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CHAPTER

4

Genomic, proteomic and metabolomic profiling of severe acute respiratory syndrome-Coronavirus-2

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4.1 Introduction

The impact of Coronavirus disease-2019 (COVID-19) on global health is unmatched in recent human history. This disease caused by severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) has cornered the public, health care workers, and scientists across the globe alike. COVID-19 started in December 2019 in Wuhan, China and within 4 months become a global pandemic. As of July 13, 2021, SARS-CoV-2 has infected over 187 million people and claimed closed to 40 million lives across the globe (WHO Coronavirus (COVID-19) Dashboard, 2021). Just as this human health challenge is unprecedented, the scientific response to it has also been incredible. The concerted effort of researchers across the globe untangling the intricate aspects of epidemiology, public health response, virus biology, and pathophysiology of the disease has helped the rapid development of diagnostic, prognostic, and control measures. Within a few months of its origin, the genome of SARS-CoV-2 was sequenced fueling the development of multiplex real-time reverse transcriptase PCR (rRT-PCR) assays for diagnosis (Mathew et al., 2021). Continued efforts to sequence genomes from diverse geographical locations are helping to keep track of the evolution of the virus and the effects of variations on pathology and epidemiology (Kupferschmidt, 2020). Studies of SARS-CoV-2 protein structures and functions have helped device immunodiagnostic methods and the development of

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therapeutics and vaccines. Efforts to understand the pathophysiology of SARS-CoV-2 infection are further augmented by metabolomic profiling of serum samples from COVID-19 patients (Doğan et al., 2021). In this chapter, we provide a comprehensive account of the genome and proteome of SARS-CoV-2 in the context of epidemiology and management of the disease. We further discuss SARS-CoV-2 induced metabolomic perturbations in the host to provide insight into the pathophysiology of the disease.

4.2 Genomics of severe acute respiratory syndrome Coronavirus 2

4.2.1 Phylogenetic relationship of severe acute respiratory syndrome Coronavirus 2 with other Coronaviruses

SARS-CoV-2 belongs to the family *Coronoviridae*. *Coronoviridae* is further divided into two subfamilies namely Letovirinae and Orthocoronavirinae. Among these, Orthocoonovirinae is divided into four genera: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus* and *Deltacoronavirus*. SARS-CoV-2 belongs to the subgenus *Sarbecovirus* of the genus *Betacoronavirus*. Betacoronaviruses are primarily known to infect mammals. Phenotypically, Coronaviruses are spherical, about 100−20 nm in diameter, and the envelope of these viruses is made of host cell membranes. It has projected spike proteins on its membrane which gives a crown-like appearance on the outer surface of virus particle giving the virus its name "Coronavirus".

Coronaviruses were mainly known to cause mild respiratory and gastrointestinal distress until the outbreak of severe acute respiratory syndrome Coronavirus 1 (SARS-CoV-1) in 2003 and then the Middle East respiratory syndrome Coronavirus (MERS-CoV) in 2012. Both these viruses were reported to have originated from bat Coronaviruses (Chan et al., 2013; Lau et al., 2005). An infection from a novel virus, belonging to the same family was reported in Wuhan City, China in December 2019 with pneumonia-like respiratory symptoms which gradually turned into a worldwide pandemic (Wu et al., 2020; Zhu et al., 2020a,b). Because of the similarity in the symptoms caused by their infection on the human body, this virus was initially thought to be closely related to SARS-CoV-1 and was named SARS-CoV-2. However, whole-genome sequence analyses of SARS-CoV-2 revealed that the virus is closer to two bat-derived SARS-like Coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC21 found in China in 2018 with a sequence identity of 88%. Eventually, phylogenetic analyses showed that the genome of SARS-CoV-2 is more similar to bat CoVRaTG13 (around 96.2% identical) rather than SARS CoV (around 79.5% identical) or MERS-CoV (around 50% identical) (Guo et al., 2020). Moreover, the percent identity of SARS-CoV2 with human Coronavirus strain HCoV-OC43 which causes the mild respiratory disease is found to be very low (40.2%) (Fig. 4.1).

4.2.2 Genetic organization of severe acute respiratory syndrome Coronavirus 2 and genome replication

SARS-CoV-2 has a positive-sense single-stranded RNA genome of 29.9 Kb. Its genome has a 5′ cap structure and a poly-A tailing at its 3′ end which allows it to function as an mRNA. It comprises 14 open reading frames (ORFs) coding for a total of 29 proteins.

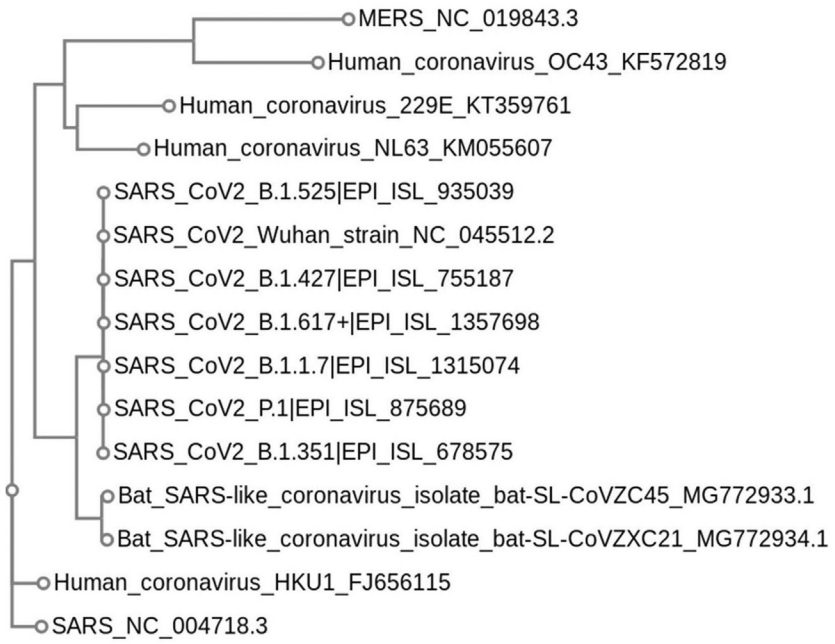

FIGURE 4.1 Phylogenetic relationship of severe acute respiratory syndrome coronavirus-2 variants and other relevant members of Coronaviridae. The phylogenetic tree was constructed using the FastaME tool available in the VIPR database. FAST uses the principle of minimum evolution to calculate phylogenetic distance.

Almost two-thirds of the genome correspond to ORFs 1ab at the 5′ end which encodes two different polyproteins 1a and 1ab which are cleaved into 16 different nonstructural proteins (NSPs). This part of the genome is also called the replicase polyprotein as it gives rise to proteins required for replication of the virus. Other than the replicase polyproteins, the viral genome encodes four structural proteins; spike protein (S), envelop protein (E), membrane protein (M), and nucleocapsid protein (N) along with nine accessory proteins. The accessory proteins are known to be mostly nonessential for replication in tissue cultures although some have been shown to be very important for pathogenesis. The genome organization of SARS-CoV-2 from 5′ to 3′ direction is 5′UTR-replicase-S-E-M-N-3′ poly-A tail and it is interspersed with transcription regulatory proteins and other accessory proteins. Another structural protein commonly found in other β-Coronaviruses, hemagglutinin esterase is absent in SARS-CoV-2 (Naqvi et al., 2020) (Fig. 4.2).

Once the genome of the virus is released into the host cell, the positive sense RNA directly acts as an mRNA and begins translation of proteins using host machinery. It translates all the structural and NSP which in turn help in viral replication and packaging (V'kovski et al., 2021). Polyprotein (pp) 1a and 1ab release 16 NSPs out of which 15 are involved in the replication of the viral genome. The main enzymatic function for RNA synthesis is brought about by NSP12−16. RdRp (NSP12) is the polymerase responsible for the RNA synthesis and NSP14 acts as a 3′−5′ exonuclease which takes care of the proofreading during the RNA synthesis (Brian & Baric, 2005; Romano et al., 2020). The replication

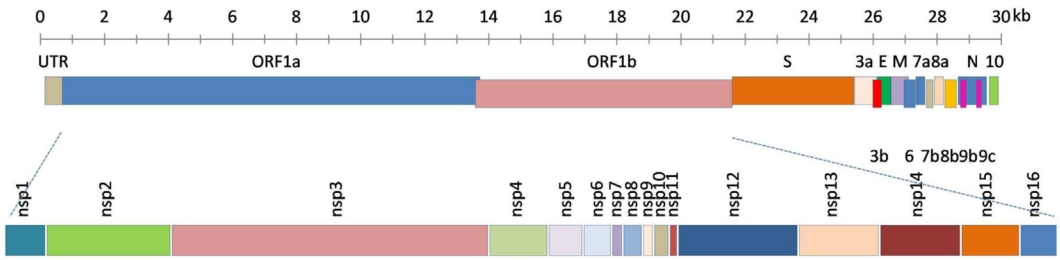

FIGURE 4.2 Architecture of by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA genome. All the 14 ORFs transcribed by the SARS-CoV-2 genome and their translation products are drawn to scale. ORF1a and ORF1b produce polyproteins 1a and 1b (pp1a and pp1b) which are cleaved by viral proteases to produce 16 nonstructural proteins. Four structural proteins; spike (S), envelope (E), membrane (M), and nucleocapsid (N), and nine accessory proteins are encoded by the rest of the ORFs, many of which overlap. *ORFs, open reading frames.*

complex proteins firstly synthesize a negative-sense RNA and use that as a template to synthesize positive-sense genomic RNA and subgenomic RNAs. The subgenomic RNAs are translated into structural, nonstructural, and accessory proteins. Genomic RNA forms complex with nucleocapsid protein and the packaging of virion particles occurs in the Golgi–endoplasmic reticulum intermediate compartment. Once assembly is completed virions are released from the cell by budding and go on to infect other host cells (Brian & Baric, 2005; Romano et al., 2020; Sawicki et al., 2007).

4.2.3 Mutations, genetic variants, and lineages of severe acute respiratory syndrome coronavirus-2

RNA viruses are known for their fast mutation rates, but Coronaviruses are known to be comparatively stable because of the proofreading ability of their replication complex (Giovanetti et al., 2021). However, many variants of SARS-CoV-2 have come up since the emergence of this virus in December 2019 as a result of substitutions, deletions, and recombination (Giovanetti et al., 2021; Graham & Baric, 2010). Sequence analysis of different SARS-CoV-2 genomes that are available in NCBI and the GISAID EpiCoV™ database revealed that RdRp, N protein, S protein, NSP3, and ORF8 genes are mutational hotspots while ORF7a, ORF7b, ORF9b, ORF14, ORF6, and ORF10 are mutational cold spots (Badua et al., 2021). Not all mutations in the circulating SARS-CoV-2 genome are of concern. Many of them are neutral or deleterious because of which not many variants exist in high frequencies in the community (Cagliani et al., 2020; Wang et al., 2021). However, mutations like L84S in ORF8, D614G in S protein, and L3606F in ORF1ab are found in unusually high frequencies among the circulating variants of SARS-CoV-2 (Badua et al., 2021). Based on the health threat posed, the different variants of the virus can broadly be grouped into three categories: variant of Interest (VOI), variant of concern (VOC), and a variant of high consequence (VOHC) (Table 4.1).

VOI is the variants that have some mutations compared to the reference genome and are associated with a reduction in the efficacy of treatments, reduced protection from previously generated antibodies, or have a predicted increase in severity and transmissibility

TABLE 4.1 Different severe acute respiratory syndrome Coronavirus 2 variants.

Group	Variant	WHO label	Origin	Spike protein mutations	Date of declaration
VOC	B.1.1.7	Alpha	United Kingdom, Sep-2020	69del, 70del, 144del, (E484K*), (S494P*), N501Y, A570D, D614G, P681H, T716I, S982A, D1118H (K1191N*)	18-Dec-20
VOC	B.1.351	Beta	South Africa, May-2020	D80A, D215G, 241del, 242del, 243del, K417N, E484K, N501Y, D614G, A701V	18-Dec-20
VOC	P.1	Gamma	Brazil, Nov-2020	L18F, T20N, P26S, D138Y, R190S, K417T, E484K, N501Y, D614G, H655Y, T1027I	11-Jan-20
VOC	B.1.617.2	Delta	India, Oct-2020	T19R, (G142D), 156del, 157del, R158G, L452R, T478K, D614G, P681R, D950N	VOI: 4 Apr-2021, VOC: 11-May-20
VOI	B.1.427/ B.1.429	Epsilon	United States, Mar-2020	D614G, S13I, W152C, L452R	5-Mar-21
VOI	P.2	Zeta	Brazil, Apr-2020	E484K, (F565L*), D614G, V1176F	17-Mar-21
VOI	B.1.525	Eta	Multiple, Dec-2020	A67V, 69del, 70del, 144del, E484K, D614G, Q677H, F888L	17-Mar-21
VOI	P.3	Theta	Philippines, Jan 2021	E484K, N501Y, D614G, P681H, E1092K, H1101Y, V1176F	24-Mar-21
VOI	B.1.526	Iota	United States, Nov-2020	(L5F*), T95I, D253G, (S477N*), (E484K*), D614G, (A701V*)	24-Mar-21
VOI	B.1.617.1	Kappa	India, Oct-2020	(T95I), G142D, E154K, L452R, E484Q, D614G, P681R, Q1071H	4-Apr-21

of the disease. So far WHO has recognized six VOIs one of which was recently recognized as a VOC in May 2021 (B.1.617.2). VOC is proven to be associated with an increase in disease severity and transmissibility, reduction in the efficacy of treatments, significantly poor neutralization effect from previously generated antibodies, and failure in the detection of the virus by available diagnostic methods. WHO has identified four such variants in the past year. VOHC is the variants against which there is clear evidence that any previously available preventive measure or medical countermeasures have remarkably reduced effect against them in comparison to the other circulating variants. So far, no such variants have been identified.

As the mutations accumulate in the SARS-CoV-2 genome and the virus evolves, different classification systems have been proposed to monitor its dynamics. Pango lineage classification is one of the most accepted classifications to identify the SARS-CoV-2 lineages, classifying it into two main lineages namely A and B. These are further classified into sublineages during the course of a pandemic, for example, lineages C and D are reassigned as the alias of lineage B (Rambaut et al., 2020). Till March 2021, 266 lineages/sublineages were identified worldwide based on the combination of mutations the variants

accumulated (Cella et al., 2021). Some of these lineages harbor mutation which has an effect on the therapeutic, prognostic, and prophylactic aspects of clinical management of SARS-CoV-2.

