International Journal of Advanced Research in Biological Sciences
ISSN: 2348-8069
www.ijarbs.com
(A Peer Reviewed, Referred, Indexed and Open Access Journal)
DOI: 10.22192/ijarbs Coden: IJARQG (USA) Volume 9, Issue 7 -2022

Review Article

DOI: http://dx.doi.org/10.22192/ijarbs.2022.09.07.014

Review on the role of Monoclonal Antibody in animal disease diagnosis

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Abstract

Monoclonal antibodies are the most effective biological reagents in the immune diagnostic assays. This is due to their high specificity and high affinity binding properties make them effective biological reagents in immunodiagnostic assays. Hybridoma technology is powerful technique to produce hybrid cell through fusion of antigen specific B-lymphocyte with myeloma cell by the treatment of polyethylene glycol (PEG).The most prominent applications of monoclonal antibodies incorporated in diagnostic techniques (Western immune blotting, enzyme linked immune sorbent assay (ELISA), Immunofluorescence test, and immunohistochemistry) for the treatment and prevention of livestock diseases. Monoclonal antibodies have proved to be extremely valuable applications in the diagnosis of wide variety of diseases such as cancer, autoimmune disease, malignancies, different infectious animal disease, allergy, metabolic disorder and asthma. Evaluating synergetic effect of antibody and chemotherapeutic drug as well as radiotherapy greatly benefits the further development of antibody therapy. Furthermore, the identification of novel biomarkers improves the efficacy and specificity of antibody-based therapy for animal diseases. In the future, studies evaluating synergistic effects of antibodies and chemotherapeutic drugs, radiotherapy or other biologic agents will greatly benefit the further development of antibody therapeutics for animal disease diagnosis and treatment. This review focuses on applications of monoclonal antibody for the treatment of animal diseases, and mechanisms of production of monoclonal antibody therapy and how monoclonal antibody based strategies have moved towards enhancing anti tumor immune responses by targeting immune cells instead of tumor antigens as well as some of the current combination therapies. The objectives of focus on the application of mab in animal disease diagnosis and to indicate the future application of mab to diagnose animal disease.

Keywords: Auto-immune disease, cancer, hybridoma, infectious disease, monoclonal antibody, technology, therapeutic application

Introduction

Monoclonal antibody is a molecule developed in a laboratory that is designed to mimic or enhance the body's natural immune system response against an invader (Elizabeth *et al.,* 2021). Monoclonal antibody production is an immunological technique with great applications in the fields of biochemistry, immunology, biotechnology and applied biology among others (Deb *et al.,* 2013). Monoclonal antibodies (mAbs) are glycoprotein capable of binding an antigen to a specific epitope and in recent years, it has been increasingly reaching maturity in therapy, with several molecules approved by regulatory agencies (Chames *et al.*, 2010). Monoclonal antibodies (mAbs) are antibodies made by clones of a unique B cell, all of which bind to specific portions of an antigen also known as an epitope (Abdullah-Al-Kamran Khan *et al.,* 2020). Initially, the immunoglobulin was produced from hybridomas, using mammalian cells by the recombinant DNA technology (Robinson *et al.*, 2015). However, despite being considered the expression system that allows a better production of mAbs in large scale because of advantages such as greater biochemical similarity, greater stability, and higher levels of expression, the use of mammalian cells implies in a longer cycle of production, which generate higher costs (Farid, 2017).

Hybridomas are cells that have been engineered to produce a desired antibody in large amounts to produce monoclonal antibodies (Hipser *et al*., 2010). Monoclonal antibodies can be produced in specialized cells through a technique now popularly known as hybridoma technology (Abdullah *et al.,* 2008). One unique merit of hybridoma production is that a mixture of antigens can be used to generate specific antibodies. Additionally, this also enables screening of antibodies of choice from a mixture of antibody populations generated by purified antigen where single cell clones can be isolated (Chowdhury *et al.*, 2013).

Monoclonal antibody technology plays a significant role in the development of specific serologic reagent towards antigen in limited amounts. They provide both highly specific and reproducible immunological assay for rapid and accurate diagnosis of different types of infectious diseases (Smith, 2012).

Monoclonal antibodies rely on the specificity and selectivity of antibodies to their antigen and exert their function through the following mechanisms: (i) by binding to cell surface receptors and inducing a signaling cascade, leading to cell death, (ii) the interference of ligand receptor interactions necessary for continued cell growth or viability, (iii) antibody dependent cellular cytotoxicity, which involves the Fc region of the antibody helping to recruit constituents of cell-mediated immunity such as natural killer (NK) cells, monocytes, and macrophages, and (iv) by complement dependent cytotoxicity arising from the activation of the complement cascade after binding to the target structure(Naran *et al.*,2018).

