National Cancer Institute

NCI CAM News

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The Newsletter of the Office of Cancer Complementary and Alternative Medicine

In this issue:

NCI Grantee Explores Vitamin C as Potential Cancer Therapy

Although it is usually associated with oranges and possibly preventing colds, vitamin C may also be a potential cancer therapy. The history of vitamin C (also known as ascorbate) and cancer spans a few decades, going back at least to the 1970s. Early experiments using high doses of vitamin C supplements and intravenously administered vitamin C suggested that vitamin C may help treat cancer. Two randomized, controlled clinical trials using vitamin C supplements found no beneficial effects on cancer and scientists lost interest in researching this vitamin as a cancer therapy. However, this issue was revisited in the mid-1990s when studies suggested that orally and intravenously administered vitamin C are not processed the same way in the body. Researchers discovered that when vitamin C is administered intravenously at high doses, resulting concentrations in the blood are much higher compared to vitamin C that is taken orally. Subsequently, a number of studies have been published indicating that high-dose (pharmacological) vitamin C may in fact help kill cancer cells and research is continuing in this area. Dr. Joseph Cullen of the University of Iowa has recently been awarded a U01* from the National Cancer Institute to investigate pharmacological ascorbate used along with radiation in pancreatic cancer.

Dr. Cullen's U01 grant is a follow-up to an earlier R21 grant** he received to examine mechanisms of ascorbate-induced death of pancreatic cancer cells. "I initially became interested in ascorbate after hearing Mark Levine (who is currently at the National Institute of Diabetes and Digestive and Kidney Diseases, part of the National Institutes of Health) present his work, which was done in collaboration with my colleague Garry Buettner at the University of Iowa. At the time, I was doing research on other oxidizing compounds in pancreatic

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* Project number: 1U01CA166800-01A1
** Project number: 5R21CA137230-02

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cancer and it made sense to pursue work with ascorbate." Dr. Cullen's results suggested that ascorbate kills pancreatic cancer cells by increasing levels of hydrogen peroxide, which is very toxic to cells. Animal studies were also conducted. In those experiments, mice were implanted with pancreatic cancer cells and then received injections of ascorbate or saline for 2 weeks. Dr. Cullen noted that the animal studies revealed "striking results with virtually no side effects." In the animals that received ascorbate treatment, tumors grew more slowly than in animals that received saline injections. On day 21 of the experiment, the tumors in saline-treated animals were three times larger than in ascorbate-treated animals. In addition, the animals that received ascorbate lived longer than animals that received saline injections.

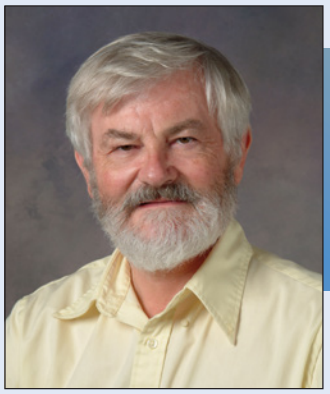
The goal of the new grant is to determine if pharmacological ascorbate can improve the effects of radiation therapy in pancreatic cancer. Dr. Cullen plans to test this by conducting experiments in pancreatic cancer cells and in animals. For the *in vitro* experiments, Dr. Cullen will determine if ascorbate makes pancreatic cancer cells more susceptible (compared to healthy cells) to radiation. He will also investigate the mechanisms behind the increased sensitivity. One way that radiation therapy is effective is by increasing levels of reactive oxygen species (such as hydrogen peroxide), which damage cells. Dr. Cullen hypothesizes that combining ascorbate with radiation will make cancer cells more vulnerable to the treatment due to increased levels of hydrogen peroxide. If the *in vitro* experiments are successful, they will be followed by work in animals. Those experiments, which will investigate if ascorbate can increase sensitivity of pancreatic cancer cells to radiation without damaging healthy cells nearby, will be critical to future clinical trials. For example, Dr. Cullen is interested in conducting a clinical trial combining ascorbate with radiation and chemotherapy in pancreatic cancer patients.

Dr. Cullen has recently published*** results of a phase I trial looking at the safety of using pharmacological ascorbate in addition to standard gemcitabine chemotherapy treatment in pancreatic cancer patients. He found that there were no serious side effects associated with the ascorbate treatment, indicating that it may be safe to use as a complementary cancer therapy. Dr. Cullen commented, "The results of this trial were surprising. Most patients with this type of cancer survive for only 6 months, but the mean survival time of patients in our study was 13 months. We even had one patient live more than 2 years." However, since the study did not include randomization with a group that received gemcitabine alone, these results cannot be used to confirm a benefit of the ascorbate.

Dr. Cullen is planning on extending this work to other cancer types. Clinical trials are underway investigating the effects of combining ascorbate with standard treatment in patients with glioblastoma and lung cancer.

Dan Xi, Ph.D., Program Director at the Office of Cancer Complementary and Alternative Medicine noted, "There is a critical need to improve the efficacy of current therapy for pancreatic cancer. Using pharmacological ascorbate to enhance pancreatic cancer cell sensitivity to death by radiation therapy is innovative and the research team led by Dr. Cullen has extensive experience in this field. If successful, the result could lead to the potential initiation of a clinical trial."

*** Welsh, J.L., Wagner, B.A., van't Erve, T.J., Zehr, P.S., Berg, D.J., Halfdanarson, T.R.,…, & Cullen, J.J. (2013). Pharmacological ascorbate with gemcitabine for the control of metastatic and node-positive pancreatic cancer (PACMAN): results from a phase I clinical trial. *Cancer chemotherapy and pharmacology*, *71*(3), 765-75.



A Conversation with:

David Newman, Ph.D.
Chief, Natural Products Branch

Please tell us about the Natural Products Branch (NPB) and your role as Chief.

