replication frequency of the virus whereas the lytic phase is characterized by high transcriptional activity and/or high replication frequency. Although the mechanism(s) involved in the switch from the latent to lytic phase is not completely understood, inhibition of the viral LTR promoter is an important strategy in AIDS treatment. The invention concerns the use of the compound carboxyamidotriazole (CAI), a calcium response modifier, and structurally related compounds that are capable of preventing the activation of the LTR promoter in the treatment of HIV infection and AIDS. In addition, CAI has antimetastatic properties and currently is being tested in clinical trials for the treatment of cancer. A further advantage is that CAI has shown no severe side effects during these trials. Therefore treatment of AIDS patients with CAI would also allow for the treatment of related cancers such as Kaposi's sarcoma. (portfolio: Infectious Diseases—Therapeutics, anti-virals, AIDS)

Diastereoselective Process Leading to a Key Intermediate for the Preparation of Fluorinated Reverse Transcriptase Inhibitors

VE Marquez, JS Driscoll, MA Siddiqui (NCI)
Serial No. 08/189,095 filed 31 Jan 94
U.S. Patent No. 5,498,719 issued 12 Mar 96

A novel process has been developed for synthesizing a key intermediate in the preparation of fluorinated reverse transcriptase inhibitors. Recently, several fluorinated dideoxynucleotides have been found to be effective inhibitors of reverse transcriptase and, thus, offer promise for replacing or augmenting current drugs for the treatment of HIV–1 infection; however, chemically synthesizing these fluorinated dideoxynucleotides is quite expensive, making it economically difficult to produce large-scale amounts for testing. This new process allows the synthesis of a key intermediate in the production of fluorinated dideoxynucleotides at much lower costs because the reaction is diastereoselective, meaning that there are fewer side reactions and more primary product is produced. (portfolio: Infectious Diseases—Therapeutics, anti-virals, AIDS)

C–C Chemokines That Inhibit Retrovirus Infection

P Lusso, R Gallo, F Cocchi, A De Vico, A Garzino-Demo (NCI)
Filed 30 Nov 95
DHHS Reference No. E–008–96/0

This invention concerns three members of the human C-C chemokine family, RANTES, macrophage inflammatory protein 1α (MIP–1α) and macrophage inflammatory protein 1β (MIP–1β), which are produced and secreted by several cell types, including CD8-positive T lymphocytes, and which act *in vitro* as HIV suppressive factors. These factors and their respective genes may be used in the diagnosis, prognosis, treatment and prevention of AIDS and other retrovirus-induced diseases. The invention provides a therapeutic preparation, methods for therapeutic and prophylactic treatment of retroviral infection, and a method of prognosis for retroviral infection. The technology was reported in *BioWorld Today* (6(234):1 (December 7, 1995) and *Science* 270(8):1560–1561 (December 8, 1995). (portfolio: Infectious Diseases—Therapeutics, anti-virals, AIDS; Infectious Diseases—Diagnostics, viral, AIDS)

Dated: July 16, 1996.
Barbara M. McGarey,
Deputy Director, Office of Technology Transfer.

[FR Doc. 96–18969 Filed 7–25–96; 8:45 am]
BILLING CODE 4140–01–M

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, HHS.

ACTION: Notice.

The inventions listed below are owned by agencies of the U.S. Government and are available for licensing in the U.S. in accordance with 35 U.S.C. 207 to achieve expeditious commercialization of results of federally funded research and development. Foreign patent applications are filed on selected inventions to extend market coverage for U.S. companies and may also be available for licensing.

ADDRESSES: Licensing information and copies of the U.S. patent applications listed below may be obtained by contacting Jaconda Wagner, J.D., at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7735 ext 284; fax: 301/402–0220). A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Methods of Treating Established Colitis Using Antibodies Against IL–12

W Strober, M Neurath, I Fuss (NIAID)
Filed 25 Oct 95
Serial No. 08/547,979

Interleukin-12 (IL–12) is a recently characterized cytokine with unique structure and pleiotropic effects. IL–12 is produced mainly by macrophages/monocytes and can be efficiently induced by intracellular parasites, bacteria and bacterial products. A method for treating the established colitis of an inflammatory bowel disease, including Cohn's disease and ulcerative colitis, by inhibiting the colitis-inducing effects of the cytokine IL–12 has been invented. Additionally, a method for treating their effectiveness in reducing the inflammatory response is also presented. (portfolio: Internal Medicine—Diagnostics, anti-inflammatory; Internal Medicine—Therapeutics, anti-inflammatory; Internal Medicine—Miscellaneous)

Truncated Hepatocyte Growth Factor Variants

AML Chan, JS Rubin, DP Bottaro, SA Aaronson, SJ Stahl,
PT Wingfield, V Cioce (NCI)
Filed 07 Jun 95
Serial No. 08/484,841 (CIP of 08/130,134, which is CIP of 07/655,502)

[HGF/NK2], a truncated form of a hepatocyte growth factor (HGF), may offer an improved method of diagnosing and treating proliferative disorders such as cancers. Elevated levels of HGF are associated with both cancerous and noncancerous conditions. This truncated form of HGF is an antagonist of HGF and can be used to effectively counteract its effects on cells. Its cDNA can also be used as a probe to detect increased levels of HGF mRNA in cells.

