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Patents and Literature

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ABSTRACT

The use of monoclonal antibodies for clinical applications has increased dramatically in the past few years. Monoclonal antibodies are used for the detection of bacterial and viral infections, determination of the presence and stage of cancer, and as diagnostics for the detection and quantitation of low molecular weight compounds of clinical and biochemical interest. The latter application has also taken place through the development of monoclonal antibody-based sensors. The ease of monoclonal antibody synthesis and their high degree of antigen specificity has made monoclonal antibodies ideal for the aforementioned clinical applications. Recent US patents and scientific literature on clinical applications of monoclonal antibodies are surveyed. Patent abstracts are summarized individually and a list of literature references are given.

INTRODUCTION

The objective of the Patents and Literature Section is to summarize and cite recent developments in industrial and academic research as portrayed within the scope of current patents and literature and to highlight emerging biotechnological research areas. Three subject areas are being surveyed in 1988: biocatalysis in nonaqueous media, monoclonal antibodies for clinical applications, and enzymatic and microbial production of optically active compounds. The subject of the second Patent and Literature Section of 1988 is Monoclonal Antibodies for Clinical Applications.

MONOCLONAL ANTIBODIES FOR CLINICAL APPLICATIONS

Patents

This section covers the US patents concerning monoclonal antibodies for clinical applications from the period of January 1986 to July 1988. The major search headings were monoclonal antibodies with the cross terms: *clinical, assay, immunoassay, probes, reagents, and diagnostic.* The major patents recovered under this search are described below. Many of the abstracts are edited for clarity. Copies of US patents can be obtained from the Commisioner of Patents and Trademarks, Washington, DC 20231.

Alderete, John F.
HYBRID CELL LINE PRODUCING MONOCLONAL ANTIBODY CYTOLYTIC TO *TRICHOMONAS VAGINALIS*
US 4,707,422, Nov. 17, 1987
Assignee: Board of Regents, University of Texas

The cytolytic monoclonal antibodies specific for *T. vaginalis* are useful in detecting the presence of *T. vaginalis* among a general population of microorganisms found in a biological sample. Detection of the *T. vaginalis* is evaluated by observing cell lysis of *T. vaginalis* after contacting the cultured microorganisms with the cytolytic monoclonal antibody specific for *T. vaginalis.* Therapeutic uses of the monoclonal antibody as an immunological antimicrobial reagent for the treatment of *T. vaginalis* infection are also disclosed.

Babu, U. M., Mia, A. S., and Pancari, G. D.
PROGESTERONE ASSAY METHOD FOR MAMMALS AND MONOCLONAL ANTIBODY THEREOF
US 4,720,455, Jan. 19, 1988
Assignee: Pitman-Moore, Inc.

A progesterone concentration level test for mammalian body fluids, particularly adapted for milk, whereby estrus and pregnancy can be determined is disclosed. The test can be carried out with a kit of several reagents, test tubes, and a dip-stick carrying an antiprogesterone monoclonal antibody.

Bauman, D. S.
COMPARATIVE ASSAY METHOD AND DEVICE
US 4,652,520, Mar. 24, 1987
Assignee: Immuno-Mycologics, Inc.

A method and device for performing comparative assay of binding and bindable substances, such as antibodies and antigens, is presented. The device includes a circulation conduit for continuously conveying a carrier fluid between a support and a detection zone. A competitive binding substance is fixed in the support zone and is capable of competitively binding a test substance and an analytical detection substance such that changes

in concentration of the test substance in the carrier fluid responsively cause changes of concentration of analytical detection substance in the carrier fluid. Each of the analytical detection substance (e.g., antigen–fluorochrome) and the test substance (e.g., antigen) are bound to the binding substance (monoclonal antibody) in proportion to the concentration of the test substance in the carrier fluid. A means is provided for detecting changes in the concentration of the analytical detection substance as the carrier fluid is conveyed through the detection zone.

Bogden, A. E.
METHOD FOR IN VIVO TESTING OF BIOLOGICAL RESPONSE MODIFIERS INCLUDING MONOCLONAL ANTIBODIES
US 4,610,869, Sep. 9, 1986
Assignee: EG&G Mason Research Institute

An in vivo method for determining the ability of biological response modifiers, including monoclonal antibodies, to interact with tumor tissue is described. A fresh, surgical tumor tissue specimen is implanted under the renal capsule of a host organism. A biological response modifier is administered to the host organism. The degree of interaction between the biological response modifier and the tumor tissue is determined. This method is particularly suitable for determining the ability of a biological response modifier to interact with fresh, surgically-obtained tumor tissue when using an immunocompetent host in an assay of short duration.

Broder, S., Matsushita, S., and Guroff, M. R.
CELL LINE PRODUCING HUMAN MONOCLONAL ANTIBODY THAT BINDS TO HTLV-I PRODUCING CELLS
US 4,722,888, Feb. 2, 1988
Assignee: US Department of Health and Human Services

The present invention is an immortalized B-cell line that produces a human monoclonal antibody IgG-Kk that specifically binds to the envelope antigen of human T-cell leukemia virus Type 1 (HTLV-I). This monoclonal antibody is useful as a diagnostic reagent by binding to the antigen specifically expressed on the surface of HTLV producing cells. Furthermore, this monoclonal antibody is useful as a therapeutic reagent, in combination with complement, for the lysis of HTLV-I producing cells.

Chang, T. W., and Chang, N. T.
METHOD OF PREPARING MURINE MONOCLONAL ANTIBODIES AGAINST CELL-FREE PRODUCTS OF ACTIVATED HUMAN T-LYMPHOCYTES
US 4,596,774, June 24, 1986
Assignee: Centocor, Inc.