One of the most notable immunotherapies of recent times has been checkpoint blockade therapy which involves the use of mAbs to disrupt the interaction between immune inhibitory receptor ligand pairs (Riley *et al.,* 2019). Immune checkpoints are cellular processes that prevent the host immunity from attacking otherwise healthy cells indiscriminately. Blocking disease associated abnormal immune checkpoint activation restores normal immune system function, thus permitting enhanced immune responses against up regulated ligands. This will help in the specific diagnosis of infectious diseases in different laboratories (Suurs *et al.*, 2019). Thus, the objective of this seminar paper is: To insight the potential applications of monoclonal antibody in animal disease diagnosis and prevention assay. To indicate the future application of monoclonal antibody to diagnose animal disease.

Literature review on the role of monoclonal antibody in animal disease diagnosis

Principle and Procedure of Production of Monoclonal Antibody

The production of monoclonal antibody using hybridoma technology was first invented by Georges Kohler and Cesar Milstein in 1975 (Buss *et al.,* 2012).To produce monoclonal antibodies by Hybridoma technology mice are first exposed to the antigen that an antibody is to be generated against. Usually, this is made by a series of injections of the antigen in question. These injections are typically followed by the use of in vivo electroporation, which significantly enhances the immune response. Once splenocytes are isolated from the mammal's spleen, the B cells are fused with immortalized myeloma cells and the fusion process achieved by Polyethylene glycol (PEG). PEG sequesters water, thus allowing cells to approach closer to one another than is normally permitted by the charges on their membranes (Naran *et al.*, 2018). The fusion of the B cells with myeloma cells can be made using electro fusion. Electro fusion causes the B cells and myeloma cells to align and fuse with the application of an electric field (Hubrecht *et al.*, 2010) (Figure1).

Monoclonal antibodies can have monovalent affinity, binding only specific epitope (the part of an antigen that is recognized by the antibody). In contrast, polyclonal antibodies bind to multiple epitopes and are usually made by several different antibody secreting plasma cell lineages (Guilfoyle and Stephen, 2020)

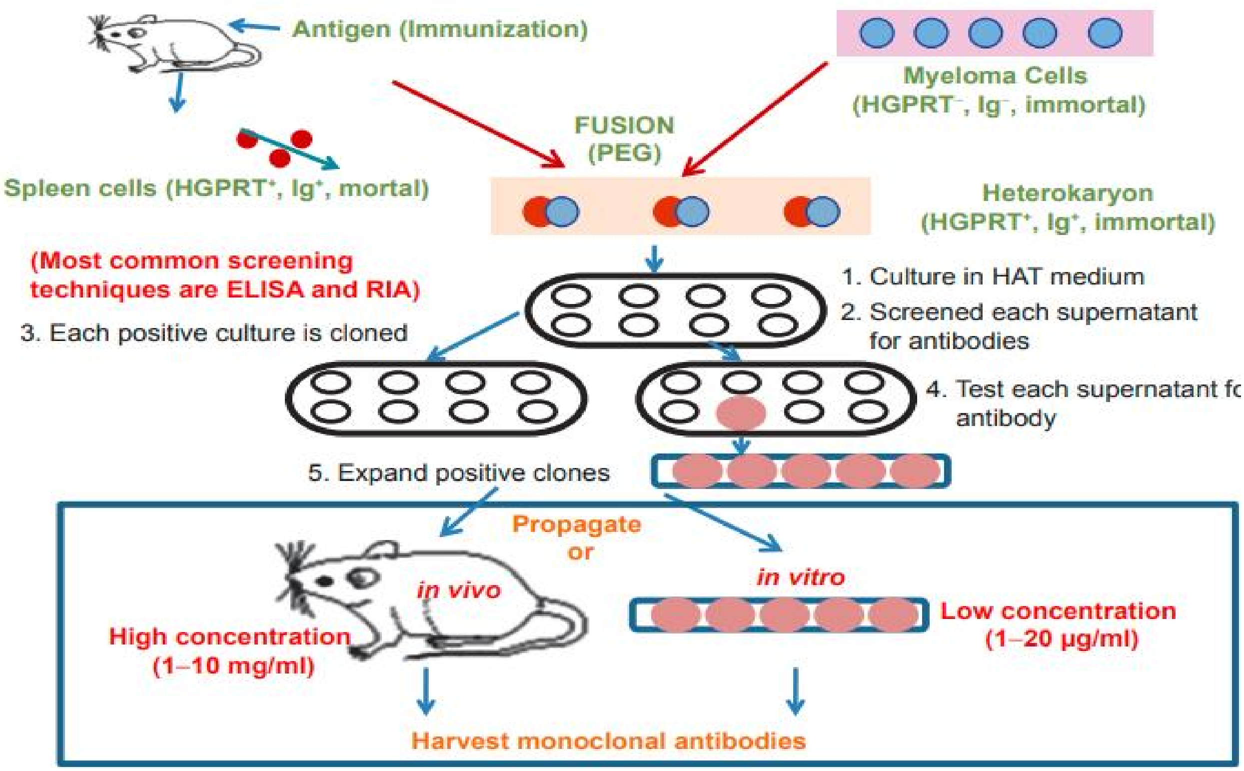

Figure.1. Production of monoclonal antibody by hybridoma technology. Source (Waliza and Shyamasreeal, 2013)

In order to achieve this, it is necessary to fuse these lymphocytes with malignant B-lymphocytes from myeloma or plasmacytoma and introduction of a selectable marker (HGPRT) allows only hybridoma cells to proliferate (Pandey, 2010). The production of specific antibody probes is a relatively straightforward process involving immunization of animals and reliance upon their immune systems to levy responses that result in biosynthesis of antibodies against the injected molecule (Chowdhury *et al.*, 2013). Even so, several factors affect the probability of inducing an immunized animal to produce useful amounts of target specific antibodies. Antigens must be prepared and delivered in a form and manner that maximizes production of a specific immune response by the animal (Figure 2). This is called immunogenic preparation. All subsequent antibodies derived this way trace back to a unique parent cell (George *et al.*, 2012).

