Evaluating Potential Broad-Spectrum Antiviral Activity using ColabFold and Docking

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December 8, 2022

Abstract

Broad-spectrum antivirals that work against many viruses provide an immediate treatment for diseases caused by novel pathogenic viruses. Notably, there is no universal drug against all four genera of the coronaviridae family, in particular d-coronaviruses, which have recently spilled over from pigs to humans. Here, we present and illustrate an in-silico strategy to evaluate potential broad-spectrum activity of an EUA-approved drug; viz., nirmatrelvir, for the porcine d-coronavirus (PDCoV) that has infected humans. First, we show that the sequence-based protein structure prediction method, ColabFold, can provide structures for the M ^{pro} dimer of a-, b-, and g-coronaviruses that are highly similar to the respective X-ray structures. Next, we validated the performance of the docking software, AutoDock Vina 1.2.3 on ColabFold-predicted SARS-CoV-2 and MERS-CoV M ^{pro} structures by showing that AutoDock Vina 1.2.3 can yield poses of nirmatrelvir that are near the catalytic Cys, as seen in the respective nirmatrelvir-bound X-ray structures. By using AutoDock Vina 1.2.3 to dock nirmatrelvir to the ColabFold-predicted M ^{pro} structure of PDCoV, we provide evidence that nirmatrelvir may inhibit PDCoV M ^{pro}. These results show the feasibility of using state-of-the-art sequence-based protein structure prediction and docking methods to assess broad-spectrum antivirals for known viruses against novel viruses lacking solved structures but sharing highly similar conserved viral domains.

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