



# Coronavirus Current and New Potential Therapeutic Targets: A Review

Jwan O. Abdulsattar<sup>1</sup>, Saad T. Mutlk<sup>2</sup>, and Ban O. Abdulsattar<sup>3</sup>

<sup>1</sup> Chemistry Department, College of Science, Mustansiriyah University, Baghdad, Iraq.

<sup>2</sup> Biology Department, College of Science, University of Anbar, Anbar, Iraq.

<sup>3</sup> Department of Biology, College of Science, Mustansiriyah University, Baghdad, Iraq.

## ARTICLE INFO

Received: 2 / 6 / 2021

Accepted: 14 / 10 / 2021

Available online: 21 / 12 / 2021

DOI: [10.37652/juaps.2022.172436](https://doi.org/10.37652/juaps.2022.172436)

### Keywords:

Coronavirus, Therapies, Structural proteins, Non-structural proteins, Antiviral drugs, Vaccines,

Copyright©Authors, 2021, College of Sciences, University of Anbar. This is an open-access article under the CC BY 4.0 license (<http://creativecommons.org/licenses/by/4.0/>).



## ABSTRACT

The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emergence in late 2019 marked the introduction of a highly spread viral pathogen threatening human population globally. The new virus is closely related genetically and clinically to severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV). There are no specific antiviral drugs approved against human coronavirus infection and all treatments are supportive. The genome of coronavirus contains several open reading frames (ORFs) that encode both non-structural proteins (nsp) and structural proteins. Most of the encoded proteins have been reported as multifunctional proteins and plays a specific role in coronavirus (CoV) replication and assembly. This review focuses on the potential vaccine and antiviral targets for coronavirus, including different proteins and genes. Understanding the current targets and discovering new possible therapeutic targets will help toward developing effective vaccines and antiviral drug against current SARS-CoV-2 outbreak and possible future outbreak.

## 1. INTRODUCTION

Coronaviruses are enveloped, single, non-segmented, and positive sense RNA viruses. The genome ranging from 27 kb - 32 kb which is considered to be one of the largest genomes among the RNA viruses (1), that are classified under the order Nidovirales, which includes four families, Coronaviridae, Roniviridae, Arteriviridae and Mesonviridae (2-4). The Coronaviridae contain two subfamilies Orthocoronavirinae and Letovirinae. The new emerged SARS-CoV-2 virus belongs to the Orthocoronavirinae subfamily (5). Within the coronaviridae family, there are four genera including alphacoronavirus, betacoronavirus, gammacoronavirus, and delta coronavirus recognized on the base of genotypic and serological differences. The coronaviruses are a group of lethal zoonotic viruses infecting both humans and animals with economic importance such as pigs and chickens, threatening domestic animal industry with great losses and human population in worldwide with multiple outbreaks (6,7). This group gained their name from the presence of a club-like spike projecting from its surface. They are commonly associated with respiratory infection in addition to enteric, hepatic, and neurological diseases with variability from mild to severe infections in multiple host species (2,8).

\*Corresponding author at: Biology Department / College of Science / University of Anbar, Anbar, Iraq Tel.: +964 7821688893; E-mail address: [saad.t.mutalk@uoanbar.edu.iq](mailto:saad.t.mutalk@uoanbar.edu.iq)

The first human coronavirus-causing outbreak occurred in November 2002 in southern China. The causative agent was named a severe acute respiratory syndrome coronavirus SARS-CoV causing severe acute respiratory syndrome (SARS) disease which was described as an epidemic disease (9,10). The second outbreak in 2012 occurred in the Middle East region (10). The etiological agent was named Middle East Respiratory Syndrome coronavirus (MERS-CoV) causing severe acute respiratory disease with multi-organ failure and high case fatality rate. Afterwards, a third coronavirus outbreak has occurred in the late of 2019 and infected human populations. In the beginning, the virus was named 2019-nCoV which was identified in Wuhan of China, in people visiting seafood or wet market (12) causing coronavirus disease 2019 (COVID-19). Special Coronaviridae Study Group (CSG) in the International Committee on Taxonomy of Viruses named the virus SARS-CoV-2 (13). The other four coronaviruses causing respiratory illness to human are (HCoV-NL63, HCoV-HKU1, HCoV-OC43 and HCoV-229E) (14). There is no proven antiviral drug by U.S Food and Drug Administration (FDA) against CoV infecting human and different vaccines are still being explored. This paper reviews different strategies on the current investigated therapeutic options against CoV infection and new promising targets for antiviral drug discovery and vaccines development.

## **2. THERAPIES AGAINST CORONAVIRUS INFECTION**

Several strategies have been developed to treat coronavirus infections. The feasible options against CoV infection can be divided into the vaccine and antiviral drug option. In the field of vaccine development, there are various strategies used to develop of an effective vaccine against CoV infection including the use of inactivated whole viruses, live-attenuated viruses (15), viral vector-based vaccines, subunit based vaccines (16,17), recombinant vectored for SARS-CoV spike protein and DNA vaccines (18–21) which were evaluated on animals only. On the other side of developing antiviral drugs against CoV infection, there are massive efforts in the production of antivirals that aimed to prevent and treat CoV infection. However, many difficulties stand up in developing effective antiviral. For example, developed drugs are tested on experimental animals, not on human, the crystal structure of all human coronavirus proteins is not solved. All licensed vaccines might control spread of the virus and reduce mortality rates but with the new emergence of new strains, the global control of COVID-19 will not be achieved and still we need to understand role of each virus gene and protein to develop fast and new systematic approaches in anti-CoV drug discovery.

In the discovery of potential anti-CoV treatment against human CoV infection, three main approaches are generally applied. The first approach includes a broad-spectrum inhibitors test that already exists and used to treat infection of other viruses. The combination of lopinavir/ ritonavir, which is used as a protease inhibitor in the treatment for human immunodeficiency virus (HIV) patients has been reported as a successful choice for the treatment of SARS and MERS patients (22–25). However, the inhibitory effect was only observed in animals and cell lines. Understanding lopinavir binding mode to the coronavirus main protease enzyme is still needed to improve inhibitory efficacy since the coronavirus genome encodes a cysteine protease (3C-like protease), not an aspartic protease related to the HIV protease (26). Several studies tested effects of Interferon (INFs) such as IFN- $\alpha$  and - $\beta$ , II (IFN- $\gamma$ ), ribavirin and cyclophilin inhibitors against SARS and MERS infection in-vitro (27–29) by using standard assays such as virus plaque formation and virus yield. Other showed that use of a broad-spectrum antiviral agent such as Nitazoxanide and teicoplanin (an inhibitor of Cathepsin L) might inhibit MERS- CoV in vitro (30,31). However, important questions such as side effects, dosing and specify remains to be answered. An anti-malarial drug chloroquine (CQ) and its derivative Hydroxychloroquine (HCQ) also revealed to inhibit SARS-2 infection that acts indirectly which decrease production of cytokines (32–34). Screening in pre-existing chemical libraries or large databases containing information

on many existing compounds (34–37) is the second approach. The advantage of this approach is based on the fast method for inhibitors identification through virtual or high-throughput screening of identified inhibitors but further evaluation such as antiviral assays, an effective concentration (EC50) and further studies are needed for developing one of these potent inhibitors. The third approach is based on developing novel, specific agents against coronavirus specific proteins and genes such as specific viral enzymes inhibitors, monoclonal antibodies and small interfering RNA (siRNA) molecules. However, further randomized clinical trials are necessary (39–41).

