Published in final edited form as:

Lancet. 2009 March 21; 373(9668): 1033–1040. doi:10.1016/S0140-6736(09)60251-8.

Monoclonal Antibodies for Cancer Immunotherapy

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Abstract

Monoclonal antibodies have emerged as effective therapeutic agents for many human malignancies. However, the ability of antibodies to initiate tumor antigen-specific immune responses has not received as much attention as other mechanisms of antibody action. Here we describe the rationale and evidence for developing anti-cancer antibodies that can stimulate host tumor antigen-specific immune responses. This may be accomplished by inducing antibody-dependent cellular cytotoxicity, by promoting antibody-targeted cross-presentation of tumor antigens or by triggering the idiotype network. Future treatment modifications or combinations should be able to prolong, amplify and shape these immune responses to increase the clinical benefits of antibody therapy of human cancer.

Keywords

Monoclonal antibody; antibody-dependent cellular cytotoxicity; dendritic cells; cross presentation; anti-idiotypic

Introduction

Monoclonal antibodies have emerged as effective therapeutic agents for an increasing number of human malignancies. They have become one of the largest classes of new agents approved for the treatment of human cancer in the last decade (Table 1). An unconjugated antibody and two radioimmunoconjugates directed against CD20 exhibit significant anti-tumor activity^{1–4}, and have been shown to improve survival in both indolent as well as aggressive B-cell non-Hodgkins lymphoma. An anti-CD33 antibody-calicheamicin conjugate has been approved for use in refractory acute myeloid leukemia⁵. Immunotoxins directed against CD22 demonstrate anti-tumor activity in hairy cell leukemia as well⁶. An unconjugated anti-HER2/*neu* antibody is widely used alone and in combination with chemotherapy agents in breast cancer^{7–9}. Recently, this antibody has been shown to significantly improve relapse-free survival when used as a component of adjuvant therapy of HER2/*neu* expressing breast cancer¹⁰. An unconjugated antibody directed against vascular endothelial growth factor improves survival in metastatic colorectal cancer¹¹. Unconjugated antibodies directed against the B-cell idiotype¹² and CD22¹³ exhibit utility in the therapy of lymphomas, and one anti-CD20 antibody has become a widely used agent to treat lymphomas. An anti-CD52 antibody that fixes complement has been approved for use in chemotherapy-refractory chronic lymphocytic leukemia¹⁴.

Antibodies directed against the extracellular domain of the epidermal growth factor receptor are clinically active in advanced colorectal cancer^{15,16}. In addition, antibodies that enhance host immune responses to self-tumor antigens by blocking the function of the CTLA-4 co-receptor on T-cells exhibit pre-clinical and clinical promise^{17,18}.

Multiple mechanisms have been proposed to explain the antitumor activity of unconjugated tumor antigen-specific monoclonal antibodies. However, in the past few years most attention has focused on the ability of such antibodies to manipulate critical signaling pathways that sustain the malignant phenotype and to trigger or enhance self-tumor antigen-specific immune responses. The capacity of antibodies to promote anti-tumor effects by modulating tumor antigen-specific immune responses has not received the attention it deserves. This review will examine the potential of monoclonal antibodies as immunotherapy vehicles. While many potential immunomodulatory mechanisms can be considered (e.g., complement activation, interference with inhibitory costimulation), we focus here on three key mechanisms: 1) mediating cellular cytotoxicity of tumor cells, 2) targeting Fc receptors on DCs to promote antigen presentation and induction of adaptive immune responses, and 3) eliciting tumor antigen-specific immune responses by triggering the idiotypic network.

