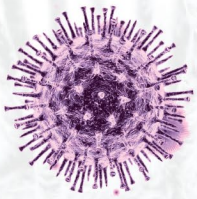
A CSR Initiative

β-Coronavirus (Covid-19)

Patent Landscape Report



Corona

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1. Introduction

An epidemic outbreak in Hubei, China, has caused global concern. It is the most lethal Coronavirus infection ever recorded with a mortality rate of 2-4% but high rates of transmission(**Chen**). Clinical findings of infection include pneumonia-like symptoms with etiological agent being a virus. Next-Generation sequencing of nucleic acids from patient samples has indicated a novel strain of Coronavirus (CoV) as a causative agent. The virus has been isolated from suspected patient samples and cultured in vitro. The virus has been designated as SARS-CoV2 and the disease is designated as Covid-19 by WHO, and is evolutionarily related to Bat SARS-like coronavirus. In this work, Covid-19 is used to denote the virus for better understanding. Coronaviruses have been found in avian, reptilian, and mammalian carriers, sporadic cross over from one species to the other has reported to cause diseases. Covid-19 is of zoonotic origin capable of human to human transmission. *Coronaviridae* family consists of four genera (α,β,γ,δ) of which only α, β CoV cause human infections. SARS and MERS belong to β-coronavirus(β-CoV) genera, according to Geng et al., CoV are common human pathogens, with 30% to 60% of the Chinese population is positive for anti-CoV antibodies(**Li, *et al.***). β-CoV are cause for about 1/3rd of common cold cases in humans(**Pillaiyar, *et al.***).

The information on Covid-19 is developing and there is no concrete information on the viral origin, epidemiology, and treatment. On 12th of March 2020, WHO has declared Covid-19 as a global pandemic, the virus has spread to more than 116 countries worldwide threatening global travel and economy as a whole(WHO). With more than 0.125 million (12th march 2020) confirmed cases and 4,500 deaths Covid-19 has dwarfed all the previous Coronavirus outbreaks.

The high-risk groups for Covid-19 infections are people with low or compromised immunity, patients with co-morbidities like cancer, people who have undergone an organ transplant. Age plays a vital role in recovery, high rates of mortality is recorded in patients above 60 years(**Wang, *et al.***).

2. Virus biology

2.1. β-CoV morphology

Viruses of the Coronaviridae family share similar morphology and are one of the largest RNA viruses ranging from 0.12-0.16μm in size. Coronaviruses are spherical and characterized by surface projections consisting of spike proteins, resembling the outer surface of the sun(corona), hence the

name Coronavirus. Genome length varies from 26-32kb, Covid-19 has 29kb genome. The RNA is polyadenylated and flanked by UTR at each end. About 300 naturally-occurring Coronaviruses are known till now, and fraction of them causing infection.

2.2. Genome

The complete genome of Covid-19 has been sequenced and is made publicly available. Covid-19 genome consists of a single-strand(+) RNA genome of 29kb length. Phylogenetic analysis has indicated that Covid-19 belongs to genus β-coronavirus, sub genus Sarbecovirus (**Randhawa, *et al.***). The genome encodes spike, envelope, membrane and nucleocapsid structural genes in order and lacks Hemagglutinin esterase gene. 70% of the genome is dedicated to non structural proteins like cysteine protease, main protease and RNA polymerase. The Covid-19 genome is flanked by two untranslated region(UTR) characteristic of β-CoV's.

Comparative analysis of genomes has shown that novel Coronavirus is similar to that of bat-SL-CoVZC45(sequence identity 87·99%), bat-SL-CoVZXC21(87·23%) and SARS-CoV (79%) (**Chan, *et al.***). Also, some of the proteins encoded by Covid-19 share similar structural and functional properties with that of bat-SL-CoVZC45 and bat-SL-CoVZXC21. Like other β-*Coronaviruses*, Covid-19 also comprises a virion surrounded by surface projections, a nucleocapsid, an envelope that contains membrane proteins which are essential for infecting host cells(**Chen, *et al.***).

2.3. Viral proteins

The viral proteins encoded by β-CoV can be grouped into structural and Nonstructural proteins(Nsp). About 15 Nsp's have been identified among β-CoV, some of these Nsp's function as helicases, IFN signaling inhibitors, nucleases. Structural proteins include Spike(S), Envelope(E), Membrane(M) and Nucleoprotein(N). Structural proteins are indispensable for viral replication.

- ⇒ S proteins of the viral envelope, homotrimers of S protein assist in the attachment of virus to host cell receptors.
- ⇒ E protein is involved in maturation and release of viral particles, an important step in progression of infection.
- ⇒ β-CoV is resistant to interferon and RNA-i, this is facilitated by the N protein. N-protein also helps in virus maturation.

⇒ M protein is a trans-membrane protein binds to nucelocapsid protein, involved in maintaining curvature of virus membrane.

3. Mode of transmission

3.1. Host

STRAIN	HOST	TARGET/VICTIM
Bovine coronavirus	Cattle	Humans, Dogs, Avian Sp.
Equine coronavirus	Horse	Horse
Human coronavirus OC43	Cattle	Humans
Porcine encephalomyelitis virus	Pigs	Pigs, Rat, Mice
Human coronavirus HKU1	Mice	Humans
SARS-related human coronavirus	Palm civets, bats	Humans
Mouse hepatitis virus	-	Mouse
Rat coronavirus	-	Rat
Pipistrellus bat coronavirus HKU5	*Japanese pipistrelle*	Humans, Camels
Rousettus bat coronavirus HKU9	*Leschenault rousette*	Humans, Camels
Middle east coronavirus	Dromedary camels, bats	Humans
***SARS-CoV2*(Covid-19)**	-	Humans

The above table indicates the know pathogenic CoV that infect humans and animals along with its carrier

3.2. Infection

Currently, the virus is believed to have first infected human subjects in a sea food market at Hubei, China. In China, majority of the initial cases had either visited the market or had contact with people who had visited the market. The market which is currently under lockdown traded sea food and other exotic live animals including bats and pangolins. Though Covid-19 genome shows similarity to bat SARS-like-CoVZXC21, the exact source of Covid-19 is still debated. Human to human transmission through respiratory droplets have been documented along with nosocomial infection. This virus can be transmitted from one individual to another by respiratory droplets, contact, and fomites.

3.3. Life cycle

⇒ Host entry- The attachment of viral particle to host is mediated by S-protein complex. Depending on the viral lineage receptor binding domain of S-protein shows selectivity to

host receptors, in case of Covid-19 Angiotensin Converting Enzyme(ACE2) is believed to assist viral attachment to ciliary epithelial cells of human lungs(**Fehr, *et al.***).

⇒ Transcription of viral genome is dependent on the formation of RTC; several Nsp are involved as cofactors for RNA polymerase. Transcription of RNA genome also involves synthesis of mRNA coding structural genes, following which the structural proteins start accumulating in the cytosol.

⇒ Translation of viral genes starts with Replicase gene, replicase is complex of two poly proteins, which regulates host cytosol to enable transcription of viral RNA genome. Accumulation of Nsp(1-15) in the cytosol signals formation replicase-transcriptase complex (RTC) enabling transcription of virus genome.

⇒ Assembly and release of virions is initiated by the Nucleocapsid protein in the presence of structural proteins. The M protein anchors the viral membrane components and accelerates the virion formation. The mature viral particles are released from Endoplasmic reticulum through budding. The viral particles are released from the affected cells by exocytosis (**Chen, *et al***.).

