Frederick National Laboratory
for Cancer Research

sponsored by the National Cancer Institute

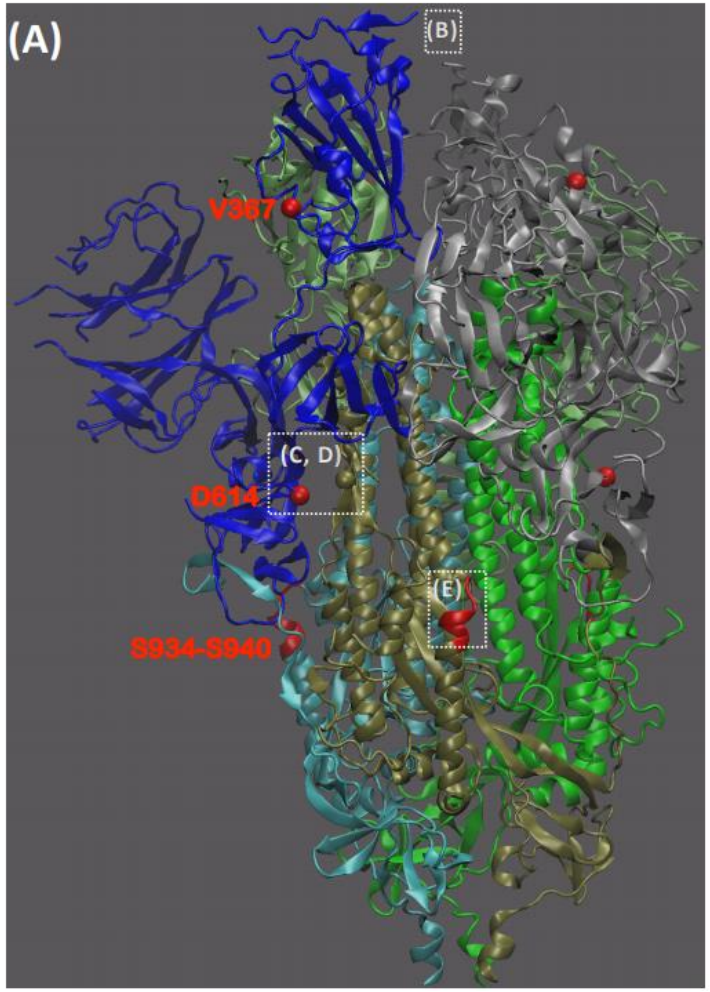
Weekly meetings and interesting papers review

S. Ravichandran, BIDS
FNLCR

May 8, 2020

Papers Eric shared

- **Spike mutation pipeline reveals the emergence of a more transmissible form of SARS-CoV-2**
- we have identified fourteen mutations in Spike that are accumulating.
- The mutation Spike D614G is of urgent concern; after beginning to spread in Europe in early February, when introduced to new regions it repeatedly and rapidly becomes the dominant form
- Used PDB structures to map the mutations



