

The Newsletter of the Office of Cancer Complementary and Alternative Medicine

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Rare Plant Compounds from China Undergo Screening at NCI



KIB's State Key Laboratory of Phytochemistry and Plant Resources

In July 2008, the United States government signed a research agreement with China to foster collaboration between researchers studying integrative and Traditional Chinese Medicine (TCM) in both countries. One of the first and most promising of these projects is a partnership between the Kunming Institute of Botany (KIB) of China Academy of Sciences and two groups at the National Cancer Institute (NCI).

The Office of Cancer Complementary and Alternative Medicine (OCCAM) began to oversee the growing collaboration after a Memorandum of Understanding (MOU) was signed between KIB and NCI in October 2008. KIB will supply rare and

promising specimens, while the Natural Products Branch (NPB) and the Developmental Therapeutics Program (DTP) will screen them in NCI's system of 60 human cancer cell lines. If any compounds show promise, more drug analysis and development would follow, said Libin Jia, M.D., health scientist administrator at OCCAM.

KIB's researchers collect and study plant specimens indigenous to their environment, a high-mountain plateau in southwest China that also extends into Tibet. Plants that thrive there could be called "extremophiles," said David Newman, Ph.D., NPB chief.

Temperatures at these altitudes fluctuate dramatically, with a range

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in temperatures between the seasons more extreme than in most areas of the world. The climate requires a natural hardiness from plants, because it winnows the supply of possible nutrients. “The ecology is unique, and also remote,” Dr. Newman noted. “We relish the opportunity to study these compounds and extracts, because we really have no idea what we may find.”

Bringing Botanical Compounds Back

Dr. Jia traveled to KIB last fall and returned with seventeen plant-derived compounds, some from plants used in TCM. He delivered the compounds to the DTP labs at NCI’s Frederick, MD, campus where the specimens are now undergoing *in vitro* screening for anti-cancer activity.

“TCM has already contributed a few compounds, like arsenic trioxide and camptothecin, which are currently used to treat cancer,” explained Dr. Jia. “It would be remarkable if we could find additional ones from the vast number of medicines China has been using for centuries.”

In his recent visit to KIB, Dr. Jia was greeted by KIB Deputy Director Jikai Liu, Ph.D., who provided a tour of the scientific organization. “He showed me their large botanical seed collection (over 1.2 million specimens), which is quite unique,” Dr. Jia recalled. KIB also developed a world-renowned botanical garden,

“We relish the opportunity to study these compounds and extracts, because we really have no idea what we may find.”

Dr. David Newman, Chief of Natural Products Branch

where they cultivate many of the plant species found in the region.

East-West Science and Vice Versa

The millennia-long history of TCM is embodied in the *Bencao Gangmu* (“Materia Medica”), explained NCI’s Dr. Newman. It is the most complete compendium ever written about TCM, compiled during the Ming Dynasty in the 16th century. “The descriptions of the plants are invariably accompanied by the associated climatic, temporal, and geographic conditions—information on where, when, and how to collect them,” he explained.

“The KIB has an extremely talented group of chemists and plant biologists,” said Dr. Newman, “who have been studying these interactions for years, and who similarly have developed a large collection of plant-associated microbes that may unlock a plant’s medicinal potential.”

Two of the compounds that Dr. Jia brought back from China have already shown promising anti-cancer activity in the KIB labs. The Chinese researchers are hoping that NPB will confirm those findings. But the real collaboration involves putting the rest of the specimens through the rigorous screening process that DTP established around 1990.

Once anti-cancer activity is detected in cells, the work may eventually progress to testing for activity in animal models of cancer. KIB has isolated thousands of compounds, and another batch is on the way to NPB’s labs.

The future of the partnership looks bright, Dr. Jia commented. OCCAM is planning a dialogue among experts on the topic of botanicals in cancer research this summer. KIB’s Dr. Liu will provide NCI researchers with more insight from and details about KIB’s work and resources at that meeting.

Discussions about how the results from some of the projects might eventually be exported back to China are also planned. One of KIB’s goals from the collaboration is to develop a greater capacity to perform its own anti-cancer screening. To facilitate this, Dr. Liu will carry back with him a functional model of the NCI-60 screening cancer cell lines. One day KIB may send scientists to train at NPB and DTP and possibly establish some of the more advanced drug screening methods and technologies, moving science from “west to east.”



Related stories:

United States and China Sign Research Agreement on Traditional Chinese Medicine
<http://www.cancer.gov/cam/newsletter/2008-fall/1.html>
From Dust to Discovery
<http://www.cancer.gov/cam/newsletter/2007-fall/1.html>



Dr. Isis Mikhail

A Conversation with:

Isis Mikhail, M.D., M.P.H., Dr.P.H.
Research Development and Support Program Director
Office of Cancer Complementary and Alternative Medicine
Division of Cancer Treatment and Diagnosis

Would you briefly describe your educational and professional background?

After graduating from Cairo University Medical School in Egypt in 1980, I came to the United States and completed my clinical boards. I then received a scholarship from the University of Alabama at Birmingham (UAB) and completed my M.P.H. in epidemiology in 1990.

After graduation, I worked on epidemiologic studies and clinical trials in many areas of health: chronic diseases (heart disease, diabetes), genetics (Alzheimer's, narcolepsy), and rheumatologic disorders (rheumatoid arthritis, lupus, fibromyalgia). While working as director of the WILLOW Project, an HIV trial funded by the National Institutes of Health (NIH), I pursued a doctoral degree in UAB's Department of Epidemiology and International Health. In 2003, I received my Dr.P.H. and was honored as the outstanding doctoral student of the year.

