Attachment I

Date Prepared: _2/15/2010___

REQUEST FOR EC/BSA CONCEPT APPROVAL
REQUESTS FOR APPLICATIONS (RFAs)/CONTRACTS (RFPs)

Title: Clinical Proteomic Technologies for Cancer Re-issuance

RFA _X__ Coop. Ag. _X___ RFP_X___ Activity Code (e.g. R01): U24

Limited Comp. _____ New ___ Reissue _X__

Division/Office/Center: OD/CSSI Division/Office/Center Co-sponsor(s): _____	Program Director: Henry Rodriguez *(Signature)* Division/Office/Center Director: *(Signature)*
Length of Award (Yrs.) 5 Anticipated Award Date: 09/01/2011	Source of Funds: RPG __ Control __ Centers __ Other Res: _X___Construct ____ NRSA _____
RFAs (Set Aside): RFA 01 Yr: $15-24M RFP 01 Yr: $2.5M (single issuance only) Amount of Set Aside 01 Year: $17.5-26.5M	Est. Number of Awards: U24 (6-8) RFP (Data Coord. Ctr., Biospecimens, Reagents) Est. Cost for Total Project Period: $87.5-132.5M
Justification for Use of RFA/RFP Mechanism: Attached: Yes Congressional Mandate:_____ Other: _____	New issuance: Are evaluation criteria included? ___ Reissuance: Is the evaluation included? Yes *(Large infrastructure only)*

NCI Clinical Proteomic Technologies for Cancer: RFA re-issuance

Overview: In the past few years we have made great strides in characterizing and sequencing the genomic alterations in statistically robust numbers of samples from several types of cancer. The Cancer Genome Atlas (TCGA), and other similar efforts to catalog this array of changes in the cancer genome, will most certainly provide a foundation for defining these myriad changes –and set the stage for the development of more molecularly targeted interventions. To achieve the promise of these rich multi-dimensional genomic data sets requires an understanding of the functional changes that derive from these genetic alterations. Proteomics offers our best hope of translating this new knowledge into effective biomarkers that can drive the development of new diagnostics and therapeutics for most cancers. However, significant problems in proteomics research such as a lack of reproducibility across laboratories, proper study design and a notable absence of standards, high-quality reagents for the field have historically represented a significant barrier to progress in achieving the vision of biomarker-driven molecularly-based personalized cancer medicine.

Proteomics methods based on mass spectrometry holds special promise for the discovery of novel protein targets that might form the foundation for new clinical tests, but to date their contribution to the diagnostic armamentarium has been disappointing. This is due in part to the lack of a coherent pipeline connecting marker discovery with well-established methods for clinical validation (qualification). As a result, among the critical challenges facing the proteomics community is the lack of an ability to accurately and reproducibly measure a meaningful number of proteins in biospecimens across institutions. Better understanding of the challenges and strategies inherent in each phase of the proteomics pipeline is required to both accelerate the pace and quality of biomarker development and facilitate the delivery and deployment of novel clinical tests.

To address many of the critical challenges facing the protein biomarker community, the NCI launched the Clinical Proteomic Technologies for Cancer (CPTC) in 2006. The overall goals of CPTC were focused on removing several of the major barriers in proteomics research to enable the accurate, efficient and reproducible identification, and quantification of meaningful numbers of proteins that could drive high value clinical biomarker qualification studies. Achieving this goal would provide a firm foundation for the field of discovery proteomics and enable the rational development of clinical biomarkers to address various needs in cancer drug development, diagnostics and clinical management.

Since its launch, CPTC has achieved significant success in developing an accurate and quantitative technology pipeline for proteomics, technology standards, standard operating procedures, data standards, molecular-based tools, critically needed reagents and an open proteomics database. The new protein biomarker workflows developed by CPTC address the variability of methods and technologies – which enables researchers to accurately and quantitatively identify large numbers of proteins. As a result, CPTC has quickly evolved into a national (and international) resource that links technologists with cancer biologists and clinicians to accelerate the development, improvement and standardization of proteomic technologies for the detection of cancer-relevant proteins/peptides in clinical biospecimens.

