Thank you for joining the

CPTAC Pre-Application Session

RFA-CA-21-023 (PCCs)
RFA-CA-21-024 (PGDACs)
RFA-CA-21-025 (PTRCs)

Start at 11:30 am EDT

CPTAC Program Overview

Henry Rodriguez, Ph.D., M.S., M.B.A.
Director, Office of Cancer Clinical Proteomics Research
National Cancer Institute, NIH

CPTAC
CLINICAL PROTEOMIC TUMOR ANALYSIS CONSORTIUM

NIH NATIONAL CANCER INSTITUTE
Office of Cancer Clinical Proteomics Research

Pre-Application Webinar (NOT-CA-21-072)

Panelist / Order of Presentations

Progress and Opportunities in Cancer Proteogenomics

Henry Rodriguez, Ph.D., M.S., M.B.A.
Office of Cancer Clinical Proteomics Research, NCI, NIH

Description of RFA-CA-21-023 (Proteome Characterization Centers)

Tara Hiltke, Ph.D.
Office of Cancer Clinical Proteomics Research, NCI, NIH

Description of RFA-CA-21-024 (Proteogenomic Data Analysis Centers)

Ana I. Robles, Ph.D.
Office of Cancer Clinical Proteomics Research, NCI, NIH

Description of RFA-CA-21-025 (Proteogenomic Translational Research Centers)

Eunkyung An, Ph.D.
Office of Cancer Clinical Proteomics Research, NCI, NIH

Pre-Application Webinar (NOT-CA-21-072)

Additional Representation

Clinical Investigations Branch, Cancer Therapy Evaluation Program
Meg Mooney, M.D., M.B.A., Chief
Elise Kohn, M.D., National Clinical Trials Network (NCTN)

Investigational Drug Branch, Cancer Therapy Evaluation Program
Jeff Moscow, M.D., Early Therapeutics Clinical Trials Network (ETCTN)

Pre-Application Webinar (NOT-CA-21-072)

Participants

Addressing Questions

- Post presentation session, there will be a 10 min break, followed by live Q&A
- Your microphone and camera will be muted/turned off
- ALL QUESTIONS to be entered via the chat function (specify whether PCC, PGDAC, or PTRC)
- Questions to be addressed at end of session. Questions not addressed during webinar, to be followed up by direct email or posted as FAQ
- Questions seen only by Panelist (email: cancer.proteomics@mail.nih.gov)
- *Webinar recording will be posted in OCCPR's website, as soon as possible following the event.*

Anticipated Number of Awards & Key Dates

RFA Number	RFA-CA-21-023	RFA-CA-21-024	RFA-CA-21-025
CPTAC Center	Proteome Characterization Centers (PCC)	Proteogenomic Data Analysis Centers (PGDAC)	Proteogenomic Translational Research Centers (PTRC)
Type of Grant	U24	U24	U01
Anticipated Number of Awards	NCI intends to fund 3 awards	NCI intends to fund 4 awards	NCI intends to fund 4 awards
Application Due Dates	June 30, 2021	June 30, 2021	July 30, 2021

Letter of Intent: 30 days prior to application due date

Anticipated Number of Awards & Key Dates

Specifics and Frequently Asked Questions (with Answers) about these FOAs at:

https://proteomics.cancer.gov/funding_opportunities

Reissuance Presentation to NCI Board of Scientific Advisors (BSA): Dec 1, 2020

- URL: https://videocast.nih.gov/watch=40096
- Time stamp: 2h:38min:12sec

Clinical Proteomic Tumor Analysis Consortium

2006-2011: standardization

2011-2016: apply to TCGA tumors

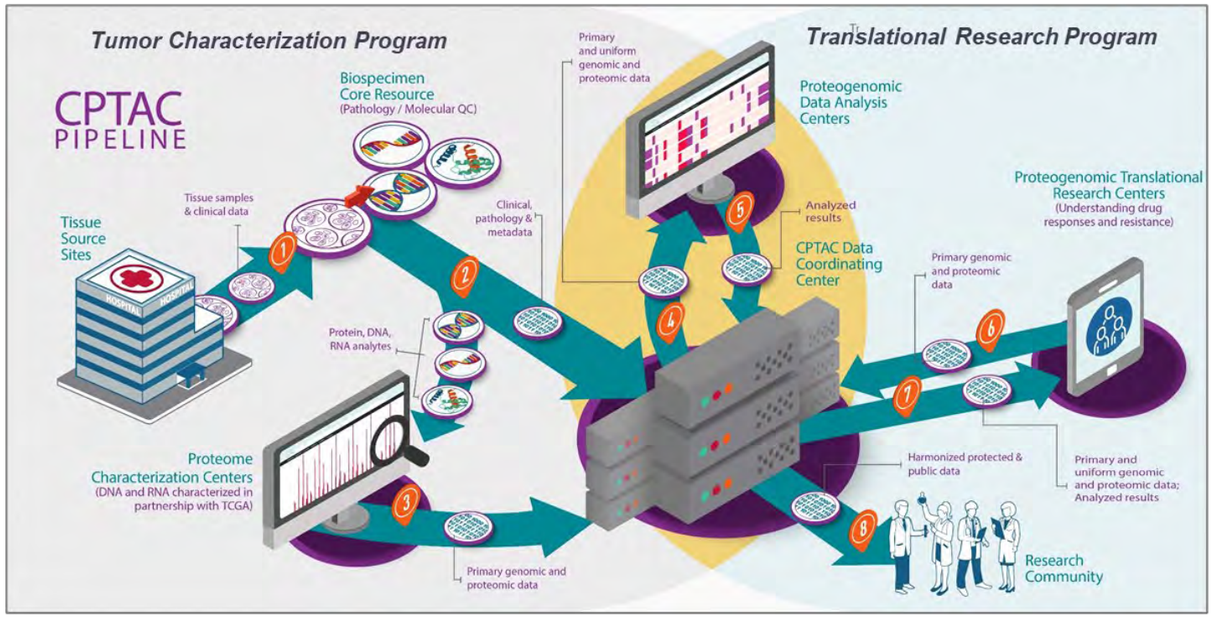
2016-2022: tumor characterization program & clinical trial translational program

multidisciplinary (team science)