A method of preparing simultaneously monoclonal antibodies specific for different cell-free products of activated human T-lymphocytes is dis-

closed. Human T-cells are activated in a medium supplemented with mouse serum rather than conventional calf serum. A supernatant prepared from the activated T-cells is used to immunize mice. The dominant immunogens in the supernatant are the cell-free products of human T-lymphocytes. The yield of hybrid cells that produce products reactive with cell-free products of human T-lymphocytes is enhanced by injecting the immunized mice with a supernatant from mitogen-activated murine splenocytes. In addition, a novel radioimmunoadsorbent assay for screening hybrids to detect production of monoclonal antibodies reactive with cell-free products of human T-lymphocytes is disclosed.

Chang, T. W., Kung, P. C., Le, J., Liu, V., and Vilcek, J.
IMMUNOASSAY FOR BIOLOGICALLY ACTIVE HUMAN INTERFERON-GAMMA EMPLOYING UNIQUE MONOCLONAL ANTIBODIES
US 4,666,865, May 19, 1987
Assignee: Centocor, Inc.

Rapid, sensitive, and accurate immunoassays for biologically active, natural, or recombinant human interferon-gamma (hulFN-gamma) based upon monoclonal antibodies that react specifically with epitopes of the biologically active form of hulFN-gamma are disclosed. The immunoassays include a sandwich immunoradiometric assay of the forward, reverse, or simultaneous type and a competitive binding assay such as radioimmunoassay. The assays are also useful for the detection of macrophage activation factor, now believed to be identical to hulFN-gamma. In addition, methods of purification of hulFN-gamma, employing the monoclonal antibodies, are described.

Cubicciotti, R. S., Karu, A. E., and Krauss, R. M.
LIPOPROTEIN MARKER
US 4,619,895, Oct. 28, 1986
Assignee: Regents of the University of California

Methods and compositions are provided for the detection of a particular low density lipoprotein that has been found to be a marker for patients suffering from type IV hypertriglyceridemia. A monoclonal antibody capable of specifically binding to a characteristic epitopic site on this LDL subspecies can be utilized in a wide variety of immunoassays. Hybridoma cell line SPL. IVA5A1 was deposited at the American Type Culture Collection on Mar. 29, 1984, and granted accession no. HB 8535.

Dedieu, A., Lockhart, C., and Jolu, E.
COMPETITIVE IMMUNOASSAY PROTOCAL FOR TARGETS INCLUDING LIPOPROTEINS AND ALPHA-FETOPROTEIN
US 4,698,298, Oct. 6, 1987
Assignee: Commissariat a l'Energie Atomique

The invention relates to a process for the immunoassay of a substance, such as an antigen, a hapten, or an antibody. This process comprises the following stages: (1) contacting a sample containing the substance to be assayed with a labeled immunoactive reagent specific to said substance, the immunoactive reagent quantity being such that the substance to be assayed is in excess compared with that labeled immunoactive reagent; (2) contacting at least part of the resulting reaction medium with a solid phase, to which an immunoactive reagent specific to the substance to be assayed is fixed; (3) separating the reaction medium from the solid phase; and (4) determining the labeled immunoactive reagent content of the solid phase. This process is more applicable to the assaying of lipoprotein and in this case, use is made of an antibody labeled by an enzyme, such as the Raifort peroxidase. It is also possible to assay a-foetoprotein by using monoclonal antibodies.

Diamond, B. A.
MONOCLONAL ANTIBODIES REACTIVE WITH SHARED IDIOTYPES ON HUMAN ANTIBODIES TO NATIVE DNA FROM PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS
US 4,692,416, Sep. 8, 1987
Assignee: Yeshiva University

The invention relates to monoclonal anti-idiotypic antibodies to human anti-DNA antibodies. Monoclonal, anti-idiotypic antibodies are produced using hybridoma technology. The antibodies are used as diagnostic reagents in methods to determine the presence of anti-native DNA antibodies in serum from patients suspected of having systemic lupus erythematosus.

Dolbeare, F. A. and Gray, J. W.
FLOW CYTOMETRIC MEASUREMENT OF TOTAL DNA AND INCORPORATED HALODEOXYURIDINE
US 4,585,736, Apr. 29, 1986
Assignee: US Department of Energy

A method for the simultaneous flow cytometric measurement of the total DNA content and the level of DNA synthesis in normal and malignant cells is disclosed. The sensitivity of the method allows a study of cell cycle traverse rates for large scale cell populations as well as single cell measurements. A DNA stain such as propidium iodide is used as the probe for the measurement of total DNA content and a monoclonal antibody reactive with a DNA precursor, such as bromodeoxyuridine (BrdU), is used as a probe for the measurement of BrdU uptake by the cells as a measure of DNA synthesis.

Dupont, B., Hoffman, M. K., Collins, N., Yang, S.-Y., Morishima, Y., and Kobayashi, M.
MONOCLONAL ANTIBODY SUBSETTING HUMAN HELPER AND KILLER T-CELLS AND METHOD

US 4,677,056, June 30, 1987
Assignee: Sloan-Kettering Institute for Cancer Research

A monoclonal antibody 4A produced by a human-mouse hybridoma cell line is described. In the presence of complement, 4A subsets both cytotoxic and helper T-cells, creating a diagnostic tool in blood biochemistry.

Epstein, A. L.
MURINE HYDRIDOMA LYM-2 AND DIAGNOSTIC ANTIBODY PRODUCED THEREBY
US 4,724,212 and 4,724,213, Feb. 9, 1988
Assignee: Northwestern University

Hybridoma Lym-1 and Lym-2 (ATCC Nos. HB 8613 and HB 8612, respectively) produces murine IgGl monoclonal antibodies specifically against normal human B-cells and derived malignancies. These antibodies have possible clinical utility for the in vivo diagnosis of human B-cell lymphomas and leukemias.

