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Review article

Breakthroughs in monoclonal antibody therapies 2024: new horizons in treatment strategies in India

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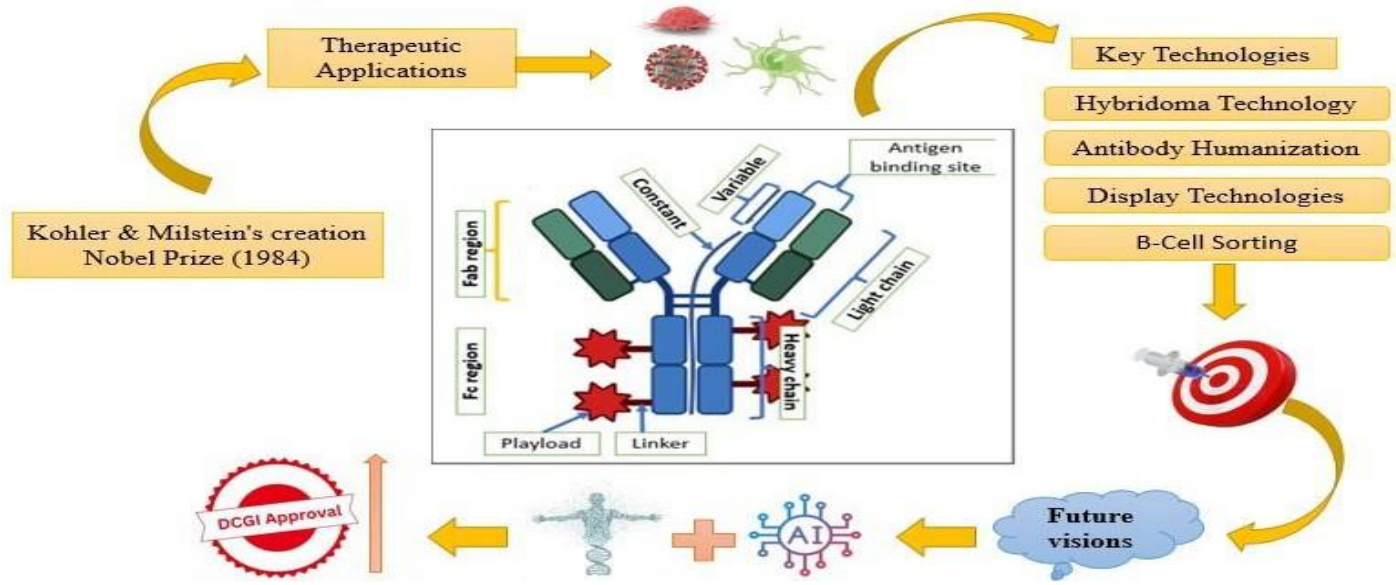
ABSTRACT

Recent advancements in biotechnology have revolutionized the development of monoclonal antibodies (mAbs). offering highly targeted therapies with fewer side effects compared to conventional treatments. As of 2024, several mAbs have been approved for import and marketing in India. Notable approvals include enfortumab vedotin for advanced urothelial cancer, nivolumab for metastatic esophageal squamous cell carcinoma and non-small cell lung cancer, and guselkumab for active psoriatic arthritis.

Furthermore, advancements in monoclonal antibody development techniques such as hybridoma technology, genetically engineered monoclonal antibodies, and phage display have resulted in the creation of highly specific antibodies. Enfortumab vedotin, for example, is an antibody-drug conjugate developed using hybridoma technology, while nivolumab is a fully human IgG4 monoclonal antibody engineered thr ough genetic modifications. This review highlights the role of monoclonal antibodies in transforming therapeutic strategies and examines the key developments in their approval and clinical use in India.



Keywords: India approvals, Hybridoma technology, Monoclonal antibodies, Targeted therapies, Therapeutic innovation.

