Focusing on the Unfolded Protein Response and Autophagy Related Pathways to Reposition Common Approved Drugs against COVID-19

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Abstract

More than 179,000 individuals have fallen ill of the Coronavirus disease (COVID-19) caused by the SARS-CoV-2 virus, which first emerged in China less than four months ago in December 2019. As of today, there exist no approved treatments against COVID-19. Vaccines are being developed, but they will take time, at least one year, to reach the population. Drug repositioning represents a fast track because already approved medicines have been broadly tested through multiple trials. We developed a repositioning strategy that mostly leads to candidates that are commonly used. The advantages are that they will facilitate proof of concept in humans through a "real-world evidence" approach and should be rapidly available to the population. We focus on the established research results that the unfolded protein response (UPR) and autophagy pathways of the host cells are essential to the life cycle of previously known coronaviruses. We performed the relevant bioinformatics analysis to understand and confirm if SARS-CoV-2 may interact with these druggable pathways. Based on these considerations, we prioritized two additional druggable pathways, which are important to the viral life cycle and tightly connected to UPR/autophagy signaling: the mitochondrial permeability transition pores (MPTP) and NLRP-3 inflammasome pathways. These four important pathways are perturbed in most major common diseases and have therefore been targeted by numerous broadly prescribed drugs. We have identified 97 approved drugs that are known to modulate these four identified pathways, and which represent, therefore, interesting repositioning candidates. Although it is indisputable that these drugs should never be used for immediate self-medication against COVID-19, we notice that some of them could also be prescribed to individuals who have COVID-19 comorbidities (e.g., hypertension). It is debated if these comorbidities are linked to the pathology itself (e.g., hypertension) or the drugs used to treat the pathology (e.g., sartans). Therefore, relevant preclinical tests and massive electronic health records (i.e., real-world evidence) must be used to pre-screen them and check the COVID-19 prognosis of individuals taking these drugs.

Keywords: COVID-2019; SARS-CoV-2; 2019-nCoV; repositioning; UPR/Autophagy; real-world evidence; pathways

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Introduction

As of March 17th, 2020, the COVID-19 disease, caused by the SARS-CoV-2 virus (a.k.a 2019-nCoV), has become a pandemic with 179,111 confirmed cases and 7,426 deaths in more than 100 countries[1]. According to multiple studies, these numbers are greatly underestimated due to the lack of systematic testing and a potentially high number of asymptomatic cases[2]. There are no approved treatments against COVID-19, and vaccines being developed are not expected to reach patients promptly[3]. Repositioning of approved drugs, or which are in ongoing clinical development, is a powerful solution to rapidly yield efficient treatments for all unmet medical needs[4,5]. To respond to the COVID-19 emergency, multiple repositioning initiatives have been launched, most of which focus on drugs known for their antiviral activity[6]. Very recent work showed that the SARS-CoV virus, which triggered the 2002-2003 Severe Acute Respiratory Syndrome (SARS) epidemic, and the MERS-CoV virus, which triggered the 2012 Middle East Respiratory Syndrome (MERS) epidemic, both coronaviruses, are closely related to the SARS-CoV-2 virus[7,8].

In this situation, because there doesn't exist enough functional studies of SARS-CoV-2, one possibility is to focus drug repositioning on host-cell pathways which are likely to be affected by all coronaviruses' life cycles, and which are targeted by an already existing wide range of drugs. Coronaviruses are beta-coronaviruses with a single-stranded RNA genome that encodes 16 nonstructural proteins, among which some are considered targetable such as several proteases, one helicase, and the RNA-dependent RNA-polymerase[3]. Beyond the protein and RNA replication machinery, classic targets of antiviral drugs[9], the lifecycle of coronaviruses relies on several host-cell encoded cellular pathways.

