Research into combating COVID-19 at BNL

J.P. Hill, Director, NSLS-II

Brookhaven Retired Employees Association February 9th 2021

U.S. DEPARTMENT OF ENERGY | Office of Science

BROOKHAVEN NATIONAL LABORATORY

Its is a collective effort!

COVID-19 is the challenge of our time, our World-War II. BNL has responded:

National Virtual Biotechnology Laboratory
Started in DOE Office of Science, coordinates COVID activities in all 17 National labs: Therapeutics, testing, manufacturing and virus transport
Kerstin Kleese van Dam, Amy Marschilok, Sean McSweeney, Bob McGraw

Brookhaven COVID S&T Working Group
Chuck Black, Mike Clancy, Cathy Cutler, Ann Emrick, Peter Ferrara, Kerstin Kleese Van Dam, Karen McNulty-Walsh, Michelle McQueen, Paul Orfin, Sergio Rescia, Timur Shaftan, Jack Shlachter

LDRDs – Kathi Barkigia, Jack Anderson and BHSO
Oleg Gang, Qun Liu, Kumaran Desigan

Departments
Biology, CAD, CFN, CSI, Environmental and Climate Science, Instrumentation, NSLS-II, Physics …

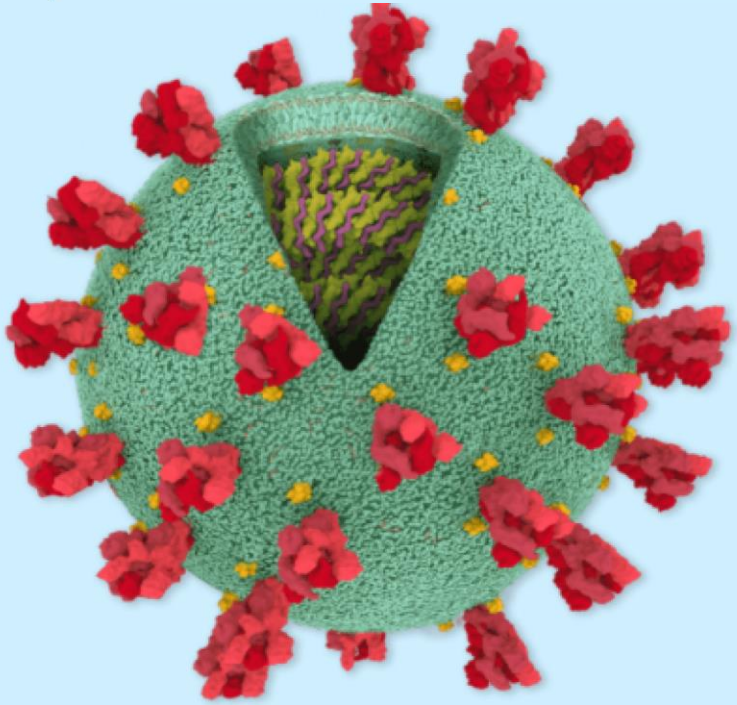
Outline

1. Introduction
   - SARS-CoV-2 and how it works
2. Drug discovery
   - Experiments
   - Computing
3. Computer modeling
   - Spread of infection
   - Flow of infectious particles
4. Sensors
   - Detecting the presence of the virus

