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Review Article

Monoclonal Antibodies: A Brief Review on Delivery Trends

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Abstract

Immunoglobulin derivatives which are derived from the monoclonal cell line and which offers a wide range of specificity are the monoclonal antibodies. They are specially produced by the hybridoma technology by the fusion of B-cells with the immortal myeloma cells in presence of PEG. Humanized mAbs are considered to be the fastest growing group in clinical trials. After development, these mAbs undergoes analytical evaluation for their efficient characterization. Developed hybridomas can be preserved for long term use through the cryopreservation techniques. Monoclonal antibodies can be delivered for the therapeutic purpose through the various systemic and non-systemic routes. Large groups of the antibodies are found to be very effective through the oral routes and the ophthalmic routes. Besides the therapeutic application for the treatment of various infectious and autoimmune diseases, these groups of therapeutics show different limitations. Monoclonal antibodies after development suffers from the stability issues and using the various techniques, the stability can be increased. With the advancement of science and technology, we can observe various advances in the monoclonal antibody development like brain targeting is possible through the antibody engineering techniques. Variability and control challenges in the serum based acquisitions, consumption of time, difficulty in the development, potential limitation in the sequence and epitope diversity etc. are some of the challenges associated with the monoclonal antibodies.

Keywords: Immunoglobulin, Hybridoma Technology, Cryopreservation, Antibody Engineering

Background:

Monoclonal Antibodies are immunoglobulin which are specially derived from the monoclonal cell line and offers a wide range of specificity. They consist of light chain and heavy chain linked with the disulfide bridges. They have wide applications in treatment that includes several infectious disease, different malignant conditions and different autoimmune disease condition. Large number of the drugs i.e. more than 250 drugs have been found to undergo clinical trials.

Adverse drug reaction is drastically reduced on using the monoclonal antibodies as therapeutic agents. Hybridoma technology is commonly adopted for the production. Such methods significantly reduce the immunogenicity. Drug interaction is highly minimized and protein targeting is specifically achieved through the antibodies therapy. Development of the bio similar antibodies has significantly reduced the higher cost of production. Wide spectrum of the disease can be targeted through the use of these techniques.

Humanized mAbs are considered to be the rapidly evolving group of monoclonal antibodies in clinical trials.[2] Chimeric and humanized antibodies have been playing a great role for minimizing the allergenicity from exposure to non-self-antibodies. Treatment of the cancer radio immunotherapy, therapy of autoimmune disease such as Crohn's disease, treatment of rheumatoid arthritis, treatment of graft-versus-host disease, therapy in the asthma, septicemia therapy is possible through the use of such techniques. Various complications of the viral infections can be treated with such moieties, for detoxifying various natural origin and synthetic toxins. Therapy of substance abuse is also another clinical application of the mAbs. In case of poisoning also they can be used.[3]

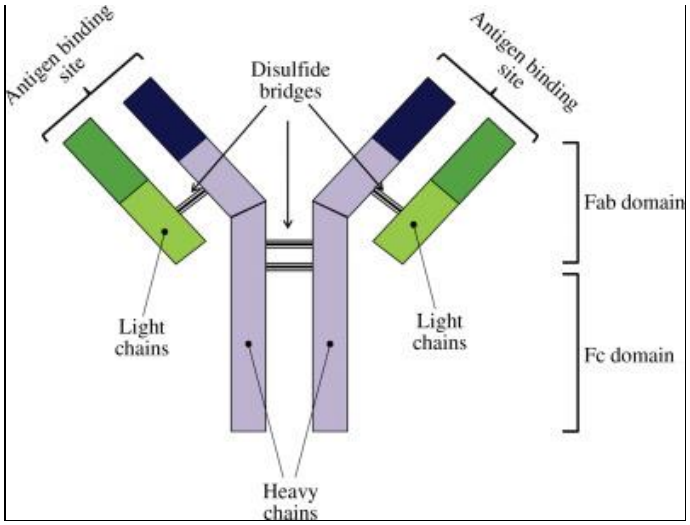

Figure 1: Antibody Structure [1]

A majority of mAbs drugs/therapeutics have been approved for the treatment of cancer, for treating rheumatoid and for prevention/treatment of autoimmune diseases.[4]

