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# MONOCLONAL ANTIBODIES USED IN THE TREATMENT OF HAEMATOLOGICAL MALIGNANCE AND SOLID TUMOUR

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## ABSTRACT

Monoclonal antibody (mAbs) are a widespread and necessary tool for biomedical science, In the haematological cancer field, since rituximab became the first mAb approved by the Food and Drug Administration for the treatment of B-cell malignancies, a number of effective mAbs targeting lineage-specific antigens (LSAs) have been successfully developed. Alongside surgery, Radiation and Chemotherapy, Monoclonal antibody shows or possesses diverse set of clinically relevant mechanism of action and in addition, antibodies can directly target tumour cells, while simultaneously promoting the induction of long-lasting antitumor immune response.

The multi-action properties of antibodies as a therapeutics platform have laid in development of a new cancer treatment strategies that will have major impact on cancer care and also they are highly specific for a particular antigen. This characteristic feature of the molecule makes them ideal tool for many application including diagnosis and therapy and autoimmune disease control with monoclonal antibodies is highly successful.

**KEYWORDS:** Monoclonal antibody, Cancer tumour, haematological cancer, Cancer treatment, Immunotherapy, Autoimmune disease.

## INTRODUCTION

Nobel laureate Paul Ehrlich proposed a concept of magic bullet in 1906, Kohler and Milestein discovered hybridoma technology in 1975 and Greq winter pioneered the technique to humanized monoclonal antibodies in 1988 monoclonal antibodies based treatment of

cancer has been established as one of the most successful therapeutic strategy for both hematologic malignancies and solid tumours in the last 20 years.

**Hematologic malignancies:** The many distinct type of Blood cells, such as red blood cells for carrying oxygen, white blood cells, and platelets for wound clotting, arises from Hematopoietic stem and progenitor cells in the bone marrow, Hematologic Malignancies are cancers that begin in these cells, There are three major group,

1. Leukemia
2. Lymphoma
3. Plasma cell neoplasm

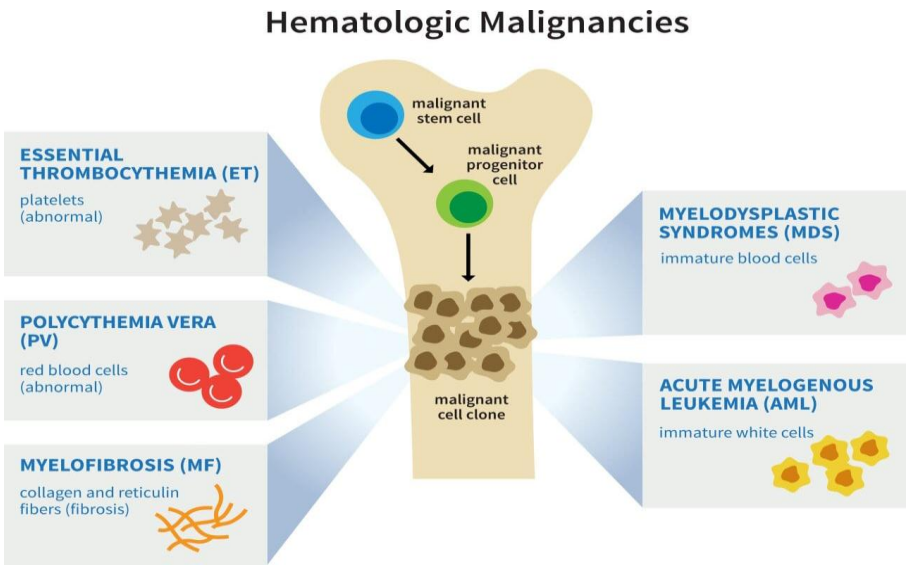


**Fig : Hematologic Malignancies.**

**Solid tumour:** An abnormal mass of tissue that usually does not contains cysts or liquid area solid tumours may be benign or solid tumors are malignant. different types of solid tumors are named for the type of cells that form them, examples, Sarcomas, Carcinomas, Lymphomas and Leukemia.