1. Introduction

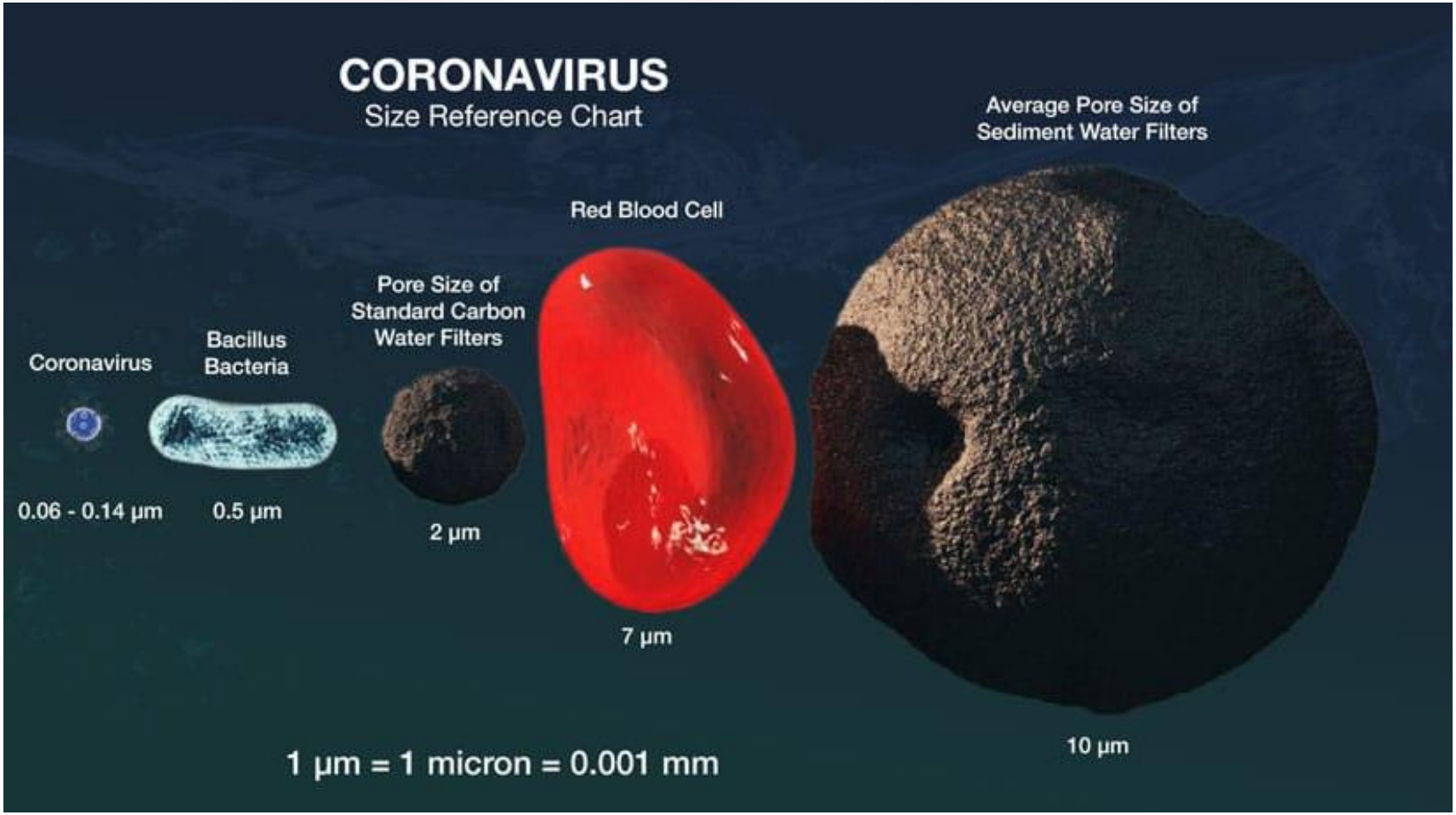
SARS-COV-2

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.

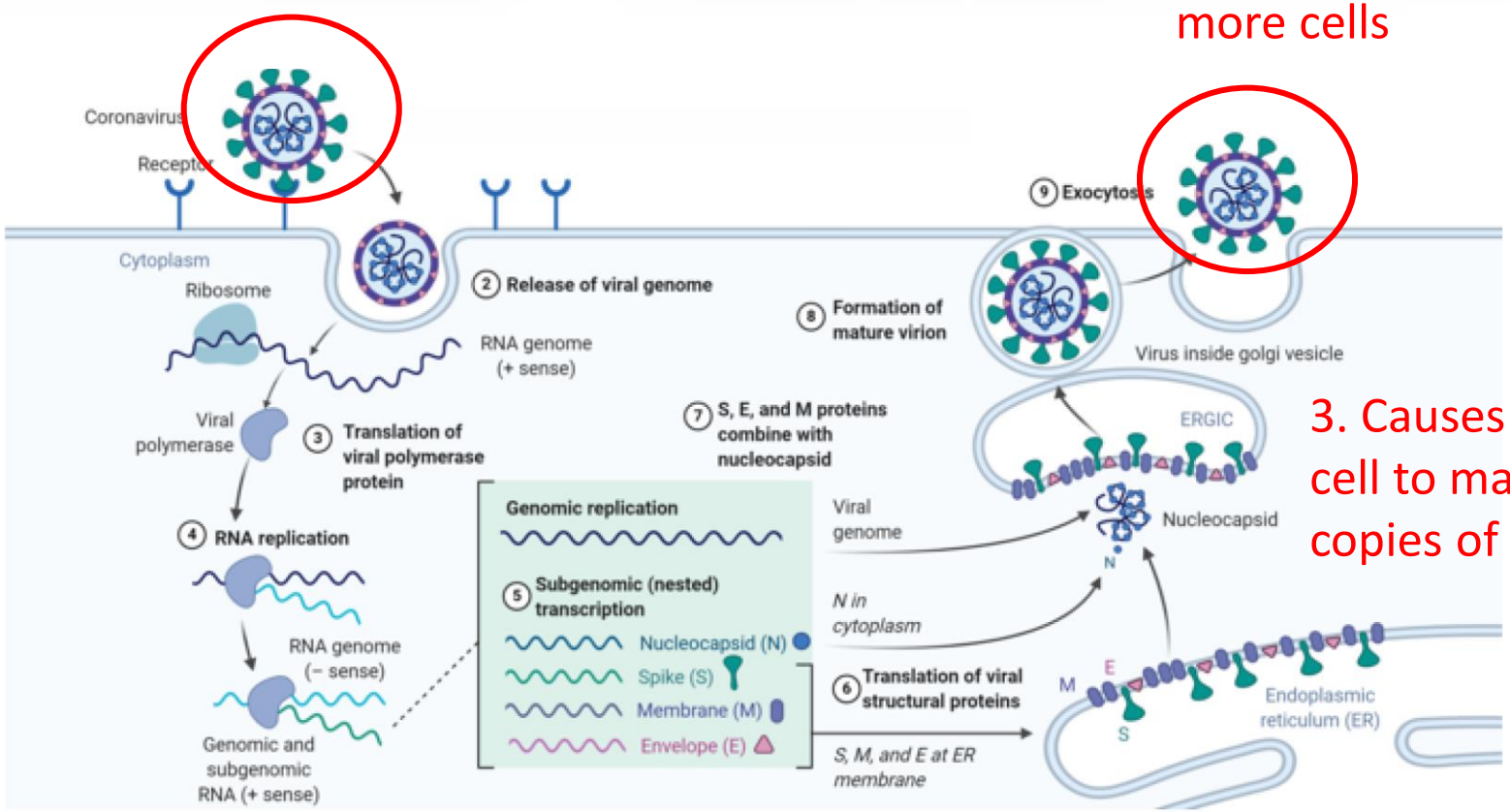
A single virus particle is SMALL!



