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(54) Antibodies for treating an immune disease
Antikörper für die Behandlung von einer Immunerkrankung
Anticorps pour le traitement d’une maladie immunitaire

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• WEYAND C.M. ET AL: ‘B cells in rheumatoid synovitis’ ARTHRITIS RESEARCH AND THERAPY vol. 7, no. SUPPL. 3, 2005, pages S9 - S12 ISSN: 1478-6354

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• CARDARELLI PINA M. ET AL: 'Binding to CD20 by Anti-B1 Antibody or F(ab')2 is sufficient for induction of apoptosis in B-cell lines' CANCER IMMUNOLOGY AND IMMUNOTHERAPY vol. 51, no. 1, 01 March 2002, pages 15 - 24, XP002308043 ISSN: 0340-7004
Description

[0001] The present invention is related to the use of an antibody or antibody fragment which targets the spleen and is disclosed against normal and malignant B-cells.


[0004] US patent 5,152,980 discloses the use of an anti-IL-2-receptor antibody for the elimination of T-cells.

[0005] International patent application WO 89/07601 discloses the use of an antigenic determinant against a species-related autoantibody.

[0006] International patent application WO 91/16069 is related to the killing of leukaemia cells for avoiding the effects arising from transplantation and graft-versus-host disease.

[0007] International patent application WO 90/06758 is related to the therapeutic use of anti-T-cell antibodies.

[0008] International patent application WO 93/13805 is related to the treatment of cancer.

[0009] US patent 4,443,427 is related to the use of an anti-T-cell antibody for the destruction of T-cells.

[0010] European patent application EP 0 274 394 is related to the use of an immunoglobulin directed against an epitope expressed on the surface of B-cells.


[0012] European patent application EP 0 330 201 is related to the use of antibody WR-2721.

[0013] European patent application EP 0 332 865 is related to the use of an anti-B-cell antibody for suppressing the immune response generated upon upministration of a therapeutic agent such as either a naked or a conjugated antibody.

[0014] International patent application WO 91/13974 is related to a combination therapy using an antibody that selectively binds to the CD19 antigen and an antibody which selectively binds to the surface of immunoglobulin of a target B-cell.

OBJECTS OF THE INVENTION

[0015] One object of the invention is to provide agents for treatment of normal organs and tissues that are hyperproliferative, remnants, or anatomically displaced.

[0016] Another object of the invention is to provide agents for ablating normal cells and tissues as part of a therapeutic intervention.

[0017] Upon further study of the specification and appended claims, further objects and advantages of this invention will become apparent to those skilled in the art.

[0018] In a first aspect the problem underlying the instant invention is solved by an antibody or antibody fragment which targets the spleen and is directed against normal and malignant B-cells for parenteral use in a method of treating normal spleen cells in immune disease by ablation of spleen cells with said antibody.

[0019] In a first embodiment of the first aspect the antibody or antibody fragment is conjugated to a toxic agent and the immune disease is immune thrombocytopenic purpura.

[0020] In a second embodiment of the first aspect, which is also an embodiment of the first embodiment of the first aspect the antibody or antibody fragment is a Fv, single chain antibody, Fab, Fab' or F(ab')2 fragment or an intact antibody.

[0021] In a third embodiment of the first aspect, which is also an embodiment of the first and second embodiment of the first aspect the antibody or antibody fragment is conjugated to a toxic agent and wherein the antibody or antibody fragment is contained in a sterile injectable composition.

[0022] In a fourth embodiment of the first aspect, which is also an embodiment of the first, second and third embodiment of the first aspect the antibody or antibody fragment is conjugated to a toxic agent.

[0023] In a second aspect, the problem underlying the instant invention is solved by the use of the antibody or antibody fragment as defined in the first aspect or any embodiment of the first aspect, for the manufacture of a medicament for parenteral use in a method of treating normal spleen cells in immune diseases by ablation of spleen cells with said antibody.

