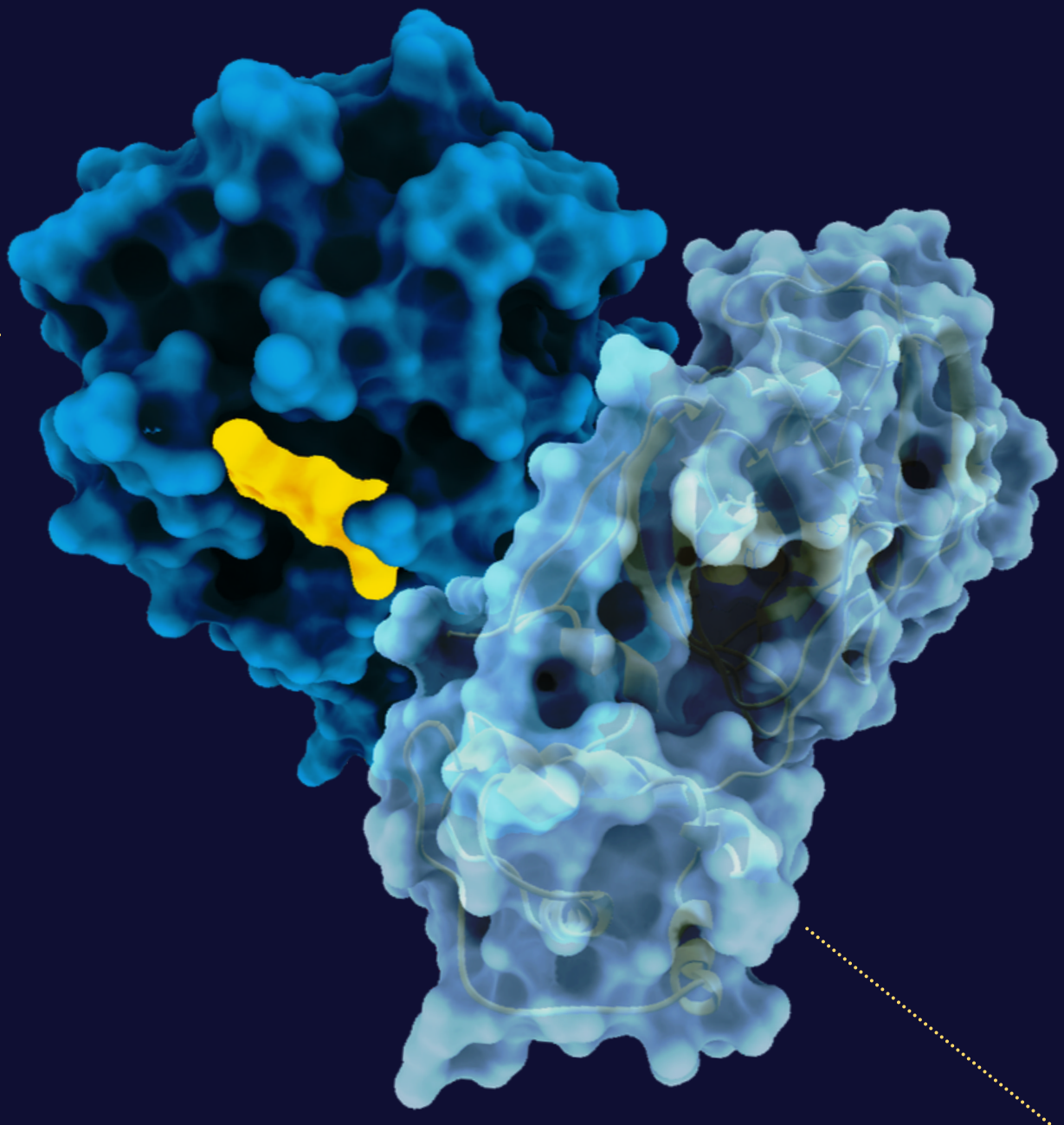
CASE STUDY

NOVEL COVID-19 INHIBITORS DESIGNED INSIDE VIRTUAL REALITY

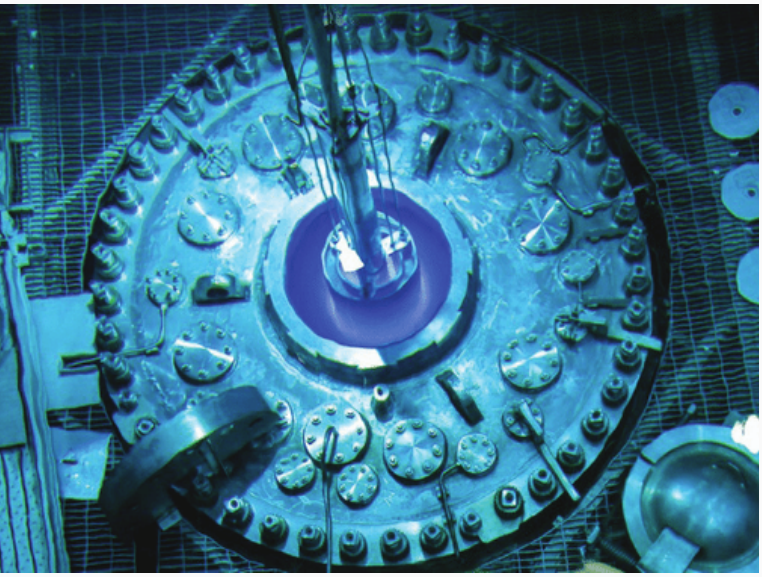
Scientists at the Oak Ridge National Laboratory use Virtual Reality to create COVID-19 inhibitors



Accelerated drug discovery to combat the pandemic

The COVID-19 pandemic challenged researchers to discover life-saving treatments at an unprecedented pace. The scientific community rose to the challenge by developing vaccines in record time. However, due to vaccine escape variants, parts of the population remain at risk, and further therapeutic solutions must be discovered.

Studying the structure and function of viral proteins is essential to developing new antiviral strategies. To leverage the information of the thousands SARS-CoV-2 structures available, scientists need tools to help them intuitively gain insights, accelerate the molecular design process, and support collaborations.



