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Article Title: Repurposing of approved drugs with potential to interact with SARS-CoV-2 receptor

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Abstract

Respiratory transmission is the primary route of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection. Angiotensin I converting enzyme 2 (ACE2) is the known receptor of SARS-CoV-2 surface spike glycoprotein for entry into human cells. A recent study reported absent to low expression of ACE2 in a variety of human lung epithelial cell samples. Three bioprojects (PRJEB4337, PRJNA270632 and PRJNA280600) invariably found abundant expression of ACE1 (a homolog of ACE2 and also known as ACE) in human lungs compared to very low expression of ACE2. In fact, ACE1 has a wider and more abundant tissue distribution compared to ACE2. Although it is not obvious from the primary sequence alignment of ACE1 and ACE2, comparison of X-ray crystallographic structures show striking similarities in the regions of the peptidase domains (PD) of these proteins, which is known (for ACE2) to interact with the receptor binding domain (RBD) of the SARS-CoV-2 spike protein. Critical amino acids in ACE2 that mediate interaction with the viral spike protein are present and organized in the

 doi:10.20944/preprints202004.0369.v2

same order in the PD of ACE1. *In silico* analysis predicts comparable interaction of SARS-CoV-2 spike protein with ACE1 and ACE2. In addition, this study predicts from a list of 1263 already approved drugs that may interact with ACE2 and/or ACE1, potentially interfere with the entry of SARS-CoV-2 inside the host cells and alleviate the symptoms of Coronavirus disease (COVID-19).

Key words: COVID-19, SARS-CoV-2, spike protein, ACE1, ACE2, host-virus interaction, drug repurposing.

Introduction

Coronavirus disease (COVID-19) is an acute infectious disease caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Xie P et al., 2020). Corona viruses are enveloped viruses with a positive-sense single-stranded ribonucleic acid (RNA) genome (Pal M et al., 2020). Respiratory transmission is the primary route of SARS-CoV-2 infection (Harapan H et al., 2020; Wu Y et al., 2020), which shares a similar mechanism with SARS-CoV (caused an outbreak in 2003) in making its way inside the host cells (Wrapp D et al., 2020; Yan R et al., 2020). Angiotensin I converting enzyme 2 (ACE2) is the known cellular receptor for both SARS-CoV and SARS-CoV-2 in human (Wan Y et al., 2020; Yan R et al., 2020). The receptor binding domain (RBD) of the surface spike glycoprotein (S protein) of these viruses interact with the extracellular peptidase domain (PD) of ACE2 using electrostatic as well as van der Waals forces (Xu X et al., 2020; Yan R et al., 2020). Despite their overall similarities in structures, SARS-COV-2 spike protein has evolved with a number of sequence variations and conformational deviations from that of SARS-CoV in the RBD that interact with ACE2 (Wan Y et al., 2020; Yan R et al., 2020). Structural analyses have revealed the key interactions between the SARS-CoV-2 spike protein RBD and ACE2 (Wan Y et al., 2020; Yan R et al., 2020). With its modified spike protein SARS-CoV-2 is assumed to bind human ACE2 more efficiently than SARS-CoV (Wan Y et al., 2020). Binding affinity of the surface spike protein to ACE2 is one of the most important

 doi:10.20944/preprints202004.0369.v2

53 determinants of SARS-CoV-2 infectivity (Wan Y et al., 2020). SARS-CoV-2 might have gained its
54 tremendous capability to infect and transmit in humans through enhanced binding to host
55 receptor.
56
57 ACE2 plays an important role in the maturation of angiotensin, which controls vasoconstriction
58 and blood pressure (Guang C et al., 2012). ACE2 is a homolog of angiotensin converting enzyme
59 (ACE1/ACE) with subtle differences in the active site (Guy JL et al., 2003; Raizada MK and
60 Ferreira AJ, 2007). Whereas ACE2 act as a carboxypeptidase that removes a single amino acid
61 from the C-terminus of susceptible substrates, ACE1 acts as a carboxy-dipeptidase (or, peptidyl-
62 dipeptidase) and removes a C-terminal dipeptide (Clarke NE and Turner AJ, 2012). A recent
63 study reported absent to low level of ACE2 expression in a variety of human lung epithelial cell
64 samples (Aguiar JA et al., 2020). Three bioprojects (PRJEB4337, PRJNA270632 and
65 PRJNA280600) invariably found very low expression of ACE2 in human lungs, whereas ACE1 was
66 found to be more abundantly expressed (Supplementary figures 1-3). Till June 30, 2020 COVID-
67 19 has spread in 216 countries and regions on earth with over 10,185,000 confirmed cases of
68 infection and more than 503,500 deaths (WHO Coronavirus disease (COVID-19) Situation
69 Report-162). Despite an urgent need to find options to help tens of thousands of patients and
70 preclude potential death, there is no decidedly proven therapy to treat COVID-19 (Kruse RL,
71 2020; Xie P et al., 2020). Repurposing of already approved drugs, if available, may be an
72 immediate and promising option to tackle COVID-19. One strategy might be the use of an agent
73 that binds to the site that is recognized by the RBD of SARS-CoV-2 surface spike protein, and
74 thus interfere with its entry into the host cells.
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76 This *in silico* study explored the possibility of SARS-CoV-2 spike protein interaction with ACE1,
77 which is more abundant than ACE2 in human lungs as well as other organs. This study also
78 explored the prospect of repurposing already approved drugs that may interact with ACE2
79 and/or ACE1 to interfere with the entry of SARS-CoV-2 inside the host cells and alongside
80 alleviate symptoms associated with COVID-19.

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Materials and methods

Comparison of X-ray crystallographic structures of ACE1 and ACE2

X-ray crystallographic structures of human ACE1 (PDB ID:1O86) (Natesh R et al., 2003), ACE2 (PDB ID: 6LZG) (Wang QH et al., 2020) and SARS-CoV-2 spike protein (PDB ID: 6VYB) (Walls AC et al., 2020) were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (PDB) (Berman HM et al., 2000). These structures were processed (*i.e.* removal of hetero atoms/HETATM, inhibitor and monomerization) using Discovery Studio Visualizer (v20.1.0.19295) (Dassault Systèmes BIOVIA Corp., 2020). 3D structures were aligned using RaptorX alignment tool (Källberg M et al., 2014). Aligned 3D models were analyzed using CCP4mg (McNicholas S et al., 2011).

Prediction of interaction between ACE1 and SARS-CoV-2 surface spike glycoprotein

Interaction of ACE1 and ACE2 with and SARS-CoV-2 surface spike glycoprotein were predicted using HADDOCK2.2 tool (van Zundert et al., 2016). Predicted protein complexes were analyzed using PyMOL (Delano WL, 2004), CCP4mg (McNicholas S et al., 2011) and Discovery Studio Visualizer (v20.1.0.19295) (Dassault Systèmes BIOVIA Corp., 2020).

