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Monoclonal Antibodies and Its Clinical Aspects

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ABSTRACT

With the emergence of various developments in determining pathophysiology behind diseases, emergence of resistance against diseases and the need to design an effective treatment against most common infectious and non-infectious diseases, the need of developing more effective drug comes under the limelight. At present, more studies are being carried out on the utilization of monoclonal antibodies as successful therapeutic agents. This include conditions which affect livelihood of people, the most common an widespread diseases, infectious diseases caused by more virulent or drug-resistant microorganisms and viruses and also inherited diseases. Current review thus targets cancer, diabetes, autoimmune diseases, hypercholesterolemia, ophthalmology and infectious diseases and briefly discusses the pathophysiology behind the mode of action of the therapeutic agents based on monoclonal antibodies and the benefits and drawbacks of such developed agents. This also focuses on the areas where studies can be carried out to determine effective use of monoclonal antibodies in the future to answer and treat major medical related issues. This review was done using the available literature on Monoclonal antibodies and its application through web and PubMed searches. According to our results, Monoclonal antibodies plays a major role as clinical and therapeutic agent in curing both communicable and non-communicable diseases.

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Introduction

Antibodies are second largest class of drugs after vaccines and they constitute the most rapidly growing class of human therapeutics. To develop antibody based therapies largest scientific effort has focused on diseases where the humeral immune system was known to contribute vital role host defense. Antibodies were first described as 'magic bullets' by Paul Ehrlich, where he further stated that they would target and destroy microorganisms and tumor cells specifically (1). Nevertheless, Köhler and Milstein proved this statement after 1975, where the production of murine Monoclonal Antibodies (mAbs) were described scientifically to be used in basic and clinical research (2). The importance of monoclonal antibody as a valuable diagnostic tool was evident in 1983 based on many animal studies and the treatment of fewer than 100 patients (3). The major drawback of developing mAbs as therapeutic agents was identified as the development of immune response in patients, which resulted in the quick inactivation of murine antibodies. The need of technical advancement in antibody generation was therefore identified as crucial to evade this problem.

One of the most important characteristics of the

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emerging immunotherapy technology is the utilization of monoclonal antibodies (mAbs) against a varying range of antigenic substances (4). Due to possessing higher possibilities of approval success, genetically engineered mAbs are generally useful for expanding the therapeutic treatment when compared to small molecule drugs. At present, more than 25 antibodies are approved for human therapy. Also, there are more than 240 antibodies in clinical development worldwide for varying range of diseases including autoimmunity and inflammation, cancer, organ transplantation, diseases of the cardiovascular system, infectious diseases, diabetes, arthritis, hypercholesterolemia and ophthalmological diseases (5).

The discovery of Hybridoma technology in 1975 generating mouse monoclonal antibodies paved the opportunity for developing therapeutic antibodies. Such developed first therapeutic monoclonal antibodies were developed during the 1980s. Due to problems associated with safety and reduced efficacy as a result of immunogenicity of the mouse-derived protein sequences, these drugs did not achieve any clinical or commercial success. Adalimumab was the first human antibody to be approved by the US Food and Drug Administration (FDA) in 2002 (6). Full human monoclonal antibodies (mAbs) are a hopeful and emerging group of targeted therapeutic agents (7-9).The clinical achievement of antibodies has created a major commercial impact, with rapidly growing annual sales that exceeded US$27 billion in 2007, which included 8 of the 20 top-selling biotechnology drugs (10). Indeed, around quarter (25~30%) of all biotechnology products under development are mAbs, were some have even been approved by the FDA as a treatment of cancer (11).

However, immunoglobulins are unique in their physical characteristics and modes of action to be regarded as a discrete therapeutic category. Antibody-based treatments on the use of human or humanized antibodies possess low toxicities and prominent specificities. The latter attribute of antibodies is both an advantage and a disadvantage. The advantage of high specificity is that antibody-based therapies can target only the microorganism that causes the disease. Nevertheless, high specificity leads to the requirement of more than one antibody type preparation to target microorganisms with high antigenic variation (12).

The therapeutic applications of MAbs are broadly grouped into 2 types:

(A) Direct use of MAbs as therapeutic agents

Due to minimal toxicity to the target tissues or the host Monoclonal antibodies can be directly used for improving the immune function of the host.

(B) MAbs as targeting agents.

In order to target a higher concentration of drugs to the desired site with minimal toxicity, the tissue-specific monoclonal antibodies can be attached or conjugated to chemicals such as Toxins, drugs, radioisotopes etc. and carried to target tissues for efficient action. This enables the use of MAbs for the correct delivery of drugs or isotopes.

Clinical applications of monoclonal antibodies

Cancer Treatment

Cancer leads to uncontrolled growth causing a lump called a tumor; this is true for all cancers except leukemia (13). It is a complex genetic disease. Its primary causative agents are known as carcinogens (or the cancer-causing agents) which can be present in food, water, air, chemicals and sunlight to which people are exposed (14) and is one of the most common causes of mortality, taking nearly 7 million lives each year worldwide (15). Even after anesthesia improved the techniques and histological control made surgery more efficient, cancer was more or less considered as incurable. Radiation therapy and antineoplastic chemotherapy are considered as the next most suited treatment method to be used for cancer (16).

