DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH
NATIONAL CENTER FOR COMPLEMENTARY
AND ALTERNATIVE MEDICINE

NATIONAL ADVISORY COUNCIL FOR COMPLEMENTARY AND ALTERNATIVE MEDICINE
MINUTES OF THE SPECIAL CONFERENCE CALL MEETING
April 4, 2005

NACCAM Members via Conference call
Dr. Carlo Calabrese, Portland, OR
Dr. Kristina Collins, McLean, VA
Dr. Deborah J. Cotton, West Roxbury, MA
Dr. Jeanette Ezzo, Takoma Park, MD
Dr. Robert E. Fullilove, New York, NY
Dr. Murray Goldstein, Washington, DC
Dr. Leslie Hillis, Dallas, TX
Dr. Tieraona Low Dog, Tucson, AR
Dr. Joel Pickar, Davenport, IA
Dr. Stefanie N. Vogel, Baltimore, MD
Dr. Larry Walker, University, MS
Dr. Benjamin Yang, San Francisco, CA

NACCAM Members Absent
Dr. Zang-Hee Cho, Irvine, CA
Dr. Gerald Cross, Washington, DC
Dr. Jonathan Davidson, Durham, NC
Dr. Michael Irwin, Los Angeles, CA
Dr. Alan Leshner, Washington, DC
Dr. Bala Manyam, Temple, TX
COL Richard Niemtzow, Clinton, MD
Dr. Barbara Timmermann, Tucson, AR

NIH Staff Present
National Center for Complementary and Alternative Medicine

Dr. Josh Berman
Dr. Margaret Chesney, Deputy Director
Ms. Linda Engel
Ms. Carol Fitzpatrick
Ms. Camille Hoover
Dr. Jane Kinsel
Dr. Qi-Ying Liu
Ms. Linda Rich
Dr. Stephen Straus, Director
Ms. Chris Thomsen
Mr. George Tucker

Members of the Public
Ms. Karen Dobin
Mr. Michael Dyer
Ms. Suzanne Niemeyer
Ms. Michelle Rodrigues
Mr. Simon Weavers

I. Open Session—Call to Order

The National Advisory Council for Complementary and Alternative Medicine (NACCAM) special conference call meeting convened at 12:30 p.m. Dr. Jane F. Kinsel, NACCAM Executive Secretary, called the meeting to order. She noted that the special Council meeting was convened in open session in accordance with all applicable regulations. She reviewed the list of documents emailed to Council members before the meeting: meeting agenda, roster of participants, and concept sheet for the initiative that was the subject of this special Council meeting. Dr. Kinsel reminded the participants of the upcoming 2005 Council meetings: June 3 and September 9.

II. Concept of Milk Thistle Request for Application

Dr. Stephen E. Straus, Director, National Center for Complementary and Alternative Medicine (NCCAM), thanked the participants. He reported that Council was meeting via teleconference rather than waiting for the next full Council meeting to expedite the review of the concept and release of the proposed Request for Application (RFA).

Dr. Straus asked Dr. Margaret Chesney, Deputy Director, NCCAM, to provide background information for the initiative. She noted that testing milk thistle ("silymarin"), a dietary supplement having shown promise in combating the effects of chronic liver disease, is a priority for NCCAM. The lack of effective conventional treatments has led many patients with hepatitis C and other forms of chronic liver disease to use silymarin

NCCAM has invested in the development of research-grade silymarin in collaboration with the National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) through the Small Business Innovation Research (SBIR) program. In addition, NCCAM issued a Notice of Opportunity in March 2005 soliciting proposals from companies to provide silymarin for studies of the treatment of liver disorders. The concept to be discussed in this special session of Council is for phase I/II clinical trials that will use the silymarin product acquired via the March 2005 solicitation. Dr. Chesney turned the discussion over to Dr. Qi-Ying Liu, Program Officer, Division of Extramural Activities, NCCAM.

Dr. Liu introduced the concept by noting that silymarin is a dietary supplement derived from the seeds of the milk thistle plant, which has been used for millennia to treat liver disease. Several recent review articles suggest that silymarin may have a role to play in the treatment of chronic hepatitis C and nonalcoholic steatohepatitis (NASH). Chronic

hepatitis C is the most common chronic liver disease in the United States and is estimated to affect 3 million people.

