Request for Project Concepts:

for public-private consortium efforts to develop novel biomarkers to understand the role of tumoral heterogeneity in the application of immunotherapies.

Cancer Steering Committee, Immuno-Oncology Working Group

A. FNIH RFP NUMBER: 002	**B. DATE ISSUED: 04/01/2021**
C. ISSUED BY: The Foundation for the NIH (FNIH) 11400 Rockville Pike, Suite 600 Bethesda, MD 20852	**D. ADDRESS RESPONSES TO** (Electronic Submissions Only): Tanya Murza, tmurza@fnih.org
E. FOR INFORMATION REGARDING THIS SOLICITATION CONTACT:	
E.1. NAME: Tanya Murza	**E.2. EMAIL:** tmurza@fnih.org
IMPORTANT: **F.** To be considered submissions must be received at the location specified in Block E.2. above by June 30, 2021 at 11:59 PM ET. Submission must be clearly identified with the solicitation number provided in Block A above.	

The Biomarkers Consortium (BC) is issuing a Request For Proposals (RFP) for novel biomarker development to support the mission of the BC Cancer Steering Committee (CSC) Immunotherapy Working Group (IO WG). The BC is a public-private partnership involving the National Cancer Institute (NCI), the U.S. Food and Drug Administration (FDA), multiple pharmaceutical, diagnostic and technology companies, non-profit and patient advocate organizations. The Biomarkers Consortium (BC) is a division of the Foundation for the National Institutes of Health (FNIH), a non-profit, 501(c) (3) charitable organization that supports the NIH in its mission to improve health by forming and facilitating public-private partnerships for biomedical research.

Purpose:

The Immunotherapy Working Group (IO WG) of the BC-CSC was initiated in 2019 to identify and validate biomarkers that can be used to improve the success rate and reduce the unintended consequences of IO application. The WG recognizes the challenges to effective immunotherapy-containing regimens posed by intra- and inter-site heterogeneity of the tumor microenvironment (TME). One goal of the group is to explore and quantify intra-tumoral heterogeneity in stromal cells, infiltrating immune/inflammatory cells, and cells intrinsic to the tumor through the retrospective examination of published data and through prospective study of tumor tissue. This pre-competitive effort seeks to set a standard for classification and quantification of heterogeneity that can be applied broadly by other research groups to achieve a more precise and nuanced understanding of the extent to which the type and degree of heterogeneity may confound or complicate understanding of tumor responses to immunotherapies alone or in combination.

The IO WG invites investigators to submit brief project concept proposals for application of novel biomarkers to public-private consortium efforts in either of two identified challenge areas. Proposals will be considered for funding under the BC precompetitive project model, described below under *Project Structure Information*.

1. Challenge area 1: <u>The impact of epigenetic changes on the interaction of the tumor and tumor microenvironment; understanding the role of epigenetics in response or resistance to immune modulatory therapy.</u>

   Studies in immuno-oncology have elucidated some of the roles of mutations and gene signatures of inflammation in response and resistance to immunotherapies, but the role and importance of epigenetic state to both the tumor and immune populations in the tumor microenvironment is only beginning to become clear. Such changes can confer plasticity or lead to a fixed state of tumor infiltrating immune populations, the importance of which can be pivotal in the activity of such populations. This RFP seeks concepts proposals focused on epigenetic changes with immunologic impact on response or resistance to immunotherapy alone or in combination.

   A successful project concept might focus on:
   - Understanding the tissue target specificity of epigenetic changes (e.g. methylation, histone marks or other alterations of interest to the investigator in DNA, RNA or microRNA) on primary versus metastatic tumor cells and/or immune cells in the tumor microenvironment;
   - Single cell approaches to epigenetic profiling of the tumor and/or components of its microenvironment; longitudinal sampling is of interest where feasible.
   - Building upon existing publications and public databases for retrospective analyses, including studies outside of oncology that define the cellular phenotypes of normal tissue (where possible to assess), tumor tissue and immune cell populations according to epigenetic state;
   - Functional studies that demonstrate the role of anti- or pro-tumor cell populations based on epigenetic state and characterization of the reversibility (or lack) of such states.
   - Development or advancement of analytic methods to assess epigenetic measures preclinically and/or in clinical datasets

   Applicants may consider the use of emerging methods, though they should either be grounded in existing data or evaluated for their quality and reliability as part of the project concept. Studies may be in any immunomodulatory therapy, including but not limited to checkpoint blockade therapy alone or in combination, cell therapy, epigenetic therapy or other therapies thought to modulate immune cell function.

