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# Novel Monoclonal Antibodies for Cancer Treatment: A Review

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## ABSTRACT

Since long time there is a search for a most promising therapy such as chemotherapy, radiation therapy and surgery for the treatment and prevention of cancers. Nowadays antibodies are also gaining importance in the treatment of most types of diseases including cancers. Antibodies are found to be important and most promising and target specific therapeutic agents for cancer due to their epitope specific interaction. Monoclonal antibodies are very specific only one type of epitope. Recently, it has become clear that antibodies possess several clinically relevant mechanisms of action. Many clinically useful antibodies can manipulate tumour-related signaling. In addition, antibodies exhibit various immunomodulatory properties and, by directly activating or inhibiting molecules of the immune system, antibodies can promote the induction of antitumour immune responses. These immunomodulatory properties can form the basis for new cancer treatment strategies.

**Keywords:** Antibody, Monoclonal Antibodies, Cancer, Mechanisms of MAb's for Cancer Treatment, FDA Approved monoclonal antibodies.

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# INTRODUCTION

## Antibody

**Antibodies** are complex protein molecules made by the immune system to identify and neutralize foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target. Antibodies belong to a family of globular proteins called **immunoglobulins**.

## The Antibody's antigenic determinants[1]

The Antibody's antigenic determinants are called Isotypes, Allotypes, and Idiotypes which determine the variability in Antibody structure.

- Isotypes are variants present in all members of a species.
- Allotypes are variants caused by intraspecies genetic differences.
- Idiotypes are variants caused by structural heterogeneity in the Antibody V regions.

## Isotypes

Humans express five groups of antibodies, called immunoglobulin (Ig), or antibody, classes. The Five classes of antibodies, designated IgG, IgA, IgM, IgD, and IgE, differ in their physicochemical (charge, size, and solubility) and serologic (in vitro reactions with antigens) properties, and in their behavior as antigens.

## Structure of Antibodies

The structure of an antibody is related to its function. The chemical structure of antibodies explains three functions of antibodies: (1) binding versatility, (2) binding specificity, and (3) biological activity.[1]

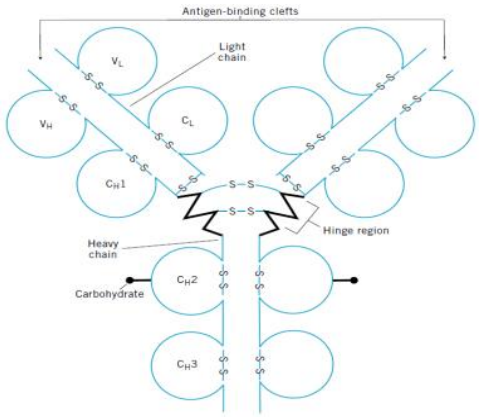


**Figure.1 Schematic representation of IgG domains**

Areas of variability and constancy divided into segments of 110 amino acid residues, within an IgG molecule (and for all antibodies) are known as domains. The IgG molecule has a V and a C domain for each light chain and one V and three C domains for each heavy chain as shown in figure1.[1]

Immunoglobulins consist of two light and two heavy chains composed of different domains. The Fab domain serves as the antigen-binding site; it is made of heavy and light variable chains. The complementarity determining regions of the variable chains define the binding site, the structure which is complementary to the epitope on the antigen that can be bound by the antibody. Antibodies achieve diversity due to variations in the amino acid sequences of the complementarity determining regions. The Fc domain structure determines the effector functions of antibodies. Fc domains are necessary for interactions with effector cells or activation of the complement cascade and the different isotypes of immunoglobulins are defined by the structures of immunoglobulin Fc domains. Human IgG1 can in particular trigger the classical complement cascade after binding to cell surfaces. The same isotype is most efficient in promoting antibody-dependent cellular cytotoxity which can be mediated by various leucocytes possessing the appropriate Fc receptors, and this mechanism is a potent mediator of lysis of cells bound by the mAb.[2,3]

**Monoclonal antibodies (mAb)**

Monoclonal antibodies (mAb) are antibodies that are identical because they were produced by one type of immune cell (B cell), all clones of a single parent cell. Monoclonal antibodies have monovalent affinity. That is, they bind to the same epitope/site.