## **3. NON-STRUCTURAL PROTEINS AS A THERAPEUTIC TARGET**

Among coronavirus nonstructural proteins, protease (nsp3 and nsp5), the RdRp (nsp12) and the helicase (nsp13) are the main targets for the development of an antiviral drug against coronavirus infection. One of the main targets is a protease (Mpro, also called the 3C-like protease, 3CLpro) and the papain-like protease (PLpro) which generates non-structural proteins involved in viral replication (38,39). The Mpro and PLpro are encoded by ORF1 of the coronavirus genome and responsible for processing the huge polyproteins pp1a and pp1ab into mature non- structural proteins (nsps) (40). Many inhibitors have been designed against coronavirus protease based on crystal structures and high throughput screening but more animal studies are needed and other preclinical studies should be included (41). For example, several natural and synthetic compounds that is known for its inhibitory activity against SARS-CoV PLpro including small molecule inhibitors, thiopurine compounds, natural products, zinc ion and zinc conjugate inhibitors and naphthalene inhibitors (42) have been developed (43–46). A recent study by Kumar et al outlined the use of different peptidomimetic inhibitors of enterovirus that could inhibit SARS and MERS 3CLpro (47).

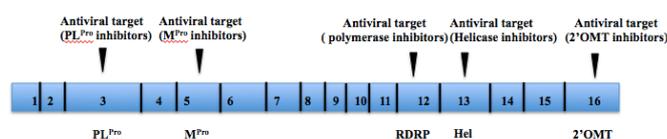
Nevertheless, some of these inhibitors have not validated in additional studies such as antiviral activity, animal studies or human in vivo evaluation. The solved crystal structure of SARS-CoV-2 main protease allowed scientist to start computationally screening in a compound library scan for over 687 million compounds for binding to the main protease of SARS-CoV-2. They reported a list of the potential drug-like compounds that are known to bind to Mpro of SARS-CoV and substructures as template molecules (48) which needs further experimental validation and optimization. The success of using available therapies for SARS-CoV and MERS-CoV to the SARS-CoV-2 with a similarity about 79% from SARS-CoV and 50% from MERS-CoV (49) is a challenge in treatment COVID-19 disease. A potential therapeutic agent Lopinavir/ritonavir (LPV/RTV) which approved since 2000 to HIV viral infection and showed a promising result against SARS-CoV

and MERS-CoV (22,50,51) is suggested to treat COVID-19 patients. A study of 199 patients confirmed with SARS-2 infection received lopinavir–ritonavir twice a day for 14 days observed no benefit from this treatment beyond standard care (52). The RNA-dependent RNA polymerase (RdRp) and helicase, which plays an important role in the transcription and replication of the virus (53,54) is another potential target for antiviral therapy. For COVID-19 and other CoV including SARS and MERS, Remdesivir (adenosine analogue) that is developed against Ebola virus originally is proposed as a promising antiviral drug. According to in-vitro studies including cultivation in cells (Vero E6 cells and Huh-7 cells), mice and non-human primates (NHP) models, Remdesivir inhibit RdRp resulting in pre-mature termination by incorporating with the new viral RNA chain (55,56).

However, to evaluate antiviral activity of this nucleoside further in-vivo studies are recommended to insure it is safety and effectiveness. Ivermectin is another approved drug used against a wide range of viruses is proposed as a treatment for COVID-19 infection. A recent study proposed Ivermectin has ability to inhibit nuclear import of coronavirus protein. The study showed that RNA of SARS-2 were reduced approximately 5000 folds within 48 hours (57). However, exact mechanism is not fully understood and further investigation is required. Ribavirin is a guanine analogue that has been known for it is antiviral activity by inhibiting viral RdRp in a variety of both a DNA and RNA viruses. However, adverse effects including hemolytic anemia limited it is use (58,59). A study developed a library of spirocyclic nucleosides that show close similarity structure to ribavirin is a promising approach to find safer and closely related ribavirin drug. The proposed nucleosides were tested in-vitro for their antiviral activity using MHV (Murine Hepatitis Virus) as a model (60). Helicase gene (nsp13) is well known as one of the most conserved protein across coronavirus four genera (61). Helicase enzyme plays a vital role in the replication and proliferation process by unwinding double-stranded nucleic acids into single strand in an ATP dependent manner. For this reason, helicase is proposed as attractive target for antiviral therapy. A study by Gordon indicted that SARS-CoV-2 helicase interact with human proteins (62). However, the lack of crystal structure for this enzyme, unsuccessful attempts to obtain the active form are the main problems to be considered when proposing helicase as a target for antiviral drug discovery.

The capping process in a variety of coronavirus is a promising target for the development of an antiviral drug against CoV infection. The capping process is an essential post-transcriptional step for viral RNA translation by host ribosomes an addition to it is role in distinguishing between self mRNA and host mRNA (63). The 2'-O

methyltransferase (2'-O MTase) enzyme that is located in non-structural protein 16 (nsp16) is one of the multiple enzymes required for cap structure formation, this enzyme is usually conserved (64). Several studies indicated that small molecules such as S-adenosyl-l-homocysteine, sinefungin, and aurintricarboxylic acid (ATA) (65–67) can inhibit nsp16 activity for CoV by interfering the interaction between nsp16/ nsp10 and nsp16/ nsp14. Another promising approach is limiting the 2'-O MTase activity by targeting active sites such as the binding site of nsp16 with nsp10 which is required for 2'-O MTase stability and activity (68). A 2'-O MTase activity of SARS-CoV could be inhibited by



short two peptides derived from the interaction domains of nsp10 (69). However, substantial research questions remain to be the answer and further understanding of 2'-O MTase activity is required for development of specific inhibitors based on targeting 2'-O MTase activity.

Figure 1. Schematic presentation of the coronavirus non-structural proteins with candidate antiviral targets. Abbreviations: PLPro, papin like protease; Mpro, main protease; RDRP, RNA dependent RNA polymerase; Hel, Helicase; 2'OMT, methyltransferase.

