



## Letter to Editor

# ACE 2 in the Context of COVID 19 – An Opportunity for us or the Virus

 Oliyath Ali,<sup>1</sup>  Ishrit Yasin<sup>2</sup>

<sup>1</sup>Department of ENT & HNS, District Hospital Kargil, Ladakh, India

<sup>2</sup>Department of Dental Surgery, District Hospital Kargil, Ladakh, India

**Cite This Article:** Ali O, Yasin I. ACE 2 in the Context of COVID 19 – An Opportunity for us or the Virus. EJMO 2020;4(2):137–138.

In 2000, a homologue of ACE was cloned by two independent groups and termed angiotensin-converting enzyme 2 which was found to be an important part of the RAS system. This trans membrane metallopeptidase, removes a single residue from Ang I to yield Ang (1–9) and cleaves a single residue from Ang II to generate Ang (1–7).<sup>[1, 2]</sup> Expression of ACE 2 has also been reported in type 2 pneumocytes,<sup>[3]</sup> and limited human pathological studies demonstrate that the respiratory tract is a major site of SARS-CoV infection and morbidity.<sup>[4, 5]</sup>

The extracellular domain of ACE 2 has been demonstrated as a receptor for the spike (S) protein of SARS-CoV,<sup>[6]</sup> human corona virus NL63<sup>[7]</sup> and recently, for the SARS-CoV-2.<sup>[8]</sup> The SARS-CoV-2 binds ACE2 with higher affinity than SARS-CoV.<sup>[9]</sup> Although ACE 2 provides cellular entry to the Corona Virus, from animal studies we know that ACE2 plays a protective role in acute lung injury. Mechanistically, the negative regulation of Ang II levels by ACE2 account, in part, for the protective function of ACE2 in ARDS.<sup>[10]</sup> This seemingly paradoxical process underlies the pathogenesis of SARS from Corona Virus which involves binding of the coronavirus spike protein to ACE2, leading to ACE2 down regulation, which in turn results in excessive production of angiotensin by the related enzyme ACE, while less ACE2 is available for converting it to the vasodilator heptapeptide angiotensin 1–7. This in turn contributes to lung injury, as angiotensin-stimulated AT1R results in increased pulmonary vascular permeability, thereby mediating increased lung pathology.<sup>[11, 12]</sup>

There is also a soluble form of ACE2 which lacks the membrane anchor and circulates in small amounts in the blood.<sup>[13]</sup> It has been found that the soluble form of ACE2, blocks association of the S1 domain and viral replication in SARS coronavirus (SARSCoV)- permissive Vero E6 cells.<sup>[14, 15]</sup>

The S protein of HCoV-NL63 virus circulating in the human population which is only modestly pathogenic in most cases, and the S proteins of SARS-CoV bind overlapping regions of ACE2 that include a critical loop between its fourth and fifth  $\beta$ -strands.<sup>[16]</sup> Potent neutralizing activity directed against NL63-S protein has been detected in virtually all sera from patients 8 years of age or older, suggesting that HCoV-NL63 infection of humans is common and usually acquired during childhood.<sup>[7]</sup>

From animal experiments we have been able to synthesise inhibitors of ACE 2 like GL1001, which is a selective and potent ACE2 inhibitor,<sup>[17]</sup> and it has been seen to exhibit anti-inflammatory effects in the upper gastrointestinal tract of the mouse<sup>[18, 19]</sup> and protects against NSAID-induced gastric damage in rats.<sup>[20]</sup>

In the light of the above information we propose the following therapeutic options for further research and testing in COVID 19.

1. Soluble ACE 2 can be a potential therapeutic option in SARS CoV 2 cases as it competes for the Viral Spike S protein making it less available for binding with the transmembrane ACE 2. It can be given in an inhaler or

**Address for correspondence:** Oliyath Ali, MD. Department of ENT & HNS, District Hospital Kargil, Ladakh, India

**Phone:** +918082891002 **E-mail:** droliyatali@gmail.com

**Submitted Date:** March 20, 2020 **Accepted Date:** April 08, 2020 **Available Online Date:** April 15, 2020

©Copyright 2019 by Eurasian Journal of Medicine and Oncology - Available online at [www.ejmo.org](http://www.ejmo.org)

**OPEN ACCESS** This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



nebulised form because the main site of SARS CoV 2 attack is the respiratory track.

2. Although attempts to make a vaccine based on viral proteins is underway, it may take more than a year to become available and may not be so useful given the ability of the virus to undergo frequent mutations. Therefore we should attempt to make an antibody against the ACE 2 receptor which can compete with the virus for binding. This can be delivered to the lungs again via inhaler or nebulizer and simultaneously ACE 2 analogues or Ag 1-7 infusion can be systemically administered to benefit from its anti-inflammatory effects.
3. A selective potent inhibitor of ACE 2 again delivered via inhalation or nebulization can prove useful.
4. Co-infection with human corona Virus NL 63 can make the disease less severe owing to same receptor binding and being less pathogenic and as most individual are already immune to NL 63.

#### Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

#### References

1. Tipnis SR, Hooper NM, Hyde R, Karran E, Christie G, Turner AJ. A human homolog of angiotensin-converting enzyme. Cloning and functional expression as a captopril insensitive carboxypeptidase. *J Biol Chem* 2000;275:33238–43. [CrossRef]
2. Douglas GC, O'Bryan MK, Hedger MP, Lee DK, Yarski MA, Smith AI & Lew RA. The novel angiotensin converting enzyme (ACE) homolog, ACE2, is selectively expressed by adult Leydig cells of the testis. *Endocrinology* 2004;145:4703–11. [CrossRef]
3. Hamming I, Timens W, Bulthuis M.L, Lely A.T, Navis G. and van Goor H. Tissue distribution of ace2 protein, the functional receptor for sars coronavirus. A first step in understanding sars pathogenesis. *J. Pathol* 2004;203:631–7. [CrossRef]
4. Franks TJ, PY Chong, P Chui, JR Galvin, RM Lourens, AH Reid, et al. Lung pathology of severe acute respiratory syndrome (SARS): a study of 8 autopsy cases from Singapore. *Hum. Pathol* 2003;34:743–8. [CrossRef]
5. Nicholls J M, L L Poon, K C Lee, W F Ng, S T Lai, C Y Leung, et al. Lung pathology of fatal severe acute respiratory syndrome. *Lancet* 2003;361:1773–8. [CrossRef]
6. Du L, He Y, Zhou Y, Liu S, Zheng B.J. and Jiang S. The spike protein of sars-cov-a target for vaccine and therapeutic development. *Nat. Rev. Microbiol* 2009;7:226–36. [CrossRef]
7. Hofmann H, P. Krzysztol, L. van der Hoek, M. Geier, B. Berkhout, and S. Pohlmann. 2005. Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. *Proc Natl Acad Sci USA* 102:7988–93. [CrossRef]
8. Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: Implications for virus origins and receptor binding. *Lancet* 2020;395:565–74. [CrossRef]
9. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL, Abiona O, et al. (2020) Cryo-em structure of the 2019-ncov spike in the prefusion conformation. *Science*, <https://doi.org/10.1126/science.abb2507>. [CrossRef]
10. Yumiko Imai, Keiji Kuba and Josef M. Penninger. The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. *Exp Physiol* 93.5 pp 543–548. [CrossRef]
11. Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature* 2005;436:112–6. [CrossRef]
12. Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Medicine* 2005;11:875–9.
13. Wysocki J, Ye M, Rodriguez E, Gonzalez-Pacheco FR, Barrios C, Evora K, et al. Targeting the degradation of angiotensin ii with recombinant angiotensin-converting enzyme 2: Prevention of angiotensin ii-dependent hypertension. *Hypertension* 2010;55:90–8. [CrossRef]
14. Li W, Moore MJ, Vasilieva N, Sui J, Wong SK, Berne MA, et al. Angiotensin-converting enzyme 2 is a functional receptor for the sars coronavirus. *Nature* 2003;426:450–4. [CrossRef]
15. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. A novel coronavirus associated with severe acute respiratory syndrome. *N Engl J Med* 2003;348:1953–1966. [CrossRef]
16. W Li, et al. The S proteins of human coronavirus NL63 and severe acute respiratory syndrome coronavirus bind overlapping regions of ACE2. *Virology* 2007;367:367–74. [CrossRef]
17. Dales NA, Gould AE, Brown JA, Calderwood EF, Guan B, Minor CA, et al. Substrate-based design of the first class of angiotensin converting enzyme-related carboxypeptidase (ACE2) inhibitors. *J Am Chem Soc* 2002;124:11852–3. [CrossRef]
18. Malstrom S, Tyler S, Ellard C, Collins H, Coopersmith R, Barnes T, White D, Tartaglia L. Use of in vivo bio-photonic imaging to identify novel therapeutic utility for use of the ACE2 inhibitor GL1001 for treating inflammatory disorders of the gastrointestinal tract. Paper presented at IBC 13th annual world congress, drug discovery & development of innovative therapeutics 2008 Aug; Boston, MA.
19. Malstrom S, Ellard C, Collins H, Coopersmith B, Barnes T, White D, Dimitrov L, Tartaglia L. Using in vivo biophotonic imaging in the repositioning of an ACE2 inhibitor. Paper presented at GTCbio conference, imaging in preclinical and clinical drug development 2007 Mar; Boston, MA.
20. Guzman LM, Odate S, Boiselle CA, Gross SB, Wallace JL, Coopersmith R, et al. GL1001 inhibition of ACE2 is gastroprotective in rat models of gastritis. *Inflamm Bowel Dis* 2008;14:S14.