**History**

Georges Kohler, Cesar Milstein, and NielsKaj Jerne who shared the Nobel Prize in Physiology in 1975 and in Medicine in 1984 for the discovery hybridoma technology.

Porter and Edelman shared the 1972 Nobel Prize in Medicine for their structural studies of antibodies.

Catumaxomab was awarded the Galen of Pergamon Prize, which recognizes pharmacological research for developing new and innovative drugs and diagnostics, in the specialist care category in 2010. The prize, which is awarded annually by Springer Medicine to honor excellence in pharmacological research in Germany, was founded in France in 1970.[1]

**Antibodies[4]**

**Table1. Difference between Polyclonal and Monoclonal antibodies.**

| Polyclonal | Monoclonal |
|---|---|
| Derived from different B Lymphocytes cell lines. | Derived from a single B cell clone. |
| Have variation in reproducibility and specificity. | mAb offer excellent reproducibility and specificity. |
| NOT Powerful tools for clinical diagnostic tests. | Enable the development of secure immunoassay systems. |
| Polyclonal antibodies are the mixture of a large number of different cells. | Monoclonal antibodies are the mixture of single line B cells. |

**Rationale**

- ❖ mAb as efficient carriers for delivery of anti-tumor agents
  - Enhanced vascular permeability of circulating macromolecules for tumor tissue and subsequent accumulation in solid tumors.
  - Normal tissue: blood vessels have intact endothelial layer that permits passage of small molecules but not permits entry of macromolecules (like mAb).
  - Tumor tissue: blood vessels leaky, so small and large molecules have access to malignant tissues.
  - Tumor tissues generally do not have a lymphatic drainage system; therefore, macromolecules are retained and can accumulate in solid tumors.
  - The applications developed at present have been primarily in cancer chemotherapy, where the greatest need arises for site-specific drug delivery.

**Types of mAb's designed[5]**

The four types of mAb's are designed dependent upon their source for therapeutic use

1) Murine mAb's
2) Chimeric mAb's
3) Humanized mAb's
4) Human mAb's

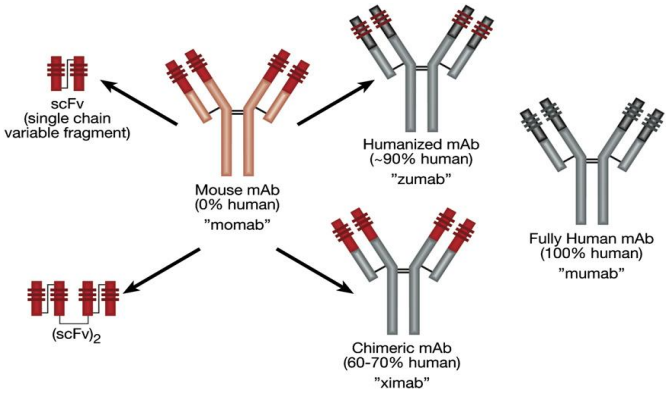


**Figure.2 Various types of Monoclonal antibodies**

**Murine mAb's**

- ❖ Rodent mAb's with excellent affinities and specificities generated using conventional hybridoma technology. Whole of the antibody is of murine origin.
- ❖ Major problems associated with murine antibodies include
  - Reduced stimulation of cytotoxicity.
  - Formation of complexes after repeated administration.

- Allergic reactions.
- Anaphylactic shock.

**Chimeric mAb's**

- ❖ Chimers combine the human constant regions with the intact rodent variable regions. Affinity and specificity unchanged.
- ❖ Antibodies are approximately 65% human.
- ❖ This reduces immunogenicity and thus increases serum half-life.

**Humanized mAb's**

- ❖ Humanized antibodies are produced by grafting murine hypervariable amino acid domains into human antibodies.
- ❖ This results in a molecule of approximately 90% human origin.

**Human mAb's**

Human monoclonal antibodies are produced by transferring human immunoglobulin genes into the murine genome, after which the transgenic mouse is vaccinated against the desired antigen, leading to the production of monoclonal antibodies.

