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A REVIEW ON MONOCLONAL ANTIBODIES IN CANCER THERAPY AND AUTO IMMUNE DISEASE

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ABSTRACT

Monoclonal antibodies are introduced as effective agents in cancer therapy and to prevent allograft rejection. They represent new pharmacological tools for the treatment of auto immune disease. The use of monoclonal antibodies (mAbs) for cancer therapy has achieved considerable success in recent years. Antibody–drug conjugates are powerful new treatment options for lymphomas and solid tumours. Immunomodulatory antibodies have also recently achieved remarkable clinical success. The development of therapeutic antibodies requires a deep understanding of cancer serology, protein-engineering techniques, mechanisms of action and resistance, and the interplay between the immune system and cancer cells. With the knowledge of immunological moments in autoimmunity, it is now possible to target each single step of the immune process, through activation of T lymphocytes in lymph nodes in the formation of immunological synapse and to cell differentiation and cytokine production. Hence it is essential to know about various monoclonal antibodies and their mechanism of action to counteract carcinoma and auto immune diseases. The present study is an over view on such monoclonal antibodies.

INTRODUCTION

Monoclonal Antibodies:

An antibody is produced by a single clone of cells. A monoclonal antibody is therefore a single pure type of antibody. It can be made in large quantities in the laboratory and are a cornerstone of immunology. Monoclonal antibodies are increasingly coming into use as therapeutic agents. Monoclonal antibody production by somatic cell fusion or hybridoma technology was introduced by Kolher and Milstein in 1975 (got Nobel Prize in 1984).[1] The technique involves fusing a normal antibody producing B cell with a myeloma cell to produce a hybrid cell or hybridoma.[2] The hybridoma would possess the immortal growth properties of the myeloma cell while secreting the antibody produced by the B cell. The resulting hybridoma could becultured indefinitely thus providing large amounts of homogeneous antibody for research purposes. The usefulness of monoclonal antibodies stems from their characteristics, specificity of binding, homogeneity, and their ability to be produced in unlimited quantities. Additionally one of the unique advantage of hybridoma production is that impure antigens can be used to produce specific antibodies. This is based on the fact that screening with the pure antigen for the antibody of choice and that antibody(Ab) is produced by isolating a single cell clone. In fact, ever if monoclonal antibodies exert selective immune modulation by targeting only cells expressing a specific origin, a wide spread perturbation of the immune system is induced, leading to a pre disposition for infection and to the occurrence of tumors.[3]

However,their success as therapeutic biologic drugs and generation of value in the Pharmaceutical market is due to the robust and flexible nature of the immunoglobulin molecule, advances in basic sciences such as molecular biology, genetics, protein engineering and cell sciences, and advances in applied sciences from the biotechnology and pharmaceutical industry. [4]mAbs are large proteins, for example immunoglobulin G (IgG) is~150kDa, and are expressed by selected, immortalized subsets of immune cells. Subsequent large scale, high-yield expression may be performed using human cell lines such as human embryonic kidney (HEK)-293, or Chinese hamster ovary (CHO) cells. They are composed of heavy and light polypeptide chains bridged through disulfide bonds and because of their (generally) murine origin, may cause self-limiting allergic reactions. IgG monomers are therefore expressed with humanized domains (‘chimeras’) or more recently as fully human IgGs. They are used to treat a wide range of disease

conditions, with cancers and autoimmune disorders being the most common targets. A cursory search across citation databases for 'therapeutic antibodies' will reveal around 200,000 peer reviewed articles. There is clearly a vast amount of literature on this subject. For the purposes of this review we have considered therapeutic monoclonal antibodies and their mechanism of action to counteract carcinoma and auto immune diseases. [5]

Monoclonal antibodies are monospecific antibodies that made by identical immune cells which are all clones of a unique parent cell. Monoclonal antibodies are a recent innovative treatment for cancer. They are considered as a form of passive immune therapy. Monoclonal antibodies are now widely used in diagnostic tests, cancer treatment and in the treatment of auto immune diseases. Most therapeutic monoclonal antibodies are of the IgG type. There are four subclasses of IgG, namely IgG1, IgG2, IgG3 and IgG4, out of which IgG4 is most abundantly found in serum. Between the four subclasses, there is a homology of 95% with respect to the amino acid sequence. The most notable difference in the structures of the subclasses lies in the hinge region. In this region; the subclasses show variation in terms of the number of disulphide bonds present between the two heavy chains. The result of these differences is that they show different susceptibility to enzyme cleavage by proteases such as papain and pepsin.

