

# Monoclonal Antibodies in Cancer Therapy

Taif Iqbal<sup>1</sup>, Piyush Choudhary<sup>2</sup>, Kashif Raza<sup>3</sup>

<sup>1,2</sup>Student, Department Of Paramedical Sciences, Jamia Hamdard University, Delhi India

<sup>3</sup>Faculty, Department Of Paramedical Sciences, Jamia Hamdard University, Delhi India

## Abstract

Cancer is a intricate ailment impacting millions of individuals globally. In recent years, there have been substantial advancements in cancer treatment, particularly in the realm of targeted therapies. Monoclonal antibodies (mAbs) have emerged as a promising category of medications for managing diverse types of cancer. Presently, Monoclonal antibody-based drugs exhibit fewer adverse effects due to their exceptional specificity. Consequently, therapeutic Monoclonal antibodies have become the predominant class of newly developed drugs.

Monoclonal antibodies offer a wide array of clinically significant mechanisms of action. Moreover, these antibodies can directly target cancerous cells while simultaneously stimulating the development of enduring anti-tumor immune responses. The multifaceted attributes of antibodies as a therapeutic platform have resulted in the creation of novel strategies for cancer treatment that will significantly impact cancer care.

The utilization of monoclonal antibody drugs has witnessed explosive growth with the approval of new drugs for the treatment of various human diseases, including numerous types of cancer, autoimmune disorders, metabolic conditions, and infectious diseases. As of December 2019, the US FDA has given its approval to 79 therapeutic mAbs, yet there remains substantial room for further expansion in this field.

**Keywords:** Monoclonal antibodies ,cancer, Immunotherapy, therapeutic antibodies,Tumor cells

**Data Source:** Peer-reviewed journal articles, book chapters, internet.

## 1. Introduction:

Monoclonal antibodies (mAbs) are synthetic molecules created in a laboratory that possess the remarkable ability to mimic the immune system's capacity to combat harmful threats, including cancer cells. These mAbs are crafted by B plasma cells from the adaptive immune system and exhibit a specific affinity for antigens. The introduction of the hybridoma technique by Köhler and Milstein in 1975 [1] revolutionized the production of mAbs, enabling the generation of large quantities of pure mAbs. This breakthrough significantly enhanced both fundamental scientific research and the potential for their clinical application.

Shortly after the discovery of hybridomas, investigations into the utilization of mAbs for cancer treatment commenced. Anti-melanoma mAbs were demonstrated to inhibit the growth of human

melanomas in nude mice, and in 1980, the inaugural human trial of mAb therapy for cancer was conducted with a lymphoma patient [2,3]. Regrettably, early therapeutic monoclonal antibodies, owing to their murine origins, provoked immune responses in humans and were ineffective at stimulating immunity in patients, thus constraining their clinical utility. In the late 1980s, techniques emerged to humanize antibodies to overcome these limitations [4]. Further advancements have led to the development of "fully-human" antibodies using transgenic mice or in vitro yeast or phage display systems [5,6]. Consequently, these innovations in antibody engineering have elevated mAbs to a pivotal role in cancer treatment.

These antibodies are designed to target specific proteins or receptors found on cancer cells, either obstructing their growth signals, instigating cell death, or prompting the immune system to attack the cancerous cells. One of the primary advantages of monoclonal antibodies is their exceptional specificity and selectivity. They can be precisely engineered to identify and attach to particular molecules present on cancer cells while avoiding healthy cells.

## 2. Structure and function of antibodies

Human immunoglobulins are shaped like a "Y" and consist of two identical light chains (LCs) and two identical heavy chains (HCs). In nature, these pairings form intact immunoglobulins, where one LC pairs with one HC to create a heterodimer. Disulfide bonds link the HC and LC within the heterodimer, and disulfide bridges link the two HCs within the heterotetramer. Human LCs can belong to one of two functionally similar classes,  $\kappa$  or  $\lambda$ , each comprising two domains: a constant domain (CL) and a variable domain (VL). On the other hand, human antibody HCs can be one of five isotypes: IgA, IgD, IgE, IgG, and IgM, each playing a distinct role in the adaptive immune system. IgAs, IgDs, and IgGs consist of three constant (C) and one variable (V) domains, while IgEs and IgMs have one variable and four constant domains. IgA and IgM isotypes have an additional component known as a J-chain, which enables the formation of dimers and pentamers, respectively. The remaining isotypes exist as monomers, defined here as HC-LC pairs [7].