CPTAC Today

Clinical Proteomic Tumor Analysis Consortium

multidisciplinary (team science)



Achieved through

TUMOR CHARACTERIZATION

Proteome Characterization Centers **(PCCs)**

Proteogenomic Data Analysis Centers **(PGDACs)**

- treatment naïve tumor / normal adjacent, prospective

TRANSLATIONAL RESEARCH

Proteogenomic Translational Res Centers **(PTRCs)**

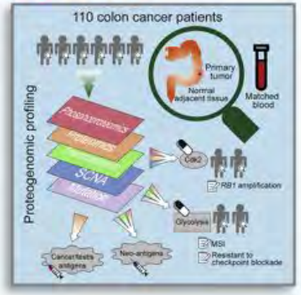
Proteogenomic Data Analysis Centers **(PGDACs)**

- pre-clinical and clinical trial samples

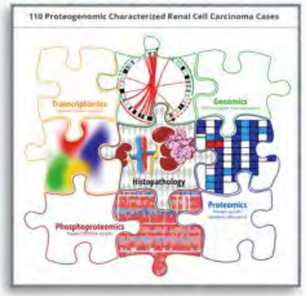
Tumor Characterization Program
(Increasing Our Understanding of Cancer)

CPTAC

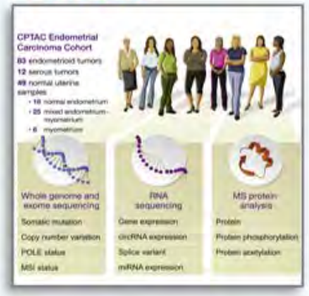
Colon
Cell 2019



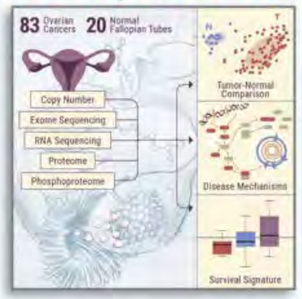
Kidney
Cell 2019



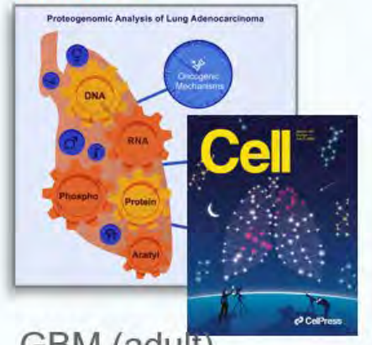
Endometrial
Cell 2020



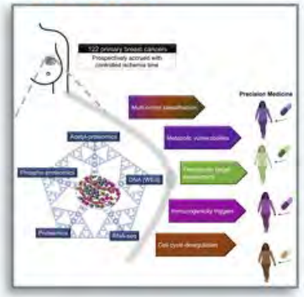
Ovarian
Cell Rep Med 2020



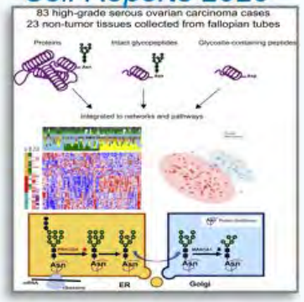
Lung adeno
Cell 2020



Breast
Cell 2020

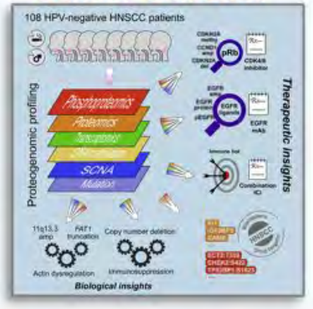


Ovarian
Cell Reports 2020

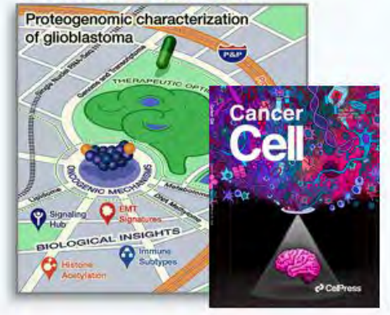


GBM (pediatric)
Cell 2020

Head & Neck
Cancer Cell 2021

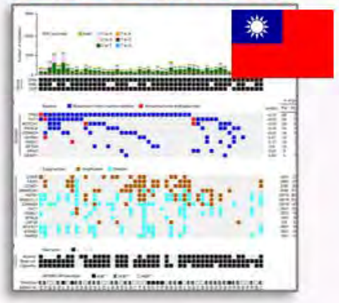


GBM (adult)
Cancer Cell 2021

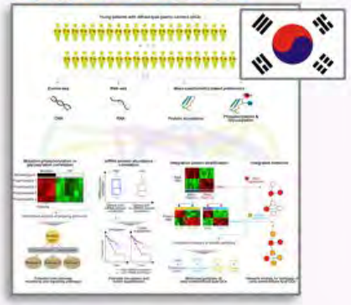


CPTAC International Collaborations

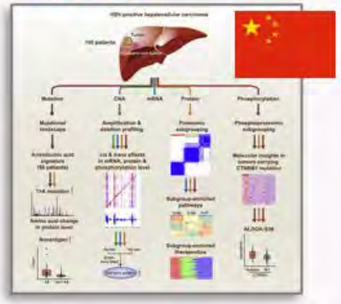
Oral squamous
Nature Comm 2017



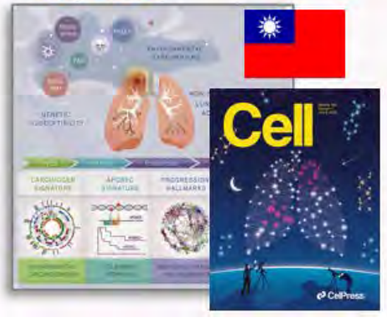
Gastric
Cancer Cell 2019



Liver
Cell 2019



Lung adeno
Cell 2020



Translational Research Program
(Bringing Proteomics to Clinical Trials)

