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Review Article

Application Of Antibody in Targeted Drug Delivery System

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ABSTRACT

Targeted drug delivery has been transformed by monoclonal antibodies (mAbs), which use their high specificity to target cells or tissues. The use of antibodies in targeted drug delivery systems is examined in this review, with an emphasis on how they can improve therapeutic efficacy and lessen side effects. We go over how antibodies can be encapsulated in delivery vehicles like liposomes and nanoparticles or conjugated to medications. We also look at the difficulties and potential applications of antibody-mediated drug delivery, such as the creation of new targeting ligands and the incorporation of cutting-edge nanotechnology. Additionally discussed is the potential of antibody-based systems in the treatment of a number of illnesses, suchas infectious diseases, autoimmune disorders, and cancer. This thorough analysis highlights the revolutionary effects of antibodies in the field of drug delivery as well as their potential to enhance the results for patients.

INTRODUCTION

A majority of therapeutic proteins are monoclonal antibodies (mAbs), which are also a major factor in the expansion of the biopharmaceutical industry [1].In clinical trials, humanized mAbs are now the group with the quickest growth [2]. The idea that certain encounters and targeting ,Paul Ehrlich initially proposed the "Magic Bullet"—the link between antibodies and antigens/receptors [3]. These customized drug transport mechanisms preferentially connect with their aims, like receptors, due to efficient ligand-receptor connections.In essence, these are designed to communicate to them particular aim and provide the majority Thismedication inserted within the aim at region while avoiding serious adverse effects [4]. At the moment, nanoparticulate delivery methods, including micelles, dendrimers, liposomes, polymeric nanoparticles, etc., are among the most studied active targeting strategies. Surface changes obtained through conjugation methods are the primary means of achieving active targeting [5].In addition to their improved efficacy and favorable safety profiles, monoclonal

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antibodies have also been shown to have greater success rates during the early stages of clinical development [6]. By 2020, it is anticipated that about 70 mAb medicines will be on the market to treat a range of illnesses [7]. The immune system produces specialized proteins called antibodies, often referred to as immunoglobulins, to recognize and eliminate foreign substances such as bacteria, viruses, and poisons. Here is a summary of their salient characteristics:

Structure:

Basic Structure: Antibodies are Y-shaped molecules a pair heavyweight and pair lightweight chains of peptides make up the four-chain structure. Disulfide ties bind such chains.

Regions:

Fab Region: The arms of the Y, responsible for binding to antigens (the foreign substances).

Fc Regio The stem of the Y, which interacts with other components of the immune system.

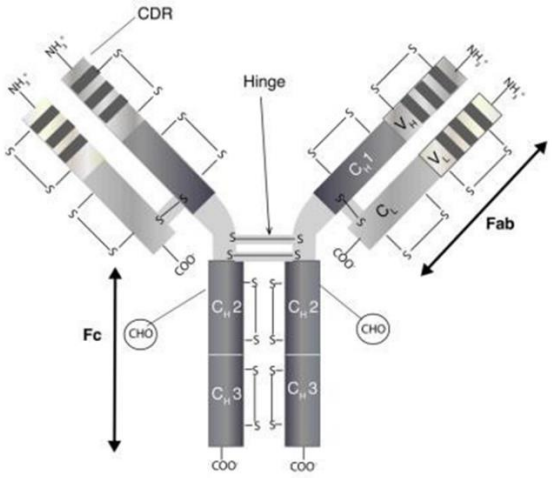

Figure 1. A schematic diagram representing the modular structure of a monoclonal antibody (mAb). (Abbreviation: CDR: complementarity-determining region; COO-: carboxy terminal; CH: constant domain, heavy chain, CL: constant domain, light chain; Fab: fragment antigen-binding; Fc: fragment crystallisable region, NH3: amino terminal end, S-S: disulfide bond; VH: variable domain, heavy chain; VL: variable domain, light chain)

Classes of Antibodies:

Human antibodies fall into five major classes, or isotypes, each of which has a specific purpose:

IgG: IgG, a very common immunoglobulin in plasma and other fluids, provides much of the immunoglobulin-based resistance towards infected cells. There are four subtypes of IgG: IgG1, IgG2, IgG3, and IgG4. is the most pertinent for treatments [8].

IgA: An essential component of mucosal immunity, it is found in secretions like saliva and breast milk as well as mucosal sites including the gut and respiratory system.

IgM: The initial immunoglobulin generated in reaction to an illness; useful in generating networks

that can be removed from the bloodstream.

IgE: Involved in parasite infection responses and allergy reactions.

B cells that have not yet been exposed to antigens use IgD primarily as a receptor.

The two primary targeting strategies utilized in nanoscale delivery systems are passive and active targeting [9]. Physical targeting, another name for passive targeting, is predicated on the pathophysiological characteristics of the sick target area as well as well as the physical-chemical properties of the medicine in addition to delivery approach [10]. The drug's and the delivery system's physicochemical characteristics include things like particle size, surface charge, solubility, and hydrophobicity/hydrophilicity. Regarding the pathophysiological characteristics of the intended regions or organisms, certain types them could

have enumerated as variations in the morphology of cells, blood flow and lymphatic drainage, and vascular structure [11]. PEGylation, the technique Some of the more popular changes to the surface for both actively and passively focusing is the combining of PEG chains to the particle's outer layer or the direct incorporation of these strands into the composition of the polymer. Increased both stealthy & hydrophilia qualities are the outcomes of PEGylation, which also provides an agent coupling platforms and ligand movement. Moreover, these traits allow a particle Method of distribution to evade RES detection and increase the likelihood that it will reach its intended cells and tissues [12]. Drug delivery systems and medications can be directed to various sick areas of the body using a variety of targeting ligand types. The most commonly utilized ligands include small compounds, proteins and peptides, aptamers, and antibodies and their components [13].

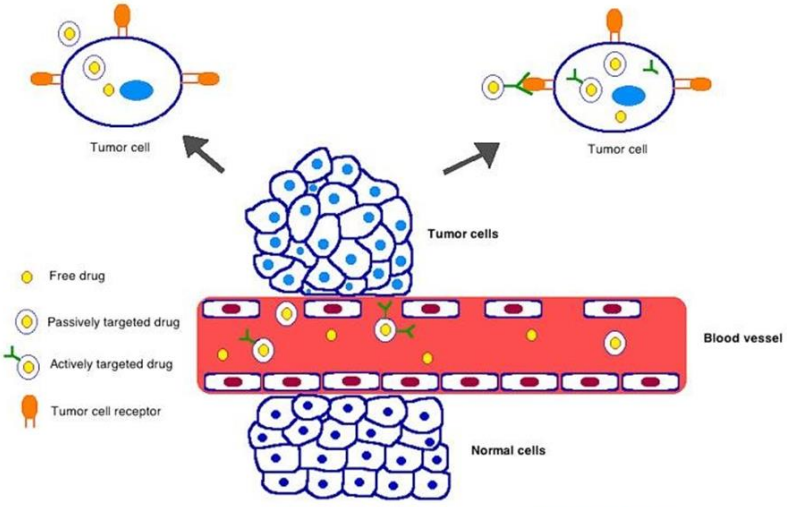

Fig. 1. EPR effect and fundamentals of passive and active targeting (Ozturk-Atar et al., 2018).

The background of immunoglobulin and how they function in specific treatments

The FDA authorized Orthoclone OKT®-3 (muromonab-CD3), an initial single-chain immune system, was derived from mice, for clinical use in humans in 1985 as an antirejection medication following kidney transplantation. However, research on "humanized" antibodies has increased due to issues with murine antibodies, including sensitization, anti-OKT3 antibody formation, and significant infection risk [14]. Through antibody-drug conjugates, antibodies might be employed to deliver the medication straight to the area of illness. alternatively, these are useful to target "actively aimed medication distribution method which include liposome nanoparticles and other drug-containing delivery systems. [15]

Function

1. Neutralization: By attaching to pathogens and blocking their ability to enter cells, antibodies can directly neutralize them.
2. Opsonization: Pathogens are marked for phagocytic cell (such as macrophage) destruction by antibodies that coat them.

Complement Activation: Pathogens can be destroyed by the complement system being activated by the Fc region of antibodies.

1. Antibodies can draw lymphocytes that try to get rid of diseased or malignant cytotoxicity caused by antibody-dependent cellular (ADCC), a mechanism that affects cells.

Production

B Cells: B lymphocytes (B cells) are a lymphocyte portion that produce immune cells. B cells can differentiate into blood vessel cells, and generate

copious quantities of immunoglobulins in reaction to a foreign substance.

Memory Cells: After an infection, some Memory cells are formed by B cells. which offer sustained immunity and a quicker reaction when the same antigen is encountered again.

Obstacles in Antibody-Based Treatments

1.**Utilizing The additives to Maintain The preparations**

A variety of The preparations composed of proteins and peptides have been made more stable by the use of excipients [16], which decrease protein motion and dynamics enhance the constancy of the shape of monoclonal antibodies, particularly at elevated levels, may prevent Clustering that depends on the connection [17–19].The use of surfactants (like By adhering to the air–liquid interface, polysorbate 20 and 80), starches (such as cyclodextrin derivatives), and amino acids (such as arginine and histidine) can aid in preventing aggregate. which is how excipients typically prevent aggregation and protect the protein [20]. Nevertheless, the application of polysorbate 80 may result in micelle formation, which raises the risk of immunogenicity [20]. Nevertheless, the application of polysorbate 80 may result in micelle formation, which raises the possibility of immunogenicity [20].

