Potential use of RNA-dependent RNA polymerase (RdRp) inhibitor against COVID-19 infection

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ABSTRACT

Favipiravir, an inhibitor of RNA-dependent RNA polymerase used against the Japanese flu, was recently suggested as a potential COVID-19 inhibitor. Since Favipiravir targets a critical and a viral specific process, using it as a treatment could be beneficial in slowing the outbreak. Though there have been many suggested antivirals to treat SARS-CoV-2 infection, most treatments target host-associated pathways that may cause adverse effects, Favipiravir or similar combination may be the best remedy against COVID-19 pandemic.

INTRODUCTION

Coronavirus Disease-2019 (COVID-19) is the disease caused by the novel severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2). SARS-CoV-2 is a member of the coronavirus family recently discovered in Wuhan, Hubei, China. The coronavirus family was initially discovered in the later part of the 1960s. Since the discovery there have been several members of this virus that have caused serious respiratory tract infections, these include Severe Acute Respiratory Syndrome (SARS-CoV) in 2003, Middle East Respiratory Syndrome (MERS-CoV) in 2012, and the current outbreak SARS-CoV-2 (previously known as 2019-nCoV).

Coronaviruses (CoVs) belong to the *Nidovirales* order and got their names from the unique “crown-like” spikes that are visible on the outer membrane of the virions. Coronaviruses are large single-stranded, enveloped RNA viruses that are broken down into four classes: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. Coronaviruses are the largest RNA viruses known with a genome ranging between 27 and 32 kb (1). Like all the *Nidovirales* members, Coronaviruses have a highly conserved genomic organization, unique enzymatic activities, and expression of nonstructural genes by ribosomal frameshifting.

Since the initial infection of SARS-CoV-2 in Wuhan the virus has spread globally. Although the mortality rate of COVID-19 is comparatively lower than previous coronavirus outbreaks (SARS-CoV- 10% and MERS-CoV- 37%), it is much higher than the 2018-2019 influenza season (0.96%). The first case in the United States was confirmed on January 20, 2020 in Washington State and has since spread to every states and territories. This outbreak has been devastating to older population (over 60) which are at higher risk and show more severe symptoms when compared with younger population. As with other coronaviruses, SARS-CoV-2 infects the lung epithelial cells of the alveola and can lead to severe complications including pneumonia (2). COVID-19 has caused a global shut down of commerce and normalcy with governments calling for social distancing and even lockdown of entire cities and countries. It is thus important for the discovery of treatments for this novel virus to slow the outbreak and shorten the disease.

VIRAL COMPONENTS AND LIFE CYCLE

SARS-CoV-2 is an enveloped single-stranded positive-sense RNA virus composed of four structural proteins, envelope (E), membrane (M), spike (S), and nuclear capsid (N) (3) (Figure 1). In addition to the structural proteins, the genome contains a 5' cap structure along with a 3' poly (A) tail that acts as a mRNA for translation of the replicase polyproteins. The replicase gene encodes the nonstructural proteins (NSPS) that form two-thirds of the genome. The genome also include several accessory proteins that are not essential for viral replication but were shown to play a role in viral pathogenesis.

Even though, the E protein is not conserved between coronaviruses, however it is important for assembly and release of the virus. The M protein gives the virion its spherical shape and is the most abundant protein. The S protein has been shown to be important in host cell interactions and virulence (4). The N protein binds to the single-strand RNA inside the capsid to protect it in a beads-on-a-string conformation. SARS-CoV-2 differs from other coronaviruses because of its S protein. The S1 domain of the S protein has been shown to have a 45% difference in the amino acid sequence compared to that of SARS-CoV.

