The Partnership for Accelerating Cancer Therapies (PACT): A Public-Private Partnership to Aid Standardization of Immune Therapy Biomarkers

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Foundation for National Institutes of Health

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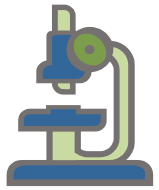
FNIH
Foundation for the National Institutes of Health

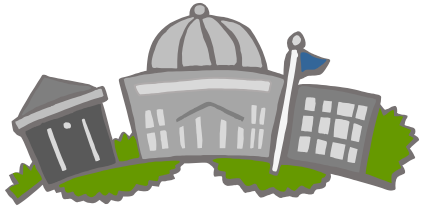
Snapshot of the Foundation for the National Institutes of Health (FNIH)

1996

established by Congress to support NIH in its mission by



advancing biomedical research and training collaborations



among government, universities, industry and not-for-profit organizations

FNIH
Foundation for the National Institutes of Health

501(c)(3)

Non-governmental not-for-profit & independent Board of Directors

Over 550

projects supported

120+

active research partnerships, scientific education/training, conferences/events and capital programs

$1 billion

raised by the FNIH since 1996

93%

of funds directly support programs

13 years

of outstanding Charity Navigator ratings

Current Public-Private Partnerships at the FNIH

- **Accelerating Medicines Partnership** — $230 million
  NIH (OD), NIA, NIAMS, NIDDK, 10 companies, 9 not-for-profit organizations
- **Partnership for Accelerating Cancer Therapies** — $220 million
  NIH (OD), NCI, PhRMA, 10+Companies, 3+ Foundations
- **Grand Challenges in Global Health (GCGH)** — $201 million
  Bill & Melinda Gates Foundation
- **Lung-MAP: Master Lung Protocol Trial** — $163 million
  NCI (SWOG), FDA, Friends of Cancer Research, 5 companies to date
- **Alzheimer's Disease Neuroimaging Initiative (ADNI)** — $148 million
  NIA, NIBIB, 25+ companies, 3 not-for-profit organizations
- **Vector-Based Control of Transmission (VCTR)** — $78 million
  VRC/NIAID, Bill & Melinda Gates Foundation
- **The Biomarkers Consortium** — $73 million
  FDA, NIH, CMS, PhRMA, BIO, pharmaceutical and nutrition companies, not-for-profit organizations
- **Comprehensive T Cell Vaccine Immune Monitoring Consortium (CT-VIMC)** — $50 million
  Bill & Melinda Gates Foundation, NIAID
- **MAL-ED: The Interactions of Malnutrition and Enteric Infections, Effect on Childhood Development** — $46 million
  Bill & Melinda Gates Foundation, Fogarty Institute Center (NIH)

