

## ADDITIONAL TECHNICAL PROPOSAL INSTRUCTIONS

**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 should follow the instructions requested here.

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 two (2) 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, plus documentation of subcontractor's expertise, qualifications and prior performance, as well as a narrative describing how the contractor 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 Government encourages offerors to be complete but succinct in their presentation and to limit the number of pages to 150. See content below:**

**TOTAL PAGE COUNT DOES INCLUDE:** Principal Investigator's (PI's) resume/*Curriculum Vitae (CV)*, with highlights of any items that are directly related to the subject project, indicated by preceding them with a double asterisk (\*\*).

**TOTAL PAGE COUNT DOES NOT INCLUDE** (some of which may be added as appendices): Title and Back Page; NIH-2043; Table of Contents; Section Dividers that do not contain information other than title of Section; Resumes/CVs of other key personnel (same information and format as used for the PI); certificates and licensures, examples of protocols, Standard Operating Procedures (SOP), Safety and Health Manual, letters of commitment by proposed consultants and subcontractors.

**PAGES THAT ARE 2-SIDED WILL COUNT AS 2 PAGES.**

**FORMATTING AND LAYOUT:**

Use your usual word processing and spreadsheet programs to prepare and format the technical and business proposals.

**Documents submitted using Adobe .pdf shall be submitted using a .pdf searchable format.**

- Type size must be 10 to 12 points.
- Type spacing should be no more than 15 characters per inch. Within a vertical inch, there must be no more than six lines of text.
- Print margins must be at least one inch on each edge of the paper.
- Print setup should be single-sided on standard letter size paper (8.5 x 11").
- Offerors shall **NOT** use 8.5 x 14 legal size paper.
- Proposals shall **NOT** include links to Internet Web site addresses (URLs) or otherwise direct readers/reviewers to alternate sources of information.
- Additional appendices may be added as needed.
- The proposal with pagination, including appendices, shall be formatted by sections, cross referenced, and include a detailed Table of Contents with page references.

**CREATING AND NAMING ELECTRONIC FILES – COMPACT DISC (CD):**

1. A separate compact disc (CD) should be submitted for the Technical and Business Proposal information. Offerors who submit both Technical and Business Proposals on the same CD will be required to resubmit them on separate CDs.
2. It is preferred that the Technical Proposal be submitted as one electronic file document.  
**Note:** if multiple files are submitted for either proposal please include the name of the section in the file name:  
EXAMPLE: XYZ Company-07-16-Technical-Approach-3-6-06
3. CDs should be named using the following format:  
Technical Proposal: Company name-RFP number-technical-date  
Business Proposal: Company name-RFP number-business-date

## **TECHNICAL PROPOSAL – TABLE OF CONTENTS**

### **General Instructions:**

#### **SECTION 1**

- 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 (NIH FORM 1688-1);
- C. GOVERNMENT NOTICE FOR HANDLING PROPOSALS;
- D. PROPOSAL SUMMARY AND DATA RECORD (NIH-2043);
- E. TABLE OF CONTENTS.

Section L of the RFP specifies the minimum documentation requirements for cost data and all cost related support. All related documentation should be included in the proposal in a clearly marked section. Cost and Pricing support should be provided for all proposed subcontractors.

#### **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.

#### **SECTION 3: TECHNICAL DISCUSSIONS**

##### **A. Personnel and Experience**

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 who is to be assigned as Key Personnel. Limit *Curricula Vitae (CV)* to 2-3 pages and provide 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 Offerer 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 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 key 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 (genomics, proteomics or metabolomics) and statistics, as necessary.

3. Certified Veterinarian (DVM): Documented participation of an American College of Laboratory Animal Medicine (ACLAM) certified veterinarian.

## **B. TECHNICAL APPROACH**

Offerors shall submit a proposal that addresses the two (02) Task Areas in the Statement of Work. Only proposals from offerors who demonstrate the capability to perform all aspects of the Statement of Work, either at their institution or through their subcontractors, will be considered for award. 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 contractor 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 1 and 2 in the Statement of Work, including 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.
3. Describe proposed plans for oversight of data management functions, including protection of intellectual property and confidentiality of compound data.
4. 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.

