



Office de la Propriété
Intellectuelle
du Canada

Un organisme
d'Industrie Canada

Canadian
Intellectual Property
Office

An agency of
Industry Canada

CA 2365636 A1 2003/06/05

(21) **2 365 636**

(12) **DEMANDE DE BREVET CANADIEN
CANADIAN PATENT APPLICATION**

(13) **A1**

(22) Date de dépôt/Filing Date: 2001/12/05

(41) Mise à la disp. pub./Open to Public Insp.: 2003/06/05

(51) Cl.Int.⁷/Int.Cl.⁷ A61K 39/395, A61K 47/48, A61K 45/00

(71) Demandeur/Applicant:
HERMAN, WILLIAM, CA

(72) Inventeur/Inventor:
HERMAN, WILLIAM, CA

(54) Titre : LIGAND MULTIFONCTIONNEL

(54) Title: MULTIFUNCTIONAL LIGAND



Multifunctional Ligand

Field of The Invention

The present invention relates to heterofunctional ligand comprising first and second moieties which have cooperating functional affinities as well as a multifunctional ligand, for example, a bi-specific antibody, having at least a first portion which binds to a 'lymphatic vessel associated' antigen/receptor and a second portion having at least one immune-affecting functionality including, without limitation, functions related to antigen presentation, immune signaling, suppression or enhancement of immune tolerance or immune stimulation, or binding to a target molecule, for example a cell surface antigen, receptor etc.

Background of the Invention

Immunotherapy has gained wide acceptance as a promising measure to address several disease states including autoimmune disease, transplant rejection, infectious disease and cancer. Despite rapid and exciting progress in approaches to treatment, the disease burden attributable to such illnesses has not significantly abated. The complex nature of the normal and pathologic immunologic processes associated with such diseases, coupled with logistical problems in evaluating and implementing methods for immunotherapy in human subjects, continue to be some of the obstacles to successful advances in treatment.

Successful approaches to immunotherapy are predicated on the ability of the immunotherapeutic molecule to be delivered in a therapeutic, sub-toxic dose at the desired therapeutic frequency. In the process of selection of a suitable immunotherapeutic molecule, it is recognized that sub-toxic doses may be insufficient for the desired therapeutic effect, especially where the antibody binds incidentally to cell populations other than the target population. In the case of an injectable preparation and especially an intravenous mode of delivery, in contrast to readily self-administered modes of delivery, the optimal dosing frequency for therapeutic purposes could impose an undesirable burden on the patient and care-giver, assuming that such optimal frequency is to begin with deemed convenient for clinical trials.

Numerous research efforts are underway to identify and test ligands including antibodies, agonists, antagonists etc. which will bind to or otherwise interact with or trigger responses in or towards immune and other cells, for example pathogenic organisms and diseased cells. A recent example is a renewed interest to find molecules and methods of triggering an interaction with CD45 (see for example Nature (2001) Vol. 409 p. 349-354).

Summary of the Invention

The present invention facilitates development, therapeutic evaluation, and delivery, particularly targeted delivery of molecules that exert therapeutic functions and particularly immune functions. In preferred aspects the invention contemplates compositions of matter and methods of delivery, in some cases using ligands that but for the targeting methods herein defined would be ineffective or have a broader effect than is desirable; or similarly, but for the severity of the disease or the absence of other therapeutic alternatives for which such ligands are useful, they would otherwise be inappropriate for therapeutic use. The present invention accommodates evaluation of such ligands for therapeutic purposes using such targeting strategies.

In one aspect the invention is directed to heterofunctional ligand comprising a first moiety which binds to a first target ligand and a second moiety which binds to a second target ligand, and wherein the affinity or avidity or both the affinity and avidity of said first moiety are selected to enable the first moiety to bind to the first target ligand independently of the ability of said second moiety to bind to the second target ligand and wherein the relative avidity or affinity or both the affinity and avidity of said second moiety are selected or adjusted to substantially reduce the probability of the second moiety binding to the second target ligand without the first moiety, first or substantially contemporaneously, binding to the first target ligand. For example, in one embodiment the first moiety is divalent and the second moiety is monovalent. In another embodiment the first moiety is trivalent and the second moiety is monovalent. In one embodiment the affinity of the first moiety for its target ligand is for example up to several orders of magnitude greater than the affinity of the second moiety for its target ligand, as discussed below. In a preferred embodiment both moieties are capable of binding to different target ligands on the same cell, for example as hereinafter specified, although in the case of tumor cell targeting, particularly with respect to cells that are growing adjacent to another the invention contemplates that the first moiety may bind to one cell and the second moiety may bind to a neighbouring cell. Accordingly, in the case of receptors requiring cross-linking for biological activity the invention contemplates that such same cell interactions and adjacent cell interactions are optionally accomplished when the second moiety is bivalent. In one embodiment, at least one of said first and second moieties comprise one or more antibody components. In another embodiment, said first moiety binds to at least one cell-surface ligand which differentiates between cells of the same population or sub-population, for example, at least one ligand which differentiates which between populations or sub-populations of immune cells (eg. see WO 01/21641, US 6156878), for example, activated vs. non-activated, disease-associated or non-disease-associated (over-expressing or uniquely expressing certain receptors or other ligands [for example cytokine or growth factor receptors, particular immunoglobulin like molecules or MHC peptide complexes] or other differentiating markers hereinafter exemplified or apparent to those skilled in the art), and said second moiety, in

virtue of its binding to the second target ligand, directly or indirectly exerts a therapeutic effect, for example an immune modulating effect. In a further preferred embodiment said second moiety has a broader target cell population than said first moiety. Eg. see Wiley H. et al. Expression of CC Chemokine Receptor-7 and Lymph Node Metastasis..., J. Natl. Cancer Inst. 93:1638-1643; Moore MA Bioessays 2001 Aug;23(8):674-6. For example, in one embodiment said first moiety binds to a tumor associated antigen on a tumor cell and said second moiety binds to a receptor which is found on the tumor cell but also on a broader population of cells. In another embodiment said first moiety binds to an antigen associated with particular population of leukocytes and said second moiety binds to a receptor which is found on that population of cells but also on a broader population of cells (eg. apoptosis mediating receptors Journal of Immunology 1998 160:3-6, Nat Med 2001 Aug; 7(8):954-960, WO 01/85782; ICAM-R WO 00/29020; see also WO 01/85768, WO 01/85908; WO 01/83755, WO 01/83560, WO 01/29020; Vitale et al. Prpc. Nat. Acad. Sci. 2001 May 8; 98(10):5754-5769; CCR2 see also USP 6,312,689; USP 6,294,655 Anti-interleukin-1 receptor antagonist antibodies and uses thereof; USP 6,262,239; USP 6,268,477). In another embodiment the second moiety does not necessarily bind with lower affinity to its target however it may bind to a first ligand which in turn binds to a second ligand on a target cell (eg. a receptor on the target cell eg. a cytokine, chemokine or growth factor receptor), for example the receptor being on the same cell to which the first moiety binds, and it binds in a manner in which it partially interferes with the binding of the first ligand to the second ligand and thereby directs or retargets that first ligand to the second ligand in a manner which accomplishes the intended interaction of the first with the second ligand (eg a signal transduction or blocking interaction ie. the second moiety causes the eg. cytokine to bind to its receptor without engendering the biological effects attributable to receptor binding eg. signal transduction, which may be assessed by assaying for effects of eg. signal transduction according to well established techniques in the art) but less competitively relative to the first moiety so that the first moiety exerts a targeting function ie. where the first ligand bound by the second moiety binds to a broader than desired population of cells. The binding of the second moiety may also be compatible with the first ligand binding to one cell surface ligand but not another eg. see WO 00/64946 the contents of which are hereby incorporated by reference. The ability to identify ligand residues of importance to binding or residues other than these, the alteration of which might interfere with binding is well established in the art. The invention contemplates varying, by high throughput techniques eg. phage display, residues of an antibody that are not involved in first ligand binding to create variants which can be tested for partial interference with first ligand binding to the second ligand eg. receptor binding.

Examples of receptors include tyrosine kinase type receptors, serine kinase type receptors, heterotrimeric G-protein coupled receptors, receptors bound to tyrosine kinase, TNF family receptors, notch family receptors, guanylate cyclase types, tyrosine phosphatase types, adhesion receptors etc. (for example receptors see those discussed in Cancer: Principles and Practice of Oncology 6th Ed. De Vita et al. Eds Lippincott 2001, including particularly Chapter 3, 7 and 18, The Autoimmune Diseases, Academic Press Third Edition, Rose/Mackay ISBN: 0125969236, Immunology 6th Edition, Mosby 2001 Roitt et al. Eds; Molecular Mimicry, Microbes & Autoimmunity by Madeleine W. Cunningham (Editor), Robert S. Fujinami (Editor) December 2000, among other references hereinbelow identified). Further mention may also be made of interleukin and interferon type receptors, HGF receptor (see for example USP 6,214,344), CD45, CXC family receptors including CXCR1 and CXCR2 receptors including IL-8 receptor, EGFRs, receptors for molecules with functions in apoptosis or homeostasis, receptors such as FGF which sensitize tumor cells to chemotherapeutic agents, etc. It is known for example to modify receptor ligands in a way which does not interfere with a signaling function (the residues important for signaling may be known or can be readily ascertained eg. see Retargeting interleukin 13 for radioimmunodetection and radioimmunotherapy of human high-grade gliomas. Debinski W, Thompson JP. Clin Cancer Res 1999 Oct;5(10 Suppl):3143s-3147s) but reduces the affinity of the ligand for this receptor (see also WO 01/19861. Alternatively, the second moiety may be an antibody which is agonistic or antagonistic and used to block, activate, neutralize etc the receptor. With respect to EGFR family, TNF family and other receptor targeting antibodies which are capable of causing apoptosis directly or indirectly, see US 5,876,158, WO 00/20576, WO96/08515, WO 01/44808 (P75AIRM1), WO 00/29020 (ICAM-R), WO 99/12973, CA 2236913 etc. The invention also contemplates that the second moiety may also be targeted to a specific portion of a receptor which differentiates it from other receptors of its class and more generally contemplates that the second moiety may contribute to the targeting ability of the multifunctional ligand.

In another aspect, the invention also contemplates that the first moiety binds to a target cell and said second moiety binds to a ligand, for example a natural ligand, (eg. a cytokine or chemokine circulating at normal levels or at higher levels attributable to a disease or treatment of a disease with another therapeutic molecule) and retargets that ligand (for example, the ligand may be retargeted from circulation) to a targeted cell. For example the invention contemplates that IL-2 may be retargeted to LAK cells or CTLs via a high affinity Leu-19 binding first moiety. For example, antibodies including fragments thereof which bind to cytokines or other natural ligands for retargeting purposes (eg. single domain antibodies) can be made by phage display against the cytokine or ligand while bound in situ to its receptor. The invention also contemplates that the affinity for the cytokine may be adjusted to regulate the degree of targeting and that serum samples may be evaluated to assess the degree of bound cytokine and the relative degree of bound and unbound cytokine. Among other methods, for example, the invention contemplates that a radiolabelled multifunctional ligand may be used to assess the amount of label associated with the multifunctional ligand when bound to the cytokine, by capturing the 'complex' with an antibody that recognizes both antigenic determinants on both the cytokine and an adjacent portion of the ligand binding thereto ie. forming a composite epitope), such as may be generated by phage display and assessing the amount of label relative to the amount of captured complex. The invention also contemplates administration of supplemental amounts of natural ligand to compensate for the degree in which the ligand is retargeted insofar as such retargeting might impact negatively on immune or other physiological processes.

In another aspect the invention contemplates that patients treated with antibodies to a particular natural ligand eg. a cytokine, for example TNF α , may preferably be treated with a multifunctional ligand having a first moiety which binds to at least one tumor type and a second moiety which binds to a natural ligand such as a cytokine for retargeting that cytokine to tumor tissues, as in a preventative method for treating cancer. In this respect the invention contemplates that the antibody is capable of binding to the cytokine but once bound the cytokine, the cytokine is incapable and/or only weakly capable of binding to its receptor and/or that the multifunctional ligand also comprises a higher affinity receptor blocking moiety to minimize retargeting of the primary disease site. In one embodiment, the first moiety binds with relatively higher functional affinity (ie. avidity, affinity, and/or relatively advantageous binding capacity in virtue of multiple ligand binding arms, each binding to different ligands on the target cell) to ensure binding to the retarget cell. In another embodiment the bound cytokine is capable of binding to the cytokine receptor at the retarget site but incapable of binding to the receptor at the disease site owing to differences in the receptors at the two sites.

For example, patients with Crohn's disease that are treated with anti-TNF α (see for example, Expert Opin Pharmacother 2000 May;1(4):615-22 and references cited therein) may be treated according to the invention with a bispecific antibody having, in addition to an anti-TNF α binding moiety, which reduces the affinity of the bound TNF for the receptor, but also an antibody moiety which binds to tumor antigen which is expressed on many different tumor types or optionally a trispecific antibody which additionally binds to a second multi-carcinomic antigen, preferably one which broadens the range of targeting against prevalent cancers. With respect to tumor antigens mention may be made of EGFR, TAG-72, CEA, H11 among other known multicarcinomic antigens (see also Cancer: Principles and Practice of Oncology 6th Ed. De Vita et al. Eds Lippincott 2001 Chapters 18 and 20.5). In another embodiment, the second moiety differentially retargets a cytokine to one receptor in preference to another, for example, to a TNF receptor over-expressed on tumor cells in preference to a TNF receptor associated with Crohns disease. In a related but also independent aspect, the invention contemplates a method of screening for an antibody which preferentially binds to a ligand when bound to a first receptor relative to another second receptor by screening for antibodies (eg. by phage display, ribosome display, etc.) which bind to the ligand eg. a cytokine, when bound in situ to the first receptor, and selecting among them those that bind to the ligand eg. cytokine but do not bind (subtractive screening) or bind with lesser affinity to the cytokine when bound to the second receptor, as well as to antibodies and multifunctional ligands created by this method (see also USP 6,046,048 and WO 99/12973 and references cited therein with respect to TNF family of receptors). Variations in the extracellular domains of such receptors are known and can be ascertained by methods known to those skilled in the art.

Further with respect to multifunctional ligands having a higher affinity targeting moiety relative to the second ie. effector moiety, the second moiety may be for example an antibody or other ligand which interferes with the binding of the regular ligand for this receptor. For example, in one embodiment, the invention contemplates that the second moiety blocks a receptor that are found on cells other than the target cell, the blockage of which leads to the apoptosis of or destruction of the cell eg. CD95 (eg. see Jung G. et al., Target cell-restricted triggering of the CD95 (APO-1/Fas) death receptor with bispecific antibody fragments Cancer Res 2001 Mar 1;61(5):1846-8). With respect to blocking insulin like growth factor receptor, insulin receptor etc. see The IGF system in thyroid cancer: new concepts. Vella V., Mol Pathol 2001 Jun;54(3):121-4; Insulin receptor isoform A, a newly recognized, high-affinity insulin-like growth factor II receptor in fetal and cancer cells. Mol Cell Biol 1999 May;19(5):3278-88; Expression of the insulin-like growth factors and their receptors in adenocarcinoma of the colon. Freier S Gut 1999 May;44(5):704-8; Pandini G., Insulin and insulin-like growth factor-I (IGF-I) receptor overexpression in breast cancers leads to insulin/IGF-I hybrid receptor overexpression: evidence for a second mechanism of IGF-I signaling. Clin Cancer Res 1999 Jul;5(7):1935-44. With respect to targeting beta-1 integrins see eg. Masumoto A, Arao S, Otsuki M. Role of beta1 integrins in adhesion and invasion of hepatocellular carcinoma cells. Hepatology. 1999 Jan;29(1):68-74. Arao S, Masumoto A, Otsuki M. Beta1 integrins play an essential role in adhesion and invasion of pancreatic carcinoma cells. Pancreas. 2000 Mar;20(2):129-37. Xie Y, Xie H. Characterization of a novel monoclonal antibody raised against human hepatocellular carcinoma. Hybridoma. 1998 Oct;17(5):437-44. Peng H, Cao Z, Zhou S, Wang Z, Lei B, Zhao L. [Production and characterization of anti-human hepatocellular carcinoma monoclonal antibodies]. Hua Xi Yi Ke Da Xue Xue Bao. 1990 Sep;21(3):259-62; Whittard JD, Akiyama SK. Activation of beta1 integrins induces cell-cell adhesion. Exp Cell Res. 2001 Feb 1;263(1):65-76 Nejari M, Hafdi Z, Dumortier J, Binguier AF, Feldmann G, Scoazec JY. alpha6beta1 integrin expression in hepatocarcinoma cells: regulation and role in cell adhesion and migration. Int J Cancer. 1999 Nov 12;83(4):518-25; Yao M, Zhou XD, Zha XL, Shi DR, Fu J, He JY, Lu HF, Tang ZY. Expression of the integrin alpha5 subunit and its mediated cell adhesion in hepatocellular carcinoma. J Cancer Res Clin Oncol. 1997;123(8):435-40.

The invention also contemplates a method of optimizing the cooperative affinities of respective binding ligands of a multifunctional ligand described herein and the length of a linker therebetween for the above and applications described below by phage or ribosome display etc. in which the multifunctional ligand is a single polypeptide chain, for example, two single chain Fvs or single domain antibodies linked in sequence, by varying the DNA sequence corresponding to amino acids that represent linker and/or for example CDR regions that are postulated to impact on affinity according to methods and strategies that well known in the art for affinity maturation. These same strategies can be employed for engineering lower affinity molecules. Accordingly, more generally the invention is directed to a phage display or similar library (eg. a ribosome display library or a microarray) in which the population of variants is a multifunctional ligand, including a multifunctional ligand according to the invention herein defined.

In another embodiment blockage of a receptor does not necessarily lead to cell death but may lead only to decreased or increased release of certain cytokines etc, for example as mediated via the IL-6 receptor. In another embodiment the second moiety may achieve the desired therapeutic effect by constituting the normal ligand for that receptor or a functional substitute. The heterofunctional ligand may also be fused or conjugated to a toxic moiety or other effector. In another or further preferred embodiment, said first moiety comprises two binding ligands (eg. one or both of which may be an antibody) which respectively bind to two different target ligands each of which contributes to its total binding capacity and neither of which are sufficient to efficiently target the cell, for example a ligand which binds to a specific MHC peptide complex and a second reduced affinity ligand which binds to a ligand on an APC. This approach also obviates the need to create high affinity ligand for a particular MHC peptide complex, although this can be accomplished. In another or further preferred embodiment the target cell is an immune cell and the second moiety binds to a molecule involved in cellular adhesion, a cytokine receptor, a ligand which stimulates the activity of said immune cell, a ligand which inhibits the activity of said immune cell, a ligand which causes one or more cytokines to be released, a ligand which prevent one or more cytokines from being released, a ligand which causes or facilitates apoptosis of said immune cell or a ligand which permits internalization of said heterofunctional ligand. In another preferred embodiment the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety that binds to a therapeutic agent (exemplified below) or a ligand which effects binding to another immune cell, for example a T cell. In another preferred embodiment, the heterofunctional ligand is a bispecific antibody, a trispecific antibody or a tetraspecific antibody. In a further preferred embodiment the first moiety binds to but is incapable of modulating the activity of said immune cell and said second moiety modulates the activity of said immune cell independently of said first moiety. In another preferred embodiment the heterofunctional ligand further comprises a moiety that binds to at least one ligand located on the intraluminal surface of a lymphatic vessel, preferably a lymphatic vessel associated ligand, as hereinafter defined. In other aspects the invention is directed to a pharmaceutical composition comprising such a heterofunctional ligand and a pharmaceutically acceptable carrier, a method of using the heterofunctional ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount.

The term heterofunctional is used broadly to refer to a ligand: 1) comprising at least two functional moieties that have different functions or different capacities to perform the same function and 2) which is typically and preferably heterospecific (having two binding specificities).

Unless the context dictates otherwise the term avidity when used in a comparative, quantifiable or controllable sense, is used to refer the valency of the binding entity or moiety. The term functional affinity is used a composite term referring to a quantitative and controllable (though not necessarily quantifiable, especially when it consists of both avidity and affinity components) propensity to specific binding attributable to one or both of avidity and affinity effects.

In another aspect, the invention contemplates that cells, particularly immune cells, that are expected to be present at or proximal to a disease site (eg. at the site where an immune cell crosses the vascular endothelial cell wall), in virtue of the disease or a therapeutic modality which is employed in relation to the disease or a concurrent disease, excluding cells that directly mediate the disease, may be targetted in virtue of a marker associated with such cells, eg. LEU-19, a marker associated with activated or killerT-cells, etc for example with an antibody, which is linked to a moiety that is capable of exerting a therapeutic effect in relation to the disease, for example, an immunoliposome or an antibody linked to another therapeutic delivery system (for example streptavidin or biotin fused, coated or conjugated entities or other payload carrying entities (see for example US patents 5439686, 6007845, 5879712, 5456917, 6165502, 5079005, 5888500, 5861159, 6193970, 6190692, 6,077, 499, WO 00/69413, WO 01/07084, etc.). For example, an immunoliposome may carry one of or a combination of cytokines, chemokines, toxins or other therapeutic molecules suitable for treating the disease directly or indirectly, for example by attracting or preventing the attraction, activating, anergizing or otherwise modulating the activity of immune cells for therapeutic or related purposes.

In another aspect the invention is directed to a heterofunctional ligand comprising a first moiety which specifically binds to at least a first target ligand on a first entity and a second moiety which specifically binds to at least a second target ligand on a second entity, and wherein the affinity or avidity or both the affinity and avidity of said first moiety are selected to enable the first moiety to bind to the at least one first target ligand independently of the ability of said second moiety to bind to the at least one second target ligand and wherein the avidity or affinity or both the affinity and avidity of said second moiety are selected to enable the second moiety to bind to the second entity in preference to the first moiety binding to the first entity when both first and second moieties are substantially contemporaneously bound to the respective first and second entities. In one embodiment the first moiety comprises at least one ligand preferably at least one antibody which binds to a first cell, for example an intraluminal lymphatic endothelial cell and the second moiety comprises a ligand, preferably at least one antibody which binds to a different cell, for example a disease associated cell (hereinafter exemplified and meaning, unless the context implies otherwise, diseased cells or disease causing, mediating (ie. having a role which is known to be intermediary or indirectly facilitating eg. antigen presenting cells) or mitigating cells (cells, typically immune cells, which directly or indirectly counteract the diseased or disease causing or mediating cells). In other aspects the invention is directed to a pharmaceutical composition comprising such a heterofunctional ligand and a pharmaceutically acceptable carrier, a method of using the heterofunctional ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount.

In another aspect the invention is directed to a heterofunctional ligand comprising a first moiety which specifically binds to at least one first target ligand on a first entity and a second moiety which specifically binds to a second target ligand or site on a second entity, and wherein the second entity binds to a third target ligand, and wherein the first and third target ligands may be on the same or different entities eg. the same or different cells, and wherein preferably the affinity or avidity or both the affinity and avidity of said first moiety are selected to enable the first moiety to bind to the first target ligand independently of the ability of said second moiety to bind to the second target ligand and independently of the ability of the second moiety to bind to the third target ligand (the first moiety optionally comprising more than one ligand (which may be the same ligand or a different ligand) one or more of which are necessary for binding and optionally each of which is sufficient for specific binding) to corresponding first target ligands) and preferably wherein 1) the avidity or affinity or both the affinity and avidity of said first moiety is/are selected to enable it to bind to the at least first target ligand in preference to the second moiety binding to the third target ligand when both said first and second moieties and the second entity are substantially contemporaneously bound to their respective target ligands eg. to effect a transfer or 2) wherein the avidity or affinity or both the affinity and avidity of said second moiety for the second entity are selected to enable the first moiety to bind to the first entity in preference to the second moiety binding to the second entity and/or 3) wherein the avidity or affinity or both the affinity and avidity of said second moiety for the second entity are selected to enable the second moiety to bind to the third target ligand in preference to the second moiety binding the second entity when both first and second moieties are substantially contemporaneously bound to the respective first and second entities and the second moiety is substantially contemporaneously bound to the third target ligand), or 4) wherein both 1) and 2) above are both operative conditions. In one embodiment, the first entity is a diseased or disease causing, mediating or mitigating cell, for example an immune cell (the first moiety preferably binding to a particular population or sub-population of the first target entity eg. the immune cell, for example activated T cells), the first moiety optionally comprising two or more ligands which may be the same or different and which bind to two or more respective first target cell surface ligands (though not necessarily to any particular effect (and in one embodiment to no effect at all) other than to better bind to and thereby target the cell, preferably in competition with the second entity, which in a preferred embodiment targets a broader population of cells), and the second entity is an entity that binds to a third target ligand, the third target ligand preferably being expressed on the surface of a cell for example the same immune cell, for example a natural cell surface ligand, to which binding yields a desired effect, for example a therapeutic advantage, the second moiety being, for example, the natural ligand for the cell surface ligand or functional mimotope or antagonist or agonist thereof, for example a cytokine, the third target ligand in this case being a cytokine receptor on the immune cell. The invention is also directed to a method of "targeted delivery" of a therapeutic entity to a cell in need of such therapy by administering said heterofunctional ligand. In this respect numerous therapeutic entities will be apparent to those skilled in the art, only some of which are mentioned herein by referring to the therapeutic entity itself or by referring to the third target ligand for which such entity is known and available or readily made by routine skill in the art. Optionally the heterofunctional ligand is delivered with the second entity, preferably in the same composition (preferably bound). In the case where the second entity is a natural ligand circulating in the path of delivery of the heterofunctional ligand, some proportion (0-100%) of the heterofunctional ligand may be delivered without supplied second entity, particularly if the treatment or the disease generates an abundance of the natural ligand. In another embodiment the first moiety binds to a target ligand on a stationary cell (for example a vascular endothelial cell or a lymphatic endothelial cell), preferably a tissue or cell type "associated" ligand (more abundantly expressed uniquely expressed on target cells relative to non-target cells), and the third target ligand and the second moiety are cell-surface target and ligand therefor as stated above, for example the second moiety binds to a cytokine and the third target ligand is a cytokine receptor, for example on an immune cell. In one embodiment the first moiety binds to at least one target ligand which differentiates between populations or sub-populations of immune cells and the second entity in virtue of its binding to the third target ligand, directly or indirectly exerts a therapeutic effect, for example by modulating the activity of said immune cell. In another or further preferred embodiment the first moiety is incapable of modulating the activity of said immune cell and said second entity modulates the activity of said immune cell independently of said first moiety. In another or further preferred embodiment the second entity binds to a molecule involved in cellular adhesion, a cytokine receptor, a ligand which stimulates the activity of said immune cell, a ligand which inhibits the activity of said immune cell (eg. via anergy or tolerance mechanisms), a ligand which causes one or more cytokines to be released, a ligand which prevent one or more cytokines from being released, a ligand which causes or facilitates apoptosis of said immune cell, a ligand which permits internalization of said heterofunctional ligand. In another preferred embodiment the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety (eg. biotin, avidin) that binds to a therapeutic agent (exemplified below) or a ligand which effects binding to another immune cell, for example a T cell. In another preferred embodiment, the heterofunctional ligand is a bispecific antibody, a trispecific antibody or a tetraspecific antibody. In another preferred embodiment the heterofunctional ligand further comprises a moiety that binds to at least one ligand located on the intraluminal surface of a lymphatic vessel, preferably a lymphatic vessel associated ligand, as hereinafter defined.

In other aspects the invention is directed to a pharmaceutical composition comprising such aforementioned heterofunctional ligand and a pharmaceutically acceptable carrier, a method of using the heterofunctional ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount. As suggested below, the foregoing strategy could be used in combination with other targeting strategies herein mentioned or known in the art. The invention contemplates making antibodies to second entities, for example, while bound to their natural receptor, by phage or ribosome display, by methods as hereinafter disclosed.

In another aspect the invention is directed to a heterofunctional ligand comprising at least a first moiety which specifically binds to a first target ligand on a cell and a second moiety which specifically binds to at least a second target ligand on the same cell, and wherein the affinity or avidity or both the affinity and avidity of said first moiety and the affinity or avidity or both the affinity and avidity of the second moiety are selected to substantially reduce the probability of the either moiety singly binding to its respective ligand for a sufficient duration or series of durations to accomplish the function of said heterofunctional ligand unless both first and second moieties are substantially contemporaneously bound to the cell. In a preferred embodiment the first moiety binds to at least one target ligand which differentiates between populations or sub-populations of immune cells and the second moiety in virtue of its binding to the second target ligand, directly or indirectly exerts a therapeutic effect, for example by modulating the activity of said immune cell. In another or further preferred embodiment the first moiety is incapable of modulating the activity of said immune cell and said second moiety modulates the activity of said immune cell independently of said first moiety. In another or further preferred embodiment the second moiety binds to a molecule involved in cellular adhesion, a cytokine receptor, a ligand which stimulates the activity of said immune cell, a ligand which inhibits the activity of said immune cell (eg. via anergy or tolerance mechanisms), a ligand which causes one or more cytokines to be released, a ligand which prevent one or more cytokines from being released, a ligand which causes or facilitates apoptosis of said immune cell, a ligand which permits internalization of said heterofunctional ligand. In another preferred embodiment the heterofunctional ligand is fused or conjugated to a therapeutic agent or a moiety (eg. biotin, avidin) that binds to a therapeutic agent (exemplified below) or a ligand which effects binding to another immune cell, for example a T cell. In another preferred embodiment, the heterofunctional ligand is a bispecific antibody, a trispecific antibody or a tetraspecific antibody. In another preferred embodiment the heterofunctional ligand further comprises a moiety that binds to at least one ligand located on the intraluminal surface of a lymphatic vessel, preferably a lymphatic vessel associated ligand, as hereinafter defined. In other aspects the invention is directed to a pharmaceutical composition comprising such a heterofunctional ligand and a pharmaceutically acceptable carrier, a method of using the heterofunctional ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount.

In other aspects the invention is directed to a method of in vivo modeling or testing using one or more foregoing targeting strategies by administering a heterofunctional / multifunctional ligand as hereinbelow disclosed as well as a method of intra-lymphatic drug delivery employing such ligand and such strategies including adaptations thereof for such purposes, as hereinafter described. In related aspects the invention is directed to a test ligand in the form of such a heterofunctional / multifunctional ligand and compositions thereof.

In one aspect, the invention is directed to a heterofunctional ligand, comprising a first moiety which specifically binds to at least one ligand located on the intraluminal surface of a lymphatic vessel and a second moiety which specifically binds to a disease associated cell and the use of such heterofunctional ligand in treating or preparing a pharmaceutical composition for treating disease associated cells, including diseased cells or disease causing, mediating (ie. having a role which is known to be intermediary or indirectly facilitating eg. antigen presenting cells) or mitigating cells (cells, typically immune cells, which directly or indirectly counteract the diseased or disease causing or mediating cells), within a lymphatic vessel. Preferably, the ligand located on the intraluminal surface of a lymphatic vessel is a lymphatic vessel associated ligand.

In another aspect, the invention is directed to a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a heterofunctional ligand comprising a first moiety which specifically binds to a ligand located on the intraluminal surface of a lymphatic vessel and a second moiety which specifically binds to said disease associated cell and the use of such ligand in treating disease associated cells, including diseased cells or disease causing or mediating cells, within a lymphatic vessel. Preferably, the ligand located on the intraluminal surface of a lymphatic vessel is a lymphatic vessel associated ligand.

In another aspect, the invention is directed to a method of treating disease associated cells, including diseased cells or disease causing or mediating cells, within a lymphatic vessel comprising administering to a subject a heterofunctional ligand comprising a first moiety which specifically binds to a ligand located on the intraluminal surface of a lymphatic vessel and a second moiety which specifically binds to said disease associated cell.

It is to be understood that disease causing cells as used herein includes diseased cells and pathogens, including micro-organisms and viruses.

In another aspect, the invention is directed to a heterofunctional ligand, comprising a first moiety which specifically binds to at least one ligand located on the intraluminal surface of a lymphatic vessel and a second moiety which specifically binds to a therapeutic entity for example a cytotoxin or cytotoxin-linked-entity or a non-toxic entity which is present in toxic amounts and to a method of reducing the toxic effect of such entity in a subject by administering said heterofunctional ligand to said subject.

In another embodiment is directed to a method of therapeutic evaluation and/or targeting / intervention in which such heterofunctional ligand is administered substantially contemporaneously with a cytotoxic substance for example a cytotoxic substance useful for treatment of cancer. The term substantially contemporaneously is used in this connection to mean in a time frame that permits both to exert their respective effects, preferably one or both exerting their respective effect optimally, or one exerting its effect dominantly. It will be appreciated that this might entail that one such entity is advanced in its delivery over the other. Optionally, one or both of these cooperating

entities are delivered proximally to their respective target cells, for example by cannulating one or more blood vessels as proximally as possible to the site(s) of a tumor and/or actual or anticipated site(s) of metastases (as discerned by using one or more tumor and vascular imaging agents, for example, one or a combination two or more agents selected from a vascular opaquing agent, a radionuclide conjugated anti-angiogenic antibody, and a radionuclide conjugated anti-vascular endothelial cell marker antibody, which cannulation may occur for example in the course of initial surgical intervention with respect to the primary tumor site) and/or at the same time cannulating one or more lymphatic vessels (which may optionally be located with the help of a radionuclide conjugated anti-lymphatic vessel marker antibody) leading to or from such tumor sites or metastases. The invention contemplates that small sections of vascular prostheses, well known to those skilled in the art (eg. Dacron types) may be grafted into those locations to permit a prolonged and secure attachment of such prosthesis to an intra-vascular cannula for secure delivery to such vascular or lymphatic locations for repeated and/or prolonged administration, optionally while the patient is mobile, optionally using one or more portable infusion devices, including micropumps designed for such purpose (see for example J Neurosci Methods 1997 Mar;72(1):35-8, US 5180365:Implantable infusion device). Numerous embodiments and improvements in vascular prosthesis and in such portable infusion devices and micropumps are described in the relevant scientific and patent literature known to those skilled in the art. The invention also contemplates delivering any multifunctional ligand herein disclosed in the above manner.

It is to be understood that targeting strategies employing the cooperative action of ligands with different affinities for their targets exemplified above, may preferably have affinities which differ, depending on the application and their avidity, by a factor of 20% up to a number of orders of magnitude which may one, two, three, four, five, six and even seven or eight order of magnitude, in order to achieve substantial advantage, as hereafter detailed in connection with one such strategy.

In another aspect the invention is directed to a heterospecific ligand comprising a first moiety which specifically binds to at least a first disease associated ligand located on a diseased or disease causing, mediating or mitigating cell for example a cancer cell or an immune cell, as well as on non-diseased or disease causing, mediating or mitigating cells (non-target cells) and at least a second moiety which specifically binds to a second different disease associated ligand on the same cell and wherein each ligand is expressed on a substantially (see definition below) different, preferably non-overlapping, subset of non-target cells, so that functional binding to a non-target tissue is substantially (see definition below) precluded. In another embodiment the functional affinities of the respective ligands may be selected in accordance with the strategies suggested above, to further facilitate targeting. In another embodiment, both different ligands are required for internalization. In other related embodiments, the heterofunctional ligand comprises at least two different pairs of binding moieties (eg. a trispecific or tetraspecific antibody which depending on its construction will permit 2, 3 or 4 such different pairs eg. a tetraspecific single domain type antibody (ie. consisting primarily of the heavy or light chain variable region or a functional fragment thereof) (see discussion below regarding its construction) allowing the greatest variation in such geometries and preferably simultaneous binding of more than one pair), wherein 1) at least three such ligands are expressed on a substantially (see definition below) different, preferably non-overlapping, subset of non-target cells, so as to further limit binding to non-target cells and/or 2) wherein at least two different pairs of ligands target a substantially different subset of cells within the same target population eg. different cells within the same tumor (eg. proliferating vs. non-proliferating cell – the respective amounts of the different types of cells will dictate the percentage of the dose that will be targeted to one population or another). In other aspects the invention is directed to a pharmaceutical composition comprising such a heterospecific ligand and a pharmaceutically acceptable carrier, a method of using the heterospecific ligand in the preparation of a pharmaceutical composition for treating a disease, and to a method of treating a subject by administering same in a therapeutically effective amount. It will be appreciated that the foregoing general strategy can be accomplished with two or more different antibodies having differing and preferably non-overlapping normal ie. non-targeted cell distributions, preferably administered in the same composition and preferably cross-linked by biotin-avidin like complementary pairs to facilitate cross-linking for internalization or targeting of therapeutic agents. In a preferred embodiment each such independent antibody carries a different complementary aspect of a toxic payload eg. a different liposome (or other payload carrying entity for example a micro or nano particle or sphere or albumin) which complement each other in virtue of their respective contents (eg. one carries the prodrug and the other the necessary converting enzyme).

In another aspect, the invention is directed to a multifunctional ("multi" meaning at least two) ligand having, at least, a first portion which binds to a lymphatic vessel associated ligand and a second portion comprising an immune function-exerting moiety.

The term lymphatic vessel is used to facilitate broader reference to ligands (eg. antigens / receptors) present on cells bordering the intra-luminal pathway through the lymphatic system including preferably the lymphatic vessels and optionally also parts of the lymph nodes, and refers in the case of the lymphatic vessels, primarily (from a functional standpoint) to the intra-luminal cell surfaces (not necessarily to the exclusion of non-luminal surfaces) on the intra-luminal endothelial cells (not necessarily to the exclusion of non-luminal lymphatic endothelial cells) of those vessels.

The term 'associated' with reference to lymphatic vessels, is used to mean differentially expressed on the surface of endothelial cells of those vessels for targeting purposes, such as to accomplish an object of the invention, but unless otherwise expressly indicated in a particular instance, it is used limitatively, to reference ligands that are predominantly, if not exclusively, found on the aforementioned endothelial cell surface (as well as in lymph nodes), such that the first portion of the multifunctional ligand is for all intents and purposes functionally targeted to the

intra-luminal surface of the lymphatic system. For instance, it is appreciated that the ligand in question may be targetted to a limited extent elsewhere eg. in the case of preferred LYVE-1 ligand discussed below, to parts of the spleen (which also provides a venue for immune cell interactions).

The invention is not concerned with imparting effects to or simply blocking a receptor on the intraluminal lymphatic endothelial cell. In this context, the multifunctional ligand of the invention is intended to exclude only, unless otherwise specifically stated in the claims, only those embodiments disclosed in WO 98/06839 or other references describing ligands, antagonists or antibodies which bind to a lymphatic vessel associated ligand or receptor (see examples of such references below), insofar as such embodiments comprise lymphatic vessel associated ligands as hereinabove limitatively defined, and to this limited extent only, the term immune function exerting moiety preferably excludes: 1) an antibody *Fc receptor*, insofar as such limitation excludes from the scope of the multifunctional ligand (per se) aspects of the invention, substantially intact naked antibodies which simply bind to a lymphatic vessel associated ligands, as well as preferably excluding 2) *cytotoxins or drugs*, insofar as this excludes from the scope of the multifunctional ligands of the invention an antibody or fragment thereof which is fused or conjugated etc. exclusively to a cytotoxic molecule (including an atom) or drug (ie. an antibody linked to a cytotoxin or drug only, which is not per se an or is not integrated with an *independent* immune function exerting component) so as to accomplish a function in relation to cells or other entities (including other multifunctional ligands) within the lymphatic other than the cell or ligand to which the multifunctional ligand is anchored.

In the same vein, the term immune function is broad in intent (as discussed below, and includes particularly any function, including binding, capable of being exerted by a ligand preferably an antibody (eg. multifunctional ligands which are bispecific antibodies) however it is to be understood that the invention and particularly the immune function exerting moiety does not have as an object (despite possible incidental effects) evaluating or exerting a disease responsive or immune function vis-à-vis ligands / cells lining the intra-luminal surface of the lymphatic system ie. insofar as such ligands have a role in disease (other than simple binding exclusively for anchoring purposes which is attributable not the immune function exerting moiety but to the first portion) *but rather*, as evident in preferred aspects of the invention, preferably an *independent* immune function which is not predicated on blocking the lymphatic endothelial receptor or treating cells bearing the receptor ie. exerted vis-à-vis targets other than the lymphatic endothelium target, for example 1) in the case of stationary diseased cells or disease causing cells or molecules, targets at the site of the disease (which may optionally be effected, for example, in case of immunization or other immune cell stimulation, inhibition etc. in the lymphatic system); and 2) in the case of non-stationary diseased or disease causing cells or molecules, at the site of those cells / molecules including, preferably, within the lymphatic system, for example by binding to or signaling those cells in the lymphatic system.

1. In one embodiment, the first portion of the multifunctional ligand is an antibody.
2. In another embodiment, the immune function exerting moiety binds to a target ligand and thereby directly or indirectly accomplishes its effect (in whole or part). For example, the target ligand may be a cytokine, for example in order to target immune cells to the lymphatic system to assist in, diseased, disease causing or other target cell ablation or phagocytic type activity (eg. by the cytokine in turn binding to a ligand, for example on an immune cell having phagocytic activity) or exerting a chemotactic effect within the lymphatic system, or to mop up cytokines, for example, when released in toxic amounts due, for example due to effects of a disease or particular immunotherapy (such as anti-CD3 therapy; see for example USP 6193969, Kummer U. et al., Immunol Lett 2001 Jan 1; 75(2):153-158) (with respect to removing disease associated antibodies from circulation see for example a bispecific dsDNAxmonoclonal antibody construct for clearance of anti-dsDNA IgG in systemic lupus erythematosus. J Immunol Methods. 2001 Feb 1; 248(1-2):125-138). (see also, for example, US 5,968,510 with respect to antibody-CTLA-4 fusion proteins for use in binding to various target ligands).
3. In another embodiment, said immune function exerting moiety comprises an antibody and optionally both the first portion and the immune function exerting moiety are antibodies (with respect to bispecific antibodies, and a recent review of some of the technologies referred to or applicable to the invention (see particularly, Journal of Immunological Methods February 2001 Vol. 248(1-2) page 1-200)
4. In another embodiment, said immune function exerting moiety binds to an immune cell, a diseased host cell or a disease causing cell or entity (eg see US6193968). The term disease is used broadly to refer to any undesirable condition. The term diseased host cell includes but is not limited to a cancerous (in the broadest sense of that term) cell and a virally infected cell (these examples are given inasmuch as the invention in a preferred embodiment involves targeting such cells for destruction) and the term disease causing cell includes but is not limited to a virus or other infectious agent and as well as immune cell which is directly or indirectly involved in mediating or causing a undesired, deleterious or pathologic consequence, including but not limited to autoimmune disorders, transplant rejection, and other immune system linked diseases. The term disease causing entity is used to refer, without limitation, to any molecule, atom, peptide, ligand, complex, chemical, component, epitope etc. that is directly or indirectly involved or associated in mediating or causing a disease or disease causing event including an antibody. Such binding to the entity may be effected through the instrumentality of one or more (same or different) multifunctional ligands and through

binding to any ligand or set of ligands, including receptors, multi-component epitopes etc, including for example, tumor *"associated"* (ie. differentially expressed to advantage for targeting purposes) epitopes which may or may not or may only be partially present on tumor associated antigens, or commonly, for example antigens / epitopes / ligands / receptors etc. which are over-expressed in association with cancer cells; or for example, antigens / epitopes / ligands / receptors etc. involved in immune signaling, stimulatory, co-stimulatory, inhibitory, adhesion or other interactions, including without limitation, cytokine receptors, ligands associated with immune cell adhesion (see for example US 5,747,035), ligands to which binding results in stimulation, activation, apoptosis, anergy or costimulation, or ligands which differentiate between different populations or subpopulations or immune cells, including sub-populations of B cells and T cells, activated versus non-activated lymphocytes, diseased or disease-causing cells versus non-diseased / disease causing lymphocytes and specific immune cell clones for example those having specific Ig type and MHC-peptide type ligands / and correlative ligands. Examples of such ligands include CCR5, CTLA-4, LFA-1, LFA-3, ICAMs eg. ICAM-1, ELAM-1, CD2, CD3, CD4 (eg see US 6,136,310), CD5, CD6, CD18, CD22, CD40, CD44; CD80, CD86, CD134 and CD154, to name only a few (see also US6087475: PF4A receptor, US6135941, WO 01/13945A1:METHODS AND COMPOSITIONS FOR IMMUNOTHERAPY OF B CELL INVOLVEMENT IN PROMOTION OF A DISEASE CONDITION COMPRISING MULTIPLE SCLEROSIS).

5. The invention is also directed to a multifunctional ligand and a method which comprises using the multifunctional ligand to assess the toxicity of directly or indirectly targeting, for example, primarily within the lymphatic vessel system (see discussion below), cells having well known markers that are associated with immune cells, for example, those exclusively associated with activated immune cells, in-so-far as such targeting has a role in prolonging or counteracting the activated state, destroying the cell (eg. where the multifunctional ligand is a immunotoxin) causing the cell to be destroyed (eg. through apoptosis (eg. see WO 01/19861, fas – fasL, U.S 6,046,048) or assisting another molecule or cell for example a T-cell or other killing or immune modulating cell to do the modulation or killing (markers such as CD23, CD25, CD26, CD28, CD30, CD38, CD49a, CD69, CD70, are just some of the markers associated with activated immune cells) etc. (for a complete listing of marker associated with activated immune cells see for example Roitt I et al. Immunology, Fifth edition, Mosby 1998 referenced below and Encyclopedia of Immunology (1998), Abbas et al. Cellular and Molecular Immunology 2000, Harcourt & Brace, the contents of which are incorporated by reference herein). Antibodies for many such ligands are known or could be readily made by eg. phage display (see references herein including *J Immunol Methods* 1999 Dec 10;231(1-2):65-81), and natural ligands for such markers or functional analogues thereof are in some cases known or could be made by recombinant DNA technologies referenced herein (see also Cellular & Molecular Immunology 4th Edition, Abbas Ak et al. WB Saunders and Company 2000, Antibody Fusion Proteins, Steven M Chamow , Avi Ashkenazi Eds. ISBN 047118358X May 1999 Wiley; Kontermann, R., et al.(Eds.) Antibody Engineering, Springer 2001. ISBN 3-540-41354-5; Antibody Engineering, Carl A. Borrebaeck Oxford University Press, 1995; Antibody Engineering:A Practical Approach David J. Chiswell, Hennie R. Hoogenboom, John McCafferty Oxford University Press,1996; Antibody Engineering Protocols, Sudhir Paul (1995) Humana Press; Antibody Expression & Engineering (1998) Henry Y. Wang, Tadayuki Imanaka, American Chemical Society). The term modulation is used broadly to refer to any change, directly or indirectly, in an immune function or effect, as broadly understood. Many such forms of modulation are well known in the art (some are exemplified herein), and therefore these need not be specifically recited (for a review of such effects see for example Roitt I et al. Immunology, Fifth Edition, Mosby 1998; Encyclopedia of Immunology ; (1998) Morgan Kaufmann Publishers, ISBN:0122267656).
6. In one aspect the invention contemplates that the multifunctional ligand exerts its function substantially (ie. upon gaining entry into lymphatic system and when bound to the lymphatic endothelial cells, which is dependant on the mode of administration) within the lymphatic system, *on cells and/or molecules circulating through the lymphatic system*, for example with respect to some embodiments, for greatest effect, to avoid an undesired degree of immunosuppression (for example, embodiments where immune cells are targeted for ablation and/or apoptosis). Preferably, such effect, is exerted at least in part, and preferably substantially to the exclusion of regions within lymphatic system that house at the time of administration non-circulating cells (eg. thymus, bone marrow, and various parts of the secondary lymphoid tissues) or/and with respect to some embodiments (excluding for example those related to immunization or mopping up toxins or antibodies) preferably, non-activated cells. This specificity of targeting can be accomplished in part to the natural distribution of the lymphatic endothelium associated marker of choice, the mode of administration and various targeting strategies herein described.
7. For example, the invention contemplates modes of delivery that to *varying degrees* ensure a greater degree of lymphatic system targeting, for example administration directly within the lymphatics, administration in tissues that drain to the lymphatics or parts thereof, intravenous delivery, as are well known to those skilled in the art, preferably in each individual case at strategic sites of administration that are most pertinent or selective for the disease in question, to the extent that selectivity is desired. The invention contemplates a variety of different size multifunctional ligands

(MRU, single domain, scFv, Fab, minibodies, F(ab)₂, F(ab')₂, substantially whole antibodies etc. and known or obvious multimers thereof referenced herein and in the referenced literature) that are most suitable (eg. for small enough or, for example, having longest half life in circulation) for particular modes of administration to the extent that this is a limitation (eg. size, where drainage into the lymphatic system is sought to be increased or optimized).

8. In a preferred embodiment the invention contemplates that the immune function exerting moiety of the multifunctional ligand comprises (eg. by way of recombinant fusion, conjugation etc.), or binds to (such antibodies are known or may be made by phage, ribosome or other such 'display' methods), so as to present the functional part of an adhesion molecule (molecule involved in cellular adhesion), for example an endothelial adhesion molecule such as a selectins, ICAMs (eg. ICAM-1, ICAM-2) V-CAM, MAdCAM-1 or functional analogues or portions thereof (see for example USP6143298, 5512660, 5861151, 5489533, 5,538,725, 6037454, 5565550, *Circulation* 2001 Feb 27; 103(8):1128-1134, and specific examples/references recited below) in order to control cell traffic including facilitating cell anchoring within the lymphatic system, including for example to facilitate interaction with another "arm" (functional moiety) of the multifunctional ligand or a second etc. multifunctional ligand or an immune cell (or a cell-sized latex sphere as described herein - for this purpose the adhesion molecule may be on the surface of another, preferably multifunctional-ligand-anchored latex sphere or on a similarly anchored cell) as well as combination therapies, for example, with therapeutic entities that enhance or inhibit leucocyte adhesion, or multifunctional ligands or antibodies that bind to one of their corresponding ligands on immune cells (eg. integrins) or other ligands eg. CD44, to facilitate control and/or some selectivity of cell entry into the lymphatic system, for example, for reactivity with the multifunctional ligands of the invention.
9. The invention also contemplates that one or more multifunctional ligands in which the immune function exerting moiety comprises an antibody type molecule targeted to a particular cell surface ligand may be able to mimic effect of such adhesion molecules, as discussed below (any such discussion of an antibody mimicking this function is unless otherwise stated not intended to limit the broader concept of utilizing any class of molecule that would facilitate anchoring or controlling, eg. slowing the passage of cells through the lymphatic vessels). It is to be understood that there may be limitations in the number of cells that can be targeted for ablation in the lymphatic system by slowing the passage of cells, particularly for the purpose herein specified of allowing them the requisite period of residence within the lymphatic system for immune cell targeting or interaction or prolonged interaction with multifunctional ligands of the invention for binding purposes while bound to the lymphatic system endothelium, for example, certain end stage lymphomas/leukemias. In this particular context it is to be understood that: 1) the invention may have greatest application when the multifunctional ligand is administered so as to primarily target cells within the circulatory system, or as an adjunct therapy, or for remission or near remission conditions, or when combined with hyaluronic acid therapy. For example, the invention contemplates that an effective amount of hyaluronic acid is pre-administered to tissues draining to the lymphatic system so as to initially occupy binding sites on LYVE-1 primarily in the smallest lymphatic vessels and thereby minimize excessive binding within the narrowest vessels.
10. In a preferred embodiment said first portion binds to LYVE-1 described below.
11. In a preferred embodiment, said first portion is fused, conjugated or otherwise linked directly or indirectly to an immunizing moiety, for example an antigen, epitope, mimotope or peptide etc. presenting/incorporating entity/scaffold that generates by itself or with the help of one or more cytokines, costimulatory molecules and/or adjuvants etc. an immune response to a desired antigenic determinant (this term is used broadly to correspond at least in scope to the overlapping groupings: antigen, epitope, mimotope or peptide), for example an anti-idiotypic antibody, an antibody component which is capable of binding to a T cell activating entity for example a cell (eg. an APC see *Int Immunol* 2000 Jan; 12(1):57-66 or other cell having eg. immune modulating activity eg. see USP 6,004,811) which is for example genetically engineered to express relevant ligands for activating (or with respect to functions not necessarily related to immunizing, anergizing, tolerizing or otherwise modulating the activity of), an immune cell for example a B cell or T-cell, for example an MHC-peptide and B7 co-stimulatory molecules for activation of T-cells (see for example *Proc Natl Acad Sci U S A* 2001 Jan 2; 98(1):241-246 see also Tham EL et al. *J of Immunological Methods* Vol. 249(1-2)(2001) p111-119 with respect to latex spheres that can be used for this purpose), or for example a CTLA-4 scaffold, a peptide fused to an Fc domain (see WO 01/18203) a HSP-peptide complex/conjugate, an MHC protein or peptide complex etc. It is also contemplated that the absence of costimulatory molecules for presentation in a co-stimulatory fashion with an MHC peptide complex will cause a tolerizing effect. Accordingly the invention is also directed to a multifunctional ligand comprising an immune function exerting moiety which comprises an MHC, preferably complexed or otherwise linked to a peptide. Peptide linking may for example be effected independently, naturally or for example through causing release of peptides from an MHC peptide or HSP peptide complex by injecting a weak acidic solution into tumor eg. just prior to excision. Suitable such solutions which may for example be combined with a cytokine , eg. IL-12 and/or adjuvant are known in the art.

12. In a preferred embodiment said immune function exerting moiety comprises an anti-idiotypic antibody, for example an antibody that a) mimics, for example, a cell surface expressed tumor associated epitope, a virus or other infectious agent associated surface epitope, a toxin, an immune stimulatory, costimulatory, inhibitory, or otherwise interactive ligand; or b) serves to bind to the idiotype (ie. paratope) bearing antibody to which it binds as an anti-idiotypic, for example an autoimmune antibody, etc. or an antibody bearing a toxic moiety for removing such antibody from passage into the circulation.
13. In a preferred embodiment, the invention contemplates that the first multifunctional ligand is used for development, therapeutic evaluation or combination therapy in conjunction with a second different multifunctional ligand of the invention, to achieve a cooperative effect (for example, in the same composition or substantially contemporaneously administered (ie. to reach the same or an interrelated destination in a cooperative time frame) or in necessary or desired sequence/interval, etc.). An example of such cooperative effect is an interaction (not necessarily simultaneously) with two different immune cell surface ligands (for example via an antibody binding interaction), or to deliver different payloads eg. toxins, to a diseased cell see (USP 6,077,499). The invention also contemplates a method of effecting substantially coordinated interactions of differing temporal and spatial complexities, ranging from a somewhat proximal and contemporaneous delivery (eg. in the same composition) of a first multifunctional ligand having, for example, a cancer cell binding second portion, and a second multifunctional ligand having, for example, a cytokine binding Ab, eg. to reduce any toxic effects associated with toxic levels of cytokine release, a cytokine component (for example to harness the effect of such component as a means to attract one or more immune cells to kill a diseased cell or to harness the inhibitory effect of such component (eg. using one or more cytokines employed by cancer cells to evade immune cell targeting) eg. on undesired immune cell elimination or immune cell elimination of the multifunctional ligand, or a T-cell binding component (eg. anti-CD3) to harness the effects of such component on cancer cell killing optionally with a concomitant object of assessing possible counterproductive immune cell elimination (eg. as would be enabled by using a radiolabelled multifunctional ligand and determining the disposition of the label over time) of the multifunctional ligand.
14. Also contemplated are methods to implement more spatially and/or temporally sensitive interactions. For example, when administered in empirically determined suitable proportions and in empirically determined sufficient total amounts for, at least, partial and/or local lymphatic-vessel-associated-ligand saturation or partial saturation to achieve proximal binding of a first to second multifunctional ligand (having regard to the route of administration eg. local saturation can be more readily accomplished by administration into the lumen of the lymphatic vessel). Two different such multifunctional ligands may be used, for example, to deliver two different immune function exerting moieties in substantial proximity to one another for contemporaneous interaction with two different ligands on an immune cell (ie. when it approaches the luminal wall of a lymphatic vessel). For example, this approach may be used to implement one or more effects including increased avidity to the cell for prolonged cell anchoring, which may positively impact on desired (in some embodiments) transfer of the multifunctional ligand from the lymphatic vessel wall to the target cell eg. for achieving an inhibitory effect via ligand binding (eg. assessed via duration of multifunctional ligand binding eg. quantitative or radioimage approximated label elimination)(N.B. this effect may be assessed with multiple copies of the same multifunctional ligand), delivery of a cooperative payload eg. different entities which contribute to the same or a different mechanism of cell killing, counterparts in a two component interaction (biotin-avidin), which preferably yields evidence (preferably quantifiable evidence) of the interaction, for example an enzyme-substrate interaction to quantitatively assay the amount of an enzyme converted substrate (eg. using a conjugated prodrug and pro-drug conversion akin to ADEPT and assessing the extent of prodrug conversion eg by labeled anti-drug specific antibody). For example, the invention contemplates the use of a respectively linked catalytic antibody component (see for example US5658753:Catalytic antibody components) and labeled substrate or RNAase and labeled RNA etc.for this purpose. Another example, discussed in more detail below is the use of one multifunctional ligand for targeting (selectivity) purposes and another for implementing directly or indirectly a desired therapeutic effect, both ligands optionally being required to give rise to a substantial probability of binding (the invention also contemplates that this strategy could be used with a single multifunctional ligand having two intra-luminally directed binding moieties).
15. The invention contemplates that such interactive entities may be conjugated fused or otherwise linked to a respective first and second multifunctional ligand for achieving a cooperative interaction between adjacently bound such ligands.
16. The invention contemplates that adjacently interacting multifunctional ligands yielding detectable evidence of the interaction, could be use in a method to assess eg. a) luminal ligand saturation for dosing, b) multiple simultaneous binding interactions, and c) perhaps most spatially sensitive, development of a process to achieve cross-linked binding with multiple eg. immune cell ligands eg. a costimulatory immune effect (ie. the effect of different simultaneous interactions eg. on stimulation,

inhibition etc. of eg. an immune cell for example combining a first multifunctional ligand capable of selectively binding to, conjugated to or fused to a B7 component (see *J Immunother* 2001 Jan-Feb; 24(1):27-36; *J Immunol* 2001 Feb 15; 166(4):2505-2513; Chalitta PM et al. *J. Immunol.* 160:3419-3426) and a second multifunctional ligand capable of selectively binding to, conjugated to or fused to an MHC molecule delivered initially with or without peptide. For example, the invention contemplates using various amounts/proportions of multifunctional ligands having antibody components fused or conjugated to or capable of binding selectively to, for example an MHC class I or II peptide complex and recombinant B7-1-Fc and/or B7-2-Fc respectively (see *Eur J Immunol* 2001 Jan; 31(1):32-38; *Eur J Immunol* 2001 Feb; 31(2):440-449) (for tumor reactive peptides see for example *J Immunother* 2001 Jan-Feb; 24(1):1-9). In this latter connection (cross-linking type interaction), and/or for permanence of binding or ease of attaching other cooperative entities (for example biotin coated or conjugated radionuclides, liposomes or other payload carrying entities (eg. see for example US patents 5439686, 6007845, 5879712, 5456917, 6165502, 5079005, 5888500, 5861159, 6193970, 6190692, WO 00/69413, WO 01/07084) the invention contemplates biotinylating the two multifunctional ligands and linking the two biotinylated cooperative multifunctional ligands with avidin, streptavidin (or other modified forms thereof eg. deglycosylated avidin or using other complementary linking components- see eg. US Patent (USP) 6,077, 499).

17. The invention also contemplates enhancing the cross-linking of the multifunctional ligands of the invention through complementary components such as biotin and avidin.
18. Preferably, with respect to, for example, increasing selectivity of targeting certain cells (eg. to induce immune tolerance), the invention also contemplates that a first multifunctional ligand is used to bind to a marker specific to a particular kind of cell (eg. activated immune cells) and a second multifunctional ligand (which may not be specific for activated immune cells) is used to modulate the activity of the immune cell (for example inactivate it or reduce its disease causing capability directly or indirectly by binding to it). For example, where the marker is used to determine the selectivity of the targeting but cannot be used for modulating its activity, it is contemplated that the functional affinity of one or both the first portion and second portions of one or both of the cooperating multifunctional ligands can be selected to at least partially control the selective modulating effect of the pair, for example both interactions would be required for the second multifunctional ligand to have an optimal opportunity to bind. For example, the functional affinity for the target cell is relatively weak for the purpose of attaching to the eg. immune cell for a sufficient duration (eg. so as to yield the effect of becoming attached to the immune cell in preference to the lymphatic vessel), compared with that of the first multifunctional ligand (ie the one that accomplishes the selective recognition through binding) to *reduce the likelihood* that the second moiety will bind in the absence of binding of the first moiety (notably a similar type of coordinated interaction ie. two binding interactions, is naturally used for cell adhesion). (NB. this type of coordination has application ie. both specificities are optimally required for binding, to a single multifunctional ligand, having a divalent immune function exerting moiety eg a triabody or tetrabody or for cross-linking and other types of coordinated interactions). In a preferred embodiment, if transfer of binding of the first multifunctional ligand to the immune cell is not desired its functional affinity of the first portion to the lymph vessel can be greater than that of its second portion, while the reverse could be true for the second multifunctional ligand. It will also be appreciated that antibodies which cross-link for example an integrin and a marker of immune cell activation could be used to limit the number of activated immune cells that migrate through the lymphatic system. For example bispecific d Abs, diabodies, etc. in which the functional affinity of each specific binding portion individually does not strongly favour binding, could be used to selectively target specific sub-populations of immune cells or even specifically activated immune cells (for example antibodies that recognize particular antigen / peptide specific T cell or B cells).
19. Accordingly, more generally speaking, the invention is directed a bispecific ligand, preferably a bispecific antibody, having a first portion which binds to a ligand which differentiates between members of the same immune cell population (eg a particular type of T cell) and a second portion which binds to a second ligand on the same cell, which binding exerts directly or indirectly a desired effect, wherein the functional affinity of said first and second portions are selected so as to substantially increase amount of immune cells in which both such portions are bound to their respective ligands relative to those which a single such portion is bound to a single ligand and preferably wherein the amount of immune cells to which the bispecific ligand is not bound is substantially greater than the number of immune cells that are not bound when compared to using a bispecific ligand having the same specificity and for example a 10^1 to 10^7 (preferably 10^1 to 10^6 , preferably 10^3 to 10^6 , preferably 10^3 to 10^5) increase in affinity of one or both portions. This invention also contemplates that binding to the ligand which differentiates between members of the same population (a particular type of T cell) does not have a negative consequence other than to cause the molecule to be ineffectual unless both of its portions are bound and that its binding is itself sufficient for binding and/or stronger relative to the second portion by two fold to 5 orders of magnitude, preferably 1 to 3 orders of magnitude. The term substantially greater imports medical

- significance and may preferably be 15% - 10000% greater. The foregoing examples are not meant to be limitative.
20. In a preferred embodiment, the invention more broadly speaking contemplates a two ligand interaction (using one or more multifunctional ligands) wherein for example both are required or increase the likelihood of interaction and wherein the interaction of at least one contributes to specificity, though not necessarily to modulation, thus permitting a broader selection of modulators including those that but for the selectivity enhancing effect of the cooperating ligand and the lymphatic system venue, would be toxic in the desired therapeutic dose. Examples of markers that could assist in selectivity include those are unique to, for example, activated B cells or T cells or those having particular specificities in virtue of unique Ig type receptors. Examples of ligands on, for example immune cells, through which modulation/inhibition/stimulation etc. (including, for example apoptosis), for example by antibody binding or supply of a natural interactive ligand, are well known. Some examples are provided herein. Combinations and permutations of markers and ligands for selectivity and exerting an immune effect such as modulation/inhibition/stimulation referred to herein or in the literature incorporated herein by reference or well known in the art are contemplated to be within the scope of the invention.
 21. It will be appreciated that a combination of factors, such as dose, using additional molecules that increase or decrease migration or adhesion optionally in a tissue targeted manner, route of administration (eg within tissue that best drain to lymphatic vessels or a portion thereof), use of cytokines, etc. and immune modulating drugs, as well combination therapies with known entities, can be employed in various combinations for strategies of harnessing the unique properties of the multifunctional ligand of the invention, to achieve a selectivity enhancing and/or modulatory/inhibitory/stimulatory etc or otherwise cooperating effects with respect to the desired target population of cells. Unless their function are self-evidently conflicting the invention contemplates all permutations of the multifunctional ligands disclosed herein or in the literature incorporated by reference hererin as well as those evident to persons skilled in the art whose mention is omitted.
 22. In a preferred embodiment, the immune function exerting moiety binds with greater functional affinity to its target ligand than said first portion binds to its target ligand. For example said immune function exerting moiety may bind with greater avidity (preferably at least 2 times greater (divalent vs. monovalent) and lesser or greater affinity (eg. within a range of 1×10^{-6} to 1×10^6 fold) or with the same avidity and greater affinity (eg. up to 1×10^6 fold). In applicable aspects, the invention contemplates that this increased functional affinity can be employed to effect transfer of a lymphatic vessel bound multifunctional ligand (eg. a bispecific antibody) to a cell passing through lymphatic system. The invention also contemplates a method comprising radiolabelling the multifunctional ligand to assess, for example, the degree to which immune cells at a disease site have passed through the lymphatic system. Certain aspects of the invention, discussed herein, relate to a multifunctional ligand based system of targeting a particular immune cell ligand for stimulation, inhibition etc. predominantly within select portions of the lymphatic system that contain migrating cells (although some general targeting can controllably occur before the multifunctional ligand binds to the lymphatic system or when the multifunctional ligand releases from the lymphatic system without having found its target within the lymphatic system) will have at least a partially selective effect on targeting disease causing/mediating immune cells (eg. activated with a specificity that causes the disease) as opposed to non-disease causing/mediating cells, in the case where such ligand is also expressed on such other immune cells eg. of the same type eg. T cells. This permits targeting of immune cells primarily within the portions of the lymphatic system that contain migrating cells particularly disease causing/mediating cells while minimizing immune system dysfunction. This effect can be even more selectively accomplished, for example, by delivering the multifunctional ligand directly into the lymphatic system and within a time frame which is shorter than the normal duration of binding of the multifunctional ligand determining the degree to which the multifunctional ligand is bound to such diseased related cells at the disease site and similarly the degree to which it is bound to the cells unrelated to the same disease eg. via radiolabel. As discussed more fully below, the invention also contemplates a multifunctional ligand based system of assessing the effects of certain types of immune stimulation eg. how stimulating enhanced migration or adhesion, will differentially affect disease activated cell migration through the lymphatic system to enhance such disease cell targeting within the lymphatic system. For example, for tumor cell targeting and stimulation of disease-activated immune cells the invention contemplates evaluating cytokine (eg. $\text{TNF}\alpha$) linked anti-angiogenic marker antibodies, optionally, preferably in combination with anti-tumor vaccination strategies, to direct disease activated immune cells to tumor site and the lymphatic system for further immune stimulation. Based on a "bait and trap" type approach, ligands such as OX40L and CD44 may also be assessed for this purpose.
 23. In this connection and more generally the invention also contemplates using a bi-specific antibody, for example having a lymphatic endothelial binding first portion and for example a cytokine binding second portion, wherein the cytokine binding portion has a lower functional affinity for the cytokine (for example 1×10^{-6} to 0.9 fold) compared with that of its natural receptor on an immune cell. It is contemplated that a multifunctional ligand of the invention could be used optionally in conjunction

with a multifunctional ligand which displays a functional adhesion molecule (a selectin, ICAM, etc.) to assess the optimal parameters for transfer of the cytokine, for example, as is known to occur by monitoring the effects of cytokine release attributable to such cytokine transfer. It will be appreciated that this information or approach could be used to optimize the binding parameters for other ligands as well (eg. anti CD3) and could be employed not only in lymphatic system but to locally deliver inhibitory or stimulatory cytokines or other ligands to certain tissue targets, for example new blood vessels forming within tumors or other tissue specific markers.

24. The foregoing strategies could be used as part of a primary, adjunct or low disease burden therapy.
25. In a preferred embodiment, the second portion comprises a ligand which is capable of binding to an immune cell for example B cells, T cells etc, preferably in one embodiment to assist in cell killing or immune modulation of a target cell (re NK cells see for example US 5770387)(see also US6071517:Bispecific heteroantibodies with dual effector functions; Bispecific antibody-mediated destruction of Hodgkin's lymphoma cells. *J Immunol Methods* 2001 Feb 1; 248(1-2):113-123; Bispecific antibody-targeted phagocytosis of HER-2/neu expressing tumor cells by myeloid cells activated in vivo. *J Immunol Methods*. 2001 Feb 1; 248(1-2):167-182 as well as *J Immunol Methods* 2001 Feb 1; 248(1-2):103-111).
26. With respect to avidity, affinity and other elements of design including size, blood clearance, additional functionality etc.the multifunctional ligand may be, for example, a bispecific antibody having a monovalent first portion and a monovalent second portion, a bispecific antibody having a divalent first portion and a divalent second portion, a trivalent trispecific antibody having a monovalent first portion and a second portion comprising a monovalent immune function exerting moiety which binds, for example, to a target ligand on a target diseased, disease causing or immune cell, and for example, a monovalent portion which binds to an immune cell which assists in killing or modulation for example anti-CD3 or anti-CD28 antibody component, a tetravalent trispecific antibody having a monovalent first portion and a second portion comprising a divalent immune function exerting moiety which binds, for example, to a target ligand on a target diseased, disease causing or immune cell, and for example, a monovalent anti-CD3 or anti-CD28 antibody component (it is contemplated that this orientation might advantageously position the anti-CD3 component for interaction with a T-cell almost exclusively when the first portion is not bound to the luminal wall of a lymphatic vessel), a trivalent bispecific antibody having a monovalent first portion and a second portion comprising a divalent immune function exerting moiety, for example, one which binds, for example, to a target ligand on a target diseased, disease causing or immune cell. The antibody subunit may be for example, a Fab, a substantially intact antibody, a single domain antibody (see also Hufton SE. *Dis Markers* 2000;16(1,2):37 Single domain human immunoglobulin fold-based biomolecules; Antigen specificity and high affinity binding provided by one single loop of a camel single-domain antibody. *J Biol Chem*. 2001 Jul 13;276(28):26285-90. Optimal Design Features of Camelized Human Single-domain Antibody Libraries. *J Biol Chem*. 2001 Jul 6;276(27):24774-24780; Recognition of antigens by single-domain antibody fragments: the superfluous luxury of paired domains. *Trends Biochem Sci*. 2001 Apr;26(4):230-5; Llama heavy-chain V regions consist of at least four distinct subfamilies revealing novel sequence features. *Mol Immunol*. 2000 Aug;37(10):579-90) a minibody an scFv or a minimal recognition unit (MRU eg see US6174691:Minimum recognition unit of a PEM mucin tandem repeat specific monoclonal antibody).
27. In a preferred embodiment, the multifunctional ligand binds to an immune cell which is associated with an autoimmune reaction, for example a CCR5-expressing cell. (see also Apoptosis genes and autoimmunity. *Curr Opin Immunol*. 2000 Dec; 12(6):719-24. for application herein)
28. In a preferred embodiment, the second portion comprises a cytokine component.
29. In a preferred embodiment, the second portion comprises a cytotoxic component.
30. In a preferred embodiment, the second portion of the multifunctional ligand comprises an internalizing antibody and a cytotoxic component.
31. In a preferred embodiment, the second portion consists of an antibody which binds to T cells, for example, an anti-CD3 antibody or an anti-CD28 antibody.
32. In a preferred embodiment, the second portion consists of a cytokine component.
33. In a preferred embodiment, the second portion comprises an antibody which binds to a target diseased, disease causing or immune cell and further comprises one or more components selected from the group consisting of a cytokine component, a cytotoxic component and an anti-CD3/CD28 component.
34. In another aspect the invention is directed to a composition comprising a multifunctional ligand and a pharmaceutically acceptable excipient.

35. In another aspect the invention is directed to a composition comprising a plurality of different multifunctional ligands.
36. In another aspect the invention is directed to methods and compositions for developing and evaluating the therapeutic value of stimulators, mediators, inhibitors etc. of immune cell signaling (eg. stimulatory, inhibitory, costimulatory), adhesion, migration, etc. including the effects of ligand/receptor blocking and supply of specific cooperative ligands, using the multifunctional ligands of the invention.
37. In a preferred aspect, the multifunctional ligands of the invention may be used to assess the effects of such compositions on the sub-population of cells that migrates into lymphatic vessels. In particular, the invention is directed to assessing the expectation that some disease causing, mediating or otherwise disease active immune cells have an enhanced ability/opportunity (and/or can be enhanced in their ability/opportunity to make their way into the lymphatic system) so that targeting of relevant ligands on that sub-population of cells within the lymphatic system will cause at least a partial selective targeting effect, preferably with positive effect on the dosing capability and choice of ligands ie. in terms of limiting more universal and/or deleterious consequences. The invention is also directed to a method of reducing the toxic side effects of a pharmaceutical composition comprising a multifunctional ligand in which the immune function exerting moiety is targeted to a ligand that is not found exclusively on disease causing, mediating or otherwise disease active immune cells, by administering said composition in a manner in which it enter more directly into the lumen of a lymphatic vessel. (It contemplated that immunization within the lymphatic system can also be enhanced in virtue of such selective targeting.) In particular, the invention is directed to a multifunctional ligand, a pharmaceutically acceptable composition thereof and method of using same for assessing enhanced migration or enhancing migration of disease-active immune cells, said multifunctional ligand comprising an immune function effecting moiety which has an immune effect on an immune cell surface ligand ie. effects including signaling (eg. stimulatory, inhibitory, costimulatory, antagonistic, agonistic), including for adhesion and migration effects, etc. This may be accomplished practically, for example through ligand/receptor blocking eg. via antibody, or by antibody fusions/conjugates etc. that supply the natural ligand or a functional fragment or chemical/biological mimotope thereof. In a preferred embodiment the invention is directed to a multifunctional ligand in which the immune function exerting moiety is an antibody that binds to a ligand selected, for example from the group consisting of CTLA-4, IL-2 receptor, CCR5, CD44, CD134, CD3, CD28, CD2.
38. In another aspect the invention is directed to a composition comprising a plurality of different multifunctional ligands which exert a potentially cooperative immune effect with respect to an immune cell, for example binding to two or more different ligands on an immune cell, wherein said ligands are selected, for example from the group consisting of CTLA-4, IL-2 receptor, CCR5, CD44, CD134, from any of the ligands herein mentioned or referenced or preferably CD3, CD28, CD2.
39. The invention is also directed to a method of preventing metastasis during the course of surgical removal of a tumor comprising administering to a patient prior to surgical treatment of the tumor site, a pharmaceutical composition comprising a multifunctional ligand in which the immune function effecting moiety binds to a tumor associated epitope on a cancer cell.
40. In another aspect the invention is directed to an immunocytokine having an anti-idiotypic antibody component which recognizes the paratope of an antibody which binds to a lymphatic vessel associated ligand and a cytokine component fused therewith or conjugated thereto. For example the cytokine component comprises IL-2 or a functional fragment thereof and/or IL-12 or a functional fragment thereof. In addition to their individual use in fusion proteins for tumor cell killing, combinations of IL-2 and IL-12 have been used successfully for this purpose. It is contemplated that such cytokine fusion could be used to target T-cells or phagocytic cells to a multifunctional ligand that has bound to its disease causing or diseased cell target, preferably having left the lymphatic vessel endothelium in preference for binding its target. In this connection it is contemplated that the functional affinity of the anti-idiotypic Ab for the first portion would be less than that of the first portion to the lymphatic endothelium, so as to minimize competition between the two. It is also contemplated that the delivery of the immunocytokine occur substantially contemporaneously but separately and after that of the multifunctional ligand, optionally by a different route of administration.
41. Similarly the invention contemplates for the same purpose, a bispecific antibody having an anti-idiotypic antibody component which recognizes the paratope of an antibody which binds specifically to a lymphatic vessel associated ligand (preferably with lower affinity than that of the Ab for its target) and for example an immune cell binding portion eg. an anti-CD3 antibody or an anti-CD28 antibody component.

42. Thus the invention is directed to a method of targeting a diseased or disease causing cell for destruction by the immune system comprising administering separately but substantially contemporaneously to a subject hosting the diseased or disease causing cell, preferably in sequence with an interposed interval and/or by different routes of administration, first a multifunctional ligand in which the immune function effecting moiety binds to a diseased or disease causing cell surface associated epitope, and an immunocytokine or bispecific antibody as described in the immediately preceding two paragraphs.
43. In a preferred embodiment the invention contemplates modification of the multi-functional ligand to substitute one or more amino acids which reduce without functional impact on the molecule the number of immunogenic MHC II class peptide sequences within the molecule. This can be accomplished through procedures available to those skilled in the art, for example through the Delimmunisation services of Biovation Limited (see also US 5821123 and related Xoma patents).
44. Inasmuch as the invention is predicated on intraluminal lymphatic system targeting such lymph association may be alternatively implemented, in suitable circumstances by the method of delivering the multifunctional ligand, for example into the lumen of a lymphatic system vessel or (where the multifunctional ligand is not of an unsuitable size (see for example Ikomi, F. et al. Lymphology 32 (1999) 90-122, within a portion of body that drains to the lymphatic system (ie a portion of the lymphatic system), for eventual migration to the lymphatic system. Particularly, with respect to embodiments of the invention in which the immune function exerting moiety is targeted with greater functional affinity to a therapeutic target (ie. not the lymphatic system target), such lymphatic system oriented modes of delivery coupled with preferred targeting to the therapeutic target may combine, absent saturated binding to the therapeutic target, to better accomplish functional lymphatic targeting. Accordingly, in a broader aspect the invention is directed a lymphatic system targeted multifunctional ligand in which the second portion is as described herein and in which the specificity of the first portion exclusively for a lymphatic system is inessential. In this connection, the invention contemplates targeting markers on lymphatic vessels that are also present, for example on blood vessel endothelial cells (eg. VEGF2). (with respect to lymph specific markers see also Birner P. et al. Clin Cancer Res 2001 Jan; 7(1):93-7 "Selective immunohistochemical staining of blood and lymphatic vessels reveals independent prognostic influence of blood and lymphatic vessel invasion in early-stage cervical cancer" and published references to the markers therein mentioned.)
45. In the case of purely sustained release aspects of the invention where the first portion is temporarily anchoring a second portion for eventual release back into the circulation, the use of term immune function affecting moiety with reference to the role of the second portion does not adequately accommodate the breadth of the invention since any form of disease palliating active moiety or entity which exerts its effect elsewhere than at the lymphatic endothelial cell may gain advantage from this form of delayed delivery (depot effect) or anchoring.
46. Furthermore, in another preferred aspect, the second portion is capable of binding directly or indirectly (eg. binding to an entity which in turn binds to a target entity) to a target entity, for example a therapeutic entity (for example to mop up excess such entity that does not immediately reach its target (eg. an entity that is toxic elsewhere in the body), a toxic entity including an entity which is not per se toxic but the presence of which is undesirable at a particular time or in particular amount or concentration (eg. a cytokine, for example when released as a result of anti-CD3 therapy), to *redirect* an entity to a target, for example a therapeutic entity, for example through the instrumentality of an antibody portion that is directed to that target (eg. a multifunctional ligand in which the second portion comprises an anti-tumor antibody portion that is conjugated to streptavidin, to retarget biotin conjugated radionuclide back to the tumor (see Martin J. et al. (1997) Cancer Chemother, Pharmacol. 40:189-201), to temporarily anchor liposomes or other carriers of entities (eg. drugs) having an direct or indirect beneficial effect elsewhere.

Detailed Description of Preferred Embodiments

In a preferred embodiment, the invention provides a multifunctional ligand having, at least, a first portion which binds to a lymphatic vessel associated antigen/receptor (and thereby exerts, not necessarily to the exclusion of other effects) at least an anchoring function, and a second portion having at least one independent immune function. The term "immune function" is broad in intent including but not limited to direct or indirect and primary or corollary effects related to simple targeting, tolerance, immunization, stimulation, inhibition, modulation or various other immune related effects (other than simply forming part of the entity which blocks the lymphatic endothelial associated ligand). The term independent is used to exclude only an effect specifically targeted towards the ligand (blocking) or cell bearing the ligand to which the first portion of the multifunctional ligand is bound, which is not contemplated as an object of the invention. The invention contemplates rather that the immune function is exerted, for example, vis-à-vis immune cells or molecules or against cancer or infected cells to affect an immune function that relates to assessment, diagnosis, therapeutic modeling, or treatment of various disease states such as autoimmune disease, transplant rejection, cancer and infectious disease. In a preferred embodiment, the invention

contemplates that the independent immune function is exerted through a physical ligand-ligand interaction. In a preferred embodiment the multifunctional ligand has an ability to bind in the manner of an antibody in virtue of at least one of the first or second portions, and preferably at least the first portion. The lymphatic system directed first portion may in some embodiments (LYVE-1) be hyaluronic acid or analogues thereof that have the appropriate binding capacity. In a further preferred embodiment the second portion binds to a target ligand on a cell or molecule (eg. a cytokine or autoimmune antibody) which passes through the lymphatic system. In a more preferred embodiment the multifunctional ligand is a bispecific antibody. The term antibody is used to refer to any antigen binding fragment of an antibody that substantially has the binding capability of an antibody including anti-idiotypic antibodies, and therefore the term bispecific antibody is used (unless the context implies a more specific usage) in a functional sense to refer to at least two different specificities (including trispecific antibodies etc.) and includes well known entities which are diabodies, triabodies, tetrabodies, minibodies, scFv dimers, etc., and entities in which one or both binding moieties are scFv or single domain type antibody fragments or dimers etc of such fragments (with respect to single domain antibodies see for example Camel single-domain antibodies as modular building units in J Biol Chem. 2000 Oct 25, & Mulligan-Kehoe U.S. patents).

The term "anchoring function" is used broadly to refer to physical attachment for a period which renders the second portion of the multi-functional ligand capable of exerting its immune function. For example where the function of the second portion is to interact with a cell passing through the lymphatic vessels, for at least a period which permits sufficient interaction for the desired effect.

The term ligand is used very broadly herein to refer to any moiety, preferably in some cases, a specifically interacting moiety including binding moieties (eg antibodies, receptors etc.) and bound moieties (eg antigens, epitopes etc) and/including otherwise interacting moieties (eg. chemotactic interactions or interactions that require multiple points of interface eg. cross-linking or multi-component epitopes). The term moiety is used broadly and non-limitatively to refer primarily to a functional part of an entity, and may refer to even the whole of the entity depending on the context in light of the broadest concept of the invention.

Optionally, depending on the mode of delivery and the relative functional affinity of the respective first and second portions, the multi-functional ligands of the present invention, may exert their immune function primarily in lymphatic system and also significantly before and optionally after entry into the lymphatic system. In a preferred embodiment the multifunctional ligand is capable of simulating a depot effect by binding for a prolonged period to the intra-luminal lymphatic endothelium for later release over time back into the circulation. The choice (avidity effect resulting from multiple binding "arms") and affinity of the binding molecule as well as various, preferably controllable factors impacting on any "undulating" movements of the lymphatic vessels (eg. water consumption) or competitive binding is contemplated to impact the binding time.

With respect to the depot and delivery aspects of the invention discussed herein, it is contemplated the second portion of the multi-functional ligand of the invention may have at least primary medicinal effects that are not immune function related as broadly understood.

It is to be understood that a use of a slash (/) means the broader of "or" or "and/or" unless to the context dictates otherwise.

Some immune interactions require, prefer or are capable of being enhanced via coordinated ligand interactions, for example for optimal immune stimulation, for example, specific costimulatory ligand interactions eg. CD80/CD86 interactions with CD28, or for example, interactions aimed at tolerizing or otherwise inhibiting or reducing immune effects or preventing such inhibition (for example using anti-CTLA-4/CD152 see related U.S. patents, for example 6,051,227, 5,844,095) (see also Hodge JW et al. Ernst Schering Res Found Workshop 2000 (30): 23-52 and Immunological Reviews Vol 172 Dec 1999, Entire Issue).

The invention contemplates modeling, evaluating and/or effecting these interactions for therapeutic intervention within the lymphatic system through the substantially contemporaneous use of different multifunctional ligands of the invention. Furthermore, control of the relative proportion of each of the different ligands permits different spatial interspersions of these ligands on the intraluminal surface of the lymphatic system (primarily) so as to provide controlled variability of spatial configurations appropriate for optimizing the coordinate interaction with multiple ligands on another entity, for example immune cells or cancer cells. This strategy also permits controls on avidity that extend beyond the choice of valency for a given single multifunctional ligand for controlling the nature and duration of the coordinate interactions including the duration of temporary anchoring, for example to allow cancer cells to be killed by immune cells, as well delivery of, for example, cytokines (through cytokine antibody fusions), superantigens etc. to the site of interaction. Such coordinate interactions may be substantially contemporaneous or sequential, for example the effect of a first interaction with a first multifunctional ligand slowing the progression of a cell or infectious agent through the lymphatic system for eventual reaction with another first multifunctional ligand (ie of the same type) or reaction with a second type of multifunctional ligand. The invention also contemplates as a strategy, alone or in combination with other strategies: 1) delivery of a multifunctional ligand of the invention to a particular site of action for the purpose of exerting, for example a local effect, with the result of causing the multifunctional ligand (whether or not it has exerted its effect, provided that or to the extent that it remains functional in at least one aspect) to subsequently be targeted to the lymphatic system for exerting a second effect (be it the same or a different disease counteracting effect) including simply elimination, or return back to the circulation (ie. where the ligand is selected (eg. based on size, immunogenicity etc.) to be preferably minimally

eliminated (at least not maximally eliminated) by the body in the course of its circulation, having regard to competing design considerations) for example, in the case of multifunctional ligand which is an anti-tumor ligand that has some residual binding to normal tissues, to set up, in effect, a site of competitive binding that advantageously impacts (ie. reduces) undesired binding more than desired target binding; 2) delivery of a multifunctional ligand of the invention or an entity that binds to a multifunctional ligand of the invention to a particular site of action eg. local disease mediating immune cells, for the purpose of simple binding with the expectation that a delayed immune or other effect will be exerted within the lymphatic system. Accordingly, the invention is also directed to a composition comprising at least one and optionally a plurality of different multifunctional ligands of the invention. The invention is also directed to such a composition when combined with a pharmaceutically acceptable carrier for example those that may be suitable for one or more of the various well known and heretofore used routes of administration including intravenous, intradermal etc which (for present purposes) are preferably not incompatible with delivering a multifunctional ligand of the invention to the lymphatic system. The invention is also directed to therapeutic compositions comprising a multifunctional ligand of the invention and to methods of treatment using such compositions. The invention is also directed to method of : 1) evaluating the therapeutic effect of a particular therapeutic entity against a particular target with reduced effect on undesired targets; 2) facilitating elimination a therapeutic entity; -- by administering the therapeutic entity as part of or in circumstances which permit interaction with, a multifunctional ligand of the invention.

The invention also contemplates cannulating particular portions of the lymphatic system to localize the delivery of a multifunctional ligand (see United States Patent 4,911,690) , for example 1) to accommodate or further accommodate the treatment of conditions in which the immune affecting molecule has an undesirable systemic or localized side-effect if delivered otherwise; 2) for the localized delivery, as required, of larger molecules, complexes (eg. for temporarily anchoring MHC-peptide complexes) or otherwise associated (at least temporarily) entities (ie. associated other than through complex formation) etc. and/or 3) for the localized delivery of additional compositional elements eg. adjuvants, cytokines (see Immunological Reviews 2000 Vol 177 p. 5-246; Nature Immunology Feb 2001 Vol 2 No. 2 page 89), or for affecting only subsets of populations of cells or molecules that pass through the lymphatic system or a desired portion of the lymphatic system. The invention also contemplates methods of selective, enhanced or localized, targeting/ delivery by administering multifunctional ligands of the invention as well as methods (including methods directly or indirectly employing the multifunctional ligands of the invention) of *enhancing / inducing* entry of cells or molecules, particularly immune cells (ie. cells having an immune system function as broadly understood) or subsets thereof, to the lymphatic system or a portion of the lymphatic system, for example for the purpose of direct or indirect interaction with the multifunctional ligands of the invention (in order to be acted on directly or indirectly, by multifunctional ligands of the invention) or for recruiting cells that will for example kill or modulate the activity of other cells, for example kill cancer cells or infected cells that will have, are having or have had direct or indirect interaction with the multifunctional ligands of the invention, as discussed further below, for example in the case of cancer, by targeting immunocytokines to the disease affected tissue eg. using cytokines eg. TNF α fused to antibody that binds specifically to tumor cell markers or markers for angiogenesis. Similarly tissue targetted as opposed to disease targeted immunocytokines could be used selectively recruit immune cells within that tissue for example a diseased tissue to enter the lymphatic system for such purposes including for example interaction with a multifunctional ligand of the invention.

It is also contemplated that a single multifunctional ligand can have multiple requisite interactive functionalities for example to stimulate, attract, anergize (or otherwise inactivate) sub-populations of B-cells of T cells via the use, for example, of trivalent or tetravalent antibodies and antibody conjugates/fusions thereof having multiple ligand interactive capabilities (see also for example technologies being developed for selection of successful binders by phage or ribosome display (see for example WO 01/00866; *Adv Protein Chem* 2000; 55:367-403). A particular application of this technology for application to this invention are antibodies which retarget T-cells to tumor cells (see for example Manzke O. et al. *Int. J. Cancer* 82, 700-708 (1999); *Br J Cancer* 2000 Jan; 82(2):472-9; *J Control Release* 2000 Feb 14; 64(1-3):229-39 as well as related references, cited therein or citing these publications.

The present invention accommodates such technology through multispecific antibodies or alternatively obviates the need for combining a T-cell receptor type molecule with the primary immune function effecting moiety (eg. a cancer cell binding moiety) by using a separate multifunctional ligand which combines, for example, a first portion and a second portion comprising a T-cell interacting moiety (eg. anti-CD3). This is accomplished by administering in the same composition or substantially contemporaneously an amount of the second multifunctional ligand that provides, as may empirically predicted by assessing the dispersion of the marker on the endothelial cell, a strong probability (eg. .001-100%, optionally 1-100%, optionally 5-100%, optionally 10-100%, etc) that the T cell will be targeted in the vicinity of a given lymphatic endothelial cell that happens be proximal to the cell sought be targeted eg the cancer cell. It is self-evident that a 50/50 proportion of the first and second multifunctional ligand will yield a strong chance that a second multifunctional ligand will be immediately adjacent on a particular given side (assuming for the sake of argument that there are sides when in reality the dispersion of the lymphatic endothelial marker is governing). It is also contemplated that adjacent multifunctional ligands may be linked for example through linkage effective pairs of ligands (avidin-biotin), the second portions having an antibody component which binds to a common ligand (eg on a liposome (see US 6197333 and refs. therein cited) or other pharmaceutically acceptable micro/nano particle/sphere of preferably selectable size for optimal spacer or endothelial cell protective purposes) and that such entities could optionally also be employed to house and deliver a payload to a given target vicinity.

In one aspect the multi-functional ligands of the present invention provide for a method and preferably a means for evaluating and/or inducing immune tolerance (with respect to B cells see strategies discussed in Immunological Reviews 2000 Vol. 176 pp. 5-247).

It is believed that immune tolerance is enhanced or prolonged through prolonged /strategic exposure to tolerance inducing and/or enhancing molecules for example prolonged antigen exposure (see Wang Y et al. Eur. J. Immunol. 2000; 30(18):2226-2234; Encyclopedia of Immunology ; (1998) Morgan Kaufmann Publishers, ISBN:0122267656; Hoyne GF *et al. Immunology* 2000 Jul; 100(3):281-8; Lerner CG et al. J Immunol. 2000 Apr. 15; 164(8): 3996-4002; Grossman Z. et al. *Semin Immunol* 2000 Jun; 12(3):197-203; discussion 257-344 Textbook of the Autoimmune Diseases by Lahita R. et al. ISBN: 0781715059 Lippincott Williams & Wilkins; Multi-Systemic Auto-Immune Diseases : An Integrated Approach Dermatological & Internal Aspects ISBN: 0444818960 Elsevier Science ; Arthritis and Allied Conditions - A Textbook of Rheumatology, Thirteenth and Fourteenth Editions, William J. Koopman, MD 14th:ISBN: 0-7817-2240-3, November 2000; Principles of Drug Development in Transplantation & Autoimmunity Landes Bioscience, ISBN:0412100614; Cancer & Autoimmunity by Gershwin M. et al.,ISBN: 0444503315 Elsevier Science ; *J Autoimmun* 2000 Jun; 14(4):278-82; The multi-functional ligands of the present invention, depending on their mode of administration (direct application by cannulating a lymphatic vessel or conventionally eg. intradermally or intravenously), can be advantageously employed to provide prolonged/strategic exposure to tolerance enhancing molecules (for example by employing a multivalent eg. bi-specific Ab fragment or diabody which has a first portion which binds to a lymph associated antigen and second portion which optionally comprises anti-idiotypic Ab portion mimicking the desired Ag or the antigen itself or a suitable portion thereof fused or conjugated to the first portion) on the intra-luminal surface of the lymphatic vessels, optionally, in addition to its conventional effects, when administered intradermally or intravenously, etc.. It is anticipated that the multi-functional ligands of the present invention would be useful to assess and/or effect tolerance induction (see Bassadona GP et al. *Proc Natl Acad Sci U S A* 1998 Mar 31; 95(7):3821-6; USP 6,106,834; USP 6,099,838; US6010902: Antibody heteroconjugates and bispecific antibodies for use in regulation of lymphocyte activity; as well as additional examples cited below with reference to examples of suitable anti-idiotypic antibodies).

It is contemplated that the present invention could be used to strategically mediate, CD45 (or variants/other PTPs) related "cell signaling", for example through signaling molecules (eg. inhibitors) using multifunctional ligands of the invention including but not limited to bispecific antibodies, antibody fusions/conjugates ie. where the immune affecting antibody portion or other moiety is conjugated, fused etc. to an antibody or fragment that binds to LYVE-1 (1999) Journal of Cell Biology Vol 144 No 4 p. 789-801) (see for example USP 5,914,111 Sievers EL, Cancer Chemother Pharmacol 2000 46 Suppl s18-22 WO9946268, Neel BG Curr Opin Immunol 1997 Jan 9(3) 405-420; Front Biosci 1998 Nov 1 3:D-1060-96, Slifka MK et al. J. Mol. Med 2000 78(2) 74-80 Goodnow CC Ciba Found Symp 1997 204: 190-202; Mustelin T. et al. Front Biosci. 1998 Nov 1; 3: D1060-96; Gaya A, Leuk Lymphoma, 1999 Oct 35 (3-4): 237-43; Sievers EL, Curr Opin Oncol. 2000 Jan 12(1): 30-5; Thomas ML, et al. Immunol. Today 1999 Sep 20(9): 406-411; Appelbaum FR, Semin. Hematol. 1999 Oct; 36 (4 suppl. 6): 2-8; Ulyanova T; Immunol. Res 1997 Feb; 16(1): 101-13; re PP32 for example USP 5,846,822 and Brody JR, et al. J Biol Chem. 1999 Jul 16; 274(29):20053-5 regarding the functional moiety of PP32 which is necessary for interaction with CD45, and for example USP 5,981,251 with respect to methods of identifying such molecules).

In preferred embodiments the invention is directed to multifunctional ligands that comprise immune function exerting moieties having functionalities of molecules currently in clinical trials or proposed for clinical trials (see for example Glennie MJ et al. Aug 2000, Immunology Today 408 Vol 21(8); see also Journal of Immunological Methods 237 (2000) 131-145; Mol Immunol 2000 Jun; 37(9) 515-526; Annu Rev Med 2001; 52:125-145; Annu Rev Med 2001 52:63-78; Q J Nucl Med 2000 Sep; 44(3) 268-83) including those that have an anti-CD2 functionality (see USP 5,795,572) anti-CD4 functionality (see for example USP 6,136,310 Herzyk D, J Infect Immun 2000 Feb; 69(2): 1032-1043) anti-CD3 functionality (for example WO 00/41474; WO 98139363; USP 6,113,901; Transplantation 2000 Dec 27 70 (12) 1707-12); Anti-CD44 functionality see for example Weiss L, et al., Proc Nat Acad Sci USA 2000; Jan 4 97(1) 285-290; Sugiyama K, Immunol Invest (1999) Mar-May 28(2-3) 185-200; Brocke S. et al. Proc Nat Acad Sci USA 1999 Jun 8 96(12) 6896; Micecz K et al. Nat Med 11995 Jun; 1(6); 558-63; Ahrens T et al., J Invest Dermatol. 2001 Jan 116(1) 93-101); with respect to control of migration of T-cell lymphocytes see Nohara C, et al. J Immunol. 2001 Feb 1; 166(3) 2108-2115), anti-CD20 functionality (see Crit Rev Oncol Hematol 2001 Jan 37(1):13-25) etc. anti-CD22 functionality see for example Newton DL, et al. Blood 2001 Jan 15; 97 (2): 528-535, USP 5,184,892; Anti-CD40/CTLA-4 see for example J Immunol 2000 Oct 1; 165(7):3612-9; Microsurgery 2000; 2c (8); 448-452; USP 5874082; USP 6056959; USP 5,801,227; USP 6004552; USP 5677165; USP 6087329; USP 5961974; USP 6051228; White CA, et al. Annu Rev Med. 2001; 52: 63-78 (see also reviews and specific applications referred to in Ditzel et al., Immunol Res. 2000; 21(2-3):185-93; USP 6,010,902, USP 5876950; USP 5876718; USP 5,601,819, USP 5981251, USP 5885579 and 5885796; Cancer Immunol Immunother 2000 Jun; 49(3):173-80; Omar K, J Neuroimmunol 2001 Feb 1, 113(1) 129-141; Bellido M, Eur J. Haematol 2001 Feb. 66(2) 100-106; Broeren et al. J Immunol (2000) Dec 15 165(12) 6908-14; Alexandroff AB et al Mol Immunol 2000 June 37(9) 515-526; Werkerle T J Immunol. 2001 Feb 15 166(4) 2311-2316; Howard LM J Immunol 2001 Feb; 116(3) 1547-53 anti-CD154; J Pharmacokinet Biopharm 1999 Aug; 27(4):397-420, J Clin Oncol 2000 Apr; 18(8):1622-36, Leukemia 2000 Mar; 14(3):474-5, Clin Cancer Res 2000 Feb; 6(2):372-80, Leukemia 2000 Jan; 14(1):129-35, J Nucl Med 1999 Nov; 40(11):1935-46, Blood 1999 Nov 15; 94(10):3340-8, Blood 1999 Aug 15; 94(4):1237-47, Cancer Res 1999 May 1; 59(9):2096-101, Vaccine 1999 Apr 9; 17(15-16):1837-45, Blood 1998 Dec 1; 92(11):4066-71, J Rheumatol 1998 Nov; 25(11):2065-76, Clin Pharmacol Ther 1998 Sep; 64(3):339-46, Mult

Scler 1996 Jul; 1(6):339-42, *Cancer Immunol Immunother* 1997 Jul; 44(5):265-72, *Transplant Proc* 1996 Dec; 28(6):3210-1, *Arthritis Rheum.* 1996 Jul; 39(7):1102-8, *Immunology* 1996 May; 88(1):13-9 and USP 5,876,718).

