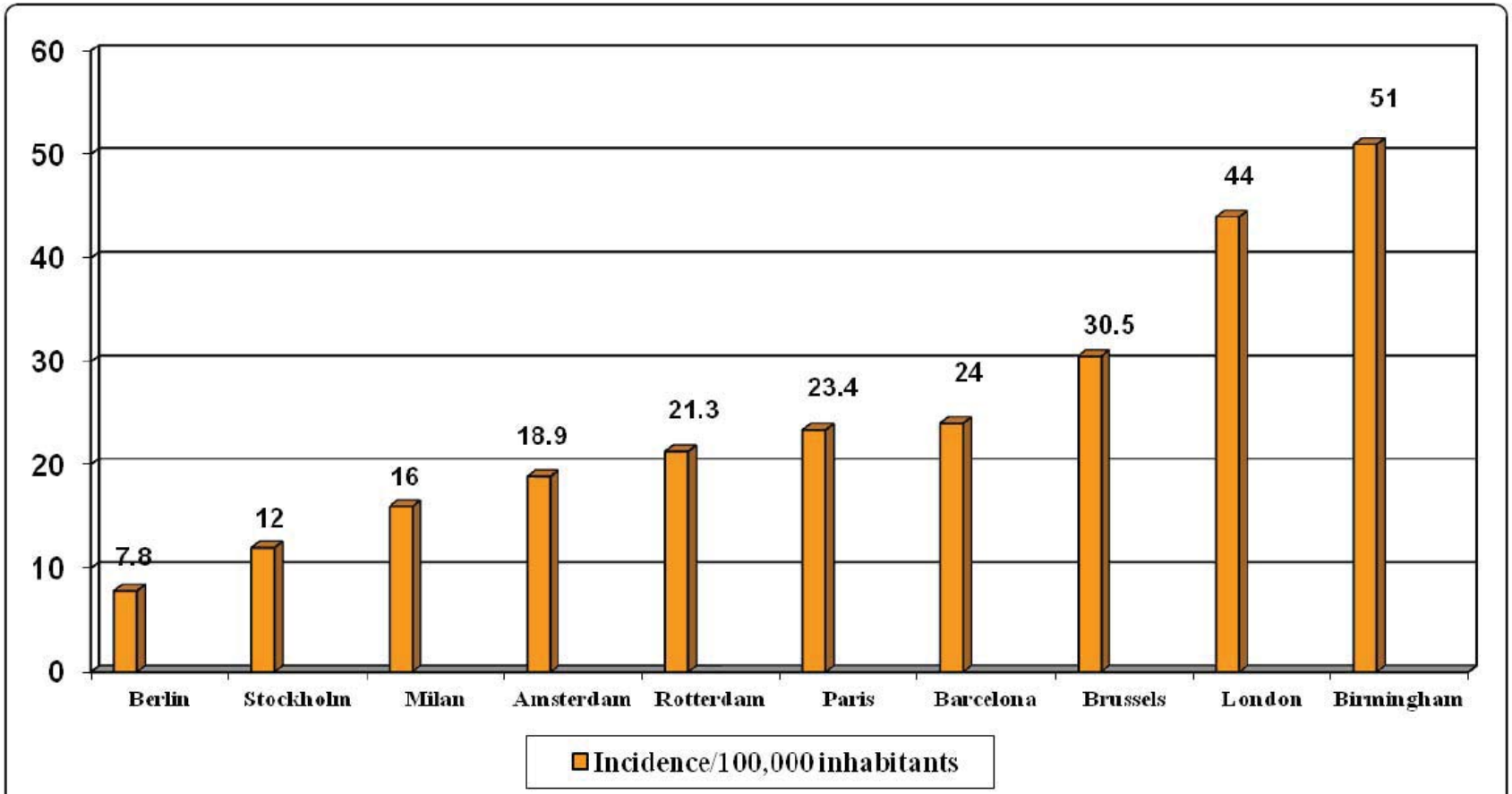


Figure 1 Incidence of tuberculosis in selected European Union cities, 2009. Incidence of this disease in cities of low-incidence European Union countries showing high level of incidence in several urban areas. Source: references [1-3].

Caylà&Orcau 2011

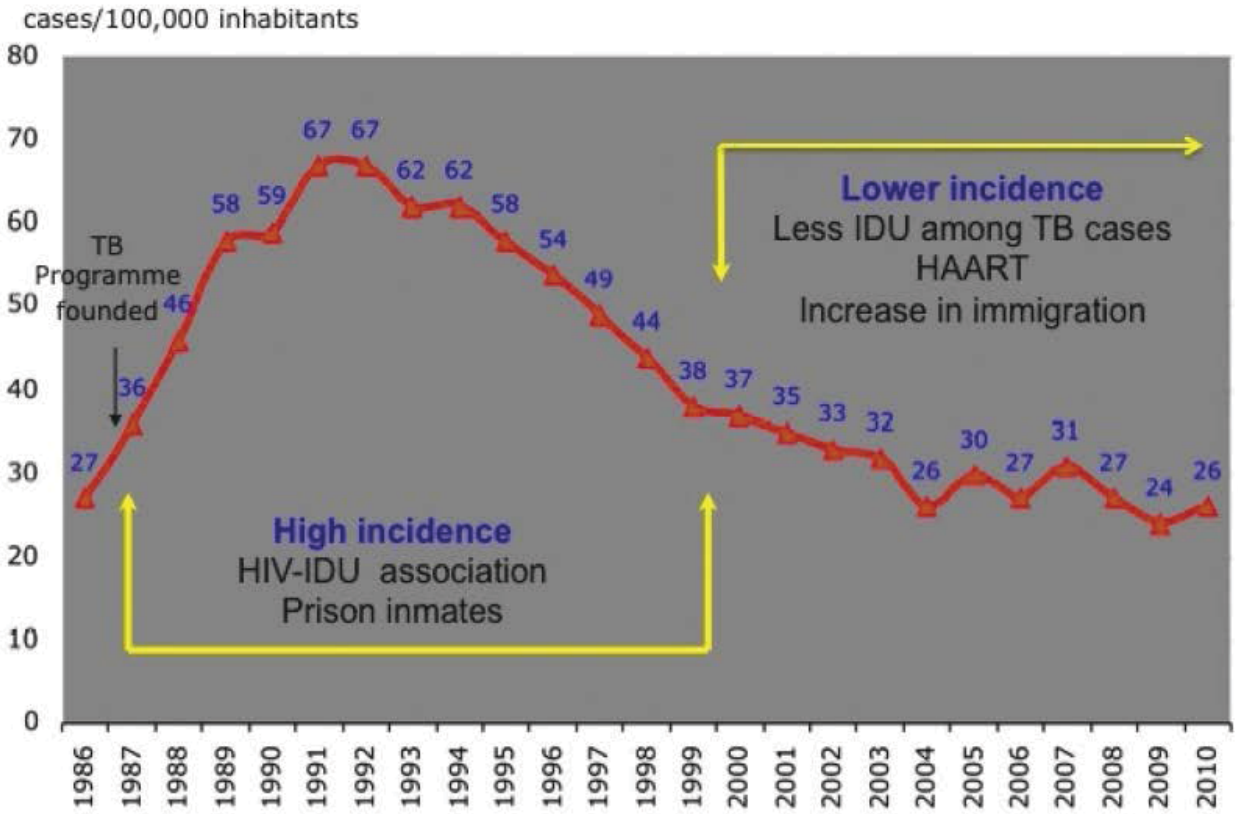
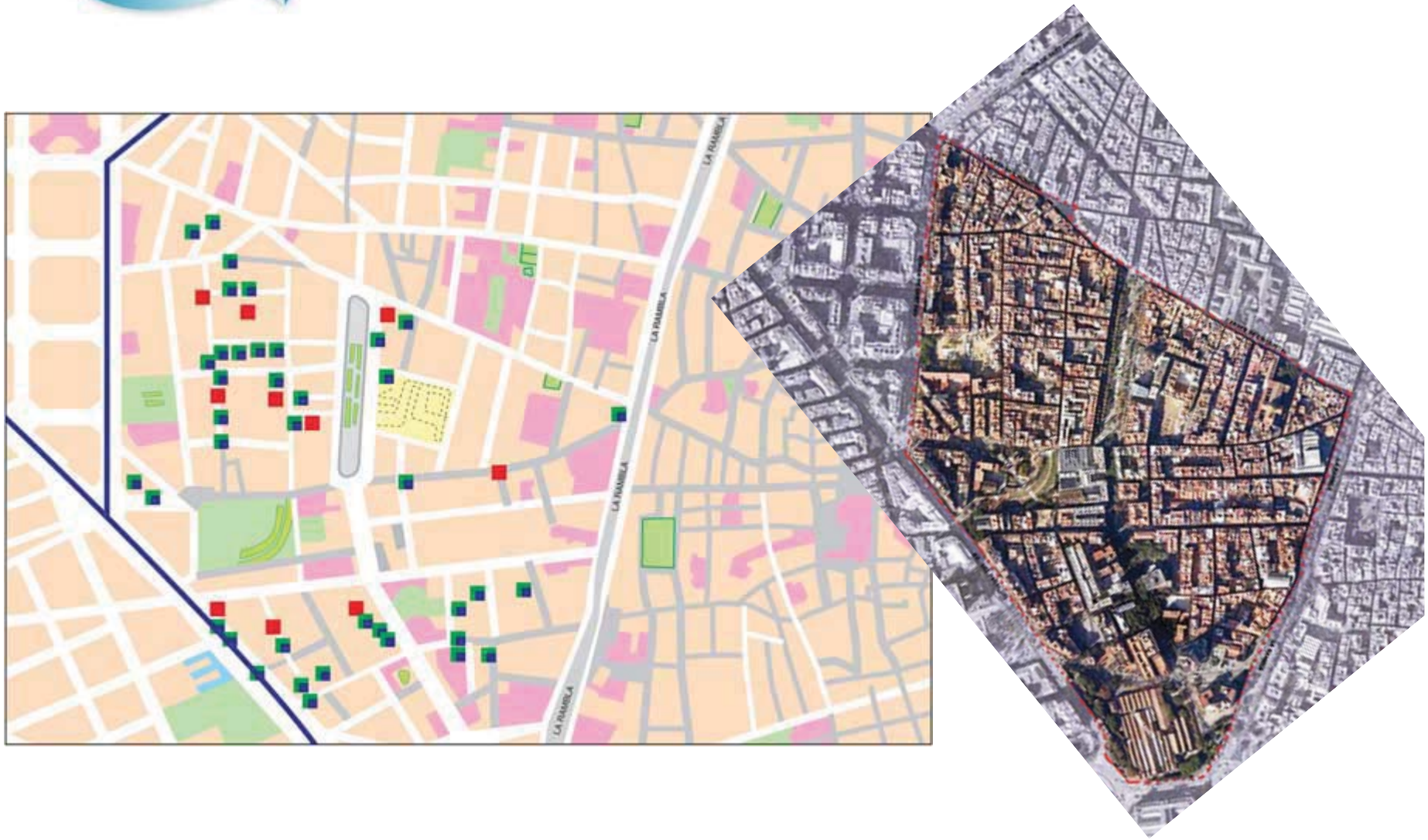


Figure 2 The evolution of tuberculosis in Barcelona, 1986-2010. The graph shows tuberculosis cases per 100, 000 inhabitants over time. During the 1990s a high incidence period was observed, mostly due to HIV-infected injecting drug users. With the implementation of control measures and the generalization of antiretroviral treatments, the annual decline was about 10%. This decline was attenuated during the low incidence period due to massive immigration from high burden countries. TB, tuberculosis; IDU, injecting drug users; HAART, highly active antiretroviral therapy.

