Team develops computational approach to redesign antibodies for broader effectiveness against viral pandemics

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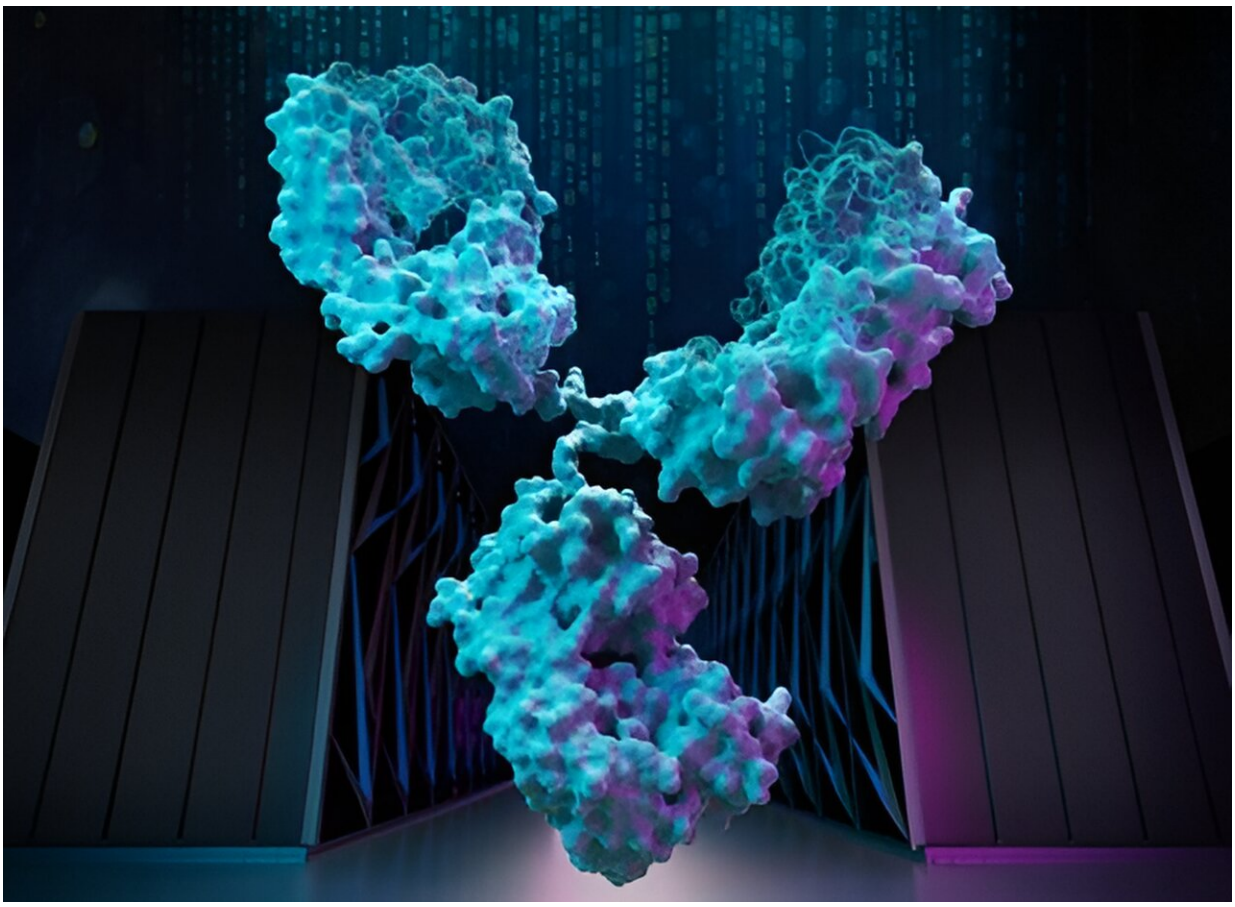

Credit: Adam Connell/LLNL.

In a new development for addressing future viral pandemics, a multi-institutional team involving Lawrence Livermore National Laboratory (LLNL) researchers has successfully combined an artificial intelligence (AI)-backed platform with supercomputing to redesign and restore the effectiveness of antibodies whose ability to fight viruses has been compromised by viral evolution.

The team's research—published in the journal *Nature*—showcases a novel antibody design platform comprising experimental data, structural biology, bioinformatics modeling, and molecular simulations—driven by a machine learning algorithm.

The interagency team used the platform to computationally optimize an existing SARS-CoV-2 antibody to restore its effectiveness to emerging SARS-CoV-2 omicron subvariants while ensuring continued efficacy against the then-dominant delta variant. Their computational approach has the potential to accelerate the drug development process and improve pandemic preparedness significantly.

