TRiC-TB
Part of IMI AMR Accelerator

EUROPEAN UNION
EU Project 853800

Reviving Ethionamide: TRICky, but possible

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GSK

JPIAMR Therapeutics Workshop 2021

imi innovative medicines initiative
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BIOVERSYS

MDR/XDR-TB: GLOBAL HEALTH EMERGENCIES

Disease	DS-TB	MDR-TB	XDR-TB
Drug	4 (INH, RIF, PZA, EMB)	≥5	≥5
Length (Months)	6	9-12	>24
Cure (%)	83	54	28

Main goals for novel TB drugs:

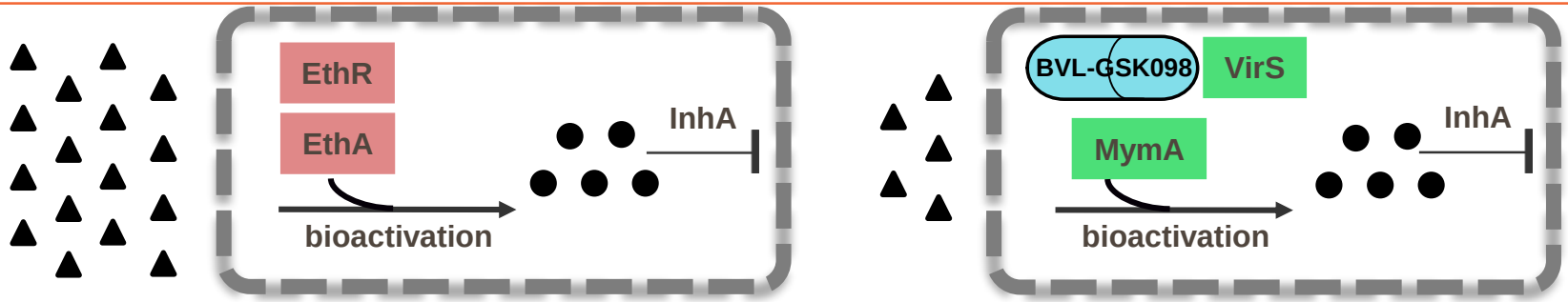
- Overcome drug resistance
- Shorten treatment time
- Safer drug profile

	MDR treatment*
A Include all	Levofloxacin OR moxifloxacin Bedaquiline Linezolid
B Add one or both	Clofazimine Cycloserine OR terizidone
C Add to complete regimens	**Ethionamide OR prothionamide** Ethambutol Delamanid Imipenem-cilastin or meropenem Pyrazinamide Amikacin p-aminosalicyclic acid

THE WORLD NEEDS A SIMPLER, SAFER AND SHORTER TB DRUG REGIMEN

* WHO guidelines 2020: Grouping of medicines recommended for use in longer MDR-TB regimens

BACKGROUND ETHIONAMIDE (ETO) AND PROTHIONAMIDE (PTO)



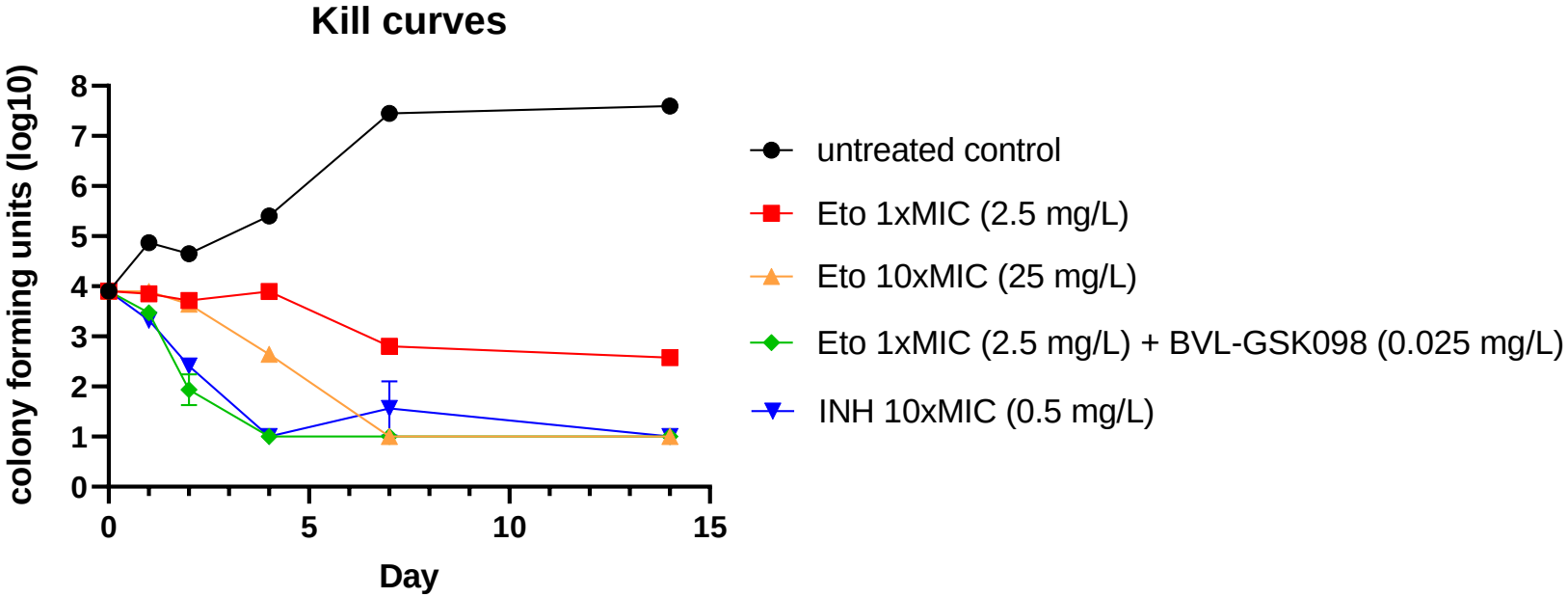
- Eto/Pto are pro-drugs ▲ that are converted inside *M. tb.* into the active form ● inhibiting InhA
- Bioactivation occurs through the enzyme EthA
- It has been recently described MymA also plays a relevant role in activating Eto*

