

The Canine-Kid Connection in Cancer

**Accelerating Discovery of Safe and More Effective Treatments
Through Comparative Oncology**

November 16, 2016



Canines-N-Kids Foundation is a recognized 501c3 Public Charity



CAC2 Values

- ❖ Put the children and their families **first** in everything we do
- ❖ Support the members and the childhood cancer community while being mindful not to compete with members or to duplicate projects/programs/services that they provide
- ❖ Be accountable and take ownership of one's commitments within the collaborative
- ❖ Be cost effective with resources
- ❖ Be inclusive and collaborative and assume positive intent
- ❖ Help give voice to the community, and amplify it in a coordinated fashion
- ❖ Stay action-oriented and flexible

Introduction

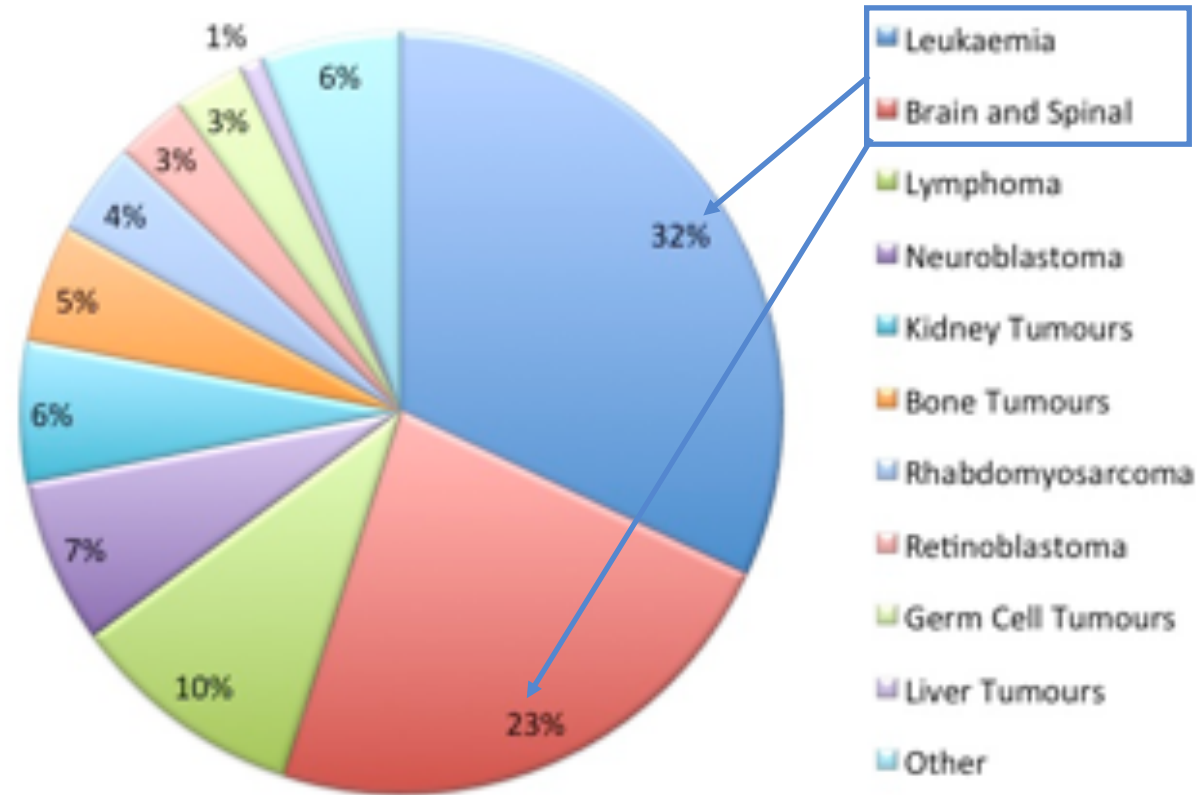
Gregory J. Aune, MD, PhD

Stephanie Edlund Distinguished Professor in Pediatric Cancer Research
St. Baldrick's Scholar
Greehey Children's Cancer Research Institute, San Antonio, TX
Canines-N-Kids Medical & Scientific Advisory Board, Board Observer

