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

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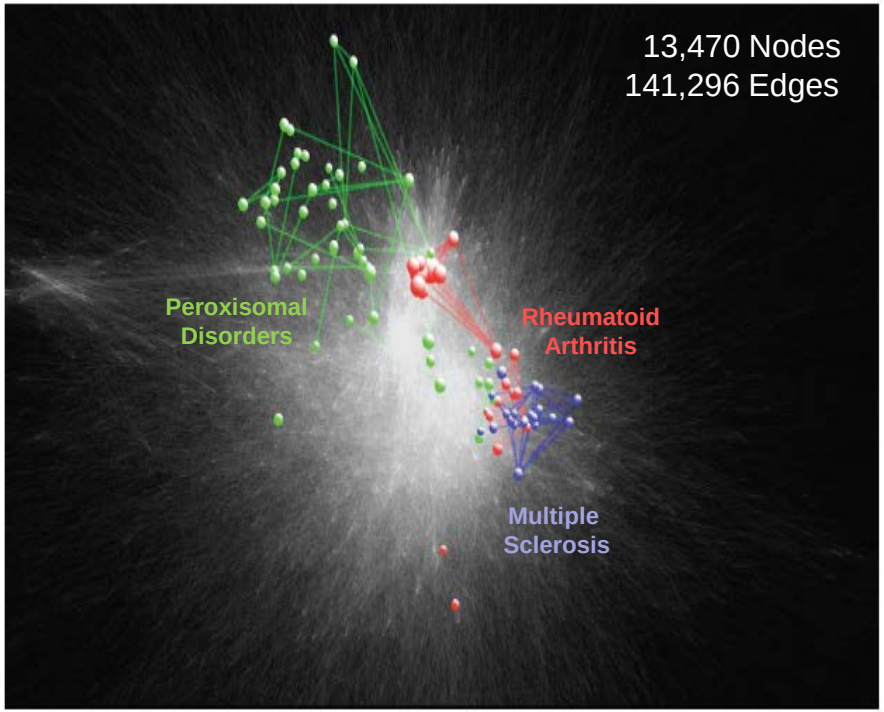
Disease Modules in the Interactome



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

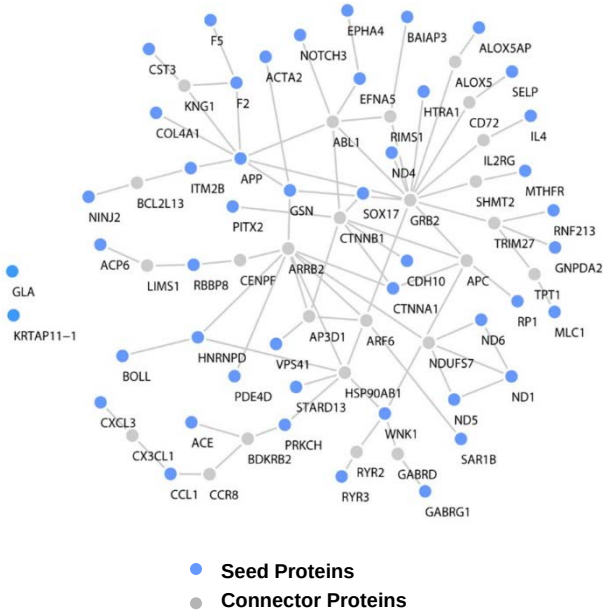
- Binary PPI (Y2H, IntAct, MINT)
- Regulatory (TRANSFAC)
- Metabolic (CORUM)
- Kinase and Signaling Networks
- Literature Curation (IntAct, MINT, BioGrid, HPRD)

--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.

