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Title: Repurposing of approved drugs with potential to block SARS-CoV-2 surface glycoprotein interaction with host receptor

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Repurposing of approved drugs with potential to block SARS-CoV-2 surface glycoprotein interaction with host receptor

Abstract

Background: Respiratory transmission is the primary route of SARS-CoV-2 infection. Angiotensin I converting enzyme 2 (ACE2) is the known receptor of SARS-CoV-2 spike glycoprotein for entry into human cells. A recent study reported absent to low ACE2 promoter activity in a variety of human lung epithelial cell samples. Three bioprojects (PRJEB4337, PRJNA270632 and PRJNA280600) invariably found abundant expression of ACE in human lungs compared to very low expression of ACE2. **Methods:** *In silico* tools were applied to assess potential interaction of SARS-CoV-2 surface spike protein with human ACE as well as predict the drugs that may block SARS-CoV-2 interaction with host receptor. **Results:** Although it is not obvious from the primary sequence alignment of ACE2 and its homolog ACE (also known as ACE1), comparison of X-ray crystallographic structures show striking similarity in the regions of these proteins which is known (for ACE2) to interact with the receptor binding domain (RBD) of SARS-CoV-2 spike protein. Critical amino acids that mediate interaction with the viral spike protein in ACE2 are organized in the same order in ACE. *In silico* analyses predicts comparable interaction of SARS-CoV-2 spike protein with ACE2 and ACE. In addition, this study predicts and selects already approved drugs from a list of 1263, which may interfere with the binding of SARS-CoV-2 spike glycoprotein to ACE2 and/or ACE.

Key words: COVID-19; SARS-CoV-2; Spike protein; ACE; ACE2.

1. Introduction

Coronavirus disease-19 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Corona viruses are enveloped viruses with a positive-sense, single-stranded ribonucleic acid (RNA) genome [1]. Respiratory transmission is the primary route of SARS-CoV-2 infection [2]. SARS-CoV-2 shares a similar mechanism with

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SARS-CoV (caused an outbreak in 2003) in making its way to the host cell [3,4]. Angiotensin I converting enzyme 2 (ACE2) is the known cellular receptor for both SARS-CoV and SARS-CoV-2 in human [3,5]. 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 [3,6]. Despite the overall similarity in structure, SARS-COV-2 spike protein has evolved with a number of sequence variations and conformational deviations from that of SARS-CoV in the RBD at the interface with ACE2 [3,5]. Structural analyses have revealed key atomic-level interactions between the SARS-CoV-2 spike protein RBD and ACE2 [3,5]. Binding ability of SARS-CoV-2 has evolved [5]. SARS-CoV-2 is assumed to bind human ACE2 more efficiently using its modified spike protein than the SARS-CoV [5]. Binding affinity of the spike protein to ACE2 is one of the most important determinants of SARS-CoV-2 infectivity [5]. SARS-CoV-2 might have gained its high capability to infect and transmit in humans through enhanced binding.

The primary physiological role of ACE2 is in the maturation of angiotensin, which controls vasoconstriction and blood pressure [7]. ACE2 is a homolog of angiotensin converting enzyme (ACE) with subtle differences in the active site [8,9]. Whereas ACE2 act as a carboxypeptidase by removing a single amino acid from the C-terminus of susceptible substrates, ACE acts as a carboxy-dipeptidase (or, peptidyl-dipeptidase) and removes a C-terminal dipeptide [10]. A recent study reported absent to low ACE2 promoter activity in a variety of human lung epithelial cell samples [11]. Three bioprojects (PRJEB4337, PRJNA270632 and PRJNA280600) invariably found very low expression of ACE2 in human lungs, whereas ACE was found to be much highly expressed (Supplementary figure 1-3) [12]. Although it is not obvious from the primary sequence alignment, ACE has striking similarity in the PD region with ACE2 that interact with the SARS-CoV-2 spike protein.

Till April 13, 2020 COVID-19 has spread in 213 countries and regions on earth with over 1,775,000 confirmed cases of infection and more than 112,000 deaths. Despite an urgent need to find options to help tens of thousands of patients and preclude potential death, there is no proven therapy to treat COVID-19 [13]. Repurposing of already approved drugs, if available, may be an immediate and promising option to tackle COVIDd-19. It is unlikely for the virus to mutate and evolve to bind an entirely different receptor within days or even months as such functional

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relationships are established by evolution over a long period of time [13]. Therefore, one strategy might be the use of an agent that binds to the receptor region recognized by the RBD of SARS-CoV-2 spike protein.

Since SARS-CoV-2 has evolved with increased affinity of the surface spike protein for its known receptor ACE2, this study explored the possibility of interaction of this spike protein with its ACE- a homolog of ACE2, which is more abundant in human lungs. This study also investigated the potential of 1263 already approved drugs to bind and interfere at the interface of ACE and ACE2 with the SARS-CoV-2 S protein.

2. Methods

2.1 Comparison of X-ray crystallographic structures of ACE and ACE2

X-ray crystallographic structures of human ACE (PDB ID:1O86) [14], ACE2 (PDB ID: 6LZG) [15] and SARS-CoV-2 spike protein (PDB ID: 6VYB) [16] were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) Protein Data Bank (*PDB*) [17]. These structures were processed (removal of HETATM, inhibitor and monomerization) using Discovery Studio Visualizer (v20.1.0.19295) [18]. 3D structures were aligned using RaptorX alignment tool [19]. Aligned 3D models were analyzed using CCP4mg [20].

