**Tissue distributions of antiviral drugs impact on their capabilities of reducing viral loads in COVID-19 treatment**

Yan Wang1,\*, Lei Chen2,\*

1Center for Translation Medicine Research and Development, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, P.R. China

2Department of Genetics, Human Genetics Institute of New Jersey, Rutgers University, Piscataway, NJ 08854, USA

**\*Correspondence:** Dr. Yan Wang, Center for Translation Medicine Research and Development, Shenzhen Institute of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, P.R. China; Phone: 86755-2641-7985; E-mail: [yan.wang@siat.ac.cn](mailto:yan.wang@siat.ac.cn); Dr. Lei Chen, Department of Genetics, Human Genetics Institute of New Jersey, Rutgers University, Piscataway, NJ 08854, USA; Phone: +1-848-445-9579; E-mail: lchen@dls.rutgers.edu.

**Abstract**

**Background and Purpose**

Previously we reported our hypothesis that the high distribution of antiviral drugs in the lung is a key factor that results in reducing viral loads in COVID-19 patients. So far, chloroquine, lopinavir, hydroxychloroquine, azithromycin, favipiravir, ribavirin, darunavir, remdesivir, and umifenovir have been tested in COVID-19 clinical trials. Here we validate our hypothesis by comparing the pharmacokinetics profiles of these drugs and their capabilities of reducing viral load in clinical trials.

**Experimental approach**

The RNA-seq data were obtained from public database and re-analyzed and visualized by Single Cell Portal and Seurat. The tissue/plasma ratio of antiviral drugs were calculated by AUC or Mean values that were compiled from publications.

**Key Results**

High expression of both *ACE2* and *TMPRSS2* makes the lung and intestine vulnerable to SARS-CoV-2. Hydroxychloroquine, chloroquine, and favipiravir, which were highly distributed to the lung, were reported to reduce viral loads in respiratory tract of COVID-19 patients. Conversely, drugs with poor lung distributions, including lopinavir/ritonavir, umifenovir and remdesivir, were insufficient to inhibit SARS-CoV-2 replication. Lopinavir/ritonavir might inhibit SARS-CoV-2 in the GI tract according to their distribution profiles.

**Conclusion and Implications**

The antiviral drugs should be distributed straight to or accumulate in the lung for reducing viral loads in respiratory tract of COVID-1 9 patients. Additionally, to better evaluate antiviral drugs that target the intestine, the stool samples should also be collected for viral RNA test in the future.