In silico assessment of drugs with potential to block SARS-CoV-2 spike protein interaction with ACE1 and ACE2

1263 approved drugs (Supplementary table 1) in 3D SDF format were retrieved from DrugBank (Wishart DS et al., 2018), BindingDB (Gilson MK et al., 2016), e-Drug3D (Douguet D, 2018) databases. Interaction of these drugs with ACE1 and ACE2 were predicted using AutoDock Vina in PyRx (Trott O and Olson AJ, 2010; Dallakyan S and Olson AJ, 2015). These structures were further analyzed using CCP4mg (McNicholas S et al., 2011).

 doi:10.20944/preprints202004.0369.v2

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Results

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Alignment of ACE1 and ACE2 X-ray crystallographic structures

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Alignment of X-ray crystallographic structures of ACE1 and ACE2 reveals striking similarities in the tertiary structures of their peptidase domains (Figure 1A). Peptidase domain of ACE2 is known to interact with the RBD of SARS-CoV-2 spike protein. Amino acid residues in this region of ACE2 (Gln24, Lys31, Glu35, Asp38, Tyr41, Gln42, Met82, Lys353, Arg357) that interact with the spike protein (Wan Y et al., 2020; Yan R et al., 2020) are also present (or, amino acids with similar polarity and structures) in the peptidase domain of ACE1 (Figure 1B). Although it is not obvious in the aligned primary sequences, these important amino acid residues in the PD of ACE1 and ACE2 are present in the same order in their tertiary structures (Figure 1B).

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Predicted interactions of SARS-CoV-2 surface spike glycoprotein with ACE1 and ACE2

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Receptor-ligand interaction analysis using molecular docking technique could predict the amino acids at the interface of ACE1 and ACE2 peptidase domains with the RBD of the spike protein (Figure 2). Although amino acid residues at the interface of ACE2 and spike proteins are already known from X-ray crystallographic analysis, this *in silico* prediction was performed as a control to assess the performance of the docking process. This also allowed the direct comparison between the interacting sites of ACE1 and ACE2 with the RBD of SARS-CoV-2 spike protein based on a common platform. The amino acid residues of ACE2 at the interface with the SARS-CoV-2 spike protein matched to the previous reports (Wan Y et al., 2020; Yan R et al., 2020). Similar residues were observed in the predicted interactions between ACE1 and the spike protein. Earlier studies have reported predominantly electrostatic interactions along with van der Waals forces between ACE2 and the RBD of spike protein (Yan R et al., 2020). The predicted interactions of ACE1 and ACE2 with the spike protein involve similar forces (Table 1).

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Drugs with potential to block SARS-CoV-2 spike protein interaction with ACE1 and ACE2

A total of 1263 approved drugs (Supplementary table 1) were assessed for potential interaction with ACE1 and ACE2 at regions that overlap with the predicted and already known binding sites for the receptor binding domain of the SARS-CoV-2 spike protein, respectively. Angiotensin II is a natural substrate of ACE2 (Clarke NE and Turner AJ, 2012). Molecular docking with AutoDock Vina predicted an interaction of angiotensin II with the peptidase domain of ACE2 with a binding energy of -6.0 kcal/mol. Drugs that bind to overlapping regions in the peptidase domains of ACE1 and/or ACE2 and, therefore, may perturb interaction with the SARS-CoV-2 spike protein, and has more stable binding than the native substrate (*i.e.,* predicted to release energy > 6.0 kcal/mol) and may provide additional health benefits to the COVID-19 patients by alleviating symptoms are listed in table 2. Table 2 also provides brief description of the drugs along with their current approval status. Some drugs have multiple statuses as these have been approved for certain condition(s), but are currently on clinical trials for one or more different indications. The listed drugs (Table 2) belong to diverse categories such as antiviral, anti-bacterial, anti-fungal, anti-hypertensive, anti-coagulant, angiotensin II analog, immunosuppressant, anti-allergic and anti-diarrheal among others. Seven of these drugs (Avatrombopag, ceruletide, natamycin, *pibrentasvir*, posaconazole, reserpine, and rifapentine) appear to bind to SARS-CoV-2 interacting sites in the PD regions of both ACE1 and ACE2. Few of these predicted interactions are shown in figure 3 and 4.

In addition to those listed in table 2, there are other antiviral drugs (supplementary table 2) with potential binding abilities to ACE1 and/or ACE2. Except baloxavir marboxil, indinavir, maraviro, nelfinavir and *pibrentasvir, the* other antiviral drugs bind to sites in ACE1 and ACE2 that do not coincide with the binding of SARS-CoV-2 spike protein. A few of these antivirals are already in clinical trials as treatment options for COVID-19 (Harapan H et al., 2020; Jiang F et al., 2020; Xie P et al., 2020). Among these bictegravir, indinavir and remdesivir bind to both ACE1 and ACE2 with >7 kcal/mol energy release.

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Discussion

Interaction between ACE1 and SARS-CoV-2 surface spike glycoprotein

Infection with SARS-CoV-2 affects multiple organs (including lung, liver, kidney, intestine and muscle) (Jiang F et al., 2020; Xie P et al., 2020). Although previous studies have reported abundant expression of ACE2 on ciliated cells of the airway epithelium and alveolar type II cells in human (Hamming I et al., 2004), a recent study reported absent to low expression of ACE2 in human lung epithelial cells (Aguiar JA et al., 2020). ACE1 appears to be more abundantly expressed in the COVID-19 affected organs (lung, liver, kidney, intestine and muscle) (Sayers EW et al., 2020). In fact, ACE1 has a wider and more abundant tissue distribution compared to ACE2 (Sayers EW et al., 2020).

