

# Individuating Possibly Repurposable Drugs and Drug Targets for COVID-19 Treatment Through Hypothesis-Driven Systems Medicine Using CoVex

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## ABSTRACT

Coronavirus disease 2019 (COVID-19), caused by the SARS-CoV-2 virus, has developed into a pandemic causing major disruptions and hundreds of thousands of deaths in wide parts of the world. As of July 3, 2020, neither vaccines nor approved drugs for effective treatment are available. In this article, we showcase how to individuate drug targets and potentially repurposable drugs in silico using CoVex a recently presented systems medicine platform for COVID-19 drug repurposing. Starting from initial hypotheses, CoVex leverages network algorithms to individuate host proteins involved in COVID-19 disease mechanisms, as well as existing drugs targeting these potential drug targets. Our analysis reveals GLA, PLAT, and GGCX as potential drug targets, and urokinase, argatroban, dabigatran etexilate, betrixaban, ximelagatran and anisindione as potentially repurposable drugs.

**Keywords:** systems medicine, network-based drug repurposing, SARS-CoV-2

## INTRODUCTION

In December 2019, the novel coronavirus SARS-CoV-2 was discovered in Wuhan, China. It causes coronavirus disease 2019 (COVID-19), which since then has developed into a pandemic with more than 10.5 million confirmed infections and more than 500 thousand confirmed deaths. As of July 3, 2020, neither vaccines nor effective drugs are available, and, consequently, researchers all over the world are working on new opportunities for treatment.

In this article, we show how to use our recently proposed computational system's medicine platform, CoVex, to identify new drug targets and possibly repurposable drugs for effective treatment.<sup>1</sup> CoVex provides an easy-to-use web interface, which allows experts from pharmacology, biomedicine, and other fields to mine the COVID-19 virus–host–drug interactome in an intuitive, hypothesis-driven way. In particular, CoVex leverages network algorithms to unravel host proteins involved in key pathways of SARS-CoV-2 infection and points the user to existing drugs targeting these proteins. CoVex is available at <https://exbio.wzw.tum.de/covex/>.

Using the interaction data and network analysis algorithms implemented in CoVex (cf. “Results and Discussion” for details), we obtained two interesting results, which we will use to exemplify how to employ CoVex for identifying potential drug targets and possibly repurposable drugs: First, we observed that the enzyme  $\alpha$ -galactosidase ( $\alpha$ -GAL), encoded by the GLA gene, is not only a direct interactor of the viral protein NSP14, but is also involved in an important pathway of angiotensin-converting enzyme 2 (ACE2), which serves as the main entry point for SARS-CoV-2.<sup>2</sup> Deficiency of  $\alpha$ -GAL causes Fabry disease, a rare genetic disorder.<sup>3</sup> Investigating further, we found that GLA is strongly expressed in lung cells

and conferred by email with Fabry disease centers across Europe (in Germany, Switzerland, Slovenia, Norway, and Denmark). None of them report a single confirmed COVID-19 case. We hence formulate the *hypothesis* that  $\alpha$ -GAL might play an important role in the life cycle of SARS-CoV-2 and, consequently,  $\alpha$ -GAL inhibitors might be effective for COVID-19 treatment.

Second, we found that 10 host proteins that directly interact with the viral proteins NSP7, NSP13, E, M, N, ORF9C, and ORF8, are also involved in coagulation pathways. Using these proteins as starting points for the analysis in CoVex, we obtained the subnetwork connecting them and identified the vitamin K-dependent gamma-glutamyl-carboxylase, encoded by GGCX, and tissue plasminogen activator, encoded by PLAT, as potential drug targets (cf. “Results and Discussion” for details). They can be targeted by existing drugs, such as argatroban, dabigatran etexilate, betrixaban, ximelagatran, and anisindione.

Several systems medicine-based approaches for COVID-19 drug repurposing have been presented recently. Zhou *et al.* constructed a coronavirus–human interactome by integrating publicly available virus–human protein–protein interaction (PPI) data for SARS-CoV, MERS-CoV, HCoV-229E, and HCoV-NL with a human PPI network and known drug–target interactions.<sup>4</sup> Subsequently, they used a network proximity algorithm to compile a list of potentially repurposable drugs. Gordon *et al.* used affinity purification mass spectrometry to generate the SARS-CoV-2-specific virus–host interactome and identified potentially promising drug candidates targeting the direct virus interactors.<sup>5</sup> Gysi *et al.* used a similar approach as Zhou *et al.*, but worked with the SARS-CoV-2-specific virus–host interactome generated by Gordon *et al.* instead of using a generic coronavirus–host interactome.<sup>6</sup>

A major advantage of CoVex w.r.t. the works of Zhou *et al.*, Gordon *et al.*, and Gysi *et al.* is that CoVex allows to explore the virus–drug–host interactome in an interactive, hypothesis-driven way. CoVex hence allows experts in the field to leverage their medical knowledge and browse the interactome in a more specific and directed fashion than by simply running generic algorithms on the data. How exactly this can be done is explained and exemplified in this article.