2.Production of Protein Scaffolds

A structure of single-chain polypeptides with a very well-organized base linked to change regions with an elevated sensitivity to conformation that permit eliminations additions, and variations is commonly referred to as a scaffold. TNF-α, CD20, VEGF, CD19, and CD3 are among the validated targets that have been used to develop the majority of scaffolds [6]. Although they can share some structural characteristics with antibodies, There have also been descriptions of frameworks unconnected to mAbs. [6]. The supports typically possess a lower molecular weight than mAbs. According to reports, protein scaffolds have improved tissue penetration, increased solubility, and thermal stability [21].

3.mAb Compositions to Increase the Length of Activity

The term "tertiary structure" refers to the three-dimensional (3D) structures found in biological macromolecules, such as mAbs. The folded structure is determined by a complex intermolecular and intramolecular balance between the functional groups of amino acids and their external surroundings. Maintaining the native folded structure requires a variety of Water-resistant, hydrogen bonding, and interactions due to van der Waals are examples of non-covalent interactions. between side chain residues and the backbone, and electrostatic interactions [22].Because biologics' Since third dimentional networks are susceptible to mechanical strain from the environment, alterations in mAb structure can happen at any stage of the manufacture procedure, from the initial release of the amino acid to its preparation and preservation.[23]

Formulation techniques, such as creating controlled release systems, have also been studied to lengthen the length of time that amino acids act (as shown in 4). More general techniques for extending the action of amino acids will be discussed here, and they are also being researched for the creation of mAb formulations with longer half-lives.

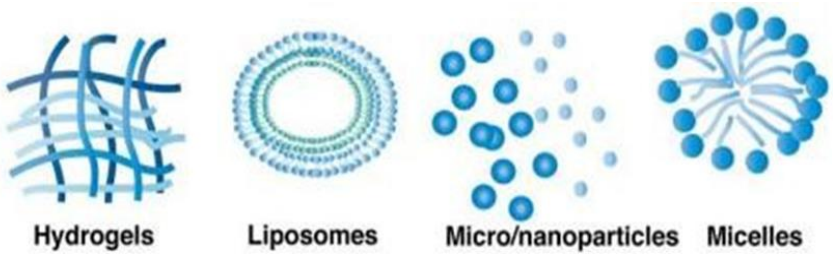

Figure 4. Common formulation strategies used to prolong protein release.

1. Alteration of Proteins to Lengthen Activity

Figure 5 summarizes the use of chemical and recombinant modifications to prolong the half- life of proteins. The majority of the tactics can be applied to long-acting mAb formulations and have been used to extend protein action. This section goes into greater detail about a few tactics that have successfully completed or begun research studies, including PEGylation, Fc Fusion, and Human Serum Albumin (HSA).

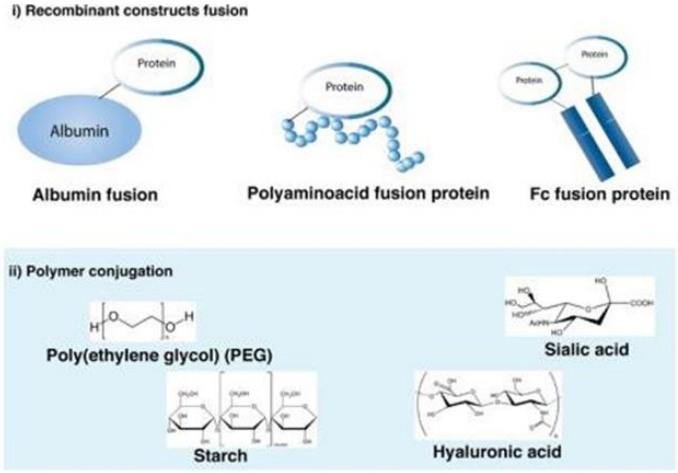

Figure 5. Methods to increase the duration of action of proteins.

Applications : Antibodies are utilized in various drug delivery systems, enhancing the efficacy and specificity of treatments.

Antibody-Drug Conjugates (ADCs):

Cancer Therapy: ADCs combine a cytotoxic medication with a monoclonal antibody. By focusing on particular antigens found in cancer cells, the antibody delivers the medication straight to the tumor while avoiding harm to healthy cells. Trastuzumab emtansine for HER2-positive breast cancer is one example

Argeted Nanoparticles: Delivery Vehicles: Immunoglobulin may be attached to a tiny molecule

allowing to targeted transmission of therapeutics (like small molecules, genes, or proteins) to specific cell or tissues. This method works well for autoimmune disorders and cancers.

Bispecific Antibodies:

Dual Targeting: Therapeutic agents can be delivered to multiple targets at once thanks to these engineered antibodies' ability to bind to two distinct antigens. Their ability to activate T cells and target them to tumors makes them especially promising for cancer treatments.

Immunoliposomes:

Liposome Targeting: Antibody-coated liposomes can encapsulate medications and transport them to their intended cells. This approach increases therapeutic efficacy and cellular uptake, particularly in the treatment of cancer.

Cell-Specific Therapy:

Autoimmune Diseases: Drugs that selectively alter immune responses can be delivered to afflicted cells via antibodies, improving the course of diseases like multiple sclerosis and rheumatoid arthritis.

Gene Therapy:

Antibody-Mediated Delivery: By guaranteeing that therapeutic genes reach their intended targets, antibodies can help deliver nucleic acids (such as plasmids or siRNA) to particular cells, improving gene therapy applications.

Vaccine Delivery:

Adjuvant Role: By focusing on antigen-presenting cells, antibodies can improve immune responses against infections or cancers and increase the effectiveness of vaccines.

Diagnosis and Monitoring:

Biosensors: Drug delivery strategies can be guided by antibodies, which can be used in diagnostic platforms to track therapeutic responses and disease progression.

These applications highlight the versatility of antibodies in enhancing drug delivery systems, leading to improved therapeutic outcomes across various medical fields.

Antibody mediated medication distribution systems:

1. Cancer medication distribution method
2. Rehumatoid medication distribution method
3. Subcutanous medication distribution method
4. Transdermal medication distribution method
5. Oral medication distribution method
6. Inflammatory bowel disease
7. Vaginal medication distribution method
8. vaccine delivery

1.Cancer drug therapy: Monoclonal Antibodies in Nanosystems as a Strategy for Cancer Treatment.

For targeted therapies, monoclonal antibodies (mAbs) are useful therapeutic tools that target tumor cells while protecting healthy tissues, reducing the likelihood of side effects. As genetic engineering has advanced, recombinant human or humanized mAbs, or singal immune are now marketed in order to manage tumors, either alone, in combination with other medications, or both. Therefore, the antitumor cytotoxic activity and potential for use in cancer immunotherapy make monovalent or bispecific mAbs useful. Immunoconjugates containing nanoparticles are less developed, despite the fact that some antibody-drug conjugates are commercially available.In this regard, nanoparticles are crucial for enhancing drug delivery because they enable site- specific delivery and controlled release both passively—by improving permeation andretention—and actively—by functionalizing nanoparticles with antibodies or antibody fragments that have a high affinity for receptors that tumor cells overexpress. Adsorption,covalent binding, or the use of adapter molecules are the primary methods for bioconjugation. To maintain its biological activity, immobilization of antibodies on the surface of nanoparticles must guarantee the appropriate antibody orientation, the required quantity of antibodies per nanoparticle, and the creation of a stable binding. This chapter will cover the primary methods for conjugating antibodies to nanoparticles using non-covalent bonds like adsorption and the biotin- avidin system, as well as covalent bonds like the chemistry of carbodiimide, maleimide, and click. In this section, we will discuss the creation of monoclonal antibodies, functionalization techniques, and antibody-receptor-targeted nanoparticles of various compositions, including lipid, polymeric, and inorganic, with an emphasis on their physicochemical characterization, preparation methods, and biological activity both in vitro and in vivo. Maleimide chemistry, which is specifically used in the functionalization of lipid nanoparticles like liposomes, the most sophisticated nanosystem, provides the primary bioconjugation methodoverall. The functionalized

nanoparticle is efficiently and specifically taken up by receptor- mediated endocytosis, according to cell culture studies. Following the success of preclinical studies using cancer xenografts, nanoparticle immunoconjugates have also shown promise for treating cancer; however, clinical trials have not yet demonstrated their safety and efficacy. As per the diverse ways in which antibodies function, certain antibodies possess the capacity to trigger the lymphocytes to identify and eradicate cancerous cells, potentially averting the development of cancer altogether. However, some antibodies have the ability to bindspecifically to Overexpression of malignant cells antigens (TAAs) in cancerous organelle, and though either not illustrated at all or only very weakly stated in healthy cells. This allows for targeted chemotherapy. impact the pathways, influencing immune cells' effectiveness. In addition to creating A melanoma microenvironment (MME) that is extremely immunogenic, cancerous tissue encourage immunosuppressive characteristics that supports Immunoevasion and the development of cancer [24]. For non-small cancer lung cancer (NSCLC), hepatocyte cancer (HCC), colon cancer, malignant melanoma lung inflammation, and carcinoma, Ipilimumab (MDX-010), a monoclonal antibody that inhibits CTLA-4 (Yervoy ®) can prevent the compounds from trigger an antitumor autoimmune reaction [25].

