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Review- Monoclonal Antibodies for Viral Diseases

Prabhat Chourasiya*, Arun Patel, Reeta Patel

B. Pharm Final Year Student, Shri Ram Group of Institution Faculty of Pharmacy,Jabalpur(M.P)
Department of Pharmaceutics,Shri Ram Group of Institution Faculty of Pharmacy, Jabalpur (M.P)
Department of Pharmaceutics, Shri Ram Group of Institution Faculty of Pharmacy, Jabalpur (M.P)

A B S T R A C T

Antibodies have a long successful history of effectiveness against viruses. Recently humanized monoclonal antibodies(mAbs) also shown success. There are many pharmaceutical companies currently working on various therapeutic against viral agents. The emergence of various new pathogens in past decades, such as Middle East respiratory syndrome coronavirus (MERS-COV), severe acute respiratory syndrome coronavirus (SARS-COV), and Ebola virus, post serious challenges to public health and therefore, need for novel antiviral approaches. Antigen-specific mAbs have been isolated using several different approaches, like hybridoma, transgenic mice, phage display, yeast display and single B-cell isolation. In this paper we summarize the recent development of fully human monoclonal antibodies and compared the various approaches to mAbs production and discussed the potential use of mAbs against viral agents. We also summarize the various mAbs for viral agents which are currently approved or in review in Europe and United States.

Keywords: MONOCLONAL ANTIBODIES, PHAGE DISPLAY TECHNIQUE, APPROVED ANTIBODY FOR VIRAL AGENT.

INTRODUCTION

Study and use of monoclonal antibodies have recently attracted great attention by the pharmaceutical industry [1].The increased interest in monoclonal antibodies (mAbs) is due to their binding accuracy (affinity and specificity) together with the original molecular structural rules that govern interaction with their corresponding antigen(Ducancel F, Muller BH, 2012). The first human monoclonal antibody (hmAbs) of predefined antigen specificity was produced by [2].Since then various method have been established to generate hmAbs. The first example of a virus outbreak, severe acute respiratory syndrome (SARS) emerged as a pandemic in 2002, was caused by severe acute respiratory syndrome coronavirus (SARS-COV), and by 2003 caused at least 812 deaths [3]. Second example, Ebola virus outbreak. Although the first recognized outbreak of Ebola virus occurred in 1967[4], after then in West African nation in March 2014, a novel variant of Ebola virus emerged. WHO estimated that this recent outbreak caused 11323 deaths [5].Third example is Middle East respiratory syndrome (MERS) which is caused by Middle East respiratory syndrome coronavirus (MERS-COV) a novel coronavirus. MERS first appeared in 2012 in Saudi Arabia and then spread to 26 other countries. MERS caused the infection in over 2000 individuals with ~35% fatality rate [6]. These three recent outbreaks clearly showed that emerging viral diseases pose a considerable threat to mankind. To cope with these emerging infectious diseases, effective treatments need to be developed. Monoclonal Antibodies-based therapy showed promising results against various viral infections. In this review we will discuss methods for the production of fully human monoclonal antibodies. And the various monoclonal antibodies are currently in use to cope with viral diseases like SARS-COV,MERS-COV, and Ebola.

* *PRABHAT CHOURASIYA.* Tel.: +918109559465
E-mail address: CHOURASIYAPRABHAT1999@gmail.com

METHODS FOR THE PRODUCTION OF FULLY HUMAN MONOCLONAL ANTIBODIES

Since the discovery of monoclonal antibodies, various methods for their production have been established but scientists have targeted to create fully human monoclonal antibodies(hmAbs) to reduce the side effects of humanized or chimeric antibodies. Immunogenicity has posted serious problem in terms of acute reactions and decreased drug efficacy attributable to decreased duration of response. Fully human monoclonal antibodies represent a new standard in monoclonal antibody drug development. [7].

