

## ADDITIONAL TECHNICAL PROPOSAL INSTRUCTIONS

### Preclinical PREVENT Cancer Program: Preclinical Efficacy and Intermediate Endpoint Biomarkers

**It is strongly recommended that Offerors use the following template as the Table of Contents for the Technical Proposal. All information presented in the Technical Proposal should be presented in the order specified below.**

These additional Technical Proposal instructions reflect the requirements of the RFP and provide specific instructions and formatting for the Technical Proposal. While Section L.2.b. of the RFP provides a generic set of Technical Proposal instructions applicable to all NIH R&D solicitations, these additional Technical Proposal instructions are tailored to the specific requirements of the RFP. The information requested in these instructions should be used, along with Section L. to format and prepare the Technical Proposal, and should be used as a Table of Contents for your Technical Proposal.

Offerors are advised to give careful consideration to the Statement of Work (SOW) and attachments, Mandatory Qualification Criteria and Technical Evaluation Criteria in Section M, and the RFP as a whole in the development of their Technical Proposals.

Offerors should submit a proposal that addresses the Mandatory Qualification Criteria and the Task Areas in the Statement of Work. If the proposed approach will involve a subcontracting arrangement, then the Offeror shall include a letter of commitment from the subcontractor(s), plus documentation of subcontractor's expertise, qualifications and prior performance, as well as a narrative describing how the Offeror will manage the subcontractor.

A detailed work plan should be submitted indicating how each aspect of the Statement of Work is to be accomplished. Your technical proposal should be in as much detail as you consider necessary to explain fully your proposed methods and rationale for their selection and should reflect a clear understanding of the nature of the work being undertaken. The technical proposal must also include information on how the project is to be organized, staffed, and managed. Information should be provided which will demonstrate your understanding of management of timeframes for planning and accomplishing the work to be performed.

Record and discuss specific factors not included elsewhere, which support your proposal. Using specifically titled subparagraphs, items may include unique arrangements, equipment, etc., which none or very few organizations are likely to have which is advantageous for effective implementation of this project.

**The Offeror must adhere to a 120 page limit. Pages in excess of this limitation will be removed from the proposal and will not be provided to the reviewers to be read or evaluated.**

**Pages shall be of standard size (8.5x11) with a font size of 10 points or larger. Proposal pages shall be numbered “Page 1 of 120”, “Page 2 of 120” and so on. Hardcopies of proposals should be printed double-sided (2 sides = 2 pages), single-spaced. The 120 page limit excludes the cover sheet, resumes, and all appendices or attachments. The 120 page limit also excludes the proposal for the sample task order.**

## **SECTION 1: COVER PAGES AND TABLE OF CONTENTS**

- A. PROPOSAL TITLE PAGE. Include RFP title and number, name of organization, DUNS number, proposal part, and identify if the proposal is an original or a copy;
- B. PROJECT OBJECTIVES;
- C. GOVERNMENT NOTICE FOR HANDLING PROPOSALS;
- D. PROPOSAL SUMMARY AND DATA RECORD (NIH-2043);
- E. TABLE OF CONTENTS. Include a Table of Contents with indicated pages of proposal sections that at a minimum uses the underlined Headings and Subheadings that appear below. Additional subheadings may be entered at the Offeror’s discretion.

## **SECTION 2: MANDATORY QUALIFICATION CRITERIA**

The Offeror should include all information which documents and/or support the mandatory qualification criteria in one clearly marked section of its technical proposal. This section related to the Mandatory Qualification Criteria must be listed in the Table of Contents with a page reference.

If the American College of Laboratory Animal Medicine (ACLAM) veterinarian is not an employee of the Offeror or the proposed subcontractor, the Offeror must include a letter of commitment from the proposed veterinarian.

## **SECTION 3: TECHNICAL DISCUSSIONS**

### **A. Personnel**

The Technical Proposal should include all information relevant to document individual training, education, experience, qualifications and expertise necessary for the successful completion of all contract requirements. Clearly identify in a list or table showing name, highest degree, organizational affiliation (employer), role on the project and percentage of effort to be committed to the project for all Personnel including any Subcontract Personnel. Include for each named person a Curricula Vitae (CV) , that is limited to 2-3 pages and which provides selected references for publications relevant to the scope of the RFP, and include experience with projects of similar scope, size and complexity carried out by the Offeror and any proposed subcontractors over the past five (5) years.

