

National Institutes of Health Botanical Research Centers Program: An Expert Panel Review

Executive Summary

This report summarizes the deliberations, findings, and recommendations of an expert panel convened in February 2003 to review the Botanical Research Centers Program, jointly funded by several offices, centers, and institutes of the National Institutes of Health (NIH). This program assessment was prompted by the approaching end of the funding cycle for the first centers that were awarded, growth and development in NIH's botanical research portfolio in the years since the centers program began, and growing public interest in the safety and efficacy of botanicals.

Charge to the Panel

The panel was asked to assess the current Botanical Research Centers Program and make recommendations for the organization of future centers and the activities they pursue. Specifically, panel members were asked to consider:

- The full range of activities carried out by current botanical research centers and whether all of those activities should continue in the future
- The role of clinical research in botanical research centers in the years ahead
- Whether future botanical research centers should organize their research around selected themes
- The most suitable funding mechanisms for research centers conducting botanical research.

Background and Partners' Perspective

NIH's Botanical Research Centers Program was initiated by the Office of Dietary Supplements (ODS) with a request for applications in early 1999 and the selection of two research center sites late that year. More awards followed in 2000 and 2002, until the program had grown to six research centers across the United States. In keeping with the major areas of emphasis established by the ODS, each center was expected to identify and characterize selected botanicals, determine their bioavailability and bioactivity, investigate active constituents and mechanisms of action, and conduct clinical and pre-clinical studies.

With the creation of this research centers program, the ODS fulfilled one of the major goals identified in its 1998 strategic plan and responded to a congressional request that it undertake a major botanical research initiative. Without grant-making authority of its own, the ODS has fulfilled its congressional mandates and strategic planning goals by joining forces with other interested NIH institutes and centers. Along with ODS, the primary partners in the Botanical Research Centers Program have been the National Center for Complementary and Alternative Medicine (NCCAM) and the National Institute of Environmental Health Sciences (NIEHS).

Since the start of FY 1999, when NCCAM was founded, a substantial portion of its research portfolio has been devoted to botanical research. By FY 2002, botanicals made up the largest single category in NCCAM's research budget, representing nearly one-third of its research spending. As NCCAM has grown, it has adopted a number of new policies and procedures to enhance the quality of its botanical research. Over the past year, NCCAM has issued detailed guidance for prospective investigators proposing research on natural products in general, and clinical trials on botanicals in particular. In addition, NCCAM is taking steps to establish an analytical resource center to analyze botanical products slated for NIH-funded clinical trials. (For more information, see <http://www.nccam.nih.gov/research/concepts/consider/analytical.htm>.)

In 2002, NCCAM solicited external input in the review of its clinical trials programs and Complementary and Alternative Medicine (CAM) Research Centers. Recognizing the unique challenges of CAM research, reviewers suggested that research centers could most effectively contribute to advancing clinical research in CAM by focusing on studies of mechanisms of action and conducting Phase I and small Phase II clinical trials. Generally, substantive Phase II and Phase III trials were thought to be better suited for settings other than research centers. Finally, the expert panel that reviewed the NCCAM Research Centers suggested that there might be scientific and fiscal advantages to supporting research centers through funding mechanisms other than the P50 specialized center award.

The involvement of NIEHS in the Botanical Research Centers Program stems, in part, from its role as the lead NIH institute for toxicology research. Because of a lack of data on possible adverse health effects of botanicals, the interagency National Toxicology Program, administered by the NIEHS, has been planning and conducting research since 1998 on a number of botanicals available as dietary supplements. These studies are investigating potential adverse effects such as neurotoxicity, immunotoxicity, and reproductive toxicity and are seeking to identify adverse effects that may result from heavy or prolonged use of botanicals. As the National Toxicology Program's botanical research activities continue, there may be benefits to increased interactions between its investigators and those in the botanical research centers.

At the time the Botanical Research Centers Program was initiated, NIEHS funding mechanisms did not include the P50 specialized center grant; as a result, the two botanical research centers with NIEHS involvement were converted to P01 program project awards. (See Appendix E for a description of funding mechanisms for NIH research centers.)

Since then, however, NIEHS funding policies have evolved to include a broader range of funding mechanisms for research centers.

Program Perspective

Reflecting its collaborative funding, the Botanical Research Centers Program is managed jointly by ODS, NCCAM, and NIEHS. Though the botanical research centers differ slightly in organization, in most cases they are expected to:

- Conduct three to four R01-like research projects
- Sponsor pilot research projects
- Be organized around a resource core devoted to administration and planning and incorporate at least two research resource cores, one of which must provide expertise in botany
- Provide research training and career development opportunities for graduate students, postdoctorates, or junior faculty
- Provide information on botanical dietary supplements to consumers and health care professionals
- Be guided by an external advisory committee
- Stimulate a sustained institutional commitment to their work

To foster greater research center productivity in the future, program staff underscored the importance of outlining requirements for botanical research centers in clear detail in the initial request for applications. Other key prerequisites for success are the experience of the center director, readily available research resources, and strong relationships among investigators.