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

Interaction of ACE and ACE2 with and SARS-CoV-2 surface spike glycoprotein were predicted using HADDOCK2.2 tool [21]. Predicted protein complexes were analyzed using PyMOL [22] and CCP4mg [20].

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2.3 *In silico* assessment of drugs with potentials to block SARS-CoV-2 spike protein interaction with ACE and ACE2

1263 approved drugs (Supplementary table 1) in 3D SDF format were retrieved from DrugBank [23], BindingDB [24], e-Drug3D [25] databases. Interaction of these drugs with ACE and ACE2 were predicted using AutoDock Vina in PyRx [26,27]. These structures were further analyzed using CCP4mg [20].

3. Results and discussion

3.1 Interaction between ACE and SARS-CoV-2 surface spike glycoprotein

Based on the sequence similarities to SARS-CoV spike proteins, it has been suggested that SARS-CoV-2 also exploits ACE2 to mediate infection in human cells [5]. Alignment of X-ray crystallographic structures of ACE and ACE2 reveals striking similarities in the tertiary structures of the PD regions that interact with the RBD of SARS-CoV-2 spike protein (Figure 1A). Critical amino acids in this region of ACE2 [3,5] that interact with the spike protein occupy similar positions in ACE (Figure 1B and C). Lys31 and Lys 353 in ACE2 are particularly considered as critical in the PD of ACE2 for interaction with the viral spike protein [5]. Although it is not obvious in the primary sequence alignment, these important amino acid residues in the PD of ACE and ACE2 are present in the same order (Figure 1B).

Receptor-ligand interaction analysis using molecular docking technique could predict the amino acids at the interface of ACE and ACE2 PD regions with 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 control to compare with the predicted analysis between ACE and S protein. The amino acid residues in ACE2 at the interface with the SARS-CoV-2 spike protein matched to the previous reports [3,5]. Similar interactions were observed in the predicted interactions between ACE and the spike

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protein. Predicted interactions of ACE and ACE2 with the spike protein involve similar forces and z-scores (Supplementary table 2). As in SARS-CoV/SARS-CoV-2 and ACE2 [5], the predicted interface between SARS-CoV-2 and ACE maintains a highly polar environment (Figure 2). In fact, the predicted interaction model suggests (Supplementary table 2) the ACE-spike protein complex to be electrostatically more stable than the ACE2-spike protein complex. As SARS-CoV-2 spike protein has evolved to bind ACE2 with higher affinity than does the SARS-CoV [4] and gained more power to transmit and infect humans, mere speculation based on sequence comparison with SARS-CoV might not be enough to define its receptor.

3.2 *In silico* assessment of drugs with potentials to block SARS-CoV-2 spike protein interaction with ACE and ACE2

A total of 1263 approved drugs (Supplementary table 1) were assessed for potential interactions with ACE and ACE2 at regions that overlap with the predicted and known binding regions of RBD of the SARS-COV-2 spike protein, respectively. Angiotensin II is a substrate of ACE2 [10]. Molecular docking with AutoDock Vina predicted an interaction of angiotensin II with the PD of ACE2 with a binding energy of -6.0 kcal/mol. Drugs that bind to overlapping regions in the PD of ACE and 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) are listed in table 1. Several of these predicted interactions are shown in figure 3 and 4. Table 1 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.

There are differences between the compositions and structures of ACE and ACE2. Based on *in silico* analysis, among the 1263 analyzed drugs in this study, only 10 may bind to regions in both ACE and ACE2 that overlap with the binding sites of the key interacting spike protein amino acid residues. Pibrentasvir is one such drug which is used to treat infection mediated by Hepatitis C Virus (HCV)- a positive-strand RNA virus [28]. *In silico* analysis could predict a few more antiviral drugs (Indinavir, *Baloxavir marboxil*, Maraviroc, Doravirine, and Nelfinavir), which

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may interfere with the binding of SARS-CoV-2 spike protein with ACE2 only. Several of the drugs may play dual roles by blocking the binding of virus to the receptor as well as fight other associated infections. For example, Azithromycin, Cefoperazone, Natamycin, Nystatin, Rifapentine, etc may be used to manage infection as well as interfere with SARS-CoV-2 binding. These may serve as a two edged sword by blocking the binding to the receptor as well as inhibiting secondary infections [29]. Two angiotensin II analogs (*Azilsartan kamedoxomil and* Saralasin) were predicted to bind with higher affinity to ACE2 than angiotensin II. These two drugs bind to regions that overlap with the binding site of SARS-CoV spike protein. Mefloquine- an anti-malarial drug may compete with spike protein for ACE2 rather than Hydroxychloroquine, which binds to other region of ACE2 (Table 1 and supplementary table 1).

4. Conclusion

Although there has been discussion on whether it would be safe to use angiotensin receptor blockers (ARB) in the treatment of COVID-19, the Council on Hypertension of the European Society of Cardiology, the American Heart Association, the Heart Failure Society of America, and the American College of Cardiology recommended that the physicians and patients should continue treatment with their usual anti-hypertensive therapy because there is no clinical or scientific evidence to suggest that treatment with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) should be discontinued because of the COVID-19 infection [30,31]. In an acid lung injury model of mice SARS-CoV worsened lung injury by down-regulation of ACE2, which was improved by treatment with angiotensin receptor blocker (ARB) [32].

No specific therapeutics for COVIDD-19 is yet available. A better understanding of the underlying pathobiology will be useful in finding a cure [33]. 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.

