Identifying compounds to target host dependency factors of SARS-CoV-2

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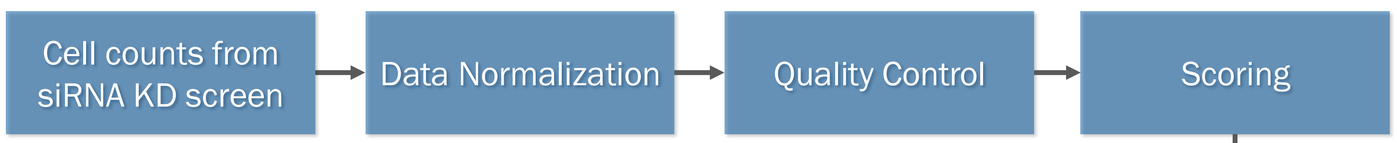
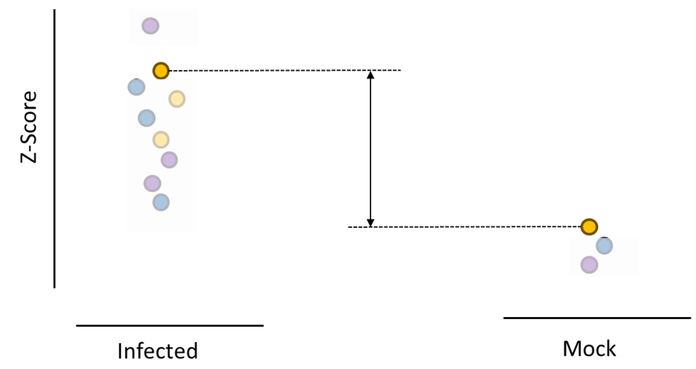
Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a highly transmissible and pathogenic coronavirus and several drug-resistant strains developed since its emergence in 2019. While CRISPR/Cas9 or RNA interference (RNAi) screens have been employed in numerous studies to identify relevant host factors (HDF), achieving robust and consistent identification poses a challenge (Edinger et al. 2014; Wagoner et al. 2022). In the present work, we screened over 27,000 small interfering RNAs (siRNAs) targeting 9,096 human genes in SARS-CoV-2 infected Caco-2 cells. To increase the robustness of potential hits, we incorporated a prioritization pipeline based on gene expression and protein-protein interaction network properties. Top-ranked host factors are enriched in transmembrane transport, energy metabolism, and the respirasome, indicating their importance for the virus. To further evaluate these results, we systematically searched drug databases to identify potential drugs targeting these processes.

Methods/Results



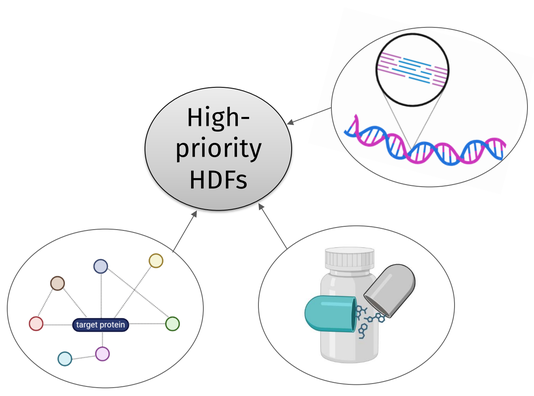
Genes are scored based on z-score difference



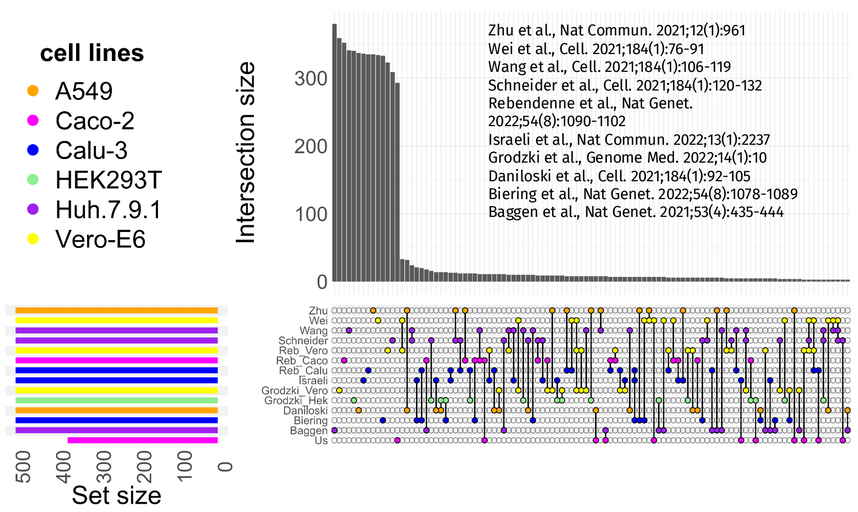
After identifying the siRNA construct with the second-best z-score difference, the z-score of the respective construct of non-infected cells was subtracted leading to the z-score difference which was used for selection.

