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

Henry Rodriguez

June 24, 2015

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

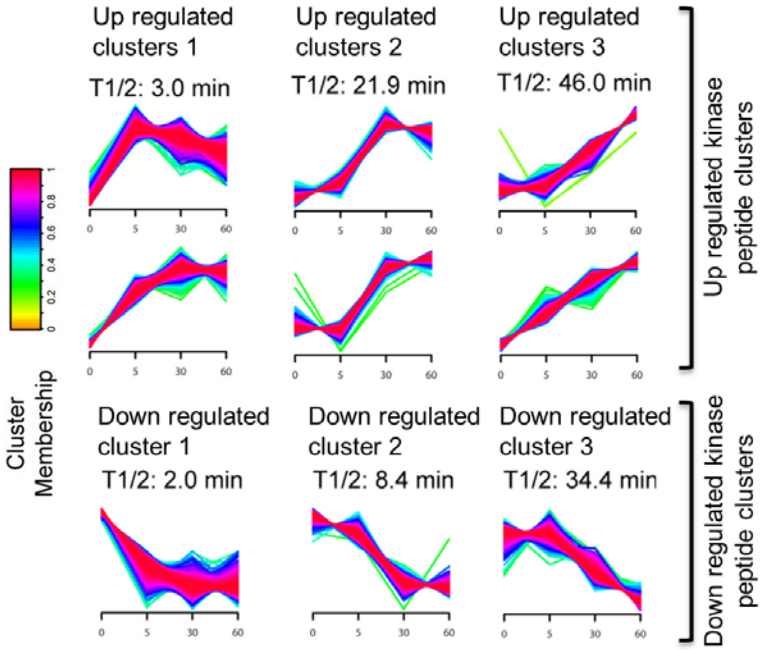
Part 1: CPTAC program current scope

- 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)