3.4. Clinical manifestation

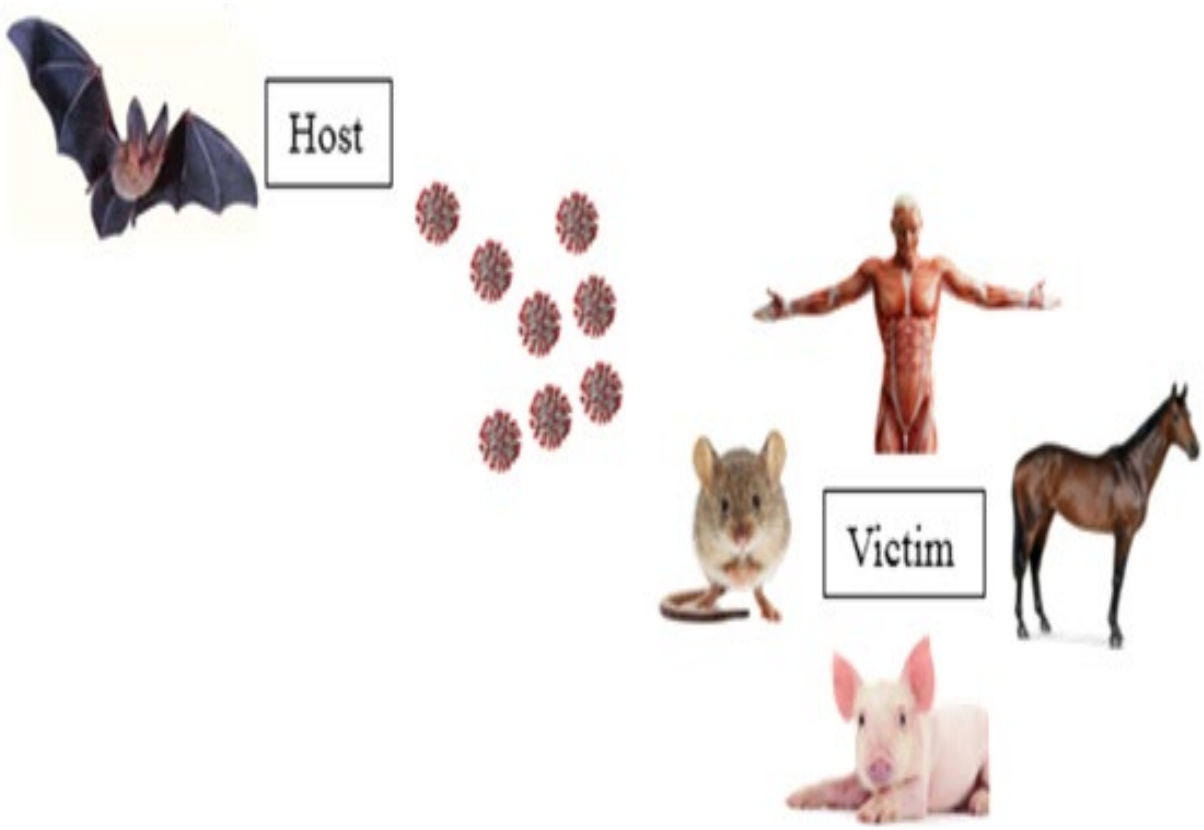
The virus has incubation time of 14 days, during which affected individuals are asymptomatic. Covid-19 is lethal in patients with comorbidities and immune-compromised adults. Initial symptoms of Covid-19 include fever, dry cough, myalgia, fatigue, dyspnea, anorexia, diarrhea, and nausea.

Patients infected with Covid-19 develop acute respiratory distress syndrome, which progresses to multisystem infection. Death is majorly caused by pulmonary edema, ARDS or multi-organ failure(**Huang, *et al***.). In severe cases, infection is associated with cytokine storm where cytokines like interleukins 2, 7, and 10, granulocyte-colony stimulating factor, interferon-γ-inducible protein, monocyte chemoattractant protein, macrophage inflammatory protein alpha, and tumor necrosis factor α are over produced. Such patients encounter lung damage and fibrosis after recovery (**Zumla, *et al***.). On infecting a human host, coronavirus is attacked by immune cells like mast cells, forming a shield to protect the body from virus invasion. However, the virus activates mast cells to produce pro-inflammatory cytokines of IL-1 family like IL-1 and IL-33, thereby leading to inflammation.

3.5. Epidemology

As of 12th Mar 2020, about 100+ countries have reported one or more cases of Covid-19 infection. Globally 0.125million cases have been recorded with more than 90% cases originating from China. Contact with nasal secretions are major cause of infection; Covid-19 infects people of all ages while the recovery is faster in pediatric cases. Pediatric cases may appear asymptomatic or present with fever, dry cough, fatigue and rare cases have upper respiratory symptoms including nasal congestion and running nose, gastrointestinal symptoms including abdominal discomfort, nausea, vomiting, abdominal pain, and diarrhea.

Infection in adults leads to acute respiratory distress syndrome (ARDS), septic shock, refractory metabolic acidosis, and coagulation dysfunction(**Shen, *et al.***). Adults with underlying chronic diseases and immune-compromised individuals are at high risk of death from Covid-19.



4. Treatment of β- Coronavirus

4.1. Chemicals claimed for treating β- Coronavirus

Based on the current knowledge of β-Coronavirus virus biology, several synthetic molecules have been tested as antivirals against the virus. The synthetic molecules have been customized to inhibit the viral structural proteins.

The molecules patented for inhibiting Coronaviruses are;

PATENT NUMBER	MECHANISM OF ACTION	CHEMICAL/ MOLECULE	TARGET ORGANISM	ASSIGNEE
CN103130710B	Protease inhibitor	Hexanolactam aldehyde	SARS	NANKAI UNIV, TSINGHUA UNIV
CN103145608B	Protease inhibitor	Hexanolactam aldehyde	SARS	NANKAI UNIV, TSINGHUA UNIV
CN104592349A	Protease inhibitor	Oxopyrollidin derivative	Coronavirus	TIANJIN INTERNAT JOINT ACADEMY OF BIOMEDICINE
CN105837487A	Protease inhibitor	M14, M18, M20	MERS	TIANJIN INT JOINT ACAD OF BIOMEDICINE
US9309284B2	Protease inhibitor	Peptidomimetic compounds	Coronavirus	UNIV KANSAS STATE , UNIV WICHITA STATE
US7462594B2	Protease inhibitor	Peptide-like compounds	Coronavirus	TAIGEN BIOTECHNOLOGY CO LTD
CN100363346C	Protease inhibitor	Small-molecule inhibitors	SARS	TSINGHUA UNIV
US20190151400A1	Protease inhibitor	-	Coronavirus	KANSAS STATE UNIV RESEARCH FOUNDATION , UNIV WICHITA STATE
CN107459511A	Protease inhibitor	Imino oxazolidine	MERS, SARS	NANKAI UNIV
US20060019967A1	Protease inhibitor	Dicyclic or multi-cyclic compounds	Coronavirus	HSIEH HSINGPANG, HSU TSUAN, LU ILIN, WU SUYING
CN102838523A	Protease inhibitor	Valerolactam	SARS	NANKAI UNIV, TSINGHUA UNIV
US9474759B2	Protease inhibitor	Peptidyl aldehydes, peptidyl α-ketoamides, peptidyl bisulfite salts, and peptidyl heterocycles	SARS	UNIV KANSAS STATE , UNIV OHIO STATE , UNIV WICHITA STATE
WO2017222935A1	Protease inhibitor	Dipeptidyl, macrocyclic derivatives	Coronavirus	KANSAS STATE UNIV RESEARCH FOUNDATION , UNIV WICHITA STATE

Coronavirus main protease is involved in processing of poly proteins into NSP's, which are essential for viral genome replication. The viral protease is one of the first viral genes to be translated in the cytoplasm of host; it is also known as M pro,3C-Like protein. Main protease is the primary target for synthetic molecules, since it conserved among β-CoVgenera.