uitb

Tuberculosis Investigation Unit of Barcelona




IGTP
Fundació Institut d'Investigació en Ciències de la Salut Germans Trias i Pujol
UTE

IGTP

Germans Trias i Pujol
Hospital

FUNDACIÓ
JOSEP CARRERAS
Contra la leucèmia

UAB
Universitat Autònoma de Barcelona

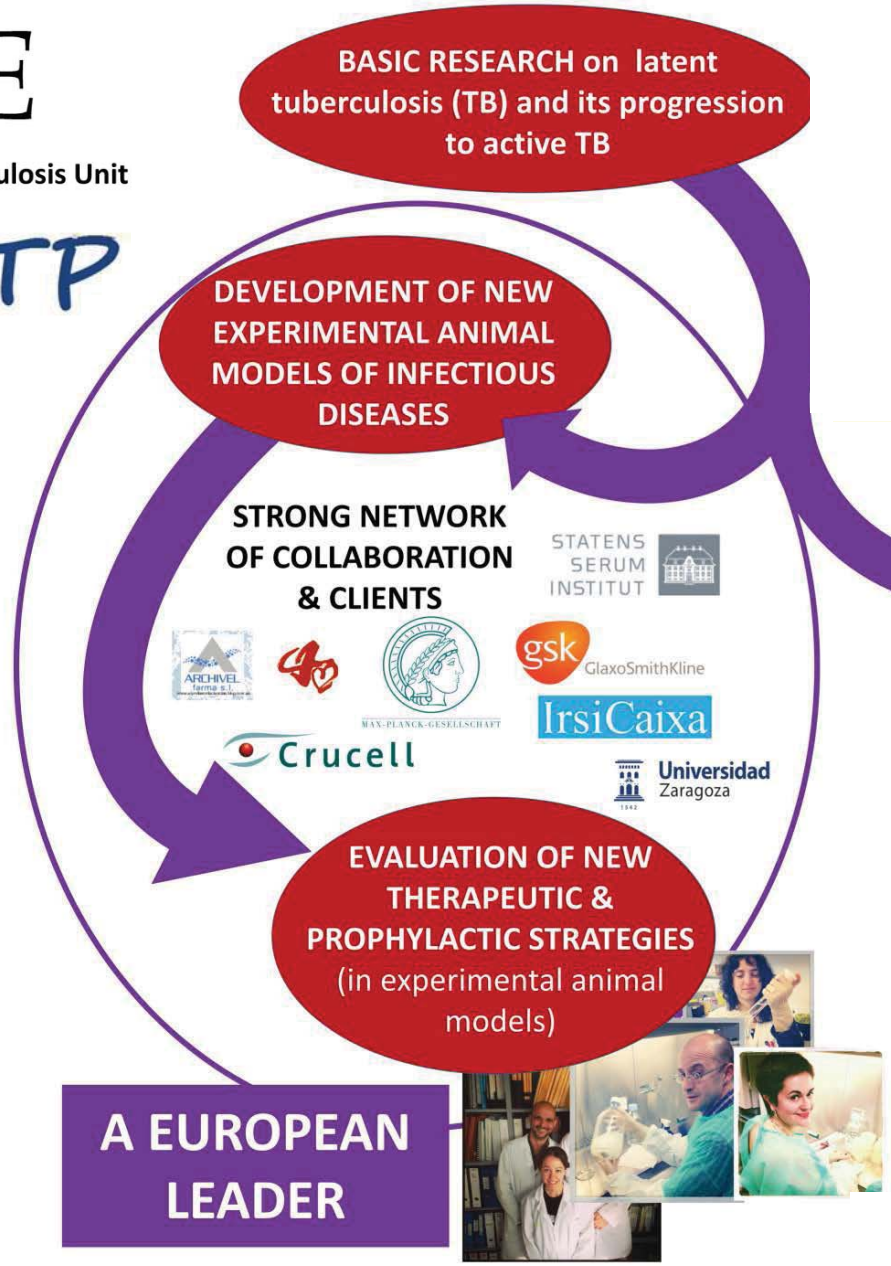
IrsiCaixa

IMPPC
Institut de Medicina Predictiva
i Personalitzada del Càncer

UTE

Experimental Tuberculosis Unit

IGTP



IN THE LAST 5 YEARS:

33 publications

6 competitive projects

collaboration contracts

DEVELOPMENT OF NEW THERAPEUTIC & PROPHYLACTIC STRATEGIES

SPIN-OFF

to develop a probiotic for TB which will be in the market in 2016

MANREMYC

http://unitatdetuberculosiexperimental.wordpress.com/

Aknowledgements

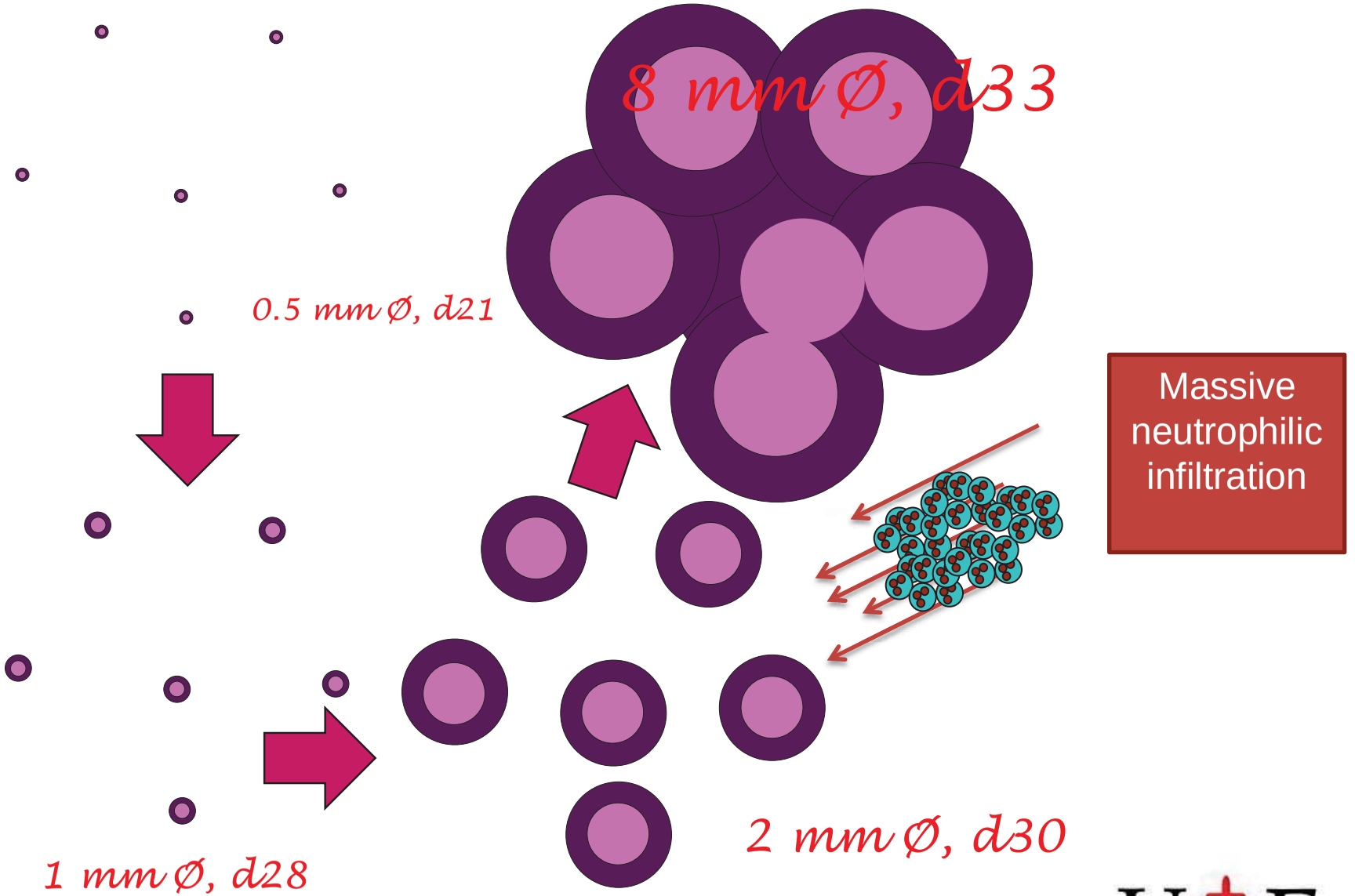
Generalitat de Catalunya
Departament de Salut

TBVI
TuBerculosis Vaccine Initiative

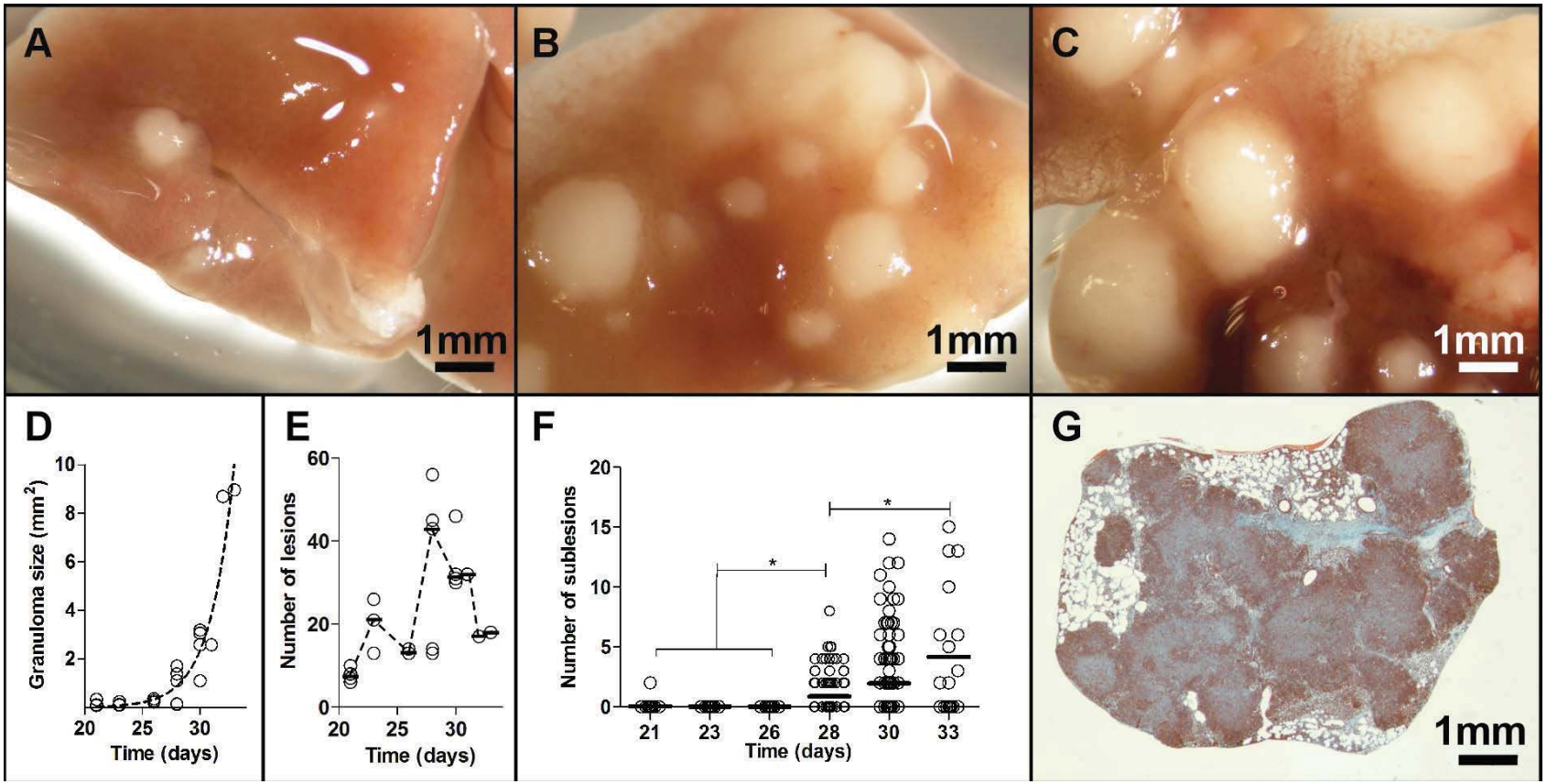
Instituto de Salud Carlos III

ciber

HORIZON 2020
THE FRAMEWORK PROGRAMME FOR RESEARCH AND INNOVATION


8 mm Ø, d33
0.5 mm Ø, d21
Massive neutrophilic infiltration
2 mm Ø, d30
1 mm Ø, d28

