How dogs are helping us understand and treat cancer: promise, progress and challenges

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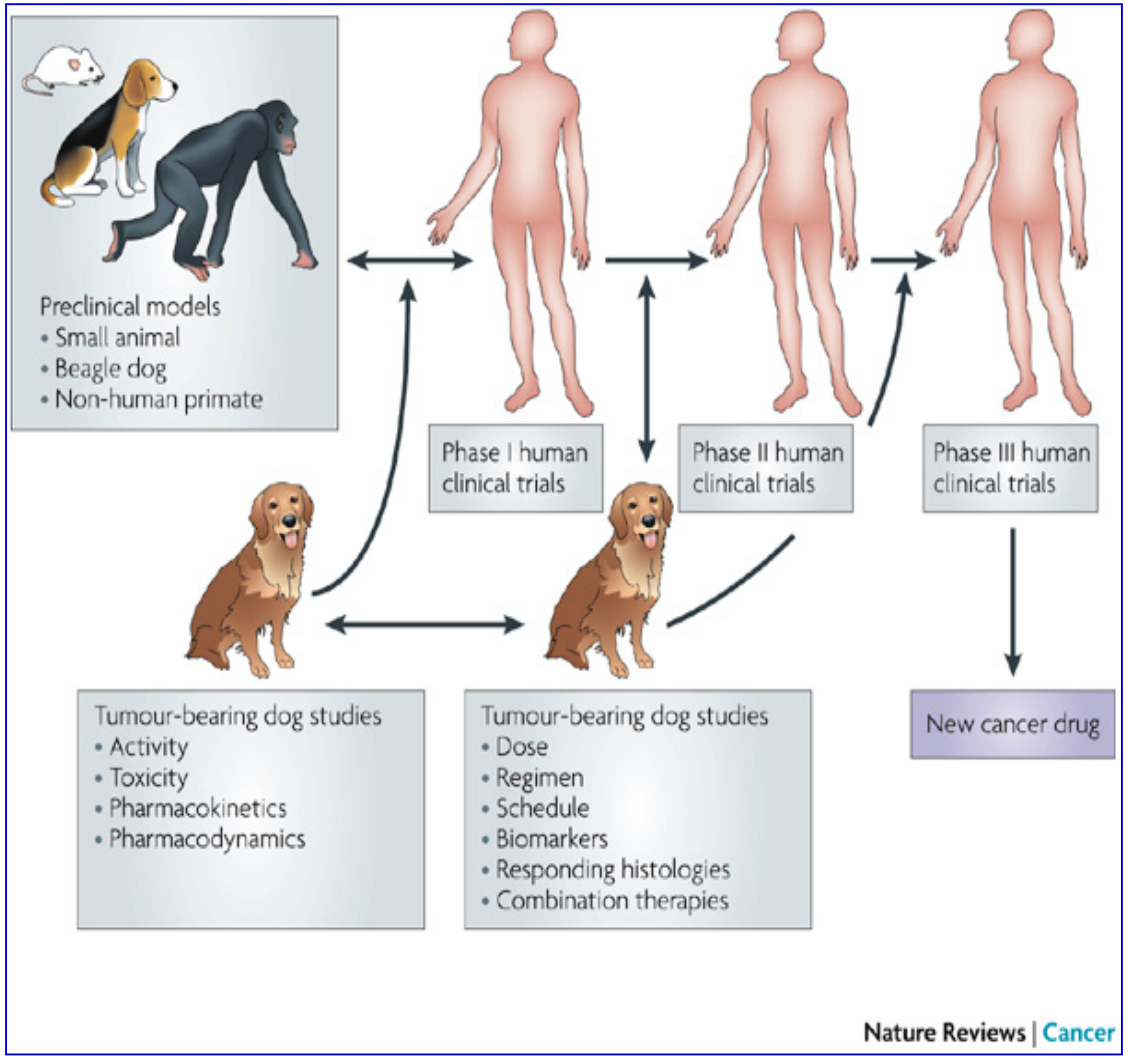
NIH NATIONAL CANCER INSTITUTE

A Comparative and Integrated Approach to Cancer Research and Drug Development: What is the Value?

- ✓ **Naturally-occurring, spontaneous cancers – solid tumors, hematologic cancers**
- ✓ **Immune-competent host**
- ✓ **Compressed disease progression, short survival**
- ✓ **Co-evolving tumor/stroma heterogeneity**
- ✓ **Application of chemotherapy, surgery, radiotherapy; single-agent and combinations**
- ✓ **Resistance to therapy and metastasis**
- ✓ **No 'standard of care'**

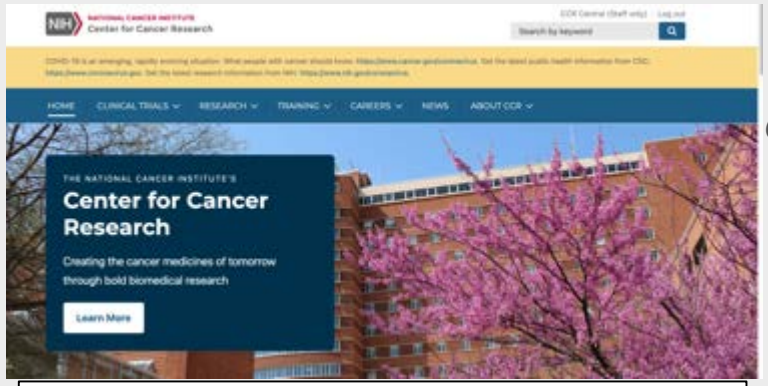


Improving human cancer therapy through the evaluation of pet dogs

Amy K. LeBlanc and Christina N. Mazcko

Abstract | Comparative oncology clinical trials play an important and growing role in cancer research and drug development efforts. These trials, typically conducted in companion (pet) dogs, allow assessment of novel anticancer agents and combination therapies in a veterinary clinical setting that supports serial biologic sample collections and exploration of dose, schedule and corresponding pharmacokinetic/pharmacodynamic relationships. Further, an intact immune system and natural co-evolution of tumour and microenvironment support exploration of novel immunotherapeutic strategies. Substantial improvements in our collective understanding of the molecular landscape of canine cancers have occurred in the past 10 years, facilitating translational research and supporting the inclusion of comparative studies in drug development. The value of the approach is demonstrated in various clinical trial settings, including single-agent or combination response rates, inhibition of metastatic progression and randomized comparison of multiple agents in a head-to-head fashion. Such comparative oncology studies have been purposefully included in the developmental plan for several US FDA-approved and up-and-coming anticancer drugs. Challenges for this field include keeping pace with technology and data dissemination/harmonization, improving annotation of the canine genome and immune system, and generation of canine-specific validated reagents to support integration of correlative biology within clinical trial efforts.

The State of Comparative Oncology in North America



Intramural + Extramural NCI – Comparative Oncology Program Focus on Cancer Drug Development, Comparative Genomics and Translational Tumor Biology

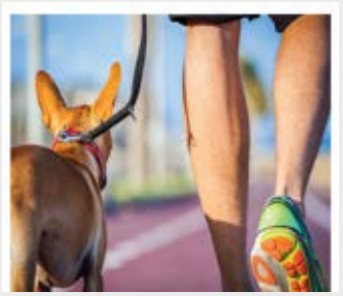
The NCI Comparative Oncology Trials Consortium (COTC)

Integration of Comparative Oncology within the Cooperative Group Structures

(Children's Oncology Group; NCI-CTEP, NeXT)

Increasing support from Pharma to conduct early phase studies with novel cancer therapeutics

Comparative Cancer Genomics
Breen Lab – NCSU
TGen
Broad Institute
Ostrander Laboratory- NIH/NHGRI



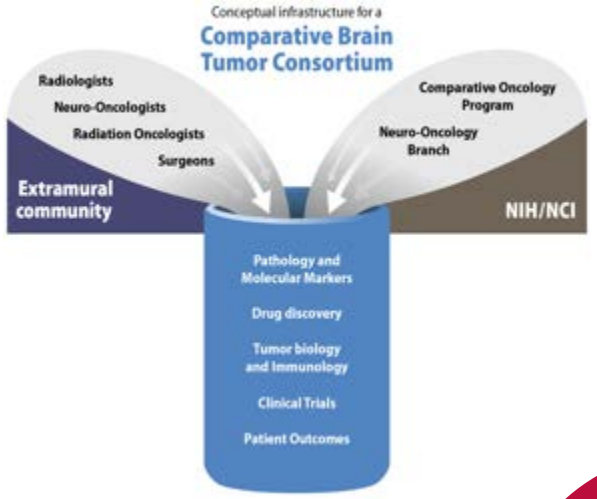
Study of gene-environment and cancer-associated risk factors