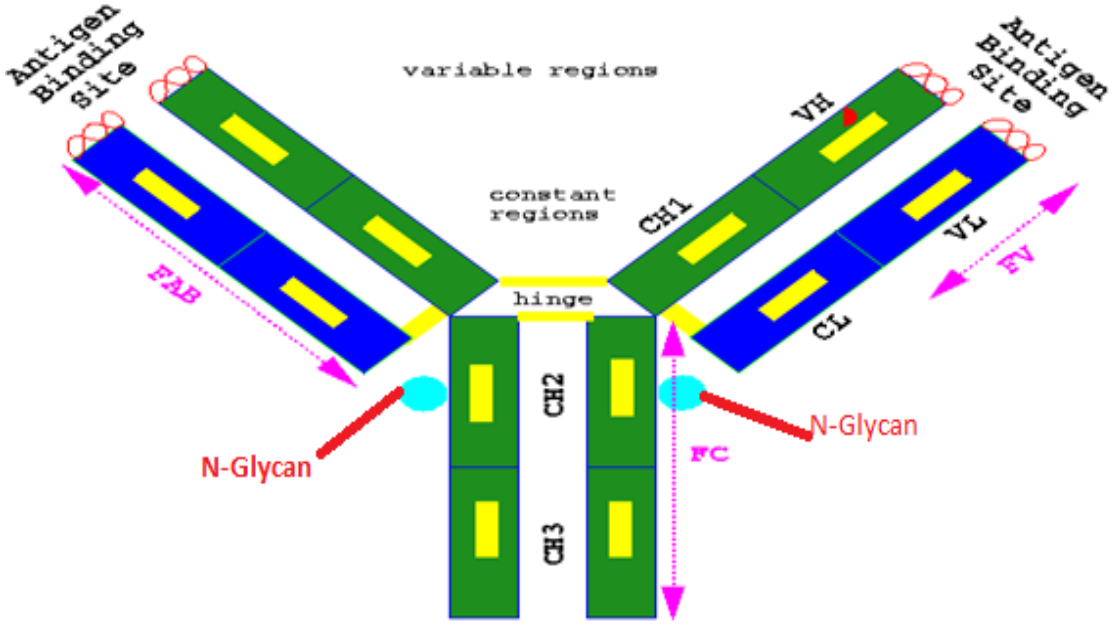

Figure 1: Structure of IgG antibody

a. Cancer treatment: IgGs (figure 1) antibodies are large molecules of about 150 kDa composed of four peptide chains. It contains two identical classes, γ heavy chains of about 50 kDa and two identical light chains of about 25 kDa, thus a tetrameric quaternary structure. [6] The two heavy chains are linked to each other and to a light chain each by disulphide bonds. The resulting tetramer has two identical halves, which together form the Y-like shape. Each end of the fork contains an identical antigen binding site. The Fc regions of IgGs bear a highly conserved N-glycosylation site. The N-glycans attached to this site are predominantly core-fucosylatedbiantennary structures of the complex type. In addition, small amounts of these N-glycans also bear bisecting GlcNAc and α-2, 6-linked sialic acid residues.

Application of mAbs:

1. Diagnostic uses: Monoclonal antibody can be used to detect the presence of antigen, endotoxins and hormones etc., The Western blot test and immuno dot blot tests detect the protein on a membrane. They are also very useful in immunohistochemistry, which detect antigen in fixed tissue sections and immunofluorescence test.

2. Therapeutic treatment:

Monoclonal antibodies binds only to cancer cell-specific antigens and induce an immunological response against the target cancer cell. Such mAb could also be modified for delivery of a toxin, radioisotope, cytokine or other active conjugate. It is also possible to design bispecific antibodies that can bind with their Fab regions both to target antigen and to a conjugate or effector cell. In fact, every intact antibody can bind to cell receptors or other proteins with its Fc region.

b. Autoimmune diseases: Monoclonal antibodies used for the treatment of autoimmune diseases include infliximab and adalimumab, which are effective in rheumatoid arthritis, Crohn's disease and ulcerative Colitis by their ability to bind to and inhibit TNF-α. Basiliximab and daclizumab inhibit IL-2 on activated T cells and thereby help to prevent acute rejection of kidney transplants. Omalizumab inhibits human immunoglobulin E (IgE) and is useful in moderate-to-severe allergic asthma.

A large variety of mAbs are therapeutically used in the treatment of various disease conditions. Such mAbs are depicted in **Table 1** .

Table 1- list of FDA approved therapeutic monoclonal antibodies

Antibody	Brand name	Company	Approval date	Type	Target	Indication
Abciximab	ReoPro	Eli Lilly	1994	Chimeric	Inhibition of glycoproteinIIb /IIIa	Cardiovascular disease
Adalimumab	Humira	Abbot	2002	Human	Inhibition of TNF-α signalling	Several auto-immune disorders
Alemtuzumab	Campath	Genzyme	2001	Humanized	CD52	Chronic lymphocytic leukaemia
Basiliximab	Simulect	Novartis	1998	Chimeric	IL-2Rα receptor (CD25)	Transplant rejection
Belimumab	Benlysta	GlaxoSmithKline	2011	Human	Inhibition of B-cell activating factor	Systemic lupus erythematous
Bevacizumab	Avastin	Genentech/Roche	2004	Humanized	Vascular endothelial growth factor (VEGF)	Colorectal cancer
Brentuximabvedotin	Adcetris		2011	Chimeric	CD30	Anaplastic large cell lymphoma(ALCL) and Hodgkin lymphoma
Canakinumab	Ilaris	Novartis	2009	Human	IL-1β	Cryopyrin-associated periodic syndrome (CAPS)
Certolizumabpegol[19]	Cimzia	UCB (company)	2008	Humanized	Inhibition of TNF-α signalling	Crohn's disease
Cetuximab	Erbitux	Bristol-Myers Squibb/Eli Lilly/Merck KGaA	2004	Chimeric	epidermal growth factor receptor	Colorectal cancer, Head and neck cancer
Daclizumab	Zenapax	Genentech/Roche	1997	Humanized	IL-2Rα receptor (CD25)	Transplant rejection
Denosumab	Prolia,Xgeva	Amgen	2010	Human	RANK Ligand inhibitor	Postmenopausal osteoporosis , Solid tumor`sbony metastases
Eculizumab	Soliris	Alexion Pharmaceuticals	2007	Humanized	Complement system protein C5	Paroxysmal nocturnal hemoglobinuria
Efalizumab	Raptiva	Genentech/Merck Serono	2002	Humanized	CD11a	Psoriasis
Gemtuzumab	Mylotarg	Wyeth	2000	Humanized	CD33	Acute myelogenousleukaemia