The invention contemplates assessment and therapeutic benefit of lymphatic localization in the case of toxic cross-reactivity of the second portion eg. antibody for its desired target with an undesired target (see eg. *Lancet* 1999 Nov 13; 354(9191):1691-5). It is contemplated that the toxic effect of a given immune affecting portion (second portion) of a multifunctional ligand of the invention, if permitted to have systematic distribution, could be avoided by confining its effects against cells passing through the lymphatic system and that heretofore (for this reason) unusable or failed target ligands due to their wide distribution on normal cells or proven toxic effects could be assessed in this lymphatic system localized context. Such other target ligands will be readily apparent to those skilled in the art.

The invention also contemplated that ligands or entities delivered to cells (the same or different entities) or preferably cooperative drug carrying entities can be cross-linked through complementary components such as biotin or avidin eg. cross-linking with avidin or streptavidin or a variant thereof, for example, *a biotin coated liposome* [or other micro/nano sphere, particle or drug carrying entity (including those adapted for slow release)] *containing a prodrug and* for example *a biotin coated liposome* [or other micro/nano sphere, particle or entity (including those adapted for slow release)] *containing the necessary pro-drug converting substance eg. enzyme* by delivering separately in succession an effective amount of complementary components, eg. a biotin type or biotin bearing component, preferably biotin or a functional variant thereof, sandwiched between the delivery two, avidin type or avidin bearing components, preferably avidin, streptavidin or a pharmaceutically acceptable variant thereof and/or by delivering as the avidin component two or more avidin (or variants thereof) subunits linked together by biotin or recombinantly fused together according to well known techniques in the art). Particularly in the case of a tumor targeting this strategy has the effect of prolonging whatever therapeutic effects or interactions are inherent in the therapeutic moieties or drug carrying entities delivered to the cells. In particular, with respect to drug carrying entities, using for example an avidin or variant to link cooperating such entities together ensures that their contents are released in the same micro-environment. The avidin component or bearing component can also be delivered between the deliveries of the two biotin bearing components (see USP 6,077, 499, USP 5,482,698, USP 5,846,537, USP 6,022,951 and their cited references). Thus according to a preferred embodiment the invention is directed to a method of targeted delivery to a target cell of the contents of two cooperating drug carrying entities, preferably biotin coated liposomes, containing respectively preferably prodrug and prodrug to drug converting substance eg. enzyme, by administering a targeting ligand eg. an antibody which is biotin coated followed by an avidin or streptavidin or variants thereof, followed by the biotin coated liposomes, followed preferably by additional avidin to further anchor the cooperating components together.

Examples of bispecific antibodies that can be evaluated for adaptation to the invention or combination therapy therewith including those with an reasonable expectation of the therapeutic application and/or effectiveness, have been reviewed (see for example van Spriel AB, van Ojik HH, van De Winkel JG. Immunotherapeutic perspective for bispecific antibodies. *Immunol Today*. 2000 Aug; 21(8):391-7; Weiner LM. Bispecific antibodies in cancer therapy. *Cancer J Sci Am*. 2000 May; 6 Suppl 3:S265-71. Barbet J, Kraeber-Bodere F, Vuillez JP, Gautherot E, Rouvier E, Chatal JF. Pretargeting with the affinity enhancement system for radioimmunotherapy. *Cancer Biother Radiopharm*. 1999 Jun; 14(3):153-66. de Wolf FA, Brett GM. Ligand-binding proteins: their potential for application in systems for controlled delivery and uptake of ligands. *Pharmacol Rev*. 2000 Jun; 52(2):207-36.; Feuring-Buske M, Buske C, Unterhalt M, Hiddemann W. Recent advances in antigen-targeted therapy in non-Hodgkin's lymphoma. *Ann Hematol*. 2000 Apr; 79(4):167-74; Wang H, Liu Y, Wei L, Guo Y. Bi-specific antibodies in cancer therapy *Adv Exp Med Biol*. 2000; 465:369-80; Staerz UD, Lee DS, Qi Y. Induction of specific immune tolerance with hybrid antibodies. *Immunol Today*. 2000 Apr; 21(4):172-6; Hoefnagel CA. Nuclear medicine therapy of neuroblastoma. *Q J Nucl Med*. 1999 Dec; 43(4):336-43. Elsasser D, Stadick H, van de Winkel JG, Valerius T. GM-CSF as adjuvant for immunotherapy with bispecific antibodies. *Eur J Cancer*. 1999 Aug; 35 Suppl 3:S25-8. Molema G, Kroesen BJ, Helfrich W, Meijer DK, de Leij LF. The use of bispecific antibodies in tumor cell and tumor vasculature directed immunotherapy. *J Control Release*. 2000 Feb 14; 64(1-3):229-39. Bodey B, Bodey B, Siegel SE, Kaiser HE. Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents. *Curr Pharm Des*. 2000 Feb; 6(3):261-76. Kudo T, Suzuki M, Katayose Y, Shinoda M, Sakurai N, Kodama H, Ichiyama M, Takemura S, Yoshida H, Saeki H, Saijyo S, Takahashi J, Tominaga T, Matsuno S. Specific targeting immunotherapy of cancer with bispecific antibodies. *Tohoku J Exp Med*. 1999 Aug; 188(4):275-88. Koelemij R, et al. Bispecific antibodies in cancer therapy, from the laboratory to the clinic. *J Immunother*. 1999 Nov; 22(6):514-24. Segal DM, Weiner GJ, Weiner LM Bispecific antibodies in cancer therapy *Curr Opin Immunol*. 1999 Oct; 11(5):558-62. Hudson PJ. Recombinant antibody constructs in cancer therapy. *Curr Opin Immunol*. 1999 Oct; 11(5):548-57. Kastenbauer E, Wollenberg B. [In search of new treatment methods for head-neck carcinoma]. *Laryngorhinootologie*. 1999 Jan; 78(1):31-5. Barth RF et al, Boron neutron capture therapy of brain tumors: an emerging therapeutic modality. *Neurosurgery*. 1999 Mar; 44(3):433-50; discussion 450-1.; Schirrmacher V, Haas C. Modification of cancer vaccines by virus infection and attachment of bispecific antibodies. An effective alternative to somatic gene therapy. *Adv Exp Med Biol*. 1998; 451:251-7. Fleckenstein G, Osmers R, Puchta J. Monoclonal antibodies in solid tumours: approaches to therapy with emphasis on gynaecological cancer, *Med Oncol*. 1998 Dec; 15(4):212-21. Schirrmacher V, et al, Immunization with virus-modified tumor cells *Semin Oncol*. 1998 Dec; 25(6):677-96. Guyre CA, Fanger MW. Macrophage-targeted killing and vaccines. *Res Immunol*. 1998 Sep-Oct; 149(7-8):655-60 available.; Cao Y, Suresh MR. Bispecific antibodies as novel bioconjugates.

Bioconjug Chem. 1998 Nov-Dec; 9(6):635-44. Farah RA, et al, The development of monoclonal antibodies for the therapy of cancer. Crit Rev Eukaryot Gene Expr. 1998; 8(3-4):321-56.: Volm M. Multidrug resistance and its reversal. Anticancer Res. 1998 Jul-Aug; 18(4C):2905-17. Rouard H, et al, Fc receptors as targets for immunotherapy. Int Rev Immunol. 1997; 16(1-2):147-85. Bookman MA Biological therapy of ovarian cancer: current directions. Semin Oncol. 1998 Jun; 25(3):381-96. et al, Bookman MA. Biological therapy for gynecologic malignancies. Cancer Treat Res. 1998; 95:115-47. Funaro A, et al, Monoclonal antibodies in clinical applications. J Biol Regul Homeost Agents. 1996 Oct-Dec; 10(4):72-82. Stocchi L, et al, Diagnostic and therapeutic applications of monoclonal antibodies in colorectal cancer. Dis Colon Rectum. 1998 Feb; 41(2):232-50. Jurcic JG, Scheinberg DA, Houghton AN. Monoclonal antibody therapy of cancer. Cancer Chemother Biol Response Modif. 1997; 17:195-216.: Makrides SC. Related Therapeutic inhibition of the complement system. Pharmacol Rev. 1998 Mar; 50(1):59-87. Tesch H, Bohlen H, Wolf J, Engert A. Pathogenesis and therapy of Hodgkin lymphoma. Med Klin. 1998 Feb 15; 93(2):82-90. Fan Z, Mendelsohn J. Therapeutic application of anti-growth factor receptor antibodies; Curr Opin Oncol. 1998 Jan; 10(1):67-73. Schirmacher V. Tumor vaccines and active specific immunotherapy Internist (Berl). 1997 Nov; 38(11):1050-4. Curnow RT. Clinical experience with CD64-directed immunotherapy. An overview. Cancer Immunol Immunother. 1997 Nov-Dec; 45(3-4):210-5. de Gast GC, et al, Clinical perspectives of bispecific antibodies in cancer. Cancer Immunol Immunother. 1997 Nov-Dec; 45(3-4):121-3. Valerius T et al, HLA class II antibodies recruit G-CSF activated neutrophils for treatment of B cell malignancies. Leuk Lymphoma. 1997 Jul; 26(3-4):261-9. Carter P, Merchant AM. Engineering antibodies for imaging and therapy. Curr Opin Biotechnol. 1997 Aug; 8(4):449-54. Pluckthun A, et al, New protein engineering approaches to multivalent and bispecific antibody fragments. Immunotechnology. 1997 Jun; 3(2):83-105. Nokihara H, et al, Overcoming of multidrug resistance by anti-P-glycoprotein monoclonal Antibody Nippon Rinsho. 1997 May; 55(5):1128-34. Renner C, Trumper L, Pfreundschuh M Monoclonal antibodies in the treatment of non-Hodgkin's lymphoma: recent results and future prospects. Leukemia. 1997 Apr; 11 Suppl 2:S55-9. Sznol M, et al, Antigen-specific agents in development. Semin Oncol. 1997 Apr; 24(2):173-86. Hayden MS, et al, Antibody engineering. Curr Opin Immunol. 1997 Apr; 9(2):201-12. Deo YM, et al, Clinical significance of IgG Fc receptors and Fc gamma R-directed immunotherapies. Immunol Today. 1997 Mar; 18(3):127-35. Rihova B. Targeting of drugs to cell surface receptors. Crit Rev Biotechnol. 1997; 17(2):149-69. Molema G et al, Tumor vascular endothelium: barrier or target in tumor directed drug delivery and immunotherapy. Pharm Res. 1997 Jan; 14(1):2-10. Haas C, et al, Immunogenicity increase of autologous tumor cell vaccines by virus infection and attachment of bispecific antibodies. Cancer Immunol Immunother. 1996 Nov; 43(3):190-4. von Mehren M, et al, Monoclonal antibody-based therapy. Curr Opin Oncol. 1996 Nov; 8(6):493-8. Two-step immunological approaches for imaging and therapy. Q J Nucl Med. 1996 Sep; 40(3):234-51. Morimoto C, et al, Selective immunomodulation: utilization of CD29/VLA molecules. Artif Organs. 1996 Aug; 20(8):828-31. Tesch H, et al, Hodgkin's disease: from basic science to clinical application. Leukemia. 1996 Jun; 10 Suppl 2:s74-7. Bodey B, et al, Human cancer detection and immunotherapy with conjugated and non-conjugated monoclonal antibodies. Anticancer Res. 1996 Mar-Apr; 16(2):661-74. Hartmann F et al, Treatment of Hodgkin's disease with bispecific antibodies. Ann Oncol. 1996; 7 Suppl 4:143-6. Wels W, et al, Intervention in receptor tyrosine kinase-mediated pathways: recombinant antibody fusion proteins targeted to ErbB2. Curr Top Microbiol Immunol. 1996; 213 (Pt 3):113-28.: Kairemo KJ. Radioimmunotherapy of solid cancers: Acta Oncol. 1996; 35(3):343-55. Verhoeyen ME, et al, Antibody fragments for controlled delivery of therapeutic agents. Biochem Soc Trans. 1995 Nov; 23(4):1067-73. Haagen IA. Performance of CD3xCD19 bispecific monoclonal antibodies in B cell malignancy. Leuk Lymphoma. 1995 Nov; 19(5-6):381-93.

In another aspect the invention is directed to presenting antigen within the lymphatic system (eg. in the form of an anti-idiotypic antibody) such as to facilitate a desired immune response eg. vaccination type responses). Optionally, adjuvants can be conventionally employed to assist initial immune stimulation eg. intradermally when appropriately delivered. Activating cytokines for example as specified above, can also be employed to enhance the immune response. Examples of antibodies having an anti-idiotypic counterpart or for which an anti-idiotypic counterpart could be made by well known techniques in the art (and that are capable of exerting the desired anti-idiotypic effect) are numerous and numerous such anti-idiotypic antibodies have application to immunization as well as applications relating to tolerance (see for example US patents: 6,146,627 Method for reducing T cell-mediated cytotoxicity in HIV using anti-idiotypic antibody; 6,132,718; Multi-stage cascade boosting vaccine; 6,117,427; 6,099,839 Gonococcal anti-idiotypic antibodies and methods compositions using them; 6,074,641 Gonococcal anti-idiotypic antibodies and methods and compositions using them; 6,063,679 Anti-idiotypic monoclonal antibodies and compositions including the anti-idiotypic monoclonal antibodies; 6,060,049 Surrogate tolerogenesis for the development of tolerance to xenografts; 6,042,827 Anti-idiotypic antibody induction of anti-tumor response; 6,007,815 Anti-idiotypic vaccination against diseases resulting from pathogenic responses by specific T cell populations; 5,981,502 Methods and compositions for inducing apoptosis in tumor cells; 5,977,316 Monoclonal antibody 1A7 and related polypeptides; 5,977,315 Murine anti-idiotypic antibody 3H1; 5,969,107 Anti-idiotypic antibodies which induce an immune response against epidermal growth factor receptor 5,965,131 Delivery of diagnostic and therapeutic agents to a target site; 5,958,408 Delivery of diagnostic and therapeutic agents to a target site; 5,939,067 Gonococcal anti-idiotypic antibodies and methods and compositions using them; 5,935,821 Polynucleotides related to monoclonal antibody 1A7 and use for the treatment of melanoma and small cell carcinoma; 5,888,509 Gonococcal anti-idiotypic antibodies and methods and compositions using them; 5,866,124 Anti-idiotypic antibodies for high molecular weight-melanoma associated antigen; 5,858,361 Monoclonal anti-idiotypic anti-CA125 antibodies and pharmaceutical compositions containing them; 5,854,069 GD2 anti-idiotypic antibodies and uses thereof; 5,849,583 Anti-idiotypic antibody and its use in diagnosis and therapy in HIV-related disease; 5,840,297 Vaccine comprising anti-idiotypic antibody to chlamydia GLXA and process; 5,817,513 Anti ganglioside monoclonal antibodies; 5,808,005 Human carcinoma antigen; 5,798,100 Multi-stage cascade boosting vaccine; 5,792,455 Anti-idiotypic antibody vaccines;

5,780,029 Antidiotypic monoclonal antibodies for treatment of melanoma; 5,766,588 Tumor immunotherapy using anti-idiotypic antibodies; 5,744,135 Method of raising an immune response with an anti-idiotypic antibody having correspondence with human hepatitis B surface antigen; 5,728,812 Anti-idiotypic antibody composition for inhibiting acute complement-mediated cytotoxicity.

According to another aspect of the invention the multi-functional ligand comprises a first portion which binds to a lymph associated antigen and a second portion which binds to a tumor cell infected cell or infectious agent. This embodiment of the invention can be used for example, to assess and affect the ability of the tumor-binding portion to more advantageously inhibit metastasis. Optionally, for example, the portion which binds to a lymph associated antigen has a lower affinity and/or avidity so that the tumor cell binding portion preferentially binds to the tumor cell and is therefore more likely to accompany its passage through the lymphatic system. This strategy also has application to bi-specific antibodies of the invention in which the second portion is for example targeted to an immune cell. Optionally, multiple such multi-functional ligands may permit sufficient tumor cell anchoring to permit the tumor cell to be killed within the lymphatic system via a toxic payload carried by the multifunctional ligand or through the recruitment of immune cells which accomplish this end (eg using the same or a different multifunctional ligand fused or conjugated to a suitable cytokine (eg IL-2, IL-12). The prolonged presence of these cells could be advantageously used to assess methods of immunization directly against the tumor cell using, for example, cytokines including cytokines fused or conjugated in whole or functional part to a lymph targeted Ab on the same, or a different multifunctional ligand delivered in a suitable dose (with respect to generation of anti-tumor antibodies and other antibody fragments for application herein as well as important related technologies see also WO 00/50008; WO 01/01137; WO 97/37791; WO 99/37791; WO 97/10003; Hoogenboom et al. Nat. Biotechnology 15(2) Feb 1997 p125-126; Fell H. et al. Journal Of Immunology Vol 146(7) Apr 1991 p2446-2452; Anderson D. et al Bioconjugate Chemistry 14(1) Jan 1993 p10-18; USP 6,172,197; USP 6,171,782; Immunological Investigations 2000 29(2) entire issue). Optionally the tumor binding portion internalizes and/or delivers a toxic payload, for example a radionuclide, or other toxin, or a cytokine to the tumor cell (with respect to selection of tumor internalizing human antibodies see for example Pool M et al. J Mol Biol. 2000 Sep 1; 301(5):1149-61, see also Kohl MD et al. J Mol. Biol. Biotechniques (2000) Vol 28(1) p162 In this way the multi-functional ligands of the invention, for example, when provided in a sufficient dose to both target the tumor and line a portion of the lymphatic system to which the target tumor is likely to drain, acts as a cancer treatment as well as a sentry system for assessing / augmenting (for example as an adjunct therapy) the ability of the tumor binding portion with/without payload to inhibit metastasis. There are numerous examples of functional cytokine and toxin fusions used for example in cancer therapy that may have application to the invention herein (for examples and reviews see references herein cited as well as WO 99/37791; WO99 53958A2 ENHANCEMENT OF ANTIBODY-CYTOKINE FUSION PROTEIN MEDIATED IMMUNE RESPONSES BY CO-ADMINISTRATION WITH PROSTAGLANDIN INHIBITOR; WO09730089A1 NOVEL ANTIBODY-CYTOKINE FUSION PROTEIN, AND METHODS OF MAKING AND USING THE SAME; WO00009150A2 CYTOKINE AND CYTOKINE RECEPTOR, AGONIST, ANTAGONIST AND/OR ANTIBODY COMBINATION FOR THERAPEUTIC; WO00/06605A2; WO 99/52562A2 ENHANCEMENT OF ANTIBODY-CYTOKINE FUSION PROTEIN MEDIATED IMMUNE RESPONSES BY CO-ADMINISTRATION WITH ANGIOGENESIS INHIBITOR; WO 99/37791A1 MULTIPURPOSE ANTIBODY; Proceeding of the IBC's 11th Annual International Conference on Antibody Engineering State of the Art Science, Technology and Applications, December 3-6, 2000; Amplification of T cell-mediated immune responses by antibody-cytokine fusion proteins. Immunol Invest. 2000 May; 29(2):117-20; Cancer Res. 1999 May 1; 59(9):2159-66.; Pharmacokinetics and stability of the ch14.18-interleukin-2 fusion protein in mice. Cancer Immunol Immunother. 1999 Aug; 48(5):219-29. Phase I study of single, escalating doses of a superantigen-antibody fusion protein (PNU-214565) in patients with advanced colorectal or pancreatic carcinoma. J Immunother. 2000 Jan; 23(1):146-53. Targeted toxin therapy for malignant astrocytoma. Neurosurgery. 2000 Mar; 46(3):544-51 (discussion @ 552); Targeting cytokines to tumors to induce active antitumor immune responses by recombinant fusion proteins. Hum Antibodies. 1999; 9(1):23-36; Lode HN, et al. Tumor-targeted IL-2 amplifies T cell-mediated immune response induced by gene therapy with single-chain IL-12. Proc Natl Acad Sci U S A. 1999 Jul 20; 96(15):8591-6; Gillies SD, et al. Improving the efficacy of antibody-interleukin 2 fusion proteins by reducing their interaction with Fc receptors. Cancer Res. 1999 May 1; 59(9):2159-66; Gan J, Kendra K, Ricci M, Hank JA, Gillies SD, Sondel PM. Specific enzyme-linked immunosorbent assays for quantitation of antibody-cytokine fusion proteins. Clin Diagn Lab Immunol. 1999 Mar; 6(2):236-42; Lode HN, et al. Synergy between an antiangiogenic integrin alpha v antagonist and an antibody-cytokine fusion protein eradicates spontaneous tumor metastases. Proc Natl Acad Sci U S A. 1999 Feb 16; 96(4):1591-6. Weiner L. et al. Oncogene (2000) 19:6144-6151; Cancer Research 60 6434-6440 Nov 15 2000; Cancer Vaccines and Immunotherapy 2000 (textbook); Immunotherapy With Intravenous Immunoglobulins P. Imbach (1991) Academic Press; Molecular Approaches to Tumor Immunotherapy (1997) World Scientific Publishing Company, Incorporated; Vaccines & Immunotherapy S. J. Cryz (1991) McGraw-Hill Ryerson, Limited *RE internalizing antibodies* see eg Biological Effects of Anti-ErbB2 Single Chain Antibodies Selected for Internalizing Function.; Biochem Biophys Res Commun. 2001 Jan 12; 280(1):274-279 and references cited therein, Immunoconjugates of geldanamycin and anti-HER2 monoclonal antibodies: antiproliferative activity on human breast carcinoma cell lines J Natl Cancer Inst. 2000 Oct 4; 92(19):1573-81; Foulon CF, et al., Radioiodination via D-amino acid peptide enhances cellular retention and tumor xenograft targeting of an internalizing anti-epidermal growth factor receptor variant III monoclonal antibody. Cancer Res. 2000 Aug 15; 60(16):4453-60. Poul MA, Becerril B, Nielsen UB, Morisson P, Marks Selection of tumor-specific internalizing human antibodies from phage libraries J Mol Biol. 2000 Sep 1; 301(5):1149-61. Vrouenraets MB, et al., Targeting of a hydrophilic photosensitizer by use of internalizing monoclonal antibodies: A new possibility for use in photodynamic therapy. Int J Cancer. 2000 Oct 1; 88(1):108-14.

In yet another aspect, the invention contemplates that the passage of tumor cells can be inhibited within the tumor vasculature using a bispecific ligand, optionally a bispecific antibody, which targets on the one hand a well known vascular endothelial marker and on the other hand binds to a ligand on the surface of the tumor. Other aspects of the invention related to tumor cell targeting are understood to be described in reference to this aspect of the invention as well. It is also contemplated that markers which are present on both the lymphatic endothelium and the tumor vasculature can be simultaneously targeted with bispecific ligands of the invention to inhibit tumor metastasis and/or immunize a subject against tumor cells.

With respect to the use of immunocytokines for antibody therapy which have application to the invention herein see also Cytokine fusion Improving the efficacy of antibody-interleukin 2 fusion proteins by reducing their interaction with Fc receptors. *Cancer Res.* 1999 May 1; 59(9):2159-66. Antibody-IL-12 fusion proteins are effective in SCID mouse models of prostate and colon carcinoma metastases. *J Immunol.* 1998 Jun 15; 160(12):6195-203. Amplification of T cell-mediated immune responses by antibody-cytokine fusion proteins. *Immunol Invest.* 2000 May; 29(2):117-20.

It is contemplated that the multifunctional ligands of the invention when used to inhibit metastasis, for example, in the manner described above, could be advantageously employed in combination with other well known therapies for example cytotoxic drugs, other tumor targeted antibodies and conjugates/fusions therewith used or currently being evaluated for immunotherapies, angiogenesis targeted drugs etc. (re angiogenesis see for example Angiogenesis in cancer and other diseases. *Nature.* 2000 Sep 14; 407(6801):249-57).

Similarly, a bi-specific antibody of the invention could be used to bind to antigens/ligands on lymphocytes which are known or become known to inhibit or enhance immune function or mediate a disease eg. CD45.

With respect to target receptors related to the inventions defined herein see also USP 6,277,962.

As discussed above, as used herein the term "lymph associated antigen" refers to antigens that are expressed significantly on lymphatic endothelial cells but not significantly expressed, if at all, on other tissues. Examples of such antigen include LYVE-1 a CD44 receptor analogue which binds to HA (February 22, 1999, Banerji et. al., *Journal of Cell Biology* Vol. 144, #4, p789-801) and which is expressed primarily on lymphatic endothelial cells. LYVE-1 specific antisera have been shown to inhibit binding of HA. The invention contemplates research and treatments using multi-functional ligands of the invention with respect to non-human mammals, including preferably agricultural animals, canine species, primates and mice having similar receptors/antigens. For example, a murine counterpart to LYVE-1 (published in Prevo R. et al. 2001 Feb 20, *J. Biol. Chem.*; Manuscript M011004200) can be employed to implement the various methods and embodiments described herein in a mouse model, for example to assess the extent of inhibition of metastasis effected by a multifunctional ligand (optionally comprising for example to a toxin, cytokine T cell receptor etc) which has a first portion which binds to LYVE-1 and a second portion which binds to, for example to GI-101, a breast tumor which is known to metastasize to the lung (see USP 6037520 and 5,693,533 see also US patents 5,643,551, 5,491,284, 5,569,812, 5,917,124 and 6,107,540 and references cited in these patents, particularly with respect to other metastatic models and methods of evaluating anticancer drugs in mice). LYVE-1 counterparts in other mammals can be identified in the manner described by Prevo R. et al. (see also Skobe M. et al. Induction of tumor lymphangiogenesis by VEGF-C promotes breast cancer metastasis *Nat. Med.* Feb; 7(2) 192-8.)

Other models of metastasis in animals are well known in the art (see for example 1: Webb CP, Vande Woude GF. Genes that regulate metastasis and angiogenesis. *J Neurooncol.* 2000 Oct-Nov;50(1-2):71-87. 2: Chirgwin JM, Guise TA. Molecular mechanisms of tumor-bone interactions in osteolytic metastases. *Crit Rev Eukaryot Gene Expr.* 2000;10(2):159-78. 3: Rusciano D. Differentiation and metastasis in melanoma. *Crit Rev Oncog.* 2000;11(2):147-63. 4: Kobaek-Larsen M, Thorup I, Diederichsen A, Fenger C, Hoitinga MR. Review of colorectal cancer and its metastases in rodent models: comparative aspects with those in humans. *Comp Med.* 2000 Feb;50(1):16-26. 5: Magnano M, Bongioannini G, Lerda W, Galvagno MB, Tondolo E, Canale G, Capogrosso B, Delsanto PP, Scalerandi M, Pescarmona GP. A physical-based model for the simulation of neoplastic growth and metastasis. *J Surg Oncol.* 2000 Jun;74(2):122-9. 6: Hoffman RM. Orthotopic metastatic mouse models for anticancer drug discovery and evaluation: a bridge to the clinic. *Invest New Drugs.* 1999;17(4):343-59. 7: Satyamoorthy K, Meier F, Hsu MY, Berking C, Herlyn M. Human xenografts, human skin and skin reconstructions for studies in melanoma development and progression. *Cancer Metastasis Rev.* 1999;18(3):401-5. 8: Fidler IJ, Schackert G, Zhang RD, Radinsky R, Fujimaki T. The biology of melanoma brain metastasis. *Cancer Metastasis Rev.* 1999;18(3):387-400. 9: Seftor RE, Seftor EA, Hendrix MJ. Molecular role(s) for integrins in human melanoma invasion. *Cancer Metastasis Rev.* 1999;18(3):359-75. 10: Yoneda T. Cellular and molecular basis of preferential metastasis of breast cancer to bone. *J Orthop Sci.* 2000;5(1):75-81. 11: Morton DL, Chan AD. The concept of sentinel node localization: how it started. *Semin Nucl Med.* 2000 Jan;30(1):4-10. 12: Groom AC, MacDonald IC, Schmidt EE, Morris VL, Chambers AF. Tumour metastasis to the liver, and the roles of proteinases and adhesion molecules: new concepts from in vivo videomicroscopy. *Can J Gastroenterol.* 1999 Nov;13(9):733-43. 13: Russo J, Russo IH. The pathway of neoplastic transformation of human breast epithelial cells. *Radiat Res.* 2001 Jan;155(1 Pt 2):151-154. 14: Uygur MC, Usulutun A, Ozen H, Ayhan A, Kendi S. Prognostic factors and the role of nephrectomy in metastatic renal cell carcinoma. *J Exp Clin Cancer Res.* 1999 Sep;18(3):397-401. 15: Schlom J, Hodge JW. The diversity of T-cell co-stimulation in the induction of antitumor immunity. *Immunol Rev.* 1999 Aug;170:73-84. 16: Thames HD, Buchholz TA, Smith CD. Frequency of first metastatic events in breast cancer: implications for sequencing of

systemic and local-regional treatment. *J Clin Oncol*. 1999 Sep;17(9):2649-58. 17: Allardyce RA. Is the port site really at risk? Biology, mechanisms and prevention: a critical view. *Aust N Z J Surg*. 1999 Jul;69(7):479-85. 18: Takahashi Y. [Experimental model for cancer metastasis]. *Gan To Kagaku Ryoho*. 1999 Feb;26(3):401-7. Japanese. 19: Voura EB, Sandig M, Siu CH. Cell-cell interactions during transendothelial migration of tumor cells. *Microsc Res Tech*. 1998 Nov 1;43(3):265-75. 20: Fidler IJ. Critical determinants of melanoma metastasis. *J Invest Dermatol Symp Proc*. 1996 Apr;1(2):203-8. 21: Duffy MJ, McCarthy K. Matrix metalloproteinases in cancer: prognostic markers and targets for therapy (review). *Int J Oncol*. 1998 Jun;12(6):1343-8. 22: Banerjee A, Quirke P. Experimental models of colorectal cancer. *Dis Colon Rectum*. 1998 Apr;41(4):490-505. 23: Demicheli R, Retsky MW, Swartzendruber DE, Bonadonna G. Proposal for a new model of breast cancer metastatic development. *Ann Oncol*. 1997 Nov;8(11):1075-80. 24: Rofstad EK, Lyng H. Xenograft model systems for human melanoma. *Mol Med Today*. 1996 Sep;2(9):394-403. 25: Boyer B, Valles AM, Thierry JP. Model systems of carcinoma cell dispersion. *Curr Top Microbiol Immunol*. 1996;213 (Pt 1):179-94. No abstract available. 26: Strieter RM, Addison CL, Ehlert JE, Keane MP, Belperio JA, Burdick MD, Arenberg DA. Use of Immunodeficient Mice for the Evaluation of CXC Chemokines in the Regulation of Tumor-associated Angiogenesis. *ILAR J*. 1999 Sep;40(4):175-182. 27: Morony S, Capparelli C, Sarosi I, Lacey DL, Dunstan CR, Kostenuik PJ. Osteoprotegerin inhibits osteolysis and decreases skeletal tumor burden in syngeneic and nude mouse models of experimental bone metastasis. *Cancer Res*. 2001 Jun 1;61(11):4432-6. 28: Korenchuk S, Lehr JE, MClean L, Lee YG, Whitney S, Vessella R, Lin DL, Pienta KJ. VCaP, a cell-based model system of human prostate cancer. *In Vivo*. 2001 Mar-Apr;15(2):163-8. 29: Johnston MR, Mullen JB, Pagura ME, Howard RB. Validation of an orthotopic model of human lung cancer with regional and systemic metastases. *Ann Thorac Surg*. 2001 Apr;71(4):1120-5. 30: Engler S, Thiel C, Forster K, David K, Bredehorst R, Juhl H. A novel metastatic animal model reflecting the clinical appearance of human neuroblastoma: growth arrest of orthotopic tumors by natural, cytotoxic human immunoglobulin M antibodies. *Cancer Res*. 2001 Apr 1;61(7):2968-73. 31: Swiercz R, Keck RW, Skrzypczak-Jankun E, Selman SH, Jankun J. Recombinant PAI-1 inhibits angiogenesis and reduces size of LNCaP prostate cancer xenografts in SCID mice. *Oncol Rep*. 2001 May-Jun;8(3):463-70. 32: Takahashi Y, Koyanagi N, Kitoh K. Effect of E7010 on liver metastasis and life span of syngeneic C57BL/6 mice bearing orthotopically transplanted murine Colon 38 tumor. *Cancer Chemother Pharmacol*. 2001;47(2):179-84. 33: Li Z, Huang X, Li J. [A study of human breast carcinoma xenografts in nude mice]. *Zhonghua Yi Xue Za Zhi*. 2000 Nov;80(11):865-8. Chinese. 34: S, Chauzy C, Martin-Vandeleet N, Delpech B, Thiberville L, Martin JP, Diarra-Mehrpour M. A model of spontaneous lung metastases visualised in fresh host tissue by green fluorescent protein expression. *Clin Exp Metastasis*. 1999;17(10):817-22. 35: Hamblin MR, Del Governatore M, Rizvi I, Hasan T. Biodistribution of charged 17.1A photoimmunoconjugates in a murine model of hepatic metastasis of colorectal cancer. *Br J Cancer*. 2000 Dec;83(11):1544-51. 36: Ciardiello F, Bianco R, Damiano V, Fontanini G, Caputo R, Pomatito G, DePlacido S, Bianco AR, Mendelsohn J, Tortora G. Antiangiogenic and antitumor activity of anti-epidermal growth factor receptor C225 monoclonal antibody in combination with vascular endothelial growth factor antisense oligonucleotide in human GEO colon cancer cells. *Clin Cancer Res*. 2000 Sep;6(9):3739-47. 37: Shinohara H, Fan D, Ozawa S, Yano S, Van Arsdell M, Viner JL, Beers R, Pastan I, Fidler IJ. Site-specific expression of transferrin receptor by human colon cancer cells directly correlates with eradication by anti-transferrin recombinant immunotoxin. *Int J Oncol*. 2000 Oct;17(4):643-51. 38: Inoue K, Slaton JW, Davis DW, Hicklin DJ, McConkey DJ, Karashima T, Radinsky R, Dinney CP. Treatment of human metastatic transitional cell carcinoma of the bladder in a murine model with the anti-vascular endothelial growth factor receptor monoclonal antibody DC101 and paclitaxel. *Clin Cancer Res*. 2000 Jul;6(7):2635-43. 39: Pulkkanen KJ, Parkkinen JJ, Kettunen MI, Kauppinen RA, Lappalainen M, Ala-Opas MY, Yla-Herttuala S. Characterization of a new animal model for human renal cell carcinoma. *In Vivo*. 2000 May-Jun;14(3):393-400. 40: Wang W, Zhou J, Xu L, Zhen Y. Antineoplastic effect of intracellular expression of a single-chain antibody directed against type IV collagenase. *J Environ Pathol Toxicol Oncol*. 2000;19(1-2):61-8. 41: Raymond MA, Tannapfel A, Schneider C, Scheidbach H, Kover S, Jung A, Reck T, Lippert H, Kockerling F. Description of an intraperitoneal tumour xenograft survival model in the pig. *Eur J Surg Oncol*. 2000 Jun;26(4):393-7. 42: Okazaki K, Nakayama Y, Shibao K, Hirata K, Sako T, Nagata N, Kuroda Y, Itoh H. Establishment of a human colon cancer cell line (PMF-ko14) displaying highly metastatic activity. *Int J Oncol*. 2000 Jul;17(1):39-45. 43: Westphal JR, Van't Hullenaar R, Peek R, Willems RW, Crickard K, Crickard U, Askaa J, Clemmensen I, Ruiter DJ, De Waal RM. Angiogenic balance in human melanoma: expression of VEGF, bFGF, IL-8, PDGF and angiostatin in relation to vascular density of xenografts in vivo. *Int J Cancer*. 2000 Jun 15;86(6):768-76. 44: Holleran JL, Miller CJ, Culp LA. Tracking micrometastasis to multiple organs with lacZ-tagged CWR22R prostate carcinoma cells. *J Histochem Cytochem*. 2000 May;48(5):643-51. 45: Hewitt RE, McMarlin A, Kleiner D, Wersto R, Martin P, Tsoskas M, Stamp GW, Stetler-Stevenson WG. Validation of a model of colon cancer progression. *J Pathol*. 2000 Dec;192(4):446-54. 46: Stein TN, Berger MR. Quantification of liver metastases from LS174T human colorectal cancer cells in nude rats by PCR. *Anticancer Res*. 1999 Sep-Oct;19(5B):3939-45. 47: Angelov L, Salhia B, Roncari L, McMahon G, Guha A. Inhibition of angiogenesis by blocking activation of the vascular endothelial growth factor receptor 2 leads to decreased growth of neurogenic sarcomas. *Cancer Res*. 1999 Nov 1;59(21):5536-41. 48: Nakanishi H, Abe A, Inada K, Tsukamoto T, Yasui K, Tatematsu M. Induction of apoptosis in metastatic foci from human gastric cancer xenografts in nude mice and reduction of circulating tumor cells in blood by 5-FU and 1-hexylcarbonyl-5-fluorouracil. *J Cancer Res Clin Oncol*. 1999 Dec;125(12):660-8. 49: Alpaugh ML, Tomlinson JS, Shao ZM, Barsky SH. A novel human xenograft model of inflammatory breast cancer. *Cancer Res*. 1999 Oct 15;59(20):5079-84. 50: Saini M, Bellinzona M, Weichhold W, Samii M. A new xenograft model of primary central nervous system lymphoma. *J Neurooncol*. 1999 Jun;43(2):153-60. 51: Howard RB, Mullen JB, Pagura ME, Johnston MR. Characterization of a highly metastatic, orthotopic lung cancer model in the nude rat. *Clin Exp Metastasis*. 1999 Mar;17(2):157-62. 52: Chikamatsu K, Reichert TE, Kashii Y, Saito T, Kawashiri S, Yamamoto E, Whiteside TL. Immunotherapy with effector cells and IL-2 of lymph node metastases of human squamous-cell carcinoma of the head and neck established in nude mice. *Int J Cancer*. 1999 Aug 12;82(4):532-7. 53: Gallo-Hendrikx E, Percy D, Copps J, McKeown B, Quinton M, McMillan I, Croy BA, Wildeman

AG. Evaluation of three lines of immunodeficient mice for the study of spontaneous metastatic tumors. *APMIS*. 1999 Feb;107(2):245-56.54: Nemeth JA, Harb JF, Barroso U Jr, He Z, Grignon DJ, Cher ML. Severe combined immunodeficient-hu model of human prostate cancer metastasis to human bone. *Cancer Res*. 1999 Apr 15;59(8):1987-93.55: Konaka H, Koshida K, Endo Y, Uchibayashi T, Sasaki T, Namiki M. A human seminoma xenograft model with regional lymph node metastasis. *J Urol*. 1999 Jan;161(1):342-8.56: Vogel I, Shen Y, Soeth E, Juhl H, Kremer B, Kalthoff H, Henne-Bruns D. A human carcinoma model in athymic rats reflecting solid and disseminated colorectal metastases. *Langenbecks Arch Surg*. 1998 Dec;383(6):466-73.57: Prewett M, Rothman M, Waksal H, Feldman M, Bander NH, Hicklin DJ. Mouse-human chimeric anti-epidermal growth factor receptor antibody C225 inhibits the growth of human renal cell carcinoma xenografts in nude mice. *Clin Cancer Res*. 1998 Dec;4(12):2957-66.58: Ellis WJ, Vessella RL, Buhler KR, Bladou F, True LD, Bigler SA, Curtis D, Lange PH. Characterization of a novel androgen-sensitive, prostate-specific antigen-producing prostatic carcinoma xenograft: LuCaP 23. *Clin Cancer Res*. 1996 Jun;2(6):1039-48.59: Triest JA, Grignon DJ, Cher ML, Kocheril SV, Montecillo EJ, Talati B, Tekyi-Mensah S, Pontes JE, Hillman GG. Systemic interleukin 2 therapy for human prostate tumors in a nude mouse model. *Clin Cancer Res*. 1998 Aug;4(8):2009-14.60: Wu TT, Sikes RA, Cui Q, Thalmann GN, Kao C, Murphy CF, Yang H, Zhau HE, Balian G, Chung LW. Establishing human prostate cancer cell xenografts in bone: induction of osteoblastic reaction by prostate-specific antigen-producing tumors in athymic and SCID/bg mice using LNCaP and lineage-derived metastatic sublines. *Int J Cancer*. 1998 Sep 11;77(6):887-94.61: Takiguchi S, Kumazawa E, Shimazoe T, Tohgo A, Kono A. Antitumor effect of DX-8951, a novel camptothecin analog, on human pancreatic tumor cells and their CPT-11-resistant variants cultured in vitro and xenografted into nude mice. *Jpn J Cancer Res*. 1997 Aug;88(8):760-9.62: Strobel T, Swanson L, Cannistra SA. In vivo inhibition of CD44 limits intra-abdominal spread of a human ovarian cancer xenograft in nude mice: a novel role for CD44 in the process of peritoneal implantation. *Cancer Res*. 1997 Apr 1;57(7):1228-32.63: Crnalic S, Hakansson I, Boquist L, Lofvenberg R, Brostrom LA. A novel spontaneous metastasis model of human osteosarcoma developed using orthotopic transplantation of intact tumor tissue into tibia of nude mice. *Clin Exp Metastasis*. 1997 Mar;15(2):164-72.64: Molpus KL, Koelliker D, Atkins L, Kato DT, Buczek-Thomas J, Fuller AF Jr, Hasan T. Characterization of a xenograft model of human ovarian carcinoma which produces intraperitoneal carcinomatosis and metastases in mice. *Int J Cancer*. 1996 Nov 27;68(5):588-95.65: Pages JC, Sordat B, Bautista D, Costa J, Benhattar J. Detection of rare circulating human colon tumor cells in a nude mouse xenograft model. *Cancer Lett*. 1996 Aug 23;106(1):139-44.66: Sakakibara T, Chen FA, Kida H, Kunieda K, Cuenca RE, Martin FJ, Bankert RB. Doxorubicin encapsulated in sterically stabilized liposomes is superior to free drug or drug-containing conventional liposomes at suppressing growth and metastases of human lung tumor xenografts. *Cancer Res*. 1996 Aug 15;56(16):3743-6.67: Kundu N, Beaty TL, Jackson MJ, Fulton AM. Antimetastatic and antitumor activities of interleukin 10 in a murine model of breast cancer. *J Natl Cancer Inst*. 1996 Apr 17;88(8):536-41).

With respect to modifying an antibody to increase its affinity see also Crystal structure of Fab198, an efficient protector of the acetylcholine receptor against myasthenogenic antibodies. *Eur J Biochem*. 2001 Jul;268(13):3685-3693.

For example, in one embodiment the invention contemplates a bispecific antibody comprising an antigen binding component specific for a tumor cell associated antigen and a relatively low affinity anti-IL-6 receptor antibody component. With respect to the anti-tumor role of IL-6 see Wei LH et al. Interleukin-6 in cervical cancer: the relationship with vascular endothelial growth factor. *Gynecol Oncol*. 2001 Jul;82(1):49-56.

The invention contemplates that TCRs and modified TCRs (see for example, WO 01/48145) may be used as ligands, in place of antibody fragments for binding to target ligands such as peptide/MHC ligands.

Techniques for generating antibodies, and methods, for example of subtractive screening useful to identify other lymphatic vessel associated antibodies, including those optionally having smaller scFv, Fab and dAb (single domain antibody or functional fragment thereof) component (more easily passaging to lymphatic vessels from tissues particularly when constructed in the form of bispecific antibodies eg. diabodies etc.) by phage or ribosome display are well known in the art (see for example Hoogenboom HR et al. *Immunol. Today* (Aug. 2000) Vol 8 p 371; Schaffitzel C. et al. *J Immunol. Methods* (Dec. 10, 1999) 231(1-2) p. 119; Roberts RW et al. *Curr Opin Chem Biol*. 1999 Jun; 3(3):268-73; Winter G. et al. *Annu Rev Immunol* 1994 12:433-55; Kontermann RE et al. *Nat Biotechnol*. 1997 Jul; 15(7):629-31; Phage Display of Peptides and Proteins, A Laboratory Manual Kay BK et al. Eds 1996 Academic Press; Immunology Methods Manual Lefkovits, I ed. 1997 Academic Press; Hoogenboom et al. *Immunotechnology* 4 (1998) 1-20; Kovar H. Ewing's sarcoma and peripheral primitive neuroectodermal tumors after their genetic union *Curr Opin Oncol* 1998 Jul; 10(4):334-42)

With respect to single domain antibodies see for example USP 5,824,520, USP 5,622,836, USP 5,702,892, USP 5,959,087, Unique single-domain antigen binding fragments derived from naturally occurring camel heavy-chain antibodies. *J Mol Recognit*. 1999 Mar-Apr; 12(2):131-40. An antibody single-domain phage display library of a native heavy chain variable region: isolation of functional single-domain VH molecules with a unique interface. *J Mol Biol*. 1999 Jul 16; 290(3):685-98 and references cited in these references.

Methods for making antibody fusion proteins and bi-specific antibodies including diabodies etc. and fusion proteins thereof are as well as uses pertinent for evaluation with this invention (including uses with a reasonable expectation of therapeutic application) also well established in the art (for reviews and particular applications see for example Adams GP et al. *Journal of Immunological Methods* 231 (1999) 249-260; USP 6,121,424, 6,027,725 and 6,025,165; EP 0654085; Hudson P. *Exp. Opin. Invest. Drugs* (2000) 9(6): 1231-1242; Antibody Fusion

Proteins Steven M Chamow , Avi Ashkenazi Eds. ISBN 047118358X May 1999 Wiley; Antibody Engineering, Carl A. Borrebaeck Oxford University Press, 1995; Antibody Engineering: A Practical Approach David J. Chiswell, Hennie R. Hoogenboom, John McCafferty Oxford University Press, 1996; Antibody Engineering Protocols, Sudhir Paul (1995) Humana Press; Antibody Expression & Engineering (1998) Henry Y. Wang, Tadayuki Imanaka, American Chemical Society; Zhu Z. Biotechnology (NY) 1996 Feb.; 14(2): 192-6; Nielsen UB et al. Cancer Res. 2000 Nov 15; 60(22):6434-40; Lawrence LJ. Et al Febs Lett. 1998 Apr. 3; 425(3) 479-84; Hollinger et al., Cancer Immunol Immunother 1997 Nov-Dec 45 (3-4) 128-30; Immunotargeting of tumors: state of the art and prospects in 2000 Bull Cancer. 2000 Nov; 87(11):777-91; Hellfrich Wet al Int. J. cancer 1998 Apr 13 76(2): 232-9; Wu AM, Q J Nuc Med. 2000 Sep.; 44(3):268-83 KrebsB. Et al. J Interferon cytokine Res 1998 Sep 18(9): 783-91; Takemura Si, et al. Protein Eng. 2000 Aug.; 13(8): 583-8; Cochlovius B et al. J Immunol. 2000 Jul 15; 165(2):888-95; Atwell JL et al. Protein Eng. 1999 Jul; 12(7) : 597-604; kiprivanov SM et al. J. Mol Biol. 1999 Oct 15, 293 (1): 41-56; Alt M. et al FEBS Lett. Jul 2 454 (1-2) 90-4. Hudson PJ et al. J Immunol Methods 1999 Dec 10; 231(1-2):177-89 Ardnt MA et al. Blood 1999 Oct 15 94(8): 2562-8; Lu D. et al. J Immunol. Methods 1999 Nov. 19; 230(1-2):159-171; Santos AD et al, Clin Cancer Res 1999 Oct 5 (10 suppl): 31185-31235 Kontermann RE et al. Nat Biotechnol. 1997 Jul; 15(7):629-31; Dolez et al. Protein eng. (2000) Aug 13 (8): 565-74; Adams GP et al. Nucl. Med. Biol (2000) May 27 (4); 339-46; Williams LE et al. Med phys 2000 may 27(5) 988-94; Fitzgerald K. Protein Eng 1997 oct 10(10): 1221-5 and the various references cited therein) as are various methods for identifying internalizing antibodies and creating toxin, radionuclide and cytokine fusions / conjugates (see ao Y et al Bioconj. Chem 1998 Nov-Dec; 9(6): 635-44) for fully exploiting various aspects of the invention herein defined (see for example Becerril B et al. Biochem Biophys Res Comm 1999 Feb 16; 255(2):386-93 see also additional references below. Triabodies and other known multivalent antibodies etc. (see for example Iliades P et al. FEBS Lett. 1997 June 16; 409(3):437-41) etc. could advantageously be employed to provide additional functionalities, as well as variation in avidity etc. for the purposes of variously exploiting the invention herein.

Methods of expressing and identifying new molecules like LYVE-1 are also well known in the art (see WO 98/06839)

Technologies for rendering the multifunctional ligands of the invention less immunogenic (eg such as employed by Biovation) are preferably applied to the multifunctional ligands of the invention.

For recent progress in the treatment of lupus nephritis see Zimmerman R. Annu Rev. Med. 2001; 52:63-78.

With respect to targeting Fas-L see US6068841:Antibodies to Fas-L for treatment of hepatitis.

The invention also contemplates using chemokines and variously targeted antibodies and fragments thereof fused or conjugated to chemokines or other molecules with for example, lymphocyte or other immune cell attractant properties (see for example Sun J. et al. Lymphology 32 (1999) 166-170; and Gerard C. et al. Nature Immunology (2001, Feb.) 2(2): p108; Immunological Reviews 1999 Vol 170 p 5-197) to attract immune cells into target tissues for eventual penetration into the lymphatic vessels for activation, signalling, binding to, inhibition, etc.. For example, for cancer treatment antibodies that bind to angiogenesis markers fused to such type such molecules eg. TNF- α can be advantageously employed optionally in conjunction with various vaccination strategies (including the use of the multi-functional ligands of the present invention) to attract immune cells including, optionally, vaccination-activated tumor targeting lymphocytes to the tumor site. In an indirectly related aspect (having independent applications as well as for combination therapy with a multifunctional ligand, the invention is also directed to an antibody that targets an angiogenesis marker fused/conjugated to a cytokine or antibody (ie a bispecific antibody) which binds to a cytokine, which cytokine augments adhesion of immune cells to blood vessels and method of using same (by administration to a subject), alone, in combination with multifunctional ligands of the invention or with other vaccination strategies to increase immune cell targeting to a solid tumor. In the case of a bispecific antibody it is contemplated that the cytokine binding portion has a relatively low functional affinity to the cytokine so as to compete unfavourably for its binding to its natural receptor.

With reference to modulating binding of leucocytes to endothelial adhesion molecules see for example US Patent No. 6,123,915 and the references therein cited.

It is well known to those in the art to make bispecific antibodies which are adapted to bind two different ligands on the same cell, for example so called antigen-forks as disclosed in USP 5,705,614 (see also Shi T et al. Murine bispecific antibody 1A10 directed to human transferrin receptor and a 42-kDa tumor-associated glycoprotein also Clin Immunol Immunopathol 1996 Feb;78(2):188-95; Amoroso AR et al., Binding characteristics and antitumor properties of 1A10 bispecific antibody recognizing gp40 and human transferrin receptor Cancer Res 1996 Jan 1;56(1):113-20; Ring DB et al., Antigen forks: bispecific reagents that inhibit cell growth by binding selected pairs of tumor antigens, Cancer Immunol Immunother 1994 Jul;39(1):41-8; Lu D et al., Complete inhibition of vascular endothelial growth factor (VEGF) activities with a bifunctional diabody directed against both VEGF kinase receptors, fms-like tyrosine kinase receptor and kinase insert domain-containing receptor. Cancer Res 2001 Oct 1;61(19):7002-8; Schmiedl A, Breitling F, Dubel S. Expression of a bispecific dsFv-dsFv' antibody fragment in Escherichia coli. Protein Eng 2000 Oct;13(10):725-34 see also Park SS, et al., Generation and characterization of a novel tetravalent bispecific antibody that binds to hepatitis B virus surface antigens Mol Immunol 2000 Dec;37(18):1123-30; Kriangkum J et al., Bispecific and bifunctional single chain recombinant antibodies Biomol Eng 2001 Sep;18(2):31-40; USPs 4,474,893, 5,989,830; WO 00/29431).

With respect to antibodies to autoantigens, ADEPT, use of anti-eotaxin antibodies, Deimmunization, antibody-cytokine fusions, ribosome display, xenomouse technology; cutting edge phage display techniques, construction of *human* antibody fragment based phage display libraries, selection of internalizing antibodies by phage-display, cancer targeting antibodies, antibody arrays, plantibodies, design of mutant IGSF domains of CD2, CD58 and TCR; oligopeptide eg. paratope mimetics, diabodies, minibodies, triabodies, tetrabodies and related size/kinetics issues, caspase activatable pro-drugs, delivery of Bismeth-213 via scFv and diabodies, anti-angiogenesis marker strategies, immunoenzyme therapy of cancer (eg. with Rnases) pancreatic antigens like CEA (TAG)-72; and related technologies see the papers and references in Proceedings of IBC's 11th Annual International Conference on Antibody Engineering, State of the Art, Science, Technology and Applications Dec 3-6 2000 La Jolla, CA.

With respect to biology of the lymphatic system having practical application herein see Ikomi, F. *Lymphology* (1999) 32:90-102; Shield JW. *Lymphology* 1999 32: 118-122 and *Lymphology* 33 (2000) 144-147, as well as the references cited therein.

The invention also contemplates control of such migration by inhibition of receptors that mediate such migration (see for example Sun J. et al. *Lymphology* 32 (1999) 166-170) for controlled application of the multifunctional ligands of the invention.

With respect to recent developments with respect to target ligands and/or immunotherapy having application herein see also WO 01/12224, WO 01/14550, WO 01/11059, WO 01/10205, WO 01/00679, WO029445A1: HUMANIZED ANTIBODY SPECIFIC FOR HUMAN 4-1BB AND PHARMACEUTICAL COMPOSITION COMPRISING SAME; WO 01/14885, WO/14564, WO 01/14558, WO 01/14224, WO 01/13945, WO 01/12840, WO 01/12781, WO 01/12674, WO 01/12670, WO 01/12224, WO 01/12646; WO 01/12223, WO 01/12218, WO 01/12217, WO 01/12216, WO 01/12154, WO 01/14557, WO 01/11059, WO 01/10912, WO 01/11040, WO 01/10888, WO 01/10460, WO 01/10205, WO 01/09611, WO 01/09328, WO 01/09186, WO 01/09192, WO 01/08635, WO 01/07481, WO 01/07082, WO 01/07084, WO 01/07081, WO 01/07484, WO 01/07466, Triggering Fc alpha-receptor I (CD89) recruits neutrophils as effector cells for CD20-directed antibody therapy. *J Immunol.* 2000 Nov 15; 165(10):5954-61. CD47 engagement inhibits cytokine production and maturation of human dendritic cells. *J Immunol.* 2000 Feb 15; 164(4):2193-9.

The invention also contemplates that a multifunctional ligand that recognizes an immune cell as a target in virtue of a particular cell marker and will be able to deliver a toxic payload to the cell, for example, in virtue of its second portion comprising such toxic component fused or conjugated thereto. The invention also contemplates attracting or supplying other immune cells or molecules to kill, or otherwise inactivate the target immune cell (eg. lymphocytes eg. by TH cell modulation or CD4 cell modulation or using antibodies including anti-idiotypic antibodies. The invention therefore contemplates that treatment of such immune cells can be accomplished by a combination of different mechanisms or drugs depending on the disease so as to reduce immunosuppression due to immune cell ablation where this is the dominant consideration. Such interactions may require interaction with one or more ligands on the surface of the targeted immune cell, as facilitated via anchoring interactions of varying affinity/avidity/duration. The invention also contemplates using multifunctional ligands comprising or bound to selectins and ICAMs etc. to facilitate such targeting, for example co-administering same in a proportion which is for example 0.01% to 25% of the targeting multifunctional ligand. The relative amounts of the selectin/ICAM etc. (including antibody mimics) bearing multifunctional ligand as compared with the targeting multifunctional ligand can be determined empirically by varying the proportions and assessing any objective indicator of successful targeting in a disease related or purely experimental context. For example successful targeting (eg. antibody binding to eg. CD3, CD28, CD2) using multifunctional ligands of the invention could be monitored by evaluating levels of cytokines normally attributable to such binding (see for example CD8 T cell activation after intravenous administration of CD3 x CD19 bispecific antibody in patients with non-Hodgkin lymphoma. *Cancer Immunol Immunother.* 1995 Jun; 40(6):390-6. Definition of a lamina propria T cell responsive state. Enhanced cytokine responsiveness of T cells stimulated through the CD2 pathway. *J Immunol.* 1995 Jan 15; 154(2):664-75.

With respect to multifunctional ligands that are used to directly or indirectly exert an immunization function, other examples of disease associated peptides that can be presented as immunogens or inhibitor/modulators of immune activity or disease progression in one of the fashions suggested above include, examples as well as technologies referenced in, for example, Knuth A, *Cancer Chemother Pharmacol* (2000); 46 suppl: 546-51; Engelhard VH, *Cancer J Sci Am* 2000 May; 6 Suppl 3: S272-80; Pietersz GA et al, *Cell Mol Life Sci.* 2000 Feb; 57(2): 290-310; Algarra I et al, *Hum Immunol.* 2000 Jan; 61(1): 65-73; Tumour vaccines: a new immunotherapeutic approach in oncology. *Ann Hematol.* 2000 Dec; 79(12):651-9; Human tumor-rejection antigens and peptides from genes to clinical research *Nippon Geka Gakkai Zasshi.* 2000 Sep; 101(9):612-7. Pinilla-Ibarz J, Cathcart K, Scheinberg DA. CML vaccines as a paradigm of the specific immunotherapy of cancer. *Blood Rev.* 2000 Jun; 14(2):111-20).

In order to present an MHC-peptide complex in proximity to a B7 co-stimulatory molecule, the invention contemplates using, in addition to varying amounts (varying from a 50/50 proportion) of adjacent multifunctional ligands (which may be a dAb, diabody etc.) preferably cross-linked by an avidin component, -- as a different strategy -- cross-linking with avidin or the like adjacent arms of a single diabody, triabody or tetrabody etc. which binds to or has been fused or conjugated individually to respective B7 and MHC peptide components (with respect

to recombinant B7 and MHC molecules and fusion proteins thereof including antibody fusions and related technologies see references above and EP 99/97477 WO 99/42597, WO 97 28191, US 6, 197, 302, US6015884 US6140113, US 6,045,796, US 5580756, EP0935607, WO 9806749 WO9803552, EP 1054984, US 5869270, Construction and characterization of bispecific costimulatory molecules containing a minimized CD86 (B7-2) domain and single-chain antibody fragments for tumor targeting; method is useful for cancer therapy Rohrbach F et al., Clin. Cancer Res.; (2000) 6, 11, 4314-22 WO 00/008057 17 Feb 2000; WO 9921572 6 May 1999; WO 9913095 18 Mar 1999; WO 9742329 13 Nov 1997; WO 9720048 5 Jun 1997; WO 9640915 19 Dec 1996; WO 00/023087; EP 610046 10 Aug 1994, USP 6056952 as well as references therein cited).

In a related aspect, the invention similarly contemplates using or more antibodies (optionally biotinylated and cross-linked by an avidin component) that bind to the same or different epitopes on a tumor including, where two such antibodies are used different proportions of MHC and B7 linked (ie fused, conjugated or capable of binding to) antibodies as well as different proportions of different epitope-specific antibodies to optimize the distribution of such cross-linked B7 and MHC peptide complexes for T-cell recognition. In this way any strongly immunogenic peptide may be used in conjunction with suitable vaccination strategies to create a universal cancer antigen. Using a tumor unrelated peptide is advantageous to avoid any tolerization effects resulting from T-cell binding to the MHC-peptide alone and does not preclude immune system recognition of a different epitope or other therapies. In a preferred embodiment, a single multifunctional ligand or pair of multifunctional ligands optionally biotinylated and cross-linked by an avidin (or variants), is used to bind to both the lumen of the lymphatic system and to a tumor cell. (using for example a trispecific antibody with monovalent linkage to both the cancer cell and lymphatic endothelial cell and a third antibody component having respective fusions to one of MHC-peptide and B7 on heavy and light chain, or a trispecific or tetraspecific tetrabody having an antibody component devoted to each of the B7 and MHC linkages). This permits a single molecule to be used for both the immunization within the lymphatic system and the tumor targeted antigen display. However, it will be appreciated that presentation of MHC-peptide complex on a tumor does not necessarily require costimulatory B7 presentation to induce a cytotoxic T cell response which is specific for the peptide and that multiple such presentations, preferably in a cross-linkable fashion may be preferable. Accordingly, strategies herein for costimulatory presentation of MHC-peptide and B7 may be differently applied to a lymphatic endothelial cell surface for immunization purposes and a tumor cell surface (primarily for recognition purposes), for example by using avidin facilitated cross-linking of in the former but not the latter (tumor) context or using different sets of molecules in each case or using modularly reconstructing the tumor cell surface with a bispecific antibody that binds to a separately administered MHC and/or B7 component.

Subject to the latter proviso, in preferred embodiments, the invention contemplates using as separate counterparts 1) separate trispecific Abs, each including for example, one antibody component which binds to each of the respective B7 and MHC molecules which are preferably together, separately administered. Such multifunctional ligands are preferably biotinylated for cross-linking – both between adjacent trispecific Abs and adjacent T-cell stimulatory/co-stimulatory arms; or 2) separate bispecific pairs of Abs each respectively having 1) either a B7 and lymphatic vessel or B7 and tumor binding portion or 2) a MHC peptide complex and a lymphatic vessel or MHC complex and tumor binding, portions which again are preferably cross-linked by an avidin, streptavidin or a variant (ie. using biotinylated antibodies). This latter embodiment permits smaller size antibody molecules to be used for better tumor targeting. Antibody components which recognize the non-T cell interactive portion of the B7 or MHC molecule can be readily generated by phage display, for example in the case of a known peptide specific antibody to an MHC peptide complex (see Chames et al. Proc Natl Acad Sci USA 97, 7969 and Chames et. al. "Affinity Maturation of TCR-Like MHC-peptide specific antibody: peptide specificity is possible over a wide affinity range" Proceedings of IBC Conference on Antibody Engineering Dec. 2000) eg. by first causing binding of the "peptide specific" antibody and then doing the phage display eg. using an array of multiple (eg. repeats of the same antibody) such peptide specific MHC antibodies, applying the MHC peptide complex to effect binding and then performing the phage or ribosome display. Alternatively a TCR (eg cell bound) or analogue/mimotope could be used for the orientation. Similarly antibodies could be generated which in effect do not compete with CD28 or a mimotope thereof to create suitable anti-B7 type antibodies. Anti-B7 antibodies are known in the art. The invention also contemplates that the MHC-peptide binding function may be supplied using a linked superantigen (US 6197299, WO 9601650 25 Jan 1996; Proc. Natl. Acad. Sci. U.S.A.; (1994) 91, 19, 8945-49) in both the tumor and lymphatic system binding sites. Optionally, the tumor antigen or one or both of the antigens are a pan-carcinomic antigen like TAG-72, CEA, H11 (WO 97/44461). The invention also contemplates using one or more phage display libraries to optimize the development of MHC/B7 costimulatory bispecific antibodies, by using cell sized latex spheres coated with an antigen eg. CEA in various surface dispersions (or a cell) and using an array of preferably biotinylated antibodies which recognize the antigen and have a "oppositely located" portion fused, conjugated or capable of binding to one or both of MHC and B7, the library optionally also presenting also variations and combinations of lengths (truncations) of one or more constant regions or for example the CDR2 generated by phage display, depending on the choice of antibody, and with microarray technology, using a signalling means to detect T-cell recognition and evaluating cytotoxicity with for example a Cr51 release assay. (with respect to protein chip or microarray technology see WO 00/63701 references, for example in the Proceedings of IBC's conference on Protein Microarray Technology March 19-21 Santiago California

The invention also contemplates use of recently published antibodies in the context of the invention (see WO 01/19861, WO 01/19990, WO 01/19860, WO 01/19987, WO 01/19990, WO 99/58678, WO 00/59943, WO 01/18014, WO 01/18016, WO 01/18204, WO 01/18042, WO 01/18021, WO 01/18014, WO 01/18046, WO 01/16166, WO 01/15731, WO 01/15728, WO 01/16183, WO 01/16170, WO 01/15732).

The invention is also directed to a method of evaluating dosing, ligand saturation, avidity effects of simultaneous ligand binding on prolonged anchoring and associated benefits (eg. to delay a cancer cell for targeted killing or facilitate transfer of the multifunctional ligand to the targeted cell), cooperative interactions, cross-linking interactions (see *J Immunol* 2001 Mar 1; 166(5):3256-3265; Nippon Rinsho. 1999 Dec; 57 Suppl:428-32; Harefuah. 2000 Jun 15; 138(12):1046-50. Leuk Lymphoma. 1998 Mar; 29(1-2):1-15) and costimulatory interactions by administering to a test subject two different multifunctional ligands of the invention with cooperating second portions.

With respect to the display of functional peptides on an antibody type scaffold see Nuttal SD; et al., *Proteins* (1999) 36: 217-227; see also Skerra A., *J. Mol. Recognition* 2000 July-Aug 13(4): 167-187. The invention also contemplates bispecific multifunctional ligands in which the immune function exerting moiety exerts its function through binding to an immunogenic component or carrier for such component as discussed above, for example an Fc domain fused to a peptide, a heat shock protein (see for example Wang XY, *Immunol Invest* 2000 May 29(2): 131-7 and references cited therein as well as US6168793; US6071956 ; US05981706; US05948646 Methods for preparation of vaccines against cancer comprising heat shock protein-peptide complexes; US05830464 Compositions and methods for the treatment and growth inhibition of cancer using heat shock/stress protein-peptide complexes in combination with adoptive immunotherapy as well as patents, scientific articles and patent applications referenced in these patents; with respect to MHC peptide complexes(see for example WO 99/64597, WO 98/03552, WO 98/06749 and references cited therein).

As described above, the invention also contemplates that the lower affinity ligand binding arm of the aforementioned multifunctional ligand (ie. having a high affinity targeting arm and a lower affinity effector arm) is constituted by a high affinity ligand, for example an high affinity antibody or functional fragment thereof, which binds to a target biological effector (eg. a cytokine, chemokine, growth factor, hormone or other biological response modifier or drug) with high affinity, in a manner which permits the effector to continue to bind to its desired target receptor while bound to the antibody (ie. the antibody binds to a portion of the effector which is not critically involved in the effector binding to its receptor) provided that when bound to the effector the antibody or fragment thereof has, when combined with the effector, a suitably lower affinity for the receptor than the ligand binding arm which functions as the high affinity binder has for its target cell marker. In one embodiment the binding moiety which binds to the biological effector binds to it with higher affinity than the affinity that the effector has for the effector receptor. The invention also contemplates that this binding arm can bind to biological effector in a manner which permits it to bind to one receptor but not a related receptor to which the effector would otherwise bind (see examples below). The invention also contemplates that antibody arrays are used to screen for antibodies which are capable of binding to such biological effectors, while bind in situ to their receptors. The invention also contemplates that such binders, when bound to the biological effector, can be used to test their ability to bind to related receptors, such as those within the same family eg. within the same family of TNF like receptors. With respect to antibody microarrays see for example Cahill DJ. Protein and antibody arrays and their medical applications. *J Immunol Methods*. 2001 Apr;250(1-2):81-91. MacBeath G. Proteomics comes to the surface. *Nat Biotechnol*. 2001 Sep;19(9):828-9. Clewley JP. Recombinant protein arrays. *Commun Dis Public Health*. 2000 Dec;3(4):311-2; Holt LJ, Enever C, de Wildt RM, Tomlinson IM. The use of recombinant antibodies in proteomics. *Curr Opin Biotechnol*. 2000 Oct;11(5):445-9. Walter G, et al. Protein arrays for gene expression and molecular interaction screening. *Curr Opin Microbiol*. 2000 Jun;3(3):298-302. de Wildt RM, Mundy CR, Gorick BD, Tomlinson IM. Antibody arrays for high-throughput screening of antibody-antigen interactions. *Nat Biotechnol*. 2000 Sep;18(9):989-94. Holt LJ, et al. By-passing selection: direct screening for antibody-antigen interactions using protein arrays. *Nucleic Acids Res*. 2000 Aug 1;28(15):E72 and the references cited therein. The term receptor as used herein for greater certainty includes decoy receptors. Examples of decoy receptors include TRAIL decoy receptors (APO-2L), CD44 decoy like receptors (hyaluronan), interleukin receptor like protein (IL-17) (see *J Biol Chem* 2001 Nov 12), CD95-Fc decoy receptor, TRAMP, IL-1 RII receptor, osteoprotegerin (OPG), IL13Ralpha2.

With respect to affinity maturation see for example Coia G, Hudson PJ, Irving RA. Protein affinity maturation in vivo using *E. coli* mutator cells. *J Immunol Methods*. 2001 May 1;251(1-2):187-93. Manivel V, Sahoo NC, Salunke DM, Rao KV. Maturation of an antibody response is governed by modulations in flexibility of the antigen-combining site. *Immunity*. 2000 Nov;13(5):611-20. Boder ET, Midelfort KS, Wittrup KD. Directed evolution of antibody fragments with monovalent femtomolar antigen-binding affinity. *Proc Natl Acad Sci U S A*. 2000 Sep 26;97(20):10701-5. Holler PD, Holman PO, Shusta EV, O'Herrin S, Wittrup KD, Kranz DM. In vitro evolution of a T cell receptor with high affinity for peptide/MHC. *Proc Natl Acad Sci U S A*. 2000 May 9;97(10):5387-92. Daugherty PS, Chen G, Iverson BL, Georgiou G. Quantitative analysis of the effect of the mutation frequency on the affinity maturation of single chain Fv antibodies. *Proc Natl Acad Sci U S A*. 2000 Feb 29;97(5):2029-34. VanAntwerp JJ, Wittrup KD. Fine affinity discrimination by yeast surface display and flow cytometry. *Biotechnol Prog*. 2000 Jan-Feb;16(1):31-7. Adams GP, Schier R. Generating improved single-chain Fv molecules for tumor targeting. *J Immunol Methods*. 1999 Dec 10;231(1-2):249-60. Review. Daugherty PS, Chen G, Olsen MJ, Iverson BL, Georgiou G. Antibody affinity maturation using bacterial surface display. *Protein Eng*. 1998 Sep;11(9):825-32. Wong YW, Kussie PH, Parhami-Seren B, Margolies MN. Modulation of antibody affinity by an engineered amino acid substitution. *J Immunol*. 1995 Apr 1;154(7):3351-8. Balint RF, Larrick JW. Antibody engineering by parsimonious mutagenesis. *Gene*. 1993 Dec 27;137(1):109-18. Schillbach JF, Near RI, Bruccoleri RE, Haber E, Jeffrey PD, Novotny J, Sheriff S, Margolies MN. Modulation of antibody affinity by a non-contact residue. *Protein Sci*. 1993 Feb;2(2):206-14. Chames P, Baty D. Engineering of an anti-steroid antibody: amino acid substitutions change antibody fine specificity from cortisol to estradiol. *Clin Chem Lab Med*. 1998 Jun;36(6):355-9. Kussie PH,

Parhami-Seren B, Wysocki LJ, Margolies MN. A single engineered amino acid substitution changes antibody fine specificity. *J Immunol.* 1994 Jan 1;152(1):146-52, as well as references cited therein.

With respect to generation of high affinity antibodies and affinity maturation of antibodies see also Hanes J. *Nat. Biotechnol.* 2000 Dec; 18(12): 1287-92; references in Hudson PJ *Exp. Opin. Invest. Drugs* (2000) 9(6) 1231-1242; Toran JL et al *Eur. J. Immunol.* 2001 Jan; 31(1) 128-137. Nielson VB et al. *Cancer Res* 2000 Nov 15; 60 (22) 6434-40 Adams Gp, *Journal of Immunological Methods* (1999) 249-260; Chowdhury PS et al (June 1999) *Nature Biotechnology* Vol 17 p. 568

With respect to strategies and recent technologies which have application to the invention see references in Hudson PJ *Exp. Opin. Invest. Drugs* (2000) 9(6) 1231-1242 and in particular references relating to strategies to achieve multivalency and multispecificity; recruitment of viruses, ADEPT, photoactivation of cytotoxic radionuclides; surface receptor cross-linking; (see also *Eur. J. Immunol* 2000 30(10) 3006), use of anti-B antibodies; immunocytokines (see also Lode HN *Immunol. Res.* 2000, 21 (2-3) 279-88; Gillies SD *Cancer Research* 59 2159-2166 May 1999; Lode HN et al *Drugs of Today* 2000 36(5) 3221-336).

With respect to practical size limitations and pharmacokinetics of various types of antibodies and fragments see Colcher D. et al. *G.J. Nucl. Med* (1999) 43: 132-139; Wu AM et al *G.J. Nucl. Med* 2000 Sep; 44(3): 268:83; Williams LE et al *Med Phys* 2000 May 27(5): 988-94 Ikomi F *Immunology* 32 (1999) 90-102.

With respect to the construction of diabodies see also Takemura SI et al. *Protein Eng.* 2000 Aug;13(8) 583-8; *Biomol. Eng.* 2001 Sept;18(2):31-40.

With respect to anti-cancer antibodies see also 6,180,357.

With respect to technologies to produce multivalent and/or multispecific antibodies see also USP 6, 172, 197; WO 92/01047; WO 93/11161; WO 94/07921; WO 94/13804; Helfrich W. et al. *Journal of Immunological Methods* 237 (2000) 131-145. Proceedings of 11th IBC Conference on Antibody Engineering; WO 01/85795

Monoclonal antibodies may be routinely produced as taught by Harlow, E. and D. Lane, (1988) *ANTIBODIES: A Laboratory Manual*, Cold Spring Harbor Laboratory, Cold Spring Harbor N.Y. Humanized antibodies may be routinely produced as taught, for example, by U.S. Pat. No. 5,585,089 and U.S. Pat. No. 5,530,101. Techniques for engineering antibodies are well known and described in Winter and Millstein (1991) *Nature* 349:293, and Larrich and Fry (1991) *Hum. Antibod. and Hybridomas* 2:17. One having ordinary skill in the art may use well known techniques and starting materials and/or commercially available expression vectors and systems that are readily available and known in the art. See e.g., Sambrook et al., *Molecular Cloning a Laboratory Manual*, Second Ed. Cold Spring Harbor Press (1989).

Examples of radionuclides useful as toxins in radiation therapy are well known. Some examples are referred to below. Auger emitters may be preferred for internalizing antibodies. As suggested above, the term antibody is used interchangeably with antibody fragment and antigen binding fragment and includes a whole antibody; antibody fragment a portion of an antibody such as a scFv F(ab')₂ F(ab)₂ Fab', Fab, dAb, microbodies (WO0029004A1: SMALL FUNCTIONAL UNITS OF ANTIBODY HEAVY CHAIN VARIABLE REGIONS) or the like or multivalent such fragments, including those itemized or referenced herein. Regardless of structure, an antibody fragment can be made to bind with the same antigen that is recognized by the intact antibody. More particularly, in addition to fragments formed by enzymatic digestion of an intact Ab the term antibody or "antibody fragment" unless otherwise stated also includes any synthetic or genetically engineered protein that acts like an antibody by binding to a specific antigen to form a complex including/as applicable, cysteine noose peptides and minimal recognition units consisting of the amino acid residues that mimic the hypervariable region. Although fully human antibodies, for example, antibodies generated via human-human hybridomas or through phage display using human antibody based libraries, are preferred, the invention does not preclude other strategies to avoid a HAMA type response.

A chimeric antibody is a recombinant protein that contains the variable domains and complementary determining regions derived from, for example, a rodent antibody, while the remainder of the antibody molecule is derived from a human antibody.

With respect to stability engineering of scFv fragments for enhanced multifunctional ligands comprising scFvs see *J Mol Biol* 2001 Feb 2; 305(5):989-1010.

Humanized antibodies are recombinant proteins in which murine LDR's of a monoclonal antibody have been

transferred from heavy and light variable chains of the murine immunoglobulin into a human variable domain.

The term therapeutic agent as used herein, is a molecule or atom which is conjugated etc. to an antibody moiety to produce combination including a conjugate which is useful for therapy. Examples of therapeutic agents include drugs, toxins, immunomodulators, chelators, boron compounds, photoactive agents or dyes, and radioisotopes.

The term "a naked antibody" may be used to refer specifically to an entire antibody, as opposed to an antibody fragment, which is not conjugated with a therapeutic agent. Naked antibodies include both polyclonal and monoclonal antibodies, as well as certain recombinant antibodies, such as chimeric and humanized antibodies.

The term immunoconjugate may be used to refer a conjugate of an antibody component with a therapeutic agent.

As used herein, the term antibody fusion protein refers to a recombinant molecule that comprises an antibody component and a second functional component for example a therapeutic agent. Examples of therapeutic agents suitable for such fusion proteins include immunomodulators ("antibody-immunomodulator fusion protein") and toxins ("antibody-toxin fusion protein").

Production of Antigen - Specific Monoclonal Antibodies, Rodent monoclonal antibodies to antigen can be obtained by methods known to those skilled in the art. See generally, for example, Kohler and Milstein, *Nature* 256:495 (1975), and Coligan et al. (eds.), *Current Protocols in Immunology*, Vol. 1, pages 2.5.1-2.6.7 (John Wiley & Sons 1991) ["Coligan"]. Briefly, monoclonal antibodies can be obtained by injecting mice with a composition comprising the antigen in a question (Ag), verifying the presence of antibody production by removing a serum sample, removing the spleen to obtain B-lymphocytes, fusing the B-lymphocytes with myeloma cells to produce hybridomas, cloning the hybridomas, selecting positive clones which produce anti-Ag antibodies, culturing the clones that produce antibodies to the antigen, and isolating the antibodies from the hybridoma cultures. Transgenic mice having for example engineered immune systems to create human antibodies such those used by Medarex and Abgenix are also contemplated for use herein to create suitably targeted antibodies.

Monoclonal antibodies can be isolated and purified from hybridoma cultures by a variety of well-established techniques. Such isolation techniques include affinity chromatography with Protein-A Sepharose, size-exclusion chromatography, and ion-exchange chromatography. See, for example, Coligan at pages 2.7.1-2.7.12 and pages 2.9.1-2.9.3. Also, see Baines et al., "Purification of Immunoglobulin G (IgG) ," in *Methods in Molecular Biology*, Vol. 10, pages 79-104 (The Humana Press, Inc. 1992).

With respect to relevant molecular biology techniques See also, for example, Ausubel et al., (eds.), *CURRENT PROTOCOLS IN MOLECULAR BIOLOGY*, pages 8.2.8 to 8.2.13 (1990) ["Ausubel"]. Also, see Wosnick et al., *Gene* 60:115 (1987); and Ausubel et al. (eds.), *Short Protocols in Molecular Biology*, 3rd Edition, pages 8--8 to 8-9 (John Wiley & Sons, Inc. 1995). Established techniques using the polymerase chain reaction provide the ability to synthesize genes as large as 1.8 kilobases in length. Adang et al., *Plant Molec. Biol.* 21:1131 (1993) Bambot et al., *PCR Methods and Applications* 2:266 (1993); Dillon et al., "Use of the Polymerase Chain Reaction for the Rapid Construction of Synthetic Genes," in *Methods in Molecular Biology*, Vol. 15: *PCR Protocols: Current Methods and Applications*, White (ed.), pages 263-268, (Humana Press, Inc. 1993).

Techniques for constructing chimeric antibodies are well-known to those of skill in the art. As an example, Leung et al., *Hybridoma* 13:469 (1994)

In yet another embodiment, an antibody of the present invention is a "humanized" monoclonal antibody. That is, mouse complementarity determining regions are transferred from heavy and light variable chains of the mouse immunoglobulin into a human variable domain, followed by the replacement of some human residues in the framework regions of their murine counterparts. Humanized monoclonal antibodies in accordance with this invention are suitable for use in therapeutic methods. General techniques for cloning murine immunoglobulin variable domains are described, for example, by the publication of Orlandi et al., *Proc. Nat'l Acad. Sci. USA* 86: 3833 (1989). Techniques for producing humanized monoclonal antibodies are described, for example, by Jones et al., *Nature* 321:522 (1986), Riechmann et al., *Nature* 332:323 (1988), Verhoeyen et al., *Science* 239:1534 (1988), Carter et al., *Proc. Nat'l Acad. Sci. USA* 89:4285 (1992), Sandhu, *Crit. Rev. Biotech.* 12:437 (1992), and Singer et al., *J. Immun.* 150:2844 (1993). The publication of Leung et al., *Mol. Immunol.* 32:1413 (1995), describes the construction of humanized LL2 antibody.

In a preferred embodiment of the invention the multifunctional ligand has a unique portion which differentiates it from other antibodies and preferably other co-administered different multifunctional ligands, which unique portion, allows the multifunctional ligand to be efficiently segregated on an immunoaffinity column. In the case of differentiating a single multifunctional ligand an anti-idiotypic (assuming the first portion consists of an antibody) or other antibody uniquely recognizing the first portion could be employed. Modifying a portion of the first portion, for example in the case where it is antibody component and creating a antibody thereto, for example by phage display, is a matter of routine skill in the arts of antibody engineering and phage display.

In another embodiment, an antibody of the present invention is a human monoclonal antibody. Such antibodies are obtained from transgenic mice that have been "engineered" to produce specific human antibodies in response to antigenic challenge. In this technique, elements of the human heavy and light chain locus are introduced into strains

of mice derived from embryonic stem cell lines that contain targeted disruptions of the endogenous heavy chain and light chain loci. The transgenic mice can synthesize human antibodies specific for human antigens, and the mice can be used to produce human antibody-secreting hybridomas. Methods for obtaining human antibodies from transgenic mice are described by Green et al., *Nature Genet.* 7:13 (1994), Lonberg et al., *Nature* 368:856 (1994), and Taylor et al., *Int. Immun.* 6:579 (1994).

Examples of Production of Antibody Fragments

Antibody fragments can be prepared, for example, by proteolytic hydrolysis of an antibody or by expression in *E. coli* of the DNA coding for the fragment.

Antibody fragments can be obtained by pepsin or papain digestion of whole antibodies by conventional methods. For example, antibody fragments can be produced by enzymatic cleavage of antibodies with pepsin to provide a 5 S fragment denoted F(ab')₂. This fragment can be further cleaved using a thiol reducing agent, and optionally a blocking group for the sulfhydryl groups resulting from cleavage of disulfide linkages, to produce 3.5 S Fab' monovalent fragments. Alternatively, an enzymatic cleavage using pepsin produces two monovalent Fab fragments and an Fc fragment directly. These methods are described, for example, by Goldenberg, U.S. Pat. Nos. 4,036,945 and 4,331,647 and references contained therein. Also, see Nisonoff et al., *Arch Biochem. Biophys.* 89:230 (1960); Porter, *Biochem. J.* 73:119 (1959), Edelman et al., in *Methods in Enzymology* Vol 1, page 422 (Academic Press 1967), and Coligan at pages 2.8.1-2.8.10 and 2.10.-2.10.4.

Other methods of cleaving antibodies, such as separation of heavy chains to form monovalent light-heavy chain fragments, further cleavage of fragments, or other enzymatic, chemical or genetic techniques may also be used, so long as the fragments bind to the antigen that is recognized by the intact antibody.

For example, Fv fragments comprise an association of V_H and V_L chains. This association can be noncovalent, as described in Inbar et al., *Proc. Nat'l Acad. Sci. USA* 69:2659 (1972). Alternatively, the variable chains can be linked by an intermolecular disulfide bond or cross-linked by chemicals such as glutaraldehyde. See, for example, Sandhu, *supra*.

Preferably, the Fv fragments comprise V_H and V_L chains which are connected by a peptide linker. These single-chain antigen binding proteins (scFv) are prepared by constructing a structural gene comprising DNA sequences encoding the V_H and V_L domains which are connected by an oligonucleotide. The structural gene is inserted into an expression vector which is subsequently introduced into a host cell, such as *E. coli*. The recombinant host cells synthesize a single polypeptide chain with a linker peptide bridging the two V domains. Methods for producing scFvs are described, for example, by Whitlow et al., *Methods: A Companion to Methods in Enzymology* 2:97 (1991). Also see Bird et al., *Science* 242:423 (1988), Ladner et al., U.S. Pat. No. 4,946,778, Pack et al., *Bio/Technology* 11:1271 (1993), and Sandhu, *supra*.

Another form of an antibody fragment is a peptide coding for a single complementarity-determining region (CDR). CDR peptides ("minimal recognition units") can be obtained by constructing genes encoding the CDR of an antibody of interest. Such genes are prepared, for example, by using the polymerase chain reaction to synthesize the variable region from RNA of antibody-producing cells. See, for example, Larrick et al., *Methods: A Companion to Methods in Enzymology* 2:106 (1991); Courtenay-Luck, "Genetic Manipulation of Monoclonal Antibodies," in *Monoclonal Antibodies: Production, Engineering and Clinical Application*, Ritter et al. (eds.), pages 166-179 (Cambridge University Press 1995); and Ward et al., "Genetic Manipulation and Expression of Antibodies," in *Monoclonal Antibodies: Principles and Applications*, Birch et al., (eds.), pages 137-185 (Wiley-Liss, Inc. 1995).

5. Preparation of Immunoconjugates

The present invention contemplates immunoconjugates to assess and effect treatment of various disease conditions. Such immunoconjugates can be prepared by indirectly conjugating a therapeutic agent to an antibody component. For example, general techniques are described in Shih et al., *Int. J. Cancer* 41:832-839 (1988); Shih et al., *Int. J. Cancer* 46:1101-1106 (1990); and Shih et al., U.S. Pat. No. 5,057,313. The general method involves reacting an antibody component having an oxidized carbohydrate portion with a carrier polymer that has at least one free amine function and that is loaded with a plurality of drug, toxin, chelator, boron addends, or other therapeutic agent. This reaction results in an initial Schiff base (imine) linkage, which can be stabilized by reduction to a secondary amine to form the final conjugate.

The carrier polymer is preferably an aminodextran or polypeptide of at least 50 amino acid residues, although other substantially equivalent polymer carriers can also be used. Preferably, the final immunoconjugate is soluble in an aqueous solution, such as mammalian serum, for ease of administration and effective targeting for use in therapy. Thus, solubilizing functions on the carrier polymer will enhance the serum solubility of the final immunoconjugate. In particular, an aminodextran will be preferred.

The process for preparing an immunoconjugate with an aminodextran carrier typically begins with a dextran polymer, advantageously a dextran of average molecular weight of about 10,000-100,000. The dextran is reacted with an oxidizing agent to effect a controlled oxidation of a portion of its carbohydrate rings to generate aldehyde groups. The oxidation is conveniently effected with glycolytic chemical reagents such as NaIO₄, according to

conventional procedures.

The oxidized dextran is then reacted with a polyamine, preferably a diamine, and more preferably, a mono- or polyhydroxy diamine. Suitable amines include ethylene diamine, propylene diamine, or other like polymethylene diamines, diethylene triamine or like polyamines, 1,3-diamino-2-hydroxypropane, or other like hydroxylated diamines or polyamines, and the like. An excess of the amine relative to the aldehyde groups of the dextran is used to insure substantially complete conversion of the aldehyde functions to Schiff base groups.

A reducing agent, such as NaBH_4 , NaBH_3CN or the like, is used to effect reductive stabilization of the resultant Schiff base intermediate. The resultant adduct can be purified by passage through a conventional sizing column to remove cross-linked dextrans.

Other conventional methods of derivatizing a dextran to introduce amine functions can also be used, e.g., reaction with cyanogen bromide, followed by reaction with a diamine.

The aminodextran is then reacted with a derivative of the particular drug, toxin, chelator, immunomodulator, boron addend, or other therapeutic agent to be loaded, in an activated form, preferably, a carboxyl-activated derivative, prepared by conventional means, e.g., using dicyclohexylcarbodiimide (DCC) or a water soluble variant thereof, to form an intermediate adduct.

Alternatively, polypeptide toxins such as pokeweed antiviral protein or ricin A-chain, and the like, can be coupled to aminodextran by glutaraldehyde condensation or by reaction of activated carboxyl groups on the protein with amines on the aminodextran.

Chelators for radiometals or magnetic resonance enhancers are well-known in the art. Typical are derivatives of ethylenediaminetetraacetic acid (EDTA) and diethylenetriaminepentaacetic acid (DTPA). These chelators typically have groups on the side chain by which the chelator can be attached to a carrier. Such groups include, e.g., benzylisothiocyanate, by which the DTPA or EDTA can be coupled to the amine group of a carrier. Alternatively, carboxyl groups or amine groups on a chelator can be coupled to a carrier by activation or prior derivatization and then coupling, all by well-known means.

Boron addends, such as carboranes, can be attached to antibody components by conventional methods. For example, carboranes can be prepared with carboxyl functions on pendant side chains, as is well known in the art. Attachment of such carboranes to a carrier, e.g., aminodextran, can be achieved by activation of the carboxyl groups of the carboranes and condensation with amines on the carrier to produce an intermediate conjugate. Such intermediate conjugates are then attached to antibody components to produce therapeutically useful immunoconjugates, as described below.

A polypeptide carrier can be used instead of aminodextran, but the polypeptide carrier must have at least 50 amino acid residues in the chain, preferably 100-5000 amino acid residues. At least some of the amino acids should be lysine residues or glutamate or aspartate residues. The pendant amines of lysine residues and pendant carboxylates of glutamine and aspartate are convenient for attaching a drug, toxin, immunomodulator, chelator, boron addend or other therapeutic agent. Examples of suitable polypeptide carriers include polylysine, polyglutamic acid, polyaspartic acid, copolymers thereof, and mixed polymers of these amino acids and others, e.g., serines, to confer desirable solubility properties on the resultant loaded carrier and immunoconjugate.

Conjugation of the intermediate conjugate with the antibody component is effected by oxidizing the carbohydrate portion of the antibody component and reacting the resulting aldehyde (and ketone) carbonyls with amine groups remaining on the carrier after loading with a drug, toxin, chelator, immunomodulator, boron addend, or other therapeutic agent. Alternatively, an intermediate conjugate can be attached to an oxidized antibody component via amine groups that have been introduced in the intermediate conjugate after loading with the therapeutic agent. Oxidation is conveniently effected either chemically, e.g., with NaIO_4 or other glycolytic reagent, or enzymatically, e.g., with neuraminidase and galactose oxidase. In the case of an aminodextran carrier, not all of the amines of the aminodextran are typically used for loading a therapeutic agent. The remaining amines of aminodextran condense with the oxidized antibody component to form Schiff base adducts, which are then reductively stabilized, normally with a borohydride reducing agent.

Analogous procedures are used to produce other immunoconjugates according to the invention. Loaded polypeptide carriers preferably have free lysine residues remaining for condensation with the oxidized carbohydrate portion of an antibody component. Carboxyls on the polypeptide carrier can, if necessary, be converted to amines by, e.g., activation with DCC and reaction with an excess of a diamine.

The final immunoconjugate is purified using conventional techniques, such as sizing chromatography on Sephacryl S-300.

Alternatively, immunoconjugates can be prepared by directly conjugating an antibody component with a therapeutic agent. The general procedure is analogous to the indirect method of conjugation except that a therapeutic agent is directly attached to an oxidized antibody component.

For application to linking MHC I/II peptide/B7 molecules to a latex which has previously conjugated to biotin, for avidin assisted linking to a multifunctional ligand, it will be appreciated that biotin can be conjugated to a part of a latex sphere which is then linked to MHC peptide and B7 molecules by placing the spheres in a confluent layer or in the spheres in a microwells such that only part of the sphere is exposed for conjugation and then coating the spheres onto avidin coated plates for the B7 and MHC linkage.

It will be appreciated that other therapeutic agents can be substituted for the chelators described herein. Those of skill in the art will be able to devise conjugation schemes without undue experimentation.

As a further illustration, a therapeutic agent can be attached at the hinge region of a reduced antibody component via disulfide bond formation. For example, the tetanus toxoid peptides can be constructed with a single cysteine residue that is used to attach the peptide to an antibody component. As an alternative, such peptides can be attached to the antibody component using a heterobifunctional cross-linker, such as N-succinyl 3-(2-pyridyldithio)propionate (SPDP). Yu et al., *Int. J. Cancer* 56:244 (1994). General techniques for such conjugation are well-known in the art. See, for example, Wong, *CHEMISTRY OF PROTEIN CONJUGATION AND CROSS-LINKING* (CRC Press 1991); Upeslakis et al., "Modification of Antibodies by Chemical Methods," in *MONOCLONAL ANTIBODIES: PRINCIPLES AND APPLICATIONS*, Birch et al. (eds.), pages 187-230 (Wiley-Liss, Inc. 1995); Price, "Production and Characterization of Synthetic Peptide-Derived Antibodies," in *MONOCLONAL ANTIBODIES: PRODUCTION, ENGINEERING AND CLINICAL APPLICATION*, Ritter et al. (eds.), pages 60-84 (Cambridge University Press 1995).

As described above, carbohydrate moieties in the Fc region of an antibody can be used to conjugate a therapeutic agent. However, the Fc region is absent if an antibody fragment is used as the antibody component of the immunoconjugate. Nevertheless, it is possible to introduce a carbohydrate moiety into the light chain variable region of an antibody or antibody fragment. See, for example, Leung et al., *J. Immunol.* 154:5919 (1995); Hansen et al., U.S. Pat. No. 5,443,953 (1995). The engineered carbohydrate moiety is then used to attach a therapeutic agent.

In addition, those of skill in the art will recognize numerous possible variations of the conjugation methods. For example, the carbohydrate moiety can be used to attach polyethyleneglycol in order to extend the half-life of an intact antibody, or antigen-binding fragment thereof, in blood, lymph, or other extracellular fluids. Moreover, it is possible to construct a "divalent immunoconjugate" by attaching therapeutic agents to a carbohydrate moiety and to a free sulfhydryl group. Such a free sulfhydryl group may be located in the hinge region of the antibody component.

Methods for determining the binding specificity of an antibody are well-known to those of skill in the art. General methods are provided, for example, by Mole, "Epitope Mapping," in *METHODS IN MOLECULAR BIOLOGY, VOLUME 10: IMMUNOCHEMICAL PROTOCOLS*, Manson (ed.), pages 105-116 (The Humana Press, Inc. 1992). More specifically, competitive blocking assays for example to determine CD22 epitope specificity are described by Stein et al., *Cancer Immunol. Immunother.* 37:293 (1993), and by Tedder et al., U.S. Pat. No. 5,484,892 (1996).

In another aspect the invention is directed to a bispecific ligand, preferably a bispecific antibody, comprising at least a first ligand, preferably an antibody component, which binds specifically to a first cell surface associated ligand and at least a second ligand, preferably a second antibody component which binds specifically to a second cell surface associated ligand on the same cell, and wherein the functional affinity of at least one and preferably both of said antibody components is selected so as to substantially limit functional binding unless both of said first and second antibody components are substantially contemporaneously bound to said cell. It is known to provide bifunctional ligands wherein functional binding, for example, to accomplish signal transduction, is predicated on both ligands being bound or cross-linking. However this effect is not contemplated to be predicated on differentially controlling the functional affinity of the respective ligands. According to a broad aspect of this invention (in which inclusion of a ligand which binds to a lymphatic vessel associated marker is optional), the invention excludes known such bispecific ligands which inherently have a suitable differential functional affinity. Such bispecific ligand are mentioned herein. By controlling the affinity of at least one of said ligands, for example where the functional affinity of one said ligands is substantially less than that of the other ligand the invention contemplates that a substantially greater percentage of the administered dose of the bispecific ligand will affect cells in which only both ligands are present, and/or that a reduced percentage of the dose administered will functionally bind to the cells in virtue only of the reduced functional affinity ligand. The invention also contemplates that functional affinity of one ligand is greatly increased to establish the functional affinity differential and that the functional affinity of both ligands is reduced relative to that of a standard, for example relative to that of a comparable ligands in hand or known in the art or identified by phage display, ribosome display or other comparable techniques using a single such ligand. The invention also contemplates that a microarray (or library) of bispecific ligands in which for example, the bispecific ligand is "tethered" (ie. immobilized) directly or indirectly in virtue of one or more amino acid residues which are positioned within the molecule to preferably minimally interfere with any binding, and in which the signal (eg its intensity) associated with a single ligand binding interaction can be differentiated from a two or more ligand interactions, for example cell surface binding (alternatively the ligands or cell may be immobilized) and that ribosome and phage display could be adapted to bispecific single domain antibodies constituting a single chain (see references herein) by elongating the end of the chain from which the molecule is tethered. The invention contemplates that the affinity of one such ligand may be fixed and that the variability in members of the library lies in the permutations of certain key residues to which binding is attributable which can readily be identified by persons skilled in the art. The invention also contemplates assessing single ligand binding capability of successful

bi-ligand binders for example by blocking the other (non-assessed at that time) ligand (eg. with correlative ligand or a mimotope thereof) and for example determining limited or non-existent such binding to as well as using inclined ligand testing surfaces for washing over the correlative ligand, for example of defined surface area, including preferably defined lengths and widths and concentrations / distributions / amounts of the bound ligand, where the degree of incline is selected to roughly simulate the micro-environment of the comparable in vivo target, be it a stationary cell with a roughly defined average shear force of bathing fluids eg. within a tumor or in the lymphatic system, or a mobile cell within a vein, artery, or lymphatic vessel, including those of different sizes. The invention is also directed to a method of generating a target ligand or improving the target specificity of any ligand by using a population of variants of that ligand within a micro-environment simulated microarray system in which the at least one of the following factors is simulated: concentration or amount or distribution of correlative ligand, shear force and shape using length and width parameters to simulate intraluminal diameter and length. The invention also contemplates in the case of a multifunctional ligand or in the case of a bispecific or multispecific ligand (as herein described) that the affinity of its component binding ligands may be selected for venous or arterial targeting or to accommodate lymphatic system targeting or targeting within or through tissues or combinations of the aforementioned eg. median, average or or weighted compromises to improve desired targeting. In a preferred embodiment the first ligand is selected on the basis of its ability to at least partially discriminate between a target population of cells (eg. a ligand that is "associated" with a target population of cells) and a non-target population of cells (in one embodiment it is selected so as to have no other effect other than binding for targeting purposes) and the second ligand is selected for its ability to modulate the activity of the targeted cell, optionally in virtue of binding alone eg. without delivering a payload (the term modulate referring broadly to any desired effect on the cell or its functionality) In this case the functional affinity for the ligand which is targeted for modulating the activity of the cell is selected so as to reduce the likelihood of binding unless binding has first or contemporaneously occurred to the first ligand targeted for selectivity (eg. the second ligand would have monovalent as opposed to divalent binding to the ligand required for selectivity and/or from 0.20 to 10^{-9} fold reduction in affinity (for example as measured by Biacore) relative to the binding affinity for the first ligand, preferably a greater than 20% reduction in affinity, preferably a greater than 20% reduction in affinity, preferably a greater than 100% reduction in affinity, preferably a greater than 200% reduction in affinity, preferably a greater than 300% reduction in affinity, preferably a greater than 400% reduction in affinity, preferably a greater than 500% reduction in affinity, preferably a greater than 600% reduction in affinity, preferably a greater than 700% reduction in affinity, preferably a greater than 800% reduction in affinity, preferably a greater than 900% reduction in affinity, preferably a greater than 1000% reduction in affinity, preferably a greater than 2000% reduction in affinity, preferably a greater than 3000% reduction in affinity, preferably a greater than 4000% reduction in affinity, preferably a greater than 5000% reduction in affinity, preferably a greater than 6000% reduction in affinity, preferably a greater than 7000% reduction in affinity, preferably a greater than 8000% reduction in affinity, preferably a greater than 9000% reduction in affinity, preferably a greater than 10000% reduction in affinity, preferably a greater than 20000% reduction in affinity, preferably a greater than 30000% reduction in affinity, preferably a greater than 40000% reduction in affinity, preferably a greater than 50000% reduction in affinity, preferably a greater than 60000% reduction in affinity, preferably a greater than 70000% reduction in affinity, preferably a greater than 80000% reduction in affinity, preferably a greater than 90000% reduction in affinity, preferably a greater than 100000% reduction in affinity, preferably a greater than 200000% reduction in affinity, preferably a greater than 300000% reduction in affinity, preferably a greater than 400000% reduction in affinity, preferably a greater than 500000% reduction in affinity, preferably a greater than 600000% reduction in affinity, preferably a greater than 700000% reduction in affinity, preferably a greater than 800000% reduction in affinity, preferably a greater than 900000% reduction in affinity, preferably a greater than 1000000% reduction in affinity, preferably a greater than 2000000% reduction in affinity, preferably a greater than 3000000% reduction in affinity, preferably a greater than 4000000% reduction in affinity, preferably a greater than 5000000% reduction in affinity, preferably a greater than 6000000% reduction in affinity, preferably a greater than 7000000% reduction in affinity, preferably a greater than 8000000% reduction in affinity, preferably a greater than 9000000% reduction in affinity, preferably a greater than 10000000% reduction in affinity, preferably a greater than 20000000% reduction in affinity, preferably a greater than 30000000% reduction in affinity, preferably a greater than 40,000,000% reduction in affinity, preferably a greater than 50000000% reduction in affinity, preferably a greater than 60000000% reduction in affinity, preferably a greater than 70000000% reduction in affinity, preferably a greater than 80000000% reduction in affinity, preferably a greater than 90000000% reduction in affinity, preferably a greater than 100,000,000% reduction in affinity, preferably a reduction in affinity of between one and two orders of magnitude, preferably a reduction in affinity of between two and three orders of magnitude, preferably a reduction in affinity of between three and four orders of magnitude, preferably a reduction in affinity of between four and five orders of magnitude, preferably a reduction in affinity of between five and six orders of magnitude, preferably a reduction in affinity of between six and seven orders of magnitude, preferably a reduction in affinity of between seven and eight orders of magnitude, preferably a reduction in affinity of between eight and nine orders of magnitude, preferably a reduction in affinity of between nine and ten orders of magnitude. It will be appreciated that a suitable reduction in affinity, if any, will depend on the valency of the respective first and second ligands and the selected affinity of the first ligand, which for example may have been augmented. The invention also contemplates a trispecific (and triavalent) ligand in which two ligands differently define its specificity to reduce the likelihood of an undesired effect attributable to the function exerting moiety binding alone. In terms of the physical constitution of a ligand having a trispecific binding capability, the invention contemplates linking three monovalent dabs, MRUs or the like or mixed combinations thereof or two bivalent dabs, MRUs or the like or mixed combinations thereof (see WO 99/42077, US 6174691, WO0029004, Camel single-domain antibodies as modular building units in J Biol Chem. 2000 Oct 25, & Mulligan-Kehoe U.S. patents including US 5702892, US 5824520; see also US 6040136) (in the latter case optionally one or both may be bispecific and linked by well known methods in the art (see WO 99/42077,

Celltech's TFM, leucine zippers, US 5,910,573, US5892020, EP 0654085B, see also EP 0318554B). The term functional binding is used to refer to binding which yields the desired effect, for example a therapeutic effect on a target cell population attributable to the binding to one or both ligands. Using the previous example, one ligand, eg. the first ligand, may be used to target activated immune cells, and the second ligand may be different and may upon being bound to, for example result in inactivation, anergy, apoptosis or reduced capacity for endothelial adhesion of the immune cell. In this case, the invention contemplates that the functional affinity of the antibody component which binds to the second ligand is selected such that binding is unlikely to occur without binding to the specificity dictating ligand, for example the ratio of targeted relative non-targeted cells affected by the dose administered is approximately 1.10 to 1, preferably approximately 1.15 to 1, more preferably approximately 1.20 to 1, more preferably approximately 1.25 to 1, more preferably approximately 1.30 to 1, more preferably approximately 1.35 to 1, more preferably approximately 1.40 to 1, more preferably approximately 1.45 to 1, more preferably approximately 1.50 to 1, more preferably approximately 1.55 to 1, more preferably approximately 1.60 to 1, more preferably approximately 1.65 to 1, more preferably approximately 1.70 to 1, more preferably approximately 1.75 to 1, more preferably approximately 1.80 to 1, more preferably approximately 1.85 to 1, more preferably approximately 1.90 to 1, more preferably approximately 1.95 to 1, more preferably approximately 2 to 1, more preferably greater than 2 to 1, more preferably approximately greater than 3 to 1, more preferably approximately greater than 4 to 1, more preferably greater than 5 to 1, more preferably greater than 6 to 1, more preferably greater than 7 to 1, more preferably greater than 8 to 1, more preferably greater than 9 to 1, more preferably greater than 10 to 1, more preferably greater than 20 to 1, more preferably greater than 30 to 1, more preferably greater than 40 to 1, more preferably greater than 50 to 1, more preferably greater than 60 to 1, more preferably greater than 70 to 1, more preferably greater than 80 to 1, more preferably greater than 90 to 1, more preferably greater than 100 to 1, more preferably greater than 500 to 1, more preferably greater than 1000 to 1, more preferably greater than 10,000 to 1, more preferably greater than 100,000 to 1, more preferably greater than 500,000 to 1 more preferably greater than 1,000,000 to 1.