Pharmacokinetics of Monoclonal Antibodies:

Clearance of the monoclonal antibodies is not regulated through the cytochrome p450 (CYP450 metabolism) nor through the interaction with the transporters present in the cell membrane. We observe the limited interactions between the small drugs and the monoclonal antibodies pharmakokinetically. However the clearance of the mAbs is affected by the other drugs though the immune response modulation. For example, the clearance of the imfliximab, golimubab and adalimubab is reduced by the anti-cancerous drug called methotrexate. The mechanism behind this phenomenon is the expression of inhibitory effect for the antibody's formation against the mAbs. Monoclonal antibodies are also called the cytokines modulator and they modify the metabolism of the drugs exerting its effect for expression of enzyme Cytochrome p450. Drugs may alter the clearance of the mAbs by either increasing or decreasing the level of expression of targets of mAbs on cell surface.[5]

These entities i.e. mAbs are considered to be the largest group of the therapeutic proteins which are being used for treatment of the disease since more than 20 years. Pharmacokinetic property of those antibodies differs widely from non-antibody drugs. Various routes can be used for the administration such as subcutaneous, intravenous and intramuscular. However oral administration is gaining the popularity. Oral administration may be hindered by the different factors that include hydrophilicity, molecular size and the degradation by the gastric enzymes. Drug distribution also becomes slow and volume of distribution also becomes low due to the large molecular size. Antibodies are reported to have both the linear and nonlinear elimination due to the target mediated disposition. Different factors plays great role for determining the elimination rate such as target antigen, patient demographics, immune reactions to the antibody, body weight and body surface area.[6]

Pharmaceutics of Orally Administered Antibody

IgY antibodies when encapsulated in the egg lecithin or cholesterol; liposomes prevent from the process called hydrolysis in the acidic condition or by the enzyme called pepsin. The stability was found to be enhanced with the procedure.[7]

Some liposomal antibodies are capable of releasing the antibodies in the areas which are extensively rich in the bile salts and thus released moieties does not get degraded in the presence of enzymes called trypsin and chymotrypsin. GI tract thus get immunized passively and gets prevented from the different viruses and bacteria.[8]

Production of Monoclonal Antibodies

Hybridoma technology is the fundamental techniques for the production of monoclonal antibody. This technique was first used by the kohler and Milstein in 1975. Mouse is carefully immunized with the specific target antigens and the immune response is developed among them. B Cells from such mouse is taken and fused with the immortalized myeloma cells which are devoid of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) making them independent on specific culture media to survive. Fusion is facilitated with the use of polyethylene glycol which produces the hybridoma cells and these are capable of producing the monoclonal antibodies[9].