High Flux Isotope Reactor (HFIR) at ORNL

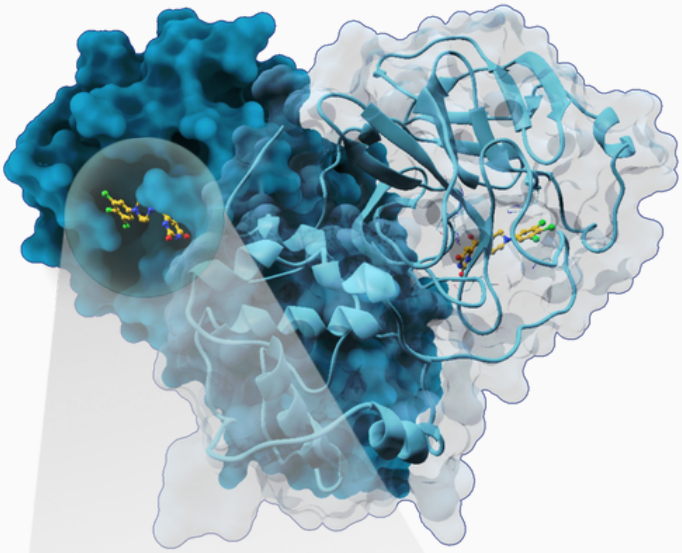
Dr. Andrey Kovalevsky, Senior Scientist at Oak Ridge National Laboratory

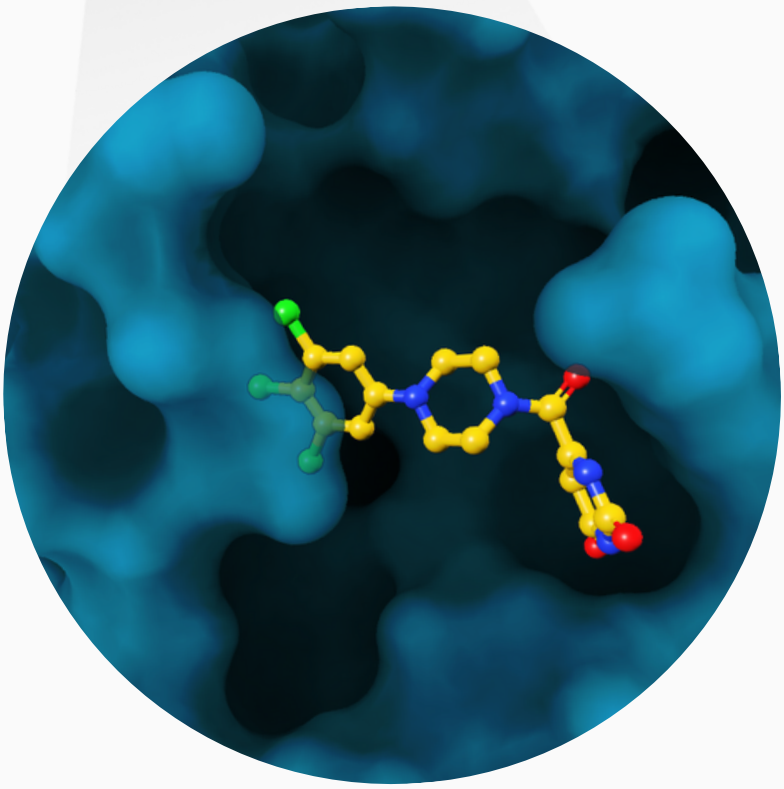
> "You can do collaborative meetings, discuss and analyze molecules while being together"

Virtual Reality meets these needs by enabling scientists to "**walk into the protein and see things how the protein sees them,** [...] do collaborative meetings in VR, discuss and analyze molecules while being together at the same time" says Dr. Andrey Kovalevsky, senior scientist at the Oak Ridge National Laboratory (ORNL). According to Kovalevsky, VR has already helped progress two structure-based drug discovery projects.

