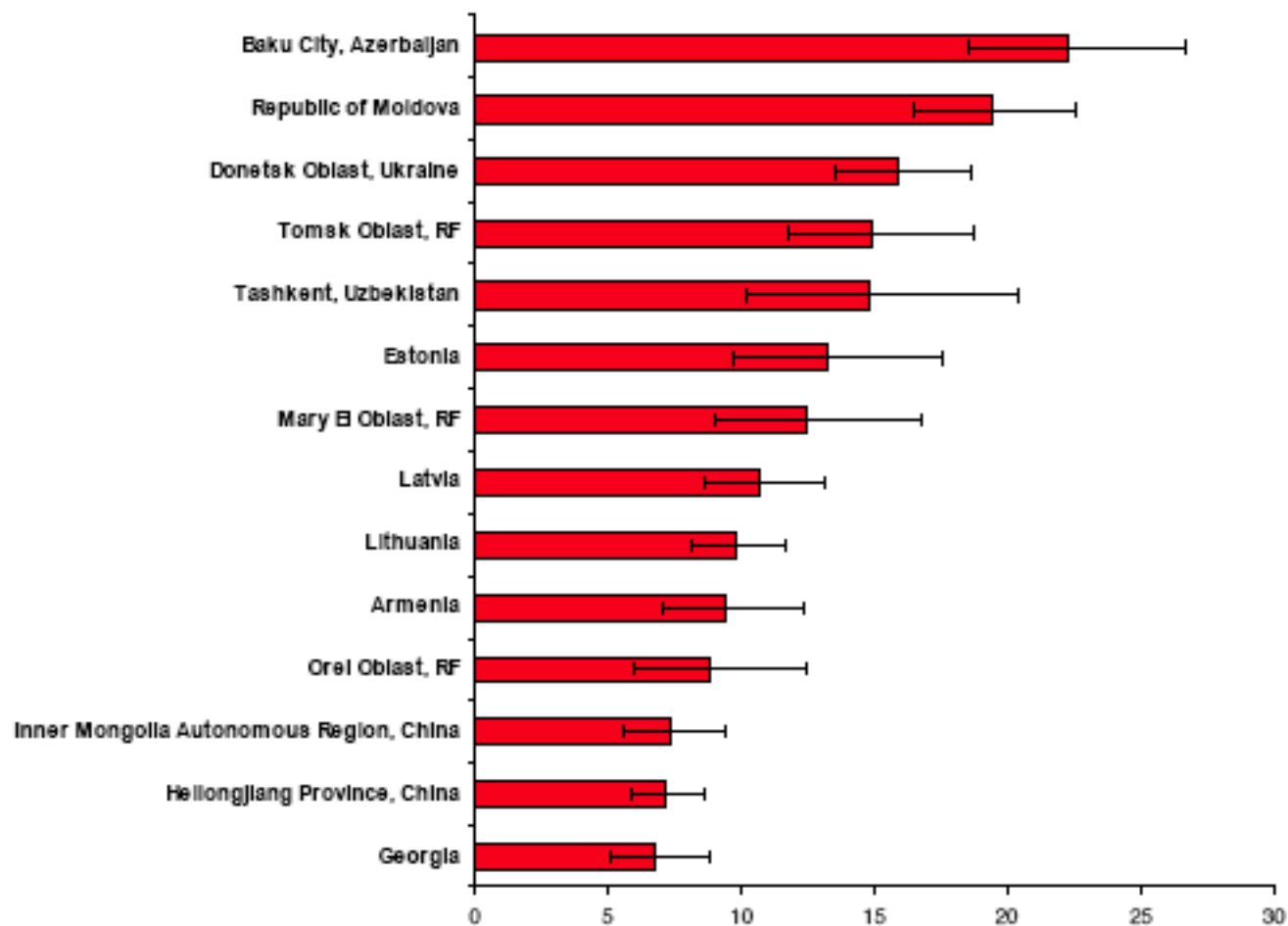


Boosting antituberculosis drugs to improve treatment compliance

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Inserm Unit 629



FIGURE 2: COUNTRIES/SETTINGS WITH MDR PREVALENCE HIGHER THAN 5.0% AMONG NEW CASES 2002-2007



Directly Observed Treatment - Short course (DOTS)