Among those pathways, the Unfolded Protein Response (UPR) and Autophagy pathways are tightly interconnected and were shown to be essential for viral infection by multiple previous studies[10–13]. Briefly, these two pathways are involved in the regulation of protein homeostasis, apoptosis, and play pivotal roles in the control of innate immunity, including the clearance of viral particles [14,15]. For example, recent work showed that the MERS-CoV virus induces reduced levels of the Beclin1 (BECN1) protein, which blocks the fusion of autophagosomes and lysosomes and the inhibition of the S-phase kinase-associated protein 2 (SKP2), an E3 ubiquitin ligase which promotes BECN1 degradation, enhances autophagy and reduces the replication of MERS-CoV up to 28,000-fold[16]. In addition, viruses are also able to modify and use the UPR/Autophagy signaling networks to complete their life cycle (e.g., enter the host cell, produce large quantities of their viral proteins)[10–13].

Moreover, therapeutic targeting of the UPR/Autophagy pathway has attracted a lot of research interests for neurodegenerative and cancer diseases. For this reason, there exists a wide range of drugs that target these pathways [17–19] and which could be immediately repositioned against COVID-19.

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In this study, we sought to assess further the putative link between COVID-19 and the UPR/autophagy pathways. To this end, we performed a bioinformatics analysis in which we relied on the aforementioned evidence that SARS-CoV-2 is closely related to the virus, which has caused the 2002-2003 SARS epidemic and to other coronaviruses. This allowed us to derive a set of host cell genes putatively involved in COVID-2019. By performing pathway enrichment analysis over those genes and identifying relevant protein-protein interactions (PPIs), we were able to list important pathways affected in infected cells. We found that several of those pathways are linked to the UPR/autophagy pathways. Furthermore, we found that a remarkably high percentage of drugs currently undergoing repositioning for COVID-19 are known modulators of the UPR/autophagy, which further supports the key role of these cellular pathways in that disease. Based on these findings, we suggest that two additional pathways, which are linked to the UPR/Autophagy pathways, are important for the viral cycle of SARS-CoV-2: the NLRP3 inflammasome signaling pathway and the pro-apoptotic mitochondrial signaling pathway. We then propose a list of drugs that are reported modulators of these four pathways, most of which are frequently prescribed and not primarily known as antiviral compounds. Finally, we indicate a global strategy to pre-screen these drugs and rapidly launch clinical trials.

Materials and Methods

Cov-SARS related gene-products

We first identified viral host gene-products (i.e., in most cases proteins) which could putatively be involved in COVID-19 by interrogating the Open Targets platform (https://www.opentargets.org/) (v3.16.1, data version 20.02) which integrates evidence from human population genetics, genomics, transcriptomics, known pathways, animal models and scientific literature data[20]. Importantly, the database integrates data from numerous diverse sources, and is, a priori, unbiased towards any specific pathway. Because COVID-19 is not yet a cataloged disease in this database, we searched for gene-products associated to the following available key terms: “coronavirus infectious disease” and “severe acute respiratory syndrome” (SARS) and combined them in one single list of “Cov-SARS” gene-products where each of them is indexed via its official symbol (Table S1).

Pathway Enrichment and Protein-Protein Interaction Analyses

We performed pathway enrichment analysis over the Cov-SARS gene-products list, a method that identifies canonical biological pathways that are significantly enriched in gene-products from this list, i.e., overrepresented, more than expected by chance[21]. This first pathway enrichment analysis was hypothesis-driven: based on our literature-supported assumption that UPR/autophagy plays an important role in coronaviruses infections, we searched for enriched pathways in our list of Cov-SARS

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gene-products. To this end, we used the bioinformatics tool IPA (Ingenuity Pathway Analysis v49932394 2019-11-15) (QIAGEN Inc., https://digitalinsights.qiagen.com/products-overview/discovery-insights-portfolio/analysis-and-visualization/qiagen-ipa/)[22] to perform a so-called "core analysis/Expression analysis" based on the Ingenuity Genes Knowledge Base reference set (Table S2). Our goal was to identify major cellular pathways putatively affected by the viral infection. We define as "statistically enriched", pathways for which the IPA reported a nominal p-value inferior to 0.05. One difficulty with pathway enrichment analysis methods is that their results can be sensitive to the manual curation of their underlying databases (e.g., which genes are in which pathway) and statistical assumptions[23].

