

cytotoxic reagents to inhibit the growth of tumor cells. This invention also describes that when these ribonucleases are expressed recombinantly they have significant increased cytotoxicity. These ribonucleases may be used to form chemical conjugates, as well as form targeted recombinant immunofusion molecules that can be used to decrease tumor cell growth. Importantly, these ribonucleases can be administered directly to patients to decrease and inhibit tumor cell growth without the use of a targeting agent. Humanized versions of these ribonucleases are described with portions of mammalian or human-derived neurotoxin, grafted to the molecule. This invention also includes methods of selectively killing cancer cells using the recombinantly expressed ribonucleases joined to a ligand to create a selective cytotoxic reagent. The method comprises contacting the cells to be killed with a cytotoxic reagent having a ligand binding moiety that specifically delivers the reagent to the cells to be killed. This method may be used for cell separation *in vitro* by selectively killing unwanted types of cells, for example, in bone marrow prior to transplantation into a patient undergoing marrow ablation by radiation, or for killing leukemia cells or T-Cells that would cause graft-versus-host disease.

The above mentioned invention is available, including any available foreign intellectual property rights, for licensing on an exclusive or non-exclusive or non-exclusive basis.

Dated: February 16, 1999.

Jack Spiegel,

Director, Division of Technology Development and Transfer, Office of Technology Transfer.
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Inventions; Availability for Licensing

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice

SUMMARY: The invention listed below is owned by an agency of the U.S. Government and is 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.

ADDRESS: Licensing information and a copy of the U.S. patent application

referenced below may be obtained by contacting J.R. Dixon, Ph.D., at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852-3804 (telephone 301/496-7056 ext 206; fax 301/402-0220; E-Mail: jd212g@NIH.GOV). A signed Confidential Disclosure Agreement is required to receive a copy of any patent application.

Entitled: Immunotoxins Directed Against Malignant B-Cells [Immunotoxins, Comprising an ONC Protein, Directed Against Malignant Cells]

Inventors: Drs. Susanna M. Rybak (NCI-FCRDC), Dianne Newton (NCI-FCRDC), and David Goldenberg (EM), DHHS Ref. No. E-157-97/0 filed 2 March 1997, [= PCT/US98/08983 filed 1 May 1998] and 09/071,672 filed 5 May 1998.

This invention relates to immunotoxins, that are useful for killing malignant B-Cells and other malignant cells and are directed to a surface marker on B-Cells and the nucleic acid constructs encoding the immunotoxins. These reagents comprise a toxic moiety that is derived from a *Rana pipiens* protein having a ribonucleolytic activity linked to an antibody capable of specific binding with a chosen tumor cell. It has been found that these immunotoxins are up to 2,000 fold more active against malignant B-Cells than their human RNase counterparts or the toxin itself. These immunotoxins when administered *in vivo* against disseminated tumors, resulted in dramatically lower side effects. These highly effective, but apparently non-toxic immunotoxins directed against such ubiquitous diseases as B-Cell Lymphomas and Leukemias and other malignancies, such as neuroblastoma, present a new and exciting therapeutic option for patients suffering from such diseases.

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Entitled: Methods for Determining the Prognosis of Breast Cancer Using Antibodies Specific for Thymidylate Synthase

Inventors: Drs. Patrick G. Johnston (NCI) and Carmen J. Allegra (NCI), Serial No. 09/152,647 filed 14 September 1998.

Thymidylate synthase provides the sole *de novo* source of thymidylate for DNA synthesis. It is also a critical therapeutic target for the fluoropyrimidine cytotoxic drugs, such as fluorouracil ("5-FU") and fluridexyureidine ("FudR"). In pre-clinical and clinical studies increased expression of thymidylate synthase protein has been associated with resistance to 5-FU. The quantitation of thymidylate synthase has traditionally been performed using enzymatic biochemical assays; however, these assays have major limitations when applied to human tumor tissue samples. Recently, monoclonal antibodies have been developed to human thymidylate synthase that have the required sensitivity and specificity to detect and quantitate thymidylate synthase enzyme in formalin-fixed tissue sections. Hence, this invention provides a method for determining the prognosis of a patient afflicted with breast cancer, by obtaining a solid breast tumor tissue sample, measuring the level of thymidylate synthase expression in the