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The Diverse Roles of Monoclonal Antibodies in Cancer Immunotherapy and Their Relative Effectiveness: A Literature Review

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Abstract

Introduction: In modern oncology, immunotherapy has emerged as a promising treatment modality for numerous cancers. At the forefront of personalized medicine, immunotherapy utilizes components of a patient's immune system to selectively target cancer cells. Numerous immunotherapy drugs have been developed thus far, including monoclonal antibodies (mAbs). mAbs are genetically identical protein antibodies often isolated and purified from animals through recombinant DNA technology. They are capable of recognizing molecules that are uniquely present on the surface of cancer cells, such as tumour-specific antigens and/or receptors. This narrative review explores the various uses of mAbs in the treatment of cancer.

Methods: A narrative literature review was conducted using Pubmed, Medline, and Embase to analyze and synthesize current and prior research surrounding the various uses of mAbs in the context of cancer treatment. Specific examples and potential shortfalls of various treatment methods were also analyzed.

Results: mAbs can be used in several distinct ways to target cancerous cells. In the native immunoglobulin G form, mAbs direct immune cells to tumours and induce cytotoxicity by initiating biochemical cascades, leading to effects such as phagocytosis, opsonization, activation of immune cells, degranulation, and cytokine release, among others. mAbs may also be conjugated with radionuclides, or traditional chemotherapeutic agents for targeted drug delivery. They can also be used to target the immune system via conjugation to cytokines or other mAbs which directly interact with immune cells for targeted recruitment. mAbs targeting immune checkpoints can also be used to enhance cancer-related immune responses. However, mAbs are not perfect, and are thus prone to a slew of limitations which are still being addressed.

Discussion: mAbs are highly useful, primarily as a result of their specific molecular recognition abilities. This property underlies all uses in cancer immunotherapy and can further be exploited in the development of new immunotherapy technologies and methodologies, along with the elucidation of novel antigens and targets in cancers, to improve the field and address limitations.

Conclusion: This literature review aims to synthesize data pertaining to the various potential uses of mAbs in cancer treatment. This approach will provide more insight into the current state of immunotherapeutics, and where additional research must be conducted.

Keywords: immunotherapy; monoclonal antibodies; mAbs; cancer; cancer therapy; molecular recognition; drugs

Introduction

Antibodies (Abs) are protein-based complexes that specialize in specific, high-affinity molecular recognition of antigens, and the initiation of immune responses. Monomeric Abs generally possess a molecular weight of ~150 kDa, consisting of two heavy chains and two light chains bound by disulfide bonds to form a Y-shaped architecture [1]. There are a variety of Ab subtypes, however all possess a constant Fc domain involved in binding immune cells/complement components to mediate cytotoxicity, and a variable Fab domain involved in recognizes and binding antigens [1]. Abs are produced and secreted by immune B-cells in response to activation by antigens and/or other immune cells [2].

Immunoglobulin G (IgG) is the most abundant Ab subtype in the body, and represents as much as 10-20% of serum protein [2]. IgG exerts its cytotoxic and immune functions in two primary ways. First, interactions with Fcγ receptors (FcγRs) can trigger antibody-dependent cell-mediated cytotoxicity (ADCC) [3]. Upon binding a target antigen via the Fab domain, the Fc region of IgG mAbs can bind to FcγRs on immune cells to mediate cytotoxicity [3]. There are many subtypes of FcγRs, with both activating and inhibitory receptor variants [3]. FcγRI (CD64) is a high affinity FcγR which can be activated by a single IgG

