SARS-CoV-2: Treatment and Therapeutic Approaches

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Abstract

Actually there are no specific treatment approach for COVID-19 and most of the cases treated with supportive conventional treatment such rest; parenteral fluids, pain reliever, cough medication and cytokines storm treatment. Many drugs used on personal experience were used and there is no clinical trial for their evaluation. In Iraq, the Ministry of Health (IMH) recommended the use of the protocol that included combination of hydroxuchloroquine, azithromycin, Tamiflu (Oseltamivir), Kaletra (Lopinavir+Ritonavir)

and antibiotics according to patients need. Additionally, in other geographical areas some expert recommended the use of Remdesivir which may be of promising clinical outcome.

Keywords: SARS-CoV-2, SARS-CoV, MERS-CoV, COVID-19, 2019-nCoV, Azithromycin, Coronaviruses, Pandemic COVID-19, Hydroxuchloroquine, Tamiflu (Oseltamivir), Remdesivir, Kaletra (Lopinavir+Ritonavir).

Introduction

Actually there are no specific treatment approach for COVID-19 and most of the cases were treated with supportive conventional treatment such rest, parenteral fluids, pain reliever, cough medication and cytokines storm treatment. Many drugs used on personal experience were used and there is no clinical trial results for their evaluation. In Iraq, the Ministry of Health (IMH) recommended the use of the protocol as shown in Table 1.

Table .1. COVID-19 Treatment protocol in Iraqi hospital [1].

Drug	Dose	Indication
Hydroxychloroquine	**400 mg BID 1st day and then 200 mg BID for 14 days**	**SARS-CoV-2 positive with pneumonia in ICU**
Azithromycin	**500 mg BID 1st day and then 250 mg BID for 14 days**	
Tamiflu (Oseltamivir)	**75 mg twice daily for 5 days**	
Kaletra (Lopinavir+ Ritonavir; 200/50 mg)	**2 tabs PO BID for 5 days**	
Antibiotics		**Accordingly**

In mild cases, there is no need to use antiviral agents, however in moderate cases IMH recommended the use of combination of Oseltamivir (Tamflu) with either Chloroquine or Hydroxychloroquine or Ribavirin. While in severe cases, the combination of Kaletra plus

Oseltamivir with either Chloroquine or Hydroxychloroquine or Ribavirin. In addition, in critical cases, course if combination of Kaletra + Oseltamivir + Ribavirin with either Chloroquine or Hydroxychloroquine. To date there are no data available that confirm their effectiveness in the treatment of COVID-19.

Drugs under testing for their Anti-SARS-CoV-2 activity

Globally, there are more than two hundreds (6 April, 2020) of clinical trials registered in the official sites of clinical trials [2] undergoing evaluation of their effectiveness as treatment approach for SARS-CoV-2 infection. COVID-19 is the first infectious health problem that takes the attention of WHO, world leaders, non-governmental organization, social media and whole world societies, even the children. The world is now desperate to find ways to slow the spread of the novel coronavirus and to find effective treatments. The drugs under evaluation included previous drugs that were used previously in the treatment of malaria, HIV, parasitic disease, and viral infections, Table 2 [3-7]. Tu et al **[7].** Fortunately, the drugs and chemical agents listed in Table 2, which are under testing for their antiviral activity, are with varied mechanisms of antiviral activity. However, to early so suggest a novel antiviral agent against SARS-CoV-2 infection.

COVID-19 treatment is the major challenge as the disease mortality is around 7% (estimated at 25th April 2020 cases). Gordon et al [3], in their study reported that human proteins interacted with SARS-CoV-2 proteins with multiple functions that include epigenetic and gene expression regulators (Nsp5, Nsp8, Nsp13, E), DNA replication (Nsp1), vesicle trafficking (Nsp6, Nsp7, Nsp10, Nsp13, Nsp15, Orf3a, E, M, Orf8), signaling (Nsp8, Nsp13, N, Orf9b), RNA processing and regulation (Nsp8, N), ubiquitin ligases (Orf10), lipid modification (Spike), nuclear transport machinery (Nsp9, Nsp15, Orf6), mitochondria (Nsp4, Nsp8, Orf9c), cytoskeleton (Nsp1, Nsp13) and extracellular matrix (Nsp9). These host virus interactome could be a novel target for drugs such as chloroquine [79,114]. However, the researcher not identified the mechanisms by which chloroquine acts in COVID-19 cases. One explanation is that chloroquine targeted Sigma 1 and Sigma 2 receptors [3]. Azithromycin, Tigecycline Linezolid and chloramphenicol antibiotics exerted their effects against human ribosomes, components of which interact with the Nsp8 protein of

SARS-CoV-2 [3,115,116]. ACE2 inhibitors and non-steroidal antiinflammatory drugs may be tested for their role as treatment approach of COVID-19.

Table 2. Drugs and Chemical Substances that modulates SARS-CoV-2 interactors.

Drug/ Compound	Human gene	Viral target	Reference
Haloperidol	SIGMAR1; TMEM97	Nsp6; Orf9c	8
JQ1	BRD2/4	Envelop	9
RVX	BRD2/4	Envelop	9
Simitasertib	CSNK2A2	Nucleocapsid	10,11
TMCB	CSNK2A2	Nucleocapsid	12
Apicidin	HDAC2	Nsp5	13
Valproic acid	HDAC2	Nsp5	14,15,16
Bafilomycin A1	ATP6AP1 ATP6V1A	Nsp6 Membrane	17
E-52862	SIGMAR1	Nsp6	18
PD-144418	SIGMAR1	Nsp6	19
RS-PPCC	SIGMAR1	Nsp6	20
Pb28	SIGMAR1 TMEM97	Nsp6 Orf9c	21
Etacapone	COMT	Nsp7	22,23
Indomethacin	PTGES2	Nsp7	24
Metformin	NDUFs	Nsp7, Orf9c	25
Ponatinib	RIPK1	Nsp12	26
H-89	PRKACA	Nsp13	27
Merimepodib	IMPDH2	Nsp14	28
Migalastat	GLA	Nsp14	29
Mycophenolic acid	IMPDH2	Nsp14	30
Ribavirin	IMPDH2	Nsp14	31
XL413	DNMT1	Orf8	32
CCT365623	LOX	Orf8	33
Midostaurin	MARK2/3	Orf9b	34
Ruxolitinib	MARK2/3	Orf9b	35
Zinc 1775962367	DCTPP1	Orf9b	36
Zinc 4326719	DCTPP1	Orf9b	37
Zinc 4511851	DCTPP1	Orf9b	38
Zinc 95559591	MARK3 TBK1	Orf9b Nsp13	39