SUMMARY OF THE INVENTION

[0024] In another embodiment, of the present invention the methods for treating ectopic tissue or organ in a mammal. The method comprises parenterally injecting a mammalian subject, at a locus and by a route providing access to said tissue or organ, with a pharmacologically effective amount of an antibody/fragment which specifically binds to said organ or tissue. The antibody/fragment is conjugated with a therapeutic agent.

[0025] In another embodiment, the invention provides a method of affecting a function of a non-malignant cell in a mammalian subject, the method comprising administering to the subject a composition comprising an antibody specific to a growth factor receptor or hormone receptor on the targeted cell, wherein the antibody affects the function and proliferation of the cell.

[0026] In another embodiment, the invention provides
an immunological method of ablating a cell in a mammalian subject, the method comprising administering to the subject requiring ablation of cell, a composition comprising an antibody or fragment specific to a hormone receptor or growth factor receptor on a cell targeted for ablation, wherein the antibody or fragment is conjugated to a chemical or radiation ablation agent.

[0027] Compositions and reagents and kits useful for practicing the methods of the invention are also provided.

DETAILED DESCRIPTION OF THE INVENTION

[0028] The above methods are beneficial for: ablation of normal spleen for therapeutic purposes, in patients with immune disease or lymphomas

[0029] The above method includes the use of a growth factor receptor antibody to target to the spleen bearing such receptor(s), the functions of which can be blocked with said antibody. An isotopic or drug conjugate of this antibody can also be used to deliver a therapeutic agent to the spleen in order to affect diseases of tissues which bear such receptors.

[0030] Many hormone and growth factor receptors are known, and frequently show sufficient organ and tissue proclivity to allow these to serve as targets for antibodies which, when bound to said receptors, affect the function of the tissues and result in an immunological or, by the use of conjugates with drugs, a chemical ablation, or a radiation ablation when used as a conjugate with therapeutic isotopes.

[0031] Where normal organs or tissues are developed abnormally or are displaced in the body, or are insufficiently removed during ablative surgery, the tissue/organ-associated antibodies may be used as tissue-targeted vehicles for delivering therapeutic agents to said tissues in order to induce their involution or chemical and/or isotopic ablation. The antibodies or their fragments (or subfragments) can be conjugated with therapeutic modalities including isotopes, drugs, toxins, photodynamic therapy agents, cytokines, hormones, autocrines, etc., which are used as cytotoxic or modulating agents, and which have hitherto been employed principally as toxic conjugates to cancer-targeting antibodies, as described in the reviews by Waldmann, T.A., Science 252:1657, 1991; Koppel, G.A., Bioconj. Chem. 1:13, 1990; Oeltmann, T.N., and Frankel, A.E., FASEB J. 5:2334, 1991; and van den Bergh, H.E., Chemistry in Britain, May 1986, 430-439.

[0032] Another therapeutic application for such organ- and tissue-targeting antibodies conjugated with a toxic agent is for the ablation of certain normal cells and tissues as part of another therapeutic strategy, such as in bone marrow ablation with antibodies against bone marrow cells of particular stages of development and differentiation, and in the cytotoxic ablation of the spleen in patients with lymphoma or certain immune diseases, such as immune thrombocytopenic purpura.

[0033] Several methods are known to those skilled in the art for producing organ or tissue-associated or specific antibodies, if existing antibodies are considered unsuitable or if different or more discriminating specificities are desired. Generally, whole cells, tissue samples and/or cell or tissue fractions, membranes, antigen extracts or purified antigens are used to challenge the immune system of a suitable animal, e.g., a mouse, rabbit, hamster, goat or the like, the antigen being rendered immunogenic by aggregation if necessary and/or by coadministration with a suitable conventional adjuvant. Hyperimmune antisera can be isolated and polyclonal antibodies prepared by conventional procedures. Alternatively, spleen cells can be fused with immortal myeloma cells to form hybridoma cells producing monoclonal antibodies, by what are now conventional procedures. See, e.g., the procedures in the above-referenced U.S. Patent Application Serial No. 609,607 for illustrative techniques. Hybridomas using animal, e.g., mouse, or human myeloma cell lines and animal or human spleen or lymph cells are all known in the art, and can be made and used for the present method. See, for example, Glassy et al., "Human Monoclonal Antibodies to Human Cancers", in "Monoclonal Antibodies and Cancer", Boss et al., Eds., 163-170 (Academic Press, 1983). The specific antisera or monoclonals are screened for specificity by methods used to screen the antilymphocyte clones in the references cited hereinabove, which methods are also conventional by now in this art.