NIH or other National Funding/Philanthropy for Comparative Oncology Research

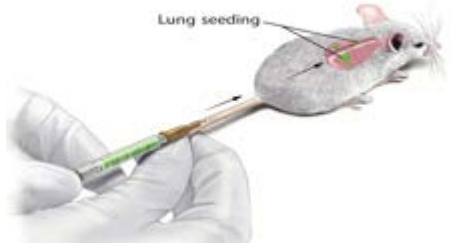
10 Veterinary Colleges with formal membership and integration to NCI Comprehensive Cancer Centers

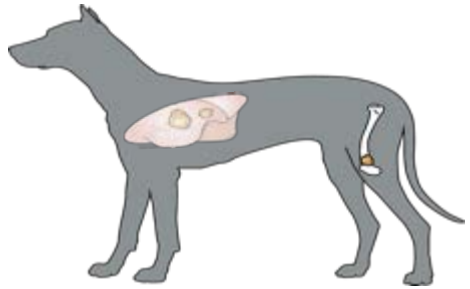
Several with informal or individual interactions

Other cooperative veterinary clinical trial groups (private practice and academic-led)



Osteosarcoma-focused laboratory research





GOAL: integration of comparative biology and clinical trial data to advance the translational relevance of canine cancer to humans

Collaborations

COTC trials

PRE-medical Cancer Immunotherapy Network for PRECINCT Canine Trials

Support to extramural NCI

DCTD/DTP

NExT

dog^2 Deciphering the Osteosarcoma Genome in Dogs

The NCI Comparative Oncology Trials Consortium (COTC)

Auburn University
Auburn, AL

Colorado State University
Ft. Collins, CO

Cornell University
Ithaca, NY

Kansas State University
Manhattan, KS

Iowa State University
Ames, Iowa

Louisiana State University
Baton Rouge, LA

Oregon State University
Corvallis, OR

Purdue University
West Lafayette, IN

Texas A&M University
College Station, TX

The Ohio State University
Columbus, OH

Tufts University
North Grafton, MA

University of California
Davis, CA

University of Georgia
Athens, GA

University of Guelph
Guelph, ON Canada

University of Illinois
Urbana, IL

University of Minnesota
St. Paul, MN

University of Missouri
Columbia, MO

University of Pennsylvania
Philadelphia, PA

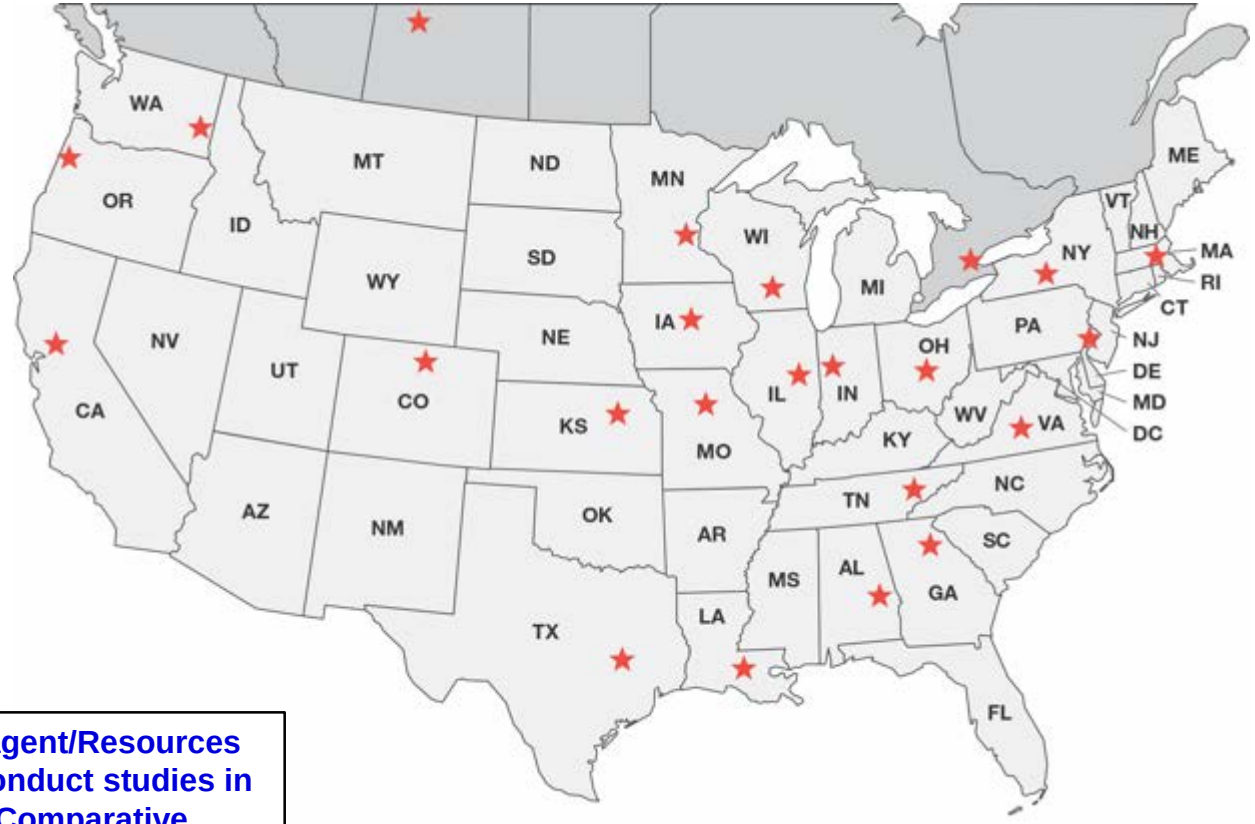
University of Saskatchewan
Saskatoon, Saskatchewan

University of Tennessee
Knoxville, TN

University of Wisconsin
Madison, WI

Virginia Tech
Blacksburg, VA

Washington State University
Pullman, WA



Reagent/Resources to conduct studies in Comparative Oncology

Integrated Canine Data Commons

PD Core - CSU
Contract Core
TMAs/Cell Lines
Biospecimen Repository

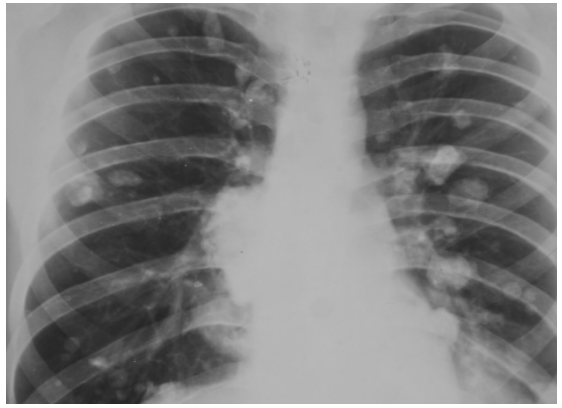
Advocacy for the Appropriate Integration of Comparative Oncology Trials