Golimumab	Simponi	Johnson & Johnson/Merck & Co, Inc.	2009	Human	TNF-alpha inhibitor	Rheumatoid arthritis, Psoriatic arthritis, and Ankylosing spondylitis
Ibritumomabtiuxetan	Zevalin	Spectrum Pharmaceuticals, Inc.	2002	Murine	CD20	Non-Hodgkin lymphoma
Infliximab	Remicade	Janssen Biotech, Inc./Merck & Co	1998	Chimeric	inhibition of TNF-α signalling	Several autoimmune disorders
Ipilimumab (MDX-101)	Yervoy		2011	Human	blocks CTLA-4	Melanoma
Muromonab-CD3	Orthoclone OKT3	Janssen-Cilag	1986	Murine	Tcell CD3 Receptor	Transplant rejection
Natalizumab	Tysabri	Biogen Idec/Élan	2006	Humanized	alpha-4 (α4) integrin,	Multiple sclerosis and Croh n's disease
Ofatumumab	Arzerra		2009	Human	CD20	Chronic lymphocytic leukaemia
Omalizumab	Xolair	Genentech/Novartis	2004	Humanized	immunoglobulin E (IgE)	mainly allergy-related asthma
Palivizumab	Synagis	MedImmune	1998	Humanized	an epitope of the RSV F protein	Respiratory Syncytial Virus
Panitumumab	Vectibix	Amgen	2006	Human	epidermal growth factor receptor	Colorectal cancer
Ranibizumab	Lucentis	Genentech/Novartis	2006	Humanized	Vascular endothelial growth factor A (VEGF-A)	Macular degeneration
Rituximab	Rituxan, Mabthera	Biogen Idec/Genentech	1997	Chimeric	CD20	Non-Hodgkin lymphoma
Tocilizumab or Atlizumab	Actemra and RoActemra		2010	Humanised	Anti- IL-6R	Rheumatoid arthritis
Tositumomab	Bexxar	GlaxoSmithKline	2003	Murine	CD20	Non-Hodgkin lymphoma
Trastuzumab	Herceptin	Genentech	1998	Humanized	ErbB2	Breast cancer

Cancer therapy:

After cardiovascular diseases, cancer represents the second most common cause of death in the Western world and hence is amajor area of focus for the pharmaceutical industry. Surgery and radiotherapy are generally used when a tumor is localized to a certain tissue, but chemotherapy is needed when metastasis has occurred. Despite extensive research, most anticancer drugs have nonspecific toxicity. By targeting the cell cycle and thereby killing rapidly proliferating cells,

they do not explicitly discriminate between healthy and tumor tissues and only gain a limited selectivity for malignant cells. Such cytotoxic drugs have a narrow therapeutic window, which limits their efficacy and results in severe side effects. Due to lack of selectivity, drug concentrations that would eradicate the tumor can often be used. In addition, tumors can develop resistance against anticancer drugs after prolonged treatment. Therefore, achieving improved tumor selectivity through targeting of cytotoxic drugs to the cancer cells is needed. A promising approach in achieving a more selective treatment is monoclonal antibodies therapy.[7]Thanks to their high binding specificity for tumor-specificantigens. mAbs can be used as vehicles to target cell-killing payloads to tumor cells. Unique or over expressed, tumor-specific antigens can be found in a wide range of human tumor cells.[8] Some mAbs have the ability to recognize and specifically bind to these tumor-associated antigens. They can be used as single agents for the treatment of cancer through binding to cancer-cell-specific antigens and induction of an immunological response against the target cancer cell.[9]

Antibody based therapy for cancer has become established over the past 15 years and is now one of the most successful and important strategies for treating patients with haematological malignancies and solid tumours. The fundamental basis of antibody-based therapy of tumours dates back to the original observations of antigen expression by tumour cells through serological techniques in the 1960s. [10] The definition of cell surface antigens that are expressed by human cancers has revealed a broad array of targets that are overexpressed, mutated or selectively expressed compared with normal tissues.[11] A key challenge has been to identify antigens that are suitable for antibody-based therapeutics. Such therapeutics can function through mediating alterations in antigen or receptor function (such as agonist or antagonist functions), modulating the immune system (for example, changing Fc function and T cell activation) or delivering a specific drug that is conjugated to an antibody that targets a specific antigen. [12-14] Molecular techniques that can alter antibody pharmacokinetics, effector function, size and immunogenicity have emerged as key elements in the development of new antibody-based therapies.

