

To the Editorial Board of Cell Reports:

Thank you for your reviews of our manuscript, “Genome-scale architecture of small molecule regulatory networks and the fundamental trade-off between regulation and enzymatic activity.” by Ed Reznik, Dimitris Christodoulou, Elad Noor, and colleagues. After carefully going through the reviewers' comments, we felt that the points they raised were fair and thoughtful. We have addressed each of the reviewers' concerns, and find that these changes have strengthened the arguments and findings of the work. In particular, we have:

- Augmented the section on metabolic control analysis to include reversible and multi-substrate reactions. The SI Text now includes a comprehensive theoretical treatment of small molecule regulation, which highlights (among other things) the fundamental trade-off between regulation and enzyme activity.
- Clarified several confusing points regarding the potential role of thermodynamics, futile cycle regulation, and feedback inhibition from biosynthesis, in selection for small molecule regulation.
- Identified a set of “high-confidence” edges in the small-molecule regulatory network of *E. coli*, which can be used as prioritized candidates for putative functional regulators in future studies.

We believe that the combination of a first-of-its-kind (open-source) genome-scale reconstruction of a small molecule regulatory network, the novel theoretical insights derived from metabolic control analysis, and the evaluation of metabolic design principles that shape the regulatory network, will have a substantial impact on the study of metabolic regulation. In this regard, we are excited for the opportunity to have our work disseminated to the interdisciplinary readership of Cell Reports.

Sincerely,  
Elad Noor