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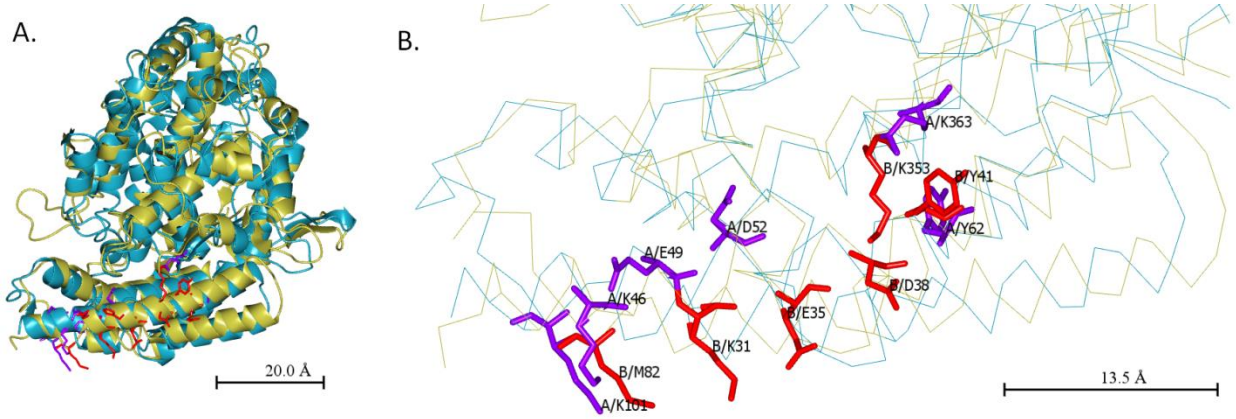

Figure 1: Alignment of X-ray crystallographic structures of ACE (PDB ID:1O86) and ACE2 (PDB ID: 6LZG). A. SARS-CoV-2 spike protein binding region (RBD) of ACE (in dark cyan) and ACE2 (in gold) have similar tertiary structures in the PD region. B. K46, E49, D52, Y62, K101, and K363 in ACE (in red) are positioned in similar order to K31, E35, D38, Y41, M82, and K353 in ACE2 (in purple). Chain A and B represent ACE and ACE2, respectively.

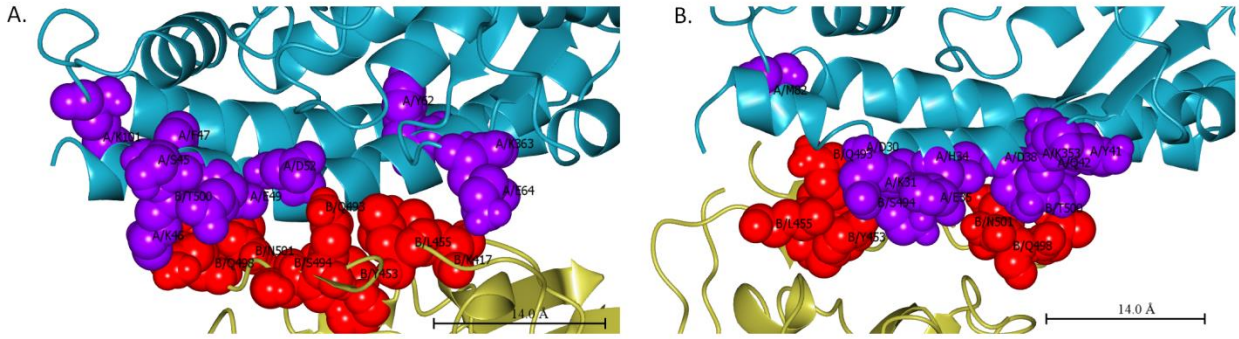

Figure 2: Predicted interactions of ACE and ACE2 with the RBD of SARS-CoV-2 surface spike protein. A and B. Interaction of ACE and ACE2 PD regions (in dark cyan) with the RBD of SARS-CoV-2 spike protein (in gold) are shown. Interacting amino acid residues in ACE and ACE2 are shown in purple, whereas those in S protein are shown in red. Chain A and B represent ACE/ACE2 and spike protein, respectively.

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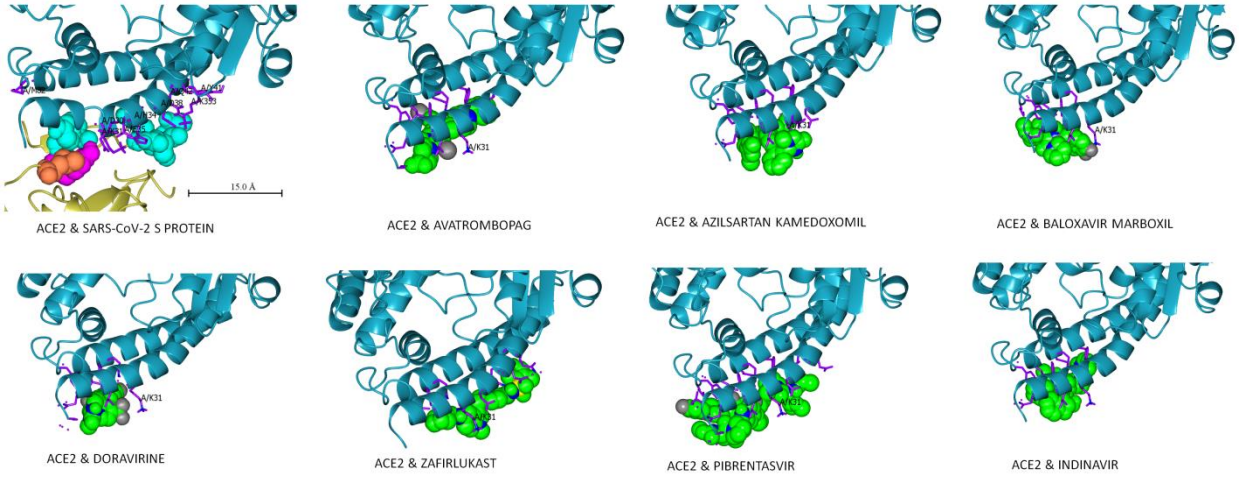

Figure 3: Drugs with potential binding abilities to ACE2 at the interface with RBD of SARS-CoV-2 surface spike protein. Interacting amino acid residues in ACE2 are shown in purple and drug molecules are shown as spheres. Chain A represents ACE2 enzyme.

