

Update on Cancer Center, SPORE, and P01 Supplements and New Initiatives for Precision Medicine

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1 Year Supplements

- **Canine Immunotherapy Research via Collaboration of NCI-Designated Cancer Centers and Veterinary Medical Colleges—For P30s**

- **Studies of How the Microenvironment of Pancreatic Ductal Adenocarcinoma Affects Immunotherapy—For P30s, P50s, and P01s**
 - *Supplement solicitations issued: April 2016*
 - *Applications received: June 2016*
 - *Applications reviewed: July 2016*
 - *Funding plans established: August 2016*
 - *Supplements awarded: September 2016*

Canine Immunotherapy Supplement

Goal: 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 for translation to the treatment of human tumors

Specifically for this 1 year supplement:

- To expand knowledge of canine cancer immunotherapy in the area of mutational load and creation of neoantigens
- To characterize the T-cell numbers and subtypes and other relevant aspects of the tumor microenvironment
- Study: **25** cases (and controls) of at least one canine tumor type: B-cell lymphoma, melanoma, bladder cancer, osteosarcoma, glioma, mammary cancer
- Cancer Center investigators were required to form collaborations with investigators at veterinary medical colleges: accession of samples, sequencing, computational analysis and testing for mutations and neoantigens (that strongly bind canine MHC antigens), and analysis of the microenvironment

Why is the canine model important?

- **Current mouse models are deficient for assessing immunotherapy response in humans**
- **Canine patients with spontaneous tumors have advantages for both immunotherapy and targeted therapy research**
 - **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 cancers in humans**
 - **Dogs are immunocompetent**
 - **Dogs are relatively outbred compared with laboratory animals, although some breeds have greater susceptibility to certain forms of cancer**
 - **Few standards of care and only 1 approved agent (a TKI) for the treatment of cancer in dogs (for mast cell tumors); investigational agents can be considered even in early or minimal residual disease states.**
 - **There is an established track record of responsiveness to known chemotherapeutic agents**
 - **For many cancers, dogs and humans share major cytogenomic aberrations in signaling pathways**
 - **Spontaneously-occurring cancers in pet dogs have been increasing as a result of increased life expectancy**

Results of the solicitation

- **17 applications were received**
- **8 funded: scored in the Exceptional and Outstanding range**
- **The 8 applications covered studies in all 6 canine tumors**

Funded Canine Supplements

Institution(s)	Project Leader	Canine Cancer(s)	Title or Aims
Baylor College of Medicine/U. Florida Vet Med College/ Texas A&M/Tech U. Denmark	Jonathan Levitt, PhD/ Alan Herron, DVM	Bladder, Mammary, Melanoma	Mutational load and predicted neoantigens in canine tumors and characterization of immune infiltrate and the tumor microenvironment
U. Colorado/Colorado State U. Vet School	Jill Slansky, PhD/ Steven Dow, DVM, PhD	B-Cell Lymphoma	Immune profiling and neoantigen discovery in canine B cell lymphoma
DFCI-HCC/Tufts University Vet Med School	Katherine Janeway, MD/Cheryl London, DVM	Osteosarcoma	A multi-institutional approach to interrogate and improve immunotherapy outcomes in osteosarcoma
Purdue University/Duke University	Deborah Knapp, DVM/ H. Kim Lyerly, MD	Bladder	Advancing immunology in dogs with naturally-occurring invasive bladder cancer: a relevant model to improve immunotherapy across molecular cancer subtypes in humans
Roswell Park Cancer Inst. /Cornell U. Vet Med	Richard Koya, MD, PhD/Kristy Richards, PhD, MD	B-Cell Lymphoma	Immunogenic mutational load analysis for adoptive T cell therapy in canine B cell lymphoma
UC Davis/UC Davis School of Vet Med	Arta Monjazeb, MD, PhD	Glioma, Melanoma, Osteosarcoma	Evaluation of the tumor mutational landscape/neoantigens and immunophenotyping the tumor microenvironment in canine cancers
Ohio State U/OSU Vet Med School/TGEN	Peter Shields, MD/Jeffrey Trent, PhD	Melanoma, Osteosarcoma	Immunogenomic profiling of canine melanoma and osteosarcoma
MD Anderson CC/Texas A&M	Amy Heimberger, MD/ Jonathan Levine, DVM	Glioma	Genomic and immunological canine glioma characterization

Pancreatic Ductal Adenocarcinoma (PDAC) Microenvironment Supplement

Goal: To understand the interaction between PDAC tumors and the tumor microenvironment (TME) in order to design new immunotherapy interventions to accommodate and build on the distinct characteristics of the interaction

Studies for this 1 year supplement could include (but were not limited to):

- Differences in the TME in inflamed and non-inflamed PDAC tumors
- Heterogeneity of PDAC TME cell populations
- Functional role of stroma and stromal cells and the mediators they secrete to produce an anti-tumor or pro-tumor milieu
- Bi-directional influences between PDAC and the TME
- Evolution of the immunosuppressive TME with all its critical components over the course of the disease
- Mechanisms that would allow the influx of immune effector cells in large numbers so that checkpoint inhibitors and other immune modulations could work
- Epitope spreading (or not) during an immune response to a vaccine and the factors or cells responsible
- Conditions in the TME or interactions between the tumor and the TME that lead to metastases, including the role of myeloid derived suppressor cells (MDSCs)

Why are these studies important?