This request for competitive reissuance of the CPTC program seeks to leverage and continue to build on the advances from the first phase of the program (e.g., proteomic technology optimization and development, technology and data standards, biospecmens, and reagents) to systematically explore the functional cancer proteome that derives from defined alterations in cancer genomes. CPTC, Phase II, will initially utilize data and biospecimens from TCGA to define and credential an array of proteins that can be further qualified and validated by other NCI programs such as the Early Detection Research Network, the Cooperative Groups and the broader cancer research community. Achievement of the goals of this reissuance for CPTC will advance the science of cancer proteomics and offers to address the growing gap between muti-dimensional data at the genomics level and the functional translational knowledge needed to support the cancer research community in their efforts to develop new clinically meaningful protein biomarkers.

Background and Accomplishments of CPTC: The overarching goals of CPTC were outlined in RFAs (CA-07-012 and -005) published in 2006. CPTC was charged by the BSA not to do biomarker discovery, but rather to address the lack of technology reproducibility and transferability across labs (technology assessment), and a lack of quality reagents (mAbs) and resources (data sets, standards) available to the cancer community. In the current funding period, these goals are being met or exceeded by the coordination of three major components of the CPTC program:

- Clinical Proteomic Technology Assessment for Cancer network (CPTAC network; U24 mechanism): provides funds for a geographically dispersed network multidisciplinary team of 5 centers to collaborate on research that would increase the understanding of experimental and analytical sources of error to existing technologies and to provide a basis for enabling proteomics science and development in the form of technology and other standards, metrics and reference datasets.
- Advanced Proteomic Platforms and Computational Sciences Program (APPCS; R01, R21, R21/33 mechanisms): provides grants for 15 individual investigators to develop novel tools and algorithms related to improving the reliability and accuracy of proteomics technologies.
- Proteomic Reagents and Resources component (PRRC; RFP mechanism): provides access to high quality, well-characterized reagents (e.g. antibodies), data, and standard reference materials for the research community.

The first 3.5 years of this program have shown the effectiveness of this multidisciplinary, multi-institutional approach in addressing the long-standing problems of variability issues in proteomics resulting in large measure from analytical platforms rather than assessing real biological differences. In this setting, the work of CPTAC network to develop new workflows that address the variability of mass spectrometric methods and technologies, enabling researchers to more confidently study protein relationships in cancer biology have been highly successful. More importantly, through this trans-network collaboration, the CPTAC centers achieved a major milestone that promises to provide support for a real level of evidence model for biomarker candidates. Known as the "verification" phase, achieved via optimized MRM mass spectrometry, this approach finally allows for a "pipeline" approach to the development of proteomic biomarkers. Given the qualification requirements by the FDA for new cancer biomarkers this approach offers a unique opportunity to stage biomarkers into qualification by FDA and validation in expanded clinical studies.

Examples of Specific CPTC Accomplishments. A major problem for the development of proteomics is the lack of inter- and intra-laboratory reproducibility. The CPTAC network has shown, through the development of performance standards, Standard Operating Procedures (SOPs), high-quality reagents, and access to historical analytical reference data, that proteomic analysis (specifically mass spectrometric measurements) is reproducible and quantitative within and across platforms and institutions. In addition, the CPTAC network developed the innovative concept of candidate "verification" via optimized MRM mass spectrometry. Verification of candidates relies upon specific, quantitative assays optimized for selective detection of target proteins, and is increasingly viewed as a critical step in the proteomics pipeline that bridges unbiased biomarker discovery to qualification. Using common materials and standardized protocols, the CPTAC network demonstrated that targeted, quantitative and multiplexed MS-based assays can be rapidly configured and deployed in multiple laboratories to yield robust and reproducible assays for proteins in biospecimens. This "bridging technology" now serves as a reliable and effective attritional process aiming to accelerate translation of new protein candidate discoveries into clinical applications. In short, the clinical proteomics pipeline developed by the CPTAC network (a metric driven characterization stage followed by a quantitative targeted multiple-reaction monitoring [MRM] verification stage, prior to candidate qualification) has achieved an unprecedented level of proteomic data quality and reproducibility across laboratories that is critical to advancing proteomics as a reliable and quantitative science - a first step in the process of moving protein discoveries from the laboratory into the clinic.

