

# National Institutes of Health Botanical Research Expert Panel Meeting

July 14, 2022

## Executive Summary

The National Institutes of Health (NIH) Office of Dietary Supplements (ODS) and the National Center for Complementary and Integrative Health (NCCIH) have supported the Consortium for Advancing Research on Botanical and Other Natural Products (CARBON) program since 1999. (Figure 1). Additional support has been or is currently being provided by the National Institute of Environmental Health Sciences, the National Cancer Institute, and the National Institute on Aging. The CARBON program currently includes Botanical Dietary Supplements Research Centers, centers which are focused on enhancing methods and resources for research on the health effects of complex natural products (NP), and related pilot projects (Figure 2). The importance of this program is clear from the prevalence of use of botanical products by the U.S. public and their prominent representation in pharmacopeias throughout the world.

In 2013, an outside expert panel reviewed the CARBON program; the panel's discussions inspired changes in the program's focus. In 2021, a new expert panel, called the Botanical Research Expert Panel (BREP), was formed to provide expert input on both the CARBON program's progress in the last decade and on future directions. The BREP held a virtual meeting on July 14, 2022, to present and discuss the results of their evaluation of the program. In each of the four main sessions of the meeting (Sessions 1 through 4), two panel members presented the session topic, and then the full panel and NIH staff discussed the issues that had been raised.

In background presentations at the beginning of the meeting, NIH staff explained that the central focus of CARBON is on elucidating the chemistry and any associated beneficial and/or deleterious effects of chemically complex NP in humans. During the first decade of CARBON, NCCIH and other NIH components supported Phase 3 clinical trials on a variety of botanicals; most of these trials did not show any evidence of benefit. Following on those results and the 2013 expert panel review, CARBON placed a greater emphasis on method development and on mechanisms of action and focused on the effects of botanicals on human resilience. The two methods-focused components of the current CARBON program are the High-throughput Functional Annotation of Natural Products (HiFAN) research center and the Natural Products Magnetic Resonance Database (NP-MRD). Dr. Barbara C. Sorkin, Office of Dietary Supplements (ODS), shared data on publications from CARBON and other botanical research projects across NIH that indicate that the impact of CARBON publications exceeds that of publications from other projects (Figure 3).

### **Session 1: Strengths and weaknesses of the program**

In what specific ways has the CARBON program (P50, U19, U24, and U41 components) over the last 8 years:

- a. Advanced understanding of the biological activity of chemically complex natural products (NP)?
- b. Developed new technologies, methods, approaches, or paradigms that have advanced this field?
- c. Rigorously trained the next generation of highly productive, independently funded and successfully collaborative (shared data and publications) investigators?
- d. Addressed the most critical gaps in knowledge about specific botanicals?

Are there components of the CARBON program that have not achieved their goals—or that are less effective? Should any of these components be discontinued or phased out?

The Expert Panel presenters noted that the centers awarded in 2015 showed strengths in phytochemical analysis, especially in areas such as separation technology, structural purity analysis, mass spectrometry, and nuclear magnetic resonance spectroscopy. These centers produced substantial numbers of publications, and three of them produced high-impact publications.

Regarding outreach, it was noted that some of the centers' websites are out of date or not fully populated. In some instances, the websites describe the projects the centers are conducting but do not present information on accomplishments, impact, or publications. The fact that information on these topics is hard to find diminishes the impact of the CARBON program. Better outreach could be particularly valuable for HiFAN and the NP-MRD because they are producing resources for use by the larger scientific community. Awareness of the NP-MRD (first funded in 2020) among potential users appears to be low. Panel members noted the importance of linking the NP-MRD to related databases and to human metabolomic and mass spectrometric data. Developing sustainable databases is important for continued progress in this field.

The strength of training programs varies among the centers, with the strongest programs at centers that have an NIH Institutional Training grant in a participating or related department. The lack of a requirement for training programs at HiFAN and the NP-MRD is a missed opportunity for the CARBON program. Moving to a cooperative agreement (U) funding mechanism has improved center operations and continued NIH oversight should be valuable.

