World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 4.223

ROLE OF MONOCLONAL ANTIBODIES IN CLINICAL RESEARCH AND THERAPY- A REVIEW

Ponnu Sarah Joseph, Jasmin Jomon, Shary Ramesh, Devi K R and Nithin Manohar*

India.

Corresponding Author: Nithin Manohar
India.

Article Received on 23/02/2017 **Article Received on 17/03/2017** **Article Accepted on 07/04/2017**

ABSTRACT

Antibodies are natural proteins with modular structure, specific pharmacodynamics and pharmacokinetics and possibly produced against any antigens, thus giving them several advantages over small drug therapeutics. Monoclonal antibodies (mAb) have been applied to the diagnosis and therapy of an array of human diseases. They are a novel and promising therapeutic class used with great results in inflammatory diseases such as rheumatoid arthritis. The initial failures of early clinical trials have been overcome through the production of a new generation of mAb which features reduced immunogenicity and improved targeting abilities. The early models of mAb therapy were focused on enhancing the cytolytic mechanisms against the tumor cells. More recently, successful mAb-based therapies were targeted to molecules involved in the regulation of growth of cancer cells. Despite all the difficulties, clinical data is outlining an increasingly significant role for antibody-mediated cancer therapy as a versatile and powerful instrument in cancer treatment. Lung cancer is the leading cause of cancer-related deaths in industrialized countries and non small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. It seems that mAbs therapy in NSCLC clearly marks the start of a new era in NSCLC treatment, with promise in improving patient survival and quality of life. Monoclonal antibodies (MAbs) are an old immunological tool with applications in the fields of immunology, biotechnology, biochemistry, and applied biology. Recently, MAbs have been widely applied in the field of clinical medicine. Currently, MAbs account for one-third of all the new therapeutic treatments for breast cancer, leukemia, arthritis, transplant rejection, asthma, and psoriasis, with many more late-stage clinical trials being conducted. In this review, we outline the
(i) production of MAbs,
(ii) application of MAbs,
(iii) antibody engineering, and
(iv) pharmaceutical application of MAbs.

KEYWORDS: Monoclonal antibody (MAb's), Immunological tool, Non SmallCell Lung Cancer(NSCLC).

INTRODUCTION

Antibodies are useful tools of research, diagnosis and therapy because they bind specifically and strongly to respective antigens.Initial models of monoclonal antibodies were used for enhancing the cytolytic mechanisms against tumour cells and recently they are also used to regulate the growth of cancer cells.The application of humanised and recombinant monoclonal antibodies (murine) for diagnostic and therapeutic purposes. Antibody mediated therapy for cancer is powerful and highly beneficial in treatment of cancer.The novel design had two folds; one was to identify the tumour specific antigens and other was to initiate lethal attack towards neoplastic cells without involving normal cells. Antibodies have now been modified and developed and new approaches have emerged. Selective immunisations against tumours have been discovered. The benefit of monoclonal antibodies is that it does more than the immediate killing effect[1]

Monoclonal Antibodies

Monoclonal antibodies has found its application in the fields of immunology, biotechnology, biochemistry and applied biology. Monoclonal antibody covers one-third of all the new therapeutic treatment methods for breast cancer, leukaemia, arthritis, transplant rejection, asthma and psoriasis.The immune system continuously evolves to protect itself from pathogens. Antigen is defined as a molecule or part of amolecule that can be recognised by the immune system as a foreign entity.Antibodies are useful tools of research, diagnosis and therapy because

they bind specifically and strongly to respectiveantigens[1]

Polyclonal and Monoclonal Antibodies

Polyclonal antibodies contain different antibodies developed in blood of immunised animal from different cell types and they can stimulate the proliferation and differentiation of variety of β-cell clones. Monoclonalantibodies are the mixture of homogenous antibody molecules with affinity towards specific antigen. This is often generated using a hybridomai.e. by fusing β-cell plus single lineage of cells containing definite antibody gene.Monoclonal antibodies are preferred over polyclonal antibodies due to high specificity and reproducibility. It is used in research, diagnosis, as therapeutic tools-cancer, immunological disorders and pharmacy.Characteristics of clinical applicability are specific binding, homogeneity, reproducibility in unlimited quantities.

Monoclonal antibodies produce four major classes of drugs:

- Stimulates body's own immune system (rituximab, infliximab)
- MAb conjugated with disrupted radio isotope (radio immune therapy, RIT)
- MAb conjugated drug activating enzyme by Antibody-directed enzyme producing therapy (ADEPT)
- MAb conjugated to liposome (Immuno-liposomes or nano-technology delivery system)

Table 1. Multi-faceted activity of therapeutic mAbs.