AC55541	**F2RL1**	**Orf9c**	**40**
AZ8838	**F2RL1**	**Orf9c**	**41**
AZ3451	**F2RL1**	**Orf9c**	**41**
Daunorubicin	**ABCC1**	**Orf9c**	**42**
GB110	**F2RL1**	**Orf9c**	**43**
S-Verapamil	**ABCC1**	**Orf9c**	**44**
ABBV-744	**BRD2/4**	**Envelop**	**45**
dBET6	**BRD2/4**	**Envelop**	**46**
MZ1	**BRD2/4**	**Envelop**	**47**
CPI-0610	**BRD2/4**	**Envelop**	**48**
Sapanisertib	**LARP1**	**Nucleocapsid**	**49,50**
Rapamycin	**LARP1** **FKBP15** **FKBP7/10**	**Nucleocapsid** **Nsp2** **Orf8**	**50,51**
Zotatifin	**EIF4E2/H**	**Nsp2**	**52**
Verdinexor	**NUPs** **RAE1**	**Nsp4** **Nsp9/Orf6**	**53**
Chloroquine	**SIGMAR1**	**Nsp6**	**54**
Dabrafenib	**NEK9**	**Nsp9**	**55**
WDB002	**CEP250**	**Nsp13**	**3**
Sanglifehrin	**IMPDH2**	**Nsp14**	**56**
FK-506	**FKBP7** **FKBP10**	**Orf8**	**57**
Pevonedistat	**CUL2**	**Orf10**	**58**
Ternatin4	**Translation**		**59**
4E2RCat	**Translation**		**60**
Tomivosertib	**Translation**		**61,62**
Compound 2	**Viral Transcription**		**63**
Compound 10	**Viral Transcription**		**64**
PS3061	**ER protein processing**		**65**
IHVR-19029	**ER protein processing**		**66,67**
Captopril	**Cell entry**		**68**
Lisinopril	**Cell entry**		**69**
Camostat	**Cell entry**		**70,71**
Nafamostat	**Cell entry**		**70,72**
Chloramphenicol	**Mitochondrial ribosome**		**73**

Tigecycline	**Mitochondrial ribosome**		**74**
Linezolid	**Mitochondrial ribosome**		**75**
Emtricitabine/ Tenovir			**2**
Hydroxychloroquine	**Blocking virus-cell membrane fusion**		**2**
Remdesivir		**RNA-dependent-RNA polymerase**	**76- 80**
Favibiravir ChiCTR2000029600		**RNA – dependent RNA polymerase**	**81**
Ivermectin		**Viral protease**	**82-85**
Lopinavir/ Ritonavir		**Viral protease**	**78,86**
APNO1 [Recombinant Human ACE2]	**Blocking virus-cell membrane fusion**		**87,88**
Hydroxychloroquine	**Blocking virus-cell membrane fusion**		**89-92**
Arbidol Hydrochloride [Umifenovir]	**Blocking virus-cell membrane fusion**		**93,94**
NK cells	**Enhancing innate immunity**		**95**
Recombinant interferon I			**96,97**
Mesenchymal Stem Cells	**Attenuating Inflammatory Response**		**98,99**
Intravenous Immunoglobulin	**Attenuating Inflammatory Response**		**100**

SARS-CoV-2-Specific Neutralizing Ab	**Attenuating Inflammatory Response**		**101,102**
Anti-C5a Monoclonal Ab	**Attenuating Inflammatory Response**		**103**
Blocking Interleukin-6 pathway	**Attenuating Inflammatory Response**		**104-108**
Thalidomide	**Attenuating Inflammatory Response**		**109,110**
Methyprednisoline	**Attenuating Inflammatory Response**		**7**
Fingolimod	**Attenuating Inflammatory Response**		**111**
Bevacizumab	**Symptomatic control**		**112**
EIDD-2801		**Nsp15, Orf1**	**113**
Combination of oseltamivir, favipiravir, and chloroquine		**Protease**	**2**
ASC09F + oseltamivir vs Ritonavir + oseltamivir vs Oseltamivir		**Protease**	**2**
Abidol hydrochloride vs Oseltamivir vs Lopinavir/Ritonavir		**Protease**	**2**

Modified from Gordon et al [3], ChEMBL [4], ZINC [5] and IUPHAR/BPS Guide to pharmacology [6], Tu et al [7]

In a recent study by Zhou et al.,[117] perform an integrative analysis of interactome networks associated with human coronaviruses and drugs targeting the components of these networks was applied to reveal 16 novel candidates for drug repurposing.

Zhou et al [117], presented a network-based methodology for systematic identification of putative repurposable drugs and drug combinations for potential treatment of SARS-CoV-2/2019-nCoV.

Integration of drug–target networks, HCoV–host interactions, HCoV induced transcriptome in human cell lines, and human protein–protein interactome network are essential for such identification. They suggested three potential drug combinations and sixteen repurposable drugs [Table.3], for targeting SARS-CoV-2/2019-nCoV. Although there is evidence reported in literature that predict their antiviral activity [Table 3], however, these suggested combinations and drug must be tested against SARS-CoV-2 in vitro and in clinical trials in animal models before their use in human.

Tu et al [7], in a review summarized the ongoing clinical trials of drugs against SARS-CoV-2 that are effective against other viruses. The drugs targets of action included: inhibition of the RNA-dependent RNA polymerase, inhibition of viral protease, blocking virus-cell fusion, enhancing the innate immunity, attenuating the inflammatory response, and symptomatic control. In addition, the evaluation of SARS-CoV-2 genome derived vaccines [Table 4]. These drugs either acting directly on virus replication, or as immunotherapy to potentiate innate immunity or by acting as inflammatory response dysregulator.

Gordon et al [3] in an extensive study identified 67 human proteins in host pathways targeted by 69 existing compounds currently being investigated or FDA-approved drugs [Table 2]. According to their study findings they suggest that SARS-CoV-2 during its replication cycle inhibit host innate immune response. Additionally, ubiquitin system may be a novel target for antiviral agents that to be tested for their activity on SARS-CoV-2. They suggested that Bafilomycin A1, Valproic acid, Apicidin, Haloperidol, Chloroquine, Centriole (CEP250), mycophenolic acid, Ribavirin, Merimepodib, Sanglifehrin A, Sapanisertib, Rapamycin and Metformin may be of predictive value in treating COVID-19.

Vaccine is the novel approach for control and prevention of viral infections including SARS-CoV-2, SARS-CoV, and MERS-CoV. However, the development of effective vaccine takes a long period. Vaccine development influenced by many factors such the safety, vaccine material antigenicity, coronaviruses diversity, and SARS-CoV-2 strains variation. At present (30th, April, 2020) there are more than 110 SARS-CoV-2 vaccines developed by universities and companies research groups under evaluation [118,125, Table 5]. In

order to induce an effective immune response that prevent infection or kill the virus after infection, 9 approaches were used in clinical trials or animal model. These approaches include: weakened virus vaccine, inactivated virus vaccine, replicating virus-vectors vaccine (weakened measles), non-replicating virus-vector vaccine (adenovirus), RNA vaccine, DNA vaccine, protein sub-unit vaccine, virus-like particles, and vaccines that used previously for other infectious diseases (BCG and polio vaccine) [118].

The vaccine activity map distribution of the active SARS-CoV-2 candidates at 9 th April, 2020, were in North America (36, 46%), in China (14, 18%), in Asia (excluding China, 14, 18%) and Australia, and in Europe (14, 18%) [119]. The vaccine development is a long lasting journey, difficult and expensive. "WHO has repeatedly warned countries against relying on a vaccine to end the current situation" [120]. However, we hope to develop an effective SARS-CoV02 to control or ameliorate the pandemic of the disease.

Sheahan et al [113] reported that EIDD-2801, a ribonucleoside -d-N4βanalog -hydroxycytidine has broad-spectrum antiviral activity against SARS-CoV, MERS-CoV, SARS-CoV-2, 2b or 2c bat-CoVs, and coronaviruses strains resistance to Remdesivir. The compound induced genetic mutations in viral RNA which attributed to inability of the virus to infect cells. In addition, to its broad-spectrum antiviral activity, the oral bioavilability of the drug addressed the suggestion of its potential antiviral activity against SARS-CoV-2 [113]. From the information mentioned in the above Tables, we concluded that the antiviral research concentrated on the drugs and compounds presented in Table 6. These compounds will induce the basic arms of the management of COVID-19 which include; antiviral activity, prevention of cytokines storm, attenuation of inflammatory responses, and enhancement of immune response.