It will be appreciated by persons skilled in the art that the foregoing aspects of the invention apply to a variety of different combinations of immune function or other therapeutic function exerting ligands and specificity dictating ligands including those involved in immune signaling, stimulatory, co-stimulatory, inhibitory, adhesion or other interactions, including without limitation, cytokine receptors, ligands associated with immune cell adhesion, ligands to which binding results in stimulation, activation, apoptosis, anergy or costimulation, or ligands which differentiate between different populations or subpopulations or immune cells (see eg. US 6135941, WO 00/63251, WO 00/61132, US 6120767), including sub-populations of B cells and T cells (see for example US 6197524) activated versus non-activated lymphocytes, diseased or disease-causing cells versus non-diseased / disease causing lymphocytes (see for example WO 01/13945A1, US 6132980,) and specific immune cell clones for example those having specific Ig type and MHC-peptide type ligands / and correlative ligands. Examples of such ligands include CCR5, CTLA-4, LFA-1, LFA-3, ICAMs eg. ICAM-1, CD2, CD3, CD4 (eg see US 6,136,310), CD18, CD22, CD40, CD44; CD80, CD86, CD134 and CD154, to name only a few (see also US6087475: PF4A receptor) (see also Glennie MJ et al. Clinical Trial of Antibody Therapy. Immunology Today Aug 2000, Vol. 21 (no. 8) p.406).

The invention also contemplates that the therapeutic function or immune function effecting ligand is also a specificity imparting ligand, which in the case of for example, an antigen presenting cell may be an antibody which recognizes and binds to a specific MHC peptide complex, as is established in the art (see pertinent Chames et al. references herein, see also WO 97/02342, Direct selection of a human antibody fragment directed against the tumor T-cell epitope HLA-A1-MAGE-A1 from a nonimmunized phage-Fab library. Proc Natl Acad Sci U S A. 2000 Jul 5; 97(14):7969-74). In this case it will be appreciated that the APC targeting ligand assist the particular MHC peptide binding antibody to bind to its target.

See also WO 97/07819 which is hereby disclaimed with respect to all relevant aspects of the invention herein insofar as inherently disclosed therein. See also US 5,770,403 with respect to antibodies which bind to cytokines.

Depending on the mode of action of the particular immunotherapeutic, functional binding may for example simply refer to a significantly reduced percentage of the total administered dose which is bound to cells that do not express both ligands and for example where internalization is part of the mode of action may refer to a significantly reduced percentage of the total administered dose which is capable of internalizing where both ligands are not present. The term "associated" is to as above to refer to a ligand which is not necessarily exclusively expressed on the target population of cells but may be expressed or over-expressed to functional (selective) advantage on a target population of cells when compared to the non-target population. Preferably said respective antibody components recognize a substantially different subset of non-targeted tissues so that functional binding to a non-targeted tissue is substantially precluded. (It will be appreciated that this strategy can be accomplished with two different antibodies have differing and preferably non-overlapping normal ie. non-targeted tissue distributions). In a preferred embodiment the target cell is a cancer cell and the respective first and second cell surface associated ligands are expressed on different subsets of normal cells, preferably non-overlapping subsets, so as to minimize deleterious normal cell targeting and distribute the undesired effects or normal cell targeting (eg. with a toxin), to different cell populations. For example in the case of tumor cell targeting one or both ligands may be expressed exclusively on a single tumor type (eg. a human sarcoma or carcinoma, e.g., fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chordoma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary

adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma; leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease) *or* a particular category of tumor types (eg. adenocarcinomas, tumors of neuroectodermal origin, *or* on multiple different tumor types or categories of tumor. One or both components (they may be the same or different) may be a dAb, a scFv, an Fab, a minibody moiety or a substantially intact antibody, for example both may be scFvs and the resulting product may be a diabody, triabody, or tetrabody. For example in a preferred embodiment the bispecific antibody comprises two dAb components comprising linked via a linker (see above) and having at least at least part of a constant region for fusion for example to a toxin (eg. at least a partial hinge region, and preferably also at least a partial CH2 domain (optionally also at least a partial CH3 domain). In another embodiment, a trispecific antibody or tetraspecific antibody with at least two different and preferably 3 or 4 subsets (preferably at least one or more of such subsets being non-overlapping subsets) of non-targeted cell reactivities may be employed in the form of a trispecific or tetraspecific antibody respectively whereby up to three or four different pairs of ligands are targeted, so as further minimize normal cell targeting and also preferably target a heterogenous population of cells within the same tumor. Ligands with distributions on normal tissues are well known, some being referenced herein, for example CEA, CD-20, P53, epidermal growth factor, including known multicarcinomic and pancarcinomic ligands (eg. see US 5, 171,665, US 4349528. The term functional binding is used to mean binding for the purpose of accomplishing the object of the binding, for example binding in a sufficient degree (% of the dose) and for a sufficient duration to inhibit or enhance a particular effect, such as cell killing, for example in the case where one both antibody components are selected for their ability to internalize, binding for a sufficient duration to permit internalization, for example to deliver a toxic payload. As discussed above, the term substantially is used to refer to a degree which provides a significant benefit from a therapeutic standpoint. Examples of tumor associated antigens (eg. WO 01/21828) and targets and related antibodies are referenced throughout the disclosure and the foregoing aspect of the invention is for greater certainty directed to bispecific antibodies (including trispecific and tetraspecific antibodies, optionally including a component which also binds to a lymphatic vessel associated ligand), which target each of the combinations and permutations of the target cell (diseased, disease causing or immune) associated antigens, ligands, epitopes or receptors well known to those skilled in the art, herein directly or indirectly referenced or referenced in the materials herein incorporated by reference (ie. permutations and combinations of pairs or where a tri- or tetra- specific antibody is used possibly permutations of (3 or 4) groups of pairs including for example pairs in which one member is used for targeting and the second is used for modulation purposes such modulation including without limitation, simple binding eg. to deliver a payload, apoptosis inducing (eg. anti-fas), modified vascular adhesion properties (eg. anti-CD44), modified cytokine binding (anti-CCR5) etc. (for relevant ligands/markers see also USP 6,010,902 and the references cited therein, Samter's Immunologic Diseases, Fifth and Sixth Edition, Lippincott, Frank Austen, MD Michael M. Frank, MD John P. Atkinson, MD Harvey I. Cantor, MD (6th-ISBN: 0-7817-2120-2); Fundamental Virology, Third and Fourth Edition, Lippincott David M. Knipe, PhD Peter M. Howley, MD Diane E. Griffin, MD, PhD Robert A. Lamb, PhD, ScD Malcolm A. Martin, MD Bernard Roizman, ScD Stephen E. Straus, MD (4th-ISBN: 0-7817-1833-3); Arthritis and Allied Conditions - A Textbook of Rheumatology, Thirteenth and Fourteenth Editions, William J. Koopman, MD 14th:ISBN: 0-7817-2240-3, November 2000; Cancer - Principles and Practice of Oncology, Fifth and Sixth Editions, Lippincott, Vincent T. DeVita, Jr., MD Samuel Hellman, MD Steven A. Rosenberg, MD, PhD ISBN: 0-7817-2229-2; Dubois' Lupus Erythematosus, Fifth Edition, Daniel J. Wallace, MD ISBN: 0-683-08665-0, December 1996; Cytokine Therapeutics in Infectious Diseases, Steven M. Holland, MD, PhD, Lippincott, ISBN: 0-7817-1625-X, US 6054561), in each of their permutations of size/valency (ie. dabs, scFv, diabodies etc herein referenced) as applied to each of the applicable disease conditions herein referenced or otherwise known to those skilled in the art.

With respect to recombinant techniques for producing Fv fragments see also WO 88/01649, WO 88/06630, WO 88/07085, WO 88/07086, and WO 88/09344.

With respect to preparing ligands for specific MHC peptide complexes see also WO 01/22083; Direct selection of a human antibody fragment directed against the tumor T-cell epitope HLA-A1-MAGE-A1 from a nonimmunized phage-Fab library. Proc Natl Acad Sci U S A. 2000 Jul 5;97(14):7969-74.

With respect to bispecific antigen binding constructs that are suitable for for binding to more than one antigen on the same cell see also Schmiedl A et al. Protein Eng 2000 Oct 13(10):725-34.

Preferred immunoconjugates include radiolabeled antibody components and conjugates of an anti-Lyve-1 antibody component and an antibody component which comprises an immunomodulator.

A radiolabeled immunoconjugate may comprise an .alpha.-emitting radioisotope, a .B.-emitting radioisotope, a gamma emitting radioisotope, an Auger electron emitter, a neutron capturing agent that emits alpha-particles or a radioisotope that decays by electron capture. Suitable radioisotopes include ¹⁹⁸ Au, ³² p., ¹²⁵ I, ¹³¹ I, ⁹⁰ Y, ¹⁸⁶ Re, ¹⁸⁸ Re, ⁶⁷ Cu, ²¹¹ At, and the like.

As discussed above, a radioisotope can be attached to an antibody component directly or indirectly, via a chelating agent. For example, ^{67}Cu , considered one of the more promising radioisotopes for radioimmunotherapy due to its 61.5 hour half-life and abundant supply of beta particles and gamma rays, can be conjugated to an antibody component using the chelating agent, p-bromoacetamido-benzyl-tetraethylaminetetraacetic acid (TETA). Chase, "Medical Applications of Radioisotopes," in Remington's Pharmaceutical Sciences, 18th Edition, Gennaro et al. (eds.), pages 624-652 (Mack Publishing Co. 1990) (see also 19th edition of Remington's). Alternatively, ^{90}Y , which emits an energetic beta particle, can be coupled to an antibody component using diethylenetriaminepentaacetic acid (DTPA). Moreover, a method for the direct radiolabeling of the antibody component with ^{131}I is described by Stein et al., Antibody Immunoconj. Radiopharm. 4: 703 (1991) (see also USP 6, 080, 384).

Alternatively, boron addends such as carboranes can be attached to antibody components, as discussed above.

In addition, therapeutic immunoconjugates can comprise an immunomodulator moiety suitable for application for the purposes herein. Broadly speaking, the term "immunomodulator" includes cytokines, stem cell growth factors, lymphotoxins, such as tumor necrosis factor (TNF), and hematopoietic factors, such as interleukins (e.g., interleukin-1 (IL-1), IL-2, IL-3, IL-6, IL-10 and IL-12), colony stimulating factors (e.g., granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF)), interferons (e.g., interferons alpha, -beta and gamma.), the stem cell growth factor designated "S1 factor," erythropoietin and thrombopoietin. Examples of suitable immunomodulator moieties include IL-2, IL-6, IL-10, IL12, interferon-gamma., TNF-alpha., and the like.

A related form of therapeutic protein is a fusion protein comprising an antibody moiety and an immunomodulator moiety.

Methods of making antibody-immunomodulator fusion proteins are known to those of skill in the art as discussed herein. For example, antibody fusion proteins comprising an interleukin-2 moiety are described by Boleti et al., Ann. Oncol. 6:945 (1995), Nicolet et al., Cancer Gene Ther. 2:161 (1995), Becker et al., Proc. Nat'l Acad. Sci. USA 93:7826 (1996), Hank et al., Clin. Cancer Res. 2:1951 (1996), and Hu et al., Cancer Res. 56:4998 (1996). In addition, Yang et al., Hum. Antibodies Hybridomas 6:129 (1995), describe a fusion protein that includes an F(ab')₂ fragment and a tumor necrosis factor alpha moiety.

Such immunoconjugates and antibody-immunomodulator fusion proteins provide a means to deliver an immunomodulator to a target cell and are particularly useful against tumor cells. The cytotoxic effects of immunomodulators are well known to those of skill in the art. See, for example, Kle et al., "Lymphokines and Monokines," in Biotechnology and Pharmacy, Pessuto et al. (eds.), pages 53-70 (Chapman & Hall 1993) as well as other references herein cited. As an illustration, interferons can inhibit cell proliferation by inducing increased expression of class I histocompatibility antigens on the surface of various cells and thus, enhance the rate of destruction of cells by cytotoxic T lymphocytes. Furthermore, tumor necrosis factors, such as TNF-alpha., are believed to produce cytotoxic effects by inducing DNA fragmentation.

Moreover, therapeutically useful immunoconjugates can be prepared in which an antibody component is conjugated to a toxin or a chemotherapeutic drug. Illustrative of toxins which are suitably employed in the preparation of such conjugates are ricin, abrin, ribonuclease, DNase I, Staphylococcal enterotoxin-A, pokeweed antiviral protein, gelonin, diphtherin toxin, Pseudomonas exotoxin, and Pseudomonas endotoxin. See, references herein as well as for example, Pastan et al., Cell 47:641 (1986), and Goldenberg, CA-A Cancer Journal for Clinicians 44:43 (1994). Other suitable toxins are known to those of skill in the art.

With respect to bispecific antibody constructs which are capable of binding simultaneously to two ligands on the same cell see also WO96/32841. Various such constructs are known in the art.

An alternative approach to introducing the combination of therapeutic antibody and toxin is provided by antibody-toxin fusion proteins. An antibody-toxin fusion protein is a fusion protein that comprises an antibody moiety and a toxin moiety. Methods for making antibody-toxin fusion proteins are known to those of skill in the art (see references cited herein); antibody-Pseudomonas exotoxin A fusion proteins have been described by Chaudhary et al., Nature 339:394 (1989), Brinkmann et al., Proc. Nat'l Acad. Sci. USA 88:8616 (1991), Batra et al., Proc. Nat'l Acad. Sci. USA 89:5867 (1992), Friedman et al., J. Immunol. 150:3054 (1993), Wels et al., Int. J. Can. 60:137 (1995), Fominaya et al., J. Biol. Chem. 271:10560 (1996), Kuan et al., Biochemistry 35:2872 (1996), and Schmidt et al., Int. J. Can. 65:538 (1996). Antibody-toxin fusion proteins containing a diphtheria toxin moiety have been described by Kreitman et al., Leukemia 7:553 (1993), Nicholls et al., J. Biol. Chem. 268:5302 (1993), Thompson et al., J. Biol. Chem. 270:28037 (1995), and Vallera et al., Blood 88:2342 (1996). Deonarain et al., Tumor Targeting 1:177 (1995), have described an antibody-toxin fusion protein having an RNase moiety, while Linardou et al., Cell Biophys. 24-25:243 (1994), produced an antibody-toxin fusion protein comprising a DNase I component. Gelonin was used as the toxin moiety in the antibody-toxin fusion protein of Wang et al., Abstracts of the 209th ACS National Meeting, Anaheim, Calif., Apr. 2-6, 1995, Part 1, BIOT005. As a further example, Dohlsten et al., Proc. Nat'l Acad. Sci. USA 91:8945 (1994), reported an antibody-toxin fusion protein comprising Staphylococcal enterotoxin-A. Numerous other examples have been reported in the literature.

Useful cancer chemotherapeutic drugs for the preparation of immunoconjugates include nitrogen mustards, alkyl sulfonates, nitrosoureas, triazenes, folic acid analogs, pyrimidine analogs, purine analogs, antibiotics, epipodophyllotoxins, platinum coordination complexes, hormones, and the like. Suitable chemotherapeutic agents are described in Remington's Pharmaceutical Sciences, 19th Ed. (Mack Publishing Co. 1995), and in Goodman and Gilman's The Pharmacological Basis of Therapeutics, 7th Ed. (MacMillan Publishing Co. 1985). Other suitable chemotherapeutic agents, such as experimental drugs, are known to those of skill in the art.

In addition, therapeutically useful immunoconjugates can be obtained by conjugating photoactive agents or dyes to an antibody composite. Fluorescent and other chromogens, or dyes, such as porphyrins sensitive to visible light, have been used to detect and to treat lesions by directing the suitable light to the lesion. In therapy, this has been termed photoradiation, phototherapy, or photodynamic therapy (Jori et al. (eds.), Photodynamic Therapy of Tumors and Other Diseases (Libreria Progetto 1985); van den Bergh, Chem. Britain 22:430 (1986)). Moreover, monoclonal antibodies have been coupled with photoactivated dyes for achieving phototherapy. Mew et al., J. Immunol. 130:1473 (1983); idem., Cancer Res. 45:4380 (1985); Oseroff et al., Proc. Natl. Acad. Sci. USA 83:8744 (1986); idem., Photochem. Photobiol. 46:83 (1987); Hasan et al., Prog. Clin. Biol. Res. 288:471 (1989); Tatsuta et al., Lasers Surg. Med. 9:422 (1989); Pelegrin et al., Cancer 67:2529 (1991). However, these earlier studies did not include use of endoscopic therapy applications, especially with the use of antibody fragments or subfragments. Thus, the present invention contemplates the therapeutic use of immunoconjugates comprising photoactive agents or dyes.

With respect to a multifunctional ligand having a first portion that binds to both lymphatic endothelial cells and tumor vasculature, the invention contemplates using phage display or ribosome display to generate an antibody that binds to vegfr-3 as well as one or both of vegfr-2 or vegfr-1, having regard to the sequences of those respective receptors (see USPs 5,776,755, 5,877,020, 5,952,199, 6,107,046, 6,130,071, 6,221,839, 6,235,713, 6,245,530; see also WO 00/21560, WO 95/33772, WO 97/05250, WO 98/33917). Preferably the antibody does not internalize, particularly in the case where the multifunctional ligand is fused or conjugated to a toxic moiety. The invention also contemplates, for example, fusing the binding domain of VEGF-C or VEGF-D to antitumor antibody. The invention also contemplates that the risk of retargeting cancer cells to non-tumor sites of angiogenesis, can be minimized by employing one or more of the following strategies pre- and/or co-treatment with inhibitors of angiogenesis, providing the multifunctional ligand with an effector function, such as a toxic moiety, cytokine or antibody component which retargets immune cells capable of killing such cancer cells. The invention also contemplates using in combination or alone a multifunctional ligand having a second portion that comprises an anti-VEGF antibody portion which binds to one or more of the VEGF family of ligands in order to inhibit lymphangiogenesis and/or angiogenesis. (see also for example, WO 00/37025, WO 98/33917, USP 6,130,071, WO 01/12669). With respect to angiogenesis and particularly lymphangiogenesis see also: 1: Shibuya M. Structure and function of VEGF/VEGF-receptor system involved in angiogenesis. Cell Struct Funct. 2001 Feb;26(1):25-35. 2: Yonemura Y, Fushida S, Bando E, Kinoshita K, Miwa K, Endo Y, Sugiyama K, Partanen T, Yamamoto H, Sasaki T. Lymphangiogenesis and the vascular endothelial growth factor receptor (VEGFR)-3 in gastric cancer. Eur J Cancer. 2001 May;37(7):918-23. 3: Ijiri K, Karkkainen MJ, Lawrence EC, Kimak MA, Uutela M, Taipale J, Pajusola K, Alhonen L, Halmekyto M, Finegold DN, Ferrell RE, Alitalo K. VEGFR3 gene structure, regulatory region, and sequence polymorphisms. FASEB J. 2001 Apr;15(6):1028-36. 4: Tang RF, Itakura J, Aikawa T, Matsuda K, Fujii H, Korc M, Matsumoto Y. Overexpression of lymphangiogenic growth factor VEGF-C in human pancreatic cancer. Pancreas. 2001 Apr;22(3):285-92. 5: Kadambi A, Carreira CM, Yun CO, Padera TP, Dolmans DE, Carmeliet P, Fukumura D, Jain RK. Vascular endothelial growth factor (VEGF)-C differentially affects tumor vascular function and leukocyte recruitment: role of VEGF-receptor 2 and host VEGF-A. Cancer Res. 2001 Mar 15;61(6):2404-8. 6: Karpanen T, Egeblad M, Karkkainen MJ, Kubo H, Yla-Herttuala S, Jaattela M, Alitalo K. Vascular endothelial growth factor C promotes tumor lymphangiogenesis and intralymphatic tumor growth. Cancer Res. 2001 Mar 1;61(5):1786-90. 7: Baldwin ME, Catimel B, Nice EC, Roufail S, Hall NE, Stenvers KL, Karkkainen MJ, Alitalo K, Stacker SA, Achen MG. The specificity of receptor binding by vascular endothelial growth factor-D is different in mouse and man. J Biol Chem. 2001 Jun 1;276(22):19166-19171. 8: Niki T, Iba S, Yamada T, Matsuno Y, Enholm B, Hirohashi S. Expression of vascular endothelial growth factor receptor 3 in blood and lymphatic vessels of lung adenocarcinoma. J Pathol. 2001 Apr;193(4):450-7. 9: Veikkola T, Jussila L, Makinen T, Karpanen T, Jeltsch M, Petrova TV, Kubo H, Thurston G, McDonald DM, Achen MG, Stacker SA, Alitalo K. Signaling via vascular endothelial growth factor receptor-3 is sufficient for lymphangiogenesis in transgenic mice. EMBO J. 2001 Mar 15;20(6):1223-31. 10: Koshida K, Konaka H, Kato H, Miyagi T, Egawa M, Uchibayashi T, Namiki M. [Correlation between expression of metastasis-related genes and lymph node metastasis in testicular cancer]. Hinyokika Kiyo. 2000 Oct;46(10):775-81. Japanese. 11: Achen MG, Williams RA, Minekus MP, Thornton GE, Stenvers K, Rogers PA, Lederman F, Roufail S, Stacker SA. Localization of vascular endothelial growth factor-D in malignant melanoma suggests a role in tumor angiogenesis. J Pathol. 2001 Feb;193(2):147-54. 12: Makinen T, Jussila L, Veikkola T, Karpanen T, Kettunen MI, Pulkkanen KJ, Kauppinen R, Jackson DG, Kubo H, Nishikawa S, Yla-Herttuala S, Alitalo K. Inhibition of lymphangiogenesis with resulting lymphedema in transgenic mice expressing soluble VEGF receptor-3. Nat Med. 2001 Feb;7(2):199-205. 13: Stacker SA, Caesar C, Baldwin ME, Thornton GE, Williams RA, Prevo R, Jackson DG, Nishikawa S, Kubo H, Achen MG. VEGF-D promotes the metastatic spread of tumor cells via the lymphatics. Nat Med. 2001 Feb;7(2):186-91. 14: Plate KH. From angiogenesis to lymphangiogenesis. Nat Med. 2001 Feb;7(2):151-2. 15: Papoutsi M, Siemeister G, Weindel K, Tomarev SI, Kurz H, Schachtele C, Martiny-Baron G, Christ B, Marme D, Wilting J. Active interaction of human A375 melanoma cells with the lymphatics in vivo. Histochem Cell Biol. 2000 Nov;114(5):373-85. 16: Mimura T, Amano S, Usui T, Kaji Y, Oshika T, Ishii Y. Expression of vascular endothelial growth factor C and vascular endothelial growth factor receptor 3 in corneal lymphangiogenesis. Exp Eye Res. 2001 Jan;72(1):71-8. 17: Clauss M. Molecular biology of the VEGF and the VEGF receptor family. Semin Thromb Hemost.

2000;26(5):561-9. Review.19: Gunningham SP, Currie MJ, Han C, Robinson BA, Scott PA, Harris AL, Fox SB. The short form of the alternatively spliced flt-4 but not its ligand vascular endothelial growth factor C is related to lymph node metastasis in human breast cancers. *Clin Cancer Res.* 2000 Nov;6(11):4278-86.20: Hamada K, Oike Y, Takakura N, Ito Y, Jussila L, Dumont DJ, Alitalo K, Suda T. VEGF-C signaling pathways through VEGFR-2 and VEGFR-3 in vasculoangiogenesis and hematopoiesis. *Blood.* 2000 Dec 1;96(12):3793-800.21: Lymboussaki A, Achen MG, Stacker SA, Alitalo K. Growth factors regulating lymphatic vessels. *Curr Top Microbiol Immunol.* 2000;251:75-82. 22: Neuhauser TS, Derringer GA, Thompson LD, Fanburg-Smith JC, Miettinen M, Saaristo A, Abbondanzo SL. Splenic angiosarcoma: a clinicopathologic and immunophenotypic study of 28 cases. *Mod Pathol.* 2000 Sep;13(9):978-87.23: Leu AJ, Berk DA, Lymboussaki A, Alitalo K, Jain RK. Absence of functional lymphatics within a murine sarcoma: a molecular and functional evaluation. *Cancer Res.* 2000 Aug 15;60(16):4324-7.24: Jones A, Fujiyama C, Turner K, Fuggle S, Cranston D, Turley H, Valtola R, Bicknell R, Harris AL. Angiogenesis and lymphangiogenesis in stage 1 germ cell tumours of the testis. *BJU Int.* 2000 Jul;86(1):80-6.25: Kubo H, Fujiwara T, Jussila L, Hashi H, Ogawa M, Shimizu K, Awane M, Sakai Y, Takabayashi A, Alitalo K, Yamaoka Y, Nishikawa SI. Involvement of vascular endothelial growth factor receptor-3 in maintenance of integrity of endothelial cell lining during tumor angiogenesis. *Blood.* 2000 Jul 15;96(2):546-53.26: Saaristo A, Partanen TA, Arola J, Jussila L, Hytonen M, Makitie A, Vento S, Kaipainen A, Malmberg H, Alitalo K. Vascular endothelial growth factor-C and its receptor VEGFR-3 in the nasal mucosa and in nasopharyngeal tumors. *Am J Pathol.* 2000 Jul;157(1):7-14.27: Karkkainen MJ, Ferrell RE, Lawrence EC, Kimak MA, Levinson KL, McTigue MA, Alitalo K, Finegold DN. Missense mutations interfere with VEGFR-3 signalling in primary lymphoedema. *Nat Genet.* 2000 Jun;25(2):153-9.28: Yokoyama Y, Sato S, Futagami M, Fukushima Y, Sakamoto T, Umemoto M, Saito Y. Prognostic significance of vascular endothelial growth factor and its receptors in endometrial carcinoma. *Gynecol Oncol.* 2000 Jun;77(3):413-8.29: Nathanson SD, Zarbo RJ, Wachna DL, Spence CA, Andrzejewski TA, Abrams J. Microvessels that predict axillary lymph node metastases in patients with breast cancer. *Arch Surg.* 2000 May;135(5):586-93; discussion 593-4.30: Paavonen K, Puolakkainen P, Jussila L, Jähkölä T, Alitalo K. Vascular endothelial growth factor receptor-3 in lymphangiogenesis in wound healing. *Am J Pathol.* 2000 May;156(5):1499-504.31: Frelin C, Ladoux A, D'angelo G. Vascular endothelial growth factors and angiogenesis. *Ann Endocrinol (Paris).* 2000 Feb;61(1):70-4. 32: Achen MG, Roufail S, Domagala T, Catimel B, Nice EC, Geleick DM, Murphy R, Scott AM, Caesar C, Mäkinen T, Alitalo K, Stacker SA. Monoclonal antibodies to vascular endothelial growth factor-D block its interactions with both VEGF receptor-2 and VEGF receptor-3. *Eur J Biochem.* 2000 May;267(9):2505-15.33: Larrivée B, Karsan A. Signaling pathways induced by vascular endothelial growth factor (review). *Int J Mol Med.* 2000 May;5(5):447-56. 34: Andre T, Kotelevets L, Vaillant JC, Coudray AM, Weber L, Prevot S, Parc R, Gespach C, Chastre E. Vegf, Vegf-B, Vegf-C and their receptors KDR, FLT-1 and FLT-4 during the neoplastic progression of human colonic mucosa. *Int J Cancer.* 2000 Apr 15;86(2):174-81.35: Shushanov S, Bronstein M, Adelaide J, Jussila L, Tchipsheva T, Jacquemier J, Stavrovskaya A, Birnbaum D, Karamysheva A. VEGF_C and VEGFR3 expression in human thyroid pathologies. *Int J Cancer.* 2000 Apr 1;86(1):47-52.36: Jacquemier J, Mathoulin-Portier MP, Valtola R, Charafe-Jauffret E, Geneix J, Houvenaeghel G, Puig B, Bardou VJ, Hassoun J, Viens P, Birnbaum D. Prognosis of breast-carcinoma lymphagenesis evaluated by immunohistochemical investigation of vascular-endothelial-growth-factor receptor 3. *Int J Cancer.* 2000 Jan 20;89(1):69-73.37: Folpe AL, Veikkola T, Valtola R, Weiss SW. Vascular endothelial growth factor receptor-3 (VEGFR-3): a marker of vascular tumors with presumed lymphatic differentiation, including Kaposi's sarcoma, kaposiform and Dabska-type hemangioendotheliomas, and a subset of angiosarcomas. *Mod Pathol.* 2000 Feb;13(2):180-5.38: Karkkainen MJ, Petrova TV. Vascular endothelial growth factor receptors in the regulation of angiogenesis and lymphangiogenesis. *Oncogene.* 2000 Nov 20;19(49):5598-605. Review.39: Skobe M, Brown LF, Tognazzi K, Ganju RK, Dezube BJ, Alitalo K, Detmar M. Vascular endothelial growth factor-C (VEGF-C) and its receptors KDR and flt-4 are expressed in AIDS-associated Kaposi's sarcoma. *J Invest Dermatol.* 1999 Dec;113(6):1047-53.40: Partanen TA, Alitalo K, Miettinen M. Lack of lymphatic vascular specificity of vascular endothelial growth factor receptor 3 in 185 vascular tumors. *Cancer.* 1999 Dec 1;86(11):2406-12.41: Petrova TV, Mäkinen T, Alitalo K. Signaling via vascular endothelial growth factor receptors. *Exp Cell Res.* 1999 Nov 25;253(1):117-30. Review.42: Lymboussaki A, Olofsson B, Eriksson U, Alitalo K. Vascular endothelial growth factor (VEGF) and VEGF-C show overlapping binding sites in embryonic endothelia and distinct sites in differentiated adult endothelia. *Circ Res.* 1999 Nov 26;85(11):992-9.43: Stacker SA, Stenvers K, Caesar C, Vitali A, Domagala T, Nice E, Roufail S, Simpson RJ, Moritz R, Karpanen T, Alitalo K, Achen MG. Biosynthesis of vascular endothelial growth factor-D involves proteolytic processing which generates non-covalent homodimers. *J Biol Chem.* 1999 Nov 5;274(45):32127-36.44: Takahama M, Tsutsumi M, Tsujiuchi T, Nezu K, Kushibe K, Taniguchi S, Kotake Y, Konishi Y. Enhanced expression of Tie2, its ligand angiopoietin-1, vascular endothelial growth factor, and CD31 in human non-small cell lung carcinomas. *Clin Cancer Res.* 1999 Sep;5(9):2506-10.45: Marchio S, Primo L, Pagano M, Palestro G, Albini A, Veikkola T, Cascone I, Alitalo K, Bussolino F. Vascular endothelial growth factor-C stimulates the migration and proliferation of Kaposi's sarcoma cells. *J Biol Chem.* 1999 Sep 24;274(39):27617-22.46: Ohta Y, Shridhar V, Bright RK, Kalemkerian GP, Du W, Carbone M, Watanabe Y, Pass HI. VEGF and VEGF type C play an important role in angiogenesis and lymphangiogenesis in human malignant mesothelioma tumors. *Br J Cancer.* 1999 Sep;81(1):54-61.47: Mandriota SJ, Pepper MS. [Lymphangiogenesis and biological activity of vascular endothelial growth factor-C]. *J Soc Biol.* 1999;193(2):159-63. 48: Marconcini L, Marchio S, Morbidelli L, Cartocci E, Albini A, Ziche M, Bussolino F, Oliviero S. c-fos-induced growth factor/vascular endothelial growth factor D induces angiogenesis in vivo and in vitro. *Proc Natl Acad Sci U S A.* 1999 Aug 17;96(17):9671-6.49: Yonemura Y, Endo Y, Fujita H, Fushida S, Ninomiya I, Bandou E, Taniguchi K, Miwa K, Ohoyama S, Sugiyama K, Sasaki T. Role of vascular endothelial growth factor C expression in the development of lymph node metastasis in gastric cancer. *Clin Cancer Res.* 1999 Jul;5(7):1823-9.50: Siemeister G, Schirner M, Weindel K, Reusch P, Menrad A, Marme D, Martiny-Baron G. Two independent mechanisms essential for tumor angiogenesis: inhibition of human melanoma xenograft growth by interfering with either the vascular endothelial growth factor receptor pathway or the Tie-2 pathway. *Cancer Res.*

1999 Jul 1;59(13):3185-91.51: Tsurusaki T, Kanda S, Sakai H, Kanetake H, Saito Y, Alitalo K, Koji T. Vascular endothelial growth factor-C expression in human prostatic carcinoma and its relationship to lymph node metastasis. *Br J Cancer*. 1999 Apr;80(1-2):309-13.52: Buhning HJ, Seiffert M, Bock TA, Scheduling S, Thiel A, Scheffold A, Kanz L, Brugger W. Expression of novel surface antigens on early hematopoietic cells. *Ann N Y Acad Sci*. 1999 Apr 30;872:25-38; discussion 38-9.53: Valtola R, Salven P, Heikkilä P, Taipale J, Joensuu H, Rehn M, Pihlajaniemi T, Weich H, deWaal R, Alitalo K. VEGFR-3 and its ligand VEGF-C are associated with angiogenesis in breast cancer. *Am J Pathol*. 1999 May;154(5):1381-90.54: Weninger W, Partanen TA, Breiteneder-Geleff S, Mayer C, Kowalski H, Mildner M, Pammer J, Sturzl M, Kerjaschki D, Alitalo K, Tschachler E. Expression of vascular endothelial growth factor receptor-3 and podoplanin suggests a lymphatic endothelial cell origin of Kaposi's sarcoma tumor cells. *Lab Invest*. 1999 Feb;79(2):243-51.55: Breiteneder-Geleff S, Soleiman A, Kowalski H, Horvat R, Amann G, Kriehuber E, Diem K, Weninger W, Tschachler E, Alitalo K, Kerjaschki D. Angiosarcomas express mixed endothelial phenotypes of blood and lymphatic capillaries: podoplanin as a specific marker for lymphatic endothelium. *Am J Pathol*. 1999 Feb;154(2):385-94.56: Fournier E, Blaikie P, Rosnet O, Margolis B, Birnbaum D, Borg JP. Role of tyrosine residues and protein interaction domains of SHC adaptor in VEGF receptor 3 signaling. *Oncogene*. 1999 Jan 14;18(2):507-14.57: Taipale J, Makinen T, Arighi E, Kukk E, Karkkainen M, Alitalo K. Vascular endothelial growth factor receptor-3. *Curr Top Microbiol Immunol*. 1999;237:85-96. Review. No abstract available.58: Cao Y, Linden P, Farnebo J, Cao R, Eriksson A, Kumar V, Qi JH, Claesson-Welsh L, Alitalo K. Vascular endothelial growth factor C induces angiogenesis in vivo. *Proc Natl Acad Sci U S A*. 1998 Nov 24;95(24):14389-94.59: Lymboussaki A, Partanen TA, Olofsson B, Thomas-Crusells J, Fletcher CD, deWaal RM, Kaipainen A, Alitalo K. Expression of the vascular endothelial growth factor C receptor VEGFR-3 in lymphatic endothelium of the skin and in vascular tumors. *Am J Pathol*. 1998 Aug;153(2):395-403.60: Ristimäki A, Narko K, Enholm B, Joukov V, Alitalo K. Proinflammatory cytokines regulate expression of the lymphatic endothelial mitogen vascular endothelial growth factor-C. *J Biol Chem*. 1998 Apr 3;273(14):8413-8.61: Jussila L, Valtola R, Partanen TA, Salven P, Heikkilä P, Matikainen MT, Renkonen R, Kaipainen A, Detmar M, Tschachler E, Alitalo R, Alitalo K. Lymphatic endothelium and Kaposi's sarcoma spindle cells detected by antibodies against the vascular endothelial growth factor receptor-3. *Cancer Res*. 1998 Apr 15;58(8):1599-604.62: Joukov V, Kumar V, Sorsa T, Arighi E, Weich H, Saksela O, Alitalo K. A recombinant mutant vascular endothelial growth factor-C that has lost vascular endothelial growth factor receptor-2 binding, activation, and vascular permeability activities. *J Biol Chem*. 1998 Mar 20;273(12):6599-602.63: Moriyama M, Kumagai S, Kawashiri S, Kojima K, Kakiyama K, Yamamoto E. Immunohistochemical study of tumour angiogenesis in oral squamous cell carcinoma. *Oral Oncol*. 1997 Sep;33(5):369-74. PMID: 9415339 [PubMed - indexed for MEDLINE]64: Achen MG, Jeltsch M, Kukk E, Makinen T, Vitali A, Wilks AF, Alitalo K, Stacker SA. Vascular endothelial growth factor D (VEGF-D) is a ligand for the tyrosine kinases VEGF receptor 2 (Flk1) and VEGF receptor 3 (Flt4). *Proc Natl Acad Sci U S A*. 1998 Jan 20;95(2):548-53.65: Wang JF, Ganju RK, Liu ZY, Avraham H, Avraham S, Groopman JE. Signal transduction in human hematopoietic cells by vascular endothelial growth factor related protein, a novel ligand for the FLT4 receptor. *Blood*. 1997 Nov 1;90(9):3507-15.66: Fielder W, Graeven U, Ergun S, Verago S, Kilic N, Stockschrader M, Hossfeld DK. Expression of FLT4 and its ligand VEGF-C in acute myeloid leukemia. *Leukemia*. 1997 Aug;11(8):1234-7.67: Fitz LJ, Morris JC, Towler P, Long A, Burgess P, Greco R, Wang J, Gassaway R, Nickbarg E, Kovacic S, Ciarletta A, Giannotti J, Finnerty H, Zollner R, Beier DR, Leak LV, Turner KJ, Wood CR. Characterization of murine Flt4 ligand/VEGF-C. *Oncogene*. 1997 Jul 31;15(5):613-8.68: Agnes F, Toux MM, Andre C, Galibert F. Genomic organization of the extracellular coding region of the human FGFR4 and FLT4 genes: evolution of the genes encoding receptor tyrosine kinases with immunoglobulin-like domains. *J Mol Evol*. 1997 Jul;45(1):43-9.69: Fournier E, Birnbaum D, Borg JP. [Receptors for factors of the VEGF (Vascular Endothelial Growth Family)]. *Bull Cancer*. 1997 Apr;84(4):397-405. Review. French.70: Liu ZY, Ganju RK, Wang JF, Ona MA, Hatch WC, Zheng T, Avraham S, Gill P, Groopman JE. Cytokine signaling through the novel tyrosine kinase RAFTK in Kaposi's sarcoma cells. *J Clin Invest*. 1997 Apr 1;99(7):1798-804.71: Kukk E, Lymboussaki A, Taira S, Kaipainen A, Jeltsch M, Joukov V, Alitalo K. VEGF-C receptor binding and pattern of expression with VEGFR-3 suggests a role in lymphatic vascular development. *Development*. 1996 Dec;122(12):3829-37. PMID: 9012504 [PubMed - indexed for MEDLINE]72: Eichmann A, Marcelle C, Breant C, Le Douarin NM. Molecular cloning of Quak 1 and 2, two quail vascular endothelial growth factor (VEGF) receptor-like molecules. *Gene*. 1996 Sep 26;174(1):3-8.73: Davis-Smyth T, Chen H, Park J, Presta LG, Ferrara N. The second immunoglobulin-like domain of the VEGF tyrosine kinase receptor Flt-1 determines ligand binding and may initiate a signal transduction cascade. *EMBO J*. 1996 Sep 16;15(18):4919-27.74: Joukov V, Pajusola K, Kaipainen A, Chilov D, Lahtinen I, Kukk E, Saksela O, Kalkkinen N, Alitalo K. A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. *EMBO J*. 1996 Apr 1;15(7):1751. No abstract available.75: Lee J, Gray A, Yuan J, Luoh SM, Avraham H, Wood WI. Vascular endothelial growth factor-related protein: a ligand and specific activator of the tyrosine kinase receptor Flt4. *Proc Natl Acad Sci U S A*. 1996 Mar 5;93(5):1988-92.76: Shibuya M. [Involvement of the VEGF-Flt-receptor family in angiogenesis]. *Nippon Yakurigaku Zasshi*. 1996 Mar;107(3):119-31. Review. Japanese.77: Joukov V, Pajusola K, Kaipainen A, Chilov D, Lahtinen I, Kukk E, Saksela O, Kalkkinen N, Alitalo K. A novel vascular endothelial growth factor, VEGF-C, is a ligand for the Flt4 (VEGFR-3) and KDR (VEGFR-2) receptor tyrosine kinases. *EMBO J*. 1996 Jan 15;15(2):290-98.78: Rousset D, Agnes F, Lachaume P, Andre C, Galibert F. Molecular evolution of the genes encoding receptor tyrosine kinase with immunoglobulin-like domains. *J Mol Evol*. 1995 Oct;41(4):421-9.79: Fournier E, Dubreuil P, Birnbaum D, Borg JP. Mutation at tyrosine residue 1337 abrogates ligand-dependent transforming capacity of the FLT4 receptor. *Oncogene*. 1995 Sep 7;11(5):921-31.80: Mustonen T, Alitalo K. Endothelial receptor tyrosine kinases involved in angiogenesis. *J Cell Biol*. 1995 May;129(4):895-8. Review. No abstract available.81: Kaipainen A, Korhonen J, Mustonen T, van Hinsbergh VW, Fang GH, Dumont D, Breitman M, Alitalo K. Expression of the fms-like tyrosine kinase 4 gene becomes restricted to lymphatic endothelium during development. *Proc Natl Acad Sci U S A*. 1995 Apr 11;92(8):3566-70.82: Borg JP, deLapeyriere O, Noguchi T, Rottapel R, Dubreuil P, Birnbaum D. Biochemical characterization of two isoforms of FLT4, a VEGF receptor-related tyrosine kinase. *Oncogene*. 1995

Mar 2;10(5):973-84.83: Hatva E, Kaipainen A, Mentula P, Jaaskelainen J, Paetau A, Haltia M, Alitalo K. Expression of endothelial cell-specific receptor tyrosine kinases and growth factors in human brain tumors. *Am J Pathol.* 1995 Feb;146(2):368-78.84: Seetharam L, Gotoh N, Maru Y, Neufeld G, Yamaguchi S, Shibuya M. A unique signal transduction from FLT tyrosine kinase, a receptor for vascular endothelial growth factor VEGF. *Oncogene.* 1995 Jan 5;10(1):135-47.85: Pajusola K, Aprelikova O, Pelicci G, Weich H, Claesson-Welsh L, Alitalo K. Signalling properties of FLT4, a proteolytically processed receptor tyrosine kinase related to two VEGF receptors. *Oncogene.* 1994 Dec;9(12):3545-55.86: Shibuya M, Seetharam L, Ishii Y, Sawano A, Gotoh N, Matsushime H, Yamaguchi S. Possible involvement of VEGF-FLT tyrosine kinase receptor system in normal and tumor angiogenesis. *Princess Takamatsu Symp.* 1994;24:162-70. Review.87: Pajusola K, Aprelikova O, Armstrong E, Morris S, Alitalo K. Two human FLT4 receptor tyrosine kinase isoforms with distinct carboxy terminal tails are produced by alternative processing of primary transcripts. *Oncogene.* 1993 Nov;8(11):2931-7.88: Finnerty H, Kelleher K, Morris GE, Bean K, Merberg DM, Kriz R, Morris JC, Sookdeo H, Turner KJ, Wood CR. Molecular cloning of murine FLT and FLT4. *Oncogene.* 1993 Aug;8(8):2293-8.89: Armstrong E, Kastury K, Aprelikova O, Bullrich F, Nezelof C, Gogusev J, Wasmuth JJ, Alitalo K, Morris S, Huebner K. FLT4 receptor tyrosine kinase gene mapping to chromosome band 5q35 in relation to the t(2;5), t(5;6), and t(3;5) translocations. *Genes Chromosomes Cancer.* 1993 Jul;7(3):144-51.90: Pajusola K, Aprelikova O, Korhonen J, Kaipainen A, Pertovaara L, Alitalo R, Alitalo K. FLT4 receptor tyrosine kinase contains seven immunoglobulin-like loops and is expressed in multiple human tissues and cell lines. *Cancer Res.* 1992 Oct 15;52(20):5738-43.91: Galland F, Karamysheva A, Mattei MG, Rosnet O, Marchetto S, Birnbaum D. Chromosomal localization of FLT4, a novel receptor-type tyrosine kinase gene. *Genomics.* 1992 Jun;13(2):475-8.92: Aprelikova O, Pajusola K, Partanen J, Armstrong E, Alitalo R, Bailey SK, McMahon J, Wasmuth J, Huebner K, Alitalo K. FLT4, a novel class III receptor tyrosine kinase in chromosome 5q33-qter. *Cancer Res.* 1992 Feb 1;52(3):746-8.)

Multimodal therapies are also contemplated within the present invention, including particularly for cancer, therapies which can be determined to be useful complementary therapies for the anti-metastatic embodiments of this invention such as anti-angiogenic Ab conjugates

In another form of multimodal therapy, subjects receive the multifunctional ligands of the present invention and standard cancer chemotherapy. For example, "CVB" (1.5 g/m² cyclophosphamide, 200-400 mg/m² etoposide, and 150-200 mg/m² carmustine) is a regimen used to treat non-Hodgkin's lymphoma. Patti et al., *Eur. J. Haematol.* 51:18 (1993). Other suitable combination chemotherapeutic regimens are well-known to those of skill in the art. See, for example, Freedman et al., "Non-Hodgkin's Lymphomas," in *Cancer Medicine*, Volume 2, 3rd Edition, Holland et al. (eds.), pages 2028-2068 (Lea & Febiger 1993). As an illustration, first generation chemotherapeutic regimens for treatment of intermediate-grade non-Hodgkin's lymphoma include C-MOPP (cyclophosphamide, vincristine, procarbazine and prednisone) and CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). A useful second generation chemotherapeutic regimen is m-BACOD (methotrexate, bleomycin, doxorubicin, cyclophosphamide, vincristine, dexamethasone and leucovorin), while a suitable third generation regimen is MACOP-B (methotrexate, doxorubicin, cyclophosphamide, vincristine, prednisone, bleomycin and leucovorin). Additional useful drugs include phenyl butyrate and brostatin-1.

In general, the dosage of administered multifunctional ligands, immunoconjugates, and fusion proteins will vary depending upon such factors as the patient's age, weight, height, sex, general medical condition and previous medical history. Typically, it is desirable to provide the recipient with a dosage of antibody component, immunoconjugate or fusion protein which is generally at least in the range of from about 1 pg/kg to 10 mg/kg (amount of agent/body weight of patient), although a lower or higher dosage also may be administered as circumstances dictate, particularly to take advantage of the depot effect of the invention.

Administration of the invention including, immunoconjugates or fusion proteins to a patient can be intravenous, intraarterial, intraperitoneal, intramuscular, subcutaneous, intrapleural, intrathecal, by perfusion through a regional catheter, or by direct intralesional injection. When administering therapeutic proteins by injection, the administration may be by continuous infusion or by single or multiple boluses.

Those of skill in the art are aware that intravenous injection provides a useful mode of administration due to the thoroughness of the circulation in rapidly distributing antibodies. Intravenous administration, however, is subject to limitation by a vascular barrier comprising endothelial cells of the vasculature and the subendothelial matrix. Still, the vascular barrier is a more notable problem for the uptake of therapeutic antibodies by solid tumors. Lymphomas have relatively high blood flow rates, contributing to effective antibody delivery. Intralymphatic routes of administration, such as subcutaneous or intramuscular injection, or by catheterization of lymphatic vessels, also provide a useful means of treating lymphomas.

For example, the multifunctional ligand of the invention can optionally be administered at low protein doses, such as 20 to 100 milligrams protein per dose, given once, or repeatedly, parenterally. Alternatively, this multifunctional ligand is administered in doses of 30 to 90 milligrams protein per dose, or 40 to 80 milligrams protein per dose, or 50 to 70 milligrams protein per dose.

With regard to "low doses" of ¹³¹I-labeled immunoconjugates, the invention includes a dosage is in the range of 15 to 40 mCi, 20 to 30 mCi. In contrast, a preferred dosage of ⁹⁰Y-labeled immunoconjugates is in the range from 10 to 30 mCi, while the more preferable range is 10 to 20 mCi.

Immunoconjugates having a boron addend-loaded carrier for thermal neutron activation therapy will normally be effected in similar ways. However, it will be advantageous to wait until non-targeted immunoconjugate clears before neutron irradiation is performed. Clearance can be accelerated using an antibody that binds to the immunoconjugate. See U.S. Pat. No. 4,624,846 for a description of this general principle.

The immunoconjugates, and fusion proteins of the present invention can be formulated according to known methods to prepare pharmaceutically useful compositions, whereby the therapeutic proteins are combined in a mixture with a pharmaceutically acceptable carrier. A composition is said to be a "pharmaceutically acceptable carrier" if its administration can be tolerated by a recipient patient. Sterile phosphate-buffered saline is one example of a pharmaceutically acceptable carrier. Other suitable carriers are well-known to those in the art. See, for example, REMINGTON'S PHARMACEUTICAL SCIENCES, 19th Ed. (1995).

For purposes of therapy, antibody components (or immunoconjugates/fusion proteins) and a pharmaceutically acceptable carrier are administered to a patient in a therapeutically effective amount. A combination of an antibody component, optionally with an immunoconjugate/fusion protein, and a pharmaceutically acceptable carrier is said to be administered in a "therapeutically effective amount" if the amount administered is physiologically significant. An agent is physiologically significant if its presence results in a detectable change in the physiology of a recipient patient. In one aspect, an agent is physiologically significant if its presence results in the inhibition of the growth of target tumor cells.

Yet another therapeutic method included in the invention is a method of treating cancer by administering to an animal suffering from cancer a pharmaceutically effective amount of one or more multifunctional ligands capable of binding to cancer cells, wherein the compound is associated with a substance capable of damaging cancer cells.

Pharmaceutical compositions herein described or alluded to include multifunctional ligands of the invention or therapeutics used in combination therapy which may be administered by a variety of routes of administration.

By administration of an "effective amount" is intended an amount of the compound that is sufficient to enhance or inhibit a response, is some embodiments particularly an immune response or cellular response to a multifunctional ligand. One of ordinary skill will appreciate that effective amounts of a multifunctional ligand can be determined empirically and may be employed in pure form or, where such forms exist, in pharmaceutically acceptable salt, ester or prodrug form. The multifunctional ligand may be administered in compositions in combination with one or more pharmaceutically acceptable excipients. It will be understood that, when administered to a human patient, the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the type and degree of the cellular response to be achieved; activity of the specific multifunctional ligand employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the agonist or antagonist; the duration of the treatment; drugs used in combination or coincidental with the specific agonist or antagonist; and like factors well known in the medical arts.

On administration parenterally, for example by i.v. drip or infusion, dosages optionally at least on the order of from 0.01 to 5 mg/kg/day, optionally 0.05 to 1.0 mg/kg/day and more preferably 0.1 to 1.0 mg/kg/day can be used. Suitable daily dosages for patients are thus on the order of from 2.5 to 500 mg p.o., optionally 5 to 250 mg p.o., optionally 5 to 100 mg p.o., or on the order of from 0.5 to 250 mg i.v., optionally 2.5 to 125 mg i.v. and optionally 2.5 to 50 mg i.v.

Dosaging may also be arranged in a patient specific manner to provide a predetermined concentration of an agonist or antagonist in the blood, as determined by the RIA technique. Thus patient dosaging may be adjusted to achieve regular on-going trough blood levels, as measured by RIA, optionally on the order of at least from 50 to 1000 ng/ml, preferably 150 to 500 ng/ml.

From above, pharmaceutical compositions are provided comprising an agonist or antagonist and a pharmaceutically acceptable carrier or excipient, which may be administered orally, rectally, parenterally, intracisternally, intravaginally, intraperitoneally, topically (as by powders, ointments, drops or transdermal patch), buccally, or as an oral or nasal spray. By "pharmaceutically acceptable carrier" is meant a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any type. The term "parenteral" as used herein refers to modes of administration which include intravenous, intramuscular, intraperitoneal, intrasternal, subcutaneous and intraarticular injection and infusion.

Optionally a composition for parenteral injection can comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, dispersions, suspensions or emulsions as well as sterile powders for reconstitution into sterile injectable solutions or dispersions just prior to use. Examples of suitable aqueous and nonaqueous carriers, diluents, solvents or vehicles include water, ethanol, polyols (such as glycerol, propylene glycol, polyethylene glycol, and the like), carboxymethylcellulose and suitable mixtures thereof, vegetable oils (such as olive oil), and injectable organic esters such as ethyl oleate. Proper fluidity can be maintained, for example, by the use of coating materials such as lecithin, by the maintenance of the required particle size in the case of dispersions, and by the use of surfactants.

Some compositions herein described may also contain adjuvants such as preservatives, wetting agents, emulsifying agents, and dispersing agents. Prevention of the action of microorganisms may be ensured by the inclusion of various antibacterial and antifungal agents, for example, paraben, chlorobutanol, phenol sorbic acid, and the like. It may also be desirable to include isotonic agents such as sugars, sodium chloride, and the like. Prolonged absorption of the injectable pharmaceutical form may be brought about by the inclusion of agents which delay absorption such as aluminum monostearate and gelatin.

In some cases, in order to prolong the effect of one or therapeutic components herein described, it is desirable to slow the absorption from subcutaneous or intramuscular injection. This may be accomplished by the use of a liquid suspension of crystalline or amorphous material with poor water solubility. The rate of absorption of the drug then depends upon its rate of dissolution which, in turn, may depend upon crystal size and crystalline form. Alternatively, delayed absorption of a parenterally administered drug form is accomplished by dissolving or suspending the drug in an oil vehicle.

Injectable depot forms are made by forming microencapsule matrices of the drug in biodegradable polymers such as polylactide-polyglycolide. Depending upon the ratio of drug to polymer and the nature of the particular polymer employed, the rate of drug release can be controlled. Examples of other biodegradable polymers include poly(orthoesters) and poly(anhydrides). Depot injectable formulations are also prepared by entrapping the drug in liposomes or microemulsions which are compatible with body tissues.

The injectable formulations can be sterilized, for example, by filtration through a bacterial-retaining filter, or by incorporating sterilizing agents in the form of sterile solid compositions which can be dissolved or dispersed in sterile water or other sterile injectable medium just prior to use.

The multifunctional ligand can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to the agonist or antagonist, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and the phosphatidyl cholesterols (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.Y. (1976), p. 33 et seq.

The present invention also contemplates a method of treatment in which immunomodulators are administered to prevent, mitigate or reverse radiation-induced or drug-induced toxicity of normal cells, and especially hematopoietic cells. Adjunct immunomodulator therapy allows the administration of higher doses of cytotoxic agents due to increased tolerance of the recipient mammal. Moreover, adjunct immunomodulator therapy can prevent, palliate, or reverse dose-limiting marrow toxicity. Examples of suitable immunomodulators for adjunct therapy include G-CSF, GM-CSF, thrombopoietin, IL-1, IL-3, IL-12, and the like. The method of adjunct immunomodulator therapy is disclosed by Goldenberg, U.S. Pat. No. 5,120,525.

For example, recombinant IL-2 may be administered intravenously as a bolus at 6×10^6 IU/kg or as a continuous infusion at a dose of 18×10^6 IU/m² /d. Weiss et al., *J. Clin. Oncol.* 10:275 (1992). Alternatively, recombinant IL-2 may be administered subcutaneously at a dose of 12×10^6 IU. Vogelzang et al., *J. Clin. Oncol.* 11:1809 (1993). Moreover, INF- γ may be administered subcutaneously at a dose of 1.5×10^6 U. Lienard et al., *J. Clin. Oncol.* 10:52 (1992). Furthermore, Nadeau et al., *J. Pharmacol. Exp. Ther.* 274:78 (1995), have shown that a single intravenous dose of recombinant IL-12 (42.5 μ g/kilogram) elevated INF- γ levels in rhesus monkeys.

Suitable IL-2 formulations include PROLEUKIN (Chiron Corp./Cetus Oncology Corp.; Emeryville, Calif.) and TECELEUKIN (Hoffmann-La Roche, Inc.; Nutley, N.J.). ACTIMMUNE (Genentech, Inc.; South San Francisco, Calif.) is a suitable INF- γ preparation.

In the preceding detailed description, reference was made to various methodologies known to those of skill in the art of molecular biology and immunology. Publications and other materials setting forth such known methodologies to which reference was made or is made below are incorporated herein by reference in their entireties along with references cited therein as though set forth in full.

Standard reference works setting forth the general principles of recombinant DNA technology include Watson, J. D. et al, *Molecular Biology of the Gene*, Volumes I and II, the Benjamin/Cummings Publishing Company, Inc., publisher, Menlo Park, Calif. (1987), Darnell, J. E. et al., *Molecular Cell Biology*, Scientific American Books, Inc., Publisher, New York, N.Y. (1986); Lewin, B. M. *Genes II*, John Wiley & Sons, publishers, New York, N.Y. (1985); Old, R. W., et al., *Principles of Gene Manipulation: An Introduction to Genetic Engineering*, 2d edition, University of California Press, publisher, Berkeley, Calif. (1981); Maniatis, T., et al., *Molecular Cloning: A Laboratory Manual*, 2nd Ed. Cold Spring Harbor Laboratory, publisher, Cold Spring Harbor, N.Y. (1989), and *Current Protocols in Molecular Biology*, Ausubel et al., Wiley Press, New York, N.Y. (1989). Standard reference works setting forth general principles and techniques of immunology include *Handbook of Experimental Immunology* Blackwell Science, Incorporated, ISBN:0632009756; *Antibody Engineering* Blackwell Science, Incorporated, ISBN:0632009756;

Therapeutic Immunology ISBN: 086542375X Blackwell Science, Incorporated ; Encyclopedia of Immunology (1998) Morgan Kaufmann Publishers, ISBN:0122267656; Immunology Mosby, Incorporated, ISBN:0723429189; Abbas AK. et al. Cellular & Molecular Immunology 4th Ed. 2000 ISBN 0721650023; Breitling F. et al. Recombinant Antibodies 1999 ISBN 0-471-17847-0; Masseyeff R. et al. Methods of Immunological Analysis Wiley-VCH ISBN 3-527-27906-7, 1992; Mountain et al. Eds, Biotechnology 2nd ed. Vol 5A 1998 ISBN 3-527-28315-3 Wiley-VCH; Campbell, A. , "Monoclonal Antibody Technology," in, Burdon, R., et al., eds, Laboratory Techniques in Biochemistry and Molecular Biology, Volume 13, Elsevier, Publisher, Amsterdam (1984);

Although the foregoing refers to particular preferred embodiments, it will be understood that the present invention is not so limited. It will occur to those of ordinary skill in the art that various modifications may be made to the disclosed embodiments and that such modifications are intended to be within the scope of the present invention.

All publications referred to herein are indicative of the level of skill of those in the art to which the invention pertains. All publications are herein (as well as references cited therein) are incorporated by reference to the same extent as if each individual publications were specifically and individually indicated to be incorporated by reference in its entirety.

The present invention, thus generally described, will be understood more readily by reference to the preceding and following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

With respect to applications of bispecific antibodies see also *Methods Mol Biol* 2001; 166:177-92; USP 6,071,517; USP 5,897,861; USP 6,096,311; USP 5,922,845, Journal of Immunological Methods February 2001 Vol. 248(1-2) page 1-200; Mol Immunol 1999 May; 36(7):433-45; Isolation and characterization of an anti-CD16 single-chain Fv fragment and construction of an anti-HER2/neu/anti-CD16 bispecific scFv that triggers CD16-dependent tumor cytotoxicity. US06051227 Blockade of T lymphocyte down-regulation associated with CTLA-4 signaling; US06143297 Methods of promoting immunopotentiality and preparing antibodies with anti-CD3 antibodies; US05977318 CTLA4 receptor and uses thereof; US05968510 CTLA4 receptor and uses thereof; US05885796 CTLA4 receptor and uses thereof; US05885579 CTLA4 receptor and uses thereof; US05869050 Methods of blocking T-cell activation using anti-B7 monoclonal antibodies; US05851795 Soluble CTLA4 molecules and uses thereof; US05747034 Methods and materials for the induction of T cell anergy; US06113901 Methods of stimulating or enhancing the immune system with anti-CD3 antibodies; US05877021 B7-1 targeted ribozymes; US05844095 CTLA4 Ig fusion proteins; US06090914 CTLA4/CD28lg hybrid fusion proteins and uses thereof; US05786152 Methods of inhibiting syp binding to a CTLA-4 receptor; US05773253 MYPPPY variants of CTL A4 and uses thereof; US05718883 Transgenic animal model for autoimmune diseases; US06045802 Enhanced immune response to an antigen by a composition of a recombinant virus expressing the antigen with a recombinant virus expressing an immunostimulatory molecule; US05855887 Blockade of lymphocyte down-regulation associated with CTLA-4 signaling; US05811097 Blockade of T lymphocyte down-regulation associated with CTLA-4 signaling; US05770197 Methods for regulating the immune response using B7 binding molecules and IL4-binding molecules; US06084067 CTLA4/CD28 ligands and uses thereof; EP01073741A2 FELINE CD80, FELINE CD86, FELINE CD28, AND FELINE CTLA-4 NUCLEIC ACID AND POLYPEPTIDES; US06130316 Fusion proteins of novel CTLA4/CD28 ligands and therefor; US06107056 SCTL A-4 gene and product; US06068984 Antibodies to lymphocyte activation antigens uses therefor; US05861310 Tumor cells modified to express B7-2 with increased immunogenicity and uses therefor; EP00865293A1 BLOCKADE OF T LYMPHOCYTE DOWN-REGULATION ASSOCIATED WITH CTLA-4 SIGNALING; US05766570 Lymphocyte activation antigens and thereto; US05710262 Nucleic acid encoding HB15 polypeptides; US05434131 Chimeric CTLA4 receptor and methods for its use; US05316920 Lymphocyte activation antigen HB15, a member of the immunoglobulin superfamily; EP01073759A1 RECOMBINANT VIRUS EXPRESSING FOREIGN DNA ENCODING FELINE CD80, FELINE CD28, FELINE CTLA-4 OR FELINE CD86 AND USES THEREOF; US06111090 Mammalian cell surface antigens; US06083751 Chimeric receptors for the generation of selectively-activatable TH-independent cytotoxic T cells; US05977303 Mammalian cell surface antigens; US05738852 Methods of enhancing antigen-specific T cell responses US05714667 Mice lacking expression of CTLA-4 receptor; Bruhl H, Cihak J, Stangassinger M, Schlondorff D, Mack M. Depletion of CCR5-Expressing Cells with Bispecific Antibodies and Chemokine Toxins: A New Strategy in the Treatment of Chronic Inflammatory Diseases and HIV. J Immunol. 2001 Feb 15; 166(4):2420-2426; Tesch H, Engert A, Mancke O, Diehl V, Bohlen H. Treatment of patients with malignant lymphomas with monoclonal antibodies. Bone Marrow Transplant. 2000 May; 26 Suppl 2:S50-3; Jung G, Brandl M, Eisner W, Fraunberger P, Reifemberger G, Schlegel U, Wiestler OD, Reulen HJ, Wilmanns W. Local immunotherapy of glioma patients with a combination of 2 bispecific antibody fragments and resting autologous lymphocytes: Evidence for in situ t-cell activation and therapeutic efficacy. Int J Cancer. 2001 Jan 15; 91(2):225-230; Kan KS, Anderson VA, Leong WS, Smith AM, Worth AT, Stevenson GT. Thioether-Bonded Constructs of Fab'gamma and Fcgamma Modules Utilizing Differential Reduction of Interchain Disulfide Bonds J Immunol. 2001 Jan 15; 166(2):1320-1326; Hahn CS, OG, Foley P, Martin EN, Taylor RP. Bispecific Monoclonal Antibodies Mediate Binding of Dengue Virus to Erythrocytes in a Monkey Model of Passive Viremia. J Immunol. 2001 Jan 15; 166(2):1057-1065; Cao Y, Suresh MR. Bispecific MAb aided liposomal drug delivery. J Drug Target. 2000; 8(4):257-66; Reynolds PN, Zinn KR, Gavriluk VD, Balyasnikova IV, Rogers BE, Buchsbaum DJ, Wang MH, Miletich DJ, Grizzle WE, Douglas JT, SM, Curiel DT. A Targetable, Injectable Adenoviral Vector for

Selective Gene Delivery to Pulmonary Endothelium in Vivo. *Mol Ther.* 2000 Dec; 2(6):562-578; Schoonjans R, Willems A, Schoonoghe S, Fiers W, Grooten J, Mertens N. Fab chains As an efficient heterodimerization scaffold for the production of recombinant bispecific and trispecific antibody derivatives *J Immunol.* 2000 Dec 15; 165(12):7050-7. 3 9: Ebbinghaus C, Al-Jaibaji A, Operschall E, Schoffel A, Peter I, Greber UF, Hemmi S. Functional and selective targeting of adenovirus to high-affinity fcgamma receptor I-positive cells by using a bispecific hybrid adapter *J Virol.* 2001 Jan; 75(1):480-9. 6 10: Mortara L, Letourneur F, Villefroy P, Beyer C, Gras-Masse H, Guillet JG, Bourgault-Villada I. Temporal loss of nef-epitope CTL recognition following macaque lipopeptide immunization and SIV challenge *Virology.* 2000 Dec 20; 278(2):551-61. 7 11: Schmiedl A, Breitling F, Dubel S. Expression of a bispecific dsFv-dsFv' antibody fragment in escherichia coli *Protein Eng.* 2000 Oct; 13(10):725-34. 2 12: Kelly FJ, Miller CR, Buchsbaum DJ, Gomez-Navarro J, Barnes MN, Alvarez RD, Curiel DT. Selectivity of TAG-72-targeted adenovirus gene transfer to primary ovarian carcinoma cells versus autologous mesothelial cells in vitro *Clin Cancer Res.* 2000 Nov; 6(11):4323-33. 0 13: Rohrbach F, Gerstmayer B, Biburger M, Wels W. Construction and characterization of bispecific costimulatory molecules containing a minimized CD86 (B7-2) domain and single-chain antibody fragments for tumor targeting *Clin Cancer Res.* 2000 Nov; 6(11):4314-22. 9 14: Schoonjans R, Willems A, Grooten J, Mertens N. Efficient heterodimerization of recombinant bi- and trispecific antibodies *Bioseparation.* 2000; 9(3):179-83. 8 15: Wallace PK, Romet-Lemonne JL, Chokri M, Kasper LH, Fanger MW, Fadul CE. Production of macrophage-activated killer cells for targeting of glioblastoma cells with bispecific antibody to FcgammaRI and the epidermal growth factor receptor *Cancer Immunol Immunother.* 2000 Nov; 49(9):493-503. 6 16: Karacay H, McBride WJ, Griffiths GL, Sharkey RM, Barbet J, Hansen HJ, Goldenberg DM. Experimental pretargeting studies of cancer with a humanized anti-CEA x murine anti- *Bioconjug Chem.* 2000 Nov; 11(6):842-54. 3 17: Koon HB, Junghans RP. Anti-CD30 antibody-based therapy *Curr Opin Oncol.* 2000 Nov; 12(6):588-93. 9 18: Foon KA. Monoclonal antibody therapies for lymphomas *Cancer J.* 2000 Sep; 6(5):273-8. 3 19: Honeychurch J, Tutt AL, Valerius T, Heijnen IA, Van De Winkel JG, Glennie MJ. Therapeutic efficacy of FcgammaRI/CD64-directed bispecific antibodies in B-cell lymphoma *Blood.* 2000 Nov 15; 96(10):3544-52. 3 20: Stockmeyer B, Dechant M, van Egmond M, Tutt AL, Sundarapandian K, Graziano RF, Repp R, Kalden JR, Gramatzki M, Glennie MJ, van De Winkel JG, Valerius T. Triggering Fcalpha-receptor I (CD89) recruits neutrophils as effector cells for CD20-directed antibody therapy *J Immunol.* 2000 Nov 15; 165(10):5954-61. 8 21: Conrath KE, Lauwereys M, Wyns L, Muyldermans S. Camel single-domain antibodies as modular building units in. *J Biol Chem.* 2000 Oct 25 [epub ahead of print] 6 22: Tomita GM, Wang Y, Paape MJ, Poulter B, Rainard P. Related Articles Influence of bispecific antibodies on the in vitro bactericidal activity of bovine neutrophils against *Staphylococcus aureus* *J Dairy Sci.* 2000 Oct; 83(10):2269-75. 7 23: Flieger D, Kufer P, Beier I, Sauerbruch T, Schmidt-Wolf IG. A bispecific single-chain antibody directed against EpCAM/CD3 in combination with the cytokines interferon alpha and interleukin-2 efficiently retargets T and CD3 + CD56 + natural-killer-like T lymphocytes to EpCAM-expressing tumor cells *Cancer Immunol Immunother.* 2000 Oct; 49(8):441-8. 1 24: Talac R, Nelson H. Current perspectives of bispecific antibody-based immunotherapy *J Biol Regul Homeost Agents.* 2000 Jul; 14(3):175-81. 9 25: Tomlinson I, Holliger P. Methods for generating multivalent and bispecific antibody fragments *Methods Enzymol.* 2000; 326:461-79. available. 8 26: Tillman BW, Hayes TL, DeGrujl TD, Douglas JT, Curiel DT. Adenoviral vectors targeted to CD40 enhance the efficacy of dendritic cell-based vaccination against human papillomavirus 16-induced tumor cells in a murine model *Cancer Res.* 2000 Oct 1; 60(19):5456-63. 8 27: Trepel M, Grifman M, Weitzman MD, Pasqualini R. Molecular adaptors for vascular-targeted adenoviral gene delivery *Hum Gene Ther.* 2000 Sep 20; 11(14):1971-81. 7 28: van Der Pol W, Vidarsson G, Vile HA, van De Winkel JG, Rodriguez ME. Pneumococcal capsular polysaccharide-specific IgA triggers efficient neutrophil effector functions via FcalphaRI (CD89) *J Infect Dis.* 2000 Oct; 182(4):1139-45. 0 29: Patel SD, Moskalenko M, Tian T, Smith D, McGuinness R, Chen L, Winslow GA, Kashmiri S, Schlom J, Stanners CP, Finer MH, McArthur JG. T-cell killing of heterogenous tumor or viral targets with bispecific chimeric immune receptors *Cancer Gene Ther.* 2000 Aug; 7(8):1127-34. 3 30: Morimoto K, Inouye K. Application of bispecific F(ab')(2&mgr;) fragments prepared from IgMs against carcinoembryonic antigen and alkaline phosphatase *Clin Chem.* 2000 Sep; 46(9):1492-3. available. 7 31: Cochlovius B, Kipriyanov SM, Stassar MJ, Schuhmacher J, Benner A, Moldenhauer G, Little M. Cure of Burkitt's lymphoma in severe combined immunodeficiency mice by T cells, tetravalent CD3 x CD19 tandem diabody, and CD28 costimulation. *Cancer Res.* 2000 Aug 15; 60(16):4336-41. 2 32: Takemura Si, Asano R, Tsumoto K, Ebara S, Sakurai N, Katayose Y, Kodama H, Yoshida H, Suzuki M, Imai K, Matsuno S, Kudo T, Kumagai I. Construction of a diabody (small recombinant bispecific antibody) using a refolding system *Protein Eng.* 2000 Aug; 13(8):583-8. 8 33: da Costa L, Renner C, Hartmann F, Pfreundschuh M. Related Articles Immune recruitment by bispecific antibodies for the treatment of Hodgkin disease. *Cancer Chemother Pharmacol.* 2000; 46 Suppl:S33-6. 5 34: Tesch H, Engert A, Manzke O, Diehl V, Bohlen H. Treatment of patients with malignant lymphomas with monoclonal antibodies *Bone Marrow Transplant.* 2000 May; 25 Suppl 2:S50-3. 9 35: Katzenwadel A, Schleier H, Gierschner D, Wetterauer U, Elsasser-Beile U. Construction and in vivo evaluation of an anti-PSA x anti-CD3 bispecific antibody for the immunotherapy of prostate cancer. *Anticancer Res.* 2000 May-Jun; 20(3A):1551-5. 9 36: van Spriel AB, van Ojik HH, van De Winkel JG. Immunotherapeutic perspective for bispecific antibodies. *Immunol Today.* 2000 Aug; 21(8):391-7 2 37: Takemura S, Asano R, Tsumoto K, Arai T, Sakurai N, Kodama H, Yoshida H, Katayose Y, Suzuki M, Matsuno S, Kudo T, Kumagai I. Functional Fv fragment of an antibody specific for CD28: Fv-mediated co-stimulation of T cells. *FEBS Lett.* 2000 Jul 7; 476(3):266-71. 6 38: Zeidler R, Mysliwicz J, Csanady M, Walz A, Ziegler I, Schmitt B, Wollenberg B, Lindhofer H. The Fc-region of a new class of intact bispecific antibody mediates activation of accessory cells and NK cells and induces direct phagocytosis of tumour cells. *Br J Cancer.* 2000 Jul; 83(2):261-6. 0 39: Hillairet de Boisferon M, Raguin O, Dussaillant M, Rostene W, Barbet J, Gruaz-Guyon A. Enhanced targeting specificity to tumor cells by simultaneous recognition of two antigens. *Bioconjug Chem.* 2000 Jul-Aug; 11(4):452-60. 5 40: Dmitriev I, Kashentseva E, Rogers BE, Krasnykh V, Curiel DT. Ectodomain of coxsackievirus and adenovirus receptor

genetically fused to epidermal growth factor mediates adenovirus targeting to epidermal growth factor receptor-positive cells. *J Virol.* 2000 Aug; 74(15):6875-84. 7 41: Renner C, Hartmann F, Jung W, Deisting C, Juwana M, Pfreundschuh M. Initiation of humoral and cellular immune responses in patients with refractory Hodgkin's disease by treatment with an anti-CD16/CD30 bispecific antibody. *Cancer Immunol Immunother.* 2000 Jun; 49(3):173-80. 7 42: Haisma HJ, Grill J, Curiel DT, Hoogeland S, van Beusechem VW, Pinedo HM, Gerritsen WR. Targeting of adenoviral vectors through a bispecific single-chain antibody. *Cancer Gene Ther.* 2000 Jun; 7(6):901-4. 1 43: Cochlovius B, Kipriyanov SM, Stassar MJ, Christ O, Schuhmacher J, Strauss G, Moldenhauer G, Little M. Treatment of human B cell lymphoma xenografts with a CD3 x CD19 diabody and T cells. *J Immunol.* 2000 Jul 15; 165(2):888-95. 3 44: Weiner LM. Bispecific antibodies in cancer therapy. *Cancer J Sci Am.* 2000 May; 6 Suppl 3:S265-71 available. 7 45: Zangemeister-Wittke U, Leech SH, Olie RA, Simoes-Wust AP, Gautschi O, Luedke GH, Natt F, Haner R, Martin P, Hall J, Nalin CM, Stahel RA. A novel bispecific antisense oligonucleotide inhibiting both bcl-2 and bcl-xL expression efficiently induces apoptosis in tumor cells *Clin Cancer Res.* 2000 Jun; 6(6):2547-55. 1 46: Schroder CP, Kroesen BJ, de Leij LF, de Vries EG. Related Articles Purging of epithelial tumor cells from peripheral blood stem cells by means of the bispecific antibody BIS-1 *Clin Cancer Res.* 2000 Jun; 6(6):2521-7. 8 47: Hufton SE, van Neer N, van den Beuken T, Desmet J, Sablon E, Hoogenboom HR. Development and application of cytotoxic T lymphocyte-associated antigen 4 as a protein scaffold for the generation of novel binding ligands. *FEBS Lett.* 2000 Jun 23; 475(3):225-31. 1 48: Ram S, Merriwether W, Buchsbaum DJ. Synthesis and biodistribution of peptide based 99mTc/186Re-MAGIPG-D612 monoclonal antibody in nude mice bearing colon cancer xenografts. *Cancer Biother Radiopharm.* 1997 Feb; 12(1):55-62. 8 49: Barbet J, Kraeber-Bodere F, Vuillez JP, Gautherot E, Rouvier E, Chatal JF. Pretargeting with the affinity enhancement system for radioimmunotherapy. *Cancer Biother Radiopharm.* 1999 Jun; 14(3):153-66 0 50: Hall N, Tomsett AB. Structure-function analysis of NADPH:nitrate reductase from *Aspergillus nidulans*: analysis of altered pyridine nucleotide specificity in vivo. *Microbiology.* 2000 Jun; 146 (Pt 6):1399-406. 8 51: Lefterova P, Marten A, Buttgerit P, Weineck S, Scheffold C, Huhn D, Schmidt-Wolf IG. Targeting of natural killer-like T immunologic effector cells against leukemia and lymphoma cells by reverse antibody-dependent cellular cytotoxicity. *J Immunother.* 2000 May-Jun; 23(3):304-10. 9 52: de Leij L, Molema G, Helfrich W, Kroesen BJ. Bispecific antibodies for treatment of cancer in experimental animal models and man. *Adv Drug Deliv Rev.* 1998 Apr 6; 31(1-2):105-129. 0 53: Zuo Z, Jimenez X, Witte L, Zhu Z. An efficient route to the production of an IgG-like bispecific antibody. *Protein Eng.* 2000 May; 13(5):361-7. 0 54: de Wolf FA, Brett GM. Ligand-binding proteins: their potential for application in systems for controlled delivery and uptake of ligands. *Pharmacol Rev.* 2000 Jun; 52(2):207-36 0 55: Feuring-Buske M, Buske C, Unterhalt M, Hiddemann W. Related Articles Recent advances in antigen-targeted therapy in non-Hodgkin's lymphoma. *Ann Hematol.* 2000 Apr; 79(4):167-74 3 56: Keler T, Wallace PK, Vitale LA, Russoniello C, Sundarapandian K, Graziano RF, Deo YM. Differential effect of cytokine treatment on Fc alpha receptor I- and Fc gamma receptor I-mediated tumor cytotoxicity by monocyte-derived macrophages. *J Immunol.* 2000 Jun 1; 164(11):5746-52. 2 57: Wang H, Liu Y, Wei L, Guo Y. Bi-specific antibodies in cancer therapy. *Adv Exp Med Biol.* 2000; 465:369-80 available. 1 58: Vander Mijnsbrugge K, Meyermans H, Van Montagu M, Bauw G, Boerjan W. Wood formation in poplar: identification, characterization, and seasonal variation of xylem proteins. *Planta.* 2000 Mar; 210(4):589-98. 2 59: Kriangkum J, Xu B, Gervais C, Paquette D, Jacobs FA, Martin L, Suresh MR. Development and characterization of a bispecific single-chain antibody directed against T cells and ovarian carcinoma. *Hybridoma.* 2000 Feb; 19(1):33-41. 9 60: Staerz UD, Lee DS, Qi Y. Induction of specific immune tolerance with hybrid antibodies. *Immunol Today.* 2000 Apr; 21(4):172-6 available. 7 61: Hoefnagel CA. Nuclear medicine therapy of neuroblastoma. *Q J Nucl Med.* 1999 Dec; 43(4):336-43 4 62: Fernandez-Arias A, Alabart JL, Folch J, Beckers JF. Related Articles Interspecies pregnancy of Spanish ibex (*Capra pyrenaica*) fetus in domestic goat (*Capra hircus*) recipients induces abnormally high plasmatic levels of pregnancy-associated glycoprotein. *Theriogenology.* 1999 Jun; 51(8):1419-30. 0 63: Wessels BW, Meares CF. Physical and chemical properties of radionuclide therapy. *Semin Radiat Oncol.* 2000 Apr; 10(2):115-22 0 64: Helfrich W, Haisma HJ, Magdolen V, Luther T, Bom VJ, Westra J, van der Hoeven R, Kroesen BJ, Molema G, de Leij L. A rapid and versatile method for harnessing scFv antibody fragments with various biological effector functions. *J Immunol Methods.* 2000 Apr 3; 237(1-2):131-45. 8 65: Gautherot E, Rouvier E, Daniel L, Loucif E, Bouhou J, Manetti C, Martin M, Le Doussal JM, Barbet J. Pretargeted radioimmunotherapy of human colorectal xenografts with bispecific antibody and 131I-labeled bivalent hapten. *J Nucl Med.* 2000 Mar; 41(3):480-7. 3 66: Loffler A, Kufer P, Lutterbuse R, Zettl F, Daniel PT, Schwenkenbecher JM, Riethmuller G, Dorken B, Bargou RC. Related Articles A recombinant bispecific single-chain antibody, CD19 x CD3, induces rapid and high lymphoma-directed cytotoxicity by unstimulated T lymphocytes. *Blood.* 2000 Mar 15; 95(6):2098-103. 0 67: Morganelli PM, Kennedy SM, Mitchell TI. Differential effects of interferon-gamma on metabolism of lipoprotein immune complexes mediated by specific human macrophage Fc gamma receptors. *J Lipid Res.* 2000 Mar; 41(3):405-15. 8 68: Muzac I, Wang J, Anzellotti D, Zhang H, Ibrahim RK. Related Articles Functional expression of an Arabidopsis cDNA clone encoding a flavonol 3'-O-methyltransferase and characterization of the gene product. *Arch Biochem Biophys.* 2000 Mar 15; 375(2):385-8. 7 69: Robins RA. Counting antigens using antibodies. *Immunol Today.* 2000 Mar; 21(3):154-5. available. 4 70: Wickham TJ. Targeting adenovirus. *Gene Ther.* 2000 Jan; 7(2):110-4 5 71: Reinagel ML, Taylor RP. Transfer of immune complexes from erythrocyte CR1 to mouse macrophages. *J Immunol.* 2000 Feb 15; 164(4):1977-85. 8 72: Molema G, Cohen Tervaert JW, Kroesen BJ, Helfrich W, Meijer DK, de Leij LF. CD3 directed bispecific antibodies induce increased lymphocyte-endothelial cell interactions in vitro. *Br J Cancer.* 2000 Jan; 82(2):472-9. 7 73: Elsasser D, Stadick H, van de Winkel JG, Valerius T. Related Articles GM-CSF as adjuvant for immunotherapy with bispecific antibodies. *Eur J Cancer.* 1999 Aug; 35 Suppl 3:S25-8 available. 8 74: Molema G, Kroesen BJ, Helfrich W, Meijer DK, de Leij LF. The use of bispecific antibodies in tumor cell and tumor vasculature directed immunotherapy. *J Control Release.* 2000 Feb 14; 64(1-3):229-39 0 75: Bodey B, Bodey B, Siegel SE, Kaiser HE. Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery

of chemotherapeutic agents. *Curr Pharm Des.* 2000 Feb; 6(3):261-76. 9 76: Kudo T, Suzuki M, Katayose Y, Shinoda M, Sakurai N, Kodama H, Ichiyama M, Takemura S, Yoshida H, Saeki H, Saijo S, Takahashi J, Tominaga T, Matsuno S. Specific targeting immunotherapy of cancer with bispecific antibodies. *Tohoku J Exp Med.* 1999 Aug; 188(4):275-88. 5 77: Lu D, Kotanides H, Jimenez X, Zhou Q, Persaud K, Bohlen P, Witte L, Zhu Z. Acquired antagonistic activity of a bispecific diabody directed against two different epitopes on vascular endothelial growth factor receptor 2. *J Immunol Methods.* 1999 Nov 19; 230(1-2):159-71. 3 78: Koelemij R, Kuppen PJ, van de Velde CJ, Fleuren GJ, Hagenaars M, Eggermont AM. Bispecific antibodies in cancer therapy, from the laboratory to the clinic. *J Immunother.* 1999 Nov; 22(6):514-24. 0 79: Ohmi Y, Shiku H, Nishimura T. Tumor-specific targeting of T helper type 1 (Th1) cells by anti-CD3 x anti-c-ErbB-2 bispecific antibody. *Cancer Immunol Immunother.* 1999 Nov; 48(8):456-62. 0 80: Amoroso AR, Alpaugh RK, Barth MW, McCall AM, Weiner LM. Related Articles Production and characterization of mice transgenic for the A and B isoforms of human Fc gamma RIII. *Cancer Immunol Immunother.* 1999 Nov; 48(8):443-55. 9 81: Vuillez JP, Kraeber-Bodere F, Moro D, Bardies M, Douillard JY, Gautherot E, Rouvier E, Barbet J, Garban F, Moreau P, Chatal JF. Radioimmunotherapy of small cell lung carcinoma with the two-step method using a bispecific anti-carcinoembryonic antigen/anti-diethylenetriaminepentaacetic acid (DTPA) antibody and iodine-131 Di-DTPA hapten: results of a phase I/II trial. *Clin Cancer Res.* 1999 Oct; 5(10 Suppl):3259s-3267s. 3 82: Kraeber-Bodere F, Bardet S, Hoefnagel CA, Vieira MR, Vuillez JP, Murat A, Ferreira TC, Bardies M, Ferrer L, Resche I, Gautherot E, Rouvier E, Barbet J, Chatal JF. Radioimmunotherapy in medullary thyroid cancer using bispecific antibody and iodine 131-labeled bivalent hapten: preliminary results of a phase I/II clinical trial. *Clin Cancer Res.* 1999 Oct; 5(10 Suppl):3190s-3198s. 3 83: Kraeber-Bodere F, Faivre-Chauvet A, Sai-Maurel C, Campion L, Fiche M, Gautherot E, Le Boterff J, Barbet J, Chatal JF, Thedrez P. Toxicity and efficacy of radioimmunotherapy in carcinoembryonic antigen-producing medullary thyroid cancer xenograft: comparison of iodine 131-labeled F(ab')₂ and pretargeted bivalent hapten and evaluation of repeated injections. *Clin Cancer Res.* 1999 Oct; 5(10 Suppl):3183s-3189s. 2 84: Gautherot E, Kraeber-Bodere F, Daniel L, Fiche M, Rouvier E, Sai-Maurel C, Thedrez P, Chatal JF, Barbet J. Immunohistology of carcinoembryonic antigen (CEA)-expressing tumors grafted in nude mice after radioimmunotherapy with 131I-labeled bivalent hapten and anti-CEA x antihapten bispecific antibody. *Clin Cancer Res.* 1999 Oct; 5(10 Suppl):3177s-3182s. 1 85: Arndt MA, Krauss J, Kipriyanov SM, Pfreundschuh M, Little M. A bispecific diabody that mediates natural killer cell cytotoxicity against xenotransplanted human Hodgkin's tumors. *Blood.* 1999 Oct 15; 94(8):2562-8. 8 86: Kipriyanov SM, Moldenhauer G, Schuhmacher J, Cochlovius B, Von der Lieth CW, Matys ER, Little M. Bispecific tandem diabody for tumor therapy with improved antigen binding and pharmacokinetics. *J Mol Biol.* 1999 Oct 15; 293(1):41-56. 4 87: Segal DM, Weiner GJ, Weiner LM. Bispecific antibodies in cancer therapy. *Curr Opin Immunol.* 1999 Oct; 11(5):558-62. 4 88: Hudson PJ. Recombinant antibody constructs in cancer therapy. *Curr Opin Immunol.* 1999 Oct; 11(5):548-57. 2 89: Koumariannou AA, Hudson M, Williams R, Epenetos AA, Stamp GW. Development of a novel bi-specific monoclonal antibody approach for tumour targeting. *Br J Cancer.* 1999 Oct; 81(3):431-9. 7 90: Pavlinkova G, Booth BJ, Batra SK, Colcher D. Radioimmunotherapy of human colon cancer xenografts using a dimeric single-chain Fv antibody construct. *Clin Cancer Res.* 1999 Sep; 5(9):2613-9. 0 91: Liu Z, Wong JT. Proliferative and regenerative capacities of CD4(+) T cells upon TCR stimulation. *Clin Immunol.* 1999 Oct; 93(1):16-23. 7 92: Wang D, Nicolle MW. Generation of acetylcholine receptor-specific human T cell lines using heterobifunctional antibody-targeted antigen presentation. *J Neuroimmunol.* 1999 Sep 1; 99(1):114-21. 4 93: Boerman OC, Kranenborg MH, Oosterwijk E, Griffiths GL, McBride WJ, Oyen WJ, de Weijert M, Oosterwijk-Wakka J, Hansen HJ, Corstens FH. Pretargeting of renal cell carcinoma: improved tumor targeting with a bivalent chelate. *Cancer Res.* 1999 Sep 1; 59(17):4400-5. 9 94: Rice DC, Chapoval AI, Porter L, Nelson H. Induction of antitumor immunity after cure of pulmonary metastases, using staphylococcal enterotoxin B and bispecific antibody. *Cancer Immunol Immunother.* 1999 Aug; 48(5):230-8. 9 95: Smans KA, Ingvarsson MB, Lindgren P, Canevari S, Walt H, Stigbrand T, Backstrom T, Millan JL. Bispecific antibody-mediated lysis of primary cultures of ovarian carcinoma cells using multiple target antigens. *Int J Cancer.* 1999 Oct 8; 83(2):270-7. 8 96: Haisma HJ, Pinedo HM, Rijswijk A, der Meulen-Muileman I, Sosnowski BA, Ying W, Beusechem VW, Tillman BW, Gerritsen WR, Curiel DT. Tumor-specific gene transfer via an adenoviral vector targeted to the pan-carcinoma antigen EpCAM. *Gene Ther.* 1999 Aug; 6(8):1469-74. 1 97: Bobrovnik SA. [The problem of determining the affinity of bivalent antibodies using ELISA and its mathematical solution]. *WMJ.* 1999 Jan-Feb; 71(1):112-4. Russian. 4 98: Schuurman J, Van Ree R, Perdok GJ, Van Doorn HR, Tan KY, Aalberse RC. Normal human immunoglobulin G4 is bispecific: it has two different antigen-combining sites. *Immunology.* 1999 Aug; 97(4):693-8. 5 99: Ruef J, Nordt TK, Peter K, Runge MS, Kubler W, Bode C. Related Articles A bispecific antifibrin-antiplatelet urokinase conjugate (BAAUC) induces enhanced clot lysis and inhibits platelet aggregation. *Thromb Haemost.* 1999 Jul; 82(1):109-14. 3 100: Rund LA, Cho BK, Manning TC, Holler PD, Roy EJ, Kranz DM. Bispecific agents target endogenous murine T cells against human tumor xenografts. *Int J Cancer.* 1999 Sep 24; 83(1):141-9. 1 101: Strehl J, Selmayr M, Kremer JP, Hultner L, Lindhofer H, Mocikat R. Gene therapy of B-cell lymphoma with cytokine gene-modified trioma cells. *Int J Cancer.* 1999 Sep 24; 83(1):113-20. 7 102: McCall AM, Adams GP, Amoroso AR, Nielsen UB, Zhang L, Horak E, Simmons H, Schier R, Marks JD, Weiner LM. Isolation and characterization of an anti-CD16 single-chain Fv fragment and construction of an anti-HER2/neu/anti-CD16 bispecific scFv that triggers CD16-dependent tumor cytotoxicity. *Mol Immunol.* 1999 May; 36(7):433-45. 6 103: Blackwell JL, Miller CR, Douglas JT, Li H, Peters GE, Carroll WR, Peters GE, Strong TV, Curiel DT. Retargeting to EGFR enhances adenovirus infection efficiency of squamous cell carcinoma. *Arch Otolaryngol Head Neck Surg.* 1999 Aug; 125(8):856-63. 1 104: Craig ML, Reinagel ML, Martin EN, Schlimgen R, Nardin A, Taylor RP. Infusion of bispecific monoclonal antibody complexes into monkeys provides immunologic protection against later challenge with a model pathogen. *Clin Immunol.* 1999 Aug; 92(2):170-80. 1 105: Wild MK, Strittmatter W, Matzku S, Schraven B, Meuer SC. Tumor therapy with bispecific antibody: the targeting and triggering steps can be separated employing a CD2-based strategy. *J Immunol.* 1999 Aug 15; 163(4):2064-72. 5 106: Zophel K,