TOTAL: $1.209 billion

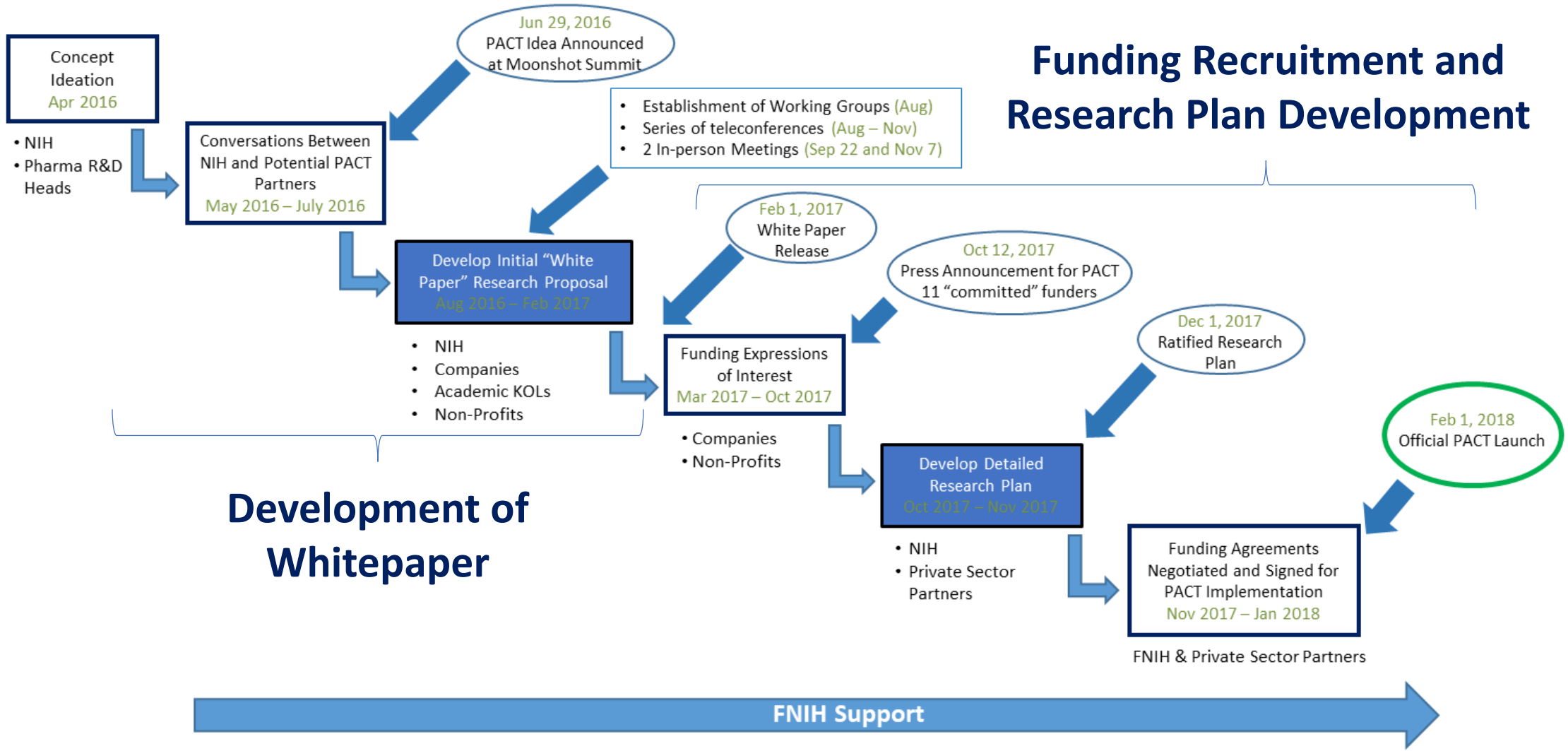
NOTE: Partnerships highlighted in green are part of the FNIH cancer portfolio.

Partnership for Accelerating Cancer Therapies (PACT)

- AbbVie
- Amgen
- BMS
- Boehringer-Ingelheim
- Celgene
- Genentech
- Gilead
- GSK
- Janssen
- Novartis
- Pfizer
- Sanofi
- NCI
- FDA
- PhRMA
- CRI
- FNIH

As a part of the Cancer Moonshot, NIH/NCI, FDA, and 12 industry partners have developed a 5-year, $220 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT) that will be managed by FNIH to enable a systematic cross-sector effort to identify and develop robust, standardized biomarkers and related clinical data that support the selection and testing of promising therapeutic combinations.

