Researchers identify 16 medicines that could be used to treat COVID-19

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In the scientific journal *Pharmaceutics*, researchers from the ESI International Chair of the CEU Cardenal Herrera University (CEU UCH) and ESI Group have just published a new computational topology strategy to identify existing medicines that could be applied to treat COVID-19 without waiting for the research and clinical trial phases

required to develop a new medicine. This mathematical model applies topologic data analysis in a pioneering way in order to compare the three-dimensional structure of the target proteins of known medicines to SARS-CoV-2 coronavirus proteins such as protein NSP12, an enzyme in charge of replicating the viral RNA.

According to ESI-CU Chair Director Antonio Falcó, "This type of analysis requires comparing a large number of parameters, which is why it is necessary to apply advanced computational techniques such as the ones we develop at the ESI-CEU Chair, which we apply to very diverse fields: from designing new materials, to optimizing manufacturing processes. Now we have used our knowledge to tackle the challenge posed by the pandemic, to find known treatments that can be effective to treat COVID-19 as fast as possible by comparing, for the first time, the topological structure of proteins."

Innovation in medicine repositioning

Even though other research groups have applied computational methods to reposition medicines to treat COVID-19, ESI Chair researcher Joan Climent says, "We are the first group on an international level to apply the latest breakthroughs in topologic data analysis (TDA), which is used to study the properties of geometric bodies, to analyze biological geometries in the context of medicine repositioning. Our starting point is the idea that known medicines that act against a certain protein as a therapeutic target can also act against other proteins that have a three-dimensional structure with a high degree of topological similarity."

In the case of COVID-19, it is known that protein NSP12, an RNA polymerase that depends on RNA and is in charge of the viral RNA replicating in the host cells, is one of the most interesting and promising pharmacological targets. "Medicines that are effective against proteins with a three-dimensional topological structure that is highly similar to

the NSP12 protein of SARS-CoV-2 could also be effective against this protein."

The study of the ESI-CEU Chair, published in Pharmaceutics, looked at the 1,825 medicines approved by the FDA, the American Food and Drug Administration. According to the Drug Bank repository, these medicines are connected to 27,830 protein structures. In the first phase of this mass analysis, the researchers compared the topological structure of these thousands of proteins available in the Protein Data Bank with the 23 proteins of the SARS-CoV-2 coronavirus. There turned out to be three viral proteins with highly significant topological similarities to target protein structures of known medicines: viral protease 3CL, endoribonuclease NSP15 and RNA-dependent RNA polymerase NSP12.

With this methodology, among the 1,825 medicines approved by the FDA, the research team was able to identify 16 medicines that act against these three proteins as their therapeutic target. Among these 16 medicines are rutin, a flavonoid that inhibits platelet aggregation; dexamethasone, a glucocorticoid that acts as an anti-inflammatory and immunosuppressor; and vemurafenib, a kinase inhibitor suited for adult patients with melanoma. With these medicines now identified, they will now have to be subjected to in vitro and in vivo clinical studies to confirm the possible efficiency detected by the mathematical model and to determine the best combination of them to treat the symptoms caused by COVID-19. Dexamethasone is currently one of the most used medicines that has the most success treating advanced COVID-19 disease.

New variant and future pandemics

The authors of the study also highlight the future usefulness of this new strategy to reposition medicines: "If we consider that half of these new virus variants have modified genes that code the Spike protein, this

technique can be useful to reposition new medicines depending on the changes of the protein structure in the new variants. Furthermore, this strategy could be applied both to the SARS-CoV-2 coronavirus and its new variants, as well as to any new viruses that may appear in the future, identifying their proteins and comparing their topological structure to that of the target proteins in known medicines, using this same strategy."

More information: A COVID-19 Drug Repurposing Strategy through Quantitative Homological Similarities Using a Topological Data Analysis-Based Framework. Pharmaceutics 2021, 13, 488. DOI: doi.org/10.3390/pharmaceutics13040488

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