(a human hair is 100 microns across)

How the virus infects you

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



2. Releases its genome inside your cell

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

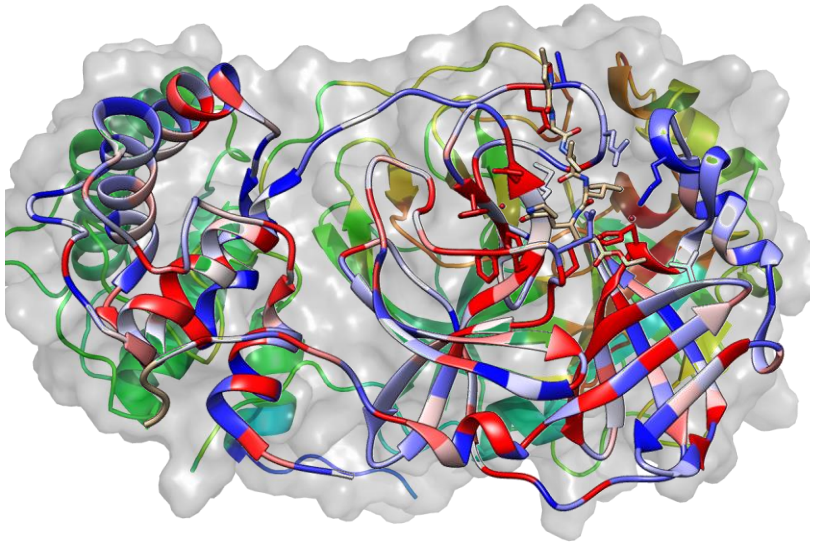
4. Ejects those copies into the body to infect more cells

2. Drug Discovery

Protein structure

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

Atomic structure of one of the viral proteins



To stop it functioning, 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

2. We need to know which drugs to try, with which pocket, of which protein. There are billions and billions of combinations.

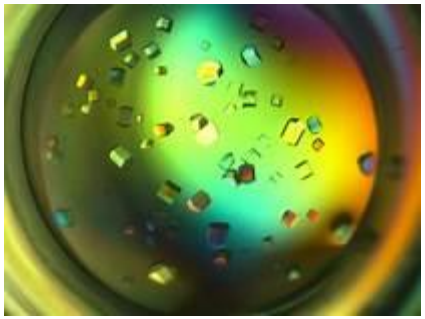
   ANSWER 1: Biologists intuition and experience from other diseases