doi: https://doi.org/10.1101/2020.04.29.069054

LEVERAGING AI TO HUNT FOR POTENTIAL TREATMENTS: A COVID-19 EXAMPLE

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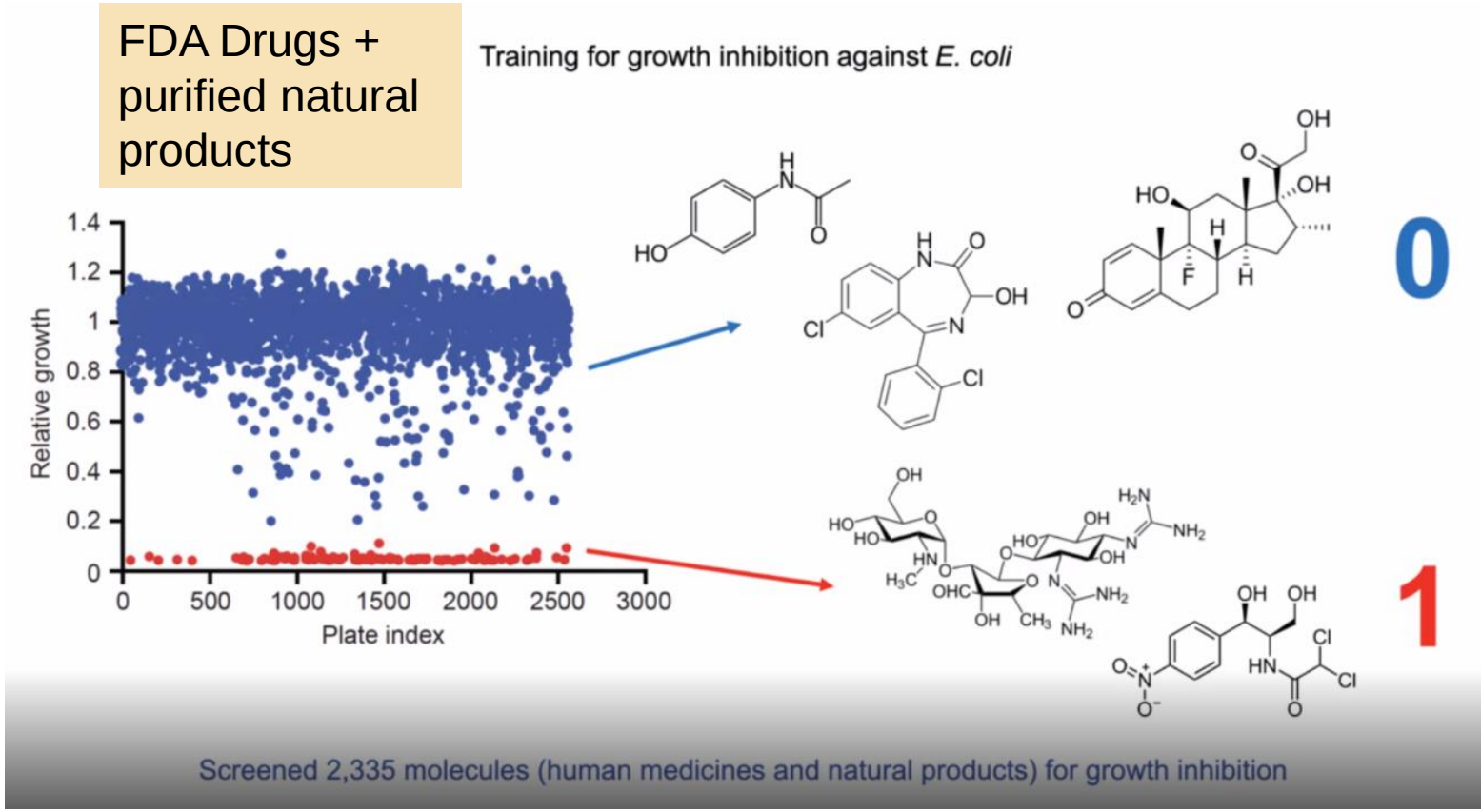
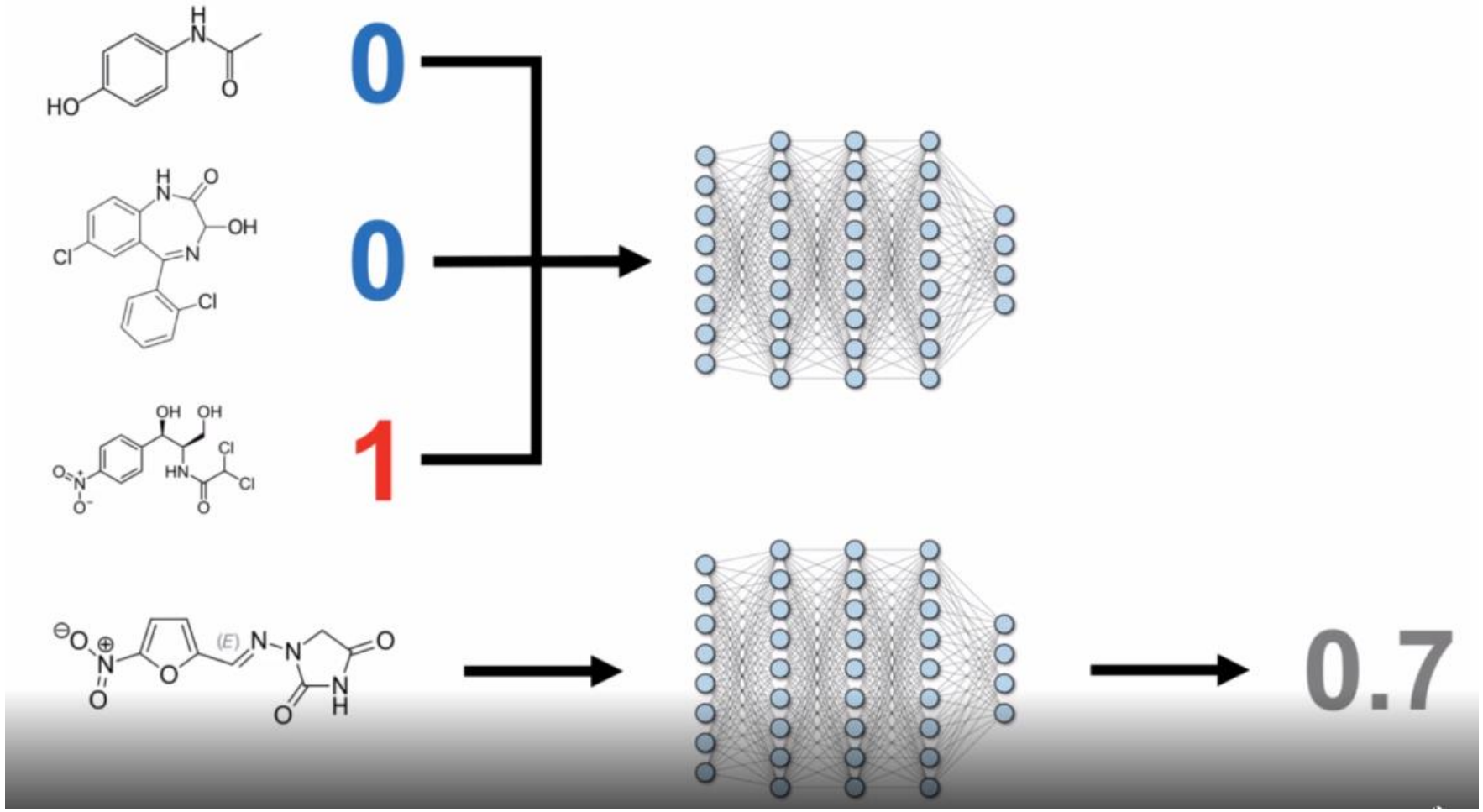
- "Attempt to identify a drug that could be active against SARS-CoV-2 (COV)."
- Repurposing effort
- **Based on a Cell paper, A Deep Learning Approach to Antibiotic Discovery Cell180, 688–702.e1–e13; February 20, 2020)**