Based on the similarities to SARS-CoV spike protein, it has been suggested that SARS-CoV-2 also exploits ACE2 to mediate infection in human (Wan Y et al., 2020). Lys31 and Lys 353 in ACE2 are considered as critical amino acid residues in the peptidase domain of ACE2 to mediate interaction with the SARS-CoV-2 spike protein (Wan Y et al., 2020). A similar configuration of these and other important amino acid residues is present in the tertiary structure of human ACE1 enzyme (Figure 1). Alike the reported interactions between SARS-CoV/SARS-CoV-2 and ACE2 (Wan Y et al., 2020; Yan R et al., 2020), the predicted interface between SARS-CoV-2 and ACE1 maintains a highly polar environment (Figure 2 and table 1). In fact, the predicted interaction model suggests the ACE1 and SARS-CoV-2 spike protein complex to be electrostatically more stable than the ACE2 and spike protein complex. As SARS-CoV-2 spike protein has evolved to bind ACE2 with higher affinity than the spike protein of SARS-CoV (Wrapp D et al., 2020) and gained more power to transmit and infect humans, mere speculation based on sequence comparison with SARS-CoV might not be adequate to define ACE2 as its sole receptor.

 doi:10.20944/preprints202004.0369.v2

Repurposing of approved drugs to block SARS-CoV-2 spike protein interaction with ACE1 and ACE2

Drug repurposing is the discovery of novel therapeutic applications for already approved drugs. This approach holds much promise as it helps to circumvent preclinical and optimization processes as well as reduce time and costs associated with drug discovery (March-Vila E et al., 2017). Molecular docking is one of the common computational approaches to repurpose established drugs towards novel therapeutic targets based on their structural complementarity (Pinzi L and Rastelli G, 2019). This approach, however, has limitations particularly arising from the use of approximate scoring functions and possible imperfect binding prediction (March-Vila E et al., 2017). Despite these limitations, molecular docking is a well-established and experimentally validated approach for predicting drug-target associations (March-Vila E et al., 2017). This technique has been successfully exploited in repurposing drugs (Kinnings SL et al., 2009; Li YY et al., 2011; Dakshanamurthy S et al., 2012). Over the last two decades, over 60 different molecular docking tools have been developed for academic and/or commercial uses. In a comparative study among these tools, AutoDock Vina, GOLD, and MOE-Dock predicted top ranking poses with best scores (Pagadala NS et al., 2017). AutoDock Vina applies a knowledge-based scoring function with a Monte Carlo sampling technique and the Broyden-Fletcher-Goldfarb-Shanno (BFGS) method for local optimization (Trott O and Olson AJ, 2010). Their simulation results showed a significant improvement in both prediction accuracy and docking time (Trott O and Olson AJ, 2010; Pagadala NS et al., 2017)

In this study, drugs were docked onto ACE1 and ACE2 with AutoDock Vina (Trott O and Olson AJ, 2010). Among the 1263 tested drugs, 12 appear to interact with ACE1, 22 with the ACE2 and 7 with both (with the release of >6.0 kcal/mol- the predicted binding energy of angiotensin II with ACE2) in the regions that overlap with the binding of the receptor binding domain of the SARS-CoV-2 spike protein. Saralasin (an angiotensin II analog and a highly specific competitive inhibitor of angiotensin II (Kim S et al., 2019)) was predicted to bind at the PD of ACE2, but not ACE1, with higher affinity than angiotensin II (Table 2).

 doi:10.20944/preprints202004.0369.v2

The most common symptoms of COVID-19 include fever, dry cough, breathing difficulties, chest pain, fatigue and myalgia (pain in muscles) (Harapan H et al., 2020). The other less common symptoms include abdominal pain, diarrhea, nausea, and vomiting (Harapan H et al., 2020). COVID-19 patients also exhibit neurological symptoms such as dizziness, headache, anosmia (smell blindness), impaired consciousness, etc (Ahmad and Rathore, 2020; Xie P et al., 2020). In severe cases, SARS-CoV-2 can lead to acute respiratory distress syndrome (ARDS), septic shock, metabolic acidosis, coagulation dysfunction, and eventually multiple organ failure (Harapan H et al., 2020; Xie P et al., 2020). No specific antiviral drugs have been confirmed decidedly effective against SARS-CoV-2 yet (Harapan H et al., 2020; Jiang F et al., 2020). At present, COVID-19 patients are given supportive care and symptomatic treatments with anti-inflammatory drugs and antibiotics for secondary infections (Harapan H et al., 2020; Jiang F et al., 2020).

Acute respiratory distress syndrome (ARDS) is the primary cause of death with COVID-19 (Li X et al., 2020). ARDS is characterized by rapid onset of widespread inflammation in the lungs which leads to respiratory failure. It is invoked by a “cytokine storm” (Li X et al., 2020) invoked by the SARS-CoV-2 stimulated systemic inflammatory response with an insurgence of pro-inflammatory cytokines (including IL-1β, IL-2,IL-6, IL7, IL-10, TNF-α, GSCF, MCP1, etc) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) (Harapan H et al., 2020; Jiang F et al., 2020). Patients with worse outcomes and multi-organ failure (lungs, heart, kidneys and liver among others), in particular, have significantly higher levels of IL-2, IL-6, IL-7, IL-10, GSCF, IP10, MCP1, and TNF-α (Harapan H et al., 2020; Jiang F et al., 2020; Xie P et al., 2020). Celecoxib and loratadine are two non-steroidal anti-inflammatory drugs that bind to the PD of ACE2 (Table 2). Sirolimus (a strong immunosuppressant), on the other hand, appears to bind to the PD of ACE1. In toxicity studies, sirolimus and loratadine have been shown to rarely cause clinically apparent liver injury (Kim S et al., 2019). These may serve as a two edged sword by blocking the binding of SARS-CoV-2 to the host receptor as well as subsiding inflammatory responses.

 doi:10.20944/preprints202004.0369.v2

Thrombotic complications (including thrombocytopenia, prolonged prothrombin time, and disseminated intravascular coagulation) have emerged as a critical issue in COVID-19 patients (Giannis D et al., 2020). Avatrombopag is a small-molecule thrombopoietin receptor agonist which increases platelet number, but does not cause platelet activation (Wishart DS et al., 2018; Kim S et al., 2019). It appears to bind at sites that overlap with the SARS-Cov-2 RBD interactions in the PD of both ACE1 and ACE2. Lusutrombopag is another anti-thrombocytopenic agent that binds to ACE2 in the PD region where the spike protein interacts. Two anti-coagulants eptifibatide and betrixaban dock onto the spike protein binding sites in ACE1 and ACE2, respectively. Among these avatrombopag, lusutrombopag and betrixaban have been reported to cause unproven but suspected rare cases of clinically apparent liver injury in toxicity assays (Kim S et al., 2019).

Pibrentasvir is an antiviral drug that seems to interact with both ACE1 and ACE2 in the PD region at sites that coincide with SARS-CoV-2 spike protein binding. Pibrentasvir is indicated for the treatment of infection mediated by Hepatitis C Virus (HCV)- a positive-strand RNA virus (Patel AB and Verma A, 2020). Several other antiviral drugs (Baloxavir marboxil, doravirine, indinavir, maraviroc, and nelfinavir) might interact only with ACE2 in the PD region and interfere with SARS-CoV-2 binding. Except indinavir, the others (Pibrentasvir, baloxavir marboxil, doravirine, maraviroc, and nelfinavir) have been shown to cause rare cases of hepatotoxicity in toxicological studies (Kim S et al., 2019).

