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REVIEW ARTICLE

International Drug Repurposing Patent Landscaping, Part 2: The Early Months of Covid-19

Hermann A. M. Mucke*

H.M. Pharma Consultancy, Vienna, Austria

***Correspondence to:** Hermann A. M. Mucke, H.M. Pharma Consultancy, Enenkelstr. 28/32, A-1160 Wien, Vienna, Austria. E-mail: h.mucke@hmpharmacon.com

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ABSTRACT

This study presents and discusses international patent applications claiming known pharmaceutical agents for repurposed use in the treatment of coronavirus disease 2019 (Covid-19). These applications were published by the World Intellectual Property Office during the second half of 2021, corresponding to filings made during the first 6 months of the pandemic (January to June 2020). Of the 93 identified documents, 46 claimed agents that were in development, or had been approved, as antiparasitics, antibiotics, anticancer agents, or immunomodulators. The remaining 47 documents concerned a wide variety of other original uses, from psychiatry to osteoporosis, and correspondingly diverse mechanisms of action. The most significant patent applications are presented and discussed in brief. The landscape of patent applications seeking to repurpose pharmaceutical agents for use in the treatment of Covid-19, filed during the early stages of the pandemic, is impressive. It provides insight into the intellectual property track pursued by industry, academia, and government organizations during this unique period.

KEYWORDS

patents; virology; Covid-19; coronavirus; drug repurposing.

INTRODUCTION

This is the second iteration of a series of papers that are intended to provide an overview of the patent landscape in specific fields of drug repurposing. It covers the international patent disclosures concerned with Covid-19 and its causative virus severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that were published by the World Intellectual Property Office during 2021. Given the approximate 18 months window period between the first national or regional filing (the priority date) and publication, this corresponds to patents with priority dates until the end of June 2020, i.e., the first 6 months of the Covid-19 pandemic. This was the most intense period of drug repurposing during the pandemic, characterized by hectic efforts to identify and test known agents that could be used to treat this disease while virological and clinical research was still ongoing.

Patent documents differ from peer-reviewed publications in many ways, the details of which have been discussed in the prologue to this landscaping series, published in the inaugural issue of this journal[1]. Briefly, it is important to understand that a patent application does not require the same degree of conclusive scientific rigor as a peer-reviewed manuscript reporting original research, that its criteria of novelty and non-obviousness are not identical to those of academic research, and that its third criterion—industrial applicability, not required for peer review

papers—is essential. Even so, patent documents often disclose new scientific information earlier than peer review papers, and once published their full content is available online free of charge (although the applicant has to bear quite significant costs). The motivations for filing a patent application are also not the same as those that apply for publishing in scientific journals: patents are filed if the inventors (or their institutions) believe that there is potential commercial applicability that can materialize within a relatively short period (patent protection expires after 20 years).

In our landscaping of the nascent drug repurposing intellectual property space for Covid-19, we have focused on documents published by the Patent Cooperation Treaty (PCT). These are not yet granted patents, but rather international publications of patent applications, usually already examined and commented on by the authorities. They afford the applicant limited and provisional protection but can evolve into defendable actual patents only when submitted to regional or national authorities. The PCT level is where the great majority of patent applications come together in a standardized format, providing an invaluable pool for research and strategic business development alike.

METHODS

We searched the RepoScope drug repurposing knowledgebase, which is currently centered around PCT patent applications published from 2010 to present, for entries with relevance to the Covid-19 pandemic that were published in 2021. RepoScope is a text-based knowledgebase designed and initiated by H.M. Pharma Consultancy, now under development within the framework of the Horizon Europe project, REPO4EU (https://repo4.eu/).

RepoScope handles its entries in three main modules: conditions, compounds, and targets. Each condition, compound, or molecular target is a named entity that can be linked to other named entities in the same module, and also in any other module. Entries can be made in any module on which the patent document is centered (and therefore seems to fit best), without compromising linkage. RepoScope does not differentiate between repurposing of an active pharmaceutical ingredient (i.e., its redevelopment for a substantially different indication) and drug repositioning (i.e., repurposing of approved or late-stage developmental drugs to indications other than those originally approved), as both types of new uses will appear in PCT documents in the same way. Given RepoScope's strict focus on drug repurposing, the only retrieval criterion was CONDITION/Covid-19 as a named entity. Entries found in the Covid-19 disease module were combined with the backlinks originating from individual compounds, and filtered by WO/2021* as a character string for the patent identifier. Patent documents were retrieved from the World Intellectual Property PatentScope database (https://patentscope.wipo.int/) and examined for claimed compounds, experimental data, and stated mode of action in SARS-CoV-2 infection.

Documents that deal with non-core symptoms of Covid-19 and post-Covid conditions were not included in this investigation.

RESULTS

A total of 93 PCT documents with drug repurposing content (by the above definition) for SARS-CoV-2 and/or Covid-19 were found to have been published in 2021. Given that the earliest publicly known cases of the disease that later came to be known as Covid-19 were not widely reported until late December 2019, and that doing drug repurposing research would take at least several weeks, no patent priority dates before late January 2020 were expected, and therefore—given the institutional 18-month delay—no PCT disclosures were expected to be published before the third quarter of 2021. With one exception, to be discussed below, this proved true: the first documents appeared online in late July and early August 2021. The number of publications increased sharply in September and October, referring to priority dates in February and March 2020.

