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Breakthroughs in SARS-CoV-2-monoclonal antibodies development

Yusuf Muhammed[1*]; Mkpouto Pius[2]; Bashiru Sani[3]; Bulus Timothy[4]; Jafar Usman[1]; Musa Garba[5]

[1]Department of Biochemistry, Federal University Gusau, Nigeria; [2]Department of Medical Genetics, University of Cambridge, United Kingdom; [3]Department of Microbiology, Federal University Lafia, Nigeria; [4]Department of Biochemistry, Kaduna State University, Nigeria; [5]Faculty of Pharmaceutical Sciences Kaduna State University, Nigeria

[*]Corresponding author E-mail: Yusufmsani1002@outlook.com

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Abstract

In December 2019, cases of unknown pneumonia-like disease connected to food markets were reported in China. The causative agent was identified as a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the disease which spread all over the world, was named COVID-19. This pandemic has negatively affected quality of life and economy worldwide, thus motivating thoughtful search for treatment and prevention strategies. Efforts have been made in drug repositioning and vaccine development as well as development of monoclonal antibodies. Monoclonal antibodies provide a long-lasting protective immunity against the pathogens, and have been at the forefront line in the therapy of some viral diseases. This study aimed to review the advances in SARS-CoV-2 monoclonal antibodies (mAbs) development. Most of the developed SARS-CoV-2 monoclonal antibodies including; B38, CR3022, 47D11, and H4, have targeted the spike protein of the virus to prevent its interaction with the host cell ACE-2 receptor. However, others such as Tocilizumab prevent the inflammation caused by the cytokine storm.

Keywords: SARS-CoV-2, Spike protein, B cells, T cells, Monoclonal antibodies

1. Introduction

COVID-19 is a major public health problem and was declared as a pandemic by the World Health Organization (WHO) in March, 2020. The disease was first reported in December, 2019, as cases of unknown pneumonia-like disease connected to a sea-food market in China were recorded, which quickly spread to different parts of the world, as reported by (Muhammed, 2020). A recent study conducted by Sun *et al*., (2020) highlighted that DNA sequencing of the lower respiratory tract of patients with the unknown pneumonia symptoms revealed a novel coronavirus, which was named as a SARS-CoV-2. Aerosolized droplet is the main route of SARS-CoV-2 transmission, although direct, oral-fecal, and mother-to-child transmissions are possible. The usual incubation period of SARS-CoV-2 is 5-14 days, but

recent studies conducted by Guan *et al*., (2020) have shown an extended incubation period of 24 days. COVID-19 infection is associated with both mild and severe symptoms such as; pneumonia, acute respiratory syndrome, fever, kidney failure, dry cough, and fatigue. Almost 80 % of the infected patients may show no symptoms or present mild symptoms. A recent study of di Mauro *et al*., (2020) reported that elevated pro-inflammatory cytokines including; IL-2, IL-6, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1α and TNFα, together with interstitial pneumonia (severe acute SARS-CoV-2 infection with high amount of inflammatory markers associated with pulmonary fibrosis) have been associated with severe COVID-19.

There is currently no definitive treatment or vaccine for COVID-19, thus necessitating the repurposing of existing drugs and strategies used for related illnesses. Importantly, broad neutralizing antibodies represent a promising approach in the management of infected patients. However, Ou *et al*., (2020) revealed that the differences in the sequences of the spike protein of coronaviruses have made the broad neutralizing antibodies to be rare. This and other limitations have resulted in little attention given to the development of monoclonal antibodies. Nevertheless, monoclonal antibodies have been isolated from the B cells of patients that recovered from SARS and COVID-19 infections, in addition to the development of mAbs from immunized mice. There have also been efforts to test for the differential efficacy of the mAbs obtained from the various sources and methods, as reported by (Jahanshahlu and Rezaei, 2020). Currently, more than 75 mAbs were licensed by the Food and Drug Administration (FDA), although only 3 of them are used in the treatment of several infections including anthrax and respiratory syncytial virus (Lu *et al*., 2020). The success recorded by the mAbs therapy in the treatment of aggressive viral infections has encouraged the development of specific mAbs for treatment of SARS-CoV-2 infection. Long half-life of immunoglobulin G 1 of up to 3 weeks would allow for single infusion, without the need for additional treatment especially in mild cases. However, Mulangu *et al*., (2019) revealed that insufficient information about the bioavailability of infused monoclonal antibodies in the lungs would be a limitation to their use in treating SARS-CoV-2 infection. Ku *et al*., (2020) highlighted that studies of monoclonal antibody development for COVID-19 are at their early stage. There is an urgent need of gap identification in mAb development to facilitate further research and effective anti-SARS-CoV-2 drug development. The objective of this article was to review the recent advances in the development of monoclonal antibodies (mAbs) against SARS-CoV-2.

