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Title: **Reducing mortality from 2019-nCoV: host-directed therapies should be an option**

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The number of confirmed cases of coronavirus 2019-nCoV reported to WHO globally has risen to 4593, with 4537 from China and 56 from 14 other countries (1). As with two other WHO priority Blueprint pathogens SARS-CoV (2) and MERS-CoV (3), the 2019-nCoV is lethal and has caused 106 deaths. There is no specific anti-viral treatment available. The mainstay of clinical management is largely symptomatic, providing supportive and symptomatic care, with organ support in intensive care for seriously ill patients. The unprecedented flurry of activity by WHO and other global public health bodies has focused on transmission, infection control measures and screening of travelers. The development of vaccines has received immediate funding. However, as with SARS, MERS and now 2019-nCoV, support for developing treatments for reducing mortality has not been forthcoming. There is an urgent need for focusing funder and scientific investments into advancing novel therapeutic interventions for coronavirus infections.

All three lethal coronaviruses, MERS-CoV, SARS-CoV and the 2019-nCoV induce excessive and aberrant non-effective host immune responses which are associated with severe lung pathology, clinical deterioration and death (2,3,4). Similar to patients with SARS-CoV and MERS-CoV, the novel Wuhan 2019-nCoV causes acute respiratory distress syndrome (ARDS) with characteristic pulmonary ground class changes on imaging, with a cytokine storm and increased plasma levels of IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα which are higher in moribund patients (2-6). In those who survive intensive care, the long-term consequences of these aberrant and excessive immune responses leads to long term suffering from lung damage and fibrosis, with functional disability, and reduction of their quality of life (7,8).

Whilst specific anti-2019-nCoV drugs will take several years to develop and evaluate, a range of potential host-directed therapies (HDTs) which are safe are already available on the market can be repurposed for use in patients with 2019-nCoV infection (9-11) (**Figure 1**). A number of already marketed drugs with excellent safety profiles such as Metformin, Glitazones, fibrates, Sartans, Atorvastin, nutrient supplements, and biologics could reduce immunopathology, boost immune responses and prevent or curb ARDS. (10,11) Zinc and other metal formulations appear to have anti-viral activity (12), are safe, cheap and readily available. These could be used as adjuncts to monotherapy or combinational therapies with cyclosporine, lopinavir–ritonavir, interferon beta-1b, ribavirin, remdesivir and/or mAbs and antiviral peptides targeting nCoV (11). Anti-IL-6 directed agents such as Tocilizumab have a good safety profile. Monoclonal and polyclonal antibodies to 2019-nCoV could be developed for post-exposure prophylaxis.

Ongoing trials of cellular therapies for treatment of ARDS could be expanded to treatment of seriously ill patients with 2019-nCoV infection. Cellular therapy (13) using mesenchymal stromal cells (MCS) from allogeneic donors has been shown to reduce non-productive inflammation, effect tissue regeneration and are being evaluated in phase I/II trials in patients with ARDS (MD Anderson, Texas, USA NCT02804945), and (Guangzhou, Guangdong, China NCT03608592). Infection with 2019nCoV appears to be initially associated with an increased Th2 response (Ref). This may reflect a physiological reaction to curb overt inflammatory responses – a well-known clinical phenomenon that guided the precise timing of IFN treatment in patients with sepsis (15) associated with increased survival. Anti-IL-17-blockade may benefit those 2019nCoV-infected patients with increased IL17 levels.

Several unique opportunities to perform studies and evaluations of a range of therapeutic and preventive interventions at the peak of the SARS and MERS outbreaks were lost due to delays and subsequent decline of the numbers of cases. Disappointingly, clinical trials registered and planned for MERS-CoV are still not yet completed and numerous questions regarding pathogenesis remains unknown due to lack of adequate numbers of cases. As the 2019-nCoV continues to spread, and evolve, and the numbers of deaths rise exponentially, reducing the number of deaths is crucial in the management of patients with 2019-nCoV infection.

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References

1. WHO 2020. Novel coronavirus (2019-nCoV) situation report 5. January 28th 2020. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports/

2. Hui DSC, Zumla A. Severe Acute Respiratory Syndrome: Historical, Epidemiologic, and Clinical Features. Infect Dis Clin North Am. 2019;33(4):869–889. doi:10.1016 /j.idc. 2019.07.001