Surgery, anti-neoplastic chemotherapy and radiation were not effective in controlling metastatic cancer and therefore still remain one of the most life-threatening diseases (16). Lack of specificity for the cancer cell was recognized as the major drawback in current cancer treatment in 1983. Therefore development of a group of agents with a greater degree of specificity for tumor cells would be a major progression in cancer treatment (17). Use of therapeutic antibodies or small molecules has made the treatment more tumor specific and less toxic (15). After 25 years, considerable progress has been made in this field and the FDA has approved 21 monoclonal antibody products, six of which are approved as biological drugs specifically for cancer (17).

Antibody-based therapy for cancer was established 15 years ago and at present the use of mAbs for cancer therapy has achieved a considerable success (18). However, there are several challenges associated with use of monoclonal antibodies for the treatment of cancer, including drug resistance, cancer stem cells, and high tumor interstitial fluid pressure (15). The first ever patient treated with monoclonal antibody therapy was from United States who had non-Hodgkin's lymphoma (19). In 1997, the first therapeutic antibody, Rituximab (Rituxan; Genentech/Biogen Idec), was approved by the US FDA for the treatment of B-cell non-Hodgkin's lymphoma (20). Since then, MAb-based therapies have become a major approach in medicine (21). Tumor-specific antibodies also provide the means to target the therapeutic agents to tumor cells, since target structures have already been identified for both hematological malignancies and solid tumors (16) and immune-modulatory antibodies also have achieved remarkable clinical success in recent times (17).

The mechanism of mAb action for cancer treatment is

not clearly known so far, but it has been proposed that mAbs possess the ability to bind or cross-link with target molecules to elicit antibody-dependent cell-mediated cytotoxicity (ADCC) and activate complement dependent cytotoxicity (CDC), and/or directly induce tumor cell apoptosis (22). Moreover, a few of mAbs can also directly induce tumor cell apoptosis through transduction of an apoptotic signal to cells (22). However, numerous pathways and characteristics of different tumor entities have been identified in the past decades. Based on this, knowledge specific tumor therapies have been generated by directly targeting the proteins involved in the neoplastic process, or by targeting drugs to the tumor. Both methods can be achieved with mAbs.

'Targeted therapy' comprises of a wide variety of different strategies, which are categorized as direct and indirect methods. Direct methods target tumor-associated or tumor-specific proteins, where their signaling is altered either by mAbs binding to the relevant antigens or by small-molecule drugs which are capable of interfering with these proteins (molecular targeting). Indirect approaches rely on tumor-associated proteins expressed on the cell surface that serve as a target device for fusion proteins containing different kinds of effector molecules. Targeting drugs to the related tumors can be actively achieved by means of tumor-specific mAbs or ligands binding to the receptors that are present on the tumor cells (16).

The efficacy of mAb immunotherapy in recent clinical trials has highlighted the potential of the mAbs in selective targeting approach to cancer therapy (23). Current attention is focused on development of new targets and new agents by recombinant engineering techniques in order to broaden greater effective anti-cancer treatments in the near future (24).

Autoimmune Diseases

Autoimmune diseases are a group of more than 80 different types of chronic, and often disabling, disorders that develop due to the underlying defects in the immune system, leading to the attack by the body to its own organs, tissues, and cells. Although the incidence and prevalence of autoimmune diseases is rising, for which the reasons are not well understood. In most autoimmune diseases, patients face a lifetime illness and there is no cure available. Since these diseases disproportionately afflict women, and are among the leading causes of death in young and middle-aged women, they impose a heavy burden on patients' families and on the society (25).

Treatments to control the symptoms associated with most of the autoimmune diseases are available at present, but a complete have not been developed yet. In general, two treatment approaches are currently available. The first involves replacing or repairing the impaired function. The second approach is to suppress the destructive autoimmune response. Global immunosuppression mostly targets a specific step in the tissue-damaging inflammatory response. Thus, efforts have been devoted in recent years to develop more targeted therapies. Numerous amounts of promising new biological agents are already in advanced clinical trials which can generate more targeted immunosuppression. Such new agents include monoclonal antibodies that decrease T cells or B cells specifically, those of which act only on activated T cells, take part in the inhibition of particular cytokine mediators of inflammation, or block the recruitment and localization of lymphocytes to the target organ. Although these targeted approaches usually have fewer side effects, the patient may become more vulnerable to infections, and therefore must be used with caution (25).

The first chimeric (human/murine) mAb approved by the FDA for the treatment of autoimmune diseases was infliximab. This anti-tumor necrosis factor (TNF)-a mAb was approved for the treatment of Crohn's disease in 1998 and rheumatoid arthritis (RA) in 1999 (26). At present, autoimmune diseases like rheumatoid arthritis, multiple sclerosis, Systemic Lupus Erythematosus and Crohn's diseases are of great concern.

