The Idea for Production of a Novel Narrow Spectrum Covid-19 Drug

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Abstract

Most drugs used in current medication for Covid-19 patient indicate several side effects due to the broad-spectrum drugs that affect the whole cells of human body (infected and healthy cells). Antiviral such as enzyme inhibitors, dideoxy, nucleoside/nucleotide analogs, amino acid analogs, even single chemical compound such as chloroquine phosphate, carboxylic acid type drugs and similar drugs may suppress some key molecules and changed pH not only in reactions which related to virus but also inevitably in the whole cells of human body. Based on all facts, then I designed the less cells destroying method to inhibit specifically SARS-CoV-2 replication in human cells. Since the sequence of single strand positive sense of SARS-CoV-2 has determined, the mechanism of its replication inside human lung cells was also well understood, the transport membrane (endocytosis) of oligonucleotides are well known and the supportive biotechnological methods are adequate to produce this type of drug then I proposed this methods and design respectively: 1) Study the specific sequence of SARS-CoV-2 RNA. 2) Synthesize the oligonucleotide using nucleotides analogs (to produce fake primers) that can specifically attach to the specific sequence of SARS-CoV-2 RNA. 3) Conduct *in vitro* experiments using the fake primers produced and the infected cells, study the efficiency of endocytosis of fake primers through cell membrane and to know the best dosage that can inhibit the SARS-CoV-2 replication. 4) Conduct clinical tests to the Covid-19 patients based on the *in vitro* test results (after passing the ethics protocol). So, the proposed novel narrow spectrum drug is the fake primer produced.

Keywords: Covid-19, Fake primer, Narrow spectrum drug

INTRODUCTION

Currently, the drugs and vaccines that have been used and been developing for medication of Covid 19 patients are mostly based on broad spectrum drugs that effect both infected cells and healthy cells. The broad-spectrum drugs also produce some metabolites that could give negative effect to metabolism then leads to several symptoms and diseases. The utilization of broad spectrum drugs inevitably generate several side effects to patient because some drugs based on monomer such as nucleotide/ nucleoside analogs, dideoxynucleotide/ dideoxynucleoside, amino acid analogs, single chemical compound drugs (carboxylic acids, Chloroquine phosphate, etc.), and enzymes inhibitors. Those types of drugs mostly effect many biochemical reactions in not only

reactions which related to the virus but also the whole cells of human body. The drugs could not avoid to be involved in transcriptions, translations, replications, enzymes production, all enzymatic reactions in metabolism, biosynthesis of biomolecules in the whole cells of human body due to each of their function as biomolecules precursor in biosynthesis. The pH changes to be more alkaline also occur in all cells not only in the infected cells. Besides that, a single type of monomer used such as nucleotide analog tends to cause fatal mutation by its end products in both infected cells and healthy cells.

Meanwhile, the vaccines which have been developing and the fact that SARS-Cov-2 viruses have been mutating from Type A to Type B, then to Type C and predictably will continue mutating due to the lack of proof reading mechanism during transcription process of the virus RNA. Some drugs also based on chemical molecule such as several types of carboxylic acid that responsible to inhibit specific reaction in virus before released from host cells exhibited several side effects to patient due to its metabolites produced in the cells. Therefore this short communication of review article aimed to propose a new method for designing and producing a novel narrow spectrum Covid-19 drug that will specifically react only inside the infected cells, relatively be more specific then predictably would reduce the side effects to the patients.

METHODS

This research was conducted by using literature review method. The results of this study were concluded as a Proposed Idea which can be used by all researchers who have been developing Covid-19 Drugs.

LITERATURE REVIEW

1. Structure of Coronaviruses

Coronaviruses (CoVs) are single stranded RNA viruses that are included in the Coronavirinae subfamily, the Coronavirdiae family, the order of Nidovirales, which is surrounded protein envelope. CoV can be divided into four genes, namely, Alphacoronavirus (αCoV), Betacoronavirus (βCoV), Deltacoronavirus (δCoV), and Gammacoronavirus (γCoV). This group of viruses originates from zoonoses with αCoV and βCoV commonly found in bats and mice, while generally δCoV and γCoV are found in poultry species (Chan *et al*, 2013). The Coronaviruses have

spike proteins which mediates membrane fusion to bind to the cellular receptors (Figure 1).

