Status of Current Resources and Experiences with Naturally Occurring Cancer in Companion Animals: Biology, Immunology and Experimental Therapeutics

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www.csuanimalcancercenter.org

Stanford One Health: Focus on Comparative Oncology
May 8, 2017

Colorado State University
Flint Animal Cancer Center
Biological Characteristics

**Companion Animal Cancer**
- Large outbred animals
- Favorable genomic characteristics
- Naturally occurring cancers
- Immune competent
- Relevant tumor histology/genetics
- Therapeutic intent and relevant outcomes
- Limited ‘standards of care’
- Compressed progression times
- Tumor heterogeneity
- Recurrence/Resistance
- Metastasis biology

Homologous Tumor Types

Lymphoma DLBCL
Osteosarcoma
Bladder
Brain
Breast
Skin cancer
Melanoma - mucosal
Sarcoma

Paoloni, et al 2009, BMC Genomics
Continuum of Cancer Care

Patients at Risk
- Risk Reduction

Patients with Cancer
- Early Detection
- Staging
  - Curative Treatment
  - Palliative Treatment
    - Hospice Care/Grieving
- Survivorship
Golden Retriever Lifetime Study

Prospective, observational lifetime study to determine risk factors for cancer over the life course of 3000 GR.

Primary Outcomes: incidence of osteosarcoma, mast cell tumor, hemangiosarcoma, and lymphoma.

Secondary Outcomes: hypothyroidism, allergies, heart disease, epilepsy, hip dysplasia, kidney failure.

Annual lifestyle and medical surveys with biosamples.

Association of outcomes with genetics, lifestyle, diet, reproductive history, environmental exposures, etc.
Owner Questionnaire

- Dog-o-graphics
- Sire and dam history
- Litter mate history
- Reproductive history
- Physical activity
- OTC meds, flea and heartworm prevention
- Dental hygiene
- Grooming
- Diet and feeding practices
- Environment and living conditions
- C-BARQ behavioral questionnaire
Gene – Environment Interactions

Exposure Source
- Toxin
- Drug
- Diet

Transport & Route
External Dose
Internal Dose

High Metabolizer genotype = lower body burden

Low Metabolizer genotype = higher body burden

Biological Effect
Altered Function

Low Detox Genotype = increased risk
High Detox genotype = decreased risk

Clinical Disease

Translational Opportunity
Time
Humans – decades; Dogs - years
Shared Exposure of Interest

Co-exposures and Risk Factors
- Obesity
- Thyroid hormone biology.
- Reproductive hormone – estrogen mimics or phytoestrogens.
- Diet – source of contaminants eg. PhIP
- Water – insecticides/herbicides/heavy metals
- Indoor air quality

Multi-generational exposures
Exposure mitigation strategies
Continuum of Cancer Care

Patients at Risk
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- Early Detection

Patients with Cancer
- Staging
  - Palliative Treatment
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Curative Treatment
- Survivorship
Drug Development Process Overview

It can take up to fifteen years to develop one new medicine from the earliest stages of discovery to the time it is available for treating patients.

- **Pre-Discovery**: 3-6 years
- **Drug Discovery**: 5,000-10,000 compounds
- **Preclinical**: 5 years
- **Clinical Trials**: 250 volunteers
  - Phase 1
  - Phase 2
  - Phase 3
- **FDA Review**: 6-7 years
- **LG-Scale Mfg**: 0.5-2 years
- **Phase 4: Post-Approval Activities**: One FDA-approved drug
Significant Failure Factors

- **Complex Commercial Viability Challenges**
  - **Pre-IND**
    - Combined overestimation of efficacy and underestimation of toxicity from in vivo data.
  - **Post-IND**
    - Clinical Trial Realities
    - Unexpected acute toxicity
    - Chronic toxicities not previously identified
    - Poor efficacy
Raising the Standards of Preclinical Cancer Research

New tools
- Robust animal systems
- Large cell line and biosample collections
- Patient selection biomarkers

Open access to all data – positive or negative
Reproducibility of published findings

Begley CG, Ellis LM  Nature 2012,  483: 531-533

*Rigor Mortis* (sloppy science) – Richard Harris, 2017
A Comparative and Integrated Approach to Cancer Drug Development

Preclinical models
- Mouse
- Dog
- Non-human primate

Dogs with cancer
- Activity
- Toxicity
- Pharmacokinetics
- Pharmacodynamics

Dogs with cancer
- Dose
- Regimen
- Schedule
- Biomarkers
- Responding histologies
- Combination therapies