Table 2- List of FDA approved mAbs for cancer therapy

Antibody	Target	FDA-approved indication	Approval in Europe*	Mechanisms of action
Naked antibodies: solid malignancies				
Trastuzumab (Herceptin; Genentech): humanized IgG1	ERBB2	ERBB2-positive breast cancer, as a single agent or in combination with chemotherapy for adjuvant or palliative treatment. ERBB2-positive gastric or gastro-oesophageal junction carcinoma as first-line treatmentin combination with cisplatin and capecitabine or 5-fluorouracil	Similar	Inhibition of ERBB2 signalling and ADCC
Bevacizumab (Avastin; Genentech/Roche): humanized IgG1	VEGF	For first-line and second-line treatment of metastatic colon cancer, in conjunction with 5-fluorouracil-based chemotherapy; for first-line treatment of advanced NSCLC, in combination with carboplatin and paclitaxel, in patients who have not yet received chemotherapy; as a single agent in adult patients with glioblastoma whose tumour has progressed after initial treatment; and in conjunction with IFNα to treat metastatic kidney cancer	Similar	Inhibition of VEGF signalling
Cetuximab (Erbitux; Bristol-Myers Squibb)‡: chimeric human–murine IgG1	EGFR	In combination with radiation therapy for the initial treatment of locally or regionally advanced SCCHN; as a single agent for patients with SCCHN for whom prior platinum-based therapy has failed; and palliative treatment of pre-treated metastatic EGFR-positive colorectal cancer	Similar	Inhibition of EGFR signalling and ADCC
Panitumumab (Vectibix; Amgen)‡: human IgG2	EGFR	As a single agent for the treatment of pre-treated EGFR-expressing, metastatic colorectal carcinoma	Similar	Inhibition of EGFR signalling
Ipilimumab (Yervoy; Bristol-Myers Squibb): IgG1	CTLA4	For the treatment of unrespectable or metastatic melanoma	Similar	Inhibition of CTLA4 signalling
Naked antibodies: haematological malignancies				

Rituximab (Mabthera; Roche): chimeric human– murine IgG1	CD20	For the treatment of CD20-positive B cell NHL and CLL, and for maintenance therapy for untreated follicular CD20-positive NHL	Similar	ADCC, direct induction of apoptosis and CDC
Alemtuzumab (Campath; Genzyme): humanized IgG1	CD52	As a single agent for the treatment of B cell chronic lymphocytic leukaemia	Similar	Direct induction of apoptosis and CDC
Ofatumumab (Arzerra; Genmab): human IgG1	CD20	Treatment of patients with CLL refractory to fludarabine and alemtuzumab	Similar	ADCC and CDC
Conjugated antibodies: haematological malignancies				
Gemtuzumabozogamicin (Mylotarg; Wyeth): humanized IgG4	CD33	For the treatment of patients with CD33-positive acute myeloid leukaemia in first relapse who are 60 years of age or older and who are not considered candidates for other cytotoxic chemotherapy; withdrawn from use in June 2010	Not approved in the European Union	Delivery of toxic payload, calicheamicin toxin
Brentuximabvedotin (Adcetris; Seattle Genetics): chimeric IgG1	CD30	For the treatment of relapsed or refractory Hodgkin's lymphoma and systemic anaplastic lymphoma	Not approved in the European Union	Delivery of toxic payload, auristatin toxin
90Y-labelled ibritumomabtiuxetan (Zevalin; IDEC Pharmaceuticals): murine IgG1	CD20	Treatment of relapsed or refractory, low-grade or follicular B cell NHL. Previously untreated follicular NHL in patients who achieve a partial or complete response to first-line chemotherapy	Similar	Delivery of the radioisotope 90Y
131I-labelled tositumomab (Bexxar; GlaxoSmithKline): murine IgG2	CD20	Treatment of patients with CD20 antigen-expressing relapsed or refractory, low-grade, follicular or transformed NHL	Granted orphan status drug in 2003 in the European Union	Delivery of the radioisotope 131I, ADCC and direct induction of apoptosis

Cancer serology:

The concept that antibodies could serve as 'magic bullets' in the diagnosis and therapy of cancer dates back to their discovery in the late 19th century. A considerable effort over the ensuing decades involved immunization of a variety of animal species with human cancer in the hope of generating antisera with some degree of cancer specificity.[15] Unfortunately, this approach had limited early success, with the notable exception of the discovery of carcinoembryonic antigen (CEA), a marker for colon and other cancers, and α-fetoprotein, a marker for hepatocellular cancer.[11]

The US Food and Drug Administration has approved 21 monoclonal antibody products, with six of these biologic drugs approved specifically for cancer (Table 2). However, rituximab became the first monoclonal antibody approved specifically for cancer therapy.[16]

Rituximab

The chimeric monoclonal antibody rituximab contains a murine derived Fab targeting CD20, a pan-B cell trans membrane protein, and a human Fc segment.[17] Features making CD20 as attractive target are having high level expression that is not down regulated by antibody binding and low plasma levels.[18] Rituximab kills normal and malignant CD20+ cells, but fortunately depletion of normal B cells is minimally toxic. Single agent rituximab was approved for relapsed/refractory indolent CD20+ non-Hodgkin lymphoma based on a response rate in heavily pre-treated patients of 48%, with median duration 13 months.[19] Given the lack of rituximab bone marrow suppression, full doses of chemotherapy and rituximab can be combined and uniformly give better outcomes than chemotherapy alone. Major randomized trials leading to the currently approved indications for rituximab include documented prolonged remissions as initial therapy for indolent non-Hodgkin lymphoma with rituximab-cyclophosphamide-vincristine-prednisone (R-CVP) or rituximab scheduled re-treatment following CVP. [20] CVP alone; and prolonged progression free and overall survival as initial therapy for aggressive B cell non-Hodgkin lymphoma with rituximab-cyclophosphamide-doxorubicin-vincristine- prednisone (R-CHOP) vs. CHOP alone.[21] Maintenance dosing of rituximab seems to prolong progression-free survival in indolent non-Hodgkin lymphoma, though dose and schedule have been variable and effects on survival require longer follow-up. Each of the three main proposed mechanisms for rituximab mediated cytotoxicity might be manipulated to enhance cytotoxicity. Cell signaling after rituximab is complex and under active investigation, but could be altered by signal pathway inhibitors. Any clinical effects, however, remain empiric. Complement activity may be enhanced by down-regulating complement inhibitory proteins such as CD55 and CD59, which is an effect of fludarabine, raising this as a possible synergistic interaction.[22] ADCC effects reflect Fc receptor binding affinities as CD16a polymorphisms alter rituximab single agent effects, however, R-chemo seemsto overcome this effect.[23] Strategies to enhance ADCC, such as blocking inhibitory signals to killer cells, are under investigation. Combination of active agents that also are immune modulating, such as lenalidomide and thalidomide, with rituximab may be