The Natural Products Branch (NPB) is part of the Developmental Therapeutics Program (DTP) and I became Branch Chief in 2006 after working at DTP in various other roles, including a chemist in charge of marine and microbial collections from 1991 to 2004 and acting chief from January 2005 until appointed chief in 2006. DTP has an overarching goal to serve as a hub of resources and drug discovery and preclinical development for anti-cancer therapeutics. The DTP is the home of the **NCI-60 Tumor Cell Line Screen**, an in vitro cell line screen designed to screen up to 3,000 compounds per year for potential anticancer activity. The NPB serves as, among other things, a repository for plant, marine, and microbial organism extracts. These extracts are tested on the NCI-60 Tumor Cell Line screen. Extracts are also available to outside researchers for use in experimental trials. Researchers must sign a Materials Transfer Agreement with NCI and will then have access to several available resources of samples through the NCI Natural Products Repository (**Open Repository; Active Repository Program**).

The DTP, of which NPB is part of, has a successful track record of chemotherapeutic agent development, including Paclitaxel (Taxol®), a compound originally extracted from the Pacific yew tree *Taxus brevifolia*. Can you speak about your program's work with natural products?

The NPB set up a screening program similar to the one based on synthetic compounds, but using extracts of plants, microbes, and marine organisms back in the early 1960s. In the early days of NPB, we had academic groups that did the extractions, and subsequent chemistry. We had contractor research groups do *in vivo* mouse assays in those days. We also had a long-time arrangement with the USDA's Economic Botany Group in Beltsville, Maryland and from these NCI screening efforts and partnerships came Paclitaxel, but those collaborations ceased in 1981.

By 1986, Dr. Michael Boyd (who was Associate Director of DTP at that time), had completely revised the screening system and instead of using animals and murine cell lines in the first tests, he set up a screen looking at 60 human cancer cell lines, which is now the NCI 60 Tumor Cell Line Screen. It was around then that we realized the flaws in the original NPB collection program. The first was "collections of opportunity" of the plants and other sources of samples. If someone was traveling somewhere in the world, they collected some plant or marine/microbial materials, but it meant that frequently they didn't get a representative sample. Sometimes, particularly in the case of microbes, they didn't even know what the sample was. So instead, we then set up the program to include collection contracts, where we competitively hired microbiologists, botanists, and marine biologists to do collections. We told the collectors, here are the resources go out and collect, and when you collect we want full details, such as the sample's geographical coordinates, taxonomy, where it came from and when, together with enough material, usually a kilo dry weight for plants, and a kilo frozen wet weight for marine organisms. With this type of contract work, we were able to set up something we didn't have before — a very large repository. We also set up the Natural Products Support Group (NPSG) lab at NCI-Frederick to process these materials in a consistent way.

The repository currently has a quarter of a million samples in it, including 160,000 plants, around 35,000 marine samples, and the rest are microbes. These are now made available to anyone in the world who signs a cooperative agreement. (See the Natural Products Repository links previously.)

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We test extracts in the 60 cell line screen and we now test "active" extracts in animals directly. If it works in an animal where we've put a tumor, there is something in that extract that is worth following. You can't do this in academia or industry; we can. When it comes to natural products per se, if someone brings something in or we obtain something, we do everything from the quality control up to producing the compound or arranging for its production usually in the source country or in the United States in conjunction with the source country. We do this with five people in NPB and a very talented group at the NCI Frederick National Laboratory for Cancer Research called the Natural Products Support Group (NPSG). The NPSG does everything from grinding and extraction, to providing the materials (both natural products and synthetic samples for the tumor cell screens). Then if active, they follow up materials that are active *in vivo*, via chemical analyses of the "active" fractions following only the biologically active materials. However, nothing gets discarded as the materials found may well be active in another type of biological screen.

People always ask what the latest, greatest drug from the rainforest is and I always say Taxol®. There has not been a single compound drug, approved from the rainforest for any disease that I am aware of since Taxol® until very recently, as now we can include Synribo®, a natural product to treat cancer that was approved in October 2012 by the FDA. Homoharringtonine, which is the trivial name for the compound, was originally isolated from the seeds of *Cephalotaxus harringtonia*, which is a coniferous bush or small tree in the plum yew family. Homoharringtonine has really been around since the early 1960s from a USDA investigation with the earlier NPB. Since enough material could not be obtained for preclinical development by NPB in the middle 1960s, due to the source tree not being indigenous to the United States, the compound languished here but work was continued in the People's Republic of China, where the source plant grew wild. The compound was in clinical trials in China for various leukemias, and was put into clinical trials in the United States in conjunction with NCI and a small company that ended up as part of TEVA Pharmaceuticals, following their recent purchase of Cephalon. It was finally approved as an anti-tumor drug, omacetaxine mepesuccinate (trade name, Synribo®), for the treatment of adults with chronic myelogenous leukemia (CML).

There are definitely significant discoveries made as a result of traditional medicine. And there will be more, but it may not necessarily be to treat an overarching disease like a specific type of cancer, it may be to treat related diseases or conditions, such as inflammation.

Has the NPB ever collaborated with OCCAM on any projects?

We have been working with OCCAM ever since your inception. And at this moment we are working with materials obtained with OCCAM through a Cooperative Agreement with Harvard University and a university in China (5U19CA128534-04) that is looking at Traditional Chinese Medicine (TCM) medicinal plants from China. This was a great agreement and it looked at 160 -200 TCM plants that were collected as they should be, following the *Inner Canon of Emperor Huangdi (Huang Di Nei Jing)*. They were collected as described and control samples taken from elsewhere (the same plant, different areas). So with help from staff at OCCAM we were able to get those materials sent to us here at the NPB. We ended up with just under a metric ton of dried plant materials, all identified taxonomically, with the correct geographical sites. What we've done now is to take a small portion of each one, treat it the way we normally do and have it tested in our 60 cell line screen, and we have seen some interesting activity. The next step is to have OCCAM scientists who are fluent in Mandarin go back and translate the traditional methodologies used for the preparation of this material in China. Our samples will be treated according to those methodologies. The traditional preparations may have been putting the plants in warm water, alkaline, acidic, or boiling water, even cold water, whatever the technique is. We will then assay those in the 60 cell line screen and this will give us an idea of whether the active potential of these samples comes from treating it one way or another. It will be interesting to see if there are similar results from the same plants taken from different areas. It

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will be the first time that I am aware of that there has been a thorough independent, blinded study of the medicinal plants.

