National Institutes of Health Support of Dietary Supplement Research

Barbara C. Sorkin, Ph.D.
Adam J. Kuszak, Ph.D.

Office of Dietary Supplements
National Institutes of Health

NCAC Spring Symposium: Safety of OTC Botanicals and Nutraceuticals
April 19th, 2017
1. NIH mission and organization
2. NIH Office of Dietary Supplements
3. Scientific review, rigor and reproducibility
4. NIH dietary supplement research support, in particular botanical safety
5. National Toxicology Program Herbal Products/Dietary Supplements Project
6. ODS Analytical Methods and Reference Materials Program
The NIH Mission - Research

NIH’s mission is to seek fundamental knowledge about the nature and behavior of living systems and the application of that knowledge to enhance health, lengthen life, and reduce illness and disability.

NIH Support of Research

- Contracts (Requests for Proposals, RFP)
- Cooperative Agreements (U’s – various flavors)
- Grants – many flavors
  - R01
  - Other Research Project Grant types/activities
Once your application arrives at NIH:

- It gets assigned to a NIH institute/center:
  - Most appropriate for the scientific topic covered in the application
  - Participates in the FOA the application was submitted to

- It gets assigned to a scientific review group:
  - Standing panel
  - Special Emphasis Panel (SEP)

Applications compliant with NIH policies are assigned for review by the Division of Receipt and Referral in the Center for Scientific Review (CSR).

CSR assigns application to an NIH Institute/Center (IC) and a Scientific Review Group (SRG).

Scientific Review Officer (SRO) assigns applications to reviewers and readers.

Initial Level of Review:
SRG members review and evaluate applications for scientific merit.

Priority Scores:
Available to Principal Investigator in eRA Commons.

Summary Statement:
Available to Principal Investigator in eRA Commons.

Second Level of Review:
Advisory council/board reviews applications.

Pre-Award Process: IC grants management staff conducts final administrative review and negotiates award.

Notification of Award: Institute/Center issues and sends Notice of Award (NoA) to applicant institution/organization.

Congratulations! Project period officially begins!

Administrative and fiscal monitoring, reporting, and compliance

Visit: http://grants.nih.gov/grants/grants_process.htm for more about the NIH grants process
NIH Institutes, Centers, and Offices

The National Institutes of Health

Office of the Director

NIH Institutes, Centers, and Offices

Source: http://www.nih.gov/
The NIH Office of Dietary Supplements (ODS) and DSHEA

Dietary Supplements Health and Education Act (1994):

• Established the NIH Office of Dietary Supplements (ODS) and defined its purpose

• Mandate for ODS to lead the development of a research initiative focused on botanical dietary supplements (now implemented as NIH CARBON Program)

• Non-DSHEA later mandate for Analytical Methods and Reference Materials Program
Dietary Supplements/DSHEA

• Product intended to supplement the diet

• Contains one or more of:
  • Vitamins
  • Minerals
  • Amino acids
  • Other dietary substances
  • Herbs or other botanicals (not tobacco)

• A DS cannot claim to prevent, diagnose, mitigate, treat or cure disease

• Structure-function claims allowed
What’s the goal?

Research that:

- improves health outcomes
- improves our understanding of what’s in the bottle and its biological effects

"Of course you can't replicate my experiments. That's the beauty of them."
Two years ago, a group of Boston researchers published a study describing how they had destroyed cancer tumors by targeting a protein called STK33. Scientists at biotechnology firm Amgen Inc. quickly pounced on the idea and assigned two dozen researchers to try to repeat the experiment with a goal of turning the findings into a drug.

It proved to be a waste of time and money. After six months of intensive lab work, Amgen found it couldn’t replicate the results and scrapped the project.

"I was disappointed but not surprised," says Glenn Begley, vice president of research at Amgen…

The US National Institute of Neurological Disorders and Stroke convened major stakeholders in June 2012 to discuss for research are not reproducible, in part because of inadequate cell lines and animal models.
NIH Rigor & Reproducibility Policy
https://grants.nih.gov/reproducibility/index.htm

WHAT ARE THE UPDATES?

