A New Class of Antibiotics Overcomes Multi-Drug Resistant Bacteria by Targeting Outer Layer Glycolipid Biosynthesis

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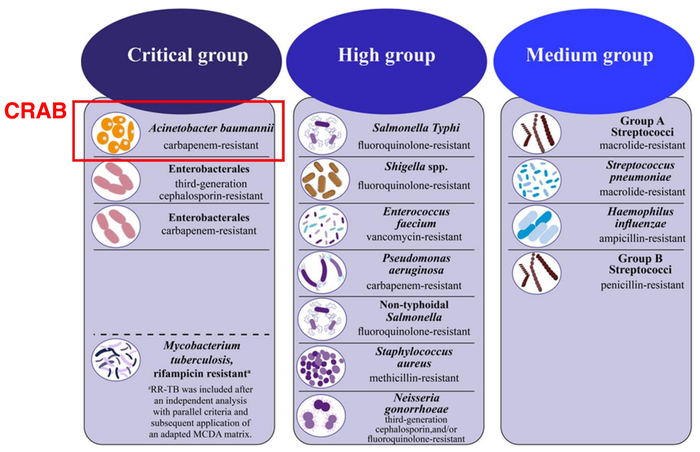
Abstract

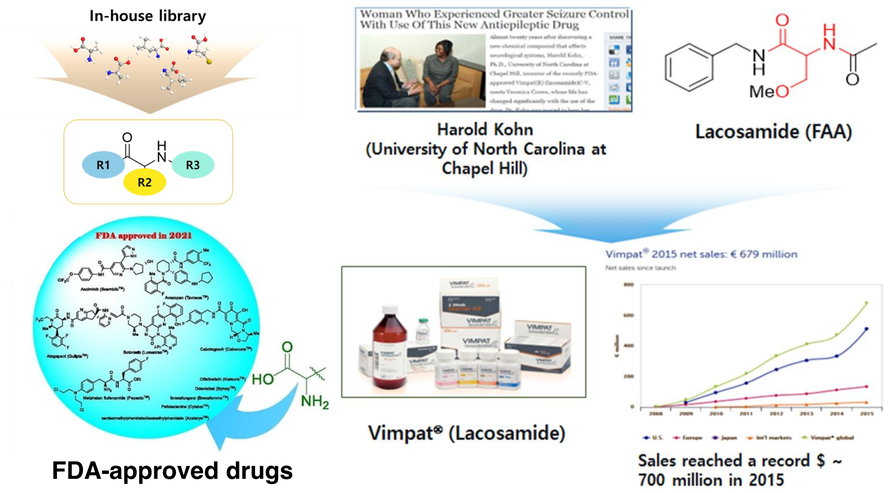
- Infectious diseases produced by multi-drug resistant bacteria (MDR) pose a significant challenge in global healthcare due to their capacity to evade treatment with antibiotics. MDR bacteria are exceptionally challenging to eradicate because their outer layers serve as significant impediments to antimicrobial agents.
- The impermeable characteristic of the outer layer arises from the presence of lipopolysaccharide (LPS) in Gram-negative bacteria, and lipoteichoic acid (LTA) in Gram-positive bacteria.
- Here, we present a novel class of antibiotics termed ASM, a functional amino acid drug class that ihibibits the production of LPS or LTA by targeting the enzyme phosphoglucomutase (PGM) in bacteria.
- Notably, ASM exhibits enhanced bactericidal efficacy relative to the last-resort antibiotic colistin and successfully eradicates clinically isolated carbapenem-resistant *Acinetobacter baumannii* (CRAB) and methicillin-resistant *Staphylococcus aureus* (MRSA).

