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

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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 though 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?

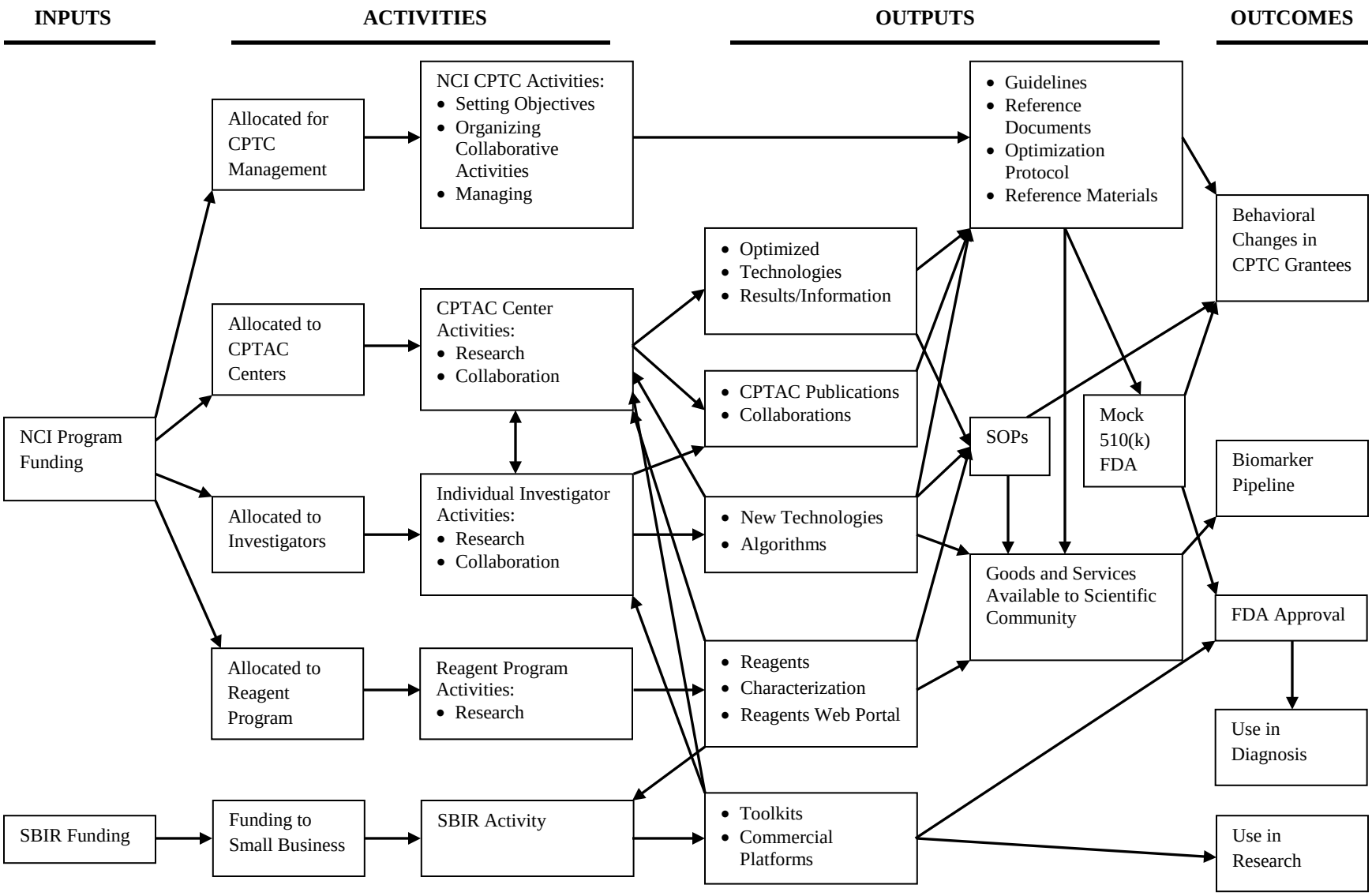
Appendix B

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

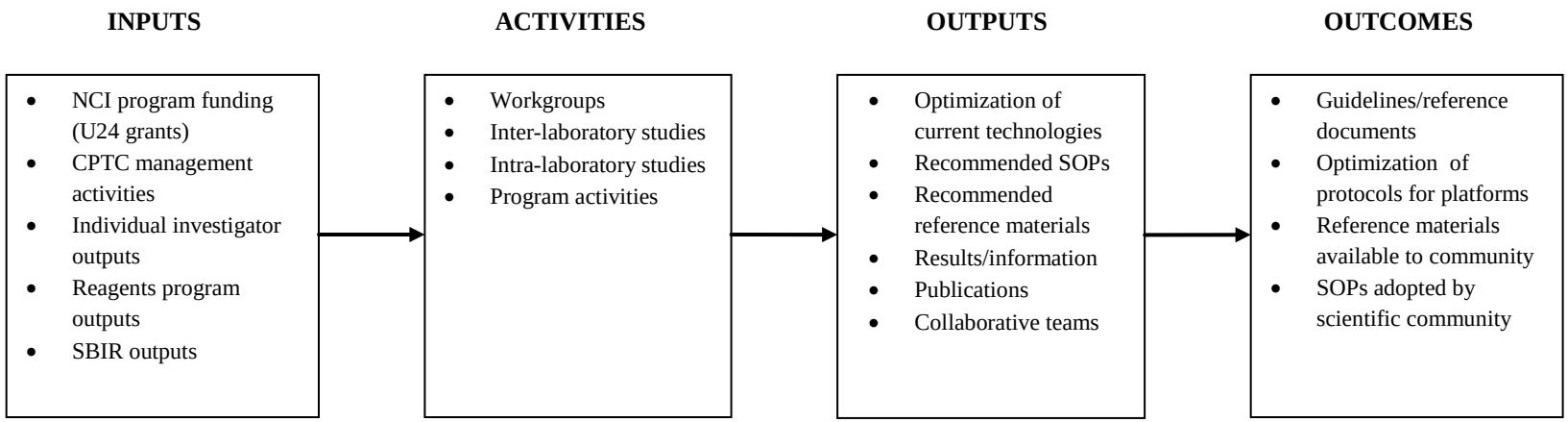
Outcomes represent behavioral changes that emerge from the program. The conceptual