

RFA Concept: Canine Immunotherapy Trials and Correlative Studies

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BSA, October 31, 2016

Goals of the RFA

■ Long-Term Goal (For the NCI)

- To establish the suitability of canine models to study single and combination immunomodulating agents, ideally with molecularly targeted drugs, chemotherapy, or radiation
- To establish whether canine cancer research will inform the design of human cancer studies, particularly with respect to immunotherapy
- If appropriate, to translate findings from dog studies to human studies

■ Short-Term Goal (Specifically for this RFA)

- To establish:
 - A network of laboratory scientists and canine clinical trialists to study the anti-tumor effect of immunotherapy agents and novel combinations of immunotherapy and other modalities
 - A coordinating center to help develop and implement the clinical protocols (from one or more sites) in immunotherapy and combinations, to assist in the standardization of immunoassays, to collect and manage data from the sites, and to create a steering committee with all the required expertise so that the best possible clinical trials are performed.

Background

- **Enormous advances in immunotherapy for treatment of some human cancers have taken place in recent years.**
- **Current mouse models are deficient in assessing the response of immunotherapy agents for humans.**
 - **GEMMs do not, in general, replicate the genetic complexity of the human tumor, including its heterogeneity**
 - **Xenografts, including PDXs, do not have an intact immune system**
 - **“Humanized” mouse models are being developed, but are not there yet.**

Background (continued)

- **Canine patients with spontaneous tumors have many 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 agent FDA-approved (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

What we know:

ABOUT CANINE IMMUNE CHECKPOINTS AND INHIBITORS:

- **Canine PD-1 and PD-L1 genes are conserved 100% among dog breeds.**
- **Recombinant canine PD-1 and PD-L1 proteins have been constructed and shown to bind to one another; anti-PD1 antibody blocks the binding of soluble PD-1 with canine PD-L1 expressing cells in a dose-dependent manner.**
- **Fresh canine tumor biopsy explant cultures mixed with activated canine PBMCs \pm anti-PD1 showed an increase in IFN-gamma production in the presence of anti-PD1.**
- **Most canine tumors express PD-L1 and increased expression is associated with the density of T cell infiltration. Immune stimuli (e.g., IFN-gamma) can further upregulate PD-L1 expression.**
- **Anti-PD-L1 treatment enhances IFN-gamma production from cultured tumor-infiltrating lymphocytes (TILs) from clinical specimens.**
- **CD8+ TIL cells from canine lymphomas have a higher PD-1 expression than CD8+ cells from normal canine lymph nodes.**
- **A clinical trial studying the effect of anti-PD1 in dogs with cancer has begun.**

What we know:

ABOUT OTHER IMMUNOMODULATING AGENTS

- **A clinical trial of canine spontaneous melanoma treated intratumorally with human CD40L (a T-helper cell stimulator via binding to CD40 on APCs) in an adenovirus vector resulted in 5 CRs, 8 PRs, 4 SDs, and 2 PDs.**
- **Blocking IDO (with 1-methyl tryptophan) reverses immunosuppression in dogs with melanoma (that were treated with radiation therapy and CpG as an in situ vaccine.)**
- **Investigational plasmid IL-12 is being used in canine sarcoma trials.**
- **Adoptive T cell therapy after treatment with CHOP has been used in dogs with B-cell lymphoma and these canine patients have shown an increase in overall survival.**
- **Canine rituximab (anti-CD20) has been approved by the USDA.**
- **A her2/neu vaccine in canine osteosarcoma that expresses her2 resulted in increased survival.**
- **An antigen presenting cell vaccine is being tested in canine lymphoma.**

What we don't know (yet):

- **Is the immunogenic mutational load associated with better survival in dogs?**
- **Will anti-PD1 or anti-PD-L1 treatment of canine cancers in clinical studies lead to increased overall survival?**

Supplements (to P30 grants)