4.3 Proteome of severe acute respiratory syndrome Coronavirus 2

Fourteen ORFs of SARS-CoV-2 collectively encode at least 29 proteins, consisting of 4 structural, 16 nonstructural, and 9 accessory proteins. Two overlapping ORFs on the 5′ of the viral genome, ORF1a and ORF1ab encode poly protein pp1a and pp1ab which are cleaved by viral proteases NSP3 and NSP5 into 16 NSPs. These proteins are involved in viral replication and transcription. NSP12, the RNA-dependent RNA polymerase (RdRp) the key protein involved in the replication/transcription along with the co-factor proteins, NSP7 and NSP8. Another important NSP from the drug discovery point of view is NSP5 also called as main protease (M^{pro}). This 33.8 kDa protein is a 3C-like protease that has at least 11 sites on pp1a including an autolytic site. The 3′ end of the viral genome encodes four structural proteins: spike (S) glycoprotein, envelope (E), membrane (M), and nucleocapsid (N) and the remaining accessory proteins, 3a, 3b, 6, 7a, 7b, 8, 9b, 9c, and 10 (Fig. 4.2). While structural proteins are required for the formation of infectious virion particles, the accessory proteins are involved in a variety of functions such as protection against host immune response and viral replication (Kim et al., 2020; Wu et al., 2020a,b). A comprehensive understanding of the molecular structures of various key viral proteins is essential for developing effective therapeutic and prophylactic measures. Numerous studies have reported the structures of key SARS-CoV-2 proteins in pure and in complex with small molecule inhibitors, peptides, or interacting partners using cryoelectron microscopy and X-ray crystallography techniques. Along with this, structure-guided in silico screening of potential inhibitors for SARS-CoV-2 have also been undertaken to find therapeutics for COVID-19. Here we have provided a detailed account of the structure and function of key nonstructural and structural proteins touted as important drug and/or vaccine targets for SARS-CoV-2. A summary of the function and their potential inhibitors/drugs for the other SARS-CoV-2 proteins can be found in Table 4.2.

4.3.1 Nonstructural proteins

4.3.1.1 Main protease (MPro, NSP5, or 3C-like proteinase)

The main protease (M^{Pro}) cleaves pp1a into at least 11 structural proteins including itself by autocleavage. It is also called 3C-like proteinase ($3CL^{pro}$) due to the similarity of its cleavage site specificity with picornavirus 3C proteinases ($3C^{pro}$) albeit limited structural similarity between these proteinases (Anand et al., 2002). M^{Pro} is highly conserved among Coronaviruses suggesting an essential role of this protein in the viral life cycle. Because of its essential role in generating NSPs required for replication and transcription of viral RNA, and the absence of a human orthologue this protein has been considered as one of the key drug targets for SARS-CoV-2 as well as other Coronaviruses. M^{Pro} is a homo-dimeric protein where each protomer consists of three domains, Domain I-III and

TABLE 4.2 Severe acute respiratory syndrome Coronavirus 2 proteins: Function and their inhibitor(s).

SARS-CoV-2 Protein	Function	Host interacting partner	Inhibitor	References
Nonstructural protein				
NSP1	host shutoff factor; suppress host innate immune function by blocking host mRNA translations	40s ribosome	Tirilazad, phthalocyanine, and Zk-806,450	de Lima Menezes & da Silva, (2021); Thoms et al. (2020)
NSP2	Unknown function			
NSP3	Papain like protease; process viral replicase polyprotein, cleaves polyubiquitin and ISGylated proteins thus preventing host inflammatory response, Modifies ER into double-membrane vesicles	The endoplasmic reticulum, ISGylated protein, polyubiquitin proteins	VIR250 and VIR251	Clementz et al. (2010); Mariano et al. (2020); Rut et al. (2020)
NSP4	Modifies ER into double membrane vescicles	Endoplasmic reticulum	–	Mariano et al. (2020)
NSP5	Main protease; cleaves pp1a into at least 11 structural proteins	–	N3, α-ketoamide, peptidomimetics inhibitors 11a, and 11b, dipyridamole, hydroxychloroquine	Li et al. (2020); Yang et al. (2005); Zhang et al. (2020)
NSP6	Modifies ER into double membrane vesicles	Endoplasmic reticulum	–	Mariano et al. (2020)
NSP7	Cofactor for NSP12	–	–	Zhai et al. (2005)
NSP8	Cofactor for NSP12	–	–	Zhai et al. (2005)
NSP9	Involved in viral replication and important for virulence	–	–	Sutton et al. (2004)
NSP10	Cofactor for NSP14 and NSP 16	–	–	Rogstam et al. (2020)
NSP11	Unknown function	–	–	–
NSP12	RNA-dependent RNA polymerase	–	Remdesivir, Sofosbuvir, Galidesivir, drugs-like compounds CID123624208 and CID11687749	Aftab et al. (2020); Yin et al. (2020)
NSP13	Helicase and NTPase		Myricetin, scultellarein, SSYA10−001, 1,2,4-triazole, 3,5-dihydroxychromone, aryl diketoacids	Yu et al. (2012); Jang et al. (2008)

(*Continued*)

TABLE 4.2 (Continued)

SARS-CoV-2 Protein	Function	Host interacting partner	Inhibitor	References
NSP14	N7-Methyltransferase and exonuclease	Host translation machinery	Patulin and aurintricarboxylic acid	Canal et al. (2021); Hsu et al. (2021)
NSP15	RNA uridylate − specific endoribonuclease			
NSP16	2′-O methyltransferase	–	Sinefungin, S-adenosyl-l-homocysteine, aurintricarboxylic acid	Decroly et al. (2011); He et al. (2004)
Structural protein				
S	Spike protein: facilitates binding and entry of the virus	ACE2 receptor	SARS-CoV2 HR2 derived peptide, lipopeptide EK1C4, nelfinavir mesylate	Musarrat et al. (2020); Xia, Cao, et al. (2020); Xia, Zhu, et al. (2020); Zhu, Wei, et al. (2020); Zhu, Yu, et al. (2020); Zhu, Zhang, et al. (2020); Zhu, Zhu, et al. (2020)
E	Envelope protein: forms a cation-selective channel across the ER-Golgi intermediate compartment (ERGIC)	ERGIC	hexamethylene amiloride (HMA), amantadine (AMT)	Mandala et al. (2020)
M	Membrane protein: involved in virus packaging and suppresses the production of both type I IFN and type III IFN	RIG-I, MAVS, and TBK1	Caffeic acid and ferulic acid	Alharbi & Alrefaei (2021); Bhowmik et al. (2020); Zheng et al. (2020)
N	Nucleocapsid Protein: Binds to viral genomic RNA to constitute RNP and helps in virion assembly	–	(−)-catechin gallate, (−)-gallocatechin gallate, 5-Benzyloxygramine (p3)	Peng et al. (2020); Roh (2012)
Accessory protein				
3a	Forms viroporins, helps in virus egress via lysosomal trafficking, induces apoptosis		–	Ghosh et al. (2020); Miao et al. (2021); Ren et al. (2020)
3b	Suppress IFN-I activity-		–	Konno et al. (2020)
6	Disrupts cell nuclear import complex formation and suppresses IFN-beta production	Nup98-Rae1 at nuclear pore complex	–	Miorin et al. (2020); Xia, Cao, et al. (2020); Xia, Zhu, et al. (2020)
7a	Immunoglobulin-like protein	can bind to CD14 + monocytes	–	Zhou et al. (2021)

(*Continued*)

TABLE 4.2 (Continued)

SARS-CoV-2 Protein	Function	Host interacting partner	Inhibitor	References
7b	Unknown function	–	–	–
8	Mediates immune evasion by downregulation of MHC I	MHC I	–	Zhang et al. (2021)
9b	Mediates immune evasion by targeting mitochondria	TOM70	–	Gordon et al. (2020)
9c	Nonprotein coding	–	–	Jungreis et al. (2020)
10	Nonprotein coding	–	–	Jungreis et al. (2020)

long loop region connecting domains II and III. Domains I and II are composed of antiparallel β-sheet and the cleft between them makes the active site of the enzyme. Domain III on the other hand is composed primarily of α helices forming the interface of protomer (Anand et al., 2002). Specific inhibitors of M^{Pro} such as N3 have been shown to inhibit viral replication without showing any toxicity to human cells (Hayden et al., 2003; Kim et al., 2016; Pillaiyar et al., 2016; Yang et al., 2005). Consequently, several groups took up the challenge of solving the structure of M^{Pro} almost immediately after COVID-19 was declared a pandemic by WHO, and several structures of this protein in native form as well as with inhibitors were available (Dai et al., 2020; Zhang et al., 2020).

Several inhibitors of M^{pro} have been identified using protein structure and/or in silico methods. M^{Pro} is a cysteine protease which unlike human proteases cleaves peptides after a glutamine residue (Muramatsu et al., 2016). Moderate size peptidomimetic scaffolds with glutamine or an isostere and a branched lipophilic group such as N3 have been shown to inhibit the activity of SARS-CoV and MERS-CoVM^{Pro} (Yang et al., 2005; Ren et al., 2013; Wang et al., 2016; Xue et al., 2008). Jin and co-workers solved the crystal structure of SARS-CoV-2 M^{Pro} in complex with N3 and showed that N3 is an irreversible inhibitor of this protein. Using structure-based in silico screening they further identified six more putative inhibitors (Jin et al., 2020). Zang et al. solved the structure of M^{Pro} in complex with an α-ketoamide inhibitor. They were successful in developing a derivative of this inhibitor with increased potency and lung tropism (Zhang et al., 2020). In another study using artificial intelligence-assisted computer virtual screening, Wu and coworkers identified several approved drugs, and natural products with known antimicrobial and antiinflammatory activities which showed high affinity to SARS-CoV-2 M^{Pro}. These compounds can be evaluated for their therapeutic potential against COVID-19 (Wu, Liu, et al., 2020). Dai et al. synthesized two peptidomimetics inhibitors of M^{Pro}, 11a, and 11b. These compounds not only strongly inhibited the activity of M^{Pro} but also showed antiviral activity in vitro and had low toxicity in vivo (Dai et al., 2020). Li et al. used a virtual screening approach with accelerated free energy perturbation-based absolute binding free energy (FEP-ABFE) predictions to identify 15 existing drugs including dipyridamole and hydroxychloroquine which showed potent in silico inhibitory activity against M^{Pro} and can be

repurposed as COVID-19 drugs (Li et al., 2020). However, the usefulness of hydroxychloroquine in managing COVID-19 is now debatable. This finding reiterates that while structure-based virtual screening and/or in vitro activity is a good start, in vivo studies are still the mainstay of drug development.

4.3.1.2 RNA-dependent RNA polymerase (RdRp) or NSP12

NSP12 or RNA-dependent RNA polymerase (RdRp) is a core component of the replication/transcription machinery with NSP7 and NSP8 acting as cofactors to enhance its activity (Ahn et al., 2012; te Velthuis et al., 2010; Ziebuhr, 2005). RdRp, therefore is considered an important drug target. Nucleotide analog remdesivir has been shown to inhibit viral replication by inhibiting RdRp function and was recommended for the management of COVID-19 in the initial phases of the pandemic (Holshue et al., 2020; Siegel et al., 2017; Wang et al., 2020; Warren et al., 2016). A cryoelectron microscope assisted three-dimensional structure of SARS-CoV-2 RdRp in complex with NSP7 and NSP8, first solved by Gao et al. is very similar to the SARS-CoV RdRp-NSP7-NSP8 complex and comprises an RdRp monomer, one NSP8 monomer, and one NSP7-NSP8 pair (Gao et al., 2020; Kirchdoerfer & Ward, 2019). SARS-CoV-2 RdRp consists of three domains; RdRp, a norovirus-unique N-terminal extension domain, also called NiRAN, and an interface domain (Gao et al., 2020). The RdRp domain has a canonical viral polymerase architecture and consists of three subdomains, the finger, the palm, and the thumb (McDonald, 2013). With eight helices and a five-stranded β-sheet, the NiRAN domain adopts a nidovirus RdRp-associated nucleotidyltransferase (NiRAN) configuration whereas the interface domain is composed of three helices and five β-strands connects the other two domains. Yin et al. solved the structure of RdRp-NSP7-NSP-8 complex with 50 bases template-primer RNA and monophosphate form of remdesivir (Lehmann et al., 2015; Yin et al., 2020). While the structure of SARS-CoV-2 RdRp was highly similar to the one solved by Gao et al., this structure provides a molecular explanation of why the RdRp complex recognizes RNA and not DNA as the template. This structure also showed remdesivir monophosphate covalently incorporated at the 3′ end of the primer in the center of the catalytic active site providing molecular detail of the mechanism of action of this antiviral drug (Yin et al., 2020).

4.3.1.3 Helicase (NSP13)

NSP13 of SARS-CoV-2 is a multifunctional protein. It acts as helicase which catalyzes the unwinding of duplex oligonucleotides (RNA or DNA) in 5′−3′ direction and also functions as an NTPase which hydrolyzes nucleotide triphosphates (NTPs) to derive the energy required for unwinding (Shu et al., 2020). NSP13 is known to have the highest sequence conservation amongst the Coronavirus family and thus could be a potential target for anti-CoV drugs (Adedeji et al., 2014; Jang et al., 2008; Shum & Tanner, 2008). Various groups have demonstrated that this helicase can unwind both double-stranded DNA and RNA (Ivanov et al., 2004; Lee et al., 2010; Tanner et al., 2003). The N-terminus of this protein is highly conserved which is postulated to form a Zn^{2+} binding cluster. This cluster was demonstrated to be very crucial for helicase activity *in vitro* (Seybert et al., 2005). NSP13 can unwind double-stranded oligonucleotide with a minimum of five

single-stranded nucleotides as overhang at the 5′ end of the oligonucleotide and is estimated to unwind them at the rate of 280 base pairs per second (Adedeji et al., 2012).

The overall structure of the protein takes a triangular pyramid shape which has five domains; domain 1A, domain 2A, domain 1B, N-terminal zinc-binding domain (ZBD) and stalk domain. The two RecA-like domains, 1A and 2A, along with domain 1B form the triangular base of the pyramidal protein while the ZBD and the stalk domain point toward the peak of the pyramid. Out of all the domains of the helicase protein, domain 1A has been suggested to have oligonucleotide unwinding properties (Jia et al., 2019).