Other drugs listed in table 2 may find purposes for other minor symptoms in COVID-19 patients. For example, loperamide and rifamycin are used as anti-diarrheal drugs without evidence of liver injury in toxicity studies. Secondary bacterial and/or fungal infection is an important factor affecting mortality in COVID-19 patients (Rawson TM et al., 2020; Zhou P et al., 2020). Although several anti-bacterial drugs (*Alatrofloxacin, azithromycin,* cefoperazone, rifapentine and

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vancomycin) might bind to the PD of ACE1 and/or ACE2 to obstruct SARS-CoV-2 binding, only rifapentine and vancomycin are unlikely to cause toxicity (Kim S et al., 2019). Vancomycin is used for the treatment of serious severe infections caused by susceptible strains of methicillin-resistant (beta-lactam-resistant) *Staphylococci* (Kim S et al., 2019). It is also used to treat *Clostridium difficile* associated diarrhea and enterocolitis caused by *Staphylococcus aureus* (Kim S et al., 2019). Among the anti-fungal drugs (Amphotericin B, anidulafungin, butenafine, candicidin, natamycin, nystatin, and posaconazole) that bind to the PD of ACE1 and/or ACE2 to affect SARS-CoV-2 binding, only anidulafungin and nystatin are not likely to cause clinically apparent hepatotoxicity (Kim S et al., 2019). Nystatin has broad-spectrum fungicidal and fungistatic activity against a number of yeasts and fungi, most notably *Candida* species, while Anidulafungin is used in the treatment of the Candidemia and other forms of *Candida* infections (intra-abdominal abscess, and peritonitis), *Aspergillus* infections, esophageal candidiasis and as an alternative for oropharyngeal canaidiasis (Wishart DS et al., 2018; Kim S et al., 2019). Both of these antifungal drugs appear to interact at the PD of ACE1 that coincide with spike protein binding sites. Posaconazole binds to the region of PDs in ACE1 and ACE2 in a manner that may impede the binding of SARS-CoV-2. Posaconazole is apparently a non-toxic drug. Although treatment with posaconazole causes transient elevations in serum aminotransferase levels in 2% to 12% of patients; these elevations are usually mild, asymptomatic and self-limited and rarely require discontinuation of the medication (Kim S et al., 2019).

There are several other drugs (Table 2) that bind to the PDs of ACE1 and/or ACE2 with potential to interfere with SARS-CoV-2 binding. These include anti-hypertensive (*Azilsartan kamedoxomil,* deserpidine, and reserpine), statins (Pitavastatin and *simvastatin*), antimigraine (*Dihydroergotamine), antiasthmatic (Zafirlukast), antihistamine (*Loratadine*), cardiac glycoside (Digoxin) and anti-malarial (*Mefloquine*).* Mefloquine (an anti-malarial drug) may compete with spike protein for binding to ACE2, rather than Hydroxychloroquine, which binds to other region of ACE2 (Table 2 and supplementary table 1). *These above mentioned drugs might find applications to tackle secondary symptoms or complications in COVID-19. All these drugs may*

play dual roles by blocking the binding of virus to the receptor as well as alleviate other complications.

Several established antiviral and other drugs have been in clinical trials to treat COVID-19. These include remdesivir, lopinavir, ritonavir, ribavirin, oseltamivir, hydroxychloroquine, dexamethasone, etc (Harapan H et al., 2020; Jiang F et al., 2020; Xie P et al., 2020). Among these remdesivir seems to bind with high affinities to both ACE1 and ACE2 at sites other that do not coincide with SARS-CoV-2 binding (Supplementary table 1). Binding affinities of 40 different anti-viral drugs along with their targets and intended applications are given in supplementary table 2.

No specific therapeutics for COVIDD-19 is yet available. A better understanding of the underlying pathobiology will be useful in finding a cure (Zhang H et al., 2020). Till then, already available potential options might be explored to bring comfort to the world.

Conflict of interests: There is no known conflict of interest.

Author contributions: AAS: conceptualization of project, data curation, data analysis, writing – original draft, review & editing.

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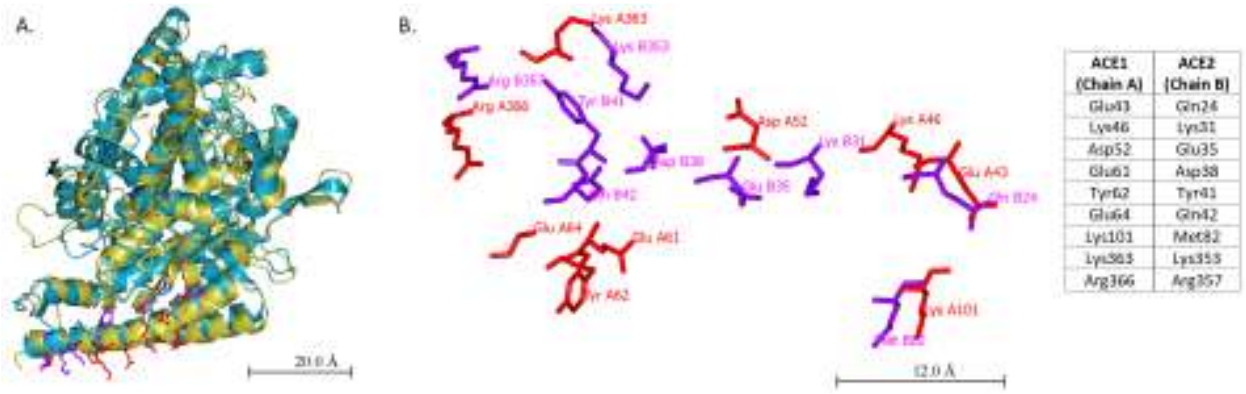

Figure 1: Alignment of X-ray crystallographic structures of ACE1 (PDB ID:1O86) and ACE2 (PDB ID: 6LZG). A. SARS-CoV-2 spike protein binding region (RBD) of ACE1 (in dark cyan) and ACE2 (in gold) have similar tertiary structures in the PD region. B. Glu43, Lys46, Asp52, Glu61, Tyr62, Glu64, Lys101, Lys363 and Arg366 in ACE1 (in red) are positioned in similar order to Gln24, Lys31, Glu35, Asp38, Tyr41, Gln42, Met82, Lys353 and Arg357 in ACE2 (in purple). Chain A and B represent ACE1 and ACE2, respectively.

