

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS), THE
NATIONAL INSTITUTES OF HEALTH (NIH) AND THE CENTERS FOR
DISEASE CONTROL AND PREVENTION (CDC) SMALL BUSINESS
INNOVATION RESEARCH (SBIR) PROGRAM**

PROGRAM SOLICITATION PHS 2016-1

Closing Date: October 16, 2015, 5:00 PM Eastern Daylight Time

Participating HHS Components:

- The National Institutes of Health (NIH)
- The Centers for Disease Control and Prevention (CDC)

IMPORTANT

Deadline for Receipt: Proposals must be received by October 16, 2015, 5:00 PM Eastern Daylight Time.

Please read the entire solicitation carefully prior to submitting your proposal.

IMPORTANT: All proposals must be submitted using the new electronic contract proposal submission (eCPS) website.

Paper proposals will not be accepted.

Please go to https://www.sbir.gov/sites/default/files/sbir_pd_with_1-8-14_amendments_2-24-14.pdf to read the SBIR/STTR Policy Directive issued by the Small Business Administration for further information.

Table of Contents

1	INTRODUCTION	1
2	PROGRAM DESCRIPTION	4
2.1	Objectives.....	4
2.2	Three Phase Program	4
2.3	Fast Track Proposals	5
2.4	Direct to Phase II Proposals	5
2.5	Grant Opportunity - Phase IIB Competing Renewal Awards (INFORMATION ONLY)	5
2.6	Awarding Components.....	6
3	DEFINITIONS.....	7
3.1	General Definitions	7
3.2	Definitions (Relating to R&D).....	10
4	PROPOSAL FUNDAMENTALS.....	16
4.1	Introduction	16
4.2	Offeror Eligibility and Performance Requirements.....	16
4.3	Multiple Principal Investigators	17
4.4	Joint Ventures and Limited Partnerships.....	17
4.5	Majority Ownership in Part by Multiple Venture Capital, Hedge Fund, and Private Equity Firms (NIH and CDC).....	17
4.6	Conflicts of Interest.....	18
4.7	Market Research.....	18
4.8	OMB Clearance.....	18
4.9	Research Involving Human Subjects	18
4.10	Inclusion of Women, Minorities, and Children in Clinical Research.....	19
4.11	Care of Vertebrate Animals.....	19
4.12	Research Involving Recombinant or Synthetic Nucleic Acid Molecules.....	20
4.13	Debriefing	20
4.14	Phase I Award Information	20
4.15	Phase II Award Information (For Fast Track and Direct to Phase II Proposals).....	21
4.16	Registrations and Certifications	21
4.17	Promotional Materials.....	22
4.18	Prior, Current, or Pending Support of Similar Proposals or Awards.....	22
4.19	Fraud and False Statements.....	22
4.20	State and Other Assistance Available	23
4.21	Payment.....	23
4.22	Proprietary Information.....	24
4.23	Identification and Marking of SBIR Technical Data in Proposals	24
5	CONTRACT REQUIREMENTS.....	25
5.1	Other Contract Requirements.....	25
5.2	Special Contract Requirements	27
5.3	Copyrights.....	27
5.4	Patents	27
5.5	Technical Data Rights	27
5.6	Invention Reporting	28

6	METHOD OF EVALUATION	29
6.1	Evaluation Process	29
6.2	Phase I Technical Evaluation Criteria	29
6.3	Phase II Technical Evaluation Criteria.....	30
6.4	Award Decisions	31
7	PROPOSAL SUBMISSION	32
7.1	Questions.....	32
7.2	Pre-Proposal Conference.....	32
7.3	Limitation on the Length of the Technical Proposal (Item 1)	32
7.4	Submission, Modifications, Revision, and Withdrawal of Proposals	32
8	PROPOSAL PREPARATION AND INSTRUCTIONS	35
8.1	Introduction	35
8.2	Fast Track Proposal Instructions (NIH Only)	35
8.3	Phase I Proposal Instructions	35
8.4	Phase II Proposal Instructions	36
8.5	Technical Proposal Cover Sheet (Item 1).....	36
8.6	Table of Contents (Item 1)	37
8.7	Abstract of Research Plan (Item 1)	37
8.8	Content of Technical Element (Item 1).....	37
8.9	Human Subjects Research and Protection from Risk.....	42
8.10	Inclusion of Women, Minorities, and Children in Clinical Research.....	47
8.11	Research Involving Human Fetal Tissue.....	51
8.12	Research Involving Vertebrate Animals	52
8.13	Content of the Pricing Proposal (Item Two).	53
8.14	Reminders	54
9	SUMMARY OF HHS COMPONENTS ANTICIPATED NUMBER OF AWARDS.....	55
10	CONTRACTING OFFICER POINTS OF CONTACT FOR QUESTIONS RELATED TO SPECIFIC TOPICS	56
	National Institutes of Health (NIH).....	56
	National Cancer Institute (NCI)	56
	National Center for Advancing Translational Sciences (NCATS).....	56
	National Heart, Lung, and Blood Institute (NHLBI).....	56
	National Institute on Alcohol Abuse and Alcoholism (NIAAA)	56
	National Institute of Allergy and Infectious Diseases (NIAID)	56
	National Institute on Drug Abuse (NIDA).....	57
	Centers for Disease Control and Prevention (CDC).....	57
	Center for Global Health (CGH).....	57
	National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	57
	National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP).....	58
	National Center for Immunization and Respiratory Diseases (NCIRD)	58
11	SCIENTIFIC AND TECHNICAL INFORMATION SOURCES.....	59
12	COMPONENT INSTRUCTIONS AND TECHNICAL TOPIC DESCRIPTIONS.....	60

National Institutes of Health.....	60
National Cancer Institute (NCI)	60
National Center for Advancing Translational Sciences (NCATS).....	99
National Heart, Lung, and Blood Institute (NHLBI).....	103
National Institute on Alcohol Abuse and Alcoholism (NIAAA)	110
National Institute of Allergy and Infectious Diseases (NIAID)	111
National Institute on Drug Abuse (NIDA)	119
Centers for Disease Control and Prevention (CDC).....	128
Center for Global Health (CGH).....	128
National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	131
National Center For HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP).....	135
National Center for Immunization and Respiratory Diseases (NCIRD)	138
13 APPENDICES.....	142
APPENDIX A — PROPOSAL COVER SHEET - USE FOR PHASE I AND FAST-TRACK PROPOSALS	142
APPENDIX B — ABSTRACT OF RESEARCH PLAN - USE FOR PHASE I, PHASE II, AND FAST-TRACK PROPOSALS	143
APPENDIX C — PRICING PROPOSAL - USE FOR PHASE I, PHASE II AND FAST-TRACK PROPOSALS	143
APPENDIX D — PHASE II TECHNICAL PROPOSAL COVER SHEET - USE FOR PHASE II AND FAST-TRACK PROPOSALS.....	143
APPENDIX E — STATEMENT OF WORK SAMPLE FORMAT - USE FOR PHASE II AND FAST-TRACK PROPOSALS	143
APPENDIX F — SUMMARY OF RELATED ACTIVITIES - USE FOR PHASE II AND FAST- TRACK PROPOSALS	143
APPENDIX G — PROPOSAL SUMMARY AND DATA RECORD - USE FOR PHASE II AND FAST-TRACK PROPOSALS	143

1 INTRODUCTION

The National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC) invite small business concerns to submit research proposals under this Small Business Innovation Research (SBIR) Contract Solicitation. Firms with the capability to conduct research and development (R&D) in any of the health related topic areas described in [Section 12.0](#), and to commercialize the results of that R&D, are encouraged to participate.

This solicitation contains opportunities to submit a proposal under a variety of different Topics, which are summarized below. Some Topics allow for only a Phase I proposal to be submitted. Some Topics allow for only a Phase II proposal to be submitted, through the ‘Direct to Phase II’ process. Some Topics allow for ‘Fast Track’ proposals, which include both a Phase I proposal and a Phase II proposal. For more information on the three phase program and the Fast Track and Direct to Phase II processes, refer to Section 2.

TOPIC NUMBER	PHASE I PROPOSAL ALLOWED? (Includes only a Phase I Proposal)	FAST TRACK PROPOSAL ALLOWED? (Includes a Phase I Proposal and a Phase II Proposal)	DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal)	TOPIC TITLE
NIH/ NCI 341	Yes	Yes	No	Development of Metabolomics Data Integration Methods and Software
NIH/ NCI 342	No	No	Yes	Validation of Mobile Technologies for Clinical Assessment, Monitoring and Intervention
NIH/ NCI 343	Yes	Yes	No	An Electronic Platform for Cognitive Assessment in Cancer Patients
NIH/ NCI 344	Yes	No	No	Technologies for Differential Isolation of Exosomes and Oncosomes
NIH/ NCI 345	Yes	Yes	No	Predictive Biomarkers of Adverse Reactions to Radiation Treatment
NIH/ NCI 346	Yes	Yes	No	Molecularly Targeted Radiation Therapy For Cancer Treatment
NIH/ NCI 347	Yes	Yes	No	Signal Amplification to Enable Attomolar Quantitation in Slide-Based or ELISA Biomarker Immunoassays
NIH/ NCI 348	Yes	Yes	No	Identification and Capture of Enriched Tumor Zones with Preservation of Labile Biomarkers from Ultra-Cold Biopsies
NIH/ NCI 349	Yes	Yes	No	Proximity Slide-Based Sandwich Immunoassay to Visualize Intramolecular Epitopes of Analytes in Tissue Sections
NIH/ NCI 350	Yes	Yes	No	Highly Innovative Tools for Quantifying Redox Effector Dynamics in Cancer
NIH/ NCI 351	Yes	No	No	Modulating the Microbiome to Improve Efficacy of Cancer Therapeutics
NIH/ NCI 352	Yes	No	No	Cell and Animal-Based Models to Advance Cancer Health Disparity Research

TOPIC NUMBER	PHASE I PROPOSAL ALLOWED? (Includes only a Phase I Proposal)	FAST TRACK PROPOSAL ALLOWED? (Includes a Phase I Proposal and a Phase II Proposal)	DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal)	TOPIC TITLE
NIH/ NCI 353	Yes	Yes	No	Cell-Free Nucleic Acid-Based Assay Development for Cancer Diagnosis
NIH/ NCI 354	Yes	Yes	No	Companion Diagnostics for Cancer Immunotherapies
NIH/ NCATS 013	Yes	No	No	Development of Stem Cell-based Assay for High-Throughput Screening of Chemicals of Toxicological Concern
NIH/ NCATS 014	Yes	No	No	Development of Smart Plate Technology
NIH/ NHLBI 094	Yes	Yes	Yes	Transcatheter Cavopulmonary Bypass Endograft
NIH/ NHLBI 095	Yes	Yes	Yes	Active MRI Transseptal Needle
NIH/ NHLBI 096	Yes	Yes	Yes	Bioabsorbable Stents for Neonatal Aortic Coarctation
NIH/ NHLBI 097	Yes	Yes	Yes	Early Detection and Monitoring of Cardiac Injury Due to Cardiotoxicity
NIH/ NIAAA 015	Yes	No	No	Development of Novel Compounds to Treat Alcohol Use Disorder
NIH/ NIAID 033	Yes	Yes	No	Precision Genome Engineering for HIV Eradication
NIH/ NIAID 034	Yes	Yes	No	High-Throughput Assay Platform for Quantifying Latent HIV Reservoirs
NIH/ NIAID 035	Yes	Yes	Yes	Method for the Detection of Minority Populations of Drug Resistant HIV
NIH/ NIAID 036	Yes	Yes	Yes	Simple, Inexpensive Device to Purify DNA from Sputum for Tuberculosis Testing
NIH/ NIAID 037	Yes	Yes	Yes	Telemonitoring for Infectious Diseases: A Remote System for Assessing Patient Parameters and Specimen Analysis
NIH/ NIAID 038	Yes	Yes	Yes	Innovative Oral Formulations for Anti-Infective Drugs
NIH/ NIAID 039	Yes	Yes	No	Vaccines against Pathogens with Small Market Potential
NIH/ NIDA 158	Yes	No	No	Development of Primer and Reference Tool to Assess Neonatal Abstinence Syndrome

TOPIC NUMBER	PHASE I PROPOSAL ALLOWED? (Includes only a Phase I Proposal)	FAST TRACK PROPOSAL ALLOWED? (Includes a Phase I Proposal and a Phase II Proposal)	DIRECT TO PHASE II ALLOWED? (Includes only a Phase II Proposal)	TOPIC TITLE
NIH/ NIDA 159	Yes	No	No	Therapeutic Cannabidiol Pulmonary Delivery Device (e.g. Nebulizer, Vaporizer, or Inhaler)
NIH/ NIDA 160	Yes	No	No	“The Pain Mobile:” Remote Pain Management System
CDC/ CGH 008	Yes	No	No	Diagnostic Tools to Support the Elimination and Control of Neglected Tropical Diseases
CDC/ NCEZID 012	Yes	No	No	De novo assembly of arthropod genomes of public health importance
CDC/ NCEZID 013	Yes	No	No	Detecting Lower Intestinal Microbiome Disruption and Multidrug Resistant Organisms
CDC/ NCHHSTP 046	Yes	No	No	Serologic measurement of hepatitis B virus cccDNA
CDC/ NCHHSTP 047	Yes	No	No	Serologic detection and quantification of hepatitis B core antigen
CDC/ NCIRD 031	Yes	No	No	Transcutaneous immunization against rotavirus using a dissolvable microneedle patch
CDC/ NCIRD 032	Yes	No	No	Thermostable Dry Powder Live Attenuated Influenza Vaccine for Nasal Delivery

All firms that are awarded Phase I contracts originating from this solicitation will be eligible to participate in Phases II and III. HHS Components will notify Phase I awardees of the Phase II proposal submission requirements. Submission of Phase II proposals will be in accordance with dates provided by individual Component instructions. The details on the due date, content, and submission requirements of the Phase II proposal will be provided by the awarding HHS Component either in the Phase I award or by subsequent notification.

The HHS is not obligated to make any awards under Phase I, Phase II, or Phase III, and all awards are subject to the availability of funds. HHS is not responsible for any monies expended by the offeror before award of any contract.

2 PROGRAM DESCRIPTION

2.1 Objectives

The objectives of the SBIR program include stimulating technological innovation in the private sector, strengthening the role of small business in meeting Federal research or research and development (R/R&D) needs, increasing private sector commercialization of innovations developed through Federal SBIR R&D, increasing small business participation in Federal R&D, and fostering and encouraging participation by socially and economically disadvantaged small business concerns and women-owned small business concerns in the SBIR program.

The basic design of the NIH/CDC SBIR program is in accordance with the Small Business Administration (SBA) SBIR Program Policy Directive dated February 24, 2014. This SBIR Contract solicitation strives to encourage scientific and technical innovation in areas specifically identified by the NIH/CDC awarding components. The guidelines presented in this solicitation reflect the flexibility provided in the Policy Directive to encourage proposals based on scientific and technical approaches most likely to yield results important to the NIH/CDC and to the private sector.

2.2 Three Phase Program

The SBIR program consists of three separate phases.

Phase I: Feasibility

The objective of Phase I is to determine the scientific or technical feasibility and commercial merit of the proposed research or R&D efforts and the quality of performance of the small business concern, prior to providing further Federal support in Phase II.

Phase II: Full R/R&D Effort

The objective of Phase II is to continue the research or R&D efforts initiated in Phase I. Funding shall be based on the results of Phase I and the scientific and technical merit and commercial potential of the Phase II proposal. *Phase I contractors will be informed of the opportunity to apply for Phase II, if a Phase II proposal was not submitted concurrently with the initial Phase I proposal under the Fast Track procedure. Only one Phase II award may result from a single Phase I SBIR contract.*

Phase III: Commercialization stage without SBIR funds

The objective of Phase III, where appropriate, is for the small business concern to pursue with non-SBIR funds the commercialization objectives resulting from the outcomes of the research or R&D funded in Phases I and II. Phase III may involve follow-on, non-SBIR funded R&D, or production contracts for products or processes intended for use by the U.S. Government.

The competition for SBIR Phase I and Phase II awards satisfies any competition requirement of the Armed Services Procurement Act, the Federal Property and Administrative Services Act, and the Competition in Contracting Act. Therefore, an agency that wishes to fund an SBIR Phase III project is not required to conduct another competition in order to satisfy those statutory provisions. As a result, in conducting actions relative to a Phase III SBIR award, it is sufficient to state for purposes of a Justification and Approval pursuant to FAR 6.302-5 that the project is a SBIR Phase III award that is derived from, extends, or logically concludes efforts performed under prior SBIR funding agreements and is authorized under 10 U.S.C. 2304(b)(2) or 41 U.S.C. 253(b)(2).

The NIH is interested in developing products and services via the SBIR program that improve the health of the American people. In its commitment to also support [Executive Order 13329](#), encouraging innovation in manufacturing-related research and development, NIH seeks, through the SBIR program, biomedical research related to advanced processing, manufacturing processes, equipment and systems, or manufacturing workforce skills and protection. This solicitation includes some topic areas that are considered relevant to manufacturing-related R&D. Additional information will be posted on the [NIH Small Business Research Funding Opportunities Web site](#) and in the [NIH Guide for Grants and Contracts](#) as it becomes available.

Small businesses may be interested in reading a U.S. Department of Commerce 2004 report, "[Manufacturing in America: A Comprehensive Strategy to Address the Challenges to U.S. Manufacturers](#)".

2.3 Fast Track Proposals

If a Topic notes that Fast Track proposals will be accepted, a Phase I proposal and a Phase II proposal may be submitted simultaneously. As described in Section 8.2 "Fast Track Proposal Instructions," a Fast Track submission consists of one complete Phase I proposal and one complete Phase II proposal, separately paginated. The Phase I proposal and Phase II proposal will be separately evaluated as set forth in Section 6.0 "Method of Evaluation."

A Fast Track submission may result in award for Phase I with a contractual option for Phase II. The Government is not obligated to fund the Phase II portion unless and until the awarding HHS Component exercises that option. This mechanism allows for streamlined processes that have the potential to minimize the funding gap between Phase I and Phase II.

If the Phase II proposal of a Fast Track submission is not found suitable to include as an option, the Phase I proposal will still be considered for Phase I only award. In this instance, the SBC is treated as other Phase I awardees are in regards to submitting a Phase II proposal in accordance with Section 1.0, "Introduction."

Refer to the table in Section 1.0 "Introduction" and [Section 12.0](#) "Research Topics," for notation of Topics allowing Fast Track proposals.

2.4 Direct to Phase II Proposals

If a Topic notes that Direct to Phase II proposals will be accepted, a small business concern that has already performed Phase I stage-type research through other funding sources (not SBIR/STTR Phase I funding) may submit a Phase II only proposal. Direct to Phase II awards allow a SBC that has already built a technology prototype and tested its feasibility (i.e. completed Phase I type R&D) to move directly into Phase II type R&D that tests the functional viability of the prototype according to scientific methods and potential for commercial development. Refer to the table in Section 1.0 "Introduction" and [Section 12.0](#) "Research Topics," for notation of Topics allowing Direct to Phase II proposals.

2.5 Grant Opportunity - Phase IIB Competing Renewal Awards (INFORMATION ONLY)

Some NIH Institutes/Centers (ICs) offer Phase II SBIR/STTR awardees the opportunity to apply for Phase IIB Competing Renewal grant awards. These are available for those projects that require extraordinary time and effort in the R&D phase and may or may not require FDA approval for the development of such projects, including drugs, devices, vaccines, therapeutics, and medical implants related to the mission of the IC. Some ICs have announced this opportunity through the NIH Guide for Grants and Contracts (see link below), and some are using this Omnibus SBIR/STTR Grant Solicitation. Only those small business concerns who have been awarded a Phase II are eligible to apply for a Phase IIB Competing Renewal award. Prospective applicants are **strongly encouraged** to contact NIH staff prior to submission. Additional requirements and instructions (e.g., submission of a letter of intent) are available in the specific IC research topics section and in the specific [IC Program Funding Opportunity Announcements](#).

The following NIH ICs will accept applications for Phase IIB Competing Renewal awards: NIA, NIAAA, NIAID (SBIR only), NICHD (SBIR only and only Competing Renewals of NICHD-supported Phase II awards), NIDA, NIDCD, NIDDK (only Competing Renewals of NIDDK-supported Phase II awards), NEI (SBIR only), NIGMS (SBIR only), NIMH (SBIR only), NCATS (SBIR only), and ORIP (SBIR only). NCI offers Phase IIB opportunities that focus on the commercialization of SBIR-developed technologies. Contact the NCI SBIR Development Center at 240-276-5300 or NCISBIR@mail.nih.gov for additional information. NHLBI offers Phase IIB Competing Renewals that focus on the commercialization of technologies requiring regulatory approval through the NHLBI Bridge Award ([RFA-HL-16-009](#)) and the NHLBI Small Market Award ([RFA-HL-14-012](#)). Contact Jennifer Shieh, Ph.D., at 301-443-8785 or jennifer.shieh@nih.gov for additional information. NINDS accepts Phase IIB SBIR/STTR Competing Renewal applications through specific opportunities that focus on the commercialization of SBIR and STTR developed technologies. These opportunities can be found on the NINDS SBIR webpage: http://www.ninds.nih.gov/funding/small-business/small_business_funding_opportunities.htm. Contact Stephanie Fertig, M.B.A., at 301-496-1779 or fertigs@ninds.nih.gov for additional information.

2.6 Awarding Components

The following awarding components are participating in this SBIR Solicitation for Contract Proposals.

National Institutes of Health (NIH) Components:

National Cancer Institute (NCI)

National Center for Advancing Translational Sciences (NCATS)

National Heart, Lung, and Blood Institute (NHLBI)

National Institute on Alcohol Abuse and Alcoholism (NIAAA)

National Institute of Allergy and Infectious Diseases (NIAID)

National Institute on Drug Abuse (NIDA)

Centers for Disease Control and Prevention (CDC) Components:

Center for Global Health (CGH)

National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)

National Center for Immunization and Respiratory Diseases (NCIRD)

3 DEFINITIONS

3.1 General Definitions

The following definitions from the SBA Policy Directive and the Federal Acquisition Regulation (FAR) apply for the purposes of this solicitation:

Applicant. The organizational entity that qualifies as an SBC at all pertinent times and that submits a contract proposal or a grant application for a funding agreement under the SBIR Program.

Affiliate. This term has the same meaning as set forth in 13 CFR part 121—Small Business Size Regulations, section 121.103. How does SBA determine affiliation? (Available at http://www.ecfr.gov/cgi-bin/text-idx?SID=b02d16dbfcddf646e5c0728d5e632a61&mc=true&node=se13.1.121_1103&rgn=div8). Further information about SBA's affiliation rules and a guide on affiliation is available at www.SBIR.gov and www.SBA.gov/size.

Animal. Any live, vertebrate animal used or intended for use in research, research training, experimentation, or biological testing or for related purposes.

Awardee. The organizational entity receiving an SBIR Phase I, Phase II, or Phase III award.

Commercialization. The process of developing products, processes, technologies, or services and the production and delivery (whether by the originating party or others) of the products, processes, technologies, or services for sale to or use by the Federal government or commercial markets.

Consultant. An individual who provides professional advice or services for a fee, but normally not as an employee of the engaging party. In unusual situations, an individual may be both a consultant and an employee of the same party, receiving compensation for some services as a consultant and for other work as a salaried employee. To prevent apparent or actual conflicts of interest, grantees and consultants must establish written guidelines indicating the conditions of payment of consulting fees. Consultants may also include firms that provide paid professional advice or services.

Contract. An award instrument establishing a binding legal procurement relationship between a funding agency and the recipient, obligating the latter to furnish an end product or service and binding the agency to provide payment therefore.

Cooperative Agreement. A financial assistance mechanism used when substantial Federal programmatic involvement with the awardee during performance is anticipated by the issuing agency. The Cooperative Agreement contains the responsibilities and respective obligations of the parties.

Covered Small Business Concern. A small business concern that:

- (1) Was not majority-owned by multiple venture capital operating companies (VCOs), hedge funds, or private equity firms on the date on which it submitted an application in response to a solicitation under the SBIR program; and
- (2) Is majority-owned by multiple venture capital operating companies, hedge funds, or private equity firms on the date of the SBIR award.

eCPS. Electronic Contract Submission (eCPS) website is a component of the Government's integrated, secure system for the electronic submission, capture, tracking, and review of contract proposals. The eCPS website will be the only way to submit proposals under this solicitation. See the Section on Proposal Submissions for further information.

Essentially Equivalent Work. Work that is substantially the same research, which is proposed for funding in more than one contract proposal or grant application submitted to the same Federal agency or submitted to two or more different Federal agencies for review and funding consideration; or work where a specific research objective and the research design for accomplishing the objective are the same or closely related to another proposal or award, regardless of the funding source.

Feasibility. The practical extent to which a project can be performed successfully.

Federal Agency. An executive agency as defined in 5 U.S.C. § 105, and a military department as defined in [5 U.S.C. 102](#) (Department of the Army, Department of the Navy, Department of the Air Force), except that it does not include any agency within the Intelligence Community as defined in Executive Order 12333, section 3.4(f), or its successor orders.

Federal Laboratory. As defined in 15 U.S.C. § 3703, means any laboratory, any federally funded research and development center, or any center established under 15 U.S.C. §§ 3705 & 3707 that is owned, leased, or otherwise used by a Federal agency and funded by the Federal Government, whether operated by the Government or by a contractor.

Fraud, Waste, and Abuse.

Fraud includes any false representation about a material fact or any intentional deception designed to deprive the United States unlawfully of something of value or to secure from the United States a benefit, privilege, allowance, or consideration to which an individual or business is not entitled.

Waste includes extravagant, careless or needless expenditure of Government funds, or the consumption of Government property, that results from deficient practices, systems, controls, or decisions.

Abuse includes any intentional or improper use of Government resources, such as misuse of rank, position, or authority or resources.

Funding Agreement. Any contract, grant, or cooperative agreement entered into between any Federal agency and any SBC for the performance of experimental, developmental, or research work, including products or services, funded in whole or in part by the Federal Government.

Funding Agreement Officer. A contracting officer, a grants officer, or a cooperative agreement officer.

Grant. A financial assistance mechanism providing money, property, or both to an eligible entity to carry out an approved project or activity. A grant is used whenever the Federal agency anticipates no substantial programmatic involvement with the awardee during performance.

Innovation. Something new or improved, having marketable potential, including: (1) development of new technologies, (2) refinement of existing technologies, or (3) development of new applications for existing technologies.

Intellectual Property. The separate and distinct types of intangible property that are referred to collectively as “intellectual property,” including but not limited to: (1) Patents; (2) trademarks; (3) copyrights; (4) trade secrets; (5) SBIR technical data (as defined in this section); (6) ideas; (7) designs; (8) know-how; (9) business; (10) technical and research methods; (11) other types of intangible business assets; and (12) all types of intangible assets, either proposed or generated by an SBC as a result of its participation in the SBIR Program.

Joint Venture. See [13 CFR 121.103\(h\)](#).

Key Individual. The principal investigator/project manager and any other person named as a “key” employee in a proposal submitted in response to a program solicitation.

Principal Investigator/Project Manager. The one individual designated by the applicant to provide the scientific and technical direction to a project supported by the funding agreement.

Program Solicitation. A formal solicitation for proposals issued by a Federal agency that notifies the small business community of its R/R&D needs and interests in broad and selected areas, as appropriate to the agency, and requests proposals from SBCs in response to these needs and interests. Announcements in the Federal Register or the GPE are not considered an SBIR Program solicitation.

Proprietary Information. Proprietary information is information that you provide which constitutes a trade secret, proprietary commercial or financial information, confidential personal information or data affecting the national security.

Prototype. A model of something to be further developed, which includes designs, protocols, questionnaires, software, and devices.

SBIR Participants. Business concerns that have received SBIR awards or that have submitted SBIR proposals/applications.

SBIR Technical Data. All data generated during the performance of an SBIR award.

SBIR Technical Data Rights. The rights an SBIR awardee obtains in data generated during the performance of any SBIR Phase I, Phase II, or Phase III award that an awardee delivers to the Government during or upon completion of a Federally-funded project, and to which the Government receives a license.

Senior/Key Personnel. The PD/PI and other individuals who contribute to the scientific development or execution of the project in a substantive, measurable way, whether or not salaries or compensation are requested under the contract.

Small Business Concern (SBC). A concern that meets the requirements set forth in [13 CFR 121.702](#):

To be eligible for award of funding agreements in the SBA's Small Business Innovation Research (SBIR) program, a business concern must meet the requirements of paragraphs (a) and (b) below:

(a) *Ownership and control.*

(1) An SBIR awardee must:

- (i) Be a concern which is more than 50% directly owned and controlled by one or more individuals (who are citizens or permanent resident aliens of the United States), other small business concerns (each of which is more than 50% directly owned and controlled by individuals who are citizens or permanent resident aliens of the United States), or any combination of these; OR
- (ii) Be a concern which is more than 50% owned by multiple venture capital operating companies, hedge funds, private equity firms, or any combination of these (for agencies electing to use the authority in 15 U.S.C. 638(dd)(1)); OR
- (iii) Be a joint venture in which each entity to the joint venture must meet the requirements set forth in paragraph (a)(1)(i) or (a)(1)(ii) of this section. A joint venture that includes one or more concerns that meet the requirements of paragraph (a)(1)(ii) of this section must comply with § 121.705(b) concerning registration and proposal requirements

- (2) No single venture capital operating company, hedge fund, or private equity firm may own more than 50% of the concern.
- (3) If an Employee Stock Ownership Plan owns all or part of the concern, each stock trustee and plan member is considered an owner.
- (4) If a trust owns all or part of the concern, each trustee and trust beneficiary is considered an owner.

(b) *Size.* An SBIR awardee, together with its affiliates, will not have more than 500 employees.

Socially and Economically Disadvantaged Individual. See [13 CFR 124.103](#) and [124.104](#).

Subcontract. Any agreement, other than one involving an employer-employee relationship, entered into by an awardee of a funding agreement calling for supplies or services for the performance of the original funding agreement.

United States. Means the 50 states, the territories and possessions of the Federal Government, the Commonwealth of Puerto Rico, the District of Columbia, the Republic of the Marshall Islands, the Federated States of Micronesia, and the Republic of Palau.

Women-Owned SBC (WOSB). A SBC that is at least 51% owned by one or more women, or in the case of any publicly owned business, at least 51% of the stock is owned by women, and women control the management and daily business operations.

3.2 Definitions (Relating to R&D)

Autopsy Materials. The use of autopsy materials is governed by applicable Federal, state, and local law and is not directly regulated by 45 CFR part 46.

Child. The NIH Policy on Inclusion of Children defines a child as an individual under the age of 21 years. The intent of the NIH policy is to provide the opportunity for children to participate in research studies when there is a sound scientific rationale for including them, and their participation benefits children and is appropriate under existing Federal guidelines. Thus, children must be included in NIH conducted or supported clinical research unless there are scientific or ethical reasons not to include them. This policy is separate from considerations of protections and consent for children to participate in research.

HHS Regulations ([45 CFR part 46, Subpart D, Sec.401-409](#)) provide additional protections for children involved as subjects in research, based on this definition: "Children are persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted." Generally, state laws define what constitutes a "child." Consequently, the age at which a child's own consent is required and sufficient to participate in research will vary according to state law. For example, some states consider a person age 18 to be an adult and therefore one who can provide consent without parental permission.

Clinical Research. NIH defines human clinical research as research with human subjects that is:

- (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are in vitro studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes:
 - (a) mechanisms of human disease,
 - (b) therapeutic interventions,
 - (c) clinical trials, or
 - (d) development of new technologies.
- (2) Epidemiologic and behavioral studies.
- (3) Outcomes research and health services research. Note: Studies falling under Exemption 4 for human subjects research are not considered clinical research by this definition.

Clinical Trial. The NIH defines a *clinical trial* as a research study¹ in which one or more human subjects² are prospectively assigned³ to one or more interventions⁴ (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes⁵.

¹ See Common Rule definition of research at 45 CFR 46.102(d).

² See Common Rule definition of human subject at 45 CFR 46.102(f).

³ The term “prospectively assigned” refers to a pre-defined process (e.g., randomization) specified in an approved protocol that stipulates the assignment of research subjects (individually or in clusters) to one or more arms (e.g., intervention, placebo, or other control) of a clinical trial.

⁴ An intervention is defined as a manipulation of the subject or subject’s environment for the purpose of modifying one or more health-related biomedical or behavioral processes and/or endpoints. Examples include: drugs/small molecules/compounds; biologics; devices; procedures (e.g., surgical techniques); delivery systems (e.g., telemedicine, face-to-face interviews); strategies to change health-related behavior (e.g., diet, cognitive therapy, exercise, development of new habits); treatment strategies; prevention strategies; and, diagnostic strategies.

⁵ Health-related biomedical or behavioral outcome is defined as the pre-specified goal(s) or condition(s) that reflect the effect of one or more interventions on human subjects’ biomedical or behavioral status, or quality of life. Examples include: positive or negative changes to physiological or biological parameters (e.g., improvement of lung capacity, gene expression); positive or negative changes to psychological or neurodevelopmental parameters (e.g., mood management intervention for smokers; reading comprehension and/or information retention); positive or negative changes to disease processes; positive or negative changes to health-related behaviors; and positive or negative changes to quality of life.

For additional information see [NOT-OD-15-015](#).

- *Phase I* clinical trials test a new biomedical intervention in a small group of people (e.g., 20-80) for the first time to evaluate safety (e.g., to determine a safe dosage range and to identify side effects).
- *Phase II* clinical trials study the biomedical or behavioral intervention in a larger group of people (several hundred) to determine efficacy and to further evaluate its safety.
- *Phase III* studies investigate the efficacy of the biomedical or behavioral intervention in large groups of human subjects (from several hundred to several thousand) by comparing the intervention to other standard or experimental interventions as well as to monitor adverse effects, and to collect information that will allow the intervention to be used safely.
- *Phase IV* studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.
- *NIH-Defined Phase III Clinical Trial*. For the purpose of the Guidelines an NIH-defined Phase III clinical trial is a broadly based prospective Phase III clinical investigation, usually involving several hundred or more human subjects, for the purpose of evaluating an experimental intervention in comparison with a standard or controlled intervention or comparing two or more existing treatments. Often the aim of such investigation is to provide evidence leading to a scientific basis for consideration of a change in health policy or standard of care. The definition includes pharmacologic, non-pharmacologic, and behavioral interventions given for disease prevention, prophylaxis, diagnosis, or therapy. Community trials and other population-based intervention trials are also included.

Data and Safety Monitoring Plan. For each clinical trial, NIH requires a data and safety monitoring plan that will provide oversight and monitoring to ensure the safety of participants and the validity and integrity of the data. The level of monitoring should be commensurate with the risks and the size and complexity of the clinical trial. A detailed data and safety monitoring plan must be submitted to the contractor’s IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. Adverse Events must be reported to the IRB, the NIH funding Institute or Center, and other required entities. This policy requirement is in addition to any monitoring requirements imposed by [45 CFR part 46](#).

Data and Safety Monitoring Board (DSMB). NIH requires the establishment of a Data and Safety Monitoring Board (DSMB) for multi-site clinical trials involving interventions that entail potential risk to the participants, *and generally for Phase III clinical trials*.

Human Subjects. The HHS regulations “Protection of Human Subjects” [45 CFR part 46](#), (administered by OHRP) define a human subject as a living individual about whom an investigator conducting research obtains:

- Data through *intervention or interaction* with the individual or
- Identifiable private information

Individually Identifiable Private Information. According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be *individually identifiable* as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through *coding* systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding system.

Interaction includes communication or interpersonal contact between investigator and subject. (45 CFR 46.102(f)).

Intervention includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes. (45 CFR 46.102(f)).

Investigational Device Exemption (IDE). An IDE is a regulatory submission that permits clinical investigation of devices. This investigation is exempt from some regulatory requirements. The term “IDE” stems from the description in 21Code of Federal Regulations (CFR) 812.1.

Investigator. The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide *coded* information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research. (See OHRP’s [Guidance on Research Involving Coded Private Information on Biological Specimens.](#))

Manufacturing-related R&D as a result of Executive Order 13329. Encompasses improvements in existing methods or processes, or wholly new processes, machines or systems. Four main areas include:

1. Unit process level technologies that create or improve manufacturing processes including:
 - Fundamental improvements in existing manufacturing processes that deliver substantial productivity, quality, or environmental benefits.
 - Development of new manufacturing processes, including new materials, coatings, methods, and associated practices.
2. Machine level technologies that create or improve manufacturing equipment, including:
 - Improvements in capital equipment that create increased capability (such as accuracy or repeatability), increased capacity (through productivity improvements or cost reduction), or increased environmental efficiency (safety, energy efficiency, environmental impact).
 - New apparatus and equipment for manufacturing, including additive and subtractive manufacturing, deformation and molding, assembly and test, semiconductor fabrication, and nanotechnology.
3. *Systems level technologies* for innovation in the manufacturing enterprise, including:
 - Advances in controls, sensors, networks, and other information technologies that improve the quality and productivity of manufacturing cells, lines, systems, and facilities.
 - Innovation in extended enterprise functions critical to manufacturing, such as quality systems, resource management, supply change integration, and distribution, scheduling and tracking.
4. Environment or societal level technologies that improve workforce abilities, productivity, and manufacturing competitiveness, including:
 - Technologies for improved workforce health and safety, such as human factors and ergonomics.
 - Technologies that aid and improve workforce manufacturing skill and technical excellence, such as educational systems incorporating improved manufacturing knowledge and instructional methods.

- technologies that enable integrated and collaborative product and process development, including computer-aided and expert systems for design, tolerancing, process and materials selection, life-cycle cost estimation, rapid prototyping, and tooling.

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be *individually identifiable* (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects. (45 CFR 46.102(f))

Coded. With respect to **private information** or human biological specimens, *coded* means that:

- a. Identifying information (such as name or social security number) that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol or combination thereof (i.e., the code); and

A key to decipher the code exists, enabling linkage of the identifying information with the private information or specimens.

Research that involves only coded private information/data or coded human biological specimens may not constitute human subjects research under the HHS human subjects regulations (45 CFR 46) if:

- The specimens and/or information/data are not obtained from an interaction/intervention with the subject specifically for the research; and
- The investigator(s) cannot readily ascertain the identity of the individual(s) to whom the coded private information or specimens pertain (e.g., the researcher's access to subject identities is prohibited).

Individuals who provide coded information or specimens for proposed research and who also collaborate on the research involving such information or specimens are considered to be involved in the conduct of human subjects research.

(See the following guidance from the Office for Human Research Protections (OHRP) for additional information and examples: <http://www.hhs.gov/ohrp/policy/cdebiol.html>.)

Research or Research and Development (R/R&D). Any activity that is:

1. A systematic, intensive study directed toward greater knowledge or understanding of the subject studied;
2. A systematic study directed specifically toward applying new knowledge to meet a recognized need; or
3. A systematic application of knowledge toward the production of useful materials, devices, and systems or methods, including design, development, and improvement of prototypes and new processes to meet specific requirements.

Research Institution. Any organization located in the United States that is:

- A university.
- A nonprofit institution as defined in Section 4(5) of the Stevenson-Wydler Technology Innovation Act of 1980.

Research Involving Vertebrate Animals

All research involving live vertebrate animals shall be conducted in accordance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals ([PHS Policy](#)).

In addition, the research involving live vertebrate animals shall be conducted in accordance with the description set forth in the Vertebrate Animal Section (VAS) of the contractor's technical proposal, as modified in the Final Proposal Revision (FPR), which is incorporated by reference. If using live vertebrate animals, HHS policy requires that offerors address the points in the Vertebrate Animal Section (VAS) of the Technical Proposal. Each of the points must be addressed in the VAS portion of the Technical Proposal. For additional information see PHS Policy and use Contract Proposal VAS Worksheet. <http://grants.nih.gov/grants/olaw/references/phspol.htm#InformationRequiredinApplications-ProposalsforAwardsSubmittedtoPHS> and <http://grants.nih.gov/grants/olaw/VAScontracts.pdf>.

Research Involving Human Subjects

All research involving human subjects, to include use of human biological specimens and human data, shall comply with the applicable federal and state laws and agency policy/guidelines for human subject protection.

Exemptions. The six categories of research exempt from the HHS human subject regulations are:

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as
 - (i) Research on regular and special education instructional strategies, or
 - (ii) Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
 - (i) Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
 - (ii) Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- (3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:
 - (i) The human subjects are elected or appointed public officials or candidates for public office; or
 - (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.
- (5) Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:
 - (i) Public benefit or service programs;
 - (ii) Procedures for obtaining benefits or services under those programs;
 - (iii) Possible changes in or alternatives to those programs or procedures; or
 - (iv) Possible changes in methods or levels of payment for benefits or services under those programs.

(6) Taste and food quality evaluation and consumer acceptance studies,

- (i) If wholesome foods without additives are consumed or
- (ii) If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Research Involving Recombinant or Synthetic Nucleic Acid Molecules. Any recipient performing research involving recombinant or synthetic nucleic acid molecules and/or organisms and viruses containing recombinant or synthetic nucleic acid molecules shall comply with the National Institutes of Health Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules, dated November 2013 as amended. The guidelines can be found at:

http://oba.od.nih.gov/rdna/nih_guidelines_oba.html. Recombinant or synthetic nucleic acid molecules are defined as:

- (i) Molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell, i.e., recombinant nucleic acids
- (ii) Nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids; or,
- (iii) Molecules that result from the replication of those described in (i) or (ii) above.

Sex/Gender. Refers to the classification of research subjects in either or both of two categories: male and female. In some cases, representation is unknown, because sex/gender composition cannot be accurately determined (e.g. pooled blood samples or stored specimens without sex/gender designation). In addition, sex/gender classification is based on the self-reporting of participants enrolled in the research study. Investigators should consider the scientific goals of their study when requesting this information, particularly if the research may include individuals whose gender identity differs from their sex assigned at birth.

Valid Analysis. This term means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are: allocation of study participants of both sexes/genders (males and females) and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization; unbiased evaluation of the outcome(s) of study participants; and use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex/gender, race, and/or ethnicity.

4 PROPOSAL FUNDAMENTALS

Unless otherwise specified, Section 4 applies to both Phase I and Phase II.

4.1 Introduction

The proposal must provide sufficient information to demonstrate to the evaluator(s) that the proposed work represents an innovative approach to the investigation of an important scientific or engineering problem and is worthy of support under the stated criteria. The proposed research or research and development must be responsive to the chosen topic, although it need not use the exact approach specified in the topic. Anyone contemplating a proposal for work on any specific topic should determine that (a) the technical approach has a reasonable chance of meeting the topic objective, (b) this approach is innovative, not routine, with potential for commercialization and (c) the proposing firm has the capability to implement the technical approach, i.e., has or can obtain people and equipment suitable to the task.

4.2 Offeror Eligibility and Performance Requirements

To receive SBIR funds, each awardee of a SBIR Phase I or Phase II award must qualify as a small business concern (SBC) at the time of award and at any other time set forth in SBA's regulations at 13 CFR 121.701-121.705. Each applicant must qualify as a small business for research or research and development purposes and certify to this on the Cover Sheet (Appendix A) of the proposal. Additionally, each awardee must submit a certification stating that it meets the size, ownership and other requirements of the SBIR Program at the time of award, and at any other time set forth in SBA's regulations at 13 CFR 121.701-705.

For Phase I, a minimum of two-thirds of the research or analytical effort must be performed by the awardee. For Phase II, a minimum of one-half of the research or analytical effort must be performed by the awardee. The percentage of work will be measured by total contract costs.

For both Phase I and II, the principal investigator must be primarily employed with the SBC. Primary employment means that more than one half (50%) of the employee's time is spent with the small business. Primary employment with the SBC precludes full-time employment at another organization.

For both Phase I and Phase II, all research or research and development work must be performed by the SBC and its subcontractors in the United States.

Phase I to Phase II Transition Benchmark. Section 4(a) of the SBIR Policy Directive calls for each Federal agency participating in SBIR to set a Phase I to Phase II transition rate benchmark in response to Section 5165 of the SBIR/STTR Reauthorization Act of 2011. The rate is the minimum required ratio of past Phase II/Phase I awards that an awardee firm must maintain to be eligible for a new Phase I award from a particular agency. The benchmark will apply to those Phase I applicants that have received 20 or more Phase I awards Program-wide. Small businesses can view their transition rate on www.sbir.gov upon completion of registration. When logging in, the Phase I to Phase II transition rate will be displayed in the welcome screen.

The HHS benchmark uses a five-year period and counts an applicant's total number of Phase I awards over the last five fiscal years, excluding the most recently completed fiscal year; and the total number of Phase II awards over the last five fiscal years, including the most recently completed year. The HHS SBIR Phase I to II Transition Benchmark, as published in the Federal Register, is as follows:

For all SBIR Program Phase I contract applicants that have received 20 or more Phase I awards over the 5-year period, the ratio of Phase II awards received to Phase I awards received must be at least 0.25.

Phase II to Phase III Commercialization Benchmark

As required by the SBIR/STTR Reauthorization Act of 2011, HHS SBIR/STTR programs are also implementing the Phase II to Phase III Commercialization Rate benchmark for Phase I applicants. The Commercialization Rate Benchmark was published in a Federal Register notice on August 8, 2013 (78 FR 48537). This requirement applies to companies that have

received more than 15 Phase II awards from all agencies over the past 10 years, excluding the two most recently-completed Fiscal Years.

Companies that meet this criterion must show an average of at least \$100,000 in revenues and/or investments per Phase II award or at least 0.15 (15%) patents per Phase II award resulting from these awards.

Applicants to this solicitation that may have received more than 15 Phase II awards across all federal SBIR/STTR agencies over the past ten (10) years should, prior to application preparation, verify that their company's Commercialization Benchmark on the Company Registry at SBIR.gov meets or exceeds the benchmark rate listed above. Applicants that fail this benchmark will be notified by SBA annually and will not be eligible to receive new Phase I, Fast-track or Direct Phase II awards for a period of one year. Information on the Phase II to Phase III Commercialization Benchmark is available at SBIR.gov.

4.3 Multiple Principal Investigators

The NIH now provides offerors the opportunity to propose a multiple Principal Investigator (PI) model on research and development contracts. The multiple PI model is intended to supplement, and not replace, the traditional single PI model. Ultimately, the decision to submit a proposal using multiple PIs versus a single PI is the decision of the investigators and their institutions. The decision should be consistent with and justified by the scientific goals of the project. At least one proposed PI must be primarily employed with the applicant, as discussed in Section 4.2 "Offeror Eligibility and Performance Requirements."

