



An Extended Feasibility Analysis of the Clinical Proteomic Technologies for Cancer Initiative



December 2, 2009

To: Henry Rodriguez
Director, Clinical Proteomic Technologies for Cancer

From: Evaluation Advisory Committee

Re: Process/Outcome Evaluation of the Clinical Proteomic Technologies for Cancer Initiative

The Advisory Committee examined the Clinical Proteomic Technologies for Cancer (CPTC) Initiative evaluation entitled "An Extended Feasibility Analysis of the Clinical Proteomic Technologies for Cancer Initiative" and is in agreement with the assessment. The program evaluation was conducted after a feasibility study (completed February, 2008) determined that the program could be evaluated in terms of its effects on the proteomic research community. The focus of the evaluation was on processes and short term outcomes, as the program is at its midway point (launched in Fall, 2006) and could not be evaluated using intermediate or long term outcomes.

Macro International (ICF Macro) conducted both the feasibility and the program evaluation. An evaluation study framework and study guides were developed and approved before the evaluation began. The program evaluation was a qualitative assessment utilizing interviews as a main source of data. The focus of the program evaluation was on cooperation within the program's centers (CPTAC), to ultimately yield high quality inter-laboratory studies which have led to multiple publications.

In short, the goal of CPTC is to enhance technical abilities to identify and measure proteins accurately and reproducibly in biological systems. Additionally, the advancement of proteomics as a reliable, quantitative field that can accelerate discovery and translational research is a goal of the program. To accomplish these goals, three integrated programs or cores within CPTC were created:

- The Clinical Proteomic Technology Assessment for Cancer (CPTAC) network – multidisciplinary team-based science conducting rigorous assessment of technologies currently used to analyze proteins and peptides
- The Advanced Platforms and Computational Sciences Program – individual investigators focused on the development of innovative new tools and algorithms for enhancing the accuracy of protein/peptide measurements
- The Proteomic Reagents and Resources Core – provides access to high quality, highly characterized, reagents (e.g. antibodies), reference materials and data.

Concurrently with this evaluation, the Program developed a 2009 annual report which provides an overview of program successes and quantitative outputs. This annual report in conjunction with the program evaluation serves as a full analysis of the CPTC program to date.

A summary of measurable programmatic outputs highlighted in both the evaluation and annual report include publications (171), standard operating procedures (27), patents (7), software tools (27), monoclonal antibodies (84), partnerships with biotechnology companies (11), partnerships with federal agencies and professional organizations (4), partnerships with academic institutions (19), leveraged funding activities (12), and a total number of organizations which make up CPTC (>60).

In summary, the Advisory Committee recognizes that CPTC has achieved significant milestones and believes that the long term potential of CPTC; will place it and the field of proteomics as a key component in initiatives for personalized medicine.

Advisory Committee (Drs. Jessup, Gallahan, Old, Blair, Solomon, Aragon, Hiltke)



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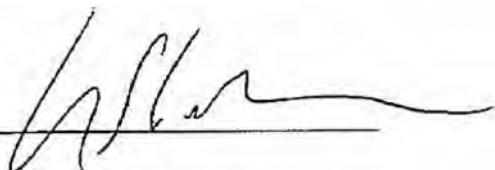


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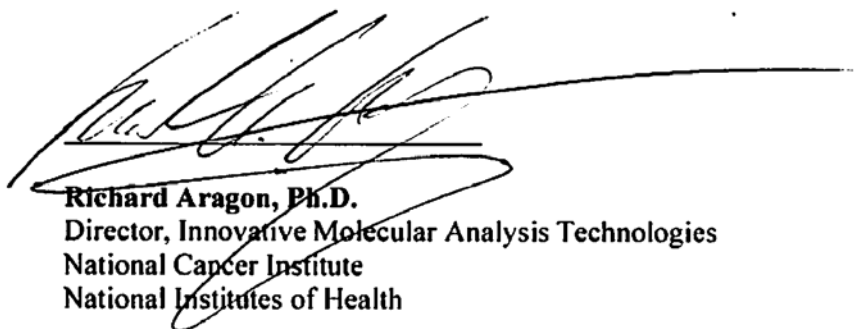
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April 2, 2009

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Dear Dr. Rodriguez:

I write in support of your proposal to evaluate the NCI Clinical Proteomic Technologies for Cancer (CPTC) initiative, a program established to address analytical and pre-analytical variables in a protein biomarker pipeline. Such a pipeline will either provide credentialed biomarker candidates for a large clinical validation study or provide an efficient means of attrition indicating that an analyte cannot be effectively verified using current technology. I understand that the proposed combination of process and short term outcome evaluation will assess the extent to which the CPTC program has been implemented as intended.

In my capacity as Program Director, Technology Development for Systems Biology, at NCRR, I can endorse both CPTC and this evaluation. NCRR supported Biomedical Technology Research Centers (BTRCs) in proteomics and glycomics and the NIH Roadmap-funded National Technology Centers for Networks and Pathways (TCNP), for which I serve as project team leader have as part of their mission the development of advanced technologies for biomarker discovery and validation, and the translation of these technologies for clinical application. CPTC complements and extends the efforts in these programs. A major challenge in proteomics is the validation of technologies and methods across laboratories and for larger study populations. The CPTC goal of creation of a systematic approach for translation of putative proteomic biomarkers from the discovery phase through validation and into a clinical setting is an area of unrealized potential which if successful will benefit both translational and basic research.

NCRR-supported BTRCs have participated in and contributed technologically to CPTC. Richard Smith, Director of the Proteomics Research Resource for Integrative Biology at Pacific Northwest National Laboratory is co-investigator on one of the CPTC teams, and Phil Andrews, Director of the National Resource on Proteomics and Pathways at the University of Michigan has applied technology created in that center to contribute significantly to the informatics infrastructure of CPTC. I expect that other relationships will continue to form as the program progresses.

I look forward to this evaluation determining which aspects of CPTC are working and which ones need modifications, defining next steps for the program.

Sincerely,

A handwritten signature in black ink, reading "Douglas M. Sheeley".

Douglas M. Sheeley, Sc.D.
Program Director, NCRR



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
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March 16, 2009

Henry Rodriguez, PhD, MBA
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National Cancer Institute

Dear Dr. Rodriguez:

This is in response to your request of writing a letter for the evaluation of the Clinical Proteomic Technology Assessment for Cancer program. I have been following with interest the National Cancer Institute initiatives in the area of proteomics and in particular the technology development initiatives that were initiated in 2004.

The field of proteomics and the development of proteomic technologies that can be applied to a clinical setting have been largely underfunded by the NIH. The NCI has been one of the few NIH institutes that have taken a leadership role in proteomics and I am very supportive of the significant investments that were made in technologies and standards development. Considering the very early stage of the proteomic field, investments in technology as they apply to cancer will benefit the community at large and will help in setting the stage for the application of proteomics also to other diseases of interest to the National Institutes of Health.

As a proteomic expert that has worked in this field for almost 20 years I should add that despite the obvious limitation of applying genomics to the diagnosis and treatment monitoring of complex diseases, proteomics has been by large less funded. This is also partially due to the technological challenges that are intrinsic to proteomic studies. It is refreshing to see that the National Cancer Institute has been taking a bold approach in tackling several of the key issues that have been hampering progress in proteomics. The Clinical Proteomic Technology Assessment for Cancer program has been a key program for the proteomic community and I certainly hope that it will continue to be fully supported by the NCI.

Sincerely,

A handwritten signature in dark ink, appearing to read "Salvatore Sechi", is written over a light blue horizontal line.

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EXECUTIVE SUMMARY

Proteomic biomarkers could provide a means for detecting cancer in its earliest stages. Although a substantial number of biomarkers have been identified, few have been reproduced, a necessary outcome for translating these discoveries to clinical settings. Reproducibility is not only affected by the technological difficulties associated with detecting proteins in low concentration but also by measurement error due to the varying technologies and methodologies used at different laboratories. The Clinical Proteomic Technologies for Cancer (CPTC) program was initiated in 2006 to address this concern. CPTC's main goal is to enhance technical abilities to identify and measure proteins accurately and reproducibly in biological systems.

The program consists of three components:

- **Clinical Proteomic Technology Assessment for Cancer (CPTAC)**—This component provides funds to five institutions to collaborate on research that would increase the understanding of experimental sources of error and to provide a basis for communicating findings to the field in the form of standard operating procedures (SOPs).
- **Advanced Proteomic Platforms and Computational Sciences (APPCS)**—This component provides grants to individual investigators to develop platforms or algorithms related to proteomic research.
- **Proteomic Reagents and Resources Core (PRRC)**—This component aims to develop high quality, well-characterized monoclonal antibodies for the research community.

In fall 2008, a feasibility study was conducted to determine whether CPTC could be evaluated in terms of its effects on the proteomic research community. The report indicated that too little time has elapsed since the program's inception for it to be evaluated on intermediate or long-term outcomes. However, the study suggested that an analysis of processes, outputs, and short-term outcomes could be conducted and would be beneficial. In late spring 2009, an assessment was funded. Research questions for the assessment are shown in the accompanying text box.

Research Questions for This Assessment

- To what extent has the program advanced collaboration in the proteomic biomarker research area?
- To what extent has CPTC had an effect on accelerating the identification of verified proteomic biomarkers for specified cancers?
- To what degree has the process of validating cancer biomarkers been facilitated?
- To what degree are program outputs used by the general cancer research community in their investigations?
- To what extent have CPTC outputs been accepted among cancer research scientists?
- To what extent has the quality of the CPTC reagents and products been demonstrated?
- To what degree are users of CPTC reagents and products satisfied with their quality and utility?
- To what extent have the outputs been used in publications relating to biomarker research?
- To what degree is the infrastructure built by CPTC sustainable?



During CPTC's three years of existence, its achievements can be gauged not merely by its knowledge generation activities, but also by its overcoming start up issues concerning the formation of an effective collaboration among the participating institutions and stakeholders. The importance of this effective collaboration lies at the basis of knowledge generation, and in current and subsequent product dissemination. To date, this collaboration constitutes one of the more important outcomes of the program, and will prove critical for also describing CPTC's success to date and in future years. During start-up, the challenges of establishing both the CPTAC and PRRC components were different from those of establishing the APPCS component in that both CPTAC and PRRC needed to establish networks of researchers, partners, and collaborators. The CPTAC component used a "U" funding mechanism in order to have substantial Federal scientific or programmatic involvement, while the PRCC operated through contracts. The APPCS component faced the more familiar management challenges faced by all of NIH's traditional "R" research grant programs, in which the grantee/principal investigator generally works alone or with an already coalesced team. Thus the focus in this latter component does not necessarily need to establish collaboration to begin their research.

Findings from our interviews and observations are summarized below for each component.

Clinical Proteomic Technology Assessment for Cancer (CPTAC)

CPTAC is a collaborative effort, applying a team science approach to understanding the variation in the technologies and methodologies of current proteomic cancer research and to developing products aimed at reducing this variation. From the onset of this effort, CPTAC faced critical challenges related to establishing a collaborative network among scientists across the five selected institutional teams. Some of these teams had been practicing team science with their chosen partners prior to submitting a proposal in response to the CPTAC request for applications, but none had been brought together with new partners in a collaborative research effort of this type. Thus, CPTAC's first challenge was to establish collaboration between the various institutional teams. Although our involvement in this project began too late to observe the formation of these relationships, we noted throughout our discussions with CPTC researchers and our observations that the following factors were important in this effort:

- NCI CPTC staff's management approach allowed collaboration to develop in an organic way, providing support where necessary but respecting the diverse perspectives of the centers. This approach also included outreach to various parts of the proteomic research community to enhance the capacities of the collaboration and to parts of the broader scientific community to create a market for the research products that would eventually be generated by the collaboration. Examples of the former include the establishment of Tranche, a massive data repository of results from mass spectrometry studies, and the involvement of the National Institute of Standards and Technology in providing standardized metrics. An example of the latter is outreach to various scientific and research-related associations, such as the American Association for Clinical Chemistry and American Association for Cancer Research.



- The Program Coordinating Committee (PCC) plays a critical role by providing a forum for discussing the larger issues associated with establishing the collaborations. These issues related not only to how the project was to progress, but also to the differing perspectives of those involved. In other words, the establishment of the PCC allowed for the development of a common basis of thought and trust that is necessary for a successful collaborative relationship.
- Intra-institutional, interdisciplinary workgroups were the engines of production for the project. They fostered collaboration on specific issues and led to the development of studies and publications in different topical areas. Their distinction from the PCC and focus on the science were critical for enhancing collaboration and meeting project objectives.

The result of CPTAC's efforts was the establishment of a collaboration to a degree that most of the researchers had not experienced prior to CPTAC. The resulting openness and trust was demonstrated when researchers suggested at a PCC meeting that they hold a special meeting to discuss the non-CPTAC research efforts they were pursuing. This was a notable instance of wanting to extend the collaborative bond beyond the CPTAC environment. The collaboration, formed in the start-up phase of the grant, was essential for progressing to the knowledge generation.

Currently CPTAC is in the midst of the knowledge-generation, with the workgroups and individual centers producing studies, publications, and standard operating procedures (SOPs). One particularly important SOP that was developed involved standardizing the collection of samples from patients—a process that if not done uniformly could affect the efforts to verify proteomic discoveries.

The next step for CPTAC is the dissemination phase, which has already begun. Thus far, products disseminated by CPTAC include SOPs, journal articles, and software. To sustain its effort, however, the program must manage several dynamics, all of which might affect its collaborative nature. These include:

- Maintaining focus on verification yet not ignoring the uses of CPTAC products for discovery and in the clinical setting
- Maintaining focus on examining existing technology, not creating new technology
- Maintaining a balance between transparency and limited access within the collaboration
- Maintaining NCI control of the aspects of the program related to achieving the goals and objectives of CPTAC while allowing CPTAC centers to conduct their research unhindered.

Each of these dynamics manifests the same overarching issue of how to reconcile researcher interests with the interests of the program. There is a natural inclination among researchers to pursue discovery, translate results to the clinical setting, become involved in engineering new technology, or otherwise pursue their own interests and perspectives, and these interests may at times conflict with achieving program objectives. The possibility of new technology also poses a threat to the current program's interests because the development of a paradigm-shifting technology that improves the resolution of detecting proteins could change the focus of the entire program.



Advanced Proteomic Platforms and Computational Sciences (APPCS)

This program has the same lifecycle as other National Institutes of Health (NIH) grants in that the grants are awarded, and the subsequent research results in publications or new products. In this case, projects are focused on platform or software development. The major difference between APPCS grants and other NIH grants is that APPCS grants are related to the overall topic of proteomic biomarker research—both in attempting to create new ways of improving the detection of proteins or in understanding information generated by current instrumentation. In this regard, CPTC has sought to integrate these researchers into the CPTAC effort. Close collaboration is already present in some cases; however, researchers indicated that they would be interested in closer involvement with the CPTAC effort.

Proteomic Reagents and Resources Core (PRRC)

The third component of the program has undergone a similar start-up and production phase as CPTAC. This component uses a combination of contracts and Interagency Agreements rather than grants. With the aim of producing high-quality reagents, the PRRC component sought to establish a network of laboratories responsible for producing and characterizing reagent materials. In addition, sites for storage and dissemination were identified. Thus, the logistics of organizing a network with many components and understanding what needed to be produced were the essential challenges for this component. To date, the program has produced a basic set of high-quality, well-characterized reagents that have been made available to researchers. The challenge in the future will be to understand which reagents are specifically needed by the research community and how to produce them more effectively.

“[CPTC] is unique because of the concentration to highly characterized antibodies for the community and empowering clinical researchers with best practices and standards.”

Saeed A. Jortani, PhD, DABCC, FACB
Director, Forensic Toxicology Program
Department of Pathology and Laboratory Medicine
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PERSPECTIVE ON CPTC'S FUTURE

A tacit goal of the CPTC initiative is to rehabilitate the image of the field of proteomics. Several interviewees said that they believed that the field initially held enormous potential in the fight against cancer but that a negative response by the public to less rigorous proteomic research conducted in the past had hindered progress in the field. They clearly felt that this program was an opportunity to change this response. There was a belief that CPTC's very clear goals would be met with the production of optimized tools, SOPs, and other resources that would enhance the ability of researchers in the field to verify proteomic biomarker discoveries. (See the callout box, "CPTC by the Numbers," for an overview of these tools and achievements.) CPTC was viewed by most of the interviewees, as least in terms of achieving its pilot goals, as a first step to the development of a robust, reliable, and quantifiable protein biomarker pipeline.

CPTC by the Numbers: An Overview of Accomplishments

- **171** Publications*
- **7** Patents
- **27** Software tools
- **84** Monoclonal antibodies
- **27** Standard Operating Procedures
- **6** Data sets publically available
- **11** Partnerships with biotechnology companies
- **4** Partnerships with federal agencies and professional organizations
- **19** Partnerships with academic institutions
- **12** Leveraged funding activities
- **>60** Number of organizations that make up the CPTC Community

*CPTC was launched in 10/2006 and awarded 20 grants (5 U24, 4 R21, 3 R21/R33, and 8 R01). RFAs were non-reissue. As of 10/2009, 15 grants encompass the CPTC portfolio (5 U24, 1 R21, 2 R33, and 7 R01).

CPTC, as one interviewee put it, should result in establishing the basis for the NCI in conducting proteomics research using the current technologies. This basis, once disseminated through publications and other means, would guide investigators in their activities. This interviewee then indicated that CPTC should be transformed to deal with other issues regarding proteomics research.

To determine what this transformative program dealing with advancing clinical proteomics through advanced protein-based technologies, metrics, standards, SOPs and team science might look like, we asked a question at the end of many interviews about whether the CPTC effort could be sustained and the potential role that CPTC could play in this. The answers were diverse but can be captured as follows:

- Several interviewees said that there needed to be a CPTC like-program that could strongly monitor and influence (one interviewee suggested a very interventionist role in setting standards) the field to prevent the sort of inferior science that had been conducted in the past. The concern was that the science would lapse back into the same siloed mindset that caused the issues in the first place without some sort of strong leadership.



- There was an expression that the program should venture and coordinate efforts dealing with other non-verification aspects of the pipeline such as facilitating the effort to transfer results to clinical settings.
- There was an expression of interest in seeing a CPTC program pursue focused goals. For instance, some interviewees thought that the CPTC reagents effort should be pursued regardless of what the program looks like in the future.

One major achievement of the program during CPTC's Phase I was collaboration. This achievement is a core result that is the basis for the necessary working relationships among institutional collaborators, and in turn, for organizing efforts to create better science. This collaboration was viewed as being critical for ensuring the viability of the pipeline, whatever the form CPTC takes in the future.

In addition to building collaborations amongst the network, CPTC has been actively involved in disseminating the latest research breakthroughs in a clear and honest manner to the cancer advocacy community. Advances have been relayed to the advocacy community through newsletters, focused areas on the program website (i.e. – Patient's Corner), and through the inclusion of advocates in the annual meeting. This communication fostered by CPTC has insured that the promise of proteomics is accurately portrayed to the current level of scientific knowledge.

Though this evaluation analyzed primarily short-term outcomes, it is clear that there is a great long-term potential for the outcomes from the CPTC. To this end, the long-term products of the pipeline developed by CPTC hold the potential of providing the community with a quantified catalog of proteins related to cancer, assays for quantitative analysis, and the possibility of diagnostic or detection biomarkers which can be used in prognosis or diagnosis of cancer. The long-term potential of CPTC; places it and the field of proteomics as a key component in developing approaches in personalized medicine.

"CPTAC is a very unique program. It is the first time people are looking at a translation technique from research laboratory into the clinical setting. It is harder than one thinks, and [CPTC] has pointed out how well thought out it has to be [to do this]. The unique cooperative structure of CPTAC has enabled it to be an order of magnitude 100 times greater than alternatives."

Martin Fleisher, PhD

*Chair, Department of Clinical Laboratories
Memorial Sloan-Kettering Cancer Center*



1. INTRODUCTION

One promising approach for detecting cancer at an early stage is through the use of proteomic biomarkers present in plasma or serum. The premise of this approach is that cancer cells “leak” proteins into the blood stream. If these proteins can be detected when they are present in low concentrations in plasma, treatment for the cancer can begin earlier with greater effect. The challenge of this approach is that current technologies cannot easily detect with a high degree of certainty proteins that are in low concentrations. Despite this challenge, researchers have discovered many promising proteomic cancer biomarkers. But few of these discoveries have been reproduced and verified, which in turn limits their value in clinical settings. Reproducibility has been hindered by the lack of technology and platform¹ standardization, high quality reagents, and, particularly, standard operating procedures (SOPs). This means that verification efforts to identify a particular protein are affected by measurement issues related to the sample collection, instrumentation, and methods for preparing and processing samples that occur in different laboratories. The Clinical Proteomic Technologies for Cancer (CPTC) program was initiated in 2006 to respond to this standardization problem by addressing the sources of experimental variation that are associated with technology and platform differences and with the methodologies that underlie SOPs. The focus of the program is to establish tools and products that will increase the ability of the proteomic research community to successfully bring its discoveries into clinical settings where they can be used for the early detection of cancer.

To assess CPTC activities and outcomes, the National Cancer Institute (NCI) sought a program evaluation. In fall and early winter 2008–2009, a study was conducted to determine whether a program evaluation was feasible. Through discussions with various NCI staff, grantees, and other individuals associated with the program and a review of program documentation, the study determined that it was premature to evaluate the program based on its effect on general proteomic research, cancer researchers, or the development of clinical assays for detecting cancer.² However, the study concluded that a more limited assessment, focused on program activities and progress, could be conducted. This report presents the results of that limited assessment.

¹ “Platform,” as conveyed in the original request for applications for the Clinical Proteomic Technology Assessment for Cancer (CPTAC) network, refers to the entire process of preparing and analyzing samples. “Technology” refers to the instrumentation.

² The report, “Feasibility Study for an Evaluation of the Clinical Proteomic Technologies for Cancer Initiative,” submitted to the National Institutes of Health (NIH) by Macro International Inc. (ICF Macro) in February 2009, is included as appendix B of this report.



2. DESCRIPTION OF CPTC

2.1. INTRODUCTION

NCI launched the CPTC initiative in 2006 to:

- Enhance technical abilities to identify and measure proteins accurately and reproducibly in biological systems
- Advance proteomics as a reliable, quantitative field that can accelerate discovery and translational research

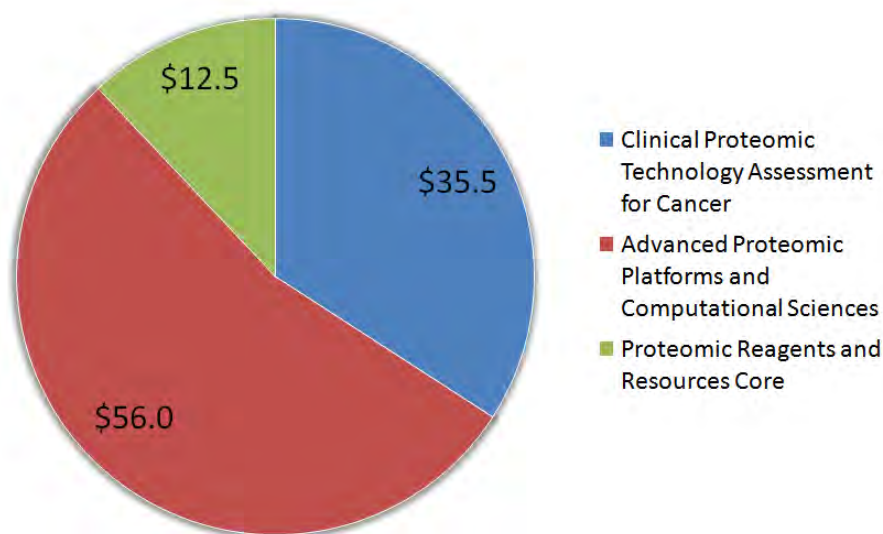
It is important to note that accomplishing the first goal is a necessary condition for achieving the second. As was indicated in CPTC documents and in interviews, the focus of the initiative is to first establish approaches for dealing with experimental variation due to differing technologies. Once the variation issue is resolved, these approaches can serve as a basis for the general proteomics community to pursue effective research in this area. This basis in turn will promote discovery and translational research. With funding of \$104 million over a 5-year span, this initiative is expected to expedite the verification of proteins with a high potential for detecting early-stage cancer. The CPTC initiative consists of three interrelated program components:

- Clinical Proteomic Technology Assessment for Cancer (CPTAC) is focused on reliably identifying, quantifying, and comparing peptides/proteins in complex biological mixtures through multidisciplinary networks of centers. CPTAC aims to develop a technological basis that supports more effective verification.
- Advanced Proteomic Platforms and Computational Sciences (APPCS) is focused on the development of highly innovative research in the quantitative analysis of peptides/proteins of interest in clinical cancer studies.
- The Proteomic Reagents and Resources Core (PRRC) is focused on producing and making available high-quality reagents to the research community.

As shown in exhibit 1, CPTAC funding makes up approximately one-third of total CPTC funding, and APPCS funding makes up more than half.



Exhibit 1. 5-Year CPTC Funding, by Program Component (in millions)



2.2. CLINICAL PROTEOMIC TECHNOLOGY ASSESSMENT FOR CANCER

The objective of the CPTAC network is to use a team-based approach to assess the performance of current protein measurement technologies and optimize the ability of those technology platforms to detect cancer biomarkers by reducing measurement variability throughout the biomarker discovery process. Sources of variability include sample collection and preparation, experimental design, instrument performance, and data management and analysis. The CPTAC network was established through a request for applications (RFA) issued in spring 2006.

As expressed in the original RFA, several factors related to establishing the CPTAC network are critical to fulfilling these goals:³

- First, the NCI/CPTC leadership recognized that a team science approach was needed to overcome measurement issues that are inherent in a proteomic research establishment in which technologies and methodologies vary across different research settings. While discovery may occur in one setting, reproducibility and verification must occur across different settings that vary in the types of platforms and instruments used. The use of multiple settings ensures that the discovery is not an artifact of the technology used by the discovering laboratory. Understanding the differences in the technologies and developing mutually agreed-on SOPs help address these variations, thus reducing experimental error. This effort involves multiple sites and collaboration.

³ The program issued several RFAs. The primary one to establish the CPTAC network was issued as a cooperative agreement. Others were established for individual researchers under R01, R21, and R33 grant award mechanisms. These were placed within the APPCS component of the program. Another component that is not addressed in this report is the Small Business Innovation Research (SBIR) awards.



- Second, the emphasis of the program is on examining how to achieve reproducibility across platforms using mass spectrometry (excluding surface-enhanced laser desorption/ionization) and affinity arrays and with high-throughput platforms that can identify very low protein concentrations. Although new approaches may be developed incidental to the exploration of the above technologies, this is not a thrust of the program.⁴
- Third, although it was recognized that the focus of CPTC is primarily verification, the activities of the initiative must address the entire range of proteomic activities, from discovery to clinical validation. For example, the standards applying to collection of sera from human subjects could have a positive effect on discovery efforts as well as later validation efforts. Information about the calibration of mass spectrometers could prove useful to researchers, regardless of whether their focus is discovery, verification, or validation. Likewise, providing standardization guidelines will enable individuals to submit well-validated applications to the Food and Drug Administration (FDA) for approval, a necessary step for translating laboratory results to the clinical setting. In this way, CPTC has an interest in the entire pipeline.⁵

2.2.1. The Centers

Of the 13 institutions that applied, 5 were awarded U24 cooperative agreement grants:

- The Broad Institute of the Massachusetts Institute of Technology (MIT) and Harvard (the Broad)
- Memorial Sloan-Kettering Cancer Center (MSKCC)
- Purdue University
- Vanderbilt University School of Medicine
- University of California, San Francisco (UCSF)

2.2.1.1. The Broad Institute of MIT and Harvard

The intent of this grant was to develop sensitive, specific, and quantitative technologies capable of measuring hundreds of candidate cancer biomarker proteins in large sets of clinical plasma samples. The team is developing methods based on multiple reaction monitoring mass spectrometry (MRM-MS) spiked in with stable isotope standards with/without capture by anti-peptide antibodies (SISCAPA), which involves sample fractionation and enrichment methods to allow for greater quantitation, specificity, and sensitivity of MRM samples.

The Broad leads a collaboration of institutions that provides a broad base of support for conducting collaborative studies as well as specialization to address specific issues associated with CPTAC goals. The major organizations and their role in this collaboration include:

⁴ The RFAs issued to individual researchers under the APPCS program allowed new methods or technologies to be developed.

⁵ The word “pipeline” is used in several contexts. Here it reflects the necessary steps to move a discovery into a clinical practice setting.



- **The Broad Institute of MIT and Harvard**—In addition to being the lead organization involved in all aspects of the effort, the Broad is heavily invested in the processing and measurement of clinical samples. The Broad has substantial resources in mass spectrometry and MRM methods. Steven Carr is the principal investigator (PI).
- **The Fred Hutchinson Cancer Research Center and the University of Washington (FHCRC)**—FHCRC is an NCI-designated comprehensive cancer center. Like the Broad, FHCRC is involved in the processing and measurement of clinical samples and has a substantial investment in mass spectrometry and sample preparation methods. It also collects plasma from women undergoing breast cancer examinations in order to provide clinical samples for this effort. FHCRC's effort is led by Amanda Paulovich.
- **Plasma Proteomics Institute (PPI)**—PPI provides expertise in a variety of areas related to the Broad effort, mostly through the participation of N. Leigh Anderson, including reagent development and use of SISCAPA technology.
- **Massachusetts General Hospital**—Provides biostatistical expertise through the participation of Steven Skates
- **University of Victoria**—Provides processing and measurement capabilities and is involved in the development of screening methods to determine whether the antibodies produced to peptide targets have good affinity and application in the team's research studies. This effort is led by Terry Pearson.

Many of the researchers from these institutions, particularly from the Broad and FHCRC, have collaborated with each other prior to their CPTAC involvement. PPI, through Dr. Anderson, had an instrumental role in bringing this team together for this effort.

The team is focusing on detecting biomarkers of breast cancer in plasma protein and has a strong interest in transitioning the results into a clinical environment. Team products are intended to demonstrate that:

- Sensitive/specific assays can be made quickly and inexpensively (particularly by comparing the SISCAPA approach to enzyme-linked immunosorbent assay and through multiplexing)
- Protocols, reagents, and technology can be formulated to provide similar results across different laboratory environments
- Protocols, reagents, and technology can be standardized and distributed

Other related and supportive initiatives by the team include activities involving 1) the collection of clinical samples from 500 women scheduled for breast cancer biopsies (FHCRC), 2) the generation of statistical, data mining, and analytic software approaches to understanding results generated by the MRM-MS methodology, 3) cross-laboratory analyses for assessing the methodology in different settings, and 4) the development of anti-peptide monoclonal antibodies for SISCAPA.



2.2.1.2. MSKCC

MSKCC, an NCI-designated comprehensive cancer center, is the lead organization in its CPTAC effort, which includes researchers from New York University (NYU). This CPTAC team has significant expertise in automated sample processing technology (robotics), a method with the potential to eliminate a significant amount of handler variability and induced error associated with protein measurements from clinical samples. In addition, the team has expertise in working with protein fragments (peptides) and assays and in the use of magnetic beads for the capture of peptides.

The CPTAC team is led by Paul Tempst. Dr. Tempst established the Protein Center at MSKCC in 1991. The center now consists of the Microchemistry and Proteomics Core Facility, a proteomics research and development laboratory, and Dr. Tempst's Laboratory of Targeted Proteomics in the Molecular Biology Program. The CPTAC team focuses on evaluating whether plasma peptide patterns or custom-designed protease assays can be measured reproducibly and whether they are valuable for cancer diagnosis. As part of this effort, the team has developed and is assessing suitability and reproducibility of both classical peptidomics and quantitative blood exopeptidases assays as new types of cancer diagnostics. They are also in the process of establishing a repository of 1,200 cancer-related plasma and serum samples and a library of substrate and reference peptides.

One of the first major efforts under the CPTAC award was to create a mirror site at the NYU Protein Analysis Facility (PAF). The NYU PAF was established in August 1998 to develop, implement, and provide cutting-edge mass spectrometry-based protein analysis services. The NYU effort is led by Thomas Neubert. After establishing the mirror site, the CPTAC team began a 2-year study to assess whether variability in peptide measurements could be attributed to the robotic, reversed-phase, magnetic-assisted sample processing or the matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) measurements.

In collaboration with a team from MSKCC breast cancer services, plasma and serum samples are being collected from women undergoing breast biopsy, following protocols established by the CPTAC biospecimen workgroup. These protocols are intended to reduce variability in sample collection. In addition to biospecimen collection, the CPTAC team compares the plasma or serum peptide profiles of women's biopsies regardless of malignant diagnosis. Analysis of samples and clinical data occur at MSKCC, and samples are contributed to the CPTAC sample repository. Samples are also being collected in collaboration with a team from MSKCC prostate cancer services. This team is assessing the value of plasma or serum peptide profiling and exopeptidase assays to predict biopsy outcomes for men undergoing prostate biopsy.

Another group of scientists from the MSKCC Human Oncology and Pathogenesis Program are working with CPTAC to explore whether exopeptidase assays show differences between control mice and genetically altered mice with prostate cancer.

In addition to the technology expertise at the MSKCC Protein Center and NYU PAF and the specific cancer center expertise of MSKCC, the CPTAC team works with the Sloan-Kettering Institute Bioinformatics Core (BIC), founded in 2003 within the Computational Biology Center.



BIC was created to provide bioinformatics services, including data analysis, software and database development, training, and high-performance computing support to MSKCC basic, clinical, and translational investigators. Over its 3 years of operations, BIC has become embedded in MSKCC research. BIC services consist primarily of microarray transcription profiling and array comprehensive genomic hybridization analyses but also include nucleotide and protein sequence analysis, software and database development, and expert advice on computational approaches and methodologies.

2.2.1.3. Purdue University

The primary goals of the Purdue CPTAC center are to:

- Demonstrate, in a high percentage of cases, with large numbers of cancer patients, that researchers can detect cancer associated protein markers in plasma
- Evaluate the performance of a variety of analytical platforms in quantifying these markers

More specifically, the center's objective is to evaluate analytical platforms for validation of breast and prostate cancer biomarker candidates in plasma or serum based on affinity selector targeting of proteins. Biomarkers selected are identified and quantified by either 1) multidimensional mass spectrometry-based methods involving electrospray ionization or MALDI, 2) ion mobility separator-based fractionation before multidimensional mass spectrometry, or 3) immunological arrays on a microfabricated BioCD. The Purdue team is led by Fred Regnier.

The strengths of this center include the capability to develop the areas of new high-throughput immunoaffinity and other mass spectrometry instrumentation and technology, biofabrication expertise, and other methods of comparing proteomics data across platforms. All these are central to overcoming the challenges in mass spectrometry-based proteomics. Another critical component that the team brings to CPTAC is the development of a microarray platform that uses interferometric analysis, which presents an opportunity for high-throughput and sensitive analysis of very small biological fluid samples. This effort has the potential to lead to the identification of useful new antibody reagents and economical antibody arrays, which could be used in both discovery and clinical proteomic work.

The capabilities of the Purdue effort are enhanced by the presence of:

- The NCI-sponsored cancer center at Purdue (renamed the Purdue University Center for Cancer Research in July 2009), which received its first award from NCI in 1978
- An oncological sciences program begun in 2004 with funding from Eli Lilly and Company

In addition, the newly established Center for Analytical Instrumentation Development brings together scientists from Purdue University, Indiana University, the Indiana University School of Medicine, and the University of Illinois in order to advance the development of new analytical instrumentation for research and clinical applications. In the context of all these efforts, Purdue's



CPTAC center acts as a component of a much broader statewide and regional cancer research effort.