HGF/NK1, another truncated form of HGF, has partial agonist/antagonist properties. Thus, it may be useful either as an antagonist of an HGF or as an agonist to reinforce the action of endogenous growth factor, depending on the circumstances. A technique has been developed to produce large quantities of biologically active HGF/NK1 and HGF/NK2 using a prokaryotic expression system. (portfolio: Cancer—Therapeutics, biological response modifiers, growth factors; Cancer—Diagnostics)

IL–13 Receptor Specific Chimeric Proteins and Uses Thereof

R Puri (FDA), W Debinski (Penn State), I Pastan (NCI), N Obiri (FDA)
Filed 15 Mar 95
Serial No. 08/404,685

A chimeric molecule that binds specifically to IL–13 receptors has been identified. The molecule, IL13–PE38QQR, targets tumor cells with less binding to healthy cells in comparison

to other chimeric molecules. The improved specific targeting of this molecule is premised upon the discovery that tumor cells overexpress IL–13 receptors at extremely high levels. This phenomena permits the use of lower dosages of chimeric molecules to deliver effecter molecules to targeted tumor cells.

This invention will be useful in the treatment of cancer. The targeting method could be used in conjunction with current methods, e.g., chemotherapy to help maintain the healthy cells. To date, the molecule has been shown to be effective against a variety of solid tumor cancers, including adenocarcinoma, colon cancer, breast cancer, ovarian cancer, kidney cancer, brain cancer and AIDS associated Kaposi's sarcoma. (portfolio: Cancer—Diagnostics, in vivo, conjugate chemistry; Cancer—Therapeutics, immunoconjugates, toxins; Cancer—Therapeutics, immunomodulators and immunostimulants)

Janus Family Kinases (JAK) and Identification of Immune Modulators

JJ O'Shea, WJ Leonard, JA Johnston, SM Russell, D McVicar, M Kawamura (NCI)
Filed 13 Jan 95
Serial No. 08/373,934

This invention relates to an isolated polynucleotide encoding the JAK–3 protein. JAK–3 is a protein tyrosine kinase having a molecular weight of approximately 125 kDa and tandem non-identical catalytic domians, lacks SH2 or SH3 domains, and is expressed in NK cells and stimulated or transformed T cells, but not in resting T cells. The JAK–3 protein itself, antibodies to this protein, and methods of identifying therapeutic agents for modulating the immune system which make use of the foregoing. (portfolio: Cancer—Research Reagents; Cancer—Diagnostics)

Pigment Epithelium Derived Factor: Characterization of its Novel Biological Activity and Sequences Encoding and Expressing the Protein

GJ Chader, SP Becerra, JP Schwartz, T Taniwaki (NEI)
Filed 07 Jun 94
Serial No. 08/257,963 (CIP of 07/952,796)

Pigment epithelium-derived factor (PEDF), which is also known as pigment epithelium differentiation factor and is a neurotrophic, neuron-survival and gliastatic protein, has been produced using recombinant DNA techniques. The invention concerns nucleic acids encoding PEDF and functional fragments thereof, vectors comprising the nucleic acids, host cells containing the vectors, a recombinant method for producing PEDF and equivalent proteins, antibodies (monoclonal and polyclonal) to PEDF, and an immunoassay for PEDF. This technology has potential therapeutic use in the treatment of inflammatory, vascular, degenerative, and dystrophic diseases of the retina and central nervous system (CNS). (portfolio: Ophthalmology—Diagnostics; Ophthalmology—Therapeutics, biological; Ophthalmology—Miscellaneous)

