Research into combating COVID-19 at BNL

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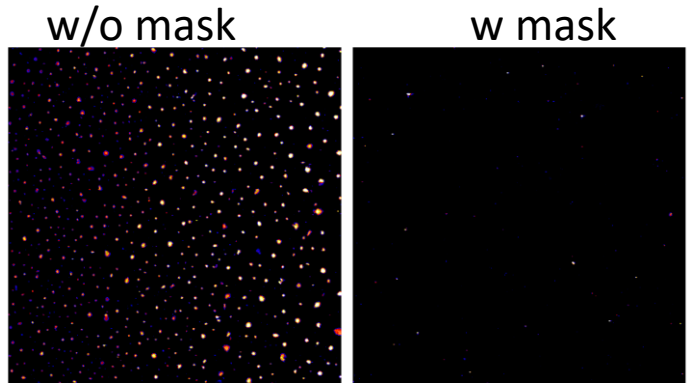
U.S. DEPARTMENT OF ENERGY | Office of Science

BROOKHAVEN NATIONAL LABORATORY

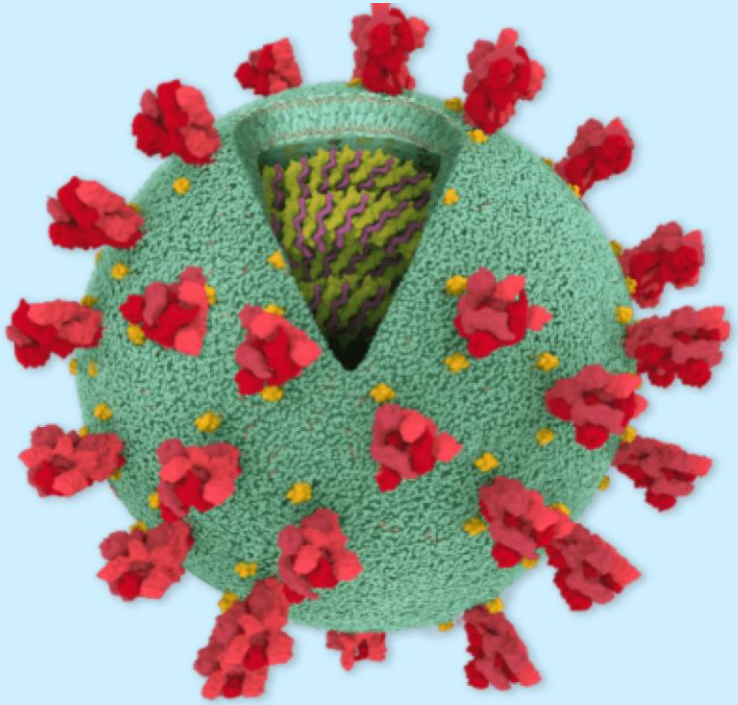
BNL is engaged in fighting COVID-19 on multiple fronts

1) **Drug discovery** (tonight's talk)
2) **Computer modeling of spread of disease**
   - A BNL model is being used by U. Illinois, Urbana-Champaign to set operating procedures to try and slow the spread of disease
   - Developing models of spread of aerosols through the air to determine how far they travel under what conditions
3) **Manufacturing techniques**
   - Looking at N95 mask materials to understand how to make them more effective
4) **Processing information**
   - Using computers to read the scientific literature and allowing scientists to search those papers using "natural language"
   - 41,000 papers in the archive
5) **Therapeutics**
   - Using nanoscience to treat COVID-19
6) **Sensing devices**
   - Using nanoscience to detect SARS-CoV-2