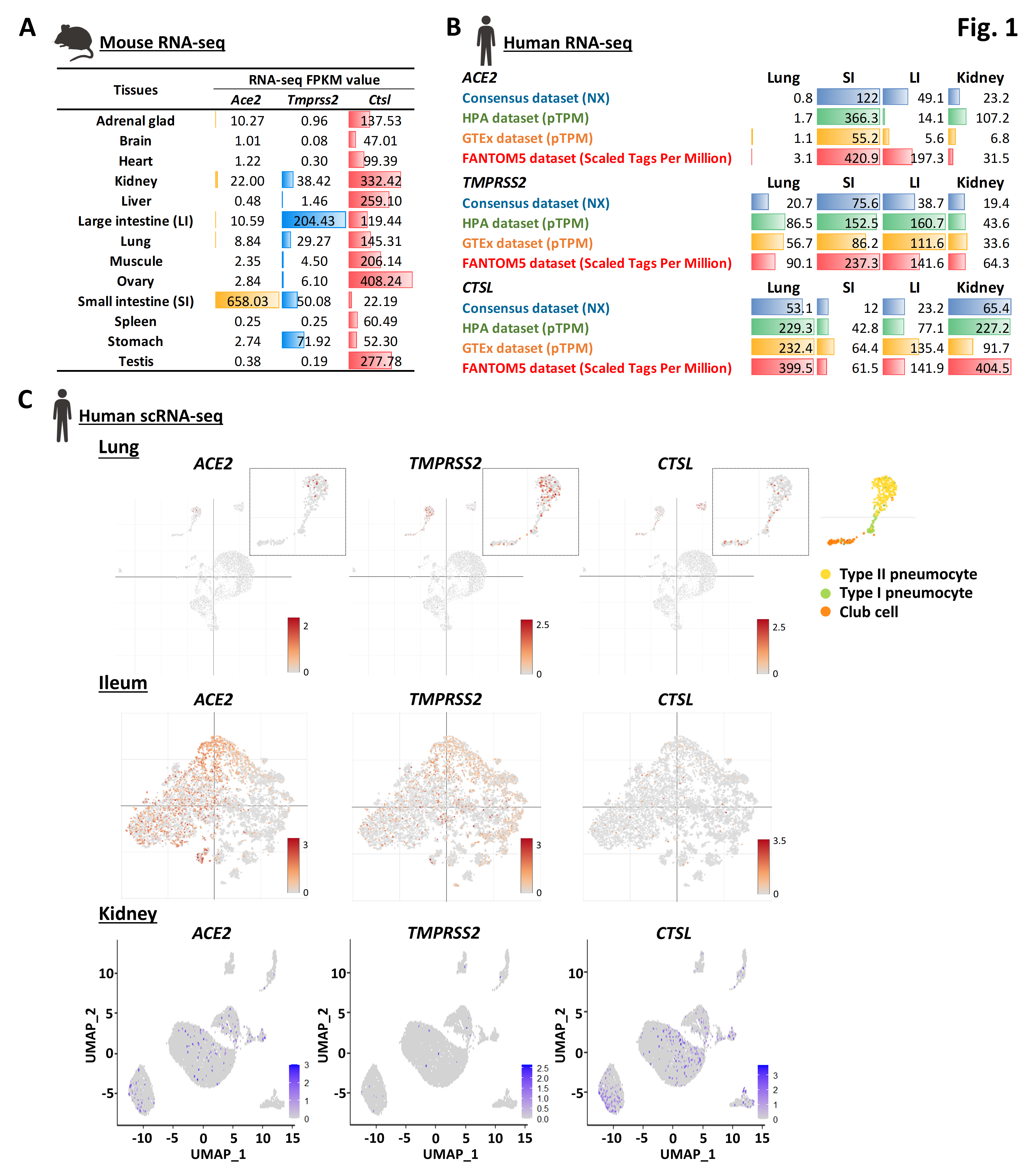
**Main**

Previously we reported our hypothesis that the high distribution of antiviral drugs in the lung is a key factor that results in reducing viral loads in COVID-19 patients ([Wang *et al.*, 2020b](#_ENREF_25)). We speculated that the disappointed clinical outcome of lopinavir might result from its low lung tissue distribution, whereas the high concentration of chloroquine in the lung might help to promote viral clearance in COVID-19 patients ([Wang *et al.*, 2020b](#_ENREF_25)). So far, many antiviral drugs, including hydroxychloroquine, azithromycin, favipiravir, ribavirin, darunavir, umifenovir and remdesivir, have been tested in COVID-19 clinical trials and the results have been released. Here we validate our hypothesis by comparing the pharmacokinetics profiles of these drugs and their capabilities of reducing viral loads in clinical trials.

**High expression of viral receptor makes tissues vulnerable to SARS-CoV-2**

Angiotensin converting enzyme 2 (ACE2) is required for SARS-CoV-2 cell entry. Spike protein of SARS-CoV-2 directly binds to ACE2 and is primed by TMPRSS2, which allows the fusion of viral membrane with the plasma membrane ([Hoffmann *et al.*, 2020](#_ENREF_10)). SARS-CoV-2 can also enter cell by endocytosis, and the endosomal cysteine protease cathepsin L primes spike protein to make the membrane fusion ([Hoffmann *et al.*, 2020](#_ENREF_10)). In this way, tissues that highly co-express ACE2, TMPRSS2 and CTLS are more likely to be attacked by SARS-CoV-2. We re-analyzed mouse and human bulk RNA-seq data and found these genes are highly expressed in the lung, kidney and intestine, indicating that these tissues are vulnerable for SARS-CoV-2 (**Fig 1A** and **B**). Consistently, COVID-19 patients exhibit cough symptom and abnormal lung findings on CT, as well as the high viral loads in their bronchoalveolar lavage fluid sample ([Liu *et al.*, 2020](#_ENREF_16)); therefore, the lung is believed to be a major target tissue that SARS-CoV-2 attacks. Diarrhea is another reported COVID-19 symptom, and the SARS-CoV-2 was also detected in the stools of COVID-19 patients ([Hindson, 2020](#_ENREF_9)).