Gruning T, Wunderlich G, Franke WG. Clinical value of a bispecific antibody binding to thyroglobulin and thyroperoxidase (TGPO-aAb) in various thyroid diseases. *Autoimmunity*. 1999; 29(4):257-62. 0 107: Brandl M, Grosse-Hovest L, Holler E, Kolb HJ, Jung G. Related Articles Bispecific antibody fragments with CD20 X CD28 specificity allow effective autologous and allogeneic T-cell activation against malignant cells in peripheral blood and bone marrow cultures from patients with B-cell lineage leukemia and lymphoma. *Exp Hematol*. 1999 Aug; 27(8):1264-70. 3 108: Manzke O, Fitzgerald KJ, Holliger P, Klock J, Span M, Fleischmann B, Hescheler J, Qinghua L, Johnson KS, Diehl V, Hoogenboom HR, Bohlen H. CD3X anti-nitrophenyl bispecific diabodies: universal immunotherapeutic tools for retargeting T cells to tumors. *Int J Cancer*. 1999 Aug 27; 82(5):700-8. 8 109: Zeidler R, Reisbach G, Wollenberg B, Lang S, Chaubal S, Schmitt B, Lindhofer H. Simultaneous activation of T cells and accessory cells by a new class of intact bispecific antibody results in efficient tumor cell killing. *J Immunol*. 1999 Aug 1; 163(3):1246-52. 0 110: Alt M, Muller R, Kontermann RE. Novel tetravalent and bispecific IgG-like antibody molecules combining single-chain diabodies with the immunoglobulin gamma1 Fc or CH3 region. *FEBS Lett*. 1999 Jul 2; 454(1-2):90-4. 2 111: Fischer R, Schumann D, Zimmermann S, Drossard J, Sack M, Schillberg S. Expression and characterization of bispecific single-chain Fv fragments produced in transgenic plants. *Eur J Biochem*. 1999 Jun; 262(3):810-6. 3 112: Kontermann RE, Muller R. Intracellular and cell surface displayed single-chain diabodies. *J Immunol Methods*. 1999 Jun 24; 226(1-2):179-88. 3 113: Yang CC, Chan HL. Preparation and characterization of beta 1-bungarotoxin bispecific monoclonal antibody. *Biochem Mol Biol Int*. 1999 Jun; 47(6):1039-48. 0 114: Hosono M, Hosono MN, Kraeber-Bodere F, Devys A, Thedrez P, Faivre-Chauvet A, Gautherot E, Barbet J, Chatal JF. Two-step targeting and dosimetry for small cell lung cancer xenograft with anti-NCAM/antihistamine bispecific antibody and radioiodinated bivalent hapten. *J Nucl Med*. 1999 Jul; 40(7):1216-21. 4 115: Posey JA, Raspet R, Verma U, Deo YM, Keller T, Marshall JL, Hodgson J, Mazumder A, Hawkins MJ. A pilot trial of GM-CSF and MDX-H210 in patients with erbB-2-positive advanced malignancies. *J Immunother*. 1999 Jul; 22(4):371-9. 9 116: Lamers CH, Gratama JW, Luider-Vrieling B, Bolhuis RL, Bast EJ. Large-scale production of natural cytokines during activation and expansion of human T lymphocytes in hollow fiber bioreactor cultures. *J Immunother*. 1999 Jul; 22(4):299-307. 1 117: Schweitzer-Stenner R, Engelke M, Licht A, Pecht I. Related Articles Mast cell stimulation by co-clustering the type I Fc epsilon-receptors with mast cell function-associated antigens. *Immunol Lett*. 1999 May 3; 68(1):71-8. 8 118: Smirnova MB, Nikulina VA, Segal OL, Kizim EA, Massino YS, Ryazanskaya NN, Kolyaskina GI, Dmitriev AD. Single-step sandwich immunoassay of myoglobin with bifunctional monoclonal antibodies. *Biochemistry (Mosc)*. 1999 Jun; 64(6):639-47. 8 119: Holliger P, Manzke O, Span M, Hawkins R, Fleischmann B, Qinghua L, Wolf J, Diehl V, Cochet O, Winter G, Bohlen H. Related Articles Carcinoembryonic antigen (CEA)-specific T-cell activation in colon carcinoma induced by anti-CD3 x anti-CEA bispecific diabodies and B7 x anti-CEA bispecific fusion proteins. *Cancer Res*. 1999 Jun 15; 59(12):2909-16. 4 120: Watanabe M, Wallace PK, Keler T, Deo YM, Akewanlop C, Hayes DF. Antibody dependent cellular phagocytosis (ADCP) and antibody dependent cellular cytotoxicity (ADCC) of breast cancer cells mediated by bispecific antibody, MDX-210. *Breast Cancer Res Treat*. 1999 Feb; 53(3):199-207. 6 121: Elsasser D, Stadick H, Stark S, Van de Winkel JG, Gramatzki M, Schrott KM, Valerius T, Schafhauser W. Preclinical studies combining bispecific antibodies with cytokine-stimulated effector cells for immunotherapy of renal cell carcinoma. *Anticancer Res*. 1999 Mar-Apr; 19(2C):1525-8. 7 122: Haas C, Herold-Mende C, Gerhards R, Schirmacher V. Related Articles An effective strategy of human tumor vaccine modification by coupling bispecific costimulatory molecules. *Cancer Gene Ther*. 1999 May-Jun; 6(3):254-62. 1 123: Nardin A, Schlimgen R, Holers VM, Taylor RP. A prototype pathogen bound ex vivo to human erythrocyte complement receptor 1 via bispecific monoclonal antibody complexes is cleared to the liver in a mouse model. *Eur J Immunol*. 1999 May; 29(5):1581-6. 2 124: Morimoto K, Inouye K. Method for the preparation of bispecific F(ab')2mu fragments from mouse monoclonal antibodies of the immunoglobulin M class and characterization of the fragments. *J Immunol Methods*. 1999 Apr 22; 224(1-2):43-50. 5 125: Tillman BW, de Gruilj TD, Luykx-de Bakker SA, Scheper RJ, Pinedo HM, Curiel TJ, Gerritsen WR, Curiel DT. Maturation of dendritic cells accompanies high-efficiency gene transfer by a CD40-targeted adenoviral vector. *J Immunol*. 1999 Jun 1; 162(11):6378-83. 0 126: Chaudri ZN, Bartlett-Jones M, Panayotou G, Klonisch T, Roitt IM, Lund T, Delves PJ. Dual specificity antibodies using a double-stranded oligonucleotide bridge. *FEBS Lett*. 1999 Apr 30; 450(1-2):23-6. 0 127: Somasundaram C, Sundarapandian K, Keler T, Deo YM, Graziano RF. Development of a trispecific antibody conjugate that directs two distinct tumor-associated antigens to CD64 on myeloid effector cells. *Hum Antibodies*. 1999; 9(1):47-54. 5 128: Denton G, Brady K, Lo BK, Murray A, Graves CR, Hughes OD, Tendler SJ, Laughton CA, Price MR. Production and characterization of an anti-(MUC1 mucin) recombinant diabody. *Cancer Immunol Immunother*. 1999 Apr; 48(1):29-38. 6 129: Pullarkat V, Deo Y, Link J, Spears L, Marty V, Curnow R, Groshen S, Gee C, Weber JS. A phase I study of a HER2/neu bispecific antibody with granulocyte-colony-stimulating factor in patients with metastatic breast cancer that overexpresses HER2/neu. *Cancer Immunol Immunother*. 1999 Apr; 48(1):9-21. 4 130: Aalberse RC, Schuurman J, van Ree R. The apparent monovalency of human IgG4 is due to bispecificity. *Int Arch Allergy Immunol*. 1999 Feb-Apr; 118(2-4):187-9. 3 131: Bauer S, Renner C, Juwana JP, Held G, Ohnesorge S, Gerlach K, Pfreundschuh M. Immunotherapy of human tumors with T-cell-activating bispecific antibodies: stimulation of cytotoxic pathways in vivo. *Cancer Res*. 1999 Apr 15; 59(8):1961-5. 7 132: DeNardo SJ, DeNardo GL, Brush J, Carter P. Phage library-derived human anti-TETA and anti-DOTA ScFv for pretargeting RIT. *Hybridoma*. 1999 Feb; 18(1):13-21. 3 133: Cochlovius B, Perschl A, Adema GJ, Zoller M. Human melanoma therapy in the SCID mouse: in vivo targeting and reactivation of melanoma-specific cytotoxic T cells by bi-specific antibody fragments. *Int J Cancer*. 1999 May 5; 81(3):486-93. 6 134: Robert B, Dorvillius M, Buchegger F, Garambois V, Mani JC, Pugnieres M, Mach JP, Pelegrin A. Tumor targeting with newly designed biparatopic antibodies directed against two different epitopes of the carcinoembryonic antigen (CEA). *Int J Cancer*. 1999 Apr 12; 81(2):285-91. 2 135: Hagenaars M, Ensink NG, Jonges LE, Chambers WH, Eggermont AM, van de Velde CJ, Fleuren GJ, Kuppen PJ. The development of a bi-specific anti-CD161A x anti-tumor antibody for rat NK cell targeting. *Immunobiology*. 1999 Feb; 200(1):31-48. 4 136: Kastenbauer E, Wollenberg B. [In search

of new treatment methods for head-neck carcinoma]. *Laryngorhinootologie*. 1999 Jan; 78(1):31-5 . 6 137: Barth RF, Soloway AH, Goodman JH, Gahbauer RA, Gupta N, Blue TE, Yang W, Tjarks W. Boron neutron capture therapy of brain tumors: an emerging therapeutic modality. *Neurosurgery*. 1999 Mar; 44(3):433-50; discussion 450-1 O 138: Sakurai N, Kudo T, Suzuki M, Tsumoto K, Takemura S, Kodama H, Ebara S, Teramae A, Katayose Y, Shinoda M, Kurokawa T, Hinoda Y, Imai K, Matsuno S, Kumagai I. SEA-scFv as a bifunctional antibody: construction of a bacterial expression system and its functional analysis. *Biochem Biophys Res Commun*. 1999 Mar 5; 256(1):223-30. 1 139: Bartlett JS, Kleinschmidt J, Boucher RC, Samulski RJ. Related Articles Targeted adeno-associated virus vector transduction of nonpermissive cells mediated by a bispecific F(ab'gamma)2 antibody. *Nat Biotechnol*. 1999 Feb; 17(2):181-6. 6 140: Becerril B, Poul MA, Marks JD. Toward selection of internalizing antibodies from phage libraries. *Biochem Biophys Res Commun*. 1999 Feb 16; 255(2):386-93. 8 141: Manzke O, Berthold F, Huebel K, Tesch H, Diehl V, Bohlen H. CD3xCD19 bispecific antibodies and CD28 bivalent antibodies enhance T-cell reactivity against autologous leukemic cells in pediatric B-ALL bone marrow. *Int J Cancer*. 1999 Mar 1; 80(5):715-22. 3 142: Wu S, Ma J, Che X, Liu Y, Wang H, Zhao J, Shen F, Xie T, Trojan J, Wu M, Guo Y. Treatment of hepatocellular carcinoma with the cellular tumor vaccines generated by in vitro modification of tumor cells with non gene transfer approaches. *Adv Exp Med Biol*. 1998; 451:283-93. 6 143: Schirmacher V, Haas C. Modification of cancer vaccines by virus infection and attachment of bispecific antibodies. An effective alternative to somatic gene therapy. *Adv Exp Med Biol*. 1998; 451:251-7 available. 2 144: Fernandez-Miguel G, Alarcon B, Iglesias A, Bluethmann H, Alvarez-Mon M, Sanz E, de la Hera A. Free in PMC , Related Articles Multivalent structure of an alphabetaT cell receptor. *Proc Natl Acad Sci U S A*. 1999 Feb 16; 96(4):1547-52. 145: Miotti S, Negri DR, Valota O, Calabrese M, Bolhuis RL, Gratama JW, Colnaghi MI, Canevari S. Level of anti-mouse-antibody response induced by bi-specific monoclonal antibody OC/TR in ovarian-carcinoma patients is associated with longer survival. *Int J Cancer*. 1999 Feb 19; 84(1):62-8. 146: Vignali DA, Vignali KM. Profound enhancement of T cell activation mediated by the interaction between the TCR and the D3 domain of CD4. *J Immunol*. 1999 Feb 1; 162(3):1431-9. 147: van Spruiel AB, van den Herik-Oudijk IE, van Sorge NM, Vile HA, van Strijp JA, van de Winkel JG. Effective phagocytosis and killing of *Candida albicans* via targeting FcgammaRI (CD64) or FcalphaRI (CD89) on neutrophils. *J Infect Dis*. 1999 Mar; 179(3):661-9. 148: Fleckenstein G, Osmers R, Puchta J. Monoclonal antibodies in solid tumours: approaches to therapy with emphasis on gynaecological cancer. *Med Oncol*. 1998 Dec; 15(4):212-21 149: Grosse-Hovest L, Brandl M, Dohsten M, Kalland T, Wilmanns W, Jung G. Tumor-growth inhibition with bispecific antibody fragments in a syngeneic mouse melanoma model: the role of targeted T-cell co-stimulation via CD28. *Int J Cancer*. 1999 Jan 5; 80(1):138-44. 150: Pfosser A, Brandl M, Salih H, Grosse-Hovest L, Jung G. Related Articles Role of target antigen in bispecific-antibody-mediated killing of human glioblastoma cells: a pre-clinical study. *Int J Cancer*. 1999 Feb 9; 80(4):612-6. 151: Kraeber-Bodere F, Faibre-Chauvet A, Sai-Maurel C, Gautherot E, Fiche M, Campion L, Le Boterff J, Barbet J, Chatal JF, Thedrez P. Bispecific antibody and bivalent hapten radioimmunotherapy in CEA-producing medullary thyroid cancer xenograft. *J Nucl Med*. 1999 Jan; 40(1):198-204. 152: Strauss G, Guckel B, Wallwiener D, Moldenhauer G. Related Articles Without prior stimulation, tumor-associated lymphocytes from malignant effusions lyse autologous tumor cells in the presence of bispecific antibody HEA125xOKT3. *Clin Cancer Res*. 1999 Jan; 5(1):171-80. 153: Autissier P, De Vos J, Liautard J, Tupitsyn N, Jacquet C, Chavdia N, Klein B, Brochier J, Gaillard JP. Dimerization and activation of the common transducing chain (gp130) of the cytokines of the IL-6 family by mAb. *Int Immunol*. 1998 Dec; 10(12):1881-9. 154: Connelly RJ, Hayden MS, Scholler JK, Tsu TT, Dupont B, Ledbetter JA, Kanner SB. Mitogenic properties of a bispecific single-chain Fv-Ig fusion generated from CD2-specific mAb to distinct epitopes. *Int Immunol*. 1998 Dec; 10(12):1863-72. 155: Hartmann F, Renner C, Jung W, Pfreundschuh M. Anti-CD16/CD30 bispecific antibodies as possible treatment for refractory Hodgkin's disease. *Leuk Lymphoma*. 1998 Oct; 31(3-4):385-92. 156: Miller CR, Buchsbaum DJ, Reynolds PN, Douglas JT, Gillespie GY, Mayo MS, Raben D, Curiel DT. Differential susceptibility of primary and established human glioma cells to adenovirus infection: targeting via the epidermal growth factor receptor achieves fiber receptor-independent gene transfer. *Cancer Res*. 1998 Dec 15; 58(24):5738-48. 157: Schirmacher V, Ahlert T, Probstle T, Steiner HH, Herold-Mende C, Gerhards R, Hagmuller E, Steiner HH. Related Articles Immunization with virus-modified tumor cells. *Semin Oncol*. 1998 Dec; 25(6):677-96 158: McLeod AL, Krause JE, Cuello AC, Ribeiro-da-Silva A. Free in PMC , Preferential synaptic relationships between substance P-immunoreactive boutons and neurokinin 1 receptor sites in the rat spinal cord. *Proc Natl Acad Sci U S A*. 1998 Dec 22; 95(26):15775-80. 159: Olafsen T, Rasmussen IB, Norderhaug L, Bruland OS, Sandlie I. IgM secretory tailpiece drives multimerisation of bivalent scFv fragments in eukaryotic cells. *Immunotechnology*. 1998 Oct; 4(2):141-53. 160: Maeda S, Okamura M, Kobayashi M, Omata T. Nitrite-specific active transport system of the cyanobacterium *Synechococcus* sp. strain PCC 7942. *J Bacteriol*. 1998 Dec; 180(24):6761-3. 161: Guyre CA, Fanger MW. Macrophage-targeted killing and vaccines. *Res Immunol*. 1998 Sep-Oct; 149(7-8):655-60 available. 162: Daniel PT, Kroidl A, Kopp J, Sturm I, Moldenhauer G, Dorken B, Pezzutto A. Immunotherapy of B-cell lymphoma with CD3x19 bispecific antibodies: costimulation via CD28 prevents "veto" apoptosis of antibody-targeted cytotoxic T cells. *Blood*. 1998 Dec 15; 92(12):4750-7. 163: Cao Y, Christian S, Suresh MR. Development of a bispecific monoclonal antibody as a universal immunoprobe for detecting biotinylated macromolecules. *J Immunol Methods*. 1998 Nov 1; 220(1-2):85-91. 164: Gautherot E, Le Doussal JM, Bouhou J, Manetti C, Martin M, Rouvier E, Barbet J. Delivery of therapeutic doses of radioiodine using bispecific antibody-targeted bivalent haptens. *J Nucl Med*. 1998 Nov; 39(11):1937-43. 165: Luo D, Geng M, Schultes B, Ma J, Xu DZ, Hamza N, Qi W, Noujaim AA, Madiyalakan R. Expression of a fusion protein of scFv-biotin mimetic peptide for immunoassay. *J Biotechnol*. 1998 Oct 27; 65(2-3):225-8. 166: Chen J, Mokotoff M, Zhou JH, Fanger MW, Ball ED. Related Articles An immunoconjugate of Lys3-bombesin and monoclonal antibody 22 can specifically induce FcgammaRI (CD64)-dependent monocyte- and neutrophil-mediated lysis of small cell carcinoma of the lung cells. *Clin Cancer Res*. 1995 Apr; 1(4):425-34. 167: Chen J, Zhou JH, Ball ED. Monocyte-mediated lysis of acute myeloid leukemia cells in the presence of the

bispecific antibody 251 x 22 (anti-CD33 x anti-CD64). *Clin Cancer Res.* 1995 Nov; 1(11):1319-25. 168: Cao Y, Suresh MR. Bispecific antibodies as novel bioconjugates. *Bioconjug Chem.* 1998 Nov-Dec; 9(6):635-44 169: Farah RA, Clinchy B, Herrera L, Vitetta ES. The development of monoclonal antibodies for the therapy of cancer. *Crit Rev Eukaryot Gene Expr.* 1998; 8(3-4):321-56 170: Yu YY, Van Wie BJ, Koch AR, Moffett DF, Davis WC. Related Articles Real-time analysis of immunogen complex reaction kinetics using surface plasmon resonance. *Anal Biochem.* 1998 Oct 15; 263(2):158-68. 171: Patrick TA, Kranz DM, Zachary JF, Roy EJ. Intracerebral bispecific ligand-antibody conjugate increases survival of animals bearing endogenously arising brain tumors. *Int J Cancer.* 1998 Nov 9; 78(4):470-9. 172: Krebs B, Ackermann B, Rose-John S. Specific targeting of cytokine-secreting cells: a bispecific diabody recognizing human interleukin-6 and CD3 induces T cell-mediated killing. *J Interferon Cytokine Res.* 1998 Sep; 18(9):783-91. 173: Klivenyi G, Schuhmacher J, Patzelt E, Hauser H, Matys R, Moock M, Regiert T, Maier-Borst W. Gallium-68 chelate imaging of human colon carcinoma xenografts pretargeted with bispecific anti-CD44V6/anti-gallium chelate antibodies. *J Nucl Med.* 1998 Oct; 39(10):1769-76. 174: Chan CH, Wang J, RR, Glennie MJ. Internalization of the lymphocytic surface protein CD22 is controlled by a novel membrane proximal cytoplasmic motif. *J Biol Chem.* 1998 Oct 23; 273(43):27809-15. 175: Kreutz FT, Wishart DS, Suresh MR. Efficient bispecific monoclonal antibody purification using gradient thiophilic affinity chromatography. *J Chromatogr B Biomed Sci Appl.* 1998 Sep 4; 714(2):161-70. 176: Shiraishi N, Croy C, Kaur J, Campbell WH. Engineering of pyridine nucleotide specificity of nitrate reductase: mutagenesis of recombinant cytochrome b reductase fragment of *Neurospora crassa* NADPH:Nitrate reductase. *Arch Biochem Biophys.* 1998 Oct 1; 358(1):104-15. 177: Russoniello C, Somasundaram C, Schlom J, Deo YM, Keler T. Characterization of a novel bispecific antibody that mediates Fcγ receptor type I-dependent killing of tumor-associated glycoprotein-72-expressing tumor cells. *Clin Cancer Res.* 1998 Sep; 4(9):2237-43. 178: Hosono M, Hosono MN, Kraeber-Bodere F, Devys A, Thedrez P, Fiche M, Gautherot E, Barbet J, Chatal JF. Biodistribution and dosimetric study in medullary thyroid cancer xenograft using bispecific antibody and iodine-125-labeled bivalent hapten. *J Nucl Med.* 1998 Sep; 39(9):1608-13. 179: Kranz DM, Manning TC, Rund LA, Cho BK, Gruber MM, Roy EJ. Targeting tumor cells with bispecific antibodies and T cells. *J Control Release.* 1998 Apr 30; 53(1-3):77-84. 180: Sforzini S, de Toter D, Gaggero A, Ippoliti R, Glennie MJ, Canevari S, Stein H, Ferrini S. Targeting of saporin to Hodgkin's lymphoma cells by anti-CD30 and anti-CD25 bispecific antibodies. *Br J Haematol.* 1998 Sep; 102(4):1061-8. 181: Volm M. Multidrug resistance and its reversal. *Anticancer Res.* 1998 Jul-Aug; 18(4C):2905-17 182: Muller KM, Arndt KM, Pluckthun A. A dimeric bispecific miniantibody combines two specificities with avidity. *FEBS Lett.* 1998 Jul 31; 432(1-2):45-9. 183: Kreutz FT, Xu DZ, Suresh MR. A new method to generate quadromas by electrofusion and FACS sorting. *Hybridoma.* 1998 Jun; 17(3):267-73. 184: Kollet O, Haimovich J, Hollander N. Idiotype-specific inhibition of LFA-1-mediated cell adhesion by anti-idiotypic x anti-LFA-1 bispecific antibodies. *Immunol Lett.* 1998 Jul; 62(3):171-6. 185: Kiprianov SM, Moldenhauer G, Strauss G, Little M. Related Articles Bispecific CD3 x CD19 diabody for T cell-mediated lysis of malignant human B cells. *Int J Cancer.* 1998 Aug 31; 77(5):763-72. 186: De Jonge J, Heirman C, de Veerman M, Van Meirvenne S, Moser M, Leo O, Thielemans K. In vivo retargeting of T cell effector function by recombinant bispecific single chain Fv (anti-CD3 x anti-idiotypic) induces long-term survival in the murine BCL1 lymphoma model. *J Immunol.* 1998 Aug 1; 161(3):1454-61. 187: Baba M, Hideshima T, Yamashita Y, Shirakusa T. Potentiation of cytotoxicity against a CEA positive cell line by the bispecific antibody OH1 using LAK cells from cancer-bearing patients. *Oncol Rep.* 1998 Sep-Oct; 5(5):1141-6. 188: Wurflein D, Dechant M, Stockmeyer B, Tutt AL, Hu P, Repp R, Kalden JR, van de Winkel JG, Epstein AL, Valerius T, Glennie M, Gramatzki M. Evaluating antibodies for their capacity to induce cell-mediated lysis of malignant B cells. *Cancer Res.* 1998 Jul 15; 58(14):3051-8. 189: Kruger K, Jochum C, Glusenka KH, Krusemann C, Lorenz P, Eberle-Adamkiewicz G, Drosdzik W, Beelen DW, Coenen HH, Rajewsky MF. New modular delivery system for diagnostic and therapeutic pre-targeting using tautomer-specific monoclonal antibody EM-6-47 and 3-substituted adenines. *Int J Cancer.* 1998 Aug 12; 77(4):610-9. 190: Barbet J, Peltier P, Bardet S, Vuillez JP, Bachelot I, Denet S, Olivier P, Leccia F, Corcuff B, Huglo D, Proye C, Rouvier E, Meyer P, Chatal JF. Radioimmunodetection of medullary thyroid carcinoma using indium-111 bivalent hapten and anti-CEA x anti-DTPA-indium bispecific antibody. *J Nucl Med.* 1998 Jul; 39(7):1172-8. 191: RR. Production of bispecific and trispecific F(ab)2 and F(ab)3 antibody derivatives. *Methods Mol Biol.* 1998; 80:121-34. available. 192: Merchant AM, Zhu Z, Yuan JQ, Goddard A, Adams CW, Presta LG, Carter P., Protein, Nucleotide An efficient route to human bispecific IgG. *Nat Biotechnol.* 1998 Jul; 16(7):677-81. 193: Rouard H, Tamasdan S, Moncuit J, Moutel S, Michon J, Fridman WH, Teillaud JL. Fc receptors as targets for immunotherapy. *Int Rev Immunol.* 1997; 16(1-2):147-85 194: Link BK, Kostelny SA, Cole MS, Fusselman WP, Tso JY, Weiner GJ. Anti-CD3-based bispecific antibody designed for therapy of human B-cell malignancy can induce T-cell activation by antigen-dependent and antigen-independent mechanisms. *Int J Cancer.* 1998 Jul 17; 77(2):251-6. 195: Quesada A, Hidalgo J, Fernandez E. Three Nrt2 genes are differentially regulated in *Chlamydomonas reinhardtii*. *Mol Gen Genet.* 1998 May; 258(4):373-7. 196: Koo K, Foegeding PM, Swaisgood HE. Development of a streptavidin-conjugated single-chain antibody that binds *Bacillus cereus* spores. *Appl Environ Microbiol.* 1998 Jul; 64(7):2497-502. 197: Zhu Z, Zapata G, Shalaby R, Snedecor B, Chen H, Carter P. High level secretion of a humanized bispecific diabody from *Escherichia coli*. *Biotechnology (N Y).* 1996 Feb; 14(2):192-6. 198: Sanna PP, De Logu A, Williamson RA, Samson ME, Altieri DC, Bloom FE, Burton DR. Rapid assay of phage-derived recombinant human fabs as bispecific antibodies. *Biotechnology (N Y).* 1995 Nov; 13(11):1221-4. 199: Neri D, de Lalla C, Petrucci H, Neri P, Winter G. Related Articles Calmodulin as a versatile tag for antibody fragments. *Biotechnology (N Y).* 1995 Apr; 13(4):373-7. 200: Bookman MA. Biological therapy of ovarian cancer: current directions. *Semin Oncol.* 1998 Jun; 25(3):381-96 201: McGuinness BT, Walter G, FitzGerald K, Schuler P, Mahoney W, Duncan AR, Hoogenboom HR. Phage diabody repertoires for selection of large numbers of bispecific antibody fragments. *Nat Biotechnol.* 1996 Sep; 14(9):1149-54. 202: Bookman MA. Biological therapy for gynecologic malignancies. *Cancer Treat Res.* 1998; 95:115-47 available. 203: Nardin A, Sutherland

WM, Hevey M, Schmaljohn A, Taylor RP. Quantitative studies of heteropolymer-mediated binding of inactivated Marburg virus to the complement receptor on primate erythrocytes. *J Immunol Methods*. 1998 Feb 1; 211(1-2):21-31. 204: Roy EJ, Cho BK, Rund LA, Patrick TA, Kranz DM. Targeting T cells against brain tumors with a bispecific ligand-antibody conjugate. *Int J Cancer*. 1998 May 29; 76(5):761-6. 205: Funaro A, Horenstein AL, Malavasi F. Monoclonal antibodies in clinical applications. *J Biol Regul Homeost Agents*. 1996 Oct-Dec; 10(4):72-82. No abstract available. 206: Kuhn SE, Nardin A, Klebba PE, Taylor RP. Escherichia coli bound to the primate erythrocyte complement receptor via bispecific monoclonal antibodies are transferred to and phagocytosed by human monocytes in an in vitro model. *J Immunol*. 1998 May 15; 160(10):5088-97. 207: Wingren C, Hansson UB. Surface properties of antigen-antibody complexes. *Scand J Immunol*. 1997 Aug; 46(2):159-67. 208: Molema G, Mesander G, Kroesen BJ, Helfrich W, Meijer DK, de Leij LF. Analysis of in vitro lymphocyte adhesion and transendothelial migration by fluorescent-beads-based flow cytometric cell counting. *Cytometry*. 1998 May 1; 32(1):37-43. 209: Haas C, Strauss G, Moldenhauer G, Iorio RM, Schirmmayer V. Bispecific antibodies increase T-cell stimulatory capacity in vitro of human autologous virus-modified tumor vaccine. *Clin Cancer Res*. 1998 Mar; 4(3):721-30. 210: Beun GD. [Immunology in clinical practice. XII. Indications for T-Cell-mediated immunotherapy of cancer]. *Ned Tijdschr Geneesk*. 1998 Feb 21; 142(8):392-6. Dutch. 211: Stocchi L, Nelson H. Diagnostic and therapeutic applications of monoclonal antibodies in colorectal cancer. *Dis Colon Rectum*. 1998 Feb; 41(2):232-50. 212: Xu D, Leveugle B, Kreutz FT, Suresh MR. Mimetic ligand-based affinity purification of immune complexes and immunoconjugates. *J Chromatogr B Biomed Sci Appl*. 1998 Mar 20; 706(2):217-29. 213: Jurcic JG, Scheinberg DA, Houghton AN. Monoclonal antibody therapy of cancer. *Cancer Chemother Biol Response Modif*. 1997; 17:195-216. No abstract available. 214: Makrides SC. Therapeutic inhibition of the complement system. *Pharmacol Rev*. 1998 Mar; 50(1):59-87. 215: Heijnen IA, Rijks LJ, Schiel A, Stockmeyer B, van Ojik HH, Dechant M, Valerius T, Keler T, Tutt AL, Glennie MJ, van Royen EA, Capel PJ, van de Winkel JG. Generation of HER-2/neu-specific cytotoxic neutrophils in vivo: efficient arming of neutrophils by combined administration of granulocyte colony-stimulating factor and Fc gamma receptor I bispecific antibodies. *J Immunol*. 1997 Dec 1; 159(11):5629-39. 216: Klein SC, van der Burg SH, Boer LH, Melief CJ, Kast WM, de Gast GC, Bast EJ. Targeting of cytotoxic T cells against leukemic B cells by bispecific antibody (aCD3 x aCD19) does not distract the T cell from its primary target. *J Immunol*. 1997 Dec 1; 159(11):5545-9. 217: Tesch H, Bohlen H, Wolf J, Engert A. [Pathogenesis and therapy of Hodgkin lymphoma]. *Med Klin*. 1998 Feb 15; 93(2):82-90. 218: Helfrich W, Kroesen BJ, Roovers RC, Westers L, Molema G, Hoogenboom HR, de Leij L. Construction and characterization of a bispecific diabody for retargeting T cells to human carcinomas. *Int J Cancer*. 1998 Apr 13; 76(2):232-9. 219: Blok VT, Daha MR, Tijsma O, Harris CL, Morgan BP, Fleuren GJ, Gorter A. A bispecific monoclonal antibody directed against both the membrane-bound complement regulator CD55 and the renal tumor-associated antigen G250 enhances C3 deposition and tumor cell lysis by complement. *J Immunol*. 1998 Apr 1; 160(7):3437-43. 220: Qi Y, Staerz UD. Specific inhibition of CD4+ T lymphocytes by a hybrid antibody. *Nat Biotechnol*. 1998 Mar; 16(3):271-5. 221: Riedle S, Rosel M, Zoller M. In vivo activation and expansion of T cells by a bi-specific antibody abolishes metastasis formation of human melanoma cells in SCID mice. *Int J Cancer*. 1998 Mar 16; 75(6):908-18. 222: Muller KM, Arndt KM, Strittmatter W, Pluckthun A. Related Articles The first constant domain (C(H)1 and C(L)) of an antibody used as heterodimerization domain for bispecific miniantibodies. *FEBS Lett*. 1998 Jan 30; 422(2):259-64. 223: FitzGerald K, Holliger P, Winter G. Improved tumour targeting by disulphide stabilized diabodies expressed in *Pichia pastoris*. *Protein Eng*. 1997 Oct; 10(10):1221-5. 224: Krebs B, Griffin H, Winter G, Rose-John S. Recombinant human single chain Fv antibodies recognizing human interleukin-6. Specific targeting of cytokine-secreting cells. *J Biol Chem*. 1998 Jan 30; 273(5):2858-65. 225: Fritzberg AR. Antibody pretargeted radiotherapy: a new approach and a second chance. *J Nucl Med*. 1998 Feb; 39(2):20N-22N, 36N. available. 226: Fernandez-Sesma A, Peluso RW, Bai X, Schulman JL, Levy DE, Moran TM. Superantigen-activated T cells redirected by a bispecific antibody inhibit vesicular stomatitis virus replication in vitro and in vivo. *J Immunol*. 1998 Feb 15; 160(4):1841-9. 227: Deo YM, Sundarapandian K, Keler T, Wallace PK, Graziano RF. Bispecific molecules directed to the Fc receptor for IgA (Fc alpha RI, CD89) and tumor antigens efficiently promote cell-mediated cytotoxicity of tumor targets in whole blood. *J Immunol*. 1998 Feb 15; 160(4):1677-86. 228: Fan Z, Mendelsohn J. Therapeutic application of anti-growth factor receptor antibodies. *Curr Opin Oncol*. 1998 Jan; 10(1):67-73. 229: Arnout J, Wittevrongel C, Vanrusselt M, Hoylaerts M, Vermeylen J. Beta-2-glycoprotein I dependent lupus anticoagulants form stable bivalent antibody beta-2-glycoprotein I complexes on phospholipid surfaces. *Thromb Haemost*. 1998 Jan; 79(1):79-86. 230: Schirmmayer V. [Tumor vaccines and active specific immunotherapy]. *Internist (Berl)*. 1997 Nov; 38(11):1050-4. available. 231: Zhu H, Jain RK, Baxter LT. Tumor pretargeting for radioimmunodetection and radioimmunotherapy. *J Nucl Med*. 1998 Jan; 39(1):65-76. 232: Curnow RT. Clinical experience with CD64-directed immunotherapy. An overview. *Cancer Immunol Immunother*. 1997 Nov-Dec; 45(3-4):210-5. 233: van Ojik HH, Repp R, Groenewegen G, Valerius T, van de Winkel JG. Clinical evaluation of the bispecific antibody MDX-H210 (anti-Fc gamma RI x anti-HER-2/neu) in combination with granulocyte-colony-stimulating factor (filgrastim) for treatment of advanced breast cancer. *Cancer Immunol Immunother*. 1997 Nov-Dec; 45(3-4):207-9. available. 234: Kroesen BJ, Nieken J, Sleijfer DT, Molema G, de Vries EG, Groen HJ, Helfrich W, The TH, Mulder NH, de Leij L. Approaches to lung cancer treatment using the CD3 x EGP-2-directed bispecific monoclonal antibody BIS-1. *Cancer Immunol Immunother*. 1997 Nov-Dec; 45(3-4):203-6. 235: Manzke O, Titzer S, Tesch H, Diehl V, Bohlen H. Related Articles CD3 x CD19 bispecific antibodies and CD28 costimulation for locoregional treatment of low-malignancy non-Hodgkin's lymphoma. *Cancer Immunol Immunother*. 1997 Nov-Dec; 45(3-4):198-202. 236: Kufer P, Mack M, Gruber R, Lutterbuse R, Zettl F, Riethmuller G. Construction and biological activity of a recombinant bispecific single-chain antibody designed for therapy of minimal residual colorectal cancer. *Cancer Immunol Immunother*. 1997 Nov-Dec; 45(3-4):193-7. 237: Weiner LM, Alpaugh RK, von Mehren M. Redirected cellular cytotoxicity employing bispecific antibodies and other multifunctional binding proteins. *Cancer Immunol Immunother*. 1997 Nov-Dec; 45(3-4):190-2. 238: Canevari S, Mezzanzanica D,

Mazzoni A, Negri DR, Figini M, Ramakrishna V, Bolis G, Colnaghi MI. Approaches to implement bispecific antibody treatment of ovarian carcinoma. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):187-9. available. 239: Renner C, Hartmann F, Pfreundschuh M. Treatment of refractory Hodgkin's disease with an anti-CD16/CD30 bispecific antibody. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):184-6. 240: Porter LE, Nelson H, Ethem Gecim I, Rice DC, Thibault C, Chapoval AI. T cell activation and retargeting using staphylococcal enterotoxin B and bispecific antibody: an effective in vivo antitumor strategy. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):180-3. 241: Wooldridge JE, Dahle CE, Weiner GJ. T-cell activation induced by anti-CD3 x anti-B-cell lymphoma monoclonal antibody is enhanced by pretreatment of lymphoma cells with soluble CD40 ligand. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):174-9. 242: Honeychurch J, Cruise A, Tutt AL, Glennie MJ. Bispecific Ab therapy of B-cell lymphoma: target cell specificity of antibody derivatives appears critical in determining therapeutic outcome. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):171-3. 243: Heijnen IA, Glennie MJ, van de Winkel JG. Lysis of murine B lymphoma cells by transgenic phagocytes via a human Fc gamma RI x murine MHC class II bispecific antibody. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):166-70. 244: De Jonge J, Heirman C, De Veerman M, Van Meirvenne S, Demanet C, Brissinck J, Thielemans K. Bispecific antibody treatment of murine B cell lymphoma. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):162-5. 245: Inouye K. Bispecific-Ab-based immunoassay of thyroid-stimulating hormone. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):159-61. 246: Gerstmayer B, Hoffmann M, Altenschmidt U, Wels W. Costimulation of T-cell proliferation by a chimeric B7-antibody fusion protein. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):156-8. 247: Taylor RP, Nardin A, Sutherland WM. Clearance of blood-borne pathogens mediated through bispecific monoclonal antibodies bound to the primate erythrocyte complement receptor. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):152-5. 248: Wickham TJ, Haskard D, Segal D, Kovsdi I. Targeting endothelium for gene therapy via receptors up-regulated during angiogenesis and inflammation. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):149-51. 249: Valerius T, Wurflein D, Stockmeyer B, Repp R, Kalden JR, Gramatzki M. Activated neutrophils as effector cells for bispecific antibodies. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):142-5. available. 250: Holliger P, Winter G. Diabodies: small bispecific antibody fragments. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):128-30. available. 251: Graziano RF, Goldstein J, Sundarapandiyan K, Somasundaram C, Keler T, Deo YM. Targeting tumor cell destruction with CD64-directed bispecific fusion proteins. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):124-7. available. 252: de Gast GC, van de Winkel JG, Bast BE. Clinical perspectives of bispecific antibodies in cancer. *Cancer Immunol Immunother.* 1997 Nov-Dec; 45(3-4):121-3. No abstract available. 253: Manzke O, Tesch H, Diehl V, Bohlen H. Single-step purification of bispecific monoclonal antibodies for immunotherapeutic use by hydrophobic interaction chromatography. *J Immunol Methods.* 1997 Oct 13; 208(1):65-73. 254: Kranenborg MH, Boerman OC, Oosterwijk-Wakka JC, de Weijert MC, Corstens FH, Oosterwijk E. Two-step radioimmunotargeting of renal-cell carcinoma xenografts in nude mice with anti-renal-cell-carcinoma X anti-DTPA bispecific monoclonal antibodies. *Int J Cancer.* 1998 Jan 5; 75(1):74-80. 255: van de Winkel JG, Bast B, de Gast GC. Immunotherapeutic potential of bispecific antibodies. *Immunol Today.* 1997 Dec; 18(12):562-4. available. 256: Luiten RM, Warnaar SO, Sanborn D, Lamers CH, Bolhuis RL, Litvinov SV, Zurawski VR, Coney LR. Chimeric bispecific OC/TR monoclonal antibody mediates lysis of tumor cells expressing the folate-binding protein (MOv18) and displays decreased immunogenicity in patients. *J Immunother.* 1997 Nov; 20(6):496-504. 257: Bohlen H, Thielemans K, Tesch H, Engert A, Wolf HJ, van Camp B, Urbain J, Diehl V. Idiotype vaccination strategies against a murine B-cell lymphoma: dendritic cells loaded with idiotype and bispecific idiotype x anti-class II antibodies can protect against tumor growth. *Cytokines Mol Ther.* 1996 Dec; 2(4):231-8. 258: Valerius T, Stockmeyer B, van Spriel AB, Graziano RF, van den Herik-Oudijk IE, Repp R, Deo YM, Lund J, Kalden JR, Gramatzki M, van de Winkel JG. Fc alpha RI (CD89) as a novel trigger molecule for bispecific antibody therapy. *Blood.* 1997 Dec 1; 90(11):4485-92. 259: Blumenthal RD, Sharkey RM, Kashi R, Sides K, Stein R, Goldenberg DM. Changes in tumor vascular permeability in response to experimental radioimmunotherapy: a comparative study of 11 xenografts. *Tumour Biol.* 1997; 18(6):367-77. 260: Gautherot E, Bouhou J, Le Doussal JM, Manetti C, Martin M, Rouvier E, Barbet J. Therapy for colon carcinoma xenografts with bispecific antibody-targeted, iodine-131-labeled bivalent hapten. *Cancer.* 1997 Dec 15; 80(12 Suppl):2618-23. 261: Klein SC, Boer LH, de Weger RA, de Gast GC, Bast EJ. Related Articles Release of cytokines and soluble cell surface molecules by PBMC after activation with the bispecific antibody CD3 x CD19. *Scand J Immunol.* 1997 Nov; 46(5):452-8. 262: Dolezal O, Coia G, Guthrie RE, Lilley GG, Hudson PJ. Related Articles Escherichia coli expression of a bifunctional Fab-peptide epitope reagent for the rapid diagnosis of HIV-1 and HIV-2. *Immunotechnology.* 1995 Dec; 1(3-4):197-209. 263: Isaacs JD, Burrows N, Wing M, Keogan MT, Rebello PR, Watts RA, Pye RJ, Norris P, Hazelman BL, Hale G, Waldmann H. Related Articles Humanized anti-CD4 monoclonal antibody therapy of autoimmune and inflammatory disease. *Clin Exp Immunol.* 1997 Nov; 110(2):158-66. 264: Libyh MT, Goossens D, Oudin S, Gupta N, Derville X, Juszczak G, Cornillet P, Bougy F, Reveil B, Philbert F, Tabary T, Klatzmann D, Rouger P, Cohen JH. A recombinant human scFv anti-Rh(D) antibody with multiple valences using a C-terminal fragment of C4-binding protein. *Blood.* 1997 Nov 15; 90(10):3978-83. 265: Raso V, Brown M, McGrath J. Intracellular targeting with low pH-triggered bispecific antibodies. *J Biol Chem.* 1997 Oct 31; 272(44):27623-8. 266: Schmitt S, Muller KP, Kyewski BA. Two separable T cell receptor signals reconstitute positive selection of CD4 lineage T cells in vivo. *Eur J Immunol.* 1997 Sep; 27(9):2139-44. 267: Keler T, Graziano RF, Mandal A, Wallace PK, Fisher J, Guyre PM, Fanger MW, Deo YM. Bispecific antibody-dependent cellular cytotoxicity of HER2/neu-overexpressing tumor cells by Fc gamma receptor type I-expressing effector cells. *Cancer Res.* 1997 Sep 15; 57(18):4008-14. 268: Taylor RP, Martin EN, Reinagel ML, Nardin A, Craig M, Choice Q, Schlimgen R, Greenbaum S, Incardona NL, Ochs HD. Bispecific monoclonal antibody complexes facilitate erythrocyte binding and liver clearance of a prototype particulate pathogen in a monkey model. *J Immunol.* 1997 Oct 15; 159(8):4035-44. 269: Hombach A, Tillmann T, Jensen M, Heuser C, Sircar R, Diehl V, Kruis W, Pohl C. Specific activation of resting T cells against CA19-9+ tumor cells by an anti-CD3/CA19-9

bispecific antibody in combination with a costimulatory anti-CD28 antibody. *J Immunother.* 1997 Sep; 20(5):325-33. 270: Lamers CH, Bolhuis RL, Warnaar SO, Stoter G, Gratama JW. Local but no systemic immunomodulation by intraperitoneal treatment of advanced ovarian cancer with autologous T lymphocytes re-targeted by a bi-specific monoclonal antibody. *Int J Cancer.* 1997 Oct 9; 73(2):211-9. 271: Valerius T, Elsasser D, Repp R, Van de Winkel JG, Gramatzki M, Glennie M. HLA class II antibodies recruit G-CSF activated neutrophils for treatment of B cell malignancies. *Leuk Lymphoma.* 1997 Jul; 26(3-4):261-9. 272: Wickham TJ, Lee GM, Titus JA, Sconocchia G, Bakacs T, Kovesdi I, Segal DM. Targeted adenovirus-mediated gene delivery to T cells via CD3. *J Virol.* 1997 Oct; 71(10):7663-9. 273: Moutel S, Birkle S, Laurence V, Michon J, Fridman WH, Aubry J, Teillaud JL. Protein, Nucleotide Generation and characterization of a mouse single-chain antibody fragment specific for disialoganglioside (GD2). *Hybridoma.* 1997 Aug; 16(4):335-46. 274: Pearce LA, Oddie GW, Coia G, Kortt AA, Hudson PJ, Lilley GG. Linear gene fusions of antibody fragments with streptavidin can be linked to biotin labelled secondary molecules to form bispecific reagents. *Biochem Mol Biol Int.* 1997 Sep; 42(6):1179-88. 275: Stepanova IP, Tsybul'skaia MV, Domogatskii SP. [Antithrombogenic effect of urokinase bound to the collagen surface with bifunctional antibodies]. *Biull Eksp Biol Med.* 1994 May; 117(5):504-7. Russian. available. 276: Goldbaum FA, Velikovskiy CA, Dall'Acqua W, Fossati CA, Fields BA, Braden BC, Poljak RJ, Mariuzza RA. Free in PMC, Related Articles Characterization of anti-anti-idiotypic antibodies that bind antigen and an anti-idiotypic. *Proc Natl Acad Sci U S A.* 1997 Aug 5; 94(16):8697-701. 277: Carter P, Merchant AM. Engineering antibodies for imaging and therapy. *Curr Opin Biotechnol.* 1997 Aug; 8(4):449-54. 278: Yukawa N, Osawa M, Saito T, Hasegawa T, Matsuda H, Takahama K, Takeichi S. Bispecific rabbit Fab'-bovine serum albumin conjugate used in hemagglutination immunoassay for beta-microseminoprotein. *J Immunoassay.* 1997 Aug; 18(3):215-33. 279: Pilson RS, Levin W, Desai B, Reik LM, Lin P, Korkmaz-Duffy E, Campbell E, Tso JY, Kerwin JA, Hakimi J. Bispecific humanized anti-IL-2 receptor alpha beta antibodies inhibitory for both IL-2- and IL-15-mediated proliferation. *J Immunol.* 1997 Aug 1; 159(3):1543-56. 280: Janevik-Ivanovska E, Gautherot E, Hillairet de Boisferon M, Cohen M, Milhaud G, Tartar A, Rostene W, Barbet J, Gruaz-Guyon A. Bivalent hapten-bearing peptides designed for iodine-131 pretargeted radioimmunotherapy. *Bioconjug Chem.* 1997 Jul-Aug; 8(4):526-33. 281: Clark JI, Alpaugh RK, von Mehren M, Schultz J, Gralow JR, Cheever MA, Ring DB, Weiner LM. Induction of multiple anti-c-erbB-2 specificities accompanies a classical idiotype cascade following 2B1 bispecific monoclonal antibody treatment. *Cancer Immunol Immunother.* 1997 Jul; 44(5):265-72. 282: Jacobs N, Mazzoni A, Mezzanzanica D, Negri DR, Valota O, Colnaghi MI, Moutschen MP, Boniver J, Canevari S. Efficiency of T cell triggering by anti-CD3 monoclonal antibodies (mAb) with potential usefulness in bispecific mAb generation. *Cancer Immunol Immunother.* 1997 Jul; 44(5):257-64. 283: Holliger P, Wing M, Pound JD, Bohlen H, Winter G. Related Articles Retargeting serum immunoglobulin with bispecific diabodies. *Nat Biotechnol.* 1997 Jul; 15(7):632-6. 284: Kontermann RE, Wing MG, Winter G. Protein, Nucleotide Complement recruitment using bispecific diabodies. *Nat Biotechnol.* 1997 Jul; 15(7):629-31. 285: Fearon D. Happy coupling: recruiting both antigen and effector function. *Nat Biotechnol.* 1997 Jul; 15(7):618-9. available. 286: Ozaki ME, Karlsson L, Peterson PA, Webb SR. Antigen specificity of dual reactive T hybridomas determines the requirement for CD40 ligand-CD40 interactions. *J Immunol.* 1997 Jul 1; 159(1):214-21. 287: Morimoto K, Inouye K. A sensitive enzyme immunoassay of human thyroid-stimulating hormone (TSH) using bispecific F(ab')₂ fragments recognizing polymerized alkaline phosphatase and TSH. *J Immunol Methods.* 1997 Jun 23; 205(1):81-90. 288: Mocikat R, Selmayr M, Thierfelder S, Lindhofer H. Related Articles Trioma-based vaccination against B-cell lymphoma confers long-lasting tumor immunity. *Cancer Res.* 1997 Jun 15; 57(12):2346-9. 289: Manetti C, Rouvier E, Gautherot E, Loucif E, Barbet J, Le Doussal JM. Targeting BCL1 lymphoma with anti-idiotypic antibodies: biodistribution kinetics of directly labeled antibodies and bispecific antibody-targeted bivalent haptens. *Int J Cancer.* 1997 Jun 11; 71(6):1000-9. 290: Renner C, Held G, Ohnesorge S, Bauer S, Gerlach K, Pfitzenmeier JP, Pfreundschuh M. Role of naive and memory T cells in tumor cell lysis mediated by bi-specific antibodies. *Immunobiology.* 1997 Jun; 197(1):122-32. 291: Kontermann RE, Martineau P, Cummings CE, Karpas A, Allen D, Derbyshire E, Winter G. Enzyme immunoassays using bispecific diabodies. *Immunotechnology.* 1997 Jun; 3(2):137-44. 292: Pluckthun A, Pack P. New protein engineering approaches to multivalent and bispecific antibody fragments. *Immunotechnology.* 1997 Jun; 3(2):83-105. 293: Shinmoto H, Kobori M, Tsushida T, Shinohara K. Competitive ELISA of bovine lactoferrin with bispecific monoclonal antibodies. *Biosci Biotechnol Biochem.* 1997 Jun; 61(6):1044-6. 294: Hombach A, Mathas S, Jensen M, Tillmann T, Menges M, Diehl V, Kruis W, Pohl C. Activation of resting T cells against the CA 72-4 tumor antigen with an anti-CD3/CA 72-4 bispecific antibody in combination with a costimulatory anti-CD28 antibody. *Anticancer Res.* 1997 May-Jun; 17(3C):2025-32. 295: Luo D, Geng M, Noujaim AA, Madiyalakan R. An engineered bivalent single-chain antibody fragment that increases antigen binding activity. *J Biochem (Tokyo).* 1997 May; 121(5):831-4. 296: Troncone L, Rufini V. 131I-MIBG therapy of neural crest tumours (review). *Anticancer Res.* 1997 May-Jun; 17(3B):1823-31. 297: Cho BK, Roy EJ, Patrick TA, Kranz DM. Single-chain Fv/folate conjugates mediate efficient lysis of folate-receptor-positive tumor cells. *Bioconjug Chem.* 1997 May-Jun; 8(3):338-46. 298: Bommhardt U, Cole MS, Tso JY, Zamoyska R. Signals through CD8 or CD4 can induce commitment to the CD4 lineage in the thymus. *Eur J Immunol.* 1997 May; 27(5):1152-63. 299: Hombach A, Tillmann T, Jensen M, Heuser C, Sircar R, Diehl V, Kruis W, Pohl C. Specific activation of resting T cells against tumour cells by bispecific antibodies and CD28-mediated costimulation is accompanied by Th1 differentiation and recruitment of MHC-independent cytotoxicity. *Clin Exp Immunol.* 1997 May; 108(2):352-7. 300: Nokihiro H, Yano S, Sone S. [Overcoming of multidrug resistance by anti-P-glycoprotein monoclonal antibody]. *Nippon Rinsho.* 1997 May; 55(5):1128-34. 301: Dolezal O, Coia G, Hudson PJ. Agglutination-inhibition assay for the detection of recombinant proteins tagged with peptide epitopes. *Biotechniques.* 1997 May; 22(5):897-904. 302: Botti C, Negri DR, Seregini E, Ramakrishna V, Arienti F, Maffioli L, Lombardo C, Boggi A, Pascali C, Crippa F, Massaron S, Remonti F, Nerini-Molteni S, Canevari S, Bombardieri E. Related Articles Comparison of three different methods for radiolabelling human activated T lymphocytes. *Eur J Nucl Med.* 1997

May; 24(5):497-504. 303: Bohlen H, Manzke O, Titzer S, Lorenzen J, Kube D, Engert A, Abken H, Wolf J, Diehl V, Tesch H. Prevention of Epstein-Barr virus-induced human B-cell lymphoma in severe combined immunodeficient mice treated with CD3xCD19 bispecific antibodies, CD28 monospecific antibodies, and autologous T cells. *Cancer Res.* 1997 May 1; 57(9):1704-9. 304: Smith JA, Tso JY, Clark MR, Cole MS, Bluestone JA. Related Articles Nonmitogenic anti-CD3 monoclonal antibodies deliver a partial T cell receptor signal and induce clonal anergy. *J Exp Med.* 1997 Apr 21; 185(8):1413-22. 305: Mack M, Gruber R, Schmidt S, Riethmuller G, Kufer P. Related Articles Biologic properties of a bispecific single-chain antibody directed against 17-1A (EpCAM) and CD3: tumor cell-dependent T cell stimulation and cytotoxic activity. *J Immunol.* 1997 Apr 15; 158(8):3965-70. 306: Renner C, Trumper L, Pfreundschuh M. Monoclonal antibodies in the treatment of non-Hodgkin's lymphoma: recent results and future prospects. *Leukemia.* 1997 Apr; 11 Suppl 2:S55-9. 307: Renner C, Held G, Ohnesorge S, Bauer S, Gerlach K, Pfitzenmeier JP, Pfreundschuh M. Role of perforin, granzymes and the proliferative state of the target cells in apoptosis and necrosis mediated by bispecific-antibody-activated cytotoxic T cells. *Cancer Immunol Immunother.* 1997 Apr; 44(2):70-6. 308: Auriol J, Chevrier D, Guesdon JL. Acetoxy-acetylaminofluorene-modified dGTP can be used to label oligonucleotides or DNA enzymatically. *Mol Cell Probes.* 1997 Apr; 11(2):113-21. 309: Sznol M, Holmlund J. Antigen-specific agents in development. *Semin Oncol.* 1997 Apr; 24(2):173-86. 310: McCormick LL, Karulin AY, Schreiber JR, Greenspan NS. Related Articles Bispecific antibodies overcome the opsonin-receptor mismatch of cystic fibrosis in vitro: restoration of neutrophil-mediated phagocytosis and killing of *Pseudomonas aeruginosa*. *J Immunol.* 1997 Apr 1; 158(7):3474-82. 311: Kreutz FT, Suresh MR. Novel bispecific immunoprobe for rapid and sensitive detection of prostate-specific antigen. *Clin Chem.* 1997 Apr; 43(4):649-56. 312: Hayden MS, Gilliland LK, Ledbetter JA. Antibody engineering. *Curr Opin Immunol.* 1997 Apr; 9(2):201-12. 313: Zhu Z, Presta LG, Zapata G, Carter P. Remodeling domain interfaces to enhance heterodimer formation. *Protein Sci.* 1997 Apr; 6(4):781-8. 314: Vuillez JP, Moro D, Brichon PY, Rouvier E, Brambilla E, Barbet J, Peltier P, Meyer P, Sarrazin R, Brambilla C. Related Articles Two-step immunoscintigraphy for non-small-cell lung cancer staging using a bispecific anti-CEA/anti-indium-DTPA antibody and an indium-111-labeled DTPA dimer. *J Nucl Med.* 1997 Apr; 38(4):507-11. 315: Guo YJ, Che XY, Shen F, Xie TP, Ma J, Wang XN, Wu SG, Anthony DD, Wu MC. Effective tumor vaccines generated by in vitro modification of tumor cells with cytokines and bispecific monoclonal antibodies. *Nat Med.* 1997 Apr; 3(4):451-5. 316: Hartmann F, Renner C, Jung W, Deisting C, Juwana M, Eichentopf B, Kloft M, Pfreundschuh M. Treatment of refractory Hodgkin's disease with an anti-CD16/CD30 bispecific antibody. *Blood.* 1997 Mar 15; 89(6):2042-7. 317: Tersikh AV, Le Doussal JM, Crameri R, Fisch I, Mach JP, Kajava AV. Free in PMC, "Peptabody": a new type of high avidity binding protein. *Proc Natl Acad Sci U S A.* 1997 Mar 4; 94(5):1663-8. 318: Vossebeld PJ, Homburg CH, Roos D, Verhoeven AJ. Related Articles The anti-Fc gamma RIII mAb 3G8 induces neutrophil activation via a cooperative action of Fc gamma RIIIb and Fc gamma RIIa. *Int J Biochem Cell Biol.* 1997 Mar; 29(3):465-73. 319: Deo YM, Graziano RF, Repp R, van de Winkel JG. Clinical significance of IgG Fc receptors and Fc gamma R-directed immunotherapies. *Immunol Today.* 1997 Mar; 18(3):127-35. 320: Stockmeyer B, Valerius T, Repp R, Heijnen IA, Buhring HJ, Deo YM, Kalden JR, Gramatzki M, van de Winkel JG. Preclinical studies with Fc(gamma)R bispecific antibodies and granulocyte colony-stimulating factor-primed neutrophils as effector cells against HER-2/neu overexpressing breast cancer. *Cancer Res.* 1997 Feb 15; 57(4):696-701. 321: Massino YS, Dergunova NN, Kizim EA, Smirnova MB, Tereshkina EB, Kolyaskina GI, Dmitriev AD. Quantitative analysis of the products of IgG chain recombination in hybrid hybridomas based on affinity chromatography and radioimmunoassay. *J Immunol Methods.* 1997 Feb 14; 201(1):57-66. 322: Coloma MJ, Morrison SL. Design and production of novel tetravalent bispecific antibodies. *Nat Biotechnol.* 1997 Feb; 15(2):159-63. 323: Hoogenboom HR. Mix and match: building manifold binding sites. *Nat Biotechnol.* 1997 Feb; 15(2):125-6. available. 324: Harris CL, Kan KS, Stevenson GT, Morgan BP. Tumour cell killing using chemically engineered antibody constructs specific for tumour cells and the complement inhibitor CD59. *Clin Exp Immunol.* 1997 Feb; 107(2):364-71. 325: Huang X, Molema G, King S, Watkins L, Edgington TS, Thorpe PE. Tumor infarction in mice by antibody-directed targeting of tissue factor to tumor vasculature. *Science.* 1997 Jan 24; 275(5299):547-50. 326: Goldstein J, Graziano RF, Sundarapandian K, Somasundaram C, Deo YM. Cytolytic and cytostatic properties of an anti-human Fc gammaRI (CD64) x epidermal growth factor bispecific fusion protein. *J Immunol.* 1997 Jan 15; 158(2):872-9. 327: Taylor RP, Sutherland WM, Martin EN, Ferguson PJ, Reinagel ML, Gilbert E, Lopez K, Incardona NL, Ochs HD. Bispecific monoclonal antibody complexes bound to primate erythrocyte complement receptor 1 facilitate virus clearance in a monkey model. *J Immunol.* 1997 Jan 15; 158(2):842-50. 328: Rihova B. Targeting of drugs to cell surface receptors. *Crit Rev Biotechnol.* 1997; 17(2):149-69. 329: Rouvier E, Gautherot E, Meyer P, Barbet J. Targeting medullary thyroid carcinomas with bispecific antibodies and bivalent haptens. Results and clinical perspectives. *Horm Res.* 1997; 47(4-6):163-7. 330: Smirnova MB, Dergunova NN, Kizim EA, Massino YS, Nikulina VA, Segal OL, Tereshkina EB, Kolyaskina GI, Dmitriev AD. Related Articles Study of antigen-binding properties of bispecific antibodies. *Biochemistry (Mosc).* 1997 Jan; 62(1):41-8. 331: Molema G, de Leij LF, Meijer DK. Tumor vascular endothelium: barrier or target in tumor directed drug delivery and immunotherapy. *Pharm Res.* 1997 Jan; 14(1):2-10. 332: Lindhofer H, Menzel H, Gunther W, Hultner L, Thierfelder S. Bispecific antibodies target operationally tumor-specific antigens in two leukemia relapse models. *Blood.* 1996 Dec 15; 88(12):4651-8. 333: Armstrong JM, Vitetta ES. The roles of Fas and perforin in LAK T-cell/bispecific antibody-mediated killing of the murine B-lymphoma cells, BCL1. *Int J Cancer.* 1996 Dec 11; 68(6):822-7. 334: Atwell JL, Pearce LA, Lah M, Gruen LC, Kortt AA, Hudson PJ. Design and expression of a stable bispecific scFv dimer with affinity for both glycophorin and N9 neuraminidase. *Mol Immunol.* 1996 Dec; 33(17-18):1301-12. 335: Thirion S, Motmans K, Heyligen H, Janssens J, Raus J, Vandevyver C. Mono- and bispecific single-chain antibody fragments for cancer therapy. *Eur J Cancer Prev.* 1996 Dec; 5(6):507-11. 336: Mazzoni A, Mezzanzanica D, Jung G, Wolf H, Colnaghi MI, Canevari S. CD3-CD28 costimulation as a means to avoiding T cell preactivation in bispecific monoclonal antibody-based treatment of ovarian carcinoma. *Cancer Res.* 1996 Dec 1; 56(23):5443-9. 337: Pericle F, Sconocchia G, Titus JA, Segal

DM. CD44 is a cytotoxic triggering molecule on human polymorphonuclear cells. *J Immunol.* 1996 Nov 15; 157(10):4657-63. 338: Gridley DS, Slater JB, Mackensen DG, Slater JM. Related Articles Effect of pre-irradiation on radiopharmaceutical localization in human colon tumor xenografts using mono- and bispecific monoclonal antibodies. *Anticancer Res.* 1996 Nov-Dec; 16(6B):3453-8. 339: Haas C, Schirrmacher V. Immunogenicity increase of autologous tumor cell vaccines by virus infection and attachment of bispecific antibodies. *Cancer Immunol Immunother.* 1996 Nov; 43(3):190-4 340: von Mehren M, Weiner LM. Monoclonal antibody-based therapy. *Curr Opin Oncol.* 1996 Nov; 8(6):493-8 341: Bardies M, Bardet S, Faivre-Chauvet A, Peltier P, Douillard JY, Mahe M, Fiche M, Lisbona A, Giacalone F, Meyer P, Gautherot E, Rouvier E, Barbet J, Chatal JF. Bispecific antibody and iodine-131-labeled bivalent hapten dosimetry in patients with medullary thyroid or small-cell lung cancer. *J Nucl Med.* 1996 Nov; 37(11):1853-9. 342: Csoka M, Strauss G, Debatin KM, Moldenhauer G. Activation of T cell cytotoxicity against autologous common acute lymphoblastic leukemia (cALL) blasts by CD3xCD19 bispecific antibody. *Leukemia.* 1996 Nov; 10(11):1765-72. 343: Robert B, Mach JP, Mani JC, Ychou M, Folli S, Artus JC, Pelegrin A. Cytokine targeting in tumors using a bispecific antibody directed against carcinoembryonic antigen and tumor necrosis factor alpha. *Cancer Res.* 1996 Oct 15; 56(20):4758-65. 344: Voliotis DL, Tesch H. [Experimental approaches]. *Internist (Berl).* 1996 Oct; 37(10):1040-8. available. 345: Hayden MS, Grosmaire LS, Norris NA, Gilliland LK, Winberg G, Tritschler D, Tsu TT, Linsley PS, Mittler RS, Senter PD, Fell HP, Ledbetter JA., Protein, Nucleotide Costimulation by CD28 sFv expressed on the tumor cell surface or as a soluble bispecific molecule targeted to the L6 carcinoma antigen. *Tissue Antigens.* 1996 Oct; 48(4 Pt 1):242-54. 346: Villa M, Durand-Gorde JM, Carayon P, Ruf J. Idiotypic study of a bispecific thyroglobulin and thyroperoxidase monoclonal antibody. *J Autoimmun.* 1996 Oct; 9(5):653-60. 347: Keck PC, Huston JS. Symmetry of Fv architecture is conducive to grafting a second antibody binding site in the Fv region. *Biophys J.* 1996 Oct; 71(4):2002-11. 348: Wickham TJ, Segal DM, Roelvink PW, Carrion ME, Lizonova A, Lee GM, Kovesdi I. Targeted adenovirus gene transfer to endothelial and smooth muscle cells by using bispecific antibodies. *J Virol.* 1996 Oct; 70(10):6831-8. 349: Devys A, Thedrez P, Gautherot E, Faivre-Chauvet A, Sai-Maurel C, Rouvier E, Auger JL, Barbet J, Chatal JF. Comparative targeting of human colon-carcinoma multicell spheroids using one- and two-step (bispecific antibody) techniques. *Int J Cancer.* 1996 Sep 17; 67(6):883-91. 350: Katayose Y, Kudo T, Suzuki M, Shinoda M, Saijyo S, Sakurai N, Saeki H, Fukuhara K, Imai K, Matsuno S. MUC1-specific targeting immunotherapy with bispecific antibodies: inhibition of xenografted human bile duct carcinoma growth. *Cancer Res.* 1996 Sep 15; 56(18):4205-12. 351: Lankester AC, Rood PM, van Schijndel GM, Hooibrink B, Verhoeven AJ, van Lier RA. Alteration of B-cell antigen receptor signaling by CD19 co-ligation. A study with bispecific antibodies. *J Biol Chem.* 1996 Sep 13; 271(37):22326-30. 352: Rosebrough SF. Two-step immunological approaches for imaging and therapy. *Q J Nucl Med.* 1996 Sep; 40(3):234-51 353: Kuwahara M, Kuroki M, Arakawa F, Senba T, Matsuoka Y, Hideshima T, Yamashita Y, Kanda H. A mouse/human-chimeric bispecific antibody reactive with human carcinoembryonic antigen-expressing cells and human T-lymphocytes. *Anticancer Res.* 1996 Sep-Oct; 16(5A):2661-7. 354: Liu L, Barth RF, Adams DM, Soloway AH, Reisfeld RA. Related Articles Critical evaluation of bispecific antibodies as targeting agents for boron neutron capture therapy of brain tumors. *Anticancer Res.* 1996 Sep-Oct; 16(5A):2581-7. 355: Faivre-Chauvet A, Mease RC, Chetanneau A, Bardies M, Sai-Maurel C, Meinken GE, Srivastava SC, Chatal JF, Geste JF. Pre-clinical and clinical studies of two new bifunctional chelating agents for immunoscintigraphy with ¹¹¹In-anti-CEA monoclonal antibody. *Nucl Med Commun.* 1996 Sep; 17(9):781-9. 356: Primus FJ, Pak RH, Richard-Dickson KJ, Szalai G, Bolen JL, Kane RR, Hawthorne MF. Bispecific antibody mediated targeting of nido-carboranes to human colon carcinoma cells. *Bioconjug Chem.* 1996 Sep-Oct; 7(5):532-5. 357: Schmidt M, Wels W. Targeted inhibition of tumour cell growth by a bispecific single-chain toxin containing an antibody domain and TGF alpha. *Br J Cancer.* 1996 Sep; 74(6):853-62. 358: Luiten RM, Coney LR, Fleuren GJ, Warnaar SO, Litvinov SV. Generation of chimeric bispecific G250/anti-CD3 monoclonal antibody, a tool to combat renal cell carcinoma. *Br J Cancer.* 1996 Sep; 74(5):735-44. 359: Shiao LD. A systematic analysis of average molecular weights and gelation conditions for branched immune complexes: the interaction between a multivalent antigen with distinct epitopes and many different types of bivalent antibodies. *Biopolymers.* 1996 Sep; 39(3):445-54. 360: Featherstone C. Bispecific antibodies: the new magic bullets. *Lancet.* 1996 Aug 24; 348(9026):536. available. 361: Luo D, Mah N, Wishart D, Zhang Y, Jacobs F, Martin L. Related Articles Construction and expression of bi-functional proteins of single-chain Fv with effector domains. *J Biochem (Tokyo).* 1996 Aug; 120(2):229-32. 362: Morimoto C, Sato T, Tachibana K. Selective immunomodulation: utilization of CD29/VLA molecules. *Artif Organs.* 1996 Aug; 20(8):828-31 363: Klonisch T, Delves PJ, Berger P, Panayotou G, Lapthorn AJ, Isaacs NW, Wick G, Lund T, Roitt IM. Relative location of epitopes involved in synergistic antibody binding using human chorionic gonadotropin as a model. *Eur J Immunol.* 1996 Aug; 26(8):1897-905. 364: Hsieh-Ma ST, Shi T, Reeder J, Ring DB. In vitro tumor growth inhibition by bispecific antibodies to human transferrin receptor and tumor-associated antigens is augmented by the iron chelator deferoxamine. *Clin Immunol Immunopathol.* 1996 Aug; 80(2):185-93. 365: Wagner CL, Mascelli MA, Neblock DS, Weisman HF, Coller BS, Jordan RE. Analysis of GPIIb/IIIa receptor number by quantification of 7E3 binding to human platelets. *Blood.* 1996 Aug 1; 88(3):907-14. 366: Thibault C, Nelson H, Chapoval AI. Tumor-infiltrating lymphocytes can be activated in situ by using in vivo activants plus F(ab')₂ bispecific antibodies. *Int J Cancer.* 1996 Jul 17; 67(2):232-7. 367: Ridgway JB, Presta LG, Carter P. 'Knobs-into-holes' engineering of antibody CH3 domains for heavy chain heterodimerization. *Protein Eng.* 1996 Jul; 9(7):617-21. 368: Jacobs N, Greimers R, Mazzoni A, Trebak M, Schaaf-Lafontaine N, Boniver J, Moutschen MP. Further characterization of cytotoxic T cells generated by short-term culture of human peripheral blood lymphocytes with interleukin-2 and anti-CD3 mAb. *Cancer Immunol Immunother.* 1996 Jul; 42(6):369-75. 369: Somasundaram C, Arch R, Matzku S, Zoller M. Development of a bispecific F(ab')₂ conjugate against the complement receptor CR3 of macrophages and a variant CD44 antigen of rat pancreatic adenocarcinoma for redirecting macrophage-mediated tumor cytotoxicity. *Cancer Immunol Immunother.* 1996 Jul; 42(6):343-50. 370: Carrithers MD, Lerner MR.

Synthesis and characterization of bivalent peptide ligands targeted to G-protein-coupled receptors. *Chem Biol.* 1996 Jul; 3(7):537-42. 371: RR, Bell AJ, Hamblin TJ, Tutt AL, Glennie MJ. Related Articles Response of B-cell lymphoma to a combination of bispecific antibodies and saporin. *Leuk Res.* 1996 Jul; 20(7):607-17. 372: Renner C, Ohnesorge S, Held G, Bauer S, Jung W, Pfizenmeier JP, Pfreundschuh M. T cells from patients with Hodgkin's disease have a defective T-cell receptor zeta chain expression that is reversible by T-cell stimulation with CD3 and CD28. *Blood.* 1996 Jul 1; 88(1):236-41. 373: Fernandez-Sesma A, Schulman JL, Moran TM. A bispecific antibody recognizing influenza A virus M2 protein redirects effector cells to inhibit virus replication in vitro. *J Virol.* 1996 Jul; 70(7):4800-4. 374: Yoshida J, Takaoka T, Mizuno M, Momota H, Okada H. Related Articles Cytolysis of malignant glioma cells by lymphokine-activated killer cells combined with anti-CD3/antiglioma bifunctional antibody and tumor necrosis factor-alpha. *J Surg Oncol.* 1996 Jul; 62(3):177-82. 375: Reinartz HW, Quinn JG, Zanker K, O'Kennedy R. Bispecific multivalent antibody studied by real-time interaction analysis for the development of an antigen-inhibition enzyme-linked immunosorbent assay. *Analyst.* 1996 Jun; 121(6):767-71. 376: Bergamaschi G, Perfetti V, Tonon L, Novella A, Lucotti C, Danova M, Glennie MJ, Merlini G, Cazzola M. Saporin, a ribosome-inactivating protein used to prepare immunotoxins, induces cell death via apoptosis. *Br J Haematol.* 1996 Jun; 93(4):789-94. 377: Tesch H, Diehl V. Hodgkin's disease: from basic science to clinical application. *Leukemia.* 1996 Jun; 10 Suppl 2:s74-7. 378: Tibben JG, Boerman OC, Massuger LF, Schijf CP, Claessens RA, Corstens FH. Pharmacokinetics, biodistribution and biological effects of intravenously administered bispecific monoclonal antibody OC/TR F(ab')2 in ovarian carcinoma patients. *Int J Cancer.* 1996 May 16; 66(4):477-83. 379: Demanet C, Brissinck J, De Jonge J, Thielemans K. Related Articles Bispecific antibody-mediated immunotherapy of the BCL1 lymphoma: increased efficacy with multiple injections and CD28-induced costimulation. *Blood.* 1996 May 15; 87(10):4390-8. 380: Ely P, Wallace PK, Givan AL, Graziano RF, Guyre PM, Fanger MW. Bispecific-armed, interferon gamma-primed macrophage-mediated phagocytosis of malignant non-Hodgkin's lymphoma. *Blood.* 1996 May 1; 87(9):3813-21. 381: Elsasser D, Valerius T, Repp R, Weiner GJ, Deo Y, Kalden JR, van de Winkel JG, Stevenson GT, Glennie MJ, Gramatzki M. Related Articles HLA class II as potential target antigen on malignant B cells for therapy with bispecific antibodies in combination with granulocyte colony-stimulating factor. *Blood.* 1996 May 1; 87(9):3803-12. 382: van Vugt MJ, Heijnen AF, Capel PJ, Park SY, Ra C, Saito T, Verbeek JS, van de Winkel JG. FcR gamma-chain is essential for both surface expression and function of human Fc gamma RI (CD64) in vivo. *Blood.* 1996 May 1; 87(9):3593-9. 383: [No authors listed] Antibody with two targets may boost immunotherapy benefit. *Oncology (Huntingt).* 1996 Apr; 10(4):620. available. 384: Renner C, Bauer S, Sahin U, Jung W, van Lier R, Jacobs G, Held G, Pfreundschuh M. Cure of disseminated xenografted human Hodgkin's tumors by bispecific monoclonal antibodies and human T cells: the role of human T-cell subsets in a preclinical model. *Blood.* 1996 Apr 1; 87(7):2930-7. 385: Berkova N, Karawajew L, Korobko V, Behrsing O, Micheel B, Shamborant O, Stukatcheva E, Shingarova L. Development of an enzyme immunoassay for the measurement of human tumour necrosis factor-alpha (hTNF-alpha) using bispecific antibodies to hTNF-alpha and horseradish peroxidase. *Biotechnol Appl Biochem.* 1996 Apr; 23 (Pt 2):163-71. 386: de Kruif J, Logtenberg T. Leucine zipper dimerized bivalent and bispecific scFv antibodies from a semi-synthetic antibody phage display library. *J Biol Chem.* 1996 Mar 29; 271(13):7630-4. 387: Holliger P, Brissinck J, Williams RL, Thielemans K, Winter G. Specific killing of lymphoma cells by cytotoxic T-cells mediated by a bispecific diabody. *Protein Eng.* 1996 Mar; 9(3):299-305. 388: Bodey B, Siegel SE, Kaiser HE. Human cancer detection and immunotherapy with conjugated and non-conjugated monoclonal antibodies. *Anticancer Res.* 1996 Mar-Apr; 16(2):661-74. 389: Weiner LM, Alpaugh RK, Amoroso AR, Adams GP, Ring DB, Barth MW. Human neutrophil interactions of a bispecific monoclonal antibody targeting tumor and human Fc gamma RIII. *Cancer Immunol Immunother.* 1996 Mar; 42(3):141-50. 390: Kroesen BJ, Wellenberg GJ, Bakker A, Helfrich W, The TH, de Leij L. The role of apoptosis in bispecific antibody-mediated T-cell cytotoxicity. *Br J Cancer.* 1996 Mar; 73(6):721-7. 391: Shpitz B, Stern H, Sandhu JS, Reilly RM, Tropak MB, Jansz G, Xu J, Gallinger S. Cytotoxicity of B72.3XOKT3 bispecific antibody recognizing human colon cancer. *J Surg Res.* 1996 Feb 15; 61(1):134-8. 392: Schmidt M, Hynes NE, Groner B, Wels W. A bivalent single-chain antibody-toxin specific for ErbB-2 and the EGF receptor. *Int J Cancer.* 1996 Feb 8; 65(4):538-46. 393: Kipriyanov SM, Little M, Kropshofer H, Breitling F, Gotter S, Dubel S., Protein, Nucleotide Affinity enhancement of a recombinant antibody: formation of complexes with multiple valency by a single-chain Fv fragment-core streptavidin fusion. *Protein Eng.* 1996 Feb; 9(2):203-11. 394: Wang Q, Chen Z, Wang W. [Anti-tumor effects of bispecific monoclonal antibody targeted human monocytes-macrophages on hepatoma cells]. *Zhonghua Yi Xue Za Zhi.* 1996 Feb; 76(2):96-9. Chinese. 395: Self CH, Cook DB. Advances in immunoassay technology. *Curr Opin Biotechnol.* 1996 Feb; 7(1):60-5. 396: Saijyo S, Kudo T, Katayose Y, Saeki H, Chiba N, Suzuki M, Tominaga T, Matsuno S. A new in vitro model of specific targeting therapy of cancer: retargeting of PWM-LAK cells with bispecific antibodies greatly enhances cytotoxicity to hepatocellular carcinoma. *Tohoku J Exp Med.* 1996 Feb; 178(2):113-27. 397: Eisenhut M, Lehmann WD, Becker W, Behr T, Elser H, Strittmatter W, Steinstrasser A, Baum RP, Valerius T, Repp R, Deo Y. Bifunctional NHS-BAT ester for antibody conjugation and stable technetium-99m labeling: conjugation chemistry, immunoreactivity and kit formulation. *J Nucl Med.* 1996 Feb; 37(2):362-70. 398: Jost CR, Titus JA, Kurucz I, Segal DM. A single-chain bispecific Fv2 molecule produced in mammalian cells redirects lysis by activated CTL. *Mol Immunol.* 1996 Feb; 33(2):211-9. 399: Shi T, Hsieh-Ma ST, Reeder J, Ring DB. Murine bispecific antibody 1A10 directed to human transferrin receptor and a 42-kDa tumor-associated glycoprotein. *Clin Immunol Immunopathol.* 1996 Feb; 78(2):188-95. 400: Batteiger BE. The major outer membrane protein of a single *Chlamydia trachomatis* serovar can possess more than one serovar-specific epitope. *Infect Immun.* 1996 Feb; 64(2):542-7. 401: Penna C, Dean PA, Nelson H. Pulmonary metastases neutralization and tumor rejection by in vivo administration of beta glucan and bispecific antibody. *Int J Cancer.* 1996 Jan 26; 65(3):377-82. 402: Galvan A, Quesada A, Fernandez E. Nitrate and nitrate are transported by different specific transport systems and by a bispecific transporter in *Chlamydomonas reinhardtii*. *J Biol Chem.* 1996 Jan 26; 271(4):2088-92. 403: Barth RF, Soloway AH, Brugger

RM. Boron neutron capture therapy of brain tumors: past history, current status, and future potential. *Cancer Invest.* 1996; 14(6):534-50. 404: Gilliland LK, Norris NA, Marquardt H, Tsu TT, Hayden MS, Neubauer MG, Yelton DE, Mittler RS, Ledbetter JA., Protein, Nucleotide Rapid and reliable cloning of antibody variable regions and generation of recombinant single chain antibody fragments. *Tissue Antigens.* 1996 Jan; 47(1):1-20. 405: Hideshima T, Iwasaki A, Baba M, Yamashita Y, Shirakusa T, Okada H. The induction of cytotoxicity by a bispecific antibody against CEA positive cell line, in vitro. *Surg Today.* 1996; 26(2):83-8. 406: Hartmann F, Renner C, Jung W, Sahin U, Pfreundschuh M. Related Articles Treatment of Hodgkin's disease with bispecific antibodies. *Ann Oncol.* 1996; 7 Suppl 4:143-6. 407: Wels W, Groner B, Hynes NE. Intervention in receptor tyrosine kinase-mediated pathways: recombinant antibody fusion proteins targeted to ErbB2. *Curr Top Microbiol Immunol.* 1996; 213 (Pt 3):113-28 available. 408: Dmitriev AD, Massino IS, Dergunova NN, Kizim EA, Segal OL, Smirnova MB, Vostrikov VM, Koliaskina GI. [Bispecific monoclonal antibodies: the isolation and study of their antigen-binding properties]. *Vestn Ross Akad Med Nauk.* 1996; (4):46-51. Russian. 409: Francois C, Dantal J, Sorel M, Cherel M, Miyasaka M, Souillou JP, Jacques Y. Antibodies directed at mouse IL-2-R alpha and beta chains act in synergy to abolish T-cell proliferation in vitro and delayed type hypersensitivity reaction in vivo. *Transpl Int.* 1996; 9(1):46-50. 410: Gorny MK, Keler T, Burda S, Williams C, Gabriel JL, Mitchell WM, Deo YM, Zolla-Pazner S. Functional studies of bispecific antibodies directed against HIV-1 and the Fc gamma I receptor type I. *Antibiot Chemother.* 1996; 48:173-83. available. 411: Kairemo KJ. Radioimmunotherapy of solid cancers: A review. *Acta Oncol.* 1996; 35(3):343-55. 412: Sahin U, Kraft-Bauer S, Ohnesorge S, Pfreundschuh M, Renner C. Interleukin-12 increases bispecific-antibody-mediated natural killer cell cytotoxicity against human tumors. *Cancer Immunol Immunother.* 1996 Jan; 42(1):9-14. 413: Reiken SR, Van Wie BJ, Sutisna H. Bispecific antibody modification of nicotinic acetylcholine receptors for biosensing. *Biosens Bioelectron.* 1996; 11(1-2):91-102. 414: Amoroso AR, Clark JI, Litwin S, Hsieh-Ma S, Shi T, Alpaugh RK, Adams GP, Wolf EJ, Ring DB, Weiner LM. Binding characteristics and antitumor properties of 1A10 bispecific antibody recognizing gp40 and human transferrin receptor. *Cancer Res.* 1996 Jan 1; 56(1):113-20. 415: DeSilva BS, Wilson GS. Solid phase synthesis of bifunctional antibodies. *J Immunol Methods.* 1995 Dec 15; 188(1):9-19. 416: Mabondzo A, Le Naour R, Le Grand R, Vaslin B, Benveniste O, Cheret A, Raoul H, Romet-Lemonne JL, Dormont D. Functional consequences of macrophage infection by human immunodeficiency virus: bispecific antibody targeting of HIV-1-infected cells to Fc gamma RI expressing effector cells. *J Hematother.* 1995 Dec; 4(6):579-85. 417: Chapoval AI, Nelson H, Thibault C, Penna C, Dean P. Related Articles Bifunctional antibody retargeting in vivo-activated T lymphocytes: simplifying clinical application. *J Hematother.* 1995 Dec; 4(6):571-7. 418: Papadopoulos NG, Gritzapis AD, Dedoussis GV, Spanakos G, Baxevas CN, Papamichail M. Production and characterization of a monoclonal antibody against epirubicin. *Hybridoma.* 1995 Dec; 14(6):593-6. 419: De Jonge J, Brissinck J, Heirman C, Demanet C, Leo O, Moser M, Thielemans K. Production and characterization of bispecific single-chain antibody fragments. *Mol Immunol.* 1995 Dec; 32(17-18):1405-12. 420: Tai MS, McCartney JE, Adams GP, Jin D, Hudziak RM, Oppermann H, Laminet AA, Bookman MA, Wolf EJ, Liu S, et al. Targeting c-erbB-2 expressing tumors using single-chain Fv monomers and dimers. *Cancer Res.* 1995 Dec 1; 55(23 Suppl):5983s-5989s. 421: Kranenborg MH, Boerman OC, Oosterwijk-Wakka JC, de Weijert MC, Corstens FH, Oosterwijk E. Development and characterization of anti-renal cell carcinoma x antichelate bispecific monoclonal antibodies for two-phase targeting of renal cell carcinoma. *Cancer Res.* 1995 Dec 1; 55(23 Suppl):5864s-5867s. 422: Li M, Meares CF, Salako Q, Kukis DL, Zhong GR, Miers L, DeNardo SJ. Prelabeling of chimeric monoclonal antibody L6 with 90yttrium- and 111indium-1,4,7,10-tetraazacyclododecane-N,N',N'',N'''-tetraacetic acid (DOTA) chelates for radioimmunodiagnosis and therapy. *Cancer Res.* 1995 Dec 1; 55(23 Suppl):5726s-5728s. 423: Ruf J, Carayon P. The molecular recognition theory applied to bispecific antibodies... *Nat Med.* 1995 Dec; 1(12):1222. available. 424: Cao Y, Vinayagamoorthy T, Noujaim AA, Suresh MR. Related Articles A rapid non-selective method to generate quadromas by microelectrofusion. *J Immunol Methods.* 1995 Nov 16; 187(1):1-7. 425: Verhoeyen ME, van der Logt CP, Beggs TS, Davis PJ. Related Articles Antibody fragments for controlled delivery of therapeutic agents. *Biochem Soc Trans.* 1995 Nov; 23(4):1067-73 available. 426: Haagen IA. Performance of CD3xCD19 bispecific monoclonal antibodies in B cell malignancy. *Leuk Lymphoma.* 1995 Nov; 19(5-6):381-93. 427: Alexandroff AB, Jackson AM, Chisholm GD, James K. Related Articles Cytokine modulation of epidermal growth factor receptor expression on bladder cancer cells is not a major contributor to the antitumor activity of cytokines. *Eur J Cancer.* 1995 Nov; 31A(12):2059-66. 428: Baxter LT, Zhu H, Mackensen DG, Butler WF, Jain RK. Related Articles Biodistribution of monoclonal antibodies: scale-up from mouse to human using a physiologically based pharmacokinetic model. *Cancer Res.* 1995 Oct 15; 55(20):4611-22. 429: Weiner LM, Clark JI, Davey M, Li WS, Garcia de Palazzo I, Ring DB, Alpaugh RK. Phase I trial of 2B1, a bispecific monoclonal antibody targeting c-erbB-2 and Fc gamma RI. *Cancer Res.* 1995 Oct 15; 55(20):4586-93. 430: Manetti C, Le Doussal JM, Rouvier E, Gruaz-Guyon A, Barbet J. Intracellular uptake and catabolism of anti-IgM antibodies and bi-specific antibody-targeted hapten by B-lymphoma cells. *Int J Cancer.* 1995 Oct 9; 63(2):250-6. 431: Canevari S, Stoter G, Arienti F, Bolis G, Colnaghi MI, Di Re EM, Eggermont AM, Goey SH, Gratama JW, Lamers CH, et al. Related Articles Regression of advanced ovarian carcinoma by intraperitoneal treatment with autologous T lymphocytes retargeted by a bispecific monoclonal antibody. *J Natl Cancer Inst.* 1995 Oct 4; 87(19):1463-9. 432: Liu L, Barth RF, Adams DM, Soloway AH, Reisfeld RA. Related Articles Bispecific antibodies as targeting agents for boron neutron capture therapy of brain tumors. *J Hematother.* 1995 Oct; 4(5):477-83. 433: Valone FH, Kaufman PA, Guyre PM, Lewis LD, Memoli V, Ernstoff MS, Wells W, Barth R, Deo Y, Fisher J, et al. Clinical trials of bispecific antibody MDX-210 in women with advanced breast or ovarian cancer that overexpresses HER-2/neu. *J Hematother.* 1995 Oct; 4(5):471-5. 434: Carter P, Ridgway J, Zhu Z. Toward the production of bispecific antibody fragments for clinical applications. *J Hematother.* 1995 Oct; 4(5):463-70. 435: Morganelli PM. Targeting lipoproteins to Fc gamma receptors with bispecific antibodies. *J Hematother.* 1995 Oct; 4(5):457-61. 436: Weiner LM, Clark JI, Ring DB, Alpaugh RK. Clinical development of 2B1, a bispecific murine monoclonal antibody targeting c-erbB-2 and Fc gamma RI. *J*

Hematother. 1995 Oct; 4(5):453-6. 437: Renner C, Pfreundschuh M. Treatment of heterotransplanted Hodgkin's tumors in SCID mice by a combination of human NK or T cells and bispecific antibodies. J Hematother. 1995 Oct; 4(5):447-51. 438: Chamow SM, Zhang D, Tan XY, Mhatre SM, Marsters SA, Peers DH, Byrn RA, Ashkenazi A, Junghans RP. A humanized, bispecific immunoadhesin-antibody that retargets CD3 + effectors to kill HIV-1-infected cells. J Hematother. 1995 Oct; 4(5):439-46. 439: De Gast GC, Van Houten AA, Haagen IA, Klein S, De Weger RA, Van Dijk A, Phillips J, Clark M, Bast BJ. Clinical experience with CD3 x CD19 bispecific antibodies in patients with B cell malignancies. J Hematother. 1995 Oct; 4(5):433-7. 440: Sforzini S, Bolognesi A, Meazza R, Marciano S, Tazzari PL, Stein H, Stirpe F, Ferrini S. Targeting of type 1 ribosome-inactivating proteins to CD30 + or CD25 + hematologic neoplasias by bispecific antibodies. J Hematother. 1995 Oct; 4(5):429-32. 441: Canevari S, Mezzanzanica D, Mazzoni A, Negri DR, Ramakrishna V, Bolhuis RL, Colnaghi MI, Bolis G. Bispecific antibody targeted T cell therapy of ovarian cancer: clinical results and future directions. J Hematother. 1995 Oct; 4(5):423-7. 442: Repp R, Valerius T, Wieland G, Becker W, Steininger H, Deo Y, Helm G, Gramatzki M, Van de Winkel JG, Lang N, et al. Related Articles G-CSF-stimulated PMN in immunotherapy of breast cancer with a bispecific antibody to Fc gamma RI and to HER-2/neu (MDX-210). J Hematother. 1995 Oct; 4(5):415-21. 443: Kroesen BJ, Janssen RA, Buter J, Nieken J, Sleijfer DT, Mulder NH, De Leij L. Bispecific monoclonal antibodies for intravenous treatment of carcinoma patients: immunobiologic aspects. J Hematother. 1995 Oct; 4(5):409-14. 444: Kranz DM, Gruber M, Wilson ER. Properties of bispecific single chain antibodies expressed in Escherichia coli. J Hematother. 1995 Oct; 4(5):403-8. 445: Belani R, Weiner GJ. T cell activation and cytokine production in anti-CD3 bispecific antibody therapy. J Hematother. 1995 Oct; 4(5):395-402. 446: Tso JY, Wang SL, Levin W, Hakimi J. Preparation of a bispecific F(ab')₂ targeted to the human IL-2 receptor. J Hematother. 1995 Oct; 4(5):389-94. 447: Grant SD, Cupit PM, Learmonth D, Byrne FR, Graham BM, Porter AJ, Harris WJ. Expression of monovalent and bivalent antibody fragments in Escherichia coli. J Hematother. 1995 Oct; 4(5):383-8. 448: Segal DM, Sconocchia G, Titus JA, Jost CR, Kurucz I. Related Articles Alternative triggering molecules and single chain bispecific antibodies. J Hematother. 1995 Oct; 4(5):377-82. 449: Chen J, Zhou JH, Mokotoff M, Fanger MW, Ball ED. Related Articles Lysis of small cell carcinoma of the lung (SCCL) cells by cytokine-activated monocytes and natural killer cells in the presence of bispecific immunoconjugates containing a gastrin-releasing peptide (GRP) analog or a GRP antagonist. J Hematother. 1995 Oct; 4(5):369-76. 450: Demanet C, Brissinck J, De Jonge J, Thielemans K. Related Articles In vivo studies using bispecific antibodies (anti-CD3 x anti-idiotypic) and CD28-induced costimulation in the BCL1 lymphoma. J Hematother. 1995 Oct; 4(5):363-8. 451: Taylor RP, Ferguson PJ. Primate erythrocyte (E) complement receptor (CR1) as an anchor site for bispecific-based therapies to clear pathogens or autoantibodies safely from the circulation. J Hematother. 1995 Oct; 4(5):357-62. 452: Heijnen IA, Van de Winkel JG. A human Fc gamma RI/CD64 transgenic model for in vivo analysis of (bispecific) antibody therapeutics. J Hematother. 1995 Oct; 4(5):351-6. 453: Fanger MW, Ball ED, Drakeman DL. Comments on the Fourth International Conference on Bispecific Antibodies and Cellular Cytotoxicity, Duck Key, Florida, March 1-5, 1995. J Hematother. 1995 Oct; 4(5):345-9. available. 454: [No authors listed] Proceedings of the 4th International Conference on Bispecific Antibodies. Duck Key, Florida, March 1-5, 1995. J Hematother. 1995 Oct; 4(5):345-483. available. 455: Smans KA, Hoylaerts MF, Narisawa S, Millan JL, De Broe ME. Bispecific antibody-mediated lysis of placental and germ cell alkaline phosphatase targeted solid tumors in immunocompetent mice. Cancer Res. 1995 Oct 1; 55(19):4383-90. 456: MacLean JA, Su Z, Colvin RB, Wong JT. Anti-CD3:anti-IL-2 receptor-bispecific mAb-mediated immunomodulation. Low systemic toxicity, differential effect on lymphoid tissue, and inhibition of cell-mediated hypersensitivity. J Immunol. 1995 Oct 1; 155(7):3674-82. 457: Negri DR, Tosi E, Valota O, Ferrini S, Cambiaggi A, Sforzini S, Silvani A, Ruffini PA, Colnaghi MI, Canevari S. In vitro and in vivo stability and anti-tumour efficacy of an anti-EGFR/anti-CD3 F(ab')₂ bispecific monoclonal antibody. Br J Cancer. 1995 Oct; 72(4):928-33. 458: Kroesen BJ, Bakker A, van Lier RA, The HT, de Leij L. Related Articles Bispecific antibody-mediated target cell-specific costimulation of resting T cells via CD5 and CD28. Cancer Res. 1995 Oct 1; 55(19):4409-15. 459: Dillehay LE, Mayer R, Zhang YG, Shao Y, Song SY, Mackensen DG, Williams JR. Prediction of tumor response to experimental radioimmunotherapy with 90Y in nude mice. Int J Radiat Oncol Biol Phys. 1995 Sep 30; 33(2):417-27. 460: Kranz DM, Patrick TA, Brigle KE, Spinella MJ, Roy EJ. Related Articles Conjugates of folate and anti-T-cell-receptor antibodies specifically target folate-receptor-positive tumor cells for lysis. Proc Natl Acad Sci U S A. 1995 Sep 26; 92(20):9057-61. 461: Tutt AL, Reid R, Wilkins BS, Glennie MJ. Activation and preferential expansion of rat cytotoxic (CD8) T cells in vitro and in vivo with a bispecific (anti-TCR alpha/beta x anti-CD2) F(ab')₂ antibody. J Immunol. 1995 Sep 15; 155(6):2960-71. 462: Boerman OC, Tibben JG, Massuger LF, Claessens RA, Corstens FH. Tumour targeting of the anti-ovarian carcinoma x anti-CD3/TCR bispecific monoclonal antibody OC/TR and its parental MOv18 antibody in experimental ovarian cancer. Anticancer Res. 1995 Sep-Oct; 15(5B):2169-74. 463: Janssen RA, Kroesen BJ, Buter J, Mesander G, Sleijfer DT, The TH, Mulder NH, de Leij L. Immunomodulatory effects of intravenous BIS-1 F(ab')₂ administration in renal cell cancer patients. Br J Cancer. 1995 Sep; 72(3):795-9. 464: Kalaga R, Li L, O'Dell JR, Paul S. Unexpected presence of polyreactive catalytic antibodies in IgG from unimmunized donors and decreased levels in rheumatoid arthritis. J Immunol. 1995 Sep 1; 155(5):2695-702. 465: Valone FH, Kaufman PA, Guyre PM, Lewis LD, Memoli V, Deo Y, Graziano R, Fisher JL, Meyer L, Mrozek-Orlowski M, et al. Related Articles Phase Ia/Ib trial of bispecific antibody MDX-210 in patients with advanced breast or ovarian cancer that overexpresses the proto-oncogene HER-2/neu. J Clin Oncol. 1995 Sep; 13(9):2281-92. 466: Thierfelder S, Mocikat R, Mysliwicz J, Lindhofer H, Kremmer E. Immunosuppression by Fc region-mismatched anti-T cell antibody treatment. Eur J Immunol. 1995 Aug; 25(8):2242-6. 467: Cheung SC, Takeda S, Notkins AL. Both VH and VL chains of polyreactive IgM antibody are required for polyreactivity: expression of Fab in Escherichia coli. Clin Exp Immunol. 1995 Aug; 101(2):383-6. 468: Chapoval AI, Nelson H, Thibault C. Anti-CD3 x anti-tumor F(ab')₂ bifunctional antibody activates and retargets tumor-infiltrating lymphocytes. J Immunol. 1995 Aug 1; 155(3):1296-303. 469: Yang J, Moyana T, Xiang J. A genetically engineered single-chain FV/TNF molecule possesses the anti-

tumor immunoreactivity of FV as well as the cytotoxic activity of tumor necrosis factor. *Mol Immunol.* 1995 Aug; 32(12):873-81. 470: Michon J, Moutel S, Barbet J, Romet-Lemonne JL, Deo YM, Fridman WH, Teillaud JL. In vitro killing of neuroblastoma cells by neutrophils derived from granulocyte colony-stimulating factor-treated cancer patients using an anti-disialoganglioside/anti-Fc gamma RI bispecific antibody. *Blood.* 1995 Aug 1; 86(3):1124-30. 471: Zhu Z, Lewis GD, Carter P. Engineering high affinity humanized anti-p185HER2/anti-CD3 bispecific F(ab')₂ for efficient lysis of p185HER2 overexpressing tumor cells. *Int J Cancer.* 1995 Jul 28; 62(3):319-24. 472: RR, Hamblin TJ, Bell AJ, Tutt AL, Glennie MJ. Related Articles Treatment of B-cell lymphomas with combination of bispecific antibodies and saporin. *Lancet.* 1995 Jul 22; 346(8969):223-4. 473: Mack M, Riethmuller G, Kufer P. A small bispecific antibody construct expressed as a functional single-chain molecule with high tumor cell cytotoxicity. *Proc Natl Acad Sci U S A.* 1995 Jul 18; 92(15):7021-5. 474: Pak RH, Primus FJ, Rickard-Dickson KJ, Ng LL, Kane RR, Hawthorne MF. Preparation and properties of nido-carborane-specific monoclonal antibodies for potential use in boron neutron capture therapy for cancer. *Proc Natl Acad Sci U S A.* 1995 Jul 18; 92(15):6986-90. 475: Limpanasithikul W, Ray S, Diamond B. Protein, Nucleotide Cross-reactive antibodies have both protective and pathogenic potential. *J Immunol.* 1995 Jul 15; 155(2):967-73. 476: Kouts S, Wang MX, Adelstein S, Krilis SA. Immunization of a rabbit with beta 2-glycoprotein I induces charge-dependent crossreactive antibodies that bind anionic phospholipids and have similar reactivity as autoimmune anti-phospholipid antibodies. *J Immunol.* 1995 Jul 15; 155(2):958-66. 477: Petruzzelli L, Maduzia L, Springer TA. Activation of lymphocyte function-associated molecule-1 (CD11a/CD18) and Mac-1 (CD11b/CD18) mimicked by an antibody directed against CD18. *J Immunol.* 1995 Jul 15; 155(2):854-66. 478: van Ravenswaay Claassen HH, Fleuren GJ. The influence of combination chemotherapy on antigen expression in ovarian cancer. *Gynecol Oncol.* 1995 Jul; 58(1):16-23. 479: Sforzini S, Bolognesi A, Meazza R, Marciano S, Casalini P, Durkop H, Tazzari PL, Stein H, Stirpe F, Ferrini S. Differential sensitivity of CD30+ neoplastic cells to gelonin delivered by anti-CD30/anti-gelonin bispecific antibodies. *Br J Haematol.* 1995 Jul; 90(3):572-7. 480: Renner C, Jung W, Sahin U, van Lier R, Pfreundschuh M. Related Articles The role of lymphocyte subsets and adhesion molecules in T cell-dependent cytotoxicity mediated by CD3 and CD28 bispecific monoclonal antibodies. *Eur J Immunol.* 1995 Jul; 25(7):2027-33. 481: Lindhofer H, Mocikat R, Steipe B, Thierfelder S. Related Articles Preferential species-restricted heavy/light chain pairing in rat/mouse quadromas. Implications for a single-step purification of bispecific antibodies. *J Immunol.* 1995 Jul 1; 155(1):219-25. 482: Flavell DJ, Cooper S, Okayama K, Emery L, Flavell SU. Related Articles Comparison of the performance of anti-CD7 and anti-CD38 bispecific antibodies and immunotoxins for the delivery of saporin to a human T-cell acute lymphoblastic leukemia cell line. *Hematol Oncol.* 1995 Jul-Aug; 13(4):185-200. 483: Wilson CC, Wong JT, Girard DD, Merrill DP, Dynan M, An DD, Kalams SA, Johnson RP, Hirsch MS, D'Aquila RT, et al. Related Articles Ex vivo expansion of CD4 lymphocytes from human immunodeficiency virus type 1-infected persons in the presence of combination antiretroviral agents. *J Infect Dis.* 1995 Jul; 172(1):88-96. 484: George AJ, RR, Glennie MJ. Measurement of kinetic binding constants of a panel of anti-saporin antibodies using a resonant mirror biosensor. *J Immunol Methods.* 1995 Jun 14; 183(1):51-63. 485: Kroesen BJ, Helfrich W, Bakker A, Wubbena AS, Bakker H, Kal HB, The TH, de Leij L. Reduction of EGP-2-positive pulmonary metastases by bispecific-antibody-redirectioned T cells in an immunocompetent rat model. *Int J Cancer.* 1995 Jun 9; 61(6):812-8. 486: Kershaw MH, Trapani JA, Smyth MJ. Cytotoxic lymphocytes: redirecting the cell-mediated immune response for the therapy of cancer. *Ther Immunol.* 1995 Jun; 2(3):173-81. 487: George AJ, Titus JA, Jost CR, Kurucz I, Perez P, Andrew SM, Nicholls PJ, Huston JS, Segal DM. Redirection of cellular cytotoxicity. A two-step approach using recombinant single-chain Fv molecules. *Cell Biophys.* 1995 Jun; 26(3):153-65. 488: Leibiger H, Hansen A, Schoenherr G, Seifert M, Wustner D, Stigler R, Marx U. Glycosylation analysis of a polyreactive human monoclonal IgG antibody derived from a human-mouse heterohybridoma. *Mol Immunol.* 1995 Jun; 32(8):595-602. 489: Renner C, Pfreundschuh M. Tumor therapy by immune recruitment with bispecific antibodies. *Immunol Rev.* 1995 Jun; 145:179-209. 490: Bakacs T, Lee J, Moreno MB, Zacharchuk CM, Cole MS, Tso JY, Paik CH, Ward JM, Segal DM. A bispecific antibody prolongs survival in mice bearing lung metastases of syngeneic mammary adenocarcinoma. *Int Immunol.* 1995 Jun; 7(6):947-55. 491: de Gast GC, Haagen IA, van Houten AA, Klein SC, Duits AJ, de Weger RA, Vroom TM, Clark MR, Phillips J, van Dijk AJ, et al. CD8 T cell activation after intravenous administration of CD3 x CD19 bispecific antibody in patients with non-Hodgkin lymphoma. *Cancer Immunol Immunother.* 1995 Jun; 40(6):390-6. 492: Haagen IA, Geerars AJ, de Lau WB, Bast BJ, de Gast BC. Related Articles The efficacy of CD3 x CD19 bispecific monoclonal antibody (BsAb) in a clonogenic assay: the effect of repeated addition of BsAb and interleukin-2. *Blood.* 1995 Jun 1; 85(11):3208-12. 493: Campbell FA, Redmond HP, Bouchier-Hayes D. The role of tumor rejection antigens in host antitumor defense mechanisms. *Cancer.* 1995 Jun 1; 75(11):2649-55. 494: Davico Bonino L, De Monte LB, Spagnoli GC, Vola R, Mariani M, Barone D, Moro AM, Riva P, Nicotra MR, Natali PG, et al. Related Articles Bispecific monoclonal antibody anti-CD3 x anti-tenascin: an immunotherapeutic agent for human glioma. *Int J Cancer.* 1995 May 16; 61(4):509-15. 495: Vossebeld PJ, Kessler J, von dem Borne AE, Roos D, Verhoeven AJ. Heterotypic Fc gamma R clusters evoke a synergistic Ca²⁺ response in human neutrophils. *J Biol Chem.* 1995 May 5; 270(18):10671-9. 496: Schondorf T, Hachtel W. The choice of reducing substrate is altered by replacement of an alanine by a proline in the FAD domain of a bispecific NAD(P)H-nitrate reductase from birch. *Plant Physiol.* 1995 May; 108(1):203-10. 497: RR, Penney CA, Browning AC, Stirpe F, George AJ, Glennie MJ. Delivery of the ribosome-inactivating protein, gelonin, to lymphoma cells via CD22 and CD38 using bispecific antibodies. *Br J Cancer.* 1995 May; 71(5):986-94. 498: Hamy A, Curtet C, Paineau J, Chatal JF, Visset J. Related Articles Feasibility of radioimmunoguided surgery of colorectal carcinoma using indium 111 CEA specific antibody and simulation with a phantom using 2 steps targeting with bispecific antibody. *Tumori.* 1995 May-Jun; 81(3 Suppl):103-6. 499: Kurucz I, Titus JA, Jost CR, Jacobus CM, Segal DM. Related Articles Retargeting of CTL by an efficiently refolded bispecific single-chain Fv dimer produced in bacteria. *J Immunol.* 1995 May 1; 154(9):4576-82. 500: Mayer R, Dillehay LE, Shao Y, Zhang YG, Song S, Bartholomew RM,