Mechanisms of action
Naked antibody—direct effects
• Neutralizing infectious agents
• Interfering with ligand-receptor interactions (antagonist activity)
• Receptor cross-linking (agonist activity)
• Sequestrating soluble mediators
• Antibody as immunogens (anti-idiotype)
Naked antibody—indirect effects
• Antibody-dependent cellular cytotoxicity (ADCC)
• Complement-dependent cytotoxicity (CDC)
Armed antibody
• Delivery of cytotoxic molecules (radionuclides, small chemotherapeutic drugs, toxins...)
• Immunomodulation (cytokine)

Most recent research of radio-immune therapy involves application to lymphomas and highly radio sensitive malignancies. Monoclonal antibodies link to drug activating enzyme used in treatment of cancer. To limit exposure of radiation, Murine antibodies are chosen which promotes rapid clearance from the body. ADEPT has provided promising results in clinical trials and therefore may be used in oncological treatments.[1]

Side-Effects of Monoclonal Antibodies

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. Other side effects of MAbs are related to the targeted antigens.

Monoclonal Antibodies in Non-Small Cell Lung Cancer

Antibodies are the natural proteins with molecular structure, specific pharmacodynamics and pharmacokinetics and possibly produced against any antigens. Antibodies have become major bio drugs for treating solid and haematological tumours.Lung cancer is the leading cause of cancer fatalities in industrialised or developed countries. The non-small cell lung cancer (NSCLC) is 85% of all lung cancers. The American Society of Clinical Oncology recommends cisplatin doublet based chemotherapy as first line treatment for NSCLC. Spiro *etal.* showed that the median survival time of patients with advanced NSCLC treated with cisplatin doublet based chemotherapy (8 months) was only 9 weekslonger than for patients had given the best supportive case (5.7 months). Treatment with MAb's has greatly prolonged the survival of patients with solid tumours like breast and colon cancers.[3]

Hybridoma Technology

MAb's include IgG's,IgG1 or IgG3 as subclasses. The molecular weight is ~15 kDa and valence of 2. Paul Ehrilch was first to consider antibodies as therapeutics in his "magic bullet" theory in 1908. Achievement of this concept became possible with the development of mouse hybridoma technology by Kohler and Milsten – 1st reliable source of MAb's. Despite the fact that they had overcome major technological problems, mouse MAb were disappointed in clinical studies because mouse MAb used had short half-life in human serum and triggered immune response in human subjects that limited possibilities of repeated injections[3]. The human anti-mouse antibody (HAMA) was reduced by engineering MAb's that lacked most of the murine sequences leading to chimeric antibodies and humanised MAb's.