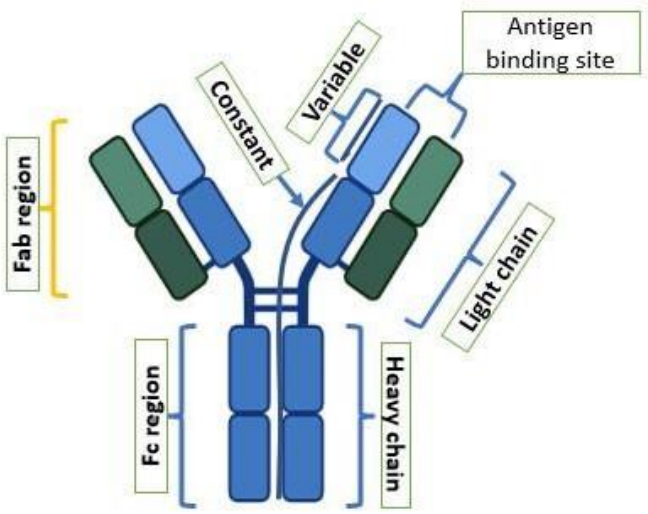
INTRODUCTION

Monoclonal antibodies (mAbs) have transformed healthcare by providing highly targeted therapies for a diverse range of medical conditions [1]. Monoclonal antibodies are specialized proteins designed to recognize and bind with exceptional accuracy to specific antigens [2]. This targeted approach focuses on addressing disease processes while reducing harm to healthy cells [3]. Recent advancements in biotechnology have revolutionized the development of monoclonal antibodies (mAbs), enhancing their efficiency, precision, and accessibility in treating a variety of diseases [4]. These innovations have provided the way for therapies that are increasingly specific, targeting only the disease causing cells while minimizing damage to healthy tissues. This targeted approach has made treatments more effective with fewer side effects. With the development of novel strategies, mAbs are now being applied to treat a broader range of diseases, including cancer, autoimmune disorders, and infectious diseases [5]. These improvements are shaping the future of medicine by offering more personalized and effective treatment options for patients worldwide. Kohler and Milstein's creation of monoclonal antibodies (mAbs) in 1975 revolutionized healthcare, leading to their Nobel Prize in 1984 [6]. The first mAb, orthoclone muromonab-CD3 (OKT3), was approved in 1986 for kidney transplant rejection. Early mAbs, produced from murine sources, faced challenges like anti-drug antibodies (ADA), leading to the development of chimeric, humanized, and fully human antibodies. The first licensed recombinant mAb, Rituxan (rituximab), launched in 1997, was produced using Chinese hamster ovary cells [7]. In 2024, India witnessed significant advancements in the import and marketing approvals of mAbs, reflecting global trends in biotherapeutics. These approvals highlight cutting-edge technologies like humanized antibodies, Fc engineering, and bispecific constructs, further expanding therapeutic options for patients. This article examines the dynamic field of monoclonal antibodies, spotlighting recent innovations, advanced development techniques, and novel therapeutic targets. It emphasizes how these breakthroughs are broadening the applications of mAbs to tackle previously unaddressed medical challenges.

Structure of Antibody

An antibody, also referred to as an immunoglobulin, is a Y-shaped molecule composed of four polypeptide chains: two heavy chains and two light chains. This unique structure allows the antibody to perform two main functions: binding to antigens and triggering immune responses. These functions are carried out by different parts of the antibody: the antigen-binding fragment (Fab) and the crystallizable fragment (Fc). The Fab region binds to antigens and consists of one variable and one constant domain from both the heavy and light chains [8]. The variable domain forms the paratope, which is the specific site for antigen recognition at the antibody's amino-terminal end. The Fc region is responsible for interacting with cell receptors known as Fc receptors and complement system proteins. This interaction helps activate the immune system.

Figure 1: Monoclonal antibody and its components



Nomenclature of Antibodies

The naming of antibodies is systematic, providing insights into their target, source (host), modifications, and any conjugation to other molecules. Guidelines established by the International Nonproprietary Name (INN) program, updated by the WHO in 2014, 2017, and 2021, define this nomenclature. The structure of an antibody name includes three main components: a prefix, a substem, and a stem.

Prefix

A unique, random element to differentiate the antibody.

Substem

Indicates the target (e.g., "ci" for cardiovascular, "ba" for bacterial, "os" for bone, "ta" for tumor, etc.) and the antibody's source. Earlier, the source was identified as “o” (murine), “xi” (chimeric), “zu” (humanized), or “nu” (fully human). However, the source indication was removed for antibodies produced after 2017.