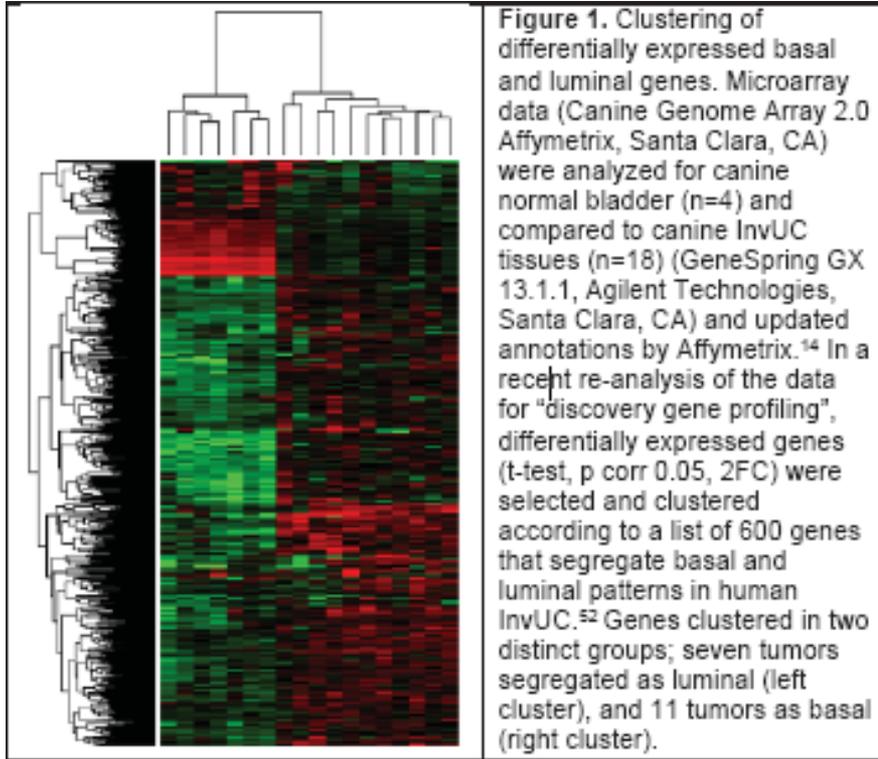
- As part of the Precision Medicine Initiative in Oncology, a number of 1-year supplements were issued including one entitled, **“Administrative Supplements for P30 Cancer Center Support Grants to Support Research in Canine Immunotherapy via Collaboration of NCI-Designated Cancer Centers and Veterinary Medical Colleges.”**
- The goals of the supplement are to:
 - Sequence (by whole exome sequencing and RNAseq) at least 25 canine tumors (and their normal controls) in one or more of the following tumors: **B-cell lymphoma, glioma, osteosarcoma, melanoma, bladder cancer, and mammary cancer**
 - Determine the mutational load in the cancers chosen for study
 - Using appropriate computational tools, characterize neoantigens that can strongly bind canine MHC antigens
 - Describe and characterize the T lymphocyte numbers and subsets, as well as other relevant aspects of the tumor microenvironment, within the canine tumors
- Seventeen (17) applications were received; 8 scored between 12 and 25.
- These 8 applications together included studies in all 6 canine tumors.

Funded 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

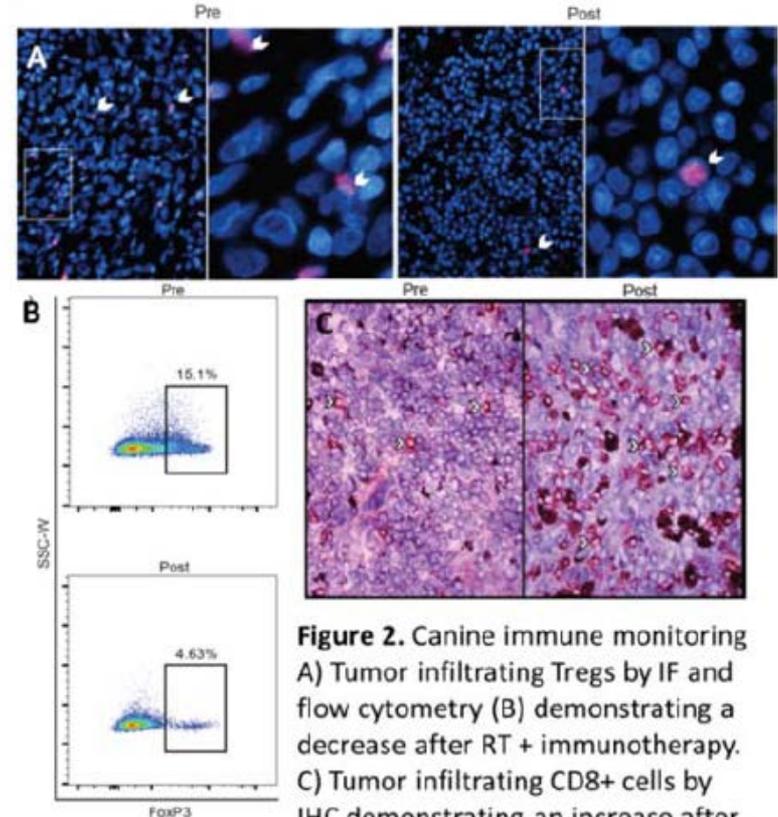
Examples of Published Preliminary Data from Supplement Applicants

