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# Effective therapy & approach to combat corona virus - Covid- 19

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## INTRODUCTION

The ideal scenario — once infected, a person is completely immune for life — is correct for a number of infections. The Danish physician Peter Panum famously figured this out for measles when he visited the Faroe Islands (between Scotland and Iceland) during an outbreak in 1846 and found that residents over 65 who had been alive during a previous outbreak in 1781 were protected. This striking observation helped launch the fields of immunology and epidemiology — and ever since, as in many other disciplines, the scientific community has learned that often things are more complicated.

One example of "more complicated" is immunity to coronaviruses, a large group of viruses that sometimes jump from animal hosts to humans: CoV is an enveloped, positive-sense single-stranded RNA (ss-RNA) virus belonging to the *Coronaviridae* family. The CoV family consists of several species and causes upper respiratory tract and gastrointestinal infections in mammals and birds. In humans, it mainly causes common cold, but complications including pneumonia and SARS can occur.[1] The known human CoV (HCoV) includes HCoV-229E, -OC43, -NL63, -HKU1, and the more widely known severe acute respiratory syndrome coronavirus (SARS-CoV) which caused a global threat with high mortality in 2003.[2] In 2012, the World Health Organization (WHO) designated a sixth type of HCoV infection identified as the Middle East respiratory syndrome coronavirus (MERS-CoV) which is associated with high fatality.[3]

SARS-CoV-2 is the third major coronavirus epidemic to affect humans in recent times, after the SARS outbreak of 2002-3 and the MERS outbreak that started in 2012.Among the many uncertainties that remain about Covid-19 is how the human immune system responds to infection and what that means for the spread of the disease. Immunity after any infection can range from lifelong and complete to nearly non-existent. So far, however, only the first glimmers of data are available about immunity to SARS-CoV-2, the coronavirus that causes Covid-19.

## MECHANISM OF INFECTION

**ACE2 as a target for SARS-CoV-2 invasion:** SARS-CoV and SARS-CoV-2 both use the same keyhole to enter cells, the ACE2 receptor. There's an abundance of this receptor in cells in the lower lung, which may explain the high incidence of pneumonia and bronchitis in those with severe COVID-19 infection. A recent study showed that ACE2 is also highly expressed in the mouth and tongue, granting the virus easy access to a new host. ACE2 receptor abundance goes down in the elderly in all these tissues, but, counter intuitively, this might place them at a greater risk of severe illness.

This is because the ACE2 enzyme is an important regulator of the immune response, especially inflammation. It protects mice against acute lung injury triggered by sepsis. And a 2014 study found that the ACE2 enzyme offers protection against lethal avian influenza. Some patients with

better outcomes had higher levels of the protein in their sera, and turning off the gene for ACE2 led to severe lung damage in mice infected with H5N1, while treating mice with human ACE2 dampened lung injury.

A fall in ACE2 activity in the elderly is partly to blame for humans' poorer ability to put the brakes on our inflammatory response as we age, according to emailed comments from Hong Peng Jia of Johns Hopkins Medicine. Reduced abundance of ACE2 receptors in older adults could leave them less able to cope with SARS-CoV-2, says Baric, though the hypothesis still needs more research.

On January 31st, Markus Hoffmann et al. in Leibniz Primate Institute, Germany, published an article entitled "The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry Into target cells" on bioRxiv. It demonstrates that SARS- CoV-2 enters the human body through the SARS- CoV receptor ACE2, and the cellular protease TMPRSS2 is used for SARS-CoV-2 spike (SARS-CoV-2-S) triggering. TMPRSS2 inhibitors prevent SARS-CoV-2 entry and are a treatment option. Finally, the study showed that serum from patients with SARS during recovery stage neutralized the entry of SARS-CoV-2-S. The findings reveal important commonalities between SARS-CoV-2 and SARS-CoV infections, and provide potential targets for antiviral intervention.

