



# Anyone can Participate

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First and foremost thanks to

***all of You !***

1.11.2020

Črtomir Podlipnik, Marko Jukić and Sebastian Pleško



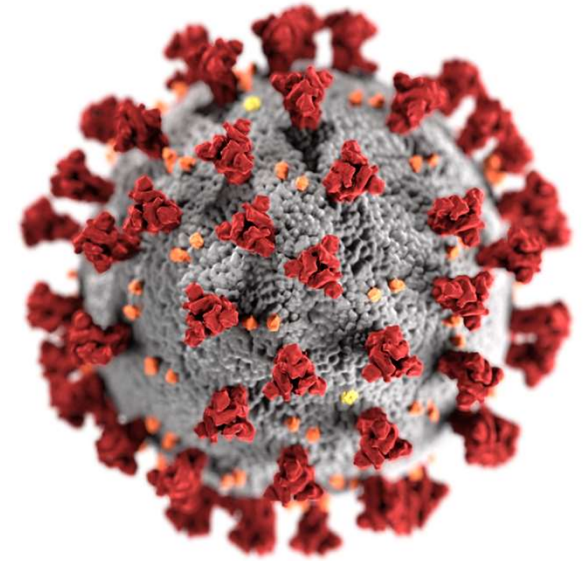
**"If you know the  
enemy and know  
yourself you  
need not fear the  
results of a  
hundred battles."**

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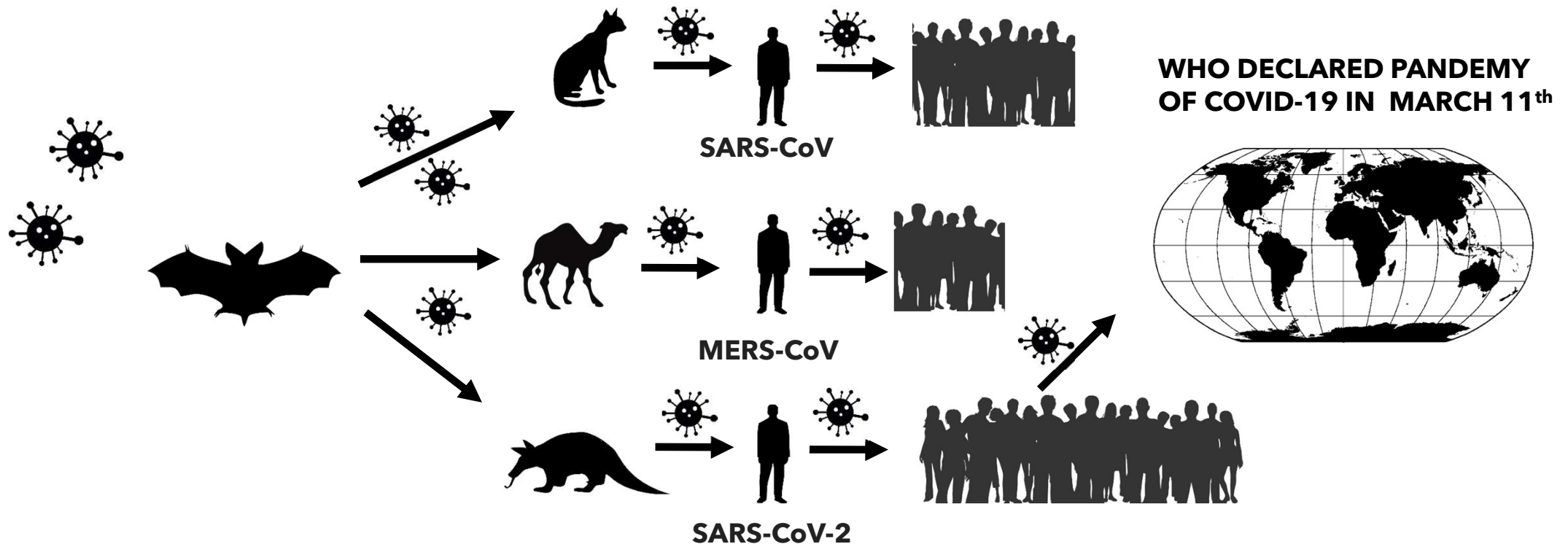
Sun Tzu

# Coronaviruses are our everyday companions

- Coronaviruses are named after crown spikes located on their surface.
- Four major subgroups of coronaviruses:  $\alpha$ ,  $\beta$ ,  $\gamma$  and  $\delta$
- 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) .

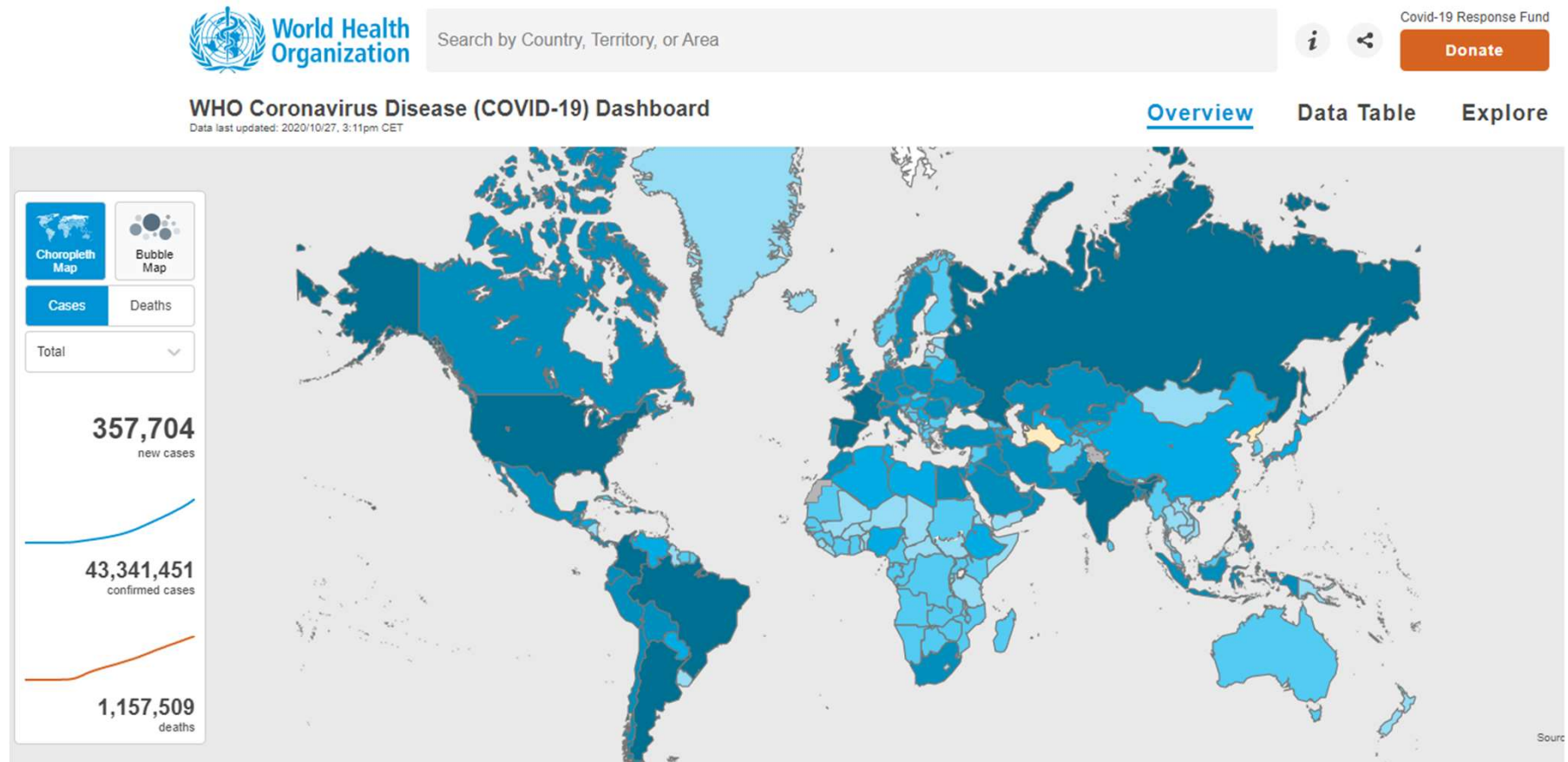


# Corona viruses are our everyday companions



- 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



Globally, as of 3:11pm CET, 27 October 2020, there have been 43,341,451 confirmed cases of COVID-19, including 1,157,509 deaths, reported to WHO.



# Worldwide Citizen Science projects to rundown SARS-CoV-2

## COVID MOONSHOT SPRINT 4

October 20, 2020  
by [John Chodera](#)

As the [COVID Moonshot](#) continues to make rapid progress, the fourth COVID Moonshot free energy calculation sprint focused on a backup lead series that suddenly pulls into the lead!



COVID Moonshot

**Help us Fight Coronavirus**

Contribute funding, compute power, or expertise to help develop a COVID antiviral

Check out our new data:

[Activity Data](#) [New](#) [Structures](#) [New](#)

It's been an incredibly busy time at Folding@home HQ, with a huge number of major projects all coming together at the same time: Between the [CUDA-enabled OpenMM core \(core22\)](#), a major update to the [SARS-CoV-2 cryptic pockets paper](#), organization of major data releases, setting up some critical new projects, and having two of our amazing scientists ([Hannah Bruce Macdonald](#) and [Matt Wittmann](#)) making previously-planned moves to new positions, it's been a hectic few weeks since our last update. But rest assured, the science has not stopped, and we're making extremely rapid progress toward a new small molecule therapy for COVID-19.



eterna

Solve Puzzles. Invent Medicine.

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You play by solving puzzles using RNAs, tiny molecules at the heart of every cell.

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**OpenVaccine: Eterna takes on COVID-19**

With the onset of the COVID-19 pandemic, the Eterna project is looking to harness online gamers toward a solution. Their mission? To develop mRNA vaccines stable enough to be deployed to everyone in the world and not just a privileged few. For more info, see the [announcement](#) and [crowdfunding campaign](#).