monomer [3]. Low affinity activating receptors include FcγRIIA (CD32A), FcγRIIIA (CD16A), FcγRIIIB (CD16B), and require multiple antibodies in an immune complex to exert effects [3]. Stimulation of these receptor subtypes by Fc/FcγR binding leads to an intracellular signalling cascade in immune cells which initiates ADCC, causing cellular effects such as phagocytosis, degranulation, and cytokine release of the immune cell (see Figure 1) [3]. Alternatively, IgGs can interact with complement proteins initiating complement-mediated cytotoxicity (CMC) via the classical pathway [4]. In this pathway, the Fc region on IgG binds and activates a variety of complement proteins, natively present in the serum in inactive form [4]. These proteins can then initiate CMC, which leads to cellular effects such as activation of nearby leukocytes, opsonization (i.e., molecular tagging) of pathogenic cells and immune complexes to facilitate their transport and removal, as well as formation of membrane attack complexes (MACs)—multi-protein complexes which form on the surface of target cells, damaging the cell and leading to cell death [4].

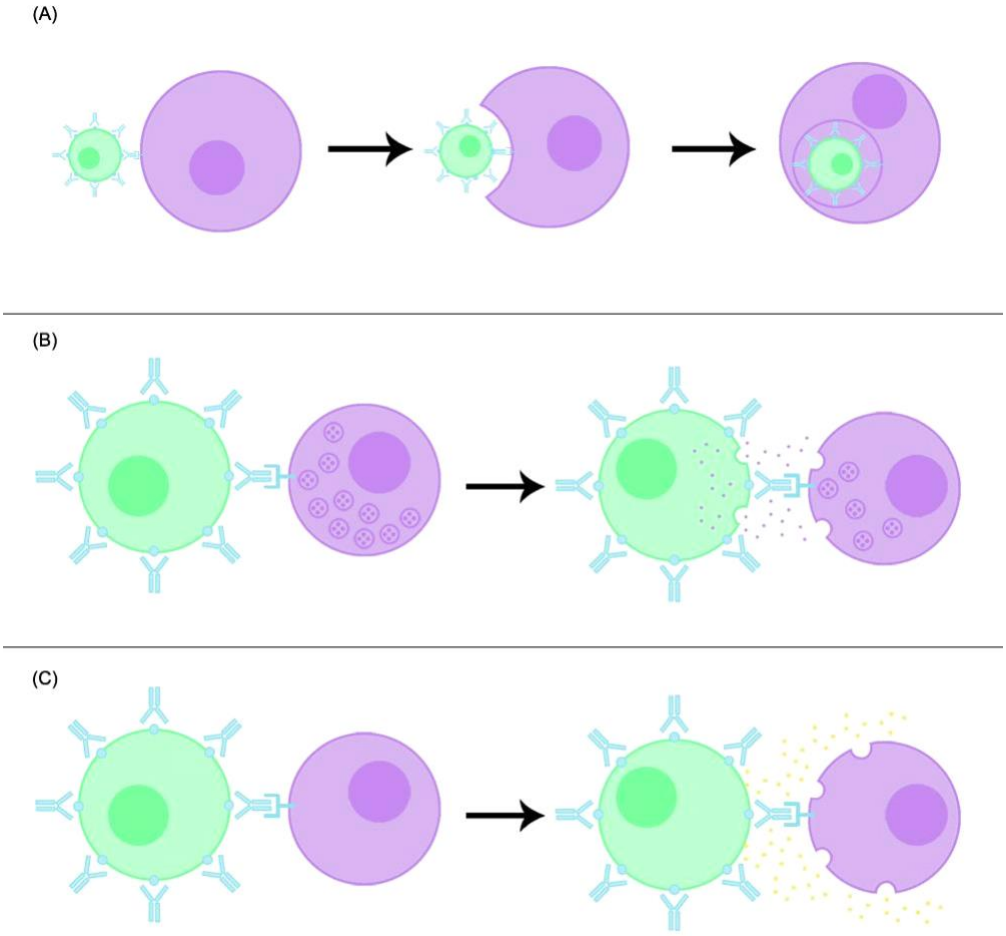

Figure 1. Antibody-dependent cell-mediated cytotoxicity (ADCC) can lead to cellular effects including (A) phagocytosis, (B) degranulation, and (C) cytokine release.

