CLINICAL PROTEOMIC TECHNOLOGIES FOR CANCER

NCI Clinical Proteomic Technologies for Cancer

Re-issuance

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NCI Board of Scientific Advisors
March 8, 2010

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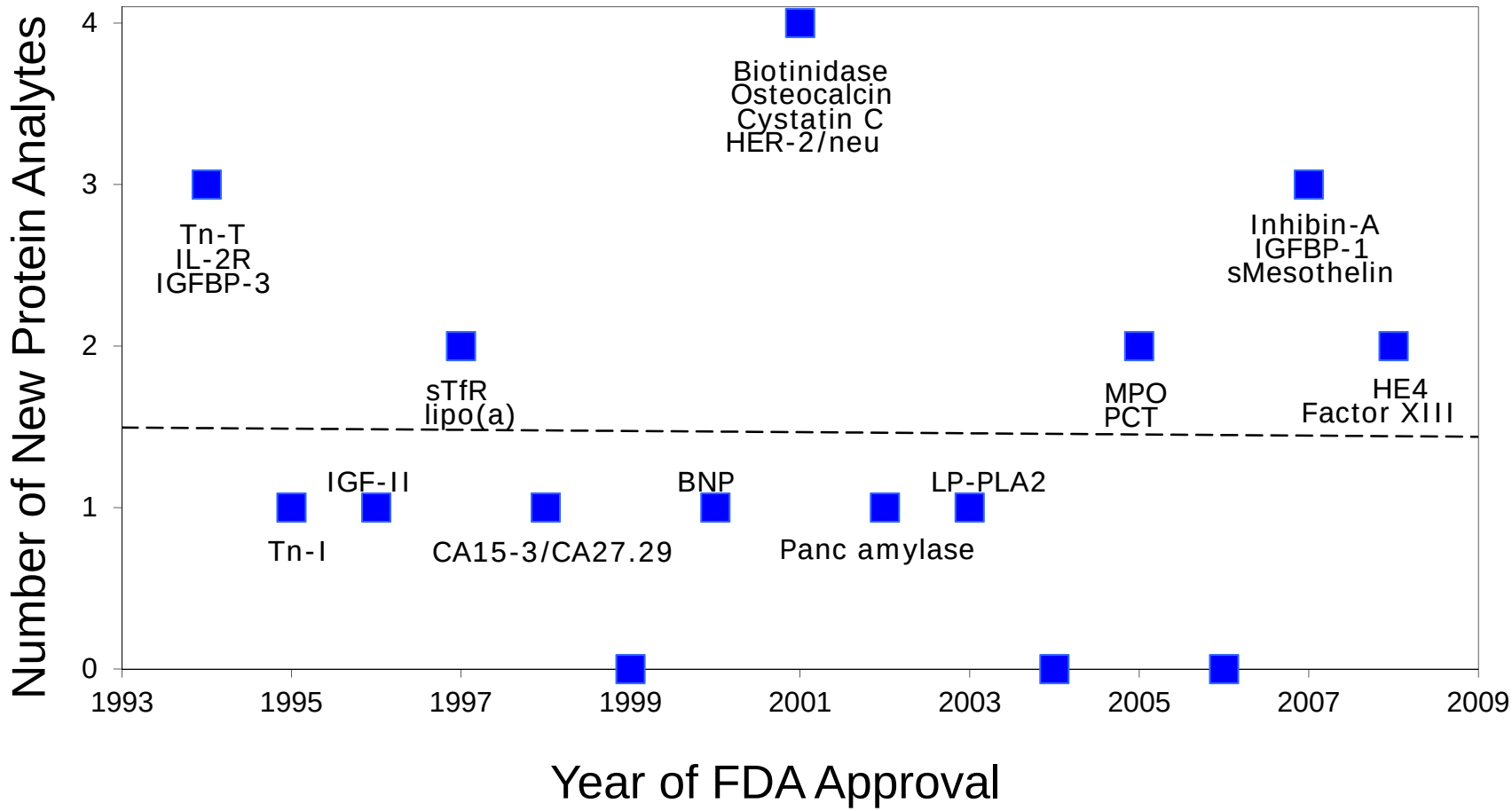
NATIONAL CANCER INSTITUTE

Only a handful of new protein biomarkers Introduced in past 15 yrs and current rate is only ~1.5/yr



"The genome is after all the instruction but it doesn't do the work – proteins do the work." ***Dr. Francis Collins, source: Catalyst, ABC 2001***

Leigh Anderson, Clin Chem (2010) in press

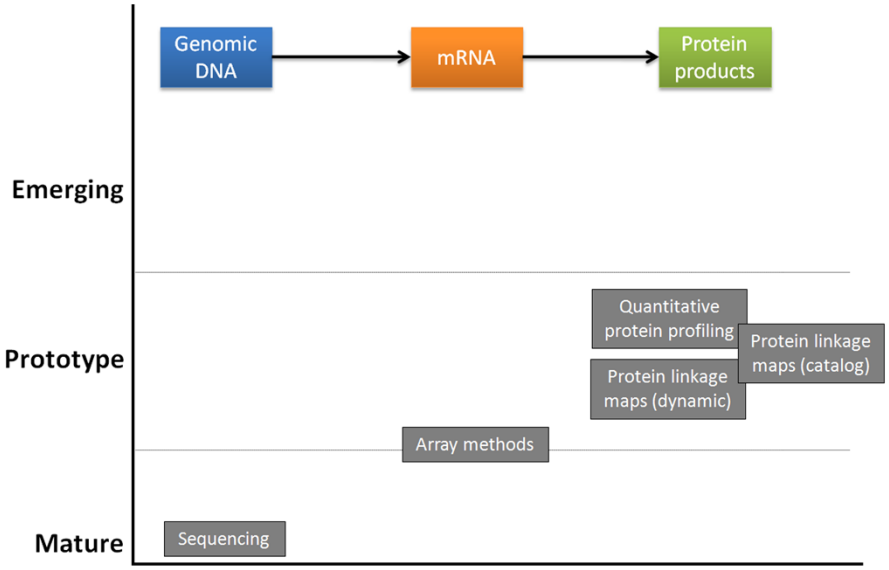
Basic Technology for Studying Cancer at the Molecular Level

