WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 14, 1345-1356. Review Article ISSN 2277– 7105

MONOCLONAL ANTIBODIES: A PROMISING SOLUTION TO INDESTRUCTIBLE DISEASES

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Article Received on
21 Sept. 2020,

Revised on 11 Oct. 2020,
Accepted on 31 Oct. 2020

DOI: 10.20959/wjpr202014-19173

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ABSTRACT

Background: Monoclonal antibodies are monovalent antibodies that are generated from a single B lymphocyte clone and binds to same epitope. From the year of 2014, FDA is approving at least 5 monoclonal antibodies per year. The therapeutic effect of monoclonal antibodies is being considered on a number of diseases like cancer, auto immune disorders, and infectious diseases and so on. The monoclonal antibodies provides precision in medicine as they are highly specific in nature. The invention of monoclonal antibodies is certainly a boon in therapy of various diseases. **Methods:** Previously published articles relating therapeutic effects of monoclonal antibodies have been collected and reviewed. **Observations:** The invention of monoclonal antibodies is really a boon to the medical field. The ongoing medical researchers on monoclonal antibodies will certainly lead to innovative treatment on incurable diseases. Monoclonal antibodies are already using in certain diseases like infections, cancers, autoimmune diseases etc. Although like other treatment modes there are certain side effects, but the benefits of monoclonal antibodies is much more than the risk.

INTRODUCTION

Monoclonal antibodies are antibodies that are made by identical immune cells. They are a mixture of homogenous antibody molecules with affinity towards a specific antigen, often generated using a hybridoma by fusing a B-cell with a single lineage of cells containing a

definite antibody gene.[1] Finally a population of identical cells (or clones) is produced that secrete the same antibody. They are essential tool for many molecular immunology investigations. They are used in combination with techniques like epitope mapping and molecular modeling.[2]

The development of hybridoma monoclonal antibody technology has a major impact on clinical and laboratory medicine. Murine monoclonal antibodies have widespread use in clinical and research laboratories especially in oncology. Antibodies are useful research tools in diagnosis and therapy, as they can recognize and bind specifically and strongly with respective antigens.[3] Due to their specificity and high reproducibility using culture techniques, MAbs offer advantage over polyclonal antibodies. Monoclonal antibodies can specifically recognize two types of epitopes. One is linear in the primary structures of proteins. The other is conformational, dependent on secondary and tertiary structures.

Humanised monoclonal antibodies are now the fastest growing group of biotechnology-derived molecules in clinical trials currently. Around the world, at least 570 therapeutic mAbs have been studied in clinical trials by commercial companies and 79 therapeutic mAbs have been approved by the United States Food and Drug Administration (US FDA) and are currently on the market, including 30 mAbs for the treatment of cancer, chronic inflammatory diseases, transplantation, infectious diseases and cardiovascular diseases.[4] Since 2008, 48 new mAbs have been approved, contributing to a total global market of 61 mAbs in clinical use at the end of 2017, according to the US FDA.

The use for which mAbs are anticipated determines the exact amount required for carrying out the different activities. Only a small amounts of mAb (0.1 g) is required for carrying out most research and analytic work. The increasing importance of therapeutic mAbs is apparent, as mAbs have become the predominant treatment modality for various diseases over the past 25 years.

Based on the mechanism of action, therapeutic mAbs can be generally divided into 2 categories, e.g., those designed to modulate immune responses by directly target immune competent cells or molecules, and those designed to target cells or molecules not belonging to the classic immune system.[5] As a major product of immune cells and an important molecule to execute the effector function of immune cells, any given mAb inevitably has some immune

regulatory effect. In short, mABs are expected to control the management of various diseases on both clinical and economical perspectives.

HISTORY

In fact, the production of monoclonal antibodies was partly accidental. Before 1975, a research was held in Dr. Milstein's Laboratory, focusing on the regulation of immunoglobulin expression, using somatic cell hybridization technique. As the first hybridoma was created, it was clear that, when a specific, antibody-producing, mortal plasma cell is hybridized or fused with an immortal, non-specific, antibody-producing, myeloma cell, the hybrid continue to produce specific antibody. Thus the era of hybridoma technology was launched.