In discussion, panel members said that tracking trainees' career paths after they finish their training would be useful. Dr. Craig Hopp, NCCIH, explained that tracking trainees is a challenge for all of NIH. Holders of training grants may not be able to follow their former trainees' whereabouts. Panel members emphasized the importance of centers sharing their data and depositing it in appropriate databases. Dr. Hopp explained that a new NIH-wide policy that goes into effect in 2023 will address many issues related to data sharing.

## **Session 2: Focus of the current program**

2013 and 2019 funding opportunity announcements (FOAs) and ensuing awards

The Botanical Center Request for Applications (RFA) for the current Botanical Research Centers required investigators to focus on addressing the most critical gaps for the conduct of optimally designed future clinical trials.

- a.** Should this remain the focus going forward?
- b.** If not, are there gaps in particular parts of the spectrum from bench to clinical research where a transdisciplinary approach is most critical to future progress in research on the health effects of botanicals?
- c.** Within the missions of ODS and NCCIH, what biological outcomes or health conditions (e.g., promotion or restoration of health or resilience, disease prevention among diverse populations) are the most promising targets for botanicals and other NP?

The High Throughput Functional Annotation of Natural Products (Hi-FAN) and Natural Products Magnetic Resonance Database (NP-MRD) Centers are focused on developing methods for facilitating discovery and subsequent elucidation of the molecular mechanisms of action of constituents of complex NP and their combinations, and on developing analytical tools and data repositories, respectively.

- a. Should these remain the foci of these two types of centers going forward?
- b. What, if any, are other critical gaps in methodology or technology for advancing the understanding of the biological mechanisms of action of complex NP which that require a transdisciplinary, multiproject approach and would benefit from additional NIH funding?

The first presenting Expert Panel member addressed the question of whether filling knowledge gaps in preparation for clinical trials should remain a focus of the CARBON program going forward. He concluded that CARBON should continue to emphasize this type of work because of the importance of clinical trials. Other panel members noted the importance of striving for answers to the public's questions about whether a given botanical is beneficial to health and of supporting the preclinical research needed to prepare for rigorous clinical trials. In discussion of the importance of focus on resilience, prevention, or wellness outcomes, it was noted that clinical trials with prevention outcomes require longer durations and thus incur higher costs, so an important focus for the CARBON program may be defining and validating mechanistic understanding of animal targets for resilience and wellness, which will be crucial for future clinical trials.

Panelists noted emerging research interest and opportunities in several arenas, with a unifying theme of moving away from a focus on single ingredients toward addressing the chemical complexity of foods and herbs, their interactions with diet as a whole and with individual genetic and metabolic differences and perhaps differences in the microbiome. It was agreed that new tools are needed to address synergies. A panel member asked whether the U.S. Department of Agriculture could be brought into the CARBON program, given that nutrition is within their mandate.

One panel member suggested screening 1,000 botanicals in humans or other animals to fully elucidate their absorption, metabolism, distribution and excretion, and, perhaps, also their impact on the microbiome and/or on immune status. Such a project could create a digitized resource that could be mined by others. Other panelists expressed concern about the high cost and utility of large-scale screening, but the panel member stated that some screening approaches, such as untargeted metabolomics, have become relatively inexpensive, such that it could be feasible to run these analyses in animal models with small sample sizes for each botanical. The more difficult challenge is building the infrastructure to make the data usable and bringing data from different sources together. Others argued that there are not 1,000 botanicals that are currently important in the U.S. consumer market, and that it may be more useful to focus on a smaller number of botanicals with the greatest prevalence of use and greatest promise. A concern was expressed that keeping the cost for individual data points down may limit the rigor and generalizability of the data, which could compromise this resource.

It was noted that the role of the gut microbiota in modulating the health effects of botanicals or food is a fundamental question, among other things in understanding individual differences in responses, and that a possibly important opportunity for the Botanical Centers is to begin to elucidate the responses of gut microbiota to botanicals and how these responses in turn affect the host's response to input. Others cautioned that so far microbiome research has not produced as much practical information as had been hoped.

Panelists agreed that both hypothesis-generating research and more focused hypothesis-testing research could be appropriate for CARBON, that information from ethnobotany, when supported by preclinical data, could be helpful in prioritizing botanicals for screening or study, and that developing the technology to tease out the complexities of synergy in appropriate models could be an appropriate focus for CARBON.