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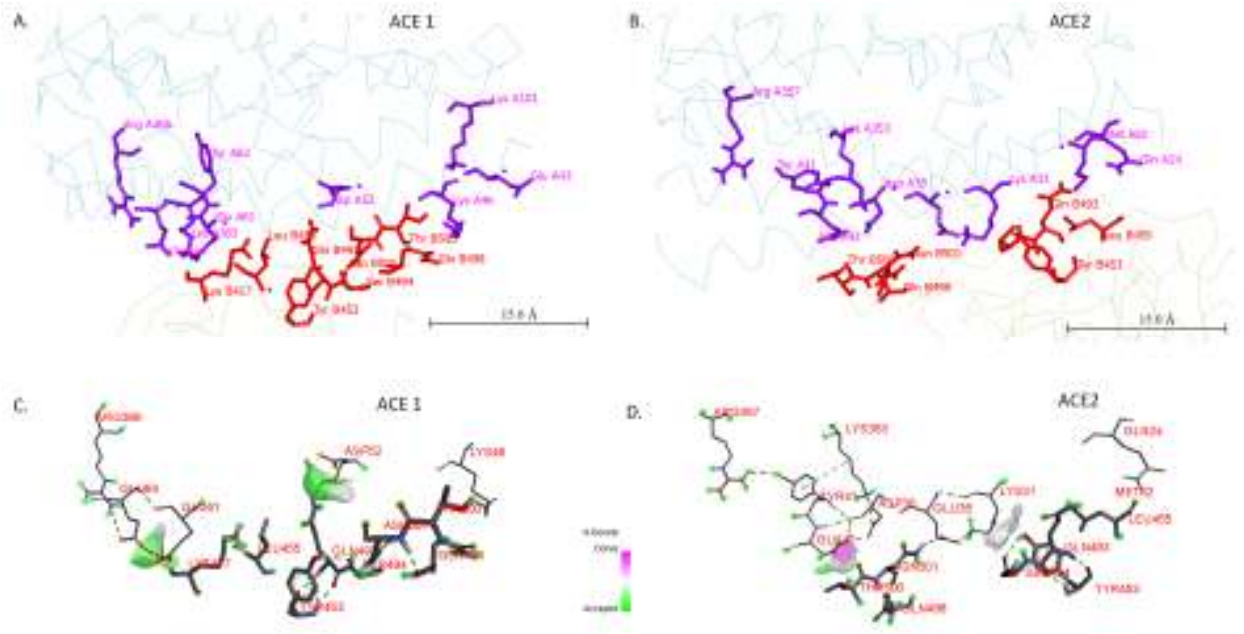

Figure 2: Predicted interactions of ACE1 and ACE2 with the RBD of SARS-CoV-2 surface spike protein. A and B. Amino acid residues at the interface of ACE1 and ACE2 PD regions (in purple) with the RBD of SARS-CoV-2 spike protein (in red). Chain A and B represent ACE1/ACE2 and spike protein, respectively. C and D. Specific interactions of ACE1 and ACE2 PD regions with the RBD of SARS-CoV-2 spike protein.

Figure 3: Drugs with potential to block SARS-CoV-2 surface glycoprotein interaction with ACE2. Interacting amino acid residues in ACE2 are shown in purple and drug molecules are shown as spheres. Chain A represents ACE2 enzyme.

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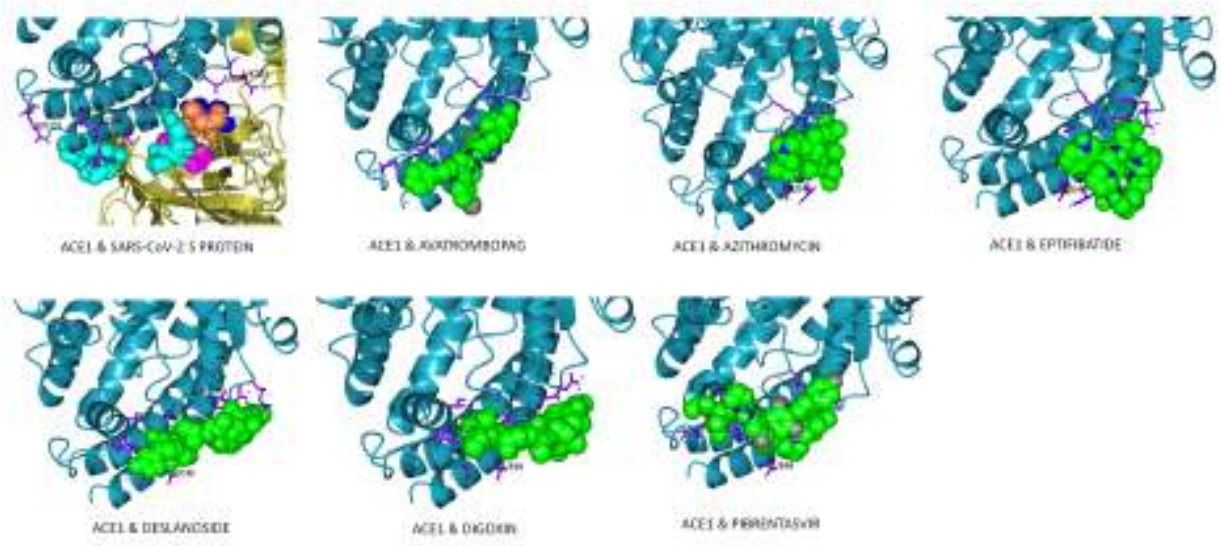

Figure 4: Drugs with potential to block SARS-CoV-2 surface glycoprotein interaction with ACE1. Interacting amino acid residues in ACE are shown in purple and drug molecules are shown as spheres. Chain A represents ACE1 enzyme.

Table 1: Predicted interactions of ACE1 and ACE2 with the RBD of SARS-CoV-2 spike protein.

Feature	ACE1 and spike protein	ACE2 and spike protein
Z-Score	-1.2	-1.4
RMSD from the overall lowest-energy structure	1.7 ± 0.3	1.1 ± 0.7
Van der Waals energy	-48.8 ± 3.3	-59.6 ± 4.7
Electrostatic energy	-319.7 ± 36.8	-122.1 ± 46.9
Desolvation energy	87.4 ± 7.4	33.8 ± 14.9
Restraints violation energy	39.4 ± 25.03	22.5 ± 14.15

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465 **Table 2:** List of drugs that bind to ACE and ACE2 PD regions and has more stable binding than
466 angiotensin II (*i.e.,* predicted to release energy > 6.0 kcal/mol).