Get the protein's point of view

Dr. Kovalevsky's team is at the forefront of COVID research, leveraging two of the world's most powerful sources of neutrons, the High Flux Isotope Reactor (HFIR) and the Spallation Neutron Source (SNS). His research focuses on elucidating the structural features of SARS-CoV-2 main protease 3CL (Mpro), which plays a central role in viral replication.





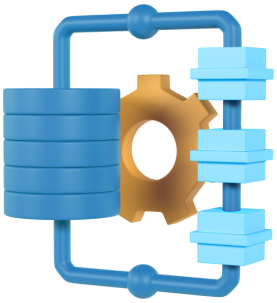
ORNL's advanced facilities allowed researchers to approach the COVID-19 drug design challenge differently from other groups. They combined data from cryogenic X-ray crystallography with room temperature crystallography and neutron crystallography to create the most accurate molecular structure of Mpro possible, down to hydrogen positioning [1, 2, 3, 4].

> "Go "inside" molecular structures and see what the protein sees"

When dealing with complex structures, the challenge lies in exhaustively comprehending the nuances of the data. The three-dimensional experience empowers users to **grasp fine details that can be easily lost in 2D visualizations**. Scientists can virtually **go "inside" molecular structures** and "see what the protein sees", which helps to better understand its structure and function [5].

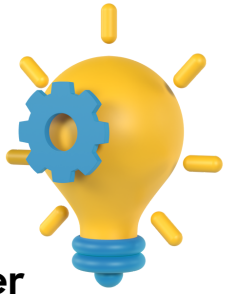
Accurate Analyses

Combine a 3D immersive environment & computational tools



Deeper Insights

In-depth understanding of molecular structures



Better Designs

Save time, innovative ideas, design more effectively

Design Better inhibitors in VR

The advantages of working in a 3D environment do not stop at visual analysis. ORNL's researchers used the full potential of VR by employing Nanome plugins for virtual reality-assisted analysis and small-molecule building, which lead to the **design of a completely novel and more effective Mpro inhibitor** [1].

"This novel chemical structure is different from what has been previously studied by the global community and could open new avenues of research with exciting possibilities for combating SARS-CoV-2," says first author Dr. Kneller [6].

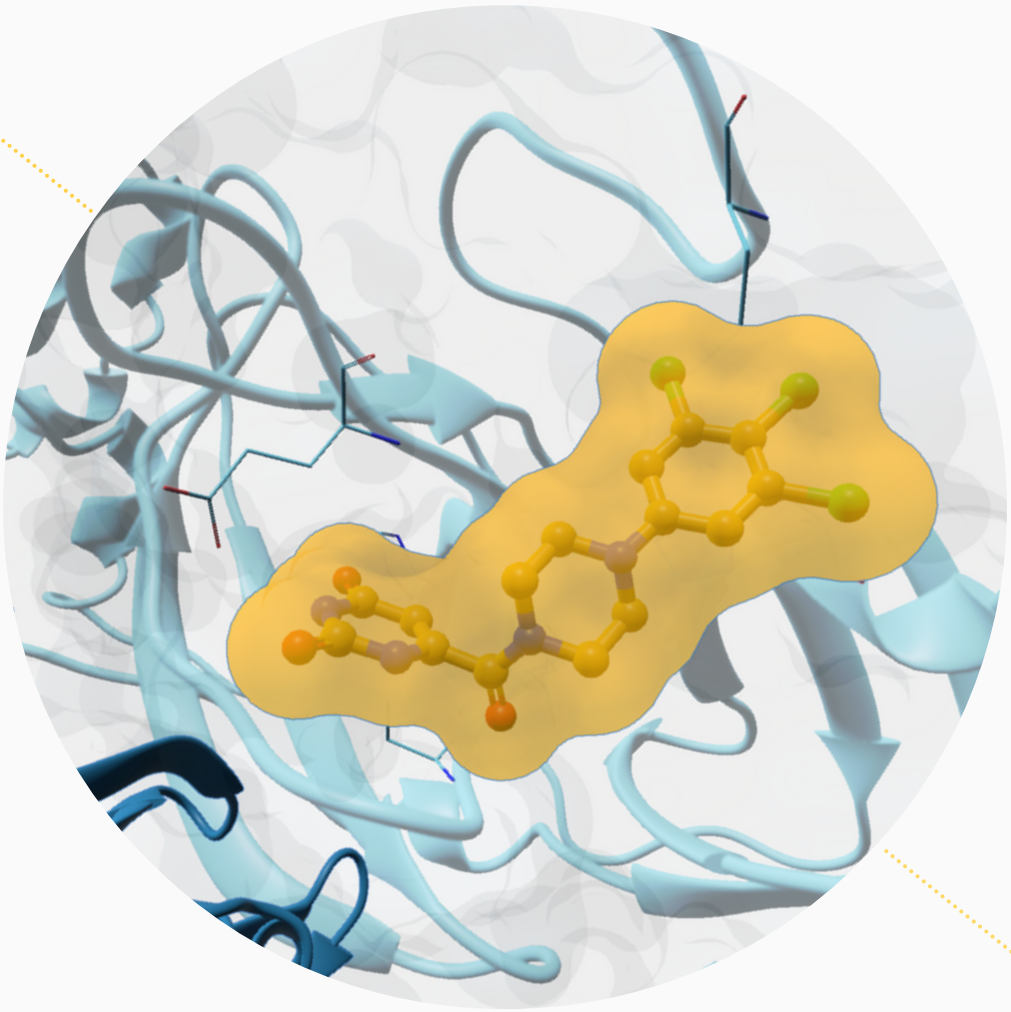
In a study published in the Journal of Medicinal Chemistry, **compounds obtained from virtual screenings were optimized by scientists inside the virtual reality environment** [1].

