National Cancer Institute

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

CLINICAL PROTEOMIC
TUMOR ANALYSIS CONSORTIUM

# 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

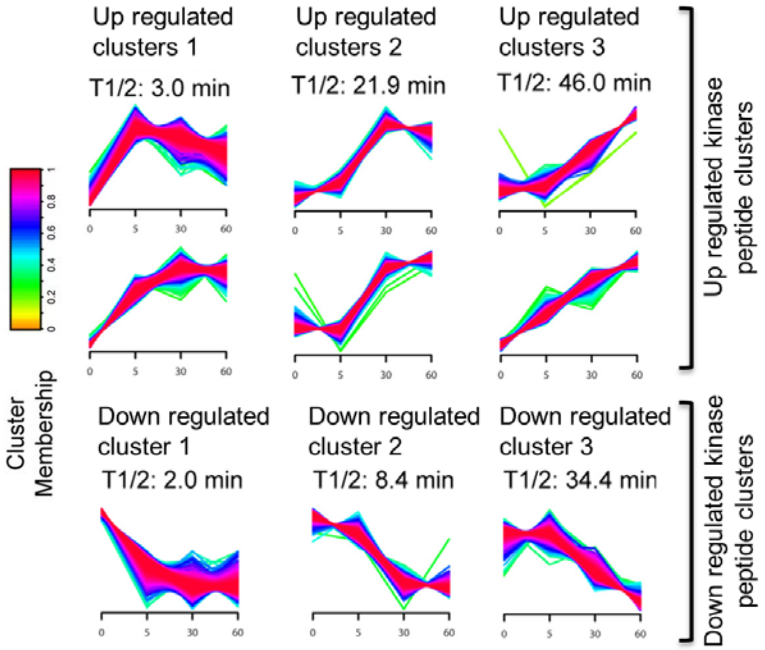
# Part 1: CPTAC program current scope

- 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

Temporal dynamics of phosphorylation changes resulting from cold ischemia during surgical procedures.