### Session 3: Investigators and diversity

Is the existing CARBON program effective in reaching out broadly to recruit the best research leaders for the program?

- a. Are there specific or unique new efforts the CARBON program could undertake to expand or diversify, whether demographically or scientifically, the investigator pool it supports?
- b. Are there particular areas of expertise, perspectives, or insights that would be valuable to the current program? To the next iteration of the program?
- c. What diversification efforts have the greatest potential to strengthen CARBON and botanical/NP research as a whole?

The lead panelists for Session 3 presented data that show that the pipeline to develop African American academic chemists is very leaky, with percentages of Black students/researchers declining at every step from undergraduate to faculty. They noted that diversifying natural products chemistry is an ongoing challenge that must be addressed via long-term efforts but is somewhat more amenable to interventions at earlier career stages, and they discussed ways to increase participation of early-career researchers and members of underrepresented groups in CARBON. In general, while support of early-career researchers has been a strength of the current CARBON program, effective outreach to members of underrepresented groups has been lacking.

Approaches that could help to plug the holes in the pipeline include institutional training awards (when associated with focused efforts to recruit diverse students and postdoctoral fellows), focused mentored research grants, special programs aimed at students from underrepresented populations (such as partnerships between minority-serving institutions, historically black colleges and universities, Hispanic-serving institutions and tribal colleges and major biomedical research institutions), and efforts to involve diverse undergraduates in research, such as summer research experiences for community college students.

The panel noted that the CARBON pilot project initiative can provide valuable training for investigators from underrepresented groups but that the publicity/outreach for these could be improved. The use of administrative supplements to stimulate research by minority scientists in the existing CARBON centers could be more strongly encouraged. Seminars similar to the National Cancer Institute's Professional Enhancement Virtual Engagement Series (<https://ncihub.org>) that provide training on topics that are challenging for investigators new to the NIH grants system could be helpful.

In discussion, Dr. Hopp mentioned the ongoing availability of diversity supplements and said that more could be done to encourage investigators to identify candidates and submit applications. Several panelists said that there are barriers that make the use of supplements challenging, including difficulty in identifying appropriate candidates, the limitation of many NIH-funding mechanisms to U.S. citizens or permanent residents, and mismatches between the timing of the funding opportunity and the timing of the student's degree program. Panelists advocated for

increasing outreach at in-person events, including seminars specifically aimed at informing junior scientists about opportunities, and for recruiting more minority scientists into the peer review process as reviewing grant applications, which helps investigators learn to write more successful applications.

The panel pointed out that only a few CARBON centers can be funded at any given time, and CARBON Center funding opportunities occur only once every 5 years. Dr. Hopp noted that strategic thinking is needed to find ways to support the natural products research community between large initiatives and to support discovery science, which is not well suited for most current funding opportunities.

Panelists said that CARBON could benefit from including more diverse types of scientific expertise. For example, there will be a continuing need for researchers trained in the rigorous utilization of large data sets. It will be important for the program to include investigators who are cross trained in both data science and other fields and to ensure that database developers work closely with their intended users.

#### **Session 4: Increasing the impact of CARBON**

- a. What critical AND inherently transdisciplinary NP research gaps within the mission of ODS/ NCCIH are not covered by the existing efforts?
- b. In what other ways, including through what shifts in organizational structure or in approaches, could the program be more responsive to research advances and/or increase its potential to achieve the program goals?

The lead presenters for this question suggested that the Consortium's impact is broadened by the inclusion of products from fungi, bacteria, viruses, and animals as well as plant products and other dietary supplements. The preclinical research programs at the CARBON centers are valuable because they can establish phenotypes for further testing and help in understanding outcomes. Developing a set of common phenotypes that are available for testing—for effects such as decreasing inflammation, relieving pain, or improving physical function—with potential for use in all the Botanical Research Centers would increase the potential to help move research toward the clinic. CARBON might also benefit from providing more clarity on the outcomes that can be studied and giving more examples of what could be included. The term “resilience” is not widely used outside of certain areas of research, so there is a risk that it could be misunderstood. Looking for opportunities to incorporate botanicals into existing trials that focus on specific health conditions or outcomes could open new avenues for research.