Molecules like flavonoids, myricetin, and scutellarin are known to inhibit the NTPase activity and thus can be used to inhibit NSP13 (Mirza & Froeyen, 2020; Yu et al., 2012). In SARS-CoV-1, the use of a compound 3-[(2-nitrophenyl)sulphanylmethyl]-4prop-2-enyl-1H-1,2,4-triazole-5-thione inhibited the helicase activity of NSP13 (Adedeji et al., 2012). Among the patented inhibitors of NSP13, SSYA10−001, 1,2,4-triazole compound, is the most characterized inhibitor. It noncompetitively inhibits the helicase and the NTPAse activity of NSP13 and has been shown to inhibit viral propagation of multiple Coronaviruses like SRAS-CoV-1, MERS-CoV, etc making it a pan-Coronavirus (pan-CoV) inhibitor (Spratt et al., 2021). Two compounds, 3,5-Dihydroxychromone and aryl diketoacids, are also patented inhibitors of NTPase activity of NSP13. Although patented inhibitors are available, the complete pharmacokinetics data is not available and also some of them contain chemical moieties that can inhibit other cellular functions (Spratt et al., 2021). Other known NSP13 inhibitors include adamantane-derived bananins, bismuth complexes, thioxopyrimidine derivatives, an acrylamide derivative [(E)-3-(furan-2-yl)-N-(4-sulfamoylphenyl)acrylamide], a purine derivative (7-ethyl-8-mercapto-3-methyl-3,7-dihydro-1 H-purine-2,6-dione), and RNA aptamers (Jang et al., 2008).

4.3.1.4 2′O-methyltransferase (NSP16)

NSP16 codes for an enzyme 2′O-methyltransferase (2′O-MTase). 2′O-MTase or NSP16 forms a protein complex with NSP10, a cofactor for the activation of NSP14 and NSP16, and adds a methyl group to the 2′ hydroxy position of the ribose sugar on the penultimate nucleotide of the viral RNA cap. This process is dependent on the methyl donor S-adenosyl-L-methionine (SAM) (Chen et al., 2011). Viral RNA cap is methylated first by NSP14 at guanosine N7 to form cap0 and then methylated by NSP10/16 complex at 2′O group of ribose forming cap1. This viral RNA cap1 mimics the 5′ cap of eukaryotic mRNA due to which the host becomes unable to recognize self/nonself mRNA and fails to activate the innate immune system (Menachery et al., 2014). SARS-CoV-2 2′O-MTase belongs to the RrmJ/fibrillarin superfamily of 2′O methyltransferases and is highly conserved among other Coronaviruses and also among viral orthologues in Flaviviruses, Alphaviruses, and Nidoviruses (Feder et al., 2003).

Upon solving the crystal structure of the NSP10/16 protein complex, it was revealed that the heterocomplex can be viewed as one molecule of NSP16 placed on top of one molecule of NSP10. NSP16 monomer comprises twelve β-strands, five 3_{10} helices, and seven α-helices. The core of the folded protein comprises seven β strands (β1- β7) which is surrounded by α-helices and loops. The N terminus of the central core comprises η1 3_{10}-helix, β8-strand, and αf-helix, η2 3_{10}-helix, and helix αD while the C terminus is decorated by three β strands (β 10−β12), 2 α-helices (αg and αh) and 3_{10}-helices (η4 and η5). NSP10 comprises three β-strands which forms the central β-sheet, three α-helices and two 3_{10}

helices (α-helices α2′−α4′ and 3_{10}-helices η1′ and η2′) which covers one side of the central sheet (Chen et al., 2011; Lin et al., 2020).

NSP16 is thought to be a very promising target for drug designing against CoVs as it has been shown that 2′O-Mtase is crucial for viral propagation and replication (Daffis et al., 2010; Decroly et al., 2008). Sinefungin, a pan-MTase inhibitor, inhibits the protein by binding to the substrate (SAM) binding pocket of the heterocomplex. If the protein is not bound to SAM, it cannot methylate the cap and hence will evoke host innate immunity. Other molecules that can inhibit 2′O-MTase activity by interfering with SAM binding are S-adenosyl-l-homocysteine, and aurintricarboxylic acid (Bouvet et al., 2010; Wang et al., 2020; Decroly et al., 2011; He et al., 2004). One limitation with using inhibitors against 2′O-MTase substrate binding is that it may also interfere with host 2′O-MTsae thereby disturbing host activities. Another strategy to inhibit viral 2′O-MTase activity is targeting the association between NSP10 and NSP16. Ke et al. showed that two peptides derived from SARS CoV-1 NSP10-NSP16 interaction domains can ablate NSP16 2′O-MTase activity (Ke et al., 2012). Another approach for inhibition is targeting N7 methylation of the 5′ cap by targeting NSP14. It is to be noted that the induction of host interferon-stimulated genes response is important for the effectiveness of the above-mentioned inhibitors and the efficacy of each inhibitor may vary depending on the interferon antagonists encoded by different Coronaviruses (Menachery et al., 2014).

4.3.2 Structural proteins

4.3.2.1 Spike (S) glycoprotein

Spike protein or simply S protein facilitates binding and entry of virus to the host cells making it the most important virulence factor, hence a key target for the development of prophylactics and therapeutics against COVID-19 (Walls et al., 2020). S protein exists as homotrimer forming a bulbous structure. These characteristic bulbous structures cover the virus particle giving the appearance of a halo around it, thus the name Coronavirus. Each monomer of spike protein consists of an N-terminal S1 subunit (head) mediating binding to cell surface receptor, angiotensin-converting enzyme 2 (ACE2), and a C-terminal S2 subunit (stalk) facilitating viral fusion to host and entry (Bosch et al., 2003; Li, 2016; Walls et al., 2017). S protein-mediated binding and entry of virus to host cell is an intricate process. A host protease, Transmembrane Serine Protease 2 (TMPRSS2) upon binding of S1 subunit to ACE2 receptors cleaves S protein which brings about substantial irreversible changes in the conformation of S2 subunit leading to membrane fusion and entry (Belouzard et al., 2009; Heald-Sargent & Gallagher, 2012; Walls et al., 2017). The structure of the SARS-CoV-2S protein trimer was solved by two different research teams using cryoelectron microscopy and demonstrates high similarity with SARS-CoV S protein (Walls et al., 2020; Wrapp et al., 2020).

The S1 subunit comprises an N-terminal domain (NTD) and a receptor-binding domain (RBD). In the prefusion state, the S1 subunit helps maintain the stability of the entire trimer and prevents conformational changes in S2 before activation (Walls et al., 2020). The RBD in S1 subunit has a core and receptor binding motif (RBM) which directly interacts with the peptidase domain of ACE2 (Kirchdoerfer et al., 2018; Song et al., 2018). The RBD in S1 subunit can shuffle between an “up” or “down” states in a hinge-like conformational

movement as in other Coronaviruses (Gui et al., 2017; Pallesen et al., 2017; Wrapp & McLellan, 2019). This movement could be asymmetrical where RBD in one S1 subunit could be in "up" confirmation while other two could be in "down." RBD in the "up" conformation is accessible to the receptor while the "down" remains inaccessible (Walls et al., 2020). Atomic structures of RBD in complex with ACE2 have been solved using cryoelectron microscopy and crystallography to provide molecular details of S1-ACE2 interaction (Lan et al., 2020; Yan et al., 2020). These structures show that RBM forms a shallow concave surface with a ridge on one side and which allows it to make contact with the arch-shaped outer surface of ACE2. While the structure of the SARS-CoV-2 RBD/ACE2 complex is very similar to the SARS-CoV RBD/ACE2 complex, biochemical studies demonstrated that SARS-CoV-2 has a significantly higher binding affinity for ACE2 receptors (Wrapp et al., 2020). Closer examination of binding interfaces of these structures provides the explanation for the higher affinity of SARS-CoV-2 RBD, where 21 residues of it directly interact with ACE2 as opposed to only 17 in the case of SARS-CoV RBD. Furthermore, mutations of key residues changing the nature of the interaction between RBD and ACE2 enhances the strength of binding in the case of SARS-CoV-2 (Lan et al., 2020; Walls et al., 2020; Wrapp et al., 2020; Wang et al., 2020).

While the binding of SARS-CoV-2 to host cell receptor ACE2 is mediated by the S1 subunit of S protein, it is the S2 subunit that brings about the fusion and entry of virus particles to the host cells. The S2 subunit is composed of a hydrophobic fusion peptide (FP), two heptad repeat regions, HR1 and HR2, a transmembrane domain (TM), and a cytoplasmic domain (Walls et al., 2020). Once the S1 subunit binds the ACE2 receptor, the S2 subunit undergoes conformational changes, FP inserts into the target cell membrane, HR1 trimer interacts with HR2 to form a 6-helical bundle. These events bring viral envelopes in proximity for viral fusion and entry (Xia et al., 2018). SARS-CoV-2 and SARS-CoV-S2 subunits are highly similar in structure as well as sequence. HR1 and HR2 domains between these two viruses share sequence identities of 92.6% and 100%, respectively, and the HR1 domain from one virus can form the 6-helical bundle with HR2 domain from the other virus (Xia et al., 2019, 2020).

Due to its role in viral fusion and entry, the essential steps in viral pathogenesis, S protein has been considered an important target for developing small molecule inhibitors of viral binding and entry. Furthermore, S protein unlike other SARS-CoV-2 proteins is antigenic and induces host immune response, and neutralizing antibodies (nAbs) against S protein can provide a protective immune response making it an excellent candidate for developing vaccines and neutralizing antibodies targeting RBD, or NTD in S1 or S2 subunit. Several human monoclonal antibodies (311mab-31B5, 311mab-32D4, 47D11, n3130, n3088, S309, P2C-1F11, P2B) have been cloned from a single memory B cell from COVID-19 recovered patient which neutralizes SARS-CoV-2 and prevents infection in vitro (Chi et al., 2020; Ju et al., 2020; Pinto et al., 2020; Wu et al., 2020; Chen et al., 2020; Wang et al., 2020). A SARS-CoV specific mAb C3022 binds SARS-CoV-2 with high affinity suggesting this can be developed into a therapeutic for COVID-19. Apart from these biologicals, several inhibitors of S protein-mediated fusion have been developed and tested for their ability to prevent SARS-CoV-2 infection. HR1 and HR2 domains are involved in viral fusion and entry to host cells. A peptide designed from SARS-CoV-2 HR2 (1168−1203 residues) was shown to inhibit viral fusion and entry (Xia et al., 2020). A pan-CoV fusion inhibitor

peptide EK1 was developed which showed an inhibitory effect against various human CoVs but in the micromolar range making it less desirable (Xia et al., 2019). Zhu et al. designed a lipopeptide derivative of EK1 called EK1C4 which was shown to inhibit SARS-CoV-2 with an IC_{50} of 15.8 nM, an improvement of approximately 149-fold over IC_{50} of EK1. They also developed another lipopeptide fusion inhibitor, IPB02 capable of potently inhibiting SARS-CoV-2 S protein-mediated cell−cell fusion and pseudovirus infection (Zhu, Yu, et al., 2020). Proteolytic cleavage by host proteases is required for the activation of S protein, making this step another important drug target. A protease inhibitor, nelfinavir mesylate (Viracept), currently used as an anti-HIV drug has been shown to inhibit S protein-mediated cell fusion in SARS-CoV-2 as well SARS-CoV suggesting that similar drugs can be designed or the available protease inhibitors can be repurposed for treatment of COVID-19 (Musarrat et al., 2020).

4.3.2.2 Nucleocapsid (N) protein

Nucleocapsid (N) protein is essential for viral replication and transmission (Zhu, Zhu, et al., 2020). It is a multivalent RNA binding protein that packages the positive-sense RNA genome into a helical ribonucleoprotein (RNP) structure and also assists in virion assembly by interacting with the viral genome and M protein (Cong et al., 2020; Masters & Sturman, 1990; Stertz et al., 2007). It shares 91% sequence homology and structural homology with the N protein of SARS-CoV-1 (Zeng et al., 2020). In comparison to S protein, which is an obvious drug target against SARS-CoV-2, the N gene sequence was found to be more stable among Coronaviruses with a fairly low mutation rate (Marra et al., 2003; Zhu et al., 2005). Among all Coronaviruses, N protein has been demonstrated to be highly immunogenic and is responsible for early antibody response in CoV infected patients (Ahmed et al., 2020; Cong et al., 2020; Liu et al., 2006). All these characteristics make this protein a very promising drug target against SARS-CoV-2.

Nucleocapsid protein of beta Coronaviruses, in general, exists in dimers and comprise mainly three highly conserved domains. The N terminal domain N1b, responsible for RNA binding, a C terminal domain N2b, responsible for dimerization and a central Ser/Arg rich disordered linker, B/N3 responsible for phosphorylation (Chang et al., 2006; Lo et al., 2013; Saikatendu et al., 2007; Wootton et al., 2002). Gao et al. reported that the secondary structure of SARS-CoV-2 N protein consists of 21.24% alpha-helix,16.71% beta folds, 6.92% beta turns, and 55.13% random coils (Gao et al., 2021). The crystal structure of the N1b domain of SARS-CoV-2 revealed is made up of a beta-sheet core that has a short alpha-helix with five antiparallel beta-strands resembling a palm, a long beta-hairpin that protrudes between β2 and β5 resembling a protruding finger and finally a long loop region that resembles a wrist. Thus the N1b protein overall resembles a right hand (Kang et al., 2020). The N2b domain is composed of a total of four-stranded beta-sheets at the dimer interface of the compactly intertwined dimerized protein. Each protomer extends two beta-strands and a short alpha-helix toward each other and packs against their hydrophobic core of the protein (Ye et al., 2020).

Because of its importance in RNA packaging, inhibition of N protein is a potential target for inhibiting viral replication. One of the strategies is to block the NTD mediated RNA binding of N protein. In HCoV-Oc34, small compounds like pJ34 and H3 have been demonstrated to reduce RNA binding at NTD of N protein (Chang et al., 2016).

The residues at the RNA binding sites of N proteins in SARS Cov2 are the same thus indicating that these compounds could also be used against SARS-CoV-2 (Peng et al., 2020). Changhyun Roh screened various polyphenolic compounds as an inhibitor against N protein in SARS CoV and found (−)-catechin gallate and (−)-gallocatechin gallate to remarkably inhibit the activity of N protein (Roh, 2012). Another strategy to inhibit N protein activity is manipulating its oligomerization. In MERS CoV, 5-Benzyloxygramine (p3) induced nonnative dimerization of N protein thus causing its aggregation. This makes it unavailable for RNP complex formation and ultimately block RNA packaging (Lin et al., 2020; Peng et al., 2020). The use of competitive peptides in HCoV 229E N protein is also known to interfere with dimer formation at the C-terminal end (Lo et al., 2013).