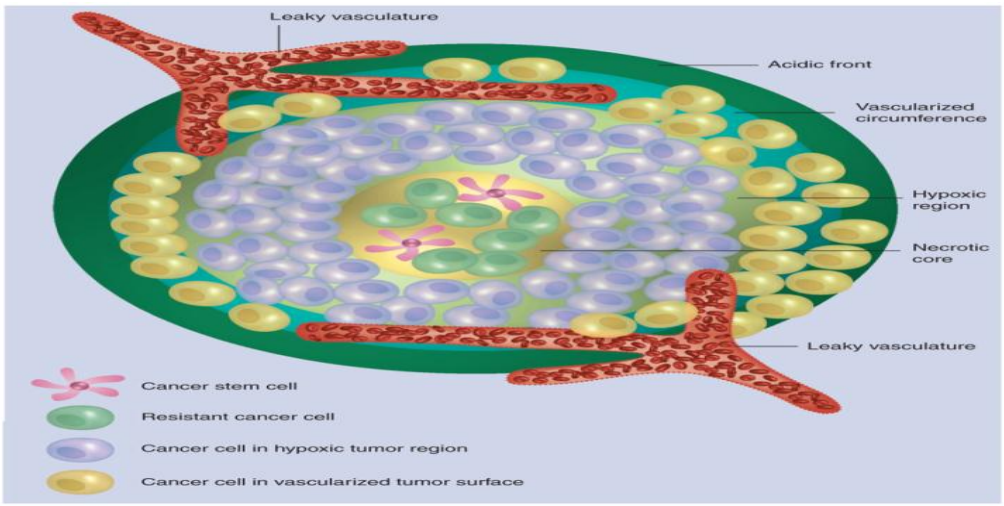


**Fig: Solid tumor.**

**Type of monoclonal antibodies**

1. **Block signals telling cancer cells to divide:** Cancer cells often make large amount of molecules called Growth factor receptors these sit on the cell surface and send signals to help the cell survive and divide. Some monoclonal antibodies stop growth factor from working property, either by blocking the signals or the receptor itself. So the cancer cell no longer receives the signals which it needs. Result in cancer cell doesn't divide.

2. **Carry cancer drug or radiation to cancer cell:** Monoclonal antibodies which carry radiotherapy or cancer drug. can be radiolabel Mab's, seek out cancer cell protein. So that the Mab's attaches to protein and radiotherapy is delivered to the cancer cell, result in the cancer cell dies.

3. **Others monoclonal antibodies**

**Flagging cancer cells:** some immune system cell depends on antibodies to locate the target of an attack. Cancer cells that are coated in monoclonal antibodies. May be more easily detected and targeted for destruction.

**Triggering cell-membrane destruction:** Some monoclonal antibodies can trigger an immune system response that can destroy the outer wall of cancer cell.

**Preventing blood vessels growth:** In order for a cancerous tumor to grow and survive, it need blood supply, some monoclonal antibody drug block protein cell interaction necessary for the development of new blood vessels.

**Delivering chemotherapy:** Some monoclonal antibodies are attached to a chemotherapeutic drug in order to deliver the treatment directly to the cancer cells while avoiding healthy cells.

**Monoclonal antibodies production**

Monoclonal antibodies production process usually start with generation of Mab's producing cell (Hybridoma) by fusing myeloma cell with desired antibody producing beta cells, these beta cells are typically source from animals, usually mice.