*Mol Cell Proteomics*. 2014 Jul;13(7):1690-1704

# Colorectal Cancer: global protein abundance (proteome subtypes identified)

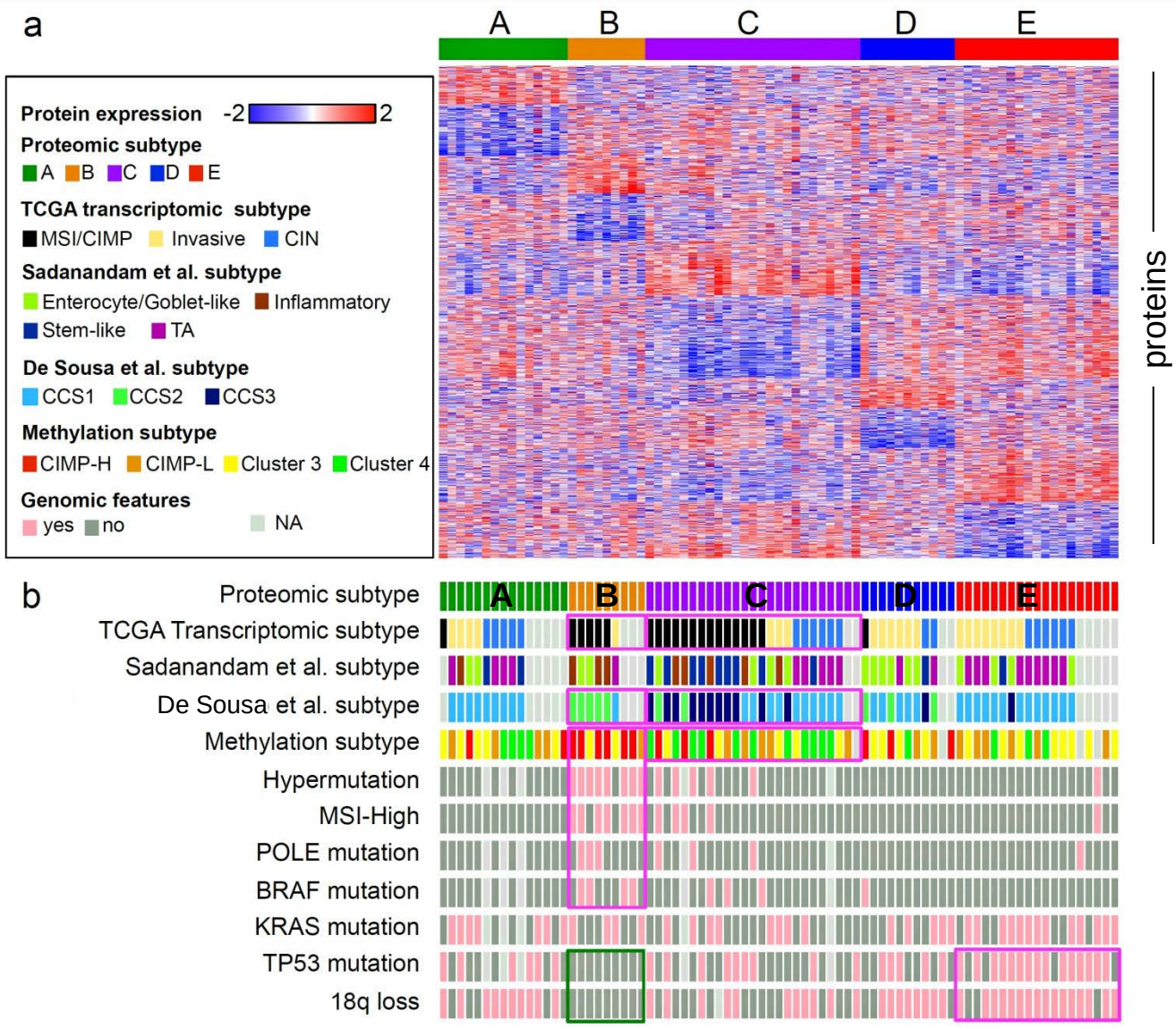
**Transcriptome Subtypes**

- MSI/CIMP
- Invasive
- CIN

**Proteome Subtypes**

A B C D E

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




*Nature*. 2014 Jul 20. doi: 10.1038/nature13438

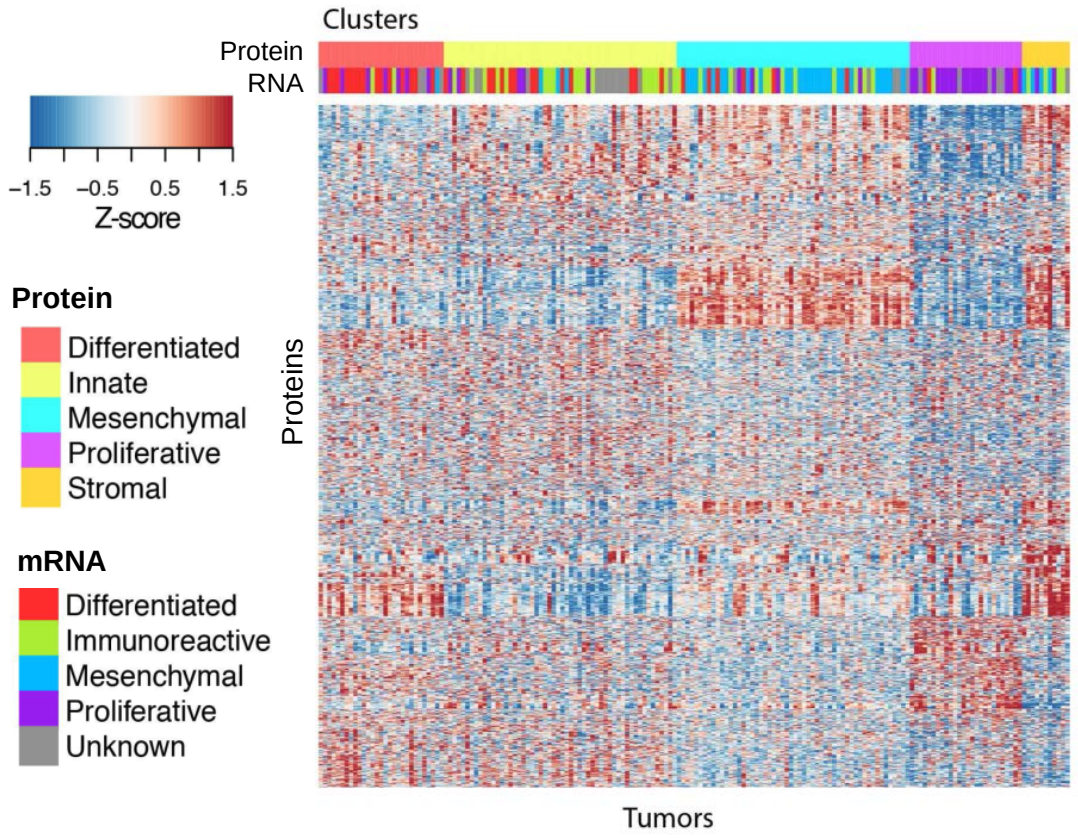
# Colorectal Cancer: global protein abundance (proteome subtypes identified)

