SANDIA REPORT
SAND2020-10755
Printed September 2020

Sandia National Laboratories

Computational Modeling To Adapt Neutralizing Antibody

Michael S. Kent

Prepared by
Sandia National Laboratories
Albuquerque, New Mexico
87185 and Livermore,
California 94550

Issued by Sandia National Laboratories, operated for the United States Department of Energy by National Technology & Engineering Solutions of Sandia, LLC.

Available to DOE and DOE contractors from
U.S. Department of Energy
Office of Scientific and Technical Information
P.O. Box 62
Oak Ridge, TN 37831

Telephone: (865) 576-8401
Facsimile: (865) 576-5728
E-Mail: reports@osti.gov
Online ordering: http://www.osti.gov/scitech

Available to the public from
U.S. Department of Commerce
National Technical Information Service
5301 Shawnee Rd
Alexandria, VA 22312

Telephone: (800) 553-6847
Facsimile: (703) 605-6900
E-Mail: orders@ntis.gov
Online order: https://classic.ntis.gov/help/order-methods/

ABSTRACT

Monoclonal antibodies (mAbs) is the leading therapy for viral infections because it provides immediate protection and can be administered at higher levels than in a natural immune response. Finding mAbs that neutralize a broad spectrum of viral targets has proven difficult because many species and strains exist and blanket targeting is a slow and laborious process to experimentally screen 108 variants. A new method is needed to rapidly redesign mAbs for homologous targets. This project speeds up redesign using structure-based computational design to reduce the mAbs search space to a manageable level and screen mutants at a much higher rate than in experiments. Computation will also provide critical knowledge about the fundamental interactions. The project will adapt S230, a human antibody that neutralizes SARS-CoV, to neutralize SARS-COV-2.

CONTENTS

LIST OF FIGURES

This page left blank

Summary: We performed computational modeling of the SARS-CoV-neutralizing antibody S230 to predict mutations needed to adapt this antibody to SARS-CoV2. The computational modeling involved a combination of Monte Carlo-based mutational analysis and molecular dynamics simulations. These two approaches are used because Monte Carlo-based mutational analysis is able to search the enormous sequence space and MD is the best approach for establishing structural fidelity. Two iterations of mutational analysis followed by MD simulation were performed. Two methods were used to assess the best mutations after the second iteration: $\Delta\Delta G$ values from the mutational analysis, and an analysis of the contacts during the second MD simulation. After selecting the best mutations and inserting them into the structure, a docking analysis was performed to compare with the docking results of the as-built structure. Based on the modeling results, 7 antibodies were purchased and testing for binding to SARS-CoV and SARS-CoV-2. The results show that 2 of the S230 variants bind to SARS-CoV-2. However, they did not compete with soluble human ACE2. Most likely the binding to SARS-CoV-2 is too weak to compete with ACE2, but it is also possible that the variants bind in a location that does not compete with ACE2.

Conclusion: Using computational modeling we successfully adapted SARS-CoV-neutralizing antibody S230 to bind to SARS-CoV-2 but the binding level is insufficient for a therapeutic-caliber antibody. Further affinity maturation is needed to improve binding to SARS-CoV-2.

External funding: External funding was secured from the Joint DOE Plan for Medical Therapeutics: Molecular Design Team to apply this methodology to two other SARS-COV2 antibodies. S230 may be chosen for that follow-on work. This funding runs through the fall of 2020. The modeling approach was also included in a proposal to DoD for improving SARS-CoV2 antibodies identified in convalescent patients' B cells. The proposal was led by Brooke Harmon and is in collaboration with researchers at Washington University School of Medicine. Finally, this new technology was briefed to a DARPA program manager on Wed July 24 for possible follow-on funding through that agency.