For this reason, we performed a complementary bioinformatics inquiry based on protein-protein interactions (PPI) referenced by IPA (Ingenuity Expert Findings + Third Party Information: BIND, Cognia, DIP, Interactome studies, MIPS, BioGRID, IntAct). Having confirmed that the UPR/autophagy linked pathways are enriched and having labelled each Cov-SARS gene to its enriched pathway (Table S2), the goal of this second analysis was to combine our Cov-SARS gene-products and their corresponding key pathways into an abstract molecular model describing the host-cell protein network possibly impacted by the SARS-CoV-2 infection. Using our Cov-SARS gene-products list, (1) we first identified all direct PPI among the proteins in the Cov-SARS list. When multiple proteins of the list directly interact together, we group them in what we call a "class I complex" (i.e., a component in standard graph language). (2) Secondly, we identified proteins, not contained in our list, which directly interact (via PPI) with at least three of our Cov-SARS proteins and which group together in what we call a "class II complex". (3) We retained only the class II complexes for which the non-Cov-SARS protein could be considered as a "master protein" because it belongs to an IPA canonical pathway (Ingenuity Expert Findings). (4) Finally, we connected class I complexes to the retained class II complexes by direct PPI (i.e. the class I complex and class II complex share common proteins) and/or by functional relations (i.e., metabolite, phosphorylation cascade, or any other IPA reference relation that is not a PPI), which are also documented by the IPA database, to delineate the most important and experimentally supported pathways affected by the SARS-CoV-2 infection ("Cov-SARS related pathways") (see Figure S1 and example "recognition receptor RIG1-like).

Drug Repositioning on candidate pathways

We identified the candidate drugs modulating the function of our selected pathways by systematic scientific literature search (see reference in Table 2)

Analysis of drugs being repositioned against COVID-19

To evaluate the results of our pathway enrichment and PPI analyses, we retrieved the latest World Health Organization (WHO) report of drugs being clinically investigated against COVID-19

(https://www.who.int/blueprint/priority-diseases/key-action/Table_of_therapeutics_Appendix_17022020.pdf?ua=1) (February 17th, 2020 version) and checked if they are modulators of the UPR/Autophagy pathways (Table 1).

Known antiviral status of our repositioning candidates

Finally, for drugs identified as putatively acting on our top Cov-SARS related pathways (Table 2), we checked their therapeutic category via IPA, Drug Bank v5.1 (https://www.drugbank.ca/) and/or the Royal Pharmaceutical Society MedecinesComplete database (https://about.medicinescomplete.com/#/).

Results and Discussion

Using the Open Targets database, we find that 274 genes are involved in coronavirus infections (Cov-SARS genes, Table S1). Numerous genes on our list are directly implicated in the host cell immune response. Including, for instance, a large group of cytokines and their receptors (e.g., IL-3, IL-15, CXCL11, TNF, TNFRSF1A, CXCR3). Expectedly, we also found the ACE2 gene, which encodes a receptor, both used by the SARS-CoV and SARS-CoV-2 viruses to enter the host cell[24].

Among the statistically enriched pathways ($p < 0.05$), our pathway enrichment analysis identified numerous signaling pathways involved in the immune response, in particular, the following pathways: “pattern recognition receptors signaling”, “interferon induction”, “inflammasome pathway” (Table S2), which are directly implicated in the antiviral innate immune response[25–28]. This further supports the link between our Cov-SARS gene-products list and coronavirus infections. Also, among those statistically enriched pathways, we found the “endoplasmic reticulum stress pathway”, the “unfolded protein response signaling,” and the “phagosome maturation pathway”, thereby supporting the aforementioned link between the UPR pathway and coronaviruses infections.

