THERAPEUTIC ANTIBODIES AND IT'S USE IN COVID-19: A REVIEW

[1]Pokalkar Ushake Monica, [2]Tera Sony

Bachlor of Pharmacy
G Pulla Reddy College of Pharmacy
Hyderabad, India.

***Abstract*- Proteins, Peptides, Monoclonal antibodies, gene therapy, cell therapy and RNAi (RNA Interference) come under large therapeutic molecules. These are progressively represented as new molecular entities registered through the FDA (Food and Drug Administration). The majority of NME's (New Molecular Entities) registered to date, are still small molecules. Under antibody-therapeutics, since 2019, in clinical trials over 82 antibody- NMEs (New Molecular Entities) have been approved to treat diseases with hundreds more. The development of antibody-based bio-pharmaceutics for effective and safe treatment of many diseases like autoimmune, oncology, transplantation and inflammatory disorders has shown noteworthy success in the last three decades. Development and significant rapid growth leading to clinical success began in the 1990s. Over 80 regulatory approvals have demonstrated this fact. Since 2015, it is estimated that more than 100 therapeutic antibodies, such as monoclonal antibodies (mAbs), have entered first-in-human (FIH) studies per year and 700 antibody-based therapeutics are currently in some stage of clinical development.**

***Keywords* - Monoclonal antibodies, Immunoglobulin G, Hybridoma technology, Covid-19, Cancer treatment**

I.INTRODUCTION Monoclonal antibodies are a combination of various antibodies mainly produced using the hybridoma technique. The main properties of mAbs are binding specificity, unlimited multiplication ability (clones) and homogeneity. Due to the advantages, mAbs are widely used in the diagnosis and treatment of illness like cancer and immunoglobulin disorders [1]. The hybrid myeloma cells, also known as Hybridomas produce long-lived antibodies. The individual cell line also called a "clone" (monoclonal), is used for the selection and sustained production of highly specific antibodies that produce desired binding characteristics to a target antigen. The development of long-lived antibody-producing hybrid myeloma cells in culture, or hybridomas, allowed for the selection and sustained production of highly specific antibodies from an individual cell line or clone (monoclonal) that exhibited the desired binding characteristics to a target antigen. Combining hybridoma screening with recombinant DNA including technology in vitro could produce IgG (immunoglobin G) antibodies with unique specificity including human sequence, leading to the development of mAbs as potential therapeutic candidates. Paul Enrlich (in the early 20th century) described these antibodies as a "magic bullet" in search of toxins [1]. Georges Kohler, Cesar Milstein and NeilsKaj Jerne used a mouse x mouse hybridoma and created the monoclonal antibody (mAb) technique in 1975. The US FDA approved the first therapeutic mAb muromonab-CD3(trade name Orthoclone OKT3) to reduce acute rejection in patients with organ transplant in the year 1992. The side effects of muromonab treatment such as rapid clearance/short half-life and high prevalence for neutralizing anti-drug antibody (ADA) response, were due to its murine sequence and isotype. The discovery of muromonab OKT3 provided the first empirical data on mAb molecules (e.g. mAb comprised murine variable region and human constant regions; nearly 67% human sequence) and sequentially "humanized" or complementary-determining region (CDR)-grafted mAbs (e.g. mAb comprised murine sequence only at antigen-binding CDR regions; > 95% human sequence), and later on fully human mAbs (100% humn sequence) ,greatly improved the clinical pharmacology of mAb therapeutics. For example, the previously marketed therapeutics mAbs ,likeRituxan(rituximab) and Remicade(infliximab), were produced as chimeric mAb formats. More than 90% of the approved antibody-based therapies developed during the past decade have been either "humanized" or fully human-sequenced [2]. FDA has approved 119 therapeutic mAbs (including two diagnostic mAb) from 1992-December 31,2020. From these FDA approved over 10 therapeutic antibodies in 2015, 10 mAbs in 2016, 17 mAbs in 2017, 15 mAbs in 2018 and 16 therapeutic antibodies in 2019. In 2020, FDA approved 13 therapeutic antibodies (during the COVID-19 pandemic). The list of FDAs approved therapeutic antibodies during the year 2020 is as follows:

TABLE 1: FDA approved therapeutic antibodies in 2020

Drug name	Active ingredients	Company	Approval date
TEPEZZ	Teprotumumab-trt	Horizon therapeutics	January 21,2020
VYEPTI	Eptinezumab-jjr	Lundbeck	February 21,2020
SARCLISA	Isatuximab-irfc	Sanofi Aventis	March 2, 2020
TRODELVY	Sacituzumabgovitecan-hziy	Immunomedics	April 22 ,2020
DARZALEX FASPRO	Daratumumab, hyaluronidase-fihj	Janssen	May 1,2020
UPLIZNA	Inebilizumab-codn	Viela	June 11,2020