PACT Design Phase Process

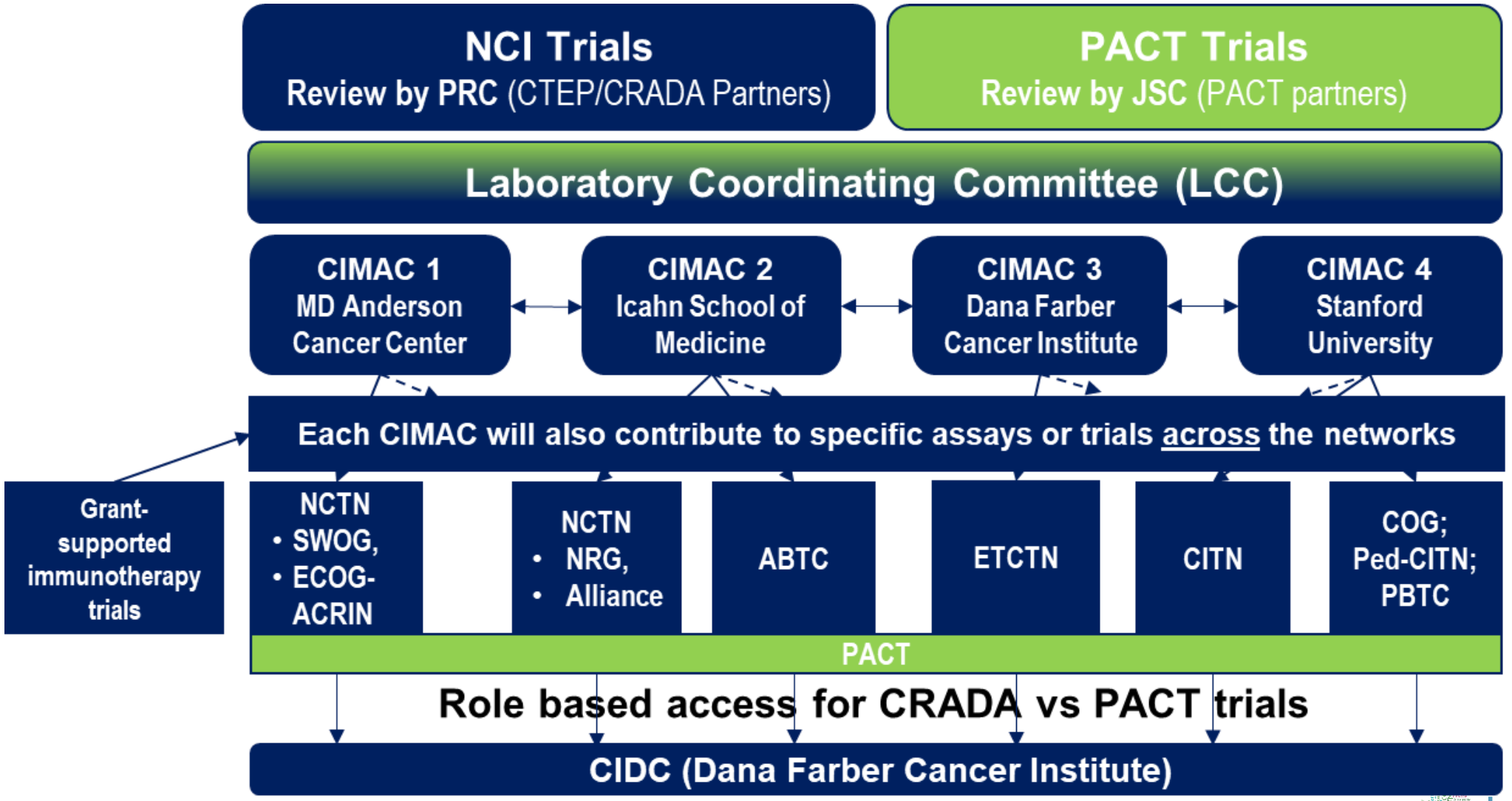


PACT Overview

***Overall goal:* Provide a systematic approach to immune and related oncology biomarker investigation in clinical trials by supporting development of standardized biomarkers and assays**

- PACT will leverage recent NCI investments in its CIMAC-CIDC Network to select basic biomarkers for uniform clinical application, develop standardized biomarkers for immunoprofiling and exploratory biomarker assays of high relevance, and make this biomarker data available to research in comprehensive database.
- PACT will provide scientific coordination by facilitating information sharing by all stakeholders to coordinate investigative approaches, avoid duplication of effort, share resources, and enable more relevant high-quality trials to be conducted via active outreach to other IO research efforts
- PACT will engage FDA in its biomarker standardization and harmonization efforts in order to enhance regulatory decision-making

