



Leidos Biomedical Research, Inc.

Agreement No.

Introduction

This Agreement, effective upon signature of Leidos Biomedical Research, Inc. (Leidos Biomed), is made between Leidos Biomed, a subsidiary of Leidos Corporation, a Delaware corporation with offices in Frederick, MD, and Insert Offeror's Name (hereinafter known as "Subcontractor"), a Insert whether Corporation or Partnership, etc. with principal offices in Insert City, State. The effort to be performed by Subcontractor under this Agreement will be part of Leidos Biomed's Prime Contract HHSN261200800001E that has been issued by the National Cancer Institute, National Institutes of Health, Frederick, MD. The provisions and clauses contained herein are influenced by and reflect the relationship of the parties in that contract, which was awarded and is administered under the provision of the Federal Acquisition Regulation (FAR).

In witness whereof and in consideration of the mutual obligations assumed under this Agreement, Leidos Biomed and Subcontractor agree to the Terms and Conditions attached hereto and incorporated by reference and represent that this Agreement is executed by duly authorized representatives as of the dates below:

Subcontractor:

Signature/Title/Date of Signature

Leidos Biomedical Research Inc:

Signature/Title/Date of Award

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Specific Terms and Conditions

A. Period of Performance

The period of performance for this Agreement shall begin on the award date and end on December 31, 2015, noting that the deadline for tissue submission is December 31, 2014. This accommodates the One Year Case Report form due 12 months from the date of tissue submission.

B. Price Schedule/Funding

B.1. Agreement Type.

This Agreement will be a hybrid combination of multiple agreement types. Firm-Fixed pricing will be utilized for milestone payments associated with Institutional Review Board (IRB) approval and executing a Material Transfer Agreement (MTA). Fixed-Unit pricing shall apply to the delivery of tumor samples, case reports/diagnostic histopathology and one-year case reports respectively. A Firm-Fixed and/or Fixed-Unit Price Agreement provides for a price that is not subject to any adjustment as a result of the Subcontractor's cost experience. The Subcontractor may not exceed the established fixed amount without the prior approval of the Contracting Officer.

For Other Direct Costs/Travel ONLY the resulting Agreement will be Cost Reimbursable as described in FAR Part 16.302. A Cost-Reimbursement Agreement provides for payment of allowable incurred costs to the extent prescribed in the Agreement. The Subcontractor may not exceed the established ceiling amount without the prior approval of the Contracting Officer.

B.2. Price Schedule.

The total ceiling amount is \$Insert \$ Amount (see Agreement --- Attachment 3 - Price Schedule).

- If at any time the Subcontractor has reason to believe that the costs accrued in performing this Agreement in the next succeeding 30 days, if added to all other payments and cost previously accrued will exceed 85% of the total amount of this Agreement, the Subcontractor shall immediately notify the Leidos Biomed Contracting Officer in writing.

C. Acceptance

Acceptance of deliverables tendered by the Subcontractor hereunder shall be made by Leidos Biomedical Research, Inc. Acceptance from other persons or entities shall not be construed as acceptance under this Agreement. Additionally, payment for services rendered, or deliverables provided, shall not be construed as acceptance by Leidos Biomed, nor does it negate or in any way diminish any rights afforded Leidos Biomed for remedies as a result of defects or nonconformance, either patent or latent, or other breach of warranty, or to make any claim for damages of any and all kind.

D. Invoices

Invoices must include adequate information to enable the Leidos Biomed Contracting Officer to determine that reasonable progress has been made, milestones or objectives have been met, and/or conditions exist that would otherwise warrant payment of an invoice tendered.

D.1. Content.

Upon award, Invoices shall be provided in the manner set forth in Agreement Attachment 2 — Invoice Instructions. All invoices shall be submitted in U.S. Dollars (\$USD).

D.2. Timing/Format.

Invoices shall be provided monthly in electronic format (pdf or other commonly used format) and submitted to: apinvoices@mail.nih.gov unless otherwise agreed upon in writing. Subcontractor shall invoice within 30 days of their invoice closing period. Failure of Subcontractor to invoice in accordance with these provisions can be considered a Breach of this Agreement under the Termination provision of this Agreement.

D.3. Certification.

The Subcontractor agrees that invoices submitted under this Agreement constitute a certification that the costs included are accurate, allocable to this Agreement, and allowable under the terms and conditions of the same.

E. Payment

Upon acceptance of a proper invoice and any required deliverables, Leidos Biomed shall pay the Subcontractor as follows:

E.1. Payment Terms.

Leidos Biomed may, at its discretion, require the Subcontractor to substantiate invoices by evidence of actual payment and by individual daily job time cards, or other substantiation approved by Leidos Biomed. Leidos Biomed shall pay the invoice, in U.S. dollars (\$USD) within 30 days after receipt of a proper invoice. Unless specifically authorized in writing by Leidos Biomed, the Subcontractor is not authorized to perform and Leidos Biomed, is not obligated to reimburse the Subcontractor for work performed on an Overtime or Shift Premium basis. FAR 52.247-34 F.O.B. Destination shall apply to any applicable deliveries made under this Agreement.

E.2. Materials, Supplies, and Other Direct Costs.

Materials, supplies, and other direct costs, including travel (if authorized), will be reimbursed on an actual-cost basis and in accordance with consistently applied Generally Accepted Accounting Principles or, if applicable, as prescribed in Section F. Travel of this Agreement. Where materials are withdrawn from inventories, cost must be determined in accordance with proper accounting practices consistently

followed by the Subcontractor. The Subcontractor shall support all material cost claims by submitting invoices, storeroom requisition receipts, expense reports, or other substantiation acceptable to Leidos Biomed

F. Advance Understanding

Throughout this Agreement document, unless a purposeful distinction is made clear and the context of the clause requires retention of the original definition, the term “Contractor” shall mean Subcontractor, the term “Contract” shall mean this Agreement, the term “Subcontractor” shall mean subcontractors of Leidos Biomed at any tier, and the terms “Government”, “Contracting Officer” and equivalent phrases shall mean Leidos Biomed and Leidos Biomed’s Contracting Officer, respectively. It is intended that the referenced clauses shall apply to Subcontractor in such manner as is necessary to reflect the position of Subcontractor as a Subcontractor to Leidos Biomed to insure Subcontractor’s obligations to Leidos Biomed and to enable Leidos Biomed to meet its obligations under its Prime Contract.

F.1. Travel

Travel including lodging, other subsistence, and incidental expenses shall be allowable only to the extent that the costs do not exceed the amounts allowed for in Agreement Attachment 3 – Price Schedule and shall be reimbursed on an actual basis and as prescribed in Agreement Attachment 4 – Travel Costs and Reimbursement Policy. All required travel not identified in the price schedule must be preapproved by the Contracting Officer before costs may be incurred.

F.2. Equipment

Leidos Biomed Contracting Officer’s advance authorization is required before any equipment is purchased under this Agreement. All equipment authorized for purchase that is either defined as “sensitive” or has a unit acquisition cost of \$5,000 or more and has an expected service life of more than two years (see the DHHS Contractor's Guide for Control of Government Property) must be reported and inventoried and remains the property of the U.S. Government.

G. Agreement Attachments/Order of Precedence

G.1. Agreement Attachments.

The following attachments are provided with this Agreement and incorporated in full force and effect as described in Section G.2—Order of Precedence:

- Attachment 1: Statement of Work
- Attachment 2: Invoice Requirements
- Attachment 3: Price Schedule
- Attachment 4: Travel Costs and Reimbursement Policy

G.2. Order of Precedence.

In the event of an inconsistency or conflict between or among the provisions of this Agreement, the inconsistency or conflict shall be resolved by giving precedence in the following order:

1. This Agreement including Leidos Biomed Standard Terms and Conditions, Exhibits thereto and provisions.
2. Specifications and/or drawings.
3. Other documents or exhibits.

H. Authorized Representatives

The following authorized representatives are hereby designated for this Agreement:

H.1. *Leidos Biomed Contracting Officer*

The following individual is designated as the Leidos Biomed Contracting Officer:

Calvin Proffitt

Leidos Biomedical Research, Inc.

PO Box B

Frederick, MD 21702

Phone: (301) 228-4022

Email: calvin.proffitt@nih.gov

Only the Contracting Officer or designee, has authority to: (1) direct or negotiate any changes to the Statement of Work; (2) modify or extend the period of performance; (3) change the delivery schedule; (4) authorize reimbursement to the Subcontractor of any costs incurred during the performance of this Agreement; or (5) otherwise change any terms and conditions of this Agreement. All changes to the Statement of Work will be accomplished by bilateral modification to the Agreement.

Important: Only the Contracting Officer or designee, as named above shall have the authority to prescribe changes to this Agreement or provide direction for which the Subcontractor will seek reimbursement. Any costs incurred by the Subcontractor not delineated herein or without the prior written approval of the Contracting Officer or designee, are incurred at the Subcontractor's significant risk of non-payment.

H.2. *Leidos Biomed Technical Project Manager (TPM)*

The following individual is designated as the Leidos Biomed Technical Project Manager (TPM) and is authorized to provide technical guidance and otherwise represent Leidos Biomedas stated herein:

TBD

Ledios Biomedical Research, Inc.

PO Box B

Frederick, MD 21702

Phone: TBD

Email: TBD

The Technical Project Manager is responsible for: (1) monitoring the Subcontractor's technical progress, including the surveillance and assessment of performance and recommending to the Contracting Officer changes in requirements; (2) interpreting the Statement of Work and any other technical performance requirements; (3) performing technical evaluation as required; (4) performing technical inspections and acceptances required by this Agreement; and (5) assisting in the resolution of technical problems encountered during performance

Important: Neither the TPM nor any person or entity other than the Contracting Officer possess any authority, implied or apparent, to provide direction that may cause or influence the Subcontractor to incur additional costs for which reimbursement may be sought. Any costs incurred by the Subcontractor not delineated herein or without the prior written approval of the Contracting Officer are incurred at the Subcontractor's significant risk of non-payment.

H.3. Leidos Biomed Subcontract Administrator

The following individual has been designated as the Leidos Biomed Subcontract Administrator for purposes of administering, processing, and handling contractual documentation:

Jessica Staley

Ledios Biomedical Research, Inc.

PO Box B

Frederick, MD 21702

Phone: (301) 228-4796

Email: jessica.staley@nih.gov

H.4. Subcontractor Authorized Representative

The following individual(s) or his or her designee is/are the designated representative of the Offeror. This will be the Official authorized to negotiate and sign the resulting Agreement:

Insert Name

Insert Company Name

Insert Address

Insert City, State, Zip

Phone: Insert Phone number

Email: Insert email address

H.5. Subcontractor Invoice Representative(s)

The following individual(s) is the designated representative to submit invoices:

Insert Name

Insert Company Name

Insert Address

Insert City, State, Zip

Phone: Insert Phone number

Email: Insert email address

H.6. Subcontractor Regulatory Affairs Representative(s)

The following individual(s) is the designated representative pertaining to Regulatory Affairs:

Insert Name

Insert Company Name

Insert Address

Insert City, State, Zip

Phone: Insert Phone number

Email: Insert email address

Contacts with Leidos Biomed that affect the price, schedule, Statement of Work, or Terms and Conditions shall be made only with the authorized contractual representative. No changes to this Agreement shall be binding upon Leidos Biomed unless incorporated in a written modification signed by the Leidos Biomed Contracting Officer, or designee. The Subcontractor will not accept any instructions issued by any person employed by, or otherwise representing, the U.S. Government.

Any notice to be given hereunder by either Party to the other shall be in writing or by common electronic means and shall be deemed received when confirmation is received. The Parties agree that notices delivered orally do not constitute official, enforceable, notices hereunder.

I. Key Personnel

For purposes of this clause, Key Personnel are those individuals who are recognized as essential to the successful completion and execution of this Agreement. Any substitution or reassignment involving the Subcontractor's Key Personnel assigned to this work shall be made only with persons of equal abilities and qualifications and are subject to prior written approval of the Leidos Biomed Contracting Officer.

Name:

Title:

Email Address:

Name:

Title:

Email Address:

J. Deliveries

- Satisfactory performance shall be deemed to occur upon written acceptance by the Leidos Biomed Contracting Officer.
- Copies of all reports identified herein shall be submitted to the individuals listed below in Sections H.2 and H.3 above.
- Deliverables are detailed in the Statement of Work. Leidos Biomed reserves the right to alter these requirements to meet programmatic objectives.

If the Subcontractor becomes unable to deliver the required reports and/or deliverables at the time points specified in the Agreement, the Subcontractor shall give the Leidos Biomed Contracting Officer immediate written notice.

K. Special Agreement Requirements

K.1. Organizational Conflict of Interest

The Subcontractor certifies that no financial, contractual, organizational, or other interest exists relating to the work under this Agreement that would constitute an Organizational Conflict of Interest or otherwise cause the Subcontractor to be unable or potentially unable to render impartial assistance or advice, impair objectivity in performing the work, or create an unfair competitive advantage for any

entity wherein the Subcontractor has an interest. The Subcontractor is personally responsible for identifying any such conflict of interest, or any relationship or actions that might give the appearance that a conflict of interest exists or could reasonably be viewed as affecting the Subcontractor's objectivity in performing the work under this Agreement. By signature the Subcontractor certifies the understanding of the above and that no Organizational Conflict of Interest exists that would affect this Agreement. The Subcontractor also indemnifies or otherwise holds harmless Leidos Biomed should an Organizational Conflict of Interest become apparent (not previously disclosed) during the life of this Agreement.

K.1.a. Financial Conflicts of Interest Certification

The Subcontractor certifies that it has a written policy and is in full compliance with the requirements of 45 CFR 94—Responsible Prospective Contractors and will maintain full compliance for the duration of this Agreement. The Subcontractor agrees to provide timely evidence of compliance upon the request of the Contracting Officer. Additionally, the Subcontractor agrees to provide written notification to the Contracting Officer of any financial conflicts of interest, as defined in 45 CFR §94.3—Definitions, related to the work under this Agreement within 30 days of learning of the conflict. The Subcontractor further agrees to submit for Contracting Officer's approval any management plan developed in response to a financial conflict of interest related to the work being performed under this Agreement.

Failure to demonstrate compliance with 45 CFR 94 or to provide timely disclosure of any financial conflict of interest to the Contracting Officer may be considered a material breach of this agreement.

K.2. Prohibition on Contractor Involvement with Terrorist Activities

The Subcontractor acknowledges that U.S. Executive Orders and Laws, including but not limited to E.O. 13224 and P.L. 107-56, prohibit transactions with and the provision of resources and support to individuals and organizations associated with terrorism. It is the legal responsibility of the contractor to ensure compliance with these Executive Orders and Laws. This clause must be included in all lower tier Agreements issued under this Agreement.

K.3. Protected Information Certification

This certification applies only to information protected under all applicable privacy laws, regulations and contract requirements used, accessed, accessible, transported, transmitted, stored, safeguarded, destroyed, or otherwise interacted with (hereinafter "used") in connection with this subcontract, even if only incidental to the work performed. Protected Information includes without limitation all information identifiable to an individual as well as protected health information as such term is defined under the Health Insurance Portability and Accountability Act of 1996 as amended. The subcontractor hereby certifies that it:

1. Has developed and implemented policies and procedures necessary to comply with all applicable privacy laws, regulation and subcontract requirements;
2. Upon request, will provide a listing of all subcontractor policies related to the use of protected information;
3. Trains any and all personnel working in connection with this subcontract regarding subcontractor protected information-related policies, and requires such individuals to take refresher training no less than annually;
4. Has a plan or procedure to validate compliance with its protected information-related policies;
5. Regularly assesses and updates its protected information-related policies; and
6. Will include this certification, in its entirety and unaltered, of each subcontractor working in connection with this subcontract.

K.4. Continued Ban on Funding of Human Embryo Research

Pursuant to the current HHS annual appropriations act, the Subcontractor shall not use Agreement 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. 289g(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 provided under this Agreement may not be used for cloning of human beings.

K.5. Needle Distribution

The Subcontractor shall not use Agreement funds to distribute any needle or syringe for the purpose of preventing the spread of blood borne pathogens in any location that has been determined by authorities to be inappropriate for such distribution.

K.6. Human Materials

It is understood that the acquisition and supply of all human biospecimen material (including fetal material) used under this Agreement will be obtained by the Subcontractor in full compliance with applicable State and local laws and the provisions of the Uniform Anatomical Gift Act in the United States and that no undue inducements, monetary or otherwise, will be offered to any person to influence their donation of human biospecimen material.

K.7. Human Subjects

The Subcontractor must comply with the NIH policy cited in these NIH announcements and any other data and safety monitoring requirements found elsewhere in this Agreement. Data and safety monitoring shall be performed in accordance with the approved data and safety monitoring plan.

The Subcontractor is directed to the full text of any and all applicable U.S. Federal and international regulations cited herein:

U.S. Food and Drug Administration (FDA).

HHS Regulations for Federally Funded Research.

HHSSAR 352-223-70 – Safety and Health.

Declaration of Helsinki.

International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

U.S. CFR.

21 CFR 11, Electronic Records, Electronic Signatures.

21 CFR 50, Human Subject Protection (Informed Consent).

21 CFR 50, Additional Safeguards for Children in Clinical Investigations of FDA-Regulated Products.

21 CFR 54, Financial Disclosure by Clinical Investigators.

21 CFR 56, Institutional Review Boards.

21 CFR 312, Investigational New Drug Application.

45 CFR Part 46, Protection for Human Subjects.

The Subcontractor warrants that all necessary licenses have been secured and regulatory requirements have been satisfied for the performance of the services covered by this Agreement or resulting Task Orders. The Subcontractor shall produce evidence of the same prior to the commencement of this Agreement or resulting Task Orders and shall provide updated accreditations, certifications, and licenses to the Leidos Biomed Contracting Officer or designee as they are required and on a timely basis.

The Subcontractor further warrants that the services performed hereunder will be performed in a manner in accordance with any and all U.S. Federal statutes, regulations, ordinances, or contracts applicable to the services covered hereunder, including but not limited to any governmental security requirements concerning classified or other material that may be involved hereunder, and will be performed in a manner in accordance with best business custom.

K.8. Privacy Act

This procurement action requires the Subcontractor to do one or more of the following: Design, develop, or operate a system of records on individuals to accomplish an agency function in accordance with the Privacy Act of 1974, Public Law 93-579, December 31, 1974 (5 USC 552a(m)(1)), and applicable agency regulations. The term “system of records” means a group of any records under the control of any agency from which information is retrieved by the name of the individual or by some identifying number, symbol, or other identifying particular assigned to the individual.

K.9. Individually Identifiable Information Standards

All clinical data and results and raw data will be collected, used, and disclosed consistent with all applicable Federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in the Code of Federal Regulations (CFR) at 45 CFR Part 164.