It has been found that the virus enters the body via droplets that travel to the respiratory tract, where it can infect cells containing angiotensin-converting enzyme 2 (ACE2) including lung epithelial cells (5). The S1 domain of the S protein has been shown to interact with ACE2 on the surface of cells (4). The S protein has also been predicted to interact with the Glucose Regulated Protein 78 (GRP78) (6). After binding to a receptor on the cell surface, the S protein is cleaved by a cellular protease: cathepsin (7) or TMPRSS2 (8) to expose the fusion peptide allowing the viral membrane to fuse with the cellular membrane. The viral genome is then released into the cytoplasm. Next, the host ribosomes translate the viral positive-sense RNA into 16 non-structural proteins (NSPS) (Table 1) (3). Some of these NSPS are involved in ensuring viral RNA is translated efficiently without host interference. Other NSPS are important for producing mature virions. The rest of the NSPS make the replicase-transcriptase complex (RTC). The RTC is composed of proteins that are required to replicate viral RNA both genomic and sub-genomic through anti-sense RNA intermediates (3).

After viral genomic RNA replication and viral protein translation from sub-genomic RNA, the viral structural proteins are inserted into the endoplasmic reticulum (ER). After this insertion, the proteins

follow the secretory pathway and form the endoplasmic reticulum-Golgi intermediate compartment (ERGIC) (8). Once the ERGIC is formed the viral RNA genomes, which are encapsulated by the N protein, are incorporated into the ERGIC which then buds into mature virions. The mature virions exit the cell via exocytosis and can infect other cells or be spread to other hosts.

VIRAL RNA REPLICATION AS A THERAPEUTIC TARGET

Currently, clinicians can only treat the various symptoms of COVID-19 because there is no targeted treatment for the SARS-CoV-2. Nevertheless, drugs used to treat Malaria and HIV-1 such as Chloroquine and Lopinavir/ritonavir, respectively, have been shown to possibly influence SARS-CoV-2 replication. Table 2 summarizes all the potential drugs that are in stage of development and the names of the pharmaceutical companies developing these drugs. Additional companies and schools launched studies aiming to develop new COVID-19 drugs/vaccine such as Pfizer, Enata Pharmaceutical, Integral Molecular, Takeda Pharmaceutical Company, Hong Kong University of Science and Technology, Columbia University, Tulane University and others (clinicaltrialsarena.com/analysis/coronavirus-mers-cov-drugs/).

Chloroquine has been shown to inhibit the glycosylation of ACE2 and thus prevent SARS-CoV-2 from binding to cells. Studies revealed no cytotoxicity *in vitro*, however the glycosylation of ACE2 is important in the regulation of the renin-angiotensin system (9). Deregulation of this system could cause some adverse effects.

Similarly, Lopinavir/ritonavir is a protease inhibitor that could block the cleavage of the S protein of SARS-CoV-2 thus preventing fusion of the viral and cellular membranes (10). However, there are many known adverse effects of this drug and it has shown no significant improvements over standard care in treating COVID-19.

Ideally, it is better to target a step of the virus life cycle preventing it from forming mature virions and infecting other cells without damaging host cell function that could cause adverse side-effects. In order to reduce adverse effects, viral-specific processes can be inhibited or reversed. SARS-CoV-2 relies on host cellular mechanisms to reproduce mature virions. However, RNA replication from an RNA template is unique to the virus thus making this step a possible therapeutic target. Inhibiting the virus at the RNA

replication step would result in 1) no genomic RNA replication, 2) no subgenomic replication and subsequent structural protein production, and 3) no mature virion formation and release essentially stopping the productive infection. By only targeting the RNA replication of the virus, NSPS can still be produced at low levels inside the cell but infection would end there. A possible drug candidate that inhibits the RNA-dependent RNA polymerase (RdRp) and would result in the inhibition of SARS-CoV-2 is Favipiravir.

