The NIH/National Cancer Institute’s Comparative Oncology Program: Past, Present and Future

Amy K. LeBlanc, DVM DACVIM (Oncology)
Director, NCI Comparative Oncology Program
NIH/NCI Center for Cancer Research
Bethesda, MD
The NCI Comparative Oncology Program

• Programmatic overview
  – Infrastructure
  – Goals
• Comparative Oncology Clinical Trials
  – Overview of policies and procedures
  – Trial examples
• New initiatives
  – Imaging agent/tool development to complement drug studies
  – Comparative Brain Tumor Consortium
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.

Major Research Funding Entities:
- DCCPS
- DCP
- DCB
- OD
- DCTD
- DCEG
- CCR

Research Infrastructure and Support:

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

- Support integration of dogs in clinical trials via the COTC mechanism and interactions with the drug development community

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

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

- Provide stewardship of COP resources
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
Approximately 78 million dogs in US households
- Over 1 million will develop cancer each year

Many cancers are similar to those that occur in people:
- NHL, OSA, TCC, STS

Owners are increasingly interested in more advanced therapeutics for their pets
- Surgery, chemotherapy, radiation therapy and now small molecule inhibitors (toceranib, masitinib) are considered standard of care
Why consider the comparative oncology approach to cancer drug development?

| Comparative genetic etiopathogenesis | Greater synteny between dog/human vs. rodent/human  
Similar gene expression alterations in cancer |
|--------------------------------------|------------------------------------------------------------------------------------------------|
| Comparable signal transduction pathways | Similar druggable targets identified  
Similar angiogenic and apoptotic pathways |
| Spontaneous tumors, outbred population | Recapitulates heterogeneity in human tumors  
Recurrence, metastasis, resistance to therapy common |
| Lower relative cost | GMP quality material not always necessary  
Pre-IND work highly valuable, particularly for early efficacy signals |
| Population less heavily pretreated | Higher patient performance status, more accurate AE assessment and less acquired resistance |
| Body size of companion species | Similar imaging and treatment modalities used  
Opportunity for repeated tissue and fluid sampling |
Species in kind approach:
Dogs are the only species with significant access to both normal and tumor bearing individuals

- Laboratory dog is a common preclinical toxicity species
- Evaluation of agents in a rapid Phase I/II setting where dose escalation and response endpoints can be included.
- Can reach MTD more quickly based on normal dog data.
- Better anticipation of adverse events; characterization of clinical toxicities likely to occur in humans
- Determination of PK/PD endpoints and surrogate markers easily transferable from normal to affected dog
- Same species therapeutic index
A Comparative and Integrated Approach to Cancer Drug Development
CANCER

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

Amy K. LeBlanc, Matthew Breen, Peter Choyke, Mark Dewhirst, Timothy M. Fan, Daniel L. Gustafson, Lee J. Helman, Michael B. Kastan, Deborah W. Knapp, Wendy J. Levin, Cheryl London, Nicola Mason, Christina Mazcko, Patricia N. Olson, Rodney Page, Beverly A. Teicher, Douglas H. Thamm, Jeffrey M. Trent, David M. Vail, Chand Khanna

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).
COTC 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
MOU/CDA
C3D data mgmt.
Drug/trial package
Protocol

MTA (drug)

IACUC

Contract for clinical case management—Contract core
Contract to perform correlative assays—PD Core

NIH/NCI COP

CDA
Protocol
Budget

Sponsor

COTC sites

IACUC
COTC Trial Development Process

Protocol Development

- Concept Discussions (Sponsor and COTC)
- 1st draft of Letter of intent & study budget (COTC)
- Review of LOI and budget (Sponsor)
- PD Core development (COTC)
- Protocol drafted (COTC)

Study Implementation

- Development of clinical database (COTC)
- Ordering of trial supplies (COTC)
- Selection of COTC sites (COTC)
- Protocol training (COTC)

Contract Process

- Study agreement between sponsor & NCI
- Contract between sponsor and PD Core
- MTA between NCI and COTC sites (NCI)
- Contracts between sponsor and COTC sites

Estimated time: 6-8 weeks.
Estimated time: 4-6 weeks. Can occur simultaneously with Contract Process
Estimated time: 6-8 weeks. Can occur simultaneously with Study Implementation