The remainder of this article is organized as follows: In the Methods section, we explain the systems medicine approach implemented in CoVex and provide a concise overview of how to use the main features. In the Results and Discussion section, we discuss GLA as a potential drug target and PLAT and GGCX as targets of possibly repurposable drugs, such as

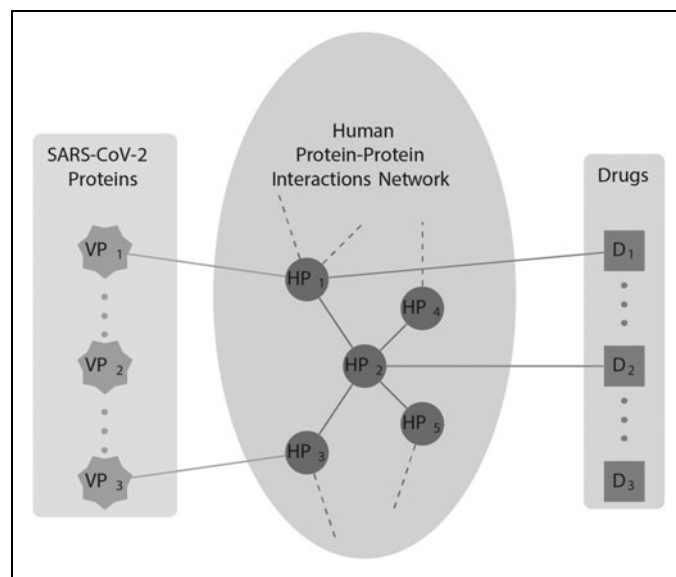
argatroban, dabigatran etexilate, betrixaban, ximelagatran, and anisindione. We conclude the article by pointing out possibilities for future work.

## METHODS

### Leveraging Systems Medicine for Drug Repurposing and Drug Target Individuation

The general paradigm of systems medicine-based drug development and repurposing is to individuate a molecular disease mechanism and to target proteins involved in the extracted mechanism through new or existing drugs.<sup>7,8</sup> In the case of SARS-CoV-2 infection, this paradigm translates into the task to unravel key virus–host pathways, which SARS-CoV-2 requires for replication or which are involved in the pathogenesis of severe COVID-19 cases.<sup>9</sup> Host proteins involved in the extracted pathways are potential drug targets and existing drugs targeting them are potentially repurposable drugs. In comparison to drug development or repurposing strategies that aim at directly targeting the viral proteins,<sup>10</sup> this approach has the advantage that drug resistances due to viral evolution are less probable.<sup>9</sup>

Figure 1 visualizes how CoVex can be used to mine the virus–host–drug interactome of SARS-CoV-2 infection in a hypothesis-driven way. Assume, for instance, that the host



**Fig. 1.** Systems medicine approach employed by CoVex. CoVex integrates experimentally validated data about interaction between SARS-CoV-2 proteins (*star nodes*) with a human PPI network (*round nodes*) and known drug–target interactions (*square nodes*). Interactions between SARS-CoV-2 and human proteins are obtained from Gordon *et al.*,<sup>5</sup> the human PPI network is taken from IID,<sup>11</sup> and the drug–host links are obtained from ChEMBL,<sup>12</sup> DrugBank,<sup>13</sup> DrugCentral,<sup>14</sup> Therapeutic Target Database,<sup>15</sup> Guide to Pharmacology,<sup>16</sup> PharmGKB,<sup>17</sup> and BindingDB.<sup>18</sup> PPI, protein–protein interaction.

proteins  $HP_4$  and  $HP_5$  are known to be involved in a pathway related to a phenotype observed in many critical COVID-19 cases. This knowledge can be leveraged in CoVex by seeding the available network algorithms with  $HP_4$ ,  $HP_5$ , and the viral proteins. CoVex then returns a subnetwork whose nodes correspond to key viral proteins for the phenotype of interest, potential drug targets, and potentially repurposable drugs. In the toy example shown in *Figure 1*, the viral proteins  $VP_1$  and  $VP_3$  are connected to the phenotype-related pathway through the direct interactors  $HP_1$  and  $HP_3$ , as well as the indirect interactor  $HP_2$ . Moreover, there are existing drugs  $D_1$  and  $D_2$  targeting  $HP_1$  and  $HP_2$ , respectively. Hence,  $HP_1$ ,  $HP_2$ , and  $HP_3$  are potential drug targets and  $D_1$  and  $D_2$  are potentially repurposable drugs.