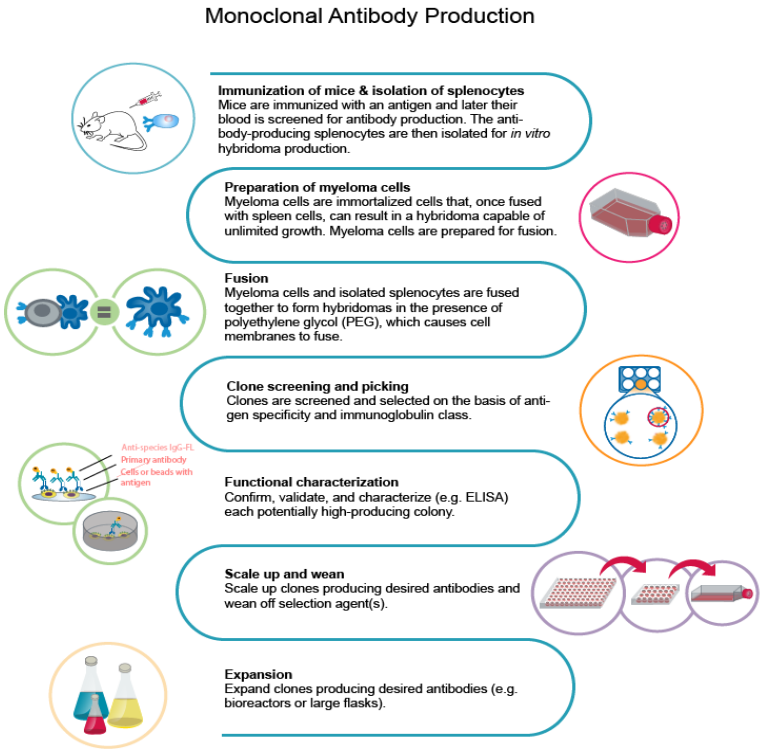


**Fig: process for monoclonal antibody production.**

1. Firstly mice are immunized with antigen and later their blood is screened for antibody production. The antibody producing beta cells are then isolated for in vitro Hybridoma production.
2. Now preparation of myeloma cells that once fused with spleen cells can result in Hybridoma capable of unlimited growth. Now ready for fusion with beta cells from Hybridoma in the presences of polyethylene glycol.
3. Cloning.
4. Screening and Picking.
5. The scale up clones produces desired antibodies.
6. Lastly expands the clones producing desired antibodies.

**Table 1**: **FDA-approved mAbs for use in oncology.**

| Name | Marketed by | Class | Target | First approved indication | Reported mechanisms of action | Approval year |
|---|---|---|---|---|---|---|
| Rituximab (Rituxan) | Biogen Idec/Genentech | Chimeric IgG1 | CD20 | Non-Hodgkin's Lymphoma | ADCC, CDC, Induction of Apoptosis4 | 1997 |
| Trastuzumab (Herceptin) | Genentech | Humanized IgG1 | HER2 | Breast Cancer | Signal Inhibition, ADCC5 | 1998 |
| Alemtuzumab (Campath) | Sanofi-Aventis | Humanized IgG1 | CD52 | B cell Chronic Lymphocytic Leukemia | CDC, Induction of Apoptosis6 | 2001 |
| Ibritumomab tiuxetan (Zevalin) | Biogen Idec | Murine IgG1 | CD20 | Non-Hodgkin's Lymphoma | Radioisotope Delivery ($^{90}$Y) | 2002 |
| Tositumomab (Bexxar) | GlaxoSmithKline | Murine IgG2a | CD20 | Non-Hodgkin's Lymphoma | Radioisotope Delivery ($^{131}$I), ADCC, CDC, Induction of Apoptosis7 | 2003 |
| Cetuximab (Erbitux) | Bristol-Myers Squibb/Eli Lilly | Chimeric IgG1 | EGFR | Squamous Cell Carcinoma of the Head and Neck | Signal Inhibition, ADCC, CDC8 | 2004 |
| Bevacizumab (Avastin) | Genentech | Humanized IgG1 | VEGF | Colorectal Cancer | Signal Inhibition9 | 2004 |
| Panitumumab (Vectibix) | Amgen | Human IgG2 | EGFR | Colorectal Cancer | Signal Inhibition, ADCC10 | 2006 |
| Ofatumumab (Arzerra) | Genmab/GSK | Human IgG1 | CD20 | Chronic Lymphocytic Leukemia | ADCC, CDC11 | 2009 |
| Denosumab (Xgeva) | Amgen | Human IgG2 | RANKL | Bone Metastases | Signal Inhibition | 2010 |
| Ipilimumab (Yervoy) | Bristol-Myers Squibb | Human IgG1 | CTLA-4 | Metastatic Melanoma | Signal Inhibition12 | 2011 |
| Brentuximab vedotin (Adcetris) | Seattle Genetics | Chimeric IgG1 | CD30 | Hodgkin Lymphoma | ADC | 2011 |
| Pertuzumab (Perjeta) | Genentech | Humanized IgG1 | HER2 | Breast Cancer | Signal Inhibition, ADCC13 | 2012 |
| Trastuzumab emtansine (Kadcyla) | Genentech | Humanized IgG1 | HER2 | Breast Cancer | ADC, Signal Inhibition, ADCC14 | 2013 |