4.4 Joint Ventures and Limited Partnerships

Joint ventures and limited partnerships are eligible, provided that each entity to the joint venture qualifies as a small business in accordance with the Small Business Act. Refer to the definition of "Small Business Concern" and "Joint Venture" in Section 3.1 "General Definitions," for further information.

4.5 Majority Ownership in Part by Multiple Venture Capital, Hedge Fund, and Private Equity Firms (NIH and CDC)

Small businesses that are owned in majority part by multiple venture capital operating companies (VCOCs), hedge funds, or private equity funds **are** eligible to submit proposals for opportunities under this solicitation, **but are required to submit a "SBIR Application VCOC Certification" at time of their application submission** per the [SBIR Policy Directive](#).

Follow the instructions below.

1. Download the "SBIR Application VCOC Certification.pdf" at the [NIH SBIR Forms](#) webpage.
2. Answer the 3 questions and check the certification boxes.
3. The authorized business official must sign the certification.
4. The signed SBIR Application VCOC Certification must be submitted as part of the Pricing Proposal.

Applicant small business concerns who are NOT owned in majority part by multiple venture capital operating companies (VCOCs), hedge funds, or private equity funds, as described above, should NOT fill out a "SBIR Application VCOC Certification" and should NOT attach it to their application package.

4.6 Conflicts of Interest

Contract awards to firms owned by or employing current or previous Federal Government employees could create conflicts of interest for those employees which may be a violation of federal law. Proposing firms should contact the cognizant Ethics Counselor from the employee's Government agency for further guidance if in this situation.

4.7 Market Research

The NIH/CDC will not support any market research under the SBIR program. Neither will it support studies of the literature that will lead to a new or expanded statement of work. Literature searches where the commercial product is a database are acceptable.

For purposes of the SBIR program, "market research" is the systematic gathering, recording, computing, and analyzing of data about problems relating to the sale and distribution of the subject of the research project. It includes various types of research, such as the size of potential market and potential sales volume, the identification of consumers most apt to purchase the products, and the advertising media most likely to stimulate their purchases. However, "market research" does not include activities under a research plan or protocol that require a survey of the public as part of the objective of the project to determine the impact of the subject of the research on the behavior of individuals.

4.8 OMB Clearance

Any research proposal involving the collection of information, such as surveys or interviews of 10 or more public respondents will require clearance by the U.S. Office of Management and Budget. Clearance may take several months to obtain and it is therefore not practical to propose any such activity for Phase I, which has a brief period of performance.

4.9 Research Involving Human Subjects

The HHS regulations "Protection of Human Subjects" ([45 CFR part 46](#), administered by OHRP) define a human subject as a living individual about whom an investigator conducting research obtains:

- data through *intervention* or *interaction* with the individual or identifiable *private information*

Notice to Offerors of Requirements of 45 CFR Part 46, Protection of Human Subjects, HHSAR 352.270-4 (January 2006)

Copies of the Department of Health and Human Services (HHS) regulations for the protection of human subjects, 45 CFR Part 46, are available from the Office for Human Research Protections (OHRP), 1101 Wootton Parkway, Suite 200, Rockville, MD 20852. The regulations provide a systematic means, based on established ethical principles, to safeguard the rights and welfare of individuals who participate as subjects in research activities supported or conducted by the HHS.

The regulations define a human subject as a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information. The regulations extend to the use of human organs, tissue, and body fluids from individually identifiable human subjects as well as to graphic, written, or recorded information derived from individually identifiable human subjects. The use of autopsy materials is governed by applicable State and local law and is not directly regulated by 45 CFR Part 46.

Activities in which the only involvement of human subjects will be in one or more of the categories set forth in 45 CFR 46.101(b)(1-6) are exempt from coverage (see section 3.2 above).

Inappropriate designations of the noninvolvement of human subjects or of exempt categories of research in a project may result in delays in the review of a proposal. The Government's Project Officer will make a final determination of whether the proposed activities are covered by the regulations or are in an exempt category, based on the information provided in the proposal. In doubtful cases, the Project Officer will consult with the Office of Extramural Programs (OEP).

In accordance with 45 CFR Part 46, prospective Contractors being considered for award shall be required to file with OHRP an acceptable Assurance of Compliance with the regulations, specifying review procedures and assigning responsibilities for the protection of human subjects. The initial and continuing review of a research project by an institutional review board shall assure that: the rights and welfare of the human subjects involved are adequately protected; the risks to the subjects are reasonable in relation to both the potential benefits, if any, to the subjects and the importance of the knowledge to be gained; and informed consent will be obtained by methods that are adequate and appropriate. HHS regulations for the protection of human subjects (45 CFR Part 46), information regarding OHRP registration and assurance requirements/processes, and OHRP contact information can be accessed at the [OHRP Website](#).

Offerors may consult with OHRP for advice or guidance concerning either regulatory requirements or ethical issues pertaining to research involving human subjects.

4.10 Inclusion of Women, Minorities, and Children in Clinical Research

NIH policy requires that women and members of minority groups and their subpopulations must be included in all NIH-supported [clinical research](#) projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. The Director, NIH, may determine that exclusion under other circumstances is acceptable, upon the recommendation of an Institute/Center Director, based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy results from the Federal law (Public Health Service Act sec. 492B. 42 U.S.C. sec. 289a-2), **and applies to research subjects of all ages**. More information on the inclusion of women and minorities may be found at http://grants.nih.gov/grants/funding/women_min/women_min.htm.

Research involving children (see definition of “child”) must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. For purposes of the NIH Inclusion of Children policy, a child is defined as an individual under the age of 21 years. This is a separate consideration from the protection of children (described above in the Human Subjects Protections section). The involvement of children as subjects in research must also be in compliance with all applicable subparts of 45 CFR part 46 as well as with other pertinent Federal laws and regulations. More information about the inclusion of children in clinical research can be found at <https://grants.nih.gov/grants/funding/children/children.htm>.

4.11 Care of Vertebrate Animals

The following notice is applicable when contract performance is expected to involve live vertebrate animals:

Notice to Offerors of Requirement for Compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals, HHSAR 352.270-5 (January 2006)

The Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (PHS Policy) establishes a number of requirements for research activities involving animals. Before award may be made to an applicant organization, the organization shall file, with the Office of Laboratory Animal Welfare (OLAW), National Institutes of Health (NIH), a written Animal Welfare Assurance (Assurance) which commits the organization to comply with the provisions of the PHS Policy, the Animal Welfare Act, and the Guide for the Care and Use of Laboratory Animals (National Academy Press, Washington, DC). In accordance with the PHS Policy, applicant organizations must establish an Institutional Animal Care & Use Committee (IACUC), qualified through the experience and expertise of its members, to oversee the institution's animal program, facilities and procedures. Applicant organizations are required to provide verification of IACUC approval prior to release of an award involving live vertebrate animals. No award involving the use of animals shall be made unless OLAW approves the Assurance and verification of IACUC approval for the proposed animal activities has been provided to the Contracting Officer. Prior to award, the Contracting Officer will notify Contractor(s) selected for projects that involve live vertebrate animals that an Assurance and verification of IACUC approval are required. The Contracting Officer will request that OLAW negotiate an acceptable Assurance with those Contractor(s) and request verification of IACUC approval. For further information contact OLAW, at NIH, 6705 Rockledge Drive, RKL1, Suite 360, MSC 7982 Bethesda, Maryland 20892-7982 (E-mail: olaw@od.nih.gov; Phone: 301-496-7163).

The PHS Policy is available on the internet at: <http://www.grants.nih.gov/grants/olaw/olaw.htm>.

4.12 Research Involving Recombinant or Synthetic Nucleic Acid Molecules

Recombinant or synthetic nucleic acid molecules are either (i) molecules that a) are constructed by joining nucleic acid molecules and b) that can replicate in a living cell, i.e., recombinant nucleic acids; (ii) nucleic acid molecules that are chemically or by other means synthesized or amplified, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules, i.e., synthetic nucleic acids; or, (iii) molecules that result from the replication of those described in (i) or (ii) above. All research involving recombinant or synthetic nucleic acid molecules that is conducted at or sponsored by an entity that receives any support for recombinant or synthetic nucleic acid molecules research from NIH shall be conducted in accordance with the [or Synthetic Nucleic Acid Molecules \(NIH Guidelines\)](#). The NIH Guidelines stipulate biosafety and containment measures for recombinant or synthetic nucleic acid molecules research and delineate points to consider in the development and conduct of human gene transfer clinical trials, including ethical principles and safety reporting requirements (See Appendix M of the Guidelines). More information about compliance with the NIH Guidelines can be found in a set of [Frequently Asked Questions](#).

The NIH Guidelines apply to both basic and clinical research studies. Prior to beginning any clinical trials involving the transfer of recombinant or synthetic nucleic acid molecules to humans, the trial must be registered with the NIH OBA and reviewed by the NIH Recombinant DNA Advisory Committee (RAC). If this contract involves new protocols that contain unique and/or novel issues, the RAC may recommend that the protocol also be discussed by the RAC in a public forum. Approval of the Institutional Biosafety Committee (IBC) and the Institutional Review Board (IRB) are necessary before the Contracting Officer's Representative (COR) and Contracting Officer may approve the protocol prior to the start of the research. The IBC approval may not occur before the NIH RAC has concluded its review of the protocol.

Failure to comply with the NIH Guidelines may result in suspension, limitation, or termination of the contract for any work related to recombinant or synthetic nucleic acid molecules research or a requirement for Contracting Officer prior approval of any or all recombinant or synthetic nucleic acid molecules projects under this contract. This includes the [requirements of the Institutional Biosafety Committee \(IBC\)](#).

As specified in Appendix M-1-C-4 of the NIH Guidelines, any serious adverse event that is both unexpected and associated with the use of the gene transfer product (i.e., there is reasonable possibility that the event may have been caused by the use of the product) must be reported to the NIH OBA and IBC within 15 days, or within 7 days if the event was life-threatening or resulted in a death. A copy of the report must also be filed with the COR and Contracting Officer. Such reports must also be submitted within their mandated time frames to the IRB, Food and Drug Administration, and, if applicable, the HHS Office for Human Research Protections.

4.13 Debriefing

An unsuccessful offeror that submits a written request for a debriefing within 3 calendar days of being notified that its proposal was not selected for award will be provided a debriefing. Please note that Component-unique debriefing processes exist; in those cases, the Component debriefing instructions supersede instructions provided here. The written request should be sent to the HHS organization that provided such notification to the offeror. Be advised that an offeror that fails to submit a timely request is not entitled to a debriefing, although untimely debriefing requests may be accommodated at the Government's discretion.

4.14 Phase I Award Information

Number of Phase I Awards. The Topic Description indicates the number of Phase I contract awards anticipated by the HHS Component. No Phase I contracts will be awarded until evaluation of all eligible proposals for a specific topic is completed.

Type of Funding Agreement. Each Phase I proposal selected for award will be funded under negotiated contracts. Firm fixed price contracts are anticipated for Phase I projects. A firm-fixed-price contract establishes a payment amount that is not subject to adjustment on the basis of the contractor's actual costs in performing the contract.

Dollar Value. Phase I contract value varies among Topics. It is therefore important for proposing firms to review the Topic description in Section 12.0, which includes a Budget for each Phase of each Topic. **The applicant's Pricing Proposal (Appendix C) may not exceed the Budget for that Topic, including all direct costs, indirect costs, and profit** (consistent with normal profit margins provided to profit-making firms for R/R&D work).

4.15 Phase II Award Information (For Fast Track and Direct to Phase II Proposals)

Number of Phase II Awards. The number of Phase II awards will depend upon the results of the Phase I (or Phase I-like) efforts and the availability of funds.

Type of Funding Agreement. Each Phase II proposal selected for award will be funded under negotiated contracts. Phase II contracts may be either firm fixed price or a cost-reimbursement type. A firm-fixed-price contract establishes a payment amount that is not subject to adjustment on the basis of the contractor's actual costs in performing the contract. A cost-reimbursement type contract provides for payment of allowable incurred costs, up to the ceiling amount established in the contract.

Dollar Value. Phase II contract value varies among Topics. It is therefore important for proposing firms to review the Topic description in Section 12.0, which includes a Budget for each Phase of each Topic. **The applicant's Pricing Proposal (Appendix C) may not exceed the Budget for that Topic, including all direct costs, indirect costs, and profit** (consistent with federal and HHS acquisition regulations and normal profit margins provided to profit-making firms for R/R&D work).

4.16 Registrations and Certifications

Registration in the System for Award Management (SAM)

Before the HHS Components can award a contract, proposing firms must be registered in the System for Award Management (SAM). If you were previously registered in CCR, your information has been transferred to SAM. However, it is in the firm's interest to visit SAM and ensure that all the firm's data is up to date from SAM and other databases to avoid delay in award. SAM replaced the Central Contractor Registration (CCR), Online Representations and Certifications Application (ORCA), and the Excluded Parties List System (EPLS). SAM allows firms interested in conducting business with the federal government to provide basic information on business capabilities and financial information. To register, visit SAM.gov.

SBA Company Registry

All applicants to the SBIR and STTR programs are required to register at the SBA Company Registry prior to application submission and attach proof of registration. Completed registrations will receive a unique SBC Control ID and .pdf file. If applicants have previously registered, you are still required to attach proof of registration. The SBA Company Registry recommends verification with SAM, but a SAM account is not required to complete the registration. In order to be verified with SAM, your email address must match one of the contacts in SAM. If you are unsure what is listed in SAM for your company, you may verify the information on the SAM site. Confirmation of your company's DUNS is necessary to verify your email address in SAM. Follow these steps listed below to register and attach proof of registration to your application.

Navigate to the SBA Company Registry.

If you are a previous SBIR/STTR awardee from any agency, search for your small business by Company Name, EIN/Tax ID, DUNS, or Existing SBIR/STTR Contract/Grant Number in the search fields provided. Identify your company and click "Proceed to Registration".

If you are a first time applicant, click the [New to the SBIR Program?](#) link on lower right of registry screen.

Fill out the required information on the "Basic Information" and "Eligibility Statement" screens.

Press "Complete Registration" on the lower right of the "Eligibility Statement" screen and follow all instructions.

Download and save your SBA registry PDF locally. The name will be in the format of SBC_123456789.pdf, where SBC_123456789 (9 digit number) is your firm's SBC Control ID.

A copy of the completed SBA Company Registration for your organization must be submitted as part of your Pricing Proposal.

Funding Agreement Certification & Life Cycle Certifications

In addition to the standard federal procurement certifications, the SBA SBIR/STTR Policy Directive requires the collection of certain information from firms at time of award and during the award life cycle.

Please go to the NIH SBIR/STTR Forms Website at: <http://grants.nih.gov/grants/forms.htm#contracts> to access the forms required to be submitted at time of the Phase I and Phase II awards and during the award life cycle.

A Funding Agreement Certification is required at the time of award and may also be required at any other time that has been identified and incorporated into the contract delivery schedule.

The Life Cycle certifications that are required prior to final payment on the Phase I award, prior to receiving 50% of the total award amount on the Phase II award, and prior to final payment on the Phase II award, will be identified as contract deliverables and incorporated into the contract delivery schedule.

4.17 Promotional Materials

Promotional and non-project related discussion is discouraged and additional information provided via Universal Resource Locator (URL) links or on computer disks, CDs, DVDs, video tapes or any other medium will not be accepted or considered in the proposal evaluation.

4.18 Prior, Current, or Pending Support of Similar Proposals or Awards

A small business concern may not submit both a contract proposal and a grant application for essentially the same project in response to NIH/CDC solicitations and funding opportunity announcements for the SBIR program.

The only exception would be the submission of a grant application after a contract proposal has been evaluated and is no longer being considered for award. In addition, a firm that receives a Phase I SBIR contract may submit a Phase II grant application.

It is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work for consideration under another federal program solicitation in addition to one NIH/CDC solicitation or funding opportunity announcements for the SBIR program.

IMPORTANT – It is unlawful to enter into contracts or grants requiring essentially equivalent effort. If there is any question concerning prior, current, or pending support of similar proposals or awards, it must be disclosed to the soliciting agency or agencies as early as possible.

4.19 Fraud and False Statements

The [Office of Inspector General Hotline](#) accepts tips from all sources about potential fraud, waste, abuse and mismanagement in Department of Health & Human Services programs. The reporting individual should indicate that the fraud, waste and/or abuse concerns an SBIR/STTR grant or contract, if relevant.

The Contractor shall not use contract funds to disseminate information that is deliberately false or misleading.

4.20 State and Other Assistance Available

State Assistance - Many states have established programs to provide services to those small business firms and individuals wishing to participate in the Federal SBIR/STTR Program. These services vary from state to state.

Contact your State STTR Support office at https://www.sbir.gov/state_services for further information.

Technical Assistance

NIH offers distinct [technical assistance programs](#) to NIH SBIR and STTR Phase I and Phase II awardees. These programs offer specialized, strategic business training and provide access to a vast network of industry experts possible through the efficiencies of scale that under a contract deliver the best value to the government and the intended small businesses seeking such assistance.

NIH and CDC Components

If you wish to utilize your own technical assistance provider, you are required to include these costs in your budget and to provide a detailed budget justification. You may request up to \$5,000 for assistance. Refer to Section 8.8 for how to include this in your Pricing Proposal. If the amount of \$5,000 is included in your cost proposal is determined to be appropriate and allowable for technical assistance, this will be in addition to the amount negotiated per award, and as specified in the topic description.

Please note, if funds are requested to utilize your own technical assistance vendor and an award is made, the awardee is not eligible to apply for the NIH-provided technical assistance program for the phase of their award. Reimbursement is limited to services received that comply with 15 U.S.C. § 638(q):

To provide small business concerns engaged in SBIR or STTR projects with technical assistance services, such as access to a network of scientists and engineers engaged in a wide range of technologies, or access to technical and business literature available through on-line data bases, for the purpose of assisting such concerns in—

- (A) making better technical decisions concerning such projects;
- (B) solving technical problems which arise during the conduct of such projects;
- (C) minimizing technical risks associated with such projects; and
- (D) developing and commercializing new commercial products and processes resulting from such projects.

4.21 Payment

The Government shall make payments, including invoice and contract financing payments, by electronic funds transfer (EFT). As a condition to any payment, the contractor is required to register in the System for Award Management before the award of a contract. Offerors must access (SAM) located at www.sam.gov.

Payments on Phase I contracts may be made based on the satisfactory completion, receipt and acceptance of contract deliverables. Advance payments may be requested, and approved on a case-by-case basis, and is dependent on Agency procedures. Offerors should indicate the need for advanced payments in Appendix C – Contract Pricing Proposal, Section III. If you are notified that your proposal is being considered for award, communicate with the point of contact named in that notification regarding procedures for requesting advanced payment. Invoices/financing requests submitted under Phase II contracts will be no more frequently than on a monthly basis unless otherwise authorized by the contracting officer.

4.22 Proprietary Information

Information contained in unsuccessful proposals will remain the property of the applicant. The Government may, however, retain copies of all proposals. Public release of information in any proposal submitted will be subject to existing statutory and regulatory requirements. If proprietary information is provided by an applicant in a proposal, which constitutes a trade secret, proprietary commercial or financial information, confidential personal information or data affecting the national security, it will be treated in confidence, to the extent permitted by law. This information must be clearly marked by the applicant with the term "confidential proprietary information" and the following legend must appear on the title page of the proposal:

"These data shall not be disclosed outside the Government and shall not be duplicated, used, or disclosed in whole or in part for any purpose other than evaluation of this proposal. If a funding agreement is awarded to this applicant as a result of or in connection with the submission of these data, the Government shall have the right to duplicate, use, or disclose the data to the extent provided in the funding agreement and pursuant to applicable law. This restriction does not limit the Government's right to use information contained in the data if it is obtained from another source without restriction. The data subject to this restriction are contained on pages ___ of this proposal."

4.23 Identification and Marking of SBIR Technical Data in Proposals

To preserve the SBIR data rights of the awardee, the legend (or statements) used in the SBIR Data Rights clause included in the SBIR award must be affixed to any submissions of technical data developed under that SBIR award. If no Data Rights clause is included in the SBIR award, the following legend, at a minimum, should be affixed to any data submissions under that award. These SBIR data are furnished with SBIR rights under Funding Agreement No. ___ (and subcontract No. ___ if appropriate), Awardee Name ___, Address, Expiration Period of SBIR Data Rights ___. The Government may not use, modify, reproduce, release, perform, display, or disclose technical data or computer software marked with this legend for four (4) years. After expiration of the 4- year period, the Government has a royalty-free license to use, and to authorize others to use on its behalf, these data for Government purposes, and is relieved of all disclosure prohibitions and assumes no liability for unauthorized use of these data by third parties, except that any such data that is also protected and referenced under a subsequent SBIR award shall remain protected through the protection period of that subsequent SBIR award. Reproductions of these data or software must include this legend."

5 CONTRACT REQUIREMENTS

5.1 Other Contract Requirements

Upon award of a contract, the contractor will be required to make certain legal commitments through acceptance of Government contract clauses. The outline that follows is illustrative of the types of clauses required by the Federal Acquisition Regulations that will be included in contracts resulting from this solicitation. This is not a complete list of clauses to be included, nor does it contain specific wording of these clauses. Copies of complete general clauses will be made available prior to award.

- a. **Inspection.** Work performed under the contract is subject to Government inspection and evaluation at all reasonable times.
- b. **Audit and Examination of Records.** The Contracting Officer and the Comptroller General, or a fully authorized representative of either, shall have the right to examine any directly pertinent records of the contractor involving transactions related to this contract.
- c. **Default.** The Government may terminate the contract if the contractor fails to perform the work contracted.
- d. **Termination for Convenience.** The contract may be terminated at any time by the Government if it deems termination to be in its best interest, in which case the contractor will be compensated for work performed and for reasonable termination costs.
- e. **Disputes.** Any dispute concerning the contract which cannot be resolved by agreement shall be decided by the contracting officer with right of appeal.
- f. **Contract Work Hours.** The contractor may not require certain classes of employees to work more than eight hours a day or forty hours a week unless the employee is compensated accordingly (that is, receives overtime pay).
- g. **Equal Opportunity.** The contractor will not discriminate against any employee or applicant for employment because of race, color, religion, sex, or national origin.
- h. **Equal Opportunity for Veterans.** The contractor will not discriminate against any employee or applicant for employment because he or she is a disabled veteran.
- i. **Equal Opportunity for Workers with Disabilities.** The contractor will not discriminate against any employee or applicant for employment because he or she is physically or mentally handicapped.
- j. **Anti-Kickback Procedures.** The contractor is prohibited from offering or accepting any money, gifts, things of value, etc. for the purpose of improperly obtaining or rewarding favorable treatment in connection with a federal contract or subcontract and shall have procedures in place to prevent and detect violations.
- k. **Covenant Against Contingent Fees.** No person or agency has been employed to solicit or secure the contract upon an understanding for compensation except bona fide employees or commercial agencies maintained by the contractor for the purpose of securing business.
- l. **Gratuities.** The contract may be terminated by the Government if any gratuities have been offered to any representative of the Government to secure the contract.
- m. **Patent Infringement.** The contractor shall report each notice or claim of patent infringement based on the performance of the contract.
- n. **Employment Eligibility Verification.** The contractor shall be enrolled as a Federal Contractor in E-Verify and verify all employees assigned to the contract as well as all new employees hired by the contractor.

- o. **Needle Distribution.** The Contractor shall not use contract funds to carry out any program of distributing sterile needles or syringes for the hypodermic injection of any illegal drug.
- p. **Acknowledgement of Federal Funding.** The Contractor shall clearly state, when issuing statements, press releases, requests for proposals, bid solicitations and other documents describing projects or programs funded in whole or in part with Federal money: (1) the percentage of the total costs of the program or project which will be financed with Federal money; (2) the dollar amount of Federal funds for the project or program; and (3) the percentage and dollar amount of the total costs of the project or program that will be financed by nongovernmental sources.
- q. **Restriction on Abortions.** The Contractor shall not use contract funds for any abortion or for health benefits coverage that includes coverage of abortion.
- r. **Continued Ban on Funding of Human Embryo Research.** The Contractor shall not use contract funds for (1) the creation of a human embryo or embryos for research purposes; or (2) research in which a human embryo or embryos are destroyed, discarded, or knowingly subjected to risk of injury or death greater than that allowed for research on fetuses in utero under 45 CFR 46.204(b) and Section 498(b) of the Public Health Service Act (42 U.S.C. 289(b)). The term "human embryo or embryos" includes any organism, not protected as a human subject under 45 CFR 46 as of the date of the enactment of this Act, that is derived by fertilization, parthenogenesis, cloning, or any other means from one or more human gametes or human diploid cells.

Additionally, in accordance with a March 4, 1997 Presidential Memorandum, Federal funds may not be used for cloning of human beings.

- s. **Limitation on Use of Funds for Promotion of Legalization of Controlled Substances.** The Contractor shall not use contract funds to support activities that promote the legalization of any drug or other substance included in schedule I of the schedules of controlled substances established under section 202 of the Controlled Substances Act, except for normal and recognized executive-congressional communications. This limitation shall not apply when the Government determines that there is significant medical evidence of a therapeutic advantage to the use of such drug or other substance or that federally sponsored clinical trials are being conducted to determine therapeutic advantage.
- t. **Dissemination of False or Deliberately Misleading Information.** The Contractor shall not use contract funds to disseminate information that is deliberately false or misleading.
- u. **Salary Rate Limitation.** None of the funds appropriated in this title shall be used to pay the direct annual salary of an individual at a rate in excess of Executive Schedule, Level II of the Federal Executive Pay Scale. **Effective January 2015, Executive Schedule, Level II of the Federal Executive Pay Scale is \$183,300.**
- v. **Anti-Lobbying.** Pursuant to the current appropriations act, except for normal and recognized executive legislative relationships, the contractor shall not use any contract funds for (i) publicity or propaganda purposes; (ii) the preparation, distribution, or use of any kit, pamphlet, booklet, publication, radio, television or video presentation designed to support or defeat legislation pending before the Congress or any State legislature, except in presentation to the Congress or any State legislature itself; or (iii) payment of salary or expenses of the Contractor, or any agent acting for the Contractor, related to any activity designed to influence legislation or appropriations pending before the Congress or any State legislature.
- w. **Gun Control.** The contractor shall not use contract funds in whole or in part to advocate or promote gun control.
- x. **Restriction on Pornography on Computer Networks.** The contractor shall not use contract funds to maintain or establish a computer network unless such network blocks the viewing, downloading, and exchanging of pornography.

5.2 Special Contract Requirements

Specific contract requirements relating to research involving the use of Human Subjects or Vertebrate Animals will be required in any contract awarded for a project involving the use of Human Subjects or Vertebrate Animals.

Contracts including the development of Electronic and Information Technology (EIT) products and services may require accessibility provisions in compliance with Section 508 of the Rehabilitation Act of 1973 (29 U.S.C.794d), as amended by the Workforce Investment Act of 1998. Information about Section 508 provisions is available at <http://www.section508.gov/>.

5.3 Copyrights

With prior written permission of the Contracting Officer, the awardee may copyright material developed with HHS support. HHS receives a royalty-free license for the Federal Government and requires that each publication contain an appropriate acknowledgment and disclaimer statement.

5.4 Patents

Small business firms normally may retain the principal worldwide patent rights to any invention developed with Government support. The Government receives a royalty-free license for its use, reserves the right to require the patent holder to license others in certain limited circumstances, and requires that anyone exclusively licensed to sell the invention in the United States must normally manufacture it domestically. To the extent authorized by 35 USC 205, the Government will not make public any information disclosing a Government-supported invention to allow the awardee to pursue a patent. See also [Invention Reporting in Section 5.6](#).

Inquiries or information about additional requirements imposed by 37 CFR 401 should be obtained from local counsel or from:

Office of Policy for Extramural
Research Administration,
Division of Extramural Inventions and
Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Drive, MSC 7980
Bethesda, MD 20892-7980
Phone: (301) 451-4235
Fax: (301) 480-0272
E-mail: hammerslaa@mail.nih.gov

See also Invention Reporting in Section 5.6.

5.5 Technical Data Rights

Rights in Data Developed Under SBIR Funding Agreement. The Act provides for “retention by an SBC of the rights to data generated by the concern in the performance of an SBIR award.”

- (1) Each agency must refrain from disclosing SBIR technical data to outside the Government (except reviewers) and especially to competitors of the SBC, or from using the information to produce future technical procurement specifications that could harm the SBC that discovered and developed the innovation.
- (2) SBIR agencies must protect from disclosure and non-governmental use all SBIR technical data developed from work performed under an SBIR funding agreement for a period of not less than four years from delivery of the last deliverable under that agreement (either Phase I, Phase II, or Federally-funded SBIR Phase III) unless, subject to paragraph (b) (3) of this section, the agency obtains permission to disclose such SBIR technical data from the awardee or SBIR applicant.

Agencies are released from obligation to protect SBIR data upon expiration of the protection period except that any such data that is also protected and referenced under a subsequent SBIR award must remain protected through the protection period of that subsequent SBIR award. For example, if a Phase III award is issued within or after the Phase II data rights protection period and the Phase III award refers to and protects data developed and protected under the Phase II award, then that data must continue to be protected through the Phase III protection period. Agencies have discretion to adopt a protection period longer than four years. The Government retains a royalty-free license for Government use of any technical data delivered under an SBIR award, whether patented or not. This section does not apply to program evaluation.

- (3) SBIR technical data rights apply to all SBIR awards, including subcontracts to such awards, that fall within the statutory definition of Phase I, II, or III of the SBIR Program, as described in section 4 of the SBIR Policy Directive. The scope and extent of the SBIR technical data rights applicable to Federally-funded Phase III awards is identical to the SBIR data rights applicable to Phases I and II SBIR awards. The data rights protection period lapses only:
 - (i) Upon expiration of the protection period applicable to the SBIR award; or
 - (ii) By agreement between the awardee and the agency.

5.6 Invention Reporting

The reporting of inventions is accomplished by submitting information through the [Edison Invention Reporting System](#) for those awarding components participating in iEdison.

Inventions must be reported promptly—within two months of the inventor’s initial report to the contractor organization—to:

Office of Policy for Extramural
Research Administration,
Division of Extramural Inventions and
Technology Resources,
National Institutes of Health (NIH)
6705 Rockledge Drive, MSC 7980
Bethesda, MD 20892-7980
Phone: (301) 451-4235
Fax: (301) 480-0272
E-mail: hammerslaa@mail.nih.gov

This should be done prior to any publication or presentation of the invention at an open meeting, since failure to report at the appropriate time is a violation of 35 U.S.C. 202, and may result in loss of the rights of the small business concern, inventor, and Federal Government in the invention. All foreign patent rights are immediately lost upon publication or other public disclosure unless a United States patent application is already on file. In addition, statutes preclude obtaining valid United States patent protection after one year from the date of a publication that discloses the invention.

If no invention is disclosed or no activity has occurred on a previously disclosed invention during the applicable reporting period, a negative report shall be submitted to the Contracting Officer.

To assist contractors in complying with invention reporting requirements of the clause, the NIH has developed "Interagency Edison," an electronic invention reporting system. NIH requires contractors to use Interagency Edison (<http://iEdison.gov>), which streamlines the reporting process and greatly reduces paperwork. Access to the system is through a secure interactive Web site to ensure that all information submitted is protected. Interagency Edison and information relating to the capabilities of the system can be obtained from the Web.

6 METHOD OF EVALUATION

All proposals will be evaluated and judged on a competitive basis. Using the technical evaluation criteria specified below, a panel of primarily nongovernment experts knowledgeable in the disciplines or fields under review will evaluate proposals to determine the most promising technical and scientific approaches. Each proposal will be judged on its own merit. The Agency is under no obligation to fund any proposals or any specific number of proposals in a given topic. It may also elect to fund several or none of the proposed approaches to the same topic.

6.1 Evaluation Process

Each proposal will be peer reviewed by an external panel of experts selected for their competence in relevant scientific and technical fields. Each peer review panel will be responsible for evaluating proposals for scientific and technical merit. When relevant, reviewers will be instructed to comment on the reasonableness of the following items, which reviewers will factor into the determination of a proposal's scientific and technical merit:

- Resource Sharing https://grants.nih.gov/grants/peer/guidelines_general/Resource_sharing_plans.pdf
 - Data Sharing Plan http://grants.nih.gov/grants/policy/data_sharing
 - Model Organism Sharing Plan http://grants.nih.gov/grants/policy/model_organism/
 - Genome Data Sharing <http://gds.nih.gov/>
- Human Subject Protection <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html>
- Data Safety Monitoring Plan <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>
- Inclusion of Women and Minorities http://grants.nih.gov/grants/funding/women_min/women_min.htm
- Inclusion of Children <https://grants.nih.gov/grants/funding/children/children.htm>
- Animal Welfare http://grants.nih.gov/grants/oer_offices/olaw.htm
- Biohazards/Select Agents/Recombinant DNA <http://grants.nih.gov/grants/guide/notice-files/not95-209.html>

The peer review panel provides a rating for each proposal and makes specific recommendations related to the scope, direction and/or conduct of the proposed research. For those proposals found technically acceptable, the peer review panel may provide a commentary about the funding level, labor mix, duration of the proposed contract project, vertebrate animal and human subject research protection, and inclusion issues. The program staff of the awarding component will conduct a second level of review. Recommendations of the peer review panel and program staff are based on judgments about not only the technical merit of the proposed research but also its relevance and potential contributions to the mission and programs of the awarding component and commercial potential. A contract may be awarded only if the proposal has been recommended as technically acceptable by the peer review panel. *Funding for any/all technically acceptable proposals is not guaranteed. Proposals that are found to be technically unacceptable by the peer review panel will not be considered further for award.*

Selection of an offeror for contract award will be based on an evaluation of proposals against two factors. The factors in order of importance are: technical and cost/price. While technical factors are of paramount consideration, cost/price may become a critical factor in source selection in the event that two or more offerors are determined to be essentially equal following the evaluation of all factors other than cost or price. In any event, the Government reserves the right to make an award to that offeror whose response provides the best overall value to the Government.

The Phase I proposal and the Phase II proposal in a Fast Track submission will be evaluated and scored individually. However, if a Phase I proposal is evaluated and found to be Technically Unacceptable, the corresponding Phase II portion of the Fast Track proposal will not be evaluated.

6.2 Phase I Technical Evaluation Criteria

Phase I proposals will be evaluated based on the criteria outlined below:

FACTORS FOR PHASE I PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach, including the identification of clear, measurable goals (<i>i.e.</i> , milestones) that have a reasonable chance of meeting the topic objective in Phase I.	25%
2. The potential of the proposed research for technological innovation.	25%
3. The potential of the proposed research for commercial application, including: <ul style="list-style-type: none"> <li data-bbox="264 569 1109 632">b. Whether the outcome of the proposed research activity will likely lead to a marketable product or process; and, <li data-bbox="264 663 1195 726">c. The offeror's discussion of the potential barriers to entry in the competitive market landscape as well as method to overcome. 	20%
4. The qualifications of the proposed Project Directors/Principal Investigators, supporting staff and consultants.	20%
5. The adequacy and suitability of the proposed facilities, equipment, and research environment.	10%

Technical reviewers will base their conclusions only on information contained in the proposal. It cannot be assumed that reviewers are acquainted with the firm or key individuals or any referenced experiments. Relevant supporting data such as journal articles, literature, including Government publications, etc., should be contained or referenced in the proposal and will count toward the page limit.

6.3 Phase II Technical Evaluation Criteria

Phase II proposals will be evaluated based on the criteria outlined below. This includes Direct to Phase II proposals, Phase II proposals included in Fast Track submissions, and Phase II proposals subsequently submitted by contractors who are awarded a Phase I contract under this solicitation.

FACTORS FOR PHASE II PROPOSALS	WEIGHT
1. The soundness and technical merit of the proposed approach, including the identification of clear, measurable goals (<i>i.e.</i> , milestones) that have a reasonable chance of meeting the topic objective in Phase II. For NIH Direct to Phase II only: Demonstrated feasibility of the methodology or technology equivalent to meeting Phase I-level objectives, providing a solid foundation for the proposed Phase II activity.	25%
2. The potential of the proposed research for technological innovation.	25%

FACTORS FOR PHASE II PROPOSALS	WEIGHT
<p>3. The potential of the proposed research for commercialization, as documented in the offeror's Commercialization Plan and evidenced by:</p> <p>(a) the offeror's record of successfully commercializing its prior SBIR/STTR or other research projects;</p> <p>(b) commitments of additional investment during Phase I and Phase III from private sector or other non-SBIR funding sources; and/or</p> <p>(c) any other indicators of commercial potential for the proposed research.</p>	25%
<p>4. The qualifications of the proposed PDs/PIs, supporting staff and consultants.</p> <p>The leadership approach (including the designated roles and responsibilities, governance, and organizational structure) being consistent with and justified by the aims of the project and expertise of each of the PDs/PIs.</p>	15%
<p>5. The adequacy and suitability of the facilities and research environment.</p>	10%

Technical reviewers will base their conclusions only on information contained in the proposal. It cannot be assumed that reviewers are acquainted with the firm or key individuals or any referenced experiments. Relevant supporting data such as journal articles, literature, including Government publications, etc., should be contained or referenced in the proposal and will count toward the page limit.

6.4 Award Decisions

For proposals recommended for award, the awarding component considers the following:

1. Ratings resulting from the scientific/technical evaluation process;
2. Areas of high program relevance;
3. Program balance (i.e., balance among areas of research);
4. Availability of funds, and.
5. Cost/Price

The Government anticipates that prospective offerors will develop unique proposals in response to the topics of research set forth in this solicitation. The agency is not under any obligation to fund any proposal or make any specific number of contract awards in a given research topic area. The agency may also elect to fund several or none of the proposals received within a given topic area.

7 PROPOSAL SUBMISSION

7.1 Questions

Offerors with questions regarding this solicitation must submit them in to the Contracting Officer point of contact identified below in Section 10 in sufficient time for receipt no later than **August 21, 2015**. The Government may issue an amendment to this solicitation including responses to submitted questions. The Government anticipates that responses would be published in sufficient time for interested offerors to consider them prior to submission of a proposal.

7.2 Pre-Proposal Conference

HHS will hold a pre-proposal conference, via webinar, on August 13, 2015 at 2:00 PM Eastern Daylight Time. This informational webinar will discuss this solicitation, and in particular will discuss the new electronic contract proposal submission (eCPS) website. For this solicitation, proposals will only be accepted via the eCPS website.

Offerors may register for the webinar at: <https://attendee.gotowebinar.com/register/1204029371162972674> . Following registration, a confirmation e-mail will be sent containing information about joining the webinar.

Presentation material from this webinar shall be posted on FedBizOpps and the NIH [SBIR/STTR webpage](#) following its completion.

7.3 Limitation on the Length of the Technical Proposal (Item 1)

SBIR Phase I technical proposals (Item 1) shall not exceed 50 pages.

SBIR Phase II technical proposals (Item 1) shall not exceed 150 pages.

All pages shall be single-sided, single-spaced pages for the entire proposal, all inclusive [including all pages, cover sheet(s), tables, CVs, resumes, references, pictures/graphics, and all enclosures, appendices or attachments, etc.]. Proposal pages shall be numbered "Page 1 of 50," "Page 2 of 50," and so on. Pages shall be of standard size (8.5" X 11") with a font size of 11 points (or larger). Two sided pages count as two pages. There are NO exclusions to the page limit – the technical proposal shall not exceed 50 pages for Phase I, and 150 pages for Phase II. Pages in excess of the page limitation will be removed from the proposal and will not be considered or evaluated.

7.4 Submission, Modifications, Revision, and Withdrawal of Proposals

- (a) Offerors are responsible for submitting proposals, including any revisions or modifications, to the electronic Contract Proposal Submission (eCPS) website at <https://ecps.nih.gov/sbirsttr> by the date and time specified on the first page of this solicitation.

Offerors must use this electronic transmission method. No other method of proposal submission is permitted.

- (b) Instructions on how to submit a proposal into eCPS are available at <https://ecps.nih.gov/sbirsttr/home/howto>. Offerors may also reference Frequently Asked Questions regarding online submissions at <https://ecps.nih.gov/sbirsttr/home/faq>.
1. Be advised that registration is required to submit a proposal into eCPS and registration may take several business days to process.
 2. The proposal must be uploaded in 2 parts: Technical and Business.

The Technical Proposal shall consist of Item 1, as described in Sections 8.3 and 8.4. The Technical Proposal must consist of a single PDF file.

The Business Proposal shall consist of Items 2, 3, and 4, as applicable, as described in Section 8.3 and 8.4. The Business Proposal must consist of a single PDF file. Offerors may also choose to submit an optional Excel Workbook spreadsheet providing a cost breakdown, in addition to the single PDF file.

3. Proposal Naming Conventions:

- (a) The ‘Proposal Name’ entered into eCPS for your proposal submission shall include, in order: (1) the Phase the proposal is for; (2) the name of the Offeror; (3) the NIH or CDC Awarding Component and the Topic being proposed under.

Examples are provided below:

- Phase I_XYZ Company_NCIRD_Topic_031
- Phase II_XYZ Company_NIAID_Topic_038

If submitting a Fast Track Proposal, include “FAST TRACK” after the Phase, as shown below:

- Phase I FAST TRACK_XYZ Company_NIAID_Topic_038
- Phase II FAST TRACK_XYZ Company_NIAID-Topic_038

- (c) Files uploaded for your proposal submission shall include, in order: (1) the name of the Offeror; (2) the NIH or CDC Awarding Component and the Topic being proposed under; and, (3) the type of proposal (i.e., Technical, Business, or Excel Workbook). Use the format set forth in the examples below when naming your files, prior to uploading them into eCPS:

- *Example for a proposal under National Institutes of Health / National Institute of Allergy and Infectious Diseases Topic 033:*

Technical Proposal: XYZ Company_NIAID_TOPIC_033_Technical.pdf
Business Proposal: XYZ Company_NIAID_TOPIC_033_Business.pdf
Excel Workbook (Optional): XYZ Company_NIAID_TOPIC_033_Business.xlsx

- *Example for a proposal under Centers for Disease Control / National Center for Immunization and Respiratory Diseases Topic 031:*

Technical Proposal: XYZ Company_NCIRD_TOPIC_031_Technical.pdf
Business Proposal: XYZ Company_NCIRD_TOPIC_031_Business.pdf
Excel Workbook (Optional): XYZ Company_NCIRD_TOPIC_031_Business.xlsx

4. To submit a Fast Track Proposal:

- Upload the Phase 1 Technical Proposal and Phase 1 Business Proposal and Submit.
- After you submit the Phase 1 proposal, then click the “Submit new/alternate Proposal” button for Phase 2 submission.
- Upload the Phase 2 Technical Proposal and Phase 2 Business Proposal and Submit.

- (d) Any proposal, modification, or revision, that is received after the exact time specified for receipt of proposals is “late” and will not be considered for award.
- (e) If an emergency or unanticipated event interrupts normal Government processes so that proposals cannot be received at the eCPS website by the exact time specified in the solicitation, and urgent Government requirements preclude amendment of the solicitation closing date, the time specified for receipt of proposals will be deemed to be extended to the same time of day specified in the solicitation on the first work day on which normal Government processes resume.
- (f) Proposals may be withdrawn by written notice at any time before award. A copy of withdrawn proposals will be retained in the contract file.

8 PROPOSAL PREPARATION AND INSTRUCTIONS

8.1 Introduction

It is important to read and follow the proposal preparation instructions carefully. The requirements for Phase I, Fast Track, and Direct to Phase II proposals are different and are outlined below. Pay special attention to the requirements concerning Human Subjects and use of Vertebrate Animals if your project will encompass either item.

8.2 Fast Track Proposal Instructions (NIH Only)

To identify the submission as a Fast Track proposal, check the box marked “Yes,” next to the words “Fast Track Proposal” shown on the Phase I Proposal Cover Sheet (Appendix A).

For a Fast Track submission, both a complete Phase I proposal and a separate, complete Phase II proposal must be submitted. The Phase I proposal shall follow the instructions set forth in Section 8.3 “Phase I Proposal Instructions.” The Phase II proposal shall follow the instructions set forth in Section 8.4. “Phase II Proposal Instructions.”

The Phase I proposal and the Phase II proposal in a Fast Track submission will be evaluated and scored individually. However, if a Phase I proposal is evaluated and found to be Technically Unacceptable, the corresponding Phase II Fast Track proposal will not be evaluated.

8.3 Phase I Proposal Instructions

A complete Phase I proposal consists of four elements:

TECHNICAL PROPOSAL

Item 1: Technical Element

- a. Proposal Cover Sheet Appendix A
- b. Table of Contents
- c. Abstract of the Research Plan, (Appendix B)
- d. Content of the Technical Element

BUSINESS PROPOSAL

Item 2: Pricing Proposal (Appendix C)

Item 3: SBIR Application VCOC Certification, if applicable

(See Section 4.5 to determine if this applies to your organization)

Item 4: Proof of Registration in the SBA Company Registry

(Refer to Section 4.16 for Directions)

IMPORTANT -- While it is permissible, with proposal notification, to submit identical proposals or proposals containing a significant amount of essentially equivalent work for consideration under numerous federal program solicitations, **it is unlawful to enter into contracts or grants requiring essentially equivalent effort.** If there is any question concerning this, it must be disclosed to the soliciting agency or agencies as early as possible. If a proposal submitted for a Phase II effort is substantially the same as another proposal that was funded, is now being funded, or is pending with any Federal Agency, you must reveal this on the Cover Sheet and provide the information required.

8.4 Phase II Proposal Instructions

A complete Phase II as part of a FAST TRACK or Direct to Phase II proposal consists of four elements:

TECHNICAL PROPOSAL

Item 1: Technical Element

- a. Technical Proposal Cover Sheet Appendix D
- b. Table of Contents
- c. Abstract of the Research Plan, (Appendix B)
- d. Content of the Technical Element
- e. Draft Statement of Work (Appendix E)
- f. Summary of Related Activities (Appendix F)

BUSINESS PROPOSAL

Item 2: Pricing Proposal (Appendix C)

Item 3: SBIR Application VCOC Certification, if applicable

(See Section 4.5 to determine if this applies to your organization)

Item 4: Proof of Registration in the SBA Company Registry

(Refer to Section 4.16 for Directions)

Phase II proposals for this solicitation will only be accepted for Topics that allow for Fast Track proposals or Direct to Phase II proposals.