PHESGO	Pertuzumab, transtuzumab and hyaluronidase- zzx	Genentech	June 29,2020
BLENREP	Belantamabmafodotin-blmf	GlaxoSmithKline	August 5, 2020
ENSPRYNG	Satralizumab-mwge	Genentech	August 14,20220
INMAZEB	Atolivimab +2	Regeneron	October 14,2020
DANYELZA	Naxitamab -gqgk	y-mAbs therapeutics	November 25,2020
MARGENZA	Margetuximab-cmkb	MacroGenics	December 16,2020
RIABNI	Rituximab-arrx	Amgen	December 17,2020
Drug name	**Disease**	**ADRs**	**Mechanism**
TEPEZZ	Thyroid eye disease	IBD worsening; hyperglycemia	IGF-1R block
VYEPTI	Migraine	Hypersensitivity	CGPR block
SARCLISA	Multiple myeloma	Neutropenia; SPM	Anti-CD38, ADCC, CDC
TRODELVY	mTNBC	Hypersensitivity neutropenia	Anti-Trop-2; SN-38; ADC
DARZALEX FASPRO	Multiple myeloma	Hypersensitivity, neutropenia	Anti – CD38, ADCC, CDC
UPLINZA	NMOSD (AQP4+)	Immune compromise	Anti-CD19
PHESGO	Breast cancer (HER2+)	Neutropenia	Anti – HER2; increases permeability
BLENREP	Multiple myeloma	Thrombocytopenia	Anti- BCMA; microtu7bule inhibitor; ADC
ENSPRYNG	NMOSD (AQP4+0)	Elevated liver enzymes	Anti- IL6 receptor
INMAZEB	Zaire ebolavirus infection	Hypersensitivity	Zaire ebolavirus glycoprotein
DANYELZA	Neuroblastoma	Neurotoxicity; hypertension	Anti-glycolipid GD2, CDC, ADCC
MARGENZA	Breast cancer	Left ventricular dysfunction	Anti-HER2, ADCC
RIABNI	NHL, CLL, GPA, MPA	IRR; TLS; PML	Anti – CD20, ADCC, CDC

IBD: Inflammatory bowel disease, IGF-1R; Insulin-like growth factor 1 (IGF-1) receptor, CGRP; Calcitonin gene-related peptide, SPM: Second primary malignances, ADCC: Antibody-dependent cell-mediated cytotoxicity, CDC: Complement-dependent cytotoxicity, ADCP: Antibody-dependent cellular phagocytosis, mTNBC: Metastatic triple-negative breast cancer, SN-38: spectrum disorder, AQP4+: Anti-aquaporin-4 antibody positive, NHL: Non-Hodgkin's lymphoma CLL: Chronic lymphocytic leukemia, GPA: granulomatosis with polyangiitis (Wegener's granulomatosis), MPA: Microscopic polyangiitis IRR: Infusion-related reaction, TLS: Tumor lysis syndrome, PML: Progressive multifocal leukoencephalopathy[3].

II.STRUCTURE AND FUNCTIONS

Antibodies belong to the superfamily immunoglobulin (ig) of glycoprotein. B Cells secreted these, identifying and neutralizing foreign organisms or antigens. An antibody is made up of two light chains and two heavy chains. These are divided into five isotypes: IgM, IgD, IgG, IgA and IgE; which are based on the type of heavy chains involved. The five types of heavy chains in mammals are:$\alpha, \delta, \varepsilon, \gamma, \mu$. These isotypes have differences in immune function and stages of the immune response [3].

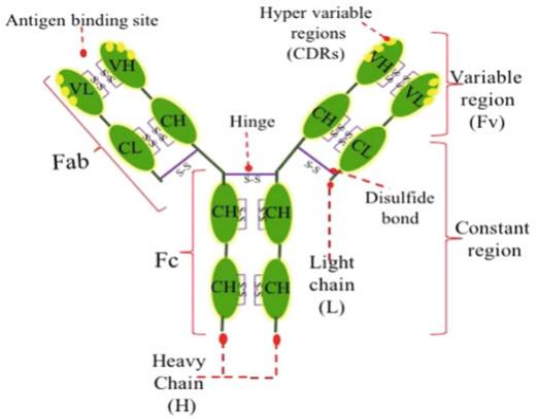

Figure 1. Structure of antibody [4]