Stem

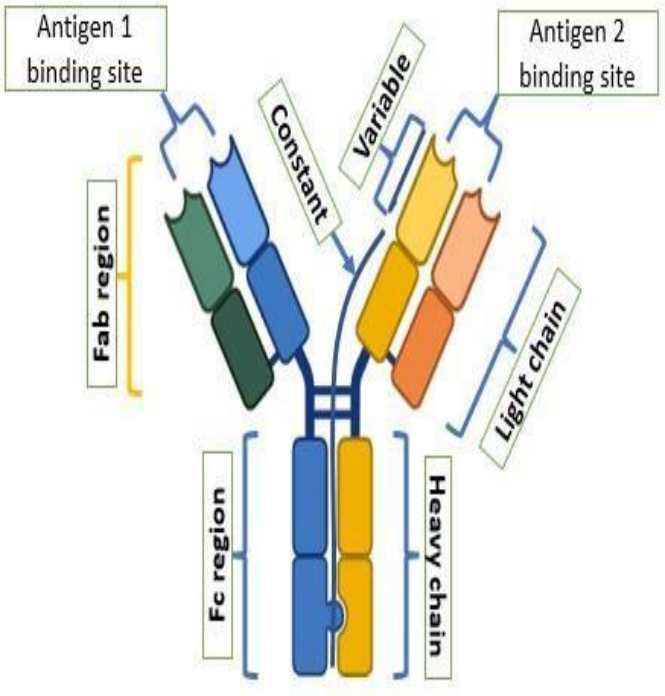
Initially, the suffix “mab” was universally applied to antibodies and their fragments. In 2021, this system was refined into four categories: Group 1, labeled as "tug," refers to natural, full-length immunoglobulins such as IgG, IgA, IgM, or IgE. Group 2, known as "bart," includes modified full-length antibodies with engineered constant domains, designed for alterations like glycation or changes in complement binding. Group 3, identified as "mig," covers multi-specific antibodies, encompassing bi- and multi-specific formats, regardless of whether they are full-length or fragments. Finally, Group 4, termed "ment," represents monospecific antibody fragments that lack the Fc region [9]. Biosimilar monoclonal antibodies (mAbs) are named using the reference drug's name with an added unique, four-letter suffix separated by a hyphen. For example, adalimumab biosimilars include names like adalimumab-atto, adalimumab-adbm, and adalimumab-bwwd.

Advancements in mAb Therapeutics

Bispecific antibodies (BsAbs)

Bispecific monoclonal antibodies (BsAbs) are engineered antibodies capable of simultaneously binding two distinct antigens or two separate epitopes on the same antigen [10]. These antibodies offer superior therapeutic benefits compared to traditional monoclonal antibodies (mAbs), especially in cancer immunotherapy and the treatment of other complex diseases. Advancements in antibody engineering, recombinant DNA technology, and protein design have significantly expanded BsAbs development [11].

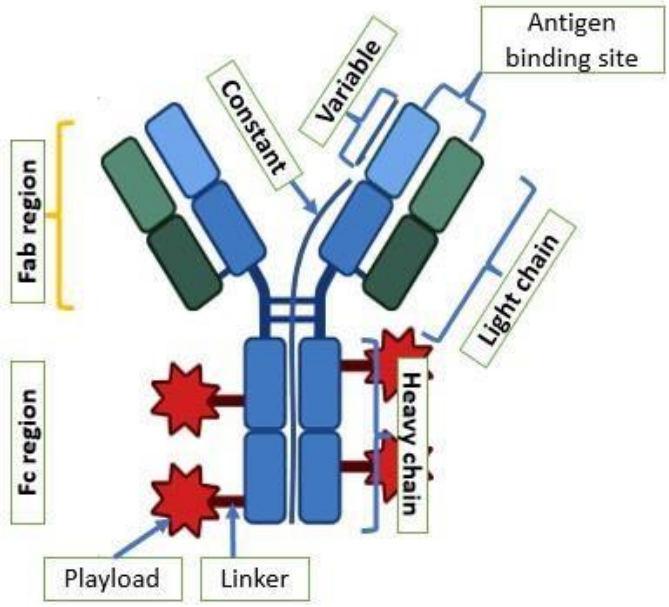
Figure 2: Bispecific Monoclonal antibody



Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates (ADCs) consist of three key components: a monoclonal antibody targeting tumor-specific antigens, a cytotoxic payload, and a linker that binds them. This design allows precise delivery of the drug to cancer cells, reducing off-target toxicity [12]. The antibody selectively binds to tumor antigens, ideally expressed more in cancer cells than normal tissues, and facilitates internalization for intracellular drug release. The linker ensures stability in circulation and efficient drug release inside the tumor, with cleavable and noncleavable types offering different mechanisms of action. The payload is a highly potent cytotoxic agent, such as tubulin inhibitors or DNA-targeting agents, designed for maximum tumor cell killing with minimal systemic exposure. Trastuzumab deruxtecan, an antibody-drug conjugate, targets HER2 (Human Epidermal Growth Factor Receptor-2) positive tumors, delivering a cytotoxic payload with a bystander effect [13]. Advances in antibody engineering, linker chemistry, and payload selection have revitalized ADC technology, resulting in approved therapies like brentuximab vedotin and ado-trastuzumab emtansine, with many others in clinical trials.