Drug	Binding energy (kcal/mol)		Status (Wishart DS et al., 2018)	Category of drug	Description (Wishart DS et al., 2018; Kim S et al., 2019)
	Human ACE1	Human ACE2			
ALATROFLOXACIN	_	-6.4	Approved, Withdrawn	Antibiotic	It is a fluoroquinolone antibiotic.
AMPHOTERICIN B	-7.1	_	Approved, Investigational	Antifungal	Used to treat potentially life threatening fungal infections.
ANIDULAFUNGIN	-6.6	_	Approved, Investigational	Antifungal	An antifungal drug used in the treatment of the following fungal infections: Candidemia and other forms of Candida infections (intra-abdominal abscess, and peritonitis), Aspergillus infections, and esophageal candidiasis. Also considered an alternative treatment for oropharyngealcanaidiasis.
AVATROMBOPAG	-6.9	-7.4	Approved, Investigational	Anti-thrombocytopenic	A small-molecule thrombopoietin receptor agonist which increases platelet number, but does not cause platelet activation.
AZILSARTAN KAMEDOXOMIL	_	-6.4	Approved, Investigational	Antihypertensive	An angiotensin II receptor antagonist indicated for the treatment of mild to moderate essential hypertension.
AZITHROMYCIN	-6.6	_	Approved	Antibiotic	A broad-spectrum macrolide antibiotic with a long half-life, which is primarily used for the treatment of respiratory, enteric and genitourinary infections.
BALOXAVIR MARBOXIL	_	-6.4	Approved, Investigational	Antiviral	An antiviral drug for the treatment of influenza A and influenza B infections.
BETRIXABAN	_	-6.5	Approved, Investigational	Anticoagulant	A non-vitamin K oral anticoagulant whose action is driven by the competitive and reversible inhibition of the factor Xa.
BUTENAFINE	_	-6.1	Approved	Antifungal	A synthetic benzylamine antifungal agent.
CANDICIDIN	_	-6.3	Approved, Withdrawn	Antifungal	An antibiotic active against some fungi of the genus Candida.
CEFOPERAZONE	_	-6.5	Approved, Investigational	Antibiotic	A semisynthetic broad-spectrum third-generation antiobiotic effective against Pseudomonas infections. It is used in the treatment of various bacterial infections, including respiratory tract infections, peritonitis, skin infections, endometritis, and bacterial septicemia.
CELECOXIB	_	-6.5	Approved, Investigational	Anti-inflammatory	A selective nonsteroidal anti-inflammatory drug (NSAID) which is known for its decreased risk of causing gastrointestinal bleeding

					compared to other NSAIDS.
CERULETIDE	-6.2	-6.2	Approved	Others	Exerts stimulatory effects on the gastric, biliary, and pancreatic secretion, as well as on certain smooth muscles.
DESERPIDINE	_	-6.6	Approved	Antihypertensive	An antipsychotic and antihypertensive agent used for the control of high blood pressure and for the relief of psychotic behavior.
DESLANOSIDE	-7.5	_	Approved	Others	A cardiotonic glycoside used for the treatment and management of congestive cardiac insufficiency, arrhythmias and heart failure
DIGOXIN	-7.7	_	Approved	Others	A commonly used agent to manage atrial fibrillation and the symptoms of heart failure.
DIHYDROERGOTAMINE	_	-7.4	Approved	Anti-migraine	Vasoconstrictor, specifically for the therapy of migraine disorders.
DORAVIRINE	_	-6.5	Approved	Antiviral	An HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) intended to be administered in combination with other antiretroviral medicines.
EPTIFIBATIDE	-7.4	_	Approved, Investigational	Anticoagulant	Synthetic cyclic hexapeptide that inhibits platelet aggregation.
ICATIBANT	-7.3	_	Approved, Investigational	others	A synthetic peptidomimetic drug that is used in acute attacks of hereditary angioedema.
INDINAVIR	_	-7.1	Approved	Antiviral	A potent and specific HIV protease inhibitor that appears to have good oral bioavailability.
LOPERAMIDE	_	-6.3	Approved	Antidiarrheal	Long-acting synthetic antidiarrheals, which has no effect on the adrenergic system or central nervous system, but may antagonize histamine and interfere with acetylcholine release locally.
LORATADINE	_	-6.3	Approved, Investigational	Antihistamine	A second generation antihistamine used to manage symptoms of allergic rhinitis.
LUSUTROMBOPAG	_	-6.5	Approved, Investigational	Anti-thrombocytopenic	An orally bioavailable thrombopoietin receptor (TPOR) agonist, which is indicated for the treatment of thrombocytopenia in adults with chronic liver disease
MARAVIROC	_	-6.3	Approved, Investigational	Antiviral	A chemokine receptor antagonist drug that is designed to act against HIV by interfering with the interaction between HIV and CCR5
MEFLOQUINE	_	-6.1	Approved, Investigational	Antimalarial	A phospholipid-interacting antimalarial drug.
NATAMYCIN	-7.4	-6.2	Approved	Antifungal	It is used for a variety of fungal infections, mainly topically.
NELFINAVIR	_	-6.2	Approved	Antiviral	A potent HIV-1 protease inhibitor.
NYSTATIN	-6.8	_	Approved	Antifungal	An antifungal drug that has broad-spectrum fungicidal and fungistatic activity against a number of yeasts

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					and fungi, most notably Candida species
PIBRENTASVIR	-7.5	-6.6	Approved, Investigational	Antiviral	A direct acting antiviral agent and Hepatitis C virus (HCV) NS5A inhibitor that targets viral RNA replication and viron assembly.
PITAVASTATIN	_	-6.1	Approved	Statin	A lipid-lowering drug belonging to the statin class of medications.
POSACONAZOLE	-7.8	-6.2	Approved, Investigational	Antifungal	An antifungal drug that is used to treat invasive infections by Candida species and Aspergillus species in severely immunocompromised patients.
RESERPINE	-6.3	-6.4	Approved, Investigational	Antihypertensive	Used as an antihypertensive and an antipsychotic drug.
RIFAMYCIN	-6.3	_	Approved, Investigational	Antidiarrheal	It is indicated for the treatment of adult patients with travelers' diarrhea caused by noninvasive strains of E. coli.
RIFAPENTINE	-6.4	-6.5	Approved, Investigational	Antibiotic	An antibiotic drug used in the treatment of tuberculosis.
RIFAXIMIN	-6.6	_	Approved, Investigational	Antidiarrheal	A semisynthetic, rifamycin-based non-systemic antibiotic used in treatment of traveller's diarrhea caused by *E. coli,*reduction in risk of overt hepatic encephalopathy recurrence as well as diarrhea-predominant irritable bowel syndrome (IBS-D) in adults.
SARALASIN	_	-7.1	Investigational	Angiotensin II analog	An octapeptide analog of angiotensin II.
SIMVASTATIN	_	-6.4	Approved	Statin	Used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver.
SIROLIMUS	-7.5	_	Approved, Investigational	Immunosuppressant	A potent immunosuppressant and possesses both antifungal and antineoplastic properties.
VANCOMYCIN	-7.7	_	Approved	Antibiotic	Antibacterial compound that inhibits bacterial cell wall assembly.
ZAFIRLUKAST	_	-7.1	Approved, Investigational	Anti-asthmatic	Used for the treatment of asthma, often used in conjunction with an inhaled steroid and/or long-acting bronchodilator.