Therapeutic antibodies (mAb) belong to the IgGisotype. IgGisotype is further divide into four subclasses (IgG1-40 based on their amount in human serum, out of which 75% of mAbs are of the IgG1 subclass (most abundant type). The immunoglobinG antibodies are about 150kDa large molecules made up of four polypeptide chains i.e., two indistinguishable heavy chains (nearly 50kDa) and two indistinguishable k or light chains (nearly 25kDa). The two heavy chains are linked to each other and one light chain, each by disulfide bonds, forming y-shaped structures with identical halves. The light chain is made up of one constant and variable region each (C_L and V_L), whereas the heavy chains are made up of three constants ($C_H1/C_H2/C_H3$) and one variable region (V_H). V_L of the light chain gets associated with C_H1 region of the heavy chain to form the antigen-binding domain or fragment of the antibody (Fab), and the regions under the flexible hinge sequence i.e. $C_H2$associated with C_H3 form the Fc domain (fragment crystallization). The structure of the four substances of IgG are similar but differ greatly in the length and composition of the C_H1 and C_H2 regions of flexible hinge sequence causing changes in molecular traits like antigen binding, proteolytic stability and Fc function of the antibody. The V_H and V_L regions are comprised of three hyper-variable amino acid sequences, known as CDRs, forming antigen-binding sites of each Fab arm. The interface of each heavy chain and light chain CRDs, along with the more constant segments (framework residues) surrounding them, forming numerous non-covalent interactions creates a highly specific three-dimensional binding structure for a distinct antigenic determinant or epitope [2].
The overall functioning of mAbs is listed as follows [5]:

- Antagonism of suitable receptor or ligand [6].
- Antibody-Dependent cellular cytotoxicity [7].
- Complement-Dependent cytotoxicity [8].
- Agonism of the receptor [9].
- Antibody-dependent cellular phagocytosis [10].
- Blockage of cell-cell interactions [11].
- Apoptosis [12].
- Non-apoptotic programmed cell death [13].

III. METHODS

Hybridoma technology: Hybridoma technology is a well-established method of producing monoclonal antibodies specific to antigens of interest and one of the most important methodological advances in biomedicine during the 1970s. In hybridoma technology we use two different kinds of cells for production of large quantity of the antibody. Hybridoma cell lines are formed via fusion between a short-lived antibody-producing B cell and immortal myeloma cell. The production of mAbs was invented by Cesar Milstein and Georges J.F.Kohler they immortalized antibody-producing cells by fusing them with the tumor cells. The Nobel Assembly of Karolinska institute awarded the Nobel prize in physiology or medicine in 1984 jointly to Neils K. Jerne, George J.F.Kohler and Cesar Milstein for theories concerning “the specificity inn development and control of the immune system” and the discovery of the principle for the production of monoclonal antibodies. The myeloma cells lack the enzyme Hypoxanthine GuanosinePhosphoribosylTransferase (HGPT) and are sensitive to HAT media. Whereas spleen B-Lymphocytes contribute the HGPRT gene to the hybrid cell end hence, unfused myeloma cells and spleen cells die in the HAT media. Monoclonal antibodies synthesis requires HAT medium. Initially mice or animal is exposed to antigen the splenocytes are developed/isolated from mice, the immortalized myeloma cells that lack HGPRT gene are fused with B cells using polyethylene glycol.
HAT medium is used for incubating the fused cells, nucleotide synthesis does not occur because the aminopterin in myeloma cells die but B-myeloma hybrids doesn’t. Then incubated medium is diluted in such a way that it includes only one cell in each well and check for the presence of the supernatant to know whether an antibody is produced or not.
Steps involved in hybridoma technology:

1. Spleen cells are prepared from animals, usually mice which have been immunized with a selected antigen.
2. These cells are fused with myeloma cells maintained in culture in the laboratory.
3. The product of this fusion is referred to as hybridoma.
4. The hybrid obtained are propagated in a highly diluted state so that colonies deriving from single hybrid cells can be isolated.
5. A particular hybridoma can be used in the future, enabling unlimited production of a highly specific antibody [14].