4.4 Alteration of host metabolome during severe acute respiratory syndrome-Coronavirus-2 infection

In the system biology approach of studying infectious disease, genomics and proteomics analyses are suggestive of the consequences of the infection. On the contrary, metabolomics provides the actual phenotypic snapshot of the disease making it arguably the most suitable approach for disease prognosis. Several comparative metabolomics studies have been conducted on blood serum samples from COVID-19 patients displaying varying degree severity to characterize the host immune and metabolic responses underlying the disease progression using nuclear magnetic resonance (NMR) spectroscopy or mass spectrometry techniques (Segers et al., 2019). A survey of available literature suggests major changes in amino acid metabolism, carbohydrate/central energy metabolism, lipid metabolism, and change in levels of metabolites linked to host immune responses.

4.4.1 Energy metabolism

Danlos et al. performed targeted and untargeted metabolomic profiling of 72 COVID-19 patients presented with varying degrees of disease severity using gas chromatography-mass spectrometry (GC-Ms) and ultra-high-pressure liquid chromatography-mass spectrometry (UHPLC-Ms). They observed that sugars such as arabinose, ribose, ribitol, mannose, maltose, raffinose, and sugar alcohols (arabitol, erythritol, and xylitol) were increased in critical patients (Danlos et al., 2021). They further demonstrated that increased levels of pyruvate and 3-hydroxybutyrate, along with the significant decrease in citrate and free amino acids such as alanine, glycine, glutamine, and histidine in COVID-19 patients indicated an impairment of energy metabolism in these patients (Danlos et al., 2021). MeoniI and coworkers made similar observations using ^{1}H NMR spectroscopy where they observed an increase in levels of sugars such3-hydroxybutyrate, mannose, glucose, pyruvate, and amino acids like isoleucine, leucine, phenylalanine, creatinine, and valine in severe patients. These patients had lower levels of many amino acids such as tyrosine, histidine, glutamine, alanine, and glycine and small fatty acid molecule such as formate, acetate, and citrate, indicative of impaired energy metabolism further supporting the findings of Danlos and coworkers (Danlos et al., 2021; Meoni et al., 2021).

A *meta*-analysis of metabolome datasets by Pang et al. also revealed perturbation in several amino acid synthesis pathways and energy metabolism including the mannose metabolism pathway. Glyoxylate and dicarboxylate metabolism pathway was found to be downregulated in severe COVID-19 patients compared to mild or moderate cases (Pang et al., 2021).

4.4.2 Immunomodulatory metabolism

Comparative metabolomics study of plasma from healthy controls, mild and severe COVID-19 patients revealed the signature of immune-suppressive metabolism in severe patients. Danlos et al. found that while tryptophan levels were down, products of tryptophan catabolism, kynurenic acid, and anthranilic acid levels were elevated in severe COVID-19 patients (Danlos et al., 2021). In a separate study, Cai et al. attributed increased propensity of human males for severe COVID-19 as compared to females to perturbation in kynurenine pathway metabolites, kynurenine, and kynurenic acid. They found that severely ill male patients had high kynurenic acid and high kynurenic acid to kynurenine ratio correlated with immune responses (Cai et al., 2021). Kynurenic acid is a competitive inhibitor of glutamate receptors and consequently, glutamate levels were found to be low in severe COVID-19 patients (Schwarcz et al., 2012; Cai et al., 2021). The kynurenine pathway has been shown to play role in neurological disorders, depression, and inflammation (Platten et al., 2005). This pathway starts with the conversion of tryptophan to kynurenine by tryptophan dioxygenase or indoleamine dioxygenase, which is then converted to kynurenic acid by kynurenine hydroxylase (Davis & Liu, 2015). Anthranilic acid is a downstream metabolite of the kynurenine pathway and has been shown to have an immunosuppressive effect (Davis & Liu, 2015; Platten et al., 2005). Diminished levels of tryptophan in mild and severe COVID-19 patients along with increased kynurenic acid and high kynurenic acid to kynurenine ratio suggest over activation of rate-limiting enzymes, tryptophan dioxygenase, or indoleamine dioxygenase. It is worthwhile to explore the therapeutic potential of the inhibitors of these enzymes for severe COVID-19 patients.

4.4.3 Lipid metabolism

Bruzzone et al. conducted a study to measure the lipidomic and metabolomic changes in the serum of symptomatic, asymptomatic COVID-19 patients and healthy controls. Their study revealed that the composition and particle sizes of lipoproteins in the SARS-CoV-2 infected patients varied greatly from healthy controls thus increasing their risk of atherosclerosis. A triglyceride-rich lipid profile is seen in COVID-19 patients with a remarkable increase in low-density cholesterol (Bruzzone et al., 2020). Such acute dysregulation, obviously pathogenic, when found in nonacute conditions like metabolic syndrome or nonalcoholic fatty liver disease fits well with increased atherosclerotic risk. Moolamalla et al. did an extensive study to see the changes in metabolism in COVID-19 patients and found major dysregulations in lipid metabolism. They found that genes for fatty acid degradation and elongation are down-regulated. Genes and enzymes involved in fatty acid synthesis like fatty acid synthase (FASN) are down-regulated in COVID-19 patients. Genes involved in steroid synthesis from cholesterol are upregulated but the genes involved in

cholesterol synthesis, HMGCS1, and HMGCR, are down-regulated in comparison to healthy controls. *De novo* synthesis of sphingolipids, synthesis of glycerophospholipids, and glycosphingolipids are significantly upregulated in COVID-19 patients (Moolamalla et al., 2020). To avoid recognition by the host, it has been observed that RNA viruses hijack the exosomal pathway. In line with this fact, a study conducted by Song et al. revealed that the overall lipid signatures in the CVID infected patients' serum mirrors that of the exosomal membrane lipid composition. They correlated the presence of monosialodihexosyl ganglioside (GM3) enriched exosomes with the pathogenesis of COVID-19 (Song et al., 2020).

Bioactive lipids such especially eicosanoids (20 carbon) and docosanoids (22 carbon) are known to modulate the immune response. While eicosanoids likely exacerbate inflammation by promoting leukocyte recruitment/activation, exudate formation, stimulating platelet aggregation, and thrombus formation, docosanoids are known to resolve inflammation by damping it. Archambault and coworkers compared the levels of bioactive lipids in the bronchoalveolar lavage (BAL) samples of healthy and severe COVID-19 patients and found that the levels of all the eicosanoids and docosanoids except Maresin-1 and -2 were elevated in severe COVID-19 patients. Some notable lipids found elevated in these patients were arachidonic acid, COX metabolites such as thromboxane, prostaglandin E2, prostaglandin D2, leukotrienes such LTB_4 and its metabolite 20-COOH-LTB_4. It is notable that levels of these lipids in the blood did not mirror their BAL levels suggesting a lung-specific bioactive lipid storm in severe COVID-19 patients (Archambault et al., 2021).

This gross perturbation of bioactive lipids in the lung of severe COVID-19 patients provides an argument for the use of lipid modulators as therapeutics for treating severe patients. Dexamethasone decreases COX-2 expression limiting the production of COX metabolites. This may in part explain the beneficial effect of this drug in managing severe COVID-19 patients (Tomazini et al., 2020). Other COX inhibitors such as aspirin may be explored for their use in subverting inflammatory lipid storms (Archambault et al., 2021). Fact that Aspirin has been shown to be beneficial in acute respiratory distress syndrome patients furthers the argument of evaluating this drug for treating COVID-19 patients (Abdulnour et al., 2018; Archambault et al., 2021; Chow et al., 2021; Merzon et al., 2021).

4.5 Conclusion

The multiomics-based approach of studying COVID-19 has helped understand SARS-CoV-2 transmission, evolution, virulence, and pathophysiology of infection enabling the design of diagnostic assays, formulation of public health policies for the containment of infection, development of vaccines and drugs as well patients management strategies. Genomics and proteomics analyses of SARS-CoV-2 have helped develop, assess and/or predict the course of the disease, diagnostic tools, and control measures. Metabolomic profiling of samples from COVID-19 patients has provided a phenotypic snapshot of the disease furthering our understanding of the pathophysiology of the disease aiding in the development of better care and management of the disease. Although the policymakers, scientists, and clinicians have risen to the occasion and responded to the pandemic brilliantly, the threat of COVID-19 is far from over. While constantly evolving virus impacting transmission dynamics and efficacy of control measures warrant the development of

pan-CoV strategies infallible to genetic variation of the virus, changing disease prognosis and post-COVID-19 complications calls for better understanding of pathophysiology to the disease. It is, therefore imperative that the efforts to better understand the virus and the disease it causes, are continued.

References

Abdulnour, R. E. E., Gunderson, T., Barkas, I., Timmons, J. Y., Barnig, C., Gong, M., Kor, D. J., Gajic, O., Talmor, D., Carter, R. E., & Levy, B. D. (2018). Early intravascular events are associated with development of acute respiratory distress syndrome a substudy of the lips-A clinical trial. *American Journal of Respiratory and Critical Care Medicine*, *197*(12), 1575–1585. Available from https://doi.org/10.1164/rccm.201712-2530OC.

Adedeji, A. O., Marchand, B., Te Velthuis, A. J. W., Snijder, E. J., Weiss, S., Eoff, R. L., Singh, K., & Sarafianos, S. G. (2012). Mechanism of nucleic acid unwinding by SARS-CoV helicase. *PLoS One*, *7*(5), e36521. Available from https://doi.org/10.1371/journal.pone.0036521.

Adedeji, A. O., Singh, K., Calcaterra, N. E., DeDiego, M. L., Enjuanes, L., Weiss, S., & Sarafianos, S. G. (2012). Severe acute respiratory syndrome Coronavirus replication inhibitor that interferes with the nucleic acid unwinding of the viral helicase. *Antimicrobial Agents and Chemotherapy*, *56*(9), 4718–4728. Available from https://doi.org/10.1128/AAC.00957-12.

Adedeji, A. O., Singh, K., Kassim, A., Coleman, C. M., Elliott, R., Weiss, S. R., Frieman, M. B., & Sarafianos, S. G. (2014). Evaluation of SSYA10-001 as a replication inhibitor of severe acute respiratory syndrome, mouse hepatitis, and Middle East respiratory syndrome Coronaviruses. *Antimicrobial Agents and Chemotherapy*, *58*(8), 4894–4898. Available from https://doi.org/10.1128/AAC.02994-14.

Aftab, S. O., Ghouri, M. Z., Masood, M. U., Haider, Z., Khan, Z., Ahmad, A., & Munawar, N. (2020). Analysis of SARS-CoV-2 RNA-dependent RNA polymerase as a potential therapeutic drug target using a computational approach. *Journal of Translational Medicine*, *18*(1). Available from https://doi.org/10.1186/s12967-020-02439-0.

Ahmed, S. F., Quadeer, A. A., & McKay, M. R. (2020). Preliminary identification of potential vaccine targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV immunological studies. *Viruses*, *12*(3). Available from https://doi.org/10.3390/v12030254.

Ahn, D. G., Choi, J. K., Taylor, D. R., & Oh, J. W. (2012). Biochemical characterization of a recombinant SARS Coronavirus nsp12 RNA-dependent RNA polymerase capable of copying viral RNA templates. *Archives of Virology*, *157*(11), 2095–2104. Available from https://doi.org/10.1007/s00705-012-1404-x.

Alharbi, S. N., & Alrefaei, A. F. (2021). Comparison of the SARS-CoV-2 (2019-nCoV) M protein with its counterparts of SARS-CoV and MERS-CoV species. *Journal of King Saud University - Science*, *33*(2), 101335. Available from https://doi.org/10.1016/j.jksus.2020.101335.

Anand, K., Palm, G. J., Mesters, J. R., Siddell, S. G., Ziebuhr, J., & Hilgenfeld, R. (2002). Structure of Coronavirus main proteinase reveals combination of a chymotrypsin fold with an extra α-helical domain. *EMBO Journal*, *21*(13), 3213–3224. Available from https://doi.org/10.1093/emboj/cdf327.

Archambault, A. S., Zaid, Y., Rakotoarivelo, V., Turcotte, C., Doré, É., Dubuc, I., Martin, C., Flamand, O., Amar, Y., Cheikh, A., Fares, H., El Hassani, A., Tijani, Y., Côté, A., Laviolette, M., Boilard, É., Flamand, L., & Flamand, N. (2021). High levels of eicosanoids and docosanoids in the lungs of intubated COVID-19 patients. *FASEB Journal*, *35*(6). Available from https://doi.org/10.1096/fj.202100540R.

Badua, C. L. D. C., Baldo, K. A. T., & Medina, P. M. B. (2021). Genomic and proteomic mutation landscapes of SARS-CoV-2. *Journal of Medical Virology*, *93*(3), 1702–1721. Available from https://doi.org/10.1002/jmv.26548.

Belouzard, S., Chu, V. C., & Whittaker, G. R. (2009). Activation of the SARS Coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. *Proceedings of the National Academy of Sciences of the United States of America*, *106*(14), 5871–5876. Available from https://doi.org/10.1073/pnas.0809524106.

Bhowmik, D., Nandi, R., Jagadeesan, R., Kumar, N., Prakash, A., & Kumar, D. (2020). Identification of potential inhibitors against SARS-CoV-2 by targeting proteins responsible for envelope formation and virion assembly using docking based virtual screening, and pharmacokinetics approaches. *Infection, Genetics and Evolution*, *84*, 104451. Available from https://doi.org/10.1016/j.meegid.2020.104451.

Brian, D. A., & Baric, R. S. (2005). Coronavirus genome structure and replication. *Current Topics in Microbiology and Immunology*, *287*, 1–30. Available from https://doi.org/10.1007/3-540-26765-4_1.

Bosch, B. J., Van der Zee, R., De Haan, C. A. M., & Rottier, P. J. M. (2003). The Coronavirus spike protein is a class I virus fusion protein: Structural and functional characterization of the fusion core complex. *Journal of Virology*, *77*(16), 8801–8811. Available from https://doi.org/10.1128/JVI.77.16.8801-8811.2003.

Bouvet, M., Debarnot, C., Imbert, I., Selisko, B., Snijder, E. J., Canard, B., & Decroly, E. (2010). In vitro reconstitution of sars-Coronavirus mRNA cap methylation. *PLoS Pathogens*, *6*(4), 1–13. Available from https://doi.org/10.1371/journal.ppat.1000863.