CLINICAL PROTEOMIC TECHNOLOGIES FOR CANCER

THE NATIONAL ACADEMIES
Advisers to the Nation on Science, Engineering, and Medicine

NATIONAL CANCER INSTITUTE

Technologies for Quantitative Analysis



- Consensus that unlike genomic technologies, proteomic technologies were not fully mature

Source: Adopted from "Defining the Mandate of Proteomics in the Post-Genomics Era: Workshop Report." *National Academy of Sciences. Molecular & Cellular Proteomics* 1:763-780, 2002.

Barriers identified (NCI workshops 2002-2005):

- Experimental design
- Analytical variability (platform assessment/optimization – MS/MS)
- Lack of standards, protocols, and reference data
- Biospecimens
- Data acquisition, analysis, and reporting
- Lack of high-quality reagents

History of CPTC

NCI Proteomics Planning Process

Oct 2006	**CPTC launched**
Dec 2005	Proteomic Affinity/Capture Methods Workshop
Feb 2005	Proteomic Technologies Informatics Workshop
Jan 2005	Clinical Proteomics Technologies Team Initiative proposal
Nov 2004 Sept 2004	Clinical Proteomics and Biomarker Discovery in Cancer Research
June 2004	***Initial draft proposal for a Clinical Proteomics/Biomarker Discovery Initiative***
April 2003	Proteomic Technologies for Early Cancer Detection
April 2002	Proteomics Planning Workshop *(NCI/NHGRI/NIGMS)*

Planning: Identification of Phase 1 CPTC Goals

- Technical barriers (platform evaluation / optimization)
  - Discovery (survey) stage
  - Verification (targeted) stage
- Biospecimen collection, handling, storage and processing
- Experimental design (Statistical Issues))
- Data acquisition, analysis and reporting
- Lack of Standards, protocols, high quality reagents

BSA recommendation, CPTC to address sources of variability and bias in clinical proteomics

CPTC Center Network
(Team Science/Multidisciplinary)

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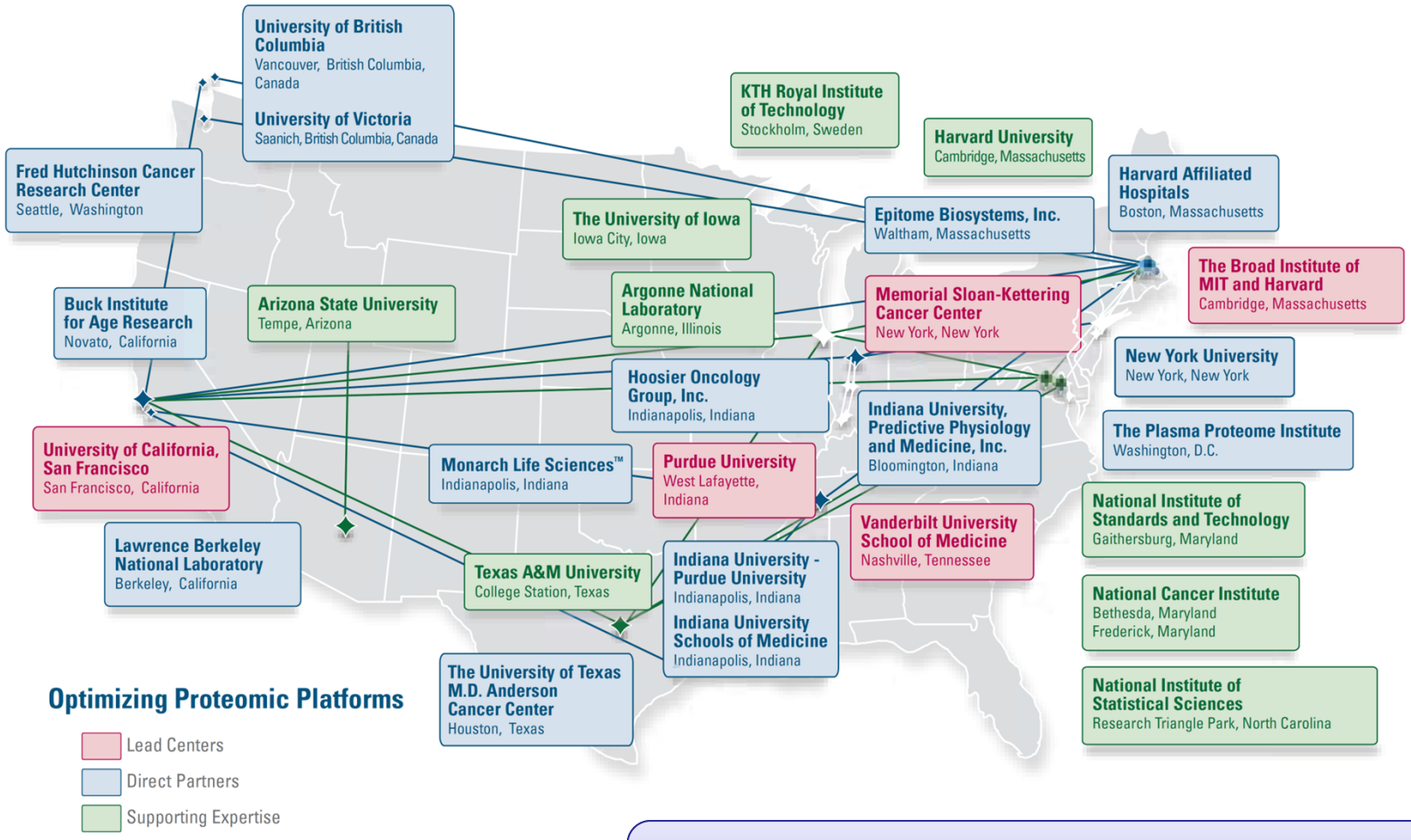

"The ultimate goal of this project will be a pipeline for biomarker discovery in which each step has been rigorously and quantitatively tested."