	AML	Breast	Ovarian
PRE-CLINICAL RESEARCH; PILOT STUDIES	• Comprehensive proteogenomics of AML cell lines with different driver mutations and subjected to FDA-approved TKIs. *Outcome: Proteomic profiles based on driver mutations* • Piloted on 16 pts from BeatAML trial. *Outcome: proteins and phosphoproteins associated with drug sensitivity*	• Developed micro-scale MS technique for comprehensive proteogenomics (breast PDX single-needle core biopsy) • Piloted on 50 HER2+ pt samples from NSABP DP-1 trial. *Outcome: HER2 phosphorylation change found based on treatment outcome*	• Comprehensive proteogenomics of intra-pt cell line pairs (pre/post-platinum resistance), refractory & sensitive PDX, and 350 pt tumors (FFPE, FF, OCT). *Outcome: Proteins associated with Pt resistance. Trained and validated on independent pt tumors (FFPE and FF)*
CLINICAL TRIAL SAMPLES	• Expanding to large cohort (200 pts from BeatAML trial) with single driver mutation (FLT3-ITD). ***APPROVED***	• Expanding to 130 HER2+ pt samples from randomized phase 3 trial. Application to NCTN trial. ***APPROVED***	• Developing MS multiplex assay; Applying to NCTN randomized phase 3 trial for samples. • CLIA lab; PD markers
	Leukemia. 2018; PMID: 29743719	*Nat Commun.* 2020; PMID: 31988290	*British J of Cancer.* 2018; PMID: 30385821

CPTAC Public Resources (data warehouse)

***Largest public repositories of proteogenomics datasets** [w/ accompanying assays and reagents]*

Proteomics Data
(Proteomic Data Commons)
620 TB total downloads
(22 TB data available)
Proteomics Data

Genomics Data
(Genomic Data Commons)
591 TB total downloads
(350 TB data available)
Genomics Data

Imaging Data
(The Cancer Imaging Archive)
5,675 images
(2 TB downloads/mth)
(1.5 TB data available)
Imaging Data

Targeted Proteomic Assays
(CPTAC Assay Portal)
2,553 assays
(7,000 users/mth)
Skyline
Panorama
Assays

mAntibodies
(CPTAC Antibody Portal)
762 mAbs
(4,953 units sold)
Antibodies

- Data Portals
- Assay Portal
- Antibody Portal

What's next for CPTAC

Recommendations: build on the achievements of CPTAC to accelerate molecularly oriented cancer research toward basic discovery and clinical impact (achieved through goals 1 and 2)

Goal 1: Tumor Characterization Program
(comprehensive proteogenomic characterization)

Proteome Characterization Centers **(PCCs)** & Proteogenomic Data Analysis Centers **(PGDACs)**

- Extend CPTAC's approach to 5-6 new cancer types where questions remain on their proteogenomic complexity

Future directions:

- Expand PTMs (beyond phosphorylation, such as acetylation, ubiquitination, and glycosylation); add metabolites (when appropriate); incorporate metastatic and rare cancers; retrospective samples (if possible)

Goal 2: Translational Program
(proteogenomics in clinical trial research)

Proteogenomic Translational Research Centers **(PTRCs)** & Proteogenomic Data Analysis Centers **(PGDACs)**

- Extend support for clinically relevant research projects with well-conceived clinical/biological questions, and a proteogenomics research approach

Future directions:

- Expand the specialized analytical expertise and infrastructure to trial experts outside of the network with cancer interests beyond those selected by PTRCs (pilot studies that address needs in clinical trials brought forward by the NCI via a DCTD Steering Committee)

Governance

- CPTAC program governed by a Steering Committee (SC)
- SC serves as the primary governing body of the CPTAC program, and oversees and coordinates the activities of all PCCs, PGDACs, and PTRCs
- The Committee is jointly established by one representative (PDs/PIs) from each awarded PCC, PGDAC, PTRC and the NCI Program Staff
- Details on the composition and functions of SC are provided in the RFAs

RFA-CA-21-023:
Proteome Characterization Centers (U24)

Tara Hiltke, Ph.D.

Office of Cancer Clinical Proteomics Research

National Cancer Institute, NIH

CPTAC
CLINICAL PROTEOMIC TUMOR ANALYSIS CONSORTIUM

NIH NATIONAL CANCER INSTITUTE
Office of Cancer Clinical Proteomics Research

Section I: Funding Opportunity Description

- Proteome Characterization Centers (PCCs) - interactive group which use standardized proteomic analysis technologies for systematic and comprehensive proteome-wide characterization of genomically-characterized samples (tumors/adjacent normal and preclinical models) provided by NCI
  - Sample types such as fresh frozen, FFPE, OCT and liquid biopsy
  - Operate as an interactive group, and leverage and use standardized proteomic analysis technologies
  - All proteomic technologies and platforms must be analytically validated, conducted in high throughput manner and deployable at start of project
- PCCs will interact with Proteogenomic Data Analysis Centers (PGDACs) and Proteogenomic Translational Research Centers (PTRCs)

RFA URL: https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-023.html

Key Dates for RFA-CA-21-023

Earliest Submission Date	Letter of Intent* Due Date	Application Due Date**
May 30, 2021	May 31, 2021	June 30, 2021

* LOI is not required, not binding, not included in review. LOI allows IC staff to estimate the potential review workload and plan the review.

** By 5:00 PM local time of applicant organization

NCI-supplied Biospecimens

- Human Biospecimens: A collective goal of PCCs is to comprehensively characterize 5-6 human cancer types
  - Anticipate 150 cases (tumor and adjacent normal) per cancer type
  - Primarily prospectively collected, but may include retrospective and metastatic/recurring samples
- Preclinical Models: A collective goal of PCCs is to comprehensively characterize preclinical samples (such as xenografts and organoids) from NCI's Patient-Derived Models Repository program
  - Anticipate up to 2000 samples
- Minimal amount available for each sample type:
  - Tumor tissue: ~25 mg wet weight per sample

PCC Research Objectives

- ***Primary Research Objective***: Utilize one or more proteomic technologies to comprehensively characterize NCI-provided specimens.
- ***Secondary Research Objective***: Improve performance of the proteomic characterization technolog(ies)/platform(s) used in Primary Research Objective. Applicants must propose specific efforts to improve the selected technolog(ies)/platform(s) used in the PCC.