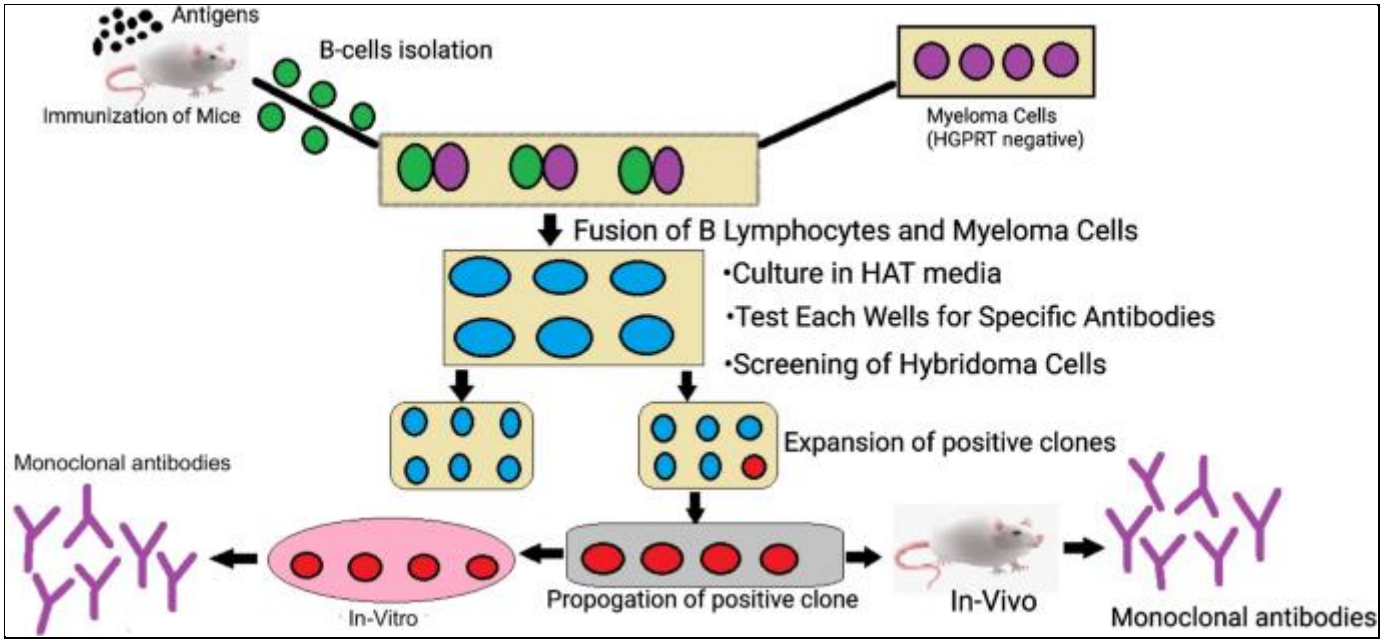

Figure 2: Hybridoma Technology [10]

Evaluation of Antibodies Formulation

Analysis of the monoclonal antibodies is a crucial part after the formulation and development. Due to the inherent complexity and the for safety purposes, powerful analytical techniques is required for their appropriate characterization. Basically electrophoresis and chromatographic techniques and their suitable combination with the mass spectroscopy are used for the identification/characterization of the mAbs. Reverse phase liquid chromatography is considered to be the popular choice from the analytical aspect. Beside this, capillary zone electrophoresis is another better option. Apart from these, adsorption is considered to be the major concern with both of the techniques i.e. chromatography and electrophoresis. IEX chromatography and size exclusion chromatography are being used historically but they have certain limitations such as low kinetic performance, limited resolving power and inability for complex coupling with powerful detection.

Identification of various quality parameters such as heterogeneity, identity, impurity level and activity should be properly monitored and investigated. It can be achieved using various techniques such as Fourier transform infrared spectroscopy (FTIR), capillary iso electric focusing (CIEF), mass spectroscopy, circular dichroism (CD), ion exchange chromatography (IEX), RPLC, Sodium dodecyl sulfate polyacrylamide gel electrophoresis, fluorescence spectroscopy, capillary zone electrophoresis etc. Major goal of using these techniques is to determine the similarity between the manufactured/formulated batches with determination of their structures which may be primary, secondary or tertiary.[11]

Preservation of Monoclonal Antibodies:

Hybridomas which are capable of producing the monoclonal antibodies can be preserved for the long term use. Cryopreservation technique is widely applicable for the storage and liquid nitrogen is extensively used. When needed they are thawed and re-cultured. There is a possibility of degradation so it is necessary to monitor the quality of the produced antibodies.[12, 13]

Therapeutics Application

For the allergy disease, various multiple factors are involved for the pathogenesis with promoting or triggering the T helper 2 (Th2) types of the immune response. It leads for the extensive development of type 2 cytokines and immunoglobulin E (IgE). These are considered to be the most critical events for the allergy and we can target these molecules through the use of monoclonal antibodies thus providing the massive relief for the patients suffered with allergy.[14]

Humanized monoclonal antibodies, anti-IgE antibodies are found to be significantly effective for treating the various conditions such as asthma which is caused by the allergy, Perennial and seasonal allergic rhinitis and allergic reactions to the peanuts. Omalizumab is such congener which has been approved in several countries in Europe and United States for the therapeutic management of the moderate to severe allergic asthma. Therapeutic anti- IgE is considered as therapeutic mast cell stabilizer which reduces the density of high affinity IgE Fc receptors FcεRI and also the density of basophils and it ultimately results the insensitiveness of them towards allergens.[15]