SBCs who receive a Phase I-only award will receive Phase II proposal instructions in a separate solicitation from the HHS Awarding Component for the Topic.

8.5 Technical Proposal Cover Sheet (Item 1)

For Phase I Proposals, complete the form identified as Appendix A and use it as the first page of the proposal. No other cover sheet should be used.

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf>)

If submitting a proposal reflecting Multiple Project Directors/Principal Investigators (PDs/PIs), the individual designated as the Contact PI should be entered here.

For Phase II proposals (including Direct to Phase II Proposals and the Phase II Proposal of a Fast Track submission), complete the form identified as Appendix D and use it as the first page of the proposal. No other cover sheet should be used.

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf>)

If submitting a proposal reflecting Multiple Project Directors/Principal Investigators (PDs/PIs), the individual designated as the Contact PI should be entered here.

- **Topic Number.** Provide the appropriate numerical designator of the research topic for which your proposal is being submitted
- **Project Title.** Select a title that reflects the substance of the project. Do not use the title of the topic that appears in the solicitation.
- **FAST TRACK or Direct to Phase II Only.** If the small business concern has received more than 15 Phase II awards in the prior 5 fiscal years, submit name of awarding agency, date of award, funding agreement number, amount, topic or subtopic title, follow-on agreement amount, source, and date of commitment and current commercialization status for each Phase II.

8.6 Table of Contents (Item 1)

Include a Table of Contents. Number all pages of your proposal consecutively. The header on each page of the technical proposal should contain your company name and topic number. The header may be included in the one-inch margin.

8.7 Abstract of Research Plan (Item 1)

Complete the form identified as Appendix B

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf>)

Do not include any proprietary information as abstracts of successful proposals will be published by NIH/CDC. The abstract should include a brief description of the problem or opportunity, specific aims, and a description of the effort. Summarize anticipated results and potential commercial applications of the proposed research. Include at the end of the Abstract a brief description (two or three sentences) of the relevance of this research to public health. In this description, be succinct and use plain language that can be understood by a general, lay audience.

NOTE: PRIOR TO PREPARING THE RESEARCH PLAN APPLICANTS SHOULD REFER TO THE SPECIFIC RESEARCH TOPIC (SEE SECTION 12.0 OF THE SOLICITATION) TO REVIEW THE DESCRIPTION AND THE OUTLINED GOALS, ACTIVITIES AND BUDGET BEFORE PREPARING THIS ELEMENT OF THEIR PROPOSAL. ALSO, IF YOUR RESEARCH IS TO INCLUDE HUMAN SUBJECTS OR VERTEBRATE ANIMALS YOU MUST ADDRESS THE REQUIREMENTS OUTLINED IN THE ‘PROPOSAL FUNDAMENTALS’. ADDRESS THESE ITEMS IN A SEPARATE SECTION OF YOUR TECHNICAL PROPOSAL AND LABEL AS REQUIRED.

8.8 Content of Technical Element (Item 1)

The Technical Item should cover the following items in the order given below.

(A) Research Plan for a Phase I Proposal

Discuss in the order indicated the following elements:

- 1) **Identification and Significance of the Problem or Opportunity.** Provide a clear statement of the specific technical problem or opportunity addressed.
- 2) **Technical Objectives.** State the specific objectives of the Phase I effort, including the technical questions it will try to answer to determine the feasibility of the proposed approach.
- 3) **Work Plan.** Provide an explicit, detailed plan for the Phase I R&D to be carried out, including the experimental design, procedures, and protocols to be used. Address how the objectives will be met and the questions stated in Item b above. Discuss in detail the methods to be used to achieve each objective or task. The plan should indicate what is planned, how, when, and where the work will be carried out, a schedule of major events, the final product to be delivered, and the completion date of the effort. The Phase I effort should determine the technical feasibility of the proposed concept.
- 4) **Related Research or R&D.** Describe significant research activities directly related to the proposed effort, including any conducted by the Project Director/Principal Investigator (PD/PI), the proposing firm, consultants, or others. Describe how these activities interface with the proposed project and discuss any planned coordination with outside sources. The PD/PI must persuade reviewers of his or her awareness of recent significant research or R&D conducted by others in the same scientific field.
- 5) **Relationship with Future R&D.**
 - a) State the anticipated results of the proposed approach, assuming project success.
 - b) Discuss the significance of the Phase I effort in providing a foundation for the Phase II R/R&D effort.
- 6) **Potential Commercial Applications.** Describe why the proposed project is deemed to have potential commercial applications (for use by the Federal Government and/or private sector markets.) Describe the market as it currently exists and how your product may enter and compete in this market. Include the potential barriers to market entry and how you expect to overcome them.
- 7) **Senior/Key Personnel and Bibliography of Directly Related Work.** Identify senior/key personnel, including their directly related education, experience, and bibliographic information. Where resumes are extensive, focus on summaries of the most relevant experience or publications. Provide dates and places of employment and some information about the nature of each position or professional experience. Resumes must identify the current or most recent position.
- 8) **Multiple PD/PI Leadership Plan.** For proposals designating multiple PDs/Pis, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/Pis and other collaborators.

If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/Pis should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.

- 9) **Subcontractors/Consultants.** Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail and identified in the cost proposal. In addition, supported by appropriate letters from each individual confirming his/her role in the project must be included. Small business concerns must perform a minimum of two-thirds for Phase I of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the

resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

- 10) **Facilities and Equipment.** Indicate where the proposed research will be conducted. One of the performance sites must be the offeror organization. Describe the facilities* to be used; identify the location; and briefly indicate their capacities, pertinent capabilities, relative proximity, and extent of availability to the project. Include clinical, computer, and office facilities of the offeror and those of any other performance sites to be used in the project.

List the most important equipment items already available for this project, noting location and pertinent capabilities of each.

Any equipment and products purchased with Government funds shall be American-made, to the extent possible.

Title to Equipment. Title to equipment purchased with Government funding by the SBIR awardee in relation to project performance vests upon acquisition in the Federal Government. However, the Government may transfer such title to an SBIR awardee upon expiration of the project where the transfer would be more cost-effective than recovery of the property.

***Whenever a proposed SBIR project is to be conducted in facilities other than those of the offeror, a letter must be submitted with the proposal stating that leasing/rental arrangements have been negotiated for appropriate research space (i.e., space that will be available to and under the control of the SBIR contractor organization).**

(B) Research Plan for Phase II proposals (including Direct to Phase II Proposals and the Phase II Proposal of a Fast Track submission)

1) **Anticipated or actual Results of the Phase I/Phase I-like Effort**

For FAST TRACK: Briefly discuss and summarize the objectives of the Phase I effort, the research activities to be carried out, and the anticipated results.

For Direct to Phase II: Summarize the specific aims of the preliminary work that forms the basis for this Direct Phase II proposal, quantitative milestones (a quantitative definition of success) for each aim, the importance of the findings, and emphasize the progress made toward their achievement. Describe the technology developed, its intended use and who will use it. Provide data or evidence of the capability, completeness of design, and efficacy along with the rationale for selection of the criteria used to validate the technology, prototype, or method Describe the current status of the product (e.g., under development, commercialized, in use, discontinued). If applicable, describe the status of FDA approval for the product, process, or service (e.g., continuing pre-IND studies, filed on IND, in Phase I (or II or III) clinical trials, applied for approval, review ongoing, approved, not approved). List the generic and/or commercial names of products.

- 2) **Detailed Approach and Methodology** - provide an explicit detailed description of the Phase II approach. This section should be the major portion of the proposal and must clearly show advancement in the project appropriate for Phase II. Indicate not only what is planned, but also how and where the work will be carried out. List all tasks in a logical sequence to precisely describe what is expected of the contractor in performance of the work. Tasks should contain detail to (1) establish parameters for the project; (2) keep the effort focused on meeting the objectives; (3) describe end products and deliverables; and (4) describe periodic/final reports required to monitor work progress under the contract. Offerors using Human Subjects or Vertebrate Animals in their research should refer to the specific instructions provided in Sections 4.9, 4.10, 8.9 and/or 8.11 of this solicitation for further guidance.

- 3) **Personnel** - List by name, title, department and organization, the extent of commitment to this Phase II effort, and detail each person's qualifications and role in the project. Provide resumes for all key staff members, describing directly related education, experience, and relevant publications. Describe in detail

- any involvement of subcontractors or consultants, and provide resumes for all key subcontractor staff. Also, include letters of commitment with proposed consultants confirming the extent of involvement and hourly/daily rate.
- 4) **Resources** - List/describe all equipment, facilities and other resources available for this project, including the offeror's clinical, computer and office facilities/equipment at any other performance site that will be involved in this project. Briefly state their capacities, relative proximity and extent of availability to this effort. (Any equipment specifically proposed as a cost to the contract must be justified in this section as well as detailed in the budget. Equipment and products purchased with Government funds shall be American-made, to the extent possible. Title to the equipment will vest in the Government.)
 - 5) **Other considerations** - Provide a brief narrative of any unique arrangements, safety procedures in place, animal welfare issues, human subjects protections, inclusion of women, minorities, and children, etc. Note: If the research plan includes the use of human subjects or vertebrate animals, refer to Sections 4.9, 4.10, 8.9 and/or 8.11 of this solicitation for further guidance.
 - 6) **Multiple PD/PI Leadership Plan**. For proposals designating multiple PDs/PIs, a leadership plan must be included. A rationale for choosing a multiple PD/PI approach should be described. The governance and organizational structure of the leadership team and the research project should be described, including communication plans, process for making decisions on scientific direction, and procedures for resolving conflicts. The roles and administrative, technical, and scientific responsibilities for the project or program should be delineated for the PDs/PIs and other collaborators.
 - 7) If budget allocation is planned, the distribution of resources to specific components of the project or the individual PDs/PIs should be delineated in the Leadership Plan. In the event of an award, the requested allocations may be reflected in Contract Award.
 - 8) **Resource Sharing Plan(s)**. NIH considers the sharing of unique research resources developed through NIH-sponsored research an important means to enhance the value and further the advancement of the research. When resources have been developed with NIH funds and the associated research findings published or provided to NIH, it is important that they be made readily available for research purposes to qualified individuals within the scientific community. If the final data/resources are not amenable to sharing (for example, human subject concerns, the Small Business Act provisions ([15 U.S.C. 631](#), et seq., as amended), etc.), this must be explained in the proposal. See http://grants.nih.gov/grants/policy/data_sharing/data_sharing_faqs.htm.
 - a) **Data Sharing Plan:** Offerors seeking \$500,000 or more in direct costs in any year are expected to include a brief 1-paragraph description of how final research data will be shared, or explain why data-sharing is not possible (for example human subject concerns, the Small Business Innovation Development Act provisions, etc.). See [Data-Sharing Policy](#) or [NIH Guide NOT-OD-04-042](#).
 - b) **Sharing Model Organisms:** Regardless of the amount requested, all proposals where the development of model organisms is anticipated are expected to include a description of a specific plan for sharing and distributing unique model organisms or state appropriate reasons why such sharing is restricted or not possible. See [Sharing Model Organisms Policy](#), and [NIH Guide NOT-OD-04-042](#).
 - c) **Genome Wide Association Studies (GWAS):** Regardless of the amount requested, offerors seeking funding for a genome-wide association study are expected to provide a plan for submission of GWAS data to the NIH-designated GWAS data repository, or an appropriate explanation why submission to the repository is not possible. GWAS is defined as any study of genetic variation across the entire genome that is designed to identify genetic associations with observable traits (such as blood pressure or weight) or the presence or absence of a disease or condition. For further information see Policy for Sharing of Data Obtained in NIH Supported or

Conducted Genome-Wide Association Studies, [NIH Guide NOT-OD-07-088](#), and [Genome-Wide Association Studies](#).

- 9) **Commercialization Plan** – Required for the Phase II portion of ALL Fast-Track or Direct Phase II proposals. The Phase II portion of Fast-Track proposals and all Direct Phase II proposals must include a Commercialization Plan. **The Commercialization Plan is limited to 12 pages.** Be succinct. There is no requirement for offerors to use the maximum allowable pages allotted to the Commercialization Plan.

Create a section entitled, “Commercialization Plan,” and provide a description in each of the following areas:

- a) **Value of the SBIR Project, Expected Outcomes, and Impact.** Describe, in layperson's terms, the proposed project and its key technology objectives. Clarify the need addressed, specifying weaknesses in the current approaches to meet this need. In addition, describe the commercial applications of the research and the innovation inherent in this proposal. Be sure to also specify the potential societal, educational, and scientific benefits of this work. Explain the non-commercial impacts to the overall significance of the project. Explain how the SBIR project integrates with the overall business plan of the company.
- b) **Company.** Give a brief description of your company including corporate objectives, core competencies, present size (annual sales level and number and types of employees), history of previous Federal and non-Federal funding, regulatory experience, and subsequent commercialization, and any current products/services that have significant sales. Include a short description of the origins of the company. Indicate your vision for the future, how you will grow/maintain a sustainable business entity, and how you will meet critical management functions as your company evolves from a small technology R&D business to a successful commercial entity.
- c) **Market, Customer, and Competition.** Describe the market and/or market segments you are targeting and provide a brief profile of the potential customer. Tell what significant advantages your innovation will bring to the market, e.g., better performance, lower cost, faster, more efficient or effective, new capability. Explain the hurdles you will have to overcome in order to gain market/customer acceptance of your innovation.
- d) Describe any strategic alliances, partnerships, or licensing agreements you have in place to get FDA approval (if required) and to market and sell your product.
- e) Briefly describe your marketing and sales strategy. Give an overview of the current competitive landscape and any potential competitors over the next several years. (It is very important that you understand and know the competition.)
- f) **Intellectual Property (IP) Protection.** Describe how you are going to protect the IP that results from your innovation. Also note other actions you may consider taking that will constitute at least a temporal barrier to others aiming to provide a solution similar to yours.
- g) **Finance Plan.** Describe the necessary financing you will require, and when it will be required, as well as your plans to raise the requisite financing to launch your innovation into Phase III and begin the revenue stream. Plans for this financing stage may be demonstrated in one or more of the following ways:
 - i) Letter of commitment of funding.
 - ii) Letter of intent or evidence of negotiations to provide funding, should the Phase II project be successful and the market need still exist.
 - iii) Letter of support for the project and/or some in-kind commitment, e.g., to test or evaluate the innovation.

- iv) Specific steps you are going to take to secure Phase III funding.
- h) **Production and Marketing Plan.** Describe how the production of your product/service will occur (e.g., in-house manufacturing, contract manufacturing). Describe the steps you will take to market and sell your product/service. For example, explain plans for licensing, internet sales, etc.
- i) **Revenue Stream.** Explain how you plan to generate a revenue stream for your company should this project be a success. Examples of revenue stream generation include, but are not limited to, manufacture and direct sales, sales through value added resellers or other distributors, joint venture, licensing, service. Describe how your staffing will change to meet your revenue expectations.
- j) Offerors are encouraged to seek commitment(s) of funds and/or resources from an investor or partner organization for commercialization of the product(s) or service(s) resulting from the SBIR contract.
- k) Your Phase III funding may be from any of a number of different sources including, but not limited to: SBIR firm itself; private investors or “angels”; venture capital firms; investment companies; joint ventures; R&D limited partnerships; strategic alliances; research contracts; sales of prototypes (built as part of this project); public offering; state finance programs; non SBIR-funded R&D or production commitments from a Federal agency with the intention that the results will be used by the United States government; or other industrial firms.

10) **Subcontractors/Consultants.** Involvement of a university or other subcontractors or consultants in the project may be appropriate and is permitted. If such involvement is intended, it should be described in detail and identified in the cost proposal. In addition, supported by appropriate letters from each individual confirming his/her role in the project must be included. Small business concerns must perform a minimum of one half for Phase II of the research and/or analytical effort (i.e., total contract price less profit/fee) conducted under the resulting contract. The Contracting Officer must approve deviations from this requirement in writing after consultation with the agency SBIR Program Manager/Coordinator.

Fast-Track proposals that do not contain all parts described above will be redirected for Phase I consideration only.

8.9 Human Subjects Research and Protection from Risk

Instructions and Required Information

If your project involves the use of Human Subjects as defined in Section 3.2 of this solicitation, this information must be submitted with the proposal.

Create a section heading entitled “**Human Subjects Research.**” Place it immediately following the “Research Plan” section of the proposal.

Instructions to Offerors Regarding Protection of Human Subjects

Offerors must address the following human subjects protections issues if this contract will be for research involving human subjects (note: under each of the following points below, the offeror should indicate whether the information provided relates to the primary research site, or to a collaborating performance site(s), or to all sites):

- a. Risks to Human Subjects
 - Human Subjects Involvement, Characteristics, and Design

- Describe and justify the proposed involvement of human subjects in the work outlined in the Research Strategy section.
 - Describe the characteristics of the subject population, including their anticipated number, age range, and health status if relevant.
 - Describe and justify the sampling plan, as well as the recruitment and retention strategies and the criteria for inclusion or exclusion of any subpopulation.
 - Explain the rationale for the involvement of special vulnerable populations, such as fetuses, neonates, pregnant women, children, prisoners, institutionalized individuals, or others who may be considered vulnerable populations. Note that 'prisoners' includes all subjects involuntarily incarcerated (for example, in detention centers) as well as subjects who become incarcerated after the study begins.
 - If relevant to the proposed research, describe procedures for assignment to a study group. As related to human subjects protection, describe and justify the selection of an intervention's dose, frequency and administration.
 - List any collaborating sites where human subjects research will be performed, and describe the role of those sites and collaborating investigators in performing the proposed research. Explain how data from the site(s) will be obtained, managed, and protected.
- Sources of Materials
 - Describe the research material obtained from living individuals in the form of specimens, records, or data.
 - Describe any data that will be collected from human subjects for the project(s) described in the application.
 - Indicate who will have access to individually identifiable private information about human subjects.
 - Provide information about how the specimens, records, and/or data are collected, managed, and protected as well as whether material or data that include individually identifiable private information will be collected specifically for the proposed research project.
 - Potential Risks
 - Describe the potential risks to subjects (physical, psychological, financial, legal, or other), and assess their likelihood and seriousness to the human subjects.
 - Where appropriate, describe alternative treatments and procedures, including the risks and potential benefits of the alternative treatments and procedures, to participants in the proposed research.

b. Adequacy of Protection Against Risks

- Recruitment and Informed Consent
 - Describe plans for the recruitment of subjects (where appropriate) and the process for obtaining informed consent. If the proposed studies will include children, describe the process for meeting requirements for parental permission and child assent.

- Include a description of the circumstances under which consent will be sought and obtained, who will seek it, the nature of the information to be provided to prospective subjects, and the method of documenting consent. If a waiver of some or all of the elements of informed consent will be sought, provide justification for the waiver. Informed consent document(s) need not be submitted to the PHS agencies unless requested.
- Protections Against Risk
 - Describe planned procedures for protecting against or minimizing potential risks, including risks to privacy of individuals or confidentiality of data, and assess their likely effectiveness.
 - Research involving vulnerable populations, as described in the DHHS regulations, Subparts B-D must include additional protections. Refer to DHHS regulations, and OHRP guidance:
 - Additional Protections for Pregnant Women, Human Fetuses and Neonates: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartb>
 - Additional Protections for Prisoners: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartc>
 - OHRP Subpart C Guidance: <http://www.hhs.gov/ohrp/policy/index.html#prisoners>
 - Additional Protections for Children: <http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html#subpartd>
 - OHRP Subpart D Guidance: <http://www.hhs.gov/ohrp/policy/index.html#children>
 - Where appropriate, discuss plans for ensuring necessary medical or professional intervention in the event of adverse effects to the subjects. Studies that involve clinical trials (biomedical and behavioral intervention studies) must include a general description of the plan for data and safety monitoring of the clinical trials and adverse event reporting to the IRB, the NIH and others, as appropriate, to ensure the safety of subjects.

Potential Benefits of the Proposed Research to Human Subjects and Others

- Discuss the potential benefits of the research to research participants and others.
- Discuss why the risks to subjects are reasonable in relation to the anticipated benefits to research participants and others.

Importance of the Knowledge to be Gained

- Discuss the importance of the knowledge gained or to be gained as a result of the proposed research.
- Discuss why the risks to subjects are reasonable in relation to the importance of the knowledge that reasonably may be expected to result.

NOTE: Test articles (investigational new drugs, devices, or biologics) including test articles that will be used for purposes or administered by routes that have not been approved for general use by the Food and Drug Administration (FDA) must be named. State whether the 30-day interval between submission of applicant certification to the FDA and its response has elapsed or has been waived and/or whether use of the test article has been withheld or restricted by the FDA, and/or the status of requests for an Investigational New Drug (IND) or Investigational Device Exemption (IDE) covering the proposed use of the test article in the Research Plan.

Data and Safety Monitoring Plan

- If the proposed research includes a clinical trial (as defined in Section 3.2. of this solicitation), create a heading entitled "Data and Safety Monitoring Plan."
- Provide a general description of a monitoring plan that you plan to establish as the overall framework for data and safety monitoring. Describe the entity that will be responsible for monitoring and the process by which Adverse Events (AEs) will be reported to the Institutional Review Board (IRB), the funding I/C, the NIH Office of Biotechnology Activities (OBA), and the Food and Drug Administration (FDA) in accordance with Investigational New Drug (IND) or Investigational Device Exemption (IDE) regulations. Be succinct. Contact the FDA (<http://www.fda.gov/>) and also see the following Web sites for more information related to IND and IDE requirements:

http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr312_01.html (IND)

http://www.access.gpo.gov/nara/cfr/waisidx_01/21cfr812_01.html (IDE)

- The frequency of monitoring will depend on potential risks, complexity, and the nature of the trial; therefore, a number of options for monitoring trials are available. These can include, but are not limited to, monitoring by a:
 - PD/PI (required)
 - Institutional Review Board (IRB) (required)
 - Independent individual/safety officer
 - Designated medical monitor
 - Internal Committee or Board with explicit guidelines
 - Data and Safety Monitoring Board (DSMB). NIH specifically requires the establishment of Data and Safety Monitoring Boards (DSMBs) for multi-site clinical trials involving interventions that entail potential risk to the participants, and generally for Phase III clinical trials. Although Phase I and Phase II clinical trials may also need DSMBs, smaller clinical trials may not require this oversight format, and alternative monitoring plans may be appropriate.
- A detailed Data and Safety Monitoring Plan must be submitted to the applicant's IRB and subsequently to the funding IC for approval prior to the accrual of human subjects. For additional guidance on creating this Plan see <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-00-038.html>.

ClinicalTrials.gov Requirements

- Public Law 110-85 (also known as the FDA Amendments Act (FDAAA) of 2007) mandates registration and results reporting of "applicable clinical trials" in ClinicalTrials.gov. Under the statute these trials generally include: (1) Trials of Drugs and Biologics: Controlled, clinical investigations, other than Phase 1 investigations, of a product subject to FDA regulation; and (2) Trials of Devices: Controlled trials with health outcomes, other than small feasibility studies, and pediatric postmarket surveillance. Review the statutory definition of applicable clinical trial to identify if registration is required to comply with the law (See PL 110-85, Section 801(a), adding new 42 U.S.C. 282(j)(1)(A)).
- NIH encourages registration of ALL clinical trials whether required under the law or not.
- Registration is accomplished at the ClinicalTrials.gov Protocol Registration System Information Web site (<http://prsinfo.clinicaltrials.gov/>). A unique identifier called an NCT number, or ClinicalTrials.gov registry number, will be generated during the registration process.
- The NIH implementation of FDAAA requires:
 - the registration of applicable clinical trials in ClinicalTrials.gov no later than 21 days after the first subject is enrolled,
 - the reporting of summary results information (including adverse events) no later than 1 year after the completion date for registered applicable clinical trials involving drugs that are approved under section 505 of the Food, Drug and Cosmetic Act (FDCA) or licensed under section 351 of the PHS Act, biologics, or of devices that are cleared under section 510k of FDCA, and
 - if an "applicable clinical trial" is funded in whole or in part by an NIH grant or cooperative agreement, grant and progress report forms shall include a certification that the responsible party has made all required submissions to ClinicalTrials.gov.
- For competing new and renewal applications that include applicable clinical trials which require registration and results reporting under FDAAA, provide the NCT number/s in the human subjects section of the Research Plan under a section heading entitled ClinicalTrials.gov. Supplemental Instructions for PHS 398 and SF424 (R&R) II-11
- The entity responsible for registering the trial is the "responsible party". The statute defines the responsible party as:
 - the sponsor of the clinical trial (as defined in 21 CFR 50.3) (<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=50.3>), or
 - the principal investigator of such clinical trial if so designated by a sponsor, grantee, contractor, or awardee (provided that "the principal investigator is responsible for conducting the trial, has access to and control over the data from the clinical trial, has the right to publish the results of the trial, and has the ability to meet all of the requirements" for submitting information under the law) (http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:publ085.110.pdf). See PL 110-85, Section 801(a), (adding new 42 U.S.C. 282(j)(1)(A)(ix)).
- For the complete statutory definitions of "responsible party" and "applicable clinical trial," refer to Elaboration of Definitions of Responsible Party and Applicable Clinical Trial.
- The signature on the application of the Authorized Organization Representative assures compliance with FDAAA.

- Additional information can be found on the ClinicalTrials.gov Web site (http://grants.nih.gov/ClinicalTrials_fdaaa/).

Collaborating Site(s)

When research involving human subjects will take place at collaborating site(s) or other performance site(s), the offeror must provide in this section of its proposal a list of the collaborating sites and their assurance numbers. Further, if you are awarded a contract, you must obtain in writing, and keep on file, an assurance from each site that the previous points have been adequately addressed at a level of attention that is at least as high as that documented at your organization. Site(s) added after an award is made must also adhere to the above requirements.

Required Education in the Protection of Human Research Participants

NIH policy requires education on the protection of human subject participants for all investigators submitting NIH proposals for contracts for research involving human subjects. This policy announcement is found in [NOT-OD-00-039](#) in the NIH Guide for Grants and Contracts Announcement dated June 5, 2000. Offerors should review the policy announcement prior to submission of their offers. The following is a summary of the Policy Announcement:

For any solicitation for research involving human subjects, the offeror shall provide in its technical proposal the following information: (1) a list of the names of the principal investigator and any other individuals proposed under the contract who are responsible for the design and/or conduct of the research; (2) the title of the education program completed (or to be completed prior to the award of the contract) for each named personnel; (3) a one sentence description of the program(s) listed in (2) above. This requirement extends to investigators and all individuals responsible for the design and/or conduct of the research who are working as subcontractors or consultants under the contract.

Curricula that are readily available and meet the educational requirement include the NIH Office of Extramural Research (OER) on-line tutorial, entitled "[Protecting Human Research Participants](#)." This course is also available in Spanish under the title "[Protección de los participantes humanos de la investigación](#)." You may take the tutorials on-line or download the information in PDF form at no cost.

If an institution already has developed educational programs on the protection of research participants, completion of these programs also will satisfy the educational requirement.

In addition, prior to the substitution of the principal investigator or any other individuals responsible for the design and/or conduct of the research under the contract, the Contractor shall provide the contracting officer with the title of the education program and a one sentence description of the program that the replacement has completed.

8.10 Inclusion of Women, Minorities, and Children in Clinical Research

Instructions for Addressing the Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations must be included in all NIH-supported [clinical research](#) projects involving human subjects, unless a clear and compelling rationale and justification establishes to the satisfaction of the relevant Institute/Center Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. The Director, NIH, may determine that exclusion under other circumstances is acceptable, upon the recommendation of an Institute/Center Director, based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. This policy results from the Federal law (Public Health Service Act sec. 492B. 42 U.S.C. sec. 289a-2), **and applies to research subjects of all ages.**

Unless otherwise specified in this solicitation, the Government has determined that the work required by this solicitation does not involve a sex/gender specific study or a single or limited number of minority population groups. Therefore, the proposed distribution of the sample by sex/gender, race, and ethnicity should be justified in the context of the scientific goals of the proposal. This section is required for all studies meeting [the NIH definition for clinical research](#), NOT just clinical trials. It is important to provide a detailed plan of who will be included (and/or excluded) and how the distributions of individuals on the

basis of sex/gender, race, and ethnicity are justified in the context of the scientific goals of the proposal. Simply stating that certain individuals will not be excluded or that individuals of either sex/gender or any race/ethnicity are eligible is not sufficient. Details about why the individuals are the appropriate individuals to accomplish the scientific goals of the study should be provided.

This solicitation contains a review criterion addressing the adequacy of: (1) the offeror's plans for inclusion of women and minorities in the research proposed; or (2) the offeror's justification(s) for exclusion of one or more groups from the research proposed.

Create a section of the proposal entitled "Inclusion of Women and Minorities" where these plans will be described. Offerors will also use the form entitled, "Planned Enrollment Report or Cumulative Inclusion Enrollment Report," when preparing your response to the solicitation requirements for inclusion of women and minorities. See this webpage for additional information in determining which form is appropriate to use:

http://grants.nih.gov/grants/funding/women_min/women_min.htm

The proposal must address, at a minimum, the following four points the following information:

1. Describe the planned distribution of subjects by sex/gender, race, and ethnicity for each proposed study and complete the Planned Enrollment Report form (Section J, Attachments). If the clinical study(s) involves US and non-US sites, at a minimum, the US sites and non-US sites should be provided on separate Planned Enrollment Reports. Additional guidance on completing the form(s) is available in Part I, Section 4.3 [here](#).
2. Describe the subject selection criteria and rationale for selection of [sex/gender](#), racial, and ethnic group members in terms of the scientific objectives and proposed study design. The description may include, but is not limited to, information on the population characteristics of the disease or condition under study.
3. Provide a compelling rationale for proposed sample specifically addressing exclusion of any sex/gender, racial, or ethnic group that comprises the population under study.
4. Describe proposed outreach programs for recruiting sex/gender, racial, and ethnic group members as subjects. This is particularly important if difficulty recruiting certain groups is anticipated.

Additional considerations for justifying inclusion:

There may be reasons why the proposed sample is limited by sex/gender, race, and/or ethnicity. This should be addressed as part of the four points detailed above.

- inclusion of certain individuals would be inappropriate with respect to their health;
- the research question addressed is only relevant to certain groups or there is a gap in the research area;
- evidence from prior research strongly demonstrates no difference on the basis of sex/gender, race, and/or ethnicity;
- sufficient data already exist with regard to the outcome of comparable studies in the excluded group(s) and duplication is not needed in this study;
- a certain group or groups is excluded or severely limited because the purpose of the research constrains the applicant's selection of study subjects (e.g., uniquely valuable stored specimens or existing datasets are limited by sex/gender, race, and/or ethnicity; very small numbers of subjects are involved; or overriding factors dictate selection of subjects, such as matching of transplant recipients, or availability of rare surgical specimens); and/or
- representation of specimens or existing datasets cannot be accurately determined (e.g., pooled blood samples, stored specimens, or data-sets with incomplete sex/gender documentation are used), and this does not compromise the scientific objectives of the research.
- In general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of particular groups. This should be considered when developing outreach plans. Establishing collaborations or other arrangements to recruit may be necessary.

Additional guidance for specific scenarios:

- **Research utilizing existing datasets or resources:** Inclusion must be addressed when conducting NIH-defined clinical research, even if the samples or data have already been collected as part of a different study. Details about the sex/gender, race, and ethnicity composition of the existing dataset/resource should be provided and justified as appropriate to the scientific goals of the proposed study. For the purposes of inclusion policy, an existing dataset may be constructed of different types of data including but not limited to survey data, demographic information, health information, genomic information, etc. Also included would be data to be derived from existing samples of cells, tissues, or other types of materials that may have been previously collected for a different purpose or research question but will now be used to answer a new research question. In general, these will be studies meeting the NIH definition for clinical research with a prospective plan to analyze existing data and/or derive data from an existing resource and where no ongoing or future contact with participants is anticipated. More information about what is considered an existing dataset or resource for inclusion policy is available [here](#).
- **Research Conducted with Non-U.S. Participants:** If conducting NIH-defined clinical research outside of the United States, design culturally appropriate data collection instruments that allow participants to self-identify their ethnic and/or racial affiliation in a way that is meaningful in the cultural and scientific contexts of the study. However, investigators must use the OMB-defined categories for reporting sex/gender, race and ethnicity to NIH, which will allow completion of the inclusion enrollment forms(s). Since the OMB categories reference world-based geographic origin, this should facilitate completion of the form(s). **Enrollment of participants at non-U.S. sites should be reported to NIH on a separate NIH inclusion enrollment form from that for reporting participants at U.S. sites, even if they are part of the same study.** For additional guidance and FAQs related to this topic, please refer to: http://grants.nih.gov/grants/funding/women_min/women_min.htm or [contact the program officer](#).
- **Delayed-Onset Human Subjects Research:** If the proposed research includes studies that meet the definition for delayed-onset human subjects research described in the Human Subjects section of the instructions, and it is not possible to describe the proposed study and provide planned enrollment on sex/gender, race, and ethnicity, then describe this in the inclusion plans sections and enter a comment on the Planned Enrollment Report(s) indicating this is a delayed-onset study. If you expect that more than one study will be delayed onset, it is acceptable to provide only one Planned Enrollment Report indicating delayed onset, but you may wish to indicate in the comments section of the Planned Enrollment Report that more than one study is anticipated under this scenario.

NOTE 1: All contractors must also report at least annually cumulative subject accrual by sex/gender, race, and ethnicity. If the clinical study(s) involves US and non-US sites, the US sites and non-US sites should be reported on separate Cumulative Inclusion Enrollment Reports.

NOTE 2: For all proposals, use the ethnic and racial categories and complete the "PLANNED Enrollment Report" in accordance with the [Office of Management and Budget \(OMB\) Directive No. 15](#).

Standards for Collecting Racial and Ethnic Data.

When you, as a contractor, are planning data collection items on race and ethnicity, you shall use, at a minimum, the categories identified in [OMB Directive No. 15](#). The collection of greater detail is encouraged. However, you should design any additional, more detailed items so that they can be aggregated into these required categories. Self-reporting or self-identification using two separate questions is the preferred method for collecting data on race and ethnicity. Collect ethnicity information first, followed by the question on race and provide participants with the option to select more than one racial category. Participants also have the option not to identify. When you present aggregate data, you shall provide the number of respondents who selected only one category, for each of the five racial categories. Participants who self-identify with more than one racial category should be reported to the NIH under the "More than one race" category of the report. Federal agencies shall not present data on detailed categories if doing so would compromise data quality or confidentiality standards.

Additional Instructions and Requirements When NIH-Defined Phase III Clinical Trials Are Proposed

If the proposed research includes an [NIH-Defined Phase III Clinical Trial](#), the section on Inclusion of Women and Minorities also MUST address plans for how sex/gender, race, and ethnicity will be taken into consideration in the design and valid analysis of the trial. Valid analysis means an unbiased assessment which will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect.

Each proposal will be assessed as being acceptable or unacceptable with regard to the scientifically justified inclusion plans, including these additional requirements for NIH-defined Phase III clinical trials.

- Applicants should address the following issues for ensuring a valid analysis:
 - inclusive eligibility criteria-- in general, the cost of recruiting certain groups and/or geographic location alone are not acceptable reasons for exclusion of particular groups;
 - allocation of study participants of both sexes/genders (males and females) and from different racial and/or ethnic groups to the intervention and control groups by an unbiased process such as randomization;
 - unbiased evaluation of the outcome(s) of study participants; and
 - use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects by sex/gender, race, and/or ethnicity, particularly if prior evidence strongly suggests that differences exist.
- Applicants also should address whether they plan to test or not test for differences in effect among sex/gender, racial, and/or ethnic groups and why that is or is not appropriate. This may include supporting evidence and/or data derived from animal studies, clinical observations, metabolic studies, genetic studies, and pharmacology studies as well as observational, natural history, epidemiology and/or other relevant studies. Additional factors may include planned primary and secondary outcomes and whether there are previous studies that support or negate the likelihood of differences between groups.

All contractors must also report at least annually cumulative subject accrual by sex/gender, race, and ethnicity, and make note of any progress in conducting analyses for sex/gender, racial, and/or ethnic differences.

Use the form entitled, "[Cumulative Inclusion Enrollment Report](#)," for reporting in the resultant contract.

Instructions to Offerors regarding the Inclusion of Children in Research Involving Human Subjects

Research involving children (see definition of “child”) must comply with the NIH Policy and Guidelines on the Inclusion of Children in Clinical Research. For purposes of the NIH Inclusion of Children policy, a child is defined as an individual under the age of 21 years. This is a separate consideration from the protection of children (described above in the Human Subjects Protections section). The involvement of children as subjects in research must also be in compliance with all applicable subparts of 45 CFR part 46 as well as with other pertinent Federal laws and regulations. Each proposal will be assessed as to whether the plans are acceptable or unacceptable with regard to the age-appropriate inclusion or exclusion of children in the proposed research project. This section is required for all studies meeting the NIH definition for clinical research, NOT just clinical trials. It is important to provide a detailed plan of who will be included (and/or excluded) based on age. Details about why the individuals in the given age/age range are the appropriate individuals to accomplish the scientific goals of the study should be provided.

Instructions for this item of the Research Plan including addressing the following points:

- Describe the age(s) or age range of all individuals to be included in the proposed study.
- Specifically discuss whether children under the age of 21 (as a whole or a subset of individuals under 21) will be included or excluded.
- The description of the plan should include a rationale for selecting a specific age range of children.
- The plan also must include a description of the expertise of the investigative team for working with children at the ages included, of the appropriateness of the available facilities to accommodate the children, and the inclusion of a sufficient number of children to contribute to a meaningful analysis relative to the purpose of the study.
- When children are involved in research, the Additional Protections for Children Involved as Subjects in Research ([45 CFR part 46 Subpart D](#)) apply and must be addressed under the Protections Against Risk subheading, not in this section.

Justifications for Exclusion of Children

For the purposes of this policy, individuals under 21 are defined as a child; however, exclusion of any specific age or age range should be justified in this section. It is expected that children will be included in all NIH-defined clinical research unless one or more of the following exclusionary circumstances apply:

- The research topic to be studied is not relevant to children.
- Laws or regulations bar the inclusion of children in the research.
- The knowledge being sought in the research is already available for children or will be obtained from another ongoing study, and an additional study will be needlessly redundant. Documentation of other studies justifying the exclusions should be provided. NIH program staff can be contacted for guidance on this issue if the information is not readily available.
- A separate, age-specific study in children is warranted and preferable. Examples include:
 - The condition is relatively rare in children, as compared to adults (in that extraordinary effort would be needed to include children, although in rare diseases or disorders where the applicant has made a particular effort to assemble an adult population, the same effort would be expected to assemble a similar child population with the rare condition); or
 - The number of children is limited because the majority are already accessed by a nationwide pediatric disease research network; or
 - Issues of study design preclude direct applicability of hypotheses and/or interventions to both adults and children (including different cognitive, developmental, or disease stages or different age-related metabolic processes). While this situation may represent a justification for excluding children in some instances, consideration should be given to taking these differences into account in the study design and expanding the hypotheses tested, or the interventions planned, to allow inclusion of children rather than excluding them.
- Insufficient data are available in adults to judge potential risk in children (in which case one of the research objectives could be to obtain sufficient adult data to make this judgment). Although children usually should not be the initial group to be involved in research studies, in some instances, the nature and seriousness of the illness may warrant their participation earlier based on careful risk and benefit analysis.
- Study designs are aimed at collecting additional data on pre-enrolled adult study subjects (e.g., longitudinal follow-up studies that did not include data on children).
- Other special cases can be justified by the investigator and assessed by the review group and the Institute/Center Director to determine if acceptable.

All offerors proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" which was published in the NIH Guide for Grants and Contracts on March 6, 1998 and is available at the following URL address: <http://www.nih.gov/grants/guide/notice-files/not98-024.html>. Offerors also may obtain copies from the contact person listed in the RFP.

For additional details and guidance, please refer to <http://grants.nih.gov/grants/funding/children/children.htm>

8.11 Research Involving Human Fetal Tissue

Human Fetal Tissue means tissue or cells obtained from a dead human fetus, including human embryonic stem cells, human pluripotent stem cells and human embryonic germ cells.

The governing federal statute is the Public Health Service Act, 42 U.S.C. 289g 1 and 289g 2. Implementing regulations and guidance for conducting research on human fetal tissue may be found at 45 CFR 46, Subpart B and [NIH Guide NOT-OD-93-235](#) and any subsequent revisions to this NIH Guide to Grants and Contracts ("Guide") Notice.

By signing the face page of the proposal, the offeror (authorized institutional official) certifies that researchers using human fetal tissue are in compliance with 42 USC 289g 2. This statute specifically prohibits any person from knowingly acquiring,

receiving, or transferring any human fetal tissue for valuable consideration. "Valuable consideration" is a concept similar to profit, and does not include reasonable payment for costs associated with the collection processing, preservation, storage, quality control or transportation of these tissues.

Research involving the transplantation of human fetal tissue must be conducted in accordance with applicable Federal, State and local law.

8.12 Research Involving Vertebrate Animals

If it is intended that live vertebrate animals will be used during performance of this contract the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals (authority derived from the Health Research Extension Act of 1985) specifies that certain information is required from offerors in contract proposals submitted to the NIH.

The following five points must be addressed in a separate section of the Technical Proposal titled "Vertebrate Animal Section" (VAS):

- Provide a detailed description of the proposed use of the animals in the work outlined in the Research Design and Methods section. Identify the species, strains, ages, sex, and numbers of animals to be used in the proposed work.
- Justify the use of animals, the choice of species, and the numbers to be used. If animals are in short supply, costly, or to be used in large numbers, provide an additional rationale for their selection and numbers.
- Provide information on the veterinary care of the animals involved.
- Describe the procedures for ensuring that discomfort, distress, pain, and injury will be limited to that which is unavoidable in the conduct of scientifically sound research. Describe the use of analgesic, anesthetic, and tranquilizing drugs and/or comfortable restraining devices, where appropriate, to minimize discomfort, distress, pain, and injury.
- Describe any method of euthanasia to be used and the reasons for its selection. State whether this method is consistent with the recommendations of the Panel on Euthanasia of the American Veterinary Medical Association. If not, present a justification for not following the recommendations.

A concise (no more than 1-2 pages), complete description addressing these five points must be provided. The description must be cohesive and include sufficient information to allow evaluation by reviewers and NIH staff. For more discussion regarding the five points in the VAS, see [NIH Guide Notice NOT-OD-10-049](#). For additional guidance see the *Worksheet for Review of the Vertebrate Animal Section under Contract Proposals*, <http://grants.nih.gov/grants/olaw/VAScontracts.pdf>.

The *PHS Policy on Humane Care and Use of Laboratory Animals* (PHS Policy) requires that offeror organizations proposing to use vertebrate animals file a written Animal Welfare Assurance with the Office of Laboratory Animal Welfare (OLAW), establishing appropriate policies and procedures to ensure the humane care and use of live vertebrate animals involved in research activities supported by the PHS. The PHS Policy stipulates that an offeror organization, whether domestic or foreign, bears responsibility for the humane care and use of animals in PHS-supported research activities. This policy implements and supplements the *U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training* and requires that institutions use the *Guide for the Care and Use of Laboratory Animals* as a basis for developing and implementing an institutional animal care and use program. This policy does not affect applicable state or local laws or regulations that impose more stringent standards for the care and use of laboratory animals. All institutions are required to comply, as applicable, with the Animal Welfare Act as amended (7 U.S.C. 2131 et sec.) and other Federal statutes and regulations relating to animals. These documents are available from the Office of Laboratory Animal Welfare, National Institutes of Health, Bethesda, MD 20892, (301) 496-7163.

The PHS Policy defines "animal" as "any live vertebrate animal used or intended for use in research, research training, experimentation or biological testing or for related purposes."

No PHS award for research involving vertebrate animals will be made to an offeror organization unless that organization is operating in accordance with an approved Animal Welfare Assurance and provides verification that the IACUC has reviewed and approved the proposed activity in accordance with the PHS Policy. Proposals may be referred by the PHS back to the IACUC for further review in the case of apparent or potential violations of the PHS Policy. No award to an individual will be made unless that individual is affiliated with an assured organization that accepts responsibility for compliance with the PHS

Policy. Foreign offeror organizations applying for PHS awards for activities involving vertebrate animals are required to comply with PHS Policy or provide evidence that acceptable standards for the humane care and use of animals will be met.

8.13 Content of the Pricing Proposal (Item Two).

Complete the Pricing Item in the format shown in the Pricing Proposal ([Appendix C](#)). Some items in the Pricing Proposal may not apply to the proposed project. If that is the case, there is no need to provide information on each and every item. What matters is that enough information be provided to allow us to understand how you plan to use the requested funds if a contract is awarded.

- List all key personnel by name as well as by number of hours dedicated to the project as direct labor.
- While special tooling and test equipment and material cost may be included under Phase I, the inclusion of equipment and material will be carefully reviewed relative to need and appropriateness for the work proposed. The purchase of special tooling and test equipment must, in the opinion of the Contracting Officer, be advantageous to the Government and should be related directly to the specific topic. These may include such items as innovative instrumentation or automatic test equipment. Title to property furnished by the Government or acquired with Government funds will be vested with the HHS Component; unless it is determined that transfer of title to the contractor would be more cost effective than recovery of the equipment by the HHS Component.
- Cost for travel funds must be justified and related to the needs of the project. Describe reason for travel, location of travel, number of travelers, and number of nights of lodging in the Description fields in Appendix C.
- Cost sharing is permitted for proposals under this solicitation; however, cost sharing is not required nor will it be an evaluation factor in the consideration of a Phase I proposal.
- All subcontractor costs and consultant costs must be detailed at the same level as prime contractor costs in regards to labor, travel, equipment, etc. Provide detailed substantiation of subcontractor costs in your cost proposal. Enter this information in the Explanatory Material section of the on-line cost proposal form.
- **NIH Policy on Threshold for Negotiation of General and Administrative (G&A)/Indirect Costs (IDC) Rates for SBIR proposals** – For SBIR offerors who propose a G&A/IDC rate of 40 percent of total direct costs or less will not be required to negotiate Final Indirect Rates with the NIH Division of Financial Advisory Services (DFAS), or other cognizant auditing agency. However, awarding Contracting Officers may require offerors to document how they calculated their IDC rate(s) in order to determine that these costs are fair and reasonable. Furthermore, the Division of Financial Advisory Services (DFAS) will retain the authority to require well-documented proposals for G&A/IDC rates on an *ad hoc* basis. If the SBC has a currently effective negotiated indirect cost rate(s) with a Federal agency, such rate(s) shall be used when calculating proposed G&A/IDC costs for an NIH proposal. (However, the rate(s) must be adjusted for IR&D expenses, which are not allowable under HHS awards.)