Antibody-dependent cellular cytotoxicity (ADCC)

ADCC occurs when antibodies bind to antigens on tumor cells and the antibody Fc domains engage Fc receptors on the surface of immune effector cells¹⁹. Several families of Fcγ receptors have been identified, and specific cell populations characteristically express defined Fcγ receptors²⁰. The engagement of activating Fcγ receptors by antibodies facilitates the recruitment of adaptor proteins and activation of immune effector cells²¹. Even though many tumor antigen-specific antibodies have been shown to mediate *in vitro* ADCC, the relevance of this putative mechanism of action to clinical efficacy has been difficult to prove. Ravetch and his collaborators have evaluated the importance of Fc domain: Fcγ receptor interactions by examining the ability of clinically effective tumor antigen-specific monoclonal antibodies to control human tumor xenografts growing in either wild-type mice or in murine FcγRII/III knockout mice. Anti-tumor activity was diminished in the Fcγ receptor knockout mice, and was preserved when only the inhibitory Fcγ receptor isoform was deleted. These data support the concept that Fc domain: Fcγ receptor interactions underlie anti-tumor efficacy in mice, and suggest that such interactions with antibodies may be important for the anti-tumor activity of selected antibodies in the clinic²². This mechanism may account for the substantially greater efficacy of rituximab in patients with lymphoma with “high responder” Fcγ receptor polymorphisms^{23,24}. Furthermore, these findings indicate that antibody Fc domain: Fc receptor interactions underlie at least some of the clinical benefit of rituximab, and imply the clinical relevance of ADCC, which depends upon such interactions. We discuss below the potential for manipulating antibody interactions with activating and inhibitory Fcγ receptors. The effector cell populations required for these effects have not been defined, but are presumed to include mononuclear phagocytes and/or natural killer cells. Manipulations of Fc domain structure can customize antibody clearance and the interaction of Fc domains with cellular Fcγ receptors^{25–27}. Considerable effort has been expended by the pharmaceutical industry to generate monoclonal antibodies that more effectively promote ADCC due to more efficient interactions with human Fcγ receptors.

Role of ADCC in anti-tumor efficacy of tumor antigen-specific antibodies

ADCC has long been viewed as a potentially independent mechanism of anti-tumor activity of tumor antigen-specific antibodies, but direct evidence supporting its relevance to the efficacy of antibody-based immunotherapy is not abundant, despite the compelling preclinical data of Ravetch and his collaborators discussed above. Therapy with an ADCC-inducing bispecific

antibody can induce HER2/*neu*-specific antibodies²⁸. Accordingly, ADCC may be viewed as a mechanism to directly induce a variable degree of immediate tumor destruction that leads to antigen presentation and the induction of “cross-primed” tumor antigen-specific T-cell responses (Figure 1). As tumor cells by themselves are poor at initiating host-protective immunity, the generation of tumor antigen-specific cytotoxic T lymphocyte (CTL) responses in vivo depends on the uptake by dendritic cells (DCs) of tumor antigens and their presentation to both CD4 helper and CD8 killer T cells. Typically, antigens derived from intracellular proteins are processed and presented on MHC I molecules to activate CD8+ killer T cells. However some antigen presenting cells such as DCs can process antigen from tumor cells and present the peptides on MHC I to CD8+ T cells, a process termed as “cross-presentation”²⁹. This model has potentially important implications for the development of unconjugated antibodies that mediate ADCC. Firstly, the model predicts that the in vivo induction of ADCC will lead to the induction of tumor antigen-specific T cell responses and host-derived antibody responses; such events could be viewed as the “footprints” of ADCC and could function as biomarkers of this antibody effect. Next, the induction of such immune responses may underlie or contribute to the clinical efficacy of unconjugated antibodies. It is plausible to assume that this vaccine-like property of antibody therapy can be exploited to selectively amplify or bias the resulting adaptive immune response by promoting the processes of antigen presentation, host antibody production, and expansion of tumor antigen-specific CTL. Such immune responses should be directed against not only the targeted tumor antigen, but also against other antigens that are processed and presented in the context of ADCC. ADCC effects also may enhance or be abetted by antibody-directed signaling perturbation and the induction of direct anti-tumor effects.