Research Objectives

- Unbiased characterization of all detectable protein forms in a sample (discovery proteomics)
- Followed by accurate quantitative proteomic determinations of selected cancer-relevant protein targets (targeted proteomics)

Main Requirements: Both types of studies are to be conducted in a high-throughput, analytically reproducible manner and with platforms/workflows deployable at the start of the project

Data Analysis Definitions

- **Level 1 (required under this FOA)**
  - *Discovery Proteomics Research* - Analysis of raw experimental data to generate results on peptide/protein identification and quantitation, post-translational modifications (PTMs) identification, site localization and quantitation using a reference genome
  - *Targeted Proteomics Research* - Analysis of raw experimental data to generate quantitative results on peptide/protein concentrations of the selected targets from *Discovery Proteomics Research*
- **Level 2:** Integration of genome-proteome data at the linear sequence level (DNA, RNA, peptides/proteins with relative quantitation obtained from Discovery Proteomics Research using personalized genomic data)
- **Level 3:** Integration, visualization and analysis of omics data mapped onto networks and pathways obtained from Discovery Proteomics Research and/or Targeted Proteomics Research

Section IV Sub-section B: Comprehensive Proteomic Data Generation

Technology/platform - reproducible, quantitative and sensitive for comprehensive proteomic characterizations. To be analytically validated must:

- Successfully been deployed and validated in at least one other laboratory;
- Capable of generating reproducible results within and across laboratories in a high-throughput, large-scale proteomic study;
- Previously published in peer-reviewed journal

Analytical Capacity

- 225 samples per year per PCC
- >7000 unique proteins using 25 mg wet tissue weight sample

Quality Assurance/Quality Control

- Detailed plan of metrics used to ensure measurement quality

Data Analysis - Level 1

- Such as data processing, ID algorithms, quantitation strategy, error rate for protein/peptide ID, PTM localization

Section IV Sub-section B: Targeted Proteomic Data Generation

Technology/platform - reproducible, quantitative and multiplexed targeted methodology that has been analytically validated. To be analytically validated must:

- Successfully been deployed and validated in at least one other laboratory;
- Involve high-throughput targeted assays capable of sampling depth of proteomes studied, span a wide dynamic range and can measure protein/peptide concentration in low fmole/ug to low fmole/mg (proteins);
- Demonstrate the analytical rigor of quantitative data obtained from within and across laboratories using standards/metrics (preferably published peer-reviewed journal);
  - It is expected that a minimum of a Tier 2 analytical characterization for mass spectrometry or an equivalent of other technologies (Reference: PMID: 24443746)

Assay Development - Describe process for targeted assay development

- 150 samples per year per PCC

Quality Assurance/Quality Control - Detailed plan of metrics used to ensure measurement quality

Data Analysis - Level 1, describe raw data analysis

Section IV Sub-section C: Improvements of Proteomic Technologies

Describe plans for technology development to improve technology(ies)/platform(s) used such as:

- Enhancing sample throughput capabilities and/or reducing sample quantity input required
- Method/Technology improvements such as detection sensitivity, quantitation accuracy, resolution, proteome coverage, software development
- Identifying sources of systematic error and bias for more reliable results
- Strategies to incorporate technology advances that may emerge during the project period, should they benefit the project
- Plans to participate on technology assessment across PCCs

Pilot Studies: No specific pilot studies to be proposed. Budget must include $30,000 direct costs/year/PCC for pilot studies

FAQs specific to RFA-CA-21-023

- **What human cancer types are to be characterized by the PCCs/PGDACs in the tumor characterization program?**

  PCCs and PGDACs are to be agnostic to the human cancer types to be characterized/analyzed in the tumor characterization program. Specific cancer types will be made available at the time of award.

- **Would applicants who may have access to biospecimens be allowed to use these samples (in addition to NCI supplied samples) in the generation of data under this RFA?**

  NCI has limited this funding mechanism to NCI-supplied samples. Applications will not be evaluated based on the inclusion and/or sharing of additional applicant-provided samples.

- **Under the list of required capabilities, it says "Extensive expertise in using a variety of biological sample types, including fresh frozen tissues, formalin fixed tissues, OCT embedded tissues, and liquid biopsies." Should a PCC demonstrate extensive experience in all of these?**

  Applicants are expected to demonstrate expertise in using a variety of biological sample types, but as indicated in the Research Objectives: Applicants seeking a PCC award *must* be able to perform comprehensive characterizations of the proteomic composition of human biospecimens and samples from preclinical models, *including fresh frozen, formalin fixed paraffin-embedded and optimal cutting temperature (OCT)-embedded*. For clarification, applicants should describe which sample types they have experience and to what extent the expertise.

FAQs specific to RFA-CA-21-023

- **Could a PCC application be a stand-alone application, or does it require that the PCC application pre-coordinate with specific PGDAC or PTRC applicants? Additionally, could/should the PCC be multi-institution?**

  PCC applications are independent of PGDAC and PTRC applications. However, PCC applications should adhere and acknowledge data sharing plan and resource sharing plan required by this FOA. PCC applications can be single or multi-institutional applications as long it meets the objectives and goals of the program.

- **Is the total amount of material stated in the RFA (25 mg wet weight) for the human biospecimens supposed to cover both discovery and targeted proteomics on each sample or will there be separate aliquots of 25 mg provided for each of the two analyses?**

  A minimum of 25 mg of wet tissue weight per sample is anticipated for both discovery and targeted proteomics. However, additional sample may be provided for samples which had more than 25 mg collected.

- **What is the purpose and timeline for PCC pilot studies?**

  Pilot studies are to improve technologies/platforms used in the primary research objective of the PCC, and are anticipated to have relatively short timeframes, i.e., on a yearly basis or at most two years.