Figures:

Figure 1

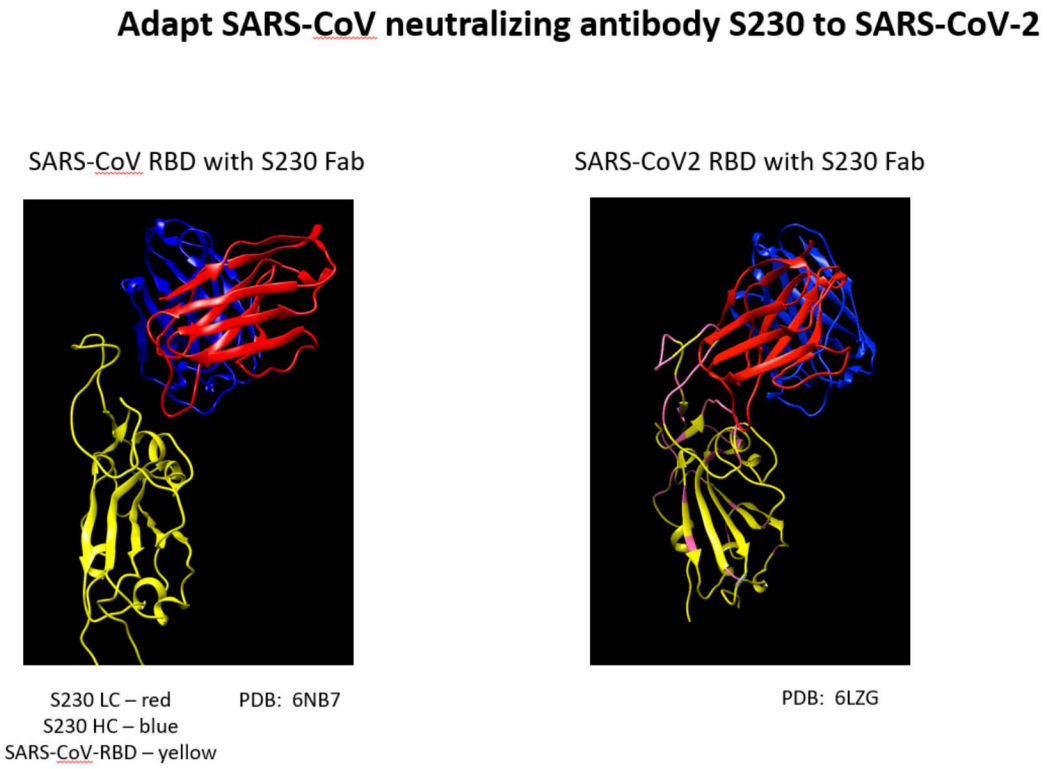


Figure 1 is comparing the structure of S230-CoV with the as-built structure of S230 with CoV2. Shown in yellow is the receptor binding domain (RBD) of the spike protein. The mutations present in CoV2 are indicated in pink.

Figure 2

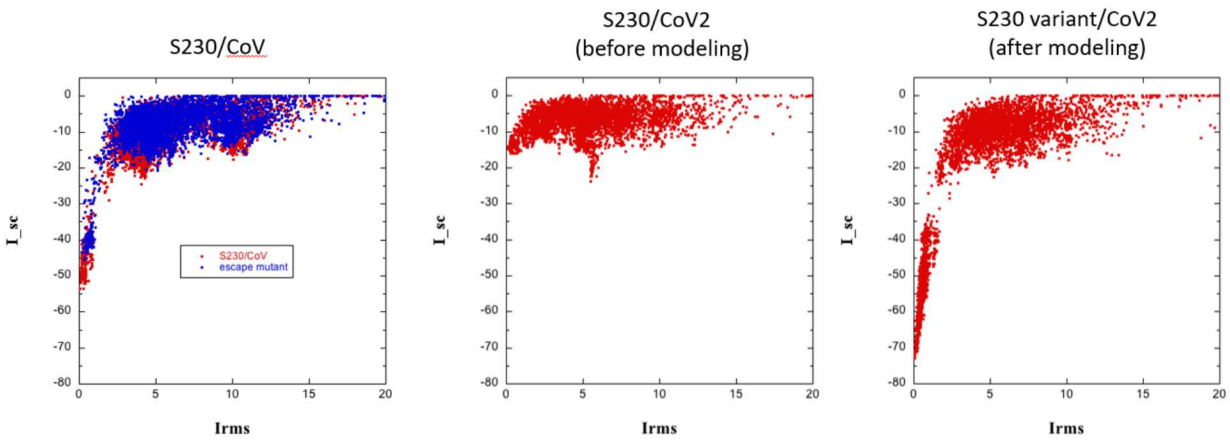


Figure 2 shows docking results for S230 with CoV (native and also with an escape mutation that blocks binding), for the as-built structure of S230 with CoV2, and for a mutated S230 variant with CoV2. The y-axis is a docking score (I_sc) and the x-axis is rms distance from input structure. A well-defined "docking funnel" with a low docking minimum score indicate a good result.

