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The Partnership for Accelerating Cancer Therapies (PACT)

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Abstract

As a part of the Cancer Moonshot, the National Cancer Institute (NCI), part of the National Institutes of Health (NIH), the Foundation for NIH (FNIH), the US Food and Drug Administration (FDA), and 12 pharmaceutical companies have formed a 5-year, \$220 million precompetitive public-private research collaboration called the Partnership for Accelerating Cancer Therapies (PACT). A systematic cross-sector effort to identify and develop robust, standardized biomarkers and related clinical data, PACT will support the selection and testing of promising immunotherapies for the treatment of cancer, with the goal of bringing effective therapy to more patients.

Background: Motivation for The Partnership for Accelerating Cancer Therapies

The National Cancer Moonshot issued a challenge to develop audacious and creative new approaches to cut in half the time needed for cancer advances, through collaboration across disciplines and sectors. In response to this challenge, scientific leadership from the National Institutes of Health (NIH), Food and Drug Administration (FDA), the Foundation for NIH (FNIH), and the private sector considered ways to work together to advance cancer prevention, diagnosis and treatment. The Partnership for Accelerating Cancer Therapies (PACT) aims to do this by bringing successful cancer immunotherapy to more patients.

Immunotherapy for cancer has emerged over the 15 years as a major addition to the traditional armamentarium of surgery, radiation and chemotherapy. In selected instances, immunotherapy has cured patients who had exhausted other options for treating cancer. T-lymphocytes trained to attack cancer cells are now an FDA-approved therapy for certain leukemias and lymphomas^(i,ii). In addition, therapies that interfere with immune checkpoint molecules, PD-1, PD-L1 and CTLA-4, uncovered through decades of dedicated basic, translational and clinical research, are now approved for the treatment of multiple cancers⁽ⁱⁱⁱ⁾, extending the lives of many patients. The development of new and successful immunoncology agents has led to an explosion of investment in the field.

These advances have offered the prospect of improved outcomes, prolonged life and even cure in the treatment of some, but not all cancer patients. There are some defined biomarkers that predict the success of specific immunotherapies. Expression levels of PD-1 and PD-L1 have been shown to correlate with the response to PD-1/PDL1 blockade. Tumors with increased somatic mutations are also more susceptible to PD-1 blockade therapy. Clinical benefit for patients receiving checkpoint inhibitors correlates with the mutational and neoantigen load in the tumor^(iv,v;vi,vii). But in addition to these, more biomarkers are

needed to predict which patients are most likely to benefit from immunotherapy, and to help dissect the mechanisms that determine success or failure. Given the novel and intensely competitive nature of the field, which has led to multiple parallel, uncoordinated, and sometimes duplicative research approaches, coordination of research efforts will be especially important for bringing precision immuno-oncology to cancer patients.

The magnitude of this task makes it impractical for a single company or research group to tackle alone. PACT represents an effort embodying the Moonshot principles of innovation, creativity, collaboration, and a rapid and open approach to data sharing^{viii}. The 12 private sector partners currently committed to PACT -- AbbVie, Amgen, Boehringer-Ingelheim, Bristol-Myers Squibb, Celgene, Genentech, Gilead, GlaxoSmithKline, Janssen, Novartis, Pfizer, and Sanofi -- together with NIH, FNIH, and FDA, will take on the challenge of the Moonshot to define biomarkers for immunotherapy, delivering information and therapeutic options to patients in less time.

Building on Success: The Accelerating Medicines Partnership (AMP)

The potential for PACT was inspired by successful existing collaborations between NIH, FDA, and industry -- in particular, the Accelerating Medicines Partnership (AMP)^{ix}. Launched in February 2014, AMP is a public-private partnership between the NIH, FDA, 10 biopharmaceutical companies, and multiple non-profit organizations to transform the current model for developing new diagnostics and treatments by jointly identifying and validating promising biological therapeutic targets. Under the management of FNIH, NIH and industry partners share expertise and resources of over \$230 million in an integrated governance structure. All partners have agreed to make the AMP data and analyses publicly accessible to the broad biomedical community.