RFA-CA-21-024: Proteogenomic Data Analysis Centers (U24)

Ana I. Robles, Ph.D.

Office of Cancer Clinical Proteomics Research

National Cancer Institute, NIH

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NIH NATIONAL CANCER INSTITUTE
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Proteogenomic Data Analysis Centers (PGDACs)

Multidisciplinary Centers that will provide data analysis and biological and clinical interpretation.

- computational biologists, software engineers, experimental research scientists

Awardees will be expected to develop computational tools for data analysis, data integration and visualization and apply these tools to CPTAC data

- Innovative bioinformatics development
- Integration of proteome and genome (linear sequence level)
- High level interpretation of data (pathway/concepts)

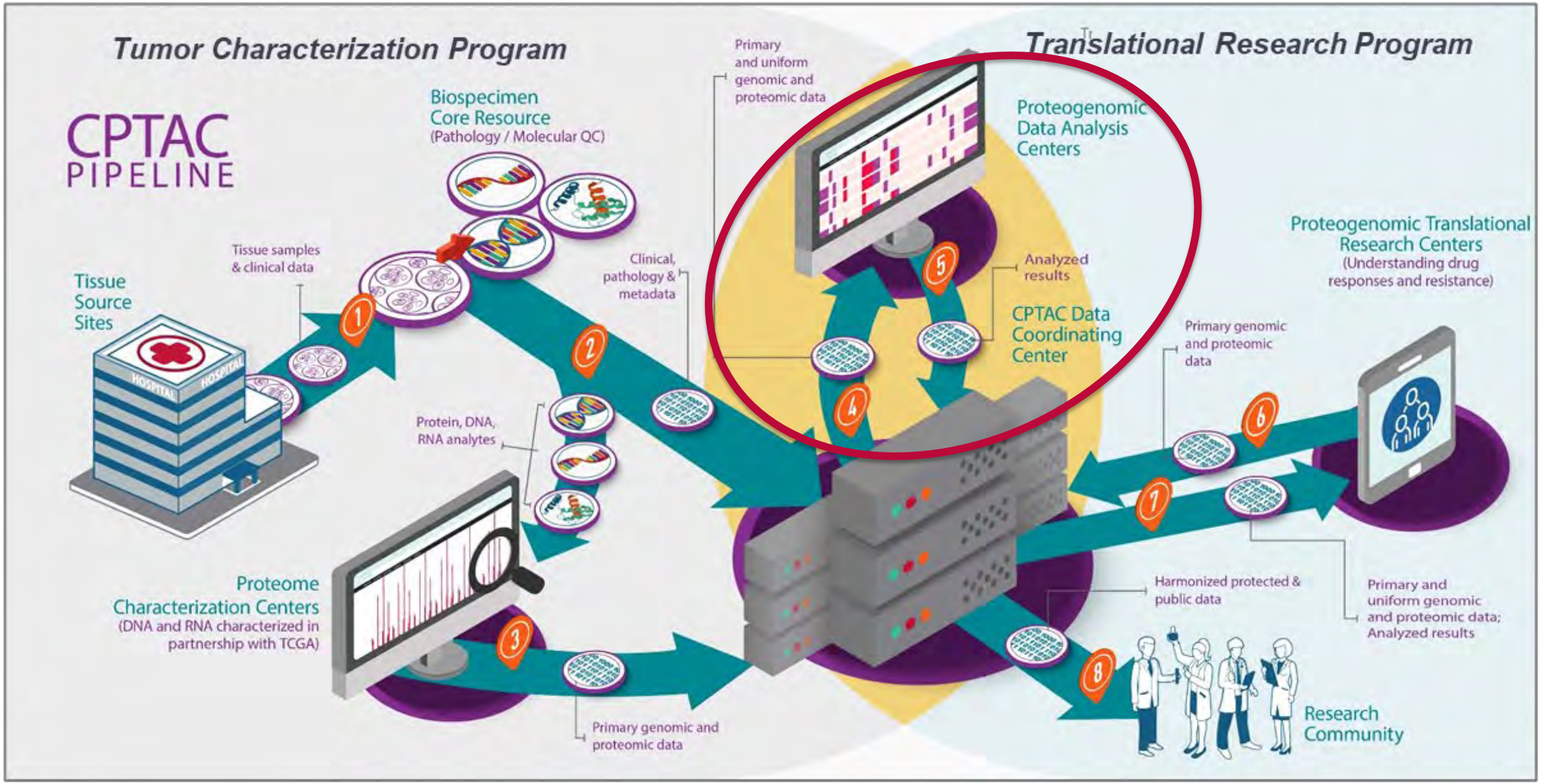
Data to be analyzed will be derived from diverse types of samples

- clinical specimens, cultured cells, animal models of human cancers

PGDACs will interact with Proteome Characterization Centers (PCCs) and Proteogenomic Translational Research Centers (PTRCs)

RFA URL: https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-024.html

PGDACs will interact with PCCs and PTRCs



Key Dates for RFA-CA-21-024

Earliest Submission Date	Letter of Intent* Due Date	Application Due Date**
May 30, 2021	May 31, 2021	June 30, 2021

* LOI is not required, not binding, not included in review. LOI allows IC staff to estimate the potential review workload and plan the review.

** By 5:00 PM local time of applicant organization

PGDAC Research Objectives
(to be responsive, scope of work must cover all)

1. Apply computational tools to CPTAC data (and other OCCPR-approved collaborations)
   i. Analyze data generated or pre-processed by Genome Characterization Center (GCC), PCC, PTRC and/or PGDACs.
   ii. Integrate CPTAC data (to include data and metadata derived from CPTAC biospecimens).
   iii. Identify potentially cancer-related molecular alterations.

2. Develop new computational tools for cancer proteogenomics
   i. New bioinformatics and computational tools to capture key biological parameters.
   ii. Pipeline and network-wide quality control methods for the system.
   iii. Processing or integration of analytical data to generate disease level findings and interpretations.