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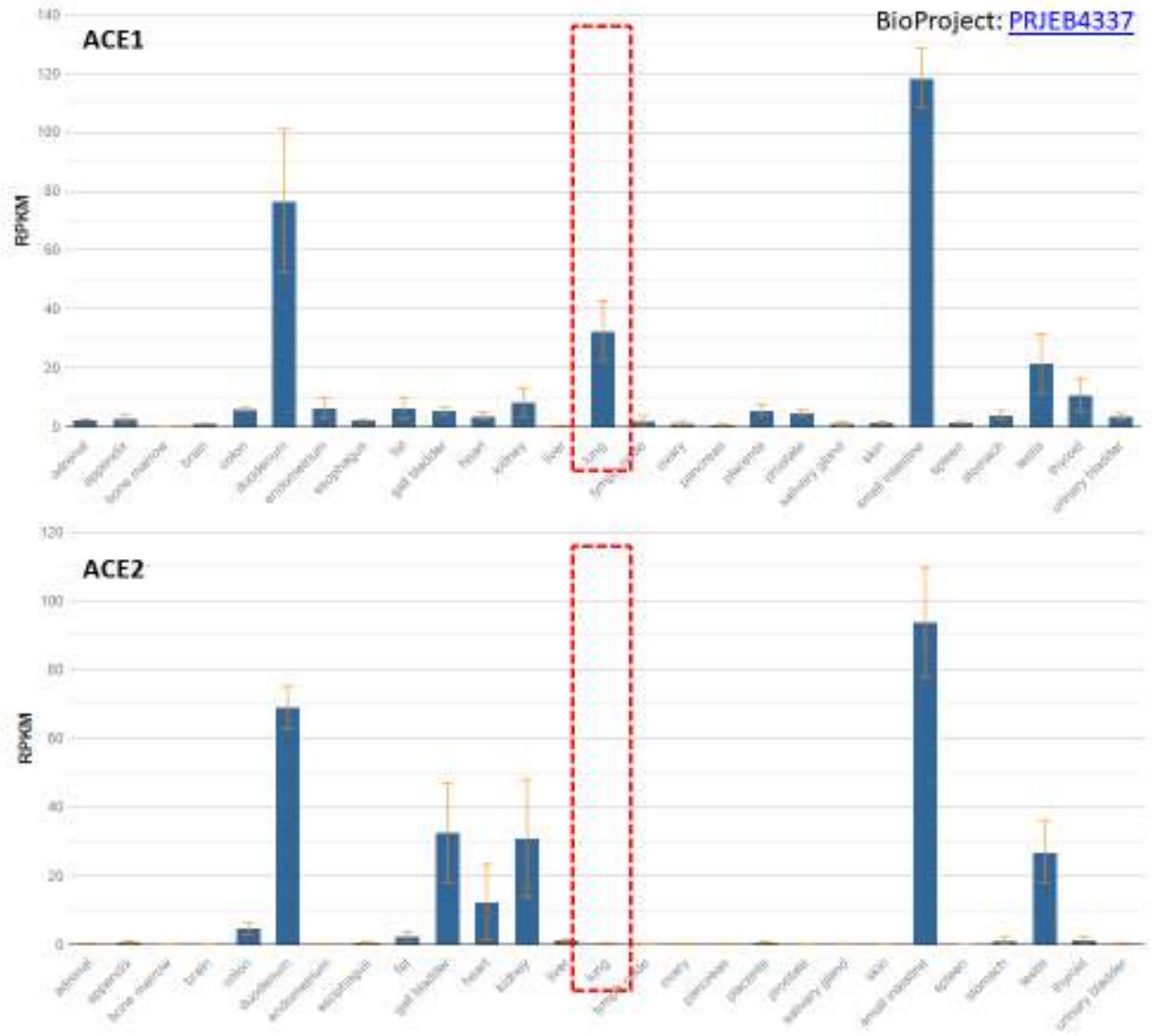
Supporting Information



Supplementary figure 1: Expression of ACE1 and ACE2 in different human tissues (BioProject accession number: PRJEB4337) (Sayers EW et al., 2020). RNA-seq was performed with tissue samples from 95 human individuals representing 27 different tissues in order to determine tissue-specificity of all protein-coding genes. The plots are adopted from (Sayers EW et al., 2020). RPKM- Reads Per Kilobase of transcript, per Million mapped reads.

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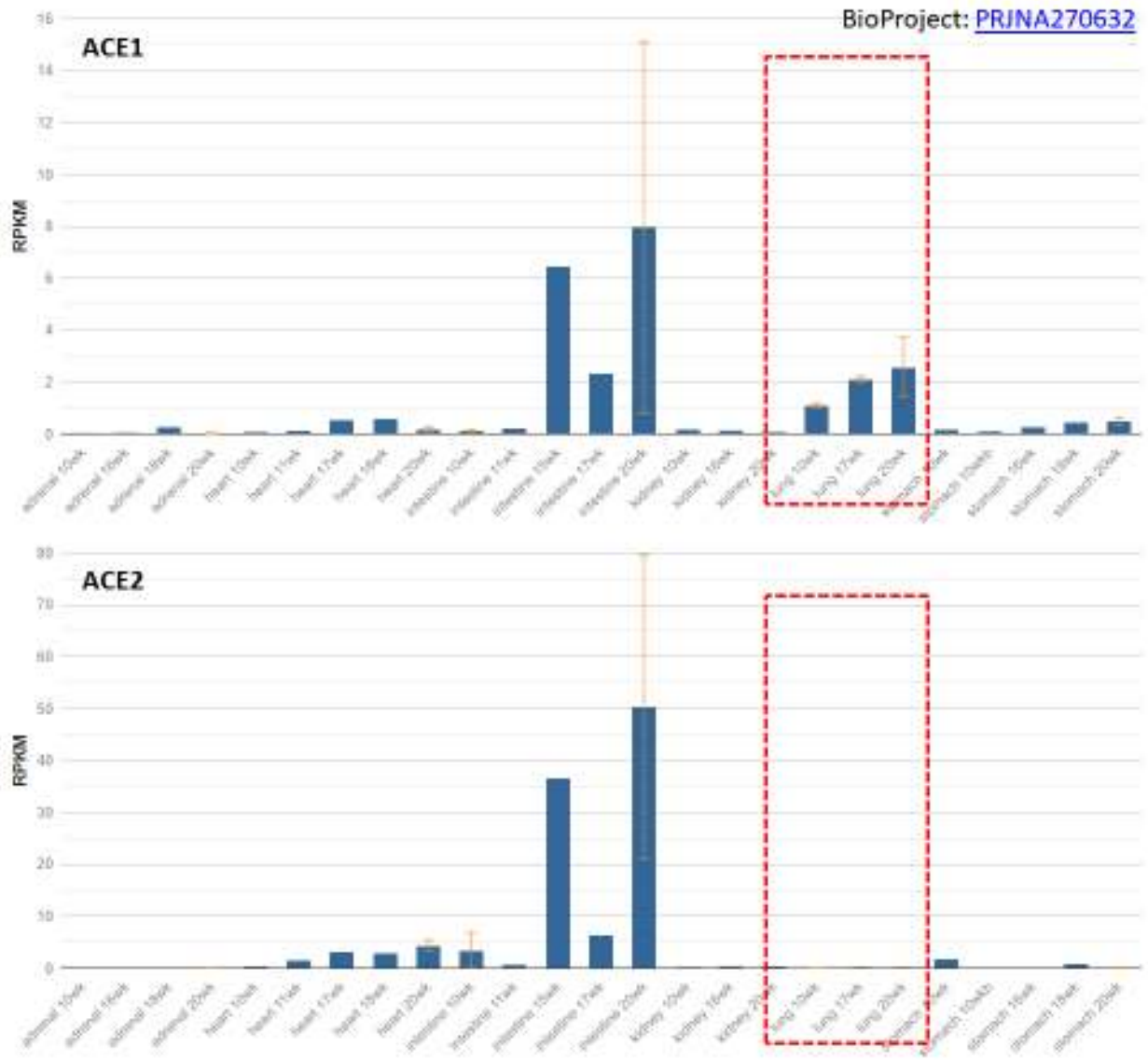