PACT Integration into CIMAC Network Structure

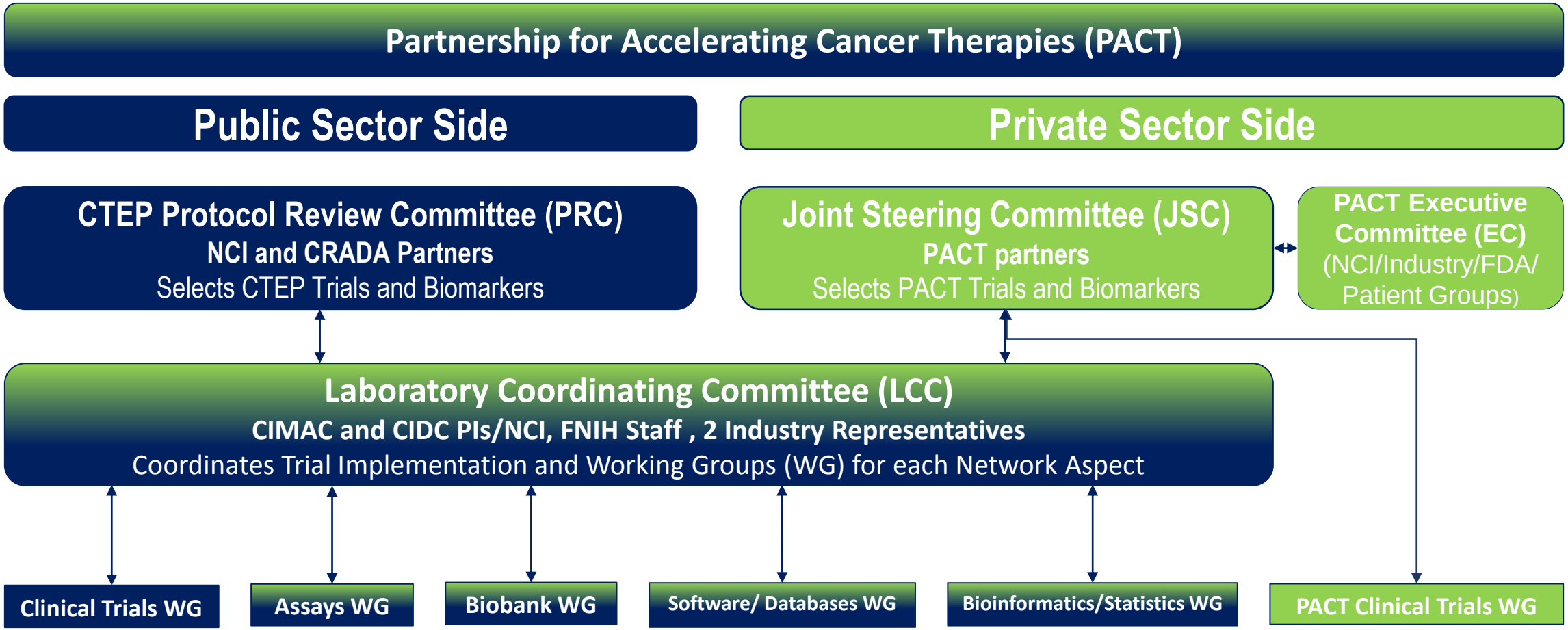


PACT Funding Will Enhance NCI Investments

PACT private sector funding will enable the following:

- Supplement NCI funding to its 4 already selected core laboratories to conduct and standardize biomarker assays in order to develop standardized biomarkers for immunoprofiling
- Develop additional exploratory IO biomarker assays of high relevance using the CIMACs
- Incorporate biomarkers and data collection standards into clinical trials prioritized through PACT
- Enhance the CIDC database by adding additional capabilities to store and manage biomarker and clinical data
- Provide a quarterly IO trial “landscape analysis” (conducted by CRI)
- Share information across all stakeholders by providing a forum for coordination with other IO research efforts

PACT Governance Structure



The JSC will select two private sector members to serve on each of the Working Groups based on qualifications of nominees submitted by participating companies.

PACT Biomarker Modules

Biomarkers were grouped in “modules”, a set of analyses built around specific biological topics or areas of inquiry.

Basic modules are fundamental to investigating specific aspects of cancer biology and building baseline data for how immunotherapy treatments effect this biology, have current clinical utility, and should be executable by the majority of trial sponsors.

Exploratory modules test novel or less well-established markers, and represent an expansion into new areas of science or technology. They are meant to address a specific biology question to each specific trial. *Exploratory modules are optional.*

PACT Proposed Biomarker Module List

Biomarker modules are comprised of two types:

1) basic biomarkers (i.e. commonly used or standard)
2) expansion biomarkers (i.e. exploratory) which can be added on an optional basis

Module	Content
1a	Immune Cell Biology – Basic (required)
1b	Immune Cell Biology – Expansion (optional)
1c	Cytokines / Chemokines Periphery – Basic (required)
2a	Cancer Genetics / Somatic Mutations – Basic (required)
2b	Cancer Genetics / Somatic Mutations – Expansion (optional)
3a	Transcriptomic Characterization of the Tumor Microenvironment – Basic (required)
3b	Transcriptomics of the Tumor Microenvironment – Expansion (optional)
4	Liquid Biopsy (CTC, cfDNA, exosomes) – Basic (required)
5	Defining the Microbiome – Basics (required)
6	Non-immune Tumor Architecture - Basics (required)

National Cancer Institute

CIMAC-CIDC Network Assays

Version date: April 13, 2018

Black text = Tier 1 assays (broadly recommended for most trials)

Gray text = Tier 2 assays (other assays, usage depends on trial)

Tissue Imaging				
Multiplex immunohistochemistry and immunofluorescence	**Dana-Farber**	**MD Anderson**	**Mt Sinai**	
Conventional immunohistochemistry	Dana-Farber	MD Anderson	Mt Sinai	Stanford
Multiplexed Ion-Beam Imaging (MIBI)			Mt Sinai (soon)	Stanford
Cell Profiling				
Mass Cytometry (CyTOF)	**Dana-Farber**		**Mt Sinai**	**Stanford**
High-dimensional flow cytometry	Dana-Farber	MD Anderson	Mt Sinai	Stanford
ELISpot	Dana-Farber	MD Anderson	Mt Sinai	
Sequencing				
RNA-Seq	**Dana-Farber**	**MD Anderson**		
NanoString	**Dana-Farber**	**MD Anderson**	**Mt Sinai**	
Whole Exome Sequencing	**Dana-Farber**	**MD Anderson**		
TCR/BCR clonality	Dana-Farber	MD Anderson	Mt Sinai	
Single-cell TCRseq	Dana-Farber			Stanford
HLA-Seq; Epitope prediction	Dana-Farber		Mt Sinai	
ISH DNA/RNA		MD Anderson		
Neoantigen Prediction	Dana-Farber		Mt Sinai	
Cell-free DNA (circulating tumor DNA)	Dana-Farber	MD Anderson		
Epigenomics (ATAC-Seq)				Stanford
HTG-EdgeSeq (gene expression)		MD Anderson		
Microbiome (16S Deep Sequencing)		MD Anderson	Mt Sinai	
Single-cell transcriptome	Dana-Farber		Mt Sinai	
Cytokines/Serum Analytes				
O-link serum cytokine analysis			**Mt Sinai**	
Luminex	Dana-Farber	MD Anderson	Mt Sinai	Stanford
Seromics-ELISA/Grand serology			Mt Sinai	
MesoScale Discovery		MD Anderson		