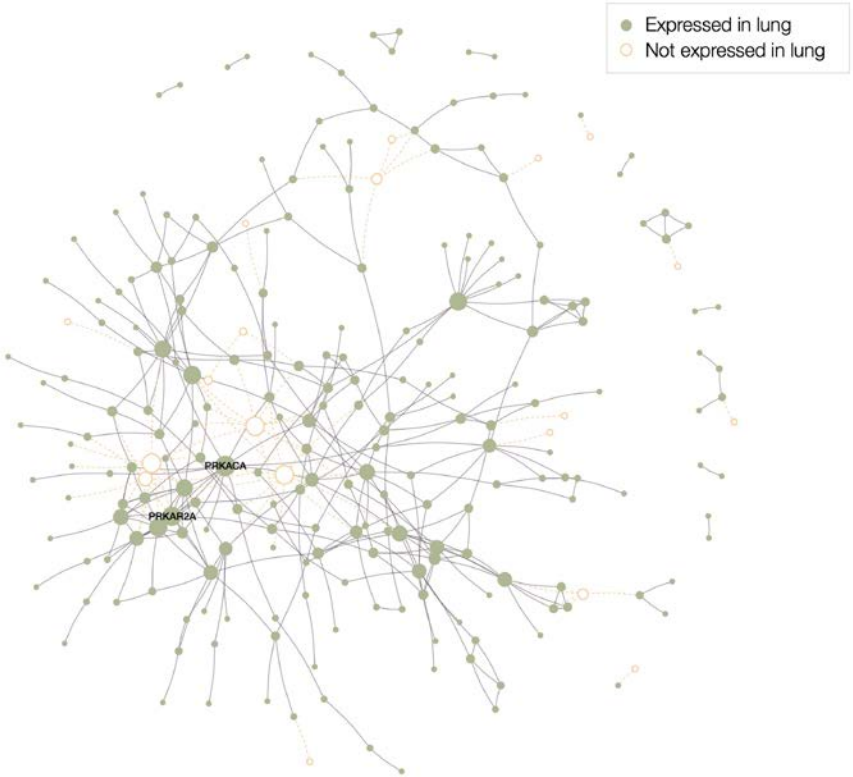
CBVD Proto-module



--Wang & Loscalzo, J Mol Biol 2018;430:2939-50

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

COVID-19 Disease Module: The Pulmonary Covidome

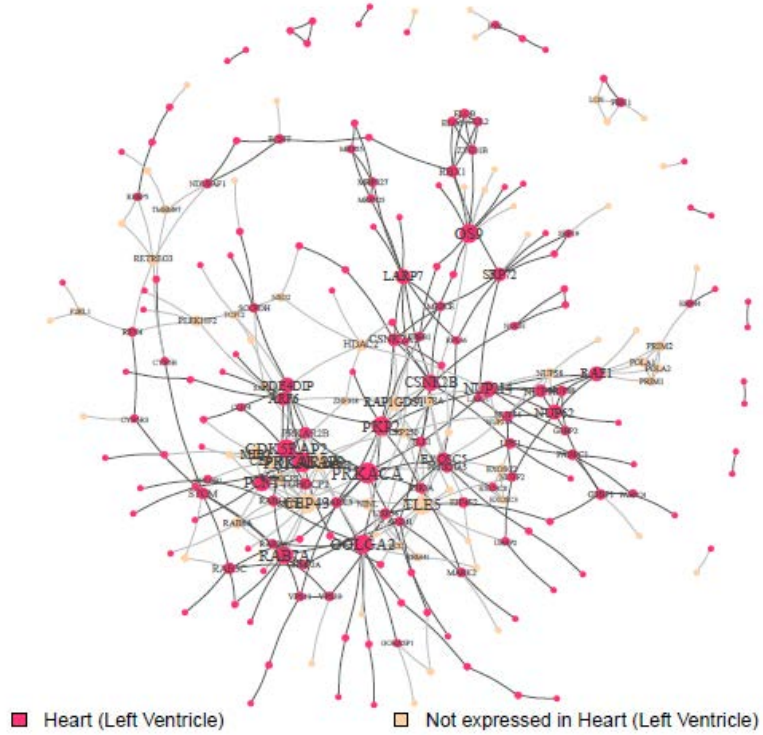


- 332 human proteins to which 26 SARS-CoV-2 proteins bind *(Gordon et al., Nature, 2020)*, mapped to the interactome