Supplementary figure 2: Expression of ACE1 and ACE2 in different human tissues (BioProject accession number: PRJNA270632) (Sayers EW et al., 2020). 35 human fetal samples from 6 tissues (3-7 replicates per tissue) collected between 10 and 20 weeks gestational time were sequenced using Illumina TruSeq Stranded Total RNA. The plots are adopted from (Sayers EW et al., 2020). RPKM- Reads Per Kilobase of transcript, per Million mapped reads.

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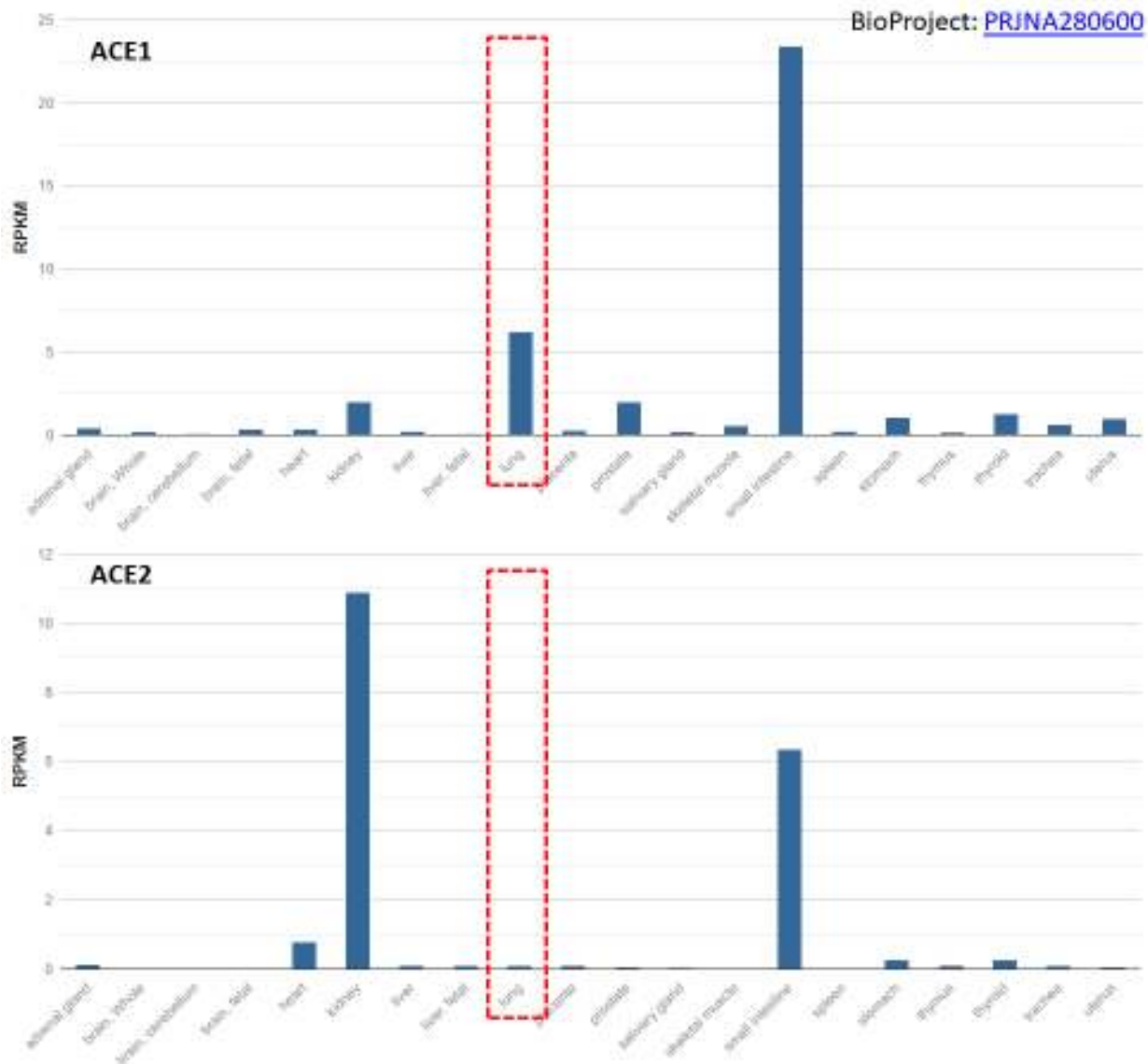

Supplementary figure 3: Expression of ACE1 and ACE2 in different human tissues (BioProject accession number: PRJNA280600) (Sayers EW et al., 2020). Transcription profiling was performed by high throughput Illumina sequencing of individual and mixture of 16 human tissues RNA. The plots are adopted and modified from (Sayers EW et al., 2020). RPKM- Reads Per Kilobase of transcript, per Million mapped reads.

Supplementary table 1: List of drugs and their binding energies to ACE1 and ACE2.

Supplementary table 2: List of anti-viral drugs that bind to ACE1 and ACE2 (Drugs listed in table 2 are shown in bold italic fonts).