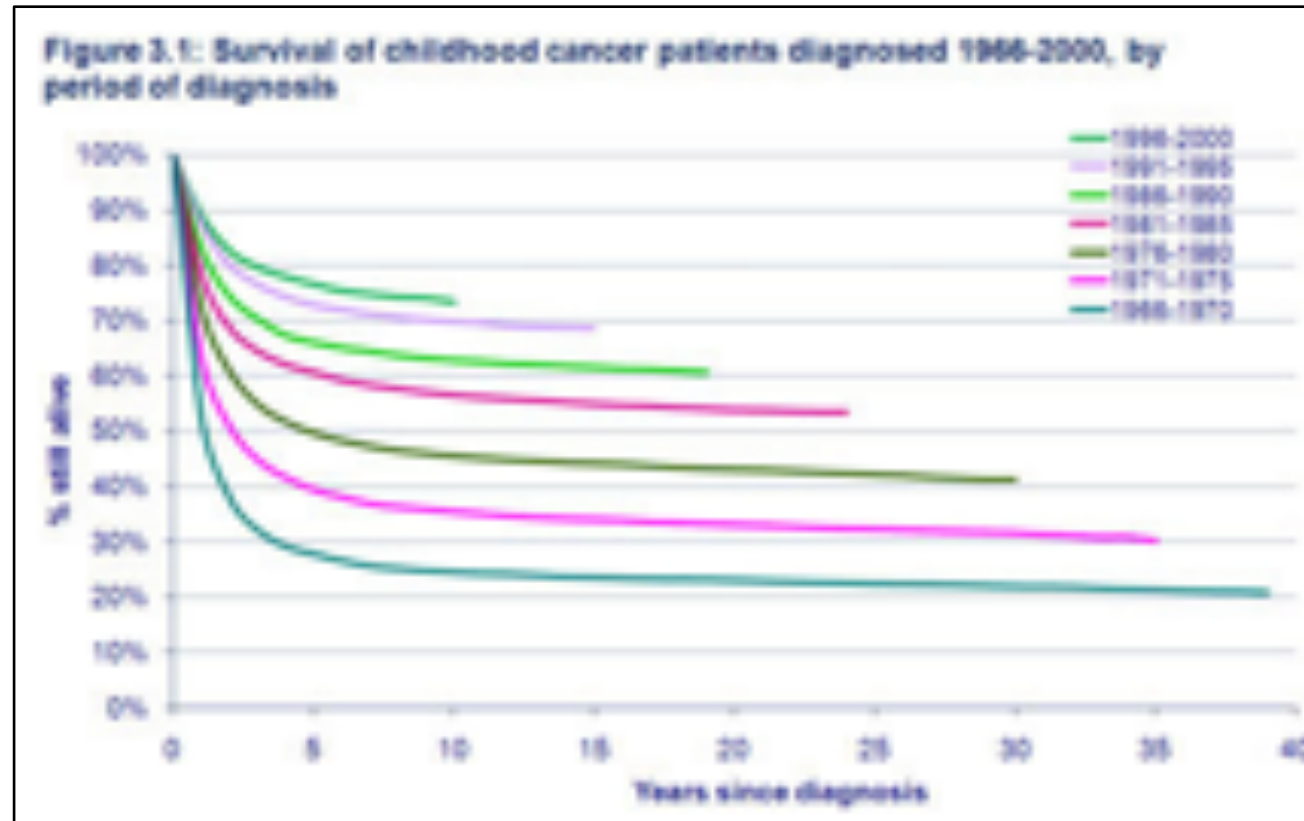


Childhood Cancer Incidence

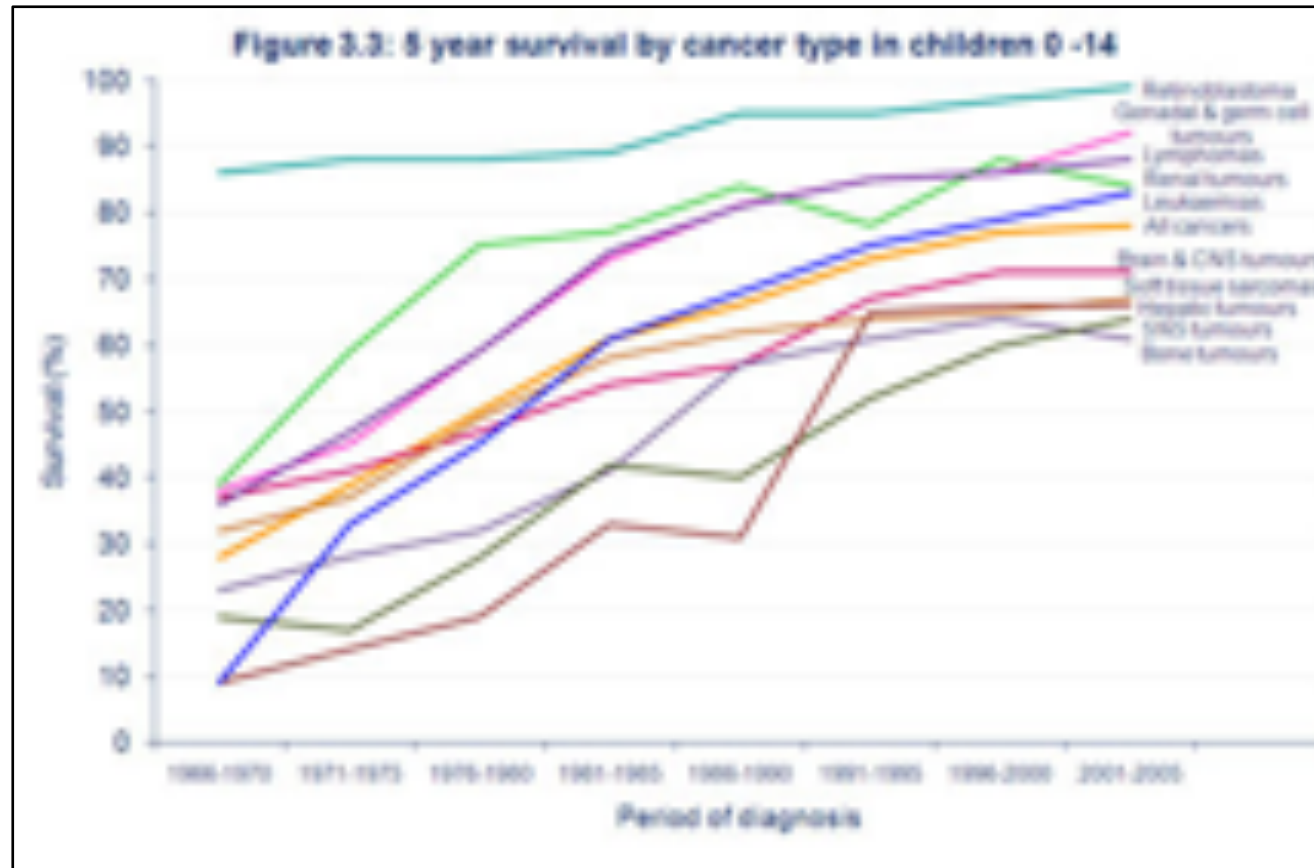
- Approximately 15,000 new patients each year in the United States
- Most common cancers are leukemia followed closely by brain tumors



Childhood Cancer Survival by Year



Survival by Cancer Type



Why are novel research programs are needed to develop better treatments for childhood cancer?

Common question I get -- Isn't childhood cancer now close to 90% curable?

- Cancer remains the #1 cause of death by disease for children in the United States.
- Worldwide over 300,000 children are diagnosed with cancer annually
- In the United States there will be over 500,000 survivors by 2020 and at least 1/3 will suffer from a life-threatening health problem caused by their prior treatments
- In the past 30 years:
 - 62 new drugs FDA approved for adult cancers (16 in 2015)
 - 3 new drugs FDA approved for pediatric cancers (0 in 2015)





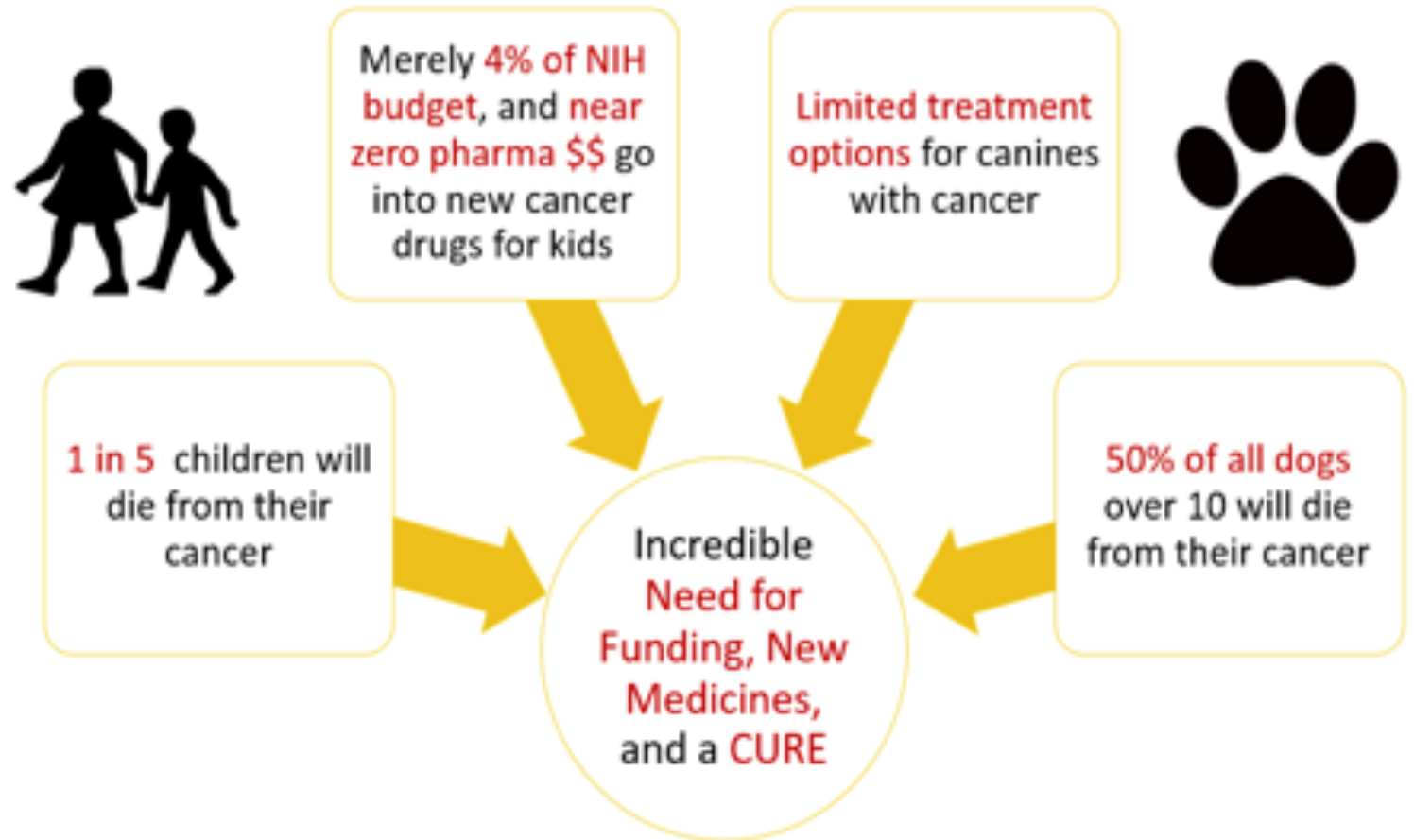
Kids & Canines: A Shared, Great Unmet Need in Cancer

Kids' cancers are "rare" by definition..

"...the 'market' for pediatric cancers is too small for pharmaceutical companies to invest in developing drugs that will specifically target these types of cancer. Furthermore, the genetics of childhood cancers differ markedly from adult cancers, therefore, most agents developed to inhibit specific pathways in adult carcinomas may have little or no benefit in the treatment of childhood malignancies." *Drs. Peter Adamson, Peter Houghton, et. al.*

- Nearly **16,000 kids** are diagnosed with cancer in the US each year – vs. 500,000 adults annually in the US
- There are about **100 different types of pediatric cancers** whose **markers are often fundamentally different** than those in adult cancer

Approx. **4,000,000 pet dogs** are diagnosed with cancer each year.





There is significant overlap in the biology of canine and childhood cancers – opportunity to develop novel research programs and spur drug development

“The dog has been man’s best friend for over 15,000 years...But the fact remains that in the 21st century, even with lots of new scientific tools to help us understand the cause and progression of cancers, we are still making incremental advancements. I believe the answers to unlocking some of nature’s most intriguing mysteries about cancer are sitting right beside us”.