Overall, the developed antivirals against protease, polymerase and methyltransferase are not effective in clinical trials (70,71) and more investigations are required.

#### 4. STRUCTURAL PROTEINS AS A THERAPEUTIC TARGET

Although coronavirus nonstructural proteins such as proteases, polymerases and helicases are the main targets for the discovery and development of antiviral drugs by scientists however, the coronavirus structural proteins that compose virus virion have also been attractive targets for development of vaccines and antivirals. Coronavirus encodes four structural proteins that are spike (S), envelope (E), membrane (M), and nucleoprotein (N). The spike protein is a large (~ 180-kDa) class I viral fusion protein that has a significant impact in binding virus to host cell surface receptors and entry processes. This protein is composed of two subunits, S1 located at the N-terminus, which is responsible for receptor binding and S2 at the C-terminus responsible for fusion activity (72,73). The S1 sequence is more variable than the conserved S2 region (74,75). The S protein is considered as a main key target for the vaccines and antiviral drugs development due to it is role in virus binding to host surface receptor, (76), entry and cell tropism (77). Developing antiviral peptides that target different regions of the spike protein is a promising strategy. A study showed that SARA-CoV plaque formation could be

inhibited up to 40–80% when peptides analogous are presented to the N terminus, pre-transmembrane domain or the loop region separating the two conserved heptad repeats (HR) located in S2 (HR1 and HR2) at micromolar concentrations (78). A pseudo type assay was used in a study by Gao et al indicating a competitive peptide for HR2 can block the fusion mechanism of MERS-CoV and prevents entry of the virus (79). Developing monoclonal antibodies that target S1, S2 and the receptor-binding domain (RBD) by neutralization structural proteins on virions is another promising approach. The developed monoclonal antibodies have usually targeted specific epitopes on the S1 domain that inhibit binding between virus and receptors of the host cell, whereas others monoclonal antibodies bind to the S2 domain and block fusion process between the virus and host cell (80).

The viral replication could be inhibited when monoclonal antibodies against MERS-CoV spike protein is administrated in humanized DPP4 mouse model (81). The RBDs contain major neutralization epitopes, which may serve as subunits for vaccine development in addition to the induction ability of the host immune responses (82–85). For the production of virus-neutralizing antibodies, the N-terminal of the spike protein is a significant target for epitopes T cell responses. The S protein can induce protective immunity when inoculated alone (86). A study showed that the SARS-CoV S protein can block virus binding and fusion by antibodies induction (87). Several studies proved that the S1 domain of the S protein remains the most successful vaccine candidate that produces antibody response to CoV (88,89). However, this might be not true for all serotypes due to the antigenic drift. Contritely, S2 domain of the S protein is immunologically silent and rare antibodies are induced to target S2 and inhibit fusion mechanism. The successful reveal of SARS-2 S protein structure enabled scientists for rapid act to optimize and evaluate vaccination strategies. Depending on reverse vaccinology and immunoinformatic methods, several potential subunit vaccines were proposed (90). Several proposed vaccines passed clinical trials successfully are now been given to peoples in many countries (91). However, side effect and duration of these vaccines are still a major concern.

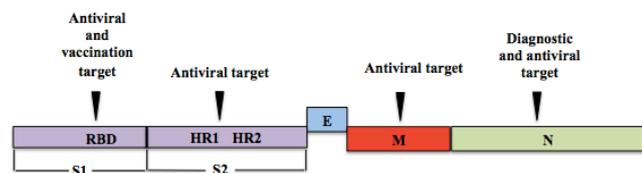
The second structural protein is the envelope protein (E). The E protein is a small polypeptide protein about 76 to 109 amino acids (92), non-glycosylated with a single hydrophobic domain (HD) present at low concentrations in virions of most CoV with exception of IBV (93,94). Due to its merits of the small size, low concentration, poor conservation across coronavirus genera (95) and no evidence is confirmed for direct interactions with the other viral structural proteins, E protein are not preferable for development of antiviral drugs against CoV infection. The

third structural protein for CoV is the membrane protein (M) (25-30 KDa) that is the most abundant integral glycoprotein in the coronavirus particle. M protein is characterized with a short amino-terminus (outside the virion membrane) followed by three transmembrane domains, and a large carboxy-terminal domain situated inside the virus particle (96,97). The structural information for M protein still limited and predicted structure is partially concluded from sequence compression and secondary structure prediction. However, a study suggested that M protein can suppress production of type I IFN mainly via blocking the formation of a functional TRAF3–TANK–TBK1/IKKe complex (98) which indicates that the M protein might be a potential target for antiviral development.

A small interfering RNA (siRNA) is another promising approach targeting envelope, membrane and some other coronavirus accessory proteins. Several in-vitro studies developed siRNAs inhibitors against E, M, ORF3a, ORF7a or ORF7b of SARS-CoV and blocking replication of the virus (67,99), however, the developed siRNAs are not ready to human use due to the lack of suitable delivery methods. The fourth protein is nucleocapsid protein (N) located inside the virus particles. N protein is a basic, heavily phosphorylated and conserved protein that contains two domains. This protein basic function is to protect viral genome by enclosing the genomic RNA in a helically symmetric ribonucleoprotein (RNP) and facilitating its replication (100,101). The N protein is composed of N-terminal domain (NTD), central linker and C-terminal domain (CTD) (102,103) which are capable of binding with RNA in-vitro with different mechanisms for each domain. Some studies suggested that the contribution of both domains are required for optimal RNA binding (104,105).

The N protein is the highly sensitive and specific diagnostic marker used to detect coronavirus disease (106,107) and has the ability to activate immune responses of the host cell (108,109). It has been proposed that MHV and SARS-CoV N protein might act as RNA chaperone (110,111) which is an essential step during template switching events. Moreover, the N protein plays an important role in the CoV assembly (112). Since N protein is considered as a multifunctional protein that plays an important role during the virus life cycle, N protein is an attractive target for antiviral drug design. A study showed that RNA-binding affinity of the N protein in HCoV-OC43 could be significantly decreased when mutations are introduced to the centre of the NTD domain and viral replication is decreased by developed RNA-binding inhibitors (113). The N protein oligomerization of the SARS-CoV could be decreased by removing 40 residues from the CTD (114). The N protein is found inside the virus particle and does not elicit neutralizing antibodies. However, N protein is considered to be a successful vaccine

candidate by their ability to generate induction of cytotoxic T lymphocytes that destroy infected cells. The SARS-CoV N protein when introduced to mice induces high cytotoxic T



lymphocytes activity (115,116). Moreover, N protein is capable of binding to ssRNA, ssDNA, and dsDNA(117,118). Also, the N protein is a sensitive diagnostic marker for SARS infection that has been used for diagnosis especially in the early stage of infection (106,119,120). The primary requirement for drug target candidate is genetic stability and conservation, which could be found in N protein. Nevertheless, additional efforts and experiments should be performed before therapeutics based on targeting N protein can be introduced to patients.