**Please provide a response to each of the Sample Task Orders of these Additional Technical Proposal Instructions:**

**See Appendix A (page 7) for details of Sample Task Orders 1 and 2.**

**Also, see Additional Business Proposal Instructions regarding development of budgets for each sample task order response.**

## **C. FACILITIES AND EQUIPMENT**

1. Facilities - The offeror shall have an operating laboratory which 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).

Discuss operation, procedures, and administration of the cell culture and animal facility and provide floor plan(s) drawn to scale (including scaling factor). Also 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 (prime) 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 and refrigerators, pathology equipment such as 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.

#### **D. ORGANIZATIONAL BACKGROUND AND EXPERIENCE**

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.

Quality Assurance - Validation studies undertaken to assure the accuracy of transmitted data for the version(s) of software shall be described.

1. Statistics - Methods of statistical analysis (parametric versus nonparametric) shall be described by the offeror for data and underlying distributions being compared.
2. Subcontracts - In the event that the offeror does not have facilities, equipment, or personnel for performing any component of the described task, then the offeror shall be prepared to implement the work through a suitable subcontractor. Letters of commitment from and qualifications of all proposed subcontractors shall be included in the proposal. The offeror shall describe any previous working relationship with proposed subcontractors. Furthermore, the offeror shall address how they will handle privity of contract issues, i.e., the offeror should explain how information will flow between the NCI, the prime contractor (offeror), and any subcontractors since the prime contractor's presence is required for any discussions.
3. Agents - to be investigated by this project are potentially hazardous. Discuss laboratory practices that will be employed which shall keep any element of risk to personnel at an absolute minimum.
4. Safety and Health for Personnel - Provide a Safety and Health Plan. Offerors' Safety and Health Plan shall include recent and ongoing organizational background and 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 SOW to insure that the work is conducted in a safe and healthful manner. All pertinent chemical and or biological hazards shall be addressed in the Plan, 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.

## APPENDIX A SAMPLE TASK ORDERS 1 AND 2

Please provide a response to each of the sample Task Orders for the following as described in the Statement of Work:

### *SAMPLE TASK ORDER 1 –*

#### **THE USE OF MICROARRAYS IN EXAMINING GENE EXPRESSION CHANGES INDUCED BY CHEMOPREVENTIVE AGENTS IN BOTH NORMAL TISSUES AND CANCERS**

**Expected Study Duration: 18 months**

#### **BACKGROUND**

The use of gene expression microarrays allows for the simultaneous examination of expression of literally thousands of genes. We have previously used microarrays to examine the relationship between agents of related structures (4HPR, 9Cis RA and Targretin) as well as to look at structurally varied RXR agonists. In addition we have used it to look at multiple structurally varied Phase I/II inducers including 1,2 dithiothione, cyclapen tadithiolthione, ethoxyquin, diallyl sulfide and 5,6 benzoflavone.. as well as to identify potential targets and biomarkers of exposure to effective and ineffective chemopreventive agents. We will use the microarray methods and analysis for 5 groups of studies. In the present study we will examine samples from bladder, mammary and lung to parallel recent results we have obtained in animal testing.

- a. **Comparison Of Control Estrogen Receptor+ (ER+) Rat Mammary Tumors And ER+ Rat Mammary Tumors Treated With Vorozole Or Atorvastatin:** The contractor shall employ analytic techniques to determine whether the gene expression changes observed in the animal tumors following short term treatment with the aromatase inhibitor Vorozole and with atorvastatin an HMG CoA synthetase inhibitor. In prior published studies we have shown vorozole to be a highly effective agent whereas atorvastatin is ineffective in this model.
  