K.10. Research Involving Recombinant DNA Molecules

In the performance of any research and/or development under this Agreement involving recombinant DNA molecules, the Subcontractor agrees to abide by all NIH Guidelines relating to such activities, that are now current, and as may be updated from time-to-time. The Contracting Officer, upon request, will provide a copy of these Guidelines to the Subcontractor.

K.11. Safety and Biosafety Standards

All work performed under this Agreement shall be conducted in accordance with the Publication entitled, “Biosafety in Microbiological and Biomedical Laboratories” (HHS Publication No. (DCD) 84-8395). This publication can be found at this address: www.cdc.gov/od/ohs/biosfty/bmb14/bmb14toc.htm.

K.12. Good Laboratory Practice

The Subcontractor shall be responsible for assuring compliance with established standards, either as required in 21 CFR 58.1-219 or by the standards established at their institution. The Subcontractor shall indicate the standard practiced and the standards include, but are not limited to, the following:

Training of personnel.

Animal care and supply facilities.

Facilities for handling test and control articles.

Laboratory operation areas.

Specimen and data storage facilities.

Standard operating procedures.

Conduct of a nonclinical laboratory study and reporting of results.

Storage, retrieval, and retention of records and data.

Additionally, the Subcontractor will supply most recent audit results as part of CLIA and CAP audits.

L. Agreement Terms and Conditions

L.1. *Quality Assurance/Inspection*

All goods furnished and services performed pursuant hereto shall be subject to inspection and testing by Leidos Biomed at all reasonable times and places during the Agreement term and in any event prior to Final Acceptance as defined in the Statement of Work. No inspection made prior to Final Acceptance shall relieve the Subcontractor from responsibility for defects or other failure to meet the requirements of this Agreement. In the event that goods furnished or services supplied are not in accordance with the Statement of Work and Schedule or other requirements, Leidos Biomed may require the Subcontractor to promptly correct, repair, replace, or re-perform the goods or services. The cost of correction, repair, replacement, or re-performance shall be determined under Section L.2. Warranty of this Agreement. If the Subcontractor fails to proceed with reasonable promptness to perform the required correction, repair, replacement, or re-performance, Leidos Biomed may terminate the Agreement for default. If the Subcontractor is unable to accomplish the foregoing, then Leidos Biomed may procure such materials and services from another source or perform such services in-house and charge to the Subcontractor's account all costs, expenses, and damages associated therewith. Leidos Biomed's approval of designs furnished by the Subcontractor shall not relieve the Subcontractor of its obligations hereunder.

L.2. *Warranty*

The Subcontractor represents and warrants (1) that the rates charged for the goods and/or services purchased pursuant hereto shall be no higher than the Subcontractor's current rates to any other customer for the same quality and quantity of such goods or services; (2) that all goods and services delivered pursuant hereto will be new, unless otherwise specified, and free from defects in material and workmanship; (3) that all goods and services will conform to applicable specifications and standards of quality and performance, and that all items will be suitable for their intended purpose; (4) that the goods covered by this Agreement are fit and safe for consumer use, if so intended. All representations and warranties of the Subcontractor together with its service warranties and guarantees, if any, shall convey to Leidos Biomed and Leidos Biomed's customers. The foregoing warranties shall survive any delivery, inspection, acceptance, or payment by Leidos Biomed.

L.3. *Changes and Suspension*

Leidos Biomed may, by written notice to Subcontractor at any time, make changes within the general scope of this Agreement in any one or more of the following: (a) drawings, designs or specifications; (b)

quantity; (c) time or place of delivery; (d) method of shipment or packing; and (e) the quantity of Subcontractor furnished property. Leidos Biomed may, for any reason, direct Subcontractor to suspend, in whole or in part, delivery of goods or performance of services hereunder for such period of time as may be determined by Leidos Biomed in its sole discretion. If any such change or suspension causes a material increase or decrease in the cost of, or the time required for the performance of any part of the work under this Agreement, an equitable adjustment shall be made in the Agreement price or delivery schedule, or both, provided Subcontractor shall have notified Leidos Biomed in writing of any claim for such adjustment within twenty (20) days from the date of notification of the change or suspension from Leidos Biomed. No such adjustment or any other modification of the terms of this Agreement will be allowed unless authorized by Leidos Biomed by means of a written modification to the Agreement. Subcontractor shall proceed with the work as changed without interruption and without awaiting settlement of any such claim.

L.4. Assignment

Neither this Agreement nor any interest herein may be assigned, in whole or in part, without the prior written consent of Leidos Biomed except that the Subcontractor shall have the right to assign this Agreement to any successor of such party by way of merger or consolidation or the acquisition of substantially all of the business and assets of the Subcontractor relating to the subject matter of this Agreement. This right shall be retained provided that such successor shall expressly assume all of the obligations and liabilities of the Subcontractor under this Agreement, and that the Subcontractor shall remain liable and responsible to Leidos Biomed for the performance and observance of all such obligations.

In the event the prime contract of Leidos Biomed with the Government is succeeded by a successor contractor selected by the Government, this Agreement may be assigned to the successor contractor.

L.5. Insurance Requirements

Prior to award, the Subcontractor must provide Certificates of Insurance, evidencing that the insurance coverages required below are in force. Subcontractor must provide no less than thirty days written notice prior to any cancellation or restrictive modification of the policies. In addition, the Certificate of Insurance shall A) certify that the Subcontractor is insured for the period of performance of this Agreement, B) shall name Leidos Biomed as "Additionally Named Insured," and C) shall identify this Agreement by number and brief description.

The Subcontractor is responsible for maintaining the minimum insurance coverage's stated herein throughout the term of this agreement including any modifications extending the period of performance or the exercising of any option periods. Should this insurance coverage lapse, be cancelled, or modified in any way Subcontractor will immediately notify Leidos Biomed. The coverage's stated herein in no way lessen nor effect the Subcontractors other obligations or liabilities set forth in this Agreement

The Subcontractor agrees to purchase and maintain at its own expense the following insurance coverages with minimum limits as stated:

- Statutory Workers' Compensation and Employer's Liability in an amount no less than that required by statute in the state of Agreement performance covering its employees, including a waiver of subrogation obtained from the carrier in favor of Leidos Biomed.
- Commercial General Liability in an amount no less than \$1 Million per each occurrence and \$2 Million in this aggregate covering bodily injury, broad form property damage, personal injury, products and completed operations, contractual liability, and independent contractors' liability. Leidos Biomed, its officers, and its employees shall be included as Additional Insureds; and a waiver of subrogation shall be obtained from the carrier in favor of Leidos Biomed.
- Automobile Liability in an amount no less than \$1 Million Combined Single Limit for Bodily Injury covering use of all owned, non-owned, and hired vehicles.
- Professional Liability in an amount no less than \$1 Million per occurrence covering damages caused by any acts, errors, and omissions arising out of the professional services performed by the Subcontractor, or any person for whom the Subcontractor is legally liable. To the extent that coverage for the Subcontractor's services are not excluded in (2) above by virtue of being deemed not of a professional nature, this requirement does not apply.
- All-Risk Property Insurance in an amount adequate to replace property, including supplies covered by this Agreement, of Leidos Biomed and/or Leidos Biomed's customer that may be in the possession or control of the Subcontractor. Leidos Biomed shall be named as a Loss Payee with respect to loss or damage to said property and/or supplies furnished by Leidos Biomed.

The required insurance coverages above shall be primary and non-contributing with respect to any other insurance that may be maintained by Leidos Biomed and notwithstanding any provision contained herein. The Subcontractor and its employees, agents, representatives, consultants, subcontractors, and suppliers, are not insured by Leidos Biomed and are not covered under any policy of insurance that Leidos Biomed has obtained or has in place.

Any self-insured retentions, deductibles, and exclusions in coverage in the policies required under this section shall be assumed by, for the account of, and at the sole risk of, the Subcontractor which provides the insurance and to the extent applicable shall be paid by the Subcontractor. In no event shall the liability of the Subcontractor be limited to the extent of any insurance or the minimum limits required herein.

L.6. Indemnification

The Subcontractor shall indemnify, defend and hold Leidos Biomed and Leidos Biomed's customers harmless from and against any and all damages, losses, liabilities and expenses (including reasonable attorneys' fees) arising out of or relating to any claims, causes of action, lawsuits or other proceedings, regardless of legal theory, that result, in whole or in part, from Subcontractor's (or any of Subcontractor's lower tiers, suppliers, employees, agents or representatives): (i) intentional misconduct, negligence, or fraud, (ii) breach of any representation, warranty or covenant made herein; (iii) breach of

the confidentiality or disclosure provisions herein; (iv) infringement of any patent, trademark, copyright, trade secret, or any other intellectual property right; or (v) violation of any law or regulation. Notwithstanding the foregoing, Subcontractor's obligations under this Section shall not apply to the extent that a claim is finally determined by a court of competent jurisdiction to be caused by the negligence or willful misconduct of Leidos Biomed.

Leidos Biomed shall promptly notify the Subcontractor of any claim that is covered by this indemnification provision and shall authorize representatives of the Subcontractor to settle or defend any such claim or suit and to take charge of any litigation in connection therewith.

Notwithstanding this section, should the deliverables or portion thereof be held to constitute an infringement and use as contemplated by this Agreement be enjoined or be threatened to be enjoined, the Subcontractor shall notify Leidos Biomed immediately, at the Subcontractor's expense; procure for Leidos Biomed the right to continue to use the deliverables or portion thereof with a version that is non-infringing, provided that the replacement or modified version meets any applicable specifications to Leidos Biomed's satisfaction. If the remedy described herein is not available to the Subcontractor, in addition to any damages or expenses reimbursed under this section, the Subcontractor shall refund to Leidos Biomed all amounts paid to Subcontractor by Leidos Biomed under this Agreement.

L.7. Confidential Information

The Subcontractor shall not at any time, up to three years after expiration or termination of this Agreement, use or disclose to any person for any purpose other than to perform this Agreement, any information it receives, directly or indirectly from Leidos Biomed in connection with this Agreement, except information that is or becomes publicly available, or is rightfully received by the Subcontractor from a third party without restriction. Upon request by Leidos Biomed, the Subcontractor shall return to Leidos Biomed all documentation and other material containing such information.

L.8. Disputes

L.8.a.

If a decision relating to the Prime Contract is made by the Frederick National Laboratory for Cancer Research Contracting Officer (FNL CO) and such decision is also related to this Agreement, said decision, if binding upon Leidos Biomed under the Prime Contract shall in turn be binding upon Leidos Biomed and the Subcontractor with respect to such matter; provided, however, that if the Subcontractor disagrees with any such decision made by the FNL CO and Leidos Biomed elects not to appeal any such decision, the Subcontractor shall have the right reserved to Leidos Biomed under the Prime Contract with the Government to prosecute a timely appeal in the name of Leidos Biomed, as permitted by the contract or by law, the Subcontractor to bear its own legal and other costs. If Leidos Biomed elects not to appeal any such decision, Leidos Biomed agrees to notify the Subcontractor in a timely fashion after receipt of such decision and to assist the Subcontractor in its prosecution of any such appeal in every reasonable manner. If Leidos Biomed elects to appeal any such decision of the NCI Contracting

Officer, Leidos Biomed agrees to furnish the Subcontractor promptly of a copy of such appeal. Any decision upon appeal, if binding upon Leidos Biomed, shall in turn be binding upon the Subcontractor. Pending the making of any decision, either by the FNL CO or on appeal, the Subcontractor shall proceed diligently with performance of this Agreement.

If, as a result of any decision or judgment which is binding upon the Subcontractor and Leidos Biomed, as provided above, Leidos Biomed is unable to obtain payment or reimbursement from the Government under the Prime Contract for, or is required to refund or credit to the Government, any amount with respect to any item or matter for which Leidos Biomed has reimbursed or paid the Subcontractor, the Subcontractor shall, on demand, promptly repay such amount to Leidos Biomed. Additionally, pending the final conclusion of any appeal hereunder, the Subcontractor shall, on demand promptly repay any such amount to Leidos Biomed. Leidos Biomed's maximum liability for any matter connected with or related to this Agreement which was the subject of a claim against the Government under the Prime Contract shall not exceed the amount of Leidos Biomed's recovery from the Government.

The Subcontractor agrees to provide certification that data supporting any claim made by the Subcontractor hereunder is made in good faith and that the supporting data is accurate and complete to the best of the Subcontractor's knowledge or belief, all in accordance with the requirements of the Contracts Disputes Act of 1978 (41USC601-613) and implementing regulations. If any claim of the Subcontractor is determined to be based on upon fraud or misrepresentation, the Subcontractor agrees to defend, indemnify, and hold Leidos Biomed harmless for any and all liability, loss, cost, or expense resulting there from.

Any dispute not addressed in paragraph (L.8.a.) above, will be subject to paragraph (L.8.b) as described below.

L.8.b.

Leidos Biomed and the Subcontractor agree to first enter into negotiations to resolve any controversy, claim, or dispute ("dispute") arising under or relating to this Agreement. The parties agree to negotiate in good faith to reach a mutually agreeable resolution of such dispute within a reasonable period of time. If good faith negotiations are unsuccessful, Leidos Biomed and the Subcontractor agree to resolve the dispute by binding and final arbitration in accordance with the Commercial Arbitration Rules of the American Arbitration Association then in effect. The arbitration shall take place in the County of Frederick, State of Maryland. The arbitrator(s) shall be bound to follow the provisions of this Agreement in resolving the dispute and may not award punitive damages. The decision of the arbitrator(s) shall be final and binding on the parties, and any award of the arbitrator(s) may be entered or enforced in any court of competent jurisdiction.

The Subcontractor hereby waives any immunity, sovereign or otherwise, that it would otherwise have to such jurisdiction and agrees that its rights, obligations, and liabilities hereunder shall be

determined in the same manner and to the same extent as those of a private litigant under like circumstances.

All costs of the arbitration shall be shared equally between the Parties, but the Parties specifically agree that each Party shall bear the expense of any costs incurred by it for its own counsel, experts, witnesses, preparation of documents, presentations, and logistics related to the proceedings.

Pending any decision, appeal, or judgment referred to in this provision or the settlement of any dispute arising under this Agreement, the Subcontractor shall proceed diligently with the performance of this Agreement.

L.9. Termination

L.9.a. Termination for Convenience

Leidos Biomed shall have the right to terminate this Agreement, in whole or in part, at any time, without cause, by providing written notice to the Subcontractor. Upon receiving notice of such termination, the Subcontractor shall:

Stop all work on this Agreement on the date and to the extent specified.

Place no further contracts hereunder except as may be necessary for completing such portions of the Agreement that have not been terminated.

Terminate all contracts to the extent that they may relate to portions of the Agreement that have been terminated.

Protect all property in which Leidos Biomed has or may acquire an interest and deliver such property to Leidos Biomed.

Within twenty (20) days from such termination, the Subcontractor may submit to Leidos Biomed its written claim for termination charges in the form prescribed by Leidos Biomed. Failure to submit such claim within such time shall constitute a waiver of all claims and a release of all Leidos Biomed's liability arising out of such termination. Under no circumstances shall the Subcontractor be entitled to anticipatory or lost profits.

Leidos Biomed reserves the right to verify claims hereunder and the Subcontractor shall make available to Leidos Biomed, upon its request, all relevant, non-proprietary books and records for inspection and audit (e.g., time cards and receipts). If the Subcontractor fails to afford Leidos Biomed its rights hereunder, the Subcontractor shall be deemed to have relinquished its claim.

L.9.b. Termination for Default

Leidos Biomed may, by written notice of default to the Subcontractor, terminate the whole or any part of this Agreement, in any one of the following circumstances:

The Subcontractor fails to make delivery of the goods or to perform the services within time specified herein or any extension thereof.

The Subcontractor fails to perform any of the other provisions of this Agreement in accordance with its terms and does not cure such failure within a period of ten (10) days after receipt of notice from Leidos Biomed specifying such failure.

The Subcontractor becomes insolvent or the subject of proceedings under any law relating to the relief of debtors or admits in writing its inability to pay its debts as they become due.

If this Agreement is so terminated, Leidos Biomed may procure or otherwise obtain, upon such terms and in such manner as Leidos Biomed may deem appropriate, goods or services similar to those terminated. The Subcontractor shall be liable to Leidos Biomed for any excess costs of such similar supplies or services.

The Subcontractor shall transfer title and deliver to Leidos Biomed, in the manner and to the extent requested in writing by Leidos Biomed at or after termination, such complete or partially completed articles, property, materials, parts, tools, fixtures, plans, drawings, information, and contract rights as the Subcontractor has produced or acquired for the performance of the terminated part of this Agreement, and Leidos Biomed will pay the Subcontractor the contract price for completed articles delivered to and accepted by Leidos Biomed and the fair value of the other property of the Subcontractor so requested and delivered.

The Subcontractor shall continue performance of this Agreement to the extent not terminated. Leidos Biomed shall have no obligation to the Subcontractor with respect to the terminated part of this Agreement except as herein provided.

L.10. Leidos Biomed Furnished Data and Materials

All items furnished, loaned, or bailed by Leidos Biomed hereunder, or fabricated, manufactured, purchased, or otherwise acquired by the Subcontractor for the performance of this Agreement and specifically charged to Leidos Biomed, are the property of Leidos Biomed.

Upon completion, expiration, or termination of this Agreement, the Subcontractor shall return all such items in good condition, reasonable wear only excepted, together with all spoiled and surplus items to Leidos Biomed, or make such other disposition thereof as may be directed or approved by Leidos Biomed. The Subcontractor agrees to replace, at its expense, all such items not so returned. The Subcontractor shall make no charge for any storage, maintenance, or retention of such items. The Subcontractor shall bear all risk of loss for all such items in the Subcontractor's possession.

The Subcontractor also agrees to use any designs or data contained or embodied in such items in accordance with any restrictive legends placed on such items by Leidos Biomed or any third party. If Leidos Biomed furnishes any material, for fabrication hereunder, the Subcontractor agrees: (1) not to substitute any other material for such fabrication without Leidos Biomed's prior written consent, and (2) that title to such material shall not be affected by incorporation in or attachment to any other property.

L.11. Publication/Publicity and Press Release

L.11.a. Publication/Publicity

Unless otherwise specified in this Agreement, the Subcontractor is encouraged to publish the results of its work under this Agreement. A copy of each article submitted by the Subcontractor for publication shall be promptly sent to the Leidos Biomed TPM and shall also inform the same when the article or other publication is published. Additionally, final manuscripts shall be submitted electronically to the NIH National Library of Medicine's (NLM) PubMed Central (PMC) (Available at: <http://www.pubmedcentral.nih.gov>). The Subcontractor shall acknowledge the support of the National Institutes of Health whenever publicizing the work under this Agreement in any media by including an acknowledgment substantially as follows:

L.11.a.(1). For Manuscripts

"This project has been funded in whole or in part with Federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. The content of this publication does not necessarily reflect the views of policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government."

