COVID.SI:

Anyone can Participate

First and foremost thanks to

all of You !

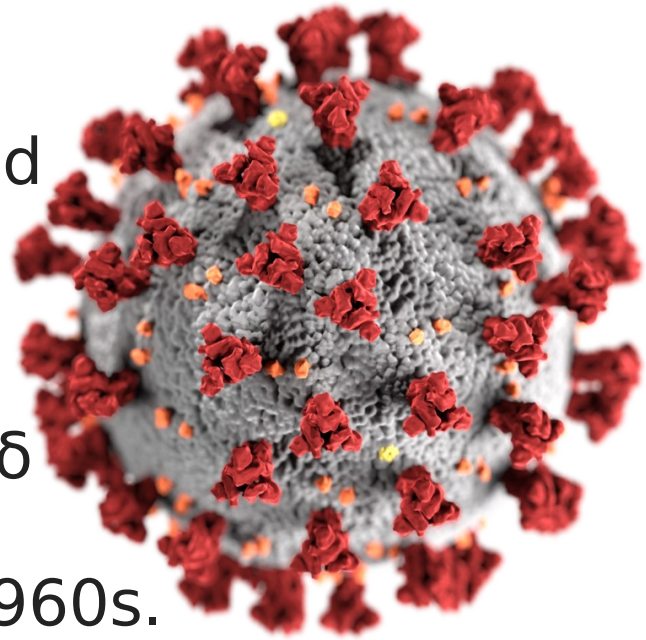
1.11.2020

Črtomir Podlipnik, Marko Jukić and Sebastian Pleško

“If you know the enemy and know yourself you need not fear the results of a hundred battles.”

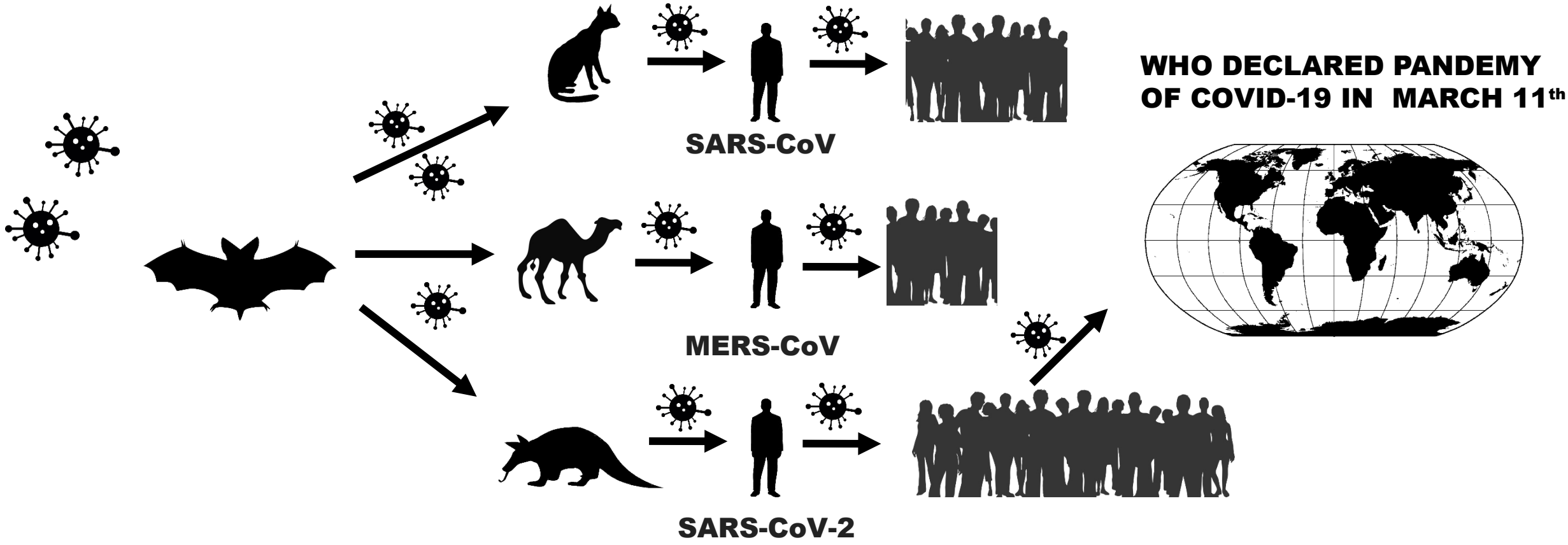
Sun Tzu

Coronaviruses are our everyday companions



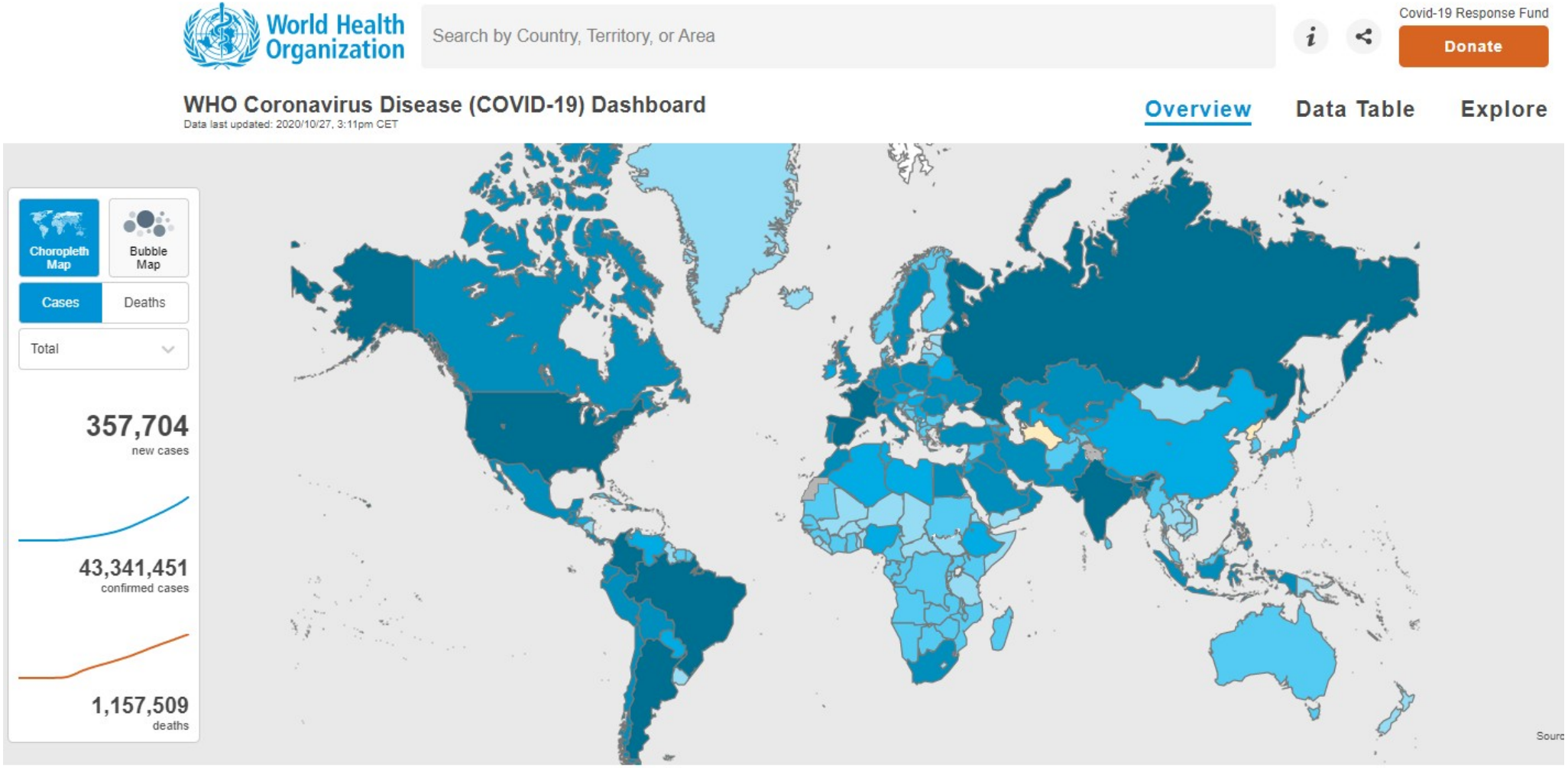
- Coronaviruses are named after crown spikes located on their surface.
- Four major subgroups of coronaviruses: α, β, γ and δ
- Human coronaviruses were discovered in the mid-1960s.
- Common human coronaviruses from the *Coronavirinae* subfamily in the *Coronaviridae* family, which often causing common colds are: 229E (alpha coronavirus); NL63 (alpha coronavirus); OC43 (beta coronavirus); HKU1 (beta coronavirus) .

Corona viruses are our everyday companions

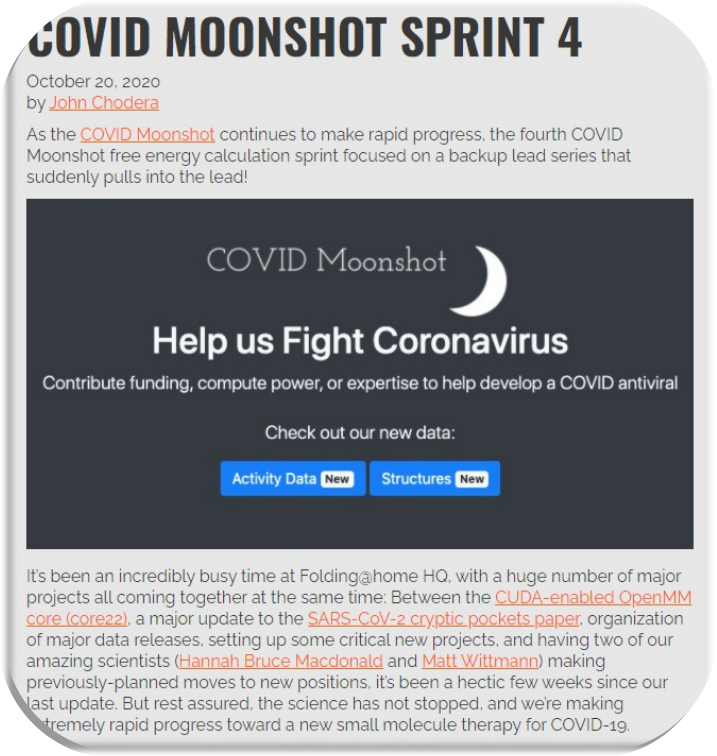


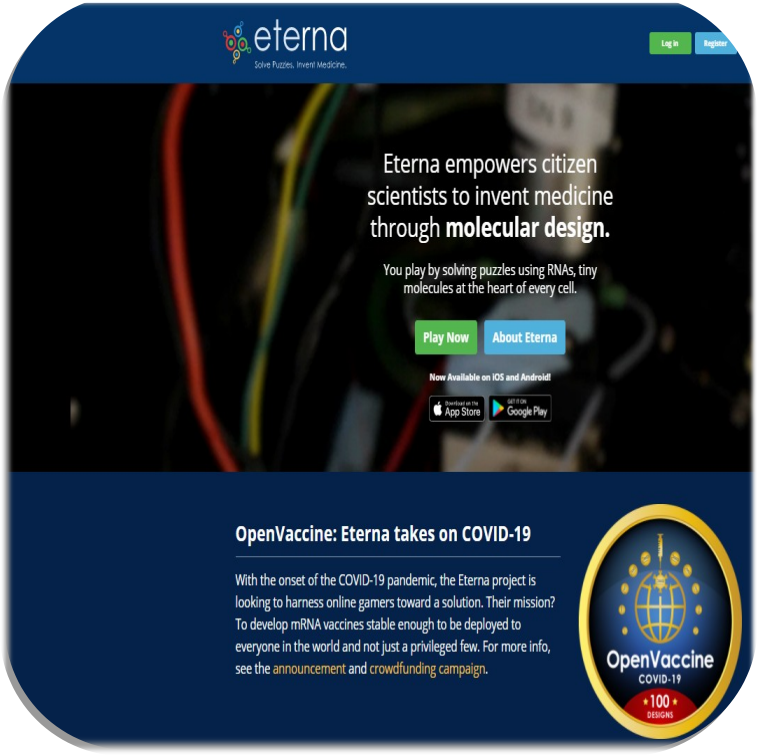
- Sometimes coronaviruses, which usually infect animals, can be skipped on humans. Such viruses are especially dangerous because humans do not yet have the mechanisms in place to defend the infection.