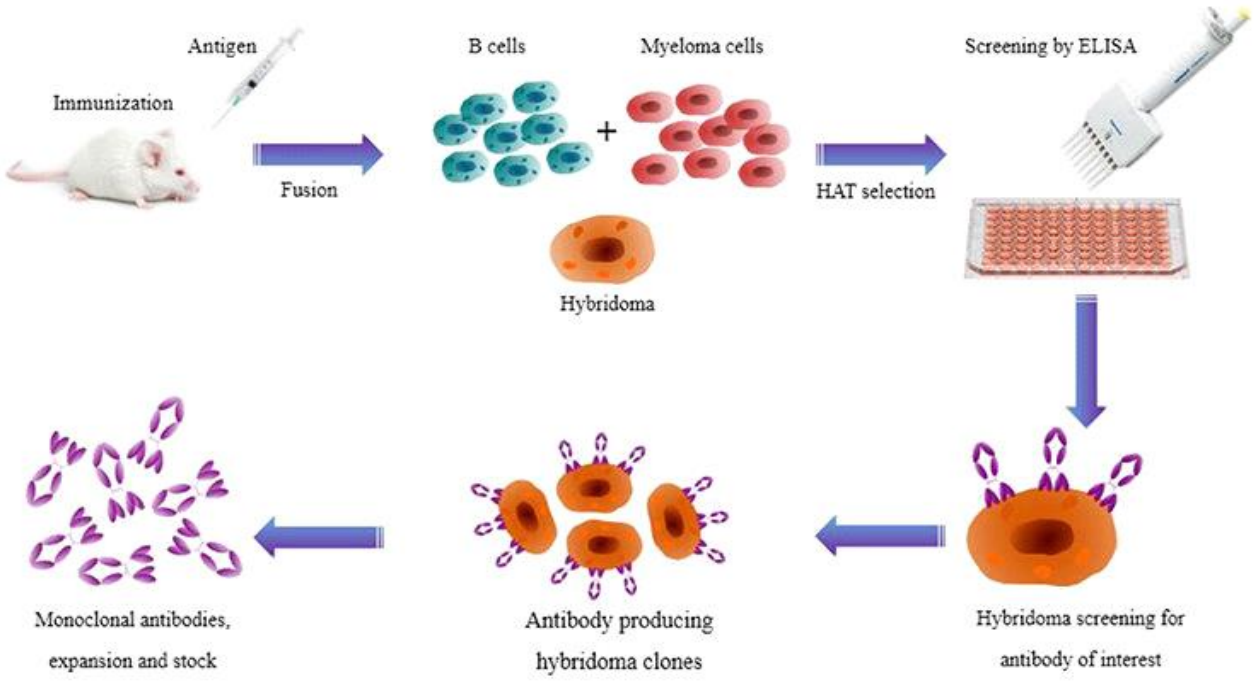

Figure 2. Diagrammatic depiction of hybridoma technology [15].

Advancement in hybridoma technology:

Hybridoma technology is an advantageous method due to its ability to be cryopreserved and be used for infinite times along with a large production rate. The advancement of stable cell line production from unstable hybridomas is currently being developed. The Chinese hamster ovary cell line is the most preferred for large-scale mAbs production. The multi-step screening process to identify antigen-specific hybridomas has advanced to robotic screening methods like microarray-based screening technology and Bio-layer interferometry [16].

Limitations:

1. The main limitation of this method is the lack of a suitable fusion partner leading to limiting its applicability to other species. To overcome this problem transgenic mice modelH-2kb-tsA58 is discovered. The model is specifically used to isolate mAbs against the filamentous phase.
2. Isolation of mAbs against various membrane proteins. The purified antigens can be generated using methods like the cell-based immunization and screening (CBIS) method for the isolation of mAbs for podoplanin (PDPN) has improved the method [16].

IV.ROLE OF MABS IN COVID-19

Covid 19 also known as SARS-CoV2 (severe acute respiratory syndrome coronavirus-2) is an airborne disease that first occurred in the month of December 22019 in a seafood market of Wuhan, China. As the name suggests this virus mainly affects the lower respiratory tract along with other body organs [17]. Coronavirus (CoV) belongs to the family "corona viridae", comprising of four types which are Alpha coronavirus, Beta coronavirus, Gamma corona virus and Delta coronavirus. The first CoV pandemic occurred in the year 2003 known as Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). Later in the year 2012, a stain of CoV caused Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Covid 19 becomes the third and largest pandemic of these [18]. Humans are affected by Gamma and Delta CoV. SARS-CoV-2 i.e., Covid 19 enters the host by receptor- mediated endocytosis and caused infection by binding to the ACE-2 surface receptors. Monoclonal antibodies bind to the protein spike (S) and prevent the viral attachment to the cells and tag it for destruction [18].

The infection is caused in the following way:

1. The spike (s) protein binds to ACE-2 receptor and enters the cell.
2. Internalisation of virus via. Host trans-membrane protease serine 2(TMPRSS2)
3. Viral RNA replication via RNA- dependent RNA polymerase
4. Viral particles produced and released [19].