Erickson, B. W., Fok, K. -F., Incefy, G. S., and Ohga, K.
RADIOIMMUNOASSAYS FOR THE SERUM THYMIC FACTOR (FTS)
US 4,634,682, Jan. 6, 1987
Assignee: Sloan-Kettering Institute for Cancer

Radioimmunossays for the quantitation of serum thymic factor (FTS), a thymic peptide hormone, are disclosed. Each assay employs an antibody specific for FTS, the monoclonal antibody or the antibody from the antiserum of a host animal; synthetic FTS or FTS analog as the hormone standard; and a radiolabeled FTS analog as the tracer. Also disclosed is a method of treating serum or other biological fluid prior to assay of FTS to remove interfering substances.

Freedman, A., Nadler, L., and Schlossman, S.
MONOCLONAL ANTIBODIES TO ANTIGEN ON ACTIVATED HUMAN B-CELLS AND ASSAY THEREFOR, PROTEIN ANTIGENIC DETERMINANT THEREFOR AND METHOD OF MAKING SAME
US 4,692,405, Sep. 8, 1987
Assignee: Dana-Farber Cancer Institute, Inc.

A monoclonal antibody recognizing an antigenic determinant on activated human B-cells is described. The antigenic determinant being characterized as a protein distinct from B-1 and BB-1, and the antibody being substantially unreactive with unactivated human B-cells.

Gay, S.
IN VITRO DIAGNOSTIC METHODS USING MONOCLONAL ANTIBODIES AGAINST CONNECTIVE TISSUE PROTEINS

US 4,628,027, Dec. 9, 1986
Assignees: Molecular Engineering Associates, Ltd.

The board of Trustees of the University of Alabama Collagen profiles of human body tissues and fluids, i.e., the types of distinct connective tissue proteins present, their distribution in human body tissues and fluids, and the concentration ratios among distinct types, are subject to change during certain pathological conditions and therapeutic regimens for the treatment of such conditions. These changes in collagen profiles can be detected by immunohistological, immunocytological, and immunoserological techniques. In vitro diagnostic methods, employing monoclonal antibodies specific for connective tissue proteins, are provided that can be used for monitoring the results of therapeutic measures taken against inflammatory diseases, fibrotic diseases and cancer, and for detecting or following the pathogenesis of such diseases.

Genco, R. J., Zambon, J. J., Christersson, A., and Neiders, M. E.
MONOCLONAL ANTIBODIES USEFUL IN THE IDENTIFICATION OF MICROORGANISMS CAUSING PERIODONTAL DISEASE
US 4,741,999, May 3, 1988
Assignee: Research Foundation of State University of New York

Actinobacillus actinomycetemcomitans has frequently been implicated in juvenile periodontitis. The present monoclonal antibodies are specific to *Actinobacillus actinomycetemcomitans*. The present monoclonal antibodies are typically employed as reagents that include an inert carrier, preferably a liquid, such as buffered saline solution and a preservative. The carrier compositions are suitably selected to provide for the proper dispersal of bacteria and to preserve the integrity of antigens and supplemental structures. The selection of the proper carrier is especially important in the detection in mixtures that include bacteria that produce large amounts of autolyltic enzymes such as *B. gingivalis*. The monoclonal antibodies of the present invention are useful in clinical testing and differentiating antigens in the gingival or subgingival sera. The method of testing and differentiating involves the steps of contacting a sample of the bacterial flora from a lesion or another site with a measured amount of monoclonal antibody specific to a single antigen site on *Actinobacillus actinomycetemcomitans* and subsequently measuring the number of antibody-antigen complexes formed.

Hampar, B., Zweig, M., and Showalter, S. D.
MONOCLONAL ANTIBODIES TO HERPES SIMPLEX VIRUS TYPE I POLYPEPTIDES
US 4,572,896, Feb. 25, 1986
Assignee: US Department of Health and Human Services

A method for producing monoclonal antibody reagents against novel proteins induced by herpes simplex virus type 1 (HSV-1) is described.

The method consists of preparing HSV-1 antigen populations by infecting mammalian cells either with HSV-1 alone or with HSV-1 in the presence of an inhibitor of protein synthesis. This is followed by allowing virus replication to proceed by reversing the action of the inhibitor, inoculating the antigen mixture in mice to induce the production of antibodies, fusing the spleen cells of the mice with myeloma cells to obtain hybrid cells, and screening said cells by radioimmunoprecipitation-polyacrylamide gel electrophoresis (RIP-PAGE). This method identifies hybrid cells producing monoclonal antibodies against HSV-1 proteins and teaches the production of unique monoclonal antibody reagents directed against novel HSV-1 proteins; including a 132,000 mol wt (mw) DNA-binding protein, a 175,000 mw immediate-early protein, and a previously unknown 110,000 mw glycoprotein.

Hellstrom, I., Brown, J. P., Hellstrom, K. E., Horn, D., and Linsley, P.
MONOCLONAL ANTIBODIES FOR HUMAN NONSMALL CELL LUNG CARINOMAS
US 4,737,579, Apr. 12, 1988
Assignee: Oncogen

The present invention is concerned with novel monoclonal antibodies that define antigens associated with human nonsmall cell lung carcinomas (NSCLC). The antibodies bind to normal human cells to a lesser degree than to tumor cells. The antibodies find use in diagnostic methods, such as the detection of malignant cells associated with NSCLC and in therapeutic methods.