1. Principal Investigator: Describe the education, training, experience, expertise, qualifications, and percentage of effort of the proposed Principal Investigator to lead and direct the activities to be carried out under this contract, including: managing an interdisciplinary team in the conduct of pharmacologic efficacy and biomarker studies

employing rodent animal models. The Principal Investigator should have a Ph.D., D.V.M. or M.D. degree or equivalent experience. The qualifications and experience of the Principal Investigator should be discussed in terms of how they are appropriate to the management of any planned subcontract(s). Discuss how the technical and scientific planning and implementation of Task Orders will be managed by the Principal Investigator.

2. **Other Scientific and Technical Personnel:** Describe the education, training, experience, expertise, qualifications, role in the project, and percentage of effort for all proposed scientific and technical personnel of the Offeror and all proposed subcontractors. Document relevant qualifications for: animal testing, chemical analysis, veterinary and pathology support, examination of potential biomarkers/signaling pathways (genomics, proteomics or metabolomics, immunohistochemistry, Western blotting and/or quantitative RT-PCT), and statistic relevance.

## **B. Technical Approach**

Offerors shall submit a proposal that addresses the Task Areas in the Statement of Work. If the proposed approach will involve a subcontracting arrangement, then the Offeror shall include a letter(s) of commitment from the subcontractor(s), plus documentation of subcontractor's expertise, qualifications and prior performance, as well as a narrative describing how the Offeror will manage the subcontractor(s).

1. Describe the procedures to be used for carrying out the types of preclinical efficacy and intermediate endpoint studies as indicated in Task Areas in the Statement of Work, which include criteria for animal handling, administering chemopreventive agents, vaccines, and adjuvant(s), moribund sacrifice, method and equipment to be used for euthanasia, collection, handling and storage of tissue, serum, and urine samples from animals, necropsy and histopathology procedures, and analytical chemistry procedures.
2. Describe the features and capabilities of data management, including software programs currently in use. Describe proposed plans for oversight of data management functions, including protection of intellectual property and confidentiality of data of chemopreventive agent(s).
3. Describe the operation of the Quality Assurance Unit within your organization concerning auditing of critical study events, raw data and study reports. Indicate when these audits take place in relation to the generation of data and reports.
4. Safety and Health for Personnel - Provide a Safety and Health Plan. Offeror's Safety and Health Plan shall include recent and ongoing experience in each task area in the Statement of Work (SOW). Offerors should describe procedures and controls to be employed during tests included in the Statement of Work to insure that the work is conducted in a safe and healthful manner. All pertinent chemical and or biological hazards shall be addressed, from receipt of test agents to ultimate disposal of contaminated waste. Details of appropriate administrative and emergency controls,

personnel, protective equipment and work practices should be addressed. All work shall comply with applicable local, State and Federal statutes relating to occupational safety and health, transportation and handling, and environmental protection. Discuss equipment and unusual operating procedures established to protect personnel from hazards associated with this project and other factors you feel are important and support your proposed approach.

5. Describe proposed methods of statistical analysis for data and underlying distributions being compared.
6. Subcontracts - Describe any previous working relationship with proposed subcontractors. The Offeror shall also address how they will handle privity of contract issues, i.e., the Offeror should explain how information will flow between the National Cancer Institute (NCI), the Offeror, and any subcontractors since the prime contractor's presence is required for any discussions.

### **C. Sample Task Order**

Provide a response to the Sample Task Order attached to these Additional Technical Proposal Instructions.

The response to the Sample Task Order should be included as a separate section (appropriately marked) in the Technical Proposal. The page limit for the Sample Task Order proposal is 14 pages. The Sample Task Order 14 page limit excludes the cover sheet, resumes, and all appendices or attachments. The Sample Task Order response does not count towards the technical proposal 120 page limit. The Offeror's response to the Sample Task Order should include discussion of technical approach, personnel proposed, facilities and equipment.