Monoclonal antibodies as adjuvants: effects on adaptive immunity

Much of the early attention on the immune effects on tumor antigen-specific monoclonal antibodies was on their ability to recruit innate mechanisms such as ADCC by Fc receptor bearing killer cells and complement activation, as discussed above. However a growing body of evidence now suggests that monoclonal antibodies may also have the capacity to recruit adaptive tumor antigen-specific immunity^{30,31}.

DCs express Fc γ receptors and are efficient at uptake of opsonized antigens such as dying antibody coated tumor cells³¹. Uptake of tumor cells by DCs can in principle lead to the induction of either immunity or tolerance, depending on the context of cell death, the nature of the phagocytic cargo and other signals from the tumor microenvironment³². As several types of tumors do not express MHC II, uptake of tumor antigens by antigen presenting cells is also important for the induction of CD4+ T helper responses. Even in some settings when tumors express MHCII (as in the case of some hematologic tumors), defects in MHCII antigen processing correlate with outcome³³. Several studies with both human and murine DCs have now shown that the uptake of opsonized tumor antigens by DCs via Fc γ receptors leads to enhancement of cross presentation and efficient generation of both tumor antigen-specific CD4+ and CD8+ T cell responses, both in vitro and in vivo^{31, 34–44}. The mechanism of Fc γ receptor mediated enhancement of cross presentation is not fully understood, but requires signaling via the activating Fc γ receptors⁴¹, and may involve access of internalized antigen to the cytosol of the antigen presenting cell⁴², or specialized signaling networks such as activation of interferon pathways⁴⁵. The ability of antibodies to enhance immunity may also enable improvements in DC therapies⁴⁶, and other cancer vaccines as well⁴⁷.

The preclinical data argue in favor of the possibility that tumor antigen-specific T cell responses may be generated in patients with malignant disease following antibody-based immunotherapy. Evidence to support this possibility has been provided by the recently described induction of MUC-1 specific T cell responses in patients treated with an anti-MUC-1 antibody⁴⁴. Similarly,

enhanced immunity to Her2 was documented in breast cancer patients treated with trastuzumab and chemotherapy⁴⁸. However at present, the data about the induction of T cell immunity in antibody treated patients are too preliminary to permit any definitive conclusions or clinical correlations. In particular, studies to evaluate the nature of the tumor antigen-specific T cell response in the tumor microenvironment after antibody therapy have not yet been described.

The ability of monoclonal antibody therapy to recruit tumor antigen-specific T cells may be particularly important for the durability of anti-tumor responses. Immunologic memory associated with T cells may also help improve responses with repeated administration of the antibody^{48,49}. It has been suggested that repeated administration of rituximab in patients with relapsed lymphoma may lead to more durable responses than those achieved after initial administration⁵⁰. While this may be explained by greater B cell depletion with repeat mAb administration in the setting of minimal residual disease, an alternate possibility is the induction of adaptive immunity and immunologic memory to tumor cells. The generation of T cell responses against antigens other than those targeted by the antibody may also help prevent the emergence of therapeutic resistance due to antigen loss variants of tumor cells⁵¹.

Effects of the balance of activating and inhibitory Fcγ receptors on the outcome of antigen presentation

As mentioned above, Fcγ receptors of the activating type allow DCs to take up and process antigens and to present antigen derived peptides on MHC class I and class II to CD8+ and CD4+ T lymphocytes, respectively. However, in addition to antigen uptake and processing, the immunologic outcome depends on the state of DC differentiation or maturation. During the steady state, DCs reside in an immature form, and can promote immune tolerance⁵². Exposure to stimuli such as pathogens activates or matures DCs and initiates immunity. The type of immunity depends upon the particular maturation stimulus that the DC encounters. Fcγ receptors not only mediate antigen uptake, but they also influence DC maturation, and the balance between activating versus inhibitory Fcγ receptors is critical to this process (Figure 2)⁵³. Conventional DCs express both activating FcγRIIa and FcγRIIIa receptors as well as inhibitory FcγRIIb receptors⁵⁴ while the subset of plasmacytoid DCs lacks inhibitory FcγRIIb, expressing only the activating isoform⁵⁵. Thus binding of immune complexes by plasmacytoid DCs in patients with systemic lupus erythematosus reliably activates these cells to produce large amounts of type I interferons, a hallmark of immune activation⁵⁶. The role of plasmacytoid DCs in immune responses following administration of tumor antigen-specific monoclonal antibodies remains to be defined. Initial studies with murine DCs demonstrated that signaling via activating Fc receptors leads to DC maturation⁵⁷ and that DCs from mice lacking the inhibitory Fcγ receptors have enhanced capacity for antigen presentation in vitro and in vivo⁵⁸. In addition to the effect on the generation of T cell responses, uptake of antigen via inhibitory Fcγ receptors on DCs can also lead to the generation of B cell responses⁵⁹.