Then, our PPI analysis confirmed the putative role of “pattern recognition receptors signaling” and “inflammasome pathway” in coronavirus infections but also allowed us to connect these two immune pathways and UPR/autophagy signaling into a single molecular framework of the host cell viral infection (Figure S1 and S2). For instance, the NLRP3 inflammasome could be activated by the RIG-I-like and TLR4 receptors-mediated signaling but is also modulated by the autophagy flux. In turn, the autophagy pathway can be activated either by the canonical ATF4 and DDIT3(CHOP) transcription factors cascade or by the RIG-I-like receptors establishing functional feedback-loops in this signaling network[29–36]. Remarkably, recent publications linked the activation of NLRP3 inflammasome to cytokine storms[37], which were reported to be involved in severe forms of COVID-19[38]. The ATF4 and DDIT3(a.k.a. CHOP) transcription factors are also involved in the regulation of intrinsic (mitochondria-mediated) apoptosis pathways through the downregulation of the BCL2

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protein (which can also modulate the autophagy flux), a constitutive component of the mitochondrial permeability transition pore complex (MPTP), a core regulator of apoptosis and target for several approved drugs [39]. Altogether, these findings confirm the important role of the UPR/Autophagy pathways in coronavirus infections and suggest it as a target to reposition drugs against COVID-19.

Also, we find that most repositioning candidate drugs (58%) under clinical investigation against COVID-19, reported by the World Health Organization, are also modulators of autophagy (Table 1) although most of them differ by their core mechanisms-of-action, e.g., the anti-malaria drug chloroquine, the hepatitis B/C treatment type-1-interferon 2a, and the anti-HIV drug Lopinavir, This holds for drugs that were approved for other diseases but shown to be effective against coronaviruses in experimental settings and not yet studied in clinical trials (Table S3). These findings suggest that effective antiviral drugs may not only work through their direct effect on viral proteins, such as lopinavir's action on the HIV protease, but also enhance their therapeutic effects by modulating the UPR/autophagy pathways and their related pathways.

In this context, we found a set of 97 drugs modulating the function of the four selected pathways (UPR, autophagy, the NLRP3 inflammasome, and MPTP (Table 2, Figure S1) by performing an extensive literature search (see references provided with Table 2). To our knowledge, most of them are novel repositioning candidates against COVID 19.

Importantly, this list contains both activators and inhibitors of autophagy. We hypothesize that they could be used to treat different types of COVID-19 patients. Indeed, based on our findings and the proposed framework (Figure S2), it is reasonable to hypothesize that some inhibitors of autophagy (e.g., chloroquine, currently undergoing clinical trial, cf. Table 1) would prevent the virus from entering the host cell and could thereby be used to prevent SARS-CoV-2 infections while activators of autophagy (e.g., interferon-alpha 2a/2b, also undergoing clinical trial, cf. Table 1), which would help the host cell clear the viral particles, could be used to treat severe forms of COVID-19. Remarkably, most drugs among our repositioning candidates are not known as antiviral, and most of them are known to be frequently prescribed drugs (Table 2). For instance, statins, anti-diabetics, and antagonists of the angiotensin receptor 1, which are used to treat hyperlipidemia, type 2 diabetes, and hypertension, respectively, all of which are very common diseases. In addition, type 2 diabetes and hypertension are known to be linked to an aggravated COVID-19 prognosis[2,40]. Therefore, it is likely that many of the patients at risk are already taking these drugs for their primary condition, and it could facilitate real-world evidence-based analyses. Such common drugs are also highly interesting candidates because they may be immediately available in large quantities, their toxicity profile is known and eminently safe (e.g. pantoprazole, metformin, cf. Table 2), and tend to be more affordable than newly developed drugs[5,41].

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Although it is indisputable that these drugs should never be used for immediate self-medication against COVID-19, we notice that some of them could also be prescribed to individuals who have COVID-19 comorbidities (e.g., hypertension). It is currently unclear if these comorbidities are linked to the pathology itself (e.g., hypertension) or the drugs used to treat the pathology. For instance, drugs directly implicated in renin-angiotensin signaling (e.g., sartans) are known to increase the SARS-CoV-2 host cell receptor expression ACE2[42]. It is also uncertain if this effect might aggravate COVID19 or if, by modifying the UPR/autophagy flux, these drugs might have a beneficial impact by, for instance, effectively blocking the virus entry. Therefore, relevant preclinical, experimental tests and massive electronic health records (i.e., real-world evidence[43]) must be used to pre-screen them and check whether their effect could potentially prevent, treat, or, on the contrary, aggravate COVID-19 before launching safe clinical trials. To this end, we must rapidly evaluate the COVID-19 prognosis of individuals taking these drugs, through an international effort to mutualize and provide such patient data, in order to respond to this health crisis with a potentially safe, efficient, available and affordable battery of repositioned drugs. The current COVID-19 urgency calls for an international evaluation and test of these drugs as fast as possible.