additive, and perhaps synergize by increasing ADCC. [24] The ability to restore the effector cell compartments with cytokines such as interleukin-2, -12 or -15 and myeloid growth factors, or potentially with cellular replacement therapy, may also enhance therapeutic antibody activity, as suggested by pre-clinical data demonstrating that IL-2 can promote NK cell development and enhance rituximab activity and clinical trials. Myeloid growth factors in combination with rituximab may also activate ADCC.[25]

Catumaxomab

Catumaxomab has two different antigen-binding specificities: one for EpCAM on tumor cells and one for the CD3 antigen on T-cells. In addition, ca-tumaxomabbinds, via its intact Fc region, to type I, IIa, and III Fcγ receptors (FcγRs) on accessory cells, e.g. natural killer (NK) cells, dendritic cells (DCs), and macrophages. Catumaxomab exerts its anti-tumor effects via T-cell mediated lysis,[26]ADCC, and phagocytosis via activation of FcγR-positive accessory cells.[27,28]Its anti-tumor activity is assisted by the induction of T-cell-secreted cytokines, such as interferon (IFN)-γ andtumor necrosis factor (TNF)-α.[29] An important aspect of catumaxomab's mode of action is that no additional activation of immune cells is required for effective tumor eradication, so it is a self-supporting system.

Gemtuzumab

This humanized monoclonal antibody to CD33 is approved for use in acute myelogenousleukemia and uses the antibody conjugated to calicheamicin, a potent enediyene antibiotic originally isolated from a Micromonosporaechoinospora.[30] Two radioisotope antibody conjugates, ytrrium-90 ibritumomabtiuxetanand iodine-131 tositumomabhave been approved. [31] The murine form of these antibodies were retained in order to expedite clearance from the circulation. Both radiolabeled antibodies target the CD20 antigen on lymphoma cells.

Trastuzumab:

A second monoclonal antibody that has proven highly effective in the clinic is trastuzumab, a humanized antibody that reacts with the second part of the human epidermal growth factor receptor 2.[32]Like rituximab, it is effective as a single agent in induction and maintenance therapy, but is used primarily in conjunction with chemotherapy for patients with human epidermal growth factor receptor 2/neu–positive breast cancer.[33,34]

Alemtuzumab:

It is a humanized monoclonal antibody targeting the CD52 antigen found on B lymphocytes and is used primarily for chronic lymphocytic leukemia.[35] Like the two previously cited monoclonal antibody therapies, alemtuzumab is effective as induction and maintenance therapy. Alemtuzumab is also reactive with T lymphocytes, and unlike the other two antibodies, it is typically not combined with chemotherapy because of the increased risk of infection. [35]

Bevacizumab:

Another humanized monoclonal antibody, bevacizumab, has been applied more broadly in human solid tumors because it targets vascular endothelial growth factor, which is the ligand for a receptor found on blood vessels.[36] Because this receptor is on endothelial cells, bevacizumab seems to be effective by reducing the blood supply to tumor nodules, thereby slowing or interrupting growth. Initially approved for advanced colorectal cancer, [37]it is now used in a variety of human solid tumors including cancers of the lung, kidney, and breast.[38-40]

The last two antibodies approved for clinical use were cetuximab(a chimeric antibody), and panitumumab (a completely human antibody).Both target the epidermal growth factor receptors found on avariety of human tumors.[41, 42]Cetuximab was originally approved for use in combination with chemotherapy in metastatic colorectal cancer.[43] It also enhances chemotherapy and radiation therapy of squamouscell cancers of the headandneck.[44] Panitumumab was approved based on its single-agent activity in refractory colorectal cancer and is being combined with chemotherapy as well.

Mechanisms of tumour cell killing:

The mechanisms of tumour cell killing by antibodies are outlined in fig.2. This cell killing can be summarized as being due to several mechanisms: direct action of the antibody (through receptor blockade or agonist activity, induction of apoptosis, or delivery of a drug or cytotoxic agent); immune-mediated cell killing mechanisms (including, complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC) and regulation of T cell function); and specific effects of an antibody on tumour vasculature and stroma. The Fc function of antibodies is particularly important for mediating tumour cell killing through CDC and ADCC. All of these approaches have been successfully applied in the clinic. The abrogation of tumour cell signalling (forexample, by cetuximab and trastuzumab)[45] the induction of effector function primarily

through ADCC (for example, by rituximab)[46]and the immune modulation of T cell function (for example, by ipilimumab)[47]are the approaches that have been most successful and that have led to the approval of antibodies using these mechanisms (discussed below).

