CHAPTER 6

PHARMACOGNOSY IN ACTION. U. S. GOVERNMENT

National Cancer Institute Molecular Targets Development Program (Laboratory of Drug Discovery Research and Development)

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Natural products discovery efforts at the U.S. National Cancer Institute were renewed and reinvigorated in the late 1980s under the leadership of Michael R. Boyd. Boyd initiated NCI's large-scale natural product collection and extraction efforts, and he established the Natural Products Repository to house the resulting raw materials and extracts. The natural product source organisms were acquired via a worldwide collection effort established by Matthew Suffness in the Developmental Therapeutics Program's Natural Products Branch, which was lead for many years by Gordon Cragg. These collections were comprised of a highly diverse taxonomic range of terrestrial plants, marine organisms, and selected microbial isolates. Raw materials from around the world were processed in Frederick, Maryland by the Natural Products Support Group under Thomas G. McCloud's supervision. A rather unique aspect of the NCI extraction protocol was that both organic solvent and aqueous extracts were prepared from each sample. To date, >80,000 individual organisms have been collected and processed, and >210,000 extracts have been prepared as a result of these efforts.[1] In addition to the renewed interest in natural products, Michael Boyd was also largely responsible for the development and implementation of the NCI 60-cell antitumor screen and the cell-based anti-HIV screen. These assays provided the principle natural products screening capabilities at the NCI for the next 15-20 years.

In addition to collection, extraction and screening operations, NCI formally established the Laboratory of Drug Discovery Research and Development (LDDRD) in 1990. The LDDRD conducted bioassay-guided natural product isolation and structural elucidation studies, as well as biological characterization of the resulting lead compounds. The Natural Products Chemistry Section was headed by John H. Cardellina II from 1990-1998, and senior chemistry staff included the current authors, as well as Yali F. Hallock (now Yali Fu) and Kirk R. Manfredi. In the early years of this program Murray H. G. Munro and John W. Blunt from the University of Canterbury, New Zealand were influential visiting scientists within the LDDRD.

Throughout the 1990s, the LDDRD natural products efforts focused primarily on extracts with selective cytotoxicity profiles in the 60-cell anticancer screen or extracts with HIV inhibitory properties in the anti-HIV screen. The microplate technology utilized in these cell-based assays was successfully employed to screen large numbers of extracts, and follow-up natural product chemistry studies resulted in the identification of a wide range of new bioactive chemotypes. In 1997, an initiative to develop higher throughput screening methodologies for molecular targets began, and in the next several years the LDDRD began to acquire new robotic equipment and implement new assay platforms. Molecularly targeted screening represented a major change from the empirical 60-cell assay, and it was designed to draw on the extensive intramural NCI expertise in cancer biology. In 2001, the LDDRD was renamed the Molecular Targets

Development Program (MTDP), and it became a part of the NCI's Center for Cancer Research. Since 2002, it has been under the leadership of James B. McMahon.

Notable HIV inhibitory natural products that were discovered since 1990 include prostratin,[2] michellamine B,[3] and calanolide A.[4] Calanolide A was licensed to Sarawak Medichem, and it progressed into Phase II clinical trials against HIV.[5] A second major success was the discovery of antiviral proteins from diverse natural sources, beginning with cyanovirin-N,[6] and later including scytovirin[7] and griffithsin.[8] All of these proteins bind avidly to specific oligosaccharides on critical viral proteins and inhibit viral entry into host cells.[9] They are currently under study for both microbicidal and treatment applications against HIV, Ebola, and influenza infection. Significant anticancer discoveries include three distinct structural types of vacuolar ATPase inhibitors, the salicylihalamides,[10] lobatamides,[11] and chondropsins,[12] from different marine sources. The schweinfurthins[13] are a notable terrestrial plant anticancer discovery.

The current focus of the MTDP is the development and application of molecularly targeted assays for screening natural product extracts, and the isolation and identification of metabolites that specifically modulate these targets. Molecular targets of recent interest include the E3 ubiquitin ligase MDM2, the multidrug resistance transporter ABCG2, the transcription factor AP-1, and HIV RNase H.