Figure 2. Schematic presentation of the coronavirus structural proteins with candidate antiviral targets. Abbreviations: S1, spike S1 domain; S2, spike S2 domain; RBD, receptor-binding domain; HR1, heptad repeat 1; HR2, heptad repeat 2; E, envelope; M, membrane; N, nucleocapsid.

At the moment, developing a vaccine or antiviral drug for SARS-CoV-2 is urgently needed since all potential drugs treat symptoms from infected patients. The rapid respond from scientist to resolve genetic map and crystal structures of some of the virus proteins have facilitated efforts for drug discovery. Moreover, discovering new targets is highly desirable in fighting this disease (125).

## 5. CONCLUSION

Despite the huge efforts in developing treatments for CoVs infections, all these treatments are tested in animal and in vitro models including inhibitors for CoV proteins, neutralizing antibodies and host immune response inhibitors. However, more research is required especially with the emergence of SARS-CoV-2 that we know little about and with the rapid threat of this virus on the human population. The key feature is by providing a complete picture of the role of each CoV protein and gene. Discovering genome difference and tracing the evolution of SARS-CoV-2 might lead to reduce and prevent more death in the human population worldwide. Furthermore, following untraditional principles in developing antiviral drug such, as large-scale screening of existing drugs seems a promising approach and increase therapeutic options. COVID-19 is a lesson to learn the necessity of developing new antiviral therapies against coronavirus and understanding function and structure of each CoV genome and protein is the most

effective way and support design of efficient drugs against SARS-CoV-2 since it will not be the last outbreak by CoV.

## 6. ACKNOWLEDGMENTS

The authors would like to acknowledge the contribution of University of Anbar, Mustansiriyah University, Iraq via their prestigious academic staff in supporting this research with all required technical and academic support.

## 7. REFERENCES

- [1] Woo PC, Lau SK, Lam CS, Lai KK, Huang Y, Lee P, et al. Comparative analysis of complete genome sequences of three avian coronaviruses reveals a novel group 3c coronavirus. *J Virol.* 2009;83(2):908–17.
- [2] De Groot,RJ, AMQ K, Adams MJ, Cartens E, Lefkowitz EJ. *Virus taxonomy, the 9th report of the international committee on taxonomy of viruses.* Vol. 9. Academic Press,San Diego,CA; 2012. 806-828 p.
- [3] Nauwynck H, Snijder EJ, Faaberg, Balasuriya U, Brinton M, Gorbalenya AE, et al. Family Arteriviridae. In: King AMQ, Adams MJ, Carstens EB, Lefkowitz EJ (eds)*Virus Taxonomy:IXth report of the International Committee of Taxonomy.* Vol. 9. 2012. 796-805 p.
- [4] Woo PC, Lau SK, Lam CS, Lau CC, Tsang AK, Lau JH, et al. Discovery of seven novel mammalian and avian coronaviruses in the genus deltacoronavirus supports bat coronaviruses as the gene source of alphacoronavirus and betacoronavirus and avian coronaviruses as the gene source of gammacoronavirus and deltacoronavirus. *J Virol.* 2012;86(7):3995–4008.
- [5] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N Engl J Med.* 2020;
- [6] Weiss SR. Forty years with coronaviruses. *J Exp Med (Internet).* 2020 May 4 (cited 2021 Jun 23);217(5). Available from: <https://rupress.org/jem/article/217/5/e20200537/151597/Forty-years-with-coronavirusesForty-years-with>
- [7] Al-Jameel W, Al-Mahmood SS. Similarities and differences of COVID-19 and avian infectious bronchitis from molecular pathologist and poultry specialist view point. *Iraqi J Vet Sci.* 2020;34(2):223–31.
- [8] Fung TS, Liu DX. Human Coronavirus: Host-Pathogen Interaction. *Annu Rev Microbiol.* 2019 Sep 8;73(1):529–57.
- [9] Drosten C, Günther S, Preiser W, Van Der Werf S, Brodt H-R, Becker S, et al. Identification of a novel coronavirus in patients with severe acute respiratory syndrome. *N Engl J Med.* 2003;348(20):1967–76.
- [10] Peiris JSM, Lai ST, Poon LLM, Guan Y, Yam LYC, Lim W, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *The Lancet.* 2003;361(9366):1319–25.
- [11] Zaki AM, van Boheemen S, Bestebroer TM,

- Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med*. 2012;367(19):1814–20.
- [12] Perlman S. Another decade, another coronavirus. *Mass Medical Soc*; 2020.
- [13] Gorbalenya AE, Baker SC, Baric RS, Groot RJ de, Drosten C, Gulyaeva AA, et al. Severe acute respiratory syndrome-related coronavirus: The species and its viruses – a statement of the Coronavirus Study Group. *bioRxiv*. 2020 Feb 11;2020.02.07.937862.
- [14] Corman VM, Muth D, Niemeyer D, Drosten C. Chapter Eight - Hosts and Sources of Endemic Human Coronaviruses. In: Kielian M, Mettenleiter TC, Roossinck MJ, editors. *Advances in Virus Research* (Internet). Academic Press; 2018. p. 163–88. Available from: <https://www.sciencedirect.com/science/article/pii/S0065352718300010>
- [15] Agrawal AS, Tao X, Algaissi A, Garron T, Narayanan K, Peng B-H, et al. Immunization with inactivated Middle East Respiratory Syndrome coronavirus vaccine leads to lung immunopathology on challenge with live virus. *Hum Vaccines Immunother*. 2016 Sep 1;12(9):2351–6.
- [16] Tai W, Wang Y, Fett CA, Zhao G, Li F, Perlman S, et al. Recombinant receptor-binding domains of multiple Middle East respiratory syndrome coronaviruses (MERS-CoVs) induce cross-neutralizing antibodies against divergent human and camel MERS-CoVs and antibody escape mutants. *J Virol*. 2017;91(1):e01651–16.
- [17] Zhang N, Tang J, Lu L, Jiang S, Du L. Receptor-binding domain-based subunit vaccines against MERS-CoV. *Virus Res*. 2015 Apr 16;202:151–9.
- [18] Chi H, Zheng X, Wang X, Wang C, Wang H, Gai W, et al. DNA vaccine encoding Middle East respiratory syndrome coronavirus S1 protein induces protective immune responses in mice. *Vaccine*. 2017;35(16):2069–75.
- [19] De Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol*. 2016;14(8):523.
- [20] Gillim-Ross L, Subbarao K. Emerging respiratory viruses: challenges and vaccine strategies. *Clin Microbiol Rev*. 2006;19(4):614–36.
- [21] Graham RL, Donaldson EF, Baric RS. A decade after SARS: strategies for controlling emerging coronaviruses. *Nat Rev Microbiol*. 2013 Dec;11(12):836–48.
- [22] Chu CM, Cheng VCC, Hung IFN, Wong MML, Chan KH, Chan KS, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004 Mar 1;59(3):252–6.
- [23] Kim UJ, Won E-J, Kee S-J, Jung S-I, Jang H-C. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome: a case report. *Antivir Ther*. 2015;21(5):455–9.
- [24] 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):1–14.
- [25] Tsang K, Zhong NS. SARS: pharmacotherapy. *Respirology*. 2003;8(s1):S25–S30.
- [26] Wu C-Y, Jan J-T, Ma S-H, Kuo C-J, Juan H-F, Cheng Y-SE, et al. Small molecules targeting severe acute respiratory syndrome human coronavirus. *Proc Natl Acad Sci U S A*. 2004;101(27):10012–7.
- [27] Falzarano D, De Wit E, Martellaro C, Callison J, Munster VJ, Feldmann H. Inhibition of novel  $\beta$  coronavirus replication by a combination of interferon- $\alpha$ 2b and ribavirin. *Sci Rep*. 2013;3:1686.
- [28] Haagmans BL, Kuiken T, Martina BE, Fouchier RA, Rimmelzwaan GF, Van Amerongen G, et al. Pegylated interferon- $\alpha$  protects type 1 pneumocytes against SARS coronavirus infection in macaques. *Nat Med*. 2004;10(3):290–3.
- [29] Ströher U, DiCaro A, Li Y, Strong JE, Aoki F, Plummer F, et al. Severe acute respiratory syndrome-related coronavirus is inhibited by interferon- $\alpha$ . *J Infect Dis*. 2004;189(7):1164–7.
- [30] Rossignol J-F. Nitazoxanide, a new drug candidate for the treatment of Middle East respiratory syndrome coronavirus. *J Infect Public Health*. 2016 Jun;9(3):227–30.
- [31] Zhou N, Pan T, Zhang J, Li Q, Zhang X, Bai C, et al. Glycopeptide Antibiotics Potently Inhibit Cathepsin L in the Late Endosome/Lysosome and Block the Entry of Ebola Virus, Middle East Respiratory Syndrome Coronavirus (MERS-CoV), and Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). *J Biol Chem*. 2016 Apr 22;291(17):9218–32.
- [32] Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov*. 2020;6(1):1–4.
- [33] Mousa YJ, Mahmood MB, Isihq FA, Mohammed AA. Are promising mechanisms of hydroxychloroquine abolish COVID-19 activity? A review study. *Iraqi J Vet Sci*. 2020;34(2):345–9.
- [34] Verma K, Kumar I. CHLOROQUINE AND HYDROXYCHLOROQUINE: A MAJOR BREAKTHROUGH FOR COVID-19. *Int J Pharm Pharm Sci*. 2020 Aug 18;1–5.
- [35] Dyal J, Coleman CM, Hart BJ, Venkataraman T, Holbrook MR, Kindrachuk J, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrob Agents Chemother*. 2014;58(8):4885–93.
- [36] Elshabrawy HA, Fan J, Haddad CS, Ratia K, Broder CC, Caffrey M, et al. Identification of a Broad-Spectrum Antiviral Small Molecule against Severe Acute Respiratory Syndrome Coronavirus and Ebola, Hendra, and Nipah Viruses by Using a Novel High-Throughput Screening Assay. *J Virol*. 2014 Apr 15;88(8):4353–65.
- [37] Kindrachuk J, Ork B, Hart BJ, Mazur S, Holbrook MR, Frieman MB, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome

- coronavirus infection as identified by temporal kinome analysis. *Antimicrob Agents Chemother.* 2015;59(2):1088–99.
- [38] Wadhwa P. MOLECULAR DOCKING STUDY OF NOVEL COVID-19 PROTEASE WITH CURRENT CLINICAL MANAGEMENT AGENTS. *Asian J Pharm Clin Res.* 2020 Jul 1;37–9.
- [39] Chen Y, Lear T, Evankovich J, Larsen M, Lin B, Alfaras I, et al. A high throughput screen for TMPRSS2 expression identifies FDA-approved and clinically advanced compounds that can limit SARS-CoV-2 entry. 2020;
- [40] Kainulainen MH, Bergeron E, Chatterjee P, Chapman AP, Lee J, Chida A, et al. High-throughput quantitation of SARS-CoV-2 antibodies in a single-dilution homogeneous assay. *Sci Rep.* 2021;11(1):1–9.
- [41] Li Q, Kang C. Progress in developing inhibitors of SARS-CoV-2 3C-like protease. *Microorganisms.* 2020;8(8):1250.
- [42] Harcourt BH, Jukneliene D, Kanjanahaluethai A, Bechill J, Severson KM, Smith CM, et al. Identification of severe acute respiratory syndrome coronavirus replicase products and characterization of papain-like protease activity. *J Virol.* 2004;78(24):13600–12.
- [43] Hilgenfeld R. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. *FEBS J.* 2014;281(18):4085–96.
- [44] Subissi L, Imbert I, Ferron F, Collet A, Coutard B, Decroly E, et al. SARS-CoV ORF1b-encoded nonstructural proteins 12–16: replicative enzymes as antiviral targets. *Antiviral Res.* 2014;101:122–30.
- [45] Xue X, Yu H, Yang H, Xue F, Wu Z, Shen W, et al. Structures of two coronavirus main proteases: implications for substrate binding and antiviral drug design. *J Virol.* 2008;82(5):2515–27.
- [46] Báez-Santos YM, John SES, Mesecar AD. The SARS-coronavirus papain-like protease: structure, function and inhibition by designed antiviral compounds. *Antiviral Res.* 2015;115:21–38.
- [47] Hilgenfeld R, Peiris M. From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses. *Antiviral Res.* 2013;100(1):286–95.
- [48] Kuo C-J, Liang P-H. Characterization and inhibition of the main protease of severe acute respiratory syndrome coronavirus. *ChemBioEng Rev.* 2015;2(2):118–32.
- [49] Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung S-H. An Overview of Severe Acute Respiratory Syndrome–Coronavirus (SARS-CoV) 3CL Protease Inhibitors: Peptidomimetics and Small Molecule Chemotherapy. *J Med Chem.* 2016;59(14):6595–628.
- [50] Zhao Q, Weber E, Yang H. Recent developments on coronavirus main protease/3C like protease inhibitors. *Recent Patents Anti-Infect Drug Disc.* 2013;8(2):150–6.
- [51] Kumar V, Shin JS, Shie J-J, Ku KB, Kim C, Go YY, et al. Identification and evaluation of potent Middle East respiratory syndrome coronavirus (MERS-CoV) 3CLPro inhibitors. *Antiviral Res.* 2017;141:101–6.
- [52] Fischer A, Sellner M, Neraanjan S, Lill MA, Smieško M. Inhibitors for Novel Coronavirus Protease Identified by Virtual Screening of 687 Million Compounds. 2020;
- [53] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *The Lancet.* 2020;395(10224):565–74.
- [54] Chan JF-W, Yao Y, Yeung M-L, Deng W, Bao L, Jia L, et al. Treatment with lopinavir/ritonavir or interferon-β1b improves outcome of MERS-CoV infection in a nonhuman primate model of common marmoset. *J Infect Dis.* 2015;212(12):1904–13.
- [55] Kim UJ, Won E-J, Kee S-J, Jung S-I, Jang H-C. Case report Combination therapy with lopinavir/ritonavir, ribavirin and interferon-α for Middle East respiratory syndrome. *Antivir Ther.* 2016;21:455–9.
- [56] 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. *N Engl J Med.* 2020 May 7;382(19):1787–99.
- [57] Kirchdoerfer RN, Ward AB. Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nat Commun.* 2019;10(1):1–9.
- [58] Lee J-M, Cho J-B, Ahn H-C, Jung W, Jeong Y-J. A novel chemical compound for inhibition of SARS coronavirus helicase. *J Microbiol Biotechnol.* 2017;27:2070–3.
- [59] Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. *Travel Med Infect Dis (Internet).* 2020 Mar 5; Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7129391/>
- [60] Zhu S, Guo X, Geary K, Zhang D. Emerging Therapeutic Strategies for COVID-19 patients. *Discoveries.* 2020;8(1).
- [61] Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved drug ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res.* 2020 Jun 1;178:104787.
- [62] Stockman LJ, Bellamy R, Garner P. SARS: Systematic Review of Treatment Effects. *PLoS Med (Internet).* 2006 Sep;3(9). Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1564166/>
- [63] Sulkowski MS. Anemia in the treatment of hepatitis C virus infection. *Clin Infect Dis.* 2003;37(Supplement\_4):S315–S322.
- [64] Cobb AJ, Dell’Isola A, Abdulsattar BO, McLachlan MM, Neuman BW, Müller C, et al. Synthesis and antiviral activity of novel spirocyclic nucleosides. *New J Chem.* 2018;42(22):18363–80.
- [65] Adedeji AO, Singh K, Kassim A, Coleman CM, Elliott R, Weiss SR, et al. Evaluation of SSSYA10-001 as a replication inhibitor of severe acute respiratory syndrome, mouse hepatitis, and Middle East respiratory syndrome coronaviruses. *Antimicrob*

