

Discovery and Development of Natural Products for Cancer Interception and Prevention

A Pilot Investment in Discovery Research

Co-sponsored by DCP, DCTD and NCATS

FOA Working Group

Bob Shoemaker, Altaf Mohammed and Phil Castle

Division of Cancer Prevention, NCI

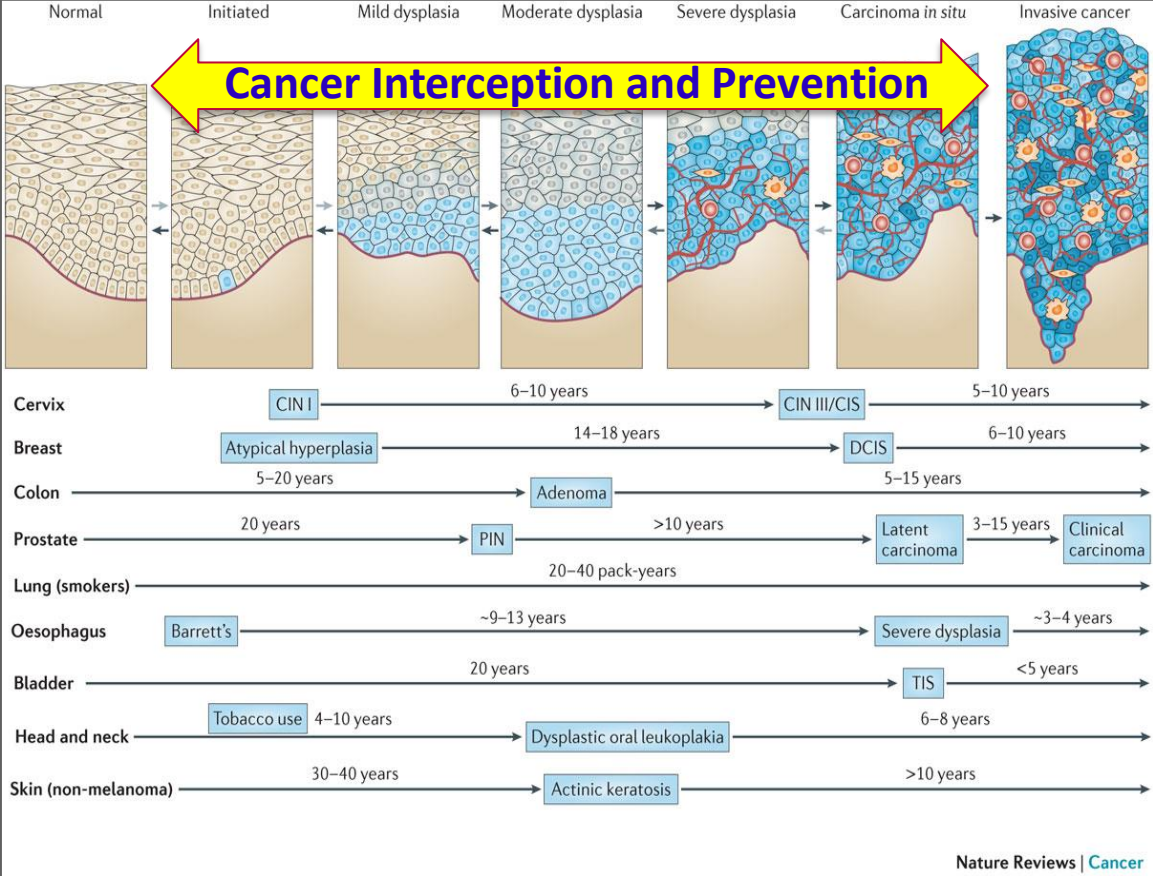
Barry R. O'Keefe

Natural Products Branch, Developmental Therapeutics Program (DTP)
Division of Cancer Treatment and Diagnosis, NCI

Matthew D. Hall

Early Translation Branch
National Center for Advancing Translational Sciences (NCATS)

Estimated Timeline of Progression of Selected Cancers and Pre-malignant Stages



Prevention is an important aspect of cancer control



Need for effective, safer, and user-friendly cancer interception and prevention agents is **HIGH**

Natural Products Discovery Research

Current Status and Challenges

- Continually seeing grants on the same natural agents (lack of innovation in discovery research)
- Current NP chemotypes (i.e. ellagic acid, quercetin etc.) have resulted in non-specific binding to numerous targets and not productive
- NP discovery research is technically demanding, especially prevention, which is inherently high-risk and potentially high reward.
- High need for initial screening efforts to identify new modalities to change the current trajectory of cancer interception and prevention research
- Lack of resources and opportunities for discovery research expansion.