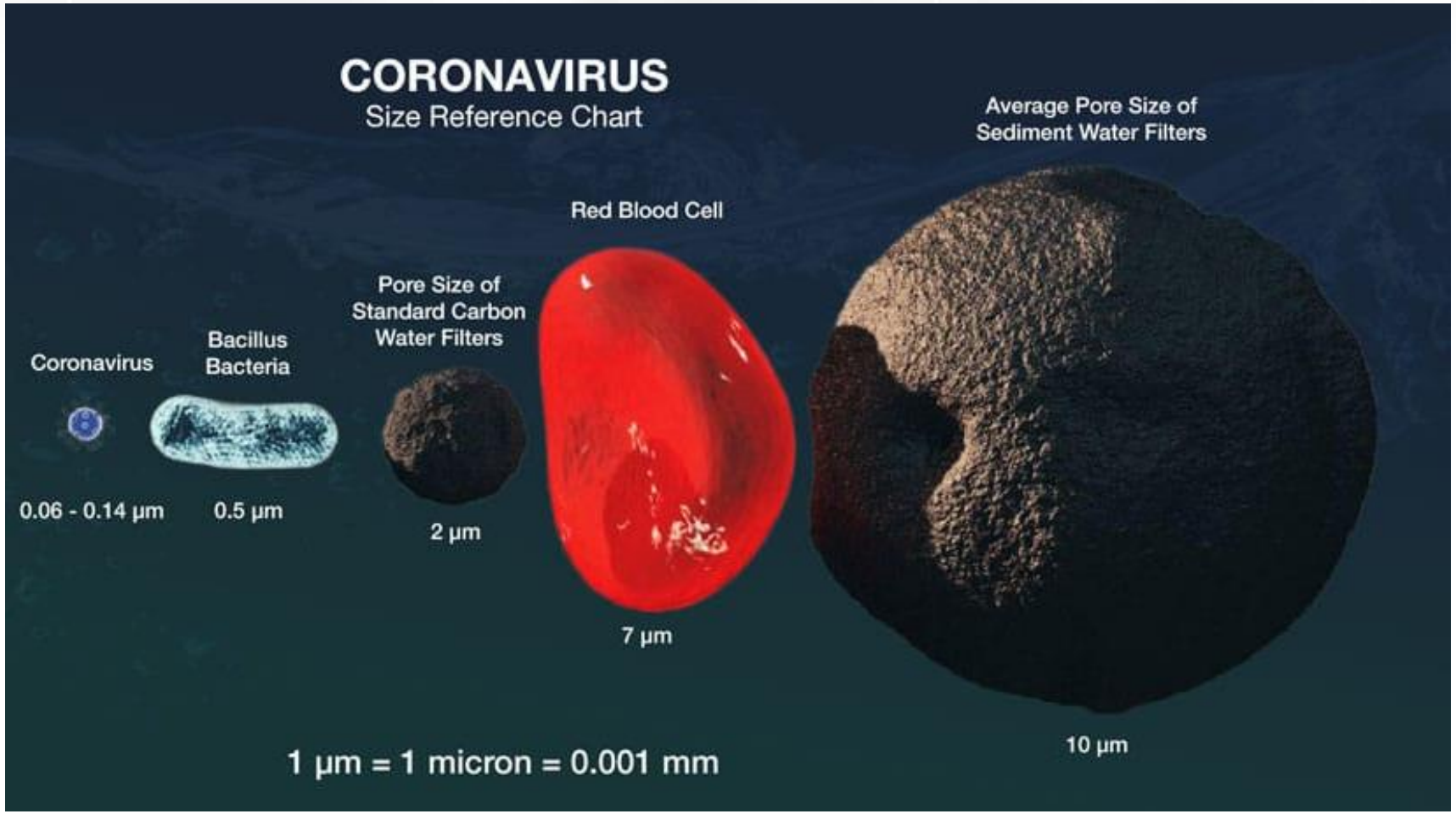
SARS-COV-2

NY Times April 3rd



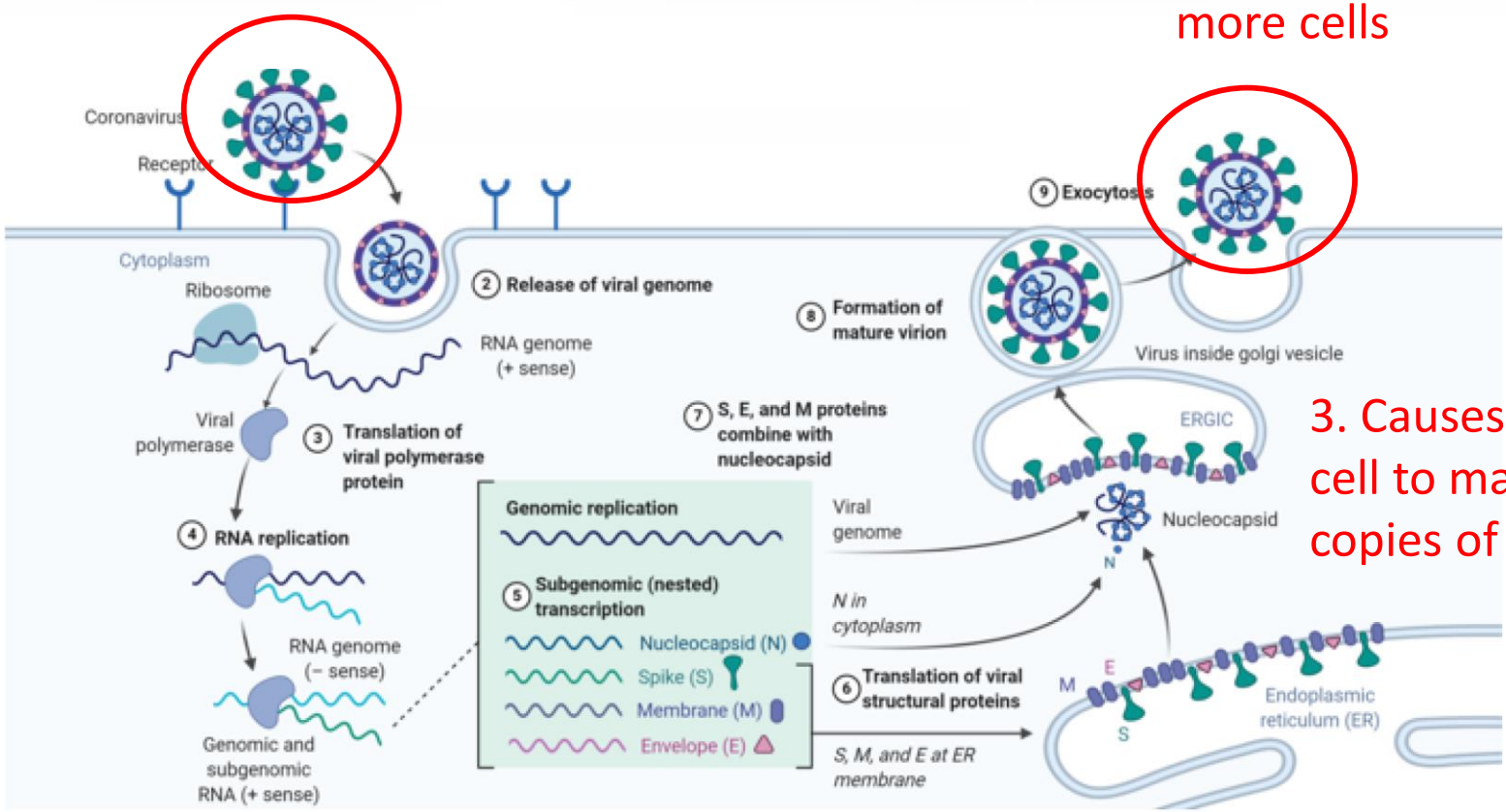
A virus is "simply a piece of bad news wrapped up in protein," the biologists Jean and Peter Medawar wrote in 1977.