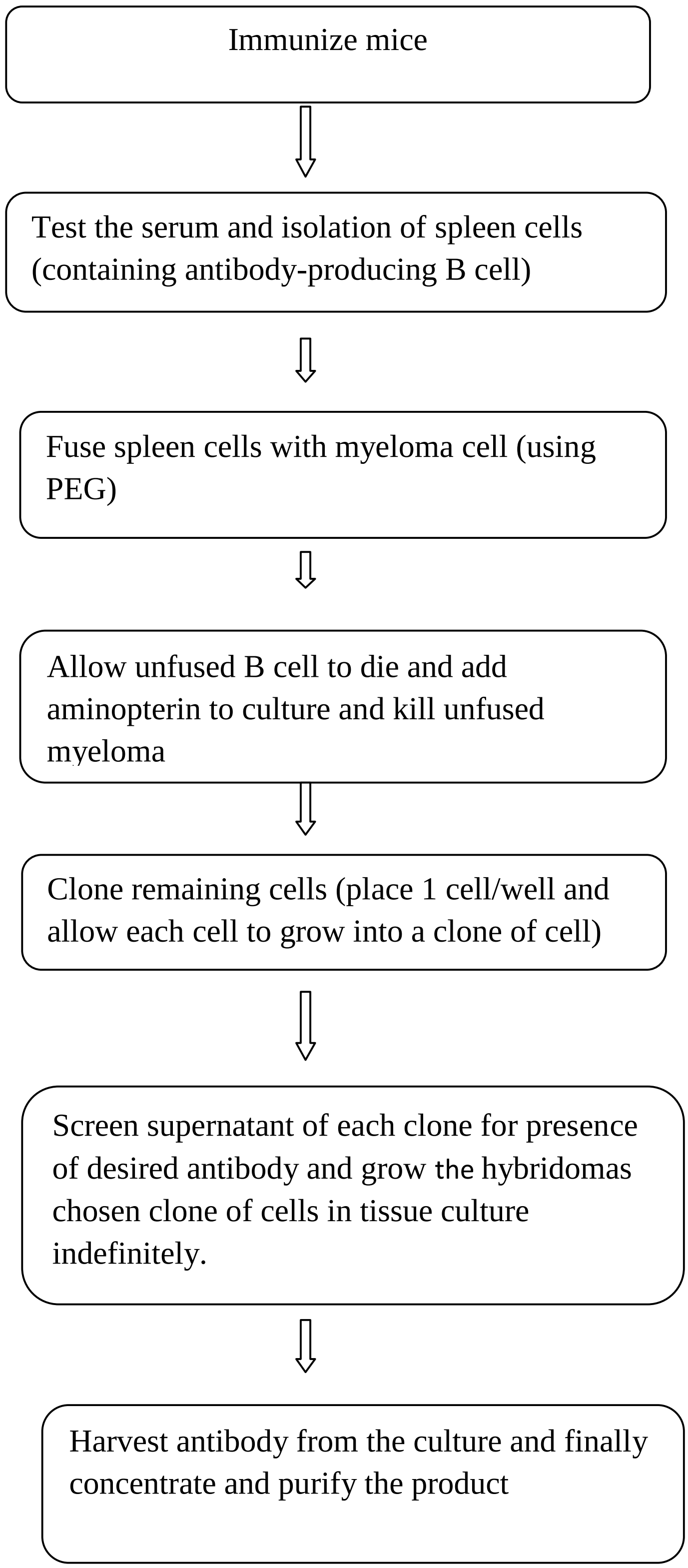

Diagram 1: procedure of monoclonal antibody production

Source :(Justinand Liu, 2014).

Application of Monoclonal Antibody to Diagnose Animal Disease

The importance of monoclonal antibodies is numerous and includes the prevention, diagnosis, and treatment of disease (Moreno *et al.,* 2013). Monoclonal antibodies have proved to be extremely valuable for basic immunological and molecular research because of their high specificity (Zola, 2010). They are used in human and animal therapy, commercial protein purification, suppression immune response, diagnosis of diseases, cancer therapy, diagnosis of allergy, hormone test, purification of complex mixtures, structure of cell membrane, identification of specialized cells, preparation of vaccines, and increasing the effectiveness of medical substances(Tyagi *et al.,*2011). An additional role of monoclonal antibodies in disease prediction and detection is promising. Monoclonal antibody technology plays a significant role in the development of specific serologic reagents towards antigen in limited amounts. They provide both highly specific and reproducible immunological assay for rapid and accurate diagnosis of different types of infectious diseases (Gupta *et al.,* 2012). Additionally, monoclonal antibodies are used for the detection of antigen as well as antibodies against bacterial diseases of livestock, for detection of antigen as well as antibodies against fungal diseases of livestock, for detection of antigen as well as antibodies against viral diseases of livestock and diagnosis of parasitic diseases (Morioka *et al.,* 2014).