Rheumatoid Arthritis

Rheumatoid arthritis (RA) is an immunologically driven long-term condition (27). It is characterized by persistent inflammation of the joints (synovitis), systemic inflammation and auto antibodies, particularly the rheumatoid factors anticyclic citrullinated peptide antibodies. Many success stories of clinical trial have been reported in the use of MAbs against T-lymphocytes and B-lymphocytes for the treatment of rheumatoid arthritis (28). The utilization of monoclonal antibodies that focus on T-cells has exhibited a few advantages when used in RA patients despite the fact that responses have been no longer robust. This is partly due to insufficient therapy following antibody immunogenicity. Since humanized antibodies are less foreign to man than conventional rodent antibodies, they are expected to make possible some advancements in treatment (28).

MAbs which have been used in RA can be broadly categorized into three main groups (29):

(1) Cytokine inhibitors

(2) MAbs that bind to adhesion molecules;

(3) MAbs that target MHC molecules and T cells.

A list of mAbs which have been used in RA is given below

E.g. cA2, CDP571/Bay103356, BIRR-1, CD5-PLUS, Campath-1H, B-F5, 16H5, VIT-4, MT151, cM-T412, VIT-4, MT151, cM-T412

Multiple Sclerosis

Multiple sclerosis (MS) is an autoimmune disease in which auto-reactive T cells cross the blood brain barrier

and attack the myelin sheath leading to a cascade of inflammation. The result is demyelination, acute axonal transaction, gliosis and subsequent axonal degeneration (30). Unpredictable episodes of neurological disability in young adults are followed by a gradual accumulation of deficits over time as the disease switches from an inflammatory to a degenerative 'secondary progressive' phase (31).

Therapeutic approaches to multiple sclerosis (MS) focuses on altering the functions of the immune system. This is achieved either by the use of a broad spectrum immunosuppressive drugs, or by modulating them more discreetly with beta interferon and synthetic amino-acid co-polymers (32). Being highly specific and potent immunosuppressive agents, mAbs may offer considerable advantages over other therapies specified against MS (32). mAbs have been used as experimental treatments of MS since the 1980s (31). During the last decade, anti-a4 integrin natalizumab became the first approved mAb for treatment of relapsing MS, after convincingly demonstrating clinically significant effects on two large Phase 3 trials (31-34). Alemtuzumab (Lemtrada®) might be the second mAb to be approved for MS (32). Of the mAbs under development for MS, alemtuzumab and rituximab have also shown promising evidence of effectiveness and potentially expanded the therapeutic horizon for the reversal of disease progression in early relapsing patients and progressive patients (32).

Systemic Lupus Erythematosus

To assess the potential role of monoclonal antibody in systemic Lupus Erythromatosus (SLE) monoclonal antibodies (mAb) are now under clinical trials. The most frequently used mAb is rituximab, which is directed against CD20, a membrane protein expressed on B lymphocytes. Uncontrolled trials reported an improvement of SLE activity in non-renal patients while some other in severe lupus nephritis which was previously unresponsive to conventional treatments. However, two randomized trials failed to show the superiority of rituximab over conventional treatment in non-renal SLE and in lupus nephritis respectively (35).

MAbs which have been used in SLE can be divided into the following categories:

B-Cell Targeted mAbs:

Selectively target and deplete B cells using mAbs. This is a promising approach to improve the efficacy of treatment for SLE at present.

Anti-CD20 mAbs:

The development of mAbs directed againstCD20 presented new insights in treating these diseases. With regard to the central role played by B cells in the pathogenesis of SLE, numerous therapeutic attempts with anti-CD20 mAbs have been conducted for this disease (36). Rituximab (Rituxan®, MabThera®) is a chimeric mAb directed against CD20 which is available in vials designed for intravenous administration. Veltuzumab is a humanized anti-CD20 monoclonal antibody similar to rituximab, Ocrelizumab also functions as a humanized mAb directed against CD20.

Anti-CD22 mAbs:

Epratuzumab is a recombinant, humanized monoclonal antibody directed against CD22.

Anti-B Lymphocyte Stimulator Protein (BLyS) mAbs:

Belimumab (Benlysta®, LymphoStat-B®) is a complete human monoclonal antibody that specifically targets and inhibits the biological activity of BLyS.

Anti-Cytokine mAb

mAnti-IL-6mAb, Anti-tumor necrosis factor alpha (TNF-alpha) mAb, Anti CD40 ligand (CD40L) mA**b**, Anti-interleukin 10 (IL-10) mAb, Anti-IL-18 mABs, Anti-complement mAbs (37).

Crohn's Disease

Crohn's disease is a type of immunologically mediated inflammatory bowel disease (IBD) which may affect any part of the digestive system, from the mouth to anus but most commonly to the end of the small bowel (the ileum) and the beginning of the colon. The exact cause of Crohn's disease is still unknown. However, researchers suggest that a combination of factors like genetics, the immune system, previous infection, smoking and environmental factors may be the key players.