**See Appendix A for details of Sample Task Order.**

**Also, see Additional Business Proposal Instructions (Attachment 16) regarding development of budgets for the sample task order response.**

### **D. Facilities and Equipment**

1. Facilities - The Offeror shall have an operating laboratory that is suitable for cell culture and laboratory animal studies using hazardous and/or carcinogenic test materials. The laboratory shall be capable of handling hazardous chemicals safely and must be able to provide appropriate facilities for housing animals required in the study. The laboratory and animal care must be sanitary and properly maintained in accordance with the criteria set forth by the animal accreditation organizations (see Mandatory Qualification Criteria in Section M).

Floor plan(s), drawn to scale, should be included for all space that is to be used for this project. The diagram of each floor plan should be adequately labelled to identify the

space for its purpose, the scale that is used, and the items of equipment or other that are portrayed. Discuss operation, procedures, and administration of the cell culture and animal facility. In addition, indicate the location (with distance) for any facilities, which are not contiguous. The Offeror should describe the facilities and equipment that belong to subcontractors. Where facilities of the Offeror are not contiguous and for any non-co-localized subcontractors, the Offeror must describe logistical plans for the transfer of materials and/or data.

Discussion shall include, as appropriate, but not be limited to:

- available room capacities;
- temperature controlled CO<sub>2</sub> incubators, sterile laminar flow hoods;
- sterile tissue culture materials and techniques;
- cryopreservation capability, microscopy capability;
- climate controls and alarm systems;
- caging and exercise;
- diet and compound storage and preparation areas;
- water systems;
- cage washing areas;
- data collection and computer systems;
- animal treatment laboratories (cardiology, ophthalmology, phlebotomy, necropsy);
- clinical and anatomic pathology laboratories and established quality control practices;
- electrical and environmental back up provisions for critical components e.g. animal rooms, chemical test article and biological samples, etc;
- data back-up systems.

2. Equipment - The Offeror shall have all the equipment necessary to accomplish the studies including but not limited to, incubators, microscopes, centrifuges, animal racks and caging, hazardous chemical storage cabinets, refrigerators and freezers to store samples at the appropriate temperature (4 degrees, -20 degrees or -80 degrees), pathology equipment such microtomes, laboratory and analytical chemistry equipment. The laboratory shall have the necessary equipment to perform the intermediate biomarker studies. The laboratory shall have or have access to appropriate terminal and computer facilities and equipment for data collection and storage.

## **E. Organizational Background and Experience**

The Offeror should include an organizational chart that describes reporting structure of the organization.

Discuss prior experience with similar tasks and provide documentation of completed studies.

Provide documentation of abilities to interact with industrial collaborators and academic researchers. Discuss the organization's experience and ability to collaborate with other individuals and organizations. In addition, describe the organization's experience in appropriate use of subcontractors to supplement areas of expertise. Discuss how the

infrastructures composed of one or more collaborating institutions will be managed.

Describe organizational experience in data collection and processing capabilities (IT systems), including statistical analysis, and an effective Quality Assurance Unit. Provide documentation of validation studies undertaken by the organization to assure the accuracy of transmitted data for the version(s) of software shall be described.

## **F. Sustainable Acquisition Definitions**

### **1. Recycled Content Products**

Recycled content products are products that are made from or contain recovered materials. That means replacing virgin materials with recycled materials, including post-consumer materials. There are currently more than 60 designated products in eight categories: paper and paper products, vehicular, construction, landscaping, park and recreation, transportation, non-paper office, and miscellaneous products. Examples of designated products include structural fiberboard, printing and writing papers. The current list of designated products, EPA's guidance, and related technical information can be found on EPA's web site at <http://www.epa.gov>.

### **2. Energy-Efficient Products: Energy Star®, FEMP-Designated, and Low Standby Power**

EPAct of 2005, Section 104 and FAR 23.203 require federal agencies to purchase Energy Star® qualified or Department of Energy's (DOE's) Federal Energy Management Program (FEMP)-designated products when procuring energy-consuming products. The technical requirements that each product must meet to become Energy Star® qualified are available at [ENERGY STAR Qualified Products : ENERGY STAR](http://www.eere.energy.gov). Information on FEMP-designated products can be found at <http://www.eere.energy.gov>. Information on low standby power products can be found on FEMP's web site at: <http://www.eere.energy.gov>.