Introduction

WHO bacterial priority pathogen list 2024

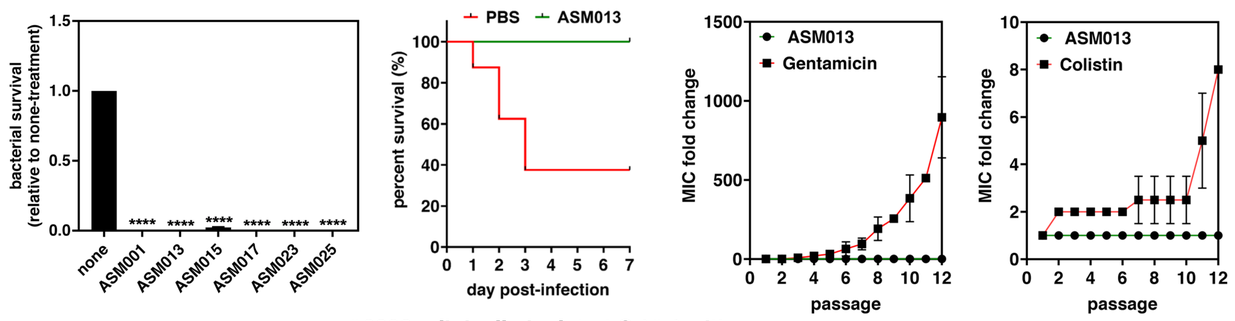


A functional amino acid derivatives possess advantage for novel drugs



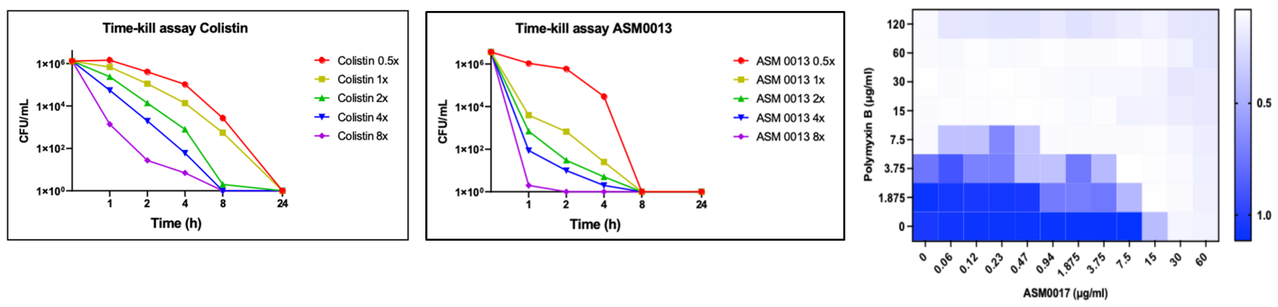
Result

1. ASM drugs can kill multidrug resistant *A. baumannii* and does not develop resistance

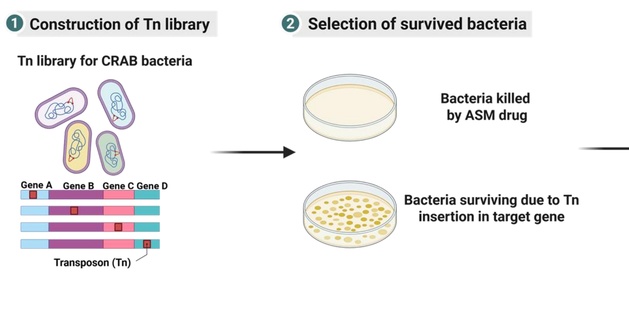


A0292: clinically isolated CRAB with high virulence

2. ASM drugs rapidly kill *A. baumannii* compared to colistin

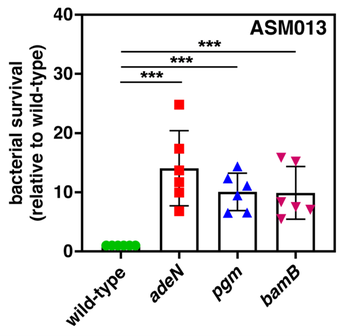


