Key Dates

Release Date: April 26, 2016
Request Receipt Date: June 20, 2016
Earliest Anticipated Start Date for Awards: August 15, 2016

Purpose

The National Cancer Institute (NCI) announces the opportunity for supplemental funding to stimulate research in the area of the pancreatic ductal adenocarcinoma (PDAC) microenvironment. The goal is to understand the interaction between tumors and the microenvironment to design new immunotherapy interventions that would accommodate and build on the distinct characteristics of this interaction. There is a need to understand more thoroughly the role of inflammation in the genesis and progression of PDAC, the roles of different effectors and suppressors of immune responses, the contribution of tumor stroma with a focus on its heterogeneity, and the function of tumor vasculature. Studying tumor-microenvironment interactions in PDAC should lead to discoveries of vulnerabilities that could be exploited in the design of immunotherapies such as cancer vaccines, checkpoint inhibitors, adoptive cellular therapies, and their combination with chemotherapy and precision medicine interventions.

Eligible grantees do not need to send a letter of intent; a full proposal of no more than 6 pages must be submitted by the request receipt date to the NCI Office of Cancer Centers (see below). Funding is contingent upon NCI approval of the proposal, which will include both a scientific and budgetary evaluation. Even though projects funded through this supplement will be generally biological in character, collaboration among cellular and molecular biologists, immunologists, pathologists, bioinformaticians, surgeons, molecular imagers, and medical and radiation oncologists will be necessary. No clinical trials will be supported by the supplement; however, the use of human specimens from clinical trials is encouraged.

Background

Despite advances in the understanding of the biology of pancreatic cancer, the disease remains a major clinical challenge claiming more than 40,000 lives yearly. PDAC is the most common type and accounts for 95% of cases of pancreatic cancers. Many risk factors including chronic inflammation, diabetes, obesity, and smoking have been established. PDAC is highly resistant to chemotherapy and radiation. The only curative intervention is surgery for localized disease; however, most patients present with locally-advanced disease and are not eligible for curative surgical approaches. The overall 5-year survival is 5%.

After decades of research, new immunotherapy approaches have resulted in unprecedentedly positive results in many types of tumors including, but not limited to lymphoma, melanoma, renal cell carcinoma, and lung adenocarcinoma. In particular, checkpoint inhibitors have produced long-term survival in approximately 20% of patients, and these findings led to FDA approval of several agents (ipilimumab, nivolumab, pembrolizumab). Cellular therapies with genetically engineered T cells (CAR-T cells or antigen-specific T cell receptors) or tumor infiltrating lymphocytes (TIL) have also proven to be efficacious in certain hematopoietic malignancies and solid tumors. Therapeutic vaccines have shown some success as well. Immunotherapy, in many cases, provides an alternative to traditional chemotherapy, and often with less severe side effects. The search for reliable predictive markers for immunotherapy is ongoing.

Immunotherapeutic approaches to PDAC, however, have not, for the most part, been successful. PDAC has a low mutational load with few neoantigens (an immunologically “cold” tumor); although...
inflammatory cells have been shown to infiltrate the tumor, these cells promote rather than inhibit PDAC growth. The tumor microenvironment is profoundly immunosuppressive with regulatory T cells, regulatory B cells, myeloid-derived suppressor cells, tumor associated macrophages, and other stromal elements that secrete suppressive factors. Despite the number of cells that surround and infiltrate the tumor, only a minority of these tumors have naturally occurring effector T cells. However, several groups have recently reported techniques that overcome the immunosuppressive milieu of PDAC and allow the host immune system to react more efficiently against the tumor.\textsuperscript{8-10}

Attempts to create accurate models of the tumor that include the PDAC microenvironment have been particularly challenging; its dense desmoplastic stroma comprises 90% of the tumor in many cases with a large variety of cells including stellate, fibroblast, endothelial, nerve, and white blood cells, all with different subtypes and functions. In addition, there is an extracellular matrix that includes collagens and fibronectin. It is believed that an important dynamic exists between PDAC and its microenvironment: factors are secreted by the tumor cells that augment the activities of the microenvironment, and growth factors and cytokines are secreted by the cells in the microenvironment that increase the growth and invasion of PDAC, as well as resistance to therapy.\textsuperscript{11} Yet, studies that depleted stromal elements in an attempt to decrease PDAC growth led to equivocal results.\textsuperscript{10}

No cell lines, genetically engineered mouse models and xenografts, or organoid cultures\textsuperscript{12} models today encompass the complete PDAC microenvironment. A deeper understanding of the complex PDAC microenvironment including its individual components, their interactions with tumor, and their potential role in facilitating immunotherapeutic interventions is needed. It has been thought that the density of the desmoplastic reaction prevented the influx of T lymphocytes, but it is now well established that this is not the case; regulatory T cells are abundant within the tumor. The effector T cells are the cells that are excluded.

