Advantages and Experiences with Trials that include Pet Animals

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Institute of Medicine Workshop 2015
Advantages and Experiences with Trials that include Pet Animals

Disclosure/Perspectives

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TO PROVIDE OPPORTUNITIES TO INCLUDE NATURALLY OCCURRING CANCER MODELS IN THE STUDY OF CANCER BIOLOGY AND THERAPY

Companion Animal Cancer Models

- Large outbred animals
- Strong genetic similarities to humans
- Naturally occurring cancers
- Immune competent and syngeneic
- Relevant tumor histology/genetics
- Relevant response chemotherapy
- No “Gold Standards”
- Compressed progression times
- Tumor heterogeneity
- Recurrence/Resistance
- Metastasis biology

Expression Profiles for Canine and Human Osteosarcoma are Indistinguishable

BMC Genomics 2009
Cross Species Comparative Approach Adds to the Totality of Data Surrounding Drug Development

- Rodent Models
  - Genetically Engineered Mouse Models
- Xenografts
- Canine Model
  - CCR - Comparative Oncology Program
- Human Model: Clinical Trials

Improved Understanding of Biology and Improved Treatment Outcomes
What is the reason for the high attrition rate for oncology drugs?
• Cancer is a complex problem
• Preclinical models are not predictive
• Pathway is linear and largely ignores opportunities to be informed
• Important questions are not sufficiently answered
A Comparative and Integrated Approach to Cancer Drug Development

Nature Reviews Cancer 2008
Tumor vaccines administered for canine lymphoma $^{13,14}$

Development of bone marrow transplantation regimes in dogs $^{11,12}$

Hyperthermia (thermoradiotherapy) techniques correlated with clinical efficacy in a canine model $^{69}$

Limb sparing optimized in canine osteosarcoma $^{71,72}$

Cytokine and chemotherapeutic inhalation strategies first assessed in dogs with cancer $^{76-79}$

Evaluation of BCG immunotherapy in canine melanoma $^{9}$

Defined toxicity, activity, PK and tumoral PD with tyrosine kinase inhibition $^{44,84}$

DNA vaccine approved for use in canine melanoma $^{37,99-100}$

Paoloni and Khanna Nature Reviews Cancer 2008
Projected “Value” of an Integrated Drug Development Path

Projected “Value” of an Integrated Drug Development Path

- **Preclinical**
  - # of Cancer Drugs Reaching This Phase in Development

- **Phase I**
  - # of Drugs in CONVENTIONAL DRUG PATH
  - # of Drugs in INTEGRATED DRUG PATH

- **Phase II**

- **Phase III**

- **Approval**
Projected “Value” of an Integrated Drug Development Path

Cumulative Cost of Cancer Clinical Trials

Projected "Value" of an Integrated Drug Development Path

# of Cancer Drugs Reaching This Phase in Development

Preclinical Phase I Phase II Phase III Approval

“Value” of an Integrated Drug Development Path is defined by the importance of questions that are now unanswered.

http://sloanreview.mit.edu
“What are the question best answered through this comparative approach: Review

LeBlanc, Khanna et al. In Preparation
Comparative Oncology Program – Center for Cancer Research

Comparative Oncology Trials Consortium (COTC)

Advocacy for the Appropriate Integration of Comparative Oncology Trials

Academia
Pharma
NCI
Regulatory Bodies

Reagent/Resources to conduct studies in Comparative Oncology

Genomics
Proteomics
Antibodies
Biospecimen Repository
PD Core
Canine Comparative Oncology and Genomics Consortium

Progress by the Comparative Oncology Trials Consortium (COTC)

Initiated of Letters of Intent 19
Initiated study protocols 11
Studies completed 9
Studies published 3
Studies in progress/in press 7

Studies of COTC are published under a “Collection” in PLoS One
Visit Date: 21-Mar-2006

ENROLLMENT

Dog's Sex

Date of Birth

Age

Initials

Breed

Dog's First Name

Dog's Last Name

Owner's First Name

Owner's Last Name

Referring DVM Name

Referring DVM Address

Referring DVM Phone Number

Date of Registration

Registering Institution

Patient ID

Patient Subgroup

Primary Disease Site

Disease Term

Stage of Disease

"MO037" - University of Missouri
"TN021" - University of Tennessee
"CO018" - Colorado State University
"PA151" - University of Pennsylvania
Guiding the Optimal Translation of New Cancer Treatments From Canine to Human Cancer Patients

Chand Khanna,³ Cheryl London,² David Vail,¹ Christina Mazcko,³ and Steven Hirschfeld⁴

Abstract
On June 20, 2008, a meeting entitled “Translation of new cancer treatments from canine to human cancer patients,” sponsored by the National Cancer Institute in Bethesda, Maryland, was convened to discuss the potential value, opportunity, risks, and rewards of an integrated and comparative drug development path for new cancer therapeutics that includes naturally occurring cancers in pet animals. A summary of this meeting and subsequent discussion are provided here to afford clarity on the conduct of these studies so as to optimize the opportunities provided by this novel drug development and modeling strategy. (Clin Cancer Res 2009;15(18):5671–7)
COTC Study Development:

1. Discuss questions not answered fully through conventional models or human trials.
   - Validation of target/drug biology in the dog
   - CCOGC Biospecimen Repository
   - PD Core

2. Determine if the dog can be used to answer questions.
   - Validation of target/drug biology in the dog
   - CCOGC Biospecimen Repository
   - PD Core

3. Iterative collaboration to define study overview/endpoints

4. Develop study protocol and data base

5. Selection of COTC sites to manage clinical study
   - Based on study completion goals and protocol intensity

6. Conduct study
   - Amend protocol with data input

7. Complete study
• Pfizer-CCOGC Biospecimen Repository is open for tissue release

• Currently houses over 2,000 patient samples
  • osteosarcoma, lymphoma, melanoma, pulmonary tumors, mast cell tumor, soft tissue sarcomas and hemangiosarcoma.
  • tumor and normal tissues (formalin fixed, snap frozen and OCT), frozen serum, plasma, urine and whole blood.

**News Release**

**FOR IMMEDIATE RELEASE**

**Date:** October 29th 2012

**Contact:** Matthew Breen, Ph.D.
**E-mail:** Biospecimens@ccogc.net
**Phone:** 919-879-8438

Canine Comparative Oncology and Genomics Consortium
and the Pfizer-CCOGC Biospecimen Repository
Announce the Availability of
Canine Cancer Patient Biospecimens for Scientific Study
Effective October 29th 2012
COTC Pharmacodynamics Core

Providing efficient access to laboratory and investigative platforms to study the biology of cancer and drug-cancer relationships in dogs

“Credential” targets and biological concepts before study launch

Support biological questions asked within COTC studies

- Clinical Pathology
- Pathology
- PARR for clonality
- IHC
- ICC
- Flow cytometry
- Cell Culture/
  Proliferation/
  Migration/Invasion
- Expression Arrays
- Proteomics
- Western Blot
- Pharmacokinetics
- Microscopy
- Metabolism
- RT-PCR

Doug Thamm and Sue Lana  CSU
**Comparative Oncology Trials Consortium: Study Examples**

**Antitumor activity and immunomodulatory effects**
“Evaluation of IL-12 and IL-2 Immunocytokines in Tumor Bearing Dogs”

**Tumor Specific Targeting – Tolerability**
“Evaluation of RGD Targeted Delivery of Phage Expressing TNF-a to Tumor Bearing Dogs”

**Modeling Personalized Medicine Delivery in Dogs**

**Pick the Winner – Biological and Antitumor activity**
“Preclinical Comparison of Three TOPO-1 inhibitors in Dogs with Lymphoma”

**Molecularly informed therapy**
AAVP-TNF Therapeutic Index (repeat dose):

• Favorable safety profile, n=18 dogs with cancer (relevant host)
  ➢ Grade 3 hypersensitivity reaction, n=9
  ➢ Grade 3 and 4 Fever, n=5 (2 on non-admin day)
  ➢ Tumoral necrosis, n=1
  ➢ No clinically relevant Hem/Biochem toxicities
  ➢ Three warm necropsies: no end organ abnormalities

AAVP-TNF Associated Tumor Regression:

➢ RECIST criteria
➢ 15 evaluable dogs
➢ Objective anti-tumor activity
  ➢ 2 Partial Response
  ➢ 6 Stable Disease
  ➢ 7 Progressive Disease
Systemic delivery of AAVP-TNF (phage) results in tumor regression

Canine Myxosarcoma (T3bN0M0)

Day 0
LD = 12.3 cm

Day 28
LD = 8.2 cm
RECIST = 33%
regression

Day 56
LD = 1.85 cm
RECIST = 85%
regression

Now surgically resectable - CR
Comparative Oncology Trials Consortium: Study Examples

**Antitumor activity and immunomodulatory effects**
“Evaluation of IL-12 and IL-2 Immunocytokines in Tumor Bearing Dogs”

**Tumor Specific Targeting – Tolerability**
“Evaluation of RGD Targeted Delivery of Phage Expressing TNF-a to Tumor Bearing Dogs”

**Modeling Personalized Medicine Delivery in Dogs**

**Pick the Winner – Biological and Antitumor activity**
“Preclinical Comparison of Three TOPO-1 inhibitors in Dogs with Lymphoma”
COTC007: Novel Topo Inhibitors: Integrated Comparative Approach to Identify Lead Agent

Low throughput selection of “lead”
Lead Candidate Discrimination/Selection Study: COTC007b

**Biological Endpoints**

**Serum Pharmacokinetics**

- Tumoral Drug Levels
- Drug Target/Modulation Biological Activity

**Circulating Tumor Cell**

- Tumor Cell Numbers
- Target Modulation Biological Activity

**Tumoral Drug Levels**

- Tumor Biopsy
- Tumor Aspirate
- BM Aspirate
- CTC collection

**Drug Target/Modulation Biological Activity**

- Tumor Biopsy 2, 6 hrs post tx
- Tumor Aspirate 2,4,6 hrs post tx
- 24 hr Serial PK
- 24 hr Serial PK