Immunotherapy makes use of artificial IgG antibody-antigen interactions to direct the immune system to various targets with high affinity and specificity [5]. Monoclonal antibodies (mAbs) are one common immunotherapy, consisting of identical antibodies which all bind the same epitope, derived from a single genetically identical B-cell lineage [6]. Since immunotherapy requires the generation of synthetic antibodies specific to a desired antigen of interest, unique technologies had to be developed to produce these antibodies [7]. This was initially made possible by hybridoma technology developed by Kohler and Milstein, in which mAbs were produced by injecting mice with a particular antigen generated through recombinant DNA technology [7]. Murine B-cells

producing antibodies against the antigen of interest were then fused with immortal myeloma cells forming a 'hybridoma' and allowing cells to grow indefinitely and secrete the desired Abs, which could then be isolated [7]. However, a problem with using mAbs secreted directly from these hybridoma cultures is that the human immune system is trained to attack anything that it recognizes as foreign, including the murine antibodies themselves [8]. This limitation was overcome by the replacement of the murine DNA sequences with their human counterparts leading to the development of chimeric, humanized and human therapeutic antibodies, generally via recombinant DNA technology [9]. Reduced immunogenicity of mAbs was accomplished by chimeric fusion of part mouse and part human antibodies (-ximab), by a small portion from mouse and a major portion of protein from human (-zumab), or only human proteins (-umab), to create mAbs with humanized backbones [10].

In order to target mAbs to a tumour, a cell surface antigen that is expressed in large quantities on the cancer cell, relative to the antigens on healthy cells, is desirable. These may include hematopoietic differentiation antigens, cell surface differentiation antigens, antigens involved in growth and differentiation signalling, antigens involved in angiogenesis, and tumour stromal and extracellular matrix antigens [11]. There is no single antigen that can be used universally, and selection is often heavily dependent on the cancer type under study. Assessment of physical and chemical properties of the antibody, detailed specificity analysis of antigen expression between tumour cells and healthy somatic cells, as well as assessment of antibody tissue localization are all essential in development of mAbs directed to cancers cells [11].

The application of immunotherapies to treat cancer has significantly improved in recent years [12]. As outlined previously, the emerging field of onco-immunology has led to the development of mAbs, the most widely implemented immunotherapeutic, especially to treat and manage cancers [13]. Following the advancement of technology, remarkable progress has been made, enabling modification of mAb's molecular size, affinity, specificity, and valency [14]. By tailoring such properties of mAbs, their clinical potential has increased as they can better target antigens without being recognized as a foreign substance by the immune system [14]. mAbs can be used to target various cancers through numerous mechanisms, which all make use of their molecular recognition properties [14]. These include directly promoting cytotoxicity via ADCC/CMC, delivery of therapeutic agents, interfering with receptor-ligand interactions, and modulating the immune response. This review aims to analyze and synthesize how and when mAbs and derivatives can be used in the treatment of cancers. In this process, we aim to answer the question, 'How can monoclonal antibodies be used to efficaciously target different cancers?' and outline and address potential limitations.

Methods

Important topics related to mAbs and immunotherapy were first identified through preliminary research in order to determine the state of the literature and identify any areas requiring additional study. Relevant sources were then identified using academic databases, including PubMed, Medline, and Embase using keywords such as 'monoclonal antibodies,' 'cancer,' 'immunotherapy,' and 'drugs.' Searches were restricted to English language papers and were selected using the following criteria:

1. *Title and abstract must be relevant to the research question* - The title and abstract of the identified sources must be relevant to the search performed and topic of interest.
2. *Main body text must be applicable to the focus of review* - The main text was examined for studies that fulfilled the criteria during title and abstract screening. The contents of the main body of text were used to determine whether the source is relevant to this review.

Using these criteria, relevant studies were included in the review. Sources were also drawn directly from citations of identified reviews by applying the same selection criteria described above. Further research was conducted in a similar manner, so as to examine the individual ways that mAbs target cancers, and their specific uses and efficacies. Additional searches were performed on Pubmed and Google Scholar in accordance with the methodology outlined above for questions that could not be answered through previously identified sources. Results that were found were critically analyzed and implications were determined.