Considering the decent expression level of *ACE2* and *TMPRSS2* in the kidney, we would think that in addition to the lung and intestine, SARS-CoV-2 should also enter the kidney. However, the prevalence of kidney involvement in COVID-19 is very low. In most cases, SARS-CoV-2 was not observed in urine samples of COVID-19 patients, and only 0.5%-9% COVID-19 patients had the acute kidney injury ([Lescure *et al.*, 2020](#_ENREF_13)). We next analyzed the public single cell RNA-seq data to visualize the distribution of *ACE2+TMPRSS2+* and *ACE2+CTSL+* cells in the human lung, intestine (ileum) and kidney. *ACE2+TMPRSS2+* cells were widely distributed in type II pneumocyte (AT2) cells of lung (**Fig 1C**, top panel) and ileum (**Fig 1C**, middle panel), as reported by others. Conversely, massive *ACE2+CTSL+* cells but not *ACE2+TMPRSS2+* were observed in the kidney (**Fig 1C**, bottom panel), indicating that if SARS-CoV-2 indeed enters kidney, the virus is more likely to use CTSL for S protein priming. The CTSL-mediated priming was reported to make coronaviruses less transmissible and toxic ([Shirato *et al.*, 2017](#_ENREF_18); [Shirato *et al.*, 2018](#_ENREF_19)), which might partially explain why the kidney damage is barely observed in the COVID-19 patients. Another possible reason is that lung and intestine could expose to SARS-CoV-2 directly, and SARS-CoV-2 might be difficult to reach kidney, as in the most cases, the plasma virus was undetectable ([Wolfel *et al.*, 2020](#_ENREF_28)). This indicates that kidney has few chances to expose to the virus. Taken together, the relatively direct exposure and high expression of both ACE2 and TMPRSS2 make lung and intestine vulnerable to SARS-CoV-2, suggesting that the antiviral drugs should take lung and intestine as priority tissue targets to reduce viral loads.



**Figure 1. RNA-seq analysis reveals transcript levels of *ACE2*, *TMPRSS2* and *CTSL* genes in lung, intestine and kidney tissues.** (A) Bulk RNA-seq data of mouse tissues are presented as mean ± SEM (n = 4 biological replicates per tissue). Data source: PRJNA375882 ([Yan *et al.*, 2017](#_ENREF_29)). (B) Bulk RNA-seq data of human tissues. Data Sources: THE HUMAN PROTEIN ATLAS ([Uhlen *et al.*, 2015](#_ENREF_23)), available from <https://www.proteinatlas.org>. SI: Small intestine; LI: Large intestine (colon); NX: Normalized eXpression; pTPM: protein-coding transcripts per million. (C) The scRNA-seq data of human lung ([Ziegler *et al.*, 2020](#_ENREF_30)) and ileum ([Ziegler *et al.*, 2020](#_ENREF_30)) are visualized by Single Cell Portal - Broad Institute, available from <https://singlecell.broadinstitute.org>. The scRNA-seq data of human kidney ([Liao *et al.*, 2020](#_ENREF_14)) (GSE131685) are re-analyzed and visualized by Seurat ([Butler *et al.*, 2018](#_ENREF_1); [Stuart *et al.*, 2019](#_ENREF_21)).

**Distribution of antiviral drugs in susceptible tissues impacts on their capabilities of reducing viral loads**

Currently, many antiviral drugs have been tested in COVID-19 clinical trials and their clinical outcomes have been reported. Here we compiled the AUC or mean concentrations of these antiviral drugs in different tissues from various animal studies and calculated tissue/plasma ratio. We then ranked these ratios and identified the major distribution tissues of these antiviral drugs (**Table 1**).