Remarkably, remdesivir appears in PCT publications only from 2021 onward. Remdesivir is an antiviral agent with a broad spectrum of activities against RNA viruses, developed for Ebola, with an emergency-use authorization for Covid-19 followed later in 2020 by a full approval.[2]

Table 1 through 5 list the respective active agents with their primary therapeutic indication (either approved, in development, or discontinued) and the commonly appreciated mode of action (MoA), the PCT patent identifiers with the publishing date and the earliest priority date (a patent application can have several if new claims are added), and a brief description of the claimed effects against SARS-CoV-2 or Covid-19. The tables group the active agents according to their originally intended or planned therapeutic class: antiprotozoals, antihelminthics, and antifungals (**Table 1**, 15 documents); antibacterials (**Table 2**, 6 documents); antineoplastic agents (**Table 3**, 11 documents); immune modulators (**Table 4**, 14 documents); and miscellaneous agents (**Table 5**, 47 documents).

First Out: Antiprotozoals, Antihelminthics, and Antifungals (Table 1)

The first patent application with an original focus on Covid-19 came from the Chinese Academy of Military Medical Sciences. With a January 21, 2020 priority it claims nitazoxanide and its active metabolite, tizoxanide. Provided data show inhibition of viral proliferation in Vero E6, an African green monkey kidney epithelial cell line that became standard for *in vitro* culturing of SARS-CoV-2. Nitazoxanide is a broad-spectrum thiazolide antiparasitic that is believed to act against several protozoa by non-competitive inhibition of pyruvate:ferredoxin oxidoreductase (PFOR). It was an obvious choice to investigate for activity against SARS-CoV-2 because *in vitro* activity against Middle East respiratory syndrome (MERS)-CoV and other coronaviruses had already been established,[3] and it had completed a phase III trial for uncomplicated influenza where it targets viral hemagglutinin at the post-translational level.[4] In Covid-19 its mechanism is mostly host-directed and multimodal[5] but could also involve impairment of SARS-CoV-2 spike glycoprotein maturation and fusion.[6]

The antimalarial chloroquine probably was the first agent to be reported in a peer-reviewed journal as an effective potential

Table 1. Antiprotozoals, Antihelminthics, and Antifungals Claimed for Covid-19

Compound(s)	Primary Indication and Commonly Known MoA	PCT Patent Code, Publishing Date, (First Priority Date)	Effect in Covid-19 or against SARS-CoV-2
Nitazoxanide Tizoxanide	Cryptosporidiosis, giardiasis PFOR inhibitor	WO/2021/147273 2021-07-29 (2020-01-21; CN)	Inhibits viral proliferation in Vero E6 cells
Chloroquine Hydroxychloroquine	Malaria Heme binding results in parasite lysis	WO/2021/155651 2021-08-12 (2020-02-03; CN)	Inhibits viral proliferation in Vero E6 cells from early endocytosis to lysosome transport
Niclosamide	Tapeworm infection Disrupts pH homeostasis of the parasite, uncouples the mitochondrial respiratory chain	WO/2021/168295 2021-08-26 (2020-02-21; US)	Antiviral EC_{50} of 150 nM in Vero E6 cells
		WO/2021/168295 2021-09-23 (2020-03-16; US)	No data disclosed Clinical study protocol provided
		WO/2021/226256 2021-11-11 (2020-05-05; US)	Clinical phase I studies with capsule formulations
Tafenoquine	Malaria Precise mechanism(s) not established	WO/2021/178346 2021-09-10 (2020-03-02; US)	Inhibits cytopathic effect in Vero E6 cells and viral replication in Calu-3 cells
Ivermectin Moxidectin	Systemic parasitosis, scabies Glutamate-gated chloride channel opener and other mechanisms	WO/2021/179050 2021-09-16 (2020-03-13; AU)	Inhibits viral proliferation in Vero/hSLAM cells and Calu-3 cells
		WO/2021/229514 2021-11-18 (2020-05-14; IN)	Ivermectin nasal and inhalation formulations
		WO/2021/247283 2021-12-09 (2020-06-04; US)	Inhalable ivermectin formulations
		WO/2021/254729 2021-12-23 (2020-06-19; GB)	Clinical trial with 3 mg ivermectin tablets shows benefit after 4–5 days
Nitazoxanide + ribavirin combo	--- PFOR inhibitor + RNA antiviral	WO/2021/180251 2021-09-16 (2020-03-09; CN)	Inhibits viral proliferation in Vero E6 cells
Emetine	Antiprotozoal, emetic	WO/2021/195521 2021-09-30 (2020-03-26; US)	No data disclosed Clinical trial protocol provided
		WO/2021/196275 2021-10-07 (2020-04-03; CN)	Inhibits viral proliferation in Vero E6 cells
Sulconazole	Topical antifungal	WO/2021/228570 2021-11-18 (2020-05-11; EP)	Furin inhibitor
Artesunate	Malaria	WO/2021/258206 2021-12-30 (2020-06-26; US)	Complex with CMC/povidone inhibits viral replication in Vero E6 cells

CMC, carboxymethyl cellulose; MoA, mode of action; PCT, Patent Cooperation Treaty; PFOR, pyruvate:ferredoxin oxidoreductase; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

repurposing candidate for Covid-19.[7] The electronic publication became available online on February 4, 2020, the day following the Chinese priority patent filing. Chloroquine and hydroxychloroquine, as well as other antimalarial agents, had long been known as immune modulators, and had been used to treat autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.[8] Investigations in obesity, diabetes, breast cancer, and HIV/AIDS have also been reported.