- Due to limited bioactivation, high dosing of Eto/Pto is required causing GI disorders
- Resistance to Eto in clinical strains is observed in the bioactivation pathway (EthA mutations)

- BVL-GSK098 acts potently on VirS rendering MymA-mediated bioactivation of Eto/Pto complete
- BVL-GSK098 can reduce therapeutic doses of Eto/Pto (side effects)
- BVL-GSK098 overcomes Eto resistance

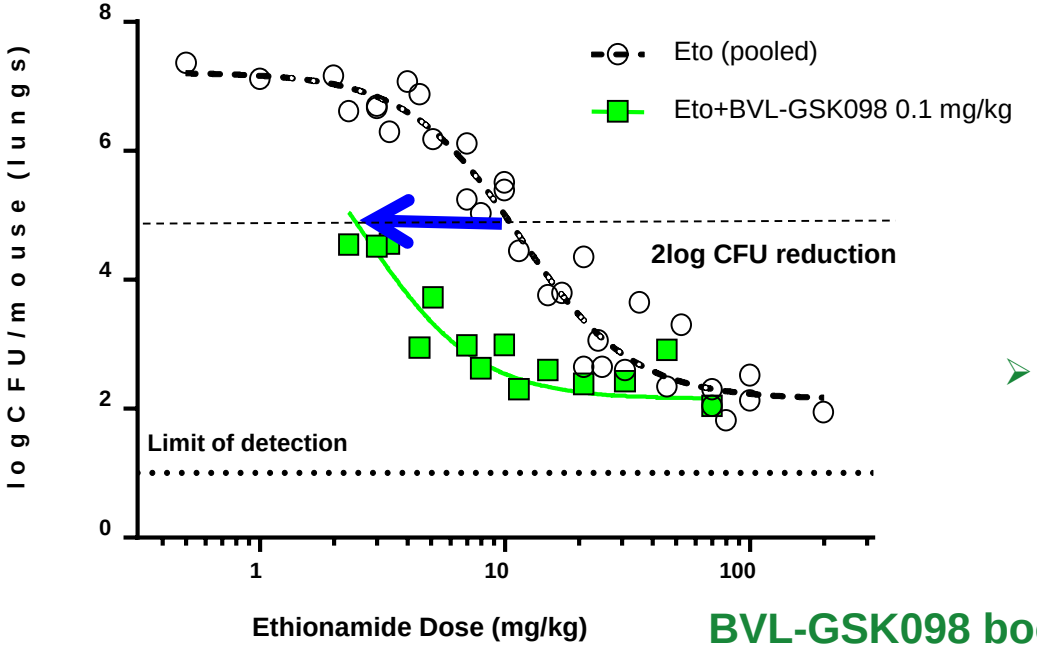
* Hung, D. et al., Cell Chem Biol. 2016 June 23; 23(6): 666–677