All of these experiences prepared me for my positions here at NCI. Before coming to OCCAM, I was a program director and epidemiologist at the Clinical and Translational Epidemiology Branch of the Division

of Cancer Control and Population Sciences at NCI. In that role, I focused on stimulating research on rare cancers and worked on projects related to chronic diseases and cancer, cancer risk, outcome, and prognosis. I served as chair of the Health Disparities Interest Group and was a member of the Special Studies Institutional Review Board.

What does your new role at OCCAM include?

My main role as director of the Research and Development Support Program (RDSP) is to coordinate, support, and expand OCCAM's extramural research activities and grant portfolio. This can be achieved by developing new initiatives and collaborative funding opportunities with other NCI and NIH programs. Also, communicating with CAM researchers and attending and organizing meetings and workshops will be important for me to build bridges with this research community. Such efforts can promote innovative research and support new investigators to conduct rigorous research.

I will also emphasize OCCAM's new research priorities, which include the identification of novel therapeutics for the pharmacopeia of traditional medical systems, as defined by the World Health Organization; the use of complementary approaches to improve the therapeutic ratio of standard and investigational anti-cancer therapies; and research on

lifestyle modifications (e.g. diet, exercise, and mind-body approaches) for their impact on cancer outcomes (e.g. response to conventional cancer therapy and survival).

How did you first become interested in CAM? How has that shaped your career?

Having grown up in Egypt, I was exposed to CAM early on. The use of CAM therapies, such as ancient Egyptian remedies, for general sicknesses is a way of life there. Also, my father owned an export business where he exported medicinal herbs to a pharmaceutical company in Germany. I can still remember hearing about herbals such as chamomile and cardamom. I also learned that certain herbs have potencies based on where they are planted, when they are planted, and the soil used.

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During my medical education, I learned that many commonly used medicines have herbal origins. However, conventional medical education did not include CAM in its curriculum. My interest in CAM was revived when I selected the topic of my doctoral dissertation—CAM use among HIV-positive women in association to their clinical disease indicators. I worked on CAM topics during my fellowship and am continuing with it here at OCCAM.

What visions do you have for the Research Development and Support Program?

I would like to expand OCCAM's extramural research portfolio and see more robust research in the field of cancer CAM. This can only be achieved through collaboration—inter- and trans-disciplinary, within and outside NIH, and both nationally and internationally. RDSP

can play an instrumental role in helping to foster such research collaborations that can result in increased recognition of CAM use by conventional health care professionals. With more rigorous and evidence-based research available in the future, I envision that CAM will be more recognized and incorporated as part of conventional cancer treatments. 🐼

News from the Field

OCCAM to Reissue Program Announcement but Adds New Priorities

Since it was first issued in 2001, the program announcement (PA) series “Developmental Projects in Complementary Approaches to Cancer Care” has been one of the most productive mechanisms for attracting new CAM grants to NCI. The series has included PAR-02-040, PA-04-053, and the soon to expire PA-06-400. To replace PA-06-400, OCCAM has revised this PA, which has been approved for reissuance and is expected to be published in May 2009.

This new PA will continue to solicit grant applications that encourage and support the development of basic and clinical complementary cancer research projects (prevention, therapeutic, and palliative) through the exploratory/developmental research grant (R21) award mechanism. For the first time in the PA series, the announcement will also foster innovative research through two new additions—the small grant (R03) mechanism and

requests for submissions that focus on OCCAM's new cancer CAM research priority areas.

The addition of the small grant (R03) mechanism allows investigators the opportunity to collect preliminary data on CAM that can provide the basis for future more extensive research. It also encourages innovative applications of CAM approaches and collaborative research for small research projects as well as between national and international studies for comparative or validation trials. These collaborations are particularly relevant to CAM practices that have been identified through the NCI Best Case Series Program and warrant NCI-initiated research but have not ascertained enough data for a larger project. Examples of such therapeutic regimens include the treatment approach of the P. Banerji Homeopathic Research Foundation, insulin potentiation therapy, and macrobiotic lifestyle as per the Kushi

UPDATE

Results of CAM Practitioners Survey Published in JSIO

The results of a survey of CAM practitioners and their interests and concerns regarding the care of cancer patients was published in the Winter 2009, Volume 7, Number 1 edition of the *Journal of the Society of Integrative Oncology*. A similar survey of cancer researchers regarding CAM was published last year in the Winter 2008 edition. Selected results from both surveys were presented at the 2nd International Conference of the Society for Integrative Oncology in October 2005.

Institute. Using the R03 mechanism, these approaches and others can be explored, creating a channel for potential promising CAM interventions to be discovered.

The addition of OCCAM's research priority areas to this announcement will encourage rigorous research in these areas that are not currently represented in the scientific knowledge:

1. Novel therapeutics in the pharmacopoeia of traditional medical systems, as defined by the World Health Organization
2. Complementary medicine approaches to improve the therapeutic ratio of standard and investigational anti-cancer therapies
3. Research on lifestyle modifications (e.g. diet, exercise, and mind-body approaches) for their impact on cancer outcomes (e.g. response to conventional cancer therapy and survival)

Additional information on this PA will be available upon its release at <http://grants.nih.gov/grants/guide/pa-files>. For extramural research questions, please contact Research Development and Support Program Director Dr. Isis Mikhail at mikhaili@mail.nih.gov.