2. Challenge area 2: <u>Mechanisms of tumor and immune system interaction, and immune cell positioning in or exclusion from tumors.</u>

   A malignant neoplasm can be viewed as a complex organ consisting of multiple cell types, including the cancer cells, stromal cells and immune/inflammatory cell populations that infiltrate the neoplasm. The latter can be a complex mixture of subsets of T lymphocytes, B lymphocytes (including antibody/autoantibody-secreting cells), natural killer cells, innate lymphoid cells, monocytes, macrophages, dendritic cells, neutrophils, eosinophils, and other cell

populations. Some of these cell types can potentially control or eliminate cancerous cells, but such actions are opposed or diverted by other cell types that have regulatory effects.

The positioning of cell types within a tumor mass is critical to the outcome of these interactions and gives rise to intra-tumor heterogeneity. A large number of small proteins have been identified that are able to stimulate directed migration of cells that bear surface receptors to which they bind. Chemokines have canonical structures that are formed in part by cysteine cross-links, and these proteins are typically 10-30kDa. They may undergo post-translational modifications, such as citrullination, which in some cases alters function and receptor specificity. Chemokines bind to G-protein-coupled receptors to initiate signal transduction. Many chemoattractants are measurable in serum and other biological fluids and are therefore potential biomarkers. Other measurable biomarkers may also reflect important components of cancer cell/stromal cell/immune cell interactions. These include cytokines, proteases, shed receptors (such as sIL2R or sICAM1/CD54), autoantibodies and other classes of molecules. A multiprotein biomarker panel of this type can measure disease activity in rheumatoid arthritis, another condition in which multiple cell types interact in the lesion.

Some cancer-associated biomarkers could become therapeutic targets as well as biomarkers that predict disease course, severity and response to treatment. To our knowledge, the comprehensive and simultaneous measurement of all known chemoattractants has not been attempted in any disease. Models and methods to predict functional consequences of multiple chemoattractants need to be developed. Heterogeneity of post-translational modifications adds daunting layers of complexity in measurement and functional analysis. Opportunities exist to measure many of these proteins by ELISA or similar assays, that can be performed on stored sera. The RFP seeks proposals to develop an omics-like study of the cancer/stromal/immune protein interactome with high relevance to disease course, treatment, and outcome.

Background:

1.Specific Objectives and Requirements*:*

This RFP solicits brief (2 – 3 page) proposals to develop novel biomarkers with the goal of advancing cancer treatment and research. Applicants with high level proposals that are of interest to the WG will be asked to provide additional justification and information after initial evaluation. Proposals should describe projects that develop biomarkers that could ultimately be incorporated into the clinical setting. Investigators should indicate the developmental level of their biomarker and proposal and be prepared to discuss the intended use of proposed platforms relative to current biological tools. Responses should outline the steps necessary to address statistical and clinical validity of a biomarker developed through an FNIH partnership.

Project Structure Information:

I. A project concept that is reviewed and approved by the IO WG, will be asked to provide additional information and meet with the WG. Successful project concepts will then be reviewed by the BC CSC, and the BC Executive Committee (EC), approved for fundraising and project execution, and administered through contracts between the FNIH and the research sites. The FNIH does not administer grants. The WG will assist the investigators to fully develop the project plan for final EC approval and launch. FNIH staff will oversee the project goals and progress, and the project team will be expanded to include two co-chairs (the principal investigator and another member); select additional CSC and IO WG members (with a minimum of three funder organization representatives); government (FDA and NCI) representatives; and representatives from academic institutions, as appropriate. Once the project plan

is complete, the FNIH will solicit funds from CSC industry partners ("funders") to support the project. The principal investigators will coordinate efforts with the project team and report results to the CSC on at least a quarterly basis. Approval of project milestone achievements linked to funding decisions are the responsibility of the project team. Applicants must agree to work with the project team to refine the overall project and specific project goals to align with the FNIH mission and the goals of the funders.