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

https://arxiv.org/abs/2004.07229

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

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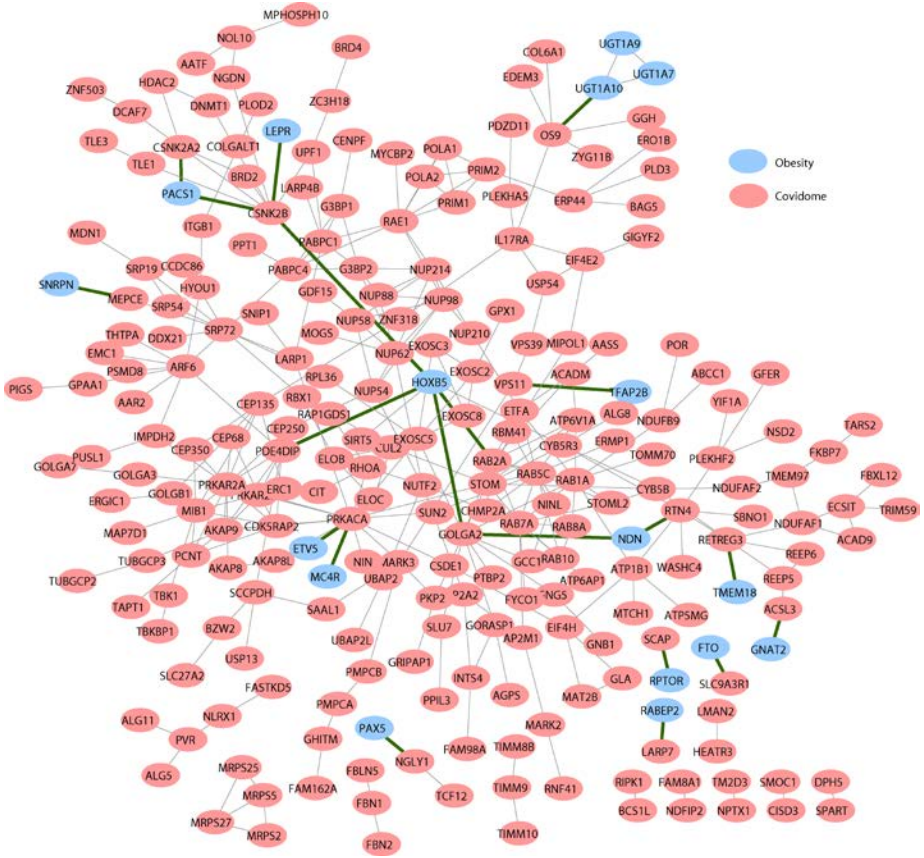
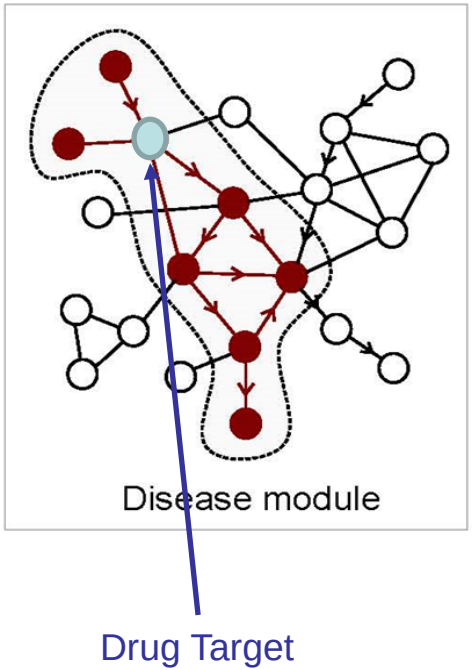
COVID-19 Disease Module: Overlap with Obesity Module



