NACCAM Members Present

Dr. Timothy Birdsall, Goodyear, AZ
Dr. Gert Bronfort, Bloomington, MN
Dr. Adam Burke, San Francisco, CA
Dr. Lupo Carlota, Memphis, TN
Dr. Daniel Cherkin, Seattle, WA
Dr. Gary Curhan, Boston, MA
Dr. Steven DeKosky, Charlottesville, VA
Dr. Stephen Ezeji-Okoye, Palo Alto, CA
Dr. Susan Folkman, San Francisco, CA
Dr. Janet Kahn, Burlington, VT
Dr. David Kingston, Blacksburg, VA
Dr. Shin Lin, Irvine, CA
Dr. Philippa Marrack, Denver, CO
Dr. Lloyd Michener, Durham, NC
Dr. Richard Niemtzow, Clinton, MD
Dr. Katherine Shear, New York, NY
Dr. Herman Taylor, Jackson, MS
Dr. Xiaoming Tian, Bethesda, MD

NACCAM Members Not Present

Dr. Brian Berman, Baltimore, MD

NIH Staff Present

Robert Bahde, NCI
John Beutler, NCI
Kirt Gustafson, NCI
Flora Katz, FIC
Qingliang Li, NCBI
Yuan Luo, CSR
Kathleen Michels, FIC
Barbara Mroczkowski, NCI
Martin Rogers, NIAID
I. Closed Session

The first portion of the forty-third meeting of the National Advisory Council for Complementary and Alternative Medicine (NACCAM) was closed to the public, in accordance with the provisions set forth in Sections 552b(c)(4) and 552b(c)(6), Title 5, U.S.C., and Section 10(d) of the Federal Advisory Committee Act, as amended (5 U.S.C. Appendix 2).

A total of 236 applications were assigned to NCCAM. Of these, 149 were reviewed by NCCAM, 90 by Center for Scientific Review. Applications that were noncompetitive, not discussed, or were not recommended for further consideration by the scientific review groups were not considered by Council.

Council agreed with staff recommendations on 111 applications, requesting $37,829,318 in total costs.

II. Open Session—Call to Order

The open session of the meeting of NACCAM convened at 10:40 a.m. Dr. Martin Goldrosen, NACCAM Executive Secretary, called the meeting to order.

The minutes of the June 3, 2011, NACCAM meeting were approved unanimously.

III. Report From the Director

NACCAM, National Institutes of Health (NIH), and National Center for Complementary and Alternative Medicine (NCCAM) News

Dr. Josephine Briggs, Director of NCCAM, welcomed Dr. Philippa Marrack to NACCAM and thanked the five departing members—Drs. Timothy Birdsall, Gert Bronfort, Lupo Carlota, Shin Lin, and Herman Taylor—for their service. Dr. Briggs congratulated NACCAM member Dr.
Janet Kahn on her presidential appointment to the Advisory Group on Prevention, Health Promotion, and Integrative and Public Health.

The U.S. Department of Health and Human Services has proposed broad-reaching changes in the oversight mechanisms that protect human research participants (generally known as the Common Rule). If implemented, these changes would streamline the oversight of low-risk research but intensify and centralize oversight of higher risk interventional research.

The directors of the Center for Scientific Review, National Center for Research Resources, and National Institute of General Medical Sciences (NIGMS) have left NIH. The new Director of NIGMS will be Dr. Chris Kaiser, Head of the Department of Biology at MIT. NCCAM is in the final stages of the search for a scientific director to lead an intramural pain program. The search committee is very enthusiastic about the final candidates, who will be interviewed within the next 2 months.

The President’s budget for NIH for FY 2012 is slightly higher than the amount appropriated for FY 2011 under a Continuing Resolution, but the actual budget may more closely match the Senate mark, which involves a small decrease in appropriations. A little less than half of NCCAM’s budget is already earmarked for noncompeting (continuing) commitments. Decisions to reduce noncompeting awards can be made on a trans-NIH basis but not by individual NIH agencies.

