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Research Article

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Patent Evaluation of Antiviral Drugs in the battle against COVID-19 & Minimization of Risks Associated with Occurrence of Dangerous viral mutations During Treatment with Antiviral Mutagenic Agents

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Introduction

It is well known that viruses are obligate parasites entirely dependent on their host cells. Such dependence poses a serious challenge to drug developers in their attempts to create medications that are able to inhibit the target virus without having an adverse effect on biochemical processes of the host macro organism. It is also a major factor contributing to the limitedness of the current antiviral arsenal. Favipiravir (favipiravir, T-705), chemical entitled 6- fluoro- 3- HYDROXYPYRAZINE -2- Methanamide, is new RNA polymerase (RdRp) the inhibitor class broad-spectrum antiviral drug that RNA relies on, itself does not have antiviral activity, is existed by metabolism Favipiravir ribonucleoside triphosphote form can be rapidly converted in vivo, by simulating guanosine triphosphate (GTP) (GTP) competitive inhibition virus The RNA polymerase that RNA relies on, suppression viral genome replicates and transcribes and play antivirus action, Favipiravir nucleoside three phosphorus Sour form also can penetrate into viral gene, plays antivirus action by inducing fatefulue mutation.Favipiravir is to A type influenza (including bird flu and influenza A H1N1 infection), virus had preferable therapeutical effect moreover it is possible to suppress the transcription of other viruses, such as Arenaviruss, yellow fever virus, west Nile viruss, Bunyavirus and hand-foot-mouth disease virus etc., nearest document report it can be effective Duplication (the IC of suppression Zaire type Ebola virus RNA_{90}For 110 μm of ol/L)

In the synthesis technique of Favipiravir mainly has following three kinds (1) patent documentation (WO00/10569) is urged through diazotising alcoholysis, palladium with 6- bromo- 3- Aminopyrazine -2- methyl formate Change lower amino to replace and the prepared 6- amino -3- methoxypyrazine -2- Methanamide of amidation process, then replace through diazotising fluorine, so Under trim, ethylchlorosilane and sodium iodide effect, demethylation is obtained Favipiravir, total recovery only 0.44% afterwards.Amino in method Replace used catalyst three (dibenzalacetone) two palladium [$Pd_2(dba)_3$] and (S)-(-) double (the diphenyl phosphine) -1,1'- of -2,2'- Dinaphthalene costly, and final step reaction be difficult to control to, yield only has 4.3%, is unfavorable for industrialized production. Reaction equation is such as Under.

The COVID-19 pandemic has brought this healthcare problem to the fore, as currently there are hardly any specific therapeutic drug options to combat the coronavirus. New vaccines against the corona virus are expected to be available in 2022. The development and approval of new pharmaceutical compounds takes in general more than 10 years. Therefore the focus is to repurpose existing drugs developed against other viral infections caused by corona viruses such as influenza or SARS and MERS [1,2]. The main goal is to provide rapid and reliable help for patients and to alleviate the course of the disease. A number of existing drugs are currently being tested for their suitability against the corona disease Covid-19, most of them being evaluated within international clinical trials. Among

these drug candidates is favipiravir, which we use as an example to show how the IP situation of a drug can be explored by using the STN Online Service.

Developing antiviral drugs in the battle against COVID-19

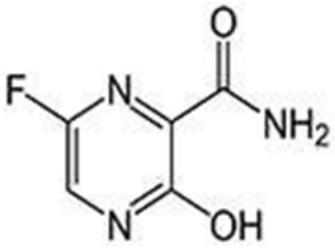
Amid the coronavirus pandemic, pioneering pharmaceutical makers, research institutes, and universities are working in collaboration to develop novel antiviral drugs that are small compounds and vaccines. Although most inventions produced this year will be disclosed when their patent applications are published next year, the inventions being developed before this pandemic have already been disclosed.

In this article, we introduce promising antiviral drugs that are small compounds and vaccines for COVID-19, and analyse the relevant patents.

Antiviral drugs

Avigan® (Favipiravir)

[Chemical structure]



Avigan is a small molecule which is a viral ribonucleic acid (RNA)-dependent RNA polymerase inhibitor and is used in the treatment of influenza. Avigan was invented and patented by Fujifilm Toyama Chemical in Japan. Fujifilm has announced that the company is going to apply for sales and market approval to the Health, Labour and Welfare Ministry (HLWM) in Japan in October 2020. They have confirmed a positive outcome from their clinical trials after controversies regarding its efficacy. It will become the first approved domestic drug for COVID-19 once the government approves it, presumably in early December.

Patent information

Avigan is protected by both a manufacturing process patent and a substance patent. However, it is possible to manufacture Avigan without the following patented manufacturing process. In contrast, it should be noted that the substance patent expired on August 18 2019, but its patent term extension (PTE) registration will expire on November 11 2031. Since the extended right has only been applied for in relation to the treatment of influenza, this right does not cover the medical treatment of COVID-19.

1. Manufacturing process patent

Japanese patent number: 5787727
Patentee: Fujifilm Corporation, Toyama Chemical
Title of invention: The pyrazino [2,3 - d] isoxazole derivative
Expiration date: November 11 2031

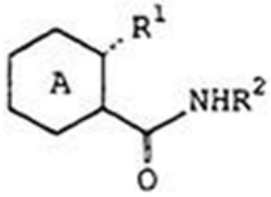
2. Substance patent

Japanese patent number: 3453362
Patentee: Toyama Chemical
Title of invention: Nitrogenous heterocyclic carboxamide derivatives or salts thereof and antiviral agents containing both
Expiration date: August 18 2024

Claim interpretation of substance patent - Japanese patent number 3453362

Claim 1

An antiviral agent comprising a nitrogen-containing heterocyclic carboxamide derivative represented by the following general formula:



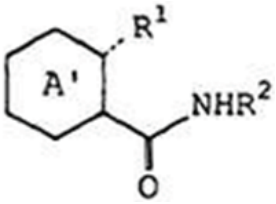
Where in ring A represents a substituted or unsubstituted pyrazine, pyrimidine, pyridazine or triazine ring; R1 represents..OH; R2 represents a hydrogen atom,..; and the broken line represents a single bond..; or a salt thereof.