Exaggerated inflammation is clue for understanding the progression from infection to active TB

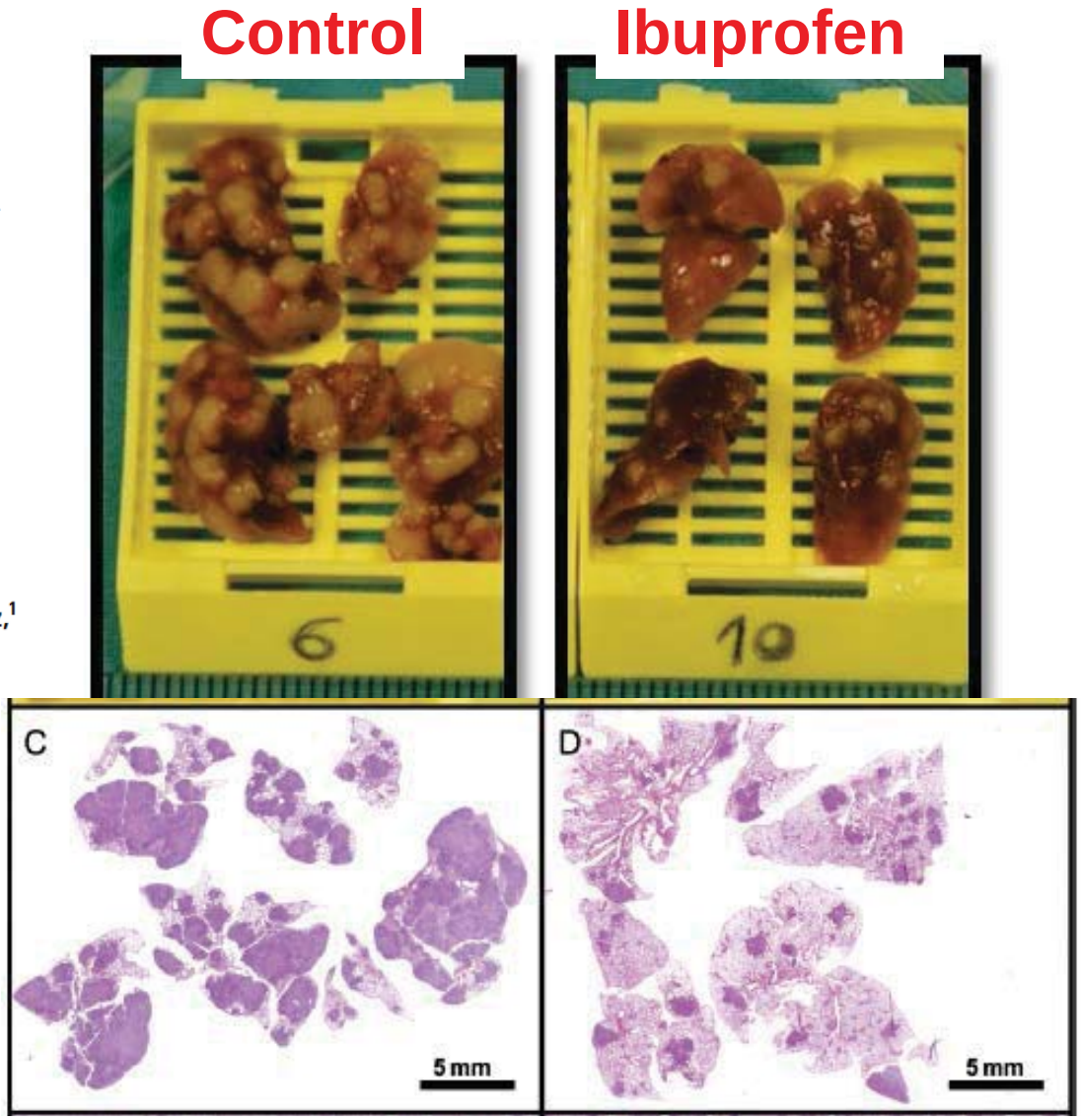


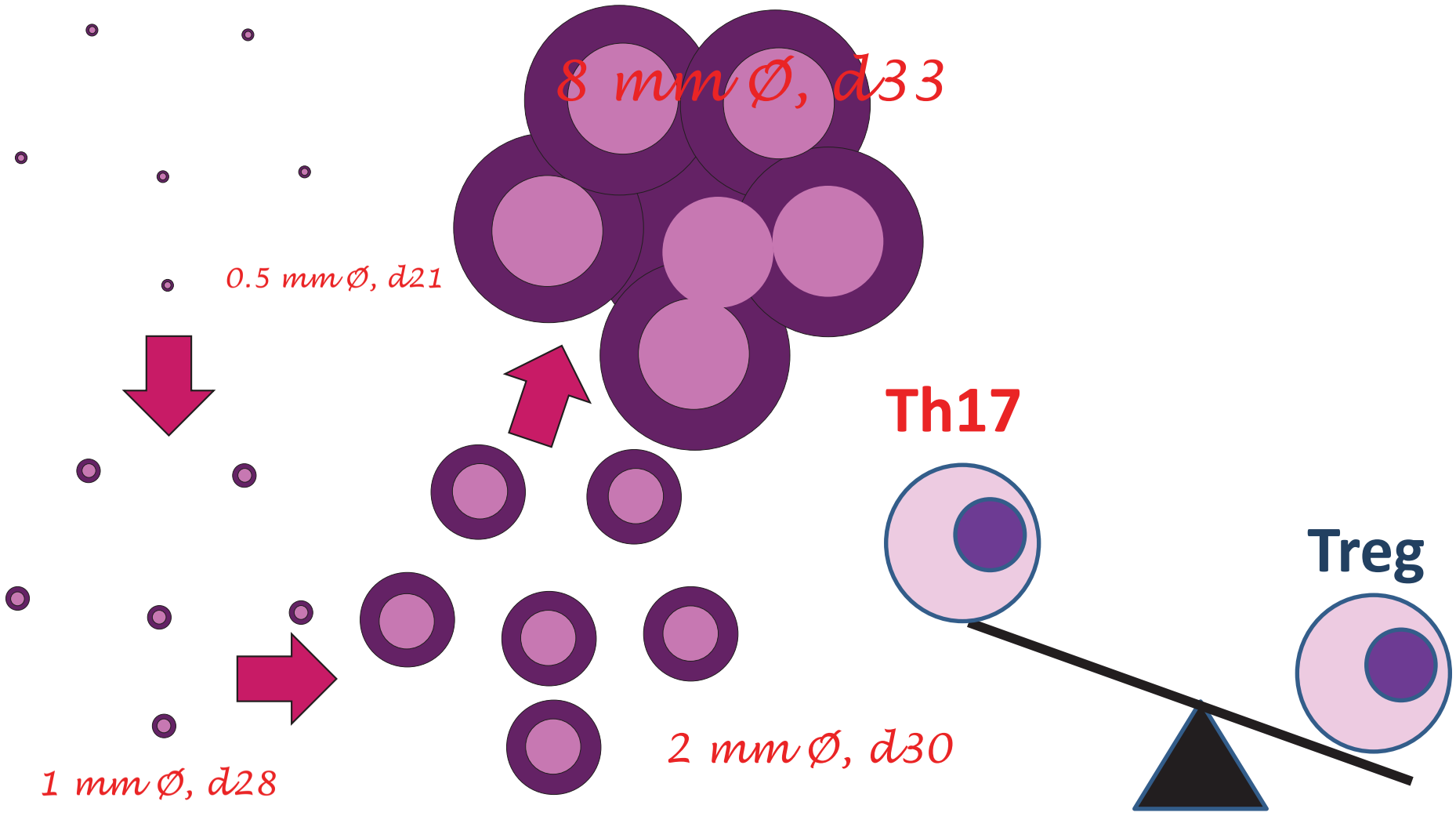
Marzo et al, Tuberculosis 2013; http://dx.doi.org/10.1016/j.tube.2013.09.004

The Journal of Infectious Diseases 2013;208:199–202

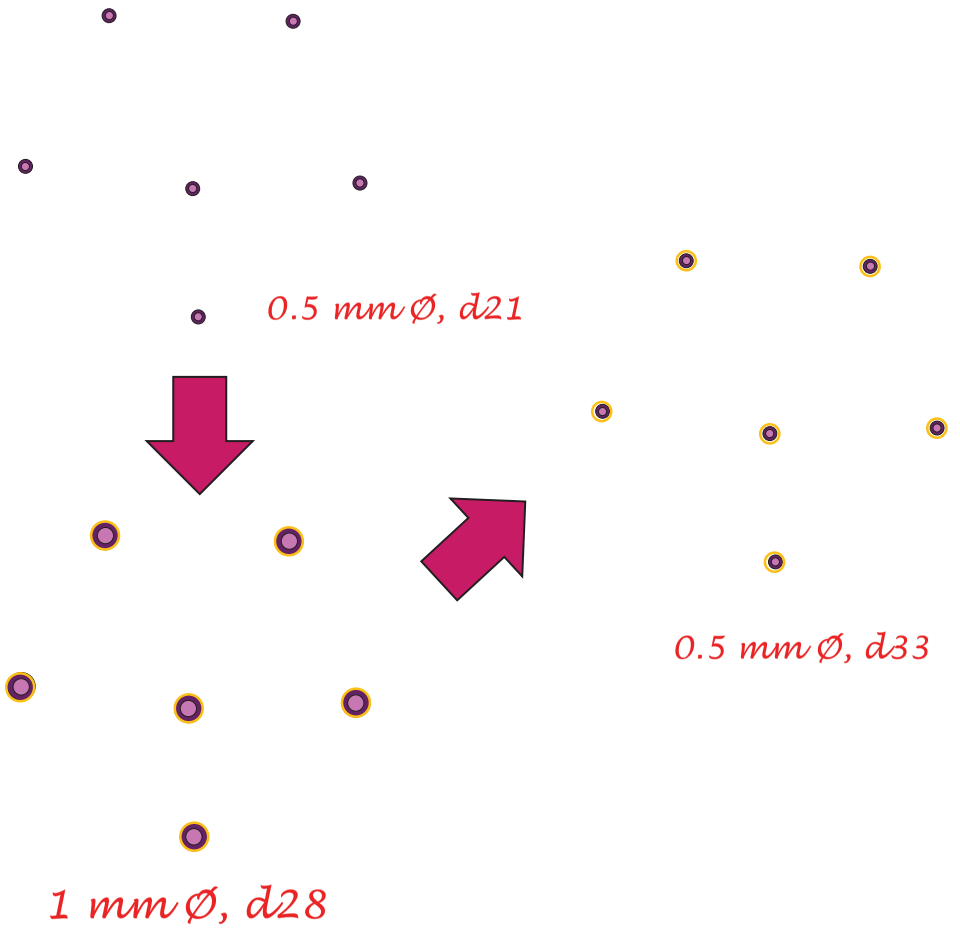
Ibuprofen Therapy Resulted in Significantly Decreased Tissue Bacillary Loads and Increased Survival in a New Murine Experimental Model of Active Tuberculosis