**Biological Activity**

- Normal tissue (Bone marrow)
- Target Modulation Biological Activity

**Timeline**

- Pre-tx
- Day 1 (1st Dose)
- Dosed daily for 5 days
- Day 5 (5th Dose)
- Day 6 (24 hrs post last dose)
- Day 29

CR/PR

SD/PD

Off Study
COTC007: Novel Topoisomerase I Inhibitors: Integrated Comparative Approach to Identify Lead Agent

Opportunities to Answer Questions to Inform Phase III Designs:

- No “Gold Standards” so ability to treat in naïve disease
- Compressed progression times
- Assess activity of drugs that uniquely target metastatic progression

Preclinical models:
- Small animal
- Beagle dog
- Non-human primate

Pharmacokinetics
Pharmacodynamics
Therapeutic Index
Minimal Residual Disease
Combinational Therapies
Novel Biomarkers

Tumour-bearing dog studies

New cancer drug
Toward a Drug Development Path That Targets Metastatic Progression in Osteosarcoma

Integrated Approach to Osteosarcoma Drug Development

Translational studies of agents that target “vulnerable” metastatic cells.

**Canine OS Trials**

- Minimal residual disease studies
  - Comparative Oncology Trials Consortium
  - 5 new agents in 5 yrs
  - Prioritize agents for human MRD/adjuvant based studies of metastatic progression

**Early Phase Trials**

**Therapeutic Approach:**

- Aminobisphosphonates
- Rapalog inhibition of mTOR
- Ezrin small molecule inhibitors

**Later Phase Trials**

- Measurable Disease
- Minimal Residual Disease
A Comparative and Integrated Approach to Cancer Drug Development

Preclinical models
- Small animal
- Beagle dog
- Non-human primate

Phase I human clinical trials
Phase II human clinical trials
Phase III human clinical trials

Tumour-bearing dog studies
- Activity
- Toxicity
- Pharmacokinetics
- Pharmacodynamics

Tumour-bearing dog studies
- Dose
- Regimen
- Schedule
- Biomarkers
- Responding histologies
- Combination therapies

New cancer drug

Nature Reviews Cancer 2008
Perceived Risks and Concerns with the Integration of a Comparative Approach

Study Duration
- Timelines are longer than those in rodent models
- **Strategic** inclusion of pet dogs should allow timely integration of data into human trials

Patient to Patient Variability
- Tumor-bearing dogs represent a different clinical population compared to research dogs
- **SNP frequency** amongst dogs is similar to that of patients in early phase cancer studies

Cancer Prevalence by Histology
- Most common: sarcomas and lymphoid neoplasms
- Less common: Breast, prostate, gastrointestinal, lung carcinomas
- Studies in the less common histologies require more time for completion and more clinical trial centers
- Histology is increasingly replaced with biology and not often a primary question for trial design

**Target biology may be unique and must be defined (“credentialed”)**
- *Canine Comparative Oncology and Genomics Consortium*
- *Pfizer - Canine Oncology and Genomics Consortium Biospecimen Repository*
- *Comparative Oncology Program Tissue Array Resource*
Drug and Budget Requirements
• Greater drug supply needed
• GMP not required
• Study costs include: clinical management, serial biopsy of tumors, imaging and other correlative endpoints

Control and reporting of data
• Good Clinical Practice guidelines
• Adverse Event reporting: Assign severity, duration, and attribution
• Compliance by pet owners and study investigators is very high

Regulatory oversight/reporting
• Pre-IND agents - guidance has been proposed and used
  • (Khanna et al Clin Cancer Res 2009)
• Post-IND agents - guidance exists

Biotech and aversion to “rocking” the development boat
Acknowledgements

Tumor and Metastasis Biology Section, Pediatric Oncology Branch, National Cancer Institute
- Ling Ren
- Arnulfo Mendoza
- Michael Lizardo
- James Morrow
- Allyson Koyen
- Tanasa Osborne
- Rhadika Gharpure
- Martin Mendoza
- Sung Hyeok Hong
- Manpreet Alhuwalia
- Jessica Cassavaugh
- Joseph Briggs

Comparative Oncology Program
CCR, National Cancer Institute
- Amy Leblanc
- Melissa Paoloni
- Christina Mazcko

Molecular Oncology Section, Pediatric Oncology Branch, National Cancer Institute
- Bob Wiltz
- Lee Helman

C3D-NCI
- Caryn Steakley
- Allison Wise
- Jeffrey Shilling
- Sawsan Sahin
- Deven Shah
- Rohit Paul

COTC
- Amy LeBlanc
- Jeffrey Phillips
- Shelley Newman
- Doug Thamm
- Susan Plaza
- Christie Anderson
- Carolyn Henry
- Kimberly Selting
- David Vail
- Ilene Kurzman
- Karin Sorenmo
- Amy LaBlanc
- Timothy Fan
- William Kisseberth
- Barb Kitchell
- Heather Wilson

CCOGC
- David Vail
- Matthew Breen
- Sue Lana
- Jaime Modiano
- Kerstin Linblad-Toh
- Elizabeth McNeil
- Phil Bergman
- Steve Withrow
- Mark Simpson
- Cheryl London
- Bill Kissebirth