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Short Communication

COVID-19; Pharmacological Approaches for Infection Prevention: Old and the New

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Severe acute respiratory virus syndrome causing virus, coronavirus 2019 (SARS CoV-2), has caused unprecedented health and economic crisis worldwide. Coronavirus disease (COVDO-19), has caused more death in the USA in the last hundred days, than the wars that the US has fought in this century. It has exceeded, the annual death records of last several decades, by the influenza virus. The genome size of this virus ranges between 27 and 34 kilobases, larger than most other RNA viruses. These viruses enter the nasal epithelia cells, through an endocytic mechanism, using surface 'spike' proteins, to bind the angiotensin-converting enzyme 2 (ACE-2) and dipeptidyl peptidase 4 (DPP4) receptors, on the bronchial epithelial cells and type 11 pneumocytes. Since there is no established cure for this disease, care givers are desperately looking for any and every remedy, that can be applied to alleviate the seriousness of this disease. Various models for the spread of the virus, infection rate, case fatality rates, modes of infection, risk assessment, risk stratification and any other topic, one writes about this disease is changing by the day. In view of these observations, it is no wonder, that there are several controversies about the pharmacological approaches for combating this menace. Deaths due to this disease in the USA has achieved a milestone, by crossing 100,000 mark in less than 100 days, from the first infection detected in this country. Compared to the global death rate, the rate of death in the USA, seems to be 30% higher in the USA, for a population, which is less than 5% of the World.

From the time the virus was reported first in Wuhan, China, the virus has mutated and evolved into new strains. Researchers from the USA and UK have sequenced thousands of SARS CoV-2 genomes, and identified all the mutations that have occurred, and developed a real-time tracking of SARS CoV-2, focusing mainly on the spike proteins. The mutation Spike D614G, seems to be the most dominant pandemic form in many countries [1]. Spike (S) proteins are of vital importance, in terms of viral infectivity as well as antibody targets. Both the S-glycoprotein and ACE_2 receptor, which is the virus biding-site for the virus, are extensively glycosylated. Spike protein has been shown, to contain 66 glycosylation sites, suggesting the importance of understanding the role of glycosylation, for the development of new vaccines [2,3]. It has been reported that angiotensin-converting enzyme-2, is the main host cell receptor of human pathogenic coronavirus [4]. Viral entry is facilitated by the presence of ACE_2, as well as transmembrane protease serine-2 (TMPRSS2) activity. Sungnak and associates, have co-detected these transcripts in specific respiratory and corneal epithelial cells, potentially explaining the high efficiency of SARS CoV-2 transmission [5,6]. When it comes to prevention strategies, apart from mitigation and social distancing, interfering with viral transmission via the ACE_2 receptors sites seems to be of primary importance. Studies with ACE_2 knockout greatly reduces viral infection and replication in mice after experimental SARS CoV infection [7].

Desperate times need desperate measures. In a rare exception, the US Food and Drug Administration (FDA) issued an emergency use authorization for the use of Hydroxychlorine (HoCl) and Chloroquine, for certain hospitalized patients diagnosed with coronavirus disease. Earlier *in vitro* studies have shown, that HoCl greatly inhibited viral replication in cells treated with this drug before, but not after the virus infection [8]. In view of this observation, the authors speculated, that HoCl preventive treatment in the area or season of dengue epidemic, might be a feasible strategy, to reduce the severity and spread of dengue virus outbreak. Several earlier studies have demonstrated, that at clinically achievable concentrations, chloroquine inhibits HIV-1 post-integrationally, by affecting

newly produced viral envelope glycoproteins, and the drug has broad-spectrum anti-HIV-1 and HIV-2 activity [9]. Chloroquine is a 9-aminoquinoline, known for its therapeutic use since 1934, to the Germans as resochin [10]. Savarino and associates from Italy, have described Chloroquine as an old drug, against today's new diseases. Originally developed against malarial parasites, these compounds have been shown to exert a variety of pharmacological function in biological systems. In the scheme of sequences, that promote malarial parasite in the red blood cells, redox-active heme moieties are generated during hemoglobin degradation, these products are toxic, and they are converted to hemozoin (malaria pigment). Chloroquine inhibits hemozoin formation, by interfering with the heme-detoxification [11,12]. Antimalarials like, chloroquine, amodiaquine, mefloquine, and quinine have a variety of targets and are known to act on heme in the parasitic food vacuole.

