CENTER FOR CANCER RESEARCH

Connecting the Cancer Community

Advantages and Experiences with Trials that include Pet Animals

Chand Khanna, DVM, PhD, Diplomate ACVIM (Oncology)

Institute of Medicine Workshop2015

NATIONAL CANCER INSTITUTE

Advantages and Experiences with Trials that include Pet Animals

Disclosure/Perspectives

Chand Khanna, DVM, PhD
Diplomate ACVIM (Oncology)

Cancer Biology/Translation
Consultant-Tumor and Metastasis Biology Section, Pediatric Oncology Branch, Center for Cancer Research, National Cancer Institute,

Comparative Oncology
Consultant-zfoundingDirector-Comparative Oncology Program, Center for Cancer Research, National Cancer Institute, Bethesda, Maryland

Veterinary Oncology
The OnciologyService, LLC
Wasington,DC
Leesberg, Springfield, Richmond VA, Wasington,DC

AnimalHelthR&D
Consultant-Ainiml Clinical Investigation,LLC
Wasington,DC

Advantages and Experiences with Trials that include Pet Animals

Disclosure/Perspectives

Chand Khanna, DVM, PhD
Diplomate ACVIM (Oncology)

AnimalHelthR&D
Consultant-Ainiml Clinical Investigation,LLC
Wasington,DC

Scientific Advisor– AbbottAnimal Health; Aratana Inc.

TGEN not-for- profit: Professor
Cancer Biology
AnimalHealth
TGEN affiliateNewco.: CSO
AnimalHelthR&D

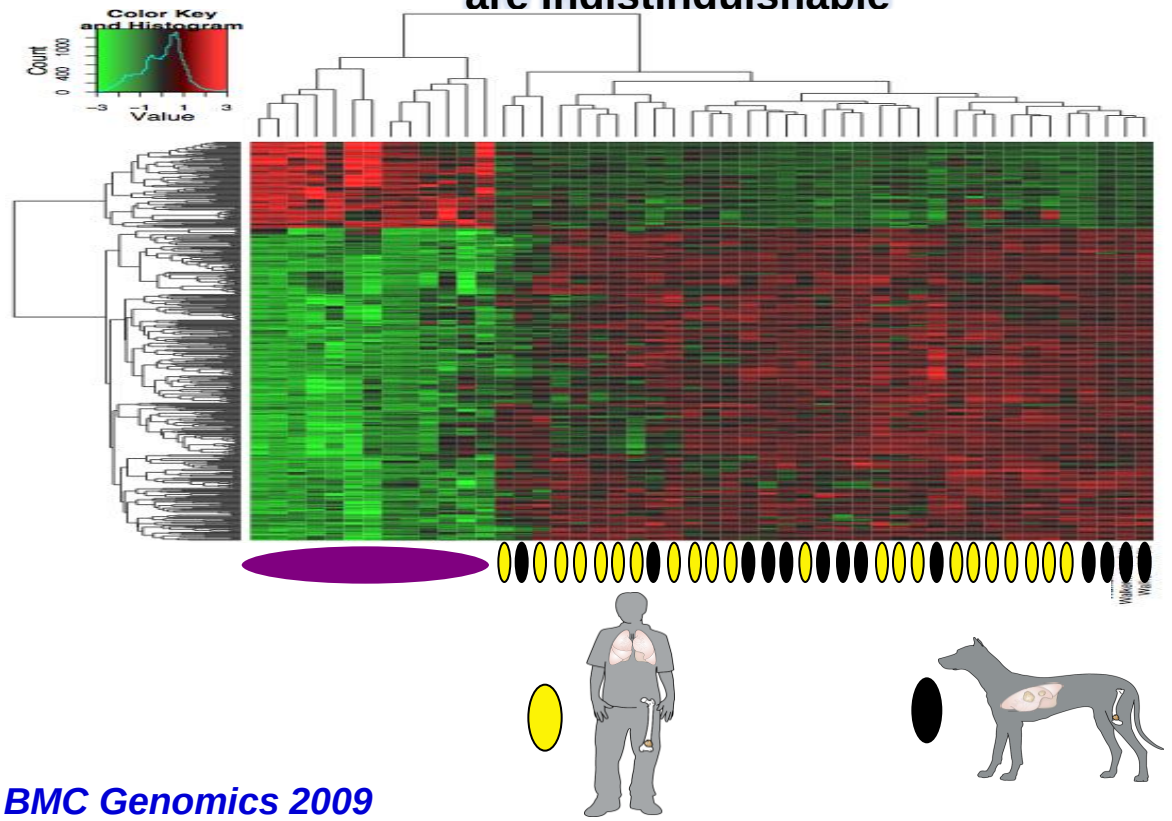
Comparative Oncology

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 competant 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

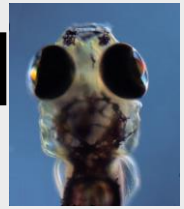


BMC Genomics 2009

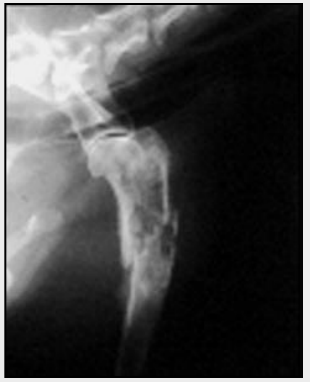
Cross Species Comparative Approach Adds to the Totality of Data Surrounding Drug Development

Rodent Models

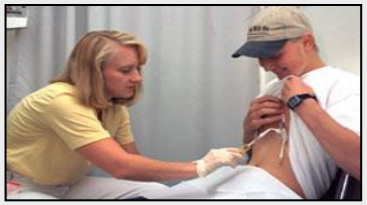
- Genetically Engineered Mouse Models
- Xenografts
- Zebra Fish