– *Dr. Matthew Breen,*
North Carolina State College of Veterinary Medicine



Finding a way forward:

A Pediatric Oncologist's Perspective

Ryan Roberts, MD, PhD

Assistant Professor, Pediatric Hematology/Oncology/BMT, Nationwide Children's Hospital
Principal Investigator, Center for Childhood Cancer, Nationwide Children's Hospital and The
James Comprehensive Cancer Center, The Ohio State University
Canines-N-Kids Foundation Board Member



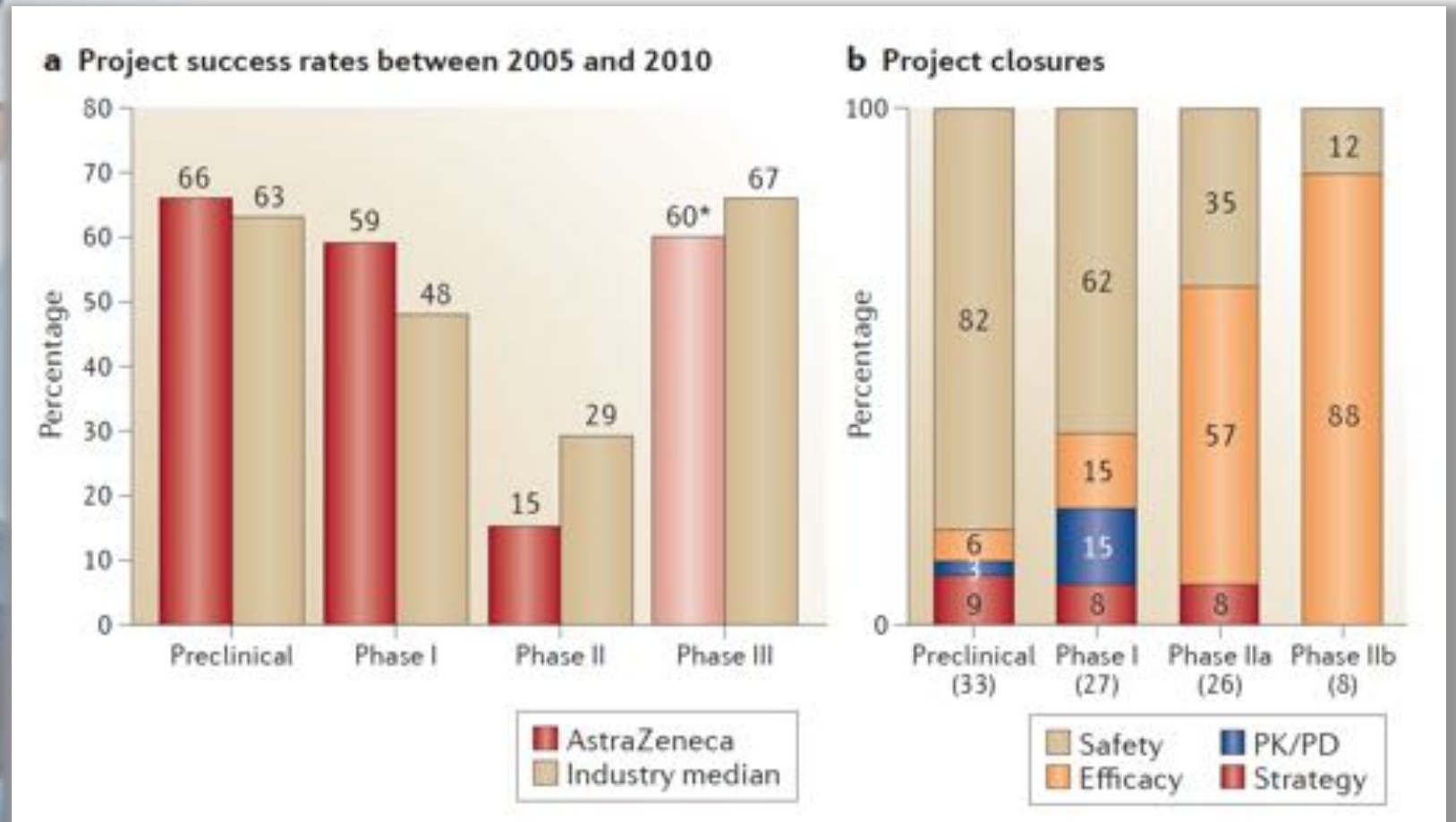
One perspective...

- Imagine yourself a scientist
- You have an idea



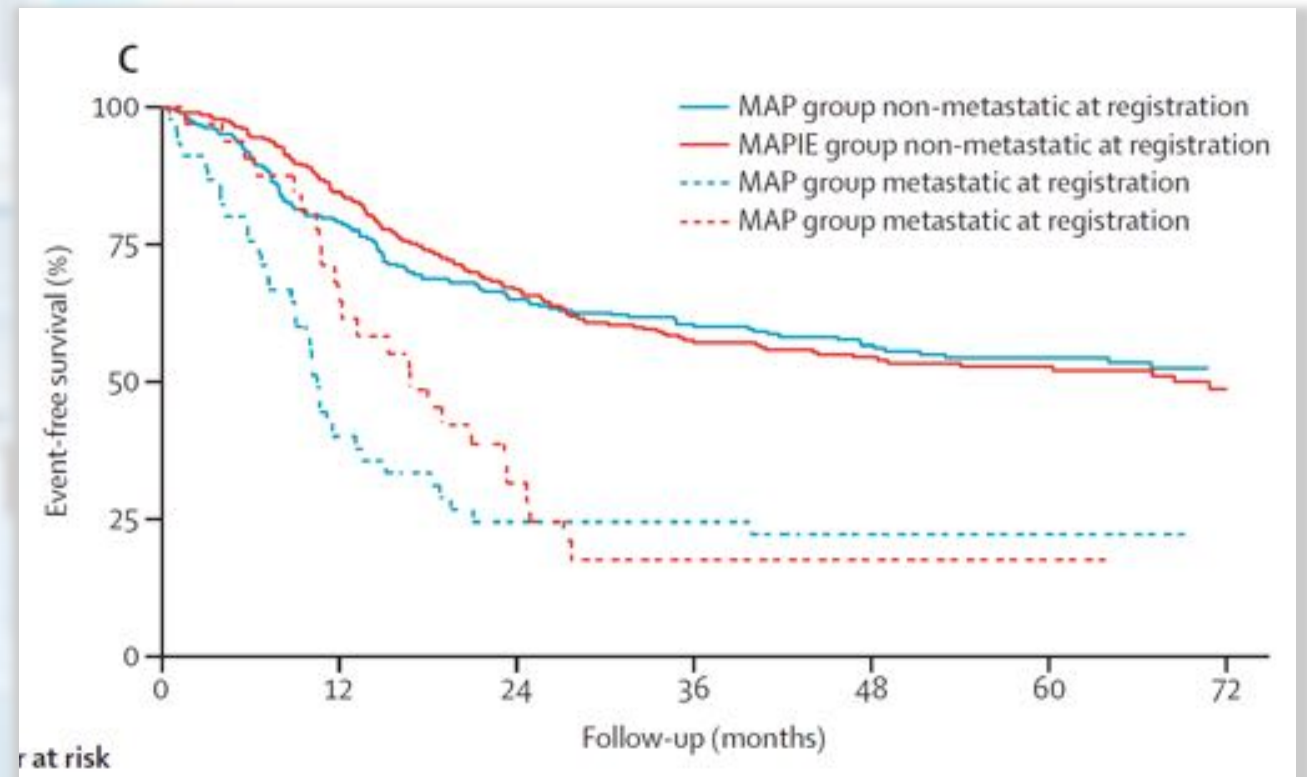


The road to success





You know...



“Proof of Concept” clinical trials require...

\$15 million

3-8 years



Bringing new therapeutics into the clinic

- Average time for clinical development of a new drug is 9 years
- Average cost of clinical development is \$1,000,000,000+
- Only 10% of investigational new drug applications submitted to the FDA are approved
- Most newly developed drugs FAIL due to LACK OF EFFICACY or unacceptable TOXICITY
- The first time drugs are tested in spontaneously developing cancers is in the human clinic (for a variety of reasons, zero will be tested first in pediatric patients, if at all!)
- Shifting the paradigm of drug development to **testing drugs earlier** in a **clinically relevant setting** will enable **selection of the most promising agents to move into the human clinic and reduce the rate of development failure**