TABLE 2: EUA (emergency use authorization drugs approved by FDA during pandemic to treat corona virus

Product name	Mode/source	ROA	Company	Target	Other uses	Reference
Bamlanivimab/etesevimab	Human	IV	Eli lilly	Surface spike protein of SARS-COV-2		20
Casirivimab/imdeviamb		IV or SC	Regeneron pharmaceuticals	SARS-COV-2 spike protein receptor binding domain (RBD)		21
Sotrovimab	Human	IV	Glaxo smith kline and Vir biotechnology	Epitope on spike protein of SARS-CO2-S		22
Regdanvimab	Human	IV	Celltrion healthcare	SARS-COV-2 spike protein of receptor binding domain		23
Tixagevimab/cilgavimab	human	IM	Astra zeneca	Spike protein of receptor binding domain of SARS-COV-2		24
Bebtelovimab	Human		AbCellera biologics and Eli Lilly	Spike protein receptor binding domain of SARS-COV-2		25
Tocilizumab	Humanized	IV		IL-6 receptor	Rheumatoid arthritis, cytokine release syndrome, Idiopathic multicentricCastleman's disease	26
Baricitinib		Oral	Eli Lilly and Incyte corp.	Janus Kinase (JAK1 & JAK2)	Rheumatoid arthritis, atopic dermatitis, alopecia areata juvenile, idiopathic arthritis idiopathic arthritis systemic lupus erythematous[28]	27

TABLE 3: FDA approved EAU (Emergency Use Authorization) drugs other than mAbs

Name	Site of Action	Other uses	ROA	Ref
Dexamethasone	GRs (glucocorticoid receptors)	Rheumatic and autoimmune diseases, leukemia, multiple myeloma and Hodgkins and non-hodgkins lymphoma	IV	29
Budesonide	GRs	Asthma	Inhaler	30
Nafamostatmesylate	TMPRSS2 (transmembrane protease serine 2)	Pancreatis, DIC, Anticoagulant, Antiplatelet	IV	31
Fresenius propoven 2% emulsion (propofol)	Upregulation of ACE-2	Anesthetic	IV	32
Colchicine	NLRP3 inflammasome	Anti-inflammatory, pericarditis	Per-oral	33
Kineset (Anakinra)	IL-1α and IL-1β (interleukin)	Rheumatoid arthritis, pericarditis, myocarditis	IV	34

Hydroxychloroquine		Malaria	Per-oral[36]	35
Favipiravir/remdesivir	RNA-dependent-RNA-polymerase (RdRp)/nsp12 protein	Influenza	IV	37

V.FDA APPROVED DRUGS

Sotrovimab neutralizes the SARS-COV-2 and other sarebecoviruses [22]. It is developed by Vir Biotechnology in collaboration with Glaxo Smith Kline. It is used for the treatment of covid-19 in adolescents aged grater or equal to 12, adults who do not require oxygen supplementation and who are at high risk to COVID. Sotrovimab received its first full approval on 17 december,2021 [38]. Tocilizumab is a recombinant humanized IL-6 receptor blocking monoclonal antibody which is administered intravenously. It is also used for the treatment of Rheumatoid arthritis, cytokine release syndrome, idiopathic multicentricCastleman's and COVID-19 [26].

Baricitinib is a Janus Kinase JAK1/JAK2 inhibitor. It is an oral medication that inhibits the Janus kinase (JAK) enzymes, Artificial intelligence played a significant role for the identification of baricitinib [27].

VI.OTHER APPLICATIONS

1. Diagnostic Testing and Identifying Pathogens: Cancers and infectious diseases i.e., reproductive and respiratory diseases can be diagnosed by mAbs some diseases are as follows: Rabies, Bovine herpes virus, cervine type 1, pneumonia, plum pox virus, HIV, AIDS, dengue, male infertility,etc. The commonly used screening systems used are enzyme-linked immunosorbent assay (ELISA), radioimmunoassay (RIA), immune fluorescence and hemolytic plaque assays, immune chromatographic card assay, etc [39].
2. Pregnancy testing: In the latest pregnancy testing the anti-hCG (monoclonal antibodies) present in kithe t binds with the hCG(human chorionic gonadotropin) present in the urine of pregnant women only giving a visible color reaction indicating the positive result of pregnancy [40].
3. Radio Immuno-Detection and Radio Immuno-Therapy: Radio Immuno-Therapy uses radio-nucleotides which have applicability for decay for the therapy. Radio Immuno detection applies to radiolabelled antibodies used for diagnosis purposes in cancer [41].
4. Cancer Treatment through Drugs: Trastuzumab containing ADC, Ado-trsatuzumabemtansine was approved by FDA in year 2013, to treat patients with metastatic breast cancer, another drug approved by FDA in the year 2017 i.e., CD19-CD3 BiTEbilnatumomab due to its significance in acute lymphoblastic leukemia patients. Alemtuzumab (naked mAb) is used to treat chronic lymphocytic leukemia (CLL) and Brentuximabemtansine (chemo-label antibodies drugs conjugates) is used to treat Hodgkin lymphoma and anaplastic large cell lymphoma [42].
5. Virus Disease Treatment: The mabs used in the treatment of the Ebola virus are single antibody mAb114; the mAb cocktails MIL77E (two mAbs combined) and MB-003, ZmAb, ZMappTM (three antibodies combined). [43] Crohn's disease (an inflammatory bowel disease) caused due to dysregulated immune response to microbiota in the gastrointestinal system. Anti-NKG2D (natural killer group 2D) mAbs are used to treat Crohn's disease [44].
6. Organ rejection: Monoclonal antibodies are commonly used in induction therapy for renal transplantation, to treat steroid-resistant acute rejection and to allow immunosuppressive minimization and treatment of chronic antibody-mediated rejection [45].