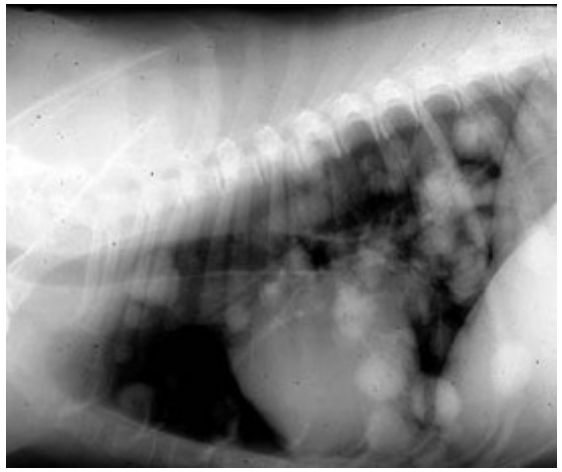
Academia
Pharma
NCI
Regulatory Bodies

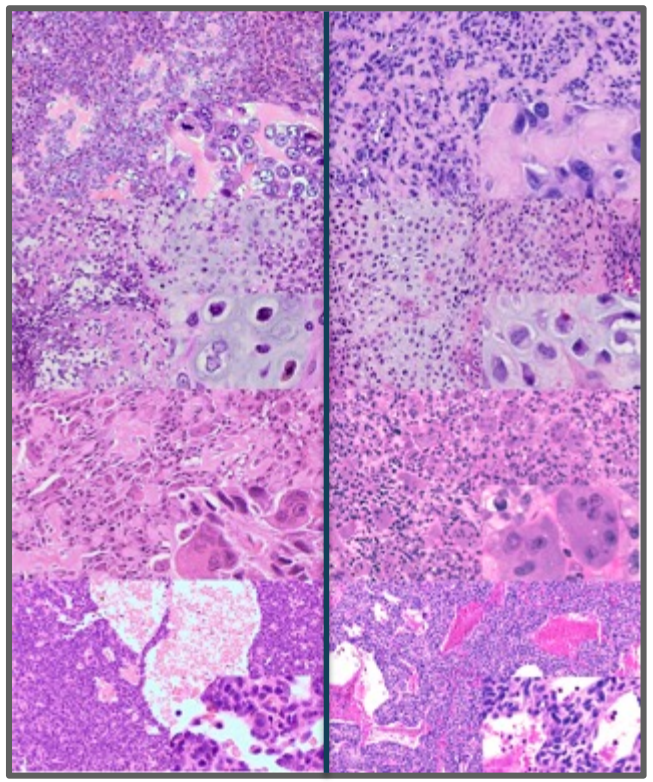
NIH NATIONAL CANCER INSTITUTE
Technology Transfer Center

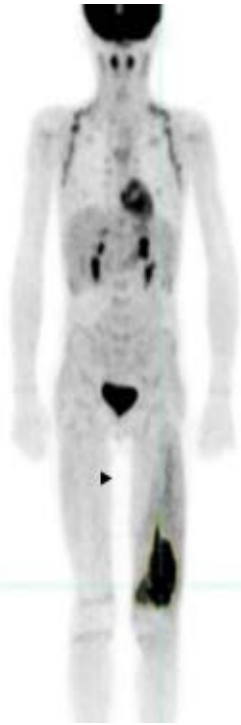
Canine Osteosarcoma

- >10,000 middle-old age, large and giant breed dogs in the US/year vs. ~ 1000 pediatric/AYA cases
- Median Survival Time: 10-14 months - majority develop **metastatic disease**
- Shares many clinical and molecular features with pediatric osteosarcoma
- Canine model recognized as a key component of discovery process for new therapies for children





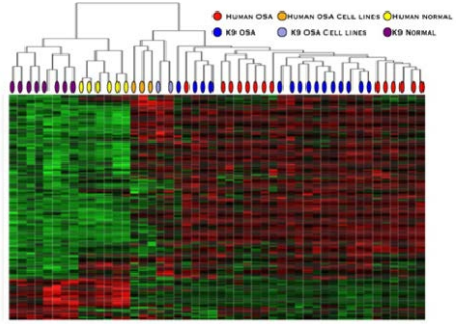




Images courtesy of Jessica Beck/NCI, Nicola Mason/UPenn and Kristen Weishaar/CSU

The National Cancer Institute
Comparative Oncology Trials Consortium

Define genomic landscape of canine OS with COP biospecimen repository



Integrate with human OS data (NCI TARGET)

TARGET

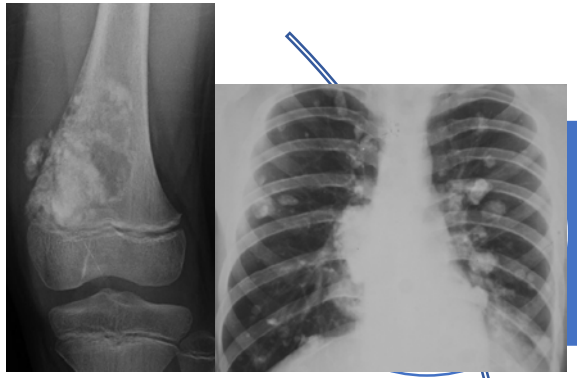
Identify new druggable targets

Interrogate with preclinical (mouse) models

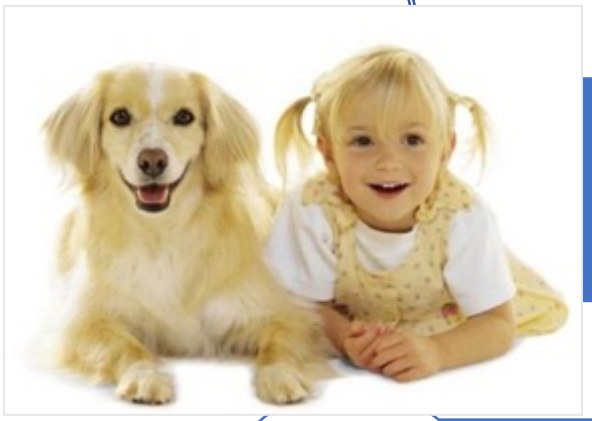
Prioritize therapeutic approaches to study in canine OS clinical trials

A Comparative Approach: Leveraging existing tools and expertise to identify new approaches for pediatric OS

How is comparative study of naturally-occurring canine osteosarcoma (OS)...



…informing drug development for human patients?

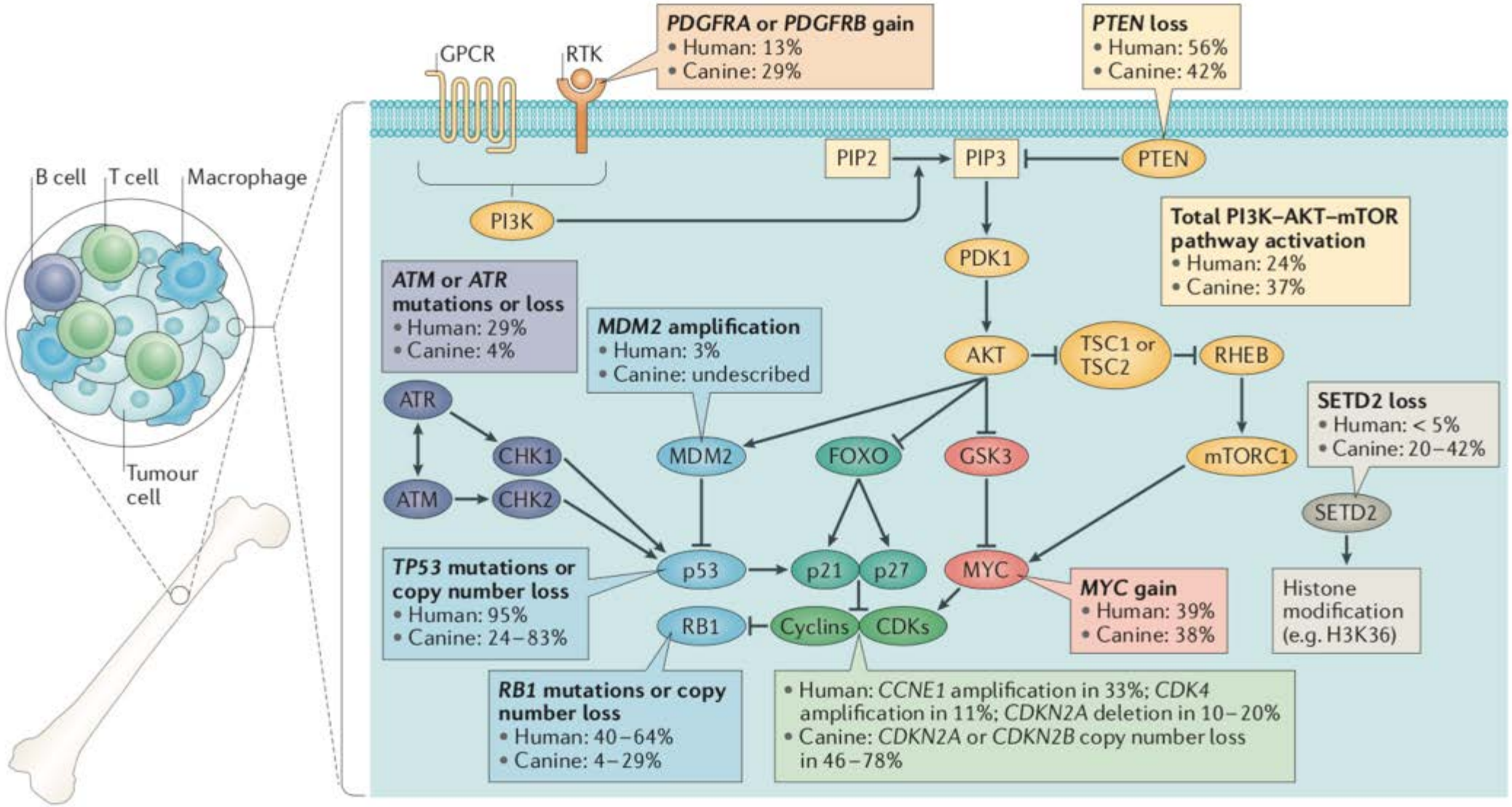


…identifying translationally relevant canine OS subtypes as models for humans?

