Frederick National Laboratory
for Cancer Research

sponsored by the National Cancer Institute

Updates and interesting papers review

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June 12, 2020

Agenda

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- **Github account for AMPL_Support**
- **Student interactions (VM image testing regarding)**
- **Amazon EC2 cloud (login regarding)**
- **NCATS assay (very interesting data)**
- **Interesting papers**

GitHub repo: https://github.com/CBIIT/AMPL_support

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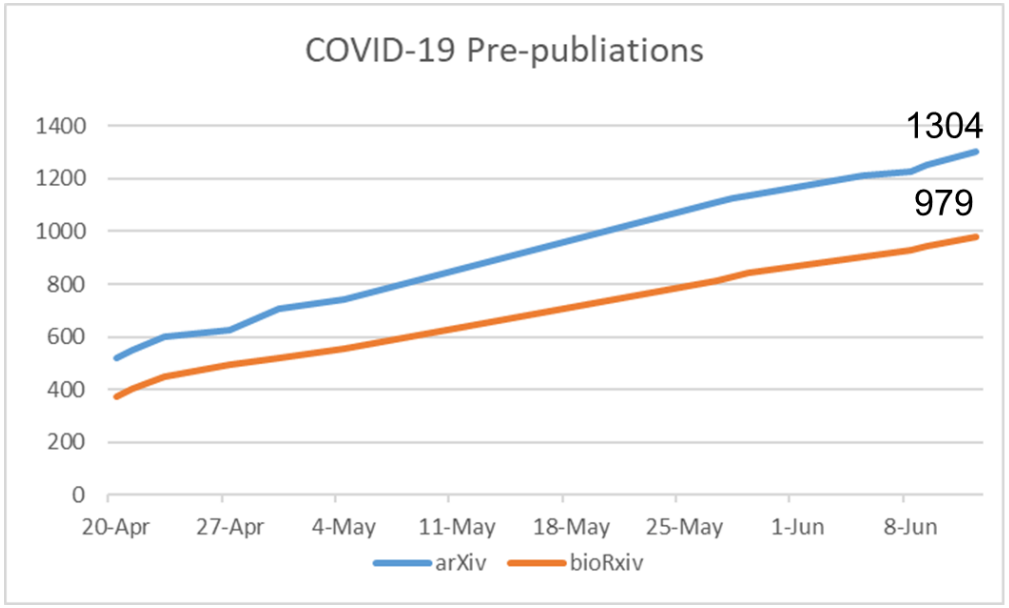
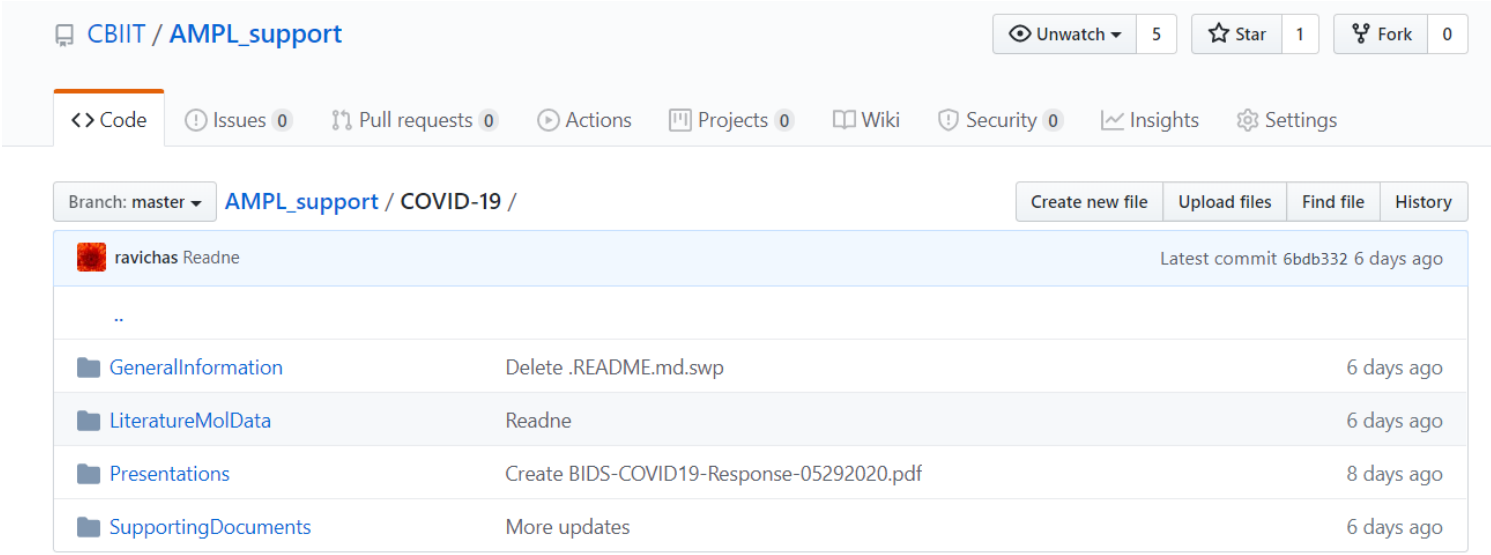
- **We have shared the repo with the ATOM team**
- **Anyone with a GitHub in the ATOM team will be added as collaborators and have the ability to edit and update the repository**





