Perspective

# ET-traps as a potential treatment for COVID-19

## 1. Introduction

COVID-19 or the coronavirus pandemic results from a novel coronavirus strain. COVID-19 is an infectious disease that has already infected more than 3.5 million individuals [1]. The majority of individuals that have contracted COVID-19 do not experience any severe respiratory problems. The elderly, and people having pre-existing health conditions, including diabetes, pulmonary disease, complications with the heart or kidney and certain cancers end up developing serious complications. There is currently no treatment for COVID-19. In this paper, we discuss the present situation of developing a treatment for COVID-19 and the potential use of ET-traps (already established proof-of-concept for diabetes) as a therapeutic for COVID-19.

## 2. Increased pro-inflammatory cytokines in a COVID-19 infection

A coronavirus infection is found to be associated with an up regulation of different cytokines that are pro-inflammatory [2–5]. Increased production of cytokines results in a cytokine storm, leading to an increased risk of excessive vascular permeability, failure of different organs, and eventually can lead to death when this increased cytokine concentration is not corrected [3].

Previous research has found that endothelin-1 (ET-1) is a stimulus of these cytokines [6]. Therefore, a tool such as ET-traps, which has been found to reduce elevated ET-1 levels, would also help with this cytokine storm.

## 3. What are ET-traps?

ET-traps are Fc fusion proteins that contain endothelin receptor ligand binding domains [7]. This includes the binding domains of the endothelin A (ETA) or endothelin B (ETB) receptors. Previous work has found that the ET-traps effectively bring down ET-1 to normal, control levels [8,9]. This was associated with the reduction in different markers of diabetes pathology. Previous animal work showed that heart and kidney functions return to normal, non-disease levels [9]. Based on current literature, the ET-traps would also restore lung function [10–12]. These studies have shown that ET-1 is elevated in disorders of the lung and explain that ET-1 is a key pathological factor. Therefore, given that ET-traps have been shown to remedy underlying health issues that escalate the risk of a serious COVID-19 infection, the ET-traps would likely offer a therapy for the COVID-19 pandemic. Furthermore, given that ET-1 acts upstream and is a stimulus of different pro-inflammatory cytokines [6,13] (Fig. 1), this tool would help control the cytokine storm.

The binding of ET-1 to its receptors results in an increase of different cytokines through various cell signaling pathways [6].

Currently, there are different therapies for COVID-19 that are being tested for use in human clinical trials. This includes repurposed drugs that are already approved for human use in other disease states, as well as vaccines. A potential problem with vaccines is that the virus may mutate and therefore the efficacy of the intended vaccine would be low if any. A group currently testing their developed vaccine for COVID-19 claims that their vaccine is so strong that it would overcome any mutations in the virus. However, a big issue here is of over stimulating the immune system, which could later lead to an autoimmune disorder [14,15]. Given the current urgency of developing a suitable treatment for COVID-19, human testing of these treatments is being expedited and unfortunately the risk of an autoimmune condition would only appear after a few years. Previous research has shown that vaccination can cause different autoimmune diseases, like type-I diabetes and multiple sclerosis [16,17]. In fact, a world health expert has stated that "Don't bet on vaccine to protect us from Covid-19" [18]. In fact, the Prime Minister of the United Kingdom, has also expressed his concerns on a vaccine offering a long term solution for the COVID-19 pandemic [19,20]. Research into drugs to control symptoms associated with COVID-19 has been touted. Furthermore, a recent report states that a third of the deaths in the UK due to COVID-19 are of diabetics [21]. The heart and kidneys can be adversely affected in diabetes [22,23]. Previous work has established the proof-of-concept for use of ET-traps in diabetes [8,9]. The ET-traps bring measures (of diabetes pathology, including poor cardiac and renal functions) return to healthy levels. Although these studies showed that the ET-traps exhibit no toxicity, more work is required to ascertain ET-traps as a therapeutic.

Repurposed drugs, being tested for COVID-19 (already approved for use in other diseases) have a caveat that many compromise the immune system and cause other health complications like problems with the heart and therefore should not be used as a treatment for an infection such as COVID-19 [24–28].