Leland Hartwell, Fred Hutchinson Cancer Research Center

Key Accomplishments
(Milestone Driven)

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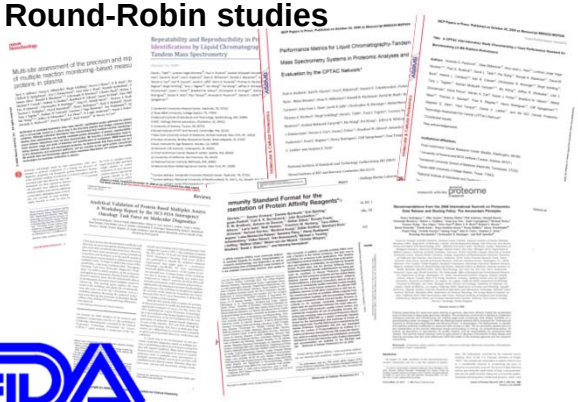
- **Standardization/Transferability of mass spectrometry**
  - 4 different LC-MS/MS platforms standardized
  - Shotgun mass spec; Targeted/Quantitative mass spec (Verification)
  - Metrics, SOPs (27), performance data sets (6), reference materials (2), computational algorithms (26) developed
  - Bias-free biospecimen collection (Ransohoff, Skates, OBBR)
  - FDA: 2 mock 510(k) presubmissions (multiplex- mass spec & affinity array)
- **Public Data Portal** (caTranche: caBIG™-silver level)
- **Community Reagents** (Antibody Characterization Lab; 84+ monoclonal antibodies)
  - International antibody characterization standards
- **Data Release Policies** (Amsterdam Principles)
- **Community Recognition:** 11public-private partnerships; NHLBI coordination, MOU with FDA, Korea Institute, American Association for Clinical Chemistry (AACC)
- **Scientific output:** 7 patents; >171+ papers
- **Leveraged funding:** additional NIH grants, philanthropy, industry, and venture investors

Round-Robin studies



FDA

U.S. National Institutes of Health | www.cancer.gov
ANTIBODY CHARACTERIZATION LABORATORY