Effector Mechanisms of Targeted mAb

There are several ways that targeted monoclonal antibodies **(mAbs)** to prevent immune cells which are specific to or excessively demonstrated by cancerous cell can kill cancer cells (Figure 1). The major effective method is to restrict growth factor binding site sensing. mechanism where several immunoglobulins cause dying of cancer cell. If mAbs bind to the cytokine receptors they are targeting , they alter of own state of activation or prevent directly binds of ligands, which disrupts indicating that promotes cancer development.

For instance, more types of cancer overexpression of the binding site for vascular endothelial growth factor (VEGF)", then signaling through VEGF causes cancer cells to proliferate, migrate, and invade. By preventing Cetuximab, an anti-EGFR mAb, induces receptor dissociation and complex formation. melanocytes to go through apoptosis [26–27]. Indirect methods include CDC, ADCC, and antibody-dependent cellular phagocytosis (ADCP). mechanisms of mAbs' activity which necessitate the participation of the host's components immune system [28].By attaching to virulence factors with of there Fab on the selected cell's surface portions now connecting the the subunit cells with their Fc portions, immunoglobulin serve as bridges. IgG1 is the greatest pertinent category of immunotherapy that fight tumor, even though IgG, IgA, and IgE can all mediate ADCC [29]. The process of creating new mAbs has changed. toward creating mAbs next to enhanced ability to mediate ADCC, as the ability of mAbs to mediate ADCC is acknowledged and this key factor that determines mAb therapy achievement. modifying the mAb's Fc region to raise its affinity for binding to the activizing FcγRIIIA through Mutations that is location, modifying the glycosylation of the Fc domain, and/or eliminating the fucosylation of the Fc domain can all improve the ADCC functionality of antibodies [30–33].

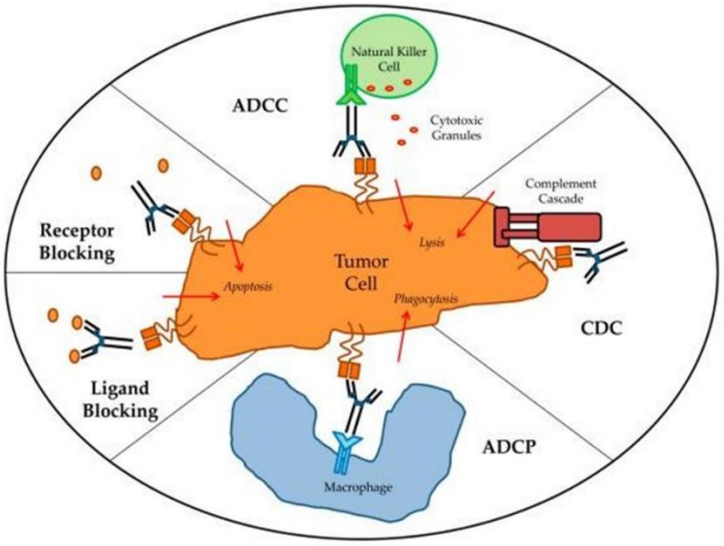

Figure 1. Antibody effector mechanisms. ADCC: antibody-dependent cellular cytotoxicity; CDC: complement-dependent cytotoxicity; ADCP: antibody-dependent cellular phagocytosis.

mAbs for Fc-mediated effector

Although you can use Fc to stimulate numerous immune paths by interacting with Fcγ receptors, and the creation of mAbs as anti - cancer medications initially relies primarily on Fab's attachment to the antigen [34].In this manner, immune cells' Fcγ receptor attaches to Fc, triggers and initiates phagocytes, effector cells, and supplement, resulting in the methods of ADCC, ADCP, and CDC that eliminate cancer cells.Following the immunoglobulin bind regarding the aim antigen, Fc attracts immune cells that express the Fcγ receptor, such as NK cells, macrophages, and T cells. It also triggers the publication of granzyme and perforin, or phagocytosis, to eliminate cancer cells. Furthermore, the The complement system is activated in order to produce the protective layer attack group and destroy the of the malignant cells. .following the binding between the C1q component and Fc [35]. A transmembrane glycoprotein called CD38 is primarily displayed on tumors of plasma cells, such as MM [36].Adult patients with MM have been treated with CD38-directed cytolytic antibodies, isatuximab and daratumumab, which cause cancer cells to undergo apoptosis and activate immune effecting method such as ADCC, ADCP, and CDC. Diarrhea, pneumonia, Neutropenia and upper respiratory tract illnesses are major frequent side effects of CD38 -directed cytolytic antibodies [37].

Antibody-drug conjugates

The antibody's great selectivity for binding and immune cells linked to tumors make it a crucial component of ADC design. Additionally, the antibody should have suitable binding properties, minimal cross-reactivity, minimal antigenicity, and well-tolerated retention. Furthermore, chemical linkers are used to keep the ADC stable and attach the cytotoxic payload to the monoclonal antibody lysine amino group on either the thiol group or the immunoglobulin that has been diminished by the disulphide bonds between chains are used by all US-FDA-approved ADCs in conjunction with the drug-linkers. By maximizing the pharmacological half-life, toxic effect, and consistency of antibodies, the payload is grafted to specific antibody sites as well as right The proportion of drug to immunoglobulin is established to obtain an outstanding therapeutic index.ADCs enter cells through receptor-mediated endocytosis after attaching to antigens that are displayed on malignant cells surfaces.Once inside, they payloads for discharge that destroy the tissue.

This is important to note that ADCs typically turn on the immune effector cells' ADCC and ADCP processes. in addition to having the effectiveness of chemotherapy [38].

mAbs in advanced medical studies for signs related to tumor

The monoclonal immunoglobulin have developed quickly due toward its benefits on treating tumors. Numerous antibody medications have started Phase-II or Phase-III clinical trials in recent years [39].

2.Rehumatoid drug delivery system

Introduction Rheumatoid arthritis (RA), a prolonged autoimmune disease, is characterized by inflammation of the joints. Conventional treatments, such as Medicines that modify arthritis (DMARDs) and non-steroidal anti-inflammatory drugs (NSAIDs), frequently have variable efficacy and systemic side effects. A viable approach to enhance treatment efficacyand specificity while reducing side effects is the use of antibody-targeted medication distribution system. Inflammation of the synovium is a hallmark of rheumatoid arthritis (RA), a systemic immune illness. Hand and foot joints are frequently severely damaged in RA patients, which can result in joint abnormalities and even disability. The autoimmune condition known as rheumatoid arthritis (RA) is typified jointly damage and persistent synovitis. Severe bone erosion may result, impairing joint function and possibly causing disability. The sufferer's longevity and the standard of living may be significantly impacted by this illness. Joint pain, swelling, and stiffness in the morning are the primary clinical symptoms of RA, which may affect extra-articular organs as well.. Furthermore, patients usually have higher indices, including anti- citrullinated protein/peptide antibody (ACPA), rheumatoid factor (RF), and additional indicators of characteristics[40]. Pathophysiology of RA is still unclear as of late. There is widespread agreement that multiple factors, including genetic and environmental factors, work together to disrupt the immune system and cause needless immune reactions. The immunologic system's reaction to self - antigens is thought to be the primary cause of the illness, is bolstered by autoreactive T and B lymphocytes. Interleukin-1 (IL-1), interleukin-17 (IL-17), and tumor necrosis factor-alpha (TNF-α) are among the many inflammatory cytokines secreted by T lymphocytes, which can develop into different subgroups of helper T-cells (Th cells). These cytokines cause infections by penetrating, clumping together, and invading the joint synovium. [41–42].Inflammation is also mediated by RFs, these are antibodies generated by B cells. The main cells of the synovium, fibroblast-like synoviocytes (FLSs), have the ability to release cytokines and chemokines and show clear signs of invasion. FLSs are therefore regarded as the essential players in synovitis.

Furthermore, patients may experience joint damage or cartilage disruption due to the production of matrix metalloproteinases (MMPS) by FLSs [43–45].Antibody-targeted drug delivery is a therapeutic approach that increases treatment efficacy and decreases side effects by using antibodies to deliver medications to particular cells or tissues. Antibodies impact targeted drug delivery in the following ways:

1.Specific Binding

Mechanism: The specific antigens displayed on the exterior of target cells, including as cancer cells, are what antibodies are made to bind to.

Example: With the help of monoclonal antibodies (mAbs), therapeutic agents can be precisely delivered to cancer cells by targeting particular tumor antigens, such as HER2 in breast cancer

2.Drug Conjugation

Mechanism: Antibody-drug conjugates (ADCs) are created when drugs and antibodies are chemically connected. When the antibody binds, the drug is delivered straight to the target cell.

Example: ADCs such as trastuzumab-emtansine (Kadcyla) target HER2-positive breast cancer cells while avoiding toxicity to healthy cells by binding the chemotherapy medication emtansine to trastuzumab

3.Enhanced Uptake

Mechanism: Endocytosis, in which the target cell absorbs the antibody-drug complex, can be facilitated by antibodies binding to their target.

Example: The antibody's internalization after binding to cancer cells enables targeted delivery of cytotoxic agents, enhancing treatment results.

4.Reduced Side Effects

Mechanism: Antibodies limit exposure to healthy tissues, thereby minimizing side effects by precisely directing drug delivery to diseased cells.

