National Cancer Institute

CLINICAL PROTEOMIC
TUMOR ANALYSIS CONSORTIUM

CPTAC Pre-Application Webinar

RFA-CA-15-022

NOTICE (NOT-CA-16-004)

(Proteogenomic Translational Research Centers)

Time/Date: 12:00 p.m. - 2:00 p.m. (ET), Jan 13, 2016

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

http://proteomics.cancer.gov

Agenda

12:00 p.m. - 12:15 p.m.

Welcome and Introductions

Henry Rodriguez, Ph.D., M.B.A.

Office of Cancer Clinical Proteomics Research, NCI, NIH

Progress and Opportunities in Cancer Proteomics

Henry Rodriguez, Ph.D., M.B.A.

Office of Cancer Clinical Proteomics Research, NCI, NIH

Agenda

12:15 p.m. – 1:20 p.m.

Description of RFA-CA-15-022

Mehdi Mesri, Ph.D.

Office of Cancer Clinical Proteomics Research, NCI, NIH

Additional representation

Investigational Drug Branch, Cancer Therapy Evaluation Program

- S. Percy Ivy, M.D., *Phase I Early Therapeutics Clinical Trials Network (ETCTN)*
- Jeff Moscow, M.D., *Phase II Early Therapeutics Clinical Trials Network (ETCTN)*
- James Zwiebel, M.D., *Chief*

Clinical Investigations Branch, Cancer Therapy Evaluation Program

- Elise Kohn, M.D., *National Clinical Trials Network (NCTN)*
- Meg Mooney, M.D., M.B.A., *Chief*

Diagnostic Biomarkers and Technology Branch, Cancer Diagnosis Program

- James Tricoli, Ph.D., *Chief*

Agenda

12:15 p.m. – 1:20 p.m.

Intellectual Property

Tom Stackhouse, Ph.D. and Charles Salahuddin, Ph.D., *Technology Transfer Center*

Financial/Grants Management

Mutema Nyankale, M.B.A., *Office of Grants Administration*

1:20 p.m. - 2:00 p.m.

Questions & Answers

Key Dates & Supporting Materials

Letter of Intent: April 11, 2016 (30 days prior to application due date)

New application receipt date: May 11, 2016, by 5:00 PM local time of applicant organization (no late applications will be accepted)

Letters of Support: At the time of application submission, applicants must provide **letter(s) of support** for access to clinical trial specimens to be used in the proposed research.

- Guidance listed in Supporting Documents: (http://proteomics.cancer.gov/aboutoccpr/fundingopportunities/current/Reissuance-of-Clinical-Proteomic-Tumor-Analysis-Consortium)

- **Reissuance Presentation to NCI Board of Scientific Advisors (BSA)**
  - June 24, 2015: http://videocast.nih.gov/summary.asp?Live=16424&bhcp=1
    - Time stamp: 4h:06min:21sec (40 min session)
- **Archived viewing of slides** (supporting documents website)

Submitting Questions and Updates

Email questions after the presentation to cancer.proteomics@mail.nih.gov

Sign up for updates at http://proteomics.cancer.gov/global/emailsignup

http://proteomics.cancer.gov

FOA Teaming & FAQ Site

Teaming Site

- Web-based system to facilitate initial communications and exploration of collaborative possibilities
  - Go to: http://proteomics.cancer.gov
  - Click on "**FOA Teaming Site**"
  - Participants submit basic set of information:
    - Position
    - Organization
    - General areas of expertise
    - Comments

Frequently Asked Questions (FAQs)

http://proteomics.cancer.gov

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Progress and Opportunities in Cancer Proteomics

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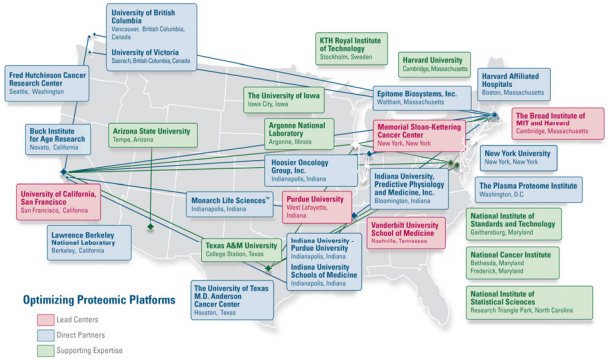
CPTAC program current scope

- NCI Signature Omics Programs (2006)
  - *Genomics:* **TCGA** - understand molecular basis of cancer through genomics. Pilot (3 cancer types) - ovarian, lung, and brain cancer
  - *Proteomics:* **CPTAC** - address lack of analytical rigor & reproducibility and community resources (data and reagents)
- Achieved through…
  - Proteomic Technology Assessment Centers - consortium of labs that coordinate, benchmark, and standardize platforms



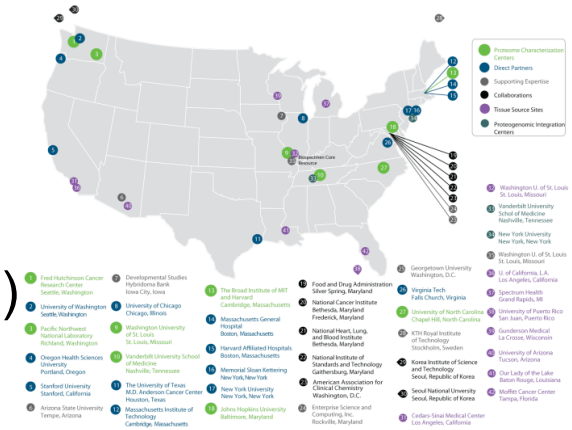
AACC FDA NIST

RIGOR & REPRODUCIBILITY

CPTAC program current scope

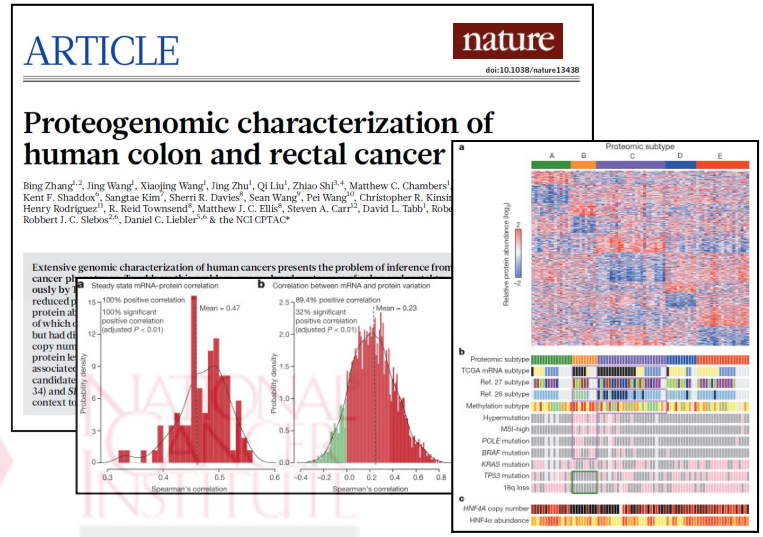
- CPTAC reissued (2011)
  - *Goal:* Elucidate proteogenomic complexity of tumors by identifying proteins that derive from alterations in cancer genomes [TCGA tumors: colorectal, ovarian and breast cancer]
  - *Underlying question:* Would additional biology be elucidated from deep proteomic analysis [CPTAC 1.0] on genomically characterized tumors [TCGA]?