**Table 1. Summary of tissue distributions of antiviral drugs in COVID-19 treatment**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Tissues** | **Tissue/Plasma Ratio (AUC\* or Mean Concentration)** | | | | | | | | |
| **Azithromycin\*** | **Hydroxychloroquine** | **Chloroquine** | **Favipiravir\*** | **Ribavirin** | **Lopinavir\*** | **Ritonavir** | **Darunavir** | **Umifenovir** |
| **Adrenal glad** |  | 56.4 |  |  | 4.6 | 1.6 | 12.8 |  |  |
| **Brain** |  | 2.1 | 4.3 | 0.2 | 7.1 | 0.0 | 1.7 | 4.6 | 0.1 |
| **Heart** | 63.9 | 12.4 | 14.1 |  | 17.5 | 0.5 | 8.2 | 0.4 | 0.1 |
| **Kidney** | 100.0 | 28.3 | 43.3 | 0.2 | 3.4 | 0.9 | 20.7 | 4.0 | 0.1 |
| **Liver** |  | 51.5 | 97.2 |  | 3.8 | 22.2 | 76.7 | 20.0 | 0.5 |
| **Large intestine** | 30.8 |  |  |  | 20.4 | 83.0 | ND |  | 6.5 |
| **Lung** | 13.6 | 50.6 | 83.1 | 0.2 | 2.2 | 0.5 | 18.4 | 0.8 | 1.7 |
| **Muscule** |  | 91.4 |  |  |  | 0.2 | 3.9 |  | 0.1 |
| **Ovary** |  |  |  |  |  |  | 11.2 |  | 0.2 |
| **Small intestine** | 137.0 |  |  |  | 18.4 | 40.8 | ND | 10.0 | 1.1 |
| **Spleen** |  | 34.9 |  | 0.2 | 2.9 | 0.4 | 10.3 | 1.4 | 0.3 |
| **Stomach** |  |  |  |  | 3.6 | 84.8 | ND | 10.0 | 10.6 |
| **Testis** |  |  |  |  | 3.8 | 0.2 | 6.4 |  | 0.0 |

Given that SARS-CoV-2 mainly attacks the lung and intestine, to enhance viral clearance, it might be more effective if the antiviral drugs could be distributed straight to or accumulate in the lung and intestine tissues. How potent the drugs are *in vitro* and how the drugs work might also impact on their capabilities of reducing viral loads in COVID-19 patients, we therefore also included cell-based antiviral EC50 results as well as mechanism of action (MOA) of antiviral drugs for our discussion (**Table 2**).

Lung is one of the major distribution tissues for chloroquine ([Ono *et al.*, 2003](#_ENREF_17)), hydroxychloroquine ([Wei *et al.*, 1995](#_ENREF_27)), favipiravir ([Gowen *et al.*, 2015](#_ENREF_8)), ritonavir ([Denissen *et al.*, 1997](#_ENREF_6)) and umifenovir ([Liu *et al.*, 2013](#_ENREF_15)). Chloroquine showed strong inhibitory effects on SARS-CoV-2 replication *in vitro* ([Wang *et al.*, 2020a](#_ENREF_24)) and was the first reported drug that can reduce viral loads and benefit COVID-19 patients ([Wang *et al.*, 2020a](#_ENREF_24)). Hydroxychloroquine, the analog of chloroquine, inhibited this coronavirus *in vitro* with EC50 at 4.51 μM ([Wang *et al.*, 2020a](#_ENREF_24)), and significantly reduced viral loads in clinical trials ([Gautret *et al.*, 2020](#_ENREF_7)). Favipiravir, a mild RdRp inhibitor of SARS-CoV-2 ([Wang *et al.*, 2020a](#_ENREF_24)), was reported to accelerate viral clearance in an open-label control study ([Cai *et al.*, 2020](#_ENREF_2)). Ritonavir was highly distributed to lung ([Denissen *et al.*, 1997](#_ENREF_6)), but it did not show anti-SARS-CoV-2 activity *in vitro* ([Choy *et al.*, 2020](#_ENREF_4)). Therefore, it is not surprising that ritonavir failed to promote viral clearance in the clinical trial. Umifenovir acts as a potent viral inhibitor *in vitro* with EC50 at 4.11 μM ([Choy *et al.*, 2020](#_ENREF_4)), and the lung is one of its major distribution organs ([Liu *et al.*, 2013](#_ENREF_15)), but still failed to reduce viral loads in the clinical trial ([Choy *et al.*, 2020](#_ENREF_4)). We speculated that although the drug distribution of umifenovir in lung is relatively high, its absolute concentration in lung is not adequate to clear the virus. Only 0.833 μg/g of umifenovir was detected in lung after 54 mg/kg P.O. in rats ([Liu *et al.*, 2013](#_ENREF_15)), whereas 13.439 μg/g of hydroxychloroquine was probed in lung after 30 mg/kg P.O. in rats ([Wei *et al.*, 1995](#_ENREF_27)).