Claim 1 is an agent claim, which specifies the use thereof, but the claimed scope is broad because the scope of ring A is broad.

Claim 6

A nitrogen-containing heterocyclic derivative represented by the following general formula:

Where in ring A' represents a pyrazine ring substituted with a halogen atom,.. ; R1 represents..OH; R2 represents a hydrogen atom..; and the broken line represents a single bond..; or a salt thereof.



Claim 6 is a compound claim which does not specify any usage.

Noteworthy point

While it takes a long time for clinical trials and pharmaceutical applications to be submitted to the Health, Labour and Welfare Ministry (HLWM), a patent on a drug can have a significant impact on both IP and society as a whole. Some patents come to draw a lot of attention when their rights are about to expire or have expired. We hope that this noble drug will help eradicate COVID-19.

Patent term extension in Japan

The substance patent referred to above (Patent No.3453362) is still valid, but its use for the extension was limited to treatment for influenza (cf. Figure 1). As a result, the patentee cannot use this right commercially for COVID-19-related treatments.

Under Japanese Patent Law, the patent term is 20 years from the filing date. However, a patent term extension (PTE) system can be utilised for inventions relating to medicines and agricultural chemicals. This is a unique system in Japan which, as an exception, allows a patent right to be maintained even after the expiration of the duration of the patent right 20 years after the filing of the application by taking into account the time required to obtain sales and marketing approval for medicines. The extended period can be up to five years.

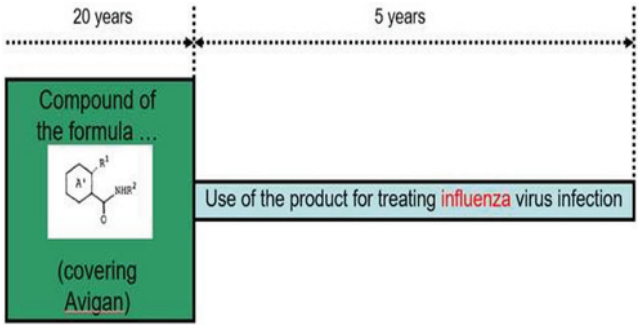
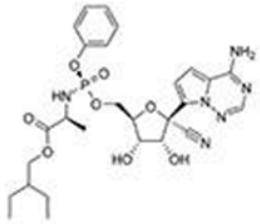


Figure 1

Veklury® (Remdesivir)

Remdesivir is a small molecule which is a pro-drug that is converted in the body into a ribonucleotide analogue and is used for treatment of the Ebola virus disease.



Patent information

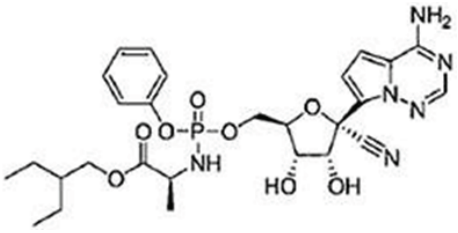
Remdesivir is protected by a substance patent which is still pending not only in Japan but also in other countries.

Japanese Patent number: 5969471
Patentee: Gilead Sciences
Title of invention: Methods and compounds for treating paramyxoviridae virus infections
Expiration date: July 22 2031

Claim interpretation

Claim 23

The compound of claim 20 that is or a pharmaceutically acceptable salt thereof.

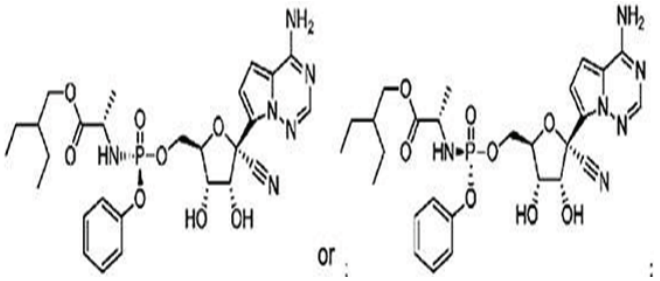


Claim 23 is a compound claim which does not specify any usage.

Amended Claim 36

A composition for treating a coronaviridae infection in a human in need thereof, comprising a compound having the following structure or a pharmaceutically acceptable salt thereof.

Claim 36 is a composition claim for treating a coronaviridae infection.
In the example, MERS-CoV and SARS-CoV antiviral activity are shown.



Comparison between Avigan and Remdesivir

Efficacy

Both compounds have a similar structure as a nucleotide (cf. Figure 2) and function as nucleotide analogues which inhibit the replication of RNA by RNA polymerase in a competitive manner (cf. Figure 3).