In discussion, panelists suggested that efforts should be redoubled to have projects within a center build on and interact with one another. Collaborations between centers could be encouraged and incentivized. The administrative supplement model has been used to encourage collaborations, with varying degrees of success. Panelists said that putting data into databases should be a requirement rather than an option. With regard to broadening the scope of the substances studied, panelists said that both innovative screening and provision of answers to the public's questions about well-known botanicals are needed. One suggestion was to generate a human microbiome project-like database cataloging all the constituents in a relatively large number of botanicals. Conversely, another suggestion was that research should be focused where there is solid evidence for a biological effect rather than dedicating limited funds where they are unlikely to yield benefit. Panelists explained that large (thousands of animals), multicenter and multispecies, or at least

multistrain, rigorous preclinical studies in both sexes of animals are needed for the field to move forward; studies of this type should be completed before clinical research begins. In such studies the validation and standardization of botanicals must be seriously addressed; biochemical differences within a plant species can be dramatic and may account for inconsistent research results.

Panelists suggested that the annual meetings of the CARBON centers could lead to group publications or dedicated journal issues. The possibility of a special session at a scientific meeting involving all the centers was also discussed. Sessions exclusively dedicated to junior researchers could be held at large meetings; they could include a presentation by an inspirational speaker working in the field, training presentations on topics such as grantsmanship, and opportunities for junior researchers to present short talks. Expanding the centers' impact through having them bring their science into the undergraduate curriculum and through creating citizen science projects was discussed.

### Session 5: Putting it all together

The panelists revisited the pros and cons of creating a large database of plant compounds or incorporating botanical data into existing efforts to develop databases on food components. They emphasized the importance of databases but cautioned that keeping a database usable requires continuous funding. The panelists supported doing molecular research but explained that the fundamental question of whether the plants that contain the molecules have health benefits should not be forgotten; at some point, the effects of natural products need to be tested in people.

NCCIH Director Dr. Helene M. Langevin asked whether the standardization of experimental animals' diet and environment limits the applicability of animal data to humans. In response, Dr. Rafael de Cabo explained that standardized tests are most easily performed in a highly controlled environment, but at later stages in research, other diets and contexts can be examined. Investigators are starting to look at the connection between diet and metabolomics, but information on diet is difficult to obtain. ODS Director Dr. Joseph Betz pointed out that there is no such thing as a perfect study. Even with animal studies, effects may differ because of coprophagy, the sex of the animal handler, and other factors. In humans, large studies with thousands of participants are performed in the hope of including enough people so that variations in environmental factors such as diet do not overwhelm the study results.

Asked to identify the top messages they would like to emphasize from their discussions, the panelists listed:

- More effectively showcasing the CARBON program's accomplishments by requiring centers to provide information on their major discoveries and methodologies annually both on a central CARBON website and on their own centers' websites
- Emphasizing synergy, improving websites, and trying to spread CARBON's message more efficiently
- Requiring that data produced by funded centers be put into databases
- Ensuring those databases are useful for the research community
- Making greater efforts to attract scientists from underrepresented groups into the field
- Broadening the scope of the program, including increasing the variety of products that can be studied and the number of people who can participate
- Emphasizing a select number of botanicals, including those that are used most frequently in the United States
- Clarifying the outcomes that can be studied and avoiding buzzwords that cannot be easily understood
- Developing methodology for clinical and preclinical research to better understand targets and mechanisms associated with prevention
- Harmonizing methods for preclinical research on botanicals

## 2022 NIH Botanical Research Expert Panel Members

Panel Member	Institution
Chair: A. Douglas Kinghorn, Ph.D., D.Sc.	Ohio State University College of Pharmacy, Medicinal Chemistry & Pharmacognosy
Wendy L. Applequist, Ph.D.	Missouri Botanical Garden
Phil Crews, Ph.D.	University of California Santa Cruz, Department of Chemistry & Biochemistry
Rafael de Cabo, Ph.D.	National Institute on Aging, Branch Chief, Translational Gerontology
Pieter C. Dorrestein, Ph.D.	Skaggs School of Pharmacy and Pharmaceutical Sciences, Director, Collaborative Mass Spectrometry Innovation Center
Jeremiah J. Faith, Ph.D.	Icahn School of Medicine at Mt. Sinai and Icahn Genomics Institute
Ilya Raskin, Ph.D.	Rutgers, The State University of New Jersey, Department of Plant Biology
Connie M. Weaver, Ph.D.	San Diego State University