### Using the Functionality Available in CoVex

*Figure 2* provides a schematic overview of CoVex' main features and the intended workflow. The analysis always starts with a set of seed proteins, which have to be selected by the user (*Fig. 2A*). There are several ways to select the seeds. The easiest option is to graphically select some or all of the viral proteins and/or direct host interactors. Alternatively, the user can select proteins with high expression in a tissue of interest (e.g., lung), or provide a custom list of seed proteins. This latter option is especially interesting, because it allows to use CoVex in a hypothesis-driven way. For instance, the user-provided list of seed proteins could contain host proteins involved in symptom-related pathways or host proteins, which are differentially expressed in COVID-19 patients.

After selecting the seeds, the user can choose among six network algorithms to individuate potential drug targets, that is, host proteins involved in virus–host pathways, which are relevant to the selected seeds (*Fig. 2B*). The following algorithms are available at this stage: degree, closeness, and betweenness centrality,<sup>19</sup> TrustRank,<sup>20</sup> KeyPathwayMiner,<sup>21</sup> and a novel multi-Steiner tree algorithm. While these algorithms differ w.r.t. their mathematical underpinnings (cf. Sadegh *et al.*<sup>1</sup> for details), they all aim at extracting pathways

that connect the selected seeds. The returned host proteins can then be displayed in UniProt<sup>22</sup> and be annotated with or filtered by tissue-specific expression values. Moreover, g:Profiler<sup>23</sup> can be called to run enrichment analysis on the found drug targets.

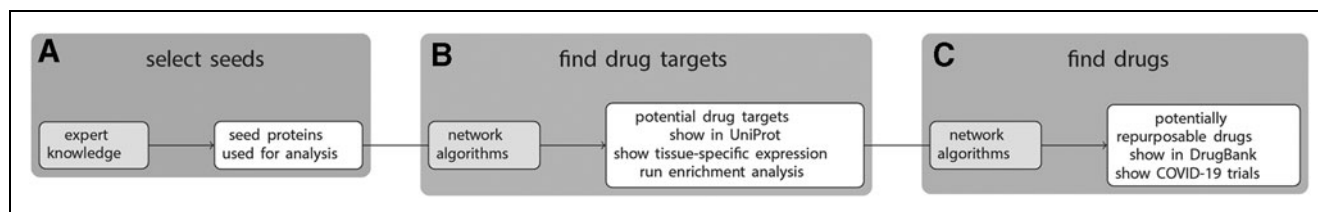
The next step is to individuate drugs targeting the discovered drug targets (*Fig. 2C*). For this, CoVex provides four different network algorithms: degree and closeness centrality,<sup>19</sup> TrustRank,<sup>20</sup> and network proximity.<sup>24</sup> All of them extract ranked lists of drugs that hit (in the close vicinity of) the found drug targets and are hence candidates for drug repurposing. The drugs can be displayed in DrugBank and it is shown which of them are currently in clinical trial for COVID-19 treatment. Note that this step (*Fig. 2C*) of the CoVex workflow can also be run from drug targets provided by the user. That is, the automated individuation of drug targets (*Fig. 2B*) can be substituted by expert knowledge. Note that CoVex—by design—is dependent on expert input, as it follows the expert-in-the-loop concept. Consequently, the final results always depend on user input at different stages of the analyses.

## RESULTS AND DISCUSSION

In this study, we show two application examples to find drug targets and drug repurposing candidates. The first example demonstrates the potential relevance of the  $\alpha$ -GAL protein as a drug target in SARS-CoV-2 infection, and the second example shows potential drug targets and possibly repurposable drugs for thromboembolic complications frequently observed in COVID-19 patients. Note that the obtained results are *hypotheses* that have not been validated through further genetic or chemical approaches and, consequently, should be treated with caution. In the present article, their main purpose is to exemplify the CoVex workflow.