- Agents Chemother. 2014;58(8):4894–8.
- [66] Gordon DE, Jang GM, Bouhaddou M, Xu J, Obernier K, White KM, et al. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature*. 2020;1–13.
- [67] Züst R, Cervantes-Barragan L, Habjan M, Maier R, Neuman BW, Ziebuhr J, et al. Ribose 2'- O -methylation provides a molecular signature for the distinction of self and non-self mRNA dependent on the RNA sensor Mda5. *Nat Immunol*. 2011 Feb;12(2):137–43.
- [68] Snijder EJ, Bredenbeek PJ, Dobbe JC, Thiel V, Ziebuhr J, Poon LLM, et al. Unique and Conserved Features of Genome and Proteome of SARS-coronavirus, an Early Split-off From the Coronavirus Group 2 Lineage. *J Mol Biol*. 2003 Aug 29;331(5):991–1004.
- [69] Bouvet M, Debarnot C, Imbert I, Selisko B, Snijder EJ, Canard B, et al. In vitro reconstitution of SARS-coronavirus mRNA cap methylation. *PLoS Pathog*. 2010;6(4).
- [70] Ferron F, Decroly E, Selisko B, Canard B. The viral RNA capping machinery as a target for antiviral drugs. *Antiviral Res*. 2012 Oct 1;96(1):21–31.
- [71] He ML, Zheng BJ, Chen Y, Wong KL, Huang JD, Lin MC, et al. Development of interfering RNA agents to inhibit SARS-associated coronavirus infection and replication. *Hong Kong Med J Xianggang Yi Xue Za Zhi (Internet)*. 2009; Available from: <https://hub.hku.hk/handle/10722/147608>
- [72] Bouvet M, Debarnot C, Imbert I, Selisko B, Snijder EJ, Canard B, et al. In vitro reconstitution of SARS-coronavirus mRNA cap methylation. *PLoS Pathog*. 2010;6(4):e1000863.
- [73] Ke M, Chen Y, Wu A, Sun Y, Su C, Wu H, et al. Short peptides derived from the interaction domain of SARS coronavirus nonstructural protein nsp10 can suppress the 2'-O-methyltransferase activity of nsp10/nsp16 complex. *Virus Res*. 2012 Aug 1;167(2):322–8.
- [74] Cheng K-W, Cheng S-C, Chen W-Y, Lin M-H, Chuang S-J, Cheng I-H, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. *Antiviral Res*. 2015;115:9–16.
- [75] Wang Y, Sun Y, Wu A, Xu S, Pan R, Zeng C, et al. Coronavirus nsp10/nsp16 methyltransferase can be targeted by nsp10-derived peptide in vitro and in vivo to reduce replication and pathogenesis. *J Virol*. 2015;89(16):8416–27.
- [76] Belouzard S, Millet JK, Licitra BN, Whittaker GR. Mechanisms of coronavirus cell entry mediated by the viral spike protein. *Viruses*. 2012;4(6):1011–33.
- [77] Heald-Sargent T, Gallagher T. Ready, set, fuse! The coronavirus spike protein and acquisition of fusion competence. *Viruses*. 2012;4(4):557–80.
- [78] Thorp EB, Boscarino JA, Logan HL, Goletz JT, Gallagher TM. Palmitoylations on murine coronavirus spike proteins are essential for virion assembly and infectivity. *J Virol*. 2006;80(3):1280–9.
- [79] Wong SK, Li W, Moore MJ, Choe H, Farzan M. A 193-amino acid fragment of the SARS coronavirus S protein efficiently binds angiotensin-converting enzyme 2. *J Biol Chem*. 2004;279(5):3197–201.
- [80] Li F. Structure, function, and evolution of coronavirus spike proteins. *Annu Rev Virol*. 2016;3:237–61.
- [81] Lu G, Wang Q, Gao GF. Bat-to-human: spike features determining “host jump” of coronaviruses SARS-CoV, MERS-CoV, and beyond. *Trends Microbiol*. 2015;23(8):468–78.
- [82] Sainz B, Mossel EC, Gallaher WR, Wimley WC, Peters CJ, Wilson RB, et al. Inhibition of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) infectivity by peptides analogous to the viral spike protein. *Virus Res*. 2006;120(1):146–55.
- [83] Gao J, Lu G, Qi J, Li Y, Wu Y, Deng Y, et al. Structure of the fusion core and inhibition of fusion by a heptad repeat peptide derived from the S protein of Middle East respiratory syndrome coronavirus. *J Virol*. 2013;87(24):13134–40.
- [84] Coughlin MM, Prabhakar BS. Neutralizing human monoclonal antibodies to severe acute respiratory syndrome coronavirus: target, mechanism of action, and therapeutic potential. *Rev Med Virol*. 2012;22(1):2–17.
- [85] Pascal KE, Coleman CM, Mujica AO, Kamat V, Badithe A, Fairhurst J, et al. Pre-and postexposure efficacy of fully human antibodies against Spike protein in a novel humanized mouse model of MERS-CoV infection. *Proc Natl Acad Sci*. 2015;112(28):8738–43.
- [86] Du L, Zhao G, Yang Y, Qiu H, Wang L, Kou Z, et al. A conformation-dependent neutralizing monoclonal antibody specifically targeting receptor-binding domain in Middle East respiratory syndrome coronavirus spike protein. *J Virol*. 2014;88(12):7045–53.
- [87] Jiang L, Wang N, Zuo T, Shi X, Poon K-MV, Wu Y, et al. Potent neutralization of MERS-CoV by human neutralizing monoclonal antibodies to the viral spike glycoprotein. *Sci Transl Med*. 2014;6(234):234ra59–234ra59.
- [88] Sui J, Li W, Murakami A, Tamin A, Matthews LJ, Wong SK, et al. Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. *Proc Natl Acad Sci U S A*. 2004;101(8):2536–41.
- [89] Ying T, Du L, Ju TW, Prabakaran P, Lau CC, Lu L, et al. Exceptionally potent neutralization of Middle East respiratory syndrome coronavirus by human monoclonal antibodies. *J Virol*. 2014;88(14):7796–805.
- [90] Cavanagh D. Coronaviridae: a review of coronaviruses and toroviruses. In: *Coronaviruses with Special Emphasis on First Insights Concerning SARS (Internet)*. Springer; 2005 (cited 2017 Feb 16). p. 1–54. Available from: <http://link.springer.com/chapter/10.1007/3-7643->