The surface of Bacillus anthraces endospores exposes a tetra saccharide containing the monosaccharide anthrose (Deb *et al.,* 2012). Production of antitetrasaccharide mAbs and anti-anthrose-rhamnose disaccharide mAbs and testing for their fine specificities in a direct spore ELISA with inactivated spores of a broad spectrum of strains of B. anthracis and related species of the Bacillus genus revealed that although the two sets of mAbs have got different fine specificities, all of them can recognize the tested B. anthracis strains and show only a limited cross-reactivity with two B. cereus strains. The detection limit of the Luminex assay is 103 to 104 spores per ml which is much more sensitive than the corresponding sandwich ELISA, instead of the fact that enzyme assay represents a useful first-line screening tool for the detection of B. anthraces spores(Tamborrini *et al.,*2010).

Diagnostic application

The diagnostic applications in various livestock and human diseases is an important area for consideration as these diseases form a major and increasingly important factor affecting health and productivity in various parts of the world (USDA, 2008). The discovery of mAbs have been used in diagnosis of many important parasitic helminthes (Zumaquero-Ríos *et al.,* 2012) and protozoan diseases (Plasmodium spp, trichinellosis, trypanosomosis, leishmanosis, anaplasmosis, etc)(Srinivasan *et al.,*2014), bacterial diseases (anthrax, brucellosis, paratuberculosis, leptospirosis, listeriosis, clostridial infections, mycoplasmosis, etc), fungal diseases (zygomycosis, cryptococcosis, histoplasmosis, etc) viral diseases (foot and mouth disease, infectious bovine rhinotracheitis, bovine viral diarrhoea, blue tongue, classical swine fever and rabies, etc (Tamborrini*et al.,* 2010).

Importance of monoclonal antibody in Immunohistochemistry: is one of the diagnostic methods which involve the process of selectively imaging antigens in cells of a tissue section by exploiting the principle of antibodies binding specifically to antigen in fixed tissue sections (Singh, 2004). The method has been used to detect in the diagnosis of cancer in humans and animal species (Casartelli-Alves *et al.,* 2014).With the help of monoclonal antibodies, immune histochemical procedures such as immune peroxidase have been improved and used as important tool for the detection of viral diseases notably the cutaneous viral infections such as the herpes viruses and papilloma viruses which are difficult to diagnose (Molina-Ruiz *et al.,* 2015). Antibody based applications depend on the specific binding of an antibody to the target epitope to generate accurate expression data.

Blocking reactive epitopes and endogenous enzymes before primary antibody incubation on specific binding and mitigates false positive error (Smith, 2012). To block nonspecific binding, the most Common buffers to block non-specific bindings are normal serum. If blocking with normal serum, the species of the animal serum is dependent on the host of the secondary antibody. For example, use goat serum if using a goat anti-mouse secondary. However, the choice of blocking buffer is contingent on the antigen type and type of detection used (Yang and Ma, 2009). Visualizing an antibody antigen interaction can be performed in several ways. In the most common instance, an antibody is conjugated to an enzyme, such as peroxidase, that can catalyze a color producing reaction. Alternatively, the antibody can also be tagged to a fluorophore, such as fluorescein(Wilson and Walker, 2010).

Importance of monoclonal antibody in Enzyme linked immune sorbent assay: is used for monitoring cellular immune responses in humans and other animals (Moreno *et al.*, 2013). It involves a polyvinylidenedifluoride (PVDF) assisted micro titer plate pre coated with antibodies specific to the antigen of interest. A capture antibody binds to the analyte of interest under precise conditions. Then, a biotinylated antibody specific to the analyte of interest is added to detect the original antibody after a wash to remove cell debris. Finally, an enzyme labeled conjugate is added after a second wash to remove unbound antibody and to visualize a colored product. The product is typically a black spot representing a single cell that produces the antigen of interest (Janetzki *et al*., 2005). Diagnostic applications include diagnosing sensitization to house dust mites (Chang *et al.*, 2016), pulmonary tuberculosis (Pang *et al.*, 2016), pleural tuberculosis (Adilistya *et al*., 2016), smear negative tuberculosis (Li *et al.*, 2015), spinal tuberculosis (Yuan *et al.*, 2015), and cytomegalovirus infection (Nesher *et al*., 2016).