Niclosamide, an anthelmintic discovered in 1958 that inhibits glucose uptake, oxidative phosphorylation, and anaerobic metabolism in tapeworms, has a very long and diverse track record of repurposing investigations. A screening campaign had identified it as having micromolar to nanomolar potency against SARS-CoV, MERS-CoV, HCV, Zika virus, and human adenovirus.[9] A small phase II clinical trial (73 participants) in mild to moderate Covid-19 showed no significant difference in oropharyngeal clearance of SARS-CoV-2 after 3 days.[10]

Ivermectin, originally a deworming agent for horses but later approved for human use, also had a long record of reports concerning *in vitro* effects against RNA viruses when the pandemic hit.[11] Despite indications of efficacy in early clinical trials (some of which were poorly designed or over-interpreted), most of the

Table 2. Antibacterial Agents Claimed for Covid-19

Compound	Primary Indication and Commonly Known MoA	PCT Patent Code, Publishing Date, (First Priority Date)	Effect in Covid-19 or against SARS-CoV-2
Bacitracin A	Dermatological infections Isoprenyl pyrophosphate complexing agent	WO/2021/203704 2021-10-14 (2020-04-07; CN)	Inhibits viral proliferation in Vero E6 cells
Fosfomycin	MurA inhibitor	WO/2021/204861 2021-10-14 (2020-04-09; DK)	No data disclosed
Doxycycline (single and combination)	30S ribosomal subunit blocker		
Eravacycline	Efflux pump inhibitor and ribosome blocker	WO/2021/209563 2021-10-21 (2020-04-16; EP)	Inhibits viral replication in Vero E6 cells; inhibits viral 3CLpro
Bismuth subcitrate, ranitidine bismuth citrate	Helicobacter gastric infection in peptic ulcers	WO/2021/244481 2021-12-09 (2020-06-01; US)	Inhibits multiple viral key cysteine enzymes, including helicase
Clofoctol	Upper respiratory tract infections Reduces intracellular ATP	WO/2021/250038 2021-12-16 (2020-06-10: EP)	Reduces viral infectivity in Calu-2 cells and in mice
Dalbavancin	MRSA infection Prevents transpeptidation during bacterial cell wall synthesis	WO/2021/253746 2021-12-23 (2020-06-14; CN)	Inhibits viral binding to ACE2

ACE2, angiotensin-converting enzyme 2; MoA, mode of action; MRSA, Methicillin-resistant *Staphylococcus aureus*; PCT, Patent Cooperation Treaty; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Table 3. Antineoplastic Agents Claimed for Covid-19

Compound	Primary Indication and Commonly Known MoA	PCT Patent Code, Publishing Date, (First Priority Date)	Effect in Covid-19 or against SARS-CoV-2
Pazopanib	Renal cell carcinoma, soft tissue sarcoma Multi-kinase inhibitor	WO/2021/101902 2021-05-27 (2019-11-20; US)	MAP3K2/3 inhibition protects against lung injury and ARDS
Veliparib Olaparib Mefuparib	Various solid tumors PARP inhibitors	WO/2021/169984 2021-09-02 (2020-02-24; CN)	Inhibits viral proliferation in Vero E6 cells, abrogates IL-6 production in PBMCs
Upamostat	Pancreatic cancer Urokinase inhibitor prodrug	WO/2021/181157 2021-09-16 (2020-03-10; US)	Inhibits viral proliferation in HBEC primary cells, and viral entry in Vero E6 and Calu-3 cells; TMPRSS2 inhibitor
Ibrutinib	Leukemias and lymphomas Irreversible Btk inhibitor	WO/2021/188837 2021-09-23 (2020-03-20; US)	Suppresses the inflammasome and promotes the differentiation of CD4+ T cells into type 1 T helper cells. Clinical trial protocol outlined
Fenretinide	Various solid tumors Inducer of apoptosis by multiple mechanisms	WO/2021/189153 2024-09-30 (2020-03-26; US)	Inhibits viral proliferation in Vero E6 cells, improves ARDS in a mouse model
Masitinib	Canine mast cell tumors Inhibitor of c-kit and other kinases	WO/2021/205029 2021-10-14 (2020-04-10; EP)	Inhibits viral proliferation in A549 cells over expressing ACE2; reduces viral load in murine lungs
Duvelisib	Leukemias and lymphomas PIK3 inhibitor	WO/2021/207230 2021-10-14 (2020-04-06; US)	Reduced cytokine storm in CLL clinical study
Cilengitide	Investigational agent for glioblastoma FAK/Src/AKT pathway inhibitor	WO/2021/224234 2021-11-11 (2020-05-04; US)	Inhibits viral entry into Vero E6 cells via its RGD motif
Orludodstat	Investigational DHODH inhibitor for glioma and leukemias	WO/2021/233966 2021-11-25 (2020-05-20; EP)	Inhibits viral replication in Vero E6 cells
Rigosertib	Investigational agent for various malignancies RAS mimetic	WO/2021/243162 2021-12-02 (2020-05-29; US)	Inhibits infection of Vero E6 cells
Romidepsin	T-cell lymphomas Histone deacetylase inhibitor	WO/2021/253338 2021-12-23 (2020-06-18; CN)	Inhibits viral replication in Vero E6 cells