Herr, J. C. and Benjamin, D. C.
MONOCLONAL ANTIBODIES AND METHOD OF IDENTIFYING SPECIES USING THE SAME
US 4,735,898, Apr. 5, 1988
Assignee: University of Virginia Alumini Patents Foundation

This new method and products recognize human serum albumin, differentiating blood and tissue from human sources from blood and tissue of other animals. The method and products are particularly useful in forensic investigations. First, mice are injected with purified human serum albumin. Then, spleen cells from the mice are fused with cells from a murine myeloma. Resulting hybridomas are screened on human serum albumin coated plates. Subcloning, stabilizing by culture, and continued assays for antihuman albumin activity produces products that recognize and differentiate blood or tissue samples from samples of other species.

Herr, J. C., Sigman, M., and Sutherland, W. M.
MONOCLONAL ANTIBODY TO MHS-5: A NEW PROBE FOR SEXUAL ASSAULT ANALYSES

US 4,741,998, May 3, 1988
Assignee: University of Virginia Alumni Patents Foundation

A new probe for forensic analysis of sexual assaults in disclosed. The probe is a monoclonal antibody to a new protein marker, MHS-5, in semen. Also disclosed is the hybridoma producing the antibody as well as an assay utilizing the antibody for forensic analysis of criminal evidence.

Huang, C.-M. and Cohen, S. N.
MONOCLONAL ANTIBODY HAVING SPECIFICITY FOR THE DOUBLE-STRANDED CONFORMATION OF NATIVE DNA AND DIAGNOSTIC METHODS USING SAME
US 4,623,627, Nov. 18, 1986
Assignee: Cetus Corp.

Monoclonal antibodies having conformation-dependent specificity for native dsDNA, as exemplified by the IgM antibody produced by murine hybridoma ATCC No. HB 8329, are used to detect DNA duplex formation in DNA hybridization tests.

Hunter, K. W. and Fischer, G. W.
HUMAN MONOCLONAL ANTIBODY REACTIVE WITH POLYRIBOSYLRIBITOL PHOSPHATE
US 4,744,982, May 17, 1988

A human monoclonal antibody produced by a self-reproducing carrier cell, the antibody being reactive with PRP capsular polysaccharide, is disclosed. Also disclosed is a process of preparing the antibody from the carrier cell that is conveniently a hybridoma. Additionally, diagnostic, prophylactic, and therapeutic compositions and methods employing the antibody are disclosed. Moreover, a laboratory reagent containing the antibody is described.

Jefferis, R. and Steensgaard, J.
IMMUNOPRECIPITATION ASSAY OF IMMUNOGLOBULINS USING MONOCLONAL ANTIBODIES
US 4,618,589, Oct. 21, 1986
Assignee: University of Birmingham

An antigen/antibody precipitate is obtained, using monoclonal antibodies. The monoclonal antibodies being selected to be specific to two distinct antigenic binding sites (L or C 2 or C 3) on a protein (IgG) in a sample under test. The proportions of subpopulations of immunoglobulins (IgG kappa, IgG lambda) in a sample is determined by reacting the sample with a combination of antibodies, both of which are specific to the heavy chains (H) of both subpopulations (IgG kappa, IgG lambda) and reacting the sample with an antibody combination specific to the heavy chain (H)

and to an antigenic determinant expressed by only one (IgG kappa) of the subpopulations.

Kettman, J. R. and Norgard, M. V.
METHODS FOR DIAGNOSING SYPHILIS
US 4,740,467, Apr. 26, 1988
Assignee: Board of Regents, University of Texas

Murine anti-Treponema pallidum monoclonal antibodies were employed in the detection of low numbers of pathogenic treponemes. Monoclonal antibodies were used as a primary antibody source in a solid-phase immunoblot assay system. All monoclonal antibodies assayed were capable of detecting ca. 1.0×10^3 to 2.5×10^3 treponemes. Of 13 monoclonal antibodies examined, 3 were able to detect 10^3 virulent treponemes, and 1 of these antibodies was able to reveal the presence of as few as 500 organisms. Western blot analyses showed that all anti-*T. pallidum* monoclonal antibodies, exhibiting high sensitivities for the detection of *T. pallidum* cells, were directed against an abundant, 47,000–48,000 dalton surface-exposed antigen of the organism. With two possible exceptions, the monoclonal antibodies tested reacted specifically with *T. pallidum,* either purified or found within a high-contaminating tissue background and not with *T. phagedenis* biotype Reiter, *Haemophilus ducreyi, Neisseria gonorrhoeae,* herpes simplex virus type 2, or normal rabbit testicular tissue.

Keydar, I.
IMMUNOASSAY FOR BREAST CANCER EMPLOYING MONOCLONAL ANTIBODIES
US 4,707,438, Nov. 17, 1987
Assignee: Tel Aviv University, Teva Pharmaceutical Industries, Ltd.

An immunoassay for diagnosing and monitoring human breast cancer is described. The assay employs a monoclonal antibody that recognizes a human mammary tumor virus derived from the T47D clone-10 breast cancer cell line (HMTV). The monoclonal antibody is produced by the hybridoma cell line deposited with the American Type Culture Collection under ATCC Accession No. HB 8630. When the immunoassay is performed on a tissue sample from a subject, the sample is contacted with monoclonal antibody ATCC Accession No. HB 8630 to form an antibody–antigen complex between the monoclonal antibody and any HMTV antigens that may be present in the sample. This antibody–antigen complex is then detected employing a second detectable antibody specific to the first monoclonal antibody. The presence or absence of the complex indicates the presence or absence of breast cancer in the subject.

Khazaeli, M. B., Beierwaltes, W. H., and England, B. G.
MONOCLONAL ANTIBODIES SPECIFIC FOR THE UNBOUND BETA SUBUNIT OF HUMAN CHORIONIC GONADOTROPIN

US 4,565,687, Jan. 21, 1986
Assignee: Regents of the University of Michigan

Hybrid-myeloma cells that produce monoclonal antibody specific to the B-subunit of human chorionic gonadotropin and methods of use of the monoclonal antibody are described.