**Cancer and Angiogenesis[6]**

Cancer has become the leading cause of death worldwide. The development of cancer is a multistep process that requires several alterations in the genome of a single cell that give it a growth advantage. The cell must also inactivate control mechanisms and tumour suppressor genes. In addition to these protective mechanisms a tumour cell must overcome other barriers: A solid tumour must be able to induce the growth of new blood vessels (angiogenesis). To be able to metastase to distant organs, the tumour needs to break through the extra cellular matrix surrounding it, move to the site of metastasis and colonialize it in order to survive. In addition, the colonialized cells must endenger angiogenesis at the target tissue[7].

Solid tumour mass cannot persist without a supply of oxygen and nutrients from blood vessels. Therefore the maximum size a tumour can grow without a blood supply is 100-200μm from a vessel. Blood vessels also transport metabolic waste products out of tumours[8]. Blood vessels, as well as lymphatic vessels, are also the route that tumour cells use for metastasis. The patterning of blood vessels within a tumour is often chaotic. The vessels are disorganized and dilated, have excessive branching and shunts and contains incomplete smooth muscle cell (SMC) coverage. Many tumour cells are also in direct contact with the blood vasculature which also advance metastasis[9].

Normally in adults, angiogenesis is minimal and takes place only in conditions such as wound

healing and female reproductive cycle. It is thought that the balance between pro-angiogenic and antiangiogenic factors and proteins define whether angiogenesis occurs or not. This is named as "angiogenic switch" which is thought to be "on" when angiogenesis occurs[10].

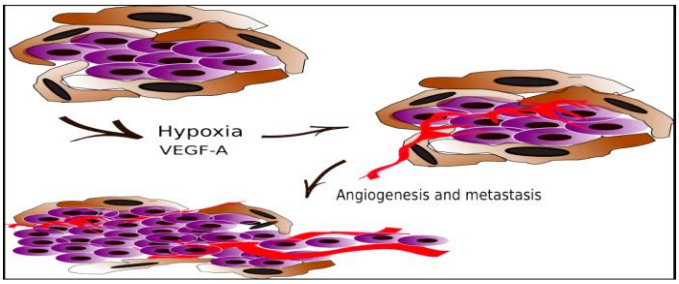


**Figure.3 Illustration of Hypoxia that leads to malignant tumour angiogenesis resulting in metastasis.**

The proteins that function in normal development but are quiescent at adulthood are thus turned on at tumour angiogenesis. These factors include the VEGF/PDGF (Vascular Endothelial Growth Factor/Placenta Derived Growth Factor) family described below, angiopoietins, that are important in adult vascular remodeling as well as factors that make space for growing blood vessels, such as MMPs (Matrix Metalloproteinases) and collagenases[11]. New blood vessels are formed by endothelial cells but also other cell types take part in vessel maturation. Also macrophages and smooth muscle cells (SMC) contribute to angiogenesis by secreting angiogenic factors as well as SMC being part of the newly formed vessels[12].

**Chemotherapy**

Shortcomings:

- Nature of cytotoxin.
- Agents lack in vivo selectivity.
- The mechanism of anti-proliferation on cells cycle, rather than specific toxicity directed towards particular cancer cell.
- Host toxicity: treatment discontinued, most of them had bad side-effects, such as no appetites, omit, and lose hair.
- Side effects of Chemotherapy[13]

**Table 2. Side effects of Chemotherapy**

| **Immediate (hours - days)** | **Early (days - weeks)** | **Delayed (weeks- months)** | **Late (months - years)** |
|---|---|---|---|
| Extravasation | Bone marrow | Cardiotoxicity | Second Cancer |
| Emesis | Mucositis | Lung fibrosis | Encephalopathy |
| Hypersensitivity | Alopecia | Periph. Neuropathy | Sterility |
| Tumour lysis | Cystitis | Hepatotoxicity, Nephrotoxicity | Teratogenicity |

**Monoclonal antibodies for cancer treatment[14-16]**

Three mechanisms that could be responsible for the cancer treatment. Monoclonal antibodies may