Center Director's Perspective

In the course of their deliberations, the panel heard from the director of one of the currently funded botanical research centers, who had been chosen by the other center directors to represent them.

The center director stressed the importance of the shared resources that a research center can supply and the economies of scale that accrue to research as a result. In the case of a developing biomedical field, such as botanical research, a major P50 center award provides a level of support and visibility that often attracts new investigators and investments. Indeed, the center director suggested that this support and visibility might account for the greater leveraging power that the botanical centers funded with P50 awards seemed to enjoy. For these reasons, the current botanical center directors suggested retaining the P50 award for funding botanical research centers, as well as maintaining the existing areas of research emphasis.

Obstacles encountered by some of the botanical research centers, such as difficulties recruiting experienced research associates, were largely attributed to the emerging nature of the field. Some centers have minimized these challenges by establishing partnerships with other institutions or with schools within their own university.

NIH Approaches to Funding Research Centers

As described in Appendix E, NIH-sponsored research centers can be supported through a variety of funding mechanisms, including P01s, U01s, U19s, P30s, P50s, and U54s. Some center funding awards, such as the P30 center core grant, limit funding to selected key aspects of research, while others, such as the P50 specialized center award and U54 specialized center cooperative agreement, generally encompass a broad range of research center activities, including research projects, core resources, pilot projects, and career development. The P50 grant mechanism is typically chosen to support research in established fields, conducted at research-intensive universities. The U54 cooperative agreement, on the other hand, is often better suited for emerging fields of research or less experienced research institutions. With the active involvement of NIH program staff they require, U54 and other U-series cooperative agreements can enhance research productivity and hasten progress.

Ultimately, however, the choice of funding mechanism is less important than the features included in a research centers program's request for applications (RFA) and operating guidelines. For example, it is the RFA that shapes the nature and organization of the research by specifying particular themes or areas of study, stipulating the inclusion of clinical research projects, requiring collaborative research or networking, or indicating whether the choice of a theme should be guided by public health needs or NIH-identified research priorities. Similarly, a program's RFA and guidelines determine the number and type of research resource cores, the level of flexibility in the use of pilot and developmental funds, and the extent to which its research centers engage in related activities such as career development and public outreach. Finally, the RFA establishes the all-important criteria for review, which should closely correspond to the program's key objectives and be weighted to emphasize the principal goals a centers program aims to achieve.

Several of the requirements originally specified in the RFAs for the current botanical research centers should perhaps be reconsidered, given the status of the field and developments at the NIH in the years since the centers were founded. For example, in an emerging field of biomedical research, such as botanicals, the career development of young investigators often requires greater attention and care than is typically provided in a research center setting. Accordingly, botanical research training and career development activities might be better accomplished under more structured circumstances, possibly by requiring a formal career development plan for each trainee within a research center. Alternatively, centers-based career development might be discontinued altogether and replaced by a series of training grants, fellowships, and career development awards in botanical research.

In addition, shaping the botanical centers program in a way that encourages—or even requires—the sharing of certain resources could prevent duplication of effort, enhance research capacity, and help expedite high-priority research goals. One option for enhancing the efficiency of the botanical research centers might be to link the centers in a network that would allow them to share research infrastructure, such as botanical resource cores. Public outreach and information dissemination activities might also be centralized, either within a single center or at the NIH.

After decisions about funding mechanisms, RFAs, and program guidelines have been made, there is still much that NIH program staff can do to foster productivity in a research centers program. Through active oversight of a centers program and judicious use of supplemental funds, program staff can help set scientific priorities, select high-quality new research projects, and foster collaboration among centers. Where management responsibilities are shared among multiple NIH institutes and centers, as is the case with the botanical research centers, consistency in oversight and priority-setting is particularly important.

Expert Panel Findings and Recommendations

Since its start in 1999, the research centers program has grown to be the NIH's leading botanical research initiative, satisfying the goals of the ODS and congressional interest in botanicals, while advancing the research interests of a number of NIH offices, centers, and institutes. A number of the program's centers have successfully generated additional funding for botanical research, further facilitating the growth and development of this area of biomedical research. Still, the expert panel recognized the value of reviewing the centers program in its early stages and considering improvements before proceeding with another round of awards, and commended the NIH sponsors for their willingness to do so.

In reviewing the features of the current Botanical Research Centers Program, the expert panel supported the requirements that research centers be guided by broad-based external advisory boards and participate in an annual centers meeting, and urged that those facets of the program be retained in the future. Panel members were also encouraged by the extent to which some of the existing centers focused their research on the needs of sensitive populations, like women and the elderly, and others used pilot project funding to draw new investigators into botanical research.