In conclusion, although there are a global research works that evaluate the effectiveness of drugs/compound as therapeutic approach for COVID-19, however, to date none found to be with promising effect. Additionally, the vaccine evaluation takes a long period until the development of novel potential vaccine. The best approach to find an effective drug against SARS-CoV-2 infection is to test new compounds, not to relay on the testing of that used in another virus's treatment. The novel drugs are that which prevent viral attachment

with the host cell to get rid of immune and inflammatory harmful responses.

Table 3. Network-predicted repurposable drugs [118].

Drug name	Clinical use	Antiviral activity
Irbesartan	Antihypertensive	HBV, HDV
Toremifene	Antineoplastic	EBOV, MERS-CoV, SARS-CoV
Camphor	Antipruritic, Anti-infective	H1N1
Equilin	Estrogen	ZEPOV-GP/HIV
Mesalazine	Anti-inflammatory	EBV
Mercaptopurine	Antimetabolite, Antineoplastic	MERS-CoV, SARS-CoV
Paroxetine	Selective serotonin reuptake inhibitor	EBOV
Sirolimus	Immunosuppressant	ANDV,HCV
Carvedilol	Beta-blocker	EMCV
Colchicine	Anti-inflammatory	EBV
Dactinomycin	Antineoplastic	FECV
Melatonin	Hormone	EBOV, RSV
Quinacrine	Antimalarial, Antibiotic	EV71, EBOV
Eplerenone	Diuretic	Viral myocarditis
Emodin	Anthraquinones	HSV-1, HSV-2, HBV, CB4, SARS-CoV
Oxymetholone	Anabolic steroid	HIV
Sirolimus plus Dactinomycin		
Toremifene plus Emodin		
Mercaptopurine plus Melatonin		

CVB4 Coxsackievirus B4, HBV hepatitis B virus, HSV-1 and -2 herpes simplex viruses, HCV hepatitis C virus, EV71 enterovirus 71, HDV hepatitis delta virus, RSV respiratory syncytial virus, EBOV Ebola viruses, FECV feline enteric coronavirus, ZEBOV-GP Zaire Ebola virus glycoprotein, EMCV encephalomyocarditis

virus, HIV human immunodeficiency virus, ANDV Andes orthohantavirus, EBV Epstein-Barr virus.

Table 4. Targeted sites/ functions of the present clinical trials [7].

Target / Function	Drug / Chemical substance
Inhibiting the RNA-dependent RNA polymerase	Remdesivir
	Favipiravir
Inhibiting the viral protease	Ivermectin
	Lopinavir/Ritonavir
Blocking Virus–Cell Membrane Fusion	Recombinant Human Angiotensin-converting Enzyme 2 (APN01)
	Hydroxychloroquine
	Arbidol Hydrochloride (Umifenovir)
Enhancing the innate immune system	Natural Killer Cells
	Recombinant interferon
Attenuating the Inflammatory Response	Mesenchymal Stem Cells
	Intravenous Immunoglobulin
	SARS-CoV-2-Specific Neutralizing Antibodies
	Anti-C5a Monoclonal Antibody
	Blocking the Interleukin (IL)-6 Pathway
	Thalidomide
	Methylprednisolone
	Fingolimod
Symptomatic Control	Bevacizumab
Vaccine	mRNA-1273
	INO-4800
	ChAdOx1 nCoV-19
	Stabilized Subunit Vaccines
	Nanoparticle-Based Vaccines
	Pathogen-Specific Artificial Antigen-Presenting Cells

Table 5. SARS-CoV-2 [COVID-19] vaccines ongoing trial

Vaccine	Clinical Trial Code	Reference
mRNA-1273	NCT04283461	7
INO-4800		7,97,98
ChAdOX1 nCoV-19	NCT04324606	7,125
Stablized- Subunit vaccine		7,121
Nanoparticle-Based vaccine		7,122
Pathogen-Specific-Artificial Antigen- Presenting Cells	NCT04299724	7, 123
CORVaX12		124
Ad5-nCoV	NCT04313127	2
LV-SMENP-D	NCT04276896	2
Adenovirus 5 vector	ChiCTR2000031781; ChiCTR2000030906	125
DNA plasmid vaccine with Electroporation	NCT04336410	125
Inactivated	ChiCTR2000031809	125
Inactivated		125
mRNA	2020-001038-36	125
LNP - encapsulated mRNA	NCT04283461	125
DNA with electroporation		125
DNA plasmid vaccine		125
DNA vaccine		125
DNA vaccine		125
DNA vaccine		125
Plasmid DNA, Needle-Free Delivery		125
DNA plasmid vaccine		125
Inactivated + alum	NCT04352608	125
Inactivated		125
TBD		125
Inactivated + CpG 1018		125
Inactivated + CpG 1018		125
Codon deoptimized live attenuated vaccines		125

Codon deoptimized live attenuated vaccines		**125**
MVA encoded VLP		**125**
Replication defective Simian Adenovirus (GRAd) encoding SARS-CoV-2 S		**125**
Ad26		**125**
MVA-S encoded		**125**
Adenovirus-based NasoVAX expressing SARS2-CoV spike protein		**125**
Ad5 S (GREVAX™ platform)		**125**
Oral Ad5 S		**125**
Adenovirus-based + HLA matched peptides		**125**
Oral Vaccine platform		**125**
MVA expressing structural proteins		**125**
Dendritic cell-based vaccine		**125**
Parainfluenza virus 5 (PIV5) –based vaccine expressing the spike protein		**125**
Recombinant deactivated rabies virus containing S1		**125**
Capsid-like Particle		**125**
Drosophila S2 insect cell expression system VLPs		**125**
Peptide antigens formulated in lipid nanoparticle formulation		**125**
S protein		**125**
S protein +Adjuvant		**125**
VLP recombinant protein + Adjuvant		**125**
Native like Trimeric subunit Spike Protein vaccine		**125**

microneedle arrays S1 subunit		**125**
Peptide		**125**
Adjuvanted protein subunit (RBD)		**125**
Peptide		**125**
S protein		**125**
Ii-Key peptide		**125**
S protein		**125**
S protein (baculovirus production)		**125**
Full length recombinant SARS CoV -2 glycoprotein nanoparticle vaccine + Matrix M		**125**
gp-96 backbone		**125**
Molecular clamp stabilized Spike protein		**125**
Peptide vaccine		**125**
S1 or RBD protein		**125**
Subunit protein, plant produced		**125**
Recombinant protein, nanoparticles (based on S protein and other epitopes)		**125**
COVID-19 XWG-03 truncated S (spike) proteins		**125**
Adjuvanted microsphere peptide		**125**
Synthetic Long Peptide Vaccine candidate for S and M proteins		**125**
Oral E.coli-based protein expression system of S and N protein		**125**
Nanoparticle vaccine		**125**
Recombinant spike protein		**125**

with Advax adjuvant		
Spike –based		**125**
Recombinant S1-Fc fusion protein		**125**
Recombinant protein		**125**
Recombinant S protein in IC-BEVS		**125**
YF17D Vector		**125**
Measles Vector		**125**
Measles Vector		**125**
Measles Vector		**125**
Measles Virus (S, N targets)		**125**
Horsepox vector expressing S protein		**125**
Live viral vectored vaccine based on attenuated influenza virus backbone (intranasal)		**125**
Recombinant vaccine based on influenza A virus (intranasal)		**125**
Influenza vector expressing RBD		**125**
Replication- competent VSV chimeric virus technology (VSVΔG) delivering the SARS-CoV-2 Spike (S) glycoprotein		**125**
VSV-S		**125**
VSV vector		**125**
M2-deficient single replication (M2SR) influenza vector		**125**
LNP encapsulated mRNA cocktail encoding VLP		**125**
LNP encapsulated mRNA encoding RBD		**125**