PATENT NUMBER	MECHANISM OF ACTION	CHEMICAL	TARGET ORGANISM	ASSIGNEE
US10226434B2	Polymerase inhibitor	Nucleoside analogue	MERS,SARS	KATHOLIEKE UNIV LEUVENLIEDEN UNIV MEDICAL CENTER RC LEIDEN , UNIV MARYLAND
EP3377045A1	Nucleoside inhibitor.	Ribavirin	Coronavirus	GLAXOSMITHKLINE , LIQUIDIA TECH INC
US20190336456A1	-	Xibornol	Human cov	ABIOGEN PHARMA SRL
CN106074506A	Entry inhibitor	Arbidol hydrochloride	MERS	GUANGZHOU MEDICAL UNIV
US10472332B2	E protein inhibitor	Acylguanidines	Coronavirus	BIOTRON LTD
US9266844B2	Helicase inhibitors	SSYA10-001	MERS, SARS	UNIV MISSOURI
US10307439B2	Polymerase inhibitor	Modified nucleosides	coronavirus	ALIOS BIOPHARMA INC
WO2006093518A3	-	Thienyl compound	Coronavirus	APATH LLC
US20130035328A1	Replication inhibition	Acylguasidines	Coronavirus	BEST WAYNE ,
US20150313909A1	Replication inhibition	Acylguasidines	Coronavirus	BIOTRON LTD
WO2012142459A1	Replication inhibition	Isoindoline	Coronavirus	ALBANY MOLECULAR RESEARCH INC , US HEALTH
US20190337981A1	Matriptase inhibitors	Peptide	Coronavirus	NEOMED INST
CN108743585A	-	Micromolecular compound	Coronavirus	YANG WEI
US20170119859A1	Cathepsin l inhibitor	-	Coronavirus	ANSUN BIOPHARMA INC
KR101944909B1	Entry inhibitor	Dihydrotanshinone	MERS	UNIVERSITY OF ULSAN
WO2019027501A1	Viral replicase inhibitor	Nucleoside analogue	Coronavirus	UNIV MARYLAND
WO2019046316A1	kinase inhibitor	-	MERS, SARS	ACURASTEM INC

PATENT NUMBER	MECHANISM OF ACTION	CHEMICAL	TARGET ORGANISM	ASSIGNEE
WO2019133712A1	NADPH oxidase inhibitors	Modified nucleosides	Coronavirus	AMBLARD FRANCK
WO2019173602A1	Transcription inhibitor	4'-halogen containing nucleotide and nucleoside	MERS, SARS	UNIV EMORY
KR20170009276A	Tyrosine kinase inhibitor	Radotinib	MERS	IL YANG PHARM CO LTD
KR10-1097189B1	Helicase inhibitor	Dihydroxychromone	SARS	KONKUK UNIV INDUSTRIAL COOPERATION CORP
WO2017077528A3	Treating inflammation	Eicosapentaenoic acid (EPA)	Coronavirus	SALZMAN LOVELACE INVEST LTD
WO2017212422A3	Viral replication inhibitor	Carbomer 980	MERS , SARS	NOVARTIS CONSUMER HEALTH SA
KR101913789B1	--	Biphenyl Compounds	Coronavirus	KOREA RESEARCH INSTITUTE OF CHEM TECHNOLOGY
US20190085024A1	Cysteine protease inhibitor	Alpha-ketoamide	Coronavirus	PHELIX THERAPEUTICS
WO2019113462A1	Nucleoside	N4-hydroxycytidine	Coronavirus	UNIV EMORY

Modified nucleosides are commonly used to treat viral infections; these molecules limit the virus replication through RNA polymerase inhibition. EP3377045A1 filed by GSK and Liquidia Technologies, claims an inhalation composition containing Ribavirin for treating RNA viruses infecting human respiratory tract. Ribavirin is an broad-spectrum anti-viral against RNA viruses including Coronavirus; it is currently marketed for treatment of RSV and Chronic Hepatitis-C infections. Ribavirin-tri-phosphate inhibits the viral polymerase, with excellent water solubility oral formulations are currently used to treat variety of viral infections. In clinical trials, almost all of the patients showed adverse reactions including bronchospasms, pyrexia of varying degrees, the molecule has low clearance from blood and is Teratogenic**(Xu, *et al.*).** Remdesivir is another nucleoside based antiviral developed by Gilead Sciences, currently investigated for treating Viral Hemorrhagic Fever like Ebola has shown promising results for inhibiting Covid-19 invitro. A patent application has been reported to be filed by Wuhan Institute of Virology, claims of which are eagerly awaited. Gilead Sciences in collaboration with Chinese health authorities, is testing Ribavirin in

severe cases of viral pneumonia, the initial results are promising. Gilead in collaboration with several researchers, had published a report in 2017 on the broad-spectrum activity of remdesivir against coronavirus, surprisingly, it included futurist CoV infections as well**(Sheahan, *et al.*).**

4.2. Drug repurposing

In any pandemic/epidemic outbreak drug repurposing, i.e., use of know therapeutic molecule for the treatment of novel infection is attractive. Remedisvir developed for treating Ebola hemorraghic fever by Gilead Sciences, has shown promising results invitro for treatment of Covid-19. Drug repurposing is advantageous as the experimental molecules with a known pharmacologic profile can progress to clinical testing directly, saving valuable time, reducing cost and accelerating development. Several studies are reported for drug repurposing studies**(Beck, *et al.*)**. Yadi Zhou et al. have identified 135 molecules based on network-based analysis and protein interactions**(Zhou, *et al.*)**. Similarly in patent literature reports the following molecules that could be used for treating β-CoV are indicated;

PATENT NUMBER	MECHANISM OF ACTION	CHEMICAL/ MOLECULE	ASSIGNEE
CN106892920B	-	Aloperine derivative	INST MEDICINAL BIOTECHNOLOGY
CN107281210A	Antibiotic/translation inhibitor	Azithromycin	INST OF MATERIA MEDICA CHINESE ACADEMY OF MEDICAL SCIENCE
US8895610B1	Viral replication	Platinum (IV)	KAY HEIDI
CN108721271A	Replication inhibitor	Monensin	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION
CN108324715A	Replication inhibitor	Phenazopyridine hydrochloride	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION
CN108478562A	Replication inhibitor	Mycophenolate mofetil and mycophenolic acid	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION
CN108721292A	Replication inhibitor	Pyrvinium pamoate	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION

PATENT NUMBER	MECHANISM OF ACTION	CHEMICAL/ MOLECULE	ASSIGNEE
CN108721293A	Viral replication	Emetine hydrochloride	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION
WO2016201692A1	Viral entry inhibitor	Teicoplanin	SUN YAT SEN UNIV
US9714271B2	Immunosuppressive	Cyclosporine analogue molecules	CONTRAVIR PHARMA INC

Immunomodulators dominate this class, particularly cyclosporine analogues. These immunomodulators reduce the adverse immune reaction caused due to septic shock and counter the abrupt release of cytokines. There are several reports of secondary bacterial infection of respiratory tract following CoV infection and pneumonia, to control such infections antibiotics are usually co-administered along with antiviral medication.