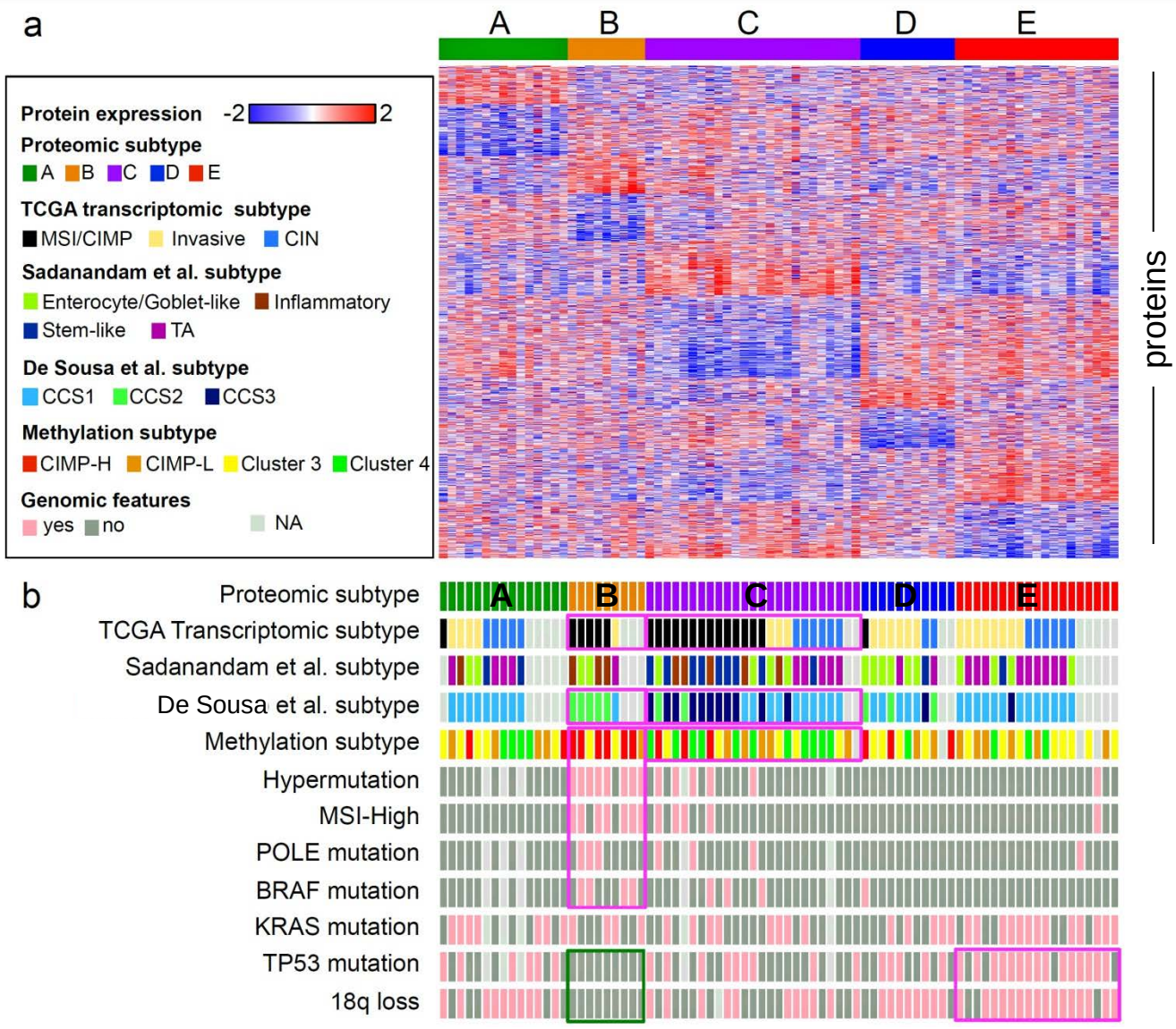
Transcriptome Subtypes

- 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

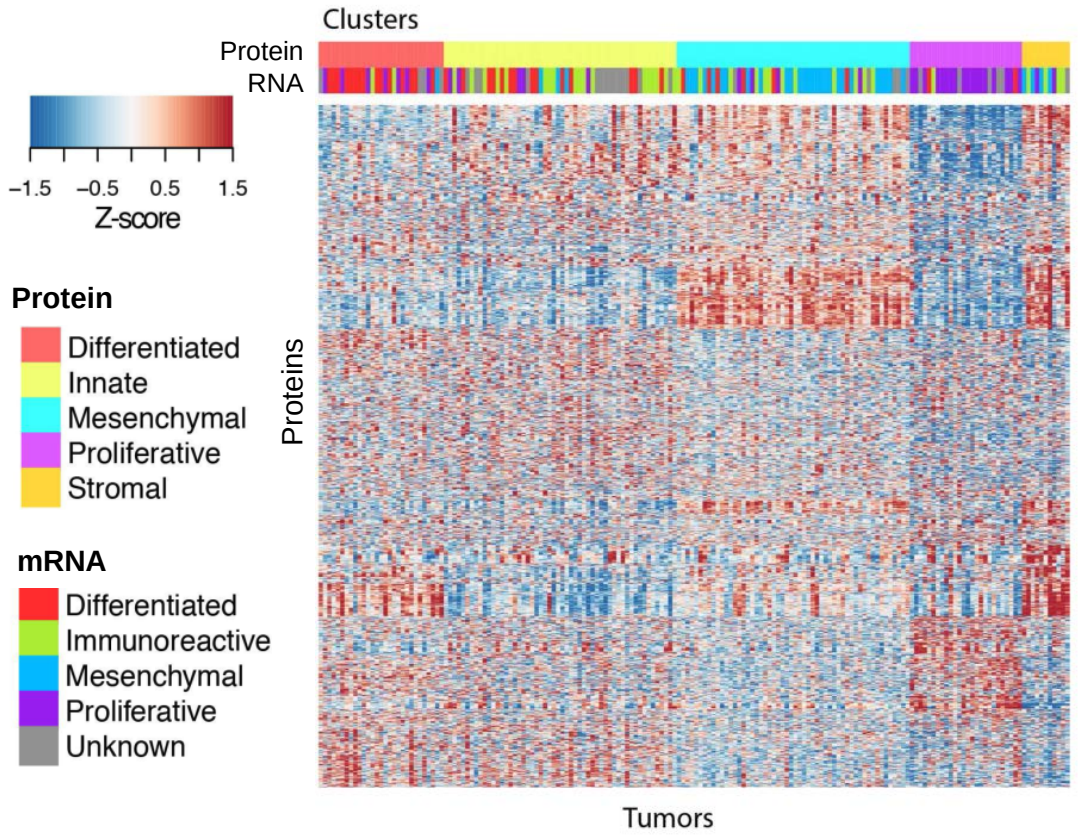
Colorectal Cancer: global protein abundance (proteome subtypes identified)

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



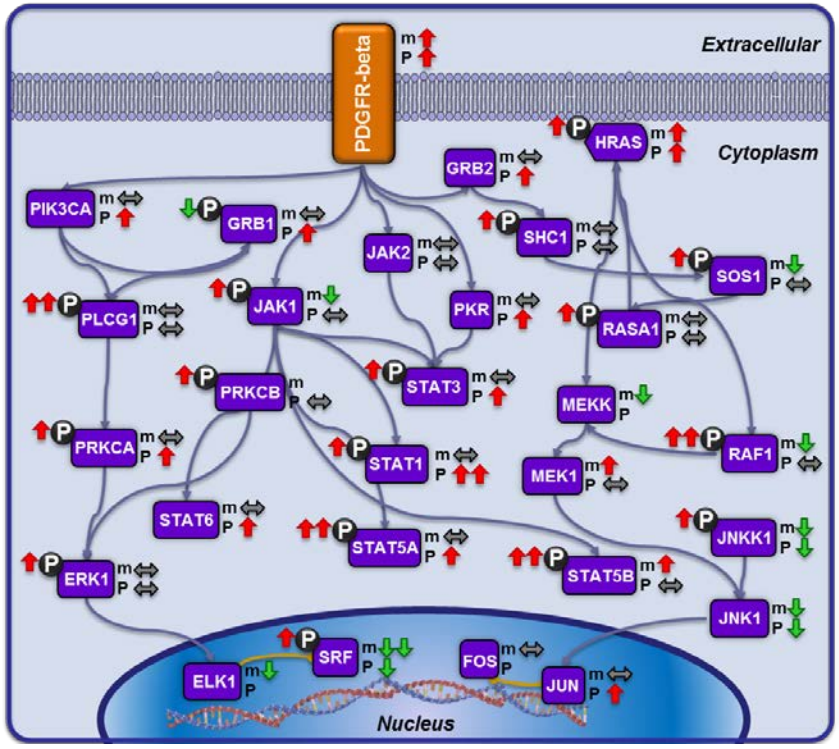
Under first round revision at *Nature*

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)