L.11.a.(2). For Abstracts:

"Funded by NCI Contract No. HHSN261200800001E."

Authors of manuscripts/abstracts have the option of using any or all of the following affiliations:

Option 1) Government laboratory name.

Option 2) Subcontractor Laboratory name.

Option 3) Subcontractor directorate name.

The selected option(s) shall be inserted into the following statement:

Author(s) Name, (Option 1, 2, and/or 3), Leidos Biomedical Research, Frederick National Laboratory for Cancer Research, Frederick, Maryland 21702.

L.11.b. Press Releases

The Subcontractor shall not, without prior written approval of the Leidos Biomed Contracting Officer, issue press releases describing or otherwise referring to this Agreement or the efforts undertaken as a result thereof. Requests for approval shall be submitted 30 days prior to any requested release date.

Any approved press releases as well as, requests for proposals, bid solicitations, and other documents describing projects or programs funded in whole or in part with Federal money shall clearly state: (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.

L.12. *General Relationship*

The Subcontractor is not an employee of Leidos Biomed for any purpose whatsoever. The Subcontractor agrees that in all matters relating to this Agreement it shall be acting as an independent contractor and shall assume and pay all liabilities and perform all obligations imposed with respect to the performance of this Agreement. The Subcontractor shall have no right, power, or authority to create any obligation, expressed or implied, on behalf of Leidos Biomed and/or the Government and shall have no authority to represent Leidos Biomed as an agent.

L.13. *Non-Waiver of Rights*

The failure of Leidos Biomed to insist upon strict performance of any of the terms and conditions in the Agreement, or to exercise any rights or remedies, shall not be construed as a waiver of its rights to assert any of the same or to rely on any such terms or conditions at any time thereafter. The invalidity in whole or in part of any term or condition of this Agreement shall not affect the validity of other parts hereof.

L.14. *Legal Construction and Interpretations*

This Agreement shall be governed by and interpreted in accordance with the principles of Federal Contract Law, and to the extent that Federal Contract Law is not dispositive, and the state law becomes applicable, the laws of the State of Maryland shall apply without regard to its conflict or choice of law provisions.

L.15. *Export Control Compliance for Foreign Persons*

The Subcontractor warrants that it has in place a system or process for compliance with all U.S. export control laws, including but not limited to the regulations of the U.S. Department of Commerce and/or U.S. Department of State. At all times, the Subcontractor shall comply with all applicable federal, state and local laws applicable to the export of any process, goods and/or technical data and information from the United States and within the U.S. to foreign nationals. Subcontractor acknowledges that when applicable, a failure to comply with all applicable laws may subject the Subcontractor to criminal liability under U.S. law and may result in termination of this Agreement. The Subcontractor shall include in all lower tier contracts similar provisions as contained herein requiring compliance with all applicable laws.

Furthermore, Subcontractor agrees that it shall not disclose, export, or re-export any Leidos Biomed information, or any process, product, or services produced under this Agreement, in violation of any

restrictive legends placed on such items by Leidos Biomed, without the prior notification to Leidos Biomed. In addition, the Subcontractor agrees to immediately notify Leidos Biomed if the Subcontractor is listed on any of the Department of State, Treasury, or Commerce proscribed persons, organizations or destinations lists, or if the Subcontractor's export privileges are otherwise denied, suspended, or revoked in whole or in part. Subcontractor shall not be required to accept any information or any work under this Subcontract that requires access to information that is subject to export controls.

L.16. *Standards of Business Ethics & Conduct*

Leidos Biomed believes in fair and open competition and is committed to conducting its business fairly, impartially, and in an ethical and proper manner. Leidos Biomed's expectation is that the Subcontractor also will conduct its business fairly, impartially, and in an ethical and proper manner. If the Subcontractor has cause to believe that Leidos Biomed or any employee or agent of Leidos Biomed has acted improperly or unethically under this Agreement, the Subcontractor shall report such behavior to the Leidos Ethics Hotline (800) 435-4234. Copies of The Leidos Corporation Code of Ethics and contacts for such reports are available on www.ledios.com under Corporate Governance.

L.17. *Audit*

At any time before final payment Leidos Biomed may request and perform an audit of the invoices and substantiating material. Each payment previously made shall be subject to reduction to the extent of amounts that are found by Leidos Biomed not to have been properly payable in accordance with the terms of this Agreement. Audit will include, but not be limited to, individual daily job time cards, invoices for material, storeroom requisitions, expense reports, and other substantiation supporting invoiced amounts.

L.18. *Compliance with Laws and Regulations*

The Subcontractor shall submit all certifications required by Leidos Biomed under this Agreement and shall at all times, at its own expense, comply with all applicable Federal, State, and local laws, ordinances, administrative orders, rules, or regulations.

L.19. *Gifts*

The Subcontractor shall not make or offer a gratuity or gift of any kind to Leidos Biomed's employees or their families. The Subcontractor should note that the providing of gifts or attempting to provide gifts under Government Agreements might be a violation of the Anti-Kickback Act of 1986 (4 U.S.C. 51-58).

L.20. *Maryland Sales and Use Tax*

The State of Maryland has issued Direct Payment Permit #3, effective date August 29, 1996, a copy of this Permit is available upon request. As a holder of a Direct Payment Permit, Leidos Biomed is authorized to make direct payment of sales and use tax to the State of Maryland. Accordingly, Subcontractors that provide goods and services to Leidos Biomed are relieved from collecting sales tax

from Leidos Biomed. Therefore, Subcontractors to Leidos Biomed shall not place a separate line item for tax on any invoice sent to Leidos Biomed. Please note that the Permit is not to be used by Subcontractors to make purchases free of sales tax, nor shall the Permit be transferred or assigned.

L.21. *Notice of Delay*

The Subcontractor agrees to immediately notify Leidos Biomed in writing of any actual or potential delay in the Subcontractor's performance under this Agreement. Such notice shall, at a minimum, describe the cause, effect, duration, and corrective action proposed by the Subcontractor to address the problem. The Subcontractor shall give prompt written notice to the Leidos Biomed of all changes to such conditions. This notification shall be informational only, and compliance with this provision shall not be construed as a waiver by Leidos Biomed of any delivery schedule or date or of any rights or remedies provided by law or under this Agreement.

L.22. *Notification of Debarment/Suspension*

By acceptance of this Agreement either in writing or by performance, the Subcontractor certifies that, as of the date of award of this Agreement, neither the Subcontractor, lower tiers, nor any of its principals, is debarred, suspended, or proposed for debarment by the Federal Government. Further, Subcontractor shall provide immediate written notice to the Leidos Biomed Contracting Officer in the event that during performance of this Agreement the Subcontractor or any of its principals is debarred, suspended, or proposed for debarment by the Federal Government.

L.23. *Security*

Under its prime contract with the Frederick National Laboratory for Cancer Research, Leidos Biomed may be required to conduct, on persons performing work on Government Owned or controlled installations, individual background checks prior to the commencement of effort. As part of this process, information will be required to enable Leidos Biomed to conduct the appropriate background checks, including name (including any aliases), daytime phone number, SSN, date of birth, and country of birth. Individuals who are unable or unwilling to provide the required information and/or receive the required authorizations will not be allowed access to the Frederick National Laboratory for Cancer Research or any controlled premises.

L.24. *Tobacco Use at the Frederick National Laboratory for Cancer Research*

In accordance with the Department of Health and Human Services (HHS) directive, the Frederick National Laboratory for Cancer Research campus is a tobacco free workplace. Use of tobacco in any form is prohibited on the entire Frederick National Laboratory for Cancer Research campus. This includes personal vehicles while on Frederick National Laboratory for Cancer Research property and all Government vehicles, regardless of their location.

This policy applies to all employees, Government and Contractor, visitors, subcontractors, vendors, and guests of the Frederick National Laboratory for Cancer Research and extends to all HHS owned or leased

facilities and properties external to the Frederick National Laboratory for Cancer Research campus where the sole tenant(s) are HHS and/or Leidos Biomed employees.

L.25. Severability

If any term contained in this Agreement is held or finally determined to be invalid, illegal, or unenforceable in any respect, in whole or in part, such term shall be severed from this Agreement, and the remaining terms contained herein shall continue in force and effect, and shall in no way be affected, prejudiced, or disturbed thereby.

L.26. Interpretation

The captions and headings used in this Agreement are solely for the convenience of the parties, and shall not be used in the interpretation of the text of this Agreement. Each party has read and agreed to the specific language of this Agreement; therefore no conflict, ambiguity, or doubtful interpretation shall be construed against the drafter.

L.27. Electronic and Information Technology Standards

The Subcontractor agrees to comply with Section 508 of the Rehabilitation Act of 1973 (29 U.S.C. 794d) as amended by P.L. 105-220 under Title IV (Rehabilitation Act Amendments of 1998). Electronic and Information Technology (EIT) developed, procured, maintained, and/or used under this contract shall be in compliance with the "Electronic and Information Technology Accessibility Standards" set forth by the Architectural and Transportation Barriers Compliance Board (also referred to as the "Access Board") in 36 CFR Part 1194. The complete text of Section 508 Final Standards can be accessed at <http://www.section508.gov/index.cfm?FuseAction=content&ID=12>. Applicable standards to this requirement are set forth in 36 CFR Part 1194.21 through 26.

The Subcontractor further agrees to include this provision in any Subcontract awarded pursuant to this Agreement. Failure to comply to these requirements may constitute cause for termination under the provisions of this Agreement.

L.28. Acceptance of Agreement and Modification of Terms

Acceptance of this Agreement by the Subcontractor may be made by signing the acknowledgement copy hereof or by partial performance hereunder, and any such acceptance shall constitute an unqualified Agreement to all terms and conditions set forth herein unless otherwise modified in writing by the parties. Any additions, deletions, or differences in the terms proposed by the Subcontractor are objected to and hereby rejected, unless Leidos Biomed agrees otherwise in writing. No additional or different terms and conditions proposed by the Subcontractor in accepting this Agreement shall be binding upon Leidos Biomed unless accepted in writing by Leidos Biomed; and no other addition, alteration, or modification to, and no waiver of, any of the provisions herein contained shall be valid unless made in writing and executed by Leidos Biomed and the Subcontractor. The Subcontractor shall

perform in accordance with the Description/Quantity schedule set forth in this Agreement and all attachments thereto.

L.29. Information Security

The Subcontractor agrees to comply with the Information Technology (IT) systems security and/or privacy specifications set forth in this Agreement and as further defined by the Federal Information Security Management Act of 2002 (FISMA), Title III, E-Government Act of 2002, Pub. L. No. 107-347 (Dec. 17, 2002); <http://csrc.nist.gov/drivers/documents/FISMA-final.pdf>.

The Subcontractor further agrees to include this provision in any Agreement awarded pursuant to the Agreement. Failure to comply with these requirements may constitute cause for termination under the provisions of this Agreement.

The Subcontractor shall be responsible for properly protecting all information used, gathered, or developed as a result of this Agreement. The Subcontractor shall establish and implement appropriate administrative, technical, and physical safeguards to ensure the security and confidentiality of sensitive Government information, data, and/or equipment. Any Subcontractor employee who may have access to sensitive information under this Agreement shall complete the form entitled, "Commitment to Protect Non-Public Information – Contractor Agreement," which may be found at the following website: <https://ocio.nih.gov/aboutus/publicinfosecurity/acquisition/Documents/Nondisclosure.pdf>.

A copy of each signed and witnessed Non-Disclosure Agreement shall be submitted to the Leidos Biomed Contracting Officer prior to performing any work under this Agreement.

The Subcontractor shall assure that each employee has completed the NIH Computer Security Awareness Training (<http://irtsectraining.nih.gov>) prior to performing any work under this Agreement.

In addition, the Subcontractor shall submit a roster, by name, position, email address, phone number, and responsibility, of all staff (including 2nd tier Subcontractor staff) working under the Agreement who will develop, have the ability to access, or host and/or maintain a Federal information system(s). The roster shall be submitted to Leidos Biomed within 14 calendar days of the effective date of the Agreement along with scanned copies of the completed training certificates for each staff member. Any revisions to the roster as a result of staffing changes shall be submitted to Leidos Biomed within 15 calendar days of the change. Additional training certifications will then be due to be submitted to Leidos Biomed every 12-months thereafter on the anniversary date of contract award.

In addition, during all activities and operations on Government premises, the Subcontractor shall comply with DHHS, including National Institutes of Health (NIH), rules of conduct. Should the Subcontractor have questions concerning these requirements or need of procedural guidance to ensure compliance they may contact the cognizant Leidos Biomed Subcontract Administrator.

L.30. Reporting Matters Involving Fraud, Waste, and Abuse

Anyone who becomes aware of the existence or apparent existence of fraud, waste, and abuse in NIH funded programs is encouraged to report such matters to the DHHS Inspector General's Office in writing or on the Inspector General's Hotline. The toll free number is 1-800-DHHS-TIPS (1-800-447-8477). All telephone calls will be handled confidentially. The email address is Htips@os.dhhs.gov and the mailing address is:

Office of Inspector General

Department of Health and Human Services

TIPS HOTLINE

P.O. Box 23489

Washington, D.C. 20026

L.31. Limitation on Use of Funds for Promotion of Legalization of Controlled Substances

Pursuant to the current HHS annual appropriations act, the Subcontractor shall not use Agreement 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 (21 U.S.C. 812), 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.

L.32. Force Majeure

Neither party shall be liable for any failure of or delay in performance of its obligations under this Agreement to the extent such failure or delay is due to circumstances beyond its reasonable control, including, without limitation, acts of God, acts of a public enemy, terrorism, fires, floods, wars, civil disturbances, sabotage, accidents, insurrections, blockades, embargoes, storms, explosions, labor disputes (whether or not the employees' demands are reasonable and/or within the party's power to satisfy), acts of any governmental body, failure or delay of third parties or governmental bodies from whom a party is obtaining or must obtain approvals, authorizations, licenses, franchises, or permits, or inability to obtain labor, materials, power, equipment, or transportation (collectively referred to herein as "Force Majeure"). Each party shall use its reasonable efforts to minimize the duration and consequences of any failure of or delay in performance resulting from a Force Majeure event and to promptly notify the other of any actual or potential Force Majeure event.

L.33. Entire Agreement

The parties hereby agree that this Agreement, including all documents incorporated herein by reference or attached hereto, shall constitute the entire Agreement and understanding between the parties hereto and shall supersede and replace any and all prior or contemporaneous representations, agreements, or understandings of any kind, whether written or oral, relating to the subject matter hereof.

L.34. Survival

The provisions for the Sections Entitled Key Personnel, Warranty, Assignment, Indemnification, Confidential Information, Disputes, Termination, Leidos Biomed Furnished Material, and Export Control shall survive the termination or expiration of this Agreement.

M. FAR/HHSAR Clauses Applicable to This Agreement

M.1. Federal Acquisition Regulation (FAR) (48CFR Chapter 1) Clauses:

This Agreement incorporates the following FAR clauses by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. Also, the full text of a clause may be accessed electronically at this address: <https://acquisition.gov/far/FAC/fac2001-01.pdf>.

Far Clause/Title:

52.203-3: Gratuities (Over \$150,000)

52.203-5: Covenant Against Contingent Fees (Over \$150,000)

52.203-6: Restrictions on Subcontractor Sales to the Government (Over \$150,000)

52.203-7: Anti-Kickback Procedures (Over \$150,000)

52.203-10: Price or Fee Adjustment for Illegal or Improper Activity (Over \$150,000)

52.203-11: Certification and Disclosure Regarding Payment to Influence Certain Federal Transactions

52.203-12: Limitation on Payments to Influence Certain Federal Transactions (Over \$150,000)

52.203-13: Contractor Code of Business Ethics and Conduct \$5,000,000

52.203-14: Display of Hotline Posters \$5,000,000

52.204-4: Printed or Copied Double-Sided on Recycled Paper (Over \$150,000)

52.204-7: Central Contractor Registration

52.209-6: Protecting the Government's Interests When Subcontracting with Contractors Debarred, Suspended, or Proposed for Debarment (over \$30,000)

52.215-2: Audit and Records – Negotiation (Over \$150,000), Alternate II

52.215-10: Price Reduction for Defective Cost or Pricing Data

52.215-12: Subcontractor Cost or Pricing Data (Over \$700,000)

52.215-14: Integrity of Unit Prices (Over \$150,000)

52.215-15: Pension Adjustments and Asset Reversions

52.215-18: Reversion or Adjustment of Plans for Postretirement Benefits (PRB) Other Than Pensions

52.215-19: Notification of Ownership Changes

52.215-21: Requirements for Cost or Pricing Data or Information Other Than Cost or Pricing Data— Modifications

52.219-9: Small Business Subcontracting Plan (over \$650,000)

52.219-16: Liquidated Damages—Subcontracting Plan (over \$650,000)

52.222-2: Payment for Overtime Premium (over \$150,000) (Note: The dollar amount in paragraph (a) of this clause is \$0 unless otherwise specified in Subcontract budget.

52.222-3: Convict Labor

52.222-21: Prohibition of Segregated Facilities

52.222-25: Affirmative Action Compliance

52.222-26: Equal Opportunity

52.222-35: Equal Opportunity for Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans

52.222-36: Affirmative Action for Workers with Disabilities

52.222-37: Employment Reports on Special Disabled Veterans, Veterans of the Vietnam Era, and Other Eligible Veterans

52.222-41: Service Contract Act of 1965

52.222-54: Employment Eligibility Verification

52.223-6: Drug-Free Workplace

52.225-1: Buy American Act—Balance of Payments Program—Supplies

52.225-13: Restrictions on Certain Foreign Purchases

52.227-1: Authorization and Consent, Alternate I

52.227-2: Notice and Assistance Regarding Patent and Copyright Infringement

52.227-11: Patent Rights – Ownership by the Contractor

52.227-14: Rights in Data - General

52.227-16: Additional Data Requirements

52.232-9: Limitation on Withholding of Payments

52.232-23: Assignment of Claims

52.232-33: Payments by Electronic Funds Transfer – Central Contractor Registration

52.237-3: Continuity of Services

52.239-1: Privacy or Security Safeguards (5 U.S.C. 552a)

52.242-13: Bankruptcy (Over \$150,000)

52.244-2: Subcontracts, Alternate I

52.244-5: Competition in Subcontracting

52.244-6: Subcontracts for Commercial Items

52.245-1: Government Property

52.245-9: Use and Charges

52.247-63: Preference for U.S. Flag Carriers

M.2. Federal Acquisition Regulation (FAR) (48 CFR Chapter 1) Contract Type Clauses:

This Agreement incorporates the following FAR clauses by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available.