***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



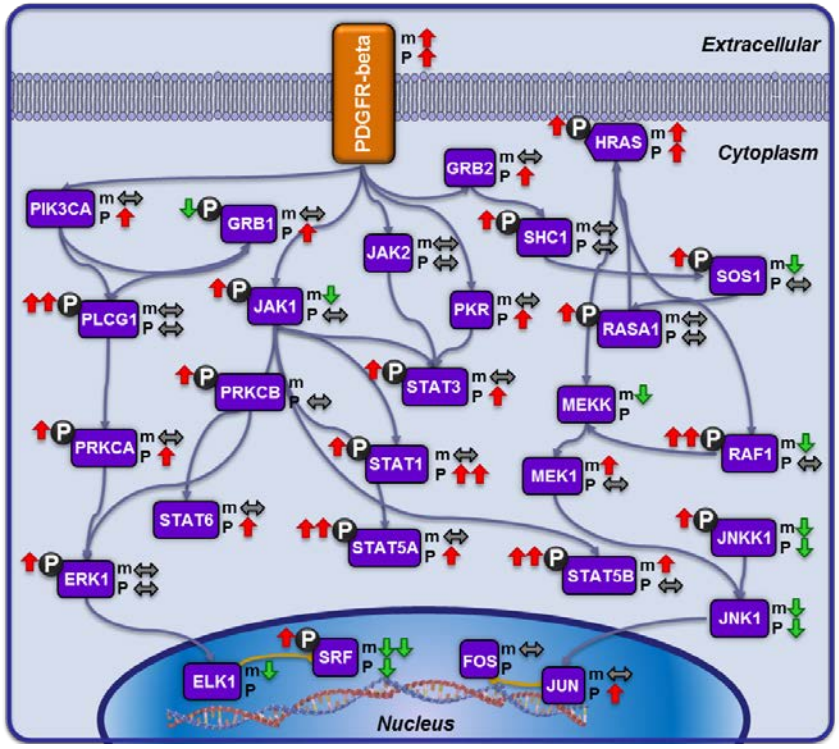

**Under first round revision at *Nature***

# 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*




Under first round revision at *Nature*

# Ovarian Cancer: Deep proteomic analysis yields pathway activation correlated with overall survival

***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)

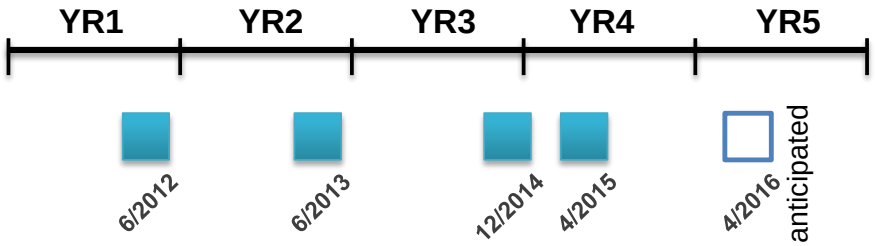
**Under first round revision at *Nature***

# What have we learned
## (observations from External Scientific Committee)

**External Scientific Committee (ESC):**

- Academia
- FDA
- NIH
- Industry

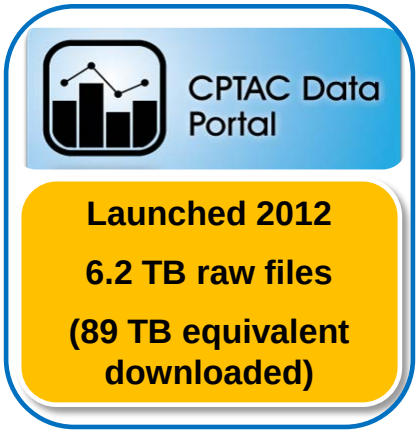
Scientific & Programmatic webinar updates



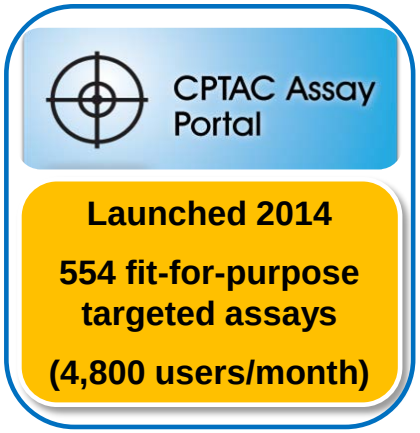

- CPTAC structure successful and innovative at addressing proteomics cancer research *(consortium of checks and balances)*
- Accelerated adoption of standardized proteomic approaches by research community; critical step in marrying two crucial disciplines
- Some PCCs better than others with innovative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

# What have we learned
## (observations from Independent Program Evaluation)

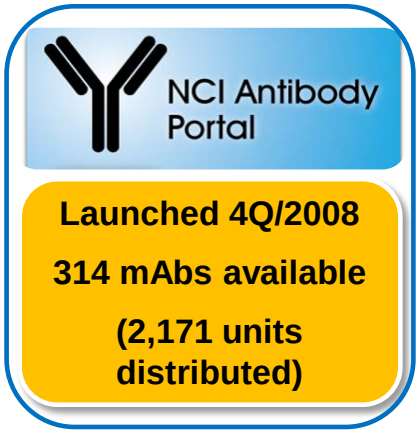
- Commissioned by the Office of Program Evaluation and Performance (NIH Office of the Director)
- Are CPTAC outputs (resources) utilized by scientific community?
  - Publication citations: too early to give a well-informed answer
    - partly due to data embargo dates:
      CRC (pub Sept 2014); BRC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




proteomics.cancer.gov




assays.cancer.gov




antibodies.cancer.gov

PubMed LinkOut

# 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)*

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- 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)*

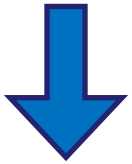
**C. Proteogenomic Data Analysis Centers (PGDACs)**

- 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)

# Key Contributors

## DCTD, Cancer Diagnosis Program

- Barbara Conley
- James Tricoli
- Tracy Lively
- Tawyna McKee
- Brian Sorg
- Irina Lubensky
- Magdalena Thurin
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