Importance of monoclonal antibody in immune fluorescence test: is described as a useful technique in the immunological diagnosis of animal disease (Carrera *et al.*, 2010). The method is used to detect antibody present in the serum of patients through binding to surface antigens or within the parasite. The reaction is read in a fluorescence microscope after adding an anti human Ig antibody conjugated to a fluorochrome. This technique (IFAT) has the advantage of providing a quantitative result by the accurate determination of antibody titer (Gupta and Singla, 2012). This method uses the specificity of antibodies to their antigen to target fluorescent dyes to specific bio-molecule targets within a cell, and therefore allows visualization of the distribution of the target molecule through the sample (Wang *et al.*, 2008). Immunofluorescence can also be used on tissue sections, cultured cell lines, and may be used to analyze the distribution of proteins, glycans, and small biological and non-biological molecules (Morioka *et al.*, 2014). To test the binding properties of the generated antibodies on cells from cultures and seawater samples, an indirect immune fluorescent labeling assay was used, where the specific antibodies were bound with secondary antibodies containing a fluorescent molecule that can be detected by fluorescent microscopy (Levenhagen and Costa-Cruz, 2014).

Importance of monoclonal antibody in Western blotting: known as protein blotting or immune blotting is a rapid and sensitive assay for the detection of proteins. It is based on the principle of immune chromatography where proteins are separated in to polyacrylamide gel according to their molecular weight (Pandey, 2010). Western blotting analysis can detect one protein in a solution that contains any number of proteins and giving the protein information, and it is widely used in protein detection. It is a method in molecular biology or immunogenetics to detect protein in a given sample of tissue homogenate or extract which is normally used with high antibody directed against a desired protein (antigen) (Yang and Ma, 2009). The proteins thus separated by Polyacrylamid gel electrophoresis are then transferred or electro transferred on to nitrocellulose membrane and are detected using a specific primary antibody and secondary enzyme labeled antibody and substrate. Western blotting has been an invaluable tool used in the detection of viruses (Naran *et al.,* 2018). Novel western blotting was developed based on monoclonal antibody for the detection of Cytomegalovirus in latently infected blood donors, pregnant women, and transplant recipients with ongoing human cytomegalovirus (Smith, 2012).

Therapeutic application

Therapeutic application of monoclonal antibodies act through multiple mechanisms, such as blocking of targeted molecule functions, inducing apoptosis in cells which express the target, or by modulating signaling pathways (Seeber *et al.*, 2014). Recent advances in genetic engineering have made possible efforts to improve the therapeutic application of mAbs by identifying new targets with improved efficacy for use in clinical practice (Xiong *et al.*, 2012). The use in immune prophylaxis or immune therapeutics has been extensively applied to infectious diseases, as carriers for toxic substances delivery to tumors or as tools for identifying, locating and target neoplasm (Mumaw *et al.,* 2015). MAbs are used in the treatment of cancer, transplantation of bone marrow and organs, autoimmune diseases, cardiovascular diseases and infectious diseases (Vyas and Dixit, 2010). Monoclonal antibodies can be directly used for enhancing the immune function of the host. Direct use of mAbs causes minimal toxicity to the target tissues or the host. MAb promotes efficient opsonization of pathogenic organisms (by coating with antibody) and enhances phagocytosis. In fact, mAbs were found to protect chimpanzees against certain viral (hepatitis B-virus) and bacterial (E. coli Haemophilus influenza, Streptococcus spp. and Pseudomonas spp.) infections (Bach and Lancet, 2011).

Cancer therapy: In the treatment of cancer, mAbs binds complement proteins, which thus lead to direct cell cytotoxicity that is, complement dependent in nature (Ribatti, 2014). One possible treatment for cancer involves monoclonal antibodies that bind to cancer cell specific antigens and induce an immune response against the target cancer cell. Such mAbs can be modified for delivery of a toxin, radioisotope, cytokine or other active conjugate or to design bispecific antibodies that can bind with their Fab regions both to target antigen and to a conjugate or effector cell. Every intact antibody can bind to cell receptors or other proteins with its Fc region (Hernandez *et al.*, 2018). Some monoclonal antibodies have been reported to function in blocking the growth factor by binding to, and inhibiting, growth factor receptors, in order to effectively arrest the proliferation of the tumor cells (Hutchings *et al*., 2010). Ibritumomab is a monoclonal antibody against the CD20 antigen on B-cells for the treatment of lymphoma patients; while Rituximab is a chimeric immunoglobulin (IgG) mAb directed against the CD20 antigen, which has been reported to be effective against B-cells malignancies (Ahmad *et al.*, 2012).Therapeutic anti-cancer mAbs against leukemia are Gemtuzumab and Alemtuzumab; while Nimotuzumab and Cituximab are for carcinomas. Bevacizumab is another is another drug (mAb) approved by the Food and Drug Administration (FDA) for use in the therapy of colorectal cancers. It binds to vascular endothelial growth factor (VEGF), thereby preventing it from binding to its receptors (Lambert *et al.*, 2014) (Table1).