ACE2, angiotensin-converting enzyme 2; ARDS, acute respiratory distress syndrome; CLL, chronic lympocytic leukemia; DHODH, dihydroorotate dehydrogenase; HBEC, human bronchial epithelial cells; IL, interleukin; MoA, mode of action; MRSA, Methicillin-resistant *Staphylococcus aureus*; PARP, poly (ADP-ribose) polymerase; PBMCs, peripheral blood mononuclear cells; PCT, Patent Cooperation Treaty; RGD, a motif of Arginine - Glycine - Aspartic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TMPRSS2, transmembrane protease, serine 2.

Table 4. Immunomodulator Agents Claimed for Covid-19

Compound(s)	Primary Indication and Commonly Known MoA	PCT Patent Code, Publishing Date, (First Priority Date)	Effect in Covid-19 or against SARS-CoV-2
Bucillamine	Antirheumatic Thiol antioxidant	WO/2021/184115 2021-09-23 (2020-03-19; US)	No mechanism stated. Ongoing clinical trial outlined
Colchicine	Gout, familial Mediterranean fever Inflammasome inhibitor, other mechanisms	WO/2021/184128 2021-09-23 (2020-03-20; CA)	No mechanism stated. Interim results from the COLCORONA trial provided
Anakinra	Rheumatoid arthritis, familial Mediterranean fever IL-1 receptor antagonist	WO/2021/185838 2021-09-23 (2020-03-16; EP)	No data provided; clinical study protocol outlined
Ozanimod	Multiple sclerosis, ulcerative colitis S1P receptor agonist	WO/2021/188326 2021-09-23 (2020-03-17; US)	No data provided
Losmapimod	Failed several developments MAPK inhibitor	WO/2021/194991 2021-09-30 (2020-03-22; US)	No data provided
Tofacitinib	Rheumatoid arthritis, ulcerative colitis JAK inhibitor, CYP3A4 inactivator	WO/2021/198980 2021-10-07 (2020-04-04; US)	Suppression of cytokine storm (reference to prior art); clinical study protocols outlined
Tocilizumab	Rheumatoid arthritis, interstitial lung disease[a] Anti-IL-6R mAb	WO/2021/202919 2021-10-07 (2020-04-01; US)	Clinical and biochemical improvements at low doses
Vidofludimus	In phase III for multiple sclerosis DHODH inhibitor, Nurr-1 activator	WO/2021/204985 2021-10-14 (2020-04-10; EP)	Inhibits viral proliferation in Vero E6 cells
		WO/2021/214033 2021-10-28 (2020-04-21; EP)	Phase II clinical trial results disclosed
Auranofin	Rheumatoid arthritis Complex mechanism	WO/2021/211792 WO/2021/211745 2021-10-21 (2020-04-15; US)	Inhibits viral proliferation in Huh7 cells
Siponimod	Multiple sclerosis S1P receptor modulator	WO/2021/214717 2021-10-28 (2020-04-23; EP)	Treats or prevents acute respiratory distress syndrome
Dexamethasone, hydrocortisone, methylprednisolone, prednisolone, cortisone, budesonide, etc.	Immune suppression Glucocorticoid receptor modulators	WO/2021/222385 2021-11-04 (2020-04-29; US)	Binding to ICAM3 mobilizes NK cells
		WO/2021/226384 2021-11-11 (2020-05-07; US)	Prevention of post-Covid pulmonary conditions

[a]Approved for Covid-19 treatment.

IL, interleukin; mAb, monoclonal antibody; MoA, mode of action; MRSA, Methicillin-resistant *Staphylococcus aureus*; NK, natural killer; PCT, Patent Cooperation Treaty; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

later phase III trials of ivermectin, and also those investigating chloroquine or hydroxychloroquine with or without azithromycin, observed no treatment benefit in Covid-19 patients.[12]

Antibiotics for Covid-19 (Table 2)

If considering use of antibacterial drugs to combat a viral disease sounds inappropriate at first sight, it must not be forgotten that many antibiotics have host effects that could qualify as a rationale for investigating them for Covid-19. For example, azithromycin had been proposed on the basis of its immunomodulatory action. However, there is no PCT disclosure claiming azithromycin as a single agent for Covid-19, and in the RECOVERY trial it did not improve survival or other prespecified clinical outcomes in hospitalized patients.[13]

Even so, only a few established antibiotics have been claimed as single-use agents for Covid-19. Evidence from clinical studies remains limited, and mostly relates to combinations with other agents in repurposed use. Several patent applications claiming antibiotics as components of complex drug cocktails without substantial evidence for a specific role of the antibiotic have been omitted from **Table 2**, such as WO/2021/194970 which claims preventing Covid-19 by administering hydroxychloroquine; azithromycin, vitamins C and D, and zinc, optionally also ivermectin and doxycycline.