Isoniazid / Rifampicine / Ethambutol / Pyrazinamide : 2 months
+
Isoniazid / Rifampicine: 4 months

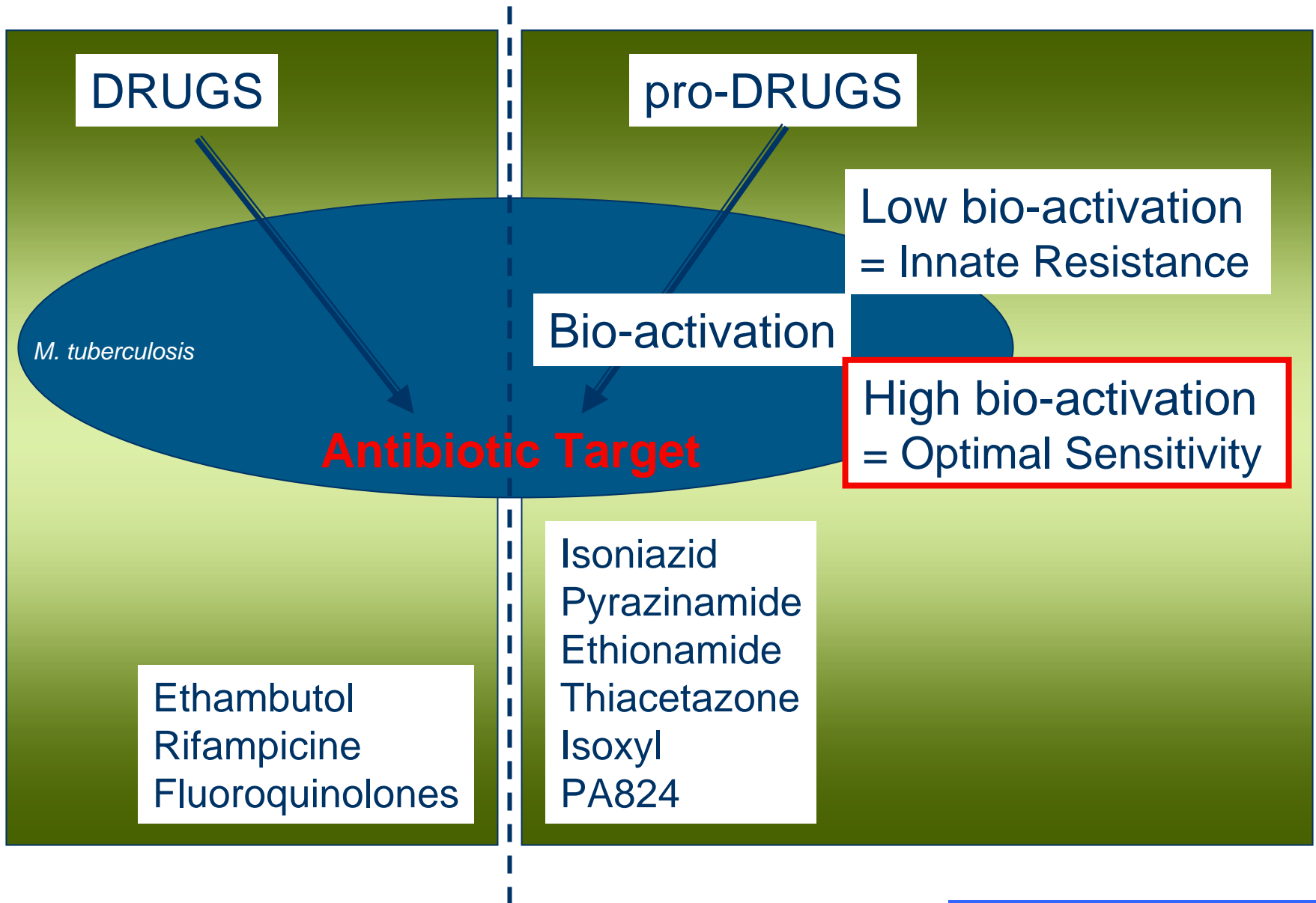
Toxicity of the treatment ==> non-compliance ==> Resistance, MDR, XDR

Objective: reducing treatment toxicity

-How?

by increasing existing-drugs efficiency...