On February 7, Dr. Robert L. Kruse from Johns Hopkins Hospital in the United States published an article "Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China". It reveals that compared to blockers binding to ACE2 receptors, the use of soluble ACE2 to fuse with the immunoglobulin Fc domain (ACE2-Fc) can block the entry of 2019-nCoV and help the immune system to build lasting immunity . In addition, ACE2-Fc treatment can also supplement the reduction of ACE2 levels in the lungs during infection, thus directly treating acute respiratory distress syndrome.

## A CYTOKINE STORM SYNDROME – COVID

An estimated 20% of individuals infected with COVID-19 are sick enough to necessitate hospitalization, with a subset of patients requiring intensive care.(4) Why some individuals become deathly ill and others don't is unknown, but is likely attributable to host factors. Early reports on the clinical (fever, confusion) and laboratory (hyperferritinemia, lymphopenia, prolonged prothombin time, elevated lactate dehydrogenase, elevated interleukin (IL) 6, elevated C-reactive protein, elevated soluble CD25) features of critically ill patients infected with COVID-19 suggest the presence of a cytokine storm syndrome (CSS) resulting in adult respiratory distress syndrome and multi-organ failure.(5-7) Indeed, many of the diagnostic criteria for CSS are reported present in those COVID-19 infected individuals under intensive care.(8-9)

### Pathophysiology & Genetics of CSS

CSS is believed to occur as a consequence of an accentuated immune response to various triggers, including certain viral infections (10). This was perhaps best modelled in mice with genetic deficiency in perforin, a protein critical to lymphocyte killing of virus- infected cells.

In 2004, Jordan et al. reported that perforin-deficient mice infected with lymphocyte choriomening it is virus died within two weeks of infection as the result of a CSS(11) Interestingly, mice in which the cytotoxic CD8 T lymphocytes were removed did not completely clear the infection, but survived (11) Similarly, neutralization of the pro- inflammatory cytokine, interferon-g (IFNg), also allowed for survival of these virally infected mice.11This strongly argues that in this scenario, the death of the mice was dependent on the immune response to the virus rather than the virus itself.

It is noteworthy that mutations in perforin and related genes important for lymphocyte cytolytic capacity were reported in some people who died during the 2009 H1N1 influenza virus pandemic (12) Thus, although we, as a population, are all at risk of infection during viral outbreaks, only a certain percentage of the population may possess genetic risk factors that contribute to frequently fatal CSS.

**Treat the Pathogen & the Host**

Over the past two decades, substantial progress has been made in understanding the clinical presentation, pathophysiology, risk factors and triggers of CSS, including such disorders as macrophage activation syndrome (MAS) and secondary hemophagocytic lymphohistiocytosis (HLH)(13) In addition, a wide array of therapeutic modalities are now available to treat CSS. In the setting of virus-trigered CSS, it is important to treat the infection (if effective antiviral therapy is available), and it may be even more critical to dampen the overly exuberant immune responses responsible for CSS-induced multi- organ dysfunction syndrome (MODS) and death.

**Progress in Diagnosis & Treatment**

CSS remains a diagnostic challenge, but several criteria have been developed that are not unique to specific inciting triggers or underlying disease (14 )Often, a clinical diagnosis of CSS can be reliably and quickly made in presence of fever, hyperferritinemia and multi-organ dysfunction syndrome (15 )The earlier therapy for CSS is instituted, the better the outcomes (19)

Novel therapies, particularly anti-cytokine approaches targeting IL-1, IL-6, IFNg and IL- 18, are now available and have all shown promise in treating various forms of CSS (16-19).IL-1 blockade for CSS has perhaps been the most reported with efficacy for a wide range of triggers, but particularly for rheumatic disease-associated CSS(13)

Currently, IL-1 blockade is being studied in a randomized and blinded clinical trial to treat children and adults with CSS [NCT02780583]. IL-6 blockade has been championed for treating CSS as a consequence of chimeric antigen receptor (CAR) T cell therapy for refractory leukemia (17) IL-18 blockade was reported to rescue an infant with a rare genetic autoinflammatory condition complicated by CSS (18) Recently, an anti-IFNg antibody was approved by the U.S. Food & Drug Administration to treat familial hemophagocytic lymph histiocytosis and is now being tested in secondary forms of CSS as well (19).