Size of virus particle



How the virus infects you

1. Virus binds to a “receptor” on your cell



4. Ejects those copies into the body to infect more cells

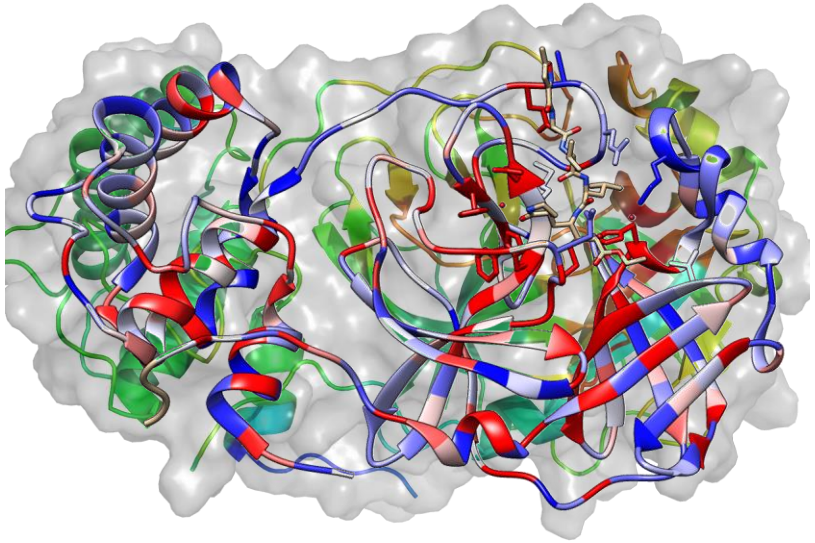
3. Causes your cell to make more copies of the virus