… exploring the molecular and biological origins of OS across species?

dog^2 Deciphering the Osteosarcoma Genome in Dogs

The Comparative Molecular Landscape of Canine and Human Osteosarcomas



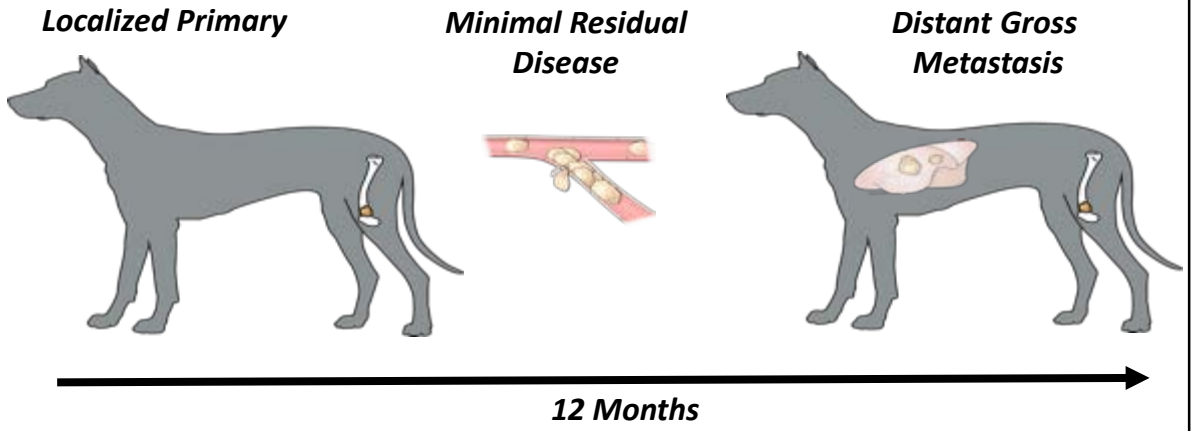
LeBlanc AK, Mazcko C. Nat Rev Cancer 2020

A Comparative Approach to Osteosarcoma Drug Development: Translational studies of agents designed to improve outcomes for dogs and humans

Canine OS Trials

Minimal residual disease studies

- ***Comparative Oncology Trials Consortium***
- ***Prioritize agents for human MRD/adjuvant based studies of metastatic progression***



The COP has enrolled ~450 canine patients on 3 trials over the last ~5 years

Therapeutic approaches include:
Novel biologics/vaccines
Rapalog inhibition of mTOR
Metabolic targeting of metastatic cells
TOP1 inhibitors
Demethylating agents

Early Phase Trials

Measurable Disease

Later Phase Trials

Minimal Residual Disease

Summary of current COTC Osteosarcoma Clinical Trials

MORRIS ANIMAL FOUNDATION

COTC-022

Standard of Care (SOC)

-Amputation

-Carboplatin x 4 @

COTC-021

Adjuvant Rapamycin

-SOC

-4 cycles of oral
cin

n/3 days off x

COTC-026

Adjuvant *Listeria* her2/neu vaccine

-SOC

-1 x 10^9 ADXS31-164 (frozen form)

-3 doses, q21 days

CLINICAL CANCER RESEARCH | CLINICAL TRIALS: TARGETED THERAPY

Adjuvant Sirolimus Does Not Improve Outcome in Pet Dogs Receiving Standard-of-Care Therapy for Appendicular Osteosarcoma: A Prospective, Randomized Trial of 324 Dogs

Amy K. LeBlanc[1], Christina N. Mazcko[1], Aswini Cherukuri[1], Erika P. Berger[2], William C. Kisseberth[3], Megan E. Brown[3], Susan E. Lana[4], Kristen Weishaar[4], Brian K. Flesner[5], Jeffrey N. Bryan[5], David M. Vail[6], Jenna H. Burton[7], Jennifer L. Willcox[7], Anthony J. Mutsaers[8], J. Paul Woods[8], Nicole C. Northrup[9], Corey Saba[9], Kaitlin M. Curran[10], Haley Leeper[10], Heather Wilson-Robles[11], Brandan G. Wustefeld-Janssens[11], Stephanie Lindley[12], Annette N. Smith[12], Nikolaos Dervisis[13,14,15], Shawna Klahn[13], Mary Lynn Higginbotham[16], Raelene M. Wouda[16], Erika Krick[17], Jennifer A. Mahoney[17], Cheryl A. London[18], Lisa G. Barber[18], Cheryl E. Balkman[19], Angela L. McCleary-Wheeler[19], Steven E. Suter[20], Olya Martin[21], Antonella Borgatti[22], Kristine Burgess[18], Michael O. Childress[23], Janean L. Fidel[24], Sara D. Allstadt[21], Daniel L. Gustafson[4], Laura E. Selmic[3], Chand Khanna[1,25,26], and Timothy M. Fan[27,28]

n 2021

11/2017 – present

n = 124 dogs

Bulk genomics

- Outcome-linked clinical biospecimen samples
- Subtypes and prognostic signatures

Biomarkers

- AI/deep learning, computational modelling
- Nanostring IO profiling of immune landscape

Tumor Heterogeneity

- Metastases and surrounding tumor microenvironment
- CTCs, ctDNA, single-nuclei sequencing

DOG² project: goals and methods

- Create a comprehensive comparative dataset describing the molecular landscape of canine OS

- Leverage existing outcome-linked biospecimen repository
  - Tumor, matched normal, biofluids; all outcome-linked
    - Exploratory: n = 12
    - Discovery: n = 55
    - Validation: n = 250
  - WGS, WES, RNAseq
  - Proteomics, methylation profiling, single-nuclei sequencing

- Integrate with human OS data generated through NCI TARGET initiative (NCI/CCR P. Meltzer, J. Khan)

- Define prognostic signatures and tumor subtypes that can be compared with humans and form the basis of the next generation of harmonized canine/human clinical trials