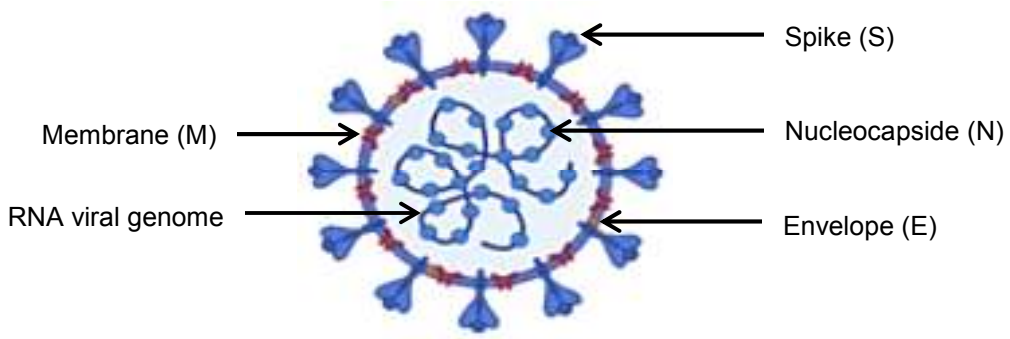

Figure 1. Structure of Coronaviruses (Source: Cascella *et al*, 2020)

SARS CoV-2 virus is a betacoronavirus which was firstly revealed in Wuhan City, Hubei Province, China in December 2019 (Li *et al*, 2020). It contains four structural proteins, namely Spike (S), Envelope (E), Membrane (M), and Nucleocapside (N). The envelope of SARS CoV-2 was built from proteins S, M, and E. The M protein is the most responsible protein for the shape of the envelope. The E protein is the smallest structural protein. The S and M proteins are important during replication, while the N proteins responsible for the formation of nucleocapside in the envelope. The N proteins are also involved in the viral infection through assembly and budding of the CoV replication cycle. In addition, the name Coronavirus comes from the S proteins which surrounded the envelope creating a crown-like appearance (Chan *et al*, 2013).

2. Genomic structure of SARS-CoV-2

The genome of SARS-CoV-2 is a single-stranded positive-sense RNA of 30kb (29891 nucleotides) encoding 9860 amino acids. The G + C content is 38%. The organization of SARS CoV-2 consists of 12 open reading frames (ORFs), one set of nine sub genomic mRNAs, nine transcription-regulatory parts, and 2 terminal regions which are untranslated. The first ORF contain almost two-thirds of the viral RNA that translates two polyproteins and encodes 16 non-structural proteins (NSP). The remaining ORFs encode structural (S, E, M, N) and accessory proteins (Perlman *et al*, 2009). In terms of whole genome sequence, it is revealed that SARS CoV-2 is closer to the SARS-like bat coronavirus (Chan *et al*,

2020). Nevertheless, mutations are found in NSP2, NSP3, and S proteins, which determined the infectious capability and replication mechanism of SARS CoV-2 (Angeletti *et al*, 2020).

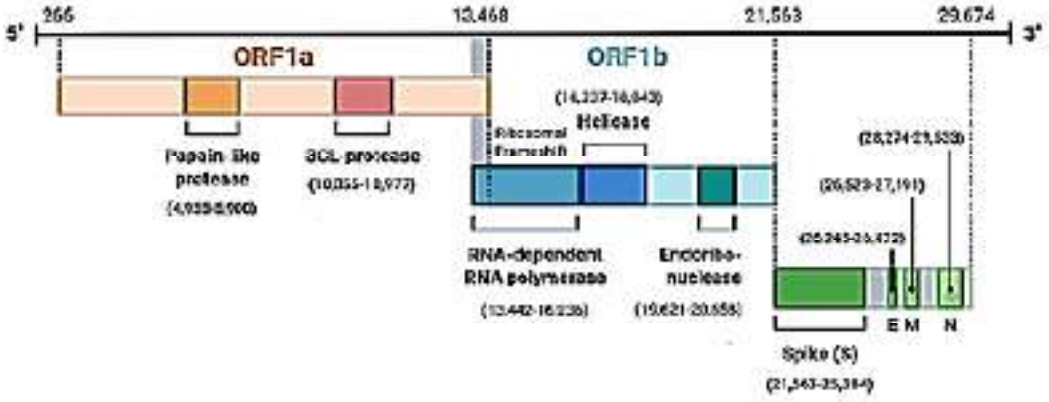

Figure 2. Genome structure of Coronaviruses (Source: Cascella *et al*, 2020)

3. Mechanisms of SARS-CoV-2 infection

There are three ways of SARS-CoV-2 transmission: droplets, contact, and aerosol transmissions (Figure 3). Droplets transmission can occur when infected patients cough, or sneeze and the droplets are inhaled or ingested by other people nearby. Contact transmission can occur when a person touches the surface or object which previously contaminated with the virus, and afterwards touches his eyes, mouth, or nose. Meanwhile, aerosol transmission can occur when droplets mix into the air and forming aerosol which is then inhaled in high dose into the lungs of nearby people. The main pathogenesis of COVID-19 infection is severe pneumonia, together with acute cardiac injury (Cascella *et al*, 2020).

