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Preclinical microbiome evaluation of novel PolC-inhibitor compounds

College of Pharmacy
UNIVERSITY OF HOUSTON

Khurshida Begum[1], Abdulwhab Shremo Msdi[1], Chenlin Hu[1], Neil Shaw, M Jahangir Alam[1], Eugenie Basseres[1], Taryn A. Eubank[1], Xiang Y. Yu[2], Lawrence I. Mortin[2], Michael H. Silverman[2], and Kevin W. Garey[1]

[1]University of Houston College of Pharmacy; [2]Acurx Pharmaceuticals, LLC

Send correspondence to:
Abdulwhab Shremo Msdi, PharmD, BCIDP
Email: ashremom@Central.UH.EDU

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Abstract: 7529

BACKGROUND

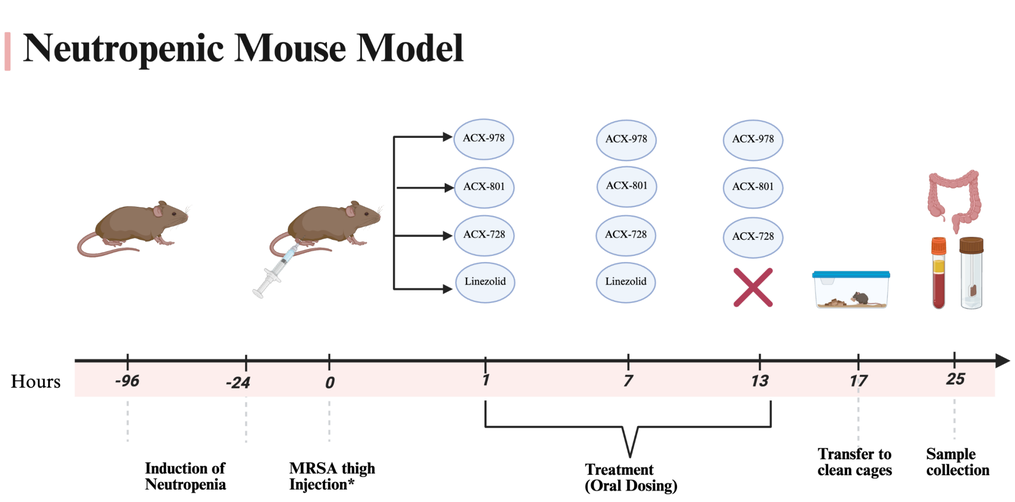
- PolC inhibition disrupts DNA replication in low GC-content Gram-positive bacteria, including priority pathogens such as Staphylococcus, Enterococcus, and Streptococcus species.[1]
- Ibezapolstat, a first-in-class PolC inhibitor for Clostridiodies difficile infection (CDI), demonstrated strong efficacy in phase 2 trial with microbiome preservation. [2, 3]
- Next-generation PolC inhibtor compounds, ACX-978, ACX-801, and ACX-728, were developed to enhance systemic exposure and Gram-positive coverage.[1]
- However, their microbiome effects have not been elucidated

METHODS

- Neutropenic CD-1 mice were infected intramuscularly with MRSA
- ACX compounds (100, 150 mg/kg, TID) and linezolid (100 mg/kg, BID) were administered orally beginning 1-hour post-infection (n=4/group)
- Controls included baseline and infection-only (placebo) groups
- Samples collected at 25 hours post-infection: plasma, feces, and thigh and colon tissue.
- Microbiome profiling: shotgun metagenomics (MetaPhlAn).
- Drug exposure quantified by LC-MS/MS.

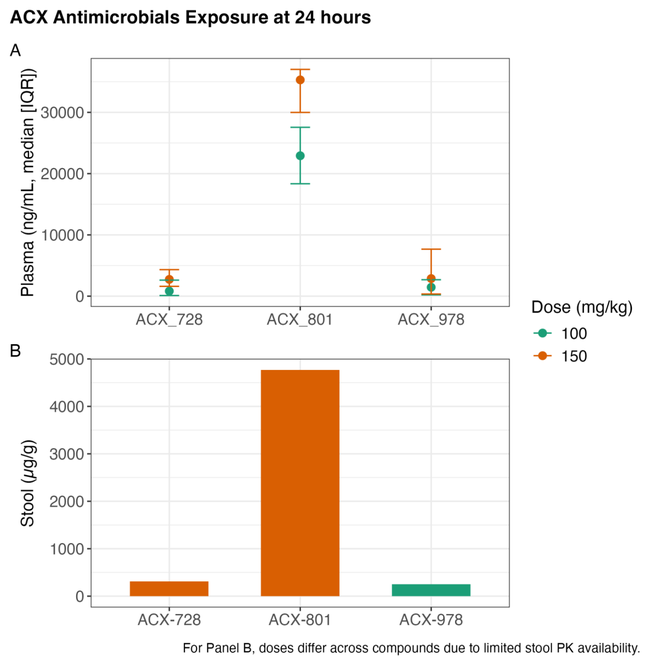
RESULTS

Figure 1. Study Design



*Induction of Neutropenia: Intraperitoneal cyclophosphamide injections

Figure 2. PolC inhibitors achieve good plasma and fecal levels at 24 hours



For Panel B, doses differ across compounds due to limited stool PK availability.