Blue designates responsibility of sponsor
<table>
<thead>
<tr>
<th>COTC Trial</th>
<th>Summary of Initiated COTC Trials</th>
<th>No. COTC Sites</th>
<th>Publication Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>COTC003</td>
<td>PK/PD (tumor) of rapamycin in OS</td>
<td>4</td>
<td>PLoS One 6/2010</td>
</tr>
<tr>
<td>COTC005</td>
<td>Tolerability and biological of tumor targeted IL-2/IL-12</td>
<td>4</td>
<td>Pending</td>
</tr>
<tr>
<td>COTC006</td>
<td>Optimizing PD endpoints sampling by cryobiopsy technique</td>
<td>2</td>
<td>Pending</td>
</tr>
<tr>
<td>COTC007a</td>
<td>Trial design validation: parent Topoisomerase I inhibitor</td>
<td>6</td>
<td>Pending</td>
</tr>
<tr>
<td>COTC007b</td>
<td>Evaluation of three novel Indenoisoquinolines</td>
<td>6</td>
<td>Complete/under analysis</td>
</tr>
<tr>
<td>COTC008</td>
<td>Tolerability and feasibility of long term parenteral rapamycin in OS</td>
<td>14</td>
<td>PLoS One 6/2010</td>
</tr>
<tr>
<td>COTC013</td>
<td>Bioavailability of orally administered rapamycin</td>
<td>2</td>
<td>Pending</td>
</tr>
<tr>
<td>COTC020</td>
<td>PK of oral rapamycin in OS (walk-in)</td>
<td>5</td>
<td>Complete/under analysis</td>
</tr>
<tr>
<td>COTC021/022</td>
<td>Adjuvant rapamycin in OS when added to SOC</td>
<td>17</td>
<td>Open trial</td>
</tr>
<tr>
<td>COTC024</td>
<td>Oncolytic virotherapy in canine cancer</td>
<td>5</td>
<td>Open trial</td>
</tr>
<tr>
<td>COTC026</td>
<td><em>Listeria</em>-based immunotherapy in OS</td>
<td>TBD</td>
<td>Under development</td>
</tr>
</tbody>
</table>
One patient, many opportunities
Canine and human melanoma may exhibit key differences in activating mutations, but demonstrate similar malignant potential, downstream pathway activation and biologic behavior in vivo.

- BRAF/NRAS mutations rare
- Role of c-kit
- Etiology

- AKT and MAPK pathway activation + loss of p16 and p53
- Aggressive biologic behavior and metastasis
- Poorly responsive to cytotoxic chemotherapy
- Responsive to immunotherapies

- BRAF/NRAS/c-kit mutations common but variable
- UV-induced
RESEARCH ARTICLE

Defining the Pharmacodynamic Profile and Therapeutic Index of NHS-IL12 Immunocytokine in Dogs with Malignant Melanoma

Melissa Paoloni1, Christina Mazcko1, Kimberly Settling2, Susan Lana3, Lisa Barber4, Jeffrey Phillips5, Katherine Skorupska5, David Vail5, Heather Wilson6, Barbara Biller7, Anne Avery7, Matti Klupfel7, Amy LeBlanc1, Anna Bernhardt8, Beatrice Brunkhorst9, Robert Tighe10, Chand Khanna*10

1 Comparative Oncology Program, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland, United States of America, 2 College of Veterinary Medicine, University of Missouri-Columbia, Columbia, Missouri, United States of America, 3 College of Veterinary Medicine and Biological Sciences, Colorado State University, Fort Collins, Colorado, United States of America, 4 School of Veterinary Medicine, Tufts University, North Grafton, Massachusetts, United States of America, 5 College of Veterinary Medicine, University of Tennessee, Knoxville, Tennessee, United States of America, 6 School of Veterinary Medicine, University of California Davis, Davis, California, United States of America, 7 School of Veterinary Medicine, University of Wisconsin-Madison, Madison, Wisconsin, United States of America, 8 College of Veterinary Medicine, Texas A&M University, College Station, Texas, United States of America, 9 College of Veterinary Medicine, Michigan State University, East Lansing, Michigan, United States of America, 10 EMD-Serono Research and Development Institute, Billerica, Massachusetts, United States of America

* khannac@mail.nih.gov

Abstract

Background

Interleukin (IL)-12 is a pro-inflammatory cytokine that mediates T-helper type 1 responses and cytotoxic T-cell activation, contributing to its utility as an anti-cancer agent. Systemic administration of IL-12 often results in unacceptable toxicity; therefore, strategies to direct delivery of IL-12 to tumors are under investigation. The objective of this study was to assist the preclinical development of NHS-IL12, an immunocytokine consisting of an antibody, which targets necrotic tumor regions, linked to IL-12. Specifically this study sought to evaluate the safety, serum pharmacokinetics, anti-tumor activity, and immune modulation of NHS-IL12 in dogs with naturally occurring cancers.