A. Trigger the immune system to attack cancer cells
B. Stop cancer cells from taking up proteins
C. Carry cancer drugs or radiation to cancer cells

**Trigger the immune system[17]**

Some monoclonal antibodies trigger the immune system to attack and kill cancer cells. Although cancer cells are abnormal, they develop from normal cells so they can be difficult for the immune system to spot. Some monoclonal antibodies simply attach themselves to cancer cells, making them easier for the cells of the immune system to find them. These include

- Rituximab (Mabthera) for non-Hodgkin's lymphoma (NHL) and some types of leukemia
- Alemtuzumab (MabCampath) for chronic lymphocytic leukemia (CLL)

**Stop cancer cells from taking up proteins[17]**

Some monoclonal antibodies work by seeking out cancer cells that have too many growth factor receptors. The mAb's then block the receptors so the cancer cell can't receive the signal to grow. This type of mAb's includes.

- Trastuzumab (Herceptin) for breast cancer and stomach cancer.
- Bevacizumab (Avastin) for advanced bowel cancer, breast cancer and some other cancers.
- Cetuximab (Erbitux) for advanced bowel cancer or in trials for other cancers.
- Panitumumab (Vectibix) for advanced bowel cancer.

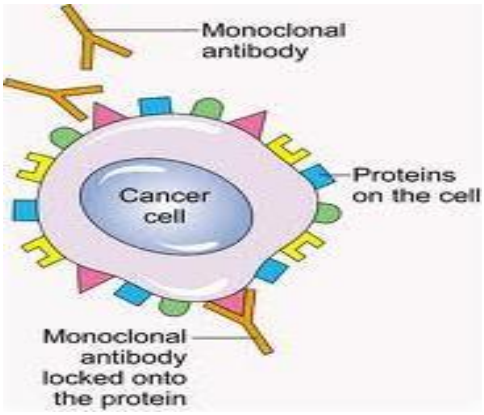


**Figure.3 Depiction of action of mAb to stop cancer cells from taking up proteins.**

**Carry anti-cancer drugs or radiation to cancer cells[18]**

Some monoclonal antibodies have drugs or radiation attached to them. The mAb finds the cancer

cells and delivers the drug or radiation directly to them. These are called conjugated mAb's. mAb's that have a radioactive substance attached. They include

- IbritumomAb (Zevalin) – for non-Hodgkin's lymphoma (NHL) and some other cancers.
- TositumomAb (Bexxar) – for non-Hodgkin's lymphoma.

MAb's that have a drug attached are still in clinical trials. They includes

- Gemtuzumabozogamicin (Mylotarg) – for acute leukemia.
- ADEPT – for bowel cancer.

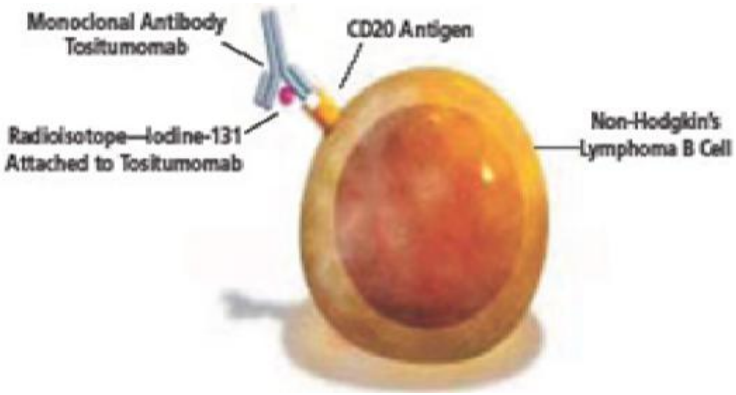


**Figure.4 Depiction of action of mAb to carry anti-cancer drugs or radiation to cancer cells.**

**Antibody-drug conjugates[14,15,19] (ADC's):**

- ADC's are a unique combination of a precise and targeted monoclonal antibody, a stable linker, and a potent cytotoxic and are designed to deliver potent anticancer agents to tumors in a targeted manner to limit systemic exposure.

