Research Supplements to P30 Cancer Center Support Grants (CCSG) and P50 Specialized Programs of Research Excellence (SPORE) Grants to Develop Autologous Human Immune Mouse Models and Organoid Systems for Cancer Immunotherapy Evaluations.

Key Dates
Release Date: March 18, 2024
Requested Receipt Date: April 29, 2024
Anticipated Start Date: May 29, 2024

PURPOSE

The National Cancer Institute (NCI) announces an opportunity to apply for an administrative supplement to support innovative research aimed at the development and sharing of *preclinical autologous human tumor-immune models and resources* to evaluate cancer immunotherapies. The research goal herein is to develop appropriate systems that can be used to assess therapeutic response and/or obtain a better understanding of the biology behind therapeutic response, therapeutic mechanism of action, immune evasion, and the interplay between the tumor and microenvironment. To address these special needs, NCI is seeking research projects that:

- Addresses current challenges in protocols to recreate human immune responses using novel PDX-based strategies, patient derived organoids, and human induced pluripotent stem cells.
- Performs preclinical immunotherapy experiments utilizing existing or newly developed PDX models and organoids as proof-of-concept. Emphasis should be on therapeutic resistance and/or disease relapse.
- Generates models and systems for dissemination to the research community through NCI Patient-Derived Models Repository (PDMR - https://pdmr.cancer.gov/).

Each concept proposed should be based on histologically and molecularly characterized PDX or organoid models that explore the relationship between mechanism of action, tumor characteristics, and drug response for immunotherapy agents. Thus, studies should include host-cell interactions to define the efficacy of mechanism-based drug combinations in genetically defined tumor subgroups that explore the genetic and host factors contributing to tumor response.

Upon successful completion of this work, participating centers will be required to share their knowledge, data, specimens, methodologies, procedures, and other research materials via the NCI Patient-Derived Models Repository (PDMR) located at the Frederick National Laboratory. Achievement of the overall goals will contribute to the establishment of a sustainable repository designed to advance immunotherapy-oncology research.

BACKGROUND

Patient-derived xenografts (PDX) have the potential to improve preclinical evaluation of novel anticancer therapies. NCI maintains programmatic interest in understanding the reproducibility and translatability of PDX drug response experiments using PDX models and organoid systems for testing therapies and in making such models available to the wider community. To further this pursuit, NCI is specifically seeking research proposals that recreate human immune responses using pluripotent stem cells and human primary tissue and the like, for immunotherapies alone or combined with cancer treatments.

The landscape in immuno-oncology has undergone profound changes since its early beginnings. The notion that immune system can recognize and destroy cancers was first hypothesized by Ehrlich in 1909 [1]. As knowledge of the immune system expanded, Thomas and Burnett proposed the hypothesis of

cancer immunosurveillance [2,3]. The development of syngeneic mouse models allowed scientists to directly observe how the immune system recognizes and destroys tumors. Dunn, Old, and Schreiber demonstrated tumors undergo immunoediting and introduced the concept of the three Es of cancer immunoediting: Elimination, Equilibrium, and Escape [4]. In recent years, the introduction of antibody-based immune checkpoint inhibitors (ICI) and chimeric antigen receptor gene modified T cells (CAR-T) as standard therapies has established immunotherapy as the 5th pillar of cancer therapy along with surgery, radio-, chemo-, and molecularly targeted- therapies [5].

There has also been a long-standing effort to create and optimize human-immune systems of mouse models. Different mouse construction protocols have been reported, all involve transplantation of human hematopoietic and/or lymphoid cells (e.g. peripheral blood lymphocytes, bone marrow cells, cord blood cells) into immunodeficient mice. As a result, most models used in human cancer immunology and immunotherapy were immunocompromised or involved allogeneic and/or xenogeneic immune responses, making the host immune environment different from that of patients. Thus, preclinical models in which both the immunity and the tumor are of human origin and genetically identical are critical to develop.

The potential to develop autologous models is supported by progress in understanding oncogenic changes causing tumorigenic transformation of normal cells though limited success on solid tumor human immune systems has been reported. Research is now underway to recreate human immune responses using novel PDX-based strategies, patient derived organoids, and human induced pluripotent stem cell (iPSC). For instance, the creation of immunodeficient NOD-SCID mice allows the establishment of PDX models. Scientists have also learned how to create the right environment for the stem cells so they can follow their own genetic instructions to self-organize, forming tiny structures that resemble miniature organs comprised of many cell types. This approach provides a unique opportunity to mimic natural T-cell differentiation *in vitro*. Research has also shown that iPSCs can be generated by reprogramming adult cells (skin fibroblast and blood cells) back into a pluripotent state through the introduction of Oct4, Sox2, Klf4, and c-Myc genes referred to as the Yamanaka factor [6]. By reprogramming cells from cancer patients, iPSCs that carry the same cancer-associated genetic mutations found in the patient's tumor cells can be generated. The combination of these platforms can create a portfolio of advanced humanized mice-tumor models appropriate for studying molecular mechanisms underlying tumorigenesis and exploring novel immunotherapeutic strategies more fully. Examples of unmet needs in cancer immunotherapies that would be enhanced by preclinical models using PDX, organoid, and iPSCs include:

