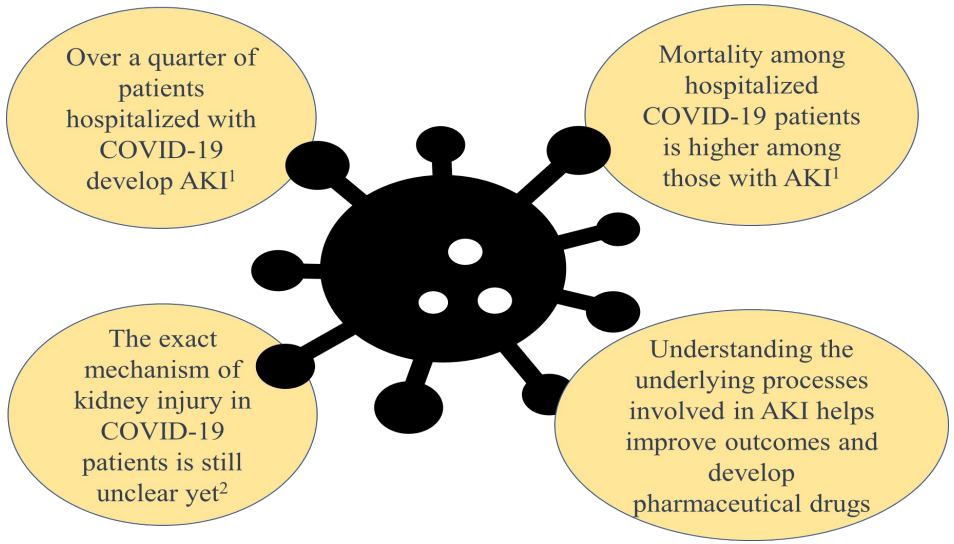
Ontological Representation and Analysis of the Molecular Interactions Related to COVID-19-associated Acute Kidney Injury

Ghida Arnous, **Yongqun "Oliver" He**, Ph.D.
University of Michigan, Ann Arbor, MI

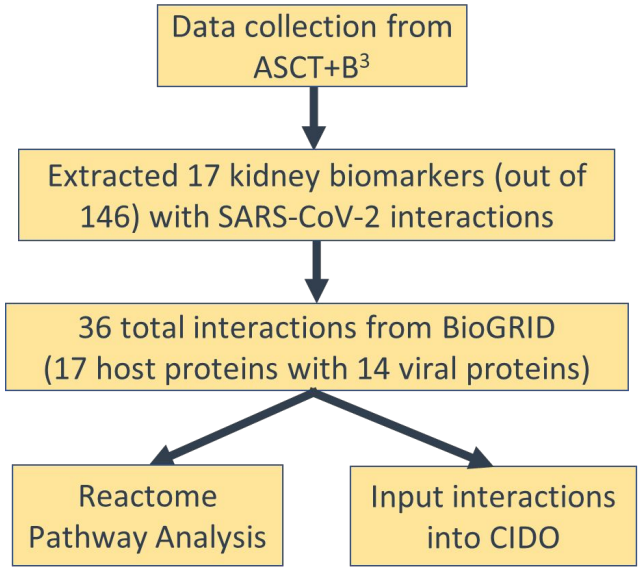
Why AKI and COVID-19?



Hypothesis:

We hypothesize that COVID-19 associated AKI is a result of protein-protein interactions between host and viral proteins.

