



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

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Abstract Introduction

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.

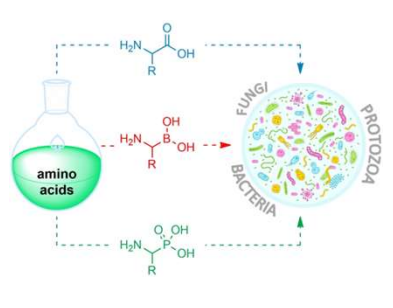
Here, we present a novel class of antibiotics termed ASM, a functional amino acid drug class that inhibit the production of LPS or LTA by targeting the enzyme phosphoglucomutase (PGM) in bacteria.

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).

WHO priority list for R&D of new antibiotics

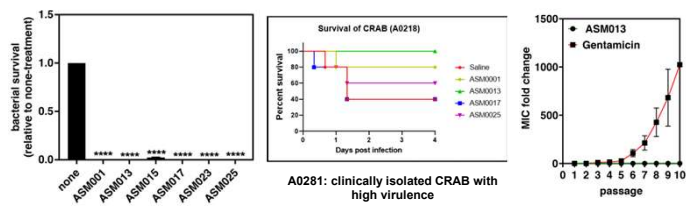
- Priority 1: CRITICAL
- Acinetobacter baumannii*, carbapenem-resistant
 - Pseudomonas aeruginosa*, carbapenem-resistant
 - Enterobacteriaceae*, carbapenem-resistant, 3rd generation cephalosporin-resistant
- Priority 2: HIGH
- Enterococcus faecium*, vancomycin-resistant
 - Staphylococcus aureus*, methicillin-resistant, vancomycin intermediate and resistant
 - Helicobacter pylori*, clarithromycin-resistant
 - Campylobacter*, fluoroquinolone-resistant
 - Salmonella* spp., fluoroquinolone-resistant
 - Neisseria gonorrhoeae*, 3rd generation cephalosporin-resistant, fluoroquinolone-resistant
- Priority 3: MEDIUM
- Streptococcus pneumoniae*, penicillin-non-susceptible
 - Haemophilus influenzae*, ampicillin-resistant
 - Shigella* spp., fluoroquinolone-resistant

Amino acid-based antimicrobial agents

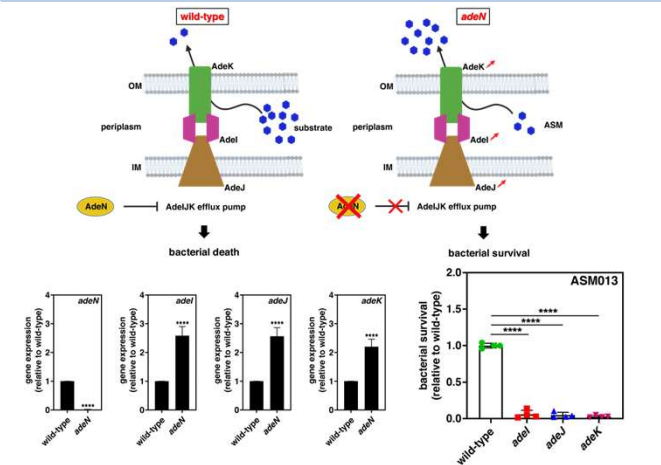


Result

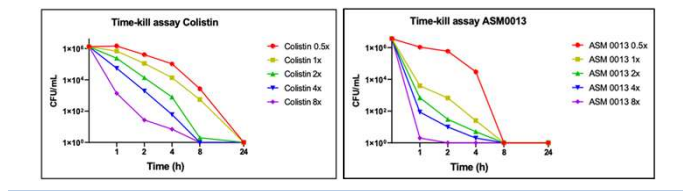
1. ASM efficiently kills *A. baumannii* and does not develop resistance



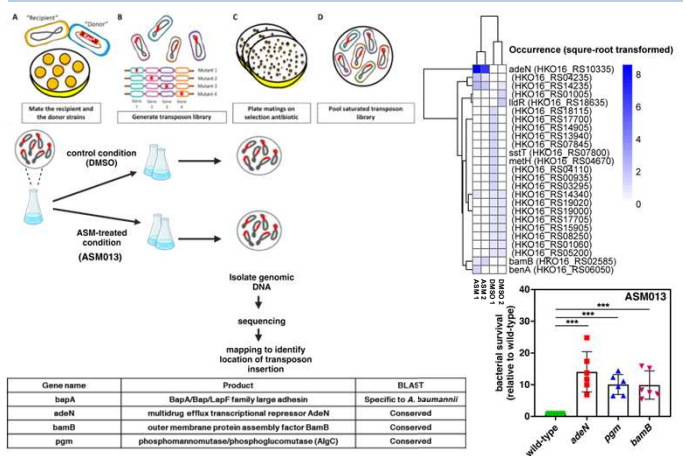
5. AdeN, a transcriptional regulator repressing expression of AdeLJK operon, is not the target for ASM



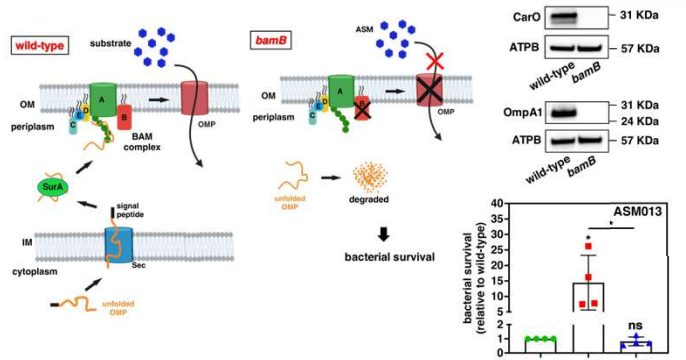
2. ASM has better bactericidal activity compared to colistin



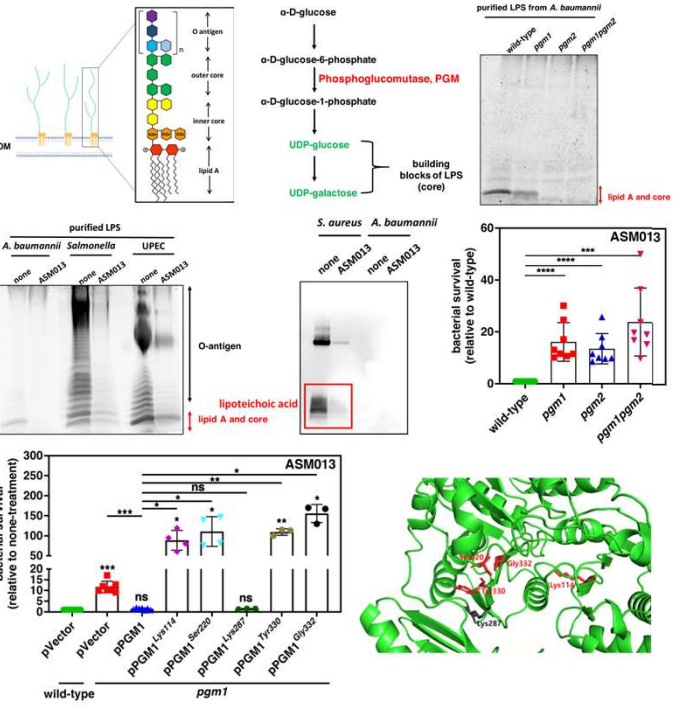
3. Identification of targets for ASM using transposon sequencing (Tn-Seq)



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



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



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