1. UPDATES TO RESEARCH STRATEGY GUIDANCE
   - The research strategy is where you discuss the significance, innovation, and approach of your research plan. Let’s look at an R01, for example:
     - The new research strategy guidelines require that you:
       - State the strengths and weakness of published research or preliminary data crucial to the support of your application
       - Describe how your experimental design and methods will achieve robust and unbiased results
       - Explain how biological variables, such as sex, are factored into research design and provide justification if only one sex is used

2. NEW ATTACHMENT FOR AUTHENTICATION OF KEY BIOLOGICAL AND/OR CHEMICAL RESOURCES
   - From now on, you must briefly describe methods to ensure the identity and validity of key biological and/or chemical resources used in the proposed studies.
   - These include, but are not limited to:
     - CELL LINES
     - ANTIBODIES
     - SPECIALTY CHEMICALS
     - OTHER BIOLOGICS
   - Standard laboratory reagents that are not expected to vary do not need to be included in the plan. Examples are buffers and other common biologicals or chemicals.
   - **DO NOT** put experimental methods or preliminary data in this section
   - **DO** focus on authentication and validation of key resources

3. NEW REVIEWER GUIDELINES
   - Here are the additional criteria the reviewers will be asked to use:
     - **Is there a strong scientific premise** for the project?
   - Have the investigators presented adequate plans to address relevant biological variables, such as sex, for studies in vertebrate animals or human subjects?
   - Have the investigators presented strategies to ensure a robust and unbiased approach, as appropriate for the work proposed?

Send inquiries to reproducibility@nih.gov
See also NIH Notice NOT-OD-16-011

Reviewers will also be asked to comment on that new attachment (see Update 2)!
## NIH Support of Botanical Research

### NIH FY11 Botanical Research Portfolio Disease/Condition Analysis

<table>
<thead>
<tr>
<th>Disease Grouping</th>
<th>NCI</th>
<th>NCCAM (now NCCIH)</th>
<th>NIAID</th>
<th>NIGMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>159</td>
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<tr>
<td>Cardiovascular</td>
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<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diabetes</td>
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<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Immune</td>
<td>1</td>
<td>11</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Infection</td>
<td>0</td>
<td>11</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Neurological</td>
<td>0</td>
<td>11</td>
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</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>41</td>
<td>2</td>
<td>28</td>
</tr>
</tbody>
</table>
Emphasis on rigor and mechanisms of action

• (in) basic research...emphasize *in vitro* and *in vivo* studies of the biological effects and mechanisms of action ..., studies characterizing the active elements of an intervention

[https://nccih.nih.gov/grants/priorities](https://nccih.nih.gov/grants/priorities)

• NCCIH Natural Product Integrity Policy

[https://nccih.nih.gov/research/policies/naturalproduct.htm](https://nccih.nih.gov/research/policies/naturalproduct.htm)
NCCIH Support of Botanical Research

Emphasis on rigor and mechanisms of action

NCCIH Natural Product Integrity Policy – in the application:

• Product (brand name, chemical or taxonomic nomenclature—e.g., genus, species, strain, as applicable)

• Ingredients of the product (both active and inactive)

• Justification/rationale for the product, including refined or complex, root, stem, leaf

• Proposed methods for product characterization and standardization and rationale

• Pharmacokinetics and pharmacodynamics of the known components of the product and any biological or chemical marker(s) of activity (if known and if applicable)

• Description of placebo or vehicle control.
Rigor and reproducibility – DNA barcoding

• Useful sources:
  - Fresh, live, dried, powdered materials
  - Crude pressed oils

• Processes that damage DNA:
  - Heat treatment
  - Distillation
  - Fermentation
  - Irradiation
  - UV light exposure
  - Supercritical fluid extraction

• Excipients/fillers

• Challenging sources:
  - Extracts, tinctures

• Methods selection:
  - More specific primers are more sensitive, but detect only target species

• Cannot:
  - Identify part of plant
  - Provide information on product-specific composition

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NIH Centers for Advancing Research on Botanicals and Other Natural Products

NIH CARBON Program – 5 Centers

3 Botanical Dietary Supplements Research Centers

- **Dietary Botanicals in the Preservation of Cognitive and Psychological Resilience**, Icahn School of Medicine at Mount Sinai, New York City
- **Botanicals and Metabolic Resiliency**, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge
- **Botanical Dietary Supplements for Women’s Health**, University of Illinois at Chicago
Botanical Dietary Supplements for Women’s Health (P50), University of Illinois at Chicago