3. Identify candidates for targeted protein assays.
   i. Prioritization of proteins/peptides of interest for targeted proteomics

Data Analysis Definitions

- **Level 1**
  - *Discovery Proteomics Research* - Analysis of raw experimental data to generate results on peptide/protein identification and quantitation, post-translational modifications (PTMs) identification, site localization and quantitation using a reference genome
  - *Targeted Proteomics Research* - Analysis of raw experimental data to generate quantitative results on peptide/protein concentrations of the selected targets from *Discovery Proteomics Research*
- **Level 2 (required under this FOA):** Integration of genome-proteome data at the linear sequence level (DNA, RNA, peptides/proteins with relative quantitation obtained from Discovery Proteomics Research using personalized genomic data)
- **Level 3 (required under this FOA):** Integration, visualization and analysis of omics data mapped onto networks and pathways obtained from Discovery Proteomics Research and/or Targeted Proteomics Research

Research Objective 1

Expected to deploy computational tools ***within six months*** of the award kick-off.

Applicants ***must*** show competencies and address capabilities in following areas:

- ***Proteogenomics:*** Integrate genome-proteome data at the linear sequence level to identify somatic/germline variation of protein sequence, correlate genomic and proteomic markers with relevant clinical parameters.
- ***Pathway/Network Analysis:*** Integration, visualization and analysis of omics data mapped onto networks and pathways obtained from Discovery Proteomics Research and /or Targeted Proteomics Research.

Applicants **may** show competencies and address capabilities in the following areas:

- **Genomics:** Apply standard pipelines and workflows to genomic data
- **Proteomics:** Apply standard pipelines and workflows to the analysis of raw proteomic data
- **Batch Effects/Integration:** Identify batch effects that might have been accrued during processing of samples
- **Digital Imaging analysis:** Utilize diagnostic histopathology to inform cellular compositions of tumor samples

What data?

Data Sources:

Biospecimens comprehensively characterized by PCCs (RFA-CA-21-023), PTRCs (RFA-CA-21-025), and GCCs (genomic)

NCI collected tumors (tumor, germline, normal adjacent tissue) with clinical data.

Preclinical Samples (xenografts, organoids) from NCI's Patient-Derived Models program.

Clinical Trial-derived specimens.

Data Types:

Global proteomics, PTMs (phosphorylation, acetylation, etc), comprehensive genomics (whole genome and whole exome sequencing, RNA sequencing, methylation), images (pathology and radiology)

Data Analyses (examples):

Differential expression of proteins, somatic/germline variation of protein sequence; Correlate genomic and proteomic markers with relevant clinical parameters; Integration, visualization and analysis of omics data mapped onto networks and pathways.

Apply standard genomic/proteomic pipelines; Identify and correct batch effects; Utilize diagnostic histopathology to inform cellular compositions of tumor samples and extract relevant features that correlate to genomic or proteomic data.

Data Generated by CPTAC

Genomic Data

Genomic Data Commons
gdc.cancer.gov

10 cancer types, ~ 1,100 cases
WGS/WXS/RNA/miRNA alignments
Methylation (coming soon)

Proteomic Data

Proteomic Data Commons
pdc.cancer.gov

10 cancer types, ~ 1,600 cases
Comprehensive proteome
Phosphoproteome
Acetylome (~ 500 cases)
Glycoproteome (~ 200 cases)
Ubiquitylome (~ 100 cases)

Imaging Data

Cancer Imaging Archive
cancerimagingarchive.net

10 cancer types, ~ 1,500 cases
~ 6,000 images
Pathology
CT, and other radiology images

General Considerations

- PGDACs are expected to extensively interact and coordinate with PCCs, PTRCs and other PGDACs, and participate of working groups and other consortium activities, in addition to conducting proteogenomic data analyses, in order to contribute to the overall interpretation and publication of results.
- PGDAC awardees will be required to upload all their data to the CPTAC DCC (private portal).
- Computer algorithms produced specifically to analyze CPTAC data, software source code or other resources made possible under the auspices of CPTAC are expected to be made broadly available, without requirement for licensing.
- A PCC or PTRC PD/PI cannot be designated as PGDAC PD/PI. However, these individuals can serve as key personnel within a PGDAC application.

FAQs specific to RFA-CA-21-024

- **What cancer types are to be characterized by the PCCs/PGDACs in the tumor characterization program?**

  PCCs and PGDACs are to be agnostic to the human cancer types to be characterized/analyzed in the tumor characterization program. Specific cancer types will be made available at the time of award.

- **Does software deployment mean sharing with the broader community, or just available for in-house use?**

  After 6 months, PGDAC software shall be fully operational within the PGDAC.

- **Can software development be the unique focus of the proposal?**

  Proposals solely focused on software development will be deemed not responsive.

- **What is the role of imaging data in CPTAC?**

  Integrating proteomic data with imaging data (pathology and radiological images) will be deemed responsive.

- **Should proposal be a combination of all three levels of data analysis, or may be focused?**

  PGDACs that focus only on data analysis levels 2 and 3 will be deemed responsive.

RFA-CA-21-025:
Proteogenomic Translational Research Centers (U01)

Eunkyung An, PhD

Office of Cancer Clinical Proteomics Research

National Cancer Institute, NIH

CPTAC
CLINICAL PROTEOMIC TUMOR ANALYSIS CONSORTIUM

NIH NATIONAL CANCER INSTITUTE
Office of Cancer Clinical Proteomics Research

Purpose of RFA-CA-21-025

- This FOA solicits applications for Proteogenomic Translational Research Centers (PTRCs).
- PTRCs are function as multidisciplinary interactive group focusing on applying *standardized state-of-the-art proteomic and genomic approaches* to understand tumor biology in clinically relevant research projects related to specific treatment(s).
- Projects should focus on *proteogenomic aspects in understanding drug response/toxicity prediction and resistance to therapies in a clinical context.* It is envisioned that these projects will facilitate a rational approach to target cancer related pathways and improve outcomes for patients with cancer.