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

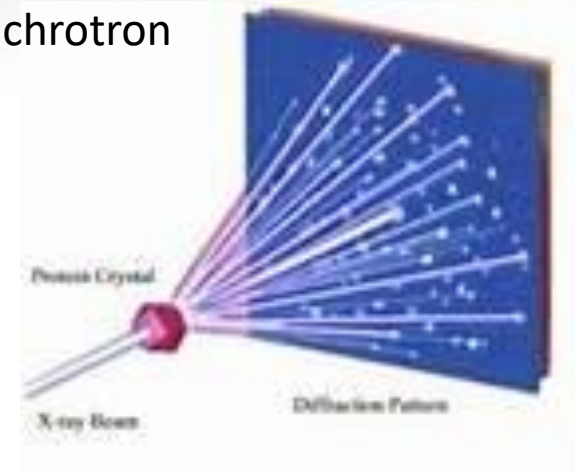
   We are doing both at BNL

How to determine the atomic structure

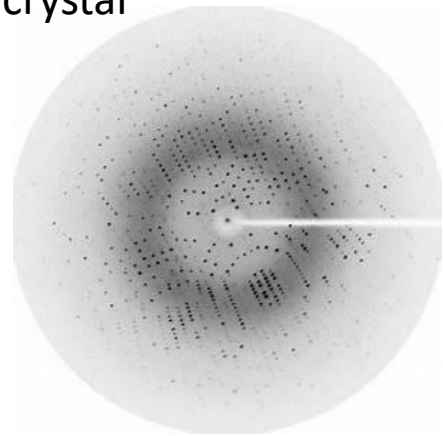
1. Protein crystals



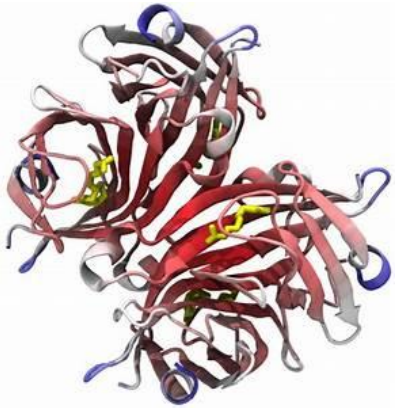
2. Synchrotron x-rays



3. X-ray diffraction pattern from crystal



4. Atomically precise protein structure

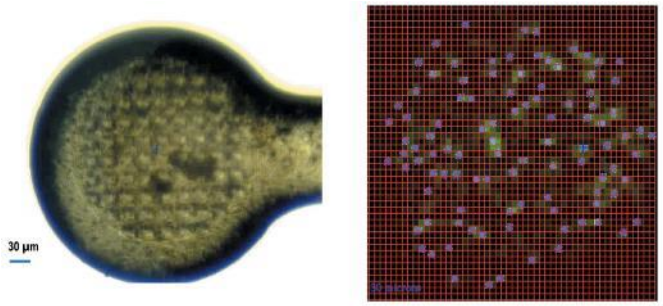


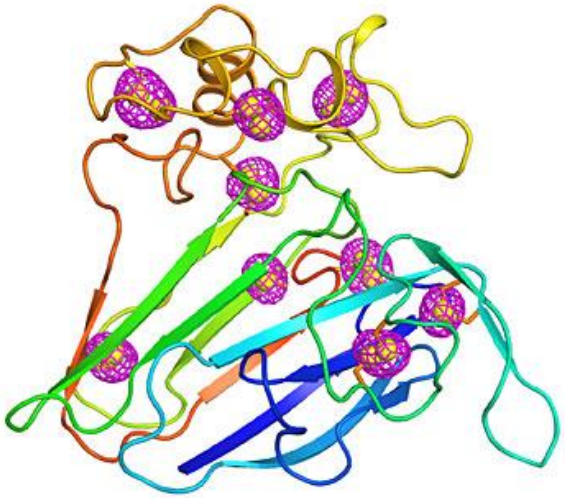
96% of all drugs approved by the FDA in the last 15 years used synchrotron x-rays.

How does NSLS-II help?

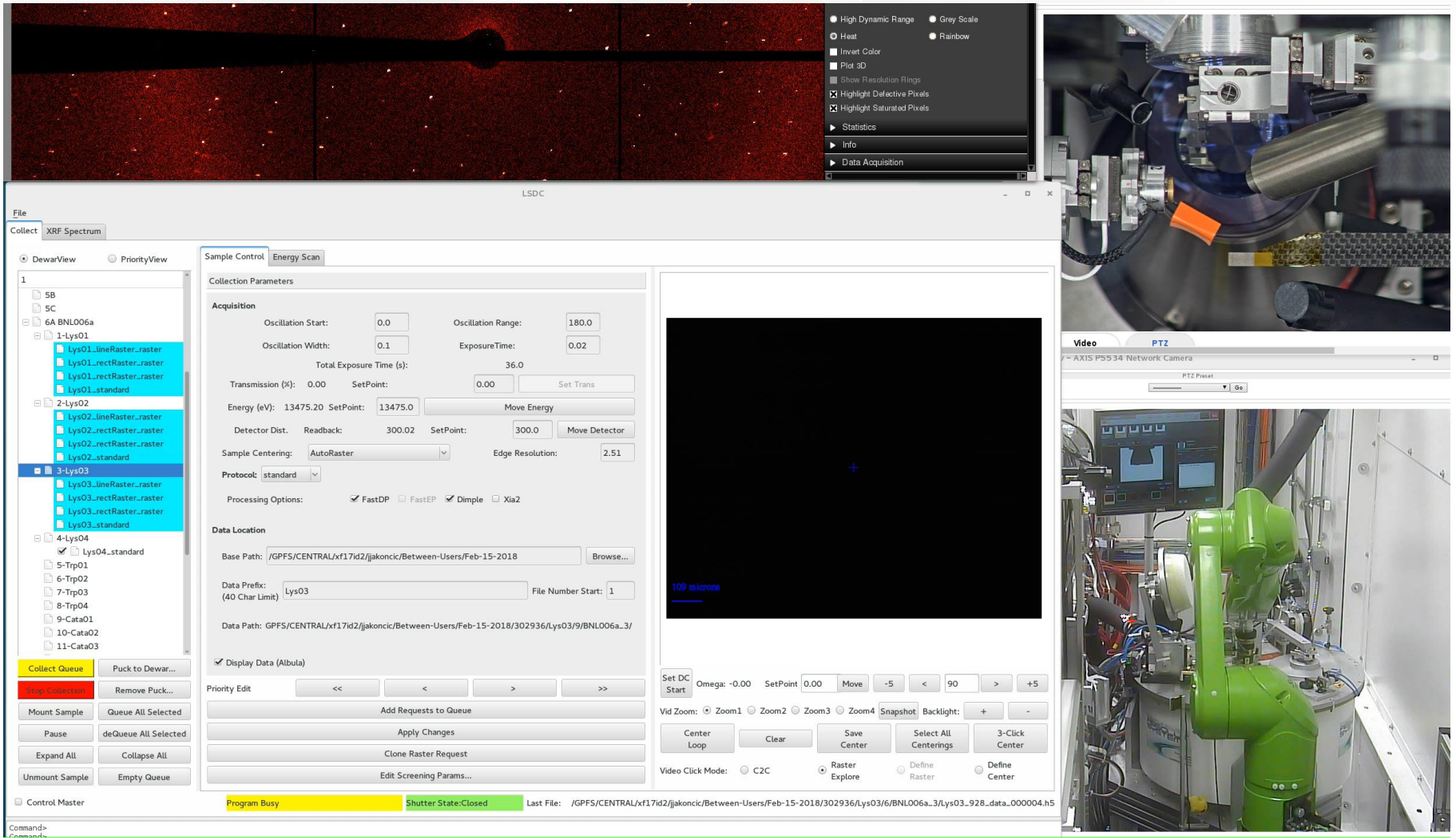
- Growing large enough single crystals is the bottleneck in determining structure
- Automation and intense x-ray beams at NSLS-II allow the study of smallest crystals in the world
- Down to ~ 1 micron (1/100th of the width of a human hair)
- 200x smaller than anyone else
- This greatly speeds up solving the structure and searching for new drugs

Guo et al. *IUCr J.* **6**, Part 4, July 2019.