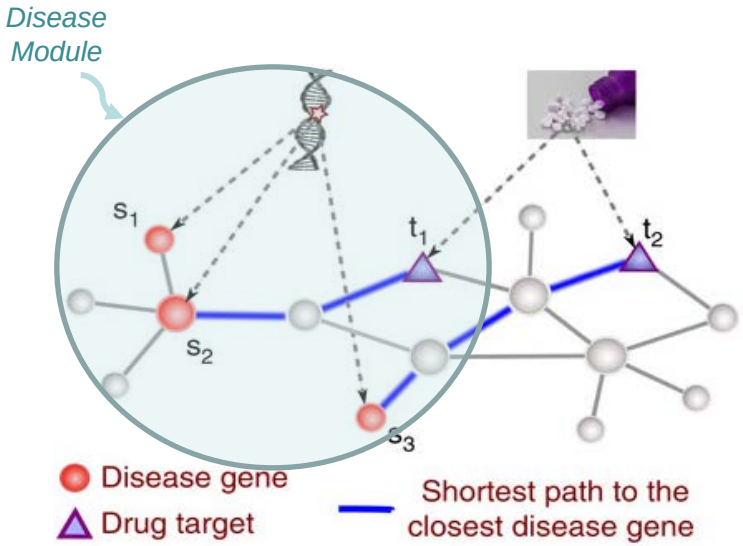
- One of four disease modules that overlap with the covidome
- Nominal statistical significance: p=0.06