VII. CONCLUSION

Until 2020, there are 119 monoclonal antibodies approved by FDA. There are five methods of production of mAbsHybridoma technology, phagedisplay, B-Cell immortalization, transgenic screening and surface display. The most widely used method is Hybridoma technology. Widely used in cancer identification, diagnosis and treatment. The mAbs are widely used in the treatment of cancer, autoimmune diseases, cardiovascular diseases, inflammation and infectious diseases. Some drawbacks of these are: inadequate pharmacokinetics, tissue accessibility as well as impaired interactions with the immune systems. In these areas, additional research is needed. The high production cost limits the wide use of these drugs. These mAbs being large, most of the administered amount remains in blood circulation and only 20% of it act together with the tumor, hence resulting in an elongated serum-half life. The large size of mAbs also causes impaired tissue penetration, especially in the case of solid tumors leading to poor diffusion causing difficulty in treating large tumor masses with mAb therapy. The "binding site binder effect" further limits the penetration of mAbs into the tumor.

Some of the side effects of the use of mAbs are general side effects include fever, nausea, vomiting and skin rashes. Serious side effects are infusion reactions, heart problems, lung problems, skin problems and bleeding. Optimization of antibodies with modified Fc region capable of overcoming some of the limitations mentioned above is being used to develop a new generation. More than 20mAbs of second generation have been approved for clinical use and third generation mAbs are being developed as potentially more efficient mAbs than the conventional mAbs. Development in other various sectors like the selection of high-responder patients, antibody delivery optimization, infusion schemes, antibody pharmacokinetics and biodistribution as well as a better control of the severe side effects generated by some antibody treatments.

REFERENCES:

1. Ansar W, Ghosh S. Monoclonal Antibodies: A Tool in Clinical Research. Indian J Clin Med [Internet]. 2013 Jan 1;4: IJCM.S11968. Available from: https://doi.org/10.4137/IJCM.S11968
2. pp. 437,438pp. 418, 438-439] Adejare A, Remington JP. Remington : the science and practice of pharmacy. London, United Kingdom: Academic Press is an imprint of Elsevier; 2021.
3. Review M. Therapeutic Monoclonal Antibodies Approved by. 2021;4(1):2020–1.