Figure 3: Monoclonal antibody with linker and Playload



Nanobody Technology

Monoclonal antibodies (mAbs) are vital tools in targeted cancer therapy, offering high specificity by binding to tumor cell antigens while sparing healthy tissues. However, their large size (150 kDa) limits tumor penetration and increases systemic accumulation, making production costly and complex. To overcome these challenges, smaller antibody formats like heavy-chain only antibodies (HcAbs, 95 kDa), single-chain variable fragments (scFv, ~30 kDa), and antigen-binding fragments (~50 kDa) have been developed [14]. Nanobodies (Nbs) are the smallest antigen-binding units derived from camelid heavy-chain antibodies (VHH) or shark immunoglobulin new antigen receptors (Ig-NARs). These single-domain antibodies (2.5 × 4 × 3 nm) exhibit high antigen specificity and binding affinity due to their elongated complementarity-determining region 3 (CDR3), which penetrates antigen cavities. Unlike conventional antibodies, nanobodies possess greater solubility, stability, and structural flexibility, attributed to hydrophilic residues and disulfide bonds. Nanobodies differ significantly from antibodies in antigen interaction, displaying higher paratope diversity and relying more on CDR3 for binding. These unique features make nanobodies promising candidates for cancer diagnosis and therapy, with enhanced tumor penetration and reduced systemic side effects.

Engineered Fc Regions

Engineering the Fc (fragment crystallizable) region of antibodies enhances their therapeutic potential by improving pharmacokinetics, immune system interactions, and target specificity [15]. Modifications can optimize effector functions like antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), strengthening immune responses against cancer or infections. Adjustments to neonatal Fc receptor (FcRn) interactions can extend antibody half-life, reducing dosing frequency [16]. For

therapies requiring minimal immune activation (e.g., in autoimmune diseases), Fc regions can be engineered to reduce effector functions by altering glycosylation patterns or specific amino acid residues [17]. Ustekinumab is a fully human IgG1 monoclonal antibody. This immunomodulator is used for conditions like Crohn's disease, plaque psoriasis, psoriatic arthritis, and ulcerative colitis. Its extended half-life (~3 weeks) is due to the neonatal Fc receptor salvage effect, allowing for less frequent dosing [18].

Gene-Encoded Antibodies

Gene encoded antibodies are an emerging strategy in immunotherapy, where genetic instructions are delivered into the body to enable cells to produce therapeutic antibodies. This approach bypasses the need for external antibody production and administration. It uses technologies like viral vectors, plasmids, or mRNA to introduce the genetic code for antibody synthesis directly into host cells [19]. Once expressed, these antibodies can specifically target disease-causing agents such as pathogens, cancer cells, or abnormal proteins. Nirsevimab is a human gene-encoded IgG1 kappa monoclonal antibody developed using in vitro display technology. It targets the prefusion conformation of the RSV fusion (F) protein, preventing the membrane fusion essential for viral entry into host cells. Engineered with a triple amino acid substitution in its Fc region, it enhances binding to the neonatal Fc receptor (FcRn), improving recycling and extending the antibody's half-life to approximately 70 days [20]. Designed for single-dose administration, it provides long-lasting protection against RSV, particularly in neonates, infants, and high-risk children.