Two Strategies for Drug Target Identification

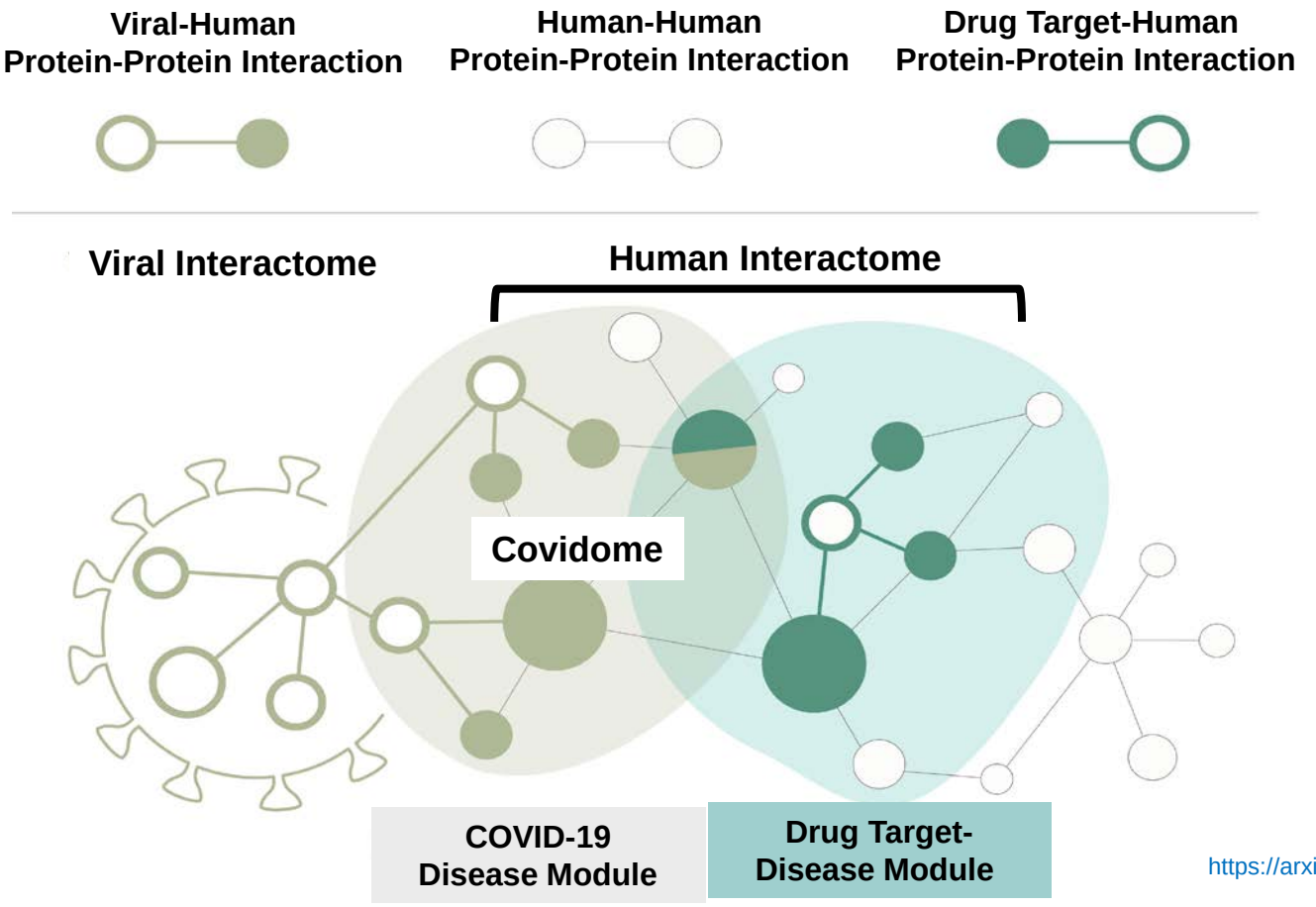
Network-based Drug Target ID



Network-based Drug Repurposing: The Proximity Hypothesis



COVID-19 Disease Module and Interactions



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General Approach to Drug Target Identification in the Covidome

Combined ROC

Methods

Network Proximity
3 pipelines

Network Diffusion
5 pipelines

Network AI
4 pipelines

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

https://arxiv.org/abs/2004.07229

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).

https://arxiv.org/abs/2004.07229

◯ # of Clinical trials from ClinicalTrials.gov

Drug	C-rank
(20) Ritonavir	1
Isoniazid	2
Troleandomycin	3
Cilostazol	4
(76) Chloroquine	5
Rifabutin	6
Flutamide	7
(2) Dexamethasone	8
Rifaximin	9
Azelastine	10
Folic Acid	16
Rabeprazole	27
Methotrexate	32
Digoxin	33
Theophylline	34
Fluconazole	41
Aminoglutethimide	42
(67) Hydroxychloroquine	44
Methimazole	47
(1) Ribavirin	49
(1) Omeprazole	50
Bortezomib	53
Leflunomide	54
Dimethylfumarate	55
(4) Colchicine	57
Quercetin	63
Mebendazole	67

Drug	C-rank
Mesalazine	69
Pentamidine	92
Verapamil	98
Melatonin	109
Griseofulvin	112
Auranofin	118
(1) Atovaquone	124
Montelukast	131
Romidepsin	138
(1) Cobicistat	141
(17) Lopinavir	146
Pomalidomide	155
Sulfinpyrazone	157
(1) Levamisole	161
Calcitriol	164
(1) Interferon-β-1a	173
Praziquantel	176
(1) Ascorbic acid	195
Fluvastatin	199
(1) Interferon-β-1b	203
Selegiline	206
(1) Deferoxamine	227
Ivermectin	235
(1) Atorvastatin	243
Mitoxantrone	250
Glyburide	259
(2) Thalidomide	262

Drug	C-rank
Sulfanilamide	265
Hydralazine	269
Gemfibrozil	281
(4) Ruxolitinib	284
Propranolol	297
Carbamazepine	301
Doxorubicin	309
Levothyroxine	329
Dactinomycin	335
Tenofivir	338
Tadalafil	339
Doxazosin	367
Rosiglitazone	397
Aminolevulinic acid	398
Nitroglycerin	418
Metformin	457
(1) Nintedanib	466
Allopurinol	471
Ponatinib	491
(1) Sildenafil	493
Dapagliflozin	504
Nitroprusside	515
Cinacalcet	553
Mexiletine	559
Sitagliptin	706
Carfilzomib	765
(1) Azithromycin	786

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

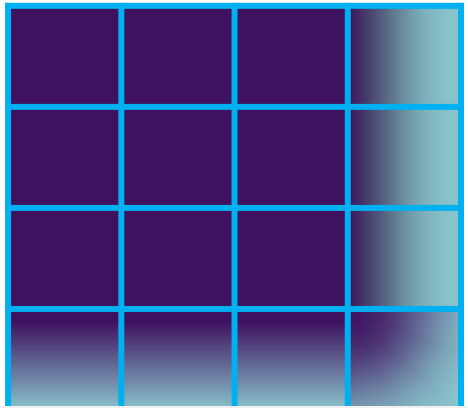
Human Proteins: 28,658 models for 14,119 proteins
Experimental structures (>35%): 7,874
Experimental structures (>10%): 9,894

M

Small Molecule Compounds: ~2M

ChEMBL:	1.5M
Approved drugs:	5,557
Foodome:	26,490
NCI60:	244,801
ZINC Biogenic:	135,335

N



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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