antibodies that react with native soluble IgE.[173/51] Further, Hellman (U.S. Patent No. 5,653,980) proposed anti-IgE vaccine compositions based on fusion of full length CεH2-CεH3 domains (approximately 220 amino acid long) to a foreign carrier protein. However, the antibodies induced by the anti-IgE vaccine compositions proposed in Hellman will most likely it result in anaphylaxis since antibodies against some portions of the CεH2 and CεH3 domains of the IgE molecule have been shown to cross-link the IgE receptor on the surface of mast cell and basophils and lead to production of mediators of anaphylaxis (See, *e.g.*, Stadler *et al.*, 1993, Int. Arch. Allergy and Immunology 102:121-126). Therefore, a need remains for treatment of IgE-mediated allergic reactions which do not induce anaphylactic antibodies.

[0036] The significant concern over induction of anaphylaxis has resulted in the development of another approach to the treatment of type I allergic disorders consisting of mimotopes that could induce the production of anti-IgE polyclonal antibodies when administered to animals (See, *e.g.*, Rudolf, *et al.*, 1998, Journal of Immunology 160:3315-3321). Kricek *et al.* (International Publication No. WO 97/31948) screened phage-displayed peptide libraries with the monoclonal antibody BSWI7 to identify peptide mimotopes that could mimic the conformation of the IgE receptor binding. These mimotopes could presumably be used to induce polyclonal antibodies that react with free native IgE, but not with receptor-bound IgE as well as block IgE from binding to its receptor. Kriek *et al.* disclosed peptide mimotopes that are not homologous to any part of the IgE molecule and are thus different from peptides disclosed in the present invention.

[0037] As evidenced by a survey of the art, there remains a need for enhancing the therapeutic efficacy of current methods of treating or preventing disorders such as cancer, autoimmune disease, inflammatory disorder, or allergy. In particular, there is a need for enhancing the effector function, particularly, the cytotoxic effect of therapeutic antibodies used in treatment of cancer. The current state of the art is also lacking in treating or preventing allergy disorders (*e.g.*, either by antibody therapy or vaccine therapy).

3. SUMMARY ~~OF THE INVENTION~~

[0038] The extracellular domains of FcγRIIA and FcγRIIB are 95% identical and thus they share numerous epitopes. However, FcγRIIA and FcγRIIB exhibit very different activities. The fundamental difference is that the FcγRIIA initiates intracellular signaling leading to cell activation such as phagocytosis and respiratory burst, whereas the FcγRIIB initiates inhibitory signaling. Prior to this ~~invention~~disclosure, to the knowledge of the inventors, antibodies known to distinguish among native human FcγRIIA and native human FcγRIIB have not been identified; in view of their distinctive activities and role in modulating immune responses, such antibodies that

recognize native FcγRIIB, and not native FcγRIIA, are needed. The present ~~invention~~disclosure is based, in part, on the discovery of such FcγRIIB-specific antibodies.

[0039] The ~~invention~~disclosure relates to an isolated antibody or a fragment thereof that specifically binds FcγRIIB, particularly human FcγRIIB, more particularly native human FcγRIIB, with a greater affinity than said antibody or a fragment thereof binds FcγRIIA, particularly human FcγRIIA, more particularly native human FcγRIIA.

[0039a] In one aspect, there is provided an isolated antibody or a fragment thereof comprising a variable domain that specifically binds the extracellular domain of native human FcγRIIB with greater affinity than said variable domain binds native human FcγRIIA, wherein said antibody is produced by hybridoma clone 1D5 (PTA-5958), 2E1 (PTA- 5961), 2H9 (PTA-5962), 2D11 (PTA-5960), or 1F2 (PTA-5959), or is a chimeric, humanized or human antibody variant of said antibody.

[0039b] In one aspect, there is provided an antibody fragment as defined herein, wherein said fragment is a F(ab')2 or a F(ab) fragment.

[0039c] In one aspect, there is provided a bispecific antibody comprising a first heavy chain-light chain pair comprising a variable domain that specifically binds FcγRIIB with greater affinity than said heavy chain-light chain pair binds FcγRIIA, and a second heavy chain-light chain pair that specifically binds a tumor antigen, wherein said variable domain is from an antibody produced by hybridoma clone: 1D5 (PTA-5958), 2E1 (PTA-5961), 2H9 (PTA-5962), 2D11 (PTA-5960), or 1F2 (PTA-5959), or is from a chimeric, humanized or human antibody variant of said antibody.