COVID-19 THE GLOBAL HEALTH PROBLEM



Worldwide Citizen Science projects to rundown SARS-CoV-2

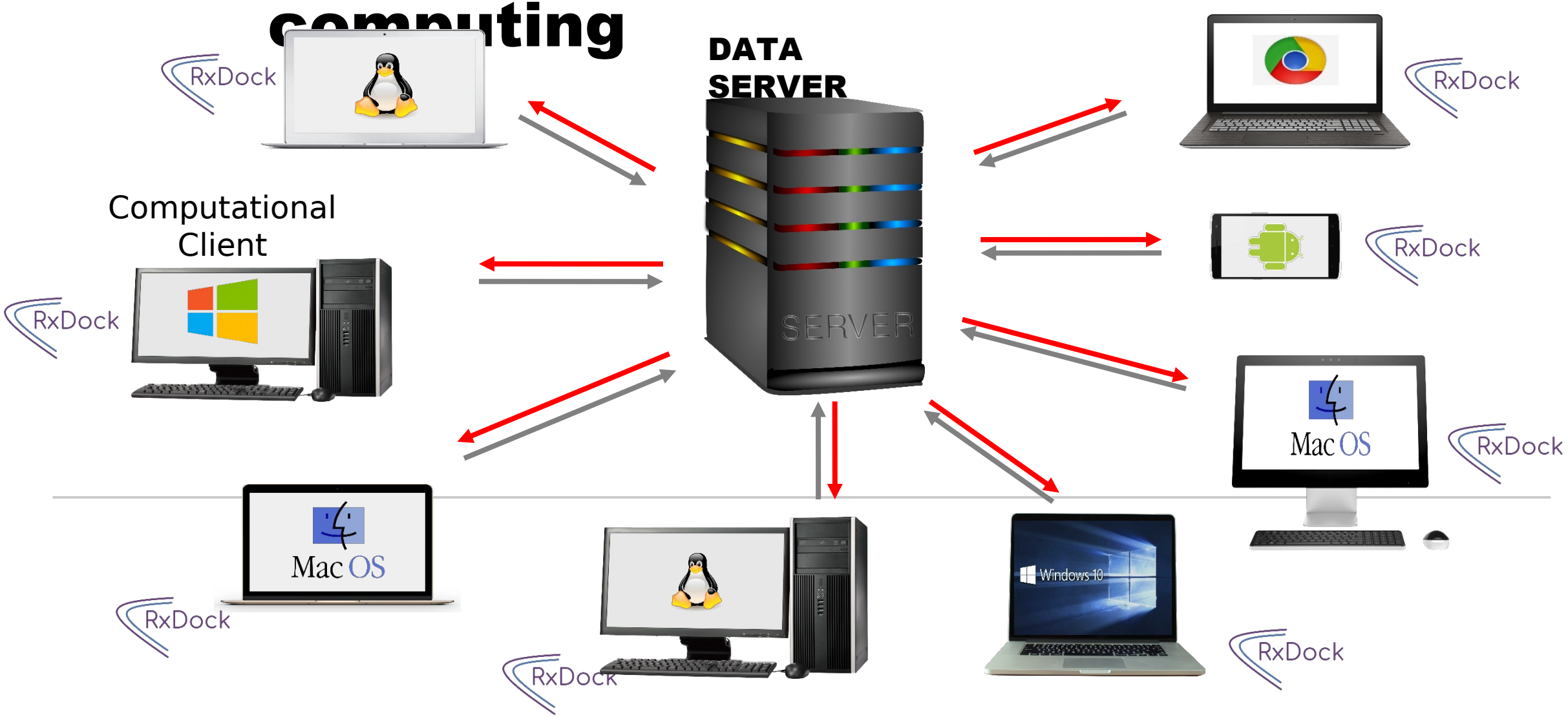




Interesting projects that engage citizens to model protein targets (Moonshot/Fold@Home, FoldIt), to develop RNA vaccines through game (Eterna), to model small proteins that inhibit binding virus to the host cell receptor (FoldIT), and to interactively design new inhibitors (Moonshot/Postera).

All these projects are well-known and well-accepted in scientific community with long history.

Scheme of community computing



From data server to client
Targets & Ligands'

From client to dataserver:
poses & docking scores

Slovenian Citizen Science projects to rundown SARS-CoV-2

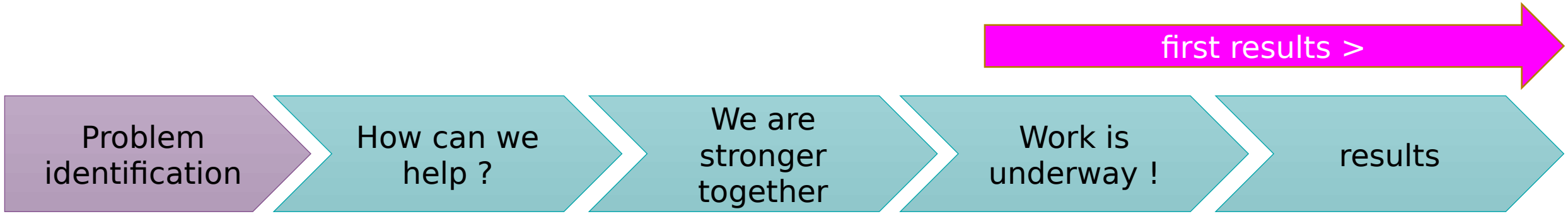
The **"COVID.SI"** - the project that allows the general public to participate in the fight against the corona virus by sharing their knowledge and computer resources. The project aims to study libraries of molecular compounds and help find a cure for the coronavirus using high-throughput virtual screening.

https://covid.si

The **"Covid-19 Tracker Slovenia"** project collects, analyses and publishes data on the spread of the SARS-CoV-2 coronavirus, the cause of COVID-19, in Slovenia. We wish to give the public a better overview of the magnitude of the issue and a proper assessment of the risk.

