The National Cancer Institute’s Laboratory of Human Carcinogenesis (LHC) has created and characterized in vitro and in vivo methods designed to screen for modulators of GADD45 polypeptide activity. Furthermore, LHC has developed methods for sensitizing proliferating cells to DNA damaging agents by inhibiting GADD45 polypeptide activity. Identification of novel inhibitors of GADD45 using LHC’s screening assays would provide potential new treatments for cancer.

**SUMMARY:** The National Cancer Institute (NCI) seeks a Cooperative Research and Development Agreement (CRADA) Collaborator to aid NCI in the screening, development and commercialization of novel compounds for the treatment of cancer. These methods focus on the identification of small molecule inhibitors of GADD45 polypeptide activity.

NCI has developed a series of in vitro and in vivo assays to screen for modulators of GADD45 polypeptide activity. These assays may identify novel small molecule inhibitors of GADD45 activity that, when used in conjunction with current chemotherapeutics, reduce the toxicity of and enhance the effectiveness of current treatments of cancer. NCI is looking for a CRADA Collaborator with a demonstrated record of success in cancer diagnostics and therapeutics. The proposed term of the CRADA can be up to five (5) years.

**DATES:** Interested parties should notify the Technology Development and Commercialization Branch of the NCI in writing of their interest in filing a formal proposal no later than May 26, 2000. Potential CRADA Collaborators will then have an additional thirty (30) days to submit a formal proposal. CRADA proposals submitted thereafter may be considered if a suitable CRADA Collaborator has not been selected.

**ADDRESSES:** Inquiries and proposals regarding this opportunity should be addressed to Holly Symonds Clark, 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) for the technology described in U.S. Provisional Patent Application Serial No. 60/126,069, filed March 25, 1999, for “Methods for Identifying Modulators of GADD45 Polypeptide Activity” (Harris et al.) should be addressed to Vasant Gandhi, J.D., Ph.D., Technology Licensing Specialist, Office of Technology Transfer, National Institutes of Health, 6011 Executive Blvd., Suite 325, Rockville, MD 20852. (Tel. 301–496–7056; 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 collaborate with NCI in the further development and commercialization of screening assays and methods relating to the analysis of small molecule inhibitors of GADD45 polypeptide activity. The expected duration of the CRADA would be from one (1) to five (5) years.

Mammalian cells cycle through a series of ordered stages that involve various cellular components during normal cellular growth (for reviews: 1, 2). A normal cell can arrest cell cycle progression when DNA damage is incurred. Cell cycle “checkpoints” exist at two different stages in cell cycle progression: the G1 to S (replication) stage and the G2–M (mitosis) stage. These checkpoints are essentially stages in which the cell “stalls” its cell cycle to repair any damaged DNA that may exist prior to entry into mitosis. The G2–M checkpoint prevents the improper segregation of chromosomes likely to be important in human tumorigenesis (3, 4). The G2-specific kinase composed of Cdk2 and cyclin B1 is a regulator of the cell cycle transition from G2 to M (1). NCI has recently reported the identification of one of the gene products that controls the G2–M checkpoint: the ubiquitously expressed polypeptide, GADD45. GADD45 was originally identified on the basis of its rapid transcriptional induction following ultraviolet (UV) irradiation (5). Induction of GADD45 has also been observed following various types of pathological stimuli including various environmental stresses, hypoxia, IR, genotoxic drugs and growth factor withdrawal (6). The GADD45-induced G2/M checkpoint is at least in part mediated through inactivation of the Cdc2/cyclin B1 kinase (1).

NCI believes that the GADD45-mediated G2–M checkpoint could be a new target for the development of anticancer agents. Inhibitors of GADD45 activity at the G2–M checkpoint could destroy the cell’s ability to stall its proliferative cycle to correct damaged DNA. Cancer cells are often deficient in the G1–S checkpoint, thus, the G2–M
checkpoint is necessary for the repair of damaged DNA in cancer cells. Currently, high levels of radiation and chemotherapy are necessary to target cancer cells that are stalled at the G2–M checkpoint. Such levels of treatment are often toxic to normal cells also undergoing proliferation. However, when both checkpoints are abolished in cancer cells, the cells proceed at a greater rate, without stalling, into mitosis where they are susceptible to DNA damaging chemotherapeutic agents. Thus, in the presence of a G2–M checkpoint inhibitor, a reduced amount of radiation or chemotherapeutic agent is needed to kill all of a population of cancer cells. A reduced level of DNA damaging agent would also lessen the toxicity to normal cells since many of these cells would be stalled at their intact G1–S checkpoints.

In effect, the use of a G2–M checkpoint inhibitor would selectively target cancer cells by “sensitizing” them to the anti-cancer treatments. NCI believes that small molecule inhibitors of GADD45 polypeptide activity could be used to abolish the G2–M checkpoint in cancer cells. Indeed, a previous report has found that blocking GADD45 expression by constitutive antisense oligonucleotide expression sensitized a human colon carcinoma cell line to killing by UV irradiation and by cisplatin, a DNA-damaging cancer chemotherapy drug (7). Thus, the identification of novel inhibitors of GADD45 activity would provide a new means to treat cancers in conjunction with current chemotherapy methods. In the clinic, such combined treatment would reduce the uncomfortable side-effects of current anti-cancer treatments, thus, improving the quality of life for cancer patients.

