Received: 7 April 2020 | Revised: 24 April 2020 | Accepted: 30 April 2020

DOI: 10.1111/bph.15102

Themed Issue: The Pharmacology of COVID-19

LETTER TO THE EDITOR

Lung tissue distribution of drugs as a key factor for COVID-19 treatment

LINKED ARTICLES: This article is part of a themed issue on The Pharmacology of COVID-19. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v177.21/issuetoc

Coronavirus Disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has killed over 254,000 people around the world (last update on May 8, 2020). It is impossible to create novel drugs against the coronavirus in a very short time, as this often takes years. Therefore the best strategy is to find new antiviral uses from approved drugs (Harrison, 2020). Not surprisingly, SARS-CoV-2 shares a highly similar viral genome sequence with SARS-CoV (Wan, Shang, Graham, Baric, & Li, 2020), suggesting that the effective treatments for SARS may also work for COVID-19 treatment.

Lopinavir, a protease inhibitor of human immunodeficiency virus type 1 (HIV-1), showed good inhibitory effects on SARS-CoV replication in cell-based assays. In clinical trials, the combination of lopinavir and ritonavir benefited the patients with SARS by reducing the viral loads (Stockman, Bellamy, & Garner, 2006). Lopinavir has been identified as a main protease inhibitor of SARS-CoV and approved for inhibiting the SARS-CoV replication (Nukoolkarn, Lee, Malaisree, Aruksakulwong, & Hannongbua, 2008). Recent docking simulation studies showed that lopinavir can also directly bind to the catalytic pocket of **SARS-CoV-2 main protease**, indicating its potential to reduce the viral loads in patients with COVID-19 (Alessandro, 2020). However, in clinical trials no benefits were observed with lopinavir–ritonavir treatment beyond standard care in patients with COVID-19 (Cao et al., 2020).

Both SARS-CoV and SARS-CoV-2 can attach to **angiotensin-converting enzyme 2** (ACE2) and then enter host cells through ACE2 (Wan et al., 2020). Given that ACE2 is highly expressed in type II alveolar (AT2) cells in lung (Xu et al., 2020), lung becomes a major organ under the coronavirus attack. Notably, ACE2 bound to the **SARS-CoV-2 spike protein** with ~15-nM affinity, which is ~10- to 20-fold higher than the binding capacity of ACE2 to SARS-CoV spike protein (Wrapp et al., 2020). This indicates that SARS-CoV-2 can enter type II alveolar cells in lung much easier than SARS-CoV. Thus, the viral loads of SARS-CoV-2 might be much higher than viral loads of SARS-CoV in the lung tissue. Therefore, it might be more effective if the anti-SARS-CoV-2 drugs could be distributed straight to or accumulate in the lung above other organs/tissues.

In a previous study, the tissue distribution of isotope-labelled lopinavir was examined in rats. The peak radioactivity levels in plasma were achieved at 4 h post-administration. Liver (52.24 μg·equiv·ml^{-1}), adrenals (4.80 μg·equiv·ml^{-1}) and thyroid (4.41 μg·equiv·ml^{-1}) exhibited greater radioactivity levels than plasma after 4 h of oral administration (lopinavir, 10 mg·kg^{-1}). The lung (1.18 μg·equiv·ml^{-1}) exhibited less radioactivity levels than plasma, indicating that the distribution of lopinavir in the lung tissue is relatively low (Kumar et al., 2004). We surmise from this that the concentration of lopinavir in the lung is far too low to inhibit SARS-CoV-2 replication. This might explain why lopinavir did not benefit the patients with COVID-19.

Unlike lopinavir, **chloroquine** exhibited clinical and virologic benefits in the treatment of COVID-19 patients, including improving lung image findings and reducing the viral loads. In preclinical studies, chloroquine showed strong inhibitory effects on SARS-CoV-2 replication in cell-based assays (EC_{50} = 1.13 μM) (Wang et al., 2020). Although chloroquine was reported to impair the endosome-mediated viral entry, the precise mechanism of action of chloroquine remains unclear. Lung is one of the major target tissues of chloroquine, as evidenced by the tissue distribution studies in rats. After an oral administration of ^{14}C-chloroquine (20 mg·kg^{-1}), the concentrations of ^{14}C-chloroquine in lung tissues were similar in albino and pigmented rats (30.76 ± 0.85 and 34.76 ± 1.56 μg·equiv·ml^{-1}, respectively) (Ono, Yamada, & Tanaka, 2003). In a long-term treatment study (16.8 mg·kg^{-1}·day^{-1}, total 32 weeks), the concentrations of chloroquine in lung tissues were 51.7 ± 3.1 and 104 ± 7.0 μg·mg^{-1} in male and female rats, respectively (McChesney, Banks, & Fabian, 1967). Both these pharmacokinetics studies showed that the concentration of chloroquine is high in the lung tissue. We believe that chloroquine can take an advantage of the high volume of the lung distribution to inhibit the viral replication in the lung. Therefore, besides the mechanism of action of antiviral drugs, the lung distributions of drugs should be considered in the COVID-19 treatment.