Figure 3

Figure 3 showing sequences corresponding to the IgGs ordered from Genscript.

Figure 4-1

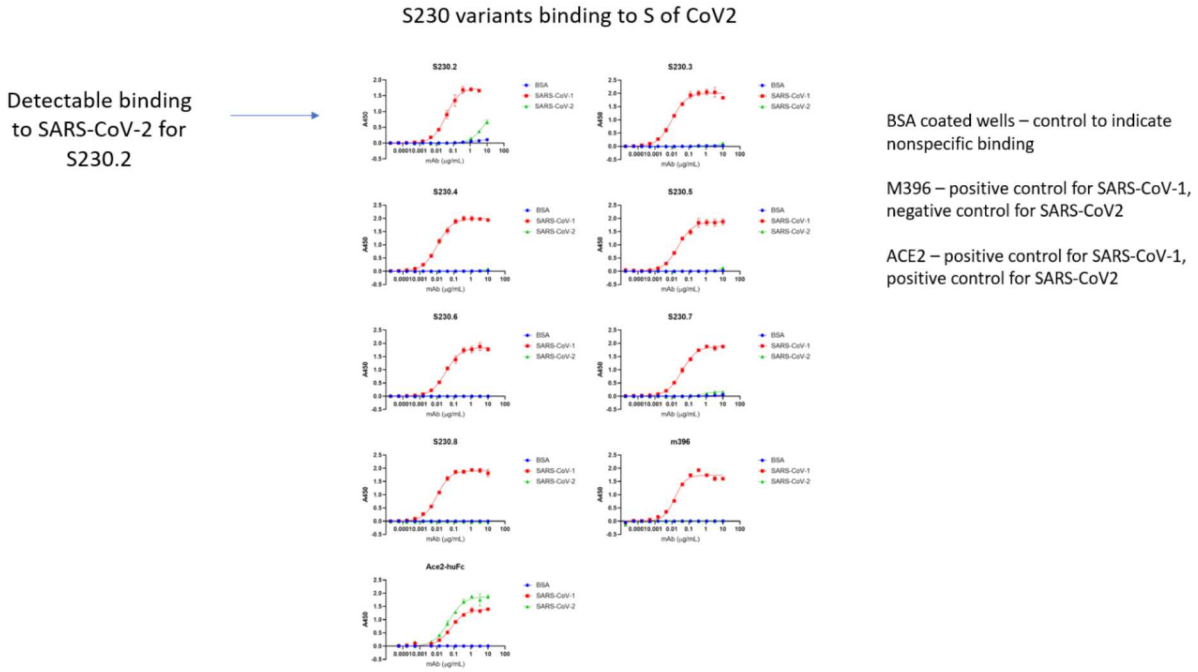


Figure 4-2

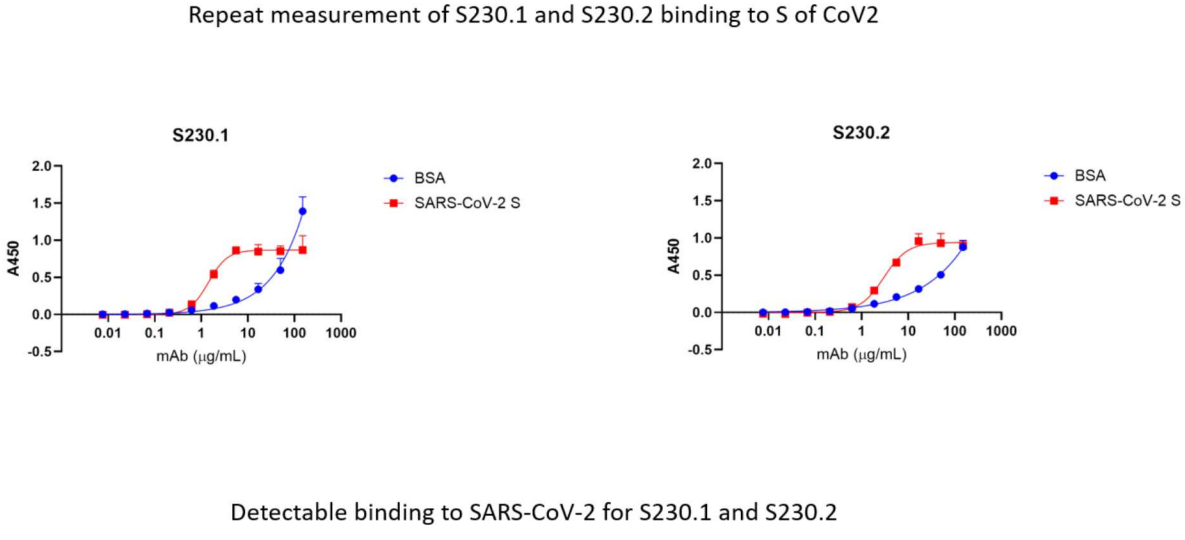
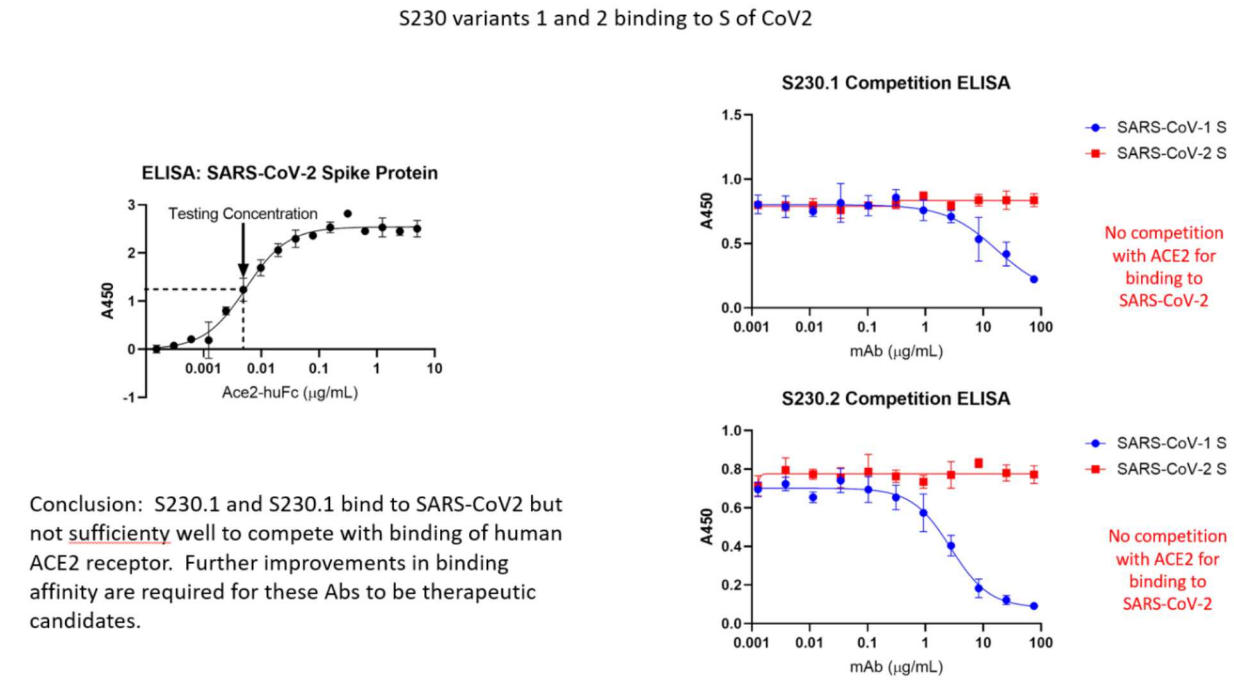


Figure 4-3



Figures 4-1, 4-2, and 4-3 summarizing binding data for S230 variants to SARS-CoV and SARS-CoV-2.

DISTRIBUTION

Email—Internal

Name	Org.	Sandia Email Address
Technical Library	01977	sanddocs@sandia.gov

This page left blank

This page left blank

Sandia National Laboratories

Sandia National Laboratories is a multimission laboratory managed and operated by National Technology & Engineering Solutions of Sandia LLC, a wholly owned subsidiary of Honeywell International Inc. for the U.S. Department of Energy's National Nuclear Security Administration under contract DE-NA0003525.