Drugs versus Prodrugs against *M. tuberculosis*



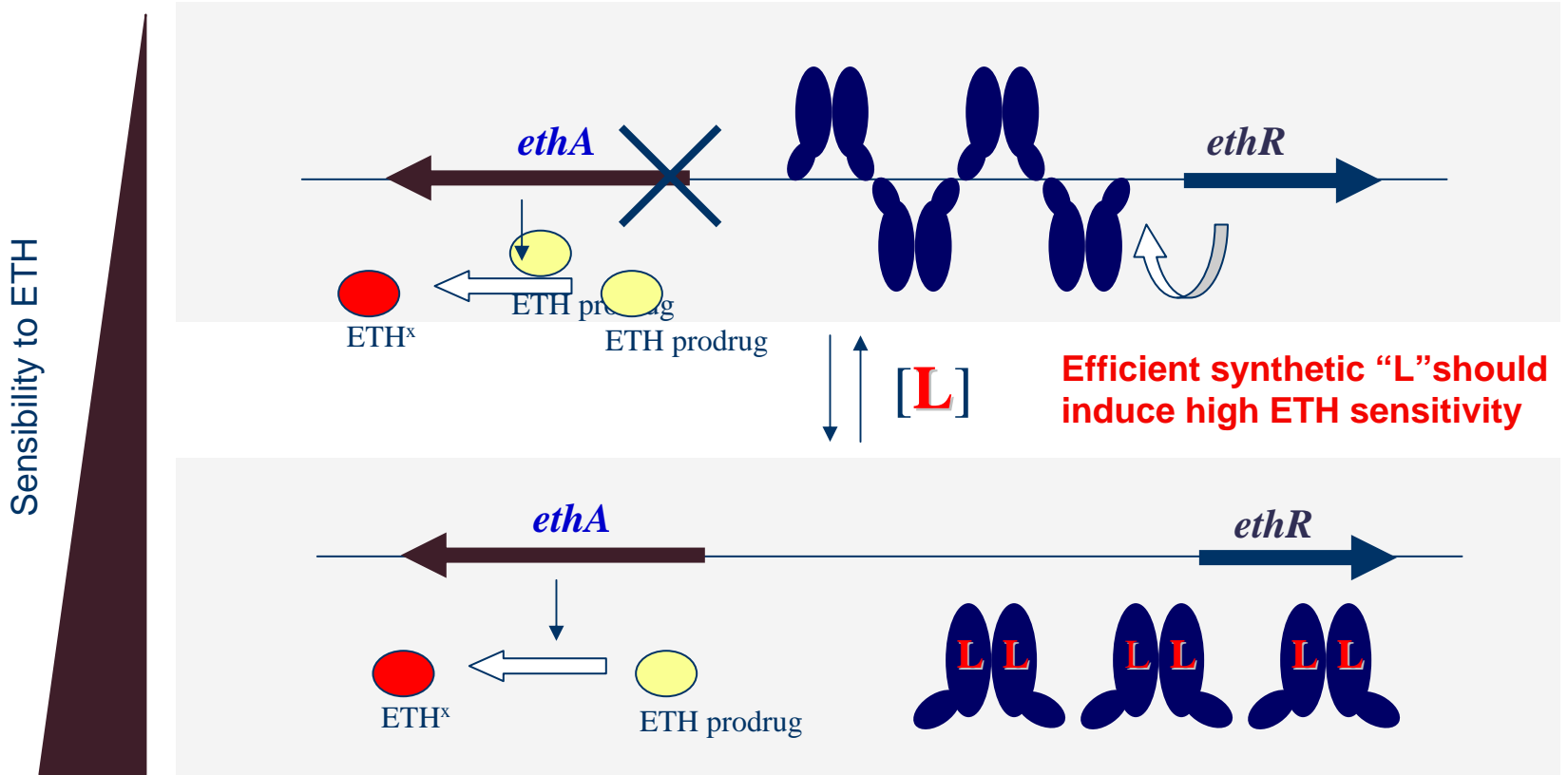
1. Identification of the **bioactivating enzymes**