Canine Model



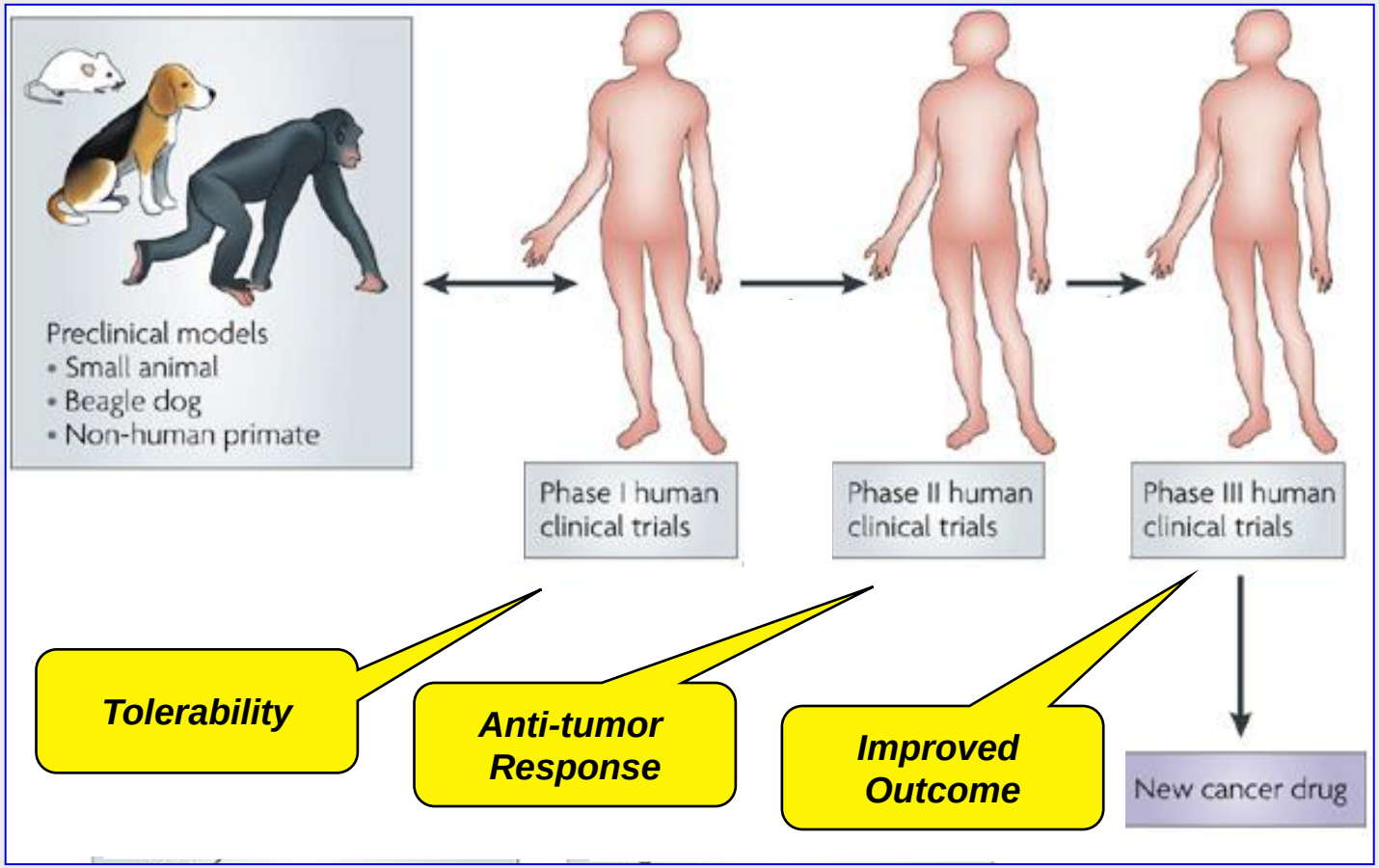
CCR - Comparative Oncology Program



Human Model: Clinical Trials

Improved Understanding of Biology and Improved Treatment Outcomes

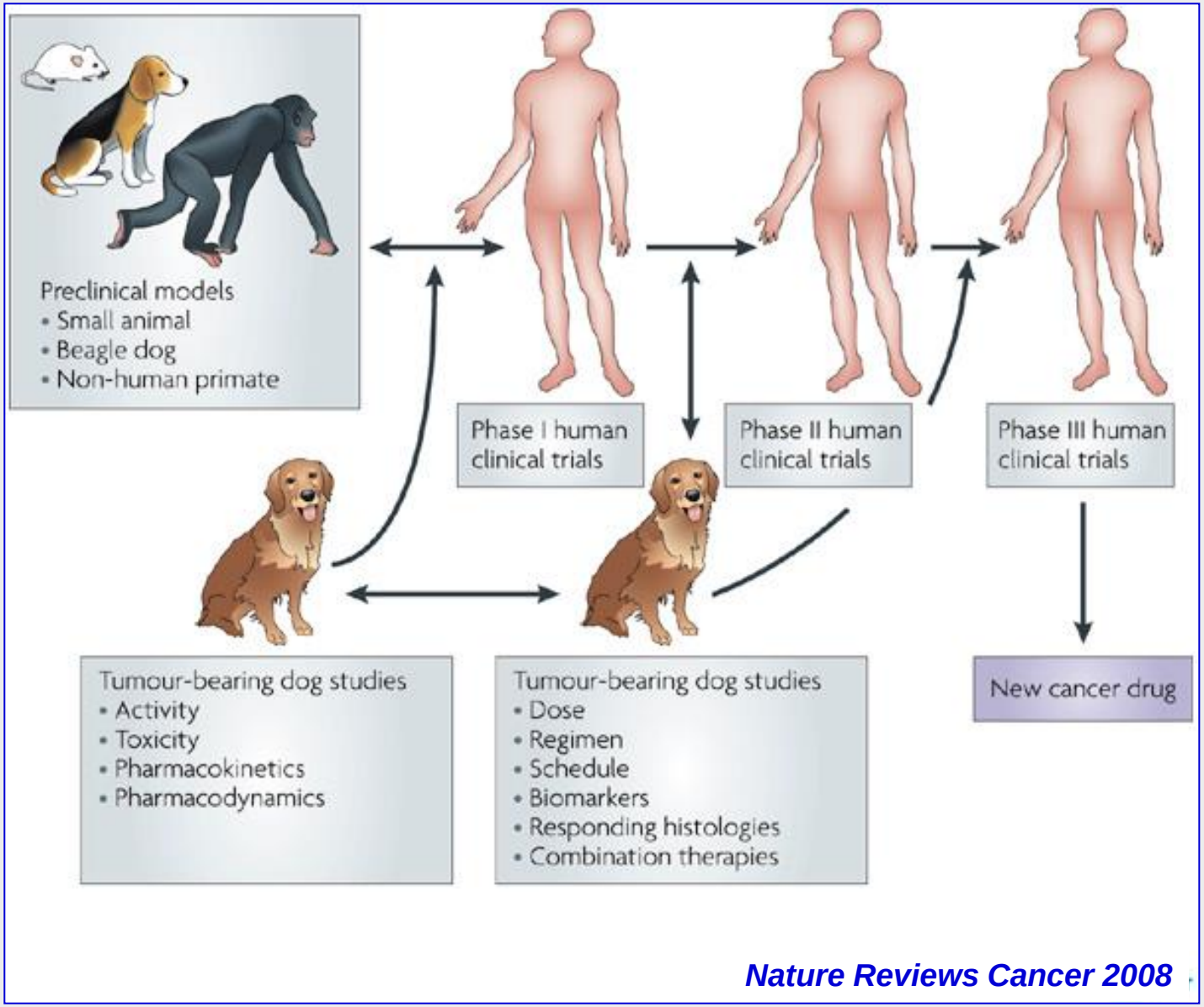
The Conventional Cancer Drug Development Path



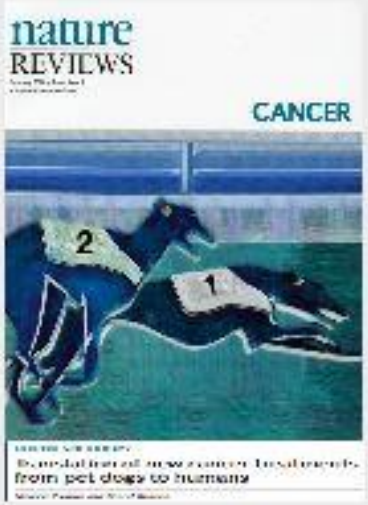
What is the reason for the high attrition rate for oncology drugs?