### Potential Drug Target: GLA

The  $\alpha$ -GAL protein, encoded by the GLA gene, was identified by Gordon *et al.*, as a direct interactor of the viral protein



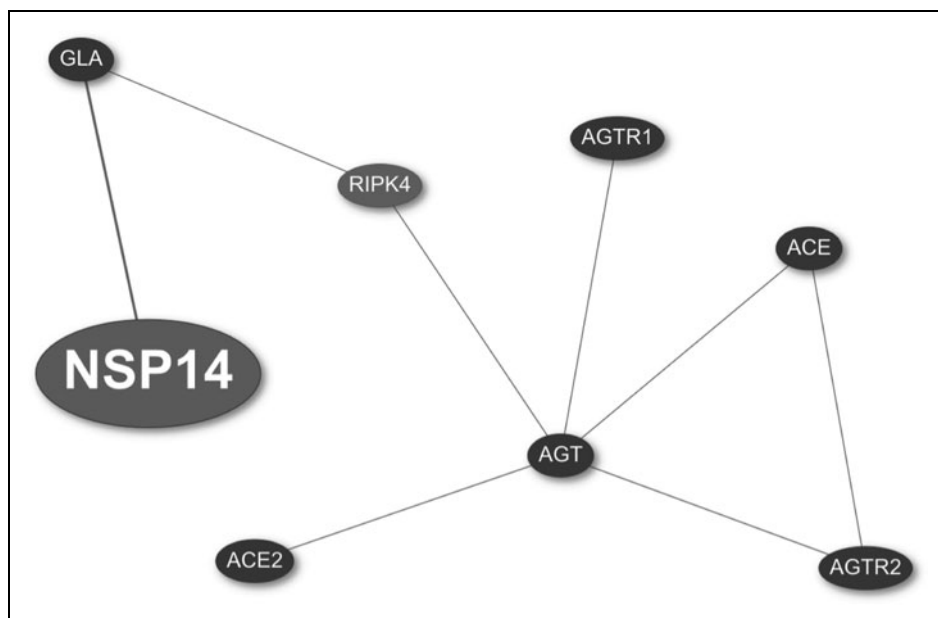
**Fig. 2.** The CoVex workflow. In the first step, the user has to select a set of seed proteins from which the analysis should be run (**A**). Subsequently, network algorithms are employed to find proteins that are putative drug targets (**B**) and potentially repurposable drugs targeting them (**C**).

NSP14 of SARS-CoV-2 virus.<sup>5</sup> The  $\alpha$ -GAL protein is a lysosomal enzyme, highly expressed in the lung<sup>25</sup> that degrades glycolipids, particularly globotriaosylceramide.<sup>26</sup> Deficiencies of this enzyme cause Fabry disease, a rare genetic disorder characterized by the accumulation of globotriaosylceramide in endothelial cells, leading to severe symptoms.<sup>3,26</sup> Fabry patients are often treated with blockers of the renin-angiotensin system, particularly angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists. Importantly, these proteins are expressed in vascular endothelial cells of the lung, kidney, and gastrointestinal tract, which are among the main tissues affected in Fabry disease and in COVID-19 patients.<sup>26,27</sup>

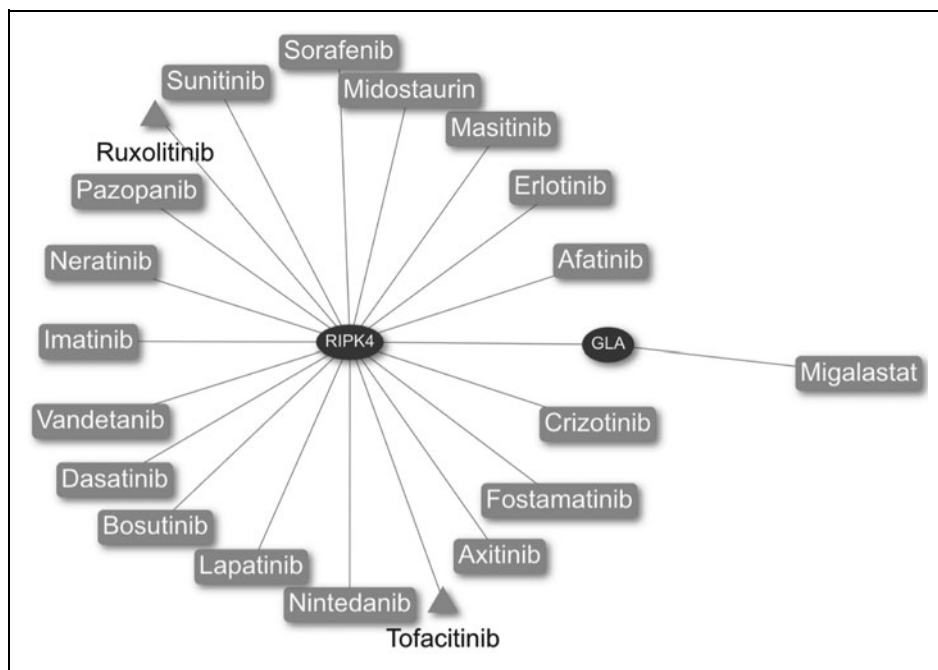
The points mentioned above raise the question whether the  $\alpha$ -GAL protein could be involved with the renin-angiotensin system in the context of SARS-CoV-2 infection. Using CoVex, we aimed at extracting a subnetwork that could link  $\alpha$ -GAL with this pathway. Thus, we used AGT, ACE, ACE2, AGTR1, and AGTR2 (main players of the renin-angiotensin system), as well as NSP14 and GLA as seeds. Next, we used the multi-Steiner algorithm to identify the connected subnetwork relevant to the seed proteins, and then ran closeness centrality to find potentially repurposable drugs.