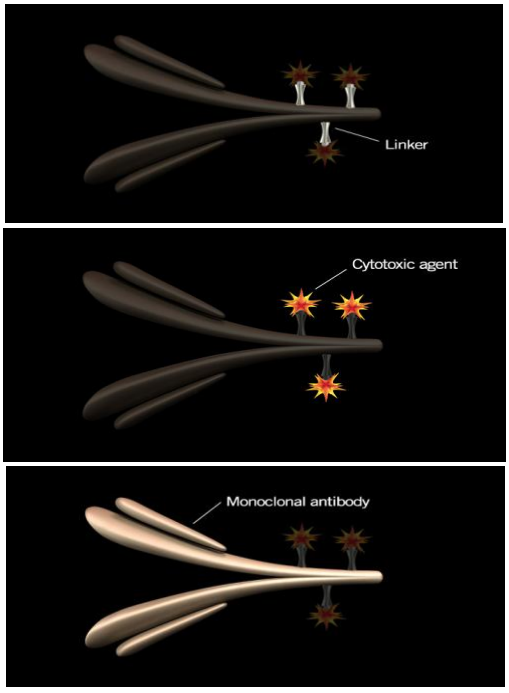


**Figure.5 Depiction of Antibody-Drug Conjugates**

- The three basic parts of ADC are
  - Monoclonal antibody
  - Cytotoxic agent
  - Linker

**Table3. FDA approved Antibody-Drug Conjugates and selected others undergoing clinical development for cancer therapy[20]**

| Generic name | Trade name | Other manipulations | Clinical status | Indication |
|---|---|---|---|---|
| Gemtuzumab ozogamicin | Mylotag® | Humanized | Approved 2000 Withdrawn 2010 | CD33+AML |
| Brentuximab vedotin | Adcentris™ | Chimeric | Approved 2011 | HL |
| Trastuzumab emtansine | MCC-DM1/ T-DM1 | Humanized | Phase III | HER-2+ MBC |
| Inotuzumab ozogamicin | CMC-544 | Humanized | Phase III Phase II | NHL DLBCL |
| Lorvotuzumab mertansine | IMGN901 | Humanized | Orphan Drug 2010; Phase II | SMLC, OC, MM |
| ---------- | SAR3419 | Humanized | Phase I | NHL |

**Legend:** AML – Acute myologenous leukemia; HL – Hodgkin's lymphoma; NHL – Non Hodglin's Lymphoma, MM – Multiple Myeloma; DLBLC – Diffuse large B cell lymphoma; OC – Ovarian cancer; MBC – Metastatic breast cancer.

**Targeting cancer cells by nanoparticles surface modified with monoclonal antibody[19]**

Targeting drugs to their sites of action is still a major challenge in pharmaceutical research. Polylactic-co-glycolic acid (PLGA) immuno-nanoparticles used for targeting invasive epithelial breast tumour cells. Monoclonal antibody (mAb) was used as a homing ligand and has attached to the nanoparticle surface either covalently or non-covalently. These nanoparticles were more likely to be bound to the targeted cells than non-coated nanoparticles. Both types of nanoparticles entered the target MCF-10A neoT cells in mono-culture. In co-culture of MCF-10A neoT and Caco-2 cells immuno-nanoparticles were localized solely to MCF-10A neo T cells, whereas non-coated nanoparticles were distributed randomly. Immunonanoparticles entered only MCF-10A neoT cells, while non-coated nanoparticles were taken up by both cell types, indicating specific targeting of the immuno-nanoparticles. In conclusion, we demonstrate a method by which mAb's can be bound to nanoparticles without detriment to their targeting ability. Furthermore, the results show the effectiveness of the new carrier system for targeted delivery of small or large active substances into cells or tissues of interest.