Bruzzone, C., Bizkarguenaga, M., Gil-Redondo, R., Diercks, T., Arana, E., García de Vicuña, A., Seco, M., Bosch, A., Palazón, A., San Juan, I., Laín, A., Gil-Martínez, J., Bernardo-Seisdedos, G., Fernández-Ramos, D., Lopitz-Otsoa, F., Embade, N., Lu, S., Mato, J. M., & Millet, O. (2020). SARS-CoV-2 infection dysregulates the metabolomic and lipidomic profiles of serum. *IScience*, *23*(10), 101645. Available from https://doi.org/10.1016/j.isci.2020.101645.

Cagliani, R., Forni, D., Clerici, M., & Sironi, M. (2020). Computational inference of selection underlying the evolution of the novel Coronavirus, severe acute respiratory syndrome Coronavirus 2. *Journal of Virology*, *94*(12). Available from https://doi.org/10.1128/JVI.00411-20.

Cai, Y., Kim, D., Takahashi, T., Broadhurst, D., Yan, H., et al. (2021). Kynurenic acid may underlie sex-specific immune responses to COVID-19. *Science Signaling*, *14*.

Canal, B., McClure, A. W., Curran, J. F., Wu, M., Ulferts, R., Weissmann, F., Zeng, J., Bertolin, A. P., Milligan, J. C., Basu, S., Drury, L. S., Deegan, T. D., Fujisawa, R., Roberts, E. L., Basier, C., Labib, K., Beale, R., Howell, M., & Diffley, J. F. X. (2021). Identifying SARS-CoV-2 antiviral compounds by screening for small molecule inhibitors of nsp14/nsp10 exoribonuclease. *Biochemical Journal*, *478*(13), 2445–2464. Available from https://doi.org/10.1042/BCJ20210198.

Cella, E., Benedetti, F., Fabris, S., Borsetti, A., Pezzuto, A., Ciotti, M., Pascarella, S., Ceccarelli, G., Zella, D., Ciccozzi, M., & Giovanetti, M. (2021). SARS-CoV-2 lineages and sub-lineages circulating worldwide: A dynamic overview. *Chemotherapy*, *66*(1–2), 3–7. Available from https://doi.org/10.1159/000515340.

Chan, J. F. W., To, K. K. W., Tse, H., Jin, D. Y., & Yuen, K. Y. (2013). Interspecies transmission and emergence of novel viruses: Lessons from bats and birds. *Trends in Microbiology*, *21*(10), 544–555. Available from https://doi.org/10.1016/j.tim.2013.05.005.

Chang, C. K., Jeyachandran, S., Hu, N. J., Liu, C. L., Lin, S. Y., Wang, Y. S., Chang, Y. M., & Hou, M. H. (2016). Structure-based virtual screening and experimental validation of the discovery of inhibitors targeted towards the human Coronavirus nucleocapsid protein. *Molecular Biosystems*, *12*(1), 59–66. Available from https://doi.org/10.1039/c5mb00582e.

Chang, C. K., Sue, S. C., Yu, T. H., Hsieh, C. M., Tsai, C. K., Chiang, Y. C., Lee, S. J., Hsiao, H. H., Wu, W. J., Chang, W. L., Lin, C. H., & Huang, T. H. (2006). Modular organization of SARS Coronavirus nucleocapsid protein. *Journal of Biomedical Science*, *13*(1), 59–72. Available from https://doi.org/10.1007/s11373-005-9035-9.

Chen, Y., Su, C., Ke, M., Jin, X., Xu, L., Zhang, Z., Wu, A., Sun, Y., Yang, Z., Tien, P., Ahola, T., Liang, Y., Liu, X., Guo, D., & Kuhn, R. J. (2011). Biochemical and structural insights into the mechanisms of SARS Coronavirus RNA ribose 2′-O-methylation by nsp16/nsp10 protein complex. *PLoS Pathogens*, *7*(10), e1002294. Available from https://doi.org/10.1371/journal.ppat.1002294.

Chen, X., Li, R., Pan, Z., Qian, C., Yang, Y., You, R., Zhao, J., Liu, P., Gao, L., Li, Z., Huang, Q., Xu, L., Tang, J., Tian, Q., Yao, W., Hu, L., Yan, X., Zhou, X., Wu, Y., & Ye, L. (2020). Human monoclonal antibodies block the binding of SARS-CoV-2 spike protein to angiotensin converting enzyme 2 receptor. *Cellular and Molecular Immunology*, *17*(6), 647–649. Available from https://doi.org/10.1038/s41423-020-0426-7.

Chi, X., Yan, R., Zhang, J., Zhang, G., Zhang, Y., Hao, M., Zhang, Z., Fan, P., Dong, Y., Yang, Y., Chen, Z., Guo, Y., Zhang, J., Li, Y., Song, X., Chen, Y., Xia, L., Fu, L., Hou, L., & Chen, W. (2020). A neutralizing human antibody binds to the N-terminal domain of the spike protein of SARS-CoV-2. *Science (New York, N.Y.)*, *369*(6504), 650–655. Available from https://doi.org/10.1126/science.abc6952.

Chow, J. H., Khanna, A. K., Kethireddy, S., Yamane, D., Levine, A., Jackson, A. M., McCurdy, M. T., Tabatabai, A., Kumar, G., Park, P., Benjenk, I., Menaker, J., Ahmed, N., Glidewell, E., Presutto, E., Cain, S., Haridasa, N., Field, W., Fowler, J. G., & Mazzeffi, M. A. (2021). Aspirin use is associated with decreased mechanical ventilation, intensive care unit admission, and in-hospital mortality in hospitalized patients with Coronavirus disease 2019. *Anesthesia and Analgesia*, 930–941. Available from https://doi.org/10.1213/ANE.0000000000005292.

Clementz, M. A., Chen, Z., Banach, B. S., Wang, Y., Sun, L., Ratia, K., Baez-Santos, Y. M., Wang, J., Takayama, J., Ghosh, A. K., Li, K., Mesecar, A. D., & Baker, S. C. (2010). Deubiquitinating and interferon antagonism

activities of Coronavirus papain-like proteases. *Journal of Virology*, *84*(9), 4619–4629. Available from https://doi.org/10.1128/JVI.02406-09.

Cong, Y., Ulasli, M., Schepers, H., Mauthe, M., V'kovski, P., Kriegenburg, F., Thiel, V., de Haan, C. A. M., & Reggiori, F. (2020). Nucleocapsid protein recruitment to replication-transcription complexes plays a crucial role in Coronaviral life cycle. *Journal of Virology*, *94*(4). Available from https://doi.org/10.1128/JVI.01925-19.

Daffis, S., Szretter, K. J., Schriewer, J., Li, J., Youn, S., Errett, J., Lin, T. Y., Schneller, S., Zust, R., Dong, H., Thiel, V., Sen, G. C., Fensterl, V., Klimstra, W. B., Pierson, T. C., Buller, R. M., Gale, M., Jr, Shi, P. Y., & Diamond, M. S. (2010). 2′-O methylation of the viral mRNA cap evades host restriction by IFIT family members. *Nature*, *468*(7322), 452–456. Available from https://doi.org/10.1038/nature09489.

Dai, W., Zhang, B., Jiang, X. M., Su, H., Li, J., Zhao, Y., Xie, X., Jin, Z., Peng, J., Liu, F., Li, C., Li, Y., Bai, F., Wang, H., Cheng, X., Cen, X., Hu, S., Yang, X., Wang, J., & Liu, H. (2020). Structure-based design of antiviral drug candidates targeting the SARS-CoV-2 main protease. *Science (New York, N.Y.)*, *368*(6497), 1331–1335. Available from https://doi.org/10.1126/science.abb4489.

Danlos, F. X., Grajeda-Iglesias, C., Durand, S., Sauvat, A., Roumier, M., Cantin, D., Colomba, E., Rohmer, J., Pommeret, F., Baciarello, G., Willekens, C., Vasse, M., Griscelli, F., Fahrner, J. E., Goubet, A. G., Dubuisson, A., Derosa, L., Nirmalathasan, N., Bredel, D., & Kroemer, G. (2021). Metabolomic analyses of COVID-19 patients unravel stage-dependent and prognostic biomarkers. *Cell Death and Disease*, *12*(3). Available from https://doi.org/10.1038/s41419-021-03540-y.

Davis, I., & Liu, A. (2015). What is the tryptophan kynurenine pathway and why is it important to neurotherapeutics? *Expert Review of Neurotherapeutics*, *15*(7), 719–721. Available from https://doi.org/10.1586/14737175.2015.1049999.

de Lima Menezes, Gabriela, & da Silva, Roosevelt Alves (2021). Identification of potential drugs against SARS-CoV-2 non-structural protein 1 (nsp1). *Journal of Biomolecular Structure and Dynamics*, *39*(15), 5657–5667. Available from https://doi.org/10.1080/07391102.2020.1792992.

Decroly, E., Debarnot, C., Ferron, F., Bouvet, M., Coutard, B., Imbert, I., Gluais, L., Papageorgiou, N., Sharff, A., Bricogne, G., Ortiz-Lombardia, M., Lescar, J., Canard, B., & Rey, F. A. (2011). Crystal structure and functional analysis of the SARS-Coronavirus RNA cap 2′-O-methyltransferase nsp10/nsp16 complex. *PLoS Pathogens*, *7*(5), e1002059. Available from https://doi.org/10.1371/journal.ppat.1002059.

Decroly, E., Imbert, I., Coutard, B., Bouvet, M., Selisko, B., Alvarez, K., Gorbalenya, A. E., Snijder, E. J., & Canard, B. (2008). Coronavirus nonstructural protein 16 is a cap-0 binding enzyme possessing (nucleoside-2′O)-methyltransferase activity. *Journal of Virology*, *82*(16), 8071–8084. Available from https://doi.org/10.1128/JVI.00407-08.

Doğan, H. O., Şenol, O., Bolat, S., Yıldız, Ş. N., Büyüktuna, S. A., Sarısmailoğlu, R., Doğan, K., Hasbek, M., & Hekim, S. N. (2021). Understanding the pathophysiological changes via untargeted metabolomics in COVID-19 patients. *Journal of Medical Virology*, *93*(4), 2340–2349. Available from https://doi.org/10.1002/jmv.26716.

Feder, M., Pas, J., Wyrwicz, L. S., & Bujnicki, J. M. (2003). Molecular phylogenetics of the RrmJ/fibrillarin superfamily of ribose 2′-O-methyltransferases. *Gene*, *302*(1–2), 129–138. Available from https://doi.org/10.1016/S0378-1119(02)01097-1.

Gao, Y., Yan, L., Huang, Y., Liu, F., Zhao, Y., Cao, L., Wang, T., Sun, Q., Ming, Z., Zhang, L., Ge, J., Zheng, L., Zhang, Y., Wang, H., Zhu, Y., Zhu, C., Hu, T., Hua, T., Zhang, B., & Rao, Z. (2020). Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science (New York, N.Y.)*, *368*(6492), 779–782. Available from https://doi.org/10.1126/science.abb7498.

Gao, T., Gao, Y., Liu, X., Nie, Z., Sun, H., Lin, K., Peng, H., & Wang, S. (2021). Identification and functional analysis of the SARS-COV-2 nucleocapsid protein. *BMC Microbiology*, *21*(1). Available from https://doi.org/10.1186/s12866-021-02107-3.

Ghosh, S., Dellibovi-Ragheb., Kerviel, A., Pak., Qiu, Q., Fisher, M., et al. (2020). Beta-Coronaviruses use lysosomes for egress instead of the biosynthetic secretory pathway. *Cell*, *183*, 1520–1535.

Giovanetti, M., Benedetti, F., Campisi, G., Ciccozzi, A., Fabris, S., Ceccarelli, G., Tambone, V., Caruso, A., Angeletti, S., Zella, D., & Ciccozzi, M. (2021). Evolution patterns of SARS-CoV-2: Snapshot on its genome variants. *Biochemical and Biophysical Research Communications*, *538*, 88–91. Available from https://doi.org/10.1016/j.bbrc.2020.10.102.

Gordon, D. E., Hiatt, J., Bouhaddou, M., Rezelj, V. V., Ulferts, S., Braberg, H., Jureka, A. S., Obernier, K., Guo, J. Z., Batra, J., Kaake, R. M., Weckstein, A. R., Owens, T. W., Gupta, M., Pourmal, S., Titus, E. W., Cakir, M., Soucheray, M., McGregor, M., & Krogan, N. J. (2020). Comparative host-Coronavirus protein interaction

networks reveal pan-viral disease mechanisms. *Science (New York, N.Y.)*, *370*(6521), eabe9403. Available from https://doi.org/10.1126/science.abe9403.

Graham, R. L., & Baric, R. S. (2010). Recombination, reservoirs, and the modular spike: Mechanisms of Coronavirus cross-species transmission. *Journal of Virology*, *84*(7), 3134–3146. Available from https://doi.org/10.1128/JVI.01394-09.

Gui, M., Song, W., Zhou, H., Xu, J., Chen, S., Xiang, Y., & Wang, X. (2017). Cryo-electron microscopy structures of the SARS-CoV spike glycoprotein reveal a prerequisite conformational state for receptor binding. *Cell Research*, *27*(1), 119–129. Available from https://doi.org/10.1038/cr.2016.152.

Guo, Y. R., Cao, Q. D., Hong, Z. S., Tan, Y. Y., Chen, S. D., Jin, H. J., Tan, K. S., Wang, D. Y., & Yan, Y. (2020). The origin, transmission and clinical therapies on Coronavirus disease 2019 (COVID-19) outbreak- A n update on the status. *Military Medical Research*, *7*(1). Available from https://doi.org/10.1186/s40779-020-00240-0.

Hayden, F. G., Turner, R. B., Gwaltney, J. M., Chi-Burris, K., Gersten, M., Hsyu, P., Patick, A. K., Smith, G. J., & Zalman, L. S. (2003). Phase II, randomized, double-blind, placebo-controlled studies of ruprintrivir nasal spray 2-percent suspension for prevention and treatment of experimentally induced rhinovirus colds in healthy volunteers. *Antimicrobial Agents and Chemotherapy*, *47*(12), 3907–3916. Available from https://doi.org/10.1128/AAC.47.12.3907-3916.2003.

He, R., Adonov, A., Traykova-Adonova, M., Cao, J., Cutts, T., Grudesky, E., Deschambaul, Y., Berry, J., Drebot, M., & Li, X. (2004). Potent and selective inhibition of SARS Coronavirus replication by aurintricarboxylic acid. *Biochemical and Biophysical Research Communications*, *320*(4), 1199–1203. Available from https://doi.org/10.1016/j.bbrc.2004.06.076.