- INH : KatG
- PZA: pyrazinamidase PncA
- **ETH / TAZ / ISO: EthA**

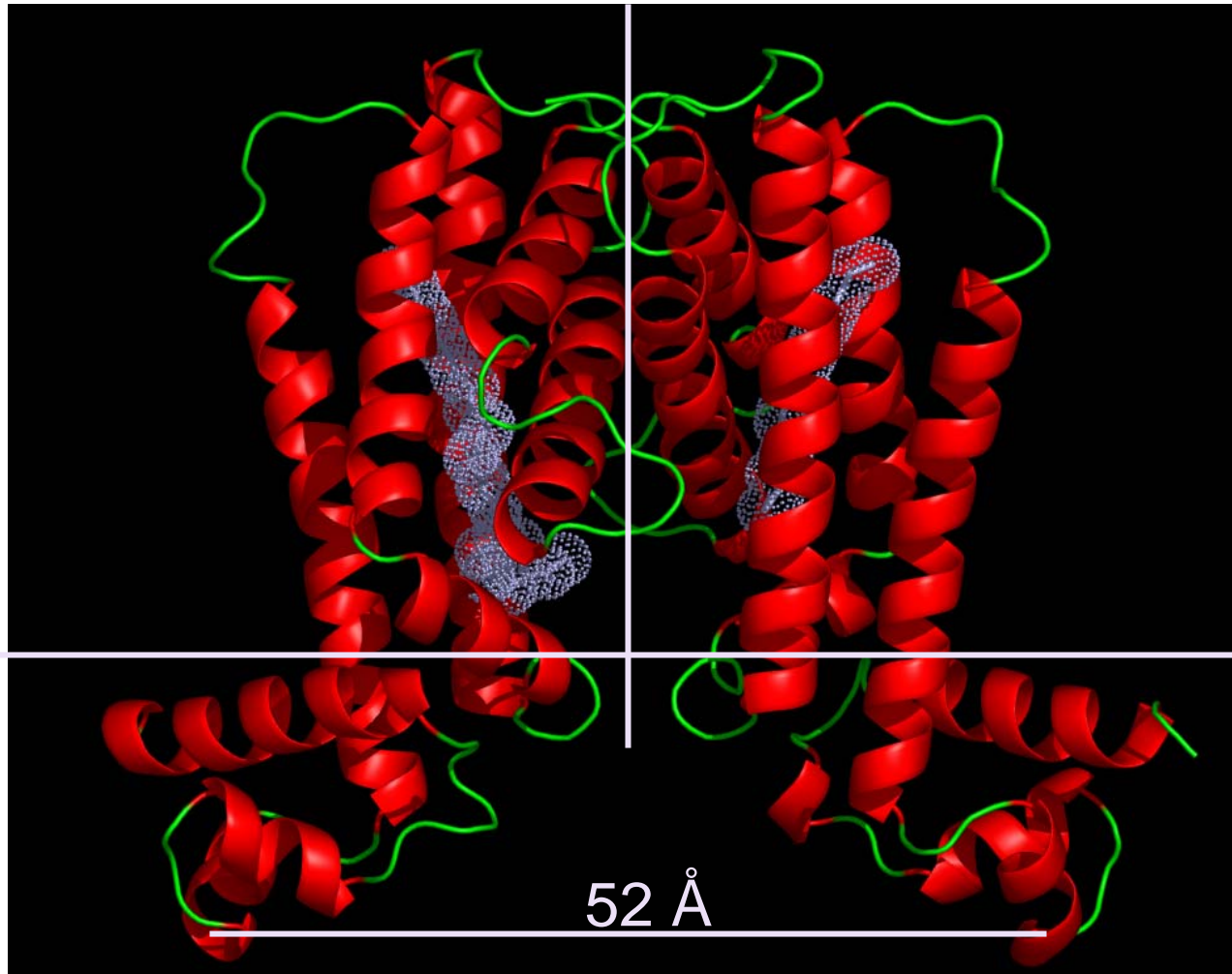
2. In all cases, **overproduction** of the bioactivating enzymes = increase of **sensitivity** to the drugs = activation is a limiting step