Example: Antibody-targeted treatments can spare healthy cells, resulting in less adverse effects compared to conventional chemotherapeutics, that can harm rapidly dividing cells.

5.Immune Modulation

Mechanism: Certain antibody-based treatments can strengthen the body's defenses against infections or tumors.

Example: Pembrolizumab and other immune checkpoint inhibitors target proteins on cancer or immune cells, improving the capacity of the immune system to recognize and destroy tumor cells.

Antibodies are necessary to the pathophysiology of rheumatoid arthritis (RA). Here is a quick summary ofthe role antibodies play in RA:

Autoantibody Production: In RA, the body's own tissues—especially the synovial tissue in joints—are mistakenly targeted through the immune system. Autoantibodies are created as a result, the most prominent of which are rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPAs).

Immune Complex Formation: Immune complexes can be formed when the antibodies attach to antigens in the joints, such as citrullinated proteins. These complexes have the ability to accumulate in joint tissues, which can lead to inflammation.

Complement Activation: A collection of proteins called the complement system, which supports the immune response, can be activated by immune complexes. Immune cell recruitment to the joint area and additional inflammation may result from this activation.

Inflammatory Cell Recruitment: Inflammatory cells, such as T cells and macrophages, are drawn to the joints by the presence of antibodies and immune complexes. These cells exacerbate inflammation and cause joint damage by releasing pro-inflammatory cytokines (such as TNF-alpha, IL-1, and IL-6).

Joint Damage: The immune response's chronic inflammation causes bone and cartilage to be destroyed, leading to the pain and function loss that characterize RA.Of course! Using concrete examples, let's examine the function of antibodies in rheumatoid arthritis (RA) in more detail:

1.Autoantibody Production

Example: Rheumatoid Factor (RF) and Anti-Citrullinated Protein Antibodies (ACPAs)

RF: Targeting the Fc region of IgG antibodies is what this antibody does. A higher severity of the disease is linked to RF, which is detected in many RA patients.

ACPAs: Citrullination, a post-translational modification, is the target of these antibodies. An autoimmune process is in motion when ACPAs are present, which is frequently thought to be more specific for RA and can manifest before clinical symptoms.

Immune Complex Formation

Example: Citrullinated Proteins in Joint TissuesImmune complexes are created when ACPAs attach to citrullinated proteins in the synovium, which lines the joints. For example, these antibodies may citrullinate fibrinogen, making it a target and causing joint inflammation.

Complement Activation

Example: C3 Activation: The complement cascade can be triggered by immune complexes attaching to immune cell receptors. As a result, inflammatory mediators C3a and C5a are produced, which draw additional immune cells to the joint and prolong the inflammatory cycle.

Inflammatory Cell Recruitment

Example: Macrophages and T Cells

TNF-alpha and IL-1, two cytokines released by activated immune cells, attract more inflammatory cells.

For example, pannus, an aberrant layer of fibrovascular tissue that erodes bone and cartilage, can develop as a result of activated macrophages producing more cytokines.

1.Joint Damage Example:Bone Erosion

The long-term inflammation causes the bone to erode and cartilage to be destroyed. For example, a characteristic of advanced RA is subchondral bone erosion that can be seen on X- rays.

3.Subcutaneous drug delivery system

the rise in monoclonal antibodies (mAbs) and the ease of subcutaneous (SC) administration. Numerous peptide and protein-based medications, including fusion proteins and monoclonal antibodies (mAbs), have emerged as a result of biotechnology advancements given that the creation of insulin, the first peptide medication [46, 47]. When compared to small molecules, mAbs' greater specificity and potency are explained by their chemical structure. This leads to decreased side effects and increased therapeutic efficacy. [48] The lymphatic system's increased permeability to big molecules is a result of its structure. For example, lymphatic vessels exhibit gaps between lymphatic endothelial cells due to their poorly defined basement membrane [49]. The development of collectors that pass via the hypodermis is caused by lymphatic capillaries, which typically are bigger than bloodstream in radius. and get bigger as they combine After that, lymph is moved into bigger lymphatic trunks, which ultimately join the blood vascular system [50]. Thus, medications are moved from the interstitial space.to the bloodstream by the lymphatic system in a one-way fashion [49]. In general, convective transport via lymphatic vessels is the physiological mechanism that results in SC absorption of mAbs Since lymph fluid enters the circulatory tissue gradually,, mAb absorption typically occurs within hours or days [51]. Furthermore, by binding to the neonatal Fc-receptor (FcRn), mAbs' fragment crystallizable (Fc) region shields them from catabolism in the system which may also account for their extended half-lives [52,53].The FcRn is specifically found in endosomes found in endothelial cells. After the drug is absorbed into these cells, mAbs bind to FcRn in slightly acidic endosomes (pH 6.0–6.5) in a pH-dependent manner, preventing lysosome catabolism. The medication can then be exposed to physiological pH once more after the endosomes are returned to the cell surface and fuse with it. In this case, the medication is released into the extracellular space because it no longer binds to FcRn [54,55].Overall, this procedure may lead to transcytosis from the SC administration site to the bloodstream in addition to shielding molecules containing Fc from bloodstream catabolism [56,57]. Designing better mAbs and drug formulations, as well as interpreting and developing pharmacokinetic and pharmacodynamic relationships, all depend on an understanding of the SC absorption process [58].

Mechanism

Antibodies can bind specifically to diseased cells or tissues (such as tumor cells or inflammatory sites) within the subcutaneous layer because of their high specificity for their target antigens**.**

Van der Waals forces and ionic interactions are examples of non-covalent interactions, and the hydroxyl groups are the main mechanism for this binding.

Endocytosis: Once the antibody has attached itself to the target antigen, endocytosis can cause the complex to be internalized into the target cell. This enhances therapeutic effects while protecting healthy cells by enabling the direct delivery of conjugated drugs into the cell.

Release of Therapeutic Agents: Antibodies may be connected to medications or medicinal substances in certain systems (e.g., cytotoxic drugs, peptides). The antibody-drug complex is internalized after binding to the target, releasing the drug inside the cell to begin its therapeutic action.

Improved Bioavailability: Antibodies can improve the bioavailability of medications that might otherwise be poorly absorbed or quickly metabolized when given systemically by directing delivery directly to particular cells.

Modulation of Immune Response: Antibodies have the ability to modulate local immune responses by targeting immune cells in the subcutaneous tissue. This can improve the effectiveness of vaccines or immunotherapies administered subcutaneously**.**

Controlled Release Mechanisms: Antibody-drug conjugates that integrate extra technologies for controlled release are used in certain delivery systems. For example, Long-term drug release can be achieved by linkers that cleave in response to certain conditions (such as pH or enzymes present in the target tissue).

4.Transdermal drug delivery system

Transdermal patches, also known as patches of skin, apply a unique cell wall to regulate the charge when the solvent drug inside the patch's reservoir can enter in bloodstream through the skin.To be used in a skin patch, certain capsules needs to be paired with ingredients, substances that improve their capacity to pierce the skin, like alcohol. Scopolamine (estrogen for menopause and to prevent osteoporosis after menopause), nitroglycerin (for angina), nicotine (for stopping smoking), lidocaine, and for motion illness (for shingles pain; herpes zoster) are among the medications that are applied as skin patches.However, insulin molecules and The size of many other materials prevents them from passing through the skin.The requirement for needle or pump-based vascular access is eliminated by applying patches to the skin. In order to treat motion sickness, The FDA initially authorized transdermal patches in 1979 after they were created in the 1970s. [59, 60].

Targeted Delivery: By using antibodies to target particular cells or tissues, the medication can be administered exactly where it is required [61]. This can lessen adverse effects and increase treatment efficacy [61].

Enhanced Penetration: Drugs can enter the body more efficiently when antibodies help break through the skin barrier [61].This is especially helpful for medications that are difficult for the skin to absorb [61].

Drug Conjugates: Drugs and antibodies can combine to create antibody-drug conjugates, or ADCs. These ADCs can be made to make the medication are controlled and persistent way once it reaches the intended location [61].

Vaccine Delivery: Vaccines can be administered via microneedle patches, a form of TDDS [62].These patches can be enhanced with antibodies to boost immunity and offer greater disease prevention [62].

Cancer Therapy: Antibody-based transdermal delivery of anticancer medications may be a Viable substitute for more conventional techniques such as oral or hypodermic administration [61].For patients who need ongoing care, this can be especially advantageous [61].

5.Oral drug delivery system

A straightforward and non-invasive method of drug delivery is oral administration. However, a variety of particles needs to be administered

intravenously to achieve the necessary Pharmacokinetics and dosages
because of inadequate ingestion and rapid Enzymatic breakdown within the digestive system. Now, we introduce an oral medicated auto-injector for liquids that can deliver doses of a bioavailable medication up to 4 mg with the quick The injection's pharmacokinetics, achieving a higher drug percentage in blood under 30minutes of dosage and an absolute bioavailability of up to 80%.Compared to our previously designed injector capsules, this method increases pharmacokinetics and dosing effectiveness by an order of magnitude.It also improves preclinical and clinical chemical permeation enhancement technologies by up to two orders of magnitude. To deliver Four clinically relevant doses frequently injected drugs—adalimumab, a GLP-1 analog, recombinant human insulin, and epinephrine—we gave the capsules to pigs. The system's translational potential is supported by these oral administration and multi-day dosages studies in lab animals that are awake.