NCATS COVID-19 OpenData Portal

- Created a new open resource
  - drug repurposing data and experiments for all approved drugs.
- Developed the portal by using SARS-CoV-2-related assays
  - "Screen over **10,000 compounds**, including the NCATS Pharmaceutical Collection of nearly **3,000** approved drugs, for their activity against the virus.
  - "This resource includes information on **assays (tests), protocols for using the assays**, **drug targets**, **mechanisms of drug action** and **screening assay data**."
  - "These data, which include **positive** and **negative** results, can be viewed, sorted, searched and exported from the portal website. Screening data are uploaded to the website as they become available. All data on the site come from NCATS-validated SARS-CoV-2 assays."

SAMPLE_ID	SAMPLE_NAME	PUBCHEM_SI	PRIMARY_MOA	AC50	LOG_AC50	AUC	EFFICACY	MAX_RESPONSE	P_HILL	R2
NCGC00181103-02	Propiverine hydrochloride	170466036	Muscarinic acetylcholine receptor Blocker			-4.234459952	-5.250000004	0	0.444283515	0.540671473
NCGC00015798-11	Dexpropranolol	170464682	Adrenergic receptor beta Antagonist			-5.474527441	-8.625737896	-8.85478158	0.087328002	0.849264105
NCGC00016902-04	Etifenin	170466635		2.119226141	-5.673822698	-107.6954004	-57.50568182	-51.35773318	0.042482977	0.901771266
NCGC00319020-01	NCGC00319020-01	225144374	Prostanoid IP receptor Agonist	10.62129087	-4.973822698	-24.62656811	-34.12996088	-31.35830073	4.2759E-06	0.999155543
NCGC00389765-01	DIBEKACIN					-9.963181453	-7.729729732	0	0.409404709	0.582637977
NCGC00178802-06	Deferoxamine mesylate	170464752	Iron Chelating Agent			-20.91044129	-17.22666294	-17.27221912	0.120834924	0.812290384
NCGC00181320-01	Mersalyl acid	144206341				-3.292880586	0	0		
NCGC00166055-04	SODIUM NITROPRUSSIDE					-2.099272148	0	0		
NCGC00390187-02	Delafloxacin (meglumine)		Staphylococcus Aureus Inhibitor			-0.798553386	-7.3	-4.75125769	0.139738775	0.794188307
NCGC00093350-05	Amikacin	174006656	30S ribosomal protein S12 Inhibitor			-22.07918393	-9.994410288	-8.32867524	0.359974785	0.562352851
NCGC00163742-05	d-LIMONENE		response to oxidative stress Modulator			-4.159709141	0	0		
NCGC00274079-01	Sodium urate	170465686				-3.764118818	0	0		
NCGC00091034-10	Captan	225144202				2.969163856	0	4.41587479		
NCGC00344534-01	Indigo carmine	225144381				-7.097470609	-6.981840196	3.8569033	0.436387816	0.549045301
NCGC00346655-02	Linagliptin		DPP-IV Inhibitor	8.436791229	-5.073822698	-25.08960504	-38.4038569	-36.94801565	0.00025816	0.993372117
NCGC00178734-06	Sitagliptin		DPP-IV Inhibitor			-26.7912557	0	-7.32252655		
NCGC00274082-01	Sodium dodecyl sulfate	170465474				-15.52269208	0	-6.76355506		
NCGC00346829-03	Fotemustine		DNA Alkylating Agent			-2.401100885	0	0		
NCGC00167558-02	Fleroxacin	170466056	Quinoline Antibiotic			-12.4370085	-12.65938606	-12.63282172	0.080791198	0.855621554
NCGC00091325-09	Dichlorophen	170465475	Indoleamine 2,3-dioxygenase Inhibit	18.88762287	-4.723822698	-42.50831311	-79.27922078	-73.3175915	0.006885834	0.964084753
NCGC00159458-05	Atorvastatin calcium	170465113	HMG-CoA Reductase Inhibitor	11.91728437	-4.923822698	-68.5305552	-54.39874674	-59.62219599	0.004172167	0.9724198
NCGC00094516-08	Coumaphos	170466302		16.8336116	-4.773822698	-32.34528107	-49.74675325	-46.39905549	0.003978676	0.973101117
NCGC00142384-03	Cholic Acid		Bile acid receptor FXR Agonist	11.91728437	-4.923822698	-65.0823461	-50.97520662	-45.21841795	0.077412197	0.85888076