Yet at the same time, the expert panel concluded that NIH program managers should take steps to more strongly encourage high standards of research productivity and efficiency throughout the Botanical Research Centers Program. As program requirements and guidelines are adapted for the next round of research center awards, panel members recommended that more attention be paid to fostering collaborations with FDA, NCI, and other NIH-funded scientists conducting botanical research, and incorporating a broader range of relevant research technologies and approaches into research centers, such as genomics, proteomics, informatics, and systems biology. Finally, recognizing the

significant challenges posed by the lack of standardization in botanical products and research materials, panel members urged that the centers further emphasize quality assurance and quality control in botanical products and that the NIH take steps wherever possible to help address these obstacles and enhance the effectiveness of botanical research.

Specific Recommendations for the Next Generation of Research Centers

In considering the structure and focus of the next generation of botanical research centers, the panelists agreed that future centers should be organized around coherent, well-justified themes. In selecting botanicals for research, for example, prospective centers might be encouraged to give special consideration to those under study, or slated for study, by the National Toxicology Program of the NIEHS.

Beyond the selection of a high-impact central research theme, panelists advised that future botanical research centers maintain the current general areas of emphasis, including identification and characterization of botanicals, studies of bioavailability and bioactivity, research on active constituents and mechanisms of action, and clinical and pre-clinical studies, but that they increasingly focus on the effects of botanicals in humans. In particular, the expert panel recommended that one of the primary goals of botanical research centers be to investigate the safety and efficacy of botanicals in humans. If a prospective research center site does not have expertise in conducting both basic and translational studies in botanical research, investigators should be encouraged to form partnerships with other institutions or schools within their own university to do so.

Translational research projects in botanical centers should test the relevance of specific botanicals or mixtures of botanicals for human health or determine the biological basis of an observation made in the clinic or a population. Whether “bench to bedside” or “bedside to bench,” translational research projects in botanical research centers should be designed to achieve definitive goals within the five-year period of the award. Examples of translational research appropriate for botanical research centers might include:

- Conducting Phase I-II trials of red clover for menopausal symptoms
- Studying the mechanism of action for the protective effects of green tea
- Determining the neuroprotective effects of grape polyphenols
- Comparing the effects of moderate and high doses of soy isoflavones on prostate cancer
- Studying the mechanism of action for the anti-inflammatory effects of turmeric
- Examining the mechanisms of action of Chinese medicine herbs in prostate cancer, administered singly and in combination

The key features the panel recommended for future botanical research centers are summarized in Table 1.

Table 1. Key Elements of Future Botanicals Research Centers

- High-impact theme
- Studies of basic mechanisms and human health, with a high level of translational interaction between the two
- Innovative technology
- Emphasis on quality assurance/quality control

Recommendations for Other Center Activities and Funding

In considering the range of other activities currently carried out by botanical research centers, the panel endorsed the continuation of pilot research projects, like those conducted by existing centers.¹ Given the many public education and outreach activities currently sponsored by the NIH ODS and NCCAM, panelists suggested that information dissemination need not be a direct responsibility of botanical research centers in the years ahead. Furthermore, before determining whether botanical research centers should be required to carry out research training and career development in the future, the NIH sponsors should consider personnel needs in botanical research and whether they would be better met by research centers or through dedicated research training and career development awards. Whatever approach is selected should provide opportunities for physicians and other health care professionals to be involved in botanical research.

Finally, at this juncture in the Botanical Research Centers Program, the expert panel recommended that its NIH sponsors consider funding mechanisms that would more readily allow NIH program staff to promote consistently high levels of research productivity and ensure that resources are directed toward the highest priorities in botanical research. The panel suggested that one such type of award is the U54 specialized center cooperative

¹ Typically limited to one to two years per project, with total annual costs of \$100,000 or less for each center.

agreement; however, other funding mechanisms could be configured to achieve the same goals. To allow an opportunity for further development to sites that might not yet be ready for a centers award, ODS and its partners might also explore a program that would combine research center and planning awards.

Conclusion

While commending the progress of the botanical research centers to date, the expert panel called on NIH program managers to work closely with investigators to foster higher standards of research productivity and efficiency throughout the Botanical Research Centers Program, by issuing program guidelines and taking steps to strengthen oversight. Furthermore, as program requirements and guidelines are adapted for the next round of research center awards, panel members recommended that more attention be paid to quality assurance and quality control in botanical products, fostering collaborations with scientists conducting botanical research at other sites, and incorporating a broader range of relevant research technologies and approaches into the centers' research. Finally, panelists agreed that future centers should be organized around coherent, well-justified themes and increasingly focus on the effects of botanicals in humans.