The Fc regions of antibodies are recognized by Fc receptors (FcRs) present on various immune cells. Antibodies can be categorized into five distinct classes based on the type of heavy chain they possess: IgA, IgD, IgE, IgG, and IgM. Among these, IgG is the most commonly used form in antibody therapy due to its ability to interact with its corresponding FcR type, Fc $\gamma$ R, which is found on neutrophils, eosinophils, monocytes, natural killer (NK) cells, dendritic cells, and This interaction facilitates specialized functions like antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Within the IgG class, subclasses like IgG1 and IgG3 can elicit ADCC and CDC, whereas IgG2 and IgG4 cannot [8].

Monoclonal antibodies (mAbs) are essentially clonal versions of a specific antibody isotype, targeted to a particular antigen epitope. Currently, in mAb therapeutics, IgG is the only class of antibodies in use. This preference is due to IgG's favorable pharmacokinetics, stability, low immunogenicity (particularly in newer, humanized/human agents), limited toxicity profiles, and the relative ease with which a large number of mAbs can be produced for various antigens. General features of antibodies include their composition with two light and heavy chains, with both types of chains containing variable and constant

domains (one variable and one constant in light chains, and one variable and three constant domains in heavy chains) [9].

**Mechanism of action mAbs**

Monoclonal antibodies (mAbs) that specifically target antigens unique to tumor cells or those that are overexpressed can trigger tumor cell death through various mechanisms (as illustrated in Figure 1). One of the primary ways in which many antibodies directly induce tumor cell death is by interfering with the signaling of growth factor receptors. When mAbs bind to their target growth factor receptors, they disrupt the signaling pathways that promote tumor growth and survival. This disruption can occur by altering the activation state of the receptor or by preventing the binding of ligands.

For instance, epidermal growth factor receptor (EGFR) is commonly overexpressed in numerous cancer types, and signaling through EGFR contributes to tumor cell proliferation, migration, and invasion. Cetuximab, an anti-EGFR mAb, prompts apoptosis in tumor cells by inhibiting ligand binding and the formation of receptor dimers [10,11].