[0039d] Preferably the antibodies of the ~~invention~~disclosure bind the extracellular domain of native human FcγRIIB. In certain embodiments of the ~~invention~~disclosure, the antibody or a fragment thereof binds FcγRIIB with at least 2 times greater affinity than said antibody or a fragment thereof binds FcγRIIA. In other embodiments of the ~~invention~~disclosure, the antibody or a fragment thereof binds FcγRIIB with at least 4 times, at least 6 times, at least 8 times, at least 10 times, at least 100 times, at least 1000 times, at least 10^4, at least 10^5, at least 10^6, at least 10^7, or at least 10^8 times greater affinity than said antibody or a fragment thereof binds FcγRIIA. In a preferred embodiment, said antibody or a fragment thereof binds FcγRIIB with 100 times, 1000 times, 10^4 times, 10^5 times, 10^6 times, 10^7 times, or 10^8 times greater affinity than said antibody or a fragment thereof binds FcγRIIA. Preferably, these binding affinities are determined with the monomeric IgG, and not the aggregated IgG, and binding is via the variable domain (*e.g.*, Fab fragments of the antibodies have binding characteristic similar to the full immunolobulin molecule).

[0040] In one embodiment, the FcγRIIB-specific antibody in accordance with the ~~invention~~disclosure is not the monoclonal antibody designated KB61, as disclosed in Pulford *et al.*, 1986 (Immunology, 57: 71-76) or the monoclonal antibody designated MAbII8D2 as disclosed in

Weinrich *et al.*, 1996, (Hybridoma, 15(2):109-6). In a specific embodiment, the FcγRIIB-specific antibody of the ~~invention~~disclosure does not bind to the same epitope and/or does not compete for binding with the monoclonal antibody KB61 or the monoclonal antibody MAbII8D2. Preferably, the FcγRIIB-specific antibody of the ~~invention~~disclosure does not bind the amino acid sequence Ser-Asp-Pro-Asn-Phe-Ser-Ile corresponding to amino acid positions 135-141 of FcγRIIb2 isoform.

[0041] The ~~invention~~disclosure relates to an isolated antibody or a fragment thereof that specifically binds FcγRIIB with a greater affinity than said antibody or a fragment thereof binds FcγRIIA, as determined by any standard method known in the art for assessing specificities. The ~~invention~~disclosure relates to an isolated antibody or a fragment thereof that specifically binds FcγRIIB with a greater affinity than said antibody or a fragment thereof binds FcγRIIA, as determined, for example, by western blot, BIAcore or radioimmunoassay. The ~~invention~~disclosure relates to an isolated antibody or a fragment thereof that specifically binds FcγRIIB with a greater affinity than said antibody or a fragment thereof binds FcγRIIA, as determined in an ELISA assay, in the linear

range for FcγRIIB binding. In one embodiment ~~of the invention~~, the ~~invention~~disclosure relates to an isolated antibody, or a fragment thereof that specifically binds FcγRIIB, produced in mammalian system, with a greater affinity than said antibody or a fragment thereof binds FcγRIIA, as determined in an ELISA assay.

[0042] In a particular embodiment, the ~~invention~~disclosure relates to an isolated antibody or a fragment thereof that specifically binds FcγRIIB with a greater affinity than said antibody or a fragment thereof binds FcγRIIA, and the constant domain of said antibody further has an enhanced affinity for at least one or more Fc activation receptors. In yet another specific embodiment, said Fc activation receptor is FcγRIII.

[0043] In one embodiment of the ~~invention~~disclosure said antibody or a fragment thereof blocks the IgG binding site of FcγRIIB and blocks the binding of aggregated labeled IgGs to FcγRIIB in, for example, a blocking ELISA assay. In one particular embodiment, said antibody or a fragment thereof blocks the binding of aggregated labeled IgGs in an ELISA blocking assay by at least 50%, 60%, 70%, 80%, 90%, 95%, 99%, or 99.9%. In yet another particular embodiment, the antibody or a fragment thereof completely blocks the binding of said aggregated labeled IgG in said ELISA assay.

[0044] In another embodiment of the ~~invention~~disclosure, said antibody or a fragment thereof blocks the IgG binding site of FcγRIIB and blocks the binding of aggregated labeled IgG to FcγRIIB, as determined by a double-staining FACS assay.

[0045] The ~~invention~~disclosure encompasses the use of antibodies that modulate (*i.e.*, agonize or antagonize) the activity of FcγRIIB. In one embodiment ~~of the invention~~, the antibodies of the ~~invention~~disclosure agonize at least one activity of FcγRIIB, *i.e.*, elicit signaling. Although not intending to be bound by any mechanism of action, agonistic antibodies of the ~~invention~~disclosure may minic clustering of FcγRIIB leading to dampening of the activating response to FcγR ligation and inhibition of cellular responsiveness.