- Achieved through…
  - Proteome Characterization Centers - labs coordinate standardized research activities
  - Community resources (data, assays, reagents)



Selected research highlights

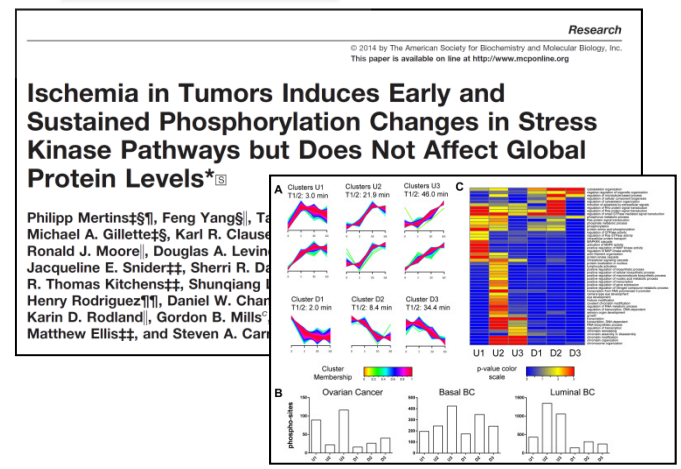
- First comprehensive proteomic characterization of a tumor, with proteogenomic integration[1]
- Completed comprehensive proteomic characterization on two other cancer types (ovarian and breast), with proteogenomic integration (manuscripts under review)
- Understanding tumor pre-analytical variables[2]
- Data publicly available (all studies)


ARTICLE

nature

doi:10.1038/nature13438

Proteogenomic characterization of human colon and rectal cancer


Research

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This paper is available on line at http://www.mcponline.org

Ischemia in Tumors Induces Early and Sustained Phosphorylation Changes in Stress Kinase Pathways but Does Not Affect Global Protein Levels*

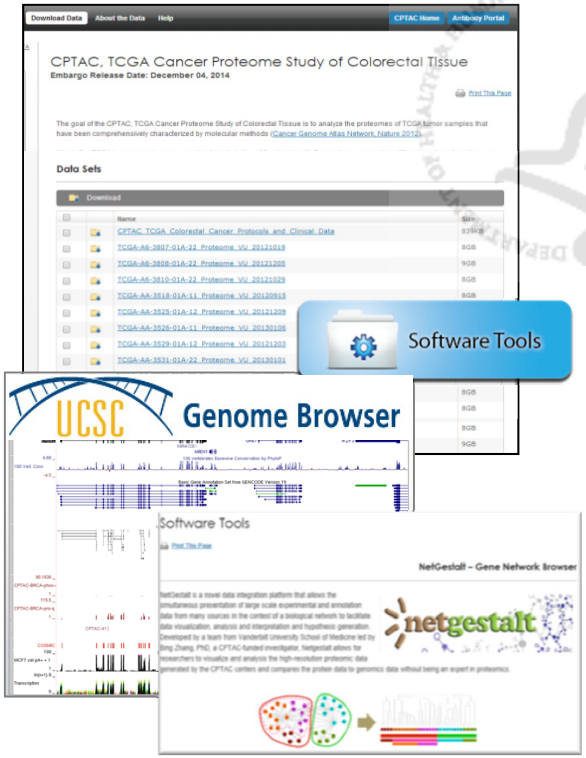
References: [1] Nature. 2014 Sep 18;513(7518):382-387; [2] Mol Cell Proteomics. 2014 Mar;13(3):907-917

Selected benchmark highlights
(generation/dissemination of community resources)

CPTAC Data Portal

6.5 TB raw files
(138 TB equivalent downloaded)

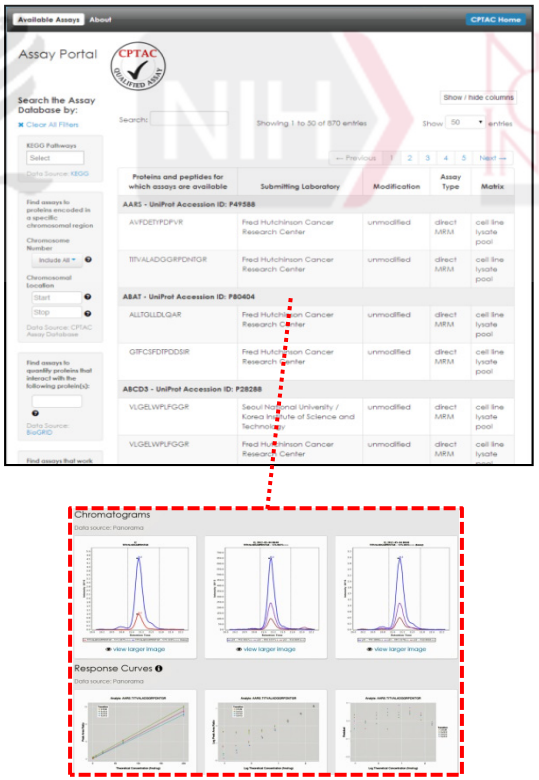
proteomics.cancer.gov



CPTAC Assay Portal

790 "fit-for-purpose" targeted assays
(4,800 users/month)

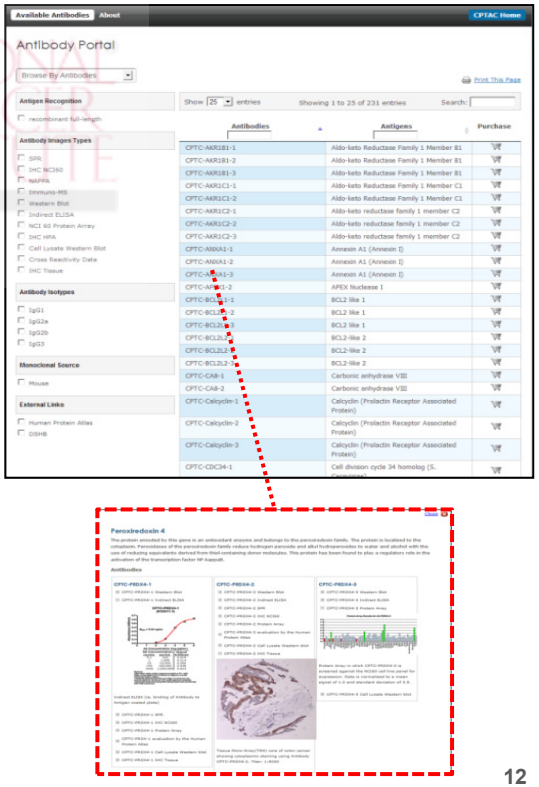
assays.cancer.gov



NCI Antibody Portal

343 mAbs available
(2,171 units distributed)

antibodies.cancer.gov



Cancer genomics aims to advance precision medicine through finding/targeting genetic alterations

- TCGA has analyzed samples from ~11,000 individuals (33 tumor types)
- Identified actionable mutations, therapies

- Not all tumors with actionable mutations respond to targeted therapy
- Many responses are temporary
- Missing biology