Mackenson DG, Williams JR. Direct measurement of intratumor dose-rate distributions in experimental xenografts treated with 90Y-labeled radioimmunotherapy. *Int J Radiat Oncol Biol Phys.* 1995 Apr 30; 32(1):147-57. Entrez-PubMed PubMedNucleotideProteinGenomeStructurePopSetTaxonomyOMIM Search PubMed Protein Nucleotide Structure Genome PopSet OMIM Taxonomy for LimitsPreview/IndexHistoryClipboard About Entrez Entrez PubMed Overview Help | FAQ New/Noteworthy PubMed Services Journal Browser MeSH Browser Single Citation Matcher Batch Citation Matcher Clinical Queries Cubby Related Resources Order Documents Grateful Med Consumer Health Clinical Alerts ClinicalTrials.gov Privacy Policy Summary Brief Abstract Citation MEDLINE ASN.1 XML/SGML LinkOut Protein Links Nucleotide Links Popset Links Structure Links Genome Links OMIM Links Show: 5 10 20 50 100 200 500 Items 501-925 of 925Page 2 of 2Select page: 501: Silla LM, Chen J, Zhong RK, Whiteside TL, Ball ED.Related Articles Potentiation of lysis of leukaemia cells by a bispecific antibody to CD33 and CD16 (Fc gamma RIII) expressed by human natural killer (NK) cells. *Br J Haematol.* 1995 Apr; 89(4):712-8. 502: Tsai CJ, Podila GK, Chiang VL., Protein, Nucleotide Nucleotide sequence of a *Populus tremuloides* gene encoding bispecific caffeic acid/5-hydroxyferulic acid O-methyltransferase. *Plant Physiol.* 1995 Apr; 107(4):1459. available. 503: Morganelli PM, Rogers RA, Kitzmiller TJ, Bergeron A.Related Articles Enhanced metabolism of LDL aggregates mediated by specific human monocyte IgG Fc receptors. *J Lipid Res.* 1995 Apr; 36(4):714-24. 504: Chatal JF, Faivre-Chauvet A, Bardies M, Peltier P, Gautherot E, Barbet J. Bifunctional antibodies for radioimmunotherapy. *Hybridoma.* 1995 Apr; 14(2):125-8 505: Moreno MB, Titus JA, Cole MS, Tso JY, Le N, Paik CH, Bakacs T, Zacharchuk CM, Segal DM, Wunderlich JR. Bispecific antibodies retarget murine T cell cytotoxicity against syngeneic breast cancer in vitro and in vivo. *Cancer Immunol Immunother.* 1995 Mar; 40(3):182-90. 506: Neri D, Momo M, Prospero T, Winter G. High-affinity antigen binding by chelating recombinant antibodies (CRAbs). *J Mol Biol.* 1995 Feb 24; 246(3):367-73. 507: Haagen IA, Geerars AJ, Clark MR, van de Winkel JG.Related Articles Interaction of human monocyte Fc gamma receptors with rat IgG2b. A new indicator for the Fc gamma RIa (R-H131) polymorphism. *J Immunol.* 1995 Feb 15; 154(4):1852-60. 508: Lamers CH, Gratama JW, Warnaar SO, Stoter G, Bolhuis RL. Inhibition of bispecific monoclonal antibody (bsAb)-targeted cytotoxicity by human anti-mouse antibodies in ovarian carcinoma patients treated with bsAb-targeted activated T-lymphocytes. *Int J Cancer.* 1995 Feb 8; 60(4):450-7. 509: Shalaby MR, Carter P, Maneval D, Giltinan D, Kotts C.Related Articles Bispecific HER2 x CD3 antibodies enhance T-cell cytotoxicity in vitro and localize to HER2-overexpressing xenografts in nude mice. *Clin Immunol Immunopathol.* 1995 Feb; 74(2):185-92. 510: Auriol J, Guesdon JL, Guibourdenche M, Riou JY.Related Articles Characterization of serogroup A *Neisseria meningitidis* strains by rRNA gene restriction patterns and PCR: correlation with the results of serotyping, subtyping and multilocus enzyme electrophoresis. *FEMS Immunol Med Microbiol.* 1995 Feb; 10(3-4):219-26. 511: Hattori K, Tsukamoto H, Ohta S, Yabe M, Yabe H, Kato S, Takakura I, Ueda R, Habu S, Nishimura T. Bispecific antibody-mediated cytotoxicity by CD4+ and CD8(+)-activated T cells generated from leukemia patients after allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 1995 Feb; 15(2):193-8. 512: Hazra DK, Britton KE, Lahiri VL, Gupta AK, Khanna P, Saran S. Immunotechnological trends in radioimmunotargeting: from 'magic bullet' to 'smart bomb'. *Nucl Med Commun.* 1995 Feb; 16(2):66-75 513: Dubel S, Breitling F, Kontermann R, Schmidt T, Skerra A, Little M., Protein, Nucleotide Bifunctional and multimeric complexes of streptavidin fused to single chain antibodies (scFv). *J Immunol Methods.* 1995 Jan 27; 178(2):201-9. 514: Kuus-Reichel K, Knott C, Sam-Fong P, Petrella E, Corvalan JR. Therapy of streptozotocin induced diabetes with a bifunctional antibody that delivers vinca alkaloids to IL-2 receptor positive cells. *Autoimmunity.* 1995; 22(3):173-81. 515: Yang J, Raju R, Sharma R, Xiang J. A genetically engineered fusion protein M4/TNF with increased bifunctional activity refolded in the presence of protein disulfide isomerase. *Hum Antibodies Hybridomas.* 1995; 6(4):129-36. 516: Kipriyanov SM, Breitling F, Little M, Dubel S. Single-chain antibody streptavidin fusions: tetrameric bifunctional scFv-complexes with biotin binding activity and enhanced affinity to antigen. *Hum Antibodies Hybridomas.* 1995; 6(3):93-101. 517: Di Mauro ME, Ager A. T-lymphocyte proliferation stimulated by alpha beta TCR/CD2 bispecific antibody is dependent on LFA-1/ICAM-1 recognition of accessory cells. *Adv Exp Med Biol.* 1995; 378:381-3. available. 518: Cosimi AB. Future of monoclonal antibodies in solid organ transplantation. *Dig Dis Sci.* 1995 Jan; 40(1):65-72 519: Schuhmacher J, Klivenyi G, Matys R, Stadler M, Regiert T, Hauser H, Doll J, Maier-Borst W, Zoller M. Multistep tumor targeting in nude mice using bispecific antibodies and a gallium chelate suitable for immunoscintigraphy with positron emission tomography. *Cancer Res.* 1995 Jan 1; 55(1):115-23. 520: Ginsberg JS, Wells PS, Brill-Edwards P, Donovan D, Panju A, van Beek EJ, Patel A. Application of a novel and rapid whole blood assay for D-dimer in patients with clinically suspected pulmonary embolism. *Thromb Haemost.* 1995 Jan; 73(1):35-8. 521: Ohta S, Tsukamoto H, Watanabe K, Makino K, Kuge S, Hanai N, Habu S, Nishimura T. Tumor-associated glycoantigen, sialyl Lewis(x) as a target for bispecific antibody-directed adoptive tumor immunotherapy. *Immunol Lett.* 1995 Jan; 44(1):35-40. 522: Weiner GJ, De Gast GC. Bispecific monoclonal antibody therapy of B-cell malignancy. *Leuk Lymphoma.* 1995 Jan; 16(3-4):199-207 523: Michon J, Perdereau B, Brixy F, Moutel S, Fridman WH, Teillaud JL. In vivo targeting of human neuroblastoma xenograft by anti-GD2/anti-Fc gamma RI (CD64) bispecific antibody. *Eur J Cancer.* 1995; 31A(4):631-6. 524: Eray M, Dogan NS, Reiken SR, Sutisna H, Van Wie BJ, Koch AR, Moffett DF, Silber M, Davis WC. A highly stable and selective biosensor using modified nicotinic acetylcholine receptor (nAChR). *Biosystems.* 1995; 35(2-3):183-8. 525: Thielemans KM. Immunotherapy with bispecific antibodies. *Verh K Acad Geneeskd Belg.* 1995; 57(3):229-47; discussion 247-8. 526: Karawajew L, Jung G, Wolf H, Micheel B, Ganzel K.Related Articles A flow cytometric long-term cytotoxicity assay. *J Immunol Methods.* 1994 Dec 28; 177(1-2):119-30. 527: Niemeyer CM, Sano T, Smith CL, Cantor CR. Oligonucleotide-directed self-assembly of proteins: semisynthetic DNA-streptavidin hybrid molecules as connectors for the generation of macroscopic arrays and the construction of supramolecular bioconjugates. *Nucleic Acids Res.* 1994 Dec 25; 22(25):5530-9. 528: Perisic O, Webb PA, Holliger P, Winter G, Williams RL.Related Articles, Protein, Structure Crystal structure of a diabody, a bivalent antibody fragment. *Structure.* 1994 Dec 15; 2(12):1217-26. 529: Poljak RJ. Production and structure of diabodies. *Structure.*

1994 Dec 15; 2(12):1121-3 530: Sconocchia G, Titus JA, Segal DM. CD44 is a cytotoxic triggering molecule in human peripheral blood NK cells. *J Immunol.* 1994 Dec 15; 153(12):5473-81. 531: Warnaar SO, De Paus V, Lardenoije R, Machielse BN, De Graaf J, Bregonje M, Van Haarlem H. Purification of bispecific F(ab')₂ from murine trinoma OC/TR with specificity for CD3 and ovarian cancer. *Hybridoma.* 1994 Dec; 13(6):519-26. 532: Chetanneau A, Barbet J, Peltier P, Le Doussal JM, Gruaz-Guyon A, Bernard AM, Resche I, Rouvier E, Bourguet P, Delaage M, et al. Pretargetted imaging of colorectal cancer recurrences using an ¹¹¹In-labelled bivalent hapten and a bispecific antibody conjugate. *Nucl Med Commun.* 1994 Dec; 15(12):972-80. 533: Haagen IA, de Lau WB, Bast BJ, Geerars AJ, Clark MR, de Gast BC. Unprimed CD4 + and CD8 + T cells can be rapidly activated by a CD3 x CD19 bispecific antibody to proliferate and become cytotoxic. *Cancer Immunol Immunother.* 1994 Dec; 39(6):391-6. 534: Marathias K, Pinto C, Rodberg G, Preffer F, Wong J, Kradin R. The T cell antigen receptor CD3:CD4 molecular complex is diminished on the surface of pulmonary lymphocytes. *Am J Pathol.* 1994 Nov; 145(5):1219-27. 535: Ruf J, Feldt-Rasmussen U, Hegedus L, Ferrand M, Carayon P. Bispecific thyroglobulin and thyroperoxidase autoantibodies in patients with various thyroid and autoimmune diseases. *J Clin Endocrinol Metab.* 1994 Nov; 79(5):1404-9. 536: Chamow SM, Zhang DZ, Tan XY, Mhatre SM, Marsters SA, Peers DH, Byrn RA, Ashkenazi A, Junghans RP. A humanized, bispecific immunoadhesin-antibody that retargets CD3 + effectors to kill HIV-1-infected cells. *J Immunol.* 1994 Nov 1; 153(9):4268-80. 537: Mikolajczyk SD, Meyer DL, Starling JJ, Law KL, Rose K, Dufour B, Offord RE. High yield, site-specific coupling of N-terminally modified beta-lactamase to a proteolytically derived single-sulfhydryl murine Fab'. *Bioconjug Chem.* 1994 Nov-Dec; 5(6):636-46. 538: Wei C, Tang ZY, Liu KD. [Targeting treatment of human HCC xenografts implanted in nude mice using bifunctional antibody HC-1 combined with mitomycin C]. *Zhonghua Yi Xue Za Zhi.* 1994 Nov; 74(11):676-9, 709-10. Chinese. 539: Renner C, Pfreundschuh M. [Antibody-conjugated cytostatic drugs. Uses of monoclonal antibodies for new strategies in tumor therapy]. *Fortschr Med.* 1994 Oct 20; 112(29):399. . available. 540: Kipriyanov SM, Dubel S, Breitling F, Kontermann RE, Little M. Recombinant single-chain Fv fragments carrying C-terminal cysteine residues: production of bivalent and biotinylated miniantibodies. *Mol Immunol.* 1994 Oct; 31(14):1047-58. 541: Kroesen BJ, Buter J, Sleijfer DT, Janssen RA, van der Graaf WT, The TH, de Leij L, Mulder NH. Phase I study of intravenously applied bispecific antibody in renal cell cancer patients receiving subcutaneous interleukin 2. *Br J Cancer.* 1994 Oct; 70(4):652-61. 542: Reid IM, Lundy JK, Donohue JH. The bispecific antibody 500A2 x 96.5 targets T-lymphocytes activated in vivo with staphylococcal enterotoxin B (SEB) against CL62 melanoma cells in vitro. *Surg Oncol.* 1994 Oct; 3(5):279-85. 543: Haagen IA, Geerars AJ, Bast EJ, de Gast GC, van de Winkel JG, de Lau WB. Evaluation of Fc gamma receptor mediated T-cell activation by two purified CD3 x CD19 bispecific monoclonal antibodies with hybrid Fc domains. *Ther Immunol.* 1994 Oct; 1(5):279-87. 544: Dietsch MT, Chan PY, Kanner SB, Gilliland LK, Ledbetter JA, Linsley PS, Aruffo A. Coengagement of CD2 with LFA-1 or VLA-4 by bispecific ligand fusion proteins primes T cells to respond more effectively to T cell receptor-dependent signals. *J Leukoc Biol.* 1994 Oct; 56(4):444-52. 545: Nunes-Duby SE, Tirumalai RS, Dorgai L, Yagil E, Weisberg RA, Landy A. Lambda integrase cleaves DNA in cis. *EMBO J.* 1994 Sep 15; 13(18):4421-30. 546: Reist CJ, Liang HY, Denny D, Martin EN, Scheld WM, Taylor RP. Cross-linked bispecific monoclonal antibody heteropolymers facilitate the clearance of human IgM from the circulation of squirrel monkeys. *Eur J Immunol.* 1994 Sep; 24(9):2018-25. 547: Makino K, Ogata T, Miyake H, Habu S, Nishimura T. Related Articles Expression of tumor-associated glycoantigen, sialyl Lewis(a), in human head and neck squamous cell carcinoma and its application to tumor immunotherapy. *Jpn J Cancer Res.* 1994 Sep; 85(9):887-91. 548: Bakacs T, Hadley AG, Kumpel BM, Segal DM, Banhidy F. Related Articles Comparison of the ability of red cells sensitized with a bispecific anti-D x anti-Fc gamma RIII Fab fragment to activate human K cells and peritoneal macrophages through Fc gamma RIII. *Immunol Lett.* 1994 Sep; 42(1-2):91-5. 549: Stmpfli MR, Miescher S, Aebischer I, Zurcher AW, Stadler BM. Inhibition of human IgE synthesis by anti-IgE antibodies requires divalent recognition. *Eur J Immunol.* 1994 Sep; 24(9):2161-7. 550: Mallender WD, Ferreira ST, Voss EW, Coelho-Sampaio T. Related Articles Inter-active-site distance and solution dynamics of a bivalent-bispecific single-chain antibody molecule. *Biochemistry.* 1994 Aug 23; 33(33):10100-8. 551: Donadel G, Calabro A, Sigounas G, Hascall VC, Notkins AL, Harindranath N. Human polyreactive and monoreactive antibodies: effect of glycosylation on antigen binding. *Glycobiology.* 1994 Aug; 4(4):491-6. 552: Whitlow M, Filpula D, Rollence ML, Feng SL, Wood JF. Related Articles Multivalent Fvs: characterization of single-chain Fv oligomers and preparation of a bispecific Fv. *Protein Eng.* 1994 Aug; 7(8):1017-26. 553: Kaneko T, Fukuda J, Teramura M, Fusauchi Y, Kakui Y, Okumura K, Mizoguchi H, Oshimi K. Combination of interleukin-2-stimulated lymphocytes and bispecific antibodies that efficiently lyse leukemic cells does not affect bone marrow CD34-positive stem cell function in vitro. *Bone Marrow Transplant.* 1994 Aug; 14(2):213-7. 554: Haagen IA, Geerars AJ, de Lau WB, Clark MR, van de Griend RJ, Bast BJ, de Gast BC. Killing of autologous B-lineage malignancy using CD3 x CD19 bispecific monoclonal antibody in end stage leukemia and lymphoma. *Blood.* 1994 Jul 15; 84(2):556-63. 555: Bohlen H, Manzke O, Engert A, Hertel M, Hippler-Altenburg R, Diehl V, Tesch H. Differentiation of cytotoxicity using target cells labelled with europium and samarium by electroporation. *J Immunol Methods.* 1994 Jul 12; 173(1):55-62. 556: Ring DB, Hsieh-Ma ST, Shi T, Reeder J. Antigen forks: bispecific reagents that inhibit cell growth by binding selected pairs of tumor antigens. *Cancer Immunol Immunother.* 1994 Jul; 39(1):41-8. 557: Roggenbuck D, Konig H, Niemann B, Schoenherr G, Jahn S, Porstmann T. Real-time biospecific interaction analysis of a natural human polyreactive monoclonal IgM antibody and its Fab and scFv fragments with several antigens. *Scand J Immunol.* 1994 Jul; 40(1):64-70. 558: Kaneko T, Fusauchi Y, Kakui Y, Okumura K, Mizoguchi H, Oshimi K. Cytotoxicity of cytokine-induced killer cells coated with bispecific antibody against acute myeloid leukemia cells. *Leuk Lymphoma.* 1994 Jul; 14(3-4):219-29. 559: Ren J, Fan DM, Zhou SJ. [Establishment of immuno-PCR technique for the detection of tumor associated antigen MG7-Ag on the gastric cancer cell line]. *Zhonghua Zhong Liu Za Zhi.* 1994 Jul; 16(4):247-50. Chinese. 560: Mabondzo A, Boussin F, Raoul H, Le Naour R, Gras G, Vaslin B, Bartholeyns J, Romet-Lemonne JL, Dormont D. Antibody-dependent cellular cytotoxicity and neutralization of human immunodeficiency virus type 1 by high affinity cross-linking of gp41 to human

macrophage Fc IgG receptor using bispecific antibody. *J Gen Virol.* 1994 Jun; 75 (Pt 6):1451-6. 561: Wallace PK, Howell AL, Fanger MW. Role of Fc gamma receptors in cancer and infectious disease. *J Leukoc Biol.* 1994 Jun; 55(6):816-26 562: Gruber M, Schodin BA, Wilson ER, Kranz DM. Efficient tumor cell lysis mediated by a bispecific single chain antibody expressed in *Escherichia coli*. *J Immunol.* 1994 Jun 1; 152(11):5368-74. 563: Demanet C, Brissinck J, Leo O, Moser M, Thielemans K. Related Articles Role of T-cell subsets in the bispecific antibody (anti-idiotypic x anti-CD3) treatment of the BCL1 lymphoma. *Cancer Res.* 1994 Jun 1; 54(11):2973-8. 564: Spooner RA, Murray S, Rowlinson-Busza G, Deonarain MP, Chu A, Epenetos AA. Genetically engineered antibodies for diagnostic pathology. *Hum Pathol.* 1994 Jun; 25(6):606-14. 565: Blum S, Milesi R, Tratkiewicz J, Olive D, Gallati H, Cerottini JC, von Fliedner V. Rapid induction of cytolytic T cells via CD28 stimulation for cellular immunotherapy. *Ther Immunol.* 1994 Jun; 1(3):143-52. 566: Nakamura Y, Russell SM, Mess SA, Friedmann M, Erdos M, Francois C, Jacques Y, Adelstein S, Leonard WJ. Heterodimerization of the IL-2 receptor beta- and gamma-chain cytoplasmic domains is required for signalling. *Nature.* 1994 May 26; 369(6478):330-3. 567: Cook AG, Wood PJ. Chemical synthesis of bispecific monoclonal antibodies: potential advantages in immunoassay systems. *J Immunol Methods.* 1994 May 16; 171(2):227-37. 568: Reason DC, Kitamura MY, Lucas AH. Induction of a protective human polysaccharide-specific antibody response in hu-PBL SCID mice by idiotypic vaccination. *J Immunol.* 1994 May 15; 152(10):5009-13. 569: Penna C, Dean PA, Nelson H. Antitumor x anti-CD3 bifunctional antibodies redirect T-cells activated in vivo with staphylococcal enterotoxin B to neutralize pulmonary metastases. *Cancer Res.* 1994 May 15; 54(10):2738-43. 570: Bashkov GV, Stepanova IP, Domogatsky SP. Collagen-targeted antibodies inhibit platelet-dependent thrombosis in vivo. *Thromb Res.* 1994 May 15; 74(4):321-34. 571: Renner C, Jung W, Sahin U, Denfeld R, Pohl C, Trumper L, Hartmann F, Diehl V, van Lier R, Pfreundschuh M. Cure of xenografted human tumors by bispecific monoclonal antibodies and human T cells. *Science.* 1994 May 6; 264(5160):833-5. 572: Morelli D, Villa E, Tagliabue E, Perletti L, Villa ML, Menard S, Balsari A, Colnaghi MI. Relevance of antibody valency in EGF receptor modulation. *Scand J Immunol.* 1994 May; 39(5):453-8. 573: Azuma A, Yagita H, Okumura K, Kudoh S, Niitani H. Related Articles Potentiation of long-term-cultured lymphokine-activated killer cell cytotoxicity against small-cell lung carcinoma by anti-CD3 x anti-(tumor-associated antigen) bispecific antibody. *Cancer Immunol Immunother.* 1994 May; 38(5):294-8. 574: Yagi J, Nakata M, Uchiyama T, Nishikawa M, Mizushima Y, Nishioka K, Ito K, Yagita H, Okumura K, Janeway CA, et al. Related Articles Superantigen-like properties of an antibody bispecific for MHC class II molecules and the V beta domain of the T cell antigen receptor. *J Immunol.* 1994 Apr 15; 152(8):3833-41. 575: Kuus-Reichel K, Knott CL, Sam-Fong P, Jue RA, Mackensen DG, Corvalan JR. Production and in vivo characterization of a bifunctional antibody (IVA039.1) with specificity for the mouse interleukin-2 receptor and vinca alkaloids. *Hybridoma.* 1994 Apr; 13(2):115-22. 576: Tada H, Kurokawa T, Seita T, Watanabe T, Iwasa S. Related Articles Expression and characterization of a chimeric bispecific antibody against fibrin and against urokinase-type plasminogen activator. *J Biotechnol.* 1994 Mar 31; 33(2):157-74. 577: Ferrini S, Sforzini S, Cambiaggi A, Poggi A, Meazza R, Canevari S, Colnaghi MI, Moretta L. The LFA-1/ICAM cell adhesion pathway is involved in tumor-cell lysis mediated by bispecific monoclonal-antibody-targeted T lymphocytes. *Int J Cancer.* 1994 Mar 15; 56(6):846-52. 578: Weiss E, Orfanoudakis G. Application of an alkaline phosphatase fusion protein system suitable for efficient screening and production of Fab-enzyme conjugates in *Escherichia coli*. *J Biotechnol.* 1994 Mar 15; 33(1):43-53. 579: Massino IS, Sukhanova LL, Kizim EA, Segal OL, Smirnova MB, Monakhov VV, Koliaskina GI, Dmitriev AD. [Preparing bifunctional antibodies to human IGG and horseradish peroxidase and their utilization for testing of antibodies to HIV]. *Biull Eksp Biol Med.* 1994 Mar; 117(3):291-3. Russian. available. 580: De Sutter K, Fiers W. A bifunctional murine:human chimeric antibody with one antigen-binding arm replaced by bacterial beta-lactamase. *Mol Immunol.* 1994 Mar; 31(4):261-7. 581: Weiner GJ, Kostelny SA, Hillstrom JR, Cole MS, Link BK, Wang SL, Tso JY. Nucleotide The role of T cell activation in anti-CD3 x antitumor bispecific antibody therapy. *J Immunol.* 1994 Mar 1; 152(5):2385-92. 582: Shen GL, Li JL, Vitetta ES. Bispecific anti-CD22/anti-CD3-ricin A chain immunotoxin is cytotoxic to Daudi lymphoma cells but not T cells in vitro and shows both A-chain-mediated and LAK-T-mediated killing. *J Immunol.* 1994 Mar 1; 152(5):2368-76. 583: Morelli D, Sardini A, Villa E, Villa ML, Menard S, Colnaghi MI, Balsari A. Modulation of drug-induced cytotoxicity by a bispecific monoclonal antibody that recognizes the epidermal growth factor receptor and doxorubicin. *Cancer Immunol Immunother.* 1994 Mar; 38(3):171-7. 584: Howell AL, Guyre PM, You K, Fanger MW. Targeting HIV-1 to Fc gamma R on human phagocytes via bispecific antibodies reduces infectivity of HIV-1 to T cells. *J Leukoc Biol.* 1994 Mar; 55(3):385-91. 585: Wang LM, Wan WH, Lu LJ. [A bispecific monoclonal antibody with versatile adaptor mediating different cytotoxicities]. *Zhonghua Zhong Liu Za Zhi.* 1994 Mar; 16(2):83-7. Chinese. 586: Kricka LJ. Selected strategies for improving sensitivity and reliability of immunoassays. *Clin Chem.* 1994 Mar; 40(3):347-57 587: Auriol J, Guesdon JL, Mazie JC, Nato F. Development of a bispecific monoclonal antibody for use in molecular hybridisation. *J Immunol Methods.* 1994 Feb 28; 169(1):123-33. 588: George AJ, Titus JA, Jost CR, Kurucz I, Perez P, Andrew SM, Nicholls PJ, Huston JS, Segal DM. Redirection of T cell-mediated cytotoxicity by a recombinant single-chain Fv molecule. *J Immunol.* 1994 Feb 15; 152(4):1802-11. 589: van Ravenswaay Claasen HH, Eggermont AM, Nooyen YA, Warnaar SO, Fieuren GJ. Immunotherapy in a human ovarian cancer xenograft model with two bispecific monoclonal antibodies: OV-TL 3/CD3 and OC/TR. *Gynecol Oncol.* 1994 Feb; 52(2):199-206. 590: Barth RF, Soloway AH. Boron neutron capture therapy of primary and metastatic brain tumors. *Mol Chem Neuropathol.* 1994 Feb-Apr; 21(2-3):139-54 591: Fanger MW, Graziano RF, Guyre PM. Production and use of anti-FcR bispecific antibodies. *Immunomethods.* 1994 Feb; 4(1):72-81 592: Mallender WD, Voss EW. Construction, expression, and activity of a bivalent bispecific single-chain antibody. *J Biol Chem.* 1994 Jan 7; 269(1):199-206. 593: Smans KA, Hoylaerts MF, De Broe ME. Requirement of monocytes and T-helper cells during development of tumor cell cytotoxicity in targeted T cells. *Cancer Immunol Immunother.* 1994 Jan; 38(1):43-52. 594: Mahana W, Jacquemart F, Ermonval M. A murine monoclonal multireactive immunoglobulin kappa light chain. *Scand J Immunol.* 1994 Jan; 39(1):107-10. 595: Beun GD, van de Velde CJ, Fleuren GJ. T-cell based

cancer immunotherapy: direct or redirected tumor-cell recognition? *Immunol Today*. 1994 Jan; 15(1):11-5 596: Wolf H, Freimann U, Jung G. Target cell induced T cell activation with bispecific antibodies: a new concept for tumor immunotherapy. *Recent Results Cancer Res*. 1994; 135:185-95 available. 597: Hansen A, Jahn S, Lukowsky A, Grutz G, Bohn J, von Baehr R, Settmacher U., Protein, Nucleotide VH/VL gene expression in polyreactive-antibody-producing human hybridomas from the fetal B cell repertoire. *Exp Clin Immunogenet*. 1994; 11(1):1-16. 598: Carter P, Rodrigues ML, Lewis GD, Figari I, Shalaby MR. Towards an immunotherapy for p185HER2 overexpressing tumors. *Adv Exp Med Biol*. 1994; 353:83-94. available. 599: Leon JA, Goldstein NI, Fisher PB. New approaches for the development and application of monoclonal antibodies for the diagnosis and therapy of human cancer. *Pharmacol Ther*. 1994; 61(1-2):237-78 600: Stevenson GT, Bell AJ, Evans TR, RR, Glennie MJ, Hamblin TJ, Kan KS, Mead GM. Mechanisms in removal of tumor by antibody. *Cell Biophys*. 1994; 24-25:45-50. 601: Horenstein A, Poiesi C, Camagna M, de Monte L, Mariani M, Albertini A, Malavasi F. Biosensor analysis of antigen-antibody interactions as a priority step in the generation of monoclonal bispecific antibodies. *Cell Biophys*. 1994; 24-25:109-17. 602: Knuth A, Bernhard H, Jager E, Wolfel T, Karbach J, Jaggle C, Strittmatter W, Meyer zum Buschenfelde KH. Induction of tumour cell lysis by a bispecific antibody recognising epidermal growth factor receptor (EGFR) and CD3. *Eur J Cancer*. 1994; 30A(8):1103-7. 603: Hayden MS, Linsley PS, Gayle MA, Bajorath J, Brady WA, Norris NA, Fell HP, Ledbetter JA, Gilliland LK. Single-chain mono- and bispecific antibody derivatives with novel biological properties and antitumour activity from a COS cell transient expression system. *Ther Immunol*. 1994 Jan; 1(1):3-15. 604: Malygin AM, Somersalo K, Timonen T. Promotion of natural killer cell growth in vitro by bispecific (anti-CD3 x anti-CD16) antibodies. *Immunology*. 1994 Jan; 81(1):92-5. 605: Ferrini S, Cambiaggi A, Sforzini S, Marciano S, Canevari S, Mezzanzanica D, Colnaghi MI, Grossi CE, Moretta L. Targeting of T lymphocytes against EGF-receptor + tumor cells by bispecific monoclonal antibodies: requirement of CD3 molecule cross-linking for T-cell activation. *Int J Cancer*. 1993 Dec 2; 55(6):931-7. 606: Hombach A, Jung W, Pohl C, Renner C, Sahin U, Schmits R, Wolf J, Kapp U, Diehl V, Pfreundschuh M. A CD16/CD30 bispecific monoclonal antibody induces lysis of Hodgkin's cells by unstimulated natural killer cells in vitro and in vivo. *Int J Cancer*. 1993 Nov 11; 55(5):830-6. 607: Reddy VS, Ford CH. Production of hybrids secreting bispecific antibodies recognising CEA and doxorubicin. *Anticancer Res*. 1993 Nov-Dec; 13(6A):2077-83. 608: Reist CJ, Combs MJ, Croft BY, Taylor RP. Antigens pre-bound to the primate erythrocyte complement receptor via cross-linked bispecific monoclonal antibody heteropolymers are rapidly cleared from the circulation. *Eur J Immunol*. 1993 Nov; 23(11):3021-7. 609: Okada H, Momota H, Okada N, Okamoto T, Azuma T. Related Articles Elimination of HIV-infected cells by lymphocytes armed with a bifunctional antibody to gp120 of HIV and CD3. *Immunol Lett*. 1993 Nov; 38(3):195-9. 610: Kroesen BJ, ter Haar A, Spakman H, Willemse P, Sleijfer DT, de Vries EG, Mulder NH, Berendsen HH, Limburg PC, The TH, et al. Local antitumour treatment in carcinoma patients with bispecific-monoclonal-antibody-redirectioned T cells. *Cancer Immunol Immunother*. 1993 Nov; 37(6):400-7. 611: Duke-Cohan JS, Morimoto C, Schlossman SF. Depletion of the helper/inducer (memory) T cell subset using a bispecific antibody-toxin conjugate directed against CD4 and CD29. *Transplantation*. 1993 Nov; 56(5):1188-96. 612: Hakalahti L, Vihko P, Henttu P, Autio-Harmainen H, Soini Y, Vihko R. Evaluation of PAP and PSA gene expression in prostatic hyperplasia and prostatic carcinoma using northern-blot analyses, in situ hybridization and immunohistochemical stainings with monoclonal and bispecific antibodies. *Int J Cancer*. 1993 Oct 21; 55(4):590-7. 613: Le Doussal JM, Chetanneau A, Gruaz-Guyon A, Martin M, Gautherot E, Lehur PA, Chatal JF, Delaage M, Barbet J. Related Articles Bispecific monoclonal antibody-mediated targeting of an indium-111-labeled DTPA dimer to primary colorectal tumors: pharmacokinetics, biodistribution, scintigraphy and immune response. *J Nucl Med*. 1993 Oct; 34(10):1662-71. 614: Bodmer M, Fournel MA, Hinshaw LB. Preclinical review of anti-tumor necrosis factor monoclonal antibodies. *Crit Care Med*. 1993 Oct; 21(10 Suppl):S441-6 615: Ramsey PS, Dean PA, Tasimowicz-Alpini A, Donohue JH, Nelson H. Interferon-gamma-induced intercellular adhesion molecule-1: expression on human tumor cells enhances bifunctional antibody-mediated lysis through a lymphocyte function-associated antigen-1 dependent mechanism. *Cancer Res*. 1993 Oct 1; 53(19):4652-7. 616: Duke-Cohan JS, Morimoto C, Schlossman SF. Targeting of an activated T-cell subset using a bispecific antibody-toxin conjugate directed against CD4 and CD26. *Blood*. 1993 Oct 1; 82(7):2224-34. 617: Garcia de Palazzo I, Klein-Szanto A, Weiner LM. Related Articles Immunohistochemical detection of c-erbB-2 expression by neoplastic human tissue using monospecific and bispecific monoclonal antibodies. *Int J Biol Markers*. 1993 Oct-Dec; 8(4):233-9. 618: Edwards CP, Aruffo A. Current applications of COS cell based transient expression systems. *Curr Opin Biotechnol*. 1993 Oct; 4(5):558-63 619: Blank-Voorthuis CJ, Braakman E, Ronteltap CP, Tilly BC, Sturm E, Warnaar SO, Bolhuis RL. Clustered CD3/TCR complexes do not transduce activation signals after bispecific monoclonal antibody-triggered lysis by cytotoxic T lymphocytes via CD3. *J Immunol*. 1993 Sep 15; 151(6):2904-14. 620: Bohlen H, Hopff T, Manzke O, Engert A, Kube D, Wickramanayake PD, Diehl V, Tesch H. Lysis of malignant B cells from patients with B-chronic lymphocytic leukemia by autologous T cells activated with CD3 x CD19 bispecific antibodies in combination with bivalent CD28 antibodies. *Blood*. 1993 Sep 15; 82(6):1803-12. 621: Bohlen H, Manzke O, Patel B, Moldenhauer G, Dorken B, von Flidner V, Diehl V, Tesch H. Cytolysis of leukemic B-cells by T-cells activated via two bispecific antibodies. *Cancer Res*. 1993 Sep 15; 53(18):4310-4. 622: Weiner LM, Holmes M, Richeson A, Godwin A, Adams GP, Hsieh-Ma ST, Ring DB, Alpaugh RK. Binding and cytotoxicity characteristics of the bispecific murine monoclonal antibody 2B1. *J Immunol*. 1993 Sep 1; 151(5):2877-86. 623: Dergunova NN, Massino IS, Kizim EA, Dmitriev AD. Related Articles [The interaction of bifunctional monoclonal antibodies with antigens studied by a radioimmunological method]. *Biull Eksp Biol Med*. 1993 Sep; 116(9):299-301. Russian. 624: Peltier P, Curtet C, Chatal JF, Le Doussal JM, Daniel G, Aillet G, Gruaz-Guyon A, Barbet J, Delaage M. Radioimmunodetection of medullary thyroid cancer using a bispecific anti-CEA/anti-indium-DTPA antibody and an indium-111-labeled DTPA dimer. *J Nucl Med*. 1993 Aug; 34(8):1267-73. 625: Holliger P, Winter G. Engineering bispecific antibodies. *Curr Opin Biotechnol*. 1993 Aug; 4(4):446-9 626: Valerius T, Repp R, de Wit TP, Berthold S, Platzer E, Kalden JR, Gramatzki M, van de Winkel JG. Involvement of the high-affinity

receptor for IgG (Fc gamma RI; CD64) in enhanced tumor cell cytotoxicity of neutrophils during granulocyte colony-stimulating factor therapy. *Blood*. 1993 Aug 1; 82(3):931-9. 627: Holliger P, Prospero T, Winter G. "Diabodies": small bivalent and bispecific antibody fragments. *Proc Natl Acad Sci U S A*. 1993 Jul 15; 90(14):6444-8. 628: Pohl C, Denfeld R, Renner C, Jung W, Bohlen H, Sahin U, Hombach A, van Lier R, Schwonzen M, Diehl V, et al. CD30-antigen-specific targeting and activation of T cells via murine bispecific monoclonal antibodies against CD3 and CD28: potential use for the treatment of Hodgkin's lymphoma. *Int J Cancer*. 1993 Jul 9; 54(5):820-7. 629: Jantschkeff P, Winkler L, Karawajew L, Kaiser G, Bottger V, Micheel B. Hybrid hybridomas producing bispecific antibodies to CEA and peroxidase isolated by a combination of HAT medium selection and fluorescence activated cell sorting. *J Immunol Methods*. 1993 Jul 6; 163(1):91-7. 630: Beun GD, van de Velde CJ, Fleuren GJ, Eggermont AM. Related Articles T-cell retargeting using bispecific monoclonal antibodies in a rat colon carcinoma model: IV. Tumor neutralization in Winn type assays. *J Immunother*. 1993 Jul; 14(1):11-5. 631: Fomin IK, Tikhonov II, Prasolov VS, Voitenok NN. Related Articles [Transfer of dominant selective genes using retroviral vectors--a simple and quick method for obtaining hybridoma hybrids]. *Mol Gen Mikrobiol Virusol*. 1993 Jul-Aug; (4):31-4. Russian. 632: Aprile C. Intraoperative radioimmunolocalization of colorectal cancer: a review. *Int J Biol Markers*. 1993 Jul-Sep; 8(3):166-71. 633: Bonardi MA, RR, Amlot P, Gromo G, Modena D, Glennie MJ. Delivery of saporin to human B-cell lymphoma using bispecific antibody: targeting via CD22 but not CD19, CD37, or immunoglobulin results in efficient killing. *Cancer Res*. 1993 Jul 1; 53(13):3015-21. 634: Tibben JG, Boerman OC, Claessens RA, Corstens FH, van Deuren M, de Mulder PH, van der Meer JW, Keijser KG, Massuger LF. Related Articles Cytokine release in an ovarian carcinoma patient following intravenous administration of bispecific antibody OC/TR F(ab')₂. *J Natl Cancer Inst*. 1993 Jun 16; 85(12):1003-4. available. 635: Link BK, Weiner GJ. Production and characterization of a bispecific IgG capable of inducing T-cell-mediated lysis of malignant B cells. *Blood*. 1993 Jun 15; 81(12):3343-9. 636: Dietsch MT, Smith VF, Cosand WL, Damle NK, Ledbetter JA, Linsley PS, Aruffo A. Bispecific receptor globulins, novel tools for the study of cellular interactions. Preparation and characterization of an E-selectin/P-selectin bispecific receptor globulin. *J Immunol Methods*. 1993 Jun 4; 162(1):123-32. 637: Tazzari PL, Zhang S, Chen Q, Sforzini S, Bolognesi A, Stirpe F, Xie H, Moretta A, Ferrini S. Targeting of saporin to CD25-positive normal and neoplastic lymphocytes by an anti-saporin/anti-CD25 bispecific monoclonal antibody: in vitro evaluation. *Br J Cancer*. 1993 Jun; 67(6):1248-53. 638: Kuppen PJ, Eggermont AM, Smits KM, van Eendenburg JD, Lazeroms SP, van de Velde CJ, Fleuren GJ. The development and purification of a bispecific antibody for lymphokine-activated killer cell targeting against the rat colon carcinoma CC531. *Cancer Immunol Immunother*. 1993 Jun; 36(6):403-8. 639: Stratieva-Taneeva PA, Khaidukov SV, Kovalenko VA, Nazimov IV, Samokhvalova LV, Nesmeyanov VA. Bispecific monoclonal antibodies to human interleukin 2 and horseradish peroxidase. *Hybridoma*. 1993 Jun; 12(3):271-84. 640: Francois C, Boeffard F, Kaluza B, Weidle UH, Jacques Y. Construction of a bispecific antibody reacting with the alpha- and beta-chains of the human IL-2 receptor. High affinity cross-linking and high anti-proliferative efficiency. *J Immunol*. 1993 May 15; 150(10):4610-9. 641: Beun GD, van de Velde CJ, Fleuren GJ. T-cell retargeting using bispecific monoclonal antibodies in a rat colon carcinoma model: III. Activation of resting T cells and tumor neutralization induced by bispecific antibodies. *J Immunother*. 1993 May 4; 13(4):223-31. 642: Mady BJ, Kurane I, Erbe DV, Fanger MW, Ennis FA. Related Articles Neuraminidase augments Fc gamma receptor II-mediated antibody-dependent enhancement of dengue virus infection. *J Gen Virol*. 1993 May; 74 (Pt 5):839-44. 643: Piran U, Silbert-Shostek D, Barlow EH. Role of antibody valency in hapten-heterologous immunoassays. *Clin Chem*. 1993 May; 39(5):879-83. 644: Somasundaram C, Matzku S, Schuhmacher J, Zoller M. Related Articles Development of a bispecific monoclonal antibody against a gallium-67 chelate and the human melanoma-associated antigen p97 for potential use in pretargeted immunoscintigraphy. *Cancer Immunol Immunother*. 1993 May; 36(5):337-45. 645: Matsuo O. [Mechanism of thrombolytic enzymes]. *Rinsho Ketsueki*. 1993 Apr; 34(4):395-402. . 646: Skerra A. Bacterial expression of immunoglobulin fragments. *Curr Opin Immunol*. 1993 Apr; 5(2):256-62. 647: Tsukamoto H, Nakamura Y, Masuko T, Hashimoto Y, Habu S, Nishimura T. Specific targeting of in vitro-activated human antitumor effector cells using anti-CD3 x anti-c-erbB-2 bispecific antibody. *Immunol Cell Biol*. 1993 Apr; 71 (Pt 2):109-15. 648: Beun GD, Gorter A, Nooyen Y, van de Velde CJ, Fleuren GJ. T cell retargeting using bispecific monoclonal antibodies in a rat colon carcinoma model. II. Syngeneic colon carcinoma CC531 is efficiently killed by retargeted cytotoxic T lymphocytes in vitro despite limited lysis in 51Cr release assays. *J Immunol*. 1993 Mar 15; 150(6):2305-15. 649: Wu S, Yang Y, Sadegh-Nasseri S, Ashwell JD. Use of bispecific heteroconjugated antibodies (anti-T cell antigen receptor x anti-MHC class II) to study activation of T cells with a full length or truncated antigen receptor zeta-chain. *J Immunol*. 1993 Mar 15; 150(6):2211-21. 650: Bruynck A, Seemann G, Bosslet K. Characterisation of a humanised bispecific monoclonal antibody for cancer therapy. *Br J Cancer*. 1993 Mar; 67(3):436-40. 651: Kaneko T, Fusauchi Y, Kakui Y, Masuda M, Akahoshi M, Teramura M, Motoji T, Okumura K, Mizoguchi H, Oshimi K. A bispecific antibody enhances cytokine-induced killer-mediated cytotoxicity of autologous acute myeloid leukemia cells. *Blood*. 1993 Mar 1; 81(5):1333-41. 652: MacLean JA, Su Z, Guo Y, Sy MS, Colvin RB, Wong JT. Related Articles Anti-CD3:anti-IL-2 receptor bispecific monoclonal antibody. Targeting of activated T cells in vitro. *J Immunol*. 1993 Feb 15; 150(4):1619-28. 653: Francois C, Boeffard F, Jacques Y. Chemically engineered bispecific antibody directed at the p55 and p75 chains of the human interleukin 2 receptor: specific high-affinity cross-linking of p55/p75 complexes and high blocking effect on IL2-induced T cell proliferation. *Transplant Proc*. 1993 Feb; 25(1 Pt 1):815-6. available. 654: Curnow SJ, Glennie MJ, Stevenson GT. The role of apoptosis in antibody-dependent cellular cytotoxicity. *Cancer Immunol Immunother*. 1993; 36(3):149-55. 655: Ferrini S, Cambiaggi A, Sforzini S, Canevari S, Mezzanzanica D, Colnaghi MI, Moretta L. Use of anti-CD3 and anti-CD16 bispecific monoclonal antibodies for the targeting of T and NK cells against tumor cells. *Cancer Detect Prev*. 1993; 17(2):295-300. 656: Malavasi F, De Monte LB, Funaro A, Magrini E, Bonino LD, Momo M, Mariani M, Horenstein A, Natali PG. Cell surface receptors and bispecific monoclonal antibodies: the link between basic science and medical oncology. *Year Immunol*. 1993;

7:74-80 available. 657: Parisi A, Bartolazzi A, Bonino C, Camagna M, DeMonte LB, Lombardi A, Natali PG, Paganelli G, Tarditi L, Vassarotto C, et al. BIS-1: a novel bispecific monoclonal antibody for CEA-expressing carcinoma radioimmunoscintigraphy and radioimmunotherapy. *Year Immunol.* 1993; 7:96-105. available. 658: Brissinck J, Demanet C, Moser M, Leo O, Thielemans K. Related Articles Bispecific antibodies in lymphoma. *Int Rev Immunol.* 1993; 10(2-3):187-94 available. 659: Kairemo K, Ljunggren K, Strand SE, Hiltunen J, Penttila P, Nikula T, Laine A, Wahlstrom T. Radioimmunotherapy with 90Y-labeled monoclonal antibodies in a nude mouse ovarian cancer model. *Acta Oncol.* 1993; 32(7-8):801-5. 660: Horenstein AL, Poiesi C, DeMonte L, Camagna M, Mariani M, Albertini A, Malavasi F. Real-time kinetic analysis applied to the production of bispecific monoclonal antibodies for radioimmunodetection of cancer. *Int J Clin Lab Res.* 1993; 23(4):199-205. 661: Fanger MW, Morganelli PM, Guyre PM. Use of bispecific antibodies in the therapy of tumors. *Cancer Treat Res.* 1993; 68:181-94 662: Weiner LM, Holmes M, Adams GP, LaCreta F, Watts P, Garcia de Palazzo I. A human tumor xenograft model of therapy with a bispecific monoclonal antibody targeting c-erbB-2 and CD16. *Cancer Res.* 1993 Jan 1; 53(1):94-100. 663: Hsieh-Ma ST, Eaton AM, Shi T, Ring DB. In vitro cytotoxic targeting by human mononuclear cells and bispecific antibody 2B1, recognizing c-erbB-2 protooncogene product and Fc gamma receptor III. *Cancer Res.* 1992 Dec 15; 52(24):6832-9. 664: Bos R, Nieuwenhuizen W. Bispecific monoclonal antibodies increase the fibrin-specific fibrinolytic activity of tissue-type plasminogen activator (tPA) and urokinase-type plasminogen activator (uPA). *Ann N Y Acad Sci.* 1992 Dec 4; 667:428-30. available. 665: Collazo P, Montoliu L, Puigdomenech P, Rigau J. Related Articles, Protein, Nucleotide Structure and expression of the lignin O-methyltransferase gene from *Zea mays* L. *Plant Mol Biol.* 1992 Dec; 20(5):857-67. 666: Smyth MJ. Generation and cytotoxic profile of human peripheral blood CD4 + T lymphocytes. *Immunol Cell Biol.* 1992 Dec; 70 (Pt 6):379-90. 667: Etienne-Julan M, Roux P, Carillo S, Jeanteur P, Piechaczyk M. The efficiency of cell targeting by recombinant retroviruses depends on the nature of the receptor and the composition of the artificial cell-virus linker. *J Gen Virol.* 1992 Dec; 73 (Pt 12):3251-5. 668: Haagen IA, van de Griend R, Clark M, Geerars A, Bast B, de Gast B. Killing of human leukaemia/lymphoma B cells by activated cytotoxic T lymphocytes in the presence of a bispecific monoclonal antibody (alpha CD3/alpha CD19). *Clin Exp Immunol.* 1992 Dec; 90(3):368-75. 669: Anderson PM, Crist W, Hasz D, Carroll AJ, Myers DE, Uckun FM. G19.4(alpha CD3) x B43(alpha CD19) monoclonal antibody heteroconjugate triggers CD19 antigen-specific lysis of t(4; 11) acute lymphoblastic leukemia cells by activated CD3 antigen-positive cytotoxic T cells. *Blood.* 1992 Dec 1; 80(11):2826-34. 670: Behrsing O, Kaiser G, Karawajew L, Micheel B. Bispecific IgA/IgM antibodies and their use in enzyme immunoassay. *J Immunol Methods.* 1992 Nov 25; 156(1):69-77. 671: Garcia de Palazzo I, Holmes M, Gercel-Taylor C, Weiner LM. Antitumor effects of a bispecific antibody targeting CA19-9 antigen and CD16. *Cancer Res.* 1992 Oct 15; 52(20):5713-9. 672: Allard WJ, Moran CA, Nagel E, Collins G, Largent MT. Related Articles Antigen binding properties of highly purified bispecific antibodies. *Mol Immunol.* 1992 Oct; 29(10):1219-27. 673: Wiener JR, Berchuck A, Bast RC. Biology and therapy with biologic agents in gynecologic cancer. *Curr Opin Oncol.* 1992 Oct; 4(5):946-54 674: Morganelli PM, Kitzmiller TJ, Hemmer R, Fanger MW. Related Articles Redirected targeting of LDL to human monocyte Fc gamma receptors with bispecific antibodies. *Arterioscler Thromb.* 1992 Oct; 12(10):1131-8. 675: De Lau WB, Boom SE, Heije K, Griffioen AW, Braakman E, Bolhuis RL, Tax WJ, Clevers H, Bast BJ. Heterodimeric complex formation with CD8 and TCR by bispecific antibody sustains paracrine IL-2-dependent growth of CD3 + CD8 + T cells. *J Immunol.* 1992 Sep 15; 149(6):1840-6. 676: Azuma A, Yagita H, Matsuda H, Okumura K, Niitani H. Related Articles Induction of intercellular adhesion molecule 1 on small cell lung carcinoma cell lines by gamma-interferon enhances spontaneous and bispecific anti-CD3 x antitumor antibody-directed lymphokine activated killer cell cytotoxicity. *Cancer Res.* 1992 Sep 15; 52(18):4890-4. 677: Ferrini S, Cantoni C, Cambiaggi A, Chen Q, Venzano P, Canevari S, Colnaghi MI, Moretta L. Induction of anti-tumor immune response by bispecific monoclonal antibodies (bimAbs). *Pharmacol Res.* 1992 Sep; 26 Suppl 2:146-7. available. 678: Bonardi MA, Tutt A, Gromo G, Modena D, Glennie M. Related Articles Activation of rat T cells in vitro and in vivo with a bispecific (anti-TCR x anti-CD2) F(ab')2 derivative. *Pharmacol Res.* 1992 Sep; 26 Suppl 2:139-40. available. 679: Nistico P, Mortarini R, De Monte LB, Mazzocchi A, Mariani M, Malavasi F, Parmiani G, Natali PG, Anichini A. Cell retargeting by bispecific monoclonal antibodies. Evidence of bypass of intratumor susceptibility to cell lysis in human melanoma. *J Clin Invest.* 1992 Sep; 90(3):1093-9. 680: Engert A, Pohl C, Diehl V. Experimental therapy in Hodgkin's disease. *Ann Oncol.* 1992 Sep; 3 Suppl 4:97-100. 681: Kontsekova E, Novak M, Kontsek P. [Bispecific antibodies: present status and possible applications]. *Bratisl Lek Listy.* 1992 Aug; 93(8):405-10 Slovak. 682: Segal DM, Qian JH, Mezzanzanica D, Garrido MA, Titus JA, Andrew SM, George AJ, Jost CR, Perez P, Wunderlich JR. Related Articles Targeting of anti-tumor responses with bispecific antibodies. *Immunobiology.* 1992 Aug; 185(2-4):390-402 683: Kontsekova E, Kolcunova A, Kontsek P. Quadroma-secreted bi(interferon alpha 2--peroxidase) specific antibody suitable for one-step immunoassay. *Hybridoma.* 1992 Aug; 11(4):461-8. 684: Curnow SJ, Glennie MJ, Stevenson GT. Cytoplasmic calcium fluxes induced in cytotoxic effector cells by engagement of Fc gamma receptors I, II, and III. *Scand J Immunol.* 1992 Aug; 36(2):221-31. 685: Deramoudt EX, Gilard C, Lepine N, Alonso JM, Romet-Lemonne JL. Bispecific anti-human red blood Rhesus-D antigen x anti Fc gamma RI targeted antibody-dependent cell-mediated cytotoxicity and phagocytosis by mononuclear leucocytes. *Clin Exp Immunol.* 1992 Aug; 89(2):310-4. 686: Massino YuS, Kizim EA, Dergunova NN, Vostrikov VM, Dmitriev AD. Construction of a quadroma to alpha-endorphin/horseradish peroxidase using an actinomycin D-resistant mouse myeloma cell line. *Immunol Lett.* 1992 Aug; 33(3):217-22. 687: Lamers CH, van de Griend RJ, Braakman E, Ronteltap CP, Benard J, Stoter G, Gratama JW, Bolhuis RL. Optimization of culture conditions for activation and large-scale expansion of human T lymphocytes for bispecific antibody-directed cellular immunotherapy. *Int J Cancer.* 1992 Jul 30; 51(6):973-9. 688: Zoller M, Schuhmacher J, Reed J, Maier-Borst W, Matzku S. Establishment and characterization of monoclonal antibodies against an octahedral gallium chelate suitable for immunoscintigraphy with PET. *J Nucl Med.* 1992 Jul; 33(7):1366-72. 689: de Palazzo IG, Kitson J, Gercel-Taylor C, Adams S, Weiner LM. Bispecific monoclonal

antibody regulation of Fc gamma RIII-directed tumor cytotoxicity by large granular lymphocytes. *Cell Immunol.* 1992 Jul; 142(2):338-47. 690: Mabondzo A, Aussage P, Bartholeyns J, Le Naour R, Raoul H, Romet-Lemonne JL, Dormont D. Bispecific antibody targeting of human immunodeficiency virus type 1 (HIV-1) glycoprotein 41 to human macrophages through the Fc IgG receptor I mediates neutralizing effects in HIV-1 infection. *J Infect Dis.* 1992 Jul; 166(1):93-9. 691: Obukhov SK, Gennie MJ, Tutt AL, Kemshead JT, Coakham HB, Beverly PC. The cytotoxic action of lymphokine activated killer cells upon the human glioma cell line U251 is stimulated by bispecific monoclonal antibody (MoAb) constructs. *J Neurooncol.* 1992 Jul; 13(3):203-10. 692: Okamoto K, Harada K, Ikeyama S, Iwasa S. Therapeutic effect of ansamitocin targeted to tumor by a bispecific monoclonal antibody. *Jpn J Cancer Res.* 1992 Jul; 83(7):761-8. 693: Zaiou M, Visvikis S, Visvikis A, Siest G. A rapid and reliable method for direct genotyping of codon 360 in the human apolipoprotein A-IV gene. *J Lipid Res.* 1992 Jul; 33(7):1061-6. 694: Nakamura Y, Tokuda Y, Iwasawa M, Tsukamoto H, Kidokoro M, Kobayashi N, Kato S, Mitomi T, Habu S, Nishimura T. Large-scale culture system of human CD4+ helper/killer T cells for the application to adoptive tumour immunotherapy. *Br J Cancer.* 1992 Jul; 66(1):20-6. 695: Affleck K, Embleton MJ. Monoclonal antibody targeting of methotrexate (MTX) against MTX-resistant tumour cell lines. *Br J Cancer.* 1992 Jun; 65(6):838-44. 696: Tarditi L, Camagna M, Parisi A, Vassarotto C, DeMonte LB, Letarte M, Malavasi F, Mariani M. Selective high-performance liquid chromatographic purification of bispecific monoclonal antibodies. *J Chromatogr.* 1992 May 22; 599(1-2):13-20. 697: Beun GD, van Eendenburg DH, Corver WE, van de Velde CJ, Fleuren GJ. T-cell retargeting using bispecific monoclonal antibodies in a rat colon carcinoma model. I. Significant bispecific lysis of syngeneic colon carcinoma CC531 is critically dependent on prolonged preactivation of effector T-lymphocytes by immobilized anti-T-cell receptor antibody. *J Immunother.* 1992 May; 11(4):238-48. 698: Imura Y, Stassen JM, Kurokawa T, Iwasa S, Lijnen HR, Collen D. Thrombolytic and pharmacokinetic properties of an immunoconjugate of single-chain urokinase-type plasminogen activator (u-PA) and a bispecific monoclonal antibody against fibrin and against u-PA in baboons. *Blood.* 1992 May 1; 79(9):2322-9. 699: Bugos RC, Chiang VL, Campbell WH. Protein Characterization of bispecific caffeic acid/5-hydroxyferulic acid O-methyltransferase from aspen. *Phytochemistry.* 1992 May; 31(5):1495-8. 700: Chen Q, Sun P, Prigione I, Xie H, Ferrini S. Targeting of "T" lymphocytes against human hepatoma cells by a bispecific monoclonal antibody: role of different lymphocyte subsets. *Tumori.* 1992 Apr 30; 78(2):79-86. 701: Taylor RP, Reist CJ, Sutherland WM, Otto A, Labuguen RH, Wright EL. In vivo binding and clearance of circulating antigen by bispecific heteropolymer-mediated binding to primate erythrocyte complement receptor. *J Immunol.* 1992 Apr 15; 148(8):2462-8. 702: Labuguen RH, Taylor RP, Zimmermann RL. E-rosette formation using heteropolymeric monoclonal antibodies. *Immunol Lett.* 1992 Apr; 32(2):175-80. 703: Shivnan E, Biffen M, Shiroo M, Pratt E, Glennie M, Alexander D. Does co-aggregation of the CD45 and CD3 antigens inhibit T cell antigen receptor complex-mediated activation of phospholipase C and protein kinase C? *Eur J Immunol.* 1992 Apr; 22(4):1055-62. 704: Flavell DJ, Cooper S, Morland B, R, Flavell SU. Related Articles Effectiveness of combinations of bispecific antibodies for delivering saporin to human acute T-cell lymphoblastic leukaemia cell lines via CD7 and CD38 as cellular target molecules. *Br J Cancer.* 1992 Apr; 65(4):545-51. 705: Heike Y, Okumura K, Tsuruo T. Augmentation by bispecific F(ab')₂ reactive with P-glycoprotein and CD3 of cytotoxicity of human effector cells on P-glycoprotein positive human renal cancer cells. *Jpn J Cancer Res.* 1992 Apr; 83(4):366-72. 706: Nishimura T, Nakamura Y, Tsukamoto H, Takeuchi Y, Tokuda Y, Iwasawa M, Yamamoto T, Masuko T, Hashimoto Y, Habu S. Related Articles Human c-erbB-2 proto-oncogene product as a target for bispecific-antibody-directed adoptive tumor immunotherapy. *Int J Cancer.* 1992 Mar 12; 50(5):800-4. 707: Kostelny SA, Cole MS, Tso JY. Protein, Nucleotide Formation of a bispecific antibody by the use of leucine zippers. *J Immunol.* 1992 Mar 1; 148(5):1547-53. 708: Neblock DS, Chang CH, Mascelli MA, Fleek M, Stumpo L, Cullen MM, Daddona PE. Conjugation and evaluation of 7E3 x P4B6, a chemically cross-linked bispecific F(ab')₂ antibody which inhibits platelet aggregation and localizes tissue plasminogen activator to the platelet surface. *Bioconjug Chem.* 1992 Mar-Apr; 3(2):126-31. 709: Xiang J, Pan Z, Attah-Poku S, Babiuk L, Zhang Y, Liu E. Production of hybrid bispecific antibody recognizing human colorectal carcinoma and CD3 antigen. *Mol Biother.* 1992 Mar; 4(1):15-23. 710: Pack P, Pluckthun A. Miniantibodies: use of amphipathic helices to produce functional, flexibly linked dimeric FV fragments with high avidity in *Escherichia coli*. *Biochemistry.* 1992 Feb 18; 31(6):1579-84. 711: Snider DP. Immunization with antigen bound to bispecific antibody induces antibody that is restricted in epitope specificity and contains antiidiotypic. *J Immunol.* 1992 Feb 15; 148(4):1163-70. 712: Smith W, Jarrett AL, Beattie RE, Corvalan JR. Immunoglobulins secreted by a hybrid-hybridoma: analysis of chain assemblies. *Hybridoma.* 1992 Feb; 11(1):87-98. 713: Bos R, Nieuwenhuizen W. Enhanced transfection of a bacterial plasmid into hybridoma cells by electroporation: application for the selection of hybrid hybridoma (quadroma) cell lines. *Hybridoma.* 1992 Feb; 11(1):41-51. 714: Koolwijk P, Van de Winkel JG, Otten I, Bast BJ. Related Articles Human monocyte-mediated cytotoxicity towards erythrocytes induced by hybrid mouse monoclonal antibodies: effect of antibody binding valency on IgG-Fc gamma R interaction. *Immunology.* 1992 Feb; 75(2):336-42. 715: Kaneko T, Oshimi K, Seto T, Okumura K, Mizoguchi H. Related Articles A bispecific antibody detects cytotoxic T lymphocytes of unknown antigen specificity in patients with granular lymphocyte-proliferative disorders. *Br J Haematol.* 1992 Feb; 80(2):151-6. 716: Nolan O, O'Kennedy R. Bifunctional antibodies and their potential clinical applications. *Int J Clin Lab Res.* 1992; 22(1):21-7. 717: Wunderlich JR, Mezzanzanica D, Garrido MA, Neblock DS, Daddona PE, Andrew SM, Zurawski VR, Canevari S, Colnaghi MI, Segal DM. Bispecific antibodies and retargeted cellular cytotoxicity: novel approaches to cancer therapy. *Int J Clin Lab Res.* 1992; 22(1):17-20. 718: Monod L, Sawamura Y, De Tribolet N. [Immunotherapy of tumors of the central nervous system]. *Neurochirurgie.* 1992; 38(2):69-79. 719: Pimm MV, Robins RA, Baldwin RW. Capture of recombinant ricin A chain by a bispecific anti-RTA:anti-CEA monoclonal antibody pre-targeted to a human gastric carcinoma xenograft in nude mice. *J Cancer Res Clin Oncol.* 1992; 118(5):367-70. 720: Chokri M, Girard A, Borrelly MC, Oleron C, Romet-Lemonne JL, Bartholeyns J. Adoptive immunotherapy with bispecific antibodies: targeting through macrophages. *Res Immunol.* 1992 Jan; 143(1):95-9. 721: Le Naour R, Raoul H,

Mabondzo A, Ripoll L, Bartholeyns J, Romet-Lemonne JL, Dormont D. Functional consequences of monocyte/macrophage infection by HIV1. *Res Immunol*. 1992 Jan; 143(1):49-56. 722: Greenman J, Hogg N, Nikolett S, Slade C, Stevenson G, Glennie M. Comparative efficiencies of bispecific F(ab'gamma)2 and chimeric mouse/human IgG antibodies in recruiting cellular effectors for cytotoxicity via Fc gamma receptors. *Cancer Immunol Immunother*. 1992; 34(6):361-9. 723: Gorter A, Kruse KM, Schrier PI, Fleuren GJ, van de Griend RJ. Enhancement of the lytic activity of cloned human CD8 tumour-infiltrating lymphocytes by bispecific monoclonal antibodies. *Clin Exp Immunol*. 1992 Jan; 87(1):111-6. 724: Fanger MW, Morganelli PM, Guyre PM. Bispecific antibodies. *Crit Rev Immunol*. 1992; 12(3-4):101-24. 725: Bolhuis RL, Lamers CH, Goey SH, Eggermont AM, Trimbos JB, Stoter G, Lanzavecchia A, di Re E, Miotti S, Raspagliesi F, et al. Adoptive immunotherapy of ovarian carcinoma with bs-MAb-targeted lymphocytes: a multicenter study. *Int J Cancer Suppl*. 1992; 7:78-81. 726: Bonardi MA, Bell A, RR, Gromo G, Hamblin T, Modena D, Tutt AL, Glennie MJ. Initial experience in treating human lymphoma with a combination of bispecific antibody and saporin. *Int J Cancer Suppl*. 1992; 7:73-7. 727: Demanet C, Brissinck J, Moser M, Leo O, Thielemans K. Related Articles Bispecific antibody therapy of two murine B-cell lymphomas. *Int J Cancer Suppl*. 1992; 7:67-8. 728: Weiner GJ. Bispecific IgG and IL-2 therapy of a syngeneic B-cell lymphoma in immunocompetent mice. *Int J Cancer Suppl*. 1992; 7:63-6. 729: Le Doussal JM, Barbet J, Delaage M. Bispecific-antibody-mediated targeting of radiolabeled bivalent haptens: theoretical, experimental and clinical results. *Int J Cancer Suppl*. 1992; 7:58-62. 730: Traunecker A, Lanzavecchia A, Karjalainen K. Janusin: new molecular design for bispecific reagents. *Int J Cancer Suppl*. 1992; 7:51-2. 731: Rodrigues ML, Shalaby MR, Werther W, Presta L, Carter P., Protein Engineering a humanized bispecific F(ab')2 fragment for improved binding to T cells. *Int J Cancer Suppl*. 1992; 7:45-50. 732: Segal DM, Qian JH, Titus JA, Moreno MB, George AJ, Jost CR, Kurucz I, el-Gamil M, Wunderlich JR. Targeted cytokine production. *Int J Cancer Suppl*. 1992; 7:36-8. 733: Ferrini S, Cambiaggi A, Cantoni C, Canevari S, Mezzanzanica D, Colnaghi MI, Moretta L. Targeting of T or NK lymphocytes against tumor cells by bispecific monoclonal antibodies: role of different triggering molecules. *Int J Cancer Suppl*. 1992; 7:15-8. 734: Bos R, Nieuwenhuizen W. The potential improvement of thrombolytic therapy by targeting with bispecific monoclonal antibodies: why they are used and how they are made. *Biotherapy*. 1992; 5(3):187-99. 735: Ball ED, Guyre PM, Mills L, Fisher J, Dinces NB, Fanger MW. Initial trial of bispecific antibody-mediated immunotherapy of CD15-bearing tumors: cytotoxicity of human tumor cells using a bispecific antibody comprised of anti-CD15 (MoAb PM81) and anti-CD64/Fc gamma RI (MoAb 32). *J Hematother*. 1992 Spring; 1(1):85-94. 736: [No authors listed] Bispecific antibodies and targeted cellular cytotoxicity. Ostuni, Italy, June 13-17, 1992. *Int J Cancer Suppl*. 1992; 7:1-81. available. 737: Shalaby MR, Shepard HM, Presta L, Rodrigues ML, Beverley PC, Feldmann M, Carter P., Protein Development of humanized bispecific antibodies reactive with cytotoxic lymphocytes and tumor cells overexpressing the HER2 protooncogene. *J Exp Med*. 1992 Jan 1; 175(1):217-25. 738: Nishimura T, Nakamura Y, Takeuchi Y, Tokuda Y, Iwasawa M, Kawasaki A, Okumura K, Habu S. Generation propagation, and targeting of human CD4 + helper/killer T cells induced by anti-CD3 monoclonal antibody plus recombinant IL-2. An efficient strategy for adoptive tumor immunotherapy. *J Immunol*. 1992 Jan 1; 148(1):285-91. 739: Fanger MW, Erbe DV. Fc gamma receptors in cancer and infectious disease. *Immunol Res*. 1992; 11(3-4):203-16. 740: Efferth T, Volm M. Antibody-directed therapy of multidrug-resistant tumor cells. *Med Oncol Tumor Pharmacother*. 1992; 9(1):11-9. 741: Segal DM, Qian JH, Andrew SM, Titus JA, Mezzanzanica D, Garrido MA, Wunderlich JR. Cytokine release by peripheral blood lymphocytes targeted with bispecific antibodies, and its role in blocking tumor growth. *Ann N Y Acad Sci*. 1991 Dec 30; 636:288-94. available. 742: Kontsekova E, Novak M, Macikova I, Kontsek P. One-step method for establishing 8-azaguanine-resistant hybridomas suitable for the preparation of triomas. *J Immunol Methods*. 1991 Dec 15; 145(1-2):247-50. 743: Kurokawa T, Iwasa S, Kakinuma A, Stassen JM, Lijnen HR, Collen D. Enhancement of clot lysis in vitro and in vivo with a bispecific monoclonal antibody directed against human fibrin and against urokinase-type plasminogen activator. *Thromb Haemost*. 1991 Dec 2; 66(6):684-93. 744: Brissinck J, Demanet C, Moser M, Leo O, Thielemans K. Related Articles Treatment of mice bearing BCL1 lymphoma with bispecific antibodies. *J Immunol*. 1991 Dec 1; 147(11):4019-26. 745: Bugos RC, Chiang VL, Campbell WH., Protein, Nucleotide cDNA cloning, sequence analysis and seasonal expression of lignin-bispecific caffeic acid/5-hydroxyferulic acid O-methyltransferase of aspen. *Plant Mol Biol*. 1991 Dec; 17(6):1203-15. 746: Weiner GJ, Hillstrom JR., Nucleotide Bispecific anti-idiotypic/anti-CD3 antibody therapy of murine B cell lymphoma. *J Immunol*. 1991 Dec 1; 147(11):4035-44. 747: Traunecker A, Lanzavecchia A, Karjalainen K. Bispecific single chain molecules (Janusins) target cytotoxic lymphocytes on HIV infected cells. *EMBO J*. 1991 Dec; 10(12):3655-9. 748: Bolhuis RL, Sturm E, Gratama JW, Braakman E. Engineering T lymphocyte antigen specificity. *J Cell Biochem*. 1991 Dec; 47(4):306-10. 749: Azuma A. [The enhancement of cytolytic activity in lymphokine activated killer cells using bispecific F(ab')2]. *Nippon Ika Daigaku Zasshi*. 1991 Dec; 58(6):663-72. . 750: [No authors listed] Fc receptors for IgG (Fc gamma Rs) on human monocytes and macrophages are not infectivity receptors for human immunodeficiency virus type 1 (HIV-1): studies using bispecific antibodies to target HIV-1 to various myeloid cell surface molecules, including the Fc gamma R. *Dis Markers*. 1991 Nov-Dec; 9(6):350-1. available. 751: Nishimura T, Nakamura Y, Takeuchi Y, Gao XH, Tokuda Y, Okumura K, Habu S. Bispecific antibody-directed antitumor activity of human CD4 + helper/killer T cells induced by anti-CD3 monoclonal antibody plus interleukin 2. *Jpn J Cancer Res*. 1991 Nov; 82(11):1207-10. 752: Greenman J, Tutt AL, George AJ, Pulford KA, Stevenson GT, Glennie MJ. Characterization of a new monoclonal anti-Fc gamma RI antibody, AT10, and its incorporation into a bispecific F(ab')2 derivative for recruitment of cytotoxic effectors. *Mol Immunol*. 1991 Nov; 28(11):1243-54. 753: Connor RI, Dinces NB, Howell AL, Romet-Lemonne JL, Pasquali JL, Fanger MW. Fc receptors for IgG (Fc gamma Rs) on human monocytes and macrophages are not infectivity receptors for human immunodeficiency virus type 1 (HIV-1): studies using bispecific antibodies to target HIV-1 to various myeloid cell surface molecules, including the Fc gamma R. *Proc Natl Acad Sci U S A*. 1991 Nov 1; 88(21):9593-7. 754: Massino IS, Kizim EA, Dmitriev AD. [A new approach to the design of hybrid hybridomas based on the use of an actinomycin D-resistant line of

murine myeloma]. *Biull Eksp Biol Med*. 1991 Nov; 112(11):511-4. Russian. 755: Mady BJ, Erbe DV, Kurane I, Fanger MW, Ennis FA. Related Articles Antibody-dependent enhancement of dengue virus infection mediated by bispecific antibodies against cell surface molecules other than Fc gamma receptors. *J Immunol*. 1991 Nov 1; 147(9):3139-44. 756: Fanger MW, Guyre PM. Bispecific antibodies for targeted cellular cytotoxicity. *Trends Biotechnol*. 1991 Nov; 9(11):375-80 757: Mezzanzanica D, Garrido MA, Neblock DS, Daddona PE, Andrew SM, Zurawski VR, Segal DM, Wunderlich JR. Human T-lymphocytes targeted against an established human ovarian carcinoma with a bispecific F(ab')₂ antibody prolong host survival in a murine xenograft model. *Cancer Res*. 1991 Oct 15; 51(20):5716-21. 758: Lustgarten J, Waks T, Eshhar Z. CD4 and CD8 accessory molecules function through interactions with major histocompatibility complex molecules which are not directly associated with the T cell receptor-antigen complex. *Eur J Immunol*. 1991 Oct; 21(10):2507-15. 759: Lloyd F, Goldrosen M. The production of a bispecific anti-CEA, anti-hapten (4-amino-phthalate) hybrid-hybridoma. *J Natl Med Assoc*. 1991 Oct; 83(10):901-4. 760: Bookman MA. Biologic therapy and immunotherapy for ovarian cancer. *Curr Opin Oncol*. 1991 Oct; 3(5):901-7 761: Jung G, Freimann U, Von Marschall Z, Reisfeld RA, Wilmanns W. Target cell-induced T cell activation with bi- and trispecific antibody fragments. *Eur J Immunol*. 1991 Oct; 21(10):2431-5. 762: Miyazaki J, Juricek M, Angelis K, Schnorr KM, Kleinhofs A, Warner RL. Protein, Nucleotide Characterization and sequence of a novel nitrate reductase from barley. *Mol Gen Genet*. 1991 Sep; 228(3):329-34. 763: Azuma A, Niitani H. [Bi-specific F(ab')₂ enhances cytolytic activities of LAK cells against human small cell lung cancer (SCLC)]. *Nihon Kyobu Shikkan Gakkai Zasshi*. 1991 Sep; 29(9):1132-7. 764: Shi T, Eaton AM, Ring DB. Selection of hybrid hybridomas by flow cytometry using a new combination of fluorescent vital stains. *J Immunol Methods*. 1991 Aug 9; 141(2):165-75. 765: Sivolapenko GB, Moreno C, Smith W, Corvalan J, Ritter MA, Epenetos AA. Xenogeneic monoclonal antibodies in the management of cancer: control of their in vivo immunogenicity and induction of specific unresponsiveness using an antibody-drug immunoconjugate. *Br J Cancer*. 1991 Aug; 64(2):281-7. 766: Azuma A, Niitani H, Okumura K. [Cancer therapy by using bispecific antibody]. *Gan To Kagaku Ryoho*. 1991 Aug; 18(10):1535-42. 767: Weil-Hillman G, Schell K, Segal DM, Hank JA, Sosman JA, Sondel PM. Activation of human T cells obtained pre- and post-interleukin-2 (IL-2) therapy by anti-CD3 monoclonal antibody plus IL-2: implications for combined in vivo treatment. *J Immunother*. 1991 Aug; 10(4):267-77. 768: Demanet C, Brissinck J, Van Mechelen M, Leo O, Thielemans K. Treatment of murine B cell lymphoma with bispecific monoclonal antibodies (anti-idiotypic x anti-CD3). *J Immunol*. 1991 Aug 1; 147(3):1091-7. 769: Flavell DJ, Cooper S, Morland B, Flavell SU. Characteristics and performance of a bispecific F(ab'gamma)₂ antibody for delivering saporin to a CD7 + human acute T-cell leukaemia cell line. *Br J Cancer*. 1991 Aug; 64(2):274-80. 770: Koolwijk P, Van de Winkel JG, Pfefferkorn LC, Jacobs CW, Otten I, Spierenburg GT, Bast BJ. Induction of intracellular Ca²⁺ mobilization and cytotoxicity by hybrid mouse monoclonal antibodies. Fc gamma RI regulation of Fc gamma RI-triggered functions or signaling? *J Immunol*. 1991 Jul 15; 147(2):595-602. 771: van Dijk J, Zegveld ST, Fleuren GJ, Warnaar SO. Related Articles Localization of monoclonal antibody G250 and bispecific monoclonal antibody CD3/G250 in human renal-cell carcinoma xenografts: relative effects of size and affinity. *Int J Cancer*. 1991 Jul 9; 48(5):738-43. 772: Snider DP, Uppenkamp IK, Titus JA, Segal DM. Processing fate of protein antigen attached to IgD or MHC molecules on normal B lymphocytes using heterocrosslinked bispecific antibodies. *Mol Immunol*. 1991 Jul; 28(7):779-88. 773: Flavell SU, Flavell DJ. The anti-mitozantrone monoclonal antibody NO-1, protects acute leukaemia cell lines from the cytotoxic effects of mitozantrone. *Br J Haematol*. 1991 Jul; 78(3):330-3. 774: Tutt A, Stevenson GT, Glennie MJ. Trispecific F(ab')₃ derivatives that use cooperative signaling via the TCR/CD3 complex and CD2 to activate and redirect resting cytotoxic T cells. *J Immunol*. 1991 Jul 1; 147(1):60-9. 775: Berg J, Lotscher E, Steimer KS, Capon DJ, Baenziger J, Jack HM, Wabl M. Bispecific antibodies that mediate killing of cells infected with human immunodeficiency virus of any strain. *Proc Natl Acad Sci U S A*. 1991 Jun 1; 88(11):4723-7. 776: Koolwijk P, Boot JH, Griep R, Bast BJ. Binding of the human complement subcomponent C1q to hybrid mouse monoclonal antibodies. *Mol Immunol*. 1991 Jun; 28(6):567-76. 777: Tutt A, Greenman J, Stevenson GT, Glennie MJ. Bispecific F(ab'gamma)₃ antibody derivatives for redirecting unprimed cytotoxic T cells. *Eur J Immunol*. 1991 Jun; 21(6):1351-8. 778: Sinoquet H, Bonhomme R. A theoretical analysis of radiation interception in a two-species plant canopy. *Math Biosci*. 1991 Jun; 105(1):23-45. 779: Ferrini S, Prigione I, Miotti S, Ciccone E, Cantoni C, Chen Q, Colnaghi MI, Moretta L. Bispecific monoclonal antibodies directed to CD16 and to a tumor-associated antigen induce target-cell lysis by resting NK cells and by a subset of NK clones. *Int J Cancer*. 1991 May 10; 48(2):227-33. 780: Bosslet K, Steinstraesser A, Hermentin P, Kuhlmann L, Bruynck A, Magerstaedt M, Seemann G, Schwarz A, Sedlacek HH. Related Articles Generation of bispecific monoclonal antibodies for two phase radioimmunotherapy. *Br J Cancer*. 1991 May; 63(5):681-6. 781: Embleton MJ, Charleston A, Robins RA, Pimm MV, Baldwin RW. Recombinant ricin toxin A chain cytotoxicity against carcinoembryonic antigen expressing tumour cells mediated by a bispecific monoclonal antibody and its potentiation by ricin toxin B chain. *Br J Cancer*. 1991 May; 63(5):670-4. 782: RR, Courtenay AE, Ingamells S, Stevenson GT, Glennie MJ. Cooperative mixtures of bispecific F(ab')₂ antibodies for delivering saporin to lymphoma in vitro and in vivo. *Cancer Res*. 1991 May 1; 51(9):2353-61. 783: Qian JH, Titus JA, Andrew SM, Mezzanzanica D, Garrido MA, Wunderlich JR, Segal DM. Human peripheral blood lymphocytes targeted with bispecific antibodies release cytokines that are essential for inhibiting tumor growth. *J Immunol*. 1991 May 1; 146(9):3250-6. 784: Erbe DV, Pfefferkorn ER, Fanger MW. Functions of the various IgG Fc receptors in mediating killing of *Toxoplasma gondii*. *J Immunol*. 1991 May 1; 146(9):3145-51. 785: Friemann A, Brinkmann K, Hachtel W. Protein, Nucleotide Sequence of a cDNA encoding the bi-specific NAD(P)H-nitrate reductase from the tree *Betula pendula* and identification of conserved protein regions. *Mol Gen Genet*. 1991 May; 227(1):97-105. 786: Taylor RP, Sutherland WM, Reist CJ, Webb DJ, Wright EL, Labuguen RH. Use of heteropolymeric monoclonal antibodies to attach antigens to the C3b receptor of human erythrocytes: a potential therapeutic treatment. *Proc Natl Acad Sci U S A*. 1991 Apr 15; 88(8):3305-9. 787: Nitta T, Nakata M, Yagita H, Okumura K. Interleukin-2 activated T

cells (T-LAK) express CD16 antigen and are triggered to target cell lysis by bispecific antibody. *Immunol Lett.* 1991 Apr; 28(1):31-7. 788: Ribeiro-da-Silva A, Pioro EP, Cuello AC. Substance P- and enkephalin-like immunoreactivities are colocalized in certain neurons of the substantia gelatinosa of the rat spinal cord: an ultrastructural double-labeling study. *J Neurosci.* 1991 Apr; 11(4):1068-80. 789: Oshimi K, Seto T, Oshimi Y, Masuda M, Okumura K, Mizoguchi H. Increased lysis of patient CD10-positive leukemic cells by T cells coated with anti-CD3 Fab' antibody cross-linked to anti-CD10 Fab' antibody. *Blood.* 1991 Mar 1; 77(5):1044-9. 790: De Lau WB, Heije K, Neefjes JJ, Oosterwegel M, Rozemuller E, Bast BJ. Absence of preferential homologous H/L chain association in hybrid hybridomas. *J Immunol.* 1991 Feb 1; 146(3):906-14. 791: Wong JT, Colvin RB. Selective reduction and proliferation of the CD4 + and CD8 + T cell subsets with bispecific monoclonal antibodies: evidence for inter-T cell-mediated cytotoxicity. *Clin Immunol Immunopathol.* 1991 Feb; 58(2):236-50. 792: Fanger MW, Segal DM, Romet-Lemonne JL. Bispecific antibodies and targeted cellular cytotoxicity. *Immunol Today.* 1991 Feb; 12(2):51-4. 793: Menard S, Canevari S, Colnaghi MI. Monoclonal antibodies as carriers for delivering cytotoxic agents. *Ann Ist Super Sanita.* 1991; 27(1):87-9. 794: Melioli G, Prigione I, Merli A, Cantoni C, Chen Q, Machi AM, Ferrini S. Induction of functional activities of human lymphocytes by monoclonal antibodies. *Ann Ist Super Sanita.* 1991; 27(1):79-85. 795: Demonte LB, Dellabona P, Nistico P, Tecce R, Camagna M, Reyna A, Momo M, Natali PG, Mariani M, Malavasi F. Retrovirus-derived shuttle vectors in the generation of murine bispecific MoAbs to be used in ex vivo and in vivo immunotherapy. *Ann Ist Super Sanita.* 1991; 27(1):133-7. 796: Mezzanzanica D, Canevari S, Colnaghi MI. Retargeting of human lymphocytes against human ovarian carcinoma cells by bispecific antibodies: from laboratory to clinic. *Int J Clin Lab Res.* 1991; 21(2):159-64. 797: Takahashi M, Fuller SA, Winston S. Design and production of bispecific monoclonal antibodies by hybrid hybridomas for use in immunoassay. *Methods Enzymol.* 1991; 203:312-27. available. 798: Bolhuis RL, Sturm E, Braakman E. T cell targeting in cancer therapy. *Cancer Immunol Immunother.* 1991; 34(1):1-8. 799: Mayer R, Stone K, Han A, Bona C. Malignant CD5 B cells--biased immunoglobulin variable gene usage and autoantibody production. *Int Rev Immunol.* 1991; 7(3):189-203. 800: Moller SA, Reisfeld RA. Bispecific-monoclonal-antibody-directed lysis of ovarian carcinoma cells by activated human T lymphocytes. *Cancer Immunol Immunother.* 1991; 33(4):210-6. 801: Cheong HS, Chang JS, Park JM, Byun SM. Affinity enhancement of bispecific antibody against two different epitopes in the same antigen. *Biochem Biophys Res Commun.* 1990 Dec 31; 173(3):795-800. 802: Bosslet K, Keweloh HC, Hermentin P, Muhrer KH, Sedlacek HH, Schulz G. Percolation and binding of MAB BW 494 to pancreatic carcinoma tissues during high dose immunotherapy and consequences for future therapy modalities. *Behring Inst Mitt.* 1990 Dec; (87):68-75. 803: de Palazzo IG, Gercel-Taylor C, Kitson J, Weiner LM. Related Articles Potentiation of tumor lysis by a bispecific antibody that binds to CA19-9 antigen and the Fc gamma receptor expressed by human large granular lymphocytes. *Cancer Res.* 1990 Nov 15; 50(22):7123-8. 804: Nitta T, Ishizawa A, Ito M, Sato K, Yagita H, Kumura K. [Induction of cytotoxicity from human lymphocytes coated with bispecific antibody against human glioma cells]. *No Shinkei Geka.* 1990 Nov; 18(11):1001-6. 805: Sahin U, Hartmann F, Senter P, Pohl C, Engert A, Diehl V, Pfreundschuh M. Specific activation of the prodrug mitomycin phosphate by a bispecific anti-CD30/anti-alkaline phosphatase monoclonal antibody. *Cancer Res.* 1990 Nov 1; 50(21):6944-8. 806: Branscomb EE, Runge MS, Savard CE, Adams KM, Matsueda GR, Haber E. Bispecific monoclonal antibodies produced by somatic cell fusion increase the potency of tissue plasminogen activator. *Thromb Haemost.* 1990 Oct 22; 64(2):260-6. 807: Wong JT, Eylath AA, Ghobrial I, Colvin RB. The mechanism of anti-CD3 monoclonal antibodies. Mediation of cytotoxicity by inter-T cell bridging. *Transplantation.* 1990 Oct; 50(4):683-9. 808: Hedlund G, Dohlsten M, Lando PA, Kalland T. Staphylococcal enterotoxins direct and trigger CTL killing of autologous HLA-DR+ mononuclear leukocytes and freshly prepared leukemia cells. *Cell Immunol.* 1990 Sep; 129(2):426-34. 809: Bosslet K, Hermentin P, Kuhlmann L, Steinstraesser A, Seemann G, Sedlacek HH. Two-phase radioimmunotherapy using bispecific monoclonal antibodies (bs MAbs). *Cancer Treat Rev.* 1990 Sep; 17(2-3):355-6. available. 810: Connor RI, Shen L, Fanger MW. Evaluation of the antibody-dependent cytotoxic capabilities of individual human monocytes. Role of Fc gamma RI and Fc gamma RII and the effects of cytokines at the single cell level. *J Immunol.* 1990 Sep 1; 145(5):1483-9. 811: Robins RA, Embleton MJ, Pimm MV, Betts DS, Charleston A, Markham AJ, Baldwin RW. Bispecific antibody that binds carcinoembryonic antigen and ricin toxin A chain cytotoxic for gastrointestinal tract tumor cells. *J Natl Cancer Inst.* 1990 Aug 1; 82(15):1295-6. available. 812: Fanger MW, Segal DM, Wunderlich JR. Going both ways: bispecific antibodies and targeted cellular cytotoxicity. *FASEB J.* 1990 Aug; 4(11):2846-9. available. 813: Nolan O, O'Kennedy R. Bifunctional antibodies: concept, production and applications. *Biochim Biophys Acta.* 1990 Aug 1; 1040(1):1-11. 814: Garrido MA, Valdayo MJ, Winkler DF, Titus JA, Hecht TT, Perez P, Segal DM, Wunderlich JR. Targeting human T-lymphocytes with bispecific antibodies to react against human ovarian carcinoma cells growing in nu/nu mice. *Cancer Res.* 1990 Jul 15; 50(14):4227-32. 815: Charpie JR, Runge MS, Matsueda GR, Haber E. A bispecific antibody enhances the fibrinolytic potency of single-chain urokinase. *Biochemistry.* 1990 Jul 10; 29(27):6374-8. 816: Bosslet K, Keweloh HC, Hermentin P, Muhrer KH, Sedlacek HH, Schulz G. Percolation and binding of monoclonal antibody BW494 to pancreatic carcinoma tissues during high dose immunotherapy and consequences for future therapy modalities. *Br J Cancer Suppl.* 1990 Jul; 10:37-9. 817: Runge MS, Bode C, Savard CE, Matsueda GR, Haber E. Related Articles Antibody-directed fibrinolysis: a bispecific (Fab')₂ that binds to fibrin and tissue plasminogen activator. *Bioconj Chem.* 1990 Jul-Aug; 1(4):274-7. 818: Lansdorp PM, Thomas TE. Purification and analysis of bispecific tetrameric antibody complexes. *Mol Immunol.* 1990 Jul; 27(7):659-66. 819: Honda S, Ichimori Y, Iwasa S. A human hybridoma producing a bispecific monoclonal antibody that can target tumor cells for attack by *Pseudomonas aeruginosa* exotoxin A. *Cytotechnology.* 1990 Jul; 4(1):59-68. 820: Snider DP, Kaubisch A, Segal DM. Enhanced antigen immunogenicity induced by bispecific antibodies. *J Exp Med.* 1990 Jun 1; 171(6):1957-63. 821: Le Doussal JM, Gruaz-Guyon A, Martin M, Gautherot E, Delaage M, Barbet J. Targeting of indium 111-labeled bivalent hapten to human melanoma mediated by bispecific monoclonal antibody conjugates: imaging of tumors hosted in nude mice. *Cancer Res.* 1990 Jun 1;

50(11):3445-52. 822: Roosnek E, Tunnacliffe A, Lanzavecchia A. T cell activation by a bispecific anti-CD3/anti-major histocompatibility complex class I antibody. *Eur J Immunol.* 1990 Jun; 20(6):1393-6. 823: James K. Human monoclonal antibodies and engineered antibodies in the management of cancer. *Semin Cancer Biol.* 1990 Jun; 1(3):243-53. 824: Karawajew L, Rudchenko S, Wlasik T, Trakht I, Rakitskaya V. Flow sorting of hybrid hybridomas using the DNA stain Hoechst 33342. *J Immunol Methods.* 1990 May 25; 129(2):277-82. 825: John MA, Elms MJ, O'Reilly EJ, Rylatt DB, Bundesen PG, Hillyard CJ. The simplified D dimer test: a novel assay for the detection of crosslinked fibrin degradation products in whole blood. *Thromb Res.* 1990 May 1; 58(3):273-81. 826: Garrido MA, Perez P, Titus JA, Valdayo MJ, Winkler DF, Barbieri SA, Wunderlich JR, Segal DM. Targeted cytotoxic cells in human peripheral blood lymphocytes. *J Immunol.* 1990 Apr 15; 144(8):2891-8. 827: Pimm MV, Robins RA, Embleton MJ, Jacobs E, Markham AJ, Charleston A, Baldwin RW. A bispecific monoclonal antibody against methotrexate and a human tumour associated antigen augments cytotoxicity of methotrexate-carrier conjugate. *Br J Cancer.* 1990 Apr; 61(4):508-13. 828: DeMonte LB, Nistico P, Tecce R, Dellabona P, Momo M, Anichini A, Mariani M, Natali PG, Malavasi F. Gene transfer by retrovirus-derived shuttle vectors in the generation of murine bispecific monoclonal antibodies. *Proc Natl Acad Sci U S A.* 1990 Apr; 87(8):2941-5. 829: Songsivilai S, Lachmann PJ. Bispecific antibody: a tool for diagnosis and treatment of disease. *Clin Exp Immunol.* 1990 Mar; 79(3):315-21. 830: Nitta T, Sato K, Okumura K, Ishii S. Induction of cytotoxicity in human T cells coated with anti-glioma x anti-CD3 bispecific antibody against human glioma cells. *J Neurosurg.* 1990 Mar; 72(3):476-81. 831: Nitta T, Sato K, Yagita H, Okumura K, Ishii S. Preliminary trial of specific targeting therapy against malignant glioma. *Lancet.* 1990 Feb 17; 335(8686):368-71. 832: Peacock JS, Colsky AS, Pinto VB. Lectins and antibodies as tools for studying cellular interactions. *J Immunol Methods.* 1990 Feb 9; 126(2):147-57. 833: Sosman JA, Hank JA, Sondel PM. In vivo activation of lymphokine-activated killer activity with interleukin-2: prospects for combination therapies. *Semin Oncol.* 1990 Feb; 17(1 Suppl 1):22-30; discussion 38-41. 834: Gherardi E, Pannell R, Milstein C. A single-step procedure for cloning and selection of antibody-secreting hybridomas. *J Immunol Methods.* 1990 Jan 24; 126(1):61-8. 835: Rylatt DB, Kemp BE, Bundesen PG, John MA, O'Reilly EJ, Cottis LE, Miles SJ, Khan JM, Dinh DP, Stapleton D, et al. A rapid whole-blood immunoassay system. *Med J Aust.* 1990 Jan 15; 152(2):75-7. 836: De Monte L, Nistico P, Tecce R, Dellabona P, Momo M, Tarditi L, Natali PG, Mariani M, Malavasi F. Gene transfer by retrovirus-derived shuttle vectors in the generation of murine bispecific MAbs. *Dev Biol Stand.* 1990; 71:15-22. 837: Pimm MV, Gunn B, Lord JM, Baldwin RW. The influence of anti-(ricin toxin A chain) monoclonal antibodies on the pharmacokinetics of ricin toxin A chain and recombinant ricin A chain in mice. *Cancer Immunol Immunother.* 1990; 32(4):235-40. 838: Smith W, Gore VA, Brandon DR, Lynch DN, Cranstone SA, Corvalan JR. Suppression of well-established tumour xenografts by a hybrid-hybrid monoclonal antibody and vinblastine. *Cancer Immunol Immunother.* 1990; 31(3):157-63. 839: Lebegue V, Joron L, Barque JP, Pancino G, Roseto A. Related Articles [Production and characterization of hybrid monoclonal antibodies with IgG1/IgG3 double isotype]. *C R Acad Sci III.* 1990; 310(9):377-82. 840: Garrido MA, Valdayo MJ, Winkler DF, Titus JA, Hecht TT, Perez P, Segal DM, Wunderlich JR. Refocusing the immune system to react with human tumors by targeting human lymphocytes with bispecific antibodies. *Dev Biol Stand.* 1990; 71:33-42. 841: Kurokawa T, Iwasa S, Kakinuma A. Enhancement of fibrinolysis by bispecific monoclonal antibodies reactive to fibrin and plasminogen activators. *Thromb Res Suppl.* 1990; 10:83-9. 842: Stevenson GT. Attack on neoplastic cell membranes by therapeutic antibody. *Mol Cell Biochem.* 1989 Nov 23-Dec 19; 91(1-2):33-8. 843: Wong JT, Pinto CE, Gifford JD, Kurnick JT, Kradin RL. Related Articles Characterization of the CD4+ and CD8+ tumor infiltrating lymphocytes propagated with bispecific monoclonal antibodies. *J Immunol.* 1989 Nov 15; 143(10):3404-11. 844: Ho BC, Ewert A, Chew LM. Interspecific competition among *Aedes aegypti*, *Ae. albopictus*, and *Ae. triseriatus* (Diptera: Culicidae): larval development in mixed cultures. *J Med Entomol.* 1989 Nov; 26(6):615-23. 845: Majsky A. [Relation of the effect of human complement in the cytotoxic test to the origin of the HLA serum]. *Vnitr Lek.* 1989 Nov; 35(11):1102-5. Czech. 846: Songsivilai S, Clissold PM, Lachmann PJ. Protein, Nucleotide A novel strategy for producing chimeric bispecific antibodies by gene transfection. *Biochem Biophys Res Commun.* 1989 Oct 16; 164(1):271-6. 847: Van Dijk J, Tsuruo T, Segal DM, Bolhuis RL, Colognola R, van de Griend RJ, Fleuren GJ, Warnaar SO. Bispecific antibodies reactive with the multidrug-resistance-related glycoprotein and CD3 induce lysis of multidrug-resistant tumor cells. *Int J Cancer.* 1989 Oct 15; 44(4):738-43. 848: Gorog G, Gandolfi A, Paradisi G, Roller E, Klasen E, Dessi V, Strom R, Celada F. Use of bispecific hybrid antibodies for the development of a homogeneous enzyme immunoassay. *J Immunol Methods.* 1989 Sep 29; 123(1):131-40. 849: Koolwijk P, Spierenburg GT, Frasa H, Boot JH, van de Winkel JG, Bast BJ. Interaction between hybrid mouse monoclonal antibodies and the human high-affinity IgG FcR, huFc gamma RI, on U937. Involvement of only one of the mIgG heavy chains in receptor binding. *J Immunol.* 1989 Sep 1; 143(5):1656-62. 850: Ferrini S, Prigione I, Mammoliti S, Colnaghi MI, Menard S, Moretta A, Moretta L. Re-targeting of human lymphocytes expressing the T-cell receptor gamma/delta to ovarian carcinoma cells by the use of bispecific monoclonal antibodies. *Int J Cancer.* 1989 Aug 15; 44(2):245-50. 851: Nitta T, Yagita H, Azuma T, Sato K, Okumura K. Bispecific F(ab')2 monomer prepared with anti-CD3 and anti-tumor monoclonal antibodies is most potent in induction of cytotoxicity of human T cells. *Eur J Immunol.* 1989 Aug; 19(8):1437-41. 853: Bode C, Kubler W. [Antibody mediated thrombolysis. A new therapeutic principle]. *Klin Wochenschr.* 1989 Jul 3; 67(13):651-8. 854: Menard S, Canevari S, Colnaghi MI. Hybrid antibodies in cancer diagnosis and therapy. *Int J Biol Markers.* 1989 Jul-Sep; 4(3):131-4. 855: Roosnek E, Lanzavecchia A. Triggering T cells by otherwise inert hybrid anti-CD3/antitumor antibodies requires encounter with the specific target cell. *J Exp Med.* 1989 Jul 1; 170(1):297-302. 856: Snider DP, Segal DM. Efficiency of antigen presentation after antigen targeting to surface IgD, IgM, MHC, Fc gamma RII, and B220 molecules on murine splenic B cells. *J Immunol.* 1989 Jul 1; 143(1):59-65. 857: Gravelle M, Ochi A. The targeting of CD4+ T lymphocytes to a B cell lymphoma. A comparison of anti-CD3-anti-idiotypic antibody conjugates and antigen-anti-idiotypic antibody conjugates. *J Immunol.* 1989 Jun 1; 142(11):4079-84. 858: Tsukada Y, Ohkawa K, Hibi N, Tsuzuki K, Oguma K, Satoh H. The effect of bispecific

monoclonal antibody recognizing both hepatoma-specific membrane glycoprotein and anthracycline drugs on the metastatic growth of hepatoma AH66. *Cancer Biochem Biophys.* 1989 May; 10(3):247-56. 859: Ribeiro-da-Silva A, Tagari P, Cuello AC. Morphological characterization of substance P-like immunoreactive glomeruli in the superficial dorsal horn of the rat spinal cord and trigeminal subnucleus caudalis: a quantitative study. *J Comp Neurol.* 1989 Mar 22; 281(4):497-15. 860: Barr IG, Miescher S, von Flidner V, Buchegger F, Barras C, Lanzavecchia A, Mach JP, Carrel S. In vivo localization of a bispecific antibody which targets human T lymphocytes to lyse human colon cancer cells. *Int J Cancer.* 1989 Mar 15; 43(3):501-7. 861: Goedegebuure PS, Segal DM, Braakman E, Vreugdenhil RJ, Van Krimpen BA, Van de Griend RJ, Bolhuis RL. Induction of lysis by T cell receptor gamma delta + /CD3 + T lymphocytes via CD2 requires triggering via the T11.1 epitope only. *J Immunol.* 1989 Mar 15; 142(6):1797-802. 862: Stevenson GT, Pindar A, Slade CJ. A chimeric antibody with dual Fc regions (bisFabFc) prepared by manipulations at the IgG hinge. *Anticancer Drug Des.* 1989 Mar; 3(4):219-30. 863: van Dijk J, Warnaar SO, van Eendenburg JD, Thienpont M, Braakman E, Boot JH, Fleuren GJ, Bolhuis RL. Induction of tumor-cell lysis by bi-specific monoclonal antibodies recognizing renal-cell carcinoma and CD3 antigen. *Int J Cancer.* 1989 Feb 15; 43(2):344-9. 864: De Lau WB, Van Loon AE, Heije K, Valerio D, Bast BJ. Related Articles Production of hybrid hybridomas based on HAT(s)-neomycin(r) double mutants. *J Immunol Methods.* 1989 Feb 8; 117(1):1-8. 865: Tada H, Toyoda Y, Iwasa S. Bispecific antibody-producing hybrid hybridoma and its use in one-step immunoassays for human lymphotoxin. *Hybridoma.* 1989 Feb; 8(1):73-83. 866: Bode C, Runge MS, Branscomb EE, Newell JB, Matsueda GR, Haber E. Antibody-directed fibrinolysis. An antibody specific for both fibrin and tissue plasminogen activator. *J Biol Chem.* 1989 Jan 15; 264(2):944-8. 867: Ferrini S, Prigione I, Mammoliti S, Colnaghi MI, Menard S, Moretta A, Moretta L. Retargeting of T-cell-receptor gamma/delta + lymphocytes against tumor cells by bispecific monoclonal antibodies. Induction of cytolytic activity and lymphokine production. *Int J Cancer Suppl.* 1989; 4:53-5. 868: Glennie MJ, Brennan DM, Bryden F, McBride HM, Stirpe F, Worth AT, Stevenson GT. Bispecific F(ab' gamma)2 antibody for the delivery of saporin in the treatment of lymphoma. *J Immunol.* 1988 Nov 15; 141(10):3662-70. 869: Gilliland LK, Clark MR, Waldmann H. Universal bispecific antibody for targeting tumor cells for destruction by cytotoxic T cells. *Proc Natl Acad Sci U S A.* 1988 Oct; 85(20):7719-23. 870: Pupa SM, Canevari S, Fontanelli R, Menard S, Mezzanzanica D, Lanzavecchia A, Colnaghi MI. Activation of mononuclear cells to be used for hybrid monoclonal antibody-induced lysis of human ovarian carcinoma cells. *Int J Cancer.* 1988 Sep 15; 42(3):455-9. 871: Fay TN, Jacobs I, Teisner B, Poulsen O, Chapman MG, Stabile I, Bohn H, Westergaard JG, Grudzinski JG. Two fetal antigens (FA-1 and FA-2) and endometrial proteins (PP12 and PP14) isolated from amniotic fluid; preliminary observations in fetal and maternal tissues. *Eur J Obstet Gynecol Reprod Biol.* 1988 Sep; 29(1):73-85. 872: Chervonsky AV, Faerman AI, Evdonina LV, Jazova AK, Kazarov AR, Gushev AI. A simple metabolic system for selection of hybrid hybridomas (tetradomas) producing bispecific monoclonal antibodies. *Mol Immunol.* 1988 Sep; 25(9):913-5. 873: Takahashi M, Fuller SA. Production of murine hybrid-hybridomas secreting bispecific monoclonal antibodies for use in urease-based immunoassays. *Clin Chem.* 1988 Sep; 34(9):1693-6. 874: Karawajew L, Behrsing O, Kaiser G, Micheel B. Production and ELISA application of bispecific monoclonal antibodies against fluorescein isothiocyanate (FITC) and horseradish peroxidase (HRP). *J Immunol Methods.* 1988 Jun 28; 111(1):95-9. 875: Mezzanzanica D, Canevari S, Menard S, Pupa SM, Tagliabue E, Lanzavecchia A, Colnaghi MI. Human ovarian carcinoma lysis by cytotoxic T cells targeted by bispecific monoclonal antibodies: analysis of the antibody components. *Int J Cancer.* 1988 Apr 15; 41(4):609-15. 876: Shinmoto H, Murakami H. [Bispecific antibodies]. *Tanpakushitsu Kakusan Koso.* 1988 Mar; 33(3):217-25. No abstract available. 877: Alkan SS, Towbin H, Hochkeppel HK. Enhanced antiproliferative action of interferon targeted by bispecific monoclonal antibodies. *J Interferon Res.* 1988 Feb; 8(1):25-33. 878: Urnovitz HB, Chang Y, Scott M, Fleischman J, Lynch RG. Related Articles IgA:IgM and IgA:IgA hybrid hybridomas secrete heteropolymeric immunoglobulins that are polyvalent and bispecific. *J Immunol.* 1988 Jan 15; 140(2):558-63. 879: Segal DM, Qian JH, Garrido MA, Perez P, Winkler DF, Wunderlich JR, Snider DP, Valdayo MJ, Titus JA. Targeting of cytotoxic cells against tumors with heterocrosslinked, bispecific antibodies. *Princess Takamatsu Symp.* 1988; 19:323-31. 880: Barr IG, Buchegger F, MacDonald HR, Carrel S, von Flidner V. Retargeting of cytolytic T lymphocytes by heteroaggregated (bispecific) antibodies. *Cancer Detect Prev.* 1988; 12(1-6):439-50. 881: Canevari S, Menard S, Mezzanzanica D, Miotti S, Pupa SM, Lanzavecchia A, Colnaghi MI. Anti-ovarian carcinoma anti-T3 heteroconjugates or hybrid antibodies induce tumor cell lysis by cytotoxic T-cells. *Int J Cancer Suppl.* 1988; 2:18-21. 882: Stevenson GT, Glennie MJ, Hamblin TJ, Lane AC, Stevenson FK. Problems and prospects in the use of lymphoma idiotypes as therapeutic targets. *Int J Cancer Suppl.* 1988; 3:9-12. 883: Yamashita T, Koyama J. Further evidence for heterogeneity of Fc gamma-receptors on guinea pig splenic B and T lymphocytes: analysis using monoclonal antibodies to two distinct types of Fc gamma-receptor. *Microbiol Immunol.* 1988; 32(2):199-210. 884: Clark MR, Waldmann H. T-cell killing of target cells induced by hybrid antibodies: comparison of two bispecific monoclonal antibodies. *J Natl Cancer Inst.* 1987 Dec; 79(6):1393-401. 885: Tiebout RF, van Bortel-Oosterhof F, Stricker EA, Zeijlemaker WP. A human hybrid hybridoma. *J Immunol.* 1987 Nov 15; 139(10):3402-5. 886: Ochi A, Worton KS, Woods G, Gravelle M, Kitagami K. Related Articles A novel strategy for immunotherapy using antibody-coupled carriers to focus cytotoxic T helper cells. *Eur J Immunol.* 1987 Nov; 17(11):1645-8. 887: Carman RJ, van Tassell RL, Wilkins TD. Production of iota toxin by *Clostridium spiroforme*: a requirement for divalent cations. *Vet Microbiol.* 1987 Oct; 15(1-2):115-20. 888: Glennie MJ, McBride HM, Worth AT, Stevenson GT. Related Articles Preparation and performance of bispecific F(ab' gamma)2 antibody containing thioether-linked Fab' gamma fragments. *J Immunol.* 1987 Oct 1; 139(7):2367-75. 889: Barr IG, MacDonald HR, Buchegger F, von Flidner V. Related Articles Lysis of tumor cells by the retargeting of murine cytolytic T lymphocytes with bispecific antibodies. *Int J Cancer.* 1987 Sep 15; 40(3):423-9. 890: Staerz UD, Yewdell JW, Bevan MJ. Hybrid antibody-mediated lysis of virus-infected cells. *Eur J Immunol.* 1987 Apr; 17(4):571-4. 891: Rammensee HG, Julius MH, Nemazee D, Langhorne J, Lamers R, Kohler G. Targeting cytotoxic T cells to antigen-specific B lymphocytes. *Eur J Immunol.* 1987 Mar; 17(3):433-6.