The incubation period of SARS-CoV-2 infection ranges from 1 day to 14 days, which is also associated with the age of the infected people (Li *et al*, 2020). Age of 60 and above usually has incubation period faster compared with others. After the virus enter the respiratory tract, it affects the alveoli. The epithelial cells in the lower respiratory tract helps the virus to attach to its receptor, hACE2, which is downregulated after the infection of SARS-CoV-2. The binding of SARS-CoV-2 S protein is believed to be the virulence key factor for viral attachment and entry.

structural and non-structural proteins responsible for viral RNA synthesis, the so-called replicase-transcriptase proteins. These replicase-transcriptase proteins are encoded in ORF1a and ORF1b which synthesized as pp1a and pp1ab.

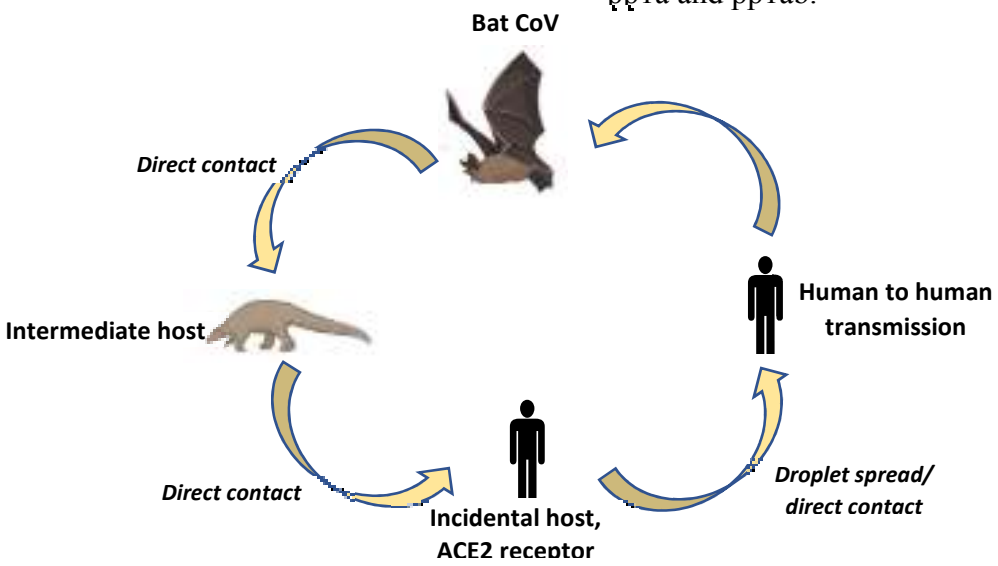

Figure 3. Transmission cycle of SARS-CoV-2 (Source: Cascella *et al*, 2020)

The S protein and hACE2 binding efficiency in SARS-CoV-2 infection is 10-20-fold higher than that of SARS-CoV infection. However, which molecules facilitate the membrane of SARS-CoV-2 endocytosis are still unclear. The S protein comprises S1 and S2 subunits. The subunit S1 is responsible for the binding via Receptor Binding Domain (RBD), while the subunit S2 helps the fusion of virus-cell membrane (Song *et al*, 2018).

The genome RNA of CoV contains about 30kb nucleotides which encodes NSP1 to NSP11 are encoded in ORF1a, while NSP12 to NSP16 are encoded in ORF1b. The complex of replicase-transcriptase (RTC) protein is composed of replicase-transcriptase protein together with other viral proteins and cellular proteins. This RTC is associated with double-membrane vesicles. The NSP3, NSP6, and NSP6 are the anchor of pp1a/pp1ab to membranes during the first step of RTC formation (Perlman and Netland, 2009). The virion-containing vesicles fuse with the plasma membrane of the cell and release the

virus which subsequently attach a new cell. So, the replication cycle is repeated.

4. Current Treatments

Drugs and Vaccines that currently used to fight the Covid-19 pandemic as seen in Figure 4.