In short, the pipeline developed by CPTC produces the highest-quality data that is reproducible and quantitative across labs and institutions. Some selected accomplishments from the first years of the program include:

- Biospecimen QA: Developed SOP for collection, processing, and storage of plasma and tissue (in coordination with OBBR and David Ransohoff); Established a blood (plasma) repository collected prior to diagnosis, to avoid bias; Developed a multisite biospecimen tracking database (DB) with strong pathology annotation; Developed a centralized biorepository (NCI-Frederick) with distribution SOPs.
- Technology Reproducibility and Transferability:
    - Global protein characterization (shotgun MS/MS): First quantitative assessment of discovery proteomics technology platforms across laboratories; Developed a standard reference material for MS/MS platforms (NIST converting into certified Standard Reference Material); Developed quality control tool to monitor and troubleshoot instrument performance (NIST developed).
    - Quantitative protein measurements (MRM-MS/MS): First large-scale, multi-institutional evaluation of targeted MS technology (MRM-MS); Demonstrated that multiplexed, quantitative MRM-MS-based

assays can be rapidly and robustly configured and deployed for measurement of proteins in biospecimen.

- High-Quality Reagents: Developed NCI's Antibody Characterization Laboratory, including public website (antibodies.cancer.gov) listing reagents and SOP-driven characterization data.
- Data Production, Analysis, and Sharing: Developed a robust, common data analysis pipeline; Developed a caBIG-silver compliant public data sharing/storage portal (caTranche); Developed international data sharing policies (Amsterdam Principles).
- Strong scientific output including: 27 SOPs, 6 publically available reference datasets, 2 analytical performance mixtures, 7 filed patents, 26 software tools developed, 4 partnerships with federal agencies, 19 partnerships with academic institutions, 11 partnerships with biotechnology companies, 12 leveraged funding activities, 84 well-characterized monoclonal antibodies against cancer-associated proteins, numerous CPTC scientific presentations (a total of 386 consisting of 286 oral presentations, and 100 posters presentations), 22 non-NIH-sponsored program staff presentations in the United States, Europe, and Asia, and over 170 peer-reviewed publications in highly regarded scientific journals.
- Successfully partnered with governmental agencies including FDA (Food and Drug Administration) and NIST (National Institutes of Standards and Technology). Work with NIST has produced two standard reference materials and a quality control software tool that monitors and troubleshoots the performance of a mass spectrometer. CPTC has established and maintains a relationship with the FDA through an MOU, which has produced guidance documents in the form of mock 510(k) applications to aid the proteomics community in understanding the FDA clearance process of multiplex *In Vitro* Diagnostic tests.
- Partnered with the American Association for Clinical Chemistry (AACC) to educate/train clinical chemists on proteomic technology standards.
- Developed associations with 15 industrial entities (ranging from PI-initiated start-up companies to collaborations with large multi-national firms), providing a vital commercial outlet for developed technologies. Through the NCI SBIR program, CPTC partners with private companies and has awarded Phase I and Phase II NCI-sponsored SBIR contracts with 11 companies.
- Successfully reached out to the advocacy community through multimedia communication on the website and also by inviting advocates to participate in a variety of NCI activities, including, but not limited to, working groups, committees and boards, meeting attendance, workshops, and site visits.

In summary, although only 3.5 years old, the CPTAC network has succeeded in addressing issues of variability reproducibility across institutions in the protein biomarker development pipeline. The re-issuance RFA will allow for the outputs developed in Phase I to be applied to high quality clinical samples from TCGA (and other robust data sets as appropriate) for quantitative analysis of protein biomarker candidates as guided by genomic information.

Alliances and Collaborations. CPTC has reached out to a large number of organizations, regulatory and standards-setting bodies and the intramural and the intramural and extramural proteomics research communities. In turn, several organizations have reached out to CPTC for proteomics expertise and adoption of its advances and output. This recognition is evident that CPTC is a leader in efforts on clinical proteomic technologies and standards. Alliances and outreach activities include: NCI Intramural (CCR works with CPTC's antibody characterization program to develop mAbs for intramural research scientists); NCI Extramural (CRCHD collaborates with CPTC on cancer health disparities and advanced technologies; OBBR collaborates with a CPTAC center on biospecimen stability studies); NIH Intramural (NCBI collaborates with CPTC on proteomic data release quality metrics); NIH Extramural (NHLBI partnered with a CPTAC center for protein verification studies, and collaborates on data release policies; NHGRI collaborates with CPTC on the development of MRM mass spec technologies); Domestic (American Association for Clinical Chemistry [AACC] works with CPTC to promote standards and metrics to clinical chemists; Canary Foundation collaborates with a CPTAC center for protein characterization studies); journal *Molecular & Cellular Proteomics* collaborates with CPTC on proteomic data policies; FDA works with CPTC on analytical validation of protein-based multiplex technologies); International (Korea Institute of Science and Technology works with CPTC to further develop/implement MRM mass spectrometry and proteomic standards; European ProteomeBinders and Wellcome Trust are collaborating with CPTC on affinity reagent