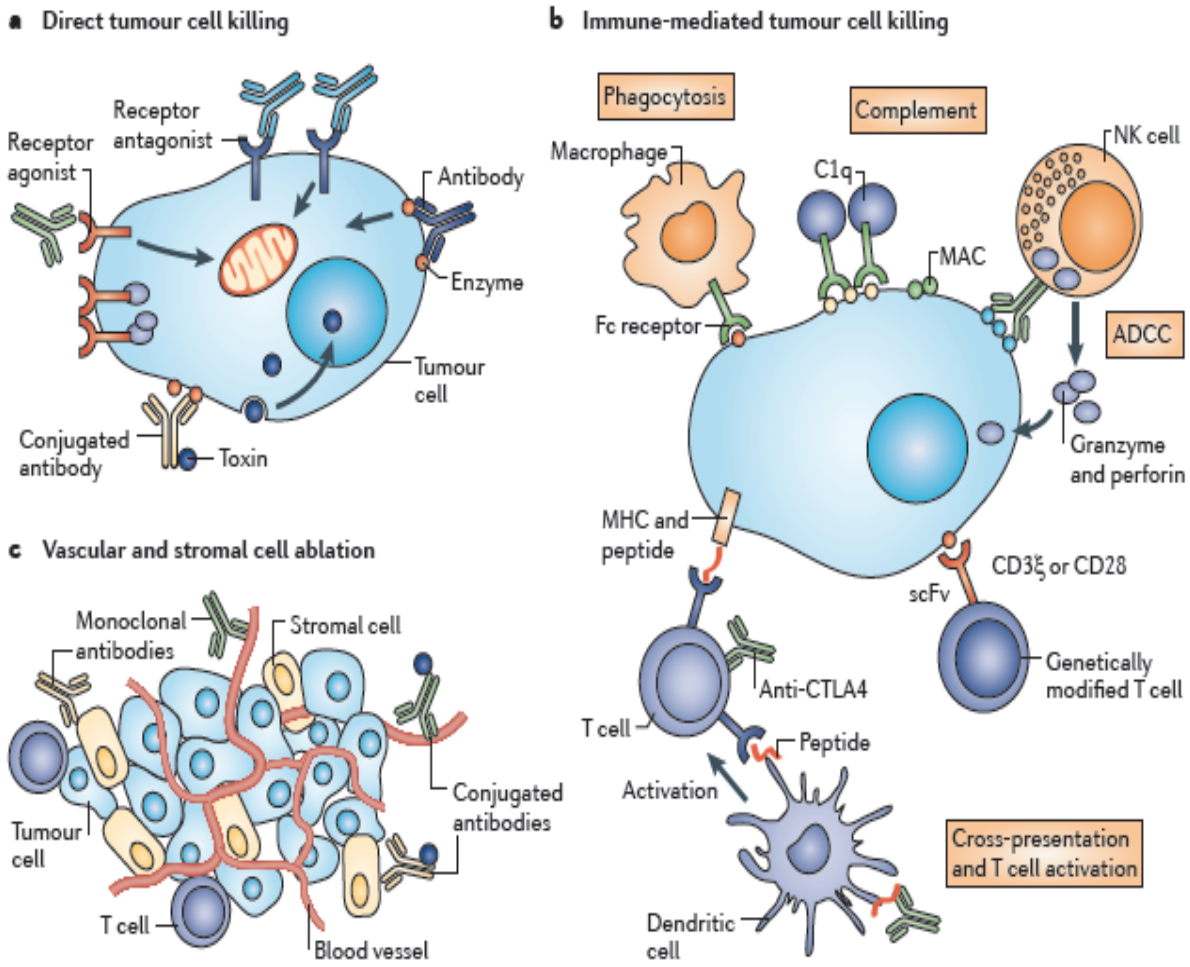

Figure 2: Mechanism of tumour cell killing

Although most of the antibodies that have been successful in the clinic are intact immunoglobulin G (IgG) molecules, multiple approaches for antibody construction and for the delivery of conjugated cytotoxic drugs have been used. [48]

Success of antibodies in the clinic: There have been twelve antibodies that have received approval from the FDA for the treatment of a variety of solid tumors and haematological malignancies. In addition, there are a large number of additional therapeutic antibodies that are currently being tested in early- and late-stage clinical trials. The early biodistribution studies of mouse anti-colon cancer antibody A33[49], the anti-CD33 antibody M195 [50], anti- CAIX

antibody G250 [51], anti-FAP antibody F19 [52], anti- GD3 antibody KM871 [53], and anti-Ley antibody hu3S193 [54]. This approach has also been applied to recent studies of trastuzumab (which targets ErbB2) biodistribution and in vivo assessment of ErbB2 expression by tumors. In non- Hodgkin lymphomas, assessment of the biodistribution of a radioconjugate in both the tumor and through whole body dosimetry was essential in initial trials exploring patient suitability for treatment and treatment dose for the United States Food and Drug Administration (FDA)-approved anti-CD20 radioimmunoconjugates tositumumab and ibritumomabtiuxetan. The use of patient biopsies can also be utilized to assess the in vivo effect of antibody abrogation of signalling pathways [55]. The evaluation of pharmacodynamics in early-phase clinical trials can also involve biological effector function of antibodies, such as ADCC (through optimized FcαR binding) and cytotoxicity. The assessment of antibodies as delivery vehicles for toxic agents can also be assessed using this clinical trial design approach. Use of therapeutic antibodies in patients with solid tumors has been most successful with classes of antibodies targeting the ErbB family (which includes EGFR) and VEGF. [56-58]