Hepatitis C can lead to cirrhosis, end-stage liver disease, and hepatocellular carcinoma. The recommended therapy for hepatitis C is the combination of pegylated interferon and ribavirin. However, many liver disease patients cannot tolerate this therapy—or have contraindications for the therapy, such as anemia—and there is an approximately 50-percent failure rate for certain hepatitis C strains. Silymarin might be beneficial as a complementary therapy for patients undergoing the currently recommended conventional therapy or as a rescue therapy for patients for whom conventional therapy has been unsuccessful. Silymarin could also be beneficial as an alternative treatment for patients with chronic hepatitis C who have failed to respond to, cannot tolerate, or have contraindications to pegylated interferon and ribavirin therapy

NASH – non-alcoholic steatohepatitis - is a common liver disease marked by the presence of fat and cellular injury (hepatitis) in the liver. It has become increasingly common with the prevalence of obesity and diabetes in the U.S. population and can lead to progressive hepatic fibrosis, cirrhosis, and end-stage liver disease. No conventional therapies for NASH have been shown to arrest or reverse the disease. Preliminary studies of insulin-sensitizing agents have yielded promising results, and these agents are now the subjects of several prospective, randomized trials. A reliable and safe means of ameliorating liver injury in NASH is an important goal for clinical research, and silymarin offers potential as a therapy. The development of more effective and better-tolerated therapies for chronic hepatitis C and NASH were areas of research listed as priorities in the *Trans-NIH Action Plan for Liver Disease Research*.

The proposed initiative will support the development of phase I/II clinical trials of silymarin. The objective of the initiative is to evaluate doses of silymarin for toxicity and efficacy against chronic hepatitis C and NASH. Efficacy and toxicity data at the optimum dose will help determine if a phase III trial is likely to be successful and, if so, the conditions under which it should be performed.

The silymarin product to be used under this initiative will be obtained under an in-kind exchange Clinical Trial Agreement (CTA). The collaborator will provide a silymarin product and product information dossier. In return, data from the NIH-funded phase I/II clinical trials generated by this initiative will be shared with the collaborator. In 2001, NCCAM awarded an SBIR grant for the development of a standardized milk thistle product. That project is almost complete and the grantee is expected to compete with other silymarin manufacturers to collaborate on silymarin clinical trials.

The proposed funding mechanism is a 4-year U01 award.

III. Council Discussion

Council members asked about basic science research on the effects of milk thistle and whether that is compatible with the pathophysiology mechanisms of chronic hepatitis C

and NASH. It was noted that the Agency for Healthcare Research and Quality (AHRQ) discussed mechanisms of milk thistle in its report, *Milk Thistle: Effects on Liver Disease and Cirrhosis and Clinical Adverse Effects*.

Dr. Josh Berman, Director, Office of Clinical and Regulatory Affairs, NCCAM, stated that researchers have not demonstrated an antiviral effect of milk thistle. He also noted that definitive preclinical work has not been done on the pathophysiology of hepatitis C and NASH.

Council asked for clarification on the patients to be enrolled in the phase I and II trials. Dr. Berman responded that discussions with NCCAM's partner, NIDDK, have led to suggestions of several potential clinical protocols that would be of interest:

- silymarin as an adjunct to standard therapy for naive hepatitis C patients;
- silymarin as a sole agent for patients who have failed standard hepatitis C therapy or are unable to use standard therapy; and
- silymarin as a sole agent for the treatment of NASH.

Responding to a question from Council on the Notice of Opportunity to supply silymarin for the NCCAM-NIDDK studies (solicitation DK-05-0130), Dr. Berman stated that the silymarin product has not yet been selected, and the receipt date for the product solicitation under the CTA will be on or around June 1, 2005. The specific choice of a product depends in part on those companies willing to adhere to requirements in the Notice of Opportunity, to follow FDA requirements, and to provide the product free of charge in exchange for clinical trial data.