The treatment of Crohn's disease has required the use of multiple modalities. With an increasing understanding related to the underlying pathogenic mechanisms and the studies on identification of specific therapeutic targets, monoclonal antibody treatment has been an ideal strategy for inducing and maintaining these patients (38). TNF-alpha is an inflammatory cytokine or pro-inflammatory mediator, the high concentration of which is responsible for the destructive inflammatory processes that occur in, particularly cartilage and bone in RA. Agents that inhibit the action of TNF-alpha therefore, will be expected to modify the inflammatory disease process.

Commonly used monoclonal antibodies for Crohn's disease are Infliximab, Adalimumab, and Certolizumab (38).

Diabetes Mellitus

Earlier, Diabetes mellitus was considered as a disease of the developed world. At present, it has become a worldwide pandemic, where two thirds of the global diabetic population living in the developing countries (39, 40). New-onset type 1 diabetes (T1D) has shown success

on immune therapy trials, but not all subjects respond, and the duration of response is limited. Number of trials has shown the use of immune therapies for the controlling of the progression of type 1 diabetes (T1D). Rituximab, and Fc receptor (FcR)–nonbinding anti-CD3 mAb treatments have reduced the fall in C peptide responses that occurs in the first 2 years after disease onset (41-43).

For type I diabetes, anti-CD3 monoclonal antibody therapy has shown promising results. Here mAbs will bind to a molecule called CD3 which in turn binds to the CD3 receptor on the immune cells (T cells) and supports the T cells in destroying the β-cells of the pancreas (which is what causes to fail to produce insulin).

Immunosuppressant of Organ Transplantation

Organ transplantation is the surgical removal of a healthy organ from one individual and using it to replace the failed or injured organ of another individual. It is often the only available treatment for end state organ failure. In normal medical practice, immunosuppressive drugs such as cyclosporine and prednisone are administered to overcome the rejection of organ transplantation by the host immune system. For this purpose MAbs specific to T-lymphocyte surface antigens are being used. The first FDA licensed monoclonal antibody used as an immunosuppressive agent after organ transplantation in humans was OKT_3. In renal and bone marrow transplantations OKT_3 specifically directed against CD_3 antigen of T-lymphocytes is used. Normally CD_3 antigen plays a key role in organ transplant rejection (destroys the foreign cells in the host) which activates T-lymphocytes. Thus use of MAb against CD_3 antigen can prevent organ transplant rejection (44).

Hypercholesterolemia

The term primary hypercholesterolemia depicts a heterogeneous group of conditions with elevated levels of Low-density lipoprotein cholesterol (LDL-C). It comprises both autosomal-dominant familial hypercholesterolemia (ADH) with an estimated frequency of one per 200–500, and polygenic non-familial hypercholesterolemia. The latter is more common and exists often in combination with adverse environmental factors, such as a hypercholesterolemic diet and obesity.

Statin therapy is a specific treatment for LDL-C, which decreases the disease by approximately 25% to 50% (45). However, this treatment for LDL-C showed some significant drawbacks. This include individuals showing inability to tolerate Statin therapy which primarily develop due to muscle-related adverse effects and also many patients remain at risk of developing cardiovascular events in the latter stages of their life (46). At present, MAbs pro-protein convertase subtilisin–kexin type 9 (PCSK9) are found to reduce low-density lipoprotein (LDL) cholesterol levels in patients who are being treated with Statins. In phase 2 studies lasting 8 to 12 weeks, the PCSK9 inhibitor alirocumab showed significant lowering of LDL cholesterol levels by 40 to 70% when added to background statin therapy (46-49). However, since this was examined in a small population, in order to establish its safety and efficacy this new treatment must be evaluated in larger populations for longer periods as a follow-up (50-53).

In 2003, the glycoprotein pro-protein convertase subtilisin/kexin type 9 (PCSK9) was discovered, followed by the discovery of 'gain of function' mutations in the PCSK9 gene leading to the causation of familial hypercholesterolemia (54, 55). PCSK9 is synthesized and secreted by the liver. It was found to be involved in the degradation of the LDL receptor by binding to the receptor in serum and targeting it for degradation intracellular in the lysosome

(56, 57). This discovery led to the development of therapeutic monoclonal antibodies that specifically bind to circulating PCSK9, neutralizing the protein and thereby inhibiting degradation of the LDL receptor (58). Currently, three monoclonal antibodies targeting PCSK9 are in Phase III development; evolocumab, alirocumab and bococizumab, which are respectively fully human IgG2 monoclonal antibody, fully human IgG1 monoclonal antibody and humanized monoclonal antibody against PCKS9.