Hybridoma Technology

Hybridoma technology, introduced by Georges Kohler and Cesar Milstein in 1975, is a groundbreaking approach for producing monoclonal antibodies (mAbs) [21]. This method involves merging antibody-producing B-cells from an immunized animal, often a mouse, with immortal myeloma cells. The fusion creates hybrid cells, known as hybridomas, which have the dual ability to produce specific antibodies and replicate indefinitely in laboratory conditions [22]. The process begins with isolating B-cells from the spleen of the immunized animal, which are then combined with myeloma cells using a fusogen like polyethylene glycol. The resulting cell mixture is cultured in a selective medium, such as HAT medium, that supports the survival of only the fused hybridomas. Each hybridoma generates a unique type of antibody corresponding to the antigen used for immunization [23]. Screening techniques are employed to identify hybridomas that produce the desired antibody. Once identified, these cells can be cloned to ensure uniformity and used to produce large quantities of the antibody. Hybridoma technology has had a transformative impact on medicine, enabling the creation of highly specific mAbs used in disease diagnostics, therapeutic interventions, and biomedical research [24]. Enfortumab vedotin is an antibody-drug conjugate (ADC) targeting nectin-4, a protein overexpressed in epithelial cancers, developed using hybridoma technology and optimized in CHO cells [25]. In 2024, the CDSCO approved enfortumab vedotin for locally advanced or metastatic urothelial cancer

Antibody Humanization

Antibody humanization is a biotechnological process aimed at modifying non-human antibodies, typically derived from rodents, to make them more compatible with the human immune system [26]. This approach is crucial for reducing immunogenicity when such antibodies are used in therapeutic applications. Humanized antibodies retain the antigen-binding specificity of the original non-human antibody while incorporating human-like structures to improve safety and efficacy [27]. The process involves identifying and preserving the complementarity-determining regions (CDRs) of the non-human antibody, which are responsible for antigen recognition [28]. These CDRs are then grafted onto a human antibody framework. Additional modifications are often made to ensure the structural integrity, binding affinity, and overall functionality of the antibody. Humanized antibodies have become essential tools in the treatment of various diseases, including cancers, autoimmune disorders, and infectious diseases [29]. For example guselkumab, a selective inhibitor of the IL-23 p19 subunit. It has demonstrated greater effectiveness than other monoclonal antibodies [30]. The HuCAL antibody library (phage display technology) was utilized to generate guselkumab.[5]

***In Vitro* Display Technologies**

In vitro display technologies are advanced tools for identifying and optimizing biomolecules like antibodies, peptides, and proteins, without relying on living systems [31]. Among these, phage display is widely used, where peptides or proteins are displayed on bacteriophage surfaces, enabling the selection of high-affinity binders and contributing significantly to therapeutic antibody discovery [32]. Similarly, yeast display presents proteins on yeast cell surfaces, allowing the simultaneous evaluation of binding properties and expression levels, making it effective for optimizing protein stability and affinity [33]. Ribosome display, a cell-free approach, synthesizes peptides or proteins linked to their mRNA on ribosomes, facilitating the selection of high-affinity binders without cellular expression limitations.[34] Another technique, mRNA display, links peptides or proteins to their encoding mRNA via a chemical bond, enabling the screening of extensive libraries for enhanced binding or enzymatic properties [35]. Additionally, DNA display attaches DNA to proteins or peptides, offering high-throughput capabilities ideal for large-scale library screening [36]. These versatile technologies have revolutionized drug discovery, diagnostics, and synthetic biology.

B-Cell Sorting and Microfluidics

B-cell sorting and microfluidics are innovative techniques used to isolate, analyze, and manipulate B-cells for applications in immunology, antibody discovery, and therapeutic development. B-cells, a type of white blood cell, are responsible for producing antibodies, making them critical targets for understanding immune responses and generating monoclonal antibodies [37]. **B-cell sorting** involves the isolation of specific B-cell populations based on their surface markers or functional properties. Techniques like fluorescence-activated cell sorting (FACS) and magnetic-activated cell sorting (MACS) are commonly used [38]. FACS employs fluorescently labeled antibodies to target surface markers and sorts cells using lasers and detectors, while MACS uses magnetic beads to capture and isolate cells of interest [39]. These methods enable the enrichment of antigen-specific B-cells, which are crucial for antibody generation and immune profiling. **Microfluidics** integrates fluid dynamics at the microscale to precisely manipulate and study individual B-cells in small volumes.[40] Microfluidic devices allow the isolation of single B-cells into tiny chambers or droplets, where they can be stimulated, monitored, and analyzed in real time [41]. Combining B-cell sorting with microfluidics has enhanced the discovery of therapeutic antibodies by enabling single-cell analyses and the efficient selection of high-affinity clones.[42] It also supports research into vaccine development and autoimmune disorders by providing insights into B-cell diversity and function.