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The National Cooperative Drug Discovery Groups (NCDDGs) and Natural Products Grant Support at the National Cancer Institute

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Following its creation in 1937, The US National Cancer Institute (NCI) established a grant awarding mechanism in 1946 as a way to stimulate creativity and to expand and apply new knowledge towards NCI's mission of coordinating research efforts relating to cancer. The Developmental Therapeutics Program (DTP) was formed in 1977 by Vincent DeVita, then Director of the Division of Cancer Treatment, NCI and who later became Director of NCI (1980 to 1988). The newly established DTP brought NCI preclinical drug research and development activities together, and the existing grants program known as the Biochemistry and Pharmacology (BP) Grant Portfolio also joined DTP. The current Grants and Contracts

Operations Branch (GCOB) was created in 1985 and headed by J. A. R. (Tony) Mead (Chief, 1985-1997) and then Mary K. Wolpert (Chief, 1997-present).

Since the inception of the grant awarding mechanism, NCI has supported extramural investigators including natural products researchers. Using investigator-initiated grant mechanisms, such as the R01, GCOB has supported a number of natural products research laboratories. Notable investigators with longstanding R01 grant support in natural products include: the late Richard E. Moore, George (Bob) Pettit, William Fenical, K.H. Lee, Jon Clardy, Chris Ireland, Phillip Crews, Rodney Croteau, Sidney Hecht and Heinz Floss. Over the years, R01s have fostered considerable innovation in the field, including increased understanding of biosynthesis and using genetic tools to map biosynthetic pathways, and the introduction of new technologies, including state-of-the-art technologies in dereplication, separation and structure identification.

The National Cooperative Drug Discovery Group (NCDDG) program was created in 1982 upon the recommendation of a Subcommittee to the former Division of Cancer Treatment's Board of Scientific Counselors chaired by Alan Sartorelli. The Chief of the Drug Evaluation Branch, John Venditti was charged with implementation of the new program. The Board recommended creating NCDDGs as a new way to support preclinical drug discovery research at the national level to place more emphasis on rational, mechanistic approaches and to augment the existing contract drug screening program. It is intended to exploit scientific and technological advances in cancer biology and related fields by multidisciplinary and often multi-institutional research teams. In 1983, the first round of NCDDG Request for Application was issued and two awards were made in 1984. In 1985, with the creation of GCOB, NCI's drug discovery and development grants, including NCDDG came under GCOB coordination and management. Since then, the NCDDG program has been re-competed at least every five years with minimal change to the basic formula. The program is an early example of bringing together academia, a government agency and industry in a concerted effort for drug discovery. The NCDDG currently funds nine consortia Groups at a total of about $10 million per year.

The NCDDGs have been instrumental in stimulating interest in drug discovery by the academic community, and have supported diverse projects which reflect the best creative ideas in small molecules, biologicals, and natural products. Since 1983, the NCDDGs have supported a number of natural products-based drug discovery consortia which have brought together talents in natural products, cancer biology and pharmacology. The program also has served as a flagship program to demonstrate natural products' potential as a source of novel drug leads. From 1985 to 1995, Matt Suffness coordinated the natural products NCDDGs before his untimely death.[1] Since 1997 to the present, Yali Fu has been responsible for the portfolio of natural products grants, including the NCDDGs and ICBG projects described below. To date the NCDDG has supported a number of natural products-based drug discovery laboratories; those supported in the past include Moore, Kinghorn (now continuing as a Program Project Grant), Hecht/Kingston, Fenical, Clardy, and the currently supported Crews[2] and Ireland[3] groups. Notable achievements of the NCDDG program include four marketed agents, one of which is topotecan, a camptothecin analog with superior properties to the parent compound that was dropped from clinical trial due to unacceptable toxicity, and is marketed by SmithKline Beecham (now GlaxoSmithKline). Twenty one more agents have entered clinical trials including four derived from natural products.

