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Methods of Preparing Lymphocytes That Express Interleukin-2 and Their Use in the Treatment of Cancer

Ke Liu and Steven Rosenberg (NCI). PCT Application No. PCT/US02/33243 filed 15 Oct 2002 (DHHS Reference No. E-297-2002/0-PCT-01).

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Adoptive immunotherapy strategies are highly dependent upon a sustained immune response to a tumor specific antigen. An effective adoptive strategy should ideally recruit and integrate into the existing components of a cancer patient's inherent immune system. However, most cancer patient's immune systems are unable to sustain the expansion of introduced tumor specific T-cells and hence cannot sustain a tumor specific response. Interleukin 2 (IL-2) is a natural cytokine that will promote the growth and expansion of introduced tumor specific T cells. Unfortunately, supplementing a patient's immune system with the systemic introduction of IL-2 has severe toxicity effects at a dose sufficient to promote T-cell growth, limiting the effectiveness of many adoptive strategies.

This invention relates to methods of preparing autologous T-lymphocytes and tumor-infiltrating lymphocytes that express IL-2. This method comprises the following steps: obtaining peripheral blood mononuclear cells (PBMC) or tumor infiltrating lymphocytes (TIL) from a patient immunized with an antigen of cancer; stimulating the PBMC's or TIL with the antigen of the cancer *in vitro*; transducing the PBMC's or TIL with a retroviral vector encoding IL-2; and reintroducing these autologous T-lymphocytes back into the patient. This method overcomes the potential toxicity issues from systemic IL-2 delivery and creates self-sufficient T-cells for an effective adoptive immunotherapy response.

Catalytic Domains of $\beta(1,4)$ -galactosyltransferase I Having Altered Donor and Acceptor Specificities, Domains That Promote In Vitro Protein Folding, and Methods for Their Use

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U.S. Provisional Application No. 60/439,298 filed 10 Jan 2003 (DHHS Reference No. E-230-2002/0-US-01);

U.S. Provisional Application No. 60/450,250 filed 23 Feb 2003 (DHHS Reference No. E-230-2002/1-US-01).

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$\beta(1,4)$ -galactosyltransferase I catalyzes the transfer of galactose from the donor, UDP-galactose, to an acceptor, N-acetylglucosamine, to form a galactose- $\beta(1,4)$ -N-acetylglucosamine bond. This reaction allows galactose to be linked to an N-acetylglucosamine that may itself be linked to a variety of other molecules. The reaction can be used to make many types of molecules having great biological significance. For example, galactose- $\beta(1,4)$ -N-acetylglucosamine linkages are very important for cellular recognition and binding events as well as cellular interactions with pathogens, such as viruses. Therefore, methods to synthesize these types of bonds have many applications in research and medicine to develop pharmaceutical agents and improved vaccines that can be used to treat disease.

The present invention is based on the surprising discovery that the enzymatic activity of $\beta(1,4)$ -galactosyltransferase can be altered such that the enzyme can make chemical bonds that are very difficult to make by other methods. These alterations involve mutating the enzyme such that the mutated enzyme can transfer many different types of sugars from sugar nucleotide donors to many different types of acceptors. Therefore, the mutated $\beta(1,4)$ -galactosyltransferases of the invention can be used to synthesize a variety of products that, until now, have been very difficult and expensive to produce.

The invention also provides amino acid segments that promote the proper folding of a galactosyltransferase catalytic domain. The amino acid segments may be used to properly fold the galactosyltransferase catalytic domains of the invention and thereby increase their activity. The amino acid segments may also be used to increase the activity of galactosyltransferases that are produced recombinantly. Accordingly, use of the amino acid segments according to the invention allows for production of $\beta(1,4)$ -galactosyltransferases having increased enzymatic activity relative to $\beta(1,4)$ -galactosyltransferases produced in the absence of the amino acid segments.

Some of the many uses for this invention are the following: synthesis of polysaccharide antigens for conjugate vaccines, glycosylation of monoclonal antibodies, and as research tools.

Targeting of the Hepatitis A Cellular Receptor To Treat Renal Cancer

Gerardo Kaplan (FDA).

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Tumor markers—receptors on the cell surface that are expressed preferentially in tumor cells—are extremely useful in the diagnosis and treatment of cancers. The inventors have discovered that hHAVcr-1 is such a tumor marker because it is overexpressed in renal cell carcinomas, and its degree of overexpression is correlated to the stage of the tumor. In addition, overexpression of this receptor appears to affect differentiation.

The inventors have also demonstrated that they can target this receptor specifically *in vitro*, using monoclonal antibodies tagged with toxins and hepatitis A virus vectors. This discovery might be useful as a tumor marker or for gene-based therapeutics. Antibodies against the receptor encoded by hHAVcr-1 might be useful in an antibody-based therapeutic for the treatment of renal cancer.

Novel 2-Alkoxy Estradiols and Derivatives Thereof

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U.S. Patent Application No. 09/041,212 filed on 12 Mar 1998, which issued as U.S. Patent 6,136,992 on 24 October 2000 (DHHS Reference No. E-188-1998/1-US-01); U.S. Provisional Application No. 60/040,540 filed 13 Mar 1997 (DHHS Reference No. E-188-1998/0-US-01).

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The present invention is directed to novel 2-alkoxy estradiols and derivatives of 2-alkoxy estradiols having anticancer activity as claimed in the U.S. Patent 6,136,992. The invention is also directed to methods of preparing these novel compounds. These compounds have improved activity against a wide variety of tumor cell lines, including lung, colon, central nervous system, melanoma, ovarian, renal, prostate and breast cancers, compared with 2-methoxy estradiols. It is expected that these compounds will be very useful in the treatment of a wide variety of cancers. In addition, the present compounds have a low affinity for the estrogen receptor and are, therefore, expected to have fewer side effects than estradiols.