[0034] Organ-associated and organ-specific antibodies can be developed by immunizing a suitable animal host with certain mammalian tumors or normal organ/tissue extracts and/or cells, as well as with purified hormone receptors or growth factor receptors. It is well known that use of tumors as immunogens can result in antibodies which not only react with neoplasia but also with normal tissue components which sometimes show an organ-restricted nature. Histogenetic and functional differences between various tissues and organs of the body of course suggest that distinct antigens are present and identifiable. A body of scientific literature already exists which claims the identification of organ-specific antigens, either using classical immunization approaches or by immunizing with specific tumors, and this is reviewed by Goldenberg et al., Cancer Res., 3455(1976), showing that such antigens are known and available.

[0035] Similar organ- and tissue-associated and specific antigens are identifiable by hybridoma methods which produce monoclonal antibodies. One recent development is the production of human hybridoma monoclonal antibodies by securing lymphocytes or plasma cells from patients showing certain organ-restricted autoimmune diseases, e.g., thyroiditis, gastritis, ulcerative colitis, myositis, and the like. These antibody-producing cells are then fused in vitro with human or murine myeloma cells and hybridomas of appropriate anti-organ and anti-tissue antibody formation are produced and propa-
gated, using well known methods. Also, patients with specific tumor types can be used as a source of such lymphocytes or plasma cells, or such patients can be further immunized with such tumor cells for stimulating the production of anti-organ and anti-tissue antibodies. The lymphatic tissue removed is then used for fusion with suitable myeloma cells, by procedures which are by now well known and conventional in the art.

[0036] Organ-associated and organ-specific antigens can be isolated for immunization of another species, e.g., subhuman primates, rodents, rabbits, goats, etc., by a number of methods known in the art, such as isolation of cell membranes or disruption of the cells, e.g., by centrifugation, sonication, etc., to obtain intracellular antigens. It is preferable, for these purposes, to use intracellular as opposed to surface and extracellular antigens. In this manner, organ-associated and organ-specific antigens can be obtained from a large number of tissues and organs of the body, including brain, thyroid, parathyroid, larynx, salivary glands, esophagus, bronchus and lungs, heart, liver, pancreas, stomach and intestines, kidney, adrenal gland, ovary, testis, uterus, prostate, etc. Of further interest is the differentiation of different tissue and cellular components within an organ, such as tubular and glomerular kidney, different regions and cell types of the brain, endocrine and exocrine pancreas, etc., especially by the identification of antigens and antigen epitopes restricted to the individual cell and tissue types in question, as accomplished with polyclonal and/or hybridoma-monoclonal antibody-production methods known in the art.

[0037] Antibodies can be produced using cells isolated from tissue obtained at autopsy. For example, mice can be immunized with such tissues for a period necessary to evoke anti-specific organ or tissue antibodies. The spleens of these mice are removed and then fused, by standard methods, with a murine myeloma cell line suitable for hybridoma production. Using methods already standard in the art, monoclonal antibody-producing hybridomas are selected and propagated, and those with organ- or tissue-associated antibody production are cloned and expanded as a source of organ or tissue antibodies. Absolute tissue specificity is not required since significant quantitative differences ordinarily suffice for operational specificity for imaging purposes.

[0038] Antibodies and fragments useful in the methods of the present invention include those against antigens associated or produced by normal organs, tissues, and cells, and may or may not be cross-reactive with certain neoplastic tissues.