framework defines outcomes that represent behavioral changes among the CPTAC organizations and investigators with grants and that affect the greater health system and the pipeline that culminates in producing diagnostic 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.

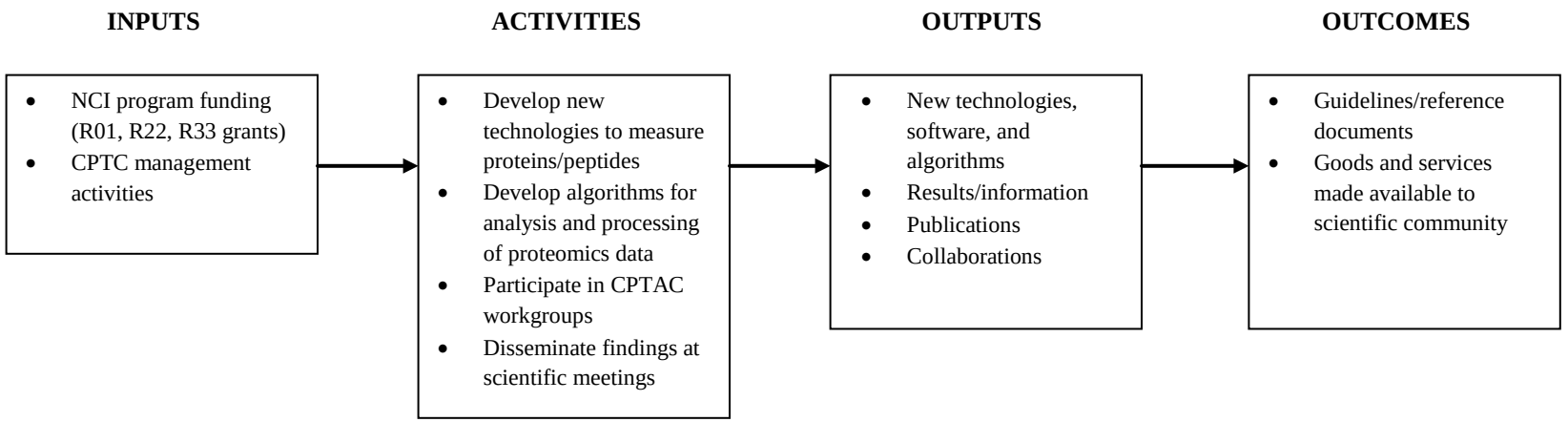
Outputs

- 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 variablilty 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.