Project 3 Specific Aims include herb-drug interactions:

SA2 - Assess *in vitro* according to FDA guidelines –

- inhibition and induction of specific phase I and phase II enzymes and drug transporters that might cause adverse interactions with therapeutic agents
- by botanical dietary supplements used by menopausal women identify compounds responsible for inhibition or induction of drug metabolizing enzymes and/or transporters

SA3 – Assess *in vivo*:

- Clinical safety studies of drug-botanical interactions to test the hypothesis that these botanicals might induce or inhibit cytochrome P450 enzymes involved in the phase I metabolism of therapeutic agents. Standardized extracts that have been predicted by *in vitro* studies to have drug interactions will be administered to women with test agents.
NIH Centers for Advancing Research on Botanicals and Other Natural Products

NIH CARBON Program – 5 Centers

2 Centers for Advancing Natural Product Innovation and Technology

- **Center for Natural Products Technologies**, University of Illinois at Chicago
- **Center for High-throughput Functional Annotation of Natural Products**, University of Texas Southwestern Medical Center, Dallas; Simon Fraser University, Burnaby, British Columbia, Canada; University of California, Santa Cruz
Center for Natural Products Technologies, University of Illinois at Chicago

- Countercurrent chromatography and development of standardized separation/purification/knockdown protocols
- Coordination and dissemination of NP community needs, standards, resources
What are the major challenges in natural product research?

- **STRUCTURE, PURITY & REPRODUCIBILITY**: unambiguous determination of the structure and purity of isolated Natural Products (NPs), and their reproducible documentation.
- **DEREPLICATION**: performance of efficient chemical dereplication strategies and broad availability of dereplication data.
- **BROAD BIOLOGICAL PROFILING**: isolation of bioactive compounds in amounts that are compatible with their biological assessment for a broad range of endpoints.
- **FRAGMENTATION & REPRODUCIBILITY**: developing methods for reproducible chemical isolation and associated biological testing protocols to promote the transparency of results.
- **MULTI-AGENT, MULTI-TARGET PHARMACOLOGY**: establishment of links between the chemical complexity and the biological outcomes of NPs.
- **METABOLIC CHARACTER**: improvement of the understanding of botanical and other NP chemical variability and complexity for biological evaluation.

What does the CENAPT do to help addressing these challenges?

Addressing the major challenges in natural product research requires...
By integrating image-based phenotypic screening ...with high-resolution untargeted metabolomics analysis, ...capable of directly predicting the identities and modes of action of bioactive constituents for any complex natural product extract library.

Integration of high-content screening and untargeted metabolomics for comprehensive functional annotation of natural product libraries

In vitro and in vivo assessment of NP-drug interactions

• Prioritized based on use prevalence, in silico and clinical data
• Analytical Core to source, acquire and characterize selected NP and analyze PK samples
• Pharmacology Core to develop SoW for in vitro and in vivo studies, develop models for further assessment of clinical relevance of results
• Informatics Core: organize, archive and disseminate data
• Mission: To evaluate agents of public health concern, by developing and applying tools of modern toxicology and molecular biology
NTP Botanical DS Program

• Received nominations to study botanical dietary supplements
• NTP conducts short- and long-term studies in rodents
  • General toxicological and carcinogenic assessment
  • Immunotoxicological evaluation
  • Developmental and reproductive toxicology

https://ntp.niehs.nih.gov/results/areas/botanical/index.html
## NTP Botanical DS Program

<table>
<thead>
<tr>
<th>Botanical Dietary Supplement</th>
<th>Rodent Study Results and Links to Select NTP Publications</th>
<th>Findings and Levels of Evidence of Carcinogenic Activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aloe Vera</strong></td>
<td>NTP Technical Report on the Toxicology and Carcinogenesis Studies of a Noncolorized Whole Leaf Extract of <em>Aloe Barbadensis</em> Miller (<em>Aloe Vera</em>) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies) <a href="http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR577_508.pdf">http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR577_508.pdf</a></td>
<td>Clear Evidence Clear Evidence No Evidence No Evidence Cancer of the large intestine in male and female rats, but not mice</td>
</tr>
<tr>
<td><strong>Green Tea Extract</strong></td>
<td>NTP Technical Report on the Toxicology Studies of Green Tea Extract in F344/N/ad Rats and B6C3F1/N Mice and Toxicology and Carcinogenesis Studies of Green Tea Extract in Wistar Han[Cr:Wl(Han)] Rats and B6C3F1/N Mice <a href="http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR585_508.pdf">http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/TR585_508.pdf</a></td>
<td>No Evidence No Evidence No Evidence No Evidence No evidence of causing cancer in rats or mice</td>
</tr>
</tbody>
</table>

