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MONOCLONAL ANTIBODIES FOR TARGETING DRUG DELIVERY SYSTEM

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ABSTRACT

Monoclonal antibodies (mAbs) are among the most important therapeutic protein types used to treat a variety of diseases (e.g., oncology, inflammation and autoimmune diseases). One major obstacle to the creation of novel antibodies is the identification of new pharmacological targets, yet monoclonal antibody technologies are still evolving to provide drugs with steadily better safety profiles. There are various prospects for producing subcutaneous formulations of antibodies, for example, to improve patient compliance, reduce costs, and control the lifespan of the drug. Nevertheless, Medication based on monoclonal antibodies has a few limitations that limit its therapeutic use. The major concerns are their short pharmacokinetic characteristics and stability problems during manufacture, transit, and storage that might result in protein aggregation and denaturation. Monoclonal antibodies (mAb) can be coupled to novel surface-functionalized cross-linked nanogels to achieve targeted drug delivery. In biomedical research, disease detection, and cancer and other types of disease treatment, monoclonal antibodies (mAb) are essential tools. A monoclonal antibody is an example of a mediator that can target nanoparticles with precision. Immune cells that produce only one kind of antibody, called monoclonal antibodies, are all clones of a single parent cell. It has a property obtained from myeloma cells, which allows it to continuously divide at the same time. A lung cancer nanoparticle targeted delivery method using a monoclonal antibody as a targeting mediator. Hybridoma technique refers to the production of monoclonal antibodies in artificial media using hybridomas that are selective for spleen and myeloma cells. They develop a hybrid cell that is capable of making several monoclonal antibodies against an antigen. Hybridoma technology is the method used to manufacture monoclonal antibodies. Due to the enormous no. of foreign substance present on the

cancer cell surface , mAb are broadly used to transport nanoparticles which helps to improve therapeutic aiming to the cancerous cells.

KEYWORDS; Monoclonal antibodies, Immunoglobulin's, Hybridoma technology, Glycoprotein.

1. TARGETED DRUG DELIVERY SYSTEM (TDDS)

A pharmaceutical Medicine is transported in the body using various techniques, formulations, technologies, and procedures in order to provide the intended therapeutic effect. This process is known as drug delivery. It includes methods for giving medication to both humans and animals to achieve therapeutic efficacy. Current advancements in DDSs have mostly accurate form on smart drug delivery, which focuses on administering drugs with the greatest level of safety and efficacy at the right time, dose, and place. And present time novel drug delivery system attracted with the TDDS for the preparation of targeted drug use in novel drug delivery system. With targeted, controlled, and sustained distribution, these systems improve the therapeutic efficacy of novel and old medications while satisfying realistic and necessary drug demand. Drug delivery systems show the total 5 Generation in developing of the generation of the drug delivery system. Targeted drug delivery systems are present in fourth generation. Over the past few decades, there has been interest in the development of sustained or controlled drug delivery systems with the goal of controlling and sustaining drug release, reducing dose frequency, or increasing therapeutic efficacy in contrast to conventional administration. Another possible advancement that may be made with delivery methods based on nanotechnology is targeted delivery to tumours. A controlled drug release is possible using nanoparticle-based drug delivery, giving medications enough time to exert their full therapeutic effect and react to various stimuli like pH, light, heat, or enzymes. Many scientific disciplines, including polymer science, pharmacology, bio conjugate chemistry, and molecular biology, are used in targeted drug delivery techniques so that a therapy can be delivered to a particular region of the body or organ rather than the complete body or organ. TDD aims to manage and regulate the pharmacodynamics, immunogenicity, aspecific toxicity, and bio recognition of medicinal medicines. There are various drug delivery system some of these are illustrated in Fig. 1.