Cristina Vilaplana,[1] Elena Marzo,[1] Gustavo Tapia,[2] Jorge Diaz,[1] Vanesa Garcia,[1] and Pere-Joan Cardona[1]

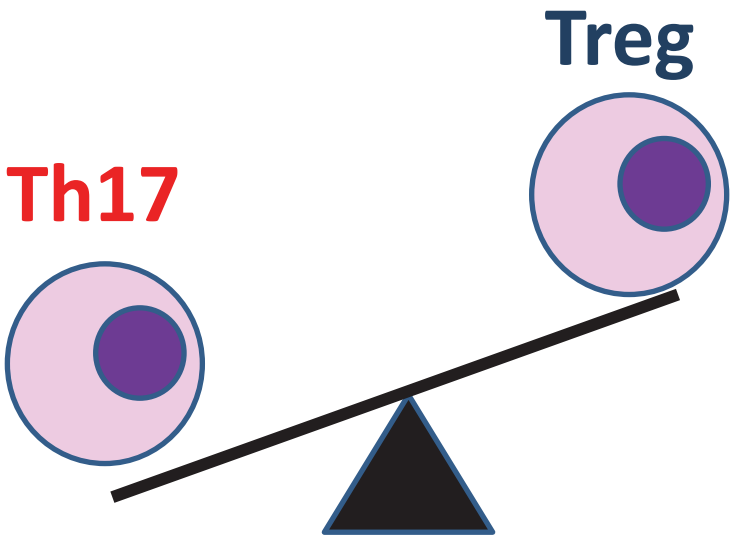




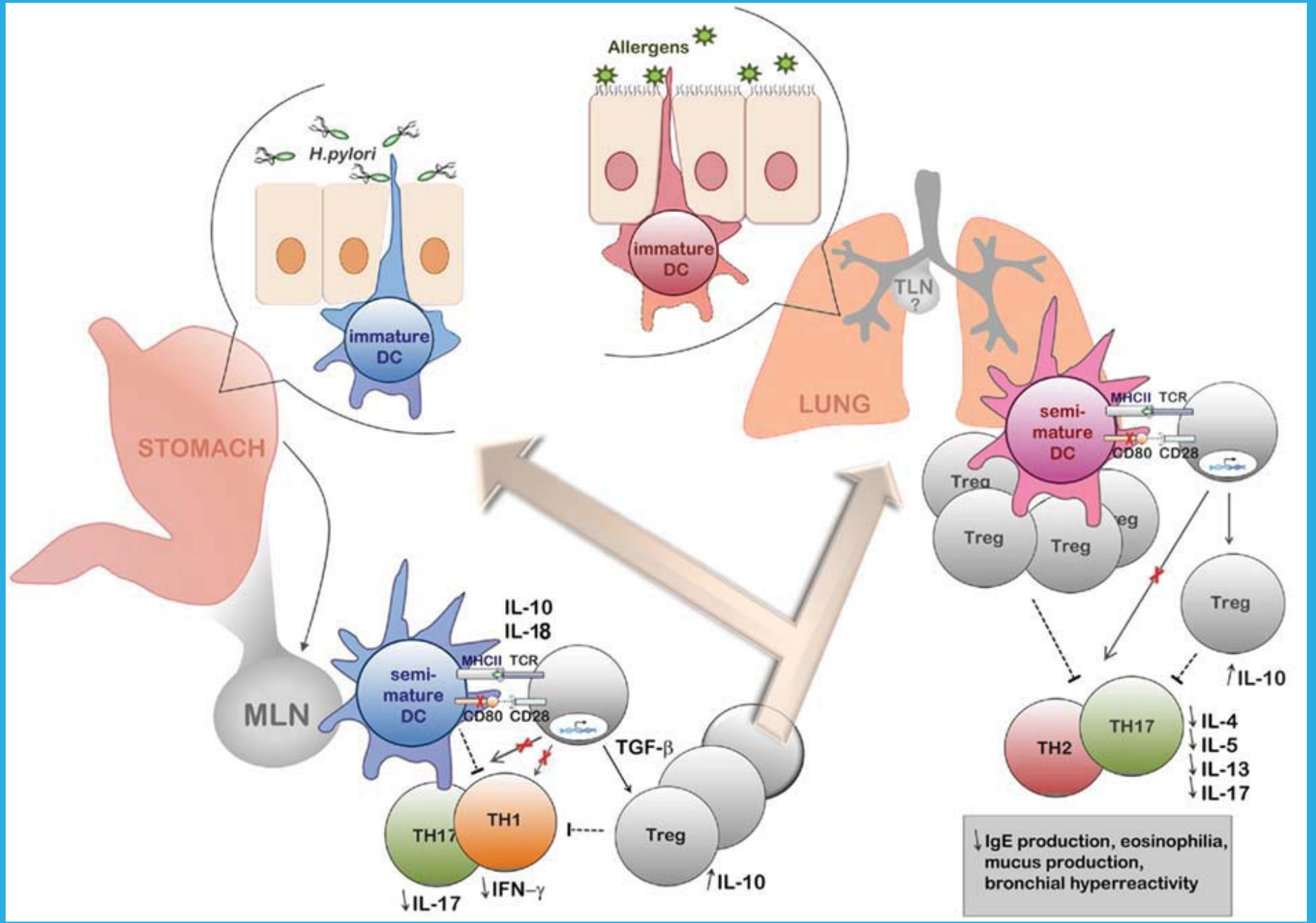
Unbalanced immune response causes TB



Encapsulation

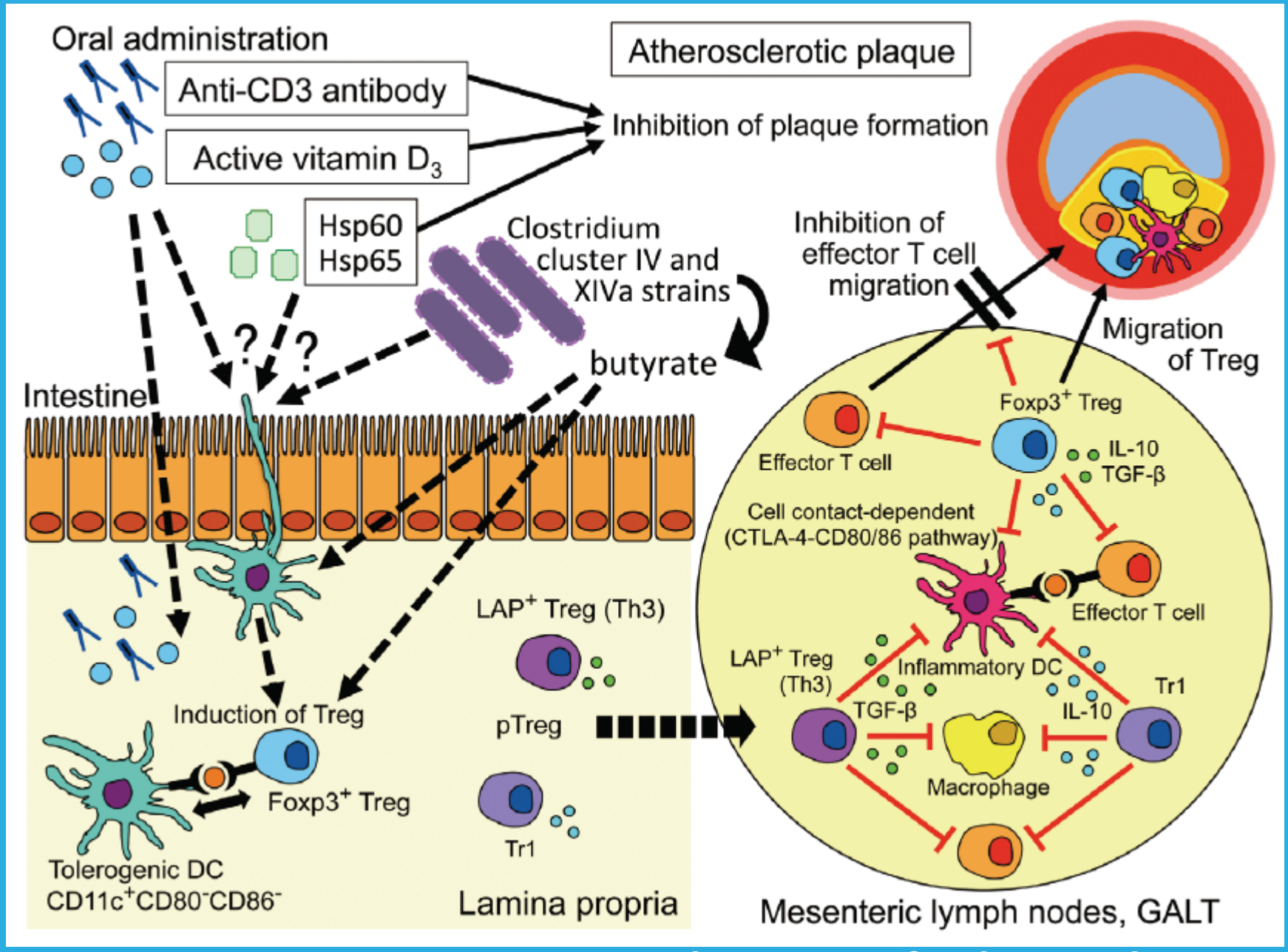


Treg induction can balance it and reduce TB risk



Arnold et al 2012

Connection GI – Lung, *H. pylori*



Yamashita et al 2015

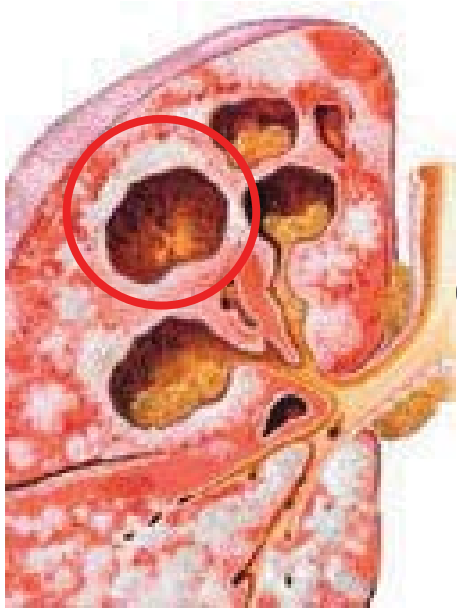
The case of atherosclerosis

Technology definition

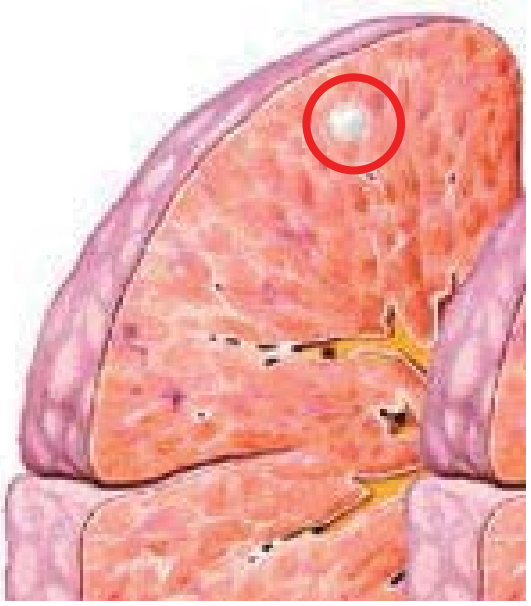
Administration of heat-killed *M.manresensis* inactivat avoids the excesive inflammatory response that causes TB.