Workflow



Results

Host protein	Entrez Gene ID	Viral protein	Evidence code/role/HT 1	ref PubMed/or DOI 1	Evidence code/role/HT 2	ref PubMed ID 2
SERPINE2	5270	ORF8	Proximity Label-MS, BAIT, High	doi: 10.1101/2020.09.03.282103		
SERPINE2	5270	M	Affinity Capture- MS, BAIT, High	33845483		
ITGAL	3683	ORF7A	Reconsituted complex, BAIT, Low	18020948		
KIT	3815	ORF3A	Affinity Capture- MS, BAIT, High	2838362		
CLDN1	9076	ORF7B	affinity Capture- MS, BAIT, High	33845483	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955
CLDN1	9076	M	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
CLDN1	9076	S	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
LRP2	4036	NSP4	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.269175
LRP2	4036	ORF3A	proximity Label-MS, BAIT, High	doi: 10.1101/2020.12.31.424961	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955
LRP2	4036	ORF3B	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
LRP2	4036	ORF7B	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
SLC5A2	6524	ORF7A	proximity Label-MS, BAIT, High	doi: 10.1101/2020.12.31.424961		
LILRB2	10288	S	reconsituted complex, HIT, High	doi: 10.1101/2020.09.09.287508		
ROBO1	6091	ORF7B	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955	proximity Label-MS, BAIT, High	doi: 10.1101/2020.09.03.282103
ROBO1	6091	M	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
ROBO1	6091	NSP4	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
ROBO1	6091	ORF3A	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
ROBO1	6091	ORF3B	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
ROBO1	6091	S	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
SATB2	23314	NSP9	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
ROBO2	6092	M	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
ROBO2	6092	ORF3A	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
ROBO2	6092	ORF7B	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
ROBO2	6092	S	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955		
MYH11	4629	NSP2	proximity Label-MS, BAIT, High	34709727		
MYH11	4629	NSP7	proximity Label-MS, BAIT, High	34709727		
MYH11	4629	NSP9	proximity Label-MS, BAIT, High	doi: 10.1101/2020.09.03.282103		
ALDOB	229	ORF3A	affinity Capture- MS, BAIT, High	32838362		
SH3GL3	6457	M	proximity Label-MS, BAIT, High	doi: 10.1101/2020.12.31.424961	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.272955
SH3GL3	6457	ORF6	affinity Capture- MS, BAIT, High	32838362		
FBLN5	10516	NSP9	affinity Capture- MS, BAIT, High	32353859	affinity Capture- MS, BAIT, High	33060197
MCAM	4162	ORF7B	affinity Capture- MS, BAIT, High	doi: 10.1101/2020.12.31.424961	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.269175
MCAM	4162	ORF3B	proximity Label-MS, BAIT, High	doi: 10.1101/2020.08.28.269175		
MCAM	4162	S	proximity Label-MS, BAIT, High	doi: 10.1101/2020.09.03.282103		
PLAT	5327	ORF8	affinity Capture- MS, BAIT, High	32353859	affinity Capture- MS, BAIT, High	33060197
SYNPO2	171024	NSP13	proximity Label-MS, BAIT, High	doi: 10.1101/2020.09.03.282103		

Table 1. Interactions between 17 ACST+B kidney biomarkers and SARS-CoV-2 proteins from BioGRID.

Pathway name	Curated found	Curated Total	Interactor found	Interactor Total	Entities found	Entities Total	Entities ratio	Entities pValue
SLIT2:ROBO1 increases RHOA activity	1	8	0	0	1	8	0	1.18E-2
Signaling by ROBO receptors	4	235	1	406	4	618	0.028	1.26E-2
Role of ABL in ROBO-SLIT signaling	1	10	0	0	1	10	0	1.47E-2
Inactivation of CDC42 and RAC1	1	12	0	0	1	12	0.001	1.76E-2
Activation of RAC1	1	15	0	0	1	15	0.001	2.19E-2
Regulation of cortical dendrite branching	2	4	0	159	2	163	0.007	2.42E-2
Transport of RCbl within the body	1	14	0	3	1	17	0.001	2.48E-2
Cargo recognition for clathrin-mediated endocytosis	2	115	0	59	2	166	0.007	2.5E-2
Sema4D induced cell migration and growth-cone collapse	1	25	0	0	1	25	0.001	3.63E-2
GRB7 events in ERBB2 signaling	0	6	1	22	1	26	0.001	3.77E-2
Sema4D in semaphorin signaling	1	31	0	0	1	31	0.001	4.48E-2
Clathrin-mediated endocytosis	2	161	0	87	2	231	0.01	4.57E-2
Signaling by KIT in disease	1	28	0	8	1	35	0.002	5.04E-2
Signaling by phosphorylated juxtamembrane, extracellular and kinase domain KIT mutants	1	28	0	8	1	35	0.002	5.04E-2
InlB-mediated entry of Listeria monocytogenes into host cell	1	19	0	22	1	38	0.002	5.46E-2
Modulation by Mtb of host immune system	0	11	1	29	1	38	0.002	5.46E-2
PLC-gamma1 signalling	0	5	1	37	1	41	0.002	5.88E-2
Cellular hexose transport	1	28	0	13	1	41	0.002	5.88E-2
PLCG1 events in ERBB2 signaling	0	6	1	37	1	42	0.002	6.02E-2
Activated NTRK3 signals through PLCG1	0	5	1	37	1	42	0.002	6.02E-2

Fig. 1. Reactome analysis of 17 AKI biomarkers found 2 genes involved in ROBO signaling (ROBO1 and ROBO2), likely important in AKI mechanism[4].