NCI's Third Annual CAM Report Now Available

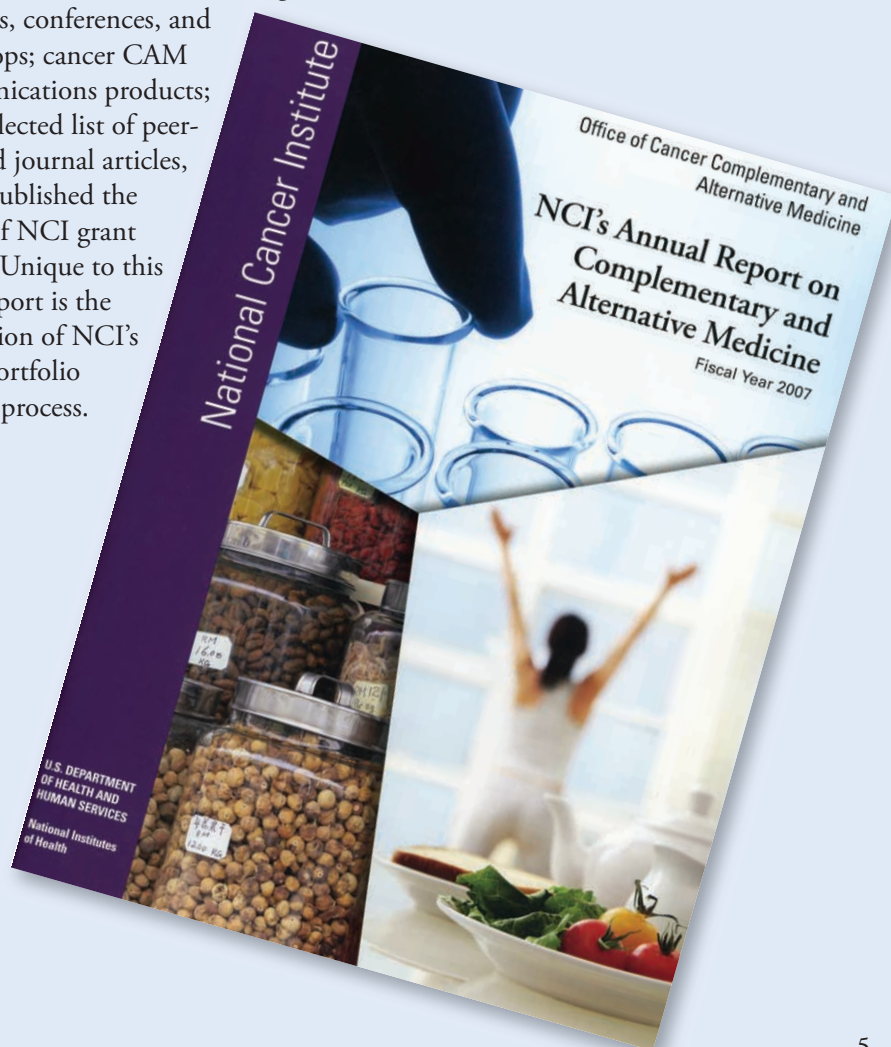
NCI has recently published its third annual report on activities relating to cancer CAM. The report, *NCI's CAM Annual Report: Fiscal Year 2007*, led by the efforts of OCCAM, covers cancer CAM communications, training, and research projects sponsored by NCI between October 1, 2006 and September 30, 2007. The primary focus of the report is to present research highlights from NCI's comprehensive grant portfolio.

To provide an overall picture of NCI's cancer CAM portfolio, the projects selected for the report represent a variety of NCI Divisions, grant mechanisms, research types, CAM therapies, research institutions, and types of cancer. Examples of project summaries featured in the report include:

- Fish Oil Studied for Possible Prevention and Treatment of Pancreatic Cancer
- Green Tea Extract and Erlotinib Explored for Prevention of Head and Neck Cancer

■ Dragon Boat Racing May Help Cancer Survivors Thrive

In addition to research project summaries, the report provides information about other NCI CAM activities from FY 2007 including meetings, conferences, and workshops; cancer CAM communications products; and a selected list of peer-reviewed journal articles, which published the results of NCI grant awards. Unique to this year's report is the description of NCI's CAM portfolio analysis process.



NCI's CAM Annual Report for fiscal year 2007 is available on the OCCAM Web site at www.cancer.gov/cam/attachments/CAMAnnualReportFY2007.pdf.

Dietary Supplement Studies Listed as One of NIH's 2008 Clinical Breakthroughs

NIH highlighted accomplishments made in 2008 by NIH-supported scientists in *NIH Research Matters*. The following dietary supplement studies were chosen as clinical breakthroughs in prevention, diagnosis, and treatment of human disease. This article is re-printed from the *NIH Research Matters* Web site: www.nih.gov/news/research_matters/december2008/12152008dietsupl_prostate.htm.

Dietary Supplements Fail to Prevent Prostate Cancer

Two large-scale clinical trials found that regular intake of vitamin E, vitamin C or selenium does not reduce the risk of prostate cancer or other cancers in older men, as some previous studies had suggested.

Prostate cancer is the second-leading cause of cancer death in American men. It's expected to kill about 29,000 people nationwide in 2008, and about 186,000 new cases are predicted for this year. Over a decade ago, a couple of clinical studies found evidence that prostate cancer risk might be reduced by taking vitamin E or selenium supplements, but these older studies weren't specifically designed to answer questions about prostate cancer. Smaller studies have hinted that vitamin C might help to prevent different types of cancer, but earlier trials haven't looked at the effects that vitamin C alone might have on prostate cancer in men at usual risk for the disease.