Results

Complement-Mediated and Antibody-Dependent Cellular Cytotoxicity

Cytotoxic therapies are mAbs used to promote cytotoxicity in cells through the following mechanisms mentioned previously: ADCC and CMC [15]. In ADCC, mAb-coated cancer cells interact directly with FcγRs on FcγR-expressing immune cells such as natural killer (NK) cells, macrophages, B-cells, dendritic cells, neutrophils and eosinophils, [16]. Upon Fc binding in activating receptors, an immunoreceptor tyrosine-based activation motif (ITAM) located either on the receptor's intracellular tail (FcγRIIA), or as a part of an accessory Fcγ subunit (other activating FcγRs), is phosphorylated by the Src family kinases [17]. The phosphorylated ITAM motif can then serve as a docking site for SH2-containing kinases. SH2 docking leads to an amplification cascade, resulting in activation of phosphatidylinositol-3-kinase (PI3-K) and phospholipase-Cγ (PLCγ), followed by protein kinase C (PKC), and sustained calcium elevation. These effects trigger ADCC, which includes phagocytosis, degranulation, and cytokine release (see Figure 1) [18]. Examples of mAbs that engage in this mechanism include cetuximab and pemtumomab.

Cetuximab is a chimeric mAb that binds epidermal growth factor receptor (EGFR), an antigen with high affinity that is overexpressed in colorectal cancers as well as head and neck cancers, inducing apoptosis in tumour cells by blocking ligand binding and receptor dimerization [19]. Pemtumomab targets the polymorphic epithelial mucin (PEM) antigen present in excess in ovarian carcinomas to elicit similar effects [20].

In CMC, following mAb binding to a target antigen on a cancer cell, antitumour immunity is initiated via binding of the IgG Fc region to the complement factor C1q— a component of the C1 complex [21]. This leads to the activation of the complement cascade and releases components that can directly interact with receptors on immune cells [22]. The anaphylatoxins, C3a and C5a complements, act as potent proinflammatory mediators, recruiting and activating leukocytes [23]. The opsonins, C3b, iC3b, and C3d complements, covalently bind to receptors on immune cells, and facilitate transport and removal of tagged target cells and immune complexes via opsonization [22]. Finally, the MAC, C5b-9 is able to directly lyse opsonized pathogens or damaged cells through pore formation. C5a is also able to downregulate FcγRIIB, induce secondary cytokine release, and increase vascular permeability [22]. Together these pathways induce cytotoxic effects via CMC. Rituximab is an example of a mAb that is highly efficient at mediating CMC [24]. By binding to the surface of the cancerous cell, the immune cells signal the formation of a membrane attack complex, which is then directed to the target [25]. Chronic Lymphocytic Leukemia (CLL) and Non-Hodgkin's Lymphoma (NHL) are among the more clinically sensitive cancer types to rituximab [24]. Obinutuzumab is another mAb that targets the CD20 protein on the surface of lymphoma and Leukemia cells [26].

Receptor-Ligand Interactions

mAbs can also interfere with numerous receptor-ligand interactions in rapidly proliferating cancer cells to elicit an antitumor response [27]. Blocking ligand-receptor interactions can inhibit the growth factor pathways which act as survival pathways for cancer cells [27]. Antagonistic mAbs' inhibition of growth factor-dependent survival pathways can also lead directly to the induction of apoptosis [28].