FAVIPIRAVIR

Favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) also known as T-705, Avigan or Favilavir, is an antiviral agent that was first developed by Toyama Chemical Co. against the Japanese flu (11). Favipiravir is a pyrazinecarboxamide derivative that can inhibit the RdRp of influenza virus and was also shown to have antiviral activities beyond Japanese flu. In animals, Favipiravir has shown activity against viruses such as Influenza, West Nile, Yellow fever, Foot and Mouth Disease, and Rift Valley as well as other Flaviviruses, Arenaviruses, Bunyaviruses, Alphaviruses (e.g. *Chikungunya* [CHIKV]; *Sindbis* [SINV]; *Western equine encephalitis* [WEEV]; and *Semliki Forest* [SFV] viruses), and Enteroviruses (12-14). Favipiravir was also shown to have an effect *in vitro* and *in vivo* against Zaire Ebola (15), Rabies (RABV) (16) and Zika viruses (17). Favipiravir was described to reduce the morbidity and mortality associated with RABV infection in mice. In Syrian hamster model that mirrors the human disease, Favipiravir reduced encephalitis, hemorrhagic fever, respiratory difficulties and mortality rate caused by Nipah virus infection (a Bat virus) (18).

Favipiravir is structurally similar to Ribavirin (antiviral drug used to treat Respiratory Syncytial Virus [RSV] infection, Hepatitis C and some viral hemorrhagic fevers) (19). Favipiravir and Ribavirin share a carboxamide (C-[O]-NH₂) moiety, however Favipiravir is a more specific version of Ribavirin. Both drugs target the viral RNA polymerase, Ribavirin primarily targets the Inosine-5'-monophosphate dehydrogenase (IMPDH), while Favipiravir interacts with RNA polymerase.

Mechanistically, Favipiravir and its form Favipiravir-RMP (favipiravir-ribofuranosyl-50-monophosphate) do not inhibit influenza RNA polymerase activity, but it is the phosphoribosylated form, favipiravir-ribofuranosyl-50-triphosphate (Favipiravir-RTP) that inhibits the enzyme. It has been

suggested that the human hypoxanthine guanine phosphoribosyl-transferase (HGPRT) plays a role in the Favipiravir activation (20). The active form of Favipiravir is recognized by the catalytic domain of the viral RNA-dependent RNA polymerase and blocks its enzymatic activity. This results in inhibition of the RNA-dependent RNA polymerase and effectively ending the infectious cycle of SARS-CoV-2 (Figure 2). Note that Favipiravir is not toxic to mammalian cells and does not inhibit RNA or DNA synthesis within these cells.

All these features make Favipiravir a broad-spectrum inhibitor of RdRp, the polymerase responsible for replicating RNA and the major functional unit of the RTC in SARS-CoV2 making this drug the best available drug to fight the spread of COVID-19.

Currently, Favipiravir has been approved in Japan as an influenza treatment (Japanese flu), while awaiting approval in the USA after successfully passing phase III clinical trials. Favipiravir has been shown to be an efficient treatment against COVID-19 in Wuhan, China . Even though, the study lacks controls (double blinded, placebo), however Favipiravir has been shown to reduce viral clearance time in 80 patients to 4 days compared to 11 days for the control group, and that 91.43% of patients had improved CT scans with few side effect. These results encouraged other countries such as Turkey to start using Favipiravir as a potential treatment against COVID-19.

CONCLUSION AND FUTURE DIRECTIONS

COVID-19 caused by the novel coronavirus, SARS-CoV-2, is currently spreading quickly across the globe. Favipiravir is an ideal targeted treatment since it is viral-specific and has already been used in clinical trials including a Phase 3 trial for the treatment of Japanese influenza. Favipiravir targets and blocks viral RNA-dependent RNA polymerase (RdRp) that is used by the virus to replicate and produce mature virions. Blocking this step in the viral life cycle won't prevent infection but will shorten the duration and reduce the severity. It may also shorten the time a patient is contagious. Clinical trials need to be completed to further explore the possibility of Favipiravir as an effective treatment for the spread and severity of SARS-CoV-2, but the previous research seems promising that Favipiravir could be a useful treatment.

In conclusion, Favipiravir has great potential to be effective in treating COVID-19 and should be fast-tracked into clinical trials in the US. A drug like Favipiravir that can shorten infection will help to reduce the number of fatalities that SARS-CoV-2 is estimated to cause in the near future.

