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Short Communication

Designing Effective Drugs Against Covid: Overcoming the Obstacles

Wanpeng Sun*

Faculty of Science, University of Alberta, Canada

***Corresponding author:** Wanpeng Sun, Faculty of Science, University of Alberta, Canada

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Abstract

Essentially, Covid disease is a retroviral infection. This kind of infection has been identified for tens of years, such as the cases of HIVs. But even now, reliable drugs to treat the retroviral infections are not available. The success of a drug design is highly dependent on the specificity to stop the retroviral infections without causing negative side effects. Ideally, this could be achieved by modern structure-based drug design with the help of computers. In the case of Covid disease, most efforts were over-focused on pro-motioning the vaccines, while the demanding research on classic drug discovery is neglected. In this mini-review, we review the difficulties associated with the drug development against Covid. Moreover, we proposed novel ways to design innovative drugs against Covid, which will lead to new and better therapeutics to end any pandemics caused either by Covid-19 or by any other retrovirus. During last pandemic, every single day, there were more than 4000 people died from Covid. It is necessary to have a drug ready to immediately stop any Covid or similar pandemics. From this point of view, this review is extremely important by proposing solutions to address this critical issue.

Keywords: Covid, Rational Drug Design, Drug Development, Structure-based Drug Design, Quantum Computer, Artificial Intelligent, Computer-aid Drug Design, Sun's Paradox

Introduction

The infectious Covid disease is caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2). Many countries have been performing genomic surveillance on Covid, and at least 96 countries have their sequencing results available [1]. Due to continuous mutations, there are significant differences among the sequencing results from different research groups from these countries. It has consumed more than 8 billion research funds in order to find a specific treatment. Most funds are used for vaccines research and only a small portion of funds is used for drug developments. In some countries, the focus on vaccines is not only for humanity, but also for economy, achieved by selling those vaccines. Because of the huge commercial profits brought by vaccine promotion, traditional research in drug discovery is often overlooked. As a matter of fact, most vaccines are only for preventative purpose. Current vaccination is insufficient to deal with an evolving virus. People who were vaccinated are still catching Covid. Additionally, all vac-cines have side effects. It is more than true for the case of Covid: during the pandemic, millions of people have side effects or "co-incidents" of health problems after being Covid vaccinated. In fact, cases of strong negative effects were being reported on all bands of Covid vaccines. To date, none of Covid vaccines is designed as therapeutics to cure the disease. Therefore, an effective therapy is in high demand. The most efficient way to treat an infective disease is still a therapy made of drugs. Unfortunately, Covid is still among the leading causes of death in the world; it is the third leading cause in USA [2]. Patients are in urgent need of better treatment. Nowadays, all of the Covid vaccines are preventive; they are produced to prevent something but not for curing purposes. The development of preventive vaccines cannot replace the development of an innovative drug. A drug tablet is still the classic and one of the most efficient ways to heal a disease. Definitely, there are obstacles and boundaries to hinder back innovative research

in drug discoveries. Hereby, we review these challenges. Moreover, we proposed novel ways to design innovative drugs against Covid, which will lead to new and better therapeutics to end a pandemic caused either by Covid-19 or by any similar virus.