4.3. Natural products claimed for treating β- Coronavirus

This section lists patents claiming natural compounds for inhibition of CoV infection. Apigenin is a flavonoid commonly found in parsley, rosemary. Berberine is an alkaloid, a known antifungal, antibacterial and anti-inflammatory. Monensin is an antibiotic isolated *Streptomyces sp.* US20190307722A1 discloses a combination of these molecules as antiviral against MERS-CoV, the mixture is administered as nasal spray. The combination has anti-inflammatory, anti-viral properties.

PATENT NUMBER	ACTIVE AGENT	ORGANISM	PLANT SOURCE	ASSIGNEE
CN105031565A	-	MERS	Honeysuckle fructus forsythia, scutellaria baicalensis, schizonepeta, radix sileris ginger, bupleurum falcatum ligusticum wallichii, mint, tuckahoe, radix angelicae pubescentis, ephedra, adenophora stricta, mulberry root-bark.	LI XIANQIANG

PATENT NUMBER	ACTIVE AGENT	ORGANISM	PLANT SOURCE	ASSIGNEE
US20150164938A1	Chitosan	Coronavirus	-	UNIV JAGIELLONSKI
WO2008105934A3	Chitosan	Coronavirus	-	OREGON BIOMEDICAL ENGINEERING
US20190060358A1	Iota or kappa-carrageenan	Coronavirus	Sea weed	MARINOMED BIOTECH AG
CN106309961A	Extract	MERS	Gypsum, almond, radix scrophulariae, raw dioscorea rhizome Radix codonopsis, snakegourd fruit, radix peucedani fritillaria cirrhosa, bamboo leaf. Lalang grass rhizome, ephedra, licorice, semen lepidii	YAN XIAOYUE
CN105079226A	-	MERS	Fructus forsythia, honeysuckle, indigowoad root, rheum officinale, herba pogostemonis, rhizoma dryopteris crassirhizomae, rhodiola rosea	BEIJING YILING PHARMA CO LTD
KR100743861B1	Pine extract	SARS	Red pine, black pine, *Pinus Koraiensis Sieb*	MOON CHI UNG , SONG CHANG SEON
KR100881035B1	-	SARS	*Celosia argentea Celosia plumose celosia cristata*	MOON CHI UNG , SONG CHANG SEON
KR101521010B1		SARS	*Reynoutria sachalinensis*	KANGWON NATIONAL UNIV INDUSTRY UNIV COLLABORATION FOUNDATION
KR20180079136A	-	SARS, MERS	Oregano herbal essential oil : rosemary herbal essential oil : olive	GREEN T IND CO LTD
KR101317318B1	Ethyl p-digallate	Coronavirus	*Galla rhois* extract	WONKWANG UNIV CT IND ACAD COOP
KR20180054029A	-	MERS	Weissella cibaria strain JW15	NAT UNIV CHONBUK IND COOP

PATENT NUMBER	ACTIVE AGENT	ORGANISM	PLANT SOURCE	ASSIGNEE
CN106822880A	Lysozyme	Coronavirus	-	JIANGYIN BENGT SAMUELSSON LIFE SCIENCE RES INST CO LTD
JP4411523B2	Polysaccharide	Coronavirus	*Green Plant Gate Chlorophyeae, Chlorococcales, Chlorococcaceae Cocccomyxaformi*	NIKKEN SOHONSHA CORP
US20190307722A1	Apigenin, Monensin, Berberine.	MERS	-	CENTRE NAT RECH SCIENT , INSTITUTE NATIONAL DE LA SANTE ET DE LA RECH MEDICALE INSERM , UNIV CLAUDE BERNARD LYON

Interesting inclusions among the natural products are polysaccharides like chitosan and carageenan. Chitosan, the second most abundant bio-polymer shows inhibitory activity against several viral strains; it acts by preventing viral replication. The polymer consists of positively charged sugar monomers which interact with the haemagglutinin protein or related surface proteins of the virus preventing viral replication. In case of Carageenan, particularly iota-carageenan from sea weeds like Kappaphycus sp. is reported to inhibit *Human Coronavirus OC43* invitro.

4.4. Antibodies claimed for treating β- Coronavirus

Neutralization of virus mediated by antibodies is an attractive approach for virus treatment. Use of convalescent serum for treating severely ill patients is one of the first approaches in therapy of any novel viral infection, the antibodies present in convalescent serum help in recovery and treatment. Antibodies are produced by humoral immunity in response to any infection in the body, antibodies confer both short term and long term immunity. In patent literature the following patents claim antibody for the treatment of β-CoV family;

PATENTS	TARGET	ANTIBODY	ASSIGNEE
CN103554235B	MERS	Ab against RBD binding domain of MERS	TSINGHUA UNIV
CN106380517B	MERS	Micromolecular Ab	AMMS CHINA
US10064934B2	β-CoV	Epitope- broad spectrum	MODERNATX INC
CN109666070A	MERS	IgG	TSINGHUA UNIV

PATENTS	TARGET	ANTIBODY	ASSIGNEE
US10421802B2	-	IgG	US HEALTH , VERITECH LTD
TWI623322B	-	Antibody	VAXSIA BIOMEDICAL INC
US10406222B2	MERS	Spike antibodies	REGENERON PHARMA
US10131704B2	MERS	Isolated antibody	DANA FARBER CANCER INST INC
CN107298712A	MERS	Antibodies	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION
CN104447986B	MERS	Antibody	INSTITUTEE OF MICROBIOLOGY CHINESE ACADEMY OF SCIENCE
AU678970B2	Coronavirus	S protein	PFIZER INC
KR10-1828794B1	MERS	Antibody	CELLTRION INC
KR10-2007161B1	MERS	Monoclonal	KOREA CENTER FOR DISEASE CONTROL PREVENTION
KR10-1969696B1	MERS	Monoclonal	KOREA CENTER FOR DISEASE CONTROL PREVENTION , OSONG MEDICAL INNOVATION FOUND
WO2019183362A1	MERS, SARS	Antibody	DANA FARBER CANCER
WO2019151632A1	MERS	Human antibody	CELLTRION INC
WO2019175606A1	Coronavirus	Fusion polypeptide	LIVERPOOL SCHOOL OF TROPICAL MEDICINE
WO2017196847A1	MERS	Antibody	UNIV MARYLAND, US HEALTH
WO2019067671A1	MERS	Synthetic antibodies	SMITH TREVOR RF
WO2019118791A1	Coronavirus	Antibodies	MOMENTA PHARMA INC
EP3576793A1	MERS, SARS	Antibody specific for CCR4.	DANA FARBER CANCER INST INC

Most of the patents claim antibodies against S-protein of the virus. The S-protein appear as petal shaped projections on the viral surface, which are anchoring points for the virus to the host cells. Antibodies are particularly directed at the Receptor Binding Domain(RBD) of S-protein, the other epitopes of S-protein targeted are S1 and S2 fragments. The antibodies bind to the S-protein and prevent viral entry, thus preventing progression of the infection. Apart from the S-protein the host cell receptors particularly DPP4/CD26 and ACE2 are employed by the virus for entry into the cell, antibodies against these receptors are also described in the literature.