[0039] Preferred are those which, prior to being labeled or conjugated, have a specific immunoreactivity to targeted cells, tissue or organs of at least 60% and a cross-reactivity to other antigens of less than 35%. Specific examples include antibodies and fragments against hormone receptors and growth factor receptors, such as of epidermal growth factor.

[0040] Antibodies that target the spleen well include the LL2 (also known as EPB-2) monoclonal antibody, disclosed in Pawlak-Byczkowska, Cancer Research, 49: 4568-4577 (1989), which is directed against normal and malignant B-cells, and which can be used for treating normal spleen cells in patients with immune diseases, lymphoma, and other diseases.

[0041] Antibodies useful in the present invention may be whole immunoglobulin of any class, e.g., IgG, IgM, IgA, IgD, IgE, chimeric or hybrid antibodies with dual or multiple antigen or epitope specificities. It can be a polyclonal antibody, preferably an affinity-purified antibody from a human or an appropriate animal, e.g., a primate, goat, rabbit, mouse or the like. Monoclonal antibodies are also suitable for use in the present method, and are preferred because of their high specificities. They are readily prepared by what are now considered conventional procedures of immunization of mammals with immunogenic antigen preparation, fusion of immune lymph or spleen cells with an immortal myeloma cell line, and isolation of specific hybridoma clones. More conventional methods of preparing monoclonals antibodies are not excluded, such as interspecies fusions and genetic engineering manipulations of hypervariable regions, since it is primarily the antigen specificity of the antibodies that affects their utility in the present invention. It will be appreciated that newer techniques for production of monoclonals can also be used, e.g., human monoclonals, interspecies monoclonals, chimeric (e.g., human/mouse) monoclonals, genetically engineered antibodies and the like.

[0042] Antibody fragments useful in the present invention are F(ab')2, F(ab)2, Fab', Fab, Fv and the like, including hybrid fragments. Also useful are any subfragments retaining the hypervariable, antigen-binding region of an immunoglobulin and having a size smaller than a Fab' fragment. This will include genetically engineered and/or recombinant proteins, whether, single-chain or multiple-chain, which incorporate an antigen binding site and otherwise function in vivo as targeting vehicles in substantially the same way as natural immunoglobulin fragments. Such single-chain binding molecules are disclosed in U.S. Patent 4,946,778, . Fab' antibody fragments may be conveniently made by reductive cleavage of F(ab)2 fragments, which themselves may be made by pepsin digestion of intact immunoglobulin. Fab antibody fragments may be made by papain digestion of intact immunoglobulin, under reducing conditions, or by cleavage of F(ab')2 fragments which result from careful papain digestion of whole Ig. The fragments may also be produced by genetic engineering.

[0043] It should be noted that mixtures of antibodies, isotopes, and immunoglobulin classes can be used, as can hybrid antibodies. The hybrids can have two different antigen specificities, e.g., one arm binding to one organ antigen and another arm binding to another antigen, or one arm could bind to one epitope on the antigen, and the other arm could bind to another epitope. The foregoing are merely illustrative, and other combinations of spe-
cificities can be envisioned that also fall within the scope of the invention.


[0046] The method of the present invention includes the use of pretargeted antibody methods, and the use of light with porphyrins and fluorescent dyes. The methods taught in the prior art are utilized in cancer therapy. However, if the antibody fragment utilized is targeted to organs and tissues specified herein, analogous procedures may be used in the present invention.

[0047] For example, Paganelli, Nucl. Med. Commun. 12:211, 1991, disclosed antibody pretargeting procedures, such as using streptavidin-conjugated antibodies, biotinylated antibodies in conjunction with avidin and biotin, bifunctional antibodies, antibody-hapten complexes, and enzyme-conjugated antibodies, in addition to delivering radiation to target cells and tissues by such 2- and 3-step procedures.