14 days of treatment reduces the risk for 1 year.

CONTROL

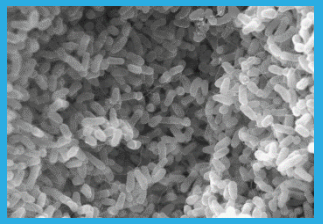


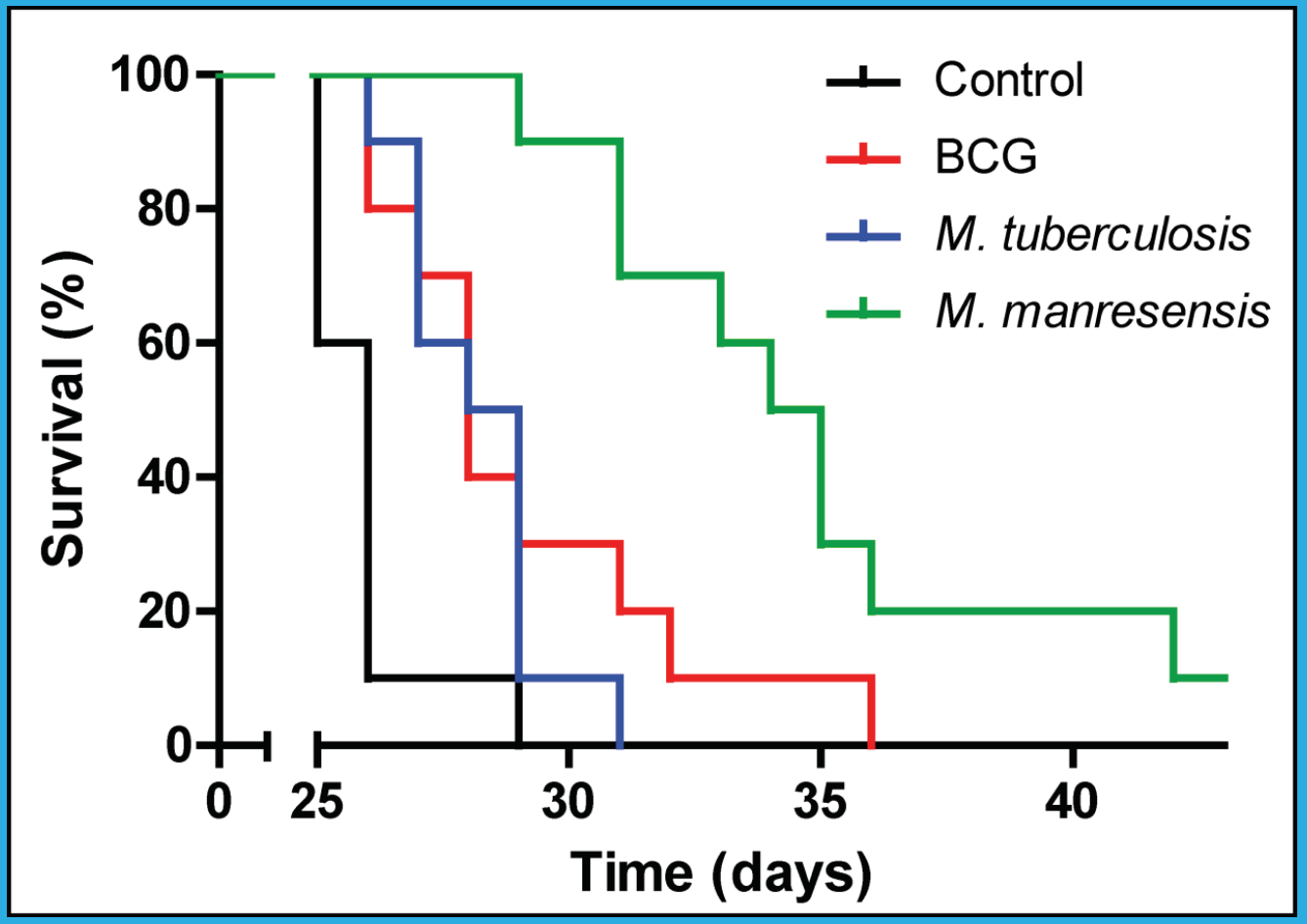
+ Nyaditum resae®



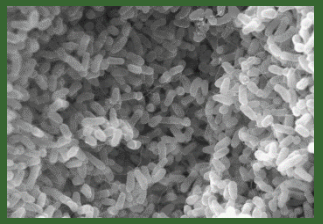
Protected technology (PCT/ES2013/000145).

Heat-killed mycobacteria stops progression towards active TB

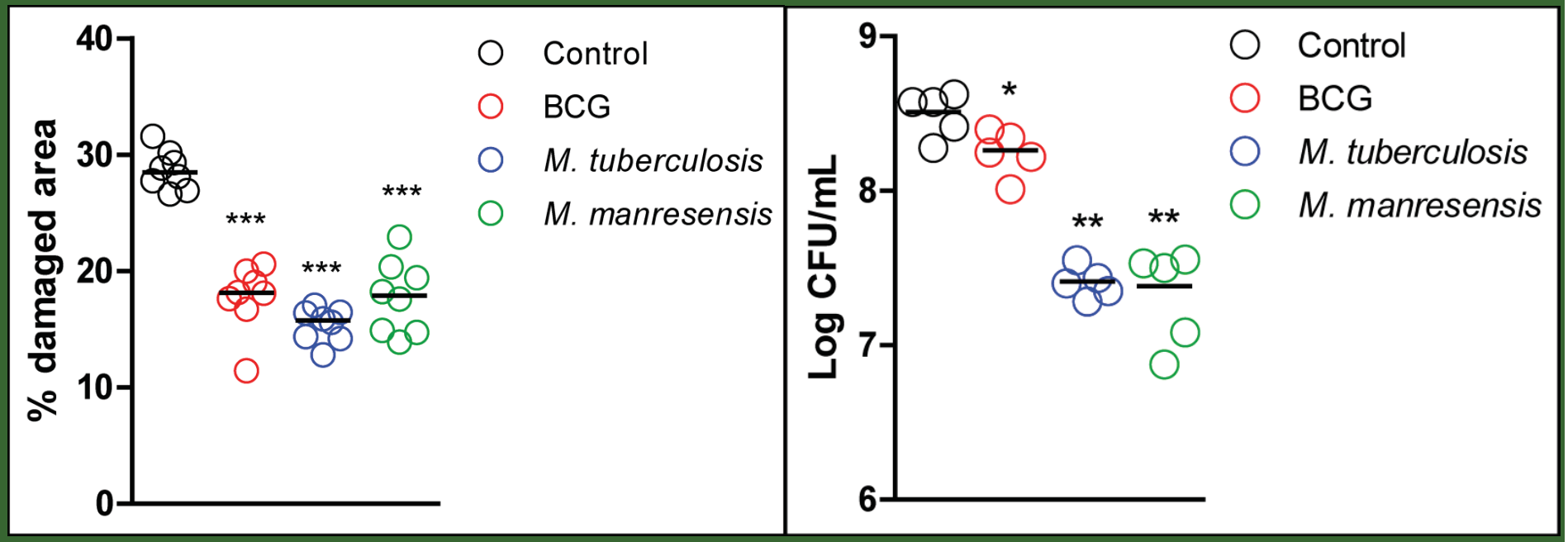




Cardona P et al submitted

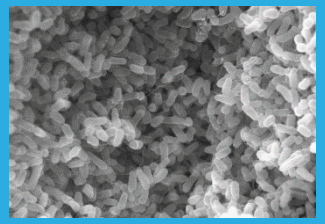


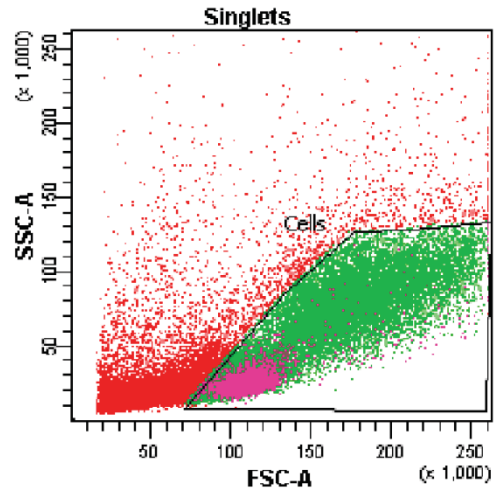
Heat-killed mycobacteria stops progression towards active TB

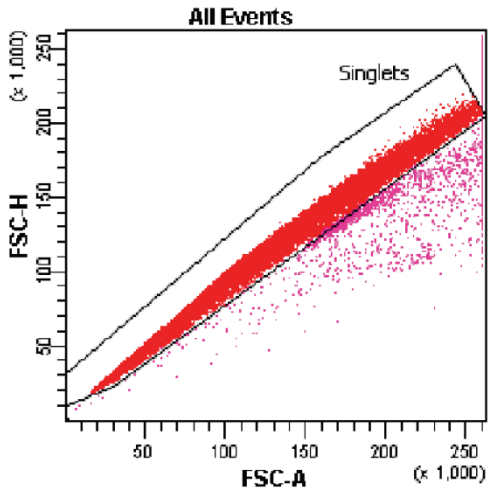


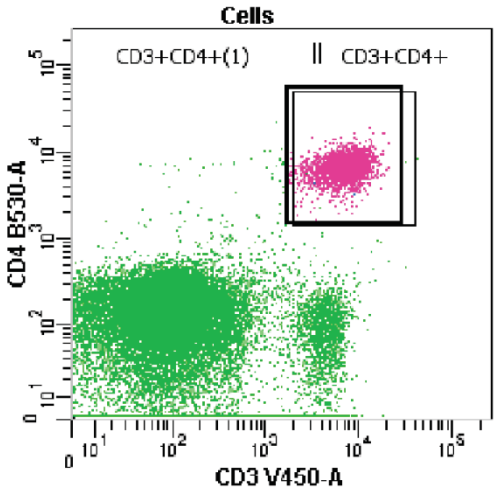
Cardona P et al submitted

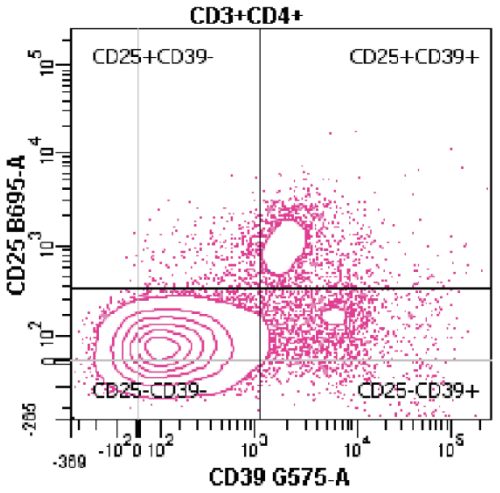
Administration of oral heat-killed mycobacteria increases Treg response