Existing NCI and NCATS datasets and expertise support dog-to-human translation

BROWSE PUBLISH ABOUT SEARCH

PLOS COMPUTATIONAL BIOLOGY

advanced search

OPEN ACCESS PEER-REVIEWED

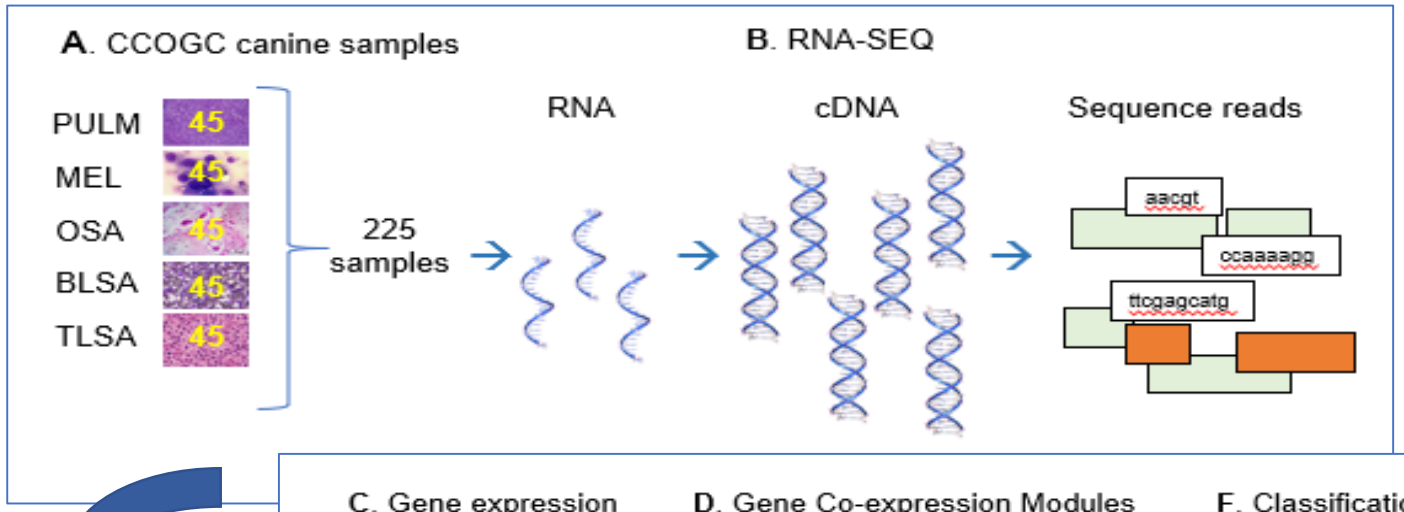
RESEARCH ARTICLE

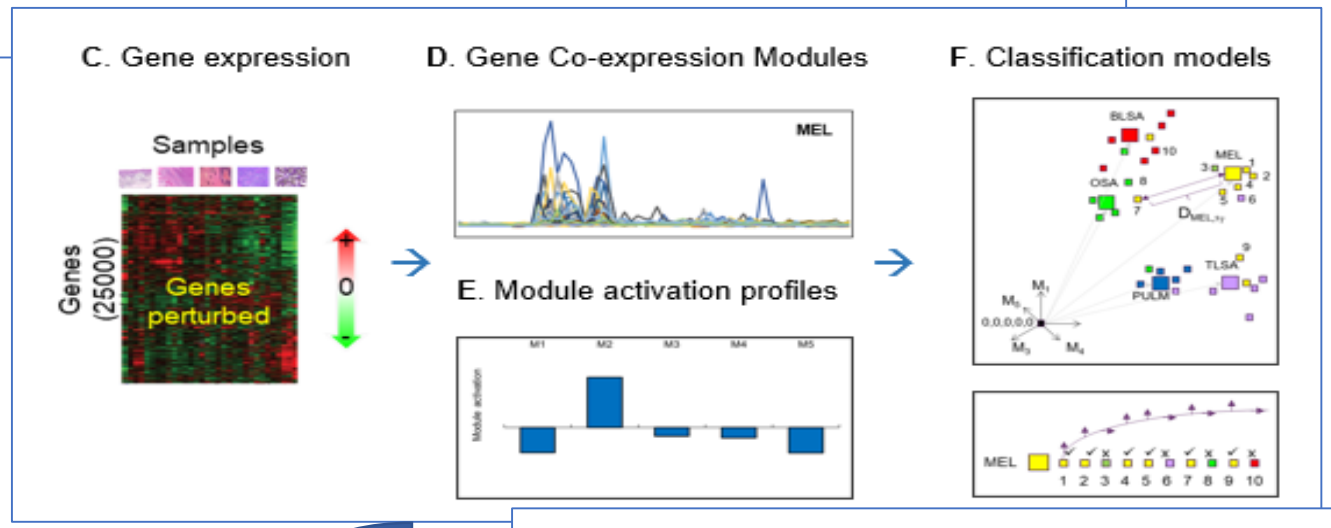
Transcriptomic profiling in canines and humans reveals cancer specific gene modules and biological mechanisms common to both species

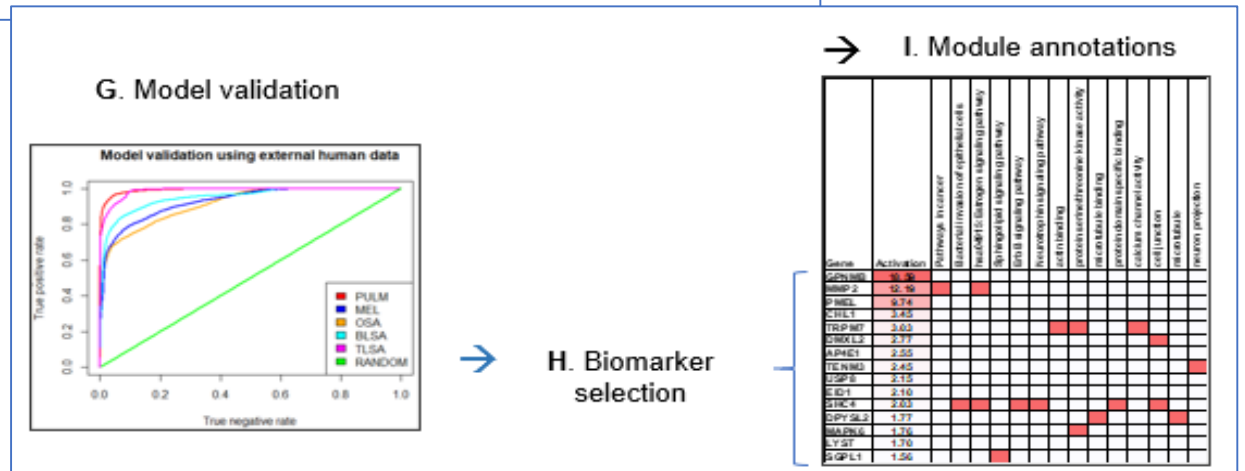
Gregory J. Tawa, John Braisted, David Gerhold, Gurmit Grewal, Christina Mazcko, Matthew Breen, Gurusingham Sittampalam, Amy K. LeBlanc

Published: September 27, 2021 • https://doi.org/10.1371/journal.pcbi.1009450

Combined experimental & bioinformatic protocol







Tawa GJ, Braisted J, Gerhold D, Grewal G, Mazcko C, et al. (2021) Transcriptomic profiling in canines and humans reveals cancer specific gene modules and biological mechanisms common to both species. PLOS Computational Biology 17(9): e1009450. https://doi.org/10.1371/journal.pcbi.1009450 https://journals.plos.org/ploscompbiol/article?id=10.1371/journal.pcbi.1009450

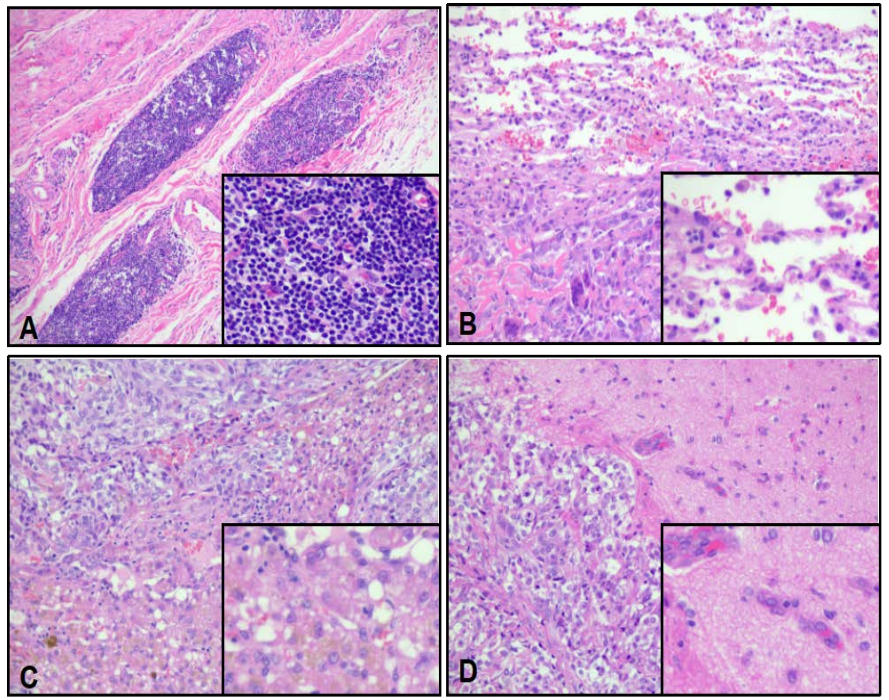
nanoString

Products Diagnostics Partnerships

Product Highlights:

- Profile 800 genes across 47 annotated pathways involved in canine immune response to IO treatments
- Overlapping content with NanoString's Human PanCancer IO 360 and PanCancer Immune Profiling Panels provides a suite of panels for comparative studies
- PanCancer coverage with tumor specific content for top canine cancers including Melanoma, Osteosarcoma, Lymphoma, Urothelial Carcinoma, and Glioblastoma

- Easy to use nCounter system provides data in 24 hours with less than 30 minutes hands on time and simple data analysis
- Easy data sharing and collaboration with a common set of genes and a panel standard