standardization and data release policies); Industry (Millipore, Bio-Rad, and ImaGenes (Germany) are commercializing CPTC's reagents on their respective proteomic platforms).

Independent Evaluation of the CPTC Program In the spring of 2009 an independent evaluation of the program was commissioned by the Office of the Director, NIH and performed by Macro International (ICF Macro). ICF Macro's evaluation of the CPTC program focused on process and outputs with particular attention to program design, effectiveness of NCI program management, strategies towards promoting collaborations and cohesion in the network, and other topics. The interviews involved several groups: investigators, trainees, and proteomics experts not participating in the program, program staff from NCI, NIH, and staff of other federal agencies. An evaluation advisory committee (composed of 4 trans-NCI staff, 1 member from National Center of Research Resources, 1 unaffiliated academic, and 1 CPTC member) was formed to examine and determine the merit of the independent program evaluation performed by ICF Macro. The committee's assessment of the program and its recommendations for the continuation of CPTC are provided in the Evaluation Report and will be used in the development of new RFA. Briefly, the committee noted:

- A successful beginning of an integrated network that operates through a joint principal investigator –NCI governance structure resulted in the achievement of significant milestones, the development of multidisciplinary teams, numerous scientific achievements, and renewed promise in the field of proteomics;
- Need for the continuation and expansion of efforts between the FDA and CPTC in translating multiplex protein-based In Vitro Diagnostic technologies (and candidates) to the clinic;
- Need for the continuation of the CPTC program beyond the five-year mark to build upon the infrastructure and quantitative protein biomarker development pipeline established during the first 3.5 years of Phase I.

Purpose and Scope of RFA Reassurance: Building upon the strong foundation developed through the current initiative, the major goal of the next phase of the program will be to apply these robust and quantitative workflows to define functional proteins using data and biospecimens from cancer genomics programs such as The Cancer Genome Atlas (TCGA) to further scientific understanding of cancer at the functional level. This reissuance recognizes that the translation from gene to protein is not a clear-cut process. For example, proteins undergo several post-translational modifications (PTM), including phosphorylation, glycosylation, lipidation and cleavage. PTMs and a myriad of other protein-protein interactions that are also known to play a significant role in cancer processes cannot be ignored. This means that genomic characterization and sequencing data must be assessed at the proteomics level with similar stringency as a direct correlation is not to be expected to uniformly exist between the levels of gene transcripts and resulting protein expression. Together, enabling our understanding of these complementary and closely connected fields, genomics and proteomics, will enable building the required foundation for personalized cancer medicine. Projects such as TCGA are and will provide a catalogue of genomic alterations in cancer, which when combined with robust, reproducible and quantitative proteomic measurement, will allow a deeper understanding of cancer at the molecular level.

In the fall of 2009, leaders and experts from the extramural community, including representatives from academic, private industry, and regulatory agencies, were convened by the NCI at a workshop entitled *Implementation of a New Cancer Biomarker Development Pipeline* to discuss how best to optimize the output from this reissuance. In short, all of the attendees agreed that the CPTAC network of multidisciplinary teams should focus future efforts to take the next step in supporting the community as hey undertake efforts to functionalize these data. To accomplish these goals, the current reissuance will undertake the systematic exploration of these high quality multi-dimensional data sets and biospecimens using the robust protein analysis tools from the CPTACs to define the proteins that derive from these genomic alterations compared with controls. The attendees agreed that TCGA's multi-dimensional data and biospecimens represents an excellent opportunity to launch such an effort to best leverage the outputs from the first phase of CPTC – and this strategy will be pursued. While ultimately dependent on the ideas and concepts solicited from the cancer research community, the following workflow represents a potential overall anticipated model for the new CPTAC network (Figure 1). This will then be further refined by assembling suggestions and inputs from an additional workshop with the new CPTAC network members to assimilate other platforms and methodologies.