Targeted Drug Delivery: To ensure that the medication is administered exactly where it is required, antibodies can be used to target particular cells or tissues in the body [63].This can lessen adverse effects and increase treatment efficacy [63]. Certain antigens, also known as markers, on the surface of cells can be recognized and bound by antibodies. An antibody-drug conjugate (ADC) is created when a drug and an antibody are combined for use in drug delivery.After being taken orally, this ADC passes through the digestive tract. The antibody component of the ADC locates and attaches itself to its target cells after absorption, enabling the drug to be released exactly where it is required. Because the medication is less likely to impact non-target cells, this improves the drug's effectiveness while lowering side effects.

Drug Conjugates: Drugs and antibodies can combine to create antibody-drug conjugates, or ADCs [64].These ADCs can be made to make available the medicines in a prolonged and regulated way after it arrives at the target site.[64].Drugs and antibodies are chemically connected in this mechanism. Until they get to the target cells, the ADCs are made to stay stable. The drug is only active in the precise location where it is needed thanks to this controlled and sustained release system, which reduces systemic exposure and possible adverse effects.For example, an ADC for cancer treatment can spare healthy tissues by delivering a strong chemotherapy medication straight to cancer cells.

Gastrointestinal Infections: Antibodies administered orally can be used to treat and prevent gastrointestinal infections brought on by bacteria like Vibrio cholerae, Escherichia coli, and rotavirus [65].Patients receiving bone marrow transplants or those with immunodeficiency
disorders will especially benefit from this [65]. Antibodies taken orally have the ability to directly neutralize pathogens in the gut. Toxins or dangerous bacteria, for example, can be bound by antibodies to stop them from sticking to or invading intestinal cells. Infections brought on by pathogens like rotavirus, E. coli, or cholera may be prevented and treated with this. This technique offers a non-invasive, efficient means of enhancing the immune system's reaction to these infections in immunocompromised people.

6.Inflammatory Bowel Disease (IBD):

To treat IBD, oral delivery of antibodies that block TNF-α, such as infliximab, is an option [64]. When compared to intravenous administration, this approach can minimize undesirable side effects [64]. persistent swelling of the gastrointestinal tract is a characteristic of diseases like ulcerative colitis and Crohn's disease,which are both types of IBD. Oral administration is an option for antibodies that target and neutralize tumor necrosis

factor-alpha (TNF-α), such as infliximab. These antibodies work on the gut's inflammatory regions when consumed, lowering inflammation and accelerating healing. Compared to intravenous administration, this may be more comfortable for patients and aid in sustaining constant drug levels.

Cancer Therapy: Antibodies can be taken orally as part of cancer treatment to specifically target and destroy cancer cells [63]. This strategy can enhance treatment results and drastically lower side effects [63]. Antibodies are used to target cancer cells specifically in oral drug delivery systems for cancer therapy. These antibodies may be connected to medications that stop cell growth or cause cell death. The drug-antibody conjugate is absorbed and moves through the body after oral administration. The conjugated medication is released locally when the antibody attaches in tumor tissue, reducing damage to healthy tissue increasing the treatment's overall effectiveness.

Example: Infliximab for IBD

Drug-Antibody Conjugation: A monoclonal antibody called infliximab targets and neutralizes

the inflammatory cytokine tumor necrosis factor-alpha (TNF-α) [66].An antibody-drug conjugate (ADC) is created when the drug and antibody are chemically connected.

Oral Administration: When taken orally, the ADC passes through the digestive tract [66].

bsorption within the duodenum : In the small intestine, the medicine is liberated from the antibody after the ADC has been absorbed [66].

Systemic Circulation: After being released, the medication travels through the bloodstream to its intended location, which in this case is the gastrointestinal tract's inflammatory regions [66].

Target Binding: In inflammatory tissues, infliximab binds to TNF-α, counteracting its effects and lowering inflammation [66].This aids in reducing Crohn's disease and ulcerative colitis, two symptoms of IBD [66].

Therapeutic Effect: Compared to systemic administration, infliximab reduces undesirable side effects and offers a more effective and targeted treatment for IBD by focusing on the particular inflammatory pathways [66].

Inflammatory bowel disease

1.Introduction

Constant relapses and remittances are hallmarks of a group of long-term inflammation digestive tract known as inflammatory bowel diseases (IBDs). Crohn's disease (CD) and ulcerative colitis (UC) are its two primary subtypes. We don't fully understand the

pathogenesis of these illnesses. The primary causes of this inflammation may be genetic predisposition, dysbiosis (changes inclimate variables, antibody response irregulation (both innate and adaptive), and the gut bacteria barrier. IBD is more common in men than women in UC, but it is equally prevalent in CD. [67]

1.Gut Barrier in IBD

To assure the protection between mucosal immune framework and to preserve gut homeostasis, The restriction of gut wall is vital. [68]. Tight junctions connect cells such as Neuroendocrine, Paneth, M, enterocytes, goblet cells, and enteroendocrine cells, to form the thick mucus layer that covers it. This layer is made up of mucin (Muc2), which is secreted by goblet cells. It has been demonstrated that spontaneous colitis develops when Muc2 is deleted [69–71].Immunoglobulin A (IgA) keeps the balance between commensal microbes and the host and contrasts pathogen invasion. On the other hand, IgA deficiency changes the gut barrier's permeability. This barrier separates the lumen's commensal bacteria from the lamina propria [72]. Following the When antigens are presented, antigen-presenting macrophages and dendritic cells, (APCs), like and recognize the host pathogenic microbes and initiate the nuclear factor-kB (NF-kB) pathways, which encourage the translation of pro-infectious genes and increase the

production of pro-inflammatory cytokines, especially TNF-α, and interleukins, like IL-12 and IL-23.. Naïve CD4+ T cells have receptors for these interleukins, which stimulate and activate the adaptive immune system and encourage Th1, Th2, and Th17 differentiation. Whereas Th2 and Th17 are more common in UC, the Th1 pathway is more common in CD. Additionally, α4β7 integrin interacts with mucosal addressing cell adhesion molecule-1 (MAdCAM-1) to transfer T cells from the vascular system to the lamina propria, raising the number of T cells unique to the gut in the lamina propria[68]. Additionally, increased TNF-α production causes gut cell damage, macrophage activation, and Paneth cell necrosis, all of which contribute to chronic intestinal inflammation [73,74].By using a novel mode of action against specific inflammatory pathways, biological therapies have completely transformed traditional treatments for IBD [75,76]. These treatments are based on immunotherapies that have the ability to target and inhibit the primary cytokines, TNF-α, and integrins. that cause inflammation. Because these treatments can directly affect the disease's primary process and enhance both clinical remission and relapse prevention, their use is recommended [77,78].

4. Antibody-Loaded DDSs

The literature reports various aptamers or Nps loaded with antibodies for a variety of uses [79]. Using Nanoparticles that self-assemble from 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000] and tannic acid Wang et al. investigated infliximab oral delivery using (DSPE-PEG2k). . Nps's capacity to shield the antibody and deliver it to the exact target location without causing premature diminishment was demonstrated by the release of infliximab at the site of inflammation [80]. Kim et al. also suggested delivering infliximab via a carrier for tetragonal nanostructure, that demonstrated its efficacy in treating IBD in a mouse model of colitis [81].

7.Vaginal drug delivery system

Systems for vaginal drug delivery present a viable means of delivering medications straight to the site of action, offering targeted therapy with little exposure to the system.[1]The efficacy of these systems can be greatly increased by antibodies due to their high specificity and capacity to target specific cells or pathogens [82,83]. In the longer - term defense in resistance to infections, topical delivery systems can deliver immunoglobulins to the wall of the mucosal surface over a long time.After giving mice vaginal antibody delivery for 30 days, we looked at the biodistribution of antibodies. Urethral rings made of polymer, which were made to deliver antibodies continuously, were used to administer various antibody preparations, such as monoclonal IgG and IgM and multiple 125I-labeled IgGs. For up to 30 days following disk insertion, there were high concentrations of antibody in the vaginal secretions; radiolabeled antibody was also detected in the blood and other tissues,albeit at a concentration that was about 100 times lower. Concentrations in the mucosa and throughout the body as a function of immunoglobulin distribution and removal rates were calculated using a basic pharmacokinetic model, which showed a reasonably good agreement with the measured concentrations. The model's results were in line with previously published measurements of antibody pharmacokinetics: the The total permeation stable for IgG vaginal absorption was ~0.01 to 0.03 h−1, The vaginal immunoglobulin exclusion ½ was roughly three hours, and the half-life for IgG1 removal from the plasma was greater than 1 day.These findings offer crucial details for the development of regulated vaginal antibody delivery systems and imply that high-dose, prolonged vaginal antibody administration might

be a sensible strategy for maintaining systemic and mucosal antibody levels. [84].

Antibodies can be applied in vaginal drug delivery systems in several innovative ways:

Targeted Therapy for Infections: Certain pathogens that cause vaginal infections can be targeted with antibodies. For instance, antibodies that target STIs, such as the herpes simplex virus (HSV) or human papillomavirus (HPV), can be administered directly to the infection site, increasing the immune response and decreasing the infection [85].

Cancer Treatment: Vaginal cancers can be targeted and treated with antibodies. To minimize systemic side effects and deliver the therapeutic agent directly to the tumor site, for example, antibodies that target antigens specific to cancer can be applied topically to the vaginal area [85].