2. Response of T and B cells to SARS-CoV-2 infection

The SARS- CoV-2 enters the host cell through attachment to angiotensin converting enzyme (ACE-2) receptor, then expresses its RNA into nucleocapsid, spike, envelop, and membrane protein to mediate replication and host infection (Fig. 1). The adaptive immunity (T and B cells), which starts about a week after the viral infection, gives rise to both protective and enduring immune responses stimulated by viral infections (Martines *et al*., 2020). Recent studies conducted by Sewell *et al*., (2020); Stephens and McElrath, (2020) revealed that understanding the features and responses of T and B cell mediated-immune response to SARS-COV-2 will aids in the forecasting of COVID-19, control strategies and therapeutics (drugs and vaccines) development. Azkur *et al*., (2020) reported that due to SARS-COV-2 similar clinical course with the previous coronaviruses and respiratory disease viruses, it stimulates the same immune responses involving T and B cells, as well as other antiviral neutralizing antibodies. T cells regulate the responses of immune cells including B cells, while antibody-producing-B cells confer and control the humoral arm of body immunity, as reported by Zhang *et al*., (2020a). A stimulated and coordinated response of four subsets of T cells including; i) CD4 (T helper cells), ii) CD8 (killer or cytotoxic T cells), iii) T cells regs (regulatory T cells) and iv) other T cells (T17 for example), help to confer effective immunity and