Analytical Issues in Botanical Supplements

• Botanical chemistry is inherently variable
  ▪ Geography, climate, harvesting, processing, etc.
  ▪ Key constituents may vary from batch-to-batch

• Dietary supplement composition can be very complex
  ▪ Individual constituents, multi-vitamin / multi-mineral, botanical extracts, and combinations thereof
  ▪ Pills, capsules, liquids, tinctures, gummies, etc.

• The ODS Analytical Methods and Reference Materials Program exists to support dietary supplement characterization and enhance rigorous research
• U.S. Senate Labor, Health & Human Services, and Education appropriations bill language (2002 & 2003):

  “...[allocate] funds to speed up ongoing collaborative efforts to develop, validate, and disseminate analytical methods, and reference materials for the most commonly used botanicals and other dietary supplements.”

https://ods.od.nih.gov/Research/AMRMProgramWebsite.aspx
ODS AMRM Program Goals

• Expand availability of validated analytical methods for DS characterization

• Produce and make available certified reference materials

• Support public-private partnerships

• Perform outreach and education activities

AMRM Program: Analytical Methods

Method development and validation

• FDA Center for Food Safety and Applied Nutrition

• USDA Food Composition and Methods Development Laboratory

• NIST Material Measurement Laboratory

• Academic researchers (grant FOA)

AMRM Program: Analytical Methods

• Methods developed/validated
  ▪ Flavonoids, catechins, phytosterols, xanthines, organic acids, citrus alkaloids in products
  ▪ Catechin & epicatechin metabolites, DHA/EPA, curcumin metabolites in plasma

• Adulteration and contamination
  ▪ PDE5 inhibitors
  ▪ Aflatoxins and ochratoxin A
  ▪ Pyrrolizidine alkaloids
  ▪ Aristolochic acid
  ▪ Pesticides
AMRM Program: Standards & QA

• NIST Standard Reference Materials
  ▪ Goal: increasing the types and availability of botanical dietary supplement reference materials and calibration solutions
  ▪ More than 20+ SRMs produced, 30+ in progress

• NIST Laboratory Quality Assurance Programs
  ▪ Inter-comparison exercises between manufacturer, 3rd party, academic, and government laboratories
  ▪ Lab results analyzed for accuracy, precision, and concordance within community
NIST Dietary Supplement Laboratory QA Program

- Nutritional compounds
  - Vitamins, minerals, fatty acids
- Botanical marker compounds
  - Phytosterols, flavonols, synephrine, anthocyanins
- Lead, arsenic, cadmium, mercury
- Aflatoxins, polycyclic aromatic hydrocarbons, acrylamide

Melissa Phillips, Catherine Rimmer, Laura Wood  http://www.nist.gov/mml/csd/dsqap.cfm
ODS AMRM Program Purposes

• AMRM is designed to help researchers, industry, and regulators
  ▪ Ensure quality of research test materials
  ▪ Enhance credibility, reproducibility, and comparability of research studies
  ▪ Provide resources for product analysis
  ▪ Develop quality standards
  ▪ Enhance the ability of FDA to enforce regulations
  ▪ Enhance the ability of industry to demonstrate compliance with regulations

https://ods.od.nih.gov/Research/AMRMProgramWebsite.aspx
Questions?

Barbara C. Sorkin, Ph.D.
Director, NIH CARBON Program
Office of Dietary Supplements
National Institutes of Health
sorkinb@mail.nih.gov
(301) 435-3605

Adam J. Kuszak, Ph.D.
Health Policy Analyst
Office of Dietary Supplements
National Institutes of Health
kuszakaj@mail.nih.gov
(301) 496-1795