**Research Highlights**

Recent findings from research funded or partly funded by NCCAM include the following:

- An updated analysis of data from the Selenium and Vitamin E Cancer Prevention Trial (SELECT) showed that vitamin E supplements significantly increased the incidence of prostate cancer in healthy men: 17 percent after 7 years of follow up.
- The Complementary and Alternative Medicine for Urological Symptoms (CAMUS) trial found that escalating doses of saw palmetto had no greater benefit than placebo in men with lower urinary tract symptoms.
- A study of patients with minor depression found that neither a relatively low dose of the drug citalopram, a standard antidepressant, nor a relatively high dose of St. John’s wort affected depression scores.
- Former NACCAM member Dr. Ted Kaptchuk and colleagues found that the drug albuterol, a placebo, and sham acupuncture all improved symptoms to a comparable extent in patients with asthma, but only albuterol improved lung function tests. Dr. Briggs noted that this pattern of differences between symptomatic and physiological responses has been a recurrent theme in the research that NCCAM supports.
- In a study of medical students, fish oil supplements reduced anxiety and inflammation in healthy people who had not been diagnosed with an anxiety disorder but had no impact on depressive symptoms.
- An important study led by NACCAM member Dr. Daniel Cherkin found significantly greater improvement in patients with chronic back pain who received either of two types of massage compared with those who received usual care.
• A study from one of the botanical centers cofunded by NCCAM showed that genetic variants in the fatty acid desaturase gene cluster may account for differences in metabolism of omega-6 fatty acids between populations of African and European descent.

• Dr. Luana Colloca, a young investigator supported by NCCAM’s intramural program, edited a special issue of Philosophical Transactions of the Royal Society that focused on the placebo effect. She also co-authored two papers in that issue.

Other NCCAM Activities

Dr. Briggs is co-chairing the trans-NIH working group that is developing the Health Care System Research Collaboratory (formerly the HMO Research Network). This group will stimulate demonstration projects to expand research partnerships with health care systems to new areas, including interventional research. NCCAM staff members are playing a major role in this effort. Dr. Briggs also served on a committee that advised on the transition of the Clinical and Translational Science Awards (CTSAs) into the proposed National Center for Advancing Translational Sciences (NCATS) and is serving on the NIH Advisory Board for Clinical Research, which faces difficult decisions about resource allocation.

Dr. Briggs is co-chairing the NIH Pain Consortium, and NCCAM Deputy Director Dr. Jack Killen and Program Officer Dr. Partap Khalsa are leading a consortium subgroup on chronic low-back pain. Among other efforts, this subgroup is working to develop research diagnostic criteria to facilitate the integration of data from multiple studies.

NCCAM is participating in a process led by the National Institute on Drug Abuse (NIDA) to develop educational curricula on pain for medical and nursing students. Ensuring that nonpharmacological methods to relieve pain receive appropriate attention is one of NCCAM’s priorities in this effort.

NCCAM is improving its clinical research oversight and has just awarded a contract for clinical study monitoring that will help ensure that all NCCAM-supported clinical research meets the best current standards. This effort will be led by Dr. Catherine Meyers, Director of NCCAM’s Office of Clinical and Regulatory Affairs. In-house clinical reviews, including reviews of statistical aspects of research design, also play a key role in NCCAM’s research oversight.

Dr. Sean Mackey of the Stanford University Pain Management Center will present the Stephen E. Straus Distinguished Lecture on November 7. His topic will be “Opening Windows to the Brain: Lessons Learned from the Neuroimaging of Pain.”

In closing, Dr. Briggs noted the recent death of Dr. Norman Farnsworth, a leader in the field of pharmacognosy, who had been supported by NCCAM as the head of a botanical center and who presented a lecture as part of NCCAM’s Distinguished Lecture Series in 2003.

IV. Symposium on Natural Product Screening

The final portion of the NACCAM meeting consisted of a symposium on natural product screening, which included four presentations followed by an open discussion. In opening the
symposium, Dr. Briggs noted that the Lasker-DeBakey Clinical Medical Research Award was recently awarded to Dr. Tu Youyou for her work on the discovery of artemisinin, a crucial antimalarial drug derived from the wormwood plant, which had long been believed to have beneficial effects against fever. Dr. Briggs explained that research on this drug succeeded only after Dr. Tu searched the ancient literature to identify the conditions under which traditional healers prepared wormwood extracts. The results of her search were applied to the extraction process, which led to discovery of the drug. This experience should serve as a reminder that traditional wisdom is a resource that should not be ignored or lost.