Hormonal Therapy: Hormonal treatments for diseases like uterine fibroids and endometriosis can employ antibodies. Antibodies can alter hormonal activity and alleviate symptoms by specifically targeting hormone receptors. [82,83].

Enhanced Drug Penetration: By acting as penetration enhancers, antibodies can improve the way other medications are delivered through the vaginal mucosa. For medications that are difficult to absorb through the vaginal tissue, this can be especially helpful. [82,83].

Vaccine Delivery: Vaccines, particularly those that target mucosal immunity, can be administered via the vaginal route. To improve the immune response and offer greater protection against infections, antibodies can be added to these vaccinations. [82,83].

Example: Antibody-Mediated Treatment for HSV (Herpes Simplex Virus)

Targeted Therapy for Infections: Vaginal discomfort and painful sores can be caused by HSV. It is possible to create monoclonal antibodies that selectively target the HSV glycoproteins. By binding to the virus and neutralizing it, these antibodies stop it from infecting healthy cells.

Topical Application: A gel or cream intended for vaginal application contains the antibody formulation. By applying this gel directly to the afflicted area, the antibodies are released and a barrier is created.

Mechanism of Action: The gel's antibodies attach to the HSV particles on the vaginal mucosa when it is applied. By doing this, the virus is neutralized and kept from infecting healthy cells.

Localized Treatment: The therapeutic effect is localized because the antibodies are delivered straight to the site of infection. This implies that greater antibody concentrations can be administered to the afflicted region without having a major negative impact on the body.

Enhanced Healing: Antibodies help to reduce inflammation and promote healing of the infected tissue in addition to neutralizing the virus. This can help with a speedier recovery and quicker symptom relief.

8.vaccine delivery

The precision and targeting properties of antibodies are used in antibody-mediated vaccine delivery to increase vaccine efficacy. Vaccines can be administered more precisely by employing antibodies to target particular cells or tissues, enhancing immune responses and minimizing side effects.

Strategies for vaccines against infectious pathogens based on antibodies

Many vaccinations produce immunoglobulin that provide protection versus a wide range of pathogens inside cells, such as bacteria, fungi, and protozoa. These include a number of vaccines made of polysaccharides and proteins, which are not eworthy due to the fact that they only produce humoral defenses against the protein-linked carbohydrate antigen of the relevant microorganism. The coupled vaccine's effectiveness, which consists of Pseudomonas

aeruginosa exotoxin covalently linked to Salmonella typhi Vi polysaccharide, has provided conclusive proof that antibody-based vaccination approaches are clinically effective against intracellular pathogens,despite the fact that most of the vaccines are experimental [86].New mechanisms of action have been discovered through research on antibody-based defense in opposition to alleged insite cellular infections. Having been consumed by phagocytes that are infected and transported intracellularly An antibody that neutralizes the toxin listerolysin was attached to the bacterial phagosome. demonstrated for intracellular toxin neutralization for Listeria monocytogenes [87]. Intracellular replication is inhibited when macrophages ingest M. tuberculosis and are incubated with specific antibodies [88].

Children's immunity to respiratory syncytial virus through antibody-mediated defense

Its more typical reason for bronchiolitis in young infants is the human respiratory syncytial virus (RSV), and the risk of a severe lower respiratory tract infection (LRTI) is highest in those under 6 months of age [89–91]. There is a continuous requirement for RSV prevention measures because of the young age at which the Immunological development may lead to unwanted reactions. after RSV exposure [92–94]. Ten genes that express eleven proteins, including fusion (F), attachment glycoprotein (G), and nucleoprotein (N), make up the RNA virus known as RSV [95]. Surface proteins F and G are important targets of neutralizing antibodies and play a role in the viral entry of host cells [96,97]. Formalin-inactivated RSV increased disease severity in early trials [98–99], which led to caution in subsequent vaccination attempts [100, -101].Some animal studies have linked low-affinity antibodies and T-helper 2 biased immune responses to enhanced respiratory disease (ERD). Antibodies contribute to ERD by changing innate immune responses and promoting monocyte uptake of RSV.[100, 102].

CONCLUSION: With its increased efficacy, decreased toxicity, and better patient outcomes, antibody-mediated targeted drug delivery is a paradigm shift in therapeutics. The possibilities of targeted delivery have been increased by developments in antibody engineering, nanotechnology, and bispecific antibodies. Current limitations will be overcome by ongoing research and development, opening the door for broad clinical adoption despite obstacles. Antibody-based drug delivery systems have enormous and potentially life-changing potential for treating infectious diseases, cancer, autoimmune disorders, and more as research advances. These cutting-edge delivery systems' accuracy and efficacy have the potential to influence medicine's future.

REFERENCES

1. Keizer, R.J.; Huitema, A.D.R.; Schellens, J.H.M.; Beijnen, J.H. Clinical pharmacokinetics of therapeuticmonoclonal antibodies. Clin. Pharmacokinet. 2010, 49, 493–507. [CrossRef] [PubMed]
2. Liu, J.K.H. The history of monoclonal antibody development—Progress, remaining challenges and future innovations. Ann. Med. Surg. 2014, 3, 113–116. [CrossRef] [PubMed]
3. (Strebhardt and Ullrich, 2008).
4. (Bae and Park, 2011; Naik et al., 2018
5. (Anarjan, 2019; Attia et al., 2019
6. Wurch, T.; Pierré, A.; Depil, S. Novel protein scaffolds as emerging therapeutic proteins: From discovery to clinical proof-of-concept. Trends Biotechnol. 2012, 30, 575–582. [CrossRef] [PubMed]
7. Ecker, D.M.; Jones, S.D.; Levine, H.L. The therapeutic monoclonal antibody market. MAbs 2015, 7, 9– 14.[CrossRef] [PubMed].
8. Vidarsson, G.; Dekkers; Rispens, T. IgG subclasses and allotypes: From structure to

effector functions. Front. Immunol. 2014, 5, 1–17. [CrossRef] [PubMed
9. (Naik et al., 2018).
10. (Naik et al., 2018; Wakaskar, 2017)
11. (Khanna, 2012; Naik et al., 2018; Narayanan and Wakaskar, 2018; Wakaskar, 2017).
12. (Attia et al., 2019; Patel, 1992).
13. Anarjan, 2019; Ozturk-Atar et al., 2018).
14. Frenzel et al., 2016; Smith, 1996)
15. Kaur et al., 2012)
16. kash, M.S.H.; Rehman, K.; Tariq, M.; Chen, S. Development of therapeutic proteins: Advances and challenges. Turk. J. Biol. 2015, 39, 343–358. [CrossRef]
17. Bhambhani, A.; Kissmann, J.M.; Joshi, S.B.; Volkin, D.B.; Kashi, R.S.; Middaugh, C.R. Formulation design and high-throughput excipient selection based on structural integrity and conformational stability of dilute and highly concentrated IgG1 monoclonal antibody solutions. J. Pharm Sci. 2012, 101, 1120–1135. [CrossRef] [PubMed]
18. Radhakrishnan, K.; Sonali, N.; Moreno, M.; Nirmal, J.; Fernandez, A.A.; Venkatraman, S.; Agrawal, R.Protein delivery to the back of the eye: Barriers, carriers and stability of anti-VEGF proteins. Drug Discov. Today 2017, 22, 416–423. [CrossRef] [PubMed]
19. Westermaier, Y.; Veurink, M.; Riis-Johannessen, T.; Guinchard, S.; Gurny, R.; Scapozza, L. Identification of aggregation breakers for bevacizumab (Avastin®) self-association through similarity searching and interaction studies. Eur. J. Pharm. Biopharm. 2013, 85, 773–780. [CrossRef] [PubMed]
20. Ratanji, K.D.; Derrick, J.P.; Dearman, R.J.; Kimber, I. Immunogenicity of therapeutic proteins: Influence of aggregation. J. Immunotoxicol. 2014, 11, 99–109. [CrossRef][PubMed].
21. Mintz, C.S.; Crea, R. Protein Scaffolds. Bioprocess. Int. 2013, 11, 40–48.
22. Roberts, C.J. Therapeutic protein aggregation: Mechanisms, design, and control. Trends Biotechnol. 2014, 32,372–380. [CrossRef] [PubMed
23. Frokjaer, S.; Otzen, D.E. Protein drug stability: A formulation challenge. Nat. Rev. Drug Discov. 2005, 4,298–306. [CrossRef] [PubMed]
24. Pardoll, DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer. 2012; 12: 252- 64
25. Bertrand A, Kostine M, Barnetche T, Truchetet ME, Schaeverbeke T. Immune related adverse events associated with anti-CTLA-4 antibodies: systematic review and meta-analysis. BMC Med. 2015; 13: 211
26. Li, S.; Schmitz, K.R.; Jeffrey, P.D.; Wiltzius, J.J.W.; Kussie, P.; Ferguson, K.M. Structural Basis for Inhibition of the Epidermal Growth Factor Receptor by Cetuximab. Cancer Cell 2005, 7, 301–311. [CrossRef] [PubMed]
27. Patel, D.; Bassi, R.; Hooper, A.; Prewett, M.; Hicklin, D.J.; Kang, X. Anti-Epidermal Growth Factor Receptor Monoclonal Antibody Cetuximab Inhibits EGFR/HER-2 Heterodimerization and Activation. Int. J. Oncol. 2009, 34, 25–32. [CrossRef] [PubMed
28. Di Gaetano, N.; Cittera, E.; Nota, R.; Vecchi, A.; Grieco, V.; Scanziani, E.; Botto, M.; Introna, M.; Golay, J.Complement Activation Determines the Therapeutic Activity of Rituximab in Vivo. J. Immunol. 2003, 171,1581–1587. [CrossRef].
29. Teillaud, J.-L. Antibody-Dependent Cellular Cytotoxicity (ADCC). In eLS; John Wiley & Sons, Ltd: Hoboken,NJ, USA, 2012. [CrossRef]
30. Liu, Z.; Gunasekaran, K.; Wang, W.; Razinkov, V.; Sekirov, L.; Leng, E.; Sweet, H.; Foltz, I.; Howard, M.;Rousseau, A.M.; et al. Asymmetrical Fc Engineering Greatly Enhances Antibodydependent