- b. **Comparison Of Control Rat Bladder Tumors And Rat Bladder Tumors; Tumors Treated With Iressa Or Low Dose Aspirin:** The contractor shall employ analytic techniques to determine gene expression changes observed in the animal tumors following short term treatment with the EGFr inhibitor Iressa and with low dose aspirin (200 ppm). In prior published studies we have shown that Iressa is highly effective whereas low dose aspirin is ineffective, SHOULD GIVE US BIOMARKERS.
  
- a. **Comparison Of Gene Expression In Control Or Treated (Vorozole Or Atorvastatin) Mammary Tumors.**

**Frozen Mammary Tumors** The contractor shall be supplied control mammary tumors [n=7] and mammary tumors treated short term [5 days] with vorozole (an aromatase inhibitor) [n=7] or with atorvastatin [n=7. Based on previous published work by the CARDG vorozole is a highly effective agent in this model whereas atorvastatin appears to be ineffective.].

- A) **RNA Preparation:** The contractor shall make RNA preparations from control or treated mammary tumors
- B) **RNA Quality :** Determine RNA quality. by examining ratios and quality of Ribosomal RNA at 28S and 18S
- C) **Determine RNA Expression Employing An Oligonucleotide Microarray.** Offereor shall propose to employ a standard commercial oligonucleotide microarray to determine gene expression. Offeror can employ an exxon array which can identify roughly 100000 different genes based on splice variant which may exist.
- D) **Determine RNAs That Are Over/Under Expressed When Comparing Control And Treated Mammary Tumors.** Using standard analytic tools determine genes which are significantly over expressed or under expressed when comparing control and treated tumors. Define the 50 genes which are most highly over expressed >2X expression and P<.001 and 150 genes which are most highly unders expressed >2 fold and P<.001 genes
- E) **Determining Molecular Pathways Which Are Modulated When Comparing Control And Treated Tumors** Employing standard analytic techniques (comparison with known pathways by GO or KeGG terms) examine gene expression changes which are related to known molecular pathways.
- F) **Confirm Over Or Under Expression Of RNAs Using Quantiative RT-PCR.** Choose at least 7 over expressed genes and 7 under expressed genes from point 1D. Determine the direction and relative magnitude of the changes in rNA expression for these specific genes.

**b. Comparison Of Gene Expression In Control Or Treated (Iressa Or Low Dose Aspirin (200 ppm) Bladder Tumors.**

**Frozen Bladder Tumors** The contractor shall be supplied control bladder tumors [n=7] and bladder treated short term [5 days] with Iressa (an EGFr1 inhibitor) [n=7] or with low dose aspirin [n=7. Based on previous published work by the CARDG irressa is a highly effective agent in this model whereas low dose aspirin appears to be ineffective.].

- A) **RNA Preparation:** The contractor shall make RNA preparations from control or treated mammary tumors
- B) **RNA Quality :** Determine RNA quality. by examining ratios and quality of Ribosomal RNA at 28S and 18S
- C) **Determine RNA Expression Employing An Oligonucleotide Microarray.** Offereor shall propose to employ a standard commercial oligonucleotide microarray to determine gene expression. Offeror can employ an exxon array which can identify roughly 100000 different genes based on splice variant which may exist.
- D) **Determine RNAs That Are Over/Under Expressed When Comparing Control And Treated Rat Bladder Tumors.** Using standard analytic tools determine genes which are significantly over expressed or under expressed when comparing control and treated tumors. Define the 50 genes which are most highly over expressed >2X expression and P<.001 and 150 genes which are most highly unders expressed >2 fold and P<.001 genes
- E) **Determining Molecular Pathways Which Are Modulated When Comparing Control And Treated Tumors** Employing standard analytic techniques (comparison with known pathways by GO or KeGG terms) examine gene expression changes which are related to known molecular pathways.

- F) **Confirm Over Or Under Expression Of RNAs Using Quantitative RT-PCR.** Choose at least 7 over expressed genes and 7 under expressed genes from point 1D. Determine the direction and relative magnitude of the changes in rNA expression for these specific genes.