Challenges and Obstacles

There are two basic approaches for drug discoveries. One is random screening. For example, ancient people performed screenings on natural products, like plants and fungi, to find herbal medicine. This is still performed by modern researchers for drug discoveries, but it is being gradually discontinued since 2000s [3]. A handful organizations still keep such screenings. For example, NCI (National Cancer Institute, USA) screens natural products as well as chemical compounds to find drug candidates. Until 1988, there are over 35000 plant species were tested [4], and the numbers are keeping increasing. Billions of dollars have been spent on the screenings. Indeed, it is a way to discovery drug. Most ancient drugs in aboriginal medicine, eastern medicine and many other cultures are discovered by that approach. It is worthy of mentioning that this could be the most efficient way for drug discovery, though it seems very rural. For discovers who either have super luck or have supernatural powers, the ideal drug candidates might be in the first batches of candidates examined; otherwise, the cost is extremely huge. This raises a paradox, which we named as the Sun's Paradox: in ancient time, there are no modern knowledge and equipment, how can human beings randomly screen millions of candidates to find medicine? In the book of Universes [5] and one paper that the author just published [6], we proposed the Sun Model of Universe and there could be parallel civilizations in addition to ours. Since the recent research finds that there was civilization in Mars which was wiped out by nuclear exposures [7,8], there were relatively high civilization that is capable to perform such screenings. In another paper that the author just published earlier this year [9], we also proposed Sun Model of Evolution, according to which human beings have higher civilization than current stage. For example, many ancient herbal medicines seem very simple, but have therapeutic effects without apparent negative effects, which is the goal for a state-of-art drug design. Realistically, in order to improve the efficiency, contemporary researchers usually refer to many literatures to carefully select a handful of candidates before performing the random screening. For example, a few scholars have referred to ancient books about herbal medicine in order to shortlist candidates from herbals. In previous research, we performed such researches and achieved some discoveries for anti-cancer candidates [10]. Nonetheless, it is a very different story for the Covid disease, since there are not such reference books. Therefore, it is not realistic to use the screening methods to find a Covid therapy.

The second but more modern approach is called the rational drug design. If researchers know the therapeutic target to treat, they will rationally design the drug to act onto the target. For example, histamine sometimes cause allergies, and antihistamines treat allergies by inhibiting histamine. Here, the histamine is referred as "target" for therapeutics. However, many drugs have side effects. The above-mentioned antihistamines not only inhibit histamine, but also bind to other molecules inside human body and cause undesired effects, which is usually called as the negative effects or the side effects. Thus, drugs with great efficacy and minimal side effects are greatly appreciated. In the rational drug design, the most effective way to achieve this goal is to design a drug that can recognize the specific structures of the target and only specifically bind to the target. This can be achieved by the Structure-based Drug De-sign (SBDD), which designs a drug based on the ultra-Nano (with resolution at angstrom level) structure of its target. It is noteworthy that such targets could be any molecules in human bodies. However, modern researchers usually focus on protein molecules that play key functions. For example, tumor suppressors and many of their interactive factors [11,12] are proteins. With advanced technologies, a structure of a large biomolecule can be resolved with the resolution as high as 0.2 nm. Based on the de-tailed structure with high resolution, smaller molecules specifically binding to that target will be de-signed. The designed drug candidates are expected to be highly specific, not binding to non-specific targets and not causing undesired effects. Nowadays, science workers use computers to facilitate the drug design. This is named as the computer-aided drug design (CADD). Due to the millions of calculations related to the structural solving process and due to the requirement of building a model in the structure solving process, the SBDD is often assisted by CADD. Theoretically, SBDD combined with CADD is the best methodology to design a specific drug with minimal negative effects; this is particular true in case of Covid drug research.

Currently, the SBDD is usually performed by well-trained chemists, because the bottle neck in SBDD is to illustrate the high-resolution structure of a therapeutic target in the ultra-Nano scale (less than 3 Å). The best way to achieve that is through the protein crystallography. Scattering the X-ray into a crystal, and then the structure can be deduced by analyzing the patterns and positions of the reflection dots. Watson and Crick got the Nobel Prize through analyzing these dots and then revealing the DNA double helix and twisted-ladder structure and this marked a milestone in the history, giving rise to modern molecular biology. There are millions of calculations, but it is not the most difficult step comparing with protein crystallization. Protein crystallization is more difficult than any other types of materials. It is hard for a protein to form a crystal, because there are no strong bonds in between their molecules. In order to form a crystal, the inside molecules have to arrange into regular arrays; in the arrays, all molecules need have equivalent orientations and positions. In protein crystals, the force of holding such arrangements are very weak, plus subjecting to the influences of many factors including gravity. Thus, protein crystals are hard to form and difficult to grow. Since the interaction between protein molecules are mainly by Van der Waals forces and weak hydrogen bonds, it is very different from salts and sugars in which there are strong bonds holding their molecules together. The