In conclusion we propose that anti-SARS-CoV-2 drug repurposing studies should pay more attentions to the lung tissue distribution of antiviral drugs. Considering the high viral loads in the lung tissue of COVID-19, the low volume of the lung distribution of antiviral drugs

might not be sufficient to inhibit the coronavirus replication. Among the anti-SARS-CoV-2 drugs in clinical trials, chloroquine is likely to be a promising drug that benefit COVID-19 patients because of its high volume of the lung distribution. So far, **remdesivir** is the most potent inhibitor of SARS-CoV-2 *in vitro* (EC_{50} = 0.77 μM) (Wang et al., 2020) but there is a lack of the tissue distribution data in the public domain. Although remdesivir was reported to reduce MERS-CoV viral lung loads in animals (de Wit et al., 2020), we are eager to see the lung tissue distribution data. This would help in determining an appropriate dosing and route of administration for remdesivir in humans. Overall pharmacodynamic markers need to be also considered in these drug repurposing studies. Thus, high-quality pharmacokinetic and pharmacodynamic (PK/PD) data could help in determining whether these drugs are truly effective or ineffective in the clinical trials.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

Yan Wang PhD[1]
Lei Chen PhD[2]

[1]*Center for Translation Medicine Research and Development, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China*
[2]*Department of Genetics, Human Genetics Institute of New Jersey, Rutgers University, Piscataway, New Jersey, USA*

Correspondence
Yan Wang, Center for Translation Medicine Research and Development, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen 518055, China.
Email: yan.wang@siat.ac.cn
Lei Chen, Department of Genetics, Human Genetics Institute of New Jersey, Rutgers University, Piscataway, NJ 08854, USA.
Email: lchen@dls.rutgers.edu

ORCID

Yan Wang https://orcid.org/0000-0003-0671-7312
Lei Chen https://orcid.org/0000-0001-7812-508X

REFERENCES

Alessandro, C. (2020). Virtual screening of an FDA approved drugs database on two COVID-19 coronavirus proteins. *ChemRxiv*, 1–6. https://doi.org/10.26434/chemrxiv.11847381

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., … Wang, C. (2020). A trial of lopinavir-ritonavir in adults hospitalized with severe COVID-19. *The New England Journal of Medicine*, *382*, 1787–1799. https://doi.org/10.1056/NEJMoa2001282

de Wit, E., Feldmann, F., Cronin, J., Jordan, R., Okumura, A., Thomas, T., … Feldmann, H. (2020). Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(12), 6771–6776. https://doi.org/10.1073/pnas.1922083117

Harrison, C. (2020). Coronavirus puts drug repurposing on the fast track. *Nature Biotechnology*, *38*(4), 379–381. https://doi.org/10.1038/d41587-020-00003-1

Kumar, G. N., Jayanti, V. K., Johnson, M. K., Uchic, J., Thomas, S., Lee, R. D., … Roberts, S. A. (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. https://doi.org/10.1023/B:PHAM.0000041457.64638.8d

McChesney, E. W., Banks, W. F. Jr., & Fabian, R. J. (1967). Tissue distribution of chloroquine, hydroxychloroquine, and desethylchloroquine in the rat. *Toxicology and Applied Pharmacology*, *10*(3), 501–513. https://doi.org/10.1016/0041-008X(67)90089-0

Nukoolkarn, V., Lee, V. S., Malaisree, M., Aruksakulwong, O., & Hannongbua, S. (2008). Molecular dynamic simulations analysis of ritonavir and lopinavir as SARS-CoV 3CL(pro) inhibitors. *Journal of Theoretical Biology*, *254*(4), 861–867. https://doi.org/10.1016/j.jtbi.2008.07.030

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. https://doi.org/10.1211/0022357022340

Stockman, L. J., Bellamy, R., & Garner, P. (2006). SARS: Systematic review of treatment effects. *PLoS Medicine*, *3*(9), 1525–1531. https://doi.org/10.1371/journal.pmed.0030343

Wan, Y., Shang, J., Graham, R., Baric, R. S., & Li, F. (2020). Receptor recognition by the novel coronavirus from Wuhan: An analysis based on decade-long structural studies of SARS coronavirus. *Journal of Virology*, *94*(7). http://doi.org/10.1128/JVI.00127-20

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., … Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Research*, *30*(3), 269–271. https://doi.org/10.1038/s41422-020-0282-0

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., … McLellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science*, *367*(6483), 1260–1263. https://doi.org/10.1126/science.abb2507

Xu, H., Zhong, L., Deng, J., Peng, J., Dan, H., Zeng, X., … Chen, Q. (2020). High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. *International Journal of Oral Science*, *12*(8), 1–5. https://doi.org/10.1038/s41368-020-0074-x