3. Study of the mode of **production** of EthA in Mtb

Production of EthA is regulated by EthR in *M. tuberculosis*



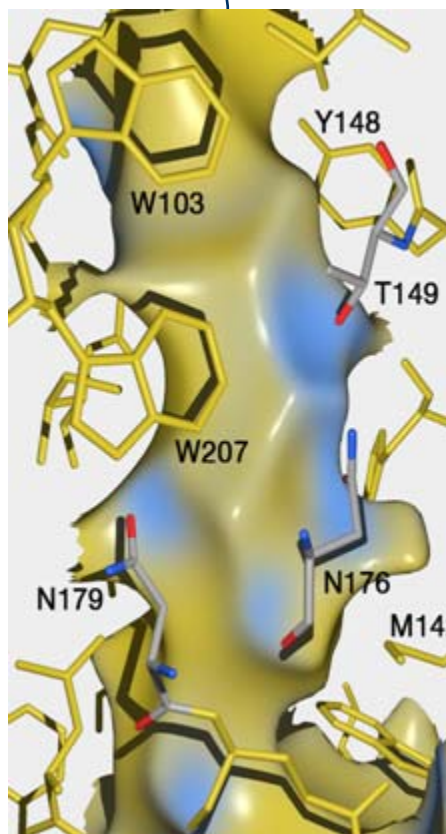
Cristal Structure of EthR



Design of test compounds

A hydrophobic tunnel

1



2

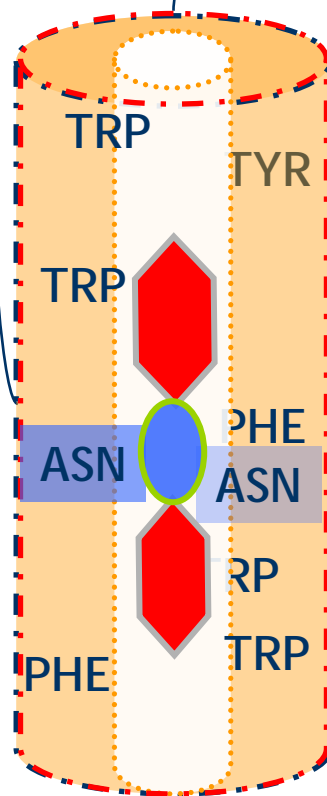
*a linker between
2 hydrophobic fragments*

131 compounds

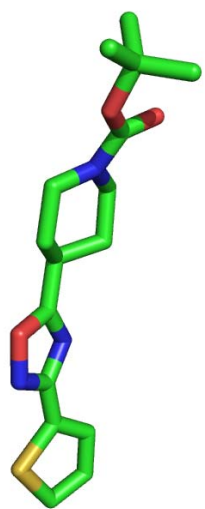
Synthesized and screened

(Sensing interaction between
DNA and EthR using BIAcore)