Morris Animal
FOUNDATION
Celebrating 65 years

5-5-5

TRIAL

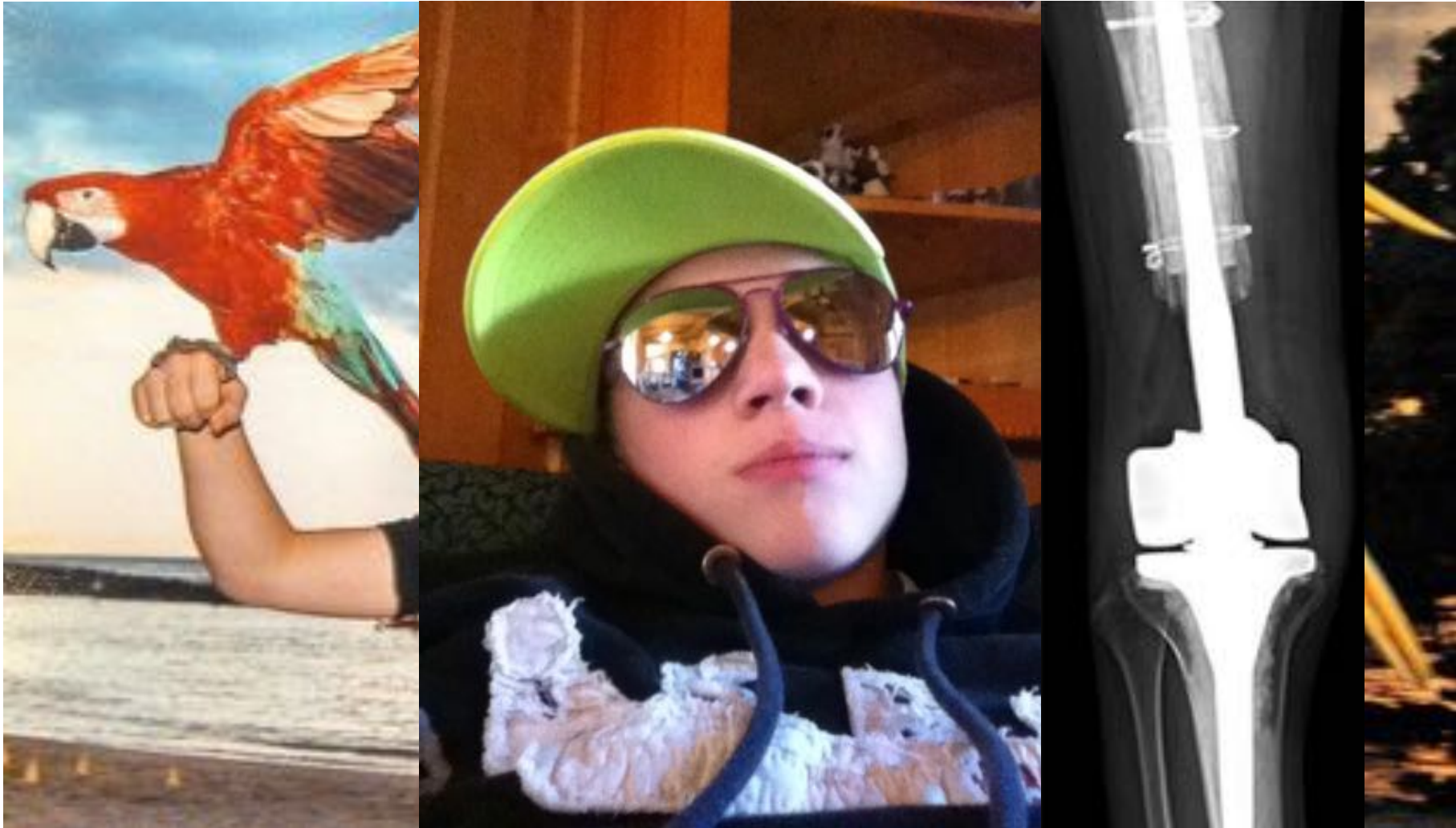


What about a clinical trial in dogs?



	Canines	Humans
Time to develop trial	<1 year	1-3 years
Time to conduct trial	1-2 years?	3-5 years
Cost to conduct trial (phase I/II)	\$1 million?	\$10-20 million
Time to accrue patients	2 months to 1 year	6 months to 4 years

Does human cancer = canine cancer?



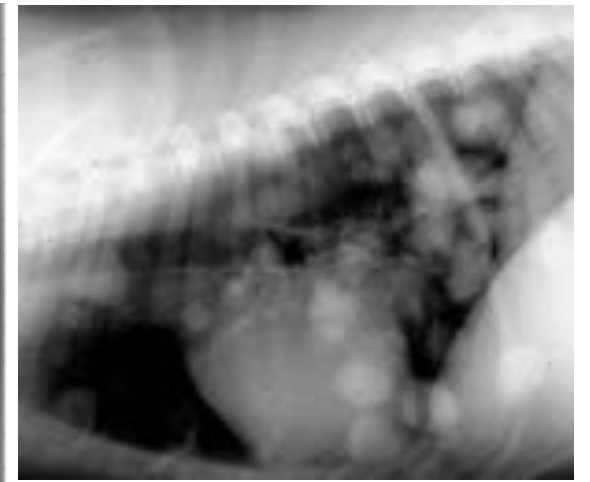
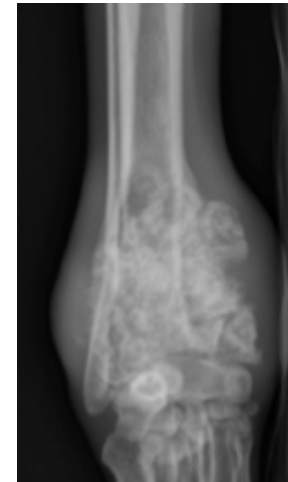
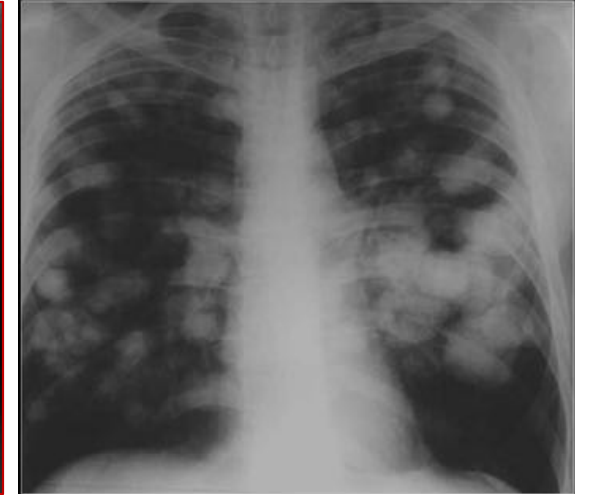
Does human cancer = canine cancer?





Osteosarcoma in Canines and Kids

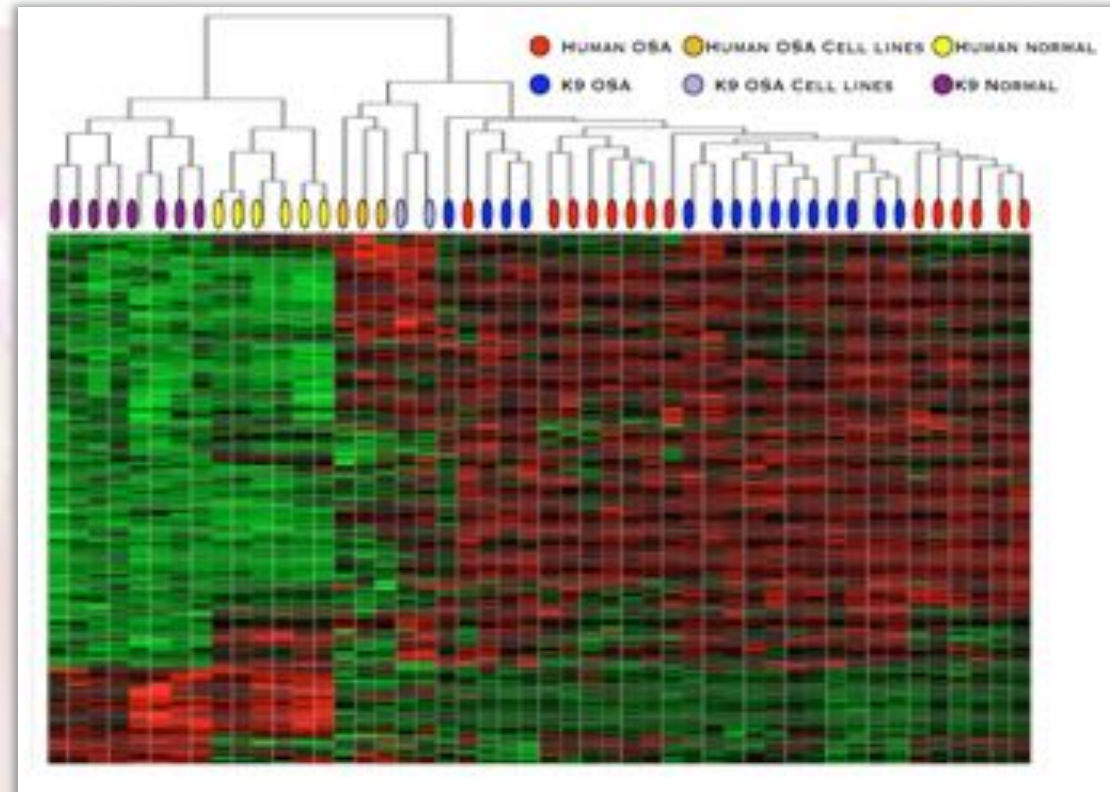
- Highly aggressive mesenchymal tumor that affects ~ 10,000 dogs and 800-1000 children per year
- Comparable tumor biology, behavior, clinical signs, treatments, and outcomes in dogs and humans
- Treatment in humans:
 - 5 year relapse free survival is ~70%; patients with mets at diagnosis or relapsed patients ~10-30% long term survival
- Treatment in dogs:
 - ~90-95% have micrometastases at diagnosis
 - 50% dogs die from metastatic disease within one year despite therapy



Does human cancer = canine cancer?