For the discovery, Georges Kohler of West Germany and Cesar Milstein of Argentina, who jointly with Niels Kaj Jerne of Denmark were awarded the Nobel Prize for Physiology and Medicine in 1984. Kohler and Milstein7 provided the most outstanding proof of the clonal selection theory from results of heterokaryons—cell hybrids formed by the fusion of normal and malignant cells.[6] Twenty-five years after Kohler and Milstein produced the first monoclonal antibodies, dramatic progress has been made in using antibodies for diagnostic purposes, but the uses of mAbs to treat disease are somewhat limited. In 1988, Greg Winter used the first humanized mAbs to avoid reactions observed in patients injected with murine derived mAbs. Monoclonal antibodies are nowadays often generated by isolating or transforming antibody-producing cells taken directly from immunized animals or patients, and transplanting the antibody - encoding genes of these cells into suitable producer cell lines, rather than using hybridoma technology.

APPLICATIONS OF MONOCLONAL ANTIBODIES

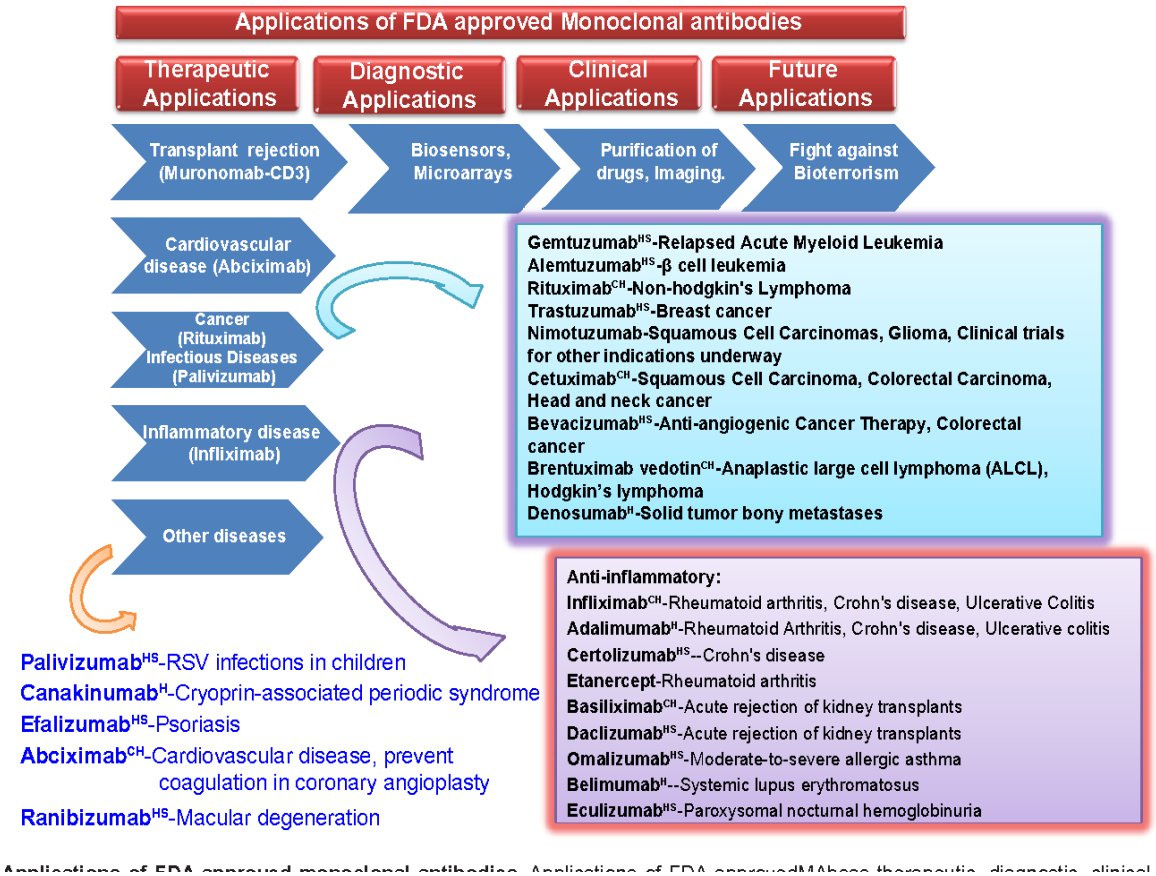

Fig. 1 Applications of FDA approved monoclonal antibodies.

mAbs are extremely valuable for immunological and molecular research because of their high specificity. They are mainly used in human therapy, commercial protein purification, suppressing immune response, diagnosis of diseases, cancer therapy, diagnosis of allergy, hormone tests, purification of complex mixtures, structure of cell membrane, identification of specialized b cells, preparation of vaccines, and increasing the effectiveness of medical substances.[7]