Purdue: Bladder Cancer—dog bladder cancer gene expression clusters into luminal and basal subgroups—as in human disease



PLoS ONE. 2015;10(9):e0136688. PMID: 26352142

UC Davis: Melanoma (treated with an indoleamine 2,3-dioxygenase [IDO] inhibitor)



Going beyond...

- **This RFA will support:**
 - Canine clinical trials using immunotherapeutic agents and novel combinations (of immune modulators, molecularly targeted agents, chemotherapy, and/or radiation)
 - 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.
- **What will this require?**
 - A network of (up to 5) academic laboratories, veterinary medicine clinical trial sites, and veterinary pharmaceutical companies (producing canine immunotherapy agents) working and sharing together (**UM1s**)
 - A single coordinating center (**U24**) assisted by the NCI's Comparative Oncology Program (**COP**) and an NCI Program Official that will:
 - 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 correlative data from all sites and work with the NCI to contribute data to a public access database
 - Provide statistical support
 - Facilitate sharing of agents, specimens, and data
 - Report progress in an annual report
- **What is the COP (Comparative Oncology Program)?** A CCR program that “complements translational research through the characterization of relevant and naturally occurring cancers that develop in pet animals as a window to evaluate novel therapies.”
- **What is the COTC (Comparative Oncology Trials Consortium)?** “A collaborative effort between the NCI and extramural academic comparative oncology centers that functions to design and execute clinical trials in dogs with cancer in collaboration with the pharmaceutical industry, academia, not-for-profit groups, and governmental agencies interested in cancer drug development.”

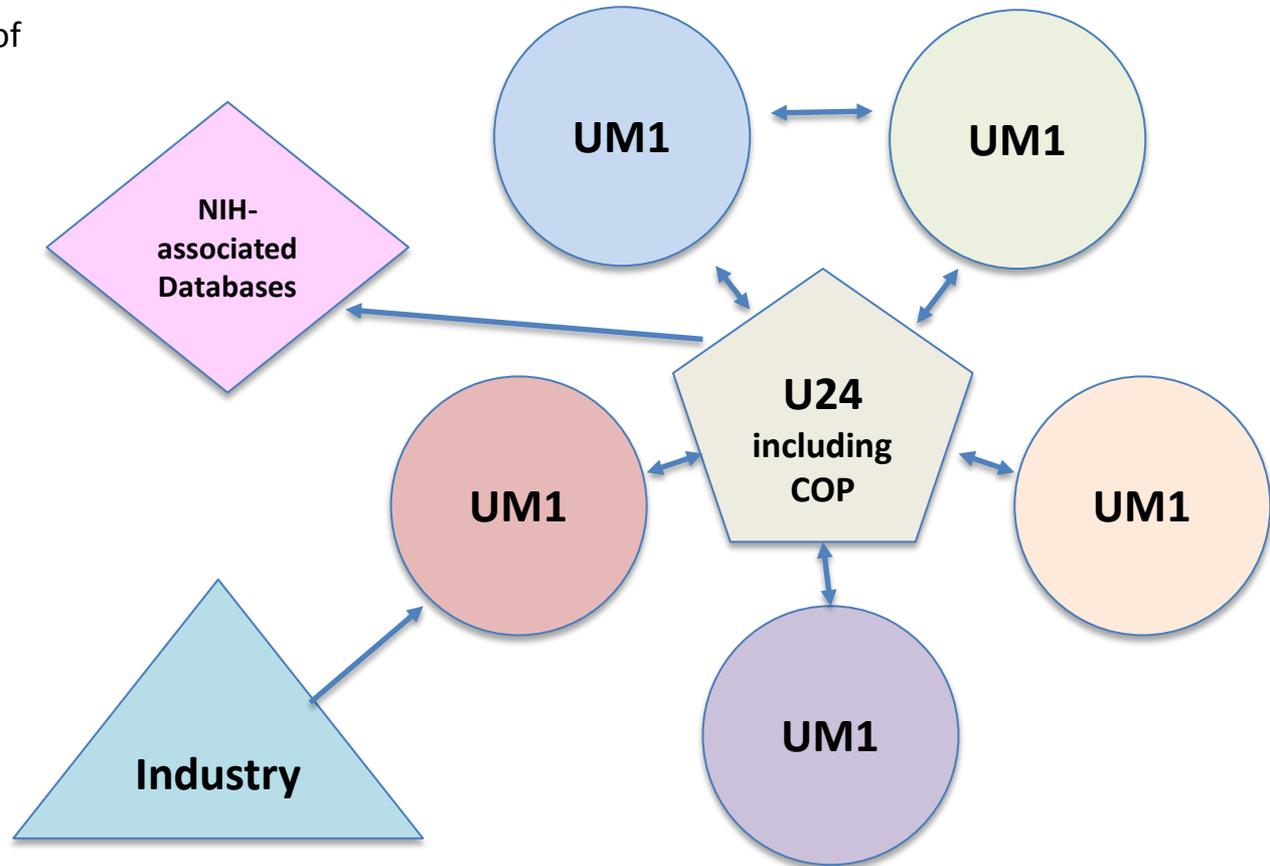
Note on availability of agents:

- **Many veterinary medical colleges already have working relationships with pharmaceutical companies that are developing and producing canine-specific immunotherapeutic agents**
- **Investigators working with canine models are often developing their own agents (antibodies, small molecules, miRNAs, T cell therapies, and vaccines) that have an immunomodulating/anti-cancer effect**
- **Canine-specific agents are being sought by the NCI; industry has expressed interest in working with the NCI**

Sharing of agents will be required in this RFA.

How will this RFA work?

Each **UM1** will consist of a PI's lab(s) and one or more vet med colleges (members of the COTC—or not) for the proposed clinical studies



In the unlikely event that no U24 application has sufficient merit for an award, one of the awarded UM1 sites will be selected for that role until a re-competition can take place.

Current Portfolio

- **Grants:**

- 20 active NCI grants in the NIH Grants Database (QVR) that perform studies in canines in at least one aim of the grant
- Only 1 grant is related to immunotherapy
 - Will study canine companion animals with sarcoma to conduct a clinical trial using autologous NK cells in combination with palliative radiotherapy or chemotherapy in order to demonstrate that NK cell and combination has anti-tumor effects targeting cancer stem cells.

- **Canine Clinical Trials through the COP's Comparative Oncology Trials Consortium (COTC: 22 veterinary medical colleges):**

- 2 active trials in pet dogs
 - One in osteosarcoma studying an mTOR inhibitor in the adjuvant setting (18 sites)
 - One defining the PK and biological activity of systemic oncolytic virus in dogs with relapsed or refractory cancer (3 sites)

Why so few trials? Funding issues! The COTC relies on funding from collaborating partners: foundations, DCTD, and pharmaceutical companies to conduct focused, biologically-rich trials. This RFA would help to do more trials at COTC member institutions.

How this will initiative be evaluated

- UM1 Sites and Network
 - Answer the question of whether canine cancer is an appropriate model for human malignant disease
 - Development of novel immunotherapy concepts including combination approaches, tested in canines
 - Successful collaboration between one or more UM1 sites in creating and implementing protocols and correlative studies/assays
 - Development of agents or ability to obtain immunotherapy agents from industry partners
 - Adequate accrual of canine patients to clinical trials
 - Discovery of new knowledge that can be translated to human patients
 - Publications and presentations at national and international meetings
- U24 Coordinating Center—including the COP
 - Assistance with the development and standardization of clinical protocols (including statistical support) and coordination of UM1 sites' activities including sharing of agents, samples, and protocols
 - Successful collaboration of the extramural site with the NCI's Comparative Oncology Program
 - Successful management of data from the various UM1 sites, contributing to a public access database
 - Evaluation of the progress and accrual of each UM1 site and recommendations to the NCI Program Officer
 - Assistance with publications

Funding Information

Network Component	Number of Sites	Total Cost/Year/Site	Total Cost/Year	Total Cost/5 Years
UM1	Up to 5	\$500,000	\$2,500,000	\$12,500,000
U24	1	\$500,000	\$ 500,000	\$ 2,500,000
		Total:	\$3,000,000	\$15,000,000



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