Replicating Defective SARSCoV-2 derived RNAs		**125**
LNP encapsulated mRNA		**125**
Liposome encapsulated mRNA		**125**
Several mRNA candidates		**125**
mRNA		**125**
mRNA		**125**
mRNA		**125**
SaRNA		**125**
mRNA		**125**
mRNA in an intranasal delivery system		**125**
Virus-like particle, based on RBD displayed on virus-like particles		**125**
Plant-derived VLP		**125**
ADDomerTM multiepitope display		**125**
Unknown		**125**
VLP		**125**
Evlp		**125**
Unknown		**125**
Unknown		**125**
Unknown		**125**

Table 6 . Suggested Antiviral agents for evaluation against SARS-CoV-2.

Agent	Target	Reference
Emodin	ACE-2	126
α-Ketoamides	Viral protease	127
Corticosteroids	Attenuate inflammation	128
Corticosteroid ciclesonide	Nsp15	129
Remdesivir+ Hydroxychloroquine	RdRp/ Block Virus-Cell membrane fusion	7,130
Remdesivir + INFb	RdRp	131
Remdesivir + Ivermectin	RdRp/ Viral protease	7,131
Remedsivir +ACE-2 inhibitors	RdRp/ ACE-2 inhibition	132
Lamivudine	RdRp	133
Tenofovir disoproxil	RdRp	132
Emtricitabine, Alovudine, Apricitabine, Zidovudine, Stavudine and / or Zalcitabine	RdRp	132
Lopinavir/Ritonavir	Protease	134-136
Nanoparticle Antiviral Agents Delivery	Multiple	137
SARS-Cov-2- specific human monoclonal antibody	RBD	138
Cyclosprin A	Protein synthesis	139
D, L-lysine acetylsalicylate+glycine	Protein synthesis, RNA polymerase, Transcription	140
Saquinavir and Beclabuvir	Protease	141
Soluble recombinant ACE-2	ACE-2	142
Plant lectin	Entry	143
Zn	RNA polymerase	144
Neutralizing Antibodies Targeting S protein	Entry	145

small interfering RNA (siRNA) or antisense oligonucleotides (ASO)	**RNA genome**	**145**
ACE2 Fc	**S protein**	**145**
Flavonoids	**Protease Enhance Immunity**	**146**
IQ-SAM (1,2,3 and 4)	**Protease Spike protein**	
Favipiravir	**RdRp**	**147**
Umifenovir (Arbidol)	**Membrane fusion**	**148**
EIDD-2801	**Genome incorporation**	**113**

References

1. Ministry of Health Document, Iraq.
2. ClinicalTrials.gov: Federally-funded clinical studies related to COVID-19; WHO Trial Registry Network: COVID-19 studies from the ICTRP database; CDC: Information for Clinicians on Therapeutic Options for COVID-19 Patients.
3. Gordon DE, Jang GW, Bouhaddou M, Xu J, Obernier K, O'Meara MJ, Guo JZ, et al. A SARS-CoV-2-Human Protein-Protein Interaction Map Reveals Drug Targets and Potential Drug-Repurposing. bioRxiv preprint doi: https://doi.org/10.1101/2020.03.22.002386.
4. Gaulton A, Hersey A, Nowotka M, Bento AP, Chambers J, Mendez M, et al. The ChEMBL database in 2017. Nucleic Acids Res. 2017;45:D945–D954.
5. Sterling T, Irwin JJ. ZINC 15--Ligand Discovery for Everyone. J. Chem. Inf. Model. 2015;55:2324–2337.
6. Armstrong JF, Faccenda E, Harding SD, Pawson AJ, Southan C, Sharman JL, et al. The IUPHAR/BPS Guide to PHARMACOLOGY in 2020: extending immunopharmacology content and introducing the IUPHAR/MMV Guide to MALARIA PHARMACOLOGY. Nucleic Acids Res. 2020;48:D1006–D1021..
7. Tu YF, Chien CS, Yarrmshyn AA, Lin YY, Luo YH, Lin YT, et al. A review of SARS-CoV-2 and the ongoing clinical trials. Int J Mol Sci 2020;21(2657):1-19.

8. Hellewell SB, Bruce A, Feinstein G, Orringer J, Williams W, Bowen WD, et al. Rat liver and kidney contain high densities of sigma 1 and sigma 2 receptors: characterization by ligand binding and photoaffinity labeling. Eur J Pharmacol 1994;268:9–18.
9. McLure KG, Gesner EM, Tsujikawa L, Kharenko OA, Attwell S, Campeau E, et al. RVX-208, an inducer of ApoA-I in humans, is a BET bromodomain antagonist. PLoS One 2013;8:e83190.
10. Pierre F, Chua PC, O'Brien SE, Siddiqui-Jain A, Bourbon P, Haddach M, Michaux J, et al. Discovery and SAR of 5-(3-chlorophenylamino) benzo[c] [2,6] naphthyridine-8- carboxylic acid (CX-4945), the first clinical stage inhibitor of protein kinase CK2 for the treatment of cancer. J Med Chem. 2011;54:635–654.
11. Siddiqui-Jain A, Drygin D, Streiner N, Chua P, Pierre F, O'Brien SE, et al. CX-4945, an orally bioavailable selective inhibitor of protein kinase CK2, inhibits prosurvival and angiogenic signaling and exhibits antitumor efficacy. Cancer Res. 2010;70:10288–10298.
12. Janeczko M, Orzeszko A, Kazimierczuk Z, Szyszka R, Baier A. CK2α and CK2α' subunits differ in their sensitivity to 4,5,6,7-tetrabromo- and 4,5,6,7-tetraiodo-1H-benzimidazole derivatives. Eur J Med Chem. 2012;47:345–350.
13. Khan N, Jeffers M, Kumar S, Hackett C, Boldog F, Khramtsov N, et al. Determination of the class and isoform selectivity of small-molecule histone deacetylase inhibitors. Biochem J 2008;409: 581–589.
14. Göttlicher M, Minucci S, Zhu P, Krämer OH, Schimpf A, Giavara S, et al. Valproic acid defines a novel class of HDAC inhibitors inducing differentiation of transformed cells. EMBO J 2001;20: 6969–6978.
15. Kramer OH, Zhu P, Ostendorff HP, Golebiewski M, Tiefenbach J, Peters MA, et al. The histone deacetylase inhibitor valproic acid selectively induces proteasomal degradation of HDAC2. EMBO J 2003; 22:3411–3420.
16. Fass DM, Shah R, Ghosh B, Hennig K, Norton S, Zhao WN, et al. Effect of Inhibiting Histone Deacetylase with Short-Chain Carboxylic Acids and Their Hydroxamic Acid Analogs on Vertebrate Development and Neuronal Chromatin. ACS Med. Chem Lett 2010;2:39–42.