The results shown in *Figure 3* reveal that GLA is closely related to important components of the renin-angiotensin system through the receptor-interacting serine/threonine-protein kinase 4 protein, encoded by the RIPK4 gene. Interestingly, the drugs ruxolitinib and tofacitinib, which are currently used in clinical trials in COVID-19 patients, also target this protein (*Fig. 4*).

To further elucidate the role of  $\alpha$ -GAL in SARS-CoV-2 infection, we



**Fig. 3.** Virus-host interaction network obtained with the multi-Steiner algorithm in CoVex. The viral protein NSP14 (*large node*) and the host proteins GLA, ACE2, AGT, ACE, AGTR1, and AGTR2 were used as seeds (*small black nodes*). The resulting subnetwork contains a new potential drug target RIPK4 (*small gray node*). ACE2, angiotensin-converting enzyme 2; RIPK4, receptor-interacting serine/threonine protein kinase 4 protein.



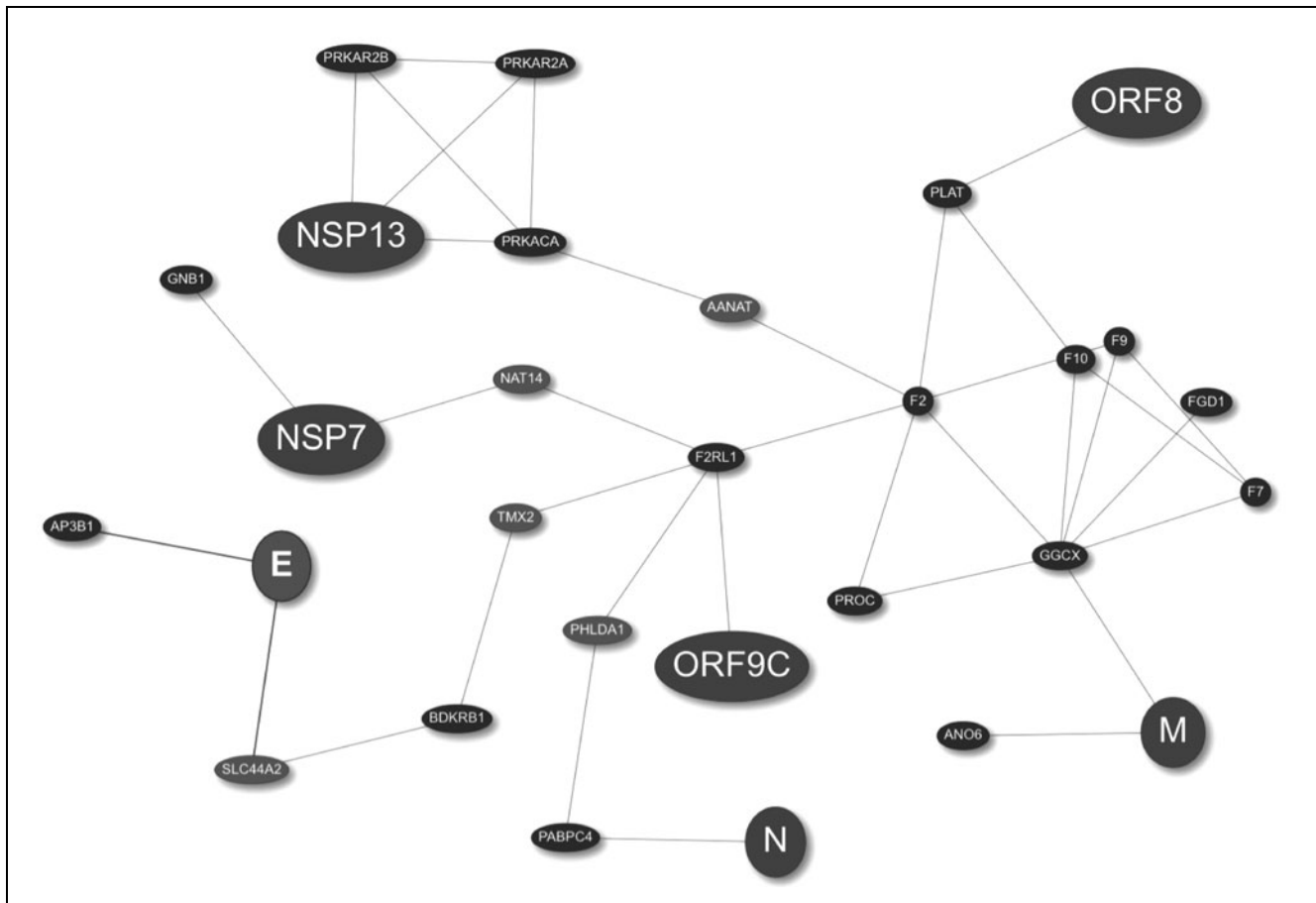
**Fig. 4.** Drug-PPI network obtained with the closeness centrality algorithm in CoVex. The host proteins RIPK4 and GLA were used as seeds (*elliptical nodes*). The resulting network contains approved drugs (*rectangular nodes*) and drugs which are in clinical trials for COVID-19 treatment (*triangular nodes*). COVID-19, coronavirus disease 2019.