4.5. Peptides claimed for treating β- Coronavirus

Peptides are unique molecules that are used for treatment were high specificity is required. The patents listed in the below table claim peptides for the treatment of β-CoV;

PATENT	TARGET	PEPTIDE	ASSIGNEE
US20070160981A1	SARS	Peptide	CHEN XIN
AU750369B2	Coronavirus	Peptides	CORTECH INC
US20040229219A1	SARS	Peptide	GALLAHER WILLIAM R
CN107022008A	SARS	Polypeptide	FUDAN UNIV
US20190262432A1	MERS	Sialidase activity	ANSUN BIOPHARMA INC
KR101912375B1	MERS, SARS	Peptide	IMMUNEMED INC
EP1623028B1	Coronavirus	Peptide	UNIV LUEBECK , UNIVERSITAET ZU LUEBECK
CN103724406A	MERS	Synthetic peptide	INST VIRAL DISEASE CONTROL PREVENTION CHINESE CT DISEASE CONTROL PREVENTION
CN107245095A	Coronavirus	Peptides	WUHAN UNIV
KR101973388B1	MERS, SARS	Virus capture protein, concanavalinA	UNIV NAT CHONNAM IND FOUND, KOREA BASIC SCIENCE INST
WO2018164573A1	MERS	Inhibitor or nucleic acid encoding inhibitor	ACADEMISCH ZIEKENHUIS LEIDEN , TORONTO UNIV , UNIV MANITOBA
WO2019135003A1	β-CoV	Polypeptides- trypsin or chymotrypsin	ENZYMATICA AB
WO2019136824A1	MERS	MERS-cov fusion inhibitor	ACAD OF MILITARY MEDICAL SCIENCE
WO2019199955A1	MERS, SARS	Viral immunogen	ADMINISTRATORS OF TULANE EDUCATIONAL FUND
WO2019202285A1	MERS	MERS-cov receptor binding domain	PROXIMA CONCEPTS LTD , SECR DEFENCE , UNIV STRATHCLYDE

Most peptides act as inhibitor of the viral protease, interfering with the viral replication. Such strategy was adopted for treating SARS virus in 2002, similarly, Andr´e Fischer et al have reported a chemical screen to find novel inhibitors for Covid-19 protease **(Fischer, *et al.*)**. The most common mechanism of viral protease inhibition is binding of the therapeutic peptide to the protease, peptides are designed to bind with specificity to cysteine residues on the protease.

4.6. Biologics claimed for treating β- Coronavirus

Vaccines including parts or whole inactivated virus are commonly used in providing long term immunity. Some of the vaccine candidates against older Coronaviruses such as SARS and MERS are in clinical stages of testing, concerns with regards to their safety persists. Developing inactivated or attenuated viral based vaccines against coronavirus is challenging due to variability of the strains.

PATENT	TARGET ORGANISM	VACCINE AGENT	ASSIGNEE
US7279327B2	Coronavirus	Attenuated virus	UNIV NORTH CAROLINA
US20180333482A1	Coronavirus	Live attenuated virus	UNIV LOYOLA CHICAGO
US7452542B2	SARS	Attenuated virus	UNIV VANDERBILT
US20070286872A1	Coronavirus	Live attenuated virus	UNIV VANDERBILT
US20060286124A1	SARS	Immunogen	ID BIOMEDICAL CORP
WO2009117134A3	Coronavirus	Aerosol vaccine	NAT INST HEALTH
US20190328865A1	MERS	Attenuated	NEW YORK BLOOD CENTER INC
WO2004091524A3	SARS	Spike protein	ACAMBIS INC
US20200030432A1	MERS	RNA vaccine	MODERNATX INC
EP3532095A1	Coronavirus	Spike proteins	DARTMOUTH COLLEGE , SCRIPPS RESEARCH INST , USA REPRESENTED BY SEC DEP OF HEALTH HUMAN SERVICE
US7618802B2	SARS	DNA vaccine	UNIV NORTH CAROLINA
US20190351048A1	MERS	mRNA vaccine	CUREVAC GMBH
US9993543B2	SARS,MERS	Silicified virus	UNIV PORTLAND STATE , PROVIDENCE HEALTH SERVICE OREGON DBA
US9889194B2	MERS	Spike protein	NEW YORK BLOOD CENTER
CN105555306B	MERS	Spike polypeptide nanopartic le	NOVARAX CO LTD
US9884895B2	Coronavirus	Spike protein	UNIV NORTH CAROLINA CHAPEL HILL 308 BYNUM HALL
US10548971B2	MERS	DNA vaccine	INOVIO PHARMA INC , UNIV PENNSYLVANIA
EP3399029A4	-	Attenuated virus	BEIJING NORMAL UNIV
US20180334480A1	SARS, MERS	Cov epitopes	UNIV RAMOT
TW201910510A	-	Attenuated virus	EMERGING VIRAL VACCINE HK LTD

PATENT	TARGET ORGANISM	VACCINE AGENT	ASSIGNEE
WO2018097603A3	MERS	S protein antigen	SK BIOSCIENCE CO LTD
CA3065177A1	Coronavirus	Attenuated virus	KERNER MATTHEW , SHACKELTON LAURA
CA3065111A1	Coronavirus	Viral nucleic acid vaccine	KERNER MATTHEW , SHACKELTON LAURA
CN107058377A	MERS	Fusion proteins	SHENZHEN HUISHENG BIOLOGICAL TECH CO LTD
EP3045181B1	MERS	Nucleocapsid as antigen	PHILIPPS UNIV MARBURG , UNIV MUENCHEN LUDWIG MAXIMILIANS
US10301377B2	MERS	Antibodies	US HEALTH
CN106928326B	SARS,MERS	RBD as antigen	INSTITUTEE OF MICROBIOLOGY CHINESE ACADEMY OF SCIENCE

US20180333482A1 discloses a live attenuated virus with a defective replicase gene, this results in low activity of NSP15. The patent was evaluated in a plaque reduction assay. US20200030432A1 filed Modernatx Inc claims an RNA vaccine encoding viral proteins, the disclosed vaccine can be used as platform for development of RNA vaccine against virus of Zoonotic origin. Several patents focus on formulation for delivery of vaccine, which is also another important factor in design of vaccine.

4.7. Gene therapy claimed for treating β- Coronavirus

PATENT NUMBER	TARGET	GENE THERAPY METHOD	ASSIGNEE
US10143709B2	MERS	Adult stem cell	INDIANA UNIV RESEARCH TECHNOLOGY CORP , USA DEPT OF VETERAN AFFAIRS REPRESENTED BY TECH TRANSFER PROGR
AU2003209766B2	Coronavirus	Gene regulation	CONSEJO SUPERIOR DE INVESTIGACIONES CIENTIFICAS , CONSEJO SUPERIOR INVESTIGACION
US20190030187A1	MERS	SiRNA	SIRNAOMICS INC
US20020150556A1	-	Gene regulation	BATEMAN ANDREW, HARRINGTON KEVIN, MURPHY STEVEN, VILE RICHARD G

PATENT NUMBER	TARGET	GENE THERAPY METHOD	ASSIGNEE
CN105543248A	Coronavirus	Synthetic gene	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION
US10434164B2	SARS, MERS	RIG receptor	UNIV WASHINGTON
CN105273067A	MERS	Spike protien as vaccine	INST VIRAL DISEASE CONTROL
AR106465A1	B-cov	RNA encoding viral genes	MODERNATX INC

US20190030187A1 claims si-RNA based therapy for treatment of MERS infection, the patent also discloses a polymeric nanoparticle based formulation for delivery of si-RNA. The composition also includes a mixture of si-RNA targeted against viral protease, RNA polymerase and spike protein.