Apparently, diverse non-canonical mechanisms contribute to the anti-coronaviral action of the claimed antibiotics. Perhaps the most interesting one is that seen with bismuth compounds that are routinely used to treat bacterial gastritis: they inhibit nsp13

Table 5. Miscellaneous Agents Claimed for Covid-19

Compound(s)	Primary Indication and Commonly Known MoA	PCT Patent Code, Publishing Date, (First Priority Date)	Effect in Covid-19 or against SARS-CoV-2
Disulfiram	Alcohol abuse Alcohol deterrent effect through ALDH inhibition	WO/2021/170093 2021-09-02 (2020-02-26; CN)	Inhibition of main viral protease
Diltiazem	Hypertonia, arrhythmia Calcium channel blocker	WO/2021/181044 2021-09-16 (2020-03-10; FR)	Inhibits viral proliferation in Vero E6 and A549-ACE2 cells
Famotidine	Gastric acid production suppressor H2 receptor antagonist	WO/2021/183259 2021-09-16 (2020-03-12; US)	Improves patient-reported outcomes in non-hospitalized Covid-19 patients. PLpro protease inhibitor
Senicapoc	Sickle cell anemia Gardos (KCa3.1) channel blocker	WO/2021/185746 2021-09-23 (2020-03-16; EP)	Protects against ventilator-induced lung injury
Idebenone	Leber's optic neuropathy Electron transport chain enhancer, lipoperoxide formation inhibitor	WO/2021/186061 2021-09-23 (2020-03-19; EP)	No data disclosed
Raloxifene	Osteoporosis Selective estrogen receptor modulator	WO/2021/187670 2021-09-23 (2020-03-18; KR)	Inhibits viral proliferation in Vero E6 cells
Multiple agents identified by FDA compound screen	Various	WO/2021/187842 2021-09-23 (2020-03-17; KR)	Inhibits viral proliferation in Vero E6 cells
Camostat	Pancreatitis, reflux esophagitis Serine protease inhibitor	WO/2021/188815 2021-09-23 (2020-03-28; US)	TMPRSS2 inhibitor No data disclosed
Camostat or nafamostat + toremifene, tamoxifen, etc.	Combined with steroid hormone receptor modulators	WO/2021/222240 2021-11-04 (2020-04-29; US)	Interaction networks with viral life cycle described but no data disclosed
Mifepristone	Abortion, Cushing's syndrome Glucocorticoid receptor antagonist	WO/2021/195119 2021-09-30 (2020-03-24; US)	Reduces ACE2 or TMPRSS2 levels, enhances immune response No data disclosed
Tradipitant	Gastroparesis, motion sickness NK1 receptor antagonist	WO/2021/195205 2021-09-30 (2020-03-26; US)	Improves clinical score during first week; trial protocol for pneumonia presented
Furosemide	Edema Loop diuretic (inhibits the Na-K-Cl cotransporter)	WO/2021/195777 2021-10-07 (2020-03-31; US)	Reduces inflammatory markers in LPS-stimulated macrophages; clinical trial protocol outlined
Ifetroban	Cardiovascular conditions TxA2 receptor antagonist	WO/2021/202437 2021-10-07 (2020-03-31; US)	Improves pulmonary function No data disclosed
Zopolrestat Epalrestat	Diabetic complications Aldose reductase inhibitors	WO/2021/202523 2021-10-07 (2020-03-31; US)	Reduces mortality and hospital stay Data from a caficrestat study disclosed
Haloperidol	Psychosis, schizophrenia D2, α1, and 5-HT2 receptor antagonist	WO/2021/202535, WO/2021/202550 2021-10-07 (2020-03-30; US)	Inhibits viral replication Sigma receptor modulation, ER stressor
Nafamostat	Anticoagulation during dialysis, pancreatitis Serine protease inhibitor	WO/2021/202708 2021-10-07 (2020-04-20; KR)	Improves symptoms Clinical study protocol provided
		WO/2021/215798 2021-10-28 (2020-03-31; US)	Inhibits viral proliferation in Calu-3 cells
Vitamin D	Rickets, osteoporosis	WO/2021/205225 2021-10-14 (2020-04-06; US)	Resolves the immunocompromised state; clinical study protocol outlined
Poliomyelitis vaccine	Poliomyelitis	WO/2021/206783 2021-10-14 (2020-04-11; US)	Case reports for protection provided
Aprepitant	NK1 receptor antagonist	WO/2021/207141 2021-10-14 (2020-04-06; US)	Inhibits viral peptide binding to NK-1R in a VZV-infected adult primary human astrocyte