antibodies.cancer.gov

caTranche

National Heart Lung and Blood Institute

AACC

KIST

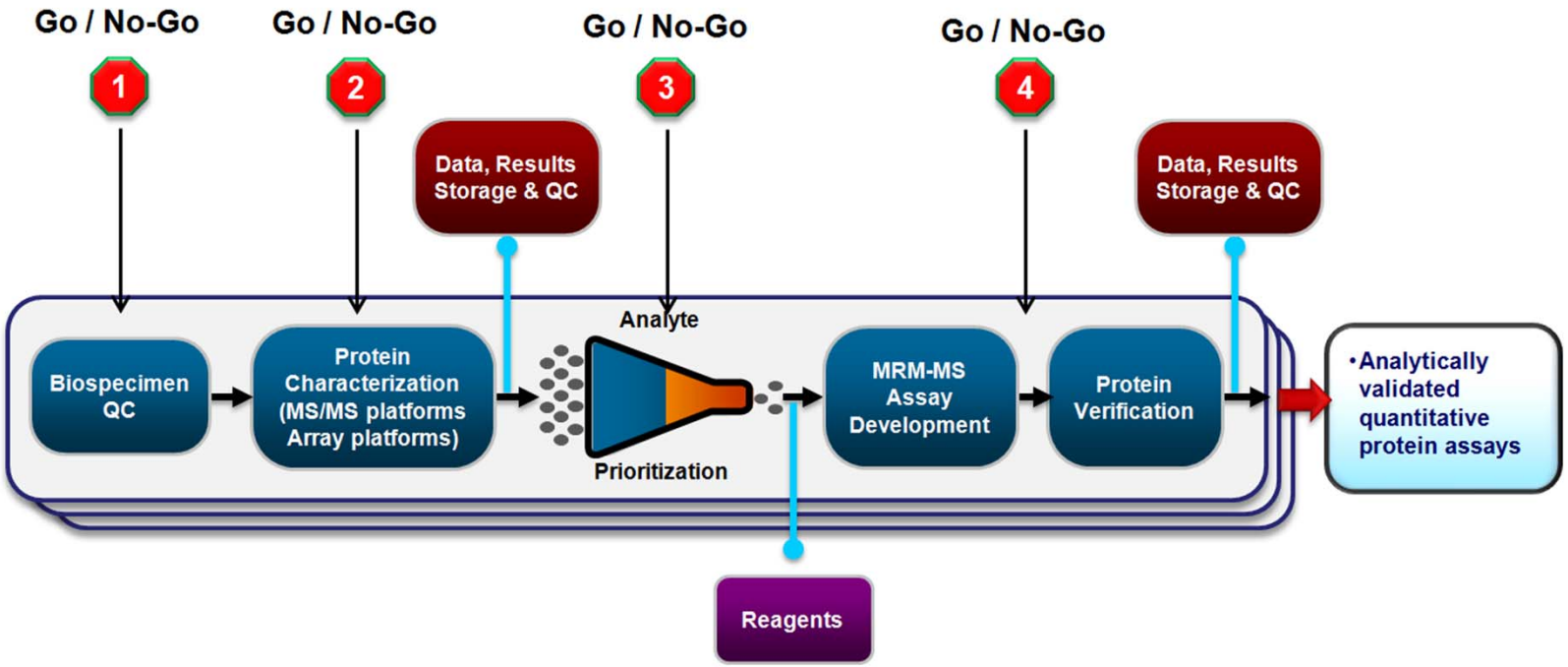
STAND UP TO CANCER

EIF

Purdue Center for Analytical Development

CPTC Phase 1 Pipeline

CPTC Proteomics Pipeline and "Go / No-Go" Decision Points

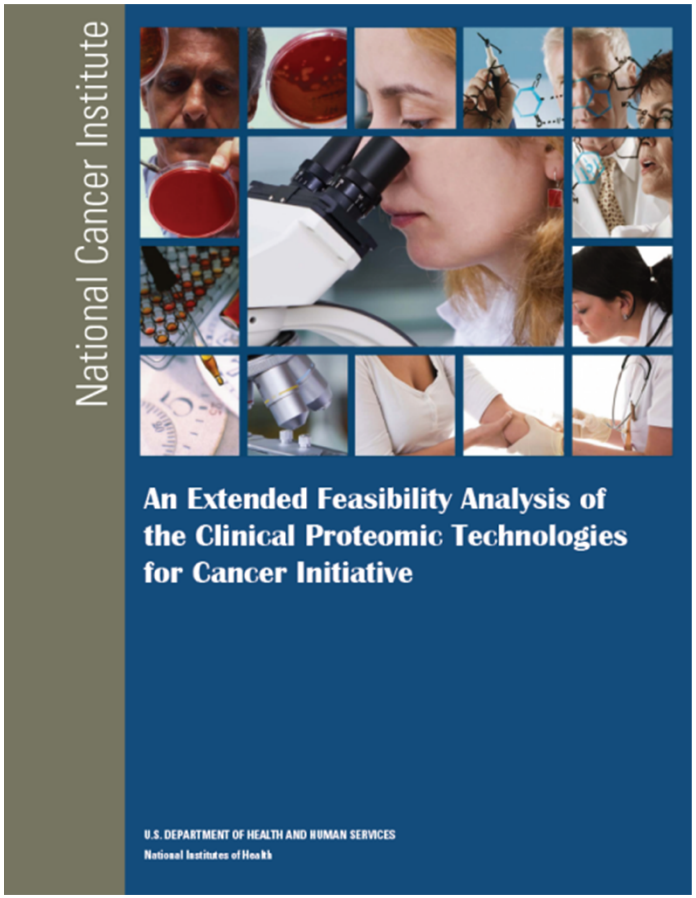


MS/MS – tandem mass spectrometry

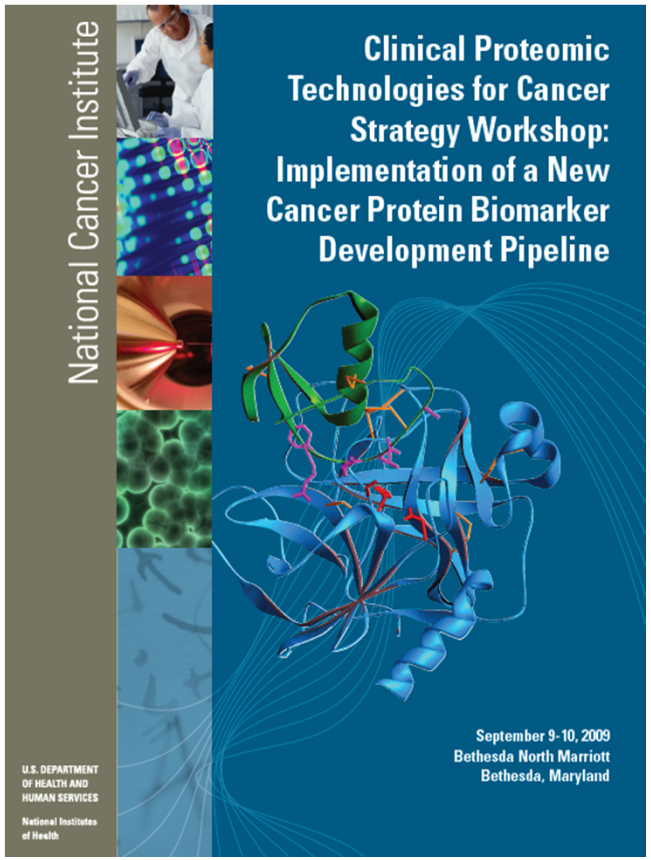
MRM-MS – multiple reaction monitoring mass spectrometry

Independent Evaluation Report

- **Commissioned by NIH Office of the Director**
- **NIH support**
  - National Institute of Diabetes and Digestive and Kidney (NIDDK)
  - National Center for Research Resources (NCRR)
- **Advisory Committee**
  - NCI: Drs. Gallahan, Jessup, Solomon, Aragon, and Hiltke
  - NCRR: Dr. Old, Senior Advisor to the Director (formerly Clinical Proteomics Director at National Heart, Lung, and Blood Institute)
  - UPenn Medical School: Dr. Blair, Vice Chair, Department of Pharmacology
- **Outcome**
  - Significant milestones achieved; long-term potential as a key component in proteomics for personalized medicine