As the center enters the second half of the award period, the main focus of its activity is to continue work on real samples from cancer patients. Specifically, this includes:

- Continuing marker quantification studies with breast cancer patient plasma samples using the small set of potential markers currently identified
- Expanding the study of prostate cancer patients in parallel with the ongoing study of breast cancer patients
- Determining the degree to which breast and prostate cancer can be differentiated from other types of cancer and inflammatory diseases by examining and analyzing a small set of colorectal, ovarian, and lung cancer patient samples along with arthritis patient samples

A number of for-profit and nonprofit organizations are involved with the Purdue CPTAC center, working together to most efficiently evaluate and roll out robust protocols and standards for mass spectrometry and affinity proteomics approaches. These include:

- **Predictive Physiology and Medicine Inc.**—This advanced analytical techniques company has a Phase I Small Business Innovation Research (SBIR) award focusing on the advancement of mass spectrometry-based technologies for proteomics.
- **Hoosier Oncology Group**—This nonprofit organization, which has access to oncology patients throughout the State of Indiana as well as the larger region, assists with cancer- and control-patient sample acquisition.
- **Quadraspec, Inc.**—This for-profit company supplies the project with instrumentation used to conduct high-throughput immunological assays needed in the validation of potential cancer marker proteins.
- **Indiana Center for Applied Protein Sciences (INCAPS)**—The CPTAC center selected this contract research company as the benchmark against which all other proteomics platforms used in cancer proteomics technology assessment will be compared.
- **Neoclone Biotechnology International**—This for-profit firm develops monoclonal antibodies using retroviral transformation, bypassing hybridoma fusion.
- **Safis Solutions**—This company provides consultation, specifically regarding the development of a framework for biomarker data presentation based on protocol formats that are familiar to FDA.
- **Sigma-Aldrich Life Science Products**—This for-profit company supplies the project with antibodies; this relationship stems from a codevelopment business arrangement that Sigma-Aldrich has with Quadraspec, Inc.

2.2.1.4. Vanderbilt University School of Medicine

In 1993 Vanderbilt University established the Vanderbilt Cancer Center (later renamed the Vanderbilt-Ingram Cancer Center) to bring together all its cancer-related research, treatment, education, and outreach activities. In 2001 the center was named a comprehensive cancer center



by NCI, and in 2007 it joined the National Comprehensive Cancer Network, further establishing it as a leading institution in the field of cancer treatment and research. Vanderbilt has an important resource in the Jim Ayers Institute for Precancer Detection and Diagnosis, which is focused on early detection of colon cancers. The Vanderbilt University CPTAC center is led by Dr. Daniel Liebler. The center has teamed with the M.D. Anderson Cancer Center in Texas to explore the use of the application of reverse phase protein array (RPPA) technology to the work pursued by Vanderbilt. RPPA was being examined at as a benchmark for comparison, cross-validation, and standardization of array- and mass spectrometry-based technologies for proteomics.

The Vanderbilt effort encompasses technological, bioinformatic, statistical, and sample-collection components and has ties both to Epitomics, Inc. for antibodies and the University of Washington for assistance in bioinformatics analytic software (Skyline). The Vanderbilt group focuses on tissue samples as well as sera samples; the group proposed examining tissue samples in its application. The group has an active program in clinical sample collection, which originally focused on colon cancer but has been realigned with other CPTAC centers in developing samples for breast cancer. Samples are also collected for pancreatic and gastric cancers. Approximately 200 plasma breast cancer samples have been collected so far, with about 15 additional samples collected each month.

The major research goals of the Vanderbilt CPTAC program are to 1) optimize shotgun proteomics technology platforms for unbiased discovery of biomarker candidates in tissues and proximal fluids, 2) develop and optimize target mass spectrometry-based assays for biomarker candidates in tissues and plasma, and 3) develop and standardize tools for proteomics data analysis. In particular, the group has focused on exploring liquid chromatography-multiple reaction monitoring mass spectrometry (LC-MRM-MS) technology. Vanderbilt-Ingram Cancer Center provides CPTAC researchers access to many core laboratory resources to help achieve these goals, including state-of-the-art mass spectrometry instrumentation and analytical methods to analyze proteins and proteomes, biostatistics resources and statistical tools, access to the Vanderbilt Monoclonal Antibody Core, and access to Vanderbilt's clinical research resources.

The center will continue to pursue its research goals over the next 2 and a half years by working to:

- Develop standardized methods for quantitative analysis of phosphoproteins
- Develop a comprehensive informatics pipeline for targeted quantitative analysis of proteins by LC-MRM-MS
- Develop a standardized method for label-free quantitation of protein biomarker candidates in tissue specimens
- Develop and standardize a hybrid immunoaffinity-LC-MRM-MS method for biomarker candidate analysis in plasma
- Extend previous research on quantitative LC-MRM-MS methods to formalin-fixed, paraffin-embedded tissue specimens
- Identify quality metrics for plasma specimens for proteomic analysis



2.2.1.5. UCSF

The CPTAC grant centered at UCSF is focused on the development of two major technologies currently used to analyze proteins and peptides: mass spectrometry and affinity capture platforms. The primary goals of the center include determining whether mass spectrometry and array platforms can be optimized, evaluating fractionation schemes, achieving reproducible protocols, and ultimately enabling quantitative proteomics.

Specific objectives include the following:

- Evaluating the performance of proteomic technology platforms and standardizing approaches to developing applications of these platforms
- Establishing systematic ways to standardize proteomic protocols and data analysis among different laboratories
- Developing and implementing uniform algorithms for sharing bioinformatics and proteomic data and analytical/data mining tools
- Developing well-characterized material and bioinformatics resources for the entire cancer research community
- Assessing proteomic platforms for their ability to analyze cancer-relevant proteomic changes in human clinical specimens

The UCSF CPTAC team is headed by co-PIs Susan Fisher of UCSF, Joe Gray of Lawrence Berkeley National Laboratory (LBNL), and Brad Gibson of the Buck Institute for Age Research.⁶ From our observations and discussions, the collaboration between UCSF and the Buck Institute is very strong, with intense joint collaborations in several areas. For example, the two institutions developed the SOPs for and evaluated the performance of discovery platforms based on LC-MALDI instruments (AB4800 and Thermo-Fisher vMALDI LTQ) using low-(NCI20) and high-complexity (yeast digest) samples. Buck Institute investigators have also been developing methods to prepare standards for post-translationally modified (PTM) proteins. The team includes:

- **LBNL**—Investigators are focusing on markers specific for metastasis-prone (basal) subtypes that are likely to have the largest impact on breast cancer survivorship.
- **M.D. Anderson Cancer Center**—The center is developing reverse phase protein array platforms for validating the results of mass spectrometry-based analyses.
- **University of British Columbia**—Center researchers have planned to work with Ron Beavis at the University of British Columbia, as well as members of the CPTAC Bioinformatics Workgroup to develop integrated informatics tools and data. Specifically, the team is

⁶ The project, as originally funded, called for LBNL to be the designee lead but was revised to have UCSF as the lead designee. This led to a delay of approximately 1 year in the official award notification. The original group included LBNL, the Buck Institute, UCSF, M.D. Anderson Cancer Center, California Pacific Medical Center, and the University of British Columbia. Some of the organizations have, thus far, been only tangentially involved, which, for some, is by design and for others a function of the timing of the work being done by the group. While the group has extensive participation with various workgroups within CPTAC, the collaboration between UCSF and the Buck Institute appears to be particularly fruitful.



proposing to develop a MS/MS spectral database specifically for PTM-modified peptides and link this tool to various resources such as the PhosphoSite® and GlycoSuiteDB online databases that have key information regarding experimental and/or predicted structural PTM sites.

2.2.1.6. Other Members of the Network

The organizations described above form the basis for the CPTAC network. The network was designed to produce collaboration not just within research teams but across multiple institutions that are openly sharing data and resources. To assist the five lead centers in their work, other institutions with particular strengths were added through contracts, interagency agreements, or collaborations.⁷ These include:

- **University of Michigan**—The University of Michigan has a proteomic research program with a very strong informatics program. This program was responsible for the development of a proteomic research site (Tranche).
- **University of Washington**—The University of Washington provides software support for analyzing the experiment results (Skyline) through a contract with Vanderbilt.
- **FDA**—FDA has an interest in protecting Americans from ineffective and misinformed diagnoses based on assays. This collaboration serves to promote the ability of proteomic biomarkers to achieve approval for clinical use.
- **National Institute of Standards and Technology (NIST)**—NIST has served in a number of capacities since the inception of CPTAC, including working on materials and informatics and analysis.
- **National Institute of Statistical Sciences (NISS)/Texas A&M University**—Because of its stature as a statistical agency that focuses on these issues, NISS currently provides expertise in statistical and experimental design. Texas A&M provided expertise during the start-up phase of CPTAC.
- **Argonne National Laboratories (ANL)**—ANL provides expertise in protein production, quantification, and characterization of peptides and proteins—in particular, customized reference protein standards for mass spectrometry studies.

2.2.1.7. Organization of the Centers

The organization of the five centers reveals distinct differences in how the centers were conceived by the center research teams. At least two of the centers (the Broad and UCSF) have built their organization around a broad coalition of external institutions, although in each case leading the effort seems to be largely shared among two institutions. Two of the centers (Vanderbilt and MSKCC) did not establish a broad coalition, instead focusing on internal institutional sources to provide support. Purdue, on the other hand, formed a broad coalition of organizations, but many of them are privately owned firms. It should be noted that these

⁷ It should be noted these are the institutions that are directly involved with the centers. There are other organizations defined as part of the network that contribute to the other two CPTC components.



examples represent how intra-team collaborations were structured but not necessarily how cross-center collaborations were carried out. Participation in the overall PCC and the workgroups did seem to mirror this intra-institutional versus inter-institutional bias somewhat.

2.2.2. Program Coordinating Committee (PCC)

The PCC is the primary organizational vehicle for bringing the five centers together and establishing research priorities. The committee consists of six voting members: the five center PIs and the NCI CPTC program director. Center co-PIs and proteomics researchers from the lead organizations and from other parts of the network also participate in PCC meetings and discussions. The PCC meets monthly via teleconference and twice annually in person. In addition to establishing priorities, the PCC monitors the progress of each center in achieving previously established objectives and approves and monitors CPTAC workgroups. NCI CPTC program managers attend all meetings and assist in coordinating program activities. As mentioned above, one of the important management areas for the PCC is the activities of the workgroups, which are cross-center collaborations on a specific topic or area. The PCC decides whether workgroups should be established or disbanded and monitors their activities.

2.2.3. Workgroups

Much of the CPTAC work is scheduled and conducted through the workgroups. Each workgroup comprises 7 to 25 members, usually with participation from all 5 centers and from others involved in the CPTAC network. Workgroups are established around particular aspects of proteomic research, typically in areas that need to be standardized across laboratories to reduce variability (see exhibit 2 for workgroups active in years 1 or 2 of the program). For example, one workgroup establishes protocols for the collection, processing, and storage of biospecimens. Another workgroup processes all collaborative study data and designs tools to make CPTAC datasets compatible and shareable. Workgroups hold monthly teleconferences, and workgroup chairs report to the PCC. Workgroups are also responsible for designing and managing the studies conducted across laboratories. Interlaboratory studies identify and reduce sources of variability by using derived SOPs and well-characterized reference materials. Thus far, there have been nine studies planned or completed. The output of these efforts (e.g., SOPs, reagents, reference materials) provide the community of scientists conducting cancer-related protein research with the resources needed to ensure that variations in protein measurement results are due to changes in the biological sample, not measurement variability.



Exhibit 2. Workgroup and Institutional Contributors

Workgroup	Year 1	Year 2	Year 3
Experimental Design and Statistics: Unbiased Discovery Studies	✓	✓	✓
Experimental Design and Statistics: Verification Studies	✓	✓	✓
Yeast Cell Lysate	✓		
Cell Line Selection and Lysates	✓		
Plasma Standard Pool	✓		
Protein Standards: Selection and Production	✓	✓	✓
Protein Standards: Post-Translational Modification Needs and Production	✓	✓	✓
Data Analysis, Storage, and Dissemination	✓	✓	
Biospecimen Collection	✓	✓	✓
Analyte Selection		✓	
Digestion Procedures		✓	

2.3. ADVANCED PROTEOMIC PLATFORMS AND COMPUTATIONAL SCIENCES

The second major program component of the CPTC program is the APPCS initiative, which consists of awards made to individual investigators via R01, R21, and R33 grants (see exhibit 3 for a description of the RFAs associated with these grants). The goals of this component are to develop new tools, reagents, and protein/peptide measurement technologies. APPCS supports two focus areas for protein measurement technology and application in cancer research:

- Development of innovative high-throughput technology for protein and peptide detection, recognition, measurement, and characterization in biological fluids that will overcome current barriers in protein/peptide feature detection, identification, quantification, and validation
- Development of computational, statistical, and mathematical approaches for the analysis, processing, and facile exchange of large proteomic datasets



Exhibit 3. Inventory of RFAs Issued Through the APPCS Component

Funding Mechanism	Project Title	Project Type	General Requirements	Number
R01	Advanced Proteomic Platforms and Computational Sciences for the NCI Clinical Proteomic Technologies Initiative (R01, R21, R21/R33)	Individual researchers—Support a discrete, specified, circumscribed research project.	Support innovative platform technology development, as well as novel data analysis methods and computational approaches, to support the identification and measurement of peptides and proteins of relevance to cancer processes from clinical cancer specimens.	RFA-CA-07-005
R21	Advanced Proteomic Platforms and Computational Sciences for the NCI Clinical Proteomic Technologies Initiative (R01, R21, R21/R33)	Individual researchers—Support exploratory/developmental studies		
R21/R33	Advanced Proteomic Platforms and Computational Sciences for the NCI Clinical Proteomic Technologies Initiative (R01, R21, R21/R33)	Individual researchers—Support phased exploratory/developmental studies		

APPCS research was intended to support individual investigators in their efforts to provide innovative solutions in the two topical areas identified above. CPTC has awarded 16 grants under the APPCS program from the 89 applications that were submitted under the Advanced Proteomic Platforms, Data Analysis Methods, and Computational Sciences RFA (see appendix A). As shown in appendix A, some of these awards are connected with institutions that are part of the CPTAC network and might be expected to collaborate within the center's CPTAC effort. In addition, the topics addressed by the awards are in many cases in line with the needs expressed by the CPTAC network, particularly the need to work within the parameters of current technologies. In order to assess the grants, they could be split into three groups, the first of which would be those that promise some chance of a major paradigm shift in how research in the area will be conducted. NCI staff identified projects that could have that type of impact (Richard Smith and Xiaolian Gao). The second group would be those grants that directly advance the objectives of CPTAC, although they were not sponsored by CPTAC. (Had these investigators not received the award, they might have been asked to conduct the same research by a CPTAC center.) D.R. Mani's and Dave Tabb's work are examples of this group. These individuals were also asked to participate in the CPTAC workgroups, so their work was likely influenced by the CPTAC effort. The third group of awards would be those that promised no new paradigm shift but still addressed problems that are important to the advancement of proteomic research. Many



of the algorithm-based grants, which were seeking to improve throughput or analysis capabilities rather than creating a new approach to computation, were of this type. The innovations addressed by this group tended to be outside the scope of CPTAC work.

2.4. PROTEOMIC REAGENTS AND RESOURCES CORE

One of the challenges facing researchers has been the lack of high-quality, well-characterized reagents for use in proteomic research. Researchers have often had to resort to using suboptimal reagents that have been poorly characterized, resulting in unverifiable results and wasted research time and money. The third CPTC program component, PRRC, addresses the research community's need for high-quality, characterized reagents by implementing and organizing a rigorous system for developing reagents such as antibodies.

In October 2008 CPTC launched the Reagents Data Portal, a searchable Web-based database of highly characterized monoclonal antibodies for cancer-associated proteins. The portal is open to the public, and the antibodies are available at a nominal cost through the Developmental Studies Hybridoma Bank (DSHB) at the University of Iowa. Most importantly, the portal provides detailed information about each protein, including SOPs, antibody production, and extensive characterization analyses. Through a series of interagency agreements and contracts, CPTC has established an antigen and antibody production program that contributes to the Reagents Data Portal and provides materials for the CPTC network and the scientific community. In addition to providing specific reagents to the community, this program establishes new quality assessment and control standards for protein and antibody development in the proteomics community.

The production pipeline starts at ANL under an interagency agreement with NCI. ANL subclones, expresses, and purifies target proteins. The purified proteins are processed (endotoxin removal) and characterized (SDS-PAGE). Again, information about the protein (e.g., sequence, molecular weight) and SOPs are included in the Reagents Data Portal. The remainder of antibody production is managed under a contract with the Advanced Technology Program of NCI-Frederick. Monoclonal antibodies are produced by institutions selected using a request for proposals (RFP) funding mechanism. Using the purified proteins provided by ANL, mice are immunized and subsequent antibodies are evaluated and selected. For each protein target, 10 antibody supernatants are evaluated, and 3 are ultimately selected for monoclonal antibody production and extensive characterization. Extensive evaluation and characterization is performed on the reagents by a variety of laboratories and researchers, including SAIC, the Harvard Institute of Proteomics,⁸ the Swedish Human Proteome Resource Program, and NCI's Center for Cancer Research. The Swedish Human Proteome Resource Program, a major European effort to explore the human proteome, is of particular note. It differs from CPTC in several major ways, most notably because it is not focused on cancer but on the normal human proteome, and it produces polyclonal rather than monoclonal antibodies, which means that its materials are nonrenewable resource. However, the overall goals and methods of the two organizations fit together well, and researchers at the Swedish Human Proteome Resource

⁸ The work at the Harvard Institute of Proteomics was being conducted by Joshua LaBaer. He has since left the Institute to accept a position at Arizona State University with the intention to continue his work in his new position.



Program feel that their characterization work on CPTC materials helps further CPTC's overall goal of providing materials to the research community.

When characterization is complete, antibodies are collected, stored, grown, and distributed by DSHB and made available to the public through DSHB and the Reagent Data Portal. DSHB was established more than 20 years ago by NIH to store and distribute hybridomas and associated antibodies and is uniquely qualified to manage the distribution of CPTC-produced antibodies.

In addition to distributing materials through DSHB, CPTC works with several for-profit firms to distribute antibodies to researchers. Millipore and imaGenes are biopharmaceutical research firms that sell materials to the research community. In 2009 CPTC and these companies established relationships that will allow the firms to distribute antibodies directly to researchers. The firms can also perform their own characterizations on the reagents and may ultimately develop kits or further materials around the antibodies and then sell these expanded materials.

2.5. OTHER INITIATIVES

The three components mentioned above—the CPTAC network, the APPCS initiative, and PRRC—constitute the focus of this study. The NIH SBIR program is another critical component for developing technology that meets the needs of the proteomic research community. The SBIR program is funded by NIH, not by the CPTC program, but the CPTC program has the ability to suggest topics for the SBIR awards. One of CPTC's three component programs, PRRC, is tasked with providing the cancer community with the tools necessary to overcome technological and methodological barriers to developing and providing such reagents. To maximize PRRC's capabilities and impact, CPTC is partnering with the biotechnology industry via NCI's SBIR program. Through the SBIR program, CPTC aims to integrate its efforts with those of the biotechnology industry by encouraging and enabling companies developing proteomic technologies and platforms to adopt standardized, well-characterized reagents—including high quality proteins and validated capture reagents (e.g., antibodies)—in the commercialization of new tools and kits for the cancer community.

Over the 3 years of CPTC's existence, 9 topics have been suggested, resulting in 14 awards. These awards are detailed in exhibit 4.



Exhibit 4. SBIR Topical Areas Sponsored by CPTC and Awards by Area

Year	Topic Number	Topic	General Requirements	Awardees	Title
2006	238	Development of Clinical Automated Multiplex Affinity Capture Technology for Detecting Low Abundance Cancer-related Proteins/Peptides	Phase 1— Demonstrate feasibility; produce prototype Phase 2— Implement strategy and project	Meso Scale Discovery	Automated Multi-Array Platform for Cancer Biomarkers
				Sequenom, Inc.	Sensitive Protein Detection Combining Mass Spectrometry
				Quadraspec, Inc.	Highest Sensitivity Cancer Marker Array on Quadraspec's Bio-CD Platform
				Rules-Based Medicine Inc.	Automated Multiplexed Immunoassays for Rapid Quantification of Low Abundance Cancer-Related Proteins
2006	239	Development of Alternative Affinity Capture Reagents for Cancer Proteomics Research	Phase 1—Identify minimum characterization criteria; demonstrate improved performance Phase 2— Implement strategy and project	Allele Biotechnology and Pharmaceuticals Inc.	Yeast Single Chain Antibodies as Capture Reagents
				Accacia International	High-Throughput of Aptamers Against Cancer Biomarkers
2007	253	Advances in Protein Expression of Post-Translationally Modified Cancer Related Proteins	Phase 1— Demonstrate feasibility; produce prototype Phase 2— Implement strategy and project	Rana Bioscience, Inc.	A Cell-Free System for High Yield Phosphoprotein Synthesis
2007	254	Development of Clinical Quantitative Multiplex High-Throughput Mass Spectrometric Immunoassay for Detecting Low Abundance Cancer Related Proteins/Peptides in Bodily Fluids	Phase I—Proof-of-concept stage Phase 2— Implement strategy and project; develop technology; validate findings	Predictive Physiology and Medicine Inc.	Immunoaffinity Capture Coupled with Ion Mobility
				Intrinsic Bioprobes, Inc.	Multiplex Mass Spectrometric Immunoassays



Year	Topic Number	Topic	General Requirements	Awardees	Title
2008	268	Novel Antibody Epitope Mapping Technologies	Phase 1— Demonstrate feasibility Phase 2— Implement strategy and project	Intrinsic Bioprobes, Inc.	High-Throughput Mass Spectrometric Epitope Mapping
				Integral Molecular	Mapping of Epitopes on Cancer Biomarkers
2008	269	Development of Novel Protein Expression Technologies for Glycosylated Cancer-Related Proteins	Phase 1— Demonstrate feasibility Phase 2— Development	Allele Biotechnology and Pharmaceuticals Inc.	Expression of Mammalian Glycoproteins Using MBEVS
				Lifesensors Inc.	Novel Protein Expression Technologies for Glycoproteins
				Rana Bioscience, Inc.	An Expression System for Synthesis of Glycoprotein with Defined O-glycan Structure
2008	270	Peptide Aptamers: New Tools to Capture and Study Protein Interactions in Lieu of Immunological Reagents	Phase 1— Demonstrate feasibility Phase 2— Implement strategy and project; develop technology; integrate platform into greater scientific community	No Award was Made	
2009	288	Development of Alternative Affinity Capture Reagents for Cancer Proteomics Research	Phase 1—Identify minimum characterization criteria; demonstrate improved performance Phase 2— Implement strategy and project	Not yet awarded	Not yet awarded
2009	289	Physical Property-Based High Throughput Protein Sequencing	Phase 1— Demonstrate feasibility Phase 2— Implement strategy and project; develop technology; integrate platform into greater scientific community	Not yet awarded	Not yet awarded



3. RESEARCH QUESTIONS AND METHODOLOGY

3.1. INTRODUCTION TO THE OVERALL DESIGN

The feasibility study, completed by Macro International Inc. (ICF Macro) in February 2009 as a precursor to this assessment, concluded that neither an impact study nor an evaluation focusing on long-term effects of the program was possible. An impact study was not feasible because of the absence of a credible counterfactual that would serve as a comparison for measuring whether the program is having an effect and whether it is cost effective. Although NCI operates other programs that have similar goals, CPTC is different enough both in goals and structure that these other programs do not provide an evaluation alternative. During the feasibility study, no other comparison was identified that would allow for an impact analysis. In addition, an outcome study focusing on intermediate and long-term effects would be premature because many CPTC products and outputs would still be in the production stage and would not be available and disseminated to the entire CPTAC community.⁹

However, the feasibility study established that an assessment of the CPTC initiative could provide useful information on 1) the degree to which the program has been implemented as intended and 2) some very short-term effects, provided that the study focused on the activities of those involved in CPTAC. This sort of assessment can provide solid information on performance, measure the progress of the CPTC program, and provide feedback to program staff and participants that can be used to help design future phases of the program.

Site visits to selected CPTAC sites and discussions with selected CPTC participants and stakeholders were the primary sources of data for the evaluation. Additional data were obtained through program reports, publications, and other available documentation. To facilitate data collection and avoid a unitary perspective on the program, ICF Macro assembled three two person teams. Each team was experienced in conducting program evaluations, and at least one person on each team had worked on the feasibility evaluation and was therefore familiar with CPTC. Analysis of the data for common themes and evidence of program activities and short-term impacts was then conducted by the team as a whole.

3.2. RESEARCH QUESTIONS

In addition to recommending the type of evaluation to be conducted, the feasibility study identified appropriate research questions. The main questions addressed in this evaluation were:

- To what extent has the program advanced collaboration in the proteomic biomarker research area?
- To what extent has CPTC had an effect on accelerating the identification of verified proteomic biomarkers for specified cancers?

⁹ The feasibility study is provided as appendix B. It contains logic models that described the outputs and outcomes for the program components.



- To what degree has the process of validating cancer biomarkers been facilitated?
- To what extent has the quality of the CPTC reagents/products been demonstrated?
- To what degree are users of CPTC reagents/products satisfied with their quality and utility?
- To what degree are program outputs used by the general cancer research community in their investigations?
- To what extent have CPTC outputs been accepted among cancer research scientists?
- To what extent have the outputs been used in publications relating to biomarker research?
- To what degree is the infrastructure built by CPTC sustainable?

To facilitate data collection and analysis, data collection guidelines were created for each of the three key components of the CPTC program: the CPTAC network, APPCS initiative, and PRRC. The guidelines outlined specific data required to address each of the main study questions. Some of the items in the guideline reflected information that would be collected from documentation, while other items had to be collected from CPTC participants. These guidelines were used during the interviews to launch discussions about the research and role of the person being interviewed. Although the primary structure of the guidelines was used in the interviews, the interviews varied considerably depending on the role of the person within the projects and his or her perspective. The resulting information was qualitative and descriptive. The data collection guidelines were drafted by ICF Macro and reviewed by NCI staff and members of the CPTC evaluation advisory committee. Final versions of the guidelines are included in appendix C.

3.3. ANALYTICAL STRATEGIES

There are two ways to measure the success of the CPTC initiative: outputs and immediate outcomes. Outputs are considered as intrinsic production results stemming from direct activities of a program, while outcomes reflect the behaviors of individuals or organizations in response to program activities. There are two ways to measure outputs and immediate outcomes for a program such as CPTC. First, the program can be measured based on scientific merit (i.e., to what degree do the products represent advances in the science). Measures of this type are usually done by surveys of the scientific community or through the number and quality of publications accepted by journals and the degree to which they are cited in subsequent studies. Also, important in assessing outcomes in this regard is the quality of publishing journal. For CPTC this intermediate measure of program success is the degree to which its publications and products are adopted by the proteomic research community or ultimately by the degree to which CPTC products facilitated the path from discovery to clinical validation. Unfortunately, the program has not been in existence for a sufficient amount of time to obtain a sense of the quality of the science or the return on the investment.

Second, there are the effects that relate to the social organization of the research. For the last several years, team science has been a focus of NIH because collaborative scientific efforts are thought to be more productive in certain circumstances. For an initiative such as CPTC, there is significant reliance on collaboration, and there is a corresponding level of risk associated with whether such collaboration can be done successfully. Therefore, the program effects can be measured in terms of how well the program facilitates collaboration and the degree to which it



does so successfully. This kind of outcome is easier to measure in the short term. The focus will be on this sort of effect, although this study will try to address the issue of scientific merit when possible. One measure that will be focused on is the degree to which CPTAC products (such as SOPs) are being used by CPTAC researchers in their non-CPTAC funded projects.

3.4. DATA SOURCES

To obtain the data elements detailed in the data collection guidelines, evaluators collected data from four main sources: CPTC documents and reports, interviews with CPTC stakeholders, CPTAC site visits, and related grant and publications data.

3.4.1. CPTC Documents and Reports

Some data items included in the data collection guidelines could be obtained through CPTC reports. For example, the major program-related activities and publications of the CPTAC centers were detailed in their annual progress reports. CPTC program highlights are also discussed on the program website and in annual reports. Much of this material was collected during the feasibility study; however, updated materials were provided by CPTC staff at the beginning of the evaluation study. CPTC program materials reviewed included the following:

- CPTC Web site
- CPTC Program Update
- CPTC governance/communications plan
- CPTC annual reports
- Overview of NCI'S CPTC programmatic requirements
- Developmental history of CPTC presentation
- Examples of SOPs
- CPTAC team summary reports from early 2009
- Workgroup progress reports
- Grant applications
- Interlaboratory Study Summaries

In addition to serving as a source of data, relevant documents were reviewed by evaluators when preparing to conduct interviews with CPTC stakeholders. Information specific to each center or researcher was used to focus evaluators' questions and provide prompts as needed.

3.4.2. Interviews With CPTC Stakeholders

CPTC program staff selected a subset of CPTC stakeholders to be contacted by the evaluators and asked to participate in phone interviews. The interviewees were selected to represent the three primary program components as well as subgroups from each component. Additional collaborators and stakeholders in the program were also included. The complete list of interviewees, including their organization and affiliation with CPTC, is included in appendix D.



Before being contacted by ICF Macro evaluators, interviewees were sent an introductory e-mail message and a consent form by Henry Rodriguez, the CPTC director. The message explained the purpose of the interviews, encouraged individuals to participate, and informed them that a member of the ICF Macro evaluation team would be contacting them. ICF Macro evaluators then e-mailed respondents, asking them to reply with a convenient time for a phone interview. Not all the interviewees responded to ICF Macro's e-mail messages, and not all those who responded were available to participate during the initial 5-week timeframe for interviews. A second round of interviews was conducted in September and October 2009 with those not initially responding. In all, discussions ranging in length from 20 minutes to 1 hour were conducted with the interviewees.

During the interviews, evaluators used the data collection guidelines to provide direction for the discussion. However, the questions asked and materials covered in each interview differed, depending on the position and practice areas of the interviewee. Evaluators requested permission to record the interview, and most phone interviews were recorded and later made available to other members of the evaluation team for analysis. Interviewers also prepared notes summarizing each interview and highlighting information sought under the data collection guidelines.

NCI staff recommended interview subjects from each of the five CPTAC centers. In addition to the PI, 4 to 7 researchers, clinicians, and other participants were chosen from each. Interviewees were drawn from both the primary grantee institution as well as from collaborating institutions.

In addition to awardees and contractors who received funding from CPTC, evaluators also spoke with individuals in the proteomic research field who are not directly involved in the CPTC program. These individuals provided insight on how the program is viewed by the larger proteomics research community, rather than the organization and operation of the program.

3.4.3. CPTAC Site Visits

During the evaluation period, NCI CPTC program staff conducted previously planned site visits at three of the five CPTAC centers: the Broad Institute, MSKCC, and UCSF.¹⁰ ICF Macro evaluators took advantage of the opportunity to join the site visits and scheduled time to interview researchers during group sessions either before or after the formal site visit activities. Two evaluators were present at each site visit. After the visit was concluded, they prepared notes detailing the discussions as well as observations made during the site visit.

In addition to site visits and interviews, ICF Macro evaluators also attended the annual CPTAC Program Coordinating Committee meeting held in June 2009 in Chicago, IL. The meeting gave evaluators the opportunity to attend presentations on program research and observe the interactions of network members, as well as participate in more informal discussions with CPTAC grantees.

¹⁰ Sites visits at the other two sites, Vanderbilt University and Purdue University, occurred earlier in the year, prior to the data collection period.



3.4.4. Related Grant and Publications Data

Data collection also focused on efforts to delineate the grant and publication activity of the investigators and centers involved in CPTC, as well as measure activities across the proteomics community. Investigators used the following sources of secondary data:

- **Information for Management, Planning, Analysis, and Coordination (IMPAC) II**—This NIH system contains information on all persons applying for or receiving grants, contracts, or cooperative agreements from NIH and other U.S. Department of Health and Human Services research agencies. It includes information related to the PI, requesting organization, review and award status, requested and awarded budget dollars, review and award dates, summary statements, abstracts, application images, and other data. The IMPAC II system contained detailed information about CPTC-related research grants.
- **Query/View/Report (QVR) system**—This system, which accesses data from the IMPAC II system, the Central Accounting System database, and the National Library of Medicine's (NLM) PubMed database, offers another important tool for monitoring the progress of the CPTC program and any developments stemming from the program. The QVR application can be used to search for and view detailed information on grant data (e.g., applications and awards). The data can be displayed in numerous formats, including Microsoft (MS) Excel spreadsheets, formatted reports, and Web page hit lists. The system contains abstracts, grant summary statements, application images, publications, PI history, and grant history.
- **PubMed**—NLM's PubMed system is a database of indexed journal citations and abstracts covering more than 4,500 journals published in the United States and more than 70 countries. PubMed includes more than 18 million citations from MEDLINE, the premier bibliographic database with a concentration on biomedicine, and other life science journals for biomedical articles. PubMed includes links to full-text articles and other related resources.

3.5. DATA AGGREGATION

Evaluators analyzed the data collected during this effort using several methods. The evaluation team held regular meetings to discuss the issues arising from the interviews and refine the data collection process, contacting CPTC program staff as necessary to clarify aspects of the program. The evaluation team also developed a matrix of themes that emerged from each interview. Examining the questions, opinions, and issues relating to each interview and logging them in a central location allowed evaluators to develop an understanding of the commonalities across centers and across larger program components.

3.6. LIMITATIONS

This effort was limited by the maturity of the CPTC program and the timeframe for data collection and analysis. At the time of this assessment, the CPTC program had been operational for less than 3 years, and some elements of the program had only recently reached full operation. For example, the consensus among interviewees was that the PRRC component had only recently reached full functionality and that reagents had not been available to the public long



enough for much data on their use or quality to be available. As indicated previously, because the program is essentially at its midpoint, its intermediate and long-term goals cannot have reasonably been attained yet. We also discovered that many of the short-term outcomes, such as utilization of the reagents produced by the program, could not be addressed.



4. ASSESSMENT OF ORGANIZATION AND COLLABORATION WITHIN THE CPTC PROGRAM

One of the principal areas of interest for this assessment is how the CPTC program organized its activities to promote team science and collaboration. During our discussions with CPTC researchers, several themes emerged related to organization and collaboration, including:

- NCI CPTC program leadership and support (Section 4.1)
- Collaboration within CPTAC (Section 4.2)
- Role of the PCC as a forum for decisions and discussions (Section 4.3)
- Workgroups as the CPTAC engines of productivity (Section 4.4)
- Development of SOPs, technologies, and platforms (Section 4.5)
- Transitioning to clinical and relevant samples (Section 4.6)

4.1. NCI CPTC PROGRAM LEADERSHIP AND SUPPORT

The success of CPTC relies heavily on how the program is administered by NCI program staff. Our observations at meetings and from interviews conducted with researchers involved in all three components resulted in our identification of the following several behaviors that supported the program's objectives:

- Developing an overall collaborative structure for the program
- Managing CPTAC relationships and collaborations
- Extending the network beyond the CPTAC centers
- Developing relationships with non-funded entities
- Ensuring that the program's achievements are recognized

4.1.1. Developing an Overall Collaborative Structure for the Program

The CPTC program's three components (CPTAC, APPCS, and PRRC) all aim to provide a basis for more effectively identifying proteomes in biological tissues and fluids, but they are different in structure and objectives and could have evolved as separate initiatives. Although the components are treated separately from an administrative perspective, our observations indicate that most individuals participating in the various components are involved to some degree with the overall program in general. The APPCS component in particular has connections with the CPTAC program as well as with the PRRC component. For example:

- Some APPCS grant awardees, particularly those who are located at CPTAC centers, have been involved in CPTAC workgroups. In particular, Dr. Mani and Dr. Tabb work with the Broad Institute and the Vanderbilt University CPTAC program. Such involvement is likely to result in greater coordination between the innovations emerging from the APPCS program and the activities of CPTAC.



- In some cases, APPCS awardees use reagents developed by the PRRC component. For example, work performed by John Chaput of Arizona State University has used CPTC reagents.
- There is an annual CPTC conference open to all researchers in all components. The papers delivered have served as a basis for some collaborations wherein individual researchers identify synergies between their research efforts and CPTAC efforts.