Council noted that hepatitis C and NASH are different diseases and are not the typical indications for use of silymarin, traditionally used for alcohol or mushroom poisoning or chemical toxicity. Dr. Berman stated that studies of alcoholic hepatitis depend on limiting alcohol intake, which would be difficult to control in a clinical trial protocol. Moreover, a protocol for chemical toxicity, requiring that a suitable number of patients be located in a short time span, would be difficult to implement. Dr. Berman stated that reviews indicate that silymarin has been used in studies of hepatitis C and alcohol-related liver disease, (Post-meeting note: The major reviews of Jacobs [Am J Med 2002; 113:506], Flora [Amer J Gastroenterol 1998; 93:139], and Saller [Drugs 2001; 61:2035] were accessed. All these reviews include reports on viral hepatitis and other causes of liver disease. The most succinct summary of the clinical literature is that of randomized placebo-controlled trials in the table in Jacobs' article, which notes seven trials for alcoholic disease, three for viral disease, three for mixed disease, and 1 for drug-induced disease.)

It was stated that silymarin is an extract and a flavonoid of *Silybum marianum* (milk thistle*)*. The term is usually used to refer to the standardization of three flavonoids. Council noted that numerous products from different manufacturers are available and emphasized the importance of referring to the specific extract selected.

Dr. Straus stated that in November 1999, NCCAM and NIDDK held a workshop on complementary and alternative approaches to chronic liver diseases. Presentations at the workshop suggested that milk thistle was the most commonly used and most promising of these approaches. Dr. Straus noted that he has met with members of chronic liver disease patient groups (most notably chronic hepatitis C), who have expressed strong interest in milk thistle. NCCAM has funded several small studies of the basic mechanisms of milk thistle and some preliminary clinical trials.

The primary response to the 1999 workshop was to fund the SBIR grant to develop a standardized product. The grant recipient has characterized the milk thistle product, including all of its chemical constituents that occur at levels greater than 1 percent. Data suggest that some of these constituents are antifibrotic and others may be anti-inflammatory. NCCAM and NIDDK identified the need to evaluate a standardized product and begin dose-range studies with patients, leading to the current concept under Council review.

In response to a question from Council, Drs. Straus and Liu stated that the results of a silymarin project conducted by Dr. Strickland at the University of Maryland were reported in *Digestive and Liver Diseases* (November 2004). Dr. Liu stated that the researchers concluded that the recommended dosage of silymarin can be taken safely for 1 year and improved symptoms and general well-being, but that it had no effect upon hepatitis C virus viremia, serum ALT, or serum and ultrasound markers for hepatic fibrosis. The researchers recommended that a more prolonged evaluation at a higher dose might be required.

Dr. Berman noted that it is important to have a standardized product *before* developing a protocol. If the reverse sequence is used (the clinical trial protocol is written and then the product is chosen), the clinical protocol would probably have to be rewritten to fit the specifics of the chosen product. In addition, additional work by the manufacturer may be required to bring its product information to FDA standards; thus, extra time after having a product but before writing the clinical protocol may be needed.

Dr. Low Dog noted that milk thistle is the most common herb she sees used in the treatment of hepatitis. She commented that milk thistle's widespread use must be considered, along with what is known about drug interactions, pharmacokinetics, and potential benefits/protection.

Council asked about the implications of treating hepatitis C with silymarin in lieu of other treatments. Dr. Berman responded that sole treatment with silymarin would be used only in patients for whom coventional treatments have been unsuccessful or not well tolerated.

Council asked for clarification on the three potential protocols noted above. Dr. Berman noted that the RFA merely suggests examples of what NIH is interested in evaluating. The actual protocols resulted from the NIH protocol-development process: potential grantees propose protocols based on NIH's suggestions but modify them based on their own knowledge and experience; the successful grantees constitute the core of the

Protocol Writing Committee; that Committee generates protocols based on what the grantees have proposed but modified by the views of the other grantees and NIH staff, with the Product Supplier as an ex-officio advisor; and the protocols so generated are further reviewed by a DSMB, IRBs, and the FDA.

Council voted unanimously by roll call vote to approve the concept.

With no additional questions or comments, Dr. Straus thanked the participants and adjourned the meeting at 1:15 p.m.

We hereby certify that, to the best of our knowledge, the foregoing minutes are accurate and complete.

Jane F. Kinsel, Ph.D.
Executive Secretary
National Advisory Council for
Complementary and Alternative
Medicine

Stephen E. Straus, M.D.
Chair
National Advisory Council for
Complementary and Alternative
Medicine