feeds already approved for an aquatic use because factors in the aquatic environment that may affect the safety and/or effectiveness of the medicated feed are so varied.

III. Availability of Medicated Feeds for Minor Species

FDA plans to continue to address the issue of lack of availability of medicated feeds for minor species. There are serious shortcomings in the legal availability of medicated feeds for minor species. These include the need for specially formulated feeds for laboratory and zoo animals and the needs of species raised in aquaculture. Future guidance will be directed specifically at these needs.

IV. Electronic Access

Persons with access to the Internet may obtain the CPG at http://www.fda.gov/cvm and http://www.fda.gov/ora.

V. Comments

As with all of FDA's guidances, the public is encouraged to submit written comments with new data or other new information pertinent to this CPG. FDA will periodically review the comments and, where appropriate, the CPG will be amended. The public will be notified of any such amendments through a notice in the **Federal Register**.

Dated: April 18, 2001.

Dennis E. Baker,

Associate Commissioner for Regulatory Affairs.

[FR Doc. 01–10164 Filed 4–19–01; 3:10 pm]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute: Opportunity for a Cooperative Research and Development Agreement (CRADA) for the Clinical Development of a Biologically Active, Epitope-Tagged Transforming Growth Factor Beta (TGF–β) Protein

The National Cancer Institute's Laboratory of Cell Regulation and Carcinogenesis (LCRC) has created and characterized a recombinant transforming growth factor-beta (TGF–β) ligand that contains the FLAG epitope tag and yet retains full biological activity.

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 preclinical and clinical development of a tagged form of the TGF–β protein. Initial studies from LCRC demonstrate that a specific, eight-amino acid tag (known as FLAG) can be inserted in at least three different sites in the TGF–β1 molecule, without interfering with its biological activity. LCRC has made three FLAG-tagged porcine TGF–β1 constructs and the identical murine FLAG–TGF–β1 cDNAs. Each construct differs only in the location of insertion of the FLAG tag, and these include either insertion immediately following the cleavage site N-terminal in the mature, processed TGF–β molecule, or between amino acids 4 and 5 or 11 and 12 of the mature TGF–β molecule. The tagged molecule can detected by using a number of different techniques, including: Immunohistochemistry, immunoprecipitation, flow cytometry, immunofluorescence microscopy, ELISA, immunoblotting (''western''), and affinity chromatography.

DATES: Interested parties should notify NCI in writing of their interest in filing a formal proposal no later than June 22, 2001. Potential CRADA Collaborators will then have an additional thirty (30) days to submit a formal proposal. Additional proposals will be considered after the posted deadline in the event that a CRADA partner is not found during the initial posted timeperiod.

ADDRESSES: Inquiries and proposals regarding this opportunity should be addressed to Holly Symonds Clark, PhD., 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 a patent license(s) needed for participation in the CRADA opportunity should be addressed to John Rambosek, PhD., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Blvd., Suite 325, Rockville, MD 20852, (Tel. 301–496–7056, ext. 270; 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 Act of 1986, NCI seeks a CRADA Collaborator to aid LCRC in the preclinical and clinical studies of a tagged form of the TGF–β protein. The expected duration of the CRADA would be from one (1) to five (5) years.

Background Information

NCI's LCRC has produced the first epitope-tagged, biologically active version of a member of the transforming growth factor-β (TGF–β) family of proteins. Transforming growth factor-β1 (TGF–β1) is the prototype for a large family of secreted polypeptides including the three mammalian TGF–β isoforms (TGF–β1, TGF–β2, TGF–β3), the bone morphogenetic proteins (BMPs), the activins and several more distantly related factors that regulate cell growth and function. The various members of the TGF–β superfamily play roles in development, immune homeostasis, cancer progression, autoimmune disorders and wound repair. TGF–βs are produced and secreted from the cell as large latent (inactive) molecules (pro-proteins). The Latency Associated Peptide (LAP) encompasses amino acids 1 through 279 (porcine TGF–β1) of the pro-protein. Association of LAP through disulfide bonds with the mature TGF–β1 sequence keeps TGF–β in a biologically inactive form. Conversion of this pro-peptide to a biologically active form can be achieved in several ways. These include disruption of the disulfide bonds (for example, mutation of two cysteine residues involved in forming this bond), cleavage of the protein to release the smaller biologically active TGF–β (amino acids 280 through 391 in TGF–β1), or denaturation of the associated LAP by acidification or heat.

The ability to track the distribution of any exogenously administered, recombinant forms of these proteins has been restricted by the inability to distinguish between the endogenous forms of the protein produced in treated cells or tissues, and because most available antibodies exhibit some degree of cross-reactivity with related family members. LCRC's invention demonstrates a successful approach to adding an opitope tag to the mature TGF–β1 molecule. Epitope tags are short stretches of amino acids to which a specific antibody can be raised, allowing one to directly identify and track the tagged protein that has been added to a living organism or to cultured cells. Examples of useful epitope tags include FLAG, HA (hemagglutinin) and myc. In principle, any of these epitope tags could be used to tag TGF–β family members, but NCI's LCRC has been the first to identify a way to retain biological function of the molecule following addition of the tag. Thus, it will be possible to track LCRC's tagged TGF–β molecule when used in

preclinical studies or when administered to patients in a clinical setting.