52.216-7: Allowable Cost and Payment

52.232-20: Limitation of Cost

52.242-1: Notice of Intent to Disallow Costs

52.242-3: Penalties for Unallowable Costs

52.242-4: Certification of Final Indirect Costs

52.246-5: Inspection of Services – Cost Reimbursement

52.232-2: Payments under Fixed-Price Research and Development Contracts

M.3. Department of Health and Human Services Acquisition Regulation (HHSAR) Clauses

This Agreement incorporates the following DEPARTMENT OF HEALTH AND HUMAN SERVICES ACQUISITION REGULATION HHSAR 48 Chapter 3 clauses by reference, with the same force and effect as if they were given in full text. Upon request, the Contracting Officer will make their full text available. Also, the full text of a clause may be accessed electronically at this address: <http://www.hhs.gov/regulations/hhsar/subpart301-1.html>.

352.242-73: Withholding of Contract Payments

352.233-71: Litigation and Claims

352.242-74: Final Decision on Audit Findings

352.242-70: Key Personnel

352.201-70: Paperwork Reduction Act

352.231-70: Salary Rate Limitation

352.270-4: Protection of Human Subjects

352.270-6: Restriction on Use of Human Subjects

Attachment 1: Statement of Work

A. Background

Despite significant progress in understanding cancer at the molecular level, the sheer complexity of the over 200 diseases that comprise “cancer” is a daunting barrier to developing the interventions needed to diagnose, treat, and prevent cancer. Vital to the progress in these areas is the discovery and understanding of cancer-specific aberrations at various molecular and cellular levels. Although proteins reflecting the genomic changes in cancer have the potential to become clinically meaningful biomarkers, their discovery and validation has proven to be challenging. As a result, few biomarker candidates have been translated into clinical utility.

Two Key Barriers

Two key barriers in the early stages of biomarker development are: 1) a limited understanding of the changes in cancer genomes that translate into functional differences at the proteomic level; and 2) insufficient technologies that could be widely applied to reproducibly detect and quantify these aberrant proteomic changes across samples from cancer and control populations. Significant barriers to the development of cancer protein biomarkers include insufficient inter-laboratory reproducibility, a lack of standards for proper study design, various analytical barriers, biospecimen collection/handling, data acquisition/analysis, and a notable absence of reference standards and high quality reagents. The progress in the field has also been hampered by the lack of a coherent “pipeline” to connect biomarker discovery with well-established methods for clinical validation. Although various cancer-related proteomic changes have been identified in numerous published studies, these studies mostly came from diverse research groups working independently. Consequently, the findings are typically based on an insufficient number of samples to have adequate statistical power needed for rigorous evaluation of the observed protein changes as specific, clinically relevant cancer biomarkers.

Launch of CPTAC

Recognizing this need for an evidence-based, efficient proteomics pipeline, the NCI launched the Clinical Proteomic Technology Assessment for Cancer program (CPTAC) in 2006. At that stage (Phase I), the CPTAC initiative focused on removing the analytical and technical barriers in order to enable the accurate and reproducible identification and quantification of a meaningful number of proteins to drive clinically-relevant biomarker qualification studies. Phase I of the CPTAC program has demonstrated the effectiveness of a multi-disciplinary, multi-institutional approach in addressing long-standing problems of analytical variability in proteomics and exploring ways to overcome the inherent variability of specific analytical platforms in order to uncover and quantify real biological differences.

Two-Step Strategy

Although discovery efforts oriented on cancer protein biomarkers identify many hundreds to thousands of candidate biomarkers, CPTAC investigators recognized that only a few would eventually prove clinically useful that can be analytically validated. Therefore, developmental strategies must allow for an efficient testing of many biomarker candidates to identify and verify those few that would be suitable for further clinical

implementation. Addressing this need, researchers involved in Phase I of the CPTAC program designed a two-step strategy (further referred to as the developmental “pipeline”) for the efficient, timely, and cost-effective development of protein (and peptide) biomarkers prior to clinical validation studies. The two steps, referred to as “Biomarker Discovery” and “Biomarker Verification,” are outlined below and in Figure 1.

Biomarker Discovery

As the first step of the CPTAC-established pipeline, cancer-specific biomarker candidates are discovered (identified) using metrics-driven protein profiling technologies that interrogate appropriate biospecimens (e.g., tumor and proximal fluid). The discovery platforms (based on mass spectrometry and affinity-based capture immunochemistry) have proved to be sufficiently robust to reveal a large number of protein biomarker candidates. These biomarker candidates identified in the Discovery step must then be evaluated in independent biospecimen collections larger than those used initially.

Biomarker Verification

Following biomarker discovery, some candidates can be further analyzed (verified) using commercially available reagents (notably, antibodies for immunoassays). However, moving candidates from discovery to clinical validation typically requires overcoming various bottlenecks reflecting a lack of commercially available, high quality affinity reagents (antibodies) in adequate numbers, their high costs, and/or lengthy production times. These limitations are addressed in a comprehensive manner by the Verification step of the CPTAC pipeline. Verification involves the development of targeted, reproducible, quantitative assays, which are commonly multiplexed and thus suitable for the examination of a larger number of biospecimens (e.g., tumor, proximal fluid, blood) to ensure appropriate statistical power. The Verification step and the established assays are meant to be cost effective and timely in terms of funneling those few biomarker candidates for further clinical validation studies. Although CPTAC teams are not involved in large scale clinical validation studies, their verified candidates will the potential to move downstream into clinical testing.

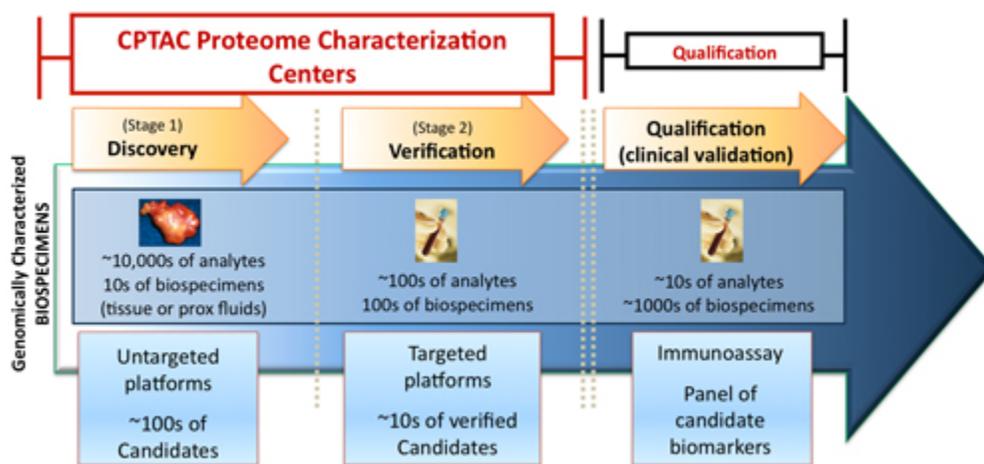


Figure 1: CPTAC Pipeline

Recently, significant progress has been made in characterizing and sequencing the genomic alterations in statistically robust numbers of samples from several types of cancer. For example, The Cancer Genome Atlas (TCGA), International Cancer Genome Consortium (ICGC) and other similar efforts are identifying genomic alterations associated with specific cancers (e.g., copy number aberrations, rearrangements, point mutations, epigenomic changes, etc.). The availability of these multi-dimensional data to the scientific community sets the stage for the development of new molecularly targeted cancer interventions. Understanding the comprehensive functional changes in cancer proteomes arising from genomic alterations and other factors is the next logical step in the development of high-value candidate protein biomarkers. Hence, proteomics can greatly advance the understanding of molecular mechanisms of disease pathology via the analysis of changes in protein expression, their modifications and variations, as well as protein-protein interaction, signaling pathways and networks responsible for cellular functions such as apoptosis and oncogenesis.

Launch of CPTAC, Phase II

Realizing this great potential, the NCI launched the second phase of the CPTC initiative in September 2011. Renamed the Clinical Proteomic Tumor Analysis Consortium, CPTAC is beginning to leverage its analytical outputs from Phase I to define cancer proteomes on genomically-characterized biospecimens. The purpose of this integrative approach is to provide the broad scientific community with knowledge that links genotype to proteotype and ultimately phenotype.

The key programmatic components of CPTAC Phase II include: Tissue Source Sites (TSS); a Biospecimen Core Resource (BCR); Proteome Characterization Centers (PCCs); a CPTAC Steering Committee (SC); a CPTAC Biomarker Candidate Selection Subcommittee (BCSS); a Data Coordinating Center (DCC); and a data portal. Each PCC consists of a discovery unit, verification unit, and administrative core. A schematic representation of the CPTAC project is shown in Figure 2.

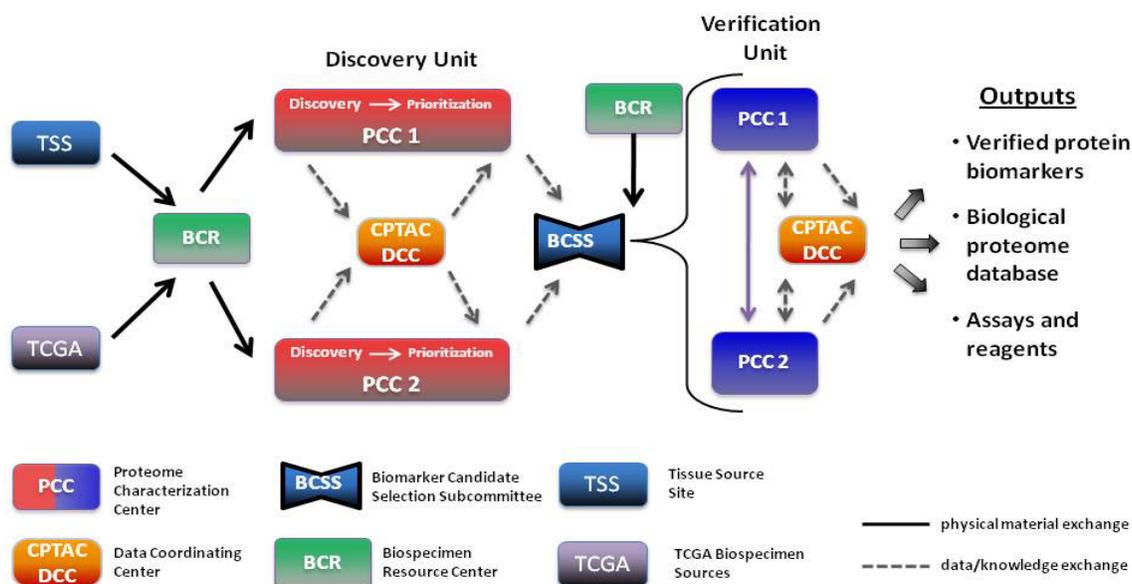


Figure 2: CPTAC Workflow

In Phase I of CPTAC, research centers shared data by depositing data files to a data repository entitled Tranche hosted by the University of Michigan. Since most of these data files were generated in technology assessment and benchmarking experiments, experimental annotation focused on the technical aspects of sample analysis and processing. However, data production Phase II of CPTAC is expected to exceed that of Phase I with the inclusion of experimental annotation of more refined descriptions of the samples involved, as well as de-identified clinical data accompanying each sample. Finally, since many of the samples have or will have undergone genomic analysis, complete data management of CPTAC data files will include connectivity between the proteomic data and genomic data. All data produced is formally hosted by the CPTAC DCC and can be found at <https://cptac-data-portal.georgetown.edu/cptacPublic/>.

B. Scope

The scope of work under this Statement of Work (SOW) encompasses the activities needed to prospectively procure high quality, clinically annotated human tumor samples and when feasible, normal tissue from volunteer patients suffering from colon, ovarian, and breast cancer. The overall programmatic goal is to procure tumor tissue meeting quality requirements from 100 cases from each cancer type. Collection will stop once those thresholds are met. The tissue will be utilized for CPTAC Program Phase II with the samples obtained under conditions optimized for proteomic analysis. The tissue procurement will be consistent with the CPTAC tissue procurement protocols (attached in Appendix 2). The scope will also encompass obtaining blood and plasma from each case along with the longer-term follow up of the clinical status of patient volunteers are procurement, as well as interacting with the CPTAC Program.

C. Place of Performance

The work will be performed at the Subcontractor's facilities

D. Objectives

At a minimum, this SOW supports the following tasks for all biospecimens and data submitted:

D.1. Obtaining Institutional Review Board Approval

The subcontractor shall provide written documentation to the Leidos Biomed Technical Project Manager (TPM) and CPTAC BCR that an Institutional Review Board (IRB) has reviewed and approved participation specifically in the CPTAC program. Such approval includes the cases when an IRB does not consider the work to be human subjects research or considers the work to be exempt; documentation of these IRB positions is still required. This approval must be documented annually and shown to be current, even after the subcontract period ends if additional follow-up data are going to be made available.

The subcontractor shall develop appropriate patient consent documents and have these reviewed and approved by an IRB. This approval must be documented with the Leidos Biomed TPM and CPTAC BCR.

D.2. Executing Material Transfer and Data Use Agreements

The Subcontractor shall develop and obtain any needed local approval for a Material Transfer Agreement (MTA) that contains a Data Use Agreement (DUA) with the CPTAC BCR. The Subcontractor shall enter into the Agreement.

D.3. Enrolling Patients

The subcontractor shall be responsible for recruiting, consenting, and enrolling patient volunteers as approved by the IRB. The Subcontractor shall also be responsible for obtaining clinical data on the volunteers and submitting a de-identified version of that data to the CPTAC BCR via an electronic interface to a clinical data repository. The specific data to be collected will be disease specific and the specific data elements determined at a later date.

D.4. Procuring, Processing, and Shipping Tissue and Blood

The Subcontractor shall obtain tumor and blood samples from consented volunteer patients. When appropriate, the Subcontractor may also obtain normal tissue. The subcontractor shall provide for the short-term storage of the tissue specimens in accordance to the protocols and standard operating procedures provided in this Attachment 1 and adhere to the instructions provided by the BCR for shipping the specimens.

D.5. Obtaining Initial Patient and Diagnostic Histopathological Data

The subcontractor shall be responsible for obtaining initial clinical data on the patient along with pathology reports for the cases submitted to the BCR. The reports shall be de-identified and electronic copies submitted to the BCR as soon as reasonably possible after the tissue has been shipped. The subcontractor shall also be responsible for obtaining high-quality electronic images of the FFPE H&E slides representative of the diagnosis in the pathology report and submit them to the BCR (or provide physical slide(s) that will be returned after imaging). For certain tumors, unstained FFPE slides will be required and submitted to the BCR.

D.6. Long-term Patient Follow Up

The subcontractor shall be responsible for obtaining patient clinical data and status at the time of tissue procurement and one year after tissue procurement.. The Subcontractor shall submit de-identified versions of that data to the CPTAC BCR via an electronic interface to a clinical data repository. The specific data to be collected will be disease specific and the specific data elements determined at a later date. The subcontractor shall also identify any patients that have been lost to follow up.

D.7. Interacting with Other Stakeholders

The subcontractor shall participate in monthly calls amongst Leidos Biomed, the NCI and other Subcontractors participating in the program. The Subcontractor shall also participate in the CPTAC

Annual Meeting.

E. Constraints

E.1. Institutional Review Board Approval

- The IRB protocol shall be based on the information contained in Appendix 3.
- Patients must give informed consent for collection of the cancer and blood samples with genetic and/or genomic research being specifically permitted.
- The subcontractor shall provide assurance of donor-specific date of consent for all cases.
- The subcontractor shall provide the Leidos Biomed TPM and CPTAC BCR copies of:
 - IRB protocols
 - The current informed consent form

E.2. Material Transfer Agreement/Data Use Agreement Approval

- A copy of the executed MTAs, with signatures, shall be provided to the Leidos Biomed TPM and the CPTAC BCR in advance of any work done under this subcontract.
- Neither the NCI nor Leidos Biomed shall be a party to the MTA.
- The MTA terms shall include the following:
 - MATERIAL shall be defined to include both the physical biospecimens and the associated annotation data.
 - MATERIAL is for research use only, i.e., not for treatment, transplant, or diagnosis.
 - All parties shall comply with relevant laws.
 - PROVIDER does not retain intellectual property reach through rights to datasets generated with MATERIALS or DERIVATIVES or to future discoveries arising from those datasets.
 - Terms shall not differentiate between nonprofit and for-profit entities being part of CTPAC operations or data generating networks.
 - Terms shall not differentiate between nonprofit and for-profit entity access to datasets.

- RECIPIENT is the custodian of the MATERIAL and acquires no ownership or intellectual property rights in the MATERIAL, derivatives, or future discoveries.
- At the end of the project, MATERIAL and derivatives shall be disposed of under the direction of NCI.
- MTA shall pre-authorize the BCR to redistribute MATERIAL and DERIVATIVES to the various centers associated with CPTAC.
- Regarding associated annotation data, MTA terms shall include:
 - A requirement that incoming data from the subcontractor shall be compliant with HIPAA-defined “Limited Data Set” with the expectation that date/timestamp and geographical data will be included. PROVIDER shall warrant that data are in compliance.
 - Language for a HIPAA-compliant “Data Use Agreement” shall be included. The data use agreement shall pre-authorize the BCR to further transmit “Limited Data Set” compliant data to CPTAC Data Coordinating Center (DCC) under an appropriate Data Use Agreement (DUA).
- MTA shall require that the RECIPIENT not attempt to identify or contact MATERIAL donor or family members.

E.3. Patient Enrollment

- Only patients suffering from breast, ovarian, and colon cancer are eligible for enrollment.
- The inclusion and exclusion criteria shall conform to those listed in the respective CPTAC Tissue Procurement Protocols.

E.4. Procuring, Processing, and Shipping Tissue and Blood Biospecimens

- Primary tumor samples:
 - The procurement of primary tumor samples for each cancer type must conform to the respective Tissue Procurement Protocol contained in Appendix 2.
 - All tissue samples must be stored at vapor phase liquid nitrogen temperature at the subcontractor’s facility until shipped to the CPTAC BCR.

E.4.a. Blood

- The procurement of plasma for biomarker analysis and blood cells for genomic analysis must conform to the respective Tissue Procurement Protocol contained in Appendix 4.

- Plasma and red cell pack shall be obtained and processed per Standard Operating Procedure “Blood Collection and Processing for Plasma and Whole Cell Components” in Appendix 4.
- Plasma and buffy coat/red cell pack shall be stored at -70° to -80°C at the subcontractor’s facility until shipped to the CPTAC BCR.

E.4.b. Normal Tissue (when available)

- Procuring normal tissue shall only be attempted when appropriate and must not compromise the generally accepted standard of patient care.
- The procurement must conform to the Tissue Procurement Protocol contained in Appendix 2.
- All tissue samples must be stored at vapor phase liquid nitrogen temperature at the subcontractor’s facility until shipped to the CPTAC BCR.