**Table4. List of FDA-Approved Monoclonal Antibodies for Therapeutic Use[20-23]**

| Generic name | Trade name | Antibody Format | Approved Indication | FDA Approval | EMEA Approval |
|---|---|---|---|---|---|
| Rituximab | Mabthera | Chimeric, $IgG_1$ | CD-20 positive, B-cell non Hodgkin's lymphoma | 26/11/97 | 02/06/98 |
| Trastuzumab | Herceptin | Humanized, $IgG_1$ | Metastatic breast cancer | 25/09/98 | 28/08/00 |
| Gemtuzumab | Mylotarg | Humanized, $IgG_4$ | CD33-positive acute myeloid leukemia | 17/05/00 | NA |
| Alemtuzumab | Mabcampath | Humanized, $IgG_1$ | B-cell chronic lymphocytic leukemia | 07/05/01 | 06/07/01 |
| Ibritomomab | Zevalin $^{90}Y$ | Mouse, $IgG_1$ | B-cell non Hodgkin's lymphoma | 19/02/02 | 16/01/04 |
| Tositumomab | Bexxar $^{131}I$ | Murine, $IgG_2a$ | CD-20 positive, B-cell non Hodgkin's lymphoma | 27/06/03 | NA |
| Cetuximab | Erbitux | Chimeric, $IgG_1$ | Metastatic colorectal and head and neck carcinoma | 12/02/04 | 29/06/04 |
| BevacizumAb | Avastin | Humanized, $IgG_1$ | Metastatic colorectal and non small-cell lung carcinoma | 26/02/04 | 12/01/05 |
| Panitumumab | Vectibix | Human, $IgG_2$ | Metastatic colorectal carcinoma | 27/09/06 | 19/12/07 |
| Ofatumumab | Arzerra | Human, $IgG_1$ | Refractory Chronic Lymphocytic leukemia | 26/10/09 | ------ |
| Ipilimumab | Yervoy | Human, $IgG_1$ | metastatic melanoma | 25/03/11 | ------ |
| Pertuzumab | Perjeta | Humanized, $IgG_1$ | Breast cancer | 08/06/12 | ------ |

**Rituximab: Anti CD-20[17,24]**

Rituximab (Rituxan) is a humanized anti-CD20 monoclonal antibody that was the first mAb to be approved by the FDA for use in human malignancy

- Acts by causing B cell apoptosis
- Used in B cell lymphomas
- Immune thrombocytopenia
- Rheumatoid arthritis

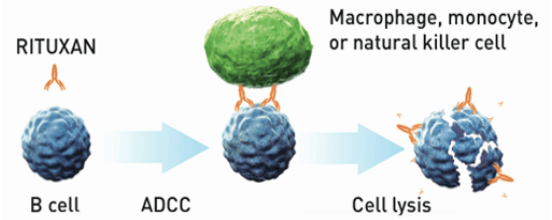


**Figure.6 Action of Rituximab (Rituxan) via antibody dependent cell-mediated cytotoxicity mechanism.**

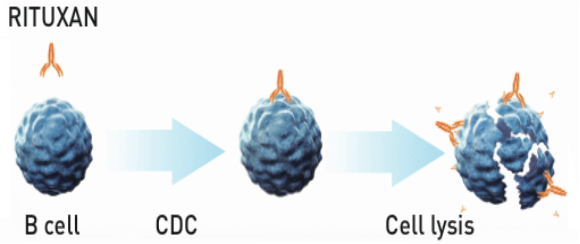


**Figure.7 Action of Rituximab (Rituxan) via Complement dependent cell lysis mechanism**

**Bevacizumab[24]**

- ❖ Bevacizumab (trade name Avastin), is an angiogenesis inhibitor drug.
- ❖ Bevacizumab was approved by the U.S.FDA for certain cancers.
- Colorectal cancer(2004)*
- Lung cancer(2006)*
- Breast cancer(2010)*
- Renal cancers(2009)*
- Brain cancers(2009)*
- Investigational trials on gastric cancer, ovarian cancer, pancreatic cancer, Osteosarcoma.