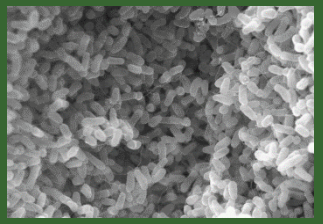


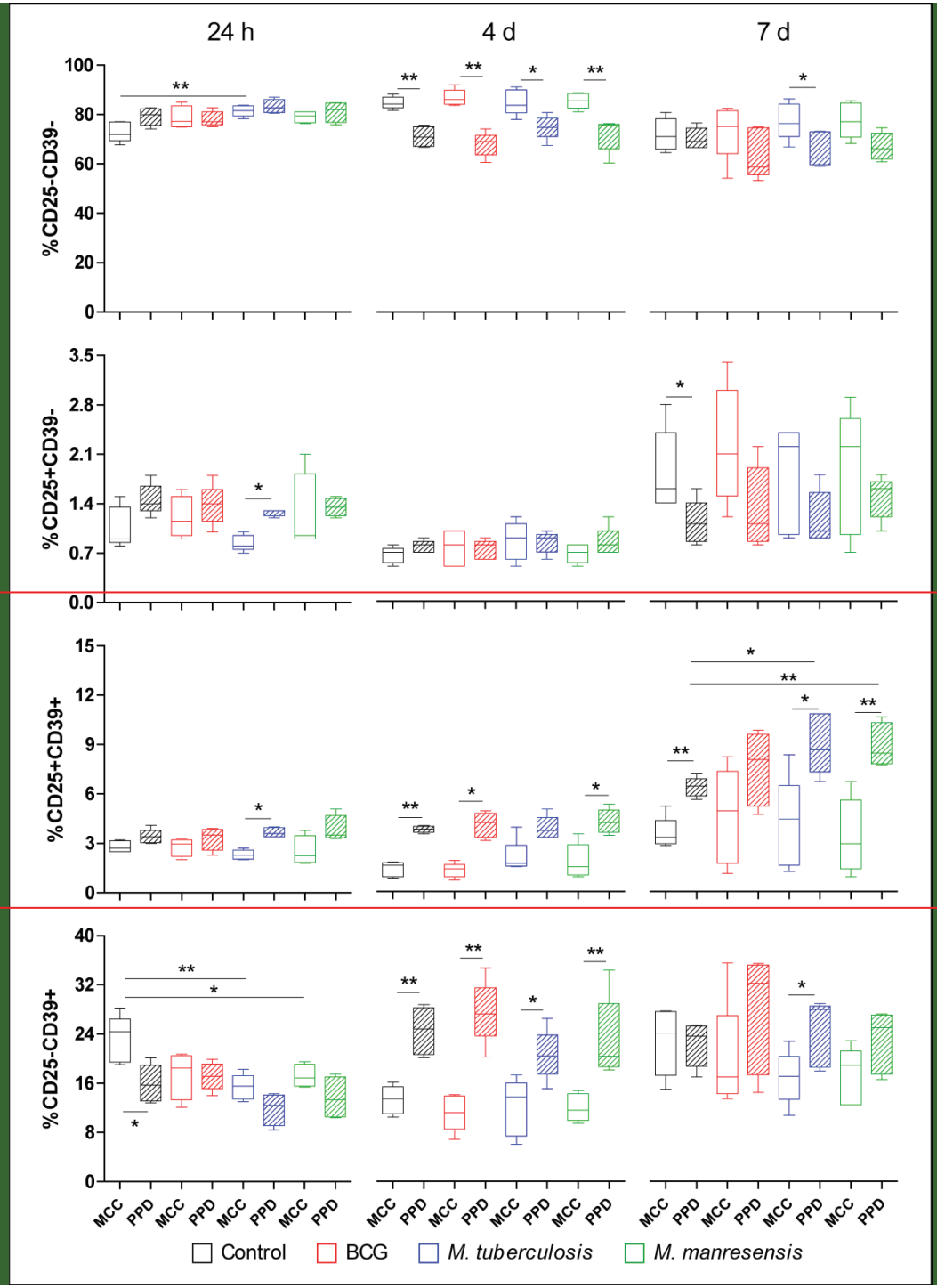
Well: E4

Population	#Events	%Parent	%Total
All Events	384,772	####	100.0
Singlets	254,124	66.0	66.0
Cells	172,857	68.0	44.9
CD3+CD4+	22,986	13.3	6.0
CD25+CD39-	318	1.4	0.1
CD25+CD39+	1,236	5.4	0.3
CD25-CD39-	19,587	85.2	5.1
CD25-CD39+	1,845	8.0	0.5
CD3+CD4+(1)	45,376	11.8	11.8

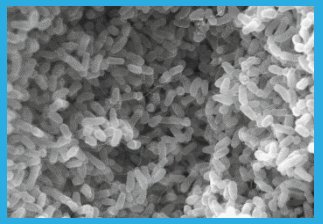
Cardona P et al submitted

Administration of oral heat-killed mycobacteria increases Treg response

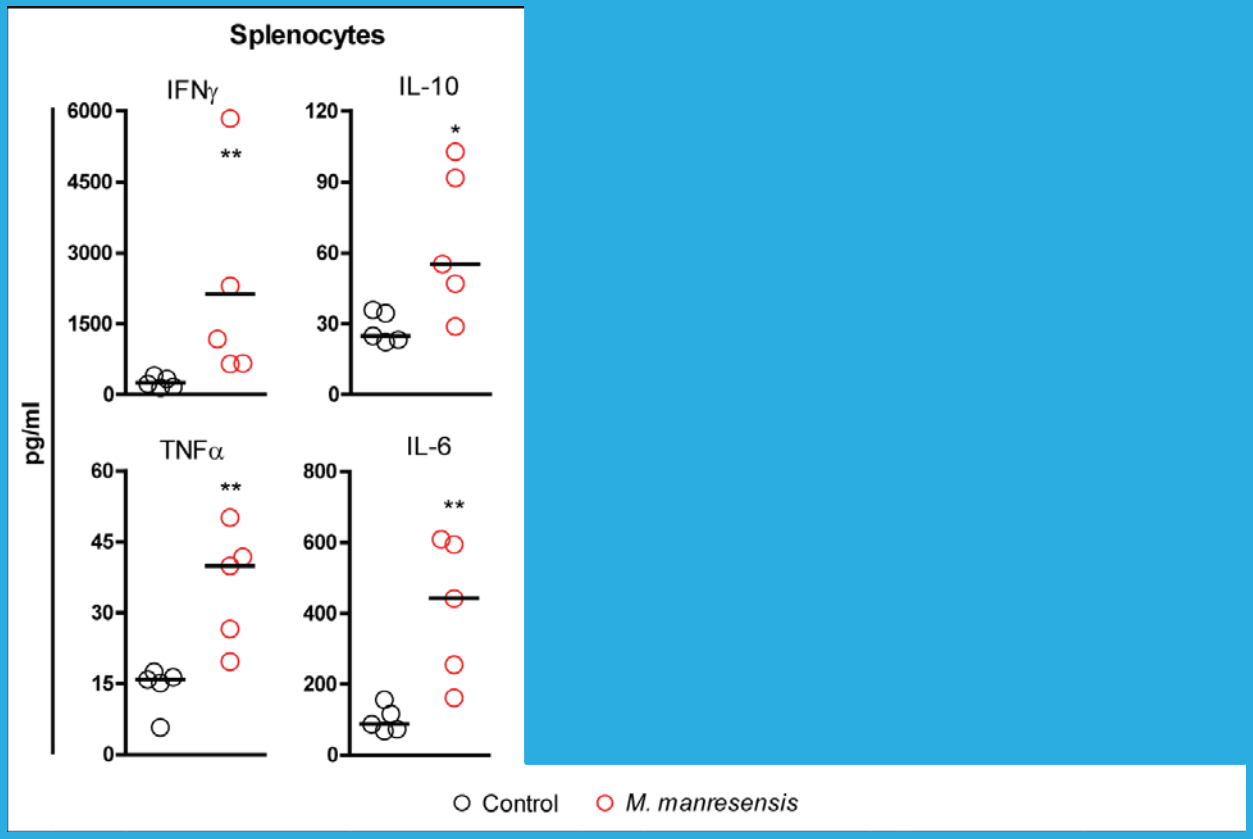




Cardona P et al submitted



Administration of oral heat-killed mycobacteria decreases the inflammatory response in the lungs



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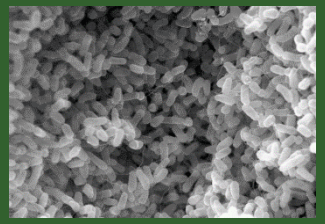
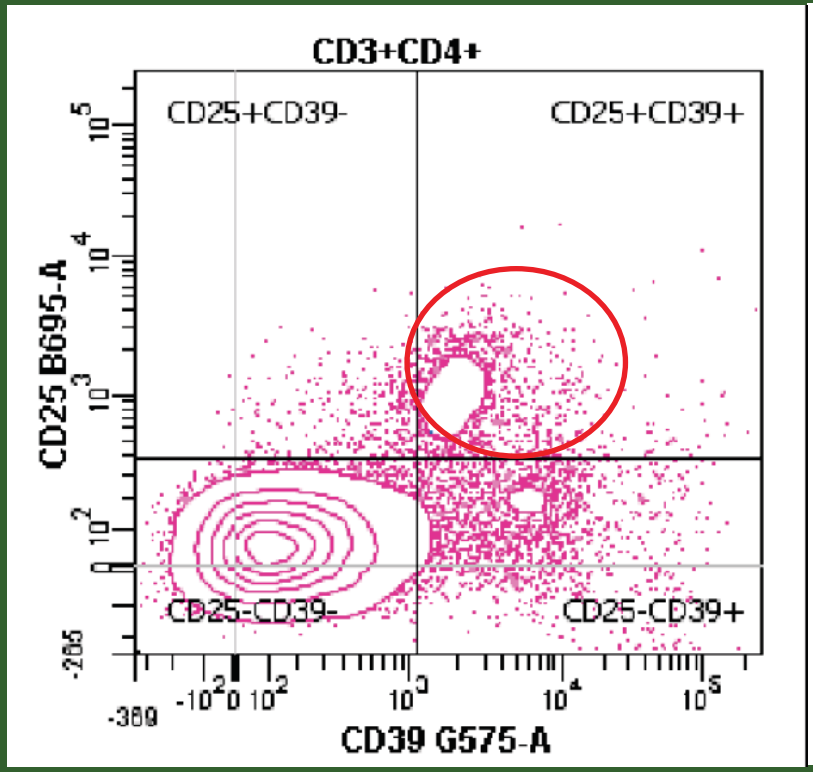
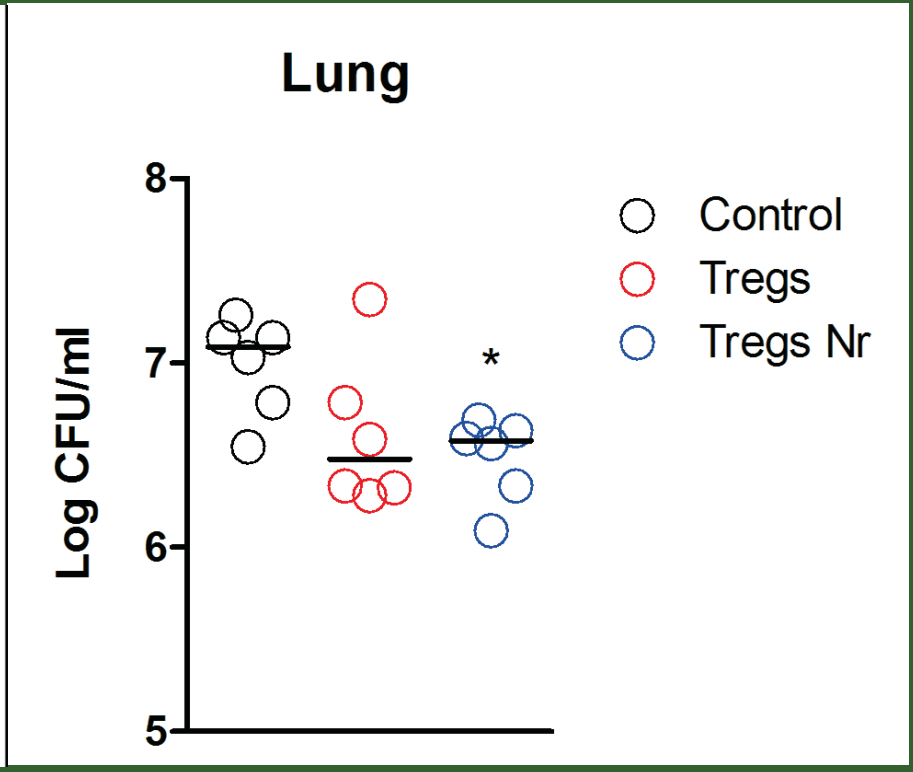