Ophthalmology

As in the past, current clinical insights has created new pharmacological questions and induced much debate among practitioners, particularly in the field of ophthalmology. The introduction of mAbs in ocular therapeutics has increased treatment alternatives in the armamentarium against some sight threatening serious conditions of the eye, which are resistant to the normal conventional treatments which are currently available (59). With more molecular pathways being defined and the drug development process getting revolutionized with the use of genetic engineering and biotechnology, newer and more important receptors will be targeted in future by the monoclonal antibodies.

The development of therapeutic monoclonal antibodies (mAbs) provided many great advances in the treatment of ocular diseases. Also they possess very effective application in ophthalmology, especially in angiogenic and inflammatory conditions. Some of these mAbs such as ranibizumab, bevacizumab, infliximab and adalimumab can control conditions such as macular degeneration, neovascularization and also inflammation. Daclizumab can effectively control recalcitrant ocular inflammation and therefore can be used long term in children and adults as a corticosteroid sparing agent to induce sustained remission (60). Rituximab, daclizumab, efalizumab, and alemtuzumab have also shown to be effective as adjunctive therapy in various ocular problems in many

preclinical and early clinical studies (59). A few other mAbs which have been tried for ophthalmic conditions are efalizumab, altemtuzumab, and basiliximab (61).

Infectious Disease

At present, most of the reagents that are available target non-infectious diseases. Interest in using antibodies to treat infectious diseases is now being fueled by factors such as the wide distribution of drug-resistant microorganisms, the emergence of new microorganisms, the relative inefficacy of antimicrobial drugs in immunocompromised hosts and the fact that antibody-based therapies are the only means to provide immediate immunity against biological weapons. Thus, passive antibody therapy was developed which is the first consistently effective antimicrobial strategy to be introduced. The ability of specific antibodies to fight against bacterial toxins was discovered by Behring and Kitasato in the early 1890s (62), and led to the rapid development of antibody therapy for the treatment of various infectious diseases (63).

An important potential advantage of using antibody therapies against bacterial and viral diseases is that they can be used in synergy or as an additive combined with conventional antimicrobial chemotherapy (63, 64). In addition, recent studies suggest in comparison using either therapy alone, or combinations of antibodies and drugs are more effective against fungal infections (65-67). In addition to being ideal therapeutic agents, antibodies play a vital role in vaccine development as well. The use of antibody therapy against an infectious disease suggests that a vaccine that elicits similar antibodies could be protective against the relevant pathogen. For example, successful passive antibody therapy against *Pneumococcal pneumonia* and *Diphtheria* preceded the development of vaccines against these diseases. More recently, the generation of protective mAbs against *C. neoformans* and *C. albicans* identified polysaccharide antigens that were then used to design effective conjugate vaccines (68-70).

Traditionally, antibodies have been effective when directed against either microbial antigens or their products, such as toxins. In some microbial diseases, antibodies act as a component of the humoral immune response to natural infection, whereas host defense against other microorganisms relies primarily on cell-mediated immune mechanisms. However, there is now considerable evidence to indicate that it is possible to generate mAbs that are protective against microorganisms such as *Mycobacterium tuberculosis*, *Listeriamono cytogenes*, *Leishmania Mexicana* and *Histoplasma capsulatum* for which the activation of humoral immunity is not important for the development of resistance to natural infection (71-73). However, monoclonal antibodies are currently being developed against certain infectious agents, including cytomegalovirus and human immunodeficiency virus. At present monoclonal antibodies are designed to be used against specific viruses; Palivizumab (Synagis) is licensed for respiratory syncytial virus (RSV) prophylaxis and Motavizumab (Numax®) which is designed as a humanized antibody with the ability to bind to RSV, and it is currently in the process of development (74).

Conclusion

The fact that these Monoclonal antibodies are extraordinarily specific in nature, not only makes them unique but also unfolds the endless possibilities of revolutionary therapeutic applications for a gamut of clinical conditions, including targeted therapy and other diagnostic applications. MAb's have dramatically changed our perception and treatment strategy for autoimmune diseases such as rheumatoid arthritis (RA), inflammatory bowel disease (IBD) and multiple sclerosis (MS). The commercial development of therapeutic monoclonal antibodies commenced in the early 1980s and since then it has continuously evolved from simple MAb products and chimeric antibodies to humanized antibodies and now to fully human MAbs. The massive success in therapeutics can be attributed to the fact that it allows us to target specific cells with pinpoint precision at a cellular level. Thus, with recent advances in the field of MAb therapeutics and a better understanding of several potential obstacles, the utility of MAbs in treatment and management of various diseases and life-threatening conditions now appears much closer to realization.

MAbs have radically transformed our understandings about the pathways of disease, enabling faster, economical and more accurate diagnostic testing on a vast scale, and have also opened up newer possibilities for the treatment of medical conditions which are difficult to treat by traditional methods. Therefore at this stage of rapid advancement in biopharmaceuticals, it would not be premature to conclude that Monoclonal antibodies (mAbs) are now established as targeted therapies for malignancies, autoimmune disorders, infectious diseases and transplant rejection.