The recent development of monoclonal antibodies that specifically block the inhibitory FcγRIIb receptor in humans has facilitated the selective manipulation of the balance of Fcγ receptors in human DCs^{60,61}. The blockade of the inhibitory Fc receptor on human DCs leads to enhanced dendritic cell maturation^{60,61} and, more importantly, augments their ability to generate tumor antigen-specific T cells in vitro⁶¹. Therefore monoclonal antibodies that preferentially target activating Fcγ receptors may serve a dual role, not only by providing an efficient pathway for the uptake of tumor antigens, but also by delivering a potent maturation stimulus to the antigen presenting DC. Together, these studies suggest that the balance of engagement of activating versus inhibitory Fcγ receptors on human DCs by monoclonal antibodies may be a critical determinant of their ability to boost adaptive immunity.

The recruitment of activating versus inhibitory Fc γ receptors by therapeutic monoclonal antibodies in vivo also depends on host-related features (e.g. Fc γ receptor polymorphisms 24 and cytokine mediated regulation of Fc γ receptors), as well as on the properties of the antibody itself (such as its isotype and glycosylation or sialylation status) ⁶². Translation of this biology into improved antibody engineering (e.g. variants with enhanced binding to Fc γ RIIa or Fc γ RIIIa), use of bispecific antibodies selectively targeting tumor antigen and activating Fc γ receptors ^{63,64} or combining current monoclonal antibodies with agents that selectively manipulate signaling via activating and inhibitory Fc γ receptors may lead to improved therapeutic outcome with the next generation of monoclonal antibody trials in patients with malignant disease.

Anti-idiotypic antibodies as tumor antigen mimics

The high diversity of the amino acid sequence of heavy and light chain variable regions of an antibody is reflected in the expression of conformational and structural antigenic determinants which are unique or expressed on a few antibody populations. These determinants, which are named idiotopes because of their restricted distribution on antibody populations, are recognized as foreign by the host immune system and therefore can trigger an immune response. Some idiotopes are located in the area of the antigen binding site of the antibody which interacts with the corresponding antigen. As a result they are complementary to the corresponding antigenic determinant. Others, although located in the combining site of the antibody, are not directly involved in its binding of the corresponding antigen and therefore have no complementarity with the corresponding epitope. According to Jerne's idiotypic network theory ⁶⁵ the induction of an antibody triggers the idiotypic cascade in a host (Figure 3). As a result the elicited antibody induces antibodies to its idiotopes which are referred to as anti-idiotypic antibodies. Some of them may recognize idiotope(s) complementary to the antigenic determinant which has triggered the idiotypic network and therefore react with the same area(s) of the antigen binding site of the antibody which binds to the nominal antigen. The similarity in reactivity between the nominal antigen and some anti-idiotypic antibodies reflects homology between the involved antigenic determinant and portion(s) of the variable regions of the anti-idiotypic antibody. This homology, which is conformational in most of the cases and structural only in a few ^{66,67,68}, accounts for the ability of some anti-idiotypic antibodies to act as surrogate antigens and to elicit an immune response to the nominal antigen (Figure 4). Anti-idiotypic antibodies which mimic tumor antigens represent attractive vaccines, since they can overcome patients' unresponsiveness to tumor antigens, most of which have low or no immunogenicity because of their self-nature. Furthermore, taking advantage of hybridoma methodology, anti-idiotypic antibodies with well defined characteristics can be produced in large amounts in a reproducible fashion, thus facilitating the standardization of vaccines for clinical use.