E.4.c. Shipping

- Shipping will be arranged by the CPTAC BCR. The CPTAC BCR will provide the shipping container and pay for the costs of shipping. A Shipping Manifest describing all the items to be shipped must be created by the Subcontractor and included with the tissue shipment..
- Except for extraordinary circumstance preauthorized by the Leidos Biomed TPM, individual shipments will be arranged for the tissues obtained from six or more cases.
- Each case shall include a completed “Submission” Form. The form shall be submitted to the CPTAC BCR via an electronic interface to a clinical data repository at the time of biospecimen submission.

E.5. Baseline Patient Data and Diagnostic Histopathological Data

- The Baseline Case Report Form will contain baseline patient data and status at the start of the initial treatment regimen. The de-identified information will be submitted to the CPTAC BCR via an electronic interface to a clinical data repository within five business days after qualification of case by BCR.
- The subcontractor shall be responsible for obtaining pathology reports for the cases submitted to the BCR. The reports shall be de-identified and electronic copies submitted to the BCR within five business days after tissue submission. The reports shall be in English.

- The subcontractor shall be responsible for obtaining high-quality electronic images of the FFPE slides on which the histology reports are based and submitting those to the BCR within five business days after qualification of case by BCR. The image format and other details will be provided by the BCR. If electronic images are not readily available, the subcontractor shall send representative glass slides of the case to the BCR where images will be created. In this case, the slides will be returned to the subcontractor.

E.6. Long-Term Patient Follow Up

- The one year Case Report Form will contain patient data and status 12 months after tissue submission. The de-identified information will be submitted to the CPTAC BCR via an electronic interface to a clinical data repository.
- The five year Case Report Form will contain patient data and status five years after start of the initial treatment regimen. The de-identified information will be submitted to the CPTAC BCR via an electronic interface to a clinical data repository. The five year follow up is not within the scope of this SOW and will be addressed at a later date.
- Reasonable efforts will be expected to find patients for each follow up. Documentation describing the efforts to find any patients that have been lost to follow up will be submitted to the CPTAC BCR.

F. Deliverables

The following table contains a list of deliverables that will be required.

Note: the end date for tissue collection is October 1, 2014.

F.1. Deliverable Summary and Due Dates

- IRB Approval – Due upon Execution
- Material Transfer Agreement/Data Use Agreement – Due upon Execution
- Participating Subject (Tumor Sample) Biospecimen and Submission Report Form – Due At time of biospecimen submission
- Participant Subject Baseline Case Report Form, Diagnostic Histopathology – Due Five business days after qualification of case by BCR
- De-identified Pathology Report - Due five business days after tissue submission
- Participant Subject One-Year Case Report Form – Due 12 months from the date of biospecimen submission

F.2. Deliverable Descriptions and Acceptance Criteria

F.2.a. IRB Approval

The subcontractor shall obtain local IRB approval for the work to be performed at their institution(s) and submit copies of the final approval and supporting documents to the CPTAC BCR and the Leidos Biomed TPM. The subcontractor shall also obtain a renewal of the approval for the second year of the Period of Performance. Electronic copies of the documents shall be submitted via email to the CPTAC BCR with a cc to the Leidos Biomed TPM.

Acceptance Criteria

Acceptable IRB approvals will be in a format consistent with local usage and allow the subcontractor to perform all the tasks in the SOW and their proposal. Scanned versions of the signed IRB approval document(s) in PDF format shall be acceptable.

F.2.b. Material Transfer Agreement/Data Use Agreement

The subcontractor shall develop a MTA/DUA using the CPTAC template (provided by the CPTAC BCR) that includes the CPTAC BCR and obtain the needed local approval(s). Electronic copies of the documents shall be submitted via email to the CPTAC BCR and Leidos Biomed TPM. Scanned versions of the fully executed agreement(s) in PDF format shall be acceptable.

Acceptance Criteria

Acceptable MTAs/DUAs shall be in a format consistent with local usage, cover all the elements noted in the CPTAC template, and provide for the transfer of the materials and data use consistent with CPTAC policy.

F.2.c. Participating Subject (Tumor Sample) Biospecimen and Submission Report Form

The subcontractor shall obtain the biospecimens (tissues and blood) from properly consented and enrolled participants and store the biospecimens locally per the appropriate tissue procurement protocol until shipping arrangements are made. For each participating subject, the subcontractor shall open a new case with the CPTAC BCR and complete the appropriate Case Submission Form via an electronic interface to the clinical data repository hosted by the CPTAC BCR. The CPTAC BCR shall ensure the completeness of the submitted form: any discrepancies noted by the CPTAC BCR shall be corrected by the TSS.

When notified by the BCR, the subcontractor shall package and ship the frozen biospecimens (tissues and blood) from each case per the instructions from the CPTAC BCR. The CPTAC BCR will provide appropriate shipping containers and pay for the costs of shipping. The frequency of shipments and the number of cases per shipment shall be determined by the CPTAC BCR.

Acceptance Criteria

All samples that have a fully completed Case Submission Form and approved for shipment from the CPTAC BCR shall be considered accepted when received by the CPTAC BCR.

Note that the performance of each TSS will be monitored over time and if a pattern emerges where major discrepancies are noted between the samples submitted and the histopathologic analyses, the acceptance criteria for this deliverable may be adjusted.

F.2.d. Participant Subject Baseline Case Report Form/Diagnostic Histopathology

The subcontractor shall complete the appropriate Case Baseline Form and submit it via an electronic interface to the clinical data repository hosted by the CPTAC BCR. The CPTAC BCR shall ensure the completeness of the submitted form; any discrepancies noted by the CPTAC BCR shall be corrected by the TSS. Once the biospecimens associated with a case submitted to the CPTAC BCR have been qualified, the CPTAC BCR shall notify the TSS that a completed Baseline Case Report Form, diagnostic histopathology materials, and a de-identified copy of the original surgical pathology report should be submitted. The subcontractor shall complete the appropriate Case Baseline Form and submit it via an electronic interface to the clinical data repository hosted by the CPTAC BCR. The CPTAC BCR shall ensure the completeness of the submitted form; any discrepancies noted by the CPTAC BCR shall be corrected by the TSS.

The subcontractor shall also obtain and submit a de-identified copy of the surgical pathology report by email to the CPTAC BCR with a cc to the Leidos Biomedical Research TPM. Finally, the subcontractor shall obtain the histopathology materials described in the relevant tissue procurement protocol (e.g., H&E slides). For the latter, electronic images may be produced and submitted to the CPTAC BCR; the TSS should consult with the CPTAC BCR regarding the details of electronic imaging (e.g., magnification, file format, etc.). If electronic images are not available, the TSS should contact the CPTAC BCR for instructions on how to ship the slides. Slides shipped to the CPTAC BCR will be imaged there and returned to the TSS.

Acceptance Criteria

Acceptable Baseline Case Report Forms will have all relevant fields completed with any discrepancies noted by the CPTAC BCR corrected.

Acceptable pathology reports must be complete, legible, and provided in English (cannot be extracted).

Acceptable histopathology slides or images must be of a quality suitable for evaluation by a pathologist and representative of the diagnosis. Images shall be submitted at the magnification and in the file format requested by the CPTAC BCR.

F.2.e. Participant Subject One Year Case Report Form

Approximately one year after the procurement of tissue from a participant, the Subcontractor shall attempt to follow up on the participant's clinical status. The subcontractor shall complete the appropriate One Year Case Report Form and submit it via an electronic interface to the clinical data repository hosted by the CPTAC BCR. The CPTAC BCR shall ensure the completeness of the submitted form; any discrepancies noted by the CPTAC BCR shall be

corrected by the TSS.

Acceptance Criteria

Acceptable One Year Case Report Forms will have all relevant fields completed with any discrepancies noted by the CPTAC BCR corrected.

In the instance where a participant appears to have been lost to follow up despite a good-faith and reasonable effort on the part of the Subcontractor to find the patient or his or her record, documentation describing the efforts taken will be accepted in lieu of the a completed One Year Case Report Form.

F.3. General Acceptance Criteria

In addition to specific acceptance criteria listed above, general quality measures, as set forth below, will be applied to each deliverable received from the subcontractor under this Statement of Work.

- Accuracy – Deliverables shall be accurate in presentation, technical content, and adherence to accepted elements of style.
- Clarity – Deliverables shall be clear and concise. Any/all diagrams shall be easy to understand and be relevant to the supporting narrative.
- Consistency to Requirements – All deliverables must satisfy the requirements of this Statement of Work.
- Timeliness – Deliverables shall be submitted on or before the due date specified in the Subcontract, or submitted in accordance with a later scheduled date determined by the Leidos Biomed TPM.

All deliverables and correspondence must be in English.

G. Meetings

Participation in the following meetings is required during the Period of Performance.

G.1. Kick Off

An initial kick off meeting will be held within 10 working days of award or as agreed to by the Leidos Biomed TPM. This will be attended by the Leidos Biomed TPM and Leidos Biomed CS, the NCI Project Officer, and representatives from the CPTAC Program Office. Key Subcontractor personnel as well as a representative from the Subcontractor's contracts organization are required to attend. The intent of the meeting is for all key personnel to meet to discuss the project's overall technical and contractual requirements.

At this meeting, the Subcontractor shall be prepared to discuss the following:

- Technical objectives.
- Deliverables and deliverable acceptance criteria.
- Reporting and invoice requirements.

G.2. Monthly Project Team Meeting

A monthly teleconference will be held amongst the project team, the Leidos Biomed TPM, the NCI Project Officer, representatives from the CPTAC Program Office, and a representative from the CPTAC BCR. The CPTAC BCR will oversee the meeting. The purpose of the meeting is to review the project's status, update the Subcontractor on the latest Program status, and ensure open and ongoing communication amongst all the stakeholders and participants in the Subcontractor-specific tissue procurement activities.

G.3. Monthly CPTAC TSS Program Teleconference

A monthly teleconference will be held amongst all the CPTAC TSSs sponsored by the CPTAC Program Office to review overall Program status and ensure open communications amongst all the participants in the CPTAC tissue procurement activities.

G.4. CPTAC Annual Meeting

The Subcontractor shall send at least one team member to the CPTAC Annual Meeting. Tentative location of the annual meeting is the Washington, D.C. metro area.

H. Reporting Requirements

None. Monthly meetings will be used to measure project's progress.

APPENDIX 1 – ACRONYMS

List of Acronyms

- BCR – Biospecimen Core Resource
- CPTAC – Clinical Proteomics Tumor Analysis Consortium
- DCC – Data Coordinating Center
- DNA – Deoxyribonucleic Acid
- DUA – Data Use Agreement
- GSC – Genomic Sequencing Centers
- HIPAA – Health Insurance Portability and Accountability Act
- IRB – Institutional Review Board
- LDS – Limited data set
- MTA – Material Transfer Agreements
- NCI – National Cancer Institute
- PCC – Protein Characterization Center
- PHI – Protected Health Information
- PMP – Project Management Plan
- QC – Quality Control
- RNA – Ribonucleic Acid
- SOP – Standard Operating Procedures
- SOW – Statement of Work
- TCGA – The Cancer Genome Atlas
- TPM – Technical Project Manager
- TSS – Tissue Source Site

APPENDIX 2

ACCEPTABLE TUMOR TYPES AND COLLECTION PROTOCOLS

Cancer Proteomics Tumor Analysis Consortium Prospective Biospecimen Collection Protocol Breast Cancer v1.8

Overview

The Clinical Proteomic Tumor Analysis Consortium (CPTAC) sponsored by the NCI Office of Cancer Clinical Proteomics Research is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of robust, quantitative, proteomic technologies and workflows. The overarching goal of CPTAC is to improve our ability to diagnose, treat and prevent cancer. To achieve this goal in a scientifically rigorous manner, the NCI launched CPTAC to systematically identify proteins that derive from alterations in cancer genomes and related biological processes, and provide this data with accompanying assays and protocols to the public.

CPTAC consists of a network of Proteome Characterizations Centers (PCC) and a Data Coordinating Center (DCC) serving as a hub and central repository for CPTAC data. CPTAC will be expanded to include 1) a network of Tissue Source Sites (TSS) to obtain clinical specimens for proteomic and genomic analysis, 2) a Biospecimen Core Resource (BCR) to serve as a repository for tissue and associated, de-identified clinical data submitted to the program, and 3) a Genomic Characterization Center (GCC) dedicated to the genomic analysis of CPTAC specimens.

Purpose

The purpose of the three options in this protocol are to establish minimum procurement parameters for ductal and lobular breast cancer stage IIA – IIIC specimens to be submitted to the CPTAC for proteomic and genomic analysis. Tissue will be obtained from newly diagnosed, untreated patients undergoing definitive surgery for breast cancer or by needle core biopsy at the time of placement of a vascular access device prior to neoadjuvant therapy for breast cancer.

The protocol builds on CPTAC experience with human tissues obtained from the TCGA programs and specifically aims for:

- Minimized specimen processing and ischemia time with the ischemia time recorded.
- Sufficient total material from each patient divided into multiple samples suitable for independent processing for proteomic and genomic analysis.
- Independent samples suitable for histopathological analysis with frozen sections obtained at the BCR.
- Improved determination of weights of individual samples for improved estimates of protein yield.

Scope

The three options described in this protocol apply to any samples submitted by a Leidos Biomedical Research, Inc. subcontractor to the CPTAC BCR.

Requirements

Patient Inclusion Criteria

- Newly diagnosed patients with invasive breast cancer undergoing definitive surgery for breast cancer or placement of a vascular access device as a prelude to neoadjuvant therapy for breast cancer. The inclusion criteria include patients with more than one newly-observed and independent breast masses.
- Patients with ductal and lobular breast cancer stage IIA – IIIC.

Patient Exclusion Criteria

- Prior history of other malignancies within the past 12 months other than treated basal cell carcinoma of the skin or treated DCIS of the contralateral breast (as long as no tamoxifen was administered).
- Other malignancies at the time of surgery.
- Prior lifetime systemic chemotherapy for any cancer.
- Prior history of radiation therapy involving the breast such as mantle field radiation for Hodgkins Disease, radiotherapy for lung cancer, etc.
- Patients who are found to have a diagnosis other than invasive breast cancer as a result of the surgery.

Regulatory (before procurement)

- IRB approval received and documented with the CPTAC BCR.
- MTA/DUA agreement received and documented with the CPTAC BCR.

Tissue Procurement and Shipping

- Signed patient consent (maintained at the tissue source site, copy to CPTAC BCR not required).
- Cancer tissue per protocol.
- Normal tissue per protocol.
- Pre-anesthesia blood per SOP.
- Shipping Manifest completed and accompanying tissue shipment.
- CPTAC Tissue Submission Form (contains details regarding procurement along with minimal patient information) completed and electronically submitted within 1-2 working days after tissue procurement Secure access to the electronic clinical data management system with the CRF to be provided by the CPTAC BCR.

- Adherence to BCR shipping instructions (the BCR will provide the shipping cryoport and cover the cost of shipping).

Patient Data

- CPTAC Baseline Case Report Form containing the patient's history and status at surgery along with diagnostic information completed and electronically submitted. Secure access to the electronic clinical data management system with the CRF to be provided by the CPTAC BCR.
- Pathology Report (de-identified) including ER, PgR, and HER2 status submitted with the Baseline Case Report Form. This may be in the form of a scanned document submitted electronically.
- When available, FFPE H&E diagnostic slides/images (at least one that is representative of the diagnosis in the pathology report; images are preferred but if slides are submitted, they will be imaged at the BCR and returned) submitted with the Baseline Case Report Form.
- If available, ten 5 micron unstained FFPE slides from the definitive surgical specimen submitted with the Baseline Case Report Form.
- CPTAC One-Year Case Report Form with updated history and status one year after the date of CPTAC tissue procurement. Secure access to the electronic clinical data management system with the CRF to be provided by the CPTAC BCR.

Tumor Specimen Inclusion Criteria

- Greater than 200 mg total of all tumor samples obtained from a patient.
- Greater than 60% tumor cell nuclei.
- Less than 20% necrosis.
- Thirty minutes or less total ischemia time.

Tissue Procurement Procedures

Option 1 – Tumor Excision at Lumpectomy/Mastectomy

In this approach the tumor in a patient who has received no neoadjuvant therapy is removed as per standard of care for a surgical resection procedure. The pathologist and/or surgeon must quickly determine what proportion of the tumor is required for clinical diagnostics and whether and what remaining tumor tissue can be sampled and frozen for research purposes. When in doubt, the surgical resection specimen must always be properly preserved for clinical assessment.

Tumor Tissue

- Excise the tumor with the goal of minimizing time of ischemia to the tissue. Record the time the tumor was excised.

- Divide the tumor which is procured for research purposes and not needed for clinical management into a minimum of two, ~100 mg segments (three preferred).
- Weigh each segment.
- Place each segment in the well of an “Intermediate” Tissue-Tek® Cryomold® (eg, Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx). Each segment shall be placed in a different cryomold. If feasible and consistent with the needs of the diagnostic pathologist, orient the cut faces of the segments as noted in Figure 1. The BCR will provide the cryomolds and labeling instructions/materials.
- Label each cryomold with an appropriate ID. Each segment/cryomold shall have a unique ID. Associate the weight of the segment and it’s relative position (e.g., 1, 2, or 3 in Figure 1) with the cryomold ID in the appropriate CRF.
- Wrap in aluminum foil and label with the same ID as on the cryomold.
- Freeze in LN2 vapor and record time for each segment.
- Record time when segments are frozen with a goal of 30 minutes or less to have elapsed from the time of excision to freezing, with no more than 30 minutes permitted.
- Store at vapor phase LN2 temperature until shipping.

Normal Tissue

- After excising the tumor, excise three, ~100 mg segments of normal breast tissue from as far from the tumor as possible. Record the time the segments were excised.
- Weigh each segment.
- Place each segment in the well of an “Intermediate” Tissue-Tek® Cryomold® (eg, Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx). Each segment shall be placed in a different cryomold. The BCR will provide the cryomolds and labeling instructions/materials.
- Label each cryomold with an appropriate ID. Each cryomold shall have a unique ID. Associate the weight of the segment with the cryomold ID in the appropriate CRF.
- Wrap in aluminum foil and label with the same ID as on the cryomold.
- Freeze in LN2 vapor and record time for each segment. Record time when segments are frozen.
- Store at vapor phase LN2 temperature until shipping.