CellularCytotoxicity (ADCC) Effector Function and Stability of the Modified Antibodies. J. Biol. Chem. 2014, 289,3571–3590. [CrossRef]Antibodies 2020, 9, 34 15 of 20

31. Umaña, P.; Jean-Mairet, J.; Moudry, R.; Amstutz, H.; Bailey, J.E. Engineered Glycoforms of an Antineuroblastoma IgG1 with Optimized Antibody-Dependent Cellular Cytotoxic Activity. Nat. Biotechnol.1999, 17, 176–180. [CrossRef]
32. Davies, J.; Jiang, L.; Pan, L.Z.; Labarre, M.J.; Anderson, D.; Reff, M. Expression of GnTIII in a Recombinant Anti-CD20 CHO Production Cell Line: Expression of Antibodies with Altered Glycoforms Leads to an Increase in ADCC through Higher Affinity for FcγRIII. Biotechnol. Bioeng. 2001, 74, 288–294. [CrossRef]
33. Shields, R.L.; Lai, J.; Keck, R.; O'Connell, L.Y.; Hong, K.; Gloria Meng, Y.; Weikert, S.H.A.; Presta, L.G.Lack of Fucose on Human IgG1 N-Linked Oligosaccharide Improves Binding to Human FcγRIII and Antibody-Dependent Cellular Toxicity. J. Biol. Chem. 2002, 277, 26733–26740. [CrossRef]
34. Goydel RS, Rader C. Antibody-based cancer therapy. Oncogene. 2021; 40: 3655-64.
35. Chen W, Yuan Y, Jiang X. Antibody and antibody fragments for cancer immunotherapy. J Controlled Release. 2020; 328: 395-406.
36. Li Y, Yang R, Chen L, Wu SF. CD38 as immunomodulator in cancer. Future Oncol. 2020; 16: 2853- 2861
37. Sanford M. Subcutaneous trastuzumab: a review of its use in HER2-positive breast cancer. Target Oncol. 2014; 9: 85-94
38. Beck A, Goetsch L, Dumontet C, Corvaia N. Strategies and challenges for the next generation of antibody-drug conjugates. Nat Rev Drug Discov. 2017; 16: 315-37.
39. Kaplon H, Chenoweth A, Crescioli S, Reichert JM. Antibodies to watch in 2022. mAbs. 2022; 14: 2014296.
40. Shams S, Martinez JM, Dawson JRD, et al. The Therapeutic Landscape of Rheumatoid Arthritis: current state and future directions. Front Pharmacol. 2021;12:680043. https://doi.org/10.3389/fphar.2021.680043. Published 2021 May 28
41. Wang Q, Qin X, Fang J, Sun X. Nanomedicines for the treatment of rheumatoid arthritis: state of art and potential therapeutic strategies. Acta Pharm Sin B. 2021;11(5):1158–74. https://doi.org/10.1016/j.apsb.2021.03.013.
42. Kondo Y, Yokosawa M, Kaneko S, et al. Review: transcriptional regulation of CD4 + T-Cell differentiation in experimentally Induced Arthritis and Rheumatoid Arthritis. Arthritis Rheumatol. 2018;70(5):653–61. https://doi.org/10.1002/art.40398
43. Matsuo Y, Saito T, Yamamoto A, Kohsaka H. Origins of fibroblasts in rheumatoid synovial tissues: implications from organ fibrotic models. Mod Rheumatol. 2018;28(4):579–82. https://doi.org/10.1080/14397595.2017.1386837
44. Chuang SY, Lin CH, Huang TH, Fang JY. Lipid-Based Nanoparticles as a Potential Delivery Approach in the Treatment of Rheumatoid Arthritis. Nanomaterials (Basel). 2018;8(1):42. Published 2018 Jan 15. doi:https://doi.org/10.3390/nano8010042
45. Araki Y, Mimura T. Matrix Metalloproteinase Gene Activation resulting from Disordred Epigenetic Mechanisms in Rheumatoid Arthritis. Int J Mol Sci. 2017;18(5):905. https://doi.org/10.3390/ijms18050905. Published 2017 Apr 2
46. J.L. Lau, M.K. Dunn, Therapeutic peptides: Historical perspectives, current development

trends, and future directions, Bioorganic Med Chem (2017)
47. C. Morrison, Fresh from the biotech pipeline - 2017, Nat Biotechnol 36 (2018) 131
48. S. Mitragotri, P.A. Burke, R. Langer, Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies, Nat Rev Drug Discov 13 (2014) 655-672
49. M.A. Swartz, The physiology of the lymphatic system, Adv Drug Deliv Rev 50 (2001) 3-20
50. K. Alitalo, T. Tammela, T.V. Petrova, Lymphangiogenesis in development and human disease, Nature 438 (2005) 946-953
51. L. Liu, Pharmacokinetics of monoclonal antibodies and Fc-fusion proteins, Protein Cell 9 (2018) 15-32
52. C.L. Anderson, C. Chaudhury, J. Kim, C.L. Bronson, M.A. Wani, S. Mohanty, Perspective - FcRn transports albumin: relevance to immunology and medicine, Trends Immunol 27 (2006) 343-348
53. R.J. Keizer, A.D. Huitema, J.H. Schellens, J.H. Beijnen, Clinical pharmacokinetics of therapeutic monoclonal antibodies, Clin Pharmacokinet 49 (2010) 493-507.
54. M.J. Borrok, Y. Wu, N. Beyaz, X.-Q. Yu, V. Oganesyan, W.F. Dall'Acqua, P. Tsui, pH-dependent Binding Engineering Reveals an FcRn Affinity Threshold That Governs IgG Recycling, J Biol Chem 290 (2015) 4282-4290
55. D.C. Roopenian, S. Akilesh, FcRn: the neonatal Fc receptor comes of age, Nat Rev Immunol 7 (2007) 715-725
56. L. Kagan, D.E. Mager, Mechanisms of subcutaneous absorption of rituximab in rats, Drug Metab Dispos 41 (2013) 248-255
57. Y.A. Yeung, M.K. Leabman, J.S. Marvin, J. Qiu, C.W. Adams, S. Lien, M.A. Starovasnik, H.B. Lowman, Engineering human IgG1 affinity to human neonatal Fc receptor: impact of affinity improvement on pharmacokinetics in primates, J Immunol 182 (2009) 7663-7671
58. D.N. McLennan, C.J. Porter, S.A. Charman, Subcutaneous drug delivery and the role of the lymphatics, Drug Discov Today Technol 2 (2005) 89-96
59. Lewis S, Udupa N. Design and evaluation of matrix type and membrane controlled transdermal delivery systems of nicotine suitable for use in smoking cessation. Indian journal of pharmaceutical sciences. 2006;68(2)
60. Naik A, Pechtold LA, Potts RO, Guy RH. Mechanism of oleic acid-induced skin penetration enhancement in vivo in humans.Journal of controlled release. 1995 Dec 1;37(3):299-306
61. Prausnitz, M. R.; Langer, R. Transdermal drug delivery. Nat. Biotechnol.2008, 26, 1261–1268.
62. Dharadhar S, Majumdar A, Dhoble S, Patravale V. Microneedles for transdermal drug delivery: a systematic review. Drug Dev Ind Pharm. 2019;45(2):188–201
63. Sung H, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49
64. Uhlig HH, Powrie F. Translating immunology into therapeutic concepts for inflammatory bowel disease. Annu Rev Immunol. 2018;36:755–81
65. Steplewski Z. Advances and outlooks for immunotherapy of cancer. Hybridoma 1993; 12: 493-500**.**
66. Reilly RM, Sandhu J, Alvarez-Diez TM, et al. Problems of delivery of monoclonal antibodies: pharmaceutical and pharmacokinetic solutions. Clin Pharmacokinet 1995; 28: 126–42