[0046] In another embodiment ~~of the invention~~, the antibodies of the ~~invention~~disclosure antagonize at least one activity of FcγRIIB, *i.e.*, block signaling. For example, the antibodies of the ~~invention~~disclosure block the binding of aggregated IgGs to FcγRIIB.

[0047] The ~~invention~~disclosure provides antibodies that inhibit FcεRI-induced mast cell activation. The ~~invention~~disclosure further provides anti-FcγRIIB antibodies that inhibit FcγRIIA-mediated macrophage activation in monocytic cells. The ~~invention~~disclosure also provides anti- FcγRIIB antibodies that inhibit B-cell receptor mediated signaling.

[0048] In one particular embodiment, the anti-FcγRIIB antibodies block the ligand binding site of FcγRIIB. In a further specific embodiment, the blocking activity can block the

negative regulation of immune complex-triggered activation and consequently enhance the immune response. In a further specific embodiment, the enhanced immune response is an increase in antibody-dependent cellular response. In another specific embodiment, the anti-FcγRIIB antibodies of the ~~invention~~disclosure block crosslinking of FcγRIIB receptors to B cell and/or Fc receptors, leading to B cell, mast cell, dendritic cell, or macrophage activation.

[0049] The present ~~invention~~disclosure encompasses methods for the production of antibodies of the ~~invention~~disclosure or fragments thereof, particularly for the production of novel monoclonal antibodies with specificities for FcγRIIB relative to FcγRIIA. The antibodies of the ~~invention~~disclosure or fragments thereof can be produced by any method known in the art for the production of antibodies, in particular, by secretion from cultured hybridoma cells, chemical synthesis or by recombinant expression techniques known in the art.

[0049a] In one aspect, there is provided a method for recombinantly producing a FcγRIIB-specific antibody, said method comprising: (i) culturing in a medium the host cell as defined herein, under conditions suitable for the expression of said antibody; and (ii) recovering said antibody from said medium.

[0049b] In one specific embodiment, the ~~invention~~disclosure relates to a method for recombinantly producing a FcγRIIB-specific antibody, said method comprising: (i) culturing under conditions suitable for the expression of said antibody in a medium, a host cell containing a first nucleic acid molecule, operably linked to a heterologous promoter and a second nucleic acid operably linked to the same or a different heterologous promoter, said first nucleic acid and second nucleic acid encoding a heavy chain and a light chain, respectively, of an antibody or a fragment thereof that specifically binds FcγRIIB with greater affinity than said antibody or a fragment thereof binds FcγRIIA; and (ii) recovery of said antibody from said medium.

[0049c] In another embodiment, the ~~invention~~disclosure provides a method for producing FcγRIIB monoclonal antibodies that specifically bind FcγRIIB, particularly human FcγRIIB, with a greater affinity than said monoclonal antibodies bind FcγRIIA, particularly human FcγRIIA, said method comprising: (a) immunizing one or more FcγRIIA transgenic mice with purified FcγRIIB or an immunogenic fragment thereof; (b) producing hybridoma cells lines from spleen cells of said one or more mice; (c) screening said hybridoma cell lines for one or more hybridoma cell lines that produce antibodies that specifically bind FcγRIIB with a greater affinity than the antibodies bind FcγRIIA. The ~~invention~~disclosure encompasses any antibody produced by said method. In one specific embodiment, the ~~invention~~disclosure provides a method for producing FcγRIIB monoclonal antibodies that specifically bind FcγRIIB, particularly human FcγRIIB,

with a greater affinity than said monoclonal antibodies bind FcγRIIA, particularly human FcγRIIA, said method comprising: (a) immunizing one or more FcγRIIA transgenic mice with purified FcγRIIB or an immunogenic fragment thereof; (b) booster immunizing said mice for a time sufficient to elicit an immune response; (c) producing hybridoma cells lines from spleen cells of said one or more mice; (d) screening said hybridoma cell lines for one or more hybridoma cell lines that produce antibodies that specifically bind FcγRIIB with a greater affinity

than the antibodies bind FcγRIIA. In a preferred embodiment, said mice are booster immunized at least four times over a period of four months. In one embodiment of the invention, said mice are immunized with purified FcγRIIB, which has been mixed with adjuvants known in the art to enhance immune response in said mice. In one particular embodiment of the invention, said immunogenic fragment is the soluble extracellular domain of FcγRIIB. The hybridoma cell lines can be screened using standard techniques known in the art (*e.g.*, ELISA).

[0050] In certain embodiments of the invention, the anti-FcγRIIB antibodies are monoclonal antibodies, synthetic antibodies, recombinantly produced antibodies, multispecific antibodies, human antibodies, chimeric antibodies, camelized antibodies, single-chain Fvs (scFv), single chain antibodies, Fab fragments, F(ab') fragments, disulfide-linked Fvs (sdFv), intrabodies, or epitope-binding fragments of any of the above.