What is one of the biggest challenges/issues in working with natural products?

One of the main issues is being certain of what you are working with. You'll find that there are groups that claim American ginseng is good for a variety of things, and there very well may be some evidence there, but the fact is what they call American ginseng has half a dozen botanical variations. This comes back to my original comments: that you've got to be certain of what you have before you test it. It can be hard to determine what herbs and plants have been grown and tested under uncontrolled conditions, there may be info worth looking at, but trying to get that from the massive numbers of people claiming everything can be hard work.

Back to TCM, it has a 3000 year history and its components have some validity, because they have been tested for centuries, on everyone from the Emperors to farmers. However, you have to be sure what you are taking today is what was originally described. Modern day CAM practitioners and researchers are building upon 3000 years of information, although the information has been a selective interpretation, without going back and looking at the original sources. Hence the reason for doing the controls in our TCM experiments. We have to use materials that are from China, gathered, and prepared in the traditional methods.

One of the problems in the case of traditional medicines in cancer is there is no defined traditional medicinal use in cancers in the history. I use a very simple methodology, say we've got this material and the traditional literature says it works against this cancer. My first thought is always is it a cancer that can be recognized without a lab or surgery? Because in ancient times, there were no x-rays or sophisticated screening tests. Skin cancer you can see, some breast cancers may be detected without invasive screening techniques, but for the major cancers that have the highest mortality (lung, colon, pancreas, and prostate) there is no way — short of invasive analysis — to identify these cancer types. So when someone comes to me saying they have a traditional remedy that is used to treat pancreatic cancer, I am skeptical. The problem is that you can't tell if the person really had cancer back in traditional times. So it is hard to take anecdotal or written histories of a TCM traditional drug that has been used for thousands of years and say it's been used to treat cancer, because how did they know these people had cancer?

It comes down to a simple truth and I know that OCCAM and NCI in general believe in this too. I want to see evidence, scientific proof of the validity of the response, which means you have to know what you started with, and this is how good experimentation with natural products begins.

Do you have any advice to new investigators starting out in the natural products field?

My advice to them would be to go in with their eyes wide open. And to ask a very simple question, in the case of the disease that a natural product they are studying is purported to help: Is this a disease that can be diagnosed in the absence of a lab test or invasive techniques? If it can be, then start looking at it.

Also, in terms of what to get training in, you can get an awful lot of info from botany, but you need chemistry and pharmacology. This doesn't mean to say you need a Ph.D. in each subject, but you need to specialize in one of them and have knowledge of the others. If you understand the botany, you know botanically it's the correct material, that's the first step. Pharmacologically, is there an effect? Chemically, how stable is it? What is it, what is in the mixtures? These are the questions you will deal with in your career in natural products whether investigating single agents as I do, or in the more complex mixtures as OCCAM, the NIH Office of Dietary Supplements and the National Center for Complementary and Alternative Medicine do. ❧

Contact Information

Office of Cancer Complementary and Alternative Medicine

9609 Medical Center Drive
Bethesda, Maryland 20892
E-mail: **ncioccam-r@mail.nih.gov**
http://cam.cancer.gov

The Big Impact of Small Nutrients: The Role of Micronutrients in Cancer Prevention Highlighted in Annual Lecture

On March 19, 2013, Dr. Susan Taylor Mayne (Yale University) gave this year's *Stars in Nutrition & Cancer* lecture, presenting research about micronutrients and cancer prevention. *Stars in Nutrition & Cancer* is a lecture series hosted by the Nutritional Science Research Group in the Division of Cancer Prevention. These lectures feature outstanding scientists or "stars" discussing the latest research about the role of nutrition in cancer prevention and progression.

Dr. Mayne began her talk with an overview of clinical trials that have helped frame our current understanding of micronutrients and cancer. Micronutrients are substances that our bodies require in small amounts and are essential for good health. Vitamins and minerals are examples of micronutrients. Studies have suggested that eating foods rich in these nutrients (particularly fruits and vegetables) is associated with a decreased risk of developing cancer. For example, a review published in 2012 suggested that individuals with high levels of carotenoids in their blood (such as beta-carotene found in carrots and lycopene found in tomatoes) have a lower risk of developing breast cancer. Earlier animal studies of cancer indicated that supplementation may provide similar benefits as eating antioxidant-rich foods, and that set the stage for human trials.

One of the first human studies examining micronutrient supplementation and cancer risk was conducted in a micronutrient-deficient population in China. The results, published in 1993, showed that participants who took the study supplement (a combination of beta-carotene, vitamin E, and selenium) had a reduction in cancer deaths. A follow-up study published in 2010 showed that benefits remained, even 10 years after participants stopped taking the supplements. However, studies published in the mid-1990s found that beta-carotene supplementation was associated with an increase in cancer deaths. Further analysis of those results revealed that the supplement doses used may have been too high for many of the study participants and that supplementation was beneficial in people who were deficient in a specific nutrient. Dr. Mayne noted that this pattern is not exclusive to beta-carotene — similar findings have been shown for selenium and folic acid as well.

Results of studies investigating the relationship between micronutrient status and chronic diseases, such as cancer, consistently show a U-shaped curve: disease risk decreases as nutrient levels increase, although at a certain point, at higher levels of nutrient status, disease risk starts to go back up. These findings indicate that nutrient supplementation may not help individuals who have high levels of a certain nutrient, rather, the greatest benefits may occur for those on the lower end of the curve.

Dr. Mayne then spoke about new technology being used in her lab that quickly determines an individual's micronutrient status and can help identify individuals who have low levels of specific micronutrients. Resonance Ramen Spectroscopy (RRS) uses a small laser to deliver light to an area of the skin. Carotenoids in the skin vibrate when they are hit with a specific wavelength of light and those vibrations indicate carotenoid levels in the skin. Carotenoids accumulate in the palm of the hand and that is where the light is directed.