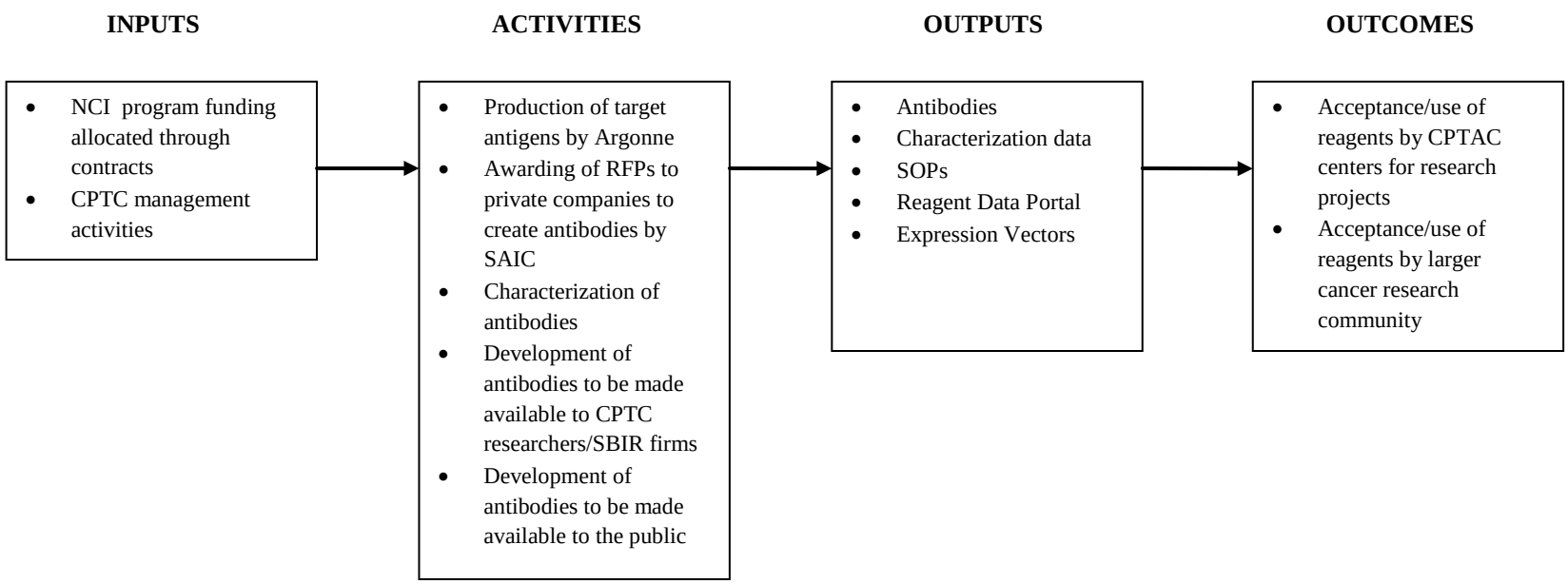
Outputs

- 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

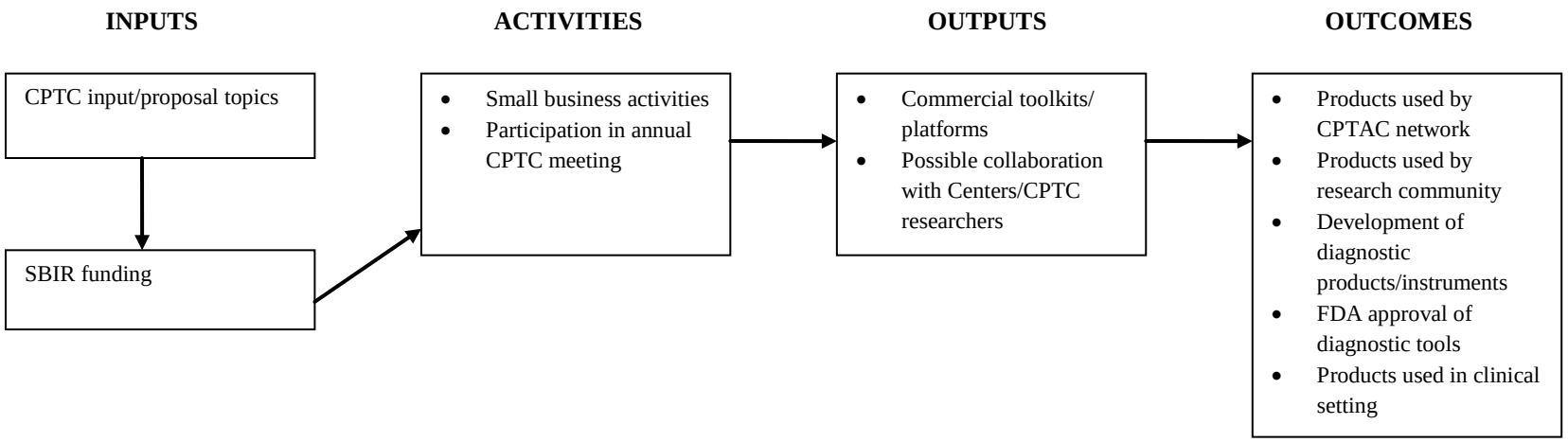
Outputs

- 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