Appendix A

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Appendix B

Expert Panel Review of the NIH's Botanical Research Centers Program

Office of Dietary Supplements
National Center for Complementary and Alternative Medicine
National Institute of Environmental Health Sciences

Doubletree Hotel
Rockville, Maryland
February 21, 2003

Agenda

8:00 a.m.	Welcome and Introductions	Bernard Goldstein, M.D.
8:10 a.m.	Charge to Committee	Paul Coates, Ph.D.
8:30 a.m.	Partner Perspective	Stephen Straus, M.D.
8:50 a.m.	Program Perspective	Christine Swanson, Ph.D.
9:05 a.m.	Center Directors' Perspective	Connie Weaver, Ph.D.
9:35 a.m.	NIH Approaches to Funding Research Centers	Brian Kimes, Ph.D.
10:00 a.m.	Break	
10:15 a.m.	Consideration of Questions and Discussion	Bernard Goldstein, M.D.
Noon	Lunch	
1:00 p.m.	Further Consideration and Discussion	Bernard Goldstein, M.D.
2:30 p.m.	Break	
2:45 p.m.	Further Consideration and Discussion	Bernard Goldstein, M.D.
3:30 p.m.	Summary of Initial Findings and Recommendations	Bernard Goldstein, M.D.
4:00 p.m.	Adjourn	

Appendix C

Botanical Research Centers Program Questions to Consider

1. Current botanical research centers are encouraged to (a) identify and characterize botanical ingredients, (b) examine their bioavailability and bioactivity, (c) identify their active constituent(s) and mechanism(s) of action, and (d) study the health effects of botanicals in humans.
 - Should these areas of emphasis be changed?
 - Should some of these areas be required, rather than encouraged?
 - Would it be more effective to take a different approach to clinical research on botanicals? For example, should clinical research be an optional activity for some centers?
2. Should future botanical research centers be structured to:
 - Foster specific research goals, such as multidisciplinary or translational research?
 - Encourage more integrative research collaborations among centers?
 - Organize their research around selected themes, such as (a) related classes of botanicals (e.g., botanicals with estrogenic activity), (b) the role of botanicals in preventing or treating specific diseases or medical conditions, or (c) the use of botanicals by certain population groups? If so, how should the areas of emphasis be selected?
3. Most of the existing botanical research centers are required to conduct a range of activities, including:
 - Basic and clinical research
 - Pilot research projects
 - Research training and career development
 - Outreach and public education

Should future centers continue to incorporate all of these activities?
4. Considering the current state of botanical research, could botanical research centers benefit more from funding mechanisms that provide:
 - Additional involvement and oversight by NIH program staff (e.g., cooperative agreements)?
 - Greater autonomy to investigators (e.g., P01s)?
5. Of the existing NIH funding mechanisms for research centers (i.e., P01s, P30s, P50s, U01s, U19s, U54s), which are best suited for the future roles likely to be played by botanical research centers?

Appendix D

Current Botanical Research Centers

<u>Center</u>	<u>Fiscal Years of Funding</u>
University of Illinois Center for Botanical Dietary Supplement Research in Women's Health	1999-2004
UCLA Center for Dietary Supplement Research: Botanicals	1999-2004
Purdue University Botanical Center for Age Related Diseases	2000-2005
University of Arizona Center for Phytomedicine Research	2000-2005
University of Missouri Center for Phytonutrient and Phytochemical Studies	2000-2005
Iowa State University Center for Research on Botanical Dietary Supplements	2002-2007

Appendix E

Selected Funding Mechanisms for NIH Research Centers

Code	Title	Features of Award
P01	Research Program Project	Broadly based, multidisciplinary research program with a well-defined central research focus or objective, consisting of at least three interrelated R01-like research projects. May also include associated infrastructure or "resource cores."
P30	Center Core Grant	Provides research infrastructure support (such as laboratories, equipment, statistical analysis, database management, patient recruitment, and administrative coordination) to enhance and extend the effectiveness of NIH-funded research projects. The core grant is integrated with the center's component research projects (generally R01s), though funded independently of them.
P50	Specialized Center	Broadly based, multidisciplinary research program with a well-defined central research focus or objective, consisting of at least three interrelated R01-like research projects and associated infrastructure or "resource cores." As a group, center grants (whether P20s, P30s, or P50s) are generally more clinically oriented than program project grants.
U01/ U19	Research Project/ Research Program Cooperative Agreement	Broadly based, multidisciplinary research program with a well-defined central research focus or objective, consisting of at least two interrelated research projects. May also include associated infrastructure or "resource cores." When using cooperative agreements, NIH institutes anticipate substantial scientific and/or programmatic involvement with the award recipient.
U54	Specialized Center Cooperative Agreement	Broadly based, multidisciplinary research program with a well-defined central research focus or objective, consisting of at least three interrelated research projects and associated infrastructure or "resource cores." When using cooperative agreements, NIH institutes anticipate substantial scientific and/or programmatic involvement with the award recipient.