RFA URL: https://grants.nih.gov/grants/guide/rfa-files/RFA-CA-21-025.html

Key Dates for RFA-CA-21-025

Earliest Submission Date	Letter of Intent* Due Date	Application Due Date**
June 30, 2021	June 30, 2021	July 30, 2021

* LOI is not required, not binding, not included in review. LOI allows IC staff to estimate the potential review workload and plan the review.

** By 5:00 PM local time of applicant organization

Research Plan

To be responsive, applications must cover BOTH preclinical studies and studies with clinical trial biospecimens.

Research Arm	Objective	Samples to use	Treatment
Preclinical Research Arm	Hypothesis generation Testing the hypothesis	Preclinical cancer model Human cancer samples	Same Tx regimen
Clinical Research Arm	Validate finding(s) from preclinical research arm	Clinical trial samples	

Research Objectives: Preclinical Research Arm

Generating and testing the hypothesis to address unmet translational needs and/or clinical question(s) related to specific treatment.

Generating Hypothesis

- Comprehensive Characterization (proteogenomics)
- Preclinical cancer model / human cancer samples with clinical outcome

Testing Hypothesis

- Develop and apply quantitative proteomics /proteogenomics approach*
- Human cancer samples with clinical outcome

*preferably in a targeted manner, and it should be used in clinical research arm.

Research Objectives: Preclinical Research Arm

Generating and testing the hypothesis to address unmet translational needs and/or clinical question(s) related to specific treatment.

Generating Hypothesis

- ✓ Hypothesis
- ✓ Protein candidate selection and prioritization

Testing Hypothesis

- Develop and apply quantitative proteomics /proteogenomics approach*
- Human cancer samples with clinical outcome

*preferably in a targeted manner, and it should be used in clinical research arm.

Research Objectives: Preclinical Research Arm

Generating and testing the hypothesis to address unmet translational needs and/or clinical question(s) related to specific treatment.

Generating Hypothesis

- ✓ Hypothesis
- ✓ Protein candidate selection and prioritization

Testing Hypothesis

- ✓ Analytically validated quantitative assay(s)*
- ✓ Statistical Analysis Plan

*preferably in a targeted manner, and it should be used in clinical research arm.

Research Objective: Clinical Research Arm

Validating a preclinical finding using clinical trial samples.

Validating Finding(s)

- Application of quantitative proteomics/proteogenomics approaches* to cancer-relevant protein targets
- NCI-supported Clinical Trial samples

*Preferably in a targeted manner.

Main Capabilities

- Scientific capabilities, infrastructure, instrumentation, quality assurance processes, etc., to conduct all the required proteomic/proteogenomic analyses as well as statistical analysis must be in place from the start of the project period
- Extensive expertise in the standardization of proposed proteomic platforms for both discovery and targeted proteomics approaches (including computational analysis)
- Operate as an interactive group
- Applicants are expected to access and obtain samples which would be used in the proposed research (*Preclinical Research Arm* and *Clinical Research Arm*)

Data Analysis Definitions

- **Level 1 (required under this FOA):**
  - *Discovery Proteomics Research* - Analysis of raw experimental data to generate results on peptide/protein identification and quantitation, post-translational modifications (PTMs) identification, site localization and quantitation using a reference genome
  - *Targeted Proteomics Research* - Analysis of raw experimental data to generate quantitative results on peptide/protein concentrations of the selected targets from *Discovery Proteomics Research*
- **Level 2 (required under this FOA):** Integration of genome-proteome data at the linear sequence level (DNA, RNA, peptides/proteins with relative quantitation obtained from Discovery Proteomics Research using personalized genomic data)
- **Level 3 (required under this FOA):** Integration, visualization and analysis of omics data mapped onto networks and pathways obtained from Discovery Proteomics Research and/or Targeted Proteomics Research

Effort Coordination

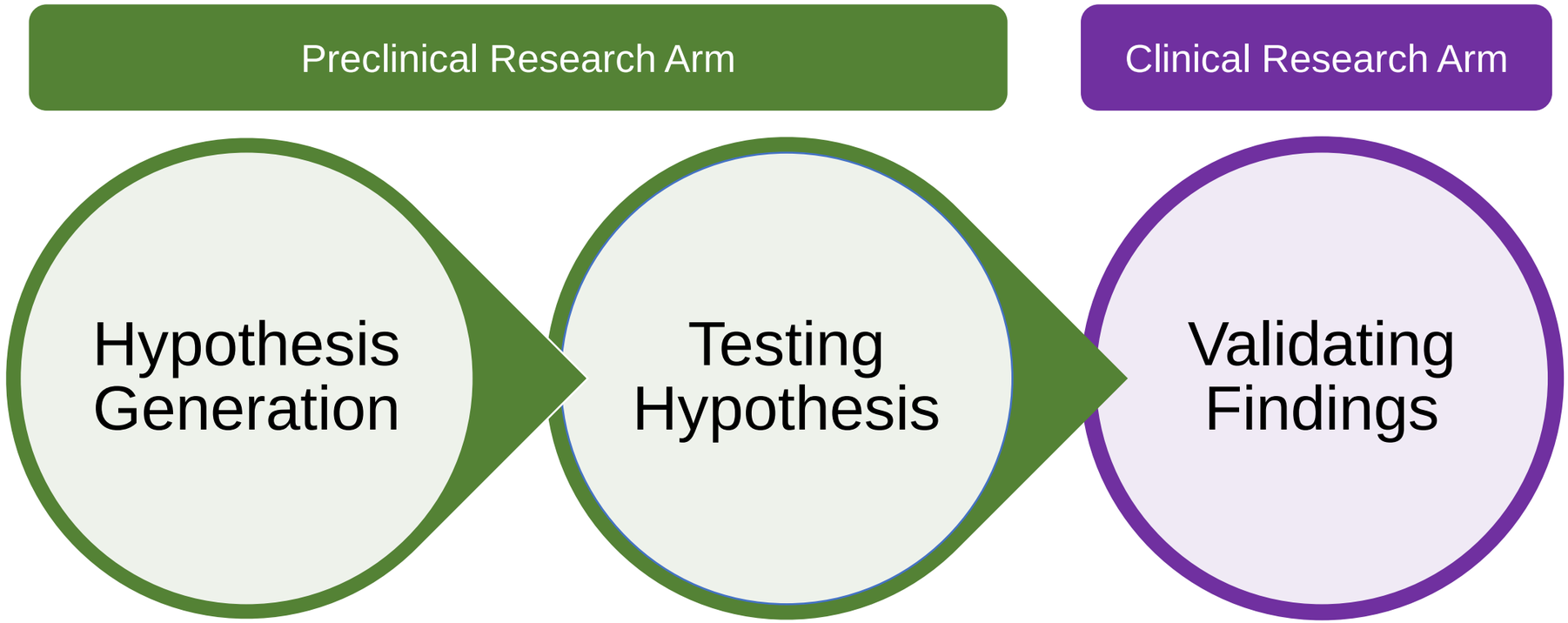
- Each PTRC must have appropriate logistical support for the expected administrative, communication, and coordination needs.
- **Coordination with PGDACs.** Levels 2-3 analysis are also to be performed by PGDACs with possible different computational omics, joint analyses are to be coordinated between PTRC and PGDAC. PTRCs will provide all data and analysis results to the CPTAC DCC where quality control and assurance of the data will be performed prior to distributing the data to the PGDACs for integrative analyses, target prioritization, and releasing the data to the public as appropriate.