4.8. Diagnosis claimed for identifying β- Coronavirus

Diagnosis of an infection is the first step in control or limiting of any epidemic/pandemic disease. In case of Covid-19 patients, screening for elevated body temperature using thermal scanners is being employed as first step. WHO has recommended the use of PCR based detection of virus in patient samples. In the USA, multiplex real-time- RT-PCR using universal primers directed against SARS like coronaviruses(N3 assay) and specific primers for Covid-19 (N1& N2 assay) is being used. Samples collected from the respiratory tract are used for analysis, due to the requirement of stringent biosafety proper handling and disposal during diagnosis adds to the complexity.

Covid-19 also leads to secondary infections; hence testing of common respiratory pathogens is simultaneously practiced along with Covid-19 detection. Poor quality of specimen and handling of the samples during shipment to lab are major challenges in diagnosis.

PATENT	DIAGNOSING AGENT	METHOD	ASSIGNEE
CN103993101A	Primers	PCR	CUI SHUJUAN
ES2303395B1	Probes	Array	INST DE SALUD CARLOS III
CN109371174A	Primers	PCR	JIANGSU UNINOVO BIOLOGICAL TECH CO LTD
CN104059997A	Primers	PCR	SHENZHEN CT FOR DISEASE CONTROL PREVENTION

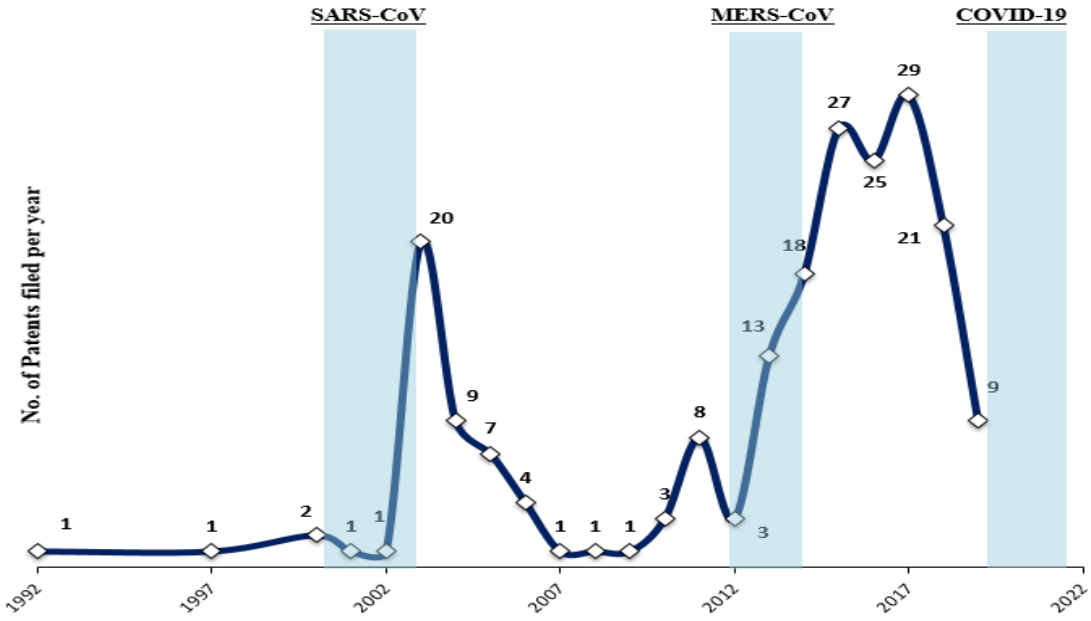
PATENT	DIAGNOSING AGENT	METHOD	ASSIGNEE
US8343718B2	IgG	ELISA	CENTRE NAT RECH SCIENT , PASTEUR INSTITUTE , UNIV PARIS
CN107475446A	Primers	PCR	CHILDREN S HOSPITAL FUDAN UNIV, JIANGSU MOLE BIOSCIENCE CO LTD
US8057993B2	Multiplex	PCR	IBIS BIOSCIENCES INC
CN103255231B	Primers	PCR	SHANDONG ACV BIOTECHNOLOGIES CO LTD
CN110724764A	Primers	PCR	INST OF PATHOGEN BIOLOGY CHINESE ACADEMY OF MEDICAL SCIENCE
CN107557496A	Flourescent probe	PCR	NINGBO INT TRAVEL HEALTH CARE CENTER
CN108060266A	Primers	PCR	BEIJING APPLIED BIOLOGICAL TECH CO LTD
US7375210B2	Primers	PCR	SAMSUNG ELECTRONIC CO LTD
CN110157839A	Flourescent probe	PCR	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION, WUXI CUSTOMS DISTR PEOPLES REPUBLIC OF CHINA
CN110144422A	Flourescent probe	PCR	INST FOR VIRAL DISEASE CONTROL PREVENTION CHINESE CENTER FOR DISEASE CONTROL PREVENTION, WUXI CUSTOMS DISTR PEOPLES REPUBLIC OF CHINA
CN109207639A	Primers	PCR	NANTONG INT TRAVEL HEALTH CARE OUTPATIENT DEPT
WO2007053165A3	Primers	Microarray	UNIV YALE
JP2017145246A	N-protein antibody	Immuno assay	KANTO KAGAKU, UNIV YOKOHAMA CITY
EP1776481A2	Primers	PCR	UNIV YALE
CN105624335B	Kit	RT- PCR	DA AN GENE CO LTD
CN102732638B	Primers	PCR	UNIV SUN YAT SEN
CN104911278A	Primers	PCR	WUXI BRANCH CT JIANGSU INTERNAT TRAVEL HEALTHCARE CT

PATENT	DIAGNOSING AGENT	METHOD	ASSIGNEE
US10295539B2	Kit	Sialic acid based receptor	MESO SCALE TECHNOLOGY LLC
US7776521B1	Primers	PCR	US HEALTH
US8106172B2	Primers	PCR	BIOMERIEUX BV
CN105039598A	Primer	PCR	HEILONGJIANG BOTENG BIOLOG SCIENCE TECHNOLOGY CO LTD
EP1639374A4	Antibody	ELISA	AGENCY SCIENCE TECH RES
CN110468234A	Multiplex primers	PCR	XIAMEN AMPLLY BIO TECH INC , NANJING ANPU PRECISION MEDICAL TEST CO LTD
EP1526175B1	Primer	PCR	AMSTERDAM INST OF VIRAL GENOMICS BV
CN110578017A	Primers	PCR	SHENZHEN STEP LIFE SCIENCE CO LTD , DONGGUAN MAIDAO BIOTECHNOLOGY CO LTD
CN110408726A	Probe	Microfluidics	ACADEMY OF MILITARY MEDICINE OF PLA ACADEMY OF MILITARY SCIENCE
CN1618983A	Probe	Gene chip	BEIJING JINDIKE INST OF BIOTEC
CN104846125B	Primers	Flourrescent PCR	BIOEASY TECHNOLOGY INC
CN103484564B	Primers	PCR	INST PATHOGEN BIOLOGY CAMS
CN105543409A	Primers	PCR	SHANGHAI ENTRYEXIT INSPECTION QUARANTINE BUREAU OF THE PEOPLES REPUBLIC OF CHINA
CN109609692B	Primers	PCR	BEIJING ZHUO CHENGHUI BIOLOGICAL POLYTRON TECHNOLOGY INC
CN104498636A	Universal primers	PCR	WUXI BRANCH CT OF JIANGSU INTERNAT TRAVEL HEALTHCARE CT
CN104232797B	Structural proteins	ELISA	BIOMEDICAL COMPANY LTD
KR100832860B1	Probes	DNA chip	KOREA CT FOR DISEASE CONTROL A
RU2504585C1	Primers	PCR	FEDERAL STATE INSTITUTION OF SCIENCE

