'Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use'' to the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist the office in processing your requests. The document may also be obtained by mail by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800, or by fax by calling the FAX Information System at 1–888–CBER–FAX or 301–827–3844. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance document.

Submit written comments on the guidance document to the Dockets Management Branch (HFA–305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Astrid L. Szeto, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a document entitled ''Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h, 'Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use.''' This guidance document is intended to provide instructions on the completion of the revised Form FDA 356h, including CMC and establishment description sections for human blood and blood components intended for transfusion or for further manufacture. The guidance announced in this notice has been revised based on comments received on the draft guidance entitled ''Guidance for Industry: For the Submission of Chemistry, Manufacturing and Controls and Establishment Description Information for Human Blood and Blood Components Intended for Transfusion or for Further Manufacture and For the Completion of the Form FDA 356h, 'Application to Market a New Drug, Biologic or an Antibiotic Drug for Human Use''' announced in the **Federal Register** of July 10, 1998 (63 FR 37401) and finalizes that draft document.

In the **Federal Register** of July 8, 1997 (62 FR 36558), FDA announced the availability of a new harmonized Form FDA 356h entitled ''Application to Market a New Drug, Biologic, or an Antibiotic for Human Use.'' The new harmonized form is intended to be used by applicants for all drug and biological products, to include blood and blood components. Manufacturers may voluntarily begin using the form for human blood and blood components. FDA will announce in the future when manufacturers are required to use this form for all products. Use of the new harmonized form will allow biological product manufacturers to submit a single application, the BLA, instead of two separate license application submissions, a product license application (PLA) and an establishment license application (ELA).

This guidance document represents the agency's current thinking on content and format of the CMC and establishment description information sections of a license application for human blood and blood components intended for transfusion or for further manufacture. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirement of the applicable statute, regulations, or both. As with other guidance documents, FDA does not intend this document to be all-inclusive and cautions that not all information may be applicable to all situations. The document is intended to provide information and does not set forth requirements.

II. Comments

Interested persons, may at any time, submit written comments to the Dockets Management Branch (address above) regarding this guidance document. Two copies of any comments are to be submitted, except individuals may submit one copy. Comments should be identified with the docket number found in the brackets in the heading of this document. A copy of the document and received comments are available for public examination in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

III. Electronic Access

Persons with access to the Internet may obtain the document using the World Wide Web (WWW). For WWW access, connect to CBER at ''http://www.fda.gov/cber/guidelines.htm''.

Dated: April 30, 1999.

William K. Hubbard,

Acting Deputy Commissioner for Policy.

[FR Doc. 99–11735 Filed 5–7–99; 8:45 am]

BILLING CODE 4160–01–F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute: Opportunity for a Cooperative Research and Development Agreement (CRADA) for the Research, Purification, and Further Development of Immunosuppressive Factor(s) Released From Human Glioblastoma Cells in Culture

The National Cancer Institute's Experimental Immunology Branch has identified and characterized the activity of a soluble factor(s) produced by human glioblastoma tumor cells that suppresses T cell responses in health donor blood samples.

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice.

SUMMARY: The National Cancer Institute (NCI) seeks a Cooperative Research and Development Agreement (CRADA) Collaborator to aid NCI in the further characterization and commercial development of the immune-suppressive factor(s) generated from glioblastoma tumor cells. The glioblastoma-generated factor(s) appear to act by causing antigen-presenting cells (APCs), such as monocytes, to undergo a change in cytokine production which induces apotosis or antigen-specific unresponsiveness (''anergy'') in T cells. NCI has partially purified and characterized the immunosuppressive factor(s). Several applications for this technology have been identified. They include (1) therapy for graft-host rejection in transplantation surgeries; (2) treatment of autoimmune diseases; and (3) suppression of severe allergic responses. NCI is looking for a CRADA Collaborator with a demonstrated record of success in protein purification and immunosuppressive therapeutics for the eventual use of this factor(s) in the clinical treatment of patients. The proposed term of the CRADA can be up to five (5) years.

DATES: Interested parties should notify this office in writing of their interest in filing a formal proposal no later than July 9, 1999. Potential CRADA Collaborators will then have an additional thirty (30) days to submit a formal proposal.

ADDRESSES: Inquiries and proposals regarding this opportunity should be addressed to Holly S. Symonds, Ph.D., Technology Development Specialist (Tel. #301–496–0477, FAX #301–402–2117), Technology Development and Commercialization Branch, National Cancer Institute, 6120 Executive Blvd., Suite 450, Rockville, MD 20852. Inquiries directed to obtaining patent license(s) needed for participation in the CRADA opportunity should be addressed to Marlene Shinn, M.S., J.D., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Blvd., Suite 325, Rockville, MD 20852, (Tel. 301–496–7056, ext. 285; FAX 301–402–0220).