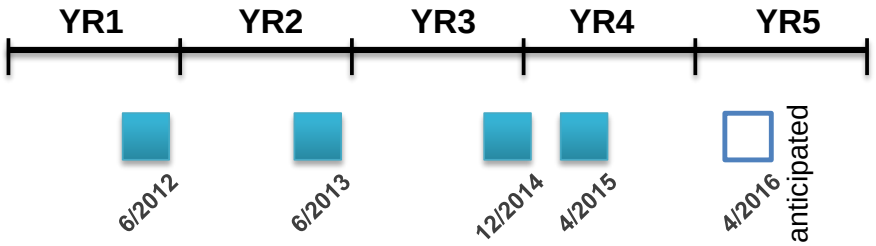
Under first round revision at *Nature*

What have we learned
(observations from External Scientific Committee)

External Scientific Committee (ESC):

- Academia
- FDA
- NIH
- Industry

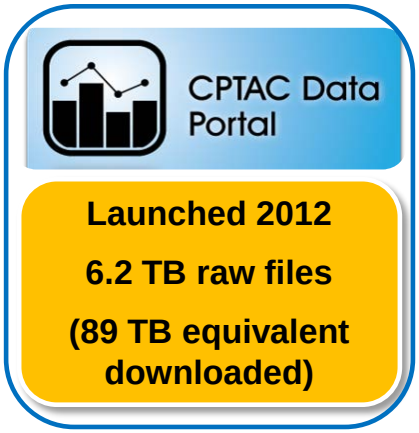
Scientific & Programmatic webinar updates



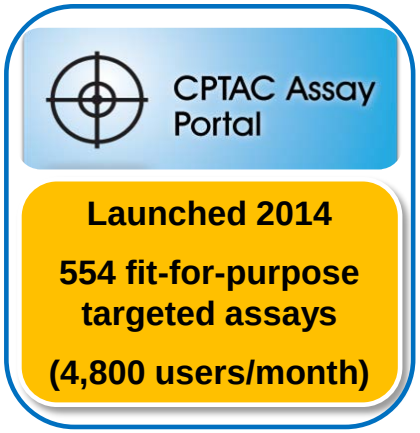
- CPTAC structure successful and innovative at addressing proteomics cancer research *(consortium of checks and balances)*
- Accelerated adoption of standardized proteomic approaches by research community; critical step in marrying two crucial disciplines
- Some PCCs better than others with innovative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

What have we learned
(observations from Independent Program Evaluation)

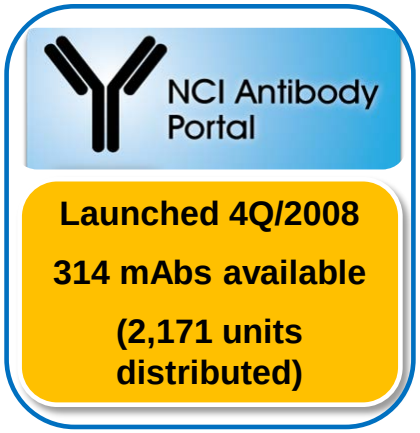
- Commissioned by the Office of Program Evaluation and Performance (NIH Office of the Director)
- Are CPTAC outputs (resources) utilized by scientific community?
  - Publication citations: too early to give a well-informed answer
    - partly due to data embargo dates:
      CRC (pub Sept 2014); BRC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

- 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)*

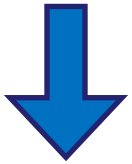
C. Proteogenomic Data Analysis Centers (PGDACs)

- 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
- Kim Jessup
- Helen Moore

DCTD, Biometric Research Branch

- Lisa McShane

DCTD, Cancer Therapy Evaluation Program

- Jeff Abrams
- Shakun Malik
- James Zwiebel
- Margaret Mooney
- Percy Ivy
- Jeffrey Moscow
- Ming Song
- Jo Anne Zujewski
- Elise Kohn

OD, Center for Cancer Genomics

- Lou Staudt
- Jean C. ZenKlusen

DCTD, Translational Research Program

- Toby Hecht
- Peter Ujhazy
- Andrew Hruszkewycz
- Tamara Walton
- Igor Kuzmin
- Steve Nothwehr
- Julia Arnold
- Leah Hubbard
- Rajeev Agarwal

NATIONAL® CANCER INSTITUTE