1. DIAGNOSTIC TOOLS

mAbs are used in different technologies like, Western blot, Immunodot blot, ELISA, RIA, flow cytometry, immunohisto chemistry, fluorescence microscopy, electron microscopy, confocal microscopy etc. mAbs can be used to detect the presence of antigens. MAb is used to detect pregnancy as early as a week or two after conception by reacting with human chorionic gonadotrophin, a hormone secreted by the placenta and found in the urine of pregnant women.[8] mAbs are available that can identify gonorrhea and Chlamydia infections

in 15–20 minutes. mAbs are also available to distinguish between the closely related herpes virus 1 and herpes virus 2.

2. GENE CLONING

mAb helps in identifying the cells containing desired genes which is a difficult step in gene cloning. So it can be used as a prob for detecting such cells in gene cloning.[9]

3. PURIFICATION OF PROTEINS

mAbs have unique specificity to desired proteins. Since the mAb-antigen complex has a single binding affinity it is possible to elute the required protein in a single, sharp peak.[10]

4. THERAPEUTIC TOOL IN CLINICAL MEDICINE

Chimerinc and humanized antibodies were produced due to overcome limitations of murine antibodies in clinical context. A chimeric antibody is a special type of therapeutic antibody made by combining genetic ingredients from a non-human animal like rat and from a human. Chimeric antibodies are composed of nearly 65% human genetic material. In human antibodies, the murine hyper variable regions are grafted onto amino acids to produce humanized antibodies.[11] This antibody molecule is nearly 95% human origin. Several drugs like infliximab, rituximab, abciximab, etc. are based on chimeric antibodies have been approved by the Food and Drug Administration (FDA) for human use and research in this field.[12] Several humanized and chimeric antibody products are currently available on the market for varied clinical diseases and some MAbs are going through clinical trials.

5. IDENTIFICATION OF CELL SURFACE MARKERS

CD and HLA are known as antigens in various immune cells. These molecules are identified using mAbs directed against a specific cell surface antigens. The mAbs also help to define the functions of immune cells. The mAbs can also be used in understanding, diagnosing and managing immune system related diseases.

6. CANCER DIAGNOSIS AND THERAPY

mAbs are used against cancer cell specific antigens, that can produce an immunological response against the target cancer cell. Availability of some mAbs that can recognize immune cell antigens resulted in diagnosis of some particular types of lymphoma, leukemia, and some solid tumors. Special mAbs are available for, colorectal cancer, ovarian cancer and lung cancer.[14] mAbs may be used not only for detecting cancer cells but to destroy them, In

cancer immunotherapy, mAbs binds complement proteins, which leads to direct cell toxicity.[15] mAb blocks growth factors released by the tumor cells by blocking growth factor receptors. This effectively arrests the proliferation of tumor cells. The FDA-regulated mAbs for cancers include bevacizumab, cetuximab, panitumumab, trastuzumab, etc.[16]

Rituximab, an IgG mAb is a chimeric antibody directed against the CD20 molecule and effective towards B-cell malignancies as CD20 antigen, which is present in significant numbers on malignant B-cells. Ibritumomab, works against the CD20 antigen on B cells, is conjugatebd to either the radioactive isotope indium-111 or yttrium-90 for treatment of lymphoma patients. Tositumomab, an mAb against CD20, is used for treating the lymphoma. For B-cell lymphoma, 131 I-Tositumomab is a single-treatment. According to clinical trials, it is evident that, mAbs have induced partial remission.[17]

Therapeutic anti-cancer MAbs against leukemia are gemtuzumab and alemtuzumab. For non-hodgkin lymphoma, rituximab is used. Trastuzumab is used for breast cancer, and nimotuzumab and cituximab for carcinomas. Complete remission of chronic lymphocytic leukemia is caused with alemtuzumab by binding to a molecule CD52 on lymphocytes.[18]

A very detailed analysis of tumor expression and normal tissue expression is required for selecting tumor antigens for antibody targeting and for understanding the role of antigen in tumor growth. If the desired mechanism of action is engagement with cell surface receptors, or to activate antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC), then it is desirable that the antigen-mAb complex should not be rapidly internalized. This allows the maximization of the availability of the Fab region to appropriately engage with surface receptors, and of the Fc region to immune effector cells and complement proteins.[19] For antibodies or proteins delivering toxins into the cancer cell, internalization is desirable. Internalization is also desirable for antibodies whose action is primarily based on down regulation of cell surface receptors.