[0048] When the cell or tissue is pretargeted by a 2- or 3-step procedure, the subject is injected with a first composition comprising, for example, a streptavidin-conjugated antibody, biotinylated antibody to be used in conjunction with avidin and biotin, bifunctional antibody, antibody-hapten complexes, or enzyme-conjugated antibody, wherein the antibody is an antibody or antibody fragment which specifically binds a marker produced by or associated with said cell or tissue. After the first composition accretes at the targeted tissue or cell, a second composition, which bears the desired therapeutic or activating principle, is administered. The second composition either activates the first composition or couples with the first composition to produce a desired effect.

[0049] When the cell or tissue is pretargeted in a 3-step procedure, the subject is injected with the first composition which comprises biotinylated antibody or fragment, is then injected with a clearing composition comprising an agent to clear circulating biotinylated antibody or fragment, and then injected with the second composition which comprises biotin conjugated with the desired imaging, therapeutic, cytoprotective or activating agent.

[0050] When the term "antibody" is used herein, all the above types of antibodies and fragments are included therein.

[0051] The use of light and porphyrins in cancer therapy has been reviewed by van den Bergh (Chemistry in Britain, May 1986, Vol. 22, pp. 430-437), and includes reference to the use of monoclonal antibodies conjugated with a photosensitizer for transporting the latter to the tumor. This has been suggested earlier by Oseroff in Photochem. Photobiol. 41:35S, 1985; Mew et al., Cancer Res. 45:4380, 1985; Hasan et al., Immunity to Cancer, II, pp. 471-477, 1989 [Alan R. Liss, Inc. publishers]; and Pelegrin et al., Cancer 67:2529, 1991 which involved tissue culture or animal studies of fluorescent dyes attached to antitumor antibodies.

[0052] Radiolabeled antibodies to markers characteristic of displaced or ectopic tissues or organs are a new kind of agent. Such agents are useful for imaging organs such as, e.g., liver, spleen, pancreas, and the like, and many antibodies which specifically bind to tissues of these organs are known and/or under current investigation and development.

[0053] Among the radioisotopes used, gamma-emitters, positron-emitters, x-ray emitters and fluorescence emitters are suitable for localization and/or therapy, while beta-emitters and alpha-emitters may also be used for therapy. Suitable radioisotopes for the methods of the present invention include: Astatine-211, Iodine-123, Iodine-125, Iodine-131, Iodine-133, Bismuth-212, Bromine-77, Indium-111, Indium-113m, Gallium-67, Gallium-68, Ruthenium-95, Ruthenium-97, Ruthenium-103, Ruthenium-105, Mercury-107, Mercury-203, Rhenium-186, Rhenium-188, Tellurium-121m, Tellurium-122m, Tellurium-125m, Thulium-165, Thulium-167, Thulium-168, Technetium-99m, Fluorine-18, Silver-111, Platinum-197, Palladium-109, Copper-67, Phosphorus-32, Phosphorus-33, Yttrium-90, Scandium-47, Samarium-153, Lutetium-177, Rhodium-105, Praseodymium-142, Praseodymium-143, Terbium-161, Holmium-166, Gold-199, Cobalt-57, Cobalt-58, Chromium-51, Iron-59, Selenium-75, Thallium-201, and Ytterbium-169. Preferably the radioisotope will emit in the 10 - 5,000 kev range, more preferably 50 - 1,500 kev, most preferably 50 - 500 kev.


[0056] Many drugs and toxins are known which have cytotoxic effects on cells. They are to be found in compendia of drugs and toxins, such as the Merck Index, Goodman and Gilman, and the like, and in the references cited above. Any such drug can be conjugated to or loaded onto the antibody by conventional means well known in the art, and illustrated by analogy to those described above.

[0057] The present invention also contemplates dyes used, for example, in photodynamic therapy, conjugated to the antibodies and fragments, and used in conjunction with appropriate nonionizing radiation.

[0058] Examples of known cytotoxic agents useful in the present invention are listed in Goodman et al., "The Pharmacological Basis of Therapeutics," Sixth Edition,
The antibodies and fragments of the invention may be radiolabeled by a variety of methods known in the art. Many of these methods are disclosed in the above-referenced U.S. Patents and Patent Applications, and include direct radionuclide labeling. See also, Rayudu, op. cit.; and Childs et al., J. Nuc. Med., 26, 293 (1985). Any conventional method of radionuclide labeling which is suitable for labeling isotopes for in vivo use will be generally suitable for labeling imaging agents according to the present invention.