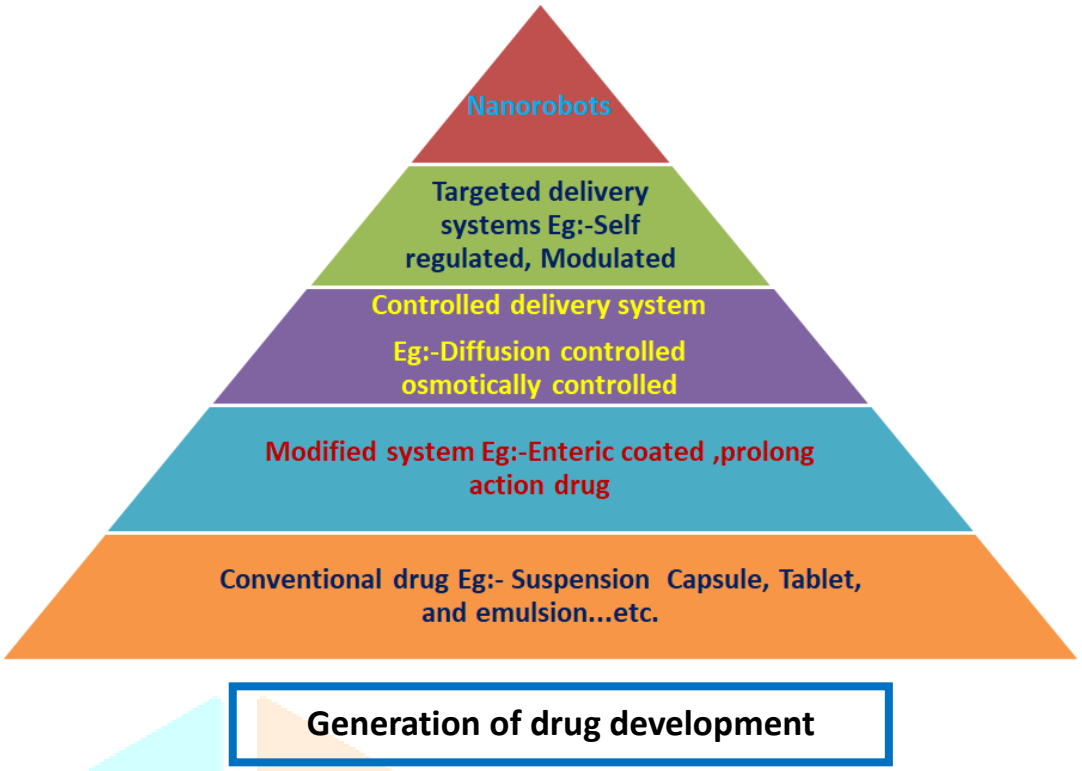

Fig.1

1.1 Importance of Targeted Drug Delivery: - The goal of a secure targeted medication distribution device is to safely extend, localize, target, and interact with the diseased tissue. The conventional drug delivery technique includes the drug being absorbed through a biological membrane, whereas the targeted release system distributes the medication in dose form. Targeted drug distribution is essential for increasing therapeutic effectiveness, but it also serves to reduce the toxicity brought on by high doses and a narrow therapeutic window.

1.2 Principles of Targeted Drug Delivery Systems: - A high dosage concentration of the medicine is administered to the desired area while a low dose concentration is administered to the unwanted area. This is the fundamental idea behind drug targeting. This tactic helps to maximise the drug's therapeutic benefits while reducing its adverse effects as a result of interactions between multiple targets, greater doses, and non-target concentrations. Drug targeting consists of coordinated drug use, a specific geographic target, and a pharmacological delivery system. The target is the specific organ, cell, or collection of cells that the medication will engage with when they are in an acute or chronic condition and need therapy. The effective transport of the loaded medication to the targeted areas depends on the carrier, a molecule or system that has been carefully developed.

1.3 LEVELS OFDRUG TARGETING

Drug targeting makes it easier for a medicine to go to the right place where it will have the intended pharmacological effect for the therapeutic need. It is simple to choose the ideal targeting moiety, ligand, or carrier system if the amount of targeting is clearly understood. Moreover, tailored delivery ensures that only a little amount of medicine enters non-target organs and tissues, resulting in a reliable and secure drug

delivery system. Generally speaking, there are three levels for medication targeting: first, second, and third, which are assigned to organs, cells, and organelles, respectively. The targeting at the molecular level is given a fourth level. Therefore, Targeted drug delivery system is classified as-