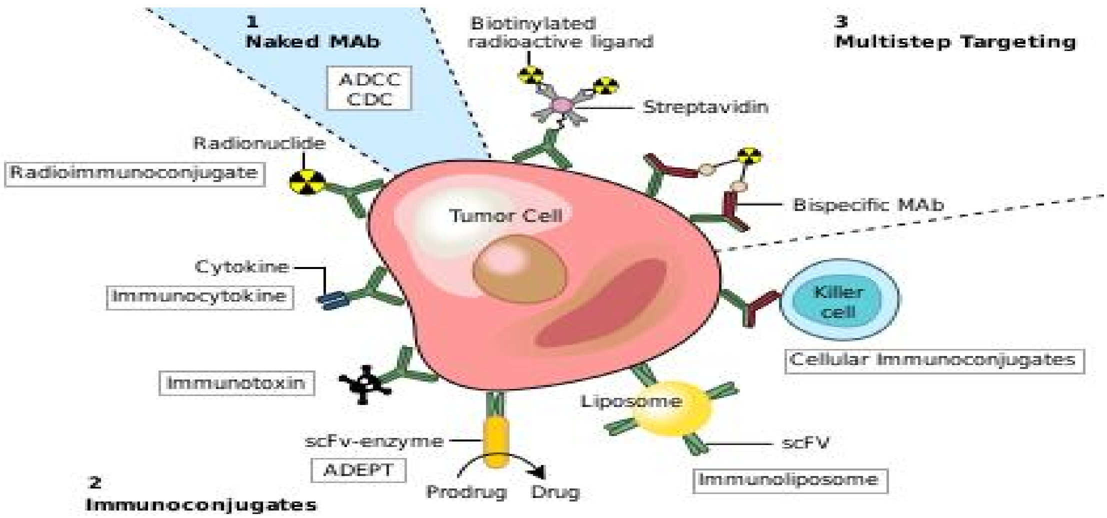

Figure 3: Monoclonal antibodies that bind to cancer-cell-specific antigens and induce an immune response against the target cancer cell. Source: (Zhang *et al.*, 2015).

Table1. Approved monoclonal antibodies for cancer therapy.

Name	**Antigen**	**Unconjugated Antibodies**	**Indications (Year of First Approval)**
Atezolizumab	PD-L1	Humanized IgG1	Bladder, Non-small cell lung (2016), and Triple-negative breast (2019) cancers (2019)
Cemiplimab	PD-1	Human IgG4	Cutaneous squamous-cell carcinoma (2018)
Avelumab	PD-L1	Human IgG1	Urothelial Carcinoma (2017) and Merkel Cell Carcinoma (2017)
Cetuximab	EGFR	Chimeric IgG1	Colorectal cancer (2004) and Head and neck squamous cell carcinoma (2006)
Necitumumab	EGFR	Human IgG1	Non-small cell lung cancer (2015)
Ipilimumab	CTLA-4	Human IgG1	Melanoma (2011) and Renal cell carcinoma (2018)
Nivolumab	PD-1	Human IgG4	Melanoma (2014), Lung (2015), and Renal (2018) cancers
Blinatumomab	CD19, CD3	Mouse BiTE	Acute lymphoblastic leukemia (2014)
Trastuzumabemtansine	HER2	Humanized ADC	Breast cancer (2013)
Isatuximab	CD38	Chimeric IgG1	Multiple Myeloma (2020)
Durvalumab	PD-L1	Human IgG1	Bladder Cancer (2017)
Dinutuximab	GD2	Chimeric IgG1	Neuroblastoma (2015)
Ramucirumab	VEGFR2	Human IgG1	Gastric cancer (2014)

Indications and year of first approval for each antibody were accessed using the FDA drug database (Rimawi *et al.*, 2015).

Auto immune disease: Monoclonal antibody used for autoimmune diseases include infliximab and adalimumab, which are effective in rheumatoid arthritis, Crohn's disease, and ulcerative Colitis due to their ability to bind to and inhibit tumor necrosis factor (TNF), TNF-α. Basiliximab and daclizumab inhibit IL-2 on activated T-cells and thereby help prevent acute rejection of kidney transplants (Hernandez *et al.*, 2018). Daclizumab is also a promising drug against T-cell lymphoma. Omalizumab inhibits human IgE and is useful in moderate to severe allergic asthma (Huang *et al.*, 2013). Several immune diseases are caused by an apparent attack of the immune system on the tissues of the body. To suppress the immune system, muromonab CD3 (OKT3), infliximab, adalimumab, omalizumab and daclizumab are the most widely used drugs (Zola *et al.,* 2010).

Metabolic disorder: One of the areas where mAbs therapeutics is applied includes metabolic disorders. G protein coupled receptors (GPCRs) are implicated in a wide variety of metabolic diseases (Dadu and Ballantyne, 2014). Thus, scientists have used GPCRs membrane fractions as a target to produce mAbs for the cure of metabolic disorders (Hipse *et al.*, 2010). Monoclonal antibodies have been produced against the human glucagon receptor (GCGR) from stable cell lines through a transgenic xeno mouse platform. These candidate mAbs were shown to display potential antagonistic activity in reducing blood glucose level with a resultant long term inhibition of GCGR signaling in a mouse model, making them effective for controlling diabetic hyperglycemia (Hutchings *et al.,* 2010). Increase low density lipoprotein cholesterol (LDL-C) levels have been reported to be a major cause of metabolic disorders (Zhang *et al.,* 2015). Evolocumab and Alirocumab were found to be safe and welltolerated (Navarese, 2015).
Clinical application