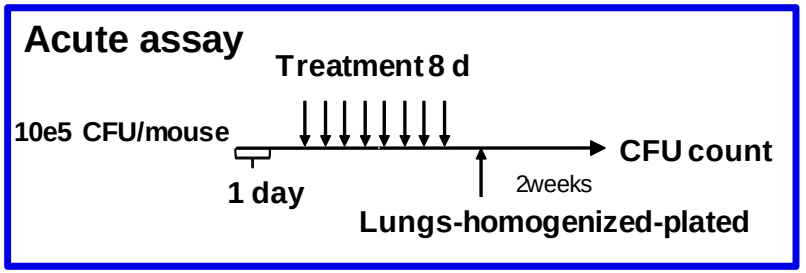
BOOSTING ETO WITH BVL-GSK098 RENDERS MAXIMUM LEVEL OF BIO-ACTIVATION



BVL-GSK098 renders Eto at 1x MIC as rapidly bactericidal as INH at 10x MIC

POTENT *IN VITRO* ACTIVITY TRANSLATES INTO *IN VIVO* EFFICACY





- ED_{99} is the dose of Eto resulting in a 2log reduction (dashed line) in lung CFUs compared to untreated control

BVL-GSK098 boosts Eto efficacy *in vivo* by >3-fold, enabling full efficacy at lower Eto exposures

All animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals

BVL-GSK098 OVERCOMES MDR-TB AND ETO RESISTANT ISOLATES

MDR Clinical Strain ID	INH	RIF	MIC Eto (mg/L)	MIC Eto (mg/L) + BVL-GSK098 (0.02 mg/L)
H37Rv	S	S	2	0.08
B1602	R	R	256	≤0.8
B1304	R	R	32	≤0.8
B1196	R	R	32	≤0.8
07MY0066	R	R	>8	≤0.8
07MY1001	R	R	32	≤0.8
07MY1166	R	R	64	≤0.8
07MY1281	R	R	16	≤0.8
08MY0089	R	R	8	≤0.8
08MY0559	R	R	>4	≤0.8
08MY1099	R	R	16	≤0.8
09MY0467	R	R	64	≤0.8
09MY1304	R	R	32	≤0.8
10MY0992	R	R	>4	≤0.8
12MY1124	R	R	>4	≤0.8
L1094	R	R	2	≤0.8

Eto: Ethionamide: **INH**: Isoniazide: **RIF**: Rifampicin: **MIC:** Minimal inhibitory concentration: **MDR:** Multi-Drug Resistant: **R**: Resistant: **S**: Susceptible

- BVL-GSK098 lowers Eto MIC on WT and MDR strains, and overcomes Eto resistance.
- MIC data based on 40 MDR/XDR clinical strains with bias towards Eto and INH resistance representing TB global lineages.

BVL-GSK098 DEPLOYS THE FULL POTENTIAL TO REVIVE ETO/PTO

- ✓ Eto/Pto are excellent drugs if their full efficacy could be exploited at better tolerated human doses
- ✓ BVL-GSK098 is a first-in-class new chemical entity with novel MoA
- ✓ *In vitro* and *in vivo* data predict that the addition of BVL-GSK098 reduces the Eto efficacious dose
- ✓ BVL-GSK098 overcomes Eto resistance in clinical strains (including MDR-TB) and makes Eto rapidly bactericidal at very low concentrations
- ✓ Addition of BVL-GSK098 to Eto/Pto regimens has the potential to play the role of INH in DS regimens in MDR/XDR regimens
- ✓ No cross resistance with current and development TB drugs
- ✓ Low risk of DDI: no inhibition/activation of CYP450s

BVL-GSK098 DEVELOPMENT: NEXT STEPS

- Pre-clinical safety evaluation in rodent and non-rodent species completed
- Phase 1 started in Dec2020 and will be hopefully completed by the end of 2021
- Funding for Phase 2a ensured through EDCTP* consortium

Next Milestone: BVL-GSK098 ready for Phase 2a studies in 1H2022

*EDCTP: European and Developing Countries Clinical Trials Partnership

ADVANTAGES OF THE TRIC-TB CONSORTIUM

- ✓ TRIC-TB is a focused, agile consortium of one SME, BioVersys and one big Pharma, GSK
- ✓ By combining an agile, fast moving SME with the experience and capabilities of a big industry partner, TRIC-TB brings innovation and a new concept of drug development
- ✓ All necessary expertise from end of pre-clinical to clinical development (microbiology, efficacy and DMPK, toxicology, CMC, drug development and clinical trials, regulatory engagement etc) is covered within the TRIC-TB consortium
- ✓ No unnecessary delays due to out of focus topics and unnecessary IP dilutions as it sometimes happens with bigger consortia

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Partnership is the key of our success

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