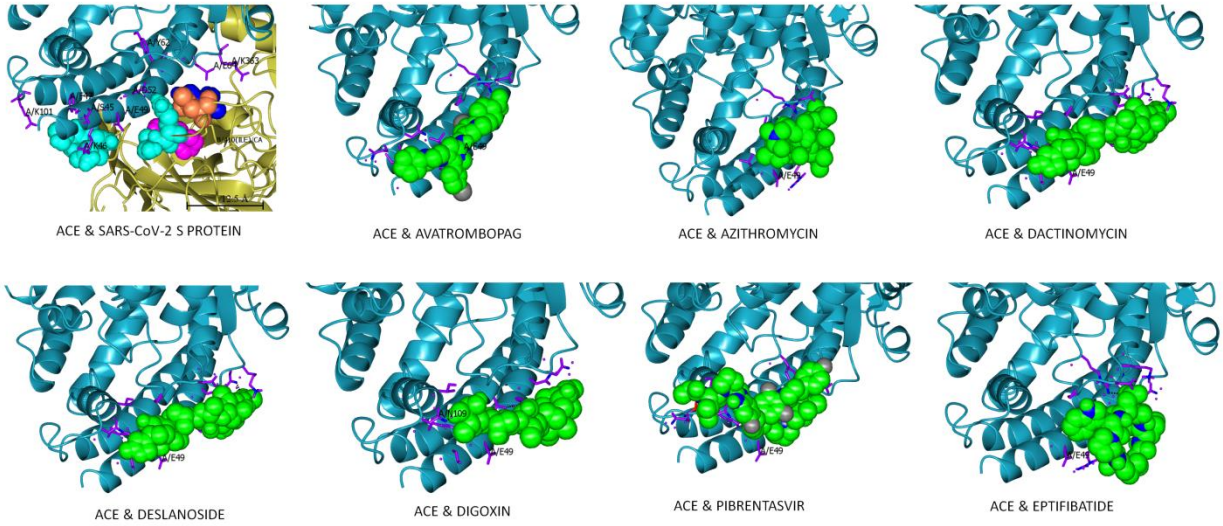

Figure 4: Drugs with potential binding abilities to ACE at the interface with RBD of SARS-CoV-2 surface spike protein. Interacting amino acid residues in ACE are shown in purple and drug molecules are shown as spheres. Chain A represents ACE enzyme.

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Table 1: List of drugs that bind to ACE and ACE2 PD regions and has more stable binding than angiotensin II (*i.e.*, predicted to release energy > 6.0 kcal/mol).

Ligand	Binding energy		Status [23]	Description [23]
	Human ACE	Human ACE2		
DIGITOXIN	–	-8	Approved	A cardiac glycoside sometimes used in place of digoxin.
NILOTINIB	–	-7.7	Approved, Investigational	A tyrosine kinase inhibitor under investigation as a possible treatment for chronic myelogenous leukemia (CML). A Phase I clinical trial showed that this drug was relatively safe and offered significant therapeutic benefits in cases of CML.
VILAZODONE	–	-7.6	Approved	A novel compound with combined high affinity and selectivity for the 5-hydroxytryptamine (5-HT) transporter and 5-HT(1A) receptors.
AVATROMBOPAG	-6.9	-7.4	Approved, Investigational	An orally administered thrombopoietin receptor (c-Mpl) agonist which increases platelet number, but not platelet activation.
DIHYDROERGOTAMINE	–	-7.4	Approved	Used as a vasoconstrictor, specifically for the therapy of migraine disorders.
ACALABRUTINIB	–	-7.2	Approved, Investigational	Indicated for the treatment of chronic lymphocytic leukemia, small lymphocytic lymphoma, and in adult patients with Mantle Cell Lymphoma (MCL).
INDINAVIR	–	-7.1	Approved	A potent and specific HIV protease inhibitor that appears to have good oral bioavailability.
SARALASIN	–	-7.1	Investigational	An octapeptide analog of angiotensin II (bovine) with amino acids 1 and 8 replaced with sarcosine and alanine, respectively.
ZAFIRLUKAST	–	-7.1	Approved, Investigational	An oral leukotriene receptor antagonist (LTRA) for the maintenance treatment of asthma, often used in conjunction with an inhaled steroid and/or long-acting bronchodilator.
PACLITAXEL	–	-6.9	Approved	Used as a treatment for various cancers.
APALUTAMIDE	–	-6.8	Approved, Investigational	A potent androgen receptor (AR) antagonist that selectively binds to the ligand-binding domain of AR and blocks AR nuclear translocation or binding to androgen response elements.
TERCONAZOLE	–	-6.8	Approved	An anti-fungal drug that is mainly used to treat vaginal yeast infections.
ABEMACICLIB	–	-6.7	Approved, Investigational	An antitumor agent and dual inhibitor of cyclin-dependent kinases 4 (CDK4) and 6 (CDK6).
DARIFENACIN	–	-6.7	Approved, Investigational	Used to treat urinary incontinence.
METOCURINE	–	-6.7	Approved	A non-depolarizing muscle relaxant.
TESTOSTERONE CYPIONATE	–	-6.7	Approved	A synthetic derivative of testosterone.
DESERPIDINE	–	-6.6	Approved	An antipsychotic and antihypertensive agent used for the control of high blood pressure and for the relief of psychotic behavior.
NERATINIB	–	-6.6	Approved, Investigational	Used as an extended adjuvant therapy in Human Epidermal Growth Factor Receptor 2 (HER2) positive breast cancer.
PIBRENTASVIR	-7.5	-6.6	Approved, Investigational	A direct acting antiviral agent and Hepatitis C virus (HCV) NS5A inhibitor that targets viral RNA replication and viron assembly.
BETRIXABAN	–	-6.5	Approved, Investigational	A non-vitamin K oral anticoagulant whose action is driven by the competitive and reversible inhibition of the factor Xa.