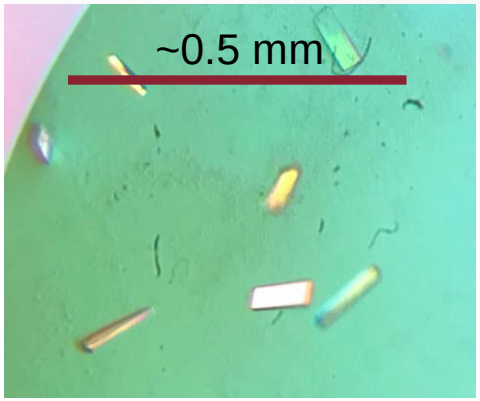


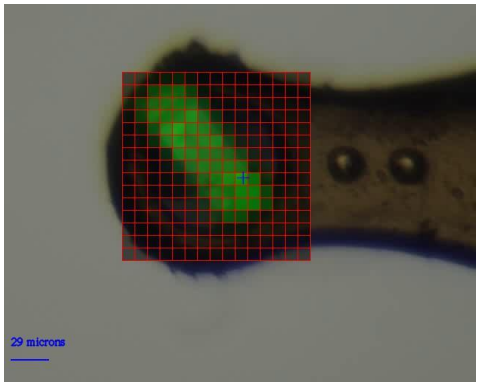


Fully Automated Data Collection

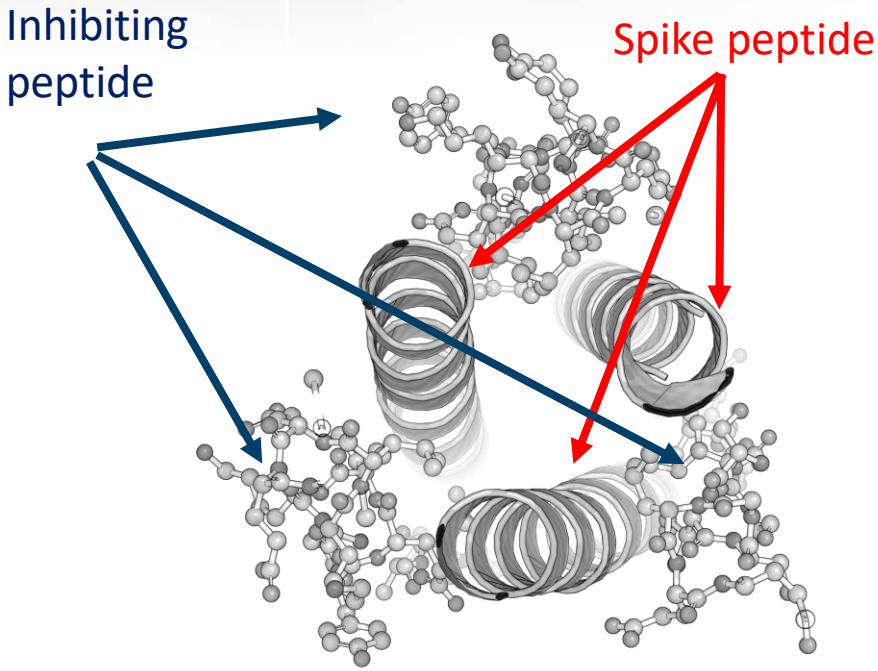


Intuition – binding with the spike protein





Crystals grown and studied at NSLS-II



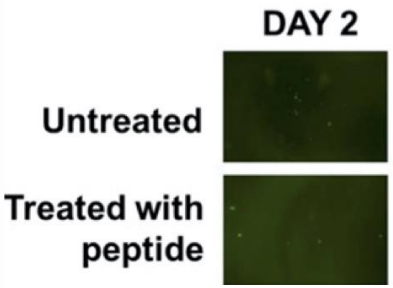
Top view

Peptide binds tightly with the spike protein and should stop it binding with receptors in your lungs.

Peptide = piece of a protein

Dale Kreitler, Alex Soares, Grace Shea-McCarthy et al.

Inhibitor peptides prevent infection in ferrets



The nasal spray prevents infections in ferrets. It has also been shown to work in human lung cells

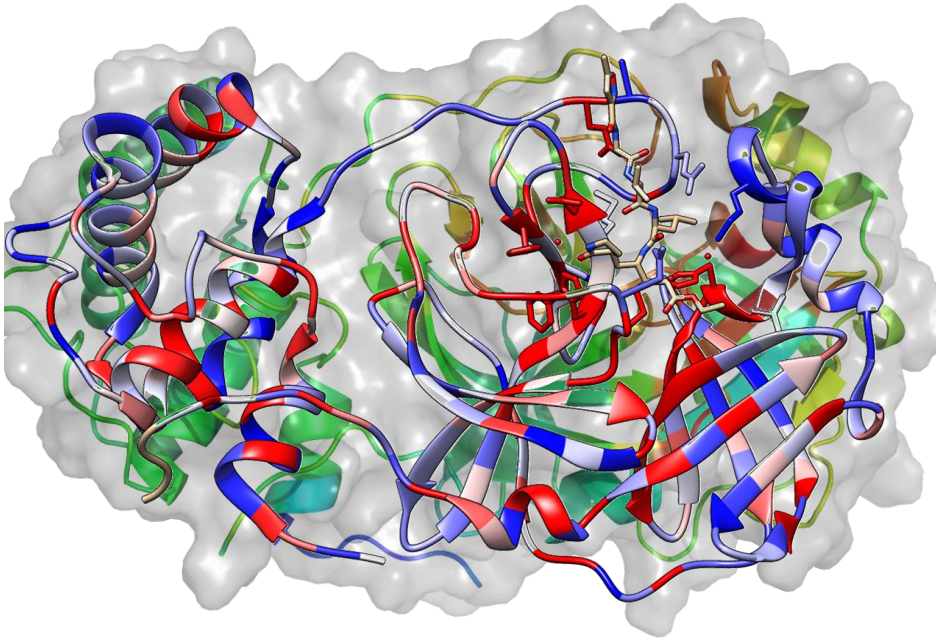
NSLS-II work shows the structure of a more strongly bound inhibitor