**Table 1. Virus–Host Interactions Related to Coagulation in Gordon *et al.*<sup>a</sup> Dataset**

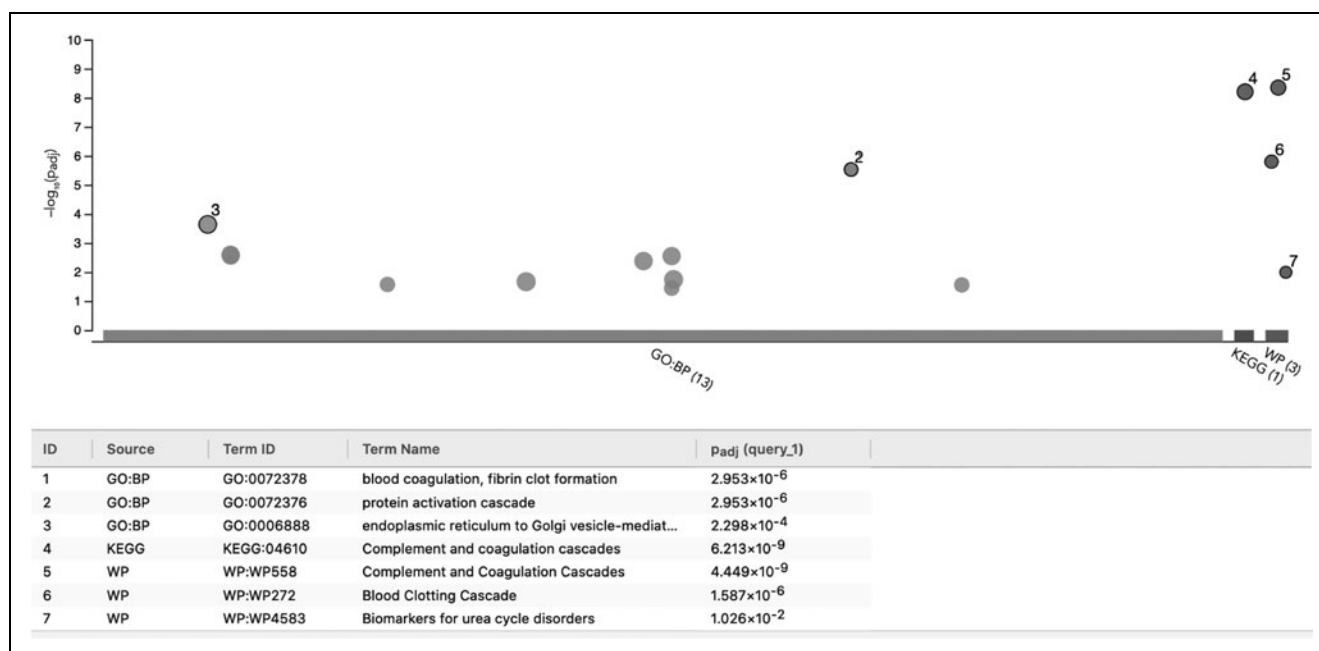
Viral proteins	Host proteins
NSP7	GNB1
NSP13	PRKAR2B, PRKACA, PRKAR2A
E	AP3B1
M	GGCX, ANO6
N	PABPC4
ORF9C	F2RL1
ORF8	PLAT