## 2022 NIH Botanical Research Expert Panel: supporting NIH program staff

D. Craig Hopp, Ph.D.,  
National Center for Complementary and Integrative Health, CARBON Co-Director

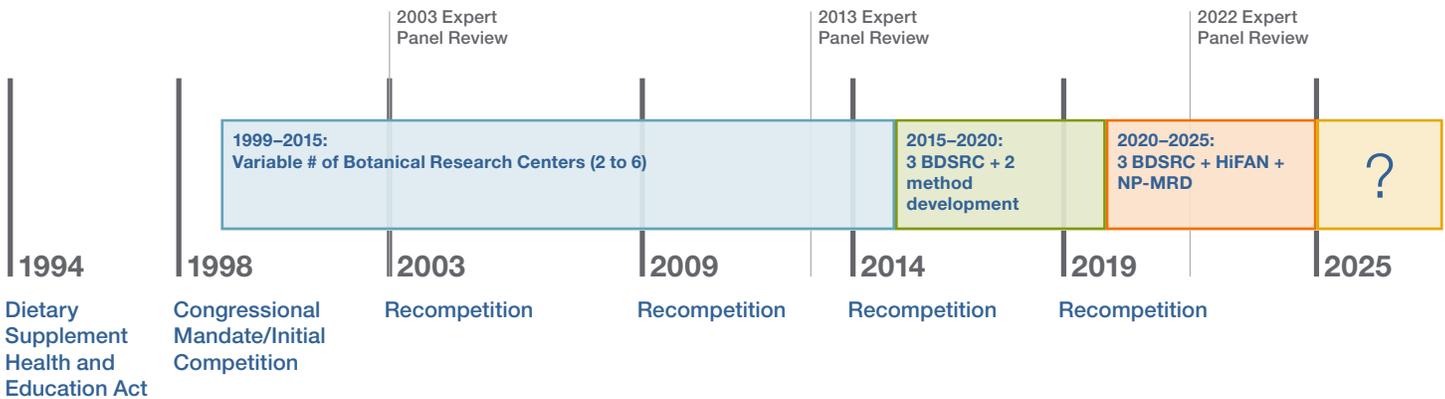
Barbara C. Sorkin, Ph.D.,  
Office of Dietary Supplements, CARBON Co-Director

LaVerne L. Brown, Ph.D.,  
Office of Dietary Supplements, Resilience Program Director

Patrick Still, Ph.D.,  
National Center for Complementary and Integrative Health, incoming CARBON Co-Director