3. Identification of targets for ASM using transposon sequencing (Tn-Seq)



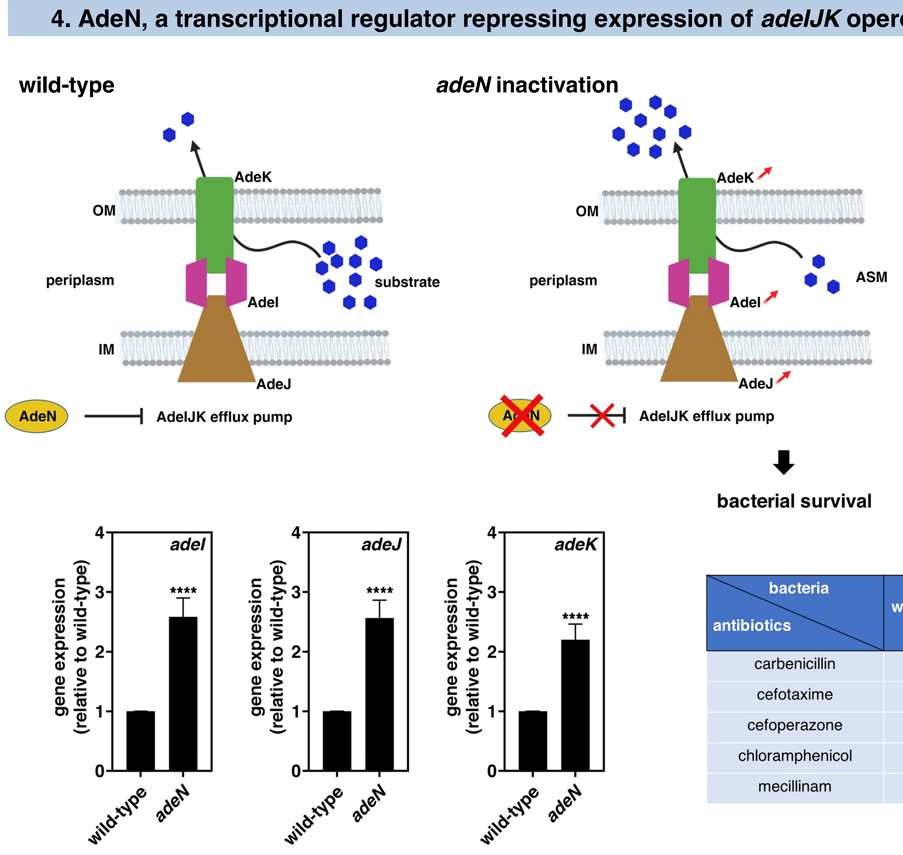
MIC (mg/L)

Strains	ASM001	ASM002
MRSA1	1	1
MRSA2	2	2
VRE1	2	1
VRE2	1	1
CRE1	16	>64
CRAB(Col R)	4	8
CRAB(Tig R)	8	16



Gene name	Product	BLAST
bapA	BapA/Bap/LapF family large adhesin	Specific to *A. baumannii*
adeN	multidrug efflux transcriptional repressor AdeN	Conserved
bamB	outer membrane protein assembly factor BamB	Conserved
pgm	phosphomannomutase/phosphoglucomutase (AlgC)	Conserved