https://covid-19.sledilnik.org

GLOBAL PROBLEM NEEDS GLOBAL SOLUTION



December 2019

Literature – media reports

January 2020

Over beer
Joint web-based workplace

February 2020

Setup of web presence
Setup of social-network

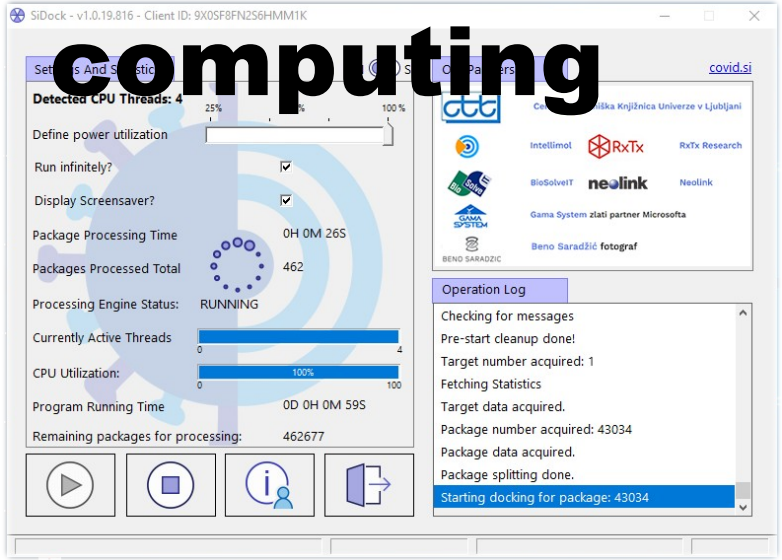
February-March 2020

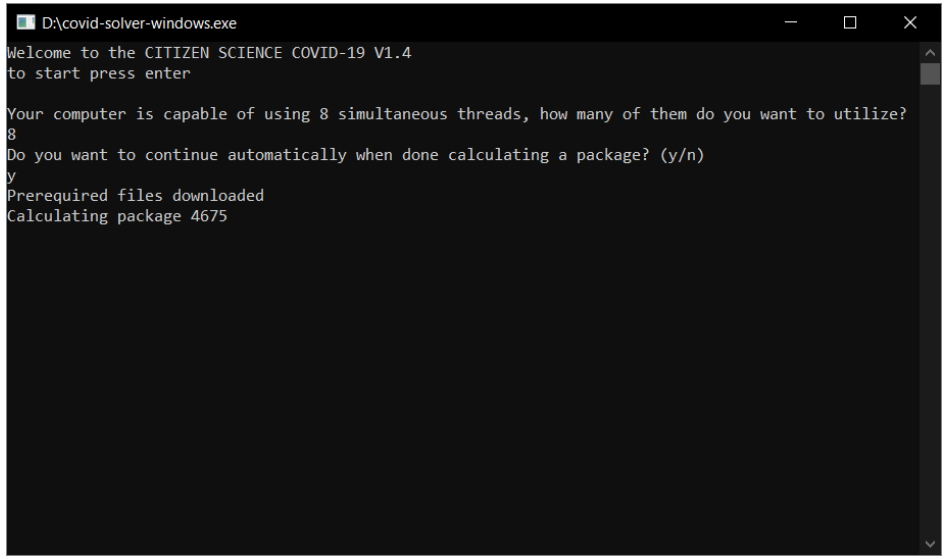
Initial community engagement

April 2020

Scientific community and private sector endorsed project

COVID.SI:
Clients for distributing computing



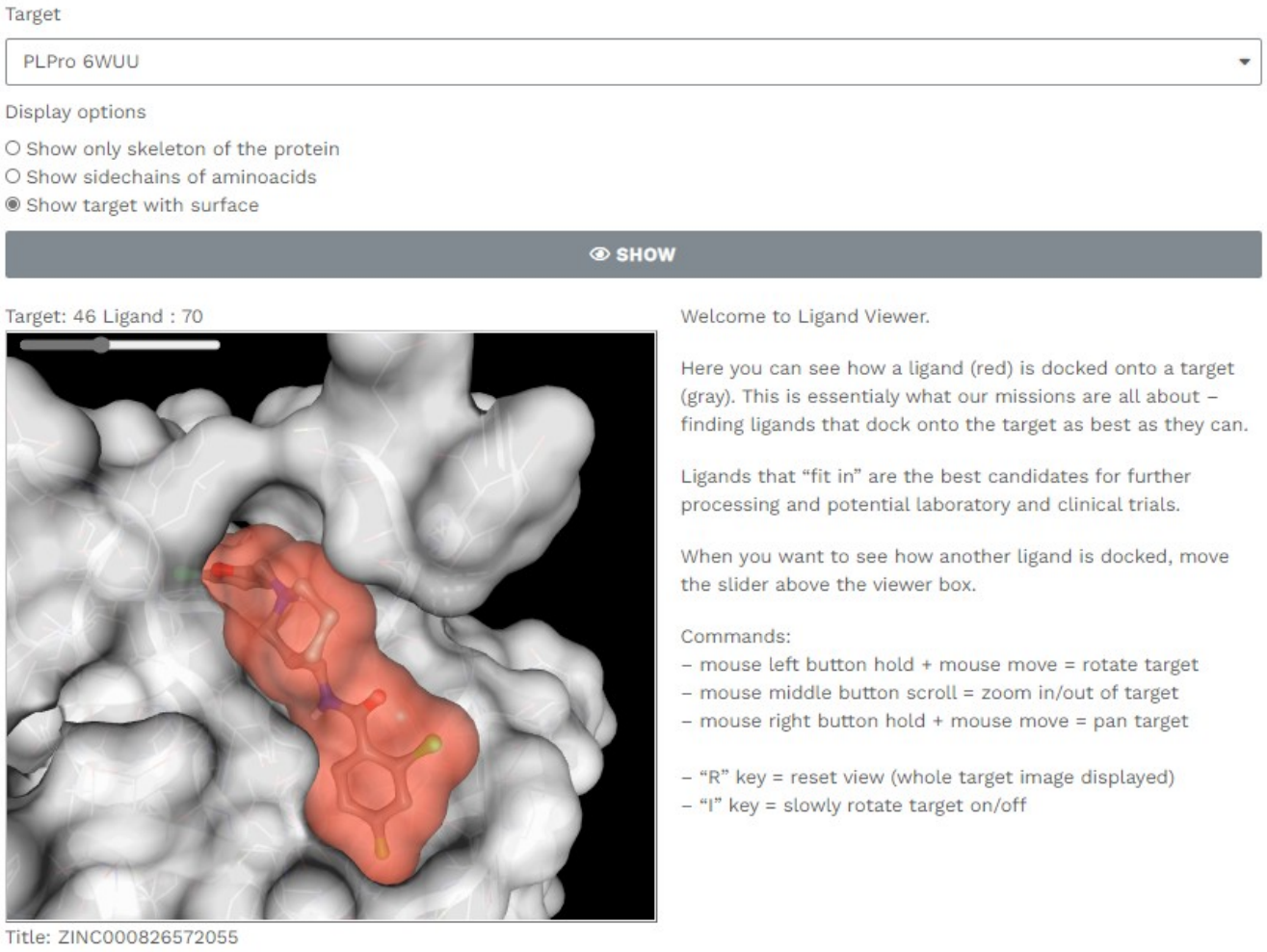


We developed the GUI Client for Winows and CLI Clients for Windows, MacOS and Linux. In all clients users can set the number of threads he wants to alocate to the project. The GUI Client has also option to switch on Screensaver which can be use for promotion of Slovenian touristic attractions.

*The instructions for using **COVID.SI** Server/Client system is available in Slovenian, English and Russian languages.*

COVID.SI:

Results' viewer based on WebGL – NGL view



- We are constantly developing new tools for analysis of the results.
- Currently, we are saving 10 000 poses for each target ranked by Total docking score to MySQL database.
- Viewer based on NGL is very useful tool for exploring complementarity between the receptor and the ligand.
- **We intend to publish some results of our missions as open data.**

COVID.SI:

Example of dissemination of the project - CSA Meeting Apr 2020

The Citizen Science Association
Law and Policy Working Group proudly presents:

COVID Webinar #2: All Hands on Deck! Citizen Science and Serious Games Tackle Covid-19

Speakers:

The Eterna OpenVaccine Challenge
Rhiju Das, Associate Professor, Stanford University

Protein-folding citizen scientists tackle Covid-19 with Foldit
Firas Khatib, Assistant Professor at the University of Massachusetts Dartmouth

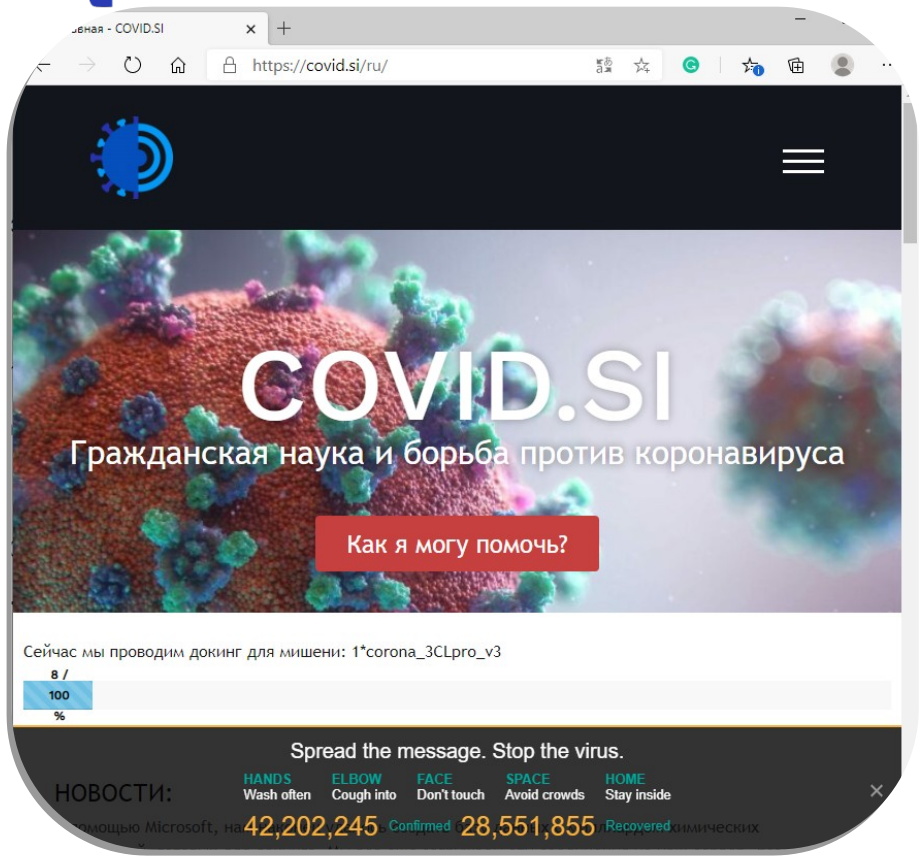
Covid Near You
Kara Seawalk, Boston Children's Hospital and Covid Near You

COVID.SI: Citizen science project to fight against NCOV-SARS-2 by distributed computing
Črtomir Podlipnik

Safecast and Responding to Covid-19 through crowdsourced data
Angela Eaton, Safecast Americas Director

COVID.SI:

Dissemination of the project - Web page



We prepared webpage for presentation of the COVID.SI project. The webpage contains brief introduction of the project, key information about our virtual screening missions, results and statistics of the project.

The site has also blog/news section – please send us your own contribution in Slovenian, English or Russian to info@covid.si

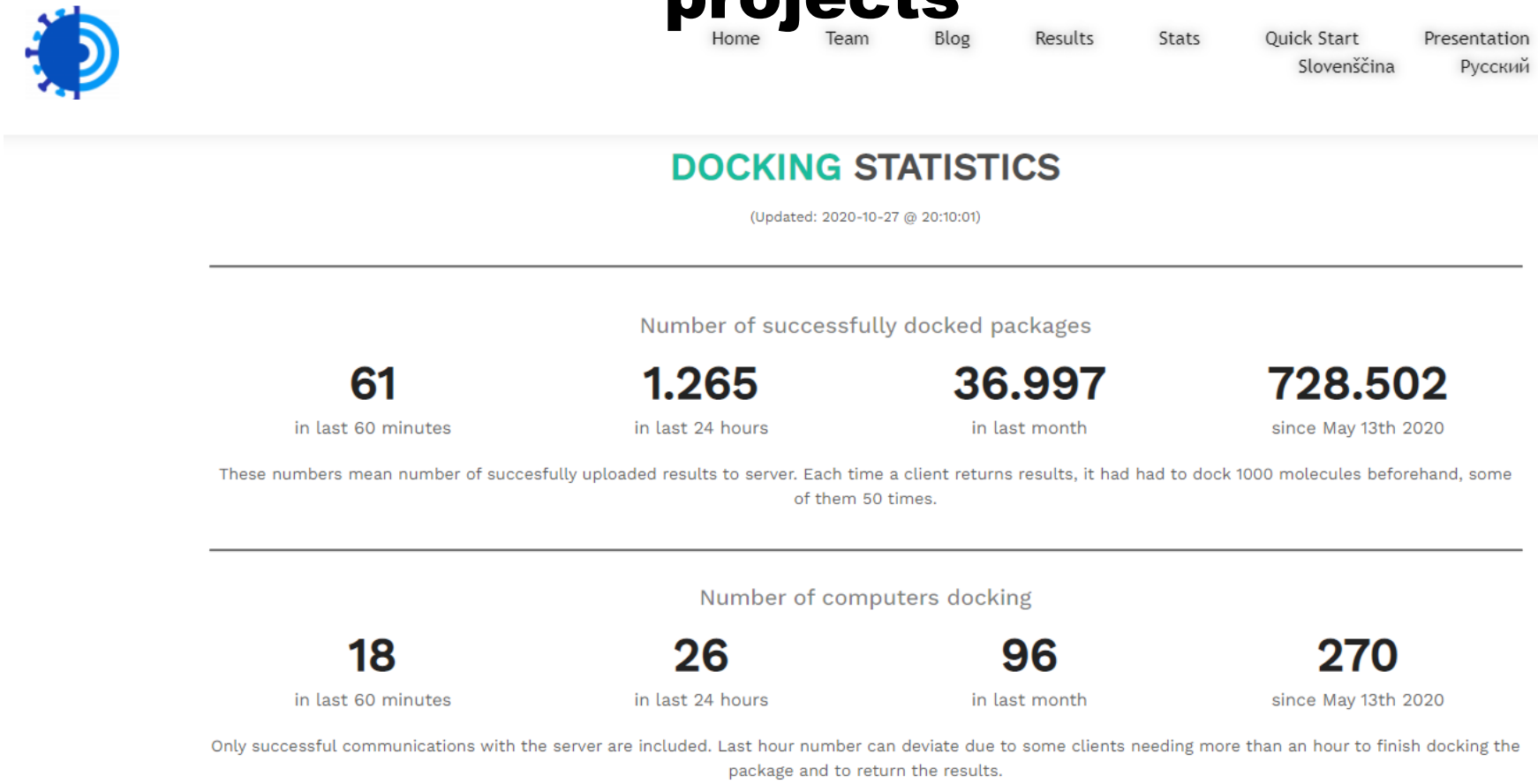
Please send also comments, suggestion and critics to

https://covid.si/

https://covid.si/en

https://covid.si/ru

Statistics of the COVID.SI projects



With current performance we could screen 10M compounds to two targets in one week.

It would be more than one year to screen per **one billion** compounds to one target.