It is clear that cells in the PDAC microenvironment play a crucial role in PDAC development and progression, and therefore the composition and function of the microenvironment in all stages of the disease need to be better understood. With the use of new staining and microimaging technologies, a better characterization of the microenvironment is possible, allowing—in a single specimen or animal—the identification and position of all cellular components of the immune response in relation to the tumor. Over the course of the disease, longitudinal specimens could show changes in the cytological signature and position of the cells in the microenvironment. The vascular architecture of PDAC is abnormal; blood vessels are highly disorganized and leaky with sluggish blood flow.\textsuperscript{13} Lymphatics within the tumor are compressed. The elevated intra-tumoral pressure results in a decreased opportunity for anticancer drugs to reach their targets.

**Administrative Supplements**

*The goal of this solicitation is to give investigators an opportunity to submit one-year supplement proposals for studies that would expand our understanding of the PDAC microenvironment and what is needed for more efficacious immunotherapy interventions.* Proposals may address, but are not limited to, studies of:

- Differences in the tumor microenvironment in inflamed and non-inflamed PDAC tumors
- The heterogeneity (in composition, function, and location) of PDAC microenvironment cell populations
- The functional role of stroma and pancreatic stellate cells and the mediators they secrete to produce an anti-tumor or pro-tumor milieu
- The bidirectional influences between PDAC and its microenvironment
- The evolution of the immunosuppressive environment with all its critical components over the course of the disease and the mechanism by which effector T cells are excluded
- Mechanisms that will allow the influx of immune effector cells in large numbers so that checkpoint inhibitors and other immune modulators can work
Epitope spreading (or not) during an immune response to a vaccine and the factors or cells responsible

Conditions in the microenvironment or interactions between the tumor and microenvironment that lead to metastases, including the role of myeloid derived suppressor cells (MDSCs)

These studies can also include the development of new models that could serve better in the study of the above.

**Eligible Institutions**

P30 Cancer Center Support Grant holders in Basic, Clinical, and Comprehensive NCI-Designated Cancer Centers are eligible to apply if immunotherapy is an integral part of the NCI-CC’s mission. Specialized Programs of Research Excellence (P50) grants involved in the study of PDAC are also eligible, as well as Program Project (P01) grants with a focus on PDAC or immune aspects of the tumor microenvironment.

**Number of Applications**

Only one application per institution is allowed. Each application must include a cover letter from the NCI-CC Director, SPORE Director, or P01 Principal Investigator, with concurrence from the Authorized Organization Official (AOR).

**Letter of Intent**

A letter of intent is not required for this supplement.

**Terms and Conditions of Funding and Allowable Costs**

The budget should justify all the direct and indirect costs. Supplements are for one year only, although a 1-year no-cost extension will be allowed. We anticipate that up to 5 awards of no more than $500,000 total cost each will be made in the 2016 fiscal year. Allowable costs include funding for the Project Leader of the study (maximum of 20% effort), who must be a member of the NCI-CC or a key personnel of the P50 or P01 grant, 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.

**Supplement Award Application Procedures**

1. **Cover Letter**
   A cover letter should accompany each application and include the following:
   a. Request for an administrative supplement to support the project
   b. Title of the supplement
   c. P30, P50 or P01 grant number
   d. Contact information for the Cancer Center Director, P50, or P01 grant Principal Investigator and the Project Leader
   e. Signatures of the Cancer Center Director and the Authorized Organization Representative (AOR)

2. **Application**
   a. Standard PHS 398 (pgs 1-5)
      i. Item 2: check yes and provide the title indicated in the cover letter, 1.b.
      ii. Item 7A-8B, denote the direct and total costs for the project.
      iii. The Authorized Organization Representative must sign the face page.
      iv. Include a detailed budget description.
3. **Summary of the Project Proposed**
   The applicant should attach a summary of the project including a description of aims including a timeline; specific approach to be used to complete this project; investigators; and environment where the work will be performed. The summary should be no more than 6 pages excluding a reference list. For the specific approach, the summary should include (a) the type of specimens, models, and methodologies to be used (b) relevance to studies in the parent grant. A full budget with justification should be included.

4. **Justification of Staff**
   Attach CV of Project Leader and any other key personnel, including any Core Leaders. Note that in order to qualify for a supplement, the name of the Project Leader must be proposed at the time of submission.

**Application Submission**

Applications may be submitted as a signed, scanned PDF to Ms. Nga Nguyen at nga.nguyen@nih.gov. Awards will be made in FY16 for a one-year period. One no-cost extension may be requested following the initial funding period for this supplement.

**Review Criteria**

Supplements will be administratively reviewed by NCI staff with appropriate expertise. There will not be a secondary review process.

**Awards**

Awards will be based on responsiveness to the goals of this announcement and the availability of funds.

**Reporting Requirements/Deliverables**

As part of the annual progress report for the parent NCI Cancer Center, P50 or P01 Grant, include information on what has been accomplished via the administrative supplement during the funding period. A copy of the annual progress report for the administrative supplement should be sent to Dr. Peter Ujhazy by email at ujhayzp@mail.nih.gov.

**Questions**

Please contact Dr. Peter Ujhazy (telephone: 240-276-5681; Email: ujhayzp@mail.nih.gov); Dr. Toby T. Hecht (telephone: 240-276-5683; Email: hecht@mail.nih.gov) or the NCI Program Director for your P30 CCSG, P50, or P01 award (telephone: 240-276-5600) for questions related to the supplement.

**References**