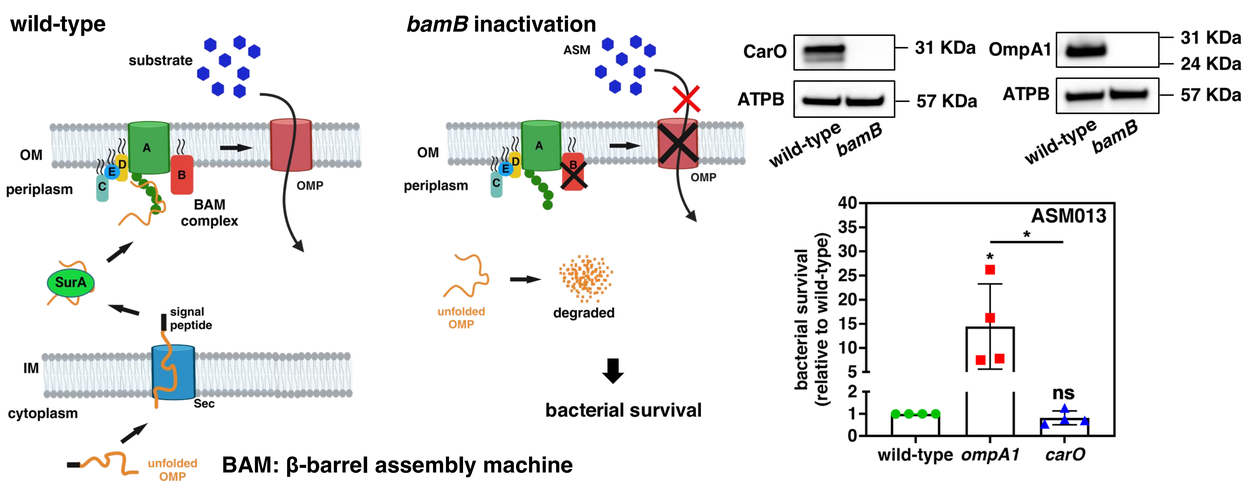
4. AdeN, a transcriptional regulator repressing expression of *adeIJK* operon, is not the target for ASM



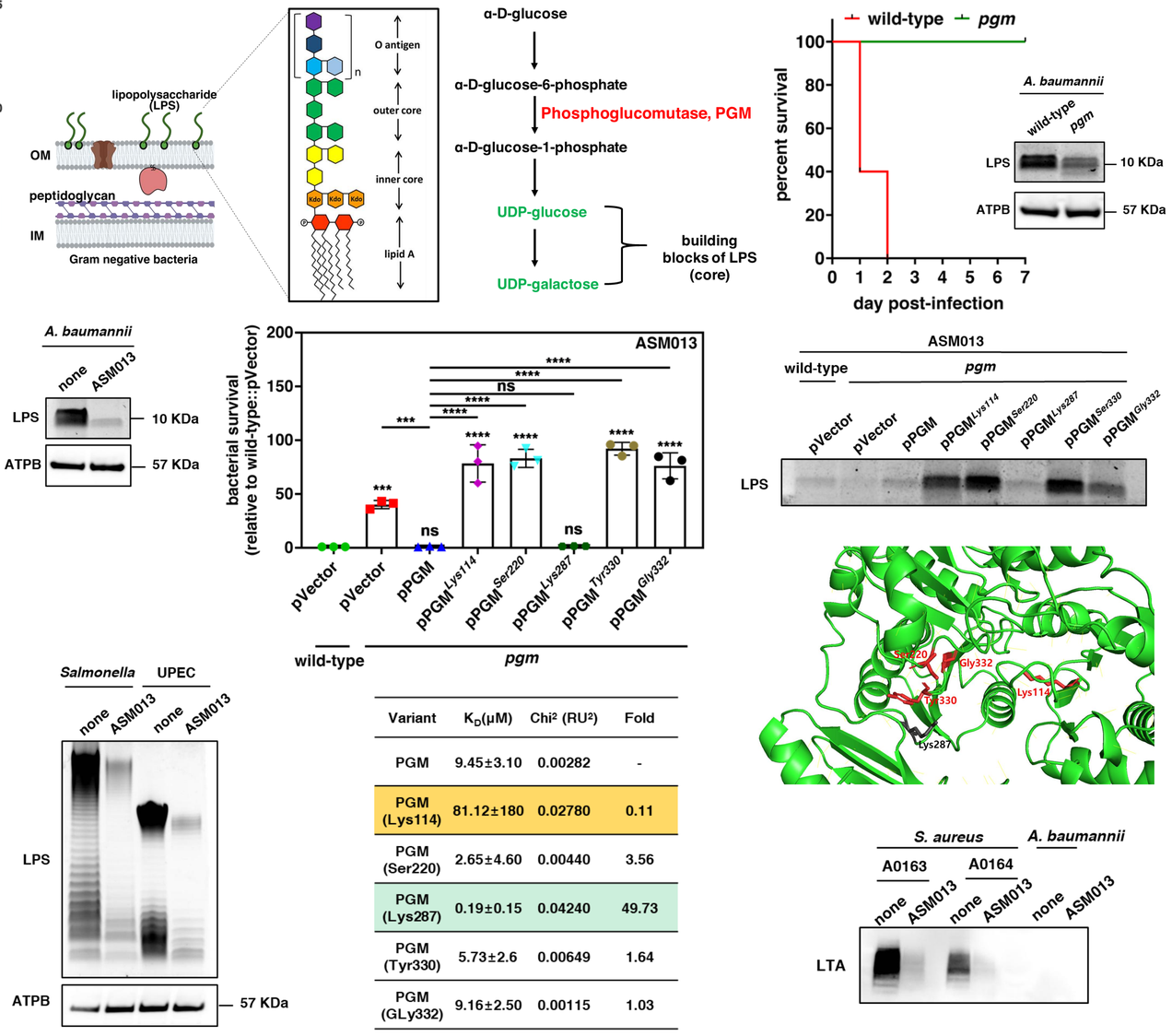
MIC (mg/L)