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Table 2. Summary of Antiviral activities of antiviral drugs in COVID-19 treatment** | | | | |
| **Antiviral Drugs** | **MOA** | **EC50** [μM] | **Major distribution organs** | **Does drug reduce viral loads in COVID-19 patients** |
| **Azithromycin** | Block endocytosis | 2.12 | Intestine, Heart, Kidney | Reduced viral loads in nasopharyngeal swabs with hydroxychloroquines |
| **Hydroxychloroquine** | Block endocytosis | 4.51 | AG, Muscule, Liver, **Lung** | Reduced viral loads in nasopharyngeal swabs |
| **Chloroquine** | Block endocytosis | 1.13-2.17 | Liver, **Lung**, Kidney | Reduced viral loads in patients |
| **Favipiravir** | Inhibit RdRp | 61.88-100 | **Lung**, Kidney, Spleen, Brain | Reduced viral loads in nasopharyngeal swabs |
| **Ribavirin** | Inhibit RdRp | 109.5-500 | Intestine, Heart | Reduced viral loads in nasopharyngeal swabs with LPV/r and interferon |
| **Lopinavir** | Inhibit 3CLpro | 26.1 | Stomach, Intestine | Failed to reduce viral loads in oropharyngeal swab |
| **Ritonavir** | Inhibit 3CLpro | >100 | Liver, Kidney, **Lung** | Failed to reduce viral loads in oropharyngeal swab |
| **Darunavir** | Inhibit 3CLpro | >100 | Liver, Intestine, Stomach | Failed to reduce viral loads in nasopharyngeal swab |
| **Umifenovir** | Unknown | 10.7 | Stomach, Intestine, **Lung** | Failed to reduce viral loads in pharyngeal swab |
| **Remdesivir** | Inhibit RdRp | 0.11-0.77 | Unknown but not lung | Failed to reduce viral loads in nasopharyngeal and oropharyngeal swab |

Both azithromycin combo (with hydroxychloroquine) ([Gautret *et al.*, 2020](#_ENREF_7)) and ribavirin combo (with LPV/r and interferon) ([Hung *et al.*, 2020](#_ENREF_11)) were reported to benefit COVID-19 patients by reducing viral loads. However, whether these two drugs can help to kill virus alone requires further validation. Lopinavir/ritonavir (LPV/r), the drug combination for HIV treatment, significantly reduced viral loads in the patients with SARS 17 years ago ([Stockman *et al.*, 2006](#_ENREF_20)). Currently, lopinavir showed a mild inhibitory effect on SARS-CoV-2 replication *in vitro* with EC50 at 26.1 μM ([Choy *et al.*, 2020](#_ENREF_4)) but LPV/r failed to promote viral clearance in the COVID-19 patients ([Cao *et al.*, 2020](#_ENREF_3)). Lopinavir was not mainly distributed to the lung and its concentration in lung is only 1.18 μg equiv/ml ([Kumar *et al.*, 2004](#_ENREF_12)). On the other hand, the concentration of ritonavir in lung is high ([Denissen *et al.*, 1997](#_ENREF_6)), but it is an inhibitor of P450 3A4, which is not active in the antiviral screening ([Choy *et al.*, 2020](#_ENREF_4)). Considering that viral loads of SARS-CoV-2 might be much higher than viral loads of SARS-CoV in lung, the low concentration of lopinavir in lung limited its capability of reducing viral loads in the respiratory tract of COVID-19 patients ([Wang *et al.*, 2020b](#_ENREF_25)). Intestine is another susceptible tissue of SARS-CoV-2, and the viral RNA has been detected in the stools ([Wolfel *et al.*, 2020](#_ENREF_28)). Lopinavir is mainly distributed to GI tract, including small intestine, large intestine and stomach ([Kumar *et al.*, 2004](#_ENREF_12)). In this context, lopinavir might reduce viral loads in GI tract rather than respiratory tract.