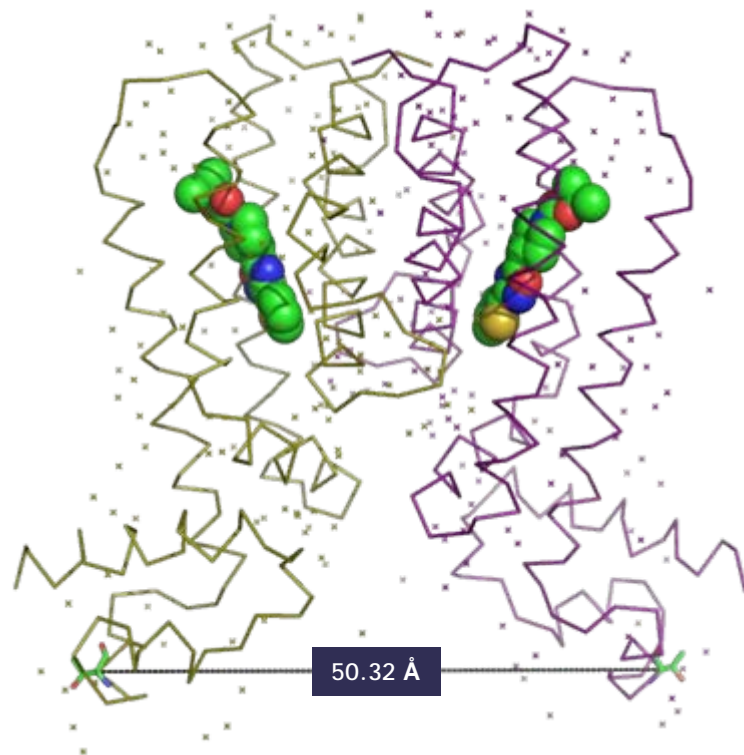
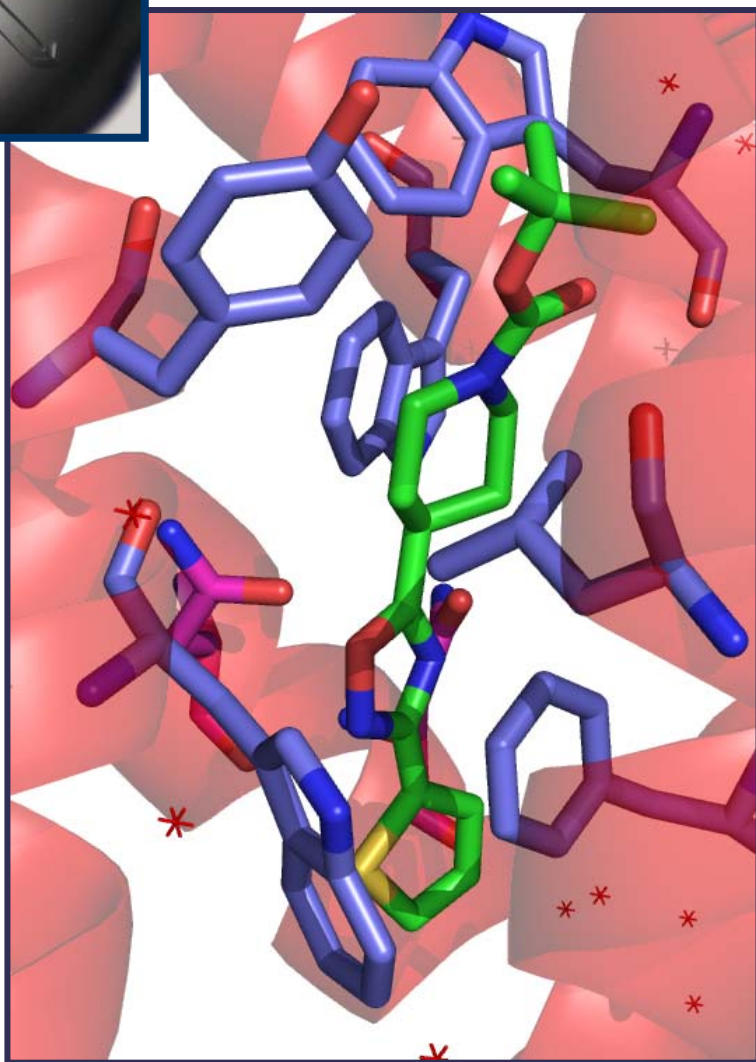
3