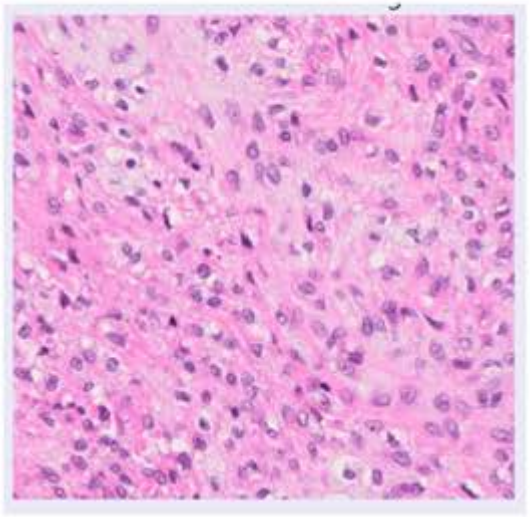


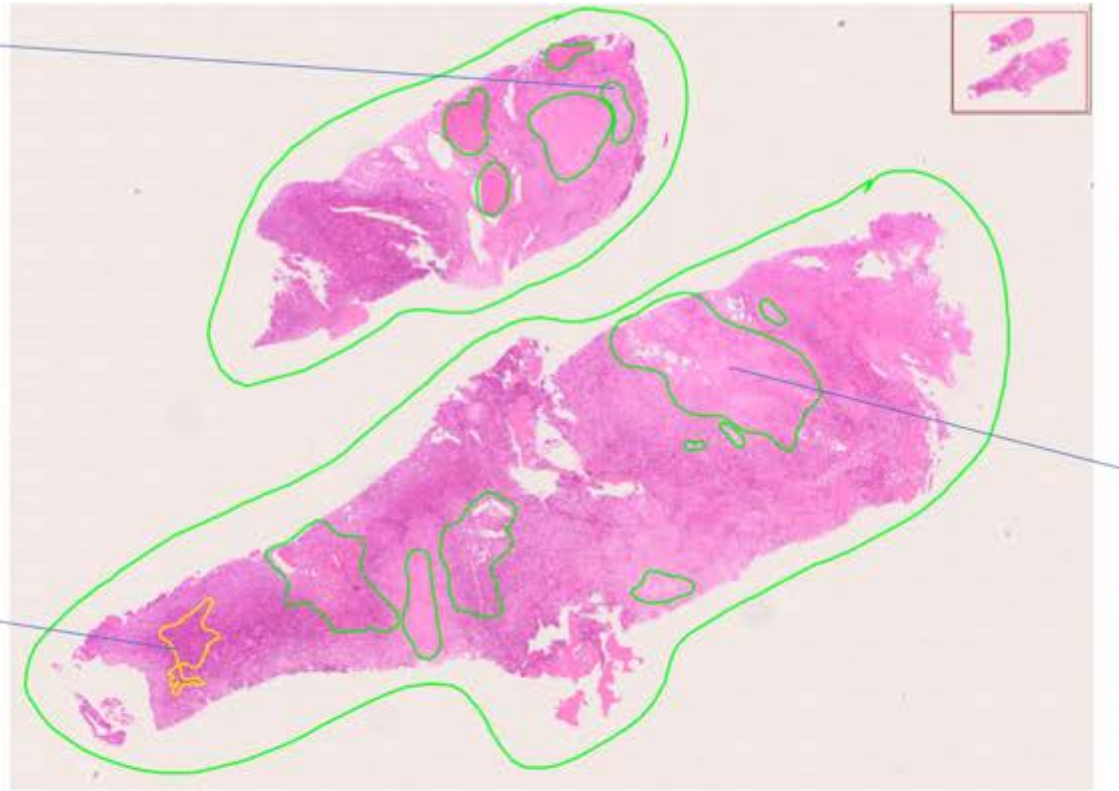
Comparative aspects of the immune landscape of canine and human OS:
-Primary tumors
-Primary tumors vs. matched metastases
-Geospatially distinct metastases

Natural canine tumor heterogeneity provides opportunities for image-based biomarker discovery and predictive computational modelling

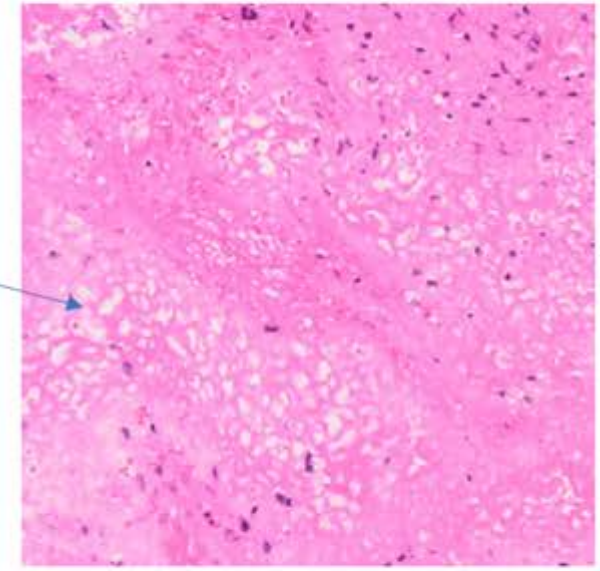
Label	Color	Description
TumorOB	yellow	entire tumor; predominantly of osteoblastic differentiation
HN	red	Hemorrhage, necrosis
Exclude	black	exclude region (i.e., multiple tissues on slide)
CB	teal	chondroblastic differentiation (enlarged cell, central nuclei, gray/blue cytoplasm)
GC	green	giant cell-rich region (multinucleated cells)
FB	purple	fibroblastic differentiation (spindle-shaped cells forming streams and bundles +/-herringbone pattern)
VR	orange	vascular-rich (telangiectatic differentiation w/ vascular spaces lined by tumor cells)

CB

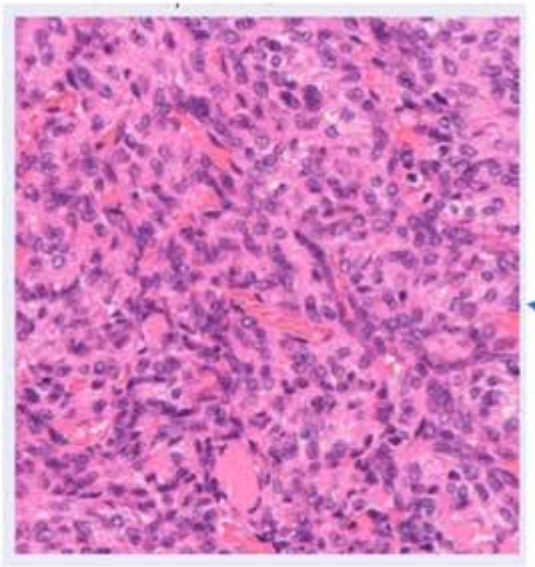




HN



VR



Images courtesy of G. Tom Brown and Sushant Patkar, NCI/MIB/AIR

AI approach to risk stratification in OS

N = 150 scanned H&E images of canine primary tumors

- Outcome-linked: predictive algorithm?
- Transferable to human OS?
- Comparative OS tumor board