**OpenVaccine**  
COVID-19  
100+ DESIGNS



foldit BETA

Solve Puzzles for Science

PUZZLES • CATEGORIES  
BLOG • FEEDBACK

**The rundown on coronavirus**

This COMPUTER GAME could help...

Poznejši o... Skupna raba

**YOU CAN HELP**

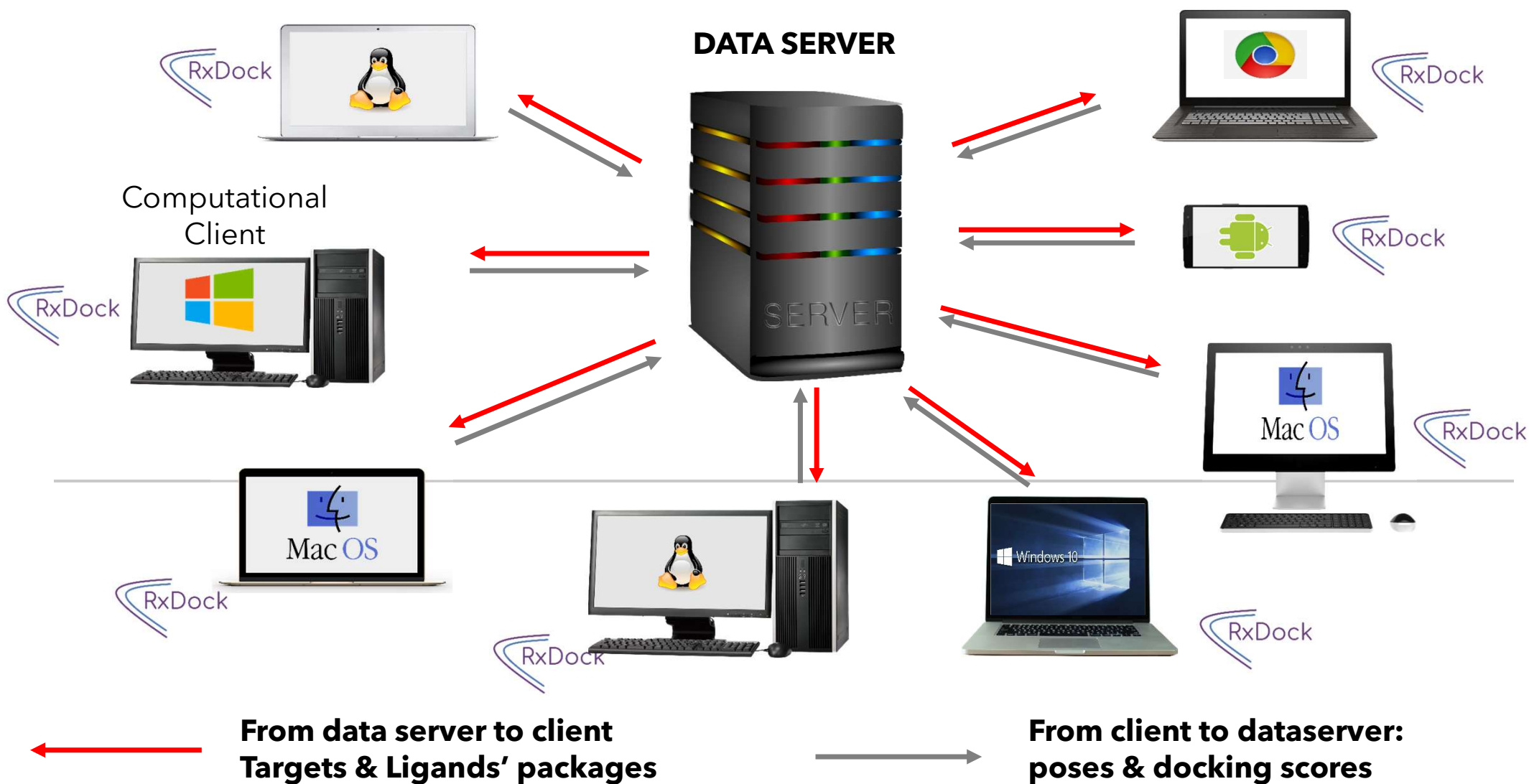
You don't have to be a scientist to do science! Download and play Foldit and you can help researchers discover new antiviral drugs that might stop coronavirus! The most promising solutions will be manufactured and tested at the University of Washington Institute for Protein Design in Seattle.

\*Foldit is run by academic research scientists. It is free to play and not-for-profit. To get started, download it and create a username!

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



# 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.

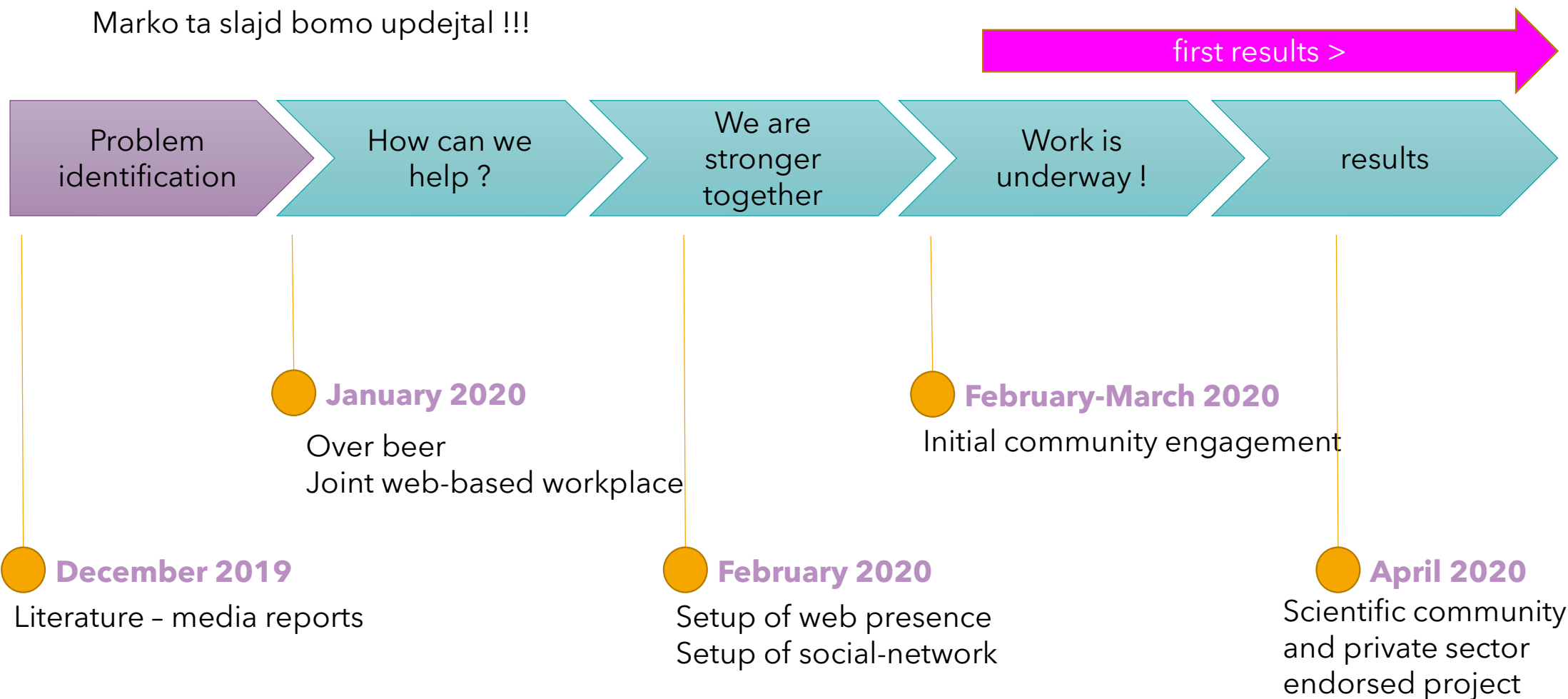
<https://covid-19.sledilnik.org>





# GLOBAL PROBLEM NEEDS GLOBAL SOLUTION

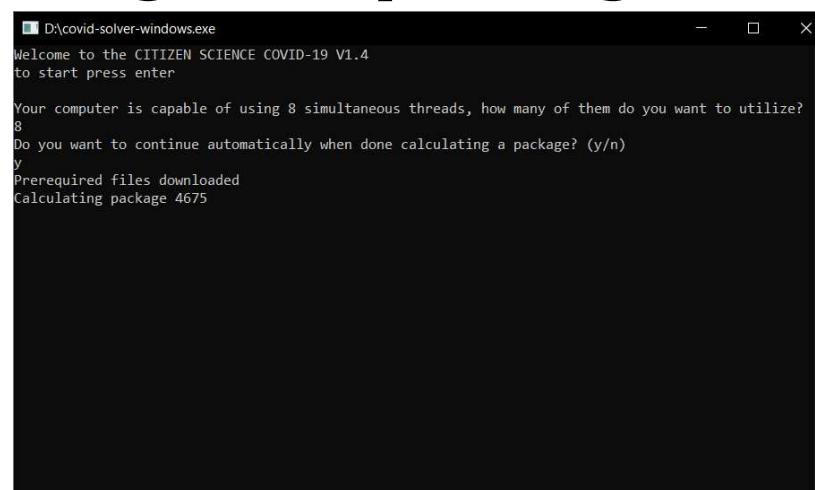
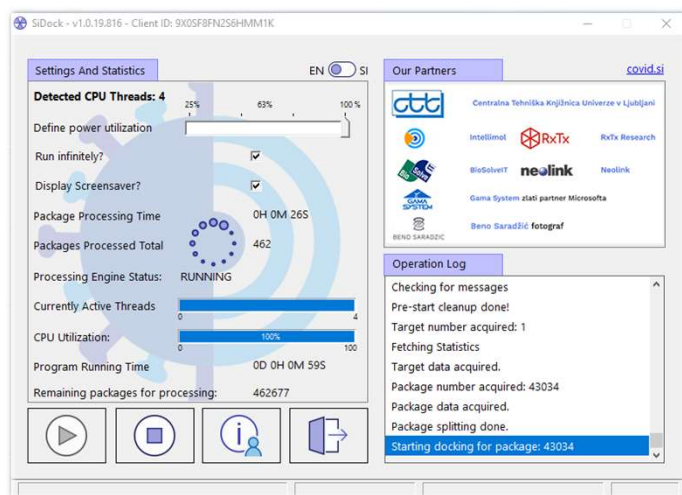
Marko ta slajd bomo updejtal !!!