The intention of program staff seems to expose major participants (i.e., CPTAC center staff) to other critical elements of the program and encourage the involvement of other participants in the total CPTC effort. Some interviewees (particularly APPCS awardees) expressed an interest in learning more about the activities under CPTAC, so there may be the potential for advancing this integration further. Thus, despite the functional and administrative boundaries between the program components, an effort is being made to bring together individuals from the various components when it is advantageous.

4.1.2. Managing CPTAC Relationships and Collaborations

Managing grant activity for a program such as CPTAC can range from a directed, hands-on approach to a flexible approach that does not interfere with the progress of the grant. In the former, the resulting interactions may stifle creativity and collaboration; in the latter, the lack of structure may result in lack of direction and a tendency to pursue non-collaborative results. Our interviews with CPTAC investigators have characterized NCI staff as pursuing a middle course for managing grant activity—i.e., collaboration was promoted without NCI staff micromanaging results or being overly involved in directing the science. The evidence from interviews seems to indicate that this approach encouraged buy-in from the various centers, thereby supporting the collaborative nature of the effort. Critical to this effort was the establishment of mechanisms such as the PCC and the workgroups that allowed grantees to work collaboratively. Discussions and decisions made within both mechanisms were led by grantees. NCI staff, at least in the PCC session that was observed, contributed to the discussions and provided information about NCI's perspectives on the program and its goals as well as about other activities at NCI (such as the use of funding from the American Recovery and Reinvestment Act of 2009).

4.1.3. Extending the Network Beyond CPTAC Centers

NCI CPTC program staff has made various efforts to extend the capability of the CPTAC network through contracts and other vehicles. Some of these efforts are integral to the functioning of CPTC. For example, expertise in statistical and experimental design and techniques is currently being provided by the National Institute of Statistical Science, a highly regarded organization in that area, and formerly by Texas A&M University. This expertise was considered necessary to provide accepted methodologies for measuring and comparing verification technology-based results in a rigorous and unbiased way. Another example is ANL's involvement in the program. ANL has the capability to develop and produce customized reference protein standards and labeled proteins for CPTAC mass spectrometry assessment studies.



Another example of extending the network beyond CPTAC centers is the support of the development of ProteomeCommons. CPTC staff established a contract with the University of Michigan to develop ProteomeCommons.org, an instance of Tranche that allows individuals to share large data and information sets. As of early summer 2009, the Web site housed 94 tools, 6,416 datasets, 22 publications, and 15 other groups aside from CPTAC; there is a total of 9.4 terabytes of information stored in more than 12 million files. The large datasets that relate to experiments using mass spectrometry and other similar technologies can be uploaded and made available to the public. The datasets are also downloadable, providing researchers with a means of reanalyzing data collected from studies conducted at other sites. Tranche provides a common forum for CPTAC centers to address their data needs, and a program management and annotation tool has been developed under the CPTAC initiative. This effort has resulted in a repository for the data produced by the various studies conducted by CPTAC and by other studies involving CPTC investigators holding APPCS grants. This results in more transparency, especially with the accompanying annotations and documentation, as well as allowing investigators to reanalyze and verify the results of other studies.

The involvement of NIST, the foremost Federal agency on measurement science, also extends the CPTAC network. Although NIST's early role in the program involved the preparation and distribution of NCI-20 and yeast-based study materials, its focus has evolved into one that emphasizes reference materials and standards for annotating large mass spectrometry datasets and the development of analyses relating to the experiments. In addition, NIST's involvement in the analyses generated by the CPTAC centers have produced approximately 50 metrics for assessing reproducibility. This activity resulted in a paper and subsequent use in CPTAC laboratories. NIST collaborates with all the CPTAC centers and workgroups, particularly with the Unbiased Discovery, Digestion, and Bioinformatics workgroups.

Two companies have recently built on NIST's work on metrics and have developed metrics software. ProteomeSoftware, makers of Scaffold, a widely used software package for proteomics, have produced MassQC, an online analysis service. Users from the international community upload data, and the software tracks performance with time in the five key areas of a proteomics workflow. All the metric "readouts" were developed by NIST under CPTAC auspices. The other company, Bioproximity, used some of the key features that CPTAC published in a paper in *Molecular and Cellular Proteomics*¹¹ to design a similar Web-based system.

4.1.4. Developing Relationships With Nonfunded Entities

Another type of relationship involves those entities that are interested in working with CPTC outside of the funding streams for grantees. (Exhibit 5 displays some of these relationships). Of particular interest are private companies, but collaboration with Federal agencies, such as the FDA is also important. NCI staff has pursued these ties with the dual aims of obtaining

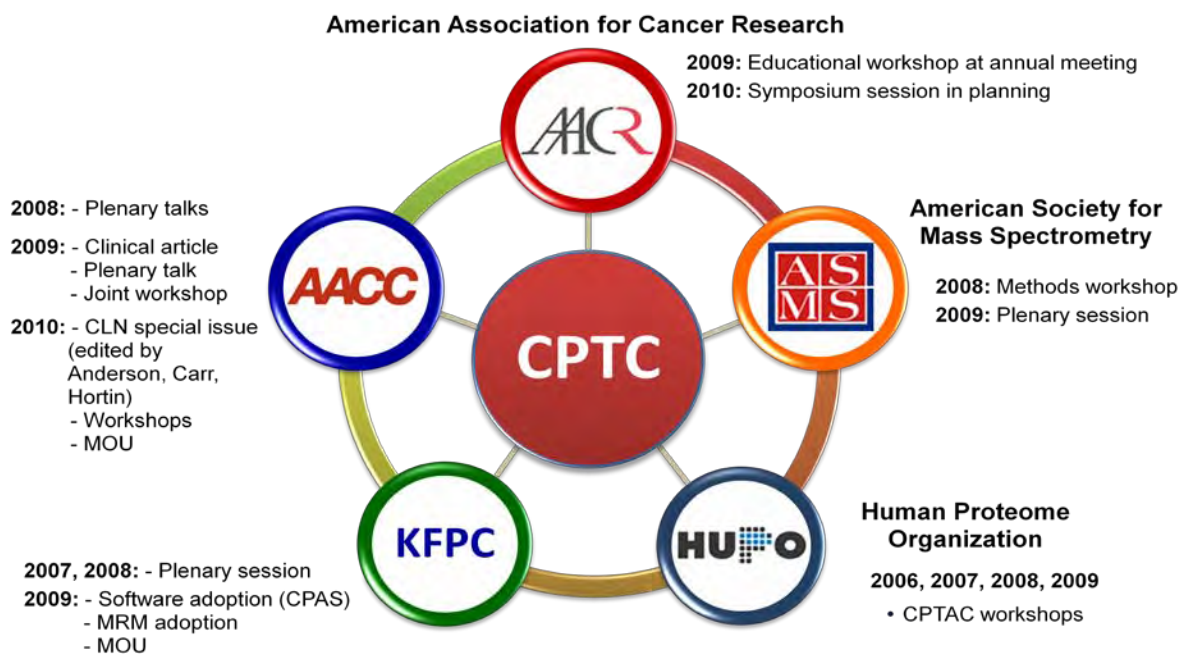
¹¹ Rudnick, PA, et al. "Performance metrics for liquid chromatography-tandem mass spectrometry systems in proteomic analyses and evaluation by the CPTAC network." *Molecular & Cellular Proteomics*. (Oct. 2009).



additional participation to further develop the pipeline and for promoting the products and results of the CPTC effort. The following examples illustrate these relationships:

- The success of any effort to translate CPTAC findings into the clinical setting depends on FDA approval. Success to obtain approval has been hindered by the inability of researchers to generate verifiable proteomic biomarkers. In addition, the methodologies being studied under CPTAC are new to FDA, which creates uncertainty both on the part of researchers in how their findings should be presented in a 510(k) approval application to the agency and on the part of FDA in evaluating the results using the methodology. To address the latter concern, NCI and FDA have established a relationship and have committed to producing mock 510(k) submissions for the community, which contain information from hypothetical experiments using methods being examined under the CPTAC grants. The Purdue University and Broad Institute teams played a lead role in preparation of these mock 510(k) submissions.
- Due to the potential impact of CPTAC consortium wide study results and implications, instrument makers have expressed interest in participating in the verification studies and other efforts. NCI officials have expressed interest in being more inclusive in recruiting these companies and others, who might be interested in developing test kits and associated products.
- As described previously, the PRRC core produces high-quality well characterized reagents. In order to market these reagents to a wider community, companies such as Millipore and imaGenes have asked to distribute its reagents to researchers in the United States and Europe.

Exhibit 5. Relationships With Non-funded Entities





4.1.5. Ensuring That the Program's Achievements Are Recognized

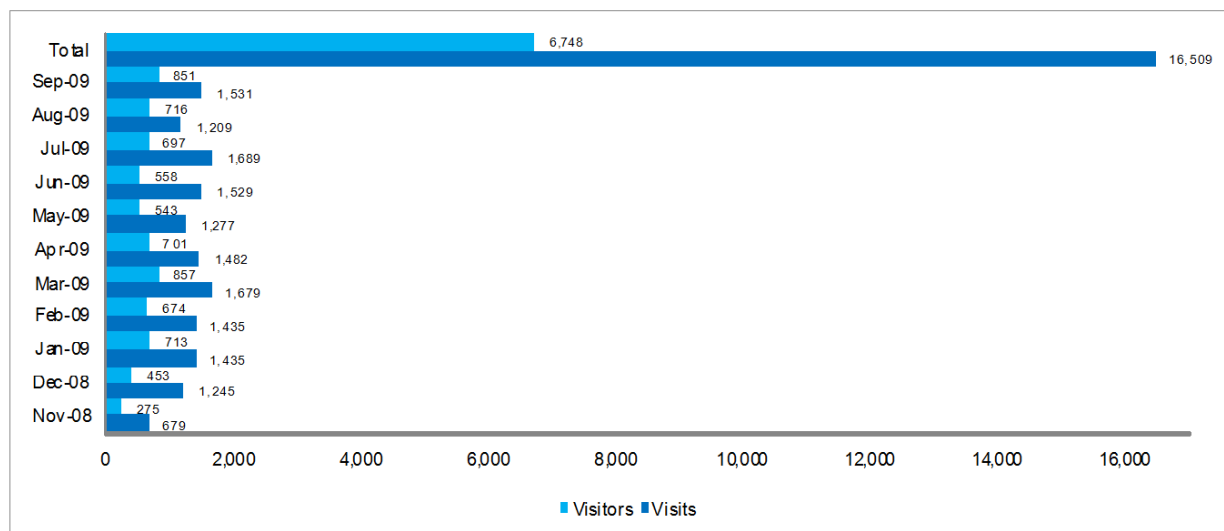
Alliances and outreach will inevitably help the CPTC program to promote interest among the general proteomics community in CPTC activities and products. Although the true effect on the more general community cannot be measured until CPTAC products have matured and been presented to the public through publication and other dissemination efforts, it is evident that NCI staff are making a concerted effort to reach out to individuals in other communities. CPTAC has close relationships with other NIH Institutes and Centers that are interested in the general technology and methodologies being developed within CPTAC and APPCS. For example, CPTC has established a relationship with the National Heart, Lung, and Blood Institute (NHLBI), which has an interest in proteomic biomarkers as indicators of cardiovascular disease. NHLBI's efforts to identify successful biomarkers would benefit from the work that CPTAC has to offer, and NHLBI recognizes the benefits of CPTC's efforts to create a repository of high-quality reagents.

Information about CPTC program achievements are also being disseminated through collaborations with associations to present CPTC activities and products. One example involves the American Association of Clinical Chemistry (AACC), which is tracking CPTC efforts and has formed relationships with CPTAC staff through meetings and other venues. The relationship between CPTC and AACC is a particularly close one, in which CPTC activities are reported to AACC members through participation in annual meetings and in editorials and special issues of the journal *Clinical Chemistry*. Other nongovernment organizations involved with CPTC include the American Association for Cancer Research, which provides the opportunity for CPTC staff to present at workshops, and Consumer Advocates in Research and Related Activities, which connects CPTC with a community of patients knowledgeable about research and technologies. Through these and other organizations, CPTC staff have presented at various sponsored workshops and conferences. Since 2007, program staff has given 22 non-NIH-sponsored presentations in the United States, Europe, and Asia.

A final indicator of outreach activities is the various publications, podcasts, and Webinars made available to the larger research community and general public. The CPTC Web site is one example of CPTC's outreach efforts. In the last year, there have been 16,509 visits to the Web site and 6,748 unique visitors. Most visits are from users in the United States and Canada (14,286), with the remainder from users in 79 other countries. Of these, users in South Korea, the United Kingdom, India, China, and Germany accounted for more than 100 visits per country. Exhibit 6 shows a relatively steady pattern of visits during this time period.



Exhibit 6. Number of Visits and Visitors to the NIH CPTC Web Site per Month for 2008–2009



4.2. COLLABORATION WITHIN CPTAC

The five cooperative agreements issued under the RFA represented a significant investment by NCI. The selection was accomplished through the NIH peer-review process and based on the responses to the RFA. All the centers were conducting work in proteomics prior to the RFA and viewed the RFA as a means of furthering their work from a different technological development and standardization perspective. For example, Vanderbilt University received funding from a private contributor to establish the Ayers Institute, the focus of which was early detection of cancer, particularly colon cancer. The methods of and approaches to Vanderbilt's discovery work focused on using mass spectrometry to identify protein signals in tissue. On the other hand, the Broad was conducting ongoing work related to identifying biomarkers using sera and had developed and focused on MRM approaches. MSKCC also had a long-standing program in proteomic research with a focus on robotic technologies.

The proteomics cancer research field is a relatively small one, especially when experience with the application of mass spectrometry instrumentation to the field is considered. However, interviews with CPTAC members indicated that aside from professional contact at conferences and other forums, there was little collaboration across center teams and that in general there had been no interaction on collaborative research prior to CPTAC. But interviewees indicated that many of the partners on the centers' teams had been working together prior to the RFA, e.g., the Broad team and FHCRC.

CPTAC added an emphasis on cooperation among the five centers and a new focus on the methods and technology that guide the process of verifying proteins, rather than discovering new proteins. The original applications and the interviews with center leads suggested that there was some concern about the requirements stated in the RFA, particularly with regard to the overall scope of work and how successful applicants would be able to merge their efforts and research



emphases within the team research model. Regarding the scope of work, there was some concern that it was not defined adequately. During the interviews, several respondents from different centers indicated that the program initially lacked a strong sense of mission or focused goals.

As a result, each center presented an approach in its application that represented the center's research priorities and agendas as applied to the general purpose specified in the RFA. Although the centers addressed the issue of collaboration, the applications were rather cautious regarding how these collaborations would proceed, given that the centers did not know who their partners would be and what approach would emerge to guide the effort. Our interviews with staff of the five centers and individuals knowledgeable about the program indicated, however, that initial caution was replaced by what was described as a useful collaborative venture. But the initial reaction of the centers highlights an important question that relates to all team science efforts: how can very accomplished researchers, each with his or her own research agenda, come together to build an infrastructure to support the generation of useful proteomic cancer biomarkers?

All those interviewed indicated that the network, working together, was able to chart a path that would allow them to work toward the program's goals. But it was clear that some CPTAC researchers felt that the initial uncertainty had hampered the early days of the program.

4.3. ROLE OF THE PCC AS A FORUM FOR DECISIONS AND DISCUSSIONS

The PCC was identified in the RFA as a mechanism for bringing together the five centers to synchronize work across the centers and make decisions about the program. The PCC has also become instrumental in what is a major outcome: establishing close working relationships among the groups.

Relative to the PCC, our perspective was limited to observing one session, held in June 2009 in Chicago, IL. The agenda was organized around workgroup research activities, with technical discussions of these activities and the results. There were also presentations and discussions centering on other CPTAC-related activities. The session was attended by the PIs from all the centers as well as other staff who gave presentations. The meeting was participatory, with individuals from the centers and others discussing and responding to the presentations. It appeared that the event was that of an equal partnership, with NCI staff contributing where they had information on other aspects of the program (e.g., informatics initiatives or the reagent initiative).

Aside from making decisions about CPTAC activities, the PCC also functions as a forum for discussing the purpose and goals of the effort. With regard to workgroup discussions and potential papers that were being generated from the interlaboratory studies, there were discussions by PCC members about clarifying the role of CPTAC verification or discovery. These discussions were not so much about the role of CPTAC in terms of creating standardized guidance for conducting proteomic research, but rather about the boundaries between establishing the framework for conducting verification and actually conducting verification (or even targeted discovery). During a later interview, one of the participants speculated that this



was important because the centers represented somewhat different perspectives on conducting proteomic research; discussions within the PCC were a way for issues to be vetted and addressed within the group context, leading to perhaps a more comfortable relationship among participating researchers through shared commonalities. Several other points were made during the session (i.e., on the use of experimental methods and animal models) that provoked discussion about the premise of CPTAC.

Our observations and the supporting information gathered from the interviews point to a group of centers whose relationships are evolving. Several individuals indicated that the activities in Year 1 focused on reaching a stage where the centers felt comfortable with each other. This related not only to learning about each other's research resources and platforms but also to the question of how to establish productive interactions supportive of team science while maintaining the research thrust, creativity, and focus of each center. This process was not unusual, in that collaborative efforts are often complicated by competing agendas and priorities, which must be reconciled. Year 2 was a period in which the science made progress. This is not to say that each of the centers does not still have its own interests and preferences related to conducting research, but rather that the centers seem to be aligned sufficiently at this point to be productive in terms of meeting CPTAC goals.

4.4. WORKGROUPS AS THE CPTAC ENGINES OF PRODUCTIVITY

Workgroups are established by the PCC and are intended to solve cross-cutting problems or facilitate interlaboratory collaborations. In general, the workgroups meet once a month via conference call. There are assigned leaders, and the groups are open to participants with an interest in the topic. The following observations were made based on interviews and documentation:

- Nine studies have been completed or are in the process of being designed and completed (exhibit 7 provides basic information on the studies). They have involved cross-center and cross-participant groups, including some organizations that are within the network but are not linked directly with a CPTAC center (e.g., NIST). The studies seem complex, not only from the perspective of the science but also from the perspective of organizing teams and participants to work on the study. Study 9, which involves cross-platform studies in 11 different laboratories, is an example.
- The workgroups seem to be the engines of collaborative team science. They consist of large groups of investigators at various levels and with different skill sets and usually meet once a month. The interdisciplinary nature of these meetings and their size allows the workgroups to tackle complex problems related to developing the science, establishing test procedures, and handling the implementation logistics.
- Taken together, the workgroups exhibit the evolution of the program's priorities and interests, including the need to end efforts in ineffective workgroup areas. For example, there was discussion of eliminating the bioinformatics workgroup at the Chicago PCC meeting. This workgroup had accomplished some specific goals earlier in the grant period, but now found itself without specific issues to address. The elimination of this group does not



necessarily mean that the group could not be reconstituted if an appropriate problem for it to address is identified.

- Issues have arisen in the functioning of the workgroups, attributed to a diversity of opinion within those groups. Most workgroups seem to function well without excessive attention to resolving group dynamics issues that sometimes pose barriers to collaboration. Issues affecting group functioning that were cited in the interviews include encouraging participation, constructing clear goals and objectives at the outset, deciding on a group's relationship as a supportive element for other groups, and producing critical experiments and studies.
- APPCS researchers not aligned with the centers expressed an interest in participating. However, there were indications at the PCC and in other site visit forums of the need to involve more organizations. For example, one presentation at the PCC meeting made it clear that it is important to extend the workgroups to instrument manufacturers. There seems to be interest on the part of these manufacturers and others who are not part of the network in becoming involved. The question then becomes how to manage a larger number of individuals who want to participate in the workgroups.

Exhibit 7. Interlaboratory Studies

Study Name	Title	Workgroup
Study 1	Measuring Variability in "Shotgun" Proteomics (No SOP)	Discovery
Study 2	Measuring Variability in "Shotgun" Proteomics (With SOP)	Discovery
Study 3	Yeast as a Model Proteome	Discovery
Study 4	Initial Multiple Reaction Monitoring (MRM, MRM of Proteins Spiked Into Plasma	Verification
Study 5	Suppressive Effects on BSA Addition on Yeast Detection Efficiency	Discovery
Study 6	Include Spikes Into Yeast of the Sigma Universal Proteomics Standard (UPS) at Five Concentrations That Differed by a Dilution Factor of 3	Discovery
Study 7.1	MRM Analysis of [$^{12}\text{C}/^{14}\text{N}$] and [$^{13}\text{C}/^{15}\text{N}$] Synthetic Peptides Spiked Into Diluted, Digested Human Plasma	Verification
Study 7.2	Single Site Digestion of Target Proteins Spiked Into Diluted, Digested Plasma	Verification
Study 7.3	Simulation of a Verification Study Across CPTAC Sites	Verification
Study 8	Tumor Tissue Proteomes and Detection of Corresponding Phenotypic Differences	Discovery
Study 9p	Pilot Study to Implement Scheduled MRM: Evaluation of Time-Targeted MRM Across Platforms	Verification
Study 9s	Run System Suitability Samples for Study 9	Verification
Study 9	Expand Study 7 to Improve Sensitivity and Multiplexing Capabilities	Verification

4.5. DEVELOPMENT OF SOPS, TECHNOLOGIES, AND PLATFORMS

One important set of products being generated by CPTAC will be SOPs, which currently provide guidance for researchers on conducting their experiments in a comparable fashion under CPTAC but will eventually be disseminated to the proteomic community at large. A variety of areas are being addressed by SOPs, including sample collection, sample preparation and storage,



equipment calibration and operation, and data analysis. In addition, there are protocols for describing how other aspects of the experiments are conducted by CPTAC members.

One important aspect of SOP development is the determination of their specificity and utility, resulting in the evolution of the SOPs. For example, study 1, which focused on measuring variability in “shotgun” proteomics, employed no SOPs, and study 2, which extended the investigations of study 1, used a limited set of SOPs. Both studies demonstrated distinctly higher levels of variability across laboratories and resulted in the need for better-defined SOPs. These and later workgroup studies clearly demonstrate the critical importance of generating well developed SOPs that are applicable across different laboratories with different technologies and methodologies. In a number of interviews and in our observations, it was apparent that SOPs are being assigned a critical role and that they are being shared among CPTAC members. An important example of an SOP developed from a workgroup collaboration is a protocol for collecting clinical samples. One source of variability involves how samples are collected, and thus there was an effort on the part of some to develop a well-defined protocol. This protocol has been instrumental in standardizing the procedures for collecting plasma samples from humans. In addition to the generation of an important protocol, this example also illustrates the group’s interactions and responses to specific needs.

Although not specifically focused on creating technology, the CPTAC teams have advanced the existing technology. Evidence indicates that each center is focused on examining how to improve its instruments and the platforms that it uses to create greater sensitivity and throughput. Our interviews and observations indicated that the groups are seeking new ways to prepare samples for more effective detection through mass spectrometry or affinity capture platforms, as well as ways to work with their instruments and interpretative software to understand the data generated by an analysis. For example, CPTAC is supporting approaches for analyzing the large, complex datasets that emerge from mass spectrometric processing of potential biomarkers. This interest is manifested in Skyline, a Windows client application for building Selected Reaction Monitoring/Multiple Reaction Monitoring methods and analyzing the resulting mass spectrometer data. Skyline is being supported through a subcontract by the Vanderbilt University team. Another example in the informatics field is the Tranche data repository. The proteomics instance was built to address how to facilitate the distribution of large datasets emerging from mass spectrometric analysis for reanalysis. A technological approach advanced by the Broad is the use of MRM with SISCAPA. Although no new technology has been developed under this contract, the program has encouraged further exploration of existing technologies.

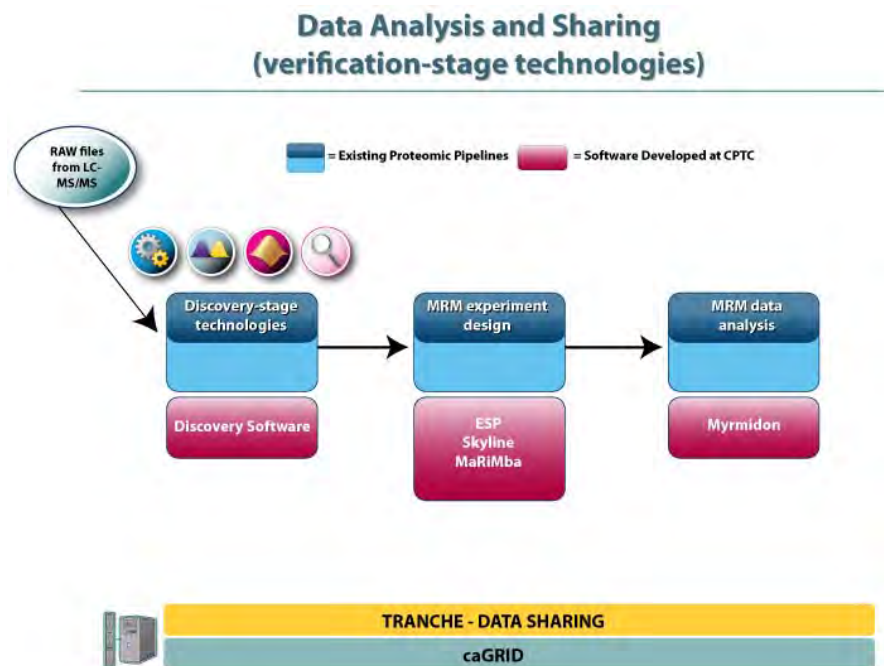
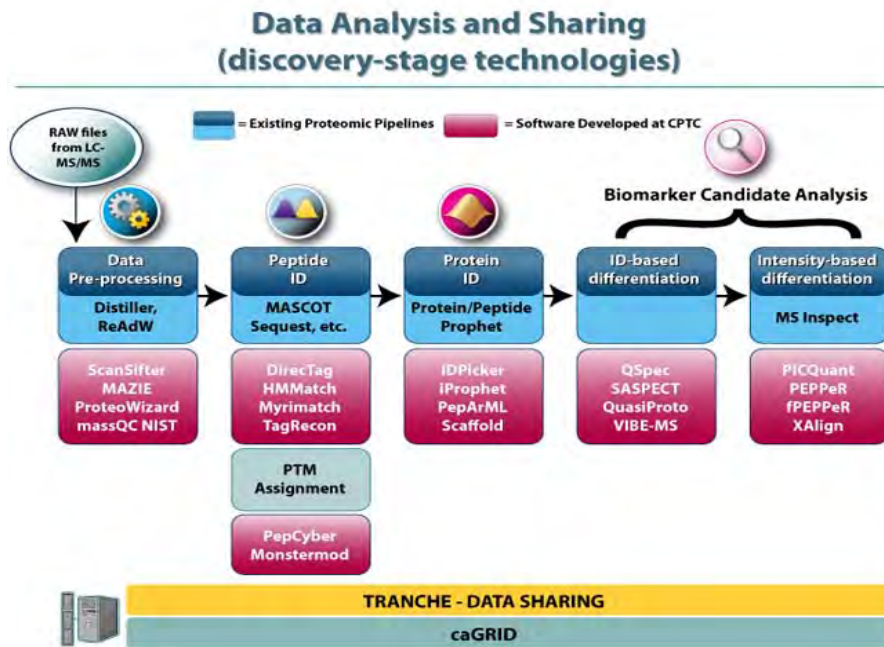
Technology also includes software development, which is one of the focuses of the APPCS component, but also involves CPTAC as a sponsor. For example, the Tranche database is an important element in disseminating study results, as is Skyline for interpreting the data. The former is supported by CPTC directly, while the latter is supported by Vanderbilt University under its CPTAC grant. In total, CPTAC is involved in supporting or assisting in the development of more than 20 software programs that meet needs from points along the entire proteomic pipeline (see exhibit 8).



Although not related to technology or platforms, the development of mock 510(k) applications is another example of the program advancing the field. CPTC has established and maintains a relationship with FDA through the NCI-FDA Interagency Oncology Task Force (IOTF). One output of this collaboration is a protocol for submitting materials for FDA approval. One of the issues with the identification of proteomic biomarkers for the clinical setting is that few assays are being verified and validated and therefore cannot meet the basic FDA requirements for approval. Those researchers submitting applications have little or no knowledge of how to assemble the evidence required by FDA. As a result, the case for verification and validation is underestimated. Another factor is the unfamiliarity on the part of FDA staff with mass spectrometry-based multiplexed proteomic methods that are being used in this research and the data generated as a result. Such familiarity would certainly lead to greater confidence in interpreting the results of tests on a particular biomarker. CPTAC leaders met with FDA staff to discuss these issues, with a number of results. The first is a white paper summarizing the IOTF Molecular Diagnostics workshop; the second is the development of two mock 510(k) applications that have been submitted for FDA critique and comments. The mock applications are a serious effort to develop an application that meets FDA requirements, without submitting an actual product or biomarker kit for approval. The FDA, on its part, will treat them as actual applications and provide feedback on their acceptability. The expectation is that the mock applications will be published in journal articles and will serve as templates for researchers submitting similar applications. FDA indicated that it is seeking to develop guidelines that will help researchers prepare more complete applications and reduce the interaction needed to process the application.



Exhibit 8. Software Packages Developed With CPTC Support





4.6. TRANSITIONING TO CLINICAL AND RELEVANT SAMPLES

The interviews and observations from the site visits indicated that CPTAC network researchers thought it was critical to begin conducting research on biological samples. There was a consensus among the interviewees that the early work on yeast cultures and the basic standardization experiments that had been conducted were important and necessary. Furthermore, many interviewees said that those experiments would never have been undertaken without the efforts of the CPTC program. However, it was made clear that it is time to graduate to samples from actual patients. In fact, some researchers said that they owed it to cancer patients to spend their time on work that could lead directly to clinical treatments. In addition, although researchers felt that the earlier work had improved standardizations and SOPs, there was the sense that these same standardization improvements and SOPs now need to be developed for human samples and protocols.



5. SUMMARY AND CONCLUSIONS

In section 3, we referenced a number of questions addressed by this report. In this section, we summarize our observations in terms of addressing the questions and present conclusions on factors that may affect the future of the program.

5.1. TO WHAT EXTENT HAS THE PROGRAM ADVANCED COLLABORATION IN THE PROTEOMIC BIOMARKER RESEARCH AREA?

Section 4 detailed the themes that emerged concerning the organization of/and collaboration within CPTC and CPTAC. In general, as was stated in some of our interviews, collaboration among scientists across institutions is difficult. However, it is considered necessary by the NCI and program for advancing the science. Our interviews with individuals within and outside of the CPTC program provide evidence that the program has been remarkable in its ability to establish a collaborative venture. One interviewee who had observed the CPTAC initiative from its inception remarked that it was unpredictably successful in this regard. Integrating distinguished and capable researchers, each with his or her own agenda and approaches, into a group capable of functioning together at a high level was a considerable achievement. Comments generally suggested that it was a remarkable accomplishment to agree on common objectives and activities to advance the program. In fact, through a review of the responses to the RFA and through retrospection on the part of interviewees, it seems that initial interactions among the CPTAC centers were rather guarded and cautious. However, the evolution of this group was demonstrated during the July PCC meeting, at which a special session devoted to examining other non-CPTAC activities pursued by the centers was proposed. Even the suggestion of a session on these works in progress implies a sense of trust among participants and can be seen as a major milestone in terms of fostering collaboration.

To some extent, this sense of cooperation may be demonstrated in the ability of the centers to pursue their own paths while focusing on the common issues and problems for which CPTC has brought them together. In other words, the centers and investigators do not seem to be in direct competition, which has been identified as one reason for an increased sharing of experiences and results. In addition, the way in which NCI staff administers the program may have also fostered cooperation. NCI staff was praised for avoiding over managing the program while still providing major support for the centers. NCI's role is a facilitating one, allowing the centers to focus on meeting program goals in their own ways. However, NCI has been on the forefront of advocating for aspects of the program where leadership was needed, such as the reagents program, the establishment of data repositories, and increasing the reach of the network by adding new participants from both the private and public sectors.



5.2. TO WHAT EXTENT HAS CPTC HAD AN EFFECT ON ACCELERATING THE IDENTIFICATION OF VERIFIED PROTEOMIC BIOMARKERS FOR SPECIFIED CANCERS?

At this early stage in CPTC's existence, the basic products needed to accelerate the identification of proteomic biomarkers within the general cancer research community cannot be evaluated. CPTC is still working on the infrastructure for doing so within the limited number of CPTAC centers. However, our interviews suggest that there are significant ongoing projects that have resulted in an advancement of SOPs that probably would not have occurred otherwise or at least in the near future. In our discussions with CPTAC researchers, we learned that CPTAC has accelerated the effort to standardize existing technology and that this work would not have been accomplished without the CPTC program, or at least it would have taken much longer to develop the technology and infrastructure for ensuring that verification is not hindered by differences in operating procedures and instrumentation. The fact that cross-institutional biological sample repositories have been established supports this assertion. Another example of CPTC's achievements is the establishment of the Tranche data repository, which allows researchers to download datasets for reanalysis. A final example is the PRRC component, which aims to provide standardized biological materials for testing.

5.3. TO WHAT DEGREE HAS THE PROCESS OF VALIDATING CANCER BIOMARKERS BEEN FACILITATED?

The validation of cancer biomarkers is a consequence of establishing or verifying that a particular protein discovery is not an artifact of the particular instrumentation or protocols used in the discovery laboratory. It should be noted that all the efforts to create standardization in verifying discovered cancer biomarkers apply to the validation stage as well. For example, SOPs established for drawing blood samples, which addressed what was found to be a significant source of variation, will possibly guide also validation efforts. Another important contribution of the CPTAC program for this stage of the pipeline is its efforts to create documents for understanding FDA requirements for 510(k) applications. In developing two mock 510(k) applications with the involvement of FDA, researchers and companies will enhance their understanding of FDA requirements and be able to set up validation tests to meet those requirements. In addition, FDA will increase its understanding of the new technology that underlies proteomic discovery, verification, and validation.

5.4. TO WHAT DEGREE ARE PROGRAM OUTPUTS USED BY THE GENERAL CANCER RESEARCH COMMUNITY IN THEIR INVESTIGATIONS? TO WHAT EXTENT HAVE CPTC OUTPUTS BEEN ACCEPTED AMONG CANCER RESEARCH SCIENTISTS?