67. Kontola, K.; Oksanen, P.; Huhtala, H.; Jussila, A. Increasing Incidence of Inflammatory Bowel Disease, with Greatest Change Among the Elderly: A Nationwide Study in Finland, 2000–2020. J. Crohn's Colitis 2023, 17, 706–711. [CrossRef]
68. Van der Sluis, M.; De Koning, B.A.; De Bruijn, A.C.; Velcich, A.; Meijerink, J.P.; Van Goudoever, J.B.; Büller, H.A.; Dekker, J.; Van Seuningen, I.; Renes, I.B.; et al. Muc2-deficient mice spontaneously develop colitis, indicating that MUC2 is critical for colonic protection. Gastroenterology 2006, 131, 117–129. [CrossRef] [PubMed]
69. Johansson, M.E.; Phillipson, M.; Petersson, J.; Velcich, A.; Holm, L.; Hansson, G.C. The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. Proc. Natl. Acad. Sci. USA 2008, 105, 15064–15069. [CrossRef] [PubMed]
70. Gustafsson, J.K.; Johansson, M.E.V. The role of goblet cells and mucus in intestinal homeostasis. Nat. Rev. Gastroenterol. Hepatol. 2022, 19, 785–803. [CrossRef]
71. Parikh, K.; Antanaviciute, A.; Fawkner-Corbett, D.; Jagielowicz, M.; Aulicino, A.; Lagerholm, C.; Davis, S.; Kinchen, J.; Chen, H.H.;Alham, N.K.; et al. Colonic epithelial cell diversity in health and inflammatory bowel disease. Nature 2019, 567, 49–55. [CrossRef]
72. Stolfi, C.; Maresca, C.; Monteleone, G.; Laudisi, F. Implication of Intestinal Barrier Dysfunction in Gut Dysbiosis and Diseases.Biomedicines 2022, 10, 289. [CrossRef
73. Ruder, B.; Atreya, R.; Becker, C. Tumour Necrosis Factor Alpha in Intestinal Homeostasis and Gut Related Diseases. Int. J. Mol.Sci. 2019, 20, 1887. [CrossRef]
74. Peyrin-Biroulet, L.; Sandborn, W.J.; Panaccione, R.; Domènech, E.; Pouillon, L.; Siegmund, B.; Danese, S.; Ghosh, S. Tumour necrosis factor inhibitors in inflammatory bowel disease: The story continues. Therap. Adv. Gastroenterol. 2021, 14, 17562848211059954.[CrossRef]
75. Rehman, M.; Cancarevic, I.; Iskander, B.; Lalani, S.; Malik, B.H. Biologics Targeting in the Treatment of Inflammatory Bowel Disease: A Conundrum. Cureus 2020, 12, e10621. [CrossRef]
76. Neurath, M.F. Targeting immune cell circuits and trafficking in inflammatory bowel disease. Nat. Immunol. 2019, 20, 970–979.[CrossRef].
77. Billmeier, U.; Dieterich, W.; Neurath, M.F.; Atreya, R. Molecular mechanism of action of anti-tumor necrosis factor antibodies ininflammatory bowel diseases. World J. Gastroenterol. 2016, 22, 9300–9313. [CrossRef]
78. Avedillo-Salas, A.; Corral-Cativiela, S.; Fanlo-Villacampa, A.; Vicente-Romero, J. The Efficacy and Safety of Biologic Drugs in the Treatment of Moderate-Severe Crohn's Disease: A Systematic Review. Pharmaceuticals 2023, 16, 1581. [CrossRef]
79. Di Rienzo, A.; Marinelli, L.; Di Stefano, A.; Vicaretti, G.; Cacciatore, I. Aptamers-based Strategies for the Treatment of Microbial Infections. Lett. Drug Des. Discov. 2024, 21, 858–865. [CrossRef].
80. Wang, X.; Yan, J.; Wang, L.; Pan, D.; Xu, Y.; Wang, F.; Sheng, J.; Li, X.; Yang, M. Oral delivery of anti- TNF antibody shielded by natural polyphenol-mediated supramolecular assembly for inflammatory bowel disease therapy. Theranostics 2020, 10,10808–10822. [CrossRef].
81. Kim, J.M.; Kim, D.H.; Park, H.J.; Ma, H.W.; Park, I.S.; Son, M.; Ro, S.Y.; Hong, S.; Han, H.K.; Lim, S.J.; etal. Nanocomposites-based targeted oral drug delivery systems with

infliximab in a murine colitis model.J. Nanobiotechnology 2020, 18, 133. [CrossRef]

82. Brannon-Peppas L (1993) Novel vaginal drug release applications. Adv Drug Deliv Rev 11:169–177.
83. Alexander NJ, Baker E, Kaptein M, Karck U, Miller L, Zampaglione E (2004) Why consider vaginal drug administration? Fertil Steril 82(1):1–12.
84. © 2000 John Wiley & Sons, Inc. Biotechnol Bioeng 67: 253–264, 2000.
85. Leyva-Gómez, G.; Piñón-Segundo, E.; Mendoza-Muñoz, N.; Zambrano-Zaragoza, M.L.; Mendoza-Elvira, S.;Quintanar-Guerrero, D. Approaches in polymeric nanoparticles for vaginal drug delivery: A review of the state of the art. Int. J. Mol. Sci. 2018, 19, 1549. [CrossRef]
86. Lin FY, Ho VA, Khiem HB, Trach DD, Bay PV, Thanh TC, Kossaczka Z, Bryla DA, Shiloach J, Robbins JB, et al. The efficacy of a Salmonella typhi Vi conjugate vaccine in two-to-five-year-old children. N Engl J Med. 2001;344:1263–1269. [PubMed] [Google Scholar]
87. Edelson BT, Unanue ER. Intracellular antibody neutralizes Listeria growth. Immunity. 2001;14:503–512. [PubMed] [Google Scholar]
88. Passwell JH, Ashkenzi S, Banet-Levi Y, Ramon-Saraf R, Farzam N, Lerner-Geva L, Even-Nir H, Yerushalmi B, Chu C, Shiloach J, et al. Age-related efficacy of Shigella O-specific polysaccharide conjugates in 1–4-year-old Israeli children. Vaccine. 2010;28:2231–2235. [PMC free article] [PubMed] [Google Scholar]
89. Shi T, McAllister DA, O'Brien KL, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: asystematic review and modelling study. Lancet 2017; 390: 946–958. doi:10.1016/S0140-6736(17)30938-8CrossRefPubMedGoogle Scholar
90. Wildenbeest JG, Billard MN, Zuurbier RP, et al. The burden of respiratory syncytial virus in healthy term-born infants in Europe: a prospective birth cohort study. Lancet Respir Med 2023; 11: 341–353. doi:10.1016/S2213-2600(22)00414-3Google Scholar
91. Li Y, Wang X, Blau DM, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: asystematic analysis. Lancet 2022; 399: 2047–2064. doi:10.1016/S0140-6736(22)00478-0CrossRefPubMedGoogle Scholar
92. Lambert L, Sagfors AM, Openshaw PJ, et al. Immunity to RSV in early-life. Front Immunol 2014; 5:466. doi:10.3389/fimmu.2014.00466CrossRefPubMedGoogle Scholar
93. Esposito S, Abu Raya B, Baraldi E, et al. RSV prevention in all infants: which is the most preferable strategy? Front Immunol 2022; 13: 880368. doi:10.3389/fimmu.2022.880368Google Scholar
94. Eichinger KM, Kosanovich JL, Lipp M, et al. Strategies for active and passive pediatric RSV immunization. Ther Adv Vaccines Immunother 2021; 9: 2515135520981516. doi:10.1177/2515135520981516Google Scholar
95. Collins PL, Fearns R, Graham BS. Respiratory syncytial virus: virology, reverse genetics, and pathogenesis of disease. Curr Top Microbiol Immunol 2013; 372: 3–38. doi:10.1007/978-3-642-38919-1_1CrossRefPubMedGoogle Scholar
96. Capella C, Chaiwatpongsakorn S, Gorrell E, et al. Prefusion F, postfusion F, G antibodies,

and disease severity in infants and young children with acute respiratory syncytial virus infection. J Infect Dis 2017; 216: 1398–1406. doi:10.1093/infdis/jix489CrossRefPubMedGoogle Scholar

97. Ngwuta JO, Chen M, Modjarrad K, et al. Prefusion F-specific antibodies determine the magnitude of RSV neutralizing activity in human sera. Sci Transl Med 2015; 7: 309ra162. doi:10.1126/scitranslmed.aac4241Abstract/FREE Full TextGoogle Scholar
98. Kim HW, Canchola JG, Brandt CD, et al. Respiratory syncytial virus disease in infants despite prior administration of antigenic inactivated vaccine. Am J Epidemiol 1969; 89: 422–434. doi:10.1093/oxfordjournals.aje.a120955CrossRefPubMedGoogle Scholar
99. Kapikian AZ, Mitchell RH, Chanock RM, et al. An epidemiologic study of altered clinical reactivity to respiratory syncytial (RS) virus infection in children previously vaccinated with an inactivated RS virus vaccine. Am J Epidemiol 1969; 89: 405–421. doi:10.1093/oxfordjournals.aje.a120954CrossRefPubMedGoogle Scholar
100. Muralidharan A, Li C, Wang L, et al. Immunopathogenesis associated with formaldehyde- inactivated RSV vaccine in preclinical and clinical studies. Expert Rev Vaccines 2017; 16: 351–360. doi:10.1080/14760584.2017.1260452CrossRefPubMedGoogle Scholar
101. Mazur NI, Higgins D, Nunes MC, et al. The respiratory syncytial virus vaccine landscape: lessons from the graveyard and promising candidates. Lancet Infect Dis 2018; 18: e295–e311. doi:10.1016/S1473-3099(18)30292-5CrossRefPubMedGoogle Scholar
102. Openshaw PJ, Culley FJ, Olszewska W. Immunopathogenesis of vaccine-enhanced RSV disease. Vaccine 2001; 20: Suppl. 1, S27–S31. doi:10.1016/S0264-410X(01)00301-2CrossRefPubMedGoogle Scholar

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