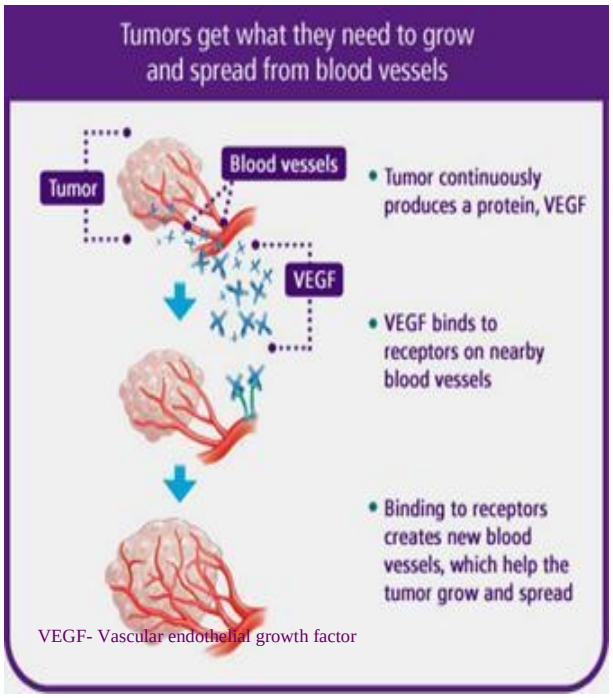


**Figure.8 Physiological growth of Cancer cells via angiogenesis.**

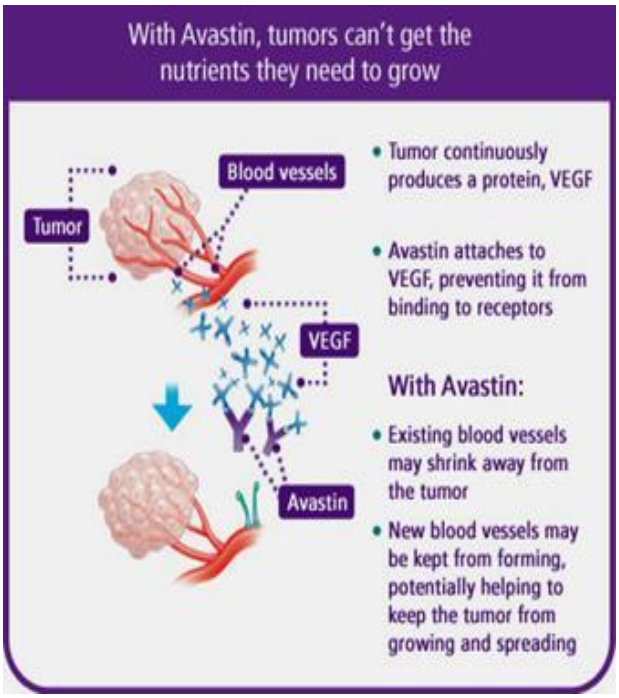


**Figure.9 Action of Bevacizumab (Avastin) over cancer cells via prevention of angiogenesis**

**Trastuzumab[24]**

- Trastuzumab (trade name Herceptin) is a humanized monoclonal antibody that interferes with the HER2 receptor.

- Its main use to treat certain breast cancers.
- The HER2 receptors are proteins that are embedded in the cell membrane and communicate molecular signals from outside the cell (molecules called EGFs) to inside the cell, and stimulate cell proliferation, HER2 is over-expressed in some breast cancer.

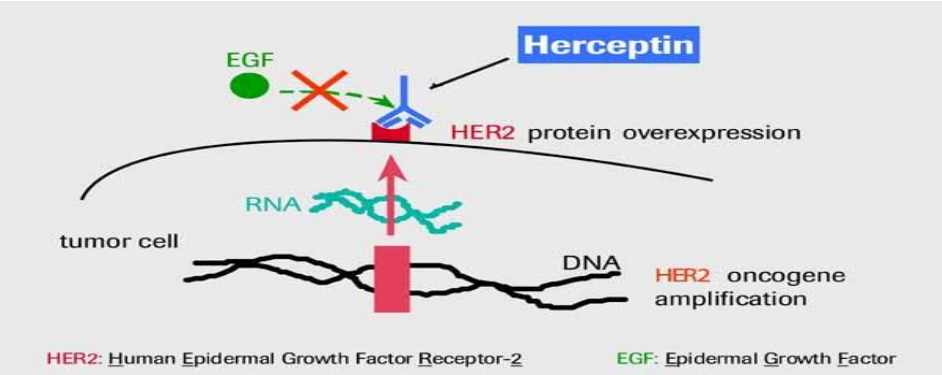


**Figure.5 Mechanism of action Trastuzumab (Hercepin)**

**Panitumumab[24]**

Panitumumab (Vectibix), formerly ABX-EGF, is a fully human monoclonal antibody specific to the epidermal growth factor receptor (also known as EGF receptor, EGFR, ErbB-1 and HER1 in humans).