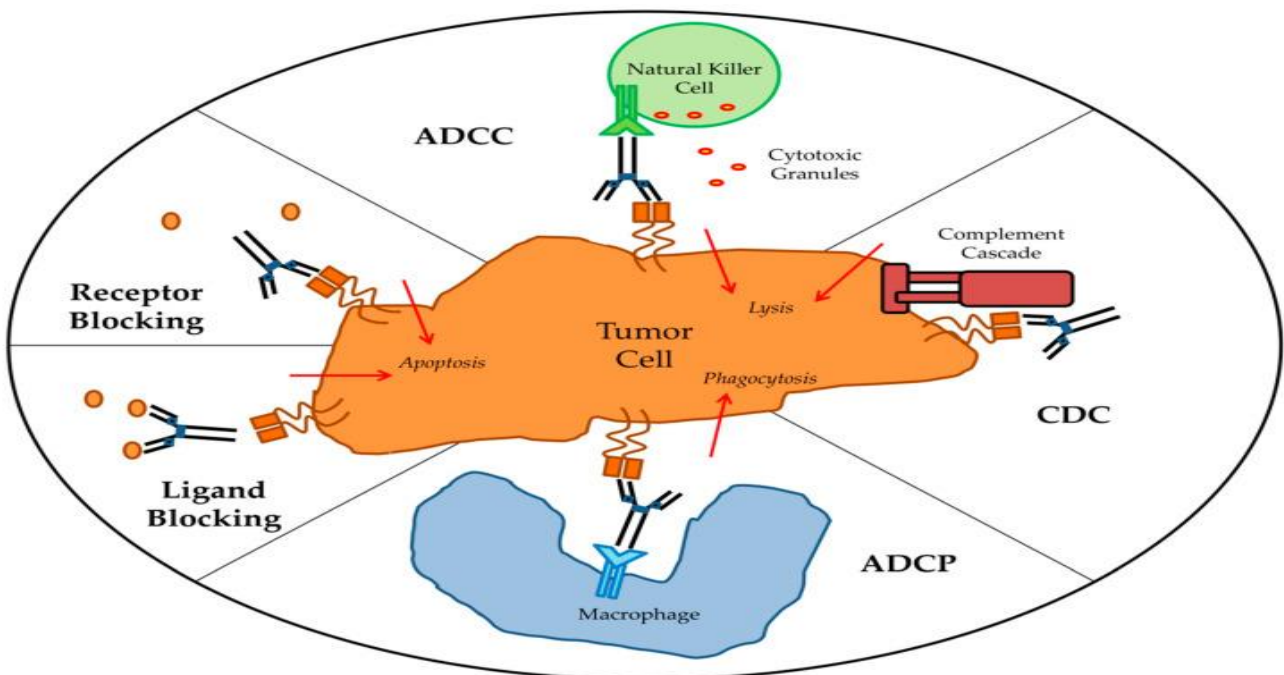


Figure 1

Antibody effector mechanisms.

ADCC: antibody-dependent cellular cytotoxicity;

CDC: complement-dependent cytotoxicity;

ADCP: antibody-dependent cellular phagocytosis

**Mechanisms of Action for Nonconjugated mAbs**

Ordinarily, when antibodies bind directly to their targets, such as pathogens, they cause an immediate disruption in structure, effectively preventing the entry of pathogens into cells. This property is highly sought after in the development of therapeutic antibodies, particularly when the goal is to block specific

signaling molecules. The binding of monoclonal antibodies (mAbs) to specific receptors can also lead to their internalization through various processes, suggesting a common regulatory mechanism. In the context of anticancer therapies, this ability to obstruct interactions and induce receptor internalization has provided a means to hinder oncogenic cellular signaling.

Furthermore, a significant portion of antibodies contains a conserved Fc (Fragment Crystallizable) domain, a term originating from earlier research, which allows them to directly engage with Fcγ-receptors (FCGR) found on various types of immune cells [12]. This capability enables mAbs to directly initiate diverse immune responses, influenced by the ratio of binding to activating and inhibitory FCGRs (A:I ratio). These ratios differ depending on the antibody isotype [13].

### **Mechanisms of Action for Conjugated mAbs**

One of the most rapidly expanding applications of monoclonal antibodies (mAbs) in cancer treatment involves their conjugation to various cytotoxic payloads, a strategy known as Antibody-Drug Conjugates (ADCs) [14]. In this approach, a cytotoxic drug is chemically linked to either the heavy or light chain domain of a mAb using various types of linkers. The unique ability of mAbs to internalize into cells enables a more precise delivery of the cytotoxic agent to tumor cells, thereby reducing the systemic toxicity associated with traditional chemotherapy. Additionally, this method is also utilized with alternatives to cytotoxic compounds, such as innate immune-stimulatory molecules like Toll-like receptor agonists, which can activate the anti-tumor immune response [15].

### **3. Classification of chemotherapeutic monoclonal antibodies**

Advancements in genetic engineering techniques have led to the development of four primary categories of Chimeric Monoclonal Antibodies (CmAbs): murine, chimeric, humanized, and fully human CmAbs.

**Murine CmAbs:** These antibodies are exclusively derived from mice and were the first to be employed in cancer chemotherapeutics [16].

**Chimeric CmAbs:** Chimeric CmAbs typically consist of variable regions sourced from mice and constant regions (about 65%) sourced from humans [17]. Some chimeric CmAbs can also be non-humanized, like chimeric trifunctional CmAbs, which are hybrid monoclonal antibodies created from a combination of rat and mouse components. They possess three distinct antigen-binding specificities: one for tumor cells, one for T lymphocyte cells, and one for accessory cells [18]. The introduction of fully human Fc portions in chimeric CmAbs significantly reduced their immunogenicity and improved their interaction with human effector cells and the complement system compared to murine CmAbs [19].

**Humanized CmAbs:** These antibodies are primarily engineered from human sources (about 90%), except for the complementarity-determining regions of the Fab portion, which are of murine origin. Humanized CmAbs are even less immunogenic than chimeric CmAbs [20].

**Human CmAbs:** Human CmAbs are entirely composed of components from humans and are engineered from transgenic mice. Compared to chimeric and humanized CmAbs, they exhibit higher affinity for human antigens and provoke minimal to no hypersensitivity responses [20].