References

1. Schwartz, Robert SMD. Paul Ehrlich's magic bullets. N Engl J Med 2004;350: 1079-80.
2. Zhiqiang An. Monoclonal antibodies – a proven and rapidly expanding therapeutic modality for human diseases. Protein Cell 2010;1(4):319-30
3. Oldham RK, Dillman RO. Monoclonal Antibodies in Cancer Therapy: 25 Years of Progress. Journal of Clinical Oncology 2008;26(11):1774-77.
4. Geng X, Kong X, Hu H, et al. Research and development of therapeutic mAbs: An analysis based on pipeline projects. Hum Vaccin Immunother 2015;11(12):2769-76.
5. Weiner LM, Surana R, Wang S. Monoclonal antibodies: versatile platforms for cancer immunotherapy. Nat Rev Immunol 2010;10(5):317-27.
6. Nelson AL, Dhimolea E, Reichert JM. Development trends for human monoclonal antibody therapeutics. Nat Rev Drug Disc 2010;9(10):767-74.
7. Reichert JM. Monoclonal antibodies as innovative therapeutics. Curr Pharm Biotech 2008; 9(10): 423-30.
8. Reichert JM, Rosensweig CJ, Faden LB, Dewitz, MC. Monoclonal

antibody successes in the clinic. Nat Biotech 2005;23(9):1073-78.
9. Reichert JM. Antibodies to watch in 2010. Mabs1)2;010 2):84-100.
10. Scolnik PA. mAbs: a business perspective. MAbs2)1;2009):179-84.
11. Breedveld FC. Therapeutic monoclonal antibodies. Lancet 2000;355(9205):735-40.
12. Buchwald UK, Pirofski L. Immune therapy for infectious diseases at the dawn of the twenty-first century: the past, present and future role of antibody therapy, therapeutic vaccination and biological response modifiers. Curr Pharm Des 2003;9(12):945-68.
13. Anonymous. Medical News Today - What is Cancer? Available from: URL: https://www.medicalnewstoday.com/info/cancer-oncology.
14. Alison MR. Cancer. eLS 2001.
15. Wu H, Chang D, Huang C. Targeted Therapy for Cancer. J Cancer Mol 2006;2(2):57-66.
16. Schrama D, Reisfeld RA, Becker JC. Antibody targeted drugs as cancer therapeutics. Nat Rev Drug Discov 2006;5(2):147-59
17. Ecker DM, Jones SD, Levine HL. The therapeutic monoclonal antibody market. MAbs 2015;7(1):9–14.
18. Scott AM, Wolchok JD, Old LJ. Antibody therapy of cancer. Nat Rev Cancer4)12;2012):278-87.
19. Motta G, Cea M, Moran E, et al. Monoclonal Antibodies for Non-Hodgkin's Lymphoma: State of the Art and Perspectives. Clin Dev Immunol 2010;2010: 428253.
20. Grillo-Lopez AJ, Hedrick E, Rashford M, Benyunes M. Rituximab: ongoing and future clinical development. Semin Oncol 2002;29(1):105-12.
21. Breedveld, FC. Therapeutic monoclonal antibodies. Lancet 2000;355(9205):735–40.
22. Wang W, Erbe AK, Hank JA, Morris ZS, Sondel PM. NK Cell-Mediated Antibody-Dependent Cellular Cytotoxicity in Cancer Immunotherapy. Front Immunol 2015;6:368.
23. Horta ZP, Goldberg JL, Sondel PM. Anti-GD2 mAbs and next-generation mAb-based agents for cancer therapy. Immunotherapy 2016;8(9):1097–1117.
24. Funaro A, Horenstein AL, Santoro P, Cinti C, Gregorini A, Malavasi F. Monoclonal antibodies and therapy of human cancers. Biotechnol Adv 2000;18(5): 385-401.
25. Bruno V, Battaglia G, Nicoletti F. The advent of monoclonal antibodies in the treatment of chronic autoimmune diseases. Neurol Sci 2011;31(3):283-8.
26. Kalden JR. Emerging role of anti-tumor necrosis factor therapy in rheumatic diseases. Arthritis Res 2002;4(2):34–S40.
27. Scott DL, Wolfe F, Huizinga, TW. Rheumatoid arthritis. Lancet 2010;376(9746):1094-108.
28. Campbell J, Lowe D, Sleeman MA. Developing the next generation of monoclonal antibodies for the treatment of rheumatoid arthritis. Br J Pharmacol 2011;162(7): 1470-84.
29. Choy EHS, Kingsley GH, Panayi GS. Monoclonal Antibody Therapy in Rheumatoid Arthritis. Brit J Rheumat 1998;37(5):484-90.
30. Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transection in the lesions of multiple sclerosis. N Engl J Med 1998;338:278-85.
31. Giovannonia G, Butzkueven H, Dhib-Jalbut S, et al. Brain health: time matters in multiple sclerosis. Mult Scler Relat Disord1)9;2016):5-48.
32. Paulo F. Monoclonal antibody therapy in multiple sclerosis, Paradigm shifts and emerging challenges. MAbs 2010;2(6):670-81.
33. Reichert JM. Monoclonal antibodies as innovative therapeutics. Curr Pharm Biotechnol 2008; 9(6):423-30.
34. Rommer PS, Dudesek A, Stüve O, Zettl UK. Monoclonal antibodies in treatment of multiple sclerosis. Clin and ExpImmunol 2014;175(3):373–84.
35. Gracia-Tello B, Ezeonyeji A, Isenberg D. The use of rituximab in newly diagnosed patients with systemic lupus erythematosus: long-term steroid saving capacity and clinical effectiveness. Lupus Sci Med 2017;4(1):e000182
36. Isenberg DA. Treating patients with lupus with B-cell depletion. Lupus 2008;17(4): 400-4.