# COVID.SI:

## Clients for distributing computing



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

Target

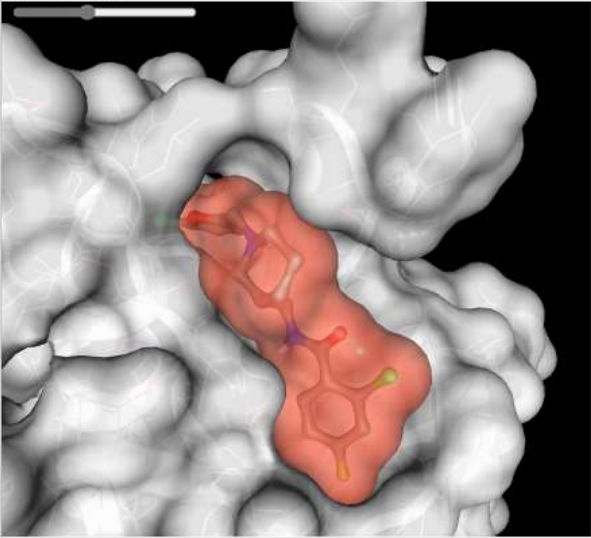
PLPro 6WUU

Display options:

- ☐ Show only skeleton of the protein
- ☐ Show sidechains of aminoacids
- ☒ Show target with surface

 SHOW

Target: 46 Ligand : 70



Welcome to Ligand Viewer.

Here you can see how a ligand (red) is docked onto a target (gray). This is essentially what our missions are all about – finding ligands that dock onto the target as best as they can.

Ligands that “fit in” are the best candidates for further processing and potential laboratory and clinical trials.

When you want to see how another ligand is docked, move the slider above the viewer box.

Commands:

- mouse left button hold + mouse move = rotate target
- mouse middle button scroll = zoom in/out of target
- mouse right button hold + mouse move = pan target
- “R” key = reset view (whole target image displayed)
- “I” key = slowly rotate target on/off

Title: ZINC000826572055

- 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

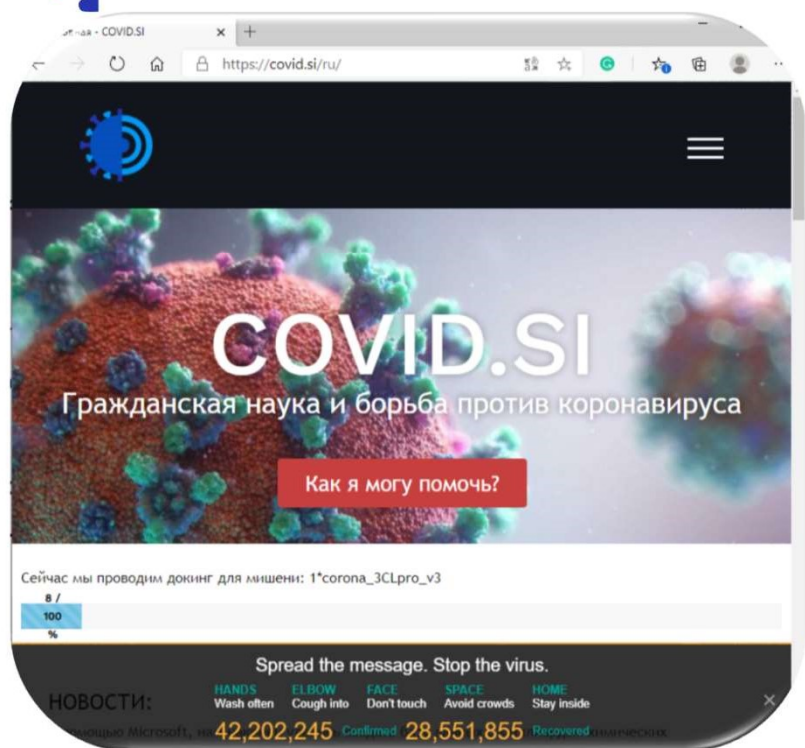
#### **Safecast and Responding to Covid-19 through crowdsourced data**

Angela Eaton, Safecast Americas Director



# COVID.SI:

## Dissemination of the project - Web page



<https://covid.si/>

<https://covid.si/en>

<https://covid.si/ru>

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](mailto:info@covid.si)

Please send also comments, suggestion and critics to [info@covid.si](mailto:info@covid.si)



# Statistics of the COVID.SI projects

[Home](#)[Team](#)[Blog](#)[Results](#)[Stats](#)[Quick Start](#)  
Slovenščina[Presentation](#)  
Русский

## DOCKING STATISTICS

(Updated: 2020-10-27 @ 20:10:01)

Number of successfully docked packages

**61**

in last 60 minutes

**1.265**

in last 24 hours

**36.997**

in last month

**728.502**

since May 13th 2020

These numbers mean number of successfully uploaded results to server. Each time a client returns results, it had had to dock 1000 molecules beforehand, some of them 50 times.

Number of computers docking

**18**

in last 60 minutes

**26**

in last 24 hours

**96**

in last month

**270**

since May 13th 2020

Only successful communications with the server are included. Last hour number can deviate due to some clients needing more than an hour to finish docking the package and to return the results.

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

[Home](#)[Team](#)[Blog](#)[Results](#)[Stats](#)[Quick Start](#)  
Slovenščina[Presentation](#)  
Русский

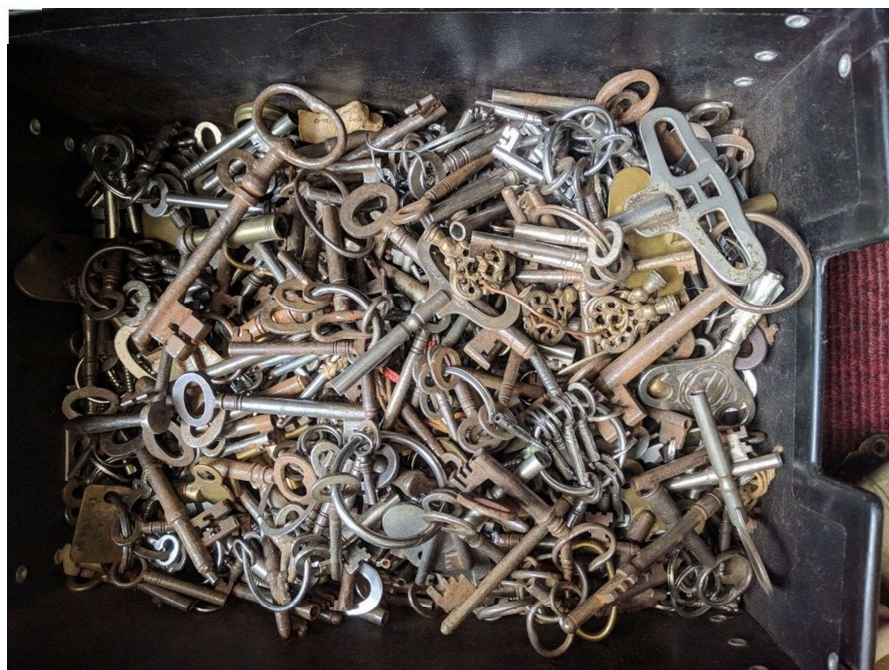
Search		Search			
Nr. of CPU threads ↕	Nr. of computers ↕	Client ID ↕	OS ↕	Uploads ↕	Last Contact ↕
40	1	TO9WMRQR5OH8ZXFD	Windows-GUI	7384	2020-10-27 20:08:41
32	1	54d961db97f0420ea3778713a2b5879b	Linux-CLI	4261	2020-10-27 20:05:57
12	2	9e255372038644cca18d597cb27cee0a	Linux-CLI	2112	2020-10-27 20:08:41
11	1	60f45e413d4c4c8b883c0e537d208fd4	Linux-CLI	1949	2020-10-27 20:08:01
10	1	fri-lrk-su2	Linux-CLI	1853	2020-10-13 11:16:03
8	6	fri-lrk-su2-2	Linux-CLI	1851	2020-10-13 11:16:23
6	1	JT7GVT5NT0NQX2IN	Windows-GUI	1602	2020-10-27 19:53:12
4	7	T4R0LDT51U0M5MKW	Windows-GUI	1447	2020-10-27 20:10:44
3	1	DKRJ42IJBRRQX615	Windows-GUI	1404	2020-10-20 13:59:02
2	3	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.