7. AUTOIMMUNE DISORDERS

mAbs can also be used for autoimmune diseases and are effective in diseases like, rheumatoid arthritis, Crohn's disease, and ulcerative colitis.[20] mAbs used include infliximab and adalimumab, etc. These mAbs are effective due to their ability to bind to and inhibit tumor necrosis factor, TNF-α. Acute rejection of kidney transplants can be prevented by, basiliximab and daclizumab by inhibiting IL-2 on activated T cells.[21] Daclizumab is also a

promising drug against T-cell lymphoma. Omalizumab is useful in asthmas it inhibits human IgE. Several immune diseases are caused by an apparent attack of the immune system on the tissues of the body. Muromonam-CD3, infliximab, adalimumab, omalizumab and daclizumab are widely used to suppress immune system.

8. ASTHMA

Bronchial hyperresponsiveness is a risk factor of asthma which may be caused due to high levels of IgE. Twice-weekly injections of recombinant humanized anti-IgE antibody, forms complexes with free IgE and blocks its interaction with mast cells and basophils and decreases serum IgE levels and helps in decreasing asthmatic symptoms.[22]

9. VIRAL INFECTIONS

Serious illness is caused by cytomegalovirus in the immunocompromised patients, such as patients with AIDS and those undergoing organ transplants. The potential treatments for CMV infection are ganciclovir, foscarnet and cytosine. Administration of anti-CMV hyperimmunoglobulin, derived from pooled sera of CMV seropositive persons is another mode of treatment. The severity of CMV and mother-to-infant transmissions can be reduced by passive immunization. Antibodies are also able to clear the virus from infected tissues. A combination of antiviral agents and immunoglobulins are used by physicians in patients, who are at the risk for CMV infection.[23] MAbs may also decrease the amount of antiviral agents required for treatment.

10. TOXINS

Toxins are poisonous proteinaceous substances. In the 1970s, antibodies were first clinically used for protection against the toxin digitalis. Humanized MAbs are used against digoxin and other toxins as the polyclonal antibodies are difficult to produce. Polyclonal antibodies can also cause hypersensitive reactions. Monoclonal antibodies also helps in alleviating poisoning due to environmental contamination. Hexachlorobiphenyl, paraquat, atrazine, 3,5,6-trichloro-2-pyridinol, triclopyr, and chloroprifosmethyl, and other chemicals can soon be detected and remediated with the help of antibodies. Antibodies may also be used in the treatment of poisoning due to paraquat, hexachlorobiphenyl, domoic acid and other contaminants that are very difficult to remove from the body.[24]

11. SUBSTANCE ABUSE

The central nervous system (CNS) is the primary target of most of the abused drugs, and immunotherapy against such chemicals must be able to penetrate the CNS. PCP or phencyclidine otherwise called angel dust affects multiple sites in the brain. It is linked to schizophrenia like violent psychotic episodes. As there is no known antagonist identified, PCP has a high volume of distribution, and about 95% of it is cleared after being metabolized, treatment is very difficult. It is found that, mAbs can bind to cocaine or PCP and can act like sponges in the bloodstream to prevent them from reaching the brain.[25] A single dose of antibody reduced PCP effects for up to 2 weeks in animals. This might be equivalent to a several months in humans.[26] The antibodies can act like a pharmacokinetic antagonist, by increasing protein binding and lowering volume of distribution of drug. Since antibodies can also reverse effects of other potent aryl cyclohexylamine drugs suggests that antibody medications can be used to treat different classes of drugs.

12. METABOLIC DISORDERS

Metabolic disorders such as diabetes, hypercholesterolemia have posed a great challenge in human medicine. Metabolic disorders is one of the areas where therapy using mAbs can be effectively used. GPCRs membrane fractions are usually used as a target to produce mAbs for the cure of metabolic disorders.[27] Monoclonal antibodies are produced against the human glucagon receptor (GCGR) from stable cell lines via transgenic XenoMouse platform. These mAbs displays potential antagonistic activity in reducing blood glucose level. This effect is caused due to long-term inhibition of GCGR signalling in a mouse model making them effective for controlling diabetic hyperglycemia.

