Clinical Proteomic Tumor Analysis Consortium

RFA renewal

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Outline

- **Part 1: What we’ve learned**
  - What was CPTAC funded to do?
  - What has CPTAC accomplished in 3.5 years?

- **Part 2: What might be next**
  - Proposed concept (overarching goals)
  - Structure, mechanisms and budget
Part 1: CPTAC program current scope

What was CPTAC funded to do?

- **Goal**: Elucidate the proteogenomic complexity of tumors by identifying proteins that derive from alterations in cancer genomes [TCGA tumors: colorectal cancer (CRC), ovarian cancer (OVC), breast cancer (BRC)]

- **Underlying question**: Would additional biology be elucidated from deep proteomic analysis [CPTAC1] on genomically characterized tumors [TCGA]?

Achieved through…

- Proteome Characterization Centers - consortium of five labs that coordinate standardized research activities
- Sample size (CRC - 95; OVC - 174; BRC - 105)
- Community resources (data, assays, reagents)
Challenges overcome in Year 1

- **Retrospective biospecimens** (samples of convenience)
  - **Scientific implication**: effects of pre-analytical variables associated with TCGA tumors on protein measurement
    - Cold ischemia (up to 60 min)
    - **Good news**: no significant change in protein levels; change in phosphorylation levels, but biologically coherent
  - **Programmatic impact**:
    - Proteomic analysis of **TCGA samples not until Year 2**
    - **Good news**: ischemic proteomic database; prospective collection (tissue); SOPs/Best Practices to be adopted by College of American Pathologists
Colorectal Cancer: global protein abundance (proteome subtypes identified)

Transcriptome Subtypes
- MSI/CIMP
- Invasive
- CIN

Proteome Subtypes
- Subtype C displayed protein network features characteristic of EMT, associated with rapid metastasis and overall poor survival
- MSI/CIMP transcriptome subtype split into two proteome subtypes

Nature. 2014 Jul 20. doi: 10.1038/nature13438
Colorectal Cancer: global protein abundance (proteome subtypes identified)

Next steps (e.g.):

• **Q1. Can we rediscover the proteome subtypes?**
  – Global analysis on independent collection (CPTAC prospective samples: 100 treatment-naïve tumors and normal)

• **Q2. Can targeted proteomic assay panels identify interesting proteome features?**
  – *Proteome Subtype Panel*: 80 proteins representing the five CRC subtypes (CPTAC prospective)

• **Q3. Can targeted proteomic assay panels identify clinically relevant features?**
  – *Proteome Subtype Panel*: evaluate ability to discriminate recurrent from non-recurrent tumors (GI SPORE: 64 treatment-naïve tumors)
Ovarian Cancer: global protein abundance (proteome subtypes identified)

- 174 ovarian HGSC tumors
  - Selection criteria:
    - Overall Survival (OS)
    - Homologous Recombination Deficiency status (HRD)

- 5 proteomic subtypes
  (4 transcriptomic subtypes)
  - Immunoreactive mRNA subtype intermixed at protein level
  - New ‘Innate’ and ‘Stromal’ subtypes emerged
Ovarian Cancer: Deep proteomic analysis yields pathway activation correlated with overall survival

- NCI Pathway Interaction Database (214 signaling pathways)
  - Significantly upregulated pathways with short OS
    - Protein data ($p<0.05$)
    - Phosphorylation data ($p<0.0001$)
    - mRNA data ($p<0.05$)

- Combining deep proteomic, phosphoproteomic and transcriptomic analysis better elucidated the proteogenomic complexity of pathway activation not obtainable at the subtype level.

**PDGFR pathway upregulation in TCGA tumors with short OS**

$m = mRNA$

$P = protein abundance$

$\uparrow = upregulated$

$\uparrow\uparrow = significantly upregulated$

$\downarrow = downregulated$

$\downarrow\downarrow = significantly downregulated$

$\leftrightarrow = no difference$

$\leftrightarrow\leftrightarrow = not observed$
Next steps (e.g.):

• Q1. Can we rediscover the proteome subtypes?
  – Deep analysis on independent collection (CPTAC prospective samples: 100 treatment-naïve tumors and normal)

• Q2. Can we rediscover the short OS up-regulated pathways?
  – Deep analysis on independent collection (CPTAC prospective)