- 7339-3\_1
- [91] Du L, He Y, Zhou Y, Liu S, Zheng B-J, Jiang S. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. *Nat Rev Microbiol.* 2009;7(3):226–36.
- [92] Jiaming L, Yanfeng Y, Yao D, Yawei H, Linlin B, Baoying H, et al. The recombinant N-terminal domain of spike proteins is a potential vaccine against Middle East respiratory syndrome coronavirus (MERS-CoV) infection. *Vaccine.* 2017;35(1):10–8.
- [93] Wirblich C, Coleman CM, Kurup D, Abraham TS, Bernbaum JG, Jahrling PB, et al. One-health: a safe, efficient, dual-use vaccine for humans and animals against Middle East respiratory syndrome coronavirus and rabies virus. *J Virol.* 2017;91(2):e02040–16.
- [94] Zhai P, Ding Y, Wu X, Long J, Zhong Y, Li Y. The epidemiology, diagnosis and treatment of COVID-19. *Int J Antimicrob Agents.* 2020 Mar 28;105955.
- [95] Yan Z-P, Yang M, Lai C-L. COVID-19 Vaccines: A Review of the Safety and Efficacy of Current Clinical Trials. *Pharmaceuticals.* 2021 May;14(5):406.
- [96] Torres J, Maheswari U, Parthasarathy K, Ng L, Liu DX, Gong X. Conductance and amantadine binding of a pore formed by a lysine-flanked transmembrane domain of SARS coronavirus envelope protein. *Protein Sci.* 2007;16(9):2065–71.
- [97] Corse E, Machamer CE. Infectious bronchitis virus E protein is targeted to the Golgi complex and directs release of virus-like particles. *J Virol.* 2000;74(9):4319–26.
- [98] Liao Y, Yuan Q, Torres J, Tam JP, Liu DX. Biochemical and functional characterization of the membrane association and membrane permeabilizing activity of the severe acute respiratory syndrome coronavirus envelope protein. *Virology.* 2006;349(2):264–75.
- [99] Masters PS. The molecular biology of coronaviruses. *Adv Virus Res.* 2006;66:193–292.
- [100] Arndt AL, Larson BJ, Hogue BG. A conserved domain in the coronavirus membrane protein tail is important for virus assembly. *J Virol.* 2010 Nov;84(21):11418–28.
- [101] Hogue BG, Machamer CE. Coronavirus structural proteins and virus assembly. *Nidoviruses ASM Press Wash DC.* 2008;179–200.
- [102] Siu K-L, Kok K-H, Ng M-HJ, Poon VK, Yuen K-Y, Zheng B-J, et al. Severe acute respiratory syndrome coronavirus M protein inhibits type I interferon production by impeding the formation of TRAF3-TANK-TBK1/IKK $\epsilon$  complex. *J Biol Chem.* 2009;284(24):16202–9.
- [103] Aakerström S, Mirazimi A, Tan Y-J. Inhibition of SARS-CoV replication cycle by small interference RNAs silencing specific SARS proteins, 7a/7b, 3a/3b and S. *Antiviral Res.* 2007;73(3):219–27.
- [104] Almazán F, Galán C, Enjuanes L. The nucleoprotein is required for efficient coronavirus genome replication. *J Virol.* 2004;78(22):12683–8.
- [105] Tylor S, Andonov A, Cutts T, Cao J, Grudesky E, Van Domselaar G, et al. The SR-rich motif in SARS-CoV nucleocapsid protein is important for virus replication. *Can J Microbiol.* 2009;55(3):254–60.
- [106] Chang C, Lo S-C, Wang Y-S, Hou M-H. Recent insights into the development of therapeutics against coronavirus diseases by targeting N protein. *Drug Discov Today.* 2016;21(4):562–72.
- [107] Ma Y, Tong X, Xu X, Li X, Lou Z, Rao Z. Structures of the N-and C-terminal domains of MHV-A59 nucleocapsid protein corroborate a conserved RNA-protein binding mechanism in coronavirus. *Protein Cell.* 2010;1(7):688–97.
- [108] Chang C, Sue S-C, Yu T, Hsieh C-M, Tsai C-K, Chiang Y-C, et al. Modular organization of SARS coronavirus nucleocapsid protein. *J Biomed Sci.* 2006;13(1):59–72.
- [109] Hurst KR, Koetzner CA, Masters PS. Identification of in vivo-interacting domains of the murine coronavirus nucleocapsid protein. *J Virol.* 2009;83(14):7221–34.
- [110] Che X-Y, Hao W, Wang Y, Di B, Yin K, Xu Y-C, et al. Nucleocapsid protein as early diagnostic marker for SARS. *Emerg Infect Dis.* 2004;10(11):1947.
- [111] Diao B, Wen K, Chen J, Liu Y, Yuan Z, Han C, et al. Diagnosis of Acute Respiratory Syndrome Coronavirus 2 Infection by Detection of Nucleocapsid Protein. *medRxiv.* 2020;
- [112] Xiong S, Wang Y-F, Zhang M-Y, Liu X-J, Zhang C-H, Liu S-S, et al. Immunogenicity of SARS inactivated vaccine in BALB/c mice. *Immunol Lett.* 2004;95(2):139–43.
- [113] Leung DTM, Hang TFC, Hung MC, Chan PKS, Cheung JLK, Niu H, et al. Antibody response of patients with severe acute respiratory syndrome (SARS) targets the viral nucleocapsid. *J Infect Dis.* 2004;190(2):379–86.
- [114] Thiel V, Herold J, Schelle B, Siddell SG. Infectious RNA transcribed in vitro from a cDNA copy of the human coronavirus genome cloned in vaccinia virus. *J Gen Virol.* 2001 Jun 1;82(6):1273–81.
- [115] Zúñiga S, Sola I, Moreno JL, Sabella P, Plana-Durán J, Enjuanes L. Coronavirus nucleocapsid protein is an RNA chaperone. *Virology.* 2007;357(2):215–27.
- [116] Hurst KR, Kuo L, Koetzner CA, Ye R, Hsue B, Masters PS. A major determinant for membrane protein interaction localizes to the carboxy-terminal domain of the mouse coronavirus nucleocapsid protein. *J Virol.* 2005;79(21):13285–97.
- [117] Lin S-Y, Liu C-L, Chang Y-M, Zhao J, Perlman S, Hou M-H. Structural basis for the identification of the N-terminal domain of coronavirus nucleocapsid protein as an antiviral target. *J Med Chem.* 2014;57(6):2247–57.
- [118] Luo H, Chen J, Chen K, Shen X, Jiang H. Carboxyl terminus of severe acute respiratory syndrome coronavirus nucleocapsid protein: self-association analysis and nucleic acid binding characterization. *Biochemistry (Mosc).* 2006;45(39):11827–35.
- [119] Zhao P, Cao J, Zhao L-J, Qin Z-L, Ke J-S, Pan W, et al. Immune responses against SARS-coronavirus