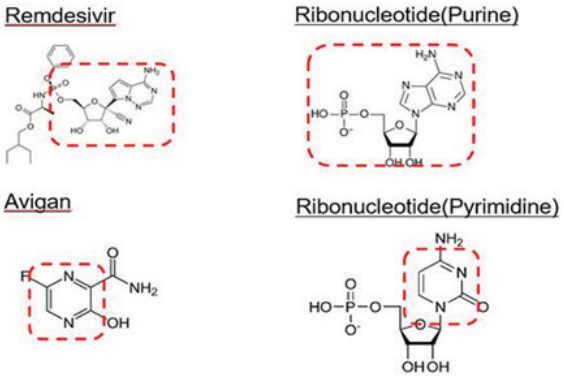


Figure 2

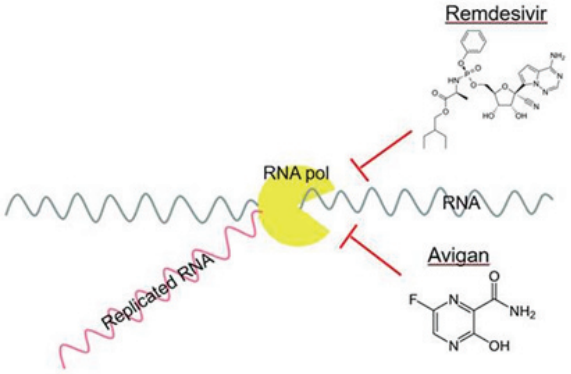


Figure 3

Patent

Regarding the legal status of both compounds, Remdesivir is protected by its patent while Avigan's patent, which protects the treatment of COVID-19, has expired (cf. Figure 4).

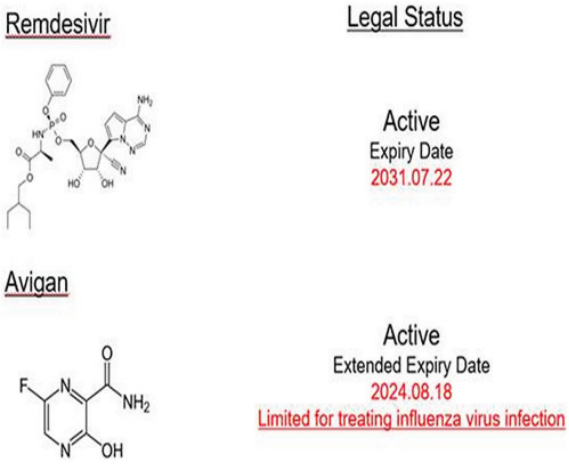


Figure 4

Vaccines

The World Health Organization (WHO) has announced that 35 vaccines are now under clinical trial and another 145 are in a preclinical evaluation stage (as of September 9 2020). Although most of the promising vaccine candidates in the WHO list have not yet been disclosed by their patent publication, pharmaceutical companies are likely to tap their existing technologies and owned patents so as to apply them to coronavirus vaccine development. We have focused on two promising COVID-19 vaccines under clinical trial from data in the DRAFT landscape of COVID-19 candidate vaccines - 9 September 2020.

1. ChAdOx1-S (AZD1222) (developer/manufacturer: University of Oxford/AstraZeneca)

This vaccine is a non-replicating viral vector. A viral vector vaccine is a non-pathogenic or a weakened viral vector where antigen protein genes are genetically introduced into the vector. Adenovirus and retrovirus are used as viral vectors. For the SARS-CoV-2 vaccine, a viral vector vaccine having a gene encoding a spike protein, which plays a crucial role in infection, is mainly being developed (cf. Figure 5).

Patent information

Patent number: 6230527

Patentee: University of Oxford

Title of invention: Simian adenovirus and hybrid adenoviral vectors

Claim interpretation

Claim 1

An adenovirus vector comprising a capsid, wherein the capsid contains one or more capsid protein derived from wild type chimpanzee adenovirus AdY25, and encapsidates a nucleic acid molecule comprising an exogeneous nucleotide sequence of interest operably linked to expression control sequences which direct the translation, transcription and/or expression thereof in an animal cell and an adenoviral packaging signal sequence, wherein nucleotide sequence coding the wild type chimpanzee adenovirus AdY25 is sequence number 1.

Noteworthy point

In the present invention, the prevalence rate of the vector-neutralising antibodies in human serum is low, and the vector, which has a target antigen, induces a sufficiently high immune system. There is no limitation in the claims to the antigen of SARS-CoV-2. Any adenovirus vector comprising one or more capsid derived from wild type chimpanzee adenovirus AdY25 would be within the claim scope. Since the present invention does not specify a target antigen, the invention could not stand out from competitors if the aforementioned vector is of no use.

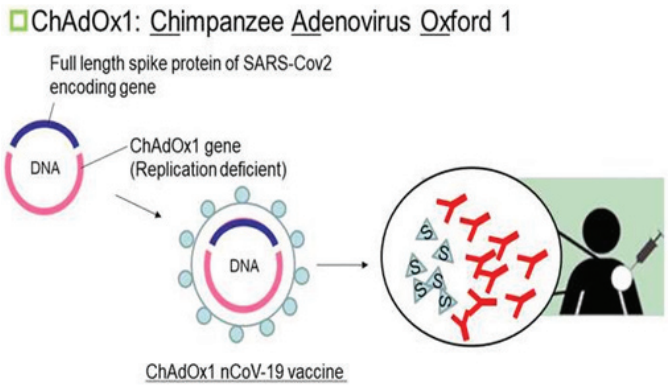


Figure 5

2. mRNA-1273 (developer/manufacturer: Moderna/NIAID)

This vaccine is an LNP-encapsulated mRNA. The mRNA vaccine for SARS-CoV-2 is engineered with the following steps: first, an artificial mRNA strand encoding a coronavirus gene is produced. Second, the mRNA is encapsuled by lipids, which are nanoparticles. Third, once the vaccine is injected into a human body, mRNAs are translated into virus proteins (virus antigen) and then, they cause the immune system to react which subsequently creates antibodies. Compared with conventional vaccines, mRNA vaccines are available in a shorter manufacturing time and are less cumbersome in culturing the virus. In recent years, there has been a lot of activity in mRNA vaccine development.