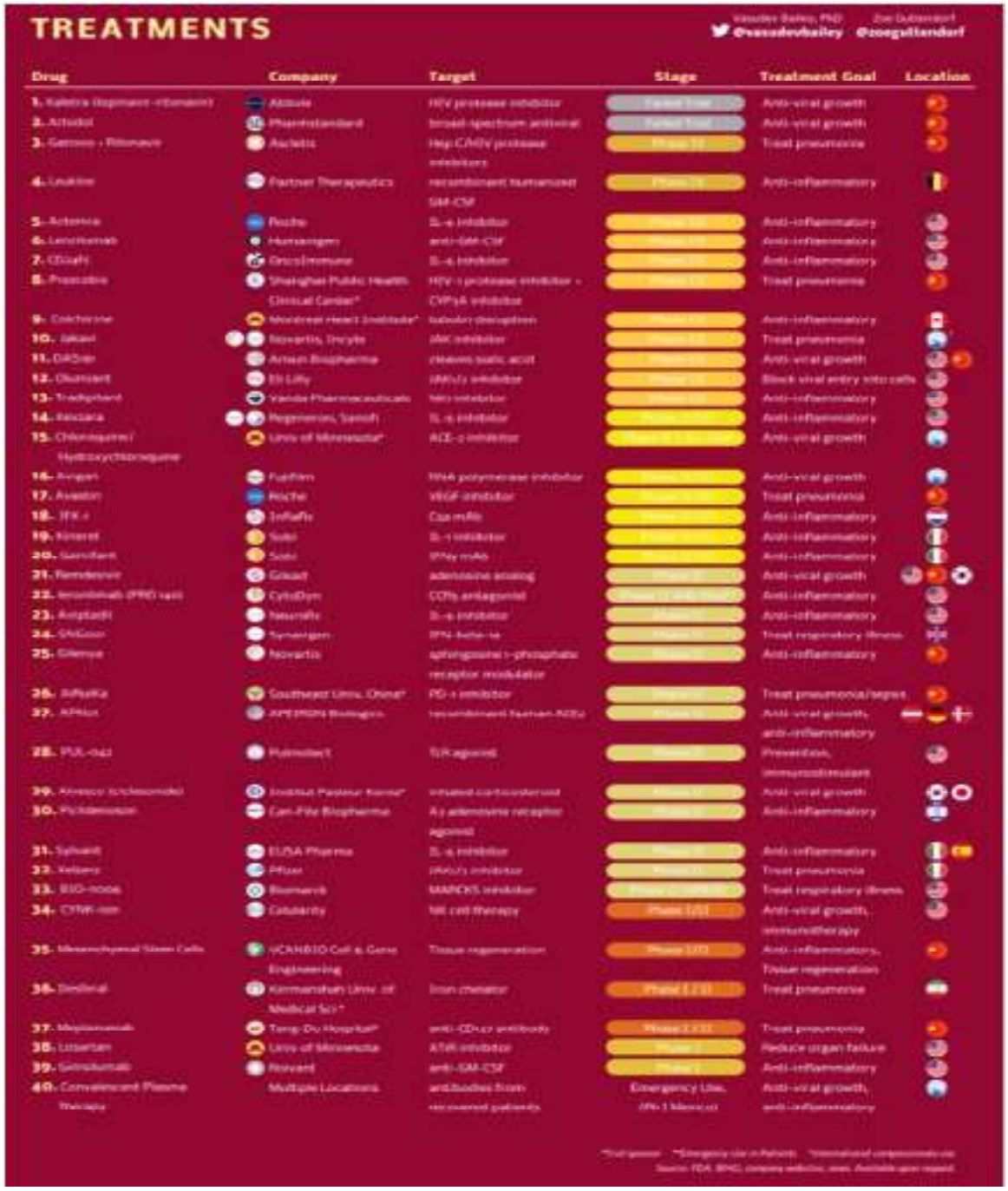

Figure 4. Several treatments of Covid-19 (Source: Artis Ventures, 2020)

RESULTS AND DISCUSSIONS

Since the mechanism of SARS-Cov-2 replication was well understood and also mostly the supportive biotechnology methods are sufficient to sequence the virus RNA, the availability of nucleotides analog, the technique to synthesis oligonucleotide as primer, then the fake primer that synthesis by using nucleotides analog can be produced. Moreover, the transport membrane and endocytosis of oligonucleotides were also known for up taking and trafficking of oligonucleotide in cytoplasm. Therefore, the fake primers produced would be the new drugs for Covid-19 patients.