[0051] Preferably, the antibodies of the ~~invention~~disclosure are monoclonal antibodies, and more preferably, humanized or human antibodies. In one specific preferred embodiment, the antibodies of the ~~invention~~disclosure bind to the extracellular domain of human FcγRIIB, particularly native human FcγRIIB. In another specific embodiment, the antibodies of the ~~invention~~disclosure specifically or selectively recognize one or more epitopes of FcγRIIB, particularly native human FcγRIIB. Another embodiment of the ~~invention~~disclosure encompasses the use of phage display technology to increase the affinity of the antibodies of the ~~invention~~disclosure for FcγRIIB. Any screening method known in the art can be used to identify mutant antibodies with increased avidity for FcγRIIB (*e.g.*, ELISA).In another specific embodiment, antibodies of the ~~invention~~disclosure are screened using antibody screening assays well known in the art (*e.g.*, BIACORE assays) to identify antibodies with K_{off} rate less than $3x10^{-3}$ s^{-1}.

[0052] In a preferred embodiment, the ~~invention~~disclosure provides a monoclonal antibody produced by clone 2B6 or 3H7, having ATCC accession numbers PTA-4591 and PTA-4592, respectively, or chimeric, humanized or other engineered versions thereof. In another preferred embodiment, the ~~invention~~disclosure provides a monoclonal antibody produced by clone 1D5, 2E1, 2H9, 2D11, and 1F2 having ATCC Accession numbers, PTA-5958, PTA-5961, PTA-5962, PTA-5960, and PTA-5959, respectively, or chimeric, humanized or other engineered versions thereof. In another embodiment, the ~~invention~~disclosure provides an isolated antibody or a fragment thereof that competes for binding with the monoclonal antibody produced by clone 2B6 or 3H7 and binds FcγRIIB, preferably native human FcγRIIB with a greater affinity than said antibody or a fragment thereof binds FcγRIIA, preferably native human FcγRIIA and/or binds to the same epitope of FcγRIIB as the monoclonal antibody produced from clone 2B6 or 3H7 and binds FcγRIIB with a greater affinity than said antibody or a fragment thereof binds FcγRIIA.

Furthermore, the ~~invention~~disclosure provides hybridoma cell line 2B6, 3H7, 1D5, 2E1, 2H9, 2D11, or 1F2 having ATCC accession numbers PTA-4591, PTA-4592, PTA-5958, PTA-5961, PTA-5962, PTA-5960, and PTA-5959, respectively. In one specific embodiment, the ~~invention~~disclosure provides the use of a 2B6, 3H7, 1D5, 2E1, 2H9, 2D11, or 1F2 antibody, or chimeric, humanized or other engineered versions thereof, to prevent, treat, manage or ameliorate a B-cell malignancy, or one or more symptoms thereof. In one particular embodiment, an engineered version comprises one or more mutations in the Fc region. The one or more mutations in the Fc region may result in an antibody with an altered antibody-mediated effector function, an altered binding to other Fc receptors (*e.g.*, Fc activation receptors), an altered ADCC activity, or an altered C1q binding activity, or an altered complement dependent cytotoxicity activity, or any combination thereof. In a preferred embodiment, a humanized 2B6 comprises a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 24 and a light chain variable domain having the amino acid sequence of SEQ ID NO: 18, SEQ ID NO: 20, or SEQ ID NO: 22. In another preferred embodiment, the Fc domain of the heavy chain of the humanized 2B6 or humanized 3H7 antibody is engineered to comprise at least one amino acid substitution at position 240, 243, 247, 255, 270, 292, 300, 316, 370, 392, 396, 416, 419, or 421 with another amino acid at that position. In a more preferred embodiment, the Fc domain of the heavy chain of the humanized 2B6 has a leucine at position 247, a lysine at position 421 and a glutamic acid at position 270; a threonine at position 392, a leucine at position 396, and a glutamic acid at position 270; or a glutamic acid at position 270, an aspartic acid at position 316, and a glycine at position 416. In certain embodiments ~~of the invention~~, the antibody is not a monoclonal antibody produced by clone 2B6 or 3H7, or chimeric, humanized or other engineered versions thereof.

[0053] In certain embodiments ~~of the invention~~, humanized 2B6 antibodies are provided, said humanized 2B6 antibodies comprising a heavy chain variable domain having the amino acid sequence of SEQ ID NO: 24 and a light chain variable domain having the amino acid sequence of SEQ ID NO: 20, wherein the Fc domain of the heavy chain of the humanized 2B6 has a leucine at position 247, a lysine at position 421 and a glutamic acid at position 270; or a glutamic acid at position 270, an aspartic acid at position 316, and a glycine at position 416.