Triggering of the idiotypic cascade by antibody-based immunotherapy

As discussed above, tumor antigen-specific antibodies can have antitumor effects by activating immunological mechanisms and/or by interfering with the function of molecules which are crucial for the survival and/or proliferation of tumor cells. Emerging evidence is compatible with the possibility that tumor antigen-specific antibodies also may contribute to anti-tumor effects by triggering the idiotypic cascade and inducing a tumor antigen-specific immune response. A variable percentage of patients with neuroblastoma, colorectal cancer, pancreas carcinoma, ovarian carcinoma, non-Hodgkin lymphoma and melanoma has been found to develop anti-idiotypic antibodies following the administration of tumor antigen-specific antibodies for diagnostic and/or therapeutic purposes ⁷¹⁻⁸¹. Although the induced anti-idiotypic antibodies may shorten the half life of the injected tumor antigen-specific antibody and interfere with its targeting of tumor cells, the triggering of the idiotypic cascade has been reported to be associated with a favorable clinical response to antibody-based therapy in

patients with neuroblastoma, colorectal carcinoma, ovarian carcinoma and non-Hodgkin lymphoma^{71,72,77,79,80,81}. This association may reflect the development of cellular and/or humoral immunity specific for the tumor antigen targeted by the administered antibody, since the induced anti-idiotypic antibodies mimic the targeted tumor antigen. In this regard, anti-idiotypic antibodies which can induce a cellular immune response to the CD55 glycoprotein in patients with colorectal carcinoma⁸² and a humoral immune response to GD₂ ganglioside and to CEA^{79,82} in xenogeneic hosts have been isolated from patients with melanoma, or pancreas carcinoma treated with antibody-based immunotherapy. Furthermore GD₂ ganglioside-specific antibodies have been induced in patients with neuroblastoma treated with GD₂ ganglioside antibodies⁸⁷ and colorectal carcinoma antigen CO17-1A-specific cellular and/or humoral immunity has been detected in patients with colorectal carcinoma treated with the monoclonal antibody CO17-1A^{78, 79}. Whether these responses can mediate tumor regressions needs further evaluation and optimization. Furthermore it remains to be determined why the idiotype cascade is not triggered in a variable proportion of the patients treated with tumor antigen-specific monoclonal antibodies. Does this reflect immunological dysfunction caused by the underlying malignant disease?

Anti-idiotypic antibodies as vaccines in malignant diseases

Anti-idiotypic antibodies which mimic tumor antigens have been utilized as immunogens in patients with malignant diseases to overcome the lack or low immunogenicity of tumor antigens, which are for the most part self-antigens expressed at higher levels by malignant cells than by their normal counterparts. The induction of self-tumor antigen-specific immune responses by anti-idiotypic antibodies reflects their ability to stimulate T and B cell clones which have not been deleted during the establishment of self-identity because their affinity for self-tumor antigens is below the threshold required for deletion. As a result the tumor antigen-specific immune responses elicited by anti-idiotypic antibodies like that induced by other types of mimics are in general weak.

Anti-idiotypic antibodies which mimic both protein and ganglioside tumor antigens have been utilized to implement active specific immunotherapy in patients with melanoma, breast, colorectal or ovarian carcinoma^{78,85,86,87,88,89,90}. With few exceptions^{78,90} the anti-idiotypic antibodies used have been mouse monoclonal antibodies. Although they have elicited high titer anti-mouse immunoglobulin antibodies, repeated administrations of mouse anti-idiotypic antibodies have not caused side effects. Most, although not all the anti-idiotypic antibodies used have elicited a tumor antigen-specific humoral immune response in a variable percentage of the immunized patients. Although there is variability in the immune response among the immunized patients as well as among the immunizing anti-idiotypic antibodies, the level of the elicited tumor antigen-specific antibodies is in general low. This finding is likely to reflect the stimulation of B cell clones with low reactivity with self-tumor antigen because the immunizing anti-idiotypic antibody resembles, but is not identical to the nominal tumor antigen. Furthermore, it remains to be determined whether the differential immunogenicity of the anti-idiotypic antibodies reflects the different extent of tumor antigen mimicry, the different immunization schedule and/or the characteristics of the immunized patient population.