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REFERENCES

1. Perlman S, Netland J. 2009. Coronaviruses post-SARS: update on replication and pathogenesis. *Nat Rev Microbiol* 7:439-450.
2. Zhou P, Yang X-L, Wang X-G, Hu B, Zhang L, Zhang W, Si H-R, Zhu Y, Li B, Huang C-L, Chen H-D, Chen J, Luo Y, Guo H, Jiang R-D, Liu M-Q, Chen Y, Shen X-R, Wang X, Zheng X-S, Zhao K, Chen Q-J, Deng F, Liu L-L, Yan B, Zhan F-X, Wang Y-Y, Xiao G-F, Shi Z-L. 2020. A pneumonia outbreak associated with a new coronavirus of probable bat origin. *Nature* 579:270-273.
3. Chen Y, Liu Q, Guo D. 2020. Emerging coronaviruses: Genome structure, replication, and pathogenesis. *J Med Virol* 92:418-423.
4. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. 2020. Structural basis for the recognition of the SARS-CoV-2 by full-length human ACE2. *Science* pii: eabb2762.
5. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, Pan P, Wang W, Hu D, Liu X, Zhang Q, Wu J. 2020. Coronavirus infections and immune responses. *J Med Virol* 92:424-432.
6. Ibrahim IM, Abdelmalek DH, Elshahat ME, Elfiky AA. 2020. COVID-19 spike-host cell receptor GRP78 binding site prediction. *J Infect* pii: S0163-4453(20)30107-9.
7. Fehr AR, Perlman S. 2015. Coronaviruses: An Overview of Their Replication and Pathogenesis. *Methods Mol Biol* 1282:1-23.
8. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu N-H, Nitsche A, Müller MA, Drosten C, Pöhlmann S. 2020. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell* pii: S0092-8674(20)30229-4.
9. Warner FJ, Lew RA, Smith AI, Lambert DW, Hooper NM, Turner AJ. 2005. Angiotensin-converting Enzyme 2 (ACE2), But Not ACE, Is Preferentially Localized to the Apical Surface of Polarized Kidney Cells. *J Biol Chem* 280:39353–39362.
10. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang L, Li C, Yuan Y, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang Y, Li H, Shang L, Wang K, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng L, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo L, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C. 2020. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med*. doi: 10.1056/NEJMoa2001282.
11. Furuta Y, Takahashi K, Fukuda Y, Kuno M, Kamiyama T, Kozaki K, Nomura N, Egawa H, Minami S, Watanabe Y, Narita H, Shiraki K. 2002. In vitro and in vivo activities of anti-influenza virus compound T-705. *Antimicrob Agents Chemother* 46:977-981.
12. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL, Gowen BB, Julander JG, Morrey JD. 2009. T-705 (favipiravir) and related compounds: Novel broad-spectrum inhibitors of RNA viral infections. *Antiviral Res* 82:95-102.
13. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. 2013. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. *Antiviral Res* 100:446-454.