Monoclonal Antibodies are extremely versatile as platforms for the development of novel therapeutics which has resulted in a large diversity of approaches. The discovery of targetable tumor specific antigens fueled interest in designing immunotherapy's (Finn, 2017). MAbs can be used in immunodiagnostic techniques as reagents to identify the antigen of the causative agents or indirectly for serological detection of antibodies against the causative agents and also used in experimental purposes ranging from molecular detection of antigenic epitopes to monoclonal antibody for utilization as a vaccine to induce protective immunity(Deb *et al.*,2013). Within vitro assays, antibodies can be used to precipitate soluble antigens, agglutinate (clump) cells, opsonize and kill bacteria with the assistance of complement, and neutralize drugs, toxins, and viruses(Shivanand ,2010).

In destroying disease causing organisms mAbs promote efficient opsonization of pathogenic organisms (by coating with antibody) and enhance phagocytosis (Justin and Liu, 2014). In the immune suppression of organ transplantation in the normal medical practice, immunosuppressive drugs such as cyclosporine and prednisone are administered to overcome the rejection of organ transplantation. In recent years, mAbs specific to T-lymphocyte surface antigens are being used for this purpose (Andrew and Otavia, 2014).

Monoclonal Antibody in the Treatment and Prevention of Animal Disease

Monoclonal antibodies are critical for immunity against infectious diseases, and extensively used for prevention and treatment of infection caused by bacteria, virus, and other infectious agents to improve public health (Graham and Ambrosino, 2015). Monoclonal antibodies are being reconsidered for the treatment of bacterial infections (Motley *et al.,* 2019). Antibodies play an important role in immune modulation during TB, evidenced by antibody profiles during latent TB infection which show enhanced Fc mediated immune effectors function and drive macrophage destruction of intracellular pathogens, highlighting the protective role of these antibodies (Lu and Chung, 2016). MEDI3902 (AstraZeneca PLC), a bi specific IgG1 antibody targeting the PcrV protein (host cell cytotoxicity) and Pslexopolysaccharide (colonization and tissue adherence) of *P. aeruginosa*, is under development for the prevention of pneumonia in high risk patients (NCT02696902) (Ali *et al.*, 2019). Furthermore, the targets are conserved across global isolates of *P. aeruginosa* and may mediate broad coverage (Tabor, 2018). AR-301 (Aridis Pharmaceuticals), a mAb with alpha-toxin (virulence factor) neutralizing capability conferred protection against alpha toxin mediated host cell damage when administered as adjunctive treatment to patients with methicillin resistant *S. aureus* (MRSA) pneumonia (NCT03816956) (François *et al.*,2018).

In the treatment of cancer mAbs, against the antigens on the surface of cancer cells, are useful for the treatment of cancer. The antibodies bind to the cancer cells and destroy them. This is brought out by antibody dependent cell mediated cytotoxicity, complement-mediated cytotoxicity and phagocytosis of cancer cells (coated with mAbs) by reticulo endothelial system (Agulnik, 2012). In the treatment of autoimmune diseases autoimmune diseases like rheumatoid arthritis and multiple sclerosis are of great concern. Some success has been reported in the clinical trials of rheumatoid arthritis patients by using mAbs directed against T-lymphocytes and B-lymphocytes (Reichert, 2011).

Therapeutic antibodies developed for the treatment of other infectious diseases include prophylaxis, anthrax, autoantibody positive, lupus, angioedema, immune thrombocytopenic purpura, macular degeneration, hemophilia A, psoriasis, alzheimer, muscle loss and weakness, optic neuritis, ulcerative colitis, pulmonary fibrosis, and asthma (Nixon *et al.*, 2014).

Immunogenicity of antibody based therapeutics

The use of mAbs in a clinical setting should have several essential biophysical properties, including high antigen binding activity, high stability, and low immunogenicity (Ducancel and Muller, 2012). Adalimumab (Humira), a human IgG1, has been reported to generate significant immune responses through eliciting anti-idiotypic antibody in a part of patients (5–89%) which varies depending on the disease and the therapy (West *et al.*, 2008). Golimumab (Simponi), a fully human anti-TNFα antibody, combining with methotrexate for treatment of rheumatoid arthritis cause 16% of patients producing anti-drug antibodies (kay *et al.*, 2018). Immunogenicity is influenced by several factors, such as drug dosage, administration strategy (route and combination), impurities contamination, aggregates arising from Ab-Ag binding complex, and structural features (sequence variation and glycosylation) (Waldmann, 2019).