Table 5. Continued

Compound(s)	Primary Indication and Commonly Known MoA	PCT Patent Code, Publishing Date, (First Priority Date)	Effect in Covid-19 or against SARS-CoV-2
Cetirizine + famotidine	H1 and H2 receptor antagonists, resp.	WO/2021/207300 WO/2021/207141 2021-10-14 (2020-04-07; US)	Reduced symptom progression in clinical study
Icosapent ethyl	Hyperlipidemia	WO/2021/207384 2021-10-14 (2020-04-07; US)	Anti-inflammatory action; clinical study protocol provided
Dantrolene	Muscle relaxant, malignant hyperthermia Ryanodine receptor antagonist	WO/2021/207443 WO/2021/207444 2021-10-14 (2020-04-10; US)	Inhibits viral replication in Vero E6 cells through intracellular Ca2+; clinical study protocol provided
Aloxistatin	Failed myopathy trials Cysteine protease inhibitor	WO/2021/209620 2021-10-21 (2020-04-16; DE)	Suppresses cytopathic effect in infected 293 ACE2 cells
Emricasan	In development for liver cirrhosis Pan-caspase inhibitor	WO/2021/211659 2021-10-21 (2020-04-14; US)	Suppresses elevated caspase-1 activity in CD4 T cells
Pirfenidone	Idiopathic pulmonary fibrosis Inhibitor of collagen formation and deposition	WO/2021/211745 2021-10-21 (2020-04-14; US)	Lowers inflammatory and prognostic markers; interim clinical study results disclosed
5-Aminolevulinic acid	Actinic keratosis Photosensitizer	WO/2021/215517 2021-10-28 (2020-04-22; US)	Inhibits viral replication in Vero E6 and Caco-2 cells
Salmeterol	Asthma, COPD Long-acting β2 adrenoceptor agonist	WO/2021/216710 2021-10-28 (2020-04-24; US)	Inhibits viral infectivity Two-pore channel inhibitor
Fluvastatin	Hypercholesterinemia HMG-CoA reductase inhibitor	WO/2021/217740 2021-11-04 (2020-04-30; CN)	Inhibits viral replication in Vero E6 cells
Dapagliflozin + ambrisentan	--- SGLT2 inhibitor + ET1 inhibitor	WO/2021/219691 2021-11-04 (2020-04-29; US)	Reduce cardiac afterload and pulmonary arterial hypertension Clinical study protocol provided
Memantine, Gliclazide, Mavorixafor, Saroglitazar, Mebrofenin, Kasugamycin, Azacytidine, Plerixafor Capreomycin, Pentamidine, Spectinomycin, Flumatinib, Darapladib, Floxuridine, Fludarabine	Various mechanisms and approvals	WO/2021/22028 2021-11-04 (2020-05-01; US)	SARS-CoV-2 E protein inhibitors SARS-CoV-2 3a protein inhibitors (Screening results in recombinant *E. coli*-based assays)
Blonanserin, Omipalisib, Tipifarnib	Various approvals and mechanisms	WO/2021/221435 2021-11-04 (2020-04-29; KR)	Mpro inhibitors and other mechanisms in combinations
Varenicline	Smoking cessation Nicotinic acetylcholine receptor agonist	WO/2021/222230 2021-11-04 (2020-04-28; US)	Data on protection of Caco-2 cells against infection and clinical study protocol for a nasal spray disclosed
Alpha1 antitrypsin	Alpha1 antitrypsin deficiency Serine protease inhibitor	WO/2021/222370 2021-11-04 (2020-04-29; US)	Inhibits infection of Caco-2 cells TMPRSS2 inhibitor
Melatonin, ramelteon, agomelatine	Sleep disorders Melatonin receptor agonists	WO/2021/224270 2021-11-11 (2020-05-05; EP)	Limit the overall levels of cytokines in the lungs of K18-hACE2 mice; inhibits viral entry by binding to ACE2
Proflavine, raloxifen, mequitazine, N-tert-butylisoquine, isofloxythepin, succinobucol, hypericin	Various approvals and mechanisms	WO/2021/224382 2021-11-11 (2020-05-06; EP)	Inhibits viral replication and cytopathic effect in Vero E6 cells
Benzimidazoles	Antihelminthics Antiacids	WO/2021/226532 2021-11-11 (2020-05-07; US)	Inhibition of viral infectivity by binding to the 5′-UTR

Table 5. Continued

Compound(s)	Primary Indication and Commonly Known MoA	PCT Patent Code, Publishing Date, (First Priority Date)	Effect in Covid-19 or against SARS-CoV-2
Icatibant, fasitibant	Hereditary angioedema C1-esterase-inhibitor	WO/2021/229100 2021-11-18 (2020-05-15; EP)	Prevents viral entry into epithelial cells
Cysteamine	Cystinosis Transamidation inhibitor	WO/2021/231570 2021-11-18 (2020-05-13; US)	Prevents infection of Huh-7 cells
Cationic amphiphilic drugs	Antipsychotics Antihistamine sedatives	WO/2021/233899 2021-11-25 (2020-05-19; EP)	Inhibitors of viral infection of Vero E6 cells; additional predictions via cheminformatics
Diquafosol Denufosol Tranilast	Dry eye disease Cystic fibrosis Allergies Purinergic receptor modulators	WO/2021/245107 2021-12-09 (2020-06-02; EP)	Suppresses viral entry in Vero E6 cells and NLRP3 inflammasome activation
Luminol	Chemiluminescent agent for identifying bloodspots	WO/2021/249667 2021-12-16 (2020-06-10; EP)	Inhibits viral replication in Vero B4 cells
Multiple diverse agents identified through screening	Various	WO/2021/251710 2021-12-16 (2020-06-09: KR)	Inhibit infection and/or replication in Vero cells; EC_{50} and CC_{50} data disclosed
Functional inhibitors of acid sphingomyelinase (FIASMA agents)	Antidepressants, antipsychotics, others	WO/2021/260152 2021-12-30 (2020-06-24; EP)	Prevent severe Covid-19 and death (as per hospital data analysis)