Figure 3. ACX compounds maintained higher microbial diversity and a community structure similar to baseline and distinct from linezolid Po

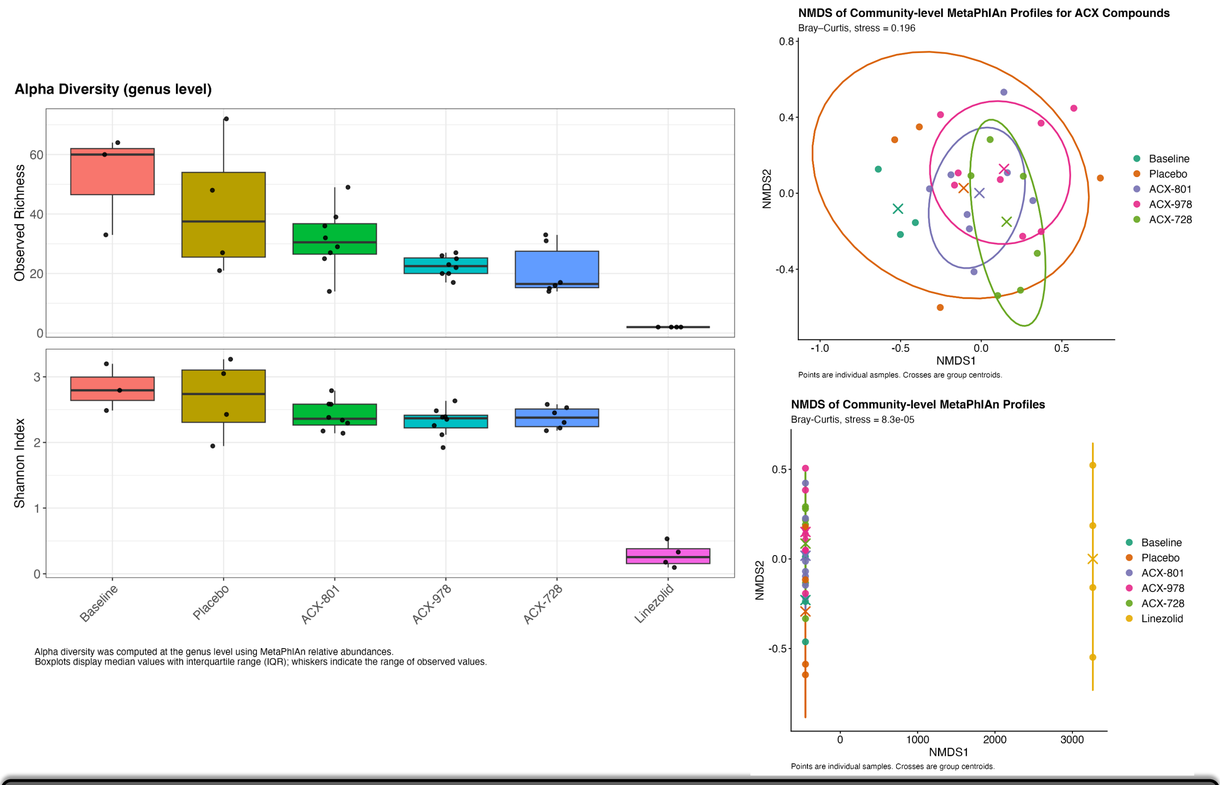


Figure 4. PolC inhibition preserves Bacteroidota-dominate community structure (Left Panel) and function (Right Panel)