Dr. Mayne described how this biomarker was developed. Accuracy of this method was determined by comparing the RRS information to data obtained from skin biopsies. In that study, hips were scanned and small skin samples were taken for analysis. Feasibility studies were

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also conducted, including one in preschool children. Children from a low-income area were scanned with the RRS and carotenoid levels were compared with fruit and vegetable intake and preference (this information was provided by parents). The data obtained from the RRS scan was significantly correlated with the intake and preference measures. Dr. Mayne also presented unpublished data that showed that the carotenoid levels obtained from RRS responded to a dietary intervention — for example, levels increased when subjects ate carotenoid-rich foods and decreased when subjects ate a low-carotenoid diet.

There is a lot of evidence that micronutrient status may affect cancer risk, but Dr. Mayne suggests that future clinical trials using supplements should target populations that have a low nutrient status, as those individuals may get the most benefit out of supplementation. Using technology, such as the new biomarker she described, may help to identify those individuals.

For more information or to view past lectures, visit ***http://prevention.cancer.gov/programs-resources/groups/ns/events/stars***.

Probiotics, Prebiotics, and Synbiotics, Oh My

The Nutritional Science Research Group at the Division of Cancer Prevention hosted a webinar titled "Exploring the Microbiome of Cancer Prevention: A Closer Look at Probiotics, Prebiotics, and Synbiotics." The microbiome is made up of the microorganisms, including bacteria and fungi, which we carry inside and outside of our bodies. These microorganisms do not normally cause disease, but work in harmony with our bodies and are involved in many processes that contribute to our state of health. Recent studies have suggested that microbes in our gut may be involved in cancer prevention and the webinar highlighted work in that area.

The first presenter was Dr. M. Andrea Azcarate-Peril, Ph.D., RD (University of North Carolina-Chapel Hill), who spoke about the role of probiotics in preventing and treating colorectal cancer (CRC). Dr. Azcarate-Peril defined probiotics as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host." While the concept of probiotics has been around since the early 1900s, the tools and technologies for microbiome analysis have been recently developed. Dr. Azcarate-Peril observed that "next generation sequencing approaches have permitted the analysis of the structure of microbial communities and a number of different types of analysis."

A few studies have compared the microbiota of healthy patients with CRC patients. Dr. Azcarate-Peril noted there was only one study that compared the microbiota in healthy intestinal mucosa with mucosa from adenomas (a pre-cancerous growth in the colon). "We showed that changes in the tumor microbiota started really early in the progression to carcinoma," she said. Studies have indicated that intestinal microbiota may produce toxic bacterial metabolites that can lead to mutations and CRC. Dr. Azcarate-Peril described a recent study that showed that CRC patients had higher levels of a certain intestinal microorganism than did healthy controls, suggesting that it may be possible to create tailored probiotics to help prevent cancer. However, Dr. Azcarate-Peril mentioned that there "is no general consensus on the role of probiotics in CRC protection." Some reasons for lack of agreement include different methods of preparing probiotics, and using various blends and doses of probiotics.

"Prebiotics and Their Role in Cancer Prevention" was the title of the presentation by Joanne L. Slavin, Ph.D., RD (University of Minnesota). She began her talk by describing the gut as a functional ecosystem and mentioned that, in addition to diet, some things that can change the make-up of microbes in the gut include stress and living conditions. Prebiotics are selectively fermented ingredients that improve health by changing the composition and/or activity of microorganisms in the colon. Examples of prebiotics include a class of dietary fibers known as fructans. Fructans are found in a number of foods such as artichokes, wheat, onions, and chickpeas. Dr. Slavin observed that in the United States, wheat is the main source of fructans.

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Prebiotics are also found in many fiber-fortified foods. According to a recent review, prebiotic administration was not associated with changes in CRC biomarkers. However, Dr. Slavin stated that "one of the conclusions from the study is while we cannot agree on what is a prebiotic and what are the best methods to measure microbiota, progress in this field is going to be difficult."

Ian Rowland, Ph.D., RD (University of Reading, United Kingdom) spoke about synbiotics. Synbiotics are mixtures of pre- and probiotics that provide benefits to the host by improving survival of microorganisms in the gut by stimulating their growth and/or metabolism. Dr. Rowland said, "In other words, it's a matter of combining pre- and probiotics with the aim of getting a benefit that is greater than from pre- and probiotics alone."

There is evidence that synbiotics may play a role in preventing cancer or slowing disease progression. Dr. Rowland described results of a study that investigated the effects of synbiotics on a rat model of CRC. In that study, rats were fed diets supplemented with a probiotic, a prebiotic, or a combination of the two. Compared to rats that were fed a normal diet, the probiotic- and prebiotic-fed animals exhibited a lower number of aberrant crypt foci (early changes in the colon which may lead to CRC) in the colon. The animals that received the synbiotic supplement showed the least amount of pre-cancerous changes in the colon. In a clinical trial, patients at high-risk or with a history of CRC received a synbiotic supplement or placebo for 12 weeks. Biopsies and stool samples were assessed for biomarkers of CRC risk. Results indicated there was less DNA damage and cell proliferation in biopsies from subjects who received synbiotics compared to subjects taking the placebo, suggesting synbiotics may have a protective effect. The exact mechanisms underlying these effects are not known, but animal studies have suggested that synbiotics may increase levels of protective enzymes in the gut and may increase programmed cell death (apoptosis) in aberrant crypt foci.

This webinar was part of the "Frontiers in Nutrition and Cancer Prevention: Online CME Series." For more information about this series and to view archived webinars, visit ***http://prevention.cancer.gov/programs-resources/groups/ns/webinars/.***

Funding Opportunities

Examination of Survivorship Care Planning Efficacy and Impact (R01 and R21)

Given the added burden of the long-term or late side effects that cancer survivors may face throughout their lifetimes, the importance of care planning is essential. In 2005, The Institute of Medicine recommended that all patients completing primary cancer treatment be provided with a comprehensive treatment summary and a survivorship care plan. This long-term care plan may also include complementary and alternative medicine (CAM). According to analyses of national surveys, cancer survivors are more likely to use CAM compared with the general population. CAM use may be a large part of the long-term care cancer survivors face throughout their life.