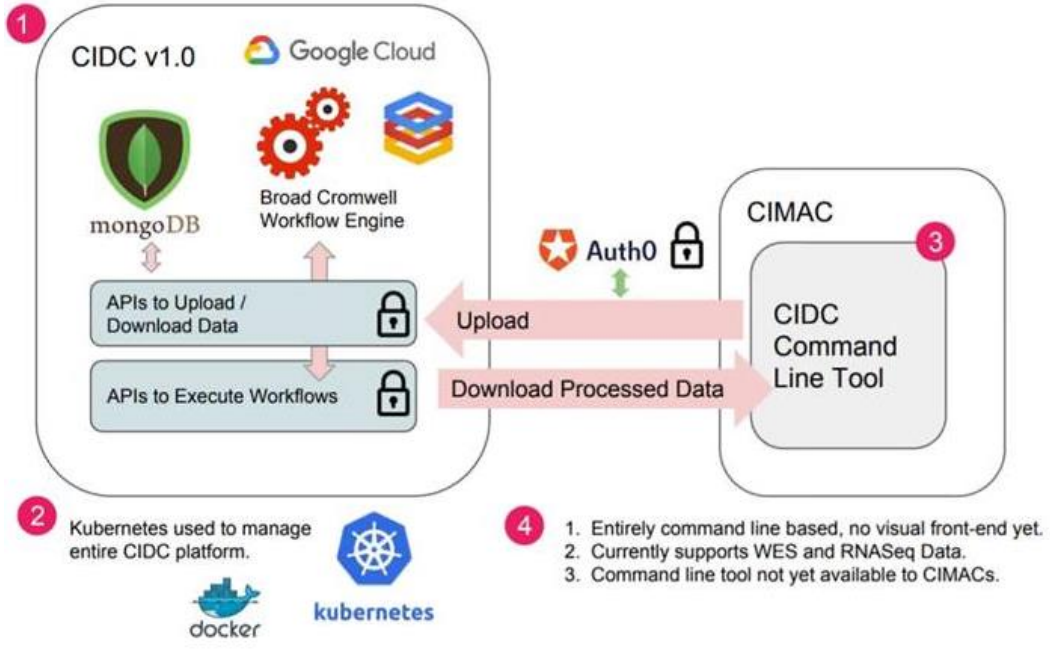
PACT Clinical Trial Selection

- CTEP trials focused on Phase Ib/early Phase II
- PACT Trial Selection Working Group will consider multiple trial types (depending on those prosed):
  - Phase Ib – Novel Combinations
  - Multi-arm Umbrella/Basket Trials of Phase Ib with a common standard of care arm
  - Small randomized Phase II
  - Large randomized Phase II/III
- Trial selection process will be nimble, flexible, and general to be able to review all types
- PACT will consider funding biomarkers in trials of IO/IO combination, IO/targeted combinations, IO single agents, and other IO therapies

National Cancer Institute

CIDC – Cancer Immunologic Data Commons

- Coordinate the adoption of assay protocols and data format standards
- Centralized Data Repository and Management System
- Centralized Sample Management and Tracking
- Uniform bioinformatics pipelines and computing infrastructure for the CIMACs
- Bioinformatics algorithms to enable integrative analysis
- Data Access and Application Programming Interfaces
- Data visualization capabilities for investigators
- CIMAC Network Logistics



Data Sharing Structure for PACT

Tiered Data Access Structure

- Trial investigators and trial Sponsors
- PACT Partners
- Public

Next Steps for PACT

- Trial Recruitment
  - Participating companies
  - Existing CTEP CRADA Trials
  - IIS Trials
  - Other clinical trial networks: Parker Institute, CRI, others
- PACT Trial Selection
  - Developing trial review process
  - Developing appropriate potential trial intake forms and other necessary documents
- Creation of an RFA to Solicit Proposals for Novel Biomarkers