The ultimate goal of AMP is to increase the number of new diagnostics and therapies for patients, while reducing the time and cost of developing them. AMP initially supported projects in three disease areas: Alzheimer's disease; Type 2 diabetes, and autoimmune disorders of rheumatoid arthritis and systemic lupus erythematosus (RA/SLE). Recently a fourth disease area was added -- Parkinson's Disease. Now nearing its 4th year, AMP has shortened time between the discovery of potential targets and the development of new drugs in each of its focus areas. In the area of Alzheimer's Disease, AMP incorporated biomarkers into clinical trials with datasets from over 2000 human brains and network models of candidate targets. For Type 2 Diabetes, a knowledge portal and tools have integrated interrogation across datasets linking human genetic data on risk and phenotypic data. Lastly, in RA/SLE, the discovery of immune cell signatures by single-cell RNAseq in synovial biopsies of patients with RA and kidney biopsies of patients with SLE offers the promise new targets for the treatment of autoimmune diseases.

PACT Development Process

The planning for PACT began in 2016 during focused discussions with an initial 12 biopharmaceutical companies, as well as multiple research foundations, philanthropies and the FDA. Multiple collaborative approaches were considered to bring new therapies to

patients in less time through precompetitive cancer research and broad data sharing. Initial focus areas for PACT included understanding responses to cancer therapies, clinical trial platforms for combination therapies, predictive modeling approaches, and therapies for rare cancers.

Fourteen companies were involved in the actual design of PACT: AbbVie, Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, Boehringer Ingelheim, Eli Lilly, EMD Serono, GlaxoSmithKline, Genentech, Merck, Novartis, Pfizer, and Takeda. Through consultation with experts in these organizations, NIH and FNIH identified two focus areas well suited to such a multi-sector and coordinated effort: (1) identification and validation of biomarkers for response and resistance to cancer therapies, with a special emphasis on immunotherapies; and (2) establishment of a platform for selecting and testing combination therapies. The first focus area sought to address fundamental gaps in understanding how cancer therapies, especially immunotherapies, work in patients. Biomarkers in patients who respond or are resistant to treatment will improve our understanding of immunotherapy and enable precision monitoring of a patient's progress during treatment. The second effort considered collaborative approaches to identify and test new combinations of the collective toolkit of the pharmaceutical industry. For both efforts, NIH was designated to coordinate efforts and sharing of information between the public and private sectors.

Interested parties who committed to invest in the full PACT effort then met and developed the more focused research plan for PACT. A white paper defining each project was presented in February 2017, and commitments and refinements took place throughout the year. Through this process, PACT partners agreed to pursue the research plan for first area of focus – the development of immuno-oncology biomarkers. Insufficient support was present for the combination therapy component. PACT was formally announced in October 12, 2017 at the National Press Club ^(x), and awards for centers supporting PACT research were made that month.

Throughout the planning process, NIH ensured that PACT aligned with [recommendations](#) of the Blue Ribbon Panel of scientific experts who engaged the research community as part of the National Cancer Moonshot ^(xi). These recommendations spanned the cancer research enterprise, including two directly relevant to PACT: the creation of a translational science network devoted exclusively to immunotherapy; and the building of a national cancer data ecosystem. Research carried out through PACT is being integrated into the National Cancer Institute (NCI)'s ongoing implementation of the Cancer Moonshot, as discussed below.

Scientific Plan

To enhance understanding of the mechanisms of response and resistance to cancer treatment, PACT will promote the robust, systematic, and uniformly conducted clinical testing of biomarkers organized into distinct modules. Both foundational and exploratory biomarker modules will be developed and made available for use both within the programs of PACT partners, and also across the research community. These modules will provide for (a) consistent generation of data, (b) access to uniform and harmonized assays to support data

reproducibility, (c) comparability of data across trials, and (d) discovery/validation of new biomarkers for combination therapies including immunotherapies and related combinations.

In addition to the development of biomarker modules, PACT will support four core laboratories to coordinate, conduct, validate, and standardize biomarker assays. These laboratories will facilitate development of both exploratory and standardized biomarkers. Standards for biomarkers and data collection for incorporation into trials will be prioritized through PACT, with the goal of broad adoption across the cancer research community. Lastly, PACT will support a comprehensive database that integrates biomarker and clinical data to enable pre- competitive correlative biomarker analyses.