- An important dynamic exists between PDAC and its TME which leads to development and progression of the tumor. This needs to be further explored particularly with respect to the future use of immunotherapy for these tumors.
- Although there have been dramatic advances in some cancer types, including long-term responses using immune checkpoint inhibitors and other immunotherapies, these approaches for PDAC have not (for the most part) been successful.
- PDAC is considered an “immunologically quiescent” tumor.
 - Low mutational load; few neoantigens
 - Inflammatory cells do infiltrate the tumor, but they generally promote rather than inhibit growth
 - The TME is highly immunosuppressive: T_{regs}, B_{regs}, MDSCs, tumor-associated macrophages, other stromal elements that secrete suppressive factors
 - A minority of PDAC tumors have naturally occurring effector T cells
- PDAC is a recalcitrant cancer and these studies address initiative #3 in the Scientific Framework for PDAC Report to Congress.

Results of the solicitation

- **36 applications were received**
- **9 funded: scored in the Exceptional range**
- **8 supplements to Cancer Centers; 1 supplement to a SPORE**

Funded PDAC Supplements

Institution(s)	Project Leader	Title or Aims
Columbia University (P30)	Kenneth Olive	Targeting the granulocyte/fibroblast axis to overcome immunosuppression in pancreatic ductal adenocarcinoma
Fred Hutchinson Cancer Research Center (P30)	Sunil Hingorani	Modifying the tumor microenvironment to enhance engineered T cell therapy for PDA
University of Nebraska (P50)	Michael (“Tony”) Hollingsworth	Effects of pancreatic cancer microenvironment on tumor immune responses
Sloan-Kettering Institute for Cancer Research (P30)	Steven D. Leach, Vinod Balachandran	Genetic and transcriptional identification of immunogenic human pancreatic cancer subtypes
University of Michigan (P30)	Howard Crawford, Marina Pasca di Magliano	Therapeutic modulation of immune microenvironment in pancreatic cancer
Massachusetts Institute of Technology (P30)	Tyler Jacks	Extracellular matrix-targeted immunocytokines for pancreatic cancer treatment
Albert Einstein College of Medicine (P30)	John Condeelis	The tumor micro-environment in early metastasis of pancreatic ductal adenocarcinoma
University of Pennsylvania (P30)	Robert Vonderheide	Integrated analysis of the transcriptional and genetic profile of metastatic PDAC in the context of cytolytic immune activity
Washington University St. Louis (P30)	David DeNardo	How the microenvironment of pancreatic ductal adenocarcinoma affects immunotherapy—reprogramming the TME to facilitate immunotherapy

New Follow-On Precision Medicine Initiatives (RFAs)

- **Canine Immunotherapy Trials and Correlative Studies**
- **Consortium for Pancreatic Ductal Adenocarcinoma (PDAC) Translational Studies on the Tumor Microenvironment**
- **Approved by the NCI Board of Scientific Advisors on October 31, 2016**

Canine Immunotherapy Trials and Correlative Studies RFA

Goal: To establish a collaborative network of laboratory scientist and canine clinical trialists to support:

- Canine clinical trials using immunotherapy agents and novel combinations of immunotherapy and other modalities in dogs (focusing mainly on spontaneous B-cell lymphoma, melanoma, glioma, bladder cancer, osteosarcoma, and mammary tumors)
- Correlative studies that seek to describe, characterize, and understand the cellular and molecular mechanisms that determine the anti-tumor response (or non-response) in dogs with spontaneous tumors

Mechanism:

- Up to **5 UM1** grants consisting of academic laboratories, veterinary medicine clinical trial sites, and veterinary pharmaceutical companies (producing canine immunotherapy agents) working and sharing together
- **1 U24** coordinating center grant (that includes the COP and an NCI PO) with the following functions:
 - Create an ad hoc steering committee of required expertise (inside and outside the UM1 grantees)
 - Help develop/implement the clinical studies in immunotherapy and combinations
 - Assist in the standardization of clinical and laboratory immune monitoring protocols
 - Manage clinical and lab data from all sites and work with the NCI to contribute data to a public access database
 - Provide statistical support and facilitate sharing of agents, specimens, and data
 - Report progress in an annual report

Pancreatic Ductal Adenocarcinoma (PDAC) Microenvironment RFA

Goal: To allow the most advanced scientific and clinical teams to perform coordinated work on aspects of the PDAC microenvironment (immune responses, role of components of the tumor stroma, tumor vascularization), with access to common resources (including clinical specimens) and with the option to conduct early clinical trials particularly with agents developed at the grantee institution or in collaboration with industry

Mechanism:

- **Up to 5 U01** grants focused on various characteristics of the PDAC TME that will enable the design of new immunotherapy and other treatment interventions. These will be predominantly pre-clinical studies with translational potential, although a pilot clinical trial could be proposed in the later years.
- **1 U24** resource center grant with the following functions:
 - Administrative support of the consortium including monthly conference calls, annual meetings, communication and oversight
 - Bioinformatics support that would allow centralization of data resources generated by the consortium (GDC)
 - Coordinating the sharing of specimens and models; distribution of consortium-generated resources
 - Creation and maintenance of the consortium website
 - Assistance with the collection of data for the NCI



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