IV. Key to the OPO Codes

The key to the acronyms used in the listings to identify OPOs and their addresses are as follows:

DCTC—WASHINGTON REGIONAL TRANSPLANT CONSORTIUM, 8110 Gatehouse Road, Suite 101 W, Falls Church, VA 22042
MAOB—NEW ENGLAND ORGAN BANK, One Gateway Center, Newton, MA 02458
MIOP—ORGAN PROCUREMENT AGENCY OF MICHIGAN, 2203 Platt Road, Ann Arbor, MI 48104
NVLV—NEVADA DONOR NETWORK, 4850 Southeastern Avenue, Suite 33, Las Vegas, NV 89119
NYAP—CENTER FOR DONATION AND TRANSPLANT, 218 Great Oaks Blvd., Albany, NY 12203
UTOP—INTERMOUNTAIN ORGAN PROCUREMENT AGENCY, 230 South 500 East, Suite 290, Salt Lake City, UT 84102
VAOP—VIRGINIA ORGAN PROCUREMENT AGENCY, 1527 Houguenot Road, Midlothian, VA 23113
WIWU—UNIVERSITY OF WISCONSIN OPO, University of Wisconsin Hospitals and Clinics, 600 Highland Avenue, Madison, Wisconsin 53792

V. Collection of Information Requirements

Under the Paperwork Reduction Act of 1995, we are required to provide 60-day notice in the **Federal Register** and solicit public comment before a collection of information requirement is submitted to the Office of Management and Budget (OMB) for review and approval. In order to fairly evaluate whether an information collection requirement should be approved by OMB, section 3506(c)(2)(A) of the Paperwork Reduction Act of 1995 requires that we solicit comment on the following issues:

- The need for the information collection and its usefulness in carrying out the proper functions of our agency.
- The accuracy of our estimate of the information collection burden.
- The quality, utility, and clarity of the information to be collected.
- Recommendations to minimize the information collection burden on the affected public, including automated collection techniques.

Therefore, we are soliciting public comment on the following issue for the information collection requirements described below.

Designation of one OPO for each service area:

Section 486.316(e) states the requirements for a Medicare or Medicaid participating hospital to qualify for a waiver permitting the hospital to have an agreement with a designated OPO other than the OPO designated for the service area in which the hospital is located. The burden associated with these requirements is currently approved under OMB 0938–0688, HCFA–R–13, Conditions of Coverage for Organ Procurement Organizations, with an expiration date of November 30, 1999.

If you comment on any of these information collection and recordkeeping requirements, please mail copies directly to the following:

Health Care Financing Administration, Office of Information Services, Security and Standards Groups, Division of HCFA Enterprise Standards, Attention: Louis Blank, HCFA–1055–NC, Room N2–14–26, 7500 Security Boulevard, Baltimore, MD 21244–1850, and

Office of Information and Regulatory Affairs, Office of Management and Budget, Attention: Allison Eydt, HCFA Desk Officer, Room 10235, New Executive Office Building, Washington, DC 20503.

Authority: Section 1138 of the Social Security Act (42 U.S.C. 1320b–8).

(Catalog of Federal Domestic Assistance Program No. 93.773, Medicare—Hospital Insurance; Program No. 93.774 Medicare—Supplementary Medical Insurance, and Program No. 93.778, Medical Assistance Program)

Dated: August 2, 1999.

Robert A. Berenson,

Director, Center for Health Plans and Providers, Health Care Financing Administration.

[FR Doc. 99–20403 Filed 8–6–99; 8:45 am]

BILLING CODE 4120–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Government-Owned Invention; Availability for Licensing: ''Novel Method and Composition to Induce Apoptosis in Tumor Cells''

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.

ADDRESSES: 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.

SUPPLEMENTARY INFORMATION: Invention Title: ''Apoptosis Inducing Agents and Methods'' Inventors: Drs. Lucio Miele (U.S.F.D.A.) and Leslie L. Shelly (NICHD) USPA SN: 60/102,816 [=DHHS Ref. No. E–176–98/0]—Filed with the U.S.P.T.O. October 2, 1998.

Apoptosis or programmed cell death is caused by many anti-tumor drugs and by radiation therapy. These treatment modalities cause apoptosis in tumor cells and in many normal cells in the body. As cancer cells progress towards more aggressive forms, they often become highly resistant to drug- or radiation-induced apoptosis, generally through the loss of function p53, a gene which can trigger apoptosis in response to DNA damage. Thus, novel strategies to induce apoptosis in tumor cells, especially p53-deficient cells, is an attractive and an active area of research.

An antisense molecule is a DNA or RNA which has the opposite beginning to end orientation compared to the ''normal'' gene. These molecules reduce the expression of the target gene by forming pairs with its ''normal'' DNA and RNA. Notch-1 is a gene which is known to be important in controlling cell differentiation in many organisms. Notch-1 is expressed at high levels in several human tumors. However, its function in tumor cells has not been characterized. So far, its role in maintaining tumor cell survival has not been identified. Using a model constituted by a p53-deficient mouse leukemia cell line, NIH scientists found that: 1.) Antisense synthetic DNA oligonucleotides and stable incorporation of an antisense gene (a model for gene therapy) targeting notch-1, when given together with a differentiation-inducing antitumor drug, cause the cells to respond by massive apoptosis rather than differentiation; 2.) stable incorporation of an antisense notch-1 gene increases apoptosis in these cells even in the absence of any antitumor drugs. This suggests that antisense notch-1 treatment, by antisense oligonucleotides or by gene therapy, may be used alone or together with anti-cancer drugs to cause apoptosis in tumor cells.