Promising and exciting, but still a long way to go

https://mbio.asm.org/content/mbio/11/5/e01935-20.full.pdf
https://www.biorxiv.org/content/10.1101/2020.11.04.361154v1.full.pdf

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

- Main protease (3CLPro)
- Papain-like protease (PLPro)
- Orf7a (replication)
- RNA dependent polymerase
- Spike protein
- Nsp15
- Nsp3 (ADRP)
- Nsp9
- Nsp10-Nsp16 complex



Computers are searching through 10 million combinations PER HOUR

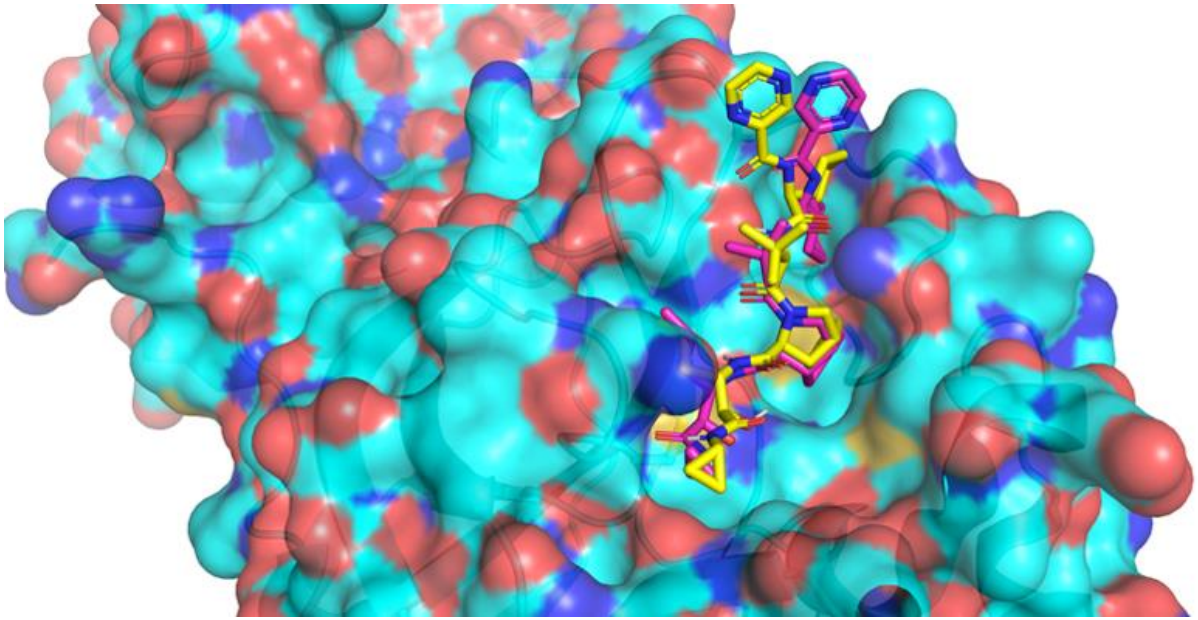
50 billion combinations searched. Top 100 hits being tested experimentally

Shantenu Jha, Li Tan

Work funded by NVBL

Computing + Experimental verification

- Modeling predicts binding, but needs to be confirmed.
- Expt at NSLS-II on nanolitres of sample (1 millionth of a teaspoon!)



1.6 A resolution

Telaprevir bound to MPro

Pink = x-rays
Yellow = computer model

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

Babak Andi, Kumaran Designan, Jan Keereetaweep

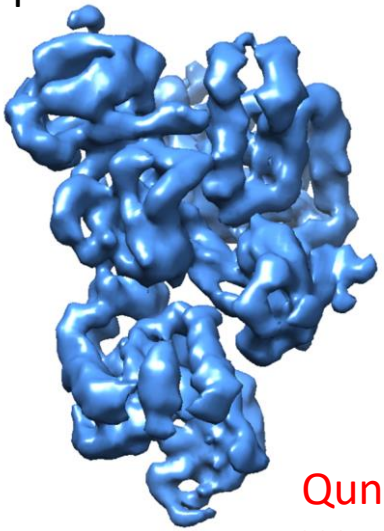
Work funded by NVBL

Another approach: Electron Microscopy

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

BNL (Julian Adams, Tom Joos, Tom Langdon and others) worked through Min-Safe period to bring the building and microscope into operations ahead of schedule

Membrane protein E bound with PALS1



3.5 A resolution

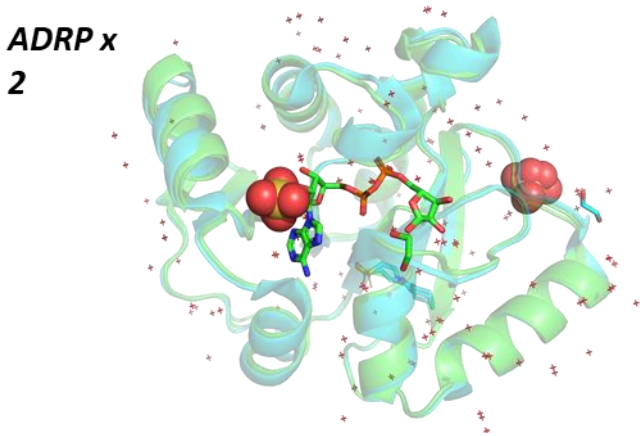
Qun Liu , Liguo Wang, Jin Chai

Membrane proteins are very difficult to solve, BUT mutate slowly so good potential targets for drugs

Work funded by LDRD

How is this research safe?