SBCs are reminded that only actual G&A/IDC costs may be charged to projects. If awarded at a rate of 40 percent or less of total direct costs, the rate used to charge actual G&A/ID costs to projects cannot exceed the awarded rate unless the SBC negotiates an indirect cost rate(s) with DFAS.

- Offerors submitting proposals may include the amount of \$5,000 for technical assistance as discussed and outlined in Section 4.20 of the solicitation.
- **Prior, Current, or Pending Support of Similar Proposals or Awards.** If a proposal submitted in response to this solicitation is substantially the same as another proposal that was funded, is now being funded, or is pending with another Federal Agency, or another or the same HHS Component, you must reveal this on the Proposal Cover Sheet and provide the following information:
 - 1) Name and address of the Federal Agency(s) or HHS Component, to which a proposal was submitted, will be submitted, or from which an award is expected or has been received.
 - 2) Date of proposal submission or date of award.

- 3) Title of proposal.
- 4) Name and title of principal investigator for each proposal submitted or award received.
- 5) Title, number, and date of solicitation(s) under which the proposal was submitted, will be submitted, or under which award is expected or has been received.
- 6) If award was received, state contract number.
- 7) Specify the applicable topics for each SBIR/STTR proposal submitted or award received.

Note: If this does not apply, state in the proposal "No prior, current, or pending support for proposed work."

8.14 Reminders

Those responding to this solicitation should note the proposal preparation tips listed below:

- Read and follow all instructions contained in this solicitation, including the instructions in Section 12.0 of the HHS Component to which the firm is applying.
- Check that the proposed price adheres to the budget set forth under each Topic.
- Check that the Project Abstract and other content provided on the cover sheets contain NO proprietary information.
- Mark proprietary information within the Technical Proposal as instructed in Section 4.22.
- Check that the header on each page of the technical proposal contains the company name and topic number.
- Ensure that if you have proposed for your research to include Human Subjects or Vertebrate Animals that you have addressed the requirements outlined in the solicitation in the Technical proposal as necessary.
- If you intend to propose surveys or other data collections in a Phase I project, you should refrain from proposing more than 9 respondents, due to OMB clearances.

9 SUMMARY OF HHS COMPONENTS ANTICIPATED NUMBER OF AWARDS

HHS COMPONENTS	ANTICIPATED NO. OF AWARDS	ANTICIPATED TIME OF AWARD
National Institutes of Health (NIH) National Cancer Institute (NCI)	32-47	Scientific and Technical Merit Review: March-May 2016 Anticipated Award Date: August 2016-March 2017
National Institutes of Health (NIH) National Center for Advancing Translational Sciences (NCATS)	4-6	Scientific and Technical Merit Review: March-June 2016 Anticipated Award Date: August-September 2016
National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI)	7-8	Scientific and Technical Merit Review: February-April 2016 Anticipated Award Date: July-September 2016
National Institutes of Health (NIH) National Institute on Alcohol Abuse and Alcoholism (NIAAA)	1-2	Scientific and Technical Merit Review: March-May 2016 Anticipated Award Date: August-September 2016
National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID)	9-16	Scientific and Technical Merit Review: March 2016 Anticipated Award Date: August 2016
National Institutes of Health (NIH) National Institute on Drug Abuse (NIDA)	3-4	Scientific and Technical Merit Review: March 2016 Anticipated Award Date: August 2016
Centers for Disease Control and Prevention (CDC) Center for Global Health (CGH)	1-2	Scientific and Technical Merit Review: May-June 2016 Anticipated Award Date: August 2016
Centers for Disease Control and Prevention (CDC) National Center for Emerging Zoonotic and Infectious Diseases (NCEZID)	2	Scientific and Technical Merit Review: May-June 2016 Anticipated Award Date: August 2016
Centers for Disease Control and Prevention (CDC) National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP)	2	Scientific and Technical Merit Review: May-June 2016 Anticipated Award Date: August 2016
Centers for Disease Control and Prevention (CDC) National Center for Immunization and Respiratory Diseases (NCIRD)	2-4	Scientific and Technical Merit Review: May-June 2016 Anticipated Award Date: August 2016

10 CONTRACTING OFFICER POINTS OF CONTACT FOR QUESTIONS RELATED TO SPECIFIC TOPICS

General Questions about the NIH SBIR Program

Email: sbir@od.nih.gov

Any small business concern that intends to submit an SBIR contract proposal under this solicitation should provide the appropriate contracting officer(s) with early, written notice of its intent, giving its name, address, telephone, e-mail, and topic number(s). If a topic is modified or canceled before this solicitation closes, only those companies that have expressed such intent will be notified.

NATIONAL INSTITUTES OF HEALTH (NIH)

NATIONAL CANCER INSTITUTE (NCI)

Ms. Rosemary M. Hamill

Procurement Analyst

Office of Acquisitions

National Cancer Institute

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NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES (NCATS)

Jeffrey R. Schmidt

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NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

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NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

Katharine C. Minker

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Contracts Management Branch, NIAAA

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NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

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Contracting Officer

Office of Acquisitions, DEA

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National Institutes of Health, DHHS

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NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

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CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

For general administrative SBIR program questions, contact:

Office of the Director, Office of the Associate Director for Science

Sean David Griffiths, M.P.H.
SBIR Program Manager
Office of Technology and Innovation
Office of the Associate Director for Science
Phone: 404-639-4641
Fax: 404-639-4903
E-mail: SGriffiths@cdc.gov

Diana Bartlett, MPH, MPP
Office of Technology and Innovation
Office of the Associate Director for Science
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CENTER FOR GLOBAL HEALTH (CGH)

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NATIONAL CENTER FOR EMERGING ZOO NOTIC AND INFECTIOUS DISEASES (NCEZID)

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NATIONAL CENTER FOR HIV/AIDS, VIRAL HEPATITIS, STD, AND TB PREVENTION (NCHHSTP)

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NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

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11 SCIENTIFIC AND TECHNICAL INFORMATION SOURCES

Health science research literature is available at academic and health science libraries throughout the United States. Information retrieval services are available at these libraries and Regional Medical Libraries through a network supported by the National Library of Medicine. To find a Regional Medical Library in your area, visit <http://nmlm.gov/> or contact the Office of Communication and Public Liaison at publicinfo@nlm.nih.gov, (301) 496-6308.

Other sources that provide technology search and/or document services include the organizations listed below. They should be contacted directly for service and cost information.

National Technical Information Service

1-800-553-6847

<http://www.ntis.gov>

National Technology Transfer Center

Wheeling Jesuit College

1-800-678-6882

<http://www.nttc.edu/>

12 COMPONENT INSTRUCTIONS AND TECHNICAL TOPIC DESCRIPTIONS

NATIONAL INSTITUTES OF HEALTH

NATIONAL CANCER INSTITUTE (NCI)

The NCI is the Federal Government's principal agency established to conduct and support cancer research, training, health information dissemination, and other related programs. As the effector of the National Cancer Program, the NCI supports a comprehensive approach to the problems of cancer through intensive investigation in the cause, diagnosis, prevention, early detection, and treatment of cancer, as well as the rehabilitation and continuing care of cancer patients and families of cancer patients. To speed the translation of research results into widespread application, the National Cancer Act of 1971 authorized a cancer control program to demonstrate and communicate to both the medical community and the general public the latest advances in cancer prevention and management. The NCI SBIR program acts as NCI's catalyst of innovation for developing and commercializing novel technologies and products to research, prevent, diagnose, and treat cancer.

It is strongly suggested that potential offerors do not exceed the total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

Unless the Fast-Track option is specifically allowed as stated within the topic areas below or the topic(s) are classified as Direct to Phase II, applicants are requested to submit only Phase I proposals in response to this solicitation.

NCI Phase IIB Bridge Award

The National Cancer Institute would like to provide notice of a recent funding opportunity entitled the SBIR Phase IIB Bridge Award. This notice is for informational purposes only and is not a call for Phase IIB Bridge Award proposals. This informational notice does not commit the government to making such awards to contract awardees.

Successful transition of SBIR research and technology development into the commercial marketplace is difficult, and SBIR Phase II awardees often encounter significant challenges in navigating the regulatory approval process, raising capital, licensure and production, as they try to advance their projects towards commercialization. The NCI views the SBIR program as a long-term effort; to help address these difficult issues, the NCI has developed the SBIR Phase IIB Bridge Award under the grants mechanism. The previously-offered Phase IIB Bridge Award was designed to provide additional funding of up to \$3M for a period of up to three additional years to assist promising small business concerns with the challenges of commercialization. The specific requirements for the previously-offered Phase IIB Bridge Award can be reviewed in the full RFA announcement:

<http://grants.nih.gov/grants/guide/rfa-files/RFA-CA-14-002.html>.

The NCI expanded the Phase IIB Bridge Award program in FY2011 to allow previous SBIR Phase II contract awardees to compete for SBIR Phase IIB Bridge Awards. Pending its planned continuation, it is anticipated that the Phase IIB Bridge Award program will be open to contractors that successfully complete a Phase I award as a result of this solicitation, and who are subsequently awarded a Phase II contract (or have an exercised Phase II option under a Fast-Track contract). Provided it is available in the future, NIH SBIR Phase II contractors who satisfy the above requirements may be able to apply for a Phase IIB Bridge Award under a future Phase IIB Bridge Award grant funding opportunity announcement (FOA), if they meet the eligibility requirements detailed therein. Selection decisions for a Phase IIB Bridge Award will be based both on scientific/technical merit as well as business/commercialization potential.

NCI Topics

This solicitation invites proposals in the following areas:

341 Development of Metabolomics Data Integration Methods and Software

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2 – 3

Budget (total costs, per award): Phase I: up to \$225,000 for up to 9 months

Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Metabolomics is the study of small molecules participating in cellular metabolism. Advances in metabolic profiling technologies have made it possible to simultaneously assay hundreds of metabolites, providing insight into an organism's metabolic status. Several studies suggest that metabolomics may identify novel biomarkers for a diverse range of disease, including cancer. Furthermore, metabolites may play important regulatory roles in disease pathways and even serve as effectors of disease processes. Metabolomics has only recently been applied to epidemiologic studies, some of which are attempting to leverage existing metabolomics data by establishing consortia such as the CONsortium of METabolomics Studies (COMETS).

There is considerable field-wide interest in the development of algorithms and methods to integrate metabolite data across laboratory platforms and analytical technologies, as is currently done for genetic variation by genome-wide association studies and next-generation sequencing. Advances in this area will help lay the foundation to support the application of metabolomics to epidemiology cohorts and consortia by facilitating replication across cohorts, enabling pooled metabolomics analyses across multiple cohorts, and rapidly scaling up sample sizes for metabolomics studies. This topic will help researchers leverage existing resources to easily compare and combine datasets to detect more subtle and complex associations among variables, thereby promoting greater collaboration, efficiency, and return on investment. In turn, it will enhance our opportunities to identify novel cancer biomarkers.

There are several analytical technologies used in metabolomics, including different separation methods [e.g., gas chromatography (GC), liquid chromatography (LC), and capillary electrophoresis (CE)] and multiple detection methods [e.g., mass spectrometry (MS) and nuclear magnetic resonance (NMR)]. Although MS and NMR are the most widely used detection methods, other methods such as ion-mobility spectrometry and electrochemical detection have been used. These detection methods differ in specificity and sensitivity, resulting in the measurement of metabolites specific to the technology. Additionally, laboratories may use the same analytical technologies, but different sample preparation, which results in the measurement of metabolites specific to the sample preparation. Therefore, there can be distinctly different metabolites measured across laboratory platforms using the same analytical technology. Both the differing analytical technologies and laboratory platforms create a complex pool of data that is challenging to integrate/harmonize without valid and reliable methods that are accessible to the research community. This, in turn, limits the ability to pool and leverage existing data for biomarker discovery.

This topic is intended to develop new and innovative bioinformatic methods to integrate metabolite data across laboratory platforms and analytical technologies and ultimately design scalable software tool(s) that apply these methods to automate the integration of metabolite data.

Project Goals

The purpose of this topic is to support the development of new and innovative methods to integrate metabolite data across analytical technologies and laboratory platforms, and in turn, design software tool(s) applying these methods for data integration.

In the short term, this topic aims to 1) develop bioinformatic methods to integrate metabolite data across various laboratory platforms and analytical technologies, including liquid-chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), and NMR; and 2) develop scalable software tool(s) to automate these methods for use by the cancer and overall public health research communities. Valid and reliable data harmonization of metabolomics data also builds a critical foundation for the longer term goal of integration of metabolomics data with other ‘omics data (e.g., genomics, proteomics, transcriptomics, epigenomics, etc.). The development of methods to integrate a wide range of -omics data will position the research community to better leverage existing data for the discovery of novel cancer biomarkers of etiology, diagnosis, and prognosis.

Responses to this topic are expected to address the development of efficient bioinformatic methods to:

1. Demonstrate bioinformatic methods for the integration of metabolite data across different laboratory platforms and analytical technologies with high accuracy;
2. Store metabolite data from the different data sources in databases that can be easily used for data integration and quality control protocols;
3. Implement valid quality control (QC) checks; and
4. Appropriately secure data at each stage of transfer and storage.

An essential task for each proposal is the development of bioinformatic tools in the form of scalable software that can be used by the research community at-large to automate complex data integration tasks for metabolomics data sources.

Phase I activities should provide evidence that metabolite data integration bioinformatic methods, using identified metabolite data, have been effectively developed, can be implemented across data inputs from diverse laboratory platforms and at least two analytical technologies, and demonstrate readiness to proceed to Phase II. Additionally, Phase I will be used to demonstrate the framework for scalable software tool(s) that apply the bioinformatic methods to automate the integration of metabolite data.

Phase I Activities and Deliverables

- Establish a project team including proven expertise in metabolomics analytical technologies, epidemiology, biostatistics/bioinformatics, and computer technology. Additionally, a team including expertise in biochemistry/clinical chemistry is preferred.
- Develop bioinformatic methods for metabolite data integration for identified metabolites across data inputs from diverse laboratory platforms and at least two analytical technologies (preferably liquid-chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), and/or NMR).
- Participate in the development of a collaboration agreement between the offeror, NCI, and NCI-identified third party sources to access relevant input data types for the proposed project. NCI staff will work with established cohort studies and consortia to provide metabolomics data (identified metabolite data) to successful offerors.
- Develop database formats that support the import and export of individual datasets and “combined” datasets, store structured data from different sources of metabolite data, and are readily used for data integration and QC protocols.
 - Finalize database formats and structure, data collection, transport and importation methods for targeted Phase I data inputs.
- Provide wireframes and user workflows for the proposed Graphical User Interface (GUI) and software functions that:
 - Support the import and export of individual datasets and “combined” datasets;
 - Implement, script or automate all features and functions of the data integration tool(s);
 - Conduct QC of “combined” datasets.
- Provide a report including a detailed description and/or technical documentation of the following:

- Specific approach to metabolite data integration;
- Specific approach to QC;
- Data standards for transfer and importation of individual metabolite data and storage of individual and “combined” metabolite data;
- Data visualization, feedback, and reporting systems for individual and “combined” metabolite data;
- Technology compatibility matrix for Phase I and Phase II metabolomics data sources by laboratory platform, analytical technology, and identified metabolites (Phase I) / unidentified metabolite peaks (Phase II).
- Software tool(s);
- Transparent, documented, and non-proprietary bioinformatic methods; and
- Description of additional software and hardware required for use of the tool.
- Finalized database formats and structure, data collection, transport, and importation methods for targeted data inputs; and
- Funds in budget to present Phase I findings and demonstrate the wireframes and user workflows for the GUI and software functions to an NCI evaluation panel.
- Develop functional prototype software that integrates data from planned Phase I technology compatibility matrix data sources using automated algorithms and methods.
- Include funds in the Phase I budget to present project deliverable and the prototype software tools to an NCI panel for evaluation.

Phase II Activities and Deliverables

- Expand the bioinformatic methods to include unidentified metabolite peaks, in addition to identified metabolite data, and demonstrate metabolite data integration across data inputs from diverse laboratory platforms and at least two analytical technologies (preferably liquid-chromatography-mass spectrometry (LC-MS), gas chromatography-mass spectrometry (GC-MS), and/or NMR).
- Participate in the development of a collaboration agreement between the offeror, NCI, and NCI-identified third party sources to access relevant input data types for the proposed project. NCI staff will work with established cohort studies and consortia to provide metabolomics data (identified metabolites and unidentified peak data) to successful offerors that would serve to: 1) train and validate the expanded bioinformatic methods; and 2) demonstrate the application of these methods through scalable software to automate complex data integration tasks for metabolomics data sources.
- Demonstrate usability of scalable software through the following:
 - Beta-test and finalize automated file transfer, database importation protocols, metabolite data integration applications and reporting tools developed in Phase I
 - Develop beta-test, finalize, and demonstrate the GUI
 - Demonstrate the software systems ability to integrate data from planned Phase II technology compatibility matrix data sources using automated algorithms and analytic methods
- Conduct usability testing of the GUI elements of the metabolite data integration tool(s).
- Develop systems documentation where applicable to support the software and bioinformatic methods.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

342 Validation of Mobile Technologies for Clinical Assessment, Monitoring & Intervention

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II proposals will be accepted.)

Phase I proposals will not be accepted. Only Direct to Phase II proposals will be accepted. Only a small business concern that has already performed Phase I stage-type research through other funding sources may submit a proposal under this topic.

Number of anticipated awards: 2-3

Budget (total costs, per award): Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Mobile health technologies have grown exponentially in the past few years. The ubiquity of mobile phone use provides a platform for health assessment, monitoring and interventions previously unavailable to health research and clinical practice. The penetration of mobile phone use, even in remote areas, provides a vehicle for health care delivery to individuals with limited access to care. Wireless sensor technologies have also rapidly expanded in availability and function in the past few years. When paired with mobile devices, these sensor technologies provide real-time data on a variety of image-based, physiological, behavioral, or environmental variables.

The range of health research and clinical practice affected by this technology revolution is quite broad. Preventive health assessment and intervention applications for cancer associated behavioral risk factors have increased dramatically. Mobile technologies have been developed for medical screening and diagnostic purposes, providing low cost and portable diagnostic tools for use in rural and underserved settings. Mobile technologies have also been used to support cancer survivorship care and improve chronic disease management for cancer risk factors such as obesity and diabetes, allowing healthcare providers to more intensively monitor patient status and intervene as needed while providing patients a resource to more effectively self-manage their disease.

The NCI Division of Cancer Control and Population Sciences aims to reduce risk, incidence, and deaths from cancer, as well as enhance the quality of life for cancer survivors. Emerging mobile technologies provide an opportunity to support innovation and progress towards NCI's mission of cancer prevention & control by 1) improving quality or access & reducing cost or burden of screening, diagnostic, treatment and follow-up care for cancer and associated chronic diseases; and 2) improving lifestyle intervention efficacy and scalability for cancer related behavioral risk factors. The number of mobile and wireless health tools grows each year, but the majority of these tools have been inadequately validated in clinical research and practice. Adoption of these technologies in support of cancer treatment and survivorship requires more evaluation in clinical and behavioral settings. This topic is not intended to support new technology development, but instead to clinically validate promising but insufficiently tested tools for cancer prevention & control.

Project Goals

The purpose of this topic is to support validation of mobile technologies for clinical assessment, screening, diagnostics, monitoring or intervention delivery focused on cancer prevention, and control objectives. Examples of technologies may include monitoring or diagnostic sensors & paired smartphone applications, cancer treatment or survivor care planning & remote monitoring systems, behavioral analytics and decision support systems, or intervention delivery systems. In the short term, the topic aims to develop research evidence to support adoption of innovative mobile technologies which support cancer prevention, treatment, disease management, or survivorship. Longer term goals are the integration of these technologies in clinical assessment, care & intervention delivery within health systems, accountable care organizations (ACO), and health research.

Within the context of this topic, "mobile" health technologies are defined broadly to include any health technologies that wirelessly transmit data and that are intended for portable use. The early focus of these technologies has primarily been devices worn on or carried by the individual throughout the day. However, devices that provide a level of portability not previously available (e.g. smaller and more portable version of a diagnostic scanner that transmits data wirelessly to the healthcare provider) is consistent with the scope of this initiative.

As noted previously, this topic is not intended to support the development of new technologies. Some additional programming may be required to customize or integrate the technology into the target clinical, health system, or related software environments, but these efforts should be sufficiently limited to retain a focus on validation and expanded evidence of commercial potential and value for health assessment or outcomes.

Responses to this topic are expected to address one or more of the following areas of mobile/wireless health research;

- 1) Evaluation of the reliability of mobile screening, diagnostic, assessment or monitoring technologies & methods
- 2) Evaluation of the validity of mobile screening, diagnostic, assessment or monitoring technologies & methods
- 3) Evaluation of the efficacy and effectiveness of mobile technology and systems for behavioral analytics, clinical decision support, or intervention delivery.

Although extension of existing usability, acceptability, and feasibility of the mobile/wireless health tool may be considered as secondary research questions, they should not be the primary objectives of applications in response to this topic.

This topic will prioritize research that will rapidly validate existing mobile technologies in clinical care & monitoring, clinical decision support or intervention applications. It is anticipated that the clinical screening, diagnostic, assessment, and monitoring technologies will provide the "gold standard" comparator for the new mobile or wireless tool being evaluated, but additional clinical measures may be needed to validate the new tool. However, in some instances, novel measures may not directly translate to existing clinical "gold standard" measures/technologies, and alternative validation approaches may be required. Validation analyses could include but are not limited to agreement rates, sensitivity/specificity, and receiver operating curves (ROC). Research evaluating the reliability of the technology is consistent with this topic. For outcome monitoring purposes, assessment of sensitivity to change are also consistent with this topic.

- Validation of mobile technologies and systems for intervention delivery or decision support are particularly encouraged. Dependent on the research question and technology under evaluation, research designs may include randomized controlled trials (RCTs), series of single case designs, optimization designs (e.g. factorial, sequential) or quasi-experimental approaches such as interrupted time series and stepped-wedge designs. Projects that integrate and automate ongoing validation and/or outcomes evaluation (e.g. automated RCTs) in the commercial product are particularly encouraged. For additional information on evaluation of mHealth technologies please see ([http://www.ajpmonline.org/article/S0749-3797\(13\)00277-8/abstract](http://www.ajpmonline.org/article/S0749-3797(13)00277-8/abstract)). Primary clinical or behavioral outcomes may be supplemented with cost-effectiveness analyses where appropriate.

Milestones for Direct-to-Phase II Technologies

All proposals submitted under this topic must provide evidence that specific mobile technology or systems development milestones have been achieved to demonstrate readiness for a Direct-to-Phase II contract. These milestones will be evaluated in addition to standard review criteria for all submissions.

1. Provide evidence that a working prototype, including all major functional components of the technology, is ready for formal validation in Phase II with minimal further development other than that required to perform the validation or outcomes research.
 - a. Products in beta version are particularly appropriate for this effort although recently released commercial products that do not have adequate validity or efficacy support are also encouraged.
2. Provide documentation that the product to be evaluated has been developed based on theory and/or empirical evidence.
3. Present evidence that appropriate focus groups, interviews, cognitive or user testing with potential end-

users of the device/software tool, etc. have been conducted to demonstrate that the feasibility, acceptability, and usability of the product have been established.

4. Provide evidence that an established project team with appropriate expertise for the scope of work is in place to advise and support the small business on Phase II activities and outcomes. This team should include, but will not be limited to, personnel with training and research experience in clinical or intervention design, implementation, and statistical methods for validation/evaluation as appropriate for the proposed project.

Phase II Activities and Deliverables

- Provide documentation that the established project team with appropriate expertise for the scope of work is in place to advise and support the small business on Phase II activities and outcomes. This team should include, but will not be limited to, personnel with training & research experience in clinical trial or intervention design, implementation, and statistical methods for validation/evaluation as appropriate for the proposed project. Provide a report outlining team member credentials, specific project roles, and timelines for performance.
- Evaluate specific IT customization requirements to support hardware, software, or communications system integration of the technology into the target clinical, health system or service, or other relevant software environment in preparation for validation. Provide a report documenting the specific IT customization requirements and timelines for implementation.
- Evaluate, enhance as necessary and provide documentation that the technology and communications systems maintain compliance with HIPAA, data security, privacy, and consent management protocols as required for the proposed solution.
- Evaluate, enhance as necessary, and provide documentation that data systems, APIs & wireless transmissions for all clinical, laboratory, or behavioral measures sent or received adhere to common data elements standards (e.g. HL7, SNOMED, LOINC, etc.) where available to facilitate data sharing and system integration.
- Evaluate, enhance as necessary, and provide a report detailing communication systems architecture and capability for data reporting to patients/subjects, care providers, clinicians/researchers, electronic medical records, and health surveillance systems as appropriate for the proposed technology solution.
- Test the integration of the technology into the target clinical, health system or service, or other relevant software environment in preparation for validation. Provide a report documenting the results of system testing and timelines for problem mitigation.
- Develop user support documentation to support all applicable potential users of the technology, including but not limited to patients/consumers, family/caregivers, and providers. Provide a report documenting user support resources, including but not limited to, links to online resources and copies of electronic or paper user support resources as appropriate.
- Prior to evaluation, provide a final report of the research plan including at a minimum
 - Appropriate human subjects protection / IRB submission packages and documentation of approval for your research plan.
 - Final study design including aims, participant characteristics, recruiting plans, inclusion and exclusion criteria, measures, primary and secondary endpoints, design and comparison conditions (if appropriate), power analyses and sample size, and data analysis plan.
 - Publication plan outlining potential research and whitepaper publications resulting from the research, including anticipated lead and co-author lists.
- Provide study progress reports quarterly, documenting recruitment and enrollment, retention, data QA/QC measure, and relevant study specific milestones.
- Prepare a tutorial session for presentation at NCI and/or via webinars describing and illustrating the technology and intended use.
- Include funds in budget to present Phase II findings and demonstrate the technology to an NCI evaluation panel.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.

In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

343 An Electronic Platform for Cognitive Assessment in Cancer Patients

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1 – 3

Budget (total costs, per award): Phase I: up to \$225,000 for up to 9 months

Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Persistent cognitive deficits are a frequent complaint of the increasing population of cancer survivors, particularly those who have undergone chemotherapy. Cancer patients experience both acute and chronic cognitive effects during both the treatment and survivorship phases of the cancer control continuum. One significant barrier to assessing cognitive symptoms in cancer populations is the inability to administer a brief, scientifically valid cognitive battery, either remotely or within a clinical visit.

The current gold standard in the field is standardized neuropsychological tests. These tests were devised for the purpose of diagnosing severe and focal cognitive impairments, such as stroke, and present consistent research challenges. First, they lack sensitivity to less severe, but still debilitating cognitive impairments such as those observed in chemotherapy patients. Second, they lack specificity; it is difficult to tell which cognitive function is responsible for poor performance. Third, they lack repeatability; tests were designed for a single diagnostic administration, and thus it is difficult or impossible to administer the same test multiple times over the course of a treatment protocol. Fourth, most such tests were originally devised decades ago and thus make no contact with the considerable advances in cognitive and neuro-scientific theory over the last thirty years. Fifth, a trained neuropsychologist must be on site to administer the test, pushing up the costs of research and limiting use in the clinical oncology setting. Therefore, there is a substantial unmet need for a suite of computerized cognitive tests, based on contemporary cognitive psychology and neuroscience research, designed for repeated testing, that could be easily administered remotely.

Project Goals

The goal of this project is to develop a scalable, secure, and privacy-compliant software system, and tools to support computerized administration of brief cognitive assessments specifically focused on measuring the subtle cognitive changes associated with cancer and cancer treatment.

The software system must support assessments of basic cognitive processes that are repeatable and can be remotely administered across diverse settings (i.e., clinic or home) using multiple technology platforms (i.e., PC, tablet, smartphone). In addition, the system must support provider/researcher portal functionality for patient management functions including (but not limited to) adding patients, ordering and scheduling assessments, automated scoring, visualization and triage of results, and standards based data reporting to third party systems. Where appropriate and relevant for project goals, the software system should integrate measures available via third party systems such as PROMIS, NIH Toolbox, and NeuroQOL rather than validate duplicative resources.

In Phase I, offerors will establish a multidisciplinary team for validation/evaluation of the proposed platform, provide documentation that appropriate software-based assessments have been developed, as well scoring protocols in the minimum specified cognitive domains. A report providing a detailed description, visual design, and technical documentation will be required, as well as a functional prototype. Phase I will also include client side user testing. Lastly, documentation detailing output reporting systems feasibility will be included in the demonstration of the final prototype to an NCI evaluation panel via webinar. In Phase II, offerors will evaluate specific IT customization requirements, test and finalize client, server, and data systems, including technical documentation for the software

systems application programming interface. Usability testing and support documentation will be provided, and submission of a research plan and presentation to NCI will be delivered via webinars.

The short term goal of this topic is to

- 1) Develop innovative software systems which support brief, remotely administered patient assessments and scoring of cognitive processes affected by cancer and cancer treatment
- 2) Develop paired provider portal tools for remote administration and management of patient assessments and results
- 3) Conduct user testing of the client side assessment tools and modes of administration
- 4) Conduct clinical validation of the cancer cognitive assessment instruments delivered via the software system

Longer term goals include the integration of these software tools in clinical assessment and monitoring in both oncology research and care settings, with the eventual goal of embedding assessment results into electronic medical records used in health systems and accountable care organizations (ACO).

This topic aims to support customized development and/or integration of information technology into the cognitive assessment process. The primary focus will be brief administration and scoring of assessments of cognitive processes affected by cancer and cancer treatments. Minimum cognitive domains to be assessed include: Attention, executive function, working memory, verbal abilities, visuospatial ability, motor function, and processing speed.

In addition to technical development, this topic is intended to support validation (e.g., efficacy and/or effectiveness) of the assessment battery, specifically with respect to reliably detecting cognitive changes in cancer populations.

Phase I Activities and Deliverables

- Establish a project team including personnel with training and research experience in cognitive psychology, neuroscience and/or neuropsychology, clinical oncology, implementation, and statistical methods for validation/evaluation as appropriate for the proposed technology platform.
- In addition, technical personnel should have experience in Health IT software standards (i.e., privacy, security, health data exchange protocols, etc.), electronic health records, cross platform client side software development, scalable server side software development, data visualization, and systems architecture that will effectively address all objectives of the current topic.
- Provide documentation that software-based assessments have been developed based on current cognitive and neuroscience findings and evidence.
- Provide a report including detailed description of proposed assessments (including relevant modification for electronic administration) and scoring protocols planned for Phase I and Phase II development. Specifically address the minimum cognitive domains required including: attention, executive function, working memory, verbal abilities, visuospatial ability, motor function, and processing speed. In addition, patient reported cognitive complaints will need to be included.
- Provide documentation that planned software-based assessments have been developed based on current cognitive and neuroscience findings and evidence.
- Provide a report including detailed description, visual design, and/or technical documentation of the proposed:
 - Database structure and data models for the proposed cognitive assessments, as well as system metadata requirements
 - Client side graphical user interface and user experience
 - Provider side graphical user interface and user experience
 - Data standards for capture, transport, importation, and storage of data between client, server, and third party application as applicable
 - Data visualization, feedback, or reporting systems, as required for target clinical monitoring and/or

- research applications
 - Systems architecture for implementation of scalable software, as required based on development and commercialization targets.
- Develop a functional prototype system that includes
 - Client software and wireframe user interface to facilitate and control the administration and transport of cognitive assessment and any associated metadata used within the system
 - Server software and wireframe provider portal that supports automated schedule, administration, data scoring, and management of patient assessments and associated metadata
 - Development release of end-to-end software system that connects client and server software & patient or provider portals for administration of planned Phase I assessments.
- Conduct user testing of client side software visual designs (or functional software) and proposed user experience for planned Phase I assessments.
- Provide a report detailing output reporting systems feasibility, proposed timelines, data standards, and communication architecture for reporting summary outputs to patients/subjects, clinicians/researchers, electronic medical records, and health surveillance systems.
- Finalize database formats and structure, data collection, transport, and importation methods for targeted cognitive assessments.
- Present Phase I findings and demonstrate the final prototype to an NCI evaluation panel via webinar

Phase II Activities and Expected Deliverables

- Evaluate specific IT customization requirements to support hardware, software, or communications system integration of the technology (e.g., HL7 compatibility); provide a report documenting the specific IT customization requirements and timeline for implementation.
- Enhance, user test and finalize client side software, patient portals and functionality listed in Phase I
- Enhance, user test and finalize server side software, provider portals and functionality listed in Phase I
- Enhance, beta test and finalize data visualization, feedback and reported systems listed in Phase I.
- Provide a report including technical documentation for the software systems application programming interface (API) for interaction with third party data systems.
- Conduct usability testing of
 - Consumer/patient facing portals or mobile applications
 - Care team/researcher facing portals or mobile applications
- Develop user support documentation for all applicable potential users of the technology, including but not limited to patients/consumers and providers. Provide a report documenting user support resources, including links to online resources and/or copies of electronic or paper user support resources as appropriate.
- Prior to evaluation/validation of software-based cognitive assessments, provide a final report of the research plan including at a minimum
 - Appropriate human subjects protection/IRB submission packages, and documentation of approval for your research plan.
 - Final study design including aims, participant characteristics, recruiting plans, inclusion and exclusion criteria, measures, design and comparison conditions (if appropriate), power analyses and sample size, and data analysis plan.
 - Publication plan outlining potential research manuscripts and whitepaper publications resulting from the research.
- Prepare a tutorial session for presentation to NCI via webinars describing and illustrating the technology and intended use.
- In the first year of the contract, provide the program and contract officers with a letter(s) of commercial interest.
- In the second year of the contract, provide the program and contract officers with a letter(s) of commercial commitment.

344 Technologies for Differential Isolation of Exosomes and Oncosomes

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning.

Number of anticipated awards: 2 – 3

Budget (total costs, per award): Phase I: up to \$300,000 for up to 9 months
Phase II: up to \$3,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Both normal and cancer tissues shed exosomes and other vesicles into body fluids. Tissue-shed exosomes are found in several body fluids including amniotic fluid, breast milk, bronchoalveolar fluid, cerebrospinal fluid, malignant ascites, plasma, saliva and urine. Exosomes collected from the blood and other body fluids of patients diagnosed with various cancers were shown to contain tumor suppressors, phosphoproteins, proteases, growth factors, bioactive lipids, mutant oncoproteins, oncogenic transcripts, microRNA and genomic DNA fragments. Exosomal trafficking and reciprocal exchange of molecular information among different organs and cell types were reported to contribute to cell-to-cell communication, horizontal cellular transformation, cellular reprogramming, functional alterations, regulation of immune response, and metastasis. In functional studies, exosomes shed by tumors, referred to as oncosomes, were reported to activate normal epithelial cells to form tumors, while exosomes from healthy individuals appear to have anti-tumor characteristics. Comparative molecular profiling of normal tissue-derived exosomes and tumor-derived oncosomes in blood and other body fluids may therefore offer a non-invasive or minimally invasive way to assess carcinogenesis; cancer risk; tumor initiation, promotion, development and progression, metastasis in tissues; survival and treatment response, and the knowledge gained may lead to better cancer prevention/care/control. The major bottleneck for using oncosomes in cancer research or clinical care is in obtaining enriched preparations of oncosomes from body fluids. Existing technologies are based on centrifugation, precipitation/centrifugation or affinity purification, which are labor intensive, time consuming, or biased because they are based on known exosomal markers. Furthermore, existing approaches impose significant stresses on these vesicles and potentially compromise their biological integrity and viability for various downstream uses. Therefore, the goal of this proposal is to accelerate the development of technologies for differential isolation and enrichment of tissue-derived exosomes and tumor-derived oncosomes which will be useful for comparative molecular profiling or therapeutic purposes. Given the potential of exosomes and oncosomes for basic research and clinical applications, proposed technology platforms should be capable of processing a large number of samples each with significant volumes and be useful for profiling multiple body fluids from multiple cancer types. Of further interest are technology proposals amenable to low-cost production, appropriate for handling large number of samples, and useful for profiling multiple body fluids from multiple cancer types to conduct molecular analysis studies in population science.

The biospecimen sources for exosomes or oncosomes isolation and enrichment can be blood, plasma, serum, urine, saliva, amniotic fluid, breast milk, bronchoalveolar lavage, cerebrospinal fluid, peritoneal fluid, malignant ascites or other types of body fluids or effusions. In Phase I, the technology development should focus on isolation and enrichment and obtaining distinct preparations of exosomes and oncosomes. In Phase II, the focus should be adopting the technology developed in phase I to isolating and enriching exosomes and oncosomes from multiple body fluids in multiple cancer types.

Project Goals

The goal of this contract proposal is 1) to support the development of large scale (capable of handling a large volume of a body fluid) or high-throughput (capable of isolating and exosomes or oncosomes from large number of samples

in a finite time) technologies for differential isolation of tissue-specific exosomes and tumor-derived oncosomes from any body fluid(s), and 2) to obtain enriched, distinct preparations useful for downstream comparative molecular profiling or therapeutic use. Applicants must propose to develop an efficient and cost effective platform for complete isolation and segregation of extracellular vesicle populations, with particular emphasis on yielding pure exosome or oncosome populations that are morphologically and functionally intact. The technology should preferably establish automated workflows and reduce human intervention to obtain enriched distinct preparations of exosomes and oncosomes.

To apply for this topic, offerors should have a proof-of-concept prototype platform with demonstrated capability for isolating exosomes from complex solutions. Preference will be given for proposals with demonstrated capability for further isolating oncosomes from the general exosome population. They should demonstrate sufficient expertise and necessary resources for robustly characterizing captured oncosomes, and verifying persistence of their biological integrity.

Applicants are required to obtain distinct preparations of exosomes and oncosomes, which originated in a specific tissue/tumor, from routinely collected fresh or archived body fluids. They should demonstrate integrity, quantity and reproducibility of isolation and separation using physicochemical and functional studies. This solicitation is not intended for developing technologies for molecular profiling exosomal or oncosomal cargo.

Phase I Activities and Deliverables

- Develop a technology for differential isolation of exosomes with highly selective isolation of oncosomes from the exosome population, which originated in a specific tissue, from body fluid(s) collected from cancer patients (e.g., breast, prostate, colon, lung or brain). High-throughput capacity or large scale abilities must be sufficient for adoption in clinical workflows (therefore demonstrate capability for processing at least 50 sample in 8 h or 10 mL of clinical fluid specimen in <1 hour)
- Demonstrate that the technology can obtain distinct preparations of ***exosomes and oncosomes*** from the routinely collected fresh/archived body fluids, and yields sufficient quantity for downstream analysis. Specifically, demonstrate sufficient yield of nucleic acids for NGS/qPCR and proteins for LC-MS/MS
- Preferably establish automated workflows sufficient to allow for minimal training for new users
- Demonstrate that the reproducibility is >90% and yield is >70%
- Demonstrate the integrity of exosomes/oncosomes is >80% using physicochemical methods (Transmission electron microscopy, AFM, dynamic light scattering, immunostaining/immunofluorescence)
- Benchmark the developed technology against at least 2 current techniques (e.g. centrifugation, density gradient, immunocapture, size-based filtration, etc.) and demonstrate comparable purity and yield from clinically appropriate sample sizes for the specific bodily fluid.
- Deliver to NCI the SOPs for exosome/oncosome isolation and the data from physicochemical characterization that demonstrates the quality of the isolated exosomes/oncosomes.

Phase II Activities and Deliverables

- Adapt the technology to multiple body fluids (i.e., stored or freeze thawed) with varying complexity
- Demonstrate that the isolated exosomes/oncosomes are morphologically intact by physicochemical methods (Transmission electron microscopy, AFM, dynamic light scattering, immunostaining/immunofluorescence), and functionally active in *in vitro* systems (transmission of information from exosomes/oncosomes to cells in culture and/or co-culture).
- Develop a production prototype kit/tool/device for the differential isolation of exosomes/oncosomes, and/or established a marketing partnership/alliance with an established strategic partner (e.g. diagnostic or device company)

345 Predictive Biomarkers of Adverse Reactions to Radiation Treatment

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2 – 3

Budget (total costs, per award): Phase I: up to \$300,000 for 6-12 months
Phase II: up to \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Radiotherapy is an important definitive and palliative treatment modality for millions of patients with cancer and is used alone or in combination with drug therapy. However, a variety of patient, tumor, and treatment-related factors will influence its outcome. Significant advances in delivery and distribution of dose for radiotherapy have been made over the years. Currently, treatment decisions in radiotherapy/radiochemotherapy are primarily defined by disease stage, tumor location, treatment volume, and patient co-morbidities, together with general guidelines concerning normal tissue tolerance for surrounding organs. However, treatment planning does not take into account an individual patient's, or a cohort of patients' sensitivities to this important modality of treatment. This is an important limitation in personalized care, as there are known variations in individual patient normal tissue sensitivities to radiation, but treatments are based on population normal tissue complication probabilities. As molecularly targeted therapy is being integrated into radiotherapy and chemotherapy, selecting the "right type of treatment" is critical to improve outcomes.

A substantial number of patients treated with radiotherapy suffer from severe to life-threatening adverse acute effects as well as debilitating late reactions. Acute side effects (e.g. skin reactions, mucositis, etc.) are often dose limiting, but may be reversible in contrast to the late effects such as fibrosis in the lung, telangiectasia, and atrophy, which are irreversible and progressive. A biomarker-based test that can predict the risk of developing severe radiotherapy-related complications will allow delivery of suitable alternative treatments. Such stratification may also allow dose escalation to the tumor in less sensitive patients. However, discovery, development, and validation of predictive biomarkers of radiation hypersensitivity are challenging, particularly due to a low incidence of normal tissue complications in the clinic, the need for long-term studies for predicting late effects, and the combination of chemotherapy with radiation as standard of care for most tumors.

Project Goals

The goal of this contract topic is to identify, develop, and validate a simple, cost-effective biomarker(s) to rapidly assess inter-individual differences in radiation sensitivity and predict early and late complications among patients with cancer prior to radiation therapy.

A predictive biomarker of individual radiation sensitivity can measure any biological changes in response to absorbed ionizing radiation, which is able to predict imminent normal tissue injury prior to radiotherapy and help determine radiotherapy suitability and outcomes. Radiation biomarkers are an emerging and rapidly developing area of research, with potential applications in predicting individual radiosensitivity, predicting severity of normal tissue injury among patients, assessing and monitoring of tumor response to radiation therapy as well as in estimating dose to accidentally radiation-exposed individuals. The purpose of this contract topic is to develop a radiation biomarker(s) to specifically identify and exclude likely "over responders" prior to radiotherapy in order to avoid severe complications and to refer them for alternative treatment modalities.

A variety of radiation biomarkers have already been explored or are currently under development at different technology readiness levels (TRLs) at different government agencies and programs. This contract topic intends to leverage on these advances. These assays include but are not limited to (i) fibroblast clonogenic assay, (ii) measurement of DNA damage foci, (iii) damaged base metabolites, (iv) various types of chromosome aberrations

studied in different phases of cell cycles, serum biomarkers, gene expression changes, (v) protein and microRNA expression changes, (vi) and genetic tests.

To be of practical value in the clinic, where radiation exposures are well-defined in terms of dose, distribution and timing, and thus quite different from radiation accidents, a predictive radiation biomarker of individual radiation sensitivity should be (i) able to predict heterogeneity of radiation responses among patients in clinic, (ii) specific to radiation, (iii) sensitive, (iv) able to show signal persistence as applicable to radiation therapy or have known time-course kinetics of signal, (v) amenable for non-invasive or minimally-invasive sampling, (vi) amenable to automation to improve quality control and assurance, (vii) have a quick turn-around time between sampling and results (though speed is not as critical as in the countermeasures scenarios), (viii) and be cost effective.

This contract topic aims to encourage the development and validation of predictive radiation biomarkers for clinical applications as described above. Both the FDA and the Centers for Medicare and Medicaid Services (CMS) through Clinical Laboratory Improvement Amendment (CLIA) regulate diagnostic tests. A reasonable predictive radiation biomarker development process for identifying likely “over-responders” to radiation treatment may involve biomarker discovery, assay design and validation, determination of assay feasibility, assay optimization and harmonization, assessing the assay performance characteristics (reproducibility, sensitivity, specificity etc.), determining the effect of confounders, if any, determination of suitable assay platforms and platform migration as may often be needed, and clinical validation with a locked-down assay before regulatory submission and commercialization. Early pre-IDE interaction with FDA is therefore critical. The following activities and deliverables are applicable to both biomarkers for acute early effects and surrogate endpoints for late effects.

Phase I Activities and Deliverables

Phase I contract proposals must describe (i) a quantitative estimate of the patient population that will benefit from the availability of such predictive radiation biomarkers for the applicable cancer type/organ site, (ii) a plan for generating evidence that the proposed biomarker or biomarkers are relevant in the prediction of radiation hyper-sensitivity among patients with cancer and logical approach in the developmental pathway to clinic from discovery, (iii) a description of assay characteristics including sensitivity and specificity and the effects of known confounders, if any, (iv) level of technological maturity, describing critical technology elements allowing technology readiness assessment by the reviewers, (v) and a description of the proposed regulatory pathway for approval and pre-IDE consultation with FDA. In such meetings with FDA it is expected that the applicant will invite NCI's participation, where applicable.

Activities and deliverables include the following:

- Discovery and early development
 - Demonstrate biomarker prevalence and utility
 - Develop a working qualitative test correlating the presence or absence of the biomarker(s) with potential outcome or a quantitative assay to assess radiation sensitivity
 - Demonstrate feasibility
- Preclinical development and technical validity
 - Provide assay characteristics, including but not limited to performance, reproducibility, specificity, and sensitivity data using frozen (or other) samples from past clinical trials, or retrospective clinical studies providing adequate power calculations
 - Illustrate the performance of the biomarker(s) with receiver operating characteristic (ROC) data
 - Demonstrate suitability of the test for use in the clinic, including kinetics of biomarker, if transient.
 - Determine the effect of confounders, such as any induction or concurrent chemotherapy regimens.
 - Provide defined metrics for measurements of success
 - Deliver the SOP of the working test or assay to NCI.