Graph showing IL-10 pg/ml versus Hours post administration with different lines for concentrations of .4 mg/m2, .8 mg/m2, 1.6 mg/m2, and 2.4 mg/m2.
Osteosarcoma Disease Free Survival

Cum. Survival vs. Time in weeks
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 Rapamycin to standard of care in the minimal residual disease setting?
Clinical Trial in Dogs with Newly Diagnosed Osteosarcoma

The Morris Animal Foundation and the National Cancer Institute are sponsoring a clinical trial in dogs with newly diagnosed Osteosarcoma. Your dog will receive standard of care as part of the study.
The Setup

Randomization

- Tumor Location in Proximal Humerus (yes/no)
- Elevated Serum ALP (yes/no)

SOC

SOC + R

Limb Amputation

4 Cycles of Carboplatin

Follow up:
- Physical exam
- Thoracic radiographs

4 Cycles of Rapamycin

Follow up:
- Physical exam
- Thoracic radiographs
Integrated and Comparative Drug Development Path: Emphasis on Imaging Endpoints and Biomarkers

**Non-Human Primate**

**Beagle Dog**

Small Animal Preclinical

Veterinary Studies

**Target Biology**

**SOP Validation**

**Assay Development**

**IMAGING: Biodistribution, new agent evaluation**

Veterinary Studies

**Dose**

**Toxicity**

**Pharmacokinetics**

**Pharmacodynamics**

**IMAGING: correlative PK/PD**

**Phase I Human Clinical Trials**

**Phase II Human Clinical Trials**

**Phase III Human Clinical Trials**

**New Human Cancer Drug**

**Veterinary Studies**

**Activity**

**Regimen**

**Schedule**

**Biomarkers**

**Responding Histologies**

**IMAGING: Clinical Response**

**IMAGING: Long term response**

**Veterinary Studies**

**Biomarkers**

**Combination therapies**

**Minimal Residual Disease**
Comparative Cancer Imaging on the Bethesda NIH campus

- Educate NCI on the opportunity to image naturally-occurring canine cancer patients – impact on biology and drug development

- Study and validate novel radiopharmaceuticals and modalities destined for human cancer imaging purposes

- Tools: $^{13}$C-hyperpolarized MRI and novel $^{18}$F-radiopharmaceuticals & techniques for T cell and metabolic imaging
Advanced imaging with pathologic correlates is readily available within COTC infrastructure

$^{18}$F-FLT PET/CT before and after exposure to GS-9219, a novel nucleoside analogue in canine lymphoma

Hyperpolarized MRI: can we turn MRI into PET?

Conventional MRI:

- Relies on magnetic resonance signal from proton nuclei within the body
- 2D/3D imaging
- Signal is linearly proportional to nuclear spin polarization
- Spectroscopic capabilities can inform on tissue biochemistry

Hyperpolarized MRI:

- Uses ultra-fast MRI sequences to detect hyperpolarized nuclear spins of biologically-relevant isotopes (\(^{13}\text{C}, \^{15}\text{N}, \^{3}\text{He}, \^{129}\text{Xe})
- Provides 4-6x signal enhancement independent of magnet strength
- Spectroscopic shift imaging in real time from parent contrast agent to downstream metabolites in vivo ~ mM concentrations
- \(^{13}\text{C}\)-pyruvate → \(^{13}\text{C}\)-lactate CSI most common clinical application
GE SpinLab™ includes sterile path, multiple patient dose capabilities, internal QC system.

Preclinical DNP polarizer: HyperSense™; optimized to support *in vivo* use.
What benefits can be gleaned from $^{13}$C-pyruvate MRI?

• A more accurate reflection of the Warburg effect?
  – Pyruvate-to-lactate shift rather than glucose uptake

• Gain greater understanding of metabolic heterogeneity *in vivo*
  – Development and monitoring of metabolically-targeted therapies

• Anatomic and metabolic data with no ionizing radiation exposure

• Gauge response to therapies where $^{18}$FDG-PET is not accurate
Creation of an NCI comparative brain tumor consortium: informing the translation of new knowledge from canine to human brain tumor patients


Sponsored by
NCI-Center for Cancer Research
-Comparative Oncology Program
-Neuro-oncology Branch
Conceptual infrastructure for a
Comparative Brain Tumor Consortium

Extramural community

Radiologists
Neuro-Oncologists
Radiation Oncologists
Surgeons

Comparative Oncology Program
Neuro-Oncology Branch

NIH/NCI

Pathology and Molecular Markers
Drug discovery
Tumor biology and Immunology
Clinical Trials
Patient Outcomes
The NCI Comparative Oncology Trials Consortium