By using ASCT+B and BioGRID, we found 17 biomarkers (out of 146) interacting with 14 SARS-CoV-2 viral proteins, yielding a total of 36 interactions.

Coronavirus Infectious Disease Ontology (CIDO) modelling

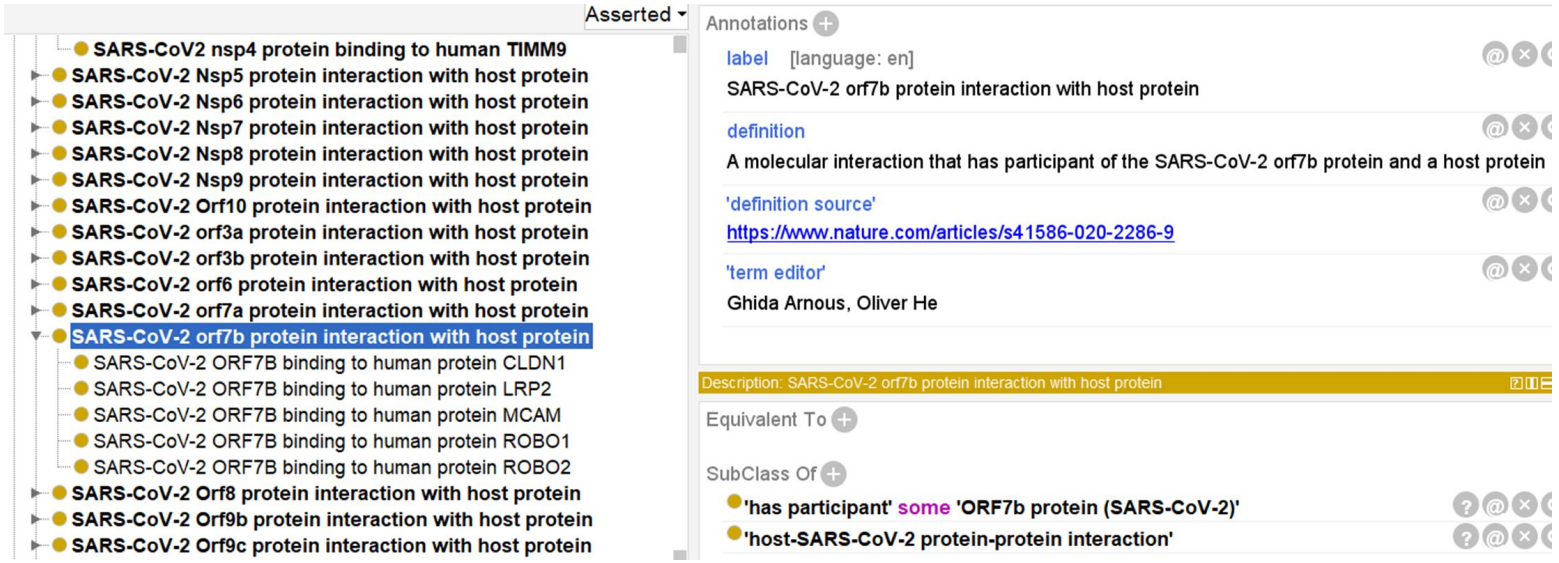


Fig. 2. CIDO-based classification and hierarchy of newly added SARS-CoV-2 and host PPIs. 5 out of 36 of the PPIs are shown in the above figure, particularly the interactions with ORF7B protein. Associated annotations are also shown on the right.

Our CIDO-based ontological representation provides a systematic and computer-interpretable logic knowledge representation of the molecular interactions related to COVID-19-associated AKI mechanisms.

Summary and next steps

We collected and analysed proteins and interactions related to COVID-19 associated AKI.

Each of the 17 kidney biomarkers recorded in ASCT+B Kidney table has demonstrated interaction(s) with SARS-CoV-2 viral protein(s), suggesting that the coronavirus closely interacts with the kidney biomarkers.

SLITs and ROBO signalling, found in our host-coronavirus interaction study, are likely associated with COVID-19 associated kidney injury.

The human-coronavirus PPIs are ontologically represented in the CIDO ontology, which can be further enhanced and used to support COVID-19 related AKI studies.