Statistics of the COVID.SI projects

Search

Nr. of CPU threads	Nr. of computers
40	1
32	1
12	2
11	1
10	1
8	6
6	1
4	7
3	1
2	3

Search

Client ID	OS	Uploads	Last Contact
TO9WMRQR5OH8ZXFD	Windows-GUI	7384	2020-10-27 20:08:41
54d961db97f0420ea3778713a2b5879b	Linux-CLI	4261	2020-10-27 20:05:57
9e255372038644cca18d597cb27cee0a	Linux-CLI	2112	2020-10-27 20:08:41
60f45e413d4c4c8b883c0e537d208fd4	Linux-CLI	1949	2020-10-27 20:08:01
fri-lrk-su2	Linux-CLI	1853	2020-10-13 11:16:03
fri-lrk-su2-2	Linux-CLI	1851	2020-10-13 11:16:23
JT7GVT5NT0NQX2IN	Windows-GUI	1602	2020-10-27 19:53:12
T4R0LDT51U0M5MKW	Windows-GUI	1447	2020-10-27 20:10:44
DKRJ42IJBRRQX615	Windows-GUI	1404	2020-10-20 13:59:02
fri-lrk-su2-3	Linux-CLI	1280	2020-10-10 14:24:39

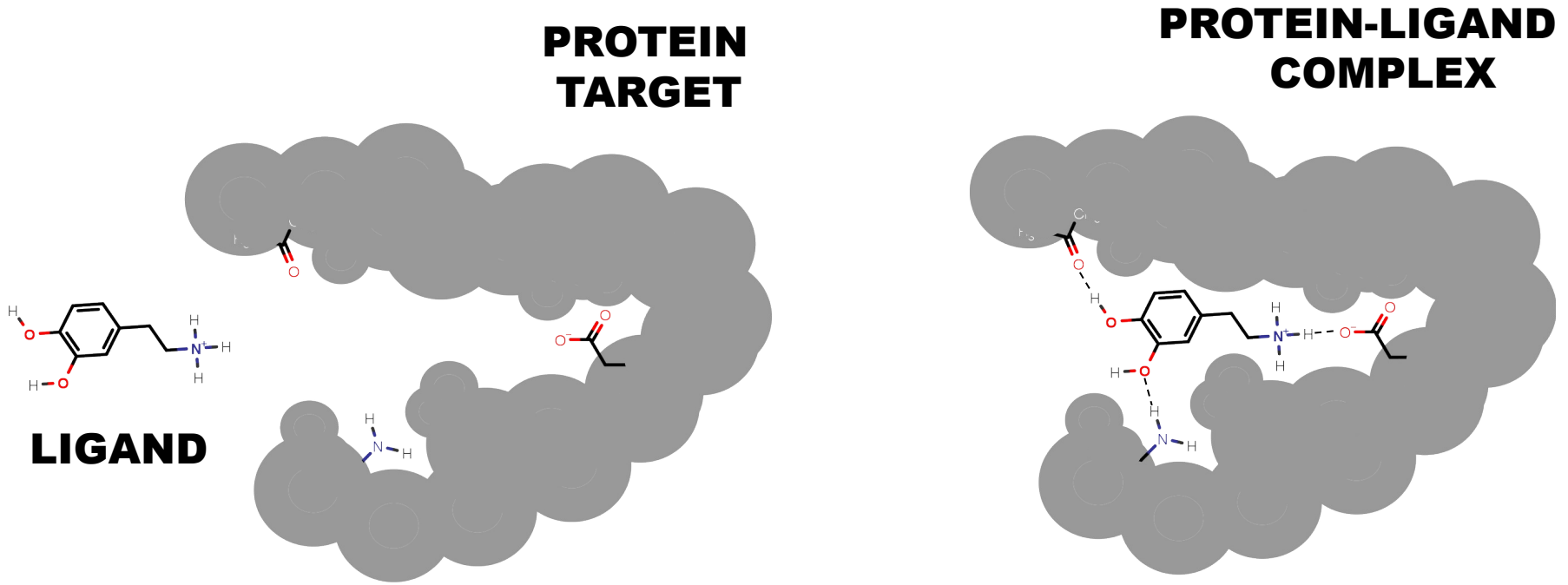
« 1 2 3 4 5 6 7 8 »

We are also monitor which computers are the most active in the project. Users can identify own computer by Client ID, which is inline with GDPR rules.

Virtual screening - Find right key for the lock

The structure based virtual screening protocol, it's like looking for a key that unlocks a lock in an Olympic pool filled with keys of all shapes and sizes, with no guarantee that the right key is in the pool.

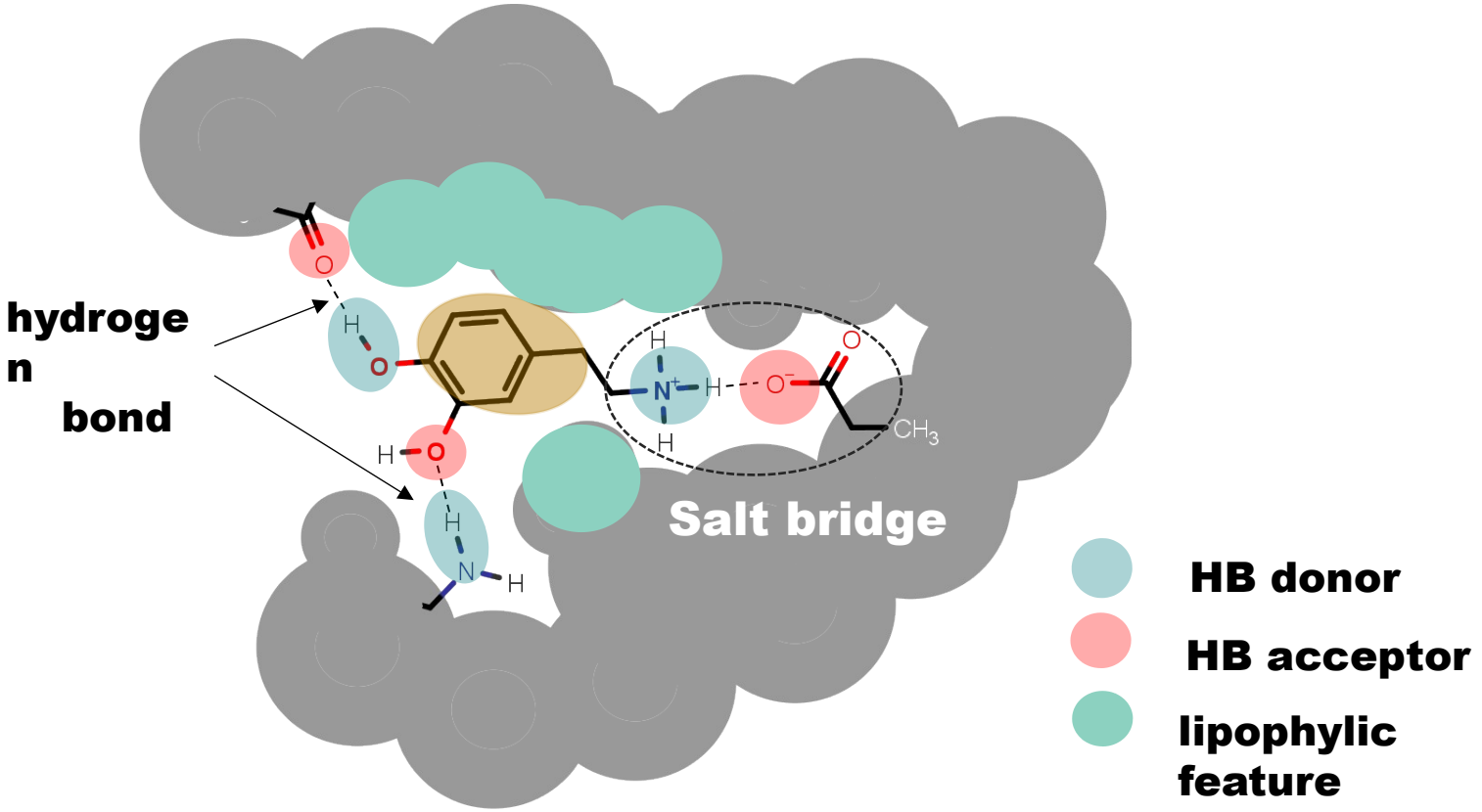
Lock-and-key aspect



The specific action of an enzyme with a single substrate can be explained using a **Lock** and **Key** analogy first postulated in 1894 by **Emil Fischer**. In this analogy, the **lock** is the enzyme and the **key** is the substrate. Only the correctly sized **key** (substrate) fits into the **key hole** (active site) of the **lock** (enzyme).

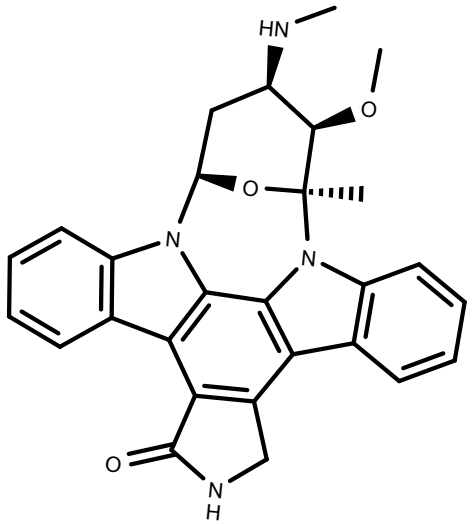
http://chemistry.elmhurst.edu/vchembook/571lockkey.ht

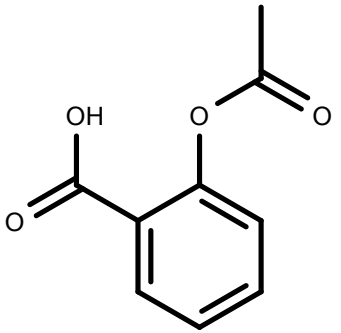
Lock-and-key aspect

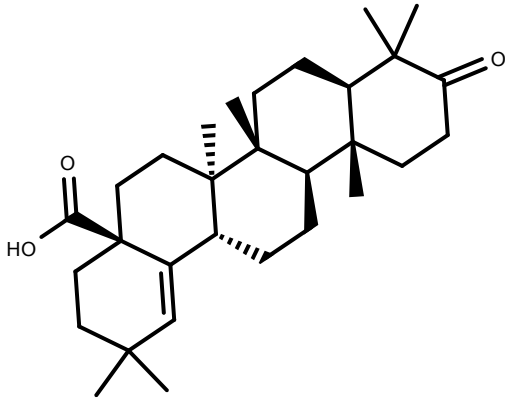


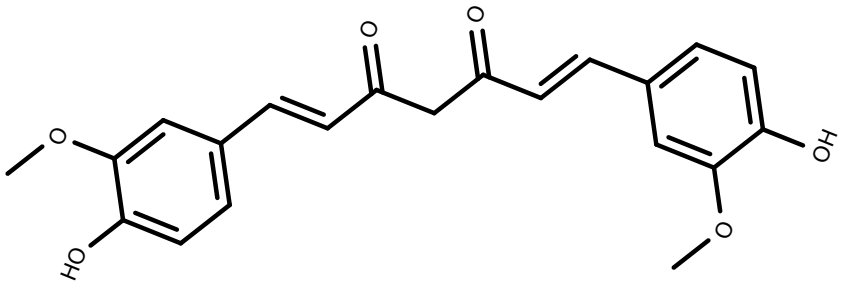
Knowing **interaction between a ligand and its host** is crucial for understanding ligand‘s biological response. Drug design involves the design of molecules that are **complementary in shape and charge** to the biomolecular target with which they interact and therefore will

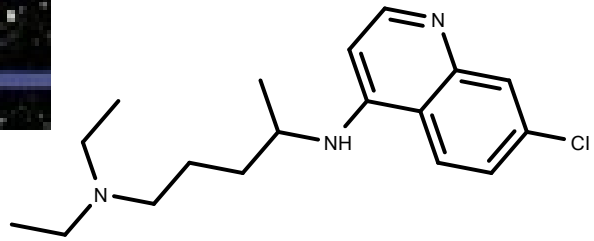
Chemical Space - infinite source of chemical stru

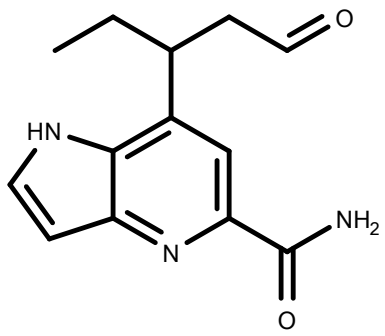


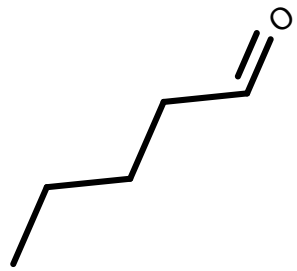












Kirkpatrick, P., & Ellis, C. (2004). Chemical space. *Nature*, *432*(7019), 823.