1. We are NOT looking at the virus itself. We are looking at pieces of some of the proteins
2. These pieces cannot infect a cell. They are inert.
3. The pieces are synthesized in a lab, knowing the gene sequence of the viral protein. They do NOT come from the virus. There is no chance of a virus particle being included in the synthesis



3. Modeling

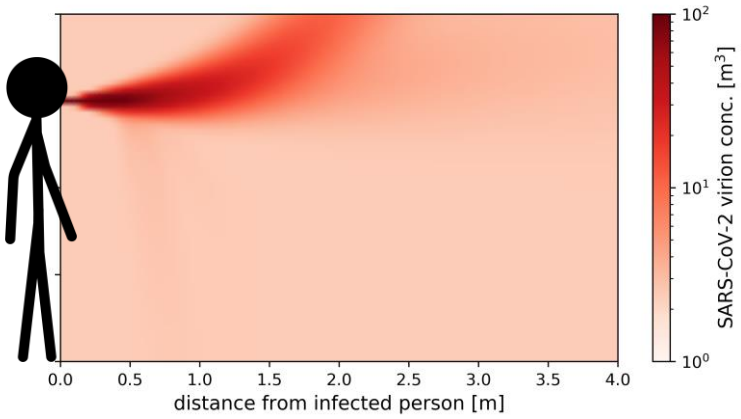
Modeling aerosol flow

Approach: Quadrature-based aerosol model coupled to turbulent jet dispersion model for simulation of near-field aerosol dispersion

Key Findings: Face masks reduce exposure to SARS-CoV-2 virions by capturing infectious particles and decreasing the velocity at which they are expelled

Significance: Efficient, well-fitting masks are particularly effective for reducing exposure to SARS-CoV-2 near infected individuals, where the risk of transmission is greatest.

Infected person **speaking**, assuming they expel one virion per second



Laura Fierce, Alison Robey, Catherine Hamilton and Bob McGraw

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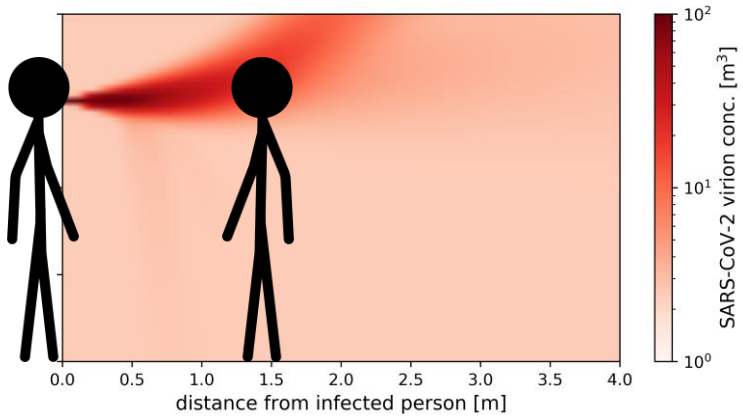
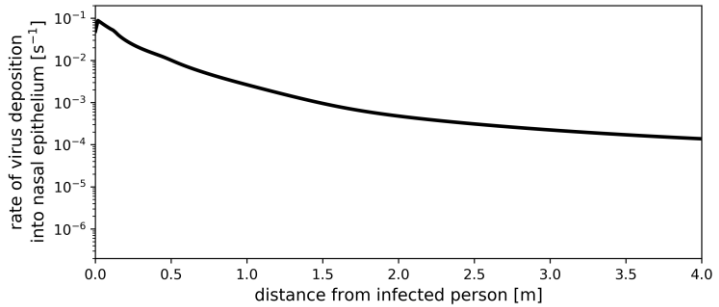
No Mask

Exposure to healthy person is reduced with distance





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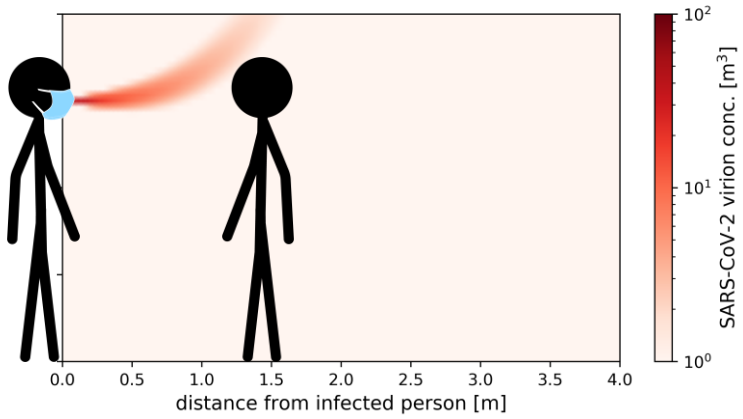
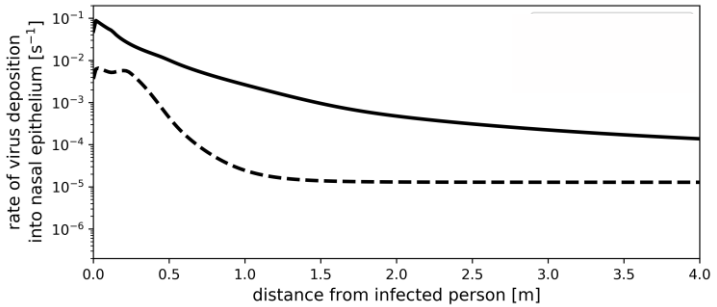
Exposure is further reduced if the **infected person wears a mask**