BACK-UP SLIDES

FNIH
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PACT Executive and Joint Steering Committees

PACT Executive Committee (EC)
(NCI/Industry/FDA/Patient Groups)

Voting Members

Francis Collins (NIH-OD)
Ned Sharpless (NCI-OD)
Jim Doroshow (NCI-DCTD)
Axel Hoos (GSK)
Edith Perez (Genentech)
Tom Hudson (AbbVie)
Nancy Roach (Fight CRC)

Non-Voting Members

Richard Pazdur (OCE)
Peter Marks (CBER)

Ex-officio Members: JSC Co-Chairs

Jeff Abrams (NCI-CTEP)
Peter Hammerman (Novartis)

PACT Joint Steering Committee (JSC)
(NCI/FDA/Industry/Patient Advocate)

Voting Members

- *Jeff Abrams (NCI-CTEP)**
- *Peter Hammerman (Novartis)**
- Helen Chen (NCI-CTEP)
- Magdalena Thurin (NCI-CTEP)
- David Patton (NCI-CBIIT)
- Tony Kerlavage (NCI-CBIIT)
- Ena Wang (AbbVie)
- Greg Friberg (Amgen)
- Michael Carleton (BMS)
- Pilar Garin-Chesa (BI)
- Derek Blair (Celgene)
- *David Shames (Genentech)+*
- *Scott Patterson (Gilead)+*
- James Smothers (GSK)
- Matt Lorenzi (Janssen)
- Darrin Beaupre (Pfizer)
- Marielle Chiron (Sanofi)
- Nancy Goodman (Kids v Cancer)
- Andrea Ferris (LUNGevity)

Non-Voting Members

- Gideon Blumenthal (FDA-OCE)
- Marc Theoret (FDA-CDER)
- Reena Philip (FDA-CDRH)
- Ke Liu (FDA-CBER)
- Eunice Lee (FDA-CDRH)
- Anand Pathak (FDA-CDRH)
- Alexander Ehlgen (BI)
- TunTun Li (Sanofi)

**Co-Chairs*
+LCC Representatives

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PACT Proposed Biomarkers

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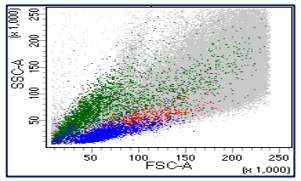
Module 1 (Basic): Immune Cell Biology – Periphery

Cell Based

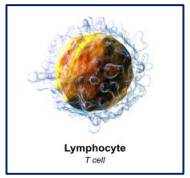


Flow Cytometry
- Immune Phenotyping
  - T-Cell phenotypes
  - T- Cell Activation
  - T-Cell Exhaustion
  - B-Cells
  - Granulocytes
  - DCs
  - MDSCS
- PD Assays for MoA
  - TCR diversity

Flow Cytometry

T cell marker panels by Flow Cytometry		
Activation	**Exhaustion**	**Functional**
Live or dead	**Live or dead**	**Live or dead**
CD3	**CD3**	**CD3**
CD4	**CD4**	**CD4**
CD8	**CD8**	**CD8**
CD45RO	**CD45RO**	**IFNg**
CD69	**LAG3**	**TNFα**
ICOS	**TIM3**	**GZMB**
OX40	**CD161**	**IL-2**
FoxP3		
CD127		

Functional

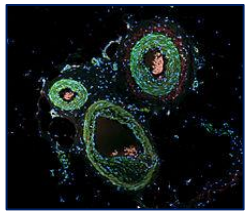


In Vitro Functional Characterization of PBMCs
- Ag recall
- Epitope Spreading
- MLRs

Necessary Specimen Collection:
- PBMCs (Blood)

Module 1 (Basic): Immune Cell Biology – Tumor

Tissue



Functional & Spatial Characterization of Immune Cells

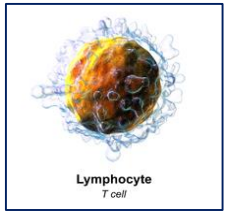
- IHC
  - Single or Multiplex
- Cell Phenotypes
- Cell:Cell Ratios
- Immunoscore
- Cytof

Markers (IHC)		
CD3	CD16	PD1
CD8	CD56	MHC-1
CD45RO	CD19	TIM3
CD4	CD68	LAG3
FoxP3		

T cell marker panels by Flow Cytometry

Activation	Exhaustion	Functional
Live or dead	Live or dead	Live or dead
CD3	CD3	CD3
CD4	CD4	CD4
CD8	CD8	CD8
CD45RO	CD45RO	IFNg
CD69	LAG3	TNFα
ICOS	TIM3	GZMB
OX40	CD161	IL-2
FoxP3		
CD127		