Using Nanome's plug-ins, they created a chemical structure characterized by an extra chlorine atom that showed a greater ability to bind Mpro. For Kneller, "Being able to create a molecule and be sure that it is sitting well in the binding pocket is a very important thing". The **VR-assisted design was the breakthrough technology that made this design possible.**

VR allowed ORNL researchers to look at the enzyme and collaboratively design and test different chemical groups on molecules while examining how the modifications affected their binding.

Inside Nanome, they **built and edited chemical structures on the fly** with the MedChem plug-in. This process was guided by built-in tools that minimize ligands, display potential clashes, and show protein-ligand interactions in real-time, providing scientists with immediate feedback while designing.

The inhibitor constructed in Nanome demonstrated a superior ability to inhibit Mpro *in-vitro* [1] and higher affinity, compared to other tests. Studies are ongoing to optimize the compound and further development is needed to assess its druggability. If the study succeeds, this will be **the first drug ever discovered in virtual reality**.



VR in the future of drug discovery

The design of more potent Mpro inhibitors in VR [1] is the **proof of concept** of the **results that can be achieved by combining virtual reality-assisted modeling with biophysics, biochemistry, and medicinal chemistry**. The integrated approach adopted by Kovalevsky helped the team to discover a novel small molecule inhibitor and laid the foundation for further steps in the process of drug design.

> **This novel chemical structure is different from what has been previously studied by the global community**

Besides the advanced technologies used by the research team, the success of the study was facilitated by effective collaboration and communication enabled by the collaborative aspects of the Nanome platform. Despite geographical distances, scientists could regularly meet in VR and work together on molecular designs.

References

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[2] Kneller, D. W., Phillips, G., Weiss, K. L., Pant, S., Zhang, Q., O'Neill, H. M., Coates, L. & Kovalevsky, A. (2020) Unusual zwitterionic catalytic site of SARS-CoV-2 main protease revealed by neutron crystallography, J Biol Chem. 295, 17365-17373.

[3] Kneller, D. W., Zhang, Q., Coates, L., Louis, J. M. & Kovalevsky, A. (2021) Michaelis-like complex of SARS-CoV-2 main protease visualized by room-temperature X-ray crystallography, IUCrJ. 8, 973-979.

[4] Kneller, D. W., Phillips, G., O'Neill, H. M., Jedrzejczak, R., Stols, L., Langan, P., Joachimiak, A., Coates, L. & Kovalevsky, A. (2020) Structural plasticity of SARS-CoV-2 3CL Mpro active site cavity revealed by room temperature X-ray crystallography, Nature Communications. 11, 3202.

[5] "Scientists at Oak Ridge National Laboratory use virtual reality to study the structure and function of the COVID-19 viral main protease and to design drug candidates", https://blog.matryx.ai/scientists-at-oak-ridge-national-laboratory-use-virtual-reality-to-study-the-structure-and-function-ad5e8b6ff5a2

[6] "Journeying 'inside' the COVID-19 viral protein to attack a weak point", https://neutrons.ornl.gov/content/journeying-%E2%80%98inside%E2%80%99-covid-19-viral-protein-attack-a-weak-point