- ***Cancer is a complex problem***
- ***Preclinical models are not predictive***
- ***Pathway is linear and largely ignores opportunties to be informed***
- ***Important questions are not sufficently answered***

A Comparative and Integrated Approach to Cancer Drug Development



Nature Reviews Cancer 2008



Development of bone marrow transplantation regimes in dogs [11,12]

Tumor vaccines administered for canine lymphoma [13,14]

Evaluation of BCG immunotherapy in canine melanoma [9]

Cytokine and chemotherapeutic inhalation strategies first assessed in dogs with cancer [76-79]

Comparative Oncology Program and Comparative Oncology Trials Consortium-NCI founded 2003

Canine Genome Release 2005

Defined toxicity, activity, PK and tumoral PD with tyrosine kinase inhibition [44, 84]

Descriptive design: size focused | ***Measurable and minimal residual disease*** | ***Integrated***

1960 1980 1990 2000 2012

Hyperthermia (thermoradiotherapy) techniques correlated with clinical efficacy in a canine model [69]

Limb sparing optimized in canine osteosarcoma [71,72]

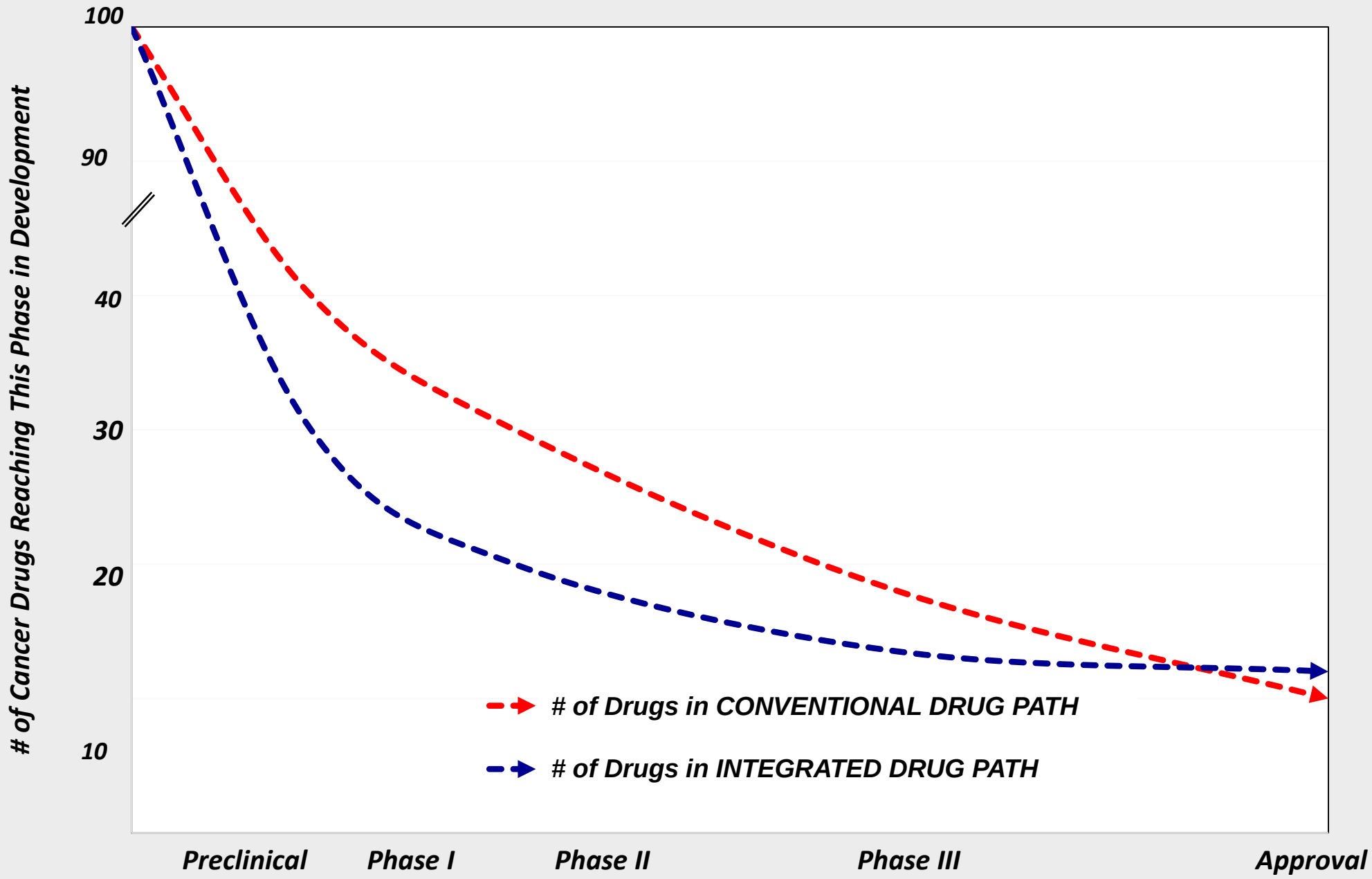
L-MTP-PE evaluated in MRD osteosarcoma guided COG studies [94]

DNA vaccine approved for use in canine melanoma [37,99-100]