COVID.SI:

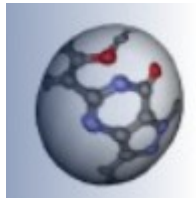
Library of one Billion Compounds

Multiple commercial and academic sources of 2D molecular structures were conglomerated, structures cleaned, checked for errors, ionised and 3D structures calculated.

Library construction was made possible by support from:

Microsoft

HPC resources and support



Balloon

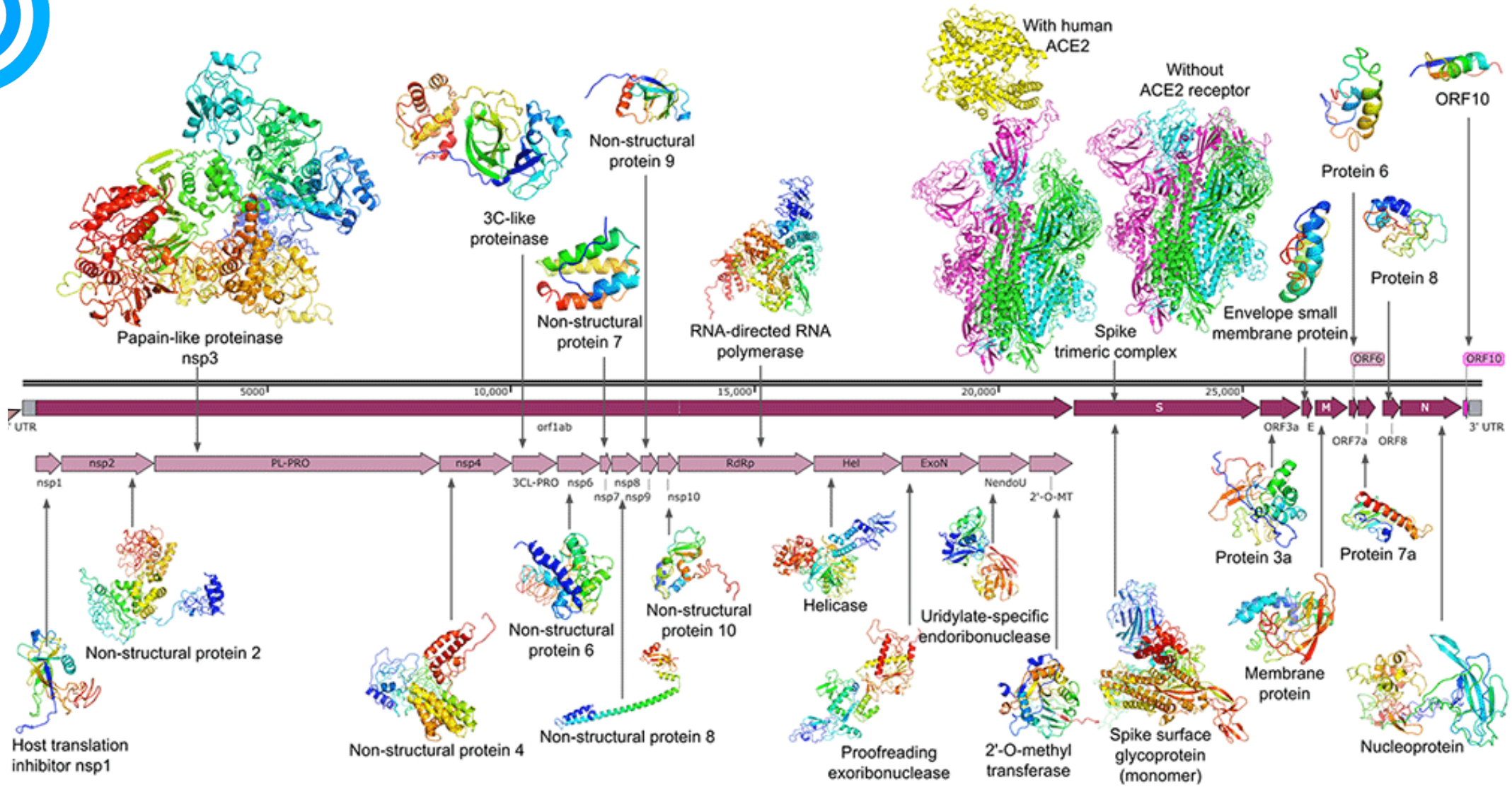
Mikko J. Vainio and Mark S. Johnson (2007) *Generating Conformer Ensembles Using a Multiobjective Genetic Algorithm.* Journal of Chemical Information and Modeling, **47**, 2462 - 2474.
The structures used for the test runs are available for download.

J. Santeri Puranen, Mikko J. Vainio, and Mark S. Johnson (2010) *Accurate conformation-dependent molecular electrostatic potentials for high-throughput in silico drug discovery.* Journal of Computational Chemistry, **31**, 1722 - 1732.

“Strategy without tactics is the slowest route to victory. Tactics without strategy is the noise before defeat.”

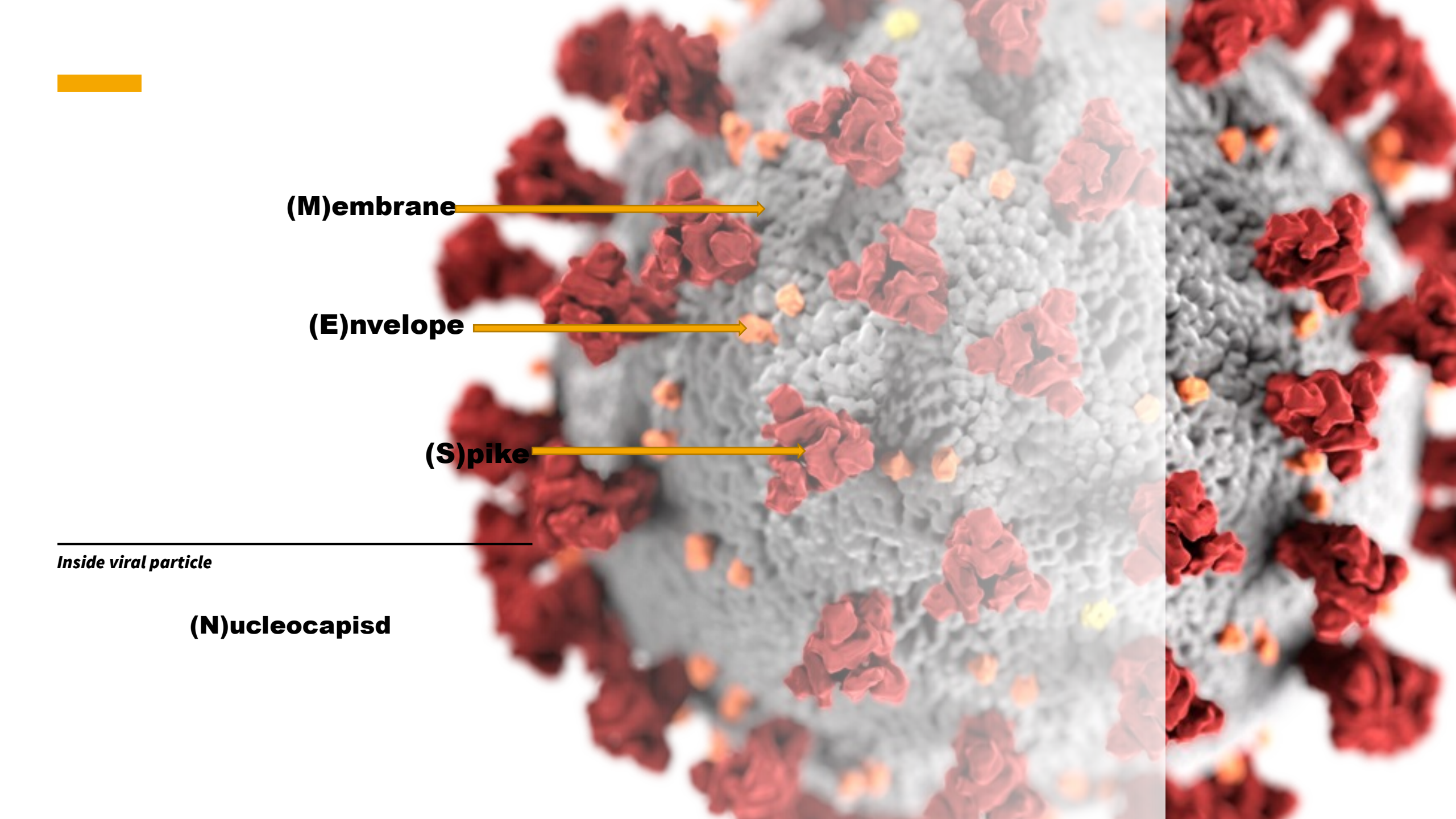
Sun Tzu

The ZOO of SARS-CoV-2



structural models and function annotation for all proteins encoded by [the genome of **SARS-CoV-2**]. Struct

modelled in **prof. Zhang Laboratory** with c-i-Tasser (https://zhanglab.ccmb.med.umich.edu/COVID-19/)

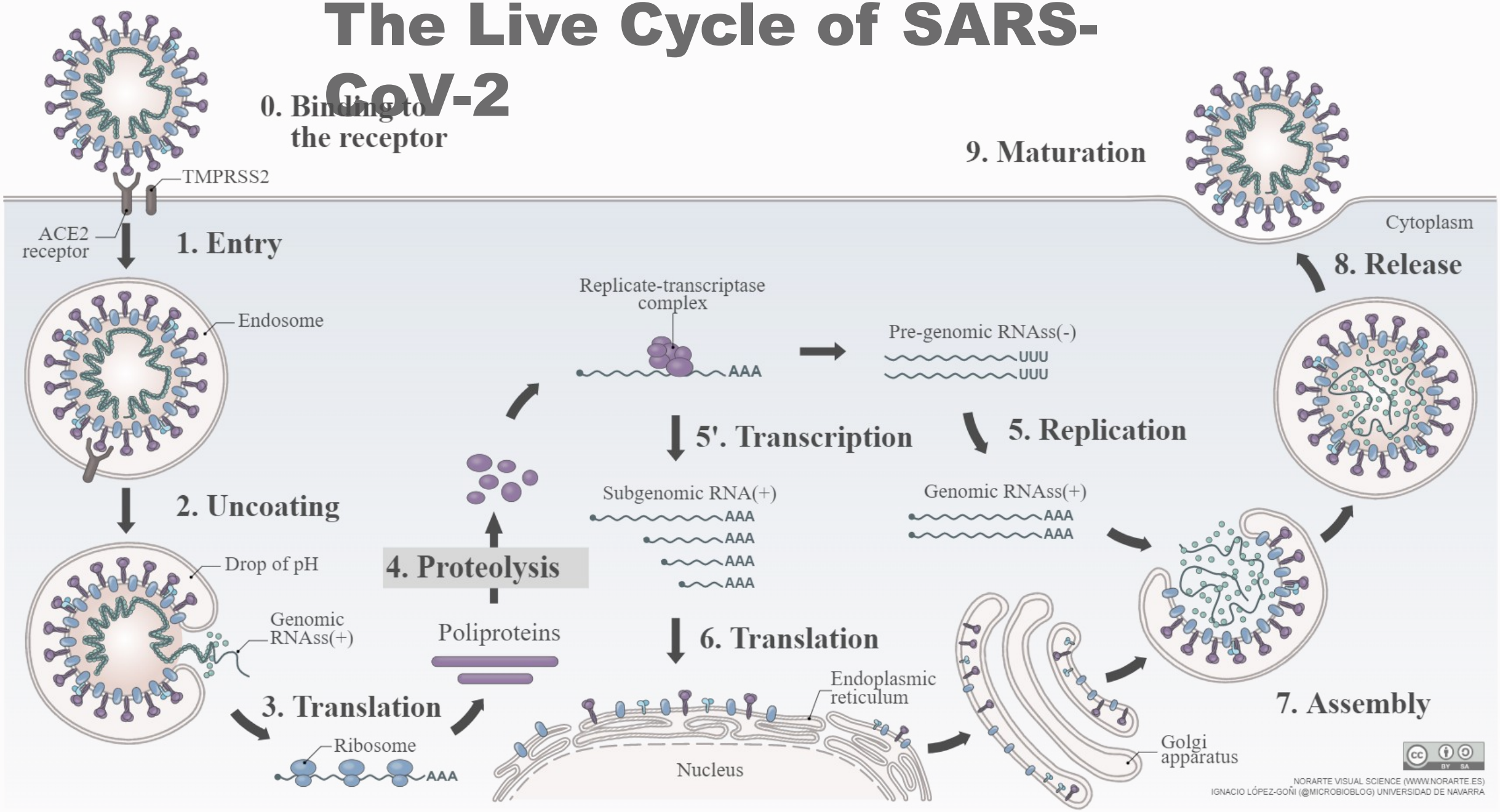

(M)embrane
(E)nvelope
(S)pike
Inside viral particle
(N)ucleocapisd

Targets related to COVID-19 studied by our methodology.