Patent information

US Patent Registration number: 10702600 (Registration date: July 7 2020)

Patentee: Moderna

Title of Invention: Betacoronavirus mRNA vaccine

Claim interpretation

Currently, there is no corresponding Japanese application. Below is an excerpt from the US patent gazette.

Claim 1

A composition, comprising a messenger ribonucleic acid (mRNA) comprising an open reading frame encoding a betacoronavirus (BetaCoV) S protein or S protein subunit formulated in a lipid nanoparticle.

Noteworthy point

BetaCoV recited in Claim 1 covers novel coronavirus (SARS-CoV2). The composition including mRNA encoding coronavirus S proteins within liquid nanoparticles, is covered in a scope of claims in the present invention. An example of the present invention describes the result that the mRNA vaccine coding MERS CoV spike protein had on immunised rabbits, successfully inducing a neutralising antibody.

Some antiviral drugs that are being developed for clinical trials are protected by their existing patents, but these protections are due to a broad claim scope or related patents such as vectors. Holding a core patent at an earlier stage is essential for helping to boost further drug discovery in this unprecedented situation.

Furthermore, patent applications directly protect antiviral drugs that are under development and will be disclosed in the near future.

Currently, there are 6 main drug development strategies to combat coronaviruses, focusing on:

1. Inhibitors of viral polymerases;
2. Inhibitors of the viral main protease (Mpro) that is involved in forming active viral polymerases;

3. Inhibitors of cell proteases involved in activation of the viral spike (S) protein that mediates the virus entry into the target cell;
4. Endosomal inhibitors of virus deproteinization;
5. Preparations based on recombinant interferons α2 and β1;
6. Preparations based on antiviral antibodies [1, 2].

Each strategy involves intense antiviral research and development.

Lately, the search for and development of antiviral agents against COVID-19 have brought antivirals of the first group into focus; these are inhibitors of the viral RNA-dependent RNA polymerase (RdRp). For instance, hopes are pinned on the antiviral known as favipiravir (FPV)-6-fluoro-3-hydroxy-pyrazinecarboxamide [3, 4]. It was synthesized and patented by Japanese researchers Y. Furuta and H. Egawa in the late 1990s [5]. During the further studies, the compound demon strated high activity against multiple viruses, including RNA viruses, such as influenza, bunya-, arena-, flavipicornaviruses and others. A serious limitation of FPV is its toxic side effects for the recipient macroorganism, which are caused by teratogenic and embryotoxic properties of the medication [6, 7]. For this reason, in the real-world clinical practice, FPV is permitted for medically supervised restricted use for patients with life-threatening influenza or COVID-19.

FPV demonstrates structural similarities to nucleosides, while competing functionally with guano-sine and adenosine (Figure 1); it can bind to viral RNA polymerases and inhibit their function [8]. As RNA polymerases of multiple viruses have a conserved structure and similar catalytic mechanism [9, 10], FPV, disrupting the RdRp specific function, demonstrates efficacy towards a wide range of RNA viruses [4, 8, 11]. Recently, virus-specific differences have been reported regarding FPV binding in the nucleotide region of the acceptor center in RNA polymerases of different viruses [12].

As a guanosine analog, FPV is efficiently recognized and modified by cellular enzymes, such as hypoxanthine-guanine-phosphoribosyltransferase (HGPRT) by attaching the ribose residue (ribosylation) [13–15]. The resulting FPV-ribosylphosphate undergoes addi¬tional phosphorylation of the ribose residue, acquiring properties of nucleoside triphosphate (FPV-ribosyl triphosphate or FPV-RTP) and the ability to become incorporated into the newly synthetized chain of nascent viral RNA through viral RdRp [16, 17]. Incorporation of nucleoside analogs into virion RNA inhibited and disrupted the complementary base pairing during template-directed synthesis of RNA strands by the viral polymerase.

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by a novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Several strategies are currently being pursued to combat the corona pandemic: (a) non-pharmaceutical measures, such as contact restrictions; (b) the development of vaccines (c) the development of new medicines, e.g. antibodies for passive immunization and existing early-stage projects for antiviral medicines, and (d) the repurposing of existing drugs by identifying and testing known active pharmaceutical ingredients already developed and approved for another disease.

Features and outcomes of the favipiravir induced mutagenic effect

Because of its mutagenic effect, FPV can cause a significant increase in the mutation rate in the genome of synthesized virions. The mutation rate is a dose-dependent parameter: At higher concentrations of the antiviral (> 100 μM), the rate is 10–1–10–2 mutations per 1 nucleotide in the genome, while at lower concentrations, the rate remains at the level of 10–3 mutations (Figure 2) [16, 26, 31]. This mutagenic effect produces two important results. At high FPV concentrations, the number of mutations is excessive and has an adverse effect on the viability of the new viral progeny – the so-called lethal effect. At low concentrations, the number of mutations decreases significantly, while being sufficient for providing a noticeable increase in the genetic diversity of the viral progeny retaining its viability [23, 31].