Given that tumour cells require new blood vessels to grow, inhibiting the growth of such vessels via an antagonistic mAb is one approach to inhibit tumour growth [29]. Blood vessels are rapidly generated in tumours by the stimulated proangiogenic factors and the vascular endothelial growth factor (VEGF) in a process known as angiogenesis [29]. mAbs such as bevacizumab can be produced to inhibit angiogenesis in tumour cells by interfering with the VEGF signalling cascade [30]. This has an antitumour response, as cancerous cells are deprived of nutrients and oxygen supplied by the blood vessels [30]. Bevacizumab has been shown to be effective in numerous cancers including colorectal, lung, breast, renal, brain, and ovarian cancer [31]. Given that mAbs that inhibit angiogenesis do not induce cell death and instead inhibit cancer growth, they generally must be coupled with agents that are cytotoxic when used in clinical settings [32].

In addition to VEGF, cetuximab is another mAb found to bind certain subtypes of EGFR, acting as a competitive antagonist to inhibit growth factor binding [33]. In effect, cetuximab inhibits ligand-induced tyrosine kinase-dependent phosphorylation and downstream signaling of the receptor, effecting an inhibition of cell proliferation in various tumour cells [33]. As such, mAbs that act as competitive inhibitors to growth factors interfere with the EGFR pathway, inhibiting the activation of the cell's survival processes [33].

Several cell surface receptors can transduce an apoptotic signal once activated with a ligand [34]. Specifically, receptors such as tumour necrosis factor receptor 1 (TNFR-1), TNF receptor-related apoptosis-mediating protein (TRAMP), and TNF-related apoptosis-inducing ligand receptor 1 and 2 (TRAIL-R1 and TRAIL-R2) carry the death domain that transduce apoptotic signals once activated [34]. This death receptor machinery serves as a means for selective killing; thus, it is targeted by the mAb TRA-8, which has been developed as an agonist of the TRAIL-R2 receptor [28]. Once TRA-8 is bound to its respective receptor on the tumour, it induces selective apoptosis. TRA-8 has been shown to elicit inhibitory effects on both solid tumours and leukemic cell lines in animal models [28].

Delivery of Therapeutic Agents

mAbs can further be used for their highly specific molecular recognition properties, acting as 'carriers' to successfully deliver therapeutic agents to cancerous cells. Once an antibody specific to the tumour of interest has been developed, immunoconjugates may be created and evaluated. Therapeutic agents that can be conjugated to mAbs include radionuclides, and chemotherapeutic drugs. Radionuclide immunoconjugates (radioimmunoconjugates) use antibody-conjugated radionuclides to deliver high energy radiation specifically to tumour cells, which damages tumour DNA and leads to cell death [35]. Conjugation of mAbs with chemotherapeutic agents (antibody-drug conjugates) can be used to deliver other cytotoxic chemical agents selectively to cancerous cells [36]. Other methods of therapeutic mAb-delivery also exist, including immunoliposomes (mAb-linked drug-containing liposomes used to deliver drugs to tumour cells) and Antibody Directed Enzyme Prodrug Therapy (ADEPT, mAb-linked enzymes used to metabolize a prodrug at the site of a tumour only), however these methods are less studied and both require further research before therapeutic use is possible [37, 38].

The majority of radioimmunoconjugates use the β-emitters ^{131}I or ^{90}Y, which is advantageous in treating larger tumour masses, due to the penetrating ability of β-radiation to deposit energy several cell diameters deep into the tissue [35]. However, α-emitters such as ^{213}Bi, ^{225}Ac, and ^{211}At have been deemed suitable for radioimmunotherapy, and deposit higher energy over a shorter range, often more effective for leukemias, and smaller clusters of cancerous cells [35]. For example, ^{131}I has been conjugated to tositumomab and ^{90}Y has been conjugated to rituximab (both antibodies directed against B-cell surface antigen CD20) [35, 39, 40]. Both of these radioimmunoconjugates have been successfully used for the treatment of NHL, and ^{131}I-tositumomab has been clinically approved in the United States [35, 39, 40]. 81C6 is another antibody directed against tenascin, a tumour-specific extracellular matrix glycoprotein, which has also been successfully conjugated to ^{131}I and ^{211}At. Both have shown promising clinical results, significantly increasing survival time in phase II clinical trials for the treatment of malignant glioma [41, 42].