• Phage display technique: In 1985, Smith et al. developed the phage display technique. In this technique, expression of a specific protein into the page surface and the integration of the protein into the phage DNA takes place [8]. This method led to the generation of phage display antibody libraries with random pairs of antibody heavy and light chains. Phage display technique enables the use of appropriate target antigen to screen specific antibodies with high affinity to the antigen[9]. The phage display technique is widely used to generate fully human monoclonal antibody libraries; this method provides a rapid and highly effective approach for obtaining specific antibodies against infectious disease.

• Humanized mouse used for production of fully human monoclonal antibody, in humanized transgenic mice; the endogenous mouse is replaced by human IG loci[10, 11].Then the transgenic mice were then immunized with the target antigen for expression of specific human antibodies. VelocImmune and Kymab mice represent transgenic mouse models that produce high affinity antibodies [10, 11].

• Many other methodologies including yeast display and single B-cell isolation have been recently used to generate human monoclonal antibodies. In the east surface display technique, the connection of the displayed antibody fragment to the C-terminus of the Aga2p subunit, which is linked Aga1P subunit by two disulphide bonds [12]. For B-cell isolation, the first step involved the selection of antigen-positive B-cell through fluorescence-activated cell sorting, antigen-coated magnetic bead system, cell-based micro-array chip system, and micro engraving [13, 14].B-cells would be immortalized through Epstein-Barr virus transformation [15]. After then heavy and light chain sequence are then obtained through reverse transcription polymerase chain reaction (RT-PCR)

TABLE 1. Comparison of techniques for generating monoclonal antibodies.

Method	Advantages	Disadvantages
Serum therapy	Easy to produce, produce large amount of antibodies.	Low safety quality issue low efficacy.
Hybridoma technology	easy to produce, high affinity antibodies.	Low safety, HAM A reaction.
Humanised mouse	Easy to produce, high affinity antibodies, fully human antibodies.	Slow process, high cost, safety issues.
Phage display	Fast method, low cost exceptionally large antibody libraries(10^8-10^{10}), fully human antibodies.	Non-native heavy and light chain pairs.
Yeast display	Fast method, relatively low cost, relatively large antibodies libraries(10^7-10^9), quantitative screening using flow cytometry, fully human antibodies.	Non-native heavy and light chain pairs.

How Monoclonal Antibodies can be used to fight against emerging viral infectious disease:

- Monoclonal antibodies can directly interfere with viral pathogenesis in multiple ways. First, binding of a neutralizing antibody to the virion can prevent target cell binding and/or fusion. Furthermore, antibody binding opsonizes the virions or infected cells for phagocytic uptake. If viral proteins are intercalated into target cell membranes during viral egress, monoclonal antibodies can facilitate target cell death via complement fixation and membrane attack complex (MAC) activation or antibody-dependent cytotoxicity. These mechanisms may result in apoptosis or necrosis of the infected cell.

- In some instances, opsonization of a virion can facilitate viral pathogenesis in a process termed 'antibody-dependent enhancement' (ADE). ADE can occur via two distinct mechanisms. First, pathogen-specific antibodies could increase infection via viral uptake and replication in Fcγ receptor (FcγR)-expressing immune cells. Secondly, ADE can be mediated via increased immune activation by Fc-mediated effector functions or immune complex formation [16].

TABLE 2 - THERAPEUTIC MONOCLONAL ANTIBODIES APPROVED

Generic name	Brand name	Target	1ST Indication approved/ reviewed	1st EU approval year	1st US approval year
Ibalizumab,ibalizumab-uiyk	Trogarzo	CD4; Humanized IgG4	HIV infection	2019	2018
Atoltivimab, maftivimab, and odesivimab-ebgn	Inmazeb	Ebola virus; mixture of 3 human IgG1	Ebola virus infection	NA	2020
Ansuvimab-zykl	Ebanga	Ebola virus glycoprotein; Human IgG1	Ebola virus infection	NA	2020
Casirivimab + imdevimab	REGEN-COV2, Ronapreve	SARS-CoV-2; Human IgG1	COVID-19	2021	In review
Regdanvimab	Regkirona	SARS-CoV-2; Human IgG1	COVID-19	COVID-19	COVID-19

[17]

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[5] https://www.cdc.gov/vhf/ebola/history/2014-2016-outbreak/index.html

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