To the Editorial Board of Cell Systems:

Please find enclosed our manuscript “Common Signatures of Tumor Metabolism Across Distinct Tissues of Origin” by Ed Reznik, Augustin Luna, Chris Sander, and colleagues for consideration for publication in Cell Systems. In it, we describe the first large-scale “pan-cancer” analysis of cancer tissue metabolomics data, spanning ~900 tissue samples across 9 cancer types.

While altered metabolism is a well-accepted hallmark of cancer, the precise metabolic changes, including shifts in metabolite abundance, underlying tumorigenesis and progression to aggressive disease remain poorly characterized. While some alterations, such as the accumulation of 2-hydroxyglutarate in *IDH*-mutant tumors and the increased uptake of glucose and production of lactate in highly glycolytic cancers are well-characterized and have found clinical utility (i.e. as a biomarker for susceptibility to therapy, and as a drug target itself), the landscape of metabolic alterations across cancers of different tissues is poorly explored.

In our manuscript, we fill a major gap in cancer research by cataloguing and analyzing the metabolic alterations associated with the development and malignant progression of cancers. The main findings of the report are as follows:

1. **Production of an atlas of metabolic variation for 935 metabolites across 900 human normal and cancer tissues.** As part of our work, we release to the cancer and computational biology research communities a dataset that has undergone multiple rounds of processing, standardization, and curation. We have made both the code and compiled data accessible as an open-source project and provide a web-application.

   Code repository: https://github.com/dfci/pancanmet_analysis
   Web application: http://sanderlab.org/pancanmet

2. **Characterization of the landscape of recurrent metabolic alterations across cancers of different cells-of-origin**. We demonstrate that metabolic reprogramming depends strongly on the tissue-of-origin. Specifically, we find that certain cancers, such as those of the pancreas, show very few metabolic differences between themselves and adjacent-normal tissue, while others (such as kidney and breast cancers) show widespread differences. Despite this variation, we identify subset of metabolites, spanning central and peripheral metabolism, which are recurrently differentially abundant across many cancer types. Additionally, we identify the metabolic sub-networks that are targetable pharmacologically.

3. **Integrative analysis with clinical data identifies metabolites associated with aggressive disease.** Using a meta-analysis technique, we integrate clinical annotations on tumor grade with our dataset, and identify a subset of metabolites whose levels in tumors are recurrently associated with high/low tumor grade across many cancers. By applying the same approach to matched adjacent-normal tissue, we unexpectedly identify a handful of metabolites whose level in normal tissue are also indicative of tumor grade. The mechanisms driving this association are unknown, and we discuss several possibilities.

Memorial Sloan-Kettering Cancer Center
1275 York Avenue, New York, New York 10021

NCI-designated Comprehensive Cancer Center

We feel that our results will be equally appealing to biologists interested in the metabolic changes in across of tumors, as well as bioinformaticists eager to understand the insights found in this integrative analysis offered by examining the dysregulation of specific metabolites of clinical interest. Additionally, we have made efforts to make this work as transparent as possible by open-sourcing both the processing and analysis code as well as producing a web-application to allow for easy exploration of the data. Thus, we feel the work is well-suited for Cancer Cell.

Thank you for your consideration,

Ed Reznik, Augustin Luna, and Chris Sander

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