The antibodies and fragments may be conjugated to therapeutic agents such as drugs, toxins, boron addends, isotopes, fluorescent dyes activated by non-ionizing radiation, hormones, autocrines, cytokines, cytotoxic agents, etc., by methods known to those skilled in the art. US Patent 5,057,313, Shih et al, teaches one such method.

Loading of drugs on to a carrier as disclosed in US Patent 5,057,313 will depend upon the potency of the drug, the efficiency of the antibody targeting and the efficacy of the conjugate once it reaches its target. In most cases, it is desirable to load at least 20, preferably 50 and often 100 or more molecules of a drug on a carrier. The ability to partially or completely detoxify a drug as a conjugate, while it is circulating, can reduce systemic side effects of the drug and permit its use when systemic administration of the unconjugated drug would be unacceptable.

Toxins will often be less heavily loaded than drugs, but it will still be advantageous to load at least 1, preferably 5, and in some cases 10 or more molecules of toxin on a carrier and load at least one carrier chain on the antibody for targeted delivery.

The conjugate will generally be administered as a sterile aqueous solution in phosphate-buffered saline. Dosage will depend on the therapeutic utilized, the desired effect and the side effects experienced by the patient.

The imaging agent will normally be administered at a site and by a means that insures that it is mobilized and taken up into the organ or tissue which will vary by the tissue or organ to be imaged.

The agent is preferable injected by a systemic route, e.g., intravenously, intraarterially, intramuscularly or subcutaneously, or by a combination of systemic routes insuring its accretion in the tissue or organ of interest.

Volumes of labeled antibody imaging agent, normally in sterile physiological saline, will normally vary somewhat depending upon the site, the concentration, and the number of injections. Activity of the agent will normally be in the range of about 10 - 40, preferably about 15 - 25 mCi per injection for a Tc-99m-labeled agent. It will be appreciated that the activity will vary for other radioisotopes, depending upon their half-lives, their imaging characteristics, i.e., energy ranges, emission intensities, scatter and the like, the stability of the labeled agent, especially antibody conjugates, their distribution and clearance, and the time at which imaging is to be done. Adjustment of these parameters will be conventional for the ordinary skilled clinician.

The conjugate will generally be administered as a sterile aqueous solution in a buffered saline. Dosage units of about 1 - 200 mg of conjugate will be administered for a duration of treatment as determined by the skilled practitioner. It may be necessary to reduce the dosage and/or use antibodies from other species and/or hypoallergenic antibodies, e.g., chimeric mouse/human, CDR-grafted (“humanized”), or primate antibodies, to reduce patient sensitivity.

Routes of administration include intravenous, intraarterial, intrapleural, intraperitoneal, intrathecal, subcutaneous or by perfusion.

The reagents are conveniently provided in kit form, adapted for use in the methods of the invention. Kits will normally contain separate sealed sterile vials of injectable solutions of labeled reagents, or lyophilized antibodies/fragments or antibody/fragment conjugates and vials of sterile conventional injection vehicles with which they will be mixed just prior to administration.

Kits may also include reagents for labeling antibodies, e.g., Chloramine-T (for I-131 or I-123 labeling), SnCl₂ (for Tc-99m labeling using pertechnetate from a commercial generator), short columns for sizing and/or purification of reagents, and other conventional accessory materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following examples are, therefore, to be construed as merely illustrative, In the following examples, all temperatures are set forth uncorrected in Celsius; unless otherwise indicated, all parts and percentages are by weight.
REFERENCE EXAMPLES