Isolated Cells



In Vitro Functional Characterization of Isolated TILS

- Multiplex immuno assays
  - Chemokines
  - Cytokines
  - Inflammatory mediators
- Flow Cytometry
  - specific intracellular signaling cascades, e.g. phosphoproteins
- Cytof

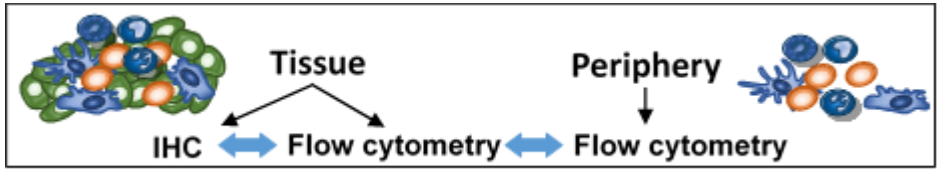
Necessary Specimen Collection:

- Multiple Tissue Biopsies
- Matched Normal and Tumor Tissue
- Tumor single-cell deconvolutions

Module 1 (Exploratory) - Immune Cell Biology – Periphery and Tissue

Tumor and Periphery

- IHC
- Flow cytometry (or CyTOF)
- Standardized SOPs and quality controlled experiments.



Cell populations / Markers (examples)
T cells (e.g. CD3, CD8, CD4, CD45RO, FoxP3, TIM3, LAG3, PD1, etc.)
NK cells (e.g. CD56, CD16, etc)
B cells (CD19, activation markers, etc)
Macrophages (e.g. CD163, CD206, CD64, etc.)
Dendritic cells (e.g. CD11c, CD1c, CD141, HLA-DR, ILT7, etc.)
MDSCs (e.g. OLR1, CD15, CD14, etc.)
Neutrophils
Mast cells
Eosinophils

Necessary Specimen Collection:

- Multiple Tissue Biopsies
- Matched Normal and Tumor Tissue
- Tumor single-cell deconvolutions
- PBMCs

Module 1 (Basic): Cytokines/Chemokines – Periphery

Soluble

Multi-Plex Immunoassays
- Immune Activation
  - Cytokines/
  - Chemokines
  - Inflammatory Mediators
- Safety'
  - CRS-targeted panel

Soluble factors	
G-CSF	IL7
GM-SCF	M-CSF
IFNg	TGFb
IL1	TNFa
IL10	GzmA
IL12	GzmB
IL13	Perforin
IL15	CCL2
IL16	CCL3
IL21	CCL8
IL17	CCL5
IL2	CX3CL1
IL4	CXCL10 (IP-10)
IL6	CXCL9 (MIG)
CXCL2	

Necessary Specimen Collection:
- Blood

Module 2 (Basic) - Cancer Genetics/Somatic Mutations

Known Markers and Analysis Platforms:

Whole Exome Sequencing (WES) at 100X coverage

Necessary Specimen Collection:

- Fresh frozen (better) versus FFPE (better suited to clinical pathology labs.
- DNA quantity
  - Practical limitations and protocol improvements allow for WES using 100ng (and less with amplification methods)
- Matched Normal Samples

Module 2 (Exploratory) - Cancer Genetics/Somatic Mutations

List of Markers:

- Copy number alterations (CNAs)
- Single Nucleotide Polymorphisms (SNPs)
- T- and B-cell receptor deep sequencing

Analysis Platforms to Include:

- WES – Can also be used for CNAs
- Illumina SNP Chips
- Adaptive Biotechnologies Receptor NGS

Necessary Tissue Collection:

- SOPs to be developed for each technology
- Matched normal and tissue samples
- Pre- and Post-treatment biopsies
- Serial biopsies

Module 3 (Basic) - Transcriptomic Characterization of Microenvironment

Known Markers and Analysis Platforms:

- RNASeq at a depth of 150 Million (?) reads across

Necessary Specimen Collection:

- Tumor biopsies
  - Fresh Frozen would be ideal
  - FFPE would be more practical
- PBMC profiling
- Matched Normal Samples
- Pre- and Post-treatment samples

Module 3 (Exploratory) - Transcriptomic Characterization of Microenvironment

List of Markers:

- Single nuclei RNAseq

Analysis Platforms to Include:

- Whole-transcriptome profiling via NGS is recommended with baseline profiling at minimum, and longitudinal samples for tumor indications where available are strongly encouraged.
- PBMD profiling is also recommended.
- Application of emerging single-cell characterization techniques are suggested to be explored and incorporated.

