National Institute of Environmental Health Sciences
Division of Extramural Research and Training
Susceptibility and Population Health Branch

NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL
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Concept Clearance

SBIR Technologies for Environmental Health Research

Introduction

As with most federal agencies with an R&D budget over $100M, the NIEHS has been mandated to allocate 2.5% of its extramural R&D budget to support small businesses via the SBIR program. With the reauthorization of the SBIR/STTR programs by Congress in December 2011, a number of key provisions are being implemented, including an increase in the set-aside requirements for federal agencies for both SBIR and STTR programs. For SBIR grants, the set-aside will increase from 2.5% in FY11 to 3.2% in FY17. For STTR grants, the set-aside increases from 0.30% in FY11 to 0.45% in FY17. In order to focus on development and commercialization of technologies that support the NIEHS mission of reducing the exposure to environmental stressors to promote healthier lives, several SBIR RFAs are proposed here, including enhancing sensor technologies for measuring multiple exposures in the personal environment, developing methods for capturing molecular information from archived formalin-fixed tissues, and a validation/commercialization effort for alternative test methods and sensor technologies. Given the increased funds set aside, particularly for SBIR projects, over the next 5 years, soliciting applications through selected RFAs will help to focus research and development of technologies and tools that have high priority for the NIEHS mission.

The NIEHS has recently released two RFAs for SBIR Phase I and Fast-track applications. RFA-ES-12-004, Novel Technologies for Rapid and Sensitive Biomonitoring in Humans (SBIR [R43/R44]) was released in December, 2011 as one of several activities extending the research goals of the Genes, Environmental and Health Initiative (GEI). A total of 10 Phase I grants were funded to develop a range of technologies to detect multiple analytes in small volumes of serum and other biological samples. A second RFA, Novel Assays for Screening the Effects of Chemical Toxicants on Cell Differentiation (SBIR [R43]) was released in November, 2012 to address the need for medium and high-throughput screening approaches for the U.S. Tox21 program, the US EPA's ToxCast program and other large-scale programs. Applications for this RFA, received on February 14, 2013, focus on the use of rodent or human pluripotent and multipotent stem cells to evaluate the effects of toxicants on cell differentiation and on altered molecular phenotypes in the differentiated cell lineages.

In addition to proposals submitted to NIEHS through the general Omnibus Solicitation of the NIH, CDC, FDA and ACF for Small Business Innovation Research Grant Applications (Parent SBIR [R43/R44]), soliciting SBIR applications through selected RFAs over the next 5 years will help to enhance the development of technologies and approaches by small businesses that support many aspects of the NIEHS mission.

Research Goals and Scope

1. **Sensor development for enhanced exposure assessment**
   The National Research Council recently issued a report on Exposure Science in the 21st Century that articulates the need for sensors that more comprehensively measure personal environment (http://www.nap.edu/catalog.php?record_id=13507). Through the GEI Exposure Biology Program and through the Omnibus Solicitation for SBIR Grant Applications, the NIEHS has supported development of wearable, lightweight sensor devices for measuring in real-time an individual's exposure to environmental agents with information on location of the exposures. Although development of several prototypes has been very successful, most of these technologies focus on a limited number of exposure classes, for example, particulate matter, volatile organic compounds, or exposure to molds or microbial toxins. In order to better and more efficiently measure exposures in the personal environment, it is important to develop point-of-contact devices that measure multiple agents or classes of chemicals simultaneously, as well as incorporating other measures, including physical activity or physiological responses to exposures. Expanding existing technologies, which are often limited to measuring one or two analytes, or developing new methods that measure multiple environmental agents in single, low-cost, user-friendly devices, will be important steps in improving exposure assessment for environmental epidemiology studies and community-based studies.