892: Karawajew L, Micheel B, Behrsing O, Gaestel M. Bispecific antibody-producing hybrid hybridomas selected by a fluorescence activated cell sorter. *J Immunol Methods*. 1987 Feb 11; 96(2):265-70. 893: Corvalan JR, Smith W, Gore VA, Brandon DR. Specific in vitro and in vivo drug localisation to tumour cells using a hybrid-hybrid monoclonal antibody recognising both carcinoembryonic antigen (CEA) and vinca alkaloids. *Cancer Immunol Immunother*. 1987; 24(2):133-7. 894: Corvalan JR, Smith W. Construction and characterisation of a hybrid-hybrid monoclonal antibody recognising both carcinoembryonic antigen (CEA) and vinca alkaloids. *Cancer Immunol Immunother*. 1987; 24(2):127-32. 895: Runge MS, Bode C, Matsueda GR, Haber E. Antibody-enhanced thrombolysis: capture of tissue plasminogen activator by a bispecific antibody and direct targeting by an antifibrin-tissue plasminogen activator conjugate in vivo. *Trans Assoc Am Physicians*. 1987; 100:250-5. available. 896: Karawajew L, Micheel B, Behrsing O, Gaestel M, Pasternak G. Use of fluorescence-activated cell sorting to select hybrid hybridomas producing bispecific monoclonal antibodies. *Hamatol Bluttransfus*. 1987; 31:367-8. available. 897: Leong MM, Milstein C, Pannell R. Luminescent detection method for immunodot, Western, and Southern blots. *J Histochem Cytochem*. 1986 Dec; 34(12):1645-50. 898: Suresh MR, Cuello AC, Milstein C. Advantages of bispecific hybridomas in one-step immunocytochemistry and immunoassays. *Proc Natl Acad Sci U S A*. 1986 Oct; 83(20):7989-93. 899: Lansdorp PM, Aalberse RC, Bos R, Schutter WG, Van Bruggen EF. Cyclic tetramolecular complexes of monoclonal antibodies: a new type of cross-linking reagent. *Eur J Immunol*. 1986 Jun; 16(6):679-83. 900: Staerz UD, Bevan MJ. Hybrid hybridoma producing a bispecific monoclonal antibody that can focus effector T-cell activity. *Proc Natl Acad Sci U S A*. 1986 Mar; 83(5):1453-7. 901: Newhall WJ, Terho P, Wilde CE, Batteiger BE, Jones RB. Related Articles Serovar determination of *Chlamydia trachomatis* isolates by using type-specific monoclonal antibodies. *J Clin Microbiol*. 1986 Feb; 23(2):333-8. 902: Suresh MR, Cuello AC, Milstein C. Bispecific monoclonal antibodies from hybrid hybridomas. *Methods Enzymol*. 1986; 121:210-28. available. 903: Paulus H. Preparation and biomedical applications of bispecific antibodies. *Behring Inst Mitt*. 1985 Dec; (78):118-32. 904: Brennan M, Davison PF, Paulus H. Preparation of bispecific antibodies by chemical recombination of monoclonal immunoglobulin G1 fragments. *Science*. 1985 Jul 5; 229(4708):81-3.

With respect to pertinent diseased cells, disease causing cells and other suitable targets for bispecific antibodies, as well as optional cytokines / toxins and methods of making and using immunotoxins and related technologies including combination therapies see references herein incorporated by reference.

With respect to anti-CCR5 antibodies used to kill CCR5-expressing cells, with for example, bi-specific antibody chemokine fusions see Bruhl H. et al. *J Immunol*. 2001 Feb 15 166(4): 2420-2426.

With respect to targeting IKAP proteins see for example US 6172195.

With respect to pertinent diseased cells, disease causing cells and other suitable targets for immunotoxins, as well as optional toxins and methods of making and using immunotoxins and related technologies see for example US05980895 Immunotoxin containing a disulfide-stabilized antibody fragment joined to a *Pseudomonas* exotoxin that does not require proteolytic activation; US05686072 Epitope-specific monoclonal antibodies and immunotoxins and uses thereof; US04956453 Antihuman ovarian cancer immunotoxins and methods of thereof; US06146631 Immunotoxins comprising ribosome-inactivating proteins; US05756699 Immunotoxins comprising ribosome-inactivating Proteins; US05744580 Immunotoxins comprising ribosome-inactivating Proteins; US06146850 Proteins encoding gelonin sequences; US05837491 Polynucleotides encoding gelonin sequences; US05578706 Methods and compositions concerning homogenous immunotoxin preparations; US05185434 Prolonged-action immunotoxins containing a glycopeptide constituent which inactivates ribosomes, modified on its polysaccharide units; US04958009 Anti-human ovarian cancer immunotoxins and methods of use thereof; US05980896 Antibodies reactive with human carcinomas; US06074644 Nucleic acids encoding immunotoxins containing a disulfide-stabilized antibody fragment replacing half or more of domain IB of *pseudomonas* exotoxin, and methods of use of the encoded immunotoxins; US05942230 Composition of immunotoxins and retinoids and use thereof; US05059413 Scintigraphic monitoring of immunotoxins using radionuclides and heterobifunctional chelators; US04919928 Conjugates in which a monovalent carboxylic ionophore is associated by means of a covalent bond with a macromolecule, their use as immunotoxin potentiators and the intermediate activated ionophores; US04911912 Ribosome-inactivating glycoproteins, modified by oxidation of their osidic units and reduction, and in vivo prolonged-action immunotoxins containing such a glycoprotein; US04911911 Ribosome-inactivating glycoproteins, modified by oxidation of their osidic units and formation of a schiff's base and in-vivo prolonged action immunotoxins containing such a glycoprotein; US05876438 Polymeric device for the delivery of immunotoxins for the prevention of secondary cataract; US05165923 Methods and compositions for the treatment of Hodgkin's disease; US04888415 2/19/1989 Gelonin immunotoxin; US04749566 Pharmaceutical composition comprising a combination of at least one immunotoxin and at least one mannose-containing polymer; US04714759 Immunotoxin therapy of allergy; WO00041474A2 ANTI-CD3 IMMUNOTOXINS AND THERAPEUTIC USES THEREFOR; US05869045 Antibody conjugates reactive with human carcinomas; US05562907 Method to prevent side-effects and insensitivity to the therapeutic uses of toxins; US04981953 Immunotoxins, process for their preparation and pharmaceutical compositions in which they are present; US04980457 Cytotoxic conjugates which can be used in therapy and process or their preparation; US04545985 *Pseudomonas* exotoxin conjugate immunotoxins; US06020145 Methods for determining the presence of carcinoma using the antigen binding region of monoclonal antibody BR96; US05792458 Mutant diphtheria toxin conjugates; US05106956 Ribosome-inactivating glycoproteins, modified by oxidation of their osidic units and reduction, and in vivo prolonged-action immunotoxins containing such a

glycoprotein; US05104976 Ribosome-inactivating glycoproteins, modified by oxidation of their osidic units and formation of a Schiff's base and in-vivo prolonged action immunotoxins containing such a Glycoprotein; US04894225 Combination therapy using antitumor immunotoxins with tumor necrosis factor; WO00061132A1 COMPOSITIONS CONTAINING IMMUNOTOXINS AND AGENTS THAT INHIBIT DENDRITIC CELL MATURATION FOR INDUCING IMMUNE TOLERANCE TO A GRAFT; US05338542 Disulfide linked immunotoxins with molecular groupings in the linker which cause steric hindrance to the disulfide linkage; US04894227 Composition of immunotoxins with interleukin-2 US04863726 Combination therapy using immunotoxins with interleukin-2; US04762707 New conjugates associating, by covalent bond, an enzyme with an antibody, and medicinal associations using the said conjugates; USRE036866 Anti-aids immunotoxins; US06099842 Recombinant immunotoxin composed of a single chain antibody reacting with the human transferrin receptor and diphtheria toxin US06071519 Immunotoxins specific for CD86 expressing cells; US06042829 Biotherapy of cancer by targeting TP-3/P80; US06004554 Methods for targeting the vasculature of solid tumors; WO09839363A2 IMMUNOTOXINS AND METHODS OF INDUCING IMMUNE TOLERANCE; US05792456 Mutant BR96 antibodies reactive with human carcinomas; US05728821 Mutant BR96 antibodies reactive with human carcinomas; US05728383 Treatment of tumors of the central nervous system with immunotoxins; US05208021 Method of preparing diphtheria immunotoxins; US05916772 Recombinant production of saporin-containing Proteins; WO09818820A1 METHODS AND COMPOSITIONS FOR RICIN FUSION PROTEIN IMMUNOTOXINS TO TREAT CANCER AND AUTOIMMUNE DISEASE; US05144009 Conjugates in which a monovalent carboxylic ionophore is associated by means of a covalent bond with a macromolecule, their use as immunotoxin potentiators and the intermediate activated ionophores; US04916213 Ribosomal inhibiting protein-immunoglobulin conjugates with specificity for tumor cell surface antigens, and mixtures thereof; US06015555 Transferrin receptor specific antibody-neuropharmaceutical or diagnostic agent conjugates; US05977307 Transferrin receptor specific ligand-neuropharmaceutical agent fusion proteins; US05821123 Modified antibody variable domains; US05770196 Modified antibody variable domains and therapeutic uses thereof; US05766886 Modified antibody variable domains; US05672683 Transferrin neuropharmaceutical agent fusion protein; US05112607 Potentiation of immunotoxin action by Brefeldin A; US04902495 IgE Fc directed delivery system; US04753894 Monoclonal anti-human breast cancer antibodies; US04485093 Immunotoxin conjugate which comprises arsanilic acid, useful for treating malignant tumors, particularly pancreatic Cancer; US06103235 Methods of inducing immune tolerance using immunotoxins; WO09964073A2 RECOMBINANT IMMUNOTOXIN DIRECTED AGAINST THE HIV-1 GP120 ENVELOPE GLYCOPROTEINS; WO09948914A1 METHODS FOR USING HEAT SHOCK PROTEINS; US05869619 Modified antibody variable domains; WO09904807A1 RECOMBINANT IMMUNOTOXIN CONTAINING A DIPHTHERIA TOXIN AND INTERLEUKIN -2(DT482-IL2) AND METHOD FOR PREPARING THE SAME; WO09858678A1 ANTI-CD40L IMMUNOTOXINS FOR THE TREATMENT OF DISEASES; US05645836 Anti-AIDS immunotoxins; US05439815 Restrictocin-like ribotoxin analogues comprising only one cysteine available for covalent linkage to a partner; US05149782 Molecular conjugates containing cell membrane-blending agents; WO09855150A1 TXU-7-PAP IMMUNOTOXIN AND USE THEREOF; WO09713529A1 IMMUNOTOXIN CONTAINING A DISULFIDE-STABIL ANTIBODY FRAGMENT; US06184043 Method for detection of specific target cells in specialized or mixed cell population and solutions containing mixed cell populations; US06147203 Recombinant disulfide-stabilized polypeptide fragments having binding specificity; WO040270A2 METHODS OF PROLONGING TRANSPLANT SURVIVAL USING IMMUNOTOXINS AND COSTIMULATION BLOCKADE OF CD154 AND D28; WO00040265A1 POTENTIATION OF ANTI-CD38-IMMUNOTOXIN CYTOTOXICITY; US06087109 Compositions that specifically bind to colorectal cancer cells and methods of using the same; US06060037 Compositions that specifically bind to colorectal cancer cells and methods of using the same; WO09953954A1 USE OF IMMUNOTOXINS TO INDUCE IMMUNE TOLERANCE TO PANCREATIC ISLET TRANSPLANTATION; US05928873 Methods of and kits and compositions for diagnosing colorectal tumors and metastasis thereof; US05879656 Methods of treating metastatic colorectal cancer with ST receptor binding compounds; US05863538 Compositions for targeting the vasculature of solid tumors; US05833988 Transferrin receptor specific antibody-neuropharmaceutical or diagnostic agent conjugates; US05759546 Treatment of CD4 T-cell mediated conditions; US05731159 Methods of and kits and compositions for diagnosing colorectal tumors and metastasis thereof; US05677171 Monoclonal antibodies directed to the HER2 receptor; US05601990 Methods of diagnosing colorectal tumors and metastasis thereof; US05518888 ST receptor binding compounds and methods of using the same; US05045451 Methods for screening antibodies for use as immunotoxins; US04865841 Methods and compositions for transient elimination of humoral immune antibodies; US04831122 Radioimmunotoxins; US04771128 Method of purifying toxin conjugates using hydrophobic interaction chromatography; US04582703 Cytotoxic medicament formed from the association of at least one immunotoxin and chloroquin; US05651986 Controlled local delivery of chemotherapeutic agents for treating solid tumors; US05644033 Monoclonal antibodies that define a unique antigen of human B cell antigen receptor complex and methods of using same for diagnosis and treatment; US05332567 Detection and treatment of infections with immunoconjugates; US04767621 Drugs comprising in association at least one immunotoxin and at least one monovalent carboxylic ionophore; US06093399 Methods and compositions for the specific coagulation of vasculature; US06036955 Kits and methods for the specific coagulation of vasculature; US06004555 Methods for the specific coagulation of vasculature; US05939531 Recombinant antibodies specific for a growth factor receptor; US5877289 Tissue factor compositions and ligands for specific coagulation of vasculature; WO09856823A1 INDUCTION OF IMMUNE TOLERANCE BY IMMUNOTOXIN; WO09850435A1 IMMUNOTOXINS, COMPRISING AN ONC PROTEIN, DIRECTED AGAINST MALIGNANT CELLS; US05830478 Method for delivering functional domains of diphtheria toxin to a cellular target; US05777078 Triggered pore-forming agents; WO09733611A1 METHOD OF KILLING TARGET CELLS IN HARVESTED CELL POPULATIONS WITH ONE OR MORE IMMUNOTOXINS; US05629197 Monoclonal anti-human breast cancer antibodies; *US05470831 1/28/1995 Angiogenic peptides; US05352447 Immunotoxins for treatment of

intracranial lesions and as adjunct to chemotherapy; JP02169523A2 IMMUNOTOXIN FOR TREATMENT OR PREVENTION OF AUTOIMMUNE DISEASE US04917888 Solubilization of immunotoxins for pharmaceutical compositions using polymer conjugation; US04904481 Method of conferring immuno-tolerance to a specific antigen; US06187536 Methods of identifying and detecting pancreatic cancer; US06165464 Monoclonal antibodies directed to the HER2 receptor; US06121424 Multivalent antigen-binding proteins; US06103889 Nucleic acid molecules encoding single-chain antigen-binding proteins; US06096862 Multimeric antiviral agent; EP01005372A1 ANTI-CD40L IMMUNOTOXINS FOR THE TREATMENT OF DISEASES; EP01000357A1 ANTIBODIES AND SCFV IMMUNOTOXINS SPECIFIC TO IMPORTED FIRE ANTS, AND THEIR APPLICATION; EP00996467A1 TXU-7-PAP IMMUNOTOXIN AND USE THEREOF; US06051230 Compositions for targeting the vasculature of solid tumors; US06033876 Anti-CD30 antibodies preventing proteolytic cleavage and release of membrane-bound CD30 antigen; US06027725 Multivalent antigen-binding proteins; US06025165 Methods for producing multivalent antigen-binding proteins; US05990296 Single chain B3 antibody fusion proteins and their uses; US05990275 Linker and linked fusion polypeptides; US05981726 Chimeric and mutationally stabilized tumor-specific B1, B3 and B5 antibody fragments; immunotoxic fusion proteins; and uses thereof; US05965132 Methods and compositions for targeting the vasculature of solid tumors; US05889157 Humanized B3 antibody fragments, fusion proteins, and uses thereof; WO09902991A1 ANTIBODIES AND SCFV IMMUNOTOXINS SPECIFIC TO IMPORTED FIRE ANTS, AND THEIR APPLICATION; US05855866 Methods for treating the vasculature of solid tumors; EP00717753B1 RIBOSOME INACTIVATING PROTEINS EXTRACTED FROM SEEDS OF SAPONARIA OCYMOIDES AND VACCARIA PYRAMIDATA, THEIR PREPARATION AND IMMUNOTOXINS CONTAINING THEM; US05824311 Treatment of tumors with monoclonal antibodies against oncogene antigens; EP00861091A1 IMMUNOTOXIN CONTAINING A DISULFIDE-STABILIZED ANTIBODY FRAGMENT; US05786457 Hormone-nuclease compounds and method for regulating hormone related diseases; US05776427 Methods for targeting the vasculature of solid tumors; US05772997 Monoclonal antibodies directed to the HER2 receptor; EP00831917A2 IMMUNOTOXINS SPECIFIC FOR CD80 AND CD86 EXPRESSING CELLS; EP00820470A1 NOVEL ANTI-AIDS IMMUNOTOXINS; US05707964 Method for treating cancer; US05705157 Methods of treating cancerous cells with anti-receptor antibodies; US05690935 Biotherapy of cancer by targeting TP-3/P80; US05665357 Antibodies recognizing tumor associated antigen CA 55.1; US05660827 Antibodies that bind to endoglin; US05631229 Method for inactivating gonadotrophs; US05608039 Single chain B3 antibody fusion proteins and their uses; US05576288 Fibroblast growth factor conjugates; US05571894 Recombinant antibodies specific for a growth factor receptor; US05529932 Isolated DNA encoding a plant ribosome inactivating protein from the leaves of saponaria officinalis; US05527527 Transferrin receptor specific antibody-neuropharmaceutical agent conjugates; US05506343 Antibodies specific for the DF3 carcinoma associated antigen; US05492893 Hormone-toxin conjugate compounds; US05491088 Monoclonal antibody BR 96 and chimeric monoclonal antibodies having the variable region of MAB BR96, which bind to a variant of ley antigen on human carcinoma cells; US05489525 Monoclonal antibodies to prostate cells; US05488036 Method for sterilizing animals using hormone-toxin conjugate compounds; JP07126187A2 CARCINOSTATIC AGENT; US05393737 Cytotoxic drug conjugates for treatment of neoplastic diseases; US05378688 GnRH analogs for destroying gonadotrophs; US05306626 Process for production of restrictocin; EP00583794A1 Recombinant pseudomonas exotoxin: construction of an active immunotoxin with low side effects; EP00577612A1 IMMUNOTOXIN FROM ANTI-CD5 MONOCLONAL ANTIBODIES; EP00561953A1 RECOMBINANT IMMUNOTOXIN COMPOSED OF A SINGLE CHAIN ANTIBODY REACTING WITH THE HUMAN TRANSFERRIN RECEPTOR AND DIPHTHERIA TOXIN; US05167956 Immunotoxin with in-vivo T cell suppressant activity; EP00365087B1 Immunotoxins for the treatment or prophylaxis of auto-immune diseases; EP00192002B1 Prolonged acting immunotoxins comprising a ribosome inactivating glycopeptide constituent having modified polysaccharide moieties; JP04069345A2 METHOD FOR REMOVING TUMOROUS CELL; EP00255424B1 Immunotoxins, process for preparing them and pharmaceutical compositions containing them; US05024834 Thioether linked immunotoxin conjugates; EP00214995B1 IMMUNOTOXIN AND METHOD OF MAKING; EP00234151B1 Glycoproteins modified by oxidation and formation of Schiff bases, inhibiting ribosomes, process for obtaining the same, and immunotoxins containing such glycoprotein; EP00229564B1 Glycoproteins modified by oxidation followed by reduction, which inhibit ribosomes, production process and immunotoxins containing such a glycoprotein; EP00327169A3 Immunotoxins from barley toxin; EP00365087A1 Immunotoxins for the treatment or prophylaxis of auto-immune diseases; US04913907 Porphycene anti-cancer agents and treatment methods; US04894226 Solubilization of proteins for pharmaceutical compositions using polyproline conjugation; EP00327169A2 Immunotoxins from barley toxin; US04806494 Monoclonal antibody against ovarian cancer cells (OVB-3); EP00255424A1 Immunotoxins, process for preparing them and pharmaceutical compositions containing them; US04698420 Antibody hybrid molecules and process for their preparation; EP00234151A1 Glycoproteins modified by oxidation and formation of Schiff bases, inhibiting ribosomes, process for obtaining the same, and immunotoxins containing such glycoprotein; EP00229564A1 Glycoprotein modified by oxidation and reduction, inhibiting the ribosomes, method for its production and immunotoxins containing said glycoprotein; US04681760 Method of conferring immunotolerance to a specific antigen; EP00214995A1 IMMUNOTOXIN AND METHOD OF MAKING; US04614650 Cytotoxic composition including at least an immunotoxin and an amine; EP00192002A1 Prolonged acting immunotoxins comprising a ribosome inactivating glycopeptide constituent having modified polysaccharide moieties; EP00086152B1 Medicines containing an association of at least one immunotoxin and at least one monovalent carboxylic ionophore; EP00086152A1 Medicines containing an association of at least one immunotoxin and at least one monovalent carboxylic ionophore; US06171588 Anti- $\alpha_v\beta_3$ integrin antibody antagonists; US06156564 Cellular apoptosis susceptibility protein (CSP) and antisense CSP; US06156321 Tissue factor methods and compositions for coagulation and tumor treatment; US06143869 CD30 ligand oligomers and polypeptides; US06132730 Combined tissue factor and factor VIIa methods and compositions for coagulation and tumor treatment; US06132729 Combined tissue factor and

chemotherapeutic methods and compositions for coagulation and tumor treatment; WO00058456A2 COMPOSITIONS AND METHODS FOR MODIFYING TOXIC EFFECTS OF PROTEINACIOUS COMPOUNDS; US06107461 Multimeric forms of human rhinovirus receptor and fragments thereof, and method of use; US06086900 Methods and compositions for using membrane-penetrating proteins to carry materials across cell membranes; US06072031 Cellular apoptosis susceptibility protein (CSP); EP00610286B1 RECOMBINANT IMMUNOTOXINS; US06017896 Purine nucleoside phosphorylase gene therapy for human malignancy; US05998587 Anti-cyanovirin antibody; US05985553 erbB-2 gene segments, probes, recombinant DNA and kits for detection; US05977322 High affinity human antibodies to tumor antigens; WO09948534A1 METHODS AND MEANS FOR THE TREATMENT OF IMMUNE RELATED DISEASES; US05928643 Method of using CD2-binding domain of lymphocyte function associated antigen 3 to initiate T cell activation; US05919764 Compounds that bind to p185 and methods of using the same; US05914111 CD2-binding domain of lymphocyte function associated antigen-3; US05911995 EGF-genistein conjugates for the treatment of cancer; US05910424 Metastatic melanoma cell lines from *Monodelphis domestica* for use in anti-cancer agent discovery; US05869620 Multivalent antigen-binding proteins; US05861156 Methods of delivering agents to target cells; WO09855623A1 TYPE-1 RIBOSOME-INACTIVATING PROTEIN; US05846565 Controlled local delivery of chemotherapeutic agents for treating solid tumors; US05843462 Diphtheria toxin epitopes; US05843425 Transplantation and graft-versus-host-disease; US05824776 Cell-targeted lytic pore-forming agents; US05821081 Nucleic acids encoding antiviral proteins and peptides, vectors and host cells comprising same, and methods of producing the antiviral proteins and peptides; US05817771 Cell-targeted lytic pore-forming agents; WO09831394A2 TISSUE FACTOR METHODS AND COMPOSITIONS FOR COAGULATION AND TUMOR TREATMENT; WO09828298A1 RICIN INHIBITORS AND METHODS FOR USE THEREOF; US05759782 Cellular apoptosis susceptibility protein (CSP) and antisense CSP; WO09817116A1 TARGETED CYTOTOXIC CELLS; US05736536 Method for treating vascular leak syndrome; US05728677 Methods of inhibiting T-cell dependent proliferation of peripheral blood lymphocytes using the CD2-binding domain of lymphocyte function associated antigen 3; US05728579 DNA encoding Mat-8; US05723326 Genome coding phytolectin antiviral protein and a recombinant expression vector therefor; US05697902 Method for imaging and treating organs and tissues; US05677430 Antibodies directed against CD30 ligand; US05670151 Method for controlling hyperproliferative diseases; US05667786 Method for treating tumors with a toxin; US05663144 Compounds that bind to p185 and methods of using the same; WO09727871A1 METHOD OF INACTIVATION OF RAS SUBFAMILY PROTEINS AND AGENTS THEREFOR; US05648234 Expression vector for Phytolectin antiviral protein; US05639863 Human monoclonal antibodies specific to cell cycle independent glioma surface antigen; US05632990 Treatment for tumors comprising conjugated antibody A5B7 and a prodrug; US05626862 Controlled local delivery of chemotherapeutic agents for treating solid tumors; US05624827 DNA sequences encoding the plant toxin gelonin; US05621083 Immunotoxins comprising ribosome-inactivating proteins; US05616122 Methods and compositions for preventing secondary cataracts; US05597569 Bryodin 2 a ribosome-inactivating protein isolated from the plant *Bryonia dioica*; WO09701636A2 RECOMBINANT MISTLETOE LECTIN; US05552311 Purine nucleoside phosphorylase gene therapy for human malignancy; US05547853 CD2-binding domain of lymphocyte function associated antigen 3; EP00717753A1 RIBOSOME INACTIVATING PROTEINS EXTRACTED FROM SEEDS OF *SAPONARIA OCYMOIDES* AND *VACCARIA PYRAMIDATA*, THEIR PREPARATION AND IMMUNOTOXINS CONTAINING THEM; EP00700444A1 IMMUNOTOXINS COMPRISING GELONIN AND AN ANTIBODY; US05480981 CD30 ligand; US05478804 Treatment of tumorigenic pathophysiological conditions with FGF-cytotoxic conjugates; US05455030 Immunotherapy using single chain polypeptide binding molecules; EP00635030A1 IMMUNOTOXINS DIRECTED AGAINST c-erbB-2 (HER-2/-neu) RELATED SURFACE ANTIGENS; EP00634938A1 IMMUNOTOXINS DIRECTED AGAINST CD33 RELATED SURFACE ANTIGENS; JP06312942A2 CARCINOSTATIC AGENT FOR HUMAN HEPATOMA CELL PRODUCING ALPHA-FETOPROTEIN; US05348865 Genome coding phytolectin antiviral protein and a recombinant expression vector therefor; EP00610286A1 RECOMBINANT IMMUNOTOXINS; EP00261671B1 Recombinant *Pseudomonas* exotoxin: construction of an active immunotoxin with low side effects; US05283344 Coupling method using selective amination of maleimide; US05191067 Fibroblast growth factor conjugates; EP00303681B1 IMMUNOSUPPRESSION IN IMMUNOTOXIN BASED HUMAN THERAPY; EP00226419B1 Anti-human ovarian cancer immunotoxins and methods of use thereof; EP00226418B1 Anti-human ovarian cancer immunotoxins and methods of use thereof; US05090914 Activated polymers and conjugates thereof; US05055289 Interferon antibody therapeutic compositions having an extended serum half-life; JP03130235A2 ANTITUMOR AGENT; US04997913 pH-sensitive immunoconjugates and methods for their use in tumor therapy; US04977280 Conjugates in which a monovalent carboxylic ionophore is associated by means of a covalent bond with a macromolecule, their use as immunotoxin potentiators and the intermediate activated ionophores; US04919927 Process for the potentiation of immunotoxins; US04911690 Treatment or diagnosis by endoscopic administration into the lymphatics; EP00186551B1 Medicament containing as a mixture at least one immunotoxin and at least one polymer containing mannose; JP02019324A2 MONOCLONAL ANTIBODY AGAINST OVARIAN CELL; EP00162781B1 Conjugates associated with a covalent bond to a monovalent carboxylic ionophore and a macromolecule, their use as potentializers of immunotoxins and the activated intermediate ionophores; JP01102032A2 IMMUNOTOXIN TREATMENT FOR ALLERGY; EP00303681A1 IMMUNOSUPPRESSION IN IMMUNOTOXIN BASED HUMAN THERAPY; US04792447 Anti-immunoglobulin toxin conjugates useful in the treatment of B cell tumors; EP00261671A2 Recombinant *Pseudomonas* exotoxin: construction of an active immunotoxin with low side effects; EP00256714A2 Combination therapy using anti-tumor monoclonal antibodies and/or immunotoxins with interleukin-2; EP00232447A1 Lectin immunotoxins; EP00089270B1 Cytotoxic medicines containing at least one immune toxin and one amine; EP00226419A2 Anti-human ovarian cancer immunotoxins and methods of use thereof; EP00226418A2 Anti-human ovarian cancer immunotoxins and methods of use thereof; EP00186551A1 Medicament containing as a mixture at least one immunotoxin and at least one polymer containing mannose; EP00088694B1 Cytotoxic medicine containing at least one immune toxin and chloroquine;

EP00162781A1 Conjugates associated with a covalent bond to a monovalent carboxylic ionophore and a macromolecule, their use as potentializers of immunotoxins and the activated intermediate ionophores; EP00130132A1 Antitumour immunotoxin, pharmaceutical compositions containing it, and its use in vitro; US06187810 Macrocytic compounds made from suboxide units; EP01073463A1 USE OF IMMUNOTOXINS TO INDUCE IMMUNE TOLERANCE TO PANCREATIC ISLET TRANSPLANTATION; US06177554 Nucleic acid transporter systems; US06177280 Ricin inhibitors and methods for use thereof; US06165750 Modified-affinity streptavidin; US06159947 Anti-RAS intracellular binding proteins and use thereof; US06156541 Compositions and methods for catalyzing hydrolysis of HIV gp120; US06156493 Modified-affinity streptavidin; US06150168 Nucleic acid transporter systems and methods of use; US06146628 Biotherapeutic agents comprising recombinant PAP and PAP mutants; US06143298 Soluble truncated forms of ICAM-1; US06127170 Multifunctional complexes for gene transfer into cells comprising a nucleic acid bound to a polyamine and having an endosome disruption agent; US06123939 Anti-neoplastic drugs in cancer therapy; US06120767 Chimeric antibody with specificity to human B cell surface antigen; US06117673 RDGB proteins and related products and methods; US06110735 Method for the preparation of a viral vector by intermolecular homologous recombination; US06103233 Cellular and serum protein anchors and conjugates; US06096303 Method to enhance treatment of cystic tumors; US06093692 Method and compositions for lipidization of hydrophilic molecules; US06089234 7/18/2000 Method for destroying residual lens epithelial cells; EP01015496A2 IMMUNOTOXINS AND METHODS OF INDUCING IMMUNE TOLERANCE; US06084084 Human metabotropic glutamate receptor; US06077675 Human metabotropic glutamate receptor; US06074836 Method of marking eukaryotic cells; US06071493 Method of screening for an agent that inhibits mononuclear phagocyte-plaque component complex formation; US06066470 Method for removing N-terminal methionine; US06060066 Method for treating tumors with a toxin; US06056959 CD40 antigen antibody complex; US06051688 Isolated human metabotropic glutamate receptor mGluR-8; US06051231 Antiviral methods and preparations; US06048717 Inhibitors of catalytic antibodies; US06043283 Tyramine compounds and their neuronal effects; US06039684 Non-lethal conditioning methods for the treatment of acquired immunodeficiency syndrome; US06037329 Compositions containing nucleic acids and ligands for therapeutic treatment; US06033884 Nucleic acid transporter systems and methods of use; US06031003 Calcium receptor-active molecules; WO00006194A2 DEPLETION OF CELLS RESPONSIBLE FOR ANTIBODY-MEDIATED GRAFT REJECTION; EP00975674A1 IMMUNOTOXINS, COMPRISING AN ONC PROTEIN, DIRECTED AGAINST MALIGNANT CELLS; US06018096 Animal model for engraftment, proliferation and differentiation of human hematopoietic stem cells; US06015876 Method of using cyanovirins; US06015556 Cytotoxic drug therapy; US06011068 Calcium receptor-active molecules; US06004812 In-vitro T-lymphopoiesis system; US06004552 Methods of blocking B cell proliferation using anti-CD40 monoclonal antibodies; US06001991 Antisense oligonucleotide modulation of MDRP-glycoprotein gene expression; US05994109 Nucleic acid transporter system and methods of use; US05990286 Antibodies with reduced net positive charge; US05981505 Compositions and methods for delivery of genetic material; US05976535 Pretargeting protocols for the enhanced localization of cytotoxins to target sites and cytotoxic combinations useful therefore; US05972901 Serpin enzyme complex receptor-mediated gene transfer; US05972900 Delivery of nucleic acid to cells; US05962653 Methods of obtaining antiviral proteins and antiviral peptides from *Nostoc ellipsosporum*; US05962428 Compositions and methods for delivery of genetic material; US05962314 Calcium receptor-active molecules; US05958770 Glycoalkaloids; JP11253181A2 RECOMBINANT PSEUDOMONAS EXOTOXIN: ACTIVE IMMUNOTOXIN STRUCTURE OF LOW SIDE EFFECTS; US05948635 Totally Synthetic Affinity Reagents; US05945100 8/31/1999 Tumor delivery vehicles; US05939070 Hybrid botulinum neurotoxins; US05922847 Methods of purifying hematopoietic cells using an antibody to a stem cell factor receptor; US05919911 Monoclonal antibodies to stem cell factor receptors; US05919457 TXU-5/B53-PAP antiviral biotherapeutic agent for the treatment of AIDS; US05917021 Stabilized monomeric protein compositions; US05916803 Target cell-specific non-viral vectors for inserting genes into cells, pharmaceutical compositions comprising such vectors and their use; US05916561 Monoclonal antibody against CD44v6; US05914127 Isolation and uses of caveolae; US05910486 Methods for modulating protein function in cells using, intracellular antibody homologues; US05906938 Method of reconstituting hematopoietic cells using monoclonal antibodies to the stem cell factor receptor; US05891689 Heme-bearing microparticles for targeted delivery of drugs; US05877210 Phosphotyrosine phosphatase inhibitors or phosphotyrosine kinase activators for controlling cellular proliferation; US05877162 Short external guide sequences; US05874082 Humanized anti-CD40 monoclonal antibodies and fragments capable of blocking B cell proliferation; US05874081 Therapeutic compositions and methods for inhibition and treatment of tumor associated angiogenesis; US05871733 Multimeric forms of human rhinovirus receptor protein; US05866570 Treatment of vascular leakage and related syndrome such as septic shock by administration of metalloproteinase inhibitors; US05863540 Adhesion molecule; US05858687 Cell bioassay of neurotoxins; US05858684 Method of screening calcium receptor-active molecules; US05856456 Linker for linked fusion polypeptides; US05854400 Monoclonal antibodies which neutralize HIV-1 infection; US05854027 Process for improving the stability of antibodies; US05852167 Totally synthetic affinity reagents; US05851991 Therapeutic use of the retinoblastoma susceptibility gene product; US05847121 Production of nitro-benzyl-dota via direct peptide cyclization; US05846535 Methods for reducing tumor cell growth by using antibodies with broad tumor reactivity and limited normal tissue reactivity; US05844076 Totally synthetic affinity reagents; US05843893 Method for inhibiting the proliferation of epithelial lens cells and implantable lens therefor; US05843882 Antiviral proteins and peptides; US05843724 Chimeric nucleic acids and proteins for inhibiting HIV-1 expression; US05843685 Production of chimeric mouse-human antibodies with specificity to human tumor antigens; US05840854 Monoclonal antibody BR110 and uses thereof; US05840300 Methods and compositions comprising single chain recombinant antibodies; US05837846 Biosynthetic binding proteins for immuno-targeting; US05837533 Complexes comprising a nucleic acid bound to a cationic polyamine having an endosome disruption agent; US05837283 Cationic lipid compositions targeting angiogenic endothelial cells; US05834599 Immunoconjugates which neutralize HIV-1 infection; US05833985 Bispecific molecules for use in inducing antibody dependent effector cell-mediated cytotoxicity;

US05831036 Soluble fragments of human intercellular adhesion molecule-1; US05830876 Genetic immunization;
 US05827934 Cytotoxic diphtheria toxin fragments; US05827655 Assay, methods and products based on n
 K + channel expression; US05824805 Branched hydrazone linkers; US05817637 Genetic immunization;
 US05817310 Inhibitory immunoglobulin polypeptides to human PDGF beta receptor;
 US05789554 Immunoconjugates and humanized antibodies specific for B-cell lymphoma and leukemia cells;
 US05773245 Methods for increasing secretion of overexpressed proteins; US05770195 Monoclonal antibodies
 directed to the her2 receptor; US05767073 D4 gene and methods of use thereof; US05763733 Antigen-binding
 fusion proteins; US05763569 Calcium receptor-active molecules; US05762921 Composition and methods for the
 treatment of tumors; US05759517 Hemoglobins as drug delivery agents; US05756097 Lymphokine activated
 effector cells for antibody-dependent cellular cytotoxicity (ADCC) treatment of cancer and other diseases;
 JP10136988 A2 RECOMBINANT PSEUDOMONAS EXOTOXIN: STRUCTURE OF ACTIVE IMMUNOTOXIN HAVING
 LESS SIDE EFFECT; US05753204 Biosynthetic binding proteins for immunotargeting; US05753203 CD30 ligand
 conjugates; US05747334 Random peptide library; US05744335 Process of transfecting a cell with a polynucleotide
 mixed with an amphipathic compound and a DNA-binding protein; US05744315 Compounds from biopolymers and
 effector substances which are linked via optically active amino acid derivatives, processes for the preparation thereof
 and the use thereof; US05739118 Compositions and methods for delivery of genetic material;
 EP00830146 A2 METHODS OF INDUCING IMMUNE TOLERANCE USING IMMUNOTOXINS;
 US05725857 Immunotoxin with in vivo T cell suppressant activity and methods of use; US05725856 Monoclonal
 antibodies directed to the HER2 receptor; US05725855 Method of treating tumors with CD8 + -depleted or CD4 + T
 cell subpopulations; US05721108 Chimeric antibody with specificity to human B cell surface antigen;
 US05720954 Monoclonal antibodies directed to the HER2 receptor; US05720937 In vivo tumor detection assay;
 US05720720 Convection-enhanced drug delivery; US05718899 Method and compositions for direct
 concentrated delivery of passive immunity; US05716990 Drug delivery systems; US05709995 Hepatitis C virus-
 derived peptides capable of inducing cytotoxic T lymphocyte responses; US05707627 Methods and compositions for
 the direct concentrated delivery of passive immunity; US05695760 Modified anti-ICAM-1 antibodies and their use in
 the treatment of inflammation; US05693627 Use of phosphotyrosine phosphatase inhibitors for controlling cellular
 proliferation; US05690928 Method of treating bladder cancer cells; US05688938 Calcium receptor-active molecules;
 US05686582 Multimeric forms of human rhinovirus receptor protein; US05686581 Multimeric form of human
 rhinovirus receptor protein; US05683694 Method for the treatment of tumors with conjugated antibody A5B7 and a
 prodrug; US05683692 Use of RIPonucleases for treating parasitic and viral diseases; US05681810 Diphtheria toxin
 fragments, conjugates and methods of use to inhibit tumors and leukemia; US05681565 Methods and compositions
 for passive immunotherapy; US05679777 Hemoglobins as drug delivery agents; US05677274 Anthrax toxin fusion
 proteins and related methods; US05677165 Anti-CD40 monoclonal antibodies capable of blocking B-cell activation;
 US05676924 In vivo assay to determine cancer treatment effectiveness; US05674982 Multimeric form of human
 rhinovirus receptor protein; US05663306 Method of conjugating an activated ester to an amine-containing biological
 material; US05658753 Catalytic antibody components; US05658568 Cytotoxic drug therapy;
 US05654267 Cooperative combinations of ligands contained within a matrix; US05645835 Therapeutic antibody
 based fusion proteins; US05641677 Method of enhancing the immunotherapeutic activity of immune cells by
 depletion of CD8 + T cells; US05625033 Totally synthetic affinity reagents; US05621002 Prodrugs for enzyme
 mediated activation; US05620013 Method for destroying residual lens epithelial cells; US05616458 Tripterygium
 wilfordii hook F extracts and components, and uses thereof; US05614611 Humanized monoclonal antibodies binding
 to IgE-bearing B cells but not basophils; US05612216 Nucleotide sequence encoding intercellular adhesion molecule-1
 and fragments thereof; US05602015 Autoantibodies which enhance the rate of a chemical reaction;
 US05601827 Diphtheria toxin vaccines; US05599538 Autoantibodies which enhance the rate of a chemical reaction;
 US05593972 Genetic immunization; US05591631 Anthrax toxin fusion proteins, nucleic acid encoding same;
 US05589453 Human rhinovirus receptor protein (ICAM-1) that inhibits rhinovirus attachment and infectivity;
 WO09641608 A2 PYRULARIA THIONIN CONTAINING IMMUNOTOXINS AND IMMUNOTOXIN-LIKE CONJUGATES;
 WO09640260 A2 IMMUNOTOXINS SPECIFIC FOR CD80 AND CD86 EXPRESSING CELLS; US05585478 D4 gene and
 methods of use thereof; US05583242 Use of phosphotyrosine phosphatase inhibitors for controlling cellular
 proliferation; US05582996 Bifunctional antibodies and method of preparing same; US05580562 Preparations and
 uses thereof for immunosuppression; WO09632416 A1 NOVEL ANTI-AIDS IMMUNOTOXINS;
 WO09632137 A2 METHODS OF INDUCING IMMUNE TOLERANCE USING IMMUNOTOXINS; US05565491 Use of
 phosphotyrosine phosphatase inhibitors for controlling cellular proliferation; US05561221 Methods and compositions
 for promoting protein folding; US05547667 Linker for bioactive agents; US05541287 Pretargeting methods and
 compounds; US05534254 Biosynthetic binding proteins for immuno-targeting; US05525337 Monoclonal antibody
 binding cell surface antigens for diagnosing cancer; US05505945 Method and compositions for the
 direct concentrated delivery of passive immunity; US05505931 Acid cleavable compounds, their preparation and use
 as bifunctional acid-labile crosslinking agents; US05498538 Totally synthetic affinity reagents; US05475091 R6-5-
 D6, an antibody which binds intercellular adhesion molecule-1; US05453271 Vaccine against ricin toxin;
 US05422339 6/06/1995 Peptides having insulin autoantibody but not insulin receptor binding capacity;
 US05420011 Cell bioassay for neurotoxins; US05416202 Materials comprising and methods of preparation and use
 for ribosome-inactivating proteins; US05405966 Trichothecene conjugates; WO09507297 A1 RIBOSOME
 INACTIVATING PROTEINS EXTRACTED FROM SEEDS OF SAPONARIA OCYMOIDES AND VACCARIA
 PYRAMIDATA, THEIR PREPARATION AND IMMUNOTOXINS CONTAINING THEM; WO09503828 A1 SINGLE-CHAIN
 IMMUNOTOXIN COMPOSITIONS AND METHODS FOR PREVENTING SECONDARY CATARACTS;
 WO09503783 A1 POLYMERIC DEVICE FOR THE DELIVERY OF IMMUNOTOXINS FOR THE PREVENTION OF
 SECONDARY CATARACT; US05387578 New linker for bioactive agents; US05376546 Analogs of ribosome-
 inactivating proteins; WO09426910 A1 IMMUNOTOXINS COMPRISING GELONIN AND AN ANTIBODY;
 WO09421813 A1 MONOCLONAL ANTIBODIES SPECIFIC FOR FIBROBLAST GROWTH FACTOR RECEPTORS,

IMMUNOTOXINS, AND USE THEREOF; US05328984 Recombinant chimeric proteins deliverable across cellular membranes into cytosol of target cells; WO09413316A1 POTENT AND SPECIFIC CHEMICALLY-CONJUGATED IMMUNOTOXINS; US05318897 Monoclonal antibody and antibody components elicited to a polypeptide antigen ground state; US05314995 Therapeutic interleukin-2-antibody based fusion proteins; JP06125912A2 ASSAY IN VIVO FOR CANCER TREATMENT; US05308626 Lymphokine activated effector cells for antibody-dependent cellular cytotoxicity (ADCC) treatment of cancer and other diseases; EP00590011A1 ABRIN VARIANTS AND IMMUNOTOXINS; US05292867 Chimeric monoclonal antibodies which bind to the extracellular segment of the membrane-bound domain of a human membrane-bound immunoglobulin; US05260416 Antigenic epitopes present on membrane-bound but not secreted IgE; WO09321232A1 IMMUNOTOXINS DIRECTED AGAINST c-erbB-2(HER-2/neu) RELATED SURFACE ANTIGENS; WO09320848A1 IMMUNOTOXINS DIRECTED AGAINST CD33 RELATED SURFACE ANTIGENS; US05254671 Extracellular segments of human immunoglobulin anchoring peptides and antibodies specific therefor; US05236836 Autoantibodies which enhance the rate of a chemical reaction; WO09315113A1 AN IMMUNOTOXIN INCLUDING A CYTOTOXIN WITH AN UNPAIRED CYSTEINE RESIDUE IN OR NEAR ITS RECEPTOR-BINDING SITE; US05229272 Catalytic antibody components; WO09307286A1 RECOMBINANT IMMUNOTOXINS; US05202252 Monoclonal antibodies against lens epithelial cells and methods for preventing proliferation of remnant lens epithelial cells after extracapsular extraction; US05194594 Modified antibodies; US05194585 Inhibitors of catalytic antibodies; US05171563 Cleavable linkers for the reduction of non-target organ retention of immunoconjugates; US05169774 Monoclonal anti-human breast cancer antibodies; EP00506854A1 AN IMPROVED TOXIN FOR CONSTRUCTION OF IMMUNOTOXINS; US05151266 Use of anionic detergents with conjugates of monoclonal or polyclonal antibodies; WO09215327A1 RECOMBINANT DOUBLE CHAIN IMMUNOTOXINS; WO09214491A1 IMMUNOTOXIN FROM ANTI-CD5 MONOCLONAL ANTIBODIES; WO09213562A1 AN IMMUNOTOXIN WITH IN VIVO T CELL SUPPRESSANT ACTIVITY; EP00489931A1 IMMUNOTOXIN COMPLEX; US05122368 Anthracycline conjugates having a novel linker and methods for their production; WO09209613A1 RECOMBINANT IMMUNOTOXIN COMPOSED OF A SINGLE CHAIN ANTIBODY REACTING WITH THE HUMAN TRANSFERRIN RECEPTOR AND DIPHTheria TOXIN; US05087616 Cytotoxic drug conjugates and their delivery to tumor cells; WO09200089A1 IMMUNOTOXIN COMPLEX; US05055291 Compositions for preventing secondary cataracts; WO09109965A1 AN IMPROVED TOXIN FOR CONSTRUCTION OF IMMUNOTOXINS; US05021343 Method for producing trichothecenes; EP00419462A1 IMPROVED IMMUNOTOXIN THERAPIES UTILIZING PURIFIED RICIN A-CHAIN SPECIES; US04994383 Method for producing trichothecenes and related materials; EP00407399A1 IMMUNOSUPPRESSION WITH ANTI-PAN T-CELL IMMUNOTOXIN COMPOSITIONS; US04975278 Antibody-enzyme conjugates in combination with prodrugs for the delivery of cytotoxic agents to tumor cells; EP00397798A1 THERAPEUTIC USE OF ANTI-T CELL IMMUNOTOXIN FOR AUTOIMMUNE DISEASES; WO09010457A1 METHOD OF TREATING HIV INFECTIONS USING IMMUNOTOXINS; US04892827 Recombinant pseudomonas exotoxins: construction of an active immunotoxin with low side effects; WO08911871A1 ONE-STEP CHROMATOGRAPHIC PURIFICATION OF IMMUNOTOXIN CONJUGATES USING A THIOPHILIC MATRIX; JP01297075A2 DEVICE FOR BLOOD TREATMENT; US04880935 Heterobifunctional linking agents derived from N-succinimido-dithio-alpha methyl-methylene-benzoates; US04880747 Fusarium sporotrichioides mutant strain capable of producing both dideacetylcalonecetrin and deacetylcalonecetrin; US04871350 Methods and compositions for preventing secondary cataracts; EP00129434B1 Immunotoxin conjugates; WO08906968A1 THERAPEUTIC USE OF ANTI-T CELL IMMUNOTOXIN FOR AUTOIMMUNE DISEASES; WO08906967A1 IMMUNOSUPPRESSION WITH ANTI-PAN T-CELL IMMUNOTOXIN COMPOSITIONS; US04853464 Hybridoma cell line XMMBR-B14 and monoclonal antibody which is specific for a non-cross reactive epitope of CEA; US04831117 Monoclonal antibody specific for human B-cells; WO08900583A1 IMPROVED IMMUNOTOXIN THERAPIES UTILIZING PURIFIED RICIN A-CHAIN SPECIES; WO08806451A1 IMMUNOSUPPRESSION IN IMMUNOTOXIN BASED HUMAN THERAPY; US04766106 Solubilization of proteins for pharmaceutical compositions using polymer conjugation; US04744981 Trichothecene antibody conjugates; WO08802401A1 RECOMBINANT PSEUDOMANAS EXOTOXIN: CONSTRUCTION OF AN ACTIVE IMMUNOTOXIN WITH LOW SIDE EFFECTS; US04672107 Cell growth inhibitor and method; US04664911 Immunotoxin conjugates employing toxin B chain moieties; WO08605098A1 IMMUNOTOXIN AND METHOD OF MAKING; US04590071 Human melanoma specific immunotoxins; US04585742 Monoclonal antibody with specificity to human small cell carcinoma and use thereof; EP00129434A2 Immunotoxin conjugates; WO08303200A1 CYTOTOXIC MEDICINES INCLUDING AT LEAST AN IMMUNOTOXIN AND AN AMINE; WO08303055A1 CYTOTOXIC DRUG FORMED BY THE ASSOCIATION OF AT LEAST ONE IMMUNOTOXIN AND CHLOROQUINE; WO08302725A1 DRUGS COMPRISING AN ASSOCIATION AT LEAST ONE IMMUNOTOXIN AND AT LEAST ONE MONOVALENT CARBOXYLIC IONOPHORE; Koon HB, Junghans RP. Anti-CD30 antibody-based therapy. *Curr. Opin. Oncol.* 2000 Nov; 12(6):588-93. Foon KA. Monoclonal antibody therapies for lymphomas. *Cancer J.* 2000 Sep; 6(5):273-8. Feuring-Buske M, Buske C, Unterhalt M, Hiddemann W. Recent advances in antigen-targeted therapy in non-Hodgkin's lymphoma. *Ann Hematol.* 2000 Apr; 79(4):167-74. Bodey B, Bodey B, Siegel SE, Kaiser HE. Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents. *Curr Pharm Des.* 2000 Feb; 6(3):261-76. Pavlinkova G, Booth BJ, Batra SK, Colcher D. Radioimmunotherapy of human colon cancer xenografts using a dimeric single-chain Fv antibody construct. *Clin Cancer Res.* 1999 Sep; 5(9):2613-9. Friedrich K, Wietek S, Lischke A, Wellbrock C, Kreitman RJ, Pastan I, Seibald W. A two-step selection approach for the identification of ligand-binding determinants in cytokine receptors. *Anal Biochem.* 1999 Mar 15; 268(2):179-86. Scherf U, Benhar I, Webber KO, Pastan I, Brinkmann U. Cytotoxic and antitumor activity of a recombinant tumor necrosis factor-B1(Fv) fusion protein on LeY antigen-expressing human cancer cells. *Clin Cancer Res.* 1996 Sep; 2(9):1523-31. Sforzini S, de Toter D, Gaggero A, Ippoliti R, Glennie MJ, Canevari S, Stein H, Ferrini S. Targeting of saporin to Hodgkin's lymphoma cells by anti-CD30 and anti-CD25 bispecific antibodies. *Br J Haematol.* 1998 Sep; 102(4):1061-8. Volm M. Multidrug resistance and its reversal. *Anticancer Res.* 1998 Jul-Aug; 18(4C):2905-17. Kruger K, Jochum C, Glusenkauf KH, Krusemann

C, Lorenz P, Eberle-Adamkiewicz G, Drosdzik W, Beelen DW, Coenen HH, Rajewsky MF. New modular delivery system for diagnostic and therapeutic pre-targeting using tautomer-specific monoclonal antibody EM-6-47 and 3-substituted adenines. *Int J Cancer*. 1998 Aug 12; 77(4):610-9. 11: Adams GP, Schier R, McCall AM, Crawford RS, Wolf EJ, Weiner LM, Marks JD. Prolonged in vivo tumour retention of a human diabody targeting the extracellular domain of human HER2/neu. *Br J Cancer*. 1998 May; 77(9):1405-12. 12: Bookman MA. Biological therapy of ovarian cancer: current directions. *Semin Oncol*. 1998 Jun; 25(3):381-96. 13: Funaro A, Horenstein AL, Malavasi F. Monoclonal antibodies in clinical applications. *J Biol Regul Homeost Agents*. 1996 Oct-Dec; 10(4):72-82. No abstract available. 14: Jurcic JG, Scheinberg DA, Houghton AN. Monoclonal antibody therapy of cancer. *Cancer Chemother Biol Response Modif*. 1997; 17:195-216. No abstract available. 15: Tesch H, Bohlen H, Wolf J, Engert A. [Pathogenesis and therapy of Hodgkin lymphoma]. *Med Klin*. 1998 Feb 15; 93(2):82-90. 16: Deonarain MP, Epenetos AA. Design, characterization and anti-tumour cytotoxicity of a panel of recombinant, mammalian ribonuclease-based immunotoxins. *Br J Cancer*. 1998 Feb; 77(4):537-46. 17: Krebs B, Griffin H, Winter G, Rose-John S. Recombinant human single chain Fv antibodies recognizing human interleukin-6. Specific targeting of cytokine-secreting cells. *J Biol Chem*. 1998 Jan 30; 273(5):2858-65. 18: Wilbur DS, Pathare PM, Hamlin DK, Weerawarna SA. Related Articles Biotin reagents for antibody pretargeting. 2. Synthesis and in vitro evaluation of biotin dimers and trimers for cross-linking of streptavidin. *Bioconjug Chem*. 1997 Nov-Dec; 8(6):819-32. 19: Goulet AC, Goldmacher VS, Lambert JM, Baron C, Roy DC, Kouassi E. Conjugation of blocked ricin to an anti-CD19 monoclonal antibody increases antibody-induced cell calcium mobilization and CD19 internalization. *Blood*. 1997 Sep 15; 90(6):2364-75. 20: Moutel S, Birkle S, Laurence V, Michon J, Fridman WH, Aubry J, Teillaud JL. Protein, Nucleotide Generation and characterization of a mouse single-chain antibody fragment specific for disialoganglioside (GD2). *Hybridoma*. 1997 Aug; 16(4):335-46. 21: Nokihara H, Yano S, Sone S. [Overcoming of multidrug resistance by anti-P-glycoprotein monoclonal antibody]. *Nippon Rinsho*. 1997 May; 55(5):1128-34. 22: Sznol M, Holmlund J. Antigen-specific agents in development. *Semin Oncol*. 1997 Apr; 24(2):173-86. 23: von Mehren M, Weiner LM. Monoclonal antibody-based therapy. *Curr Opin Oncol*. 1996 Nov; 8(6):493-8. 24: Robert B, Mach JP, Mani JC, Ychou M, Folli S, Artus JC, Pelegri A. Cytokine targeting in tumors using a bispecific antibody directed against carcinoembryonic antigen and tumor necrosis factor alpha. *Cancer Res*. 1996 Oct 15; 56(20):4758-65. 25: Voliotis DL, Tesch H. [Experimental approaches]. *Internist (Berl)*. 1996 Oct; 37(10):1040-8. available. 26: Schmidt M, Wels W. Targeted inhibition of tumour cell growth by a bispecific single-chain toxin containing an antibody domain and TGF alpha. *Br J Cancer*. 1996 Sep; 74(6):853-62. 27: RR, Bell AJ, Hamblin TJ, Tutt AL, Glennie MJ. Related Articles Response of B-cell lymphoma to a combination of bispecific antibodies and saporin. *Leuk Res*. 1996 Jul; 20(7):607-17. 28: Bergamaschi G, Perfetti V, Tonon L, Novella A, Lucotti C, Danova M, Glennie MJ, Merlini G, Cazzola M. Saporin, a ribosome-inactivating protein used to prepare immunotoxins, induces cell death via apoptosis. *Br J Haematol*. 1996 Jun; 93(4):789-94. 29: Tesch H, Diehl V. Hodgkin's disease: from basic science to clinical application. *Leukemia*. 1996 Jun; 10 Suppl 2:s74-7. 30: Bodey B, Siegel SE, Kaiser HE. Human cancer detection and immunotherapy with conjugated and non-conjugated monoclonal antibodies. *Anticancer Res*. 1996 Mar-Apr; 16(2):661-74. 31: Schmidt M, Hynes NE, Groner B, Wels W. A bivalent single-chain antibody-toxin specific for ErbB-2 and the EGFR receptor. *Int J Cancer*. 1996 Feb 8; 65(4):538-46. 32: Saijyo S, Kudo T, Katayose Y, Saeki H, Chiba N, Suzuki M, Tominaga T, Matsuno S. A new in vitro model of specific targeting therapy of cancer: retargeting of PWM-LAK cells with bispecific antibodies greatly enhances cytotoxicity to hepatocellular carcinoma. *Tohoku J Exp Med*. 1996 Feb; 178(2):113-27. 33: Gilliland LK, Norris NA, Marquardt H, Tsu TT, Hayden MS, Neubauer MG, Yelton DE, Mittler RS, Ledbetter JA. Protein, Nucleotide Rapid and reliable cloning of antibody variable regions and generation of recombinant single chain antibody fragments. *Tissue Antigens*. 1996 Jan; 47(1):1-20. 34: Mota G, Marches R, Cialacu V, Roman V, Kozma E, Margineanu M, Dima S, Moraru II. Mouse multivalent IgG(2a, b) antibody-ricin A-chain immunotoxins combined with homologous or heterologous interleukin 2 in the treatment of a murine malignant lymphoproliferation (EL4). *Arch Immunol Ther Exp (Warsz)*. 1996; 44(2-3):131-6. 35: Wels W, Groner B, Hynes NE. Intervention in receptor tyrosine kinase-mediated pathways: recombinant antibody fusion proteins targeted to ErbB2. *Curr Top Microbiol Immunol*. 1996; 213 (Pt 3):113-28. available. 36: Sforzini S, Bolognesi A, Meazza R, Marciano S, Tazzari PL, Stein H, Stirpe F, Ferrini S. Targeting of type 1 ribosome-inactivating proteins to CD30+ or CD25+ hematologic neoplasias by bispecific antibodies. *J Hematother*. 1995 Oct; 4(5):429-32. 37: Michon J, Moutel S, Barbet J, Romet-Lemonne JL, Deo YM, Fridman WH, Teillaud JL. In vitro killing of neuroblastoma cells by neutrophils derived from granulocyte colony-stimulating factor-treated cancer patients using an anti-disialoganglioside/anti-Fc gamma RI bispecific antibody. *Blood*. 1995 Aug 1; 86(3):1124-30. 38: RR, Hamblin TJ, Bell AJ, Tutt AL, Glennie MJ. Related Articles Treatment of B-cell lymphomas with combination of bispecific antibodies and saporin. *Lancet*. 1995 Jul 22; 346(8969):223-4. 39: Sforzini S, Bolognesi A, Meazza R, Marciano S, Casalini P, Durkop H, Tazzari PL, Stein H, Stirpe F, Ferrini S. Differential sensitivity of CD30+ neoplastic cells to gelonin delivered by anti-CD30/anti-gelonin bispecific antibodies. *Br J Haematol*. 1995 Jul; 90(3):572-7. 40: Flavell DJ, Cooper S, Okayama K, Emery L, Flavell SU. Related Articles Comparison of the performance of anti-CD7 and anti-CD38 bispecific antibodies and immunotoxins for the delivery of saporin to a human T-cell acute lymphoblastic leukemia cell line. *Hematol Oncol*. 1995 Jul-Aug; 13(4):185-200. 41: George AJ, RR, Glennie MJ. Measurement of kinetic binding constants of a panel of anti-saporin antibodies using a resonant mirror biosensor. *J Immunol Methods*. 1995 Jun 14; 183(1):51-63. 42: RR, Penney CA, Browning AC, Stirpe F, George AJ, Glennie MJ. Delivery of the ribosome-inactivating protein, gelonin, to lymphoma cells via CD22 and CD38 using bispecific antibodies. *Br J Cancer*. 1995 May; 71(5):986-94. 43: Eason JD, Wee S, Kawai T, Hong HZ, Powelson JA, Widmer MB, Cosimi AB. Inhibition of the effects of TNF in renal allograft recipients using recombinant human dimeric tumor necrosis factor receptors. *Transplantation*. 1995 Jan 27; 59(2):300-5. 44: Wei C, Tang ZY, Liu KD. [Targeting treatment of human HCC xenografts implanted in nude mice using bifunctional antibody HC-1 combined with mitomycin C]. *Zhonghua Yi Xue Za Zhi*. 1994 Nov; 74(11):676-9, 709-10. Chinese. 45: Renner C, Pfreundschuh M. [Antibody-conjugated cytostatic drugs. Uses of monoclonal antibodies for new strategies in tumor therapy]. *Fortschr Med*. 1994 Oct 20; 112(29):399. available. 46: Ring DB, Hsieh-Ma

ST, Shi T, Reeder J. Antigen forks: bispecific reagents that inhibit cell growth by binding selected pairs of tumor antigens. *Cancer Immunol Immunother.* 1994 Jul; 39(1):41-8.47: De Sutter K, Fiers W. A bifunctional murine::human chimeric antibody with one antigen-binding arm replaced by bacterial beta-lactamase. *Mol Immunol.* 1994 Mar; 31(4):261-7.48: Shen GL, Li JL, Vitetta ES. Bispecific anti-CD22/anti-CD3-ricin A chain immunotoxin is cytotoxic to Daudi lymphoma cells but not T cells in vitro and shows both A-chain-mediated and LAK-T-mediated killing. *J Immunol.* 1994 Mar 1; 152(5):2368-76.49: Wang LM, Wan WH, Lu LJ. [A bispecific monoclonal antibody with versatile adaptor mediating different cytotoxicities]. *Zhonghua Zhong Liu Za Zhi.* 1994 Mar; 16(2):83-7. Chinese.50: Carter P, Rodrigues ML, Lewis GD, Figari I, Shalaby MR. Related Articles Towards an immunotherapy for p185HER2 overexpressing tumors. *Adv Exp Med Biol.* 1994; 353:83-94. available.51: Deonarain MP, Epenetos AA. Targeting phosphodiesterases as a strategy for killing tumor cells. *Cell Biophys.* 1994; 24-25:249-57.52: Hayden MS, Linsley PS, Gayle MA, Bajorath J, Brady WA, Norris NA, Fell HP, Ledbetter JA, Gilliland LK. Single-chain mono- and bispecific antibody derivatives with novel biological properties and antitumor activity from a COS cell transient expression system. *Ther Immunol.* 1994 Jan; 1(1):3-15.53: Duke-Cohan JS, Morimoto C, Schlossman SF. Depletion of the helper/inducer (memory) T cell subset using a bispecific antibody-toxin conjugate directed against CD4 and CD29. *Transplantation.* 1993 Nov; 56(5):1188-96.54: Duke-Cohan JS, Morimoto C, Schlossman SF. Targeting of an activated T-cell subset using a bispecific antibody-toxin conjugate directed against CD4 and CD26. *Blood.* 1993 Oct 1; 82(7):2224-34.55: Bonardi MA, RR, Amlot P, Gromo G, Modena D, Glennie MJ. Delivery of saporin to human B-cell lymphoma using bispecific antibody: targeting via CD22 but not CD19, CD37, or immunoglobulin results in efficient killing. *Cancer Res.* 1993 Jul 1; 53(13):3015-21.56: Tazzari PL, Zhang S, Chen Q, Sforzini S, Bolognesi A, Stirpe F, Xie H, Moretta A, Ferrini S. Targeting of saporin to CD25-positive normal and neoplastic lymphocytes by an anti-saporin/anti-CD25 bispecific monoclonal antibody: in vitro evaluation. *Br J Cancer.* 1993 Jun; 67(6):1248-53.57: Brissinck J, Demanet C, Moser M, Leo O, Thielemans K. Related Articles Bispecific antibodies in lymphoma. *Int Rev Immunol.* 1993; 10(2-3):187-94. available.58: Fanger MW, Morganelli PM, Guyre PM. Use of bispecific antibodies in the therapy of tumors. *Cancer Treat Res.* 1993; 68:181-94.59: Wiener JR, Berchuck A, Bast RC. Biology and therapy with biologic agents in gynecologic cancer. *Curr Opin Oncol.* 1992 Oct; 4(5):946-54.60: Engert A, Pohl C, Diehl V. Experimental therapy in Hodgkin's disease. *Ann Oncol.* 1992 Sep; 3 Suppl 4:97-100.61: Okamoto K, Harada K, Ikeyama S, Iwasa S. Therapeutic effect of ansamitocin targeted to tumor by a bispecific monoclonal antibody. *Jpn J Cancer Res.* 1992 Jul; 83(7):761-8.62: Affleck K, Embleton MJ. Monoclonal antibody targeting of methotrexate (MTX) against MTX-resistant tumor cell lines. *Br J Cancer.* 1992 Jun; 65(6):838-44.63: Choe S, Bennett MJ, Fujii G, Curmi PM, Kantardjieff KA, Collier RJ, Eisenberg D. , Protein, Structure The crystal structure of diphtheria toxin. *Nature.* 1992 May 21; 357(6375):216-22.64: Flavell DJ, Cooper S, Morland B, R, Flavell SU. Related Articles Effectiveness of combinations of bispecific antibodies for delivering saporin to human acute T-cell lymphoblastic leukaemia cell lines via CD7 and CD38 as cellular target molecules. *Br J Cancer.* 1992 Apr; 65(4):545-51.65: Monod L, Sawamura Y, De Tribolet N. [Immunotherapy of tumors of the central nervous system]. *Neurochirurgie.* 1992; 38(2):69-79.66: Pimm MV, Robins RA, Baldwin RW. Capture of recombinant ricin A chain by a bispecific anti-RTA:anti-CEA monoclonal antibody pre-targeted to a human gastric carcinoma xenograft in nude mice. *J Cancer Res Clin Oncol.* 1992; 118(5):367-70.67: Fanger MW, Morganelli PM, Guyre PM. Bispecific antibodies. *Crit Rev Immunol.* 1992; 12(3-4):101-24.68: Efferth T, Volm M. Antibody-directed therapy of multidrug-resistant tumor cells. *Med Oncol Tumor Pharmacother.* 1992; 9(1):11-9.69: Bookman MA. Biologic therapy and immunotherapy for ovarian cancer. *Curr Opin Oncol.* 1991 Oct; 3(5):901-7.70: Azuma A, Niitani H, Okumura K. [Cancer therapy by using bispecific antibody]. *Gan To Kagaku Ryoho.* 1991 Aug; 18(10):1535-42.71: Flavell DJ, Cooper S, Morland B, Flavell SU. Characteristics and performance of a bispecific F(ab')₂ antibody for delivering saporin to a CD7 + human acute T-cell leukaemia cell line. *Br J Cancer.* 1991 Aug; 64(2):274-80.72: Embleton MJ, Charleston A, Robins RA, Pimm MV, Baldwin RW. Recombinant ricin toxin A chain cytotoxicity against carcinoembryonic antigen expressing tumor cells mediated by a bispecific monoclonal antibody and its potentiation by ricin toxin B chain. *Br J Cancer.* 1991 May; 63(5):670-4.73: RR, Courtenay AE, Ingamells S, Stevenson GT, Glennie MJ. Cooperative mixtures of bispecific F(ab')₂ antibodies for delivering saporin to lymphoma in vitro and in vivo. *Cancer Res.* 1991 May 1; 51(9):2353-61.74: Menard S, Canevari S, Colnaghi MI. Monoclonal antibodies as carriers for delivering cytotoxic agents. *Ann Ist Super Sanita.* 1991; 27(1):87-9.75: Margineanu M, Marches R, Dima S, Cialacu V, Kozma E, Savi G, Stavri H, Badea E, Bancu A, Mota G. Interleukin 2 enhances the efficiency of immunotoxins in the treatment of mice with ascitic tumors. *Neoplasma.* 1991; 38(6):633-8.76: Honda S, Ichimori Y, Iwasa S. A human hybridoma producing a bispecific monoclonal antibody that can target tumor cells for attack by *Pseudomonas aeruginosa* exotoxin A. *Cytotechnology.* 1990 Jul; 4(1):59-68.77: Le Doussal JM, Gruaz-Guyon A, Martin M, Gautherot E, Delaage M, Barbet J. Targeting of indium 111-labeled bivalent hapten to human melanoma mediated by bispecific monoclonal antibody conjugates: imaging of tumor hosted in nude mice. *Cancer Res.* 1990 Jun 1; 50(11):3445-52.78: Pal R, Singh O, Rao LV, Talwar GP. Bionutralization capacity of the antibodies generated in women by the beta subunit of human chorionic gonadotropin (beta hCG) and beta hCG associated with the alpha subunit of ovine luteinizing hormone linked to carriers. *Am J Reprod Immunol.* 1990 Mar-Apr; 22(3-4):124-6.79: Marches R, Mota G, Margineanu M, Stavri H, Savi G, Nicolae M, Bancu A, Moraru I. Treatment of murine EL4 leukemia in ascitic form with anti-Thy 1.2 specific immunotoxins. *Neoplasma.* 1990; 37(5):573-8.80: Smith W, Gore VA, Brandon DR, Lynch DN, Cranstone SA, Corvalan JR. Suppression of well-established tumor xenografts by a hybrid-hybrid monoclonal antibody and vinblastine. *Cancer Immunol Immunother.* 1990; 31(3):157-63.81: Winkler MA, Price JO, Foglesong PD, West WH. Biodistribution and plasma survival in mice of anti-melanoma monoclonal antibody cross-linked to OKT3. *Cancer Immunol Immunother.* 1990; 31(5):278-84.82: Weiner LM, O'Dwyer J, Kitson J, Comis RL, Frankel AE, Bauer RJ, Konrad MS, Groves ES. Phase I evaluation of an anti-breast carcinoma monoclonal antibody 260F9-recombinant ricin A chain immunoconjugate. *Cancer Res.* 1989 Jul 15; 49(14):4062-7.83: Nardelli B, McHugh L, Mage M. Polyacrylamide-streptavidin: a novel reagent for simplified construction of soluble multivalent macromolecular conjugates. *J Immunol Methods.* 1989 Jun 21; 120(2):233-9.84: Tsukada Y, Ohkawa K, Hibi N, Tsuzuki K, Oguma

K, Satoh H. The effect of bispecific monoclonal antibody recognizing both hepatoma-specific membrane glycoprotein and anthracycline drugs on the metastatic growth of hepatoma AH66. *Cancer Biochem Biophys*. 1989 May; 10(3):247-56.85: Srinivasachar K, Neville DM. New protein cross-linking reagents that are cleaved by mild acid. *Biochemistry*. 1989 Mar 21; 28(6):2501-9.86: Mota G, Margineanu M, Marches R, Nicolae M, Bancu A, Moraru I. Experimental model for testing the efficiency of immunotoxins administered in vivo: evaluation of two ricin A-chain-multivalent antibody immunotoxins. *Immunol Lett*. 1989 Mar; 20(4):283-91.87: Glennie MJ, Brennan DM, Bryden F, McBride HM, Stirpe F, Worth AT, Stevenson GT. Bispecific F(ab' gamma)2 antibody for the delivery of saporin in the treatment of lymphoma. *J Immunol*. 1988 Nov 15; 141(10):3662-70.88: Moa G, Nicolae M, Laky M, Bancu A, Moraru I. In vivo follow up of the cytotoxic effect of ricin toxin vectorized by multivalent hybrid antibody on target cells. *Immunol Lett*. 1988 Feb; 17(2):177-82.89: Petrella EC, Wilkie SD, Smith CA, Morgan AC, Vogel CW. Related Articles Antibody conjugates with cobra venom factor. Synthesis and biochemical characterization. *J Immunol Methods*. 1987 Nov 23; 104(1-2):159-72. Laky M, Mota G, Moraru I, Ghetie V. Binding and cytotoxic effect of ricin toxin on multivalent hybrid antibody-coated target cells. *Immunol Lett*. 1987 Jan; 14(2):127-32.