change to get a good-quality protein crystal with a decent size for X-ray is far less than 1 in 1,000,000 and usually performed by well-trained chemists for several and even tens of years. A supervising committee member of the author, Dr. Delbaere, the former executive of American Crystallographic Association, had performed research by growing crystals in space in order to achieve bigger-size crystals with lesser influences of gravity [13,14]. However, a spaceship is out of the scope of most labs.

There are other ways to study proteins structure, but not comparable with the classic X-ray Crystallography. Nuclear magnetic resonance (NMR) is applicable only for a small target, e.g. a truncated domain usually less than 120 amino acids. The computer simulation requires a highly similar model, which is originally from the X-crystallography. Further, the accuracy in silico modeling is always lower than the real experimental structures like X-ray Crystallography and NMR. In addition, the technology of cryo-genic electron microscopy (cryo-EM) is very promising, but not mature – no drugs that are designed based on cryo-EM are approved by FDA. It is important to note that we cannot only reply on cryo-EM data for serious drug design, since cryo-EM got the protein structures in ultra-low temperature, where the subtle conformations of macromolecules are not exactly like those in normal temperature. Previously, cryo-EM is slightly over-evaluated since its resolution can be occasionally achieved as good as 1-2 Å; however, its resolution is usually above 3 Å, not as good as X-ray Crystallography in most cases. Practically, non-specificity is always reported for drugs designed purely based on the cryo-EM structures. In clinical situations, such non-specificity caused negative effects in patients by allowing the drugs to bind unknown targets in human bodies. Thus, traditional X-ray Crystallography is still the golden standard for large domains. It is not surprising that more than 50 Nobel Prize winners got this worldly Number One top prize based on their structural studies by Crystallography [15]. As aforementioned, the SBDD is usually performed by well-trained chemists, who does not necessary know the details in molecular and cell biology. Thus, they might not choose the right target sequences to study. Moreover, the target that was "carefully" chosen to study is mainly based on the relative easiness of getting a decent crystal, rather than the importance for therapeutic purpose. For example, if there is a previous report about the crystallization conditions for a protein that is homological to the target protein, it will be much easier to get the crystal by playing with known conditions rather than randomly screening mil-lions of conditions.

Attitude is the essential for drug development (Figure 1). Attitude of the workers involved in a drug development can sometime create a strong boundary. In above-mentioned structural studies, even scientific workers choose a wrong target, they can still publish decent papers and attract funds as long as the researches are related to a good topic, like Covid. For a "successful" career, that is enough. On the other hand, if they choose a tough target which took more tens of years to get a crystal, even if the target is right, their career is gone. It was very common to see PhD candidates dedicated on protein crystallography finally gave up academic careers after 8-10 years of hard work, simply because they cannot get the protein crystalized, no mentioning the following jobs. In old generations, it is not uncommon for a professor to use such PhD candidates, who are committed on science, as expendables. The author is one of these expendables; but miracles happen, and the author get protein crystallized [16,17]. In old days, scientists usually pray to God for help in extremely difficult projects, like protein crystallization. Now-adays, people are "smart", and they usually take easier projects since science commitment is not a value affecting their decisions. As to the structural research against Covid, many scholars choose protease, which is not an essential target. Some scholars also choose the Spike Protein, which is continuously evolving with mutated sequences. The speed of drug-development research is far behind the speed of their mutations. In another, wrong targets were often selected in the SBDD against Covid. A tiny mistake costs huge waist. During pandemic, every single day, there are more than 4000 people died from Covid. Existing methodology on spike protein studies is far lagging behind to reveal the structures of any variant derived from this virus in a timely manner. Can artificial intelligence (AI) compensate this? Not Now, but maybe in future. Current AI and machine learning are very low, without the equipment of a quantum computer. We will discuss this in the latter text.