It is somewhat premature to gauge the acceptance of CPTC outputs among cancer research scientists because the program's research efforts are still ongoing. Interviews conducted with researchers not directly funded by CPTAC indicated that although there is some knowledge of the CPTC program, there seems to be little or no detailed knowledge of its products (See



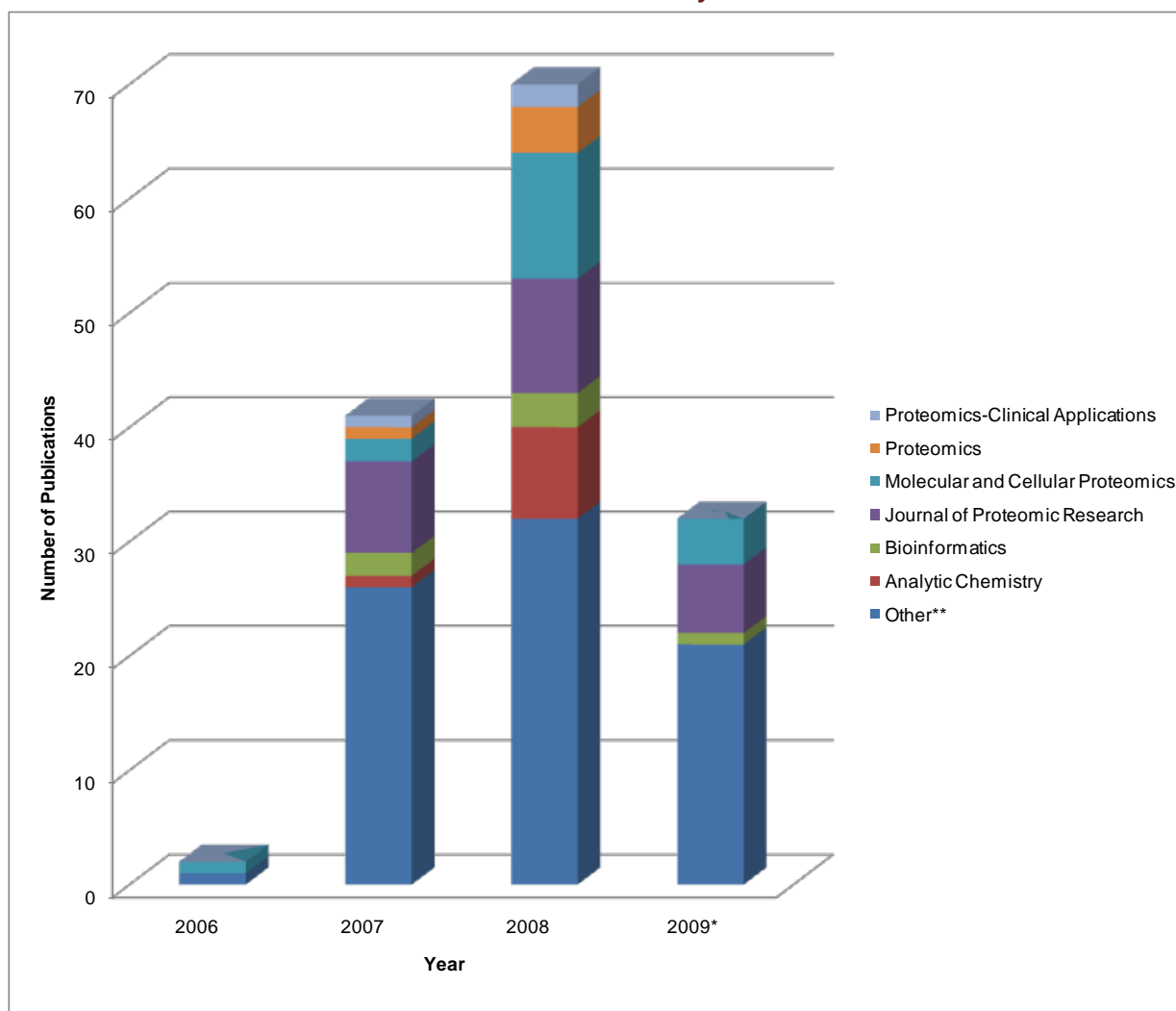
appendix D). However, among those funded by the program, interviews indicated that the researchers used or planned to use SOPs and other CPTAC products in their non-CPTAC work. At least two of the sites used SOPs generated at other laboratories, although they had been modified slightly to fit the site's instrumentation. With regard to the APPCS and PRRC components, there seems to be some sharing of outputs with the broader community, although it is difficult to determine the level of acceptance. For example, there has been some interest shown in the PRRC program that indicates acceptance of the products; however, it is uncertain whether the researchers were curious about the utility of the products or saw them as a necessary component of their research. There is also evidence that some of the algorithms generated under the individual research grants have been disseminated to other researchers. However, these products, like the reagent core outputs, are still in the earliest stages of reaching the research community at large.

5.5. TO WHAT EXTENT HAVE THE OUTPUTS BEEN USED IN PUBLICATIONS RELATING TO BIOMARKER RESEARCH?

To a large extent, publications reflect the main channel for disseminating the results of CPTC efforts. Again, it is too early to determine the impact of publications on the general community, but there has been significant publication activity by those involved in the program. As of June 2009, there were 145 journal articles published by individuals associated with CPTC since the program's inception. Exhibit 9 presents the number of articles by year and journal in which they were published. The data indicate that the number of articles has increased dramatically since 2006, with 70 articles published in 2008. (The 32 articles published in 2009 only include those published as of June, and the number as of that time is consistent with the 2008 total.) If the 2006–2009 period is used as a benchmark, this number compares with the 353 articles that were published on cancer proteomic biomarkers, 319 articles that were published in the area of cancer proteomic biomarkers and mass spectrometry, and approximately 23 articles published in the area of cancer proteomic biomarkers and affinity platforms in the field as a whole. These benchmarks demonstrate the overall contribution of CPTAC authors to the general field as well as an increase in published articles since 2006, which likely reveals an increased interest in this area, perhaps a result of CPTC's involvement. The journals these studies were most frequently published in are the *Journal of Proteomic Research* (24 articles) and *Molecular and Cellular Proteomics* (18 articles). CPTC publications have also appeared in journals of bioinformatics, mass spectrometry, and analytic chemistry. In addition to these publications, there are the products of the workgroups themselves. These have been somewhat slower to reach the dissemination stage because of the lead time to perform the research and the original dissemination strategy, which was attempting to publish CPTC-related papers as a group.



Exhibit 9. Number of Publications by Year and Journal



* Includes only those publications actually published as of June 2009.

** Other includes those journals with less than 6 total CPTC publications during the 5-year period.

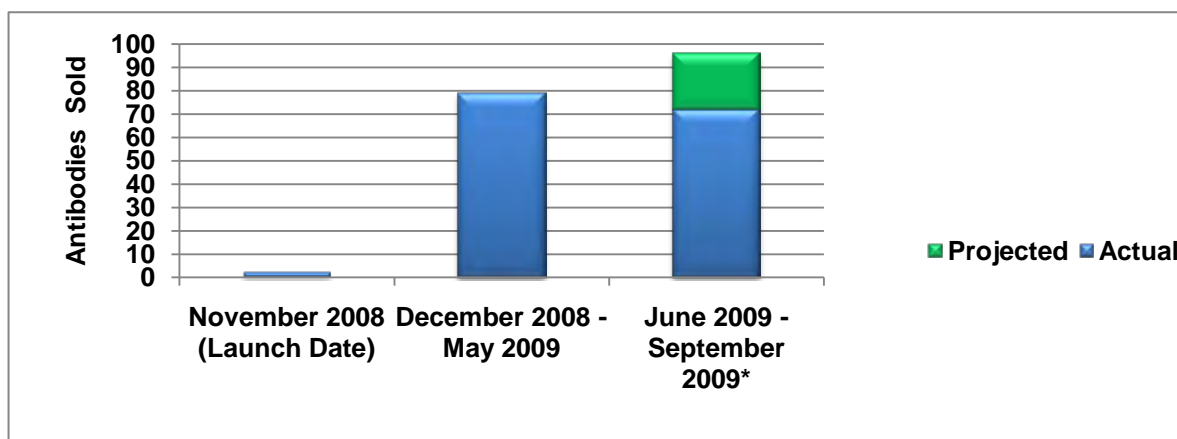
5.6. TO WHAT EXTENT HAS THE QUALITY OF THE CPTC REAGENTS AND PRODUCTS BEEN DEMONSTRATED? TO WHAT DEGREE ARE USERS OF CPTC REAGENTS AND PRODUCTS SATISFIED WITH THEIR QUALITY AND UTILITY?

The PRRC component has the goal of making well-characterized monoclonal antibodies available to researchers. This component has only recently reached a stage at which products have appeared, and the number of products on the market is still comparatively low. In general, the reagents have not yet been used in CPTAC interlaboratory studies, nor are they in widespread use among proteomic researchers. As of July 2009, based on information from DSHB, 48 researchers have inquired about the products made available through this program component, and 130 units have been sold. DSHB only began receiving orders in late 2008, and this coincides with the launch of the CPTC reagents portal (<http://antibodies.cancer.gov>).



DSHB provided an update of the products sold as of September 4, 2009. In all, 23 additional antibodies had been purchased. Eighty-one of the total antibodies sold were purchased by domestic researchers, and 72 were purchased by foreign researchers. Ninety-two of the purchasers were from universities, 28 from various institutes, and 6 from for-profit companies. To date, none of the customers purchased an antibody more than once.

Exhibit 10. Number of Antibodies Purchased Through September 4, 2009



There appear to be several reasons for these reagent dissemination patterns. First, the CPTC emphasis on producing well-characterized and high-quality reagents has resulted in lower throughput. The number and types of characterization required by CPTC increases the time needed to ready the product for distribution. It should be noted, however, that this strategy is likely to result in less time and resources spent by researchers using these reagents as opposed to other alternatives. Second, the current selection of reagents would be expected to limit the number of users to those who had an interest in the proteins that those reagents address. (A few researchers indicated that the current reagents were not ones of interest). As the number of reagents increases, we expect to see more interest from the community. Third, the reagents have not yet been heavily promoted. In our interviews, some of the individuals who knew about or had been involved with the CPTAC program did not know about the reagent program, or if they did, they knew little of the specifics.

One effort to create a wider distribution is with two companies, Millipore and imaGenes, to distribute monoclonal antibodies created and characterized by NCI. This benefits the CPTC program because it leverages the marketing resources of these companies to help distribute the antibodies to the widest possible audience. At the same time, these companies have found that their customers are interested in well-characterized antibodies; there are so many non-validated and unreliable antibodies on the market that these companies believe that there is a market for products with the level of documentation and publication history of the CPTC antibodies. The amount of work that CPTC has invested in these antibodies and the name recognition of the program in the community are both valuable assets to these for-profit firms. At this time, the



relationships between CPTC and these firms are new, and the companies have not yet started selling the antibodies.

Efforts to increase the antibody target lists through individual investigator comments and suggestions as well as through the creation of protein target subcommittees would ensure that the targets selected represent the demands of the scientific community. In addition, increasing the characterization throughput would shorten the time required for selected antibodies to appear on the reagents portal. Lastly, in collaboration with DSHB and the communications team at NCI, the reagents will continue to be promoted to the research community. It is likely that the dissemination of the antibody reagents to the community will increase exponentially once materials are cited in publications and used by members of the program.

5.7. TO WHAT DEGREE IS THE INFRASTRUCTURE BUILT BY CPTC SUSTAINABLE?

The CPTC program has not been in existence for long and has faced the startup challenges that all similar programs face, in addition to those related to establishing a collaborative working relationship among a set of institutions and individuals with different roles and perspectives. Our observations indicate that the program seems to have overcome these initial challenges and has now entered a more advanced phase in which knowledge creation and dissemination are the primary focuses. This is particularly true for the CPTAC and PRRC components. For CPTAC, the initial challenge was to encourage the centers to forge strong collaborative relationships, and the component is now moving ahead with creating the substantive products that will create a less biased environment for verification. For PRRC, the initial challenge was developing a base set of antibodies that could effectively meet the demands of the research community.

The CPTAC program, more so than the other two program components, provides an example of how the infrastructure will fare in the future. Currently there seems to be a high level of collaboration among the centers, although collaboration is, as would be expected, still higher within center teams than across center teams. But given that at least two of the centers consist of a number of institutional team members, this within-center collaboration occurs at different levels—within institution and across institution, with close collaborations reflecting strong cross-institutional relationships. There are two aspects of note concerning sustainability: first, whether CPTC is sustainable as a **program** in the near future or at least until it meets its objectives and second, whether the idea of CPTC as a **collaborative effort** to facilitate verification and generate proteomic biomarkers for use in clinical settings is sustainable.

With regard to the first aspect, we observed the following four dynamics that may affect sustainability:

- **Dynamic between discovery, verification, and clinical translation**—This dynamic was manifested in our interviews and observations at various meetings, and it is clearly an issue that may cause the centers, depending on their orientation, to extend the scope of CPTAC. First, it is important to note that all participants recognize that the goal of CPTAC is to create an environment for proteomic discovery and verification that would reduce sources of



variation other than the sample itself. However, each center and its associated investigators have certain preferences. For example, Vanderbilt University is interested in targeted discovery, while the Broad has an interest in using its technologies to establish clinical efficacy. UCSF, in contrast, is eager to move from yeast studies to cancer plasma studies. Therefore, although the centers adhere to the scope of the CPTAC program, each center attempts to push that scope in a direction that supports its own preferences. As we stated earlier, the PCC seems to be a strong forum for maintaining consistency and a high level of coordination by focusing on the CPTAC scope. As long as it continues to do so without establishing a dominance hierarchy among centers, the infrastructure can be sustained.

- **Dynamic between examining available technology versus creating new technology**—The primary technology being examined is mass spectrometry, although each center has its own variation. In some cases, new ways of performing experiments are being developed, particularly with regard to preparing materials for spectrometric analysis. Justification for examining such new approaches may suggest the generation of an SOP that takes into account all aspects of sample preparation and analysis. For example, the Broad is using SISCAPA to intensify the sample sera, and MRM is being examined fairly closely in this context. The methods used at Vanderbilt University relate to digestion methodologies and techniques for developing shotgun discovery. The impression is that although the centers are focused on verification issues, there is also a sense that new technologies and methodologies are being developed to more clearly identify cancer-related peptides and proteins. The ability to maintain a balance between examining current technologies and investigating newer technologies may eliminate the possibility that this program will turn into a technology program. A threat to this process may be the development of a novel technology that provides greater resolution for identifying proteins and creates the potential need for a whole new set of studies.
- **Dynamic between transparency and limited access**—To a great extent, the program has been evolving toward a transparency that all participants consider useful and productive. As indicated, this trend demonstrates that the participants have established bonds of trust. Associated with this is a dynamic between inclusion and exclusion, particularly as it applies to recruiting others for workgroups for specifying new studies, providing insight on problems, and conducting experiments on a greater number of platforms. Another associated dynamic is to provide a venue for junior researchers to be recognized within larger group efforts. Concern was expressed that younger researchers who participate in large science programs have few opportunities to become lead authors and may jeopardize their career advancement by participating in collaborative work. The researcher interviewed suggested that talented junior scientists may leave the program unless internal processes are established to encourage and recognize their individual efforts. National Research Service Fellowships and Traineeships provide one vehicle for exposing young scientists to this field, as does the Emerging Technologies Continuing Umbrella of Research Experience, which is directed at exposing underserved students and investigators to the field.
- **Dynamic between a controlling versus a facilitating management approach by NCI**—Program participants credited NCI's CPTC leadership with allowing researchers the freedom they consider necessary to maximize the research effort. Researchers felt that NCI's facilitating and supportive perspective is crucial to maintaining CPTAC's spirit of collaboration, and they gave credit to NCI for not trying to dictate the science. Interestingly,



a few researchers felt that the program suffers from a lack of basic research direction. These participants felt that devoting more time to basic research would result in more numerous and higher-quality publications. According to these few researchers, NCI's role in this should be seen as providing a direction for the program. It should be noted that NCI's approach reflects the management style of the NCI CPTC staff and the programs emphasis to applied research, and therefore will not likely change. But such a directive approach suggests a dynamic that could discourage collaborative research. NCI's current role appears to have struck a good balance.

With regard to the second aspect of program sustainability—i.e., sustaining the CPTC as an approach for improving verification and translating discoveries to the clinical setting—we were able to gather little evidence from this evaluation. The important dynamic related to this aspect is how the collaborative infrastructure and CPTC products are used to create an establishment that supports the biomarker pipeline. Part of the support for this pipeline, both in terms of funding and direction, will need to be provided by other organizations. Thus far, some of the CPTAC center collaborations have leveraged additional sources of funding. For example, the Canary Foundation has provided funding to the Broad and UCSF. There are also instances of private funding from companies whose interests would be served by CPTAC research. At the Broad Institute team meeting, there was discussion about involving a private company in the program through an initiative to generate information kits for college students interested in exploring this area of research.

Finally, an unspoken goal of the CPTC initiative is to rehabilitate the image of the field of proteomics. Several interviewees said that they believed that the field initially held enormous potential in the fight against cancer but that a negative response by the public to less rigorous proteomic research conducted in the past had hindered progress in the field. They clearly felt that this program was an opportunity to present a public image of rigorous, scientific proteomic research. One interviewee said that there needed to be a permanent group or network that could police the field to prevent the sort of inferior science that had been conducted in the past. The permanent presence of the CPTC group, with a somewhat different focus, was recommended by a number of interviewees.

APPENDIX A

CPTC INDIVIDUAL INVESTIGATOR AWARDS

Area of RFA	Title	Institution	Principal Investigator	Research Focus
Computational Sciences	Proteomic Characterization of Alternate Splicing and cSNP Protein Isoforms	Georgetown University Medical Center	Nathan J. Edwards, Ph.D.	To develop an infrastructure to enable characterization of alternative splicing and coding isoforms of single nucleotide polymorphisms to improve the current proteomic workflows
	Enhancement of MS Signal Processing Toward Improved Cancer Biomarker Discovery	College of William and Mary	Dariya Malyarenko, Ph.D.	To increase the effectiveness of cancer protein/peptide detection from label-free MALDI-TOF mass spectra for verification and identification. To develop computational tools that can be used across all laboratories employing this mass spectrometry technology.
	A Platform for Pattern-Based Proteomic Biomarker Discovery	Massachusetts Institute of Technology	Denkanikota Mani, Ph.D.	To construct and validate a software system for protein/peptide pattern discovery, the research team will combine peptide identity and pattern information obtained from high-resolution and high-mass accuracy spectra. Application involves the use of peptide identifications via tandem mass spectrometry throughout the processing of the data, while still allowing quantification and comparison of unidentified peptide signals.
	Analysis and Statistical Validation of Proteomic Datasets	University of Michigan	Alexey I. Nesvizhskii, Ph.D.	To build more reliable statistical algorithms and models for analyzing large proteomic datasets. These algorithms and models are necessary to make peptide assignments to spectra from MS/MS, inferring proteins by assembling identified peptides, estimating quantitative changes, assessing the quality of MS/MS data and spectra, and analyzing MS/MS data from cross-laboratory multiple studies.

Area of RFA	Title	Institution	Principal Investigator	Research Focus
Computational Sciences	Quantitative Methods for Spectral and Image Data in Proteomics Research	Fred Hutchinson Cancer Research Center	Timothy W. Randolph, Ph.D.	To address the rapidly growing need for rigorous quantitative methods that increase the power to perform comparative proteomics for current and upcoming platforms in proteomic research. This team hopes to meet that need through the use of wavelet scale functions to define peaks and a penalized regression model to align spectra.
	Computational Tools for Cancer Proteomics	University of Colorado at Boulder	Katheryn A. Resing, Ph.D.	To analyze melanoma progression biology, differentiation of K562 cultured cells into erythrocyte or megakaryocyte lineages, and changes in response to MKK1/2 or MKK5 in neuronal cells, specifically in hippocampus and PC12 cells. Computational methods needed to quantify protein expression changes, increase the accuracy of peptide and protein identification from MS/MS spectra, improve phosphoproteomics analysis, and cluster multidimensional peptides and proteins between many samples will be the focus of this group of scientist.
	New Proteomic Algorithms to Identify Mutant or Modified Proteins	Vanderbilt University	David L. Tabb, Ph.D.	To develop new proteomic algorithms to identify protein mutations and modifications is a critical need. If successful, this research team's efforts could lead to a highly useful methodology and computer infrastructure with high-throughput for accurate identification of mutations and modifications.

Area of RFA	Title	Institution	Principal Investigator	Research Focus
Computational Sciences	PICquant—An Integrated Platform for Biomarker Discovery	University of Virginia	Dennis J. Templeton, Ph.D.	To realize the potential of peptide diagnostics in clinical medicine by merging clinical informatics, quantitative proteomics, and automated data processing routines to allow the rapid analysis of data from dozens of individual patients that would be impractical using manual analysis. One promising proteomic application is the potential for a complete analytic platform for urine biomarker discovery. Using PIC labeling, this research team seeks to develop a new labeling reagent for peptides, in addition to a clinical registry that links acquired urine specimens to current and prospective clinical information, including outcomes. The registry enables multivariate clustering of disease states with quantified protein families.
Advanced Proteomic Platforms	Developing Synthetic Antibodies for Array-based Cancer Detection	The Biodesign Institute at Arizona State University	John C. Chaput, Ph.D.	To develop a chemical approach to obtaining protein affinity reagents that does not require animal immunization or iterative selection steps. This team will use this technology to accelerate the rate of protein affinity reagent discovery and will increase the availability of high-quality antibodies to large numbers of proteins, which has become a major bottleneck in proteomics research.

Area of RFA	Title	Institution	Principal Investigator	Research Focus
Advanced Proteomic Platforms	Proteomic Phosphopeptide Chip Technology for Protein Profiling	University of Houston	Xiaolian Gao, Ph.D.	To develop a novel proteomic phosphopeptide microchip technology platform that can profile proteins carrying phosphopeptide binding domains, this research group is taking a comprehensive approach to build all the necessary parts, including software development, chip fabrication, and construction of analytic tools.
	Global Production of Disease-Specific Monoclonal Abs	Northeastern University	Barry L. Karger, Ph.D.	To demonstrate the feasibility of a global approach to the generation of disease-specific monoclonal antibodies (mAbs) to low-level proteins for the discovery and validation of biomarkers to cancer
	Top-Down Mass Spectrometry of Salivary Fluids for Cancer Assessment	University of California, Los Angeles	Joseph A. Loo, Ph.D.	To develop a new type of ion source, electrospray-assisted laser desorption, for top-down sequencing of salivary proteins
	A New Platform to Screen Serum for Cancer Membrane Proteins	Institute for Systems Biology	Daniel B. Martin, M.D.	To develop and implement a proteomic platform for the capture and analysis of membrane glycoproteins in cell culture models of the disease. The goal of this work is to define a rapid, specific, reliable, and inexpensive strategy to identify and validate prostate cancer protein markers.
	A Proteomics Approach to Ubiquitination	Emory University	Junmin Peng, Ph.D.	To use high-resolution mass spectrometry to providing a new and powerful preparative proteomic technology to capture and isolate this interesting and largely uninvestigated class of molecules, resulting in an accurate and quantitative biochemical analysis of the ubiquitination proteome of mammalian tissues and human brain tumors

Area of RFA	Title	Institution	Principal Investigator	Research Focus
Advanced Proteomic Platforms	A Proteomics Platform for Quantitative, Ultra-High Throughput, and Ultra-Sensitive Measurements	Battelle Pacific Northwest Laboratories	Richard D. Smith, Ph.D.	To develop a cancer protein/peptide assessment platform for analyses of clinically relevant samples that will provide measurements that are much more robust; are of higher sensitivity; provide more than order-of-magnitude throughput; and have improved quantitative utility, particularly for low-abundance proteins, compared with existing platforms
	Aptamer-Based Proteomic Analysis for Cancer Signatures	Michigan State University	Stephen P. Walton, Ph.D.	To test the potential for aptamers to detect specific proteins in biological samples, using bead-based or oligonucleotide arrays of molecular barcodes to detect protein-binding aptamers containing molecular barcodes

APPENDIX B
CPTC FEASIBILITY STUDY

Feasibility Study for an Evaluation of the Clinical Proteomic Technologies for Cancer Initiative

February 2009

prepared for

**National Institutes of Health
National Cancer Institute**

by



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EXECUTIVE SUMMARY

Proteomic biomarkers offer great potential for the early detection of cancer. Harnessing this potential, however, has been challenging in part because of a lack of standardization in the technologies used in the discovery and verification process. The National Cancer Institute's (NCI) Clinical Proteomic Technologies for Cancer (CPTC) initiative was established to address the standardization issue, with a focus on the following goals:

- Enhancing technical abilities to identify and measure proteins accurately and reproducibly in biological systems
- Advancing proteomics as a reliable, quantitative field that can accelerate discovery and translational research

CPTC consists of three components:

- **Clinical Proteomic Technology Assessment for Cancer (CPTAC) network**—This set of grants establishes five centers and a network of collaborators to work together on improving the technology for identifying and verifying proteomic biomarkers. An important emphasis of this effort is collaboration among the centers.
- **Advanced Proteomic Platforms and Computational Sciences initiative**—This area consists of grants to investigators to develop 1) innovative high-throughput technology for protein and peptide detection, recognition, measurement, and characterization and 2) computational, statistical, and mathematic approaches for the analysis, processing, and exchange of proteomic datasets.
- **Proteomic Reagents and Resources Core**—This component organizes tools, reagents, enabling technologies, and other critical resources to support protein/peptide measurement and analysis efforts. It is supported by contracts.

CPTC's short-term outcomes, such as eliminating the variability in mechanisms and processes for detecting potentially useful protein biomarkers, may have a considerable effect on longer-term outcomes, such as being able to diagnosis cancer in its earliest stages. As a precursor to an evaluation of the program, Macro International Inc. was contracted to perform a feasibility study that was to identify key questions to be addressed by the evaluation, define the measures and data sources that could answer the questions, develop a viable evaluation strategy, and provide guidelines on how that evaluation strategy would be implemented.

The feasibility study included developing a conceptual framework through an analysis of materials provided by CPTC staff; interviews with CPTC staff, grantees, and contractors participating in the program; and an examination of various administrative data sources that might contribute to answering questions about the efficacy of CPTC. Conceptual frameworks for the three components and for the CPTC program overall allowed us to identify key outcome variables, classify them as short-term or intermediate or long-term, and identify outputs and program products and activities.

The following major questions were addressed in the study:

- Is an impact evaluation possible, or is the evaluation strategy limited to an outcome evaluation?
- Is the program effective in terms of achieving intermediate or long-term outcomes?
- Is the program effective in terms of achieving short-term outcomes?
- Did the program achieve projected program outputs?
- What are the costs and benefits associated with particular outcomes/outputs?

Within each of these questions, we posed several particular questions that relate to measuring the effect of the programs on a number of outcomes related to program success. In general, we found the following:

- An impact study (i.e., a study of the causal links between CPTC and its effects) is not feasible because of the absence of a credible counterfactual.
- An outcome study focusing on intermediate and long-term effects could not be conducted effectively until a number of years after CPTC Phase I ends.
- An outcome study focusing on short-term effects is feasible, provided that the focus is largely on those involved in CPTAC. It is possible, however, to involve other proteomic discovery investigators in a dose-response study and to evaluate the prevalence of use and acceptance of CPTC standards on a limited basis.
- An analysis of outputs and activities (i.e., a process evaluation) is feasible and would provide strong information on performance.
- A return on investment study is not feasible because it would be difficult to ascribe dollar values to intermediate or long-term outcomes. However, information on program costs, allocations, and savings can be collected and analyzed.

The evaluation study design we recommend should focus on documenting specific questions related to outputs and their relationship to the goals and objectives of the program and activities, on assessing short-term program outcomes, and on describing the costs, savings, and cost effectiveness of the program. It should also primarily focus on evaluating outcomes of participants in the CPTAC network. Such outcomes would include not only achievements realized as part of the CPTAC network, but also achievements in discovery work outside the network. The hypothesis is that CPTAC outputs will be used heavily by investigators within the network. We recommend site visits to CPTAC sites to collect data, as well as a review of secondary material. The Advanced Proteomic Platforms and Computational Sciences initiative and the Proteomic Reagents and Resources Core component should be examined in terms of their activities and the usefulness of their outputs. Those assessments should be carried out through interviews or focus groups with principal leads/investigators within these components, as well as through interviews with CPTAC participants on the usefulness of outputs emerging from these components. One important focus of the evaluation should be on collaborative efforts made within CPTAC.

This proposed study should be scheduled for at least a 6-month period. One critical point is that the proposed design expressed in this feasibility report will require further elaboration and specification before being conducted; therefore, time should be set aside for the development of

that design. In addition to evaluation staff, the project will need an individual well versed in proteomics—particularly if, as recommended, one of the study’s focuses is on outputs and activities. We estimate the maximum budget for the evaluation to be \$300,000. This includes staff time and travel for nine site visits and focus groups. Not included are any costs associated with bringing individuals to the focus groups. The focus groups will either be combined with other activities that bring participants to the Washington, DC, area or be conducted through the Web or a teleconference.

1. INTRODUCTION

Proteomic biomarkers offer great potential for the early detection of cancer. However, while many potential biomarkers have been discovered, few have been verified. Verification, or the ability to ensure that protein detection and measurement can be replicated, is subject to a variety of procedures, reagents, and technologies used by different researchers, and it is difficult to determine whether the lack of successful biomarker verification arises from the material being analyzed or from issues with the platforms used in conducting the verification.

The National Cancer Institute's (NCI) Clinical Proteomic Technologies for Cancer (CPTC) initiative was established to facilitate the development of technology for using proteomic biomarkers in the detection of early-stage cancers. The goals of CPTC are to:

- Enhance technical abilities to identify and measure proteins accurately and reproducibly in biological systems
- Advance proteomics as a reliable, quantitative field that can accelerate discovery and translational research

Specifically, CPTC seeks to produce reagents, standards and guidelines, and information that can be made available to all proteomic cancer researchers and will allow for consistency in the identification of proteomic biomarkers across various laboratories. Funded for \$104 million over a 5-year span, this initiative will expedite the verification of proteins with a high potential for detecting early-stage cancer.

Within the CPTC initiative, three interrelated program components were designed to address the overall goals:

- Clinical Proteomic Technology Assessment for Cancer (CPTAC) network
- Advanced Proteomic Platforms and Computational Sciences initiative
- Proteomic Reagents and Resources Core

CPTAC network—The objective of CPTAC is to assess the performance of current proteomic platforms and optimize the performance of those platforms by reducing measurement variability. Sources of variability include experimental design, sample collection and preparation, protein/peptide identification, and data analysis. NCI determined that the best way to address the issue of variability in proteomic research was to establish a network of proteomic research teams to conduct collaborative assessments and verification studies. Five multidisciplinary, multi-institution centers led by established proteomics researchers were awarded 5-year U24 cooperative agreement grants.

The Program Coordinating Committee (PCC), the CPTAC governing body, establishes research priorities for the CPTAC network. Voting members of the committee include the five center leads and the NCI CPTC program director. Center co-principal investigators (co-PIs) and other respected proteomics researchers also participate in PCC meetings and discussions. The PCC meets monthly via teleconference and twice a year in person. In addition to establishing

priorities, the PCC monitors the progress of each center in achieving previously established objectives and approves and monitors CPTAC workgroups.

Cross-center collaborations are organized and managed through workgroups. There are several workgroups included in the CPTAC program, each comprising 7–25 members from across the 5 centers. Workgroups are established around particular aspects of proteomic research, typically areas that need to be standardized across laboratories to reduce variability. For example, one workgroup established protocols for the collection, processing, and storage of biospecimens. Another workgroup processes all collaborative study data and designed tools to make CPTAC datasets compatible and shareable. Workgroups teleconference monthly, and workgroup chairs report to the PCC. Workgroups are also responsible for designing and managing studies conducted across laboratories.

Eight inter-laboratory studies were designed and conducted to identify and address the source of variability in measuring protein mixtures. The first set of experiments designed and implemented under the direction of the discovery workgroup compared mass spectrometry measurements for various reference materials and reduced variability through a series of procedural refinements. The second set of experiments was designed and implemented under the verification topic areas. The technique of multiple reaction monitoring was employed to measure absolute amounts of proteins in spiked plasma samples across laboratories. Four papers reporting the outcomes of these studies have been written and submitted by the research teams for publication.

Inter-laboratory studies identify and eliminate sources of variability by using derived standard operating procedures (SOPs) and well-characterized reference materials. The output of these efforts (e.g., SOPs, reagents, reference materials) will provide the community of scientists conducting cancer-related protein research with the resources needed to ensure that variations in protein measurement results are due to changes in the biological sample and not to measurement variability.

Under an NCI cooperative agreement grant, substantial programmatic involvement is anticipated between the Institute and research teams. In the case of CPTAC, NCI program managers are highly involved in network activities. They attend all workgroup meetings and assist in coordinating program activities. CPTC program managers also facilitate scientist participation from other components of the CPTC program in the CPTAC network and pursue agreements with public sector institutions or contracts with private enterprise to meet program needs (e.g., providing reagents and reference materials).

Advanced Proteomic Platforms and Computational Sciences initiative—The 16 R01, R21, and R33 grants awarded so far in the Advanced Proteomic Platforms and Computational Sciences initiative allow individual investigators to explore new technologies and methods in proteomic research. Specifically, these grants support investigators in the development of 1) innovative high-throughput technology for protein and peptide detection, recognition, measurement, and characterization and 2) computational, statistical, and mathematic approaches for the analysis, processing, and exchange of proteomic datasets. Some of the investigators are connected to institutions involved in the CPTAC network and work in collaboration with network members; others work independently to develop new technologies and strategies.

Proteomic Reagents and Resources Core—The Proteomic Reagents and Resources Core addresses the community’s need for high-quality, characterized reagents. Antibodies developed in this initiative are thoroughly tested and characterized and then made available to the public through the Reagent Data Portal. This program component differs from the others in that it is funded through Interagency Agreements and contracts rather than grant awards, and the contractors involved work closely with CPTC staff to determine how best to proceed with the production, testing, and distribution of materials.

In addition to the three program components, the CPTC program has been able to leverage the National Institutes of Health’s (NIH) Small Business Innovation Research (SBIR) program to further advance the proteomic field by suggesting topics for SBIR requests for proposals. Although not an official component of the CPTC program, SBIR funding opportunities allow the CPTC community to connect with small businesses and encourage the business sector to work on topics of interest to the program. These awards focus largely on supporting commercial technologies and toolkits that facilitate discovery.

The effectiveness of the CPTC program depends on both meeting its immediate program objectives and changing aspects of how proteomic research is conducted. An evaluation of this program will lead to conclusions about CPTC’s effectiveness and could also suggest strategies for possible future modification of the program. This report contains information on the feasibility of conducting an evaluation of CPTC to determine whether the program has achieved its goals—both short- and long-term—and the cost-effectiveness of the program. The report is not intended to be an evaluation or an assessment of the program, but rather a statement on whether an evaluation should be conducted and, if so, what form it should take.

2. APPROACH AND ANALYSIS

This study answers the following questions:

- Is it feasible to conduct an outcome evaluation of the CPTC program, or is an analysis of program outputs preferable?
- What are the primary evaluation questions that need to be addressed?
- Which of these questions can be addressed within the evaluation strategy?
- What measures and data sources can be used to answer the evaluation questions?
- Are there any comparison groups that provide a basis for assessing CPTC effects, and, if so, how should the study be designed to make use of these groups?
- What is the most appropriate and cost-effective method for collecting and analyzing the data?
- What is the length of time needed to complete the study?
- What are the limitations inherent in conducting an evaluation of the CPTC program?

To address these questions, Macro International Inc. developed a conceptual framework linking program goals and objectives together with inputs, activities, outputs, and outcomes. This conceptual framework was developed after gaining an understanding of the program, both from the perspective of individuals involved in administering the program and from those participating in the program as grantees or other interested stakeholders. Macro gained this understanding by reviewing materials related to the program and interviewing CPTC program staff, grantees, contractors, and other stakeholders who could provide a greater sense of the context and goals of the program. The interviews were conducted to identify potential sources of data as well as to construct a valid conceptual framework for this feasibility study; the focus was not on eliciting information to assess the performance of CPTC.

2.1. REVIEW OF BACKGROUND AND OTHER MATERIALS

As a first step, Macro reviewed a series of Web sites and documents describing various aspects of the program. Materials reviewed included:

- CPTC Web site
- CPTC governance/communications plan
- CPTC 2007 annual report
- Overview of NCI'S CPTC programmatic requirements
- Developmental history of CPTC presentation
- 2008 *New York Times* articles regarding the OvaSure test
- Examples of SOPs
- CPTAC team summary reports from early 2009

These materials provided information on the goals and objectives of the program, program components and how they interact, the cancer biomarker pipeline and other elements of the scientific discovery process, and some of the challenges facing the program and the larger CPTC community.

2.2. MEETING WITH CPTC STAFF

On December 2, 2008, Macro staff members Donald McMaster, Richard Mantovani, Kinsey Gimbel, and Kathryn Harper met with CPTC program staff at NCI's Bethesda, MD, office for the feasibility study kickoff meeting. The discussion included:

- Origins and history of the CPTC program
- Current status and components of the program
- How program components interact
- Goals of the overall program
- Goals of each of the program components

Among other points raised at the meeting, CPTC staff members emphasized something that would be echoed in later interviews: the goal of this program is not to discover proteomic biomarkers, but rather to develop, optimize, and standardize technologies and methods in order to support unbiased discovery.