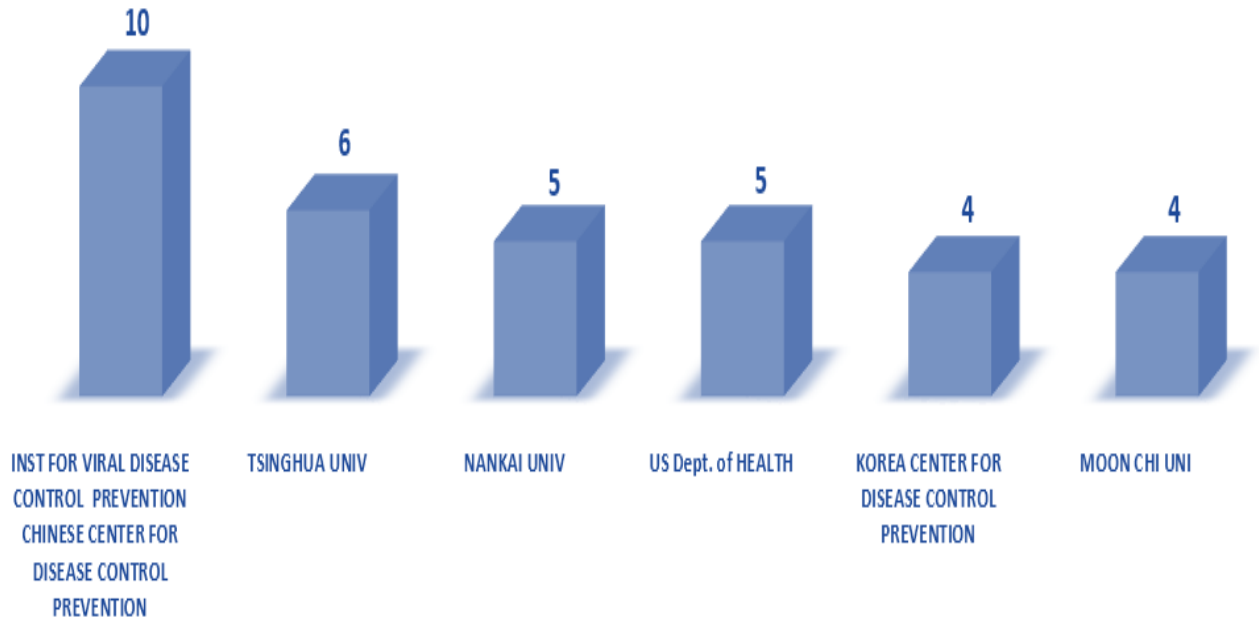
PATENT	DIAGNOSING AGENT	METHOD	ASSIGNEE
CN103710462B	Primers	PCR	SHENZHEN INTERNATIONAL TRAVEL HEALTH CARE CENTER
KR10-2018079B1	Primers	PCR	NAT UNIV CHUNGBUK IND ACAD
KR101916899B1	Primers	PCR	BIONANO HEALTH GUARD RES CENTER , KOREA RES INST BIOSCIENCE BIOTECHNOLOGY
KR100832867B1	Monoclonal Ab	Immuno assay	REPUBLIC OF KOREA MANAGEMENT RURAL DEVELOPMENT
KR100832870B1	Monoclonal Ab	Immuno assay	REPUBLIC OF KOREA MANAGEMENT RURAL DEVELOPMENT
KR101775984B1	Non-structural protein 3 (nsp3) gene region of MERS	Molecular beacon	SEOUL NAT UNIV HOSPITAL
KR10-1857685B1	Primers	PCR	KOGENE BIOTECH CO LTD , KOREA CENTER FOR DISEASE CONTROL PREVENTION
KR100438006B1	Ab	ELISA	GREEN CORSS VETERINARY PORDUCT
KR101895228B1	Spike protein of MERS	Monoclonal antibody	KOREA CENTER FOR DISEASE CONTROL PREVENTION
KR20190035542A	Nc fusion protein of a nucleocapsid	Monoclonal antiboides	KOREA RES INST BIOSCIENCE BIOTECHNOLOGY
KR102017217B1	Antibody	Immunoassay	YONSEI UNIV INDUSTRY ACADEMIC COOPERATION
WO2006076007A3	Nucleocapsid	Antibody-ELISA	UNIV VANDERBILT
WO2016080591A1	Nucleocapsid	Ab-ELISA	BIONOTE INC
CN206273830U	Primers	PCR	BEIJING INT TRAVEL HYGIENE CENTER GENERAL ADMINISTRATION OF QUALITY SUPERVISION INSPECTION QUARA, SHAANXI INT TRAVEL HEALTHCARE CENTER, SHENZHEN ACAD OF INSPECTION QUARANTINE, SHENZHEN UNIMEDICA TECH CO LTD

PCR based detection of Covid-19 is most commonly claimed in patents, apart from PCR antibody based ELISA is also reported. CN110468234A claims a multiplex PCR kit for diagnosis of 19 different respiratory pathogens, detection is based on fluorescence. WO2017078421A1 discloses a Molecular Beacon based detection of MERS, it is based on the use of aptamer for binding the Virus RNA particularly the NSP3 region.

5. Patent Analysis

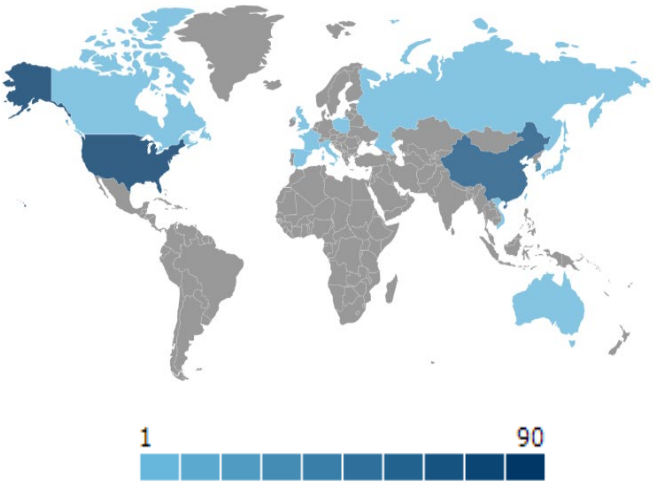


Year on Year filling trend of patents relating to β-CoV is represented in the above chart, interestingly spike in patent filling is observed following an outbreak. The numbers in the inset refer to the patents filed in that particular year. Currently, about 40% of patents are granted and an equal number of applications are awaiting examination and grant.

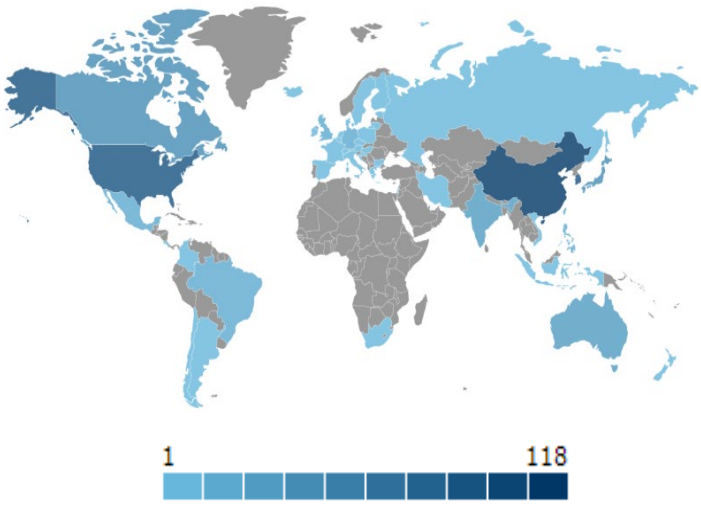


Institute for Viral Disease Control-Prevention, China leads in terms number of patents assigned. It is interesting to note that China has significantly invested in research for prevention of coronavirus infections, 3 out of 5 top assignees are located in China.