Canine Comparative Oncology and Genomics Consortium founded 2006

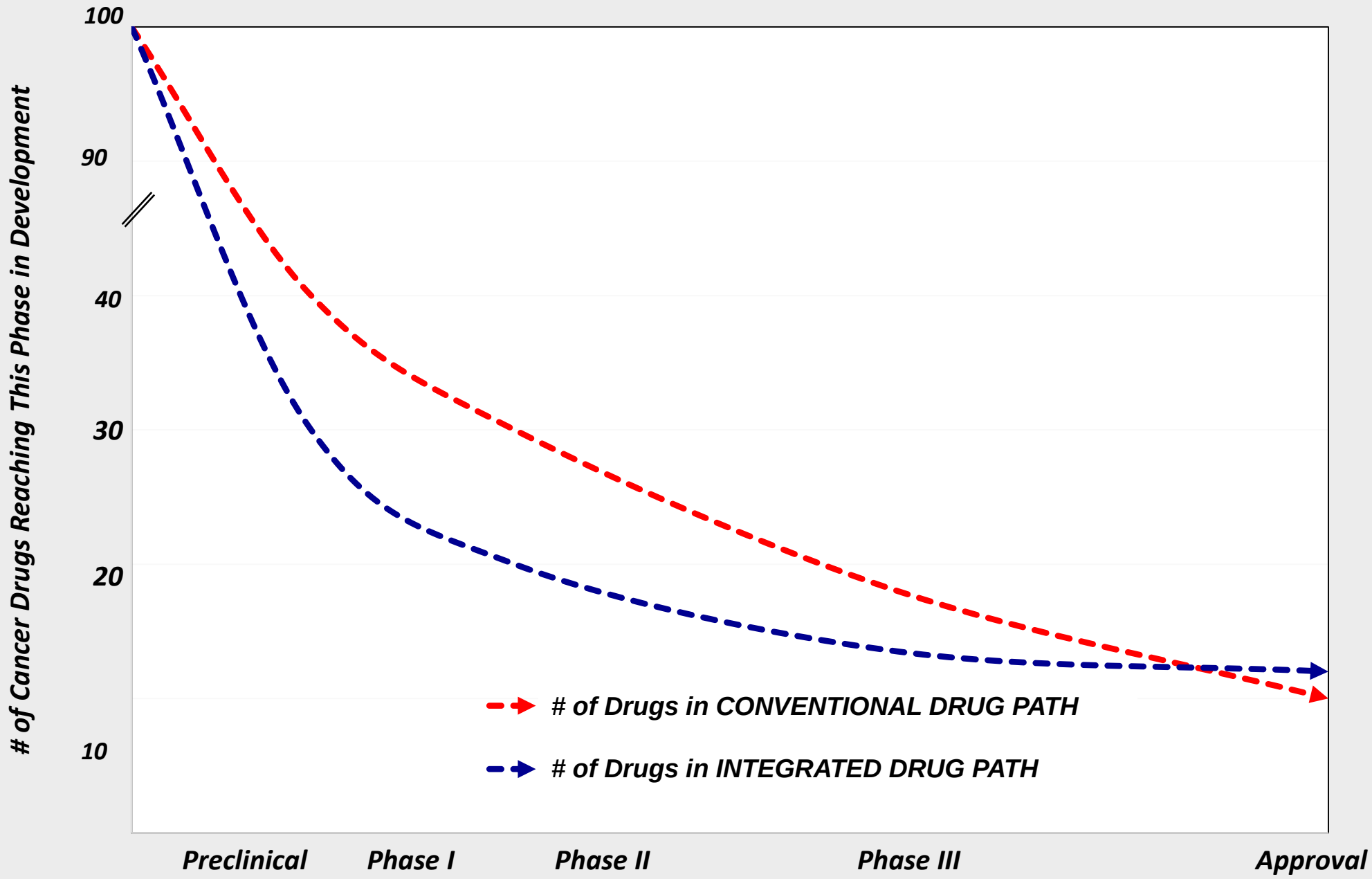
Paoloni and Khanna Nature Reviews Cancer 2008

