David J. Gonzalez, PhD

*Associate Professor*

[djgonzalez@ucsd.edu](mailto:djgonzalez@ucsd.edu)

31 October 2024

Dear Editorial Board,

My coauthors and I are pleased to resubmit our manuscript, titled **“Multi-omic Signatures of Host Response Associated with Presence, Type, and Outcome of Enterococcal Bacteremia,”** for consideration in *mSystems*. We have revised the manuscript in response to the reviewers' constructive feedback, which has enhanced its clarity and rigor. This updated version includes a machine learning analysis, as recommended by the reviewers, providing an alternative validation of our findings and reinforcing the strength of our conclusions.

In this study, we conducted a comprehensive multi-omic investigation of the systemic host responses to enterococcal bacteremia (EcB), a topic that we believe aligns closely with *mSystems*’ scope and interests. In brief, we analyzed human plasma samples enriched with clinical metadata using high-resolution tandem mass spectrometry-based proteomics and metabolomics to identify and evaluate features that (1) distinguish EcB from healthy controls, (2) differentiate infections by *E. faecalis* and *E. faecium*, and (3) correlate with patient survival outcomes. Our findings reveal several features capable of distinguishing EcB plasma from that of healthy controls with near-perfect discriminatory accuracy. By comparing these features with those identified in *Staphylococcus aureus* bacteremia, we provide insights into both conserved and distinct host responses relative to homeostasis. While significant distinctions were observed between *E. faecalis* and *E. faecium* bacteremia, these differences may not exceed the effectiveness of current clinical tests. Finally, we identified HRG and FETUB abundances as promising biomarkers for distinguishing survivors from non-survivors, offering potential clinical utility in prognosis.

In summary, our manuscript provides new insights into the systemic host responses underlying EcB and suggests potential clinical applications. We are confident that our findings will engage *mSystems* readers and advance the understanding of these clinically relevant enterococcal infections. Thank you for considering our manuscript, and we look forward to the opportunity to share our research through *mSystems*.

Sincerely,



David Gonzalez, Ph.D.