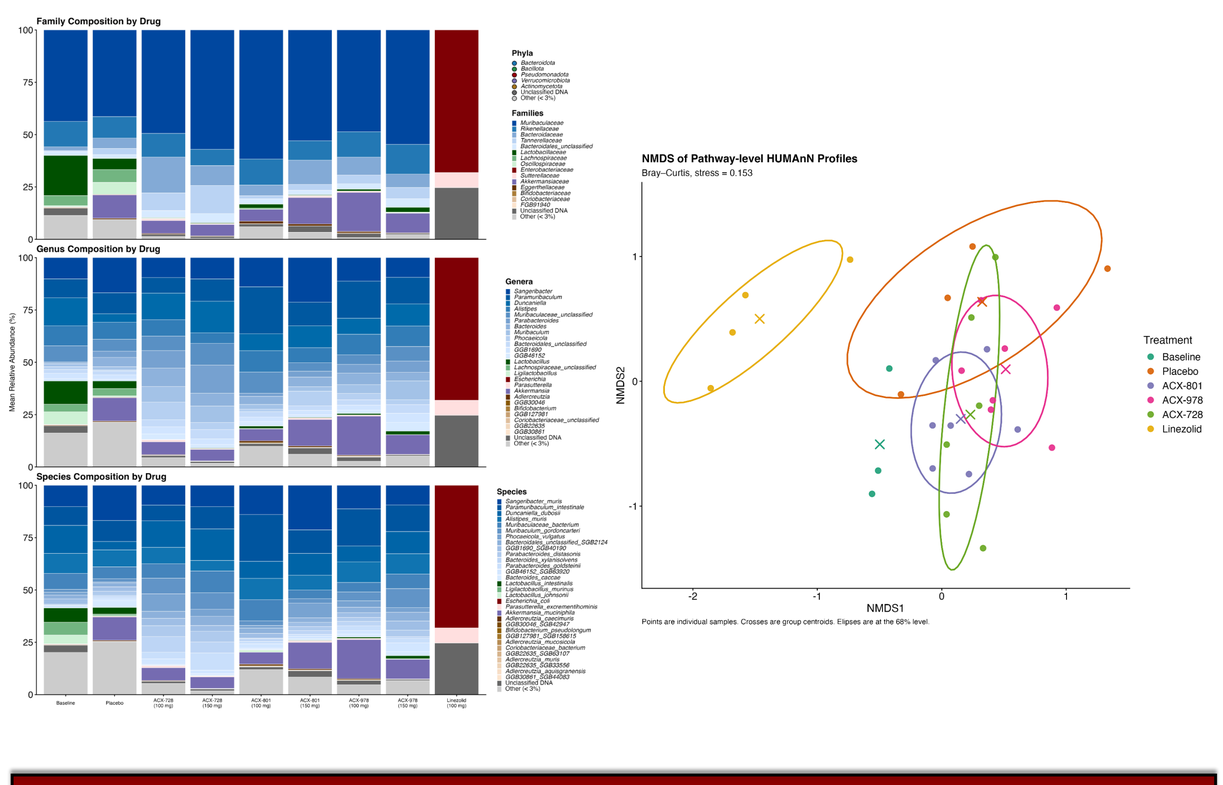
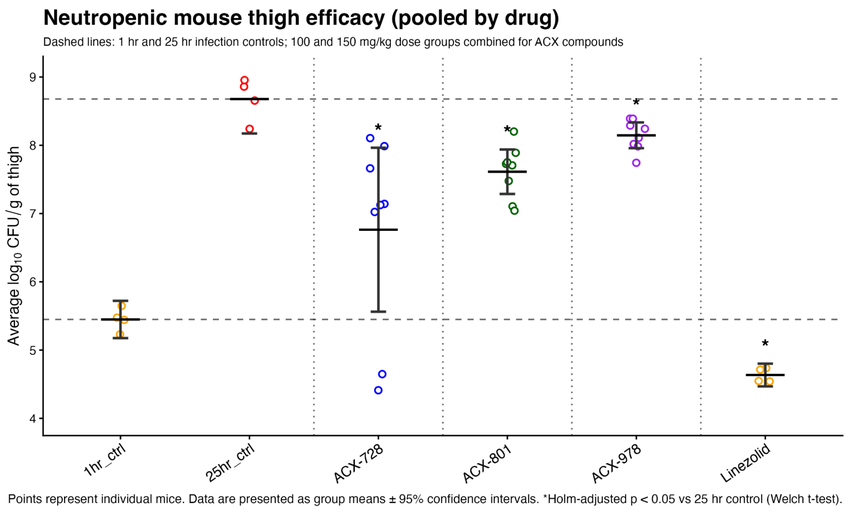


Figure 5. PolC inhibitors reduced MRSA burden in neutropenic mouse model



CONCLUSION

- PolC inhibitors demonstrate class-consistent microbiome preservation in concert with antibacterial activity (0.5 to 2.0 $\log_{10}$ reduction in CFU/g)
- Unlike linezolid, ACX compounds maintain Bacteroidota-dominant community structure and prevent Proteobacteria expansion.
- ACX-801 shows favorable systemic exposure with microbiome stability.
- PolC compounds represent a targeted strategy to treat resistant Gram-positive infections while preserving microbiome structure, minimizing downstream complications associated with antibiotic-induced dysbiosis

FUNDING

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3. Eubank TA, Jo J, Alam MJ, et al. Efficacy, safety, pharmacokinetics, and associated microbiome changes of ibezapolstat compared with vancomycin in adults with Clostridioides difficile infection: a phase 2b, randomised, double-blind, active-controlled, multicentre study. Lancet Microbe. Aug 2025;6(8):101126. doi:10.1016/j.lanmic.2025.101126