The NCI's experience and commitment in exploring natural products as a source for new drug leads, and its leadership in developing a benefit-sharing framework has benefited others in this field. The NCI has been co-funding the International Cooperative Biodiversity Group (ICBG),[4] a natural products program supported by multiple US Government agencies and NIH Institutes, since its inception. NCI staff George Johnson, Gordon Cragg, Yali Fu, Mary Wolpert and Dave Newman has been actively participating in the management and coordination of those ICBGs with cancer drug screening activities. The NCDDG model has been used by NIAID in a TB and malaria drug discovery program as well.

Beyond the traditional discovery of new drug leads, the GCOB's grant portfolio includes biosynthesis, mechanism of action, and all other aspects of preclinical development of natural products such as medicinal chemistry, formulation, pharmacology and toxicology. Modern drug discovery and translational research is a costly and complex process, and calls for more interdisciplinary collaborations across the traditional institutional barriers. The NCDDG model, which brings together academia, government and industry, continues to serve as a successful and viable mechanism for discovering and developing new cancer drug leads. (The opinions expressed are those of the authors and not the US Government.)

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National Cancer Institute Natural Products Branch

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The National Cancer Institute (NCI) was established in 1937, its mission being "to provide for, foster and aid in coordinating research related to cancer." In 1955, NCI set up the Cancer Chemotherapy National Service Center (CCNSC) to coordinate a national voluntary cooperative cancer chemotherapy program, involving the procurement of drugs, screening, preclinical studies, and clinical evaluation of new agents. By 1958, the initial service nature of the organization had evolved into a drug research and development program with input from academic sources and substantial participation of the pharmaceutical industry. The responsibility for drug discovery and preclinical development at NCI now rests with the Developmental Therapeutics Program, a major component of the Division of Cancer Treatment and Diagnosis. Thus, NCI for the past 54 years has provided a resource for the preclinical screening of compounds and materials submitted by grantees, contractors, pharmaceutical and chemical companies, and other scientists and institutions, public and private, worldwide, and has played a major role in the discovery and development of many of the available commercial and investigational anticancer agents.

From the outset, natural products were off interest to NCI largely due to the commitment of Jonathan A. Hartwell (1906-1991), who joined in 1939 and served for 36 years until his retirement in 1975. Among his positions were Assistant Chief of the Cancer Chemotherapy National Service Center (CCNSC), and Head, Natural Products Section, Drug Research and Development Branch, and he was personally responsible for the initiation and early development

of the research programs giving impetus to the creation of a systematic search for plants and marine animals with anticancer activity, an ongoing project for close to 50 years. His influence in organizing the natural products research programs at NCI led to the initial and continuing funding of major research groups. He did extensive laboratory work at the NCI in the area of lignans, particularly those derived from *Podophyllum peltatum*, which were the basis for the subsequent discovery of the anticancer drug, etoposide. He compiled a thorough work on traditional and folkloric uses of plants for treatment of cancer, covering references to literature from ancient Chinese, Egyptian, Greek, Indian and Roman eras through the period of European discovery in the Americas and Africa to the 1900s; originally published in 11 installments in Lloydia from 1967-1971, it was reprinted in a single volume, *Plants Used Against Cancer: A Survey*.[1]

On Hartwell's retirement in 1975, John Douros was appointed Chief of the newly-formed Natural Products Branch (NPB), and he promoted the investigation of microbial sources, strengthening interactions with pharmaceutical companies, and establishing a fruitful contract with the Institute of Microbial Chemistry in Tokyo under the direction of Hamao Umezawa. In 1976, Matt Suffness joined NPB, and became Chief in 1986 before becoming natural products grants program coordinator for the NCI Grants and Contracts Branch in 1989. Matt (ASP President, 1989-1990) played a major role in the evolution of the natural products program as we know it today. Shortly before his untimely death in 1995, he edited the book, *Taxol, Science and Applications*.[2]

