cytotoxic reagents to inhibit the growth of tumor cells. This invention also describes that when these ribonucleases are expressed recombinantly they have significant increased eytotoxicity. 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.

[FR Doc. 99–4656 Filed 2–24–99; 8:45 am]

BILLING CODE 4140–01–M

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.

The above mentioned invention is available, including any foreign intellectual property rights, for licensing on an 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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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 flurodeoxyureidine (''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

tissue sample using antibody specific for thymidylate synthase. This invention further provides a method for predicting the benefit of chemotherapy for a patient afflicted with breast cancer. The above mentioned invention is derived from the discovery that high thymidylate synthase expression is associated with a poor prognosis in node-positive, but not in node-negative, breast cancer patients. Further, with some 2,504 patients, thymidylate synthase expression was not found to be correlated with other prognostic factors including tumor size, ER status, PR Status, tumor grade, vessel invasion, and histology.

The above mentioned invention is available for licensing on an 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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BILLING CODE 4140–01–M

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 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 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 Richard U. Rodriguez, M.B.A., at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7056 ext. 287; fax: 301/402–0220; e-mail: rr154z@nih.gov. A signed Confidential Disclosure Agreement will be required to receive copies of the patent applications.

Use Of Calreticulin And Calreticulin Fragments To Inhibit Endothelial Cell Growth And Angiogenesis, And Suppress Tumor Growth

G Tosato, SE Pike (FDA), DHHS Reference No. E–082–98/0 filed 06 Oct. 98

Tumor growth and invasion into normal tissues is dependent upon an adequate blood supply, and agents that target tumor blood supply have been shown to prevent or delay tumor formation and to promote the regression or dormancy of established tumors in preclinical models. It has been shown that EBV-immortalized cell lines can promote regression of experimental Burkitt's lymphoma, colon carcinoma and other human malignancies established in athymic mice through a vascular-based process. The inventors analyzed the cultured-media from EBV-immortalized cells and isolated a unique and potent factor which inhibits angiogenesis and tumor cell growth. This novel compound was named vasostatin. Vasostatin is an NH_2-terminal fragment of human calreticulin, and it can inhibit endothelial cell proliferation *in vitro*, suppress neovascularization *in vivo* and prevent or reduce growth of experimental tumors while having minimal effect on other cell types. Vasostatin is the most conserved domain among calrecticulins so far cloned and has no homology to other protein sequences. Data suggests that the antitumor effects of vasostatin are related to inhibition of *new* vessel formation rather than to a toxic effect on established tumor vascular structures. Vasostatin has key differences from other inhibitors of angiogenesis. It is small and soluble, and it is stable for greater than 19 months in aqueous solution. It is easily produced and delivered. By comparison, angiostatin, endostatin and thrombospondin can be difficult to isolate, purify and deliver. Additionally, studies have shown that the effective dose of vasostatin is 4–10 fold lower than the effective doses of endostatin and angiostatin. Therefore, this new and potent anti-angiogenic molecule should prove highly useful for the prevention and treatment of human cancers.

Polynucleotide Inhibition Of RNA Destabilization And Sequestration

DJ Lipman (NLM)
DHHS Reference No. 3–130–97/1 filed 19 Aug 98; PCT/US98/17261

A variety of mechanisms are available in eukaryotic cells for regulating gene expression such that each gene product is produced at appropriate times and in appropriate quantities. It is well established that a significant amount of control over gene expression can be exerted at the level of RNA processing and RNA stability. Evidence exists that suggests a role for antisense RNA transcripts (countertranscripts) in RNA destabilization and nuclear sequestration which promotes down-regulation of protein expression. Countertranscript-RNAs are encoded by the complementary-strand of a gene, and they are sometimes found in different tissues or developmental stages than their corresponding sense or transcript-RNAs, and these different expression patterns yield different gene-product expression patterns. Therefore, transcript-countertranscript complexes can play a critical role in the degradation and sequestration of RNAs and thus affect protein expression. The disclosed invention provides a means whereby defined polynucleotides can be introduced into a cell or tissue in order to prevent transcript-countertranscript interactions and thereby inhibit this degradation and nuclear sequestration of transcript RNA. This methodology could enhance the expression of a target gene-product encoded by a transcript-RNA by preventing transcript-countertranscript association. The polynucleotides themselves can be introduced or expression vectors can be created containing the polynucleotide sequence in order to express the defined polynucleotides in the cells or tissue of choice. These polynucleotides can also be used in *in vivo* and *ex vivo* regimens. As an example, these polynucleotides could be used to treat tumorigenic cells in such a way as to promote the expression of known apoptotic proteins whereby the tumorigenic cells are selectively killed. In summary, this technology could be used in any number of applications where the promotion of the expression of a particular gene-product is desirable.

Labeling DNA Plasmids With Triplex-Forming Oligonucleotides and Methods for Assaying Distribution of DNA Plasmids in Vivo

IG Panyutin, RD Neumann, O Sedelnikova (CC), DHHS Reference No. E–142–98/0 filed 26 May 98.

Monitoring the intracellular distribution of circular plasmids that have been introduced into cells is problematic because labeling moieties are not readily attached to covalently closed circular DNA molecules. Monitoring the biodistribution of DNA vectors that are introduced into a host animal, e.g., to determine the efficiency of transfection of target tissues in developing a method for gene therapy,