14. Caroline AL, Powell DS, Bethel LM, Oury TD, Reed DS, Hartman AL. 2014. Broad Spectrum Antiviral Activity of Favipiravir (T-705): Protection from Highly Lethal Inhalational Rift Valley Fever. *PLoS Negl Trop Dis*. 8:e2790.
15. Kerber R, Lorenz E, Duraffour S, Sissoko D, Rudolf M, Jaeger A, Cisse SD, Camara AM, Miranda O, Castro CM, Akoi Bore J, Raymond Koundouno F, Repits J, Afrough B, Becker-Ziaja B, Hinzmann J, Mertens M, Vitoriano I, Hugh Logue C, Böttcher JP, Pallasch E, Sachse A, Bah A, Cabeza-Cabrerizo M, Nitzsche K, Kuisma E, Michel J, Holm T, Zekeng EG, Cowley LA, Garcia-Dorival I, Hetzelt N, Baum JHJ, Portmann J, Carter L, Yenamaberhan RL, Camino A, Enkirch T, Singethan K, Meisel S, Mazzearelli A, Kosgei A, Kafetzopoulou L, Rickett NY, Patrono LV, Ghebregiorghis L, Arnold U, Colin G, Juchet S, Marchal CL, Kolie JS, Beavogui AH, Wurr S, Bockholt S, Krumkamp R, May J, Stoecker K, Fleischmann E, Ippolito G, Carroll MW, Koivogui L, Magassouba N, Keita S, Gurry C, Drury P, Diallo B, Formenty P, Wölfel R, Di Caro A, Gabriel M, Anglaret X, Malvy D, Günther S. 2019. Laboratory Findings, Compassionate Use of Favipiravir, and Outcome in Patients With Ebola Virus Disease, Guinea, 2015-A Retrospective Observational Study. *J Infect Dis* 220:195-202.
16. Yamada K, Noguchi K, Komeno T, Furuta Y, Nishizono A. 2015. Efficacy of Favipiravir (T-705) in Rabies Postexposure Prophylaxis. *J Infect Dis* 213:1253-1261.
17. Cai L, Sun Y, Song Y, Xu L, Bei Z, Zhang D, Dou Y, Wang H. 2017. Viral polymerase inhibitors T-705 and T-1105 are potential inhibitors of Zika virus replication. *Arch Virol* 162:2847-2853.
18. Dawes BE, Kalveram B, Ikegami T, Juelich T, Smith JK, Zhang L, Park A, Lee B, Komeno T, Furuta Y, Freiberg AN. 2018. Favipiravir (T-705) protects against Nipah virus infection in the hamster model. *Sci Rep* 8:7604.
19. Drabikowska AK, Dudycz L, Shugar D. 1979. Studies on the mechanism of antiviral action of 1-(beta-D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (ribavirin). *J Med Chem* 22:653-657.
20. Naesens L, Guddat LW, Keough DT, van Kuilenburg AB, Meijer J, Vande Voorde J, Balzarini J. 2013. Role of human hypoxanthine guanine phosphoribosyltransferase in activation of the antiviral agent T-705 (favipiravir). *Mol Pharmacol* 84:615-629.

FIGURES LEGENDS

Figure 1. ***Schematic presentation of the COVID-19 structure.*** Structural Proteins of SARS-CoV 2 where the location and names of the viral proteins are shown (S= spike; N= nucleocapside; M= membrane; E= Envelope). Structure was created using Biorender software.

Figure 2. ***Favipiravir Mechanism of Action.*** Numbers in black indicate the normal life cycle of SARS-CoV2 from 1) binding to ACE2 receptors and then fusion with the cellular membrane, 2) release of the viral genome in the form of (+) sense RNA and the subsequent production of non-structural proteins (NSPS), 3) translation and formation of the replicase-transcriptase complex (RTC), 4) RNA replication of genomic and subgenomic RNA, 5) transcription of subgenomic RNA, 6) translation of that RNA into structural proteins, 7) nucleocapsid combination with S, E, and M proteins in the ERGIC, 8) budding of the ERGIC into a mature virion, and 9) exocytosis of mature virions. Numbers in red indicate the mechanism of action of Favipiravir from 1) entry into the cell in the inactive form, 2) converted to active form by phosphoribosylation, and 3) binding to RNA-dependent RNA polymerase to block its active site.

Table 1. List of viral NSPS and their known functions.

Table 2. ***List of Potential or in development drugs, pharmaceutical companies and mechanisms of action.*** Yellow shaded- drugs developed to treat different diseases but was used to treat COVID-19; White shaded- names of major drugs/vaccine that have the potential to become drugs in various stage of development; Light Green shaded- drugs in various stages of development globally.