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Competing Interests

SN, AEP, JB and DC are employees of Pharnext S.A.

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Tables

Table 1. Drugs ongoing COVID-19 preclinical and clinical development according to the World Health Organization, whether they modulate the UPR/Autophagy pathways and the supporting published evidence (listed below by corresponding reference number). For Thalidomide, although the drug does not induce autophagy itself, it enhances the pro-autophagic effect of another drug.

Drug name	UPR/autophagy modulator	Reference(s)
Interferon alfa-2a / 2b	yes	1
Chloroquine	yes	2
Corticosteroids	yes	3, 4
Darunavir	no	-
Cobicistat	no	-
Emtricitabine	yes	5
Tenofovir	yes	6
Ruxolitinib	yes	7
Rapamycin	yes	8
Mycophenolate mofetil	yes	9
FN-β1a (IFNB1)	yes	1
IFN-gamma	yes	10, 11
Ribavirin	yes	12
Lopinavir	yes	13, 14
Ritonavir	yes	15
Baloxavir marboxil	no data	-
Favipiravir	no data	-
Enisamium iodide	no data	-
Arbidol (Umifenovir)	no data	-

Remdesivir	no data	-
IFN-λ1a	yes	16, 17
Thalidomide	yes *	18
Camostat	yes	19
BCX4430	no data	-
Relacatib	no data	-
Lycorine	yes	20
Asterivir	no data	-
UDA/lectin	no data	-
Hiltonol Poly-IC:LC (poly IC)	yes	21
RTD-1 peptide	no data	-
NHC (EIDD-1931) - β-D-N4 - hydroxycytidine	no data	-

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Table 2. Full list of the repositioning candidates (n = 97), and for each drug: the targeted Cov-SARS related pathway, its mechanism of action, its therapeutic category, and the supporting published evidence (listed below by corresponding reference number). In some instances, we kept on our list drugs targeting the same targets (e.g., Temsirolimus, Tacrolimus, Everolimus) because they could have different side-effects profiles. In addition, and especially for further experimental investigations, mechanisms of action mentioned for each drug should be considered with caution since the functional effects of a drug can be influenced by experimental settings, especially the cell type selected for drug screening.

CANDIDATE DRUG	MECHANISM OF ACTION	THERAPEUTIC CATEGORY	REFERENCE(S)
Rapamycin	activator of autophagy	immunosuppressant; anticancer agent	1
Temsirolimus	activator of autophagy	anticancer agent	1
Tacrolimus	activator of autophagy	immunosuppressant	1
Everolimus	activator of autophagy	immunosuppressant; anticancer agent	1
Metformin	activator of autophagy	antidiabetic drug	1
Trehalose	activator of autophagy	dietary supplement	1
Resveratrol	activator of autophagy and mitophagy	dietary supplement	1
Lithium	activator of autophagy	antipsychotic agent; mood stabilizers	1
Carbamazepine	activator of autophagy	antiepileptic drug; analgesic agent	1
Sodium valproate	activator of autophagy	antiepileptic drug; mood stabilizers	1
Verapamil	activator of autophagy	antianginal drug; antiarrhythmic; antihypertensive	1
Nimodipine	activator of autophagy	cardiovascular drug	1
Nitrendipine	activator of autophagy	antihypertensive drug	1
Fluspirilene	activator of autophagy	antipsychotic drug	2
Trifluoperazine	activator of autophagy	antipsychotic drug	2
Nicardipine	activator of autophagy	antianginal drug; antihypertensive drug	2
Tamoxifen	activator of autophagy	hormonal antineoplastic drug	2
Pimozide	activator of autophagy	antipsychotic drug	2
Amiodarone	activator of autophagy	antianginal drug; antiarrhythmic drug	2
Loperamide	activator of autophagy	antidiarrheal drug	2
Rilmenidine	activator of autophagy	antihypertensive drug	3
Clonidine	activator of autophagy	antihypertensive drug; non-narcotic analgesic	3
Calcifediol	activator of autophagy	calcium regulator; vitamin source drug	3
Nitazoxanide	activator of autophagy	anti-infective agent	3
Nortriptyline	activator of autophagy	tricyclic antidepressant	3
Simvastatin	activator of autophagy	anticholesteremic agent	3
Minoxidil	activator of autophagy	antihypertensive drug; vasodilator; antialopecia drug	4
Bromperidol	activator of autophagy	antipsychotic drug	4,5
Metergoline	activator of autophagy	CNS drug; anti-hyperprolactinemic agent	4,5
Chlorpromazine	activator of autophagy	antiemetic drug; antipsychotic drug	4,5