bacteria / antibiotics	wild-type	*adeI*	*adeJ*	*adeK*
carbenicillin	16	1	2	1
cefotaxime	8	1	1	1
cefoperazone	512	32	64	32
chloramphenicol	15.6	7.8	7.8	7.8
mecillinam	128	32	32	32

5. BamB, a lipoprotein critical for outer membrane protein (OMP) insertion, is not the target for ASM



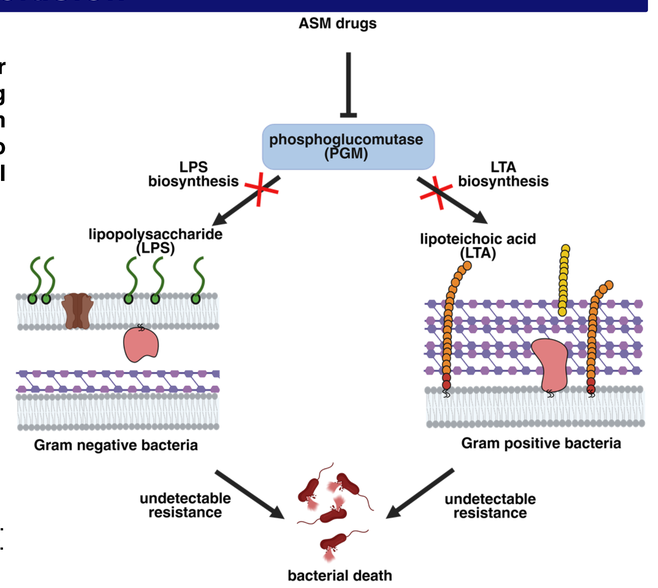
6. Phosphoglucomutase (PGM), an enzyme essential for LPS and LTA biosynthesis, is the target for ASM



Variant	K_D(μM)	Chi² (RU²)	Fold
PGM	9.45±3.10	0.00282	-
PGM (Lys114)	81.12±180	0.02780	0.11
PGM (Ser220)	2.65±4.60	0.00440	3.56
PGM (Lys287)	0.19±0.15	0.04240	49.73
PGM (Tyr330)	5.73±2.6	0.00649	1.64
PGM (GLy332)	9.16±2.50	0.00115	1.03

Conclusion

ASM signifies a possible therapeutic approach for patients with invasive infections caused by multi-drug resistant bacteria, such as CRAB and MRSA, for whom existing treatment options are insufficient, while also recognizing PGM as a viable target for antimicrobial drug development.



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