Example 1 - Imaging Pancreatic Cells

[0072] Hybridoma-monoconal antibodies are made in the mouse to the Langerhans cells of the endocrine pancreas, derived from a human autopsy specimen shortly after death. The monoclonal F(ab')2 reactive against the antigen epitope showing relatively high specificity for Langerhans cells of the pancreas, as demonstrated, e.g., by immunohistology, are labeled with a gamma-emitting isotope, such as with I-123, and injected, e.g. 0.15 mg monocolonal against endocrine pancreas antigen, labeled using Chloramine-T with I-123, at a dose of 3.0 mCi, injected i.v. in a 3-month-old male suspected of having pathology of the endocrine pancreas. External gamma-camera imaging is performed at 6, 24, and 48 hours after injection, without subtraction. In this specific case, decreased to almost absent accretion of 1-123 radioactivity in the pancreas is suggestive of endocrine pancreas pathology in an infant presenting with pancreas hormone deficiency shortly after birth.

Example 2 - Bone Marrow Ablation and Cancer Therapy

[0073] A middle-age woman with advanced breast cancer, including bone and bone marrow invasion, has an aliquot of her bone marrow removed and harvested for regrafting after clearing the marrow of the cancer cells in vitro. The bone marrow in the patient is then destroyed by i.v. infusion of 20 mg NP-2 monoclonal antibody F (ab')2 labeled with 200 mCi Rhenium-188 according to the method of Griffiths et al. (Cancer Res. 51:4594, 1991). Approximately 3 weeks later, there is evidence of severe bone marrow toxicity which requires the infusion of the autologous bone marrow which was previously cleared of cancer cells, in combination with hematopoietic growth factor administration, in this case with GM-CSF given repeatedly before and after marrow grafting. Six weeks later, the patient has renewed bone marrow function and an MN3-Fab' (Tc-99m) bone marrow scan shows good bone marrow imaging without evidence of metastatic defects. She is now a candidate for treatment of other sites of her metastatic breast cancer.

Example 3 - Endometriosis Detection

[0074] A woman complains of amenorrhea and infertility and is suspected of having endometriosis. She is injected with 1 mg of anti-endometrial tissue monoclonal antibody Fab' labeled with Tc-99m (20 mCi) intravenously. Four hours later, a total body planar scan reveals abnormal foci of radioactivity in the right lower chest and in the retroperitoneum, which are confirmed by single photon emission computer tomography immediately thereafter. The patient is then referred to ablation therapy.

Example 4 - Endometriosis Therapy

[0075] A woman is diagnosed to have endometriosis and is referred to her gynecologist for treatment. An endometrial tissue-associated monoclonal antibody IgG and a monoclonal antibody IgG against FSH receptor are labeled with I-131 by the chloramine-T method at a specific activity of 10 mCi/mg, and the combination is then infused i.v. to deliver a dose of 100 mCi I-131. After monitoring her peripheral blood cells during the next month, a repeat therapy is given 6 weeks later. After an additional 6 weeks, the patient shows a complete remission of her symptoms.

Claims

1. An antibody or antibody fragment which targets the antigen of endometrial tissue and is directed against normal and malignant B-cells for parenteral use in a method of treating normal spleen cells in immune diseases by ablation of spleen cells with said antibody.
2. The antibody or antibody fragment of claim 1, wherein the antibody or antibody fragment is conjugated to a toxic agent and wherein the immune disease is immune thrombocytopenic purpura.
3. The antibody or antibody fragment of claims 1 to 2, wherein the antibody or antibody fragment is Fv, single chain antibody, Fab, Fab' or F(ab')2 fragment or an intact antibody.
4. The antibody or antibody fragment of any one of claims 1 to 3, wherein the antibody or antibody fragment is conjugated to a toxic agent and wherein the target cell is at least 60% and a cross reactivity to other antigens of less than 35% prior to labelling.
5. The antibody or antibody fragment of any one of claims 1 to 5, wherein the antibody or antibody fragment has a specific immunoreactivity to said target cell of at least 60% and a cross reactivity to other antigens of less than 35% prior to labelling.
6. The antibody or antibody fragment of any one of claims 1 to 5, wherein the antibody or antibody fragment is conjugated to a toxic agent.
7. Use of an antibody or antibody fragment as defined
Patentansprüche

1. Antikörper oder Antikörperfragment, der/das die Milz targetiert und gegen normale und maligne B-Zellen gerichtet ist, für die parenterale Verwendung in einem Verfahren zur Behandlung normaler Milzzellen bei Imunerkrankungen durch Ablation von Milzzellen mittels des Antikörpers.