• Q3. Can targeted proteomic assay panels identify interesting proteome features?
  – e.g. Growth Factor Panel: >30 proteins (non-modified and phospho) up-regulated in PDGFR & VEGFR associated with short OS (CPTAC prospective)
What have we learned
(observations from External Scientific Committee)

External Scientific Committee (ESC):
- Academia
- FDA
- NIH
- Industry

Scientific & Programmatic webinar updates

- CPTAC structure successful and innovative at addressing proteomics cancer research (*consortium of checks and balances*)
- Accelerated adoption of standardized proteomic approaches by research community; critical step in marrying two crucial disciplines
- Some PCCs better than others with innovative data analysis
- Retrospective samples should be avoided, if possible
What have we learned
(observations from Independent Program Evaluation)

- Commissioned by the Office of Program Evaluation and Performance (NIH Office of the Director)
- Are CPTAC outputs (resources) utilized by scientific community?
  - Publication citations: too early to give a well-informed answer
    - partly due to data embargo dates: CRC (pub Sept 2014); BRC (May 2015); OVC (Sept 2015)

- **Other metrics**…

  - **CPTAC Data Portal**
    - Launched 2012
    - 6.2 TB raw files (89 TB equivalent downloaded)
    - proteomics.cancer.gov

  - **CPTAC Assay Portal**
    - Launched 2014
    - 554 fit-for-purpose targeted assays (4,800 users/month)
    - assays.cancer.gov

  - **NCI Antibody Portal**
    - Launched 4Q/2008
    - 314 mAbs available (2,171 units distributed)
    - antibodies.cancer.gov
Part 2: What’s next for CPTAC

• *Process*: Extensive input from External Scientific Committee members, Think Tank participants, and ongoing discussions with NCI Divisions, Centers and Offices program staff

• *Consensus recommendations*: Leverage investments in cancer genomics, by building on current achievements in cancer proteomics
  
  – (a) Supports an understanding of tumor proteogenomic complexity
  
  – (b) Addresses clinical/biological questions of drug response/toxicity prediction and resistance
  
  – (c) Accelerates proteomics science through community resources
Two Overarching Goals Addressing Specific Questions of Cancer

• **Goal 1**: Improve our understanding of the proteogenomic complexity of tumors
  – Q. What’s the association between genome and proteome?
  – Q. How do signaling pathway components crosstalk (DNA, RNA, and protein/PTMs)?
  – Q. What’s the impact of genetic alterations on the proteome?

A. **Proteome Characterization Centers (PCCs)**: extend CPTAC’s approach to additional cancer types where questions remain on their proteogenomic complexity

  • 5-6 cancer types; 100+ cases each (treatment-naïve CPTAC prospective collection); *(selection by extramural community - ESC members, CPTAC PIs, TCGA PIs, Think Tank participants)*

  • Patient-Derived Models Repository program *(coordination with DCTD)*
  • Human Cancer Models Initiative *(coordination with CCG, DCTD, and DCB)*
Two Overarching Goals Addressing Specific Questions of Cancer

• **Goal 2:** Improve our understanding of tumor resistance to therapy, and predicting treatment response (role of non-genetic factors)
  - Q. Why do some individuals not respond or relapse to therapies, when genomics indicated otherwise?
  - Q. What are the underlying mechanisms of resistance to therapies?

B. **Proteogenomic Translational Research Centers (PTRCs):**
CPTAC’s approach to research models and clinical trial samples
  - Applications to include well-conceived clinical/biological questions, access to clinical trial samples, and a proteogenomics research approach (*coordination with NCI’s DCTD - CTEP and CDP*)

C. **Proteogenomic Data Analysis Centers (PGDACs)**
  - Work hand-in-hand with PCCs/PTRCs to develop innovative tools that process and integrate data across the entire proteome Data*, assays and resources (goals 1 & 2) - community resources. (*coordination with CCG and CBIIT*)
Structure and Budget

- Current total FY2015 budget is $13M/yr (U24 PCCs)

- Proposed path forward and recommended budget is $13M/yr
  - Reduce and optimize **PCCs** by focusing on data generation. Budget is $4.0M/yr (U24)
  - Proteogenomic translation to be performed by **PTRCs**. Budget is $4.5M/yr (U01)
  - Data integration/analysis to be performed by specialized **PGDACs**. Budget is $4.5M/yr (U01)
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