**Mechanism of action of chemotherapeutic monoclonal antibodies**

Chemotherapeutic monoclonal antibodies target cancer cell by binding to cell surface antigen. Cell surface antigen include antigen associated with growth and differentiation, such as cluster of differentiation (CD; e.g., CD20, CD30, CD33, CD52) Carcino-embryonic antigen (CEA), Epidermal growth factor (EGFR), Receptor activator of nuclear factor kappa-B-ligand, 2HER, VEGF, FAP and Extracellular matrix metalloproteinase inducers i.e. EMMPRIN.

**Key characteristics:** In order for monoclonal antibodies to be successful in cancer therapy, a number of key characters must be met.

- **Specificity:** Target antigen must be present on malignant cells only.
- **Density:** The quantity of target antigen expression directly relates to tumor response.
- **Modulation:** Modulating antigen internalize the antibody/ antigen complex once binding has taken place, this is required for toxin conjugated monoclonal antibodies and is less desirable when it occurs rapidly for Unconjugated monoclonal antibodies.
- **Function:** The role of target antigen in cell survival and proliferation is instrumental in cell destruction. Both Unconjugated and conjugated monoclonal antibodies are approved for clinical use in cancer therapy.
- Conjugated monoclonal antibodies carry radio immune conjugate, chemo immune conjugates or immunotoxins to a specific target antigen, they are capable of killing cells and do not require any host immune mechanism, conjugated monoclonal antibodies E.g., Gemtuzumab ozogamicin, Y90 ibritumomab Huxetan, 1131 tositimomab.
- Unconjugated monoclonal antibodies target a specific anti- tumor antigen initiating immunologic response reliant on the host. Immune mechanism to destroy the target cells. E.g. rituximab, trastuzumab, alemtuzumab.

**Pharmacokinetics:** MAB's are administered intravenously, intramuscularly or subcutaneously, oral administration is normal in use, distribution into tissue is slow because of the molecular size of MAB's and Volume of distribution is also slow. MAB's are metabolized to peptides and amino acids in several tissues, by circulating phagocytic cells or by their target antigen-connecting cell. Elimination both linear and non linear elimination. Metabolic drug-drug interactions are rare for MAB's.

**Pharmacodynamic:** MAB's can target soluble or membrane bound and the corresponding downstream effect by effecter function such as ADCC (Antibody dependent cell mediated cytotoxicity) and CDC (Complement dependent cytotoxicity) Depending on mechanism of action of MAB's, type of Pharmacodynamic response impact on cell signaling by blocking receptor.

**Adverse effect:** compared with conventional chemotherapy. The adverse effects of Unconjugated CMAB's are usually mild while conjugated CMAB's severe adverse effect. E.g. bevacizumab target tumor blood vessels growth and cause adverse effect such as hypertension and kidney damage. Above 90% of patient on rituximab therapy experienced infusion related reaction such as cytokine release syndrome and tumor lysis syndrome. I.V. administration of alemtuzumab is associated with lymphoneia, and concomitant immunosupression. Also myelosupression is the main toxicity of 131-I-tositumab and 90Y-ibritumomab tiuxeton 24. other adverse effect common most CMAB's are chills, weakness, headache, nausea, vomiting, diarrhea, hypotension and rashes. The cost to the user in 2012 the calculated per patient cost of treatment of colorectal cancer with CMAB's was US $30 400 in comparison to US $17 500 for the use of conventional chemotherapeutics drug (Oxaliplatin, irinotecan, fluorouracil and leucovorin).

## CONCLUSION

In this review, we have summarized the monoclonal antibodies used for cancer treatment, including mechanism action, production, pharmacokinetics, Pharmacodynamic and adverse effect. Monoclonal antibodies may be considered to be an important class of anti-cancer agent with 14 MAB's in current clinical use, and with many more in development. this drug class, which achieve effects through a variety of mechanism and provides several advantages over the traditional chemotherapeutics agents, including slow rates of elimination, high efficacy, and low target toxicity, based on the promise of agent of development. It is anticipitated that anti-cancer MAB's will continue to grow in importance over the next 5-10 years.

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