



Editors

Molecular Systems Biology

Submission Date: June 30, 2021

Dear Editors:

Enclosed is our submission of a manuscript entitled, “Novel metabolic drivers of virulence in *Clostridioides difficile* identified through genome-scale metabolic network analysis” for consideration in Molecular Systems Biology. We report (1) novel metabolic network reconstructions for two strains of this important pathogen, (2) integrate transcriptomic data new to this manuscript to predict metabolic trends associated with virulence, and (3) experimentally validate these novel, conserved shifts in metabolism. This is the first time that potential drivers of virulence expression have been identified across both *in vivo* and *in vitro* conditions using metabolic networks and then tested in the laboratory. We also anticipate these validated, well-curated computational models will be of significant value to those studying *C. difficile* and that the pipeline we present here will serve as a model for other microorganisms. In addition, the model-driven discovery of metabolic regulation of virulence-related phenotypes could enable the development of therapeutic strategies.

We appreciate the attention to our submission, and all raw data and code associated with this study are hosted on the NCBI Sequence Read Archive or GitHub respectively.

With best regards,

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