2,335 compounds from the primary training dataset were binarized as hit or non-hit. After binarization, we used these data to train a binary classification model that predicts the probability of whether a new compound will inhibit the growth of E. coli based on its structure

Stokes team developed a software ChemProp

Software
https://github.com/chemprop/chemprop



Since then used two PubChem Assays

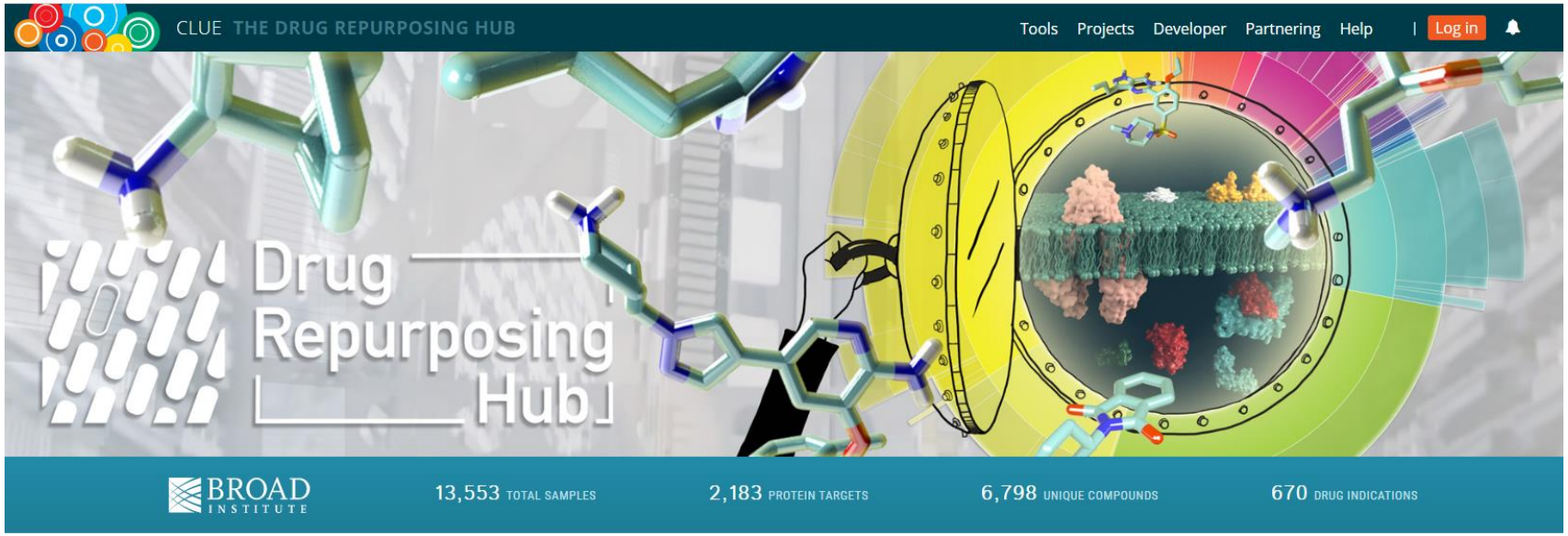
ChemProp

Playing with ChemProp

3CLpro Inhibition prediction from SARS-CoV model

Drug Name	SMILES	Activity Probability
Zafirlukast	Cc1ccccc1S(=O)(=O)NC(=O)c2cc(OC)c(cc2)Cc3cn(C)c4ccc(cc43)NC(=O)OC5CCCC5	0.72431216
Montelukast	CC(C)(C1=CC=CC=C1CCC(C2=CC=CC(=C2)C=CC3=NC4=C(C=CC(=C4)Cl)C=C3)SCC5(CC5)CC(=O)O)O idasanutlin	0.60056485
Ritonavir	CC(C)C1=NC(=CS1)CN(C)C(=O)NC(C(C)C)C(=O)NC(CC2=CC=CC=C2)CC(C(CC3=CC=CC=C3)NC(=O)OCC4=CN=CS4)O	0.51782315
Remdesivir	CCC(CC)COC(=O)C(C)NP(=O)(OCC1C(C(C(O1)(C#N)C2=CC=C3N2N=CN=C3N)O)O)OC4=CC=CC=C4	0.46806238
Indinavir	CC(C)(C)NC(=O)C1CN(CCN1CC(CC(CC2=CC=CC=C2)C(=O)NC3C(CC4=CC=CC=C34)O)O)CC5=CN=CC=C5	0.42568066