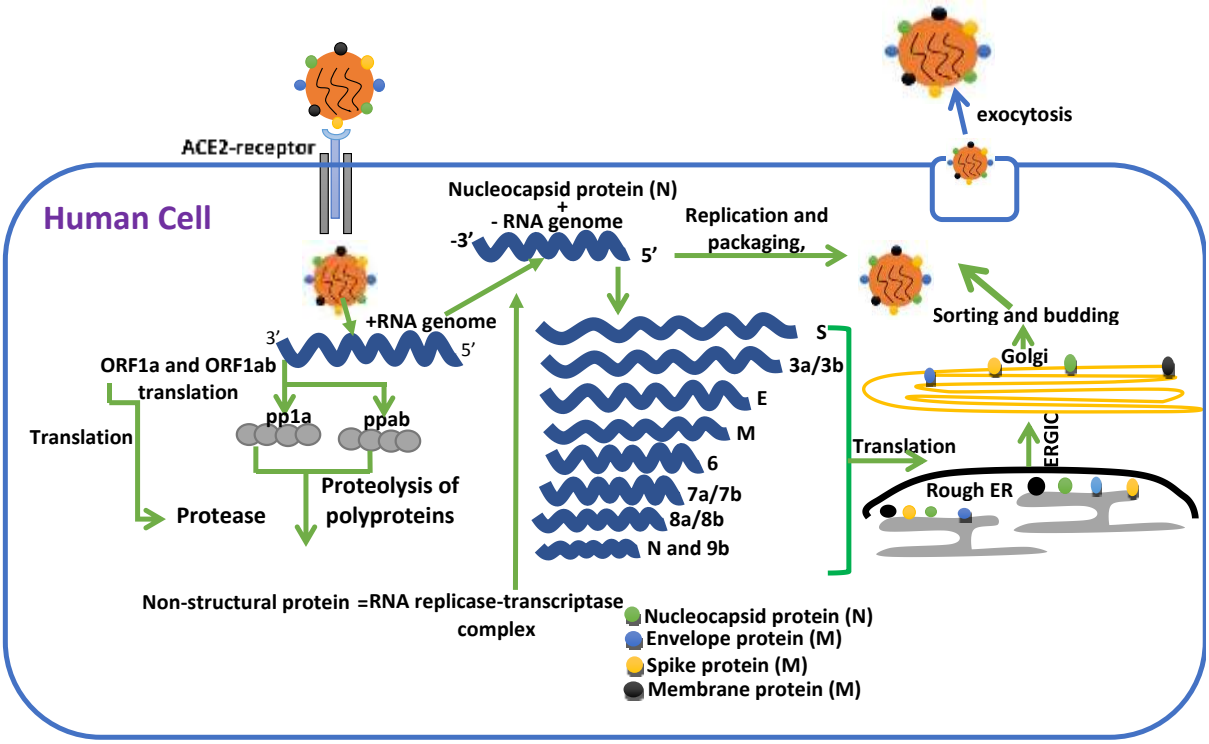

Fig. 1. The binding, entry and replication of SARS-CoV-2 in a human cell. The ACE-2 receptor mediates binding and entry of SARS-CoV-2 into the human cell, the virus releases its RNA, followed by viral RNA ORF1a and ORFab translation into polyproteins (polyprotein ab and 1a). The protease enzyme is encoded by ORF1a, which generates non-structural protein upon cleavage of polyprotein, this is the basis of RNA replicase-transcriptase formation for structural protein biosynthesis. The genomic RNA is then fragmented by discontinuous transcription into fragments that yield spike, membrane, nucleocapsid, and envelope protein. The structural proteins are biosynthesized in the rough endoplasmic reticulum, processed, sorted, and then finally released outside the cell.

immune response to SARS-COV-2, as reported by Stephens and McElrath, (2020).

As recently described by the study of Azkur *et al*., (2020), SARS-COV-2 invades and attaches to its receptor sites on the host cells and then replicates. Upon further entry into tissues of respiratory epithelial cells, antigen presenting cells (APCs) via MHC (major histocompatibility complex) class 1 molecules present SARS-COV-2 peptides to the T cells. This activates CD8 T cells, which initiates division, clonal expansion and stimulation of T effector and memory cells specific to SARS-COV-2. The infected tissue is then lysed by CD8, and the viral particles are shortly afterwards recognized by the macrophages and dendritic cells, and then presented via MHC class 2 to CD4 T cells (Jansen *et al*., 2019).

On the other hand, the B cells recognise and interact directly with the virus and CD4 T cells (Long *et al*., 2020). A recent work conducted by Walls *et al*., (2020) added that B cells produce different classes of antibodies, with focus on IgA, IgG and IgM that neutralise the spike (S) and other structural proteins of the SARS-CoV-2 by binding to them, thereby preventing viral attachment and infection to the susceptible cells. Samrat *et al*., (2020) added that this directed attack of the neutralizing antibodies on the S

protein is the major focus of most COVID-19 vaccines currently been developed, and are at various stages of clinical trials.

Lymphopenia, a condition of significant reduction in blood lymphocytes population and cross reactivity; however, have been observed in positive and negative patients, respectively. Lymphopenia has been thought to arise from over-secretion of T cells and T cell apoptosis, leading to decrease in CD8 T cells and memory T cells. However, the exact cause of this phenomenon is yet to be unravelled and understood (Jafarzadeh *et al*., 2020). Detection of memory and helper T cells as well as B cells specific to SARS-COV-2 have also been reported in patients with no case or contact with the virus. Recently, Azkur *et al*., (2020); Xiong *et al*., (2020a) attributed this to the cross reactivity of immune cells resulting from prior exposure to similar pneumonic and coronavirus-based infections such as; SARS and Middle East Respiratory Syndrome Coronavirus (MERS-CoV).

3. Advances in the development of mAbs for SARS-CoV-2

Monoclonal antibodies (mAbs) are essential parts in host immune responses to viral infections. They are developed as drugs to treat infectious diseases such as HIV, Rabies, Influenza, HCMV, and Ebola. Interestingly, there is well established strategy for the development of antibodies for viral infection as clear in Fig. (2), and reported by Tabrizi *et al*., (2009); Ducry and Stump, (2010); Zhou and Mascelli, (2011). Recently, scientists from different parts of the world have launched programs for the development of SARS-CoV-2 monoclonal antibodies (Fig. 3) (Ku *et al*., 2020). Antiviral antibodies typically target viral surface-exposed antigens to inhibit its infection. The viral spike protein that mediates viral attachment to the host angiotensin converting enzyme is the target for the development of monoclonal antibodies. According to Shanmugaraj *et al*., (2020), *in vivo* analysis showed that antibodies directed against the spike protein conferred protection against the virus.