A variety of chemotherapeutic agents can be conjugated to antibodies to form antibody-drug conjugates. Antibody-drug conjugates are most commonly formed covalently at interchain disulfide bridges and surface-exposed lysine residues, which are stable at physiological pH but can be released as a cytotoxic payload once internalized into the cancer cells' lysosomal system [36, 43]. In producing these conjugates it is important that the cytotoxicity of the drug and the specificity of the antibody both remain intact [36]. The drug-antibody ratio for antibody-drug conjugates in the clinic averages at 4:1, allowing for a more potent payload [44]. This class of conjugated mAbs can be used to treat a diverse range of cancers, depending on the antigen chosen, including leukemias, and smaller clusters of cancerous cells [43]. For example, polatuzumab vedotin-piiq is an antibody directed against B-cell surface receptor CD79b (to elicit cellular internalization), covalently linked to the cytotoxic drug monomethyl auristatin (MMAE) [45]. Polatuzumab vedotin-piiq has shown a large amount of success and has been clinically approved in the United States for use in treating diffuse large B-cell lymphoma (DLBCL), and is currently being developed for use in the treatment of NHL [46]. BR96 is another antibody directed against the Lewis-Y antigen, expressed on 75% of breast cancers, and has been successfully conjugated to doxorubicin [47]. This antibody-drug conjugate has shown limited clinical antitumour activity in phase II clinical trials [47].

Immune Modulation

Immune modulation by mAbs uses a variety of the approaches to target the immune system and immune response to tumour cells. These approaches include mAbs targeting molecules involved in immune checkpoints, and immunocytokines (mAb-mediated delivery of cytokines to tumour cells) and bispecific mAbs (BsAbs) which may both activate and direct immune cells to tumour cells.

Immune checkpoint inhibitors (ICIs) are drugs that are used to modulate the immune response to tumours, primarily through the regulation of T-cell activation [48]. T-cells are essential in the immunosurveillance of cancers, however it has been found that many cancers are able to evade a T-cell response by overexpressing inhibitory immune effectors [48]. These include cytotoxic T-lymphocyte antigen 4 (CTLA4) which interacts with T-lymphocyte CD80/CD86 receptors, and the ligand(s) of programmed cell death protein 1 (PD-L1 and/or PD-L2) which interact with the programmed cell death T-lymphocyte receptor (PD-1) [17]. Many mAb ICIs targeting these pathways are currently in clinical use in the United States [49]. Ipilimumab is successfully used to treat metastatic melanoma, and selectively binds CTLA4 on cancer cells, preventing the inhibitory interaction with CD80/CD86 [49]. Pembrolizumab and Nivolumab both selectively bind PD-1 on T-cells to prevent interaction with its ligands, and are used in the treatment of both metastatic melanoma and non-small cell lung cancer (NSCLC) [49].

Immunocytokines are mAbs conjugated to inflammatory cytokines, predominantly interleukin-2 (IL-2), interleukin-12 (IL12), and tumour necrosis factor (TNF) [50]. Cytokines localize d to the tumour surface by mAbs are then able to interact with cytokine receptors on nearby immune cells (e.g., T-cells, NK cells), and enhance a cytotoxic, pro-inflammatory immune response directed at the tumour cells [50]. For example, Hu14.18-IL2 is an IL-2 conjugated mAb that recognizes the GD2 disialoganglioside expressed on neuroblastoma cells [51]. Hu14.18-IL2 showed promising results that warrant further study in a phase II clinical trial in children with non-bulky high-risk neuroblastoma [51].