Autoimmune Diseases:

Autoimmune Diseases occur when the body's immune system recognize itself as non-self and acts against it as foreign particle or pathogen. It reacts against some of its own cells and tissue (s) by producing antibodies against it known as autoantibodies. Examples of autoimmune diseases include rheumatoid arthritis, systemic lupus erythematous, myasthenia gravies, multiple sclerosis, psoriasis juvenile diabetes, antiphospholipid syndrome,alopecia, crohn's disease, and cardiomyopathy. Auto immune diseases are broadly categorized into organ –specific and systemic auto immune diseases. Five to seven percentage of the world population is affected by auto immune diseases, mostly causing chronic debilitating ailments. It is expected that the treatment for autoimmune diseases should be aimed at particularly reducing the auto immune response without causing any side effects to the rest of the immune system.

Treatment of severe antibody mediated autoimmune disorders remains a difficult clinical problem. Treatment usually requires the long term use of corticosteroids alone or combined with cytotoxic agents.[59-61] The combinations ofcorticosteroids with cytotoxic chemotherapeutic agents, though frequently effective, have broad immunosuppressive effects involving phagocytic cells, T and B lymphocyte function. This lack of specificity, coupled with other systemic effects,

may cause considerable toxicity and treatment related morbidity. [61] Patients refractory to standard treatment present an even more complex therapeutic challenge. Therefore, agents that would specifically target B lymphocytes might provide a safer and more effective treatment of the antibody associated autoimmune disorders. Rituximab (Rituxan, IDEC Pharmaceuticals Corp, San Diego, CA) is a chimeric monoclonal antibody that targets the pan-B lymphocyte antigen CD20.CD20 is a B cell antigen that is present on the pre-B cells, and persists through all stages of B cell differentiation, being present on mature B cells as well as most B cell neoplasms.[62]Rituximab has been remarkably effective in the treatment of relapsed or refractory low grade non-Hodgkin's lymphoma. [63] The mechanisms by which rituximab exerts its lymphotoxic activity include complement dependent cytotoxicity, antibody dependent cellular cytotoxic and induction of apoptosis. [64]

The blockade of cytokines inducing inflammatory responses:

Currently, there are 3 major TNFα-blockers available for patients who do not react well tostandard therapies like methotrexate or other disease modifying anti-rheumatic drugs(DMARDs), these are: etanercept, infliximab and adalimumab(Table 3). Most common side effects of anti-TNFαtherapy are a higher susceptibility for infections, possible flares of TB.

Etanercept:

It is a fusion protein consisting of two extracellular binding domains of the TNFreceptor 2 and the Fc-part of a human IgG1 molecule is acting like a soluble decoy receptor byinhibiting ligand-binding to TNF-receptors, only with an extended *in vivo* half-life due to thepresence of the Fc-part. It is licensed by the FDA for the treatment of RA, polyarticular juvenileidiopathic arthritis (JIA), psoriatic arthritis, ankylosing spondylitis and plaque psoriasis.[65]

Infliximab (Remicade):

It is a chimeric monoclonal antibody specific for TNFαthat wasapproved by the FDA in 1998 for thetreatment of Crohn's disease. [66] Its use has beenextended since then to the treatment of psoriasis, ankylosing spondylitis, psoriatic arthritis,rheumatoid arthritis and ulcerative colitis.

Adalimumab (Humira):

Another monoclonal antibody of fully human origin was derived by a phage display library and used to treat RA patients first. Since then, clinical trials proved its effectiveness in psoriatic arthritis, ankylosing spondylitis, Crohn's disease, psoriasis and juvenile idiopathic arthritis.[67]

Infliximab and adalimumab were shown to neutralize biological activity of TNFαby binding to its soluble, membrane- or receptor-bound forms, while etanercept is unable to neutralize the receptor-bound form of TNFαdue to its structural features. Additionally, the anti-TNF monoclonal antibodies can induce Fc-receptor-mediated cell lysis and infliximab has been also shown to induce apoptosis of lamina propria T cells in Crohn's patients in a TNFαdependent manner.In a follow-up comparative study Bacquet-Deschryver et al. evaluated the effects of the three different anti-TNFαbiologics on the re-emerginig of anti-nuclear antibodies (ANA), antidsDNAantibodies, RF and anti-CCP in rheumatoid arthritis and spondyloarthropathypatients.[67] They found that the response to treatment is independent of the induction ofANA production and anti-dsDNA autoantibody variations regardless of the rheumatismand the anti-TNFαtreatment prescribed.Another study conducted in human TNFαtransgenic mice showed that in a strictly TNFαdriven model of RA the number of CD3+CD25+FoxP3+ Treg cells is initially lower than inwild-type counterparts, but gets elevated during the course of the disease. This populationof regulatory T cells is attenuated in its suppressor activity, which can be restored witheither passive (infliximab treatment) or active (TNF-K immunization) TNFαblockingapproaches. Moreover, the differentiation of a CD62L-regulatory T cell population is induced. [68]

Blockade of IL-6:

IL-6 is a widely expressed pleiotropic cytokine, best known as main mediator of fever and acute phase reactions alongside IL-1 and TNFα. In hepatocytes it strongly induces production of acute phase proteins e.g. C-reactive protein, mannose-binding lectin, or serum amyloid protein A, and it also causes immobilization of neutrophil granulocytes from the bone marrow. Besides supporting B cell differentiation into antibody plasma cells, it has been shown to be essential in Th17 cell differentiation as well. The IL-6R consists of two chains, the 80-kDa IL-6-binding subunit and the 130-kDa membrane glycoprotein gp130 thatis responsible for signal transduction.[69] The expression of membrane bound IL6R is restricted to only few cell types including macrophages, neutrophils, some T-cell subpopulations and hepatocytes. On the other hand, gp130 is ubiquitously expressed. IL-6R is either shed from the cell surface by matrix metalloproteases or in human, expressed as a result of alternative splicing. Association of the IL-6/sIL-6R complex to gp130 mediatesagonistic signaling events (trans-signaling).[70]

Excessive levels of the IL-6/sIL-6R complex can be detected in the synovial fluid of many RA patients, which could highly contribute to osteoclast-like cell formation and therefore, joint destruction.[71] Also, IL-6 production of synovial fibroblasts induces excess production of vascular endothelial growth factor (VEGF) resulting in enhanced angiogenesis and increased vascular permeability of synovial tissue. Serum IL-6 levels were found to be elevated in other autoimmune conditions e.g. in SLE as well.[72]

Tocilizumab:

It is a humanized IL6R-specific monoclonal antibody that blocks IL-6 mediated signal transduction via the inhibition of ligand-binding to the IL-6Rs. Phase III clinical studies showed a remarkable inhibition of radiological damage of joints. It has been approved as a therapeutic drug for the treatment of RA and in Japan for Castelman's disease and systemic juvenile idiopathic arthritis. Tocilizumab is a potential candidate drug for the therapy of several other disorders including SLE, Crohn's disease or multiple sclerosis.[73]

Table 3: List of FDA approved mAbsfor autoimmune disease

Monoclonal antibodies	Type	Target molecules	Auto immune diseases
Adalimumab(Humira)	Human	TNF α	RA, Psoriatic arthritis, Ankylosing spondylitis
Belimumab(Benlysta)	Human	BAFF	SLE
Certolizumab(Cimzia)	Humanized	TNF α	RA, Crohn's disease
Epratuzumab	Humanized	CD22	SLE
Infliximab(Remicade)	Chimeric	TNF α	Crohn's disease, Psoriasis
Natalizumab(tysabri)	Humanized	α Integrin	Multiple Sclerosis, Crohn's disease
Rituximab(Rituxan)	Chimeric	CD20	RA
Toclizumab(Acetemab)	Humanized	IL-6R	RA, Castelman's disease

Inhibition of the IL-1 mediated responses with a recombinant IL-1R antagonist Like TNFα or IL-6, IL-1α and β also induce a wide spectrum of biological responses that contribute to fight infections: these include the production of acute phase proteins, raising body temperature (hence the term endogenous pyrogens) or mobilization of neutrophils, thus promoting microbe clearance by phagocytosis. The main source for IL-1α and β are macrophages and epithelial cells, whereas IL-1Ra, a naturally occurring IL-1R antagonist is released also by monocytes and hepatocytes. [74] The IL-1 receptors CD121a and b are expressed on different subsets of lymphocytes, monocytes and macrophages.

Recombinant IL-1a (anakinra) is an approved therapeutic drug for RA that mimics the effects of endogenous IL-1Ra, thus blocking the IL-1 binding site on the receptor without inducing any further signaling events. The treatment with anakinra is well tolerated, with less occurring opportunistic infections than in case of TNF blockage, and it was shown to improve joint swelling, pain and inflammation, although with less efficacy. [75-77]

Induction of alterations in IL-21 mediated cellular responses:

IL-21 is a type I cytokine expressed by activated CD4+ T cells and NKT cells, and induces the differentiation and activation of NK cells, promotes NKT proliferation, enhances the differentiation of Th17 cells and was found to regulate mature B cell responses depending on the type of co stimulation (within a wide range of inducing proliferation to cell death). IL21R-/-mice showed no defects in B cell development, but had severe problems with class-switch to IgG1 and IgG2b, and the down-regulation of the germinal centre reaction. As a consequence they experienced a decrease in the number of plasma cells and an increase in memory B cells.[78]

CONCLUSION

The use of mAbs for the therapy of cancer is one of the great success stories of the past decade. This success builds on a long history of scientific investigation that aimed to understand the complexities of antibody serology, target selection, antibody–receptor function and immune regulation of tumour growth. Since the development of the hybridoma technique, several monoclonal antibodies have been approved for the treatment of autoimmune diseases. Immunogenicity of murine sequences caused initial complications, which could be attenuated and finally overcome by the production of chimeric and humanized antibodies and with the generation of transgenic mouse strains for human Ig-sequences. One of the crucial steps by the design of amonoclonal antibody for therapeutic applications is the selection of the right target molecule. In autoimmune disorders several options exist: the blockade of the proinflammatory cytokines TNFα, IL-1 or IL-6, the inhibition of T cell-B cell interactions, B cell depletion to reduce autoantibody production and the establishment of ectopic lymphoid structures or the blockade of B cell survival factors.

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