Lastly, targeting inflammatory cytokine signalling via JAK-STAT inhibition to treat CSS is being reported (20). The relative low risk of co-infections and worsening viral infection with anti-cytokine therapies is mitigated by the benefits afforded by these targeted approaches to treating CSS.

**Cytokine-Targeted Therapy**

Early reports emanating from China indicate favourable outcomes in a series of severely ill COVID-19 patients treated with a regimen that included therapy with tocilizumab, which leads to blockade of the IL-6 receptor. Moreover, high doses of glucocorticoids (typically available worldwide) are therapeutic options to dampen a detrimental immune response in desperate settings (21).

While we are attempting to develop vaccines and trailing novel or repurposed antiviral therapies, let’s also not forget to treat the patient with all we have to offer to help save lives. As rheumatologists, we have much to offer on the front lines to recognize and treat these critically ill individuals with complications of hyper-inflammation.

**Effective Therapies:**

The novelty of this strain of virus means that there are so many uncertainties surrounding its behaviour, therefore it is too early to determine whether herbal plants or compounds could in fact contribute to society as prophylactic agents or as suitable substances in anti- coronavirus drugs against Covid-19.

So far, there has been no effective treatment of COVID-19. Several potential drug candidates, including lopinavir/ritonavir (Kaletra$^{R}$ ), nucleoside analogues, neuraminidase inhibitors, remdesivir, umifenovir (Arbidol$^{R}$ ), DNA synthesis inhibitors (such as tenofovir disoproxil and lamivudine), chloroquine and Chinese traditional medicines (such as ShuFeng JieDu or Lianhua Qing- wen capsules), have been proposed [22,23]. In addition, an angiotensin-converting enzyme 2 (ACE2)-based peptide, 3CLpro inhibitor (3CLpro-1) and a novel vinylsulfone protease inhibitor, theoretically, appear to show potential for antiviral activity against SARS-CoV-2 [24]. Chloroquine has been well described with in vitro effects on inhibition of uncoating and/or alteration of post-translational modifications of newly synthesised proteins, especially inhibition of glycosylation in many viruses, including human immunodeficiency virus (HIV) [25].

Preliminary in vivo clinical studies suggest that chloroquine alone or in combination with antiretroviral agents might play an interesting role in treating HIV infection [25]. A recent study by Wang et al. revealed that remdesivir and chloroquine were highly effective in the control of 2019-nCoV in vitro [23]. In addition to the one case of SARS- CoV-2 pneumonia with a promising clinical response to remdesivir [26] and two clinical trials in China, further case-controlled clinical studies of remdesivir therapy are warranted to verify its therapeutic efficacy.