3.1. 47D11 antibody

Investigation of mechanisms used by 47D11 antibody (Ab) to interfere with the host receptors is a new area of research. Using hybridoma technology, mAb against SARS-CoV-2 RBD can be generated from mice after immunization with Receptor-Binding Domain (RBD) of SARS-CoV-2 (Shanmugaraj *et al*., 2020; Xiong *et al*., 2020b) Identification of 47D11 cross reactivity in supernatants (obtained from H2L2 transgenic mice producing chimeric antibodies) after its production was achieved by enzyme linked immunosorbent assay (ELISA), in which cross reactivity was observed in 4 of the 51 hybridoma supernatants (Wang *et al*., 2020). The 47D11 Ab neutralizes both SARS-CoV-2 and SARS-CoV infection in VeroE6 cells. The spike protein of both SARS-CoV-2 and SARS-CoV is the target of 47D11 Ab development (Wang *et al*., 2020). The region of the viral spike protein used in mAb development is the RBD, which is divided into S1 and S2 (Tian *et al*., 2020). A recent study of Wang *et al*., (2020) has shown that through ELISA, the region of S1 responsible for antibody interaction is S1b. However, from the same study, 47D11 Ab has higher affinity to SARS-CoV (Kd [Equilibrium Dissociation constant] = 0.745nM) spike protein, than to SARS-CoV-2 (Kd= 10.8nM). This difference in affinity is attributed to variation in the accessibility of epitopes between the spike protein of SARS-CoV-2 with that of SARS-CoV. The S1 of the RBD spike protein is divided into core domain (receptor engager) and a receptor-binding sub domain. The receptor binding sub domain of SARS-CoV-2 and SARS-CoV has lower sequence similarities, which makes the 47D11 Ab to poorly neutralize the virus (Jahanshahlu and Rezaei, 2020). Furthermore, 47D11 Ab can be useful in the detection of SARS-CoV-2 antigen, and for serological assays (Wu et al., 2020a; Wang *et al*., 2020). The design and production of the mAb involve cloning of cDNA coding for the mAb (RBD encoding gene) variable region of the heavy and light chain, into a plasmid containing heavy chain of human IgG1 and light chain of Ig kappa.

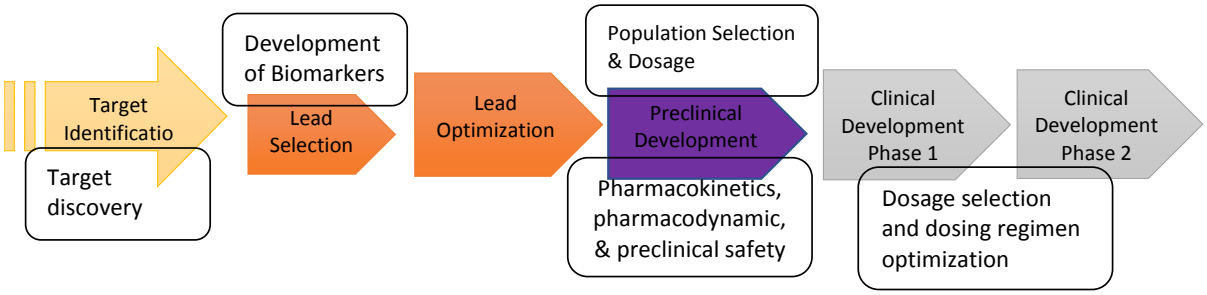

Fig. 2. An overview of steps involved in monoclonal antibody drug development from the scratch