Stimulation of mutagenesis of the viral genome results in acceleration of the virus microevolution. Firstly, the increased mutagenesis boosts the rate of occurrence of viral mutations resistant to the mutagenic agent, which are otherwise known as viral escape mutations [8, 11, 22]. Secondly, newly generated viral mutations contribute to the overall genetic diversity of the viral population, thus significantly increasing the occurrence probability regarding dangerous virus variants characterized by high contagiousness and pathogenicity for humans, along with an expanded host range facilitating the transmission of mutant variants to domestic and farm animals as well as generating cross-species transmission between humans and animals. This can give rise to new migration flows of the virus transmitted among different species of animals and humans. The increased occurrence of viral mutations resulting from

extensive therapeutical use of a mutagenic agent or agents can trigger a dangerous epidemic problem. This problem associated with occurrence of dangerous viral mutations poses a real-life risk, if antiviral mutagenic agents are used indiscriminately, especially when they are easily accessible and their use and therapeutic dosage are not supervised or monitored.

Minimization of risks associated with occurrence of dangerous viral mutations during treatment with antiviral mutagenic agents

The administration of antiviral mutagenic agents suggests three implementable options aimed at increasing the mutagenesis threshold, which would inhibit the genetic diversity of the infectious virus and the occurrence of dangerous viral mutations.

The first option aimed at minimization of the adverse mutagenic effect on the virus implies improvement of the structure of the antiviral agent. Modification of the structure of a mutagenic agent such as FPV should result in eliminating its ability to incorporate into a nascent RNA stand and to cause both the termination of its elongation and the disruption of the further synthesis of a non-defective molecule. This task can be fulfilled by increasing the affinity of the nucleoside component of the agent for the polymerase to make their complexing irreversible. The other solution implies modification of the structure of the ribosyl-triphosphate group to prevent building of the phosphodiester bond between the antiviral agent and the subsequent nucleotide base, which would discontinue elongation and cause disruption of the RNA synthesis.

The second option aimed to inhibit the occurrence of dangerous viral mutations involves using of combinations of antiviral agents having different mechanisms of action, being directed at different viral and/or cellular targets. Numerous data on multiple antiviral-agents, which affect different viral proteins (enzymes), including viral polymerases, demonstrate that passaging of viruses in the presence of one antiviral agent (the so-called monotherapy) boosts the generation of viral mutants resistant to that particular agent [8, 11, 22]. Generally, the resistant strain had a mutation in the viral gene of the protein, at which the antiviral agent was targeted. However, the concurrent (parallel) application of 2 and more antiviral agents directed at different viral and/or cellular targets does not result in any occurrence of mutant strains even after the virus was passaged for a long time in the presence of combined antiviral agents [34–37]. These data suggest that application of antivi¬ral agents, including FPV, in combinations where the agents are directed at different targets should be seen as rational and well justified. Furthermore, using a combination of antiviral agents is generally characterized by significantly higher therapeutic efficacy and a synergistic antiviral effect [38–42].

The third option aimed to prevent dangerous consequences of the FPV mutagenic effect focuses on the range of optimal doses of the agent in the recipient. The range parameters can be based on the level of permanent concentration of min 75 μM (~30 mg/kg of body weight) [23, 26]. The estimation of mutagenic FPV concentrations in the influenza-virus-infected cell culture shows that the concentration of 125 μM and higher concentrations provide effective termination of the synthesis of viral RNAs and their lethal mutagenesis, thus notably inhibiting the generation of viable virions [8, 16, 21, 22, 26, 43]. Extrapolation of this concentration, taking into account the bioavailability in a human body, makes it possible to estimate the maintaining therapeutic dose of the antiviral agent, which is equal to 20– 50 mg/kg of body weight, or higher, when administered daily [44]. If therapeutic concentrations of FPV are de¬creased, large amounts of threatening viral mutations with different infectivity levels and unpredictable behavior will be synthesized in the body of the infected patient.

Challenges for the global distribution of a medicine – an IP focused view on favipiravir As soon as the approval process for a drug candidate is successful further important steps are required for the rapid introduction into patient care. Since it will have to be produced in large quantities, even for existing drugs the production process with its production capacity limits will be challenging as well as the worldwide distribution under existing IP rights. The experience and resources of companies that have been developing and selling medicines for many years will be essential. We are in particular interested in who developed the drug and who holds IP-rights. What is the current patent situation, how long does patent protection last and in which countries? This allows, for example, to deduce whether cost-effective generics can be produced when there is a high level of demand. It is also interesting to find out, if newer patent applications exist, from which companies and in which countries. To answer these questions, we performed a thorough patent search and analysis in renowned databases on STN®. Favipiravir (brand name Avigan®) is a broad-spectrum antiviral drug currently considered in several clinical trials to assess the safety and efficacy in patients with COVID-19. Figure 1 -Avigan tablets (KAZUHIRO NOGI/AFP). Favipiravir was discovered through

screening chemical library for anti-viral activity against the influenza virus by Toyama Chemical Co., Ltd. (now FUJIFILM Toyama Chemical Co., Ltd.) [3]. The drug was launched in Japan in 2014 exclusively for emergency use in severe infectious diseases like avian flu or Ebola for which there are no viable options [4]. In the context of the coronavirus pandemic the Japanese government intends to stockpile two million treatment courses of Avigan® and FUJIFILM Toyama Chemical revealed it will engage with other countries after consultation with the Japanese government [5]. As this drug is considered a promising potential therapeutic approach against SARSCoV-2 the German Ministry of Health (Bundesministerium für Gesundheit) recently initiated central purchasing of Avigan® for COVID-19-patients in Germany - favipiravir, CAS Registry Number 259793-96-9. From a chemical and pharmacological point of view favipiravir (T-705; 6-fluoro-3-hydroxy-2-pyrazinecarboxamide) is a small-molecule prodrug which is metabolized in vivo by an intracellular enzyme to its active form, favipiravir ribofuranosyl-5′-triphosphate (favipiravir-RTP). Favipiravir-RTP acts as a substrate for viral RNA-dependent RNA polymerase (RdRp) thereby preventing replication by inhibiting the viral RNA-dependent polymerase activity of RNA viruses [6]. Since the catalytic domain of RdRp is conserved among various types of RNA viruses, this mechanism of action underpins a broader spectrum of anti-viral activities of favipiravir. Favipiravir is effective against a wide range of types and subtypes of influenza viruses, including strains resistant to existing anti-influenza drugs.