The FLAG epitope tag is short amino acid sequence of just eight amino acids (DYKDDDDK). Because of its small size, LCRC hypothesized that addition of this sequence to a region of the mature TGF–β1 molecule where structural constraints were minimal would result in no loss of biological activity. LCRC chose to add the FLAG tag independently in two different locations, creating two FLAG-tagged versions of the molecule. The mature, cleaved TGF–β molecule should thus possess the FLAG epitope tag. Evaluation of the biological activities of the FLAG-tagged versions of TGF–β1 indicate that there is no loss of biological activity as a consequence of inserting the FLAG epitope tag. In principle, the FLAG epitope tag can be added in an analogous way to any of the other TGF–β isoforms or to closely related family members (e.g. the BMPs).

The described methods are the subject of a U.S. provisional patent application filed on October 20, 2000 by the Public Health Service on behalf of the Federal Government.

Under the present proposal, the goal of the CRADA will be to further characterize and develop the flag-tagged TGF–β molecule in the following areas:

1. Additional pre-clinical studies.

(a). These studies would include, but not be limited to analyses of functionality of the epitope-tagged TGF–βs. Of particular interest are the relative effects of different sites of tag insertion on the processing of the latent TGF–β precursor, on receptor affinity, and on the dose-dependent effects of TGF–β in a variety of functional assays, such as in vitro assays of leukocyte chemotaxis, epithelial and hematopoietic cell growth and differentiation, and lymphocyte activation. In addition, the epitope-tagged TGF–βs offer the unique potential to use immunofluorescence and confocal microscopy techniques to follow receptor trafficking and disposition following ligand binding.

(b). The availability of the epitope-tagged TGF–β also allows for a more quantitative evaluation of the pharmacodynamics of the peptide ligand. In vivo studies of plasma half-life, tissue distribution, CNS penetration, and elimination will be pursued. These studies will include assessment of both enteral and perenteral administration of TGF–β. Other studies currently proposed include the generation of a ''knock-in'' mouse, in which the epitope-tagged TGF–β is used to replace the endogenous TGF–β gene in mice, to confirm the absence of a deleterious effect of the epitope tag on normal function throughout development and in the adult organism. Such studies will allow for assessment of the transplacental transfer and distribution of maternal TGF–β during gestation.

(c). LCRC investigations also plan to focus on the development of diagnostic tools and screens based on the epitope-tagged TGF–β1. These experiments will include assays to provide a quantitative assessment of the level of functional TGF–β receptor expression in both normal and tumor tissues by quantitative histochemical techniques and flow cytometric analysis. ELISA-based screens for the epitope tag will be developed as tools for pharmacokinetic studies of the epitope-tagged TGF–β1 following either systemic, enteral, or local administration.

2. Clinical trials focused on the applications of functional epitope-tagged TGF–β ligands in the treatment of cancer, wound healing, and immune disorders.

There are several important implications of this discovery for the development and application of TGF–β family members for therapeutic purposes. To date, TGF–β family members have been studied in clinical trials in the treatment of rheumatoid arthritis, multiple sclerosis, wound healing, and in the prevention of chemotherapy-induced mucositis. Preclinical studies in animal models predict that a number of applications will be tested in the near future. These include the evaluation of TGF–β in the treatment of bronchial asthma, uveitis, osteoinduction following irradiation, management of inflammatory bowel disease, and a variety of autoimmune disorders and neuropathies having an autoimmune etiology. The ability to administer an epitope-tagged TGF–β to a patient in a clinical setting would allow the researcher to accurately follow drug (FLAG–TGF–β) distribution, half-life, elimination, and circulating levels without the complication of detecting the endogenous TGF–β that is already present in the patient's tissues. The epitope-tagged molecule now provides a unique and novel tool to detect receptors for the TGF–β proteins in tissues. The progression of many pathologic conditions, including cancer and immune system disorders, is often associated with loss of expression of these receptors.

Following the completion of the preclinical studies described in section 1 above, LCRC plans to test the epitope-tagged TGF–β in the following settings in the clinic:

(a). LCRC plans to study the utility of epitope-tagged TGF–β as a diagnostic tool for the quantitative, real-time measure of receptor expression in diseases in which altered expression of TGF–β receptors and binding proteins have been described, such as cancer and immune disorders. These studies will include, but not be limited to the following:

(i). Malignancies including lymphoid and those of the gastrointestinal tract, in which loss of receptor expression has been linked to disease pathogenesis.

(ii). Autoimmune disorders, such as Systemic Lupus Erthematosis (SLE) and Sjogren's Syndrome, where altered production and responsiveness to TGF–β may play a role in disease progression.