A recent development has found that children infected with COVID-19 have gone on to develop serious symptoms, including septic shock [29]. Septic shock or sepsis is most commonly caused by a severe infection [30]. Septic shock is associated with an increase of ET-1 levels in the plasma [31]. Kaffarnik et al. (2017) have found that these increased levels of ET-1 are a pathological factor in sepsis. Endotoxins in pathological conditions stimulate increased ET-1 levels. These increased ET-1 levels contribute to the pro-inflammatory response, the cytokine storm discussed before. This leads to damage of various organs such as liver, lung, heart and kidney [30]. Previous animal work has found that use of ET-traps restores liver, heart and kidney functions [9].
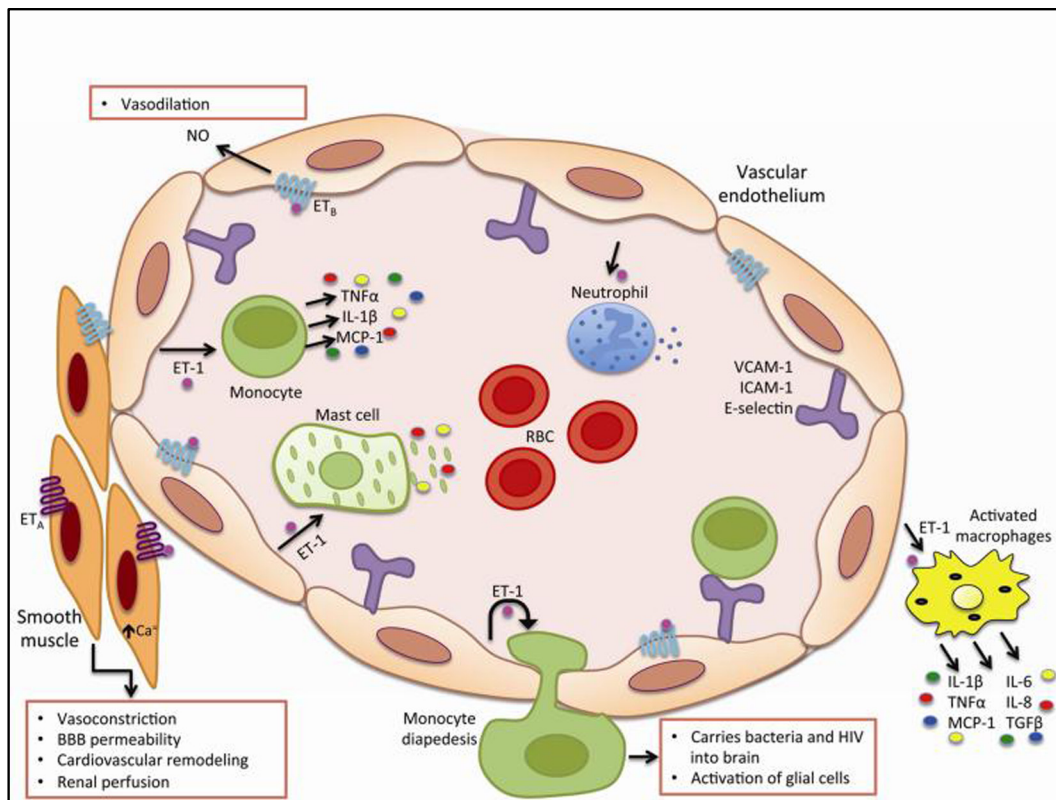
**Fig. 1.** Effects of ET-1 on the cytokine storm.

ET-1 is clearly an important pathological factor in COVID-19 and therefore an important therapeutic target. Therefore, endothelin receptor antagonists (ERAs) already approved for use in other disease areas may provide a therapeutic for COVID-19. One issue here is that ERAs, such as Macitentan, are not currently approved for use in children or women of childbearing age because of teratogenicity. This issue has been discussed in a previous publication [32] and is because ET-1 has an essential role in different physiological processes and so the ET-system cannot be fully blocked as would an ERA. With ET-traps, we are merely sequestering high ET-1 levels that are associated with pathology, without fully blocking ET-1 functions. Previous studies have shown a therapeutic effect of the ET-traps at the working concentration [8,9]. Furthermore, ET-traps show stronger binding affinity that is about a 1000-fold higher than the strongest ERA [32]. This is in addition to the ET-traps showing no toxicity [9].

## 4. Conclusion

Therefore, the ET-traps would provide a therapeutic for the COVID-19 pandemic. This would require further evaluation at both the cell and animal levels in appropriate models. Previous research has shown that the ET-traps are a potential therapy for diabetes with diabetics being at a higher risk of a serious COVID-19 complication, they would also help tackle the cytokine storm that previous research has shown can be induced by ET-1 and they would also help improve cardiac and renal functions (both of which are compromised in a COVID-19 infection). Experts in the field of ET-1 research have commended the value of ET-traps [33,34]. The ET-traps may provide a much needed, life-saving therapeutic for use in COVID-19.

## Conflict of interest

Both authors are a part of Accelerate Cambridge.