Subtype	PIK3CA	TP53	MAP3K1	MAP2K4	GATA3	MLL3	CDH1	PTEN	PIK3R1	AKT1	RUNX1	CBFB	TBX3	NCOR1	CTCF	FOXA1	SF3B1	CDKN1B	RB1	AFF2	NF1	PTPN22	PTPRD
All	36%	37%	8%	4%	11%	7%	7%	3%	3%	2%	4%	2%	3%	3%	3%	2%	2%	1%	2%	3%	3%	1%	2%
Luminal A	45%	12%	13%	7%	14%	8%	9%	4%	0.4%	4%	5%	2%	3%	5%	4%	2%	3%	1%	0.4%	1%	2%	0.4%	2%
Luminal B	29%	29%	5%	2%	15%	6%	5%	4%	2%	2%	2%	2%	4%	2%	2%	2%	0%	1%	3%	2%	4%	2%	4%
HER2-enriched	39%	72%	4%	2%	2%	7%	5%	2%	4%	2%	4%	2%	0%	0%	2%	2%	4%	2%	0%	5%	0%	5%	4%
Basal-like	9%	80%	0%	0%	2%	5%	0%	1%	0%	0%	0%	0%	1%	2%	1%	0%	1%	0%	4%	4%	2%	0%	1%

Percentages of cases with mutation by expression subtype

Integration science for precision medicine/oncology – combining proteomic, genomic & transcriptomic analysis better elucidates the underlying biology of cancer biology and at the subtype level.

What's next for CPTAC (3.0)

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)?

- ***Goal 2:*** **Improve our understanding of tumor resistance /toxicity to therapy, predicting treatment response**
  - Q. Why do some individuals not respond or relapse to therapies, when genomics indicated otherwise?

Overarching Structure of CPTAC 3.0

A. Proteome Characterization Centers

additional cancer types where questions remain on their proteogenomic complexity

5-6
new treatment-naïve cancer types

B. Proteogenomic Translational Research Centers

research models and clinical trial samples

C. Proteogenomic Data Analysis Centers

develop innovative tools that process and integrate data across the entire proteome

Data, assays and resources - community resources

Overarching Structure of CPTAC 3.0

A. Proteome Characterization Centers

additional cancer types where questions remain on their proteogenomic complexity

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B. Proteogenomic Translational Research Centers

research models and clinical trial samples

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C. Proteogenomic Data Analysis Centers

develop innovative tools that process and integrate data across the entire proteome

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Data, assays and resources - community resources

Overarching Structure of CPTAC 3.0

B. Proteogenomic Translational Research Centers

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research models and clinical trial samples

Data, assays and resources - community resources

Governance
(Clinical Proteomic Tumor Analysis Consortium)

- 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, PTRCs, and PGDACs.
- The Committee will be 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 each of the RFAs.**

National Cancer Institute

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RFA-CA-15-022: Proteogenomic Translational Research Centers (U01)

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Purpose of RFA-CA-15-022

[Section I]

- Proteome Translational Research Centers (PTRCs) – multidisciplinary interactive group focused on applying *standardized state-of-the-art proteomic and genomic approaches* to clinically-relevant research projects.

- Projects should focus on proteogenomic aspects in <u>understanding</u> drug responses and resistance to therapies in a clinical context, which <u>may enable</u> better evaluation of novel targeted therapeutics and identification of predictive biomarkers in early stages of drug development/treatments. Therefore, <u>elucidating biological mechanisms of response/resistance</u> that implicate potential predictive biomarkers that would require downstream clinical validation (beyond the scope of this RFA), <u>is responsive</u>.

PTRC Function

- Projects are to be conducted in collaboration with clinical researchers and use human biospecimens from clinical trials.
- Research should involve relevant preclinical models of cancer, integration of proteomic with genomic characterization data, targeted proteomic assay development and application on clinical trial samples.
- PTRCs will interact with two CPTAC sub-programs: Proteogenomic Data Analysis Centers (PGDACs) and Proteome Characterization Centers (PCCs).

PTRC Eligibility Capabilities

Extensive expertise in the standardization of proteomic platforms for both discovery and targeted proteomics required, including

- Ability to ensure rigor and reproducibility in all types of analyses;
- Ability to use a comprehensive proteogenomics-based approach to prioritize proteins/peptides for targeted assay development;
- Expertise in computational proteomic and proteogenomic analysis methods for Level 1-3; and
- Ability to perform complex bioinformatic analyses and interpretation of omics data.

<u>Must designate at least two PDs/PIs</u>: one expert in proteomics and one expert in clinical trials, due to the "team science" approach of the projects.

PTRC Structure

Applications must cover BOTH preclinical studies (using cancer model systems) and studies with clinical biospecimens

Preclinical Research Arm

- Comprehensively characterize and quantitatively measure proteins and their variants along with associated genomics in preclinical cancer model samples

Clinical Research Arm

- Develop and apply quantitative proteomic assays to cancer-relevant proteins identified in Preclinical Research Arm or preliminary data, to clinical trial samples

PTRC Preclinical Research Arm
(Biospecimens)

- Preclinical cancer models such as cell lines and patient-derived xenografts are to be provided by each applicant.
- Established cancer cell lines with documented evidence of preserved phenotypic attributes, with corresponding patient sample molecular signatures may be proposed.
- Models must have corresponding genomic characterization which meets TCGA or equivalent platform standards

  (http://proteomics.cancer.gov/aboutoccpr/fundingopportunities/current/Reissuance-of-Clinical-Proteomic-Tumor-Analysis-Consortium)

PTRC Preclinical Research Arm
(Characterization)

- Comprehensively characterize proteins, PTMs and genetic/genomic aberrations in preclinical cancer models including proteo-genomic integration for the therapeutic agents of interest (pre- and post-treatments).
- Studies expected to build foundation for and drive the design of Clinical Research Arm
- Applicants should plan accomplishing respective preclinical goals early enough to allow for sufficient time (such as at least 2-3.5 years) for the conduct of the clinical studies based on those preclinical findings.

PTRC Preclinical Research Arm
(Characterization)

Explaining "….sufficient time (such as at least 2-3.5 years) for the conduct of the clinical studies…" from previous slide:

- Applicant has adequate preclinical data addressing review criteria, and trial samples at beginning of award period. Applicant can start clinical research arm with no waiting period.
- Applicant to conduct preclinical research. Expected that a PTRC completes preclinical research within 18 months to allow sufficient time to develop/optimize targeted assays and process/analyze trial samples.
- Applicant to develop additional pilot studies to initiate new trials. Expected that all preclinical research be completed by the end of Year 3 to allow sufficient time to accrue and process/analyze trial samples.

PTRC Preclinical Research Arm
(Technology and Platforms)

[Section IV. Sub-section B]

Technology Eligibility Criteria – Analytically Validated

- Successfully deployed in at least one other site (peer-reviewed article);
- Discovery proteomics: capable of generating reproducible results across laboratories in a high-throughput setting;
- Targeted proteomics: capable of generating reproducible, quantitative, and multiplexed assays detecting low abundant proteins.

Quality Assurance/Quality Control

- Detailed plan of metrics used to ensure measurement quality.

Throughput

- Describe analytical capacity and assay development throughput capability.

Data Analysis

- Perform three levels of proteomic data analysis (Level 1-3). Coordination with PGDACs required.