From 1955-1982, more than 500,000 chemicals, both synthetic and natural, and over 180,000 microbial-derived, some 16,000 marine organism-derived, and over 114,000 plant-derived extracts were screened for antitumor activity, mainly by the NCI, leading to the discovery of many novel active compounds, and the development of a number of clinically effective chemotherapeutics.[3] In 1982, the NCI de-emphasized natural products, but through the efforts of Michael Boyd, a new program was initiated in the mid-1980s. In 1986, contracts for the cultivation and extraction of fungi and cyanobacteria and for the collection of marine invertebrates and terrestrial plants were initiated, and with the exception of fungi and cyanobacteria, these programs continue to operate in various forms today. Marine organism collections, originally focused in the Caribbean and Australasia, expanded to the Central and Southern Pacific and to the Indian Ocean through a contract with the Coral Reef Research Foundation based in Palau. Terrestrial plant collections have been carried out in over 25 countries in tropical and subtropical regions worldwide through contracts with the Missouri Botanical Garden (Africa and Madagascar), the New York Botanical Garden (Central and South America), and the University of Illinois at Chicago (Southeast Asia), and expanded to the territorial United States through contracts with the Morton Arboretum and World Botanical Associates. In carrying out these collections, the NCI contractors work closely with qualified organizations in each of the source countries, and NCI is committed to policies of "fair and equitable collaboration and benefit-sharing" through its Letter of Collection (http://ttc.nci.nih.gov/forms/loc.doc) which predated the 1992 United Nations Convention on Biological Diversity by some four years.

The second and continuing phase of the NPB program started in 1986 under the leadership of Matt Suffness and transferred to Gordon Cragg (ASP President, 1998-1999), who became Branch Chief in 1990 until his retirement in early 2005. From late 1985 to 1987, Janice Thompson coordinated the marine program; she was followed by Ken Snader who also managed

large-scale isolation contracts before moving to the NCI Pharmaceutical Resources Branch in 1995. Ralph Collins came from U. Connecticut in 1989 to coordinate the microbial programs before moving in 1993 to manage the fungal cultivation program serving NPB at Science Applications International Corporation (SAIC). David Newman joined NPB in 1991 to manage the marine and microbial programs, and assumed leadership of the Branch in 2005, becoming Chief in 2006. In 1986, the Natural Products Support Group (NPSG; http://npsg.ncifcrf.gov/) under the management of Tom McCloud was set up; over 200,000 extracts of plant, marine and microbial origin have been prepared and are stored in the Natural Products Repository at -20^{o}C. These are distributed through the Active and Open Repository Programs (http://dtp.nci.nih.gov/branches/npb/repository.html), managed by Erma Brown, to researchers worldwide for studies aimed at the discovery of novel drugs for the treatment of human diseases, subject to signing of a Material Transfer Agreement protecting the rights of the source countries.

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Natural Products Research at the National Heart, Lung, and Blood Institute

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Natural products research at the National Heart, Lung, and Blood Institute (NHLBI; then just the National Heart Institute) was initiated in the 1950s, largely due to the efforts of James Shannon, then NIH's Director. Shannon was aware of the very successful application of *Rauwolfia serpentina* extracts in the treatment of certain mental diseases and he felt that there must be many other medically useful natural products just waiting to be discovered. He prevailed upon Evan Horning, an organic chemist at the University of Pennsylvania who had just finished publishing the latest version of Organic Synthesis, then the synthetic chemist's bible, to gather a group of chemists to form the Laboratory for the Chemistry of Natural Products in the Heart Institute in 1950. Among those hired were Bernard Witkop, who shortly switched to the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK; then the National Institute of Arthritis), and William Wildman from Princeton University. It might be noted that in those days the distinction between biochemists, and synthetic and natural product chemists was not as clear as it is today, and Horning pursued the more biochemical approaches with Melvin Fish, Sidney Goodwin and others, leaving Wildman to the chemistry aspects. Wildman with this author explored the synthesis of lycorine, an Amaryllidaceae alkaloid, but soon switched to structure determination of the entire Amaryllis family of over 100 alkaloids, using the expertise of Fales, Robert Highet, and Edgar Warnhoff.