Garadicimab which is an anti-activated factor XII is considered to be very effective and efficacious for subcutaneous prophylaxis in patients with HAE-C1-INH (C1 esterase inhibitor deficient hereditary angioedema.[16]

Monoclonal antibody can be used for the other various purposes. Due the high specificity property of them, they are being widely used for the immunological and biological research. Treatment of various disease in human as a therapeutic agents, purification of the protein in commercial scale, effective suppressing of the immunological response, identification and diagnosis of the various disease, therapy for the tumors and cancerous cells, as a aid for the purification of the complex mixtures, vaccine development and utilization for assessment of the effectiveness of the medical substance are the applications of mAbs.[17]

Various technologies utilizes the monoclonal antibodies such as western blot test for the detection of specific proteins in the blood or the tissue, ELISA test for the detection of antigen antibody in the given sample, immune dot blot test for the detection of the antibodies, radio immuno assay, immunohistochemistry test for the detection of the antigens, electron microscopy, fluorescence microscopy along with the various biotechnical related applications.[17]

Monoclonal antibody which recognizes the availability of the gene product, can be used as probe for the appropriate detection of the cells and thus for the detection of genes.[18]

Cells which get participated in the immune response, different types of T cells such as suppressor T cells and helper T cells can be distinguished in the lymphocytes with the help of B cells. Monoclonal antibodies helps for defining the different changes in T-cells and B-cells that take place during the development phase.[17, 18]

They have unique specificity for desired protein and we observe very low contamination level by the unwanted protein species. Due to the single binding affinity of complex formed by the monoclonal antibody and antigen, it is possible to have an elution of the desired protein in the sharp single peak. Single relative protein to the total protein concentration is very low. Utilization of the immune affinity column is evident in the protein purification and we can observed the leak of immunoglobulin in the column thus the gaining the 100 percent pure protein is difficult.[17, 18]

Combinational use of Omalizumab along with the other oral immunotherapy has been assessed as safe than in the isolated immunotherapy. It has been studied that the quality of life of the patients gets enhanced.[19]

Systemic and Local Administration:

Systemic administration is done through the parenteral routes and subcutaneous routes where as other routes also have been developed such as transdermal, nasal, oral and inhalation routes. Local delivery of the monoclonal antibodies through the various noninvasive routes like transdermal, inhalational, nasal, intraviteral, vaginal, Intratumoral etc. can be achieved. These offers high efficacy and less systemic effects.[20]

Oral Delivery of Monoclonal Antibodies:

Oral absorption of the large macromolecules is very poor due to the large molecular weight. Also they encounter the low stability in the GI tract. Various approaches such as chemical conjugation, utilization of absorption enhancers and moreover using of particulate systems, have played a significant role for expanding the clinical use of such macromolecules. Lipophilicity and intestinal permeability of the macromolecules can be altered by targeting the receptor mediated transport pathways or transporters in the intestine through the chemical conjugation of the macromolecular drugs to the small molecules. Modification of the tight junction barriers and thus the enhancement of the permeability and lipophilicity of the drugs through the co-administration with the absorption enhancers can be achieved. Transportation of nano/micro particulate systems to the intracellular site can be achieved via the M cells and via the enterocytes.[21]

Monoclonal antibodies have been formulated as powder of reconstitution using the spray dried technique at the high concentration of mAbs. Humanized IgG4 monoclonal antibody was used for the formulation.[22]

Anti CD3 monoclonal antibody was successfully administered orally for the purpose of inhibition of autoimmune diabetes and was successful.[23]

Self-assembled, pH responsive delivery system in the form of nanoparticle was developed for loading and delivering of antibodies through the oral route. Nano precipitation technique was used for synthesizing the Nano-particles using the copolymers which are pH responsive. Polymers bears the hydrophobic nature due to this property, it is possible to deliver the antibody via the self-assembly.[24]

Single domain antibodies have been used for controlling the gastrointestinal pathogens which are caused by the different viruses, parasites and pathogens. They can be delivered as a native soluble protein to the gastrointestinal tract and using the delivery vehicles using different transgenic plants or using the bacteria.[25]