Anti-idiotypic antibodies which mimic CD55 and high molecular weight-melanoma associated antigen have been found to elicit HLA class I antigen restricted, tumor antigen-specific cytotoxic T-lymphocytes^{91,92}. This finding, which challenges the general belief that anti-idiotypic antibodies cannot elicit a tumor antigen-specific cytotoxic T-cell response, appears to reflect the presence in the anti-idiotypic antibody variable region of amino acid sequence stretches with HLA class I anchor motifs and with structural or conformational homology with the amino acid sequence of the nominal tumor antigen⁹³.

The tumor antigen-specific immune response elicited by anti-idiotypic antibodies has been found to be associated with regression of metastases and/or with survival prolongation in patients with melanoma or colorectal or ovarian carcinoma^{85, 89, 90}. The association between clinical benefit and induction of tumor antigen-specific immunity, which is not absolute, as observed in other types of active specific immunotherapy, requires further studies.

Future Directions

The induction of adaptive tumor antigen-specific immune responses continues to hold enormous promise for cancer prevention and therapy. Monoclonal antibodies provide underappreciated opportunities for immunization against cancer. This may be accomplished by tumor-directed antibodies, by anti-idiotypic antibodies or by combinations that include these approaches in concert with other immune manipulations strategies. Monoclonal antibody therapy-promoted ADCC can directly cause tumor destruction, and subsequent antigen uptake, processing and presentation by DCs and related professional antigen presenting cells, leading to adaptive T-cell-mediated immune responses. Monoclonal antibodies can be engineered to mediate improved ADCC, which should enhance antigen presentation and T cell activation. This can be accomplished by increasing antibody affinity for tumor antigen targets, or by manipulating antibody Fc γ domains to increase their affinity for Fc γ receptor(s). As discussed above, it may prove possible to further refine such antibody engineering to selectively engage activating, as opposed to inhibitory Fc γ receptors. Alternatively, it may be advantageous to generate antibodies that selectively block the interactions of tumor antigen-specific antibodies with inhibitory Fc γ receptors. Antibody structures can be further modified to contain immunostimulatory motifs that selectively induce, shape and amplify antigen processing, presentation and costimulation to favor the induction of clinically effective host anti-tumor immune responses. In lieu of direct modification of antibody structures, tumor antigen-specific antibodies might be combined with other agents that promote antigen presentation (e.g., toll receptor agonists), costimulation (e.g., anti-CTLA-4 antibody), or T-cell activation or expansion (e.g., interleukin-2). Antibody therapy may also help enhance the efficacy of other immune therapies such as DC vaccines⁴⁶. It should not be forgotten that several clinically useful antibodies that mediate ADCC are routinely combined with chemotherapy agents; further studies are required to determine if chemotherapy-based tumor destruction cooperates with monoclonal antibody therapy to promote adaptive, tumor antigen-specific immunity.

The association between tumor antigen-specific immune responses elicited by anti-idiotypic antibodies and clinical responses emphasizes the need for randomized clinical trials to obtain clinical proof-of-concept about the validity of this immunization strategy. Furthermore approaches should be developed to enhance the ability of anti-idiotypic antibodies to elicit a strong tumor antigen-specific immune response with the expectation that this will improve its anti-tumor effects. These studies will benefit from the characterization of the structural basis of tumor antigen mimicry by the corresponding anti-idiotypic antibodies and of the relationship between the extent of antigen mimicry and immunogenicity of a mimic. This information, in turn, will facilitate the replacement of anti-idiotypic antibodies with peptide mimics which are more amenable to manipulations to enhance their immunogenicity.