Knowles, R. W., Dupont, B., Naito, K., and Morishima, Y.
METHOD FOR DIFFERNTIAL DIAGNOSIS OF T-CELL LEUKEMIAS USING MONOCLONAL ANTIBODIES
US 4,645,738, Feb. 24, 1987
Assignee: Memorial Sloan-Kettering Institute Cancer Center

Two monoclonal antibodies (3-3 and 3-40) were produced which identify two new leukemia associated antigens. Both antibodies reacted with most cell lines derived from patients with T lymphoblastic leukemia (T-ALL), but were not detected on suspensions of normal hematopoietic cells. Analysis of fresh leukemic cells indicated that mAb 3-3 only reacted with T-ALL cells, while mAb 3-40 reacted with some non-T non-B ALL cells and a few acute myelocytic leukemia (AML) cells, as well as T-ALL cells. The 3-40 antigen was also found histopathologically in frozen sections of several normal tissues, including the epithelial cells and a few lymphoid cells of the thymus, and some malignant tissues, while the 3-3 antigen was not found in any tissue studied. A "double absorption" assay provided additional serological evidence that the two antibodies identify different antigenic determinants.

Knowles, W. J., Marchesi, V. T., and Haigh, W.
PEPTIDES USEFUL IN PREPARING HEMOGLOBIN A(1c)IMMUNOGENS
US 4,647,654, Mar. 3, 1987
Assignee: Molecular Diagnostics, Inc.

Monoclonal antibodies specific for the glucosylated *N*-terminal peptide residue in Hb A(1c), a method for producing such antibodies, hybridoma cell lines secreting such antibodies, a method for their production, and immunoassay methods and reagent systems using such antibodies for the determination of Hb A(1c) in human blood samples is presented. The monoclonal antibodies are secreted by hybridomas obtained from the fusion of a myeloma cell and a lymphocyte that has been taken from an animal, preferably a mouse, immunized with a synthetic peptide immunogen and which produces antibody specific for the glucosylated *N*-terminal peptide residue in Hb A(1c). The synthetic peptide immunogen comprises an *N*-terminal glucosylated peptide residue having at least 2 amino acid units corresponding to the *N*-terminus of the beta-subunit of human hemoglobin and an immunogenic carrier to which the glucosylated peptide residue is linked.

Kortright, K. H.
METHOD FOR ENHANCING AND/OR ACCELERATING IMMUNOASSAY DETECTION OF HUMAN CARCINOMA TUMOR ASSOCIATED ANTIGEN IN A PATHOLOGY SAMPLE
US 4,743,543, May 10, 1988
Assignee: Coulter Corp.

Detection of an identified human carcinoma tumor antigen in a pathological sample by means of a labeled monoclonal antibody specific to the determinant site on the antigen has been found to be enhanced and/or accelerated at an earlier development stage than heretofore achieved by removing a carbohydrate steric hindrance for monoclonal antibody availability to bind the antigen of the tumor for which it is specific. The carbohydrate steric hindrance for monoclonal binding to the antigen is identified as sialic acid. The method of the invention involves selective removal of sialic acid from the antigen's determinant site by enzymatic digestion using neuraminidase.

Kung, P. C. and Goldstein, G.
HYBRID CELL LINE FOR PRODUCING MONOCLONAL ANTIBODY TO HUMAN EARLY THYMOCYTE ANTIGENS, ANTIBODY, AND METHODS
US 4,624,925, Nov. 25, 1986
Assignee: Ortho Pharmaceutical Corp.

The development of a hybrid cell line for production of monoclonal antibody to an antigen found on approximately 10% of normal human thymocytes is disclosed. The hybrid is formed by fusing splenocytes from immunized CAF(1)mice with P3X63Ag8U1 myeloma cells. Diagnostic and therapeutic uses of the monoclonal antibody are also disclosed.

Kung, P. C. and Goldstein, G.
HYBRID CELL LINE FOR PRODUCING MONOCLONAL ANTIBODY TO A HUMAN T-CELL ANTIGEN, ANTIBODY, AND METHODS
US 4,614,720, Sep. 30, 1986
Assignee: Ortho Pharmaceutical Corp.

The development of a hybrid cell line for production of monoclonal antibody to an antigen, found on essentially all normal human T-cells and on approximately 95% of normal human thymocytes, is disclosed. The hybrid is formed by fusing splenocytes from immunized CAF(1)mice with P3X63Ag8U1 myeloma cells. Diagnostic and therapeutic uses of the monoclonal antibody are also disclosed.

Kung, P. C. and Goldstein, G.
HYBRID CELL LINE FOR PRODUCING MONOCLONAL ANTIBODY TO HUMAN CYTOTOXIC AND SUPPRESSOR T-CELLS, ANTIBODY, AND METHODS

US 4,637,983, Jan. 20, 1987
Assignee: Ortho Pharmaceutical Corp.

Hybrid cell line for production of monoclonal antibody to an antigen found on normal human cytotoxic and suppressor T-cells is described. The hybrid is formed by fusing splenocytes from immunized CAF(1)mice with P3X63Ag8U1 myeloma cells. Diagnostic and therapeutic uses of the monoclonal antibody are also disclosed.

Kung, P. C. and Goldstein, G.
METHODS AND COMPOSITIONS USING MONOCLONAL ANTIBODY TO HUMAN HELPER T-CELLS
US 4,652,447, Mar. 24, 1987
Assignee: Ortho Pharmaceutical Corp.