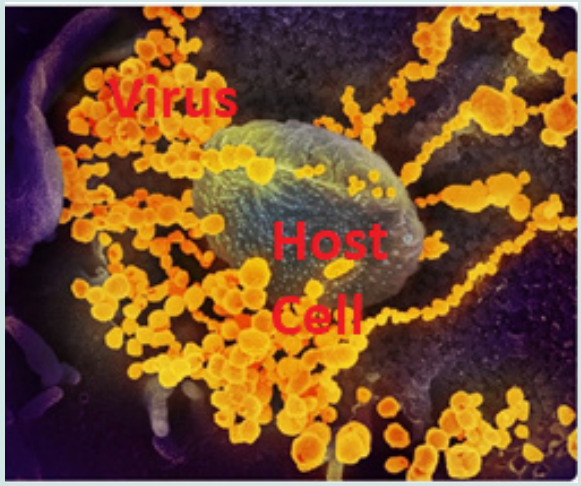

Figure 1

Scientific Expectations

Hereby, we proposed novel ways to design innovative drugs by SBDD and CADD against Covid. As long as we can break boundaries mentioned above, it is just a matter of time to discover the new and better therapeutics in order to end the pandemics caused either by Covid-19 or by any similar virus.

First of all, the optimal strategy for Covid drug development is to design a drug that not only treats Covid diseases, but also treats all diseases caused by retrovirus including the virus originated from Covid and similar virus like SARS and HIV. By examining the essential

enzymes for the retroviral pro-duction, we found hints to stop the virus from proliferation in host cells: for retroviruses including those caused the Covid diseases, their cDNA has to integrate into the host genome to proliferate. The Covid virus is a positive-sense single-stranded RNA virus. In order to spread, it needs to survive in host cells. In order to survive, its viral RNA has to been retro-transcribed to DNA by the reverse transcriptase (RT). RT has both ribonuclease activity and DNA polymerase activity. Collectively, these activities enable the enzyme to convert single-stranded RNA into cDNA. In retroviruses like COVID-19, SARS and HIV, this cDNA will integrate into the host genome. By eliminating the possibility of the integration of viral cDNA into the host genome, a new drug (therapy) can be developed so as to make human completely "immunized" from Covid and similar virus. Furthermore, the retro-transcription mechanism is only present in retrovirus, not innate in human. A cutting-edge drug designed against the retrovirus can be very specific without apparent side effects on patients.

Figure 2: The Idea Situations for the development an innovative drugs. Through multidisciplinary and interdisciplinary re-search, good drug candidates can be designed, move through the pipeline, get approved as a pharmaceutical drug, and help patients as a medicine. Throughout these steps, the most important issue is the attitude of the drug developers. A negative attitude can block or ruin the whole process.

Despite of the fast evolution of Covid virus, its sequence encoding the RT, which is essential for its own survive, is conserved. There are minor variations in the codons that still represent same amino acids and stop signals. The RT sequence is relative conserved, comparing with those evolving mutations in other parts of genome. Based on the published sequence encoding the RT, we can synthesize the plasmid con-taining the sequence of RT. With the commercialization of synthesis services, we can synthesize the re-quired sequence with professional design e.g. including the promotor region for expression and the necessary tags for downstream isolation. Since the cost of synthesis for a 5kb plasmid is around 50 USD, this synthesis approach is better than the traditional approaches, like DNA recombination and cloning [17-19], which involve large amount of work. We can transform this plasmid to cell lines, and then express and purify the RT in-vitro. Via this process, we can get large amount of RT for study purposes. It is noteworthy that this approach only has RT expressed without infectious elements; it is safer and easier for downstream purification, comparing with the expression of the whole sequence of Covid virus that also encodes infectious proteins. Sub-sequentially, cryo-EM (good for a preview), NMR (good for truncated domains less than 120 amino acids) and X-ray crystallography will be performed to solve the structure of each domain of RT. The high-resolution structure will be resolved. After resolving the de-tailed structure, structure-based molecular design can be performed and molecules can be designed to exclusively bind the reverse transcriptase and inhibit the RT enzyme activity. Without RT, the viral RNA cannot be reversely translated to DNA and its RNA will be quickly eliminated