NCI has developed several in vitro and in vivo methods for assaying for modulators of GADD45 polypeptide activity. The methods focus on the ability to assess the binding activities of the GADD45 polypeptide during the cell cycle. NCI has identified a functional domain of GADD45 that is involved in the G2–M checkpoint and in binding to the cell cycle regulator, cdc2. Deletion analysis indicates that the central region of this functional domain mediates the G2/M arrest. Specifically, the central region contains a unique acidic motif that appears to be important for the induction of a G2/M arrest because changes in the acidic residues abolish the G2/M checkpoint. Small molecule compounds that are designed to target the region of the GADD45 polypeptide would affect 1. GADD45/cdc2 binding, 2. the GADD45 polypeptide-mediated dissociation of the cdc2/cyclinB1 protein complex, and 3. the ability of the cdc2/cyclinB1 complex to phosphorylate histone H1. NCI suggests that the small acidic motif may, in itself, be a possible small molecule, dominant negative inhibitor of GADD45 activity. Once other small molecule GADD45 modulators are identified, NCI would be interested in a collaboration to further characterize all candidate GADD45 modulators using preclinical and clinical assays.

NCI is seeking a CRADA Collaborator to aid in the screening, development and commercialization of small molecule inhibitors of GADD45 polypeptide activity for use in the preclinical and clinical treatment of cancer. NCI has developed various in vitro and in vivo methods that could be applied to a drug screening protocol in which potential modulators of GADD45 could be identified and characterized. Once identified and characterized, novel GADD45 inhibitors may be administered to candidate cancer patients and evaluated in their ability to treat various tumors in conjunction with current chemotherapeutic treatments. The described methods are the subject of U.S. provisional patent application, US/6/126,069, filed on March 25, 1999 by the Public Health Service on behalf of the Federal Government.

Furthermore, the initial report and characterization of the invention is described in Wang, X.W. et al, PNAS, vol. 96: 3706–3711.

References

Under the present proposal, the overall goal of the CRADA collaboration will involve the following:
1. To use the current technology developed by NCI to screen for modulators of GADD45 polypeptide activity.
2. To conduct preclinical and clinical assays to test the effectiveness of the candidate GADD45 polypeptide modulators in the treatment of different cancers.

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 methods developed to assess the activity of the GADD45 polypeptide.
3. Planning research studies and interpreting research results.
4. Carrying out research to validate the use of the GADD45-related methods and candidate GADD45 polypeptide modulators in preclinical, diagnostic and clinical settings.
5. Publishing research results.
6. Developing additional potential applications of the screening methods.

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.

Selection criteria for choosing the CRADA Collaborator may include, but not be limited to:
1. A demonstrated record of success in the screening of chemotherapeutic agents.
2. A demonstrated background and expertise in cancer research and treatment.
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.
DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Office of the Director, National Institutes of Health; Notice of Meeting

Pursuant to section 10(a) 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 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 Heart, Lung, and Blood Institute Special Emphasis Panel, Mouse Phenotyping RFA.

Date: April 12, 2000.

Time: 8:00 a.m. to 6:00 p.m.

Agenda: To review and evaluate grant applications.

Place: Holiday Inn Bethesda, 8120 Wisconsin Ave, Bethesda, MD 20814.

Contact Person: Virginia P. Wray, PhD, Scientific Review Administrator, Grants Review Branch, Division of Extramural Activities, National Cancer Institute, 6116 Executive Boulevard, Room 8046, Rockville, MD 20895–7405, 301/496–9236.

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.

(Catalogue of Federal Domestic Assistance Program Nos. 93.392, Cancer Construction; 93.393, Cancer Cause and Prevention Research; 93.394, Cancer Detection and Diagnosis Research; 93.395, Cancer Treatment Research; 93.396, Cancer Biology Research; 93.397, Cancer Centers Support; 93.398, Cancer Research Manpower; 93.399, Cancer Control, National Institutes of Health, HHS)


LaVerne Y. Stringfield, Director, Office of Federal Advisory Committee Policy.

[FR Doc. 00–7374 Filed 3–24–00; 8:45 am]

BILLING CODE 4140–01–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute; 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 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 Cancer Institute Initial Review Group, Subcommittee C—Basic & Preclinical.

Date: April 12–14, 2000.

Time: 7:30 p.m. to 12:00 p.m.

Agenda: To review and evaluate grant applications.

Place: Holiday Inn, 8120 Wisconsin Avenue, Bethesda, MD 20814.

Contact Person: Virginia P. Wray, PhD, Scientific Review Administrator, Grants Review Branch, Division of Extramural Activities, National Cancer Institute, 6116 Executive Boulevard, Room 8046, Rockville, MD 20895–7405, 301/496–9236.

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LaVerne Y. Stringfield, Director, Office of Federal Advisory Committee Policy.

[FR Doc. 00–7370 Filed 3–24–00; 8:45 am]

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