These different types of CmAbs offer varying degrees of human components and immunogenicity, allowing for tailored approaches in cancer therapy depending on the desired level of immune response and interaction with human cells.

**Clinical uses of chemotherapeutic monoclonal antibodies**

Antibodies have proven to be highly adaptable platforms for the development of innovative therapeutics, resulting in a wide array of approaches. The discovery of target able tumor-specific antigens sparked significant interest in the creation of immunotherapies [21].

With the emergence of monoclonal antibodies (mAbs), it was envisioned that using them to target tumor cell antigens could potentially offer a more effective and less toxic treatment option compared to traditional chemotherapy. In 1988, scientists identified a protein called CD20, which was specifically present on mature B cells. CD20 was found to be abundantly expressed on cancerous B cells in non-Hodgkin's lymphoma but absent on healthy immature B cells. Consequently, the development of a mAb therapy that targeted CD20 held the promise of eliminating cancerous cells while leaving immature B cells intact to replenish the supply of healthy cells. This marked a significant milestone as CD20 became the first target for mAb therapy, and rituximab, the anti-CD20 mAb, was the inaugural mAb approved for the treatment of cancer [22].

CmAb	Type	Year approved
	<b>Unconjugated</b>	
Rituximab	Chimeric IgG1	1997
Trastuzumab	Humanized IgG1	1998
Alemtuzumab	Humanized IgG1	2001
Tositumomab	Murine IgG2a	2003
Cetuximab	Chimeric IgG1	2004
Bevacizumab	Humanized IgG1	2004
Panitumumab	Human IgG2	2006
Catumaxomab*	Chimeric mouse-rat hybrid	2009
Ofatumumab	Human IgG1	2009
Ipilimumab	Human IgG1	2011
Pertuzumab	Humanized IgG1	2012
Denosumab	Human IgG2	2013
	<b>Conjugated</b>	
Ibritumomab tiuxetan	Murine IgG1 Radio-nucleotide (Yttrium90 or Indium111)	2002
Tositumomab	Murine IgG2a Radio-nucleotide (Iodine131)	2003

CmAb	Type	Year approved
	<b>Unconjugated</b>	
Brentuximab vedotin	Chimeric IgG1 Drug (Auristatin E)	2011
Trastuzumab emtansine	Humanized IgG1 Drug (Mertansine)	2013

For a comprehensive list of Chimeric Monoclonal Antibodies (CmAbs) approved by the United States Food and Drug Administration (FDA) for use in oncology, categorized by type and year of approval, please refer to Table 1.

Monoclonal antibodies for cancer therapy that have received FDA approval, categorized as unconjugated and conjugated forms.

Approved by European Medicines Agencies and undergoing trials in the USA. CmAb: chemotherapeutic monoclonal antibody. Source: [23, 24]

#### 4. Clinical successes

CmAb	Antigenic target	MOA	Main cancer indication(s)
Rituximab	CD20	ADCC, CMC, induces apoptosis	Non-Hodgkin's lymphoma
Alemtuzumab	CD52	Induces apoptosis, CMC, ADCC	Chronic lymphocytic leukaemia
Tositumomab	CD20	ADCC, induces apoptosis	Non-Hodgkin's lymphoma
Cetuximab	EGFR	ADCC, inhibition of EGFR signaling	Colorectal cancer.
Bevacizumab	VEGF	Inhibition of VEGF signaling	Lung cancer, renal cancer, colorectal cancer, brain cancer, breast cancer
Panitumumab	EGFR	Inhibition of EGFR signaling	Colorectal cancer
Catumaxomab*	EpCAM	ADCC, T-cell mediated lysis, phagocytosis via FcγR accessory cells	Malignant ascites in patients with EpCAM +ve cancers
Ofatumumab	CD20	ADCC, CMC	Chronic lymphocytic leukaemia
Denosumab	RANKL	Inhibition of RANKL signaling	Breast cancer, prostate cancer
Ipilimumab	CTLA-4		Melanoma