[0054] The ~~invention~~disclosure also encompasses polynucleotides that encode the antibodies of the ~~invention~~disclosure. In one aspect, there is provided an isolated nucleic acid comprising a nucleotide sequence encoding a heavy chain or a light chain of the antibody or fragment thereof as defined herein. In one embodiment, the ~~invention~~disclosure provides an isolated nucleic acid sequence encoding a heavy chain or a light chain of an antibody or a fragment thereof that specifically binds FcγRIIB with greater affinity than said antibody or a fragment thereof binds FcγRIIA.

In one aspect, there is provided~~The invention also relates to~~ a vector comprising the~~said~~ nucleic acid molecule as defined herein. In a further aspect, there is provided a vector comprising a first nucleic acid molecule encoding a heavy chain and a second nucleic acid molecule encoding a light chain, said heavy chain and light chain being of the antibody or fragment thereof as defined herein.

In one embodiment, the~~The invention further provides a~~ vector comprisinges a first nucleic acid molecule encoding a heavy chain and a second nucleic acid

molecule encoding a light chain, said heavy chain and light chain being of an antibody or a fragment thereof that specifically binds FcγRIIB with greater affinity than said antibody or a fragment thereof binds FcγRIIA. In one specific embodiment, said vector is an expression vector. The ~~invention~~disclosure further provides host cells containing the vectors of or poylucleotides encoding the antibodies of the ~~invention~~disclosure. In one aspect, there is provided a host cell containing the vector as defined herein. In one aspect, there is provided a host cell containing a first nucleic acid operably linked to a heterologous promoter and a second nucleic acid operably linked to the same or a different heterologous promoter, said first nucleic acid and second nucleic acid encoding a heavy chain and a light chain, respectively, of the antibody as defined herein.

In one embodiment~~Preferably~~, the ~~invention~~disclosure encompasses polynucleotides encoding heavy and light chains of the antibodies produced by the deposited hybridoma clones, 2B6, 3H7, 1D5, 2E1, 2H9, 2D11, or 1F2 having ATCC accession numbers PTA-4591, PTA-4592, PTA-5958, PTA-5961, PTA-5962, PTA-5960, and PTA-5959, respectively, or portions thereof, *e.g.*, CDRs, variable domains, etc. and humanized versions thereof.

[0055] Activating and inhibitory Fc receptors, *e.g.*, FcγRIIA and FcγRIIB, are critical for the balanced function of these receptors and proper cellular immune responses. The ~~invention~~disclosure encompasses the use of the antibodies of the ~~invention~~disclosure for the treatment of any disease related to loss of such balance and regulated control in the Fc receptor signaling pathway. Thus, the FcγRIIB antibodies of the ~~invention~~disclosure have uses in regulating the immune response, *e.g.*, in inhibiting immune response in connection with autoimmune or inflammatory disease, or allergic response. The FcγRIIB antibodies of the ~~invention~~disclosure can also be used to alter certain effector functions to enhance, for example, therapeutic antibody-mediated cytotoxicity.

In one aspect, there is provided the use of a therapeutically effective amount of said antibody or a fragment thereof as defined herein for the manufacture of a medicament for treating cancer.

[0056] The antibodies of the ~~invention~~disclosure are useful for prevention or treatment of cancer, for example, in one embodiment, as a single agent therapy. In a preferred embodiment, the antibodies of the ~~invention~~disclosure are used for the treatment and/or prevention of melanoma. In another embodiment, the antibodies are useful for prevention or treatment of cancer, particularly in potentiating the cytotoxic activity of cancer antigen-specific therapeutic antibodies with cytotoxic activity to enhance tumor cell killing and/or enhancing antibody dependent cytotoxic cellular ("ADCC") activity, complement dependent cytotoxic ("CDC") activity, or phagocytosis of the therapeutic antibodies. The ~~invention~~disclosure provides a method of treating cancer in a patient having a cancer characterized by a cancer antigen, said method comprising administering to said patient a therapeutically effective amount of a first antibody or a fragment thereof that specifically binds

FcγRIIB with greater affinity than said antibody or a fragment thereof binds FcγRIIA, and a second antibody that specifically binds said cancer antigen and is cytotoxic. The ~~invention~~disclosure also provides a method of treating cancer in a patient having a cancer characterized by a cancer antigen, said method comprising administering to said patient a therapeutically effective amount of an antibody or a fragment thereof that specifically binds FcγRIIB, particularly native human FcγRIIB with greater affinity than said antibody or a fragment thereof binds FcγRIIA, preferably native human FcγRIIA, and the constant domain of which further has an increased affinity for

one or more Fc activation receptors, when the antibody is monomeric, such as FcγRIIIA, and an antibody that specifically binds said cancer antigen and is cytotoxic. In one particular embodiment, said Fc activation receptor is FcγRIIIA. In particular embodiments, the antibody of the ~~invention~~disclosure is administered at a dose such that the antibody does not detectably bind to neutrophils.