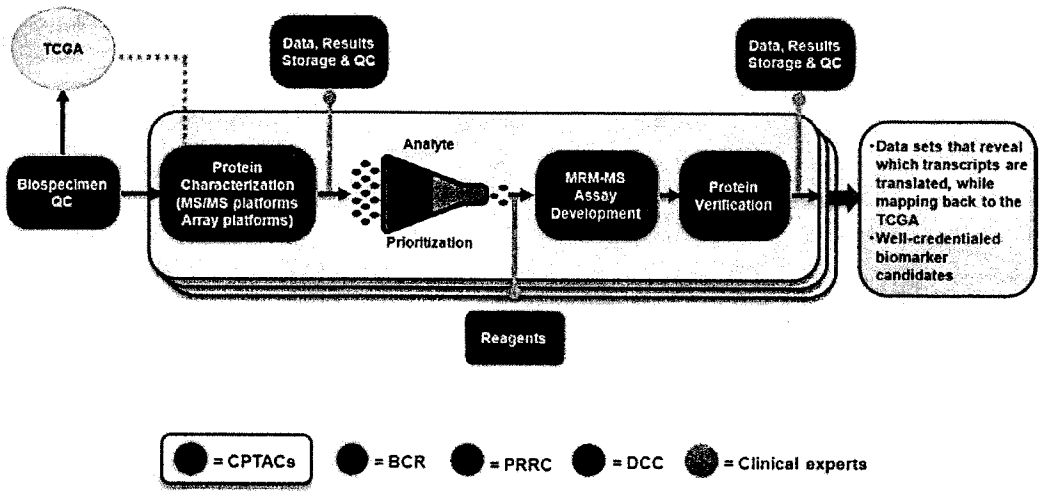

Figure 1. Proposed CPTC Phase II Workflow

A few expected outcomes of the project include (1) A proteome "map" based on large scale, high quality data and biospecimens corroborating, or complementing genomic findings in multiple tumor types; (2) a quality-ensured public database that stores, organizes, and makes accessible all data from the effort; (3) Development of validated multiplexed, quantitative protein assays, each with: biological evidence for its role in cancer, rigorous assay performance metrics provided by multiple laboratories, and statistically-powered, preliminary clinical data to demonstrate feasibility in the clinic; (4) Well-credentialed biomarker candidates that have been verified by the CPTC network that can then be handed off to enter the process of clinical qualification and validation for therapeutic response, prognostic indication, and/or early detection.

It is anticipated that the proteomic data, standard operating procedures, standards, etc. generated by this reissuance will stimulate advances in cancer research and provide opportunities for the discovery and development of new biomarkers and potential targets for cancer therapeutics. As in TCGA, this reissuance of CPTC will allow cancer researchers to develop the biomarkers needed to develop personalized treatment plans for each patient and allow clinical trials to focus on patients who are most likely to respond to specific treatments.

To implement all of the activities above, an *open competition* RFA will be reissued to solicit new CPTAC applications for the second phase of the CPTC program to ensure the proper influx of new ideas, technologies, and investigators. The proposed CPTAC centers will continue its current model of a multidisciplinary approach with milestone-driven programs consisting of two components:

- Network of CPTAC centers (U24 mechanism): In addition to continued activities of technology/software assessment and development, these U24 centers will consist of multidisciplinary teams that perform two primary functions:
  - Proteomic characterization. CPTAC centers will analyze common tumor tissues and blood for their protein content and correlate the results with those of TCGA and other large-scale genomics initiatives. Subsequently, within the context of cancer biology, the network will prioritize protein candidates for verification assay development.
  - Targeted verification of protein candidates. In the verification phase, centers will use the prioritized list of protein candidates to develop quantitative, multiplexed mass spectrometry (+/- affinity) assays for detection in tissue and blood. These assays will be analytically validated by multiple centers and verified in a statistically-powered number of biospecimens.
- Reagents and Resources Cores (RFP mechanisms): As in CPTC Phase I, several RFPs will be used to solicit applications to support the development of publicly accessible monoclonal antibodies and other reagents, begin development of a Data Coordinating Center with publicly accessible data, and biospecimen core resource in collaboration with caHUB.