Does human cancer = canine cancer?



Howling at the Moonshot

- Establish a network for direct patient involvement
- Create a translational science network devoted exclusively to immunotherapy
- Develop ways to overcome cancer's resistance to therapy
- Build a national cancer data ecosystem
- Intensify research on the major drivers of childhood cancers
- Minimize cancer treatment's debilitating side effects
- Expand the use of proven cancer prevention and early detection strategies
- Mine past patient data to predict future patient outcomes
- Develop a 3D cancer atlas
- Develop new cancer technologies





Canine Cancer Patients: Translational models in the Pediatric Cancer Drug Development Continuum

Nicola J. Mason PhD, BVetMed

Associate Professor of Medicine & Pathobiology, University of Pennsylvania School of
Veterinary Medicine
Canines-N-Kids Foundation Board Member



Perspectives on Mouse Models of Cancer



- Most cancers in mice are induced – not spontaneous
- Range from human xenografts (human tumors implanted into immune deficient mice) to genetically engineered mouse models (GEMM)
- Useful for modelling cancer and for the early evaluation of novel therapies. But....
 - these tumors grow very rapidly
 - do not re-capitulate the complex interaction between tumor cells and their environment (the tumor microenvironment)
- Mice are often immune deficient and tumors develop without immune pressure; not suitable for testing immunotherapies
- Mice tend to be easily cured by test therapies
- Frequently do NOT predict possible side effects of novel therapies



Canine Patients with Cancer: A Clinically Relevant Translational Intermediate

- Bridge the gap between murine models and human patients
- Approx. 75 million dogs in USA
- \$14.37 billion spent on vet care in 2014
- 4 million new cases of canine cancer per year
- Outbred population
- Selective breeding has led to restricted genetic heterogeneity **within breeds**
 - Strong genetic predisposition to develop malignancies
 - Increased incidence
 - Easier to identify driver mutations
 - Easier to identify molecular signatures



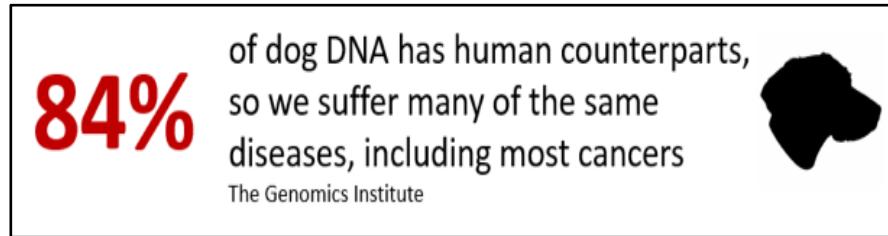
A Kid's Best Friend in the Fight Against Cancer

"Strong similarities between the biology of cancer in dogs and humans have been shown, including patterns of response to therapies and cancer recurrence...Specific types of cancer are functionally identical between dogs and humans, and in some cases the cancers can be considered indistinguishable between the species."




Dr. Chand Khanna, former Senior Scientist at NCI's Center for Cancer Research, Doctor of Veterinary Medicine and Ph.D. in Pathobiology



Dogs develop spontaneous cancers that mimic their human/pediatric counterparts



Canine vs. Human Incidence

	8X more Bone Cancer
	2X more Brain Cancer
	Up to 5X more Lymphoma

- **Bone cancer** (osteosarcoma)
- **Lymphomas**
- **Brain Cancer**
- **Leukemia**

Striking similarities, sometimes indistinguishable:

- **Clinically** (Develop over long periods of time, in immune competent environment)
- **Biologically** (Recurrence, chemoresistance, distant metastases to relevant sites)
- **Molecularly/cytogenetically** (Somatic mutations, gene expression profiles, chromosomal translocations, etc.)

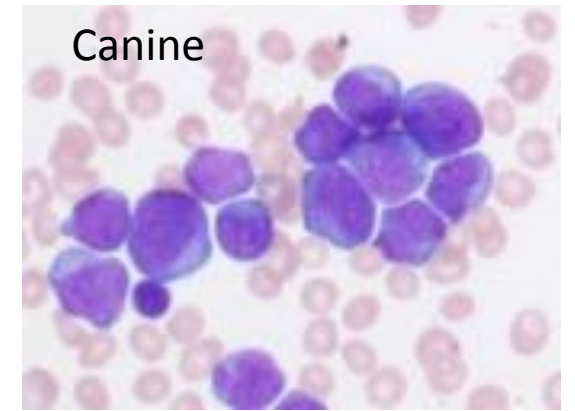
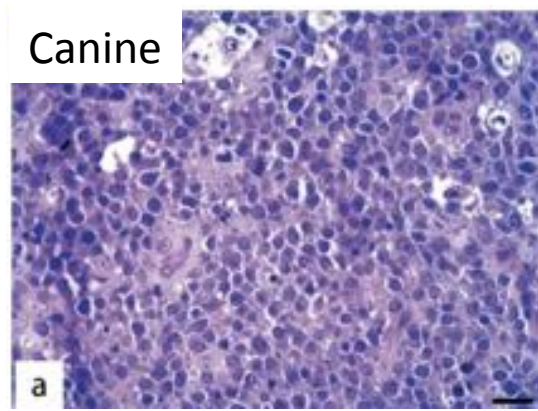
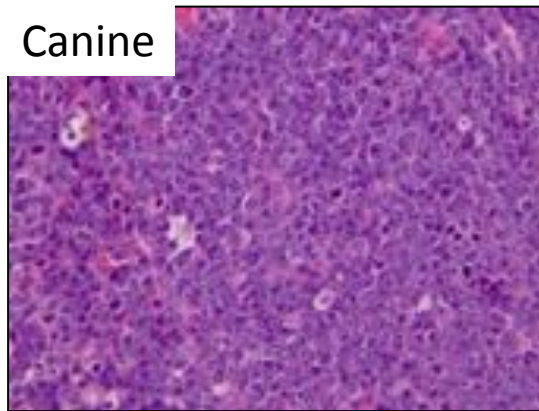
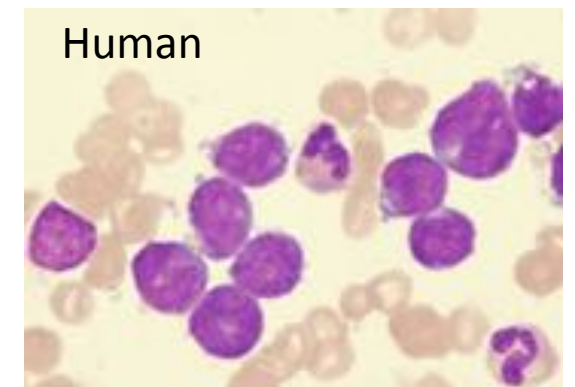
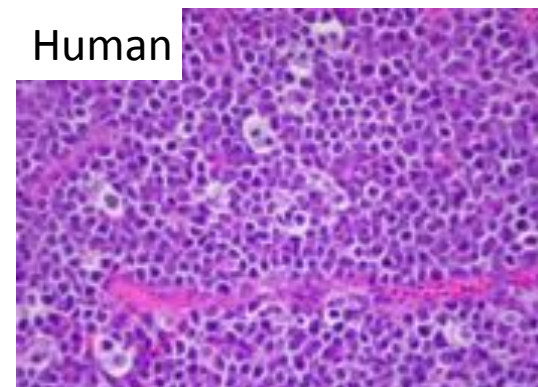
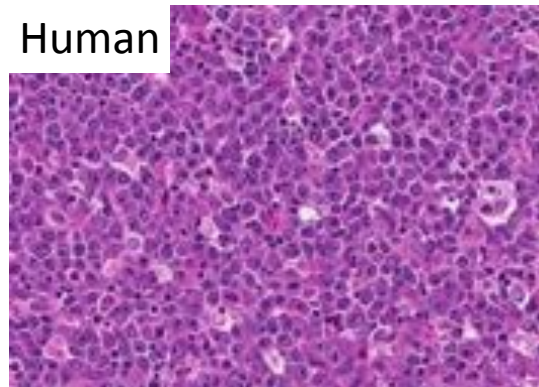