The idea of using fake primer as the drug for Covid-19 patients based on following mechanism (Figure 5):

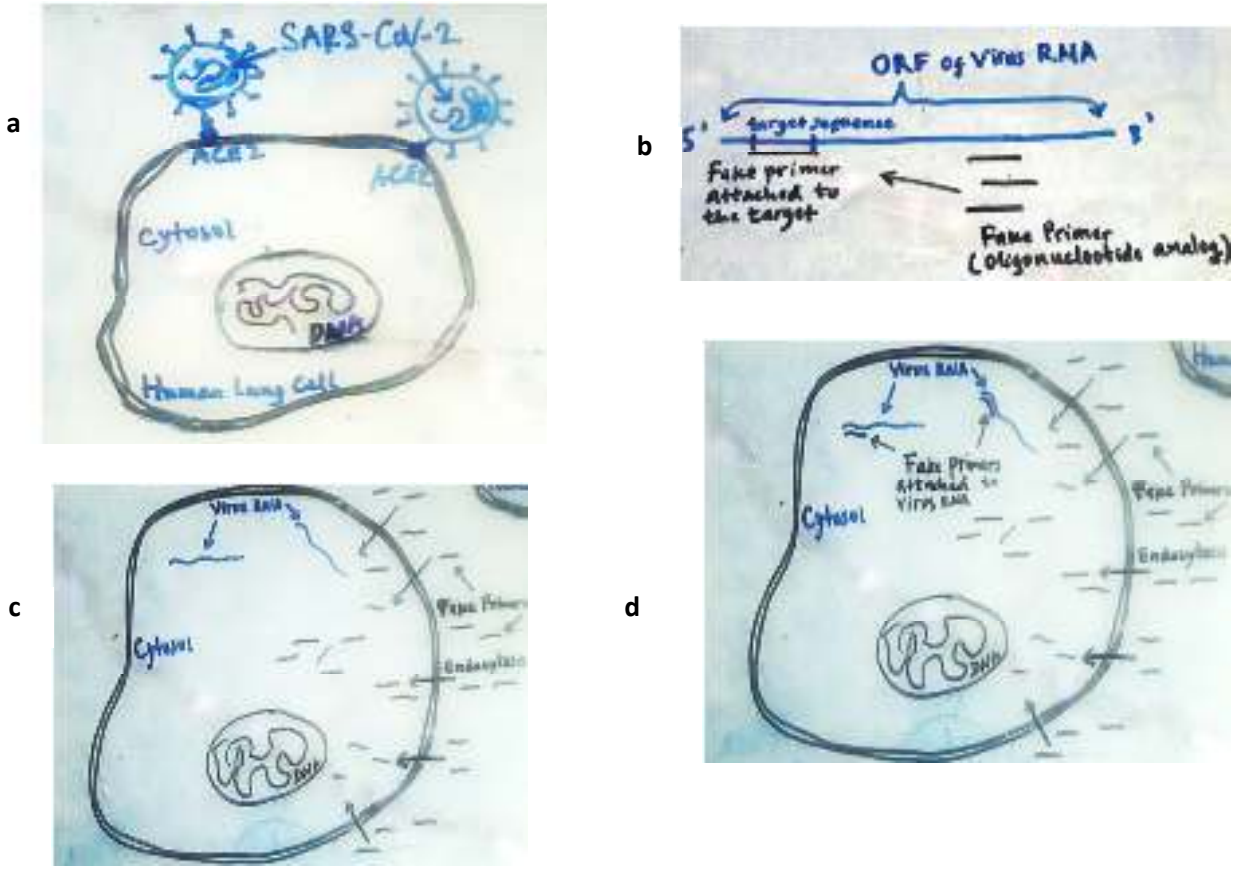

Figure 5. (a). Viruses inject their RNA to cytosol of human lung cell. (b) Fake primer (oligonucleotide analog) attach to the virus RNA. (c) Fake primers attach to viruses RNAs then will stop the working of RNA dependent RNA polymerase inside the infected cell. (d) So, the new virions will not be formed.

The virus RNA which has an attached fake primer will not be processed further to produce vital protein for new virions. The aggregate of RNA and fake primer then naturally destroyed by cell's mechanism.

CONCLUSIONS

I proposed the methods and design respectively: 1) Study the specific sequence of SARS-CoV-2 RNA. 2) Synthesize the oligonucleotide using nucleotides analogs (to produce fake primers) that can specifically attach to the specific sequence of SARS-CoV-2 RNA. 3) Conduct *in vitro* experiments using the fake primers produced and the infected cells, study the efficiency of endocytosis of fake primers through cell membrane and to know the best dosage that can inhibit the SARS-CoV-2 replication. 4) Conduct clinical tests (after passing the ethics protocol) to the Covid-19 patients based on the *in vitro* test results. So, the proposed novel narrow spectrum drug is the fake primer.

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