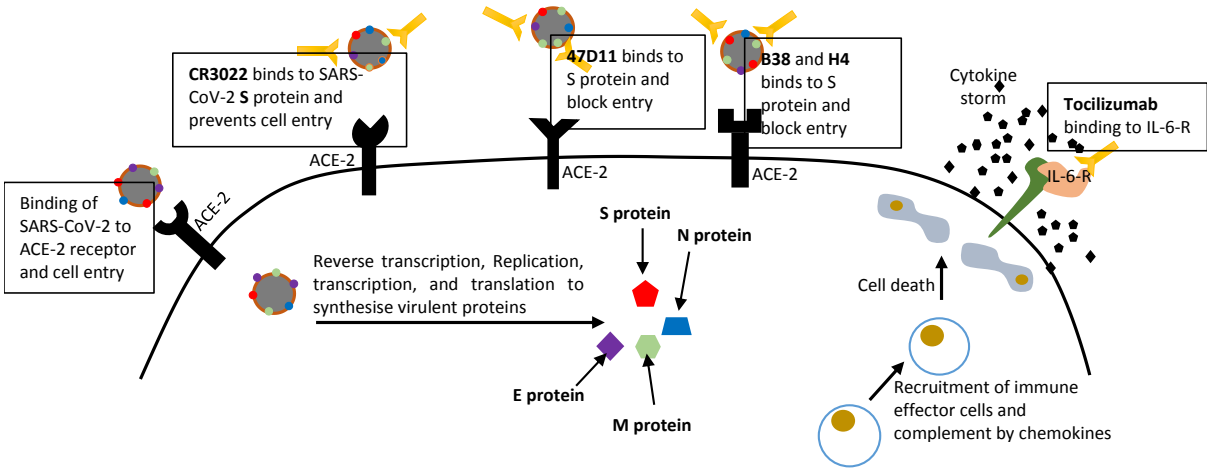

Fig. 3. An overview of monoclonal antibodies repositioned to target SARS-CoV-2 virulent proteins and reduce inflammation mediated by IL-6-R. The CR3022, 47D11, B38, and H4 were developed to target spike protein (S protein) that mediates viral entry into the host cell. However, tocilizumab binds to interleukin-6 receptor (IL-6-R) and prevents cascades of signalling, which mediate cytokine storm and inflammation. Where; N = nucleocapsid protein, M = membrane protein, and E = envelope protein.

The plasmid is also designed with 2 signal sequence from interleukin to allow efficient release of the protein (Wang *et al*., 2020). Production of the Ab will takes place after transfection into HEK-293T mammalian cell lines, as discussed by Wang *et al*., (2020). Apart from interfering with receptor binding by 47D11 Ab, other unknown mechanisms such as inactivation of spike protein used by 47D11 Ab are proposed to affect the interaction of SARS-CoV-2 with ACE2 receptor (Wang *et al*., 2020).

3.2. CR3022 Ab

The CR3022 mAb with heavy, light, and complementary regions neutralizes epitopes used by SARS-CoV-2 to mediate the infection. The epitope is located in the RBD of the spike protein, which was isolated recently from patient's convalescent plasma (Rattanapisit *et al*., 2020). In an early study, Ye *et al*., (2013) reported that CR3022 Ab heavy and light chain were found to be encoded by germline genes including; IGHV for heavy chain, IGHD for diversity,

IGHJ for joining, IGKV4-1 for light chain variable region, and IGKJ2 for joining region. The DNA-encoded monoclonal antibodies (DmAb) can be generated from CR3022 Ab through modification and optimization of the epitope sequence. According to Parzych and Weiner, (2020), upon infection of the mice with the engineered CR3022 Ab, isolated sera from the mice contain the antibody that binds to RBD of the S1 subunit of the spike protein. The crystal structure of SARS-CoV-2 interacting with CR3022 Ab showed that the antibody binds through hydrophobic interaction. The binding affinity of CR3022 Ab and its neutralisation efficacy are well investigated in both SARS-CoV-2 and SARS-CoV (Tian *et al*., 2020). CR3022 Ab binds to the spike S domain-RBD of both SARS-CoV and SARS-CoV-2, with higher affinity of binding to SARS-CoV (Kd=1nM) than SARS-CoV-2 (Kd=115nM). This is attributed to the conservation of 24 out of 28 epitope amino acid residue of SARS-CoV-2 and SARS-CoV-2. Although CR3022 Ab has the potential of neutralizing SARS-CoV-2, however *in vitro* studies by microneutralization assay showed no neutralizing effect. This proved the lower affinity of CR3022 Ab to SARS-CoV-2. Alignment of SARS-CoV-2-ACE2 and SARS-CoV complexes revealed that CR3022 epitopes and ACE2 do not overlap and never compete. Apart from CR3022 Ab, other RBD targeted Abs compete with ACE2. Thus, CR3022 Ab can be used only or synergistically with other SARS-CoV-2 mAbs for treatments. The up (enable binding to ACE2) and down (do not permit ACE2 binding) conformational hinges are among the main characteristics of the studied SARS-CoV-2 RBD, as reported by Wrapp *et al*., (2020). Recently, Yuan *et al*., (2020) reported that binding of CR3022 Ab can still be hindered by the up conformation, which can be avoided by slight rotation of the targeted-RBD in the double up configuration according to the structural modelling. The binding of CR3022 Ab to RBD was supported by the research work conducted by Tian *et al*., (2020). They found that using ELISA and Bio-Layer Interferometry (BLI), CR3022 Ab binds potently to RBD of SARS-CoV-2. Even though there are possibilities of CR3022 Ab binding to RBD *in vivo*, the difference in binding of CR3022 Ab to RBD *in vitro* and *in vivo* requires further investigation using different animal models and *in vitro* techniques.