In the 1950s Horning, Charles Sweeley and William VanDenHeuvel began their extensive work on the gas chromatography of steroids, and Wildman's group immediately applied this technique to the alkaloid and drug field. NMR analysis evolved shortly after, with Robert Highet as the lab's local expert. In 1961, Horning and Wildman left for Baylor University and the University of Iowa, respectively, and the interests of the laboratory shifted to the biosynthesis of the amaryllis alkaloids and methylenebis-phloroglucinols (Aneri Pentilla), along with studies on phytanic acid as the cause of Refsum's disease with Daniel Steinberg, Later, Fales and Govind

Kapadia worked extensively on alkaloids of peyote and melochia families, before turning to studies of the alkaloids of the fire ants (*Solenopsis*). During this time the group also engaged in several studies on mass spectrometric methods (chemical Ionization, GC/MS, etc), which have proven so useful in natural product work. More recently, the group has been concerned almost exclusively with mass spectrometry of peptides and proteins which are, of course, just another set of natural products.

Natural Products Research at the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK)

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Natural products research at NIDDK started in earnest in the 1950s with the project on the blow dart poison, batrachotoxin, initiated by Bernhard Witkop, Chief of the Laboratory of Chemistry in National Institute of Arthritis and Metabolic Diseases (NIAMD, a precursor to NIDDK). . After John Daly joined the Witkop group in 1958, he scaled up collections of the poison frog source from Colombia, which allowed structural elucidation work to proceed in collaboration with Isabella Karle using X-ray diffraction on a derivative of batrachotoxin, batrachotoxinin-A (BTX-A)-*p*-bromobenzoate, synthesized and crystallized by Takashi Tokuyama. The structure was ultimately determined as a 2,4-dimethyl-3-pyrrole ester of BTX-A by John and Takashi using mass spectrometry and NMR analyses.

In 1978, John Daly became the founding chief of the Laboratory of Bioorganic Chemistry (LBC), serving from 1978-1997. One of the authors (T. S.) joined him in 1980, and they and a team of pharmacologists continued to work on frog skin alkaloids, being joined by Martin Garraffo from Argentina in 1987. This team led by Daly became world leaders in research on the chemistry and pharmacology of amphibian alkaloids, and characterized over 800 different alkaloids from species of four families of brightly colored poison frogs, and the arthropods from which most sequester their alkaloids.[1] The program was the result of years of collecting frogs by John under hazardous conditions, preparing the extracts following a uniform protocol, and painstaking GC-MS, GC-IR, and LC-MS work. The meticulous nature of the work is described in the brief review of "The Discovery, Structure and Biological Activity of Epibatidine" in the Milestones Section of this volume. The group did occasionally explore other areas, such as bufadienolides, peptides (the hunting magic peptide), ants, beetle, millipede and mite alkaloids, and even some ryanodines in a "spider moth" (unpublished work). The Daly maxim was "if it has biological activity and hasn't been looked at, we are good to go on it." With the passing of John Daly in 2008, his group continues the study of amphibian and arthropod alkaloids. A current member of the group is Nirina R. (Rabe) Andriamaharavo, a visiting scientist from Madagascar, who worked closely with Daly over the years.[2]

The tradition of natural products is also being continued by the LBC natural products chemistry section headed by Carole Bewley. One of her primary research interests is the isolation and complete structure elucidation of natural product inhibitors of mycobacterial enzymes and HIV-1 membrane fusion, coupled with mechanism of action studies and structure-guided design and synthesis of natural product mimics or analogs.

The Laboratory of Chemistry once headed by Witkop is now fragmented, but programs of the original LC continue, with a steroid laboratory in NIDDK under Stoney Simons, a successor to the famous laboratory once headed by Erich Mosettig (where many plant sterols and vitamin D

intermediates were discovered in the 1940s and 50s. An equally eminent Laboratory of Medicinal Chemistry, started under Lyndon Small and continued by Everette May, is now under Kenner Rice, and, although it is in in a different institute, (the National Institute on Drug Abuse/National Institute on Alcohol and Alcoholism; NIDA/NIAAA), the focus is still on the synthetic and mechanistic aspects of opioid analgesia.