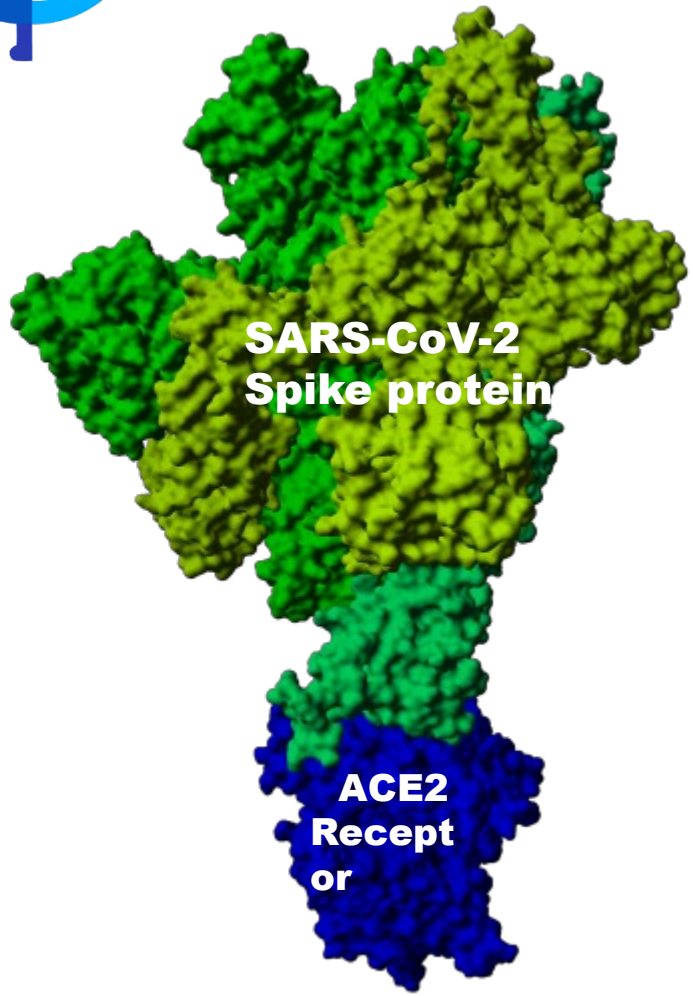
Target ID	The protein	Organism	Source of structure	PDB Code
1-21	3CL Pro	SARS-2	Snapshots from MD trajectory	
26-34	Spike Protein	SARS/MERS/SARS-2	Crystalographic structures	2AJF,2DD8, 3SCL, 5X58,6ACK,6LZG, 6M0J,6M17,6VW1
35-37	DHODH	Human	Crystalographic structures	4IGH,4JTU,4OQV
41-48	PL Pro	SARS/MERS/SARS-2	Crystalographic structures	2FE8,3MP2,4OW0, 6W9C,6WRH,6WUU, 6WX4,6WZU
49-50	FURIN	Human	Crystalographic structures	5JXH, 5MIM
51-54	Methyl Transferase	SARS2	Crystalographic structures	6W4H,6W61,7C2I,7C2J
55-56	E Protein	SARS / SARS2	NMR/Homology model	5X29 (SARS) 5X29 – Homology (SARS2)
58-59	PL Pro	SARS2	Homology models	based on 3E9S based on 5E6J based on 6W9C

Table 1: Targets related to COVID-19 studied by our methodology.

The Live Cycle of SARS-CoV-2



Strategy 1: Prevent virus entry into the host cell



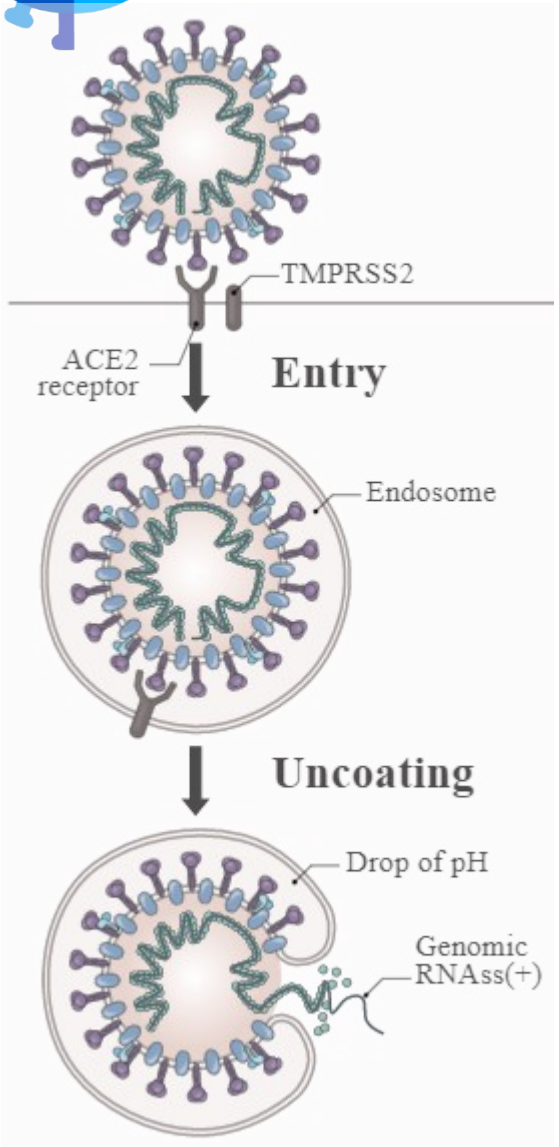
The complex between SARS-CoV-2 S protein and host ACE2 Receptor taken from Zhang Lab, rendered with YASARA.

Development molecules that hinder interactions between SARS-CoV-2 Spike protein and ACE2 or other receptors (tactics):

- **Screening a library of small molecules to find binders to Spike Recognition binding domain (RBD);**
- **Screening a library of small molecules to find ACE2 inhibitors (host target) .**
- **Designing small peptides or proteins that prevent binding of Spike protein to host receptor.**

Other host receptors which are possibly involved in virus entry: TMPRSS2, GRP-78, CD-147

Strategy 2: Prevent virus to escape from endosome



Lysosomotropic agents targeting endosomal/lysosomal pH

Therapy with **CQ**, a well-known anti-malarial drug, which is lysosomotropic agent that accumulates in the acidic organelles such as endosomes and lysosomes and neutralizes their pH.

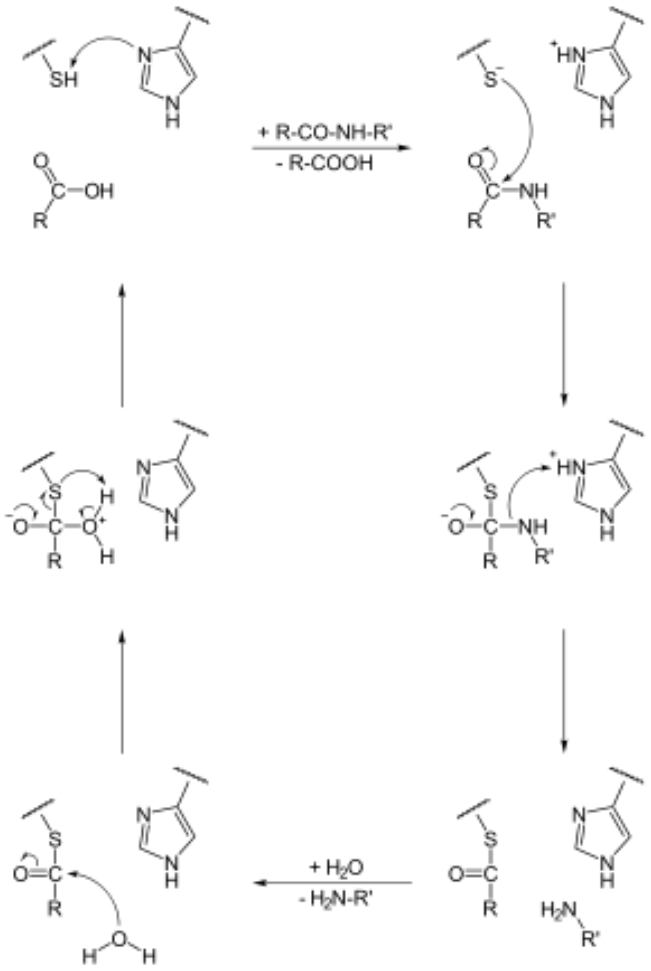
Endosomal-lysosomal protease inhibitors

Inhibition of **Cathepsins**, endosomal and lysosomal cysteine proteases that play important roles in protein degradation in various cellular processes including both the endocytic pathway and autophagy.

Inhibitors for clathrin-mediated endocytosis

Searching for new inhibitors of clathrin-mediated endocytosis which is one of the key mechanisms for viral entry into the host cells.

Strategy 3: Disarmament of viral proteases

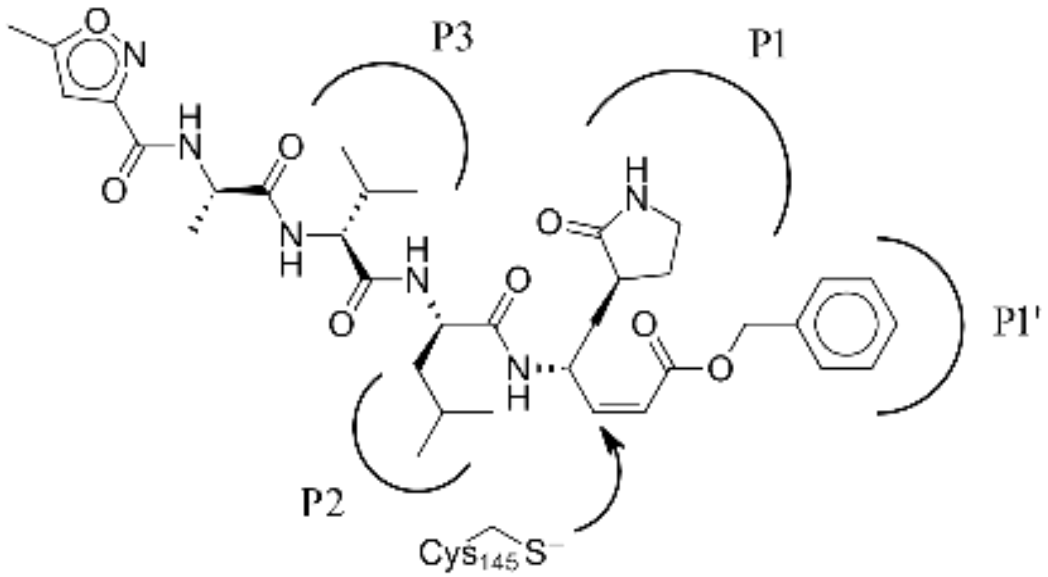


Virus uses its proteases to process initial transated polyproteins into functional protein molecules. Currently the most researched protease is the **C30 Endopeptidase** or the **3C-like proteinase** (**3CL^{pro}**). It is a cysteine protease under clan PA, MEROPS classification C30.