BsAbs work via a similar but distinct mechanism in which a mAb is selective for a tumour surface antigen on one Fab arm, and is selective for another antigen (generally an immunomodulating antigen) on the other Fab arm [52]. The most common and well-studied use for BsAbs is as cytotoxic effector cell redirectors which bind tumour surface antigens and stimulate activating immune receptors such as CD3 in T-cells, and FcγRIII in NK cells, among others, leading to a broad-spectrum, acute immune response [52]. For example, Blinatumomab is a cytotoxic effector cell redirector BsAb targeted to CD19 × CD3 that is currently used in the United States as a treatment for B-cell Acute Lymphoblastic Leukemia (B-ALL) [52]. Alternately, BsAbs can be used as tumour-targeted immunomodulators to selectively stimulate immune receptors and activate a smaller pool of tumour-specific T-cells (which is more likely to induce immunological memory), or act as dual immunomodulators and bind two distinct immunomodulating targets simultaneously, potentially generating additive immune effects [52]. However, the

latter two classes of BsAb require significant additional study before clinical applications will be possible [52].

General Limitations

While mAbs have proven very effective as cancer immunotherapies in many areas, they can face a host of limitations. These include pharmacokinetic limitations; namely short *in vivo* half- lives, difficulty penetrating into tissues, restriction to lymphatic absorption due to large molecular weight, excretion by the kidneys, liver, and spleen, and protease degradation [53]. Additionally, mAbs are particularly susceptible to adverse immune events such as allergic reactions, immune-related reactions, and/or organ toxicity, depending on the patient's immune system and the target antigen (potential for cross-reactivity) [54]. The development of antibody-drug antibodies (ADAs) is a significant challenge that can vastly change the efficacy of mAb immunotherapies and lead to unpredictable changes in pharmacokinetic properties [53]. Changes in protein folding or mAb denaturation can further disrupt the mechanism of action, and promote protein aggregation, potentially leading to adverse effects, although this may be minimized via proper formulation [53]. Acquired resistance to immunotherapeutics (e.g., via antigen mutation/ underexpression) is another limitation, and may necessitate the future discovery and characterization of mAbs raised against new antigens [55]. Cellular fate of mAbs (uptake into cells) must also be considered, as this can affect the properties of drug delivery positively or negatively depending on the mAb treatment option in question [35].

However, some of these properties may be addressed via additional structural modification to mAbs. This can include conjugation to polyethylene glycol (PEG) to slow excretion and resist protease digestion, and/or fusion to albumin or addition of Fc fusion proteins to hijack recycling mechanisms and increase half-life [53]. Use of slow-release delivery methods such as hydrogels, nanoparticles, and liposomes can also be used to encourage longer half-lives [53]. Exploration of lower molecular weight, non-IgG protein scaffolds with molecular-recognition properties akin to mAbs, is another promising area of inquiry to address some of these limitations [56].

Discussion

As evidenced by the sheer number of effective uses for mAbs in cancer immunotherapy, they are a highly versatile tool in medicine. This versatility stems from the relative ease of mAbs development that can selectively bind to a desired ligand. By learning from natural processes harnessed by the human adaptive immune system, we have been able to develop a tool that is only limited to the imagination in terms of potential uses. However, these uses all have one factor in common—selective molecular recognition. Whether through natural stimulation of FcγRs following antigen binding, selective modulation of receptor-ligand interactions, delivery of various therapeutic agents to tumour cells specifically, or secondary modulation of the immune system, the importance of this property is apparent in cancer immunotherapy.

This property can be used to inspire further methodologies and technologies for immunotherapy, potentially leading to the development of novel treatment paradigms. Furthermore, the characterization and identification of ideal target antigens for immunotherapy is another significant endeavor. Given the vastness of potential pathways that biochemically interact and could be exploited in immunotherapy, this is a difficult but essential task. The combination of increased understanding of biochemical pathways with novel methodology could revolutionize the field even further. Development of a large-scale screening assay may be of use in this regard, so as to preclude the need for extensive testing for various antigens only to hit dead ends later on. This could potentially lead to advancements in personalized medicine, such as personalised immunotherapy based on tissue biopsies and genetic screenings for specific mutations, so as to address a given cancer in a minimally invasive way.