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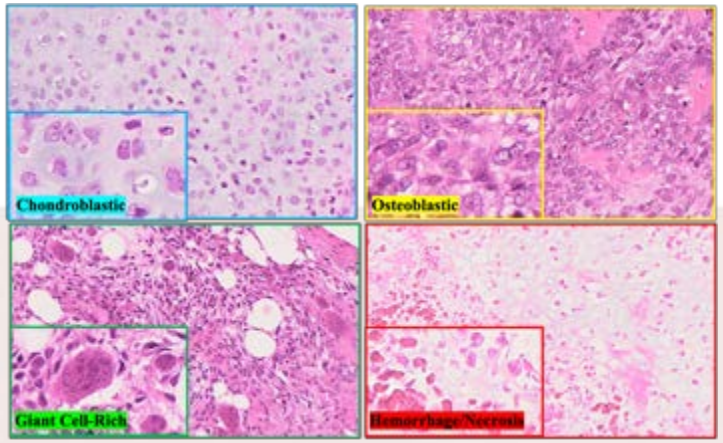
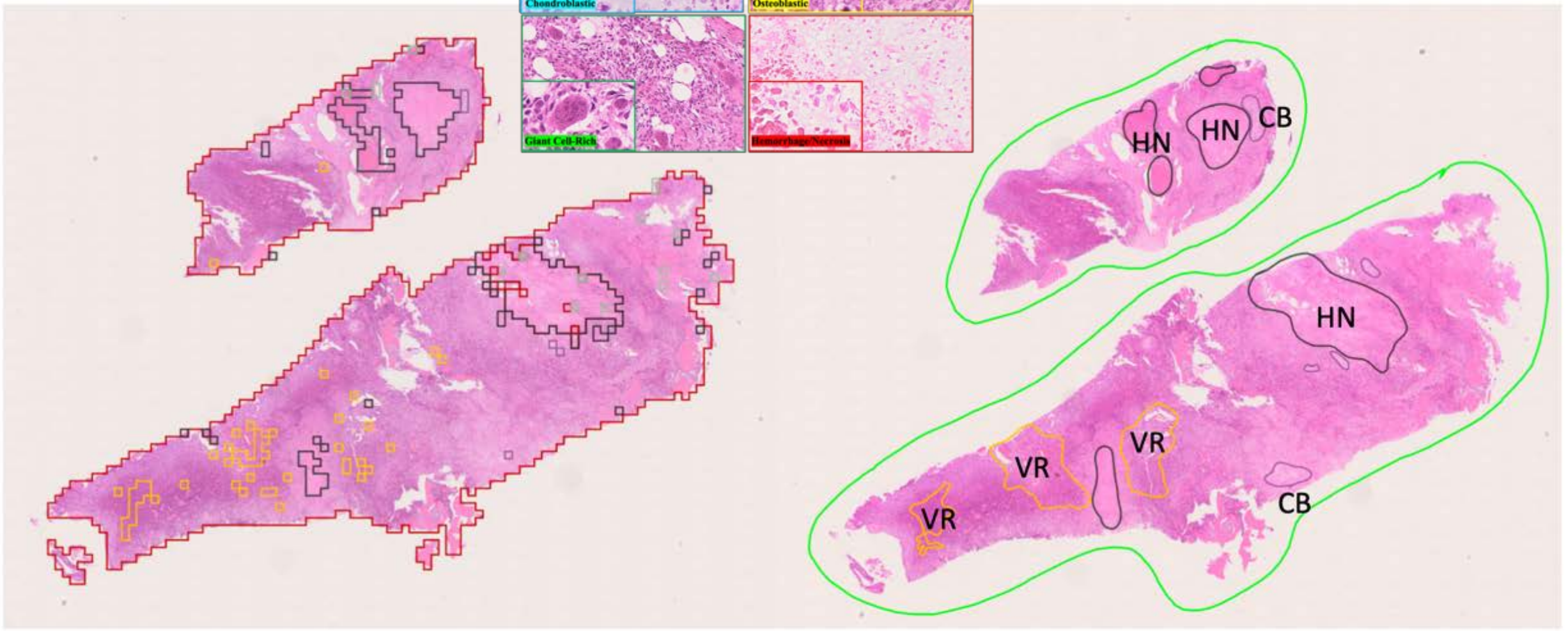
OSTR | Office of Science and Technology Resources

Artificial Intelligence Resource (AIR)



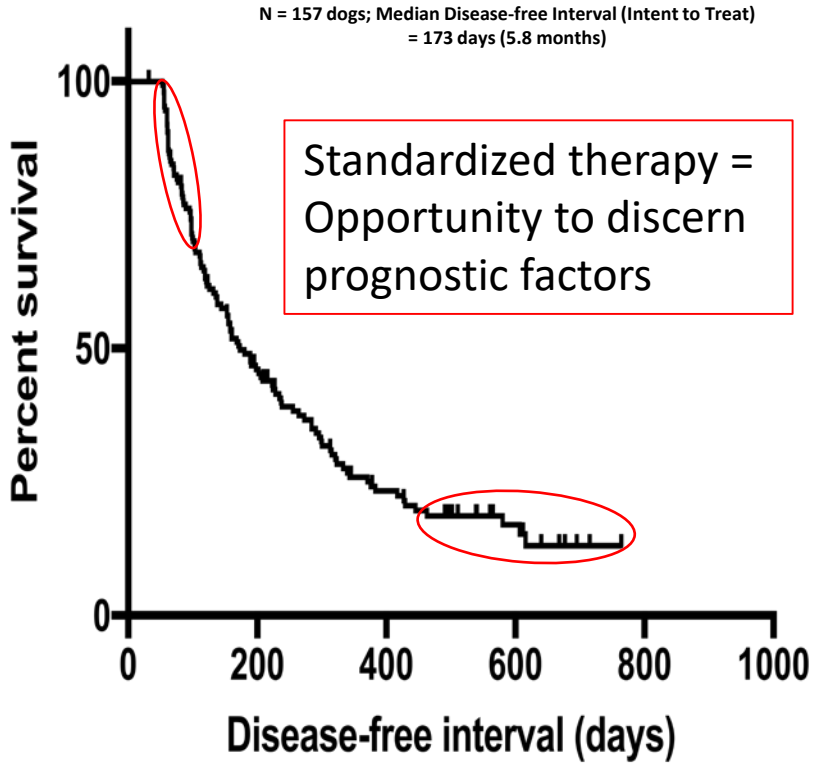


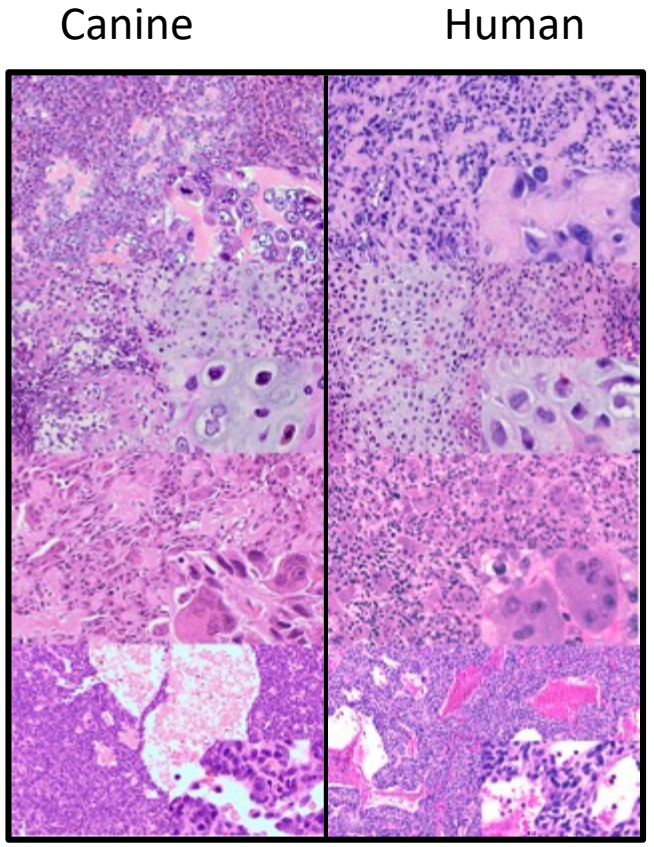
predictions

Images courtesy of Jess Bock/NCI/COB and G. Tom Brown and Sushant Patkar, NCI/MIP/AIR

Ground truth

Natural canine tumor heterogeneity provides opportunities for image-based biomarker discovery and **cross-species** predictive computational modelling





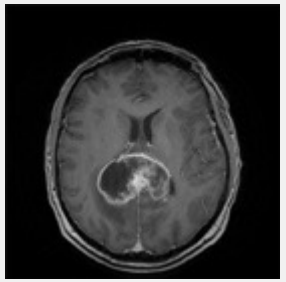
- Algorithm performance will be developed and tested in scanned canine OS lesions, then assessed in human OS image sets
  Key question: Can we inform beyond % necrosis after neoadjuvant chemotherapy for humans?
- Exploration of relationships between imaging, clinical outcome, genomic data
- Future direction: relationships between matched primary/metastatic pairs

NCI's Integrated Canine Data Commons (ICDC)

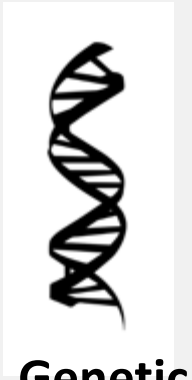
"Further research on human cancers through comparative analysis with canine cancer."