The proposed re-issuance will solicit centers in the form of U24s focusing on implementing the newly enhanced technology foundations and advancing the field of cancer proteomics to empower cancer researchers to progress more rapidly toward the development of high quality biomarkers that are critical to realizing the promise of cancer

genomics and new clinical interventions. Applicants will be encouraged to assemble team with experts in genomics, proteomics, and other advanced emerging technologies.

As with the first phase, the program will continue to leverage experience and resources available at a multitude of other NCI programs and all of the Centers and Divisions as well as other NIH institutes.

3. Current Portfolio Analysis

NCI's investment in proteomics over the past 5 years has gone from $132M in 2005 to $269.3M in 2009. The current funding level of CPTC comprises less than 4.2% of the total NCI investment in proteomics in FY 2009 (Table 1).

Table1: NCI's Investment in Proteomics

FY	Total Awarded (million)	Total Awards
2005	$132.0	352
2006	$217.8	411
2007	$258.5	519
2008	$229.4	545
2009	$269.3	646

4. Justification for Use of Funding Mechanism

RFA Mechanism: The organizational complexity of CPTAC centers and diversity of involved science requires the use of special review panels, as for the previous CPTAC RFA. Given the wide range of expertise required to review these applications, it would be difficult for any existing CSR study sections to review submissions to this FOA. As such, an appropriate special emphasis panel built by NCI DEA would be required. In addition, to drive robust protein characterization and verification, significant infrastructure will need to be developed to facilitate sharing of protein candidates, data, and methodologies, all of which would be difficult to accomplish using an investigator-initiated mechanism.

Cooperative Agreement: CPTC is a highly integrated network in which the NCI's role goes well beyond the normal stewardship of awards. Developing scores of biomarker candidate assays requires a level of inter-laboratory coordination unparalleled in typical academic research. NCI program staff members interact frequently with awardees in order to coordinate inter-laboratory studies, to develop baseline protocols, to promote a collaborative environment across the CPTC network, and to help maintain the scientific vision of the program. Direct communication between an investigator and NCI program staff allows for substantive involvement to guide project direction and preempt any possible delays or complications concerning achievement of project aims and milestones. The U24 mechanism allows for an *active program management* structure ensuring frequent and close communication between investigators and the NCI program staff members. The U24 is specifically designed for grants developing research resources. As such, continuation of this initiative under the U24 mechanism is the best forward strategy.

RFP Mechanism: Contracts will be used for reagents and resources. This includes monoclonal antibodies, a Data Coordinating Center and biospecimens. The materials and services acquired through this mechanism will support the CPTAC network as well as the greater cancer proteomics community. Because an RFP mechanism enables the NCI to better insure sufficient quality of these reagents, and since the materials acquired through this component do not require new innovation or research, an RFP is believed to the best mechanism to support these efforts.

5. Budget

The requested funding will allow for 1) a sufficient number of NCI's CPTAC centers to advance proteomics science through the network, and 2) providing reagents and resources for the CPTAC network as well as reproducible protein-based assays for the greater cancer community. The budget requested for the re-issuance is proposed as follows: 6 to 8 (U24) centers, and contracts to support reagents and resources (Table 2). Estimated total project period (5 years), would be $87.5-132.5M.

Table 2. Original and Projected Re-issuance Budget for CPTC

Mechanism	Total/year	Total budget
• CPTC Initiative	$21M	$104M
• CPTC Re-issuance	$17.5-26.5M	$87.5-132.5M

6. Evaluation Criteria for RFA

A. Evaluation of the CPTC Program by the NCI CSSI

The initial goals of the CPTC plan have been met or exceeded including the development of several SOPs, analysis tools, and a robust trans-network verification pipeline. To evaluate the second phase of the CPTC program on an ongoing basis, a matrix of quantitative performance measures will be added in addition to those established in the first phase of the program.

(1) The number of genetic aberrations confirmed by proteomic data,
(2) The number of protein candidates considered for quantitative verification,
(3) The number of new platforms and methodologies matured through trans-network testing,
(4) The number of quantitative protein assays developed and analytically validated,
(5) The number of well-credentialed biomarkers delivered for qualification studies.