- Enhancing exploration and testing immune stimulatory and regulatory modulation as therapeutic approaches across different tumor types.
- Testing efficacy of human immunotherapy agents within a reconstituted human tumor microenvironment (TME).
- Enhancing understanding of regulatory components leading to primary or secondary immunotherapy resistance.
- Improving trafficking of effector cell therapies into the TME.

REFERENCES

1. Ehrlich P. Ueber den jetzigen Stand der Karzinomforshung. *Ned Tijdschr. Geneeskd*. 1909; 5 (part 1) 273-90.
2. Thomas L. Discussion. In *Cellular and Humoral Aspects of the Hypersensitivity States*. Ed. HS Lawrence, 1959; 529-32.
3. Burnet FM. The concept of immunological surveillance. Prog Exp Tumor Res. 1970; 13:1-27.

4. Dunn GP, Old LJ, Schreiber RD. The three Es of cancer immunoediting. Annu Rev Immunol. 2004; 22:329-60.
5. Couzin-Frankel J. Breakthrough of the year 2013. Cancer immunotherapy. Science. 2013 Dec 20;342(6165):1432-3.
6. Takahashi K., Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006 Aug 25;126(4):663-76.

SUPPLEMENT RESEARCH GOALS

The proposed collaborative project must develop custom models, if not established, for screening or characterizing therapeutic drugs for indications that have previously been difficult to study, or platform technologies that enable the generation of phenotypically relevant iPSC-derived human disease models, or iPSC platform enabling the generation of sustainable disease cell models. The proposed collaborative project must utilize autologous tumor/blood or fibroblasts to generate functional immune models to test immunotherapy agents. Researchers should leverage investigator developed and PDMR resources to make research materials available to the extramural community at large. The PDMR maintains many PDXs and organoids across several histologies (e.g., breast, renal cell, head and neck squamous cell carcinomas) that can be matched with patient derived organoids including cancer associated fibroblast for co-culture experiments. Awardees will retain custody of, and have primary rights to, the data developed under these awards, subject to Government rights of access consistent with current DHHS, PHS, and NIH policies. Participating centers may also collaborate with members of the NCI-funded PDX Network to contribute ideas and share resources.

Examples of scientific needs are as follows:

1. Research and model development focused solely on therapeutic evaluations of any human malignancy.
2. Research and model development that reflects the clinical, histological, and genetic heterogeneity representing refractory diseases.
3. PDX-models or organoids created from patients with intrinsic and acquired resistance to targeted- and immune-therapies
4. Research and model development leading to functionally active patient antigen-specific T-cells from iPSCs.

Models to Study. Examples include PDX*, in vivo* patient-derived tumor cell cultures, cancer-associated fibroblasts, and patient-derived organoids. Validation studies involving *ex vivo* models as well as *in vivo* disease-specific models performed at a single center will be considered.

***Interactions with NCI-Frederick PDMR*.** Enhancement of this resource will involve donating PDX models (tissues) to the repository, collaborating in the development and testing of methods for cross-validation of studies, and testing reproducibility of results within the research project. Researchers are also expected to develop and abide by standard operating procedures and quality control measures acceptable to PDX generation and for drug response testing procedures.

ELIGIBLE INSTITUTIONS

NCI-Designated Cancer Centers and SPORE awardees with NCI are eligible to apply if translational immunotherapy research is an integral component of the center's mission or grant program. The P30 or P50 administrative supplements are limited to a project period of one year. Therefore, at least one full year on the parent award or partnering collaborator award (if not utilizing a sub-award mechanism)

must remain at the time of funding. Awards that are in a cost-extension or a no-cost extension are not eligible for this supplement.

In addition, the PI(s) or designated Project leader must have demonstrated expertise in PDX or organoid model development and associated iPSC research. Arrangements between the NCI-funded centers and any other participating institution(s) including intellectual property rights should also be defined by the institutions involved prior to submission of this supplement application. For supplements to parent awards that include multiple program directors/principal investigators (PD/PIs), the supplement may be requested by any or all the PD/PIs on that award (in accordance with the existing leadership plan) and must be submitted by the awardee institution of the parent award. Collaborations with foreign institutions are allowed, but investigators must provide a justification for the collaboration. Please note that some foreign collaborations will require U.S. State Department approval by the NCI, and that may delay receipt of funding beyond FY2024.