Currently, remdesivir showed the most potent inhibitory effect on SARS-CoV-2 replication *in vitro* with EC50 at 0.11-0.77 μM ([De Meyer *et al.*, 2020](#_ENREF_5); [Wang *et al.*, 2020a](#_ENREF_24)). Notably, as compared with placebo, remdesivir did not accelerate the viral clearance in the COVID-19 patients ([Wang *et al.*, 2020c](#_ENREF_26)). Because of the poor distribution profiles in the lung , it was believed that remdesivir and its active metabolites might not be adequate to inhibit SARS-CoV-2 in the lung ([Sun, 2020](#_ENREF_22)).

We conclude here that the antiviral drugs should be distributed straight to or accumulate in the lung for reducing viral loads in respiratory tract of COVID-19 patients. Some antiviral drugs, like LPV/r, might inhibit SARS-CoV-2 in the GI tract according to their distribution profiles. However, most of samples for viral RNA test were collected from nasopharyngeal swabs and oropharyngeal saliva in the clinical trials. To better evaluate antiviral drugs that target GI tract, the stool samples should also be collected for viral RNA test in the future.

**Acknowledgment Statement**

This study was supported by the National Natural Science Foundation of China (81903875).

**Conflict of Interest Statement**

The authors declare that they have no conflict of interest.

**References**

Butler A, Hoffman P, Smibert P, Papalexi E, Satija R (2018). Integrating single-cell transcriptomic data across different conditions, technologies, and species. *Nature biotechnology* **36**(5)**:** 411-420.

Cai Q, Yang M, Liu D, Chen J, Shu D, Xia J*, et al.* (2020). Experimental Treatment with Favipiravir for COVID-19: An Open-Label Control Study. *Engineering*.

Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G*, et al.* (2020). A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *The New England journal of medicine* **382**(19)**:** 1787-1799.

Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KPY*, et al.* (2020). Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. *Antiviral research* **178:** 104786.

De Meyer S, Bojkova D, Cinatl J, Van Damme E, Meng CB, Van Loock M*, et al.* (2020). Lack of Antiviral Activity of Darunavir against SARS-CoV-2. *International Journal of Infectious Diseases***:** DOI: https://doi.org/10.1016/j.ijid.2020.1005.1085.

Denissen JF, Grabowski BA, Johnson MK, Buko AM, Kempf DJ, Thomas SB*, et al.* (1997). Metabolism and disposition of the HIV-1 protease inhibitor ritonavir (ABT-538) in rats, dogs, and humans. *Drug metabolism and disposition: the biological fate of chemicals* **25**(4)**:** 489-501.

Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M*, et al.* (2020). Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *International journal of antimicrobial agents***:** 105949.

Gowen BB, Sefing EJ, Westover JB, Smee DF, Hagloch J, Furuta Y*, et al.* (2015). Alterations in favipiravir (T-705) pharmacokinetics and biodistribution in a hamster model of viral hemorrhagic fever. *Antiviral research* **121:** 132-137.

Hindson J (2020). COVID-19: faecal-oral transmission? *Nature reviews. Gastroenterology & hepatology* **17**(5)**:** 259.

Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S*, et al.* (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* **181**(2)**:** 271-280 e278.

Hung IF, Lung KC, Tso EY, Liu R, Chung TW, Chu MY*, et al.* (2020). Triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *Lancet* **395**(10238)**:** 1695-1704.