**SAMPLE TASK ORDER 2 –**

**SCREENING FOR CHEMOPREVENTIVE AGENTS EMPLOYING TRANSGENIC MICE:**

- 1. NEU OVEREXPRESSION AND A MUTATION OF THE P53 TUMOR SUPPRESSOR GENE**
- 2. EXPRESSING T ANTIGEN IN PROSTATE OR MAMMARY GLAND**

**Expected Study Duration: 18 months**

**BACKGROUND**

The development of transgenic mouse models allows one to employ rodents with specific alterations, expressed oncogenes or loss of specific tumor suppressor genes, which may be particularly relevant to the human disease. One mouse model which has been developed recently involves the expression of a nonmutated Neu gene under the control of the MMTV promoter (Gury et al PNAS 89, 10578). Since results in ER negative tumors Neu overexpression drives one of the two major forms of ER breast cancer, use of this model would appear to be particularly relevant in screening potential agents for ER negative breast cancer. Interestingly, roughly 60% of human ER negative breast cancer have a mutation in P53. Therefore the use of a model which both overexpresses Neu and has a mutation in P53 appears to be particularly relevant. The second mouse model entails use of a mammary tumor model which overexpresses T antigen and which is by gene array analysis similar to human basal type tumors.

**A. Generation of Transgenic Mice with a Neu Transgene and a Knockout (KO) of P53:**

1. Contractor shall generate breeding mice which are either heterozygous or homozygous for KO of the P53 tumor suppressor gene on an FVB background;
2. Contractor shall generate breeding mice which are homozygous for expression of Neu under the control of the MMTV promoter(Neu/Neu);
3. Contractor shall generate F1 mice from groups 1 and 2 above which are heterozygous for expression of Neu and which have a heterozygous KO of P53(Neu/WT; P53/WT). All of the female mice resulting from such a cross should have the proper genotype;
4. Generate 60 female mice for the control group;
5. Generate 30 female mice per group for the chemoprevention studies;
6. The initiation of treatment shall begin when mice are 10 weeks of age;
7. Mice shall be checked weekly for the development of palpable mammary tumors which shall be noted;
8. Mice shall be sacrificed when they develop large palpable mammary tumors;
9. All mice shall be sacrificed at 9 months of age. Alternatively mice shall be sacrificed when 80% of control mice develop large palpable lesions;
10. Four hours prior to sacrifice animals shall be administered BudR so that proliferation indices can be determined in tumors.

***Prevention Protocol***

<b>No. of Animals Per Group</b>	<b>Chemopreventive Agent</b>	<b>Duration of Treatment</b> (Weeks of Age)
60	None	10-36
30	Iressa Hi Dose	10-36
30	Lapatinib	10-36

**B. Generation of Transgenic Mice Expressing C31Tag in Mammary:**

11. Contractor shall generate breeding mice which are homozygous for expression of C31 T antigen on an FVB background;
12. Contractor shall generate F1 mice from groups 10 by crossing these homozygous mice with FVB wild type mice. The resulting mice should be heterozygous for the C31 Tag.. All of the mice resulting from such a cross should have the proper genotype;
13. Generate 60 female mice per group for the control group;
14. Generate 30 female mice per group for the chemoprevention studies;
15. The initiation of treatment shall begin when mice are 6 weeks of age;
16. Mice shall be checked weekly for the development of palpable mammary tumors which shall be noted;
17. Mice shall be sacrificed when they develop a large palpable mammary tumors;
18. All mice shall be sacrificed at 8 months of age. Alternatively mice shall be sacrificed when 80% of control mice develop large palpable lesions;
19. Four hours prior to sacrifice animals shall be administered BudR so that proliferation indices can be determined in tumors.

***Prevention Protocol***

<b>N. of Animals Per Group</b>	<b>Chemopreventive Agent</b>	<b>Duration of Treatment</b> (Weeks of Age)
60	None	10-36
30	Tarceva Hi Dose	10-36
30	Targretin	10-36
30	UAB 30	10-36
30	SAHA	10-36

The doses of the individual preventive agents shall be determined by agreement between the contractor and the NCI personnel.

**See also the Additional Business Proposal Instructions regarding development of budgets for each sample task order response.**