New Program Justification

- Currently, there are no NCI programs or initiatives supporting these types of research activities.
- The unique resources available from the NCI and NCATS overcome many of the deficiencies of historical natural product discovery approaches.
- No other program in the community, including the pharma is doing work in this field.
- Need to expand the base of discovery knowing that there is a high rate of attrition.

Purpose of FOA

The overall goal of this UG3/UH3 Exploratory/Developmental phased initiative is to support the discovery and development of novel natural products that are safe, non-toxic, and efficacious for cancer interception and prevention.

1. **Purpose of UG3**: Select clinically relevant targets and develop and validate assays for bioactivity as well as toxicity screening
2. **Purpose of UH3 phase**: Screening libraries, structure elucidation, full-scale characterization, efficacy testing, and development of the screened agents

NCI Natural Product Collections

The NCI has one of the world's largest, most diverse collections of natural product extracts (>500,000 extracts).



Plant Extract Library



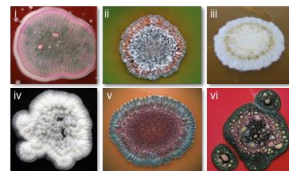
- ~161,000 extracts (organic + aqueous)
- ~44,000 plants, including 81,400 raw materials (leaves, roots, fruit, etc.) collected from Africa and Madagascar; North, Central and South America; and Southeast Asia.

Marine Extract Library



- ~41,000 extracts (organic + aqueous)
- ~20,500 organisms collected from the Indo-Pacific region.

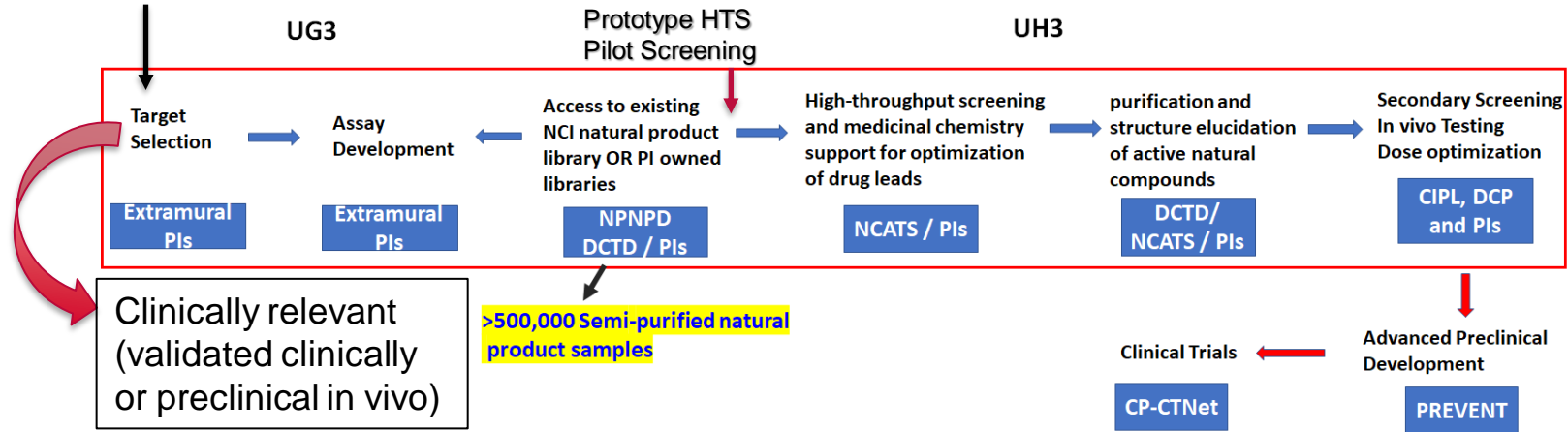
Microbial Extract Library



- ~30,000 extracts (organic + aqueous)
- ~26,000 organisms collected from US
- **New Collection:** 20,000 Fungal strains from USA (Univ. of Oklahoma)