- nucleocapsid protein induced by DNA vaccine. Virology. 2005;331(1):128–35.
- [120] Zhu M-S, Pan Y, Chen H-Q, Shen Y, Wang X-C, Sun Y-J, et al. Induction of SARS-nucleoprotein-specific immune response by use of DNA vaccine. Immunol Lett. 2004;92(3):237–43.
- [121] Takeda M, Chang C, Ikeya T, Güntert P, Chang Y, Hsu Y, et al. Solution structure of the c-terminal dimerization domain of SARS coronavirus nucleocapsid protein solved by the SAIL-NMR method. J Mol Biol. 2008;380(4):608–22.
- [122] Tang T-K, Wu MP-J, Chen S-T, Hou M-H, Hong M-H, Pan F-M, et al. Biochemical and immunological studies of nucleocapsid proteins of severe acute respiratory syndrome and 229E human coronaviruses. Proteomics. 2005;5(4):925–37.
- [123] Di B, Hao W, Gao Y, Wang M, Qiu L, Wen K, et al. Monoclonal antibody-based antigen capture enzyme-linked immunosorbent assay reveals high sensitivity of the nucleocapsid protein in acute-phase sera of severe acute respiratory syndrome patients. Clin Diagn Lab Immunol. 2005;12(1):135–40.
- [124] Surjit M, Lal SK. The SARS-CoV nucleocapsid protein: a protein with multifarious activities. Infect Genet Evol. 2008;8(4):397–405.
- [125] Al-Aalim AM, Hamad MA, AL-ledani Ali A. Some insights of novel COVID 19 virus: structure, pathogenicity and immunity aspects. Iraqi J Vet Sci. 2020;34(2):287–93.

## الأهداف العلاجية الحالية والجديدة المحتملة لفيروس كورونا

جوان عدي عبد الستار<sup>1</sup> و سعد طه مطلق<sup>2</sup> و بان عدي عبد الستار<sup>3</sup>  
<sup>1,3</sup>الجامعة المستنصرية – كلية العلوم ، <sup>2</sup>جامعة الأنبار – كلية العلوم

Email: [jwan.abdulsattar@uomustansiriyah.edu.iq](mailto:jwan.abdulsattar@uomustansiriyah.edu.iq) , [saad.t.mutalk@uoanbar.edu.iq](mailto:saad.t.mutalk@uoanbar.edu.iq) , [banoday@uomustansiriyah.edu.iq](mailto:banoday@uomustansiriyah.edu.iq)

### الخلاصة:

ظهر فيروس كورونا الجديد 2 المسبب المرض المتلازمة التنفسية الحادة الوخيمة في أواخر عام ٢٠١٩، والذي شهد إدخال أحد مسببات الأمراض الفيروسية عالية الانتشار التي تهدد السكان على مستوى العالم. يرتبط الفيروس الجديد ارتباطاً وثيقاً وراثياً وسرياً بفيروس كورونا المتلازمة التنفسية الحادة الوخيمة (SARS-CoV) وفيروس كورونا الشرق الأوسط التنفسي (MERS-CoV). لا توجد أدوية محددة مضادة للفيروسات معتمدة ضد عدوى فيروس كورونا البشري وجميع العلاجات داعمة. يحتوي جينوم الفيروس التاجي على العديد من اماكن القراءة المفتوحة (ORFs) التي تشفر كلاً من البروتينات غير الهيكلية (nsp) والبروتينات الهيكلية. لقد ذكرت التقارير ان معظم البروتينات المشفرة تعمل كبروتينات متعددة الوظائف وتلعب دوراً محدداً في تكرار وتجميع فيروس كورونا (CoV). تركز هذه المراجعة على اللقاح المحتمل والأهداف المستهدفة ضد الفايروسات وخصوصاً فايروس كورونا، بما في ذلك البروتينات والجينات المختلفة. إن فهم الأهداف الحالية واكتشاف أهداف علاجية جديدة محتملة سيساعد في تطوير لقاحات فعالة وأدوية مضادة للفيروسات ضد تفشي SARS-CoV-2 الحالي واحتمال تفشي المرض في المستقبل.