PTRC Clinical Research Arm
(Biospecimens)

- Human specimens from clinical trials provided by each applicant
- **Letters of Support:** At the time of application submission, applicants must provide letter(s) of support for access to clinical trial specimens to be used in the proposed research.
  - For ETCTN and NCTN studies, guidance for letter(s) [URL below]
  - For other NCI-sponsored trials, approval process for obtaining clinical specimens collected during the trial and the investigator's commitment to fulfill these requirements, are to be described.
- Samples can be retrospective from a completed or open (ongoing) trial, prospective from an open trial, or a combination of retrospective with prospective samples.
- Specimens must have clinical data and corresponding genomic characterization which meets TCGA or equivalent platform standards

  (http://proteomics.cancer.gov/aboutoccpr/fundingopportunities/current/Reissuance-of-Clinical-Proteomic-Tumor-Analysis-Consortium)

PTRC Clinical Research Arm
(Characterization)

- Using Preclinical Research Arm data (or other preliminary data), justify/prioritize proteogenomic determinants (e.g. proteins/pathways) implicated in tumor response , resistance, and/or toxicity to treatment.
- Develop and apply targeted quantitative proteomic assays to implicated proteins (e.g. tumor response and/or resistance), in clinical trial samples.
- Studies <u>may address</u> the following types of concepts (Section IV, Sub-section C)
  - Correlative studies (linking proteogenomic patterns before treatment with therapeutic outcomes after such treatment;
  - Comparative proteogenomic analyses (e.g., pharmacogenomic determinations to examine the effects of treatment on specific proteins or pathways before AND after such treatment.

PTRC Clinical Research Arm
(Technology and Platforms)

[Section IV. Sub-section C]

Technology Eligibility Criteria – Analytically Validated

- Successfully deployed in at least one other site (peer-reviewed article)
- Targeted proteomics: capable of generating reproducible, quantitative, and multiplexed assays detecting low abundant proteins.

Quality Assurance/Quality Control

- Detailed plan of metrics used to insure measurement quality.

Throughput

- Describe assay development throughput capability.

Data Analysis

- Perform data analysis of targeted protein measurements in clinical trial in combination with genomic information (coordination with PGDACs required)

PTRC Clinical Research Arm
(Coordination and Pilot Studies)

- Internal program management and coordination of PTRC efforts
- Timeline and milestones
- Communication plan
- Scientific project manager
- Pilot projects (Section IV, Sub-section D)
  - List and justify the areas for which pilot studies are anticipated;
  - No pilot studies are to be proposed in the applications (will be proposed and evaluated for funding post-award)

Experimental Therapeutics Clinical Trials Network

Team Driven. Cancer Therapy Focused.

ETCTN and the early clinical development of NCI-IND agents

Jeff Moscow, M.D.

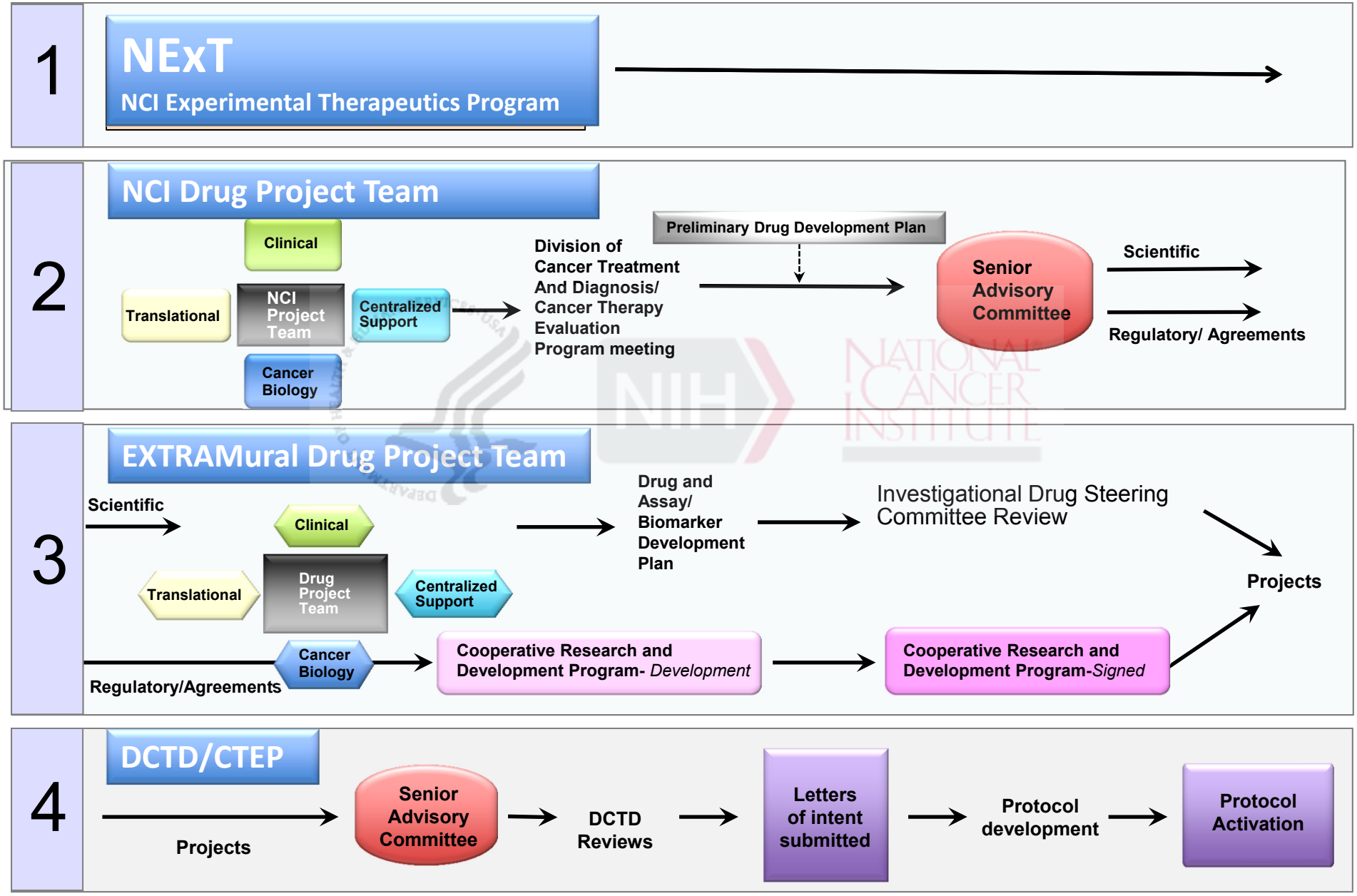
Role of NCI/DCTD in Early Clinical Development of New Cancer Therapies

- NCI/DCTD forms collaborations with Pharma and academic medical centers to develop new anticancer agents and new combinations of agents.
- Underlying concept is that important public health needs are not met by Pharma activities alone – role of NCI/DCTD is to expand indications of novel agents as well as the understanding of their biology
- Many interrelated NCI programs are devoted to this effort, from initial evaluation of proposed collaborations and preclinical development through initial clinical evaluation.
- When NCI agrees to a partnership to develop an agent, NCI assumes regulatory responsibility for the trials it sponsors, and holds IND for these agents (NCI IND agents)

Role of ETCTN in NCI Drug Development

- The Experimental Therapeutics Clinical Trials Network (ETCTN) is a UM1-funded network of clinical trial sites, and associated clinical trials support infrastructure, that is solely devoted to the conduct of the earliest clinical studies of NCI IND agents.
- The ETCTN assures the clinical development of NCI IND agents up to the point of hand-off to NCTN and/or back to Pharma: defining dose, schedule, target expression, engagement and modulation, identification of relevant biomarkers, and demonstration of clinical activity
- The ETCTN maintains a network of experienced investigators focused on mechanism-based early phase studies that require intensive monitoring for safety and intensive intervention for correlative studies

Development Cycle for new NCI-IND agents



ETCTN FAQs

Where are ETCTN sites?