2. Antikörper oder Antikörperfragment nach Anspruch 1, wobei der Antikörper oder das Antikörperfragment mit einem toxischen Agens konjugiert ist, und wobei die Imunerkrankung immunthrombocytopenische Purpura ist.

3. Antikörper oder Antikörperfragment nach Anspruch 1 bis 2, wobei der Antikörper oder das Antikörperfragment ein Fv, Einzelkettenantikörper, Fab-, Fab'- oder \( F(ab')_2 \)-Fragment oder ein intakter Antikörper ist.

4. Antikörper oder Antikörperfragment nach einem der Ansprüche 1 bis 3, wobei der Antikörper oder das Antikörperfragment mit einem toxischen Agens konjugiert ist, und wobei der Antikörper oder das Antikörperfragment in einer sterilen injizierbaren Zusammensetzung enthalten ist.

5. Antikörper oder Antikörperfragment nach einem der Ansprüche 1 bis 5, wobei der Antikörper oder das Antikörperfragment eine spezifische Immunreaktivität mit der targetierten Zelle von wenigstens 60% und eine Kreuzreaktivität mit anderen Antigenen von weniger als 35% vor dem Markieren aufweist.

6. Antikörper oder Antikörperfragment nach einem der Ansprüche 1 bis 5, wobei der Antikörper oder das Antikörperfragment mit einem toxischen Agens konjugiert ist.

7. Verwendung eines Antikörpers oder Antikörperfragments wie in einem der Ansprüche 1 bis 6 definiert, zur Herstellung eines Medikamentes für die parenterale Verwendung in einem Verfahren zur Behandlung normaler Milzzellen bei Imunerkrankungen durch Ablation von Milzzellen mit dem Antikörper.

Revendications

1. Anticorps ou fragment d’anticorps dont la cible est la rate et qui est dirigé contre des lymphocytes B normaux et cancéreux destiné à une utilisation parentérale dans un procédé de traitement de cellules spléniques normales dans des maladies immunitaires par l’ablation de cellules spléniques avec ledit anticorps.

2. Anticorps ou fragment d’anticorps selon la revendication 1, où l’anticorps ou le fragment d’anticorps est conjugué à un agent toxique et où la maladie immunitaire est le purpura thrombopénique immunitaire.

3. Anticorps ou fragment d’anticorps selon les revendications 1 à 2, où l’anticorps ou le fragment d’anticorps est un fragment Fv, un anticorps à simple chaîne, un fragment Fab, Fab’ ou \( F(ab')_2 \) ou un anticorps intact.

4. Anticorps ou fragment d’anticorps selon l’une quelconque des revendications 1 à 3, où l’anticorps ou le fragment d’anticorps est conjugué à un agent toxique et où l’anticorps ou le fragment d’anticorps est contenu dans une composition stérile injectable.

5. Anticorps ou fragment d’anticorps selon l’une quelconque des revendications 1 à 5, où l’anticorps ou le fragment d’anticorps possède une immunoréactivité spécifique à ladite cellule cible d’au moins 60 % et une réactivité croisée à d’autres antigènes inférieure à 35 % avant le marquage.

6. Anticorps ou fragment d’anticorps selon l’une quelconque des revendications 1 à 5, où l’anticorps ou le fragment d’anticorps est conjugué à un agent toxique.

7. Utilisation d’un anticorps ou fragment d’anticorps selon l’une quelconque des revendications 1 à 6, pour la fabrication d’un médicament destiné à une utilisation parentérale dans un procédé de traitement de cellules spléniques normales dans des maladies immunitaires par l’ablation de cellules spléniques avec ledit anticorps.
REFERENCES CITED IN THE DESCRIPTION

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