Another major risk factors for cardiovascular diseases is hypercholesterolemia. Increase in low-density lipoprotein cholesterol levels is probably the major cause of metabolic disorders. Studies are aiming to inhibit the proprotein convertase type 9. Evolocumab and Alirocumab were found to be safe and well tolerated in this context.[28] These antibodies were reported to substantially reduce the LDL level by over 50%, increase HDL level and result in favourable changes in other lipids to lower LDL levels, through the development of mAbs.

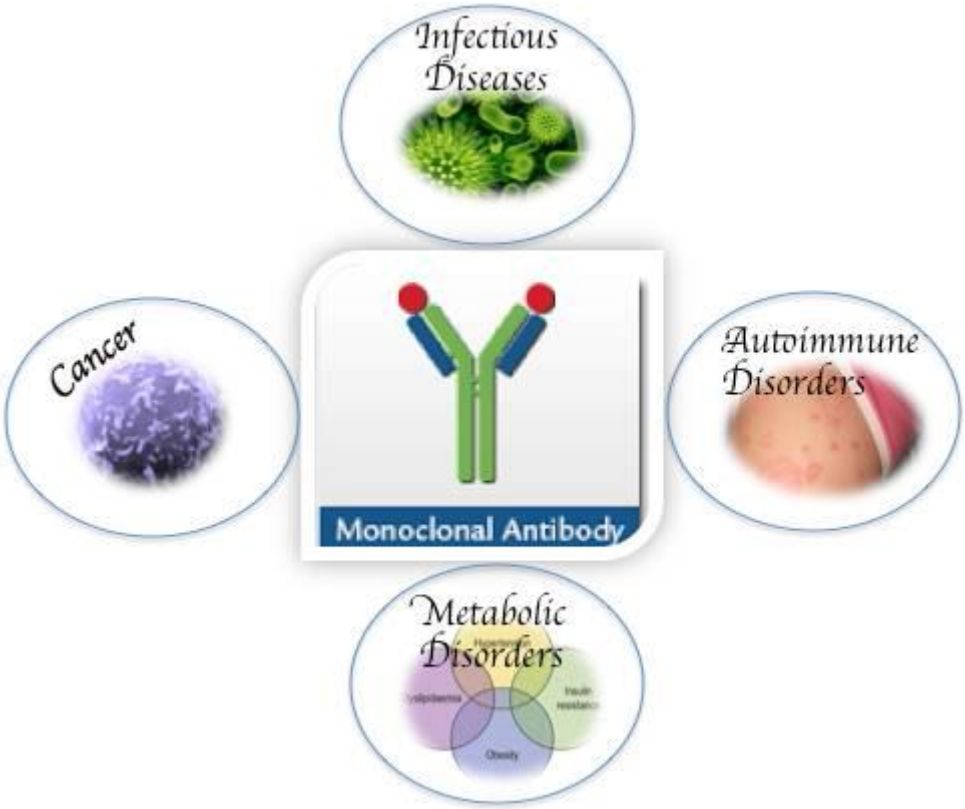

Fig 2. Pharmaceutical applications of Monoclonal antibodies.

PHARMACEUTICAL APPLICATIONS OF mAbs

mAbs are mainly used to produce four major classes of drugs. These classes include:

- The first group that stimulates the body's own immune system (rituximab, infliximab etc).
- The second class includes mAb drugs conjugated with a disruptive compound such as radioisotope (radio-immunotherapy, RIT).
- The third class includes mAb drugs conjugated with drug-activating enzyme by antibody-directed enzyme prodrug therapy.
- The fourth classes of MAbs are conjugated to liposomes (immuno-liposomes).

As lymphomas, are highly radio-sensitive malignancies, RIT is very important in treating them. Murine antibodies are specially chosen to limit the exposure of radiation due to their high immunogenicity. This promotes rapid clearance from the body. For eg, to situ momab is used for non-Hodgkin lymphoma.[29] In antibody-directed enzyme pro-drug therapy, mAbs are linked to this drug-activating enzyme for its application in cancer. The clinical trial of ADEPT treatments is ongoing, as it is quite promising in future treatment of cancer. Immuno-liposomes are antibody-conjugated liposomes, which carry drugs or therapeutic nucleotides

and when conjugated with mAbs, may be directed against malignant cells. Thus, immune-liposomes have been successfully used in vivo to tumors to achieve targeted delivery of tumor-suppressing genes, using an antibody fragment against the human transferrin receptor. The delivery of tissue-specific gene using immune-liposomes has also been achieved in brain and breast cancer tissue.[30]