- Benchmark the technology against quantitative milestones proposed by offers to measure success
- Provide description of proposed regulatory pathway for approval and pre-IDE consultation with FDA

Phase II Activities and Deliverables

Phase II contract proposals must describe (i) the setting and intended use of the predictive biomarker(s) in retrospective or prospective studies using human tissue samples (frozen or fresh), (ii) a logical approach to regulatory approval, (iii) a description of assay platform and platform migration, if necessary, (iv) a demonstration of clinical utility and clinical validation, (v) a proposed schedule for meeting with FDA regulators regarding approval. In such meetings with FDA it is expected that the applicant will invite NCI's participation, where applicable.

Activities and deliverables include the following:

- Provide a schedule of proposed meetings with FDA regarding approval
- Early-trial development
 - Retrospective tests using archived, frozen samples from past clinical trials, or prospective trials using fresh human samples.
- Full development
 - Demonstrate clinical utility
 - Demonstrate clinical validity in a large prospective randomized clinical trial

346 *Molecularly Targeted Radiation Therapy for Cancer Treatment*

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2 – 3

Budget (total costs, per award): Phase I: up to \$300,000 for up to 9 months
 Phase II: up to \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Targeted radionuclide therapy (TRT) enables personalized cancer treatment by combining the therapeutic effect of radiation therapy with the targeting capability of molecular therapies. In TRT, a cytotoxic dose of a radioactive isotope is attached to monoclonal antibodies, receptor ligands, or synthetic molecules that target malignant tumor cells selectively. The ability of these molecules to bind specifically to a tumor-associated structure ensures that the tumor gets a lethal dose of radiation, while normal tissue gets only a minimal dose. This minimizes toxicity to normal tissues and can increase therapeutic efficacy (therapeutic index) leading to a reduction of overall treatment costs.

Currently available TRT compounds such as Zevalin and Bexxar have been developed and approved in the United States for use in the treatment of non Hodgkins Lymphoma (NHL). Although these drugs have shown a response rate of approximately 80%, they have failed to show a survival advantage in patients. Large multicenter trials to study long- term survival are currently underway. Because these drugs have had modest commercial success to date, private investment in molecularly-targeted radiation pharmaceuticals remains at low levels. As this class of

treatments shows tremendous clinical potential, there is a need to encourage the development of next-generation technologies (see below) for cancers other than NHL, including solid tumors, where the clinical need is most acute.

Project Goals

This contract solicitation seeks to stimulate research, development, and commercialization of innovative TRT techniques that could potentially shorten treatment cycles and reduce toxicity to normal tissues. Proposals addressing the following technology areas are encouraged: new treatment strategies; design, synthesis and evaluation of innovative ligands and radiotracers for TRT; novel radioisotope generators and radioisotope production techniques; dosimetry techniques; and new conjugation chemistries that can link the radioisotopes to targeting agents other than antibodies (e.g. existing small molecule chemotherapeutic drugs) are also encouraged.

The short-term goal of the project is to perform feasibility studies for development and use of possible radioimmunotherapeutics for the treatment of cancer. The long-term goal of the project is to enable a small business to bring a fully developed TRT compound to the clinic and eventually to the market.

Phase I Activities and Deliverables

Phase I activities should support the technical feasibility of the innovative approach. Specific activities and deliverables during Phase I should include:

- Proof-of-concept of the conjugation or attachment of the radioisotope to the antibody or other targeting moiety.
- Radiation dosimetry studies in an appropriate small animal model
- Proof-of-concept small animal studies demonstrating an improved therapeutic efficacy and improved therapeutic index, assessment of toxicity to normal tissues, and pharmacokinetic/pharmacodynamic studies utilizing an appropriate animal model.

Phase II Activities and Deliverables

Where cooperation of other vendors or collaborators is critical for implementation of proposed technology, the offeror should provide evidence of such cooperation (through written partnering agreements, or letters of intent to enter into such agreements) as part of the Phase II proposal.

Specific activities and deliverables during Phase II should include:

- Demonstration of the TRT manufacturing and scale-up scheme
- IND-enabling studies, preferably in consultation with FDA, carried out in a suitable pre-clinical environment.
- When appropriate, demonstration of similar or higher specificity and sensitivity of the technology when compared to other technologies.
- Offerors are encouraged to demonstrate knowledge of appropriate FDA regulations and strategies for securing insurance reimbursement.

347 Signal Amplification to Enable Attomolar Quantitation in Slide-Based or ELISA Biomarker Immunoassays

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2-3

Budget (total costs, per award): Phase I: up to \$225,000 for up to 6 months

Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Accurate detection of specific markers is crucial for the diagnosis of malignant disease, monitoring drug therapy and patient screening. The development of sensitive and reliable strategies for the detection of biomarkers at ultra-low concentration is of particular importance to cancer medicine. Efforts have been made to develop techniques for the amplification of signals, but there is still a paucity of novel approaches used specifically to improve the simplicity, selectivity and sensitivity of cancer biomarker assays, especially for the interrogation of tumor tissue.

The current work focus of this SBIR topic is for incorporation of an existing or novel signal amplification system into high value cancer biomarker antibody based assays (ELISA type or slide-based IFA/IHC) to enable an increase in accuracy and sensitivity (at least 100-fold) for detection of the specific analyte at the lowest possible concentration level. Detection at attomolar/sub-femtomolar concentrations is desired. These assays must be optimized for performance on tumor tissues and tissue extracts, which requires a fundamentally different approach than those commonly used for high-sensitivity serum assays already in use in the field.









In vitro immunoassays are probably the most common, simple and relatively inexpensive methods used in clinical laboratories for the diagnosis and management of disease. Despite continued efforts to improve the performance of immunoassays, there is an urgent need for assays with increased sensitivity (i.e., attomolar sensitivity) and accuracy for detection of low-level disease markers specifically in tumor tissue.

There are many amplification systems that have been published in the past 10-15 year but most have limited effect, demonstrating improved sensitivity < 10 fold, and have not been widely adopted in the clinical lab. One issue is low signal-to-noise ratio; noise often increases with signal amplification. There is a big technological gap as we learn more and more about signaling molecules in cancer; many are tightly regulated with low levels of protein expression. Simply put, the existing assays are not of sufficient sensitivity to detect low abundance biomarkers. Finally, the most commonly requested utility for these existing assays is on serum or cell line lysates, not solid tumor tissues. There is a great need for the development of highly sensitive/specific antibody based assays that can detect analytes in tumor lysates (ELISA) and in tumor tissue sections (IFA/IHC).

The current techniques used in molecular tag detection assays use radiolabels, electrical, light scattering, fluorescent, and chemiluminescent molecules—see table below. Most of the commercially available labels have inherent limitations in signal strength. These assay limitations lead to numerous drawbacks in our ability to measure low abundant biomarkers to improve the clinical care of the patient – to include:

- The assay is limited (i.e., the sensitivity of an assay is not sufficient to detect biomarkers in majority of clinical specimens) to the measurements of biomolecules in clinical situations where they are present in high abundance (e.g., protein overexpression or high gene copy number)
- The assays can only be applied to biological samples where biomolecules are more abundant such as tumor tissue, but not to more easily obtained non-invasive specimens, such as blood, where the biomolecules are often present but in extremely low- abundance.
- The current lower sensitivity of antibody based assays limits detection of many signaling molecules, and where they can be detected, often it will not be possible to detect a drug-mediated decrease in the signal (e.g., for pharmacodynamics [PD] applications).
- If the biomarker is of low abundance, then the reliable measurement via an ELISA assay requires the consumption of large amounts of biological samples (e.g., tumor needle biopsies) to bring up the protein level high enough to quantitate biomarkers at the limits of detection (i.e., in the process, large amount of precious tumor biopsy is lost to further molecular analyses) .

Table 1 | Detection of protein biomolecules

Tool or technique	Read-out	Illustration	Detection limit*	Molecules per drop (60 μ l)	In clinical use
Colorimetry	Visual		150 pM	10^9	Yes
Carbon nanotubes	Electrical		100 pM	10^9	No
Chemi-luminescence	Luminescence		30 pM	10^9	Yes
ELISA	Luminescence		1-10 pM	10^7	Yes
Quantum dots	Fluorescence		500 fM	10^7	No
Silicon nanowires	Electrical		1 fM	10^4	No
Metal nano-particles	Scanometric and/or light (bio-barcode)		30 aM	900	Yes
Immuno-PCR	Fluorescence		20 aM	700	Yes

*Detection limits are best-case examples from the literature and can vary substantially depending on the target and the assay conditions.

*David A. Giljohann & Chad A. Mirkin. *Nature* 462, 461-464, 2009

Recently, a few new technologies have been described in the literature that is reported to achieve 10^2 - 10^6 fold improvement in signal strength. Many of the technologies bring together large aggregates of immune complexes to produce amplified detection signals several magnitudes greater than reagents in which unitary labels are coupled directly to the secondary antigen or antibody without using multi-label scaffolds. A short description of some of the more promising technologies is listed below with greater details found in Appendix A. These technologies described below are representative, but not exclusive; offerors are welcome to propose solution technologies not listed below, provided they address the aims of this solicitation.

Plasmonic absorbers, especially in the infrared (IR) range, have potential applications for biochemical sensing, imaging, energy conversion, and other medical diagnostics. One technology referred to as “Nanobar shaped disk-coupled dots-on-pillar antenna-array” (Bar-D2PA) claims up to 1 million fold improvement of immune sensitivity. – see [DocLINK](#). The D2PA is composed of an array of dense three-dimensional nanoantennas that can be layered with immunological reagents to create a specific assay. The benefits of the bar-D2PA technology are:

- (a) low manufacturing costs;
- (b) multiple identifying resonance peaks;
- (c) tunable transmission with high absorption; and
- (d) high-field regional cross-section for analyte detection. The bar-D2PA structure shows unique mid-IR light response with polarization-dependent plasmonic resonances.

Nanoparticle-based bio-bar codes for the ultrasensitive detection of proteins have attomolar sensitivity. This ultrasensitive method for detecting protein analytes is referred to as the bio-barcode method and has been shown to amplify the signal from extremely low levels of protein or oligonucleotide in solution as published by Mirkin and colleagues ([Nam et al., 2003](#)). The principle is to get low-abundant proteins to bind to particles containing a target specific antibody – this particle is also tagged with thousands of identical single strands of DNA to the target analyte gene which is used to amplify the signal. A magnetic particle tagged with another analyte specific antibody

(different epitope) pulls the analyte-particle complex out of solution, and the DNA is separated from the captured particle and quantified.

Another approach of amplification technology is 3DNA® developed by Genisphere which is a 3-dimensional structure made entirely out of DNA. For many applications, a four-layer arrangement is used, which has an average of 280 +/- 20 arms per molecule. The arms are modified with labels and targeting moieties. As examples, the labels can be fluorescent, enzymatic (HRP, AP), nanogold, or a hapten (biotin, FITC, DIG); and the targeting moiety may be an antibody, peptide, specified RNA/DNA sequence, aptamer, PNA, or a hapten (biotin, FITC, DIG). Mixing and matching a variety of labels and targets on the same 3DNA core creates a highly customized reagent. Genisphere's 3DNA technology has been used to improve the limit of detection by up to 100-fold in a variety of assay platforms, including microarray, ELISA, bead-based flow cytometry, and lateral flow.

Another novel signal amplification strategy in lateral flow immunoassay (LFIA) utilizes three amplification steps: (a) biotin-streptavidin amplification; (b) polylysine amplification; and (c) fluorescence dye signal amplification. The resulting conjugates achieved a detection limit 100-fold lower than that of the magnetic beads-based ELISA and gold-based LFIA.

The Enzyme-cascade-amplification strategy (ECAS-CIA) allows detection of low-abundance proteins by coupling with enzyme cascade amplification strategy ([DocLINK](#)). In the presence of target analyte, the labeled alkaline phosphatase on secondary antibody catalyzes the formation of palladium nanostructures, which catalyze 3,3',5,5'-tetramethylbenzidine-H₂O₂ system to produce the colored products, thus resulting in the signal cascade amplification.

It is believed that these technologies and other new technologies could have broad applicability to improving the sensitivity of ELISA and slide-based immunoassays for target proteins as well as for nucleic acid detection assay platforms. However, most of these reagents and associated instrumentations are not commercially available to laboratory researcher or adapted to clinical quality assays.

References:

David A. Giljohann & Chad A. Mirkin *Nature* 462, 461-464, 2009

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Enhanced Colorimetric Immunoassay Accompanying with Enzyme Cascade Amplification Strategy for Ultrasensitive Detection of Low-Abundance Protein Zhuangqiang Gao,1, Li Hou,1, Mingdi Xu1, & Dianping Tang1, *Scientific Reports*4, Article number:3966 Volume

Project Goals

With rapid advances in biomedical research and the growing biotechnology industry, development of highly sensitive and economical assays will meet an unmet need and serve to promote the use of biomarkers in the personalized care of patients. These enhanced detection technologies can also be directed towards designing fully automated, highly sensitive assays to identify multiple disease markers in a single clinical specimen using multiple assay platforms and to improve the amount of molecular information that a clinician obtains for more precise care of the cancer patients.

The increasing demand for screening assays at the early stage of disease development and from minimally-sized specimens calls for ultrasensitive detection of biologically relevant biomarkers at an extremely low level of expression. To keep pace with expectations in clinical assays, there is still the quest for more flexible, yet highly sensitive, quantitative, and easy-to-use methods. This SBIR topic is to support assay development that pushes the level of analyte detection to the absolute maximum.

The **goal** of this SBIR topic is to incorporate recent advances in signal amplification methods into the development of quantitative ELISA and/or slide-based antibody assays (IFA/IHC) to low abundance but high value cancer biomarkers. The amplification system could be chemical, bio-chemical, nano-particle, or any other component based. The desired aim is to improve the sensitivity of an assay by at least 100-fold and preferably thousand-fold. Demonstrating the diagnostic potential of existing or novel amplification systems (i.e., platform, tagging, enrichment) in antibody based assays to protein analytes will provide the foundation for their use in other molecular assays (FISH, RNA in situ, etc) – i.e. this SBIR will support a significant technological advance in molecular test development in general by promoting the integration of emerging technology into the diagnostic paradigm.

There are two objectives:

Objective 1. Select an appropriate signal enhancing system to improve the signal strength /sensitivity of an ELISA or slide-based antibody assays (IFA/IHC) using tumor tissue by 10^2 - 10^6 fold (preferably at attomolar levels) for two high value cancer biomarkers, preferably a NCI designated target listed below .

BIOMARKER	ASSAY TYPE
MET	N-Terminal or C-Terminal non-phosphorylated epitopes and coupled with specific phosphorylated sites (pY1234/pY1235, pY1235, pY1236, pY1349 or pS1009)
ERK	ERK1 and ERK2 specific epitopes and phosphorylated sites (ERK1-pY202pT204, and ERK2-pY185pT187)
AKT	AKT 1, 2, & 3 specific epitopes and phosphorylated sites (pT308 or pS473)
Apoptosis Biomarkers	Bim
HIF1 alpha	Use the polyclonal/monoclonal provided in the DUOSet IC ELISA Kit, for detection of human/mouse total HIF-1 alpha (R&D Systems, Inc., Cat#: DYC1935-5 or DYC1935E)

NCI may advise on the appropriate assay reagents and non-clinical models. In special cases, NCI may provide reagents to selected PD biomarkers and/or the associated xenograft tumors or cell line models to awardees.

Objective 2. The enhanced sensitivity system must maintain the integrity of ELISA and/or slide-based antibody assay designs and be easily adaptable to widely used formats/platforms in clinical laboratories (i.e., 96 well

microtiter plate assay, detection instrumentation, bead based detection, automated slide strainers, fluorescent microscopes, etc.).

Phase I Activities and Deliverables

- The amplification technology must provide a significant improvement in assay sensitivity (10^2 - 10^6 fold) to high value low abundant cancer biomarkers using tumor tissue. Two assays are to be developed with the new amplification system.
- The amplification technology must be consistently manufacturable, and if new instrumentation is required, size and cost of prototype instrumentation should be within reach of a clinical lab.
- Any alteration in the assay design or assay protocol as an attempt to increase the sensitivity of the assay constitutes a critical issue and introduces bias resulting from the changes made. The assay design must be adjusted to optimize the analytic performance of the assay for clinical utility while ensuring analytic validity using proper controls to minimize false results. Suggested activities to test for optimal assay performance are:
 - Optimize the assay to increase signal over background noise and maintain the optimal kinetics of the assay (in fact faster assays with improved kinetics should be possible with a strong amplification system). Appropriate controls and calibrators are to be used.
 - Evaluate the specificity of the higher sensitivity assay to make sure that it is unchanged by challenging the system with interfering substances and related proteins.
 - The reproducibility and precision of the enhanced antibody based assay are to be evaluated by calculating the intra- and inter-batch variation coefficients (CVs of the assays using the same batch of signal enhancing reagent should be <20%).
 - The batch-to-batch reproducibility using at least 2 different batches of the signal enhancing reagent, performed on different days with different operators should have CV <20%.
- Assay performance must be tested in the appropriate non-clinical models for the chosen immunoassay analytes. NCI will recommend at least two models and expects that at least 6 separate specimen preparations from the models will be tested for statistical determinations.
- The assay, associated methodology, and if applicable, instrumentation will be independently verified by an external laboratory (NCI may be available for this activity).

Phase II Activities and Deliverables

- Expand and 'optimize' enhanced detection for the selected ELISA or slide-based antibody assays (at least 100 fold to bring analysis in attomolar range) to at least 4 high value oncology biomarkers, preferably from NCI's list of desired analytes. Test in appropriate models using target specific calibrators and controls. The assays/associated equipment must be affordable and easily adaptable to standard clinical laboratories.
- Reproducibly manufacture signal amplification reagents for the 4 high value oncology biomarkers (3 lots) and do at least 6 months stability testing under different storage conditions. If new instrumentation or equipment is required, then the design and manufacture must be optimized.
- Show reproducibly/robustness of the antibody-based assay quantitation of the designated biomarkers in selected models/tumor specimens performed by 2 users on 3 different days.
- Statistical quantification of the signal should be provided to demonstrate the enhanced sensitivity and the reliability of the technique.
- The assay, associated methodology, and if applicable, instrumentation should be independently verified by an external laboratory (NCI may be available for this activity).
- Show adaptability of the signaling reagents for use in other assay formats (e.g., FISH).

- Provide the program and contract officers with a letter of commercial interest.

348 Identification and Capture of Enriched Tumor Zones with Preservation of Labile Biomarkers from Ultra-Cold Biopses

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 for up to 9 months
Phase II: up to \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

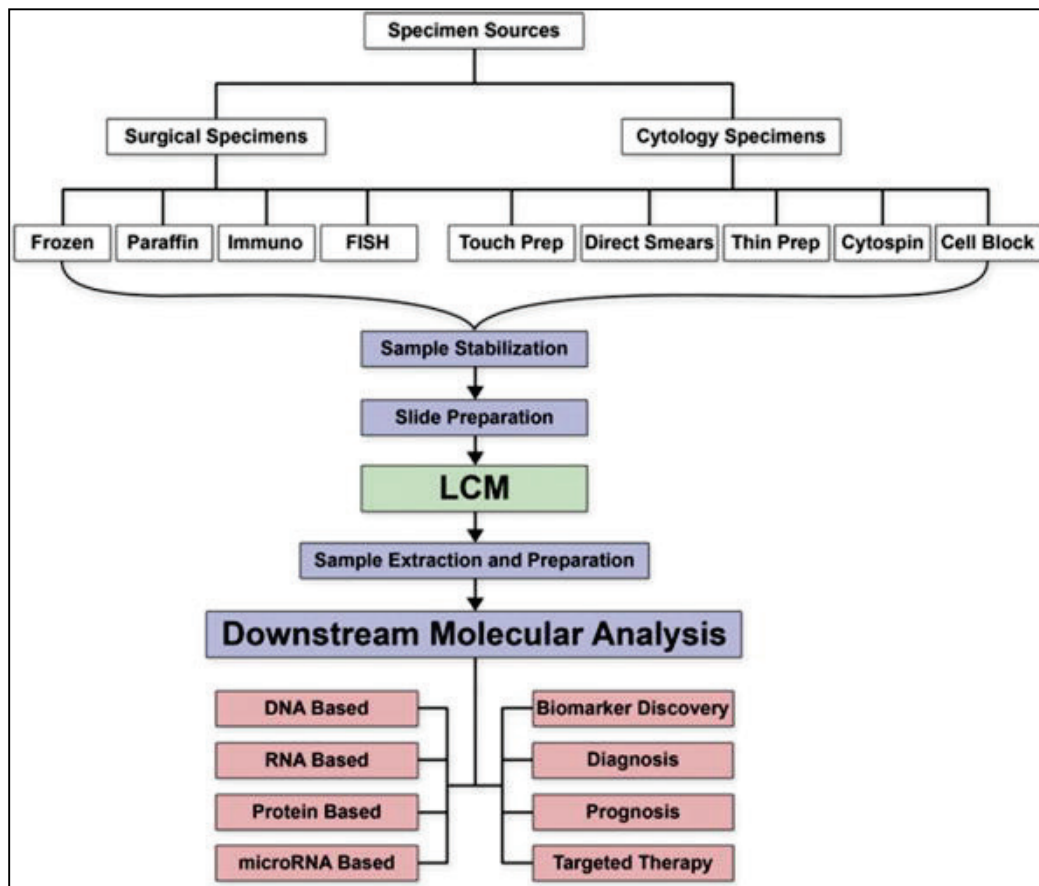
Summary

Personalized medicine approaches allow the treatment of patient tumors with drugs tailored to their tumors, which increase the probability of a beneficial response. In the last decade, a number of pharmacodynamic (PD) markers have been identified that help the physician know that the drug is hitting the target or target pathway in the patient's tumor. Recently approved cancer treatments target either the cell surface receptors at the head of these signaling pathways or the intermediate phosphoproteins and kinases in the pathway signaling cascades. Understanding the phosphoprotein activation state of key signaling molecules in tumor cells can yield critical information on the type, stage and status of those cells, aiding in the diagnosis, prognosis and treatment of an individual's disease. Unfortunately, target analyte lability, especially with phosphoproteins, requires adoption of rapid and highly controlled tissue collection and handling before widespread clinical use of the assays in predicting drug response. Also, in some cases, the magnitude of drug modulation of biomarker may be small but still significant in correlating to overall tumor response, which mandates the use of quantitative assays in enriched samples of tumor. NCI/DCTD has developed analytic multiplexed ELISA type immunoassays to cancer drug targets/pathways that quantitate actual analyte levels in tumor lysates.

However, there is an inherent problem in the use of tissue lysates in that a tissue is comprised not only of tumor cells but also of normal parenchyma, stromal cells, inflammatory cells, vessels, and often significant necrosis, so when a specimen sample is homogenized the macromolecules extracted is a sum of all cellular/matrix components, proportional to each representative element. Thus, the presence of non-target cells and necrosis can significantly affect the quantification of protein levels in 'viable' tumor cells. Even the most sophisticated testing methods are of limited value when the input DNA, RNA, or protein is contaminated or diluted by non-target cells and necrotic/acellular matrix. The requirement for relatively pure cell populations has led to various technical solutions, most notable Laser Capture Microdissection (LCM). Microdissection techniques permit analysis of various molecular signatures within a specific cell population of a tissue and reduce the interference from non-target cell populations and acellular matrix such as fibrosis/necrosis. Although there are numerous reports of genetic and gene expression analyses of microdissected tumor populations, and of proteomic assessment using Western blot, 2D-PAGE, mass spectrometry, and peptide sequencing, studies using ELISA/immunoassay quantitation of key drug targets are limited. Tumor enrichment techniques that allow the rapid capture of tumor rich zones from core needle biopsies (not sections) have the potential to provide sufficient tumor amounts for analyte quantitation in tumor cells residing within a tissue with the sensitivity and specificity of ELISA. This technology will have significant clinical value.

The **purpose/goal** of this SBIR topic is the development and commercialization of a visualization/microdissection system that is capable of identifying and capture of 'viable' tumor rich zones in frozen solid tumor biopsies under conditions that preserve labile pharmacodynamics (PD) biomarkers for antibody mediated quantitation.

Microdissection technologies are powerful tools for the isolating enriched populations of tumor cells from cellular heterogeneous tissues. It has been shown that the harvested cells can be used for many molecular investigations including DNA, RNA, protein, microRNA, and protein analyses (See Figure 1 below). The **goal** of this SBIR topic is to adapt / improve existing visualization strategies for frozen solid tumor needle biopsies allowing microdissection of large tumor rich zones with 50% tumor region enrichment while preserving labile biomarkers. The desire is to include quantitative ELISA/immunoassay in the list of molecular analyses (see chart below) that can be performed reliably on microdissected cell populations by developing a system for the rapid identification and dissection of enriched tumor cell zones from frozen biopsies. These tumor rich zones should provide sufficient material for multiplex ELISA quantitation of biomarkers. This system will be much more time-effective and productive than the labor intensive microdissection of multiple tissue sections from a biopsy. The ability to quantify biomarkers via immunoassay of isolated biopsy zones enriched for 'viable' tumor cells is especially important when a biomarker is only modulated to a small extent requiring very sensitive and specific analytic assays. Of note, the development of this technology has the potential to improve the 'specificity' of any molecular test that involves homogenization of the tissue and macromolecular isolation.



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Project Goals

ELISA/Immunoassays have the capacity to quantify the levels of a specific analytes in a specimen. There are two important considerations in the reliability of immunoassays to accurately measure the levels of PD biomarkers and the use of the information in clinical care:

1. Many of the drug biomarkers are very labile and require immediate processing after collection which usually involves rapid freezing or lysis in buffers with specific inhibitors (e.g., phosphatase inhibitors).
2. Tumors are not of a homogeneous cell type and often contain significant amounts of necrotic and normal cell zones which will impinge on the accurate measurement of an analyte in the tumor population if the entire tissue sample is homogenized.

It is believed that the development of microdissection techniques for identification and collection of viable tumor zones with at least 50% tumor enrichment from frozen solid tumor biopsies under conditions that preserve the stability of labile biomarkers can lead to detailed quantitative assessment of key protein targets modulated by drugs in tumor cells in their natural microenvironment and increase the PD utility of selected biomarkers.

The use of an appropriate visualization technologies and microdissection method such laser capture microdissection (LCM) is proposed. The LCM process has the advantage of working with tissue in various physical states, particular frozen (a state that would preserve labile phosphoprotein biomarkers), and does not alter the morphology or biochemistry of the sample collected. LCM has demonstrated success in collecting selected cells for molecular analyses, particular when frozen sections are used. Limitations of LCM include difficulties of microdissection due to decreased optical resolution of tissue sections. Possible options to improve cell resolution include the use of specialized optics to identify tumor zones via architectural/morphometric/light refraction/density parameters or the use of special stains or immunohistochemistry/immunofluorescence. This topic goal is to develop ‘identification’ or visualization and capture methods for frozen solid tumor needle biopsies or thick sections. These techniques must not impinge on the stability of the labile biomarkers (i.e., frozen conditions must be maintained).

The **goal** of this SBIR topic is to develop a reliable visualization approach to identify and capture zones of ‘viable’ tumor cells from frozen solid tumor biopsies that lead to at least 50% enrichment of tumor zones. The technology should focus on distinguishing tumor regions from non-tumor zones and acellular matrix, such as necrosis, upon scanning frozen solid tumor biopsies or thick sections. This technology will result in the collection of relatively large areas of biopsy material that is enriched in tumor cells with preserved labile biomarkers and of sufficient amounts to be amenable to quantitation by ELISA/Immunoassay.

The **first objective** should be to develop reliable methods to distinguish enriched ‘viable’ tumor zones from necrotic zones or viable tumor zones from normal cell types in frozen solid tumor biopsies or thick sections. Malignant

transformation is associated with structural, genotypic/phenotypic cellular modifications, and biochemical changes, which as a consequence, alter the spectroscopic, metabolic and microscopic properties. These and other alterations may be exploited to develop a means to scan frozen solid tumor biopsies /thick sections and identify zones that correlate to cellular/acellular areas in the biopsy. The optimal scanning system should be able to extract information about the morphological/ architecture/ spectroscopic properties in the frozen biopsy that may be used to distinguish normal and malignant areas; such as, the measurement of color, overall density or light reflectance which may correlate to cellular density and/or vascularity which in turn may reflect tumor zones.

The **second objective** is to microdissect and capture the enriched tumor zones from frozen solid tumor biopsies/thick sections in a manner that preserves the label PD biomarkers, while maintaining the tumor zone as frozen throughout the process. Such a product will enable the reliable identification and capture of relatively large amounts of pure populations of tumor cells from frozen solid tumor biopsies which are amenable for quantification of label biomarkers via immunoassays, thus increasing the sensitivity and specificity of the assays for the target in tumor cells and their PD utility.

Phase I Activities and Deliverables

The essential characteristics of a tumor enrichment microdissection system of frozen solid tumor biopsies should include all or some of the following features:

- 1) a biopsy/thick section scanning/microdissection method that is adaptable for use with most common microscopic/microdissection systems with the capability to maintain the specimens under freezing temperatures;
- 2) able to generate an easily interpretable signal indicative of parameters that can distinguish between necrotic and viable tumor, and if possible, also between tumor and non-tumor tissue;
- 3) be capable of microdissection of enriched tumor zones without inducing significant cellular damage or change in labile PD biomarkers (i.e. maintain frozen state); and
- 4) able to perform as designed and intended in fit-for-purpose studies in relevant clinical veterinary models (i.e. the method has to produce tumor tissue of sufficient quantity and quality for ELISA based immunoassay).

To accomplish the goal of this SBIR topic to develop microdissection techniques that reliably identifies and captures tumor-rich ‘viable’ zones in frozen, unfixed tumor biopsy cores or thick sections in a manner that preserves labile drug target/pathway PD biomarkers for quantitative ELISA/Immunoassay analyses, the Phase I deliverables are:

- Develop a microscopic visualization/microdissection method to identify and capture ‘viable/cellular’ tumor zones from frozen tumor biopsies/thick sections from at least two solid tumor types while maintaining the frozen state of the specimen. The use of the entire needle tumor biopsy is preferred. Any gauge needle biopsy can be used for Phase I development, but 18 gauge is desired for Phase II. The readout from the visualization/scan of the frozen biopsy should be easily interpretable (e.g. cellular rich or acellular rich) and is associated with the level of necrosis and ‘viable’ cell-rich tumor zones, and if possible, between tumor and non-tumor ‘normal’ zones. Xenograft tumors may be used for developing this technology. NCI can recommend specific xenografts that have sufficient levels of specific labile PD biomarkers and are known for developing necrosis. (See Table 1 below).
- The purity and cellularity of the captured zones can be assessed by H&E staining and imaging. Initially the histology of the entire biopsy will need to be analyzed to associate the visualization measurement with the histology (i.e. the cellular quantity and cellular types present throughout the biopsy). One option is that during the development phase, the biopsy can be cut longitudinally into 2 halves with one side being subjected to frozen sectioning and H&E staining for histological evaluation and the 2nd half to being scanned via the visualization method. This will allow the visualization measures to be related to the histology of the biopsy. As to the quantitative needs, it will depend on the assay; for example, for the DCTD apoptosis multiplex immunoassay, 20 ug of protein is required per panel, preferably with 50% tumor cell content.

- Demonstrate that the visualization/capture technology preserves in the enriched tumor cells at least one of labile protein biomarkers of interest to NCI (see Table 1 below). Maintaining the biopsy specimen under freezing conditions is mandatory and it is preferred that the enriched tumor zones be kept frozen. If specimen loss after capture is an issue, then the use of special lysis buffer may be approved by NCI. NCI may provide assistance in the analysis of the biomarker levels in isolated tumor zones.
- The device and methodology need to be independently tested at a different laboratory. NCI may be willing to perform the independent validation/field testing of the breadboard prototype device and associated methodology.

Table 1: Suggested Phospho-protein PD biomarkers and associated xenograft models

Priority	Name	Phospho-Site(s)	Xenograft Models
1	MET Receptor	pY1234/1235, pY1356	MKN45, GTL16
2	Akt1 Kinase	pT308, pS473	Calu-1, H-23
3	ERK1/ERK2 Kinases (* Internal control for one and two)	ERK1: pY202, pT204 ERK2: pY185, pT187	Calu-1, H-23

Phase II Activities and Deliverables

The Phase II activities should be focused on the design criteria/specification and fabrication of the alpha prototype biopsy visualization/microdissection system. The size of the needle biopsy is recommended to be 18 gauge for Phase II activities. The activities/deliverables are:

- Processes/instrumentation should be optimized to reproducibly identify and allow microdissection of ‘viable’ cell rich tumor zones from frozen tumor biopsies/thick sections of at least 4 different tumor types, evaluating a minimum of 6 specimens from each type (e.g., xenograft models). Reproducibility should be demonstrated by 2 users on 3 different days. Images of H&E stained slides of the isolated tumor zones should be provided to demonstrate reliability of the technique.
- Demonstrate preservation of 2 labile PD biomarkers via ELISA/immunoassay. NCI may provide assistance in this task.
- The alpha prototype device and associated methodology should undergo independent validation/field testing at a separate laboratory. NCI may be willing to do this.
- Provide the program and contract officers with a letter of commercial interest.

349 Proximity Slide-Based Sandwich Immunoassay to Visualize Intramolecular Epitopes of Analytes in Tissue Sections

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 2-3

Budget (total costs, per award): Phase I: up to \$300,000 for up to 6 months
Phase II: up to \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

The cancer community has developed a series of single-plex and multiplex immunofluorescent assays (IFA) to evaluate oncology biomarkers in tumor sections on slides. Many of the assay targets are key DNA damage response and signaling molecules (γ H2AX, Nbs1, ERCC1, RAD51, RAD50, pATR, pchk2, cdk/PY15, pKAP, MET – total-pY1234/pY1235-pY1236, AKT- pT308pS473, ERK1-pY202pT204, and ERK2-pY185pT187). Our understanding of DNA damage response and signaling in tumors is critically dependent on our ability to visualize and quantify specific signaling molecules with high spatial resolution in the cellular context. However, these slide-based assays are at most semi-quantitative. ELISA/Immunoassays have the capacity to precisely quantify the levels of a specific analytes in a specimen. ELISA analysis of whole tissue homogenates would be more informative if the analysis could be done on a pure population of tumor cells; however, tumors are not of a homogeneous cell type and often contain significant amounts of necrotic and normal cell zones which will impinge on the accurate measurement of an analyte in the tumor population if the entire tissue sample is homogenized. So, there is an **un-met need** to improve the specificity and sensitivity of slide-based immunoassays that visualize analytes on single cell types to approach or exceed that of quantitative ELISAs. It is clear that the current proximity technology has the potential to provide a robust foundation for significant improvements in the design and construction of cell type specific quantitative slide-based, cancer biomarker, IFA for the interrogation of tumor sections.

The applications of proximity technology such as Fluorescence Resonance Energy Transfer (FRET) or Radio Frequency have expanded tremendously in the last 25 years. Proximity technology has enabled the quantitative analysis of molecular dynamics in biophysics and in molecular biology, such as monitoring of protein-protein interactions, protein-DNA interactions, and protein conformational changes.

Proximity technology shows great promise for further development in the utility and scope of biological applications due to dramatic improvements in instrumentation, particularly with respect to time-resolved techniques. Advances in signaling tag such as fluorescent probe development have produced smaller and more stable molecules with new mechanisms of attachment to biological targets. For example, fluorophores have also been developed with a wide range of intrinsic excited state lifetimes, and a significant effort is being placed on development of a greater diversity in genetic variations of fluorescent proteins. Entirely new classes of tag materials, many of which are smaller than previous fluorophores, allow for the evaluation of molecular interactions at lower separation distances, promise to improve the versatility of labeling and lead to new applications of the proximity techniques.

This topic is focused on developing slide-based proximity technologies using two specific antibodies at different epitopes of the target to enable more accurate quantitation of cancer biomarkers in tumor cells in tissue sections. Initial focus should be on epitopes within the same target molecule. This new technological approach has the potential to improve slide-based IFA sensitivity and specificity to approach or exceed that of sandwich ELISA testing of tissue homogenates and have the advantage of visualization of the cell types that express the biomarker and enable the quantitation of the state biomarker (e.g., activation) in specific cell types.

It is believed that the development of the proximity reagents for dual antibody staining of tissue sections to high value cancer biomarkers will have great research value and have a significant clinical impact; i.e., direct visualization and quantitation of informative biomarkers in the tumor population that the drug targets.

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Project Goals

Over the past decade, biosensors based on fluorescent proteins, FRET, and recently radio-frequency tags have emerged as major classes of probes that are capable of tracking a variety of cellular signaling events, such as second messenger dynamics and enzyme activation/activity, in time and space. For example, a donor chromo/fluorophore, initially in its electronic excited state, may transfer energy to an acceptor chromo/fluorophore through nonradiative dipole–dipole coupling. The efficiency of this energy transfer is inversely proportional to the sixth power of the distance between donor and acceptor, making FRET extremely sensitive to small changes in distance. Depending on the types of detection probes used, the distance /proximity between donor and acceptor can be between 1 nm and 10 nm to generate a signal.

There is increased use of proximity biosensors, particularly tagged-antibodies in combination with signaling factors (electric, optical, etc.) to provide a specific signal directly related to the concentration of an analyte. These proximity reagents have the potential to allow rapid detection of the target with the sensitivity and specificity of a sandwich assay.

The **goal** of this topic is to develop reagents/methods for use of dual primary antibodies to different epitopes of the same analyte or to different subunits of a target that, upon binding of the molecule(s) in cells within a tissue section, will generate a proximity signal due to close spatial association of the antibody reagents containing donor/acceptor tags, respectively (e.g., fluorochromes). This signal can be captured and visualized to cell types as well as quantitated via conventional microscopy.

The benefit is that antibody based proximity assays to high value cancer biomarkers will represent a significant advancement in detection capabilities for slide-based immunoassays of tumor sections. These assays will provide specific, sensitive and reliable detection of targets in a cell specific manner and approach or exceed ELISA level quantitation which has significant clinical applications.

Phase I Activities and Deliverables

The **goal** is to replicate or exceed the sensitivity and specificity of an ELISA in slide-based immunoassays of tumor specimens. The **objective** is to develop and test the applicability of double antibody labeling using proximity technology for the detection of two epitopes on TWO high value oncology biomarkers, preferably choosing NCI designated biomarkers. This may involve the development of new proximity tags adapted for use in dual antibody labeling of histological sections. The readout will be the successful localization of protein based analytes in the appropriate cell type when expressed at varying levels (i.e., specificity/sensitivity) and quantitation of the cell specific signal that agrees with known protein levels measured by other biochemical methods – initially using non-clinical models to evaluate.

Biomarkers important to NCI are oncology-relevant proteins that have two epitopes of interest; for example, one could select epitope specific antibodies to allow for cell specific visualization and quantitation of the amount of a receptor in a cell that is also phosphorylated at a specific epitope.

The NCI biomarkers and possible epitopes of interest for developing these assays are listed below:

TARGETS	EPITOPE 1	EPITOPE 2
CTNNB1 (Beta Catenin)	N-Terminus C-Terminus	pS45, pY142, pS33, pS37, pY86, pS675, others?
AKT (v-AKT [AK mice with thymoma]; also called Protein kinase B [PKB])	AKT 1, 2, & 3 specific epitopes	pT308 or pS473 specific antibodies
MET	N-Terminal or C-Terminal non-phosphorylated epitopes or specific phosphorylated sites such as pS1009	biphosphorylated pY1234/pY1235, pY1235, pY1236, pY1349 or pS1009
PKM2 (Pyruvate kinase isozymes M1/M2 also known as pyruvate kinase muscle isozyme (PKM),)	N-Terminus	C-Terminus (may distinguish between isozymes) Internal Domain

NCI is available to advise on biomarker reagents and xenograft models. In special cases, NCI may provide antibody reagents to selected PD biomarkers and the associated xenograft tumors to awardees.

Phase I Activities and Deliverables

- Reagent parameters [proximity tags], assay parameters, imaging platform parameters, and image capture and analysis strategy for the proximity measurements (e.g. FRET) are to be developed.
- Select appropriate donor and acceptor probes for the 2 analyte specific antibodies chosen for each target and determine the manner in which they are employed as molecular labels to obtain optimal energy transfer/signal.
- Detailed SOPs written for each of **TWO** high value oncology biomarkers, preferably choosing from NCI designated biomarkers.
- Optimize reaction and stabilization conditions.
- Develop measurement strategy for capturing the intensity of signal.
- Relate the proximity signal to the quantitation provided by other biochemical measurements in appropriate non-clinical models.
- Prove that proximity signals are emanating from the same protein molecules, rather than adjacent or nearby protein molecules.
- Carry out independent verification of prototype assay reagents/instrument (NCI may be available to do this).

Phase II Activities and Deliverables

- Develop ‘optimized’ dual antibody proximity assays to two epitopes on each of **THREE** high value oncology biomarkers, preferably choosing from NCI designated biomarkers.
- Reproducibly manufacture proximity-reagents and do at least 6 months stability testing.
- Show reproducibly/robustness of the proximity -dual antibody staining and quantitation in sections of a human tumor xenograft(s).
- Provide images of the dual antibody stained xenograft tumor sections and quantification of the signal to demonstrate reliability of the technique.
- Carryout independent verification of performance of reagents/ instrumentation (NCI may be available to do this).

- Provide the program and contract officers with a letter of commercial interest.

350 Highly Innovative Tools for Quantifying Redox Effector Dynamics in Cancer

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 3-4

Budget (total costs, per award): Phase I: up to \$225,000 for up to 9 months

Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

The generation and dynamic interplay of redox effector molecules (e.g., oxygen, free radicals, peroxides, nitrogen oxides, and hydrogen sulfide) are fundamental features underlying the genomic, structural, metabolic and functional alterations observed in cancers. Alterations in redox balance impact all phases of disease including carcinogenesis, disease progression, response to treatment and prevention. For example, the DNA damaging effects of free radicals can mutagenize key oncogenic sites. Redox imbalances occur by abnormalities commonly associated with cancers including mutations in p53, myc and ras pathways. Redox effectors operate to modify protein function at the post-translational level, which plays a significant mechanistic role in the phenotypic plasticity cancer cells demonstrate in the face of oxidative and reductive (hypoxia) stresses. Redox tone is a key regulator of the self-renewal properties of stem-like cancer cells, which has been shown to contribute to tumor resistance to current therapies.

Progress in the cancer biology and pre-clinical space has been limited by the lack of tools that can accurately measure redox parameters in animal models with sufficient spatio-temporal resolution and minimal perturbation of the system. NCI seeks input from the small business community to develop and optimize a new generation of quantitative and specific technologies that will enable and accelerate basic research aimed at understanding basic redox effector mechanisms and the roles they play in the cellular adaptations and complex biology of tumors.

Supporting the development of these technologies will allow researchers to validate and benchmark data obtained across different 3D cell culture platforms and pre-clinical animal model systems with the goal of accurately mimicking tumor environments experienced by patients with cancer. Moreover, an enhanced ability to screen, manipulate, or analyze redox dynamics is an invaluable index in the evaluation of cancer cell-tumor responses to therapeutic interventions in the critical pre-clinical testing phase. These redox data have potential to significantly improve our understanding of tumor biology and ability to better predict treatment responses and long-term efficacy when translated into patients.

Project Goals

There is an unmet need in basic cancer research for probes or technologies that can better measure, characterize, profile, or resolve the spatiotemporal dynamics of redox effectors at the subcellular to cellular levels. Genomic profiles, for instance, cannot capture post-translational redox regulation that occurs with changes in the tumor microenvironment. Redox probes have been traditionally reliant on organic dyes that experience spectral shifts with redox. The current state of the art is genetically encoded redox indicators that couple redox responsive enzyme motifs with indicator proteins. These genetically engineered redox probes have improved response kinetics, but may have limited optical qualities. Given the critical role played by redox effectors, developing a range of new tools will help us better understand how redox effectors regulate cell phenotypes in functional tumor populations.

The goal of this FOA is to develop quantitative tools to measure redox dynamics in biological systems. Ideally, probes or biosensor tools should be minimally invasive as to not significantly perturb the system. The technical approach should: (1) allow for *in vivo* measurements of redox effector spatiotemporal dynamics; and/or (2) be useable in high throughput systems, for example to allow the screening of cellular response to experimental perturbations, such as exposure to cytotoxic agents. The long term goal is that the technologies developed through this contract can help validate whether data gathered in model experimental systems faithfully represents the redox dynamics of human tumors.

To successfully meet this goal, offerors shall develop a technology for the minimally to non-invasive measurement of one or more redox effectors, including but not limited to oxygen, free radicals, reactive oxygen species, peroxides, nitrogen oxides, and hydrogen sulfide. Phase I studies should focus on developing the technology and demonstrating proof of concept in an *in vitro* system. Phase II studies further refine the technology and demonstrate the use of the technology to measure redox effectors. Offerors shall justify their choice of approach with respect to the scientific utility and commercial potential, and specify quantitative milestones that can be used to evaluate the success of the technology being developed.

It is anticipated that offerors shall develop a probe or similar agent that facilitates the measurement of redox effectors by one or more imaging modalities; however, offerors are not restricted to any particular technical approach and label or probe free approaches that can meet the requirements of this contract are welcome.

Offerors are not restricted to any particular technical approach and can propose resource and tool development that incorporates high-risk/high-impact technologies. Examples can include, but are not limited to:

- Redox probes that provide significant advances in sensitivity, selectivity, ratiometric capability, or resolution in reporting the spatial concentration gradients and temporal dynamics of redox effectors at the subcellular, cellular and/or tissue compartment levels.
- Genetically encoded redox biosensors that are expressed in a cell or tissue selective manner in small animal models of cancer for interrogation by non-invasive to minimally invasive imaging modalities.
- Biology-inspired redox sensors (e.g., based on bacterial chemosensors) that through synthetic biology techniques are genetically encoded for expression in a cell or tissue selective manner.
- Nanotechnology scaffolds multiplexed with sensors that permit functional parallel profile analyses of a combination of redox effectors (i.e., oxygen, nitric oxide, hydrogen peroxide, superoxide) and/or related species (e.g., proton, glutathione, ascorbate) across both time and space at the subcellular, cellular and/or tissue compartment levels.

Technologies that have the potential for *in vivo* use, especially those with potential clinical applications in the long term will be of particular interest, but methods that will be restricted to pre-clinical research applications are also of interest.