[0056a] In one aspect, there is provided the use of a therapeutically effective amount of said antibody or fragment thereof as defined herein for the manufacture of a medicament for treating or ameliorating a B-cell malignancy.

[0057] In one~~another~~ preferred embodiment ~~of the invention~~, the antibodies of the ~~invention~~disclosure are useful for prevention or treatment of B-cell malignancies, particularly non-Hodgkin's lymphoma or chronic lymphocytic leukemia. Accordingly, the present ~~invention~~disclosure provides methods of treating, managing, preventing, or ameliorating a B-cell malignancy by administering, either alone or in combination with one or more other therapeutics, antibodies that specifically bind FcγRIIB, and, preferably, do not specifically bind FcγRIIA, as well as derivatives, analogs and antigen binding fragments of such antibodies. In particular embodiments, the cancer of the subject is refractory to one or more standard or experimental therapies, particularly, to Rituxan treatment. The methods of the ~~invention~~disclosure may be used for the treatment, management, prevention, or amelioration of B-cell diseases, such as, B-cell chronic lymphocytic leukemia (B-CLL), non-Hodgkin's lymphoma, diffuse large B cell lymphoma, follicular lymphoma with areas of diffuse large B cell lymphoma, small lymphocytic lymphoma, mantle cell lymphoma, and diffuse small cleaved cell lymphoma.

[0058] In another embodiment, the ~~invention~~disclosure provides for the use of a FcγRIIB-specific antibody conjugated to a therapeutic agent or drug. Examples of therapeutic agents which may be conjugated to an anti-FcγRIIB antibody or an antigen-binding fragment thereof include, but are not limited to, cytokines, toxins, radioactive elements, and antimetabolites.

[0059] In one embodiment, the ~~invention~~disclosure provides for the use of an FcγRIIB-specific antibody in combination with a standard or experimental treatment regimen for B-cell malignancies (*e.g.*, chemotherapy, radioimmunotherapy, or radiotherapy). Such combination therapy may enhance the efficacy of standard or experimental treatment. Examples of therapeutic agents that are particularly useful in combination with a FcγRIIB-specific antibody or an antigen-binding fragment thereof, for the prevention, treatment, management, or amelioration of B-cell malignancies, include, but are not limited to, Rituxan, interferon-alpha, and anti-cancer agents. Chemotherapeutic agents that can be used in combination with a FcγRIIB-specific antibody or an antigen-binding fragment thereof, include, but are not limited to alkylating agents,

antimetabolites, natural products, and hormones. The combination therapies of the ~~invention~~disclosure enable lower dosages of an anti-FcγRIIB antibody or an antigen-binding fragment thereof and/or

less frequent administration of anti-FcγRIIB antibody or an antigen-binding fragment thereof to a subject with a B-cell malignancy, to achieve a therapeutic or prophylactic effect.

[0060] In another embodiment, the use of an anti-FcγRIIB antibody or an antigen-binding fragment thereof prolongs the survival of a subject diagnosed with a B-cell malignancy.

[0061] In another embodiment, the ~~invention~~disclosure provides a method of enhancing an antibody mediated cytotoxic effect in a subject being treated with a cytotoxic antibody, said method comprising administering to said patient an antibody of the ~~invention~~disclosure or a fragment thereof, in an amount sufficient to enhance the cytotoxic effect of said cytotoxic antibody. In yet another embodiment, the ~~invention~~disclosure provides a method of enhancing an antibody-mediated cytotoxic effect in a subject being treated with a cytotoxic antibody, said method comprising administering to said patient an antibody of the ~~invention~~disclosure or a fragment thereof, further having an enhanced affinity for an Fc activation receptor, when monomeric, in an amount sufficient to enhance the cytotoxic effect of said cytotoxic antibody. In yet another embodiment, the ~~invention~~disclosure provides a method further comprising the administration of one or more additional cancer therapies.

[0062] The ~~invention~~disclosure encompasses the use of the antibodies of the ~~invention~~disclosure in combination with any therapeutic antibody that mediates its therapeutic effect through cell killing to potentiate the antibody's therapeutic activity. In one particular embodiment, the antibodies of the ~~invention~~disclosure potentiate the antibody's therapeutic activity by enhancing antibody-mediated effector function. In another embodiment ~~of the invention~~, the antibodies of the ~~invention~~disclosure potentiate the cytotoxic antibody's therapeutic activity by enhancing phagocytosis and opsonization of the targeted tumor cells. In yet another embodiment ~~of the invention~~, the antibodies of the ~~invention~~disclosure potentiate the antibody's therapeutic activity by enhancing antibody-dependent cell-mediated cytotoxicity ("ADCC") in destruction of the targeted tumor cells. In certain embodiments, the antibodies of the ~~invention~~disclosure are used in combination Fc fusion proteins to enhance ADCC.