The production of a hybrid cell line for production of monoclonal antibody to an antigen found on all normal human helper T-cells is described. The hybrid is formed by fusing splenocytes from immunized CAF(1)mice with P3X63Ag8U1 myeloma cells. Diagnostic and therapeutic uses of the monoclonal antibody are also disclosed.

Kuo, G., Masiarz, F. R., Truett, M., Valenzuela, P., Rasmussen, M. E., and Favaloro, J.
MONOCLONAL ANTIBODIES TO FACTOR VIIIC
US 4,716,117, Dec. 29, 1987
Assignee: Chiron Corp.; Nordisk Gentofte

Hybridomas producing monoclonal antibodies specific for polypeptide fragments derived from human Factor VIIIC are provided. Class I hybridomas produce monoclonal antibodies reactive with a 80/77 kD doublet fragment or with both the 80/77 kD doublet and a 240 kD polypeptide. Class III hybridomas produce monoclonal antibodies reactive with the 240 kD polypeptide as well as a 92.5 kD fragment and its precursors. Class III antibodies show additional reactivity with a 40 kD thrombin digestion product. The monoclonal antibodies are useful for the separation of Factor VIIIC and its constituent polypeptides, as well as for the immunoassay of Factor VIIIC in biological samples.

Lee, J. P., Salcedo, F. B., and Robins, M. F.
IMMUNOASSAYS USING MULTIPLE MONOCLONAL ANTIBODIES AND SCAVENGER ANTIBODIES
US 4,722,889, Feb. 2, 1988
Assignee: Leeco Diagnostics, Inc.

A method and reagent kit are provided for assay of a selected antigen such as hCG or CEA in an aliquot of body fluid. The method requires constituting the aliquot in a mixture comprising tracer (that may be an enzyme or a radioactive tracer) conjugated with monoclonal antibody and a

separate immobilized monoclonal antibody. The mixture is incubated to enable separation of a solid phase antigen-antibody conjugate in sandwich relation, and the tracer content measured giving the corresponding antigen content of the aqueous or solid phase. The antibody (conjugated and/or immobilized) comprises multiple monoclonal antibodies from different cell lines so that the specificity of the assay is enhanced, and the possibility of unrecognized antigen fragments is reduced. Also, as a preferred option, the incubation may be carried out with a scavenger monoclonal antibody so that, as an example, in the context of hCG assay, the scavenger chosen for beta subunit selectivity, but low hCG affinity is present in the reaction to prevent any possible cross-reactivity from analogs of homologous reactivity.

Lemelson, J.H.
DRUG COMPOSITIONS AND METHODS OF APPLYING SAME
US 4,674,480, Jun. 23, 1987

A composition and method for targeting and applying drugs or medication to a select location(s) within a living being is provided. Drug units are produced, each of which is formed of at least one antibody, such as a monoclonal antibody, a small quantity of a medication such as a chemical or organic material and a small quantity of a nuclide that is normally inactive, but may be rendered explosively radioactive when targeted within a living body by external radiation passed through the body to the drug unit. When rendered radioactive, the medication is released to infiltrate or be absorbed by surrounding tissue. In a particular form, the system also includes means for detecting the location(s) of such drug units within the body and controlling the generation and direction of activating radiation passed through the body from an external source to cause the nuclide material existing in each drug unit to become radioactive.

Loor, R., Mtimkulu, T., and DeWitt, S. K.
PROCESS FOR SIMULTANEOUSLY DETECTING MULTIPLE ANTIGENS USING DUAL SANDWICH IMMUNOMETRIC ASSAY
US 4,690,890, Sep. 1, 1987
Assignee: Cetus Corp.

The detection of at least two antigens in a sample using an immunometric dual sandwich assay containing an effective amount of at least one monoclonal antibody against each antigen is described. These antibodies are separately conjugated with the same or different signal moieties as labels, and an effective amount of at least one unlabeled monoclonal antibody against each antigen are immobilized on a single support. Preferably, the antibodies are all products of different cell lines and the antigens are prostatic acid phosphatase and prostate antigen.

Lundblad, K. A.
MONOCLONAL ANTIBODY FORMULATION FOR DIAGNOSTIC USE
US 4,618,486, Oct. 21, 1986
Assignee: MonoCarb AB

Aqueous formulations containing monoclonal antibodies active against cell-bound antigens, particularly human red cell antigens is described. The said formulations contain a soluble salt in a concentration of not less than about 200 mmol/1.

Lutz, H.
HYBRIDOMAS PRODUCING MONOCLONAL ANTIBODIES SPECIFIC FOR FeLV p27
US 4,713,325, Dec. 15, 1987
Assignee: Regents of the University of California

Compositions and methods are described for the detection of feline leukemia virus. Hybridomas are prepared, producing monoclonal antibodies specific for at least one determinant site for the protein p27 of feline leukemia virus (FeLV). The antibodies are used in an enzyme immunoassay for determination of feline leukemia virus.

Mattes, M, J., Lewis, Jr., J. L., Lloyd, K. O., Old, L. J., and Cordon, C. C.
MONOCLONAL ANTIBODIES TO OVARIAN, CERVICAL, AND UTERINE HUMAN CANCERS AND METHOD OF DIAGNOSIS
US 4,666,845, May 19, 1987
Assignee: Sloan-Kettering Institute

Mouse monoclonal antibodies to several cell antigens of human ovarian, cervical, and endometrial carcinomas have been produced and characterized. The distribution of the antigens was determined by mixed hemagglutination assays on 153 normal and malignant cell cultures of various types and by immunoperoxidase staining of frozen sections of 27 normal adult and 24 fetal tissues. Five monoclonal antibodies, representative of five classes of monoclonal antibodies (mAb) raised to restricted ovarian, cervical, and endometrial cells, were tested extensively producing mAb reactive with cancer, but not normal cells. One such mAb, MF116 was readily detected in the spent culture medium of metabolically radiolabeled cells. These antibodies, reacting with relatively restricted cell surface antigens, are useful in the analysis of epithelial cell differentiation, cancer diagnosis and therapy, and tissue typing of normal or abnormal cells.