### **3. Biobased Products**

Biobased products are products determined by the Secretary of Agriculture to be commercial or industrial products (other than food or feed) that are composed in whole, or in significant part, of biological products or renewable domestic agricultural materials and forestry materials. Examples of USDA-designated biobased products include mobile equipment, hydraulic fluids, roof coatings, diesel fuel additives, and towels. USDA is responsible for implementing the BioPreferred<sup>SM</sup> procurement preference program. Information on these designated products, USDA's guidance, and related documentation can be found at USDA's web site at <http://www.biopreferred.gov>. (The FAR is being revised to require that Federal agencies procure designated items composed of the highest percentage of biobased content practicable [FAR Case 2010-004].)

#### **4. Environmentally Preferable Products and Services**

Environmentally Preferable Products (EPP) are products or services that have a lesser or reduced effect on human health and the environment when compared with competing products or services that serve the same purpose. This comparison may consider raw materials acquisition, production, manufacturing, packaging, distribution, reuse, operation, maintenance, or disposal of the products or services. Examples of environmentally preferable products include cleaning products that are non-toxic, non-volatile, and biodegradable; and paint with no or low volatile organic compounds. This program is managed by EPA which maintains a database of products and specifications defined by federal, state, and local agencies, and other nations. The database can be found at <http://www.epa.gov/epp> along with EPA's **Guidance on the Acquisition of Environmentally Preferable Products and Services** located at <http://www.epa.gov/epp/pubs/index.htm>

#### **5. Electronic Product Environmental Assessment Tool (EPEAT) Products**

EPEAT is a tool for evaluating the environmental performance of electronic products throughout their life cycle. EPEAT is intended to help purchasers in the public and private sectors evaluate, compare and select desktop computers, notebooks and monitors based on their environmental attributes. EPEAT also provides a clear and consistent set of performance criteria for the design of products, and provides an opportunity for manufacturers to secure market recognition for efforts to reduce the environmental impact of its products. Available at: <http://www.epeat.net/>

#### **6. Water-Efficient Products**

A water-efficient product is in the upper 25% of water efficiency for all similar products, or is at least 10% more efficient than the minimum level meeting U.S. Federal Government standards. Examples of products that have met the EPA WaterSense label include: high efficiency toilets, sink faucets, showerheads, urinals, and landscape irrigation systems. Information about the WaterSense Program is available at [www.epa.gov/watersense](http://www.epa.gov/watersense).

#### **7. Non-Ozone Depleting Substances**

E.O. 13423 and the Council on Environmental Quality (CEQ) Implementing Instructions require that each agency give preference to the purchase of non-ozone depleting substances, as identified in EPA's Significant New Alternatives Policy (SNAP) program. **FAR 23.803** states that agencies shall give preference to the procurement of alternative products that reduce overall risks to human health and the environment by lessening the depletion of ozone in the upper stratosphere. It further requires that in preparing specifications and purchase descriptions, and the acquisition

of supplies and services, agencies shall comply with the requirements of the Clean Air Act and substitute safe alternatives to ozone-depleting substances.

SNAP provides lists of acceptable and unacceptable substitutes in the following sectors: fire suppressants, aerosol solvents and propellants, refrigeration and air conditioning equipment, and adhesives and coatings. SNAP is managed by EPA. Information about the SNAP Program is available on <http://www.epa.gov/ozone/strathome.html>

## **8. Alternative Fuel Vehicles and Alternative Fuels**

Under EPCRA, alternative fuel vehicles are defined as any dedicated, flexible-fuel, or dual-fuel vehicle designed to operate on at least one alternative fuel. As defined by EPCRA, alternative fuels are substantially non-petroleum based fuels and include (but are not limited to) the following: ethanol at a 85% blend or higher (E85); liquefied petroleum gas (propane); compressed natural gas (CNG); biodiesel; electricity; hydrogen; and P-series fuels. DOE's FEMP manages this program. Information on these federal fleet requirements can be found at [http://www1.eere.energy.gov/femp/program/fedfleet\\_requirements.html](http://www1.eere.energy.gov/femp/program/fedfleet_requirements.html).