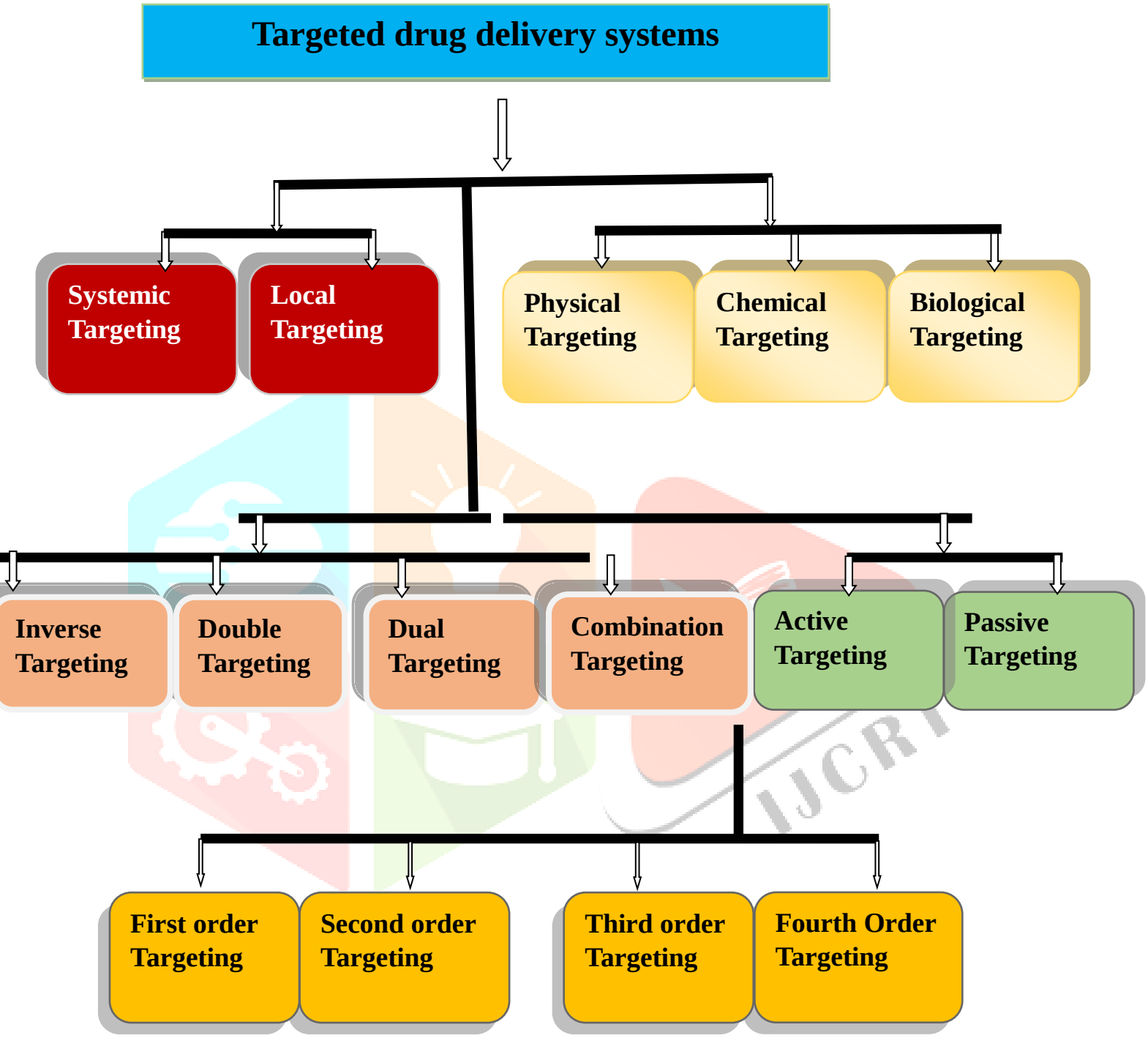

Fig. 2

1.4 METHODS OF DRUG TARGETING

1.4.1 Passive Targeting: - The therapeutic agent is incorporated into a macromolecule or nanoparticle that passively goes to the target area to achieve passive targeting. The effectiveness of the medicine in passive targeting is closely correlated with the length of circulation. By covering the nanoparticle with a coating, this is accomplished. This may be accomplished by a number of chemicals, polyethylene glycol being one of them (PEG). PEG is used to make the nanoparticle's which is have hydrophilic surface, which enables water molecules to engage with the O_2 molecules on PEG through H_2 bonding. A layer of hydration forms around the nanoparticle as a result of this interaction, making the material antiphagocytic. The particles' hydrophobic interactions with the reticuloendothelial system (RES) give them this feature, which allows the drug-loaded nanoparticle to circulate for a longer duration. In order complete this passive targeting mechanism. And nanoparticles are having the 10 to 100 size in nm. Drug delivery with passive targeting seeks to influence systemic circulation. In this approach, drug targeting results from the body's biochemical response to the physical characteristics of the drug [3].

1.4.2 Active Targeting: - Targeted nanoparticles will be better absorbed into the tumour microenvironment through active transport pathways than through more passive ones like the EPR effect, according to predictions. In this kind of active targeting, it has been proven successful to use transferrin as the cell-specific receptor. To precisely target tumour cells that had membrane-based transferrin-receptor driven endocytosis pathways, transferrin was linked to the nanoparticle. Contrary to non-conjugated nanoparticles, it was discovered that this method of targeting increased absorption. The Arginylglycylaspartic acid (RGD) motif is another cell-specific ligand that attaches to integrin V_3. In tumour and activated endothelial cells, this integrin is increased. It has been demonstrated that adding Arginylglycylaspartic acid (RGD) to chemotherapeutic-loaded nanoparticles increases cancer cell absorption both invitro and in-vivo [3].

1.4.3 Systemic Targeting: - Any form of cancer treatment that concentrates on the complete body is referred to as systemic therapy. For instance, chemotherapy, the most popular type of systemic cancer therapy, travels throughout the bloodstream and kills malignant cells throughout the body. Chemotherapy drugs can be delivered in a variety of ways (for E.g.as a tablet, an injection, or an intravenous infusion), but once the drugs reach the bloodstream, they spread out and kill aberrant cells everywhere. Chemotherapy is therefore frequently used to treat malignancies that have progressed from their initial site of development [3]

1.4.4 Local Targeting: -The goal of improving overall survival and quality of life using local targeting technologies is to increase the bioavailability of drugs at the site of disease, restrict delivery to malignant tissues, boost drug solubility, and reduce systemic adverse effects. Depending on how they are managed and how they work, existing systems may be categorised into two categories. The first uses nanomaterials including dendrimers, liposomes, and polymer nanoparticles for systemic administration. [3]

1.4.5 Physical Targeting: - Physical targeting systems, as opposed to those that are specifically targeted at a biological receptor, localise agents to target places based on their size, content, or other characteristics.

1.4.6 Chemical Targeting: - Chemical targeting entails the localisation of substances through the use of prodrugs designed for a particular spot. It is also possible to direct agents to particular areas using enzymes or chemical processes that target a vehicle or cause a regulated release or action of the agent.

1.4.7 Biological Targeting: - Localized agents can target areas via biological targeting by utilising antibodies, peptides, proteins, or other bio molecules that have a specific preference for receptors, sites, or other biological targets. Gene expression can also be limited to particular areas of interest using cells, organs, or other specialised promoters in vector systems. [3, 4]

1.4.8 Inverse Targeting: - Inverse targeting is the process of suppressing the body's natural defensive systems by inhibiting the reticuloendothelial system's normal function in order to reduce passive drug absorption.

1.4.9 Dual Targeting: -Delivery of a carrier molecule with its own therapeutic action is known as dual targeting, and it increases the (synergistic) therapeutic efficacy of the medication.

1.4.10 Double Targeting: -Double targeting combines geographical and temporal approaches, i.e., placement at precise locations and controlled temporal delivery.

1.4.11 Combination Targeting: -Combination targeting is a method of direct approach to a target equipped with carriers, polymers, and homing devices of molecular specificity.