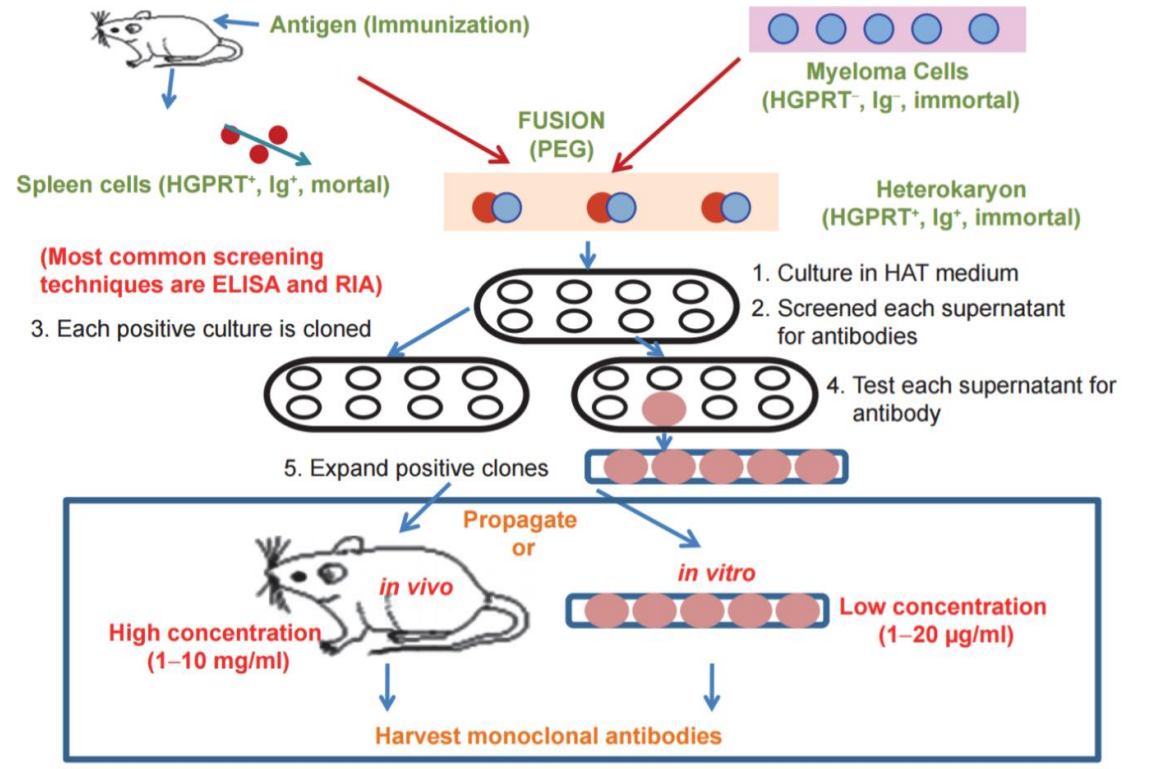

Figure 1. Production of monoclonal antibody by hybridoma technology. The hybridoma technology outline involves the isolation of spleen cells from immunized mice, their fusion with immortal myeloma cells and the production and further propagation of monoclonal antibodies from the hybrid cells.[2]

Applications of Monoclonal Antibodies

As mentioned earlier monoclonal antibodies are extremely valuable in basic immunological or molecular research due to its high specificity. It has been found to be useful in human therapy, suppressing immune response, diagnosis of allergy, hormone test, identification of specialized cells. Major applications are diagnostic tools in research and laboratory, gene cloning, to identify cell types, protein purification, as a therapeutic tool, cancer diagnosis and therapy. Pharmaceutical applications of monoclonal antibodies (MAb's) are arthritis, β-cell malignancies-Antibodies against CD20 antigen produced, autoimmune diseases, breast cancer-Antibodies against inflammatory cytokine TNF and HER-2[1].

Others applications include western blotting, immune histochemistry, immunocytochemistry, immunoprecipitation, ELISA, flow cytometric analysis.

Antibodies are also designed for therapeutic applications such as suppression of immune system after organ transplantation, cancers, leukemia and inhibition of angiogenesis. They are also used for the explanation of a variety molecule which monitors and control cell replication and differentiation. MAb's are important precursors in biomedical field, diagnosis of diseases such as hepatitis, AID's, herpes simplex, influenza and cancers.[2]

CONCLUSION

Antibodies have been reconfigured, and new therapeutic approaches have emerged and mAb are increasingly emerging as a powerful component of many therapeutic protocols. The future role of mAb may thus best envisaged as an adjunct to conventional therapy.

Recent successes in clinical applications have revived the interest of scientists, and also of the biotechnological companies which represent a driving force in the development of new immunotherapeutics. Current attention is focused on defining the possibilities offered by the new targets and new agents being generated by recombinant engineering techniques in order to develop more effective anti-cancer therapies in the near future. NSCLC is a cancer with poor prognosis refraction to anti-cancer treatments. MAb's may be used to treat NSCLC. The development of MAb's clearly marks the start of a new era in NSCLC treatment though there are more trials or studies to be done to use them as optional target in lung cancer. Through processes of genetic engineering and innovative ideas and approaches, the monoclonal antibodies based therapy for cancer has begun to evolve.

REFERENCES

1. Waliza Ansar and Shyamasree Ghosh, Asutosh College, Post Graduate Department, Kolkata; Indian Journal of Clinical Medicine, 2013; 4: 9–21.

2. Muhammad Saleem and Mustafa Kamal Pharmaceutical Research Center, Pakistan. Department of Biotechnology, University of Karachi; African Journal of Biotechnology, 17 April, 2008; 7(8): 923-925.
3. L. Guilleminault[1,2,3], E. Lemarié[1,2,3], N. Heuzé-Vourc'h[1,2] Université François Rabelais, Tours, France; [2]Centre d'Etude des Pathologies Respiratoires, Tours, France; [3]Service de Pneumologie; Journal of Cancer Therapy, 2012; 3: 1170-1190.
4. Ada Funaroa, Alberto L. Horensteina, PieraSantoroa, Cristina Cintib, Armando Gregorinib, Fabio Malavasib,Department of Genetics, Biology and Biochemistry, University of Turin, Turin, Italy,Institute of Biology and Genetics, University of Ancona, Via Ranieri 65 (Montedago), 60131 Ancona, Italy; Biotechnology Advances, 2000; 18: 385–401.