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National Center for Agricultural Utilization Research

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The Northern Regional Research Laboratory (NRRL), now National Center for Agricultural Utilization Research (NCAUR), a laboratory maintained by the US Department of Agriculture (USDA), Agricultural Research Service (ARS), was established by an Act of Congress in 1938 and the building in Peoria, Illinois was dedicated in October 1939. Among the objectives of the Laboratory were the development of new products from agricultural commodities and the discovery of new crops to replace those, such as corn and soybeans, where surpluses were a continuing problem.

NRRL was quickly called upon to develop methods for the production of penicillin. Key contributions to large-scale penicillin production included the introduction of submerged culture fermentation, the use of precursors and the discovery of a mold strain more productive of penicillin.[1] Pioneering research at NRRL allowed rapid advances in the antibiotic industry and has contributed to the production of numerous antibiotics. NCAUR also maintains the NRRL Culture Collection, one of two major culture collections in the U.S., with the primary function of maintaining pure cultures of microorganisms (bacteria, yeasts and fungi) that are known to produce useful products by fermentation.[2] The collection has proved essential to the discovery of newer antibiotics, in studies of mycotoxins (including tricothecenes and fumonisins), and in discovery of numerous metabolites having antifungal, antiinsectan and other biological activities.

The search for new crops that would yield products of higher value to farmers, and that could be used for industrial purposes rather than food led to a survey of plants growing in the United States and to a large collection of germplasm (seeds) at NRRL. This was supplemented by seeds of many unusual and little known plant species assembled by USDA botanists from a number of countries throughout the world.

Of primary interest to the program were potential new crop species containing unusual lipids as sources of specialty chemicals. Several dozen previously unknown fatty acids were revealed during these studies, including those having unusual chain lengths, various positions of double bonds and/or conjugated double bonds, acetylenic fatty acids and those having hydroxy or epoxy groups at various positions along the fatty acid chain. Kleiman[3] has summarized the more important species identified as new industrial oilseed crops during this work, and provided information on their potential uses in commerce. The research on seed lipids also led to the discovery of crepenynic acid,[4] an acetylenic analogue of linoleic acid and previously unrecognized biosynthetic intermediate of many polyacetylenic compounds, and the nitrogen containing cyanolipids.[5]

Collateral research on seed extracts, in cooperation with the NCI and other researchers, resulted in discovery of several potentially useful antileukemic, antitumor and cytotoxic compounds. Most notable of these were homoharringtonine from *Cephalotaxus harringtonia*,[6] cephalomannine (a Taxol® analogue) from *Taxus wallichiana*,[7] maytansinoids from *Trewia nudiflora*,[8] sesbanimide from *Sesbania drummondii*[9] and acetogenins from *Asimina triloba*.[10] The initial research attracted widespread and continuing interest in these and related compounds as potential pharmaceutical agents, and the full impact of these studies is yet to be determined.

Of particular importance to plant science was the identification and structure determination of brassinolide by Grove, et al.[11,12] Brassinolide is the first plant growth substance shown to have a steroidal structure and is the first naturally occurring steroid that has a seven-membered lactone ring as part of the fused ring system.

Tall fescue grass (*Festuca arundinacea*), widely grown as forage in the U. S., was known to produce a toxic syndrome in cattle in some places during certain times of the year, and particularly under stressful environmental conditions. The problem was traced to an endophyte that produced ergot-type alkaloids, and the primary causative agent identified as ergovaline.[13] The loline group of pyrrolizidine alkaloids was also present in endophyte-infected tall fescue.[14] Both alkaloid types were then demonstrated to occur often in endophyte-infected grasses.[15] Sleepygrass (*Stipa robusta*) from the Sacramento and Sierra Blanca mountains of New Mexico was known to produce a profoundly somnolent or stuporous condition in horses lasting up to several days. The primary active constituent in this latter case was demonstrated to be lysergic acid amide.[16]

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The NIH Office of Dietary Supplements

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The U.S. National Institutes of Health (NIH) has a long record of supporting research on natural products. In response to public interest, the US Congress created two entities within NIH for the purpose of investigating natural remedies for human health. The NIH Office of Alternative Medicine was created in October of 1991, and became the National Center for Complementary and Alternative Medicine (NCCAM) in October of 1998[1]. NCCAM's mission is to explore complementary and alternative healing practices in the context of rigorous science, train CAM researchers, and disseminate authoritative information to the public and professional communities. The Dietary Supplement Health and Education Act of 1994 (DSHEA),[2] created the Office of Dietary Supplements (ODS) within the Office of the Director at NIH. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the US population[3]. The ODS in collaboration with NCCAM has several programs[4] relevant to pharmacognosy. The two major efforts include a program of dietary supplement research centers focused on botanicals and an Analytical Methods and Reference Materials Program (AMRM).