Fludrocortisone	activator of autophagy	mineralocorticoid replacement agent	4,5
Noscapine	activator of autophagy	antitussive drug	4,5
Clemastine	activator of autophagy	anti-allergic agent; antipruritics	4
Deferiprone	activator of autophagy	chelating agent; metabolic disorder drug	6
Temozolomide	activator of autophagy	alkylating antineoplastic drug	7
Gefitinib	activator of autophagy	anticancer drug	7
Sertindole	activator of autophagy	antipsychotic drug	8
Olanzapine	activator of autophagy	antipsychotic drug	8
Fluphenazine	activator of autophagy	antipsychotic drug	8
Methotrimeprazine	activator of autophagy	antipsychotic drug	8
Niclosamide	activator of autophagy	antihelmintic drug	9
Prochlorperazine	activator of autophagy	antiemetic drug; antipsychotic drug	5
Clozapine	modulator of autophagy	antipsychotic drug	8
Baclofen	modulator of autophagy	skelatal muscle relaxant	10
Quinacrine	inhibitor of autophagy	antihelmintic drug; antiprotozoal drug	11,12
Bortezomib	inhibitor of autophagy	anticancer agent	7
Pantoprazole	inhibitor of autophagy	gastrointestinal drug	7
Celecoxib	inhibitor of autophagy	non-narcotic analgesic; anticancer agent; NSAID	7
Azithromycin	inhibitor of autophagy	macrolide antibiotic	4
Verteporfin	inhibitor of autophagy	ocular drug	4
Clomipramine	inhibitor of autophagy	tricyclic antidepressant	4
Chloroquine	inhibitor of autophagy	antiprotozoal drug	3
Hydroxychloroquine	inhibitor of autophagy	antiprotozoal drug	3
CANDIDATE DRUG	**MECHANISM OF ACTION**	**THERAPEUTIC CATEGORY**	**REFERENCES**
Phenylbutyrate	suppressor of UPR stress	urea cycle disorder agent	7,13
Pioglitazone	suppressor of UPR stress	antidiabetic drug	13
Isoproterenol	suppressor of UPR stress	bronchodilator; cardiotonic agent	13
Pravastatin	suppressor of UPR stress	hypolipidemic drug	13
Etanercept	suppressor of UPR stress	antiarthritic drug; immunomodulator	13
Sunitinib	suppressor of UPR stress	anticancer agent	13
Curcumin	suppressor of UPR stress	dietary supplement	13
Exenatide	suppressor of UPR stress	antidiabetic drug	14
Vildagliptin	suppressor of UPR stress	antidiabetic drug	14
Fenofibrate	suppressor of UPR stress	hypolipidemic drug	14
Valsartan	suppressor of UPR stress	antihypertensive drug	14
Losartan	suppressor of UPR stress	antihypertensive drug	14
Olmesartan	suppressor of UPR stress	antihypertensive drug	14
Telmisartan	suppressor of UPR stress	antihypertensive drug; cardiovascular agent	14
Guanabenz	suppressor of UPR stress	antihypertensive drug	15
Trazodone	suppressor of UPR stress	antidepressant	16
Berberine	suppressor of UPR stress	antimicrobial agent; antidiabetic agent	17
Bisoprolol	suppressor of UPR stress	antihypertensive drug; cardiovascular agent	17
Propranolol	suppressor of UPR stress	antihypertensive drug; antianginal drug; antiarrhythmic drug	17
Metoprolol	suppressor of UPR stress	antianginal drug; antihypertensive drug	17