To address the issues of long-term survivorship care planning, NCI has announced new R01 and R21 Funding Opportunity Announcements (FOA): "Examination of Survivorship Care Planning Efficacy and Impact." This FOA seeks applications that are expected to assess whether care planning renders added benefits in terms of patient morbidity, adherence to follow-up guidelines and self-management of late effects, as well as appropriate utilization of follow-up care. Studies relating to how successful care planning initiatives are implemented in a variety of healthcare and community practice settings are also encouraged, including family and caregiver outcomes in addition to survivor outcomes.

Research areas of interest include, but are not limited, to:

- What is the impact of survivorship care planning on cancer survivors' post-treatment psychosocial and physiologic morbidity?

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- What is the effect of survivorship care planning on adherence to screening recommendations, preventive behaviors, and self-management of late and long-term effects of cancer?
- Does provider participation in the development of care plans and the care planning process affect implementation of care planning?

For more information about this FOA please visit: ***http://grants.nih.gov/grants/guide/pa-files/PA-12-275.html.***

Questions related to this funding announcement can be directed to Carly Parry, Ph.D., MSW (301-435-4540, carla.parry@nih.gov).

Funding Opportunity: Translational Research at the Aging/Cancer Interface (TRACI) (R01)

Age is a major risk factor for cancer. As life expectancy in the United States continues to rise, there will be a larger number of individuals reaching older age and the public health burden of cancer in the elderly will increase. The National Cancer Institute is co-sponsoring a funding opportunity designed to improve translational research relevant to the care of older cancer patients.

Examples of research areas include, but are not limited to:

- Developing innovative translational interventions designed to increase efficacy and/or tolerance of treatment
- Exploring ways in which geriatric syndromes (such as frailty and unexplained anemia) and general health problems (for example, nutritional status) affect treatment outcomes
- Investigating interventions to help manage post-therapy health issues in elderly cancer survivors

Go to ***http://grants.nih.gov/grants/guide/pa-files/PA-12-136.html*** for a detailed description of this funding opportunity.

For questions related to this funding announcement, please contact T. Kevin Howcroft, PhD (301-496-7815, howcrofk@mail.nih.gov).

Funding Opportunity Announcement: Mechanisms, Models, Measurement, & Management in Pain Research (R01, R03, R21)

Pain is the most common reason people visit the doctor and costs this country over $500-650 billion each year in health care and lost productivity. Pain has a profound impact on quality of life and can negatively affect sleeping, cognition, mobility, and overall functional status. It is also a common side effect of cancer and cancer treatment and can persist in cancer survivors after treatment ends.

The National Institutes of Health is seeking applications for all aspects of pain research. Topic areas include, but are not limited to:

- Epidemiology of pain
- Biobehavioral pain
- Pain management, including non-pharmacological interventions
- Molecular and cellular mechanisms of pain

For more information about this funding opportunity, go to ***http://grants.nih.gov/grants/guide/pa-files/PA-13-118.html*** (R01), ***http://grants.nih.gov/grants/guide/pa-files/PA-13-117.html*** (R03), or ***http://grants.nih.gov/grants/guide/pa-files/PA-13-119.html*** (R21).

For specific questions regarding this funding opportunity, please contact Partap S. Khalsa, DC, PhD, DABCO (301-594-3462, khalsap@mail.nih.gov).

A Plethora of Research Resources For You

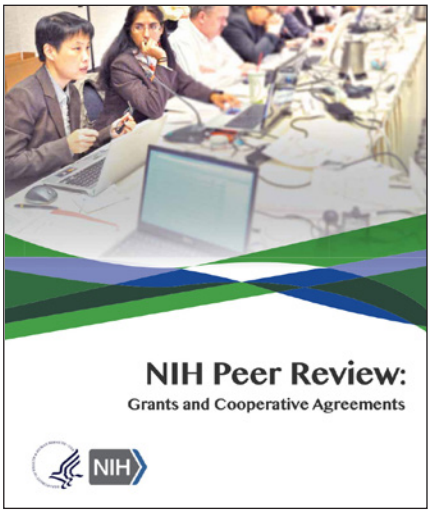
The Office of Extramural Research has announced several important updates of interest to both new and seasoned investigators

NIH Regional Seminar on Program Funding and Grants Administration

The NIH is holding one regional seminar this year on program funding and grants administration from June 26-28, 2013, in Baltimore, MD. The seminar is intended to help clarify the application and review process, explain Federal regulations and policies, and highlight current areas of special interest or concern to grantees. More information about the seminar and a link for registration is available on the following site: ***http://grants.nih.gov/grants/seminars.htm.***

Unclear about the NIH Peer Review process?

The peer review process can be hard to understand, but it doesn't have to be. This concise PDF outlines several aspects of the NIH review process, as well as the Center for Scientific Review and the individuals that oversee it, and the rules that apply to reviews such as transparency, confidentiality, and impartiality. Important links and contact information are also provided. View the document online: ***http://grants.nih.gov/grants/PeerReview22713webv2.pdf.***



Why read, when you can listen

The NIH Office of Extramural Research (OER) has recently released two new podcasts as part of their "All About Grants" series. Designed for investigators, fellows, students, research administrators, and others, the podcasts provide brief glimpses and insights into the application and awards process.

The latest podcasts are parts 3 & 4 of a four-part series called "Who Should I Contact at NIH?"

- Who Should I Contact at NIH? – Part 3 of 4: Application Submission through Review (**MP3** and **transcript**)
- Who Should I Contact at NIH? – Part 4 of 4: Life After Peer Review (**MP3** and **transcript**)

The entire list of OER podcasts can be found at the All About Grants website: ***http://grants.nih.gov/podcasts/All_About_Grants/.***

Giving credit where credit is due

An important part of the NIH grants policy is a stipulation concerning how grantees should acknowledge NIH in their publications. In a nutshell, all grantee publications including research publications, press releases, and other publications or documents about research that is funded by NIH, must include a specific acknowledgment of NIH grant support.