Macro worked closely with CPTC staff throughout the development of this feasibility report. In addition to the formal interviews that were part of our study, we exchanged e-mail messages and telephone calls with CPTC staff, who provided feedback on initial concepts and ideas, explained scientific concepts and processes, and confirmed and clarified statements made in some of the interviews that were conducted with CPTC stakeholders. These discussions proved particularly useful for understanding the state of proteomic research and defining scientific concepts critical for describing the program and its outcomes.

2.3. INTERVIEWS

Various groups of stakeholders involved with the CPTC program were interviewed to provide a more thorough understanding of the goals and objectives of the program as a whole and of each program component, the activities that were pursued in accomplishing these objectives, and the role of participants involved in the overall CPTC effort and in each component. The interviews also led to a greater understanding of how different members of the community view the goals and long-term potential of the program. Six groups of stakeholders were identified: 1) CPTC staff, 2) CPTAC center leads, 3) investigators in the Advanced Proteomic Platforms and Computational Sciences initiative, 4) the Science Applications International Corporation (SAIC) contractor who serves as lead contact for the Proteomic Reagents and Resources Core, 5) recipients of SBIR awards, and 6) stakeholders who serve as ad hoc members of the PCC. Macro interviewed CPTC staff first and then, based on the findings from those interviews and other background information, developed protocols for the interviews with external stakeholders. Stakeholders to be interviewed were identified by CPTC staff. A list of interviewees and interview protocols are included in the appendixes.

2.3.1. CPTC Staff

Prior to developing protocols and scheduling interviews with non-NCI stakeholders, Macro conducted one-on-one interviews with the CPTC program director and three program managers. These interviews were conducted to provide more detailed information about the CPTC program components, particularly recent activities that may not yet have been documented, and to document program management processes.

CPTC staff reported that they work as a team, with some delegation of responsibility based on expertise. Staff members communicate on a daily basis and meet as a group once a week. The program managers also attend all CPTAC workgroup meetings. Because NCI staff are involved in all aspects of the program, it is easier to reallocate staffing resources as needed to meet the program goals. Due to this level of communication, program staff, particularly the three program managers, are perceived as a unit by awardees. Not all program staff have been with the program from its inception, and there are plans for additional hires; this is another reason why the allocation of responsibilities is a dynamic process. The program director, Henry Rodriguez, attends many of the workgroup meetings but is also part of the program governing body, the PCC. He authorizes the budget and delegates activities to the program managers.

Program staff are actively involved in the management of the CPTAC and Proteomic Reagents and Resources Core components of the CPTC program. Dr. Rodriguez works with the members of the PCC to establish priorities for inter-laboratory studies and authorize the formation of additional workgroups. Program managers facilitate the activities of workgroups by planning meetings, presenting agendas, and serving as a point of contact for obtaining external resources from contractors, such as reagents and resource materials.

NCI CPTC staff establish contracts with industry and interagency agreements as part of the Proteomic Reagents and Resources Core component and manage the activities under those agreements. The Reagents program was developed to organize and acquire the tools and resources needed to support CPTAC's protein/peptide measurement and analysis efforts, as well as to make the reagents available to the greater scientific community. For example, through an interagency agreement, the National Institute of Standards and Technology provides reference materials for use in inter-laboratory studies, and SAIC was contracted to manage the Antibody Characterization Pipeline. CPTC program managers make requests for reagents and services under these agreements on behalf of center researchers and direct the inclusion of target antigens, based on CPTAC recommendation, in the antibody pipeline. Program managers monitor the characterization of data and field community requests through the reagent portal.

A similar interagency relationship, not directly related to supporting center studies, has been established with the Food and Drug Administration (FDA). NCI is working with FDA to advance the agency's understanding of cancer-related proteomic research and inform scientists of the requirements for FDA applications. FDA approval of diagnostic tests is one of the program's long-term goals.

CPTC staff also:

- Update materials such as the program Web site, the annual report, and presentation slides
- Manage program monitoring activities such as collecting center and workgroup annual reports and conducting center site visits
- Submit ideas for SBIR awards that will enhance proteomic technology development to the NCI SBIR bureau

Compared with the CPTAC network and Proteomic Reagents and Resources Core components, the CPTC program staff have little interaction with awardees under the Advanced Proteomic Platforms and Computational Sciences initiative. Although the intent is for awardees to be involved in the CPTAC network, there is no requirement for participation under the initiative's noncollaborative research awards. However, some researchers under this component are performing collaborative work with center teams and are participating in CPTAC workgroups. The NCI CPTAC staff encourage collaborations with CPTAC centers and the reagents core when possible.

2.3.2. CPTAC Center Leads

Telephone interviews were conducted with the CPTAC lead in all five centers; in one case a co-PI was interviewed at the same time as the team leader (see appendix A for a list of interviewees). In collaboration with the CPTC program managers, a 15-question open-ended interview protocol was developed (see appendix A). This protocol provided a foundation for the interviews, but interviewers frequently asked followup questions to clarify a response or pursue an issue that the interviewee introduced. Some interview questions addressed specifics of the research being conducted by each team, but most addressed how the CPTC program and the organization of the CPTAC component has facilitated program and center goals.

Center leads largely agreed that the cooperative agreement approach was the best way to meet the goals of assessing technologies and standardizing procedures and that the CPTC staff and their efforts were critical to the success of this approach. When asked their opinion of the collaborative centers format, all center leads acknowledged that there are several challenges in trying to make this collaborative network succeed:

- Researchers, at least in this field, are not used to collaborating.
- Verification of technologies and standardization of protocols are not where a scientist is going to earn his or her reputation, particularly in a collaborative project.
- The five centers do not have the same level of experience and resources in all areas.
- The level of organization and management needed to perform collaborative work is significant.

Despite acknowledging the challenges of cooperative agreements, all interviewees agreed that collaboration was the best approach to achieving the program objectives and that the program has made significant steps in the verification of proteomic technologies. The interviewers also

agreed that the inter-laboratory verification process would not have been attempted without the encouragement of NCI and the organizational efforts of CPTC staff.

The interviews generally suggested the following outcomes:

- Centers are meeting their individual goals of improving measurement sensitivity, developing assays, and collecting biospecimens.
- The program has increased the amount of time that center leads spent working with researchers outside their centers. They are not necessarily extending their network beyond people they know, because it is a relatively small research community, but it has created a more active community.
- The centers are working well together. This is due primarily to the narrow focus of the program. Teams are already using the same techniques.
- Centers would not have completed the extensive level of documentation for platform procedures if they were working on their own.
- Other than the few researchers receiving awards under the Advanced Proteomic Platforms and Computational Sciences initiative that are already associated with a CPTAC center, center researchers are not interacting with other grantees performing work under that program component.
- Not surprisingly, the center leads, who are all respected researchers, give many presentations at research conferences. They all discuss CPTAC during these presentations.

When asked about participation in workgroups, center leads primarily discussed the Unbiased Discovery and Verification workgroups in which the inter-laboratory studies originated. Center leads mentioned several workgroups but did not provide details about the goals or activities of most groups, perhaps because other team members were participating in these groups. A full-scale evaluation should therefore seek input from CPTAC members who are not center leads. It might be particularly informative to speak to junior scientists, who might have a different perspective on cross-center interactions. A few center leads mentioned that they do not engage in much informal collaboration with other centers but that members of their team frequently work with other centers outside formal workgroups.

2.3.3. Investigator Grantees Receiving an Award Under the Advanced Proteomic Platforms and Computational Sciences Initiative

Three of the 16 grantees receiving awards in the Advanced Proteomic Platforms and Computational Sciences initiative were interviewed. These awardees described their work and how their independent research projects address the program goals of advancing technical abilities in the field of proteomics. All said that they were already doing work in areas related to the goals of the requests for applications prior to the receipt of their grant, so this program was a natural fit with the research. They also all felt that CPTC funding has allowed them to expand into new areas of research and provided new opportunities for collaboration and making connections within the cancer research community. All agreed that this has been a valuable result of receiving the award.

The investigators who were interviewed reported having some involvement and interaction with the rest of the CPTC community. One awardee said that more interaction with CPTC would encourage further collaboration and technological development and that the plan to transfer new technologies from the individual investigators to the centers had not yet been realized. But they all agreed that collaboration was a key element of the program. However, program staff indicated that many of the investigators receiving these awards are not in touch with the network and have little contact with the CPTC community outside the annual meeting. For a full-scale evaluation, we would recommend that interviews be conducted and data be collected from these investigators, who we feel will provide valuable information on program outcomes, as well as from those working with CPTAC researchers. Because a significant amount of the program's portfolio is allocated to individual investigator awards, it will be important to understand the achievements of both those investigators who interact with the CPTAC centers and those involved in more independent research.

2.3.4. Lead Contact for the Proteomic Reagents and Resources Core

During the stakeholder interviews, Gordon Whiteley was interviewed as the representative of the Proteomic Reagents and Resources Core component of the program. He provided detailed information on the process of producing and characterizing antibodies and on who uses these materials and for what purposes. He also described some of the challenges related to translating this kind of research into a marketable product and suggested that the program may want to conduct a market survey at some point in order to better understand what the community needs in terms of reagent production.

The Proteomic Reagents and Resources Core is the program component that CPTC staff have perhaps the most control over and that has the most straightforward, measurable outputs. Assessing such basic information as the number of reagents produced, types of characterization completed, and number of users/customers will be fairly straightforward. However, a full-scale evaluation may also want to examine the extent to which this component of the program is meeting the needs of the community. In addition, this element of the program involves a significant number of other institutions and organizations, including subcontractors who produce the antigens and the external laboratories that perform the characterizations. Their input and value to this component should also be examined.

2.3.5. SBIR Recipients

While not a funded component of the CPTC program,¹ the SBIR awards provide an opportunity for the program to leverage current work in the field by small businesses in the scientific community. Both awardees interviewed reported that their companies were already working in this research area and that the SBIR awards were a good fit for their businesses. These awards allowed them to advance their companies' goals while also venturing into new areas of interest. One awardee said that the annual program meetings provided a helpful opportunity to network with other researchers and helped them develop their business strategy.

¹ SBIR awards are funded by NCI and not by the program. However, the program provides input to the announcements for applications.

The CPTC program may not have the same level of investment in or control over the SBIR awards as it does with the three program components, but this population may still be important to consider in a full-scale evaluation. These awardees can offer insight into the networking occurring in the community, how technology is transferring from the research institutions to small businesses, and the types of products that are being advanced by the business community. It will also be informative to determine the impact that the program has on this segment of the small business community. During the interviews, one awardee expressed some concern over schedule delays due to slow delivery of materials from NCI; during a full evaluation, interviewing all SBIR recipients will ensure that information is collected on issues such as program administration, impacts on awardees, and any scientific/technological matters that arise during the course of the program.

2.3.6. PCC Stakeholders

Leigh Anderson of the Plasma Proteome Institute and Lee Harwell of the Fred Hutchinson Cancer Research Center were interviewed to provide a broad perspective of the scientific problem space and CPTC's role in addressing the issues within that space. In addition, interview questions were directed at identifying considerations that would affect the feasibility of an evaluation. Both are leaders in the field of proteomics and were involved in developing the CPTC program. The following summarizes comments made by each.

Dr. Anderson—Dr. Anderson described the current proteomic biomarker discovery situation as one in which biomarkers were being discovered in a form that could not be used by the diagnostic community. He described a divide between the research community, which considered their results to be self-evident, and the diagnostic community, which viewed the results as failing to meet clinical standards. Dr. Anderson said that CPTC aims to understand the technical aspects of this problem and demonstrate that the existing technology is robust enough to provide useful results. This latter purpose is particularly critical because there are many in the general cancer-research community who are skeptical of the CPTC program. Dr. Anderson also emphasized the collaboration and organization needed to achieve the program's goals. He described the need to organize individuals around the pipeline and stressed the organization required to push the technology ahead.

Dr. Hartwell—Dr. Hartwell agreed with Dr. Anderson about the problem being the lack of useful results from proteomic discovery research and further described the problem as a lack of reproducibility of discovered biomarkers due to technological uncertainties. He said that it is not known how well the technology of detecting proteins at low blood concentration works or what the best technologies are. Dr. Hartwell believed that the benchmark for assessing whether CPTAC is a success is whether a pipeline for biomarker discovery is established and presented to the proteomic research community. He said that coordination was important because this goal can only be achieved through a team effort. He also discussed the importance of structuring needed comparisons across the centers, which bring different perspectives and approaches to solving the technology problem. Dr. Hartwell said that the field would eventually arrive at the same solution, albeit through a "Brownian random walk." He added, however, that he thought that "the field" is not a good standard on which to build a comparison for the evaluation. He said

that he thought that publications were a viable way to judge success if they were present in sufficient numbers by the end of the Phase I effort.

These interviewees also stressed some concepts that would need to be considered in an evaluation, including:

- An important outcome for CPTC consists of demonstrating the value of the pipeline to skeptical researchers in the field. However, in addition to convincing this audience, it is also critical that the pipeline be adopted by the general research community in order to advance unbiased discovery.
- Collaboration around and organization of the pipeline are important benchmarks for success. A team effort was needed to address the issue of biomarker verification from a number of perspectives, and the organization of this process was critical. Both interviewees, however, stressed that collaboration was not an explicit goal for CPTC.
- There are no counterfactual or viable comparison groups for measuring CPTC's success.
- Publications and discoveries using pipeline methodologies should appear before Phase I of the program is completed.
- CPTAC will evolve into something else (possibly a project involved in discovery, implementation, or another activity) in Phase II of the program.

3. DEVELOPMENT OF THE CONCEPTUAL FRAMEWORK AND KEY EVALUATION QUESTIONS

Conceptual frameworks (or logic models) are approaches for describing the operating characteristics of programs or initiatives with regard to goals and objectives, inputs or resources, activities and outputs, and outcomes. Appendix B contains the conceptual frameworks developed for this project. The frameworks established a basis for identifying key questions that a full-scale evaluation of the CPTC program should address, along with program-related challenges in conducting an evaluation.

3.1. MAJOR EVALUATION QUESTIONS

The five major evaluation questions are described below.

3.1.1. Is an impact evaluation possible, or is the evaluation strategy limited to an outcome evaluation?

An impact evaluation generally consists of an attempt to link outcomes causally to a program. It would provide the strongest confirmation that CPTC is effective. It also includes the use of a strong counterfactual representing what would occur if the program did not exist. Outcome studies, on the other hand, are less effective in making inferences about program effectiveness. Strong outcome studies will use quasi-experimental designs using comparison groups; weaker outcome studies will only focus on describing the outcomes, relying on contextual information to assess whether these outcomes are acceptable. This question will assess whether an impact evaluation is feasible.

3.1.2. Is the program effective in terms of achieving intermediate or long-term outcomes?

Program outcomes are those measured elements that provide evidence on how well program goals are being realized. Outcomes will be classified into one of two groups: those goals realized and measured in the intermediate and long term and those that are realized and measured in the short term. In general, we refer to intermediate and long-term outcomes as those realized beyond CPTC's current Phase I funding.

Intermediate or long-term outcomes can be measured in two ways. First, we can ask whether the short-term outcomes of the 5-year effort are sustained over time. For example, are the guidelines, reference documents, and other CPTC outputs effective several years from now, either on their own or in promoting further efforts to produce similar kinds of outputs? This question points not to the immediate short-term impact of CPTC but to whether that impact is sustained over the long term, both in terms of the original outputs or products and of influencing new operating procedures, platforms, technologies, and other advances related to the original CPTC mission.

Second, we can ask what impact the program has on long-term outcomes, ones not realized within a few years of the intervention. Outcomes could relate to the overall modification in how cancer is diagnosed or to effects on the research community during biomarker discovery, verification, and validation efforts.

Examples of questions related to outcome evaluations include the following:

- How many grants are submitted specifying protocols based on CPTC guides and platform information? What is the success rate of these grants compared with other grant applications? (An intermediate term outcome)
- How does the program affect the success of FDA approval? (An intermediate to long-term outcome)
- How does the program affect diagnostic success in identifying cancer? (A long-term outcome)

3.1.3. Is the program effective in terms of achieving short-term outcomes?

Short-term outcomes are realized almost immediately or, at the most, within a year or two. In some cases, such outcomes may not be statistically measureable in the short term, even if their presence is realized. For example, we might expect verified cancer proteomic biomarkers to be identified within the 5-year period. This result, although not a direct goal of the program, is facilitated by CPTC through its emphasis on standardization. However, such biomarkers will be continually developed after Phase I using the CPTC platforms, and only after a body of work has been established can we judge the effectiveness of these platforms.

The following are some specific questions relating to short-term goals:

- Has the process of validating cancer biomarkers been facilitated?
- Did CPTC have an effect on accelerating the identification of verified proteomic biomarkers for specified cancers?
- To what degree are program outputs used by the general cancer research community in their investigations?
- What is the general acceptance of the CPTC outputs among cancer research scientists?
- To what extent have the outputs been used in publications relating to biomarker research?
- To what extent has the program advanced collaboration in the proteomic biomarkers research area?

3.1.4. Did the program achieve projected program outputs?

Outputs include actual products or results produced by the program. The program staff have control over outputs, something they do not have in the case of outcomes. It should be noted, however, that although the program has control over the outputs, the final outputs may be very different than what was originally specified. The differences stem largely from production challenges, such as funding, technical difficulties, or competing priorities.

The distinction between outputs and outcomes is sometimes subtle. For example, peer-reviewed journal publications generated under the auspices of the program are outputs, while those that are generated as a side effect of the program by consortia members are outcomes.

Specific questions that could be addressed by the evaluation include:

- Are outputs consistent with program goals?
- Are outputs consistent with program activities?
- Do the outputs reflect collaborative activity?

3.1.5. What are the costs and benefits associated with particular outcomes/outputs?

Cost-benefit analysis and return on investment (ROI) are critical components to an evaluation, and they should be examined in terms of the portfolio of projects supported and the inherent risks associated with the projects. The CPTC program is a two-level portfolio. The first level is the program as a whole and consists of CPTAC, the Advanced Proteomic Platforms and Computational Sciences initiative, and the Proteomic Reagents and Resources Core. (The SBIR program is not funded by CPTC; although fostering program goals and facilitating program outcomes, it is a budget allocation by NCI and should be considered separately from a cost/benefit perspective.) The second level consists of the elements within each of the components. Each of the projects or grants within the portfolio carries with it a return and a risk. The sum of returns and risks determines the cost/benefits of the portfolio for that component.

ROI reflects the costs/investments associated with the outcomes generated. In many cases, these outcomes will not be known for years, so a good ROI estimate should focus on long-term outcomes. The analysis should also specify the cost benefits relative to opportunity costs (i.e., investments in alternatives) and factor in depreciation costs (i.e., developing a present value calculation or discounting for the fact that the dollar declines in relative value).

Specific questions related to evaluating the cost/benefits include:

- What is the overall program cost?
- What is the return for CPTC investments?
- What is the cost effectiveness of various program components?
- Have program resources been allocated optimally across components? Have program resources been allocated optimally within each component?

3.2. CPTC CHARACTERISTICS INFLUENCING FEASIBILITY

In addition to suggesting key evaluation questions, the conceptual framework provides a basis for understanding some of the challenges of completing an evaluation of CPTC. The following are descriptions of CPTC characteristics that would influence the feasibility of an evaluation and its design.

The nature of outcomes associated with program success—The CPTC program aims to produce platforms that are useful in the discovery and verification of proteomic biomarkers. Such platforms, if adopted, provide the opportunity to identify proteomic cancer biomarkers more quickly. In addition to the concrete products generated by the program, the program implicitly seeks to modify how proteomic discovery is conducted more generally, with the result that many more validated proteomic biomarkers are identified, which in turn will have an effect on cancer detection. This is all accomplished within a collaborative context. Thus, outcomes for the program are diverse, ranging from those that are targeted specifically in the verification process to those related to the larger issues of early detection of cancer and how science is conducted. This diversity is difficult to capture within the context of a time-limited evaluation and presents challenges for deriving one single measure of program effectiveness.

Program timeframe—CPTC was provided with \$104 million in funding for the 5 years referred to as Phase I. Stakeholders and program staff generally thought that the technologies and platforms should be in place at the end of the 5-year period and that the program should transform itself with somewhat different goals and objectives for the following phases. The program, as defined by its current goals, is therefore focused on the products generated during the initial 5-year period. Outcomes, although realized in some forms during the period, will persist beyond 5 years because they will be present in ongoing research work. The CPTC successor program, if it has any resemblance to the current Phase I program, could through its activities affect intermediate or long-term outcomes and therefore confound the ability to identify the unique effects of the Phase I program.

Participants—Current CPTC participants include scientists at the five institutions receiving grants and their collaborators, investigators receiving grants under the Advanced Proteomic Platforms and Computational Sciences initiative, investigators receiving reagents from the Proteomic Reagents and Resources Core, and companies that received SBIRs issued to advance the aims of the program. Effects could be measured in terms of the platforms produced and the outcomes realized by these participants. This would probably suggest a focus similar to that of a case study, primarily because of the diversity and small number of investigators and laboratories involved. Another possibility would be to expand the definition of participants to include those in the general proteomic research community focused on the discovery of biomarkers.

Dissemination—The success of CPTC will ultimately be judged by whether the platforms developed by CPTC or developed as a consequence of the CPTC effort will assist in disseminating proteomic products to the diagnostic community. A necessary condition of success is that the platforms be adopted by the general research community. Dissemination and adoption will largely occur after Phase I.

Diversity of CPTC components—The three CPTC-funded components have different specific objectives, although they are integrated and work in support of common overall objectives. CPTAC is the component that is most essential to the Phase I effort. The other components, although advancing proteomic research on their own, provide essential support for CPTAC in the form of new technologies, algorithms, and tested and reliable reagents. From one evaluation perspective, it is important to treat all components in a uniform way, capturing how total

program goals are achieved. From another evaluation perspective, it is important to examine each component separately, with an understanding of the interactions between components.

4. DATA SOURCES FOR THE EVALUATION

We have identified several sources of existing secondary data that could be useful in conducting a full-scale evaluation.

4.1. IMPAC II

The Information for Management, Planning, Analysis, and Coordination (IMPAC) II system contains information on all persons applying for or receiving grants, contract, or cooperative agreements from NIH and other U.S. Department of Health and Human Services (HHS) research agencies. The IMPAC II system includes information related to the PI, requesting organization, review and award status, requested and awarded budget dollars, review and award dates, summary statements, abstracts, application images, and other data. The system contains all the detailed information about CPTC-related research grants (R01s), phased innovation awards (R21s/R33s), SBIR grants, and cooperative agreements (U24s).

The IMPAC II system could be used to describe the background of individuals applying for or receiving other NCI funding. Many investigators associated with CPTAC will move onto other grants outside the program but will continue in the same area of research. The IMPAC II system can facilitate the tracking of these individuals to determine whether any of the processes or platforms developed while working under the CPTAC program are being used on subsequent grants (i.e., in subsequent research).

4.2. QVR

The Query/View/Reporting (QVR) system, which pulls data from the IMPAC II system, the Central Accounting System database, and the National Library of Medicine's PubMed database, offers another important tool for monitoring the progress of the CPTC program and any developments from the program. The QVR system is an application that can be used to search and view detailed information on grant data (e.g., applications and awards). The data can be displayed in numerous formats, including Microsoft (MS) Excel spreadsheets, formatted reports, and Web page hitlists. The system contains abstracts, grant summary statements, application images, publications, PI history, and grant history.

One NIH requirement is that grantees submit data to the NIH manuscript submission system at PubMed Central (www.nihms.nih.gov) when a paper is published. The QVR module may facilitate the identification of publications produced as a result of CPTC grants (or any subsequent grant(s) from a CPTC PI). The link to the associated publication information is a useful feature of the QVR system, but there will be a time delay between the conduct of any research and the subsequent publication on that research. There may still be an issue with PIs being fully compliant with the NIH Public Access Policy.

Two additional facets of the grants that may be useful in tracking current and future work in this area are the Data Sharing Plan and the Sharing Research Resources Plan. Both are required as part of the grant application. CPTC-funded grants, like other research grants at NIH, have a

requirement to share research data and resources. The ultimate responsibility resides with the funding organization to monitor these data-sharing policies. As researchers move onto other grants outside the CPTC program, it will be important that this monitoring continue in order to track the use and proliferation of any CPTC-related research or resources in other work.

4.3. PUBMED

The National Library of Medicine's PubMed system (www.pubmed.gov) is a database of indexed journal citations and abstracts covering more than 4,500 journals published in the United States and more than 70 countries. PubMed includes more than 18 million citations from MEDLINE, which is the premier bibliographic database with a concentration on biomedicine, and other life science journals for biomedical articles. PubMed includes links to full-text articles and other related resources.

The PubMed system will allow for a broader survey of the proteomic research being conducted (and published) because it is not limited to just NIH. It became clear from the searches we performed during the feasibility study that terms such as "proteomics platform" and "proteomics protocols" were not new areas entering the field as a result of the CPTC program. Some of the published articles dated back 8–10 years.

4.4. CRISP

The Computer Retrieval of Information on Scientific Projects (CRISP) system (<http://crisp.cit.nih.gov>) is a searchable database of federally funded biomedical research projects conducted at universities, hospitals, and other research institutions. The CRISP system contains information on research projects and programs supported by HHS. Most of the research falls within the broad category of extramural projects, grants, contracts, and cooperative agreements. The CRISP system also contains information on the intramural programs of NIH and FDA.

The CRISP system could be useful as a starting point on the types of proteomic research. Because it allows for searching on keywords/terms, an evaluation should consider this tool as a preliminary gauge on the amount of research currently occurring in the extramural community. Most of the information returned from CRISP will likely be directly or closely linked to the CPTC program, but other related research can quickly be linked through this tool via the grant number.

5. FEASIBILITY ASSESSMENTS

In this section, we discuss the feasibility of various evaluation strategies. Our discussion will consider impact studies, evaluations focusing on intermediate and long-term outcomes, evaluations focusing on short-term outcomes, studies of outputs and activities, and costs and benefits. For each, we will discuss how we will answer specific research questions in terms of study design, measures, and data sources.

5.1. FEASIBILITY OF AN IMPACT STUDY

Impact studies assess a program's effect through a comparison with a counterfactual. The factors discussed above would suggest that a viable counterfactual would be difficult to construct given the complicated nature of the program (i.e., three different components) and the high probability that the program, if successful, would be adopted throughout the proteomic research community, thereby possibly contaminating any control group that could be established. For these reasons we recommend against an impact evaluation.

5.2. FEASIBILITY OF AN EVALUATION FOCUSING ON INTERMEDIATE AND LONG-TERM OUTCOMES

Outcomes studies generally focus on results or achievements by the program in relation to a comparison group. Causal inferences are precluded by this type of study. Any effort to judge the effects of CPTC using intermediate or long-term measures should answer the following questions:

- **How many grants are submitted specifying protocols based on CPTC guides and platform information? What is the success rate of these grants compared with other grant applications?**

These questions relate to the adoption of the CPTC platforms by the general research community, either with regard to the specific cancers used to develop the platforms or as modified to address other cancers. Grant awards from NIH provide the basis for much of the biomedical research performed in this country. Adoption of the CPTC platforms in research, in one form or another, is an indication that such platforms are being used and that the proteomic biomarker pipeline contains elements that will ensure the verification of potential biomarkers. Just as important is the degree to which these platforms are represented in grant applications. This provides an idea of the degree to which the general investigator community views these platforms as critical in obtaining grants. The application-to-award ratio also provides information on the extent to which peer reviewers view these platforms as essential elements in their evaluations of grant applications.

The classification of grant outcomes as an intermediate measure reflects the lag between the discovery of a new problem space and the substantial funding of that problem space. In this case, CPTC must generate the platforms for conducting unbiased discovery, and then the

research community must adopt them, formulate grant applications, and wait for the grant applications to be funded. The critical component in classifying this measure is determining when a large enough sample of grant applications will exist to provide meaningful data.

Information on grants can be collected from NIH administrative databases. Information on the grant application may have to be abstracted to identify whether the platforms were discussed within the applications. This approach has its limits because it depends on the submitting investigators providing information on the technologies and platforms used to pursue their investigation. Alternatively, information can be gathered on grant activity from investigators through a survey focused on those doing work in proteomic cancer biomarker research. The survey would include questions about their research, the role of the CPTC platforms in their research, and information on NIH and non-NIH grant applications and awards. Comparison groups could theoretically be established to examine the success of grant applications among those planning to use CPTC platforms versus alternative discovery approaches, although the potential for contamination among groups would need to be considered.

- **How does the program affect the success of FDA approval?**

Because FDA is involved in approving biomedical diagnostic tools, one measure of success in proteomic biomarker identification is the number of proteomic biomarker tests approved by FDA for use in clinical settings, or a change in FDA approval rates among proteomic-based biomarker tests. CPTC platforms provide a basis for biomarker verification, thus providing more support for approval as well as accelerating the approval process. Success would be measured by the number of applications receiving approval and the amount of time between identification of the biomarker and approval. Data on this process could be drawn from three sources:

- **Patents**—This source could provide all potential candidates for FDA approval, although patents could yield some misclassification and omission biases. The first bias occurs when the evaluators err in their recognition of the relevant problem space that the patent addresses. The second bias occurs when a tool or test has not been submitted for patent approval, and thus the patent database does not optimally define all the activity in this area. In addition, it can be years before a provisional patent can serve as a meaningful denominator.
- **FDA approvals**—This source would provide information on any proteomic-based biomarker tests that obtain approval. A rate can be generated using those tests submitted as a denominator.
- **Survey results**—A survey would be targeted to researchers who are involved in biomarker investigations, perhaps with a frame consisting of patent holders or academics and businesses participating in proteomic biomarker discovery. The survey would collect information on the biomarker approval process directly from individuals and could even focus on their intentions to put a test on the market. One issue related to conducting a survey of this nature is the difficulty of obtaining information from individuals who have a financial stake in keeping their research activities and submissions from public scrutiny. Comparisons could be made between the groups that used CPTC platforms and those that

did not. These groups would have to be defined through the survey. The threat of contamination to the controls is a factor, because the comparison groups will probably adopt the platforms if they prove successful.

- **How does the program affect long-term diagnostic success in identifying cancer?**

The basic aim of CPTC is to eliminate some of the barriers that prevent proteomic biomarkers from being adopted by clinicians for the early detection of cancer. If the program is successful in creating a basis for facilitating approval and thus establishing proteomic biomarkers as early detectors of cancer, fewer cancer-related deaths will occur and health care costs may be decreased. Measures at this level could include prevalence, morbidity, and other health status indicators gleaned from cancer surveillance databases or through surveys such as the National Health Interview Survey (NHIS) or the Behavioral Risk Factor Surveillance System. For example, information on prostate-specific antigen screening is collected through NHIS. It is possible that once proteomic biomarker diagnostic tests receive approval, NHIS will add questions pertaining to these screening tests.

Intermediate and long-term outcomes are important for gauging the success of CPTC, and although its immediate goals are related to establishing platforms for better verification of proteomic biomarkers, the ultimate goal is to increase the efficiency of the pipeline in order to enable the successful identification of proteomic biomarkers and promote the early detection of cancer. However, there are several issues that make an evaluation focused on these intermediate to long-term goals infeasible, including:

- The evaluation would have to extend at least 5 years past the current funding lifespan of the program. Thus it would become a major effort that may involve multiple data collections and continued monitoring. In addition, such an evaluation, although providing useful information on the CPTC initiative in terms of fostering collaboration and standardization, would not provide results in enough time to help guide the next steps within the area of proteomic cancer biomarker research.
- Another issue relates to the challenge of isolating CPTC effects from other confounding factors. This issue becomes more problematic in longer-term evaluations because the CPTC effect may decline as new technologies and methodologies take hold in future years, making it more difficult to disentangle effects in the intermediate or long term without some effort to monitor these new technologies. Further, if CPTC is successful, it will be because it has an effect on the general research community and not just on the CPTC network, which would work against establishing an uncontaminated comparison group.

For these reasons, we recommend against conducting an evaluation examining CPTC effects on intermediate or long-term outcomes. We recommend collecting data (such as grant activity) to establish a context for comparison.

5.3. FEASIBILITY OF AN EVALUATION FOCUSING ON SHORT-TERM OUTCOMES

The discussion in this section focuses on short-term outcomes, or outcomes that are realized and measureable within the program's life span or within a year thereafter. Although these outcomes are expected to occur as long as the program outputs exist and may in fact vary in their effect as time passes, they also provide a good benchmark for evaluating the program in the short term. Research questions therefore focus on results that may occur within the third year of CPTC's Phase I funding period to possibly a year after Phase I funding has ended. The focus on short-term outcomes would likely concentrate on those institutions involved with the network because it would take time for the results of the CPTC effort to disseminate to the more general proteomic-focused cancer research community. This does not mean, however, that information collected outside the network could not provide useful background information.

Questions to address in this type of evaluation include the following:

- **Has the process of validating cancer biomarkers been facilitated?**

The CPTC program focuses on establishing platforms that will reduce variability in the identification of potential proteomic cancer biomarkers, which will lead to greater confidence in the verification process and allow for biomarker validation. This question is related to examining whether CPTC activities lead to better validation results, i.e., whether the results are positive or negative (in terms of being a biomarker test with acceptable sensitivity and specificity rates). This effect may be measureable within Phase I, especially within the CPTAC centers and collaborators, although a better measurement would be achieved as more biomarker test data are accumulated. The measure must reference the validation process and include data from those performing validation. The measure reflects whether validation leads to a higher level of positive confirmations when using verified biomarkers (using CPTC-produced SOPs and platforms) than biomarkers produced outside these protocols. The comparison must be done with care because other researchers may be using non-CPTC, possibly standardized technologies for verification, thus obscuring the results. Data for addressing this question can be obtained through surveys of researchers performing proteomic biomarker verification. We expect that the frame for this survey will be the general community of proteomic researchers.

- **Did CPTC have an effect on accelerating the identification of verified proteomic biomarkers for specified cancers?**

This question would be answered by examining how quickly proteomic biomarkers are produced for validation within those investigator groups using CPTC platforms compared with groups not using CPTC platforms. Specific measures would use the number of verified biomarkers submitted for validation, standardized by a denominator that would control the actual activity for biomarker research. That denominator could be the number of biomarkers identified within the CPTAC group and within the comparison group.

- **To what degree are program outputs used by the general cancer research community in their investigations?**

One indicator of CPTC success is the degree to which the program outputs (platforms, guidelines, SOPs, reagents, and other innovations) fostered by the program are used by both CPTC investigators and the general cancer research community. Greater use means that there will be greater success in identifying potential proteomic-based cancer biomarkers through verification and greater success in their validation and acceptance by FDA and the diagnostic community. We expect this use to increase as time passes, although as the platforms age and new technologies and algorithms are developed, the platforms themselves may be amended. Addressing this question involves measuring the use of each program output by investigators and researchers. Data for addressing this question could be derived from a survey of CPTC participants, as well as researchers involved in identifying proteomic biomarkers. It is feasible to get a measurement of this indicator before Phase I ends, although we expect the impact to be more notable after Phase I has ended.

- **What is the general acceptance of the CPTC outputs among cancer research scientists?**

This question is different from the previous one in that it measures acceptance, not use. This was one criterion that was discussed in our interviews with Dr. Anderson and Dr. Hartwell. Acceptance means that CPTC outputs are seen as standards or critical guidelines that should be taught and followed by researchers in this field. The measurement can be collected through a survey similar to the one described for measuring use.

- **To what extent have the outputs been used in publications relating to biomarker research?**

Publications are both outputs (when the program pays for their production) and outcomes (when they result as a consequence of the investigators' actions). Publications provide a gauge of both dissemination into and acceptance by the scientific community and can be used to measure the development of standards, technologies, procedures, and algorithms, as well as findings. Evaluations of publications generally consider the prestige of the journals that publish the papers as a way to measure acceptance. Information on publications can be generated from the Thomson Reuters Web of Science (which catalogs publications) or PubMed or by querying researchers in the field through a survey. The latter approach has the advantage of collecting information on publications in progress. We have classified publications as short-term outcome measures because we believe that before the project ends there should be adequate results that are disseminated through peer-reviewed journals. Citations of these publications by other researchers would be an additional measure, although it may not be realized as quickly and may be more of an intermediate outcome.