Auburn University
Auburn, AL

Oregon State University
Corvallis, OR

Tufts University
North Grafton, MA

University of Guelph
Guelph, ON Canada

University of Pennsylvania
Philadelphia, PA

Colorado State University
Ft. Collins, CO

Purdue University
West Lafayette, IN

University of California
Davis, CA

University of Illinois
Urbana, IL

University of Tennessee
Knoxville, TN

Cornell University
Ithaca, NY

Texas A&M University
College Station, TX

University of Florida
Gainesville, FL

University of Minnesota
St. Paul, MN

University of Wisconsin
Madison, WI

Kansas State University
Manhattan, KS

The Ohio State University
Columbus, OH

University of Georgia
Athens, GA

University of Missouri
Columbia, MO

Virginia Tech
Blacksburg, VA

North Carolina State University
Raleigh, NC

Washington State University
Pullman, WA
The NCI-Comparative Brain Tumor Consortium leads cross-disciplinary research in naturally-occurring canine brain tumors to advance diagnostic and therapeutic strategies to benefit both human and canine patients.

**Basic Research**

**What data are needed to more fully validate canine brain tumors as models for humans?**

- How does the histologic and molecular landscape of canine glioma and meningioma compare to that of humans?
- What comparable drug sensitivities exist among the available canine brain cancer cell lines?
- How can we construct a multi-center prospective bio-banking effort to support basic research in canine brain tumor biology?

**Translational/Clinical Research**

**What opportunities exist to include dogs with brain tumors in cancer drug and imaging agent development?**

- How are canine brain tumor patients diagnosed and managed in today’s veterinary practice climate?
- How can we standardize best practices in support of multicenter brain tumor clinical trials in dogs?
- What mechanisms exist to increase awareness and acceptance of the canine model of brain cancer?
- What types of clinical trial designs are most impactful within a comparative model of brain cancer?
- Do we need natural history studies of canine cancer patients?
The NCI-Comparative Brain Tumor Consortium leads cross-disciplinary research in naturally-occurring canine brain tumors to advance diagnostic and therapeutic strategies to benefit both human and canine patients.

Basic Research

What data are needed to more fully validate canine brain tumors as models for humans?

- How does the histologic and molecular landscape of canine glioma and meningioma compare to that of humans?

- Canine Glioma Pathology Board
  - Combined MD/DVM review of 150 FFPE cases
  - H&E + 5 IHC markers
  - 18 member board
  - 19 institutions

- Comparative high-throughput drug screening of canine and pediatric glioma cell lines

- Whole-exome sequencing of canine glioma and meningioma (collaboration with NCI, NCATS and CBTC membership institutions)
The NCI-Comparative Brain Tumor Consortium leads cross-disciplinary research in naturally-occurring canine brain tumors to advance diagnostic and therapeutic strategies to benefit both human and canine patients.

Translational/Clinical Research

- What opportunities exist to include dogs with brain tumors in cancer drug and imaging agent development?
  - How are canine brain tumor patients diagnosed and managed in today’s veterinary practice climate?
  - How can we standardize best practices in support of multicenter brain tumor clinical trials in dogs?
  - What types of clinical trial designs are most impactful within a comparative model of brain cancer?

- Survey instrument to veterinarians
- MRI consensus document
- PAC-1/^{18}F-CP18 apoptosis imaging and therapy clinical trial in meningioma
Summary and points for consideration

• The NCI COP provides a robust, facile mechanism to generate high-quality comparative oncology clinical trial data
• Leverage the past successes and support to advance new concepts

• Intent:
  – 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
Acknowledgements

NIH-NCI Center for Cancer Research
- Office of the Director (Dr. Tom Misteli)
- Molecular Imaging Program (Drs. Peter Choyke, Elaine Jagoda)
- Pediatric Oncology Branch (Drs. Kathy Warren, Rosandra Kaplan, Fernanda Arnaldez)
- Radiation Biology Branch (Drs. Murali Cherukuri, Kazu Yamamoto)
- NeuroOncology Branch (Dr. Mark Gilbert)

NIH-NCI Comparative Oncology Program
- Dr. Chand Khanna
- Christina Mazcko
- Dr. Ling Ren
- Dr. Shan Huang
- Dr. Hongsheng Wang
- Dr. Arnulfo Mendoza
- Christine Tran Hoang
- Anusha Kambala

NCI Division for Cancer Treatment & Diagnosis (DCTD)

COTC member institutions, investigators, and support staff: past, present and future

University of Queensland Center for Advanced Imaging