CmAb	Antigenic target	MOA	Main cancer indication(s)
Pertuzumab	HER2	Inhibition of HER2 signaling	Breast cancer
90Y-ibritumomab tiuxetan	CD20	Radioisotope (90-Yttrium) delivery	Non-Hodgkin's lymphoma
131-I tositumomab	CD20	Radioisotope (131-Iodine) delivery	Non-Hodgkin's lymphoma
Brentuximab vedotin	CD30	Cytotoxic drug (auristatin E) delivery	Hodgkin's lymphoma, anaplastic large cell lymphoma
Trastuzumab emtansine	HER2	Inhibition of HER2 signaling, ADCC	Breast cancer

\*Monoclonal antibodies authorized by the European Medicines Agency (EMA) and currently under clinical trials in the United States.. Source: [23, 24, 25]

### 5. Side effects

It's important to note that all treatments, including monoclonal antibodies (mAbs), can have side effects, and the specific side effects can vary depending on the type of mAb being used. Allergic Reactions: One common side effect associated with some mAbs is an allergic reaction to the drug. This reaction is most likely to occur during treatment and particularly when you receive the treatment for the first time. To prevent such reactions, your healthcare provider may administer paracetamol (a pain reliever), a steroid (anti-inflammatory medication), and an antihistamine drug (to reduce allergic reactions) before your treatment. Allergic reactions to mAbs can manifest as symptoms such as breathlessness, fever, chills, an itchy rash, and feeling faint. Your nurse will closely monitor you during treatment and provide prompt treatment for any allergic reaction symptoms that may arise. General Side Effects: In addition to allergic reactions, mAbs can cause general side effects that can vary in intensity. These may include: Skin

**Changes:** Some individuals may experience skin changes, such as redness, soreness, or an itchy rash.

**Diarrhea:** Diarrhea can be a side effect of certain mAbs.

**Tiredness:** Fatigue or tiredness is a common side effect reported by some patients undergoing mAb treatment.

**Flu-Like Symptoms:** Flu-like symptoms such as chills, fever, dizziness, and nausea may occur in response to mAb therapy.

**Nausea and Vomiting:** Feeling or being sick (nausea and vomiting) can also be side effects associated with mAbs. It's crucial to discuss potential side effects and their management with your healthcare team before starting mAb treatment. Your medical team can provide guidance on how to manage and alleviate these side effects, ensuring that you have a more comfortable and effective treatment experience. They

will closely monitor you during treatment to address any side effects promptly. Specific side effects Some MABs have specific side effects which can sometimes be serious. For example, some MABs are responsible for heart problems or increase risk of bleeding. Clinical team will tell you about this before your start treatment. For more information about the side effects of your treatment, go to the individual drug pages.[26]

Contact your Clinical team if you have these symptoms, particularly if you have diarrhoea, a rash or flu-like symptoms. They can decide whether you need treatment.

## 6. Limitation of CmAb-Based Therapy

The success of monoclonal antibodies (mAbs) in therapeutic applications has been mixed, with some achieving significant clinical success like Rituximab, while others face challenges, including drug resistance. Here are some key considerations:

**Development of Drug Resistance:** One major challenge with therapeutic mAbs is the development of drug resistance, which highlights the need to gain a deeper understanding of their mechanisms of action. To combat this resistance, various strategies have been explored, such as combining mAbs with other compounds, modifying the Fc region to enhance activation of natural killer (NK) cells and macrophages, or using them in conjunction with conventional therapies [27, 28].

**Complex Production Process:** mAbs are complex proteins with a molecular weight of 150 kDa and contain disulfide bonds and N-linked glycans as post-translational modifications. Their production involves the use of sophisticated eukaryotic machinery, making them relatively expensive and less accessible to all patients. To address this issue, cost reduction strategies have been developed for commercial antibodies like Rituximab [29].

**Immunogenicity and Poor Immune Response:** Historically, the first therapeutic mAbs derived from mice often resulted in side effects such as immunogenicity (provoking immune responses) and poor immune responses in patients, limiting their clinical use. However, biotechnological advancements have addressed these drawbacks. Techniques have been developed to translate the murine Fc region into a fully human Fc or to completely delete this region to generate other antibody formats, thus circumventing these challenges [30].

In summary, while some therapeutic mAbs have achieved significant success, challenges like drug resistance, production costs, and immunogenicity have been encountered. Ongoing research and advancements in biotechnology are focused on overcoming these hurdles and further enhancing the efficacy and accessibility of monoclonal antibody therapies.