SUPPLEMENTARY INFORMATION: A Cooperative Research and Development Agreement (CRADA) is the anticipated joint agreement to be entered into with NCI pursuant to the Federal Technology Transfer Act of 1986 and Executive Order 12591 of April 10, 1987 as amended by the National Technology Transfer Advancement Act of 1995. NCI is looking for a CRADA partner to aide NCI in characterization and commercial development of the tumor cell-derived immune-suppressive factor(s). The expected duration of the CRADA would be from one (1) to five (5) years.

Cancer patients frequently demonstrate an impaired *in vitro* and *in vitro* T cell immune activity. This deficiency is often reflected in animal models and affects both tumor antigens and non-tumor antigens. Cytokine dysfunction appears to contribute to tumor-associated immune dysregulation, with decreases of IL–2 and/or IFN-gamma production and increases in IL–4, IL–5, IL–6, and/or IL–10 production. Human gliomas are frequently very immunosuppressive and provide an interesting example of tumor-associated immune dysfunction. T cells from glioma patients are impaired in their ability to respond *in vitro* to antigens and to T cell mitogens by proliferation and IL–2 production. *In vitro* and clinical findings suggest that one or more factors released into the glioma culture supernatant (GCS) elicit immunoregulatory effects on systematic cellular immunity.

To test this hypothesis, NCI scientist investigated whether GCS would affect monocyte-generated cytokines and T cells from healthy donors of human peripheral blood mononuclear cells (PBMCs). Incubation of PBMC with GCS decreased production of IL–12, IFN-gamma, and TNF-alpha, and increased production of IL–6 and IL–10. The GCS-induced underproduction of IL–12 and overproduction of IL–10 in monocytes was correlated with a decrease in IL–12 p40 and an increase in IL–10 mRNA expression. Incubation with GCS also resulted in reduced expression of MHC class II and CD80/86 costimulatory molecules on monocytes. Experiments using exogenous IL–6, TGF-beta-1, TGF-beta-2, or CDGP, either singly or in combination, did not elicit the changes in with IL–12 or IL–10 production.

NCI scientists have shown that the immunosuppressive effects found in GCS are due to a factor(s) that is resistant to extremes in pH, differentially susceptible to temperature, susceptible to trypsin, and has a minimum molecular mass of 40 kDa. NCI scientists have also demonstrated that the glioblastoma factor(s) alter the cytokine profiles of monocytic APC(s) that, in turn, inhibit T cell function. Thus, the scientists have shown that monocytes can serve as an intermediate between tumor-generated immune-suppressive factors and the T cell responses that are suppressed in glomas. NCI scientists are currently exploring the possibility that T cells that recognize antigens presented on treated monocytes will undergo apoptosis or anergy, while T cells that do not recognize those antigens will retain their normal activities.

NCI predicts that the therapeutic use of the glioblastoma-generated immunosuppressive factor(s), once fully characterized and purified, will be applicable to a wide variety of fields. For example, there is a great need for immunosuppressive therapy following transplantation surgeries. A major challenge of tissue transplantation is to selectively deplete the immune system of responses against antigens found on the surface of grafted foreign tissue without concomitantly compromising immunity to antigens of infectious agents or tumors. At present, the standard approach is to continuously treat the transplant recipient with immunosuppressive drugs that are non-specific rendering the patient susceptible to opportunistic infections and/or cancer. By treating transplant recipients with donor antigen-presenting cells (APCs) that have been incubated ex vivo with glioblastoma culture supernatant (GCS), the recipient may be able to be depleted of all donor-specific T lymphocytes that are responsible for initiating graft rejection while at the same time maintaining immune integrity.

Immunnosuppressive drugs are also used to treat autoimmune diseases in which the autoantigen is known. Thus, it may be possible to delete autoimmune-specific T cells by treating the patient with autologous antigen-presenting cells that have been incubated with GCS and pulsed with the antoantigen *ex vivo.* Such an approach may eliminate the need for, or reduce the use of, immunosuppressive drugs in both tissue transplantation and autoimmune diseases.

The described methods are the subject of a U.S. provisional patent application filed on March 24, 1999 by the Public Health Service on behalf of the Federal Government. Furthermore, the initial report and characterization of the invention is described in: Zou et al, Journal of Immunology, vol. 162: 4882–4892 (1999).

Under the present proposal, the goal of the CRADA will be to enhance the development of the GCS-generated immunosuppressive factor(s) in the following areas:

1. Further purification and characterization of the factor(s).

2. Examination of the ability of the purified immunosuppressive factor to induce apoptosis or anergy in T cells through a monocyte intermediate using *in vitro* and *in vivo* models.

Party Contributions

The role of the NCI in the CRADA may include, but not be limited to:

1. Providing intellectual, scientific, and technical expertise and experience to the research project.

2. Providing the CRADA Collaborator with information and data relating to the glioblastoma-generated immunosuppressive factor(s).

3. Planning research studies and interpreting research results.

4. Carrying out research to validate the immunosuppressive activities of the GCS-generated factor(s).

5. Publishing research results.

6. Developing additional potential applications of the factor(s).

The role of the CRADA Collaborator may include, but not limited to:

1. Providing significant intellectual, scientific, and technical expertise or experience to the research project.

2. Planning research studies and interpreting research results.

3. Providing technical and/or financial support to facilitate scientific goals and for further design of applications of the technology outlined in the agreement.