<sup>a</sup>Reference.<sup>5</sup>

contacted several Fabry disease centers across Europe by email. We received numbers of Fabry disease patients and confirmed COVID-19 cases among them from Germany, Switzerland, Slovenia, Norway, and Denmark. Interestingly, all centers reported zero confirmed COVID-19 cases among their patients. Hence, we formulate the *hypothesis* that  $\alpha$ -GAL might play a role in COVID-19 pathogenesis and could hence be an attractive drug target for treatment. However, one should note that Fabry disease is a rare disease and these centers follow only a few thousand patients such that the evidence of not having a single COVID-19 case among them is rather weak. We followed up this thread because of the observed molecular interaction between  $\alpha$ -GAL and the viral protein NSP14.



**Fig. 5.** Virus–host interaction network obtained with the TrustRank and multi-Steiner algorithms in CoVex. The viral protein (*large nodes*) and the host proteins shown in Table 1 were used for the initial analysis with TrustRank, the resulting network (*small black nodes*) was further analyzed with the multi-Steiner algorithm, which identified additional connector proteins (*small gray nodes*).

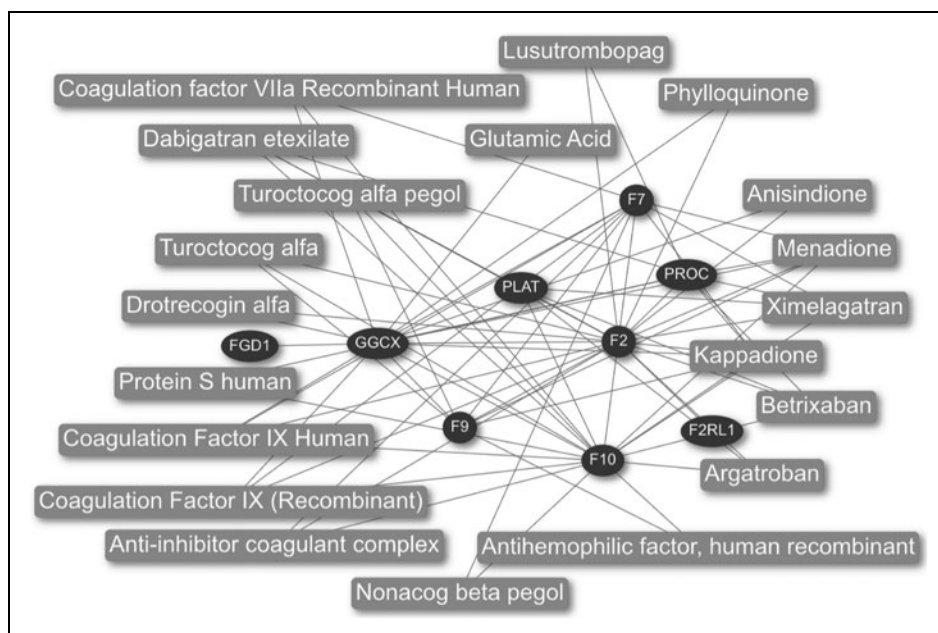


**Fig. 6.** Functional enrichment analysis of the coagulation-related interaction network in CoVex. The nonseed host proteins from the coagulation-related network (Fig. 5) were analyzed with g:Profiler using GO biological process, KEGG pathways, and Wiki-Pathways as data sources. The *upper panel* shows the significantly enriched terms for each data source, and the *lower panel* shows the terms with the smallest *p*-values. BP, biological process; GO, Gene Ontology; KEGG, Kyoto Encyclopedia of Genes and Genomes; WP, Wikipathways.

**Potential Drug Targets: PLAT and GGCX**

Several studies reported an increased incidence of cardiovascular complications and venous thrombotic events in hospitalized COVID-19 patients irrespectively of disease severity as well as abnormal coagulation parameters.<sup>28,29</sup> While the mechanism of COVID-19 coagulopathy remains unclear, the cytokine storm syndrome<sup>30,31</sup> and the endothelial dysfunction occurring in COVID-19 have been suggested as a possible main driver.<sup>32</sup> In this second application example of CoVex, we hypothesize that the virus is directly involved in the disruption of the coagulation process, which, to some extent, could contribute to the observed hypercoagulable states.

To evaluate this hypothesis, we used SARS-CoV-2 host interactors and viral proteins involved in coagulation as seeds (proteins mapping to the Gene Ontology (GO) term coagulation GO:0050817, cf. Table 1). Next we ran the “Find drug target” analysis using TrustRank and the



**Fig. 7.** Drug-PPI network obtained with the closeness centrality algorithm in CoVex. The resulting network contains host seed proteins (*elliptical nodes*) and approved drugs (*rectangular nodes*).

multi-Steiner algorithms to extract the corresponding subnetwork (Fig. 5), which is enriched with genes involved in coagulation (Fig. 6). This means that CoVex was capable of identifying new genes in a network, which are also involved with the biological process of interest.