37. Claudio P, Gabriella M. Monoclonal Antibodies for Systemic Lupus Erythematosus (SLE). Pharmaceuticals 2010;3:300-22.
38. Brijen S, Lloyd M. Current status of monoclonal antibody therapy for the treatment of inflammatory bowel disease. Expert Rev Clin Immunol 2010; 6(4): 607-20.
39. Wild RG, Green A, Sicree R, King H. Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diabetes Care 2004;27(10):1047-53.
40. 40. King H, Aubert RE, Herman WH. Global burden of diabetes, 1995-2025: prevalence, numerical estimates and projections. Diabetes Care 1998;21(9):1414–31.
41. International Diabetes Federation. World Diabetes Foundation. Diabetes Atlas: executive summary. 2nd ed. Brussels: IDF Executive Office; 2003. p7–11.
42. Herold KC, Hagopian W, Auger JA, et al. Anti-CD3 monoclonal antibody in new-onset type 1 diabetes mellitus. N Engl J Med 2002;346(22):1692-98.
43. Mark DP, Carla JG, Heidi KS, et al. Rituximab, B-Lymphocyte Depletion, and Preservation of Beta-Cell Function. N Engl J Med 2009;361:2143-52.
44. Keymeulen B, Vandemeulebroucke E, Ziegler AG, Mathieu C, Kaufman L, Hale G. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. N Engl J Med 2005;352(25):2598-608
45. Wadhera RK, Steen DL, Khan I, Giugliano RP, Foody JM. A review of low-density lipoprotein cholesterol, treatment strategies, and its impact on cardiovascular disease morbidity and mortality. Journal of Clinical Lipidology. 2016;10(3):472-489.
46. Mancini GB, Tashakkor AY, Baker S, et al. Diagnosis, prevention, and management of statin adverse effects and intolerance: Canadian Working Group Consensus update. Can J Cardiol 2013;29(12):1553-68.
47. McKenney JM, Koren MJ, Kereiakes DJ, Hanotin C, Ferrand AC, Stein EA. Safety and efficacy of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 serine protease, SAR236553/ REGN727, in patients with primary hypercholesterolemia receiving ongoing stable atorvastatin therapy. J Am Coll Cardiol 2012;59(25):2344-53.
48. Roth EM, McKenney JM, Hanotin C, Asset G, Stein EA. Atorvastatin with or without an antibody to PCSK9 in primary hypercholesterolemia. N Engl J Med 2012;367(20):1891-900.
49. Stein EA, Gipe D, Bergeron J, et al. Effect of a monoclonal antibody to PCSK9, REGN727/SAR236553, to reduce low-density lipoprotein cholesterol in patients with heterozygous familial hypercholesterolemia on stable statin dose with or without ezetimibe therapy: a phase 2 randomised controlled trial. Lancet 2012;380(9836): 29-36.
50. Colhoun HM, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab, a fully human PCSK9 monoclonal antibody, in high cardiovascular risk patients with poorly controlled hypercholesterolemia on maximally tolerated doses of statins: rationale and design of the ODYSSEY COMBO I and II trials. BMC Cardiovasc Disord 2014;14:121.
51. Kastelein JJ, Robinson JG, Farnier M, et al. Efficacy and safety of alirocumab in patients with heterozygous familial hypercholesterolemia not adequately controlled with current lipid-lowering therapy: design and rationale of the ODYSSEY FH studies. Cardiovasc Drugs Ther 2014;28(3):281-89.
52. Moriarty PM, Jacobson TA, Bruckert E, et al. Efficacy and safety of alirocumab, a monoclonal antibody to PCSK9, in statin-intolerant patients: design and rationale of ODYSSEY ALTERNATIVE, a randomized phase 3 trial. J Clin Lipidol 2014;8(6):554-61.
53. Robinson JG, Colhoun HM, Bays HE, et al. Efficacy and safety of alirocumab as add-on therapy in high-cardiovascularrisk patients with hypercholesterolemia not adequately controlled with atorvastatin (20 or 40 mg) or rosuvastatin (10 or 20 mg): design and rationale of the ODYSSEY OPTIONS Studies. Clin Cardiol 2014;37(10):597-604.
54. Seidah NG, Benjannet S, Wickham L, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. Proc Natl AcadSci USA 2003;100(3):928-33.
55. Abifadel M, Varret M, Rabes JP, et al. Mutations in PCSK9 cause autosomal dominant hypercholesterolemia. Nat Genet 2003;34(2):154-6.
56. Horton JD, Cohen JC, Hobbs HH. PCSK9: a convertase that coordinates LDL catabolism. J Lipid Res 2009;50(Suppl):S172-7.
57. Qian YW, Schmidt RJ, Zhang Y, et al. Secreted PCSK9 downregulates low density lipoprotein receptor through receptor-mediated endocytosis. J Lipid Res 2007;48:1488-98.
58. Chan JC, Piper DE, Cao Q, et al. A proprotein convertase subtilisin/kexin type 9 neutralizing antibody reduces serum cholesterol in mice and nonhuman primates. Proc Natl Acad Sci USA 2009;106(24):9820-5.
59. Rodrigues EB, Farah ME, Maia M, et al. Therapeutic monoclonal