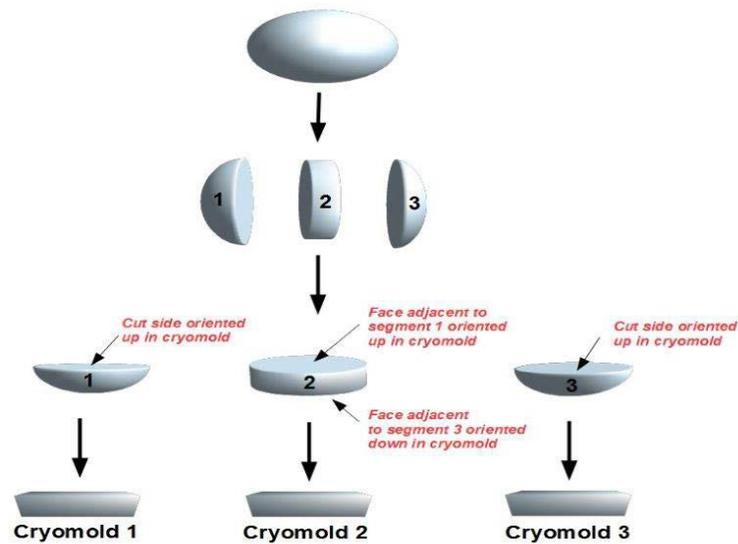


Figure 1: Orientation of tissue segments to track adjacent cut faces.

Option 2 - Large-Bore Percutaneous Tumor Coring Before Lumpectomy/Mastectomy

In this approach the tumor in a patient who has received no neoadjuvant therapy is sampled by needle core biopsy in situ prior to being removed as per standard of care for a surgical resection procedure. It is the clinical judgement of the surgeon to determine whether the tumor is of sufficient size to perform a needle core biopsy prior to surgical excision and pathological evaluation without compromising the diagnostic integrity of the specimen. When in doubt, the surgical resection specimen must always be properly preserved for clinical assessment.

Tumor Tissue Cores

- Obtain the large-bore (~10 ga.) samples to be submitted to the CPTAC BCR from the tumor (minimum of 2 attempts, 3 or more preferred).
- Record the time each core is obtained.
- Weigh each core and record weight.
- Place each core in the well of an “Intermediate” Tissue-Tek® Cryomold® (eg, Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx). Each core shall be placed in a different cryomold. The BCR will provide the cryomolds and labeling instructions/materials.
- Label each cryomold with an appropriate ID. Each core/cryomold shall have a unique ID. Associate the weight of the core with the cryomold ID in the appropriate CRF.
- Wrap in aluminum foil and label with the same ID as on the cryomold.
- Freeze in LN2 vapor and record time for each core.

- Store at vapor phase LN2 temperature until shipping.

Normal Tissue Cores from the Same Patient

- Identify normal appearing breast tissue as far from the tumor as possible.
- Obtain the large-bore (~10 ga.) samples to be submitted to the CPTAC BCR from the tumor (minimum of 2 attempts, 3 or more preferred) without interfering with potential surgical-margin analysis.
- Record the time each core is obtained.
- Place each core in the well of an “Intermediate” Tissue-Tek® Cryomold® (eg, Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx). Each core shall be placed in a different cryomold. The BCR will provide the cryomolds and labeling instructions/materials.
- Label each cryomold with an appropriate ID. Each core/cryomold shall have a unique ID. Associate the weight of the core with the cryomold ID in the appropriate CRF.
- Wrap in aluminum foil and label with the same ID as on the cryomold.
- Freeze in LN2 vapor and record time for each core.
- Store at vapor phase LN2 temperature until shipping.

Option 3 - Large-Bore Percutaneous Coring During Port Placement

Tumor Tissue Cores

- Obtain the large-bore (~10 ga.) samples to be submitted to the CPTAC BCR from the tumor (minimum of 2 attempts, 3 or more preferred).
- Record the time each core is obtained.
- Weigh each core and record weight.
- Place each core in the well of an “Intermediate” Tissue-Tek® Cryomold® (eg, Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx). Each core shall be placed in a different cryomold.
- Label each cryomold with an appropriate ID. Each core/cryomold shall have a unique ID. Associate the weight of the core with the cryomold ID in the appropriate CRF.
- Wrap in aluminum foil and label with the same ID as on the cryomold.
- Freeze in LN2 vapor and record time for each core.
- Obtain at least one additional core and process for H&E staining.

- Store tissue for shipping at vapor phase LN2 temperature.

Normal Tissue Cores from the Same Patient

- Obtain the large-bore (~10 ga.) samples from the contralateral breast (minimum of 2 attempts, 3 or more preferred).
- Weigh each core and record weight.
- Place each core in the well of an “Intermediate” Tissue-Tek® Cryomold® (eg, Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx). Each core shall be placed in a different cryomold.
- Label each cryomold with an appropriate ID. Each core/cryomold shall have a unique ID.
- Associate the weight of the core with the cryomold ID in the appropriate CRF.
- Wrap in aluminum foil and label with the same ID as on the cryomold.
- Freeze in LN2 vapor and record time for each core.
- Store at vapor phase LN2 temperature until shipping.

Reference: Wilson, R and Kavin, S, Comparison of Large-Core Vacuum-Assisted Biopsy and Excision Systems *In* Brun del Re, R. (Ed.) Minimally Invasive Breast Biopsies, Springer, pp. 23-41, 2010. (<http://www.google.com/url?sa=t&rct=j&q=bard%20large%20core%20biopsy%20instrument%20vacuum&source=web&cd=4&sqi=2&ved=0CEcQFjAD&url=http%3A%2F%2Fwww.springer.com%2Fcd%2Fcontent%2Fdocument%2Fcd%2Fdownloaddocument%2F9783540314035-c1.pdf%3FSGWID%3D0-0-45-796504-p150492838&ei=EUI4UcvvLOq10QGgg4C4Cg&usg=AFQjCNGzx8IYPToq2SPF9e-ZhY6lw&cad=rja>)

Blood Collection Procedure

- Obtained pre-anesthesia.
- 10 ml lavender top vacutainer with the blood processed per SOP.

Prospective Biospecimen Collection Protocol

Colon Cancer v1.5

Overview

The Clinical Proteomic Tumor Analysis Consortium (CPTAC) sponsored by the NCI's Office of Cancer Clinical Proteomics Research is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of robust, quantitative, proteomic technologies and workflows. The overarching goal of CPTAC is to improve our ability to diagnose, treat and prevent cancer. To achieve this goal in a scientifically rigorous manner, the NCI launched CPTAC to systematically identify proteins that derive from alterations in cancer genomes and related biological processes, and provide this data with accompanying assays and protocols to the public.

CPTAC consists of a network of Proteome Characterizations Centers (PCCs) and a Data Coordinating Center (DCC) serving as a hub and central repository for CPTAC data. CPTAC will be expanded to include:

1. a network of Tissue Source Sites (TSS) to obtain clinical specimens for proteomic and genomic analysis,
2. a Biospecimen Core Resource (BCR) to serve as a repository for tissue and associated, de-identified clinical data submitted to the program, and
3. a Genomic Characterization Center (GCC) dedicated to the genomic analysis of CPTAC specimens.

Purpose

The purpose of this protocol is to establish the minimum procurement parameters for colon adenocarcinoma (biopsy proven) specimens to be submitted to the CPTAC for proteomic and genomic analysis. The tissue source will be from newly diagnosed, untreated patients undergoing definitive surgery for colon cancer.

The protocol builds on CPTAC experience with human tissues obtained from the TCGA programs and specifically aims for:

- Minimized specimen processing and ischemia time with the ischemia time recorded.
- Sufficient total material from each patient divided into multiple samples suitable for independent processing for proteomic and genomic analysis.
- Independent samples suitable for histopathological analysis with frozen sections obtained at the BCR.
- Improved determination of weights of individual samples for improved estimates of protein yield.

Scope

The protocol applies to any samples submitted by a Leidos Biomedical Research, Inc. subcontractor to the CPTAC BCR.

Requirements

Patient Inclusion Criteria

- Newly diagnosed, untreated patients undergoing primary surgery for colon adenocarcinoma.

Patient Exclusion Criteria

- Prior history of other malignancies within the past 12 months except basal cell carcinoma of the skin.
- Other malignancies at the time of surgery.
- Prior lifetime systemic chemotherapy for any cancer.
- Radiation or chemotherapy for the colon cancer.
- Prior radiation therapy to the abdomen or pelvis for any cancer.

Regulatory (before procurement)

- IRB approval received and documented with the CPTAC BCR
- MTA/DUA agreement received and documented with the CPTAC BCR

Tissue Procurement and Shipping

- Signed patient consent (maintained at the tissue source site, copy to CPTAC BCR not required).
- Cancer tissue per protocol.
- Normal tissue per protocol.
- Pre-anesthesia blood per SOPs.
- Shipping Manifest completed and accompanying tissue shipment.
- CPTAC Tissue Submission Form (contains details regarding procurement such as ischemia times along with minimal patient information) completed and electronically submitted within 1-2 working days after tissue procurement.
- Adherence to BCR shipping instructions (the BCR will provide the shipping cryoport and cover the cost of shipping).

Patient Data

- CPTAC Baseline Case Report Form (CRF) containing the patient' history and status at surgery along with diagnostic information (specific data to be collected to be determined) completed and electronically submitted prior to tissue shipment.
- Pathology Report (de-identified) submitted prior to tissue shipment.

- FFPE H&E diagnostic slides/images (at least one that is representative of the diagnosis in the pathology report; slides will be returned) submitted prior to tissue shipment.
- CPTAC One-Year CRF with updated history and status one year after completion of the initial treatment regimen. Secure access to the electronic clinical data management system with the CRF to be provided by the CPTAC BCR.
- CPTAC Five-Year CRF with updated history and status five years after completion of the initial treatment regimen. Secure access to the electronic clinical data management system with the CRF to be provided by the CPTAC BCR.

Tumor Specimen Inclusion Criteria

- Greater than 300 mg total of all segments obtained from a patient.
- Greater than 60% tumor cell nuclei.
- Less than 20% necrosis.
- Less than 30 minutes total ischemia time.

Tissue Procurement Procedure

- Record the time point for initial ligation of the arterial blood supply to the tumor.
- Remove the particular section of the colon of interest with the goal of minimizing time of ischemia to the tissue. Record the time of removal.
- Excise a >300 mg portion of the tumor mass and a separate >300 mg portion of adjacent normal colonic tissue. Place both specimens into separate specimen containers.
- To minimize total ischemia time for the tumor, process the tumor material first.
 - Divide the tumor specimen into >100 mg segments for submission to the CPTAC BCR..
 - Weigh each tumor segment.
 - Place each segment in the well of an “Intermediate” Tissue-Tek® Cryomold® (ef, Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx).. Each segment shall be placed in a different cryomold.
 - Label each cryomold with an appropriate ID. Each segment/cryomold shall have a unique ID. Associate the weight of the segment with the cryomold ID in the appropriate CRF.
 - Wrap in aluminum foil and label with the same ID as on the cryomold.
 - Freeze in LN2 vapor.

- Record time when segments are frozen with the goal of **20 minutes** or less to have elapsed from the time of initially dividing the mesentery to freezing and no more than **30 minutes** permitted.
- After processing the tumor material, process the normal tissue for freezing.
 - Divide the normal specimen into >100 mg segments for submission to the CPTAC BCR.
 - Weigh each normal segment.
 - Place each segment in the well of an “Intermediate” Tissue-Tek® Cryomold® (ef, Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx).. Each segment shall be placed in a different cryomold.
 - Label each cryomold with an appropriate ID. Each segment/cryomold shall have a unique ID. Associate the weight of the segment with the cryomold ID in the appropriate CRF.
 - Wrap in aluminum foil and label with the same ID as on the cryomold.
 - Freeze in LN2 vapor.
 - Record time when segments are frozen with the goal of **20 minutes** or less to have elapsed from time of initial time of initially dividing the mesentery to freezing and no more than **40 minutes** permitted.
- Additional samples may be obtained for local use.
- Store all segments at vapor phase LN2 temperature until shipping.
- The CPTAC BCR should be consulted if questions arise regarding this protocol.

Blood Collection Procedure

- Obtained pre-anesthesia
- 10 ml lavender top vacutainer with the blood processed per SOP.

Prospective Biospecimen Collection Protocol

Ovarian Cancer v1.6

Overview

The Clinical Proteomic Tumor Analysis Consortium (CPTAC) sponsored by the NCI's Office of Cancer Clinical Proteomics Research is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of robust, quantitative, proteomic technologies and workflows. The overarching goal of CPTAC is to improve our ability to diagnose, treat and prevent cancer. To achieve this goal in a scientifically rigorous manner, the NCI launched CPTAC to systematically identify proteins that derive from alterations in cancer genomes and related biological processes, and provide this data with accompanying assays and protocols to the public.

CPTAC consists of a network of Proteome Characterizations Centers (PCCs) and a Data Coordinating Center (DCC) serving as a hub and central repository for CPTAC data. CPTAC will be expanded to include a 1) network of Tissue Source Sites (TSSs) to procure clinical specimens for proteomic and genomic analysis, 2) Biospecimen Core Resource (BCR) to serve as a repository for tissue and associated, de-identified clinical data submitted to the program, and 3) Genomic Characterization Center (GCC) dedicated to the genomic analysis of CPTAC specimens.

Purpose

The purpose of this protocol is to establish the minimum procurement parameters for high-grade serous ovarian, fallopian tube, and peritoneal cancer specimens to be submitted to the CPTAC for proteomic and genomic analysis. The tissue source will be from newly diagnosed, untreated patients undergoing definitive surgery for ovarian cancer.

The protocol builds on CPTAC experience with human tissues obtained from the TCGA programs and specifically aims for:

- Minimized specimen processing and ischemia time with the ischemia time recorded.
- Sufficient total material from each patient divided into multiple samples suitable for independent processing for proteomic and genomic analysis.
- Independent samples suitable for histopathological analysis with frozen sections obtained at the BCR.
- Improved determination of weights of individual samples for improved estimates of protein yield.

Scope

The protocol applies to any samples submitted by a Leidos Biomedical Research, Inc. subcontractor to the CPTAC BCR.

Requirements

Patient Inclusion Criteria

- Newly diagnosed, untreated patients undergoing primary cytoreductive surgery for serous ovarian cancer.
- Tumor from ovary, pelvic mass or omentum only (other anatomic sites not acceptable).

Patient Exclusion Criteria

- Prior history of other malignancies within the past 12 months except non-melanomatous skin cancer and in situ cervical cancer.
- Other malignancies at the time of surgery.
- Prior lifetime systemic treatment (cytotoxic or molecular) for any malignancy.
- Prior radiation therapy for any prior malignancy that involves treatment to the abdomen or pelvis.
- Prior hormonal therapy within the last five years for cancer.
- Patients who are found to have low-grade (grade 1) or low stage (stage I or II) serous ovarian, fallopian tube, or peritoneal cancer based on final pathology (typically 5-10 days after surgery).

Regulatory (before procurement)

- IRB approval received and documented with the CPTAC BCR.
- MTA/DUA agreement received and documented with the CPTAC BCR.

Tissue Procurement and Shipping

- Signed patient consent (maintained at the tissue source site, copy to CPTAC BCR not required).
- Cancer tissue per protocol.
- Normal fallopian tube fimbriae if possible (per Crum protocol).
- Pre-anesthesia blood per SOP.
- Shipping Manifest completed and accompanying tissue shipment.
- CPTAC Tissue Submission Form (contains details regarding procurement such as ischemia time along with minimal patient information) completed and electronically submitted within 1-2 working days after tissue procurement.
- Adherence to BCR shipping instructions (the BCR will provide the shipping cryoport and cover the cost of shipping).

Patient Data

- CPTAC Baseline Case Report Form (CRF) containing the patient's history and status at surgery along with diagnostic information completed and electronically submitted prior to tissue shipment.
- Pathology Report (de-identified; example content at <http://www.cancer.gov/cancertopics/factsheet/detection/pathology-reports>) submitted prior to tissue shipment.
- FFPE H&E diagnostic slides/images (at least one that is representative of the diagnosis in the pathology report; images are preferred but if slides are submitted, they will be imaged at the BCR and returned) submitted prior to tissue shipment.
- CPTAC One-Year CRF with updated history and status one year after completion of the initial treatment regimen (specific data to be collected to be determined).
- CPTAC Five-Year CRF with updated history and status five years after completion of the initial treatment regimen (specific data to be collected to be determined).

Tumor Specimen Inclusion Criteria

- Greater than 300 mg total of all segments obtained from a patient.
- Greater than 60% tumor cell nuclei.
- Less than 20% necrosis.
- Less than 12 minutes total ischemia time.

Tissue Procurement Procedure

Tumor Tissue

- Identify a 1-2 cc nodule that appears to be mostly tumor, with little or no intervening normal tissue.
- Dissect free from surrounding attachments leaving main blood supply intact for as long as possible unless specimen is to be excised immediately from within a larger tumor mass.
- Start timer when blood supply transected.
- Take nodule off operating field onto back table, bisect to confirm apparent tumor.
- Cut at least three strips (segments) of tumor each weighing ≥ 100 mg segments for submission to the CPTAC BCR.
- Weigh each segment.

- Place each segment in the well of an “Intermediate” Tissue-Tek® Cryomold® (e.g., Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx). Each segment shall be placed in a different cryomold.
- Label each cryomold with an appropriate ID. Each segment/cryomold shall have a unique ID. Associate the weight of the segment with the cryomold ID in the appropriate CRF.
- Wrap in aluminum foil and label with the same ID as on the cryomold.
- Freeze in LN2 vapor.
- Record time when segments are frozen with the goal of **seven minutes** or less to have elapsed from resection to freezing and no more than **twelve minutes** permitted.
- Store at vapor phase LN2 temperature until shipping.
- Note that the CPTAC BCR should be consulted if questions arise regarding this protocol.

Normal Tissue (Fallopian tube submitted for SEE-FIM sectioning)

- Record the time of excision.
- If a fallopian tube grossly looks normal, collect up to 3 individual fimbria from that tube.
- Weigh each piece destined for the BCR.
- Place each tissue in the well of an “Intermediate” Tissue-Tek® Cryomold® (e.g., Product No. 27183; http://www.tedpella.com/embed_html/27110.htm.aspx). Each tissue shall be placed in a different cryomold.
- Label each cryomold with an appropriate ID. Each segment/cryomold shall have a unique ID. Associate the weight of the tissue with the cryomold ID in the appropriate CRF.
- Wrap in aluminum foil and label with same ID as on the cryomold.
- Freeze in LN2 vapor.
- Record time when samples are frozen, with the goal of **seven minutes** or less to have elapsed from resection to freezing and no more than **twelve minutes** permitted.
- Store at vapor phase LN2 temperature until shipping.
- Note that the CPTAC BCR should be consulted if questions arise regarding this protocol.

Blood Collection Procedure

- Obtained pre-anesthesia.
- 10ml lavender top vacutainer with blood processed per SOP.

APPENDIX 3 – IRB GUIDANCE DOCUMENT

The purpose of this document is to assist Institutional Review Boards (IRBs)/Ethics Boards and/or Privacy Boards at participating clinical sites in their review of protocols that include submission of tissues and associated clinical data to The Clinical Proteomics Tumor Analysis Consortium (CPTAC) Project of the National Cancer Institute (NCI) of the National Institutes of Health (NIH). This document provides summary information on the project and how it works, followed by a discussion of key points of interest to this audience.