The following is an example of such a statement: "Research reported in this [publication/press release] was supported by [name of the Institute(s), Center, or other NIH

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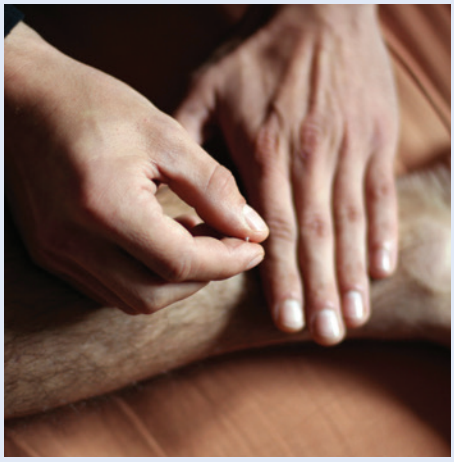
offices] of the National Institutes of Health under award number [specific NIH grant number(s) in this format: R01GM987654]."

The NIH created a webpage specific to this issue called "Communicating and Acknowledging Federal Funding" and contains information for researchers and Public Information Officers. For more examples and tips visit the website: ***http://grants.nih.gov/grants/acknow.htm.***

Research Highlights

A Mixed Bag When it Comes to Acupuncture Randomized Control Trials Reporting

Acupuncture is a relatively safe complementary and alternative medicine modality and has been used for centuries. Acupuncture, as a part of cancer care, is increasing in availability at cancer centers. A recent systematic review* by M. Kay Garcia Dr.P.H., M.S.N., LAc of the University of Texas MD Anderson Cancer Center, and colleagues, identified prospective randomized clinical trials (RCT) investigating the use of acupuncture for symptom management among patients with cancer, along with evaluating each study's inherent risk of bias. The authors also provided recommendations for physicians and researchers regarding the use and study of acupuncture. This research was supported in part by a cooperative agreement and grant from the National Cancer Institute**.



Prospective RCTs using acupuncture with needle insertion for symptom management in patients with cancer were screened for inclusion in the systematic review. Studies using therapies similar to acupuncture, but that did not involve needle insertion (such as acupressure or laser acupuncture) or trials that compared only two types of acupuncture to each other were excluded. Forty-one studies were deemed acceptable for inclusion; four of the studies were written in Chinese and were read by study authors fluent in the language. Some studies included treatment for more than one symptom.

Risk of bias (ROB) in the studies was determined according to the Cochrane ROB criteria, which included criterion relating to missing data, lack of blinding of participants, and small study sample size, among others. Meeting the criterion for high risk in any of these categories caused a study to be rated as having high ROB, and alternatively, meeting criterion for low risk in all categories allowed studies to be rated as low ROB. Issues with ROB appeared throughout most of the studies. Of the 41 studies included in the review, only one trial was categorized as having low ROB (positive trial). Of the remaining trials, eight had unclear ROB (four positive, three negative, one unclear), and 33 had high ROB (19 positive, 11 negative, 3 both positive and negative outcomes). Issues with small sample size were also found throughout, with 39% of trials having had fewer than 60 participants.

The analysis of studies showed that the majority of symptoms treated with acupuncture included pain, nausea, postoperative ileus, and xerostomia (dry mouth). Other symptoms studied included hot flashes, fatigue, mood disturbances, and sleep disturbance. Pain was the most common symptom treated, and was represented by 11 RCTs. Problems with high ROB included lack of blinding of patients and small sample size. One trial tested acupuncture in a small group for the management of aromatase-inhibitor-associated joint

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* Garcia, M.K., McQuade, J., Haddad, R., Patel, S., Lee, R., Yang, P., …& Cohen, L. (2013). Systematic review of acupuncture in cancer care: a synthesis of the evidence. *Journal of Clinical Oncology, 31*(7), 952-60.

** Project numbers: 5 U19 CA121503; P30CA016672

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pain, with initial positive results of reduced joint symptoms and improved functional ability. The subsequent blinded, sham-control trials showed that worst pain scores were significantly lower in the true acupuncture group.

Nausea and vomiting are common side effects associated with cancer treatment. A three- arm study (n=104) to help control myeloablative chemotherapy-induced emesis (vomiting) among women with breast cancer was assessed by the authors. All patients were receiving the same chemotherapy regimen and antiemetic drugs. The three arms of the study included: electroacupuncture at sites indicated for nausea and emesis control; minimal needling away from emesis acupuncture sites; and antiemetic medication only. This trial had low ROB, and showed that at the end of the 5-day study period, the electroacupuncture group had significantly fewer episodes of emesis versus minimal needling. Also the minimal needling group had significantly fewer episodes of emesis than the medication-alone group.

Postoperative ileus, or the inhibition of muscular contractions in the wall of the intestine responsible for pushing along the gastrointestinal (GI) tract contents, which can cause abdominal distention, nausea, vomiting, and diet intolerance, can be a common side effect of many surgical operations. Eight RCTs investigating acupuncture and postoperative ileus met inclusion criteria, though six had high ROB. One study in patients with intestinal tumors, randomizing 35 participants to acupuncture and 35 to usual care, did show a positive effect. No studies of acupuncture to treat diarrhea, constipation, or loss of appetite met the inclusion criteria.

According to the authors, the strongest evidence for use of acupuncture was for the control of nausea and vomiting. At least two studies provided positive results with low or unclear ROB.

High ROB due to a lack of complete reporting was an issue across studies, and given the strong placebo effect associated with acupuncture, the authors noted it is important to know more about the therapeutic ritual, who provided the treatments, and if different practitioners were used in different groups. These details would lead to a better understanding of any placebo component in the patient-practitioner relationship. Authors noted that "studies in which a single unblinded acupuncturist provides all treatments may be at risk of introducing bias, especially if one individual provides treatment to both active and inactive groups in a sham-controlled trial." The authors continued that "regardless of the specific molecular basis of the effects, acupuncture for nausea/vomiting is a safe and inexpensive treatment that can relieve considerable suffering and may be an especially important option for patients who do not get good symptom control with pharmaceuticals."

However, the authors cautioned that "for other symptoms such as pain, hot flashes, xerostomia, anxiety, or fatigue, efficacy is undetermined largely owing to high ROB among studies."