Atorvastatin	UPR stress modulator	anticholesteremic agent	17
Liraglutide	UPR stress modulator	antidiabetic drug; anti-obesity agent	17
Alpha-lipoic acid	UPR stress modulator	nutritional supplement; antioxidants; anti-neuropathic agent	17
Melatonin	UPR stress modulator	CNS drug; anti-insomnia agent	18
Quercetin	UPR stress modulator	dietary supplement	19
CANDIDATE DRUG	**MECHANISM OF ACTION**	**THERAPEUTIC CATEGORY**	**REFERENCES**
Haloperidol	MPTP modulator	antipsychotic drug; antiemetic drug	20, 21, 22
Pentazocine	MPTP modulator	narcotic analgesic	20, 21, 22
Ifenprodil	MPTP modulator	vasodilator	20, 21, 22
Donepezil	MPTP modulator	anti-Alzheimer's drug; CNS drug	20, 21, 22
Carbetapentane	MPTP modulator	antitussive	20, 21, 22
Dextromethorphan	MPTP modulator	antitussive	20, 21, 22
Edaravone	MPTP modulator	neuroprotective agent; anti-ALS drug	23,24
Cyclosporin A	MPTP modulator	immunosuppressant	24, 25, 26
Diazoxide	MPTP modulator	antihypertensive drug; vasodilator	24, 25, 26
Nicorandil	MPTP modulator	antianginal drug	24, 25, 26
Tadalafil	MPTP modulator	impotence drug; antihypertensive drug	24, 25, 26
Perhexiline	MPTP modulator	antianginal drug	24, 25, 26
Carvedilol	MPTP modulator	antihypertensive drug	24, 25, 26
Etifoxine	MPTP modulator	antipsychotic drug	27, 28
Pramipexole	MPTP modulator	antiparkinsonian drug	29
CANDIDATE DRUG	**MECHANISM OF ACTION**	**THERAPEUTIC CATEGORY**	**REFERENCES**
Glyburide	NLRP3 Inflammasome inhibitor	antidiabetic drug	30, 31
Tranilast	NLRP3 Inflammasome inhibitor	anti-inflammatory agent;	31, 32
Anakinra	NLRP3 Inflammasome inhibitor	antiarthritic drug; antiinflammatory agent	31
Thalidomide	NLRP3 Inflammasome inhibitor	anticancer agent; antiemetic drug; immunomodulator	31

Supporting References for Table 2.

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List of Supplementary Figures and Tables

Table S1. List of Open Targets derived Cov-SARS gene-products referenced via their official symbol and ordered alphabetically.

Table S2. IPA pathway enrichment analysis (core analysis/expression analysis). We give the IPA canonical pathway names, the p-value of a Fisher's exact test (which test the enrichment of the pathway in our Cov-SARS gene-products list compared to the null hypothesis of the enrichment of the same pathway in all the genes cataloged by IPA) and the Cov-SARS gene-products which belong to that pathway. Finally, we highlight in yellow pathways related to the UPR/Autophagy pathways.

Table S3. Drug effective against other coronaviruses (SARS-CoV, MERS-CoV), not in clinical development, whether they modulate the UPR/Autophagy pathways and the supporting published evidence.

Figure S1. Summary of the bioinformatics search approach, using the RIG-I-Like receptor signaling pathway as an example.

Figure S2. The four Cov-SARS related pathways putatively involved in the viral infection. The corresponding Cov-SARS proteins are in blue, the non-Cov-SARS master proteins from the IPA canonical pathways are in grey. Between proteins, up-regulation interactions are shown with blue arrows. Down-regulations are shown in red, and modulations (i.e., up or down) are shown in black. The RIG-I-Like receptor signaling module from Figure S1 is shown next to its corresponding pathway.