Coronavirus Drug Shows Global Hurdles To Patent Protection

By **Ping Wang, Michael Ye, John Murray and Peter Brunovskis** (February 13, 2020)

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Recently, Gilead Sciences Inc. developed a nucleotide analog prodrug, Remdesivir, also known as GS-5734, as a treatment for Ebola virus and other pathogenic infections.[1] It was subsequently found that Remdesivir also inhibits infections by arenaviruses and coronaviruses, such as SARS and Middle East respiratory syndrome.

Initially, Gilead filed provisional U.S. patent applications in 2015, followed by utility applications the following year, to cover methods of treating coronavirus and arenavirus infections with Remdesivir. These applications were published in 2017. A later-filed continuation application, U.S. Application No. 16/265,016, was allowed on Feb. 6, 2020, with issued claims specifically directed to a method for treating a coronavirus infection in a human with Remdesivir.

COVID-19 is a new coronavirus, first identified in Wuhan, China, which has caused a widespread outbreak in China, infecting more than 10,000 and killing hundreds of people to date. Researchers from the Wuhan Institute of Virology, or WIV, and the Academy of Military Medical Sciences, or AMMS, who discovered this new virus published their initial findings, including characterization of this new virus, then known as 2019-nCoV, as a betacoronavirus with sensitivity to Remdesivir.[2][3][4]

The reports suggest that the Chinese researchers jointly filed a Patent Cooperation Treaty patent application based on treatment of COVID-19 with Remdesivir, among others.[5] Nevertheless, in view of Gilead's earlier disclosures and publications, these recent developments raise questions about patentability of the WIV and AMMS applications in the U.S., particularly in view of the admissions made by the inventors of the WIV and AMMS subject matter to publish and obtain intellectual property protection.

Under U.S. patent law, to obtain a patent, an invention needs to meet all requirements of patentability. In this case, Section 103 of the Patent Act requires that the invention is nonobvious over the prior art. Obviousness is determined by considering what would have been obvious "to a person having ordinary skill in the art to which the claimed invention pertains."

To reach a proper determination under Section 103, an assessment is made from the viewpoint of a hypothetical person of ordinary skill in the art when the invention was unknown and just before it was made. In view of all factual information, it is determined whether the claimed invention as a whole would have been obvious at that time to that person.

In this case, Gilead filed patent applications to attempt to cover methods for treating coronavirus infections with Remdesivir. Subsequently published research findings providing a strong impetus for applying the use of Remdesivir for treatment of coronavirus applications, especially those caused by betacoronaviruses, such as the SERS-CoV and MERS-CoV (along with other betacoronaviruses described in the Gilead patent).

Indeed, a joint research effort by Gilead and collaborators determined that GS-5734 was effective against a diverse array of human and zoonotic CoVs in primary human airway epithelial cell cultures, among the most biologically relevant in vitro models for human lung infections, which were the cell type used to isolate the virus.[6][7]

In particular, the joint researchers found that GS-5734 treatment inhibited the replication of a diverse group of coronaviruses, including those sharing a close structural relationship to COVID-19. Additionally these researchers presciently highlighted that the tested strains "pose particular concern as 'prepandemic strains', which can infect human airway epithelial cultures without adaptation and are thus, poised for emergence in humans," precisely like COVID-19.[8] These researchers further found that GS-5734 was effective in reducing replication and spread of SARS-CoV in mice, both prophylactically and therapeutically.[9]

Under U.S. patent law, if a prima facie case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the prima facie case.[10] Rebuttal evidence may consist of a showing that the claimed invention possesses unexpected properties or improvements.[11]

A showing of unexpected results must be based on evidence, not argument or speculation.[12] To determine whether a patent is directed to a species that yielded unexpected results, it is necessary to look to the patent's disclosures to assess what results were expected at the time the patent application was filed.[13]

For example, a showing of unexpected results for a single member of a claimed subgenus, or a narrow portion of a claimed range would be sufficient to rebut a prima facie case of obviousness if a skilled artisan "could ascertain a trend in the exemplified data that would allow him to reasonably extend the probative value thereof."[14]