3. Azhar EI, Hui DSC, Memish ZA, Drosten C, Zumla A. The Middle East Respiratory Syndrome (MERS). Infect Dis Clin North Am. 2019;33(4):891–905. doi:10.1016/j.idc.2019.08.001
4. Huang C, Wang Y, Li X. Clinical features of patients infected with 2019 coronavirus in Wuhan, China. Published online January 24, 2020 https://doi.org/10.1016/ S0140-6736(20)30183-5.
5. Li G, Fan Y, Lai Y, et al. Coronavirus Infections and Immune Responses [published online ahead of print, 2020 Jan 25]. J Med Virol. 2020;10.1002/jmv.25685. doi:10.1002/jmv.25685
6. Channappanavar R, Perlman S. Pathogenic human coronavirus infections: causes and consequences of cytokine storm and immunopathology. Semin Immunopathol. 2017;39(5):529–539. doi:10.1007/s00281-017-0629-x
7. Batawi S, Tarazan N, Al-Raddadi R, et al. Quality of life reported by survivors after hospitalization for Middle East respiratory syndrome (mers). Health Qual Life Outcomes 2019; 17(1): 101.
8. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. Respirology 2010; 15(3): 543-50.
9. Zumla A, Chan JF, Azhar EI, Hui DS, Yuen KY. Coronaviruses - drug discovery and therapeutic options. Nat Rev Drug Discov 2016; 15(5): 327-47.
10. Beigel JH, Nam HH, Adams PL, et al. Advances in respiratory virus therapeutics - a meeting report from the 6th ISIRV antiviral group conference. Antiviral Res 2019; 167: 45-67.
11. Zumla A, Azhar EI, Arabi Y, et al. Host-directed therapies for improving poor treatment outcomes associated with the middle east respiratory syndrome coronavirus infections. Int J Infect Dis. 2015;40:71–74. doi:10.1016/j.ijid.2015.09.005
12. Barnard DL, Wong MH, Bailey K, et al. Effect of oral gavage treatment with ZnAL42 and other metallo-ion formulations on influenza A H5N1 and H1N1 virus infections in mice. Antivir Chem Chemother. 2007;18(3):125–132. doi:10.1177/095632020701800302
13. Horie S, Gonzalez HE, Laffey JG, Masterson CH. Cell therapy in acute respiratory distress syndrome. J Thorac Dis 2018; 10(9): 5607-20.

Figure 1

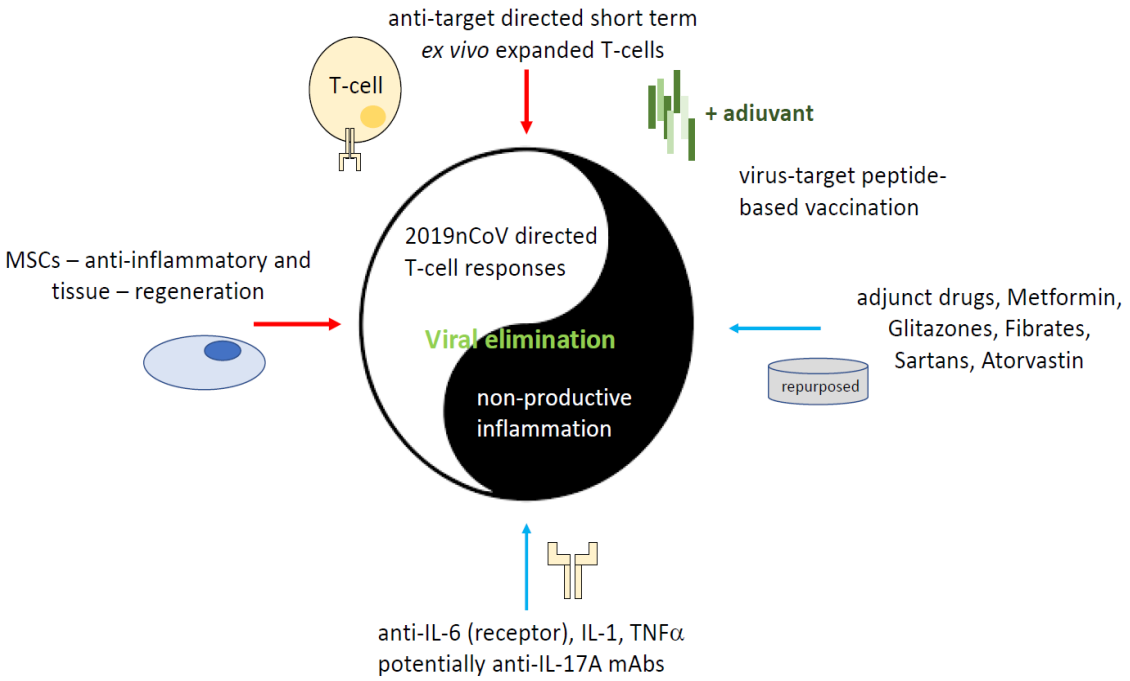

Figure Legend

A key clinical feature in 2019nCoV infection is the balance of increasing or maintaining anti-pathogen-specific immune responses while avoiding overt inflammation. Short term ex vivo expansion of viral - specific T-cells is commonly used in patients with aHSCT and can be used to tailor anti-coronavirus specific T-cells. MSCs reduce inflammation and have tissue-remodeling capacities, mAbs directed inflammatory cytokines curb a 'cytokine storm' and 'repurposed drugs' may be considered to reduce harmful inflammation without loss of immunocompetence. Peptide-based vaccines can be safely and swiftly produced with the advantage to incorporate viral isolate-directed information. Such biological therapy is to be guided by smart sampling that allows to define clinically and biologically relevant biomarkers.