However, as described above, mAbs can have major limitations in use. While several methods to overcome these limitations have been proposed, the field is still far from perfect. Future research could explore these limitations further and determine how they may be addressed moving forward. Relevant areas of inquiry include characterization of further therapeutic targets for mAbs, and perhaps the exploration of novel therapeutics that take advantage of molecular recognition without necessitating the shortfalls posed by protein-based drugs. This could include the development of highly modified peptides, or even small molecules that are able to act as biomimetic agents. Of course, this must accompany a better understanding of the origins of molecular recognition properties in mAbs, and scale easily through synthesis to be applicable to therapeutics. Further studies could also focus on analysis of the intersections between the various pathways influencing and acting on mAbs *in vivo*, so as to better understand relevant protein interactions and avoid the potential for cross-reactivity and aggregation. By obtaining a greater breadth of knowledge on the biochemical pathways underpinning mAbs, new approaches can then be identified to increase clinical efficacy.

Conclusions

There are several distinct roles which mAbs may take on in cancer immunotherapy. Most traditionally, mAbs may make use of the natural immune processes of ADCC or CMC to kill cancer cells. Alternatively, mAbs can modulate relevant receptor-ligand interactions, resulting in cancer cell death or inhibition of further tumour growth. mAbs may also be used for their molecular recognition properties, as a selective delivery agent of radio- and/or chemotherapies. Finally, mAbs can be used to modulate the immune response, via direct inhibition of immune checkpoints, as a

selective delivery agent for cytokines, and/or in a bispecific capacity, leading to enhanced immune cell activation. mAbs do face some limitations, however many new techniques and methodologies continue to emerge to address these challenges, and mAbs are still successfully in use to treat cancers globally.

List of Abbreviations Used
Ab: antibody
Fab domain: antigen binding domain
Fc domain: constant domain
IgG: Immunoglobulin G
FcγRs: Fcγ receptors
ADCC: antibody-dependent cell-mediated cytotoxicity
CMC: complement-mediated cytotoxicity
MAC: membrane attack complex
mAb: monoclonal antibody
NK cells: natural killer cells
ITAM: immunoreceptor tyrosine-based activation motif
PI3-K: phosphatidylinositol 3-kinase
PLCγ: phospholipase-Cγ
PKC: protein kinase C
EGFR: epidermal growth factor receptor
PEM: polymorphic epithelial mucin
CLL: Chronic lymphocytic leukaemia
NHL: Non-Hodgkin's Lymphoma
VEGF: vascular endothelial growth factor
TNFR-1: tumour necrosis factor receptor 1
TRAMP-TNF receptor: related apoptosis-mediating protein
TRAIL-R1: TNF-related apoptosis-inducing ligand receptor 1
TRAIL-R2: TNF-related apoptosis-inducing ligand receptor 2
ADEPT: Antibody Directed Enzyme Prodrug Therapy
MMAE: monomethyl auristatin
DLBCL: Diffuse Large B-cell Lymphoma
BsAbs: bispecific mAbs
ICI: immune checkpoint inhibitor
CTLA4: cytotoxic T-lymphocyte antigen 4
CD-L1: ligand 1 of programmed cell death protein 1
CD-L2: ligand 2 of programmed cell death protein 1
PD-1: programmed cell death protein 1
NSCLC: non-small cell lung cancer
IL-2: interleukin-2
IL-12: interleukin-12
TNF: tumour necrosis factor
B-ALL: B-cell Acute Lymphoblastic Leukaemia
ADA: antibody-drug antibody
PEG: polyethylene glycol

Conflicts of Interest
The authors declare that they have no conflicts of interest.

Ethics Approval and/or Participant Consent
This study did not require ethics approval and/or participant consent as no experiments were performed, and no participants were recruited for this literature review.

Authors' Contributions
RI: contributed to the design of the study, drafted the manuscript, critically appraised, and revised the manuscript, and gave approval of the final version to be published.
KH: contributed to the design of the study, drafted the manuscript, critically appraised, and revised the manuscript, and gave approval of the final version to be published.

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