antibodies in ophthalmology. Prog Retin Eye Res 2009;28(2): 117-44.
60. Bhat P, Castañeda-Cervantes RA, Doctor PP, Foster CS. Intravenous daclizumab for recalcitrant ocular inflammatory disease. Graefes Arch Clin Exp Ophthalmol 2009;247(5): 687-92.
61. Bonnekoh B, Böckelmann R, Pommer AJ, Malykh Y, Philipsen L, Gollnick H. The CD11a binding site of efalizumab in psoriatic skin tissue as analyzed by Multi- Epitope Ligand Cartography robot technology. Introduction of a novel biological drug-binding biochip assay. Skin Pharmacol Appn Skin Physiol 2007;20: 96-111.
62. Casadevall A. Passive Antibody Administration (Immediate Immunity) as a Specific Defense Against Biological Weapons. Emerg Infect Dis 2002;8(8): 833-41.
63. Oral HB, Akdis CA. Antibody-Based Therapies in Infectious Diseases. In: George A.J.T., Urch C.E. (eds) Diagnostic and Therapeutic Antibodies. Methods in Molecular Medicine 2000;40. Humana Press.
64. Buchwald UK, Pirofski L. Immune therapy for infectious diseases at the dawn of the twenty-first century: the past, present and future role of antibody therapy, therapeutic vaccination and biological response modifiers. Curr Pharm Des 2003;9(12): 945-68.
65. Nosanchuk JD, Steenbergen JN, Shi L, Deepe GS, Casadevall, A. Antibodies to a cell surface histone-like protein protect against Histoplasma capsulatum. J Clin Invest 2003;112(8):1164–75.
66. Matthews RC, Rigg G, Hodgetts S, et al. Preclinical assessment of the efficacy of mycograb, a human recombinant antibody against fungal HSP90. Antimicrob Agents Chemother 2003;47(7):2208–16.
67. Bowen A, Wear MP, Cordero RJ, Oscarson S, Casadevall A. A Monoclonal Antibody to Cryptococcus neoformans Glucuronoxylomannan Manifests Hydrolytic Activity for Both Peptides and Polysaccharides. J Biol Chem. 2017;292(2):417-34.
68. Rachini A, Pietrella D, Lupo P, Torosantucci A, Chiani P, Bromuro C, et al. An Anti-β-Glucan Monoclonal Antibody Inhibits Growth and Capsule Formation of Cryptococcus neoformans In Vitro and Exerts Therapeutic, Anticryptococcal Activity In Vivo. Infect Immun 2007;75(11):5085-94.
69. Bugli F, Cacaci M, Martini C, et al. Human Monoclonal Antibody-Based Therapy in the Treatment of Invasive Candidiasis. Clin Dev Immunol 2013;2013:403121.
70. Al-Sayyed B, Piperdi S, Yuan X, Li A, Besra GS, Jacobs WR, et al. Monoclonal antibodies to Mycobacterium tuberculosis CDC 1551 reveal sub cellular localization of MPT51. Tuberculosis (Edinb) 2007;87(6):489-97.
71. Pethe K, Alonso S, Biet F, et al. The heparin-binding haemagglutinin of M. tuberculosis is required for extrapulmonary dissemination. Nature 2001; 412(6843):190–94.
72. Mohamed W, Sethi S, Darji A, Mraheil MA, Hain T, Chakraborty T. Antibody Targeting the Ferritin-Like Protein Controls Listeria Infection. Infect Immun 2010;78(7):3306-14
73. Nejad-Moghaddam A, Abolhassani M. Production and Characterization of Monoclonal Antibodies Recognizing a Common 57-kDa Antigen of Leishmania Species. Iranian Biomedical Journal 2009;13(4): 245-251.
74. Rogovik AL, Carleton B, Solimano A, Goldman R. Palivizumab for the prevention of respiratory syncytial virus infection. Can Fam Physician 2010; 56(8):769–772.