Purpose of FOA

Cancer Interception

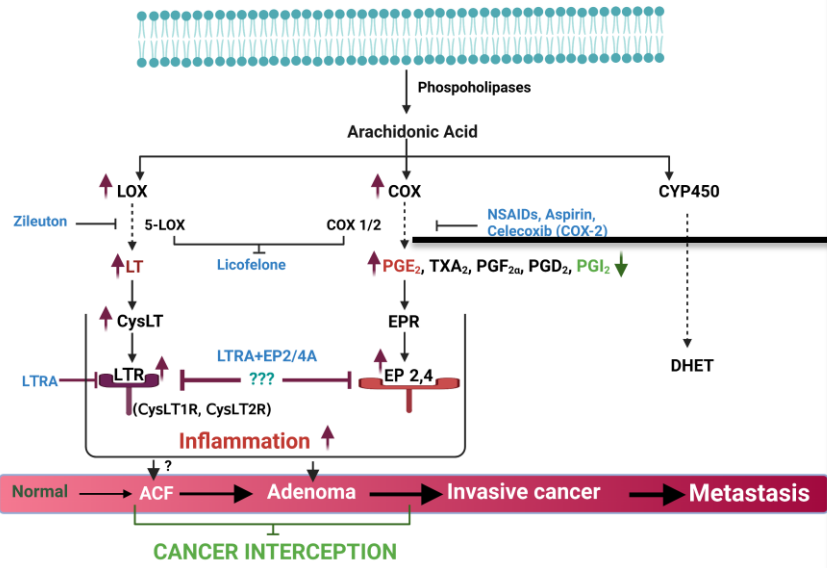


This FOA will utilize a bi-phasic, milestone-driven mechanism of the award.

- UG3 phase (up to 3 yrs): Target selection, verification (preclinical and clinical samples), assay development/validation, prototype HTS, pilot screening.
- UH3 phase (2-yrs): Full-scale screening libraries and characterize, evaluate PK, bioavailability, and assessment of the screened natural product's effect/MOA in vitro and in vivo.

Example: Molecular Targets for Cancer Interception

HTS of NP regulating activity of EP2/EP4, LTR



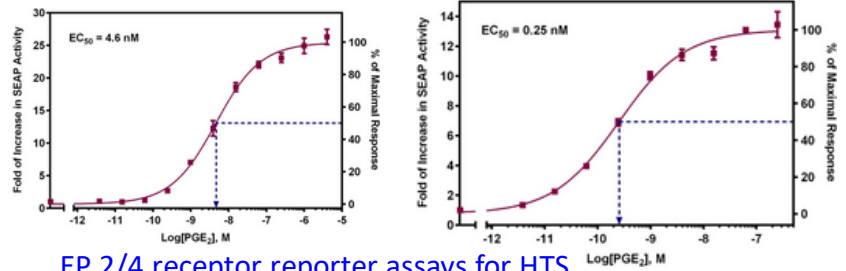
mPGES-1 ↑

CRISPR-based, liver-derived reporter cells for screening of mPGES-1 inhibitors

Fluorescence imaging strategy to monitor the expression of mPGES-1

PMID: 30879343

Mohammed & Shoemaker, *Cancer Prev Res* 2022;15:637–40



EP 2/4 receptor reporter assays for HTS

Application Submission to Funding: Process

- PI proposes a target and screening approaches for UG3
- Peer review evaluates and scores the application
- NCI staff (DCP and DCTD) proposes Funding Plan
- Customized milestones negotiated by NIH Staff with PIs (establishment of a robust and scalable HTS a key milestone)
- NIH Staff evaluate progress towards UG3 milestones and recommend awards for the UH3 phase
- NIH Staff monitor UH3 phase progress and integrate development efforts

Expectations of PI for Natural Product Drug Discovery for Cancer Interception and Prevention RFA

UG3 Phase

- Selection/justification of clinically relevant target
- Generation of research plan
- Development of pilot screening assay and conduct of pilot screens
- Development of secondary assays for selectivity and toxicity
- Development of mechanistic assays to characterize screening leads
- HTS strategy that meets NCATS HTS requirements

UH3 Phase

- Development/optimization of animal models
- Secondary testing of screening leads
- Mechanistic characterization of screening leads
- Conduct/collaboration on medicinal chemistry/formulation of purified natural products
- Conduct/collaboration on PK, PD, and cancer preventive efficacy testing

Potential NIH Contributions to Natural Product Drug Discovery for Cancer Interception and Prevention

UG3 Phase

- Advice on development of high-throughput screening assays (NCATS and NCI)
- Advice and assistance with generation of key reagents
- Provision of prototype natural product libraries for pilot screening (NCI)
- Advice on optimization of screening assay for technology transfer to HTS lab (NCATS)