## **SAMPLE TASK ORDER:**

### **USE SMALL MOLECULE INHIBITOR(S) OF MDM2/MDMX TO PREVENT CANCER**

**PERIOD OF PERFORMANCE:** 24 months

#### **BACKGROUND**

Cancer is the leading cause of mortality worldwide in developing and developed countries and the second leading cause of death. About half of the demise is due to tumors at following organs: lung, breast, colorectal, pancreas, and prostate. According to World Health Organization (WHO), 14.1 million people developed and 8.2 million died of cancer in 2012. The burden of cancer is notable heavier in the developed countries due to factors including age, lifestyle choices such as smoking, physical inactivity/obesity, environmental carcinogens exposure, and infectious agents etc., many of these cancers should be largely preventable. Cancer arises as the result of usually a series of mutations in DNA that may be either germline (inherited) or somatic (acquired during life), resulting in uncontrollable cell growth, proliferation, and death. Germline genetic variants are likely to account for small attributable to highly penetrant mutations such as in *BRCA1* or mismatch repair genes. In the past decades, the knowledge regarding public awareness of cancer and chemoprevention has made significant progress, albeit the number of new cancer cases is still on the rise. Should this trend continue, 16.5 million new cases of cancer are expected to be diagnosed in 2020 with an approximate 10 million deaths expected, two-thirds of which are likely to occur in developing nations. Since the prevalence of cancer incidences is a growing problem, primary prevention is an effective—and probably cost-effective—way to decrease cancer incidence, with about a third of cancers being preventable. Hence, it is important to understand how and why cancers develop in order to devise feasible, effective regimen to preventing, reversing tumorigenesis as a priority for fighting this insidious disease.

About 50% of all human cancers have mutations in the p53 tumor suppressor gene. The p53 plays significant roles in cell-cycle arrest and apoptosis when cells exposed to various forms of stress, including DNA damage. The transcriptional activity of p53 leads to the activation of downstream target genes, which are responsible for inducing cell-cycle arrest, DNA repair, senescence, or apoptosis. P53 is one of the most commonly altered genes in human tumors. The studies of P53 mutations lead the understanding of human malignancy. These studies also demonstrate a link between exposure to various types of carcinogens, specific mutational events in the P53 gene and development of cancers in specific organs. For example, p53 is often inactivated in breast and lung cancer cells due to gene mutation or overexpression of its repressors, such as Mdm2 and MdmX. These mutations, exhibit dominant-negative activity through hetero-oligomerization with wild-type p53 expressed from the remaining allele, generally lead to a loss or diminution of the wild-type functions of p53. Furthermore, mutant p53 can enhance signaling through receptors such as transforming growth factor  $\beta$  (TGF- $\beta$ ) receptor, epidermal growth factor receptor, and MET, etc. There is increasing evidence indicating the indirect effect of mutant p53 on gene expression through binding to other transcription factors underlies the unique activities of these mutant p53. In addition, the biological functions of p53 protein are tightly controlled via an auto-regulatory feedback loop, which block p53 tumor suppressive activities in both normal and malignant cells via Mdm2/MdmX heterodimers. These

proteins bind p53 with their structurally dissimilar N-terminal domains and effectively inhibit p53 transcriptional activity. Additionally, some tumors amplify and/or overexpress Mdm2, an E3 ubiquitin ligase, which accelerate p53 for degradation. In some cases, tumors in which p53 is not mutated have evolved other mechanisms to deregulate this pathway.