Kumar GN, Jayanti VK, Johnson MK, Uchic J, Thomas S, Lee RD*, et al.* (2004). Metabolism and disposition of the HIV-1 protease inhibitor lopinavir (ABT-378) given in combination with ritonavir in rats, dogs, and humans. *Pharmaceutical research* **21**(9)**:** 1622-1630.

Lescure FX, Bouadma L, Nguyen D, Parisey M, Wicky PH, Behillil S*, et al.* (2020). Clinical and virological data of the first cases of COVID-19 in Europe: a case series. *The Lancet. Infectious diseases*.

Liao J, Yu Z, Chen Y, Bao M, Zou C, Zhang H*, et al.* (2020). Single-cell RNA sequencing of human kidney. *Scientific data* **7**(1)**:** 4.

Liu X, Pei K, Chen XH, Bi KS (2013). Distribution and excretion of arbidol hydrochloride in rats. *Chinese Journal of New Drugs* **22**(7)**:** 829-833.

Liu Y, Yang Y, Zhang C, Huang F, Wang F, Yuan J*, et al.* (2020). Clinical and biochemical indexes from 2019-nCoV infected patients linked to viral loads and lung injury. *Science China. Life sciences* **63**(3)**:** 364-374.

Ono C, Yamada M, Tanaka M (2003). Absorption, distribution and excretion of 14C-chloroquine after single oral administration in albino and pigmented rats: binding characteristics of chloroquine-related radioactivity to melanin in-vivo. *The Journal of pharmacy and pharmacology* **55**(12)**:** 1647-1654.

Shirato K, Kanou K, Kawase M, Matsuyama S (2017). Clinical Isolates of Human Coronavirus 229E Bypass the Endosome for Cell Entry. *Journal of virology* **91**(1).

Shirato K, Kawase M, Matsuyama S (2018). Wild-type human coronaviruses prefer cell-surface TMPRSS2 to endosomal cathepsins for cell entry. *Virology* **517:** 9-15.

Stockman LJ, Bellamy R, Garner P (2006). SARS: systematic review of treatment effects. *PLoS medicine* **3**(9)**:** e343.

Stuart T, Butler A, Hoffman P, Hafemeister C, Papalexi E, Mauck WM, 3rd*, et al.* (2019). Comprehensive Integration of Single-Cell Data. *Cell* **177**(7)**:** 1888-1902 e1821.

Sun D (2020). Remdesivir for Treatment of COVID-19: Combination of Pulmonary and IV Administration May Offer Aditional Benefit. *The AAPS Journal* **22:** 77.

Uhlen M, Fagerberg L, Hallstrom BM, Lindskog C, Oksvold P, Mardinoglu A*, et al.* (2015). Proteomics. Tissue-based map of the human proteome. *Science* **347**(6220)**:** 1260419.

Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M*, et al.* (2020a). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell research* **30**(3)**:** 269-271.

Wang Y, Chen L (2020b). Lung tissue distribution of drugs as a key factor for COVID-19 treatment. *British Journal of Pharmacology***:** DOI: https://doi.org/10.1111/bph.15102.

Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y*, et al.* (2020c). Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* **395**(10236)**:** 1569-1578.

Wei Y, Nygard GA, Ellertson SL, Khalil SK (1995). Stereoselective disposition of hydroxychloroquine and its metabolite in rats. *Chirality* **7**(8)**:** 598-604.

Wolfel R, Corman VM, Guggemos W, Seilmaier M, Zange S, Muller MA*, et al.* (2020). Virological assessment of hospitalized patients with COVID-2019. *Nature* **581**(7809)**:** 465-469.

Yan KS, Janda CY, Chang J, Zheng GXY, Larkin KA, Luca VC*, et al.* (2017). Non-equivalence of Wnt and R-spondin ligands during Lgr5(+) intestinal stem-cell self-renewal. *Nature* **545**(7653)**:** 238-242.

Ziegler CGK, Allon SJ, Nyquist SK, Mbano IM, Miao VN, Tzouanas CN*, et al.* (2020). SARS-CoV-2 receptor ACE2 is an interferon-stimulated gene in human airway epithelial cells and is detected in specific cell subsets across tissues. *Cell***:** DOI: https://doi.org/10.1016/j.cell.2020.1004.1035.