Dr. David Kingston, University Distinguished Professor in the Department of Chemistry at Virginia Tech, and Dr. Craig Hopp, a program officer in NCCAM’s Division of Extramural Research chaired the symposium. In his opening comments, Dr. Kingston explained that natural products have been responsible for about half of all new drugs and are a valuable cultural resource in many settings. Recently, however, the pharmaceutical industry has discontinued most natural products research.

Natural products cover a complementary chemical space to synthetic compounds, and their potential has not been exhausted. They have a proven track record and represent a significant proportion of today’s marketed drugs. Roughly 35 percent of all new drugs and 42 percent of new anticancer drugs introduced since 1981 are either natural products or chemically modified compounds of natural origin. One reason drugs from natural sources have been so useful is that they are complex compounds with chirality that fit well in protein folds. They were produced by enzymes and are “designed” to interact with enzymes; therefore, they have natural enzymatic binding sites that can be exploited to interact with target proteins. Natural products have better drug-like properties than a random sample of compounds prepared by combinatorial chemistry.

Dr. Hopp explained that natural products have played a pivotal role in the pharmaceutical age of health care during the last century, but that serious questions have been raised about what role they will play in the future and what role the Federal Government should play in shaping that future. With the retreat of major pharmaceutical companies from natural products research, important questions are being asked about whether public funds, including NCCAM funds, should be directed toward this area.

Dr. Hopp hypothesized that pharmaceutical companies have withdrawn from natural products research because the high-throughput capacity of the modern biotechnology laboratory is a poor match for the more deliberate pace of natural products discovery. Important discoveries about natural products can still be made, but it may not be possible to make them quickly enough to suit the business model of pharmaceutical companies.

NCCAM has initiated a small pilot-scale project to explore the utility of the former Merck natural products library. This large collection of samples from a wide variety of natural sources has been donated to a nonprofit organization and is now available to researchers from around the world. Before NCCAM considers larger scale investments in this area, it is important to understand the basis for industry’s decision to withdraw from natural products work and the barriers to and tools for natural products research. Dr. Hopp emphasized that research on natural products should continue to adhere to good botanical practices and to respect and protect the
indigenous cultures from which some products originate. The goal of this symposium was to highlight the opportunities and challenges in natural products research and identify ways in which the public sector can facilitate progress in natural products science.

**Industry Experience with Natural Product Screening**

In the first symposium presentation, Dr. Sheo Singh of Merck Research Laboratories explained that Merck and other companies have discontinued natural products discovery not because of a lack of interest but because the cost of this type of work became unsustainable. In the current industry environment, the long-term investment necessary for natural products research could not be justified. Development is continuing, however, on some previously discovered compounds from natural sources at Merck and other large pharmaceutical companies. These compounds were primarily derived from fermentation. Less work has been done on compounds of plant origin because concerns about the environmental impact of harvesting plants for drug production have led to a negative public image. The plant-derived samples in the Merck collection may be particularly valuable because they represent an almost entirely untapped resource.

Dr. Singh presented some examples of potentially valuable natural products that are currently under early development, including platensimycin, which was first studied as an antibiotic but proved to be of more value for its antidiabetic effects; kibdelomycin, the first novel antibiotic (that inhibits bacterial gyrase) in its class discovered in five decades; and the parnafungins and enfumafungin, which are antifungal agents.

One of the major challenges of natural products research is that as time goes on, an exponentially increasing proportion of compounds identified by screening prove to be known substances. In addition, natural products do not fit well into the current ultra-high-throughput screening model. Nevertheless, opportunities for natural products may exist in the antibacterial, antifungal, anticancer, immunosuppressant, and antiparasitic therapeutic areas. To take advantage of these opportunities, modern screening technologies are needed, and all the components of the discovery and development process need to be in place, ideally under one roof.

**New Methods in Natural Product Research**

The second presentation of the symposium was made by Dr. Kingston, who focused on four problems in natural product screening and their possible solutions.