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CEFOPERAZONE	–	-6.5	Approved, Investigational	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	A selective nonsteroidal anti-inflammatory drug (NSAID) which is known for its decreased risk of causing gastrointestinal bleeding compared to other NSAIDS.
DOCETAXEL	–	-6.5	Approved, Investigational	An anti-mitotic chemotherapy medication used mainly for the treatment of breast, ovarian, and non-small cell lung cancer.
DORAVIRINE	–	-6.5	Approved	An HIV-1 non-nucleoside reverse transcriptase inhibitor (NNRTI) intended to be administered in combination with other antiretroviral medicines.
ESTROPIPATE	–	-6.5	Approved, Investigational	It is a form of estrogen.
IDARUBICIN	–	-6.5	Approved	It has activity against breast cancer, lymphomas and leukemias, together with the potential for reduced cardiac toxicity.
LUSUTROMBOPAG	–	-6.5	Approved, Investigational	An orally bioavailable thrombopoietin receptor (TPOR) agonist.
RIFAPENTINE	-6.4	-6.5	Approved, Investigational	An antibiotic drug used in the treatment of tuberculosis. It inhibits DNA-dependent RNA polymerase activity in susceptible cells.
ALATROFLOXACIN	–	-6.4	Approved, Withdrawn	It is a fluoroquinolone antibiotic.
AZILSARTAN KAMEDOXOMIL	–	-6.4	Approved, Investigational	An angiotensin II receptor antagonist indicated for the treatment of mild to moderate essential hypertension.
BALOXAVIR MARBOXIL	–	-6.4	Approved, Investigational	An antiviral drug for the treatment of influenza A and influenza B infections.
BRIGATINIB	–	-6.4	Approved, Investigational	A reversible dual inhibitor of anaplastic lymphoma kinase (ALK) and epidermal growth factor receptor (EGFR).
CLOFAZIMINE	–	-6.4	Approved, Investigational	A fat-soluble riminophenazine dye used for the treatment of leprosy.
GANIRELIX	-6.2	-6.4	Approved	Ganirelix is an injectable competitive gonadotropin-releasing hormone antagonist.
RESERPINE	-6.3	-6.4	Approved, Investigational	Used as an antihypertensive and an antipsychotic drug.
SIMVASTATIN	–	-6.4	Approved	Used to lower the risk of cardiovascular disease and manage abnormal lipid levels by inhibiting the endogenous production of cholesterol in the liver.
CANDICIDIN	–	-6.3	Approved, Withdrawn	An antibiotic active against some fungi of the genus Candida.
LOPERAMIDE	–	-6.3	Approved	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	Loratadine is a second generation antihistamine used to manage symptoms of allergic rhinitis.
MARAVIROC	–	-6.3	Approved, Investigational	A chemokine receptor antagonist drug that is designed to act against HIV by interfering with the interaction between HIV and CCR5
PIPECURONIUM	–	-6.3	Approved	A non-depolarizing neuromuscular blocking agent.
PLICAMYCIN	–	-6.3	Approved, Investigational, Withdrawn	An antineoplastic antibiotic used in the treatment of testicular cancer, Paget's disease of bone, and, rarely, the management of hypercalcemia.
CERULETIDE	-6.2	-6.2	Approved	Exerts stimulatory effects on the gastric, biliary, and pancreatic secretion, as well as on certain smooth muscles.