Cardona P et al In preparation

Transference of Tregs has stopped the progression towards active TB

This is the origin of Manremyc, a spin-off of IGTP


Manremyc is developing Nyaditum resae® a galenic formulation of *M. manresensis*


PPF
planta
pilot
fermentació
Leading its optimized
production


PPF
planta
pilot
fermentació
Scale-up
production


Nyaditum resae
Batch C14
10e5 CFUs
#00043
and it's widest distribution

अयं मे विश्व भेषज :

Tablets (India) Limited

REIG JOFRE

Elena Ramón

El consejero delegado de Reig Jofre, Ignasi Biosca.

Reig Jofre se alía con la 'biotech' Manremyc

ACUERDO/ El laboratorio catalán distribuirá en Europa un complemento nutricional de la 'start up' contra la tuberculosis.

Gabriel Trindade. Barcelona

La farmacéutica Reig Jofre apuesta por las biotecnológicas catalanas. La compañía ha llegado a un acuerdo con la *start up* Manremyc para el desarrollo comercial en Europa del *Nyaditum resae*, un

LA ENFERMEDAD

La **tuberculosis** es la segunda causa de mortalidad en el mundo por agente infeccioso. Cada año,

tes de la fusión con Natraceutical.

El acuerdo muestra el compromiso de la firma con el sector biotecnológico en el proceso de transferencia de conocimiento al mercado. "Es imprescindible que las

ClinicalTrials.gov

A service of the U.S. National Institutes of Health

Safety and Immunogenicity of Nyaditum Resae® Probiotic to Protect From Tuberculosis

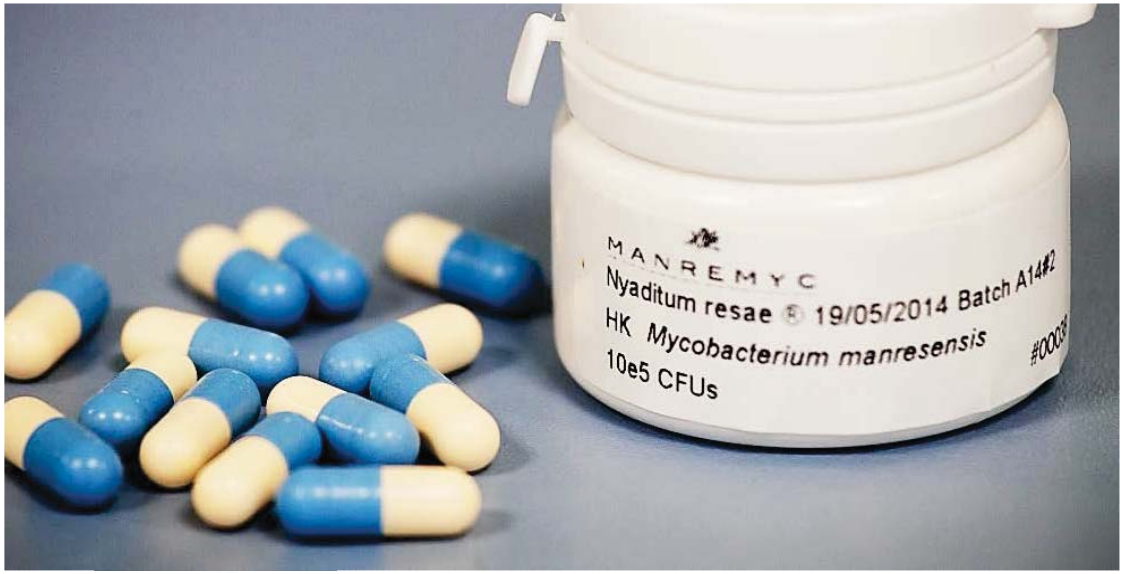
This study has been completed.

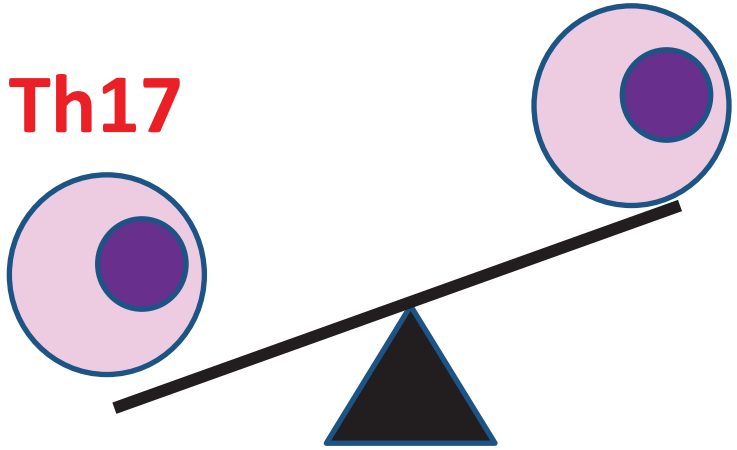
Sponsor:
Manresana de Micobacteriologia, SL

Information provided by (Responsible Party):
Manresana de Micobacteriologia, SL

ClinicalTrials.gov Identifier:
NCT02076139

First received: February 20, 2014
Last updated: August 24, 2015
Last verified: August 2015
History of Changes





U E

M


1st day in NYADATREG

NYADATREG

The **tolerability** of the food supplement **Nyaditum resae® was excellent**. The AE recorded were mostly gastrointestinal and mild, and no statistically significant differences were found between the treated groups with Nyaditum resae® and the Placebo group.

The analysis of the **immunogenicity showed** a significant **increase** in the population **of** specific effector and memory **Tregs** in the groups treated with Nyaditum resae® in both PPD pos & neg subjects. It has been experimentally demonstrated that these cells are the responsible for balancing the excessive inflammatory response that led to the induction of active TB.

45th Union World Conference on Lung Health
BARCELONA, SPAIN · 28 OCTOBER-1 NOVEMBER 2014
International Union Against Tuberculosis and Lung Disease
COMMUNITY-DRIVEN SOLUTIONS FOR THE NEXT GENERATION

NYADATREG

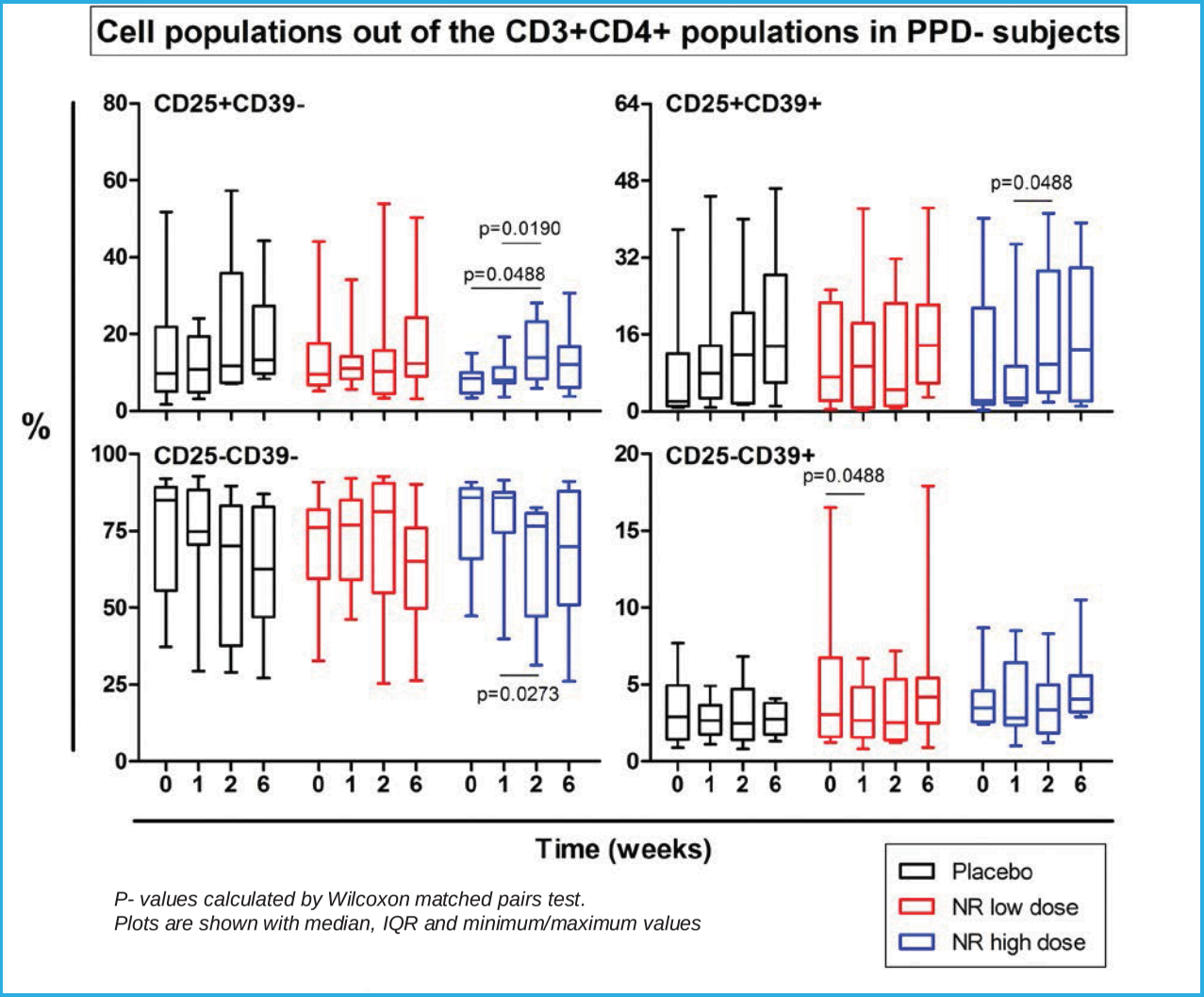
Total Adverse Events per subject, Median (IQR)

	Gastrointestinal	Non-gastrointestinal	Total	*p*
PLACEBO	4 (2 - 6)	2 (1 - 3)	6 (4 - 9)	*NS*
Nyaditum resae® low dose	2,5 (1,3 - 4)	2 (1,3 - 4,5)	4,5 (4 - 9)	*NS*
Nyaditum resae® high dose	2 (1,0 - 3,5)	2 (1 - 4,5)	5 (2,5 - 7,5)	*NS*