Geographical Distribution–Priority data



Geographical Distribution –Publication data



China tops in the number of patents filed, a significant chunk of application originate in Asia

6. Search Strategy

The search was conducted individually in multiple commercial databases and MCPaIRS® database with search fields limited to Title, Abstract, and Claims. One member per patent family was considered for analysis. The resulting documents were de-duplicated, followed by manual categorization and grouping into new chemical entities, vaccines, gene therapy, and diagnostic groups based on the focus of independent claims. Patents related only to the production method of viral particles or vaccines were not considered for analysis.

6.1. Keywords

BETACORONAVIRUS ; SARBECOVIRUS; MIDDLE EAST RESPIRATORY SYNDROME ; MURINE HEPATITIS VIRUS; MURINE CORONAVIRUS ; HEDGEHOG CORONAVIRUS; MIDDLE EAST RESPIRATORY SYNDROME RELATED CORONAVIRUS; SEVERE ACUTE RESPIRATORY SYNDROME RELATED CORONAVIRUS; SARS; HKU5; HKU4; HKU1; HKU9; HCOV; TYLONYCTERIS PIPISTRELLUS; BAT CORONAVIRUS; HUMAN CORONAVIRUS; ROUSETTUS; PI BATCOV ; OC43; RHINOLOPHUS; COVID 19; 2019 NCOV ; NCOV; WUHAN VIRUS; 424/221.1; A61K 39/215; C07K 14/165; C12N 15/50; C12N2770/20011; C12Y304/22069; G01N2333/165

7. Resources

- ⇒ The Lancet: Coronavirus Resource Centre was designed by the lancet for providing daily updates on the recent outbreak of Covid-19 by collecting information which is being published in the lancet journal.
- ⇒ Centers for disease control and prevention (CDC) : CDC provides latest statistics and news regarding Covid-19 in order to create awareness and provide knowledge for research purpose.
- ⇒ Center for Infectious Disease Research and Policy: University of Minnesota maintains center for infectious disease research and policy for revising information and data on Covid-19.
- ⇒ NIH Fogarty International Center: Fogarty international center is a part of U.S. National Institutes of Health supplies updates on global health and emerging concern about Covid-19.
- ⇒ WHO: WHO is providing situation reports on the recent outbreak of coronavirus, and helping in tracking the progress with respect to treatments ad diagnosis.
- ⇒ OSHA: Occupational Safety and Health Administration guides employers and researchers by supplying facts about preventing the spread and latest treatments available for Covid-19.
- ⇒ BC Centre for Disease Control: BCCDC helps in providing measures for preventing and/ or containing the disease as well as providing latest news about the global outbreak.
- ⇒ FDA: FDA provides details about diagnosis, treatment and prevention of the disease along with situation reports on the spread of Covid 19 globally.
- ⇒ ISARIC: ISARIC is an international resource which collects clinical data of patients suffering from Covid-19.
- ⇒ American hospital association: AHA is a national organization which records impact on hospitals and health systems and progress of the disease at global level.
- ⇒ Johns Hopkins CSSE: Johns Hopkins maintains a website providing information on real-time mapping of Covid-19 cases based on country wise reporting and tracking the numbers of recovered cases.

8. Conclusion

The Covid-19 is spreading its tentacles infecting millions, threatening global supply chains. In this research paper, we have analyzed all Patents/Applications citing β-coronavirus treatment or diagnosis published untill February 2020.

A comprehensive search strategy was designed to cover all patents claiming treatment and diagnosis of strains in β-CoV genre, to which Covid-19 is part of. Since the outbreak of SARS, China has invested significant efforts in therapy and diagnosis of CoV & three out of top five assignees are from China. The publication trend indicates a constant increase in numbers, though there is variation in the filling activity every year. Based on the analysis, it takes an average of 424 days for a patent to be published form the priority date.

During the outbreak of SARS and MERS in the past, the patent application filing upsurged by almost 1000%. A similar increasing filing trend is exptectd in the case of COVID-19 in next couple of months. Since the very beginning of the outbreak, the pharmaceutical industry and the medical community have been focusing their efforts on investigating drugs that can be repurposed to treat the symptoms, as well as developing new vaccines to limit the virus.

From patent filling trends, it is evident that the efforts in finding new therapy and diagnosis need to be scaled up, and sustained research is the need of the hour.

Molecular Connections is committed to collaborating researchers to serve their communities during this difficult time. We will continue to monitor the patent filing activity actively and help organisations accelerate their research needs.

Further, the entire list of Patents that were analyzed to derive insights as part of this research paper is provided at this link. Molecular Connections will continue to update this list weekly, depending on the publication of new Patents/Patent families claiming treatment or diagnosis of β-Coronavirus.

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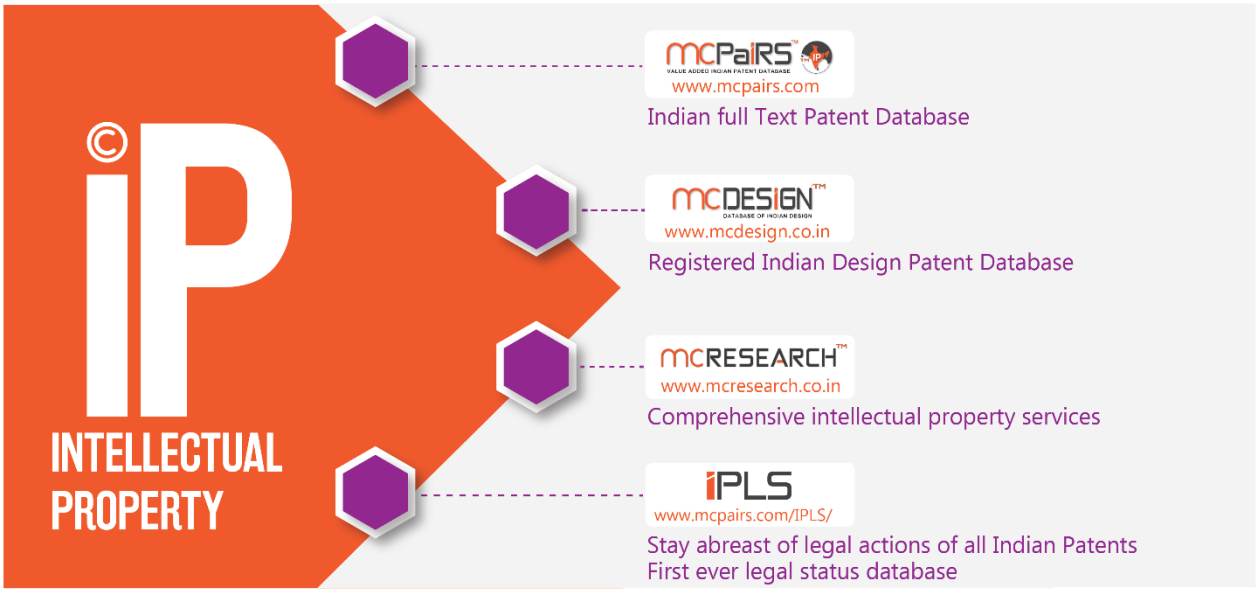

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