## Combined Therapies

Combination therapies involving monoclonal antibodies (mAbs) have indeed shown great promise in improving treatment outcomes for cancer patients. These combinations, which can include mAbs along with chemotherapy, radiation therapy, or other targeted therapies, often result in synergistic effects, enhancing the overall effectiveness of cancer treatment.

**Synergy through Targeted Approach:** One of the key advantages of combining mAbs with other treatments is the ability to target cancer from multiple angles. For instance, pairing a mAb that specifically targets a particular protein on cancer cells with a chemotherapy drug designed to disrupt DNA replication can lead to more potent and comprehensive cancer cell destruction.

**Signaling Pathway Inhibition:** Monoclonal antibodies are increasingly important



in clinical oncology because they can specifically inhibit signaling pathways crucial for tumor growth. Combining mAbs allows the simultaneous targeting of multiple pathways, potentially leading to additive or synergistic effects. This is a powerful approach as it addresses the complexity of cancer biology, where multiple signaling pathways may contribute to tumor development and progression. Complementary Mechanisms: Monoclonal antibodies are often favorable for combination therapy because they tend to have limited overlapping toxicity with other treatments and do not typically interfere with each other's pharmacokinetics (how drugs are absorbed, distributed, metabolized, and eliminated). This makes them highly compatible with various treatment modalities [31]. For a more detailed overview of some mAb combinations used in the treatment of tumors and malignancies, you can refer to the specific resource or reference [32]. These combinations offer exciting prospects in the field of oncology, providing patients with more effective and well-tolerated treatment options.

<b>Combination of antibodies (target)</b>	<b>Indication</b>	<b>Type of research</b>	<b>Results</b>
Bevacizumab (VEGF) and panitumumab (EGFR)	Metastatic colorectal cancer	Clinical (phase II and III) and meta-analysis	Addition of panitumumab to bevacizumab and chemotherapy (oxaliplatin- and irinotecan-based) resulted in decreased progression-free survival and increased toxicity [33]
Bevacizumab (VEGF) and cetuximab (EGFR)	Metastatic colorectal cancer	Preclinical, clinical (phase II and III)	Cetuximab added to bevacizumab and chemotherapy as first line treatment resulted in worse progression-free survival (9.4 vs 10.7 months), more skin toxicity and lower quality of life [34],[35]
Cetuximab (EGFR) and dalotuzumab (IGF-1R)	Advanced colorectal cancer	Clinical (phase I)	In this study the combination of dalotuzumab with cetuximab and irinotecan was well tolerated. No pharmacokinetic interactions were seen [36]
Panitumumab (EGFR) and ganitumab (IGF-1R)	Advanced colorectal cancer	Clinical (phase I)	The addition of ganitumab (up to doses of 12 mg/kg) to panitumumab was well tolerated and no pharmacokinetic interactions were found[37]
Cetuximab (EGFR) and	Advanced solid tumors	Clinical (phase II)	A study where paclitaxel and carboplatin was combined with

cixutumumab (IGF-1R)			cetuximab (arm A), cixutumumab (arm B) or both (arm C), was prematurely closed, because an excessive number of grade 5 events in arm A and C; thirteen of the 140 patients died during treatment [38]
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**7. Conclusion:**

Monoclonal antibodies have indeed brought about a revolution in the field of cancer treatment. They offer a more targeted and less toxic approach compared to traditional chemotherapy. Their unique ability to precisely target cancer cells and augment the immune response has demonstrated significant potential in improving patient outcomes. Combination therapies involving monoclonal antibodies, whether in conjunction with chemotherapy, radiation therapy, or other targeted treatments, have shown the power of synergy. By addressing different facets of cancer growth and progression, these combinations can enhance treatment effectiveness and potentially overcome resistance mechanisms. Nonetheless, there is still ongoing research needed to optimize the use of monoclonal antibodies, identify predictive biomarkers for treatment response, and develop even more effective combination therapies. The future of monoclonal antibody therapy in cancer appears promising. Advances in antibody engineering techniques and the discovery of novel therapeutic targets continue to expand the horizons of targeted cancer therapies. This ongoing innovation holds great potential for further improving cancer care and patient outcomes.

**8. Conflict of Interest**

There is no conflict of interest between authors.

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