Administrative Supplements for P30 Cancer Center Support Grants (CCSG) to Support Research in Canine Immunotherapy via Collaboration of NCI-Designated Cancer Centers and Veterinary Medical Colleges

Key Dates

Release Date: April 12, 2016
Request Receipt Date: June 13, 2016
Earliest Anticipated Start Date for Awards: August 15, 2016

Purpose

The National Cancer Institute (NCI) announces the opportunity for supplemental funding to promote expanding knowledge of canine cancer immunotherapy in the area of mutational load and neoantigens of a small number of specific canine organ-site tumors (short-term goal). The long-term goal is to understand the interaction between tumors and the microenvironment (immune cells) in canine cancers, so that this species can be used to test combination therapies—either (a) two (or more) immune modulating agents, or (b) an immune modifier and a targeted agent or chemotherapy—for translation to the treatment of human cancers. This endeavor will require NCI-designated Cancer Centers (NCI-CCs) to form collaborations with veterinary oncologists, translational researchers, and geneticists at veterinary medical colleges to accession and sequence canine specimens, analyze the specimens for mutations and neoantigens, determine the dog major histocompatibility complex (MHC) context of the neoantigen epitopes across cancer types, and characterize the T lymphocyte numbers and subtypes, as well as other relevant aspects of the tumor microenvironment, within the canine tumors.

All NCI-CCs are eligible for funding. A letter of intent is not required; a full proposal of no more than 6 pages must be submitted by the request receipt date to the NCI Office of Cancer Centers. Funding is contingent upon NCI approval of the proposal, which will include both a scientific and budgetary evaluation. These administrative supplements are designed to provide funds that will allow NCI-CC investigators to collaborate with veterinary medical college investigators who are actively involved in canine immunotherapy investigations, have access to canine cancer biospecimens for study, and have translational perspectives of comparative oncology.

Background

The past several years have seen an enormous advance in the use of immunotherapy approaches for cancer treatment in humans. In particular, the use of checkpoint inhibitor antibodies, such as anti-CTLA4 and anti-PD1, which bind to suppressor elements on immune cells and increase the magnitude and extent of effector cell immune responses, has achieved responses in at least 20% of patients with certain organ-site malignancies, such as melanoma, renal cell carcinoma, bladder cancer, and non-small cell lung cancer (NSCLC), with durable responses in a significant number of these patients. Initially, it was thought that the expression of PD-L1 on the surface of tumor cells could serve as a biomarker for responsiveness to anti-PD1 therapy, but several studies have shown that the correlations between expression and response are complex; the majority of patients with PD-L1 expressing tumors do not respond to PD-1/PD-L1 pathway blockade, while responses are occasionally seen in PD-L1 non-expressers. In 2015, Rizvi and colleagues[1] reported that sensitivity to PD-1 blockade in NSCLC depends primarily on a high non-synonymous mutation load in the tumor (generating neoantigens) and less on the expression of PD-L1 on the tumor surface—although that does play some role. Certain mutations, such as mismatch repair defects in colon cancer, appear to predict susceptibility to the effects of checkpoint inhibitors, as shown by longer progression-free survival in patients with these mutations[2]. The magnitude of T cell infiltration of tumor is also a factor, but not an independent biomarker[3]. The specificity and affinity of the engagement of T cells with tumor cell neoantigens in the context of the patient's HLA haplotype is probably important as well.

Animal models have been tremendously important tools in human cancer research. Immunocompetent mouse models, including syngeneic, transgenic, and genetically engineered mouse models (GEMMs), as well as a number of immunodeficient xenograft models, have been employed for decades. GEMMs carry many of the same mutations as do the corresponding human tumors and often develop tumors on a compressed timeline compared with the natural history of the human tumor; but these tumors are of mouse origin, not human, and do not—in general—replicate the genetic complexity of the human tumor, including its heterogeneity[4]. GEMMs therefore are not optimal for testing the response of drugs and immunotherapeutic agents to be used in humans. Immune deficient models, including patient-derived xenografts (PDXs) carrying human primary tumors, have been used to predict patient response to drugs, but they lack an intact immune system and are therefore inadequate for testing the effect of immunotherapies. In addition, Bondarenko[5] and others have shown that solid human tumors engrafted into NSG and NOG mice have a high probability of forming both B and T cell lymphoid tumors. More recently, "humanized" mouse models have been developed that accept and engraft human tissue, specifically human hematopoietic stem cells, and express human cytokine genes. However, a "perfect" humanized mouse model appropriate for immunotherapy studies would require specific human MHC class I and II elements to match those of the patients' tumors; these models would require considerable time to develop.