Highly expressed, central proteins are prioritized

Genes known to be targets for available compounds were prioritized based on gene expression and cellular network properties derived from generic and virus specific protein-protein interactions.

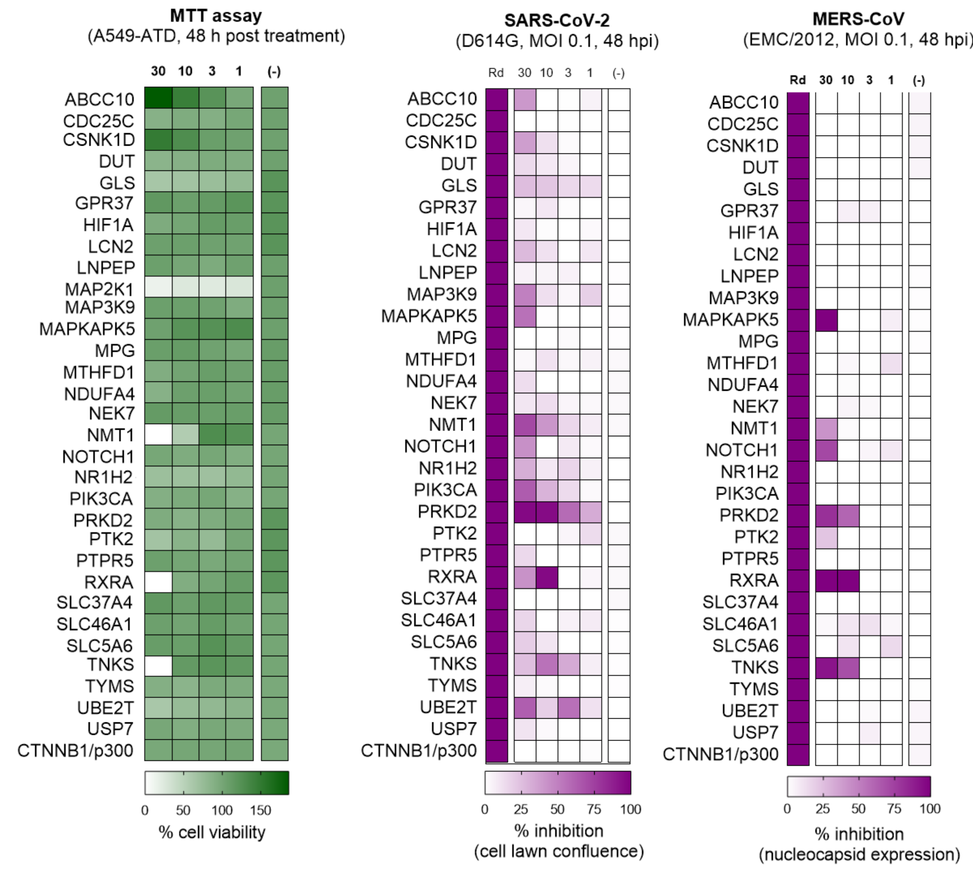


Identified HDFs are more consistent

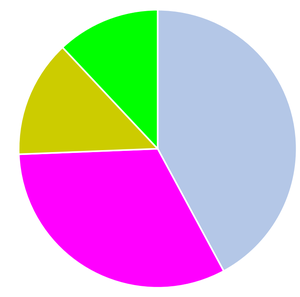


Compounds selected to inhibit HDFs

To experimentally validate our predictions, drug databases (e.g., DrugBank, ChEMBL, BindingDB) were systematically screened to identify the most promising inhibitors from over 500,000 compounds. Cell viability assays where performed with the treated cells .



Enrichment of HDFs in transmembrane transport, energy metabolism and the respirasome



Term Name	p-Value
carboxylic acid transmembrane transporter activity	2.49E-02
organic acid transmembrane transporter activity	2.64E-02
nuclear envelope	2.71E-03
nuclear membrane	4.63E-02
protein serine kinase activity	1.66E-05
protein serine/threonine kinase activity	1.04E-06
nucleoside diphosphate metabolic process	1.57E-03
aspartate family amino acid metabolic process	1.05E-02
glycolytic process	1.10E-02
ATP generation from ADP	1.21E-02

Discussion

A systematic siRNA knock-down screen and prioritizion approach was performed to identify potential host dependency factors for SARS-CoV-2. The enrichment of top-ranking HDFs in processes related to transmembrane transport, energy metabolism and the respirasome implies a crucial role of these cellular processes in the SARS-CoV-2 infection cycle. While further experimental validations of the identified inhibitors of these HDFs is ongoing, these findings may pave the way for identifying SARS-CoV-2 host dependency antivirals opening new perspectives to improved treatment options.

References

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