Projected “Value” of an Integrated Drug Development Path



Gordon, I et al. PLoS Med 6(10): e1000161. doi:10.1371/journal.pmed.1000161

Projected “Value” of an Integrated Drug Development Path



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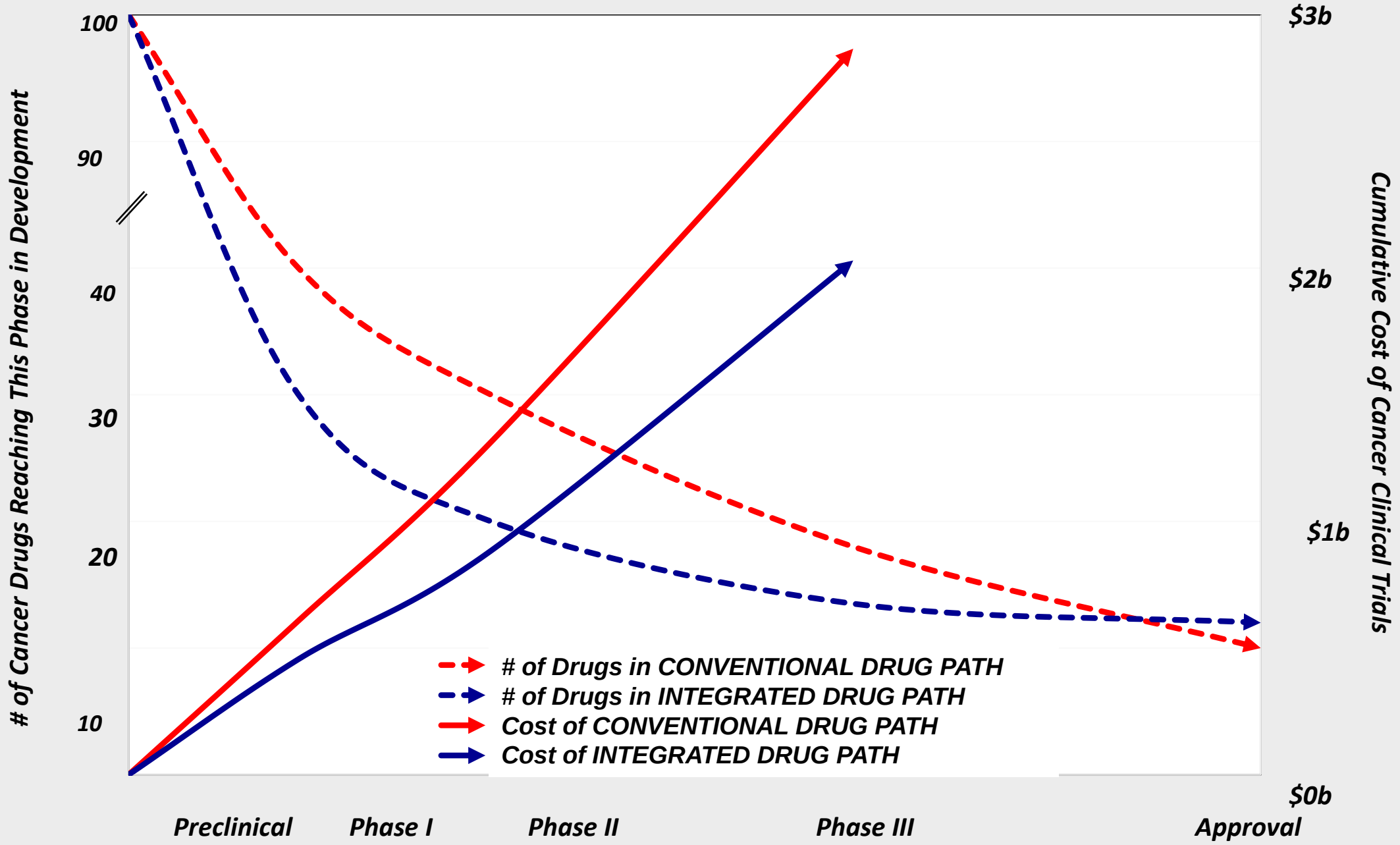
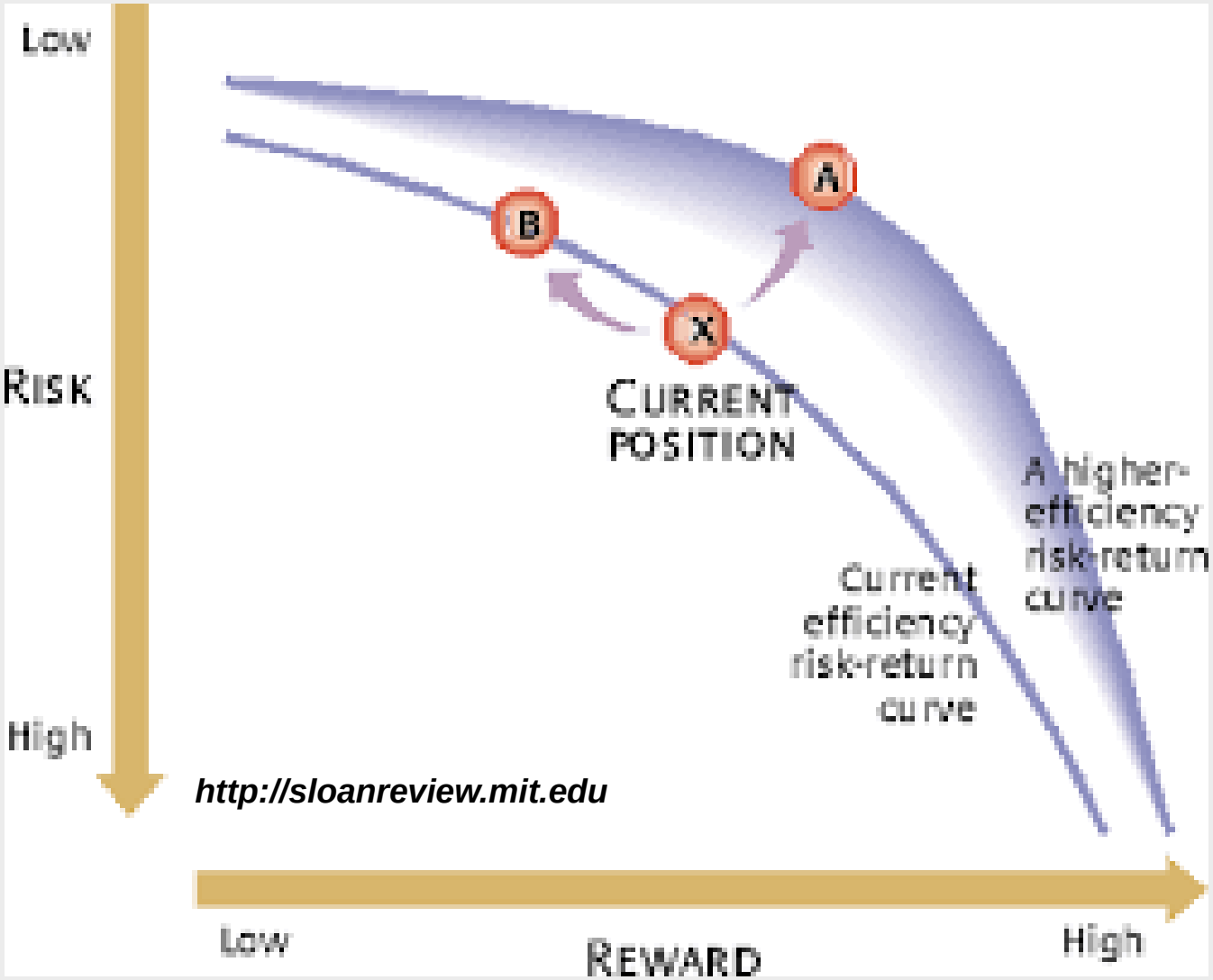
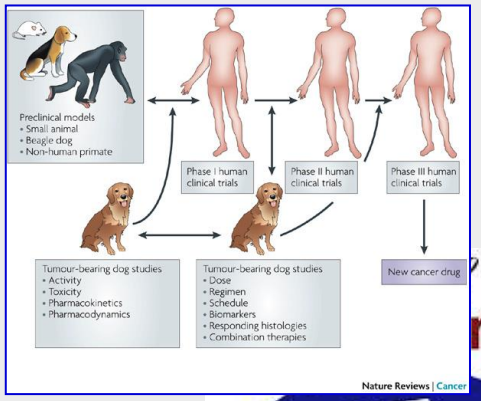


Gordon, I et al. PLoS Med 6(10): e1000161. doi:10.1371/journal.pmed.1000161

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

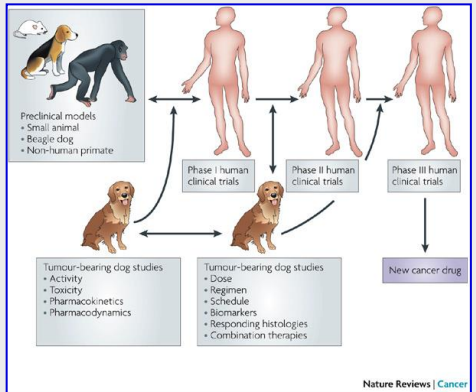


http://sloanreview.mit.edu



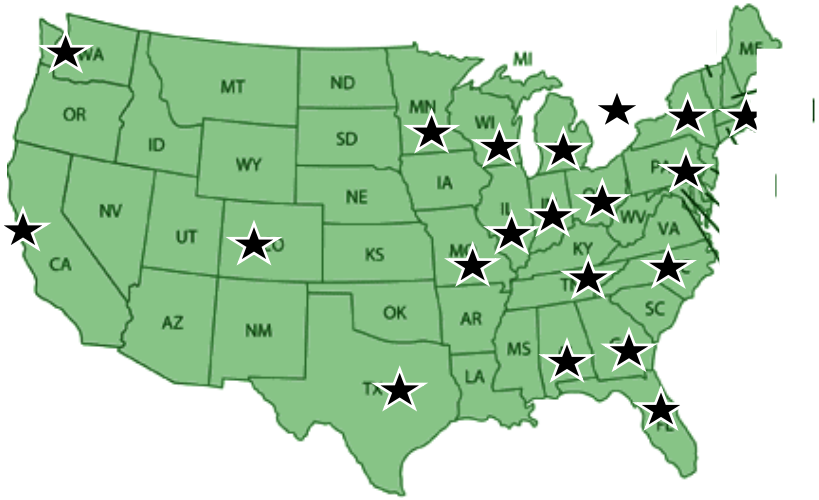
“What are the question best answered through this comparative approach:Review