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CETRORELIX	–	-6.2	Approved, Investigational	A synthetic hormone that blocks the effects of Gonadotropin Releasing Hormone.
ESTRAMUSTINE PHOSPHATE	–	-6.2	Approved, Investigational	Used to treat prostatic neoplasms; also has radiation protective properties.
FOSNETUPITANT	–	-6.2	Approved	An alternative treatment option for patients experiencing chemotherapy-induced nausea and vomiting.
NATAMYCIN	-7.4	-6.2	Approved	It is used for a variety of fungal infections, mainly topically.
NELFINAVIR	_	-6.2	Approved	A potent HIV-1 protease inhibitor.
POSACONAZOLE	-7.8	-6.2	Approved, Investigational	An antifungal drug that is used to treat invasive infections by Candida species and Aspergillus species in severely immunocompromised patients.
ROMIDEPSIN	_	-6.2	Approved, Investigational	A selective inhibitor of histone deacetylase for the treatment of cutaneous T-cell lymphoma (CTCL) or/and peripheral T-cell lymphoma (PTCL).
SOLIFENACIN	_	-6.2	Approved	A competitive muscarinic receptor antagonist indicated to treat an overactive bladder with urinary incontinence, urgency, and frequency.
BUCLIZINE	–	-6.1	Approved	An antihistamine medication with both antiemetic and anticholinergic effects.
BUTENAFINE	_	-6.1	Approved	A synthetic benzylamine antifungal agent.
ETOPOSIDE PHOSPHATE	–	-6.1	Approved	A semisynthetic derivative of podophyllotoxin that exhibits antitumor activity. Etoposide inhibits DNA synthesis by forming a complex with topoisomerase II and DNA.
MEFLOQUINE	–	-6.1	Approved, Investigational	A phospholipid-interacting antimalarial drug (anti-malarials).
NAFARELIN	–	-6.1	Approved	A potent synthetic agonist of gonadotropin-releasing hormone.
PITAVASTATIN	–	-6.1	Approved	A lipid-lowering drug belonging to the statin class of medications.
DIGOXIN	-7.7	–	Approved	Used to manage atrial fibrillation and the symptoms of heart failure.
DACTINOMYCIN	-7.7	_	Approved, Investigational	It binds to DNA and inhibits RNA synthesis (transcription), with chain elongation more sensitive than initiation, termination, or release.
VANCOMYCIN	-7.7	–	Approved	Antibacterial compound that inhibits bacterial cell wall assembly.
HISTRELIN	-7.5	–	Approved	A gonadotropin releasing hormone agonist that acts as a potent inhibitor of gonadotropin
DESLANOSIDE	-7.5	_	Approved	A cardiotonic glycoside.
SIROLIMUS	-7.5	_	Approved, Investigational	Acts by selectively blocking the transcriptional activation of cytokines, thereby inhibiting cytokine production.
TEMSIROLIMUS	-7.4	-6.1	Approved	Used in the treatment of renal cell carcinoma.
EPTIFIBATIDE	-7.4	–	Approved, Investigational	Synthetic cyclic hexapeptide that binds to platelet receptor glycoprotein and inhibits platelet aggregation.
TRIAZOLAM	_	-6.1	Approved	A short-acting benzodiazepine used in the treatment of insomnia. (Withdrawn in the United Kingdom due to risk of psychiatric adverse drug reactions.)
ICATIBANT	-7.3	_	Approved, Investigational	A synthetic peptidomimetic drug that acts as an effective and specific antagonist of bradykinin B2 receptors and approved in the EU for use in hereditary angioedema.
AMPHOTERICIN B	-7.1	_	Approved, Investigational	Shows a high order of *in vitro* activity against many species of fungi and without effect on bacteria, rickettsiae, and viruses.
NYSTATIN	-6.8	_	Approved	A polyene antifungal drug that has broad-spectrum fungicidal and fungistatic activity against a number of yeasts and fungi, most notably Candida species

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ANIDULAFUNGIN	-6.6	–	Approved, Investigational	An anti-fungal drug with similar safety profile to caspofungin.
AZITHROMYCIN	-6.6	–	Approved	A broad-spectrum macrolide antibiotic with a long half-life, which is primarily used for the treatment of respiratory, enteric and genitourinary infections.
GOSERELIN	-6.6	–	Approved	A synthetic hormone that stops the production of the hormone testosterone in men.
RIFAXIMIN	-6.6	–	Approved, Investigational	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 adult.
RIFAMYCIN	-6.3	–	Approved, Investigational	The first antibiotic used intravenously for the treatment of tuberculosis.
TRIPTORELIN	-6.3	–	Approved	A synthetic decapeptide agonist analog of luteinizing hormone releasing hormone.
VASOPRESSIN	-6.1	–	Approved	Antidiuretic hormone.

