Repurposing Drugs for Treatment of Cardiovascular Disease Caused by SARS-CoV-2

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Disease Modules in the Interactome

Curation of all experimentally validated protein-protein interactions in the human cell that form the human interactome

- Binary PPI (Y2H, IntAct, MINT)
- Regulatory (TRANSFAC)
- Metabolic (CORUM)
- Kinase and Signaling Networks
- Literature Curation (IntAct, MINT, BioGrid, HPRD)

--Menche, et al., Science 2015;347:1257601
Disease Module Derivation: Cerebrovascular Disease

- Identify disease phenotype of interest (CBVD).
- Ascertain disease network components (‘seed’ proteins).
- Map ‘seed’ proteins to interactome.
- Identify disease module(s) within interactome network.

The interactome provides the ‘missing links’ among disease-associated proteins in the disease module.

--Wang & Loscalzo, J Mol Biol 2018;430:2939-50
COVID-19 Disease Module: The Pulmonary Covidome

- 332 human proteins to which 26 SARS-CoV-2 proteins bind (Gordon et al., Nature, 2020), mapped to the interactome

- Repurposing candidates must target proteins within the covidome or very near it.

COVID-19 Disease Module: The Cardiac Covidome

- 332 human proteins to which 26 SARS-CoV-2 proteins bind (Gordon et al., Nature, 2020), mapped to the interactome

- Repurposing candidates must target proteins within the covidome or very near it.
COVID-19 Disease Module: Overlap with Obesity Module

- One of four disease modules that overlap with the covidome
- Nominal statistical significance: $p=0.06$
Two Strategies for Drug Target Identification

Network-based Drug Target ID

Network-based Drug Repurposing: The Proximity Hypothesis

Disease Module

Drug Target
COVID-19 Disease Module and Interactions

Viral-Human Protein-Protein Interaction

Human-Human Protein-Protein Interaction

Drug Target-Human Protein-Protein Interaction

Viral Interactome

Human Interactome

Covidome

COVID-19 Disease Module

Drug Target-Disease Module

General Approach to Drug Target Identification in the Covidome

Methods

Network Proximity
3 pipelines

Network Diffusion
5 pipelines

Network AI
4 pipelines

Combined ROC

Individual methods offer complementary information harnessed by the combined ranking algorithm for optimal predictive power.

Curated Drug Ranking & HTS

--Drugs in clinical trials shown in green--greater intensity indicates greater number of trials.

--Drugs with reported positive effects (e.g., ritonavir, ivermectin) appear in list.

--We cannot tell whether a drug on this list will suppress the infection or worsen it; in vitro testing is essential.

--This list does not provide information on other drug targets, which may lead to adverse effects (such as with hydroxychloroquine).

--HTS for SARS-CoV-2 in vitro viricidal activity yielded ~50% success rate (far greater than the <1% hit rate of random screenings).

Creating a Comprehensive Atlas of Human Protein-Drug (Small Molecule) Interactions

Lawrence Livermore National Laboratory—Sierra System (near exa-scale)

Center for Accelerated Drug Discovery

Human Proteins: 28,658 models for 14,119 proteins
Experimental structures (>35%): 7,874
Experimental structures (>10%): 9,894

Small Molecule Compounds: ~2M
ChEMBL: 1.5M
Approved drugs: 5,557
Foodome: 26,490
NCI60: 244,801
ZINC Biogenic: 135,335

Specific interactions between drugs and protein targets will be used to map the drug targets to the PPI, which should yield comprehensive information on the breadth of disease treatments and adverse effects.
Ongoing Work

--Test top hits in human cell assays with SARS-CoV-2: HuH-7, Calu-3, pericytes, ECs, CMs.

--Study repurposed drug combinations.

--LLNL--CADD high-performance computing analysis of potential repurposed drug targets in or near the covidome

--Proposed human trials
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