Hematologic Malignancies Shared by Canines & Kids

Diffuse Large B Cell Lymphoma

Burkitt Lymphoma

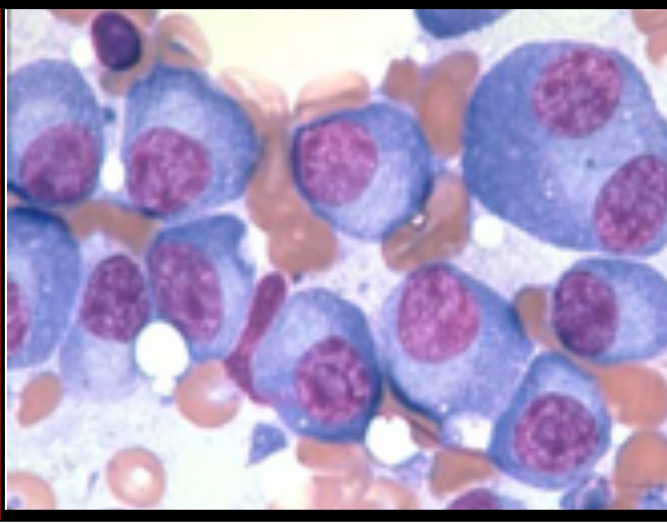
Acute Lymphoblastic Leukemia



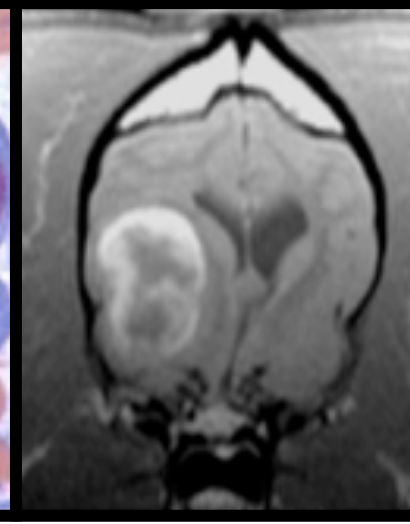
Similar Treatment Options for Canines and Kids with Cancer



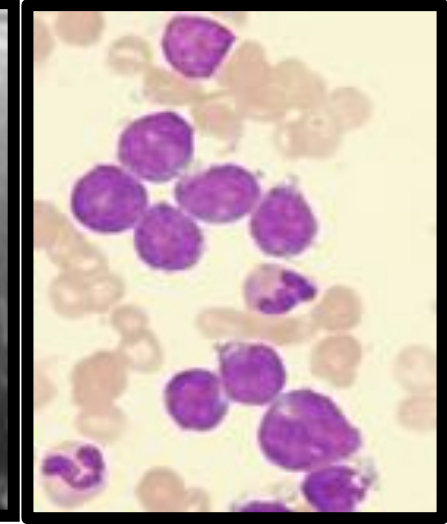
Surgery



Chemotherapy



Radiation therapy



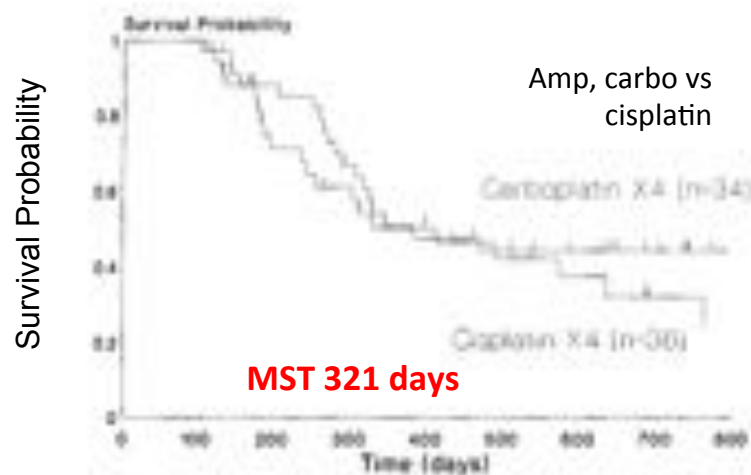
Immunotherapy



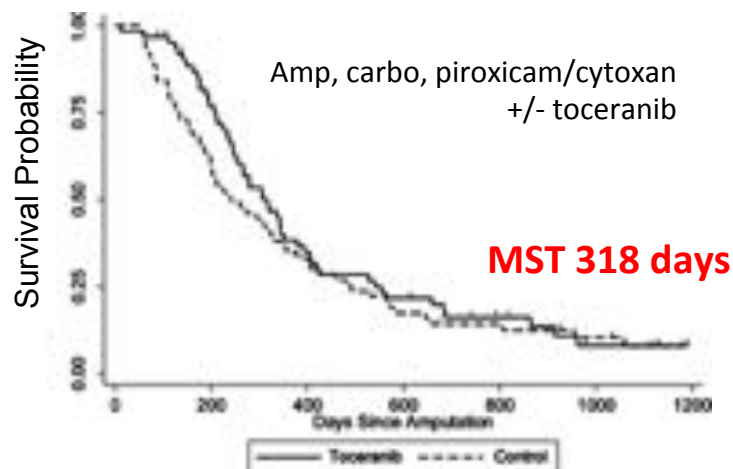
Immunotherapies More Promising in Canine Osteosarcoma