The successful development of antibody drugs from phage display

Phage display has the advantage of allowing researchers to tailor critical characteristics of successful antibody drugs (e.g. affinity, specificity, cross-reactivity and stability) (Kennedy *et al.*, 2018). Adalimumab (Humira) was developed Bioresearch Corporation and Cambridge Antibody Technology. It was not only the first phage display derived antibody granted a marketing approval, but adalimubab was also the first approved (2002) fully human mAb drug (Arrieta *et al.*, 2017). Adalimumab binds and suppresses TNF-α and is approved to treat inflammatory diseases, such as rheumatoid and psoriatic arthritis, Crohn’s disease, and psoriasis. Adalimumab is the world’s best selling drug (Lindsley, 2019). Many researchers have begun to take advantage of these free technologies (Sheehan and Marasco, 2015). According to (Lu *et al.*, 2011) also established a phage displayed human naive scFv library at the Institute of Cellular and Organismic Biology (ICOB) in Academia Sinica in Taiwan. The antibody gene repertoires of the ICOB phage antibody library were isolated from the PBMCs of 50 healthy human donors, producing a library size of 60 billion individual scFv clones (Lee *et al.*, 2016). This collection has been successfully used to select antibodies that bind a wide spectrum of target antigens, including pure recombinant proteins, glycans, cancer cells and virus particles (Wu *et al.*, 2019) (Table 2).

Table.2. some examples of monoclonal antibody therapies currently in use and the conditions treated.

Drug Therapy	Disease Condition Treated
Etanercept Brand name: Enbrel	Rheumatoid arthritis
Abciximab Brand name: Reopro	Prevents blood clots in coronary angioplasty
Infliximab Brand name: Remicade	Rheumatoid arthritis, Chrohn's disease
Rituximab Brand names: Rituxan and MabThera	Non-Hodgkin's lymphoma
Trastuzumab Brand name: Herceptin	Specific kind of breast cancer
Bevacizumab Brand name: Avastin	Several types of cancer
Basiliximab Brand name: Simulect	Rejection of kidney transplants
Alemtuzuab Brand name: Campath	B cell leukemia
Paliviziumab Brand name: Synagis	Respiratory syncitial virus (RSV) infections in children

Source :(MargiePatlak, 2009).

Future Application of Monoclonal Antibody in Animal Disease Diagnosis

In recent years, the development of monoclonal antibody by means of laboratory animals has become a vital approach to protect against a number of pathogenic contagions (Marasco and Sui, 2017). However, there is still significant growth potential for the therapeutic antibody field. Traditionally, antibodies have been used for the treatment of cancer, autoimmune diseases, and infectious diseases (Saunders, 2019). These immune protective molecules provide defense against transmissible diseases and can eliminate the infection. If the molecular mechanisms of a specific disease can be clearly elucidated and the specific proteins or molecules involved in pathogenesis can be identified, antibodies may provide an effective therapeutic option (Ohradanova *et al.,* 2018).

Anti-proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies (evolocumab or alirocumab) are used for the treatment of hypercholesterolemia. Anti-fibroblast growth factor 23 (FGF23) antibodies (burosumab) are used to treat X-linked hypophosphatemia(Neri, 2019). Anti-IL6R antibody (sarilumab and tocilizumab) can be used for the treatment of rheumatoid arthritis. Anti-Factor IXa/Xa antibody (emicizumab) is a valuable treatment for hemophilia A. Anti-von Willebrand factor antibody (caplacizumab) is approved for the treatment of thrombotic thrombocytopenic purpura, and other antibodies will be approved for new indications in the near future(Labrijn *et al.,*2019). Immune checkpoints have proven to be valuable targets for cancer treatment (Park *et al.*, 2018). In the future, studies evaluating synergistic effects of antibodies and chemotherapeutic drugs, radiotherapy or other biologic agents will greatly benefit the further development of antibody therapeutics. Furthermore, the identification of novel biomarkers may improve the efficacy and specificity of antibody-based therapy for animal diseases.

Conclusion and Recommendations

Monoclonal antibodies are specialized proteins produced by immune system B cells. Their unique structure and function allow them to bind to highly specific targets or receptors. Therapeutic mAbs are designed specifically to prevent or treat particular diseases or clinical conditions. The mechanisms of action are varied and can include killing of cells, immune modulation, or neutralization of an infectious agent. Monoclonal antibodies have emerged as a major class of therapeutic agents.

Since monoclonal antibody production is a very sophisticated process, it requires immunization of antibody against a specific antigen, collection of spleen cells from immunized mice, and fusing the spleen cells with myeloma cell with an immortal myeloma cell. The technology is referred to as hybridoma technology which targets to produce a monoclonal antibody against a specific epitope of antigen as opposed to a polyclonal antibody which is specific to multiple epitopes in an antigen. Monoclonal antibodies have been utilized for diagnostic applications like western blotting, immuneflorescent, immunehistochemistry, and ELISA. Based on the above conclusion the following recommendations forwarded:

- ❖ Taking maximum attention in all segmented process of monoclonal antibody production.
- ❖ Improve the production and use of monoclonal antibody for the target foreign antigen highly applicable for animal disease treatment.
- ❖ Continuous improvement and further advancements in this field of research is important.

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DOI:10.22192/ijarbs.2022.09.07.014	

How to cite this article:
Belay Walelig Moges, Tekalign Woldehana Uro. (2022). Review on the role of Monoclonal Antibody in animal disease diagnosis. Int. J. Adv. Res. Biol. Sci. 9(7): 144-160.
DOI: http://dx.doi.org/10.22192/ijarbs.2022.09.07.014