SMARt (Small Molecule Aborting Resistance) in combination with ethionamide resets innate and acquired ethionamide resistance in *Mycobacterium tuberculosis*
Disclosures

M. Gitzinger, C. Kemmer and S. Lociuro are employees of BioVersys AG

V. Trebosc is a Ph.D. student seconded at BioVersys AG

A. Boulard is at Institute Pasteur of Lille

B. Deprez and N. Willand are professors at the University of Lille2
Tuberculosis in the 21st century

Tuberculosis is still a Neglected Disease

10.4 million people in the world developed TB

1.4 million people in the world died from TB

580,000 people developed MDR-TB

WHO Global TB Report 2016

25.04.2017

Treating tuberculosis in the era of drug resistance
The pipeline of marketed drugs

First-line regimen
- Isoniazid
- Pyrazinamide
- Ethambutol
- Rifampicin

Second-line regimen
- Streptomycin
- Ethionamide
- Capreomycin
- Amikacin
- Ofloxacin

TB treatment averted 49 million deaths globally between 2000 and 2015

- 83% DS-TB treatment success rate
- 52% MDR-TB treatment success rate
- 28% XDR-TB treatment success rate
Rational for choosing ethionamide

- Ethionamide (ETH) and prothionamide (pETH) are currently second line approved molecules to treat MDR/XDR TB.
- **WHO recommends ETH as part of the treatment of MDR-TB patients.**
- In China, pETH is widely used in the treatment of TB in general.
- As efficient as Isoniazid.
- Cross blood/brain barrier.

**Can ETH/pETH activity/efficacy be improved?:**
- High dose needed, due to inefficient bio-activation (Innate resistance)
- Main source of resistance is within the bio-activation pathway (Acquired resistance)
- ETH and pETH suffer of dose dependent side effects mainly related to nausea.

**Objectives of BioVersys’ booster program:**
- Reverse resistance in MDR/XDR strains to ETH/pETH.
- Increase ETH Probability of Target Attainment (PTA)
- Reduce the clinical dose/exposure of ETH.
Innate bacterial resistance

- Baulard et al, 2000
- DeBarber et al, 2000

ETH - NAD

Mycobacterium tuberculosis

Treating tuberculosis in the era of drug resistance
Innate bacterial resistance

Inhibition of EthR

InhA

EthA

EthR

INH-β-D-NAD

M. tuberculosis

Ethionamide

Baulard et al 2000; DeBarber et al, 2000

25.04.2017

Treating tuberculosis in the era of drug resistance
**BDM 41906**

A first interesting EthR inhibitor

BDM 41906

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IV infection
4-week treatment
5 days/week
ETH per OS
BDM41906 per OS 20mpk

**(Clin. Isol. ID | INH | Rif | Emb | ETH | ETH+41906)**

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"All animal studies were ethically reviewed and carried out in accordance with European Directive 86/609/EEC"


25.04.2017

Treating tuberculosis in the era of drug resistance
A good reason for target hopping?

Affinity to target vs. activity against *Mycobacterium tuberculosis*

Target affinity $\Delta T_m$ in °C

Cellular activity ($\text{pEC}_{50}$)

BDM41420

BDM41906
Back to the genes


25.04.2017
Treating tuberculosis in the era of drug resistance
Innate bacterial resistance

Ethionamide

\[
\text{Ethionamide} = \text{H}_2\text{N} - \text{S} - \text{C}_6\text{H}_4 - \text{CH}_3
\]

\[
\text{InhA}^+ \rightarrow \text{ETH-NAD} \rightarrow \text{InhA}^-
\]

Blondiaux et al, Science, 2017

25.04.2017  Treating tuberculosis in the era of drug resistance
Innate bacterial resistance

**EthR2 inhibition**

Ethionamide

\[
\text{H}_2\text{N}-\text{C} = \text{N}-\text{S}\text{CH}_3
\]

**EthA**

**EthR**

**ETH-NAD**

InhA

**BDM41420**

*Mycobacterium tuberculosis*


25.04.2017  
Treating tuberculosis in the era of drug resistance
Acquired bacterial resistance

M. tuberculosis

EthR

Mutated EthA

EthA2

EthR2

Mycobacterium tuberculosis

Blondiaux et al, Science, 2017

Combating AntiMicrobial Resistance

25.04.2017

Treating tuberculosis in the era of drug resistance
Acquired bacterial resistance
Reversion of ETH-resistance by EthR2 inhibition

Blondiaux et al, Science, 2017

Treating tuberculosis in the era of drug resistance
## MIC of ETH on MDR-TB clinical isolates

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**TB strains**
- H37Rv

**MDR strains ETH-R**
- B1150
- B1602
- B0775
- B0057
- L3556
- B0467
- L0728
- P379
- P395
- P359
- P351
- LPN4
- B1166
- B1001
- B1304
- B0383
- B1196
- B1004
- B0391
- B0089

**Table Note:**
- **INH:** INH (INH)
- **RIF:** RIF (INH)
- **EMB:** EMB (INH)
- **OFLO:** OFLO (INH)
- **AMI:** AMI (INH)
- **ETH:** ETH (INH)
- **ETH + BDM41906:** MIC of ETH on MDR-TB clinical isolates
- **ETH + BDM41420:** MIC of ETH on MDR-TB clinical isolates

**Notes:**
- **BDM41906** and **BDM41420** are the MIC values for the drugs in question.
- **MIC of ETH on MDR-TB clinical isolates**

---

**References:**
- Treating tuberculosis in the era of drug resistance

**Date:** 25.04.2017
In vivo efficacy

H37RV

H2N

CH3

S

N

C

EthA

EthR

EthA2

EthR2

BDM41420

EthA mutated strain: E1

H2N

CH3

S

N

C

EthA

EthR

EthA2

EthR2

BDM41420

"All animal studies were ethically reviewed and carried out in accordance with European Directive 86/609/EEC"

25.04.2017

Treating tuberculosis in the era of drug resistance
## Target Product Profile

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<td>• Effective with low dose of ETH</td>
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<td>✔</td>
<td>• Stable PhysChem properties</td>
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<td>• Low-cost production</td>
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<td>• No drug-drug interaction</td>
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<td>✔</td>
<td>(Tb : rifampicin HIV : ritonavir)</td>
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<td>• No toxic issues</td>
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<td>• Comb. Active on MDR-XDR TB</td>
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- Approved in 1956
- Bactericidal
- Key in MDR tx
- Inexpensive
- Cross-R with INH
- ETH\(^r\) strains exist

- Oral administration
- Max Once a day
- Effective with low dose of ETH
- Stable PhysChem properties
- Low-cost production
- No drug-drug interaction (Tb : rifampicin HIV : ritonavir)
- No toxic issues
- Comb. Active on MDR-XDR TB
Acknowledgements