17. Gagliardi S, Nadler G, Consolandi E, Parini C, Morvan M, Legave MN, et al. 5-(5,6-Dichloro-2-indolyl)-2-methoxy-2,4-pentadienamides: novel and selective inhibitors of the vacuolar H+-ATPase of osteoclasts with bone antiresorptive activity. J Med Chem 1998;41:1568–1573.
18. Diaz JL, Fernandez A, Luengo M, Bordas M, Enrech R, Carro M, et al. Synthesis and biological evaluation of the 1-arylpyrazole class of σ(1) receptor antagonists: identification of 4-{2-[5-methyl-1-(naphthalen-2-yl)-1H-pyrazol-3-loxy]ethyl}morpholine (S1RA, E-52862). J Med Chem. 201;55:8211–8224.
19. Akunne HC, Whetzel SZ, Wiley JN, Corbin AE, Ninteman FW, Tecle H, et al. The pharmacology of the novel and selective sigma ligand, PD 144418. Neuropharmacology 1997;36:51–62.
20. Prezzavento O, Campisi A, Ronsisvalle S, Li Volti G, Marrazzo A, Bramanti V, et al. Novel sigma receptor ligands: synthesis and biological profile. J Med Chem. 2007;50:951–961.
21. Azzariti A, Colabufo NA, Berardi F, Porcelli L, Nisco M, Simone GM, et al. Cyclohexylpiperazine derivative PB28, a sigma2 agonist and sigma1 antagonist receptor, inhibits cell growth, modulates P-glycoprotein, and synergizes with anthracyclines in breast cancer. Mol Cancer Ther. 2006;5:1807–1816.
22. Nissinen E, Linden IB, Schultz E, Pohto P. Biochemical and pharmacological properties of a peripherally acting catechol-O-methyltransferase inhibitor entacapone. Naunyn Schmiedebergs Arch Pharmacol. 1992;346:262–266.
23. De Santi C, Giulianotti PC, Pietrabissa A, Mosca F, Pacifici GM. Catechol-O-methyltransferase: variation in enzyme activity and inhibition by entacapone and tolcapone. Eur J Clin Pharmacol. 1998;54:215–219.
24. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nat New Biol. 1971;231:232–235.
25. Wheaton WW, Weinberg SE, Hamanaka R, Soberanes S, Sullivan LB, Anso E, et al. Metformin inhibits mitochondrial complex I of cancer cells to reduce tumorigenesis. Elife 2014;3: e02242.
26. Najjar M, Suebsuwong C, Ray SS, Thapa RJ, Maki JL, Nogusa S, et al. Structure guided design of potent and selective ponatinib-based hybrid inhibitors for RIPK1. Cell Rep. 2015;10:1850–1860.

27. Chijiwa T, Mishima A, Haqiwara M, Sano M, Hayashi K, Inoue T, et al. Inhibition of forskolin-induced neurite outgrowth and protein phosphorylation by a newly synthesized selective inhibitor of cyclic AMP-dependent protein kinase, N-[2-(pbromocinnamylamino)ethyl]-5-isoquinolinesulfonamide (H-89), of PC12D pheochromocytoma cells. J Biol Chem. 1990;265:5267–5272.
28. Sintchak MD, Nimmesgern E. The structure of inosine 5'-monophosphate dehydrogenase and the design of novel inhibitors. Immunopharmacology 2000;47:163–184.
29. Asano N, Ishii S, Kizu H, Ikeda K, Yasuda K, Kato A, et al. In vitro inhibition and intracellular enhancement of lysosomal alpha-galactosidase A activity in Fabry lymphoblasts by 1-deoxygalactonojirimycin and its derivatives. Eur J Biochem. 2000; 267:4179–4186.
30. Carter SB, Franklin TJ, Jones DF, Leonard BJ, Mills SD, Turner RW, et al. Mycophenolic acid: an anti-cancer compound with unusual properties. Nature 1969;223:848–850.
31. Wittine K, Stipkovic BM, Makuc D, PLavec J, Kraljevic S, Sedic M, et al. Novel 1,2,4-triazole and imidazole derivatives of L-ascorbic and imino-ascorbic acid: synthesis, anti-HCV and antitumor activity evaluations. Bioorg Med Chem. 2012;20:3675–3685.
32. Koltun ES, Tsuhako AL, Brown DS, Aay N, Arcalas A, Chan V, et al. Discovery of XL413, a potent and selective CDC7 inhibitor. Bioorg Med Chem Lett. 2012;22:3727–3731.
33. Leung L, Niculescu-Duvaz D, Smithen D, Lopes F, Callens C, McLeary R, et al. Anti-metastatic Inhibitors of Lysyl Oxidase (LOX): Design and Structure-Activity Relationships. J Med Chem 2019;62:5863–5884.
34. Karaman MW, Herrgard S, Treiber DK, Gallant P, Atteridge CE, Campbell BT, et al. A quantitative analysis of kinase inhibitor selectivity. Nat Biotechnol. 2008;26:127–132.
35. Davis MI, Hunt JP, Herrgard S, Ciceri P, Wodicka LM, Pallares G, et al. Comprehensive analysis of kinase inhibitor selectivity. Nat Biotechnol. 2011;29:1046–1051.
36. Llona-Minguez S, Höglund A, Jacques SA, Johansson L, Calderón-Montaño JM, Claesson M, et al. Discovery of the First

Potent and Selective Inhibitors of Human dCTP Pyrophosphatase 1. J Med Chem. 2016;59:1140–1148.
37. Llona-Minguez, S, Höglund A, Wiita E, Almlöf I, Mateus A, Calderón-Montaño JM, et al. Identification of Triazolothiadiazoles as Potent Inhibitors of the dCTP Pyrophosphatase 1. J Med Chem. 2017;60:2148–2154.
38. Llona-Minguez S, Haggblad M, Martens U, Johansson L, Sigmundsson K, Lundback T, et al. Diverse heterocyclic scaffolds as dCTP pyrophosphatase 1 inhibitors. Part 2:Pyridone- and pyrimidinone-derived systems. Bioorg Med Chem Lett. 2017;27: 3219–3225.
39. McIver EG, Bryans J, Birchall K, Chugh J, Drake T, Lewis SJ, et al. Synthesis and structure-activity relationships of a novel series of pyrimidines as potent inhibitors of TBK1/IKKε kinases. Bioorg Med Chem Lett. 2012;22:7169–7173.
40. Seitzberg JG, Knapp AE, Lund BW, Mandrup Bertozzi S, Currier EA, Ma JN, et al. Discovery of potent and selective small-molecule PAR-2 agonists. J Med Chem. 2008;51:5490–5493.
41. Cheng RKY, Fiez-Vandal C, Schlenker O, Edman K, Aggeler B, Brown DG, et al. Structural insight into allosteric modulation of protease-activated receptor 2. Nature 2017;545:112–115.
42. Priebe W, Marta Krawczyk M, Kuo T, Yamane M, Savaraj N, Ishikawa T. Doxorubicin- and Daunorubicin-Glutathione Conjugates, but Not Unconjugated Drugs, Competitively Inhibit Leukotriene C4Transport Mediated byMRP/GS-XPump. Biochemical Biophysical Res Communications 1998;247:859–863.
43. Barry GD, Suen JY, Le GT, Cotterell A, Reid RC, Fairlie DP, et al. Novel agonists and antagonists for human protease activated receptor 2. J Med Chem. 2010;53:7428–7440.
44. Perrotton T, Trompier D, Chang XB, Di Pietro A, Baubichon-Cortay H. (R)- and (S)-verapamil differentially modulate the multidrug-resistant protein MRP1. J Biol Chem. 2007;282: 31542–31548.
45. Faivre EJ, McDaniel KF, Albert DH, Mantena SR, Plotnik JP, Wilcox D, et al. Selective inhibition of the BD2 bromodomain of BET proteins in prostate cancer. Nature 578;306–310.
46. Xu L, Chen Y, Mayakonda A, Koh L, Chong YK, Buckley DL, et al. Targetable BET proteins- and E2F1-dependent