The first of these is the incompatibility of crude extracts from natural sources with high-throughput screening. Plant extracts contain tannins that bind to proteins and interfere with assays. This problem can be solved either by detanninizing the crude extracts or by preparing libraries of partially purified natural product extracts that are compatible with high-throughput screening.

The second problem is re-isolation of known compounds. Methods for “dereplication”—that is, the differentiation of novel metabolites in an extract from known natural products—are needed. Classical methods for dereplication are slow and inefficient, but more rapid techniques involving
a combination of high-performance liquid chromatography and nuclear magnetic resonance (NMR) spectroscopy are possible.

Difficulty in isolating compounds is the third problem. Chemoselective enrichment can be useful here. Pure compounds can also be prepared in an automated way if resources are available.

The fourth problem is the difficulty of structure determination when only small amounts of the active compound are available, as may be the case with substances derived from plants. Recent advances in NMR, including capillary NMR and cryoprobe NMR, have addressed this issue. It also may be possible to synthesize the active compound in some instances.

Although new techniques, such as those described above, have facilitated natural products isolation and structure elucidation, natural products research is still a long-term undertaking that requires an infrastructure of advanced equipment that may not be available in all academic laboratories. Given adequate equipment and facilities, natural products research can continue to be a fruitful approach to drug discovery. Some of major advances are likely to come from the combination of natural products chemistry and new bioassays.

**Discussion.** In response to a question from Dr. Briggs, Dr. Singh said that dereplication needs to be addressed in two ways—by determining whether the extract contains previously known compounds and by determining whether a particular compound has the desired activity. Database mining can be helpful in addressing the first issue but not the second. In response to a question from Dr. Marrack about the value of molecular biology in dereplication, Dr. Singh explained that pharmaceutical companies are looking for knowledge that can be applied and that molecular biological approaches have not yet been developed to the point where they would be practical and cost-effective for dereplication.

The cost of goods is a major issue in the development of antiparasitics. Plants are a questionable source of antiparasitics because of supply and cost, but the example of artemisinin shows that some exceptions to this rule exist. In some instances, it may be necessary to develop a synthetic form of an antiparasitic drug if yields from the plant are low or the plant is not readily available.

In response to a question from Dr. Hopp, Dr. Kingston explained that conservation and public image issues related to plant-derived drugs can sometimes be overcome by producing the drug in ways that do not involve harvesting plants. For example, taxol is now produced by plant tissue culture. However, such approaches are possible only for a proven natural product, for which the investment in the development of new production techniques can be justified.

**Advances in Methodology for Natural Product Screening**

Dr. Louis Barrows, Professor in the Department of Pharmacology and Toxicology, College of Pharmacy, University of Utah, described some of his research group’s experiences with natural product screening, including work performed in Papua New Guinea. He explained that many complex issues exist in natural products discovery, ranging from collection and agreement issues to working with industry partners on the development of the most promising leads. Much research has been performed in academic settings that lack the power and resources of industry.
Dr. Barrows and his colleagues worked in partnership with Papua New Guinea institutions to carry out a botanical survey of plant diversity in that country, which led to the establishment of a collection library at the University of Utah. To prepare plant samples for analysis, they used the approaches of prefractionation and phenotypic or cell-based screening. In addition to collecting natural products that may be valuable for drug discovery, the project has identified new plant species and distributed type specimens of many species to major herbaria around the world. The researchers are now focusing on the collection of plants with traditional medicinal uses.

Cell-based screening programs at the University of Utah have emphasized activity against tuberculosis, HIV, and malaria. Fractions are also screened for cytotoxicity because cytotoxic substances cannot be used in the treatment of infectious diseases. Approximately 2,000 extracts can be tested in each of the four assays (activity against the three diseases and cytotoxicity) in 6 months. Some promising compounds have been identified, but a slow timeline, supply problems, and a lack of chemistry support have limited their development.

In summary, for natural product testing high throughput strategies are not the best fit. While we can prepare "peak" libraries of largely purified natural products, cell based or "phenotypic" screens are still the most compatible and informative with natural products.

**Discussion.** In response to questions, Dr. Barrows emphasized that a source of frustration for academic groups involved in drug discovery is that their projects progress to a point where they need to be handed off to others, but the path for doing this is not clear.