Additionally, the resulting network shows new identified target proteins connected to the viral proteins, M, ORF8, and ORF9C, and to the host interactors, PLAT and GGCX. These new targets are of special interest because they are among the main proteins in the coagulation cascade (F2, F7, F9, F10, and protein C [PROC]).<sup>33</sup> Proteins F2, F7, F9, and F10 correspond to the clotting factors thrombin (II), proconvertin (VII), Christmas factor (IX), and Stuart-Prower factor (X), respectively; and they are necessary to induce thrombus formation.<sup>33</sup> On the other hand, PROC plays an important role in the inhibition of thrombi formation; similarly, PLAT is involved in fibrinolysis (degradation of thrombi).<sup>33</sup> Finally, GGCX is expressed in the liver and catalyzes a vitamin K-dependent post-translational modification required by several coagulation proteins to properly function.<sup>34</sup> We selected PLAT and GGCX as potential drug targets from the network analysis because they directly interact with viral proteins and are key regulators of coagulation. A dysfunction of these proteins could explain, at least in part, the thromboembolic complications observed during SARS-CoV-2 infection.

Next, we obtained approved drugs with the “Find drugs” analysis using closeness centrality (Fig. 7). The analysis shows the top 20 drugs identified by the network analysis. Attractive drugs are argatroban, dabigatran etexilate, betrixaban, ximelagatran, and anisindione, because they exhibit anticoagulant effects and additionally target the proteins PLAT and GGCX; thus these drugs could be considered as additional treatment in COVID-19. Of note, dabigatran is an approved anticoagulant drug routinely used in different settings. Our data provide pathophysiological insights concerning the benefit of anticoagulant treatment during SARS-CoV-2 infection, which may reduce the impact of COVID-19 coagulopathy. Clinical trials investigating different antiplatelet therapies are ongoing worldwide and may validate our *in silico* findings.

In summary, we showed that CoVex is capable of extracting biologically relevant networks useful to put the interactors of SARS-CoV-2 into molecular context by integrating drug-PPI information and network-based drug repurposing methods.

## CONCLUSIONS AND OUTLOOK

Systems medicine is a powerful emerging paradigm for drug discovery and drug repurposing, which aims at targeting the molecular disease mechanisms. In this article, we show-

ed how to leverage systems medicine for individuating putative drug targets and potentially repurposable drugs for COVID-19 treatment using the SARS-CoV-2 systems medicine platform CoVex. We individuated GLA, PLAT, and GGCX as putative drug targets and argatroban, dabigatran etexilate, betrixaban, ximelagatran, and anisindione as potentially repurposable drugs. Since CoVex is designed to allow easy incorporation of expert knowledge, we hope that more and more researchers from pharmacology and related fields will use it to unravel further promising strategies for COVID-19 treatment.

## ACKNOWLEDGMENTS

The authors are grateful for support by Harald H.H.W. Schmidt and Frank Weidemann for establishing the contacts to Fabry disease experts across Europe.

## DISCLOSURE STATEMENT

No competing financial interests exist.

## FUNDING INFORMATION

J.B. and S.S. are grateful for financial support from H2020 grant REPO-TRIAL (no. 777111). M.S.-A. is a doctoral student from “Programa de Maestría y Doctorado en Ciencias Bioquímicas, UNAM” and is grateful for a PhD fellowship funding from CONACYT (CVU659273 and 312021) and the German Academic Exchange Service, DAAD (ref. 91693321). J.B. and J.M. acknowledge financial support from H2020 grant FeatureCloud (no. 826078) and BMBF grant Sys\_CARE (no. 5103388). D.B.B. gratefully acknowledges financial support from the German Center for Cardiovascular Research, DZHK (no. 81X3600606).

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## Abbreviations Used

$\alpha$ -GAL	= $\alpha$ -galactosidase
ACE2	= angiotensin-converting enzyme 2
BP	= biological process
COVID-19	= coronavirus disease 2019
GGCX	= gamma-glutamyl carboxylase
GO	= Gene Ontology
KEGG	= Kyoto Encyclopedia of Genes and Genomes
PLAT	= tissue plasminogen activator
PPI	= protein–protein interaction
PROC	= protein C
RIPK4	= receptor-interacting serine/threonine-protein kinase 4 protein
WP	= Wikipathways