- **To what extent has the program advanced collaboration in the proteomic biomarkers research area?**

This question reflects two interests: the collaboration fostered in the CPTAC program and the potentially increased collaboration relative to generating verified results. The first is

addressed in the next section on outputs. The second reflects an assumption that has been emphasized by NIH in recent years through its Roadmap activities. The degree to which this is a short-term goal, however, can be debated because the scientific community must accept the benefits of collaboration, which is a substantial shift in the research paradigm. Collaboration may be measured through a survey with questions on the degree to which researchers interact with researchers in other institutions or disciplines and about what issues. Analysis could be accomplished through network methodologies, which are statistical methods for charting the linkages between various researchers and centers in a network. The resulting measure would be a network strength measure that can be measured against a comparison group of individuals doing work in a closely aligned field.

A short-term outcome evaluation of the project is feasible, although some of the measures will not be fully realized for statistical analysis until after Phase I ends. The most useful strategy would be to focus on what has transpired in the CPTAC centers relative to those researchers with little involvement in that network. One approach for doing this evaluation would be a dose-response model, in which the dose is the degree of exposure to CPTAC and the response is researchers' behavior in terms of using CPTAC outputs and being successful in various outcomes within the pipeline (e.g., having their biomarker verified and validated). These data would also be useful in an analysis of collaboration using a network analysis methodology.

5.4. FEASIBILITY OF A PROCESS EVALUATION STUDY FOCUSING ON OUTPUTS AND ACTIVITIES

The evaluation of outputs, which for CPTC consists of the platforms for biomarker identification, should be a direct reflection of specific program goals regarding performance. As we mentioned before, there are overall CPTC performance goals as well as CPTC component performance goals, and there are different outputs for each. Currently all outputs are scheduled to be completed by the end of the Phase I funding period because they are linked to program-specific activities.

Questions to address in this type of evaluation include the following:

- **Are the outputs consistent with program goals?**

CPTC program goals and output-related objectives provide a framework for specifying what is to be produced by the program within Phase I. In general terms, the CPTAC program will produce a variety of materials on technology platforms, the grant component will produce new technologies and algorithms, the reagent component will produce materials for use in testing and discovery, and the SBIR program will produce specific technologies and toolkits for use by researchers. In more specific terms, the products reflect a dynamic, iterative process, in which decisions are made throughout the project on how best to meet goals and objectives. For example, the workgroups within the CPTAC program will work together to identify new research emphases; sometimes research will veer off in unexpected directions due to circumstances or new discoveries and findings. In some cases these new directions are consistent with program goals; in other cases, they are interesting detours that are not

consistent with program goals and objectives. This question aims to evaluate whether the program's products advance program goals.

Measures of consistency could be conducted as simply as by assessing whether a particular product supports the program goals and objectives, or more complexly, determining the degree to which the product provides support. In the former case, the measure would be a simple yes or no, while in the latter case, the measure would be continuous, ranging from "not in support" to "fully in support." This measure would rate individual outputs, and an overall index measure would need to be established to ensure consistency among all products within a CPTC component. There would be two sources for establishing these measures, and both would involve working with individuals familiar with proteomic research. First, CPTAC researchers who use products from the other components could be asked to provide information on those products. The second source would be nonstakeholders because we believe that CPTAC products should be assessed by independent observers/researchers. Both sources can be reached through focus groups.

- **Are outputs consistent with program activities?**

Outputs are related to program goals and objectives but are generated from actual activities. This research question assesses whether program activities result in outputs, either directly or indirectly. Outputs can take on various forms and be developed in a variety of ways, some of which may be more efficient than others. The various program components comprise different strategies and approaches for generating outputs, and because collaboration is an important element of the program, these strategies should link with each other. This question addresses duplication, efficiency, and productivity. Measures addressing this particular question would be developed from information collected through site visits and more qualitatively framed interviews. To effectively conduct these interviews, it would be necessary to employ individuals associated with the subject matter areas who also possess program evaluation expertise.

- **Do the outputs reflect collaborative activities?**

Collaboration across centers is an important element of the CPTAC program, and while collaboration itself is an activity, it can also be viewed as an output. Collaboration can also occur when individual grantees from the Advanced Proteomic Platforms and Computational Sciences initiative component work with CPTAC centers. The degree of collaboration can be measured through common activities, and the results of this collaboration can be measured by the common products produced. Questions related to this collaboration should not focus only on the activities or obvious interactions, but also on the importance placed by researchers on this mode of research. This requires information from center investigators and those participating in the grant program about the strength of ties generated by this common effort and the kinds of activities that are most amenable to such collaboration. Such information can be placed in the context of researchers not associated with CPTC and be examined to determine whether the collaboration generated by the program reflects the set of participants involved or whether it represents a model that can be translated to the general

cancer research community. Discussions with grantees who are not involved with any CPTAC activities could provide a contrasting point of view.

An examination of outputs and activities is feasible up to the end of the Phase I project. These areas of evaluation do not need comparison groups because their terms are internally set and acted on, although information provided by others not involved in CPTC may be useful to provide a context and perhaps a contrast, particularly for examining collaboration activities. The evaluation is not focused on the effect of the program, but rather on whether the program produced what it said it would produce. Each of the components could be examined alone or with regard to their interaction.

5.5. FEASIBILITY OF ANALYZING THE COSTS AND BENEFITS ASSOCIATED WITH PARTICULAR OUTCOMES/OUTPUTS

Questions to address in this type of evaluation include the following:

- **What is the overall program cost?**

Costs reflect staff involvement in activities and the purchasing of materials, as well as funds allocated to the awards in the three program components. Although costs for the overall CPTC initiative and its components are known, costs for specific activities are not. While performing a full cost analysis detailing specific amounts spent on specific activities would lead to a greater understanding of what it costs to produce certain outputs, obtaining the information from those involved in the program would be burdensome. Also, many outputs may be generated from the same activities, thereby leading to problems in allocating funds. We believe that this issue might be more pronounced for the CPTAC network than for the other components because of its collaboration activities as well as a diversity of other interrelated activities that are difficult to disentangle from a cost perspective. The Advanced Proteomic Platforms and Computational Sciences initiative, although covering a range of different activities, can be characterized by the individual awards and the results they are supposed to achieve. The Proteomic Reagents and Resources Core component involves contracts calling for specific products and results. One approach would be to allocate costs by center to those activities and outputs produced by the centers and then create a common pool that represents the amount spent on “common” activities and outputs. Under this scenario, a measure could be developed for each center along with a common cost measure covering the entire CPTC program.

Another consideration related to evaluating cost pertains to savings. The Advanced Proteomic Platforms and Computational Sciences initiative and Proteomic Reagents and Resources Core components and the SBIR grantees provide technologies, algorithms, reagents, and toolkits to both the general cancer research community and CPTAC participants. In other words, the components’ focus and perhaps their efficiency in performing this work may be translated into savings for the CPTAC research teams as well as for members of the general cancer research community.

Overall program costs reflect not only the amounts budgeted for the various components, but also additional costs associated with other program components. The costs should be described for the program as a whole and for each component. If possible, costs should also be examined by the expenditures within components (i.e., by grant or contract). The subsequent cost breakdown would provide a basis for a cost-effectiveness analysis. This information can be supplied by program staff, and estimates can be performed following interviews with CPTAC grantees and the SAIC contract project director.

- **What is the return for CPTC investments?**

CPTC investments can be easily identified and characterized, although outside of the particular components they may be difficult to associate with particular products. Returns (in terms of dollars) are more difficult to identify and characterize. The ultimate measure of a return is the net benefit in terms of reducing cancer; however, this is a long-term measure that can only be measured using economic assumptions about the effects of proteomic biomarkers in the specific disease areas over a number of years, beginning with their adoption in clinical settings. Short-term returns may be more easily characterized, particularly with information provided by the CPTAC centers on savings due to the presence of characterized proteins generated by the Proteomic Reagents and Resources Core component.

- **What is the cost effectiveness of various program components?**

ROI analysis implies an analysis using a monetary return, whereas cost-effectiveness analysis views the return as an outcome measure. Thus a cost-effectiveness measure might involve measuring the percentage of researchers using CPTC guidelines for verification over the costs of generating those guidelines. One barrier is whether costs can be broken down by specific output. It may be the case that a composite outcome measure is generated that can be used to examine cost effectiveness; therefore, one might consider the aggregated activities of the CPTAC program, weighted to emphasize their importance relative to program goals. Information would be derived from the cost analysis and from surveys and site visits. One issue, however, is how to assess the cost effectiveness without a baseline or point of comparison. One approach could be to assess the cost of performing discovery as it is performed outside the CPTAC network. Gross information could be gathered by reviewing the expenditures of grants undertaking proteomic discovery in particular disease domains or more subjectively by asking investigators involved in proteomic discovery within a survey.

- **Have program resources been allocated optimally across components? Have program resources been allocated optimally within each component?**

These questions pertain to extending the cost-effectiveness analysis to attempt to value particular decisions. For example, we can ask whether allocations should have stressed the Proteomic Reagents and Resources Core component over the Advanced Proteomic Platforms and Computational Sciences initiative. This can be accomplished by comparing outcomes with costs relative to the contributions to overall program goals. Data to address these questions include survey responses and a cost analysis.

A true ROI analysis is probably not feasible because program outcomes needed for such an analysis cannot be realized without examining intermediate and long-term benefits. However, the following short-term cost-effectiveness measures can be generated:

- Obtaining a general gauge of investments, not only to major components but also to output categories within each component
- Evaluating the cost savings of some components compared with others
- Estimating the effect of the cost savings on facilitating the discovery of new verified biomarkers

We therefore recommend that an evaluation consider these three limited objectives.

6. RECOMMENDED STUDY DESIGN

After considering the various options available for conducting a CPTC evaluation, our conclusion is that the study should focus to the extent possible on how short-term outcomes are satisfied. One practical limitation that influences our recommendation is CPTC's desire to conclude the evaluation by November 2009, which would not allow adequate time to conduct an Office of Management and Budget (OMB)-approved survey. With this in mind, we believe that the analysis should focus on evaluating CPTAC activities and outputs associated with the program, as well as on CPTAC researchers' activities and achievements occurring outside of CPTAC funding. The first set of activities and outputs focus on establishing standards, guidelines, and products that will promote unbiased discovery; the latter set of activities will focus on actual discovery-related activity. The measurement for success will be the degree to which CPTAC activities are translated to other activities pursued by these research teams. While a more comprehensive examination of the influence of CPTAC outputs would focus on the general research community, we believe that a quantitatively testable measurement of this influence would require a survey of researchers outside CPTAC. Regarding the other CPTC components, we propose a design that largely focuses on an assessment of these components' outputs by CPTAC investigators, as well as on collecting information from the participants in each of the components. We recommend that we not address the SBIR program because there are few grants to date, and the impact of these programs will not be realized in the short term.

The design will focus on collecting the following information from CPTAC investigators:

- Grant applications and awards for discovery and verification
- Publications in peer-reviewed journals
- Presentations at conferences or participation in workshops
- CPTAC outputs and use of these outputs during discovery performed outside the CPTAC grant
- Collaborative contact and interactions
- Enumeration and classification of CPTAC outputs
- Issues with collaboration or use of products generated from other CPTC components
- Interactions with other investigators outside the CPTAC network
- Cost savings

These data will be collected through the following mechanisms:

- Reports submitted by the grantees
- Observations of workgroup and PCC activities
- Site visits to the major grantees and to other participating institutions to the degree permitted by OMB restrictions (nine total visits)
- Interviews with selected other members of the network (up to nine interviews)
- Review of publications and grant-related activities from PubMed and IMPAC II

For investigators receiving grants under the Advanced Proteomic Platforms and Computational Sciences initiative, we will chart activities related to the development of the technology or

informatics products they proposed, publications and grants, and collaboration with the CPTAC community. We believe that the best way to collect data on collaboration and activities is through a focus group. We propose two focus groups segmented by area of research or a limited survey of up to nine participants.

For the Proteomic Reagents and Resources Core component, we propose interviews with staff in Maryland and Iowa, as well as a limited set of interviews with others involved in providing reagent characterizations and other information. We also recommend that statistics on inquiry and requests be obtained and evaluated and that these data identify the requesting investigators.

It may be possible to conduct a focus group with investigators working in the field who are not associated with the CPTAC network. This group could provide a context for information collected from CPTAC members.

The scope of work will require the following tasks:

- 1. Development of a task plan and research design**—This task will discuss in specific terms how the research will be carried out, the research questions, the specific approaches for addressing the questions, the data collection design, the data collection protocols, and analysis plans. It will also contain completion dates for various deliverables both in draft and final form. This task will require 2 months of effort.
- 2. Data collection**—Data collection will include all activities related to collecting data from site visit respondents and focus groups. This task will begin in month 2 with the identification of individuals to be interviewed and scheduling of events and will end in month 4.
 - Two to three-day site visits (including travel) will provide detailed evidence on program activities, outcomes, and outputs. Interviews will be conducted with senior members of the CPTAC centers. Other non-CPTAC individuals associated with the institution may be interviewed to examine how CPTAC activities affect other similar efforts, such as other cancer-related grant projects supported by CPTC or the institutions.
 - Focus groups will be assembled consisting of individuals who can assess the products or outputs in terms of the activities and goals of the program. This activity provides information on specific outputs and outcomes and their relative importance in the field.
- 3. Analysis**—This task will include activities focused on describing the programs by research questions, making comparisons, and performing the cost analysis. The analysis will provide both quantitative and qualitative indicators of program performance. This task will end in month 5.
- 4. Reporting**—This task will include activities related to generating interim reports, draft and final reports, and materials for presentations. In addition to monthly progress reports, we envision two versions of a draft final report, each incorporating NCI staff comments, and a final version. We also propose a presentation of program results. This task will begin in month 5 and end in month 6.

7. SCHEDULE, COST, AND STAFFING

7.1. SCHEDULE

The evaluation project we propose could be completed in 6 months, although a more realistic timeframe allowing for a more thorough analysis of the data and a more complete review of the draft reports would be 8 months.

7.2. COST

We estimate that the total hours spread across various staff to be about 2,000 hours, which when combined with costs for nine site visits will cost approximately \$300,000. This figure is intended for planning purposes and allows CPTAC some discretion in fashioning tasks and activities within the evaluation. Not included are any costs associated with bringing individuals to the focus groups. The focus groups will either be combined with other activities that bring participants to the Washington, DC, area or be conducted through the Web or a teleconference.

7.3. STAFFING

Evaluation staff will include the following:

- Project director with NIH program and evaluation experience
- Senior staff for site visits
- Senior programmer/database developer
- Data collection staff
- Senior research analyst(s)
- Junior data/research analyst
- Scientific researcher with experience in proteomic discovery

Appendix A

Stakeholder Interviews

Appendix A1

List of Interviewees

Clinical Proteomic Technologies for Cancer (CPTC) Program Leadership Office of the Director, National Cancer Institute

- Henry Rodriguez, Ph.D., M.B.A., Director
- Tara Hiltke, Ph.D., Program Manager
- Mehdi Mesri, Ph.D., Program Manager
- Christopher Kinsinger, Ph.D., Program Specialist

Clinical Proteomic Technology Assessment for Cancer (CPTAC) Network Team Leaders

- Steve Carr, Ph.D., Senior Scientist, Proteomics and Biomarker Discovery, The Broad Institute of MIT and Harvard
- Susan Fisher, Ph.D., Professor of Cell and Tissue Biology, University of California, San Francisco
- Dan Liebler, Ph.D., Director, Jim Ayers Institute for Precancer Detection and Diagnosis, Vanderbilt University
- Paul Tempst, Ph.D., Member of the Sloan-Kettering Institute; Professor, Gerstner Sloan-Kettering Graduate School of Biomedical Sciences
- Fred Regnier, Ph.D., J.H. Law Distinguished Professor, Analytical Chemistry, Purdue University

Advanced Proteomic Platforms and Computational Sciences Initiative Principal Investigators (PIs)

- Dave Tabb, Ph.D, Assistant Professor, Vanderbilt University Medical Center
- D.R. Mani, Ph.D., Senior Computational Biologist, Cancer Program & Proteomics, The Broad Institute of MIT and Harvard
- Richard D. Smith, Ph.D., Battelle Fellow and Chief Scientist, Director of Proteomics Research, Biological Sciences Division, Pacific Northwest National Laboratory

Proteomic Reagents and Resources Core Component Contractor Representative

- Gordon Whitely, Ph.D, RM (CCM), Director of the Clinical Proteomics Reference Library, SAIC-Frederick, Inc.

Ad Hoc Program Coordinating Committee (PCC) Members

- Leigh Anderson, Ph.D., Chief Executive Officer, Plasma Proteome Institute
- Lee Hartwell, Ph.D., President and Director of Fred Hutchinson Cancer Research Center and Professor of Genome Sciences, University of Washington

Small Business Innovation Research (SBIR) Awardees

- John Kenten, Ph.D, Scientific Director, Meso Scale Diagnostics
- Karri L. Ballard Ph.D., Director, Diagnostic Initiatives, Rules-Based Medicine, Inc.

Appendix A2

Interview Questions

CPTAC Team Leader Interviews

1. What are the objectives of your center under this grant? Have any objectives been achieved?
2. Describe your center's participation in the CPTAC workgroups.
3. Does your center communicate with other centers/PIs outside of the workgroups? How could this communication be improved?
4. How do the inter-laboratory studies enhance/complement your individual research project(s) and vice versa?
5. How does the scientific research developed by the individual PIs and/or SBIR within this program assist you in your research? How can this be improved?
6. How will you integrate the methodologies and reagents being generated within the CPTC program into your current and future research?
7. As the program is currently at its half way mark, please describe how the program has impacted the development of your center? Your individual laboratory?
8. Has the NCI staff created a network that will achieve the overall goals of the pilot project? Is the NCI management team efficient in facilitating communication and fulfilling CPTC needs?
9. What do you envision would be the next scientific aims to further the goals of this program?
10. Describe how you/your center communicates/promotes the program to the greater community.
11. How is the center approach (cooperative agreement-based) beneficial to accelerating the progress of cancer technology research and/or translational research? What are the major strengths and weaknesses of the current model?
12. Do you work with any other organizations, apart from the other centers? What organizations? How do outputs from the CPTC program integrate into your other projects?
13. Do you have funding from other sources to do work in this area? From whom and approximately how much support do you receive?
14. Who do you consider to be your audience? Other researchers, the public, etc.?
15. From your perspective, what do you think needs to be accomplished in order for your center to be successful?

Advanced Proteomic Platforms and Computational Sciences Initiative PI Interviews

1. Why did you decide to apply for this award?
2. Could you describe the work you're doing under this award?
3. What are the objectives of this research?
4. Has your work changed from what was in your original grant application?
5. How long have you been doing this kind of research? Before you received the award, what were you working on?
6. Do you have funding from other sources to do work in this area? If so, from whom and approximately how much?
7. Do you do research in other areas, as well? If yes, does work on this grant enhance or complement your other areas of research? How?
8. What do you expect the final result of this work to be (e.g., a product? a process?)
9. What plans do you have, beyond this grant, for meeting your research goals?
10. Describe leverage opportunities developed by this grant (e.g., other research opportunities, collaborations within or outside of CPTC network, networking within the field, financial (other grants, university funds)).
11. Do you have any recommendations for increasing interactions within the CPTC network, particularly for R01 awardees?

SBIR Awardee Interviews

1. How long has your company been in business?
2. Before you received the SBIR award, what were you working on?
3. Why did you decide to apply for the SBIR?
4. Can you describe the work you're doing under the SBIR award? What are the objectives?
5. Are you currently a Phase I, II, or III SBIR?
6. What kind of product(s) do you hope results from this work?
7. When do you envision products becoming commercially available?
8. How does your work within this program enhance your company's goals?
9. Who would the audience or consumers be for this product?
10. Do you work with any other organizations on this research?
11. Please describe your interactions with the CPTC centers/PIs.
12. What recommendations do you propose for greater interactions within the program between SBIR and the CPTC grant holders?
13. Please describe how you will integrate the reagents being generated within the CPTC program (i.e., antibodies) into your platform/assay.
14. Has your work changed from what you proposed in your original application?
15. Does your company perform research in other areas?

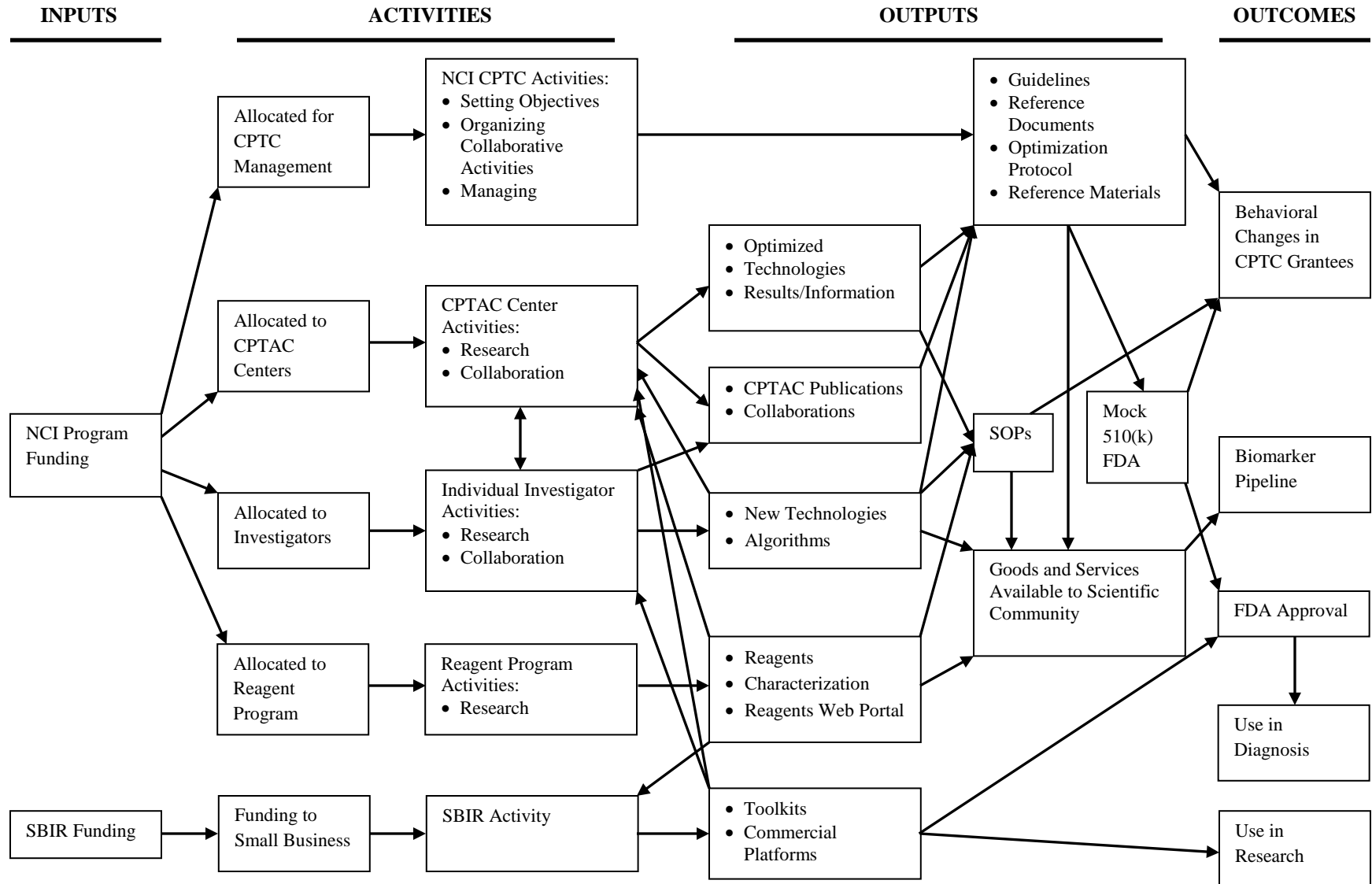
Appendix B

Conceptual Framework

Appendix B1

Clinical Proteomic Technologies for Cancer (CPTC) Program

THE CLINICAL PROTEOMIC TECHNOLOGIES FOR CANCER (CPTC) PROGRAM CONCEPTUAL FRAMEWORK



CPTC Program Conceptual Framework

Inputs

Inputs refer to external resources devoted to the program or initiative. They could exist in the form of direct funding, leveraged funding, staff time contributed from external organizations or agencies, and shared facilities and infrastructure. The CPTC program has the following three types of inputs:

- National Cancer Institute program funding: The total amount of funding is \$104 million over a 5-year period.
- Staff: This category would include individuals providing some sort of input to CPTC, but who fall outside of the above funding. For example, researchers participating on peer review panels assess CPTC grant applications for scientific merit, and in doing so affect which grants obtain funding.
- SBIR funding: SBIR projects are supported by non-CPTC funds, but because these projects address program objectives, they should be identified as an input.

Activities

The first set of activities relates to how program funding is allocated among the three components. There are four functions that require funds:

- The Clinical Proteomic Technology Assessment for Cancer (CPTAC) network constitutes multiyear grants to five centers or institutions and their partners. Foci and specific activities vary across centers, but they cooperate in their aim to establish platforms that will enhance verification of samples.
- The Advanced Proteomic Platforms and Computational Sciences initiative includes grants awarded to investigators through the R01, R21, and R33 award programs. Grants are ranked on scientific merit and other considerations through a peer review process, and funding is established according to these rankings. Each grant represents an investment that carries both returns on the investment and associated risks.
- The Proteomic Reagents and Resources Core is the third component. These are funds allocated to a contract for production of reagents and for specialized services in support of the CPTAC program.
- Management activities include the overhead of the program activities, as well as funds provided for some of the common activities associated with carrying on collaboration and other activities.

Outputs

Outputs are the products that emerge from program initiatives and are largely under the control of the program. For example, publications that emerge as a result of CPTAC activity would usually be characterized as an output, but publications that are produced separately (but reflecting the authors' CPTC work) would probably qualify as an outcome.

The above framework lists some outputs that are generated as a result of CPTC activities. The framework at this point is notable because it displays a variety of outputs that feed back into activities of other components, while also leading to other outputs of greater sophistication. For example, the reagent program feeds into CPTAC activity—providing the basic samples to be analyzed. This dynamic demonstrates not only the intended integration among the components, but also a structure that is intended to provide the CPTAC program with needed platforms and tools. It becomes clear that the CPTAC component is a primary focus of current activities.

Outcomes

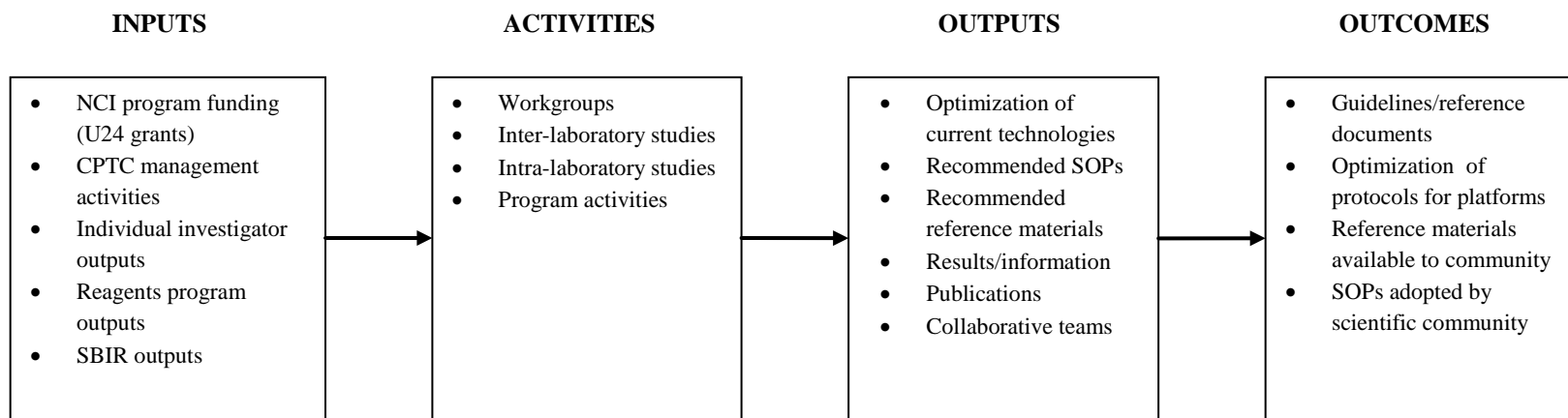
Outcomes represent behavioral changes that emerge from the program. The conceptual framework defines outcomes that represent behavioral changes among the CPTAC organizations and investigators with grants and that affect the greater health system and the pipeline that culminates in producing diagnostic biomarkers for cancer. With regard to the first, outcomes represent the ways the various centers interact with each other, produce publications in response to their work on CPTC, and to submit grants to further CPTC efforts. With regard to the second, the audience includes researchers who use CPTC guidelines, reference documents, optimization protocols, and reagents and diagnosticians who benefit from the improvement in identifying useful proteomic biomarkers from verification.

The framework considers the CPTAC component as the centerpiece of CPTC activity, with the other components supporting CPTAC as well as providing viable products that forward CPTC aims on their own. This is especially true of the Reagents component. It is less true of the Investigator and SBIR programs. Grants allow the investigator to pursue projects with merit, but they do not compel the investigator to generate a specific output or product. From this perspective, it might be interesting to examine the behavior of researchers receiving grants through these mechanisms and consider the outputs of that process as outcomes with regard to the program as a whole.

Appendix B2

CPTC Program Components

THE CLINICAL PROTEOMIC TECHNOLOGY ASSESSMENT FOR CANCER (CPTAC) NETWORK CONCEPTUAL FRAMEWORK



CPTAC Conceptual Framework

The objective of CPTAC is to assess the performance of current proteomic platforms and optimize the performance of those platforms by reducing measurement variability. Sources of variability include experimental design, sample collection and preparation, protein/peptide identification, and data analysis. Inter-laboratory studies identify and eliminate sources of variability by using derived standard operating procedures (SOPs) and well-characterized reference materials. The outputs of this effort (e.g., SOPs, reagents, reference materials) will provide the community of scientists conducting cancer-related protein research with the resources needed to ensure that protein measurement results are due to changes in the biological sample and not to measurement variability.

Inputs

- NCI program funding: U24 Cooperative Agreement grants (RFA-CA-07-012) with five multidisciplinary research teams
- CPTC management activities: Under an NCI cooperative agreement grant, substantial programmatic involvement is anticipated between the Institute and research teams. In the case of CPTAC, NCI program managers attend most inter-laboratory meetings and work with network members to determine research objectives and assist in coordinating program activities. CPTC program managers also facilitate participation by scientists from other components of the CPTC program and pursue agreements with public sector institutions or contracts with private enterprise to meet program needs.
- Individual investigator outputs: New protein detection technologies, analyses software, and algorithms that can be verified and standardized within CPTAC network
- Reagents program outputs: Products and characterization data created within the Reagent component are used by CPTAC teams for inter-laboratory research projects.
- SBIR outputs: The toolkits, platforms, and other technologies created by SBIR firms will be available to researchers in the CPTAC network, as facilitated by the program management.

Activities

- Workgroups (WG): There are several workgroups included in the CPTAC program each comprising 7–12 members from across the five centers. WG chairs typically rotate every year. WGs teleconference monthly and chairs report to the PCC. There are two main WGs that were created at the program's inception: the Unbiased Discovery WG and the Verification WG. Other WGs were largely established based on the needs of these groups. Many WGs are anticipated to remain active across the life of the program. However, some WGs have been established for very specific short-term projects and have already been disbanded, having met their objectives. WGs submit annual reports summarizing activities. The following is a list of current and past WGs. Descriptions are provided when available.
 - Unbiased Discovery
 - Verification

- Biospecimens: Establish protocols for collection, processing, and storage of biospecimens and fields for establishing a database that was implemented across all CPTAC sites
 - Bioinformatics: Process study data, characterize database search identification algorithms, design tools to make CPTAC datasets compatible with caBIG and sharable
 - Post-Translational Modifications
 - Cell Lysate
 - Analyte Selection
 - Yeast Production
 - Plasma
 - Protein Standards
 - Digestion
 - Cell Line
- Inter-laboratory studies: Two inter-laboratory studies to identify and address the source of variability in measuring protein mixtures have been designed and conducted so far. The first set of experiments designed and implemented under the direction of the Unbiased Discovery WG compared mass spectrometry (MS) measurements for various reference materials and reduced variability through a series of procedural refinements. The second set of experiments was designed and implemented under the direction of the Verification WG. The technique of Multiple Reaction Monitoring was employed to measure absolute amounts of proteins in spiked plasma sample across labs. In addition to conducting these studies, CPTAC centers were engaged in detailed documentation for the production of future standards and protocols.
 - Intra-laboratory studies: In addition to the inter-laboratory studies, each team is continuing their own research programs and implementing CPTAC procedures.
 - Program activities:
 - Program Coordinating Committee (PCC): A committee of team leads and the CPTC program director, with participation from some center co-PIs and other respected proteomics researchers, participate in the committee. The PCC chair is a center lead and the chair rotates every year. The committee monitors the progress of each center, establishes priorities for the CPTAC network, and facilitates communication between network members. The PCC meets monthly via teleconference and twice a year in person.
 - Annual review: Centers submit a summary of activities and outputs each year in January in preparation for site visits conducted by CPTC program managers in the spring.
 - CPTAC meetings: Center representatives are asked to attend and present at the annual program meeting held in the fall. Additionally, they are asked to participate in occasional ad hoc workshops and planning meetings.

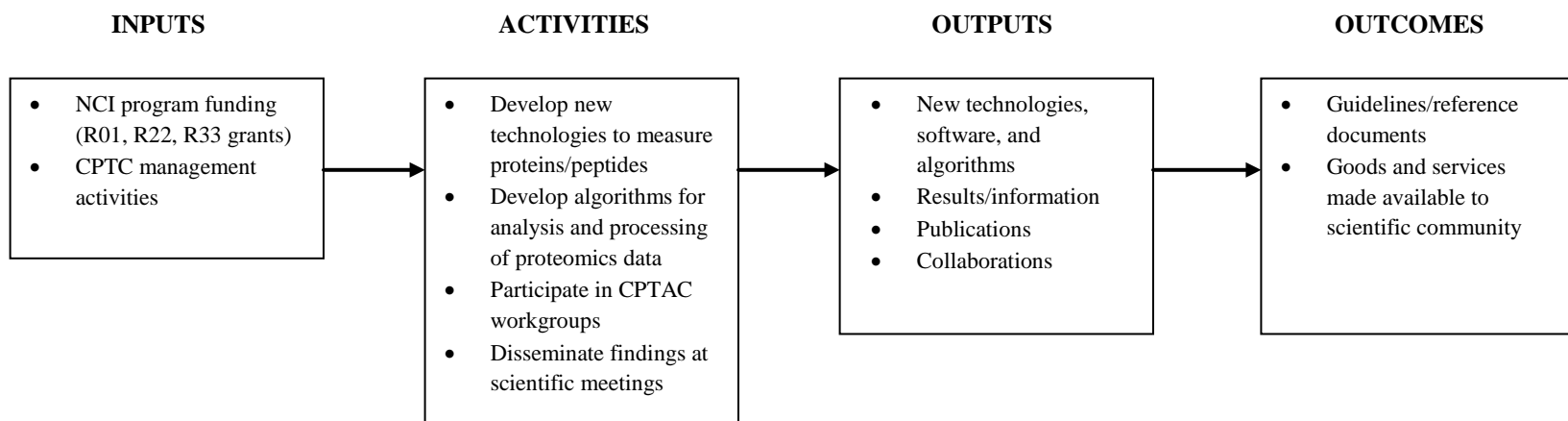
Outputs

- Optimization of current technologies: Standardized approaches to developing applications of proteomic platforms to maximize the ability to analyze cancer-relevant proteomic changes in human clinical specimens
- Recommended SOPs: Documented systematic approaches, based on the outcomes of inter-laboratory studies and workgroups, to reducing measurement variability through experimental design, platform protocols, specimen collection and preparation, and data analysis
- Recommended reference materials: Well-characterized biological materials such as a protein mixtures used in inter-laboratory studies used to compare the performance of MS platforms using established SOPs
- Results/information: Study outcomes, including protocols and materials, disseminated outside of formal publications (e.g., presentations, NCI reports, media, conversations with colleagues)
- Publications: Inter- and intra-laboratory study findings published in peer-reviewed proteomic, cancer research, or other science journals
- Collaborative teams: Collaborative teams with members of the CPTAC or with other proteomics researchers that continue or are formed outside the requirements of the program

Outcomes

- Guidelines/reference documents: Protocols from the verification study provide a foundation for proteomics investigators to develop similar MS-based protein assays in their own lab.
- Optimization of protocols for platforms: Taking the protocols adopted as a result of the CPTAC studies and optimizing them for new or verified proteomic technologies
- Reference materials available to community: Reference materials used in inter-lab studies and recommended by CPTAC researchers that are produced by CPTC contractors or independent private firms
- SOPs adopted by scientific community: SOPs recommended by CPTAC adopted and expanded by other proteomic cancer researchers

ADVANCED PROTEOMIC PLATFORMS AND COMPUTATIONAL SCIENCES INITIATIVE CONCEPTUAL FRAMEWORK



Advanced Proteomic Platforms and Computational Sciences Initiative Conceptual Framework

The Advanced Proteomic Platforms and Computational Sciences initiative allows individual investigators to explore new technologies and methods in proteomic research. Since these are research grants without a collaboration requirement, CPTC staff have less communication with these awardees and there are no requirements for participation in the CPTAC network. The objectives of these awards, as established by NCI, are applied discovery in the areas of proteomic platforms and algorithms. This differs from the CPTAC goals of verifying and standardizing procedures for current technologies.