BUDGET AND ALLOWABLE COSTS

Supplement requests may not exceed $750,000 in total costs and the project period is for one year. The budget should justify all the direct and indirect costs. Institutions may waive indirect costs, but it is not required. Allowable costs include funding for the Project Leader of the study (maximum of 20% effort), who must be a member of the Cancer Center or SPORE grant program, funding for required expertise to complete this project, as well as costs for the procurement of tissues, sequencing, and analysis. The purchase of large pieces of equipment through this supplement will not be permitted. If supporting students and/or postdocs, please indicate if they are already working in the lab or when they will be recruited. It is not appropriate to have TBN personnel listed as part of the budget request. A statement of how the new student/postdoc will be supported after the conclusion of the one-year supplement must be included.

AWARDS

NCI anticipates funding two supplement projects in fiscal year 2024 pending responsiveness to the goals of this announcement. Awards will be made in FY2024 for a one-year period. One no-cost extension may be requested following the initial funding period for this supplement. The earliest anticipated start date is May 29, 2024.

LETTER OF INTENT

Eligible applicants are asked to submit a letter of intent via email to Ms. Molly Maher at molly.maher@nih.gov for CCSGs, and to Ms. Tamara Walton at waltont@mail.nih.gov for SPOREs by the receipt date with the following information:

Title of proposed activity
Name(s), address(es), and telephone number(s) of the PD(s)/PI(s)
Participating institution(s)

APPLICATION SUBMISSION FORMAT

P30 or P50 supplement applications must be submitted electronically via eRA Commons to the parent award using PA-20-272 “Administrative Supplements to Existing Grants and Cooperative Agreements (Parent Admin Supplement)” no later than 5:00pm (local time) on the receipt date. Your submission should follow the instructions in this funding announcement with the following emphasis:

1. A cover letter from the NCI-Cancer Center or SPORE PI awardees with concurrence from the Authorized Organization Official (AOR).
2. Project Summary/Abstract and Specific Aims
3. Research Plan (4 pages) that describes:
    - Novel concepts and approaches to provide preclinical evidence.
    - Overall capabilities in terms of the scale of operation, types of xenograft/organoid procedures used, blood- and fibroblast-derived iPSCs, types of drug testing conducted, reuse capabilities.
    - Steps to ensure that models and resources are shared with the PDMR-FNLCR and allows cross-validation of experimental results and to enhance the diversity of tumor models.
    - Human cell lines/organoid collections unique to the institution for research.
    - An appropriate project timeline.
4. Budget and budget justification using SF424 forms. Appendices are not allowed.
5. Describe the qualifications of the individual(s) who will conduct the work. Include the Project Leader and key personnel with expertise in model development, cancer immunotherapy, and molecular analyses. Note: Separate SF424 forms will be needed for biosketches.

EVALUATION CRITERIA

Supplements will be administratively evaluated by NCI staff with appropriate expertise. There will not be a secondary review process. Proposals will be reviewed for quality and responsiveness to the requirements outlined in this announcement with an emphasis on:

- Potential to develop sustainable autologous human systems to investigate immunotherapy agents.
- Feasibility to achieve proposed research plans and goals.
- Suitability of models to test immunotherapies and/or combination anti-cancer therapies.
- Expertise and disease targets selected for development.
- Ability to use PDMR established banked material for broader dissemination.
- Logistics involved in sharing resources through a collaboration with the PDMR.

EXPECTATIONS FOR DATA MANAGEMENT AND SHARING

Sharing models and data with the broad scientific community is a central goal of the supplement. NCI expects awardees to adhere to the NIH Data Management and Sharing policy to the extent feasible and in a timely manner. Awardees will be required to abide by the NIH DMS policy and meet the PDMR program expectations/procedures.

REPORTING REQUIREMENTS

As part of the annual progress report of the parent NCI-CCSGs or SPORE grant, include information on what has been accomplished via the administrative supplement during the funding period. NCI expects the supplement reporting of any data sharing progress to be included in the annual progress report.

QUESTIONS

Please contact Dr. Lori Henderson (Email: hendersonlori@mail.nih.gov) or Dr. Marc Ernstoff (Email: marc.ernstoff@nih.gov) from the Division of Cancer Treatment and Diagnosis at NCI for questions related to the supplement.