The notch gene belongs to a family of epidermal growth factor (''EGF'') like homeotic genes, which encode transmembrane proteins with a variable number of cystgeine-rich EGF-like repeats in the extracellular region. Four notch genes have been described in mammals, which include notch-1, notch-2, notch-3, and notch-4 (Int-3), which have been implicated in the differentiation of the nervous system and other structures. The EGF-like proteins Delta and Serrate have been identified as ligands of notch-1.

Mature notch proteins are heterodimeric receptors derived from the cleavage of notch pre-proteins into an extracellular subunit (N^{EC}) containing multiple EGF-Like repeats and a transmembrane subunit including intracellular region (N^{tm}). Notch activation results from the binding of ligands expressed by neighboring cells, and signaling from activated notch involves a network of transcription regulators.

Alteration of notch-1 signaling or expression may contribute to tumorigenesis. Deletions of the extracellular portion of human notch-1 are associated with about 10% of the cases of T-Cell acute lymphoblastic leukemia. Truncated forms of notch-1 cause T-Cell lymphomas when introduced into mouse bone marrow stem cells and are onogenic in rat kidney cells. The human notch-1 gene is in a chromosomal region (9q34) associated with hematopoietic malignancies of lymphoid, myeloid, and erythroid lineage. Additionally, strikingly increased expression of notch-1 has been documented in a number of human tumors including cervical cancer, colon tumors, lung tumors, and pre-neoplastic lesions of the uterine cervix.

Notch antisense oligonucleotides (or other molecules that interfere with the expression or function of notch) could be therapeutically administered to treat or prevent tumors. It has not been found that administration of notch antisense oligonucleotide alone is ineffective as an anti-neoplastic treatment. The present invention has overcome this problem by combining the administration of a cell differentiation agent with a molecule that interferes with the expression or function of a notch protein (such as the notch-1 protein). This combination of approaches has unexpectedly been found to induce apoptosis in neoplastic cells, and provide a useful therapeutic application of this technology. The method of the present invention includes inducing apoptosis in a target cell by inhibiting a cell fate determining function of a notch protein in the target cell at a time when the cell is undergoing differentiation. In particular, the target cell is induced to differentiate and upregulate notch expression, so that interference with notch expression or function causes the target cell to commit to an apoptotic pathway. Inhibition of notch expression or interference with its function can include exposing the cell to a notch protein antisense oligonucleotide that includes at least six nucleotides that comprise a sequence complementary to at least a portion of the RNA transcript of a notch gene (such as the notch-1 gene), and is hybridizable to the RNA transcript. Although the antisense oligonucleotide can be hybridizable to any region of the RNA transcript, particular oligonucleotides that have been found to be useful are antisense oligonucleotides to the notch-1 EGF repeat region, Lin/notch region, or ankyrin region. Alternatively the molecule can be a monoclonal antibody that antagonizes the function of a notch protein in the cell.

In particular the tumor cell is one that is characterized by increased activity or increased expression of a notch protein, such as a notch-1 or notch-2 protein. Examples of tumor types that over express notch-1 include cervical cancer, breast cancer, colon cancer, melanoma, seminoma, lung cancer and hematopoietic malignancies, such as erythroid leukemia, myeloid leukemia, (such as chronic or acute myelogenous leukemia), neuroblastoma and medulloblastoma. The differentiation inducing agent to which the cell is exposed can be selected from a broad variety of agents, including retinoids, polar compounds (such as hexamethylene bisacetanmide), short chain fatty acids, organic acids, Vitamin D derivatives, cyclooxygenase inhibitors, arachidonate metabolism inhibitors, ceramides, diacylglycerol, cyclic nucleotide derivatives, hormones, hormone antagonists, biologic promoters of differentiation, and derivatives of any of these agents.

Technology

This invention provides a method and pharmaceutical composition for treating a tumor by causing apoptosis in tumor cells that expresses notch-1 protein, and in particular cells that exhibit increased expression of notch-1. Hence, this technology discloses methods and compositions to induce apoptosis in cells that over express the notch proteins. A cell fate determining function of notch is specifically disrupted at a time when the cell is undergoing differentiation, which causes the cell to undergo apoptosis. The invention includes therapies for tumors that over express a notch protein (such as notch-1) by inducing differentiation of the cells in the tumor with a differentiation inducing agent such as hexamethylene bisacetamide and other such differentiation agents. At a time during which differentiation has been promoted, and the cell is susceptible to interference with the anti-apoptosis effect of notch, the function of the notch protein is disrupted. Disruption of notch function can be achieved, for example, by the expression of antisense oligonucleotides that specifically interfere with expression of the notch protein on the cell, or by monoclonal antibodies that specifically bind to notch and inactivate it. This technology represents a novel method to induce apoptosis in tumor cells.

The above mentioned invention is available, including any available foreign intellectual property rights, for licensing.

Dated: August 3, 1999.

Jack Spiegel,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 99–20455 Filed 8–6–99; 8:45 am]

BILLING CODE 4140–01–P

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 writing to the indicated licensing contact at the Office of Technology Transfer, National Institutes of Health, 6011 Executive Boulevard, Suite 325, Rockville, Maryland 20852–3804; telephone: 301/496–7057; fax: 301/402–0220. A signed Confidential Disclosure Agreement will