LeBlanc ,Khanna et al.In Preparation



Comparative Oncology Program – Center for Cancer Research

Comparative Oncology Trials Consortium (COTC)



Reagent/Resources to conduct studies in Comparative Oncology

Genomics
Proteomics
Antibodies
Biospecimen Repository
PD Core

Canine Comparative Oncology and Genomics Consortium

Advocacy for the Appropriate Integration of Comparative Oncology Trials

Academia
Pharma
NCI
Regulatory Bodies

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 Blank Comment

Enroll | COM

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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

"MO037" - University of Missouri

"TN021" - University of Tennessee

"CO018" - Colorado State University

"PA151" - University of Pennsylvania

Primary Disease Site

Disease Term

Stage of Disease

Review

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 Hirschfeld[4]

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.

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

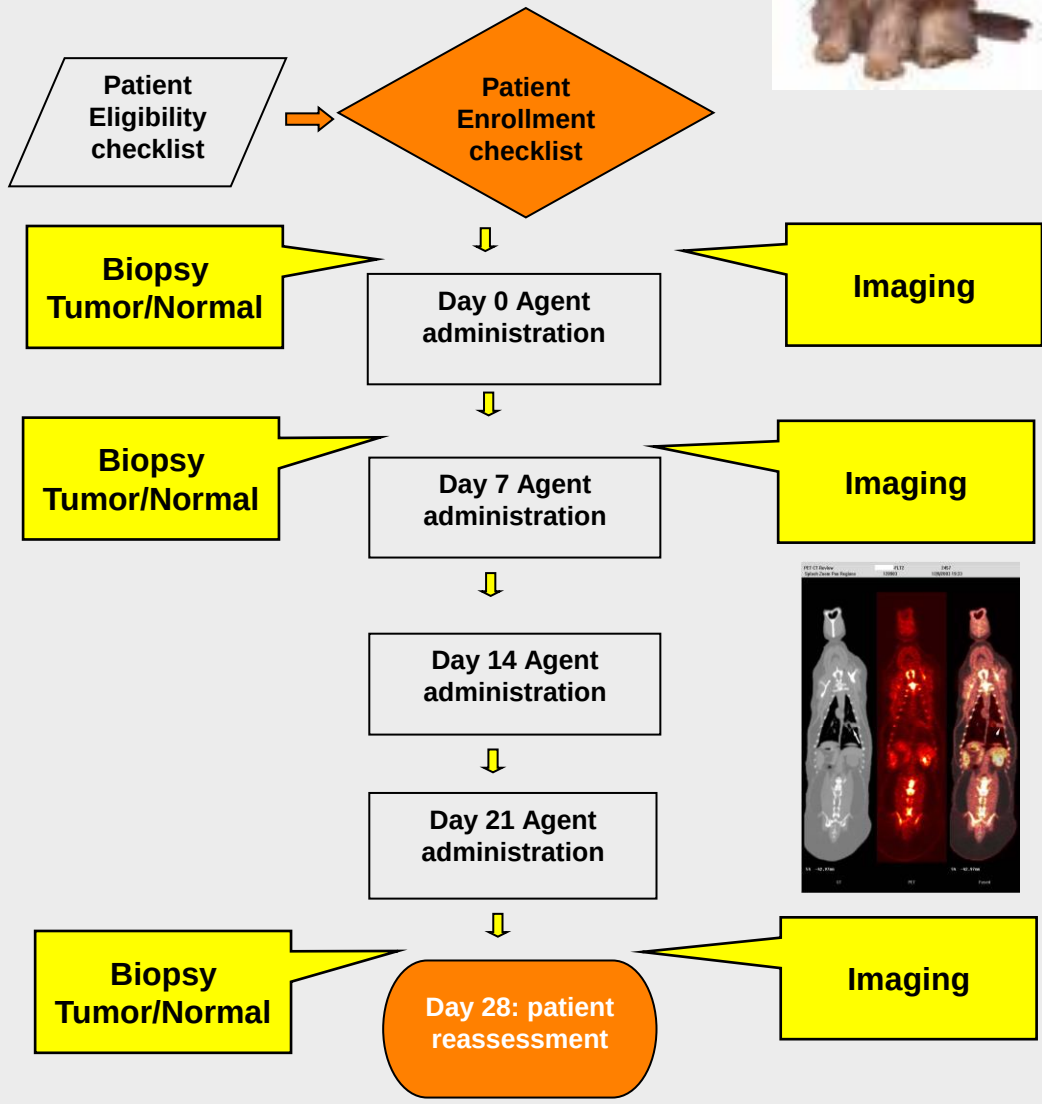
3. Iterative collaboration to define study overview/endpoints

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



Canine Comparative Oncology & Genomics Consortium (CCOGC)

- **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.

CANINE COMPARATIVE ONCOLOGY & GENOMICS CONSORTIUM ***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

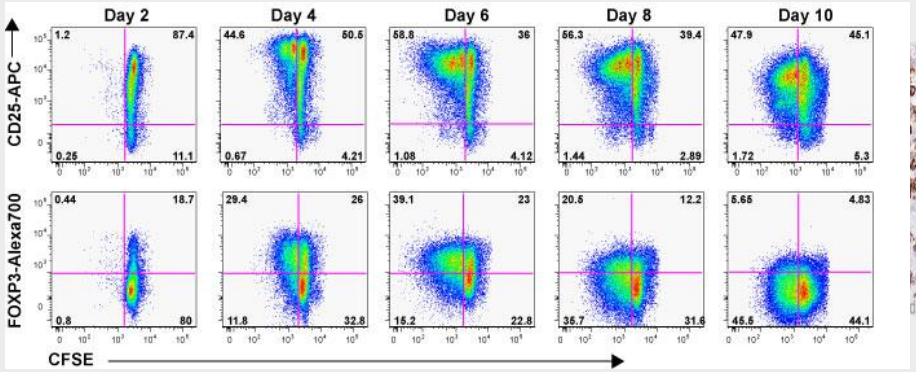
COTC Pharmacodynamics Core

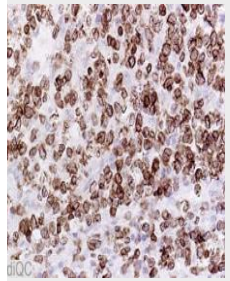
Providing efficient access to laboratory and investigative platforms to study the biology of cancer and drug-cancer relationships in dogs