- **Share** your data in the Cancer Research Data Commons' canine-specific cloud-based repository

- **Access** many types of comparative oncology data sets including:

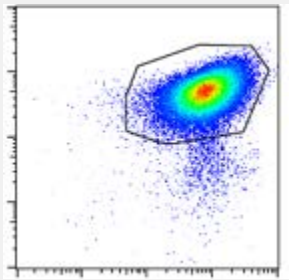


Imaging



Genetic
genomic/ transcriptomic

Clinical



Immunological

- **Analyze** data with more than 1,000 tools and workflows in the cloud resources

Find, Then Analyze data

canine.commons.cancer.gov/#/cases

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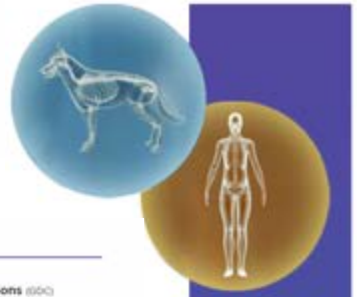
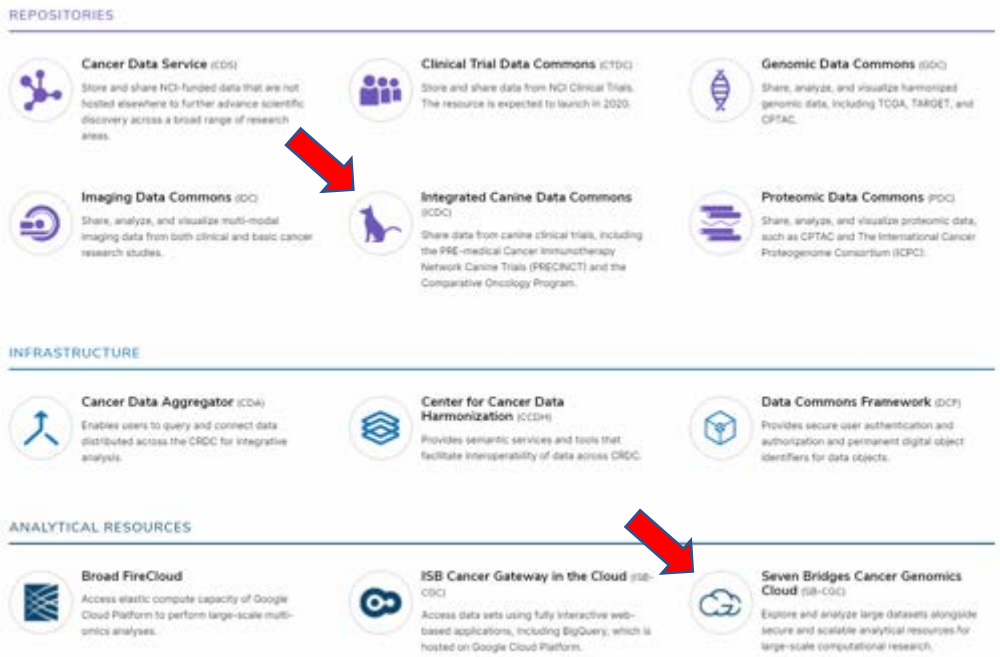
Cancer Research Data Commons



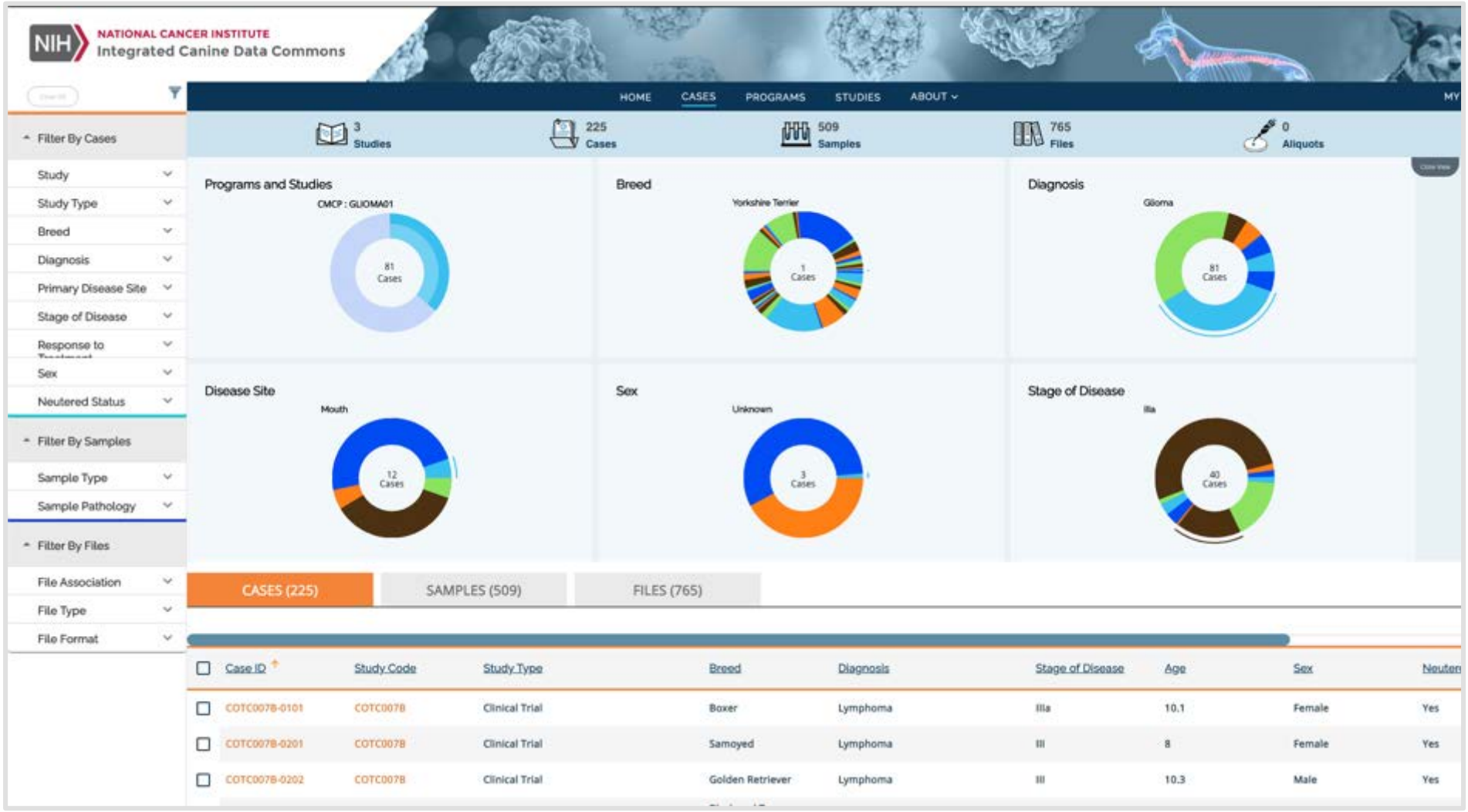
- ICDC is a node in NCI Cancer Research Data Commons. Use filters to find data to use in analysis
- NCI Cloud Resources provide analytics and are hosted by The Broad Institute, The Institute for Systems Biology, and Seven Bridges
- Users can also use their own AWS account and analytical tools
- Researchers can bring their own data and tools to the cloud, and combine with data in the CRDC for integrative analysis



Non-CRDC analytical access:

aws jupyter

Access data: Web & API (caninecommons.cancer.gov)



Submit data: caninecommons.cancer.gov/#/submit
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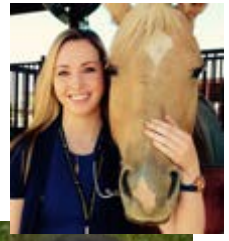
Thank you to current and former COP members!

Christina Mazcko, BS
Ling Ren, PhD
Shan Huang, MD PhD
Erika Berger, DVM DACVIM
Joshua Mannheimer, PhD
Jessica Beck, DVM PhD DACVP



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-Molecular Imaging Branch and Artificial Intelligence Resource (AIR)
-Genetics Branch (Dr. Paul Meltzer, Bob Walker)
-Pediatric Oncology Branch (Dr. Troy McEachron)
-Radiation Oncology and Biology Branches (Drs. Murali Cherukuri, Kazu Yamamoto)
-NeuroOncology Branch (Drs. Mark Gilbert, Mioara Larion, Adrian Lita, Tyrone Dowdy, Victor Ruiz-Rodado)

NIH-NCATS Therapy for Rare and Neglected Diseases (TRND) Program and Division of Preclinical Innovation (DPI)
NCI Division for Cancer Treatment & Diagnosis (DCTD)
NIH Divisions of Veterinary Resources (DVR) and Radiation Safety (DRS)
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Dr. Chand Khanna
COTC member institutions, investigators, and support staff: past, present and future
Hope Veterinary Referral Center – BluePearl of Rockville, MD

Questions?

Thank you for your attention

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