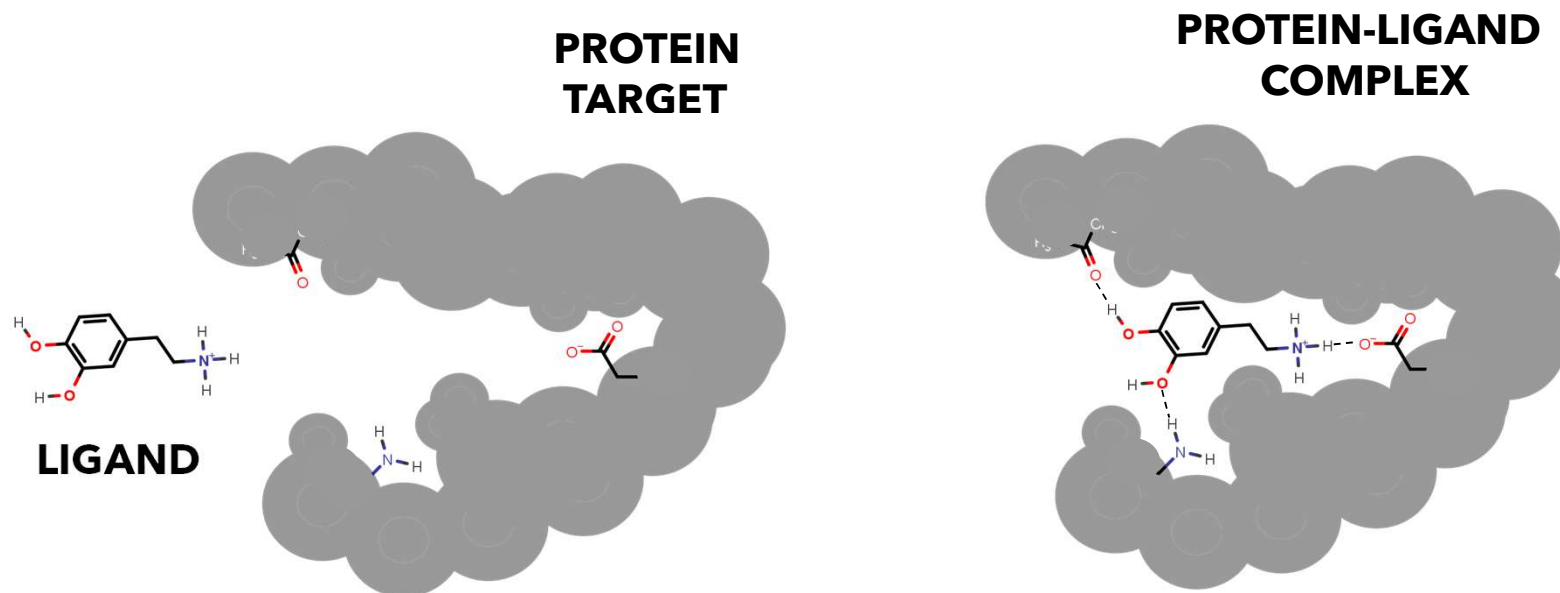
## Virtual screening - Find right key for the lock



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

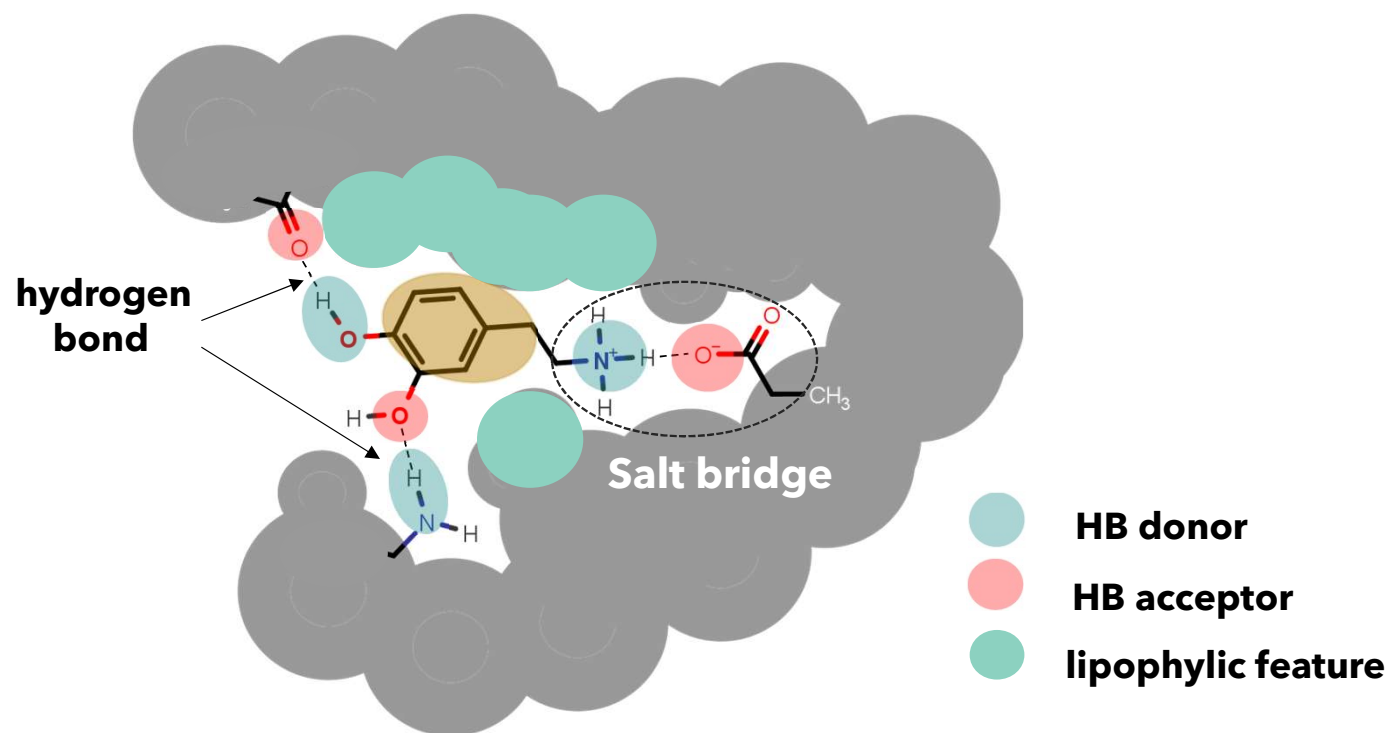


The specific action of an enzyme with a single substrate can be explained using a **Lock** and **Key** analogy first postulated in 1894 by **Emil Fischer**. In this analogy, the **lock** is the enzyme and the **key** is the substrate. Only the correctly sized **key** (substrate) fits into the **key hole**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

<http://chemistry.elmhurst.edu/vchembook/571lockkey.html>



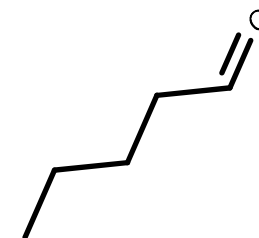
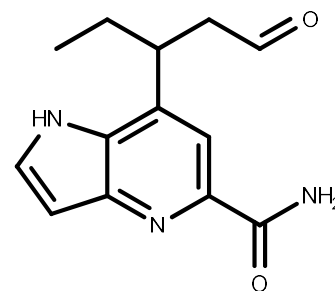
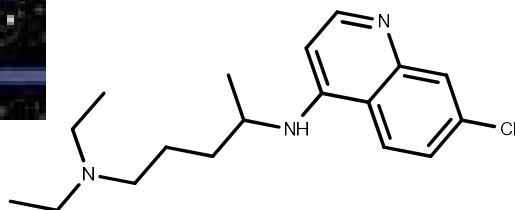
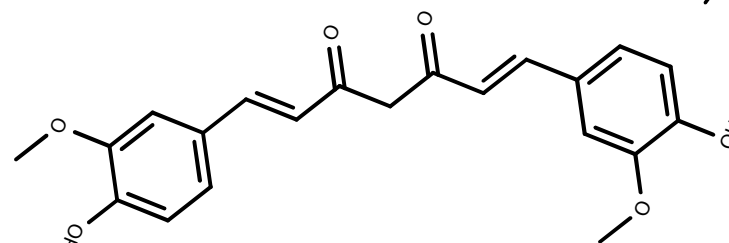
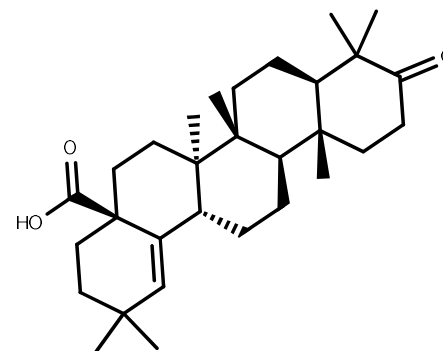
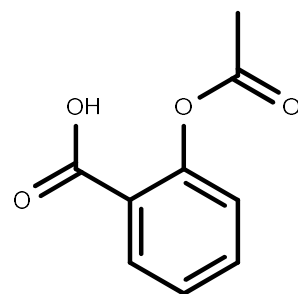
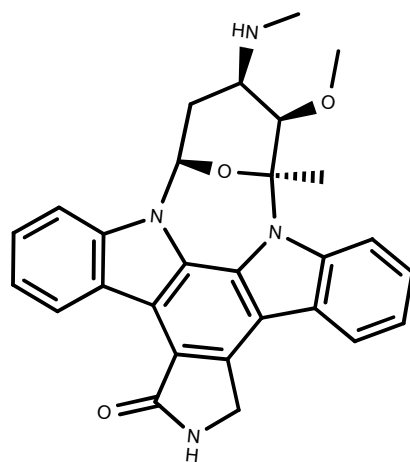
## Lock-and-key aspect



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 bind to it.



# Chemical Space - infinite source of chemical structures



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



# COVID.SI:

## Library of one Billion Compounds

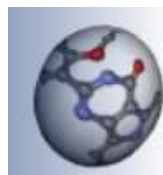


Multiple commercial and academic sources of 2D molecular structures were conglomerated, structures cleaned, checked for errors, ionised and 3D structures calculated. Library construction was made possible by support from:



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.