What agents are being developed using the ETCTN?

What clinical trials are active in the ETCTN?

ETCTN agents (NCI-IND agents)

Follow link at:

http://ctep.cancer.gov/protocolDevelopment/agents_drugs.htm

Active ETCTN trials

Doc Number	Principal Investigator	Title
7870	George, Saby	Phase I/II Study of High Dose Interleukin 2, Aldesleukin, in Combination with the Histone Deacetylase Inhibitor Entinostat in Patients with Metastatic Renal Cell Carcinoma
7977	LoRusso, Patricia Mucci	A Phase I Dose-Escalation Study of Oral ABT-888 (NSC #737664) Plus Intravenous Irinotecan (CPT-11, NSC#616348) Administered in Patients with Advanced Solid Tumors
8329	Menefee, Michael E.	A Phase I/II Trial of ABT-888, an Inhibitor of Poly(ADP-ribose) Polymerase (PARP), and Topotecan (TPT) in Patients with Solid Tumors (Phase I) and Relapsed or Refractory Ovarian Cancer or Primary Peritoneal Cancer (Phase II) After Prior Platinum Containing First-Line Chemotherapy
8348	Liu, Joyce Fu	Phase I/II Study of Cediranib and Olaparib in Combination for Treatment of Recurrent Papillary-Serous Ovarian, Fallopian Tube, or Peritoneal Cancer or for Treatment of Recurrent Triple-Negative Breast Cancer
8445	Gajewski, Thomas Frank	A Randomized Phase II Study of Multipeptide Vaccination with or Without IL-12, then Combined with Regulatory T Cell Depletion Using Daclizumab in Patients with Metastatic Melanoma
8484	Shapiro, Geoffrey Ira	Phase 1 Trial of ABT-888 and SCH727965 in Patients with Advanced Solid Tumors
8628	Tarhini, Ahmad A.	A Randomized Phase II Study of Sequential Biotherapy with Aflibercept and High Dose IL-2 Versus High Dose IL-2 Alone in Patients with Inoperable Stage III or Stage IV Melanoma: Efficacy and Biomarker Study
8808	Tawbi, Hussein Abdul-Hassan	An Early Phase 1 Study of ABT-888 in Combination with Carboplatin and Paclitaxel in Patients with Hepatic or Renal Dysfunction and Solid Tumors
8850	Mehnert, Janice M.	A Phase I Trial of Riluzole and Sorafenib in Patients with Advanced Solid Tumors and Melanoma
8871	Ueno, Naoto Tada	Phase I and Phase I Trastuzumab Cohort Study of Entinostat, Lapatinib and Trastuzumab in Patients with Her2-Positive Metastatic Breast Cancer in Whom Trastuzumab Has Failed
8992	Pratz, Keith William	A Pilot Study of Sorafenib in Patients with Acute Myeloid Leukemia as Peri-Transplant Remission Maintenance
9012	Hussain, Maha H. A.	A Randomized Gene Fusion Stratified Phase 2 Trial of Abiraterone with or Without ABT-888 for Patients with Metastatic Castration-Resistant Prostate Cancer
9076	Bible, Keith Christopher	Pharmacokinetic-Driven Individualization of Pazopanib Therapy in Patients with Solid Tumors: A Phase I Study
9157	Kumar, Shaji K.	Phase 1 Clinical Trial of a Novel CDK Inhibitor Dinaciclib (SCH 727965) in Combination with Bortezomib and Dexamethasone in Relapsed Multiple Myeloma
9182	Wahner Hendrickson, Andrea E.	A Phase I Trial of the Combination of the PARP Inhibitor ABT-888 with Intraperitoneal Floxuridine (FUDR) in Epithelial Ovarian, Primary Peritoneal and Fallopian Tube Cancers
9197	Tuscano, Joseph M.	A Phase I Study of Ipilimumab in Combination with Rituximab in Patients with Relapsed/Refractory CD20+ B-Cell Lymphoma
9204	Davids, Matthew Steven	A Phase I/IB Study of Ipilimumab in Patients with Relapsed Hematologic Malignancies After Allogeneic Hematopoietic Cell Transplantation
9214	Smith, B. Douglas	A Phase 1 Study of Ipilimumab in Relapsed and Refractory High Risk Myelodysplastic Syndrome and Acute Myeloid Leukemia with Minimal Residual Disease
9231	Azad, Nilofer Saba	A Phase I Trial of Dinaciclib (SCH727965) and MK-2206 in Metastatic Pancreatic Cancer with an Expansion Cohort in Advanced Pancreatic Cancer
9254	Pollyea, Daniel A.	A Dose Escalation Study of Ibrutinib with Lenalidomide for Relapsed and Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
9268	Jones, Jeffrey Alan	A Multicenter Phase 2 Study of the Bruton's Tyrosine Kinase Inhibitor PCI-32765 (Ibrutinib) for Treatment of Relapsed Hairy Cell Leukemia
9312	Shah, Manisha H.	Phase II Study of Cabozantinib in Patients with Radioiodine-Refractory Differentiated Thyroid Cancer Who Progressed on Prior VEGFR-Targeted Therapy
9322	Dhani, Neesha	A Phase 2 Study of XL184 (Cabozantinib) in Recurrent or Metastatic Endometrial Cancer
9342	Fanale, Michelle Anne	A Phase 1 Trial of MLN8237 Plus Romidepsin for Relapsed/Refractory Aggressive B-Cell and T-Cell Lymphomas

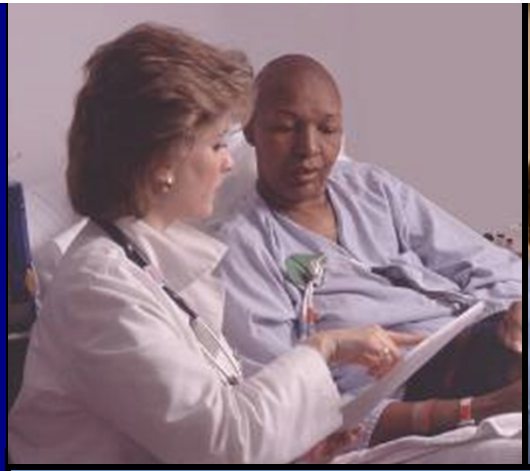
Active ETCTN trials (continued)