transcriptional program maintains the malignancy of glioblastoma. Proc Natl Acad Sci. USA. 2018;115:E5086–E5095.
47. Zengerle M, Chan KH, Ciulli A. Selective Small Molecule Induced Degradation of the BET Bromodomain Protein BRD4. ACS Chem Biol 2015;10:1770–1777.
48. Albrecht BK, Gehling VS, Hewitt MC, Vaswani RG, Côté A, Leblanc Y, et al. Identification of a Benzoisoxazoloazepine Inhibitor (CPI-0610) of the Bromodomain and Extra-Terminal (BET) Family as a Candidate for Human Clinical Trials. J Med Chem. 2016; 59:1330–1339.
49. Schenone S, Brullo C, Musumeci F, Radi M, Botta M. ATP-competitive inhibitors of mTOR: an update. Curr Med Chem. 2011;18:2995–3014.
50. Fonseca BD, Jia JJ, Hollensen AK, Pointet R. LARP1 is a major phosphorylation substrate of mTORC1. bioRxiv (2018).
51. Toral-Barza L, Zhang WG, Lamison C, Larocque J, Gibbons J, Yu K, et al. Characterization of the cloned full-length and a truncated human target of rapamycin:activity, specificity, and enzyme inhibition as studied by a high capacity assay. Biochem Biophys Res Commun. 2005;332:304–310.
52. Thompson PA, Ernst JT, Eam B, Young NP, Fish S, Chen J, Barrera M, et al. Abstract 2698: eFT226, a potent and selective inhibitor of eIF4A, is efficacious in preclinical models of lymphoma. in Experimental and Molecular Therapeutics 2698–2698 (American Association for Cancer Research, 2019).
53. Jorquera PA, Mathew C, Pickens J, Williams C, Luczo JM, Tamir S, et al. Verdinexor (KPT-335), a Selective Inhibitor of Nuclear Export, Reduces Respiratory Syncytial Virus Replication In Vitro. J Virol. 2019;93(4): e01684-18.
54. Tesei A, Tesei A, Cortesi M, Zamagni A, Arienti C, Pignatta S, Zanoni M, Paolillo M, et al. Sigma Receptors as Endoplasmic Reticulum Stress 'Gatekeepers' and their Modulators as Emerging New Weapons in the Fight Against Cancer. Front Pharmacol. 2018;9:711.
55. Phadke M, Remsing Rix LL, Smalley I, Bryant AT, Luo Y, Lawrence HR, et al. Dabrafenib inhibits the growth of BRAF-WT cancers through CDK16 and NEK9 inhibition. Mol Oncol. 2018;12:74–88.

56. Pua KH, Stiles DT, Sowa ME, Verdine GL. IMPDH2 Is an Intracellular Target of the Cyclophilin A and Sanglifehrin A Complex. Cell Rep. 18, 432–442 (2017).
57. Nakamura T, Yabe D, Kanazawa N, Tashiro K, Sasayama S, Honjo, T. Molecular cloning, characterization, and chromosomal localization of FKBP23, a novel FK506-binding protein with Ca2+-binding ability. Genomics 1998;54:89–98.
58. Soucy TA, Smith PG, Milhollen MA, Berger AJ, Gavin JM, Adhikari S, Brownell JE, et al. An inhibitor of NEDD8-activating enzyme as a new approach to treat cancer. Nature 2009;458:732–736.
59. Carelli JD, Sethofer SG, Smith GA, Miller HR, Simard JL, Merrick WC, et al. Ternatin and improved synthetic variants kill cancer cells by targeting the elongation factor-1A ternary complex. Elife 2015;4: e10222.
60. Cencic R, Desforges M, Hall DR, Kozakov D, Du Y, Min J, et al. Blocking eIF4E-eIF4G interaction as a strategy to impair coronavirus replication. J. Virol. 85, 6381–6389 (2011).
- Reich SH, Sprengeler PA, Chiang GG, Appleman JR, Chen J, Clarine J, et al. Structure-based Design of Pyridone-Aminal eFT508 Targeting Dysregulated Translation by Selective Mitogen-activated Protein Kinase Interacting Kinases 1 and 2 (MNK1/2) Inhibition. J Med Chem. 2018;61:3516–3540.
62. Xu Y, Poggio M, Jin HY, Shi Z, Forester CM, Wang Y, et al. Translation control of the immune checkpoint in cancer and its therapeutic targeting. Nat Med. 2019;25:301–311.
63. Mackman RL, Steadman VA, Dean DK, Jansa P, Poullennec KG, Appleby T, et al. Discovery of a Potent and Orally Bioavailable Cyclophilin Inhibitor Derived from the Sanglifehrin Macrocycle. J Med Chem. 2018;61:9473–9499.
64. Rutaganira FU, Fowler ML, McPhail JA, Gelman MA, Nguyen K, Xiong A, et al. Design and Structural Characterization of Potent and Selective Inhibitors of Phosphatidylinositol 4 Kinase IIIβ. J Med Chem. 2016;59:1830–1839.
65. Shah PS, Link N, Jang GM, Sharp PP, Zhu T, Swaney DL, et al. Comparative Flavivirus-Host Protein Interaction Mapping Reveals Mechanisms of Dengue and Zika Virus Pathogenesis. Cell 2018;175:1931–1945.e18.

66. Ma J, Wu S, Zhang X, Guo F, Yang K, Guo J, et al. Ester Prodrugs of IHVR-19029 with Enhanced Oral Exposure and Prevention of Gastrointestinal Glucosidase Interaction. ACS Med. Chem. Lett. 2017;8:157–162.
67. Ma J, Zhang X, Soloveva V, Warren T, Guo F, Wu S, et al. Enhancing the antiviral potency of ER α-glucosidase inhibitor IHVR-19029 against hemorrhagic fever viruses in vitro and in vivo. Antiviral Res. 2018;150:112–122.
68. Michaud A, Williams TA, Chauvet MT, Corvol P. Substrate dependence of angiotensin Iconverting enzyme inhibition: captopril displays a partial selectivity for inhibition of N-acetyl-seryl-aspartyllysyl-proline hydrolysis compared with that of angiotensin I. Mol Pharmacol. 1997;51:1070–1076.
69. Natesh R, Schwager SLU, Sturrock ED, Acharya KR. Crystal structure of the human angiotensin-converting enzyme-lisinopril complex. Nature 2003;421:551–554.
70. Hoffmann M, Weber HK, Kruger N, Muller M, Drosten C, Pohlmann S. The novel coronavirus 2019 (2019-nCoV) uses the SARS-coronavirus receptor ACE2 and the cellular protease TMPRSS2 for entry into target cells. bioRxiv 2020.01.31.929042.
71. Kawase M, Shirato K, van der Hoek L, Taguchi F, Matsuyama S. Simultaneous treatment of human bronchial epithelial cells with serine and cysteine protease inhibitors prevents severe acute respiratory syndrome coronavirus entry. J Virol. 2012;86:6537–6545.
72. Yamamoto M, Yamamoto M, Matsuyama S, Li X, Takeda M, Kawaguchi Y, et al. Identification of Nafamostat as a Potent Inhibitor of Middle East Respiratory Syndrome Coronavirus S Protein-Mediated Membrane Fusion Using the Split-Protein-Based Cell-Cell Fusion Assay. Antimicrob. Agents Chemother. 2016;60:6532–6539.
73. Kandasamy J, Atia-Glikin D, Shulman E, Shapira K, Shavit M, Belakhov V, et al. Increased selectivity toward cytoplasmic versus mitochondrial ribosome confers improved efficiency of synthetic aminoglycosides in fixing damaged genes: a strategy for treatment of genetic diseases caused by nonsense mutations. J Med Chem. 2012;55:10630–10643.