MICROGLOBULIN FUSION PROTEINS AND HIGH AFFINITY VARIANTS; WO09803552A2 A MULTIVALENT MAJOR HISTOCOMPATIBILITY COMPLEX PEPTIDE FUSION PROTEIN FOR MODULATING SPECIFIC T CELL FUNCTION; US05997869 Peptides containing a fusion joint of a chimeric protein encoded by DNA spanning a tumor-associated chromosomal translocation and their use as immunogens; **US05753262** Cationic lipid acid salt of 3beta[N-(N',N'-dimethylaminoethane) - carbamoyl]cholesterol and halogenated solvent-free preliposomal lyophilate thereof; **US06090914** CTLA4/CD28 Ig hybrid fusion proteins and uses thereof; **US05994318** Cochleate delivery vehicles; **US05844095** CTLA4 Ig fusion proteins; **US05643599** Intracellular delivery of macromolecules; **WO09806749A2 SOLUBLE MONOVALENT AND MULTIVALENT MHC CLASS II FUSION PROTEINS, AND USE THEREFOR; US06004811** Redirection of cellular immunity by protein tyrosine kinase chimeras; **US05985275** β -Lactoglobulin modified with aromatic anhydride compound for preventing HIV infection; **US05977318** CTLA4 receptor and uses thereof; **US05968510** CTLA4 receptor and uses thereof; **US05955422** Production of erythropoietin; **US05885796** CTLA4 receptor and uses thereof; **US05885579** CTLA4 receptor and uses thereof; **US05871732** Anti-CD4 antibody homologs useful in prophylaxis and treatment of AIDS, ARC and HIV infection; **US05851828** Targeted cytolysis of HIV-infected cells by chimeric CD4 receptor-bearing cells; **US05851795** Soluble CTLA4 molecules and uses thereof; **US05770197** Methods for regulating the immune response using B7 binding molecules and IL4-binding molecules; **US05707626** Methods of treating HIV infection using antibodies to the U2 small nuclear ribonuclear protein; **WO09724446A2 GENE DELIVERY VEHICLE-TARGETING LIGANDS; US05434131** Chimeric CTLA4 receptor and methods for its use; **US05348878** Class I MHC-restricted T-T hybridomas, and a CD8-transfected BW5147, fusion partner therefor; **US06165502** Protein-lipid vesicles and autogenous vaccine comprising the same; **US06147192** Tub interactor (TI) polypeptides and uses therefor; **WO00058452A1 sCrry TRANSGENIC MICE AND USES THEREOF; US06123915** Methods for using agents that bind to VCAM-1; **US06083751** Chimeric receptors for the generation of selectively-activatable TH-independent cytotoxic T cells; **EP00997477A2** MHC complexes and uses thereof; **US05958907** Pharmaceutical compositions and uses of inorganic pyrophosphates; **WO09942597A1 MONOVALENT, MULTIVALENT, AND MULTIMERIC MHC BINDING DOMAIN FUSION PROTEINS AND CONJUGATES, AND USES THEREFOR; EP00935607A2 SOLUBLE MONOVALENT AND MULTIVALENT MHC CLASS II FUSION PROTEINS, AND USES THEREFOR; WO09918129A1 SOLUBLE SINGLE-CHAIN T-CELL RECEPTOR PROTEINS; US05863797** Gene fusion encoding a hypersecretor protein; **US05834015** Protein-lipid vesicles and autogenous vaccine comprising the same; **US05827670** Methods of isolating and detecting bone marrow stromal cells with VCAM-1-specific antibodies; **US05804191** Sperm as immunogen carriers; **WO09811914A1 TARGETING ANTIGENS TO THE MHC CLASS II PROCESSING PATHWAY WITH ANTHRAX TOXIN FUSION PROTEIN; US05698679** Product and process for targeting an immune response; **US05686114** Uses of inorganic pyrophosphates; **WO09728191A1 MHC COMPLEXES AND USES THEREOF; US05580756** B7 Ig fusion protein; **US05521288** CD28 Ig fusion protein; **US05206345** IL-4 and TNF induce mAb 6G10-recognized expression on bone marrow stromal cells; **US06184025** Viral isolates associated with multiple sclerosis; **US06183745** Subunit papilloma virus vaccine and peptides for use therein; **US06165335** Biosensor device and method; **EP01054984A1 MONOVALENT, MULTIVALENT, AND MULTIMERIC MHC BINDING DOMAIN FUSION PROTEINS AND CONJUGATES, AND USES THEREFOR; US06143298** Soluble truncated forms of ICAM-1; **US06107461** Multimeric forms of human rhinovirus receptor and fragments thereof, and method of use; **US06096862** Multimeric antiviral agent; **US06071512** Infective protein delivery system; **US06071736** Process and culture medium for the production of cells infected by a multiple sclerosis-associated virus; **US06063759** Conjugate of biologically active compound and polar lipid conjugated to a microparticle for biological targeting; **US05869270** Single chain MHC complexes and uses thereof; **WO09905269A2 TRANSCRIPTIONAL SILENCER PROTEIN NRF; US05861290** Methods and polynucleotide constructs for treating host cells for infection or hyperproliferative disorders; **US05849586** Infective protein delivery system; **US05843640** Method of simultaneously detecting amplified nucleic acid sequences and cellular antigens in cells; **US05843446** Immunogenic LHRH peptide constructs and synthetic universal immune stimulators for vaccines; **US05837510** Methods and polynucleotide constructs for treating host cells for infection or hyperproliferative disorders; **US05830850** Methods for the treatment of bone resorption disorders, including osteoporosis; **US05827819** Covalent polar lipid conjugates with neurologically active compounds for targeting; **US05827516** Immunomodulatory peptides; **US05820866** Product and process for T cell regulation; **US05817315** Recombinant vaccine; **US05800980** Detection of MSRV1 virus and MSRV2 pathogen and/or infective agent associated with multiple sclerosis, by nucleic acid hybridization; **US05776746** Gene amplification methods; **US05773253** MYPPPY variants of CTL A4 and uses thereof; **US05759551** Immunogenic LHRH peptide constructs and synthetic universal immune stimulators for vaccines; **US05728540** Cytotoxic factor as is associated with multiple sclerosis, its detection and its quantification; **WO09807441A1 ALLOGENEIC HISTOCOMPATIBILITY COMPLEXES AS MEDIATORS OF CELL**

DESTRUCTION; US05705732 Universal donor cells; US05693522 Anti-cancer immunotherapeutics; US05679784 Recombinant mutants for inducing specific immune responses; US05679345 Method for preventing complement-dependent rejection of organ or tissue transplants; US05658568 Cytotoxic drug therapy; US05624895 Treatment and/or prevention of type I diabetes mellitus with gamma interferon administration; US05409825 Expansion of human hematopoietic progenitor cells in a liquid medium; US05352576 Method of determining the presence and titer of anti HIV-1 ag27 bodies; US05002869 Monoclonal antibody specific to a novel epitope of the LFA-1 antigen of human T lymphocytes; US06143298 Soluble truncated forms of ICAM-1 US05288854 Functional derivatives of ICAM-1 which are substantially capable of binding to LFA-1... US05962424 Methods and compositions for targeting selectins US05852175 P-selectin glycoprotein ligand blocking antibodies US05800815 Antibodies to P-selectin and their uses; US06130202 Antiviral methods; US06033667 Method for detecting the presence of P-selectin US05880091 Glycoprotein ligand for P-selectin and methods of use thereof US05612216 Nucleotide sequence encoding intercellular adhesion molecule-1 and fragments thereof US05891841 Methods of using intercellular adhesion molecule-3 (ICAM-3)... US05605821 Expression control sequences of the P-selectin gene US05977080 Sulfated disaccharide inhibitors of selectins,... US05834425 Use of chimeric selectins as simultaneous blocking agents... US05831036 Soluble fragments of human intercellular adhesion molecule-1 US05808025 Chimeric selectins as simultaneous blocking agents for component selectin function US05783693 Methods for synthesizing sulfated disaccharide inhibitors of selectins US05475091 R6-5-D6, an antibody which binds intercellular adhesion molecule-1 US05695760 Modified anti-ICAM-1 antibodies and their use in the treatment of inflammation US05514788 Oligonucleotide modulation of cell adhesion; US05464778 Glycoprotein ligand for P-selectin and methods of use thereof; US05919637 Method for identifying reduced binding between GMP-140 and GMP-140 ligand; US05891645 Porcine E-selectin; US05591623 Oligonucleotide modulation of cell adhesion; US06124267 O-glycan inhibitors of selectin mediated inflammation derived from PSGL-1; US06111094 Enhanced antisense modulation of ICAM-1; US05985852 Inhibition of selectin binding; WO09821591 A1 P-SELECTIN ASSAYS AND METHODS OF USE THEREOF; US05472849 Method for detecting inflammation; US05972625 Assays for inhibitors of leukocyte adhesion; US05840679 Method of inhibiting P-selectin ligand activity; US06008335 Methods of screening for ulcerative colitis and Crohn's disease; WO09943834 A2 P-SELECTIN LIGAND PROTEIN INCLUDING TETRAMERIC FUSION PROTEINS; US05916748 Method of diagnosing a clinical subtype of Crohn's disease with features of ulcerative colitis; US06191271 Synthetic divalent sLex containing polylactosamines and methods for use; US06111065 Peptide inhibitors of inflammation mediated by selectins; US06075004 Peptide compositions which induce immunotolerance and methods of use; US06037324 Inhibitors of MAdCAM-1-mediated interactions and methods of use thereof; US05962660 Sialyl Lewis X mimetics incorporating fucoseptides; US05827817 P-selectin ligand protein; US05786322 Peptides and compounds that bind selectins including endothelium leukocyte adhesion molecule 1; US05728802 Peptides and compounds that bind selectins including endothelium leukocyte adhesion molecule 1 (ELAM-1); JP09227410 A2 SUPPRESSANT FOR REJECTION IN ORGAN TRANSPLANTATION; US05643873 Peptides and compounds that bind selectins including endothelial leukocyte adhesion molecule 1; US05614615 Sialyl Lewis X mimetics incorporating fucoseptides; US05235049 Nucleic acid sequences encoding a soluble molecule (SICAM-1) related to but distinct from ICAM-1; US06037454 Humanized anti-CD11a antibodies; US06020152 Lymphocyte-associated cell surface protein; US05965544 Synthetic multivalent sLex containing polylactosamines and methods for use; WO09943353 A2 COMBINATION ANTI-SELECTIN AND IMMUNOSUPPRESSANT THERAPY; US05849699 Soluble molecule related to but distinct from ICAM-1; WO09853852 A1 P-SELECTIN TRANSLOCATION TO VASCULAR EPITHELIAL LUMEN BY IONIZING RADIATION; US05843885 ICAM-1/LFA-1 short-chain peptides and method of using same; US05843707 Nucleic acid encoding a novel P-selectin ligand protein; US05830471 Methods and compositions comprising anti-lam-1 antibodies; US05807734 Monoclonal antibodies and FV specific for CD2 antigen; US05795572 Monoclonal antibodies and FV specific for CD2 antigen; US05753631 Intercellular adhesion mediators; US05708141 Neutrophil inhibitors; US05695752 Treating inflammation via the administration of specific sulfatase enzymes and/or sulfation inhibitor; US05681699 Methods of diagnosing ulcerative colitis and Crohn's disease; US05629162 Method of identifying agents which modulate ICAM-3 binding to LFA-1; US05622701 Cross-reacting monoclonal antibodies specific for E- and P-selectin; US05622700 Method for treating a LFA-1-mediated disorder; JP06209788 A2 IMMUNOASSAY OF HUMAN SOLUBLE ICAM-1, ANTIBODY AND KIT FOR MEASUREMENT THEREOF; JP03072430 A2 ANTIVIRAL AGENT BY USING FUNCTIONAL DERIVATIVE OF INTERCELLULAR ADHESIVE MOLECULE; JP01135724 A2 TREATMENT FOR NONSPECIFIC INFLAMMATION; US06123915 Methods for using agents that bind to VCAM-1; WO09929706 A2 DISALICYLATE ANALOG BASED SIALYL LEWIS X MIMETICS; WO09918442 A1 DIAGNOSIS OF THROMBOTIC EVENTS BY DETECTING P-SELECTIN; US05877295 Antibodies which bind a subpopulation of Mac-1 (CD11b/CD18) molecules which mediate neutrophil adhesion to ICAM-1 and fibrinogen; US05869460 Sulfated and phosphorylated saccharide derivatives, process for the preparation of the same and use thereof; US05858994 Carbohydrate conjugates as inhibitors of cell adhesion; US05811405 Multiply fucosylated dicarboxylic acids possessing antiadhesive properties; US05654282 Selectin binding glycopeptides; US05632991 Antibodies specific for E-selectin and the use thereof; US05599676 Method for isolating a novel receptor for alpha.4 integrins; US05580862 Sulfate ligands for L-selectins and methods of preventing sulfate addition; US05508387 Selectin binding glycopeptides; US06177547 Antibodies to P-selectin glycoprotein ligand; WO00079010 A1 COMPOSITIONS AND METHODS FOR PREVENTING TRANSEPIITHELIAL TRANSMISSION OF HIV; US06096722 Antisense modulation of cell adhesion molecule expression and treatment of cell adhesion molecule-associated diseases; US06030947 Methods of treating p150,95-mediated inflammation and ICAM-1-mediated viral infection; US05948821 Methods of using ajoene; US05883082 Compositions and methods for preventing and treating allograft rejection; US05874233 Methods of diagnosing a clinical subtype of Crohn's disease with features of ulcerative colitis; US05854218 Sialyl Lex analogues as inhibitors of cellular adhesion; US05849896

.alpha.-subunit of the Mac-1 leukocyte adhesion receptor; US05827670 Methods of isolating and detecting bone marrow stromal cells with VCAM-1-specific antibodies; US05756095 Antibodies with specificity for a common epitope on E-selectin and L-selectin; JP10101699A2 PREPARATION OF HYBRIDOMA PRODUCING ANTIBODY BINDING TO ICAM-L OR ITS FUNCTIONAL FRAGMENT; US05658880 Sialic acid/fucose based medicaments; US05622937 Compositions and methods of inhibiting the binding of E-selectin or P-selectin or sialyl-Lewis x or sialyl-Lewis a; JP09077686A2 REMEDY OF ANESTHETIC INJURY; US05565550 Antibodies to ICAM-2, and fragments thereof; US05489578 Sulfated ligands for I-selectin and methods of treating inflammation; US05444050 Binding of E-selectin or P-selectin to sialyl-Lewis x or sialyl-Lewis a; US05272263 DNA sequences encoding vascular cell adhesion molecules (VCAMs); US05206345 IL-4 and TNF induce mAb 6G10-recognized expression on bone marrow stromal cells; US06121233 Methods for the inhibition of cancer metastasis mediated by endothelial adhesion molecules; WO00041711A1 METHODS FOR INHIBITING TUMOR METASTASIS, AND PEPTIDES USEFUL THEREFOR; WO00034255A1 SUBSTITUTED THIAZOLES FOR TREATMENT OF HUMAN DISEASES INVOLVING MODULATORS OF P-, L- AND E- SELECTIN; WO00033836A1 5-MEMBERED HETEROCYCLES FOR THE TREATMENT OF HUMAN DISEASES INVOLVING MODULATORS OF SELECTINS; WO09961033A1 BIFUNCTIONAL MOLECULES FOR BINDING AND REGULATING E-SELECTINS AND METHODS DETECTING SAME; WO09941363A1 PODOCALYXIN LIKE SIALOMUCINS HAVING SELECTIN LIGAND ACTIVITY; US05750508 Sialic acid/fucose based medicaments; US05739300 Antiadhesive piperidine- and pyrrolidinecarboxylic acids; US05736143 Anti-inflammatory, tolerogenic and immunoinhibiting properties of carbohydrate binding-peptides; US05728685 Methods of treating inflammation using cell adhesion inhibitors; US05679346 Methods of blocking adhesion with anti-lam-3 antibody; US05660992 Sialic acid/fucose based assay reagents and assay methods; US05602230 Peptide inhibitors of selectin binding; US05593882 Selectin variants; US05591835 Substituted lactose derivatives; US05576305 Intercellular adhesion mediators; US06162432 Method of prophylaxis or treatment of antigen presenting cell driven skin conditions using inhibitors of the CD2/LFA-3 interaction; US06153395 ICAM-related protein; US06132994 Lactosamine oligosaccharides and method for producing the same; US06117977 Type C lectins; EP00986401A1 P-SELECTIN TRANSLOCATION TO VASCULAR EPITHELIAL LUMEN BY IONIZING RADIATION; EP00919563A2 Synthetic Core 2-Like Branched Structures as Ligands for Selectins; US05889156 TNF deletion muteins; US05888814 Recombinant host cells encoding TNF proteins; US05874077 Human TIL cells expressing recombinant TNF pro-hormone; US05863889 ICAM-1/LFA-1 short-chain peptides and method of using same; US05863797 Gene fusion encoding a hypersecretor protein; US05861290 Methods and polynucleotide constructs for treating host cells for infection or hyperproliferative disorders; US05852170 ICAM-4 materials and methods; US05840302 Treatment of bacterially-induced inflammatory diseases; US05837822 Humanized antibodies specific for ICAM related-protein; US05837510 Methods and polynucleotide constructs for treating host cells for infection or hyperproliferative disorders; US05833990 Anti-inflammatory, tolerogenic and immunoinhibiting properties of carbohydrate binding peptides; US05830871 Inhibitors of E-, P- and L-selectin binding; EP00871670A2 INHIBITORS OF MAdCAM-1-MEDIATED INTERACTIONS AND METHODS OF USE THEREFOR; US05821340 Inducible endothelial surface protein mediating lymphoid and tumor cell adhesion: antibodies and uses; US05773293 Anti-ICAM-4 antibodies and hybridomas; - US05770686 ICAM-related protein fragments; US05756291 Aptamers specific for biomolecules and methods of making; - US05747040 Anti-inflammatory, tolerogenic and immunoinhibiting properties of carbohydrate binding-peptides US05712102 Method of screening compounds which inhibit P. gingivalis lipopolysaccharide from inhibiting the extravasation of leukocytes; US05702917 Polynucleotides encoding human ICAM-4; US05700658 ICAM-4 materials and methods; US05686265 Leukocyte adhesion receptors; WO09731625A1 INHIBITION OF SELECTIN BINDING; WO09707809A1 SULFATED DISACCHARIDE INHIBITORS OF SELECTINS METHODS FOR SYNTHESIS AND THERAPEUTIC USE; EP00759769A1 PEPTIDES AND COMPOUNDS THAT BIND SELECTINS INCLUDING ENDOTHELIUM LEUKOCYTE ADHESION MOLECULE 1 (ELAM-1); EP00758243A1 BINDING OF E-SELECTIN, P-SELECTIN OR L-SELECTIN TO SIALYL-LEWIS x OR SIALYL-LEWIS a; JP09040582A2 THERAPEUTIC AGENT FOR NEUROPATHY; US05589465 Glycolipid derivatives acting as ligands for selectins; EP00745852A1 Use of functional derivatives of the intercellular adhesion molecule ICAM-1 in anti-viral therapy; EP00720619A1 SELECTIN BINDING GLYCOPEPTIDES; US05527785 Selectin receptor modulating compositions; US05512660 Purified ICAM-2 and fragment thereof; US05484891 Selectin ligands; US05453272 Lectin derived carbohydrate binding-peptide; EP00670734A1 A SUBPOPULATION OF MAC-1 (CD11B/CD18) MOLECULES WHICH MEDIATE NEUTROPHIL ADHESION TO ICAM-1 AND FIBRINOGEN; EP00668871A1 AMINO-ACID SEQUENCE HOMOLOGIES BETWEEN SELECTINS AND B. PERTUSSIS TOXIN-PEPTIDES DERIVED THEREFROM, ANTIBODIES THERETO AND PHARMACEUTICAL COMPOSITIONS; EP00666914A1 NOVEL P-SELECTIN LIGAND PROTEIN; EP00642356A1 ANTIBODIES TO P-SELECTIN AND THEIR USES; US05395929 Isolated nucleic acid encoding the alpha subunit of the human leukocyte adhesion receptor; EP00314863B1 Use of ICAM-1 or its functional derivatives for the treatment of non-specific inflammation; US05367056 Endothelial cell-leukocyte adhesion molecules (ELAMs) and molecules involved in leukocyte adhesion (MILAs); US05304640 DNA sequence encoding a selectin ligand; EP00584229A1 GLYCAM-1 (Sgp 50), A SELECTIN LIGAND; EP00544815A1 Peptides from the GMP-140 lectin binding domain and selectin binding ligands on carbohydrates; US06193979 Compositions comprising complement receptor type 1 molecules having carbohydrate structures that are selectin ligands; EP01037653A1 COMPOSITIONS AND METHODS FOR REGULATING PHAGOCYTOSIS AND ICAM-1 EXPRESSION; US06106834 Use of anti-CD45 leukocyte antigen antibodies for immunomodulation; EP01026250A1 DNA-constructs of blood clotting factors and P-selectin; US06100383 Fusion proteins comprising ICAM-R polypeptides and immunoglobulin constant regions; US06099838 Pharmaceutical compositions comprising anti-CD45RB antibodies for the inhibition of T-cell mediated immune responses; US06090914 CTLA4/CD28 Ig hybrid fusion proteins and uses thereof; US06090840 Peptidyl compounds having MMP and TNF inhibitory activity; EP00639224B1 LECTIN DOMAIN VARIANTS OF SELECTIN; EP01010762A1 DNA constructs of blood clotting factors and P-Selectin;

EP00840606B1 DI- AND TRIVALENT SMALL MOLECULE SELECTIN INHIBITORS; WO00027420A1 COMPOSITIONS AND METHODS FOR TREATMENT OF CANCER; WO00025808A1 INHIBITION OF DIFFERENTIATION OF CYTOTOXIC-CELLS BY P-SELECTIN LIGAND (PSGL) ANTAGONISTS; US06040428 Porcine E-selectin; US06040176 Antibodies to ICAM-related protein; US06004565 Compositions and methods of using compositions with accelerated lymphocyte homing immunosuppressive properties; US05994311 Cell adhesion peptides for modifying the adhesion capacity of eukaryotic cells between each other; US05977318 CTLA4 receptor and uses thereof; US05976877 Proteins produced by human lymphocytes DNA sequence encoding these proteins and their pharmaceutical and biological uses; US05968510 CTLA4 receptor and uses thereof; US05962422 Inhibition of selectin binding; US05958705 Cytoplasmic modulators of integrin regulation/signaling; JP11246396A2 IMMUNOPOTENTIATOR; US05939525 Methods of treating inflammation and compositions therefor; US05929036 Ligand or GMP-140 selectin and methods of use thereof; EP00929670A1 P-SELECTIN LIGAND PROTEINS; US05925531 Human bone marrow endothelial cell line and methods of use thereof; US05916876 Peptide inhibitors of leukocyte adhesion; US05916803 Target cell-specific non-viral vectors for inserting genes into cells, pharmaceutical compositions comprising such vectors and their use; WO09930730A1 METHODS AND COMPOSITIONS FOR IMPROVING THE SUCCESS OF CELL TRANSPLANTATION IN A HOST; US05914112 Anti-CD18 antibodies in stroke; EP00902681A1 INHIBITION OF SELECTIN BINDING; US05885796 CTLA4 receptor and uses thereof; US05885579 CTLA4 receptor and uses thereof; US05880268 Modulators of the interaction between ICAM-R and α_d /CD18; US05879712 Method for producing drug-loaded microparticles and an ICAM-1 dosage form so produced; US05874548 Regioselective sulfation; US05874250 DNA encoding for a protein containing the extracellular domain of lymphocyte activation gene 3; US05869262 Method for monitoring an inflammatory disease state by detecting circulating ICAM-R; US05859212 Method of isolating and purifying sICAM-1; US05853722 Use of C5-specific antibodies for reducing immune and hemostatic dysfunctions during extracorporeal circulation; US05851795 Soluble CTLA4 molecules and uses thereof; EP00689599B1 CHIMERIC SELECTINS BY EXCHANGE OF DOMAINS USES THEREOF; US05844095 CTLA4 Ig fusion proteins; US05837542 Intercellular adhesion molecule-1 (ICAM-1) ribozymes; EP00488061B1 The MAC-1 binding site of ICAM-1; US05821341 Antibodies to sICAM-1; US05811517 ICAM-related protein variants; US05776707 Method for identifying and isolating cells expressing leukocyte adhesion molecule-1; EP00850243A2 PEPTIDE AND O-GLYCAN INHIBITORS OF SELECTIN MEDIATED INFLAMMATION; US05773578 Proteins produced by human lymphocytes, DNA sequence encoding these proteins and their pharmaceutical and biological use; US05773253 MYPPPY variants of CTLA4 and uses thereof; US05773218 Method to identify compounds which modulate ICAM-related protein interactions; US05770197 Methods for regulating the immune response using B7 binding molecules and IL4-binding molecules; EP00840606A1 DI- AND TRIVALENT SMALL MOLECULE SELECTIN INHIBITORS; EP00833650A1 P-SELECTIN LIGANDS AND RELATED MOLECULES AND METHODS; EP00804235A1 ANTIBODIES TO P-SELECTIN AND THEIR USES; US05652343 Method for purification of L-selectin ligands; US05648458 Peptides and compounds that bind to ELAM-1; US05648344 Methods of treating inflammation using selection binding compounds; JP09183789A2 NEW SULFATED AND PHOSPHATED SUGAR DERIVATIVE, ITS PRODUCTION AND USE; US05646248 E-selection binding soluble lamp-1 polypeptide; EP00771795A1 New glycomimetics as Selectin antagonists and anti-inflammation pharmaceutical compositions; US05624909 Derivatives of triterpenoid acids as inhibitors of cell-adhesion molecules ELAM-1 (e-selectin) and LECAM-1 (l-selectin); EP00765172A1 CROSS-REACTING MONOCLONAL ANTIBODIES SPECIFIC FOR E-SELECTIN AND P-SELECTIN; US05616488 IL-5 targeted ribozymes; EP00762886A1 ICAM-1/LFA-1 SHORT-CHAIN PEPTIDES AND METHOD OF USING SAME; US05595737 Methods for using monoclonal antibodies specific for cell-surface bound LAM-1; WO09701335A1 DI- AND TRIVALENT SMALL MOLECULE SELECTIN INHIBITORS; EP00391088B1 Use of functional derivatives of the intercellular adhesion molecule ICAM-1 in anti-viral therapy; US05580756 B7IG fusion protein; US05521288 CD28IG fusion protein; US05519008 Derivatives of triterpenoid acids as inhibitors of cell-adhesion molecules ELAM-1 (E-selectin) and LECAM-1 (L-selectin); EP00379904B1 A soluble molecule related to but distinct from ICAM-1; US05489533 Isolated nucleic acid molecules encoding ICAM-2; US05487112 Method and apparatus for time-resolved measurements of lymphocyte function and aggregate structure using computer-automated microscopy; EP00691813A1 DERIVATIVES OF TRITERPENOID ACIDS AS INHIBITORS OF CELL-ADHESION MOLECULES ELAM-1 (E-SELECTIN) AND LECAM-1 (L-SELECTIN); EP00689599A1 CHIMERIC L- AND P-SELECTIN BY EXCHANGE OF DOMAINS - USES THEREOF; EP00671951A1 HUMANIZED ANTIBODIES REACTIVE WITH L-SELECTIN; EP00668907A1 GLYCOPROTEIN LIGAND FOR P-SELECTIN AND METHODS OF USE THEREOF; US05434131 Chimeric CTLA4 receptor and methods for its use; EP00656904A1 PEPTIDE INHIBITORS OF SELECTIN BINDING; EP00652897A1 PEPTIDE INHIBITORS OF SELECTIN BINDING; EP00639224A1 LECTIN DOMAIN VARIANTS OF SELECTIN; US05389520 Specific detection of cell surface receptor leukocyte adhesion molecule-1; EP00608260A1 PEPTIDE INHIBITORS OF INFLAMMATION MEDIATED BY SELECTINS; US05324510 Use of antibodies to intercellular adhesion molecule-1 (ICAM-1) in the treatment of asthma; EP00602194A1 PEPTIDE INHIBITORS OF INFLAMMATION MEDIATED BY SELECTINS; US05318890 Assays for inhibitors of leukocyte adhesion; US05316913 Neutrophil LECAM-1 as indicator of neutrophil activation; US05284931 Intercellular adhesion molecules, and their binding ligands; EP00488061A3 The MAC-1 binding site of ICAM-1; EP00488061A2 The MAC-1 binding site of ICAM-1; EP00391088A3 Use of functional derivatives of the intercellular adhesion molecule ICAM-1 in anti-viral therapy; EP00391088A2 Use of functional derivatives of the intercellular adhesion molecule ICAM-1 in anti-viral therapy; EP00379904A1 A soluble molecule related to but distinct from ICAM-1; US06194557 Nucleic acid molecules encoding Bap-1 proteins; US06183988 Leukocyte-specific protein and gene, and methods of use thereof; US06177475 Methods of using integrin modulators for treatment of inflammation; US06174914 Method of inhibiting cytokine release from human ocular cells; US06156878 Ligand (ACT-4-L) to a receptor on the surface of activated CD4+ T-cells; US06136790 Carbohydrate mimetics having antiadhesive properties; US06133239 Carbohydrate ligands (myelorrillin) that

cause E-selectin dependent cell rolling and adhesion under dynamic flow system; US06132764 Targeted polymerized liposome diagnostic and treatment agents; WO00060055A1 MODIFIED DENDRITIC CELLS AND USES THEREFOR; US06114517 Methods of modulating tumor necrosis factor α -induced expression of cell adhesion molecules; US06111093 CD19 coding sequences; US06111084 Fuo peptide mimetics; US06110922 Cell adhesion-inhibiting antiinflammatory and immune-suppressive compounds; US06110897 Antiinflammatory cell adhesion inhibitors; US06107365 Biomimetic hydrogel materials; US06107046 Antibodies to α , a receptor tyrosine kinase and uses thereof; WO00043023A1 PHARMACEUTICAL COMPOSITION WITH ADHESION MOLECULE EXPRESSION REGULATING ACTIVITY; US06068829 Method of identifying molecules that home to a selected organ in vivo; US06066321 Method for antagonizing vascular adhesion protein-1 (VAP-1)-mediated binding of endothelial cells to lymphocytes; US06063906 Antibodies to integrin α subunit; US06063585 TRAF Inhibitors; US06060588 Bap-1 proteins; US06060303 TRAF inhibitors; US06060056 Composition for inducing humoral energy to an immunogen comprising a T cell epitope-deficient analog of the immunogen conjugated to a nonimmunogenic valency platform molecule; US06057423 Integrin α subunit; US06051598 Amino ceramide-like compounds and therapeutic methods of use; US06051428 Rapid production of autologous tumor vaccines; US06046046 Compositions, methods and devices for maintaining an organ; US06043094 Therapeutic liposome composition and method; US06040332 Amino ceramide-like compounds and therapeutic methods of use; US06040147 Systemic inflammatory markers as diagnostic tools in the prevention of atherosclerotic diseases and as tools to aid in the selection of agents to be used for the prevention and treatment of atherosclerotic disease; US06034238 Heterocyclic compounds, their preparation and their use as leucocyte adhesion inhibitors and VLA-4-antagonists; US05998598 Immuno adhesins and methods of production and use thereof; US05997865 Agonist antibodies against the flk2/flt3 receptor and uses thereof; US05993816 Methods to inhibit humoral immune responses, immunoglobulin production and B cell activation with 5c8-specific antibodies; US05993800 Methods for prolonging the expression of a heterologous gene of interest using soluble CTLA4 molecules and an antiCD40 ligand; US05977303 Mammalian cell surface antigens; US05968755 Methods for determining T-cell profiles of immunocompromised subjects; EP00948597A1 HUMAN MUCOSAL ADDRESSIN CELL ADHESION MOLECULE-1 (MAdCAM-1) AND SPLICE VARIANTS THEREOF; US05955291 Antibodies recognizing tie receptor tyrosine kinase and uses thereof; US05932214 Treatment for inflammatory bowel disease with VLA-4 blockers; US05928643 Method of using CD2-binding domain of lymphocyte function associated antigen 3 to initiate T cell activation; US05922570 Cytoplasmic Modulators of Integrin Binding/Signalling; US05919768 Di- and trivalent small molecule selectin inhibitors; US05914111 CD2-binding domain of lymphocyte function associated antigen-3; US05904920 Regulation of systemic immune responses utilizing cytokines and antigens; US05888969 Use of cytokine restraining agents to treat inflammatory bowel disease; US05876715 Antibodies that bind novel carbohydrate ligands (myelorollins) that cause E-selectin dependent cell rolling, and uses thereof; US05871734 Treatment for asthma with VLA-4 blocking agents; US05869619 Modified antibody variable domains; US05869453 Cytotoxic T-cell epitopes; US05861151 Soluble fusion molecules with binding specificity for cell adhesion molecules; US05851989 Method of extending the plasma half-life of vascular endothelial cell growth factor; US05843441 Use of endothelial-leukocyte adhesion molecule-1 specific antibodies in the treatment of asthma; WO09853049A1 VASCULAR ADHESION PROTEIN-1 HAVING AMINE OXIDASE ACTIVITY; JP10295375A2 SOLUBLE LFA-1 PROTEIN; US05831029 Human α 2232; integrin α subunit; US05821332 Receptor on the surface of activated CD4 + T-cells: ACT-4; US05821123 Modified antibody variable domains; EP00868197A1 ANTI-SELECTIN ANTIBODIES FOR PREVENTION OF MULTIPLE ORGAN FAILURE AND ACUTE ORGAN DAMAGE; US05817515 Human B2 integrin α subunit antibodies; WO09842750A1 ANTIGENIC FUSION PROTEIN CARRYING GAL. α 1,3 GAL EPI TOPES; US05811300 TNF- α ribozymes; US05807745 Method of inhibiting PADGEM-mediated or ELAM-1-mediated leukocyte adhesion using an inhibitor comprising a Lex core component; US05792444 Labeled chemotactic peptides to image focal sites of infection or inflammation; EP00528931B1 HUMANIZED CHIMERIC ANTI-ICAM-1 ANTIBODIES, METHODS OF PREPARATION AND USE; US05776775 Anti-LAM 1-3 antibody and hybridoma; US05776755 FLT4, a receptor tyrosine kinase; US05766850 Human α 2232; integrin α subunit; US05766585 Systemic gene treatment of connective tissue diseases with IRAP-1; US05759855 Methods for modifying the binding activity of cell adhesion receptors; JP10130240A2 INHIBITOR OF ICAM-1-PRODUCTION; US05741667 Tumor necrosis factor receptor-associated factors; US05730983 Use of intercellular adhesion molecules, and their binding ligands in the treatment of asthma; US05730978 Inhibition of lymphocyte adherence with lpha.4 α 2231; α -specific antibodies; US05728533 Human β 2 integrin α subunit; US05693483 Cytoplasmic modulators of integrin binding/signalling; US05688656 Cytokine-induced marker for inflammatory response; JP09216902A2 NOVEL CARBOHYDRATE LIGAND (MYE LOROLLIN) THAT CAUSES E-SELECTIN DEPENDENT CELL ROLLING AND ADHESION UNDER DYNAMIC FLOW SYSTEM; US05650396 Methods of modulating inflammatory cytokines in the CNS using TGF- β ; US05629412 Synthetic glycoamines that promote or inhibit cell adhesion; US06068829 Method of identifying molecules that home to a selected organ in vivo; US06066321 Method for antagonizing vascular adhesion protein-1 (VAP-1)-mediated binding of endothelial cells to lymphocytes; US06063906 Antibodies to integrin α subunit; US06063585 TRAF Inhibitors; US06060588 Bap-1 proteins; US06060303 TRAF inhibitors; US06060056 Composition for inducing humoral energy to an immunogen comprising a T cell epitope-deficient analog of the immunogen conjugated to a nonimmunogenic valency platform molecule; US06057423 Integrin α subunit; US06051428 Rapid production of autologous tumor vaccines; US06043094 Therapeutic liposome composition and method; US06034238 Heterocyclic compounds, their preparation and their use as leucocyte adhesion inhibitors and VLA-4-antagonists; US05998598 Immuno adhesins and methods of production and use thereof; US05997865 Agonist antibodies against the flk2/flt3 receptor and uses thereof; US05993816 Methods to inhibit humoral immune responses, immunoglobulin production and B cell activation with 5c8-specific antibodies; US05993800 Methods for prolonging the expression of a heterologous gene of interest using soluble CTLA4 molecules and an antiCD40

ligand; US05968755 Methods for determining T-cell profiles of immunocompromised subjects; EP00948597A1 HUMAN MUCOSAL ADDRESSIN CELL ADHESION MOLECULE-1 (MAdCAM-1) AND SPLICE VARIANTS THEREOF; recognizing tie receptor tyrosine kinase and uses thereof; US05951982 Methods to suppress an immune response with variant CD44-specific antibodies; US05932214 Treatment for inflammatory bowel disease with VLA-4 blockers; US05928643 Method of using CD2-binding domain of lymphocyte function associated antigen 3 to initiate T cell activation; US05904920 Regulation of systemic immune responses utilizing cytokines and antigens; US05888978 Method for reducing the severity of gastro-intestinal damage; US05888969 Use of cytokine restraining agents to treat inflammatory bowel disease; US05876715 Antibodies that bind novel carbohydrate ligands(myelorrins) that cause E-selectin dependent cell rolling, and uses thereof; US05871734 Treatment for asthma with VLA-4 blocking agents; US05869619 Modified antibody variable domains; US05869453 Cytotoxic T-cell epitopes; US05861151 Soluble fusion molecules with binding specificity for cell adhesion molecules; US05851989 Method of extending the plasma half-life of vascular endothelial cell growth factor; US05843441 Use of endothelial-leukocyte adhesion molecule-1 specific antibodies in the treatment of asthma; WO09853049A1 VASCULAR ADHESION PROTEIN-1 HAVING AMINE OXIDASE ACTIVITY; JP10295375A2 SOLUBLE LFA-1 PROTEIN; US05831029 Human α 2232; integrin .alpha. subunit; US05821332 Receptor on the surface of activated CD4 + T-cells: ACT-4; US05821123 Modified antibody variable domains; EP00868197A1 ANTI-SELECTIN ANTIBODIES FOR PREVENTION OF MULTIPLE ORGAN FAILURE AND ACUTE ORGAN DAMAGE; US05817515 Human B2 integrin alpha subunit antibodies; US05807745 Method of inhibiting PADGEM-mediated or ELAM-1-mediated leukocyte adhesion using an inhibitor comprising a Lex core component; EP00528931B1 HUMANIZED CHIMERIC ANTI-ICAM-1 ANTIBODIES, METHODS OF PREPARATION AND USE; US05776775 Anti-LAM 1-3 antibody and hybridoma; US05776755 FLT4, a receptor tyrosine kinase; US05770196 Modified antibody variable domains and therapeutic uses thereof; US05766886 Modified antibody variable domains; US05766854 Method for identifying active domains and amino acid residues in polypeptides and hormone variants; US05759855 Methods for modifying the binding activity of cell adhesion receptors; US05741667 Tumor necrosis factor receptor-associated factors; US05730983 Use of intercellular adhesion molecules, and their binding ligands in the treatment of asthma; US05730978 Inhibition of lymphocyte adherence with α 42231; -specific antibodies; US05728533 Human β 2 integrin .alpha. subunit; US05693483 Cytoplasmic modulators of integrin binding/signalling; US05688656 Cytokine-induced marker for inflammatory response; JP09216902A2 NOVEL CARBOHYDRATE LIGAND (MYELOTOLLIN) THAT CAUSES E-SELECTIN DEPENDENT CELL ROLLING AND ADHESION UNDER DYNAMIC FLOW SYSTEM; US05650396 Methods of modulating inflammatory cytokines in the CNS using TGF- β ; US05648465 Cloning and expression of neurocan, chondroitin sulfate proteoglycan; US05646250 Cadherin polypeptides; US05646123 Time dependent administration of oligosaccharide glycosides related to blood group determinants having a type I or type II core structure in reducing inflammation in a sensitized mammal arising from exposure to an antigen; US05629412 Synthetic glycoamines that promote or inhibit cell adhesion. Examples of tumor specific antigens are numerous and are referred to in the hereinabove cited references and as well as the in the following references. US0608370307/04/2000 Identification of TRP-2 as a human tumor antigen recognized by cytotoxic T lymphocytes; US0613298010/17/2000 Antibodies specific for TRP-2 a human tumor antigen recognized by cytotoxic T lymphocytes; US0583101611/03/1998 Identification of TRP-2 as a human tumor antigen recognized by cytotoxic T lymphocytes; US0593221008/03/1999 Recombinant adenoviral vector and methods of use; US0590707805/25/1999 Transgenic mouse model for prostate cancer; US0569352212/02/1997 Anti-cancer immunotherapeutics; US05635473 06/03/1997 Inhibitor of hepatitis B virus replication; US0608711007/11/2000 Alternative open reading frame DNA of a normal gene and a novel human cancer antigen encoded therein; US0607465006/13/2000 Membrane anchor/active compound conjugate, its preparation and its uses; US0576658806/16/1998 Tumor immunotherapy using anti-idiotype antibodies; US0575634905/26/1998 Production of erythropoietin; US0561461003/25/1997 Tumor immunotherapy using anti-idiotype antibodies; US0535484710/11/1994 Chimeric antibody with specificity to human tumor antigen; US0530681104/26/1994 Squamous cell carcinoma-like immunoreactive antigen from human female urine; US0520814605/04/1993 Murine monoclonal anti-idiotype antibodies; US0491816404/17/1990 Tumor immunotherapy using anti-idiotype antibodies; US0440304009/06/1983 Diagnostic test for the detection of a specific tumor antigen with CoA-SPC; US0616546412/26/2000 Monoclonal antibodies directed to the HER2 receptor; US0615630512/05/2000 Implanted tumor cells for the prevention and treatment of cancer; US06096520 08/01/2000 Brain glycogen phosphorylase cancer antigen; US0605456104/25/2000 Antigen-binding sites of antibody molecules specific for cancer antigens; US0602496402/15/2000 Membrane anchor/active compound conjugate, its preparation and its uses; US0600454812/21/1999 Analogs of pluripotent granulocyte colony-stimulating factor; US0595197509/14/1999 Induction of CTLs specific for natural antigens by cross priming immunization; US0587730503/02/1999 DNA encoding biosynthetic binding protein for cancer marker; US0584083911/24/1998 Alternative open reading frame DNA of a normal gene and a novel human cancer antigen encoded therein; US0583070511/03/1998 Method for recombinant production of human pluripotent granulocyte colony-stimulating factor; US0582431110/20/1998 Treatment of tumors with monoclonal antibodies against oncogene antigens; US0580798909/15/1998 Methods for treatment or diagnosis of diseases or disorders associated with an APB domain; US0578896308/04/1998 Isolation and/or preservation of dendritic cells for prostate cancer immunotherapy; US0567694110/14/1997 Methods of enhancing bone marrow transplantation and treating burn wounds comprising administering human pluripotent granulocyte colony-stimulating factor; US0566290709/02/1997 Induction of anti-tumor cytotoxic T lymphocytes in humans using synthetic peptide epitopes; US0553222007/02/1996 Genetic mechanisms of tumor suppression; US0552767606/18/1996 Detection of loss of the wild-type P53 gene and kits therefor; US0549683103/05/1996 Inhibition of insulin-induced adiposis; US0524867109/28/1993 Methods and compositions for treatment of cancer using oligonucleotides; US0484950907/18/1989 Monoclonal antibodies against melanoma-associated antigens and hybrid cell lines producing these antibodies; US0459155205/27/1986 Detection of hepatitis B surface antigen (or antibody

to same) with labeled synthetic peptideUS0458427804/22/1986 Antigen derived from human ovarian tumors andradioimmunoassay using the antigenUS0404375708/23/1977 Method for detection of human mammarycarcinomaUS0619775403/06/2001 Suppression of tumor growth by a mini-E1AgeneUS0618730702/13/2001 Cancer immunotherapy with semi-allogeneiccellsUS0618374602/06/2001 Immunogenic peptides from the HPV E7 proteinUS0618061201/30/2001 Methods and compositions for targeting DNAmetabolic processes using aminoglycoside derivativesUS0617726701/23/2001 Acetyl-CoA carboxylase from wheatUS0614687711/14/2000 Identification of the progression elevatedgene-3 and uses thereofUS0614329711/07/2000 Methods of promoting immunopotential andpreparing antibodies with anti-CD3 antibodiesUS0614012610/31/2000 Antisense modulation of Y-box binding protein 1expressionUS0614005810/31/2000 Activation of p53 proteinUS0614005010/31/2000 Methods for determining breast cancer andmelanoma by assaying for a plurality of antigens associatedtherewithUS0613658010/24/2000 β -1-6-N-acetylglucosaminyltransferase thatforms core 2, core 4 and I branchesUS0613271810/17/2000 Multi-stage cascade boosting vaccineUS0611390109/05/2000 Methods of stimulating or enhancing the immunesystem with anti-CD3 antibodiesUS0611074408/29/2000 Diminishing viral gene expression by promoterreplacementUS0611074308/29/2000 Development and use of human pancreatic celllinesUS0610747408/22/2000 Nucleotide sequence encoding a 14 kDa proteinfrom goat liverUS0609078907/18/2000 Synthesis of the breast tumor-associatedantigen defined by monoclonal antibody MBr1 and uses thereofUS0608744107/11/2000 Structurally modified peptides that areresistant to peptidase degradationUS0608717107/11/2000 Method for inducing DNA synthesis in neuronsUS0608408507/04/2000 Inducing resistance to tumor growth withsoluble IGF-1 receptorUS0608040906/27/2000 Immunostimulatory methodUS0608039906/27/2000 Vaccine adjuvants for immunotherapy ofmelanomaUS0607795006/20/2000 Methods for enhancing an immune response from a43 KD human cancer antigenUS0606923105/30/2000 PR domain peptidesUS0606390005/16/2000 Isolated tumor rejection antigen precursorMAGE-2 derived peptides, and uses thereofUS0606337905/16/2000 Anti-idiotypic monoclonal antibodies andcompositions including the anti-idiotypic monoclonal antibodiesUS0606023805/09/2000 Method and composition for regulatingapoptosisUS0605446704/25/2000 Down-regulation of DNA repair to enhancesensitivity to P53-mediated apoptosisUS0605169304/18/2000 CLNH11-specific antibodiesUS0605139604/18/2000 Method for producing retinoblastoma geneprotein productsUS0605138704/18/2000 Methods of determining the presence of aneoplasm with CLNH5- and CLNH11-specific antibodiesUS0605122904/18/2000 Human-human hybridom for neoplasms CLNH5 andCLNH11 specific antibody compositionsUS0605122604/18/2000 MN-specific antibodies and their use in cancertreatmentUS0604600704/04/2000 Method and composition for regulatingapoptosisUS0603713403/14/2000 Methods that detect compounds that disruptreceptor tyrosine kinase/GRB-7 complexesUS0603421403/07/2000 Isolated nonapeptides which bind to HLAmolecules and provoke lysis by cytolytic T cellsUS0602792402/22/2000 Isolated nucleic acid molecule coding for tumorrejection antigen precursor MAGE-C1 and uses thereofUS0602791602/22/2000 Galectin 9 and 10SV PolynucleotidesUS0602547402/15/2000 Isolated nucleic acid molecules coding fortumor rejection antigen precursor mage-3 and uses thereofUS0602295802/08/2000 cDNAs coding for members of thecarcinoembryonic antigen familyUS0602269202/08/2000 Method for screening for possible presence ofcancerUS0602014502/01/2000 Methods for determining the presence ofcarcinoma using the antigen binding region of monoclonal antibodyBR96US0601998702/01/2000 Isolated, MAGE-3 derived peptides which complexwith HLA-A2 molecules and uses thereofUS0601754001/25/2000 Prevention and treatment of primary andmetastatic neoplastic diseases and infectious diseases with heatshock/stress protein-peptide complexesUS0601566501/18/2000 Method and composition for regulatingapoptosisUS0601556701/18/2000 HER2 extracellular domainUS0601377201/11/2000 Antibody preparations specifically binding tounique determinants of CEA antigens or fragments thereof and use ofthe antibody preparations in immunoassaysUS0601348101/11/2000 Isolated, nucleic acid molecules which code forage tumor rejection antigen, the tumor rejection antigen, and usesthereofUS0601325801/11/2000 Immunogenic peptides from the HPV E7 proteinUS0600799112/28/1999 Antisense oligonucleotides formitogen-activated protein kinases as therapy for cancerUS0600158312/14/1999 Methods for disrupting GRB-7 complexesUS0599820512/07/1999 Vectors for tissue-specific replicationUS0599412611/30/1999 Method for in vitro proliferation of dendriticcell precursors and their use to produce immunogensUS0599406211/30/1999 Epithelial protein and DNA thereof for use inearly cancer detectionUS0598527011/16/1999 Adoptive immunotherapy using macrophagessensitized with heat shock protein-epitope complexesUS0598157511/09/1999 Inhibition of fatty acid synthase as a means toreduce adipocyte massUS0598089611/09/1999 Antibodies reactive with human carcinomasUS0595527509/21/1999 Methods for identifying nucleic acid sequencesencoding agents that affect cellular phenotypesUS0595507509/21/1999 Method of inhibiting tumor growth usingantibodies to MN proteinUS0595248809/14/1999 Androgen regulation with DNA sequences of ratprobasin geneUS0593242108/03/1999 Methods and cell lines for identification ofregulators of integrin activationUS0591976407/06/1999 Compounds that bind to p185 and methods ofusing the sameUS0591712406/29/1999 Transgenic mouse model of prostate cancerUS0591438906/22/1999 E6 associated proteinUS0591214306/15/1999 Polynucleotides encoding a human mage proteinhomologUS0591062606/08/1999 Acetyl-CoA carboxylase compositions and methodsof useUS0587456002/23/1999 Melanoma antigens and their use in diagnosticand therapeutic methodsUS0587221702/16/1999 Antibodies which specifically bind a cancerrelated antigenUS0586963602/09/1999 Immunoreactive peptide sequence from a 43 kDhuman cancer antigenUS0586904502/09/1999 Antibody conjugates reactive with humancarcinomasUS0586612402/02/1999 Antiidiotypic antibodies for high molecularweight-melanoma associated antigenUS0586401101/26/1999 Cancer related antigenUS0586138101/19/1999 Pharmaceutical composition for the treatment ofa malignant tumorUS0585611201/05/1999 Method for selectively inducing biomarkerexpression in urologic tumor tissue for

diagnosis and treatment thereof US05856091 01/05/1999 Isolated nucleic acid sequence coding for a tumor rejection antigen precursor processed to at least one tumor rejection antigen presented by HLA-A2 US05851991 12/22/1998 Therapeutic use of the retinoblastoma susceptibility gene product US05851764 12/22/1998 Human prostate tumor inducing gene-1 and use thereof US05851523 12/22/1998 Isolated, peptides derived from MAGE tumor rejection antigen precursors which complex with HLA-A2 molecules and uses thereof US05849517 12/15/1998 Method and composition for preserving antigens and nucleic acids and process for utilizing cytological material produced by same US05847083 12/08/1998 Modified p53 constructs which enhance DNA binding US05844075 12/01/1998 Melanoma antigens and their use in diagnostic and therapeutic methods US05843685 12/01/1998 Production of chimeric mouse-human antibodies with specificity to human tumor antigens US05843648 12/01/1998 P15 and tyrosinase melanoma antigens and their use in diagnostic and therapeutic methods US05840854 11/24/1998 Monoclonal antibody BR110 and uses thereof US05837846 11/17/1998 Biosynthetic binding proteins for immunotargeting US05837231 11/17/1998 GM-CSF administration for the treatment and prevention of recurrence of brain tumors US05831008 11/03/1998 Retinoblastoma protein-interacting zinc finger proteins US05830470 11/03/1998 Humanized antibodies to ganglioside GM2 US05830464 11/03/1998 Compositions and methods for the treatment and growth inhibition of cancer using heat shock/stress protein-peptide complexes in combination with adoptive immunotherapy US05827666 10/27/1998 Synthetic multiple tandem repeat mucin and mucin-like peptides, and uses thereof US05824658 10/20/1998 Topical composition containing hyaluronic acid and NSAIDS US05821070 10/13/1998 Antibodies reactive with retinoblastoma binding proteins and methods of using same US05817513 10/06/1998 Anti ganglioside monoclonal antibodies US05811304 09/22/1998 Nucleic acid molecules encoding retinoblastoma protein-interacting zinc finger proteins US05811099 09/22/1998 Method and composition for preserving antigens and process for utilizing cytological material produced by same US05808005 09/15/1998 Human carcinoma antigen US05801233 09/01/1998 Nucleic acid compositions encoding acetyl-coacetylase and uses thereof US05798229 08/25/1998 Bispecific molecules recognizing lymphocyte antigen CD2 and tumor antigens US05798090 08/25/1998 Enhancement of the cellular immune response US05792456 08/11/1998 Mutant BR96 antibodies reactive with human carcinomas US05783681 07/21/1998 Androgen regulation with DNA sequences of rat probasin gene US05773579 06/30/1998 Lung cancer marker US05772997 06/30/1998 Monoclonal antibodies directed to the HER2 receptor US05770374 06/23/1998 Methods for identifying oncogenes and anti-oncogenes US05770195 06/23/1998 Monoclonal antibodies directed to the her2 receptor US05766910 06/16/1998 Expression of the developmental I antigen by a cloned human cDNA encoding a member of a beta-1,6-N-acetylglucosaminyltransferase gene family US05766571 06/16/1998 Method of treating human breast cancer by administration of radiolabeled antibody and unsaturated fatty acids US05763224 06/09/1998 Decay accelerating factor (DAF) and nucleic acids encoding it US05759837 06/02/1998 Chemotherapy for cancer by inhibiting the fatty acid biosynthetic pathway US05759791 06/02/1998 Cancer related antigen US05753260 05/19/1998 Vaccines against sterols US05753204 05/19/1998 Biosynthetic binding proteins for immunotargeting US05750395 05/12/1998 DNA encoding MAGE-1 C-terminal cytotoxic lymphocyte immunogenic peptides US05747650 05/05/1998 P53AS protein and antibody thereof US05747268 05/05/1998 Tumor marker control US05747072 05/05/1998 Adenoviral-mediated gene transfer to synovial cells in vivo US05744144 04/28/1998 Synthetic multiple tandem repeat mucin and mucin-like peptides, and uses thereof US05741648 04/21/1998 Cell analysis method using quantitative fluorescence image analysis US05733721 03/31/1998 Cell analysis method using quantitative fluorescence image analysis US05731420 03/24/1998 Antibodies to human I-branching beta-1,6-N-acetylglucosaminyltransferase US05728821 03/17/1998 Mutant BR96 antibodies reactive with human carcinomas US05725856 03/10/1998 Monoclonal antibodies directed to the HER2 receptor US05723333 03/03/1998 Human pancreatic cell lines: developments and uses US05721340 02/24/1998 p53 proteins with altered tetramerization domains US05720954 02/24/1998 Monoclonal antibodies directed to the HER2 receptor US05720937 02/24/1998 In vivo tumor detection assay US05714170 02/03/1998 Method of inducing resistance to tumor growth US05705159 01/06/1998 Immunoreactive peptide sequence from a 43 KD human cancer antigen US05705157 01/06/1998 Methods of treating cancerous cells with anti-receptor antibodies US05695994 12/09/1997 Isolated cytolytic T cells specific for complexes of MAGE related peptides and HLA molecules US05693763 12/02/1997 Antibodies to human carcinoma antigen US05693617 12/02/1997 Inhibitors of the 26S proteolytic complex and the 20S proteasome contained therein US05693511 12/02/1997 Immortalized human fetal osteoblastic cells US05691175 11/25/1997 Immortalized human fetal osteoblastic cells US05688488 11/18/1997 Composition and method for tumor imaging US05686068 11/11/1997 Isolated peptides derived from MAGE-2, cytolytic T cells specific to complexes of peptide and HLA-A2 molecules, and uses thereof US05684134 11/04/1997 Antibody specific for ࢷ.fw.darw.6N-acetylglucosaminyltransferase US05683886 11/04/1997 Tumor rejection antigens which correspond to amino acid sequences in tumor rejection antigen precursor bage, and uses thereof US05681701 10/28/1997 Immortalized human fetal osteoblastic cells US05681562 10/28/1997 Lymphokine gene therapy of cancer US05677171 10/14/1997 Monoclonal antibodies directed to the HER2 receptor US05674486 10/07/1997 Cancer immunotherapy with carrier cells US05665874 09/09/1997 Cancer related antigen US05665357 09/09/1997 Antibodies recognizing tumor associated antigen CA 55.1 US05663144 09/02/1997 Compounds that bind to p185 and methods of using the same US05658778 08/19/1997 ࢷ.6 N-acetylglucosaminyl, transferase, its acceptor molecule, leukosialin, and a method for cloning protein having enzymatic activity US05658774 08/19/1997 IRF-1 DNA expression inhibits growth of cells expressing c-myc or FosB US05648226 07/15/1997 Isolated peptides derived from tumor rejection antigens, and their use US05645835 07/08/1997 Therapeutic antibody based fusion proteins US05633142 05/27/1997 WT1 monoclonal antibodies and methods of use thereof US05624832 04/29/1997 ࢷ.6 N-acetylglucosaminyltransferase, its acceptor molecule, leukosialin, and a method for cloning protein having enzymatic activity US05624820 04/29/1997 Episomal expression vector for human gene therapy US05622836 04/22/1997

Monoclonal antibodies which recognize malignant cells from bladder carcinomas US0562088604/15/1997 Isolated nucleic acid sequence coding for a tumor rejection antigen precursor processed to at least one tumor rejection antigen presented by HLA-A2 US0561001303/11/1997 Method for diagnosing a disorder by determining expression of a tumor rejection antigen precursor US0559143001/07/1997 Isolated, MAGE-3 derived peptides which complex with HLA-A2 molecules and uses thereof US0558957912/31/1996 Gene sequence and probe for a marker of non-small cell lung carcinoma US0557392511/12/1996 P53 proteins with altered tetramerization domains US0557171111/05/1996 Isolated nucleic acid molecules coding for BAG tumor rejection antigen precursors US0556554810/15/1996 Pre-S gene coded peptide hepatitis B immunogens and synthetic lipid vesicle carriers US0555472409/10/1996 Isolated tumor rejection antigen precursor MAGE-2 derived peptides, and uses thereof US0555450609/10/1996 Isolated, MAGE-3 derived peptides which complex with HLA-A2 molecules and uses thereof US0555229309/03/1996 Tumor antigen specific antibody US0554553208/13/1996 Human carcinoma antigen (HCA), HCA antibodies, HCA immunoassays and methods of imaging US0553425407/09/1996 Biosynthetic binding proteins for immuno-targeting US0553234807/02/1996 E6 associated protein and methods of use thereof US0552128505/28/1996 CTAA 28A32, the antigen recognized by MCA28A32 US0549500202/27/1996 Tumor associated monoclonal antibody 123AV16 US0548952502/06/1996 Monoclonal antibodies to prostate cells US0548645601/23/1996 Method of diagnosing ovarian, endometrial, and colon cancers with monoclonal antibodies OXA and OXB US0548459001/16/1996 Expression of the developmental I antigen by a cloned human cDNA encoding a member of α -1,6-N-acetylglucosaminyltransferase gene family US0547475512/12/1995 Tumor associated monoclonal antibodies US0546079710/24/1995 Method for fixing tissues and cells for analysis using oxazolidine compounds US0545907310/17/1995 Method and composition for preserving antigens and process for utilizing cytological material produced by same US0541188405/02/1995 Monoclonal antibody L53 which recognizes a human tumor-associated antigen US0537454812/20/1994 Methods and compositions for the attachment of proteins to liposomes using a glycosphospholipid anchor US0535903110/25/1994 Unique protein marker for bladder cancer US0533883208/16/1994 Antigen recognized by MCA 16-88 US0522715907/13/1993 Anti-idiotypic antibodies reactive with shared idiotopes expressed by B cell lymphomas and autoantibodies US0522161206/22/1993 Unique protein marker for bladder cancer US0521786406/08/1993 Replication initiator protein complex and methods of use thereof US0520409604/20/1993 Pre-S gene coded peptide hepatitis B immunogens, vaccines, diagnostics, and synthetic lipid vesicle carriers US0520050804/06/1993 Cell surface antigen that binds with L6 monoclonal antibody US0519253703/09/1993 Method of treating renal cell carcinoma using activated mononuclear cells, renal tumor antigen and cimetidine US0517166512/15/1992 Monoclonal antibody to novel antigen associated with human tumors US0513407507/28/1992 Monoclonal antibody to novel antigen associated with human tumors US0503961108/13/1991 Monoclonal antibodies to superficial papillary bladder tumor cells US0502655706/25/1991 Adjuvant composition US0501938305/28/1991 Fatty acid carriers for synthetic peptides US0501664405/21/1991 Urine testing module and method of collecting urine antigen US0500304603/26/1991 Monoclonal antibody producing hybridoma and corresponding antibody specific for human breast fibroblast tumor antigen US0496071610/02/1990 Monoclonal antibodies specific for 330 KDa breast tumor antigen and assay using said monoclonal antibodies US0495932009/25/1990 Monoclonal antibody, process for preparing same, reagent for detecting cancer antigen containing the monoclonal antibody and process for preparing same US0492179005/01/1990 Tumor specific assay for CA125 ovarian cancer antigen US0484708007/11/1989 Pre-S gene coded peptide hepatitis B immunogens, vaccines, diagnostics, and synthetic lipid vesicle carriers US0482899105/09/1989 Tumor specific monoclonal antibodies US0474354305/10/1988 Method for enhancing and/or accelerating immunoassay detection of human carcinoma tumor associated antigen in a pathology sample US0469100909/01/1987 Hybrid proteins produced by an ultrahigh prokaryotic expression system US0468320007/28/1987 Monoclonal antibody to human cancer antigen and method for producing same US0467038606/02/1987 Cancer tests using tumor antigen generated lymphokines and compositions USRE03241705/12/1987 Radiolabeled antibody to anti-tumor associated antigen and process US0456216012/31/1985 Melanoma tumor antigen and autologous antibody US0455410111/19/1985 Identification and preparation of epitopes on antigens and allergens on the basis of hydrophilicity US0447237109/18/1984 Radiolabeled antibody to anti-tumor associated antigen and process US0440159208/30/1983 Pharmaceutical composition having antitumor activity US0431585102/16/1982 Pharmaceutical composition having antitumor activity US0424366301/06/1981 Glycolipid compositions for transplanted tumor immunotherapy US0413276901/02/1979 Cancer antigen, cancer therapy, and cancer diagnosis JP01044856A202/17/1989 ANTI-CANCER ANTIGEN ANTI-SERUM WO00006595A102/10/2000 HLA-A2 RESTRAINT TUMOR ANTIGEN PEPTIDE ORIGINATING IN SART-1 WO09940837A208/19/1999 COMPOSITIONS FOR DETECTING AND SURGICALLY REMOVING LYMPHOID TISSUE INVOLVED IN TUMOR PROGRESSION WO00032770A106/08/2000 NOVEL TUMOR ANTIGEN PROTEIN ART-1 AND TUMOR ANTIGEN PEPTIDE THEREOF WO00012701A103/09/2000 NOVEL TUMOR ANTIGEN PROTEIN SART-3 AND TUMOR ANTIGEN PEPTIDE THEREOF JP63012963A201/20/1988 CANCER ANTIGEN JP62163686A207/20/1987 METHOD FOR ESTABLISHING ANTIBODY-FORMING CELL STRAIN JP62012718A201/21/1987 LABELED T-CELL ANTIGEN RECEPTOR EP00974653A201/26/2000 Human gastric cancer antigen gene and protein WO09967288A112/29/1999 TUMOR ANTIGEN PEPTIDES ORIGINATING IN CYCLOPHILIN B WO09942140A108/26/1999 DETECTOR MOLECULE FOR USE IN A METHOD FOR DETECTING AND SURGICALLY REMOVING LYMPHOID TISSUE INVOLVED IN TUMOR PROGRESSION WO09746676A112/11/1997 TUMOR ANTIGEN PROTEINS, GENES THEREOF, AND TUMOR ANTIGEN PEPTIDES WO09735008A109/25/1997 METHODS AND COMPOSITIONS OF CHIMERIC POLYPEPTIDES FOR TUMOR ANTIGEN VACCINES JP63047664A202/29/1988 METHOD FOR MEASURING CANCER ANTIGEN AND KIT THEREFOR JP62238464A210/19/1987 QUANTIFICATION OF HUMAN LUNG CANCER ANTIGEN EP01055684A111/29/2000 TUMOR ANTIGEN PEPTIDE DERIVATIVE SEP01041146A110/04/2000

TUMOR ANTIGEN PROTEIN, GENE THEREOF, AND UTILIZATION THEREOF WO00052165A209/08/2000
 COMPOSITIONS AND METHODS FOR BREAST CANCER THERAPY AND DIAGNOSIS JP00184880A207/04/2000
 PROPAGATION AND ACTIVATING INDUCTION OF CYTOTOXIC T-CELL SPECIFIC TO CANCER CELL AND DEVICE
 THEREFOR JP00116383A204/25/2000 HUMAN CANCER REGRESSION ANTIGEN
 PROTEIN WO00002907A101/20/2000 TUMOR ANTIGEN PEPTIDE ORIGINATING IN SART-
 1 WO09933977A107/08/1999 TUMOR ANTIGEN PROTEIN, GENE THEREOF, AND UTILIZATION
 THEREOF WO09929715A106/17/1999 TUMOR ANTIGEN PEPTIDE DERIVATIVES WO09918206A204/15/1999
 NOVEL HUMAN CANCER ANTIGEN NY ESO-1/CAG-3 AND GENE ENCODING SAME WO09906834A202/11/1999
 METHODS FOR IDENTIFYING LIGAND SPECIFIC BINDING MOLECULES WO09804282A102/05/1998 CANCER
 IMMUNOTHERAPY USING AUTOLOGOUS TUMOR CELLS COMBINED WITH ALLOGENEIC CYTOKINE-SECRETING
 CELLS JP07089873A204/04/1995 BISPECIFIC TRIGGER MOLECULE RECOGNIZING LYMPHOCYTE ANTIGEN CD2
 AND TUMOR ANTIGEN JP63041427A202/22/1988 HUMAN CANCER ANTIGEN JP61216683A209/26/1986 B-
 LYMPHOCYTE STRAIN ORIGINATED FROM BLOOM SYNDROME PATIENT HAVING COMMON CANCER
 ANTIGEN WO00111044A102/15/2001 TUMOR ANTIGEN WO00054807A109/21/2000 LIGAND-BONDED
 COMPLEX WO00030680A106/02/2000 TUMOR ANTIGEN-SPECIFIC ANTIBODY-GP39 CHIMERIC PROTEIN
 CONSTRUCTS JP00000092A201/07/2000 ANTI-HUMAN BREAST CANCER
 MONOCLONAL ANTIBODY WO00000591A101/06/2000 HUMAN MONOCLONAL ANTIBODIES AGAINST THE
 TUMOR ANTIGEN UK114 AND LYMPHOCYTE CELLS AND HYBRIDOMAS FOR
 THEIR PRODUCTION WO09943857A109/02/1999 DETECTION OF METASTATIC CANCER CELLS USING PCTA-
 1 WO09936094A207/22/1999 COMPOSITION AND METHOD FOR TREATING METASTATIC TUMORS OR CANCER
 INDUCED BY CELLS EXPRESSING SV40 TUMOR ANTIGEN JP11160318A206/18/1999 DETECTION AND
 DIAGNOSIS METHODS OF TUMOR ANTIGEN OF SMALL ANIMAL JP11118805A204/30/1999 MEASURING
 VESSEL, MEASURING KIT AND MEASUREMENT METHOD OF CANCER-ANTIGEN SPECIFIC CELLULAR IMMUNO-
 RESPONSE EP00911397A104/28/1999 TUMOR ANTIGEN PROTEINS, GENES THEREOF, AND TUMOR ANTIGEN
 PEPTIDES WO09822825A205/28/1998 A WHOLE BLOOD/MITOGEN ASSAY FOR THE EARLY DETECTION OF A
 SUBJECT WITH CANCER AND KIT WO09822582A105/28/1998 HUMAN CANCER REGRESSION ANTIGEN
 PROTEIN WO09729195A208/14/1997 HUMAN CANCER ANTIGEN OF TYROSINASE-RELATED PROTEIN 1 AND 2
 AND GENES ENCODING SAME JP09151200A206/10/1997 PEPTIDE CAPABLE OF INDUCING IMMUNE
 RESPONSE TO HUMAN GASTRIC CANCER, THERAPEUTIC AND PREVENTIVE AGENT FOR HUMAN GASTRIC
 CANCER CONTAINING THE SAME WO09704802A102/13/1997 ISOLATION AND/OR PRESERVATION OF
 DENDRITIC CELLS FOR PROSTATE CANCER IMMUNOTHERAPY JP06308126A211/04/1994 DEVICE AND METHOD
 FOR EXAMINING MOLECULAR SPECIMEN IN BIOLOGICAL FLUID AND COLLECTING CELL
 COMPONENT JP02172923A207/04/1990 METHOD FOR TREATING CANCER JP01163130A206/27/1989
 VACCINE CONTAINING TUMOR ANTIGEN AND ADJUVANT JP01045397A202/17/1989 CANCER
 ANTIGEN JP61277635A212/08/1986 DIAGNOSTIC AGENT JP61234358A210/18/1986 ASSAY OF HUMAN LUNG
 CANCER ANTIGEN JP56065829A206/03/1981 ANTITUMOR AGENT JP56065828A206/03/1981 ANTITUMOR
 AGENT EP01072272A101/31/2001 METHOD FOR PRODUCING A SPECIFIC ANTISERUM AGAINST THE
 UNIVERSAL TUMOROUS ANTIGEN AND METHOD FOR DIAGNOSING MALIGNANT TUMOURS USING SAID
 ANTISERUM EP01062335A112/27/2000 BREAST CANCER ANTIGEN WO00052463A109/08/2000 METHOD OF
 DIAGNOSING AND MONITORING MALIGNANT BREAST CARCINOMAS WO00047228A108/17/2000 METHODS
 FOR TREATMENT OF TUMORS AND METASTASES USING A COMBINATION OF ANTI-ANGIOGENIC AND
 IMMUNOTHERAPIES WO00044782A208/03/2000 EWING'S TUMOUR ANTIGEN, NUCLEIC ACID
 AND ANTIBODIES EP01021535A207/26/2000 HUMAN CANCER ANTIGEN NY ESO-1/CAG-3 AND GENE ENCODING
 SAME WO00026676A105/11/2000 CANCER-ASSOCIATED ANTIGENS AND METHODS OF THEIR
 IDENTIFICATION WO00024778A105/04/2000 HLA-A2 AND HLA-DR SPECIFIC PEPTIDE EPITOPES FROM THE
 MELANOMA ANTIGEN TRP2 WO00020460A104/13/2000 METHODS FOR PRODUCING HUMAN TUMOR
 ANTIGEN SPECIFIC ANTIBODIES JP00072693A203/07/2000 MEDICINE TO BE INJECTED INTO
 SPLEEN WO00009691A202/24/2000 BPC-1: A SECRETED BRAIN SPECIFIC PROTEIN EXPRESSED AND SECRETED
 BY PROSTATE AND BLADDER CANCER CELLS WO09964590A112/16/1999 POLYMORPHIC MARKERS OF
 PROSTATE CARCINOMA TUMOR ANTIGEN-1 (PCTA-1) WO09962942A212/09/1999 NOVEL TUMOR ANTIGEN
 USEFUL IN DIAGNOSIS AND THERAPY OF PROSTATE AND COLON CANCER WO09951263A210/14/1999
 METHODS AND MODIFIED CELLS FOR THE TREATMENT OF CANCER WO09949034A109/30/1999 BREAST
 CANCER ANTIGEN WO09946392A109/16/1999 METHODS AND COMPOSITIONS OF CHEMOKINE-
 TUMOR ANTIGEN FUSION PROTEINS AS CANCER VACCINES JP11237381A208/31/1999 METHOD FOR FITTING
 HUMAN OR ANIMAL TRANSPLANTATION TISSUE TO RECIPIENT AND METHOD FOR DETECTING TUMOR ANTIGEN
 IN HUMAN OR ANIMAL WO09938954A108/05/1999 A UNIVERSAL IMMUNOMODULATORY CYTOKINE-
 EXPRESSING BYSTANDER CELL LINE AND RELATED COMPOSITIONS AND METHODS OF MANUFACTURE AND
 USE WO09924566A105/20/1999 TUMOR-SPECIFIC ANTIGENS, METHODS FOR THEIR PRODUCTION AND THEIR
 USE FOR IMMUNIZATION AND DIAGNOSIS EP00910646A104/28/1999 BRAIN GLYCOGEN PHOSPHORYLASE
 CANCER ANTIGEN EP00882130A212/09/1998 HUMAN CANCER ANTIGEN OF TYROSINASE-RELATED PROTEIN 1
 AND 2 AND GENES ENCODING SAME WO09850551A111/12/1998 RAGE1-LIKE
 PROTEIN WO09846769A110/22/1998 COMPOSITION AND METHOD FOR INDUCING AN IMMUNE RESPONSE
 AGAINST TUMOUR-RELATED ANTIGEN EP00521842B109/16/1998 Tumor antigen specific
 antibody WO09833511A108/06/1998 STRUCTURALLY MODIFIED PEPTIDES RESISTANT TO PEPTIDASE
 DEGRADATION WO09816246A104/23/1998 CYTOKINE ENHANCED IMMUNOTHERAPY FOR
 BRAIN TUMORS WO09816238A204/23/1998 CANCER IMMUNOTHERAPY USING TUMOR CELLS COMBINED WITH
 MIXED LYMPHOCYTES WO09800163A101/08/1998 INDUCTION OF CTLs SPECIFIC FOR NATURAL ANTIGENS BY
 CROSS-PRIMING IMMUNIZATION WO09749817A112/31/1997 BRAIN GLYCOGEN PHOSPHORYLASE CANCER
 ANTIGEN WO09749421A112/31/1997 GM-CSF ADMINISTRATION FOR THE TREATMENT AND PREVENTION OF

RECURRENCE OF BRAIN TUMORSEP00721504A107/17/1996 IMMUNOREACTIVE PEPTIDE SEQUENCE FROM A
 43 KDHUMAN CANCER ANTIGENJPO7318562A212/08/1995 ANTIBODY HAVING SPECIFICITY TO
 ANTIGENRELATING TO MAMMARY CANCER AND ANTIGEN MEASURING METHODJPO7092160A204/07/1995
 COLLECTING DEVICE, TESTING AND COLLECTINGDEVICE, TESTING METHOD, AND MEASURING
 METHODWO09506725A103/09/1995 IMMUNOREACTIVE PEPTIDE SEQUENCE FROM A 43 KDHUMAN CANCER
 ANTIGENEP00266663B101/18/1995 Chimeric antibody with specificity to humantumor
 antigenJPO6157347A206/03/1994 SELECTIVE CARCINOSTATIC AGENTJPO6157346A206/03/1994 SELECTIVE
 CARCINOSTATIC AGENTJPO6141884A205/24/1994 AMINO ACID SEQUENCE OF ANTICANCER
 HUMANMONOCLONAL ANTIBODY AND DNA BASE SEQUENCE CAPABLE OF CODING
 THESAMEEP00521842A301/26/1994 Tumor antigen specific antibodyEPO0521842A201/07/1993 Tumor antigen
 specific antibodyJPO4212063A208/03/1992 ASSAY OF HUMAN LUNG TUMOR ANTIGEN AND
 REAGENTTHEREFORJPO4159290A206/02/1992 GM3-ANALOGOUS COMPOUND AND METHOD
 FORTHESYNTHESIZING THE SAMEJPO4054131A202/21/1992 SYNTHETIC VACCINE FOR SPECIFICALLY
 INDUCINGCYTOTOXIC T-LYMPHOCYTEJPO4001138A201/06/1992 ANTITUMOR
 AGENTJPO2306923A212/20/1990 NEW ANTIBODY TRANSPORT SYSTEM FOR BIORESPONSEREGULATORY
 SUBSTANCEEP00171083B111/14/1990 Monoclonal antibody, process for preparing same, reagent for detecting
 cancer antigen containing the monoclonalantibody and process for preparing sameJPO1309677A212/14/1989
 MICROORGANISMJPO1291790A211/24/1989 NOVEL MONOCLONAL ANTIBODY AND
 HYBRIDOMAJPO1238542A209/22/1989 ANTISERUM AND PRODUCTION THEREOFJPO1156928A206/20/1989
 ANTI-CANCER ANTI-SERUM AND PRODUCTIONTHEREOFJP63290898A211/28/1988 HUMAN IMMUNOGLOBULIN
 PRODUCING HUMAN/HUMANHYBRIDOMA SPECIFIC TO CANCER-RELATED ANTIGEN AND ANTIBODY
 PRODUCEDTHEREBYEP00288082A210/26/1988 A tumor specific assay for CA125 ovariancancer
 antigenJP63251093A210/18/1988 NOVEL MONOCLONAL ANTIBODY AGAINST SMALL CELLLUNG CANCER
 ANTIGEN AND MOUSE-HYBRIDOMA PRODUCING THEABOVE-MENTIONED ANTIBODYJP63139134A206/10/1988
 T CELL ACTIVATOREP00266663A105/11/1988 Chimeric antibody with specificity to humantumor
 antigenWO08803145A105/05/1988 CHIMERIC ANTIBODY WITH SPECIFICITY TO HUMANTUMOR
 ANTIGENEP00259773A203/16/1988 A novel antibody specific for a cancerantigenJP62238465A210/19/1987
 QUANTIFICATION OF ADENOCARCINOMATOUSANTIGENJP61234357A210/18/1986 ASSAY OF HUMAN LUNG
 CANCER ANTIGENJP61044900A203/04/1986 MONOCLONAL ANTIBODY AND REAGENT FOR
 DETECTINGCANCER ANTIGENEP00171083A202/12/1986 Monoclonal antibody, process for preparing same,
 reagent for detecting cancer antigen containing the monoclonalantibody and process for preparing
 sameJP59142466A208/15/1984 MEASURING METHOD OF MATERIAL PROVIDED WITHANTIGEN- DETERMINING
 GROUPJP59090052A205/24/1984 MELANOMA DIAGNOSIS MEDICINE USING MONOCLONALSPECIFIC
 ANTIBODYJP55092325A207/12/1980 ANTITUMOR AGENT AND ITS PREPARATION1: Graadt van Roggen JF, van
 Velthuysen ML, Hogendoorn PC.The histopathological differential diagnosis of gastrointestinal stromaltumours.J
 Clin Pathol. 2001 Feb; 54(2):96-102 22: Roth W, Weller M.Chemotherapy and immunotherapy of malignant
 glioma: molecular mechanisms andclinical perspectives.Cell Mol Life Sci. 1999 Oct 30; 56(5-6):481-506 03: Ferrer
 I.[Pathology of paraneoplastic syndromes of the central and peripheral nervoussystem and muscle].Rev Neurol.
 2000 Dec 16-31; 31(12):1228-36 Spanish.04: Alvira-Dupla MR, Mayayo-Artal E.[Paraneoplastic syndromes with
 peripheral nerve involvement].Rev Neurol. 2000 Dec 16-31; 31(12):1223-5 Spanish.45: Dalmau J, Porta-Etessam
 J.[Paraneoplastic cerebral syndromes with oto-neuro-ophthalmologicmanifestations].Rev Neurol. 2000 Dec 16-31;
 31(12):1213-9 Spanish.26: Lum LG.T cell-based immunotherapy for cancer: a virtual reality?CA Cancer J Clin.
 1999 Mar-Apr; 49(2):74-100, 65 97: Radich J, Sievers E.New developments in the treatment of acute myeloid
 leukemia.Oncology (Huntingt). 2000 Nov; 14(11A):125-31 68: von Mensdorff-Pouilly S, Snijdwint FG, Verstraeten
 AA, Verheijen RH,Kenemans P.Human MUC1 mucin: a multifaceted glycoprotein.Int J Biol Markers. 2000 Oct-Dec;
 15(4):343-56 29: Phipps RP, Pollock SJ, Kaur K, Kaufman J, Borrello MA, Graf BA, Nazarenko D,Roberts LJ,
 Morrow JD, Palis J, Ryan DJ, Bennett JM.Expression of cyclooxygenase-2 and prostaglandins by B-1 cells and B-
 CLL cells.Curr Top Microbiol Immunol. 2000; 252:293-300 available.410: Ravaud A.[Cell therapy in solid
 tumors].Bull Cancer. 2001 Jan; 88(1):91-100 . available.811: Rousseau R, Soria JC.[Telomerase, a universal
 target in immunotherapy strategies against tumor]?Bull Cancer. 2000 Dec; 87(12):895-901 .912: Frankel AE,
 Sievers EL, Scheinberg DA.Cell surface receptor-targeted therapy of acute myeloid leukemia: a review.Cancer
 Biother Radiopharm. 2000 Oct; 15(5):459-76 813: Jager D, Jager E, Knuth A.Vaccination for malignant melanoma:
 recent developments.Oncology. 2001; 60(1):1-7 114: Riethmuller D, Seilles E.[Immunity of the female genital tract
 mucosa and mechanisms of papillomavirusevasion].J Gynecol Obstet Biol Reprod (Paris). 2000 Dec; 29(8):729-740
 .815: Goel A, Batra SK.Antibody constructs for radioimmunodiagnosis and treatment of human
 pancreaticcancer.Teratog Carcinog Mutagen. 2001; 21(1):45-57 016: Kuroki M, Arakawa F, Khare PD, Kuroki M,
 Liao S, Matsumoto H, Abe H,Imakiire T.Specific targeting strategies of cancer gene therapy using a single-
 chainvariable fragment (scFv) with a high affinity for CEA.Anticancer Res. 2000 Nov-Dec; 20(6A):4067-71 417:
 Potter M, Melchers F.Opinions on the nature of B-1 cells and their relationship to B cell neoplasia.Curr Top Microbiol
 Immunol. 2000; 252:307-24 available.918: Potter M, Jones G, Dubois W, Williams K, Mushinski E.Myeloma
 proteins that bind Hsp65 (GroEL) are polyreactive and are found in highincidence in pristine induced
 plasmacytomas.Curr Top Microbiol Immunol. 2000; 252:265-71 419: Carcenac M, Gutowski M, Rouanet P,
 Larroque C, Pelegrin A.[Cancer immunophotodetection and immunophototherapy].Bull Cancer. 2000 Nov;
 87(11):804-12 .920: Penault-Llorca FM, Balaton AJ.[Monoclonal antibodies in oncology: applications in diagnosis,
 prognosis andprediction of response to therapy on tissue specimens].Bull Cancer. 2000 Nov; 87(11):794-803
 .821: Ochsenbein AF, Zinkernagel RM.Natural antibodies and complement link innate and acquired
 immunity.Immunol Today. 2000 Dec; 21(12):624-30 322: Deveci MS, Deveci G, Gunhan O, Finci R.Oncocytic
 mucoepidermoid carcinoma of the parotid gland: report of a case withDNA ploidy analysis and review of the
 literature.Pathol Int. 2000 Nov; 50(11):905-9 823: Scher HI.HER2 in prostate cancer--a viable target or innocent

bystander? *J Natl Cancer Inst.* 2000 Dec 6; 92(23):1866-8 available. 924: Mohrmann RL, Arber DA. CD20-Positive peripheral T-cell lymphoma: report of a case after nodular sclerotic Hodgkin's disease and review of the literature. *Mod Pathol.* 2000 Nov; 13(11):1244-52 325: Rogers BE, Zinn KR, Buchsbaum DJ. Gene transfer strategies for improving radiolabeled peptide imaging and therapy. *Q J Nucl Med.* 2000 Sep; 44(3):208-23 626: Zochbauer-Muller S, Minna JD. The biology of lung cancer including potential clinical applications. *Chest Surg Clin N Am.* 2000 Nov; 10(4):691-708 027: Koon HB, Junghans RP. Anti-CD30 antibody-based therapy. *Curr Opin Oncol.* 2000 Nov; 12(6):588-93 928: Flynn JM, Byrd JC. Campath-1H monoclonal antibody therapy. *Curr Opin Oncol.* 2000 Nov; 12(6):574-81 729: Turner HE, Wass JA. Are markers of proliferation valuable in the histological assessment of pituitary tumours? *Pituitary.* 1999 May; 1(3-4):147-51 230: Weisberger J, Wu CD, Liu Z, Wong JY, Melamed MR, Darzynkiewicz Z, Gorczyca W. Differential diagnosis of malignant lymphomas and related disorders by specific pattern of expression of immunophenotypic markers revealed by multiparameter flow cytometry (Review). *Int J Oncol.* 2000 Dec; 17(6):1165-77 231: Bocchia M, Bronte V, Colombo MP, De Vincentiis A, Di Nicola M, Forni G, Lanata L, Lemoli RM, Massaia M, Rondelli D, Zanon P, Tura S. Antitumor vaccination: where we stand. *Haematologica.* 2000 Nov; 85(11):1172-206 832: Dubensky TW, Liu MA, Ulmer JB. Delivery systems for gene-based vaccines. *Mol Med.* 2000 Sep; 6(9):723-32 833: Scheinberg DA. Speed bumps on the road to antibody therapy. *Cancer J.* 2000 Mar-Apr; 6(2):64-5. 34: Antoine JC. Immunological mechanisms in paraneoplastic peripheral neuropathy. *Clin Rev Allergy Immunol.* 2000 Aug; 19(1):61-72 35: Rogemond V, Honnorat J. Anti-CV2 autoantibodies and paraneoplastic neurological syndromes. *Clin Rev Allergy Immunol.* 2000 Aug; 19(1):51-9. 36: Bradwell AR. Paraneoplastic neurological syndromes associated with Yo, Hu, and Ri autoantibodies. *Clin Rev Allergy Immunol.* 2000 Aug; 19(1):19-29. 37: Kawai Y, Shimizu N, Ujii M, Takeshita E, Todoroki T, Mitsunashi T, Watanabe K. [Morphology and immunophenotyping in hematological malignancies]. *Rinsho Byori.* 2000 Aug; 48(8):694-701. 38: Gong MC, Chang SS, Watt F, O'Keefe DS, Bacich DJ, Uchida A, Bander NH, Reuter VE, Gaudin PB, Molloy PL, Sadelian M, Heston WD. Overview of evolving strategies incorporating prostate-specific membrane antigen as target for therapy. *Mol Urol.* 2000 Fall; 4(3):217-22; discussion 223. 39: Salgaller ML. Prostate cancer immunotherapy at the dawn of the new millennium. *Expert Opin Invest Drugs.* 2000 Jun; 9(6):1217-29. 40: Ziebold JL, Hixon J, Boyd A, Murphy WJ. Differential effects of CD40 stimulation on normal and neoplastic cell growth. *Arch Immunol Ther Exp (Warsz).* 2000; 48(4):225-33. 41: Kostler WJ, Brodowicz T, Hejna M, Wiltchke C, Zielinski CC. Detection of minimal residual disease in patients with cancer: a review of techniques, clinical implications, and emerging therapeutic consequences. *Cancer Detect Prev.* 2000; 24(4):376-403. 42: Desai PR. Immunoreactive T and Tn antigens in malignancy: role in carcinoma diagnosis, prognosis, and immunotherapy. *Transfus Med Rev.* 2000 Oct; 14(4):312-25 available. 643: Morris JC, Waldmann TA. Advances in interleukin 2 receptor targeted treatment. *Ann Rheum Dis.* 2000 Nov; 59 Suppl 1:i109-14 044: van Houten VM, Tabor MP, van den Brekel MW, Denkers F, Wishaupt RG, Kummer JA, Snow GB, Brakenhoff RH. Molecular assays for the diagnosis of minimal residual head-and-neck cancer: methods, reliability, pitfalls, and solutions. *Clin Cancer Res.* 2000 Oct; 6(10):3803-16 [] 245: Ruffner KL, Matthews DC. Current uses of monoclonal antibodies in the treatment of acute leukemia. *Semin Oncol.* 2000 Oct; 27(5):531-9 146: Weiner GJ. The immunobiology and clinical potential of immunostimulatory CpG oligodeoxynucleotides. *J Leukoc Biol.* 2000 Oct; 68(4):455-63 547: Dummer R, Heinzerling L, Schmid MH, Burg G. [Immuno-intervention in cutaneous lymphomas]. *Schweiz Rundsch Med Prax.* 2000 Sep 14; 89(37):1471-6 .948: Ferrans VJ, Yu ZX, Nelson WK, Valencia JC, Tatsuguchi A, Avila NA, Riemenschn W, Matsui K, Travis WD, Moss J. Lymphangioma myomatosis (LAM): a review of clinical and morphological features. *J Nippon Med Sch.* 2000 Oct; 67(5):311-29 049: Tamada K, Chen L. T lymphocyte costimulatory molecules in host defense and immunologic diseases. *Ann Allergy Asthma Immunol.* 2000 Sep; 85(3):164-75; quiz 175-7 050: Matthey B, Engert A, Barth S. Recombinant immunotoxins for the treatment of Hodgkin's disease (Review). *Int J Mol Med.* 2000 Nov; 6(5):509-14 551: Kosmas C, Stamatopoulos K, Stavroyianni N, Zoi K, Belessi C, Viniou N, Kolli P, Yataganas X. Origin and diversification of the clonogenic cell in multiple myeloma: lessons from the immunoglobulin repertoire. *Leukemia.* 2000 Oct; 14(10):1718-26 652: Lopez M, Beaujean F. Positive selection of autologous peripheral blood stem cells. *Baillieres Best Pract Res Clin Haematol.* 1999 Mar-Jun; 12(1-2):71-86 453: Iftikharuddin JJ, Miele LA, Rosenblatt JD, Ryan CK, Sahasrabudhe DM. CD-20 expression in post-transplant lymphoproliferative disorders: treatment with rituximab. *Am J Hematol.* 2000 Oct; 65(2):171-3 754: Bhattacharya-Chatterjee M, Chatterjee SK, Foon KA. Anti-idiotypic vaccine against cancer. *Immunol Lett.* 2000 Sep 15; 74(1):51-8 855: Eisenbach L, Bar-Haim E, El-Shami K. Antitumor vaccination using peptide based vaccines. *Immunol Lett.* 2000 Sep 15; 74(1):27-34 456: Cebon J, MacGregor D, Scott A, DeBoer R. Immunotherapy of melanoma: targeting defined antigens. *Australas J Dermatol.* 1997 Jun; 38 Suppl 1:S66-72 757: Cornelison TL. Human papillomavirus genotype 16 vaccines for cervical cancer prophylaxis and treatment. *Curr Opin Oncol.* 2000 Sep; 12(5):466-73 558: Ling M, Kanayama M, Roden R, Wu TC. Preventive and therapeutic vaccines for human papillomavirus-associated cervical cancers. *J Biomed Sci.* 2000 Sep-Oct; 7(5):341-56 359: Chu PG, Chang KL, Arber DA, Weiss LM. Immunophenotyping of hematopoietic neoplasms. *Semin Diagn Pathol.* 2000 Aug; 17(3):236-56 960: Morrison CD, Prayson RA. Immunohistochemistry in the diagnosis of neoplasms of the central nervous system. *Semin Diagn Pathol.* 2000 Aug; 17(3):204-15 661: Milosevic D. Potential diagnostic, prognostic and therapeutic implications of some new regulatory proteins in hematologic malignancies. *J Exp Clin Cancer Res.* 2000 Jun; 19(2):175-81 562: Fonsatti E, Altomonte M, Coral S, De Nardo C, Lamaj E, Sigalotti L, Natali PG, Maio M. Emerging role of protectin (CD59) in humoral immunotherapy of solid malignancies. *Clin Ter.* 2000 May-Jun; 151(3):187-93 463: Knuth A, Jager D, Jager E. Cancer immunotherapy in clinical oncology. *Cancer Chemother Pharmacol.* 2000; 46 Suppl:S46-51 864: Sievers EL. Targeted therapy of acute myeloid leukemia with monoclonal antibodies and immunoconjugates. *Cancer Chemother Pharmacol.* 2000; 46 Suppl:S18-22 265: Chester KA, Mayer A, Bhatia J, Robson L, Spencer DI, Cooke SP, Flynn AA, Sharma SK, Boxer G, Pedley RB, Begent RH. Recombinant anti-carcinoembryonic antigen antibodies for targeting cancer. *Cancer Chemother Pharmacol.* 2000; 46 Suppl:S8-12 066: Rolinski J, Rupniewska ZM, Dmoszynska A, Wasik-Szczepanek E, Bojarska-Junak A. [CD43 in B-cell chronic lymphocytic leukemia]. *Pol Arch Med Wewn.* 1999 Sep; 102(3):753-62

Polish.267: Dammacco F, Sansonno D, Piccoli C, Racanelli V, D'Amore FP, Lauletta G. The lymphoid system in hepatitis C virus infection: autoimmunity, mixed cryoglobulinemia, and Overt B-cell malignancy. *Semin Liver Dis.* 2000; 20(2):143-57 068: McCluskie MJ, Weeratna RD, Davis HL. The role of CpG in DNA vaccines. *Springer Semin Immunopathol.* 2000; 22(1-2):125-32 769: Weiner GJ. Immunostimulatory DNA sequences and cancer therapy. *Springer Semin Immunopathol.* 2000; 22(1-2):107-16 available.570: Bendandi M. Anti-idiotypic vaccines for human follicular lymphoma. *Leukemia.* 2000 Aug; 14(8):1333-9 571: Urban T. [Clinical and molecular epidemiology of lymphangioleiomyomatosis and pulmonary pathology in tuberous sclerosis]. *Rev Mal Respir.* 2000 Jun; 17(2 Pt 2):597-603 172: van Spriel AB, van Ojik HH, van De Winkel JG. Immunotherapeutic perspective for bispecific antibodies. *Immunol Today.* 2000 Aug; 21(8):391-7 273: Green MC, Murray JL, Hortobagyi GN. Monoclonal antibody therapy for solid tumors. *Cancer Treat Rev.* 2000 Aug; 26(4):269-86 274: Buchegger F, Roth A, Allal A, Dupertuis YM, Slosman DO, Delaloye AB, Mach JP. Radioimmunotherapy of colorectal cancer liver metastases: combination with radiotherapy. *Ann N Y Acad Sci.* 2000 Jun; 910:263-9; discussion 269-70 975: Coiffier B. Monoclonal antibodies in the treatment of non-Hodgkin's lymphoma patients. *Haematologica.* 1999 Jun; 84:14-8 available.776: Stevenson FK, King CA, Spellerberg MB, Zhu D, Rice J, Sahota S, Thompson A, Radl J, Hamblin TJ. DNA vaccines against haematological malignancies. *Haematologica.* 1999 Jun; 84:11-3 677: Sharon J, Sarantopoulos S, Den W, Kao CY, Baecher-Allan CM, Santora KE, Sompuram SR, Petersen-Mahrt S, Williams BR. Recombinant polyclonal antibody libraries. *Comb Chem High Throughput Screen.* 2000 Jun; 3(3):185-96 878: Garcia G, Petrovic LM, Vierling JM. Overview of hepatitis B and transplantation in the hepatitis B patient. *Semin Liver Dis.* 2000; 20 Suppl 1:3-6 779: Rossi G, Ferrari G, Longo L, Trentini GP. Epithelioid sarcoma of the penis: a case report and review of the literature. *Pathol Int.* 2000 Jul; 50(7):579-85 480: Jurcic JG, Cathcart K, Pinilla-Ibarz J, Scheinberg DA. Advances in immunotherapy of hematologic malignancies: cellular and humoral approaches. *Curr Opin Hematol.* 2000 Jul; 7(4):247-54 181: Kipps TJ. Chronic lymphocytic leukemia. *Curr Opin Hematol.* 2000 Jul; 7(4):223-34 882: Berman E. Recent advances in the treatment of acute leukemia: 1999. *Curr Opin Hematol.* 2000 Jul; 7(4):205-11 583: Bhattachary-Chatterjee M, Nath Baral R, Chatterjee SK, Das R, Zeytin H, Chakraborty M, Foon KA. Counterpoint. Cancer vaccines: single-epitope anti-idiotypic vaccine versus multiple-epitope antigen vaccine. *Cancer Immunol Immunother.* 2000 Jun; 49(3):133-41 284: Melief CJ, Toes RE, Medema JP, van der Burg SH, Ossendorp F, Offringa R. Strategies for immunotherapy of cancer. *Adv Immunol.* 2000; 75:235-82 available.685: Ozaki S, Kosaka M. [The treatment of multiple myeloma: a new molecular target therapy]. *Rinsho Ketsueki.* 2000 May; 41(5):421-5 available.486: Engelhard VH, Bullock TN, Colella TA, Mullins DW. Direct identification of human tumor-associated peptide antigens and a preclinical model to evaluate their use. *Cancer J Sci Am.* 2000 May; 6 Suppl 3:S272-80 887: Weiner LM. Bispecific antibodies in cancer therapy. *Cancer J Sci Am.* 2000 May; 6 Suppl 3:S265-71 available.788: Schmutzler C, Koehle J. Innovative strategies for the treatment of thyroid cancer. *Eur J Endocrinol.* 2000 Jul; 143(1):15-24 689: Gong MC, Chang SS, Sadelain M, Bander NH, Heston WD. Prostate-specific membrane antigen (PSMA)-specific monoclonal antibodies in the treatment of prostate and other cancers. *Cancer Metastasis Rev.* 1999; 18(4):483-90 190: Dillman RO. Infusion reactions associated with the therapeutic use of monoclonal antibodies in the treatment of malignancy. *Cancer Metastasis Rev.* 1999; 18(4):465-71 991: Wikstrand CJ, Cokgor I, Sampson JH, Bigner DD. Monoclonal antibody therapy of human gliomas: current status and future approaches. *Cancer Metastasis Rev.* 1999; 18(4):451-64 892: Saffran DC, Reiter RE, Jakobovits A, Witte ON. Target antigens for prostate cancer immunotherapy. *Cancer Metastasis Rev.* 1999; 18(4):437-49 793: Ditzel HJ. Human antibodies in cancer and autoimmune disease. *Immunol Res.* 2000; 21(2-3):185-93 694: Hirano T, Ishihara K, Hibi M. Roles of STAT3 in mediating the cell growth, differentiation and survival signals relayed through the IL-6 family of cytokine receptors. *Oncogene.* 2000 May 15; 19(21):2548-56 395: White CA. Rituximab immunotherapy for non-Hodgkin's lymphoma. *Cancer Biother Radiopharm.* 1999 Aug; 14(4):241-50 096: Takekawa Y, Ugajin W, Koide H, Nishio S, Yamamoto T, Sawada T. Pathologic, cytologic and immunohistochemical findings of an intra-abdominal desmoplastic small round cell tumor in a 15-year-old male. *Pathol Int.* 2000 May; 50(5):417-20 297: Davis ID. An overview of cancer immunotherapy. *Immunol Cell Biol.* 2000 Jun; 78(3):179-95 698: Matic G, Schutt W, Winkler RE, Tiess M, Ramlow W. Extracorporeal removal of circulating immune complexes: from non-selective to patient-specific. *Blood Purif.* 2000; 18(2):156-60 699: Feuring-Buske M, Buske C, Unterhalt M, Hiddemann W. Recent advances in antigen-targeted therapy in non-Hodgkin's lymphoma. *Ann Hematol.* 2000 Apr; 79(4):167-74 3100: Posner JB, Dalmau JO. Paraneoplastic syndromes of the nervous system. *Clin Chem Lab Med.* 2000 Feb; 38(2):117-22 8101: Lake DF, Huynh WC, Hersh EM. Natural and induced human antibody response to cancer. *Cancer Invest.* 2000; 18(5):480-9 available.2102: Dworzak MN, Fritsch G, Panzer-Grumayer ER, Mann G, Gadner H. Detection of residual disease in pediatric B-cell precursor acute lymphoblastic leukemia by comparative phenotype mapping: method and significance. *Leuk Lymphoma.* 2000 Jul; 38(3-4):295-308 6103: Watanabe R, Takiguchi Y, Kuriyama T. [Serum tumor markers for primary lung carcinoma]. *Nippon Rinsho.* 2000 May; 58(5):1070-3 1104: Maxwell P. Carcinoembryonic antigen: cell adhesion molecule and useful diagnostic marker. *Br J Biomed Sci.* 1999; 56(3):209-14 2105: Livingston PO, Ragupathi G, Musselli C. Autoimmune and antitumor consequences of antibodies against antigens shared by normal and malignant tissues. *J Clin Immunol.* 2000 Mar; 20(2):85-93 9106: Berke Z, Dalianis T. Studies on polyomavirus persistence and polyomavirus-induced tumor development in relation to the immune system. *Adv Cancer Res.* 2000; 79:249-76 available.3107: Dalgleish AG. Cancer vaccines. *Br J Cancer.* 2000 May; 82(10):1619-24 available.3108: Yip D, Strickland AH, Karapetis CS, Hawkins CA, Harper PG. Immunomodulation therapy in colorectal carcinoma. *Cancer Treat Rev.* 2000 Jun; 26(3):169-90 0109: Wang H, Liu Y, Wei L, Guo Y. Bi-specific antibodies in cancer therapy. *Adv Exp Med Biol.* 2000; 465:369-80 available.1110: Haseman MK, Rosenthal SA, Polascik TJ. Capromab Pendetide imaging of prostate cancer. *Cancer Biother Radiopharm.* 2000 Apr; 15(2):131-40 8111: Slifka MK, Whitton JL. Clinical implications of dysregulated cytokine production. *J Mol Med.* 2000; 78(2):74-80 2112: Illidge TM, Johnson PW. The emerging role of radioimmunotherapy in haematological malignancies. *Br J Haematol.* 2000 Mar; 108(4):679-88 available.9113: Canfield PJ, Hemsley S. The roles of histology and immunohistology in the investigation of marsupial disease and normal lymphoid tissue. *Dev Comp Immunol.* 2000 Jul; 24(5):455-71 1114:

Inuzuka T. Autoantibodies in paraneoplastic neurological syndrome. *Am J Med Sci.* 2000 Apr; 319(4):217-26 6115: Grima KM. Therapeutic apheresis in hematological and oncological diseases. *J Clin Apheresis.* 2000; 15(1-2):28-52 available. 0116: Noack F, Schmitt M, Bauer J, Helmecke D, Kruger W, Thorban S, Sandherr M, Kuhn W, Graeff H, Harbeck N. A new approach to phenotyping disseminated tumor cells: methodological advances and clinical implications. *Int J Biol Markers.* 2000 Jan-Mar; 15(1):100-4 0117: Witz IP. Differential expression of genes by tumor cells of a low or a high malignancy phenotype: the case of murine and human Ly-6 proteins. *J Cell Biochem Suppl.* 2000; 34:61-6 6118: Loudon JA, Billy ML, DeYoung BR, Allen CM. Angiosarcoma of the mandible: a case report and review of the literature. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 2000 Apr; 89(4):471-6 9119: Brinkmann U. Recombinant antibody fragments and immunotoxin fusions for cancer therapy. *In Vivo.* 2000 Jan-Feb; 14(1):21-7 7120: Nozawa Y, Wakasa H, Abe M. Production and usefulness of monoclonal antibodies against B cells. *Fukushima J Med Sci.* 1999 Jun; 45(1):1-11 1121: Abe A, Emi N. [The current status and future applications of gene therapy and immunogenetherapy for malignant lymphoma]. *Nippon Rinsho.* 2000 Mar; 58(3):715-9 .2122: Johno M, Ono T. [Clinicopathological differential diagnosis of mycosis fungoides/Sézary syndrome from the cutaneous type of adult T-cell leukemia/lymphoma]. *Nippon Rinsho.* 2000 Mar; 58(3):660-4 .2123: Nakamura S, Ichimura K, Sasaki K, Suzuki R. [Ki-1 lymphoma]. *Nippon Rinsho.* 2000 Mar; 58(3):650-4 .0124: Hathway DE. Toxic action/toxicity. *Biol Rev Camb Philos Soc.* 2000 Feb; 75(1):95-127 4125: Laheru DA, Jaffee EM. Potential role of tumor vaccines in GI malignancies. *Oncology (Huntingt).* 2000 Feb; 14(2):245-56; discussion 259-60, 265 1126: Taylor ST, Hickman JA, Dive C. Survival signals within the tumour microenvironment suppress drug-induced apoptosis: lessons learned from B lymphomas. *Endocr Relat Cancer.* 1999 Mar; 6(1):21-3 2127: Talwar GP, Diwan M, Razvi F, Malhotra R. The impact of new technologies on vaccines. *Natl Med J India.* 1999 Nov-Dec; 12(6):274-80 0128: Hoefnagel CA. Nuclear medicine therapy of neuroblastoma. *Q J Nucl Med.* 1999 Dec; 43(4):336-43 4129: Skinnider BF, Connors JM, Sutcliffe SB, Gascoyne RD. Anaplastic large cell lymphoma: a clinicopathologic analysis. *Hematol Oncol.* 1999 Dec; 17(4):137-48 9130: Tsunoda S, Tsutsumi Y, Nakagawa S, Mayumi T. [Targeting therapy using a monoclonal antibody against tumor vascular endothelium]. *Yakugaku Zasshi.* 2000 Mar; 120(3):256-64 .7131: Rowe JM. Treatment of acute myelogenous leukemia in older adults. *Leukemia.* 2000 Mar; 14(3):480-7 6132: Bernstein ID. Monoclonal antibodies to the myeloid stem cells: therapeutic implications of CMA-676, a humanized anti-CD33 antibody calicheamicin conjugate. *Leukemia.* 2000 Mar; 14(3):474-5 4133: Tait BD. HLA class I expression on human cancer cells. Implications for effective immunotherapy. *Hum Immunol.* 2000 Feb; 61(2):158-65 9134: Schat KA, Xing Z. Specific and nonspecific immune responses to Marek's disease virus. *Dev Comp Immunol.* 2000 Mar-Apr; 24(2-3):201-21 8135: Treon SP, Shima Y, Grossbard ML, Preffer FI, Belch AR, Pilarski LM, Anderson KC. Treatment of multiple myeloma by antibody mediated immunotherapy and induction of myeloma selective antigens. *Ann Oncol.* 2000; 11 Suppl 1:107-11 0136: Waldmann TA. T-cell receptors for cytokines: targets for immunotherapy of leukemia/lymphoma. *Ann Oncol.* 2000; 11 Suppl 1:101-6 9137: Hammel P, Soussi T. [Serum p53 antibody assay: evaluation in colorectal cancer]. *Rev Med Interne.* 2000 Feb; 21(2):167-73 .3138: Kuwahara S, Kawada M, Uga S, Mori K. [A case of cerebellar meningoencephalitis caused by Epstein-Barr virus (EBV): usefulness of Gd-enhanced MRI for detection of the lesions]. *No To Shinkei.* 2000 Jan; 52(1):37-42 .9139: Sievers EL. Clinical studies of new "biologic" approaches to therapy of acute myeloid leukemia with monoclonal antibodies and immunoconjugates. *Curr Opin Oncol.* 2000 Jan; 12(1):30-5 6140: Takamori M, Maruta T, Komai K. Lambert-Eaton myasthenic syndrome as an autoimmune calcium-channelopathy. *Neurosci Res.* 2000 Mar; 36(3):183-91 2141: Sikic BI. New approaches in cancer treatment. *Ann Oncol.* 1999; 10 Suppl 6:149-53 7142: Thiele J, Kvasnicka HM. [Reactive lymphoid nodule or malignant lymphoma. A brief guideline for the differential diagnosis of bone marrow infiltrates in non-Hodgkin lymphomas]. *Pathologe.* 2000 Jan; 21(1):16-23 .5143: Ryu DD, Nam DH. Recent progress in biomolecular engineering. *Biotechnol Prog.* 2000 Jan-Feb; 16(1):2-16 3144: Mihara H, Kato Y, Tokura Y, Hattori Y, Sato A, Kobayashi H, Imamura A, Daimaru O, Miwa H, Nitta M. [Epstein-Barr virus-associated hemophagocytic syndrome during mid-term pregnancy successfully treated with combined methylprednisolone and intravenous immunoglobulin]. *Rinsho Ketsueki.* 1999 Dec; 40(12):1258-64 .9145: Chang MH, Chen DS. Prospects for hepatitis B virus eradication and control of hepatocellular carcinoma. *Baillieres Best Pract Res Clin Gastroenterol.* 1999 Dec; 13(4):511-7 6146: Scholzen T, Gerdes J. The Ki-67 protein: from the known and the unknown. *J Cell Physiol.* 2000 Mar; 182(3):311-22 7147: Mayer A, Chester KA, Flynn AA, Begent RH. Taking engineered anti-CEA antibodies to the clinic. *J Immunol Methods.* 1999 Dec 10; 231(1-2):261-73 3148: Molema G, Kroesen BJ, Helfrich W, Meijer DK, de Leij LF. The use of bispecific antibodies in tumor cell and tumor vasculature directed immunotherapy. *J Control Release.* 2000 Feb 14; 64(1-3):229-39 0149: Lacronique J, Urban T. [Current aspects of lymphangioliomyomatosis]. *Rev Pneumol Clin.* 1999 Oct; 55(5):263-9 .2150: Bodey B, Bodey B, Siegel SE, Kaiser HE. Genetically engineered monoclonal antibodies for direct anti-neoplastic treatment and cancer cell specific delivery of chemotherapeutic agents. *Curr Pharm Des.* 2000 Feb; 6(3):261-76 9151: Takahashi H. [Dendritic cells and tumor specific immunity]. *Gan To Kagaku Ryoho.* 1999 Dec; 26(14):2121-6 .3152: Pierres A, Benoliel AM, Bongrand P. [Adhesion molecules and cancer]. *Rev Med Interne.* 1999 Dec; 20(12):1099-113 .2153: Ashmore SM, Thomas DG, Darling JL. Does P-glycoprotein play a role in clinical resistance of malignant astrocytoma? *Anticancer Drugs.* 1999 Nov; 10(10):861-72 3154: Seneviratne U, de Silva R. Lambert-Eaton myasthenic syndrome. *Postgrad Med J.* 1999 Sep; 75(887):516-20 3155: Ilangumaran S, Borisch B, Hoessli DC. Signal transduction via CD44: role of plasma membrane microdomains. *Leuk Lymphoma.* 1999 Nov; 35(5-6):455-69 3156: Welt S, Ritter G. Antibodies in the therapy of colon cancer. *Semin Oncol.* 1999 Dec; 26(6):683-90 1157: Balzar M, Winter MJ, de Boer CJ, Litvinov SV. The biology of the 17-1A antigen (Ep-CAM). *J Mol Med.* 1999 Oct; 77(10):699-712 5158: Sinkovics JG, Horvath JC. Vaccination against human cancers (review). *Int J Oncol.* 2000 Jan; 16(1):81-96 2159: Kudo T, Suzuki M, Katayose Y, Shinoda M, Sakurai N, Kodama H, Ichiyama M, Takemura S, Yoshida H, Saeki H, Saijo S, Takahashi J, Tominaga T, Matsuno S. Specific targeting immunotherapy of cancer with bispecific antibodies. *Tohoku J Exp Med.* 1999 Aug; 188(4):275-88 5160: Hwang LC, Fein S, Levitsky H, Nelson WG. Prostate cancer vaccines: current status. *Semin Oncol.* 1999 Apr; 26(2):192-