Inputs

- NCI program funding: 15 individual R01, R21, or R21/R33 grants (RFA-CA-07-005)
- CPTC management activities: At least 3 of the 15 individual awardees were involved with one of the CPTAC teams or members of that team prior to receiving the current award and therefore contribute to the network through their participation in the CPTAC team. Also, if appropriate, CPTC program staff will facilitate collaborations between individual research awardees and collaborative centers.

Activities

- Develop new technologies to measure proteins/peptides: The development of innovative high-throughput technology for protein and peptide detection
- Develop algorithms for analysis and processing of proteomics data: The development of computational, statistical, and mathematical approaches for the analysis, processing, and transfer of large proteomic datasets
- Participate in CPTAC workgroups: Individual researchers who are collaborating with centers or are developing a technology relevant to a particular workgroup might participate in workgroups, but this is not a required activity.
- Disseminate findings at scientific meetings: Individual researchers are invited to report findings at the CPTC annual meeting and may present at other conferences.

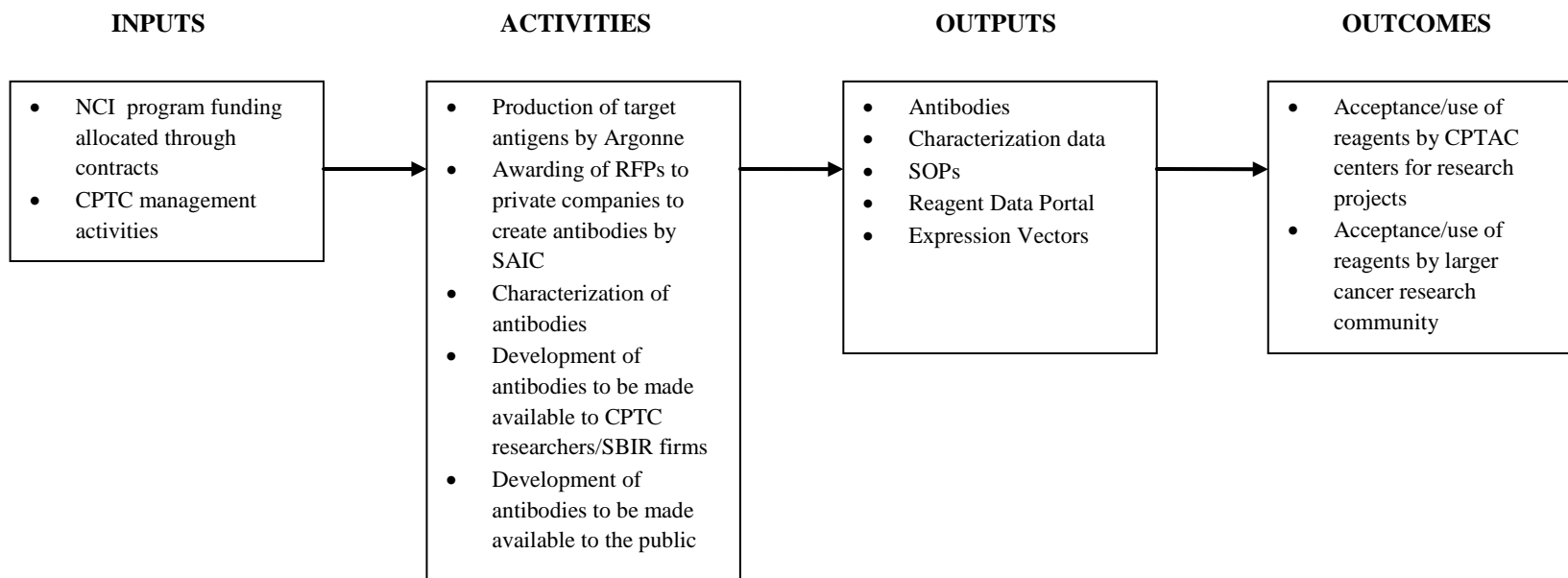
Outputs

- New technologies, software, and algorithms: Technologies and algorithms are developed and made available for verification by other researchers, possibly within CPTAC.
- Results/information: Study outcomes, including protocols and materials, disseminated outside of formal publications (e.g., presentations, NCI reports, conversations with colleagues)
- Publications: Study findings published in peer-reviewed proteomic, cancer research, or other science journals
- Collaborations: Collaborations with members of the CPTAC

Outcomes

- Guidelines/reference documents: Protocols for the implementation of new technologies
- Goods and services made available to scientific community: Software using algorithms for analysis of protein/peptide measurements or services for processing proteomic datasets

PROTEOMIC REAGENTS AND RESOURCES CORE COMPONENT CONCEPTUAL FRAMEWORK



Proteomic Reagents and Resources Core Component Conceptual Framework

Inputs

- NCI program funding allocated through contracts: Contracts awarded by NCI to SAIC and other institutions/organizations/businesses for reagent production, characterization, and the other activities performed in this program component
- CPTC management activities: Guidance, direction, and instructions provided by CPTC staff to SAIC and the other institutions involved in the reagent component

Activities

- Production of target antigens by Argonne: Target proteins produced by Argonne National Lab (or other labs, if applicable) and delivered to Reagent component staff
- Awarding of RFPs to private companies to create antibodies by SAIC: Subcontracts awarded by SAIC to companies to make reagents and return them to SAIC for evaluation
- Characterization of antibodies: Evaluations and characterizations performed on antibodies by SAIC staff, Harvard Institute of Proteomics, NCI'S Center for Cancer Research, and other researchers
- Development of antibodies to be made available to CPTC researchers/SBIR firms: Products and characterization data that the CPTC program provides for interlaboratory research projects, SBIR work, and other program-related activities
- Development of antibodies to be made available to public: Products and characterization data available for purchase by the research community through the Reagent Data Portal

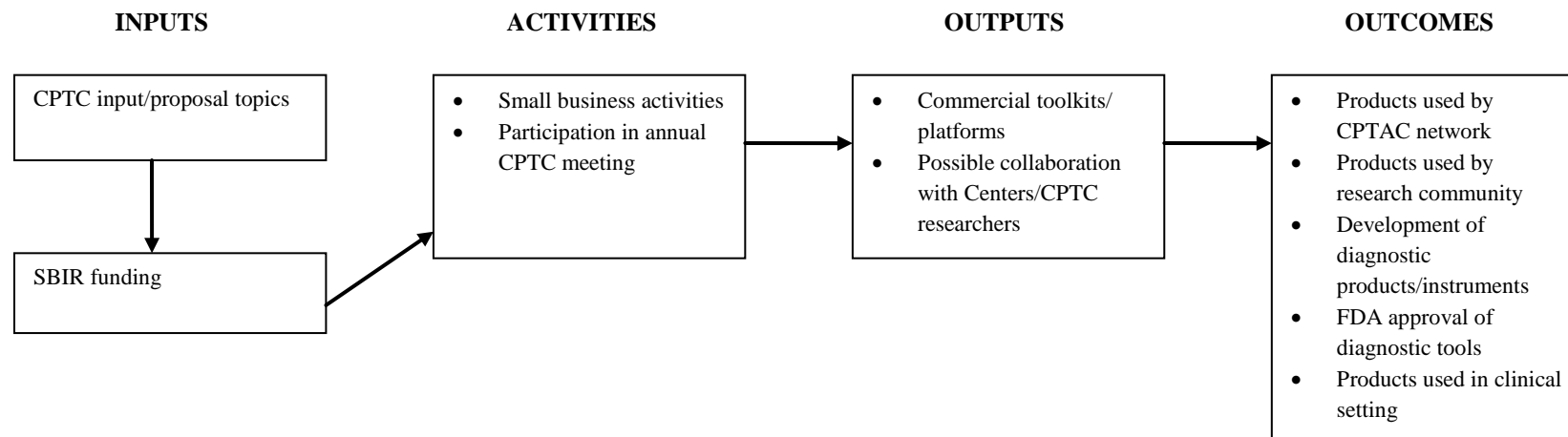
Outputs

- Antibodies: Well-characterized, renewable, reasonably-priced reagents that are made available to researchers through the Reagent Data Portal
- Characterization data: Data obtained during the characterization process that informs researchers about the reagents
- SOPs: Standard operating procedures and other documentation produced during the antibody production and characterization process and made available to researchers
- Reagent Data Portal: Web site that researchers access to request samples from the biorepository
- Expression Vectors: Replicated or cloned proteins available to CPTC researchers

Outcomes

- Acceptance/use of reagents by CPTAC centers for research projects: Products and characterization data created by the Reagent component are used by CPTC community members for inter-laboratory research projects, SBIR work, and other program-related activities.
- Acceptance/use of reagents by larger cancer research community: Products and characterization data available for purchase by the research community through the Reagent Data Portal are used by researchers in the larger cancer research community.

SMALL BUSINESS INNOVATION RESEARCH (SBIR) PROGRAM CONCEPTUAL FRAMEWORK



SBIR Program Conceptual Framework

As the SBIR program is not a funded component of the CPTC program, the program has little control over the outputs and outcomes of the SBIR awardees. This framework represents the overall process of SBIR research and development, and these awards should be examined in a full evaluation. However, the CPTC program's lack of direct funding and input in this area should be kept in mind when evaluating the outcomes of this group of awards.

Inputs

- CPTC input/proposal topics: Ideas for SBIR awards proposed by CPTC program. CPTC staffers also have input into which awards advance past Phase 1.
- SBIR funding: RFPs issued and awards made by the SBIR program

Activities

- Small business activities: Work done by grant winners to carry out research proposed in their grant applications, with the ultimate aim of developing products for the marketplace
- Participation in annual CPTC meeting: Attending the meeting and producing a presentation or poster, as appropriate. Attendees also use this time to network, learn about other researchers' projects, and develop relationships that may lead to future collaborations.

Outputs

- Commercial toolkits/platforms: Products produced by SBIR firms for the marketplace. May include antibodies, research toolkits, platforms, software, and other materials
- Possible collaboration with Centers/CPTC researchers: SBIR researchers may work with other members in the CPTC community to develop strategies and research plans. Additionally, scientific discoveries made by the Centers may be transitioned to SBIR businesses that will put them into the marketplace.

Outcomes

- Products used by CPTAC network: The toolkits, platforms, and other technologies created by SBIR firms that will be available to researchers in the CPTAC network, as facilitated by the program
- Products used by research community: The toolkits, platforms, and other technologies created by SBIR firms that will be available to researchers throughout the community, whether they are associated with the CPTC program or not
- Development of diagnostic products/instruments: The extent to which SBIR firms become involved in developing tests and instruments that can be used in cancer diagnosis
- FDA approval of diagnostic tools: The receipt of necessary FDA approval for diagnostic tools developed
- Products used in clinical setting: Any tests, tools, or products developed for use in the diagnostic, clinical setting

APPENDIX C
DATA COLLECTION GUIDELINES

This appendix present the three data collection guidelines for the study, each directed at a particular component of the study. The questions were developed to outline potential data needs for the assessment. They were reviewed by the Evaluation Advisory Committee for the National Cancer Institute's Clinical Proteomic Technologies for Cancer program and revised accordingly. The guidelines provide a general platform for embarking on discussions with interviewees. They were not constructed to assist the interviewers in understanding the kinds of information needed from the interview, nor to serve as an interview protocol. There were several reasons why this particular approach was taken, not the least of which was the limited time available to conduct a discussion. For the most part, the interviews were scheduled to last half an hour, which was not adequate for addressing even half of the questions.

I. Interview and Data Collection Guide for CPTAC Center Network

Resources

1. What is the grant amount? (External Sources)
2. How is the grant funds allocated to support:
 - a. Overall center functions?
 - b. Different topical areas or objectives?
 - c. Partners?
3. How many FTEs is supported solely from grant funds
 - a. Researchers?
 - b. Supporting staff (computer, instrumentation and laboratory specialists)?
 - c. Trainees (Post-docs and pre-doc)?
 - d. Administrative staff?
4. How much of the grant has allocated for travel?
5. How much of the grant is spent obtaining samples (reagents) and other materials?
6. What other sources of funding are directed at achieving CPTAC aims (include in-kind resources)? Do these other funds support:
 - a. Facilities?
 - b. Staffing?
 - c. Instrumentation?
7. How critical are these extra funding sources for carrying out the CPTAC aims.

Objectives

1. What are your program or grant objectives? (Note: each objective should be followed relative to stating inputs/resources, activities, outputs, and outcomes)
2. Can you describe how the objectives were arrived at and how you formulated the strategy for carrying the objectives out?
3. What are the primary activities that are pursued by researchers under this program? Can you describe the activities by whether and to what extent they are pursued:
 - a. With CPTAC supported personnel?
 - i. At this institution?
 - ii. At a partner institution?
 - b. In collaboration with
 - i. Independently funded researchers at this institution?
 - ii. CPTAC funded researchers from other CPTAC grantees?
 - iii. Independently funded researchers at partner institutions?
4. Has the objective been achieved?
 - a. What are the criteria for assessing this?
 - b. What were limitations or barriers that were encountered and how were they mitigated?

Outputs

1. Can you provide a list of achievements that were developed under this grant?
 - a. Peer reviewed publications
 - b. Other journal or peer reviewed articles, notes, or reports
 - c. Presentations
 - d. Awards
2. Can you describe the meetings in which you are involved under CPTAC grant auspices?
 - a. Professional meetings
 - b. CPTAC workgroups
3. Can you describe tools or toolkits (computer programs, SOPs, instruments) that were generated by your program?
4. Did you conduct bioanalytical validation of any cancer biomarkers that were identified? If so, describe how this was done.
5. Did you conduct clinical validation of any cancer biomarkers? If so, describe how this was done.
6. Did any biomarkers that were identified meet the accepted bioanalytical criteria for biomarker validation?
7. What was the clinical specificity and sensitivity for the biomarkers that passed the bioanalytical validations?
8. Describe the impact of your research on the fields of cancer biology and cancer therapeutics.
9. Can you describe other achievements that were realized in proteomic cancer research outside of the CPTAC grant

Can you tell us about your prior Discovery and Research Efforts? (Note: This section provides information on what individuals are doing outside of CPTAC. The information will be used to assess the degree to which CPTC affects these investigators in non-CPTAC activities. We would expect that of any group, this one would be using the technologies, methodologies and standards fostered by CPTAC, and would confirm that the program can have an effect).

1. What other proteomic research efforts were you involved in prior to CPTAC?
2. Did you identify potential biomarkers?
3. Were these biomarkers verified? Validated?
4. Did you submit an application to FDA for approval? If so, what is the status of your application?
5. Since the award of the CPTAC grant, can you describe grant applications to NIH or other agencies and foundations that you applied for? Can you describe these in terms of the objectives of the research and relationship to CPTAC?
6. Which of these other grants or projects relating to proteomic research that you have been awarded?
7. How did you use of CPTAC methodologies, collaborations, etc. play a role in any new grant opportunities?

8. How did you use of CPTAC generated “outputs/products” for these grants?
 - a. Utility of Outputs/Products
 - b. Improvements made to CPTAC effort
9. Please describe products generated from these other efforts?

Inputs

1. Have you used information, samples or protocols from other CPTAC groups?
 - a. What information or materials was provided?
 - b. What is the utility of the materials supplied?
 - c. What were the limitations of the materials?
2. How have you use information, samples or protocols from CPTC Reagents Program
 - a. What information or materials was provided?
 - b. What is the utility of the materials supplied?
 - c. What were the limitations of the materials?
3. How have you used such inputs from other sources?
 - a. What was the input?
 - b. Who were the other sources?
 - c. What were the materials used for?

Collaboration

1. Which CPTAC workgroups do you participate on?
 - a. How does participation affect your current work?
2. How have you participated in any inter-laboratory studies?
 - a. Who are your colleagues in these studies?
 - b. What is your role?
 - c. How do these studies affect your other work?
3. Are you collaborating with your partners, or with researchers at other institutions on discovery, and verification (outside the CPTAC focus)?

Reflections on CPTC

1. Please describe how the program has impacted the development of your center?
2. Has the CPTC program provided the mechanisms for creating an environment for achieving project objectives? If so, how?
3. Has the collaborative activities supported by CPTC been useful in pursuing:
 - a. CPTC objectives?
 - b. Other research objectives? If so how?
4. Which mechanisms prove to be effective in supporting your efforts? How?
5. What other CPTC activities that do not currently exist would help in supporting your efforts?
6. How does your center communicate what you are doing to the clinical and general proteomic research community?

Perceptions of Activities by Other Researchers

1. Do you know of any other research groups using the CPTC methodologies, reagents and technologies that you are developing? What are these? How do they work?
2. Do you know of any other research groups using CPTC reagents or other technologies? What are these? How do they work?
3. Have you had intensive discussions with these individuals? What was the nature of these discussions?
4. What level of satisfaction have they reported with the methods?

II. Data Collection Guide for Individual Investigators and Non-CPTC Proteomic Investigators, Organized by Assessment Goal

Note to team: most individuals in this category are software developers, thus the questions must be related to these individuals. Reagent questions have no relevance for them.

- A. Evaluate the performance of proteomic technology platforms and standard approaches to developing applications for these platforms.
 - a. Number of publications including this author citing CPTC funding? Other inputs or outputs (e.g., SOPs, CPTAC studies).
 - b. Number of grants applications submitted, and awarded?
 - c. Are you collaborating with investigators as a result of CPTC? Describe these collaborations and any jointly-achieved results. (both CPTC and non-CTPC)
 - d. Have these collaborations advanced your research? How? (both CPTC and non-CTPC)
 - e. Have these collaborations resulted in joint publications or studies? (both CPTC and non-CTPC) Please describe.
 - f. Do you foresee continuing these collaborations? (both CPTC and non-CTPC) If no, why not?
- B. Assess proteomic platforms and software for their ability to analyze cancer relevant proteomic changes in human clinical specimens.
 - a. What is your primary research focus?
 - b. What have you produced (papers, software, protocols) from this research? Please elaborate on these products?
 - c. For those who are involved in discovery?
 - i. Are you identifying or verifying specific cancer biomarkers as part of their research? (both CPTC and non-CPTC)
 - ii. If yes, has the research resulted in any biomarkers being in use in correlative research studies in early phase clinical trials? If so, what are these?
 - iii. Has CPTC had an effect upon accelerating the bioanalytical or clinical validation of this biomarker?
 - iv. If yes, what is your verification of the biomarker? How were the bioanalytical and clinical validations conducted?
- C. Develop well characterized reagents and bioinformation resources for the entire cancer research community. For platform developers.
 - a. Have antibodies been purchased by this investigator? If so, which ones and for what applications?
 - b. If none purchased, is the investigator familiar with the **CPTC Reagents & Resources web portal**? (Non-CPTC only)? How did the portal work?
 - c. Have they personally accessed the portal? Someone from their lab?

- d. If no record of purchase, have they or someone from their lab purchased antibodies through the biorepository?
- e. If reagents purchased, were they satisfied with the quality of the reagents? Why/why not?
- f. Do you approve of CPTCs choices for the first groups of antigens to add to the reagents portal and made available through DSHB (University of Iowa)? If yes, why? If no, why not?
- g. Do you think CPTC has directed enough money and effort to the reagents portal? Too much?

For software developers:

- 1. What specific software products have you produced under your CPTC grant? Can you describe it and its applicability, and potential and actual end users?
- 2. What other software products have you produced in the recent past to facilitate proteomic research? Is the software made available to the scientific community? If yes, how is it disseminated?
- 3. Will this software be generalizable to the proteomic community? Will it succeed without CPTAC?
- 4. Have there been any efforts to ensure caBIG capability?

III. Data Collection Guidelines for Reagent Pipeline Investigators, Reagent Pipeline Users, and Other Individuals Associated With Reagent Activities

Data to be collected regarding the following program goal: Develop well-characterized reagents and bioinformatics resources for the entire cancer research community.

Reagent Pipeline Investigators

How many reagents have been produced and/or characterized at your facility?

1. Explain the characterization process for the reagents? What characterization methodologies are used?
2. Are your reagents used for quantitative proteomics? If so, how were they validated
3. What supporting documentation is created for the reagents?
4. How do investigators decide which reagents will be characterized?
5. What is the funding amount for producing these reagents? How many people are supported by it? What is the typical per reagent cost? What are the characterization costs per reagent?
6. What are the goals of this program? How is progress towards meeting those goals measured? What are the results of measuring this progress?
7. What are the internal and external barriers to achieving these goals? How might these be mitigated?
8. What could the CPTC program be doing to further advance the goals that are not being met?
 - a. OR while you are meeting your goals, how could the CPTC program do so more cost- and time efficiently?
9. How sustainable would this work be without CPTC support? If the CPTC program were not there, would the characterization work be carried out by other organizations/agents? How do you believe characterization would be affected?
10. Describe the types and characteristics of contact do reagent investigators have with users who are in the CPTAC network or are otherwise related to CPTC? With users from the larger research community?
11. How are CPTAC researchers using these products? How are researchers from the larger community using these products?
12. From your perspective and interactions, what is the perception of the reagents within the CPTAC network? In the larger research community? (Note: David Soll could provide information through customers on this).
13. What kinds of feedback on the quality and applicability of the reagents does the CPTAC network provide? The general research community?
14. Do you measure user satisfaction with the products? How? Overall, are users satisfied or dissatisfied? Are there other products or characterization information that they need?
15. What impact does this part of the CPTC program have on the larger research community in terms of carrying out work in discovery, verification, or validation?
16. How many researchers have inquired about reagents? How many have ordered? How many ordered more than once? (From DSHB)

17. Which reagents have been ordered? How often? Any repeat orders of same product? (From DSHB)
18. What was the timeline of the orders? How long does it take to fill an order, or how long did it take for initial orders to be placed? Can this process be more efficient? (From DSHB)
19. In addition to other types of characterization, how do you determine the stability of your reagent, the effects of different matrices on your reagent(s) and in addition to reactivity in gels and the various assays the shelf life of your reagent?
20. What IP surrounds the reagents that you produce and can the reagents be used for more than basic research?
21. Describe the impact of your reagents on the fields of cancer biology and cancer therapeutics

Reagent Pipeline Users

1. How do researchers learn about the Reagent Data Portal? How many hits has the portal received? (Mike Loss – Web portal Designer and CPTC staff)
2. How do researchers use the antibodies/antigens in their research?
3. If the products were not available from the Portal, where would researchers get them?
4. What did researchers think of the quality of the products?
5. What did researchers think of the quality of the supporting documentation/characterization data?
6. Have researchers used reagents from other sources before? If so, from where? When? What was their experience with those products?
7. Do researchers plan to use the Portal to purchase reagents again in the future? Why or why not?
8. Are any additional reagents or products needed? Why/what kinds?
9. How could the products themselves be improved?
10. CPTC currently provides the following characterizations. Are you aware that they are being provided?
 - a. isotyping,
 - b. western blot,
 - c. ELISA,
 - d. Immuno – Mass Spectrometry,
 - e. Immuno histochemistry,
 - f. Surface Plasmon Resonance,
 - g. Nucleic Acid programmable protein arrays (NAPPA)
11. What additional characterizations would be of interest to your group?
12. How do you delineate these reagents from others that are produced through similar means or a similar pipeline?
13. How do the CPTC-produced reagents offer a significant advancement (and I know that they do!) over what currently exists?

Other Individuals Associated With Reagent Activities (FDA, NIST, etc.)

1. How is this organization/individual connected to CPTC (or to CPTAC?) (From CPTC staff)
2. How long has the relationship existed? (From CPTC staff)
3. What is the contractual/legal nature of the relationship? Is there any funding from CPTC involved? (From CPTC staff)
4. What does the organization/individual get from the relationship?
5. Does CPTC benefit from this relationship? How?
6. What are the goals of the strategic relationship? How are these goals measured?
7. How do these goals relate to the overall program goals?
8. Are these goals being met?
9. What are the barriers to meeting these goals and how are they mitigated?
10. What kinds of outputs are expected from this relationship? Are these being produced? If so, how are they perceived/measured?
11. What is the relationship with the CPTC staff?
12. What is the relationship with others in the CPTC community, such as network members or researchers?

APPENDIX C
DATA COLLECTION GUIDELINES

This appendix present the three data collection guidelines for the study, each directed at a particular component of the study. The questions were developed to outline potential data needs for the assessment. They were reviewed by the Evaluation Advisory Committee for the National Cancer Institute's Clinical Proteomic Technologies for Cancer program and revised accordingly. The guidelines provide a general platform for embarking on discussions with interviewees. They were not constructed to assist the interviewers in understanding the kinds of information needed from the interview, nor to serve as an interview protocol. There were several reasons why this particular approach was taken, not the least of which was the limited time available to conduct a discussion. For the most part, the interviews were scheduled to last half an hour, which was not adequate for addressing even half of the questions.

I. Interview and Data Collection Guide for CPTAC Center Network

Resources

1. What is the grant amount? (External Sources)
2. How is the grant funds allocated to support:
 - a. Overall center functions?
 - b. Different topical areas or objectives?
 - c. Partners?
3. How many FTEs is supported solely from grant funds
 - a. Researchers?
 - b. Supporting staff (computer, instrumentation and laboratory specialists)?
 - c. Trainees (Post-docs and pre-doc)?
 - d. Administrative staff?
4. How much of the grant has allocated for travel?
5. How much of the grant is spent obtaining samples (reagents) and other materials?
6. What other sources of funding are directed at achieving CPTAC aims (include in-kind resources)? Do these other funds support:
 - a. Facilities?
 - b. Staffing?
 - c. Instrumentation?
7. How critical are these extra funding sources for carrying out the CPTAC aims.

Objectives

1. What are your program or grant objectives? (Note: each objective should be followed relative to stating inputs/resources, activities, outputs, and outcomes)
2. Can you describe how the objectives were arrived at and how you formulated the strategy for carrying the objectives out?
3. What are the primary activities that are pursued by researchers under this program? Can you describe the activities by whether and to what extent they are pursued:
 - a. With CPTAC supported personnel?
 - i. At this institution?
 - ii. At a partner institution?
 - b. In collaboration with
 - i. Independently funded researchers at this institution?
 - ii. CPTAC funded researchers from other CPTAC grantees?
 - iii. Independently funded researchers at partner institutions?
4. Has the objective been achieved?
 - a. What are the criteria for assessing this?
 - b. What were limitations or barriers that were encountered and how were they mitigated?

Outputs

1. Can you provide a list of achievements that were developed under this grant?
 - a. Peer reviewed publications
 - b. Other journal or peer reviewed articles, notes, or reports
 - c. Presentations
 - d. Awards
2. Can you describe the meetings in which you are involved under CPTAC grant auspices?
 - a. Professional meetings
 - b. CPTAC workgroups
3. Can you describe tools or toolkits (computer programs, SOPs, instruments) that were generated by your program?
4. Did you conduct bioanalytical validation of any cancer biomarkers that were identified? If so, describe how this was done.
5. Did you conduct clinical validation of any cancer biomarkers? If so, describe how this was done.
6. Did any biomarkers that were identified meet the accepted bioanalytical criteria for biomarker validation?
7. What was the clinical specificity and sensitivity for the biomarkers that passed the bioanalytical validations?
8. Describe the impact of your research on the fields of cancer biology and cancer therapeutics.
9. Can you describe other achievements that were realized in proteomic cancer research outside of the CPTAC grant

Can you tell us about your prior Discovery and Research Efforts? (Note: This section provides information on what individuals are doing outside of CPTAC. The information will be used to assess the degree to which CPTC affects these investigators in non-CPTAC activities. We would expect that of any group, this one would be using the technologies, methodologies and standards fostered by CPTAC, and would confirm that the program can have an effect).

1. What other proteomic research efforts were you involved in prior to CPTAC?
2. Did you identify potential biomarkers?
3. Were these biomarkers verified? Validated?
4. Did you submit an application to FDA for approval? If so, what is the status of your application?
5. Since the award of the CPTAC grant, can you describe grant applications to NIH or other agencies and foundations that you applied for? Can you describe these in terms of the objectives of the research and relationship to CPTAC?
6. Which of these other grants or projects relating to proteomic research that you have been awarded?
7. How did you use of CPTAC methodologies, collaborations, etc. play a role in any new grant opportunities?

8. How did you use of CPTAC generated “outputs/products” for these grants?
 - a. Utility of Outputs/Products
 - b. Improvements made to CPTAC effort
9. Please describe products generated from these other efforts?

Inputs

1. Have you used information, samples or protocols from other CPTAC groups?
 - a. What information or materials was provided?
 - b. What is the utility of the materials supplied?
 - c. What were the limitations of the materials?
2. How have you use information, samples or protocols from CPTC Reagents Program
 - a. What information or materials was provided?
 - b. What is the utility of the materials supplied?
 - c. What were the limitations of the materials?
3. How have you used such inputs from other sources?
 - a. What was the input?
 - b. Who were the other sources?
 - c. What were the materials used for?

Collaboration

1. Which CPTAC workgroups do you participate on?
 - a. How does participation affect your current work?
2. How have you participated in any inter-laboratory studies?
 - a. Who are your colleagues in these studies?
 - b. What is your role?
 - c. How do these studies affect your other work?
3. Are you collaborating with your partners, or with researchers at other institutions on discovery, and verification (outside the CPTAC focus)?

Reflections on CPTC

1. Please describe how the program has impacted the development of your center?
2. Has the CPTC program provided the mechanisms for creating an environment for achieving project objectives? If so, how?
3. Has the collaborative activities supported by CPTC been useful in pursuing:
 - a. CPTC objectives?
 - b. Other research objectives? If so how?
4. Which mechanisms prove to be effective in supporting your efforts? How?
5. What other CPTC activities that do not currently exist would help in supporting your efforts?
6. How does your center communicate what you are doing to the clinical and general proteomic research community?

Perceptions of Activities by Other Researchers

1. Do you know of any other research groups using the CPTC methodologies, reagents and technologies that you are developing? What are these? How do they work?
2. Do you know of any other research groups using CPTC reagents or other technologies? What are these? How do they work?
3. Have you had intensive discussions with these individuals? What was the nature of these discussions?
4. What level of satisfaction have they reported with the methods?

II. Data Collection Guide for Individual Investigators and Non-CPTC Proteomic Investigators, Organized by Assessment Goal

Note to team: most individuals in this category are software developers, thus the questions must be related to these individuals. Reagent questions have no relevance for them.

- A. Evaluate the performance of proteomic technology platforms and standard approaches to developing applications for these platforms.
 - a. Number of publications including this author citing CPTC funding? Other inputs or outputs (e.g., SOPs, CPTAC studies).
 - b. Number of grants applications submitted, and awarded?
 - c. Are you collaborating with investigators as a result of CPTC? Describe these collaborations and any jointly-achieved results. (both CPTC and non-CTPC)
 - d. Have these collaborations advanced your research? How? (both CPTC and non-CTPC)
 - e. Have these collaborations resulted in joint publications or studies? (both CPTC and non-CTPC) Please describe.
 - f. Do you foresee continuing these collaborations? (both CPTC and non-CTPC) If no, why not?
- B. Assess proteomic platforms and software for their ability to analyze cancer relevant proteomic changes in human clinical specimens.
 - a. What is your primary research focus?
 - b. What have you produced (papers, software, protocols) from this research? Please elaborate on these products?
 - c. For those who are involved in discovery?
 - i. Are you identifying or verifying specific cancer biomarkers as part of their research? (both CPTC and non-CPTC)
 - ii. If yes, has the research resulted in any biomarkers being in use in correlative research studies in early phase clinical trials? If so, what are these?
 - iii. Has CPTC had an effect upon accelerating the bioanalytical or clinical validation of this biomarker?
 - iv. If yes, what is your verification of the biomarker? How were the bioanalytical and clinical validations conducted?
- C. Develop well characterized reagents and bioinformation resources for the entire cancer research community. For platform developers.
 - a. Have antibodies been purchased by this investigator? If so, which ones and for what applications?
 - b. If none purchased, is the investigator familiar with the **CPTC Reagents & Resources web portal**? (Non-CPTC only)? How did the portal work?
 - c. Have they personally accessed the portal? Someone from their lab?

- d. If no record of purchase, have they or someone from their lab purchased antibodies through the biorepository?
- e. If reagents purchased, were they satisfied with the quality of the reagents? Why/why not?
- f. Do you approve of CPTCs choices for the first groups of antigens to add to the reagents portal and made available through DSHB (University of Iowa)? If yes, why? If no, why not?
- g. Do you think CPTC has directed enough money and effort to the reagents portal? Too much?

For software developers:

- 1. What specific software products have you produced under your CPTC grant? Can you describe it and its applicability, and potential and actual end users?
- 2. What other software products have you produced in the recent past to facilitate proteomic research? Is the software made available to the scientific community? If yes, how is it disseminated?
- 3. Will this software be generalizable to the proteomic community? Will it succeed without CPTAC?
- 4. Have there been any efforts to ensure caBIG capability?

III. Data Collection Guidelines for Reagent Pipeline Investigators, Reagent Pipeline Users, and Other Individuals Associated With Reagent Activities

Data to be collected regarding the following program goal: Develop well-characterized reagents and bioinformatics resources for the entire cancer research community.

Reagent Pipeline Investigators

How many reagents have been produced and/or characterized at your facility?