**Figure 1**

## Consortium Advancing Research on Botanicals and Other Natural Products Program



BDSRC: Botanical Dietary Supplements Research Centers

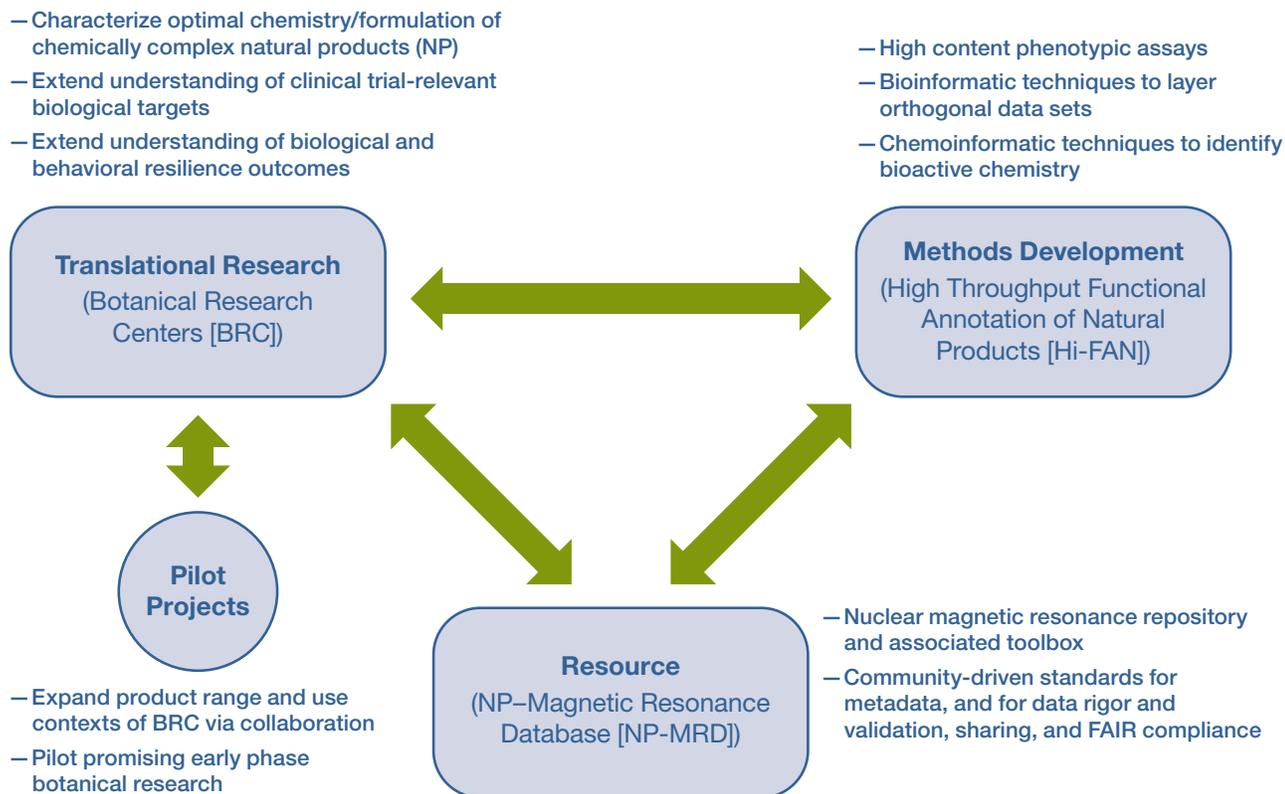
Hi-FAN: High Content Functional Annotation of Natural Products

NP-MRD: Natural Products Magnetic Resonance Database

See also: [https://ods.od.nih.gov/Research/CARBON\\_prior\\_awards.aspx](https://ods.od.nih.gov/Research/CARBON_prior_awards.aspx)