The NIH currently funds six Dietary Supplement Research Centers focused on botanicals, collectively referred to as the Botanical Research Centers Program (BRCP). The DSHEA assured consumers ready access to a wide variety of products, including many containing botanical ingredients.[2] However, despite widespread availability of these products and promising science,[5,6,7] biomedical research in this area was relatively limited. Thus, the efficacy and safety of many botanicals had not been adequately evaluated. In 1999 the ODS received funding to develop a botanical research initiative. NCCAM collaborated in the development and funding of the initiative, resulting in the creation of the BRCP. The program is intended to advance the spectrum of botanical research activities ranging from plant identification to early-phase clinical studies, with preclinical research encouraged as the primary focus of center activities. From the outset it was clear that the complexity of botanicals poses unique research challenges. For example, in contrast with synthetic drugs, botanicals are complex mixtures of bioactive constituents that may have synergistic or antagonistic effects. Pharmacognosists within the centers appreciated this complexity and have done much to advance the science conducted under the umbrella of the BRCP. The work of the centers is relevant to health maintenance, disease prevention, and disease treatment. The centers provide: (1) a balance across clinical areas; (2) proficiency in natural products research focused on botanicals; and (3) expertise in using contemporary methodologies. Each center has a thematic focus with high potential for being translated into benefits for human health. For example, one center studies actions of botanical oils rich in omega-3 fatty acids and their potential to prevent inflammatory diseases. Another group studies the molecular and cellular processes that influence the development of metabolic syndrome. All centers operate under a funding mechanism that supports a broad collaborative, interdisciplinary research program consisting of highly integrated activities and associated research infrastructure. The BRCP provides a rich environment for training the next generation of scientists in a number of disciplines including pharmacognosy. Building multidisciplinary

research teams, using contemporary technologies, and conducting research that considers the complexity of human biology are very much in line with the philosophy of the NIH Roadmap.[8]

Quality of botanical products is an uncertainty faced by consumers, clinicians, regulators, and researchers. In response to quality concerns and the need for validated methods for Dietary Supplement analysis, the US Congress directed the ODS to allocate funds for methods validation, and the AMRM Program was created. The program taps into the origins of pharmacognosy as it seeks to create, validate, and disseminate modern quality assurance tools for natural products. The program was constructed from stakeholder input and incorporates several activities in a coordinated framework.[9] The major accomplishments of the program are methods validation and reference material development in partnership with the US Food and Drug Administration and the National Institute of Standards and Technology (NIST).[10] To date, seven supplement methods have been approved as first action AOAC Official Methods.[11] In addition to progress on Official Methods, the past five years marked the emergence of a community of researchers interested in dietary supplement analysis. In the two years before the start of the AMRM, there were no DS publications in the Journal of AOAC International. Since the program's launch in 2002, there have been over 100 DS methods published in the journal. The program has also partnered with NIST for the development of reference materials to complement the analytical method activities. The materials are intended for use in evaluation of analytical methods performance and are useful tools in laboratory proficiency testing.[12] There are currently 15 suites of NIST Standard Reference Materials (SRM™) in process, with five now available.[13]

Enormous challenges remain in evaluating safety and efficacy and developing quality assurance tools for dietary supplements for the projected 40,000 supplement products expected to be on the US market by 2010.[14] Acceleration and expansion of the programs are expected to continue as interest in supplements grows.

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(3) http://dietary-supplements.info.nih.gov/
(4) http://dietary-supplements.info.nih.gov/Research/research.aspx
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