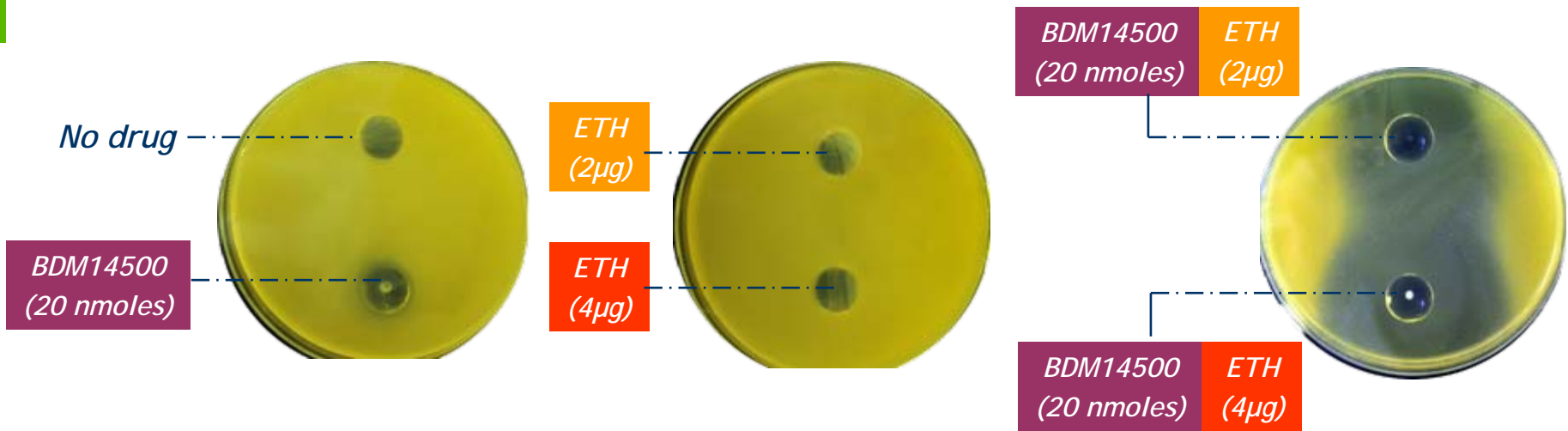
First hit identified



BDM14500

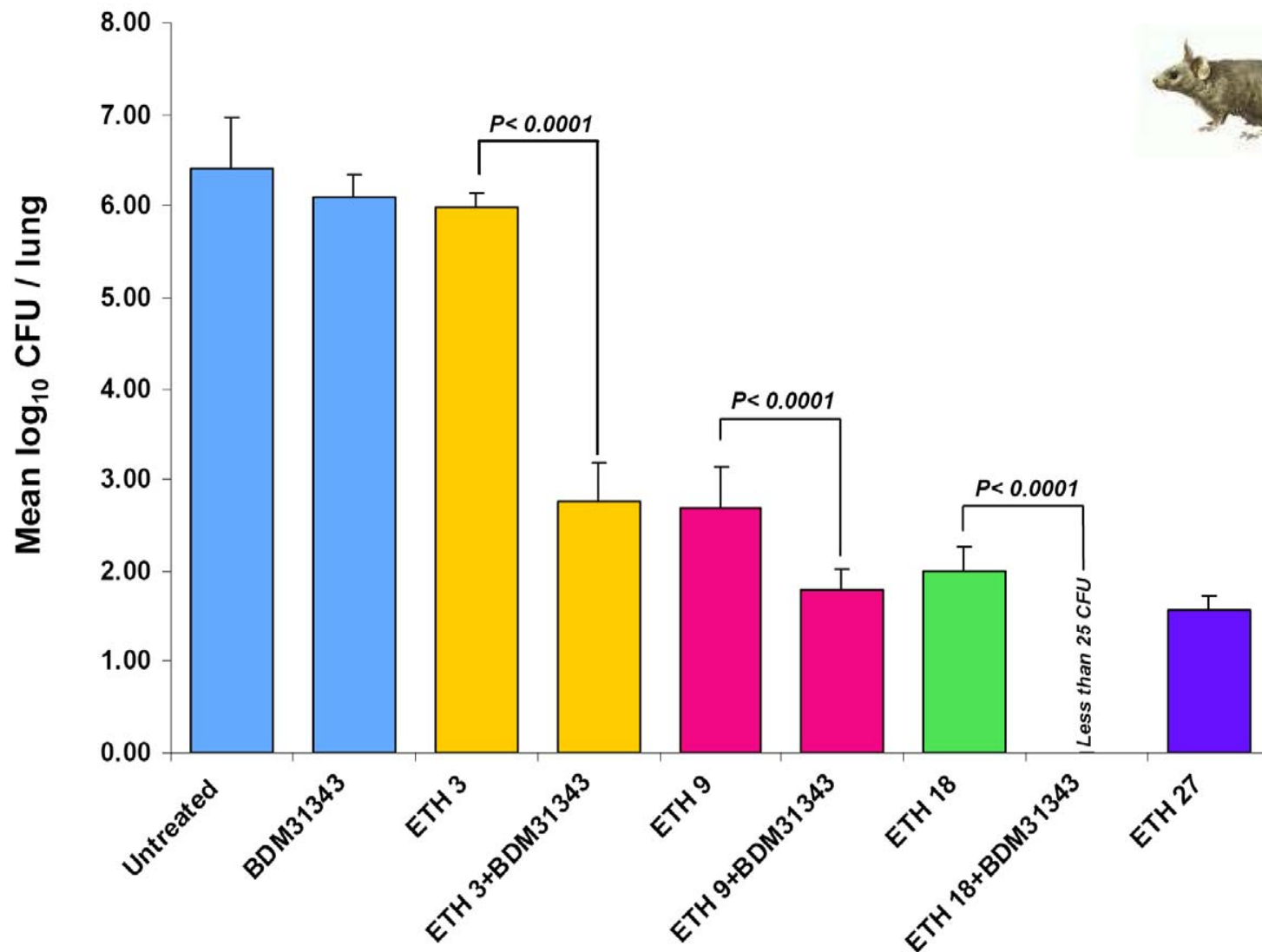


Effect of EthR-inhibitors on *M. tuberculosis* in culture



ETH activity is boosted by BDM14500

ETH-boosting effect of EthR inhibitor BDM31343 on a TB-mouse model IP administration



Partners in France

A. Baulard : Molecular Mechanisms of Bacterial Pathogenesis, U629 INSERM - Institut Pasteur de Lille

B. Déprez: Biostructure et Découverte de Médicament, U761 Inserm – Université de Lille II – Institut Pasteur de Lille

V. Villeret: Groupe radiocristallographie UMR8161 – Université de Lille I & II –IBL- Institut Pasteur de Lille

P. Brodin : Biology of Intracellular Pathogens. Institut Pasteur Korea

P. Bifani : Molecular Pathology of Tuberculosis. Institut Pasteur, Brussels. Belgium (Present Address: Novartis; Singapur)

Inserm

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Université du Droit
et de la Santé

RÉGION
NORD
PAS DE CALAIS

 USTL
Lille 1

 CRS

 INSTITUT PASTEUR KOREA

Proposition of a new association: INH+ETH&booster to tackle MDRs

Treatment (original)	Genotype	Percentages	Phenotype	Treatment (proposed)
INH	katG ⁻	±70%	INH^R ETH ^S	} (ETH+INH) boosted
	inhA ⁻	±25%	INH^RETH^r	
ETH*	inhA ⁻	±15%	(INHx3 ^s)	
	ethA ⁻	±80%	ETH^R INH ^S	

* based on clinical and in vitro data