Heald-Sargent, T., & Gallagher, T. (2012). Ready, set, fuse! the Coronavirus spike protein and acquisition of fusion competence. *Viruses*, *4*(4), 557–580. Available from https://doi.org/10.3390/v4040557.

Holshue, M. L., DeBolt, C., Lindquist, S., Lofy, K. H., Wiesman, J., Bruce, H., Spitters, C., Ericson, K., Wilkerson, S., Tural, A., Diaz, G., Cohn, A., Fox, L. A., Patel, A., Gerber, S. I., Kim, L., Tong, S., Lu, X., & Lindstrom, S. (2020). First case of 2019 novel Coronavirus in the United States. *New England Journal of Medicine*, *382*(10), 929–936. Available from https://doi.org/10.1056/NEJMoa2001191.

Hsu, J. C. C., Laurent-Rolle, M., Pawlak, J. B., Wilen, C. B., & Cresswell, P. (2021). Translational shutdown and evasion of the innate immune response by SARS-CoV-2 NSP14 protein. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(24). Available from https://doi.org/10.1073/pnas.2101161118.

Ivanov, K. A., Hertzig, T., Rozanov, M., Bayer, S., Thiel, V., Gorbalenya, A. E., & Ziebuhr, J. (2004). Major genetic marker of nidoviruses encodes a replicative endoribonuclease. *Proceedings of the National Academy of Sciences of the United States of America*, *101*(34), 12694–12699. Available from https://doi.org/10.1073/pnas.0403127101.

Jang, K. J., Lee, N. R., Yeo, W. S., Jeong, Y. J., & Kim, D. E. (2008). Isolation of inhibitory RNA aptamers against severe acute respiratory syndrome (SARS) Coronavirus NTPase/Helicase. *Biochemical and Biophysical Research Communications*, *366*(3), 738–744. Available from https://doi.org/10.1016/j.bbrc.2007.12.020.

Jia, Z., Yan, L., Ren, Z., Wu, L., Wang, J., Guo, J., Zheng, L., Ming, Z., Zhang, L., Lou, Z., & Rao, Z. (2019). Delicate structural coordination of the severe acute respiratory syndrome Coronavirus Nsp13 upon ATP hydrolysis. *Nucleic Acids Research*, *47*(12), 6538–6550. Available from https://doi.org/10.1093/nar/gkz409.

Jin, Z., Du, X., Xu, Y., Deng, Y., Liu, M., Zhao, Y., Zhang, B., Li, X., Zhang, L., Peng, C., Duan, Y., Yu, J., Wang, L., Yang, K., Liu, F., Jiang, R., Yang, X., You, T., Liu, X., & Yang, H. (2020). Structure of Mpro from SARS-CoV-2 and discovery of its inhibitors. *Nature*, *582*(7811), 289–293. Available from https://doi.org/10.1038/s41586-020-2223-y.

Ju, B., Zhang, Q., Ge, J., Wang, R., Sun, J., Ge, X., Yu, J., Shan, S., Zhou, B., Song, S., Tang, X., Yu, J., Lan, J., Yuan, J., Wang, H., Zhao, J., Zhang, S., Wang, Y., Shi, X., & Zhang, L. (2020). Human neutralizing antibodies elicited by SARS-CoV-2 infection. *Nature*, *584*(7819), 115–119. Available from https://doi.org/10.1038/s41586-020-2380-z.

Jungreis, Sealfon, & Kellis, M. (2020). SARS-CoV-2 gene content and COVID-19 mutation impact by comparing 44 Sarbecovirus genomes.

Kang, S., Yang, M., Hong, Z., Zhang, L., Huang, Z., Chen, X., He, S., Zhou, Z., Zhou, Z., Chen, Q., Yan, Y., Zhang, C., Shan, H., & Chen, S. (2020). Crystal structure of SARS-CoV-2 nucleocapsid protein RNA binding domain reveals potential unique drug targeting sites. *Acta Pharmaceutica Sinica B*, *10*(7), 1228–1238. Available from https://doi.org/10.1016/j.apsb.2020.04.009.

Ke, M., Chen, Y., Wu, A., Sun, Y., Su, C., Wu, H., Jin, X., Tao, J., Wang, Y., Ma, X., Pan, J. A., & Guo, D. (2012). 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 Research*, *167*(2), 322–328. Available from https://doi.org/10.1016/j.virusres.2012.05.017.

Kim, Y., Liu, H., Kankanamalage, A. C. G., Weerasekara, S., Hua, D. H., Groutas, W. C., Chang, K.-O., & Pedersen, N. C. (2016). Correction: Reversal of the progression of fatal coronavirus infection in cats by a broad-spectrum Coronavirus protease inhibitor. *PLoS Pathogens*, e1005650. Available from https://doi.org/10.1371/journal.ppat.1005650.

Kim, D., Lee, J. Y., Yang, J. S., Kim, J. W., Kim, V. N., & Chang, H. (2020). The architecture of SARS-CoV-2 transcriptome. *Cell*, *181*(4), 914–921, e10. Available from https://doi.org/10.1016/j.cell.2020.04.011.

Kirchdoerfer, R. N., & Ward, A. B. (2019). Structure of the SARS-CoV nsp12 polymerase bound to nsp7 and nsp8 co-factors. *Nature Communications*, *10*(1). Available from https://doi.org/10.1038/s41467-019-10280-3.

Kirchdoerfer, R. N., Wang, N., Pallesen, J., Wrapp, D., Turner, H. L., Cottrell, C. A., Corbett, K. S., Graham, B. S., McLellan, J. S., & Ward, A. B. (2018). Stabilized Coronavirus spikes are resistant to conformational changes induced by receptor recognition or proteolysis. *Scientific Reports*, *8*(1). Available from https://doi.org/10.1038/s41598-018-34171-7.

Konno, Y., Kimura, I., Uriu, K., Fukushi, M., Irie, T., Koyanagi, Y., Sauter, D., Gifford, R. J., Nakagawa, S., & Sato, K. (2020). SARS-CoV-2 ORF3b is a potent interferon antagonist whose activity is increased by a naturally occurring elongation variant. *Cell Reports*, *32*(12), 108185. Available from https://doi.org/10.1016/j.celrep.2020.108185.

Kupferschmidt, K. (2020). Genome analyses help track Coronavirus' moves. *Science (New York, N.Y.)*, *367*(6483), 1176–1177. Available from https://doi.org/10.1126/science.367.6483.1177.

Lan, J., Ge, J., Yu, J., Shan, S., Zhou, H., Fan, S., Zhang, Q., Shi, X., Wang, Q., Zhang, L., & Wang, X. (2020). Structure of the SARS-CoV-2 spike receptor-binding domain bound to the ACE2 receptor. *Nature*, *581*(7807), 215–220. Available from https://doi.org/10.1038/s41586-020-2180-5.

Lau, S. K. P., Woo, P. C. Y., Li, K. S. M., Huang, Y., Tsoi, H. W., Wong, B. H. L., Wong, S. S. Y., Leung, S. Y., Chan, K. H., & Yuen, K. Y. (2005). Severe acute respiratory syndrome Coronavirus-like virus in Chinese horseshoe bats. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(39), 14040–14045. Available from https://doi.org/10.1073/pnas.0506735102.

Lee, N. R., Kwon, H. M., Park, K., Oh, S., Jeong, Y. J., & Kim, D. E. (2010). Cooperative translocation enhances the unwinding of duplex DNA by SARS Coronavirus helicase nsP13. *Nucleic Acids Research*, *38*(21), 7626–7636. Available from https://doi.org/10.1093/nar/gkq647.

Lehmann, K. C., Gulyaeva, A., Zevenhoven-Dobbe, J. C., Janssen, G. M. C., Ruben, M., Overkleeft, H. S., Van Veelen, P. A., Samborskiy, D. V., Kravchenko, A. A., Leontovich, A. M., Sidorov, I. A., Snijder, E. J., Posthuma, C. C., & Gorbalenya, A. E. (2015). Discovery of an essential nucleotidylating activity associated with a newly delineated conserved domain in the RNA polymerase-containing protein of all nidoviruses. *Nucleic Acids Research*, *43*(17), 8416–8434. Available from https://doi.org/10.1093/nar/gkv838.

Li, F. (2016). Structure, function, and evolution of coronavirus spike proteins. *Annual Review of Virology*, *3*, 237–261. Available from https://doi.org/10.1146/annurev-virology-110615-042301.

Li, Z., Li, X., Huang, Y. Y., Wu, Y., Liu, R., Zhou, L., Lin, Y., Wu, D., Zhang, L., Liu, H., Xu, X., Yu, K., Zhang, Y., Cui, J., Zhan, C. G., Wang, X., & Luo, H. B. (2020). Identify potent SARS-CoV-2 main protease inhibitors via accelerated free energy perturbation-based virtual screening of existing drugs. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(44), 27381–27387. Available from https://doi.org/10.1073/pnas.2010470117.

Lin, S., Chen, H., Ye, F., Chen, Z., Yang, F., Zheng, Y., Cao, Y., Qiao, J., Yang, S., & Lu, G. (2020). Crystal structure of SARS-CoV-2 nsp10/nsp16 2′-O-methylase and its implication on antiviral drug design. *Signal Transduction and Targeted Therapy*, *5*(1). Available from https://doi.org/10.1038/s41392-020-00241-4.

Lin, S. M., Lin, S. C., Hsu, J. N., Chang, C. K., Chien, C. M., Wang, Y. S., Wu, H. Y., Jeng, U. S., Kehn-Hall, K., & Hou, M. H. (2020). Structure-based stabilization of non-native protein-protein interactions of Coronavirus nucleocapsid proteins in antiviral drug design. *Journal of Medicinal Chemistry*, *63*(6), 3131–3141. Available from https://doi.org/10.1021/acs.jmedchem.9b01913.

Liu, S., Leng, C., Lien, S., Chi, H., Huang, C., Lin, C., Lian, W., Chen, C., Hsieh, S., & Chong, P. (2006). Immunological characterizations of the nucleocapsid protein based SARS vaccine candidates. *Vaccine*, *24*(16), 3100–3108. Available from https://doi.org/10.1016/j.vaccine.2006.01.058.

Lo, Y. S., Lin, S. Y., Wang, S. M., Wang, C. T., Chiu, Y. L., Huang, T. H., & Hou, M. H. (2013). Oligomerization of the carboxyl terminal domain of the human Coronavirus 229E nucleocapsid protein. *FEBS Letters*, *587*(2), 120–127. Available from https://doi.org/10.1016/j.febslet.2012.11.016.

Mandala, V. S., McKay, M. J., Shcherbakov, A. A., Dregni, A. J., Kolocouris, A., & Hong, M. (2020). Structure and drug binding of the SARS-CoV-2 envelope protein transmembrane domain in lipid bilayers. *Nature Structural and Molecular Biology*, *27*(12), 1202–1208. Available from https://doi.org/10.1038/s41594-020-00536-8.

Mariano, G., Farthing, R. J., Lale-Farjat, S. L. M., & Bergeron, J. R. C. (2020). Structural characterization of SARS-CoV-2: Where we are, and where we need to be. *Frontiers in Molecular Biosciences*, *7*. Available from https://doi.org/10.3389/fmolb.2020.605236.

Marra, M. A., Jones, S. J. M., Astell, C. R., Holt, R. A., Brooks-Wilson, A., Butterfield, Y. S. N., Khattra, J., Asano, J. K., Barber, S. A., Chan, S. Y., Cloutier, A., Coughlin, S. M., Freeman, D., Girn, N., Griffith, O. L., Leach, S. R., Mayo, M., McDonald, H., Montgomery, S. B., & Roper, R. L. (2003). The genome sequence of the SARS-associated Coronavirus. *Science (New York, N.Y.)*, *300*(5624), 1399–1404. Available from https://doi.org/10.1126/science.1085953.

Masters, P. S., & Sturman, L. S. (1990). Background paper: Functions of the Coronavirus nucleocapsid protein. *Advances in Experimental Medicine and Biology*, *276*, 235–238. Available from https://doi.org/10.1007/978-1-4684-5823-7_32.

Mathew, B. J., Vyas, A. K., Khare, P., Gupta, S., Nema, R. K., Nema, S., Gupta, S., Chaurasiya, S. K., Biswas, D., & Singh, A. K. (2021). Laboratory diagnosis of covid-19: Current status and challenges. *Iranian Journal of Microbiology*, *13*(1), 1–7. Available from https://ijm.tums.ac.ir/index.php/ijm/article/view/2843/1309.

McDonald, S. M. (2013). RNA synthetic mechanisms employed by diverse families of RNA viruses. *Wiley Interdisciplinary Reviews: RNA*, *4*(4), 351–367. Available from https://doi.org/10.1002/wrna.1164.

Menachery, V. D., Debbink, K., & Baric, R. S. (2014). Coronavirus non-structural protein 16: Evasion, attenuation, and possible treatments. *Virus Research*, *194*, 191–199. Available from https://doi.org/10.1016/j.virusres.2014.09.009.

Meoni, G., Ghini, V., Maggi, L., Vignoli, A., Mazzoni, A., Salvati, L., Capone, M., Vanni, A., Tenori, L., Fontanari, P., Lavorini, F., Peris, A., Bartoloni, A., Liotta, F., Cosmi, L., Luchinat, C., Annunziato, F., Turano, P., & Subbarao, K. (2021). Metabolomic/lipidomic profiling of COVID-19 and individual response to tocilizumab. *PLoS Pathogens*, *17*(2), e1009243. Available from https://doi.org/10.1371/journal.ppat.1009243.

Merzon, E., Green, I., Vinker, S., Golan-Cohen, A., Gorohovski, A., Avramovich, E., Frenkel-Morgenstern, M., & Magen, E. (2021). The use of aspirin for primary prevention of cardiovascular disease is associated with a lower likelihood of COVID-19 infection. *FEBS Journal*. Available from https://doi.org/10.1111/febs.15784.

Miao, G., Zhao, H., Li, Y., Ji, M., Chen, Y., Shi, Y., Bi, Y., Wang, P., & Zhang, H. (2021). ORF3a of the COVID-19 virus SARS-CoV-2 blocks HOPS complex-mediated assembly of the SNARE complex required for autolysosome formation. *Developmental Cell*, *56*(4), 427–442, e5. Available from https://doi.org/10.1016/j.devcel.2020.12.010.