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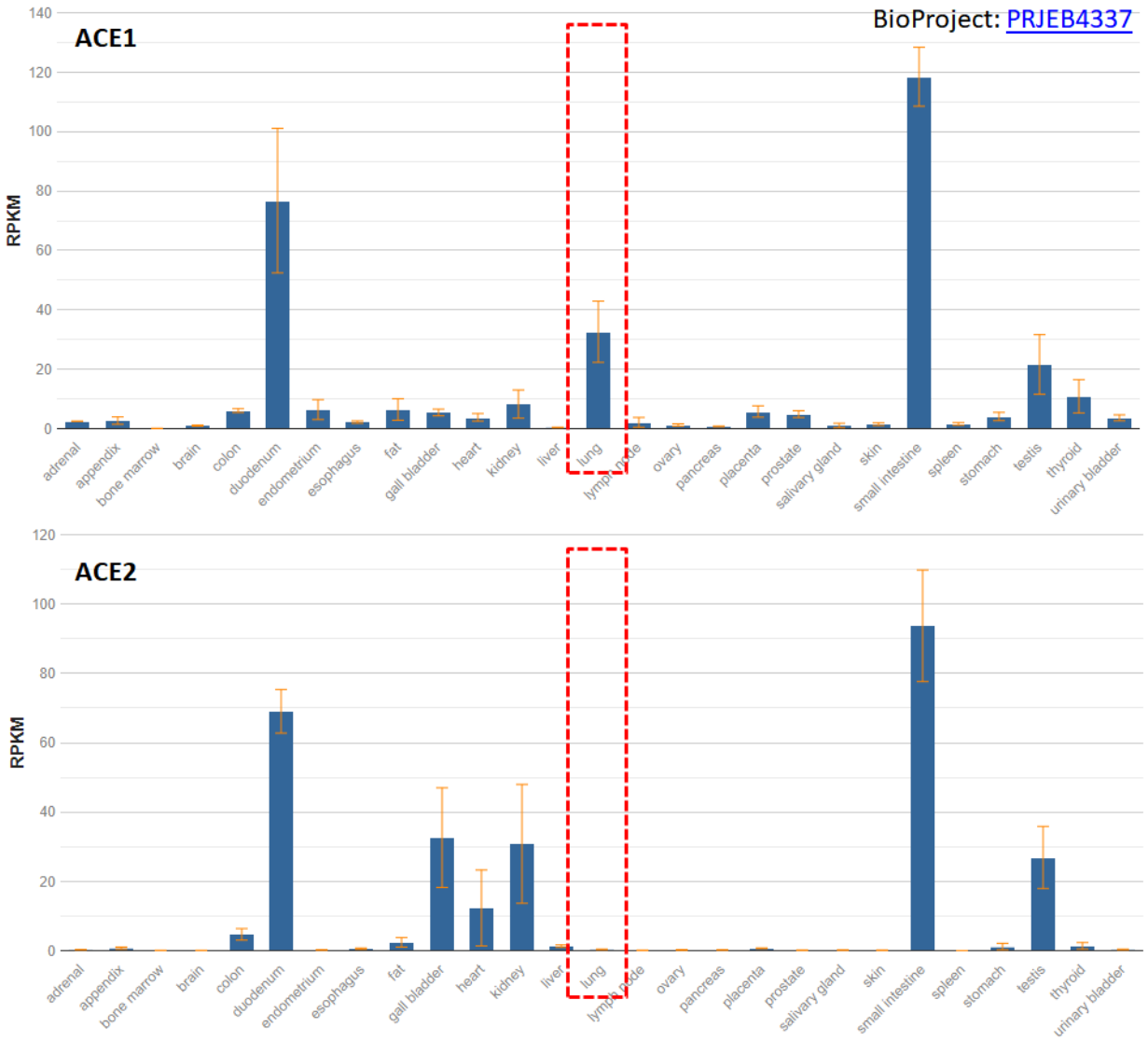

Supplementary figure 1: Expression of ACE and ACE2 in different human tissues (BioProject accession number: PRJEB4337) [12]. RNA-seq was performed of tissue samples from 95 human individuals representing 27 different tissues in order to determine tissue-specificity of all protein-coding genes. The plots are adopted and modified from [12]. RPKM- Reads Per Kilobase of transcript, per Million mapped reads.

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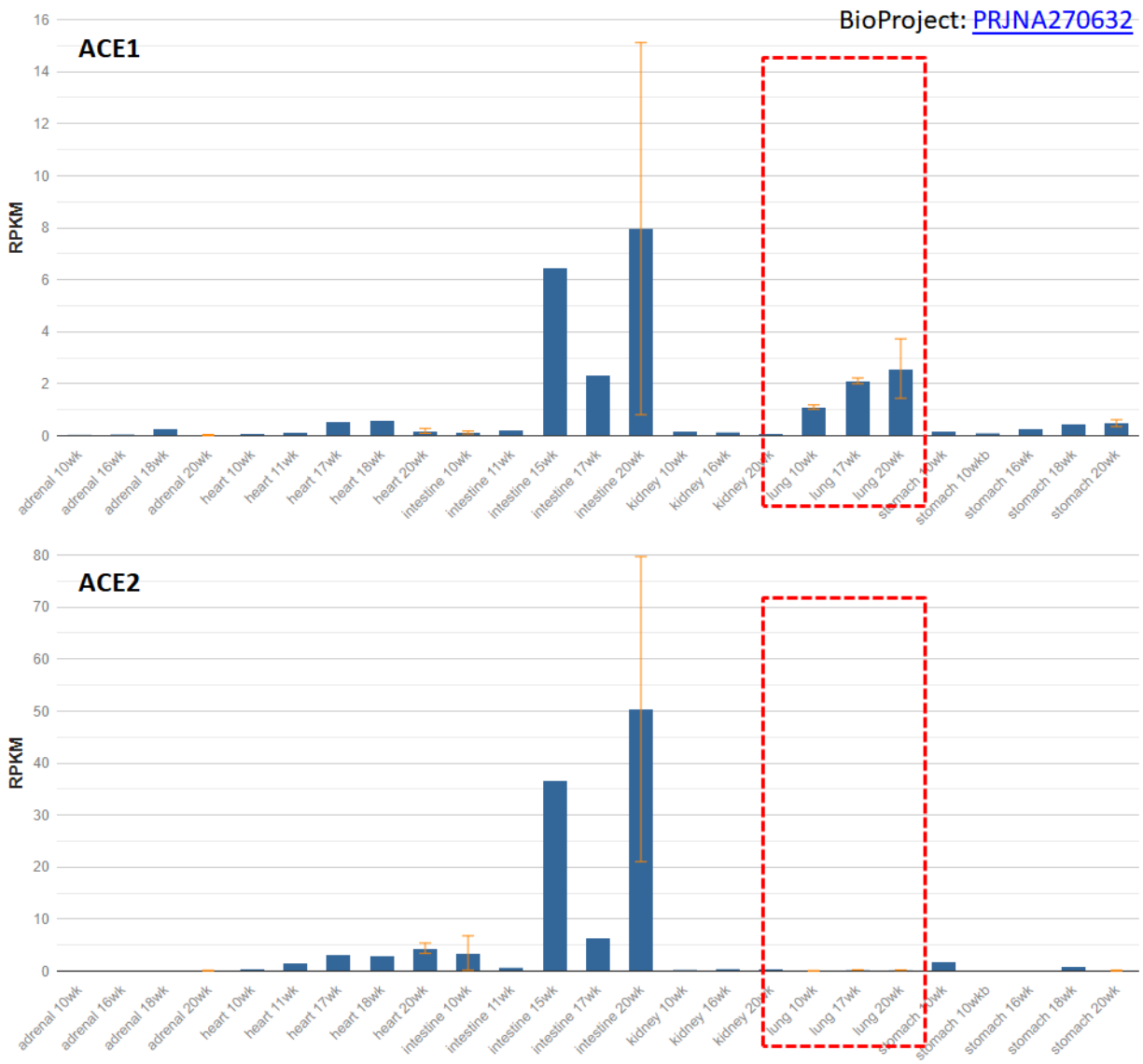