2. Releases its genome inside your cell

Protein structure

We need to understand the precise shape of the proteins involved in the replication of the virus in order to stop it

Atomic structure of one of the viral proteins



We need to find a drug (a molecule) that will bind with the protein and prevent it from doing its job

Think of two jigsaw puzzle pieces. If you fill one notch with something else, it can't fit into its partner

Two problems:

1. We need to know the structure of these tiny, tiny proteins with atomic precision
   ANSWER: NSLS-II (our giant x-ray microscope)

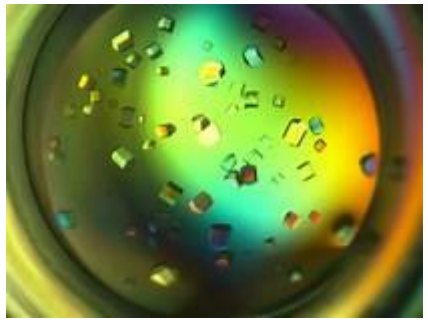
2. We need to know which drugs to try, with which pocket, of which protein. There are billions and billions of combinations.
   ANSWER 1: Biologists intuition and experience from other diseases

   ANSWER 2: Computers search through the combinations and predict the most likely

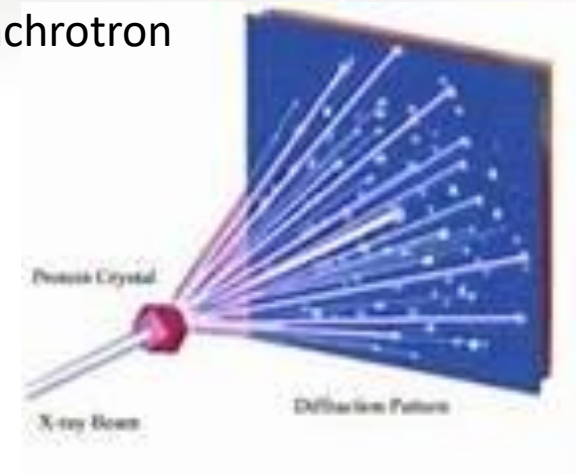
   We are doing both at BNL

How to determine the atomic structure

1. Protein crystals

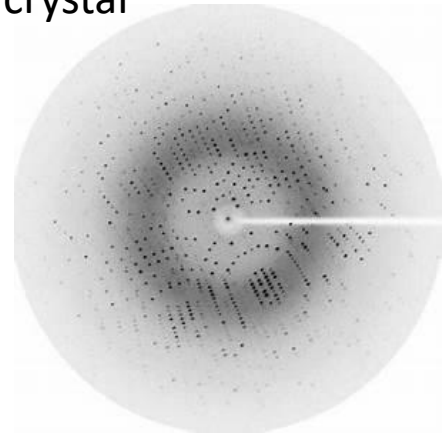


2. Synchrotron x-rays

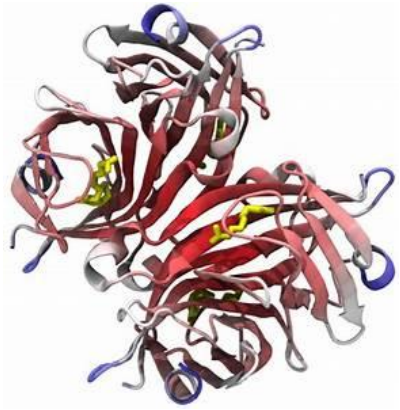


93% of all drugs approved by the FDA in the last 15 years used synchrotrons

3. X-ray diffraction pattern from crystal

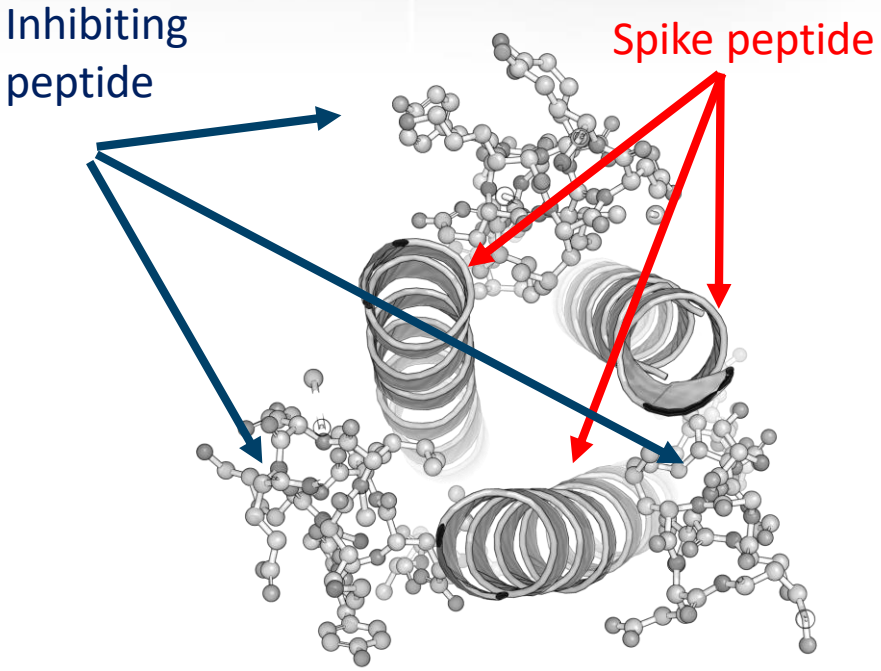


4. Atomically precise protein structure



We have looked at **5500** COVID related samples so far, including many with pharma companies

Intuition – binding with the spike protein



Top view

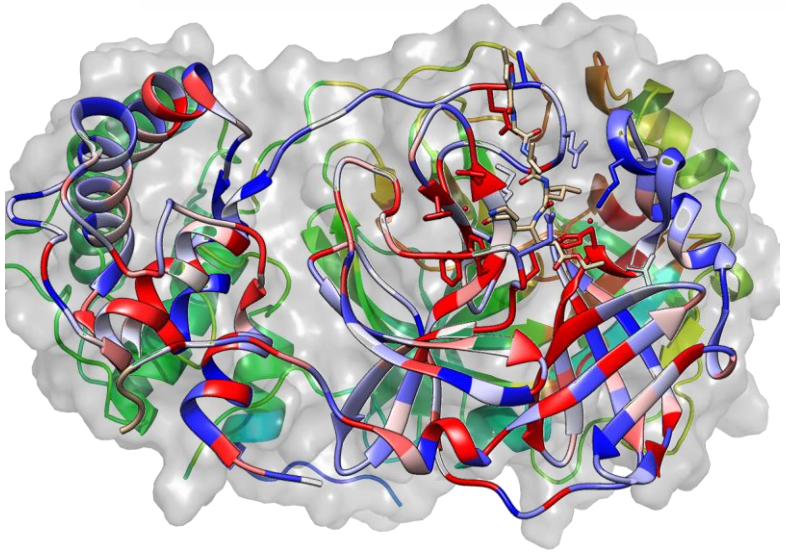
Peptide = piece of a protein

Goal is to find something that binds with the spike protein and prevents it fusing with our cell membrane.