Despite this knowledge, at the time of this unprecedented COVID-19 pandemic, studies on HoCl have been the most controversial. The authors of a small clinical study in Marseille, France, wrote; "For ethical reasons, and because our results are so significant, we decided to share our findings with the medical community, given the urgent need for an effective drug against SARS CoV-2 in the current pandemic" [13]. Studies by the US and Canadian scientists have demonstrated; processing of the spike protein was effected by furin-like convertases and that inhibition of this cleavage by a specific inhibitor, abrogated cytopathicity and significantly reduced the virus titer of SARS CoV [14]. Based on their own observations, and that of others the authors concluded, "that the cell surface expression of under glycosylated ACE_2 and its poor affinity to SARS-CoV spike protein, may be the primary mechanism by which infection is prevented by drug pretreatment of cells to prior to infection". Furthermore, earlier studies have shown, that viruses use sialic acid moieties as receptors. Considering the higher transmissibility of SARS CoV2 on cell surface attachment, there is considerable speculation that Chloroquine and HoCl bind readily to sialic acid with high affinity, as well as to the sialic acid containing gangliosides [15].

As the controversies continue, there are scientific reports coming out now, which suggest that these drugs may not be beneficial for use in the treatment of COVID-19 patients. Mehra and associates from the Harvard University, reported the results of one of the largest studies, on hydroxychloroquine in the journal Lancet. They were unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone, or with a macrolide, on in-hospital outcomes for COVID-19 [16]. Is this the final nail in the coffin of Hydroxychloroquine-COVID-19 story? Not necessarily. According to the Nobel Laureate (1958), Joshua Lederberg, our wits have so far afforded us increased longevity and reduced mortality from infectious disease, but the defenses we have mounted to make these gains are no match, over the long run, for the rapidly changing adaptable genomes of microbial pathogens" [16]. Influenza virus over a century ago, created havoc worldwide (Spanish Flu 1918-19). The virus infected quarter of the world population (500 million) and killed 50 million individuals worldwide. Since then, we have seen several viruses emerging, and remerging like dengue, Ebola, Avian influenza, severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), hepatitis C, Chikungunya (CHIKV), human immunodeficiency virus (HIV). *In vitro* studies have revealed that Chloroquine is effective at both entry and at post entry stages of SARS CoV-2 infection in Vero E6 cells [17,18]. It is worth exploring the preventive role if any of these drugs on viral infections, rather than therapeutic effects on severely ill COVID-19 patients.

Now that we have discussed briefly, the use of an old drug for the prevention of a new and novel coronavirus infection, let us take a look at what is going on in the realm of innovation in the field of modern biotechnology, in terms of developing preventive strategies for the SARS CoV-2 infection. There are global efforts underway to diagnose, treat, and prevent SARS CoV-2 infections. Pharmaceutical companies are working globally to combat COVD-19. In the last two decades, therapeutic antibodies have rapidly become the leading products in the Biopharmaceutical market. In 2013, therapeutic antibodies represented 50% of the 40 billion market. There are currently more than thirty therapeutic antibodies approved by the US FDA [19]. There is a great rush to develop anti-viral compounds as well as other potent drugs, to combat Covid-19. Remdesivir is a known antiviral compound, that has emerged as a leading candidate for the treatment of Covid-19 [20]. However not many know of the story behind the development of this promising anti-viral drug. Remdesivir is developed by Gilead Science of California. It is named after Ramesh E.M. Desigan of Tamil Nadu, India, the lead scientist of the research and development team. Initially it was called Ebpantuvir, the name was changed in honor of the inventor to REMDesiVir.

In this section of the guest editorial, we are not talking about the drug discovery and development, but about the recent advancements in the development of CoV vaccines. According to World Health Organization (WHO), currently 124 candidates (Vaccines) are at various stages of development with eight different technologies or platforms, of which 10 are undergoing human trials. At the time of this writing, China's CanSino adenovirus vaccine, Oxford University's adenovirus vaccine, Moderna's mRNA vaccine and Novavax have emerged as the top promising candidates. Merck, one of the largest pharmaceutical company in the world, has initiated two studies to develop SARS CoV-2 vaccines. The first approach is to use, the vesicular stomatitis virus (VSV) surface protein, or spike, for SARS-CoV-2, the virus that causes COVID-19. Vesicular stomatitis virus has been extensively studied and serves as a model for the replication of (-) RNA viruses. For the second project, Merck has acquired an Austrian company (Themis), plans to use a weakened, safe version of that virus, and adding the spike gene from SARS-CoV-2 to this attenuated virus. Researchers are using a variety of approaches, to develop coronavirus vaccine including, whole virus vaccine, recombinant vaccine, antibody vaccine, nucleic acid vaccine, and spike protein vaccine. Recombinant protein subunits do not carry the risk of any infection in recipients, because they do not contain any live pathogens. Scientists are trying to make recombinant proteins, that targets a protein called spike (S-) protein.