The 2 new studies, funded in part by NIH's National Cancer Institute (NCI) and several other NIH

components, were designed to look specifically at how prostate cancer and total cancer risk is affected by different dietary supplements. The results of both trials were published on December 9, 2008, in the online edition of the *Journal of the American Medical Association*.

The larger study—the Selenium and Vitamin E Cancer Prevention Trial (SELECT)—recruited more than 35,000 men, age 50 and older, who had no evidence of prostate cancer. Participants were randomly assigned to receive selenium, vitamin E, the 2 in combination or inactive placebo pills for comparison. Researchers originally intended to follow each participant for at least 7 years. But in October 2008, after an average follow-up of about 5.5 years, the participants were asked to stop taking their pills. That's because an independent monitoring committee found that the supplements seemed to offer no cancer-related benefits. In fact, preliminary analyses hinted at some possible harm.

Overall, the researchers reported no significant differences between the 4 groups in the rates of prostate cancer or other types of cancer. The men taking vitamin E alone had a slightly raised prostate cancer risk, and those taking selenium trended toward a

higher risk of type 2 diabetes. In both cases, though, the differences weren't large enough to prove they weren't due to chance. Although the study participants are no longer taking their assigned treatments, the researchers plan to continue monitoring their health for at least 3 more years to detect any long-term effects of supplement use. The second trial, Physicians' Health Study II, looked at how the long-term use of vitamin E or C supplements affect the risk of prostate or other cancers. More than 14,000 male doctors, age 50 or older, were randomly assigned to take either vitamin E, vitamin C, both vitamins, or a placebo. After an average follow-up of about 8 years, the scientists found that neither vitamin—alone or in combination—significantly reduced the risk of prostate or other cancers compared to the placebo group. No significant negative effects were associated with vitamin use.

The results of these studies highlight the fact that, while dietary supplements can often seem beneficial in small observational studies, large, carefully controlled trials are needed to test whether they really live up to their hoped-for benefits. 🐼

Related stories:

- *SELECT Press Release*
<http://www.cancer.gov/newscenter/pressreleases/SELECTJAMAResults2008>
- *Prostate Cancer*
<http://www.nci.nih.gov/cancerinfo/types/prostate/>
- *Selenium and Vitamin E Cancer Prevention Trial (SELECT)*
<http://www.cancer.gov/newscenter/pressreleases/SELECTQanda>
- *Supplementing Your Diet: Vitamins, Minerals and Beyond*
http://newsinhealth.nih.gov/2006/March/docs/01features_01.htm

Request for Applications on Botanical Supplements Released



RFA-OD-001 supports research on foods of plant origin such as broccoli.

The National Cancer Institute (NCI), the National Center for Complementary and Alternative Medicine (NCCAM), and the Office of Dietary Supplements (ODS) have released RFA-OD-09-001, titled “Dietary Supplement Research Centers: Botanicals (P50).” The purpose of this Request for Applications (RFA) is to promote collaborative interdisciplinary study of botanicals, particularly those used in dietary supplements. This initiative is intended to advance the spectrum of botanical research activities, ranging from plant identification and characterization to early phase clinical studies.

The NCI Division of Cancer Prevention is interested in supporting research focused on the mechanisms by which botanically derived bioactive food components might influence cancer risk and tumor behavior. Only investigators who submitted a pre-application in

response to PAR-09-091 and received notification are eligible to submit full applications under this RFA.

Botanicals of particular interest include traditional herbal medicines or phytomedicines (e.g., ginkgo, echinacea, valerian), many of which are widely available in the U.S. as dietary supplements. This RFA also supports research on foods of plant origin (e.g., cranberry, broccoli, garlic) which by virtue of biologically active components may provide health benefits beyond basic nutrition; these bioactive constituents are appearing with increasing frequency as ingredients in dietary supplements.

For more information, review the following announcement at <http://grants.nih.gov/grants/guide/rfa-files/RFA-OD-09-001.html> or contact Dr. Harold Seifried at seifried@mail.nih.gov.

Program Announcement for Basic and Preclinical CAM Research Reissued

In October 2008, NCI, NCCAM, and ODS published the Program Announcement (PA) PA-09-010, “Basic and Preclinical Research on Complementary and Alternative Medicine (CAM) (R01).” A reissue of PA-07-007, this announcement’s purpose is to encourage researchers to study CAM with an aim of understanding the mechanisms and the biomedical scientific basics behind CAM clinical practices.

There are four categories into which these practices can be grouped: mind-body medicine, biologically based practices, manipulative and body-based practices, and energy medicine. The focus should be on basic, mechanistic, and preclinical research. NCI is particularly interested in interactions between bioactive dietary components and CAM modalities.

Researchers are encouraged to contact the program directors listed for each participating Institute prior to submitting their applications. The NCI contact for this PA is Cindy Davis, Ph.D., of the Nutritional Science Research Group; contact Dr. Davis at davisci@mail.nih.gov. OCCAM welcomes questions as well; contact Research Development and Support Program Director Dr. Isis Mikhail at mikhail@mail.nih.gov.

For more information on this PA, visit <http://grants.nih.gov/grants/guide/pa-files/PA-09-010.html>.