[0063] In some embodiments, the ~~invention~~disclosure encompasses use of the antibodies of the ~~invention~~disclosure in combination with a therapeutic antibody that does not mediate its therapeutic effect through cell killing to potentiate the antibody's therapeutic activity. In a specific embodiment, the ~~invention~~disclosure encompasses use of the antibodies of the ~~invention~~disclosure in combination with a therapeutic apoptosis inducing antibody with agonistic activity, *e.g.*, anti-Fas antibody. Therapeutic apoptosis-inducing antibodies may be specific for any death receptor known in the art for the modulation of apoptotic pathway, *e.g.*, TNFR receptor family member or a TRAIL family member.

[0064] The ~~invention~~disclosure encompasses using the antibodies of the ~~invention~~disclosure to block macrophage mediated tumor cell progression and metastasis. The antibodies of the ~~invention~~disclosure are particularly useful in the treatment of solid tumors, where macrophage infiltration occurs. The antagonistic antibodies of the ~~invention~~disclosure are particularly useful for controlling, *e.g.*, reducing or eliminating, tumor cell metastasis, by reducing or eliminating the population of macrophages that are localized at the tumor site. The ~~invention~~disclosure further encompasses antibodies that effectively deplete or eliminate immune effector cells other than macrophages that express FcγRIIB, *e.g.*, dendritic cells. Effective depletion or elimination of immune effector cells using the antibodies of the ~~invention~~disclosure may range from a reduction in population of the effector cells by 50%, 60%, 70%, 80%, preferably 90%, and most preferably 99%. In particular embodiments, the antibody of the ~~invention~~disclosure is administered at a dose such that the antibody does not detectably bind to neutrophils.

[0065] In some embodiments, the agonistic antibodies of the ~~invention~~disclosure are particularly useful for the treatment of tumors of non-hematopoietic origin, including tumors of melanoma cells.

[0066] In some embodiments, the ~~invention~~disclosure encompasses use of the antibodies of the ~~invention~~disclosure in combination with therapeutic antibodies that immunospecifically bind to tumor antigens that are not expressed on the tumor cells themselves, but rather on the surrounding reactive and tumor supporting, non-malignant cells comprising the tumor stroma. In a preferred embodiment, an antibody of the ~~invention~~disclosure is used in combination with an antibody that immunospecifically binds a tumor antigen on a fibroblast cell, *e.g.*, fibroblast activation protein (FAP).

[0067] The ~~invention~~disclosure provides a method of treating an autoimmune disorder in a patient in need thereof, said method comprising administering to said patient a therapeutically effective amount of one or more antibodies of the ~~invention~~disclosure. The ~~invention~~disclosure also provides a method of treating an autoimmune disorder in a patient in need thereof, said method further comprising administering to said patient a therapeutically effective amount of one or more anti-inflammatory agents, and/or one or more immunomodulatory agents.

[0068] The ~~invention~~disclosure also provides a method of treating an inflammatory disorder in a patient in need thereof, said method comprising administering to said patient a therapeutically effective amount of one or more antibodies of the ~~invention~~disclosure. The ~~invention~~disclosure also provides a method of treating an inflammatory disorder in a patient in need thereof, said method further comprising administering to said patient a therapeutically effective amount of one or more anti-inflammatory agents, and/or one or more immunomodulatory agents.

[0069] The ~~invention~~disclosure provides a method of enhancing an immune response to a vaccine composition in a subject, said method comprising administering to said subject an antibody or an antigen-binding fragment thereof that specifically binds FcγRIIB with greater affinity than said antibody or a fragment thereof binds FcγRIIA, and a vaccine composition, such that said antibody or a fragment thereof is administered in an amount effective to enhance the immune response to said vaccine composition in said subject. The antibodies of the ~~invention~~disclosure may be used to enhance a humoral and/or cell mediated response against the antigen(s) of the vaccine composition. The antibodies of the ~~invention~~disclosure may be used in combination with any vaccines known in the art. The ~~invention~~disclosure encompasses the use of the antibodies of the ~~invention~~disclosure to either prevent or treat a particular disorder, where an enhanced immune response against a particular antigen or antigens is effective to treat or prevent the disease or disorder.