Acknowledgments

CA51008, CA50633, CA121033, (LMW); CA106802, CA109465, Damon Runyon Cancer Research Fund, Dana Foundation (MVD); and CA 105500 (SF).

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Figure 1. A proposed model for the induction of adaptive immune responses by ADCC
 An anti-tumor monoclonal antibody binds to an antigen on a tumor cell, and engages an Fc receptor on a killer cell. This induces antibody-promoted phagocytosis or direct cytotoxicity, resulting in antigen processing and presentation via MHC Class I or Class II molecules on antigen-presenting cells. This leads to the induction of host anti-tumor immunity manifested by either the production of tumor-directed host cytotoxic T-lymphocytes and/or antibodies.

Figure 2. Fc receptors and immune balance

Signaling via Fc γ receptors (Fc γ R) is regulated by a balance of activating versus inhibitory Fc γ R, which carry immune tyrosine activating motif (ITAM) versus immune tyrosine inhibitory motifs (ITIM). Fc domains of monoclonal antibodies can generally engage both forms of receptors. The balance of net engagement of activating versus inhibitory receptors depends on both host and antibody related factors and determine antibody mediated activation of immunity.

Figure 3. Triggering of the idiotype network by immunization with a tumor antigen

The antibody, referred to as Ab1, elicited by a tumor antigen induces anti-idiotypic antibodies to the idiotopes expressed on its variable region. Some anti-idiotypic antibodies, referred to as Ab2β, react with the area of the Ab1 variable region, which binds to the nominal antigen. These anti-idiotypic antibodies bear the internal image of the nominal antigen and therefore can induce tumor antigen binding antibodies, referred to as Ab3. Other anti-idiotypic antibodies, referred to as Ab2γ, react with areas of the Ab1 variable region, which do not bind to the nominal antigen. They can interfere with the binding of Ab1 to the nominal antigen, and induce anti-anti-idiotypic antibodies which do not bind to the nominal antigen. Other anti-idiotypic antibodies, referred to as Ab2α, react with areas of the Ab1 variable region outside its antigen combining site. They do not interfere with the binding of Ab1 to the nominal antigen, and induce anti-anti-idiotypic antibodies which do not bind to the nominal antigen.

Figure 4. Molecular basis of tumor antigen mimicry by an anti-idiotypic antibody

The mimicry of a tumor antigen by an anti-idiotypic antibody may reflect the homology of an amino acid sequence stretch of a tumor antigen with a stretch of the anti-idiotypic antibody variable region amino acid sequence or conformational similarity between a tumor antigen determinant and an anti-idiotypic antibody idiotope.

Table 1
Therapeutic Monoclonal Antibodies Approved for Use in Oncology

Generic Name (Trade Name)	Species of Origin	Isotype	Toxic Payload	Target	Indication	Refs
Unconjugated Antibodies						
Trastuzumab (Herceptin)	Humanized	IgG1	-	HER2/ <i>neu</i>	Breast Cancer	7-10
Rituximab (Rituxan)	Murine-human Chimeric	IgG1	-	CD20	Lymphoma	1-2
Cetuximab (Erbix)	Murine-human Chimeric	IgG1	-	EGF Receptor	Colorectal Cancer	15
Bevacizumab (Avastin)	Murine-human Chimeric	IgG1	-	Vascular Endothelial Growth Factor	Colorectal, Lung, Breast Cancers	11
Alemtuzumab (Campath-1H)	Humanized	IgG1	-	CD52	Chronic Lymphocytic Leukemia	14
Immunoconjugates						
Ibritumomab tiuxetan (Zevalin) plus	Murine	IgG1	90 Yttrium	CD20	Lymphoma	3
Rituximab	Human	IgG1				
¹³¹ I-Tositumomab plus Tositumomab (Bexxar)	Murine	IgG2a	¹³¹ Iodine	CD20	Lymphoma	4
Gemtuzumab (Myelotarg)	Human	IgG4	Calicheamicin	CD33	Acute myelogenous	5