4. Sadeghalvad M, Rezaei N. Introduction on Monoclonal Antibodies. In: Rezaei N, editor. Rijeka: IntechOpen; 2021. p. Ch. 1. Available from: https://doi.org/10.5772/intechopen.98378
5. Strohl WR, Strohl LMBT-TAE, editors. 8 - Monoclonal antibody targets and mechanisms of action. In: Woodhead Publishing Series in Biomedicine [Internet]. Woodhead Publishing; 2012. p. 163–595. Available from: https://www.sciencedirect.com/science/article/pii/B9781907568374500087
6. Heath H, Qin S, Rao P, Wu L, LaRosa G, Kassam N, et al. Chemokine receptor usage by human eosinophils. The importance of CCR3 demonstrated using an antagonistic monoclonal antibody. J Clin Invest. 1997 Jan;99(2):178–84.
7. Tai Y-T, Dillon M, Song W, Leiba M, Li X-F, Burger P, et al. Anti-CS1 humanized monoclonal antibody HuLuc63 inhibits myeloma cell adhesion and induces antibody-dependent cellular cytotoxicity in the bone marrow milieu. Blood. 2008 Aug;112(4):1329–37.
8. Baig NA, Taylor RP, Lindorfer MA, Church AK, Laplant BR, Pavey ES, et al. Complement dependent cytotoxicity in chronic lymphocytic leukemia: ofatumumab enhancesalemtuzumab complement dependent cytotoxicity and reveals cells resistant to activated complement. Leuk Lymphoma. 2012 Nov;53(11):2218–27.
9. Prat M, Crepaldi T, Pennacchietti S, Bussolino F, Comoglio PM. Agonistic monoclonal antibodies against the Met receptor dissect the biological responses to HGF. J Cell Sci. 1998 Jan;111 (Pt 2:237–47.
10. Kurdi AT, Glavey S V, Bezman NA, Jhatakia A, Guerriero JL, Manier S, et al. Antibody-Dependent Cellular Phagocytosis by Macrophages is a Novel Mechanism of Action of Elotuzumab. Mol Cancer Ther. 2018 Jul;17(7):1454–63.
11. Keizer GD, Visser W, Vliem M, Figdor CG. A monoclonal antibody (NKI-L16) directed against a unique epitope on the alpha-chain of human leukocyte function-associated antigen 1 induces homotypic cell-cell interactions. J Immunol. 1988 Mar;140(5):1393–400.
12. Gribben JG, Freeman GJ, Boussiotis VA, Rennert P, Jellis CL, Greenfield E, et al. CTLA4 mediates antigen-specific apoptosis of human T cells. ProcNatlAcadSci U S A. 1995 Jan;92(3):811–5.
13. Hattori K, Takano N, Kazama H, Moriya S, Miyake K, Hiramoto M, et al. Induction of synergistic non-apoptotic cell death by simultaneously targeting proteasomes with bortezomib and histone deacetylase 6 with ricolinostat in head and neck tumor cells. OncolLett. 2021 Sep;22(3):680.
14. Pandey S. Hybridoma technology for production of monoclonal antibodies. Int J Pharm Sci Rev Res. 2010;1(2):88–94.
15. Saeed AFUH, Wang R, Ling S, Wang S. Antibody Engineering for Pursuing a Healthier Future [Internet]. Vol. 8, Frontiers in Microbiology . 2017. Available from: https://www.frontiersin.org/articles/10.3389/fmicb.2017.00495
16. Parray HA, Shukla S, Samal S, Shrivastava T, Ahmed S, Sharma C, et al. Hybridoma technology a versatile method for isolation of monoclonal antibodies, its applicability across species, limitations, advancement and future perspectives. IntImmunopharmacol. 2020 Aug;85:106639.
17. Yuki K, Fujiogi M, Koutsogiannaki S. COVID-19 pathophysiology: A review. Clinical immunology. 2020 Jun 1;215:108427.
18. Lloyd EC, Gandhi TN, Petty LA. Monoclonal Antibodies for COVID-19. Vol. 325, JAMA. United States; 2021. p. 1015.
19. Yousefi H, Mashouri L, Okpechi SC, Alahari N, Alahari SK. Repurposing existing drugs for the treatment of COVID-19/SARS-CoV-2 infection: A review describing drug mechanisms of action. Biochemical pharmacology. 2021 Jan 1;183:114296.
20. Dougan M, Nirula A, Azizad M, Mocherla B, Gottlieb RL, Chen P, Hebert C, Perry R, Boscia J, Heller B, Morris J. Bamlanivimab plus etesevimab in mild or moderate Covid-19. New England Journal of Medicine. 2021 Oct 7;385(15):1382-92.
21. Deeks ED. Casirivimab/imdevimab: first approval. Drugs. 2021 Nov;81(17):2047-55.
22. Gupta A, Gonzalez-Rojas Y, Juarez E, CrespoCasal M, Moya J, Falci DR, Sarkis E, Solis J, Zheng H, Scott N, Cathcart AL. Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. New England Journal of Medicine. 2021 Nov 18;385(21):1941-50.
23. Syed YY. Regdanvimab: first approval. Drugs. 2021 Dec;81(18):2133-7.
24. Levin MJ, Ustianowski A, De Wit S, Launay O, Avila M, Templeton A, Yuan Y, Seegobin S, Ellery A, Levinson DJ, Ambery P. Intramuscular AZD7442 (tixagevimab–cilgavimab) for prevention of COVID-19. New England Journal of Medicine. 2022 Jun 9;386(23):2188-200.
25. Westendorf K, Žentelis S, Wang L, Foster D, Vaillancourt P, Wiggin M, Lovett E, van der Lee R, Hendle J, Pustilnik A, Sauder JM. LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. Cell Reports. 2022 May 17;39(7):110812.
26. Morena V, Milazzo L, Oreni L, Bestetti G, Fossali T, Bassoli C, Torre A, Cossu MV, Minari C, Ballone E, Perotti A. Off-label use of tocilizumab for the treatment of SARS-CoV-2 pneumonia in Milan, Italy. European journal of internal medicine. 2020 Jun 1;76:36-42.
27. Marconi VC, Ramanan AV, de Bono S, Kartman CE, Krishnan V, Liao R, Piruzeli ML, Goldman JD, Alatorre-Alexander J, de Cassia Pellegrini R, Estrada V. Efficacy and safety of baricitinib for the treatment of hospitalised adults with COVID-19 (COV-BARRIER): a randomised, double-blind, parallel-group, placebo-controlled phase 3 trial. The Lancet Respiratory Medicine. 2021 Dec 1;9(12):1407-18.
28. Stebbing J, Krishnan V, de Bono S, Ottaviani S, Casalini G, Richardson PJ, Monteil V, Lauschke VM, Mirazimi A, Youhanna S, Tan YJ. Mechanism of baricitinib supports artificial intelligence-predicted testing in COVID-19 patients. EMBO molecular medicine. 2020 Aug 7;12(8):e12697.
29. Mehta J, Rolta R, Mehta BB, Kaushik N, Choi EH, Kaushik NK. Role of dexamethasone and methylprednisolone corticosteroids in coronavirus disease 2019 hospitalized patients: a review. Frontiers in Microbiology. 2022 Feb 15;13:46.