## Credit Author Statement

**Arjun Jain:** Contributed to writing and revising the manuscript.
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## References

[1] WHO. Coronavirus disease (COVID-19) pandemic. World Health Organisation; 2020.
[2] Channappanavar R, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection outcomes. J Clin Invest. 2019;130:3625–39.
[3] Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020.
[4] Mehta P, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.
[5] Sarah B. What Is a Cytokine Storm? Doctors Explain How Some COVID-19 Patients' Immune Systems Turn Deadly. Available from: https://www.health.com/condition/infectious-diseases/coronavirus/cytokine-storm; 2020.
[6] Freeman BD, et al. Endothelin-1 and its role in the pathogenesis of infectious diseases. Life Sci. 2014;118(2):110–9.
[7] Jain A, et al. Creating a Soluble Binder to Endothelin-1 based on the natural ligand binding domains of the endothelin-1 (G-protein-coupled) receptor. Int J Pept Res Ther. 2017:107–14.
[8] Arjun J, et al. Endothelin-1 traps potently reduce pathologic markers back to basal levels in an in vitro model of diabetes. J Diabetes Metab Disord. 2018.
[9] Jain A, et al. In vivo studies demonstrate that endothelin-1 traps are a potential therapy for type I diabetes. J Diabetes Metab Disord. 2019:133–43.
[10] Fagan KA, McMurtry IF, Rodman DM. Role of endothelin-1 in lung disease. Respir Res. 2001;2(2):90–101.

[11] Swigris JJ, Brown KK. The role of endothelin-1 in the pathogenesis of idiopathic pulmonary fibrosis. BioDrugs. 2010;24(1):49–54.

[12] Wilkins MR. Pulmonary hypertension: the science behind the disease spectrum. Eur Respir Rev. 2012;21(123):19–26.

[13] Teder P, Noble PW. A cytokine reborn? Endothelin-1 in pulmonary inflammation and fibrosis. Am J Respir Cell Mol Biol. 2000;23(1):7–10.

[14] Callier V. Autoimmune diseases may be side effect of a strong immune system. New Scientist; 2016.

[15] Blach-Olszewska Z, Leszek J. Mechanisms of over-activated innate immune system regulation in autoimmune and neurodegenerative disorders. Neuropsychiatr Dis Treat. 2007;3(3):365–72.

[16] Vadalà M, et al. Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon? EPMA J. 2017;8(3):295–311.

[17] Segal Y, Shoenfeld Y. Vaccine-induced autoimmunity: the role of molecular mimicry and immune crossreaction. Cell Mol Immunol. 2018;15(6):586–94.

[18] McKie R, Helm T, Savage M. Don't bet on vaccine to protect us from Covid-19, says world health expert. The Guardian; 2020.

[19] Agencies N. Boris Johnson: Coronavirus vaccine 'might not come to fruition'. Aljazeera News; 2020.

[20] Agency SN. Coronavirus vaccine may never be found, Boris Johnson says. Sky News; 2020.

[21] Agency IN. Almost a third of patients to die with Covid-19 had diabetes – NHS England. ITV News; 2020.

[22] Pecoits-Filho R, et al. Interactions between kidney disease and diabetes: dangerous liaisons. Diabetol Metab Syndr. 2016;8:50.

[23] Kenny HC, Abel ED. Heart Failure in Type 2 Diabetes Mellitus Impact of Glucose-Lowering Agents, Heart Failure Therapies, and Novel Therapeutic Strategies. Circ Res. 2019;124(1):121–41.

[24] Ye B, et al. Effects of BTK signalling in pathogenic microorganism infections. J Cell Mol Med. 2019;23(10):6522–9.

[25] Calquence(Acalabrutinib Capsules) side effects drug center. Available from: https://www.rxlist.com/calquence-side-effects-drug-center.htm; 2019.

[26] Covid-19: VA Study Points to Increased Mortality with Hydroxychloroquine. PhysiciansWeekly; 2020.

[27] Boseley S. Hydroxychloroquine: Trump's Covid-19 'cure' increases deaths, global study finds. The Guardian; 2020.

[28] Communication, F.D.S. FDA cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems; 2020.

[29] Taylor C. Coronavirus could be causing new inflammatory condition in children, UK health officials warn. CNBC; 2020.

[30] Kowalczyk A, et al. The role of endothelin-1 and endothelin receptor antagonists in inflammatory response and sepsis. Arch Immunol Ther Exp (Warsz). 2015;63(1):41–52.

[31] Kaffarnik MF, et al. Correlation between plasma endothelin-1 levels and severity of septic liver failure quantified by maximal liver function capacity (LiMAx test). A prospective study. PLoS One. 2017;12(5):e0178237.

[32] Jain A, et al. Endothelin-1 traps as a potential therapeutic tool: from diabetes to beyond? Drug Discov Today. 2019;24(9):1937–42.

[33] Barton M, Yanagisawa M. Endothelin: 30 Years From Discovery to Therapy. Hypertension. 2019;74(6):1232–65.

[34] Wernly B, Jung C. Trapping endothelin-1 to hunt down cardiovascular disease? Drug Discov Today. 2019;24(11):2108–10.