Pancreatic Cancer Prevention Supported Through Program Announcement

Pancreatic cancer affects around 37,000 Americans a year. It is difficult to detect and is considered largely incurable. The American Cancer Society estimates the one-year survival rate is 20% and the five-year rate is 10%.

NCI and the National Institute on Alcohol Abuse and Alcoholism released PA-08-032, “Molecular Approaches to Diet and Pancreatic Cancer Prevention (R01),” which is a re-release of PA-07-257. The goal of this PA is to encourage researchers who have ideas for “innovative preclinical and clinical studies to determine how dietary energy intake and bioactive food components, including alcohol, influence pancreatic cancer development and prevention.”

The agencies releasing the PA hope to promote collaboration among “nutritional scientists, cancer biologists, oncologists and gastroenterologists to jointly examine

key mechanisms in the pancreatic cancer process”. Examples of appropriate research ideas include, but are not limited to, the following:

- Nutritional genomic, epigenomic, proteomic, and metabolomic approaches to examining energy metabolism and/or bioactive food component activity in relevant pancreatic cancer models;
- Relationship between diet, genetic polymorphisms (e.g., enzymes that influence energy metabolism) and pancreatic cancer risk.
- Mechanistic studies on the impact of oxidative stress, dietary antioxidants in pancreatic cancer (e.g., apoptosis, IGF-1 signaling);
- Understanding synergistic relationships between bioactive food components in

signaling pathways relevant to pancreatic cancer;

- Development of relevant animal models for pancreatic cancer and application of such models to studies on dietary prevention of pancreatic cancer; and
- Understanding the molecular mechanisms by which dietary fat, oxidative stress, acetaldehyde, cytokines, and other factors contribute to the pathogenesis of chronic alcoholic pancreatitis.

For more information on this PA, contact NCI’s Division of Cancer Prevention Program Director Dr. Sharon Ross at rossha@mail.nih.gov and visit <http://grants.nih.gov/grants/guide/pa-files/PA-08-032.html>. 📄

Research Resources

What’s New with NIH Peer Review?

The National Institutes of Health (NIH) has a world-renown peer review system designed to enable NIH to assess the merit of each grant application in a consistent and non-biased way. After a year of assessment, NIH identified four priority areas of change needed for the current peer review system: engaging the best reviewers; improving the quality and transparency of review; ensuring balanced and fair reviews across

scientific fields and career stages, while reducing administrative burden; and continuing to review the system of peer review. Enhancements to the NIH peer review system based on the priority areas are now underway.

NIH’s Center for Scientific Review has been setting the stage for these changes with both NIH staff and the broader scientific research community through

communications such as policy notices in the Guide for Grants and Contracts, briefings to NIH Councils, training for NIH staff, press releases, newsletter articles, and listserv communications. In addition to providing these resources, the Enhancing Peer Review Web site is continually updated with new content, such as a video presentation that was posted in March 2009. Scientific Review Officers have been communicating with reviewers and preparing them for the training

they will receive as the spring review meetings commence.

For an overview of the timetable for implementing the changes to the peer review system, see NOT-OD-09-023

(<http://grants.nih.gov/grants/guide/notice-files/NOT-OD-09-023.html>).

For more information, please visit the Enhancing Peer Review Web site at <http://enhancing-peerreview.nih.gov>.

Learn More About NCI Funded Research Projects

Each year, NCI supports approximately 450 cancer CAM research projects. If you are interested in learning more about these NCI projects or other CAM research projects funded by other Institutes at NIH, you will find multiple federal Web sites and databases designed to help in your search. Three public resources that are available to help you to locate this type of information are the Research Portfolio Online Reporting Tool (RePORT)

(<http://report.nih.gov/index.aspx>), Computer Retrieval of Information on Scientific Projects (CRISP) (<http://report.nih.gov/crisp/index.aspx>), and the NCI Funded Research Portfolio (<http://fundedresearch.cancer.gov/>).

RePORT

RePORT is an NIH Web site that provides access to reports, data, and analyses related to the comprehensive NIH research portfolio. Launched in February 2008, RePORT includes the NIH biennial report, strategic plans for the individual NIH Institutes and Centers, budget and

spending information, success rates, funded investigators, and extramural institution data. It also showcases the NIH's new, consistent and transparent process for categorizing and reporting research projects called the Research, Condition, and Disease Categorization (RCDC). RCDC uses 215 categories to describe research projects, one of which is Complementary and Alternative Medicine.

By selecting *Categorical Spending* from the RePORT home page, you can find the RCDC table, which displays fiscal year funding amounts for grants, contracts, and other funding mechanisms. By clicking on the *FY 2008 Actual* link in the category Complementary and Alternative Medicine, the system will populate a list of all of the NIH-funded CAM projects. You will find the name of the primary funding NIH Institute, project number, project title, principle investigator's name, institution, state, and funding amount available for each project.

CRISP

RePORT now also hosts the CRISP database. CRISP contains information on federally funded research projects and programs supported by agencies within the Department of Health and Human Services (DHHS). These research projects are primarily extramural and are conducted by universities, hospitals, and other research institutions. In addition to information on extramural projects, grants, contracts, and cooperative agreements, you will also find information on intramural programs of the NIH and U.S. Food and Drug Administration.

The best way to search CRISP for cancer CAM projects funded by NCI is to choose NCI from the Institutes and Centers list and use the Search Terms box to search for specific topics within CAM. Watch over the next year for new features in CRISP, as the database is updated to include budget information and links to publications and patents that are a result of the NIH-funded research.