2. VARIOUS VEHICLES THAT ARE USED IN TDDS FOR TARGETING ARE-

2.1 CARRIER BASED TARGETING

2.1.1 Liposome's: - Liposome is tiny vesicles that are intentionally created and range in size from 20 to 10,000 nm. They are made of phospholipids bilayers around them. Many liposome formulations are quickly absorbed by macrophages, and this property can be utilised for either drug delivery to macrophages specifically or passive drug targeting, allowing drug release from these cells into the bloodstream to occur gradually over time. [5]

2.1.2 Nanoparticles: - Biocompatible polymers make up nanoparticles, which can be either soluble or particle-type carriers. Nanoparticles are less capable of carrying drugs than soluble polymers due to their tiny size (0.2–0.5 m). Depending on the physicochemical properties of the drug, drug formulation might take place at the particle surface or in the nucleus. They are promptly distributed to the target site after systemic injection or transportation, and then the phagocytic system's cells take them inside. In addition to being utilised to deliver medications to specific cells, nanoparticles have more recently been investigated for use in the oral administration of peptides and peptidomimetics.

2.1.3 Microspheres: - Microspheres are show the synthetic polymer property and consist by proteins. This is having biodegradable nature. And they have the less than 200µm particle size. Microsphere are developed by different-2 method like emulsion techniques, spray drying, solvent evaporation.

2.2 LIGAND BASED TARGETING

The NTDDS (Nanoparticle-mediated targeted drug delivery system) may spread throughout the tumor mass by feeding arteries before fenestrating by the EPR (Enhanced permeability and retention) effect and accumulating in the tumor interstitial fluid. What's more, the precise NP-cell surface contacts are essential for aiding the internalization of NPs into the intended tumor cells. One of the most popular methods used by HCC (Hepatocellular carcinoma) to further enhance the targeting property is receptor-mediated endocytosis.

MONOCLONAL ANTIBODIES: -The bulk of techniques based on antibodies' ability to recognise antigens have been created particularly for the treatment of cancer. These tactics primarily target the presence or, more precisely, the expression of tumour cell-expressed antigens. The compound of a medication and a monoclonal antibody known as an antibody-drug conjugate (ADC) allows for the selective targeting of tumour cell masses or lymphomas. Under physiological circumstances, enzymatic breakage of the linker releases the medication. Monoclonal antibodies are briefly described as-

3. ANTIBODIES

An antibody sometimes referred to as an immunoglobulin, which is a large, Y-shaped protein(also known as glycoprotein's) that the immune system utilises to recognise and destroy foreign substances like harmful bacteria and viruses. The pathogen's distinctive molecule, known as an antigen, is recognised by the antibody. Mainly, Glycoprotein's comprising 4-18% Carbohydrates and 82-96% Polypeptides. With the help of disulfide bonds, these glycoprotein chains contains about 110 amino acids that form the immunoglobulin (Ig) fold. Two 50-kD heavy chains (H chains) disulfide-bonded to two 25-kD light chains make up the structural core of each Ig molecule. (L chains).Antibodies always represented by Symbol **Ab**[6]. Structure of antibody is best shown in fig. 3

3.1 TYPES OF ANTIBODIES

3.1.1 IgG- **ϒ** IMMUNOGLOBULINS (**ϒ** IS A HEAVY CHAIN)

IgG1,IgG2,IgG3 and IgG4

3.1.2 IgA- **α** IMMUNOGLOBULINS (**α** IS A HEAVY CHAIN)

IgA1 and IGA2

3.1.3 IgM- **µ** IMMUNOGLOBULINS (µ IS A HEAVY CHAIN)

3.1.4 IgE- **€** IMMUNOGLOBULINS (**€** IS A HEAVY CHAIN)

3.1.5 IgD- **δ** IMMUNOGLOBULINS (δ IS HEAVY CHAIN)

Each heavy and light chain mixture binds to a specific antigenic site [6]

3.2 STRUCTURE OF ANTIBODIES

A. The B lymphocytes are responsible for producing antibodies.
B. Immunoglobulin G is the common (IgG) type of antibody
C. IgG a protein made up of two primary structural components functional regions.

1**. Fab region**: Contains the antigen (Ag) binding site that differs between various antibodies.

2. **Fe region**: A area with a consistent structure within an antibody class [6]