PACT will also promote scientific coordination among partners by facilitating information sharing. Enhanced coordination of clinical/translational oncology programs, aligned investigative approaches, reduced duplication, and shared resources will allow NIH and industry to prioritize more relevant high-quality trials.

Modules

Foundational/Core Modules

PACT defined a core series of modules to study biomarkers in the partnership. Core modules were selected to serve as a solid knowledge base for cross-comparison of clinical trials that are testing cancer immunotherapies. Core modules are based on well-developed techniques, and can be achieved through standardized assay platforms and analysis techniques to be selected by PACT partners in consultation with the NCI.

Module 1: Immune Cell Biology—Given the importance of immune processes in the response to cancer immunotherapy, the first module will focus on measures of immune response and activity of different components of the immune system. Peripheral samples of blood, serum or plasma will be collected at multiple time points throughout the course of treatment to allow for longitudinal evaluation of changes in immune biology and, if possible, to correspond with measures of drug exposure. Multiplex cell-based and cytokine evaluations will test several circulating cytokines in the plasma/serum. The markers will include mediators of immune activation, inflammation, target cell killing, and safety signals.

In addition to these measures, multiple samples of tumor tissue will be collected throughout the course of a patient's treatment to allow for longitudinal evaluation of the immune response to treatment. Cancer tissues will be collected by resection and/or biopsy, fixed, frozen, or used immediately for IHC, gene expression and cellular analyses by flow cytometry. Similarly, purified Tumor-Infiltrating Lymphocytes (TILs) can be used for in vitro stimulations for cytokine analyses. Specific protocols for sample collection and assay execution will be defined.

Module 2: Cancer Genetics/Somatic Mutations—Advances in low-cost genome sequencing technologies and bioinformatics have led to enormous progress in the field of cancer genetics. Analysis of cancer genomes has identified new cancer genes and pathways, advanced the molecular classification of tumors, and enabled novel target-based drug

discovery programs and approaches to match therapies with patient-specific genetic alterations. Genetic mutations are especially important to the immune response to cancer, as clinical benefit for patients receiving checkpoint inhibitors frequently correlates with mutational and neoantigen loads, although notable exceptions have been observed, such as the frequent response to the treatment of virus-positive Merkel cell carcinomas, which typically have fewer than 20 mutations ^(xii,xiii;xiv;xv). To expand our knowledge of the interplay between novel somatic mutations and immunotherapy, PACT will consider use of whole exome sequencing (WES) as a core biomarker module. Implementation of plans for WES will take into account considerations such as the availability of matched normal tissue, and define needs for sequence coverage, mutation calling, copy number alterations, and algorithms for predicting neoepitopes.

Module 3: Transcriptomic Characterization of the Tumor and

Microenvironment—Transcriptional programs in the both the tumor and surrounding tumor microenvironment provide valuable information about biological and immune processes central to the response to immunotherapy. Changes in immune gene expression signatures in blood have been shown to correlate with response to treatment ^(xvi). Expression profiles of interest include signatures of T-cell activation and exhaustion, Type I interferon, interferon gamma, Th1 and cytolytic activity. Signatures of extrinsic immune suppression highlight mechanisms that may supplement immune checkpoint blockade as ways tumors overcome resistance through combination therapy. For this module, PACT will consider methodologies with a range of complexity, such as qRT-PCR, Nanostring, targeted NGS (next generation sequencing) panels, as well as genome-wide RNA sequencing. Systematic profiling of tumor samples and the primary tumor prior to treatment, during treatment or upon relapse, will provide insight into mechanisms of resistance and opportunities for combination therapies.

Module 4: Liquid Biopsy – cell free DNA (cfDNA)—Real-time information about the response to cancer treatment, of interest to researchers, clinicians and patients, is limited by access to solid tumors through tissue biopsy. Technologies for obtaining information about the patient's response through liquid biopsy, including next generation qPCR and sequencing capabilities, rare cell detection and analysis, ultra-sensitive protein detection, and informatics have enabled the collection of unprecedented multi-dimensional data. Specimens derived from relevant body fluids (e.g., blood, CSF, pleural fluid, etc.) have the potential to enable clinical decision-making, provide for surrogate endpoints, and allow for broader immunoprofiling of patients at more time points before and after therapy. But the full potential of data from liquid biopsy for solid tumors will not be reached until researchers can integrate data across cfDNA, exosomes, and circulating tumor cells in a standardized way. NGS-DNA-seq was selected as the primary experimental screening platform for this module.