A. CPTAC Aim and Summary

The overarching goal of CPTAC is to improve our ability to diagnose, treat, and prevent cancer. To achieve this goal in a scientifically rigorous manner, the National Cancer Institute (NCI) launched CPTAC to systematically identify proteins that derive from alterations in cancer genomes and related biological processes, and provide this data with accompanying assays and protocols to the public.

Genomics initiatives such as The Cancer Genome Atlas (TCGA) have characterized and sequenced the genomic alterations from several types of cancer. These efforts are providing a catalogue of alterations in the cancer genomes and setting the stage for the development of more molecular interventions. CPTAC will leverage its analytical outputs from Phase I in the coming years by producing a unique continuum that defines the proteins translated from cancer genomes in order to link genotype to proteotype and ultimately to phenotype. This goal will be met through four overarching objectives. They are:

Objective 1: Identify and characterize the protein inventory from tumor and normal tissue biospecimens

Objective 2: Integrate genomic and proteomic data from analysis of common cancer biospecimens

Objective 3: Develop assays against proteins prioritized in the discovery stage as potential biomarker candidates

Objective 4: Perform testing of verification assays in relevant cohorts of biospecimens

For the cancer types studied, approximately 100 cases of tumor tissue with a case-matched germline DNA source that have been or will be genomically analyzed across multiple genomic platforms will be characterized by large-scale, quantitative protein profiling via mass spectrometry. When possible, matched normal tissue for each case will be included in the analyses. Each case will be obtained with demographic and clinical annotation, along with follow-up information minimally sufficient to correlate molecular profiles with survival.

CPTAC is operating as a network of grant and contract funded entities. With regard to prospective human sample collection, clinically annotated tissue specimens will be collected from several participating CPTAC Tissue Source Sites (TSS), and sent to the CPTAC Biospecimen Core Resource (BCR).

The BCR will perform quality control on the tissues and will send qualified samples to the CPTAC Protein Characterization Centers (PCC) for proteomic analysis. The BCR will use uniform protocols to isolate nucleic acids that will be sent to a Genomic Sequencing Center (GSC) within the network for genomic analysis. The PCC and GSC data are sent to the CPTAC Data Coordination Center (DCC), where the data are made available to other investigators via the internet. Raw sequencing data may be maintained by a separate DCC than the rest of the CPTAC data. The BCR will also standardize and quality control the participant clinical data that are subsequently sent directly to the central DCC.

The GSC molecular characterizations will include whole-exome sequencing, micro- and messenger-RNA expression profiling (sequenced based), and chromosomal structure and copy number alteration (low pass sequence and/or chip based). Since both tumor and germline DNA are sequenced from each case, somatic single nucleotide variants are discovered. However, the germline information is also available for which investigators can use for their research. Proteomic characterization of these samples by the PCCs will include mass spectrometry-based profiling of the proteome, phosphoproteome, and glycoproteome of these specimens. A subset of selected samples may also be characterized by protein microarray and/or reverse-phase protein

B. Key Human Subjects Policies

This document was written to provide guidance to Principal Investigators and IRB staffs at the CPTAC TSSs at which the participants are enrolled and their tissue specimens and clinical data are collected. CPTAC will collect tissues and associated clinical data from US-based organizations using Leidos Biomed subcontracting mechanisms.

U.S.-based sites are subject to federal regulations covering human subjects research (45 CFR 46, the “Common Rule”) and are also HIPAA “Covered Entities.” The following sections describe key CPTAC protocols and policies relevant to human subject research and participant protection policies.

C. Minimal Risk Protocol

To date, most IRBs have considered protocols providing clinically annotated tumor tissues to programs such as The Cancer Genome Atlas (TCGA) program sponsored by the National Cancer Institute (NCI) and National Human Genome Research Institutes (NHGRI) to be “minimal risk.” The CTPAC program will mimic TCGA program in all aspects relating to patient risk. The CPTAC program will employ a series of prospective protocols for tissue acquisition that are non-interventional and will employ a “surgical remnant” or “surgical discard” approach; i.e., the tissues to be collected will be obtained during the normal course of care for cancer patients that would normally be discarded or used in other research programs. Participants are at some “social risk” from potential loss of privacy or the possibility of a security breach resulting in a loss of confidentiality of their medical information. Participation in CPTAC holds an additional social risk: the project generates individually unique proteomic and genetic information (see Section G [Genetic Data: Open vs. Controlled-Access Tiers] below) and there is a theoretical risk that such data combined with third-party databases could result in re-identification of a participant.

With “minimal risk” protocols, IRBs may wish to consider applications or amendments to existing protocols under an expedited review process.

D. Linked Protocol and “Coded” Identifiers

Similar to TCGA, CPTAC will operate as a “linked” protocol, with each participant ID being doubly de-referenced (i.e., “coded” twice) before tissue or data are distributed by the Network. The first linking key is retained by the TSS at which the participants are enrolled. Access to this key is the purview of TSS institutional policies and the local IRB. The second linking key is retained by the CPTAC BCR and is only made available within the program for quality control purposes upon approval by the Director, Office of Cancer Clinical Proteomics Research. The second key will also be provided to the TSS Principal Investigator upon presentation of IRB approval to have this second key. As a result of these policies, investigators using CPTAC data are prevented from seeing participant direct identifiers or from linking backwards to the primary participant identifiers at the TSS clinical sites by both technical systems and contractual obligations.

“45 CFR 46.101(b)(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”

E. HIPAA and Collection of a Limited Data Set (LDS)

Clinical data will be provided by the CPTAC TSS to the CPTAC BCR in a form compliant with a HIPAA-defined Limited Data Set (LDS) (The 16 traditional direct identifiers as defined by HIPAA under 45 CFR 164.514(e)(2), name, social security number, etc. are excluded). Additionally, CPTAC will not collect geographic information at the level of detail permitted by an LDS. CPTAC will collect specific demographic and clinical event date information, for example, country of origin, dates of birth, death, admission, diagnosis, surgery, treatment, and release. These data are necessary for quality control purposes and to enable correlation of molecular profiles with time-based patient characteristics such as survival. It is expected that the organization hosting the BCR will be a subcontractor to Leidos Biomed and the BCR and Leidos Biomed will enter into HIPAA-compliant Data Use Agreements (DUA) with the clinical Tissue Source Sites (the HIPAA “Covered Entity”) to enable this process.

However, LDS data will **not** be distributed beyond the CPTAC DCC to any other CPTAC network component, (PCC and GSC) nor to the broader research community. Prior to data distribution, the DCC will convert all dates to intervals and/or modify dates to being no more specific than one year. As a result, distributed participant data meet the HIPAA test of being De-Identified (45 CFR 164.514(b)(2)(i)).

F. Informed Consent

CPTAC policy is that subjects enrolled for tissue collections must be consented under a protocol that does not expressly conflict with any key concepts related to participation in CPTAC.

G. Genetic Data: Open vs. Controlled-Access Tiers

In addition to proteomic data, CPTAC will generate individually unique genetic data (“genetic fingerprints”, or genotypes). These data will not be directly tied to an identified individual, and the clinical information associated with these data are de-identified as described above. Nevertheless, a theoretical risk exists that the genetic data in conjunction with third party databases (e.g., forensic genetic profile databases) could lead to the re-identification of a participant or relative. Consequently, NIH policy for CPTAC will be the same as for TCGA in that individual genetic data from the characterization studies will be kept in a restricted-access database. (More information on segmentation of all CPTAC data between the open-access and restricted-access tiers is in Section I2 below.)

To be authorized to access the restricted tier of data, Investigators will be required to submit an application to the project’s Data Access Committee (DAC). Upon approval by the DAC that the access request is for bona fide research purposes, the Investigator and their institution will be required to subscribe to a Data Use Certification that controls their ability to access the data, and places requirements for data security upon them, scientists directly under their control, and their institutions. Data use for these controlled-access data are for any legitimate research use (i.e. there are no data use restrictions and users may apply data to non-cancer research-related discovery).

H. IRB documentation of approval to participate

NIH policy regarding TSS participation in CPTAC places 45CFR46 compliance responsibility on the local IRB. Nevertheless, to participate, each TSS Principal Investigator must have some level of IRB review and document such review to Leidos Biomed, the NCI, and the BCR. Such review can range from a full IRB protocol submission and approval, amendment to an existing protocol, or an expedited/administrative review. The IRB may determine that participation is either Exempt or grant a Waiver, either of which is acceptable to NIH. Also, the IRB may determine that participation is not human subjects research, if, for example, the subjects are deceased.

Regardless of the IRB finding, however, program policy is that a TSS Principal Investigator must document to Leidos Biomed, NCI and the BCR that their IRBs have either:

1. approved their participation specifically in the CPTAC project, through an approved protocol, amendment, exemption, or waiver, and the documentation must include **specific mention of CPTAC**; or
2. provided documentation that the IRB does not consider participation to constitute “human subjects research,” and therefore does not have purview.

I. Additional information on CPTAC Policies

I.1. Human Subjects and Participant Protection

CPTAC expects investigators, their institutions, and their IRBs to consider, based on their own standards of research practice, whether or not research involving coded and potentially re-identifiable information in CPTAC datasets meets the definition of “human subjects research” or not. The NCI presumes that this determination will be made consistent with institutional policies and under the auspices of the local IRB.

I.1.a. Contents of Informed Consent, additional information

For the purpose of reviewing the content of Informed Consents for prospective collections, the following key concepts pertinent to CPTAC should be considered for inclusion and disclosure to participants:

- genetic research, including proteomic analysis and DNA sequencing
- sharing of biospecimens, including to collaborators at other institutions
- sharing of clinical data, including to collaborators at other institutions
- possibility of future research use
- use of internet-connected electronic database with restricted public access
- the risk of loss of privacy or confidentiality of their personal information
- there will be no return of individual results to the participant
- should a patient withdraw, the project cannot retrieve or delete data once they have been distributed. Residual tissue at the BCR will no longer be used.

CPTAC may develop Informed Consent templates with suggested language that includes the concepts above, with specific nuances for prospective tissue procurement protocols.

I.2. Data Sharing and Access

I.2.a. Rapid and Broad Data Release

CPTAC policy is to promote wide dissemination of all project data for use by the biomedical research community and to assure their maximum utility. Accordingly, CPTAC is committed to the rapid and complete release of its datasets for use by all investigators throughout the global scientific community who, along with their institutions, certify their agreement with CPTAC policies.

I.2.b. Data Access: open- versus restricted-access tiers

To minimize the risk of participant identification, the CPTAC Project Team established a policy that CPTAC data be made available from a two-tiered data access system.

- The Open-Access Data Tier will be publicly accessible to anyone on the internet and contain only proteomic, genomic, and clinical data that cannot be analyzed to generate a dataset unique to an individual. These data may include:
 - Tissue pathology data
 - HIPAA de-identified clinical data
 - Gene expression data
 - Copy-number alterations for non-genetic platforms
 - Proteomic data
 - Data summaries, such as genotype frequencies
 - DNA sequence data of single amplicons
- The Controlled-Access Data Tier will contain genomic and clinical data that are associated to a unique, but not directly identified, person. However, there is a risk that these data could be analyzed to potentially identify a person through reference to 3rd party databases. They will therefore be managed with both additional technical security and a qualification and access authorization process for investigators and their institutions. They will be made available to any qualified researcher for the purpose of biomedical research, once the investigator, along with his/her institution, has certified agreement to the statements within TCGA Data Use Certification (DUC). The DUC can be found at:
http://dbgap.ncbi.nlm.nih.gov/aa/wga.cgi?page=DUC&view_pdf&stacc=phs000178.v4.p4

J. Description of CPTAC Components and Operations

This appendix provides a more detailed description of the CPTAC network, specifically the various institutions that operate the “pipeline” that ultimately results in the CPTAC data sets being made available as a community resource.

In addition to the Tissue Source Sites (TSS), the TCGA Network is comprised of the following entities, working under a combination of grants and contracts from NCI and Leidos Biomed.

J.1. Biospecimen Core Resource (BCR)

A CPTAC BCR will be established as a central site for the receipt, review and processing of tissues and associated clinical data. The BCR will be the primary interface between the TSSs and the CPTAC Network.

Tissue samples, after screening against inclusion and exclusion criteria at the TSS, will be shipped to the BCR. Samples of tumor and, if available, normal tissue will be shipped from the BCR to the PCCs for proteomic analysis. In addition, nucleic acids will be isolated at the BCR. Subsequent proteomic and genomics analyses will be performed on tissues or analytes from samples that meet pathology quality control (QC) using uniform protocols. All protein, DNA, and RNA will be co-isolated from samples from the same individual such that characterizations are effectively performed on the same sample. These analytes are also subject to several QC processes. Subsequently, DNA and RNA will be distributed to the CPTAC GCC.

Clinical data associated with the samples will be collected from the TSS via electronic case report forms. At the BCR, the data will be quality controlled and transformed into a standardized caBIG-based terminology and a uniform data model, and then sent to the CPTAC DCC. Note that samples and associated data sent by the BCR to the PCCs and GSC for characterization are De-Identified.

The BCR will also ensure and verify that CPTAC human subjects protections policies, procedures, and regulations are followed.

The Biospecimen Core Resources for CPTAC has been established under subcontract by Leidos Biomed under the Federally-Funded Research and Development Center arrangement with the NCI to the Washington University, St. Louis, MO.

J.2. Genomic Sequencing Center (GSC)

The Genomic Sequencing Centers (GSC) will conduct DNA- and RNA-based molecular characterizations.

The GSC will perform large-scale DNA sequencing using the latest sequencing technologies. All CPTAC samples will be analyzed by whole exome sequencing to reveal mutations within coding regions.

The GSC will receive samples from the CPTAC BCR and log them into local material management / laboratory information system (LIMS) databases. The GSC will also have access to sample logistics and QC data from the BCR, as necessary, and may store local copies of such data for operational support. Center databases will maintain the link between the CPTAC IDs provided by the BCR and the derived data. The sequence data will be stored in the TCGA CGHUB; other molecular characterization data generated by the GSC will be sent to the CPTAC Data

Coordinating Center (DCC), where they will be integrated with the clinical and tissue specimen data sent by the BCR.

The Genomic Sequencing Center for CPTAC will be established under subcontract by Leidos Biomed under the Federally-Funded Research and Development Center arrangement with the NCI.

J.3. Proteome Characterization Centers (PCCs)

The CPTAC consists of five teams that create a network of PCCs. The PCCs are:

- Boise State University, Boise, ID
- Broad Institute, Cambridge, MA
- Fred Hutchinson Cancer Research Center, Seattle, WA
- Harvard Affiliated Hospitals, Boston, MA
- Johns Hopkins University, Baltimore, MD
- Massachusetts Institute of Technology, Cambridge, MA
- Massachusetts General Hospital, Boston, MA
- Memorial Sloan-Kettering Cancer Center, New York, NY
- New York University, New York, NY
- Oregon Health & Science University, Portland, OR
- Pacific Northwest National Laboratory, Richland, WA
- Stanford University, Stanford CA
- University of California at San Diego, San Diego, CA
- University of Chicago, Chicago, IL
- University of Connecticut Health Center, Farmington, CT
- University of North Carolina, Chapel Hill, NC
- University of Texas M.D. Anderson Cancer Center, Houston, TX
- University of Washington, Seattle, WA
- Vanderbilt University, Nashville, TN

- Virginia Polytechnic Institute and State University, Northern Virginia Center, Fall Church, VA
- Washington University in St. Louis, St. Louis, MO

J.4. Data Coordination Center (DCC)

The Data Coordination Center (DCC) is the main data repository of CPTAC, and coordinates technical data standards across the entire project. The DCC collects, stores and distributes the proteomic, clinical, and genomic data generated by the project. The DCC links together all data generated by the project into a single integrated resource, including clinical information that will be extracted from medical records by TSSs (via the BCR) and the raw results from the PCCs and GSC

To help ensure the protection of participants consistent with the policies of CPTAC, the DCC software includes security systems to control access, and data verification and modification tools to prevent content from being readily used to identify participants. In no case will the DCC database include any direct identifiers such as name, medical record number, address, social security numbers, or contact information. The Limited Data Set received from any TSS is immediately modified to meet the HIPAA definition of De-Identified by exclusion of all the 18 identifiers cited in the Privacy Rule.

While CPTAC employs one main DCC, data may actually be housed at multiple databases at the National Institutes of Health, with the data divided up according to the technical requirements for storage. For example, some CPTAC sequence data may also be deposited in the NIH Database of Genotypes and Phenotypes (dbGAP). The overall data access restriction policies developed by CPTAC apply to CPTAC data regardless of where they are technically stored.

The main CPTAC Data Coordinating Center is housed at the Georgetown University under a direct government contract to ESAC, Inc., Rockville, MD.

K. Additional Information

CPTAC is a program within the NCI Office of Cancer Clinical Proteomics Research. Additional information can be found on the project's website: <http://proteomics.cancer.gov/programs/cptacnetwork>.

The CPTAC Program Office can be contacted at:

Chris Kinsinger, Ph.D.

Program Manager

General Contact

kinsingc@mail.nih.gov

301-451-8883

Office of Cancer Clinical Proteomics Research

cancer.proteomics@mail.nih.gov

301-594-9016

National Cancer Institute:

Harold Varmus, M.D.; Director, National Cancer Institute

Douglas Lowy, M.D.; Deputy Director, National Cancer Institute

Henry Rodriguez, Ph.D., MBA; Director, Office of Cancer Clinical Proteomics Research

APPENDIX 4 - STANDARD OPERATING PROCEDURES

Prospective Biospecimen Collection Protocol Blood Collection and Processing for Plasma and Whole Cell Components v2.0

Overview

The Clinical Proteomic Tumor Analysis Consortium (CPTAC) sponsored by the NCI's Office of Cancer Clinical Proteomics Research is a comprehensive and coordinated effort to accelerate the understanding of the molecular basis of cancer through the application of robust, quantitative, proteomic technologies and workflows. The overarching goal of CPTAC is to improve our ability to diagnose, treat and prevent cancer. To achieve this goal in a scientifically rigorous manner, the NCI launched CPTAC to systematically identify proteins that derive from alterations in cancer genomes and related biological processes, and provide this data with accompanying assays and protocols to the public.

CPTAC consists of a network of Proteome Characterizations Centers (PCCs) and a Data Coordinating Center (DCC) serving as a hub and central repository for CPTAC data. CPTAC will be expanded to include

1) a network of Tissue Source Sites (TSS) to obtain clinical specimens for proteomic and genomic analysis, 2) a Biospecimen Core Resource (BCR) to serve as a repository for tissue and associated, de-identified clinical data submitted to the program, and 3) a Genomic Characterization Center (GCC) dedicated to the genomic analysis of CPTAC specimens.