No Mask
Mask on source

Laura Fierce, Alison Robey, Catherine Hamilton and Bob McGraw

Work funded by NVBL

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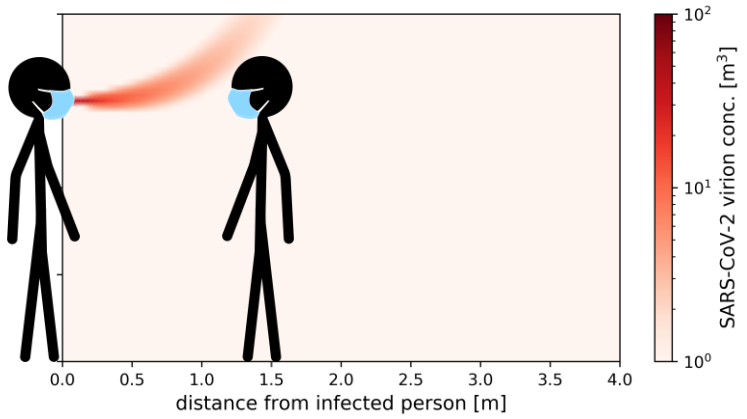
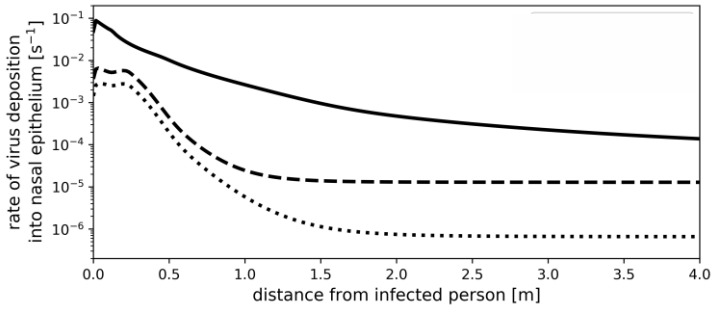
Greatest reduction in exposure when **both people wear masks**





No Mask
Mask on source
Masks on both

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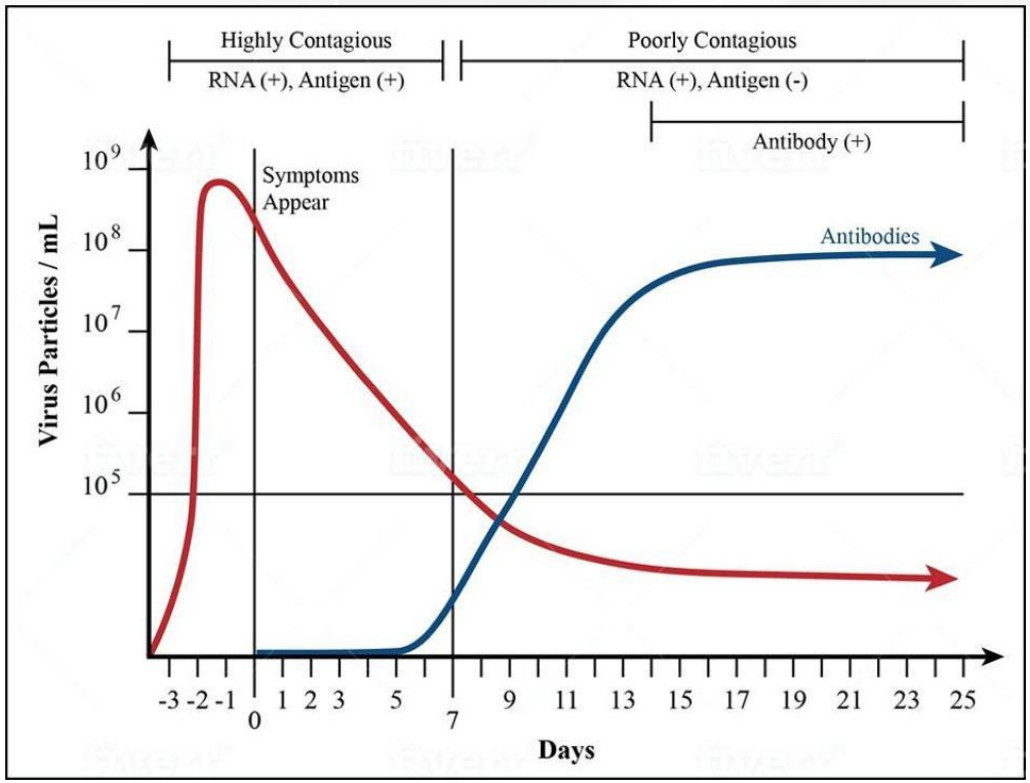
4. Sensors

Nanosensors for home-based virus tests



- PCR tests are slow and labor intensive
- Antigen tests are fast, but too late

Needed:

- Fast, cheap, highly sensitive and suitable for POC or home setting

CFN developing a new approach:

- Designed nanostructures to provide significantly enhanced sensing

Benefits:

- Detect a single virus
- Quantitative
- Simple and inexpensive
- Suitable for point-of-care and personal at-home use
- Can use the same platform to sense different pathogens

Oleg Gang, CFN, Biology, Instrumentation and external collaboration with U. Tennessee and Columbia

Summary

- The DOE National labs are working together to combat the challenge of COVID-19
- Many of our capabilities and expertise at BNL can be brought to bear on these challenges
- BNL is part of the fight
  - Drug discovery
  - Computer modeling
  - Virus transport
  - Materials manufacturing
- COVID-19 will be beaten and BNL will have played a role