In view of Gilead's research activities, the Chinese researchers had good reason to investigate the therapeutic potential against COVID-19 using GS-5734. In fact, their recent letter to Cell Research suggests that their strategy was predicated on exactly what a person having ordinary skill in the art would have pursued:

> An efficient approach to drug discovery is to test whether the existing antiviral drugs are effective in treating viral infections. The 2019-nCoV belongs to Betacoronavirus which also contains SARS-CoV and Middle East respiratory syndrome CoV (MERS-CoV).[15][16]

The letter to Cell Research further notes that "Remdesivir has been recently recognized as a promising antiviral drug against a wide array of RNA viruses (including SARS/MERS-CoV infection in cultured cells, mice and nonhuman primate (NHP) models."[17]

Once the Patent Cooperation Treaty patent application, filed by WIV, enters into the U.S., genus-species counter-arguments couched with proclamations of unexpected results may likely follow. Indeed, WIV could argue that there was no expectation of success for treating COVID-19 considering that Remdesivir was expected to cure Ebola, similarly based on successful in vitro results that nevertheless failed in subsequent clinical trials.[18]

Nevertheless, such arguments merely beg the question of whether the alleged reports of treating the species here, COVID-19, using GS-5734 is actually unexpected. In fact, it is noteworthy that Gilead and its collaborators previously showed that the susceptibility of SARS-CoV and MERS-CoV to Remdesivir (GS-5734) is largely mediated by their RNA-

dependent RNA polymerase, RdRp, also known as nsp12.[19]

However, it turns out that the amino acid sequences from the RdRps of SARS-CoV and MERS-CoV are 96% identical to the RdRp predicted amino acid sequence of COVID-19.[20][21][22] Moreover, pairwise alignments of the amino acid sequences in the critical core domain of RdRp (amino acid numbers 385-887[23]) are virtually identically shared (98% identity in each case) between COVID-19, SARS-CoV and bat-SL-CoVZC45, which was characterized as the most closely related known coronavirus to COVID-19.[24][25][26]

It is important to apply IP protection for innovation. On the other hand, not all discoveries can be translated into patents. An invention must meet all patentability requirements of a jurisdictions to be patentable in that jurisdiction. Here, the recent interplay between the Gilead applications and the WIV and AMMS applications demonstrates how the requirements in differing jurisdictions may complicate efforts to obtain patent protection.

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[2] Zhu, N. et al., (2020) Jan. 24, N. Eng. J. Med., Doi: 10.1056/NEJMoa2001017. [Epub ahead of print].

[3] Lu, R. et al., (2020) Jan. 30, Lancet, Doi: 10.1016/S0140-6736(20)30251-8. [Epub ahead of print].

[4] Huang, C. et al., (2020) Jan. 24, Lancet, Doi: 10.1016/S0140-6736(20)30183-5. [Epub ahead of print].

[5] The New York Times, February 6, 2020, https://www.nytimes.com/aponline/2020/02/06/business/bc-as-china-outbreak-us-drug.html.

[6] Zhu, N. et al., (2020) Jan. 24, N. Eng. J. Med., Doi: 10.1056/NEJMoa2001017. [Epub ahead of print].

[7] Sheahan, T.P. et al., (2017) Sci. Transl. Med., 9(396): doi: 10.1126/scitranslmed.aal3653.

[8] Id.

[9] Id.

[10] See, e.g., In re Dillon, 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).

[11] Dillon, 919 F.2d at 692-93, 16 USPQ2d at 1901.

[12] Abbvie Inc. v. Mathilda & Terence Kennedy Inst. of Rheumatology Trust, 764 F.3d 1366, 1380 (Fed. Cir. 2014).

[13] Id.

[14] In re Clemens, 622 F.2d 1029, 1036, 206 USPQ 289, 296 (CCPA 1980).

[15] Lu, R. et al., (2020) Jan. 30, Lancet, Doi: 10.1016/S0140-6736(20)30251-8. [Epub ahead of print].

[16] Wang, M. et al., (2020) Jan. 25, Cell Research, 0:1-3; https://doi.org/10.1038/s41422-020-0282-0.

[17] Id.

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[21] NCBI Accession No. P0C6X7.1.

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