T Cell Receptor Ligands, And Methods For Use

RN Germain, L Racioppi (NIAID)
Filed 15 Jan 93
Serial No. 08/004,936

T lymphocytes are key cellular elements of the immune system. The growth, effector functions (cytokine secretion, cytotoxicity), and survival of these cells are regulated by signals arising from the interaction of ligands consisting of polypeptide-MHC molecule complexes with specific receptors (TCR) on the cell membrane. All antigen-specific attempts at modulation of T-cell dependent immunity involve this key TCR-ligand interaction. This application describes a novel class of TCR ligands (called variant TCR ligands, a sometimes referred to in the scientific literature as altered peptide ligands) with selective antagonist or mixed agonist-antagonist properties that can modulate the function of T cells in unique ways. For example, these compounds can induce T lymphocyte unresponsiveness while preventing T cell effector activity or can permit secretion of some cytokines while inhibiting the secretion of others typically produced upon exposure to the normal stimulatory ligand of the TCR in question. These effects can thus modulate *in vivo* immune responses by inactivating T cells or by changing the effector response of such cells from a damaging to a benign pattern. These properties should be extremely useful in the development of antigen-specific immunotherapies for various autoimmune diseases, including but not limited to diabetes, rheumatoid arthritis, and multiple sclerosis. These compounds could also be useful in modifying responses to tumor antigens, to vaccine components, or tissue transplants. Because these novel immunomodulatory compounds are produced by slight alteration of the normal peptide-MHC molecule ligand for the TCR, it is believed that all current attempts to modify such diseases using as antigen either species variants or synthetic variants rather than native, unmodified human self-antigens involve materials whose properties and mode of action fall within the scope of this patent application. (portfolio: Cancer—Therapeutics, immunomodulators and immunostimulants)

Macrophage Stimulating Protein

EJ Leonard, AH Skeel, T Yoshimura, E Appella, S Showalter, S Tanaka (NCI)
Serial No. 07/586,085 filed 21 Sep 90
U.S. Patent No. 5,219,991 issued 15 Jun 93 and
Serial No. 08/076,880 filed 6/15/93 (DIV of 07/586,085)
U.S. Patent No. 5,527,685 issued 18 Jun 96

Macrophage stimulating protein (MSP), a relative of the hepatocyte growth factor (HGF), is a component of human and animal (mammalian) blood plasma which accelerates the movement and increases the activity of macrophages. Macrophages, when activated, can kill foreign microorganisms and tumor cells.

This invention describes the preparation of highly purified MSP and the production of antibodies to the purified MSP. These methods overcome the primary problem with natural MSP, i.e., that its concentration in the plasma is too low for purification by conventional techniques and for use as an effective therapeutic agent. The highly purified MSP and/or its antibodies can be used as a diagnostic and therapeutic agent and a basic research tool for diseases characterized by macrophage-mediated inflammation. The invention also describes a bioassay for the detection of antibodies to that bind MSP. (portfolio: Internal Medicine—Diagnostics; Internal Medicine—Therapeutics; Internal Medicine—Miscellaneous)

75 Kilodalton Interleukin-2 Receptor Proteins and Their Use

KA Smith
Serial No. 06/944,337 filed 19 Dec 86
U.S. Patent 5,352,772 issued 04 Oct 94

A cellular protein produced by activated T cells and involved in high affinity binding of interleukin-2 has been discovered. The protein is substantially unreactive with anti-Tac antibodies and is believed to interact with the previous 55,000 dilaton receptor protein to form high affinity interleukin-2 receptor which triggers the growth and mitosis of T cells during an immune response. Methods for isolating and purifying the protein and raising monoclonal antibodies to the proteins

are included as well as techniques for cloning and expressing the protein in related materials.

T cells play a central role in the induction and regulation of the immune response. Thus, the structure of IL–2 receptors and their relationship to T cell growth and proliferation is on considerable scientific and clinical importance. The present technology could be used in the development of T cell antagonists compounds which could be to treat a wide range of autoimmune diseases, such as rheumatoid arthritis and other T cell-driven inflammatory diseases. The technology could also be used to develop immunosuppressants, which could be useful in combating tissue and organ graft rejection in kidney, liver, heart and other transplants and so-called ''graft versus host'' disease in bone marrow transplants without the side effect associate with conventional immunosuppressants. (portfolio: Internal Medicine—Miscellaneous; Internal Medicine—Diagnostics, anti-inflammatory; Internal Medicine—Therapeutics, anti-inflammatory)

Soluble Interleukin-2 Receptor as a Disease Indicator and a Method of Assaying the Same

D Nelson, W Biddison, L Rubin, W Greene, W Leonard, R Yarchoan (NCI)
Serial No. 06/724,897 filed 19 Apr 85
U.S. Patent No. 4,707,443 issued 17 Nov 87

Soluble IL–2 receptor is produced in response to immune activation and by some malignant cells. For instance, elevated levels of IL–2 have been detected in patients with adult T-cell leukemia, Sezary syndrome, Hodgkin's disease, chronic lymphocytic leukemia, multiple myeloma, and solid tumors. The systemic level of IL–2 receptor is also relevant in the diagnosis and treatment of such diseases as rheumatoid arthritis and systemic lupus erythematosis and may be used to titrate immunosuppressive therapy in such applications as graft rejection.