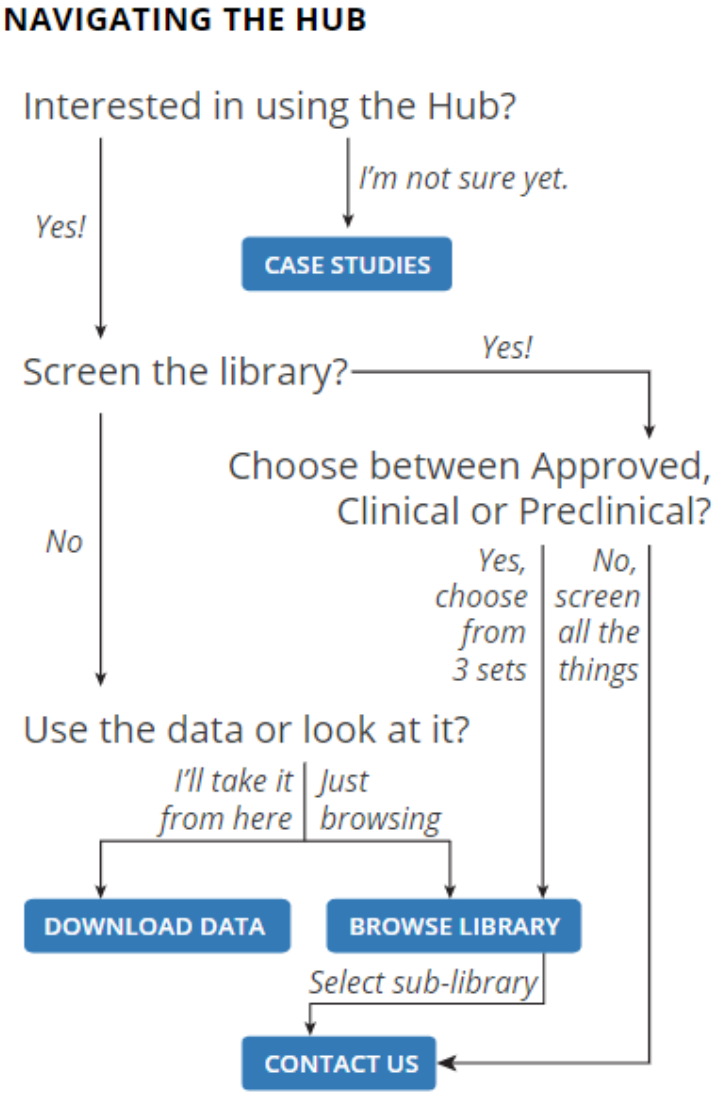
Follow up efforts



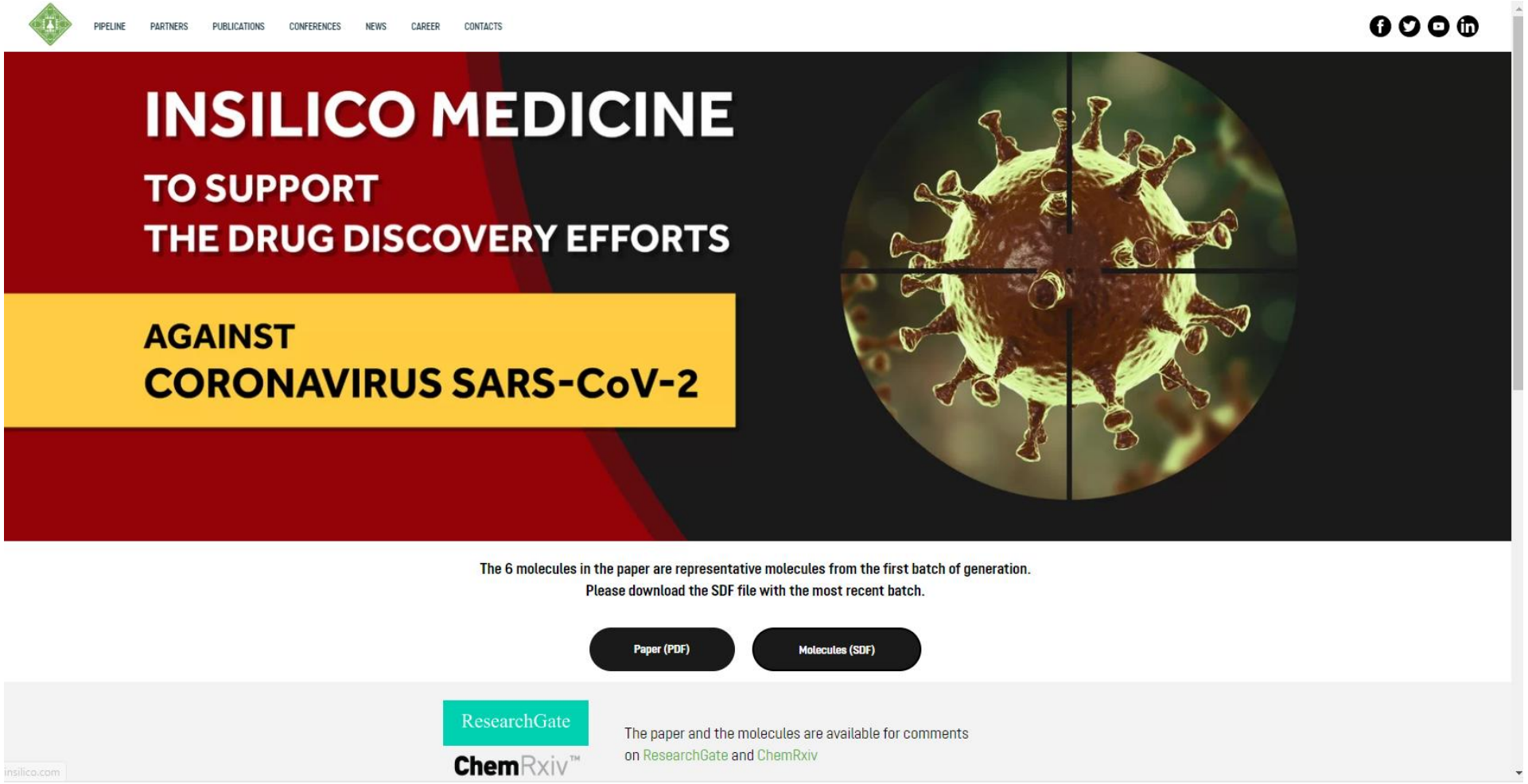
Go to: Home | About | Case Studies | Conduct a Screen | Download Data | Explore the Data App | Contact Us