4. Publishing research results.

Selecting criteria for choosing the CRADA Collaborator may include, but not be limited to:

1. A demonstrated record of success in the areas of protein purification, characterization and therapeutic development.

2. A demonstrated background and expertise in immunological sciences.

3. The ability to collaborate with NCI on further research and development of this technology. This ability will be demonstrated through expertise and expertise in this or related areas of technology indicating the ability to contribute intellectually to ongoing research and development.

4. The demonstration of adequate resources to perform the research and development of this technology (e.g., facilities, personnel and expertise) and to accomplish objectives according to an appropriate timetable to be outlined in the CRADA Collaborator's proposal.

5. The willingness to commit best effort and demonstrated resources to the research and development of this technology, as outlined in the CRADA Collaborator's proposal.

6. The demonstration of expertise in the commercial development and production of products related to this area of technology.

7. The Level of financial support the CRADA Collaborator will provide for CRADA-related Government activities.

8. The willingness to cooperate with the National Cancer Institute in the timely publication of research results.

9. The agreement to be bound by the appropriate DHHS regulations relating to human subjects, and all PHS policies relating to the use and care of laboratory animals.

10. The willingness to accept the legal provisions and language of the CRADA with only minor modifications, if any. These provisions govern the distribution of future patent rights to CRADA inventions. Generally, the rights of ownership are retained by the organization that is the employer of the inventor, with (1) the grant of a license for research and other Government purposes to the Government when the CRADA Collaborator's employee is the sole inventor, or (2) the grant of an option to elect an exclusive or nonexclusive license to the CRADA Collaborator when the Government employee is the sole inventor.

Dated: April 30, 1999.

Kathleen Sybert,

Chief, Technology Development and Commercialization Branch, National Cancer Institute, National Institutes of Health.

[FR Doc. 99–11658 Filed 5–7–99; 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.

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: .

Title: "Monoclonal Antibodies Specific for Human Thymidylate Synthase"—Prognosticator of Breast and Colorectal Cancer Survival

Inventors: Drs. Patrick G. Johnston (NCI), Carmen J. Allegra (NCI), Bruce A. Chabner (NCI) and Chi-Ming Liang (NCI).

DHHS Ref. No.: E–137–90/0 [= USPA SN: 07/690,841—Filed April 24, 1991].

The fluoropyrimidines are an important group of antineoplastic agents that are widely used in the treatment of gastrointestinal tumors, breast tumors, and epithelial tumors of the upper aerodigestive tract. Thymidylate synthase (''TS'') catalyzes the methylation of deoxyurdine monophasphate (''dUMP'') to deoxythymidine monphosphate (''dTMP''). The de novo synthesis of dTMP is an essential step in the synthesis of pyrimidine nucleotides and DNA biosynthesis. Thymidylate synthase (''TS'') enzyme inhibition is one of the main biochemical events underlying the antineoplastic action of the fluropyrimidines 5-fluorouracil (''5-FU'') and fluorodeoxyuridine (''FudR'').

The clinical importance of Thymidylate synthase (''TS'') has been noted by several investigators who have demonstrated *in vivo* as well as *in vitro* that TS enzyme levels in neoplastic cells rise rapidly when cells are exposed to 5-fluorouracil. Thus, the ability of a tumor to acutely over express the TS enzyme may play a key role in the development of tumor resistance and may represent an important protective mechanism in response to this drug.

The quantitation and detection of TS in human tissues has traditionally been performed by enzymatic biochemical assays that either measure catalytic activity or measure the amount of radiolabeled FdUMP binding to TS following extraction of the enzyme from cells and tissue. These assays have several limitations when applied to the measurement of TS activity in human tissue samples. While the assays have the required sensitivity for quantitating enzyme *in vitro* malignant cells in culture, they lack adequate sensitivity to measure the lower levels of enzyme activity in human tumors. 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. These monoclonal antibodies to TS provide a method for determining the prognosis of a patient afflicted with breast cancer or with primary colorectal cancer by measuring the level of TS expression in biopsy tissue samples by using these antibodies specific to thymidylate synthase.

These monoclonal antibodies further provide a method for predicting the benefit of chemotherapy for a patient afflicted with breast cancer. The aforementioned methodology 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 2,500 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 expression of TS is also an important independent prognosticator of disease-free survival and overall survival in patients with colorectal cancer. In a study of the prognostic importance of the level of thymidylate synthase (''TS'') expression in patients with primary colorectal cancer, the level of TS expression in the primary rectal cancers of 294 of 801 patients was immunohistochemically assessed with the TS–106 monoclonal antibodies. Forty-nine percent of patients whose tumors had low TS levels were disease free at 5 years compared with 27% of patients with high levels of TS. Moreover, 60% of patients with low TS