June 3, 2020; DOI: 10.1056/NEJMoa2016638

Randomized Control trial

ORIGINAL ARTICLE

A Randomized Trial of Hydroxychloroquine as Postexposure Prophylaxis for Covid-19

David R. Boulware, M.D., M.P.H., Matthew F. Pullen, M.D., Ananta S. Bangdiwala, M.S., Katelyn A. Pastick, B.Sc., Sarah M. Lofgren, M.D., Elizabeth C. Okafor, B.Sc., Caleb P. Skipper, M.D., Alanna A. Nascene, B.A., Melanie R. Nicol, Pharm.D., Ph.D., Mahsa Abassi, D.O., M.P.H., Nicole W. Engen, M.S., Matthew P. Cheng, M.D., et al.

We enrolled 821 asymptomatic participants. Overall, 87.6% of the participants (719 of 821) reported a high-risk exposure to a confirmed Covid-19 contact. The incidence of new illness compatible with Covid-19 did not differ significantly between participants receiving hydroxychloroquine (49 of 414 [11.8%]) and those receiving placebo (58 of 407 [14.3%]); the absolute difference was −2.4 percentage points (95% confidence interval, −7.0 to 2.2; P=0.35). Side effects were more common with hydroxychloroquine than with placebo (40.1% vs. 16.8%), but no serious adverse reactions were reported.

https://arxiv.org/ftp/arxiv/papers/2006/2006.06523.pdf

Predicting inhibitors for SARS-CoV-2 RNAdependent RNA polymerase using machine learning and virtual screening.

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- **Procedure**
  - RdRp inhibitors from PubChem, ChEMBL bioassays (SMILES)
    - Targets HCV, Poliovirus, Dengue Virus and Influenza virus
  - Filter only the data with IC50/EC50
    - Cutoff 5 µM
  - Dataset 1356 (656 in active, 700 active)
  - Unusual compounds which contained only a single atom, or no carbon atoms were removed
  - Training/Validation (80%/20%); Testset was chosen (20 known RdRp and 20 unrelated molecules (mostly kinases))
  - Another set of FDA approved and clinical antiviral/anti inflammatory drugs as test sets for drug repurposing effort

PubChem ChEMBL FDA

IC50/EC50

https://arxiv.org/ftp/arxiv/papers/2006/2006.06523.pdf

Table 1.1: Model performance on the validation set.

Model	AUROC	ACC	Confidence Interval (alpha=0.05)
GraphConv	0.898	0.825	[0.780, 0.870]
Weave	0.790	0.670	[0.614, 0.726]
MPNN	0.849	0.768	[0.718, 0.818]
RandomForest (Circular)	0.921	0.840	[0.796, 0.884]
SVM (Circular)	0.794	0.787	[0.738, 0.836]
Ridge (Circular)	0.802	0.799	[0.751, 0.847]
Lasso (Circular)	0.752	0.742	[0.690, 0.794]
MLP (2 layers) (Circular)	0.794	0.791	[0.743, 0.839]
MLP (3 layers) (Circular)	0.831	0.829	[0.784, 0.874]
XGBoost (Circular)	0.773	0.765	[0.715, 0.815]
RandomForest (Topological)	0.825	0.818	[0.772, 0.864]
SVM (Topological)	0.780	0.772	[0.722, 0.822]
Ridge (Topological)	0.741	0.738	[0.686, 0.790]
Lasso (Topological)	0.801	0.799	[0.751, 0.847]
MLP (2 layers) (Topological)	0.758	0.753	[0.702, 0.804]
MLP (3 layers) (Topological)	0.725	0.715	[0.661, 0.769]
XGBoost (Topological)	0.816	0.810	[0.763, 0.857]

Abbreviations: AUROC, area under the receiver operating characteristic curve; ACC, accuracy.

NRP1 joins the potential host-cell targets, TMPRSS2 and ACE2 !

- “Peter Cullen and Yohei Yamauchi at the University of Bristol, UK, and their colleagues showed that a fragment of the Spike protein can bind to NRP1 (L. Cantuti-Castelvetri *et al.* Preprint at bioRxiv http://doi.org/dx5c; 2020).” Nature News
- Second paper finds similar role for NRP1
  - **Neuropilin-1 is a host factor for SARS-CoV-2 infection**
  - https://www.biorxiv.org/content/10.1101/2020.06.05.134114v1