New Cohorts to Assess Environmental Exposures and Cancer Risk

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Purpose

- RFA will support new cancer etiology cohorts that use **innovative strategies and approaches** to
  - Address knowledge gaps between environmental exposures, genetics, and other molecular factors and cancer etiology across diverse populations
  - Ensure rigor and reproducibility of data and biospecimen collections

- RFA responsive to NCI NCAB Cohort Subcommittee Report (2019)
  - Need for new etiology cohorts to address research gaps on exposures
Goal

- Fund approximately five new cohorts:
  - Assess new and understudied exposures with innovative designs and measures
  - Focus on both short-term and longer-term research questions
  - Investigators required to collaborate—facilitated by Coordinating Center
  - **Common data elements and biospecimen collection**
  - Priority for innovative, significant, and actionable research
Need for New Etiology Cohorts

- Environmental exposures (e.g., new exposures, persistent chemicals, and chemical mixtures) understudied
- IARC and NTP have identified several “Group 1” or “Known Carcinogens” to humans, but many more environmental exposures lack adequate evidence to properly classify
- Identification of the key carcinogenic hallmarks of environmental exposures needed in prospective designs
- Challenge with existing cohorts include blood collected at the appropriate time point to assess new exposures; appropriate age; limited research on life-course exposures; diversity

Resources of existing cohorts (data and biospecimens) -- R01/R21/R03 applications
Example of New Exposure

- Emerging classes of chemicals are persistent in the environment and accumulate in humans [e.g., per- and polyfluorinated alkyl substances (PFAS) and endocrine disrupting chemicals (EDC)]
- Novel or understudied exposures
- Answers are needed regarding their potential to increase risk for cancer

Cancer Etiology Cohorts

Extramural Program
DCCPS

Aging cohorts

DCEG
AHS
USRT
Connect

NIEHS
Sister Study

Relevance to NIH All of Us
- Not focused on cancer or environmental exposures
- Collected biological samples could be relevant
- Open resource available for research investigations

AHS – Agricultural Health Study (started 1993) – occupational cohort
USRT - U.S. Radiologic Technologists (following technologists since 1983) – occupational cohort
Connect - Comprehensive Oncology Network Evaluating Tumors – conducted within a set of integrated health care systems
Sister Study (started 2004) – study of women whose sister had breast cancer
Short-Term Research Examples

- Use IARC framework to assess biological mechanisms to support classification of environmental exposures
- Other bioassays
- Building cohort
- Use incident cases for case-control/case-cohort studies in the initial years

<table>
<thead>
<tr>
<th>Biological Mechanisms (Carcinogenic characteristics)</th>
<th>Measures</th>
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<tbody>
<tr>
<td>Metabolic activation</td>
<td>DNA and Protein Adducts</td>
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<tr>
<td>Is genotoxic</td>
<td>DNA damage; Gene mutations, Cytogenic changes</td>
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<tr>
<td>Induces chronic inflammation</td>
<td>Elevated WBC; altered cytokine/chemokine production</td>
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<tr>
<td>Is immunosuppressive</td>
<td>Decreased immunosurveillance; immune dysfunction</td>
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<tr>
<td>Alters cell proliferation</td>
<td>Cell proliferation; Angiogenesis</td>
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Smith et al. Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. Env Health Persp 124(6):713-21, 2016
Longer-Term Research Questions

- What chemical, physical, lifestyle and genetic factors interact to affect cancer risk in understudied populations?
- How are timing of environmental exposures, multiple exposures, and chronic low-dose exposures associated with cancer development?
Sustainability

Options to Enhance and Sustain New Cancer Etiology Cohorts

- Cohort Infrastructure Support PAR
- SEER Virtual Pooled Registry Cancer Linkage System
- Human Health Exposure Analysis Resource (HHEAR)
- Innovative Molecular Analysis Technologies (IMAT)
- R01 Grants
NCI Portfolio Analysis

- NCI currently provides infrastructure-only support for 16 etiology cohorts (2 are in phased close-out; 2 are not US-based; 3 started as RCTs)

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<tr>
<th>Issue</th>
<th>Description</th>
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<tr>
<td>Age</td>
<td>majority 75 years and older</td>
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<tr>
<td>Attrition</td>
<td>due to deaths approx. 62%</td>
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<tr>
<td>Racial/Ethnic</td>
<td>majority Whites (75%); African Americans (16%)</td>
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<tr>
<td>New Exposures</td>
<td>cannot be adequately addressed</td>
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- NCI active grants portfolio show scarcity of funding research focused on environmental exposures
Coordinating Center (U01)

Biospecimen and data collection

- Standard Operating Procedures
- Support data harmonization
- Facilitate deposition of data to NIH
- Communication & Meeting support
- Project website
- Coordinate assessment across cohorts

COORDINATING CENTER
UG3/UH3 Research Mechanism

- UG3 phase PI sets milestones for recruitment and data collection (requires approval from Program and NCI leadership)
- UH3 phase focused on completing research
Evaluation Criteria

- **Innovation**: Priority to innovative and novel projects and study designs using technological and molecular innovation to address identified research gaps related to environmental exposures.

- **Inclusivity**: Representation of understudied and diverse populations.

- **Strong scientific justification for research questions to be addressed, approach, and population**: Willingness to collect core data and biospecimens.

- **UG3/UH3 milestones must be appropriate**.

- **Data sharing – compliance with NIH policies**.

- **Proposals for the CC will be evaluated on the evidence of having provided administrative and logistic support for cohorts**.
RFA Justification and Budget

- Set aside funds
- Specialized review - scientific expertise with diverse reviewers

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<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>All Years</th>
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<tbody>
<tr>
<td><strong>Total Costs</strong></td>
<td>6.5M</td>
<td>6.5M</td>
<td>12.5M</td>
<td>12.5M</td>
<td>12.5M</td>
<td>12.5M</td>
<td>63M</td>
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<td>(5 cohorts)</td>
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<th>All Years</th>
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<tr>
<td><strong>Total Costs: CC</strong></td>
<td>0.8M</td>
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Reviewer Comments and Responses (Seewaldt, Robison, and Bondy)

- **Emphasize innovative strategies** – RFA will be modified to emphasize innovation in scientific questions, design, and assessments

- **Rigor and reproducibility** – RFA will emphasize rigor and reproducibility in biospecimen and data collection and require core collections

- **Rationale for new cohorts** – New exposures; appropriate population-relevant to research questions; diversity

- **Clarify population-based** – appropriately defined and relevant to research questions; International allowed with relevance to US populations

- **Coordinating Center** – PI will be part of the collaborative steering committee