3.3. Tocilizumab Ab

SARS-CoV-2 pathogenesis and infection are associated with excessive release of pro-inflammatory cytokines, a condition often called cytokine storm or hypercytokinemia. This results in respiratory distress syndrome, and subsequent failure of organs and respiration, as proposed by Tang *et al*., (2020). As a result of studying the cytokine storm, an Ab called Tocilizumab was developed and approved in China for the reduction of complication of lungs associated with cytokine release. Tocilizumab makes interleukin-6 receptor inaccessible to ligands (di Mauro *et al*., 2020). There is growing interest in the use of Tocilizumab Ab in immunotherapy for treatment of patients with chronic infection of COVID-19 (Patel *et al*., 2020). The disease has different presentations including severe respiratory defects that require invasive mechanical ventilation. Pedersen and Ho, (2020) highlighted that one of the classic responses to COVID 19 infection is a cytokine storm in which the body overreacts and releases large amounts of cytokines to attack the virus, and this overload often cause long term tissue damage especially to the lungs. This accounts for the multiple organ failure and acute respiratory distress syndrome that occur in these patients. After SASR-CoV-2 infection, hyper-inflammation occurs driven by cytokine release syndrome (CRS). This is defined as systematic response to infection or chemical substances like drugs in which there is increase in the amount of pro-inflammatory cytokines, and is often seen in immuno-therapy and viral infections (Winkler *et al*., 2020). According to Zhang *et al*., (2020b), SAR-COV-2 triggers the release of these cytokines by binding to the alveolar cells with a consequent enhanced flow of blood and fluid into the alveolar cells, which accounts for much of the disease severity. This increased expression of inflammatory markers such as C reactive protein and interleukin-6 in these patients are positively correlated with the increased death rates

(Henry *et al*., 2020). There are currently no drugs produced to treat COVID-19, and the current therapeutic approaches use antiviral and immunoactive combination therapy such as Tocilizumab Ab. The antibody is an IgG1 humanized monoclonal antibody. It targets Interleukin-6 (IL-6) receptors in the soluble and membrane-bound form. It is used to treat several forms of arthritis and potentially fatal cytokine release syndromes (Guaraldi *et al*., 2020). A previous study conducted by Tanaka *et al*., (2014) reported that IL-6 is produced by macrophages and monocytes when an infection occurs, and plays both of anti- and pro-inflammatory roles. It participates in a signal transduction pathway in which it binds to its receptors and sets off a downstream cascade of reactions. In particular, when IL-6 binds to its receptor in the classic signal transduction pathway which only takes place in cells that express the receptor, it complexes with glycoprotein 130 (gp130), resulting in a downstream activation of pathways. Tocilizumab binds to the IL-6R thereby inhibiting this signal transduction and thus truncating the storm, as reported by Campbell *et al*., (2014). Recently, Fu *et al*., (2020) revealed that elevated levels of serum IL-6 content over 20 pg/ ml mandate the use of the Tocilizumab immunotherapy, which temporarily raises the levels of this IL-6 due to the block of the receptor.