It was approved by the U.S. Food and Drug Administration (FDA) for the first time in September 2006, for "the treatment of EGFR-expressing metastatic colorectal cancer with disease progression" despite prior treatment.[19] Panitumumab was approved by the European Medicines Agency (EMEA) in 2007, and by Health Canada in 2008 for "the treatment of refractory EGFR-expressing metastatic colorectal cancer in patients with non-mutated (wild-type) KRAS".

EGFR is a transmembrane protein. Panitumumab works by binding to the extracellular domain of the EGFR preventing its activation. This results in halting of the cascade of intracellular signals dependent on this receptor.[5]

**Cetuximab[24]**

Cetuximab (Erbitux) is a chimeric (mouse/human) monoclonal antibody, an epidermal growth factor receptor (EGFR) inhibitor, given by intravenous infusion for treatment of metastatic colorectal cancer and head and neck cancer.

When growth factors bind to their receptors on the surface of the cell, the receptors give a signal that causes cells to divide. Some cancers are caused by mutated receptors that give a signal to divide even without growth factor. That causes the cells to divide uncontrollably. Cetuximab binds to such receptors and turns off that signal.

The EGFR sends a signal down a pathway that includes another protein; KRAS (also spelled K-ras). In some cancers, the EGFR is mutated, and is present to a larger or smaller degree. In these cancers, the KRAS protein may either be "wild type" or mutated. If mutated, KRAS sends a signal to divide uncontrollably, even if EGFR has been blocked by Cetuximab.

Therefore, before Cetuximab is used, the standard of care is that the KRAS gene in the cancer cells is tested for mutation.

A genetic test for the KRAS mutation was approved by the FDA as an indication for Erbitux treatment of colon cancer in July, 2009 (this also applied to the EGFR antibody Panitumumab).[25] This was the first genetic test to guide treatment of cancer.[26]

**Catumaxomab (Removab)[2]**

The trifunctional antibody (trAb) Catumaxomab is characterized by a unique ability to bind three different cell types: tumor cells; T-cells; and accessory cells. It binds to epithe-lial cell adhesion molecule (EpCAM) on tumor cells, the CD3 antigen on T-cells, and to type I, IIa, and III Fcγ receptors (FcγRs) on accessory cells (e.g. natural killer cells, den-dritic cells, and macrophages). Catumaxomab exerts its anti-tumor effects via T-cell-mediated lysis, antibody-dependent, cell-mediated cytotoxicity, and phagocytosis via activation of FcγR-positive accessory cells. Catumaxomab represents a self-supporting system, as no additional immune cell activation is required for tumor eradication.

Catumaxomab was approved for the treatment of Malignant Ascites in patients with EpCAM-positive carcinomas where standard therapy is not available or no longer feasible in the European Union in April 2009. It is the first trAb and the first drug in the world approved specifically for the treatment of Malignant Ascites.

**Future Scope**

- It is possible to create a mAb specific to almost any extracellular/ cell surface target, and thus a large amount of research and development is currently being undergone to create monoclonals for numerous serious diseases (such as rheumatoid arthritis, multiple sclerosis and most importantly to different types of cancers).
- Researchers hope to define the optimal combinations of the use of mAb with conventional chemotherapeutic agents and with radiation therapy.

## CONCLUSIONS

The clinical studies with mAb identified several areas that promise to make significant contributions to the management of cancer. The promising results of the mAb discussed here

represent the future of mAb's in cancer treatment. The novel mAb's are under clinical trials. Such studies are being done in most clinical disciplines.

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