Secretory IgA and systemic IgG antibody response has been enhanced after performing the oral immunization with the biodegradable antigen containing micro particles.[26]

Ophthalmic Delivery of Antibodies

Monoclonal Antibodies are being used as therapeutic agents in the ophthalmology. Ophthalmic delivery of the antibodies can be achieved through the targeting of various biochemical factors such as platelet derived growth factor, tumor necrosis factor (TNF), vascular endothelial growth factor (VEGF) receptor, epithelial growth factor receptor, basic fibroblast growth factor receptor and cluster of differentiation antigens. They are beneficial for treatment of the inflammatory ophthalmic conditions and angiogenic conditions. Various monoclonal antibodies such as ranibizumab, bevacizumab which are the group of anti-VEGF monoclonal antibodies are used. Besides these other antibodies belonging to the class of anti-TNF agents such as adalimubab, inflixamab and etanercept are used for controlling the ocular neovascularization and intraocular inflammation. Similarly various other monoclonal antibodies such as efalizumab, rituximab, alemtuzumab and daclizumab are also found to have positive effects on lymphomas and inflammation in ocular regions and they can be used as adjuvant therapeutic agents.[27]

Side Effects of Monoclonal Antibody Therapeutics: [28]

Abciximab which is a chimeric antibody fragment: c7E3 Fab, approved by FDA in the year 1994 and indicated for the purpose of preventing the ischemic heart complications and unstable angina, targeting the platelet glycoprotein IIb and IIIa shows the various side effects such as immune genecity, hypersensitivity, Thrombocytopenia and increase the hemorrhage.

Adalimumab was developed with targeting the tumor necrosis factor-alpha, is a fully human antibody which was approved by FDA in 2002 under the name of Humira is indicated for treating the various complications such as rheumatoid arthritis shows the various side effects such as hypersensitivity reaction, immunogenicity, worsening of the cardiac failure, elevated liver transaminases, leukopenia, anemia etc. Similar side effects can be seen with other antibodies such as humanized PEGylated antibody called certolizumab (Approved by FDA in 2008), chimeric antibody such as infliximab (approved in 1998).

Alemtuzumab for treatment of multiple sclerosis, graft-versus-host disease, behcet's disease, vasculitis, multiple myeloma etc. shows various side effects such as thyroid disorders, tumor lysis syndrome, autoimmune hemolytic anemia, immunogenicity and hypersensitivity, cardio toxicity etc. It was approved by FDA on 2001.

Chimeric antibody such as Basiliximab and Humanized antibody Daclizumab, which are used for the prophylaxis of renal transplant allograft rejection, shows various types of side effects such as different types of local skin reactions, hypersensitivity, immunogenicity, immunosuppression etc. Interleukin 2 receptor alpha on activated lymphocytes are the target of these antibodies.

Another humanized antibody called eculizumab, approved in 2007 and indicated for the proximal nocturnal haemoglobinuria shows various side effects such as intravascular hemolysis and meningococcal infection.

Tocilizumab which targets the interleukin-6 receptor and is a humanized antibody, approved in 2009 for treatment of various diseases such as castleman's disease and unresponsive active rheumatoid arthritis shows various side effects such as headache, anaphylaxis and anaphylactoid reactions, UTRI and abnormal liver functions.

Palivizumab which is a humanized antibody and approved in 1998 for the prevention of RSV complications in high-risk infants shows various side effects such as fever, anaphylaxis and apnoea reactions.

While studying the safety profile of the monoclonal antibodies they exhibit the positive response with enhancement in efficacy, also exhibit the higher rate of success in the early clinical development.[29]

Stability of Antibody Formulations:

Stability of the antibody is the major concern after the formulation and development. Various parameters such as binding affinity and specificity, thermal stability, purity, aggregation, degradation, unfolding etc. are measured as an attribute of the stability. These tests are performed using various techniques such as binding, affinity and specificity can be measured using the ELISA test, unfolding and thermal stability can be measured using the differential scanning caloriemetry/ fluorimetry and dye binding technique, purity, aggregation and degradation can be measured using the dynamic light scattering techniques, size exclusion chromatography techniques and SDS-PAGE techniques. Binding specificity can be measured using the western blot test. Various equipment such as NMR, mass spectroscopy and circular dichroism etc. can be used.[30]

Effects of Structure of Antibody on Stability

Normally monoclonal antibodies contain light and heavy chain with both variable and constant domains. They are considered to be more stable than the fragments of the antibody which are smaller.