Doc Number	Principal Investigator	Title
9377	Ott, Patrick Alexander	A Sequential Safety and Biomarker Study of BRAF-MEK Inhibition on the Immune Response in the Context of Combined CTLA-4 Blockade and PD-1 Blockade for BRAF Mutant Melanoma
9407	Oza, Amit M.	A Phase I Study of the Wee 1 Kinase (Wee 1) Inhibitor AZD1775 (MK-1775) in Combination with Cisplatin and Radiation in Cervical Cancer (10041848, 10008224, 10008328)
9416	Winquist, Eric William	A Randomized Phase II Trial of Cisplatin with or Without Wee1 Kinase Inhibitor AZD1775 (MK-1775) for First-Line Treatment of Recurrent or Metastatic Squamous Cell Cancer of the Head and Neck (RM-SCCHN)
9426	Christian, Beth Ann	A Phase I Study of Ibrutinib (PCI-32765) in Combination with Lenalidomide in Relapsed and Refractory B-Cell Non-Hodgkin's Lymphoma
9434	Kunos, Charles Andrew	Randomized Phase II Study of Intravenous 3-Aminopyridine-2-Carboxaldehyde Thiosemicarbazone (3-AP, Triapine® NSC #663249) Cisplatin-Radiochemotherapy Versus Intravenous Cisplatin-Radiochemotherapy in Women Diagnosed with Stage IB-IVA Cervical Cancer and Stage II-IVA Vaginal Cancer
9443	Jain, Nitin	A Phase 2 Study of MEK 1/2 Inhibitor Trametinib in Combination with AKT Inhibitor GSK2141795 in Acute Myeloid Leukemia (AML) with RAS Mutations
9445	Shoushtari, Alexander Noor	A Randomized Two-Arm Phase II Study of Trametinib Alone and in Combination with GSK2141795 in Patients with Advanced Uveal Melanoma
9448	Lin, Steven H.	A Phase 1 Study of Trametinib in Combination with Chemoradiation for KRAS Mutant Non-Small Cell Lung Cancer
9455	Ramaswamy, Bhuvaneswari	A Single Arm, Phase II Study of Single Agent Trametinib Followed by Trametinib in Combination with GSK2141795 in Patients with Advanced Triple Negative Breast Cancer
9458	Wuthrick, Evan John	A Phase 1 Study of Trametinib in Combination with Radiation Therapy for Brain Metastases from KRAS-, BRAF-, NRAS- or HRAS- Mutant Malignancies
9460	Trudel, Suzanne	A Phase 2 Study of Sequential Trametinib and GSK2141795 in Relapsed or Refractory Multiple Myeloma
9466	Sullivan, Ryan Joseph	Phase I/II Study of Dabrafenib, Trametinib, and Navitoclax in BRAF Mutant Melanoma and Other Solid Tumors
9524	Gojo, Ivana	A Phase I Study of Pomalidomide Given at the Time of Lymphocyte Recovery Following Induction Timed Sequential Chemotherapy with Cytarabine, Daunorubicin and Etoposide (AcDVP16) in Patients with Newly Diagnosed Acute Myeloid Leukemia (AML) and High-Risk MDS
9525	Corcoran, Ryan Bruce	An Open Label, Two-Part, Phase Ib/II Study to Investigate the Safety, Pharmacokinetics, Pharmacodynamics, and Clinical Activity of the MEK Inhibitor Trametinib and the BCL2-Family Inhibitor Navitoclax (ABT-263) in Combination in Subjects with KRAS Mutation-Positive Advanced Solid Tumors
9543	Burger, Jan A.	A Phase 2 Study to Determine the Efficacy of the BTK Inhibitor Ibrutinib (PCI-32765) in Patients with Relapsed or Refractory Precursor-B Lymphoblastic Leukemia (B-ALL)
9552	Nayak, Lakshmi	A Phase 1 Study of MLN0128 and Bevacizumab in Patients with Recurrent Glioblastoma and Other Solid Tumors
9557	Sullivan, Ryan Joseph	Phase I Study of AT13387 in Combination with Dabrafenib and Trametinib in BRAF-Inhibitor Resistant Patients with BRAF-Mutant Melanoma and Other Solid Tumors.
9568	Oza, Amit M.	A Randomized Placebo-Controlled Phase II Trial Comparing Gemcitabine Monotherapy to Gemcitabine in Combination with AZD 1775 (MK 1775) in Women with Recurrent, Platinum Resistant Epithelial Ovarian, Primary Peritoneal or Fallopian Tube Cancers
9585	Naing, Aung	Phase I Study of MLN0128 (NSC# 768435) in Combination with Ziv-Aflibercept (NSC# 724770) in Patients with Advanced Cancers
9603	Hofmeister, Craig C.	Pilot Trial Evaluating Viral Protein Production from the Combination of Reolysin and Carfilzomib in Multiple Myeloma
9604	Yao, James C.	Perfusion CT as Predictive Biomarker in a Phase II Study of Ziv-Aflibercept in Patients with Advanced Pancreatic Neuroendocrine Tumors
9676	Hodi, Frank Stephen	A Phase 1 Trial of MK-3475 Plus Ziv-Aflibercept in Patients with Advanced Solid Tumors
9571	Lieu, Christopher Hanyoung (48508)	A Phase IB Study of the Combination of AZD6244 Hydrogen Sulfate (Selumetinib) and Cyclosporin A (CsA) in Patients with Advanced Solid Tumors with an Expansion Cohort in Metastatic Colorectal Cancer
9608	Costello, Brian A. (44889)	A Phase I Trial of ABT-263, a Bcl-2 Inhibitor, and Sorafenib (Nexavar) in Patients with Relapsed or Refractory Solid Organ Tumors

Active ETCTN trials (continued)

Doc Number	Principal Investigator	Title
9653	Sadeghi, Sarmad (51958)	Phase II Trial of Gemcitabine-Eribulin (GE) in Cisplatin Ineligible Patients with Advanced or Unresectable Urothelial Carcinoma of the Bladder
9591	Siu, Lillian L. (26530)	A Phase I Trial of Single Agent Trametinib (GSK1120212) in Advanced Cancer Patients with Hepatic Dysfunction
9343	Ramanathan, Ramesh (26095)	A Phase 1 and Pharmacokinetic Study of Dabrafenib (GSK2118436B) in Patients with BRAFV600X Mutations and Renal or Hepatic Dysfunction
9676	Hodi, Frank Stephen (28040)	A Phase 1 Trial of MK-3475 Plus Ziv-Aflibercept in Patients with Advanced Solid Tumors
9672	George, Suzanne (32628)	Phase II Trial of Nivolumab in Advanced Uterine Leiomyosarcoma
9673	Eng, Cathy (31954)	A Multi-Institutional Phase 2 Study of Nivolumab in Refractory Metastatic Squamous Cell Carcinoma of the Anal Canal **Closed to Patient Accrual**
9008	Connolly, Roisin M. (47379)	A Phase 1 and Pharmacokinetic Single Agent Study of Romidepsin in Patients with, Lymphomas, Chronic Lymphocytic Leukemia and Select Solid Tumors and Varying Degrees of Liver Dysfunction
9846	Doroshow, James H. (12131)	Patient-Derived Models Tissue Procurement Protocol for the National Cancer Institute (NCI)
9706	Liu, Hongtao (42318)	Randomized Phase II Study to Assess the Role of Nivolumab as Single Agent to Eliminate Minimal Residual Disease and Maintain Remission in Acute Myelogenous Leukemia Patients After Chemotherapy
9681	Apolo, Andrea Borghese (46793)	Phase 1 study of CaboNivo or CaboNivoIpi in Metastatic Urothelial and Genitourinary Cancer
9742	Ma, Brigette Buig-Yue (34980)	Multicenter Phase II Study of Nivolumab in Previously Treated Patients with Recurrent and Metastatic Nasopharyngeal Carcinoma (NPC)
9782	Wisinski, Kari Braun (42375)	A Phase 1 Study of BMN 673 in Combination with Carboplatin and Paclitaxel in Patients with Advanced Solid Tumors
9837	Koczywas, Marianna (27105)	Phase I Study of TRC102 in Combination with Cisplatin and Pemetrexed in Patients with Advanced Solid Tumors, with Expansion Cohort in Mesothelioma / Phase II Study of TRC102 with Pemetrexed in Patients Refractory to Cisplatin and Pemetrexed
9853	Danielle Shafer (39691)	A Phase I Trial of Belinostat and AZD-1775 in Relapsed/Refractory AML, CML-BC or MDS and Selected Poor-Prognosis Subsets of Patients with Previously Untreated AML
9824	Goff, Laura Williams (41055)	A Phase 1 Study of Alisertib in Combination with mFOLFOX in Gastrointestinal Tumors
9855	Patel, Sapna Pradyuman (46800)	A Phase 2 Study of Glembatumumab Vedotin for Metastatic Uveal Melanoma
9874	Hope, Andrew J. (41569)	A Phase I Trial of AT13387 in Patients with Locoregionally Advanced Squamous Cell Carcinoma of the Head and Neck (LA-SCCHN) Receiving Concurrent Radiation and Cisplatin **Temporary Closure**
9844	Connolly, Roisin M. (47379)	A Phase 1 Study Evaluating Safety, Tolerability, and Preliminary Antitumor Activity of Entinostat and Nivolumab with or without Ipilimumab in Advanced Solid Tumors
9825	Liu, Joyce Fu (42430)	A Phase 2 Study of Olaparib and Cediranib for the Treatment of Recurrent Ovarian Cancer