Miorin, L., Kehrer, T., Sanchez-Aparicio, M. T., Zhang, K., Cohen, P., Patel, R. S., Cupic, A., Makio, T., Mei, M., Moreno, E., Danziger, O., White, K. M., Rathnasinghe, R., Uccellini, M., Gao, S., Aydillo, T., Mena, I., Yin, X., Martin-Sancho, L., & García-Sastre, A. (2020). SARS-CoV-2 Orf6 hijacks Nup98 to block STAT nuclear import and antagonize interferon signaling. *Proceedings of the National Academy of Sciences of the United States of America*, *117*(45), 28344–28354. Available from https://doi.org/10.1073/pnas.2016650117.

Mirza, M. U., & Froeyen, M. (2020). Structural elucidation of SARS-CoV-2 vital proteins: Computational methods reveal potential drug candidates against main protease, Nsp12 polymerase and Nsp13 helicase. *Journal of Pharmaceutical Analysis*, *10*(4), 320–328. Available from https://doi.org/10.1016/j.jpha.2020.04.008.

Moolamalla, S.T.R., Chauhan, R., Priyakumar, U.D., & Vinod, P.K. (2020). Host metabolic reprogramming in response to SARS-Cov-2 infection. *BioRxiv*. <https://www.biorxiv.org/content/10.1101/2020.08.02.232645v1>

Muramatsu, T., Takemoto, C., Kim, Y. T., Wang, H., Nishii, W., Terada, T., Shirouzu, M., & Yokoyama, S. (2016). SARS-CoV 3CL protease cleaves its C-terminal autoprocessing site by novel subsite cooperativity. *Proceedings of the National Academy of Sciences of the United States of America*, *113*(46), 12997–13002. Available from https://doi.org/10.1073/pnas.1601327113.

Musarrat, F., Chouljenko, V., Dahal, A., Nabi, R., Chouljenko, T., Jois, S. D., & Kousoulas, K. G. (2020). The anti-HIV drug nelfinavir mesylate (Viracept) is a potent inhibitor of cell fusion caused by the SARSCoV-2 spike (S) glycoprotein warranting further evaluation as an antiviral against COVID-19 infections. *Journal of Medical Virology*, *92*(10), 2087–2095. Available from https://doi.org/10.1002/jmv.25985.

Naqvi, A. A. T., Fatima, K., Mohammad, T., Fatima, U., Singh, I. K., Singh, A., Atif, S. M., Hariprasad, G., Hasan, G. M., & Hassan, M. I. (2020). Insights into SARS-CoV-2 genome, structure, evolution, pathogenesis and therapies: Structural genomics approach. *Biochimica et Biophysica Acta - Molecular Basis of Disease*, *1866*(10). Available from https://doi.org/10.1016/j.bbadis.2020.165878.

Pallesen, J., Wang, N., Corbett, K. S., Wrapp, D., Kirchdoerfer, R. N., Turner, H. L., Cottrell, C. A., Becker, M. M., Wang, L., Shi, W., Kong, W. P., Andres, E. L., Kettenbach, A. N., Denison, M. R., Chappell, J. D., Graham, B. S., Ward, A. B., & McLellan, J. S. (2017). Immunogenicity and structures of a rationally designed prefusion MERS-CoV spike antigen. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(35), E7348–E7357. Available from https://doi.org/10.1073/pnas.1707304114.

Pang, Z., Zhou, G., Chong, J., & Xia, J. (2021). Comprehensive *meta*-analysis of covid-19 global metabolomics datasets. *Metabolites*, *11*(1), 1–14. Available from https://doi.org/10.3390/metabo11010044.

Peng, Y., Du, N., Lei, Y., Dorje, S., Qi, J., Luo, T., Gao, G. F., & Song, H. (2020). Structures of the SARS-CoV-2 nucleocapsid and their perspectives for drug design. *EMBO Journal*, *39*(20). Available from https://doi.org/10.15252/embj.2020105938.

Pillaiyar, T., Manickam, M., Namasivayam, V., Hayashi, Y., & Jung, S. H. (2016). An overview of severe acute respiratory syndrome-Coronavirus (SARS-CoV) 3CL protease inhibitors: Peptidomimetics and small molecule chemotherapy. *Journal of Medicinal Chemistry*, *59*(14), 6595–6628. Available from https://doi.org/10.1021/acs.jmedchem.5b01461.

Pinto, D., Park, Y. J., Beltramello, M., Walls, A. C., Tortorici, M. A., Bianchi, S., Jaconi, S., Culap, K., Zatta, F., De Marco, A., Peter, A., Guarino, B., Spreafico, R., Cameroni, E., Case, J. B., Chen, R. E., Havenar-Daughton, C., Snell, G., Telenti, A., & Corti, D. (2020). Cross-neutralization of SARS-CoV-2 by a human monoclonal SARS-CoV antibody. *Nature*, *583*(7815), 290–295. Available from https://doi.org/10.1038/s41586-020-2349-y.

Platten, M., Ho, P. P., Youssef, S., Fontoura, P., Garren, H., Hur, E. M., Gupta, R., Lee, L. Y., Kidd, B. A., Robinson, W. H., Sobel, R. A., Selley, M. L., & Steinman, L. (2005). Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. *Science (New York, N.Y.)*, *310*(5749), 850–855. Available from https://doi.org/10.1126/science.1117634.

Rambaut, A., Holmes, E. C., O'Toole, Á., Hill, V., McCrone, J. T., Ruis, C., du Plessis, L., & Pybus, O. G. (2020). A dynamic nomenclature proposal for SARS-CoV-2 lineages to assist genomic epidemiology. *Nature Microbiology*, *5*(11), 1403–1407. Available from https://doi.org/10.1038/s41564-020-0770-5.

Ren, Y., Shu, T., Wu, D., Mu, J., Wang, C., Huang, M., Han, Y., Zhang, X. Y., Zhou, W., Qiu, Y., & Zhou, X. (2020). The ORF3a protein of SARS-CoV-2 induces apoptosis in cells. *Cellular and Molecular Immunology*, *17*(8), 881–883. Available from https://doi.org/10.1038/s41423-020-0485-9.

Ren, Z., Yan, L., Zhang, N., Guo, Y., Yang, C., Lou, Z., & Rao, Z. (2013). The newly emerged SARS-Like Coronavirus HCoV-EMC also has an \Achilles' heel\: Current effective inhibitor targeting a 3C-like protease. *Protein and Cell*, *4*(4), 248–250. Available from https://doi.org/10.1007/s13238-013-2841-3.

Rogstam, A., Nyblom, M., Christensen, S., Sele, C., Talibov, V. O., Lindvall, T., Rasmussen, A. A., André, I., Fisher, Z., Knecht, W., & Kozielski, F. (2020). Crystal structure of non-structural protein 10 from severe acute respiratory syndrome Coronavirus-2. *International Journal of Molecular Sciences*, *21*(19), 1–15. Available from https://doi.org/10.3390/ijms21197375.

Roh, C. (2012). A facile inhibitor screening of SARS Coronavirus N protein using nanoparticle-based RNA oligonucleotide. *International Journal of Nanomedicine*, *7*, 2173–2179. Available from https://doi.org/10.2147/IJN.S31379.

Romano, M., Ruggiero, A., Squeglia, F., Maga, G., & Berisio, R. (2020). A structural view of SARS-CoV-2 RNA replication machinery: RNA synthesis, proofreading and final capping. *Cells*, *9*(5). Available from https://doi.org/10.3390/cells9051267.

Rut, W., Lv, Z., Zmudzinski, M., Patchett, S., Nayak, D., Snipas, S. J., Oualid, F. E., Huang, T. T., Bekes, M., Drag, M., & Olsen, S. K. (2020). Activity profiling and crystal structures of inhibitor-bound SARS-CoV-2 papain-like protease: A framework for anti–COVID-19 drug design. *Science Advances*, *6*(42). Available from https://doi.org/10.1126/sciadv.abd4596.

Saikatendu, K. S., Joseph, J. S., Subramanian, V., Neuman, B. W., Buchmeier, M. J., Stevens, R. C., & Kuhn, P. (2007). Ribonucleocapsid formation of severe acute respiratory syndrome Coronavirus through molecular action of the N-terminal domain of N protein. *Journal of Virology*, *81*(8), 3913–3921. Available from https://doi.org/10.1128/JVI.02236-06.

Sawicki, S. G., Sawicki, D. L., & Siddell, S. G. (2007). A contemporary view of Coronavirus transcription. *Journal of Virology*, *81*(1), 20–29. Available from https://doi.org/10.1128/JVI.01358-06.

Schwarcz, R., Bruno, J. P., Muchowski, P. J., & Wu, H. Q. (2012). Kynurenines in the mammalian brain: When physiology meets pathology. *Nature Reviews. Neuroscience*, *13*(7), 465–477. Available from https://doi.org/10.1038/nrn3257.

Segers, K., Declerck, S., Mangelings, D., Heyden, Y. V., & Eeckhaut, A. V. (2019). Analytical techniques for metabolomic studies: A review. *Bioanalysis*, *11*(24), 2297–2318. Available from https://doi.org/10.4155/bio-2019-0014.

Seybert, A., Posthuma, C. C., Van Dinten, L. C., Snijder, E. J., Gorbalenya, A. E., & Ziebuhr, J. (2005). A complex zinc finger controls the enzymatic activities of nidovirus helicases. *Journal of Virology*, *79*(2), 696–704. Available from https://doi.org/10.1128/JVI.79.2.696-704.2005.

Shu, T., Huang, M., Wu, D., Ren, Y., Zhang, X., Han, Y., Mu, J., Wang, R., Qiu, Y., Zhang, D. Y., & Zhou, X. (2020). SARS-Coronavirus-2 Nsp13 possesses NTPase and RNA helicase activities that can be inhibited by bismuth salts. *Virologica Sinica*, *35*(3), 321–329. Available from https://doi.org/10.1007/s12250-020-00242-1.

Shum, K. T., & Tanner, J. A. (2008). Differential inhibitory activities and stabilisation of DNA aptamers against the SARS Coronavirus helicase. *Chembiochem: A European Journal of Chemical Biology*, *9*(18), 3037–3045. Available from https://doi.org/10.1002/cbic.200800491.

Siegel, D., Hui, H. C., Doerffler, E., Clarke, M. O., Chun, K., Zhang, L., Neville, S., Carra, E., Lew, W., Ross, B., Wang, Q., Wolfe, L., Jordan, R., Soloveva, V., Knox, J., Perry, J., Perron, M., Stray, K. M., Barauskas, O., & Mackman, R. L. (2017). Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine C-nucleoside (GS-5734) for the treatment of ebola and emerging viruses. *Journal of Medicinal Chemistry*, *60*(5), 1648–1661. Available from https://doi.org/10.1021/acs.jmedchem.6b01594.

Song, W., Gui, M., Wang, X., Xiang, Y., & Heise, M. T. (2018). Cryo-EM structure of the SARS Coronavirus spike glycoprotein in complex with its host cell receptor ACE2. *PLoS Pathogens*, *14*(8), e1007236. Available from https://doi.org/10.1371/journal.ppat.1007236.

Song, J. W., Lam, S. M., Fan, X., Cao, W. J., Wang, S. Y., Tian, H., Chua, G. H., Zhang, C., Meng, F. P., Xu, Z., Fu, J. L., Huang, L., Xia, P., Yang, T., Zhang, S., Li, B., Jiang, T. J., Wang, R., Wang, Z., & Shui, G. (2020). Omics-driven systems interrogation of metabolic dysregulation in COVID-19 pathogenesis. *Cell Metabolism*, *32*(2), 188–202, e5. Available from https://doi.org/10.1016/j.cmet.2020.06.016.

Spratt, A. N., Gallazzi, F., Quinn, T. P., Lorson, C. L., Sönnerborg, A., & Singh, K. (2021). Coronavirus helicases: Attractive and unique targets of antiviral drug-development and therapeutic patents. *Expert Opinion on Therapeutic Patents*, *31*(4), 339–350. Available from https://doi.org/10.1080/13543776.2021.1884224.

Stertz, S., Reichelt, M., Spiegel, M., Kuri, T., Martínez-Sobrido, L., García-Sastre, A., Weber, F., & Kochs, G. (2007). The intracellular sites of early replication and budding of SARS-Coronavirus. *Virology*, *361*(2), 304–315. Available from https://doi.org/10.1016/j.virol.2006.11.027.

Sutton, G., Fry, E., Carter, L., Sainsbury, S., Walter, T., Nettleship, J., Berrow, N., Owens, R., Gilbert, R., Davidson, A., Siddell, S., Poon, L. L. M., Diprose, J., Alderton, D., Walsh, M., Grimes, J. M., & Stuart, D. I. (2004). The nsp9 replicase protein of SARS-coronavirus, structure and functional insights. *Structure (London, England: 1993)*, *12*(2), 341–353. Available from https://doi.org/10.1016/j.str.2004.01.016.

te Velthuis, A. J. W., Arnold, J. J., Cameron, C. E., van den Worm, S. H. E., & Snijder, E. J. (2010). The RNA polymerase activity of SARS-Coronavirus nsp12 is primer dependent. *Nucleic Acids Research*, *38*, 203–214. Available from https://doi.org/10.1093/nar/gkp904.

Tanner, J. A., Watt, R. M., Chai, Y. B., Lu, L. Y., Lin, M. C., Peiris, J. S. M., Poon, L. L. M., Kung, H. F., & Huang, J. D. (2003). The severe acute respiratory syndrome (SARS) Coronavirus NTPasefhelicase belongs to a distinct class of 5′ to 3′ viral helicases. *Journal of Biological Chemistry*, *278*(41), 39578–39582. Available from https://doi.org/10.1074/jbc.C300328200.

Thoms, M., Buschauer, R., Ameismeier, M., Koepke, L., Denk, T., Hirschenberger, M., Kratzat, H., Hayn, M., Mackens-Kiani, T., Cheng, J., Straub, J. H., Stürzel, C. M., Fröhlich, T., Berninghausen, O., Becker, T., Kirchhoff, F., Sparrer, K. M. J., & Beckmann, R. (2020). Structural basis for translational shutdown and immune evasion by the Nsp1 protein of SARS-CoV-2. *Science (New York, N.Y.)*, *369*(6508), 1249–1255. Available from https://doi.org/10.1126/science.abc8665.

Tomazini, B. M., Maia, I. S., Cavalcanti, A. B., Berwanger, O., Rosa, R. G., Veiga, V. C., Avezum, A., Lopes, R. D., Bueno, F. R., Silva, M. V. A. O., Baldassare, F. P., Costa, E. L. V., Moura, R. A. B., Honorato, M. O., Costa, A. N., Damiani, L. P., Lisboa, T., Kawano-Dourado, L., Zampieri, F. G., & Azevedo, L. C. P. (2020). Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: The CoDEX randomized clinical trial. *JAMA - Journal of the American Medical Association*, *324*(13), 1307–1316. Available from https://doi.org/10.1001/jama.2020.17021.