NCI Funded Research Portfolio

If you are only interested in locating information about NCI research projects, use the NCI Funded Research Portfolio, which was introduced last summer as a replacement for the Cancer Research Portfolio. The search functions and overall navigation make this database a user-friendly way to access information about NCI-funded research grants, contract awards, and intramural research projects.

To find grants investigating a specific CAM therapy, for example acupuncture, use the keyword search on the home page. The Portfolio's *Advanced Search* page allows you to search more specifically with options including: fiscal year, research topic, project type, cancer type, funding mechanism, NCI Division, project number, principal investigator, and research institution.

To locate information on CAM using the *Advanced Search* page, select one of the following complementary and alternative approaches drop-downs under *Research Type* (Common Scientific Outline [CSO]):

- Complementary and Alternative Prevention Approaches

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- Complementary and Alternative Treatment Approaches
- Complementary and Alternative Approaches for Supportive Care of Patients and Survivors
- Behavior Related to Cancer Control
- Interventions to Prevent Cancer: Personal Behaviors that Affect Cancer Risk
- Nutritional Sciences
- Patient Care & Survivorship Issues

Before you begin, determine whether you want to search for NCI-funded projects or projects funded by other Institutes at NIH. These three resources will provide helpful instructions and answers to frequently asked questions to guide you as you search. [🔗](#)

The above list does not include all of NCI's CAM projects, so also try searching other Research Types including:

Research Highlights

Vitamin C as a Potential Anti-Cancer Agent: Progress and Controversies

Vitamin C is commonly known to be essential to human health. However, specifically as it relates to cancer treatment, the value of vitamin C is debated and often considered a topic of scientific controversy. Cancer researchers have investigated various ways of administering high-dose vitamin C, including both orally and intravenously. Researchers have also examined different forms of vitamin C—ascorbic acid (AA) and dehydroascorbic acid (DHA)—which may well be a comparison of apples and oranges.



Researchers Debate the Role of IV Vitamin C as a Cancer Treatment

History of Vitamin C Research

In 1952, William J. McCormick, M.D. speculated that vitamin C could be useful as an anti-cancer agent by strengthening collagen and thereby preventing the spread of metastases. The idea was revisited in the early 1970s by Ewan Cameron, M.D. and his Scottish colleagues. They administered high dose AA to patients

with advanced cancer. Linus Pauling, Ph.D., winner of two Nobel prizes, and Cameron coauthored two retrospective case series that suggested high doses of vitamin C as a treatment agent substantially prolonged life and improved well being in some patients with advanced cancer. However, two

double-blind, placebo-controlled clinical trials performed in the late 1970s and early 1980s at the Mayo clinic showed no anti-cancer effects from high-dose vitamin C, and interest in the field waned.

More recent research shed light on why the Mayo clinic trials were not

comparable to the earlier case series of Cameron and Pauling. Cameron administered AA both orally and intravenously, but the Mayo clinic investigators used only oral AA. Research over the past decade has shown that vitamin C concentrations in humans are carefully regulated, in part by diminished absorption in the intestine as doses increase. Intravenous administration produces concentrations that can be more than 100 fold higher than concentrations produced by maximal oral doses. Thus, most of the 10 gram oral dose administered in the Mayo clinic trials—approximately 100 times the Recommended Dietary Allowance—would have been directly excreted, unable to reach the targeted cancer cells.

Current Research

Recently, researchers at NIH have revisited the potential of vitamin C as an anti-cancer agent. To circumvent the absorption problem seen with oral dosing, researchers from the NIH's National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), led by Mark Levine, M.D., tested intravenous or intraperitoneal injections of high-dose AA in mouse models of ovarian cancer, pancreatic cancer, and glioblastoma.

In all three tumor types, the injections reduced tumor growth by approximately half compared with untreated mice. In addition, metastases were found in about 30 percent of untreated mice, but in none of the mice injected with AA. The study was published in the August 12, 2008 *Proceedings of the National Academy of Science*.

In additional work, investigators at the University of Kansas Medical Center led by Jeanne Drisko, M.D., were able to achieve similar concentrations of AA as those achieved in the mice by using intravenous injections in human subjects with ovarian cancer. This work has since been confirmed in a phase I clinical trial led by L. John Hoffer, M.D., Ph.D.

“The way that the body handles oral and intravenous vitamin C differently raises the question of whether or not the clinical trials that were done with only the oral formulation were adequate to help us understand the role, if any, vitamin C has in cancer treatment,” said Dr. Jeffrey D. White, director of OCCAM.

More questions were recently raised by a study from the Memorial Sloan-Kettering Cancer Center about using vitamin C in combination with traditional chemotherapeutic drugs. In that study led by Mark Heaney M.D., Ph.D., published in the October 1, 2008 issue of *Cancer Research*, investigators injected tumor-bearing mice with a combination of DHA, the oxidized form of vitamin C, and the chemotherapy drug doxorubicin.

They found that mice receiving the combination had tumors four times larger than the tumors in mice treated with doxorubicin alone. Corresponding studies in cell lines suggested that the DHA may have protected the cancer cells' mitochondria from doxorubicin-induced damage.

Incomparable Results

In assessing the value of vitamin C as a cancer treatment, comparisons of the NIDDK and Memorial Sloan-Kettering studies have been made. However, there are some problems with making these comparisons. Two different forms of vitamin C, AA and DHA, were used in the studies. The studies had different aims. One looked at AA's anti-cancer effects as a stand-alone therapy, while the other looked at the effects of DHA when used with certain chemotherapy agents. In addition, different dose ranges were examined, which would be similar to comparing pharmaceutical concentrations of vitamin C levels to that of an oral supplement.