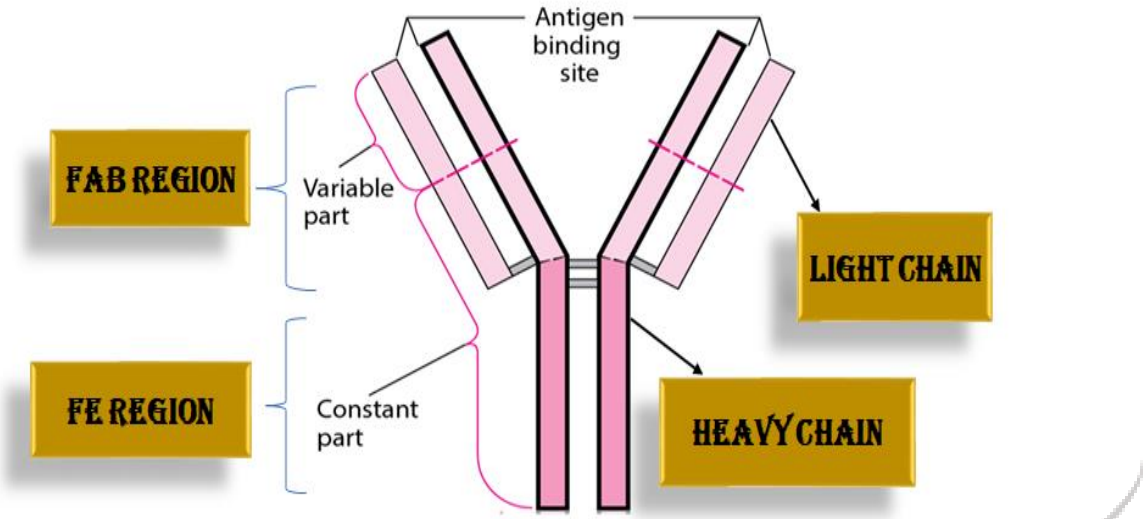

Fig. 3 Structure of Antibody

4. MONOCLONAL ANTIBODIES

Monoclonal antibodies are immune cells that are all just one kind of antibody which is produced by these single-parent cell clones. Monoclonal antibodies are represented by symbol **(MAb)** or **(mAb)** basically, produced by white blood cells (WBC) which is also known as plasma cells[7].Monoclonal antibodies (mAb) are crucial tools used in biomedical research, disease detection, and cancer and other types of disease treatment. These antibodies are created by cell lines or clones derived from animals that have received vaccinations against the research chemical. B cells taken from the vaccinated animal are fused with myeloma cells to make the cell lines (Köhler and Milstein 1975). The cells must be cultivated in one of two methods in order to create the necessary mAb: in vitro tissue culture or injection into the peritoneal cavity of mouse (the in vivo, or mouse ascites, approach).Monoclonal antibodies are produced by the technology which is known as **HYBRIDOMA TECHNOLOGY**[8]

Georges J.F. Kohler and Cesar Milstein created this technology in 1975.Additionally, they shared the Nobel Prize in 1984 for this discovery. They create a hybrid cell that can produce a variety of monoclonal

antibodies against an antigen. Spleen cell and myeloma cell specific hybridomas can produce monoclonal antibodies in artificial media; this process is known as hybridoma technology. The hybrid cell is capable of producing antibodies from B-cells (spleen cell). It can continually divide at the same time because to a quality derived from myeloma cells. This approach ensures large-scale, single-specificity antibody synthesis by fusing the desired characteristics of both cells[8]

4.1 CRITERIA CONSIDERING FOR THE CREATION OF COMPLEX DRUG- MONOCLONAL ANTIBODY

1. The surface of the cell should have the monoclonal antibody's recognition site.

2. 2. The antibodies need to be specific enough for cancer tissue.

3.Degree to which the antibody is localised at the target site.

4. The conjugate must not trigger an immune response and be biodegradable [9]

4.2 ADVANTAGES OF MONOCLONAL ANTIBODIES

1. Hybridoma act as an immortal source of monoclonal antibody.

2. Same quality of the antibody is maintained among all the different production batches.

3. Highly reproducible and unlimited production source.

4. Speed and sensitivity, specificity of assays.

5. Production of antibodies Will take place when needed [10]

4.3DISADVANTAGES OF MONOCLONAL ANTIBODIES

1. Time consuming process it takes about 6 months to 9 months.

2. Very expensive and needs more effort for production.

3. Hybridoma culture may be subject to contamination.

4. System is only well developed for mice and rat and not for other animals.

5. More than 99% of the cells do not survive during the fusion process [10]

5. RECENT APPLICATIONS OF MONOCLONAL ANTIBODIES

5.1 Lung cancer nanoparticle targeted delivery method using monoclonal antibody as a targeting mediator [11,12]

The most frequent type of cancer is lung cancer, behind breast cancer. Among all cancer kinds, it has the highest fatality rate. One lung cancer treatment uses nanoparticle technology, which is still under development. However, conjugation with particular ligands is capable of Enhancing nanoparticle targeting

performance still needs to be done in order to deliver medications more precisely to cancer areas. A monoclonal antibody is one kind of mediator that may target nanoparticles precisely. Because cancer cells have a large number of antigens on their surface, monoclonal antibodies are widely used to transport nanoparticles and improve therapeutic targeting to cancer cells. Many of them are therefore designed as nanoparticles to reduce their main limitations and improve drug targeting.

5.1.1 DIFFERENT TYPES OF MONOCLONAL ANTIOBODY I.E USED IN TARGETED DELIVERY FOR THE TREATMENT OF LUNG CANCER

Fig. 4 summarises by using certain antigens that are widely distributed on the covering of lung cancerous cells, monoclonal antibodies are utilised to treat lung cancer. These antibodies are employed as ligands to assist direct nanoparticles to a particular population of cells.