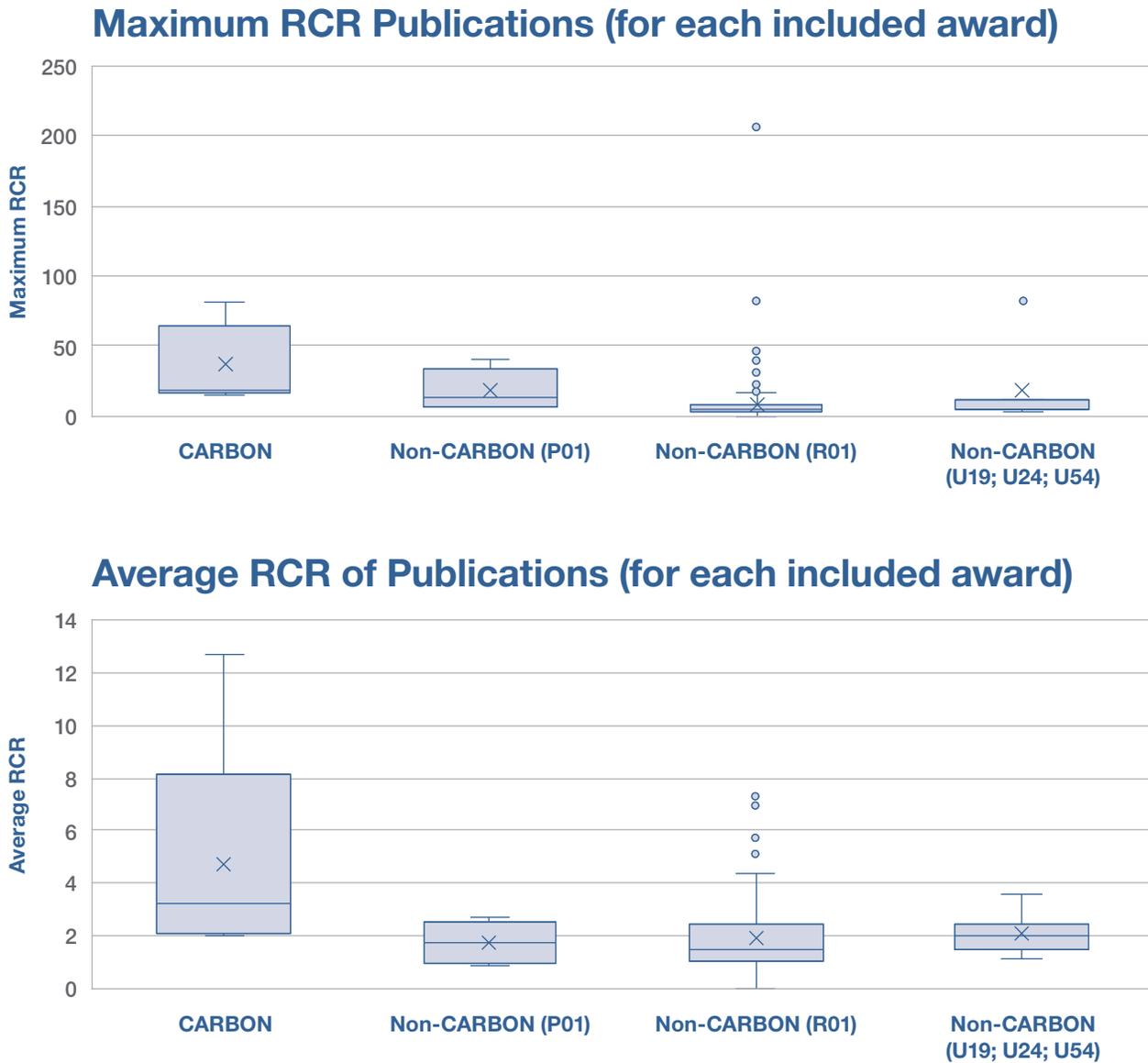
**Figure 2**

## Schematic: Structure of Current CARBON



**Figure 3**

**Comparison of Relative Citation Rates (RCRs)\* of CARBON-Supported Publications With Contemporaneous Publications From Other National Institutes of Health (NIH) Botanical Research Awards**



Ns for each category in the above graphs are as follows:

	CARBON	Non-CARBON (All types)	Non-CARBON (P01)	Non-CARBON (R01)	Non-CARBON (U19; U24; U54)
# of Pubs	264	3,009	348	2,467	194

**Figure 3 legend:**

NIH natural products research awards (P01 or other Centers and R01s, each separately) are included for comparison. Awards included were active between 2015 and 2020 and were selected using the MeSH terms Natural Products; Drugs, Chinese Herbal; Teas, Medicinal; Medicinal Herbs; Herbal Supplements; Dietary Supplements; Plants, Medicinal; and/or Herbal Medicine. Administrative supplements and grants with the MeSH term “probiotic” were excluded. The publications and awards included are listed in 7b. Only research and review papers published from 2015 through 2020 (inclusive) are included.

\*RCR ([https://icite.od.nih.gov/user\\_guide?page\\_id=ug\\_infl](https://icite.od.nih.gov/user_guide?page_id=ug_infl)) is an NIH Office of Portfolio Analysis metric of scientific influence. RCR represents the field- and time-normalized citation rate and is benchmarked to 1.0 for a typical (median) NIH paper in the corresponding year of publication. A paper with an RCR of 1.0 has received the same number of cites/year as the median NIH-funded paper in its field, a paper with an RCR of 2.0 has received twice as many cites/year as the median NIH-funded paper in its field, while an RCR of 0.5 means that it is receiving half as many citations per year. The methodology is described in detail in Hutchins et al., PLoS Biol. 2016;14(9):e1002541.

RCRs for papers published in the previous 2 years are flagged as “provisional” to reflect that citation metrics for newer articles are not necessarily as stable as for older articles. Provisional RCRs are provided for papers published in the previous year if they have received five citations or more.