The invention disclosed in the patent is a sandwich immunoassay useful for determining the amount of IL–2 receptor in a sample. The invention also discloses a method of detecting such disturbed or abnormal conditions in humans which release soluble IL–2 receptor in bodily fluids. (portfolio: Internal Medicine—Diagnostics, anti-inflammatory; Internal Medicine—Therapeutics, anti-inflammatory; Cancer—Diagnostics; Cancer—Therapeutics, biological response modifiers)

Enhanced Stem Cell Engraftment Using Cytokines

M. Mardiney III, HL Malech (NIAID)
Filed 21 Jul 95
Serial No. 60/001,386

The invention relates to be a method for establishing high levels of chimerism of transplanted hematopoietic stem cells in humans to treat disease, more particularly, to accomplish this with a significant reduction in the level of recipient conditioning prior to transplantation. This technology can be used to achieve successful engraftment in individuals who must undergo bone marrow transplantation.

The practice of bone marrow transplantation or peripheral blood stem cell transplantation involves placing a suspension of allogeneic or autologous hematopoietic pluripotent cells into the blood stream of the recipient. Successful engraftment of these cells requires conditioning of the recipient prior to transplantation. This is accomplished by subjecting the recipient to systemic radiation, or chemotherapy, or a combination of radiation and chemotherapy. This treatment kills bone marrow cells, including stem cells, and open spaces for transplanted stem cells to engraft. However, current conditioning regimens used to ensure successful engraftment are associated with immune deficiency, multi-organ toxicity, secondary malignancies, and increased risk of death.

The current invention provides a method for successful transplantation by enhancing radiation or chemotherapy potentiated engraftment at doses which are much smaller than those used in current practice. The mechanism of this process relates, in part, to the ability of cytokines to upregulate receptors necessary for homing of transplanted hematopoietic stem cells. Thus, successful transplantation can be performed with minimal conditioning-related morbidity. (portfolio: Cancer—Therapeutics, biological response modifiers, growth factors; Infectious Diseases—Miscellaneous; Internal Medicine—Miscellaneous)

Depigmenting Activity of Agouti Signal Protein and Peptides Thereof

VJ Hearing (NCIA)
Filed 23 Jun 95
DHHS Reference No. E–165–95/0

Pigmentation is controlled at many levels in mammals. One important regulatory protein known to be physiologically active is the Agouti signal protein (ASP), which has depigmenting activity. This invention provides biologically active peptides of ASP and a method of using ASP and its peptides to inhibit melanin synthesis by down regulating the melanogenic enzymes involved in melanin synthesis. Using a method also provided in this invention, ASP and its peptides can be used to treat hyperpigmentary conditions, such as melasma photoaging spots, solar keratosis, and hyperpigmentation at wound healing sites. ASP and its peptides are also useful for cosmetic purposes. These compounds may potentially be used for other therapeutics in the prevention or treatment of damaged skin. The invention also gives a pharmaceutical composition of ASP or its peptides and a screening method for ASP peptides. Issuance of a patent for this invention is currently pending. (portfolio: Internal Medicine—Therapeutics, skin disorders, other)

Selective Elimination of T-Cells That Recognize Specific Preselected Targets

A Rosenberg (FDA)

Filed 30 Aug 95

DHHS Reference No. E–116–95/0

The invention relates to methods and compositions for the elimination of T cells that recognize specific preselected targets which can be used to treat autoimmune diseases and graft rejection.

The invention provides a method for selectively inhibiting or killing T cells that recognize a specific preselected target molecule and also for modified killer cells that bear a signal transduction molecule to which is attached the preselected target molecule. Recognition of the preselected molecule by a T-cell activates the killer cell which then kills or inhibits the T cell. Where the preselected molecule is an extracellular domain of an MHC from a xenograft or an allograft, treatment of the graft recipient with the modified killer T-cells delays or inhibits graft rejection. Similarly, where the preselected molecule is an MHC that binds the antigenic determinant of the autoimmune disease, treatment of the organism with the modified T-cells mitigates the autoimmune response directed against that antigenic determinant. (portfolio: Internal Medicine—Miscellaneous; Internal Medicine—Therapeutics, anti-inflammatory)

Dated: July 16, 1996.

Barbara M. McGarey,

Deputy Director, Office of Technology Transfer.

[FR Doc. 96–18970 Filed 7–25–96; 8:45 am]

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