CPTC Phase 2 Strategy Workshop



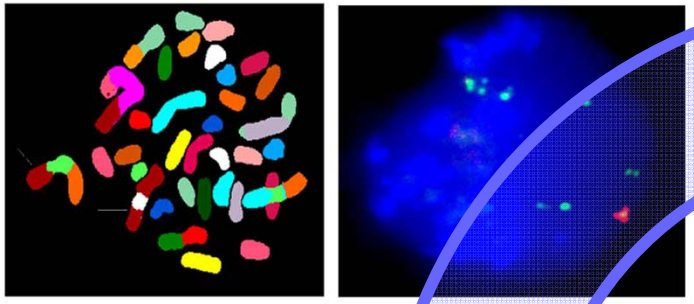
- **Recommendations**
- Phase 1 of CPTC will achieve goals – set the stage for rational biomarker discovery pipeline
- TCGA and other large scale genomic characterization/sequencing programs have shown that a large scale, systematic approach can identify most genomic alterations
- CPTC is poised to build upon the outputs of TCGA (and similar efforts) in the context of protein biology (protein mapping)
- Phase 2 of CPTC should employ results of Phase 1 – develop network to systematically verify relevant proteins using known genomic alterations as starting point – enable technology development
- **Participants**
  - Genomicists, oncologists, technologists, biologists, informatics, clinical chemists, diagnostics, therapeutics, regulatory, patient advocates, NCI Divisions

TCGA: Building Multi-Dimensional Data to Identify All Relevant Genomic Changes in Specific Cancers

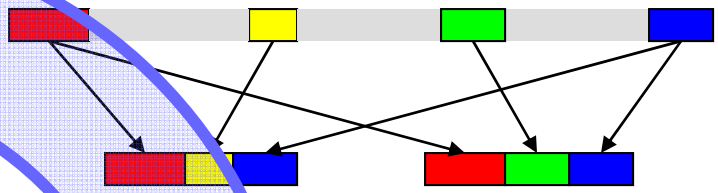
THE CANCER GENOME ATLAS

From Ron DePinho

Aneuploidy; Re-arrangement; Translocation



Gene splicing alterations



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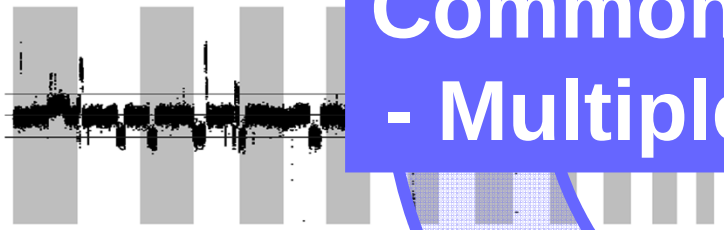
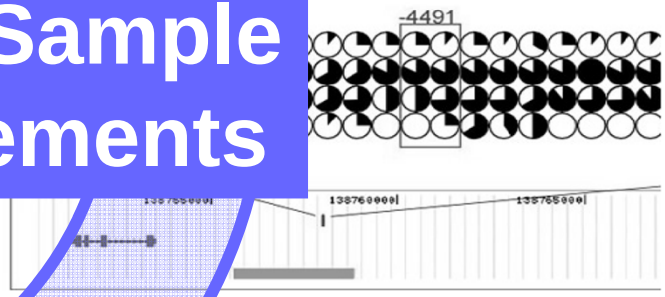
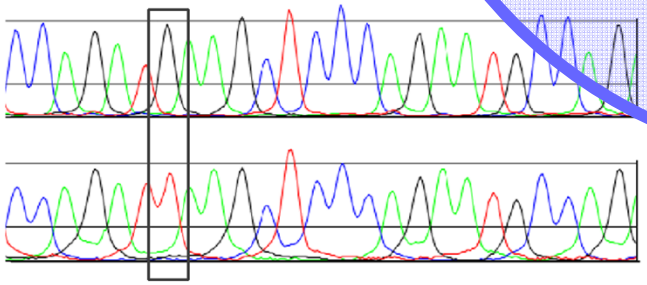


Methylation or modification

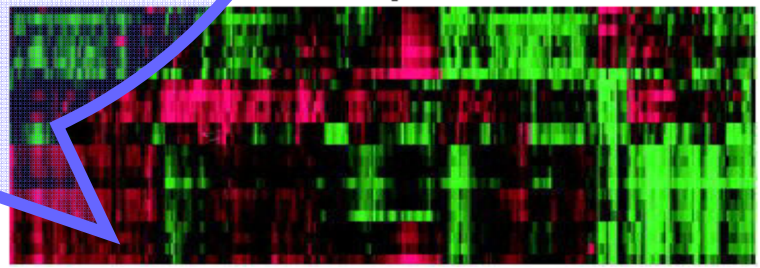


Common Clinical Sample - Multiple Measurements

Somatic mutations



Altered expression



Adopted from Cameron Brennan

Significant Opportunity to Leverage Progress in CPTC – Employ TCGA and Other Genomic Data to Define Cancer Proteomes