Key Person Profile

Expertise in

- Proteomics
- Clinical research
- Other disciplines such as genomics, cancer biology, molecular oncology, clinical oncology, biostatistics
- Bioinformatics

Deliverables and Preliminary Data



Hypothesis	Analytically validated quantitative assay(s)
Protein candidate selection and prioritization	Statistical Analysis Plan

Section IV. Application and Submission Information

Preclinical Research Arm

Clinical Research Arm

Hypothesis generation

Testing Hypothesis

Validating finding(s)

Do you have working hypothesis and protein list to test?

Yes

Do you have analytically validated assay(s) for those protein list?

Yes

Do you have statistical analysis plan?

Yes

You can bypass Preclinical Research Arm.

No

1. Plan for **Preclinical Research Arm** (generating and testing hypothesis)
2. Plan for **Clinical Research Arm**
3. **Letter(s) of Support**

No

1. Data from the hypothesis generation **(Preclinical Research Arm)**
2. Plan for how to develop and validate assay(s)
3. Plan for how to test the hypothesis **(Preclinical Research Arm)**
4. Plan for **Clinical Research Arm**
5. **Letter(s) of Support**

No

1. Data from the hypothesis generation **(Preclinical Research Arm)**
2. Description of analytically validated assay
3. Plan for how to test the hypothesis **(Preclinical Research Arm)**
4. Plan for **Clinical Research Arm**
5. **Letter(s) of Support**

1. Data from **Preclinical Research Arm**
2. Description of analytically validated assay(s)
3. Statistical Analysis Plan
4. Plan for **Clinical Research Arm**
5. **Letter(s) of Support**

Letters of Support (required)

Provide Letter(s) of Support that identify clinical trials with samples that would fulfill the next step of clinical validation.

If proposing to start with Preclinical Research Arm

- the proposed research questions are clinically aligned/clinically relevant to trial(s)
- appropriate samples (in quality and quantity) may be available.

If proposing to start with Clinical Research Arm

- evidence of secured access to NCI-supported clinical trial samples.
- describe the required approval process for obtaining clinical specimens and the investigator's commitment to fulfill these requirement at the start of the program.

- # of specimens and amount
- Timing of the availability
- Specimen nature
- Types of accompanying data

FAQs specific to RFA-CA-21-025

- **What qualifies as an NCI-supported trial?**

  "NCI-Supported" in the context of clinical trials for this FOA means all clinical trials that are funded in full or in part by NCI. This includes all NCI network trials, trials that are supported by NCI grants, and trials at the NIH Clinical Center in Bethesda, Maryland. Clinical trials that are wholly funded by private entities (and in which the data from the clinical trial belong to the private funder) are not considered to be NCI-supported even if such studies are conducted at the NCI-designated Cancer Centers and benefit from the Cancer Center infrastructure.

- **Are Non-NCI-supported trial samples allowed?**

  Non-NCI-supported clinical trials may be used in an auxiliary role. However, NCI-supported clinical trial samples are required in Clinical Research Arm.

FAQs specific to RFA-CA-21-025

- **Would an NCI-sponsored intramural trial be permissible for this RFA?**

  Yes. NCI intramural trials are responsive to RFA-CA-21-025. Intramural trials are to be coordinated through Dr. William Dahut, Clinical Director of NCI's Center for Cancer Research (dahutw@mail.nih.gov).

- **Can NCI intramural investigators participate in RFA-CA-21-025?**

  It is allowable for NCI intramural investigators to participate as sub-awardees on RFA-CA-21-025. Please note that any salaries for, expenses of, and/or work done by intramural investigators is to be paid for by the intramural program. Also, intramural investigators cannot be the PI or Contact PI (if multiple PIs) on the application and award.

FAQs specific to RFA-CA-21-025

- **Are PTRCs to focus only on molecularly targeted "nextgen" cancer therapies, or would conventional chemotherapies, radiation therapy, and/or preventative vaccine trials also be considered responsive?**

  With the exception of vaccine cancer prevention trials, all the other aforementioned therapies are considered to be responsive.

- **Can PTRCs be included in the GCC agreements? (from the RFA, “Genomic Characterization Center (GCC) that will genomically characterize the same biospecimens provided by CPTAC to PCCs for proteomic characterization”)**

  No. This does not apply to PTRCs. In RFA-CA-21-025 under section [Overall CPTAC structure and functions/ Additional Resources Supported by NCI], it states that the GCC genomically characterize the same biospecimens provided by CPTAC to PCCs for proteomic characterization.

CPTAC Pre-Application Session

RFA-CA-21-023 (PCCs)
RFA-CA-21-024 (PGDACs)
RFA-CA-21-025 (PTRCs)

Grab some coffee

We will be back in 10 minutes to address questions...