According to this review, future acupuncture trials should focus on standardizing comparison groups and treatment methods, ensuring that at least single blinding is used, use multiple acupuncturists, identify biologic mechanisms, and conduct trials with adequate statistical power.

NCI Researchers Presented *in vitro* and *in vivo* Research at the American Association of Cancer Research 2013 Annual Meeting

As part of an intramural research collaboration with Guang An Men Hospital, China Academy of Chinese Medical Sciences in Beijing, China, the NCI Laboratory of Cancer Prevention within the Center for Cancer Research is currently hosting Guang An Men visiting fellow, Weidong Li, M.D., Ph.D. Dr. Li, supported in part by OCCAM, is working with NCI staff scientist Matthew R. Young, Ph.D. and scientist emeritus and former Laboratory Chief, Nancy H. Colburn, Ph.D. on research designed to explore the potential for certain compounds used in Traditional Chinese Medicine (TCM) to prevent colon cancer and investigate their related mechanisms.

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"OCCAM is interested in traditional medical systems, especially understanding and verifying drug efficacy against cancer," said Libin Jia, M.D., scientific program manager at OCCAM managing this project. "This study is the fourth collaboration project between Guang An Men Hospital and NCI on the research of Chinese medicine and cancer. The other projects looked at several TCM products such as **Sheng Qi Formula** and **Kushen Injection**, but this is the first one on cancer prevention."

Dr. Li's work, which was accepted for a poster presentation at the 2013 AACR annual meeting, consisted of both *in vitro* colorectal cancer cell lines and *in vivo* mouse studies testing berberine. Berberine is an isoquinoline alkaloid isolated from plants. It can be found in plants such as the Oregon grape, barberry, goldenseal, Chinese goldthread and others. It has been used for many purposes from traditionally dying fabric to use as an antibiotic. It has also shown anti-diabetic, anti-inflammatory, and anti-tumor effects. Berberine is often used clinically in China as one of the traditional drug components for cancer patients for symptom management, such as diarrhea control.

Three human colorectal cancer cell lines were treated with berberine to evaluate inhibitory effects on cell growth. Dr. Li and colleagues tested berberine on the AMP-activated protein kinase, or AMPK. AMPK is a cellular energy sensor that is a potential therapeutic target for cancer. Previous research by others has shown that berberine displays beneficial effects in the treatment of diabetes and obesity in part by stimulating AMPK activity. Dr. Li's work tested whether berberine, when used to treat colon cancer, is also linked to the activation of the AMPK pathway.

The three human colorectal cancer cell lines were treated with escalating doses of berberine and cell growth was monitored. It was found that berberine inhibited the growth of the three cell lines and activated AMPK in a dose-dependent manner. The experiment also showed that berberine down-regulated other colorectal cancer targets related to cell growth, such as mTOR (mammalian target of rapamycin, which regulates cell growth, proliferation, and other processes).

An *in vivo* mouse model of colitis-induced colon cancer was used to explore the effects of berberine against colon cancer. Mice were divided into two groups and treated with either berberine or water for 10 weeks. Results showed that berberine-treated mice experienced a significant reduction in the number of tumors present compared to control mice (60%). The researchers also compared the sizes of tumors that were present in the animals at the end of the experiment. Berberine-treated mice did not have any tumors that were larger than 4mm. Compared to control animals, berberine-treated mice had 94% less tumors between 2-4mm and 49% less tumors that were smaller than 2mm.

Dr. Li and colleagues noted that their data suggests that berberine suppresses colon cancer cell proliferation via inhibition of the mTOR protein through activation of AMPK. Interestingly, the antidiabetic drug Metformin has shown anticancer activity via similar mechanisms.

"To elucidate the berberine mechanism of action on the molecular level is important. We are very impressed to see the progress within a short time from this collaborative research project by Drs. Li, Young, and Colburn on TCM cancer prevention," praised Dr. Jia.

Dr. Li and colleagues noted that berberine may become a promising candidate for chemoprevention, and possibly treatment, of colon cancer but further studies in humans are needed. "Clinical studies in humans would most likely include using berberine in combination with another conventional cancer therapy, like chemotherapy. This may be a possibility for the future," noted Dr. Li.

NCI's CAM FY 2011 Annual Report Released

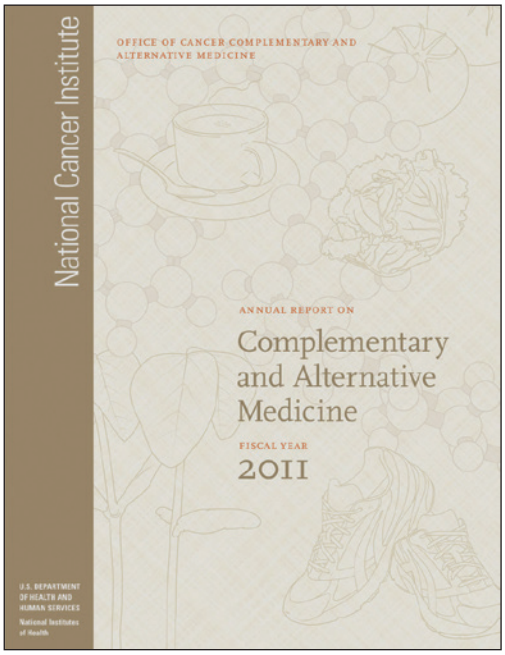
The National Cancer Institute's Office of Cancer Complementary and Alternative Medicine (OCCAM) announces the release of the seventh NCI CAM Annual Report. NCI's *Annual Report on Complementary and Alternative Medicine: Fiscal Year 2011* provides an overview of NCI-supported CAM research and highlights research studies, projects, and grants that are supported by NCI's extramural and intramural grant funding divisions.