However, due to Covid-19's high similarity with the previously reported SARS-CoV and MERS-CoV viruses, previous published research on herbal compounds, which have been proven to exert anti- coronavirus effects, may be a valuable guide to Pending anti- coronavirus herbal plants, which may be active against the SARS- CoV-2 virus. After the breakout of SARS-CoV, Prst reported in early 2003[27], scientists have been vigorously trying to exploit several antiviral compounds against SARS-CoV. This had led a group of experts in China to screen more than 200 Chinese medicinal herb extracts for antiviral activities against this coronavirus strain. Previously reported saikosaponins (A, $B_2$, C, and D), which are naturally occurring triterpene glycosides isolated from medicinal plants such as *Bupleurum* spp. (Chái Hú), *Heteromorpha* spp., and *Scrophularia scorodonia* (Xuán Shēn), exert antiviral activity against HCoV-22E9.[ 28 ] Upon co-challenge with the virus, these natural compounds effectively prevent the early stage of HCoV-22E9 infection, including viral attachment and penetration. Extracts from *Lycoris radiata* (Shí Suàn), *Artemisia annua* (Huáng Huā Hāo), *Pyrrosia lingua* (Shí Wěi), and *Lindera aggregata* (Wū Yào) have also been documented to display anti–SARS-CoV effect from a screening analysis using hundreds of Chinese medicinal herbs.[ 29] Natural inhibitors against the SARS-CoV enzymes, such as the nsP13 helicase and 3CL protease, have been identified as well and include myricetin, scutellarein, and phenolic compounds from *Isatis indigotica* (Bǎn Lán Gēn) and *Torreya nucifera*(Fěi).[ 30, 31,32. ] Other anti-CoV natural medicines include the water extract from *Houttuynia cordata*(Yú Xīng Cǎo), which has been observed to exhibit several antiviral mechanisms against SARS-CoV, such as inhibiting the viral 3CL protease and blocking the viral RNA-dependent RNA polymerase activity..[ 33]

Amongst these, other four extracts exhibited moderate to potent inhibition effects against SARS-CoV – *Lycoris radiata* (Red Spider Lily), *Pyrrosia lingua* (a fern), *Artemisia annua* (Sweet wormwood) and *Lindera aggregate* (an aromatic evergreen shrub member of the laurel family). The antiviral effects of these were dose dependant and ranged from low concentrations of the extract to high, varying for each herbal extract. In particular *Lycoris radiata* exhibited the most potent anti-viral activity against the virus strain.[34]

This result was consistent with that of two other research groups, which suggested that an active constituent contained in Licorice roots, Glycyrrhizin, has been proven to have an anti-SARS-CoV activity by inhibiting its replication.[35] [36] In another study, Glycyrrhizin also exhibited antiviral activity when tested for its *in vitro* antiviral effects on 10 different clinical isolates of SARS coronavirus. Baicalin – a constituent of the plant *Scuttelaria baicalensis* (Skullcap) – has also been tested in this study under the same conditions and has also shown antiviral action against the SARS coronavirus.[37] Baicalin has also been shown to inhibit the replication of the HIV-1 virus *in vitro* in previous studies.[38] [39] However it should be noted that *in vitro* findings may not correlate with *in vivo* clinical efficacy. This is because the oral dose of these agents in humans may not achieve a blood serum concentration similar to that tested *in vitro.*

Lycorine has also demonstrated potent antiviral action against SARS- CoV.3 Several previous reports suggest that Lycorine seems to have broad antiviral activities and has been reported to have demonstrated an inhibitory action on the Herpes Simplex virus (type I)[40] and the Poliomyelitis virus also.[41] Other herbs which have been reported to have shown antiviral activity against SARS-CoV are *Lonicera japonica* (Japanese Honeysuckle) and the commonly- known Eucalyptus plant, and *Panax ginseng* (a root) through its active component Ginsenoside-Rb1."[42]

Evidence from the above-mentioned studies and several other worldwide studies report that many medicinal herbal constituents have exhibited antiviral activities against coronaviruses[43] [44] and their main mechanism of action seems to be through the inhibition of viral replication.[45] China has extensively used traditional Chinese medicinal herbs for the treatment of SARS effectively in many cases.[46] However there is no substantial evidence yet on the clinical effectiveness of these for Covid-19 infected patients.

Although natural products have been marginalized by major pharmaceutical companies all over the world in the last 30+ years, the changing landscape of drug discovery — as Pharma strives to develop innovative and highly effective new drugs — will eventually now favour a greatly enhanced role for natural products as valued sources of novel leads whose further drug development.

Moreover, cancer therapy may be helpful in treating patients with coronavirus disease 2019 (COVID-19). On April 2, 2020, the FDA granted an investigational new drug application (NDA) to CYNK-001 for the treatment of adults with COVID-19, according to Celularity Inc., the manufacturer of the immunotherapy.(47) CYNK-001 will be evaluated in an upcoming phase I/II clinical trial including up to 86 patients with COVID-19.