Mulshine, J. L. and Minna, J. D.
MONOCLONAL ANTIBODIES AGAINST NONSMALL CELL LUNG CANCER
US 4,569,788, Feb. 11, 1986
Assignee: US Department of Health and Human Services

Monoclonal antibodies 703D4 and 704A1 have been prepared to detect human nonsmall cell lung cancer (nonSCLC) and distinguish nonSCLC from all other types of lung cancer and normal tissue cells. These two antibodies may be utilized in kit form to distinguish nonSCLC from other forms of lung cancer. These monoclonal antibodies bind to S(35)methionine-incorporating protein doublets under reduced and unreduced conditions. The determinants bound by these antibodies on the 31 kD protein are independent of each other as determined in radiolabeled competition assays.

Murray, K. A.
ASSAY OF IMMUNOGLOBULIN A PROTEASE AND THE RAPID DIAGNOSIS OF GONORRHEA
US 4,582,699, Apr. 15, 1986
Assignee: Magbon Test Co.

A method for rapid diagnosis of gonorrhea is set forth comprising the assay of the enzyme immunoglobulin A protease (IgAP). Immunoassays, including radioimmunoassay and enzyme-linked immunoassay with monoclonal antibodies to IgAP, are disclosed. A kit for early detection of gonorrhea is given. The assay and kit of the present invention may also be used in the detection of meningitis.

Pestka, S.
IMMUNOASSAY FOR PEPTIDE AND PROTEIN OLIGOMERS
US 4,623,621, Nov. 18, 1986
Assignee: Hoffman-La Roche, Inc.

A convenient immunoassay for detecting the presence of oligomeric forms of peptides and proteins is described. The assay employs the sandwich technique with a monoclonal antibody selective for a single epitope on the peptide or protein bound to a solid phase and the same monoclonal antibody labeled with a detectable label in the solution phase.

Reisfeld, R. A. and Schulz, G.
MONOCLONAL ANTIBODY DIRECTED TO HUMAN GANGLIOSIDE GD(2)
US 4,675,287, June 23, 1987
Assignee: Scripps Clinic and Research Foundation

A nonhuman, mammalian monoclonal receptor produced and secreted by a hybridoma having the ATCC accession number HB 8568 and methods of preparing and using same, as well as diagnostics utilizing the receptor, are disclosed. The monoclonal receptor reacts with cells, such as human neuroectodermal tumors, having ganglioside GD(2)antigen expressed on their cellular membrane surfaces.

Ring, D. B.
ASSAY KIT AND METHOD FOR THE DETERMINATION OF ANTIBODY CLASS AND SUBCLASS
US 4,727,037, Feb. 23, 1988
Assignee: Cetus Corp.

A method of rapid determination of the isotype class for a panel of monoclonal antibodies is described. The assay comprises adsorbing on a solid support medium antibodies directed to specific immunoglobulin heavy and light chains. Once such isotype-specific antibodies are bound to the nitrocellulose paper, the treated strips can be incubated with the monoclonal antibody of interest. Upon formation of a complex between the specific iso-type antisera and the monoclonal antibody, the complex is visualized by reaction with a chromogenic substance. In the preferred embodiment of the invention, the treated nitrocellulose strips are stored in kit form. Using these prepared strips, the isotyping assay can be performed in less than two hours with a minimum of technical manipulation and expenditure of reagents.

Robert, G. M. and Gallo, R. C.
METHOD FOR DETECTING HTLV-III NEUTRALIZING ANTIBODIES IN SERA
US 4,755,457, July 5, 1988
Assignee: US Department of Health and Human Services

This invention relates to a method to measure natural human antibodies in sera that will neutralize HTLV-III infection in an in vitro assay. Basically, cell-free virus is incubated with serum and used to infect H9 cells, that are then put in culture for 3 d, and viral infectivity is assayed using a monoclonal antibody specific for HTLV-III p24 in an immune fluorescent assay.

Sadowski, P. L.
USE OF MONOCLONAL ANTIBODIES AGAINST BACTERIAL ADHESINS
US 4,652,448, Mar. 24, 1987
Assignee: Molecular Genetics, Inc.

Monoclonal antibodies specific for surface antigens of bacteria that act as adhesins between prokaryotic and eukaryotic cells and, in particular, K-99 pili, and methods for production thereof are described. These monoclonal antibodies may be used for the prophylactic and therapeutic treatment of diseases induced by adhesin-bearing pathogens in animals and humans and for the diagnostic identification of adhesion-bearing bacteria.

Sakamoto, J., Cordon, C. C., Friedman, E., Finstad, C. L., Enker, W. E., Melamed, M. R., Lloyd, K. O., Oettgen, H. F., and Old, L. J.

MONOCLONAL ANTIBODIES TO HUMAN GASTROINTESTINAL CANCERS AND HYBRIDOMA METHOD OF PRODUCTION OF THE MONOCLONAL ANTIBODIES
US 4,579,827, Apr. 1, 1986
Assignee: Sloan-Kettering Institute for Cancer Research

A panel of monoclonal antibodies produced from human gastrointestinal tumors as immunogen is used to diagnose the presence of colon cancer. The antibody panel subsets the human gastrointestinal tract in its reactivity vis-à-vis esophagus, stomach, small intestine, and colon. The panel is useful as a diagnostic probe for cancer.