Another approach to both targeted therapy and immunotherapy research is the use of companion animals, such as dogs. Canine subjects with spontaneous tumors have a number of advantages over mice as therapeutic models as summarized by Paoloni and Khanna[6]. Briefly, the canine genome is similar to that of human; dogs are immunocompetent; spontaneously-occurring cancers in pet dogs have been increasing as a result of increased life expectancy; dogs are relatively outbred compared with laboratory animals (although some breeds have greater susceptibility to certain forms of cancer); the complexity of canine tumors in terms of heterogeneity, their relationship to the tumor microenvironment, and the development of resistance to treatment are closely related to cancer in human patients; and there are few standards of care and few agents approved for the treatment of cancer in dogs, and therefore investigational agents can be considered even in early or minimal residual disease states. In addition, Maekawa and colleagues demonstrated that canine PD-1 and PD-L1 genes were conserved among dog breeds and that the pathway is associated, as in humans, with T cell exhaustion that can be overcome with PD-1 or PD-L1 blockade[7].

Although it has not been demonstrated in dogs, it is probable that blockade of the PD-1/PD-L1 pathway will not result in a strong anti-tumor effect unless there is a high tumor mutational load that translates into the expression of neoantigens recognizable by the canine immune system. Mutations in human tumors do not necessarily parallel the equivalent mutations in canine tumors. For example, although both human and canine melanomas are similar in their activation of the AKT/mTOR pathway and other pathway dysregulation, B-raf mutations are rare in canine melanoma[8]. Conversely, the frequency of BRAF mutations is higher in canine urothelial carcinoma and prostate cancer compared with human tumors[8]. It is therefore important to identify the specific somatic mutations in canine cancers and understand why some of them become tumor neoantigens important for effective immunotherapy.

References

1. Rizvi, NA, MD Hellmann, A Snyder, et. al., Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer, Science 348, 2015, 124-128.
2. Le, DT, JN Uram, H Wang, et. al., PD-1 blockade in tumors with mismatch-repair deficiency, N Engl J Med 372, 2015, 2509-2520.
3. Taube, JM, A Klein, JR Brahmer, et.al., Association of PD-1, PD-1 ligands, and other features of the tumor immune microenvironment with response to anti-PD-1 therapy, Clin Cancer Res 20, 2014, 5064-5074.
4. Richmond, A and Y Su, Mouse xenograft models vs GEM models for human cancer therapeutics, Disease Models and Mechanisms 1, 2008, 78-82.

5. Bondarenko, G, A Ugolkov, S Rohan, et.al., Patient-derived tumor xenografts are susceptible to formation of human lymphocytic tumors, Neoplasia 17, 2015, 735-741.
6. Paoloni, M and C Khanna, Translation of new cancer treatments from pet dogs to humans, Nature Reviews Cancer 8, 2008, 147-156.
7. Maekawa, N, S Konnai, R Ikebuchi, et. al., Expression of PD-L1 on canine tumor cells and enhancement of IFN-γ production from tumor-infiltrating cells by PD-L1 blockade, PLOS One, 2014, DOI: 10.1371/journal.pone.0098415.
8. Mochizuki, H, K Kennedy, SG Shapiro, and M Breen, BRAF mutations in canine cancers, PLOS One, 2015, DOI: 10.1371/journal.pone.0129534.

Administrative Supplements

Currently, many NCI-CCs have an affiliation or are in a position to collaborate with investigators at veterinary medical colleges that are performing or are capable of performing genomic studies, including sequencing and analysis, on canine tumors. ***The goal of this solicitation is to give investigators at NCI-Designated Cancer Centers an opportunity to submit one-year supplement proposals for genomic studies (sequencing and analysis) in one or more of 6 different canine cancers: B-cell lymphoma, melanoma, bladder cancer, osteosarcoma, glioma, and breast cancer (and their normal cell equivalents).*** The goal is to characterize the immunogenic mutational load (neoantigens that can strongly bind canine MHC type I antigens) in 25 cases of each of these tumors in advance of testing the suitability of canine models for the study of single and combination immunomodulating agents, molecularly targeted drugs or chemotherapeutics.

Eligible Institutions

P30 CCSG 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 and is included as a component of the grant. The NCI-CCs must be able to work with one or more veterinary medical colleges to obtain and sequence canine tumor specimens and normal controls, and to analyze the results. Arrangements between the NCI-CC and the veterinary medical college concerning intellectual property and publications should be defined by the institutions involved prior to submission of this supplement application.

Number of Applications

Only one application per NCI-CC is allowed. Each application must include a cover letter from the NCI-CC Director, 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 6 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, 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 grant number
   d. Contact information for the Cancer Center Director 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 AOR must sign the face page.
      iv. Include a detailed budget description.
      v. Provide NIH biographical sketches for the P30 principal investigator and the principal leader of the sub-award.

3. **Summary of the Project Proposed**
   The applicant should attach a summary of the project including a description of aims; 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 and number of the canine tumors and controls that will be studied, and (b) a detailed description and rationale for the selected genomic methodologies (whole exome sequencing, RNA-seq, or combinations of methods) and computational tools that will be used to identify and analyze somatic mutations and the subsets that are predicted to be immunogenic. For the description of the investigators, the track record/experience of the proposed NCI-CC-Veterinary Medical College collaborators with this type of analysis is essential. For the environment discussion, the organizational relationships between the NCI-CC and the Veterinary Medical College should be described. 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 that will provide genomic analyses and bioinformaticians providing the computation analyses. 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 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 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. Toby T. Hecht by email at hechtt@mail.nih.gov.

Questions

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