2. **Technologies for omics studies using formalin-fixed, paraffin embedded tissue samples**
   Over the last 30 years the National Toxicology Program has collected and maintained one of the largest repositories in the world of formalin-fixed paraffin embedded (FFPE) tissue samples collected from nearly every NTP rodent toxicity study. Detailed pathology has been performed on all samples in the repository, which are often accompanied by serum chemistries and observational measures. However, little is known about molecular changes that accompany the pathology changes in these archived tissues. With the advent of numerous next-generation sequencing technologies, as well as improvements in extracting protein, DNA, RNA, and metabolites from both FFPE tissues and frozen biological samples, there are significant opportunities for measuring transcriptional, epigenetic, proteomic, or metabolomic alterations with specific toxicant exposures. Novel technologies are needed to expand the capability for molecular analyses of archived organs and tissues. In addition, improved tissue fixatives and preservation methods that maintain histologic features while preserving high quality DNA, RNA, protein and small molecules in archived tissue from rodent and human studies are also needed.

3. Validation of alternative toxicological methods and sensor technologies through the Phase IIb grant mechanism

The goal of the SBIR/STTR programs to develop commercializable products is often hampered, in the case of ES-supported technologies, by the "Valley of Death", i.e., the gap in funding between development of assays or sensor prototypes and the commercialization phase. Validation efforts for both bioassays and sensor technology are usually beyond the scope of a Phase II grant and often require additional time and effort to carry out studies needed for commercialization and acceptance by the end-user communities.

Phase IIb competing renewal applications are accepted by several NIH Institutes for projects that require additional time and effort, for example, for FDA approval of new drugs, devices, vaccines, or medical implants. This mechanism allows small businesses with Phase II grants to apply for up to 3 years of support for developing products that require approval of a regulatory agency and for facilitating the transition of the SBIR Phase II projects to the commercialization stage. However, there are important technologies that would not be subject to such regulation, but that still require extraordinary time and effort to develop. Two such examples of NIEHS-funded SBIR research are alternative toxicological assays submitted to the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) for evaluation and the development, manufacture and field testing of sensor technology. Both novel assays and sensor prototypes require validation and commercialization efforts prior to acceptance by either regulatory agencies in the case of assays or testing methods, or by the wider environmental health research community, in the case of sensor technology.

NIEHS-funded SBIR grants have developed in vitro assays, human organotypic models, and other tools for measuring responses to environmental toxicants that meet the goals of NICEATM/ICCVAM to refine, reduce or replace animal use in toxicity testing. To be eligible to apply for Phase IIb funding, current Phase II grantees developing alternative toxicological methods would have to demonstrate support/ interest from federal agencies, and meet the criteria for the validation and regulatory acceptance for new and alternative test methods as outlined in the report ***Validation and Regulatory Acceptance of Toxicological Test Methods*** (ICCVAM 1997) [**PDF**]. As a condition of the Phase IIb grant, test method sponsors would be required to consult with NICEATM throughout the validation process. The objective of these interactions is to maximize the likelihood that validation studies and submissions will adequately characterize the usefulness and limitations of the proposed test method.

Other ES-supported SBIR projects have developed wearable sensor devices for measuring exposures in the personal environment. To be eligible for Phase IIb support for sensor validation, Phase II grantees would need to demonstrate appropriate sensitivity and specificity for the device from laboratory studies and

usability and reliability from initial field testing. Also important is the demonstration of commercialization potential for the technology through either a history of successfully bringing a product to market or a committed partnership with manufacturing/commercialization entity.

Mechanism and Justification

Phase I (R43) and Fast Track applications will be solicited for initial development of novel technologies for integrated measures of the personal environment, and new methods for molecular analysis of FFPE tissue. Subsequent RFAs will solicit Phase II (R44) applications for these topics and for current Phase I grantees from RFA-ES-12-004 and RFA-ES-13-003 . For the validation and commercialization efforts, Phase IIb applications will be accepted from Phase II grantees through a separate RFA solicitation. Applicants will need to meet criteria for submitting Phase IIb applications demonstrating that assays or sensor devices are ready for multi-laboratory testing for alternative toxicological methods or for field-testing, manufacture, and commercialization for sensor devices.

Soliciting applications from small businesses through selected RFAs in these scientific areas will help to focus technology development in areas that support many aspects of the NIEHS mission.