30. Liew F, Openshaw PJ. Inhaled corticosteroids: not just for asthma, but for COVID-19?. The Lancet Respiratory Medicine. 2022 Jun 1;10(6):526-7.
31. Quinn TM, Gaughan EE, Bruce A, Antonelli J, O'Connor R, Li F, McNamara S, Koch O, MacKintosh C, Dockrell D, Walsh T. Randomised controlled trial of intravenous nafamostatmesylate in COVID pneumonitis: Phase 1b/2a experimental study to investigate safety, Pharmacokinetics and Pharmacodynamics. EBioMedicine. 2022 Feb 1;76:103856.
32. Wei P, Zheng Q, Ye H, Lyu W, Li J, Yang JJ. Putative antiviral effects of propofol in COVID-19. British Journal of Anaesthesia. 2021 May 1;126(5):e188-91.
33. Deftereos SG, Siasos G, Giannopoulos G, Vrachatis DA, Angelidis C, Giotaki SG, Gargalianos P, Giamarellou H, Gogos C, Daikos G, Lazanas M. The Greek study in the effects of colchicine in COvid-19 complications prevention (GRECCO-19 study): Rationale and study design. Hellenic journal of cardiology. 2020 Jan 1;61(1):42-5.
34. Khani E, Shahrabi M, Rezaei H, Pourkarim F, Afsharirad H, Solduzian M. Current evidence on the use of anakinra in COVID-19. International Immunopharmacology. 2022 Jul 20:109075.
35. •• Fantini J, Di Scala C, Chahinian H, Yahi N. Structural and molecular modelling studies reveal a new mechanism of action of chloroquine and hydroxychloroquine against SARS-CoV-2 infection. Int J Antimicrob Agents Published online. 2020:1–https://doi.org/10.1016/j.ijantimicag.2020.105960Evaluates novel mechanism supporting the use of HCQ in COVID-19.
36. Faraone I, Labanca F, Ponticelli M, De Tommasi N, Milella L. Recent clinical and preclinical studies of hydroxychloroquine on RNA viruses and chronic diseases: a systematic review. Molecules. 2020 Nov 14;25(22):5318.
37. Shannon A, Selisko B, Le NT, Huchting J, Touret F, Piorkowski G, Fattorini V, Ferron F, Decroly E, Meier C, Coutard B. Rapid incorporation of Favipiravir by the fast and permissive viral RNA polymerase complex results in SARS-CoV-2 lethal mutagenesis. Nature communications. 2020 Sep 17;11(1):4682.
38. Heo YA. Sotrovimab: first approval. Drugs. 2022 Mar;82(4):477-84.
39. Siddiqui MZ. Monoclonal antibodies as diagnostics; an appraisal. Indian J Pharm Sci. 2010 Jan;721.
40. Jones RE, Lopez KH. Chapter 10 - Pregnancy. In: Jones RE, Lopez KHBT-HRB (Fourth E, editors. San Diego: Academic Press; 2014. p. 175–204. Available from: https://www.sciencedirect.com/science/article/pii/B9780123821843000106 (1):12–7.
41. Larson SM, Carrasquillo JA, Reynolds JC. Radioimmunodetection and Radioimmunotherapy. Cancer Invest [Internet]. 1984 Jan 1;2(5):363–81. Available from: https://doi.org/10.3109/07357908409040313
42. Zahavi D, Weiner L. Monoclonal Antibodies in Cancer Therapy. Antibodies (Basel, Switzerland). 2020 Jul;9(3).
43. Moekotte AL, Huson MAM, van der Ende AJ, Agnandji ST, Huizenga E, Goorhuis A, et al. Monoclonal antibodies for the treatment of Ebola virus disease. Expert OpinInvestig Drugs. 2016 Nov;25(11):1325–35.
44. Vadstrup K, Bendtsen F. Anti-NKG2D mAb: A New Treatment for Crohn's Disease? Vol. 18, International Journal of Molecular Sciences. 2017.
45. Zaza G, Tomei P, Granata S, Boschiero L, Lupo A. Monoclonal antibody therapy and renal transplantation: focus on adverse effects. Toxins (Basel). 2014 Feb;6(3):869–91.