1. Explain the characterization process for the reagents? What characterization methodologies are used?
2. Are your reagents used for quantitative proteomics? If so, how were they validated
3. What supporting documentation is created for the reagents?
4. How do investigators decide which reagents will be characterized?
5. What is the funding amount for producing these reagents? How many people are supported by it? What is the typical per reagent cost? What are the characterization costs per reagent?
6. What are the goals of this program? How is progress towards meeting those goals measured? What are the results of measuring this progress?
7. What are the internal and external barriers to achieving these goals? How might these be mitigated?
8. What could the CPTC program be doing to further advance the goals that are not being met?
 - a. OR while you are meeting your goals, how could the CPTC program do so more cost- and time efficiently?
9. How sustainable would this work be without CPTC support? If the CPTC program were not there, would the characterization work be carried out by other organizations/agents? How do you believe characterization would be affected?
10. Describe the types and characteristics of contact do reagent investigators have with users who are in the CPTAC network or are otherwise related to CPTC? With users from the larger research community?
11. How are CPTAC researchers using these products? How are researchers from the larger community using these products?
12. From your perspective and interactions, what is the perception of the reagents within the CPTAC network? In the larger research community? (Note: David Soll could provide information through customers on this).
13. What kinds of feedback on the quality and applicability of the reagents does the CPTAC network provide? The general research community?
14. Do you measure user satisfaction with the products? How? Overall, are users satisfied or dissatisfied? Are there other products or characterization information that they need?
15. What impact does this part of the CPTC program have on the larger research community in terms of carrying out work in discovery, verification, or validation?
16. How many researchers have inquired about reagents? How many have ordered? How many ordered more than once? (From DSHB)

17. Which reagents have been ordered? How often? Any repeat orders of same product? (From DSHB)
18. What was the timeline of the orders? How long does it take to fill an order, or how long did it take for initial orders to be placed? Can this process be more efficient? (From DSHB)
19. In addition to other types of characterization, how do you determine the stability of your reagent, the effects of different matrices on your reagent(s) and in addition to reactivity in gels and the various assays the shelf life of your reagent?
20. What IP surrounds the reagents that you produce and can the reagents be used for more than basic research?
21. Describe the impact of your reagents on the fields of cancer biology and cancer therapeutics

Reagent Pipeline Users

1. How do researchers learn about the Reagent Data Portal? How many hits has the portal received? (Mike Loss – Web portal Designer and CPTC staff)
2. How do researchers use the antibodies/antigens in their research?
3. If the products were not available from the Portal, where would researchers get them?
4. What did researchers think of the quality of the products?
5. What did researchers think of the quality of the supporting documentation/characterization data?
6. Have researchers used reagents from other sources before? If so, from where? When? What was their experience with those products?
7. Do researchers plan to use the Portal to purchase reagents again in the future? Why or why not?
8. Are any additional reagents or products needed? Why/what kinds?
9. How could the products themselves be improved?
10. CPTC currently provides the following characterizations. Are you aware that they are being provided?
 - a. isotyping,
 - b. western blot,
 - c. ELISA,
 - d. Immuno – Mass Spectrometry,
 - e. Immuno histochemistry,
 - f. Surface Plasmon Resonance,
 - g. Nucleic Acid programmable protein arrays (NAPPA)
11. What additional characterizations would be of interest to your group?
12. How do you delineate these reagents from others that are produced through similar means or a similar pipeline?
13. How do the CPTC-produced reagents offer a significant advancement (and I know that they do!) over what currently exists?

Other Individuals Associated With Reagent Activities (FDA, NIST, etc.)

1. How is this organization/individual connected to CPTC (or to CPTAC?) (From CPTC staff)
2. How long has the relationship existed? (From CPTC staff)
3. What is the contractual/legal nature of the relationship? Is there any funding from CPTC involved? (From CPTC staff)
4. What does the organization/individual get from the relationship?
5. Does CPTC benefit from this relationship? How?
6. What are the goals of the strategic relationship? How are these goals measured?
7. How do these goals relate to the overall program goals?
8. Are these goals being met?
9. What are the barriers to meeting these goals and how are they mitigated?
10. What kinds of outputs are expected from this relationship? Are these being produced? If so, how are they perceived/measured?
11. What is the relationship with the CPTC staff?
12. What is the relationship with others in the CPTC community, such as network members or researchers?

APPENDIX D

CPTC STAKEHOLDER INTERVIEWS

Individual	Relevant CPTC Program Element	Location
Susan Fisher	UCSF CPTAC center	University of California, San Francisco
Joe Gray	UCSF CPTAC center	Lawrence Berkeley National Laboratory
Brad Gibson	UCSF CPTAC center	Buck Institute for Age Research
Steve Hall	UCSF CPTAC center	University of California, San Francisco
Ewa Witkowski	UCSF CPTAC center	University of California, San Francisco
Birgit Schilling	UCSF CPTAC center	Buck Institute for Age Research
Rich Niles	UCSF CPTAC center	University of California, San Francisco
Steve Carr	Broad CPTAC center	Broad Institute of MIT and Harvard
Leigh Anderson	Broad CPTAC Center	Plasma Proteome Institute
Steven Skates	Broad CPTAC center	Dana-Farber Cancer Research Institute
D.R. Mani	Broad CPTAC center and individual awardee	Broad Institute of MIT and Harvard
David Ransohoff	Broad CPTAC center	The University of North Carolina at Chapel Hill School of Medicine
Mandy Paulovich	Broad CPTAC center	Fred Hutchinson Cancer Research Center
Dan Liebler	Vanderbilt CPTAC center	Vanderbilt University
Dave Tabb	Vanderbilt CPTAC center and individual awardee	Vanderbilt University
Amy Ham	Vanderbilt CPTAC center	Vanderbilt University
Lisa Zimmerman	Vanderbilt CPTAC Center	Vanderbilt University
Fred Regnier	Purdue CPTAC center	Purdue University
Charles Buck	Purdue CPTAC center	Purdue University
Mu Wang	Purdue CPTAC center	Indiana University School of Medicine
Predrag Radivojac	Purdue CPTAC center	Indiana University
Paul Tempst	MSKCC CPTAC center	Memorial Sloan-Kettering Cancer Center
Tom Neubert	MSKCC CPTAC center	New York University Langone Medical Center
Mousumi Ghosh	MSKCC CPTAC center	Memorial Sloan-Kettering Cancer Center
Hans Lilja	MSKCC CPTAC center	Memorial Sloan-Kettering Cancer Center
Martin Fleisher	MSKCC CPTAC center	Memorial Sloan-Kettering Cancer Center
Joseph Loo	Individual awardee	University of California, Los Angeles
Xiaolian Gao	Individual awardee	University of Houston
Dariya Malyarenko	Individual awardee	College of William and Mary
Alexey Nesvizhskii	Individual awardee	University of Michigan
Richard Smith	Individual awardee	Battelle Pacific Northwest Research Laboratory
John Chaput	Individual awardee	Arizona State University
Phil Andrews	Tranche developer	University of Michigan
Elizabeth Mansfield	Organization with a strategic alliance with the CPTC program	Food and Drug Administration
Steve Stein	Organization with a strategic alliance with the CPTC program	National Institute of Standards and Technology

Individual	Relevant CPTC Program Element	Location
David Bunk	Organization with a strategic alliance with the CPTC program	National Institute of Standards and Technology
Willie May	Organization with a strategic alliance with the CPTC program	National Institute of Standards and Technology
Stephen Wise	Organization with a strategic alliance with the CPTC program	National Institute of Standards and Technology
Lee Hartwell	Ad Hoc Program Coordinating Committee member	Fred Hutchinson Cancer Research Center.
Saeed Jortani	Current American Association for Clinical Chemistry Proteomics Division president	University of Louisville
Pothur Srinivas	Part of the larger proteomic research community	National Heart, Lung, and Blood Institute, National Institutes of Health
David Agus	Part of the larger proteomic research community	University of California, Los Angeles
Sandy Markey	Part of the larger proteomic research community	National Institute of Mental Health
Gordon Whiteley	PRRC program	SAIC/NCI-Frederick
Craig Reynolds and Walter Hubert	PRRC program	NCI-Frederick
Stephen Hewitt	PRRC program	National Cancer Institute Center for Cancer Research
Joshua La Baer	PRRC program	Previously at Harvard University, now at Arizona State University
David Soll	PRRC program	Developmental Studies Hybridoma Bank, University of Iowa
James Holberg	Involved in the distribution of reagents developed under PRRC	Millipore
Johannes Mauer	Involved in the distribution of reagents developed under PRRC	ImaGenes-Bio
Fredrik Ponten	PRRC program	KTH Biotechnology

APPENDIX E

PROGRAM COMMENTS AND RESPONSES TO EVALUATION ADVISORY COMMITTEE QUESTIONS

Program Comments and Responses to Evaluation Advisory Committee Questions

Reviewer 1

Question: The Clinical Proteomic Technologies for Cancer (CPTC) program is a \$104 million program that has been in existence for only 3 years, and is composed of three interdependent activities (the Clinical Proteomic Technology Assessment for Cancer (CPTAC) - a network of 5 institutions with subsets of institutions and investigators that is the backbone of CPTC; Advanced Proteomic Platforms and Computational Sciences (APPCS) - a grants program that supports independent investigator research in proteomic technologies; and the Proteomic Reagents and Resources Core (PRRC) - a program to provide high quality antibodies and recombinant peptides to the external community for research purposes). Macro International - has provided a high-level review of the program that is detailed and seemingly complete. There are a number of publications that are used as metrics and by that criterion the program is highly successful. The amount of effort to get the three parts of the CPTC functional and operational is prodigious and to be complimented. Hopefully, the program can be sustained because it is just beginning to be productive.

Areas not directly addressed in the review, which need clarification are as follows: Overall focus of the program - As this reviewer understood from discussions with the Project Manager over the years, the primary focus was to improve the quality, stability and overall usability of mass spectrometry as a discovery platform to identify proteins/peptides that are useful in clinical research in oncology. It is clear that standard operating procedures (SOPs) were created and adopted, that tests were performed within a consortium on a standard set of samples and that with intensive training, all participants eventually correctly identified the peptides by understanding the sources of variability in the analytical protein biomarker discovery pipeline. What is not clear is what mass spectrometry platform is the best for this purpose, the lessons learned in broad strokes (a manuscript will contain the details) and how this will be used to move the field forward and what exactly that means.

Program Response: The 2009 Annual Report is to accompany the Evaluation Report, as it contains the tangible milestones/outcomes achieved by the CPTC. In brief, page 3 of the Annual Report states the goals of CPTC initiative - To address barriers in translating proteomic discoveries to clinical utility (barriers include experimental design, technical/analytical barriers, biospecimen, and data analysis). To effectively address these barriers, the NCI and its scientific advisory boards agreed that it would require a highly collaborative effort as it is far too great an endeavor for a single institution.

Specific deliverables to date include:

- Bias-free biospecimen collection procedures (in collaboration with NCI's Office of Biorepositories and Biospecimen Research [OBBR]);

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- Performance metrics for proteomic discovery platforms (in collaboration with National Institutes of Standard and Technology [NIST] and of which are available through NIST or commercial vendors);
- Standardize methods for targeted (quantitative) proteomic multiplex verification platforms (in collaboration with the Food and Drug Administration [FDA]);
- Uniform algorithms for sharing bioinformatics and proteomic data and analytical/data mining tools across the scientific community along with a caBIG silver compliant data sharing portal to foster the rapid dissemination of proteomics research information to the scientific community and the public (in collaboration with CBIIT); and the
- Development of standard/reference materials and reagents for the proteomic community (in collaboration with NIST, National Institute of Statistical Sciences [NISS], NCI's Center for Cancer Research [CCR], and public-private partnerships).

Several key round-robin papers discussing the robustness of platforms and methodologies across multiple institutions in the context of the protein biomarker discovery pipeline developed by the CPTAC network are cited in the 2009 Annual Report (and referenced here^{1,2,3}).

Question: Do the SOPs for preanalytic processing and stabilization created within the CPTAC correspond with similar protocols developed under other NCI-supported efforts such as the OBBR/caHUB?

Program Response: At the outset of the CPTC initiative, (OBBR) facilitated a meeting among the CPTAC network biospecimen collection sites. The purpose was to compare existing biospecimen collection and storage SOPs from these respective institutions, along with those from other programs within and outside the NCI. It was agreed upon by the CPTC Governing Body to consolidate these protocols into one consensus SOP to be used at all collection sites.

¹ Addona, T., Abbatiello, S.E., Skates, S.J., Bunk, D.M., Schilling, B., Spiegelman, C.H., Zimmerman, L.J., Ham, A-J.L., Keshishian, H., Hall, S.C., Allen, S., Anderson, N.L., Blackman, R.K., Borchers, C.H., Buck, C., Cardasis, H.L., Cusack, M.P., Dodder, N.G., Gibson, B.W., Held, J.M., Hiltke, T., Jackson, A., Johansen, E.B., Kinsinger, C.R., Li, J., Mani, D.R., Mesri, M., Neubert, T.A., Niles, R.K., Paulovich, A.G., Pulsipher, T.C., Rodriguez, H., Rudnick, P.A., Smith, D., Tabb, D.L., Tegeler, T.J., Variyath, A.M., Vega-Montoto, L.J., Wahlander, A., Waldemarson, S., Wang, M., Whiteaker, J.R., Fisher, S.J., Liebler, D.C., Regnier, F.E., Tempst, P., Carr, S.A., CPTAC Network. (2009) Multi-site Assessment of the Precision and Reproducibility of Multiple Reaction Monitoring-based Measurements of Proteins in Plasma. *Nature Biotechnology*. Jul;27(7):633-644.

² Rudnick, P.A., Clauser, K.R., Kilpatrick, L.E., Tchekhovskoi, D.V., Neta, P., Blonder, N., Billheimer, D.D., Blackman, R.K., Bunk, D.M., Cardasis, H.L., Ham, A-J.L., Jaffe, J.D., Kinsinger, C.R., Mesri, M., Neubert, T.A., Schilling, B., Tabb, D.L., Tegeler, T.J., Vega-Montoto, L., Variyath, A.M., Wang, M., Wang, P., Whiteaker, J.R., Zimmerman, L.J., Carr, S.A., Fisher, S.J., Gibson, B.W., Paulovich, A.G., Regnier, F.E., Rodriguez, H., Spiegelman, C., Tempst, P., Liebler, D.C., and Stein, S.E. (in press). Performance Metrics for Evaluating Liquid Chromatography-Tandem Mass Spectrometry Systems in Shotgun Proteomics. *Mol. Cellular Proteomics*.

³ Tabb, D.L., Vega-Montoto, L., Rudnick, P.A., Variyath, A.M., Ham, A-J.L., Bunk, D.M., Kilpatrick, L.E., , Billheimer, D.D., Blackman, R.K., Cardasis, H.L., Carr, S.A., Clauser, K.R., Jaffe, J., Kowalski, K.A., Neubert, T.A., Regnier, F.E., Schilling, B., Tegeler, T.J., Wang, M., Wang, P., Whiteaker, J.R., Zimmerman, L.J., Fisher, S.J., Gibson, B.W., Kinsinger, C.R., Mesri, M., Rodriguez, H., Stein, S.E., Tempst, P., Paulovich, A.G., Liebler, D.C., Spiegelman, C. (in press) Repeatability and Reproducibility in Proteomic Identifications by Liquid Chromatography - Tandem Mass Spectrometry. *Mol. Cellular Proteomics*.

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Question: It is not clear how other major agencies such as NIST and FDA interact with this program. What is the role of NIST? One hopes that the creation of reagents and reference materials in the PRRC is coordinated with NIST in some mutually beneficial way that might allow these materials to become SRMs for the NIST program.

Program Response: Page 24 of 2009 Annual Report discusses these points. CPTC has an interagency agreement with NIST to develop assessment materials to be used by the CPTAC teams. These materials, designed to assess the performance metrics of various instruments, will be the first of their kind developed by the NCI and will help to evaluate and compare existing proteomic technologies and compare these with emerging proteomic technologies of interest to the clinical cancer community. A well-characterized yeast lysate used in CPTAC round-robin studies (publication in press⁴), has been developed by NIST and is now available to the research community. This material serves as a model proteome of moderate complexity intended for evaluating the measurement quality of protein-based mass spectrometry investigations (SRM 3952). A second performance mixture is currently being evaluated by the CPTAC network of which has also been approved by NIST. This performance mixture (SRM 3592) consists of a complex mixture of peptides intended for evaluating the performance of mass spectrometry instruments/components performing quantitative data-dependent acquisition – specifically, multiple reaction monitoring (MRM) technology. Interactions with the FDA are further outlined in the following question.

Question: The Macro International review suggests that the CPTC is supporting the development of clinically useful biomarkers with “mock” 510(k) submissions to the FDA. This seems to be an entirely new direction from that discussed with this reviewer that may be entirely appropriate. However, while the stress on the regulatory aspects of data submission to the FDA is an important step, there are other more important steps that are entirely glossed over in the review. To be clinically useful a biomarker and its assay must have valid analytical performance within its matrix and then shown to be clinically useful in medical decision-making within its clinical context. If the marker is to be cleared by the Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD), retrospective data may be useful but if the marker is connected to a drug or biological, then prospective data sets are necessary. Since a focus of the CPTC was to improve the performance of mass spectrometry platforms for peptide analysis where they may be sufficiently reliable and robust that it might perform in a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory, then it is possible that the mass spectrometry approach may be ultimately successful as an analytical platform.

Program Response: A central goal of the CPTC initiative was to address the technical barriers (analytical) in protein-based platforms. In early discussion with OIVD at the FDA, it was

⁴ Paulovich, A.G., Billheimer, D.D., Ham, A-J.L., Vega-Montoto, L., Rudnick, P.A., Tabb, D.L., Wang, P., Blackman, R.K., Bunk, D.M., Cardasis, H.L., Clauser, K.R., Kinsinger, C.R., Schilling, B., Tegeler, T.J., Variyath, A.M., Wang, M., Whiteaker, J.R., Zimmerman, L.J., Carr, S.A., Fisher, S.J., Gibson, B.W., Mesri, M., Neubert, T.A., Regnier, F.E., Rodriguez, H., Spiegelman, C., Stein, S.E., Tempst, P., Liebler, D.C., and the NCI Clinical Proteomic Technology Assessment for Cancer (CPTAC) Network. (in press) A CPTAC Inter-laboratory Study Characterizing a Yeast Performance Standard for Benchmarking LC-MS Platform Performance. *Mol. Cellular Proteomics*.

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learned that there are currently no guidelines to protein-based multiplex analytical platforms. Because the CPTC initiative addresses the barriers in translating proteomic to clinical application, a MOU was established among the two organizations with a focus on analytical barriers. This is referenced on page 36 of the 2009 Annual Report and discussed in the CPTC eProtein Newsletter Spring 2009 (enclosed in the June 2009 NCI BSA update report). Briefly, CPTC worked with the FDA on a workshop to identify what are the analytical validation questions that need to be addressed for protein-based multiplex "bridge" technologies to be used in the context of clinical utility. A workshop report was developed and submitted for publication in the journal of *Clinical Chemistry* (currently in press⁵). Additionally, two "mock" 510(k) documents emerged as outputs of the FDA workshop. These mock 510(k) documents were jointly written by members of CPTAC and FDA and are anticipated to help orient the FDA to the use of protein-based multiplex assays (a multiplex immunoaffinity mass spectrometry platform, and an immunological array platform) in novel diagnostics and serve as a springboard for guidance to the proteomics community (submitted for publication in the journal of *Clinical Chemistry* and currently in press⁶).

Lastly, as CPTC goal is to advance the application of clinical proteomics to personalize cancer care, it firmly believes that the sharing of proteomic information on a broad scale will play a vital role in the translation of protein discoveries to clinical utility. CPTC is leading international efforts to address the lack of widely followed policies governing the rapid release of large-scale proteomic data into the public domain. CPTC is working with NCI Center for Biomedical Informatics and Information Technology, National Center for Biotechnology Information, other NIH ICs, policy makers, and industry to address this topic. A recent outcome are the Amsterdam Principles that provide recommendations for rapid proteomics data release and sharing policies that are similar to the Bermuda Principles⁷.

Question: It is this reviewer's understanding that a major hurdle that is not discussed in the review is that mass spectrometry cleared for newborn screening uses a platform and technology for small metabolites that is distinct from that used for the analysis of peptides in complex solutions. Thus, the specific technology and the approach used to standardize the original harmonization project and its advantages and disadvantages for moving into clinical use should be described more fully. Also, other components of biomarker development that are described in

⁵ Rodriguez, H., Težak, Z., Mesri, M., Carr, S.A., Liebler, D.C., Fisher, S.J., Tempst, P., Hiltke, T., Kessler, L.G., Kinsinger, C.R., Philip, R., Ransohoff, D.F., Skates, S.J., Regnier, F.E., Anderson, N.L., Mansfield; E., on behalf of the Workshop Participants. (in press) Analytical Validation of Protein-Based Multiplex Assays: A Workshop Report by the NCI-FDA Interagency Oncology Task Force on Molecular Diagnostics. *Clinical Chemistry*.

⁶ Regnier, F.E., Skates, S.J., Mesri, M., Rodriguez, H., Težak, Z., Kondratovich, M.V., Alterman, M.A., Levin, J.D., Roscoe, D., Reilly, E., Callaghan, J., Kelm, K., Brown, D., Philip, R., Carr, S.A., Liebler, D.C., Fisher, S.J., Temps, P., Hiltke, T., Kessler, L.G., Kinsinger, C.R., Ransohoff, D.F., Mansfield, E., Anderson, N.L. (in press) Protein-Based Multiplex Assays: Mock Presubmissions to the U.S. Food and Drug Administration. *Clinical Chemistry*.

⁷ Rodriguez, H., Snyder, M., Uhlén, M., Andrews, P., Beavis, R., Borchers, C., Chalkley, R.J., Cho, S.Y., Cottingham, K., Dunn, M., Dylag, T., Edgar, R., Hare, P., Heck, A.J.R., Hirsch, R.F., Kennedy, K., Kolar, P., Kraus, H.J., Mallick, P., Nesvizhskii, A., Ping, P., Pontén, F., Yang, L., Yates, J.R., Stein, S.E., Hermjakob, H., Kinsinger, C.R., Apweiler, R. (2009) Recommendations from the 2008 International Summit on Proteomics Data Release and Sharing Policy – The Amsterdam Principles. *Journal of Proteome Research*. 8:3689–3692.

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the Pepe et al 2001 manuscript are not discussed nor are the issues raised by both the STARD (The Standards for Reporting of Diagnostic Accuracy) initiative as well as the REMARK (Reporting Recommendations for Tumor Market Prognostic Studies) documents that outline the steps needed to improve biomarker analytical validation. The REMARK documents were created in collaboration with members of OIVD and should be important guidelines for biomarker development.

Program Response: A goal of the CPTC initiative was to address the technical barriers (analytical) in protein based multiplex platforms, not the identification or qualification of a particular biomarker. In terms of mass spectrometric platforms for newborn screening, you are correct that targeted MRM mass spectrometry has been used very successfully for quantifying small molecules (e.g., hormones, drugs and their metabolites) in pharmaceutical research and in clinical laboratories in applications such as screening newborns for disease. More recently, the merits of MRM for quantifying peptides derived from proteins in plasma have been demonstrated in several laboratories. These studies have, however, only addressed assay performance at a single laboratory, and thus were not able to demonstrate the multisite robustness needed in large-scale biomarker research and ultimately in preclinical and clinical applications. CPTAC landmark paper assessing the analytical characteristics of a multiplexed, MRM assay across eight laboratories using target proteins spiked into human plasma was published in *Nature Biotechnology* (see Addona, T., et. al. cited above). In terms of the REMARK, STARD, and Pepe et al. documents, it is our understanding that these documents pertain to clinical validation (qualification). The CPTC initiative is in the process of collecting SOP-driven blood (plasma) samples from patients prior to breast biopsy diagnosis (unbiased) in collaboration with OBBR for verification studies (not biomarker qualification), and as such welcome opportunities to work closely with the Division of Cancer Treatment and Diagnosis (DCTD) in exploring how best to integrate protein-based multiplex platforms into clinical validation studies.

Question: If the focus of the CPTC is to develop clinically useful biomarkers, what efforts have been made regarding Intellectual Property (IP) issues? This reviewer applauds any help in creating safe harbors or consortium approaches to IP handling that CPTC may be able to provide.

Program Response: Program agrees that IP rights related to diagnostics; therapeutics, etc. are an issue that needs to be addressed. However, as the CPTC initiative worked in the pre-clinical environment, its IP focused more on minimizing the utility of its reagents (RUO - research use only). As the scope of CPTC broadens, it anticipates and looks forward in coordinating its activities with respective parties at the NCI and NIH on matters of in vitro diagnostic IP. Preliminary (informal) discussions with the FDA are currently ongoing.

Question: The Strategic Partnering to Evaluate Cancer Signatures (SPECS) program includes the Vanderbilt site as one of 6 molecular profiling centers and the only one that is focused on proteomics for the creation of a prognostic or predictive molecular profile. Vanderbilt is also an original site in the CPTAC. Define the interaction between the CPTAC investigators and the SPECS investigators in the same institution, and possibly other NCI-supported programs such as the EDRN and the SPORE programs. Please note that this reviewer firmly believes that it is way too early to be concerned with such impact criteria - especially if the program clearly defines the

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optimal approaches to standardization of mass spectrometry for discovery research and possibly clinical use.

Program Response: CPTC has been active in finding areas of collaboration, information sharing, and shared meetings with program that share similar focuses. With regards to SPECS, EDRN, and SPORES the following activities have taken place:

- **SPECS:** CPTC has had several discussions with Jim Jacobson, more recently, Tracy G. Lively on identifying mechanisms to foster collaboration. A recent development is the invitation of Dan Liebler (CPTAC PI at Vanderbilt) to give a key talk at the upcoming pan-SPECS meeting set to take place at UC Irvine January 17-19, 2010. The basis is to (a) expose pan-SPECS members to CPTAC's outputs (metrics and standards), and potentially identify collaborative projects among Dan Liebler and David Carbone at Vanderbilt (PI of the Lung consortium).
- **EDRN:** To foster collaboration and knowledge sharing, CPTC investigators have presented at EDRN governing body and annual meetings, and vice versa. In addition, Henry Rodriguez and Sudhir Srivastava have been involved in several scientific conference joint sessions.
- **SPORES:** CPTC leadership has presented programmatic updates at annual SPORE meetings over the years, and vice versa. Lastly, members of the CPTAC network are involved with SPORE sites (e.g. UCSF and Vanderbilt) and EDRN sites.

Question: The CPTC is to be applauded for its creation of programs that can assess and standardize different approaches to proteomic platforms. This program will be forever valued if it can clearly define how to standardize and harmonize results across different platforms and perhaps delineate what the advantages and disadvantages of each platform are. The creation of calibrators and reference materials for mass spectrometry that may also be used by other investigators for their assays is also a major advance. A major effort for the future may be to evaluate whether mass spectrometry will be sufficiently robust and reliable as a clinical tool or whether effort should be put toward other high throughput platforms that are currently cleared for use in the clinical laboratory such as the various bead-based analytical platforms. The review did not clearly describe the effort in translating the discovery research in mass spectrometry to other platforms (this is the genesis of the PRRC after all). However, the choice of platform for measuring peptides in the clinical laboratory may involve alternative platforms and possibly technologies that are not necessarily based on antibodies. It may be important in the future to consider what the best strategy is for moving forward the identification of peptides or other small molecules as pharmacodynamic, prognostic or predictive biomarkers.

Program Response: It is agreed that that CTPC initiative should explore the utility of other commercially available platforms. As a result, CPTC works closely with the SBIR Development Center to have topics which allow for technologies incorporating CPTC reagents/targets to be developed for comparison with existing CPTC assessed platforms. A description of the topics and companies awarded is available on page 30 of the 2009 Annual Report. Several SBIR companies use bead based or similar affinity capture platform and are/will be evaluating CPTC reagents/targets, with their performance compared to existing methodologies developed within

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the program. Additionally, alternative affinity capturing reagents (e.g. yeast single chain, synbodies) are also being developed in collaboration with the SBIR Development Center, and being compared to current monoclonal antibodies against the same targets.

Reviewer 2

Question: With regard to the extended feasibility study, it seems quite comprehensive from its description of the CPTC program. A question is how one ensures utilization of CPTC resources outlined in the study. What mechanisms are in place to accomplish dissemination of, say, CPTC-produced reagents and antibodies vis-a-vis other potential and/or competing sources of such reagents?

Program Response: Program agrees that dissemination and utilization of the CPTC reagents is a critical measure of the reagent component success. All reagents and resources produced within the CPTC program are made available to the scientific community through the Reagents Data Portal (<http://antibodies.cancer.gov>), a Web-based service created by NCI-Frederick. The goal of the Antibody Characterization Program is to have three monoclonal antibodies produced for each successfully expressed/purified recombinant antigen. Each antibody is fully characterized using SOP-driven assays (e.g. ELISA, Western, IHC, ImmunoMS, SPR and NAPPA), with all protocols and characterization made fully available to the scientific community. Specifically, the antibody portal was launched in late 2008 and since inception we currently have 91 antibodies to 29 cancer related targets. To date, over 80 antibodies have been sold to universities, companies and private institutions to both domestic and foreign researchers. In addition to the Developmental Studies Hybridoma Bank (DSHB) at the University of Iowa, companies, such as Millipore and imaGenes are in the process of distributing CPTC reagents. Several smaller biotechnology companies are also working with these antibodies and expect to release commercial assays in the coming year through the SBIR funding mechanism. Together these various relationships broaden the exposure and research audience for our reagents. The CPTC name will be retained to allow for program recognition and tracking through publications and other media outlets. The antibodies will be marketed by DSHB, Millipore and imaGenes, as well as future companies who may be interested. Additionally, new antibodies are described in each edition of CPTC's quarterly publication, eProtein, as well as a poster and oral presentations given by program staff at a variety of venues.

Question: What is the potential or envisioned impact of CPTC in terms of individual health outcomes?

Program Response: CPTC firmly agrees that the potential impact of well characterized reagents in a clinical setting is one way to translate discoveries from the bench to the patient. In his NIH town hall speech shortly after assuming the directorship of NIH, Dr. Francis Collins mentioned that one of the strategic objectives of the new NIH administration is the implementation of provisions associated with the national health care reform process, one of which is improved individual health outcomes by linking specific NIH outputs to specific health outcomes. This is further echoed in language in a bill currently in the Senate specifically addresses the need for better methods of earlier detection and biomarker discovery/validation. CPTC is a prime vehicle

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by which to accomplish these sorts of activities, particularly since the infrastructure is already up and running and initial flow of outputs through CPTC's pipeline has already begun (provides the means for testing, evaluation, and improving efficiency and adaptability of the pipeline). CPTC also works with representatives from the advocacy community, including NCI's Office of Advocacy Relations (OAR) page 37 of the 2009 Annual Report describes how the CPTC website has a section entitled Patient Corner, which highlights the link between proteomics research and patient outcomes using podcasts, webinars, brochures and tutorials. Additionally, CPTC has established communication with investigators, clinicians, researchers as well as advocacy outreach groups by involving members of these groups to participate in a variety of NCI activities, including, but not limited to, working groups, committees and boards, meeting attendance, workshops and site visits. CPTC has a myriad of outputs that while their connection to patient care is longer term, the program recognizes their impact.

Reviewer 3

Question: The program has gotten off to a good start. As with all programs, it takes time to build trust – which needs to be established prior to true collaboration. The NCI staff has also done a good job in balancing the needs of the government (NCI) and the research team. Congratulations on a great program. I hope that it continues to meet the needs of the cancer community and NCI. Regarding the SOPs developed in this initiative, are they intended for discovery or clinical utility?

Program Response: CPTC has developed SOPs for separate groups and purposes. The reagent SOPs are created for the research community and pertain to the specific method or instrumentation used to create the data, typically characterization data associated with an antigen or antibody as part of our reagents component. The mass spectrometry SOPs are predominantly made for pre-clinical studies (this refers to the newly introduced stage of Verification by the CPTC program). CPTC believes that to study the variability of biology, one need to first understand the variability of the methods and technologies. This requires access to common performance standards, analysis SOPs, reference to historical analytical reference data, and data standards. SOPs developed in this stage empower researchers to optimize the accuracy and measurement capability of their platforms by benchmarking their analytical performance data to those obtained by the CPTAC network. The “mock” 510(k) documents and accompanying SOPs serve as a baseline for the research community and clinical laboratories interested in bridging the gap between the research and clinical world. These were done in collaboration with clinical laboratories, instrument manufacturers, and the FDA.

Lastly, the blood collection SOP developed in the CPTC initiative is for use in clinical laboratories. At the outset of the CPTC initiative, NCI's Office of Biorepositories and Biospecimen Research (OBBR) facilitated a meeting among the CPTAC network biospecimen collection sites. The purpose was to compare existing biospecimen collection and storage SOPs from these respective institutions, along with those from other organizations. This was also done in collaboration with clinical laboratories (hospitals and blood drawing centers) to help design an SOP that is practical in practice. It was agreed upon by the CPTC Governing Body to consolidate these protocols into one consensus SOP to be used at all collection sites.

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Question: Another metric that might be useful is invited talks requested on CPTC. Is there a number that can be provided?

Program Response: A total of 386 talks have been requested on CPTC. This consists of 286 oral presentations, and 102 posters presentations.

Reviewer 4

Question: What mechanisms/approaches were effective in involving APPCS into the CPTC?

Program Response: CPTC has developed several mechanisms to engage APPCS investigators with the CPTAC network and PRCC, and vice versa. They are:

- **Governing Body:** The CPTAC has an official governing body called the Program Coordinating Committee (PCC). The PCC oversees the integration of the CPTAC centers as part of the entire CPTC. Voting members of the PCC include the Team Leader (or a team leader designated senior scientist) from each CPTAC and one person representing CPTC Program staff (the CPTC Program Director). One of the responsibilities of the PCC is to be aware of efforts by APPCS researchers in order to implement promising technologies and software as they become available. To facilitate this interaction, investigators from APPCS were frequently asked to attend or participate in PCC meetings. APPCS researchers directly aligned with CPTAC centers had an easier time integrating within the CPTAC work groups and studies.
- **APPCS Research Highlights:** To foster the development of collaborative projects among APPCS and CPTAC, CPTC Program Staff developed an Annual Research Highlight Report for distribution to the CPTAC. These reports have been extremely useful in providing a quick synopsis of promising technologies or software/algorithms that could be directly employed into the CPTAC network.
- **Annual Meetings:** CPTC annual meetings incorporate oral presentations and poster abstracts from all of its investigators (CPTAC, APPCS, and PRRC). This mechanism has been successful in allowing APPCS investigators to learn about newly developed reagents and resources through the PRRC, some of which are now used by APPCS investigators.

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Question: Non-CPTAC activities are mentioned on page 38, does this include other non-CPTAC Principal Investigator activity and should it?

Program Response: CPTC annual meetings provide an open forum whereby investigators from CPTAC and non-CPTAC (APPCS and PRRC) are able to present their latest research findings, while also discussing non-CPTC work which is relevant to the goals of CPTC. In addition, non-CPTC investigators are frequently invited to present outside research as a way to foster knowledge sharing and new collaborative projects. The Non-CPTAC activities mentioned on page 38 refer to a workshop that was held among the CTAC investigators with inclusion of APPCS investigators (non-CPTAC).

Question: To what extent are SOPs and other products (reagents) being used outside or within CPTAC?

Program Response: CPTC has developed SOPs for separate groups and purposes. The research SOPs are predominantly made for mass spectrometry pre-clinical studies (verification of protein candidates). These SOPs empower researchers to optimize the accuracy and measurement capability of their platforms by benchmarking their analytical performance data to those obtained by the CPTAC network. The research SOPs and accompanying reagents are used through the network (both in the inter-lab studies and intra-lab studies).

In addition to research SOPs, reagent SOPs are created for the research community and pertain to the specific method or instrumentation used to create the data, typically characterization data associated with an antigen or antibody as part of our reagents component. These SOPs linked to a specific reagent (example, monoclonal antibody) have proven to be highly sought by the research community and private sector, as evidenced with the recent Material Transfer Agreements between CPTC and private companies seeking access to the high-quality reagents linked to the SOPs.

While the adoption of SOPs and reagents usually takes time by the research community, a testament to their potential is the recent interaction with the American Association for Clinical Chemistry (AACC). AACC is an international society comprised of medical professionals with an interest in clinical chemistry, clinical laboratory science, and laboratory medicine. CPTC was approached by representatives of AACC to learn how to work together in the further development of CPTC proteomic technologies and standards for translation into clinical laboratories. This interaction is currently being formulated into a memorandum of understanding between the AACC and NCI. Furthermore, the “mock” 510(k) documents and accompanying SOPs have served as a baseline for the research community and clinical laboratories interested in bridging the gap between the research and clinical world. The 510(k) documents were done in collaboration with clinical laboratories, instrument manufacturers, and the FDA. The interactions with AACC and the “mock” 510(k) documents represent the initial extent and great interest of the SOPs and products (reagents) produced by the network, which are now gaining acceptance and use in the larger proteomics community.



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