by ribonuclease intracellularly in the infected cells. Since RT is very unique to retrovirus and there is no RT in mammalians, the designed drug will selectively kill the virus with minimal negative effects on patients. Moreover, without the RT activity to make cDNA, the virus cannot integrate into human genome and cannot continuously produce the protein envelope, which is essential to protect its genetic materials during transmission. Further, human has innate immunity - there are protective ribonuclease activity throughout human body: e.g. in blood plasma and skin surface, so there is no chances for this virus to spread by RNA itself. The remaining virus particles with previously-packed envelopes will demolish by themselves since they cannot survive for several days by themselves. My research will completely stop the spread of the COVID-19 or similar virus.

Last but not lease, we did not completely disagree with the aforementioned spike protein research. Nevertheless, the spike protein mutates extremely faster than expected, the way faster than the current speed of scientific discoveries. Our opinion is: human beings need an extremely super computation power to catch up the speed of its mutations. Nowadays, a couple of quantum computers are developed. The calculations that used to take a modern high-end computer thousands of years can be easily achieved by a quantum computer in tens of seconds. Before quantum computers are invented, the fastest computer is HP Frontier (#1 supercomputer), which can have over 1018 operations per second [20]. The #1 supercomputer will take more than 47 years to achieve the operations that achieved by the Google's quantum computer in a few seconds [21]. With such super computation power, scientists will be able to investigate the key structures in the host-interacting spike protein, which is responsible for the invasion of host cell. In fact, the spike proteins have many variants. This is the root cause that many people, who completed Covid vaccination, are still infected by Covid virus. All variants of spike proteins from Covid virus should be studied in detail. This provides essential clues for rational drug designs. Subsequently, precise therapeutic molecules that target on selective regions of spike proteins will be designed via SBDD based on the resolved high-resolution structures. Those drug molecules will act as inhibitors to deactivate spike proteins, so that the virus will not able to "spike" host cells. Nonetheless, it is extremely difficult to reveal the structures of each variant of the spike proteins due to the huge amount of work involved in structural research and due to the fast evolution of this virus. CBDD will be applied to assist the drug discovery. In addition to traditional work performed by CBDD, an effective AI with super computation power will be introduced to accurately predict the evolving structure of this fast-evolving virus, saving valuables time and saving lives. It is not worthy that the spike protein variants have relatively limited complexity, even though it keeps mutating. For spike proteins, most known variations happen in the receptor-interacting regions. With a quantum computer that can calculate far more than quintillions of quintillion times per second, researchers should be able to precisely reveal the structures of any variant derived from spike protein in a timely manner and stop the spread by well-designed therapies, which provide broad collaboration opportunities.

Conclusion

Hereby, we proposed novel ways to design innovative drugs against Covid, which will lead to new and better therapeutics to end any pandemics caused either by Covid-19 or by any similar virus. Definitely, there are obstacles and boundaries hindering back the research. Theoretically, the approaches that we proposed are the most efficient and effective ways to treat Covid infections and remove it from the list of life-threatening diseases. Currently, Covid is one of the leading causes of death in North America, and patients are in urgent need of better treatment. During pandemic, every single day, there are more than 4000 people died from Covid. Human beings should be prepared for this kind of disasters. It is a must to have a drug ready to immediately stop such pandemics. From this point of view, this review is extremely important by proposing solutions to address this critical issue.

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