UH3 Phase

- Assistance with technology transfer to NCATS
- Conduct of primary HTS of the NCI Natural Products Library (NCATS)
- Follow-up testing to support bioassay-directed isolation of active natural products (NCATS and NCI)
- Medicinal chemistry/formulation support for isolated natural products (NCATS and NCI)

Portfolio Analysis

- NIH RePORTER (as of 06/2022): There were 88 unique multi-year active projects identified when searched using “natural products cancer prevention” as keywords.
- 39 projects (~\$16 million) funded by the NCI are predominantly the investigator-initiated R01 and other grants focusing on specific agents. Some of these projects are therapeutics.
- Only one project specifically applies a screening platform for the discovery of novel noncytotoxic compounds from cyanobacteria - antimetastatic activity.
- None of these projects focuses on screening and development of NPs for cancer interception and prevention.

Proposed Budget

- UG3 is capped at 250K direct cost/year for ~3 years; UH3 at 400K direct costs/year for 2 years
- One receipt date/year in FY 24, 25, 26; n=4/yr, thus two opportunities for A1 submissions
- NCI controlled collaborative supplements with an emphasis on UH3 projects

NPDD Program	FY2024	FY2025	FY2026	FY2027	FY2028	FY2029	Total
UG3 (n=4/yr; total 12)	\$1.5M	\$3M	\$4.5M	\$3M	\$1.5M	-	\$13.5M
UH3 (n=2 total)	-	-	-	\$0.6M	\$1.2M	\$0.6M	\$2.4M
Supplements (UH3)	-	-	-	\$0.2M	\$0.5M	-	\$0.7M
NCATS Resources	\$0.25M	\$0.4M	\$0.4M	\$0.4M	\$0.4M	\$0.4M	\$2.25M
CIPL Resources Frederick	\$0.25M	\$0.4M	\$0.4M	\$0.4M	\$0.4M	\$0.4M	\$2.25M
DCTD Resources Frederick	\$0.25M	\$0.4M	\$0.4M	\$0.4M	\$0.4M	\$0.4M	\$2.25M
Total (Direct + Indirect)	\$2.25M	\$4.2M	\$5.7M	\$5M	\$4.4M	\$1.8M	\$23.35M

* Go back to SPL if >2 UG3 grants progress to UH3 phase to request additional funds

Justification for RFA & Cooperative Agreement

- There is no NIH parent announcement for the UG3/UH3 mechanism.
- The RFA mechanism will enable the solicitation of high-risk and high-impact research proposals. This risk will be mitigated by the milestone-driven UG3/UH3 transition.
- This RFA mechanism will also allow for a dedicated NCI Special Review Panel essential for the wide range of expertise proposed for these applications.
- Substantial programmatic involvement by NCI and NCATs.
- Foster and support the communication, and collaboration between this program and other relevant NCI research programs.

Selected Reviewers' Comments (Drs. Robertson, Flaherty, & Grandis) & Responses

The availability of the NCI libraries and making them more accessible to investigators needs to be critical in the proposed RFA.

- ✓ We will explicitly state in the FOA that the NCI libraries will be available for successful projects at no cost.

Is the NCI offering services to help set up these programs or is it expected that each team has to have all the expertise on hand to be successful?

- ✓ NIH staff will work with PIs before proposal submission and the awardees in the UG3 and UH3 phases providing the required assistance. NCI/NIH services are listed on slide 12.

The proposed RFA seems to focus on exploratory activities. What is the expectation to have a successful proposal reviewed by the special emphasis panel?

- ✓ Expectations of a successful proposal and criteria for review will be described in the FOA. A few of them are listed on Slide 11.

Selected Reviewers' Comments & Responses

How would NIH help investigators enhance target specificity?

- ✓ Depending on the research plan proposed and the milestones agreed upon, NIH would work with individual investigators (e.g. secondary screens to prove the specificity of active compounds). Further, NIH will share information when an identified active fraction has previously tested positive in another assay (both biochemical and cell-based).

The initial screens seem to be with sub-fractions of natural compounds. How will you help with the isolation of the specific reactive compound?

- ✓ NCI (DCTD NPB) will provide direct support for the isolation, identification, and structural characterization of bioactive fractions/active natural products throughout the purification process. A set-aside budget is allocated for these activities.

The budget seems limited and unclear based on the number provided in the table.

- ✓ The budget slide is revised to provide better clarity.



**NATIONAL
CANCER
INSTITUTE**

www.cancer.gov

www.cancer.gov/espanol