Spontaneous canine malignancies:
Models for precision cancer medicine

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What is comparative oncology and how can this approach improve and inform the cancer research and drug development process, with precision medicine in mind?

Comparative Oncology Program @ NCI
- Infrastructure and goals
- Comparative oncology clinical trials
  - Trial examples
  - New NCI-funded initiatives
The NCI’s Center for Cancer Research (CCR) is part of the Intramural Research Program (IRP) of NIH.

The NCI supports its mission through a combination of extramural funding (grants) and intramural (on-site) research.

- Molecular Imaging Program
- Comparative Oncology Program
NCI Comparative Oncology Program Goals

-Support integration of pet dogs with cancer in clinical trials via the COTC mechanism and advocate for the comparative approach within the drug development community

-Link COP laboratory efforts to consortium-based clinical trials
  -current focus: metastasis biology and metabolism in osteosarcoma

-Develop molecular imaging tools to support drug development and clinical trial activities

-Provide stewardship of COP resources
The remarkable similarity in cancers shared by human and dog

approx. 1.66 million diagnoses each year (approx. 500 cases/100 000 population)

approx. 4.2 million diagnoses each year (approx. 5300 dogs/100 000 population)

one pathogenesis

Joshua D. Schiffman, and Matthew Breen
Phil. Trans. R. Soc. B 2015;370:20140231
Reagent/Resources to conduct studies in Comparative Oncology
Genomics
Proteomics
Antibodies
PD Core
Contract Core
TMAs/Cell Lines

Canine Comparative Oncology and Genomics Consortium

Advocacy for the Appropriate Integration of Comparative Oncology Trials
Academia
Pharma
NCI
Regulatory Bodies
Antitumor activity and immunomodulatory effects
“Phase I evaluation of NHS-IL-12 Immunocytokine in Canine Melanoma”

Defined PK/PD, tolerability and efficacy across several dosing cohorts in naturally-occurring canine malignant melanoma; led directly to NCI-held IND in human patients.
Phase 3 assessment of anti-metastatic activity
“Impact of mTOR inhibition on metastatic progression in Canine Osteosarcoma”

What improvement in disease-free interval is seen with addition of sirolimus therapy to standard of care in the minimal residual disease setting?
Comparative Oncology Clinical Trials: Intent and Value

- Data generated in response to specific need in human drug development

- Trial design reflects specific questions being asked of the disease model in dogs
  - Tumor biology or drug target > histology
  - Dose/schedule, selection of lead compound, PK/PD relationships, biomarker validation
  - Efficacy often not primary endpoint

- Value of the data is a function of its novelty and relevance to human drug development
  - viewed in context by FDA as **important but supplementary**

What role can comparative oncology trials play in precision medicine?
Comparative oncology is the study of naturally-cancer that develop spontaneously in pet dogs in the context of intact immunity, correlative environmental exposures, and the natural species lifespan.

Questions we must address:

How to establish the genetic landscape of canine cancer?

Who will develop therapies that match genetic abnormalities?
  - Re-purposing
  - New discovery and development

Access to:
  - Analytical tools and expertise
  - Biologic samples
  - Clinical/demographic data
  - Agents to test in a clinical trial infrastructure
A first step: P30 Supplements to characterize the molecular landscape of selected canine cancers

- As part of the Precision Medicine Initiative in Oncology: “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 were to:
  - Sequence (by whole exome sequencing and RNAseq) at least 25 canine tumors (and their normal controls) in one of 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
  - 8 awards totaling ~ $4M
A second step: create a new RFA to investigate utility of dogs with cancer as models for immunotherapy development

- **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, and translate the findings 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 and to collect and manage data from the sites
How will this RFA work?

UM1 awardees will study:
✓ Glioma x 2
✓ Metastatic Osteosarcoma
✓ Melanoma
✓ Lymphoma

U24 awardee will work with the COP to standardize clinical protocols, foster collaboration and sharing of SOPs, reagents, data, etc.

5 awards totaling ~ $15M
Prioritization of lead(s) for human studies @ NCI

What are the distinct mechanistic differences in how different agents perform in canine cancer?
Target modulation, methylation profiling, synthetic lethality, etc.

New for 2018 and beyond:
NCI-sponsored Phase 0 studies in canine cancers

5 COTC member institutions

Biopsy → treat → biopsy schema

Peripherally-accessible disease to facilitate repeated tumor sampling

Short-term drug exposures

✓ PK/PD
✓ Tolerability
✓ Efficacy signal
Creation of an NCI comparative brain tumor consortium: informing the translation of new knowledge from canine to human brain tumor patients

Perspectives from man’s best friend: National Academy of Medicine’s Workshop on Comparative Oncology

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Scientists gather to survey comparative oncology research and pinpoint potential contributions to human therapeutics.

Collective experience within the cancer drug-development community suggests that conventional animal models and early-phase clinical studies in patients fail to provide seminal therapeutic insights needed to enhance the low rates of overall success and to reduce the late-stage failures in cancer drug discovery efforts. Dogs develop a broad spectrum of naturally occurring cancers that share strong similarities with human cancers, and, like human patients, pets receive state-of-the-art medical care that can include experimental therapeutics, thus offering a singular opportunity for preclinical modeling (1). A growing alliance of scientists involved in cancer research

The U.S. National Academy of Medicine’s National Cancer Policy Forum, which operates at the intersection of scientific research, science policy, and strategy development for cancer treatment and prevention, convened a workshop to analyze gaps in the optimal setting for clinical studies that include dogs with naturally occurring cancers (Fig. 1). The workshop provided a framework within which potential or perceived deficiencies in the field of comparative oncology could be defined and explored. A goal of the workshop was to apply a gap analysis to fashion an agenda designed to advance the role of dogs in preclinical drug development. Sessions on

Fig. 1. Conquering cancer: Walking the path together. The workshop, held in June 2015 in Washington, D.C., was entitled “The role of clinical studies for pets with naturally occurring tumors in translational cancer research” and had as its key goal to carry out a gap analysis of comparative oncology research. (http://iom.nationalacademies.org/Activities/Disease/NCPF/2015-JUN-08.aspx).

Summary and points for consideration

• Success in precision medicine is predicated on in-depth knowledge of the disease in question
  – More work to be done on genetic profiling of canine cancers and how they are/aren’t similar to human cancers
  – Screening/confirmatory diagnostic testing must be integrated with drug development and methods to rationally select treatment on a patient-by-patient basis

• Comparative oncology studies can:
  – Inform and enhance human cancer drug development
    • Small molecules, immuno-oncology, combination strategies
  – Increase the technical success of preclinical modelling and biomarker discovery
  – Provide valuable supplemental data to IND filings
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