Phase I Activities and Deliverables

- Identify and justify development of a sensing tool or probe for specific redox effector species from both a cancer biology and commercial perspective.
- Offerors shall describe the current state of the art technologies for sensing and measuring the redox effector being addressed by their proposal, and outline the advantages that their approach will offer.
- Develop and characterize a redox probe or biosensor. Offerors shall specify quantitative milestones that can be used to evaluate the success of the technology being developed, and justify these milestones from the viewpoint of both scientific utility and commercial value.
- Develop an assay or system that demonstrates proof-of-concept testing and benchmarking of specificity and sensitivity parameters of the agent or system for a range of redox effector species (e.g., oxygen, free

- radicals, hydrogen peroxide, nitric oxide, hydrogen sulfide).
- For each redox effector or parameter, a technical description of methodology for each assessment shall be provided that includes how each measurement is calibrated. If measurements are collected serially, the rationale for the order of measurements shall be specified.
- Demonstrate feasibility to sense, interrogate, detect or resolve the spatiotemporal dynamics of redox effector species in live cells or animal model, ideally with a minimally invasive perturbation of the system.
- Provide NCI with proof-of-concept assay SOP.

Phase II Activities and Deliverables

The goal of the Phase II product is an optimized commercial resource, product, reagent, kit or device that can allow researchers to measure the relevant redox effector molecules in their laboratory. Decisions for continued project development into Phase II will be based on probes, biosensors, assays or systems that:

- Can demonstrate reliability and robustness. Offerors shall provide a technical evaluation and quality assurance plan with specific detail on shelf life, best practices for use, and equipment required for use.
- Can be scaled up at a price point that is compatible with market success and widespread adoption by the basic research community.
- Have potential to benchmark data obtained across different cancer model systems (e.g. 2D and 3D tissue culture systems, and *in vivo* animal models of cancer).

Deliverables for the Phase II projects are:

- Scaled up synthesis or manufacture of necessary agents, chemicals, device, or products.
- Design and implementation of quality assurance controls and assays to validate production.
- Validate scaled up device, chemical or product. Offeror shall demonstrate the utility, reliability and sensitivity of their device, chemical or product across *in vitro* and/or *in vivo* models relevant to cancer research.
- Refine SOPs to allow for user friendly implementation of technology by the target market for the agents, chemicals, device, or products.

351 Modulating the Microbiome to Improve Efficacy of Cancer Therapeutics

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning

Number of anticipated awards: 3-4

Budget (total costs, per award): Phase I: up to \$300,000 for up to 9 months
Phase II: up to \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Metagenomic studies in humans and animal models have established that there are alterations of the GI microbiota community during development of neoplastic and pre-neoplastic disease, and in tumor-bearing vs. healthy individuals. Understanding the impact of human host/microbiota interactions on the initiation, progression and treatment of cancer, and the molecular mechanisms that govern the outcomes of these interactions, will provide new therapeutic strategies and new targets for the treatment of many human tumors.

One promising approach emerging from recent research is alteration of microbiome function designed to enhance the efficacy of cancer therapies. Recent work demonstrated that individual variability in patient drug response to chemo (and other) therapies can be attributed to actions of the gastrointestinal (GI) microbiota, either through direct metabolic activity on the agent itself, or by effects on host barrier function and immunomodulation that affect drug bioavailability. For example, microbial β -glucuronidase activity results in re-activation of toxic metabolites that affect the dose-limiting range of CPT-11, a prodrug form of the topoisomerase inhibitor Irinotecan that is widely used to treat a variety of solid tumors. Antibiotic co-therapy and specific inhibition of bacterial β -glucuronidase activity reduced chemotherapy-induced GI toxicity in several animal models. Other studies have shown that depletion of NOX-inducing *Lactobacillus* species by antibiotics, results in reduced tumoricidal activity of platinum based drugs, which rely on induction of reactive oxygen species (ROS) to mediate tumor cell killing. Similarly, the antitumor effects of radiotherapy and several cytotoxic chemotherapeutic drugs such as cyclophosphamide (CTX), oxaliplatin, and CpG-ODN, are achieved in part by an immune-mediated bystander effect that requires the recruitment and activation of an intense inflammatory infiltrate to regress tumors.

As we learn more about how the microbiome affects disease progression and response to treatments, the opportunity to exploit the microbiome for therapeutic benefit is an exciting new approach that should be explored.

Project Goals

The purpose of this SBIR contract solicitation is to develop innovative technologies and methods designed to modulate the GI microbiota in order to enhance the therapeutic efficacy of existing or novel cancer therapies, or ameliorate side effects of these therapies. The goal is to develop effective adjuvant strategies that specifically target critical microbial activities or populations that affect drug efficacy and/or tolerability. Ultimately, this activity will accelerate the development of novel strategies based on the rational targeting and manipulation of human GI microbiome functions for the treatment of human tumors.

To successfully meet this goal, applicants will need to demonstrate that their approach accomplishes the specific perturbation or modulation of the microbiome that is desired, and that these approaches have demonstrable benefits in addressing a significant unmet medical need relevant to cancer (e.g. reduction of off-target toxicity). Phase I studies should focus on developing and refining the approach that will be used to modulate GI microbiota or functions performed by the microbiota (such as metabolic activity). Applicants should establish appropriate criteria to benchmark or evaluate the success of their approach, and these should be related to the expected level of perturbation or modulation that is required to have therapeutic benefits. Phase II studies should focus on demonstrating that the approaches developed in Phase I studies are effective in an appropriate *in vivo* model system. Lead candidates should be developed and tested for efficacy in appropriate animal models, and Phase II studies should also measure drug delivery (e.g., probiotics, engineered phage, lipids, nano-particles) and pharmacokinetic targeting (e.g., reduction/increase of specific microbial enzyme activity, signaling ligand, or host interaction) in addition to measured endpoints of tumor regression and/or ablation *in vivo*.

Applicants are not limited to specific cancer types, but are required to identify and justify a cancer type and unmet medical need that can be addressed by their approach. They should also provide a scientifically justified rationale for exploring particular approach(es) for perturbing or modulating the microbiome, and justify the choice of model system to evaluate their approach(es).

It is anticipated that applicants will test perturbations of the GI microbiome, such as antibiotic treatments, bacteriophage therapies, probiotic supplements, dietary metabolites, drug metabolizing enzymes, modulators of bacterial metabolism, and immunomodulators. However, applicants are free to employ any approach.

The focus of this contract topic is not to search for new mechanisms or effects by which the microbiome affects cancer therapy or progression, but rather to explore microbiome directed intervention strategies that have a rational basis. The contract topic is not intended to develop screening approaches, though applicants may propose to refine or optimize lead compounds or other agents designed to modulate or perturb GI microbiota.

Phase I Activities and Deliverables

- Define and characterize a microbial activity/interaction that affects therapeutic efficacy, demonstrated through appropriate *in vitro* and *in vivo* experiments.
- Develop targeted microbiota regulated/directed intervention strategies designed to improve, either alone or in combination, patient outcomes for new or current therapeutic agents. *Approaches may involve, but are not limited to:*
 - Narrow spectrum antibiotics
 - Bacteriophage therapies
 - Probiotics/Prebiotics
 - Dietary metabolites
 - Expression or delivery of novel drug metabolizing enzymes
 - Inhibitors of bacterial enzymes
 - Immunomodulators/vaccines
- Test and refine therapeutic approaches in order to identify lead candidates or agent (e.g. bacteriophage, bacterial strain, enzyme, dietary metabolite, vaccine, *etc.*) to develop further in Phase II studies
- The lead candidate or agent should be able to successfully accomplish the desired perturbation or modulation of the microbiome to a level that can reasonably be expected to have an impact on the efficacy of the therapeutic interventions and demonstrate proof of concept for the efficacy of their approach
 - Offeror should demonstrate proof of concept in an appropriate *in vivo* model
- Offeror should determine and justify the assays and endpoints that will be used to evaluate the success of their approach (e.g., biomarkers, enzymatic activity, presence or absence of specific microbial populations)
 - If needed, offeror should develop alternative tools/methods to evaluate candidate effects on microbiome function.
- Submit a statement to NCI that specifies the metrics and criteria used to evaluate the success of the approach being developed, and justification for these metrics and criteria from a commercial and scientific perspective.

Phase II Activities and Deliverables

- Demonstrate the efficacy of lead candidate(s) or agent(s) from Phase I studies in an appropriately characterized *in vivo* model
 - Identify and measure appropriate pharmacokinetic, pharmacodynamics, and therapeutic endpoints
 - Evaluate toxicity and efficacy of therapeutic candidate(s) or agent(s)
 - Evaluate immune response to therapeutic approach where appropriate
- Determine the toxicology and safety profile of the lead candidate(s) or agent(s) using appropriate animal models and assays relevant to the specific therapeutic approach being pursued
- Optimize or scale up lead candidate(s) or agent(s) (e.g. bacteriophage, bacterial strain, enzyme, dietary metabolite, vaccine, *etc.*) from Phase I studies. Activities may include, but are not restricted to:
 - Medicinal chemistry to optimize small molecules for *in vivo* studies
 - Scale up production of lead therapeutic candidate(s) or agent(s)
 - Optimize delivery method for therapeutic candidate(s) or agent(s)
- Develop a plan for obtaining regulatory approval to conduct human studies. Offerors should provide plans and a detailed time table for obtaining this regulatory approval

352 Cell and Animal-Based Models to Advance Cancer Health Disparity Research

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning

Number of anticipated awards: 3-4

Budget (total costs, per award): Phase I: up to \$225,000 for up to 9 months
Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Cancer health disparities (CHDs) are defined as differences in the incidence, prevalence, morbidity, and mortality that contribute to an unequal burden of cancer and represent a major public health concern both nationally and globally. In the United States, several racial/ethnic populations demonstrate increased incidence and/or more aggressive disease for numerous cancer types. The causes of these CHDs are multifactorial, including differences in access to health care, diet and lifestyle, cultural barriers, environmental exposures, and ancestry-related factors. Recent data suggest that biological factors may contribute to CHDs. The NCI specifically encourages and funds investigations of such biological factors to better understand mechanisms that contribute to CHDs. One limitation in conducting basic, translational, and clinical research investigating the causes of CHDs is a substantial lack of relevant *in vitro* and *in vivo*-based models. The development and validation of appropriate models to study underrepresented population groups would greatly advance this field of research.

Program Goals

The primary goal of this topic is to develop new, commercially available models relevant to diverse racial/ethnic populations. These models may be used to enhance research capabilities of basic scientists and/or provide novel tools to pharmaceutical companies for preclinical oncology studies. Establishing these novel models may influence CHD research in multiple ways including 1) attracting additional researchers to this largely underexplored area of research, 2) improving the quality and acceptance of CHD research data, and 3) improving validation and commercialization of cancer therapeutics relevant to diverse patient populations. Lastly, achieving these goals will contribute to the overarching goal of facilitating the reduction of CHDs.

Small businesses are invited to submit proposals to develop a panel of cell lines, primary cells, or patient-derived xenograft (PDX) mouse models established from racially/ethnically diverse patient populations. Additionally, competitive applications may propose novel genetically engineered mouse (GEM) models to investigate cancers or co-morbid conditions that are more frequent and aggressive amongst diverse racial/ethnic populations.

- **Cancer cell lines and primary cancer cells**: The scientific integrity of cancer cell lines and primary cells is critical for maintaining high standards in research. Any cells established via this solicitation must be fully confirmed through a rigorous and validated authentication and be contamination-free. Furthermore, offerors must have access to fully annotated tumor tissues from diverse racial/ethnic populations with appropriate approval(s) in place (i.e., IRB).
- **PDX Mouse Models**: PDX models have recently gained huge recognition in clinical and preclinical oncology research. Molecular profiling studies have shown the similarity between patient tumor and PDX models is greater than between patient tumor and traditional cell lines. Therefore, new initiatives have been proposed to use PDX models in a number of clinically relevant research areas including characterization of tumor heterogeneity, *in vivo* therapeutic target validation studies, clinically relevant mechanism of action studies, and sensitivity and resistance to therapy studies. Furthermore, PDX models have even been suggested to be a

useful tool to mimic human clinical trials using animals. Similarly, offerors must have access to fully annotated tumor tissues from diverse racial/ethnic populations with appropriate approval(s) in place (i.e., IRB).

- **GEM Models:** Numerous cancer types are more prevalent in specific racial/ethnic populations. An example of one such disease is triple negative breast cancer (TNBC). Although diagnosed less often, breast cancer in African American women display different characteristics compared to breast cancer in Caucasian women, including earlier onset, less favorable clinical outcome, and an aggressive tumor phenotype. The reason for this aggressive phenotype is currently widely studied however progress is hampered by the lack of suitable TNBC model systems. Development of GEMs (including knock-in mice, knock-out mice, and mice with chemically induced mutations) to study cancers disproportionately effecting racial/ethnic populations would advance the field. Offerors must provide data or cite literature justifying the GEMs proposed and have relevant technical expertise.

Phase I Activities and Deliverables

- Establish an experimental model relevant to CHD research. This may include one of the following:
 - Cancer cell line or primary cells established from racial/ethnic minorities
 - PDX animal model established from racial/ethnic minorities
 - GEM model
- **Cancer cell line and primary cells deliverables:** Establish a stable cell line from tumor cells and passage the cells in culture to determine viability.
 - Detailed documentation must be provided including patient clinical characteristics, passage history, mycoplasma testing results, and appropriate growth/preparation conditions.
 - Develop a standardized, working protocol for establishment of additional cell culture models.
- **PDX animal model deliverables:** Establish a serially transplantable, phenotypically stable, human cancer xenograft model in immunocompromised mice.
 - Transplant fresh surgical tissue or biopsy (either subcutaneous or intraperitoneal) into recipient immunodeficient mice (Transplant generation 1)
 - Subsequent serial transplantations must be conducted following establishment of initial xenograft outgrowths, typically >10mm in diameter (A minimum of three generations of transplantation is required to establish a stable line)
 - After three generation of transplantations, confirm genetic and phenotypic heterogeneity of the tumors.
 - Freeze and bank tumors.
 - Develop a standardized, working protocol for establishment of additional models.
 - Perform comprehensive molecular characterization of patient samples and earliest PDXs, including whole exome sequencing and mutational status analysis using a CLIA-approved panel.
- **GEM model deliverables:** Develop a GEM model to support investigations on cancers disproportionately effecting racial/ethnic populations.
 - Develop transgenic constructs and strategy to create GEM models
 - Transfer fertilized mouse embryos with transgenic constructs to foster mouse mothers
 - Identify potential transgenic founders and mate to generate F1 progeny
 - Analyze to identify and confirm successful transgenic mice
 - Determine validation and development plan for transgenic mice
- Validate the genetic ancestry of patients (if applicable) from which a model was established using a panel of ancestry informative makers (AIMs). The AIM panel(s) selected should be relevant to the patient populations being investigated and capable of specifying admixture proportions.

Phase II Activities and Deliverables

- Cancer cell lines and primary cells: Generate a panel of no less than 50 cell lines from different patient sources.
- PDX animal models: Generate a panel of no less than 20-50 models (depending on tumor type being used) from unique patient sources using established protocols.
- GEM Models: Demonstrate preclinical utility and merit of the generated transgenic mouse model(s) by conducting sufficient experiments.

353 Cell-Free Nucleic Acid-Based Assay Development for Cancer Diagnosis

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 3-4

Budget (total costs, per award): Phase I: up to \$300,000 for up to 6 months
Phase II: up to \$2,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

The evidence that cell-free circulating DNA is present in cancer patient's blood was first reported over half century ago. Since then studies that addressed the clinical significance of the cell free DNA quantification in plasma/serum for cancer diagnosis have grown steadily. Research findings indicated that most patients with solid tumors in lung, breast, prostate, colon, cervix, ovary, testes, and bladder have increased DNA levels that allow for discriminating patients with malignancies from those with non-malignant disease. The first application of cell free circulating nucleic acids (cfNA) in the diagnosis and prognosis of cancer was demonstrated in 1977 when higher level of circulating DNA was detected in the serum of cancer patients; these levels decreased in response to radiation therapy.

In recent years, it has been recognized that circulating DNA may be altered in fragmentation pattern, microsatellite stability, and DNA methylation. In addition, the cfNA sequences may be mutated and tumor-specific allowing for increased sensitivity and specificity in evaluation and detection of cancer compared to mere quantification of cfNA levels. Besides circulating cell free DNA, evidence has indicated that tumor-derived RNA, (especially the quantification of the tumor-derived microRNA in plasma/serum) may be an excellent biomarkers for the diagnosis and prognosis of cancer. Furthermore, alterations of cfNA are also found in other sources of body fluids or effusions such as urine or sputum. Clearly, cfNA as a biomarker, which is easily accessible, reliable, and reproducible, can offer many advantages in their implementation into clinical use.

To date, however, there are no currently effective cfNA-based assays that are approved for clinical use in the diagnosis or prognosis of cancer. The low abundance of cfNA from all body fluids and effusions remains a major challenge in the assay development. Many early developments need to be further verified and validated before they can be translated to clinical use. With the latest technology advancement in sample collection, processing, and analysis for nucleic acids, the likelihood of clinical utilization of cfNA becomes more reachable.

The purpose of this initiative is to provide much needed support for the development of a cfNA-based assay for cancer diagnosis and/or prognosis. The selected applicants will develop an assay for detection of cancer or its

subtype, so that cancer or subtypes can be identified specifically. Since a single alteration in cfNA may not be sufficient to detect a specific cancer, offerors are encouraged to use a panel of cfNA alterations that could be more robust for their assay development. The cfNA alterations may include, but not limited to, cfNA concentration, fragmentation pattern, microsatellite stability, and DNA methylation, tumor-specific sequences, DNA mutations or tumor-derived RNA. The sources for cfNAs can be from plasma, serum, urine, sputum or other types of body fluids or effusions. In Phase I, the development of molecular diagnostic assay should focus on proof of concept. In Phase II, the assay developed in Phase I will be validated in the clinic setting under a plan developed with the NCI project officer.

Program Goals

The goal of the project is to develop a cfNA-based assay for clinical use in the evaluation of cancer diagnostics, prognostics, and response to therapy. The levels of sensitivity and specificity required will depend on the clinical question and unmet need the assay is attempting to answer. The assay may also be used to provide a better mechanistic understanding of tumor development and progress with the idea that this knowledge may lead to better therapeutic targets and improve patient outcome. Preference will be given to the assays that are platform driven, meaning that the technology platform should be portable and easily used for diagnosis of multiple cancer types.

To apply for this topic, offerors need to outline and indicate the clinical question and unmet clinical need that their assay will address. Offerors are also required to use validated cfNA markers. This solicitation is not intended for biomarker discovery.

Phase I Activities and Expected Deliverables

- Select one or a set of validated cfNA markers with samples of a choice (e.g., plasma, serum or/and urine) for detection of a cancer or subtype (e.g., breast cancer or triple negative breast cancer). If novel or proprietary markers are used, offerors must show that the markers have been validated.
- Develop an assay to identify these markers effectively to distinguish the cancer samples from healthy samples. The offerors should also demonstrate that the assay is able to differentiate the cancer from other cancer types.
- Demonstrate high reproducibility and accuracy with the assay.
- Demonstrate high specificity and sensitivity of the assay. Specificity and sensitivity will depend on the application (e.g., high specificity will be required if the assay is used to provide specific molecular information for the lesion that was detected by CT imaging).
- Deliver to NCI the SOPs of the cfNA-based assay for cancer diagnosis.
- Demonstration of a plan that is necessary to file a regulatory application.

Phase II Activities and Expected Deliverables

- Demonstrate the assay that enables a test to be finished within one day.
- Validate the assay in the clinical setting.
- Submit a regulatory application to obtain approval for clinical application.

354 Companion Diagnostics for Cancer Immunotherapies

(Fast-Track proposals will be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 3-4

Budget (total costs, per award): Phase I: up to \$225,000 for 6-9 months; Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

The field of cancer immunotherapy has expanded rapidly over the last few years with the development of several new immunomodulatory agents that have shown promising clinical results. As one example, in 2011, the FDA approved a therapeutic antibody for the treatment of melanoma, ipilimumab (YERVOY®), which blocks cytotoxic T-lymphocyte antigen 4 (CTLA-4), a receptor found on T-cells that downregulates the immune system. In 2014, the FDA approved another agent for the treatment of melanoma, pembrolizumab (KEYTRUDA®), which is the first approved therapeutic antibody targeting the programmed cell death protein 1 (PD-1), another T-cell receptor that plays a role in immune inhibition. These two therapeutic antibodies are representative of a major class of cancer immunotherapies known as immune checkpoint inhibitors, and several other therapeutic agents are currently in development targeting CTLA-4, PD-1, and other immune checkpoint proteins. Other major classes of cancer immunotherapies currently being developed include therapeutic cancer vaccines, as well as therapeutic approaches that involve *ex vivo* manipulation and engineering of immune cells, including chimeric antigen receptor (CAR) therapy.

Cancer immunotherapies offer several advantages over current standard-of-care cancer treatments, including the potential to eradicate cancer cells not visible to the surgeon, as well as disseminated metastases that remain undetectable using current imaging modalities. Immunotherapy approaches may also prove effective at targeting slowly dividing or quiescent tumor cells that do not respond well to chemotherapy and/or radiation, and certain immunotherapy approaches are expected to suppress re-emergence of the cancer (following initial treatment) by exploiting the immune system's memory. In fact, early results have shown positive and dramatic clinical outcomes for some of the more recent cancer immunotherapies, even in patients with advanced disease; however, it is often the case that only a subset of patients respond to such therapies for reasons that are often poorly understood.

As the field of cancer immunotherapy continues to evolve, and as more cancer immunotherapies advance through clinical development, there will be an increasing need for companion diagnostic assays capable of predicting responders (and non-responders) to cancer immunotherapies. Moreover, such assays will become critically important as these therapies are eventually utilized as part of routine clinical practice.

Program Goals

The goal of this contract topic is to develop companion diagnostic assays and technologies capable of identifying individual patients for whom a particular cancer immunotherapy regimen will be safe and effective. This includes cancer immunotherapies that have already received marketing approval from the FDA, as well as cancer immunotherapies currently in clinical development. This topic is specifically intended to address cancer immunotherapies that depend upon eliciting an immune response. Projects that do not meet this requirement will not be considered responsive. For example, a monoclonal therapeutic antibody that exerts a direct antitumoral effect either by neutralizing the antigen or by activating signaling pathways within the target tumor cell, but does not elicit an immune response for its clinical activity, is not considered an immunotherapy and would not be considered responsive.

The goal of this contract topic is NOT to solicit any particular technology or approach, i.e., this contract topic is technology agnostic. Technologies employed may include, but are not limited to, genetic analysis, other molecular diagnostic approaches, cell culture and cell expansion technologies, imaging modalities, radio-labeling approaches, and data science/analytics. This contract topic is specifically intended to support the development of assays that provide predictive and/or prognostic information for a specific cancer immunotherapy. Projects that do not meet this requirement will not be considered responsive. For example, development of an assay for the sole purpose of measuring whether an agent modulates its intended molecular target (e.g., pharmacodynamic assay) would not be considered responsive. Likewise, development of an assay for providing information that is useful in cancer diagnostics or prognostics but not in determining the safe and effective use of a therapeutic product/regimen would also not be considered responsive. Noninvasive and minimally invasive sampling methods (e.g., body fluids and mouth swab) are preferred. Other sampling methods are acceptable if they provide significantly improved predictive value, accuracy, and clinical applicability.

Phase I Activities and Expected Deliverables

- Develop a working companion diagnostic test for a specific cancer immunotherapy regimen, which meets the criteria described above
- Characterize the variation, reproducibility, and accuracy of the test, and implement a QA/QC plan
- Demonstrate suitability of the test for use in the clinic, and conduct benchmarking studies against current tests (if available); algorithms must be tested with datasets other than those used for their development
- In cases where a companion diagnostic test is proposed for a specific immunotherapeutic that is not yet commercially available (i.e., approved for marketing), the applicant must provide proof of collaboration or partnership with the entity that is developing the therapeutic agent or with an established diagnostic company
- All offerors must establish a collaboration or partnership with a diagnostic and/or pharmaceutical company and/or clinical/research institution that can provide relevant clinical trial specimens; offerors must provide a letter of support from the partnering organization in the Phase II application
- Deliver the SOP of the working test to NCI for evaluation

Phase II Activities and Expected Deliverables

- Incorporate the assay into a standard kit for clinical testing and eventual distribution and sale
- Demonstrate clinical utility and value by testing sufficient numbers of patients from multiple sites to unequivocally demonstrate statistical significance with regard to patient selection for the therapy
- If the primary conclusions reached during the Phase I studies were based on animal experiments or *ex vivo* modeling, then a correlation study between these models and treatment in human subjects is expected
- Establish marketing partnership or alliance with the company developing the therapy, unless the therapy is already approved for marketing
- It is preferred that the test be performed in at least one independent CLIA-certified laboratory
- Deliver the final SOP to NCI for evaluation

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It is strongly suggested that potential offerors not exceed the total costs (direct costs, facilities and administrative (F&A)/indirect costs, and fee) listed under each topic area.

013 Development of Stem Cell-based Assay for High-Throughput Screening of Chemicals of Toxicological Concern

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II proposals will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning

Number of anticipated awards: 2-3

Budget (total costs, per award): Phase I: up to \$225,000 for up to 12 months
Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Adverse human health outcomes – a.k.a., “toxicity” – caused by pharmaceutical or environmental compounds are a major cause of drug development failure and public health concern. Methods to evaluate the potential of chemical compounds to induce toxicity are based largely on animal testing, are low-throughput and expensive while giving little insight into mechanisms of compound toxicity, and have not changed appreciably in the last 50 years despite enormous advances in science. Multiple efforts, including Tox21 program in the U.S., REACH Program in the E.U., and multiple industrial collaborations, are attempting to develop *in vitro* methods using induced pluripotent stem cell (iPSC)-derived cells to assess chemical toxicity. Stem cells or iPSC-derived cell types have great potential to provide more physiological relevance than immortalized/transformed cell lines and to provide larger quantities and higher assay reproducibility than primary cells. These programs must assess toxicity potential in every organ system and identify pathways and/or targets affected.

Given the protean nature of these effects, it is likely that hundreds of *in vitro* assays will need to be developed and evaluated for their ability to profile chemical effects on particular cell types and pathways. Progress in the field is currently limited by the relatively small number of pathways and cell types that have been developed into high-throughput screening (HTS)-ready assays, and the artificial nature of many of the assays that have been developed (e.g., immortalized/transformed cell lines, heterologous expression with lack of physiologically accurate regulation).

The development of HTS-ready assays using stem cells or iPSC-derived cells, which can report on particular pathways and cellular phenotypes across the full spectrum of pathway space and toxicological outcomes, is needed. Such assays would need to meet strict performance criteria of robustness, reproducibility, and physiological relevance. The assays developed would need to be capable of being run in 384-well or (ideally) 1536-well format and must allow the testing of >100,000 samples per week.

Main requirements

The outcome of this contract is expected to be one or more novel assays that can be performed in stem cells or iPSC-derived cells for targets, pathways, and cellular phenotypes related to any type of xenobiotic toxicity. These assays would utilize human cells, including primary cells and stem cell derived cells, and must be functional in multi-well format with characteristics suitable for automated high-throughput screening. Such assays should be novel, having metabolic capability, reflecting new pathways or cellular endpoints than are currently available, and be clearly connected to some type of human toxicological response. Such assays could find utility as in chemical assessment and risk management after validation.

Deliverables Phase 1

An assay that meets the requirements listed above and also meets the following:

- Develop a working assay in 96-well or denser (384, 1536) micro-well format
- Characterize the sensitivity, specificity, variability, reproducibility, signal: background, dynamic range, and accuracy of the assay, utilizing standard positive and negative controls, Z' values >0.5
- Demonstrate the utility of the assay by characterizing its ability to detect the effects of compounds known to affect the pathway/cellular phenotype, with a throughput of at least 10,000 samples/day with workstation automation
- Are not duplicative of assays already available commercially
- Deliver the assay/SOP to NCATS for evaluation

Deliverables Phase 2

- Demonstrate miniaturization of assay to work in at least 384-well (preferably 1536-well) format with same technical specifications as listed above
- Demonstrate amenability for HTS by successful testing of >100,000 samples/day in fully automated robotic format with maintenance of assay performance

- Deliver final assay/SOP to NCATS for evaluation.

014 Development of Smart Plate Technology

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning.

Number of anticipated awards: 2-3

Budget (total costs, per award): Phase I: up to \$225,000 for up to 9 months

Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary:

Microtitre plates are nearly ubiquitous in many life sciences laboratory settings, used as a standard tool to act as the vessel in which a wide variety of experiment types are performed. There are a variety of key parameters that dictate the application a particular plate type will be used for, such as the number of wells present on a plate, the color of the plate depending upon the detection method to be used, the material the plate is made from to ideally be as chemically inert as possible, the surface treatment or coating of the wells within a plate geared towards a specific experiment type and other parameters for more specialty plate types.

One nearly universal parameter regardless of plate type is that these plates are typically assumed to be a consumable product, used once and then discarded, making them in effect a disposable item. Depending on the laboratory in question, it is not uncommon for thousands if not tens of thousands of these plates to be consumed and discarded within a single year. Given the disposable nature of these parts, they have been manufactured with the idea that each plate will be a consumable product, and are typically made out of a variety of polymers using injection molding techniques, most commonly polystyrene and polypropylene. Given the consumable nature of the product and the materials used to manufacture them on a large scale at low cost, the typical features that distinguish one plate from another typically come down to the physical properties of the materials the plates are made of and any additional additives to them, potentially limiting the plate from being anything more than a vessel for an experiment.

Over the last ten years, High-Throughput Experimental Sciences (High-Throughput Screening) have evolved at a very rapid pace- mostly enabled by ever more sensitive assay constructs, and the evolution of detection and miniaturization schemes. Ten years ago a typical high-throughput assay would have 2-3 reagent constituents and a single absorbance or fluorescence-based readout. Today, modern screening facilities are commonly running very high-content, very data rich assays with optical microscopy- based readouts. These assays produce terabytes of data leading to information that is uncovering cellular behavior characteristics never before measured. These progressive steps have far out-paced the evolution of the microplate—as a “dumb” article made of plastic. The microplate component of the “system” needs to be significantly updated in its’ ability to harvest data, monitor environmental and atmospheric conditions, and report in real time any micro-climate variances-which are critical systemic contributors to cell performance.

Main Requirements:

The purpose of this project is to treat a microtitre plate not as a disposable product meant to act as a vessel for one experiment, but instead to potentially be a resource that can be used multiple times against a variety of different experiments. Instead of limiting these plates to only being a variety of plastics with a lifespan of one use, if different

materials and manufacturing techniques were utilized it could greatly impact what a plate could be used for. Imagining the plate as being used for a variety of monitor and control applications be built directly into the plate, such as temperature, relative humidity, CO₂ and O₂ levels etc., instead of relying on external pieces of instrumentation to perform these measurements.

The title of this solicitation is 'Smart Plate' in reference to idea of the Smart Phone; once a platform was built to create a phone that could perform a variety of functions as opposed to simply one a huge amount of innovative ideas sprang forth. The goal of this SBIR solicitation is to do the same, to fundamentally transform the idea of a microtitre plate from being a single use vessel for an experiment to nearly becoming an instrument itself which could provide more data about the samples under test to actually providing measurements in the plate itself. A key goal tied to this is to break the idea of a plate being completely disposable and instead treating each plate as a resource that can be used many times.

One important point of this solicitation is that we are **NOT** looking for the creation of a plate that only works with a specific piece of instrumentation; the goal is a feature rich plate that can be used in a variety of existing instrumentation.

Phase I Activities and Expected Deliverables:

- Develop a prototype that has the following features:
- Adheres as closely as possible to current ANSI/SLAS Microplate Standards
 - ANSI/SLAS 1-2004 (R2012) Microplates – Footprint Dimensions (formerly ANSI/SBS 1-2004)
 - ANSI/SLAS 2-2004 (R2012) Microplates – Height Dimensions (formerly ANSI/SBS 2-2004)
 - ANSI/SLAS 3-2004 (R2012) Microplates – Bottom Outside Flange Dimensions (formerly ANSI/SBS 3-2004)
 - ANSI/SLAS 4-2004 (R2012) Microplates – Well Positions (formerly ANSI/SBS 4-2004)
- The plate should provide the ability to work with different well types, shapes and materials.
 - The wells do not necessarily have to store sample; they could in fact be components that perform various functions within a plate.
- Incorporates automated sensing of variables such as temperature, relative humidity, volume, CO₂, O₂, pH and others of the samples within a well. Not all variables are represented and the prototype is not required to monitor all of these, these are just given as examples.
 - The values should ideally be accessible in real time; so in the best case scenario the 'Smart Plate' would have some sort of integrated messaging capabilities over common network protocols such as SMS, MMS, RFID or TCP/IP.
 - If messaging is not an option in real time, the ability to store these values to memory for retrieval at a later time is required.
- The device will ideally have some capacity to allow flow between wells through microfluidic channels. The pumps or devices used to generate the flow are not required as part of the plate itself but access ports should be available.
- Provide a detailed requirements and design document for the device, including mechanical and electrical drawings, in addition to hardware specifications and communications protocols used.
- Cost estimates to manufacture a device capable of meeting the specifications listed above.
- Provide NCATS with all data resulting from Phase I Activities and Deliverables.

Phase II Activities and Expected Deliverables:

- Build a prototype plate that meets the Phase I specifications.
- Provide a test plan to evaluate every feature of the device

- Provide NCATS with all data from each executed test to properly evaluate each test condition
- Develop a robust manufacturing plan for the device, using off the shelf OEM components where possible to minimize expense.
- Provide NCATS with all data resulting from Phase II Activities and Deliverables.

NATIONAL HEART, LUNG, AND BLOOD INSTITUTE (NHLBI)

The NHLBI plans, conducts and supports research, clinical trials and demonstration and education projects related to the causes, prevention, diagnosis, and treatment of heart, lung, and blood (including blood vessel), and sleep disorders. It also supports research on the clinical use of blood and all aspects of the management and safety of blood resources. The NHLBI SBIR/STTR program fosters basic, applied, and clinical research on all product and service development related to the mission of the NHLBI.

For more information on the NHLBI SBIR/STTR programs, visit our website at: <http://www.nhlbi.nih.gov/sbir>

NHLBI Phase IIB Programs

The NHLBI would like to provide notice of two SBIR Phase IIB funding opportunities. This notice is for informational purposes only and is not a call for Phase IIB proposals. This informational notice does not commit the government to making such awards to contract awardees.

The NHLBI offers Phase IIB opportunities through the NHLBI Bridge Award and the NHLBI Small Market Award using separate funding opportunity announcements (Bridge Award: [RFA-HL-16-009](#); Small Market Award: [RFA-HL-14-012](#)). The purpose of the NHLBI Bridge and Small Market Awards is to accelerate the transition of SBIR Phase II projects to the commercialization stage by promoting partnerships between SBIR or STTR Phase II awardees and third-party investors and/or strategic partners. The Small Market Award is designed to support technologies addressing rare diseases or pediatric populations. The Bridge and Small Market Awards encourage business relationships between applicant small business concerns and third-party investors/strategic partners who can provide substantial financing to help accelerate the commercialization of promising new products and technologies that were initiated with SBIR/STTR funding. In particular, applicants are expected to leverage their previous SBIR/STTR support, as well as the opportunity to compete for additional funding through the NHLBI Bridge Award or Small Market Award programs, to attract and negotiate third-party financing needed to advance a product or technology toward commercialization.

Budgets up to \$1 million in total costs per year and project periods up to three years (a total of \$3 million over three years) may be requested. Development efforts may include preclinical R&D, which is needed for regulatory filings (e.g., IND or IDE) and/or clinical trials.

An SBIR Phase IIB Bridge or Small Market Award application must represent a continuation of the research and development efforts performed under a previously funded SBIR or STTR Phase II award. The NHLBI welcomes applicants previously funded by any NIH Institute or Center or any other Federal agency, as long as the proposed work applies to the NHLBI mission. Applications may be predicated on a previously funded SBIR or STTR Phase II grant or contract award. Applicants with Phase II contracts or awards from another Federal agency must contact the NHLBI to ensure their application can be received.

Applicants are strongly encouraged to contact Jennifer Shieh, Ph.D. at 301-443-8785 or jennifer.shieh@nih.gov for additional information.

Limited Amount of Award

For budgetary, administrative, or programmatic reasons, the NHLBI may not fund a proposal and does not intend to fund proposals for more than the budget listed for each topic.

This solicitation invites proposals in the following areas.

094 Transcatheter Cavopulmonary Bypass Endograft

(Fast-Track proposals will be accepted.)

(Direct-to-Phase II proposals will be accepted.)

Number of anticipated awards: 2

Budget (total costs): Phase I: up to \$250,000 for up to 12 months; Phase II: up to \$3,000,000 for up to 36 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Extra-anatomic bypass or vascular shunts divert blood flow. In congenital heart disease, these surgical procedures are critical for management. Children born with one functional ventricle or cardiac pumping chamber require two to three major cardiac surgery procedures for palliation. The management goal is to divert systemic venous return (deoxygenated blood) from the heart directly to pulmonary artery circulation such that the single ventricle can pump oxygenated blood returning to the heart from the lungs to the body. These multiple surgical procedures carry significant morbidity and mortality, as well as incur substantial hospital costs secondary to lengthy hospital stays. A minimally invasive transcatheter approach would revolutionize the management of these children with congenital heart disease. No commercial alternatives exist for off-label medical use. Children born with “single ventricle physiology” represent 7.7% of congenital heart disease diagnosed in childhood and have a birth incidence of approximately 4–8 per 10,000. In the United States, this represents approximately 2,000 children born each year. The commercial market is small enough to discourage the early development costs of a transcatheter cavopulmonary bypass endograft. There is a considerable unmet need for a purpose-built cavopulmonary anastomosis device.

Project Goals

The goals of this project are to develop and test a transcatheter cavopulmonary bypass endograft prototype in vivo in Phase I, and to develop a clinical device and obtain an FDA Investigational Device Exemption (IDE) for first-in-human testing in the United States in Phase II.

Phase I Activities and Expected Deliverables

Expected deliverables are transcatheter endografts to be delivered using conventional interventional cardiovascular techniques including guiding catheters or sheaths, trans-lesional guidewires, and balloon-expandable or self-expanding delivery systems. Conventional and novel approaches are welcomed.

Specific requirements of the endografts include:

- Delivery systems (10-12 French or smaller);
- Sufficient radial force to resist elastic recoil (with specific focus at anastomosis site);
- Nominal calibers suitable for the most common lesions;
- Freedom from “pull-through” of the anastomosis once deployed; and
- Accommodation for growing children (ultimately dilatable to adult size vessels).

Proposed endograft nominal geometry should be diameter 10-14mm, length range 25-50mm, and delivery system 10-12 French or smaller. The radial hoop strength of the deployed device should approach that of commercial endovascular stent grafts such as Gore Viabahn or Atrium iCast. Percutaneous vascular access routes would be trans-venous. The implant and the delivery system should be conspicuous under the intended image-guidance modality; MRI compatibility is considered important. Offerings should specifically provide the high radial force required to overcome immediate recoil of the intended applications, and should allow “direct stent” treatment technique.

Considerable detail should be supplied about the intended mechanical and biological performance of the graft-pulmonary anastomosis, including resistance to inadvertent separation and pull-through, hemorrhage, thrombosis, neointimal overgrowth, angulation, distortion or failure by patient and cardiovascular motion, and anticipated flow characteristics.

Phase I should focus on mechanical and biological performance of the proposed endograft, taking into account the mechanical strength required for the application; geometry of the access vessels and geometry and morphology of target vessels; “growth” accommodation to achieve larger size and delivery, implantation, and visualization strategies.

At the conclusion of Phase I, a candidate device design should be selected for clinical development based on in vivo performance of a mature prototype resembling a final design. Consideration for transition to Phase II funding will include progress toward regulatory clearance. Consideration may include the status of the contractor’s interactions with the Food and Drug Administration (FDA); therefore, contractors are encouraged to provide a detailed report of pre-IDE interactions with the FDA identifying requirements for IDE development under Phase II, including the summary of mutual understanding, if available. NHLBI encourages contractors to consider requesting designation to the FDA’s Expedited Access for PMA Devices (EAP) program (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>) during the Phase I award period.

The sponsoring NHLBI laboratory is willing to perform a limited number in vivo proof-of-principal experiments in swine (by mutual agreement) to confirm mechanical performance.

Phase II Activities and Expected Deliverables

The activities in Phase II should align with the required testing and development milestones agreed upon with the FDA in Phase I. The device should fit the specifications as described in the Phase I Activities and Expected Deliverables. The offeror should provide clear project milestones.

At the conclusion of Phase II, the offeror should submit an IDE for a US-based first-in-human research protocol, involving at least 10 subjects.

If the IDE is not granted during Phase II, the offeror must provide an FDA response that indicates that the specific deficiencies are limited to Current Good Manufacturing Design Verification and Validation, and that the offeror-proposed plan to address these deficiencies would be considered acceptable.

Offerors are encouraged to consider the NHLBI Phase IIB Small Market Award program (<http://www.nhlbi.nih.gov/research/funding/sbir/small-market-awards.htm>) to support additional development beyond Phase II. The NHLBI Phase IIB Small Market Awards provide up to an additional \$3M over 3 years, with an expectation that applicants secure independent third-party investor funds.

The sponsoring NHLBI laboratory is willing to perform a limited number of in vivo proof-of-principal experiments in swine (by mutual agreement).

NHLBI offers, but does not require, to perform the clinical trial at no expense to the offeror, to participate in the development of the clinical protocol, and to provide clinical research services. The vendor is expected to perform or obtain safety-related in vivo experiments and data to support the IDE application.

095 Active MRI Transseptal Needle

(Fast-Track proposals will be accepted)

(Direct-to-Phase II proposals will be accepted)

Number of anticipated awards: 2

Budget (total costs): Phase I: up to \$200,000 for up to 12 months; Phase II: up to \$2,000,000 for up to 36 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Catheter access to the left atrium is a fundamental step to numerous transcatheter therapies including catheter ablation of rhythm disorders, diagnostic catheterization in pediatric and structural heart disease, and future treatments for mitral valve and left atrial appendage disease. MRI operation would enable radiation free catheterization and superior image guidance that are expected to enhance clinical outcomes. No MRI safe and conspicuous atrial transseptal needle is commercially available. “Active” MRI catheter devices contain electronic elements to produce MRI visibility. This topic aims to support the development of an active MRI transseptal needle catheter and accessories.

Project Goals

The goals of this project are to develop and test an active MRI transseptal needle catheter prototype and accessories in vivo in Phase I, and in Phase II to develop a clinical device and obtain an FDA Investigational Device Exemption (IDE) for first human testing in the United States.

Phase I Activities and Expected Deliverables

A Phase I award would support the development and testing of actively visualized atrial transseptal needle system prototypes.

The deliverable is a complete clinically-relevant system including:

1. A transseptal needle;
2. Accompanying electronics, if needed to enable safe active visualization and interface to the host MRI hardware;
3. A transseptal introducer sheath, which should be visualized passively or actively using real-time balanced steady state free precession MRI;
4. A matched dilator to allow safe delivery of the introducer sheath over the needle, which must also be clearly visualized, preferably using active visualization. “Active” refers to visualization by virtue of serving as a resonant antenna connected or coupled to the MRI hardware system.

The system should be free from clinically-important heating during continuous MRI at 1.5T. Proposals for novel alternative visualization and heat-mitigation strategies are welcomed.

The sheath should be 8.5Fr or smaller and approximately 71cm in length. Shapes should be available to accomplish transseptal puncture in a range of clinical applications; a deflectable sheath would be attractive.

The transseptal “needle” functionality can be conferred using any combination of mechanical, electrical, acoustic, or photonic energy.

A solution must be provided for visualization of the “active” electronic components using a real-time MRI system.

At the conclusion of Phase I, a candidate device design should be selected for clinical development based on in vivo performance of a mature prototype resembling a final design. Consideration for transition to Phase II funding will include progress toward regulatory clearance. Consideration may include the status of the contractor’s interactions with the Food and Drug Administration (FDA); therefore, contractors are encouraged to provide a detailed report of pre-IDE interactions with the FDA identifying requirements for IDE development under Phase II, including the summary of mutual understanding, if available. NHLBI encourages contractors to consider requesting designation to the FDA’s Expedited Access for PMA Devices (EAP) program

<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>) during the Phase I award period.

The contracting DIR lab is willing to provide feedback about design at all stages of development. The contracting DIR lab will test the final deliverable device for success in vivo in swine. This requires specific hardware compatibility with the NIH Siemens Aera 1.5T MRI system.

Phase II Activities and Expected Deliverables

Phase II activities should include testing and regulatory development for the device with specifications as described in the Phase I Activities and Expected Deliverables section to be used in first-in-human investigation in the United States, whether under IDE or 510(k) marketing clearance. IDE license or 510(k) clearance would constitute the deliverable.

096 Bioabsorbable Stents for Neonatal Aortic Coarctation

(Fast-Track proposals will be accepted.)

(Direct-to-Phase II proposals will be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$400,000 for up to 12 months; Phase II: up to \$3,000,000 for up to 36 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Aortic coarctation is a common congenital heart condition that is usually recognized during the neonatal period early after birth. The usual treatment is open surgery. Non-surgical catheter-based stent therapy is not available to treat neonatal aortic coarctation because children outgrow commercially available metallic stents. Absorbable stents might revolutionize the treatment of aortic coarctation in children, especially in neonates. Neonates require small delivery systems for relatively large nominal diameter implants, which is technically challenging. No commercial alternatives are available for off-label medical use. There is a considerable unmet need for a purpose-built, absorbable scaffold stent for neonatal aortic coarctation.

Project Goals

The Phase I award is intended to support the development of a mature prototype with the requisite geometry, strength, deliverability, and absorption characteristics required for the clinical product.

The Phase II award is intended to result in an Investigational Device Exemption (IDE) for a first human clinical test in the United States.

Phase I Activities and Expected Deliverables

Expected deliverables are transcatheter stents to be delivered using conventional interventional cardiovascular techniques including guiding catheters or sheaths, trans-lesional guidewires, and balloon-expandable or self-expanding delivery systems. Conventional and novel approaches are welcomed.