Number of subjects presenting possible or probable-related adverse events

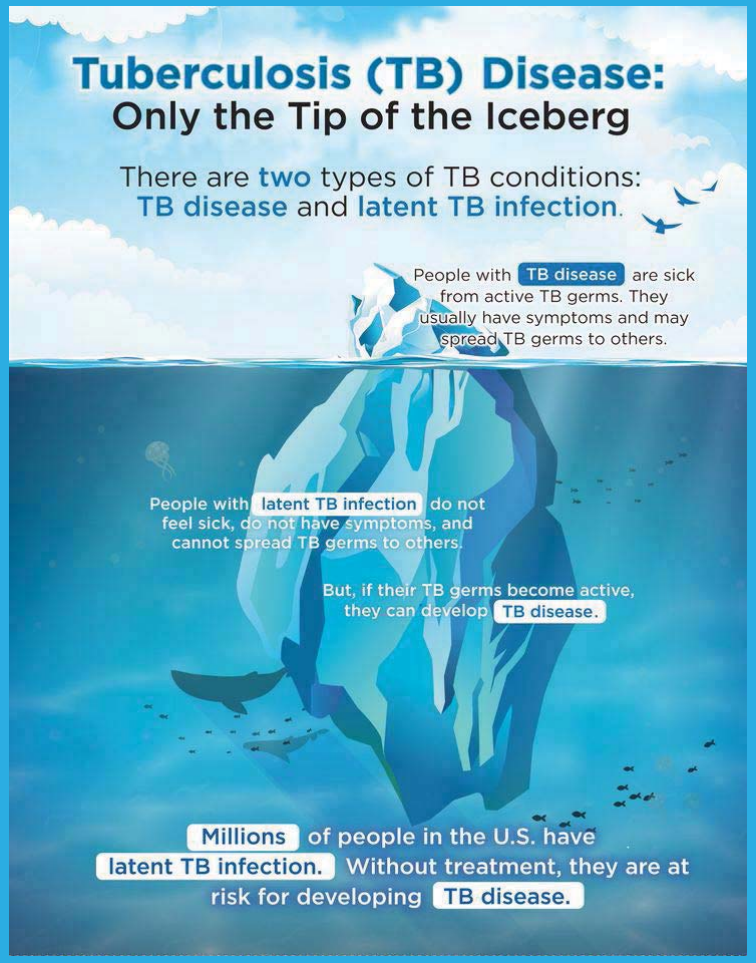
ADVERSE EVENTS			Participants N	Participants %	PLACEBO (n=18)	Nyaditum resae® Low dose (n=16)	Nyaditum resae® High dose (n=17)	*p*
Gastrointestinal	Abdominal pain		18	35.3	8	3	7	*NS*
	Faeces deposition	Increased	18	35.3	8	6	4	*NS*
	Faeces consistency	Decreased	14	27.5	5	5	4	*NS*
	Nausea		9	17.6	6	2	1	*NS*
	Diarrhoea		6	11.8	3	2	1	*NS*
	Dispepsia		4	7.8	1	3	0	*NS*
	Faeces deposition	Increased	3	5.9	3	0	0	*NS*
	Faeces consistency	Decreased	3	5.9	3	0	0	*NS*
	Vomits		2	3.9	1	0	1	*NS*
	Flatulence		2	3.9	1	1	0	*NS*
	Constipation		1	2	1	0	0	*NS*
	Epigastralgia		1	2	1	0	0	*NS*
	Rectal Tenesmus		1	2	0	1	0	*NS*
Non-Gastrointestinal	Hepatic alterations		7	13.7	1	4	2	*NS*
	Hematologic alterations		5	9.8	3	1	1	*NS*
	Cephalea, migraine		4	7.9	1	3	0	*NS*
	Respiratory Infection		3	5.9	1	1	1	*NS*
	Hyperglycemia		3	5.9	0	1	2	*NS*
	Others		5	9.8	1	3	1	*NS*

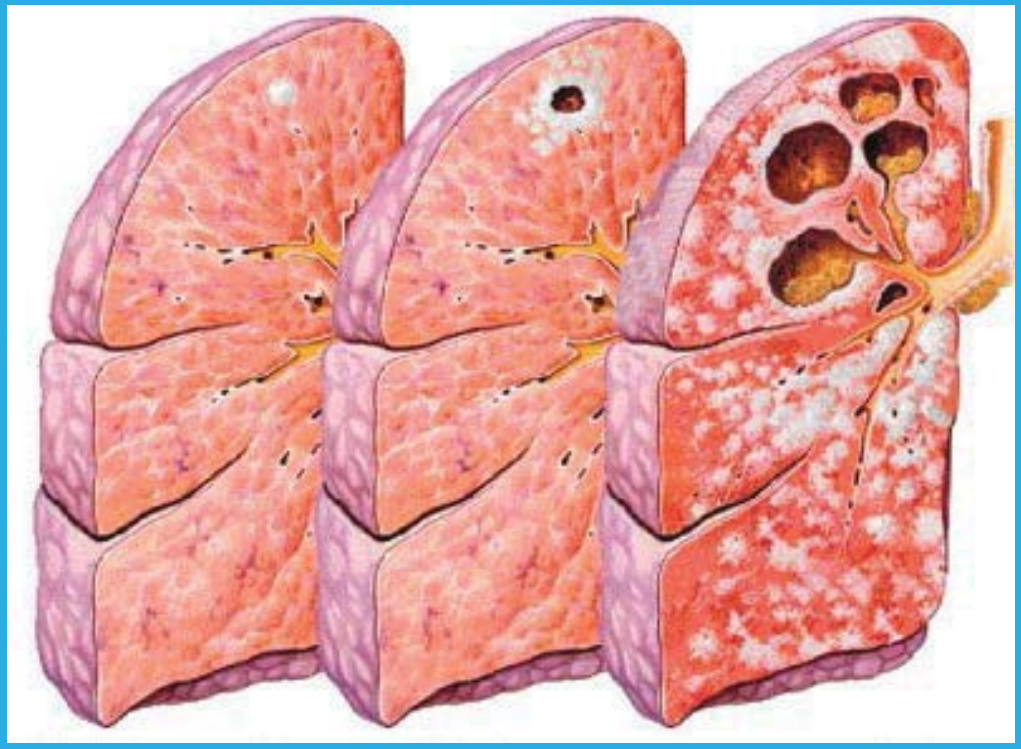
NYADATREG



NR® is a **unique product**:

There are no competitive products. It ***is not a vaccine***, **it is a nutraceutical**, thus it has a lot of regulatory advantages.





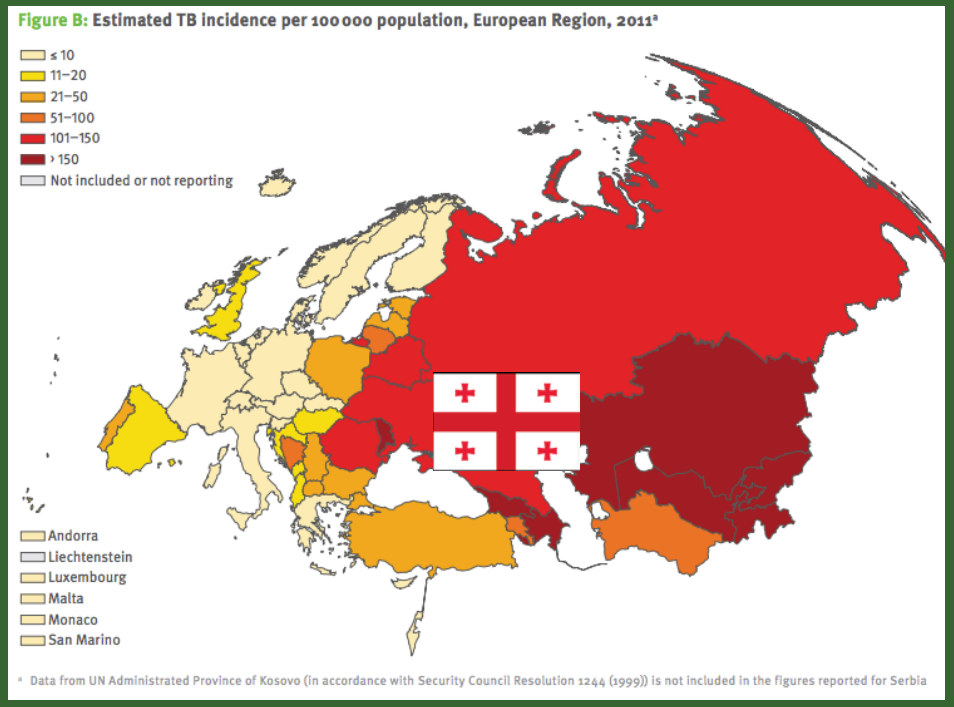
TARGETS?

Contacts of active TB cases

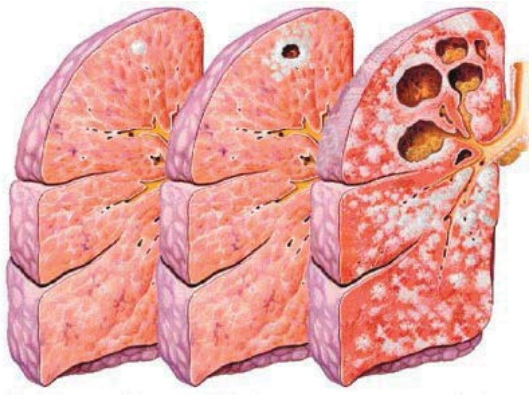
Active TB cases

Subjects in risk: i.e. DM, HIV

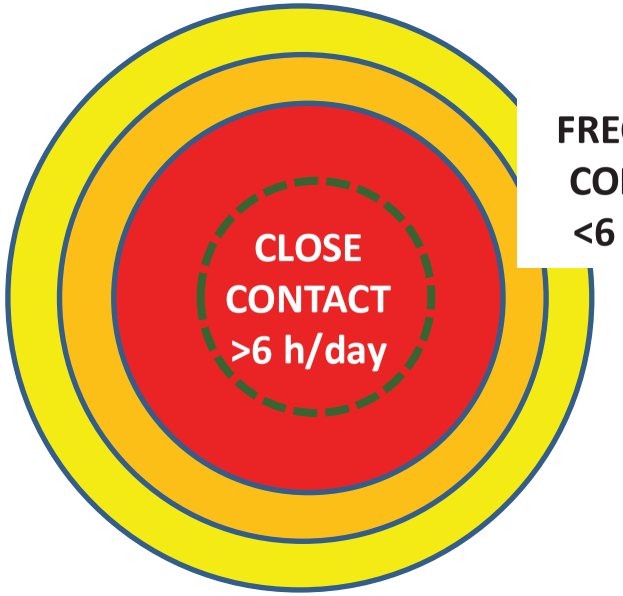
EFFICACY CLINICAL TRIALS to be launched



IGTP



1650 subjects



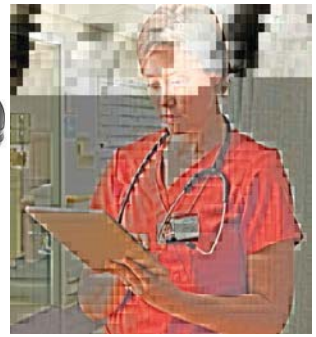
FREQUENT
CONTACT
<6 h/day

1650 subjects

2 years

3%

5%



NYADAGEORG

THANKS A LOT !!!