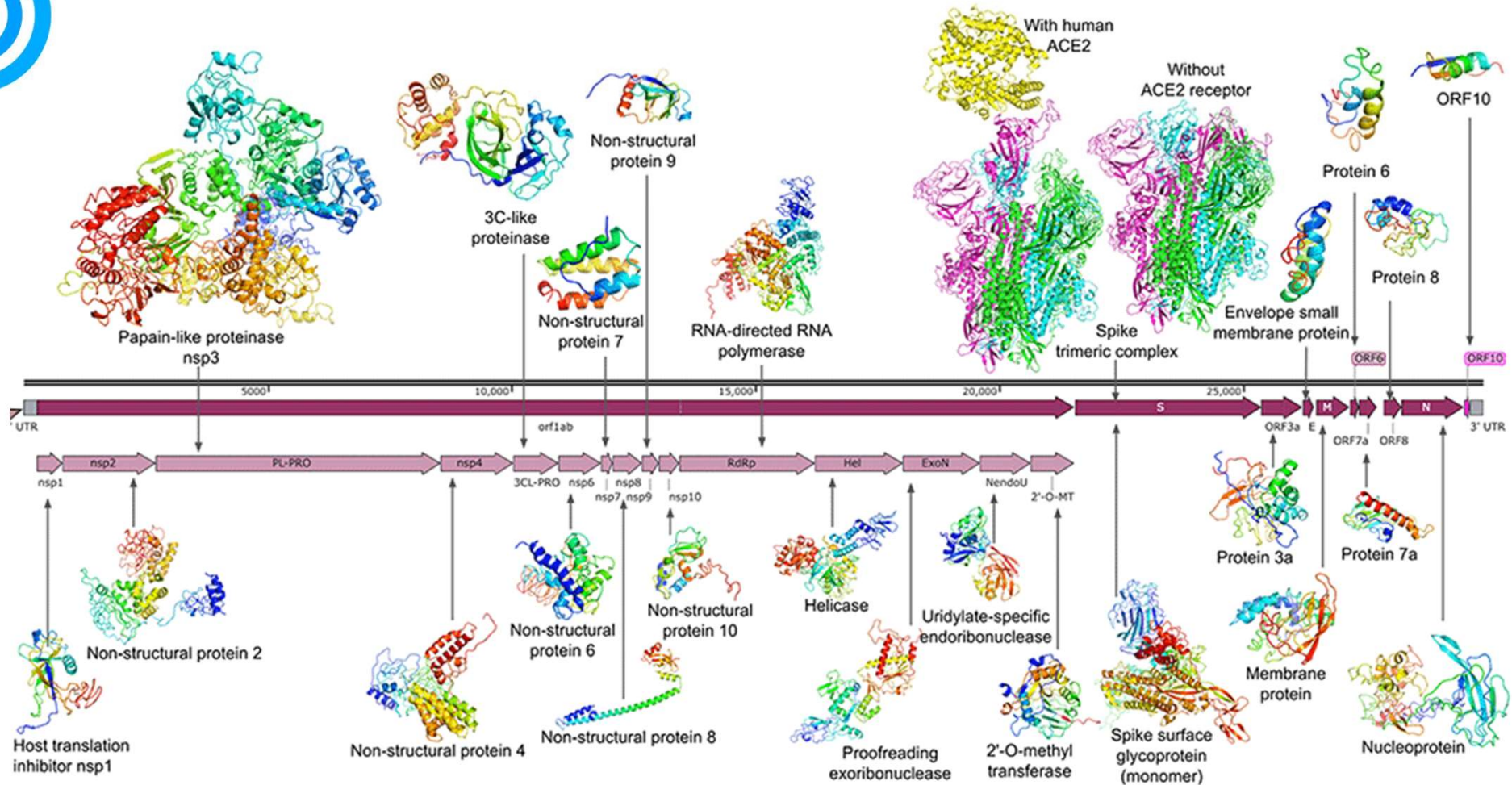
**"Strategy without tactics is the slowest route to victory. Tactics without strategy is the noise before defeat."**

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Sun Tzu



# The ZOO of SARS-CoV-2 proteins



3D structural models and function annotation for all proteins encoded by [the genome of SARS-CoV-2](https://zhanglab.ccmb.med.umich.edu/COVID-19/). Structures are modelled in **prof. Zhang Laboratory** with c-i-Tasser (<https://zhanglab.ccmb.med.umich.edu/COVID-19/>)



**(M)embrane** →

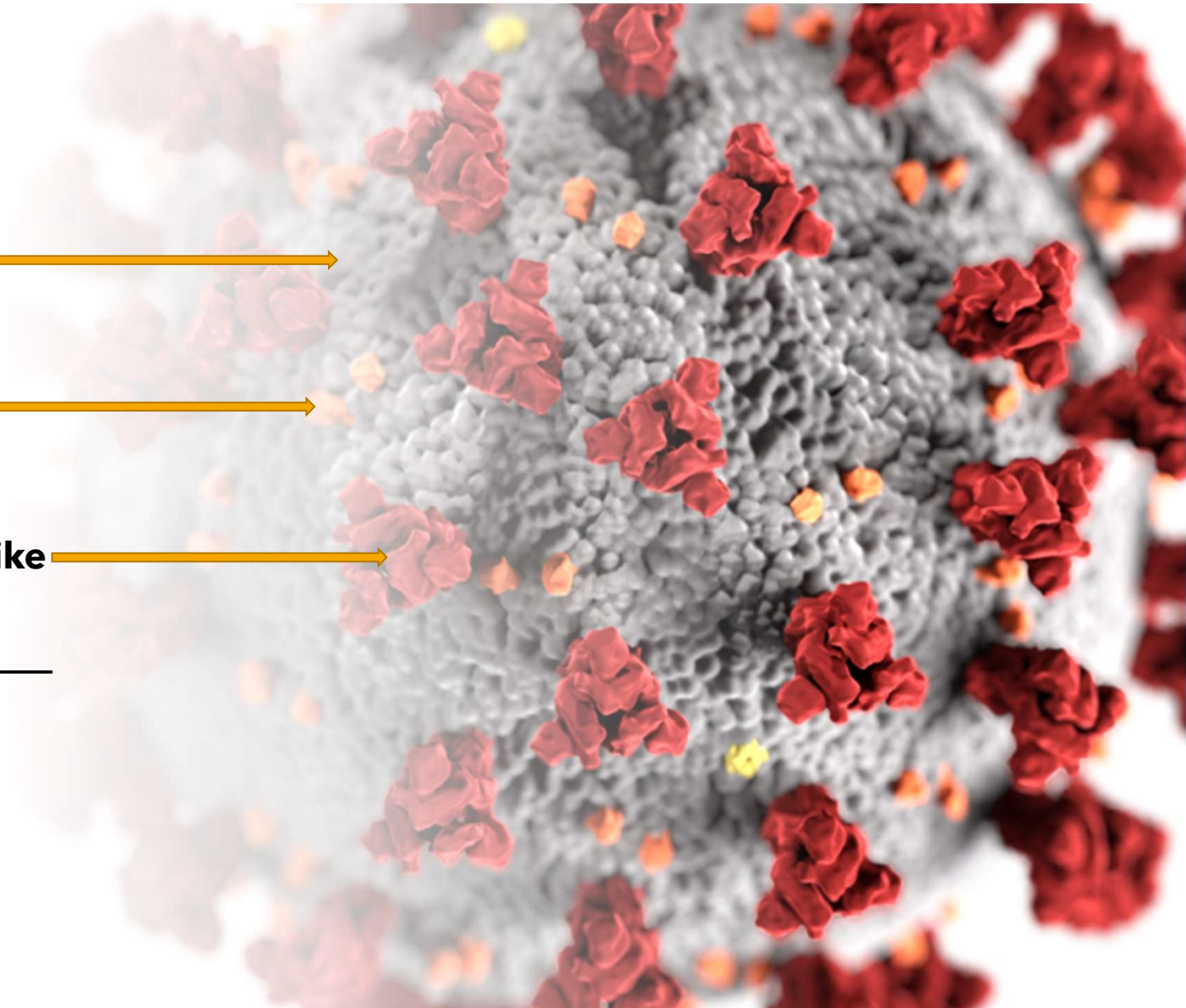
**(E)nvelope** →

**(S)pike** →

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*Inside viral particle*

**(N)ucleocapsid**





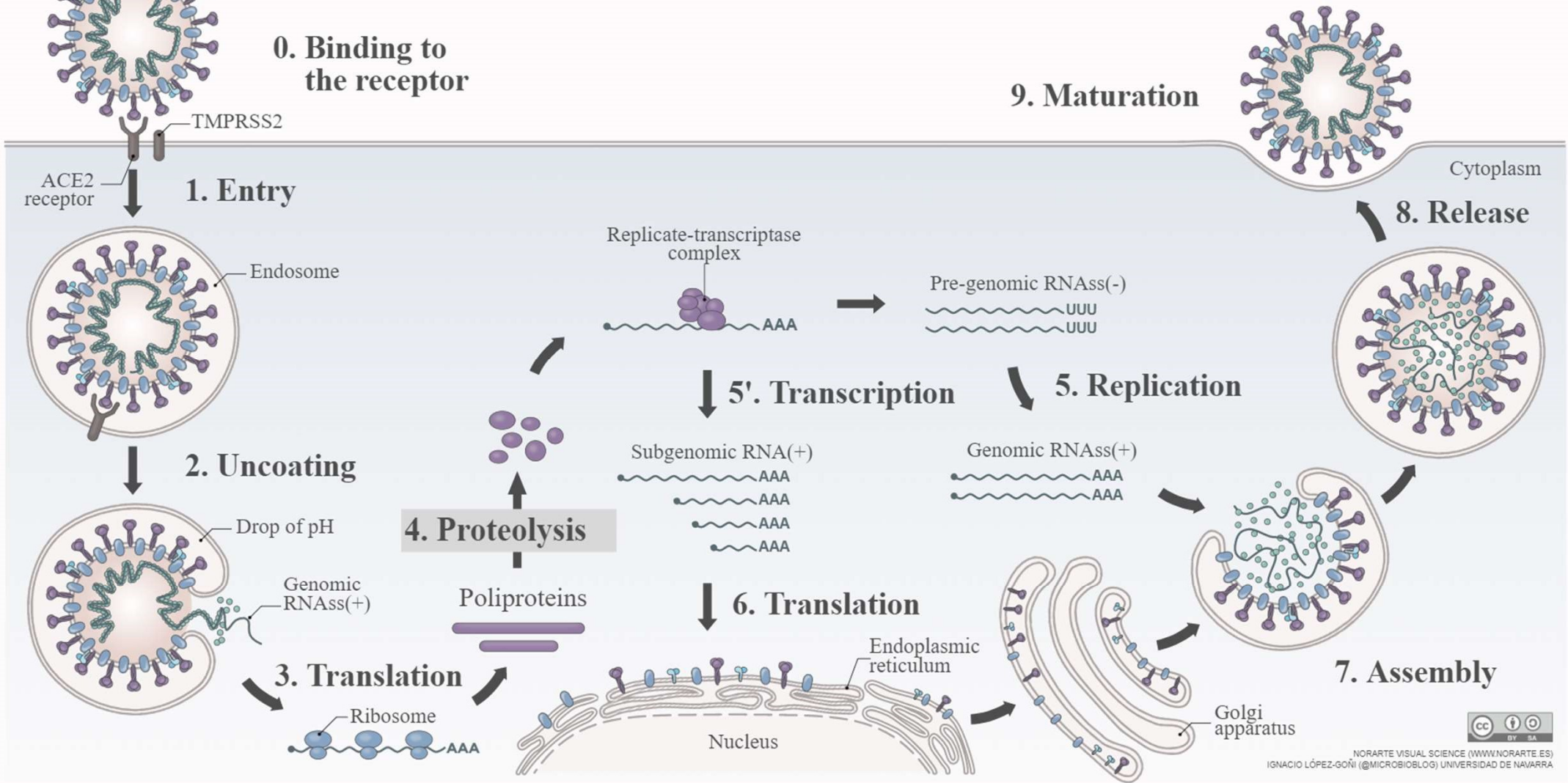
## Targets related to COVID-19 studied by our methodology.