Chemotherapies

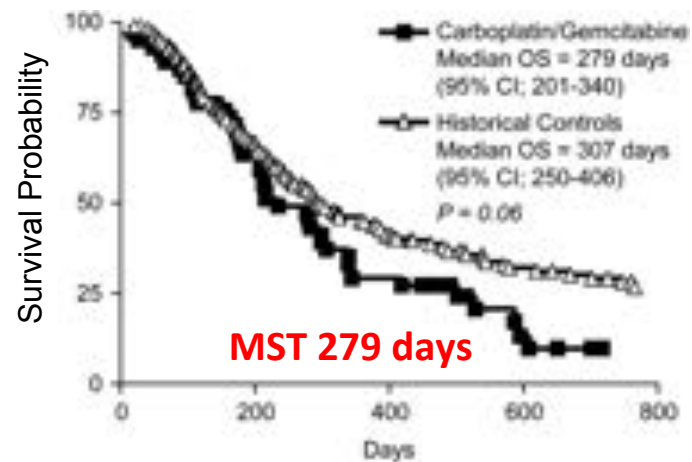
Bergman et al. 1996



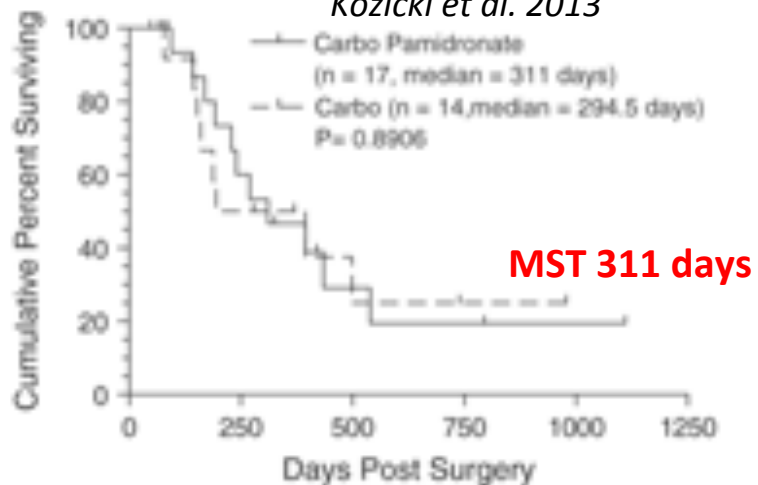
London C et al. 2015



Vail et al. 2015

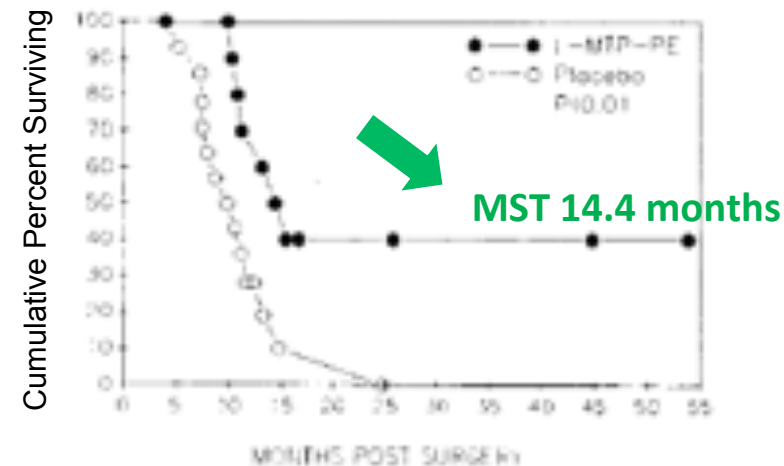


Kozicki et al. 2013

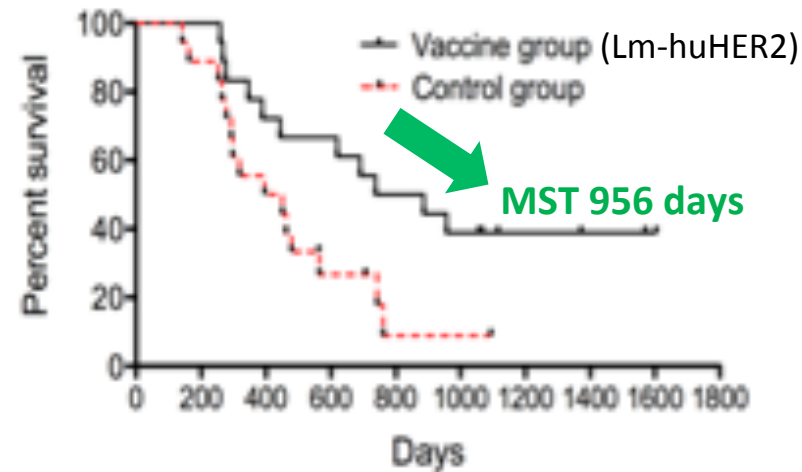


Immunotherapies

Kurzman et al. 1995

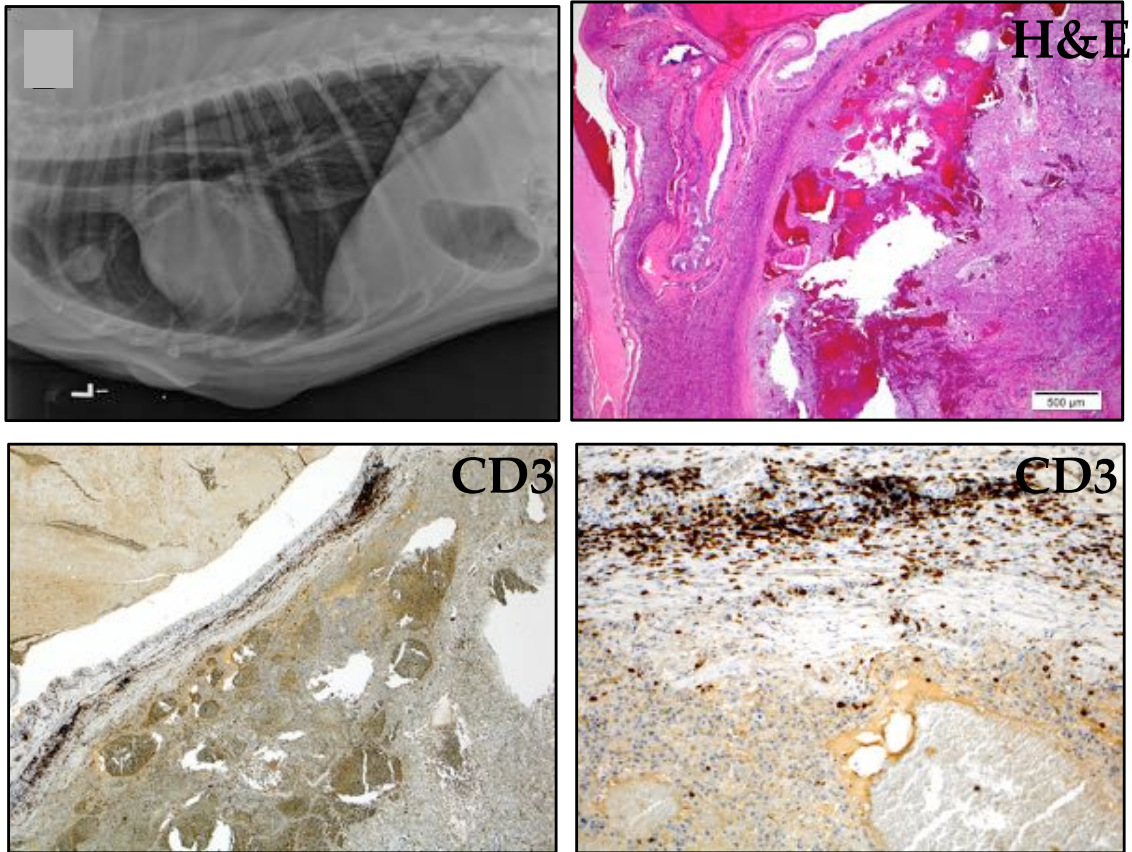


Mason et al. 2016



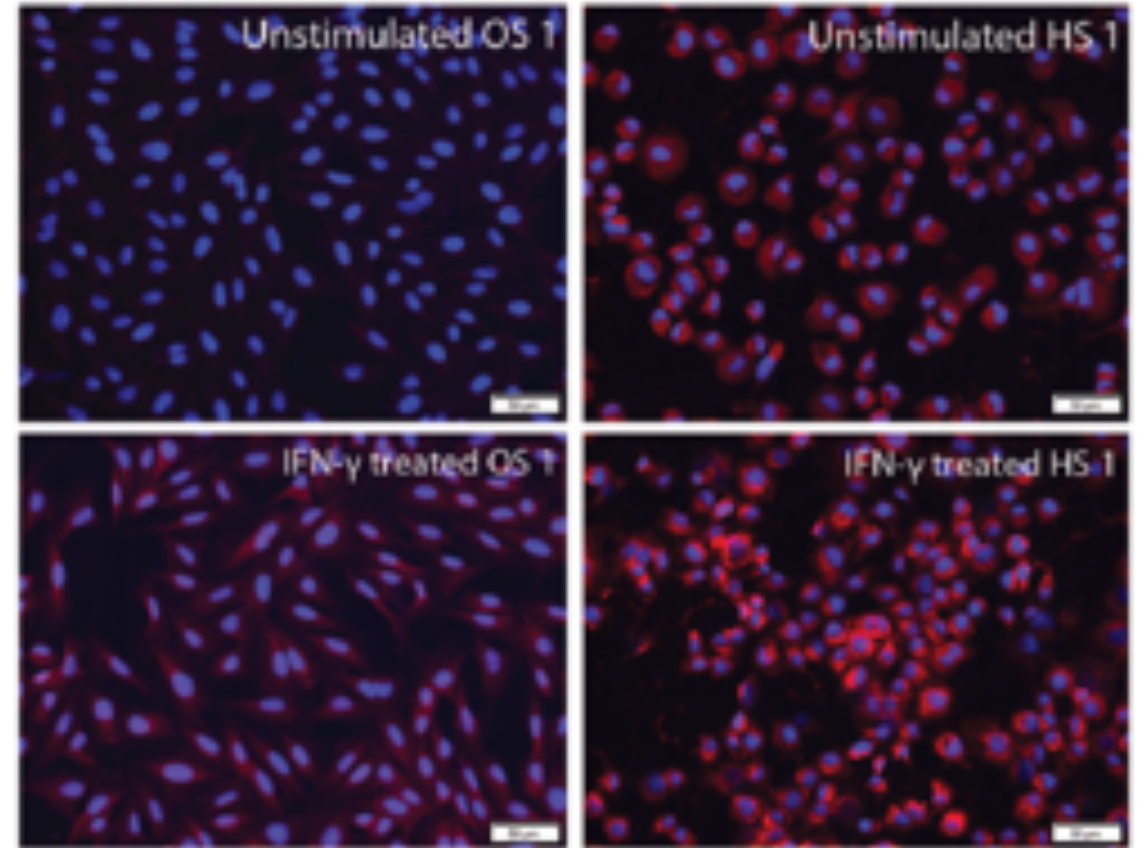
Comparable Barriers to Effective Immunotherapy

T cell exclusion from tumor site



Mason et al. Clin Cancer Research 2016; 1; 22 (17) p4380

IFN- γ up-regulates checkpoint expression (PDL-1)