Necessary Tissue Collection:

- SOPs to be developed for each technology
- Matched normal and tissue samples
    - Large enough samples to do single-cell isolates to test subpopulations
- Pre- and Post-treatment biopsies
- Serial biopsies
- Leverage ICGC/TCGA Learnings

Module 4 (Basic and Exploratory) - Cell Free Components - CTC, cfDNA, cfRNA, exomes

List of Known Markers:

- Specific biomarkers TBD (many), but will include:
  - Mutation analysis in cfDNA
  - RNA expression in exosomes (mRNA, non-coding RNA)
  - Circulating tumor cells
- PACT effort to focus on immunotherapy related biomarkers, it may be appropriate to focus predominantly on cfDNA, cfRNA (or whole blood RNA), and exosomes.

Analysis Platforms to Include:

- qPCR – research tool that is readily translatable into commercial and regulatory viable IVD
- NGS – DNA-seq and RNA-seq – good for biomarker discovery/research, LDT approaches; also may be preferred technology in specific settings (e.g. detection of minimal residual disease in certain heme malignancies)
- Epic Biosciences and Rarecyte CTC platforms – selection agnostic CTC approaches, broader potential across many tumor types

Necessary Tissue Collection:

- cfDNA - EDTA plasma will likely suffice for most targets.
- Exosomes - serum or plasma (EDTA plasma preferred)
- CTC collection, each approach has a particular blood collection tube required due to the need for a fixative to limit pre-analytical variables.

Module 5 (Exploratory) - Defining role of the microbiome in modulating CI responses

List of Known Markers:

- The principal activity will focus on bacterial communities measurable in fecal samples.
- Project could be expanded to include multiple microbial communities across different mucosal surfaces.
- Potential Markers
  - Levels of bacterial taxa (16S sequence data)
  - Levels of bacterial metabolites (SCFAs, Bile acids, ect.)
  - Levels of bacterial enzymes (GUS, Bile acid hydrolases, etc.)
  - Levels of serum LPS, MDP
  - Host inflammatory cytokines/host molecular signatures of dysbiosis

Analysis Platforms to Include:

- Enzyme activity screens (480-well) for detecting bacterial enzyme levels
- Micro-array or Elisa for detecting cytokine profiles
- High throughput Mass spec. for detecting bacterial metabolites
- Quantative IHC for detecting immune checkpoint receptor levels after probiotic treatement

Define Tissue Collection and Banking Required:

- Serum
- Mucosal (Oral swabs, endoscope…)
- Urine/Fecal – Primary focus of “Basic” module
- Tumor

Module 6 (Exploratory) - Non-Immune Cell Characterization of Tumor Microenvironment

List of Known Markers:

- Small particles (exosomes, ectosomes, microvesicles) - blood and tumor microenvironment
- Antibodies selective for mesenchymal stromal to isolate these for single cell characterization
- Markers of blood vessels (i.e. CD34, CD31 and endoglin), effective angiogenesis, and tumor hypoxia
- Representative non-immune cell genes (DNA and RNA) could be used to assess the signature of vasculature, stroma and other non-immune cells in tumor microenvironment.
- Baseline serum VEGF demonstrated the correlation with clinical outcome in melanoma patients treated with CTLA-4 blockade.

Analysis Platforms to Include:

- Flow cytometry, IHC, DNA and RNA sequencing

Define Tissue Collection and Banking Required:

- Baseline tumor, during treatment, and post treatment (when possible):
- Bulk tumor resection (fresh)
- Core biopsy materials
- Standard tissue processing procedures (FFPE, Snap frozen, RNAlater, single cell suspension)
- Emerging tissue processing approaches such as those that recover single nuclei for RNA-seq
- Single cell suspensions from tumor sample
    - Tissue process with or without enzyme digestion
    - Cell freezing media and standard operation procedure
- Plasma collection and banking protocol

PACT Trial Selection Process

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DRAFT NCI LCC Review Process for Biomarker Proposals involving CIMACs

"Proposals for Correlative Studies in Collaboration With CIMAC" (developed by CIMAC and Trial Investigators)

↓

Review and refined by WG (with assay group as needed)

↓

Present to LCC for comments and CIMAC assignment

Non-NCTN trials (e.g. ETCTN): Biomarker proposal to be submitted by the PI and CIMAC

NCTN trials: The Biomarker Proposals will be submitted by the Groups

CTEP Protocol Review Committee Reviews for Comments/Approval

↓

- **For <u>New</u> trials**
  - Incorporate CIMAC in the LOI or protocol
- **For <u>Ongoing</u> trials with samples**
  - Protocol amendment to include CIMAC work → Biospecimen accession
- **For <u>Completed</u> trials with banked specimens**
  - CTEP to triage the proposal for review, if needed by the appropriate core correlative science review committee → Biospecimen accession

PACT Trial Selection Approval Process