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

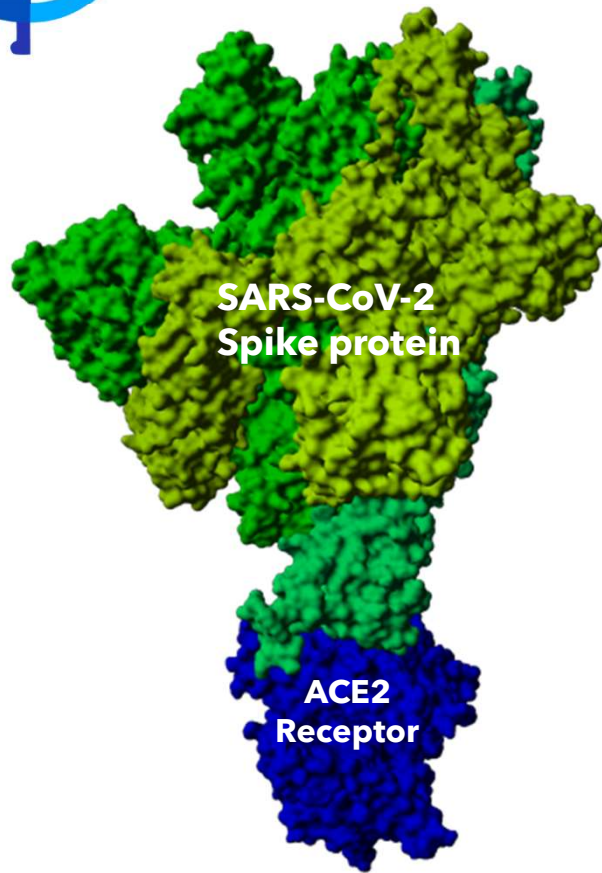


# The Live Cycle of SARS-CoV-2





# Strategy 1: Prevent virus entry into the host cell



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

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





## Strategy 2: Prevent virus to escape from endosome

### Lysosomotropic agents targeting endosomal/lysosomal pH

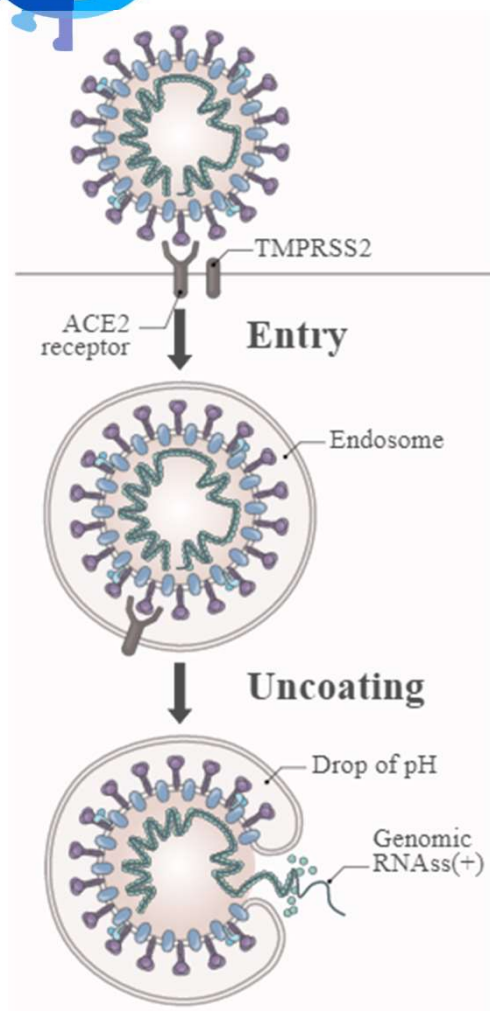
Therapy with **CQ**, a well-known anti-malarial drug, which is lysosomotropic agent that accumulates in the acidic organelles such as endosomes and lysosomes and neutralizes their pH.

### 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.



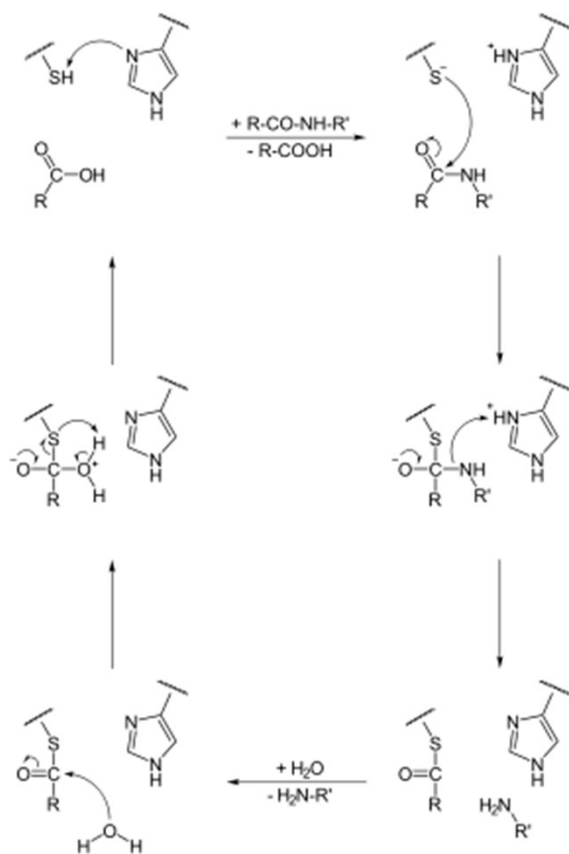


## Strategy 3: Disarmament of viral proteases

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

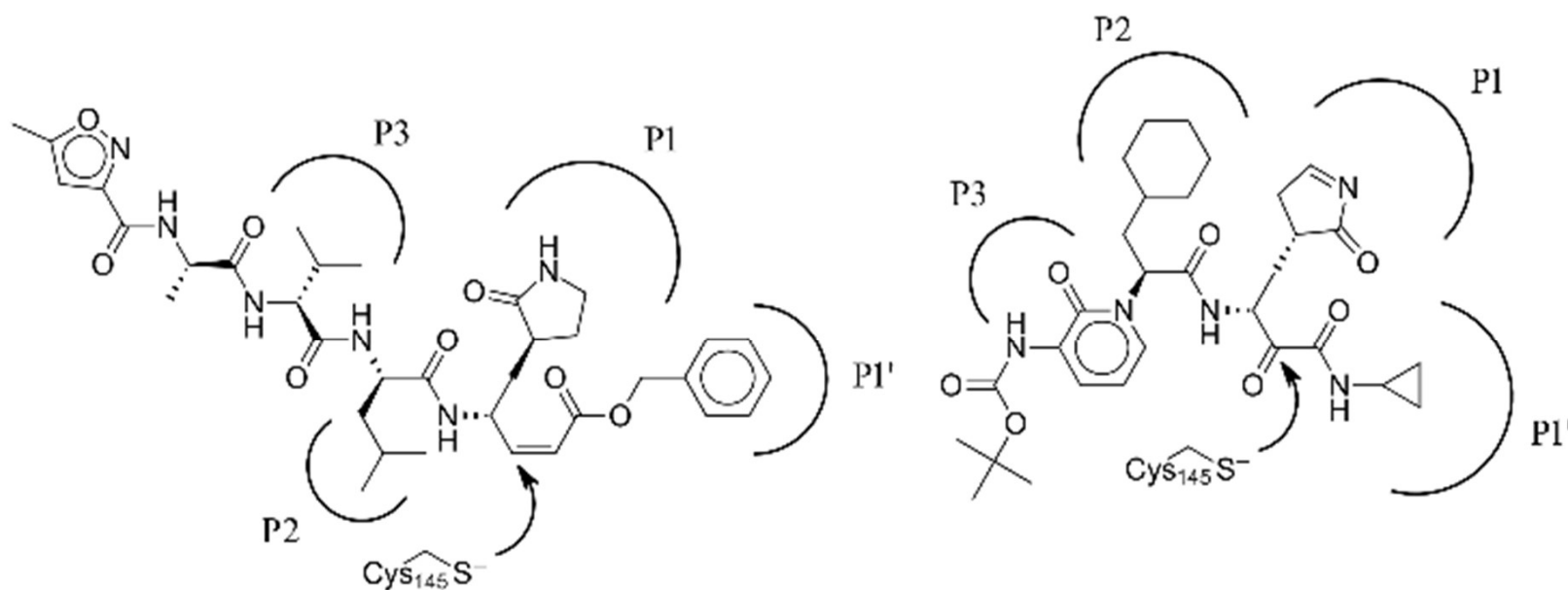
Therefore routes towards protease inhibition are of paramount importance in virus lifecycle inhibition and key approaches are:

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





## Strategy 3: Disarmament of viral proteases

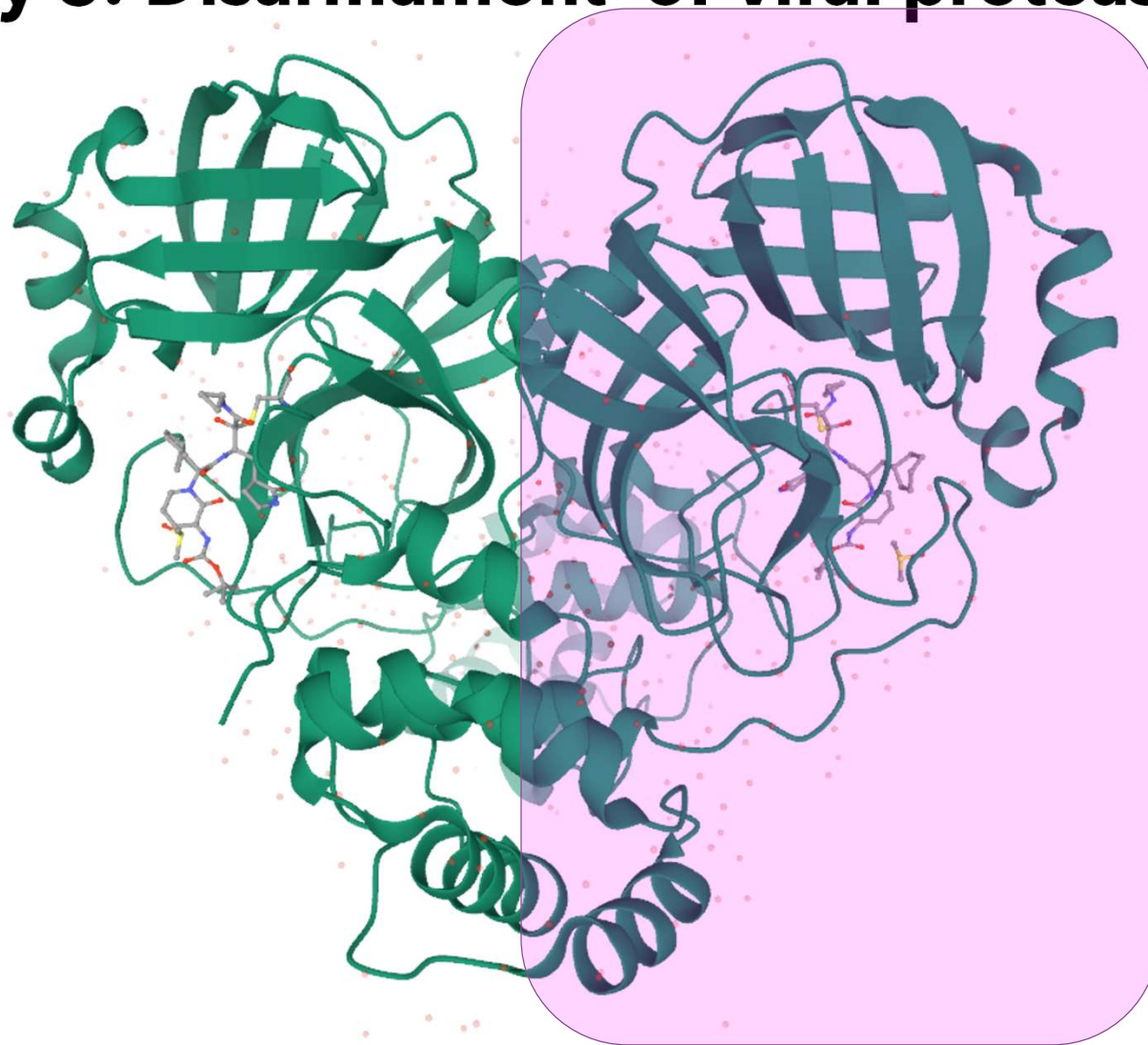


PRD\_002214 (PDB ID: 6LU7)

OEW (PDB ID: 6Y7M)