3.4. B38 and H4 Abs

A study conducted by Jahanshahlu and Rezaei, (2020) highlighted that the two convalescent human mAbs that compete with binding of SARS-CoV-2 to ACE2 receptor are B38 and H4. Both of B38, H4 and other SARS-COV-2 neutralizing mAbs are developed by isolating a single B cell from the peripheral blood mononuclear cells that express the RBD of SARS-CoV-2. After that, PCR amplification of the single B cell DNA encoding heavy chain and light chain takes place. The amplified DNA are then cloned separately into a pCAGGS vector (mammalian expression vector with CMV IE promoter; amp resistance; restriction enzyme cloning) containing a gene for a constant region, which will result in the formation of a IgG1 Ab after host expression (Wang *et al*., 2019). Then co transfection of pCAGGS vectors (expressing the right heavy and light chains) into human embryonic kidney 293T expressing mutated T cell gene (HEK 293T) occurs to produce mAbs. To screen for the binding ability of the specific Ab to RBD, the supernatant was subjected to bio-layer interferometry (Wu *et al*., 2017). Recently, Wu *et al*., (2020b) carried out a number of investigations on human neutralizing Abs that block binding of SARS-CoV-2 to its ACE2 receptor, part of their investigation revealed that B5, H2, B38, and H4 Abs bind to SARS-CoV-2 RBD. They have also shown that these antibodies did not bind to SARS-CoV RBD, suggesting differences in the epitopes of these viruses. The complete competition of B8 and H4 Abs to block ACE-2 receptor interaction with the spike protein RBD has been observed from fluorescence activated sorting. Nevertheless, binding of B5 to the RBD of SARS-CoV-2 is less; however, H2 Ab did not show any competition for binding with RBD. In the same studies, investigation of the efficacies of B38 and H4 Abs has been examined 12 hours after Abs administration to mice. These Abs have shown protection against SARS-CoV-2 infection *in vivo*, by administering a single dose of B38 (25 mg/ kg) to a SARS-CoV-2-treated-transgenic mice (hACE2). On the other hand, H4 was also administered to transgenic mice using the same dose. Results have shown that B38 treated group recovered after 3 days with better outcome than the control (treated with phosphate buffer) and H4 treated groups. The research further quantified the amount of RNA in the lungs of B38 (32.8% reduction in SARS-CoV-2 RNA) and H4 (26% reduction in the viral RNA) treated groups, which clearly revealed the neutralizing ability of both Abs. Furthermore, histopathological screening of mice groups treated with B38 and H4 revealed mild bronchopneumonia in H4 treated group, with no any symptoms in B38 group. The control group (treated with phosphate buffer saline) demonstrated the presence of several symptoms such as; bronchial epithelia, oedema and infiltration of lymphocytes in the spaces of the alveoli. In other studies, investigation of the complex formed by B38 Ab RBD, comparison of B38 epitopes and hACE2

were carried out by Emsley and Cowtan, (2004); Adams *et al*., (2002), which revealed that 21 residues (from heavy chain) and 15 residues (from light chain) were involved in the interaction with the host receptor (hACE2).

3.5. Using combination of mAbs and mAbs-transporters

One major challenge identified in harnessing mAbs for SAR-CoV-2 is the high propensity of viral particles to mutations, leading to viral diversity and the possible emergence of mAbs-resistant viruses. This causes a great challenge to the development of mAbs therapy. Such challenge may be tackled by employing a combination of two or more mAbs designed to target different site of the viral antigenic protein. The paucity of information on the bioavailability of passively infused IgG in diseased tissues such as the lungs, could also limits the mAb therapy (Jahanshahlu and Rezaei, 2020). An early study conducted by Ducry and Stump, (2010) revealed that another possible strategy that could aid in bioavailability of mAb, is to enhance the delivery of effective mAbs to target tissues through linking them to tissue-specific transporters/ conjugates. This approach which has been taught of for cancer therapy; if applied to SAR-CoV-2 may greatly enhance the therapeutic strategy.

4. SARS-CoV-2 mAbs on clinical investigation

The Chinese Antibody Academy have collaborated with the Antibody Society in March, 2020, to globally track the COVID-19 Abs that are either under clinical trial; clinical evaluation, requested for emergency use by the FDA, research and development. Most of the Abs targeting spike (blocking viral entry) protein are on preclinical stages. More than 8 mAbs demonstrated in Table (1) got approval from the FDA (Yang *et al*., 2020) The US president was treated with one of the mAbs (REGN-COV2 cocktail) that got approval from FDA, which forms a part of his treatment. Other Abs shown in Table (2) are currently undergoing clinical trials, while some are at the stage of discovery research. DeFrancesco, (2020) reported that in addition to COVID-19 treatment and vaccine, anti-SARS-CoV-2 mAbs are promising adjunct to conventional treatments.