Patent Protection of Favipiravir Patent Search in Value-added Patent Databases

Searching for specific drugs in the patent literature is a challenging task, as it requires expert knowledge of how the drug is represented in the different types of patents. While patents in the early development of the drug (e.g. chemical synthesis patents) use chemical structures to describe the drug, later patents (e.g. formulation patents) often use development codes, generic drug names or trade names. For favipiravir, either the prodrug itself or the metabolized active drug could be part of the patent application.In this case study we searched the renowned databases of Chemical Abstracts Service and Derwent on STN® to access the worldwide patent literature for favipiravir. This includes the Derwent World Patents IndexTM with the associated structure databases Derwent Chemistry Resource and Derwent Markush Resource, and also CAplus® together with CAS REGISTRY® and MARPAT®. An exhaustive structure search based on the powerful STN® retrieval capabilities was complemented with a keyword search, considering the different terminologies used for the drug favipiravir. The structure search covered all patents with favipiravir (prodrug and active drug) represented as a specific or generic (Markush) structure. This drug search does not claim to be exhaustive, but will give a good overview of the key patents of favipiravir. Another major challenge was to reliably determine the legal status of the respective patents. For this task we consulted the database INPADOC on STN® and the national registers of the patent offices. Analysis of Key Patents covering Favipiravir

A total of 148 inventions [7] were identified with favipiravir either playing a central role in the invention (orange bars) or being an optional component of a formulation (blue bars) and thus less relevant for our case study (Figure 3). While patenting activities started more than twenty years ago on a low level, they have seen a major increase over the last decade. Only 40% of the overall inventions mentioning favipiravir have been ranked as highly relevant.

The following patent analysis concentrates on those 60 inventions in which favipiravir plays a major role. When looking at the inventions that were filed over time, five major categories could be identified (Figure 4).

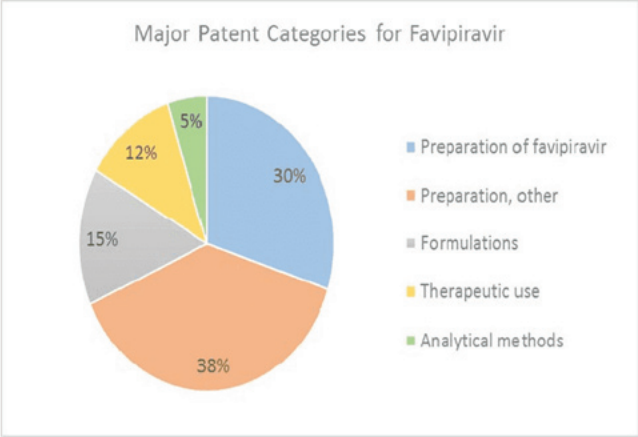


Figure 6: *Patenting activities for favipiravir (number of inventions vs priority year, first).*

About two thirds of the inventions relate to the synthesis of favipiravir (Figure 4, Preparation of favipiravir) or its nucleotide variants or reaction intermediates (Figure 4, Preparation, other), only 27% relate to new formulations or new therapeutic indications. For most approved drugs the percentage of inventions regarding

new formulations and therapeutic indication is much higher. This supports the fact that favipiravir is a drug which has its potential as an emergency drug and companies do not expect favipiravir to be approved for use in standard antiviral medicine.

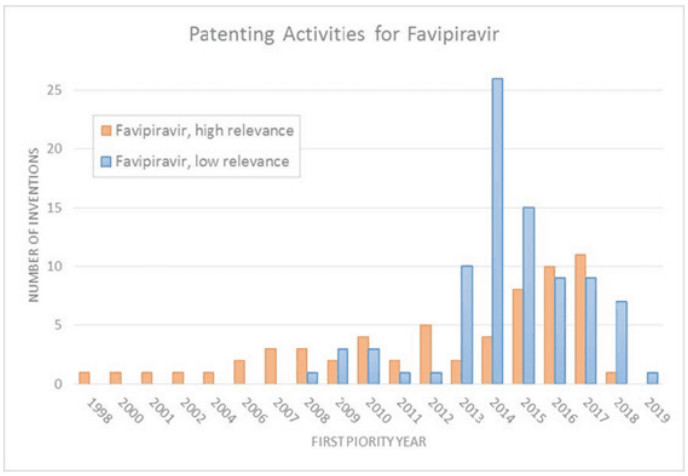


Figure 7: *Major patent categories for favipiravir (number of relevant inventions per category).*

Innovation around favipiravir concentrates on improved methods for the synthesis of the drug and its derivatives, making the large-scale manufacture of the drug more cost-effective and more environmentally friendly. Formulation patents mainly cover tablets with enhanced drug release, but there is also an invention combining favipiravir with a traditional Chinese medicine (Radix Isatidis) which should have antiviral activity [8]. While the original patent of favipiravir claimed the treatment against influenza, later patents protect new indications like Ebola infections.

In 1998 the original patent was filed by FUJIFILM Toyama Chemical, claiming the preparation and antiviral use of a substance class covering favipiravir. In the following years until 2014 the chemical synthesis of favipiravir, its intermediates and derivatives dominated the filing activities. As part of the life-cycle management relevant formulation patents and new therapeutic use patents have been filed in the years that followed (Figure 5).