Future Directions

Future directions for monoclonal antibodies include enhancing their precision and efficacy through advanced engineering techniques, such as bispecific and multispecific designs. Efforts are also focused on improving delivery systems, reducing immunogenicity, and exploring novel therapeutic targets for complex diseases. Additionally, integrating artificial intelligence and high-throughput screening can accelerate the discovery process of monoclonal antibodies [43].

Furthermore, Artificial Intelligence (AI) can optimize manufacturing processes, reducing costs and improving scalability. In clinical settings, AI-driven predictive models assist in identifying patient populations likely to benefit from specific mAb therapies, enabling precision medicine.

Table 1: List of Monoclonal antibodies approved for import and marketing in India in 2024

Monoclonal antibody	Year of approval	Indication	Type of monoclonal Antibody/Developmental technique
Enfortumab vedotin[43]	2024	Locally advanced or metastatic urothelial cancer	Antibody-drug conjugate Developed by hybridoma technology
Nivolumab	2024	Unresectable advanced or metastatic Esophageal squamous cell carcinoma (ESCC) Adjuvant treatment of adult patients with urothelial carcinoma (UC) who are at high risk of recurrence after undergoing radical resection of UC Non-Small Cell Lung Cancer (NSCLC)	Fully human IgG4 monoclonal antibody (mAb) Genetically engineered monoclonal antibody
Guselkumab	2024	Active psoriatic arthritis	Fully human monoclonal antibody (mAb) Phase display technology HuCAL (Human Combinatorial Antibody Library)
Pembrolizumab	2024	Stage III melanoma and lymph node involvement Metastatic microsatellite instability-high (MSI-H) or mismatch repair deficient (MMR) colorectal cancer in adults Relapsed or refractory classical Hodgkin lymphoma	Humanized monoclonal anti-PD1 antibody
Trastuzumab deruxtecan	2024	Locally Advanced or Metastatic Gastric Cancer HER2-Low Metastatic Breast Cancer T	Antibody-drug conjugate Humanized anti-HER2 monoclonal antibody
Erenumab	2024	Prophylaxis of migraine	Fully human monoclonal antibody (IgG2) Anti-calcitonin gene-related peptide monoclonal antibodies
Ustekinumab	2024	Moderate to severe active ulcerative colitis	Fully human IgG1 monoclonal antibody Neonatal Fc receptor salvage effect
Toripalimab	2024	Metastatic or with recurrent, locally advanced nasopharyngeal carcinoma (NPC)	Fully human monoclonal antibody
Nirsevimab	2024	Prevention of Respiratory Syncytial Virus (RSV) lower respiratory tract disease in: Neonates and infants born during or entering their first RSV season	Human gene-encoded IgG1 kappa monoclonal antibody in vitro display technology neonatal Fc receptor (FcRn)
Mirikizumab	2024	Psoriatic arthritis Ankylosing spondylitis Non-radiographic axial spondylarthritis	Humanized IgG4 monoclonal antibody (mAb) Engineered using recombinant DNA technology
Durvalumab	2024	Non-Small Cell Lung Cancer (NSCLC)	Human monoclonal antibody (IgG1 subtype) Engineered using recombinant DNA technology [42].
Benralizumab	2024	Add-on maintenance treatment for severe asthma with an eosinophilic phenotype in adult patients	Humanized monoclonal antibody (IgG1 subtype) Developed using glycoengineering to create afucosylated antibodies for enhanced ADCC (antibody-dependent cell-mediated cytotoxicity) [43].

CONCLUSION

The monoclonal antibody (mAb) landscape in 2024 is marked by significant advancements, with a diverse range of therapeutic applications spanning oncology, autoimmune diseases, respiratory conditions, and more. Notable approvals in India, includes

antibody-drug conjugates (e.g., enfortumab vedotin and trastuzumab deruxtecan), genetically engineered and humanized mAbs (such as nivolumab, pembrolizumab, and guselkumab), and human gene-encoded antibodies (like nirsevimab). These therapies leverage cutting-edge technologies, including hybridoma, phage display, recombinant DNA technology, and glycoengineering, to enhance efficacy and target specificity. As more mAbs receive approval, they are paving the way for more personalized and effective treatments, offering hope for better outcomes in conditions that were once challenging to treat. The future of mAb therapeutics holds promise for continued innovation, particularly in targeting previously unmet medical needs with improved safety profiles and precision medicine approaches.

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