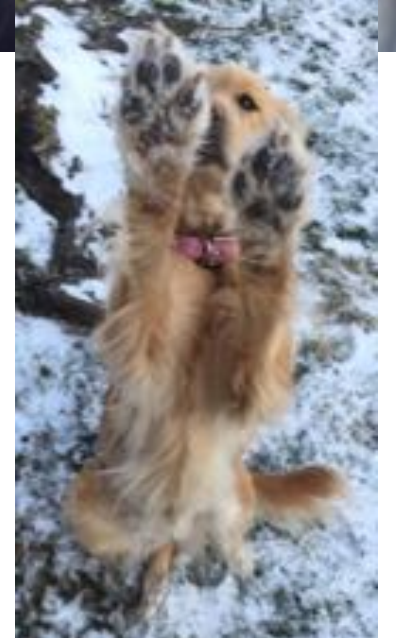
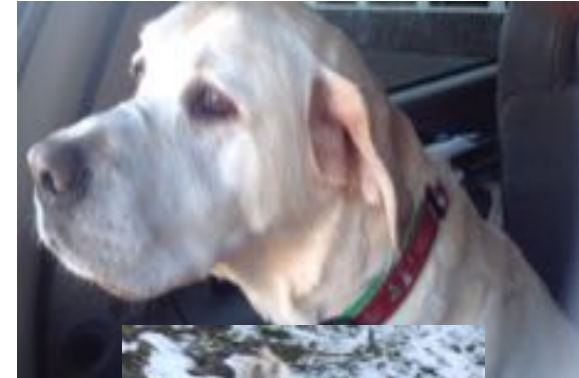


Hartley et al. Vet Comp Oncol 2016 Feb 4 [Epub]

Clinical Trials in Dogs with Spontaneous Cancer

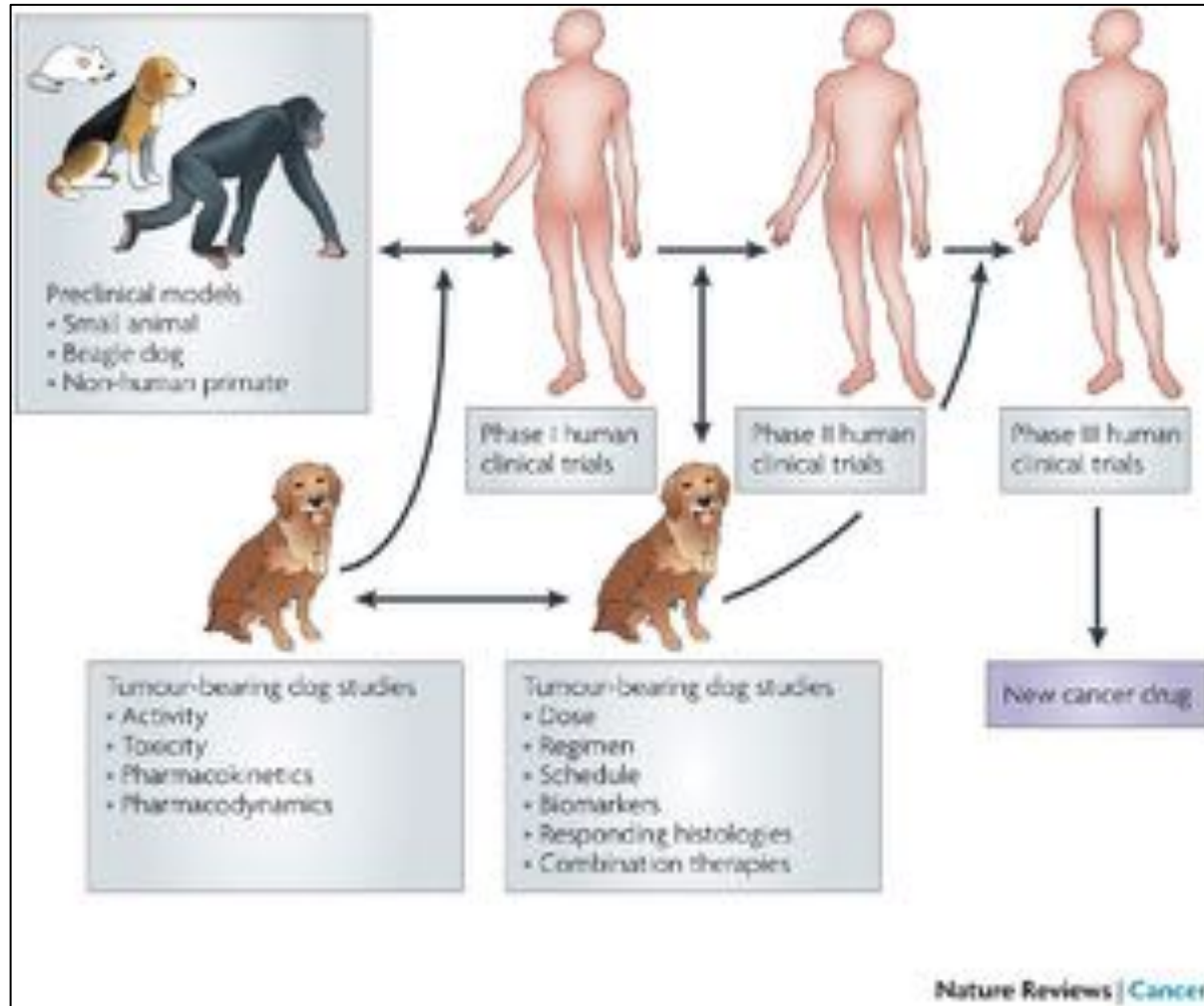
- Safe, **more effective treatments** needed for pet dogs with cancer
- **Relatively easy to perform** clinical trials in client-owned pet dogs
 - Decreased regulatory burden
 - Recruitment rapid and relatively easy
 - Relatively cheap to perform
 - Rapid realization of therapeutic effect
- Data obtained in canine clinical trials **can be used to support applications for human use**
- Rapidly expanding veterinary market
 - Pathway to drug approval less cumbersome
 - Biological agents regulated by the USDA
 - Cell-based therapies governed by FDA
- Accelerate the most promising, safe and effective into **both human and veterinary arenas**

“Scooby Doo” OSA – 4.5 yr + survival



“Isabelli” DLBCL –
7mth + survival

Integrating Canine Cancer Patients into the Drug Development Continuum (Bench to Bedside)



Rudolf Virchow M.D.
1821-1902



“Between animal and human medicine there are no dividing lines - nor should there be.”



Meaningful Comparative Trials with Maximum Potential

Fund well-designed cross-disciplinary, cross-institutional **canine clinical trials** with best prospects for translation to pediatrics

- Consolidate expert opinions into research priorities
 - Tumor biology
 - Comparative genomics (e.g fusion onco-proteins as drivers, shared/common markers)
 - Efficacy
 - Combination therapies, immunotherapies
- Asking the right questions, executing with rigor, getting meaningful results
- Collaborative multidisciplinary and multi-institutional trials



Embracing Comparative Research



- Agency has not taken regulatory action (e.g., clinical hold) in response to a safety signal observed from a canine clinical trial
- Despite this, formal guidance on clinical trials for pet patients sought - none exists
- Drugs approved by FDA for human use could also become available for veterinary use – benefitting both human and animal patients



Industry



- Increased recognition of comparative oncology's value, more engagement/investment needed
- Examples of therapeutic advances in human oncology that have derived in part from clinical trials in dogs include:
 - improvements in understanding radiation response for head and neck cancers;
 - a limb-sparing surgical technique that became the standard in human osteosarcoma patients; and
 - a new drug that improves the survival rate for children with bone cancer by delaying metastasis.

Embracing Comparative Research

- Includes Comparative Oncology Trials Consortium
- Coordinates canine cancer trials among 20 veterinary teaching hospitals housing dedicated oncology centers
- Valuable organizational platform for standardized protocols and the pooling of available patients
- Centers work collaboratively to design and execute clinical trials for dogs with naturally occurring cancers, then share results.
- Traditionally “Intra-murally” focused, but just announced outward grant-making for comparative immunotherapy (See photo)
- Significant additional dedicated resources required



Sick as a dog: canines with cancer could be key to unlocking the mysteries of immunotherapy

People and dogs share some cancer-causing genetic mutations. Now the government is funding an effort to learn from that.

TECHNOLOGYREVIEW.COM | BY EMILY MULLIN



**NATIONAL
CANCER
INSTITUTE**

From Here to there

- **Raising awareness** of the great shared unmet need, and **comparative oncology** as a promising approach to benefit two of our most vulnerable and beloved populations affected by cancer
- **Mobilizing & raising funds among new constituencies** to increase pool of \$\$ in support of tackling pediatric cancer
- **Embracing Moonshot:** compelling comparative model/approach as critical to moving science and cost effective pediatric oncology research forward
- **Fostering collaboration to facilitate great science** across many disciplines & stakeholders: pediatric & veterinary oncology translational research, genomics, immunology, industry (human & animal health), pediatric and animal health advocacy communities
- **Inspiring the Next Generation of Researchers**

COMMUNICATE, COLLABORATE, CURE





Additional Information

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