PURPOSE

The purpose of this protocol is to establish a uniform procedure for collecting and processing blood samples obtained as part of the CPTAC prospective tissue procurement project. The blood samples are intended to provide 1) plasma for subsequent biomarker discovery and 2) cellular blood components for germ line genetic analysis of tissue donors. This protocol applies to TSSs collecting tissues from breast, colon, and ovarian cases.

This procedure was originally developed to provide plasma samples for CPTAC-wide experimentation collected under similar blood collection and plasma processing conditions, to assure, as much as possible, that differences in molecular profiles of such specimens will not be due primarily to different collection and processing conditions. The common procedure for obtaining plasma was developed after analysis of many protocols in use and an examination of the available scientific rationales for different steps in these protocols, as well as the reasonable accommodations to a common protocol required by the different program sites. Note in particular that the use of refrigeration in processing, as prescribed here, can result in platelet activation and thus may result in molecular profiles that are distinct from protocols performed at room temperature. The original procedure has been expanded to include the collection and storage of the cellular blood components remaining after fractionation to be used for determining the germ line genetics of patients providing tumor and normal tissue to the CPTAC.

The original procedure was adapted from the NCI/EDRN/SPORE Lung Cancer Biomarkers Group SOP for Collection of Serum and Plasma Samples for Proteomic Analysis HUPO's recommended SOP for EDTA-Plasma Specimen Collection (Plasma Proteome Project, 2006).

Scope

The protocol applies to any samples obtained by a Leidos Biomedical, Inc. CPTAC Tissue Source Site subcontractor for submission to the CPTAC Biospecimen Core Resource (BCR) in conjunction with the submission of tumor and corresponding normal tissue for proteomic analysis.

Procedures

Blood Collection Requirements

1. Blood must be collected before any anesthesia is administered prior to commencing the procurement.
2. Patient consent must have been obtained.
3. All other requirements for the respective CPTAC Tissue Procurement protocol have been satisfied
4. Preferred Method for Collecting Blood
 - a. Venipuncture from a readily accessible peripheral vein using a conventional blood collection system and the appropriate Vacutainer® (Product Number BD366643; provided by the BCR).
5. Acceptable Alternative Methods for Collecting Blood
 - a. Venipuncture from a readily accessible peripheral vein using a syringe and needle/butterfly with the contents of the syringe immediately transferred to the appropriate Vacutainer® (Product Number BD366643; provided by the BCR).
 - b. Withdrawal via syringe from a peripheral intravenous catheter with the contents of the syringe immediately transferred to the appropriate Vacutainer®. (Product Number BD366643; provided by the BCR). If this method is used, the TSS shall employ best practices for obtaining blood samples from a peripheral intravenous catheter (e.g., Heyer N.J. et al. Effectiveness of practices to reduce blood sample hemolysis in EDs: a laboratory medicine best practices systematic review and meta-analysis, Clin Biochem. 45, pp. 1012-32, 2012 [PMID 22968086]).
6. Other Requirements
 - a. Regardless of the collection method employed, slowly and gently invert the Vacutainer® 8-10 times after filling.
 - b. Keep the Vacutainer® on wet ice after mixing.

Sample Processing Steps (must be completed within 90 minutes of collection)

1. Centrifugation 1
 - a. Within 30 minutes of collection, centrifuge at 1500 g for 15 min in a refrigerated centrifuge (4° C).

- b. .Transfer plasma using sterile disposable 10 mL pipette to centrifugation tubes (Product Number 352196; 15 mL polypropylene Falcon tube; provided by the BCR), taking care to not disturb the buffy coat.
 - c. Recap Vacutainer® tube containing buffy coat and red cell mass and return to wet ice.
2. Centrifugation 2
 - a. Centrifuge the 15 ml tube containing the plasma at 2000 g at 4° C for 15 minutes to remove all potentially remaining cells.
 - b. Transfer the top 2.5 ml of the supernatant into 2.0 mL cryovials (~1.25 ml per vial; Corning Product Number 430488; provided by the BCR with a blue cap insert).
 - c. Product Number 430488; provided by the BCR with a blue cap insert).
 3. Transfer buffy coat and red cell mass (using sterile disposable 10 mL pipette) into 2.0 mL cryovials (~1.50 mL per vial; Corning Product Number 430488; provided by the BCR with a white cap insert).
 4. Immediately freeze tubes containing the processed plasma and buffy coat/red cell mass and freeze in LN2 vapor.
 5. Complete the appropriate section of the CPTAC Submission CRF.
 6. Store at vapor phase LN2 temperature until shipping to the CPTAC BCR.

Attachment 2: Invoice Instructions

Cost Reimbursement

Format: Invoice requests may be submitted on the payee's letterhead or self-designed form provided that it contains the information described herein.

Submission: Invoices shall be provided in electronic format (pdf or other commonly used format) and submitted to: apinvoices@mail.nih.gov.

Frequency: Invoice requests submitted in accordance with the Payment Clause shall be submitted no more frequently than monthly unless otherwise authorized by the Leidos Biomedical Research, Inc. (Leidos Biomed) Contracting Officer.

Cost Incurrence Period: Costs incurred must be within the Agreement performance period or covered by pre-contract cost provisions.

Billing of Costs Incurred: If billed costs include: (1) costs of a prior billing period, but not previously billed; or (2) costs incurred during the contract period and claimed after the contract period has expired, the amount and month(s) in which such costs were incurred shall be cited.

Subcontractor's Fiscal Year: Invoices shall be prepared in such a manner that costs claimed can be identified with the Subcontractor's fiscal year.

Currency: All Leidos Biomed agreements are expressed in United States (U.S.) dollars. When payments are made in a currency other than U.S. dollars, billings on the Agreement shall be expressed, and payment shall be made, in that other currency at amounts coincident with actual costs incurred. Currency fluctuations may not be a basis of gain or loss to the Subcontractor. Notwithstanding the above, the total of all invoices paid under this Agreement may not exceed the U.S. dollars authorized.

Costs Requiring Prior Approval: Costs requiring the Contracting Officer's approval, which are not set forth in an Advance Understanding in the contract shall be so identified and reference the Leidos Biomed Contracting Officer's Authorization. In addition, any cost set forth in an Advance Understanding shall be shown as a separate line item on the request.

Invoice Submission: Each invoice shall be identified as either:

- **Interim Invoice:** These are interim payment requests submitted during the performance period.
- **Final Invoice:** A final invoice may be required after the amounts owed have been settled between Leidos Biomed and the Subcontractor (e.g., resolution of all suspensions and audit exceptions).

Cost Reimbursement Invoice Preparation and Documentation Requirements

The Subcontractor shall furnish the information set forth in the explanatory notes below.

- (a) **Designated Billing Office Name and Address** — Enter the designated billing office name and address, identified in the Invoice Submission Instructions, on all copies of the invoice.
- (b) **Invoice Number** — Insert the appropriate serial number of the invoice.
- (c) **Date Invoice Prepared** — Insert the date the invoice is prepared.
- (d) **Agreement (and, if applicable, Task Order) Number and Date** — Insert the Agreement (and, if applicable, Task Order) number and the effective date of the Agreement (or Task Order).
- (e) **Payee's Name and Address** — Show the Subcontractor's name (as it appears in the Agreement), correct address, and the title and phone number of the responsible official to whom payment is to be sent. When an approved assignment has been made by the Subcontractor, or a different payee has been designated, then insert the name and address of the payee instead of the Subcontractor.
- (f) **Total Estimated Cost of Agreement** — Insert the total estimated cost of the Agreement (or Task Order), exclusive of fixed-fee. For incrementally funded Agreements, enter the amount currently obligated and available for payment.
- (g) **Total Fixed-Fee** — Insert the total fixed-fee (where applicable). For incrementally funded Agreements (or Task Orders), enter the amount currently obligated and available for payment.
- (h) **Billing Period** — Insert the beginning and ending dates (month, day, and year) of the period in which costs were incurred and for which reimbursement is claimed.
- (i) **Amount Billed for Current Period** — Insert the amount billed for the major cost elements, adjustments, and adjusted amounts for the current period.
- (j) **Cumulative Amount from Inception** — Insert the cumulative amounts billed for the major cost elements and adjusted amounts claimed during this Agreement.
- (k) **Direct Costs** — Insert the major cost elements. For each element, consider the application of the paragraph entitled "Costs Requiring Prior Approval" on page 1 of these instructions.
 - 1. **Direct Labor** — Provide breakdown of each labor category, hours worked (or percentage of effort), and hourly rate (or annual salary) charged and amount billed. (Time cards may be requested on a random basis.)
 - 2. **Fringe Benefits** — Cite rate, amount, and base to which it is applied and amount billed. If rate has changed since award, explain the rationale for the change.

3. **Accountable Personal Property** — Include permanent research equipment and general purpose equipment having a unit acquisition cost of \$5,000 or more and having an expected service life of more than two years, and sensitive property regardless of cost (see the DHHS Contractor's Guide for Control of Government Property). Show permanent research equipment separate from general purpose equipment. Prepare and attach form entitled Report of Capitalized Nonexpendable Equipment, which may be requested from the Leidos Biomed Subcontract Administrator.

List each item for which reimbursement is requested. A reference shall be made to the following (as applicable):

- The item number for the specific piece of equipment listed in the Property Schedule.
- Leidos Biomed Contracting Officer's approval letter and number if the equipment is not covered by the Property Schedule.
- Be preceded by an asterisk (*) if the equipment is below the approval level.

Further itemization of invoices shall only be required for items having specific limitations set forth in the Agreement.

4. **Overhead** — Cite rate, amount, and base to which it is applied and amount billed. If rate has changed since award, explain the rationale for the change.
5. **Materials and Supplies** — Include equipment with unit costs of less than \$5,000 or an expected service life of two years or less, and consumable material and supplies regardless of amount. Attach invoices from vendors or a consolidated listing providing individually listed equipment/supplies and the amount paid.
6. **Premium Pay** — List remuneration in excess of the basic hourly rate and attach the Contracting Officer's approval letter.
7. **Consultant Fee** — List fees paid to consultants. Identify consultant by name, hours worked, rate charged, and amount. (Attach consultant's invoice.)
8. **Travel** — Identify travelers, dates, destination, purpose of trip, and amount. Include domestic and foreign travel. Foreign travel is travel outside of the United States, and its territories and possessions. However, for an organization located outside the United States, and its territories and possessions, foreign travel means travel outside that country. Foreign travel must be billed separately from domestic travel. (Attach travel expense report.)
9. **Agreement Costs** — List the Subcontractor(s) by name and amount billed. Describe services provided. (Attach the Subcontractor invoices.)

10. **Other** — List all other direct costs in total unless exceeding \$1,000 in amount. If over \$1,000, list cost elements and dollar amounts separately. If the Agreement contains restrictions on any cost element, that cost element must be listed separately. All costs related to specific protocols must be itemized by protocol number as a subsection of each Agreement (and, if applicable, Task Order).
- (l) **Cost of Money (COM)** — Cite the COM factor and base in effect during the time the cost was incurred and for which reimbursement is claimed.
- (m) **Indirect Costs** — Overhead or General and Administrative Costs (G&A) Cite rate, amount, and base to which it is applied and amount billed. If rate has changed since award, explain the rationale for the change.
- (n) **Fixed-Fee Earned** — Cite the formula or method of computation for the fixed-fee (if any). The fixed-fee must be claimed as provided for by the Agreement. Any withholding amount must be shown separately.
- (o) **Total Amounts Claimed** — Insert the total amounts claimed for the current and cumulative periods.
- (p) **Adjustments** — Include amounts conceded, outstanding suspensions, and/or disapprovals subject to appeal. (Provide explanation and rationale for adjustment.)
- (q) **Grand Totals**

Fixed Price Invoice Instructions

General: The Subcontractor shall submit Invoices as prescribed herein.

Format: Invoice requests may be submitted on the payee's letter-head or self-designed form provided that it contains the information described herein.

Submission: Invoices shall be provided in electronic format (pdf or other commonly used format) and submitted to: apinvoices@mail.nih.gov.

Frequency: Invoices shall be submitted upon delivery of goods or services unless otherwise authorized by the Leidos Biomed Contracting Officer.

Preparation and Itemization of the Invoice: The invoice shall be prepared in ink or typewritten as follows:

- (a) Designated billing office and address.
- (b) Invoice number.
- (c) Date of invoice.
- (d) Agreement (and, if applicable, Task Order) number and date.
- (e) Payee's name and address. Show the Subcontractor's name (as it appears in the Agreement), correct address, and the title and phone number of the responsible official to whom payment is to be sent. When an approved assignment has been made by the contractor, or a different payee has been designated, then insert the name and address of the payee instead of the contractor.
- (f) Description of goods or services, quantity, unit price (where appropriate), and total amount.
- (g) Charges for freight or express shipments other than F.O.B. destination. (If shipped by freight or express and charges are more than \$25, attach prepaid bill.)
- (h) Equipment. If the purchase of equipment is authorized, invoice shall include a list of equipment purchased with associated receipts (regardless of purchase price) and a completed Capitalized Nonexpendable Equipment form, which may be requested from the Leidos Biomed Subcontract Administrator.

Currency: All Leidos Biomed Agreements are expressed in United States (U.S.) dollars. When payments are made in a currency other than U.S. dollars, billings on the Agreement shall be expressed, and payment shall be made, in that other currency at amounts coincident with actual costs incurred. Currency fluctuations may not be a basis of gain or loss to the Subcontractor. Notwithstanding the above, the total of all invoices paid under this Agreement may not exceed the U.S. dollars authorized.

Attachment 3: Price Schedule

Attachment 4: Travel Costs and Reimbursement Policy

Domestic Travel

Total expenditures for domestic travel (transportation, lodging, subsistence, and incidental expenses) incurred in direct performance of this Agreement shall not exceed the amount agreed to in approved Price Schedule without prior written approval of the Leidos Biomed Contracting Officer. Domestic travel encompasses all trips within the continental United States, Alaska, Hawaii, Puerto Rico, the Northern Mariana Islands, and the territories and possessions of the United States. Additionally, domestic travel will be reimbursed in accordance with the Federal Acquisition Regulation (FAR) and the Federal Travel Regulations (FTR), prescribed by the General Services Administration, as defined below:

Foreign Travel

Total expenditures for foreign travel (transportation, lodging, subsistence, and incidental expenses) incurred in direct performance of this Agreement shall not exceed the amount agreed to in approved Price Schedule without prior written approval of the Leidos Biomed Contracting Officer. Foreign travel encompasses all trips outside the continental United States, except for travel to Alaska, Hawaii, Puerto Rico, the Northern Mariana Islands, and the territories and possessions of the United States. All other destinations, including Canada and Mexico, are considered to be foreign travel. Additionally, foreign travel will be reimbursed in accordance with the FAR and the FTR, prescribed by the U.S. Department of State as defined below:

Documentation (i.e., itemized receipts) to support all actual travel costs incurred will be provided with each invoice request. In addition, identify all travelers, dates of travel, destination, and purpose of trip.

Lodging

Domestic and foreign lodging will be reimbursed for actual expenses, not to exceed the maximum lodging per diem permitted by the FTR. All requests for reimbursement of lodging expenses must be supported by a receipt. Domestic lodging per diem rates can be accessed at the General Services Administration website <http://www.gsa.gov> by clicking on "Per Diem Rates". Foreign lodging per diem rates can be accessed at the U.S. Department of State website <http://www.state.gov> by clicking on "Per Diem Rates" under Quick Links. Domestic per diem rates do not include lodging taxes. Actual taxes associated with lodging will be reimbursed provided a receipt is made available. Foreign per diem rates include all lodging taxes. Actual lodging expenses will only be reimbursed up to the FTR foreign lodging per diem amount.

A deviation from the allowable lodging per diem may be requested in certain situations. Examples of situations warranting such a deviation are: (1) when a conference, seminar, or meeting is held at a hotel that does not offer rates within the FTR, (2) lodging expenses are offset by savings in transportation expenses, and (3) Government per diem rates are not available or obtainable at the destination. All requests for deviations from the maximum lodging per diem rate require Leidos Biomed Contracting Officer approval prior to travel.

In the event the traveler deviates from the allowable lodging per diem rate in effect at the time of travel, and is not a result of the warranted deviations suggested above, the traveler will be reimbursed up to the maximum lodging per diem rate and will absorb any excess cost over the approved per diem rate. The Subcontractor will be responsible for excess costs and any additional expenses incurred for personal preference or convenience. A receipt must still be provided for reimbursement up to the maximum allowable per diem rate.

Meals and Incidental Expenses

Meals and incidental expenses (M&IE) for domestic and foreign travel will be reimbursed according to the maximum allowable per diem for meals and incidental expenses as determined by the FTR. Domestic meals and incidental per diem rates can be accessed at the General Service Administration website <http://www.gsa.gov> and by clicking on "Per Diem Rates". Foreign meals and incidental per diem rates can be accessed at the U.S. Department of State website <http://www.state.gov> by clicking on "Travel and Business" and then clicking on "Foreign Per Diem Rates." M&IE rates cover expenses for breakfast, lunch, dinner, and related tips and fees. Incidentals are used for fees and tips given to porters, baggage carriers, bellhops, hotel maids, and dining room stewards/stewardesses. The allowance for M&IE on the first and last day of travel will be 75% of the applicable M&IE rate for both domestic and foreign travel. Specifically excluded costs that are non-reimbursable are alcoholic beverage and entertainment expenses, and any expenses incurred for other persons.

Airfare Costs

For air travel, coach-class or equivalent must be utilized. All travel, both foreign and domestic, must use a U.S. flag air carrier service. In special or unusual situations, airfare costs in excess of coach-class or equivalent may be allowable only upon a written and warranted justification for use of the higher amounts. All requests for accommodations other than coach-class or equivalent require Leidos Biomed Contracting Officer approval prior to travel.

Mileage Costs

The cost of using a private automobile will be reimbursed in accordance with the current "Privately Owned Vehicle (POV) Reimbursement Rate" as set forth in the FTR, prescribed by the General Service Administration <http://www.gsa.gov>. (Click on "POV Mileage Reimbursement Rates.") The rate covers all costs of operation of the automobile. Mileage is based on the standard miles of the "shortest route" as indicated by commercially available websites providing driving directions. Provide the printout from the website used which shows the resulting mileage.

Automobile Rentals

Requests for rental cars are to be included in the original travel package with appropriate justification. Approval from the Leidos Biomed Contracting Officer must be obtained prior to any automobile rentals. Costs specifically excluded and non-reimbursable are the costs of purchasing extra collision or personal liability insurance, GPS systems, bike racks, or ski racks.

Miscellaneous Costs

The use of taxis, shuttles, and other public transportation will be reimbursed at actual cost. Parking and tolls incurred while traveling will be reimbursed at actual cost; however, the most economical means for parking must be utilized. Garage or valet parking will not be reimbursed, unless this is the only option or a special need justifies this sort of parking. Receipts are required for reimbursement of all transportation expenses.