on the nature and degree of performance. More specifically, they depend on the—

+ Relative overall performance compared to other contractors;

+ Number of criteria in which deficient performance occurs;

+ Extent of each deficiency;

+ Relative significance of the requirement for which deficient performance occurs within the overall evaluation program; and

+ Efforts to improve program quality, service, and efficiency.

• Deciding the assignment or reassignment of providers and designation of regional or national intermediaries for classes of providers.

We make individual contract action decisions after considering these factors in terms of their relative significance and impact on the effective and efficient administration of the Medicare program.

In addition, if the cost incurred by the intermediary or carrier to meet its contractual requirements exceeds the amount which the Secretary finds to be reasonable and adequate to meet the cost which must be incurred by an efficiently and economically operated intermediary or carrier, such high costs may also be grounds for adverse action.

VII. Response to Public Comments

Because of the large number of items of correspondence we normally receive on **Federal Register** documents published for comment, we are unable to acknowledge or respond to them individually. We will consider all comments we receive by the date and time specified in the **DATES** section of this preamble, and, if we proceed with a subsequent document, we will respond to the comments in the preamble of that document.

In accordance with the provisions of Executive Order 12866, this notice was reviewed by the Office of Management and Budget.

We have reviewed this notice under the threshold criteria of Executive Order 13132 of August 4, 1999, Federalism, published in the **Federal Register** on August 10, 1999 (64 FR 43255). The Executive Order is effective November 2, 1999, which is 90 days after the date of this Order. We have determined that the notice does not significantly affect the rights, roles, and responsibilities of States.

Section 202 of the Unfunded Mandates Reform Act of 1995 requires that agencies assess anticipated costs and benefits before issuing any rule that may result in an expenditure by State, local, or tribal governments, in the aggregate, or by the private sector, of $100 million in any one year. This notice will not have an effect on the governments mentioned, and the private sector costs will not be greater than the $100 million threshold.

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

Dated: October 6, 1999.

Michael M. Hash,

Deputy Administrator, Health Care Financing Administration.

[FR Doc. 99–31361 Filed 12–2–99; 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, 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: ''Anti-Notch-1 Monoclonal Antibodies for Inducing Cellular Differentiation and Apoptosis'' Inventors: Drs. Lucio L Miele (U.S.F.D.A.) and Chana Y. Fuchs (U.S.F.D.A.) USPA SN: 60/124,119—Filed with the U.S.P.T.O. March 12, 1999

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.

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, PHS 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 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 oligonucleotides alone is effective as an anti-neoplastic treatment. The present invention has overcome this problem by combining the administration of a cell differentiation agent with an antibody that antagonizes the function of a notch protein and hence 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.

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 compositions, pharmaceutical compositions, and methods for stimulating/increasing cell differentiation, and is particularly related to the treatment of tumors which have increased notch-1 expression. A polyclonal and/or monoclonal antibody generated against human Notch-1 Epidermal Growth Factor (''EGF'') that recognizes an extracellular epitope of notch-1 and that stimulates target cell differentiation in the presence of an effect amount of differentiation inducing agent is disclosed as is the hybridoma which produces these antibodies. 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: November 24, 1999.

Jack Spiegel,

Director, Division of Technology Development & Transfer, Office of Technology Transfer.

[FR Doc. 99–31343 Filed 12–2–99; 8:45 am]

BILLING CODE 4140–01–P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Diseases; Notice of Closed Meetings

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meetings.

The meetings will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The grant applications and the discussions could disclose confidential trade secrets or commercial property such as patentable material, and personal information concerning individuals associated with the grant applications, the disclosure of which would constitute a clearly unwarranted invasion of personal privacy.

Name of Committee: National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel. ZDK1 GRB–7 J3 P.

Date: December 6–8, 1999.

Time: 7:00 p.m. to 12:00 p.m.

Agenda: To review and evaluate grant applications.

Place: Radisson Hotel at Gateway, 651 Huron Road, Cleveland, OH 44115.

Contact Person: Lakshmanan Sankaran, Scientific Review Administrator, Review Branch, DEA, NIDDK, Natcher Building Room 6AS25F, National Institutes of Health, Bethesda, MD 20892–6600, (301) 594–7799.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

Name of Committee: National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel. ZDK1 GRB C (J1).

Date: December 7–9, 1999.

Time: 7:30 p.m. to 11:00 a.m.

Agenda: To review and evaluate grant applications.

Place: New Haven Hotel, 229 George Street, New Haven, CT 06510.

Contact Person: Dan E. Matsumoto, Scientific Review Administrator, Review Branch, DEA, NIDDK, Natcher Building Room 6AS37B, National Institutes of Health, Bethesda, MD 20892–6600, (301) 594–8894.

This notice is being published less than 15 days prior to the meeting due to the timing limitations imposed by the review and funding cycle.

Name of Committee: National Institute of Diabetes and Digestive and Kidney Diseases Special Emphasis Panel. ZDK1 GRB–C J3 P.

Date: December 16–18, 1999.

Time: 7:00 p.m. to 12:00 p.m.

Agenda: To review and evaluate grant applications.

Place: Holiday Inn, 5 Blossom Street, Boston, MA 02114.

Contact Person: Dan E. Matsumoto, Scientific Review Administrator, Review Branch, DEA, NIDDK, Natcher Building Room 6AS37B, National Institutes of Health, Bethesda, MD 20892–6600, (301) 594–8894.

(Catalogue of Federal Domestic Assistance Program Nos. 93.847, Diabetes, Endocrinology and Metabolic Research; 93.848, Digestive Diseases and Nutrition Research; 93.849, Kidney Diseases, Urology and Hematology Research, National Institutes of Health, HHS)

Dated: November 24, 1999.

LaVerne Y. Stringfield,

Director, Office of Federal Advisory Committee Policy.

[FR Doc. 99–31340 Filed 12–2–99; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Institute of Diabetes and Digestive and Kidney Disease; Notice of Closed Meeting

Pursuant to section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is hereby given of the following meeting.

The meeting will be closed to the public in accordance with the provisions set forth in sections 552b(c)(4) and 552b(c)(6), Title 5 U.S.C., as amended. The contract proposals and the discussions could disclose