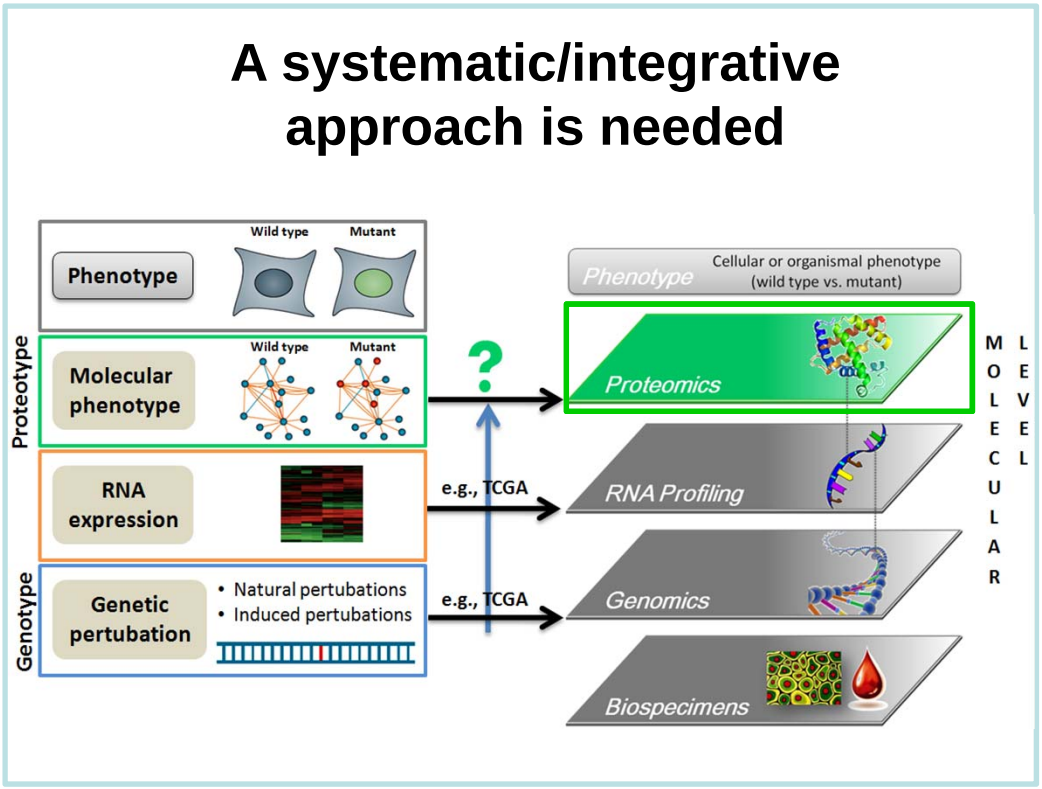
- **TCGA and similar efforts provides rational basis for cancer proteomics**

Biological mechanisms:

- Are genetic aberrations detectable at protein level?
  - *qualitative and quantitative*
- What is their effect on protein function?
  - *e.g. protein-protein interaction; structure-function relationship*

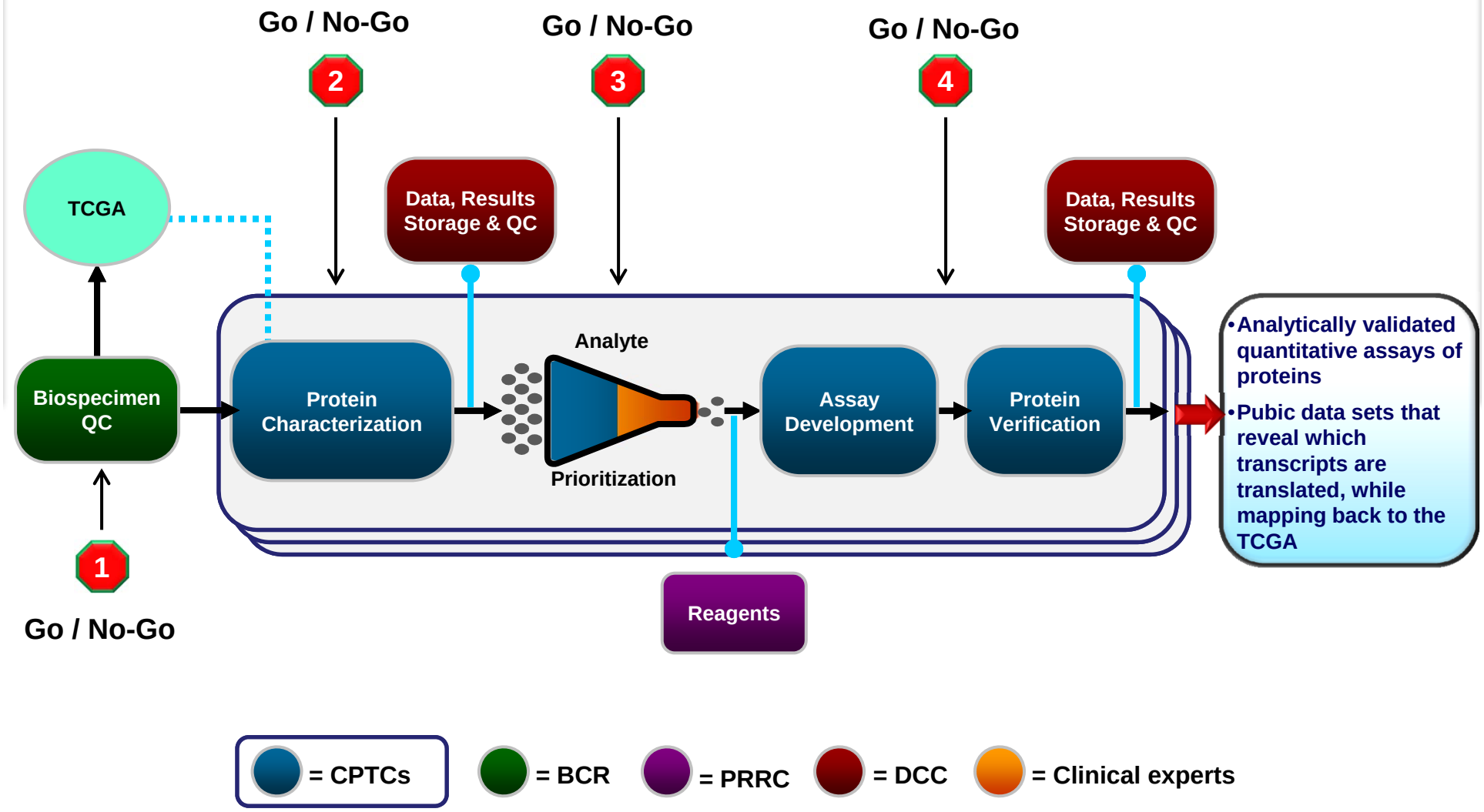
Clinical applications:

- Can genotypic information guide protein biomarker development?
- Are these candidates involved in specific biological pathways?
  - *e.g., cancer development & progression; predictive/drug response*



Source: Adopted from – Gstaiger, M., Aebersold, R. Applying mass spectrometry-based proteomics to genetics, genomics and network biology. *Nature Reviews Genet.* 2009 Sep;10(9):617-27.

Proposed CPTC Phase 2 Pipeline



Emerging Proteomics Pipeline

(A Paradigm Shift in Technology)

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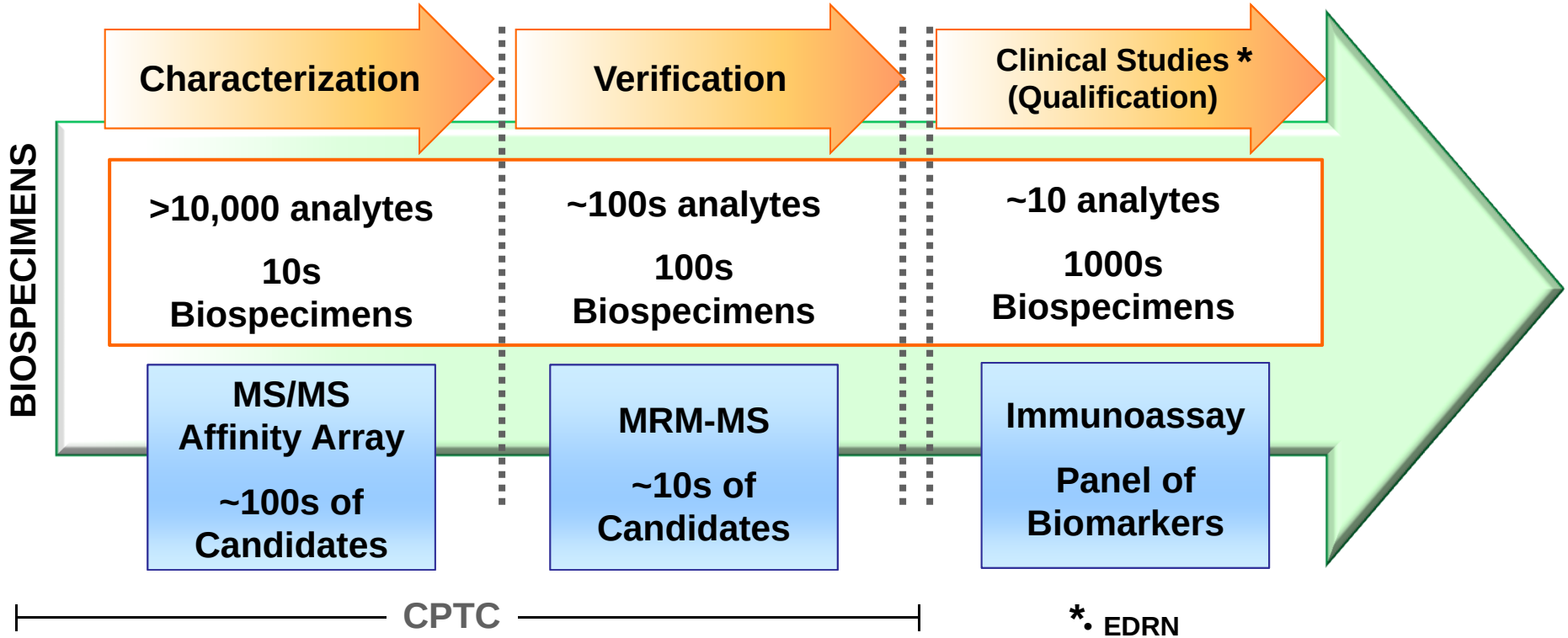