Monoclonal antibodies which are glycosylated are found to be more stable than the monoclonal antibodies with unglycosylated form as they undergo extensive aggregation more easily. Glycans are found to aid for the protein folding and thus stabilize the folded structure. Folded structure resist the proteolysis and aggregation.[30]

Thermodynamic stability of single chain variable fragments (scFb) varies widely. They are found to have the moderate to poor stability without engineering techniques. Stability of such scFb can be improved by adopting the various strategies of the protein engineering such as chain shuffling, point mutations, addition of different tags, grafting procedure of their CDR region onto stable variable domain frameworks, reducing the potential for aggregation and through the storage condition optimization.

Strategies for increasing stability

Development of the aggregation and unwanted immunogenicity has created challenges during the manufacturing and clinical stages. With the help of different types of the excipients and suitable amino acids they can be made more stable. Also by the development of the more stable constructs such as protein scaffolds and bi-specific molecules, they can be made more stable. Many techniques such as Fc fusions and PEGylation have been effective for the improvement of the safety profile and pharmacokinetic profiles.[31]

Advances in monoclonal antibody development

Fully human antibodies are considered to be the safest form of the antibody as all the sequences come from the human sources and the human anti-murine antibody reactions are not induced. Technology involved with the genetic engineering and in parallel the technology of flow cytometry coupled to single B cells gene amplification has made easier for the production of safest fully human monoclonal antibodies.[32]

Adalimubab is the first monoclonal antibody. Other antibodies approved are canakinumab, denosumab, panitumumab, ofatumumab, golimumab and ustekinumab.[33]

Antibody Engineering

Antibody engineering is the key aspect for humanization of the murine antibodies. In 1983, anti-CD3 murine mAbs (OKT-3) was first approved as therapeutic antibody. But it did not succeed and encountered a transplantation rejection due to generation of severe human-anti murine antibody (HAMA) response in the patients. For the purpose of reduction of such immunogenicity, chimeric antibodies with the human constant regions and mouse variable regions were constructed. Humanized antibody were constructed by the protein engineering.[34]

Phage Display technique is extensively used for the production of the human antibody as through the hybridoma technology, fully human antibody development is not possible. Additionally, the transgenic mice which contains human immunogenic germ line locus can be used as the alternative strategic technique for the production of the human antibody. When we immunize the transgenic mice, human antibody response is generated and later by the utilization of hybridoma technology, hybridomas which are capable of producing the human antibody can be prepared. First fully human mAbs drug, used for the treatment of the disease called rheumatoid arthritis was Humira and it was successfully launched in the year 2003.[13]

Brain Targeting of Antibodies

Crossing of the blood brain barrier is the major challenges associated with the monoclonal antibodies. They show their inability to cross BBB i.e. blood brain barrier thus targeting of the monoclonal antibodies can solve such issues. Brain targeted liposomal drug delivery can enhance the delivery of the monoclonal antibodies across the blood brain barrier and allows them into the neurons and thus facilities the treatment of the Parkinson disease. Transferrin can be used for decorating the brain targeting liposomes which improves the brain targeting through the overexpressed

different transferrin receptors. SynO4 is loaded with the brain targeting liposomes which inhibits the alpha synuclein aggregation a pathological hall mark of the Parkinson disease. Behavioral motor function gets improved when treated with the brain targeting liposomes. Various neurological condition such as neuron degeneration can be treated through the targeted nanotechnologies.[35]

Challenges of Antibody Production

Variability and control challenges in the serum based acquisitions, time consuming, difficulty, potential limitation in the sequence and epitope diversity etc. are some of the challenges associated with the monoclonal antibodies.

Conclusion:

Advancement of the science and technology has highly increased the potential of the antibody therapeutics for the treatment of the various disease conditions. Large scale research is being carried out for the delivery of the antibodies through the oral and topical routes. Highly challenging brain targeting of the antibodies is also being possible through the antibody engineering.

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