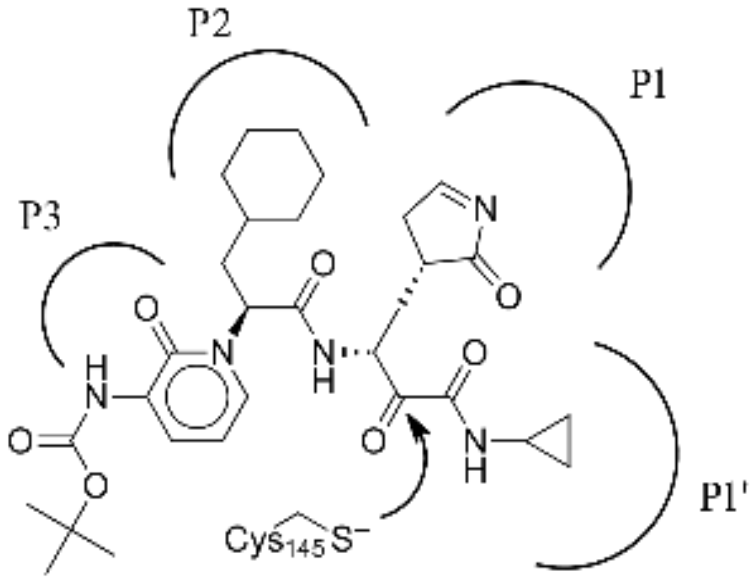
Therefore routes towards protease inhibition are of paramount importance in virus lifecycle inhibition and key approaches are:

- **Design small molecule covalent and**
- **Design of small molecule non covalent inhbitors**

Strategy 3: Disarmament of viral proteases

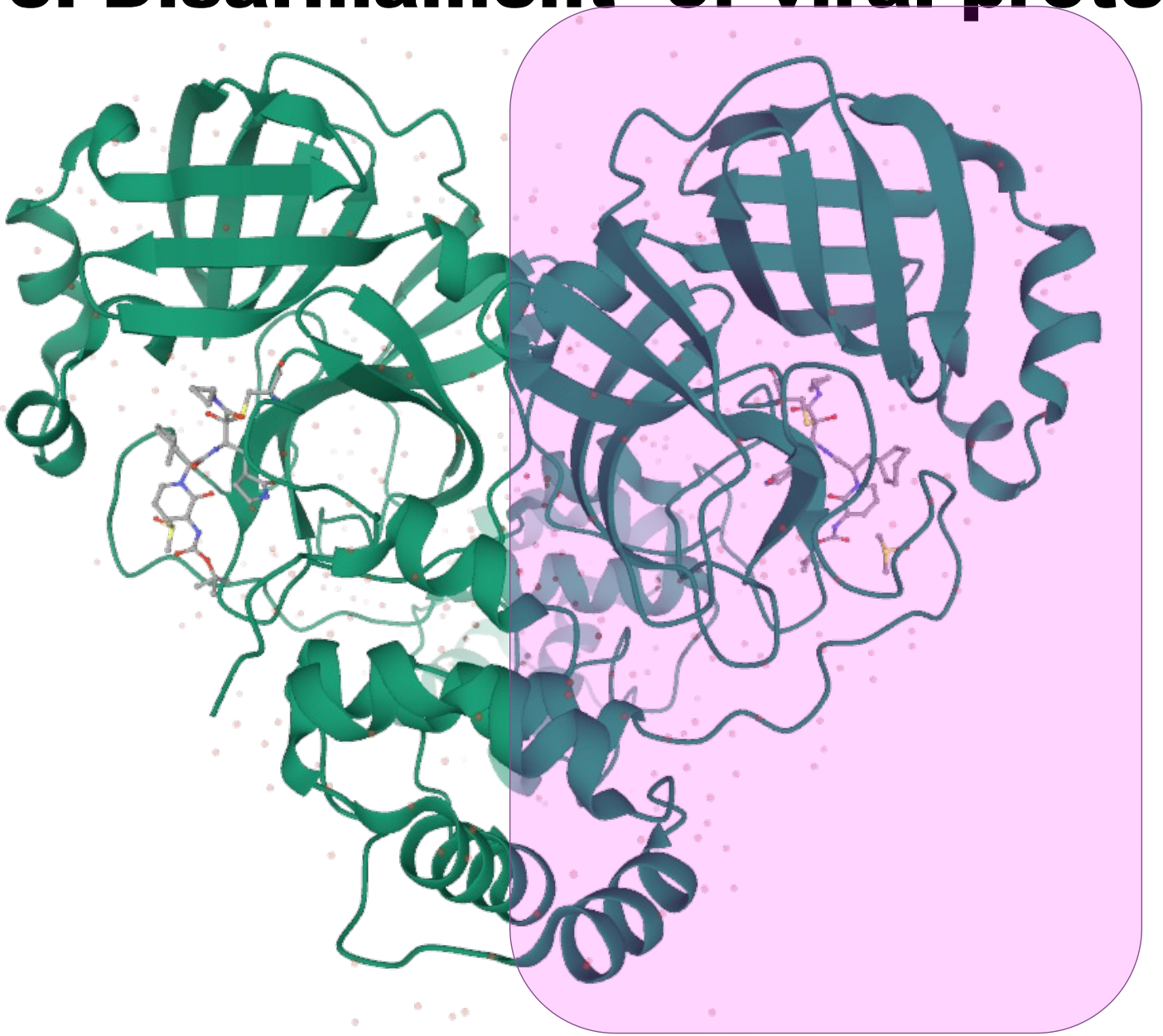


PRD_002214 (PDB ID: 6LU7)

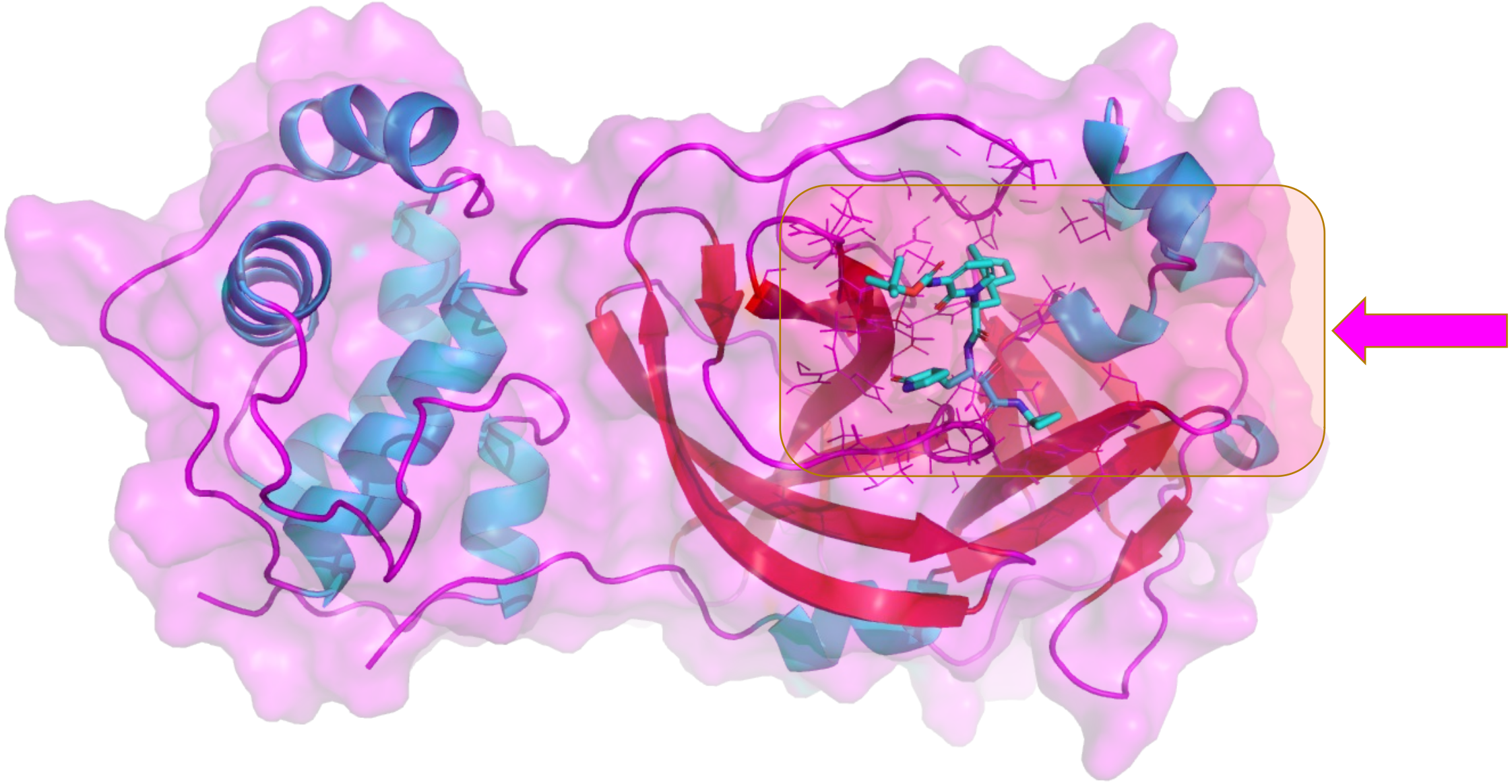


OEW (PDB ID: 6Y7M)