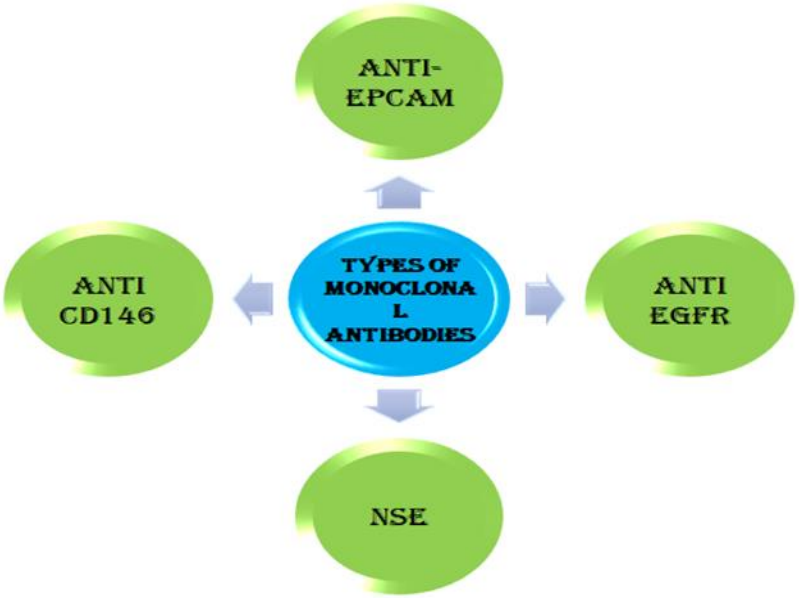

Fig. 4 Different Types of Monoclonal antibodies

Where, ANTI-EPCAM stands for- Epithelial cell adhesion molecule, ANTI-EGFR stands for- epidermal growth factor receptor, NSE stands for- Neuron Specific Enolase and CD-146 stands for CD146 (MCAM) is an integral membrane glycoprotein belonging to the immunoglobulin family.

5.2 5.2 Monoclonal antibody-adorned polyelectrolyte nanogels for targeted drug delivery

Monoclonal antibodies (mAb) can be conjugated to cutting edge surface-functionalized cross-linked nanogels as a surface for targeted drug delivery. Poly (ethylene glycol)-b-poly (methacrylic acid) (PEG-b-PMA) diblock copolymers having clearly identifiable PEG terminal. By using atom transfer radical polymerization (ATRP), aldehyde functionality was created, and it was then examined using GPC and 1H

NMR. These copolymers were used to create nanogels by combining PEG-b-PMA with Ca2+ ions to form aggregates that resemble micelles, cross-linking the PMA/Ca2+ cores, and removing the Ca2+ ions. The resulting nanogels are spherical polyelectrolyte particles that have undergone significant swelling and have free terminal aldehyde functionalities at non-ionic PEG chains. Between mAb's amino groups and aldehyde groups, there is a reductive amination process resulted in the efficient conjugation of mAb CC49 against tumour-associated glycoprotein 72 to nanogels. Surface plasmon resonance demonstrated that the mAb maintained its affinity for binding to bovine submaxillary mucin following conjugation. As a result, an easy, one-step procedure can be used to attach aldehyde functionalized nanogels to mAb. They might be able to deliver diagnostic and therapeutic substances to tumours in a targeted manner [13,14]

5.3 Monoclonal antibodies for the treatment of innate defence diseases

Rheumatoid arthritis, Crohn's disease, and ulcerative colitis can all be effectively treated with the monoclonal antibodies Infliximab and Adalimumab. They tend to bind and limit the release of tumour necrosis factor (TNF), tumour necrosis factor-alpha (TNF-), and interleukin-2 (IL-2) from activated T-cells, which are likewise blocked by basiliximab and daclizumab, assisting in the prevention of acute rejection of kidney transplants. Omalizumab's effective human IgE inhibition makes it useful in the treatment of many forms of allergic asthma, whereas Daclizumab, another effective mAb drug, is effective in treating T-cell lymphoma. OKT3 (Muromonab, Orthoclone) is the first therapeutic monoclonal antibody (mAb) licensed by the FDA (murine IgG2a; CD3-specific), and is presently utilized in patients with steroid resistance whose solid organ transplants are refractory. This medication is frequently administered to kidney transplant recipients in order to promote immunosuppression and avoid the rejection of the foreign tissue. The T-cells that lead to rejection are known to be attacked by the (OKT-3) mAb [15,16]

6. PRODUCTION OF MONOCLONAL ANTIBODIES[17,18,19]

Monoclonal antibodies are produced from a single B-lymphocyte which are used to bind to the same epitope. In 1975, a hybridoma approach was used to create them for the first time in mice. In order to create hybridomas, a certain species must be immunised against a particular antigen epitope and have its spleen harvested for its B-lymphocytes. Shown in fig. 5