Shockman, G. D., Jackson, D. E., and Wong, W.
MONOCLONAL ANTIBODIES TO PEPTIDOGLYCAN AND METHODS OF PREPARING SAME
US 4,596,769, June 24, 1986
Assignee: Temple University

Several novel hybridoma cell lines, ATCC HB-8510, 8511, 8512, 8513, 8514, 8515, 8516, and 8517 that produce monoclonal antibody peptidoglycan, a normal structural component of nearly all true bacteria, is described. Each antibody reacts not only with peptidoglycan from the immunizing bacterial strain, but also peptidoglycan from other strains. Certain members of the hybridoma panel produce monoclonal antibody that reacts with peptidoglycan from substantially any peptidoglycan-possessing bacterium. The hybridomas are formed by fusing spleen cells from immunized Balb/c mice with SP2/O-Ag14 myeloma cells. Diagnostic and therapeutic uses of the monoclonal antibodies are provided.

Siebert, G. R. and Armstrong, J.
MONOCLONAL ANTIBODIES RECOGNIZING L-THYROXINE
US 4,636,478, Jan. 13, 1987
Assignee: Becton, Dickinson and Co.

The development of monoclonal antibodies specific for thyroxine (T(4)) that are produced by two new and separate hybridoma cell lines are described. Combinations of the monoclonal antibodies from the two cell lines are used in an immunoassay for T(4)of high accuracy over the range of T(4)concentrations encountered in serum samples.

Steplewski, Z., Koprowski, H., and Herlyn, M.
LEWIS BLOOD GROUP PHENOTYPE ASSAY
US 4,607,009, Aug. 19, 1986
Assignee: The Wistar Institute

An assay for determining the Lewis blood group of a patient is described and consists of testing a body sample for the presence of Lewis(a)and Lewis(b)antigens. Monoclonal antibodies, specific for either of these anti-

gens, are employed that do not cross-react with other related antigens, such as the H blood antigen. Body samples that may be tested include: saliva, serum, urine, and paraffin-embedded tissue samples. Hybridoma cell lines, and the antibody compositions they produce, specific for these antigens are provided for use in the assay.

Stuart, W. D. and Frank, M. B.
MONOCLONAL ANTIBODIES FOR DNA-RNA HYBRID COMPLEXES AND THEIR USES
US 4,732,847, Mar. 22, 1988
Assignee: University of Hawaii

Monoclonal antibodies are provided that are capable of distinguishing DNA-RNA hybrid complexes from single stranded DNA and RNA and double stranded DNA and RNA. The antibodies find particular use in determining the presence of a specific nucleic acid sequence on a solid surface. Single stranded polynucleotide is fixed to a solid (gel) surface and then hybridized with the complementary probe. The hybrid complex specific monoclonal antibody is then added to bind to any hybrid complexes that have formed. By appropriate label, the hybrid complex may be visualized in a variety of ways.

Talle, M. A., Newman, W., Rao, P. E., and Goldstein, G.
MONOCLONAL ANTIBODY THERAPY
US 4,731,244, Mar. 15, 1988
Assignee: Ortho Pharmaceutical Corp.

A method of seriatim administration to a patient of a plurality of ligands, each of which contains an antigen combining site of a monoclonal antibody of distinct idiotype, is disclosed. This method is useful for therapeutic as well as diagnostic purposes.

Terasaki, P. I., Hirota, M., Fukushima, K., Wakisaka, A., and Iguro, T.
SIALYLATED LEWIS(X)EPITOPE, ANTIBODIES AND DIAGNOSIS
US 4,752,569, June 21, 1988
Assignee: Regents of the University of California

Detection of sialylated Lewis(x)antigen in sera is employed as diagnostic of the presence of cancer. Conveniently, monoclonal antibodies are provided that are shown to be useful in the diagnosis of a neoplastic condition, with a wide variety of different tumors. The hybridoma CSLEX1 was deposited at the ATCC (Accession No. HB8580) on June 20, 1984.

Thompson, R. E., Rubin, R. H., Rubin, N. T., and Chan, T. H.
DISEASE DIAGNOSIS BY DETECTION OF SHED NORMAL TISSUE ANTIGENS
US 4,731,326, Mar. 15, 1988
Assignee: Ortho Diagnostic Systems, Inc.

Methods are provided for the detection of proximal convoluted tubule-causing diseases or kidney harmful drug monitoring by detecting the presence of shed normal proximal tubule-associated antigens in a body fluid such as urine. The preferred embodiment employs an ELISA sandwich format wherein one monoclonal antibody, specific for a first epitopic site on said antigen, is immobilized on a solid phase and a second antibody, specific for a second epitopic site on said antigen, is directly or indirectly labeled.

Wang, L., and Inbar, M.
PREPARATIONS FOR USE IN SOLID PHASE IMMUNOASSAYS COMPRISING MONOCLONAL ANTIBODIES COVALENTLY EMBEDDED IN THEIR IMMOBILIZED HYBRIDOMA CELLS
US 4,727,023, Feb. 23, 1988
Assignee: I.D.L. International Diagnostic Laborates Ltd.

A reagent for use in solid phase immunoassay diagnostics is described. This reagent comprises a matrix of nonactive hybridoma cells embedded with its self-produced, covalently bound, actively presented monoclonal antibodies. The solid phase reagent, according to the invention, is prepared by incubating, in vitro, a culture medium containing active hybridoma cells capable of producing monoclonal antibodies, separating and washing the cells, resuspending the cells in a buffer solution, and adding to the resulting suspension an inactivator substance capable of converting active hybridoma cells into the nonactive state.

LITERATURE

This section surveys the literature in the area of monoclonal antibodies for clinical applications from January 1986–July 1988. The major headings and cross terms are the same as listed in the patent search. This section is not intended to be all encompassing and lists both review articles and research publications that highlight the varied nature of research in this field during the specified time period.

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