201 0161: Trueb RF, Trueb RM.[Cutaneous paraneoplastic syndrome as an immunologic phenomenon exemplified by paraneoplastic subacute cutaneous lupus erythematosus]. *Schweiz Rundsch Med Prax.* 1999 Oct 28; 88(44):1803-10 .0162: Chang SS, Bander NH, Heston WD.Monoclonal antibodies: will they become an integral part of the evaluation and treatment of prostate cancer--focus on prostate-specific membrane antigen? *Curr Opin Urol.* 1999 Sep; 9(5):391-5 6163: Jochmus I, Schafer K, Faath S, Muller M, Gissmann L.Chimeric virus-like particles of the human papillomavirus type 16 (HPV 16) as a prophylactic and therapeutic vaccine. *Arch Med Res.* 1999 Jul-Aug; 30(4):269-74 7164: Haraguchi S, Fukuda Y, Sugisaki Y, Yamanaka N.Pulmonary carcinosarcoma: immunohistochemical and ultrastructural studies. *Pathol Int.* 1999 Oct; 49(10):903-8 5165: Taylor-Papadimitriou J, Burchell J, Miles DW, Dalziel M.MUC1 and cancer. *Biochim Biophys Acta.* 1999 Oct 8; 1455(2-3):301-13 0166: Biragyn A, Kwak LW.B-cell malignancies as a model for cancer vaccines: from prototype protein to next generation genetic chemokine fusions. *Immunol Rev.* 1999 Aug; 170:115-26 6167: Gorter A, Meri S.Immune evasion of tumor cells using membrane-bound complement regulatory proteins. *Immunol Today.* 1999 Dec; 20(12):576-82 9168: Keating MJ.Chronic lymphocytic leukemia. *Semin Oncol.* 1999 Oct; 26(5 Suppl 14):107-14 5169: Maloney DG.Preclinical and phase I and II trials of rituximab. *Semin Oncol.* 1999 Oct; 26(5 Suppl 14):74-8 1170: Grillo-Lopez AJ, White CA, Varns C, Shen D, Wei A, McClure A, Dallaire BK.Overview of the clinical development of rituximab: first monoclonal antibody approved for the treatment of lymphoma. *Semin Oncol.* 1999 Oct; 26(5 Suppl 14):66-73 0171: Press OW.Radiolabeled antibody therapy of B-cell lymphomas. *Semin Oncol.* 1999 Oct; 26(5 Suppl 14):58-65 9172: Dyer MJ.The role of CAMPATH-1 antibodies in the treatment of lymphoid malignancies. *Semin Oncol.* 1999 Oct; 26(5 Suppl 14):52-7 8173: Winter JN.Prognostic indicators in diffuse, aggressive non-Hodgkin's lymphomas: regulators of growth fraction and programmed cell death. *Semin Oncol.* 1999 Oct; 26(5 Suppl 14):26-33 5174: Gopal AK, Press OW.Clinical applications of anti-CD20 antibodies. *J Lab Clin Med.* 1999 Nov; 134(5):445-50 available. 6175: Friesen C, Fulda S, Debatin KM.Cytotoxic drugs and the CD95 pathway. *Leukemia.* 1999 Nov; 13(11):1854-8 2176: Abbondanzo SL.Paraffin immunohistochemistry as an adjunct to hematopathology. *Ann Diagn Pathol.* 1999 Oct; 3(5):318-27 1177: Carbone DP.Molecular modalities in the treatment of lung cancer. *Oncology (Huntingt).* 1999 Oct; 13(10 Suppl 5):142-7 9178: Wiseman GA, White CA, Witzig TE, Gordon LI, Emmanouilides C, Raubitschek A, Janakiraman N, Gutheil J, Schilder RJ, Spies S, Silverman DH, Grillo-Lopez AJ.Radioimmunotherapy of relapsed non-Hodgkin's lymphoma with zevalin, a 90Y-labeled anti-CD20 monoclonal antibody. *Clin Cancer Res.* 1999 Oct; 5(10 Suppl):3281s-3286s 6179: Robinson HL.DNA vaccines: basic mechanism and immune responses (Review). *Int J Mol Med.* 1999 Nov; 4(5):549-55 0180: Moiseenko VM.[The use of monoclonal antibodies in the treatment of solid tumors]. *Vopr Onkol.* 1999; 45(4):458-62 Russian. available. 4181: Vose JM.Antibody-targeted therapy for low-grade lymphoma. *Semin Hematol.* 1999 Oct; 36(4 Suppl 6):15-20 2182: Appelbaum FR.Antibody-targeted therapy for myeloid leukemia. *Semin Hematol.* 1999 Oct; 36(4 Suppl 6):2-8 0183: Zangemeister-Wittke U, Stahel RA.Novel approaches to the treatment of small-cell lung cancer. *Cell Mol Life Sci.* 1999 Sep; 55(12):1585-98 6184: Allison AC.Squalene and squalene emulsions as adjuvants. *Methods.* 1999 Sep; 19(1):87-93 3185: Pal'tsev MA.[Current approaches to studying the pathogenesis of diseases]. *Vestn Ross Akad Med Nauk.* 1999; (9):22-5 Russian. available. 9186: Braun S, Pantel K.Micrometastatic bone marrow involvement: detection and prognostic significance. *Med Oncol.* 1999 Sep; 16(3):154-65 5187: Seilles E, Riethmuller D, Mouglin C.[Biology of the papillomavirus infections: V. Vaccine developments]. *Ann Biol Clin (Paris).* 1999 Sep-Oct; 57(5):517-24 .3188: Li Q, Chang AE.Adoptive T-cell immunotherapy of cancer. *Cytokines Cell Mol Ther.* 1999 Jun; 5(2):105-17 3189: Trail PA, Bianchi AB.Monoclonal antibody drug conjugates in the treatment of cancer. *Curr Opin Immunol.* 1999 Oct; 11(5):584-8 1190: Cragg MS, RR, Glennie MJ.Signaling antibodies in cancer therapy. *Curr Opin Immunol.* 1999 Oct; 11(5):541-7 9191: Jager E, Jager D, Knuth A.CTL-defined cancer vaccines: perspectives for active immunotherapeutic interventions in minimal residual disease. *Cancer Metastasis Rev.* 1999; 18(1):143-50 2192: Sharp JG, Chan WC.Detection and relevance of minimal disease in lymphomas. *Cancer Metastasis Rev.* 1999; 18(1):127-42 1193: Del Vecchio M, Parmiani G.Cancer vaccination. *Forum (Genova).* 1999 Jul-Sep; 9(3):239-56 1194: Cao Y, Abbas J, Wu X, Dooley J, van Amburg AL.Anti-Yo positive paraneoplastic cerebellar degeneration associated with ovarian carcinoma: case report and review of the literature. *Gynecol Oncol.* 1999 Oct; 75(1):178-83 0195: Whiteside TL.Signaling defects in T lymphocytes of patients with malignancy. *Cancer Immunol Immunother.* 1999 Oct; 48(7):346-52 6196: Landman WJ, Koch G.[Avian leukosis: an old problem in a new coat: diagnostic possibilities and limitations]. *Tijdschr Diergeneesk.* 1999 Sep 1; 124(17):496-502 Dutch. 0197: Vincent A, Willcox N.The role of T-cells in the initiation of autoantibody responses in thymoma patients. *Pathol Res Pract.* 1999; 195(8):535-40 3198: Kaiser R.[Paraneoplastic neurologic syndromes. Diagnostic and pathogenetic significance of autoantibodies]. *Nervenarzt.* 1999 Aug; 70(8):688-701 .9199: Borden EC, Esserman L, Linder DJ, Campbell MJ, Fulton AM.Biological therapies for breast carcinoma: concepts for improvement in survival. *Semin Oncol.* 1999 Aug; 26(4 Suppl 12):28-40 2200: Slovin SF, Scher HI.Peptide and carbohydrate vaccines in relapsed prostate cancer: immunogenicity of synthetic vaccines in man--clinical trials at Memorial Sloan-Kettering Cancer Center. *Semin Oncol.* 1999 Aug; 26(4):448-54 7201: Belling O, Ottesen K, Meyer W, Feller AC, Merz H.[Comparative analysis of various standard immunohistochemical procedures]. *Pathologe.* 1999 Jul; 20(4):242-50 .7202: Naschitz JE, Rosner I, Rozenbaum M, Zuckerman E, Yeshurun D.Rheumatic syndromes: clues to occult neoplasia. *Semin Arthritis Rheum.* 1999 Aug; 29(1):43-55 4203: Eyden B.Electron microscopy in tumour diagnosis: continuing to complement other diagnostic techniques. *Histopathology.* 1999 Aug; 35(2):102-8 3204: Mierau GW.Electron microscopy for tumour diagnosis: is it redundant? *Histopathology.* 1999 Aug; 35(2):99-101 2205: Chorzelski T, Hashimoto T, Maciejewska B, Amagai M, Anhalt GJ, Jablonska S.Paraneoplastic pemphigus associated with Castleman tumor, myasthenia gravis and bronchiolitis obliterans. *J Am Acad Dermatol.* 1999 Sep; 41(3 Pt 1):393-400 2206: Caligaris-Cappio F, Hamblin TJ.B-cell chronic lymphocytic leukemia: a bird of a different feather. *J Clin Oncol.* 1999 Jan; 17(1):399-408 9207: Liang R, Lau GK, Kwong YL.Chemotherapy and bone marrow transplantation for cancer patients who are also chronic hepatitis B carriers: a review of the problem. *J Clin Oncol.* 1999 Jan; 17(1):394-8 8208: Shih IM.The role of CD146 (Mel-CAM) in biology and pathology. *J Pathol.* 1999 Sep; 189(1):4-11 1209: Jungblut PR, Zimny-

Arndt U, Zeindl-Eberhart E, Stulik J, Koupilova K, Pleissner KP, Otto A, Muller EC, Sokolowska-Kohler W, Grabher G, Stoffler G. Proteomics in human disease: cancer, heart and infectious diseases. *Electrophoresis*. 1999 Jul; 20(10):2100-10 2210: Onrust SV, Lamb HM, Balfour JA. Rituximab. *Drugs*. 1999 Jul; 58(1):79-88; discussion 89-90 1211: Ditzel HJ. Human monoclonal antibodies: a tool for cancer detection in vivo. *APMIS Suppl*. 1999; 94:5-42 available. 9212: Costello RT, Gastaut JA, Olive D. [Mechanisms of tumor escape from immunologic response]. *Rev Med Interne*. 1999 Jul; 20(7):579-88 8213: Colcher D, Goel A, Pavlinkova G, Beresford G, Booth B, Batra SK. Effects of genetic engineering on the pharmacokinetics of antibodies. *Q J Nucl Med*. 1999 Jun; 43(2):132-9 8214: Apostolopoulos V, Sandrin MS, McKenzie IF. Carbohydrate/peptide mimics: effect on MUC1 cancer immunotherapy. *J Mol Med*. 1999 May; 77(5):427-36 2215: Yuste JR, Belouqui O, De la Pena A, Prieto J. [Antiphospholipid syndrome]. *Rev Med Univ Navarra*. 1998 Oct-Dec; 42(4):194-207 Spanish. 1216: Kuroda N, Yamasaki I, Nakayama H, Tamura K, Yamamoto Y, Miyazaki E, Naruse K, Kiyoku H, Hiroi M, Enzan H. Prostatic signet-ring cell carcinoma: case report and literature review. *Pathol Int*. 1999 May; 49(5):457-61 1217: Setterfield J, Shirlaw PJ, Lazarova Z, Bryant BM, Bhogal BS, Harman K, Challacombe SJ, Black MM. Paraneoplastic cicatricial pemphigoid. *Br J Dermatol*. 1999 Jul; 141(1):127-31 8218: Colcher D, Pavlinkova G, Beresford G, Booth BJ, Batra SK. Single-chain antibodies in pancreatic cancer. *Ann N Y Acad Sci*. 1999 Jun 30; 880:263-80 2219: Mittal K. Utility of proliferation-associated marker MIB-1 in evaluating lesions of the uterine cervix. *Adv Anat Pathol*. 1999 Jul; 6(4):177-85 1220: Nemoto Y, Irimura T. [Tumor metastases and adhesion molecules carbohydrates and lectins]. *Gan To Kagaku Ryoho*. 1999 May; 26(6):849-56 8221: Acha-Orbea H, Finke D, Attinger A, Schmid S, Wehrli N, Vacheron S, Xenarios I, Scarpellino L, Toellner KM, MacLennan IC, Luther SA. Interplays between mouse mammary tumor virus and the cellular and humoral immuneresponse. *Immunol Rev*. 1999 Apr; 168:287-303 1222: Norkin LC. Simian virus 40 infection via MHC class I molecules and caveolae. *Immunol Rev*. 1999 Apr; 168:13-22 1223: Evans SV, Roger MacKenzie C. Characterization of protein-glycolipid recognition at the membrane bilayer. *J Mol Recognit*. 1999 May-Jun; 12(3):155-68 6224: Kadagidze ZG. [The immunodiagnosis and immunotherapy of tumors]. *Vestn Ross Akad Med Nauk*. 1999; (5):19-22 Russian. 5225: Mukherjee AB, Kundu GC, Mantile-Selvaggi G, Yuan CJ, Mandal AK, Chattopadhyay S, Zheng F, Pattabiraman N, Zhang Z. Uteroglobin: a novel cytokine? *Cell Mol Life Sci*. 1999 May; 55(5):771-87 2226: Kowalczyk DW, Ertl HC. Immune responses to DNA vaccines. *Cell Mol Life Sci*. 1999 May; 55(5):751-70 1227: Abelev GI. [Immunology of cancer]. *Vestn Ross Akad Med Nauk*. 1999; (4):21-5 Russian. 9228: Lendeckel U, Arndt M, Frank K, Wex T, Ansorge S. Role of alanyl aminopeptidase in growth and function of human T cells (review). *Int J Mol Med*. 1999 Jul; 4(1):17-27 2229: Filez L, Penninckx F, Ectors N, Van Cutsem E, Geboes K, Aerts R, D'Hoore A, Kerremans R. Radioimmunoguided surgery for colorectal carcinoma. *Hepatogastroenterology*. 1999 Mar-Apr; 46(26):691-700 available. 7230: Moffat FL, Gulec SA, Serafini AN, Sfakianakis GN, Pop R, Robinson DS, Franceschi D, Boggs J, Livingstone AS. A thousand points of light or just dim bulbs? Radiolabeled antibodies and colorectal cancer imaging. *Cancer Invest*. 1999; 17(5):322-34 0231: van Dalen A. TPS monitoring in metastatic breast cancer. *Int J Biol Markers*. 1999 Jan-Mar; 14(1):45-8 0232: Yokozaki H, Yanagawa E, Harada M, Tahara E. Cutaneous ciliated cyst of the right lower leg. *Pathol Int*. 1999 Apr; 49(4):354-7 7233: Spencer JO, Dunn-Walters DK. Somatic hypermutation and B-cell malignancies. *J Pathol*. 1999 Jan; 187(2):158-63 0234: Wagner U, Kohler S, Prietl G, Giffels P, Schmidt-Nicolai S, Schlebusch H, Grunn U, Bender H, Biersack HJ, De Potter C, Krebs D, Wallwiener D. [Monoclonal anti-idiotypic antibodies in immunotherapy of ovarian carcinoma (MAbACA125) and breast carcinoma (MAb ACA14C5)]. *Zentralbl Gynakol*. 1999; 121(4):190-5 6235: Neipel F, Fleckenstein B. The role of HHV-8 in Kaposi's sarcoma. *Semin Cancer Biol*. 1999 Jun; 9(3):151-64 7236: Miles DW, Taylor-Papadimitriou J. Therapeutic aspects of polymorphic epithelial mucin in adenocarcinoma. *Pharmacol Ther*. 1999 Apr; 82(1):97-106 0237: Xiang J. Targeting cytokines to tumors to induce active antitumor immune responses by recombinant fusion proteins. *Hum Antibodies*. 1999; 9(1):23-36 3238: Maxwell-Armstrong CA, Durrant LG, Scholefield JH. Immunotherapy for colorectal cancer. *Am J Surg*. 1999 Apr; 177(4):344-8 8239: Tempero M. Biologic therapy of gastrointestinal cancer. *Cancer Treat Res*. 1998; 98:227-37 1240: Moul JW. Angiogenesis, p53, bcl-2 and Ki-67 in the progression of prostate cancer after radical prostatectomy. *Eur Urol*. 1999; 35(5-6):399-407 6241: Engberg J, Krogsgaard M, Fugger L. Recombinant antibodies with the antigen-specific, MHC restricted specificity of T cells: novel reagents for basic and clinical investigations and immunotherapy. *Immunotechnology*. 1999 Mar; 4(3-4):273-8. 242: Nap M. Immunohistochemistry of CA 125. Unusual expression in normal tissues, distribution in the human fetus and questions around its application in diagnostic pathology. *Int J Biol Markers*. 1998 Oct-Dec; 13(4):210-5 243: O'Brien TJ, Tanimoto H, Konishi I, Gee M. More than 15 years of CA 125: what is known about the antigen, its structure and its function. *Int J Biol Markers*. 1998 Oct-Dec; 13(4):188-95. 244: Bast RC, Xu FJ, Yu YH, Barnhill S, Zhang Z, Mills GB. CA 125: the past and the future. *Int J Biol Markers*. 1998 Oct-Dec; 13(4):179-87. 245: Takamori M. An autoimmune channelopathy associated with cancer: Lambert-Eaton myasthenic syndrome. *Intern Med*. 1999 Feb; 38(2):86-96 246: Kosmas C, Stamatopoulos K, Stavroyianni N, Belessi C, Viniou N, Yataganas X. Molecular analysis of immunoglobulin genes in multiple myeloma. *Leuk Lymphoma*. 1999 Apr; 33(3-4):253-65. 247: Herlyn D, Birebent B. Advances in cancer vaccine development. *Ann Med*. 1999 Feb; 31(1):66-78. 248: Wu JT. Review of circulating tumor markers: from enzyme, carcinoembryonic protein to oncogene and suppressor gene. *Ann Clin Lab Sci*. 1999 Apr-Jun; 29(2):106-11. 249: Pandey M, Mathew A, Nair MK. Cancer vaccines: a step towards prevention and treatment of cancer. *Eur J Surg Oncol*. 1999 Apr; 25(2):209-14. 250: Werner M, Mueller J, Walch A, Hofer H. The molecular pathology of Barrett's esophagus. *Histol Histopathol*. 1999 Apr; 14(2):553-9 251: Nawrocki S, Mackiewicz A. Genetically modified tumour vaccines--where we are today. *Cancer Treat Rev*. 1999 Feb; 25(1):29-46 8252: Qiu J, Luo P, Wasmund K, Steplewski Z, Kieber-Emmons T. Towards the development of peptide mimotopes of carbohydrate antigens as cancer vaccines. *Hybridoma*. 1999 Feb; 18(1):103-12 253: Hombach A, Pohl C, Reinhold U, Abken H. Grafting T cells with tumor specificity: the chimeric receptor strategy for use in immunotherapy of malignant diseases. *Hybridoma*. 1999 Feb; 18(1):57-61. 254: Ernst P. Review article: the role of inflammation in the pathogenesis of gastric cancer. *Aliment Pharmacol Ther*. 1999 Mar; 13 Suppl 1:13-8. 255: Guy J, Aptsiauri N. Treatment of paraneoplastic visual loss with intravenous immunoglobulin: report of 3 cases. *Arch Ophthalmol*.

1999 Apr; 117(4):471-7. 256: Verheijen RH, von Mensdorff-Pouilly S, van Kamp GJ, Kenemans P. CA 125: fundamental and clinical aspects. *Semin Cancer Biol.* 1999 Apr; 9(2):117-24. 257: Dalmay JO, Posner JB. Paraneoplastic syndromes. *Arch Neurol.* 1999 Apr; 56(4):405-8. 258: Buske C, Engert A, Schnell R, Diehl V, Hiddemann W. [Monoclonal antibodies in therapy of malignant lymphomas]. *Internist (Berl).* 1998 Dec; 39(12):1205-14. 259: Chan JK. Mesenchymal tumors of the gastrointestinal tract: a paradise for acronyms (STUMP, GIST, GANT, and now GIPACT), implication of c-kit in genesis, and yet another of the many emerging roles of the interstitial cell of Cajal in the pathogenesis of gastrointestinal diseases? *Adv Anat Pathol.* 1999 Jan; 6(1):19-40. 260: Busam KJ, Jungbluth AA. Melan-A, a new melanocytic differentiation marker. *Adv Anat Pathol.* 1999 Jan; 6(1):12-8. 261: Chu PG, Chang KL, Arber DA, Weiss LM. Practical applications of immunohistochemistry in hematolymphoid neoplasms. *Ann Diagn Pathol.* 1999 Apr; 3(2):104-33. 262: Gomez-Duarte OG, Bumann D, Meyer TF. The attenuated *Salmonella* vaccine approach for the control of *Helicobacter pylori*-related diseases. *Vaccine.* 1999 Mar 26; 17(13-14):1667-73. 263: Bakkus MH. Ig gene sequences in the study of clonality. *Pathol Biol (Paris).* 1999 Feb; 47(2):128-47. 264: Hersey P. Impediments to successful immunotherapy. *Pharmacol Ther.* 1999 Feb; 81(2):111-9. 265: Ockert D, Schmitz M, Hampl M, Rieber EP. Advances in cancer immunotherapy. *Immunol Today.* 1999 Feb; 20(2):63-5. 266: Rubin MA, Buzyounouski M, Bagiella E, Sharir S, Neugut A, Benson M, de la Taille A, Katz AE, Olsson CA, Ennis RD. Microvessel density in prostate cancer: lack of correlation with tumor grade, pathologic stage, and clinical outcome. *Urology.* 1999 Mar; 53(3):542-7. 267: Schultze JL, Nadler LM. T cell mediated immunotherapy for B cell lymphoma. *J Mol Med.* 1999 Mar; 77(3):322-31. 268: Tuteja R. DNA vaccines: a ray of hope. *Crit Rev Biochem Mol Biol.* 1999; 34(1):1-24. 269: Ordonez NG. The immunohistochemical diagnosis of epithelial mesothelioma. *Hum Pathol.* 1999 Mar; 30(3):313-23. 270: Descamps V, Belaich S. [Paraneoplastic pemphigus]. *Presse Med.* 1999 Feb 20; 28(7):363-7. 271: Morse MA, Lysterly HK. Cellular and biological therapies of gastrointestinal tumors: overview of clinical trials. *Ann Surg Oncol.* 1999 Mar; 6(2):218-23. 272: Braun S, Pantel K. Prognostic significance of micrometastatic bone marrow involvement. *Breast Cancer Res Treat.* 1998; 52(1-3):201-16. 273: Thurnher M, Rieser C, Holtl L, Papesh C, Ramoner R, Bartsch G. Dendritic cell-based immunotherapy of renal cell carcinoma. *Urol Int.* 1998; 61(2):67-71. 274: Bendall LJ, Gottlieb DJ. CD44 and adhesion of normal and leukemic CD34+ cells to bone marrow stroma. *Leuk Lymphoma.* 1999 Feb; 32(5-6):427-39. 275: Foon KA, Yannelli J, Bhattacharya-Chatterjee M. Colorectal cancer as a model for immunotherapy. *Clin Cancer Res.* 1999 Feb; 5(2):225-36. 276: Koike K. [Co-infection of HBV with HCV and a possible role of HBV DNA in hepatocarcinogenesis]. *Nippon Rinsho.* 1999 Jan; 57(1):213-9. 277: Pers JO, Jamin C, Predine-Hug F, Lydyard P, Youinou P. The role of CD5-expressing B cells in health and disease (review). *Int J Mol Med.* 1999 Mar; 3(3):239-45. 278: Rinaldi M, Ciafre SA, Parrella P, Signori E, Farace MG, Saglio G, Fazio VM. Strategies to elicit anti-idiotypic immune response in B-lymphoma patients. Peptide and genetic immunization. *Adv Exp Med Biol.* 1998; 451:323-30. 279: Schirrmacher V, Haas C. Modification of cancer vaccines by virus infection and attachment of bispecific antibodies. An effective alternative to somatic gene therapy. *Adv Exp Med Biol.* 1998; 451:251-7. 280: Findley HW, Zhou M. The clinical significance of Fas expression in leukemia: questions and controversies. *Leukemia.* 1999 Feb; 13(2):147-9. 281: Chan JK. Advances in immunohistochemical techniques: toward making things simpler, cheaper, more sensitive, and more reproducible. *Adv Anat Pathol.* 1998 Sep; 5(5):314-25. 282: Chan JK. Anaplastic large cell lymphoma: redefining its morphologic spectrum and importance of recognition of the ALK-positive subset. *Adv Anat Pathol.* 1998 Sep; 5(5):281-313. 283: Goldenberg DM, Nabi HA. Breast cancer imaging with radiolabeled antibodies. *Semin Nucl Med.* 1999 Jan; 29(1):41-8. 284: Hancock JC, Wells A, Halling KC, Tilashalski K, Conner MG, Johns C, Listinsky CM. Composite B-cell and T-cell lymphoma arising 24 years after nodular lymphocyte predominant Hodgkin's disease. *Ann Diagn Pathol.* 1999 Feb; 3(1):23-34. 285: Sharifi J, Khawli LA, Hornick JL, Epstein AL. Improving monoclonal antibody pharmacokinetics via chemical modification. *Q J Nucl Med.* 1998 Dec; 42(4):242-9. 286: Tabata M, Sugihara K, Matsui R, Yonezawa S, Abeyama K, Maruyama I. Angiosarcoma of the tongue: report of a case with immunohistochemical findings. *J Oral Pathol Med.* 1999 Feb; 28(2):92-5. 287: Jager E, Jager D, Knuth A. Strategies for the development of vaccines to treat breast cancer. *Recent Results Cancer Res.* 1998; 152:94-102. 288: Butel JS, Lednický JA. Cell and molecular biology of simian virus 40: implications for human infections and disease. *J Natl Cancer Inst.* 1999 Jan 20; 91(2):119-34. 289: Greil R, Egle A, Villunger A. On the role and significance of Fas (Apo-1/CD95) ligand (FasL) expression in immune privileged tissues and cancer cells using multiple myeloma as a model. *Leuk Lymphoma.* 1998 Nov; 31(5-6):477-90. 290: Chorvath B, Sedlak J. Hematopoietic cell differentiation antigens (CD system 1997). Cancer research relevance. *Neoplasma.* 1998; 45(5):273-6. 291: Sekiguchi I, Suzuki M, Sato I, Ohkawa T, Kawashima H, Tsuchida S. Rare case of small-cell carcinoma arising from the endometrium with paraneoplastic retinopathy. *Gynecol Oncol.* 1998 Dec; 71(3):454-7. 292: Leach M, Vora AJ, Jones DA, Lucas G. Transfusion-related acute lung injury (TRALI) following autologous stem cell transplant for relapsed acute myeloid leukaemia: a case report and review of the literature. *Transfus Med.* 1998 Dec; 8(4):333-7. 293: Ohnishi K, Ohno R. [New antitumor drugs for non-Hodgkin's lymphoma]. *Gan To Kagaku Ryoho.* 1998 Dec; 25(14):2223-8. 294: Rees J. Paraneoplastic syndromes. *Curr Opin Neurol.* 1998 Dec; 11(6):633-7. 295: Link BK, Weiner GJ. Monoclonal antibodies in the treatment of human B-cell malignancies. *Leuk Lymphoma.* 1998 Oct; 31(3-4):237-49. 296: Schirrmacher V, Ahlert T, Probstle T, Steiner HH, Herold-Mende C, Gerhards R, Hagmuller E, Steiner HH. Immunization with virus-modified tumor cells. *Semin Oncol.* 1998 Dec; 25(6):677-96. 297: Livingston P. Ganglioside vaccines with emphasis on GM2. *Semin Oncol.* 1998 Dec; 25(6):636-45. 298: Dranoff G. The use of gene transfer in cancer immunotherapy. *Forum (Genova).* 1998 Oct-Dec; 8(4):357-64. 299: Hoskin DW, Williams B, Fitzpatrick L, Makrigiannis AP. Cell biology and possible therapeutic applications of anti-CD3-activated killer-T cells (review). *Int J Mol Med.* 1998 May; 1(5):893-902. 300: Guyre CA, Fanger MW. Macrophage-targeted killing and vaccines. *Res Immunol.* 1998 Sep-Oct; 149(7-8):655-60. 301: Murphy GP, Elgamal AA, Su SL, Bostwick DG, Holmes EH. Current evaluation of the tissue localization and diagnostic utility of prostate specific membrane antigen. *Cancer.* 1998 Dec 1; 83(11):2259-69. 302: Gotoda T, Matsumura Y, Kokawa A, Kondo H. [The prognostic factors of pancreatic cancer--adhesion molecule CD44]. *Gan To Kagaku Ryoho.* 1998 Nov; 25(13):2036-42. 303: Grob PJ, Frei PC. [Hepatitis B virus and

pathogenesis]. *Soz Präventivmed.* 1998; 43 Suppl 1:S5-9, S79-83 .304: Elgamal AA, Troychak MJ, Murphy GP. ProstaScint scan may enhance identification of prostate cancer recurrences after prostatectomy, radiation, or hormone therapy: analysis of 136 scans of 100 patients. *Prostate.* 1998 Dec 1; 37(4):261-9 .305: Maloney DG, Press OW. Newer treatments for non-Hodgkin's lymphoma: monoclonal antibodies. *Oncology (Huntingt).* 1998 Oct; 12(10 Suppl 8):63-76 .306: Roselli M, Buonomo O, Piazza A, Guadagni F, Vecchione A, Brunetti E, Cipriani C, Amadei G, Nieroda C, Greiner JW, Casciani CU. Novel clinical approaches in monoclonal antibody-based management in colorectal cancer patients: radioimmunoguided surgery and antigen augmentation. *Semin Surg Oncol.* 1998 Dec; 15(4):254-62 .307: Weinberg AD, Vella AT, Croft M. OX-40: life beyond the effector T cell stage. *Semin Immunol.* 1998 Dec; 10(6):471-80 .308: Leget GA, Czuczman MS. Use of rituximab, the new FDA-approved antibody. *Curr Opin Oncol.* 1998 Nov; 10(6):548-51 .309: Multani PS, Grossbard ML. Monoclonal antibody-based therapies for hematologic malignancies. *J Clin Oncol.* 1998 Nov; 16(11):3691-710 .310: Piette JC. Towards improved criteria for the antiphospholipid syndrome. *Lupus.* 1998; 7 Suppl 2:S149-57 .311: Gharavi AE, Pierangeli SS. Origin of antiphospholipid antibodies: induction of aPL by viral peptides. *Lupus.* 1998; 7 Suppl 2:S52-4 .312: Kim TJ, Park SH. Immunotherapeutic potential of JL1, a thymocyte surface protein, for leukemia. *J Korean Med Sci.* 1998 Oct; 13(5):455-8 .313: Ordonez NG. Desmoplastic small round cell tumor: II: an ultrastructural and immunohistochemical study with emphasis on new immunohistochemical markers. *Am J Surg Pathol.* 1998 Nov; 22(11):1314-27 .314: Farah RA, Clinchy B, Herrera L, Vitetta ES. The development of monoclonal antibodies for the therapy of cancer. *Crit Rev Eukaryot Gene Expr.* 1998; 8(3-4):321-56 .315: Adkins JC, Spencer CM. Edrecolomab (monoclonal antibody 17-1A). *Drugs.* 1998 Oct; 56(4):619-26; discussion 627-8 .316: McGregor J, Berdeaux A, Bonnet J, Cambien F, Fitzgerald D, Lacolley P, Lu H, Le Saux Narjoz A, Miossec P, Netter P, Poston R, Laurent S. [Cell adhesion molecules and pharmacologic applications. Round Table No 3 at Giens XIII]. *Therapie.* 1998 Jul-Aug; 53(4):371-9 .317: Schipper DL, Wagenmans MJ, Peters WH, Wagener DJ. Significance of cell proliferation measurement in gastric cancer. *Eur J Cancer.* 1998 May; 34(6):781-90 .318: Butera J, Malachovsky M, Rathore R, Safran H. Novel approaches in development for the treatment of pancreatic cancer. *Front Biosci.* 1998 Nov 1; 3:E226-9 .319: Agrawal B, Gendler SJ, Longenecker BM. The biological role of mucins in cellular interactions and immune regulation: prospects for cancer immunotherapy. *Mol Med Today.* 1998 Sep; 4(9):397-403 .320: Solal-Celigny P. [Treatment of malignant low-grade lymphoma. Follicular Lymphoma Study Group]. *Rev Med Interne.* 1998; 19 Suppl 1:18S-20S . available. .321: Cerilli LA, Huffman HT, Anand A. Primary renal angiosarcoma: a case report with immunohistochemical, ultrastructural, and cytogenetic features and review of the literature. *Arch Pathol Lab Med.* 1998 Oct; 122(10):929-35 .322: Mitchell EP. Role of carcinoembryonic antigen in the management of advanced colorectal cancer. *Semin Oncol.* 1998 Oct; 25(5 Suppl 11):12-20 .323: Hakomori S. Cancer-associated glycosphingolipid antigens: their structure, organization, and function. *Acta Anat (Basel).* 1998; 161(1-4):79-90 .324: Ordonez NG. Role of immunohistochemistry in distinguishing epithelial peritoneal mesotheliomas from peritoneal and ovarian serous carcinomas. *Am J Surg Pathol.* 1998 Oct; 22(10):1203-14 .325: Matthews DC. Immunotherapy in acute myelogenous leukemia and myelodysplastic syndrome. *Leukemia.* 1998 Sep; 12 Suppl 1:S33-6 .326: Seitz HK, Simanowski UA, Homann N, Waldherr R. Cell proliferation and its evaluation in the colorectal mucosa: effect of ethanol. *Z Gastroenterol.* 1998 Aug; 36(8):645-55 .327: Hollowood K, Goodlad JR. Germinal centre cell kinetics. *J Pathol.* 1998 Jul; 185(3):229-33 .328: Brambilla E, Brambilla C. p53 and lung cancer. *Pathol Biol (Paris).* 1997 Dec; 45(10):852-63 .329: Taylor DD, Gercel-Taylor C. Tumor-reactive immunoglobulins in ovarian cancer: diagnostic and therapeutic significance? (review). *Oncol Rep.* 1998 Nov-Dec; 5(6):1519-24 .330: Smitt PA, de Leeuw B, Vecht CJ. [Immunology in the clinical practice. XVI. Paraneoplastic syndromes of the nervous system: pathogenesis and diagnosis]. *Ned Tijdschr Geneesk.* 1998 Jul 18; 142(29):1652-8 . Dutch. .331: Sweat SD, Pacelli A, Murphy GP, Bostwick DG. Prostate-specific membrane antigen expression is greatest in prostate adenocarcinoma and lymph node metastases. *Urology.* 1998 Oct; 52(4):637-40 .332: Rittenhouse HG, Finlay JA, Mikolajczyk SD, Partin AW. Human Kallikrein 2 (hK2) and prostate-specific antigen (PSA): two closely related, but distinct, kallikreins in the prostate. *Crit Rev Clin Lab Sci.* 1998 Aug; 35(4):275-368 .333: Palacio A, Tamariz L, Berger J, Patarca R. Enteropathy-associated T-cell lymphoma and its immunocarcinogenic correlates: case report and review of the literature. *Crit Rev Oncog.* 1998; 9(1):63-81 .334: Greslin I, Mougin C, Seilles E. [The biology of papillomavirus infections. III. Immune response]. *Ann Biol Clin (Paris).* 1998 May-Jun; 56(3):267-76 .335: Coiffier B, Salles G. [Update on lymphomas: 1997, a profitable year]. *Bull Cancer.* 1998 Jan; 85(1):45-7 . available. .336: Maloney DG. Advances in immunotherapy of hematologic malignancies. *Curr Opin Hematol.* 1998 Jul; 5(4):237-43 .337: Guglielmi A, Frameglia M, Iuzzolino P, Martignoni G, De Manzoni G, Laterza E, Veraldi GF, Girlanda R. Solitary fibrous tumor of the liver with CD 34 positivity and hypoglycemia. *J Hepatobiliary Pancreat Surg.* 1998; 5(2):212-6 .338: Yamaguchi A. [Expression of variant CD44 in colorectal cancer and its relationship to liver metastasis]. *Nippon Geka Gakkai Zasshi.* 1998 Jul; 99(7):409-14 .339: Meier F, Satyamoorthy K, Nesbit M, Hsu MY, Schitteck B, Garbe C, Herlyn M. Molecular events in melanoma development and progression. *Front Biosci.* 1998 Sep 15; 3:D1005-10 .340: Cserni G, Boross G, Baltas B. [The role of the histopathological analysis of sentinel lymph nodes in breast cancer. Preliminary findings]. *Orv Hetil.* 1998 Aug 9; 139(32):1899-903 . Hungarian. .341: Ng IO. Prognostic significance of pathological and biological factors in hepatocellular carcinoma. *J Gastroenterol Hepatol.* 1998 Jun; 13(6):666-70 .342: Ellem KA, Schmidt CW, Li CL, Misko I, Kelso A, Sing G, Macdonald G, O'Rourke MG. The labyrinthine ways of cancer immunotherapy--T cell, tumor cell encounter: "how do I lose thee? Let me count the ways" . *Adv Cancer Res.* 1998; 75:203-49 . available. .343: Ruiz-Arguelles A, Duque RE, Orfao A. [1st Latin American consensus conference on immunologic typing of leukemias]. *Rev Invest Clin.* 1997 Jul-Aug; 49(4):317-22 . Spanish. .344: Totterman TH, Gidlof C, Ragnarsson L, Hogbom E, Lindeberg M, von der Lehr N, Einarsson A, Soegaard M, Kristensson K, Kalland T, Dohlsten M. Targeted superantigens for immunotherapy of haematopoietic tumours. *Vox Sang.* 1998; 74 Suppl 2:483-7 .345: Sandler SG. Management of patients with hematologic malignancies and aplastic anemia who are refractory to platelet transfusions. *Haematologia (Budap).* 1998; 29(1):1-11 .346: Zhong RZ, Lazarovits AI. Monoclonal antibody against CD45RB for the therapy of rejection and autoimmune diseases. *J Mol Med.* 1998 Jul; 76(8):572-80 .347: Mahler V, Antoni C, Anhalt GJ, Koch HJ, Peters KP, Manger B, Kalden

JR, Hornstein OP. Graft-versus-host-like mucocutaneous eruptions with serological features of paraneoplastic pemphigus and systemic lupus erythematosus in a patient with non-Hodgkin's lymphoma. *Dermatology*. 1998; 197(1):78-83 348: Matker CM, Rizzo P, Pass HI, Di Resta I, Powers A, Mutti L, Kast WM, Carbone M. The biological activities of simian virus 40 large-T antigen and its possible oncogenic effects in humans. *Monaldi Arch Chest Dis*. 1998 Apr; 53(2):193-7 349: Guarino M, Giordano F, Pallotti F, Polizzotti G, Tricomi P, Cristofori E. Malignant mixed müllerian tumor of the uterus. Features favoring its origin from a common cell clone and an epithelial-to-mesenchymal transformation mechanism of histogenesis. *Tumori*. 1998 May-Jun; 84(3):391-7 350: Bonneville M, Scotet E, Peyrat MA, Saulquin X, Houssaint E. Epstein-Barr virus and rheumatoid arthritis. *Rev Rhum Engl Ed*. 1998 Jun; 65(6):365-8 available. 351: Steen R, Egeland T. CD34 molecule epitope distribution on cells of haematopoietic origin. *Leuk Lymphoma*. 1998 Jun; 30(1-2):23-30 352: Ozdemirli M, Fanburg-Smith JC, Hartmann DP, Shad AT, Lage JM, Magrath IT, Azumi N, Harris NL, Cossman J, Jaffe ES. Precursor B-Lymphoblastic lymphoma presenting as a solitary bone tumor and mimicking Ewing's sarcoma: a report of four cases and review of the literature. *Am J Surg Pathol*. 1998 Jul; 22(7):795-804 353: Hadden JW. The immunopharmacology of head and neck cancer: an update. *Int J Immunopharmacol*. 1997 Nov-Dec; 19(11-12):629-44 354: Aarli JA, Skeie GO, Mygland A, Gilhus NE. Muscle striation antibodies in myasthenia gravis. Diagnostic and functional significance. *Ann N Y Acad Sci*. 1998 May 13; 841:505-15 available. 355: Dropcho EJ. Principles of paraneoplastic syndromes. *Ann N Y Acad Sci*. 1998 May 13; 841:246-61 available. 356: Niho Y, Asano Y. Fas/Fas ligand and hematopoietic progenitor cells. *Curr Opin Hematol*. 1998 May; 5(3):163-5 357: Maio M, Brasoveanu LI, Coral S, Sigalotti L, Lamaj E, Gasparollo A, Visintin A, Altomonte M, Fonsatti E. Structure, distribution, and functional role of protectin (CD59) in complement-susceptibility and in immunotherapy of human malignancies (Review). *Int J Oncol*. 1998 Aug; 13(2):305-18 358: Torbenson M, Dhir R, Nangia A, Becich MJ, Kapadia SB. Prostatic carcinoma with signet ring cells: a clinicopathologic and immunohistochemical analysis of 12 cases, with review of the literature. *Mod Pathol*. 1998 Jun; 11(6):552-9 359: Baum RP, Brummendorf TH. Radioimmunolocalization of primary and metastatic breast cancer. *Q J Nucl Med*. 1998 Mar; 42(1):33-42 360: Laytragoon-Lewin N. Programmed cell death: the influence of CD40, CD95 (Fas or Apo-1) and their ligands. *Med Oncol*. 1998 Apr; 15(1):15-9 361: Bookman MA. Biological therapy of ovarian cancer: current directions. *Semin Oncol*. 1998 Jun; 25(3):381-96 362: Ablin RJ. A retrospective and prospective overview of prostate-specific antigen. *J Cancer Res Clin Oncol*. 1997; 123(11-12):583-94 363: Resser JR, Carbone DP. Immunotherapy of head and neck cancer. *Curr Opin Oncol*. 1998 May; 10(3):226-32 364: Antonini C, Forgiarini O, Chiara A, Briani G, Belmonte P, Zucconelli R, Fiaccavento G, Sacchi G. [Stromal tumor of the ileum (GIST) at the same time as a renal carcinoma. Description of a case and review of the literature]. *Pathologica*. 1998 Apr; 90(2):160-4 Italian. 365: Nakamura T, Tabuchi Y, Ohno M. Relations of nm23 expression to clinicopathologic variables and proliferative activity of gastric cancer lesions. *Cancer Detect Prev*. 1998; 22(3):246-50 366: Fradet Y. Phenotypic characterization of bladder cancer. *Eur Urol*. 1998; 33 Suppl 4:5-6 available. 367: Denis MG. Characterization, cloning and expression of the Tage4 gene, a member of the immunoglobulin superfamily. *Int J Oncol*. 1998 May; 12(5):997-1005 368: McKeever PE. Insights about brain tumors gained through immunohistochemistry and in situ hybridization of nuclear and phenotypic markers. *J Histochem Cytochem*. 1998 May; 46(5):585-94 369: Klein U, Goossens T, Fischer M, Kanzler H, Braeuninger A, Rajewsky K, Kuppers R. Somatic hypermutation in normal and transformed human B cells. *Immunol Rev*. 1998 Apr; 162:261-80 370: Stevenson F, Sahota S, Zhu D, Ottensmeier C, Chapman C, Oscier D, Hamblin T. Insight into the origin and clonal history of B-cell tumors as revealed by analysis of immunoglobulin variable region genes. *Immunol Rev*. 1998 Apr; 162:247-59 371: Maraj BH, Whelan P, Markham AF. Prostate-specific membrane antigen. *Br J Urol*. 1998 Apr; 81(4):523-8 available. 372: Lin BT, Bonsib SM, Mierau GW, Weiss LM, Medeiros LJ. Oncocytic adrenocortical neoplasms: a report of seven cases and review of the literature. *Am J Surg Pathol*. 1998 May; 22(5):603-14 373: Bhattacharya-Chatterjee M, Foon KA. Anti-idiotypic antibody vaccine therapies of cancer. *Cancer Treat Res*. 1998; 94:51-68 available. 374: Chiron MF. [Recombinant immunotoxins and chimeric toxins for targeted therapy in oncology]. *Bull Cancer*. 1997 Dec; 84(12):1135-40 375: Wikstrand CJ, Reist CJ, Archer GE, Zalutsky MR, Bigner DD. The class III variant of the epidermal growth factor receptor (EGFRvIII): characterization and utilization as an immunotherapeutic target. *J Neurovirol*. 1998 Apr; 4(2):148-58 376: Majewski S, Jablonska S. Immunology of HPV infection and HPV-associated tumors. *Int J Dermatol*. 1998 Feb; 37(2):81-95 available. 377: Reisfeld RA, Becker JC, Gillies SD. Immunocytokines: a new approach to immunotherapy of melanoma. *Melanoma Res*. 1997 Aug; 7 Suppl 2:S99-106 378: Adams GP. Improving the tumor specificity and retention of antibody-based molecules. *In Vivo*. 1998 Jan-Feb; 12(1):11-21 379: Lamb HM, Faulds D. Capromab pendetide. A review of its use as an imaging agent in prostate cancer. *Drugs Aging*. 1998 Apr; 12(4):293-304 380: Guzman-Rojas L, Alcocer-Gonzalez JM, Madrid-Marina V. [Perspectives for the development of vaccines and immunotherapy against cervico-uterine cancer]. *Salud Publica Mex*. 1998 Jan-Feb; 40(1):38-46 Spanish. 381: Wesche WA, Wilimas J, Khare V, Parham DM. Renal medullary carcinoma: a potential sickle cell nephropathy of children and adolescents. *Pediatr Pathol Lab Med*. 1998 Jan-Feb; 18(1):97-113 382: Stocchi L, Nelson H. Diagnostic and therapeutic applications of monoclonal antibodies in colorectal cancer. *Dis Colon Rectum*. 1998 Feb; 41(2):232-50 383: Dighiero G. Autoimmunity and B-cell malignancies. *Hematol Cell Ther*. 1998 Feb; 40(1):1-9 384: Resta R, Yamashita Y, Thompson LF. Ecto-enzyme and signaling functions of lymphocyte CD73. *Immunol Rev*. 1998 Feb; 161:95-109 385: Joseph-Silverstein J, Silverstein RL. Cell adhesion molecules: an overview. *Cancer Invest*. 1998; 16(3):176-82 386: Falini B, Terenzi A, Liso A, Flenghi L, Solinas A, Pasqualucci L. Targeted antibodies in the treatment of lymphomas. *Cancer Surv*. 1997; 30:295-309 387: Weller M, Kleihues P, Dichgans J, Ohgaki H. CD95 ligand: lethal weapon against malignant glioma? *Brain Pathol*. 1998 Apr; 8(2):285-93 388: Benharroch D, Meguerian-Bedoyan Z, Lamant L, Amin C, Brugieres L, Terrier-Lacombe MJ, Haralambieva E, Pulford K, Pileri S, Morris SW, Mason DY, Delsol G. ALK-positive lymphoma: a single disease with a broad spectrum of morphology. *Blood*. 1998 Mar 15; 91(6):2076-84 389: Treon SP, Anderson KC. Interleukin-6 in multiple myeloma and related plasma cell dyscrasias. *Curr Opin Hematol*. 1998 Jan; 5(1):42-8 390: Zbar AP, Lemoine NR, Wadhwa M, Thomas H, Snary D, Kmiet WA. Biological therapy: approaches in colorectal cancer. Strategies to

enhance carcinoembryonic antigen (CEA) as an immunogenic target. *Br J Cancer*. 1998 Mar; 77(5):683-93 available. 391: Clatch RJ, Foreman JR, Walloch JL. Simplified immunophenotypic analysis by laser scanning cytometry. *Cytometry*. 1998 Feb 15; 34(1):3-16 392: Dropcho EJ. Neurologic paraneoplastic syndromes. *J Neurol Sci*. 1998 Jan 8; 153(2):264-78 393: Gregorakis AK, Holmes EH, Murphy GP. Prostate-specific membrane antigen: current and future utility. *Semin Urol Oncol*. 1998 Feb; 16(1):2-12 394: Yonezawa S, Sato E. Expression of mucin antigens in human cancers and its relationship with malignancy potential. *Pathol Int*. 1997 Dec; 47(12):813-30 395: Maxwell-Armstrong CA, Durrant LG, Scholefield JH. Colorectal cancer vaccines. *Br J Surg*. 1998 Feb; 85(2):149-54 396: Parfitt AM, Wang Q, Palnitkar S. Rates of cell proliferation in adenomatous, suppressed, and normal parathyroid tissue: implications for pathogenesis. *J Clin Endocrinol Metab*. 1998 Mar; 83(3):863-9 397: Lenickova L, Smid F. [Glycosphingolipids as tumor markers]. *Cas Lek Cesk*. 1997 Nov 5; 136(21):655-61 Czech. 398: Pritsch O, Maloum K, Dighiero G. Basic biology of autoimmune phenomena in chronic lymphocytic leukemia. *Semin Oncol*. 1998 Feb; 25(1):34-41 399: Heatley MK. What is the value of proliferation markers in the normal and neoplastic cervix? *Histol Histopathol*. 1998 Jan; 13(1):249-54 400: Illiger HJ. [Monoclonal antibody 17-1A (Panorex). A new approach to adjuvant therapy of colonic carcinoma]. *Internist (Berl)*. 1997 Oct; 38(10):1001-6; discussion 1006 . No abstract available. 401: Berumen J, Villegas N. [Recombinant therapeutic vaccines against cancer of the uterine cervix]. *Salud Publica Mex*. 1997 Jul-Aug; 39(4):288-97 Spanish. 402: Viviani S, Jack A, Bah E, Montesano R. [Hepatocellular carcinoma: a preventable cancer]. *Epidemiol Prev*. 1997 Apr-Jun; 21(2):129-36 Italian. 403: Niederkorn JY. Immunoregulation of intraocular tumours. *Eye*. 1997; 11 (Pt 2):249-54. 404: Schirmacher V. [Tumor vaccines and active specific immunotherapy]. *Internist (Berl)*. 1997 Nov; 38(11):1050-4 405: Nicolas JC, Marechal V, Dehee A. [Epstein-Barr virus]. *Bull Acad Natl Med*. 1997 Jun-Jul; 181(6):981-96; discussion 996-7. 406: Gokden M, Roth KA, Carroll SL, Wick MR, Schmidt RE. Clear cell neoplasms and pseudoneoplastic lesions of the central nervous system. *Semin Diagn Pathol*. 1997 Nov; 14(4):253-69 407: Nakayama H, Kimura A, Okumichi T, Miyazaki E, Kajihara H, Enzan H. Metaplastic shadow cells in rectal adenocarcinoma: report of a case with immunohistochemical study. *Jpn J Clin Oncol*. 1997 Dec; 27(6):427-32 408: Iwasa K, Komai K, Yasukawa Y, Maruta T, Takamori M. [Molecular immunology of voltage-gated calcium channel and Lambert-Eaton myasthenic syndrome]. *Nippon Rinsho*. 1997 Dec; 55(12):3322-30 . 409: Curnow RT. Clinical experience with CD64-directed immunotherapy. An overview. *Cancer Immunol Immunother*. 1997 Nov-Dec; 45(3-4):210-5 410: de Gast GC, van de Winkel JG, Bast BE. Clinical perspectives of bispecific antibodies in cancer. *Cancer Immunol Immunother*. 1997 Nov-Dec; 45(3-4):121-3 available. 411: Ordonez NG. Value of the Ber-EP4 antibody in differentiating epithelial pleural mesothelioma from adenocarcinoma. The M.D. Anderson experience and a critical review of the literature. *Am J Clin Pathol*. 1998 Jan; 109(1):85-9 412: Masutani K, Fujimaru M, Tsubota Y, Matsui N, Okamura T. [Double negative adult T-cell leukemia with hemophagocytic syndrome]. *Rinsho Ketsueki*. 1997 Nov; 38(11):1199-205 . 413: Matz LR, Latham BI, Fabian VA, Vivian JB. Collecting duct carcinoma of the kidney: a report of three cases and review of the literature. *Pathology*. 1997 Nov; 29(4):354-9 414: Arlen M, Tsang A, Wang T. Immunotherapy of colon cancer using chimeric mAb 31.1. *Crit Rev Immunol*. 1998; 18(1-2):133-8 415: Chen MF, Jeng LB. Partial hepatic resection for hepatocellular carcinoma. *J Gastroenterol Hepatol*. 1997 Oct; 12(9-10):S329-34 416: Sheu JC. Molecular mechanism of hepatocarcinogenesis. *J Gastroenterol Hepatol*. 1997 Oct; 12(9-10):S309-13 417: Wick MR. Immunophenotyping of malignant mesothelioma. *Am J Surg Pathol*. 1997 Dec; 21(12):1395-8 available. 418: Schlimok G. [Adjuvant and palliative immunotherapy of colorectal carcinoma]. *Schweiz Rundsch Med Prax*. 1997 Sep 24; 86(39):1517-9 . 419: Stewart CC, Behm FG, Carey JL, Cornbleet J, Duque RE, Hudnall SD, Hurtubise PE, Loken M, Tubbs RR, Wormsley S. U.S.-Canadian Consensus recommendations on the immunophenotypic analysis of hematologic neoplasia by flow cytometry: selection of antibody combinations. *Cytometry*. 1997 Oct 15; 30(5):231-5 available. 420: Chen YH, Shiao RT, Labayog JM, Modi S, Lavelle D. Modulation of interleukin-6/interleukin-6 receptor cytokine loop in the treatment of multiple myeloma. *Leuk Lymphoma*. 1997 Sep; 27(1-2):11-23 421: Buchsbaum DJ. Experimental tumor targeting with radiolabeled ligands. *Cancer*. 1997 Dec 15; 80(12 Suppl):2371-7 422: Raz E. Introduction: gene vaccination, current concepts and future directions. *Springer Semin Immunopathol*. 1997; 19(2):131-7 available. 423: Dachs GU, Dougherty GJ, Stratford IJ, Chaplin DJ. Targeting gene therapy to cancer: a review. *Oncol Res*. 1997; 9(6-7):313-25 424: Santa Cruz DJ, Hamilton PD, Klos DJ, Fernandez-Pol JA. Differential expression of metalloproteinase/S27 ribosomal protein in melanocytic lesions of the skin. *J Cutan Pathol*. 1997 Oct; 24(9):533-42 425: Hounsell EF, Young M, Davies MJ. Glycoprotein changes in tumours: a renaissance in clinical applications. *Clin Sci (Colch)*. 1997 Oct; 93(4):287-93 426: Myers DE, Jun X, Clementson D, Donelson R, Sicheneder A, Hoffman N, Bell K, Sarquis M, Langlie MC, Turner N, Uckun FM. Large scale manufacturing of TXU(anti-CD7)-pokeweed antiviral protein (PAP) immunoconjugate for clinical trials. *Leuk Lymphoma*. 1997 Oct; 27(3-4):275-302 427: Durrant LG. Cancer vaccines. *Anticancer Drugs*. 1997 Sep; 8(8):727-33 428: Gurski KJ, Steller MA. Progress and prospects in vaccine therapy for gynecologic cancers. *Oncology (Huntingt)*. 1997 Nov; 11(11):1727-34, 1739-40; discussion 1740, 429: Oh SJ, Dropcho EJ, Claussen GC. Anti-Hu-associated paraneoplastic sensory neuropathy responding to early aggressive immunotherapy: report of two cases and review of literature. *Muscle Nerve*. 1997 Dec; 20(12):1576-82 430: Skarin AT, Dorfman DM. Non-Hodgkin's lymphomas: current classification and management. *CA Cancer J Clin*. 1997 Nov-Dec; 47(6):351-72 431: Scott AM, Welt S. Antibody-based immunological therapies. *Curr Opin Immunol*. 1997 Oct; 9(5):717-22 432: Sahin U, Tureci O, Pfreundschuh M. Serological identification of human tumor antigens. *Curr Opin Immunol*. 1997 Oct; 9(5):709-16 433: Brodie A, Lu Q, Nakamura J. Aromatase in the normal breast and breast cancer. *J Steroid Biochem Mol Biol*. 1997 Apr; 61(3-6):281-6 434: Livingston PO, Ragupathi G. Carbohydrate vaccines that induce antibodies against cancer. 2. Previous experience and future plans. *Cancer Immunol Immunother*. 1997 Oct; 45(1):10-9 available. 435: Livingston PO, Zhang S, Lloyd KO. Carbohydrate vaccines that induce antibodies against cancer. 1. Rationale. *Cancer Immunol Immunother*. 1997 Oct; 45(1):1-9 available. 436: Davis HL. Plasmid DNA expression systems for the purpose of immunization. *Curr Opin Biotechnol*. 1997 Oct; 8(5):635-46 437: Kratzer SS, Ulbright TM, Talerman A, Srigley JR, Roth LM, Wahle GR, Moussa M, Stephens JK, Millos A, Young RH. Large cell calcifying Sertoli cell tumor of the

testis: contrasting features of six malignant and six benign tumors and a review of the literature. *Am J Surg Pathol*. 1997 Nov; 21(11):1271-80 438: Mahle C, Schwartz M, Popek E, Bocklage T. Intra-abdominal lymphangiomas in children and adults. Assessment of proliferative activity. *Arch Pathol Lab Med*. 1997 Oct; 121(10):1055-62 439: Sunderkotter C, Kalden H, Luger TA. Aging and the skin immune system. *Arch Dermatol*. 1997 Oct; 133(10):1256-62 440: Lam KS, Zhao ZG. Targeted therapy for lymphoma with peptides. *Hematol Oncol Clin North Am*. 1997 Oct; 11(5):1007-19 441: Liu SY, Press OW. The potential for immunoconjugates in lymphoma therapy. *Hematol Oncol Clin North Am*. 1997 Oct; 11(5):987-1006 442: O'Leary CP, Willison HJ. Autoimmune ataxic neuropathies (sensory ganglionopathies). *Curr Opin Neurol*. 1997 Oct; 10(5):366-70 443: Shaw PM, Sivanandham M, Bernik SF, Ditaranto K, Wallack MK. Adjuvant immunotherapy for patients with melanoma: are patients with melanoma of the head and neck candidates for this therapy? *Head Neck*. 1997 Oct; 19(7):595-603 444: Valerius T, Elsasser D, Repp R, Van de Winkel JG, Gramatzki M, Glennie M. HLA class II antibodies recruit G-CSF activated neutrophils for treatment of B-cell malignancies. *Leuk Lymphoma*. 1997 Jul; 26(3-4):261-9 445: Penichet ML, Harvill ET, Morrison SL. Antibody-IL-2 fusion proteins: a novel strategy for immune protection. *Hum Antibodies*. 1997; 8(3):106-18 446: Suhrbier A. Multi-epitope DNA vaccines. *Immunol Cell Biol*. 1997 Aug; 75(4):402-8 447: Reichardt VL, Okada CY, Stockerl-Goldstein KE, Bogen B, Levy R. Rationale for adjuvant idiotypic vaccination after high-dose therapy for multiple myeloma. *Biol Blood Marrow Transplant*. 1997 Aug; 3(3):157-63 448: Furukawa F, Fujii K, Horiguchi Y, Matsuyoshi N, Fujita M, Toda K, Imamura S, Wakita H, Shirahama S, Takigawa M. Roles of E- and P-cadherin in the human skin. *Microsc Res Tech*. 1997 Aug 15; 38(4):343-52 449: Springer GF. Immunoreactive T and Tn epitopes in cancer diagnosis, prognosis, and immunotherapy. *J Mol Med*. 1997 Aug; 75(8):594-602 450: Chan DW, Sokoll LJ. Prostate-specific antigen: update 1997. *J Int Fed Clin Chem*. 1997 Sep; 9(3):120-5 451: Danzig M, Cuss F. Inhibition of interleukin-5 with a monoclonal antibody attenuates allergic inflammation. *Allergy*. 1997 Aug; 52(8):787-94 452: Bartges JW. Therapeutic plasmapheresis. *Semin Vet Med Surg (Small Anim)*. 1997 Aug; 12(3):170-7 453: Kuhn CA, Hanke CW. Current status of melanoma vaccines. *Dermatol Surg*. 1997 Aug; 23(8):649-54; discussion 654-5 454: Segal-Eiras A, Croce MV. Breast cancer associated mucin: a review. *Allergol Immunopathol (Madr)*. 1997 Jul-Aug; 25(4):176-81 455: Fonseca R, Tefferi A, Strickler JG. Follicular dendritic cell sarcoma mimicking diffuse large cell lymphoma: a case report. *Am J Hematol*. 1997 Jul; 55(3):148-55 456: Meager A. Natural autoantibodies to interferons. *J Interferon Cytokine Res*. 1997 Jul; 17 Suppl 1:S51-3 457: Fair WR, Israeli RS, Heston WD. Prostate-specific membrane antigen. *Prostate*. 1997 Jul 1; 32(2):140-8 458: Sonneveld P, Wiemer E. Assays for the analysis of P-glycoprotein in acute myeloid leukemia and CD34 subsets of AML blasts. *Leukemia*. 1997 Jul; 11(7):1160-5 459: Bolla L, Palmer RM. Paraneoplastic cerebellar degeneration. Case report and literature review. *Arch Intern Med*. 1997 Jun 9; 157(11):1258-62 460: Moelling K. DNA for genetic vaccination and therapy. *Cytokines Cell Mol Ther*. 1997 Jun; 3(2):127-35 461: Schendel DJ, Oberneder R, Falk CS, Jantzer P, Kressenstein S, Maget B, Hofstetter A, Riethmüller G, Nossner E. Cellular and molecular analyses of major histocompatibility complex (MHC) restricted and non-MHC-restricted effector cells recognizing renal cell carcinomas: problems and perspectives for immunotherapy. *J Mol Med*. 1997 Jun; 75(6):400-13 462: Bastian BC. Annexins in cancer and autoimmune diseases. *Cell Mol Life Sci*. 1997 Jun; 53(6):554-6 463: Dalmau JO, Posner JB. Paraneoplastic syndromes affecting the nervous system. *Semin Oncol*. 1997 Jun; 24(3):318-28 464: Galili U, LaTemple DC. Natural anti-Gal antibody as a universal augmentor of autologous tumor vaccine immunogenicity. *Immunol Today*. 1997 Jun; 18(6):281-5 available. 465: Kilpatrick SE, Inwards CY, Fletcher CD, Smith MA, Gitelis S. Myxoid chondrosarcoma (chordoid sarcoma) of bone: a report of two cases and review of the literature. *Cancer*. 1997 May 15; 79(10):1903-10 466: Oberling F. Monocyte/macrophages as effector cells in cancer immunotherapy. *Transfus Sci*. 1997 Jun; 18(2):243-50 467: Muroi K, Amemiya Y, Sievers EL, Miura Y, Hakamori SI, Loken MR. Expression of sialosyl-T and disialosyl-T antigens in erythroid cells. *Leuk Lymphoma*. 1997 May; 25(5-6):403-14 468: Yabana M, Takagi N, Kihara M, Muto R, Tamura K, Maemoto S, Minamisawa M, Nakatani Y, Ishii M. [A case of nephrotic syndrome after bone marrow transplantation]. *Nippon Jinzo Gakkai Shi*. 1997 May; 39(4):414-20 469: Begent RH, Chester KA. Single-chain Fv antibodies for targeting cancer therapy. *Biochem Soc Trans*. 1997 May; 25(2):715-7 available. 470: Anderson DR, Grillo-Lopez A, Varns C, Chambers KS, Hanna N. Targeted anti-cancer therapy using rituximab, a chimeric anti-CD20 antibody (IDEC-C2B8) in the treatment of non-Hodgkin's B-cell lymphoma. *Biochem Soc Trans*. 1997 May; 25(2):705-8 available. 471: Bond A, Corlett L, Nagvekar N, Jacobson L, Pantic N, Beeson D, Nicolle M, Vincent A, Newsom-Davis J, Spack E, Willcox N. Heterogeneity and immunotherapy of specific T-cells in myasthenia gravis. *Biochem Soc Trans*. 1997 May; 25(2):665-70 available. 472: Scott AM, Cebon J. Clinical promise of tumour immunology. *Lancet*. 1997 May; 349 Suppl 2:S119-22 available. 473: Israeli RS, Grob M, Fair WR. Prostate-specific membrane antigen and other prostatic tumor markers on the horizon. *Urol Clin North Am*. 1997 May; 24(2):439-50 474: Nishimoto N, Shima Y, Sasai M, Danno N, Yoshizaki K. [Clinical application of interleukin-6 receptor antibody]. *Nihon Rinsho Meneki Gakkai Kaishi*. 1997 Apr; 20(2):87-94 475: el-Ghorr AA, Norval M. Biological effects of narrow-band (311 nm TL01) UVB irradiation: a review. *J Photochem Photobiol B*. 1997 Apr; 38(2-3):99-106 476: Fischer S, Scheffler A, Kabelitz D. Stimulation of the specific immune system by mistletoe extracts. *Anticancer Drugs*. 1997 Apr; 8 Suppl 1:S33-7 477: Renner C, Trumper L, Pfreundschuh M. Monoclonal antibodies in the treatment of non-Hodgkin's lymphoma: recent results and future prospects. *Leukemia*. 1997 Apr; 11 Suppl 2:S55-9 478: Takakura K. [Interleukin-2 receptor]. *Nippon Rinsho*. 1997 Apr; 55 Suppl 2:520-5 available. 479: Goodnow CC, Cyster JG. Lymphocyte homing: the scent of a follicle. *Curr Biol*. 1997 Apr 1; 7(4):R219-22 480: Eldor J. Urotherapy for patients with cancer. *Med Hypotheses*. 1997 Apr; 48(4):309-15 481: Altenschmidt U, Moritz D, Groner B. Specific cytotoxic T lymphocytes in gene therapy. *J Mol Med*. 1997 Apr; 75(4):259-66 482: Huang YW, Baluna R, Vitetta ES. Adhesion molecules as targets for cancer therapy. *Histol Histopathol*. 1997 Apr; 12(2):467-77 483: Goldsmith SJ. Receptor imaging: competitive or complementary to antibody imaging? *Semin Nucl Med*. 1997 Apr; 27(2):85-93 484: Morris JC. Structure and function of the TSH receptor: its suitability as a target for radiotherapy. *Thyroid*. 1997 Apr; 7(2):253-8 485: Sznol M, Holmlund J. Antigen-specific agents in development. *Semin Oncol*. 1997 Apr; 24(2):173-86 486: Karius D, Marriott MA. Immunologic advances in monoclonal antibody therapy: implications for oncology nursing. *Oncol Nurs Forum*.

1997 Apr; 24(3):483-94; QUIZ 495-6 487: Ivanyi JL, Marton E, Szabo F, Mahunka M, Kelenyi G.[Anaplastic large cell lymphoma based on our clinicopathological cases].Orv Hetil. 1997 Mar 30; 138(13):779-84 Hungarian.488: Goldenberg DM, Juweid M, Dunn RM, Sharkey RM.Cancer imaging with radiolabeled antibodies: new advances withtechnetium-99m-labeled monoclonal antibody Fab' fragments, especially CEA-Scanand prospects for therapy.J Nucl Med Technol. 1997 Mar; 25(1):18-23; quiz 34 489: Bene MC, Faure GC.CD10 in acute leukemias. GEIL (Groupe d'Etude Immunologique des Leucemies).Haematologica. 1997 Mar-Apr; 82(2):205-10 490: Carter JJ, Galloway DA.Humoral immune response to human papillomavirus infection.Clin Dermatol. 1997 Mar-Apr; 15(2):249-59 available.491: Howett MK, Christensen ND, Kreider JW.Tissue xenografts as a model system for study of the pathogenesis ofpapillomaviruses.Clin Dermatol. 1997 Mar-Apr; 15(2):229-36 available.492: Komada Y, Sakurai M.Fas receptor (CD95)-mediated apoptosis in leukemic cells.Leuk Lymphoma. 1997 Mar; 25(1-2):9-21 493: Dalquen P, Baschiera B, Chaffard R, Dieterich H, Feichter GE, Krmer K,Torhorst J.MIB-1 (Ki-67) immunostaining of breast cancer cells in cytologic smears.Acta Cytol. 1997 Mar-Apr; 41(2):229-37 494: Itoh C, Katono J.[B cell function and its evaluation].Nippon Rinsho. 1997 Mar; 55 Suppl 1:166-71. 495: Deo YM, Graziano RF, Repp R, van de Winkel JG.Clinical significance of IgG Fc receptors and Fc gamma R-directedimmunotherapies.Immunol Today. 1997 Mar; 18(3):127-35 496: Hakomori S, Zhang Y.Glycosphingolipid antigens and cancer therapy.Chem Biol. 1997 Feb; 4(2):97-104 497: Wang ZY, Shen ZX.Megakaryocytes and platelets in immune thrombocytopenic purpura.Baillieres Clin Haematol. 1997 Feb; 10(1):89-107 498: O'Reilly PE, Raab SS, Niemann TH, Rodgers JR, Robinson RA.p53, proliferating cell nuclear antigen, and Ki-67 expression in extrauterineleiomyosarcomas.Mod Pathol. 1997 Feb; 10(2):91-7 499: Molinie V, Pouchot J, Vinceneux P, Barge J.Osteoclastoma-like giant cell tumor of the renal pelvis associated withpapillary transitional cell carcinoma.Arch Pathol Lab Med. 1997 Feb; 121(2):162-6 500: Behr TM, Goldenberg DM, Becker WS.Radioimmunotherapy of solid tumors: a review " of mice and men".Hybridoma. 1997 Feb; 16(1):101-7 Ligands on immune or other cells which may be targeted with bispecific ligands in which one ligand of the pair dictates specificity for a population of cells or particular sub-population of those cells and a second ligand with reduced functional affinity is used to effect a specific immune function include those referenced in the following patents and publications therein referenced: US0613299210/17/2000 Expression vectors encoding bispecific fusionproteins and methods of producing biologically active bispecificfusion proteins in a mammalian cell; US0612076709/19/2000 Chimeric antibody with specificity to human Bcell surface antigen; US0609091407/18/2000 CTLA4/CD28Ig hybrid fusion proteins and usesthereof; EP00721469B101/05/2000 ANTI-GP39 ANTIBODIES AND USES THEREFOR; US0601090201/04/2000 Antibody heteroconjugates and bispecificantibodies for use in regulation of lymphocyte activity; US0599380011/30/1999 Methods for prolonging the expression of aheterologous gene of interest using soluble CTLA4 molecules and anantiCD40 ligand; US0597731811/02/1999 CTLA4 receptor and uses thereof; US0596851010/19/1999 CTLA4 receptor and uses thereof; US0594551308/31/1999 Fusion proteins comprising gp39 and CD8; WO09942077A208/26/1999 COMPOSITIONS AND METHODS FOR REGULATINGLYMPHOCYTE ACTIVATION; US0591656006/29/1999 Methods for inhibiting an immune response byblocking the GP39/CD40 and CTLA4/CD28/B7 pathways and compositionsfor use therewith; EP00757099A305/26/1999 CTLA4 mutant molecules and uses thereof; US0588579603/23/1999 CTLA4 receptor and uses thereof; US058857903/23/1999 CTLA4 receptor and uses thereof; US0587671803/02/1999 Methods of inducing T cell non-responsiveness to transplanted tissues and of treating graft-versus-host-diseasewith anti-gp39 antibodies; EP00892643A101/27/1999 METHODS FOR INHIBITING AN IMMUNE RESPONSE BYBLOCKING THE GP39/CD40 AND CTLA4/CD28/B7 PATHWAYS AND COMPOSITIONSFOR USE THEREWITH; EP00445228B101/20/1999 IMMUNOTHERAPY INVOLVING CD28 STIMULATION; US0585179512/22/1998 Soluble CTLA4 molecules and uses thereof; US0584409512/01/1998 CTLA4 Ig fusion proteins; US0580773409/15/1998 Monoclonal antibodies and FV specific for CD2antigen; EP00606217B109/02/1998 CTL4A RECEPTOR, FUSION PROTEINS CONTAINING ITAND USES THEREOF; US0579557208/18/1998 Monoclonal antibodies and FV specific for CD2antigen; US0578645607/28/1998 Bp 50-specific antibodies and fragmentssthereof; US0577325306/30/1998 MYPPPY variants of CTL A4 and uses thereof; US0577019706/23/1998 Methods for regulating the immune responseusing B7 binding molecules and IL4-binding molecules; US0574703705/05/1998 Anti-GP39 antibodies; US0574630605/05/1998 Switch having stackable fuses; EP00832227A104/01/1998 METHOD FOR PROLONGING THE EXPRESSION OF AGENE OF INTEREST USING SOLUBLE CTLA4 MOLECULES; US0572110802/24/1998 Chimeric antibody with specificity to human Bcell surface antigen; EP00585943B102/11/1998 Soluble ligands for CD40; US0570985901/20/1998 Mixed specificity fusion proteins; US0567718010/14/1997 Chimeric antibody with specificity to human Bcell surface antigen; WO09734633A109/25/1997 METHODS FOR INHIBITING AN IMMUNE RESPONSE BYBLOCKING THE GP39/CD40 AND CTLA4/CD28/B7 PATHWAYS AND COMPOSITIONSFOR USE THEREWITH; US0563748106/10/1997 Expression vectors encoding bispecific fusionproteins and methods of producing biologically active bispecificfusion proteins in a mammalian cell; WO09720048A206/05/1997 MODIFIED SFV MOLECULES WHICH MEDIATE ADHESIONBETWEEN CELLS AND USES THEREOF; US0560924503/11/1997 Modular switch interior assembly and method of assembling same; EP00613944A303/05/1997 Methods for regulating the immune responseusing CTLA4-binding molecules and IL4-binding molecules; EP00757099A202/05/1997 CTLA4 mutant molecules and uses thereof; WO09639514A112/12/1996 METHOD FOR PROLONGING THE EXPRESSION OF AGENE OF INTEREST USING SOLUBLE CTLA4 MOLECULES; US0558075612/03/1996 B7IG fusion protein; US0554092607/30/1996 Soluble and its use in B cell stimulation; EP00721469A107/17/1996 ANTI-GP39 ANTIBODIES AND USES THEREFOR; US0552128805/28/1996 CD28IG fusion protein; EP00610046A304/24/1996 Expression vectors encoding bispecific fusionproteins and methods of producing biologically active bispecificfusion proteins in a mammalian cell; US0550036203/19/1996 Chimeric antibody with specificity to human Bcell surface antigen; EP00336379B102/07/1996 Antibody heteroconjugates for use inregulation of lymphocyte activity; EP00682039A111/15/1995 CTLA4 molecules and IL4-binding molecules anduses thereof; US0543413107/18/1995 Chimeric CTLA4 receptor and methods for itsuse; JP07069928A203/14/1995

INHIBITION OF TUMOR CELL GROWTH BY ADMINISTRATION OF B7-TRANSFECTED CELLS; JP07069914A203/14/1995 IMMUNE RESPONSE-REGULATING COMPOSITION; EP00600591A303/01/1995 Inhibition of tumor cell growth by administration of B7-transfected cells; EP00595659A301/11/1995 Extracellular matrix receptor ligands that modulate leukocyte function; EP00626447A111/30/1994 Monoclonal antibodies and Fv specific for cd2 antigen; EP00613944A209/07/1994 Methods for regulating the immune response using CTLA4-binding molecules and IL4-binding molecules; US0534127308/23/1994 Electrical load center; EP00610046A208/10/1994 Expression vectors encoding bispecific fusion proteins and methods of producing biologically active bispecific fusion proteins in a mammalian cell; EP00606217A107/20/1994 CTL4A RECEPTOR, FUSION PROTEINS CONTAINING IT AND USES THEREOF; EP00585943A307/06/1994 Soluble ligands for CD40; EP00308936B107/06/1994 Antibody heteroconjugates for the killing of HIV-infected cells; EP00600591A206/08/1994 Inhibition of tumor cell growth by administration of B7-transfected cells; EP00555880A305/11/1994 The CD40CR receptor and ligands therefor; EP00595659A205/04/1994 Extracellular matrix receptor ligands that modulate leukocyte function; EP00585943A203/09/1994 Soluble ligands for CD40; US0524706909/21/1993 Ligands and methods for augmenting B-cell proliferation; EP00555880A208/18/1993 The CD40CR receptor and ligands therefor; EP00507256A306/16/1993 Tyrosine phosphorylation in protozoa; JP05132429A205/28/1993 TYROSINE PHOSPHORYLATION IN PROTOZOA; EP00537293A104/21/1993 LIGAND FOR CD28 RECEPTOR ON B CELLS AND METHODS; US0518236801/26/1993 Ligands and methods for augmenting B-cell proliferation; WO09300431A101/07/1993 CTL4A RECEPTOR, FUSION PROTEINS CONTAINING IT AND USES THEREOF; EP00507256A210/07/1992 Tyrosine phosphorylation in protozoa; US0513454307/28/1992 Electrical load center; WO09200092A101/09/1992 LIGAND FOR CD28 RECEPTOR ON B CELLS AND METHODS; EP00445228A109/11/1991 IMMUNOTHERAPY INVOLVING CD28 STIMULATION; USD031885408/06/1991 Combined housing and bus bar support panel for an electrical load center; WO09101583A102/07/1991 IMPROVED ELECTRICAL LOAD CENTER; WO09005541A105/31/1990 IMMUNOTHERAPY INVOLVING CD28 STIMULATION; EP00308936A302/14/1990 Antibody heteroconjugates for the killing of HIV-infected cells; EP00336379A301/31/1990 Antibody heteroconjugates for use in regulation of lymphocyte activity; EP00274394A301/17/1990 Chimeric antibody with specificity to human B cell surface antigen; JP01304356A212/07/1989 ANTIBODY HETEROCONJUGATE FOR REGULATING LYMPHOCYTE ACTIVITY; EP00336379A210/11/1989 Antibody heteroconjugates for use in regulation of lymphocyte activity; JP01163134A206/27/1989 ANTIBODY HETEROCONJUGATE FOR KILLING HIV-INFECTED CELL; EP00308936A203/29/1989 Antibody heteroconjugates for the killing of HIV-infected cells; WO08804936A107/14/1988 CHIMERIC ANTIBODY WITH SPECIFICITY TO HUMAN B CELL SURFACE ANTIGEN; EP00274394A207/13/1988 Chimeric antibody with specificity to human B cell surface antigen; US0467706106/30/1987 T-cell lymphocyte subset monitoring of immunologic disease. 2: Rosenthal KS, Mao H, Horne WI, Wright C, Zimmerman D. Immunization with a LEAPS heteroconjugate containing a CTL epitope and a peptide from beta-2-microglobulin elicits a protective and DTH response to herpes simplex virus type 1. Vaccine. 1999 Feb 12; 17(6):535-42. 93: Jensen ON, Kulkarni S, Aldrich JV, Barofsky DF. Characterization of peptide-oligonucleotide heteroconjugates by mass spectrometry. Nucleic Acids Res. 1996 Oct 1; 24(19):3866-72. 4: Jost CR, Titus JA, Kurucz I, Segal DM. A single-chain bispecific Fv2 molecule produced in mammalian cells redirects lysis by activated CTL. Mol Immunol. 1996 Feb; 33(2):211-9. 5: Shi T, Hsieh-Ma ST, Reeder J, Ring DB. Murine bispecific antibody 1A10 directed to human transferrin receptor and a 42-kDa tumor-associated glycoprotein. Clin Immunol Immunopathol. 1996 Feb; 78(2):188-95. 6: Hideshima T, Iwasaki A, Baba M, Yamashita Y, Shirakusa T, Okada H. The induction of cytotoxicity by a bispecific antibody against CEA positive cell line, in vitro. Surg Today. 1996; 26(2):83-8. 7: Kol'tsova SV. [Effect of electrostatic interactions on formation and properties of soluble heteroprotein conjugates based on proteolytic enzymes]. Bioorg Khim. 1995 Jun; 21(6):408-20. Russian. 8: Kol'tsova SV, Boiko EV, Kuznetsova NP, Danilichev VF. [Soluble heteroprotein conjugates based on recombinant pro-urokinase for ophthalmology]. Vopr Med Khim. 1995 May-Jun; 41(3):13-7. Russian. 9: Zhu Z, Ghose T, Lee SH, Fernandez LA, Kerr LA, Donohue JH, McKean DJ. Tumor localization and therapeutic potential of an antitumor-anti-CD3 heteroconjugate antibody in human renal cell carcinoma xenograft models. Cancer Lett. 1994 Oct 28; 86(1):127-34. 10: Deans JP, Ledbetter JA, Pilarski LM. Differential modulation of human multilineage (CD3-4-8-) thymocyte proliferation by monoclonal antibodies to CD45RA or to CD45. Immunol Cell Biol. 1994 Aug; 72(4):292-9. 11: Smans KA, Hoylaerts MF, De Broe ME. Requirement of monocytes and T-helper cells during development of tumor cell cytotoxicity in targeted T cells. Cancer Immunol Immunother. 1994 Jan; 38(1):43-52. 12: Malygin AM, Somersalo K, Timonen T. Promotion of natural killer cell growth in vitro by bispecific (anti-CD3 x anti-CD16) antibodies. Immunology. 1994 Jan; 81(1):92-5. 13: Bernhard H, Karbach J, Strittmatter W, Meyer zum Buschenfelde KH, Knuth A. Induction of tumor-cell lysis by bi-specific antibody recognizing ganglioside GD2 and T-cell antigen CD3. Int J Cancer. 1993 Sep 30; 55(3):465-70. 14: Smyth MJ, Ortaldo JR. Mechanisms of cytotoxicity used by human peripheral blood CD4+ and CD8+ T cell subsets. The role of granule exocytosis. J Immunol. 1993 Jul 15; 151(2):740-7. 15: Hess SD, Oortgiesen M, Cahalan MD. Calcium oscillations in human T and natural killer cells depend upon membrane potential and calcium influx. J Immunol. 1993 Apr 1; 150(7):2620-33. 16: Wu S, Yang Y, Sadegh-Nasseri S, Ashwell JD. Use of bispecific heteroconjugated antibodies (anti-T cell antigen receptor x anti-MHC class II) to study activation of T cells with a full length or truncated antigen receptor zeta-chain. J Immunol. 1993 Mar 15; 150(6):2211-21. 17: Hsieh-Ma ST, Eaton AM, Shi T, Ring DB. In vitro cytotoxic targeting by human mononuclear cells and bispecific antibody 2B1, recognizing c-erbB-2 protooncogene product and Fc gamma receptor III. Cancer Res. 1992 Dec 15; 52(24):6832-9. 18: Smyth MJ. Generation and cytotoxic profile of human peripheral blood CD4+ T lymphocytes. Immunol Cell Biol. 1992 Dec; 70 (Pt 6):379-90. 19: Anderson PM, Crist W, Hasz D, Carroll AJ, Myers DE, Uckun FM. G19.4(alpha CD3) x B43(alpha CD19) monoclonal antibody heteroconjugate triggers CD19 antigen-specific lysis of t(4; 11) acute lymphoblastic leukemia cells by activated CD3 antigen-positive cytotoxic T cells. Blood. 1992 Dec 1; 80(11):2826-34. 20: Higgins PJ, Paradis T, Potts BJ, White-Scharf ME, Rusche JR, Scott CF. In vitro inhibition of a variety of human immunodeficiency virus isolates by a broadly reactive,

V3-directed heteroconjugate antibody. *J Infect Dis.* 1992 Jul; 166(1):198-202.21: Reid I, Lundy J, Monson J, Nelson H, Ramsay P, Ilstrup D, Donohue J. Heteroconjugated antibodies enhance lymphocyte-mediated tumour cell lysis invitro and in vivo. *Br J Surg.* 1992 Jul; 79(7):628-32.22: Reid I, Lundy J, Donohue JH. Enhancement of in vitro tumor-infiltrating lymphocyte cytotoxicity by heteroconjugated antibodies. *J Immunol.* 1992 Apr 15; 148(8):2630-5.23: Voss LM, David CS, Showalter SD, Paya CV, Leibson PJ. Heteroconjugate antibodies enhance cell-mediated anti-herpes simplex virus immunity in vivo. *Int Immunol.* 1992 Mar; 4(3):417-20.24: Montgomery AM, Wing MG, Lachmann PJ. The targeting of T-helper cells and tumourcidal macrophages to a B-cell lymphoma using a PPD-monoclonal antibody heteroconjugate. *Immunology.* 1992 Feb; 75(2):217-23.25: Smyth MJ, Norihisa Y, Ortaldo JR. Multiple cytolytic mechanisms displayed by activated human peripheral blood T cell subsets. *J Immunol.* 1992 Jan 1; 148(1):55-62.26: Mittler RS, Rankin BM, Kiener PA. Physical associations between CD45 and CD4 or CD8 occur as late activation events in antigen receptor-stimulated human T cells. *J Immunol.* 1991 Nov 15; 147(10):3434-40.27: Mansfield PF, Salmeron MA, Rosenblum MG, Itoh K. Effects of HC antibody in autologous tumor-specific cytotoxicity by human melanoma tumor-infiltrating lymphocytes. *Int J Cancer.* 1991 Sep 30; 49(3):356-61.28: Smyth MJ, Strobl SL, Young HA, Ortaldo JR, Ochoa AC. Regulation of lymphokine-activated killer activity and pore-forming protein gene expression in human peripheral blood CD8 + T lymphocytes. Inhibition by transforming growth factor-beta. *J Immunol.* 1991 May 15; 146(10):3289-97.29: Davignon JL, Vallin-Davignon M, Cohen PL, Eisenberg RA. Targeting of T-B interaction using heteroconjugate antibody. *Immunology.* 1991 May; 73(1):1-7.30: Gilliland LK, Teh HS, Uckun FM, Norris NA, Teh SJ, Schieven GL, Ledbetter JA. CD4 and CD8 are positive regulators of T cell receptor signal transduction in early T cell differentiation. *J Immunol.* 1991 Mar 15; 146(6):1759-65.31: Smyth MJ, Ortaldo JR. Comparison of the effect of IL-2 and IL-6 on the lytic activity of purified human peripheral blood large granular lymphocytes. *J Immunol.* 1991 Feb 15; 146(4):1380-4.32: Smans KA, Hoylaerts MF, Hendrickx HF, Goergen MJ, De Broe ME. Tumor-cell lysis by in-situ-activated human peripheral blood mononuclear cells. *Int J Cancer.* 1991 Feb 1; 47(3):431-8.33: Nelson H, Ramsey PS, McKean DJ, Dozois RR, Donohue JH. Anti-tumor X anti-lymphocyte heteroconjugates augment colon tumor cell lysis invitro and prevent tumor growth in vivo. *Dis Colon Rectum.* 1991 Feb; 34(2):140-7.34: Mansfield PF, Rosenblum MG, Murray JL, Itoh K. Augmentation of interleukin-2-induced activation of human melanoma tumor-infiltrating lymphocytes by heteroconjugate antibody. *Cancer Immunol Immunother.* 1991; 33(4):247-54.35: de Palazzo IG, Gercel-Taylor C, Kitson J, Weiner LM. Potentiation of tumor lysis by a bispecific antibody that binds to CA19-9 antigen and the Fc gamma receptor expressed by human large granular lymphocytes. *Cancer Res.* 1990 Nov 15; 50(22):7123-8.36: Montgomery AM, Wing MG, Lachmann PJ. A novel strategy for targeting CD4 + PPD-reactive T cells against tumour cells using PPD monoclonal antibody heteroconjugates. *Clin Exp Immunol.* 1990 Nov; 82(2):200-7.37: Wing MG, Montgomery AM, Harley C, Lachmann PJ. Cytostasis of different tumours by a murine PPD-reactive CD4 + T lymphocyte clone is mediated by interferon-gamma and tumour necrosis factor alone or synergistically. *Clin Exp Immunol.* 1990 Nov; 82(2):208-13.38: Hedlund G, Dohlsten M, Lando PA, Kalland T. Staphylococcal enterotoxins direct and trigger CTL killing of autologous HLA-DR + mononuclear leukocytes and freshly prepared leukemia cells. *Cell Immunol.* 1990 Sep; 129(2):426-34.39: Garrido MA, Valdayo MJ, Winkler DF, Titus JA, Hecht TT, Perez P, Segal DM, Wunderlich JR. Targeting human T-lymphocytes with bispecific antibodies to react against human ovarian carcinoma cells growing in nu/nu mice. *Cancer Res.* 1990 Jul 15; 50(14):4227-32.40: Moran TM, Usuba O, Shapiro E, Rubinstein LJ, Ito M, Bona CA. A novel technique for the production of hybrid antibodies. *J Immunol Methods.* 1990 May 25; 129(2):199-205.41: Kerr L, Huntoon C, Donohue J, Leibson PJ, Bander NH, Ghose T, Luner SJ, Vessella R, McKean DJ. Heteroconjugate antibody-directed killing of autologous human renal carcinoma cells by in vitro-activated lymphocytes. *J Immunol.* 1990 May 15; 144(10):4060-7.42: Nelson H, McKean DJ, Kerr LA, Donohue JH. Anti-tumor x anti-CD3 heteroconjugates direct human peripheral blood lymphocytes to lyse colon tumor cells. *J Surg Res.* 1990 Apr; 48(4):284-90.43: June CH, Fletcher MC, Ledbetter JA, Samelson LE. Increases in tyrosine phosphorylation are detectable before phospholipase C activation after T cell receptor stimulation. *J Immunol.* 1990 Mar 1; 144(5):1591-9.44: Yefenof E, Benizri R, Reiter Y, Klein E, Fishelson Z. Potentiation of NK cytotoxicity by antibody-C3b/iC3b heteroconjugates. *J Immunol.* 1990 Feb 15; 144(4):1538-43.45: Bellet D, Bidart JM, Rougier P, Bohuon C. [Use of monoclonal antibodies in the treatment of cancer of the pancreas: towards new progress]? *Bull Cancer.* 1990; 77(3):283-8.46: Winkler MA, Price JO, Foglesong PD, West WH. Biodistribution and plasma survival in mice of anti-melanoma monoclonal antibody cross-linked to OKT3. *Cancer Immunol Immunother.* 1990; 31(5):278-84.47: Van Dijk J, Tsuruo T, Segal DM, Bolhuis RL, Colognola R, van de Griend RJ, Fleuren GJ, Warnaar SO. Bispecific antibodies reactive with the multidrug-resistance-related glycoprotein and CD3 induce lysis of multidrug-resistant tumor cells. *Int J Cancer.* 1989 Oct 15; 44(4):738-43.48: Kolber MA, Quinones RR, Henkart PA. Target cell lysis by cytotoxic T lymphocytes redirected by antibody-coated polystyrene beads. *J Immunol.* 1989 Sep 1; 143(5):1461-6.49: Snider DP, Segal DM. Efficiency of antigen presentation after antigen targeting to surface IgD, IgM, MHC, Fc gamma RII, and B220 molecules on murine splenic B cells. *J Immunol.* 1989 Jul 1; 143(1):59-65.50: Nardelli B, McHugh L, Mage M. Polyacrylamide-streptavidin: a novel reagent for simplified construction of soluble multivalent macromolecular conjugates. *J Immunol Methods.* 1989 Jun 21; 120(2):233-9.51: Staerz UD, Bevan MJ. Redirecting the cellular immune response. *Int Rev Immunol.* 1989 May; 4(2):159-73.52: Reiter Y, Fishelson Z. Targeting of complement to tumor cells by heteroconjugates composed of antibodies and of the complement component C3b. *J Immunol.* 1989 Apr 15; 142(8):2771-7.53: Hathcock KS, Segal DM, Hodes RJ. Activation of Lyt-2 + (CD8 +) and L3T4 + (CD4 +) T cell subsets by anti-receptor antibody. *J Immunol.* 1989 Apr 1; 142(7):2181-6.54: Quinones RR, Segal DM, Henkart P, Perez P, Gress RE. Inhibition of cytotoxic T cell lysis by anti-CD8 monoclonal antibodies: studies with CD3-targeted cytotoxicity of nominal antigen-negative targets. *J Immunol.* 1989 Apr 1; 142(7):2200-6.55: Goedegebuure PS, Segal DM, Braakman E, Vreugdenhil RJ, Van Krimpen BA, Vande Griend RJ, Bolhuis RL. Induction of lysis by T cell receptor gamma delta + /CD3 + T lymphocytes via CD2 requires triggering via the T11.1 epitope only. *J Immunol.* 1989 Mar 15; 142(6):1797-802.56: Ledbetter JA, Norris NA, Grossmann A, Grosmaire LS, June CH, Uckun FM, Cosand WL, Rabinovitch PS. Enhanced transmembrane signalling activity of monoclonal antibody heteroconjugates suggests

molecular interactions between receptors on the T cell surface. *Mol Immunol.* 1989 Feb; 26(2):137-45.57: Paya CV, McKean DJ, Segal DM, Schoon RA, Showalter SD, Leibson PJ. Heteroconjugate antibodies enhance cell-mediated anti-herpes simplex virus immunity. *J Immunol.* 1989 Jan 15; 142(2):666-71.58: Foglesong PD, Winkler MA, Price JO, Marshall GD, Reagh SH, Bush DA, Hixson KS, West WH. Preparation and analysis of bifunctional immunoconjugates containing monoclonal antibodies OKT3 and BABR1. *Cancer Immunol Immunother.* 1989; 30(3):177-84.59: Reiter Y, Fishelson Z. Killing of human tumor cells by antibody C3b conjugates and human complement. *Targeted Diagn Ther.* 1989; 2:119-35.60: Colombatti M, Bisconti M, Dell'Arciprete L, Gerosa MA, Tridente G. Sensitivity of human glioma cells to cytotoxic heteroconjugates. *Int J Cancer.* 1988 Sep 15; 42(3):441-8.61: Jung G, Eberhard HJ. An in-vitro model for tumor immunotherapy with antibody heteroconjugates. *Immunol Today.* 1988 Sep; 9(9):257-60 available.62: Mezzanzanica D, Canevari S, Menard S, Pupa SM, Tagliabue E, Lanzavecchia A, Colnaghi MI. Human ovarian carcinoma lysis by cytotoxic T cells targeted by bispecific monoclonal antibodies: analysis of the antibody components. *Int J Cancer.* 1988 Apr 15; 41(4):609-15.63: Zarling JM, Moran PA, Grosmaire LS, McClure J, Shriver K, Ledbetter JA. Lysis of cells infected with HIV-1 by human lymphocytes targeted with monoclonal antibody heteroconjugates. *J Immunol.* 1988 Apr 15; 140(8):2609-13.64: Emmrich F, Rieber P, Kurrle R, Eichmann K. Selective stimulation of human T lymphocyte subsets by heteroconjugates of antibodies to the T cell receptor and to subset-specific differentiation antigens. *Eur J Immunol.* 1988 Apr; 18(4):645-8.65: Eichmann K, Emmrich F. Selective induction of T-cell subsets by antibodies to the T-cell antigen receptor and to the subset-specific differentiation antigens CD8 and CD4. *Vaccine.* 1988 Apr; 6(2):85-8.66: Ledbetter JA, June CH, Rabinovitch PS, Grossmann A, Tsu TT, Imboden JB. Signal transduction through CD4 receptors: stimulatory vs. inhibitory activity is regulated by CD4 proximity to the CD3/T cell receptor. *Eur J Immunol.* 1988 Apr; 18(4):525-32.67: Segal DM, Qian JH, Garrido MA, Perez P, Winkler DF, Wunderlich JR, Snider DP, Valdayo MJ, Titus JA. Targeting of cytotoxic cells against tumors with heterocrosslinked, bispecific antibodies. *Princess Takamatsu Symp.* 1988; 19:323-31.68: Canevari S, Menard S, Mezzanzanica D, Miotti S, Pupa SM, Lanzavecchia A, Colnaghi MI. Anti-ovarian carcinoma anti-T3 heteroconjugates or hybrid antibodies induce tumor cell lysis by cytotoxic T-cells. *Int J Cancer Suppl.* 1988; 2:18-21.69: Leo O, Foo M, Henkart PA, Perez P, Shinohara N, Segal DM, Bluestone JA. Role of accessory molecules in signal transduction of cytolytic T lymphocyte by anti-T cell receptor and anti-Ly-6.2C monoclonal antibodies. *J Immunol.* 1987 Dec 1; 139(11):3556-63.70: Titus JA, Perez P, Kaubisch A, Garrido MA, Segal DM. Human K/natural killer cells targeted with heterocross-linked antibodies specifically lyse tumor cells in vitro and prevent tumor growth in vivo. *J Immunol.* 1987 Nov 1; 139(9):3153-8.71: Jung G, Martin DE, Muller-Eberhard HJ. Induction of cytotoxicity in human peripheral blood mononuclear cells by monoclonal antibody OKT3. *J Immunol.* 1987 Jul 15; 139(2):639-44.72: Jung G, Ledbetter JA, Muller-Eberhard HJ. Induction of cytotoxicity in resting human T lymphocytes bound to tumor cells by antibody heteroconjugates. *Proc Natl Acad Sci U S A.* 1987 Jul; 84(13):4611-5.73: Staerz UD, Yewdell JW, Bevan MJ. Hybrid antibody-mediated lysis of virus-infected cells. *Eur J Immunol.* 1987 Apr; 17(4):571-4.74: Jung G, Honsik CJ, Reisfeld RA, Muller-Eberhard HJ. Activation of human peripheral blood mononuclear cells by anti-T3: killing of tumor target cells coated with anti-target-anti-T3 conjugates. *Proc Natl Acad Sci U S A.* 1986 Jun; 83(12):4479-83.75: Staerz UD, Bevan MJ. Hybrid hybridoma producing a bispecific monoclonal antibody that can focus effector T-cell activity. *Proc Natl Acad Sci U S A.* 1986 Mar; 83(5):1453-7.76: Staerz UD, Bevan MJ. Targeting cells for attack by cytotoxic T lymphocytes using heteroconjugates of monoclonal antibodies. *Symp Fundam Cancer Res.* 1986; 38:31-4. available.77: Staerz UD, Kanagawa O, Bevan MJ. Hybrid antibodies can target sites for attack by T cells. *Nature.* 1985 Apr 18-24; 314(6012):628-31. Other references highlighting targets for immune cell therapy which are relevant for application to the strategies herein are: 1: Huang JL, Lee WY, Chen LC, Kuo ML, Hsieh KH. Changes of serum levels of interleukin-2, intercellular adhesion molecule-1, endothelial leukocyte adhesion molecule-1 and Th1 and Th2 cell in severe atopic dermatitis after intravenous immunoglobulin therapy. *Ann Allergy Asthma Immunol.* 2000 Mar; 84(3):345-52.12: Liles WC, Dale DC, Price TH, Gaviria JM, Turner T, Saoud J, Frumkin LR. Inhibition of in vivo neutrophil transmigration by a novel humanized anti-CD11/CD18 monoclonal antibody. *Cytokines Cell Mol Ther.* 2000 Sep; 6(3):121-6.03: Rhee P, Morris J, Durham R, Hauser C, Cipolle M, Wilson R, Luchette F, McSwain N, Miller R. Recombinant humanized monoclonal antibody against CD18 (rhuMAb CD18) intraumatic hemorrhagic shock: results of a phase II clinical trial. *Traumatic Shock Group. J Trauma.* 2000 Oct; 49(4):611-9; discussion 619-20.74: Coulter SA, Cannon CP, Ault KA, Antman EM, Van de Werf F, Adgey AA, Gibson CM, Giugliano RP, Mascelli MA, Scherer J, Barnathan ES, Braunwald E, Kleiman NS. High levels of platelet inhibition with abciximab despite heightened platelet activation and aggregation during thrombolysis for acute myocardial infarction: results from TIMI (thrombolysis in myocardial infarction) 14. *Circulation.* 2000 Jun 13; 101(23):2690-5.55: Fredrickson BJ, Turner NA, Kleiman NS, Graziadei N, Maresh K, Mascelli MA, Efron MB, McIntire LV. Effects of abciximab, ticlopidine, and combined Abciximab/Ticlopidine therapy on platelet and leukocyte function in patients undergoing coronary angioplasty. *Circulation.* 2000 Mar 14; 101(10):1122-9.86: Gottfried I, Seeber A, Anegg B, Rieger A, Stingl G, Volc-Platzer B. High dose intravenous immunoglobulin (IVIG) in dermatomyositis: clinical responses and effect on sIL-2R levels. *Eur J Dermatol.* 2000 Jan-Feb; 10(1):29-35.47: Lorenz HM, Grunke M, Hieronymus T, Antoni C, Nusslein H, Schaible TF, Manger B, Kalden JR. In vivo blockade of tumor necrosis factor-alpha in patients with rheumatoid arthritis: longterm effects after repeated infusion of chimeric monoclonal antibody cA2. *J Rheumatol.* 2000 Feb; 27(2):304-10.98: Braun S, Hepp F, Kentenich CR, Janni W, Pantel K, Riethmuller G, Willgeroth F, Sommer HL. Monoclonal antibody therapy with edrecolomab in breast cancer patients: monitoring of elimination of disseminated cytokeratin-positive tumor cells in bone marrow. *Clin Cancer Res.* 1999 Dec; 5(12):3999-4004.19: Neumann FJ, Zohlhofer D, Fakhoury L, Ott I, Gawaz M, Schomig A. Effect of glycoprotein IIb/IIIa receptor blockade on platelet-leukocyte interaction and surface expression of the leukocyte integrin Mac-1 in acute myocardial infarction. *J Am Coll Cardiol.* 1999 Nov 1; 34(5):1420-6.710: Harder S, Kirchmaier CM, Krzywanek HJ, Westrup D, Bae JW, Breddin HK. Pharmacokinetics and pharmacodynamic effects of a new antibody glycoprotein IIb/IIIa inhibitor (YM337) in healthy subjects. *Circulation.* 1999 Sep 14; 100(11):1175-81.711: Jacob MC, Agrawal S, Chaperot L, Giroux C, Gressin R, Le Marc'Hadour F, Favre M, Sotto JJ, Bensa JC,