Strategy 3: Disarmament of viral proteases

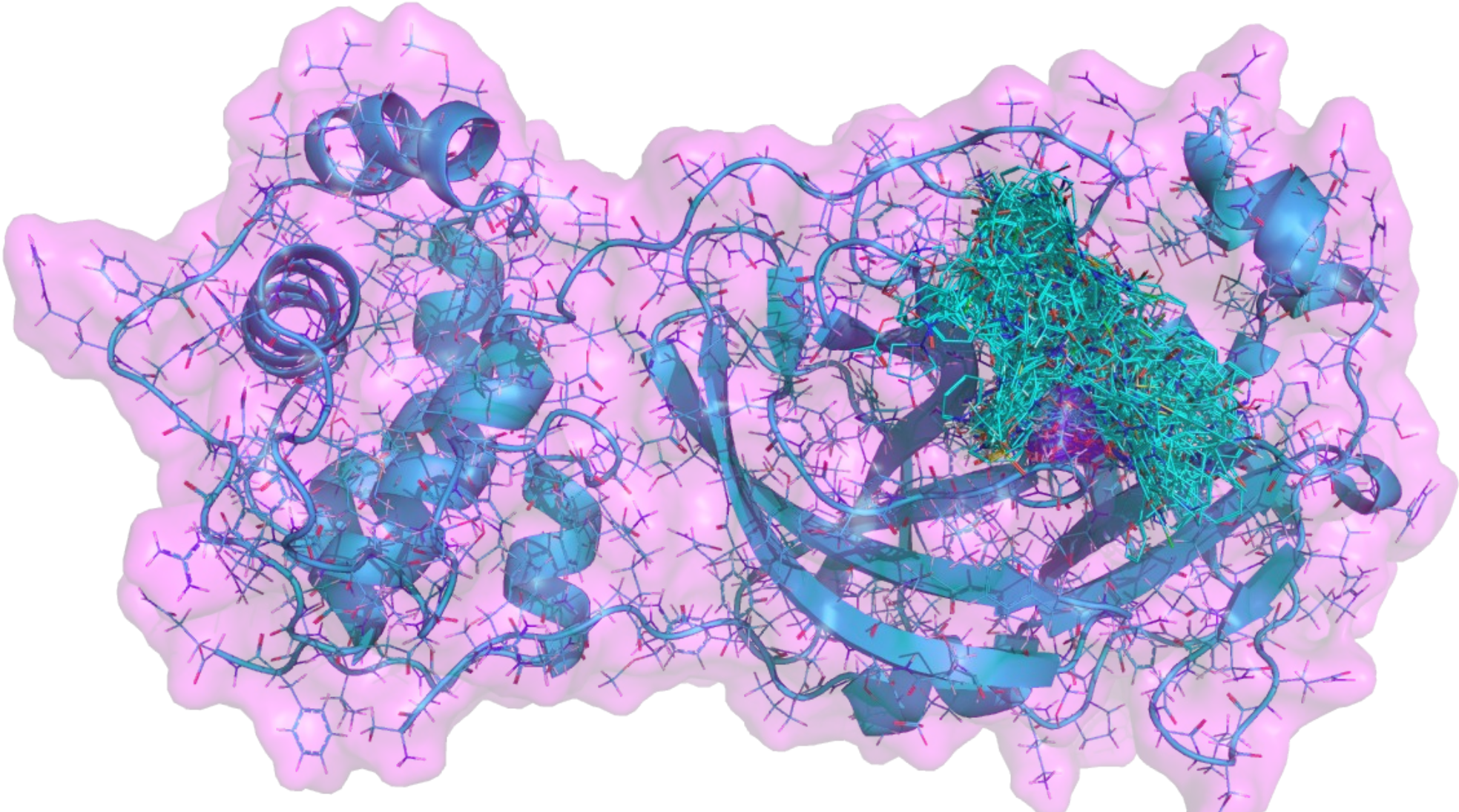


Strategy 3: Disarmament of viral proteases



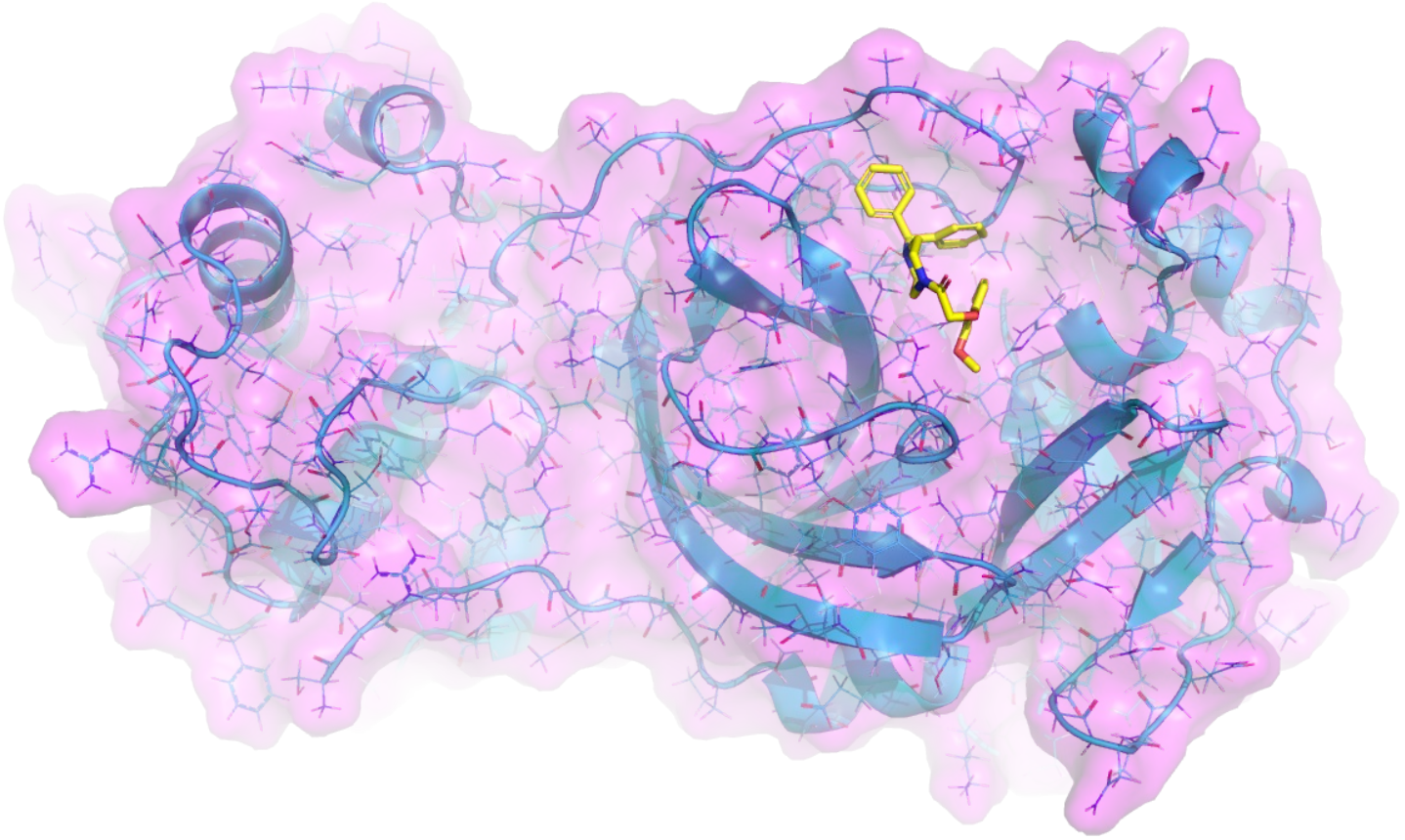
Strategy 3: Disarmament of viral proteases

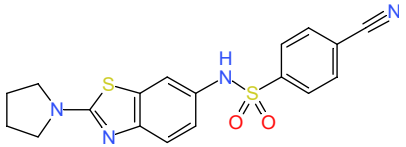
Searching the universe of compounds …

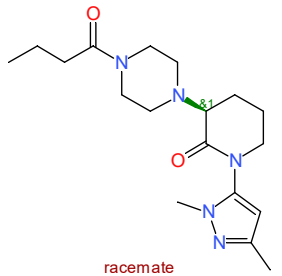


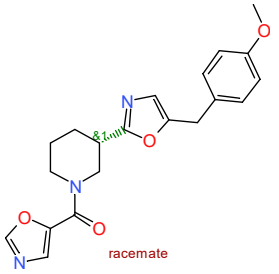
Strategy 3: Disarmament of viral proteases

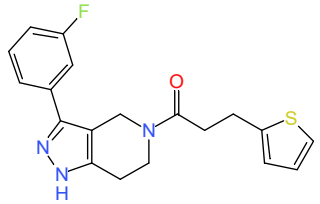
Results in ongoing research ...

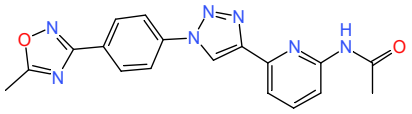






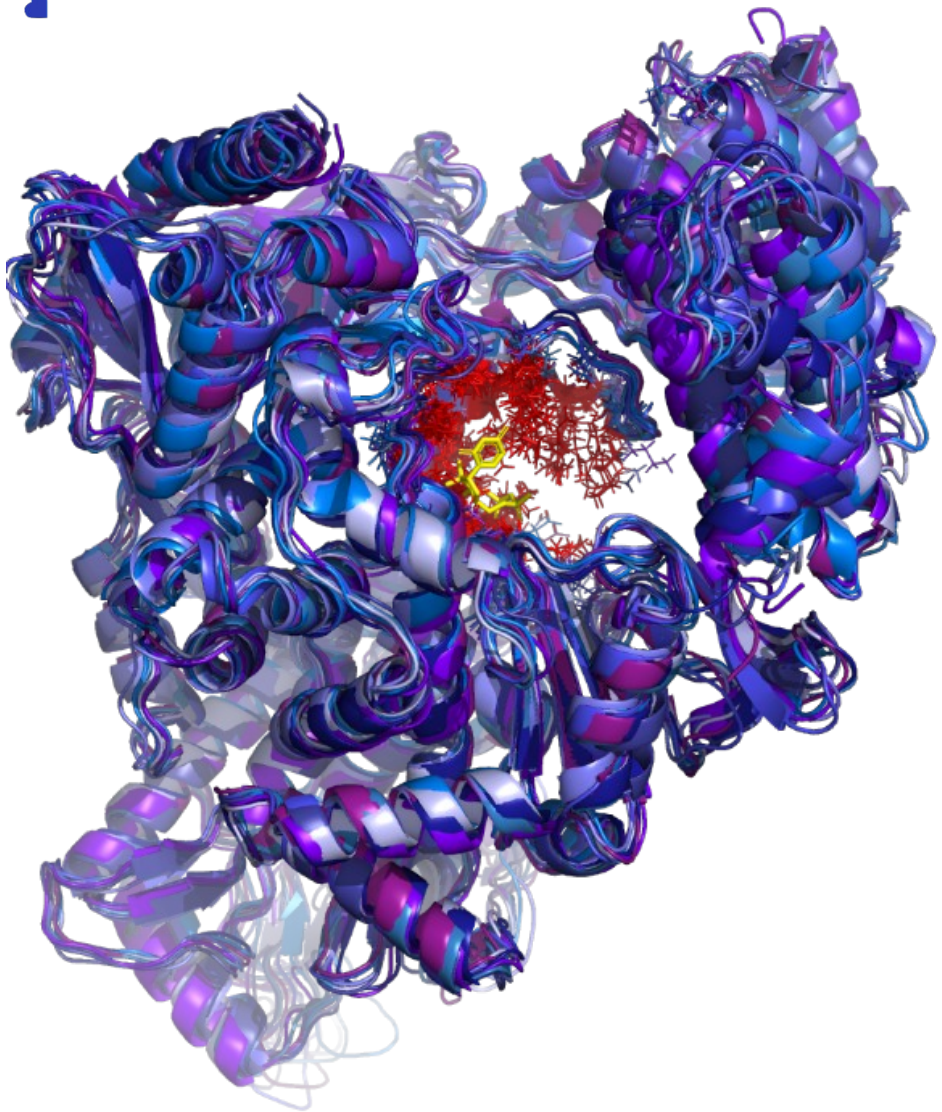






Compounds are underway for biological evaluatio

Strategy 4: Inhibition of other potential therapeutic targets



- The viral **protein E** is 75 amino acids long and forms a pentamer, which acts as a viral trans-envelope protein. It functions as an ion channel, most likely for Na+, but also seems to be important for the release of virions from cells .

- **S Protein** A protein precursor that is cleaved into the glycosylated subunits S1 and S2. S1 binds to the host cell receptor, ACE2, whereas S2 mediates the
  fusion of virus and host membrane.

- **TMPRSS2** Transmembrane protease, serine 2, SARS-CoV-2 uses the SARS-CoV receptor ACE2 for entry and the serine protease TMPRSS2 for S protein priming

Project will soon be available to everyone:

SiDock@home

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What is SiDock@home test?

COVID.SI is a citizen science project to fight against SARS-CoV-2 by distributed computing. SiDock@home is a BOINC-based extension of the project COVID.SI to engage the BOINC community into the drug search.

You can help with your computer. With the help of BOINC, you will download a subset of compounds on your computer, examine the compounds in the context of the studied target and send the results to a server where they are collected for later analysis.

For account creation please use a **Crunch_4Science** invitation code. It is not needed when registering by BOINC Manager.

Windows application requires the Microsoft Visual C++ Redistributable for Visual Studio 2019.

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News is available as an RSS feed RSS

COVID.SI project wholehartedly thanks all participants for their support and help !

Together we are more effective in fighting this global crisis!

Thank You for your attention.