Exploratory Module/Assay Development

Exploratory biomarkers and novel assays are necessary for the continued development of biomarkers integrated with treatment, and may become part of basic modules over time. Depending on resources, availability of samples from the periphery and tissue, and the

specific objectives of the relevant clinical trial, PACT partners can choose to fund exploratory biomarker modules. The first four proposed areas for exploratory marker development are the same as the areas chosen for biomarker development, but modules 5 and 6 are completely exploratory: (1) Immune Cell Biology: single-cell sequencing of tumor cells and immune cell subsets and immune cell characterization, cell trafficking, and spatial co-localization of multiple cell types in the tumor microenvironment; (2) Cancer Genetics/Somatic Mutations: Copy number alterations, single-nucleotide polymorphisms (SNP), and T- cell-receptor (TCR) and B-cell receptor (BCR) deep sequencing; (3) Transcriptomic Characterization: Whole-transcriptome profiling at baseline and following treatment; (4) Liquid Biopsy: techniques for better analyzing CTCs, cfRNA, and exosomes; (5) Microbiome analysis: Bacterial communities measurable in fecal samples, with possible expansion to include multiple microbial communities across different mucosal surfaces; and (6) Characterization of the nonimmune tumor microenvironment including stromal cells, blood vessels, and small particles (e.g., exosomes, ectosomes, microvesicles), cytokines, and enzyme or adhesive properties.

PACT Infrastructure

Research infrastructure and academic grants from the NCI will support key components of PACT, including the core laboratories, assay development, and core database functions. The first of these grants were awarded in September 2017 to four Cancer Immune Monitoring and Analysis Centers (CIMACs), a Cancer Immunologic Data Commons (CIDC), and several related initiatives that create integrated multidisciplinary research cores with basic, translational and computational expertise as part of the Precision Oncology Initiative and Cancer Moonshot. The CIMACs are located at MD Anderson Cancer Center, Mount Sinai Medical Center, Stanford University, and Dana Farber Cancer Institute. The Dana Farber Cancer Institute in collaboration with the Broad Institute will house the CIDC. Research at these centers will incorporate PACT biomarkers into a wide range of immunotherapy trials across the NCI clinical trials network, and provide a framework for evolution of the Data Commons into a sustainable resource for immuno-oncology data serving the larger research community.

The CIMAC Network provides an infrastructure for PACT research within NCI-sponsored trials involving immunotherapies. The four CIMACs will use state of the art standardized methodologies to perform assays and analyses for biomarkers associated with NCI-funded clinical trials, including early immunotherapy trials (Phase I and phase II), other trials in the Cancer Therapy Evaluation Program (CTEP) network, and trials funded through NCI grants. One coordinating committee will oversee the four centers, and each center will contribute to specific assays and/or trials across the networks. Established relationships between each center and 1–2 trial networks will facilitate collaboration in scientific planning, biobanking, and other ongoing efforts.

PACT Governance

To maintain close involvement of all partners in PACT decision making, a joint governance structure has been established with equal voting participation among government, private

sector, and patient advocate partners. This structure will include 1) an Executive Committee to provide strategic direction, communication with partner leadership, and resolution of policy issues; and 2) a Joint Steering Committee to direct execution of the research plan. All PACT data will be released as promptly and broadly as possible, in keeping with NIH's mission and the spirit of the Cancer Moonshot, and consistent with any restrictions in underlying clinical trial and grant agreements.

Conclusion and Next Steps

PACT originated as a framework for joining efforts between the public and private sectors to fulfill the promise of effective immunotherapy for more tumors and more patients. Through lengthy deliberation, a series of initial plans and investments have been made, and the selection of basic biomarker panels, assays and analytical pipelines to support the research, and existing trials as pilot projects, is now underway. Testing of the first assays is expected to begin in mid-2018, and the first datasets will be generated by the end of 2018. Through this plan, the systematic, and uniformly conducted clinical testing of biomarkers should yield enhanced understanding of the mechanisms of response and resistance to cancer treatment, and ultimately should help provide effective therapy for more patients with cancer.

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