Although non-essential lab work has been temporarily suspended at Broad Institute and on-site staff are limited, we are dedicated to prioritizing COVID-19 related screens. We will continue to provide the Repurposing Library, via single concentration assay ready plates, to the worldwide research community to aid COVID-19 studies. We will endeavor to accelerate all requests.

I am planning to follow-up up Drug Repurposing Hub soon

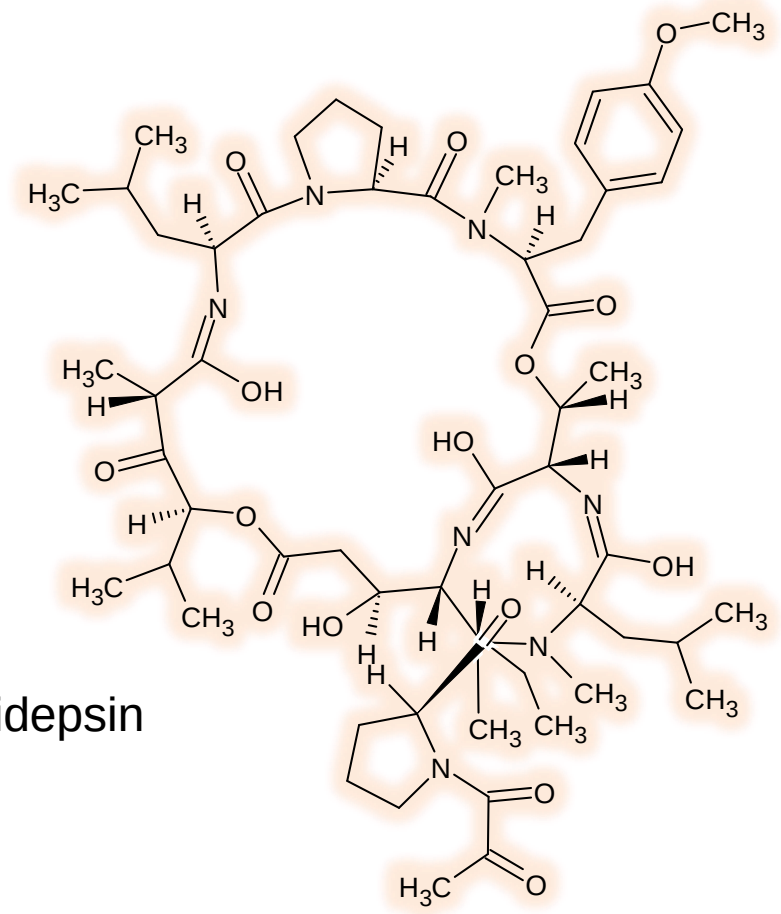


InSilico Medicine

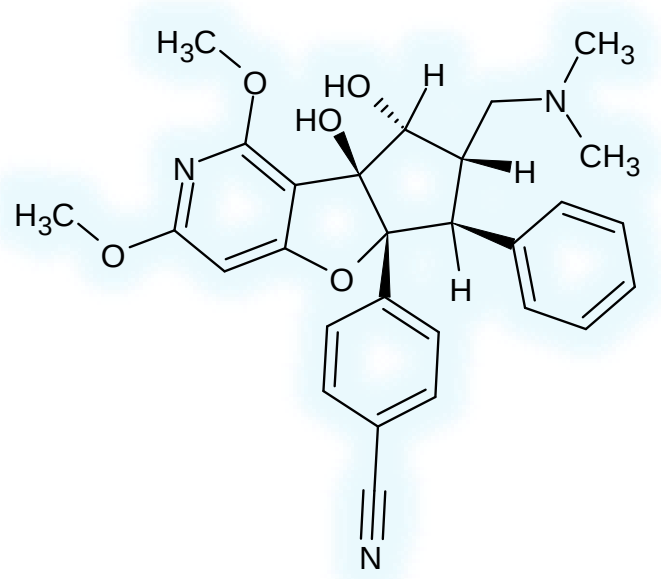


Novel Approach-Drug repurposing

- Protein translation inhibitors Zotatifin (currently in a Phase I trial for cancer therapy)
- Ternatin-4 (plitidepsin) which is used clinically for multiple myeloma.



Plitidepsin



Zotatifin

What drugs could be pursued?

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- Multiple drugs are known to modulate Sigma1 and Sigma2 receptors, and several of them showed efficacy against SARS-CoV-2;
- Antihistimines (cloperastine and clemastine)
- Antipsychotics (haloperidol and melperone),
- Antimalarial (hydroxychloroquine)
- Hormone (progesterone)
- Antianxiety (siramesine), and two preclinical compounds.
- Sigma1 and Sigma2 receptor modulators perturb the virus through different mechanisms than the translation inhibitors—potentially through cell stress response. They suggest that this may point to a combination drug approach, including other antivirals such as remdesivir.

Interesting works

- **The race to find a SARS-CoV-2 drug can only be won by a few chosen drugs: a systematic review of registers of clinical trials of drugs aimed at preventing or treating COVID-19**
  - “The objective of this comprehensive systematic review is to gather and synthesize the information included in the clinical trial registers of candidate drugs to prevent and treat COVID-19 according to the pharmacological group and specific drugs name, study design, main outcomes, number and characteristics of participants recruited, and It is made available under a CC-BY-NC-ND 4.0 International license . (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. medRxiv preprint doi: https://doi.org/10.1101/2020.05.05.20091785.this version posted May 9, 2020. The copyright holder for this preprint expected completion date. In addition, we graphically represent which drugs are most likely to achieve consistent results over the coming months of 2020”
  - https://www.medrxiv.org/content/10.1101/2020.05.05.20091785v2

Congratulations! We have done it again! Disease name and Gene Name confusion

- **What is the disease?**
  - COVID-19
  - Coronavirus disease
- **What is the virus that is causing the disease?**
  - SARS-CoV-2
    - Severe Acute Respiratory Syndrome Coronavirus 2
- **Who names these virusus?**
  - ICTV
  - How this name was chosen?
    - This name was chosen because the virus is genetically related to the coronavirus responsible for the SARS outbreak of 2003. While related, the two viruses are different.

Disease: AIDS
Virus that causes AIDS: HIV