ACE2, angiotensin-converting enzyme 2; ALDH, aledyde dehydrogenase; COPD, chronic obstructive pulmonary disease; ER, endoplasmic reticulum; FDA, Food and Drug Administration; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LPS, lipoplysaccharide; MoA, mode of action; NK1, neurokinin-1; NLRP3, NLR family pyrin domain containing 3; PCT, Patent Cooperation Treaty; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGLT-2, sodium-glucose cotransporter 2; TMPRSS2, transmembrane protease, serine 2; UTR, untranslated region.

unwinding activity via disrupting the binding of ATP and the DNA substrate to viral helicase.[14]

Oncology Agents: Fishing in a Large Pool (Table 3)

Anticancer agents represent one of the broadest fields in applied pharmacology. Not only are many of them approved (and more in development), their mechanisms also are as diverse as the conceivable ways to inhibit the rapid proliferation of mutated cells, and to address the abnormal inflammatory and immunologic responses that are associated with cancer. In some cases this includes interference with the "host" of the cancer. It is therefore no surprise that antineoplastics were among the first agents to be investigated for the treatment of Covid-19.[15]

Actually, the very first patent application to be filed (and to subsequently reach the PCT publication stage) shows November 20, 2019 as its single priority date, which is as amazing as it is controversial at first sight. The earliest known patient with symptoms later attributed to Covid-19 reported sick on November 17, 2019 but these earliest known cases were not linked to a novel coronavirus until 6 weeks later. At first sight this seems perplexing: How could Yale University not only know about this but even secure a priority date for the use of the multi-kinase inhibitor pazopanib 3 days after the first unappreciated Chinese case occurred? How is it possible that the inventors not only mentioned a "*novel coronavirus … that afflicted a large number of people in Wuhan, China in December 2019*" but also referred to the virus as SARS-CoV-2, a name that was not assigned to it until the first months of 2020?

It is easy to see how suspicion of foul play could arise, fueling conspiracy theories. But the answer lies in a peculiarity of the PCT system. PCT Articles 19 and 34 permit amendments during the international phase, provided that they do not introduce new subject matter beyond what was originally disclosed in the priority application (in which case a second priority date would be assigned). Specifically, terminology in PCT publications may reflect current nomenclature due to modifications introduced during the publication or administrative stages. In this case, it is likely that Yale updated the terminology and provided clarifications to reflect the then-current understanding of the virus, while carefully maintaining the scope and claims of the original invention, making a second priority date unnecessary.

Looking at the supporting scientific data provided by the other applications, we see that almost all limited themselves to show that infection of, and/or viral replication in, Vero E6 cells is inhibited. Only a few make reference to a molecular mechanism, such as host angiotensin-converting enzyme 2 (ACE2) receptor blockade or the TMPRSS2 protease on which viral entry depends.[16] This does not imply that no mechanistic data were available at the time of filing; showing efficacy in cell culture would have been sufficient to support the claims, given that demonstrating a particular mechanism is not integral to patentability. This makes disclosure of additional data unnecessary, and possibly a hindrance for later, more specific patent applications.

The Immune Modulators: Increasing Rational Repurposing (Table 4)

The primary cause of Covid-19 mortality is inflammatory dysregulation and overactivation of the immune system which, in a runaway effect, can lead to the cytokine release syndrome (commonly referred to as a "cytokine storm") and the acute respiratory distress

syndrome (ARDS). This was evident even with the first hospitalized cases, and it was already known not only from the MERS coronavirus epidemic of the early 2000s, but also from severe cases of influenza, especially the devastating 1918 H1N1 pandemic.

While some antiparasitics and antihelminthics became the earliest repurposing candidates for Covid-19 because of their known immunomodulating effects, it was not before March 2020 that the first patent applications were filed claiming agents that held approvals on the basis of such activities. Possible explanations for this relative delay include restricted availability and high price. This is certainly true for the immunosuppressive monoclonal antibody tocilizumab, which blocks the interleukin-6 receptor. On December 7, 2021 the European Medicines Agency approved it for treatment of adults with severe Covid-19 who are treated with corticosteroids and require extra oxygen or mechanical ventilation; the Food and Drug Administration (FDA) issued the same use extension a year later, having allowed emergency use earlier. (A small molecule immune modulator, the JAK inhibitor baricitinib, which is approved for the treatment of rheumatoid arthritis and atopic dermatitis, had been approved for the treatment of hospitalized Covid-19 patients in November 2020 by the FDA, but the market authorization application in Europe had been withdrawn.)