II. Funds Available and Anticipated Number of Projects

The number of projects contracted and the amount per project is contingent upon evaluation by the IO WG members and industry funder support. These are dependent in part on the submission of meritorious applications and proper budget justification within the proposals. Concepts received are not in competition and there is no limit to the number of successful concept proposals. Selection of a proposal for consideration does not guarantee funding until the project is favorably reviewed by the FNIH CSC and EC and industry funding is secured.

III. Project Budget

Application budgets are typically $2 to 3 million over 2 – 4 years and must reflect the requirements of the project plan to develop the proposed biomarker. Scientific and budget justification should be provided for evaluation. The committee reserves the right to award at a lower amount than requested.

IV. Contract Project Period

The scope of the proposed project should determine the award project period. The typical project period is 2 – 4 years with the potential for a no-cost extension to complete necessary analyses.

V. Eligibility Information

Organizations eligible to apply are:

- Private or public sector
- US-based or international
- All applicants will be expected to comply with the FNIH Policies and Guidelines previously established by the Biomarkers Consortium (https://fnih.org/what-we-do/biomarkers-consortium/about/policies).

VI. Application and Submission Instructions

Submission Deliverables

Complete applications will include the information below, provided in the application response template (IO WG Project Concept Application Form, Appendix 1):

- Summary of the project with the clinical challenge to be addressed, technological approach, specific aims, outcomes, and deliverables.
- The scientific strategy, overall experimental plan and the definition of success given the stated aims, outcomes, and deliverables.
- Rationale for why this effort would benefit clinical oncology as described in the two clinical challenges outlined under Purpose.
- Current status of the effort, background and supporting data.
  High level project timeline and budget (accounting for project stages as appropriate, personnel, reagents and materials, equipment, sample acquisition, other requirements for work proposed as appropriate).

Page Limit: Please keep responses to 2–3 pages in length (single spaced, 11 pt. font). Proposals of interest will be asked to provide additional information in follow up.

VII. Project Contract Reporting

Principal investigators for awarded applications should expect to submit progress updates for the project at least quarterly to the Project Team. The format for progress reports will be agreed upon before launch and described in the award agreements.

VIII. Additional Information Required

Please provide any existing IP or patent information that may affect the contracting of a public-private partnership, or the banking of any resulting data funded by this effort in a public but controlled-access resource.

IX. Submission Instructions

Send responses via e-mail to tmurza@fnih.org with a copy to dconnors@fnih.org. You may email with questions regarding the RFP or the submission process.

Key Dates

Application Due Date: June 30, 2021, 11:59 PM ET*

Targeted Application Review Period: July 1 - August 31, 2021

Potential Oral Presentations from Finalists (if needed):

Applicants will be informed by email after September 1, 2021, of the result of the initial review of proposals and whether they will be asked to provide an oral presentation to the IO WG by teleconference with the ability for Q&A. An invitation to present the proposal does not guarantee a selection for project development. Final selection of proposals to recommend for review by the CSC and EC will be made in the Fall of 2021. Pending a positive review by these committees, a project team will be formed as described above under *Project Structure Information.*

*If no adequate submissions are received in this timeline, the FNIH reserves the right to extend the target deadline.

About the Foundation for the NIH and the Biomarkers Consortium

Established by the United States Congress to support the mission of the NIH – improving health through scientific discovery in the search for cure – the FNIH is a leader in identifying and addressing complex scientific and health issues. The Foundation is a non-profit, 501(c) (3) charitable organization that raises private-sector funds for and manages a broad portfolio of unique programs that complement and enhance NIH priorities and activities. For additional information about the FNIH, visit www.fnih.org. The BC is a public-private biomedical research partnership managed by the FNIH. The mission of the Biomarkers Consortium is to help create a new era of precision medicine, with more highly predictive markers that have an impact during a patient's illness or lifespan. Its goal is to combine the forces of the public and private sectors to accelerate the development of biomarker-based technologies, medicines and therapies for prevention, early detection, diagnosis and treatment of disease. Visit https://fnih.org/what-we-do/biomarkers-consortium.