National Cancer Institute



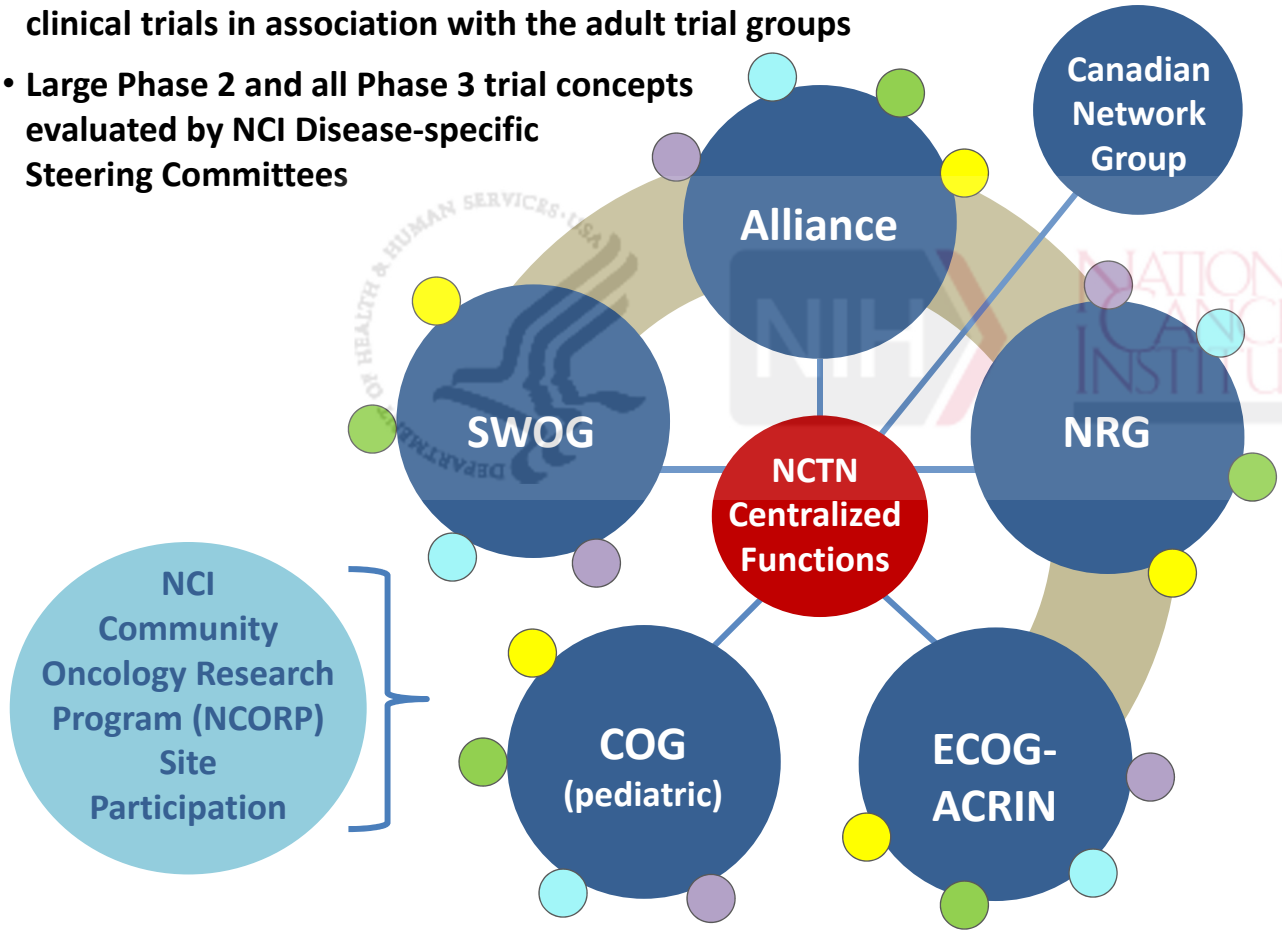
NCI National Clinical Trials Network (NCTN)
Brief Overview

Meg Mooney, M.D., M.B.A.

NCTN Structure as of March 1, 2014

- 5 US groups (4 adult & 1 pediatric) and 1 Canadian group
- Centralized functions for operational efficiencies
- Optimized use of scientific innovations
- 30 Lead Academic Participating Sites (LAPS) provide leadership in development and accrual & conduct of clinical trials in association with the adult trial groups
- Large Phase 2 and all Phase 3 trial concepts evaluated by NCI Disease-specific Steering Committees

≈ 2400 enrolling sites across North America (plus other international sites)



LEGEND:

- Centralized Functions:
  - Centralized Institutional Review Board
  - Cancer Trials Support Unit
  - Radiotherapy/Imaging Cores
  - Common Data Management System Central Hosting
- 30 Lead Academic Participating Sites (LAPS)
- Operations
- Statistics & Data Management
- Tumor Banks
- Member Sites

http://www.cancer.gov/clinicaltrials/nctn

NCTN Group Operations Center & Associated Statistics/Data Mgt Centers Awardees

Network Group Operations Ctrs		Associated Network Group Stats/Data Ctrs	
Name	**Institution (PI)**	**Name**	**Institution (PI)**
Children's Oncology NCTN Network Group Operations Ctr	Children's Hospital of Pennsylvania Adamson, Peter	Children's Oncology Group Statistics & Data Center	U of Florida Devidas, Meenakshi
NRG Oncology Network Group Operations Ctr	NRG Oncology Foundation Wolmark, Norman (contact)	NRG Oncology Network Group Statistics & Data Mgt Center	University of Pittsburgh) Costantino, Joseph (contact)
SWOG Network Group Operations Ctr of the NCTN	Oregon Health & Sci U Blanke, Charles (contact)	SWOG Statistics & Data Mgt Center	Fred Hutch CRC LeBlanc, Michael
Alliance for Clinical Trials in Oncology Operations Ctr	Brigham & Women's Bertagnolli, Monica (contact)	Statistics and Data Ctr for the Alliance for Clinical Trials in Oncology	Mayo Clinic Sargent, Daniel
ECOG- ACRIN Operations Ctr	ECOG-ACRIN Medical Research Foundation Comis, Robert (contact)	ECOG-ACRIN Network Group Statistics & Data Mgt Ctr	Dana-Farber CI Gray, Robert
NCIC-Clinical Trials Group Ctr (Canadian Collaborating Clinical Trials Network Group)	Queen's University at Kingston, Ontario, CA Dancey, Janet	(included in single grant)	