The original Patent of Favipiravir

The original patent of FUJIFILM Toyama Chemical protects the compound, the preparation and the use of favipiravir as an antiviral drug especially against influenza infections. The drug itself is claimed as part of a generic chemical structure (Markush) covering a broad range of similar structures (Figure 6).

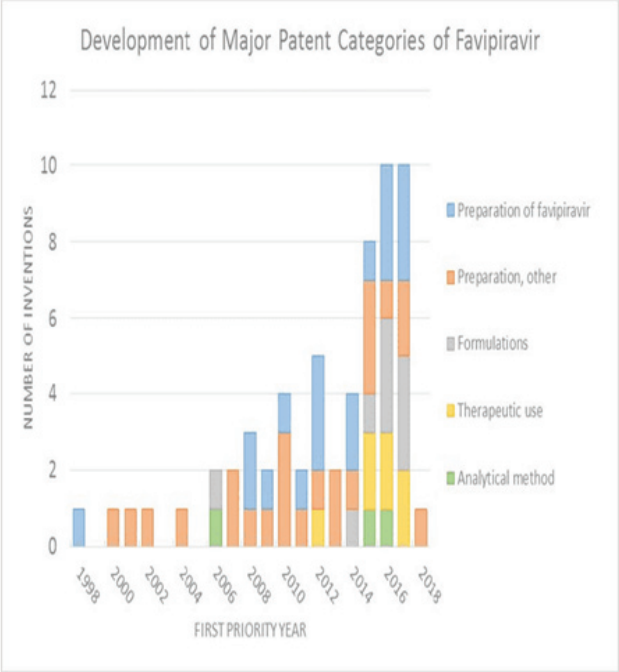


Figure 8: *Major patent categories for favipiravir developing over time (no of inventions vs priority year first).*

FUJIFILM Toyama Chemical filed an international PCT application (WO2000/10569 A1) at the Japanese Patent Office on August 18, 1999. This first filing was the basis for the worldwide patent protection in Asia, Europe, Australia, America and South Africa, including 27 patent authorities in total. 20 years later in August 2019 the original patent lost its patent protection in China, Europe and many other countries [9]. Due to a 5-year patent term extension, the patent will still be valid in Japan until August 2024 [10]. Our research also revealed a patent term extension in Brazil until November 2023.

The patent situation in the U.S.A. regarding US6787544 B2 (US43748 E) is unclear. According to the patent register of the USPTO the patent is still valid, even though all facts suggest that the US patent expired [11].

In 2016 FUJIFILM Toyama Chemical concluded a license agreement concerning favipiravir with the Chinese company Zhejiang Hisun Pharmaceutical [12]. This agreement was cancelled in 2019. Due to the corona pandemic and the loss of patent protection in China, Chinese companies may be preparing to bring favipiravir on the generics market. In February 2020 the Chinese company Zhejiang Hisun Pharmaceutical obtained official approval to produce a

generic version of favipiravir [13]. Favipiravir Patents of FUJIFILM Toyama Chemical The original patent holder FUJIFILM Toyama Chemical stands out with 17 inventions which have been applied over the last twenty years. The timeline below sums up the patent development in more detail

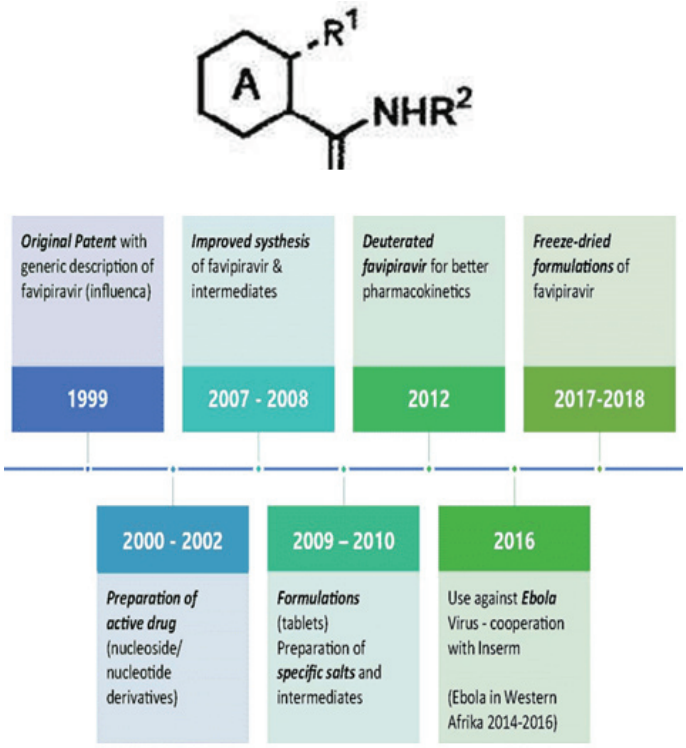


Figure 9: *Generic structure of favipiravir claimed in WO2000/10569 A1. (nucleoside/ nucleotide derivatives).*

Preparation of active drug

Figure 7 -Development of favipiravir patents of Fujifilm Toyama Chemical according to application year In the 10 years following the original patent, several patents concerning preparations of nucleoside/nucleotide derivatives, intermediates and also improved synthesis of favipiravir were filed.

In March 2011, FUJIFILM Toyama Chemical submitted favipiravir for approval of treating influenza (type A and B) in Japan [14]. Shortly before that time, Toyama had started to file pharmaceutical formulation patents, in particular tablets (WO2010/104170 A1, patent expiry in 2030).