74. Martin TD, Cook DR, Choi MY, Li MZ, Haigis KM, Elledge SJ, et al. A Role for Mitochondrial Translation in Promotion of Viability in K-Ras Mutant Cells. Cell Rep. 2017:20:427–438.
75. Nagiec EE, Wu L, Swaney SM, Chosay JG, Ross DE, Brieland JK, et al. Oxazolidinones inhibit cellular proliferation via inhibition of mitochondrial protein synthesis. Antimicrob Agents Chemother. 2005;49:3896–3902.
76. Mulangu S, Dodd LE, Davey RT, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of Ebola virus disease therapeutics. N Engl J Med. 2019;381:2293–2303.
77. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. Sci Trans Med. 2017; 9: eaal3653.
78. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. mBio 2018;9(2): e00221-18.
79. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. Cell Res. 2020; 30:269–271.
80. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First Case of 2019 Novel Coronavirus in the United States. New Engl J Med. 2020;382:929–936.
81. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. Proc Jpn Acad Ser. B 2017;93:449–463.
82. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin alpha/beta-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. Biochem J. 2012;443:851–856.
83. Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, Jans DA. The broad spectrum antiviral ivermectin targets the host nuclear transport importin alpha/beta1 heterodimer. Antiviral Res 2020;104760.
84. Caly L, Wagstaff K, Jans DA. Nuclear trafficking of proteins from RNA viruses: Potential target for antivirals? Antivir Res. 2012;95:202–206.

85. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. Antivir. Res. 2020;104787.
86. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. New Engl J Med. 2020. NEJM.org.
87. Vanessa Monteil HK, Patricia P, Astrid H, Reiner A, Wimmer MS, Alexandra L, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell Press 2020.
88. Khan A, Benthin C, Zeno B, Albertson TE, Boyd J, Christie JD, et al. A pilot clinical trial of recombinant human angiotensin-converting enzyme 2 in acute respiratory distress syndrome. Crit Care 2017;21(1):234.
89. Savarino A, Boelaert JR, Cassone A, Majori G, Cauda R. Effects of chloroquine on viral infections: An old drug against today's diseases. Lancet Infect Dis. 2003;3:722–727.
90. Vincent MJ, Bergeron É, Benjannet S, Erickson BR, Rollin P, Ksiazek TG, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virol J 2005;2:69.
91. Gautret P, Lagier JC, Parola P, Hoang VT, Meddeb L, Mailhe M, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: Results of an open-label non-randomized clinical trial. Int. J. Antimicrob. Agents 2020;105949.
92. Molina JM, Delaugerre C, Goff JL, Mela-Lima B, Ponscarme D, Goldwirt L, de Castro N. No benefit of hydroxychloroquine and azithromycin in people hospitalised with COVID-19. Med Mal Infect. 2020. pii: S0399-077X(20)30085-8.
93. Kadam RU, Wilson IA. Structural basis of influenza virus fusion inhibition by the antiviral drug Arbidol. Proc Natl Acad Sci. USA 2016;114:206–214.
94. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. medRxiv 2020.
95. Chen J, Lau YF, Lamirande EW, Paddock CD, Bartlett JH, Zaki SR, et al. Cellular Immune Responses to Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) Infection in Senescent BALB/c Mice: CD4+ T Cells Are Important in Control of SARS-CoV Infection. J Virol. 2009;84:1289–1301.

96. Cinatl J, Morgenstern B, Bauer G, Chandra P, Rabenau H, Doerr HW. Treatment of SARS with human interferons. Lancet 2003; 362:293–294.
97. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, Brown AJ, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nat Commun. 2020;11:1–14.
98. Lee JW, Gupta N, Serikov V, Matthay MA. Potential application of mesenchymal stem cells in acute lung injury. Expert Opin Boil. 2009;9:1259–1270.
99. Li Y, Xu J, Shi W, Chen C, Shao Y, Zhu L, et al. Mesenchymal stromal cell treatment prevents H9N2 avian influenza virus-induced acute lung injury in mice. Stem Cell Res. 2016;7:159.
100. Jolles S, Sewell WAC, Misbah SA. Clinical uses of intravenous immunoglobulin. Clin Exp Immunol. 2005;142:1–11.
101. Zhou G, Zhao Q. Perspectives on therapeutic neutralizing antibodies against the Novel Coronavirus SARS-CoV-2. Int J Boil Sci. 2020;16:1718–1723.
102. Love JC, Gupta NT, Ogunniyi AO, Zimnisky RM, Qian F, Yao Y, et al. Neutralizing antibodies against West Nile virus identified directly from human B cells by single-cell analysis and next generation sequencing. Integr Boil. 2015;7:1587–1597.
103.Guo RF, Ward PA. Role of c5a in inflammatory responses. Ann Rev Immunol. 2005;23:821–852.
104. Voiriot G, Razazi K, Amsellem V, Van Nhieu JT, Abid S, Adnot S, et al. Interleukin-6 displays lung anti-inflammatory properties and exerts protective hemodynamic effects in a double-hit murine acute lung injury. Respir Res. 2017:18:64.
105. Herold T, Jurinovic V, Arnreich C, Hellmuth JC, Bergwelt-Baildon M, Klein M, et al. Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. medRxiv 2020.
106. Rose-John S, Waetzig GH, Scheller J, Grotzinger J, Seegert D. The IL-6/sIL-6R complex as a novel target for therapeutic approaches. Expert Opin. Ther Targets 2007;11:613–624.
107. Rose-John S. IL-6 Trans-Signaling via the Soluble IL-6 Receptor: Importance for the Pro-Inflammatory Activities of IL-6. Int J Boil Sci. 2012;8:1237–1247.

108. Shirley M, Deeks ED. Sarilumab: A Review in Moderate to Severe Rheumatoid Arthritis. Drugs 2018;78:929–940.
109. Vargesson, N. Thalidomide-induced teratogenesis: History and mechanisms. Birth Defects Res. Part C. Embryo Today Rev. 2015;105:140–156.
110. Zhu H, Shi X, Ju D, Huang H, Wei W, Dong, X. Anti-Inflammatory Effect of Thalidomide on H1N1 Influenza Virus-Induced Pulmonary Injury in Mice. Inflamm. 2014;37:2091–2098.
111. Pelletier D, Hafler DA. Fingolimod for Multiple Sclerosis. New Engl J Med. 2012;366:339–347.
112. Thickett D, Armstrong L, Christie SJ, Millar AB. Vascular Endothelial Growth Factor May Contribute to Increased Vascular Permeability in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2001;164:1601–1605.
113. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, Agostini ML, et al. An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. Science Translational Medicine 2020:12(541): eabb5883.
114. Gao J, Tian Z, Yang X. Breakthrough: Chloroquine phosphate has shown apparent efficacy in treatment of COVID-19 associated pneumonia in clinical studies. Biosci Trends 2020;14: 72–73.
115. McKee EE, Ferguson M, Bentley AT, Marks TA. Inhibition of mammalian mitochondrial protein synthesis by oxazolidinones. Antimicrob Agents Chemother.2006; 50:2042–2049.
116. Skrtić M, Sriskanthadevan S, Jhas B, Gebbia M, Wang X, Wang Z, et al. Inhibition of mitochondrial translation as a therapeutic strategy for human acute myeloid leukemia. Cancer Cell 2011;20:674–688.
117. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. Cell Discov 2020;6:14–18.
118. Gallawy E. The race for coronavirus vaccines: a graphical guide. Nature 2020;580:576-577.
119. Le TT, Andreadakis Z, Kumar A, Roman RG, Tollfsen S, Saville M, et al. The COVID-19 vaccine development landscape. Nature