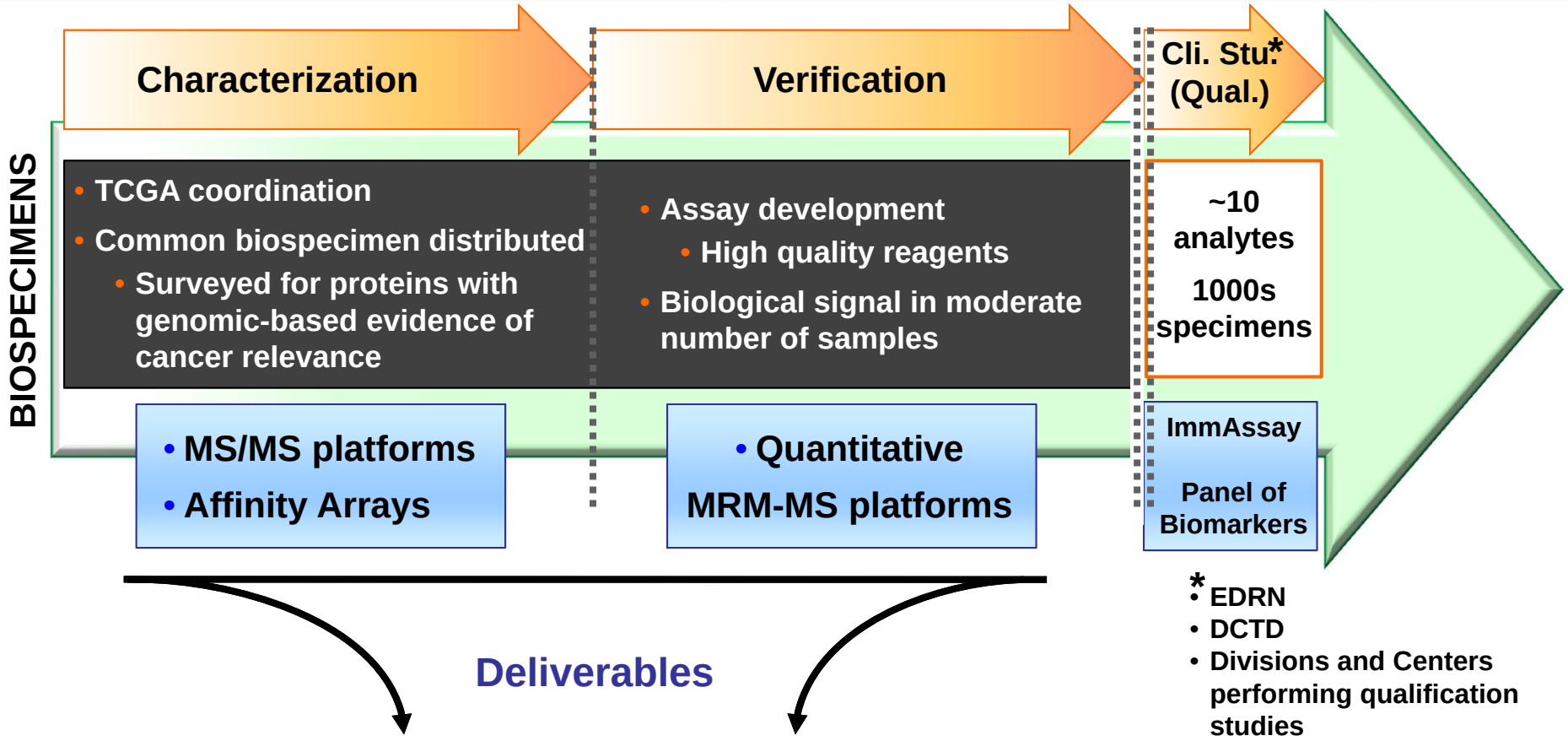
*
- EDRN
- DCTD
- Divisions and Centers performing qualification studies

"This is a first step in the long march to move protein biomarkers from the laboratory into the clinic."

Steven A. Carr, Broad Institute of MIT and Harvard

- **Pipeline enables delivery of highly-credentialed protein biomarker candidates for clinical studies (qualification).**

Re-issuance: CPTC Pipeline



- Highly credentialed biomarker candidates for qualification studies
- Library/catalog of characterized & verified protein analytes (genomic correlation)
- Quantitative multiplex assays, with data sets, reagents and SOPs

Re-issuance: Components – Deliverables

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CPTC center network

Characterization Phase

- MS/MS platforms – protein survey
- Array platforms – protein function
- TCGA coordination
- Common biospecimen distributed across centers (tissue; proximal fluid)
- Pathway/network focus

candidate prioritization

Verification Phase

- Quantitative MRM-MS/MS platforms
- Stage gates (basic biology and clinical potential; clinically driven evidence; and clinical cohort)
- Prospectively-designed biospecimen collections; clinical utility

Reagents & Resources

Biospecimens (caHUB)	Data Coord. Ctr. (CBIIT)	Reagents core

CPTC Deliverables

- Library/catalog of characterized & verified protein analytes (genomic correlation)
- Highly credentialed biomarker candidates for qualification studies

- Quantitative multiplex assays, with data sets, reagents and SOPs

Re-issuance:
Proposed Mechanism and Budget

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CPTC center network:

- RFA (U24: Resource-Related Research Project-Cooperative Agreements)
- 6-8 Centers
- Annual budget: $15-24M, Total budget: $75-120M

Reagents and Resources:

- RFP (contracts)
- (e.g., performance mixtures, antibodies)
- Common biospecimens
- Biomarker candidate library/database
- Data Coordination Center
- Annual budget: $2.5M, Total budget: $12.5M

Re-issuance: Milestones

To evaluate the second phase of the CPTC program on an ongoing basis, a matrix of quantitative performance measures will be used. Milestones will depend to some extent on the members of the phase 2 network – and may require adjustment based on the cancer type being studied. Benchmarks that will be utilized to launch the program include the following:

- The number of genetic aberrations successfully confirmed by proteomic data
- The number of verified proteins that emerge from the program
- The number of new platforms and methodologies matured through trans-network testing
- The number of quantitative protein assays developed and analytically validated (verification stage)
- The number of cancer types studied

Re-issuance: Phase 2 Summary

- **Develop a network to systematically characterize and verify proteins with a basis of known genomic alterations**
- **Enable technology development**
- **Analytically validate quantitative multiplex assays, with associated data sets, reagents and SOPs**
- **Enable the R01 and/or clinical communities to pursue rational biomarker discovery and development**

In short, CPTC Phase 2 will provide a resource of **well-characterized** and robust protein candidates, **orthogonally verified** using advanced technology platforms, **cross-tested within a network**, and **shared with the public** quickly for further development as potential cancer biomarkers. In this process, **promising candidates could most certainly be discovered**, but it is not the main goal/mission of the pipeline as the overall mission is to facilitate exploration of relevant portions of the cancer proteome at one level by CPTC and more exensively by the research communities