Dr. Levine's laboratory is planning further preclinical studies to measure the effects of AA injections in combination with chemotherapy agents and to understand the mechanisms behind why high-dose AA affects some cancer cells but not normal cells. He hopes to use that information “to figure out which types of cancer may be sensitive to ascorbate [AA] and which wouldn't be,” he explained. In addition, in the near future, “We think this work needs to go forward to targeted clinical trials, and we're looking for clinical partners to help us do that,” said Dr. Levine.

Whether these DHA results in mice will translate to intravenous AA injections in people remains to be determined, said Dr. Heaney. “I think vitamin C could turn out to be something of a double-edged sword. DHA may protect tumor cells, and depending on how you're giving AA, there are times when it may have some therapeutic properties.” 🐼

Ten-Year Mark Brings New Commitment to Patients' CAM Information Needs

For the past decade, OCCAM has successfully worked to stimulate cancer CAM research by focusing much of its communication efforts on cancer researchers and CAM practitioners. For the next ten years, OCCAM has made a commitment to continue its progress in research while expanding its efforts in the area of patient outreach and communication. The goals outlined to address this commitment include positioning NCI as the authoritative and unbiased voice on the topic of cancer CAM. To meet this goal, OCCAM will produce additional resources for cancer patients that will fill in the existing information gaps and address cancer patients' information needs.

In order to develop resources that will best serve the needs of patients,

OCCAM will conduct a qualitative needs assessment to identify the CAM issues and topics most important to cancer patients. "We recognize the need for improved patient communication and information on cancer and CAM. The information collected in our assessment will help shape a dialogue about cancer patients' needs related to CAM. It will also help us determine high priority areas for new patient-focused publications and resources." said Dr. Jeffrey D. White, director of OCCAM.

To prepare for the needs assessment, OCCAM reviewed the following:

- data from focus groups that addressed cancer patients and caregivers cancer CAM information needs
- literature published in peer-reviewed journals on cancer patients' information-seeking behaviors
- existing information resources that NCI and other agencies offer on cancer CAM

OCCAM's qualitative needs assessment will target groups who work closely with patients including cancer patient educators, oncology social workers, nurses, and patient advocates. After analyzing the results, OCCAM hopes to work with representatives from these and other groups to produce resources that will meet the needs identified. 🗣️

Sign-up for OCCAM's Listserv

Stay up-to-date on the latest cancer CAM news at NCI with OCCAM's listserv, OCCAM Announcements. As a listserv subscriber, you will receive a monthly email about upcoming workshops and lectures, new funding opportunities, publications, and other resources. To subscribe, simply visit OCCAM's Web site:

<http://cancer.gov/cam/news/occam-announcements.html>

Meetings Fruitful for NCI Collaborations with China

Libin Jia, M.D., health scientist administrator in the Office of the Director at OCCAM, attended two conferences in China during October 2008. The first was sponsored by the Cancer Foundation of China, titled “The Progress and Prospect of Traditional Chinese Medicine (TCM) Cancer Therapy and Prevention.” The conference was held from October 22-24, in Zhangjiajie, Hunan Province. Dr. Jia was invited to the conference by the Foundation to share the projects on CAM and cancer that NCI is currently supporting, particularly on TCM related to cancer therapy or prevention. The attendees, who were primarily doctors trained in conventional medicine, were interested in learning about OCCAM’s projects and updated

Web site. During this meeting, Dr. Jia also learned about current TCM cancer research in China.

The second conference was the “2nd International Congress of TCM and Integrated TCM-Western Medicine (WM) Oncology”, held in Beijing on October 24-26. Dr Jia was invited by the World Federation of Chinese Medicine Society to be a plenary session speaker and a chairperson. In his talk, Dr. Jia again gave an overview of current NCI investments in CAM and cancer. He discussed specific projects, which highlight the importance of scientific research on TCM drug mechanisms. For example, he talked about the successful cooperative study on Sheng Qi Formula taking place between NCI and Guang An Men, a

hospital in Beijing. This collaboration has led to some new findings on the regulatory function of this TCM drug on the immune system.

During his travels, Dr. Jia also had the opportunity to meet with Dr. Hongsheng Lin, chairman of the Beijing meeting and the chief of the Oncology Department at the Guang An Men hospital of the China Academy of Chinese Medical Sciences. They discussed the continuation of cooperative research between NCI and Guang An Men hospital, future TCM-related projects, postdoctoral training offered by NCI, and information exchange between two institutions.

Five Years of NCI Funding Support for SIO’s International Conference

For the past five years, NCI has provided grant support for the international conference of the Society of Integrative Oncology (SIO). The 2008 conference was held in Atlanta, Georgia in November and was supported, in part, by an R13 conference grant from OCCAM. This 2-day meeting drew almost 225 attendees and included presentations and discussions on recent advances in the field covering topics such as botanicals, Traditional Chinese Medicine (TCM), CAM therapies for symptom management, and integrative survivorship.

Isis Mikhail, M.D., M.P.H., Dr.P.H., director of OCCAM’s Research Development and Support Program, commented about her experience as a

first time attendee, “I was working previously at OCCAM when SIO was in the early stages of being established. I was glad to see the organization fully operational and witness the number of attendees interested in cancer CAM research.”