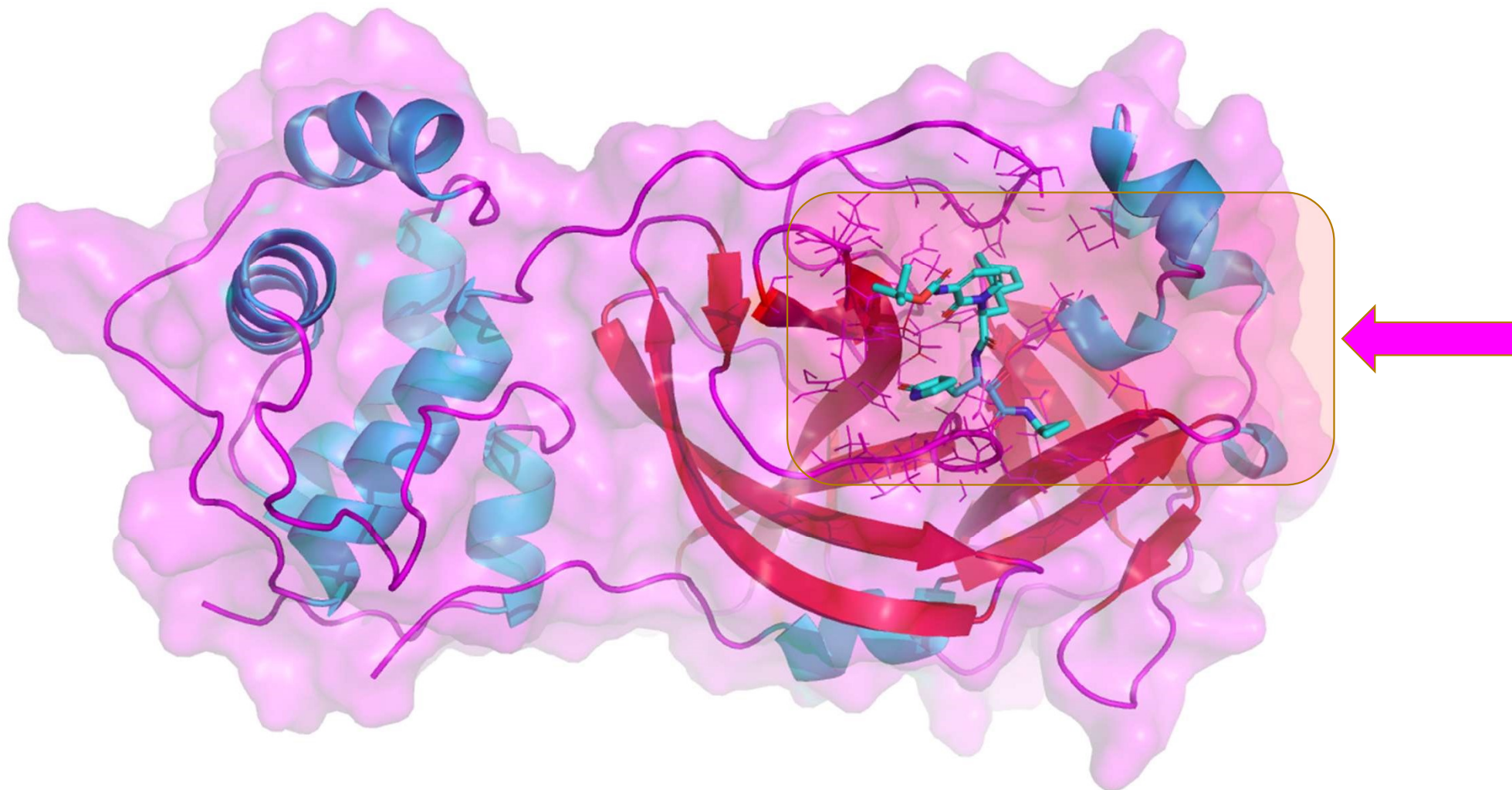


## Strategy 3: Disarmament of viral proteases





## Strategy 3: Disarmament of viral proteases

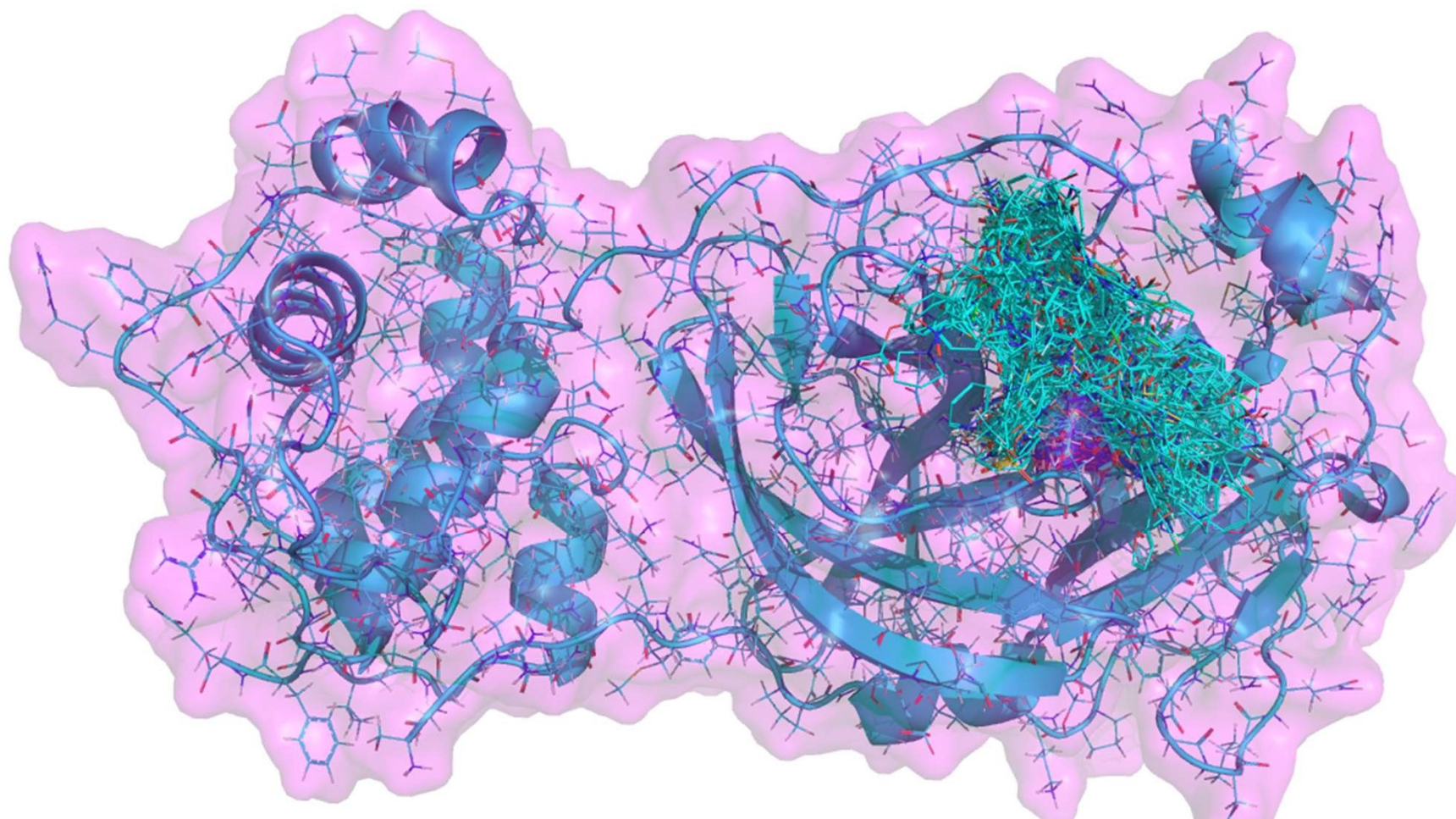






## Strategy 3: Disarmament of viral proteases

### Searching the universe of compounds ...

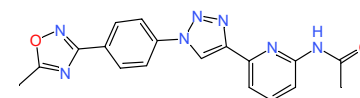
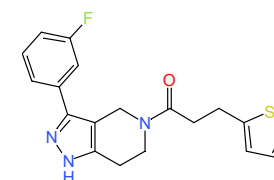
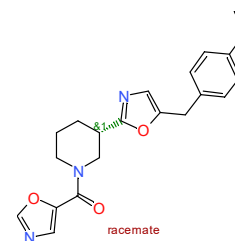
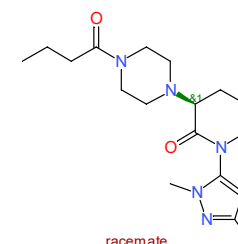
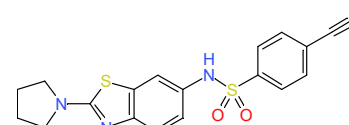
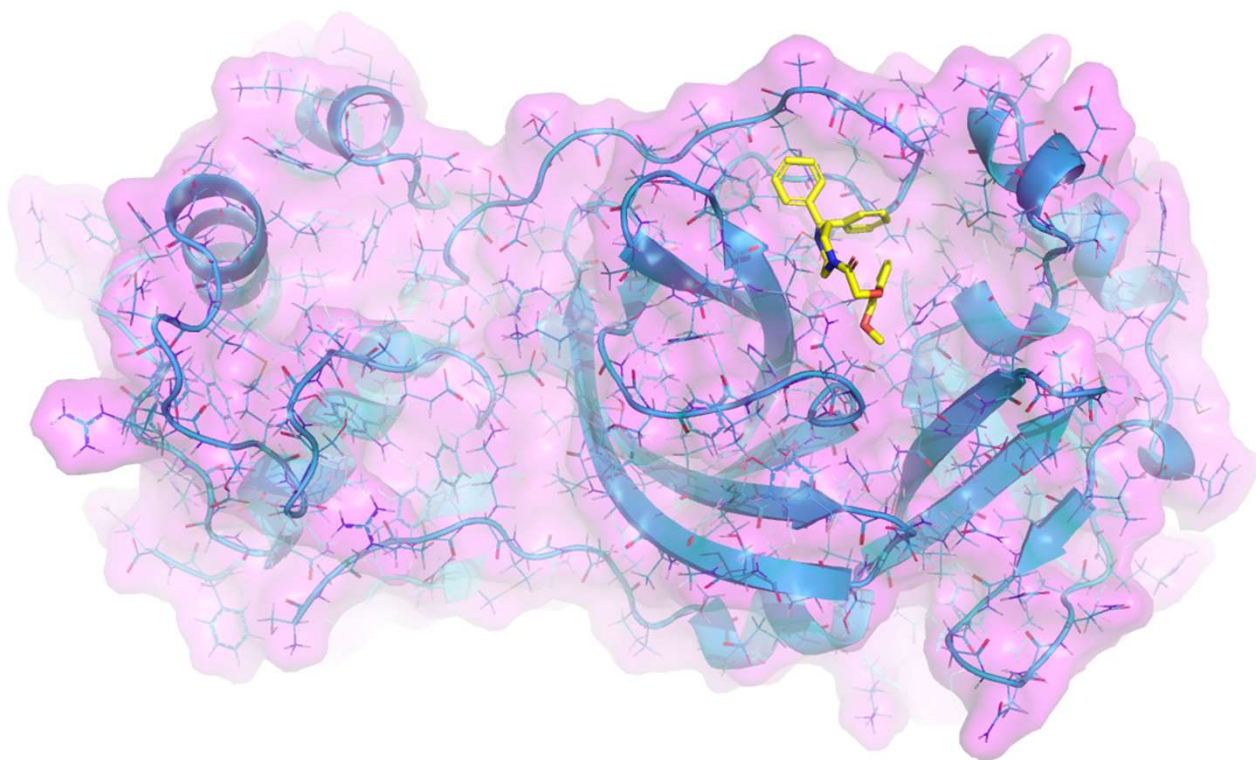






# Strategy 3: Disarmament of viral proteases

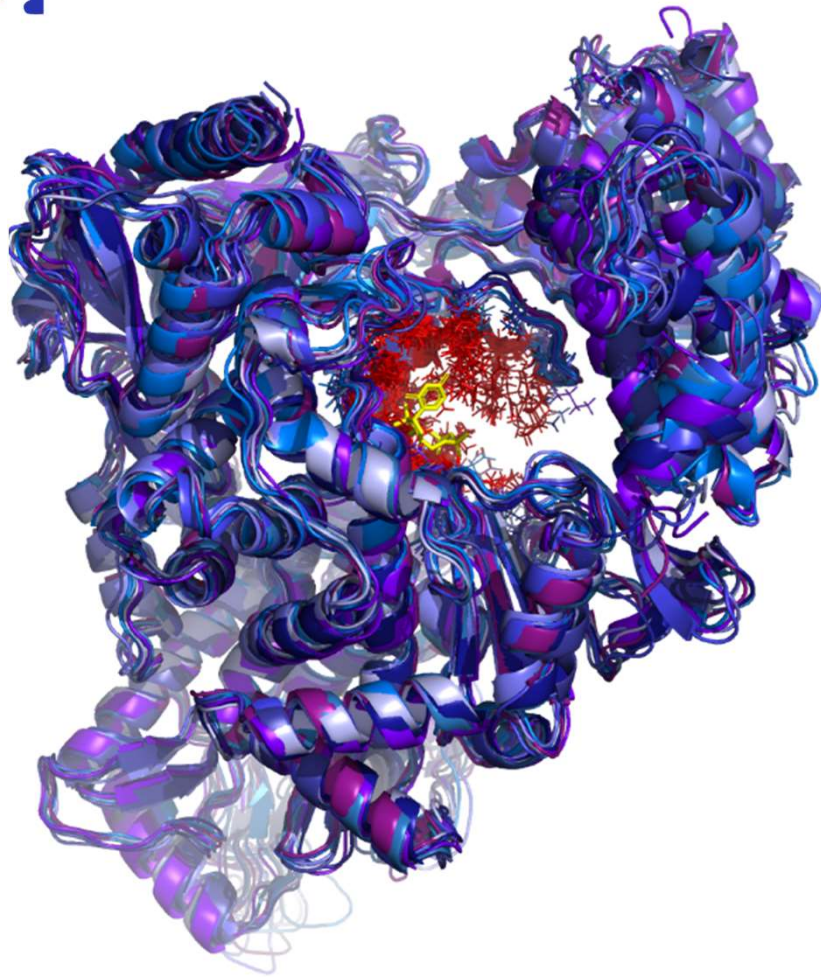
## Results in ongoing research ...



Compounds are underway for biological evaluation



## Strategy 4: Inhibition of other potential therapeutic targets

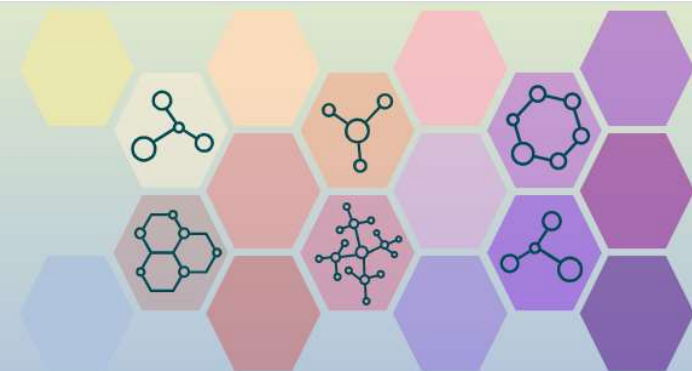


- The viral **protein E** is 75 amino acids long and forms a pentamer, which acts as a viral trans-envelope protein. It functions as an ion channel, most likely for  $\text{Na}^+$ , but also seems to be important for the release of virions from cells .
- **Sprot**
- **TMPRSS2** Transmembrane protease, 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



SiDock@home test Project ▾ Computing ▾ Community ▾ Site ▾

[Join](#) [Login](#)

### 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](#).

[Join SiDock@home test](#)

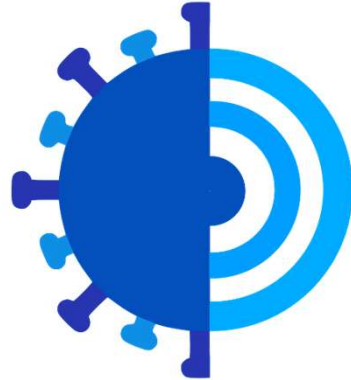
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**COVID.SI project wholeheartedly thanks all participants for their support and help !**

**Together we are more effective in fighting this global crisis!**



***Thank You for your attention.***