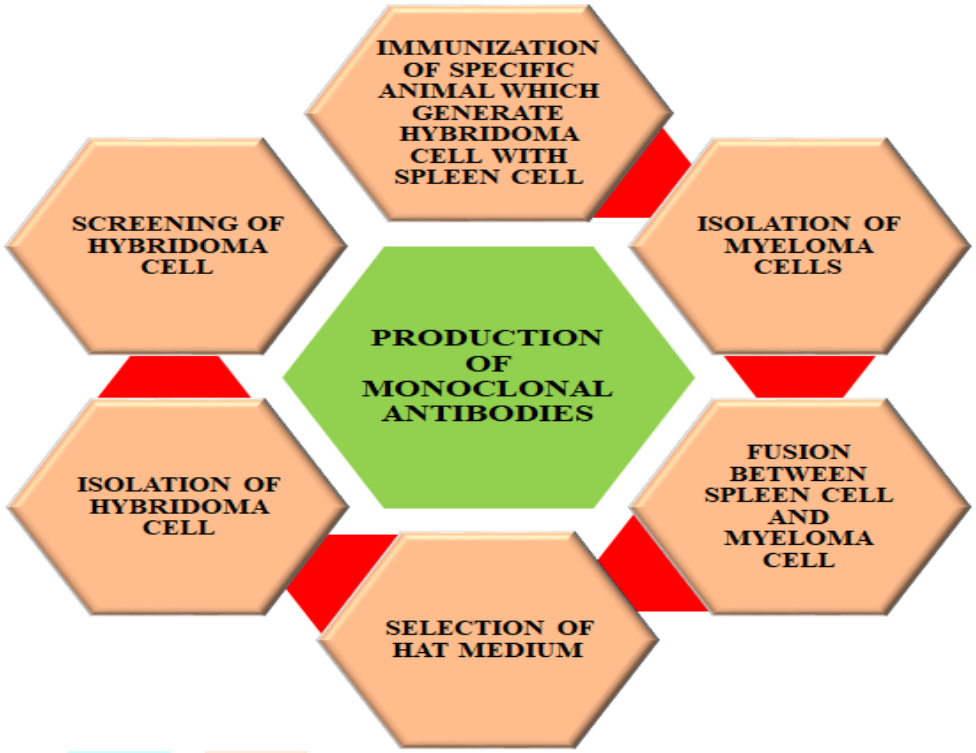

Fig. 5 Steps for the production of Monoclonal Antibodies

6.1 STEPS INVOLVED ARE-

6.1.1 IMMUNIZATION OF SPECIFIC ANIMAL WHICH GENERATE HYBRIDOMA CELL WITH SPLEEN CELL

AnAntigen administered intravenously to immunise an animal (such as mice).

↓

Where in spleen it activates B-cell which produces plasma cell or spleen cell(splenocytes)

↓

Plasma cells to produce monoclonal antibodies

↓

Isolation of plasma cells from spleen of animal

6.1.2 ISOLATION OF MYELOMA CELLS

Cancerous cells called myeloma are extracted from bone marrow. In general, myeloma cells have the ability to multiply and are immortal in nature[20]

6.1.3 FUSION OF SPLEEN AND MYELOMA CELL

PEG(Polyethylene glycol) is required for fusion. It can also be done by electro-fusion Fusion between myeloma cell and spleen cell produced 5 different types of cells-

1. Fused plasma
2. fused myeloma
3. Hybridoma
4. Unfused plasma
5. Unfused myeloma

6.1.4 SELECTION OF HAT MEDIUM

HAT STANDS FOR **(HYPOXANTHIN, AMINOPTERIN, and THYMIDINE)** before multiplication of antibody, it has to synthesize new copy of DNA and for that it requires synthesis of nucleotide.

For synthesis of nucleotide, it follows 2 pathways i.e.

1.Salvage pathway

2. De-novo synthesis

Salvage pathway requires degraded part of old nucleotide to produce new nucleotide.

Whereas,

In de-novo synthesis it is synthesised from new nucleotide by small molecules.

As a result, Aminopterin, which blocks the Di-hydro folate enzyme required for these synthesises, is present in HAT media, which prevents cells from synthesising via de novo synthesis. For synthesis in the salvage pathway, the HGPRT enzyme is necessary (Hypoxanthine Guanine Phospho-Ribosyl Transferase). whereby thymidine and hypoxanthine are utilised as precursors

6.1.5 ISOLATION OF HYBRIDOMA CELL

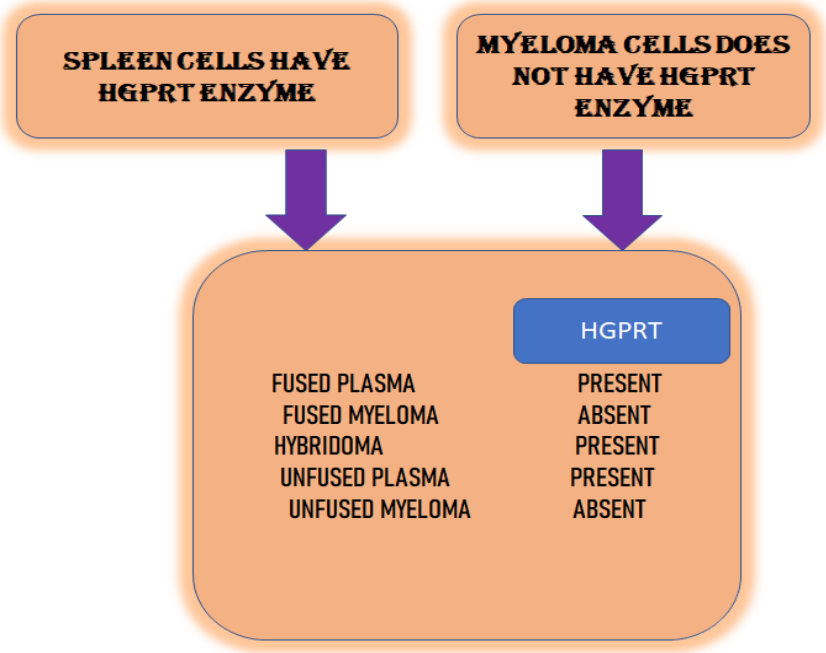

Fig. 6 Role of HGPRT Enzyme

Because they lack the HGPRT enzyme, fused and unfused myeloma cannot thrive on HAT medium. Both fused and unfused plasma contain the HGPRT enzyme, although neither have a lengthy shelf life.

The ability to repeatedly divide as myeloma cells is shared by hybrid cells, which also contain the HGPRT enzyme from spleen cells.

Because it is the only cell that can survive in HAT media, hybrid cells must be isolated.