Specific requirements of the stents include:

- small delivery systems (5 French or smaller);
- sufficient radial force to resist elastic recoil for the coarctation;

- sustained radial strength suited to the application for at least 6 months;
- controlled degradation within 6-12 months;
- inflammatory response that does not cause significant stenosis, restenosis, or aneurysm;
- resistance to downstream embolization or toxicity;
- geometry that does not threaten patency of the subclavian artery;
- nominal calibers suitable for aortic coarctation.

Proposed stent nominal geometry should be diameter 6-10mm, length range 10-25mm, delivery system 5-6 French or smaller. The radial hoop strength of the deployed device should approach that of commercial balloon-expandable stent such as the Cordis Palmaz Genesis. Percutaneous vascular access routes for aortic coarctation application include transvenous-transeptal antegrade and retrograde transfemoral artery. The implant and the delivery system should be conspicuous under the intended image-guidance modality to allow precise positioning. Offerings should specifically provide the high radial force required to overcome immediate recoil of the target tissue, and should allow “direct stent” treatment technique for native and iatrogenic lesions.

Phase I should focus on mechanical and biological performance of the proposed biodegradable stents in the intended use for aortic coarctation, taking into account mechanical strength required for the application; geometry of the access vessels and geometry and morphology of target vessels; strategies to avoid inflammatory restenosis or constriction; and delivery, implantation, and visualization strategies.

At the conclusion of Phase I, a candidate device design should be selected for clinical development based on in vivo performance of a mature prototype resembling a final design. Consideration for transition to Phase II funding will include progress toward regulatory clearance. Consideration may include the status of the contractor’s interactions with the Food and Drug Administration (FDA); therefore, contractors are encouraged to provide a detailed report of pre-IDE interactions with the FDA identifying requirements for IDE development under Phase II, including the summary of mutual understanding, if available. NHLBI encourages contractors to consider requesting designation to the FDA’s Expedited Access for PMA Devices (EAP) program (<http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM393978.pdf>) during the Phase I award period.

The sponsoring NHLBI laboratory is willing to perform a limited number in vivo proof-of-principal experiments in swine (by mutual agreement) to confirm mechanical performance.

Phase II Activities and Expected Deliverables

The activities in Phase II should align with the testing and development requirements agreed upon with the FDA in Phase I. The device should fit the specifications as described in the Phase I Activities and Expected Deliverables. The offeror should provide clear project milestones.

The sponsoring NHLBI laboratory is willing to perform a limited number of in vivo proof-of-principal experiments in swine (by mutual agreement).

At the conclusion of Phase II, the offeror should obtain an IDE for a US-based first-in-human research protocol, involving at least 10 subjects.

NHLBI offers, but does not require, to perform the clinical trial at no expense to the offeror, to participate in the development of the clinical protocol, and to provide clinical research services. The vendor is expected to perform or obtain safety-related in vivo experiments and data to support the IDE application.

Offerors are encouraged to consider the NHLBI Phase IIB Small Market Award program (<http://www.nhlbi.nih.gov/research/funding/sbir/small-market-awards.htm>) to support additional development beyond Phase II. The NHLBI Phase IIB Small Market Awards provide up to an additional \$3M over 3 years, with an expectation that applicants secure independent third-party investor funds.

097 Early Detection and Monitoring of Cardiac Injury Due to Cardiotoxicity

(Fast-Track proposals will be accepted.)

(Direct-to-Phase II proposals will be accepted.)

Number of anticipated awards: 2-3

Budget (total costs): Phase I: up to \$250,000 for up to 12 months; Phase II: up to \$750,000 for up to 36 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Summary

Cardiotoxicity is increasingly recognized as a significant challenge to many existing therapies and as a potential barrier to the development of new therapies. For example, despite improved survival from cancer, chemotherapy-induced cardiotoxicity has emerged as a significant problem. Cardiovascular complication, particularly heart failure, is an important cause of morbidity and mortality among cancer survivors. In small studies, cardioprotective strategies against cancer therapy-induced cardiac dysfunction are effective if implemented early at the subclinical phase. However, detection of the frequency of subclinical disease and subsequent ability to protect against further functional decline are limited by inadequacy of current technologies to accurately assess and monitor changes in cardiac structure and function. Novel non-invasive strategies that detect early subclinical changes in cardiac structure, function, and/or tissue are needed to improve detection and monitoring of cardiac injury in order to improve cardioprotection and effectiveness of cancer therapeutics or other toxic exposure. Studies that demonstrate increased sensitivity and precision of existing or enhanced imaging technologies with respect to normal and altered cardiac structure, function, energetics, and metabolism are sought. Pre-clinical or patient studies using molecular changes or biomarkers to enhance early detection of cardiac derangements are also responsive.

Project Goals

The goal of this initiative is to encourage the development of innovative methods to detect and monitor cancer therapy-induced cardiac injury as early as possible through minimally invasive means. Early monitoring of cardiac injury will enhance both cardiac safety and treatment efficacy of cancer therapies.

Phase I Activities and Expected Deliverables

Phase I activities include proof-of-concept studies to demonstrate the feasibility of the method that will be fully developed in the Phase II. Examples of Phase I research and expected deliverables may include, but are not limited to:

- Design, testing, and initial *in vivo* validation of imaging methods or probes capable of assessing subclinical myocardial injury by cardiac MR, PET, or x-ray based imaging
- Identification, selection, and initial testing of biomarker-based monitoring methods of cardiac injury, specifically aimed for cardiac injury due to chemotherapy
- Studies to demonstrate innovative advances in ultrasound-based methods, including echocardiography, to improve sensitivity and resolution in order to assess early cardiac structural or functional changes

Phase II Activities and Expected Deliverables

Phase II activities are expected to include full development of the method whose feasibility was successfully demonstrated in Phase I, including additional validation in order to apply for regulatory approval and attract funding from industry. A detailed report of interactions with the Food and Drug Administration (FDA) identifying the

requirements for regulatory clearance or approval of the method is needed. Examples of Phase II activities may include, but are not limited to:

- Development and validation of imaging methods to assess subclinical myocardial injury by cardiac MR, PET, or x-ray based imaging
- Validation of biomarker-based monitoring methods of cardiac injury, specifically aimed for cardiac injury due to chemotherapy
- Development of novel ultrasound-based methods, including echocardiography, to assess early cardiac structural or functional changes

NATIONAL INSTITUTE ON ALCOHOL ABUSE AND ALCOHOLISM (NIAAA)

The mission of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) is to conduct and support biomedical and behavioral research, health services research, research training, and health information dissemination with respect to the prevention of alcohol abuse and the treatment of alcoholism, and to conduct a study of alternative approaches for alcoholism and alcohol abuse treatment and rehabilitation.

This solicitation invites proposals in the following area.

015 Development of Novel Compounds to Treat Alcohol Use Disorder

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning.

Number of anticipated awards: 1-2

Budget (total costs, per award): Phase I: up to \$225,000 for 6-12 months
Phase II: up to \$1,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Efforts to develop medications for the treatment of alcohol use disorder have expanded rapidly in recent years. Developing novel compounds for alcohol treatment is high priority for NIAAA Medications Development Program. Three agents directed at the addictive behavior in the use of alcohol—disulfiram, naltrexone, and acamprosate—are now approved for use in the United States and many other countries. Still, these medications do not work for everyone. Because of this, further research is needed to develop additional medications to treat Alcohol Use Disorder and organ damage caused by alcohol consumption.

During the past decade, many new targets in the brain and liver have evolved that alter alcohol-seeking and drinking behavior. Brain effects and behavior may be influenced by agents directed at CRF, adrenergic, opioid kappa, vasopressin V1b, NK1, orexin, NPY, NOP, glutamate mGluR2/3, mGluR5, GABA α -1 and α -5 receptors. Several intracellular targets in additional (peripheral) organs have also been identified that alter outcomes of chronic alcohol use, including ALDH-2; PKC; PPAR γ ; epigenetic modulators, (HDAC inhibitors, methylases, demethylases, and microRNAs); rapamycin complex 1; and GDNF. Tissue damage induced by the influence of alcohol or acetaldehyde on any of the above have serious negative consequences including development of steatohepatitis, cirrhosis or

hepatocellular carcinoma. Agents affecting these, and any other validated targets, may be synthetically derived or developed from plant materials.

Summary

This solicitation seeks to support the preliminary work required for the development of novel compounds to interact with recently identified targets to alter alcohol-seeking, drinking behavior and/or organ tissue damage caused by excessive alcohol consumption.

Project Goals

The goal of this solicitation is to provide support for the development of novel therapeutic agents to treat alcohol use disorder and tissue damage caused by excessive alcohol consumption.

Phase I Activities

If compounds have not yet been identified, activities include conducting high-throughput screening of libraries for novel compounds for further development. For identified candidate compounds, conducting preclinical animal studies to demonstrate proof of concept and safety; drug formulation and pharmacokinetic testing; drug optimizations and GMP manufacturing; IND-directed animal toxicology.

Phase I Expected Deliverables

- Conduct animal toxicology and pharmacology studies as appropriate for the agent(s) selected.
- Develop a detailed plan for future regulatory activities.

Phase II Activities and Expected Deliverables

- Complete IND-enabling experiments and assessments according to the plan developed in Phase I (e.g., demonstration of desired function and favorable biochemical and biophysical properties, PK/PD studies, safety assessment, preclinical efficacy, GMP manufacturing, and commercial assessment). The plan should be re-evaluated and refined as appropriate.
- Develop and execute an appropriate regulatory strategy. If warranted, provide sufficient data to file an IND or an exploratory IND for the candidate therapeutic agents (i.e., oncologic indications for CSCs).
- Demonstrate the ability to produce a sufficient amount of clinical grade material suitable for an early clinical trial.

NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES (NIAID)

The National Institute of Allergy and Infectious Diseases (NIAID) conducts and supports basic and applied research to better understand, treat, and ultimately prevent infectious, immunologic, and allergic diseases. For more than 60 years, NIAID research has led to new therapies, vaccines, diagnostic tests, and other technologies that have improved the health of millions of people in the United States and around the world. To learn more about the NIAID, please visit our web page at <http://www.niaid.nih.gov/about/whoWeAre/Pages/moreWhoWeAre.aspx>.

033 Precision Genome Engineering for HIV Eradication

(Fast-Track proposals will be accepted.)

(Direct to Phase II proposals will **not** be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: up to \$300,000 for up to one year; Phase II: up to \$2,000,000 for up to 3 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Highly active antiretroviral therapy is now optimized to control HIV-1 replication long-term, but the virus remains integrated into the host genome in a latent form and poses a threat for re-emergence. In search for more potent therapeutic agents geared towards HIV cure, newly developed chimeric nucleases, which allow the precise modification of viral and human genomes, have recently been explored for HIV reservoir elimination. These designer enzymes have the ability to disrupt the integrated HIV genome by double-stranded DNA break, so integrated proviruses become permanently defective, and to modify host genes essential for HIV replication, so cells become resistant to HIV infection. The gene-editing enzymes currently available to the scientific community are zinc finger nucleases (ZFNs), transcription activator like-effector nucleases (TALENs), homing endonucleases, and clustered regulatory interspaced short palindromic repeats (CRISPR)/Cas9. Each of these restriction enzymes is associated with unique strengths, but also with off-target effects.

Project Goals

The primary goal is to design improved nucleases for disruption of integrated HIV provirus and/or modification of host genes, so HIV replication is no longer supported. There is also a need for alternative delivery strategies for these nucleases to substitute for lentiviral gene delivery or plasmid transfections. An additional goal is to evaluate off-target effects and immune responses induced by the delivered nucleases and their vectors.

Phase 1 activities may include

- Design and test chimeric nucleases that irreversibly disrupt or excise HIV provirus in infected cell lines and peripheral blood mononuclear cells (PBMC)
- Design modified host genes and test their ability to impede HIV infection
- Evaluate off-target effects in cell lines and primary PBMC
- Develop strategies for eliminating off-target effects, including software tools for designing nucleases with reduced off-target sites

Phase 2 activities may include

- Develop and test improved delivery strategies
- Evaluate efficacy and adverse reactions of delivered nucleases in humanized mouse and nonhuman primate models
- Evaluate immune responses against nucleases and vectors *in vivo* and develop strategies to reduce the immunogenicity of the delivered constructs

034 High-Throughput Assay Platform for Quantifying Latent HIV Reservoirs

(Fast-Track proposals will be accepted.)

(Direct to Phase II proposals will **not** be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: \$300,000 for up to one year; Phase II: \$2,000,000 for up to 3 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

One of the most significant hurdles to overcome in evaluating strategies to cure HIV infection is the lack of a simple method for quantifying changes in the size of the latent reservoir of replication-competent HIV in resting CD4+ memory T cells in individuals on highly effective antiretroviral therapy. Most of the HIV DNA in these cells represents defective virus; less than 0.01% of highly purified resting CD4 cells harbor replication-competent provirus. As a result, PCR-based methods tend to over-estimate the size of the reservoir and do not correlate with the number of cells producing functional virus in a viral outgrowth assay. However, viral outgrowth assays are labor-intensive and require large volumes of blood.

Project Goal

The goal of this project is to design a high-throughput assay platform that can be used to reproducibly quantify changes in the size of the replication-competent latent HIV reservoir in resting CD4+ memory T cells isolated from individuals on highly effective antiretroviral therapy. Applicants must provide a plan for validating the assay by demonstrating correlation with quantitative viral outgrowth assays (QVOA) and/or functional non-induced HIV proviruses using cells isolated from virally suppressed HIV+ individuals on optimized antiretroviral therapy.

Phase 1 activities

- Development of technologies for detecting replication-competent latent proviruses
- Validation of detection methods using standardized controls
- Optimization of sensitivity to detect low-frequency latently infected cells
- Demonstration of correlation with replication-competent provirus vs. defective provirus

Phase 2 activities

- Further optimization of the assay platform technology and validation of assay reproducibility
- Increased throughput
- Comparison of assay to other methods published in the literature
- Testing of clinical samples from diverse cohorts of HIV+ individuals with varying levels of residual viral reservoirs
- Comparison of blood vs. tissue samples from virally suppressed individuals
- Modification of assay to detect latent HIV in humanized mouse models and latent SIV in nonhuman primate models in the context of optimized antiretroviral therapy
- Use of assay to demonstrate changes in the size of the latent HIV/SIV reservoir in response to an intervention

035 Method for the Detection of Minority Populations of Drug Resistant HIV

(Fast-Track proposals will be accepted.)

(Direct to Phase II proposals will be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: up to \$300,000 for up to 1 year; Phase II: up to \$3,000,000 for up to 3 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Antiretroviral therapy (ART) reduces mortality and morbidity in HIV-infected individuals. With successful therapy HIV RNA becomes undetectable, but drug resistance may occur. Specific HIV mutations are associated with resistance and these mutations can be detected through standard genotypic resistance tests, which have the ability to detect mutations only when they are present in approximately 20% of the virus population within an individual.

Importantly, it is now known that the presence of certain resistance mutations, even at very low concentrations within a patient's virus population (1% or more), can contribute to virological failure. These drug resistant minor variants can reflect the early emergence of acquired resistance during therapy, and can also be transmitted to newly infected individuals. These minor variants are not detected by standard drug resistance assays and methods to detect minor variants that contribute to HIV virological failure are needed. These assays would need to detect mutations causing resistance to each of the antiretroviral drug classes (NRTI, NNRTI, PI and INI) in all HIV subtypes, and must be inexpensive, since large numbers of patients would need to be screened.

Project Goal

The goal of this solicitation is to develop an assay to detect minor populations of resistant variants in blood specimens from HIV-infected individuals with HIV RNA viral loads above 1000 copies/ml. The test must detect resistant variants that comprise 1% or more of the virus population or quasispecies, and must detect mutations causing resistance to NNRTIs, NRTIs, PIs and INIs in all subtypes of HIV. Sensitivity for qualitative detection of the minor variant at 1% or more must be at least 95% and specificity at least 98%, but the method must also yield quantitative results, showing the percentage of each resistant variant in the overall quasispecies. Methods that detect a set of relevant point mutations and methods that collect full sequences are both acceptable. For methods that detect point mutations, a set of relevant mutations should be proposed in the application, but will be finalized in cooperation with DAIDS program staff. The method must be appropriate for use in centralized clinical laboratories with a target turn-around-time of less than 1 week and an initial target cost of \$100 or less.

Phase I activities

- Development of a method for the quantitative detection of minor populations of HIV resistance mutations comprising 1% or more of the viral quasispecies
 - a. Must detect major mutations causing resistance to all drug classes (NNRTI, NRTI, PI and INI)
 - b. Sensitivity must be at least 95%, specificity at least 98%
 - c. Must be suitable for clinical laboratory use, with turn-around time of less than 1 week
 - d. Cost must be less than \$100 per test
- Initial testing of the product with combinations of drug-susceptible and –resistant laboratory strains of HIV spiked into HIV-negative blood
- Additional testing on clinical isolates

Phase II activities

- Validation testing with controls as well as clinical isolates, including assessment of sensitivity, specificity, precision, accuracy, and linearity
 - Production of the test under good manufacturing practices (GMP)
 - Development of a quality control program to ensure lot-to-lot consistency
- Multi-site evaluation

036 Simple, Inexpensive Device to Purify DNA from Sputum for Tuberculosis Testing

(Fast-Track proposals will be accepted.)

(Direct to Phase II proposals will be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: up to \$300,000 for up to 1 year; Phase II: up to \$3,000,000 for up to 3 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Tuberculosis (TB) continues to cause significant mortality and morbidity throughout the world, especially in HIV-infected individuals. Increases in drug resistant TB cases have been occurring in many high endemic countries that have limited resources to identify and diagnose patients. Standard diagnostic techniques for TB include sputum smear microscopy to detect acid fast bacilli and microbiological culture confirmation. As a result, diagnosis of TB is both difficult and time consuming, especially in smear-negative, HIV-infected and pediatric patients. Molecular technologies are under development for TB case detection and identification of drug resistance mutations in lower levels of the health care system. These technologies will make use of sputum samples, the most important specimen type for TB diagnosis. Processing of sputum prior to PCR amplification will be necessary. A simple, inexpensive device to purify DNA from sputum and re-suspend the DNA in a buffer along with a compatible transfer system to molecular diagnostic assays is being sought. The purified DNA sample from the device should be compatible with many different technologies, thus removing the very difficult step of sample processing from development of the molecular test for Mtb detection and drug resistance testing. This would also allow the sputum processing and molecular testing to be delinked, with processing done immediately at the point-of-care.

Project goal

The goal of this solicitation is to develop an inexpensive (less than \$10), easy to use device for processing sputum samples to obtain purified DNA for TB testing to be used in a rural clinic setting with minimal infrastructure. Processing of the sputum must be performed in less than 30 minutes, without the need for external electricity (battery power can be proposed). The resulting material must: 1) be stable over a wide range of ambient temperatures in TB endemic areas (approximately 5 to 50°C), 2) must provide DNA comparable in quality and quantity to DNA prepared using standard laboratory methods, and 3) must provide results comparable to those obtained using DNA from standard laboratory methods in molecular assays for Mtb.

NOTE: The use of TB positive sputum samples may be proposed, but due to the difficulty in obtaining these samples, the use of spiked TB negative sputum samples from donors or artificial sputum samples may also be proposed for initial studies.

Phase I activities

- Development of a method for processing sputum to purify DNA for TB testing.
 - a. Sample processing time must be no more than 30 minutes with no more than 2-3 steps performed by the operator.
 - b. DNA recovery must be at least 50% compared to a gold standard laboratory method and must allow detection of Mtb in sputum containing at least 5-20 CFU/ml using a standard molecular detection method.
 - c. The CV for inter-operator variability must be no more than 20%.
 - d. Processed specimens must be stable for at least 7 days at temperatures ranging from 5 to 50°C.
- Initial evaluation of the product compared to DNA obtained using standard laboratory methods with at least one molecular TB test technology

Phase II activities

- Production of a small lot to be used for validation testing with at least one molecular Mtb test. Pre-defined validation targets should be specified.
- Validation testing with at least one Mtb test, to include precision, accuracy, sensitivity, and specificity with a standard laboratory method of DNA preparation as the comparator
- Manufacture of the product under good manufacturing practices (GMP) and compliant with the requirements of ISO 13485
- Development of a quality control program to ensure lot-to-lot consistency

037 Telemonitoring for Infectious Diseases: A Remote System for Assessing Patient Parameters and Specimen Analysis

(Fast-Track proposals will be accepted.)

(Direct to Phase II proposals will be accepted.)

Number of anticipated awards: 2-3

Budget (total costs): Phase I: up to \$225,000 for up to 1 year; Phase II: up to \$1,500,000 for up to 3 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Traditional methods for the diagnosis and clinical management of infectious diseases require the direct assessment of a patient's symptoms, vital signs, and often the collection and analysis of clinical specimens by health care practitioners, usually in a health care setting. Recent scientific advances in mobile and remote monitoring technologies have enabled home-based telemonitoring of multiple physical parameters in patients with chronic medical conditions including cardiovascular disease, diabetes, hypertension, and asthma. Additionally, advances in rapid diagnostic platforms to detect pathogens have also been recently realized. There is now a unique opportunity to leverage and integrate the advances made in these two areas of research and their associated technologies and to apply them to the development of portable and continuous monitoring systems to revolutionize the early detection, progression, and/or effects of treatment of patients with infectious diseases.

The emerging development of portable monitoring devices and technologies have yet to be applied to infectious diseases and may have a significant impact on clinical management. Systems that are able to remotely monitor and report physiological status with minimally-invasive specimen collection would be useful ways to inform and support the clinical management of disease, e.g., in premature infants at risk for (or already diagnosed with) RSV, in elderly individuals with chronic illness. Remote monitoring of patients for the occurrence or worsening of an infectious disease may result in early clinical intervention and optimize the use of available therapies. Such "real-time" monitoring of symptoms and/or disease progression would also add value by avoiding unnecessary trips to the ER/physician, and reducing healthcare costs. While this type of monitoring system is envisioned to be broadly applicable, some patient populations (infants, elderly adults, and immunocompromised individuals) may have greater benefit as they may not show symptoms on examination, yet they may have an increased chance of developing infections due to recent medical procedures or to rapid worsening of a previously diagnosed infectious disease.

Project goal

The overall goal of this solicitation is to develop a device that can, in a non-clinical setting, monitor and report data that reflects the emergence and/or progression of an infectious disease. The complexity of such a device, and its operation, should allow for its use in patient environments such as a home or a nursing facility and be capable of communicating "actionable" data to professional healthcare workers. Ideally, such a device would have an integrated architecture consisting of a physiological monitoring component, and/or a specimen collection apparatus with equipment to analyze the sample, and a communications functionality for data transmission; however, the capability for specimen collection is not required for applications that involve physiological measurements only (i.e. that do not require evaluation of analytes). A highly desirable feature for a device that requires sample collection might be a visual menu that provides simple instructions for outpatient specimen collection when needed, so that family members or care providers could support the analytical device with minimal training. The types of information to be collected may include, but are not limited to: physiological measurements (vital signs), analytes (biomarkers) that are present in bodily fluids or breath and measures of behavioral responsiveness to environmental stimuli. Evidence must be presented that the data collected by the device is directly relevant to the occurrence and/or progression of an infectious disease and that its ultimate use will be to support clinical decision-making.

Phase I activities include but are not limited to:

- Development of appropriate tests / physiological measurements to be used for monitoring of disease
- Proof of concept that the information can be used to infer a clinically-relevant change in disease state
- Initial design of integrated device for outpatient monitoring including, if proposed, specimen collection / analysis

Phase II activities include but are not limited to:

- Development of prototype device for monitoring and reporting of infectious disease status
- Development of analytic software (beta version) to evaluate and report results
- Optimization of any reagents that are required for analytic tests
- Validation of test procedures to address issues of reproducibility, sensitivity and specificity
- Proof of concept that device can integrate measurement / analysis steps with data transmission

038 Innovative Oral Formulations for Anti-Infective Drugs

(Fast-Track proposals will be accepted.)

(Direct to Phase II proposals will be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: up to \$225,000 for up to one year; Phase II: up to \$1,500,000 for up to 3 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

There is a persistent need to develop alternative, simple to administer formulations of FDA approved anti-infective agents for use by children and by adults who have difficulty taking traditional tableted drugs. These formulations will simplify administration for caretakers and patients and ensure compliance.

There are few child-friendly formulations of pediatric anti-infective medications available to practitioners in the U.S. and especially globally. It is standard practice to cut or crush un-scored adult tablets and administer them to children in juice or other palatable substances, such as food. This practice has significant potential to deliver incorrect and highly variable doses to children, contributing to ineffective treatment. For some adult patients, especially those with difficulty swallowing or those with dementia or other mental impairments, taking standard pills or syrups may be problematic and also affect compliance.

For infectious diseases, completion of drug therapy is critical to assure cure and reduce development of resistance. Resistance often develops when therapy is terminated early or drugs taken intermittently, rather than the prescribed daily doses. Furthermore, for infectious diseases that require long term dosing such as tuberculosis or HIV/AIDS, there is evidence of decrease of patient compliance as time goes on, particularly if drugs are not very palatable. Customized oral formulations are needed that facilitate long term compliance and are of sufficient stability to be suitable for use in resource limited countries.

Examples of the types of oral formulations that may address these issues include, but are not limited to:

- Oral thin-films
- Porous, chewable matrix systems (scorable “Taffy” based on patient weight)
- Candy-like formulations, including gummies and jellybeans

It is recognized that these formulations may only be suitable for highly active anti-infective drugs.

While consideration of pediatric applications is a recent regulatory requirement for novel drugs in general, this requirement does not apply to a majority of anti-infective drugs that are already off patent and therefore, development of new formulations should be an attractive commercial goal for small businesses. In addition, offering these easier to take formulations to adults who have difficulty taking oral tablets would further expand the utility of these innovative dosing forms, as well as facilitate overall compliance with taking medicines.

Project Goal

The goal of this project is to develop innovative oral formulations for FDA approved anti-infective agents (antibacterials, antifungals, antiparasitics, and antivirals, including anti-retrovirals for HIV/AIDS) other than nanoparticles or pills to facilitate administration to patients who are either too young or have difficulty taking oral medications. The final product should be simple to manufacture, stable under ambient conditions and ready for testing in Phase I bioequivalence and PK studies.

Phase I activities include but are not limited to

- Develop prototype formulations that address the goals of this solicitation
- Develop analytical assays to characterize the chemical composition, purity and stability of prototype formulations
- Assess the pharmacokinetic profile and safety of the formulations when delivered in the intended way, in appropriate systems
- Conduct or develop drug potency assays for bioequivalence studies

Phase II activities include but are not limited to

- Scale-up the formulations (activity need not be compliant with cGMP) for further preclinical studies
- Conduct additional pharmacology and toxicology evaluations of the formulations in appropriate systems
- Conduct other pre-clinical studies necessary for subsequent human bioequivalence studies

This SBIR will not support:

- The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial>) for the NIH definition of a clinical trial). For SBIR phase II clinical trial support, see the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#).

039 Vaccines against Pathogens with Small Market Potential

(Fast-Track proposals will be accepted.)

(Direct to Phase II proposals will **not** be accepted.)

Number of anticipated awards: 2-3

Budget (total costs): Phase I: up to \$225,000/year for up to two years
Phase II: up to \$1,000,000/year for up to 3 years

Proposals that exceed the budget or project duration listed above may not be funded. In all cases, applicants should propose a budget that is reasonable and appropriate for completion of the proposed research project.

Background

There is an urgent need to develop vaccines against pathogens affecting a relatively small segment of the US population. While the market or segment of the overall population affected may be statistically small, the morbidity and mortality in some cases can be quite substantial. NIAID is interested in receiving proposals to develop vaccines against small or limited market-type pathogens. Specific examples of unmet vaccine needs that would fit this request would be Coccidioidomycosis/San Joaquin Valley Fever (VF), Lyme disease, as well as vaccines for selected high risk populations.

Project Goal

- To promote identification, characterization, validation, and ultimately product development of potential vaccines against pathogens with limited market potential.
- To encourage collaboration between academic researchers and small business entities to discover, validate and produce vaccines for pathogens with small market potential.

Phase I activities include but are not limited to

- Identification, characterization, and validation of vaccine candidates
- Development of in vitro assays to qualify vaccine candidates for future product development
- Selection of adjuvant, as appropriate, for further development and antigenicity testing

Phase II activities include but are not limited to

- Additional testing of the lead vaccine candidate(s) in the vaccine product development pathway leading to IND-enabling studies, including but not limited to testing to improve safety, efficacy, and QA/QC
- Pilot lot of cGMP manufacturing for further refinement of the vaccine candidate(s)
- Formulation, stability, and toxicology studies, as appropriate, for later stages of the vaccine product development pathway

This SBIR will not support:

- The design and conduct of clinical trials (see <http://www.niaid.nih.gov/researchfunding/glossary/pages/c.aspx#clintrial>) for the NIH definition of a clinical trial). For SBIR phase II clinical trial support, see the [NIAID SBIR Phase II Clinical Trial Implementation Cooperative Agreement program announcement](#).
- Platform development such as vehicle or delivery systems.

NATIONAL INSTITUTE ON DRUG ABUSE (NIDA)

NIDA's mission is to lead the nation in bringing the power of science to bear on drug abuse and addiction, through support and conduct of research across a broad range of disciplines and by ensuring rapid and effective dissemination and use of research results to improve prevention, treatment, and policy.

This solicitation invites proposals in the following areas:

158 Development of Primer and Reference Tool to Assess Neonatal Abstinence Syndrome

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning.

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: up to \$150,000 for up to 6 months; Phase II: up to \$1,000,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Objective

This topic addresses the demand to promote awareness and knowledge of the best practice in management of Neonatal Abstinence Syndrome (NAS). The need is caused by clinical rigor and raised concerns among neonatal and pediatric practitioners regarding a constellation of various withdrawal symptoms and treatment approaches. The ultimate goal of this solicitation is to develop a skill-building Primer and Reference Tool to assist clinicians in identifying, interpretation, scoring and responding to NAS symptoms toward improving neonatal outcomes.

Background

NAS is a group of withdrawal problems that occur in a newborn who was exposed to addictive drugs while in the mother's womb. NAS characterized by gastrointestinal, respiratory, autonomic, and central nervous system disturbances from drug withdrawal that affect critical regulatory areas for postnatal life adaptation. Withdrawal signs may develop in 37% to 94% of neonates exposed by various addictive substances including illegal drugs or prescribed analgesics and antidepressants.

In the past decade, the use of prescription opioids and the incidence of opioid addiction among women of childbearing age increased substantially. According the American Academy of Pediatrics, the number of opioid-dependent NAS diagnoses increased threefold reaching more than 13,000 babies across the United States annually. Currently, the consistent use of pain relievers with other drugs become more common that causes the NAS symptoms to be more severe and poorly manageable. At the consequence, newborns with NAS present new challenges for the neonatal hospitals and may require prolonged hospitalization in order to alleviate the symptoms. The national health cost to care for such infants jumped from \$190 million in 2000 to \$720 million per year in 2009. In addition, there is the growing concern, that hospitals may discharge some newborns before the symptoms appearance, if newborns were exposed by long-acting opioids with five or more days to show signs of withdrawal. These newborns present the significant challenge for diagnostics at hospital emergency rooms or out-patient pediatric units outside of the nation's epicenters of drug abuse.

To date, there is neither a standard diagnostic tool, preventive treatment strategy, nor a comprehensive educational program to manage NAS. Among educational resources, few existing online applications (Neonatal Drug Withdrawal Protocol App, Kaiser Permanente; Neonatal Abstinence Syndrome CE581, Nurse.com) are limited in the context and provide general text-based information with no interactivity rather than helping practitioners to adapt the clinical symptoms to the established diagnostic and treatment guidelines.

Responding to the demand for NAS awareness and medical care standardization, the National Institute on Drug Abuse (NIDA) supports development of a medical Primer and Reference Tool to specifically address the information gap in this critical pediatric health problem. With the long-term goal of improving neonatal health care, NIDA is soliciting proposals for a SBIR contract to develop and evaluate a bedside assisting App for NAS management.

Currently, the modified Neonatal Abstinence Scoring System (or Modified Finnegan Scoring system) is the predominant scoring tool used in the United States. Despite of its complexity and bulkiness as the 21-item related observation checklist, the Modified Finnegan Scoring remains more comprehensive system. The value of NAS severity, calculated by this tool, is a critical feature for any NAS assessment which serves as the basis for treatment selection and start. Recently, the Modified Finnegan Scoring was incorporated into the electronic medical record (EMR) platforms in the national centers of pediatric care excellence and the nation's epicenters of drug abuse. However, outside the recognized medical centers, most nurses and pediatricians have little experience in NAS evaluation and Finnegan Scoring. These hospital codes are unfamiliar with the criteria of NAS and may give the neonatal an alternative diagnosis that shares signs with NAS such as infection, hypoglycemia, hypocalcemia, hyperthyroidism, intracranial hemorrhage, hypoxic-ischemic encephalopathy, and hyperviscosity. At presentation, signs of NAS vary and usually include excessive cry, irritability, short sleep, tremors, stiffened muscles, gastro-

intestinal and respiratory problems. NAS unawareness or different practice standards cases the number of challenges in diagnostics and therapeutic strategies.

Thus, the lack of the standard management and bed-side references causes bias and subjectivity in NAS scoring and assessment. To address this problem, the new electronic tool should adapt and unify the existing knowledge regarding NAS risks, symptoms, Finnegan Scoring, diagnostic and therapeutic approaches. New tool is sought to better explain the withdrawal symptoms in newborns and provide bed-side instructions how to assess the Modified Finnegan Score. The primary target audience for the proposed tool includes neonatal practitioners, pediatricians, and nurses. However, the material are sought to be useful for a wide range of health care professionals from family or GYN physicians, pain prescription provides to medical and nurse students who wish to continue their medical carrier to pediatrics.

Phase I Activities and Expected Deliverables:

Technical Requirements

1. Assemble a consultant team and determine availability of data, references, educational and clinical guidelines, and presentation strategies. *Offerors are expected to have in house capabilities or the established practice or experience to contact consultative and CME educational services, neonatal centers, hospitals, professional associations and medical practitioners including but not limited to neonatal providers, nurses, pediatricians, and pain prescription physicians.*
2. Develop a curriculum for education modules and interactive resources. An electronic Tool should adapt the skill-building multimodal Primer and serve as a bed-site Reference Tool for neonatal and pediatric providers.

A Primer and Reference Tool proposed in response to this solicitation should provide the repository of necessary information in following areas:

- a. *Epidemiology and pathophysiology of NAS.*
 - b. *The clinical phenomenon of NAS symptoms. Clinical signs, frequency, severity and duration of NAS. Mechanisms of opioids withdraw. Clinical facts of multi-drug exposures and their impact to NAS development and representation.*
 - c. *Interpretation of the Modified Finnegan Score system. Guidelines in assessment and scoring.*
 - d. *Overview of available and appropriate toxicology tests to determine the exposure level. All drug screening procedures should contain corresponding references to the test sensitivity, efficiency, time for analysis, cost and diagnostic limitations.*
 - e. *Description of pharmacologic and non- pharmacologic interventions. Interactive referral and references how to select the appropriate therapy based on the symptoms appearance and NAS scoring. The materials should describe the importance of breastfeeding in stable mothers.*
3. Define and collect all reference materials such as medical publications, scientific references, best-practice guidelines, and other downloadable tools. A Tool may be built with the option for interactive questions.
4. Identify an electronic platform for the software implementation. A Tool's App should have full compatibility with both Flash and FULL compatibility with HTML5 standards.
5. Develop a detailed project plan for Phase II activities which includes, but is not limited to:
 - a. Project Gantt
 - b. Task linked budget for Phase II Activities
 - c. Mock Ups outlining of Phase I Deliverables 2 (a-e) and Description of the Software

- d. Plan for the case study recording
- e. Examples of surveys to be used in Phase II Activities
- f. Plan for piloting, evaluation, and refinement of draft modules
- g. Plan to address FDA-regulations if a Tool is to be disseminated as a NAS scoring and a clinical/treatment reference device w/wo compatibility with electronic medical records (EMR) software.

Phase I Activities and Expected Deliverables:

Technical Requirements

1. Develop a multimodal awareness building program of a Primer and Reference Tool:
 - a. Collect case presentations (video and descriptive) to supplement tool's modules and address the challenges in NAS symptoms recognition and interpretation;
 - b. Create reliable software as required. Code the device as needed.
2. Conduct a Pilot study of the draft module with professionals representing the target audience to a Primer and Reference Tool. Conduct community's feedback survey and analyze data.
3. Revise and improve software in response to perceived needs. Complete the web-based lesson context, iterative design and development of the software operation tools.
4. Conduct efficiency study and evaluate the effectiveness of a Primer and Reference Tool. Complete satisfaction and acceptance testing.
5. Prepare strategy for implementation and dissemination.

159 Therapeutic Cannabidiol Pulmonary Delivery Device (e.g. Nebulizer, Vaporizer or Inhaler)

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning.

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: up to \$225,000 for up to 6 months; Phase II: up to \$1,500,000 for up to 2 years

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED

- All studies conducted using Cannabidiol (CBD) must be conducted in accordance with appropriate Federal laws and regulations. At the present time this means a Schedule 1 license under the Controlled Substances Act would be required. Such a license would not be a requirement at the time of submission (but would be required to hold and work with CBD).
- All CBD used in conducting these studies must be obtained in accordance with Federal law, for example to be supplied by the National Institute on Drug Abuse, or from another party with the appropriate license under the Controlled Substances Act.

Objective

To develop a pulmonary delivery device that can administer therapeutic doses of the non-psychoactive cannabinoid CBD. The ultimate goal is to generate a sufficiently characterized clinical tool such that the Food and Drug Administration (FDA) would allow it to be used to evaluate the efficacy of inhaled CBD as a therapeutic agent in clinical trials.

This opportunity is open to all Small Business Innovation Research (SBIR) award-eligible organizations. However, it is anticipated that a Small Business Concern (SBC) best equipped to produce such a characterized device and data package within the time and budget constraints might currently be marketing a similar or related inhalation product.

Aspects of a Market analysis

The NIDA foresees a niche for the SBC with a pulmonary CBD delivery device that has previously successfully undergone Federal IND review. This product would be marketed to clinical researchers wishing to conduct clinical studies into potential therapeutic effects of CBD. The SBC would supply the researchers with devices and allow them to cross-reference the original IND in their own FDA application(s). All proprietary information would be kept between the SBC and the FDA.

- **Diversified Income Stream-** Clinical researchers in the US (and beyond) represent limited / no-competition market niche, protected by the costs involved in characterizing the device and obtaining an IND.
- **In a market where designs are rapidly evolving** this represents a situation where a stable device design is prized and minimal future R&D investment will be required.
- **Informing Product Development-** Characterizing your existing product will aid future design efforts and perhaps “future-proof” against a scenario where greater regulatory oversight might require characterization.
- **“Free” Clinical Data Studies** The product would be described as a generic NIH device, but the SBC would be welcome to reveal their involvement in NIH clinical studies in their marketing materials.

Background

CBD is a compound found in marijuana that has no euphoric properties but appears to have other pharmacological activities. Current understanding of CBD pharmacology is limited; a number of laboratory studies have been conducted and a few have progressed into early clinical phase investigations, the most successful demonstrating CBD as an anxiolytic agent. Potential applications for the anxiolytic properties of CBD include reduction of craving and relapse in Substance Use Disorders, and reduction of anxiety in Post-Traumatic Stress Disorder. In addition, CBD is currently under clinical investigation for the treatment of childhood intractable epilepsies, where it is added to the existing medication regimen (usually, to 2-3 other drugs). However, CBD is well known as an inactivator of drug metabolizing enzymes and so can significantly disturb the patient’s exposure to their current medications and potentially contribute to serious drug interactions. If CBD is to be administered via a pulmonary (inhaled) mechanism rather than via oral route, the liver exposure would be much lower, resulting in less enzyme inactivation and drug-drug interactions. Furthermore, inhaled CBD provides 2-3x greater bioavailability and shows substantially lower inter-dose and inter-subject variability than with oral administration. when used in a clinical trial a pulmonary delivery device would result in more reproducible CBD dosing, less risk of drug interactions and ultimately less variable and more reproducible clinical data.

Project Overview

- The solicitation is open to all small businesses. SBCs with similar / related existing technologies are especially encouraged to apply.
- Products based on herbaceous material will not be acceptable, all formulations will need to be liquids or solids manufactured according to current Good Manufacturing Practices (cGMP).
- The delivery device could be in the form of a vaporizer, nebulizer, dry-powder inhaler or any other FDA-approvable pulmonary delivery device.

- Phase 1 of the project characterizes the quantity and reproducibility of CBD delivered in a single 5-second puff, as well as the identities and the amounts of all other agents in the vapor/aerosol.
- All components of the device and liquid are to be manufactured according to Good Manufacturing Practices (cGMP) or when such standards do not exist manufacturing should be performed according to the “spirit of GMP”.
- Analytical Studies are to generate Certificates of Analyses demonstrating an appropriate and reproducible CBD output as well as quantities of all other emissions. Studies are to be conducted by an ISO 17025 laboratory.
- The Phase I deliverables also include the minutes of an FDA pre-IND submission meeting outlining FDA expectations for any additional studies / data that would be required for a successful IND application.
- If selected to progress into phase II, the SBC is to conduct the studies required by the FDA to achieve a successful IND to examine the pharmacokinetics of CBD delivery by the device in normal healthy adults. In addition, in Phase II, a 10 person study would be conducted to evaluate the pharmacokinetics of single dose/session administration of CBD using the device. It is recognized that a pharmacokinetic study may not always require an IND, but a protocol is required for the FDA to consider the suitability of the data package for issuance of IND. Once the data package has been allowed for one study, that IND can then be cross-referenced in future studies.
- It is expected that the data from the pharmacokinetic study would be published in a peer reviewed journal).
- Phase II projects will also require elucidation of the strategy that will be used to move the proposed research tool to a marketable product. Evidence of a track record of commercialization and / or commitment of additional investment from private sector or other non-SBIR funding sources will be expected.
- Phase II would consist of studies aimed to satisfy FDA requirements for issuing an IND and the conduct of a 10 person study to evaluate the pharmacokinetics of single dose/session administration of CBD using the device. It is recognized that a pharmacokinetic study may not always require an IND, but a protocol is required for the FDA to consider the suitability of the data package for issuance of IND.
- The SBC would agree to market this device as characterized (without further change) to all clinical researchers who have been granted NIH funds to conduct the relevant studies.
- The device would be available for a sufficient period after the completion of the project to allow clinical studies to be conducted (i.e. 5-10 y).
- The SBC would retain the proprietary data held within the Drug Master File but would allow NIH researchers (and other customers) to cross reference the original Investigational New Drug Application (IND) using that data in order when seeking FDA approval for their study.
- The battery used in the device must be rechargeable using a USB port and not meet the definition of hazardous waste as described in 40 CFR 261, subpart C.
- The device should deliver at least 40 mg CBD to the vapor / aerosol over 10 minutes of use
- Availability of other formulations such as a placebo formulation would be desirable, but not essential. If several formulations are proposed, the budget may potentially be modified accordingly during the negotiation phase (if the government determines negotiations are necessary). A formulation that contains a defined low amount of THC in combination with the required CBD delivery would also be viable as an additional formulation, although NIDA would need to be the source of the THC during the course of the contract.
- Phase II would consist of studies aimed to satisfy FDA requirements for issuing an IND and the conduct of a 10 person study to evaluate the pharmacokinetics of single dose/session administration of CBD using the device. It is recognized that a pharmacokinetic study may not always require an IND, but a protocol is required for the FDA to consider the suitability of the data package for issuance of IND.

The Phase I contract proposal must include:

- A description of the device appearance and characteristics, including (but not limited to)
 - The liquid reservoir volume
 - The device dimensions and weight
 - An image of the device
- Information regarding protections to prevent a user's exposure to the CBD containing liquid.
- Estimation of the number of puffs per cartridge, tank fill or disposable device (as appropriate) using a defined puffing topography (see Phase I Activities and Expected Deliverables).
- Estimation of the number of 5 sec puffs on a single battery charge (where applicable). The number of times a battery can be discharged to less than 20% of full charge and then recharged to >90% of specified full charge (estimation of battery life) should be described.
- Estimation of device time to failure.
- Concentration of CBD in the liquid formulation(s).
- Indicate the differential characteristics of each formulation (if several formulations are planned).
- Describe and provide examples of the data output, if the device possesses a data recording capability (not a requirement).
- The number units developed under this contract that are anticipated to be supplied annually and an indication of number of related units sold in a similar market place over last 1-2 years
- Documentation regarding capability to provide the device for a minimum of 5 years after the end of the development contract.
- Demonstration of the knowledge and capability to provide cGMP reagents in the completed device (see Guidance for Industry Q7A Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients).
- The anticipated cost of the device and any required accessories such as cartridges or battery chargers (where applicable). Cost should also be described in terms of equivalence to a typical herbal extract / nicotine vaporizer as well as the cost over the lifetime of a single device.
- It is recommended (but not essential) to describe experience of the key investigators or organization in the development of marketing of similar products to that proposed in this project.
- Demonstration of manufacturing and supply chain stability, is strongly advised including letters of support where applicable.

Phase I Activities and Expected Deliverables

This phase focuses on characterizing the chemical and mechanical characteristics of the device, including:

- Number of puffs per cartridge, tank fill (as appropriate). This is to be determined using a standardized puffing topography: 10 sec per puff, 60 ml puff volume, 20ml/sec flow rate, 30 sec puff interval. Grantees should also describe and test the optimal puff topography for their device, if different.
- The approximate number of 10 sec puffs, using the standard puffing topography, on a single battery charge (where applicable).
- Analysis of device time to failure.