SARS has many similarities with the COVID-19, as they are caused by the same family of viruses, -coronavirus. Scientists have demonstrated, that the antibodies that neutralize the SARS-causing virus, can also limit the spread of the new, novel CoV-2 virus. Nucleic acid vaccines use genetic material, such as DNA or RNA. Modern approach to the vaccine development includes, the use of gene-based information on possible identification of potential antigens for vaccine development. Although laboratories have several gene-based vaccines, none have been commercialized for use in combating human illness. In this novel approach, scientists use instructions from the genome of the virus, to create a 'blueprint' of select antigens. Then the scientists inject the DNA or RNA into the human cells. The cells biological machinery uses this instruction, to make virus antigens that stimulate the immune system. The current focus is to find ways and means, to train human cells to make antigens called, SARS CoV-2 spike protein. Using nucleic acid to deliver immunity is a novel approach, and three Pharma companies are using this approach: Inovio Pharmaceuticals, Moderna Therapeutics and Curevac. Inovio's DNA plasmid trial went into human clinical trial in mid-April, within three months after the Chinese sequenced SARS CoV-2 genome. Moderna has begun a small human trial of its RNA vaccine, with a huge US grant of over 480 million dollars. Barouch's laboratory developed a prototype of adenovirus vaccine in just four weeks. Johnson and Johnson committed more than a billion USD to fund a large human clinical trial.

AstraZeneca was the recipient of a 1.2 billion grant from Biomedical Advanced Research and Development Authority (BARDA), a U.S. Department of Health and Human Service (HHS) office, responsible for procurement and development of medical countermeasures. The company is responsible for producing millions of doses of the University of Oxford's front-runner COVID-19 vaccine. AstraZeneca and Oxford BioMedica have signed up a one-year deal covering "multiple batches" of the University of Oxford's adenovirus-based vaccine candidate, AZD1222. The US Pharma giant, Pfizer, is conducting clinical trials in the US and Europe for the BNT162 vaccine, which represents a different combination of mRNA format and target antigen. Russian scientists are working on 50 different vaccine projects. According to Kremlin, tests are underway, and the clinical trials will start in the coming weeks. Researchers from the Harvard University in collaboration with Jannsen Vaccines and Prevention BV, Leiden, The Netherlands, have developed a series of DNA vaccine candidates, expressing different forms of the SARS CoV-2 spike (S) protein. They have evaluated these candidate vaccines in 35 rhesus monkeys, demonstrated the effective vaccine protection against SARS CoV-2, and defined neutralizing antibody titers as an immune correlate of protection [21]. The US biotechnology company, Novavax has become the latest to announce, that it has started human clinical trials of its NVX-CoV2373 vaccine for COVID-19 in Australia. The biotech company uses genetic engineering technology, to grow harmless copies of the CoV virus spike protein in giant vats of insect cells.

Chinese researchers of Wuhan, China, did a dose-escalation, single-center, open-label, non-randomized, phase 1 trial of an Ad5 vectored COVID-19 vaccine expressing the spike glycoprotein of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) strain [22]. They interpreted their findings as follows: The Ad5 vectored COVID-19 vaccine is tolerable and immunogenic at 28 days

post-vaccination. Humoral responses against SARS CoV-2 peaked at day 28 post-vaccination in healthy adults, and rapid specific T-cell responses were noted from day 14 post-vaccination. Our findings suggest, that the Ad5 vectored COVID-19 vaccine warrants further investigation. Beijing Institute of Biological Products and China National Biotec Group has completed phase 11 testing and may be ready for marketing their vaccines by the end of the year. New York researchers Trogen and associates, commenting on the consequences of rushing a SARS CoV-2 vaccine, concluded, "Physicians should not administer inadequately vetted vaccines; researchers should not endorse them without sufficient data. The likelihood of achieving that goal depends on convincing evidence that assures vaccine safety and efficacy" [23].

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