V'kovski, P., Kratzel, A., Steiner, S., Stalder, H., & Thiel, V. (2021). Coronavirus biology and replication: Implications for SARS-CoV-2. *Nature Reviews. Microbiology*, *19*(3), 155–170. Available from https://doi.org/10.1038/s41579-020-00468-6.

Walls, A. C., Park, Y. J., Tortorici, M. A., Wall, A., McGuire, A. T., & Veesler, D. (2020). Structure, function, and antigenicity of the SARS-CoV-2 spike glycoprotein. *Cell*, *181*(2), 281–292, e6. Available from https://doi.org/10.1016/j.cell.2020.02.058.

Walls, A. C., Tortorici, M. A., Snijder, J., Xiong, X., Bosch, B. J., Rey, F. A., & Veesler, D. (2017). Tectonic conformational changes of a Coronavirus spike glycoprotein promote membrane fusion. *Proceedings of the National Academy of Sciences of the United States of America*, *114*(42), 11157–11162. Available from https://doi.org/10.1073/pnas.1708727114.

Wang, H., Pipes, L., & Nielsen, R. (2021). Synonymous mutations and the molecular evolution of SARS-CoV-2 origins. *Virus Evolution*, *7*(1). Available from https://doi.org/10.1093/ve/veaa098.

Wang, M., Cao, R., Zhang, L., Yang, X., Liu, J., Xu, M., Shi, Z., Hu, Z., Zhong, W., & Xiao, G. (2020). Remdesivir and chloroquine effectively inhibit the recently emerged novel Coronavirus (2019-nCoV) in vitro. *Cell Research*, *30*(3), 269–271. Available from https://doi.org/10.1038/s41422-020-0282-0.

Wang, C., Li, W., Drabek, D., Okba, N. M. A., van Haperen, R., Osterhaus, A. D. M. E., van Kuppeveld, F. J. M., Haagmans, B. L., Grosveld, F., & Bosch, B. J. (2020). A human monoclonal antibody blocking SARS-CoV-2 infection. *Nature Communications*, *11*(1). Available from https://doi.org/10.1038/s41467-020-16256-y.

Wang, F., Chen, C., Tan, W., Yang, K., & Yang, H. (2016). Structure of main protease from human Coronavirus NL63: Insights for wide spectrum anti-Coronavirus drug design. *Scientific Reports*, *6*. Available from https://doi.org/10.1038/srep22677.

Wang, Q., Zhang, Y., Wu, L., Niu, S., Song, C., Zhang, Z., Lu, G., Qiao, C., Hu, Y., Yuen, K.-Y., Wang, Q., Zhou, H., Yan, J., & Qi, J. (2020). Structural and functional basis of SARS-CoV-2 entry by using human ACE2. *Cell*, *181*(4), 894–904, e9. Available from https://doi.org/10.1016/j.cell.2020.03.045.

Warren, T. K., Jordan, R., Lo, M. K., Ray, A. S., Mackman, R. L., Soloveva, V., Siegel, D., Perron, M., Bannister, R., Hui, H. C., Larson, N., Strickley, R., Wells, J., Stuthman, K. S., Van Tongeren, S. A., Garza, N. L., Donnelly, G., Shurtleff, A. C., Retterer, C. J., & Bavari, S. (2016). Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature*, *531*(7594), 381–385. Available from https://doi.org/10.1038/nature17180.

WHO Coronavirus (COVID-19) Dashboard. (2021). <https://covid19.who.int/>.

Wootton, S. K., Rowland, R. R. R., & Yoo, D. (2002). Phosphorylation of the porcine reproductive and respiratory syndrome virus nucleocapsid protein. *Journal of Virology*, *76*(20), 10569–10576. Available from https://doi.org/10.1128/JVI.76.20.10569-10576.2002.

Wrapp, D., & McLellan, J. S. (2019). The 3.1-angstrom cryo-electron microscopy structure of the porcine epidemic diarrhea virus spike protein in the prefusion conformation. *Journal of Virology*, *9*(23). Available from https://doi.org/10.1128/JVI.00923-19.

Wrapp, D., Wang, N., Corbett, K. S., Goldsmith, J. A., Hsieh, C. L., Abiona, O., Graham, B. S., & McLellan, J. S. (2020). Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. *Science (New York, N.Y.)*, *367*(6483), 1260–1263. Available from https://doi.org/10.1126/science.aax0902.

Wu, C., Liu, Y., Yang, Y., Zhang, P., Zhong, W., Wang, Y., Wang, Q., Xu, Y., Li, M., Li, X., Zheng, M., Chen, L., & Li, H. (2020). Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods. *Acta Pharmaceutica Sinica B*, *10*(5), 766–788. Available from https://doi.org/10.1016/j.apsb.2020.02.008.

Wu, F., Zhao, S., Yu, B., Chen, Y. M., Wang, W., Song, Z. G., Hu, Y., Tao, Z. W., Tian, J. H., Pei, Y. Y., Yuan, M. L., Zhang, Y. L., Dai, F. H., Liu, Y., Wang, Q. M., Zheng, J. J., Xu, L., Holmes, E. C., & Zhang, Y. Z. (2020). A new Coronavirus associated with human respiratory disease in China. *Nature*, *579*(7798), 265–269. Available from https://doi.org/10.1038/s41586-020-2008-3.

Wu, Y., Li, C., Xia, S., Tian, X., Kong, Y., Wang, Z., Gu, C., Zhang, R., Tu, C., Xie, Y., Yang, Z., Lu, L., Jiang, S., & Ying, T. (2020). Identification of human single-domain antibodies against SARS-CoV-2. *Cell Host & Microbe*, *27*(6), 891–898, e5. Available from https://doi.org/10.1016/j.chom.2020.04.023.

Xia, H., Cao, Z., Xie, X., Zhang, X., Chen, J. Y.-C., Wang, H., Menachery, V. D., Rajsbaum, R., & Shi, P.-Y. (2020). Evasion of type I interferon by SARS-CoV-2. *Cell Reports*, *33*(1), 108234. Available from https://doi.org/10.1016/j.celrep.2020.108234.

Xia, S., Xu, W., Wang, Q., Wang, C., Hua, C., Li, W., Lu, L., & Jiang, S. (2018). Peptide-based membrane fusion inhibitors targeting HCOV-229E spike protein HR1 and HR2 domains. *International Journal of Molecular Sciences*, *19*(2). Available from https://doi.org/10.3390/ijms19020487.

Xia, S., Yan, L., Xu, W., Agrawal, A. S., Algaissi, A., Tseng, C. T. K., Wang, Q., Du, L., Tan, W., Wilson, I. A., Jiang, S., Yang, B., & Lu, L. (2019). A pan-Coronavirus fusion inhibitor targeting the HR1 domain of human Coronavirus spike. *Science Advances*, *5*(4). Available from https://doi.org/10.1126/sciadv.aav4580.

Xia, S., Zhu, Y., Liu, M., Lan, Q., Xu, W., Wu, Y., Ying, T., Liu, S., Shi, Z., Jiang, S., & Lu, L. (2020). Fusion mechanism of 2019-nCoV and fusion inhibitors targeting HR1 domain in spike protein. *Cellular and Molecular Immunology*, *17*(7), 765–767. Available from https://doi.org/10.1038/s41423-020-0374-2.

Xue, X., Yu, H., Yang, H., Xue, F., Wu, Z., Shen, W., Li, J., Zhou, Z., Ding, Y., Zhao, Q., Zhang, X. C., Liao, M., Bartlam, M., & Rao, Z. (2008). Structures of two Coronavirus main proteases: Implications for substrate binding and antiviral drug design. *Journal of Virology*, *82*(5), 2515–2527. Available from https://doi.org/10.1128/JVI.02114-07.

Yan, R., Zhang, Y., Li, Y., Xia, L., Guo, Y., & Zhou, Q. (2020). Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science (New York, N.Y.)*, *367*(6485), 1444–1448. Available from https://doi.org/10.1126/science.abb2762.

Yang, H., Xie, W., Xue, X., Yang, K., Ma, J., Liang, W., Zhao, Q., Zhou, Z., Pei, D., Ziebuhr, J., Hilgenfeld, R., Yuen, K. Y., Wong, L., Gao, G., Chen, S., Chen, Z., Ma, D., Bartlam, M., Rao, Z., & Bjorkman, P. (2005). Design of wide-spectrum inhibitors targeting coronavirus main proteases. *PLoS Biology*, e324. Available from https://doi.org/10.1371/journal.pbio.0030324.

Ye, Q., West, A. M. V., Silletti, S., & Corbett, K. D. (2020). Architecture and self-assembly of the SARS-CoV-2 nucleocapsid protein. *Protein Science*, *29*(9), 1890–1901. Available from https://doi.org/10.1002/pro.3909.

Yin, W., Mao, C., Luan, X., Shen, D. D., Shen, Q., Su, H., Wang, X., Zhou, F., Zhao, W., Gao, M., Chang, S., Xie, Y. C., Tian, G., Jiang, H. W., Tao, S. C., Shen, J., Jiang, Y., Jiang, H., Xu, Y., & Xu, H. E. (2020). Structural basis for inhibition of the RNA-dependent RNA polymerase from SARS-CoV-2 by remdesivir. *Science (New York, N.Y.)*, *368*(6498), 1499–1504. Available from https://doi.org/10.1126/science.abc1560.

Yu, M. S., Lee, J., Lee, J. M., Kim, Y., Chin, Y. W., Jee, J. G., Keum, Y. S., & Jeong, Y. J. (2012). Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS Coronavirus helicase, nsP13. *Bioorganic and Medicinal Chemistry Letters*, *22*(12), 4049–4054. Available from https://doi.org/10.1016/j.bmcl.2012.04.081.

Zeng, W., Liu, G., Ma, H., Zhao, D., Yang, Y., Liu, M., Mohammed, A., Zhao, C., Yang, Y., Xie, J., Ding, C., Ma, X., Weng, J., Gao, Y., He, H., & Jin, T. (2020). Biochemical characterization of SARS-CoV-2 nucleocapsid protein. *Biochemical and Biophysical Research Communications*, *527*(3), 618–623. Available from https://doi.org/10.1016/j.bbrc.2020.04.136.

Zhai, Y., Sun, F., Li, X., Pang, H., Xu, X., Bartlam, M., & Rao, Z. (2005). Insights into SARS-CoV transcription and replication from the structure of the nsp7–nsp8 hexadecamer. *Nature Structural & Molecular Biology*, *12*(11), 980–986. Available from https://doi.org/10.1038/nsmb999.

Zhang, L., Lin, D., Sun, X., Curth, U., Drosten, C., Sauerhering, L., Becker, S., Rox, K., & Hilgenfeld, R. (2020). Crystal structure of SARS-CoV-2 main protease provides a basis for design of improved a-ketoamide inhibitors. *Science (New York, N.Y.)*, *368*(6489), 409–412. Available from https://doi.org/10.1126/science.abb3405.

Zhang, Y., Chen, Y., Li, Y., Huang, F., Luo, B., Yuan, Y., Xia, B., Ma, X., Yang, T., Yu, F., Liu, J., Liu, B., Song, Z., Chen, J., Yan, S., Wu, L., Pan, T., Zhang, X., Li, R., & Zhang, H. (2021). The ORF8 protein of SARS-CoV-2 mediates immune evasion through down-regulating MHC-I. *Proceedings of the National Academy of Sciences of the United States of America*, *118*(23). Available from https://doi.org/10.1073/pnas.2024202118.

Zheng, Y., Zhuang, M.-W., Han, L., Zhang, J., Nan, M.-L., Zhan, P., Kang, D., Liu, X., Gao, C., & Wang, P.-H. (2020). Severe acute respiratory syndrome Coronavirus 2 (SARS-CoV-2) membrane (M) protein inhibits type I and III interferon production by targeting RIG-I/MDA-5 signaling. *Signal Transduction and Targeted Therapy*, *5*(1). Available from https://doi.org/10.1038/s41392-020-00438-7.

Zhou, Z., Huang, C., Zhou, Z., Huang, Z., Su, L., Kang, S., Chen, X., Chen, Q., He, S., Rong, X., Xiao, F., Chen, J., & Chen, S. (2021). Structural insight reveals SARS-CoV-2 ORF7a as an immunomodulating factor for human CD14 + monocytes. *IScience*, *24*(3), 102187. Available from https://doi.org/10.1016/j.isci.2021.102187.

Zhu, Y., Liu, M., Zhao, W., Zhang, J., Zhang, X., Wang, K., Gu, C., Wu, K., Li, Y., Zheng, C., Xiao, G., Yan, H., Zhang, J., Guo, D., Tien, P., & Wu, J. (2005). Isolation of virus from a SARS patient and genome-wide analysis of genetic mutations related to pathogenesis and epidemiology from 47 SARS-CoV isolates. *Virus Genes*, *30*(1), 93–102. Available from https://doi.org/10.1007/s11262-004-4586-9.

Zhu, G., Zhu, C., Zhu, Y., & Sun, F. (2020). Minireview of progress in the structural study of SARS-CoV-2 proteins. *Current Research in Microbial Sciences*, *1*, 53–61. Available from https://doi.org/10.1016/j.crmicr.2020.06.003.

Zhu, H., Wei, L., & Niu, P. (2020). The novel Coronavirus outbreak in Wuhan, China. *Global Health Research and Policy*, *5*(1). Available from https://doi.org/10.1186/s41256-020-00135-6.

Zhu, N., Zhang, D., Wang, W., Li, X., Yang, B., et al. (2020). A novel Coronavirus from patients with pneumonia in China, 2019. *New England Journal of Medicine*, *382*(8), 727–733. Available from https://www.nejm.org/doi/10.1056/NEJMoa2001017?url_ver = Z39.88-2003&rfr_id = ori:rid:crossref.org&rfr_dat = cr_pub%20%200http://www.ncbi.nlm.nih.gov.

Zhu, Y., Yu, D., Yan, H., Chong, H., He, Y., & Pfeiffer, J. K. (2020). Design of potent membrane fusion inhibitors against SARS-CoV-2, an emerging Coronavirus with high fusogenic activity. *Journal of Virology*, *94*(14). Available from https://doi.org/10.1128/jvi.00635-20.

Ziebuhr, J. (2005). The Coronavirus replicase. *Current Topics in Microbiology and Immunology*, *287*, 57–94. Available from https://doi.org/10.1007/3-540-26765-4_3.