In the past decade, intensive studies on Mdm2 and MdmX proteins have indicated that a major oncogenic role of Mdm proteins is to block p53 transcriptional activities. Both Mdm2 and MdmX contain three well-conserved domains: an N-terminal domain that is responsible for p53 binding, a zinc-finger domain, and a C-terminal Really Interesting New Gene (RING) domain. The RING domain is accountable for the formation of homo-heterodimers and confers E3 ubiquitin ligase activity. In addition to proteasomal degradation of p53, Mdm2 and MdmX bind to the N-terminal transactivation domain of p53 and prevent its interaction with the transcriptional machinery, which result in the inhibition of p53-regulated gene expression. Furthermore, Mdm2 promotes p53 nuclear export and suppress p53 acetylation by co-activator p300 protein.

The p53 protein orchestrates a plethora of signaling pathways that prevent a damaged or abnormal cell from undergoing malignant transformation. Under physiological condition, p53 protein is maintained at low levels due to the negative regulation by Mdm2/MdmX. Hence, controlling and maintaining full-scale of p53 biological activities are critical for normal homeostasis and malignance surveillance. One of the strategies to restore p53 functions involves elevating wild-type p53 protein levels and transcriptional activities by targeting p53-Mdm2/MdmX network and preventing Mdm2-mediated proteasomal degradation of p53. The first reported small molecules capable of displacing p53 from Mdm2 *in vitro* with nanomolar potency were the nutlin and its derivatives. Currently, many novel molecules with innovative molecular mechanisms, based on dissimilar structures between MDM2 and MDMX in their p53-binding pockets, are entering in clinical investigations, and numerous molecules are in late stage of preclinical evaluation. Therefore, it is imperative to assess this hypothesis, enhancement of wild-type p53 functions, for an avenue to prevent carcinogenesis.

## **STATEMENT OF WORK**

### **Objective:**

The overall objective of this Task Order shall be to evaluate preclinical chemopreventive efficacy of *novel* small molecule(s) that inhibits Mdm2/MdmX-mediated ubiquitylation and proteasomal degradation of p53 protein in appropriate animal model(s).

### **The Offeror shall perform the following tasks:**

#### **Task Area 1**

1. The Offeror shall nominate at least one novel and specific inhibitor of Mdm2/MdmX from literature for initiating a dose finding *in vivo* study. In addition, the Offeror shall conduct an initial PK study to demonstrate blood levels of molecule over 24-hour period.

- The Offeror shall conduct an extensive literature search and identify novel and specific inhibitor, which demonstrates its potency to elevate/restore wild-type p53 transcriptional function activities by targeting p53-Mdm2/MdmX binding and inhibiting/disrupting Mdm2/MdmX-mediated proteasomal degradation of p53 protein. The Offeror shall *not* use nutlin, its derivatives, CP-31398, Prima-1 and derivatives as test agents.
- The Offeror shall provide detailed characteristics of the test agent.
- Regarding the PK study of the test agent, the Offeror shall conduct 24-hour measurements of the molecule. The blood samples should be collected at 0, 2, 4, 8, 16, and 24 hours after first dose.

## Task Area 2

1. The Offeror shall choose one preclinical efficacy model and conduct detailed pharmacodynamic study to demonstrate such molecule's effectiveness in preventing carcinogenesis.
  - The Offeror shall propose one preclinical animal model with one target organ, such as breast, pancreas, lung, colon, urothelial bladder carcinoma, which has a strong biological relevance to p53-MDM-mediated pathway of tumorigenesis, and evaluating test agent in preventing the process of tumorigenesis.
2. The Offeror shall explore and delineate the connection of pharmacodynamic endpoints, such as tumor multiplicity, incidence, and pathway-mediated intermediate endpoints.
  - The Offeror shall design and perform additional studies, based on the preclinical efficacy mode, to explicate downstream molecular pathway, as intermediate endpoints, to connect an inhibition of p53-Mdm2/MdmX and pharmacodynamic endpoints. For example, the offeror could use samples from target tumor tissue to delve specific molecular signaling of p53 and/or Mdm2/MdmX, which shall be able to correlate with inhibition of tumor incidence or multiplicity, etc.
  - The Offeror shall provide scientific rationale which could delineate a margin-of-safety of testing agent to avoid on-target potential adverse effects.
3. Travel - One (1) staff member/PI shall travel to a scientific meeting one (1) time in the final year of the Task Order for the purposes of presentation of the results for the Task Order.