6.1.6 SCREENING OF HYBRIDOMA CELL

The hybridoma culture is incubated using the ELISA screening method, which results in the development of coloured product that indicates the presence of hybridoma. Hybridoma cells are inserted into the peritoneal cavity of the animal during an in-vivo technique, and antibodies are then extracted from ascetic fluid. The in-vitro approach requires cultivating hybridoma cells in the appropriate growth conditions, followed by the isolation and purification of antibodies. A hybridoma colony that has been created will continue to expand and manufacture antibodies in a culture medium like RPMI-1640. STORAGE- Liquid Nitrogen. The whole process is best shown in fig. 7 [21]

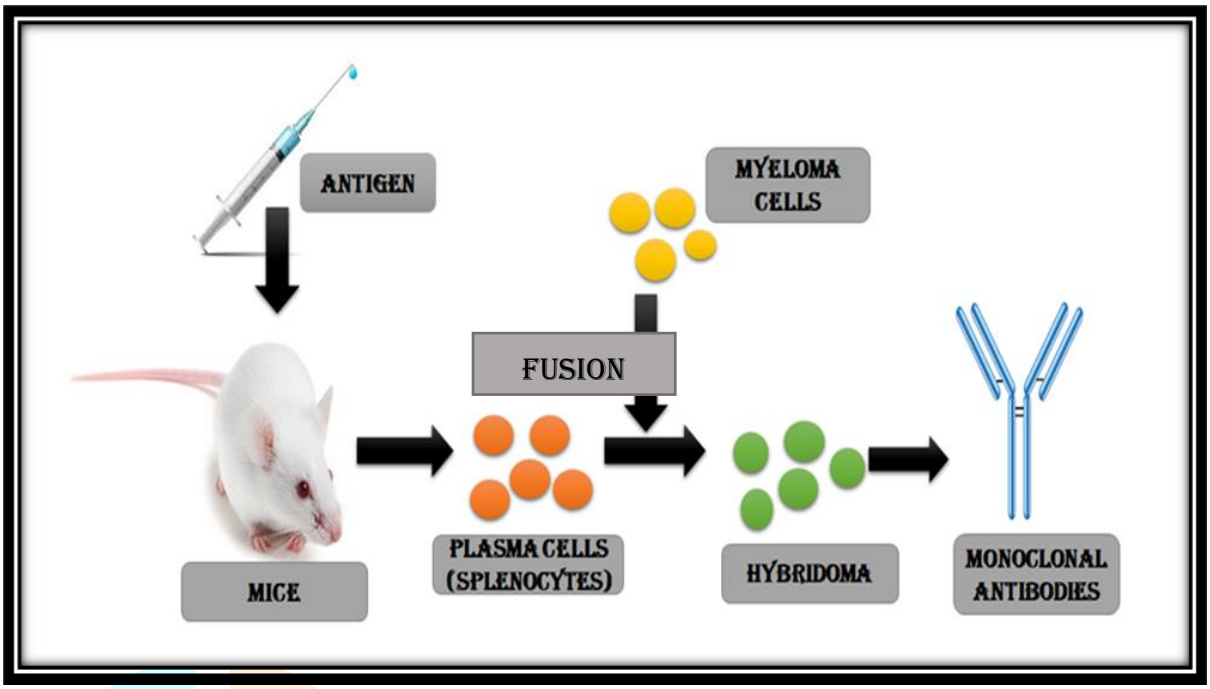

Fig. 7 Process for the production of Monoclonal Antibody

DIFFERENCE BETWEEN MONOCLONAL AND POLYCLONAL ANTIBODIES

S.NO	MONOCLONAL ANTIBODIES	POLYCLONAL ANTIBODIES
1	THESE ARE PRODUCED FROM ONE TYPE OF IMMUNE CELLS	THESE ARE PRODUCED FROM DIFFRERNT TYPES OF IMMUNE CELLS
2.	EXPENSIVE TO PRODUCE	LESS EXPENSIVE TO PRODUCE
3.	INTERACTS WITH PARTICULAR EPITOPES	INTERACTS WITH DIFFERENT EPITOPES ON THE SAME REGION
4.	THE WILL BIND TO SINGLE SPECIFIC REGION	MAY BIND TO DIFFERENT AREAS OF TARGET MOLECULE
5.	REQUIRE TIME TO PRODUCE	FAST PRODUCTION OCCURS

Tab. 1

MARKET MONOCLONAL ANTIBODIES APPROVED BY THE USFDA

S.NO	MAb	BRAND NAME	COMPANY	TECHNOLOGY	INDICATION	YR OF APPROVAL
1.	Crizanlizumab	Adakveo	Novartis Pharmaceutical Corps.	Hybridoma	Sickle cell disease	2019
2.	Romosozumab	Evenity	Amgen/UCB	Hybridoma	Osteoporosis	2019
3.	Galcanezumab	Emgality	Eli Lilly	Hybridoma	Migraine prevention	2018
4.	Sarilumab	Kavzara	Regeneron pharmaceuticals inc.	Transgenic mice	Rheumatoid arthritis	2018
5.	Atezolizumab	Tecentiq	Roche,f.hoffman-laroche,ltd/genentech	Hybridoma	Bladder cancer	2016
6.	mepolizumab	Nucala	Centocor inc./gsk	Hybridoma	Severe eosinophilic asthma	2015
7.	vedolizumab	Entyvio	Genentech inc./millennium pharmaceuticals inc./	Hybridoma	Ulcerative colitis	2014

Tab. 2

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