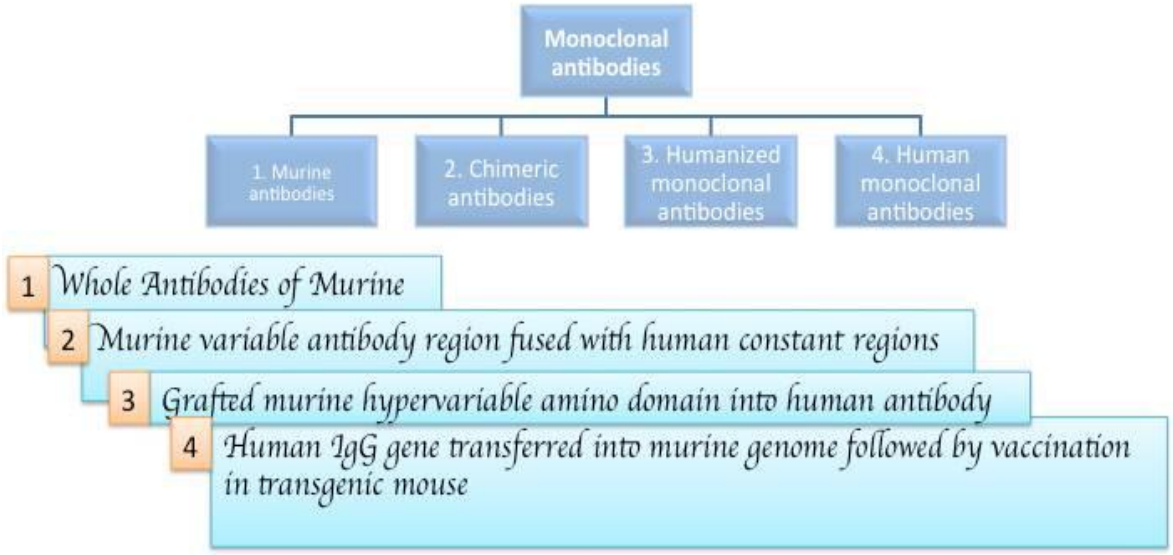

Fig 3. Major classes of monoclonal antibody drugs.

LIMITATIONS OF mAbs.

- MAbs given intravenously have usually mild side effects as compared with chemotherapy. A mild allergic reaction (rash) may be occurs with first administration of the drug. Common side effects include fever, headache, weakness, chills, nausea with vomiting and diarrhea, and low blood pressure.
- mAb used against tumor blood vessel growth can present numerous side effects, some of which include renal failure, bleeding with poor wound healing and high blood pressure.
- MAb drugs have always been costly, as only a few of nearly 22 FDA regulated drugs are available in the market.
- The huge demand to increase production of the drugs and the drive to lower the cost of the expensive medicines is a continuous challenge to the present industry.
- Researches regarding mAbs are time consuming. It takes about 6 to 9 months.

- For effective action antibodies usually needs to get bound with certain elements of the immune system like receptors. As they are of murine nature, the antibodies cannot interact properly with components of the human immune system and their biological efficacy is severely restricted.
- mAbs are usually produced by immunizing the mice. But the patients treated with the mice antibody may make antibodies against mice Ig, called HAMA. This may block the function of mAb and cause serum sickness.
- The production of mAbs are labour intensive, expensive and technically complex to generate.
- Ethical issues regarding production of mAbs via mice.
- Lack of efficient mAb generation models

CONCLUSION

The field of immunology is evolving at a rapid pace and is yielding many critical developments day by day. The development of mAbs that use the specificity of immunological responses is one of course the most successful applications of immunology to date. Developments in radiology and pharmacology have allowed radiolabeled and immune conjugated antibodies to be produced. These promising developments may soon allow mAbs to be used to treat afflictions as varied as substance abuse, cancer, asthma, viral infection, septicemia, and poisoning.[31] Although the first mAbs approved as human therapeutic agent were generally reported to be intolerable as therapeutics, advances in hybridoma technology have resulted in mAbs that are currently more effective and safe. The ability to engineer variable regions that encode multiple specificities into a single molecular entity has been an advantage for optimizing antigenbinding capabilities. There is no doubt that the future of mAbs will sway the treatment of infectious diseases, cancers and other conditions like Alzheimer and Parkinsonism.

FUNDING: No funding.

DECLARATION OF COMPETING INTEREST: None declared.

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