Early results look promising and this drug is now in animal trials with U. Texas

Computers: Nine target proteins – each with a distinct role in viral life-cycle

1. Main protease (3CLPro)
2. Papain-like protease (PLPro)
3. Orf7a (replication)
4. RNA dependent polymerase
5. Spike protein



6. Nsp15
7. Nsp3 (ADRP)
8. Nsp9
9. Nsp10-Nsp16 complex

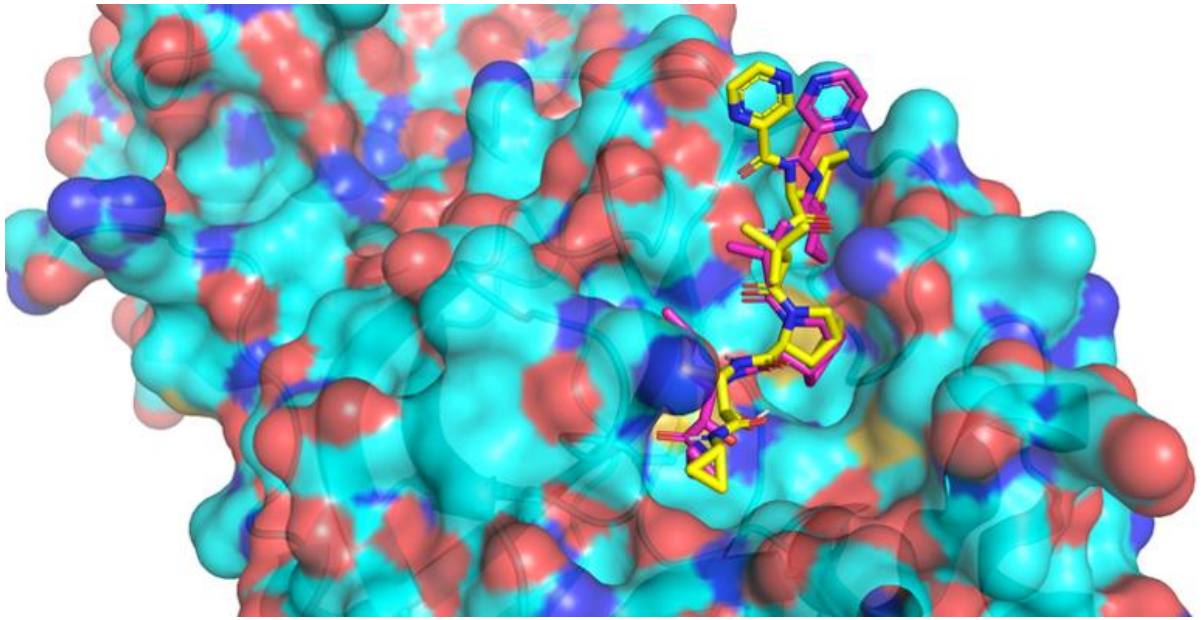
Computers are searching through 45 million combinations PER HOUR

The computer models were originally developed to find cancer fighting drugs. The COVID efforts have sped them up 100-1000x. It is hoped that this will also benefit cancer research in the future

Work funded by National Virtual Biotechnology Laboratory

Drug discovery

- Computational modeling, but needs to be confirmed.
- Experiment at NSLS-II on nanolitres of sample (1 millionth of a teaspoon!):



1.6 A resolution

Drug bound to MPro

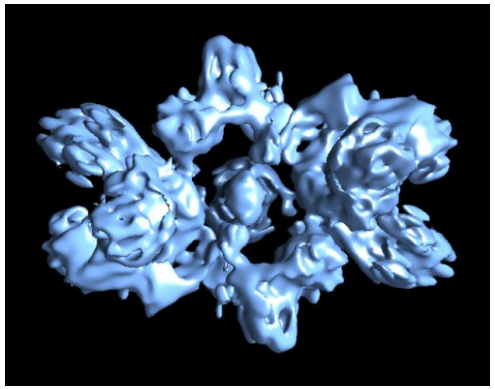
Pink=x-rays,
yellow=computer model

Work funded by National Virtual Biotechnology Laboratory

Another approach: Electron Microscopy

Very high-resolution electron microscopes can be used when you can't get crystals

- **Empire State Development Corporation** funded a new building and 1 microscope ($15 M)
- Construction was accelerated to tackle COVID-19
- Operations began in July. DOE is paying for these



- First COVID-19 protein structure from new microscope 9/9/20
- Stay tuned for results!!

Summary: Some good news

- We understand a lot about Coronaviruses
- A solution will be found. Better anti-virals, then vaccines
- We have many good avenues to explore, verify and move forward
- The DOE National labs are working together
- International cooperation is happening
- BNL is part of the fight
  - Drug discovery
  - Computer modeling
  - Virus transport
  - Materials manufacturing