When Western Africa was hit by the Ebola epidemic between 2014 and 2016, FUJIFILM Toyama Chemical signed a partnership agreement with Inserm (French national institute of health and medical research) to investigate the antiviral efficacy of favipiravir against the Ebola virus [15]. The cooperation resulted in joint patenting of WO2016/120301 A1 in 2016. The patent was granted in the United States (US10098879 B2) with Inserm being the current patent owner.

The most recent inventions of FUJIFILM Toyama Chemical were filed in 2017/2018, covering new methods to produce freeze-dried formulations of favipiravir (WO2018/3946 A1, WO2019/131223 A1) which show enhanced drug stability and solubility. FUJIFILM Toyama Chemical holds 15 active patent families around favipiravir, most of them filed with relevant patent offices worldwide. So far, patent protection has been extended to 2036 for new preparations (WO2016/199824 A1) and to 2031 for another three inventions related to new salts/new preparations of favipiravir (WO2012/63931, WO2012/43700, WO2012/43696). Favipiravir Patents of other Companies and Institutions

Taking a look at other patent applicants, it is striking that most inventions are from Chinese companies and institutions, which apply for patent protection in China only. The majority of these patents is related to the preparation of favipiravir and new formulations, while Chinese universities also protect the new therapeutic use of favipiravir (canine distemper virus, enterovirus EV-D68). These filing activities in China started in 2012 and are still ongoing.

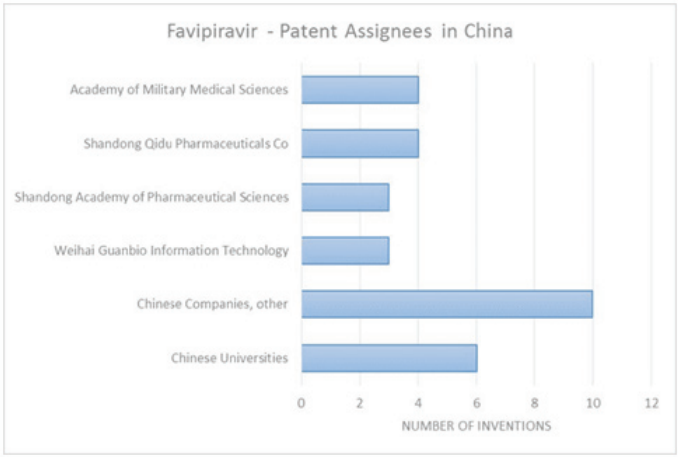


Figure 10: *Patent assignees in China and the no of inventions related to favipiravir.*

There are only 11 favipiravir inventions from patent assignees outside Japan and China, 7 of which are from US assignees (and one with a French cooperation), with 4 of them being universities. The

other four assignees are from Singapore, Sweden, France and Austria. Most of the non-Japanese or non-Chinese inventions concern preparations of nucleotides/nucleosides derivatives or the therapeutic use against the Ebola virus or Leishmania.

Current clinical Trials Several clinical trials for COVID-2019 infections are ongoing in the US, China, the Middle East and Japan [16]:

- Phase III, Japan, COVID-2019 infections

Phase II, United States, COVID-2019 infections April 2020:

- FUJIFILM Corporation initiated a phase II proof-of-concept trial to evaluate the safety and efficacy of favipiravir with standard of care (SoC) or SoC alone in patients with COVID-2019 infections [17].
- Clinical development for treatment of COVID-2019 infections was underway in the Middle East. Results from clinical studies in COVID-2019 infections in China were generally positive [18].

March 2020:

- FUJIFILM Toyama Chemical initiated a phase

III trial in Japan, to assess the safety and efficacy of favipiravir, for patients afflicted with COVID-2019 infections [19].

- Zhejiang Hisun Pharmaceutical conducted a clinical trial in collaboration with Zhongnan Hospital in 120 patients with COVID-2019 infections and another trial in collaboration with Third People's Hospital of Shenzhen in 80 patients with COVID2019 infections. For both trials results were released [20] .

February 2020: Sihuan Pharmaceutical Holdings Group initiated clinical trials for favipiravir tablet for COVID-2019 infections. A total of 60 cases of regular COVID-19 patients are planned to be recruited for a treatment period of 10 days [21].

Summary

In-depth patent searching for favipiravir requires the value-added patent databases of Chemical Abstract Service and Derwent on STN to achieve reliable and fast access to relevant inventions.

Many of the key inventions of favipiravir could not be retrieved with a simple keyword search in patent full text databases, in particular patents claiming new methods for the synthesis of the drug. The FPV-induced increase in the synthesis of mutantvirions poses a risk of occurrence of new dangerous viral strains characterized by high pathogenicity both for humans and animals and by acquired resistance to antiviral agents. The mutagenic effect of FPV can be minimized through the synthesis of new FPV modifications deprived of their ability to incorporate into the molecule of the synthesized RNA; by using FPV in combination with antiviral agents having other mechanisms of action and directed at different viral and/or cellular targets; by continuous and medically supervised therapy with high therapeutic FPV doses to boost a lethal mutagenic effect on the infectious virus in the recipient body to prevent occurrence of its mutations

Favipiravir is an antiviral drug which has only been approved for emergency use in Japan. This special situation accounts for the rather unusual patent development of favipiravir which has a strong focus on enhanced manufacturing solutions.

Although the original favipiravir patent lost its patent protection in many countries, FUJIFILM Toyama Chemicals can still commercially exploit their original invention worldwide with a series of valid chemical process and formulation patents.

On the one hand the corona pandemic may have revived interest in producing generic versions of the drug. On the other hand, however, favipiravir may not be attractive for traditional generic companies due to its restricted approval, its unclear effectiveness and its potentially severe side effects.

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