(iii). In patients with Hereditary Hemorrhagic Telangiectasia (HHT), a disorder that exists in two forms and results from mutational inactivation of specific cell surface receptors. FLAG–TGF–β 1 can serve as the basis for a number of new diagnostic tools that may be useful in determining disease severity and prognosis in each of these disorders.

(b). LCRC's tagged TGF–β provides an example of how the members of the extended TGF–β family might be tagged. Thus, an additional goal of the clinical phase of the research is to determine whether or not adding an epitope tag to other members of the extended TGF–β family will allow for efficient tracking of the tagged molecule.

(c). In the future, LCRC intends to examine the feasibility of inserting tag sequences that will not only allow for tracking, but will also enhance the delivery of these proteins by ferrying them into target tissues without loss of function. The latter represents an important area of ongoing research at NCI that will aim to reduce the incidence of adverse effects associated with the systemic administration of TGF–β and related proteins. This avenue of research is of primary importance, as the widespread expression of TGF–β receptors throughout vascular endothelia, and the rapid clearance of either active or latent forms from the circulation make the development of new delivery strategies essential.

(d). LCRC intends to test the therapeutic application of the above functionalized, tagged TGF–β molecules in the treatment of disorders, including, but not limited to the following:

- Disorders of chronic/delayed wound healing,
- Lymphoproliferative and autoimmune syndromes,
- Inflammatory disorders of the gastrointestinal tract, and

• Hematopoietic and epithelial malignancies.

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 development and characterization of the epitope-tagged TGF–β ligands, *in vitro* and *in vivo* assays of TGF–β function, techniques for the detection and quantitation of epitope-tagged TGF–β proteins in biological specimens.
3. Planning research studies and interpreting research results.
4. Carrying out research to evaluate the pharmacokinetics and toxicity profiles of epitope-tagged TGF–β ligands.
5. Publishing research results.
6. Developing additional potential applications of the FLAG-tagged TGF–β molecule.

The Role of the CRADA Collaborator May Include, But Not Be 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.
5. Providing resources and support for production and purification of the recombinant, epitope-tagged TGF–β ligands.

Selection Criteria for Choosing the CRADA Collaborator Will Include

1. A demonstrated record of success in the areas of cytokine expression systems, large scale purification of recombinant proteins and the evaluation of cytokine function.
2. A demonstrated background and expertise in the preclinical development of biological response modifiers and in the design and execution of clinical trials.
3. The ability to collaborate with NCI on further research and development of this technology. This ability will be demonstrated through experience 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 or joint inventor.

Dated: April 12, 2001.

Kathleen Sybert,

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

[FR Doc. 01–9924 Filed 4–20–01; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

White House Commission on Complementary and Alternative Medicine Policy; Notice of Meeting

Pursuant to Section 10(a) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2), notice is given of a meeting of the White House Commission on Complementary and Alternative Medicine Policy.

The purpose of the meeting is to convene the Commission for a public hearing to receive public testimony from individuals and organizations interested in the subject of Federal policy regarding complementary and alternative medicine. The major focus of the meeting is coverage and reimbursement by the private and public sectors for Complementary and Alternative (CAM) practices and products and the coordination of research on Complementary and Alternative Medicine practices and products. Comments received at the meeting may be used by the Commission to prepare the Report to the President as required by the Executive Order.

Invited speaker discussions focusing on the coverage and reimbursement for CAM practices and products on May 14–15 will include the following: Trends in the United States health care system including the underinsured and uninsured; Federal, state, and private sector providers' perspectives on the financing of health care and providing coverage and reimbursement for CAM practices and products; Employer coverage and reimbursement programs; and Health plans and CAM benefits. Invited speaker discussions focusing on the coordination of CAM research on May 15–16 will include the following: Not-for-profit support for CAM research; Approaches to evaluating research literature; Challenges of CAM research and research training—research methodology and the training of conventional and CAM research investigators; and Publication of peer-reviewed CAM research results.

Some Commission members may participate by telephone conference. Opportunities for oral statements by the public will be provided on May 16, from about 4:00 p.m.–5:00 p.m. (Time approximate).

Name of Committee: The White House Commission on Complementary and Alternative Medicine Policy.

Date: May 14–16, 2001.

Time: May 14—8:15 a.m.–6:00 p.m., May 15—8:15 a.m.–6:00 p.m., May 16—8:15 a.m.–5:00 p.m.

Place: Academy for Educational Development Conference Center, 1825 Connecticut Avenue, NW., Room 800, Washington, DC 20009–5721.

Contact Persons: Michele M. Chang, CMT, MPH, Executive Secretary, or, Stephen C. Groft, Pharm.D., Executive Director, 6701 Rockledge Drive, Room 1010, MSC 7707, Bethesda, MD 20817–7707, Phone: (301) 435–7592, Fax: (301) 480–1691, E-mail: WHCCAMP@mail.nih.gov.

Because of the need to obtain the views of the public on these issues as soon as possible and because of the early deadline for the report required of the Commission, this notice is being provided at the earliest possible time.