The work was completed within the GUIDE program, one of LLNL's largest strategic partnerships with DOD. The paper includes multiple collaborators from government and academia, including Los Alamos National Laboratory, Vanderbilt University Medical Center, the Washington University School of Medicine, the Fred Hutchinson Cancer Center, and the JPEO-CBRND.

The GUIDE program was developed to address the urgent need for a rapid and agile approach to responding to biological threats, including the relentless mutation of the SARS-CoV-2 virus. SARS-CoV-2 evolution has led to the emergence of subvariants that have eluded existing clinical antibody therapeutics.

GUIDE researchers said the achievement could potentially lower drug

development costs, reduce developability risks, and accelerate the timeline to clinical use when compared to a novel drug-product screen with comparable breadth and efficacy. This acceleration continues to be relevant as SARS-CoV-2 variants continue to emerge, researchers said.

"Using LLNL's supercomputing capabilities and our modeling platform, we identified just a few key amino acid substitutions necessary to restore the antibody's potency," explained Tom Desautels, a machine learning expert and first author of the paper.

"The original antibody had been authorized by the Food & Drug Administration for emergency use as pre-exposure protection—which is especially critical for immune-compromised patients—but suffered a substantial reduction in potency against omicron variants, rendering it no longer protective."

The LLNL GUIDE team virtually assessed the mutated antibodies' ability to bind to the virus and selected just 376 proposed antibody candidates for laboratory evaluation from a theoretical design space of over 10^{17} possibilities.

"We were able to start with an antibody that had already been authorized and known to work safely and modify it to compensate for viral escape," Desautels said, stressing that the antibodies the team developed are not potent against the newest strains of the SARS-CoV-2 virus. The research published in the new paper used models from 2020—since then, the team's capabilities have progressed.

Recent work has expanded the breadth of a different SARS-CoV-2-targeting antibody to neutralize against 22 different variants, including potential future escape variants.

In a biosecurity first, the National Nuclear Security Administration's

Sierra supercomputer, sited at LLNL, calculated the molecular dynamics of individual substitutions or mutant antibodies using one million graphics-processing hours (GPU hours). LLNL researchers also utilized other LLNL high performance computing (HPC) systems to perform the computational re-design, a promising strategy to recover antibody functionality and avoid the time-consuming process of discovering entirely new antibodies.

An effective antibody has dozens of locations on its amino-acid sequence that interact with the SARS-CoV-2 protein, meaning the team had a vast number of available sites to propose mutations to enable binding, according to LLNL principal investigator Dan Faissol.

"Our binding predictions are driven by advanced structural bioinformatics and large-scale molecular simulations, which allows us to optimize for far more antigen targets than laboratory-based evaluations directly," Faissol said. "The design space in this work was 10^{17} possibilities—it's not infinite, but it is far too many to evaluate even with the world's most powerful supercomputers."

"To put it into context, the space of possibilities for the Powerball lottery is more like 10^{8}. We aren't going to succeed by hoping to get lucky. You can't 'design' your lottery numbers to win, but you can now redesign an antibody to recover from viral escape."

Once the LLNL team produced their list of potential antibody candidates, LLNL and Vanderbilt's biologists synthesized, produced, purified, screened, and characterized the designs to determine if the binding was improved. After the redesigned antibodies were produced for real-world testing, the LLNL and Vanderbilt teams each rapidly evaluated a combined 376 antibody candidates for binding to multiple variants of concern.

The rapid screening capability at LLNL was made possible in large measure through a related Laboratory Directed Research and Development (LDRD) project aimed at assisting with developing monoclonal SARS-CoV-2 antibodies.

"We were able to perform our work much faster and more accurately than past attempts, using just a tiny amount of protein," said biomedical scientist Kathryn Arrildt, a principal investigator for the experimental evaluation phase of the project. "Everyone on the team was excited to be working on this."

Washington University later confirmed the top candidates' potency with authentic neutralization assays and in vivo studies. Structural characterization of the top antibody performed at Vanderbilt confirmed that the predicted structure was consistent with the LLNL team's predictions.

"SARS-CoV-2 is a difficult microbial target because the sequence of the virus is changing so fast that we face the need to update the antibody therapeutics that served us so well at the beginning of the pandemic," said Vanderbilt Vaccine Center Director James Crowe.

"The work performed here in this collaborative network rapidly accomplished a historic leveraging of supercomputing resources and expertise to update an important therapeutic model. Clearly, this is a new method for how we will keep future antibody drugs up to date in the future against highly variable viruses."

Faissol added that a "huge benefit of GUIDE is that it also enables the pre-emptive optimization of antibodies to increase robustness to potential future viral escape, extending the clinically useful life of a therapeutic."

More information: Daniel Faissol, Computationally restoring the potency of a clinical antibody against Omicron, *Nature* (2024). DOI: 10.1038/s41586-024-07385-1.
www.nature.com/articles/s41586-024-07385-1

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