- Chemical and Manufacturing Control (CMC) information for filing a Drug Master File (DMF) with the FDA. Batch reproducibility will also be covered in the CMC. Data will be generated from an ISO 17025 accredited laboratory.
- Information to be included in the DMF should be in agreement with the following FDA guidelines:
 - Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances.
 - Guideline for the Format and Content of the Chemistry, Manufacturing, and Controls Section of an Application.
 - Guideline for Submitting Documentation for the Manufacture of and Controls for Drug Products.
 - Guideline for Submitting Samples and Analytical Data for Methods Validation.
 - Guidance for Industry INDs for Phase 2 and Phase 3 Studies - Chemistry, Manufacturing, and Controls Information.
- List of ingredients and a Certificate of Analysis (CoA) for each liquid formulation. Constituents analyzed must include: CBD, other cannabinoids present, cannabinoid breakdown products and vehicle components, for example, ethanol, propylene glycol, glycerin, acrolein and formaldehyde. Reproducibility of liquid constituents should be demonstrated for at least 3 consecutive lots
 - CoA will be generated from an ISO 17025 accredited laboratory.
 - CoA for the vapor /aerosol produced by the device using the standardized puffing topography. Data should show the amount of CBD in the inhalant collected from the first 10 puffs and the amounts of all constituents (above 1 µg) present in the vapor collected from the first 150 puffs.
 - Indicate highest temperature of vapor / aerosol exiting device during a standard puff.
 - Indicate aerosol droplet size range where appropriate.
 - Indicate variation in the vapor constituents over the lifetime of the device.
- Long term and accelerated stability that will be initiated in Phase I for the final device with each of the different liquid formulations. To be included in the Phase I report is the 30 day accelerated (40°C, 75% relative humidity) stability testing. The testing should be conducted in a manner consistent with the following FDA guidance: Guidance for Industry Q1A(R2) Stability Testing of New Drug Substances and Products.
- A Drug Master File for the device including all liquid formulations, completed to FDA specifications.

160 “The Pain Mobile”: Remote Pain Management System

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Phase II budget and duration information is provided to assist Phase I offerors with their long-term strategic planning.

Number of Anticipated Awards: 2-3

Budget (total costs): Phase I: up to \$150,000 for up to 6 months; Phase II: up to \$1,000,000 for up to 2 years.

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Objective

Provide in-home access to coordinated comprehensive pain treatment through a mobile treatment platform. This platform may range from a fully equipped mobile clinic, to a mobile extension of a traditional pain clinic, or a virtual network of mobile treatment services. Note that opioids may be part of this comprehensive treatment plan and may be prescribed, if warranted, but will not be delivered through the pain mobile platform.

Background

Pain is a major health crisis in America, where chronic pain afflicts nearly a third of our population. Opioids can be a powerful tool in fighting pain; however they are too often used as substitute for a comprehensive interprofessional pain treatment program. Patients are merely sent home with a bottle of pills. The result is pain is often inadequately treated and opioids are over used.

In an effort to improve pain treatment and reduce dependence on opioids, NIDA is soliciting applications to create a mobile pain management system. Core to this solicitation is the delivery of a comprehensive pain treatment system to a pain patient's home, as it is difficult for many pain patients to make numerous needed visits to clinical settings. Opioids may be prescribed as part of this comprehensive treatment plan, but will not be dispensed. The patients will have to get opioids from pharmacies (either in person or via a delivery system).

This "pain mobile" can be an actual portable clinic that is equipped and staffed to treat pain. Alternatively, it can be more of a virtual remote pain treatment system, where health care providers get to patients homes using various means other than a devoted vehicle. It can also be a hybrid of these approaches. However, it is crucial that visits and treatments are coordinated in a way that delivers comprehensive and appropriate pain treatment. This coordination can be done from the actual pain mobile or *via* a remote site.

The health care providers that visit the pain patients need to have appropriate training (e.g. nurse practitioner); but they do not have to be clinicians. However, it is essential that clinicians are involved in many aspects of the patients care, including assessment, diagnosis, and management, planning, and prescribing of drugs. This clinician input can take many forms, and can include occasional office visits by the patients and having the clinician remotely see the patients using various telemedicine technologies (e.g., Skype).

In many cases, as part of a complete pain treatment program, we expect that various other health care providers would visit the pain patients in a coordinated fashion. These may include acupuncturists, physical therapists, massage therapists, cognitive/behavioral psychologists and others depending on patient needs. Again, these visits need to be coordinated, and progress needs to be monitored. Further, this treatment systems needs to be flexible and change with the needs of the patients.

Given that the "pain mobile" approach involves going to the patients' homes, it offers some unique opportunities not available with visits to clinics. With home visits, it is possible to assess the home environment and also to educate patient and those living with the patient. As part of the "pain mobile" program, we expect that at least one of the health care providers that go to the patient's residence be trained to evaluate the living conditions of the patient and when appropriate, suggest improvements that will allow the patient to function better in their home environment despite their condition. If the patient is using opioid pain medications, how these drugs are stored and secured will be examined. The health care provider will also be expected to educate the pain patient and co-inhabitants of the home about the safe use of opioids.

While this is a small scale project, we would like the chosen model to be economically viable and potentially expanded. To make this more likely, the offeror must describe a plan of how they will make this project not only self-sustaining, but also expandable. Agreements with existing health care providers, health insurance companies, health services providers or the like is required. If the pilot project funded under this contract is shown to be economically viable on a small scale, we envision that this will encourage provider partners to expand this system within their existing networks, and thus expand the impact of this effort.

Phase I Activities and Expected Deliverables:

Technical Requirements

1. Assemble a team of professionals to work together to provide comprehensive pain treatment.
2. Develop a plan to deliver coordinated comprehensive pain treatment, including determined the frequency of home visits, the need for in clinic consultations and testing, the coordination plan of treatment delivery (who goes where and when), the development of hardware and software needed in the coordination of care and store/access data, and a plan to insure data security.
3. Built/equip the pain mobile itself with all the needed medical and communication requirements.
4. Develop a plan for compensation of services that does not sole or largely rely on the patient paying for services out of pocket. This may take many forms but could include a contractual relationship with a health care insurer.
5. Recruit a patient population.
6. Perform pilot testing of the system and services for feasibility.

Phase II Activities and Expected Deliverables:

Technical Requirements

1. Provide pain treatment from the pain mobile full-time on a cohort of chronic pain patients.
2. Test for efficacy of the pain mobile. This could include surveys of patient satisfaction as well as impact of treatment on the patient's pain and quality of life. These measures could include measures of pain, depression, mood, function, level of use of opioids, activity levels and other indicators of successful pain treatment. These data could be compared across time within this cohort of pain patients, and/or related to a comparison group of pain patients treated in a traditional clinical setting.
3. Results from the above testing should be disseminated *via* conference presentations and manuscript publications.

CENTERS FOR DISEASE CONTROL AND PREVENTION (CDC)

CENTER FOR GLOBAL HEALTH (CGH)

The Center for Global Health (CGH) leads the execution of the CDC's global strategy; works in partnership to assist Ministries of Health to plan, manage effectively, and evaluate health programs; achieves U.S. Government program and international organization goals to improve health, including disease eradication and elimination targets; expands CDC's global health programs that focus on the leading causes of mortality, morbidity and disability, especially chronic disease and injuries; generates and applies new knowledge to achieve health goals; and strengthens health systems and their impact.

CGH Internet site: <http://www.cdc.gov/globalhealth/>

For this solicitation CGH invites Phase I proposals in the following area:

008 Diagnostic Tools to Support the Elimination and Control of Neglected Tropical Diseases

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1-2

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Neglected tropical diseases (NTDs) are bacterial, parasitic, and viral infections that disproportionately affect poor and underserved populations around the world, and are primarily associated with high levels of morbidity due to the chronic nature of the infections. Adults affected by NTDs often have decreased productivity. School aged children are also affected by NTDs, resulting in decreased physical and scholastic performance. A subset of NTDs, including lymphatic filariasis (1 billion people at risk in 73 countries), onchocerciasis (120 M people at risk in 37 countries), schistosomiasis (700 M at risk in 74 countries), trachoma (540 M at risk in 55 countries) and soil transmitted helminth (STH) infections (4 billion at risk, 1 billion infected, worldwide), can be targeted effectively through mass drug administration (MDA). In recent years, there have been significant increases in the number of countries implementing public health programs to combat NTDs, and in the number of persons being treated for NTDs. This progress is the direct result of generous donations of drugs from pharmaceutical manufacturers as well as funding support from the U.S. Agency for International Development (USAID) and the UK Department for International Development (DFID), among others. Reducing the morbidity caused by NTDs is an objective of the U.S. Government Global Health Initiative (GHI) with specific targets for the global elimination of lymphatic filariasis and trachoma.

Currently available laboratory and epidemiological tools to achieve the new elimination goals set for several NTDs require improvement. For example, there is significant geographic overlap in the distribution of most NTDs, but programs continue to use disease-specific and labor intensive clinical or parasitologic exams for mapping and surveillance. This approach does not maximize the limited resources available to these programs. Treatment drugs for some NTDs can cause serious adverse events if other infections are also present. For example, serious neurologic adverse events can result when MDA takes place with the use of ivermectin in regions where onchocerciasis and Loa loa overlap (i.e., Central and West Africa). An integrated diagnostic platform for NTDs could produce significant cost-savings for mapping and surveillance and improved safety for MDA programs.

Project Goal

Field-compatible antibody and antigen (as appropriate for the particular disease, as delineated in the table below) tests can be used to define treatment areas, guide MDA program implementation and to conduct post-treatment surveillance. Development of multiplexed strip tests would facilitate integrated, cost-effective surveillance and mapping activities.

NTD	Antigen	Antibody
Lymphatic filariasis (LF)	-	+
Onchocerciasis	+	+
Loa loa	+	+
LF/onchocerciasis	+	+
Schistosomiasis	-	+
Soil Transmitted Helminth (STH)	+	+

(+) = test is needed

The specific project goal is to have prototype field-compatible tests that can address the following issues currently faced by national NTD programs

- the need for rapid determination of infection prevalence in support of micro mapping;
- the detection of co-infections that hamper MDA activities (for example lymphatic filariasis endemicity in areas where ivermectin has been previously used for onchocerciasis MDA, *Loa loa* infections in areas endemic for onchocerciasis);
- epidemiological surveillance, evaluation of program impact through serological monitoring, and surveillance for infection or exposure following apparent interruption of transmission.

The proposed assays should be developed towards use of a standard platform, therefore opening opportunities for integrated surveillance for NTDs.

Phase I Activities and Expected Deliverables

- 1) Prototype device or methodology for point of care application (field compatible) for simultaneous or consecutive detection of one or more NTDs. A rapid diagnostic, field compatible serological assay is highly desirable. Such a device will help identify infected persons in specific areas, therefore facilitating fast mapping could be the basis of program monitoring and evaluation activities. A desirable prototype should include either two or more of the NTDs listed above, including but not limited to:
 - Schistosomiasis and lymphatic filariasis
 - *Loa loa* and onchocerciasis
 - *Loa loa* and LF
 - Schistosomiasis and intestinal helminth infections (e.g. *Strongyloides stercoralis*)
- 2) Determination of basic assay performance characteristics: preliminary sensitivity and specificity desired but not required.
- 3) Field compatibility characteristics: performance outside a fully equipped laboratory and the stability, shelf life, and storage requirements of the tests.

Projected Phase II activities

Phase II activities for a successful Phase I prototype will include expanded testing for sensitivity and specificity, and small-scale production of beta prototypes for field testing. Following this, modifications of the beta prototypes towards a final field-compatible test will be done. Finally, data will be generated to further characterize the test performance characteristics and assay compatibility with NTD program needs for mapping and program monitoring and evaluation, including post-treatment surveillance.

Impact

Development of improved diagnostic tools supports CDC's efforts to address lymphatic filariasis in the Americas and the NTD GHI targets. These tools would also encourage the commitment of donors and policy makers to NTD control and elimination programs by allowing program integration across diseases and enhanced efficiency. New devices or assays may provide more reliable detection of infection rates, which would lead to increased confidence towards meeting public health goals. Significant savings in human and financial resources could be obtained through the development of improved diagnostic tools.

Commercialization Potential

NTDs are by definition neglected and diagnostic tests for NTDS are not necessarily compatible with standard commercialization strategies. However, there is a need for new diagnostic methods. Small businesses are the frontrunners on developing novel technologies and approaches for addressing unmet needs. Market opportunities

arise from the presence of donors and policy makers already committed in NTD elimination and control efforts, who could encourage manufacturers to promote production and commercial availability of these devices.

NATIONAL CENTER FOR EMERGING ZOOONOTIC AND INFECTIOUS DISEASES (NCEZID)

The mission of the National Center for Emerging and Zoonotic Infectious Diseases aims to prevent disease, disability, and death caused by a wide range of infectious diseases. NCEZID focuses on diseases that have been around for many years, emerging diseases (those that are new or just recently identified), and zoonotic diseases (those spread from animals to people). NCEZID's work is guided in part by a holistic "One Health" strategy, which recognizes the vital interconnectedness of microbes and the environment. Through a comprehensive approach involving many scientific disciplines, NCEZID can attain better health for humans and animals and improve our environment.

NCEZID's Web site: <http://www.cdc.gov/ncezid>

For this solicitation NCEZID invites Phase I proposals in the following areas:

012 De novo assembly of arthropod genomes of public health importance

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Long range de novo genome assembly from short sequence reads is still one of the greatest challenges in genomics despite vast and rapid improvements in obtaining those short reads. Numerous viral, bacterial, and parasitic agents causing human and veterinary diseases are carried and transmitted by arthropods including but not limited to ticks, mosquitos, triatomids, sandflies, mites, lice, and fleas. The prevalence, diversity, and range of these arthropod disease vectors render them an important subject of study for improving our understanding of their roles in human disease transmission, and consequently for the prevention of those diseases. The impact of assembly of the human genome sequence on medicine has been tremendous. Similarly, high-quality genome assemblies of arthropod vectors are a critical precondition to new approaches to studying vector-pathogen interactions and for controlling vector populations. Such genome assemblies will be used to underpin demographic, phylogenetic, host/parasite, and population genetic analyses. Unfortunately, very few reference or even draft-quality assemblies exist for arthropod vectors of public health importance, with the exception of species with small genomes like mosquitoes. This is true despite the huge economic and public health impacts of many other vector species. Assemblies of larger, more complex arthropod genomes, such as ticks, were first proposed in 2006 (Lyme disease vector) but they are still very poor despite their importance to public health. A consequence of the lack of cost-effective assembly technologies to complete even single sequences is that large-scale comparative assembly efforts are virtually nonexistent. This is partly a consequence of the costs required to generate high-quality assemblies for this massively diverse phylum, even as the cost per read has declined. However, the read length of efficient sequencers with contemporary libraries is too short for effective construction of chromosome length assemblies. Higher order assembly requires very expensive and cumbersome approaches that are still being applied to correction of the human genome sequence. New approaches may substantially reduce the time and effort required for higher order genome assemblies and thus make fuller and more cost effective use of the short read sequence libraries which are the norm for NextGeneration Sequencers but quite inadequate for achieving the goal of accurate full genome assemblies. Currently genomes are

often released as assemblies containing tens of thousands of contigs (e. g., *Rhodnius prolixus*, the triatomine vector of Chagas Disease, even at 8 X coverage has 58,559 contigs and 27,872 supercontigs).

Two recent Institute of Medicine of the National Academies Workshops by expert panels have focused on the costs and public health threats associated with vector-borne disease. The more general 2008 workshop was entitled “Vector-Borne Diseases, Understanding the Environmental, Human Health, and Ecological Connections, Workshop Summary (Forum on Microbial Threats).” And published by the National Academy Press. This was followed by another more focused National Academy Press publication in 2011 of a workshop proceeding which was entitled “Critical Needs and Gaps in Understanding Prevention, Amelioration, and Resolution of Lyme and Other Tick-Borne Diseases: The Short-Term and Long-Term Outcomes - Workshop Report.” These lengthy documents fully explore the public health problem, costs, and research directions needing effort in order to reduce the health burden posed by vector-borne diseases. Suffice it to say, greater genetic understanding of the target species, the focus of this solicitation, was fully addressed as a pressing need in these publications. Those same considerations apply to a wide range of arthropods of veterinary and agricultural importance.

Project Goals

The goals of the proposed research are to rapidly and cost-effectively assemble high-quality arthropod genomes de novo. The innovation should ultimately enable large numbers of genomes to be assembled in multi-megabase scaffolds rapidly and affordably. A scalable, parallelizable approach will enable much broader surveys and targeted studies of arthropod genomes to better understand their role in disease transmission and myriad costs to society. Technologies designed to meet these needs will need to employ computational and assay-based innovations. Projects must start with input DNA and yield assembled genomes, not just data from which assembly may be done eventually. This will be the first such effort attempted with large arthropod genomes for higher order and more complete assemblies. Technologies previously found to be effective for human and alligator genome assemblies (e.g., Chromosome-scale shotgun assembly using an in vitro method for long-range linkage ArXiv: 1502.05331v1 [q-bio.GN] 18 Feb 2015) using emerging sequencing and bioinformatic technologies may be used to achieve this goal.

Phase I Activities and Expected Deliverables:

Phase I must demonstrate the feasibility of an advanced methodology pipeline for rapid and high-quality de novo genome assembly of several arthropod genomes. Specifically, at least three tick vector genomes of public health importance (e. g., *Ixodes scapularis*, *Dermacentor variabilis*, *Amblyomma americanum*) with different genomic characteristics (total estimated genome sizes of >1 Gbp and different amounts of repetitive DNA families) must be assembled to reasonable contiguity (N50 > 200 Kbp) and quality by the responder to the solicitation. For Phase I, only the final data demonstrating successful de novo assembly of these targets will need be provided. Additional high quality conventional annotation and chromosome mapping confirmation that these assemblies are indeed correct will be required in Phase II for each of these three targets as well as the additional genomes to be analyzed in Phase II.

Projected Phase II activities

Phase II projects must demonstrate the scalability and cost-effectiveness of the technology approach demonstrated in Phase I, as well as quality annotations for the assemblies. For each respective year of the phase II project period, a total of 8 (including the three Phase I targets) (Phase II-yr1) and 10 (Phase II-yr2) additional arthropod vector genome assemblies and annotations, including other arthropod species of public health interest in at least four arthropod orders (e. g., fleas, ticks, lice, mites, triatomines) with genomes > 500 Mbp, must be produced that meet the same annotation quality, N50 and contiguity criteria established for the three Phase I assemblies. Furthermore, each assembly in the second phase must be completed, or a credible roadmap demonstrated to reach, a total reagent cost reduced to less than \$10,000 per assembly for those performed in the last year of Phase II. Generated assemblies must be released to the public domain, and applicant must perform and demonstrate gene annotation and synteny comparisons of qualities comparable to the state of the art generally achieved for well-assembled reference vertebrate genomes.

Impact

Higher-quality arthropod genome assemblies will support public health research and interventions on a number of fronts. Better assemblies and broader sampling are highly conducive to comparative analyses for understanding phylogenetic relationships between closely and distantly related disease vectors. Population genetic analyses will become more powerful by allowing for more accurate characterization of population growth or decline, changes in geographic distribution through time, and evolutionary forces such as selection and drift. Higher-quality assemblies also allow better genome annotation via both syntenic and computational analyses, which in turn offer insight into host/symbiont relationships and the genetic basis of disease transmission. All of these benefits positively impact the ability to understand arthropod-borne disease transmission and, consequently, capabilities for effective prevention and intervention. Arthropods are increasingly resistant to pesticides used in their control. A fundamental understanding of the genetics of vectors is essential to developing new strategies for reducing the huge economic and public health burdens they cause. The first step in this process is to obtain high quality reference genome sequences which can provide the basis for development of other novel methodologies applicable to related species and diverging populations. The methods demonstrated should be applicable to a much wider selection of species of interest, both vertebrate and for other invertebrate groups, and provide a commercially viable future for a successful responder to this solicitation.

Commercialization Potential

More than 5000 arthropod genomes have been proposed for sequencing (i5K project) and numerous pests of agricultural importance as well medically important vectors are on this list. Insects alone comprise the largest number of species of any life form except bacteria and arthropods are the most successful animals on the planet. Given the importance of arthropods in disease transmission, the vast diversity of the phylum, and the importance of high quality genome assemblies for effective scientific investigations, the proposed technologies embody substantial market potential. Whereas the i5K project is estimated to take 5 or 10 years to complete, our goal is to use advanced technologies to obtain results sooner than this and of better quality. The ultimate service or product provided will find extensive use with all eukaryotic subjects of genomics research. Thorough characterization of the many important arthropod genomes will be a long term effort by the scientific community providing an ongoing need for the proposed product from the solicitation responder for many years to come.

013 Detecting Lower Intestinal Microbiome Disruption and Multidrug Resistant Organisms

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Antibiotic resistance causes over 2 million infections and 23,000 deaths annually in the United States alone and is a global public health challenge that has reached critical levels in healthcare settings, and the evolution of multidrug-resistant organisms (MDROs) threaten to move the care of hospitalized patients into a pre-antibiotic era. These MDROs include organisms such as vancomycin-resistant enterococcus (VRE), carbapenem-resistant Enterobacteriaceae (CRE), extended-spectrum beta-lactam resistant Enterobacteriaceae (ESBLs), and *Clostridium difficile*, all of which primarily colonize patients in the lower intestine where they undergo clonal expansion and often dominate the microbiome. Prerequisite for colonization by these intestinal MDROs are disruption and shift in diversity of the lower intestinal microbiome that usually result from exposure to antibiotics, but may be contributed to by other medications, dietary changes, and diarrhea from viral and non-infectious causes. Following colonization, dominance of the lower intestinal microbiome by a particular MDRO (as defined by constituting >30% of the

microbiome) is a risk factor for infection. Moreover, intestinal MDRO dominance, over and above low-level colonization, is associated with increased skin and environmental contamination, and risk of transmission.

Investigations are underway to identify critical taxonomic and functional components of the intestinal microbiome that, when absent, confer risk for colonization or infection with MDROs. Meanwhile, current infection control and public health recommendations often include active surveillance testing to detect and contain transmission from patients who are asymptotically colonized with the aforementioned MDROs.

Project Goals

Develop a proof of concept assay that could be used as the basis of a diagnostic method for stool that quantitatively detects not only the presence and relative amount of one or more of the previously described MDROs (i.e., CRE, VRE, ESBL, and/or *C. difficile*), but also the taxonomic components and diversity of the gut microbiome. The approach to both MDRO detection and microbiome description may utilize a number of different existing technologic platforms and combinations thereof including, but not limited to, single or multiplex PCR platforms, 16S ribosomal RNA-encoding DNA amplification and sequencing, deep DNA sequencing, or other advanced metagenomic or metabolomic methods.

The overall objectives are to: 1) detect colonization by one or more MDRO(s) using a molecular approach expected to yield a clinically meaningful sensitivity and specificity; 2) determine the abundance of the MDRO(s) relative to important taxonomic components of the lower intestinal microbiome (e.g., degree of dominance); 3) determine relative abundance and diversity of the important taxa of the lower intestinal microbiome to describe disruptions that may portend future near-term risk of MDRO colonization or, if already colonized, the future risk for transmission and infection and; 4) generate results with a clinically useful turnaround time.

Phase I Activities and Expected Deliverables

1. Determine a workable strategy to achieve the above outlined goals.
2. Develop pertinent wet-lab protocols to identify and modify, if necessary, any existing software or bioinformatics tools necessary for interpretation, and
3. Demonstrate, using spiked human stool or waste clinical specimens from which MDRO have been cultured, the detection of MDROs and, using stool from antibiotic-naïve and antibiotic-experienced patients, the ability to discern major microbiome disruptions.

Projected Phase II Activities

1. Build-out of modular components for commercialization of a clinical assay including adaptation of assay and results interpretation for use with rectal swabs
2. Perform a clinical demonstration study divided into two phases:
 - a. Testing at-risk patients periodically throughout their hospitalization, correlating results of the combined microbiome and MDRO assay performed on a rectal swab with antibiotic and other drug exposures as well as microbiologic evidence (i.e., perform sampling) of patient skin, patient care area environment (i.e., high-touch surfaces), and healthcare worker hand contamination caused by the target MDRO. Select patient population (based on underlying clinical risk) and power the sample size to examine the capability of assay to predict ongoing risk for colonization (in the previously non-colonized) and transmission or infection events among those already colonized. No clinical or infection control intervention will be based upon assay results, observational only. The goal will be to demonstrate the predictive capability of the combined assay results of microbiome disruption and MDRO detection (and the degree of MDRO dominance in the microbiome), over and above qualitative MDRO detection alone, for the likelihood of colonization or, if already colonized, the likelihood to serve as a source for transmission.

- b. A proof of concept infection control intervention focused on enhanced environmental cleaning and glove use triggered by assay results, examining its impact on transmission and compared to either a historic (i.e., quasi-experimental) or concurrent ward, unit, or facility control.
3. Engage either developers of an advanced probiotic or academic investigators studying fecal microbiota transplantation (under an FDA IND) to design study for future implementation in which one of these interventions is offered to patients on the basis of assay results as a means to reduce their risk for colonization and infection as well as transmission to other patients.

Impact

Having a means to monitor the level of microbiome disruption in a patient, while simultaneously detecting colonization with selected MDROs, will allow proactive identification of the infection control risk of patients, both in terms of their vulnerability to colonization with an MDRO (i.e., if they are disrupted) and their risk of transmission if they are already MDRO-colonized or (especially) if they are MDRO-dominated. Moreover, because MDROs are pathobionts, it is likely the identification of MDRO domination will become regarded as an important independent risk factor (along with others) for infection in many, if not all, patient populations. Meanwhile, microbiome restorative therapies are currently under clinical development. The data generated from assays such as this, once integrated into clinical care, will provide not only direction to antibiotic stewardship and infection control but also form the basis for an entirely new frontier of patient management. It is not an over statement that the development and use of ‘microbiome disruption indexes’ in patient management will revolutionize current infection control and MDRO prevention in all of healthcare.

Commercialization Potential

With the appropriate level of intellectual and fiscal capital invested into a relatively easy to use, straightforward platform with good bioinformatics support, the commercialization potential is tremendous. At least in the case of *C. difficile* there are already national third-party payer incentives for hospitals to reduce publically reported rates, such that it is plausible that hospitals will utilize available advanced diagnostics that stratify patient risks for colonization, transmission, and infection. In addition, it is likely that advanced probiotics and other microbiome restorative therapies will become available in the next 5-10 years and, coupled with the appropriate risk-stratifying diagnostics, these may become administered routinely to patients with microbiome disruption following antibiotic or other drug therapies.

NATIONAL CENTER FOR HIV/AIDS, VIRAL HEPATITIS, STD, AND TB PREVENTION (NCHHSTP)

The mission of the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention (NCHHSTP) is to maximize public health and safety nationally and internationally through the elimination, prevention, and control of disease, disability, and death caused by HIV/AIDS, Viral Hepatitis, other Sexually Transmitted Diseases, and Tuberculosis.

NCHHSTP Web site: <http://www.cdc.gov/nchhstp/>

For this solicitation NCHHSTP invites Phase I proposals in the following areas:

046 Serologic measurement of hepatitis B virus cccDNA

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Hepatitis B virus (HBV) infection is a global public health concern. Worldwide more than 350 million people are chronically infected with hepatitis B virus. HBV infection causes acute and chronic hepatitis leading to liver cirrhosis and hepatocellular carcinoma. After HBV infection, viral DNA is transferred to nuclei of the infected hepatocytes and the double-stranded, open circular DNA is converted to covalently closed circular DNA (cccDNA). Persistence of cccDNA remains an obstacle to clearing HBV in chronically infected people, who remain at risk of developing advanced liver disease. This is because cccDNA acts as a template for continued virion production in the hepatocyte nucleoplasm. As long as the infected hepatocyte survives, cccDNA remains in the nucleus, maintaining a viral 'pool'. Further, in patients undergoing antiviral therapy who discontinue treatment, HBV can reactivate from cccDNA. To monitor the persistence of cccDNA in the liver, repeated liver biopsies are required, which are hazardous and uncomfortable to the patient, and costly.

Previous studies have shown the presence of cccDNA in serum of chronically infected patients. Serum cccDNA levels correlate well with intrahepatic cccDNA content. Serum cccDNA may thus be used for sequential monitoring of intrahepatic cccDNA levels without the requirement for repeated liver biopsies. Further, the appearance of cccDNA in the serum can be a marker of liver damage.

Quantitative detection of cccDNA in serum thus has potential to evaluate the severity of liver damage and the efficacy of antiviral therapy. Methodologies for the detection of HBV cccDNA in serum have been reported but assays for its detection and quantification are not commercially available. Development of a facile quantitative assay is required for quantitative detection of cccDNA in peripheral blood, whose manufacture can be scaled up and marketed to diagnostic laboratories.

Project Goal

The purpose of this project is to identify a panel of sera from treated and untreated HBV-infected patients, validate and develop an assay for quantitative detection of cccDNA in serum or plasma, establish the performance characteristics of assay, and establish and validate the cccDNA detection kit.

Phase I Activities and Deliverables

1. Design assay for quantitative detection of HBV cccDNA in serum or plasma from HBV-infected patients.
2. Validate assay and determine sensitivity and specificity using seroconversion panels.

Projected Phase II Activities:

1. Validation of the assay using specimens from HBV-infected patients and controls; optimize and validate the assay using clinical samples from patients and controls and establish and improve performance characteristics of assay.
2. Validation of the assay using specimen from HBV infected patients and Report Writing; produce prototype HBV cccDNA assay and explore feasibility of transferring technology to commercial and state and public health laboratories.

Impact

After infection or antiviral therapy, HBV remains dormant in the infected person by adopting the cccDNA form in the liver. As cccDNA can also be found in the blood, especially after liver damage, its detection in serum or plasma allows the efficacy of antiviral therapy and the extent of liver damage to be evaluated without resorting to liver biopsies. Worldwide more than 350 million people are chronically infected with HBV. Improved antivirals are in the pipeline that potentially cure instead of suppress HBV. In the next 5-10 years, a substantial proportion of HBV

infected persons who undergo antiviral therapy will benefit from access to a facile diagnostic method for the detection of cccDNA.

Commercialization Potential

Assays for detection and quantification of cccDNA in serum are not available. A simple, cost-effective and sensitive test kit, whose manufacture is then scaled up, should become marketable for use in diagnostic laboratories.

047 Serologic detection and quantification of hepatitis B core antigen

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Hepatitis B is a major public health problem in United States, where 1.4 million persons are estimated to be infected with the virus. HBV surface antigen (HBsAg) is the mainstay serological marker used for identifying HBV infection and evaluating the efficacy of antiviral therapy. However, it is not a reliable marker of HBV found in blood, as it is shed from the liver in much greater abundance than HBV virions. Further, HBsAg can be shed from HBV even when it is residing in the liver in the latent (non-replicating) state.

HBV core antigen (HBcAg) is a constituent of the HBV nucleocapsid, which after encapsidation is released into the circulation. HBcAg in serum or plasma is a better indicator than HBsAg of the extent of shedding of HBV virions from the liver to peripheral blood, i.e., 'productive' HBV infection. Critically, as transcription and translation of HBcAg production are not inhibited by nucleotide analogues currently used for antiviral therapy, patients treated with these drugs continue to produce HBcAg for considerable periods of time. Immunoassays to detect HBcAg can therefore help in identifying HBV infections without resorting to HBsAg or HBV DNA testing.

Previous studies have shown that HBc antigenemia correlates positively with HBcAg production in the liver. Several methodologies for the detection of HBcAg core antigen in serum have been published but assays for its detection and quantification are not commercially available for use in diagnostic procedures. Development of a reliable immunoassay that can also be an alternative to HBsAg and HBV DNA testing, is needed.

Project Goals

- Identify a panel antibodies that have the potential to detect HBV core antigen in clinical samples.
- Validate and develop a serological assay for quantitative detection of HBV core antigen
- Validate the performance characteristics of the assay using commercial panels of serum samples from HBV-infected persons.
- Validate the performance characteristics of the assay using with prospectively obtained serum samples from HBV-infected persons.
- Establish protocols to scale up production of validated assay.

Phase I Activities and Deliverables

Deliverable: Design and develop a simple immunoassay for detection and quantification of HBcAg in human serum or plasma from persons with acute and chronic HBV infection

Activity: Identify a panel of antibodies with the potential to be capture agents for HBcAg in serum or plasma.

Projected Phase II Activities

Deliverable: Optimize and validate the assay using clinical samples from HBV infected patients and controls

Activity: Establish sensitivity and specificity of the assay, continue to refine the assay and improve performance characteristics of the assay

Deliverable: Establish and validate prototype assay.

Deliverable: Produce final report and explore feasibility of transferring technology to commercial and state and public health laboratories.

Impact

Serologic testing for hepatitis C virus (HCV) core antigen is increasingly being used to identify persistent HCV infection and evaluating the efficacy of anti-HCV therapy. Similarly, testing for HBcAg has potential for use to identify productive HBV infection and evaluating the efficacy of anti-HBV therapy. Worldwide more than 350 million people are chronically infected with HBV. Improved antivirals are in the pipeline that potentially cure instead of suppress HBV. In the next 5-10 years, a substantial proportion of HBV-infected persons can then benefit from access to testing for HBVcAg. This start- up initiative, when funded and successfully developed, should lead to a marketable product for use in commercial and publically funded diagnostic laboratories.

Commercialization Potential

A simple assay for serologic detection and quantification of Hepatitis B virus core antigen with high sensitivity and specificity and low cost can lead to a marketable product for use in commercial and publically-funded diagnostic laboratories. The market potentially comprises the 350 million people who are chronically living with HBV worldwide.

NATIONAL CENTER FOR IMMUNIZATION AND RESPIRATORY DISEASES (NCIRD)

The mission of the National Center for Immunization and Respiratory Diseases (NCIRD) is the prevention of disease, disability, and death through immunization and by control of respiratory and related diseases. Our challenge is to effectively balance our efforts in the domestic and global arenas as well as accommodate the specific needs of all populations at risk of vaccine preventable diseases from children to older adults.

NCIRD Web site: <http://www.cdc.gov/ncird/>

For this solicitation NCIRD invites Phase I proposals in the following areas:

031 Transcutaneous immunization against rotavirus using a dissolvable microneedle patch

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Currently licensed live oral rotavirus vaccines, RotaTaq and Rotarix, are effective in preventing severe diarrhea among children in developed and middle income countries, but are significantly less effective in the developing world. While the causal mechanisms for this lower efficacy have not been clearly defined, we hypothesize that multiple factors, such as high titers of pre-existing maternal antibody, breast feeding and interference by other flora and viruses in the gut, might play a role in reduced vaccine efficiency among children. Consequently, rotavirus remains a major killer among children in low-income countries of Africa and Asia. In addition, both vaccines are associated with a low risk of diarrhea and intussusception (i.e., blockage of the small intestine) among infants who receive the first dose of vaccine. To improve the safety and efficacy of oral rotavirus vaccines, CDC scientists have developed a proprietary inactivated rotavirus vaccine (IRV) technology (new human strains and a novel method for rotavirus inactivation) and demonstrated the immunogenicity and protective efficacy in piglets of this IRV by intramuscular (IM) injection and transcutaneous administration using microneedles. With the establishment of proof of concept for parenteral (i.e., non-oral) immunization, CDC has licensed this technology to a number of vaccine manufacturers for further R&D and clinical development of an IM IRV.

We now propose a SBIR topic for the formulation and fabrication of a dissolving microneedle patch to deliver an IRV for transcutaneous immunization against rotavirus in collaboration with a contract manufacturing organization. We have recently demonstrated enhanced immunogenicity of our IRV using an innovative metal microneedle patch technology, achieving comparable antibody titers with a 1/10th of the antigen dose compared to those induced by a full IM dose of vaccine. Microneedles provide a simple and painless method to administer vaccines without using hypodermic needles. They are inexpensive to manufacture and may not need the cold chain with large volume of cold storage and high cost, a major advantage for immunization campaigns in the developing world.

Transcutaneous immunization using a dissolvable microneedle patch is a novel and innovative approach to the prevention against infectious diseases, but no such vaccines have been licensed for use in humans yet. Currently this technology to deliver influenza vaccine is being tested and evaluated in phase I clinical trials. Similar clinical trials for inactivated polio vaccine (IPV) using a dissolvable microneedle patch are being planned for the next few years. However, no development and proof of concept work have been done for IRV.

Project Goal

The goal of this project is to conduct formulation and process development and a feasibility study to manufacture a dissolving microneedle patch for skin immunization against rotavirus. This program area will provide small business companies with opportunities to apply for necessary funds and work with CDC scientists to further optimize the fabrication process and prepare a dissolving microneedle patch for clinical trials of a patch IRV.

Phase I Activities and Expected Deliverables

1. Develop an outline for the project goals described above.
2. Develop a draft scalable manufacturing process for a dissolving microneedle patch, including formulation and fabrication of IRV and necessary assays.

Expected Phase II Activities

1. Develop and validate a scalable manufacturing process for a dissolving microneedle patch.
2. Develop and implement manufacturing methods to make microneedle patches for IRV vaccination under good manufacturing practice (GMP) conditions.

3. Support regulatory approval to conduct a phase I clinical trial of IRV vaccination using a microneedle patch.
4. Support for a phase I clinical trial to assess the safety, immunogenicity, reactogenicity, and acceptability of IRV vaccination using a microneedle patch.

Impact

The findings from this SBIR research may allow us to enhance public health through the development of a low cost vaccine with an improved safety and efficacy profile and thus help advance CDC's Global Immunization Winnable Battle that includes increasing Global Health Impact of rotavirus vaccination.

Commercialization Potential

Demonstration of the feasibility for the manufacture of a dissolving microneedle patch for IRV will bode well for a serious investment and more expeditious and effective development of this new and innovative IRV for commercialization. This IRV would be more efficacious in resource-poor settings because of its parenteral administration. As the world is transitioning to IPV from oral polio vaccine (OPV), a combined IPV and IRV in the expanded program on immunization (EPI) would ultimately increase global health impact through large immunization campaigns and help save more lives.

032 **Thermostable Dry Powder Live Attenuated Influenza Vaccine for Nasal Delivery**

(Fast-Track proposals will **not** be accepted.)

(Direct to Phase II will **not** be accepted.)

Number of anticipated awards: 1-3

Budget (total costs): Phase I: up to \$150,000 for up to 6 months

PROPOSALS THAT EXCEED THE BUDGET OR PROJECT DURATION LISTED ABOVE MAY NOT BE FUNDED.

Background

Ongoing disease and death associated with seasonal influenza and the threat of an influenza pandemic are two of the highest priority issues for global public health. Vaccination is a powerful tool for preventing influenza, however, current vaccines have several limitations. Inactivated influenza vaccines (IIV) given by needle injection require skilled health care workers and can lead to needle-associated injuries and infections. Liquid nasal live attenuated influenza vaccine (LAIV) is needle-free but has limitations which can result in restricted distribution of vaccine. The limitations of IIV and LAIV are critical because unlike many other vaccines, almost everyone needs flu vaccine every year. Also, efficient rapid distribution is essential especially in a pandemic situation. An ideally distributable vaccine could be shipped without restriction, by mail for example, and self-administered. Every step away from this ideal decreases the accessibility of the vaccine. Both IIV and liquid LAIV require strict adherence to cold chain requirements (shipping and storage at 2-8⁰C) which restricts distribution to facilities with monitored refrigeration. This is expensive in the developed world and can significantly restrict distribution in the developed world, where cold chain capacity is stretched by routine EPI vaccination requirements and has little or no surge capacity for influenza vaccines or pandemic situations.

While the needle-free nasal administration LAIV is an advantage over vaccination by injection the liquid delivery format has several limitations. The FluMist™ LAIV available in the US is shipped and delivered in a prefilled liquid in a glass syringe which imposes shipping requirements and increases shipping costs. More importantly vaccine by liquid nasal spray results in suboptimal vaccine deposition. The large droplets administered by liquid nasal spray devices accumulate in the nares and much the dose is wasted by dripping out of the nose does not reach the target

nasopharyngeal tissues. Also, liquid nasal sprays require an experienced vaccinator as differences in the force and speed of plunger depression results in variable droplet size and the placement of the spray tip can significantly affect vaccine deposition. LAIV based on the Leningrad donor virus is also delivered as a liquid nasal spray. This vaccine is shipped as a lyophilized cake and requires reconstitution with a separate liquid diluent, which adds another layer of complexity to vaccine delivery. These two limitations in the distributability of liquid LAIV, cold chain requirements and inefficient liquid delivery are the gaps this project seeks to address.

Recent studies in anatomic models of nasal airways have shown dry powder nasal delivery provides markedly improved distribution and retention compared to liquid nasal spray delivery. Dry powder nasal delivery was also less sensitive to vaccinator variability and can potentially be self-administered. (CDC unpublished data) A nasal thermostable dry powder LAIV would retain the advantages of needle-free nasal delivery and improve upon them by removing cold chain restrictions and improving the consistency and efficiency of delivery and reducing the skill level needed to deliver nasal LAIV.

Project Goal

The goal of the proposed research is to develop a thermostable dry powder LAIV for nasal delivery as a platform technology and assess immunogenicity following nasal powder vaccination in a ferret model. It is expected that this platform technology of thermostable dry powder nasal vaccine will be expanded to use for other vaccines.

Phase I Activities and Expected Deliverables

1. Create dry powder LAIV
 - a. Acquire high titer single strain LAIV bulk lot vaccine
 - b. Dry LAIV into a thermostable format
 - c. Process dry LAIV into a powder with a size suitable for nasal delivery (approximately 20 micron average particle size)
2. Assess potency and 1 month thermostability of the dry powder LAIV
 - a. Freeze aliquots of bulk lot vaccine at -70°C for potency test controls
 - b. Store samples of powder vaccine at $4-8^{\circ}\text{C}$, 24° and 37°C for testing
 - c. Compare potency of powder vaccine at various temperatures to frozen and lyophilized LAIV potency at 1 week, 2 weeks, 1 month
 - d. Test powder vaccine potency by EID_{50} and TCID_{50} compared to frozen LAIV
 - e. Assess formulation and process parameters for optimum thermostability

Projected Phase II Activities

1. Optimize formulation and process parameters
2. Package powder into a nasal delivery device
3. Assess potency and 1 year thermostability of the optimum dry powder LAIV
 - a. Freeze aliquots of bulk lot vaccine at -70°C for potency test controls
 - b. Store samples of powder vaccine at $4-8^{\circ}\text{C}$, 24° and 37°C for testing
 - c. Store samples of powder vaccine in nasal delivery packages at $4-8^{\circ}\text{C}$, 24° and 37°C for testing
 - d. Test powder vaccine by EID_{50} and TCID_{50} compared to frozen LAIV
 - e. Test packaged powder vaccine by EID_{50} and TCID_{50} compared to frozen LAIV
 - f. Compare potency of powder vaccine at various temperatures to frozen and lyophilized LAIV potency at 1 week, 2 weeks, 1 month and then every other month for one year total storage time.
4. Assess immune responses to and efficacy of dry powder LAIV in the ferret model, which is the gold standard animal model for assessing the influenza vaccines
 - a. Package powder into nasal powder delivery system
 - b. Adapt delivery system to ferret nasal delivery if needed
 - c. Vaccinate ferrets with dry powder LAIV and Liquid LAIV
 - d. Assess serologic immune response
 - e. Challenge with homologous influenza virus and measure viral load

Impact

The increased distributability of thermostable dry powder nasal LAIV could significantly improve coverage in the developed and developing world. In addition to the reduction in influenza morbidity and mortality, it is intended that this platform technology be expanded to other vaccines, increasing their accessibility and decreasing the morbidity and mortality of the respective diseases. New thermostable vaccines could be stored and delivered at ambient temperatures, without refrigeration, decreasing energy usage and equipment costs for refrigeration and lightening loads for vaccine transport and delivery. This would be especially helpful in the developing world where hauling icepacks and coolers can make an already rough journey to a village more difficult. Thermostable vaccines can also eliminate the potentially catastrophic loss of vaccine potency that results when cold-chain methods fail, and facilitate distribution in pandemic responses, mass-vaccination campaigns, and agricultural applications. The disadvantages of liquid vaccine delivery format- increased shipping requirements and costs, suboptimal vaccine deposition, need for experienced vaccinators and onsite reconstitution are described above. A thermostable powder vaccine could be potentially be shipped by mail or hand carried by anyone and self-administered or administered by people with minimal skill level. This is the ideal in making vaccines accessible to everyone who needs them.

Commercialization Potential

The Advisory Committee on Immunization Practices (ACIP) recommends every person over age 6 months receive annual flu vaccination, with few exceptions, which would require over 300 million doses a year. In recent seasons over 130 million doses of flu vaccine were distributed annually in the US, almost equaling the total of all other vaccines combined. Over the recent years, the global influenza vaccine market has witnessed double digit growth rate due to fear of an impending pandemic and is expected to cross USD 4 billion in 2015. The high volume demand for influenza vaccine fosters competition which is leading to increased innovation in vaccine delivery. Vaccine manufacturers are willing to invest in improved delivery systems to increase market share by making their vaccines more acceptable and accessible to the population. Recent licensed innovations influenza vaccine include needle-free nasal spray LAIV (MedImmune FluMist™ AccuSpray syringe), intradermal delivery using minineedles (Sanofi Fluzone ID™ with Soluvia™ minineedles), and vaccination by jet injection (bio CSL's Afluria™ with PharmaJet Stratis™ jet injector).

The most likely business model for the small business developer of a formulation and process for thermostable dry powder LAIV would be to license the technology to vaccine manufacturers for fees and or royalties.

13 APPENDICES

APPENDIX A — PROPOSAL COVER SHEET - USE FOR PHASE I AND FAST-TRACK PROPOSALS

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixA.pdf>)

APPENDIX B — ABSTRACT OF RESEARCH PLAN - USE FOR PHASE I, PHASE II, AND FAST-TRACK PROPOSALS

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixB.pdf>)

APPENDIX C — PRICING PROPOSAL - USE FOR PHASE I, PHASE II AND FAST-TRACK PROPOSALS

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixC.pdf>)

APPENDIX D — PHASE II TECHNICAL PROPOSAL COVER SHEET - USE FOR PHASE II AND FAST-TRACK PROPOSALS

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixD.pdf>)

APPENDIX E — STATEMENT OF WORK SAMPLE FORMAT - USE FOR PHASE II AND FAST-TRACK PROPOSALS

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixE.pdf>)

APPENDIX F — SUMMARY OF RELATED ACTIVITIES - USE FOR PHASE II AND FAST- TRACK PROPOSALS

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixF.pdf>)

APPENDIX G — PROPOSAL SUMMARY AND DATA RECORD - USE FOR PHASE II AND FAST-TRACK PROPOSALS

MS Word (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.docx>)

PDF (<http://grants.nih.gov/grants/funding/SBIRContract/ContractAppendixG.pdf>)

The Appendices noted above are in Microsoft Word and Adobe Acrobat Reader fillable format.

NOTE: Other software packages for completing these proposals may be available from other sources; however, it is essential that the type size and format specifications are met or the proposal may be returned without review.

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