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.

[FR Doc. 99–4658 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 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,

is also problematic because commonly used assays based on detecting marker gene expression do not provide accurate biodistribution data due to failure to obtain a signal in those tissues in which the marker gene is not expressed. This invention obviates these deficiencies by disclosing the use of triplex-forming-oligonucleotides (TFO) which bind to their target sequences in circular plasmid DNA and thereby creating stable readily detectable triplex-complexes when introduced into living eukaryotic cells. These fluorescent or radio-labled polypurine TFOs can provide a noninvasive way to study the biodistribution of a plasmid of interest *in vivo* using tools developed for probe detection and radioimaging. In summary, this technology allows one to quantitatively monitor the whole-body distribution of labeled-vectors in living animals or patients.

Extension of a Protein-Protein Interaction Surface To Inactivate the Function of a Cellular Protein

CR Vinson, D Krylov (NCI), DHHS Reference No. E–113–95/1 filed 29 May 96, Related cases: Serial No. 08/690,111 filed 31 Jul 96; PCT/US96/12590 filed 31 Jul 96.

This invention uses sequence-specific DNA binding proteins as eukaryotic transcription factors, i.e., transcription regulatory proteins. Specifically, multimeric proteins having nucleic acid (DNA or RNA) binding domains in which the binding domain or protein interaction surface is engineered or modified to be acidic in nature. The acidic nature of the protein increases the stability of heteromultimeric or heterodimeric complexes that are formed. This type of nucleic acid binding protein should be capable of regulating the function of a target nucleic acid sequence or gene to which it is bound, thereby acting as a potent dominant-negative regulator of gene transcription, cell growth and cell proliferation. These proteins would be useful as drugs, inhibitory molecules or growth-controlling agents that can inhibit the expression,and thus the activity, of cellular proteins which have harmful, deleterious and even lethal effects on cell growth and survival. These proteins could also be used in gene therapy by using appropriate constructs to allow expression of a regulatory protein to treat suitable disease states. The constructs could also be used to create transgenic animals or plants in which the dominant-negative protein interacts with the wild-type protein to provide viable phenotypes to evaluate and assess the *in vivo* effects of the protein. In summary, this technology provides for useful tools and therapeutics which are capable of regulating specific target gene expression and gene-product activity.

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.

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Activity Dependent Neurotrophic Factor III (ADNP)

DE Brenneman (NICHD), Ilana Gozes (Tel Aviv University)
M Bassan
Serial No. 09/187,330 filed 06 Nov 1998 and claiming priority to PCT/US98/02485 and 60/037,404.
Licensing Contact: Susan S. Rucker; 301/496–7056 ext. 245; e-mail: sr156v@nih.gov

These application(s) disclose the identification, isolation, cloning and sequencing of a newly discovered gene which encodes a product known as ADNF III (Activity Dependent Neurotrophic Factor III)/ADNP (Activity Dependent Neuroprotective Protein). The gene has been localized to the long arm of chromosome 20 at 20q13.2—a region which has previously been associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). In addition to describing ADNF III/ADNP, the applications describe an eight (8) amino acid peptide fragment NAP which is an active region ADNF III/ADNP.

ADNP and NAP exhibit neuroprotective activity, the ability to protect neurons from cell death, with an EC50 in femtomolar range. Neuronal cell death is suggested as one mechanism in operation in Alzheimer's disease making ADNP or NAP attractive as candidates for the development of therapeutics for prevention or treatment of Alzheimer's disease. Early work using Apo-E deficient mice indicates that NAP can ameliorate learning and memory deficiencies normally exhibited in these mice. Other diseases involving neuronal cell death where ADNP or NAP may be useful include stroke, Huntington's disease, epilepsy, Parkinson's disease and Tourette's syndrome.

A Mutant OF TEV Protease That Is Resistant To Autoinactivation

David S. Waugh (NCI)
Serial No. 60/104,799 filed 19 Oct 98
Licensing Contact: Kai Chen; 301/496–7056 ext. 247; e-mail: kc169a@nih.gov

This invention concerns a mutant of the tobacco etch virus (TEV) proteinase. Due to its high degree of sequence specificity, the TEV protease is valuable reagent for cleaving fusion proteins. However, the wild-type TEV protease also cleaves itself to yield a truncated enzyme with greatly reduced proteolytic activity. As a result, more protease must be used to achieve complete digestion of a fusion protein substrate, and the stability of the enzyme during long term storage becomes problematic. This invention provides a means of avoiding autoinactivation of TEV, thereby enhancing its utility as a reagent for cleaving fusion proteins at a specific, predetermined site.

Fluorescent Pteridine Adenosine Analogs As DNA Probes Not Requiring Separation of Products

ME Hawkins, FM Balis, W Pfledierer (NCI)
Serial No. 60/099,487 filed 08 Sep 98
Licensing Contact: Manja Blazer; 301/496–7056 ext. 224; e-mail; mb379e@nih.gov

These are part of a series of nucleic acid analogs to be used as fluorescent probes for DNA analysis. Their site-specific incorporation into DNA through a deoxyribose linkage causes them to be much more sensitive to changes in the DNA than traditional fluorophores.