Basic Network Operating Principles

- Network Groups maintain their individual research agendas and internal processes for many activities (e.g., group membership requirements, contract/agreements with their members)
- Clinical trials are conceived, developed, & conducted during the project period for NCTN Program (competitive renewal Q 5 years)
- All qualified full members of any Network Group can participate in any Network phase 3 trial & select phase 2 trials
- All phase 3 trials and most phase 2 studies are reviewed by the NCI Central IRB
- All active trials use centralized regulatory system & centralized patient enrollment system and new trials are developed in the Network's common, electronic data management system (Medidata RAVE)

NCTN Group Operations Center Grants

- All NCTN grants are Cooperative Agreements (U10s)
- Scientific evaluation by peer-review at time of grant application is of the NCTN Group's role in national network, overall scientific strategy, innovation and quality
- Review criteria also focus on operational efficiency & collaborative management of Network
- Individual phase 3 and large phase 2 trials are evaluated and prioritized during the grant's project period by NCI Disease-specific Steering Committees
- Associated Tumor Banks for the NCTN Groups are funded via U24 grants

Integrated National Biospecimen Banks for NCTN

- **In general, all data & biospecimen collection go to the lead Network Group conducting the trial and are stored in the associated NCTN Group Bank**
- **Biospecimens are collected for integral and integrated studies as defined in the study protocol with full statistical analysis plans**
- **Optional collections of biospecimens are also included in select trials & are available for future correlative science projects after primary results are released from the trial**

New Uses of Specimens Collected in NCTN Trials

- Per the Terms of Award for NCTN grants:
  - ✓ On-going trials may be amended to include an integral or integrated correlative science aim that requires biospecimens
  - ✓ Access to optional collections may be requested for new correlative science studies after primary results of the trial have been released; these requests are evaluated by the NCTN Core Correlative Science for scientific merit
- For the CTPAC RFA, applicants must submit a Letter of Support from the NCTN Group Chair (PI) confirming that the NCTN Group will collaborate with the investigator to either submit an amendment for an on-going NCTN trial to NCI/CTEP for approval or an ancillary correlative science proposal for a trial with banked specimens available to the NCTN Core Correlative Science Committee for approval should the CTPAC proposal be selected.
- Please Note: Approval of an CTPAC project does NOT guarantee approval by the appropriate NCTN process/procedure.

FAQs specific to RFA-CA-15-022

What qualifies as an NCI-sponsored trial?

Answer: "NCI-sponsored" in the context of clinical trials means all clinical trials either financially supported by the NCI for any part of research (excluding support for infrastructure and grants for NCI-designated Cancer Centers), or carried out under an NCI-held IND. 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.

FAQs specific to RFA-CA-15-022

Are non-NCI-sponsored trial samples allowed?

Answer: Other types of human biospecimens from non-NCI-sponsored clinical trials may be used in an auxiliary role.

Are applicants allowed to partner with one or more clinical trials?

Answer: Yes, permitting that the PTRC allows for the complete interrogation (data production and analyses) of all samples within the timeline specified in this FOA.

FAQs specific to RFA-CA-15-022

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

Answer: Yes. NCI intramural trials are responsive to RFA-CA-15-022. Intramural trials are to be coordinated through Dr. William Dahut, Clinical Director of NCI's Center for Cancer Research (dahutw@mail.nih.gov)

FAQs specific to RFA-CA-15-022

Are PTRCs to focus only on molecularly targeted "nextgen" cancer therapies (e.g. specific monoclonals or TKIs), or could conventional chemotherapies (e.g. cisplatinum, Doxorubicin, Fluorouracil), preventative vaccine trials and/or radiation therapy also be considered responsive?

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

FAQs specific to RFA-CA-15-022

With respect to chemotherapies, are all of the drugs (conventional and nextgen) listed on the NCI site (http://www.cancer.gov/about-cancer/treatment/drugs) eligible for study by a CPTAC PTRC?

Answer: Yes, provided they are in a NCI-sponsored trial. In addition, a listing of approved agents for ETCTN trials are referenced in a file located at http://proteomics.cancer.gov/aboutoccpr/fundingopportunities/current/Reissuance-of-Clinical-Proteomic-Tumor-Analysis-Consortium, under Supporting Documents (File Name: Active ETCTN trials), while additional agents that include investigational agents under NCI's Cancer Therapy Evaluation Program IND are listed at the following website http://ctep.cancer.gov/protocolDevelopment/agents_drugs.htm (File Name: CTEP Agents and Active Agreements, MS Excel).

FAQs specific to RFA-CA-15-022

Preclinical Research Arm: Must it be cell lines or mouse models?

Answer: It could be either or both.

Data analysis: What level of data analysis are required by PTRCs and how is it related to PGDAC (RFA-CA-15-023) analysis?

Answer: Data analyses by a PTRC are required for all three levels as defined in the RFA. PTRC awards are expected to interact with PGDAC awardees to coordinate prioritization of protein candidates ultimately approved by the Protein Candidate Selection Sub-committee and the Steering Committee to avoid duplicative efforts for targeted assay development.

FAQs specific to RFA-CA-15-022

For PTRCs, please clarify whether the goal is to identify predictive biomarkers of response/resistance/toxicity to therapies (requiring clinical testing and appropriate statistical power), or is the goal to elucidate biological mechanisms of response/resistance/toxicity and thereby implicate potential predictive biomarkers that would require downstream clinical validation (beyond the scope of this RFA)?

Answer: Elucidating biological mechanisms of response / resistance / toxicity that implicate potential predictive markers that would require downstream clinical validation (beyond the scope of RFA-CA-15-022), would be responsive.

FAQs specific to RFA-CA-15-022

In Section IV. 2. PHS398 Research Plan the PTRC RFA mentions drug toxicity, whereas the rest of the RFA only discusses response/resistance. Would a study of mechanisms of toxicity to cancer therapies be considered responsive to this RFA, or only studies of response/resistance?

Answer: Yes – mechanisms of toxicity would be responsive.

FAQs specific to RFA-CA-15-022

How do non-clinical applicants team up with clinicians? Are pathologists considered as a qualified clinician PI?

Answer: Yes, as long as the pathologist is familiar with unmet clinical needs, clinical trials, and access to trial samples (see section SF424(R&R) Senior/Key Person Profile). In addition, a FOA Teaming Site at http://proteomics.cancer.gov has been developed to facilitate interactions between proteomicists, genomicists, and clinicians. In addition, applicants are encouraged to contact NCI's clinical trial point-of-contacts listed in the RFA.