Highlights of articles in the report include:

- **Finding a Healthy Dietary Ratio for Prostate Cancer Prevention**
- **High-Fat Diet May Enhance Cancer Patients' Response to Treatments**
- **Impact of Exercise on Ovarian Cancer Prognosis Studied**
- **Acupuncture Studied to Prevent Radiation-Induced Chronic Dry MouthPatients**

NCI's Annual Report on Complementary and Alternative Medicine: Fiscal Year 2011 is available for viewing on the OCCAM Website at ***http://www.cancer.gov/cam/cam_annual_report_fy10.pdf.***

Past reports are also available for viewing at ***http://www.cancer.gov/cam/cam_annual_report.html.***



Focused CAM Information You Can Use

OCCAM recently launched a new initiative to help patients and health care professionals receive targeted cancer complementary and alternative medicine (CAM) information. *CAM Highlights from NCI* is an email and web page that includes information about a specific issue related to cancer care and CAM. Research is presented in a concise and helpful format for patients, health care providers, and the general public.

The first issue, *Fatigue and CAM*, focused on the often debilitating side effect of cancer-related fatigue. Several CAM modalities have been researched in an attempt to alleviate this condition, especially in cases where pharmacological treatments do not help or are undesirable.

Visit the **CAM Highlights at NCI page** to see all of the latest targeted CAM highlights.

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://www.cancer.gov/cam/news_listserv.html.***

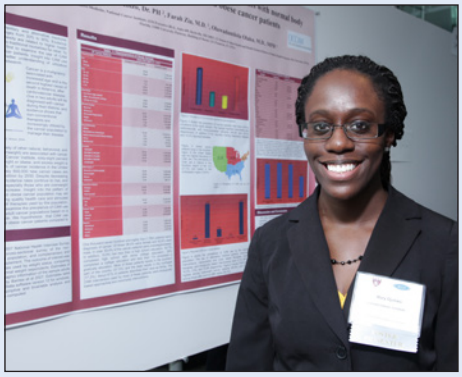
OCCAM Fellow Researches Weight Status and CAM Use

The use of complementary and alternative medicine (CAM) can be influenced by many factors including a person's age, economic status, and health status. Mary Ojukwu, B.S., a Cancer Research Training Award (CRTA) fellow at OCCAM, has decided to look at another factor that could be related to CAM use: a person's Body Mass Index (BMI). BMI is an approximation of body fat based on height and weight. A BMI of 25–29.9 indicates a person is overweight; a BMI of greater than 30 indicates obesity.

Ms. Ojukwu is delving into the wealth of knowledge available to researchers from the National Health Interview Survey (NHIS), a population-based survey of U.S. households completed in 2007. The 2007 NHIS is the latest survey to date that contains a special supplement specifically related to CAM. The outcome of interest for Ms. Ojukwu was the frequency of use of CAM modalities by those survey respondents who indicated they had a prior diagnosis of cancer. The frequencies were determined for groups of individuals based on weight status, comparing overweight, obese, and normal weight respondents. Ms. Ojukwu and coauthors, Drs. Farah Zia and Oluwadamilola Olaku from OCCAM and Dr. Justice Mbizo of the University of West Florida, state that the purpose of this research is "to examine the prevalence of CAM use in overweight and obese U.S. adult cancer populations based on a nationally representative sample."

Prior literature states that the prevalence of CAM use is low in the overweight and obese population and high in the cancer population. For example, one study found that adults with obesity were less likely to use most individual CAM modalities compared to normal weight adults and another study found that cancer survivors used more CAM compared to the general population after controlling for other factors. Furthermore, cancer survivors used CAM at levels similar to those with chronic symptomatic illness. There has been no study to date on a sample population that reveals the prevalence and pattern of the use of CAM in cancer patients who are overweight. The literature suggests that chronic disease is a major determinant for CAM use. By virtue of the fact that there is a higher likelihood of comorbid conditions, like diabetes, among the overweight and obese cancer population, Ms. Ojukwu hypothesized that CAM use will be higher in overweight and obese cancer patients compared to normal weight cancer patients in order to improve symptoms associated with their cancer as well as their comorbid disease.

Ms. Ojukwu has presented her work at the New England Science Symposium at Harvard Medical School in Boston, MA. Recently, she was accepted to present her work as a poster at the Academy Health Annual Research Meeting in Baltimore, MD on June 23-25, 2013.



Mary Ojukwu presents her research.

Of the 1,785 patients that had a diagnosis of cancer, 59.4% were overweight or obese. Of the total cancer patient population, 89% stated they used CAM, and the CAM interventions used by most of these patients were predominantly biologically-based approaches (70.5%) and mind-body interventions (69%). Biologically-based approaches include dietary supplements such as herbal extracts and vitamins and mind-body interventions include meditation, hypnosis, cognitive behavioral therapy, support groups, and relaxation therapy. Those with a BMI that labeled them as overweight or obese used CAM at a slightly higher percentage than the total sample at 92.9% and 90%, respectively. Eighty-eight percent of underweight and normal weight respondents used CAM and only 58% of respondents whose BMI

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could not be determined used CAM. The association between overweight BMI status and CAM use was significant based on a multivariate logistic regression model. Interestingly, Ms. Ojukwu looked at other non-BMI variables of the data and noted, "In contrast to previous findings in the literature, income, education, and race were not significant predictors of CAM use within the cancer population."

While not related to CAM use, it is telling that many cancer patients did report comorbidities, which may affect their use of CAM. The highest reported comorbidities were cardiovascular and musculoskeletal ailments (44% and 43% respectively). In addition, 17% of patients reported having respiratory disease and 14% reported diabetes.

"Based on our findings, CAM use was highly prevalent among cancer patients regardless of BMI status. The association was significant only for the overweight cancer patients, thus, due to our findings, our hypothesis was not supported. We concluded that CAM use is high among the cancer population, and prospective clinical studies are needed to evaluate the efficacy and safety of these non-conventional interventions, with a focus on the biologically based therapies, for the well-being of the cancer population within the United States," Ms. Ojukwu noted. She added, "Future directions of this research study include looking at the data again more closely with different variables such as physical activity status and causal reasons for CAM use. This will provide a better characterization of the relationship between CAM use and weight status within the U.S. adult cancer population.

For inquiries on cancer and CAM, please contact
1-800-4-CANCER (1-800-422-6237)

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