[0070] The ~~invention~~disclosure further provides a method for treating or preventing an IgE-mediated allergic disorder in a patient in need thereof, comprising administering to said patient a therapeutically effective amount of the agonistic antibodies of the ~~invention~~disclosure. The ~~invention~~disclosure also provides a method for treating or preventing an IgE-mediated allergic disorder in a patient in need thereof, comprising administering to said patient the antibodies of the ~~invention~~disclosure in combination with other therapeutic antibodies or vaccine compositions used for the treatment or prevention of IgE-mediated allergic disorders.

[0071] The ~~invention~~disclosure also provides a method for enhancing immune therapy for an infectious agent wherein the antibodies of the ~~invention~~disclosure are administered to a patient that is already infected by a pathogen, such as HIV, HCV or HSV, to enhance opsonization and phagocytosis of infected cells.

[0072] The ~~invention~~disclosure provides a method of treating diseases with impaired apoptotic mediated signaling, *e.g.*, cancer, autoimmune disease. In a specific embodiment, the ~~invention~~disclosure encompasses a method of treating a disease with deficient Fas-mediated apoptosis, said method comprising administering an antibody of the ~~invention~~disclosure in combination with an anti-Fas antibody.

[0073] The ~~invention~~disclosure encompasses the use of the antibodies of the ~~invention~~disclosure to detect the presence of FcγRIIB specifically (*i.e.*, FcγRIIB and not FcγRIIA) in a biological sample.

[0074] In another embodiment, the ~~invention~~disclosure provides a method of diagnosis of an autoimmune disease in a subject comprising: (i) contacting a biological sample from said subject with an effective amount of an antibody of the ~~invention~~disclosure; and (ii) detecting binding of said antibody or a fragment thereof, wherein detection of said detectable marker above a background or standard level indicates that said subject has an autoimmune disease.

[0075] In one aspect, there is provided a pharmaceutical composition comprising (i) a therapeutically effective amount of said antibody or fragment thereof as defined herein; and (ii) a pharmaceutically acceptable carrier. In one embodiment, the~~The invention further provides a~~ pharmaceutical composition comprisinges (i) a therapeutically effective amount of the antibody or a fragment thereof that specifically binds FcγRIIB with greater affinity than said antibody or a fragment thereof binds FcγRIIA; and (ii) a pharmaceutically acceptable carrier. The ~~invention~~disclosure additionally provides a pharmaceutical composition comprising (i) a therapeutically effective amount of the antibody or fragment thereof that specifically binds FcγRIIB with greater affinity than said antibody or fragment thereof binds FcγRIIA; (ii) a cytotoxic antibody that specifically binds a cancer antigen; and (iii) a pharmaceutically acceptable carrier.

[0076] In certain embodiments~~ of the invention~~, pharmaceutical compositions are provided for use in accordance with the methods of the ~~invention~~disclosure, said pharmaceutical compositions comprising an anti-FcγRIIB antibody or an antigen-binding fragment thereof, in an amount effective to prevent, treat, manage, or ameliorate a B-cell malignancy, or one or more symptoms thereof, and a pharmaceutically acceptable carrier. The ~~invention~~disclosure also provides pharmaceutical compositions for use in accordance with the methods of the ~~invention~~disclosure, said pharmaceutical compositions comprising an anti-FcγRIIB antibody or an antigen-binding fragment thereof, a prophylactic or therapeutic agent other than a FcγRIIB antagonist, and a pharmaceutically acceptable carrier.

3.1 DEFINITIONS

[0077] As used herein, the term "specifically binds to FcγRIIB" and analogous terms refer to antibodies or fragments thereof (or any other FcγRIIB binding molecules) that specifically bind to FcγRIIB or a fragment thereof and do not specifically bind to other Fc receptors, in particular to FcγRIIA. Further it is understood to one skilled in the art, that an antibody that specifically binds to FcγRIIB, may bind through the variable domain or the constant domain of the antibody. If the antibody that specifically binds to FcγRIIB binds through its variable domain, it is understood to one skilled in the art that it is not aggregated, *i.e.*, is monomeric. An antibody that specifically binds to FcγRIIB may bind to other peptides or polypeptides with lower affinity as determined by, *e.g.*, immunoassays, BIAcore, or other assays known in the art. Preferably, antibodies or fragments that specifically bind to FcγRIIB or a fragment thereof do not cross-react with other antigens. Antibodies or fragments that specifically bind to FcγRIIB can be identified, for example, by immunoassays, BIAcore, or other techniques known to those of skill in the art. An antibody or a fragment thereof binds specifically to a

FcγRIIB when it binds to FcγRIIB with higher affinity than to any cross-reactive antigen as determined using experimental techniques, such as western blots, radioimmunoassays (RIA) and enzyme-linked immunosorbent assays (ELISAs). See, *e.g.*, Paul, ed., 1989, Fundamental