Phase I/II human clinical trials

Phase III human clinical trials

Phase IV/post-marketing surveillance

New cancer drugs

Better cancer drugs

Adapted from: Nature Reviews Cancer – 2008

<table>
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<tr>
<th>Risk factor</th>
<th>Canine Clinical Study Mitigation Plan</th>
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<tr>
<td>Non-optimal dose selection</td>
<td>Supplement preclinical studies with single and repeat-dose escalation studies in dogs with naturally occurring cancers. Include tissue biopsy to assess target effects.</td>
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<tr>
<td>Delayed or cumulative toxicity</td>
<td>Clinical phase I/II trials in companion animals with associated PK/PD assessments at delayed endpoints. Clinical observation (nausea) and clin path (e.g. liver enzymes or bx) in aged or co-morbid patients.</td>
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<tr>
<td>Lack of relevant biomarkers</td>
<td>Serial biopsies of both tumor and adjacent normal tissue. Biological sampling (serum, plasma, urine, feces) can provide treatment-related changes for identification of predictive indicators of drug response or toxicity.</td>
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<td>Hepatic toxicity</td>
<td>Elderly canine patients with cancer/concurrent disease better reflect the hepatic vulnerability of human patients during drug studies.</td>
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# Drug Development Challenges and Mitigation

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<td>Limited predictability from traditional animal systems.</td>
<td>Develop evidence of relevance through enabling efficacy studies as proof of concept.</td>
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<td>Rare cancers lack patient numbers or market share.</td>
<td>Companion animals with rare human-relevant diseases could be surrogate clinical trial subjects.</td>
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<td>Equivocal safety/efficacy profile for an exciting new product</td>
<td>Phase II trial canine/feline trials may provide balanced assessment of risk/benefit.</td>
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<td>Personalized therapy approaches not supported by traditional animal systems</td>
<td>Understanding of disease personalization or disease-modifying therapeutic targets through focused study of susceptible stages of disease, challenging co-morbidities or immunologic genotypes.</td>
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Comparative Oncology: The Emerging Business Case

Honigberg et al, PNAS. 2010

Mkt cap: $260M

Mkt cap: $8B
Immuno-Pathology Core

Develop and Validate Canine Reagents
- Preclinical immunotoxicology
- Immune responses to interventions

Characterize Immunologic Landscape of Canine Neoplasia

Determine binding site characteristics of Canine MHC molecules
Ed Gillette/Steve Withrow ’78
NIH PPG CSU ‘85-’96
NIH PPG Duke/NCSU 86-2005
CSU Center Status 2001
VTH Extension ’02 (35K SqFt)
Ca Bio PhD for DVM’s ‘05
CU-CSU Consortium ’07,’12
Endowment Fund ’07 - current
5 Endowed Chairs
CSU Cancer Res Funding ’07-15
VTH Remodel ‘16 (~ 7K Sq Ft)
Clinical Service and Research at the FACC

32 Faculty, House Officers and Staff

Multi-Disciplinary Care -

1600 new cancer patient referrals annually

(25-30% of all hospital appointments)

3500 - 3700 rechecks annually

Frequently seen cancer types

- Osteosarcoma (~200/yr)
- Lymphoma (~200/yr)
- Invasive MCT (~100/yr)
- Soft tissue sarcoma (~125/yr)
- Carcinoma (~125/yr)
- Melanoma (~30/yr)

- Strategically recruit as needed per protocol
Dedicated Clinical Trials Program

Dedicated faculty coordinator
Dedicated DVM’s, nursing/archiving staff, grant admin & hospital space

Experience:
20-30 active trials/yr
250-300 patients eval/yr
>700 appts/yr

Diverse Research Core support

Dr. Kristen Weishaar
Clinical Trials Director
Current FACC Research Strengths
40 Research Faculty, students, staff

Pharmacology
Immunology/Immunotherapy
Radiation Biology/Onc
Dev Ther and Clin Trials
Musculoskeletal Onc
Molecular Bio/Genomics
Cell Lines & Archive

RESOURCES:

CU-CSU Collaboration
NCI-60 Cell Lines
FACC Cell Lines
COXEN Algorithm
FACC Biorepository with outcome data.
Prospective COXEN-Driven Clinical Trial in Canine OSA

$300 K + Owner Cost-Share.

**FIGURE 6.** Predictivity of human-based COXEN models in canine cell lines and clinical outcome in canine osteosarcoma patients. A) COXEN scores of all 6 drugs are correlated to actual IC50 data from the ACC-16 using Spearman correlation. B) Survival curves of predictions from the NCI60-COS49 tumor models. The COXEN prediction for “Responder” or “Non-responder” is based on a sensitive or resistant prediction to either DOX, CARBO, or CIS. The Log Rank test was performed for significance.