The majority of the other immunomodulator agents listed in **Table 4** have entered advanced clinical trials that were either prematurely terminated or showed limited response: bucillamine (NCT04504734, terminated); colchicine (several trials as a single agent and in combination with ivermectin or tocilizumab), anakinra (several trials, also in combination with ruxolitinib); ozanimod (NCT04405102, terminated); losmapimod (NCT04511819, terminated); tofacitinib (single agent and in combination with hydroxychloroquine); vidofludimus (NCT04379271, completed).

The Uncategorized Segment: Ingenious Pharmacology and Serendipity (Table 5)

Half of the agents in our pool of repurposing patent applications do not fit in any of the above categories. Instead, their approved therapeutic indications cover almost all known classes of medical conditions, and so do the molecular mechanisms for which they are known. In some cases the activity against SARS-CoV-2 was a chance finding made during *in vitro* experiments, as with the classical antipsychotic, haloperidol[17]; sometimes evidence came from hospital records or registries; others resulted from targeted screening efforts or from *in silico* docking once the interactions between viral and host proteins and the respective structures had been characterized. Still other discoveries were made by ingeniously combining seemingly disparate evidence with known mechanisms, and confirming the line of thought experimentally. Sometimes a combination of factors contributed to investigations that are still ongoing, as was the case with the loop diuretic, furosemide: originally proposed in an inhalable presentation to treat pulmonary edema in Covid-19 ARDS, it was soon found not only to improve fluid balance but also to act as a potent inhibitor of pro-inflammatory cytokine release.[18]

Available space is insufficient to individually address the large number of claimed compounds and the associated evidence; the reader is referred to the original patent documents listed in **Table 5**.

DISCUSSION

The initial phase of the COVID-19 pandemic saw a surge in drug repurposing efforts, during which a vast array of potential therapies was rapidly considered, and hundreds underwent evaluation. The interest in antiparasitic and antihelminthic agents during this period was primarily fueled by their previously documented broad-spectrum antiviral activities, immunomodulatory properties, accessibility for repurposing, and their affordability on a global scale. In contrast, theoretical mechanistic considerations appear to have been a relatively minor influence on these early investigations.

A notable example of the rapid response during this period was the patent application for nitazoxanide, filed by the China Institute of Military Medicine on January 21, 2020. This filing occurred only 22 days after the Wuhan Municipal Health Commission publicly acknowledged the outbreak of a novel viral pneumonia and informed the World Health Organization, and just 11 days after a consortium of Chinese universities, hospitals, the Chinese Center for Disease Control, and the University of Sydney released the genome sequence of what became known as SARS-CoV-2.

The cases of chloroquine/hydroxychloroquine and ivermectin highlight different aspects of drug repurposing during the pandemic. These drugs became the focus of intense public discourse, ultimately overshadowing objective assessments of their potential benefits. In March 2020, then U.S. President Donald Trump publicly endorsed hydroxychloroquine, both as a stand-alone treatment and in combination with azithromycin, as a promising measure against COVID-19, later disclosing that he personally took the drug. This endorsement led to a surge in off-label prescriptions, only to collapse shortly thereafter amid reports of drug shortages and the absence of robust clinical evidence supporting its use.

Ivermectin experienced a different but equally problematic trajectory. It became a symbol within alternative medicine and anti-vaccine circles, with conspiracy theories alleging that pharmaceutical companies, regulatory authorities, and governments were suppressing data that demonstrated ivermectin's efficacy. In some countries, particularly in South America, ivermectin was authorized for emergency use, while mainstream media outlets ridiculed its use as a "horse dewormer," disregarding the limited and controversial scientific evidence available at the time. The ensuing whirlwind of political influence, misinformation, irrational advocacy, and inconsistent scientific findings transformed ivermectin into a prime example of how drug repurposing should not be conducted. This serves as a critical lesson to consider in the implementation of improved pandemic preparedness strategies.

Immunomodulatory agents, on the other hand, largely avoided the public controversies that engulfed antiparasitic treatments. This might have been due to the much more sophisticated *in vivo* testing required for this type or agents. Their accelerated clinical

investigations were conducted with relatively limited public scrutiny and ultimately led to the second of only two successful cases of repurposed drugs approved for the treatment of COVID-19. Kinase inhibitors, in particular, emerged as a focal point in patent filings for repurposing anticancer agents, a natural extension of their established immunomodulatory capabilities, but also due to their dominance in modern cancer therapy.

The section concerning miscellaneous agents might be the one with the most lessons to teach, the primary lesson being diversity. This section is reminiscent of the early days of the AIDS epidemic in the early 1980s, when researchers rushed to their freezers and tested whatever compound libraries they had available. Ultimately, rationally designed compounds prevailed; however, rational repurposing had not yet taken root at that time. Today, repurposing for Covid-19 is far from finished, and efforts are underway to integrate it into pandemic preparedness strategies that, together with advanced artificial intelligence tools, should make humanity's response to a new pathogen quicker and more targeted.

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CONFLICTS OF INTEREST

The author declares no conflict of interest.

DATA AND CODE AVAILABILITY

Data and code availability does not apply.

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