Conclusion

COVID-19 has reached the nooks and crannies of many countries across the globe in 2020 due to its widespread ability, resulting in an unanticipated disruption of educational, social, and economic activities worldwide. The urgent need to curtail and exterminate the SARS-CoV-2 virus has led to the exploration and production of a number of medications. Although attention has been focused on drug repositioning and vaccine development to fight the present pandemic; however, there are several studies initiated on the development of mAb for SARS-CoV-2. It is highly valuable to strengthen research on the development and scale up of SARS-CoV-2 mAbs production as a way forward to diversify treatment for COVID-19. The good character of mAb is the recruitment of the human endogenous immune system, to induce protective immunity that can lasts for a long time. Development of mAbs for SARS-CoV-2 infection will benefit the health care systems, patients, and revolutionise the antiviral mAb-based vaccine.

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Conflicts of interest

The authors declare no conflict of interests.

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Ethical approval

Non-applicable

Table 1: Ant-SARS-CoV-2 mAbs granted emergency use by the FDA

Drug name	Company requesting for FDA approval	Antibody origin	Molecular target	Date of approval
LY-CoV555	Eli Lilly	Human	Spike protein	November 9, 2020
REGN-COV2	Regeneron Pharmaceutical, Inc.	Human Cocktail	Receptor binding domain of SARS-CoV-2	November 20, 2020
VIR-7831/GSK4182136	Vir Biotechnology, Inc., and GlaxoSmithKline plc	Human	Spike protein	-
AZD7442(AZD8895 + AZD1061)	AstraZeneca/ Vanderbilt University	-	Spike protein	-
TY027	Tychan Pt Ltd, Singapore	-	Spike protein	-
COVI-GUARD (STI-1499)	Sorrento Therapeutics Inc.	-	Spike protein	-
ADM03820	Ology Bioservices	-	Spike protein	-
BRII-96, BRII-98	Brii Biosciences	-	Spike protein	-
JS016	Junshi Biosciences	-	Spike protein	-
CT-P59	Celltrion	-	Spike protein	-

Table 2: Clinical evaluation of some of the anti-SARS-CoV-2 mAbs

mAbs	Company	Clinical trial phase	Trial start date	Trial completion date
CT-P59	Celltrion	-	7/18/2020	Nov 2020
AZD7442	AstraZeneca	3	8/17/2020	Sep 2021
TY027	Tychan Pte. Ltd.	3	6/9/2020; 12/4/2020	Oct 2020; 8/31/2020
SCTA01	Sinocelltech Ltd.	3/2	7/24/2020; 2/10/2021	Nov 2020; 5/10/2021
MW33	Mabwell (Shanghai)Bioscience Co., Ltd.	2	8/7/2020; Nov 2020	Dec 2020; May 2021
JS016, LY3832479, LY-CoV016	Junshi Biosciences /Eli Lilly and Company	2	6/5/2020; 6/19/2020; 6/17/2020	Dec2020; 10/2/2020; 3/11/2021
BGB DXP593	Beigene	2	8/31/2020; 10/30/2020	10/15/2020; 2/28/2021
COVI-AMG (STI-2020)	SorrentoTherapeutics, Inc.	1/2	Dec 2020	Dec 2020
BRII-196	Brii Biosciences	1	7/12/2020	7/12/2020
BRII-198	Brii Biosciences	1	7/13/2020	7/13/2020
ABBV-47D11	AbbVie	1	11/27/2020	11/27/2020
COVI-GUARD(STI-1499)	SorrentoTherapeutics, Inc.	1	9/17/2020	9/17/2020
HFB30132A	HiFiBiO Therapeutics	1	Oct 2020	Oct 2020
ADM03820	Ology Bioservices	1	12/4/2020	12/4/2020
HLX70	Hengenix Biotech Inc	1	12/9/2020	12/9/2020
DZIF-10c	U.Cologne/Boehringer Ingelheim	1/2	11/23/2020; 11/23/2020	6/30/2021; 6/30/2021

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