"With our initial clinical study, we will gain an understanding of the impact CYNK-001 can have on patients recently diagnosed with COVID-19. We are hopeful to contribute to flattening the COVID-19 curve, expanding on the promising early results we've seen in our clinical studies in devastating cancers to patients with coronavirus," said Robert Hariri, MD, PhD, Founder, Chairman and CEO at Celularity, in a statement.
The drug is a cryopreserved allogenic, off-the-shelf Natural Killer (NK) cell therapy that is being developed from placental hematopoietic stem cells. NKs are immune cells that can target cancer cells and affect immunity.

Cellularity states that CYNK-001 is safe and versatile. In fact, it is also being investigated for the treatment of acute myeloid leukemia, multiple myeloma, and glioblastoma multiforme. Last week, the Society for Immunotherapy in Cancer (SITC) published a statement on the promise of tocilizumab for COVID-19.

"Studies have established that there is robust activation of NK cells during viral infection regardless of the virus class," says Celularity's Chief Scientific Officer, Xiaokui Zhang, PhD, in the statement.

"CYNK-001 demonstrates a range of biological activities expected of NK cells, including expression of activating receptors such as NKG2D, DNAM-1 and the natural cytotoxicity receptors NKp30, NKp44 and NKp46, which bind to stress ligands and viral antigens on infected cells. They also show the expression of cytolytic molecules perforin and granzyme B, which kill recognized infected cells. These functions suggest that CYNK-001 could provide a benefit to COVID-19 patients in terms of limiting SARS-CoV-2 replication and disease progression by eliminating the infected cells."

Paclitaxel one the efficient anti- cancer drugs inhibits adhesion molecule expression resulted in impaired NK cell binding to target cells, which may have a negative impact on immune surveillance. Activated NK cells are crucial for the elimination of virus- infected cells during the early stages of viral infection (48) and are also involved in the maturation of antigen-presenting dendritic cells (49). In addition, NK cell recognition and cytolysis of tumor target cells is critical for the induction of tumor-specific cytotoxic T lymphocytes (50). Since adhesion interactions between LFA-1 and ICAM-1 are an essential initial step in activating the cytolytic machinery of NK cells (51), paclitaxel-induced reductions in LFA-1 and ICAM-1 expression are likely to at least contribute to decreased NK cell function following paclitaxel treatment (52-55). The inhibitory effect of paclitaxel on NK cell function should therefore be taken into account when designing immune-based cancer therapies that will be employed concurrently with paclitaxel-based chemotherapy.

Paclitaxel has also been reported to have both immunostimulatory and immunosuppressive properties (56). In mice, paclitaxel is a lipopolysaccharide mimetic that induces the synthesis of pro-inflammatory interleukin (IL)-12 by macrophages via an autocrine signaling pathway involving macrophage-derived nitric oxide (57). Paclitaxel, in combination with interferon- Á, also induces nitric oxide-dependent killing of P815 mastocytoma cells by murine macrophages (58). In addition, paclitaxel causes increased secretion of pro-inflammatory IL-1, by unprimed human monocytes (59). Collectively, these findings suggest that paclitaxel-mediated enhancement of certain immune effector mechanisms may contribute to the anti-neoplastic activity of paclitaxel. However, there is also evidence that paclitaxel suppresses the function of other immune effector cells, which may result in impaired immune surveillance (60)-(69). The proliferative capacity of T cells from normal and tumor-bearing animals is reduced by paclitaxel, although the inhibitory effect is reversed by exogenous IL-12 (70). Paclitaxel also inhibits IL-2 synthesis and the induction of cytotoxic T cells in response to alloantigen, leading to prolonged survival of rat cardiac allografts (71). Interestingly, paclitaxel treatment of dendritic cells results in impaired dendritic cell-activated proliferation of mouse T lymphocytes (72), suggesting that paclitaxel exerts an inhibitory effect on T cell function at the level of dendritic cell-T cell interactions. In vitro exposure to paclitaxel also impairs the cytotoxic function of major histocompatibility complex unrestricted T cells and natural killer (NK) cells, as well as their activation by IL-2 (73, 74, 75). In addition, a transient decrease in NK cell activity has been reported for patients with non-small cell lung cancer undergoing weekly paclitaxel therapy (76).