FIGURE 1

FIGURE 2

TABLE 1

Protein	Function(s)
nsp1	Causes degradation of Host cell mRNA
nsp2	Function currently unknown
nsp3	Multi-domain transmembrane protein which interacts with the viral N protein, promotes cytokine expression, cleaves viral polypeptides, and blocks host innate immunity
nsp4	Transmembrane protein that is important for double-membrane vesicle (DMV) formation
nsp5	Cleaves viral polyproteins
nsp6	Transmembrane protein
nsp7	One part of the RNA polymerase clamp
nsp8	One part of the RNA polymerase clamp, possible primase
nsp9	RNA binding protein
nsp10	nsp14 and nsp16 cofactor
nsp11	Function currently unknown
nsp12	RNA dependent RNA polymerase
nsp13	RNA helicase
nsp14	MTase and exoribonuclease
nsp15	Viral endoribonuclease
nsp16	Protects viral RNA

TABLE 2

Name	Company	Targets/Mechanisms
Chloroquine	SANOFI	Malaria /Arthritis
Favipiravir	Toyama Chemical	Japanese Flu
TJM2	I-Mab Biopharma	Targets GM-CSF (responsible for acute or chronic inflammation)
No name	Medicago and Laval University's Infectious Disease Research Centre	Virus-Like Particles (VLP) of the coronavirus
AT-100 (rhSP-D)	Airway Therapeutics / NIH	Reduces inflammation and infection in the lungs; Generates an immune response against various respiratory diseases
TZLS-501	Tiziana Life Sciences	Anti-interleukin-6 receptor; Prevents lung damage and elevated levels of IL-6
OYA1	OyaGen	Prevents viral replication in cell culture
BPI-002	BeyondSpring	Small molecule, activates CD4+ helper T cells and CD8+ cytotoxic T cells; Generates an immune response in the body
Intranasal vaccine	Altimune	Similar to NasoVAX, an influenza vaccine
INO-4800	Inovio Pharmaceuticals/ Beijing Advaccine Biotechnology	Activates immune system to generate a robust targeted T cell and antibody response
NP-120 (Ifenprodil)	Algernon Pharmaceuticals	N-methyl-d-aspartate (NDMA) receptor Glutamate receptor antagonist
mRNA-1273 vaccine	Moderna and Vaccine Research Center-NIAID	Targets the Spike (S) protein of the coronavirus
APN01	University of British Columbia and APEIRON Biologics	Targets ACE2 in SARS
Avian Coronavirus Infectious Bronchitis Virus (IBV) vaccine	MIGAL Research Institute	Treats avian coronavirus; Modified to treat COVID-19
TNX-1800	Tonix Pharmaceuticals and Southern Research	Modified Horsepox virus designed to express a protein derived from the virus that causes the coronavirus infection
Brilacidin	Innovation Pharmaceuticals	Antibacterial, anti-inflammatory and immunomodulatory properties
Oral recombinant vaccine	Vaxart	No Info
Recombinant subunit vaccine	Clover Biopharmaceuticals	Targets the trimeric S protein (S-Trimer) of the COVID-19 (responsible for binding with the host cell and causing a viral infection)
Leronlimab (PRO 140)	CytoDyn	CCR5 antagonist
Linear DNA Vaccine	Applied DNA Sciences and Takis Biotech	No Info
BXT-25	BIOXYTRAN	Supplies oxygen to the vital organs
MERS vaccine	Novavax	Binds to the major surface S-protein
AmnioBoost	Lattice Biologics	Reduces the production of pro-inflammatory cytokines while boosting the production of anti-inflammatory cytokines
SNG001	Synairgen Research	An interferon- β , which is delivered directly to the lungs to reduce the infection
REGN3048/51 and Kevzara	Regeneron	Both antibodies bind to S-protein of MERS coronavirus; Kevzara blocks interleukin-6 pathway
Galidesivir (BCX4430)	Biocryst Pharma	Nucleoside RNA polymerase inhibitor
Actemra	Roche	Prevents cytokine storms or overreaction of the immune system
Remdesivir (GS-5734)	Gilead Sciences	Developed against Ebola but ineffective