Supplementary figure 2: Expression of ACE and ACE2 in different human tissues (BioProject accession number: PRJNA270632) [12]. 35 human fetal samples from 6 tissues (3 - 7 replicates per tissue) collected between 10 and 20 weeks gestational time were sequenced using Illumina TruSeq Stranded Total RNA. The plots are adopted and modified from [12]. RPKM- Reads Per Kilobase of transcript, per Million mapped reads.

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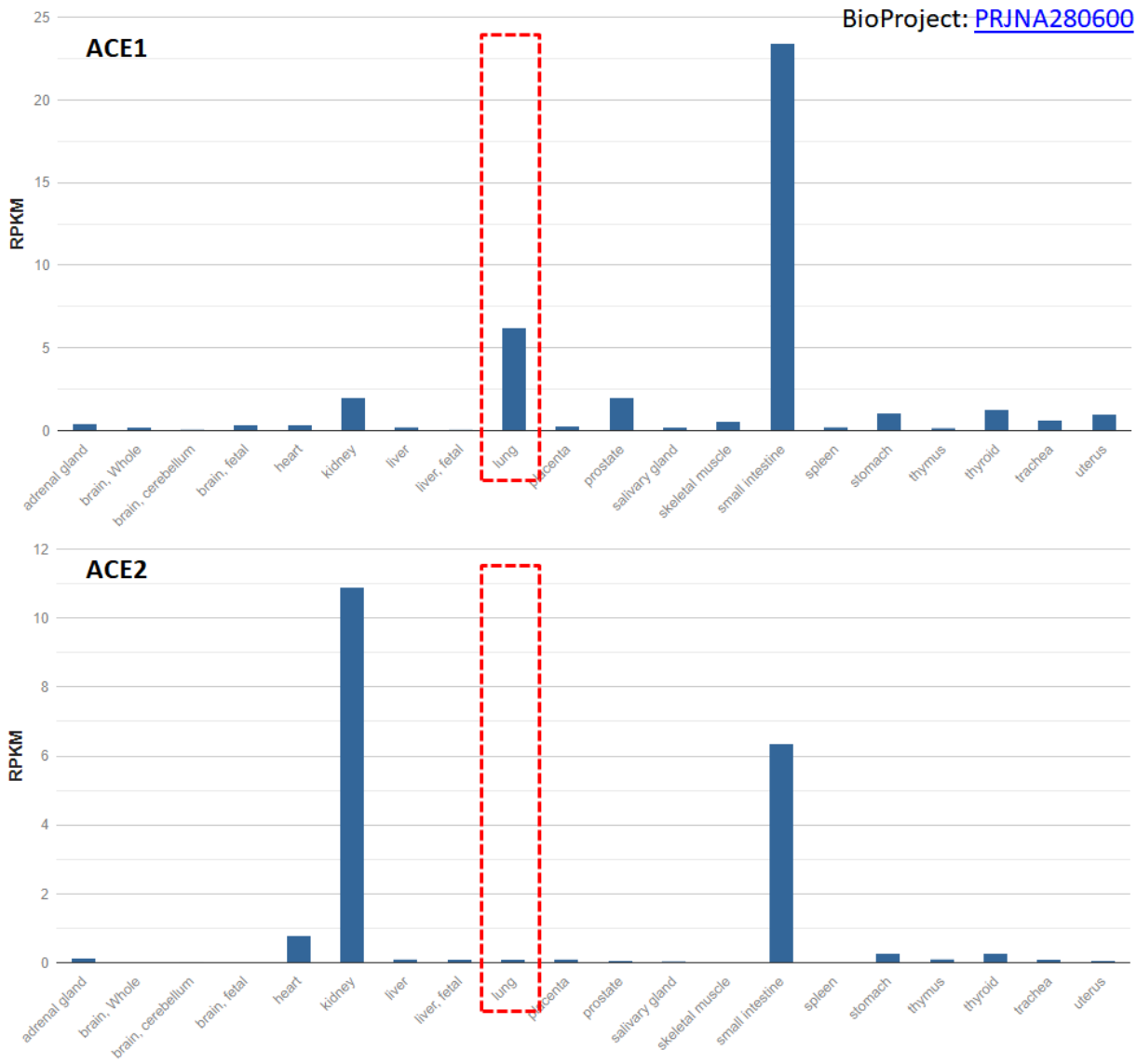

Supplementary figure 3: Expression of ACE and ACE2 in different human tissues (BioProject accession number: PRJNA280600) [12]. Transcription profiling by high throughput Illumina sequencing of individual and mixture of 16 human tissues RNA. The plots are adopted and modified from [12]. RPKM- Reads Per Kilobase of transcript, per Million mapped reads.

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

Supplementary table 2: Predicted interactions of ACE and ACE2 with RBD of SARS-CoV-2 spike protein.