Opening day topics on integrative oncology included research challenges, communication issues, addressing the whole person, and practical implications. Dr. Mikhail commented on the conference program, “Several of the session topics corresponded to OCCAM’s research priority areas, specifically the ones on botanicals and TCM.”

Two of NCI’s staff members were part of the conference program.

John Milner, Ph.D., chief of the Nutritional Science Research Group, gave a presentation titled “Nutrition for the Cancer Survivor.” Joseph Kelaghan, M.D., M.P.H., of the Community Oncology and Prevention Trials Research Group, gave an update on NCI’s Community Clinical Oncology Program.

The program, abstracts, and selected videos from the 2008 conference are available on the SIO Web site at www.integrativeonc.org/events.html.

SIO’s 6th International Conference will take a place in New York City on November 12-13, 2009.

IOM and U.S. Senate Hold Events on Integrative Medicine

On February 25-27, 2009, the Institute of Medicine (IOM), in partnership with The Bravewell Collaborative, held a summit to examine the role that integrative medicine (IM), a marriage between conventional medicine and CAM therapies, can play in the nation's health agenda. The three-day summit gathered participants from academia, clinical centers, advocacy organizations, government agencies, health insurance providers, as well as patients. The main purpose of the summit was to bring the different parties together to share knowledge and work toward U.S. health reform that includes IM.

Dr. Harvey V. Fineberg, president of the IOM, opened the summit by reflecting on the current state of IM and providing the many different dimensions of IM. As Dr. Fineberg described it, IM:

- Fulfills the World Health Organization (WHO) definition of health: "A state of complete physical, mental, and social well-being, and not merely the absence of disease"
- Extends across the whole spectrum of medicine, caregivers, and institutions
- Focuses on the individual to create patient-centered care
- Conveys openness to multiple modalities of care

The summit's keynote addresses and panel discussions covered topics such as innovative health care models, the science of IM, current and future health care workforce and education needs, and the economic state of the

U.S. health care system. Speakers included Senator Tom Harkin (D-IA), Dean Ornish, M.D., and Mehmet Oz, M.D. Over the course of three days, the summit addressed the definition of IM, how to incorporate IM into conventional medicine, and how to use the concept of IM to advance health reform in the U.S. A review of all of the panel discussions and a commitment to produce a thorough meeting summary ended the summit. The agenda, presentation slides, white papers, and videocast of the summit are available on IOM's Web site:

www.iom.edu/CMS/28312/52555.aspx.

During the same week as the summit, the Senate Committee on

Health, Education, Labor and Pensions held two hearings to discuss IM. The hearings were chaired on Monday, February 23 by Senator Barbara Mikulski (D-MD) and on Thursday, February 26 by Senator Michael B. Enzi (R-WY), the ranking member of the Committee; Senator Harkin; and Senator Mikulski. Each hearing had a panel with four IM experts, who gave opening statements and then answered questions posed by the attending Senators. Several of the panelists were also speakers at the IOM summit, including Dr. Oz and Dr. Ornish. Panelists commented on the need for a special office in the White House to oversee health reform and the importance of health coaches to insure a continuum of care for patients. 🗣️

New NCI Factsheet!



Calcium and Cancer Prevention: Strengths and Limits of the Evidence

This factsheet discusses whether a relationship exists between higher calcium intakes and reduced risks of certain types of cancer.

www.cancer.gov/cancertopics/factsheet/prevention/calcium

OCCAM's Monthly Lecture Series

The OCCAM Monthly Lecture Series will be held
from 1:00 – 2:00 pm ET
on the second Wednesday of each month at
6130 Executive Plaza
1st Floor, Conference Room H
Bethesda, MD 20892

Upcoming Lectures

Date	Speaker	Topic
May 13, 2009	Dr. Ming You Department of Surgery, Washington State University	Anti-tumor B and Lung Cancer
June 10, 2009	Dr. Mian Ying Department of Pathology, University of Illinois College of Medicine	Breast Cancer Prevention and Treatment With Noni Juice
July 8, 2009	Dr. Wei Jia Department of Nutrition, University of North Carolina at Greensboro	To Be Determined
August 12, 2009	Dr. Constantinos Koumenis Department of Radiation Oncology, University of Pennsylvania	Phenolic Antioxidants as Tumor Radio/Chemosensitizers
September 9, 2009	Dr. Susan Zunino United States Department of Agriculture, California	Evaluation of Resveratrol and Curcumin as Therapeutics Against High Risk Leukemia

Featured Scientific Meetings

Date	Meeting	Location	OCCAM Staff Attending
April 6-9, 2009	8 th Annual Oxford International Conference on the Science of Botanicals*	Oxford, MS	Shea Buckman Dr. Isis Mikhail
April 18-22, 2009	American Association for Cancer Research Annual Meeting*	Denver, CO	Dr. Libin Jia Dr. Isis Mikhail
May 12-15, 2009	North American Research Conference on Complementary and Integrative Medicine*	Minneapolis, MN	Shea Buckman
May 29-June 2, 2009	American Society for Clinical Oncology Annual Meeting	Orlando, FL	Dr. Farah Zia
September 8-11, 2009	NIH Mind-Body Week	Bethesda, MD	Lauren Rice
November 12-13, 2009	Society for Integrative Oncology*	New York City, NY	Shea Buckman Dr. Isis Mikhail

**Indicates that an OCCAM staff member will be at the NCI or OCCAM exhibit booth.*

To obtain a copy of this newsletter or for inquiries on cancer and CAM, please contact
1-800-4-CANCER (1-800-422-6237).



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