Dr. Hopp noted that some of the compounds shown on Dr. Barrows’ slides were at the “greasy” end of the liquid chromatogram and may be interesting because they are primary metabolites. Dr. Singh added that similar compounds have been identified in his research and that they were active in isolated cells but might not be effective in the human body. Dr. Hopp observed that in some instances, developing probes to investigate the biology of a system, rather than developing a drug, may be a worthwhile goal.

In response to a question about combining several compounds for therapeutic purposes, Dr. Barrows noted that this is being done in some instances. In the bush, people are experimenting with medicinal plants for HIV. In one instance, two peaks of activity were discovered in an extract from one plant, suggesting the possibility of developing a combination product.

**Good Botanical Practices in Natural Products Research**

Dr. Michael Balick, Vice President and Director of the Institute of Economic Botany at the New York Botanical Garden, discussed the roles of good botanical practices, environmental issues, and intellectual property rights in natural products drug discovery and in efforts to use evidence-based traditional medicines to improve public health in various parts of the world. Correctly identifying plant sources is crucial for the reproducibility of research. Currently, plant voucher specimens are the “gold standard” of botanical reference materials. Confirming a plant’s identity requires a preserved specimen deposited in a properly curated collection and assignment of the correct name to that specimen. Unfortunately, many published papers on natural products do not
identify plants adequately, which impedes replication of the research findings, or makes it totally impossible to know on what materials the researcher based their study.

Dr. Balick described the plant collection program that was operated by the New York Botanical Garden and National Cancer Institute (NCI) in 16 Neotropical countries (New World Tropics--Central and South America as well as the Caribbean) from 1986 to 1996. Issues that needed to be addressed during this program included environmental concerns—such as ensuring sustainable harvest and production of medicinal plants—and permitting issues, which involved government agencies in the countries where samples were collected, international permits, and U.S. Department of Agriculture import permits for samples brought to the United States, as well as full disclosure of all activities and their consequences to the communities involved. During this program, NCI took the lead in establishing benefit-sharing systems and intellectual property rights. The letter of collection and materials transfer agreement developed at that time are still in use today.

To encourage local communities to have interest in plant collection projects it is essential to find ways to share benefits in the short term as well as the long term. This is an essential part of the program and must be budgeted for from the beginning. To provide short-term benefits from their plant collection program, Dr. Balick offered a few examples of how he and his colleagues provided short and medium term benefits including local participants as co-authors on research papers; developing guidebooks and other materials to encourage and support ecotourism; collaboration with Departments of Health and other state agencies in the preparation of primary health care manuals based on traditional remedies; and supporting local environmental conservation efforts.

Dr. Balick concluded his presentation by explaining that only 1 to 5 percent of all higher plants have been thoroughly evaluated for their chemical composition or therapeutic properties. This is for many reasons, including that most plants have not been screened against all the multiple targets available, as well as ca. 100,000 new plant species are expected to be discovered and described in the next 50 years, so there is a great deal of opportunity for improving public health by identifying new and valuable active compounds.

**Discussion.** In the future, genetic barcoding may play an important role in identifying plants, but we can assume that plant voucher specimens will remain the gold standard for positively identifying plants, in combination with chemical profiles, DNA barcoding and other techniques that are currently being developed.

Belief systems in other cultures may not correspond to Western diagnostic entities, e.g. as discussed in the DSM-IV, and this should be taken into account when studying the therapeutic effects of medicinal plants. There may be mind/body effects going on along with effects from biological chemical compounds. Understanding traditional systems of healing is particularly challenging in cultures in which traditions are primarily oral, and fast disappearing, as compared with systems such as traditional Chinese medicine or Ayurveda in India, where a centuries old body of literature can be consulted. Also, workers in the field of gathering indigenous knowledge report that it can take many years to obtain the confidence of local healers and their
genuine collaboration in order that researchers can gain access to orally transmitted ethnomedical knowledge and begin to evaluate the plants upon which this is based.