As anti-HIV drugs have already been recommended for the Coronovirus – Covid 19 patients , Paclitaxel becomes a potent thing as there are few reports on the antiviral activity of paclitaxel (Krawczyk et al. 2005[77];Stebbing et al. 2003[78]), in particular, there are very few reports on anti-HIV activity of microbial paclitaxel by molecular imprinted polymer. the potential of paclitaxel in the prevention and treatment of AIDS: HIV-1 viral invasion, HIV-1 protease activity, and HIV-1 integrase activity.

Paclitaxel sample has shown to inhibit the entry of HIV-1 virus into TZM-BL cells, and addition of the pre-invasive drug had a higher inhibition rate on the virus, indicating that in future practice, the method of preventive dosing can be employed to prevent and treat AIDS more effectively

Interestingly, the paclitaxel sample not only acts on the process before the virus invades, but also has an inhibitory effect upon viral invasion of the host cells. is result provides a theoretical basis for the subsequent inhibition of HIV-1 protease and integrase activity by paclitaxel samples.

Results have shown that the paclitaxel sample had different inhibitory activities against the two enzymes and had stronger HIV-1 protease inhibitory activity. The body is in an immune-regulated state under normal conditions, and once stimulated by the outside world, the immune system will be disordered (Yuan et al. 2010[79]). Therefore, we can detect the effect of paclitaxel samples from the aspect of cytokine changes. Under normal conditions, the body's immune cells 1/ 2 are in dynamic equilibrium (Yuan et al. 2010[79]).

Many studies have disclosed that in the early stage of HIV-1 virus-infected host, the immune balance is disrupted, causing the immune cells 1 to shift to 2, and the immune-related cytokines are characterized by down-regulation of IL-2 and up-regulation of IL-4 and IL-10, and e pro-inflammatory factor TNF-α, which is closely related to the virus, is activated, allowing NF-kB to bind to the LTR of HIV-1 virus, thereby activating viral replication, causing immune imbalance and disease progression Paclitaxel can down regulate the expression of IL-10 and up-regulate the up-regulation of IL-6, which has a certain positive effect on balancing the cytokines in immune imbalance. (Coghill et al. 2017[80]; Otiti-Sengeri et al. 2018[81]).

## CONCLUSION

As therauptic options are underway to dampen a detrimental immune response of the Covid -19 , paclitaxel could prove to be an efficient therauptic approach for the individuals with complications of hyper inflammation, as the paclitaxel has the capacity of suppressing the function of immune effector cells, which may result in impaired immune surveillance., anti-inhibitory effect of NK cells, inhibitory effect of T-cell function at the dendritic T-cell interaction, impairs the cytotoxic function of major histocompatibility complex unrestricted T cells and natural killer (NK) cells, as well as their activation by IL-2, down regulate the expression of IL-10 and up-regulate the up-regulation of IL-6, which has a certain positive effect on balancing the cytokines in immune imbalance. As anti-HIV drugs have already been recommended for the Coronovirus – Covid 19 patients , Paclitaxel becomes a potent thing as there are few reports on the antiviral activity of paclitaxel -on anti-HIV activity of microbial paclitaxel by molecular imprinted polymer. the potential of paclitaxel in the prevention and treatment of AIDS: HIV-1 viral invasion, HIV-1 protease activity, and HIV-1 integrase activity. Keeping in view the same, the present review highlights that paclitaxel can translate into applications in the current pandemic 2019-nCov infection – public health , safety , its crucial role should be intensively evaluated as conventional treatment.

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