Review Drug Discovery, 9 April, 2020. https://www.nature.com/articles/d41573-020-00073-5

120. Mahase E. Covid-19: What do we know so far about a vaccine? BMJ 2020;369:m1679 doi: 10.1136/bmj.m1679.
121. Chappell K, Watterson D, Young P. Rapid response pipeline for stabilized subunit vaccines. In Proceedings of the Vaccine Technology VII, Mont Tremblant, QC, Canada, 17–22 June 2018.
122. Al-Halifa S, Gauthier L, Arpin D, Bourgault S, Archambault D. Nanoparticle-Based Vaccines Against Respiratory Viruses. Front Immunol. 2019;10:22.
123. Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, Xu H. Positive RT-PCR Test Results in Patients Recovered From COVID-19. JAMA 2020.
124. https://thefly.com/landingPageNews.php?id=3065899&headline=ONCS-OncoSec-jumps-as-traders-circulate-CORVax-vaccine-fact-sheet. https://www.who.int/blueprint/priority-diseases/key-action/Novel_Coronavirus_Landscape_nCoV_11April2020.PDF
125. WHO. DRAFT landscape of COVID-19 candidate vaccines – 30 April 2020. https://www.who.int/who-documents-detail/draft-landscape-of-covid-19-candidate-vaccines (Accessed 2/5/2020).
126. Schwarz S, Wang K, Yu W, Sun B, Schwarz W. Emodin inhibits current through SARS-associated coronavirus 3a protein. Antiviral Res. 2011 Apr;90(1):64-9. doi: 10.1016/j.antiviral.2011.02.008. Epub 2011 Feb 26. PMID: 21356245; PMCID: PMC7114100.
127. Zhang L, Lin D, Kusov Y, Nian Y, Ma Q, Wang J, et al. α-Ketoamides as Broad-Spectrum Inhibitors of Coronavirus and Enterovirus Replication: Structure-Based Design, Synthesis, and Activity Assessment. J Medicinal Chemistry, 2020;acs. jmedchem. 9b01828.
128. Russell B, Moss C, George G, Santaolalla A, Cope A, Papa S, Van Hemelrijck M. Associations between immune-suppressive and stimulating drugs and novel Covid-19 – a systematic review of current evidence ecancer 14 1022 https://doi.org/10.3332/ecancer.2020.1022.
129. Matsuyama S, Kawase M, Shimojima M, Fuku S, Ujike M, Kamitani W, et al. The inhaled corticosteroid ciclesonide blocks

coronavirus RNA replication by targeting viral NSP15. bioRxiv 2020:03.11.987016.
130. Sheahan TP, Sims AC, Graham RL, Menachery VD, Gralinski LE, Case JB, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses Sci Transl Med. 2017; 9(396): doi:10.1126/scitranslmed.aal3653.
131. Sheahan T, Sims A, Leist S, Schäfer A, Won J, Brown A, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. Nature Communications. 2020;11:222. 10.1038/s41467-019-13940-6.
132. Chhikara BS, Rathi B, Singh J, Poonam G. Corona virus SARS-CoV-2 disease COVID-19: Infection, prevention and clinical advances of the prospective chemical drug therapeutics. Chem Biol Lett. 2020;7(1):63-72.
133. Chang Y, Tung Y, Lee K, Chen T, Hsiao Y, Chang H, et al. Potential Therapeutic Agents for COVID-19 Based on the Analysis of Protease and RNA Polymerase Docking. Preprints 2020, 2020020242. (doi: 10.20944/preprints202002.0242.v1).
134. Singh J, Chhikara BS. Comparative global epidemiology of HIV infections and status of current progress in treatment. Chem Biol Lett 2014;1(1):14–32.
135. Yao TT, Qian JD, Zhu YZ, Wang Y, Wang GQ. A Systematic Review of Lopinavir Therapy for SARS Coronavirus and MERS Coronavirus-A Possible Reference for Coronavirus Disease-19 Treatment Option. J Med Virol. 2020;10.1002 /jmv.25729.
136. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the index patient who caused tertiary transmission of coronavirus disease 2019 in Korea: The application of lopinavir/ritonavir for the treatment of COVID-19 pneumonia monitored by quantitative RT-PCR. J Korean Med. Sci.2020, 35 (6), e79–e79.
137. Chhikara BS, Varma RS. Nanochemistry and Nanocatalysis Science: Research advances and future perspective. J Mater Nanosci. 2019;6(1):1–6.
138. Tian X, Li C, Huang A, Xia S, Lu S, Shi Z, et al. Potent binding of 2019 novel coronavirus spike protein by a SARS coronavirus-

specific human monoclonal antibody. Emerg. Microbes Infect. 2020;9(1):382–385.
139. de Wilde AH, Zevenhoven-Dobbe , Meer Y, Thiel V, Narayanan K, Makino S, et al. Cyclosporin A inhibits the replication of diverse coronaviruses. J Gen Virol 2011;92:2542-8.
140. Muller C, Karl N, Ziebuhr J, Pleschka S. D. L-lysine acetyldsalicylate+glycine impairs coronavirus replication. J Antivir Antiretrovir 2016;8(4):142-50.
141. Talluri S. Virtual High Throughput Screening Based Prediction of Potential Drugs for COVID-19. Preprints 2020;2020020418 (doi: 10.20944/preprints202002.0418.v1).
142. Daniel Batlle, Jan Wysocki, Karla Satchell; Soluble angiotensin-converting enzyme 2: a potential approach for coronavirus infection therapy?. Clin Sci (Lond) 2020; 134 (5): 543–545.
143. Mitchell CA, Ramessar K, O'Keefe BR. Antiviral lectins: Selective inhibitors of viral entry. Antiviral Res. 2017;142:37-54.
144. te Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog. 2010;6(11):e1001176.
145. Kruse RL. Therapeutic strategies in an outbreak scenario to treat the novel coronavirus originating in Wuhan, China. F1000Res. 2020 Jan 31;9:72. doi: 10.12688/f1000research.22211.2. PMID: 32117569; PMCID: PMC7029759.
146. Sawikowska A. Meta-analysis of flavonoids with antiviral potential against coronavirus. Biometrical Letters.2020; 10.2478/bile-2020-0002.
147. Bryner J. Flu drug used in Japan shows promise in treating COVID-19.live Science, 18/3/2020. https://www.livescience. com/flu-drug-could-treat-coronavirus.html
148. Chen C, Huang J, Cheng Z, Wu J, Chen S, Zhang Y, et al. Favipiravir versus Arbidol for COVID-19: A Randomized Clinical Trial. https://www.medrxiv.org/content/10.1101/2020.03.17. 20037432 v1.full.pd