Symposium Discussion

Dr. Briggs introduced Dr. James Doroshow, Director of the Division of Cancer Treatment and Diagnosis (DCTD) at NCI; Dr. Jerry Collins, Associate Director of DCTD’s Developmental Therapeutics Program; and Dr. M. John Rogers, Preclinical Parasite Drug Development Project Officer at the National Institute of Allergy and Infectious Diseases, and asked them to comment on their Institutes’ thinking on natural products drug development.

Dr. Doroshow explained that NCI has tried to keep natural products alive in cancer therapeutics activity because major pharmaceutical companies have abandoned it. NCI’s most recent activities have involved reformatting natural product extract libraries to make them more suitable for high-throughput screening. Dr. Collins noted that NCI’s natural product repository is available for research on any disease within the NIH mission, not just cancer. Government may be able to fill a niche that industry is not filling by keeping natural products research alive and working with academia in this area. Dr. Rogers explained that antiparasitics face a special problem because of the lack of a commercial market. However, with the increasing interest in tropical diseases, public-private partnerships have been established and have become productive; natural products could become part of these partnerships.

Dr. Briggs explained that although NCCAM has a responsibility to include some international activities in its portfolio, the Center does not have the resources to continue investing in human subject research in other countries. She suggested that NCCAM’s limited funds might be better spent asking questions about natural products-derived remedies for neglected diseases, and this idea was part of the motivation for the day’s symposium. Another impetus for the discussion was the availability of the former Merck natural products library. Although NCCAM does not have the resources to develop drugs, it could pursue interesting compounds that could then be handed off to others at NIH. Plant-based remedies are of particular interest to NCCAM, and experience has shown that mechanistic studies should precede clinical ones. Dr. Briggs asked Council members and guests for their thoughts on these topics.

In response to questions, Dr. Kingston noted that a few pharmaceutical companies are still involved in natural products research, but to a very limited extent. Companies in Asia have been trying to isolate active compounds from TCM mixtures but have had little success, possibly because the activity of a TCM mixture may not be attributable to a single substance.

Dr. Briggs noted that NIH is in negotiations with pharmaceutical industry partners on the issue of repurposing drugs with expired patents and those that failed for one purpose but could be used for another; a similar model could perhaps be developed around natural products.

Dr. Singh reemphasized that the timeline is the biggest obstacle to natural product drug development.
Dr. Collins commented on the need to change the ratio of biology to chemistry in drug development. NCI has created a consortium of chemical biologists in the extramural community, but this venture is only 2 years old and cannot yet be declared a success.

Dr. Rogers noted that NIH is not a pharmaceutical company or a public-private partnership. A more appropriate role for NIH is to develop projects to the point where they are attractive enough to be handed off to others.

Dr. Xiaoming Tian suggested that a less expensive and simpler approach to the study of natural products would be to demonstrate whether products currently in use, such as herbal dietary supplements, are safe and effective and to determine optimal dosages.

The issue of patenting natural products was raised, and Council members and speakers agreed that the intellectual property issues surrounding natural products are very complex.

Dr. Susan Folkman suggested that bacteria that accompany natural products in their environment may contribute to or be responsible for their effects. Dr. Hopp concurred; he noted that in some instances when the activity of a product seems to be lost during purification, the removal of microorganisms responsible for the activity could be the explanation. Dr. Folkman also raised the issue of how expectations affect effectiveness, suggesting that some natural products may lose their effectiveness when taken out of their cultural context. Dr. Hopp added that human genetic diversity, including single nucleotide polymorphisms, may account for some of the instances in which a natural product seems more effective in one culture than another.

In response to a member’s question, Dr. Balick noted that when studying traditional remedies, it is important to prepare them in the same way that they would be prepared by a healer from the culture of origin, so that the same chemical composition is obtained. He gave an example where the omission of a seemingly irrelevant component from a complex product led to a loss of activity, which was restored when the component was reintroduced.

V. Public Comment Session and Closing

No public comments were offered. Dr. Briggs thanked Council members and adjourned the meeting at 3:45 p.m.

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

Martin Goldrosen, Ph.D.
Executive Secretary
National Advisory Council for Complementary and Alternative Medicine

Josephine Briggs, M.D.
Chairperson
National Advisory Council for Complementary and Alternative Medicine