"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***



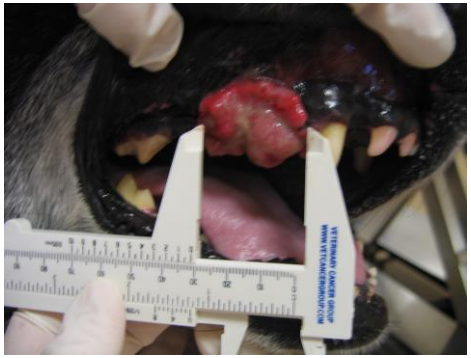


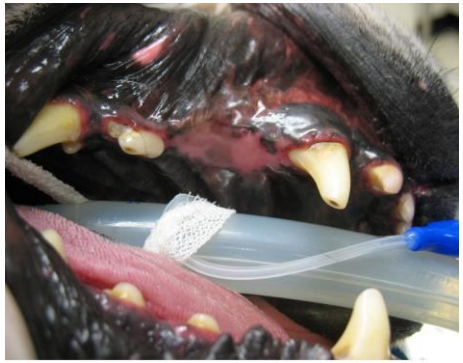
Doug Thamm and Sue Lana CSU

Comparative Oncology Trials Consortium: Study Examples

Antitumor activity and immunomodulatory effects

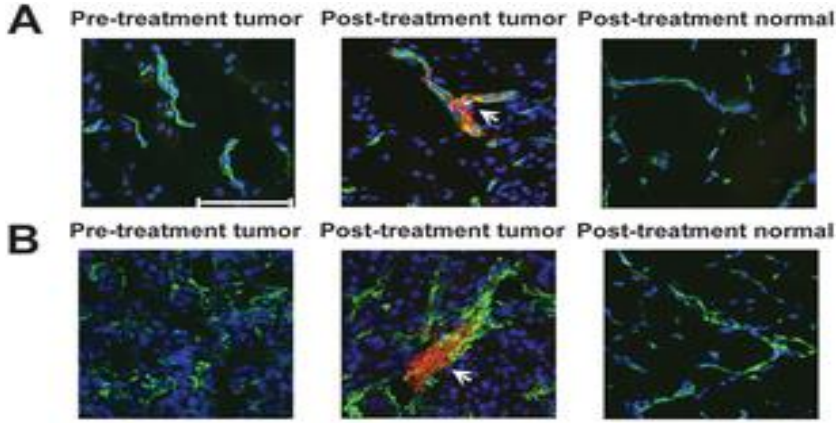
“Evaluation of IL-12 and IL-2 Immunocytokines in Tumor Bearing Dogs”



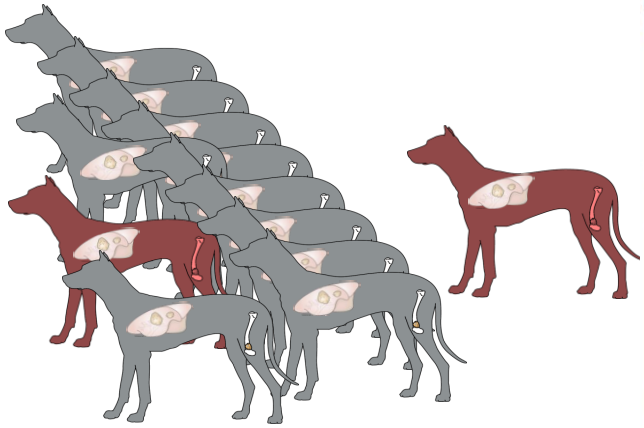


Tumor Specific Targeting – Tolerability

“Evaluation of RGD Targeted Delivery of Phage Expressing TNF-a to Tumor Bearing Dogs”



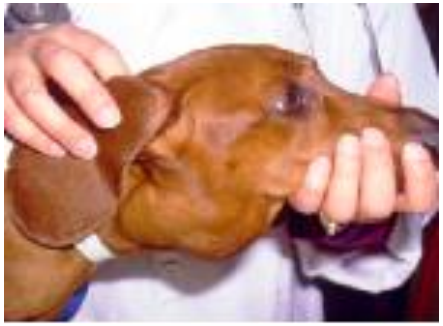
Modeling Personalized Medicine Delivery in Dogs



Molecuiarly informed therapy

Pick the Winner – Biological and Antitumor activity

“Preclinical Comparison of Three TOPO-1 inhibitors in Dogs with Lymphoma”



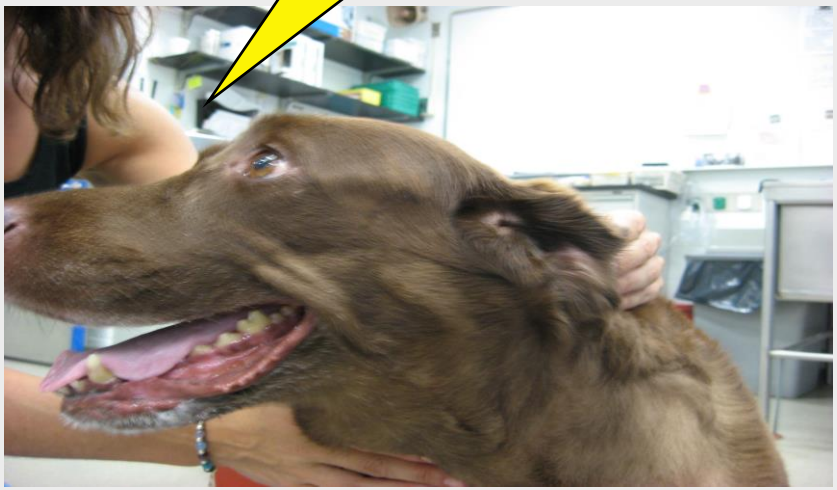
AAVP-TNF Therapeutic Index (repeat dose):

- **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***

Single species Assessment of Therapeutic Index

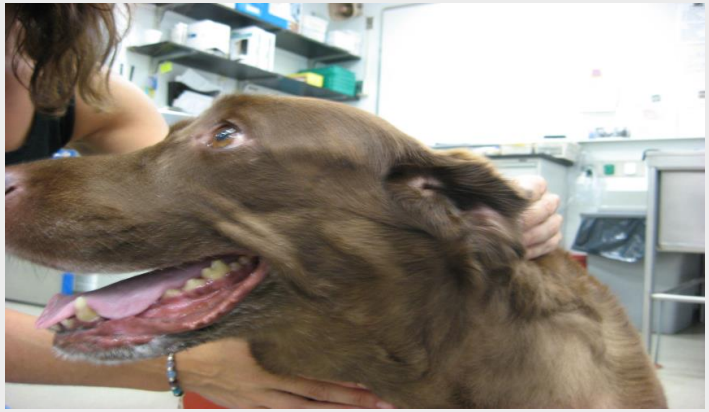
AAVP-TNF Associated Tumor Regression:

- **RECIST criteria**
- **15 evaluable dogs**
- **Objective anti-tumor activity**
  - **2 Partial Response**
  - **6 Stable Disease**
  - **7 Progressive Disease**

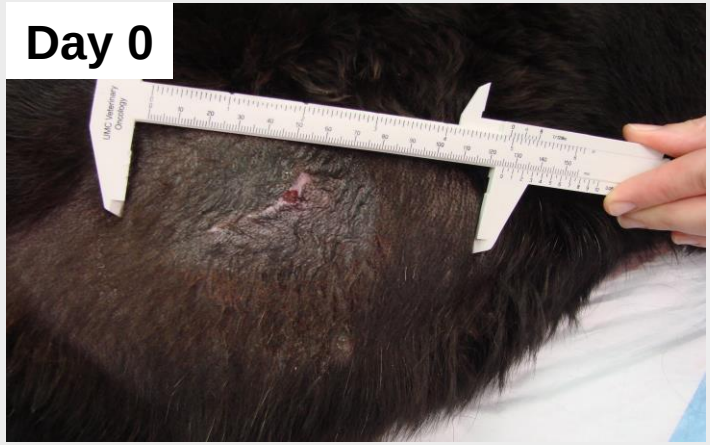


Systemic delivery of AAVP-TNF (phage) results in tumor regression

Canine Myxosarcoma (T3bN0M0)

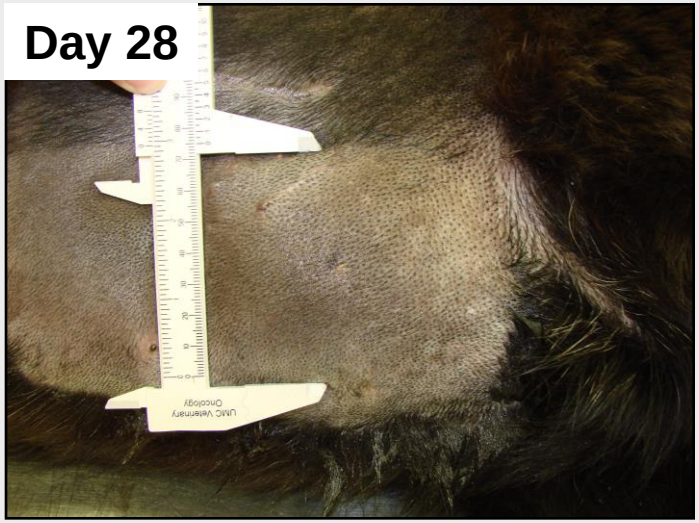


Day 0



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

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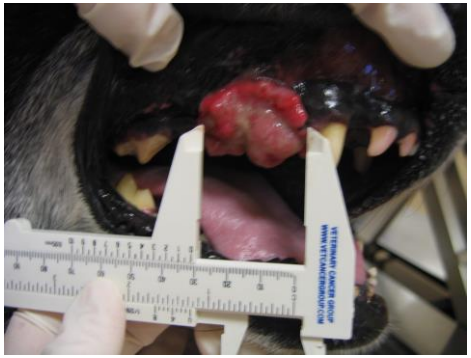

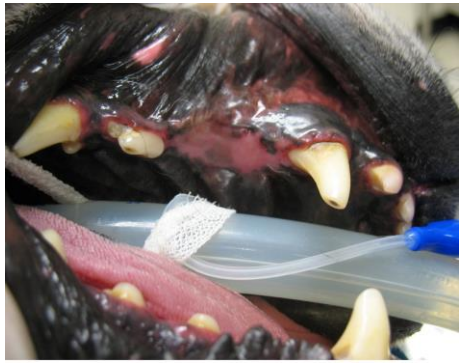

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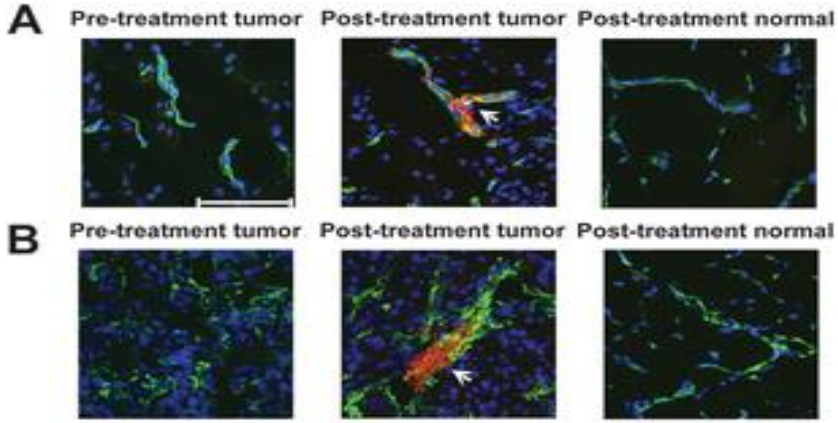

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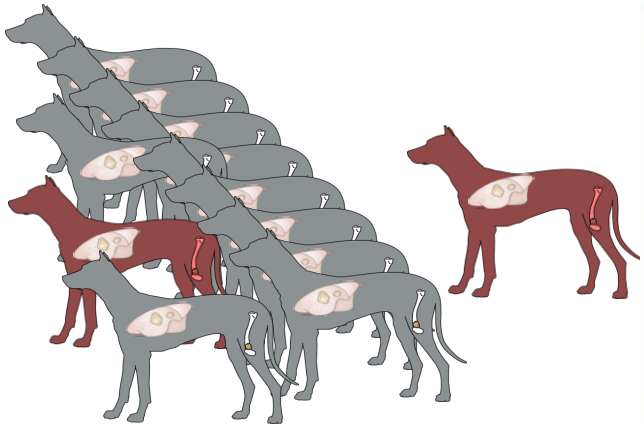

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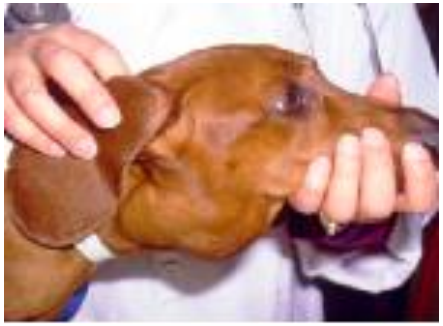
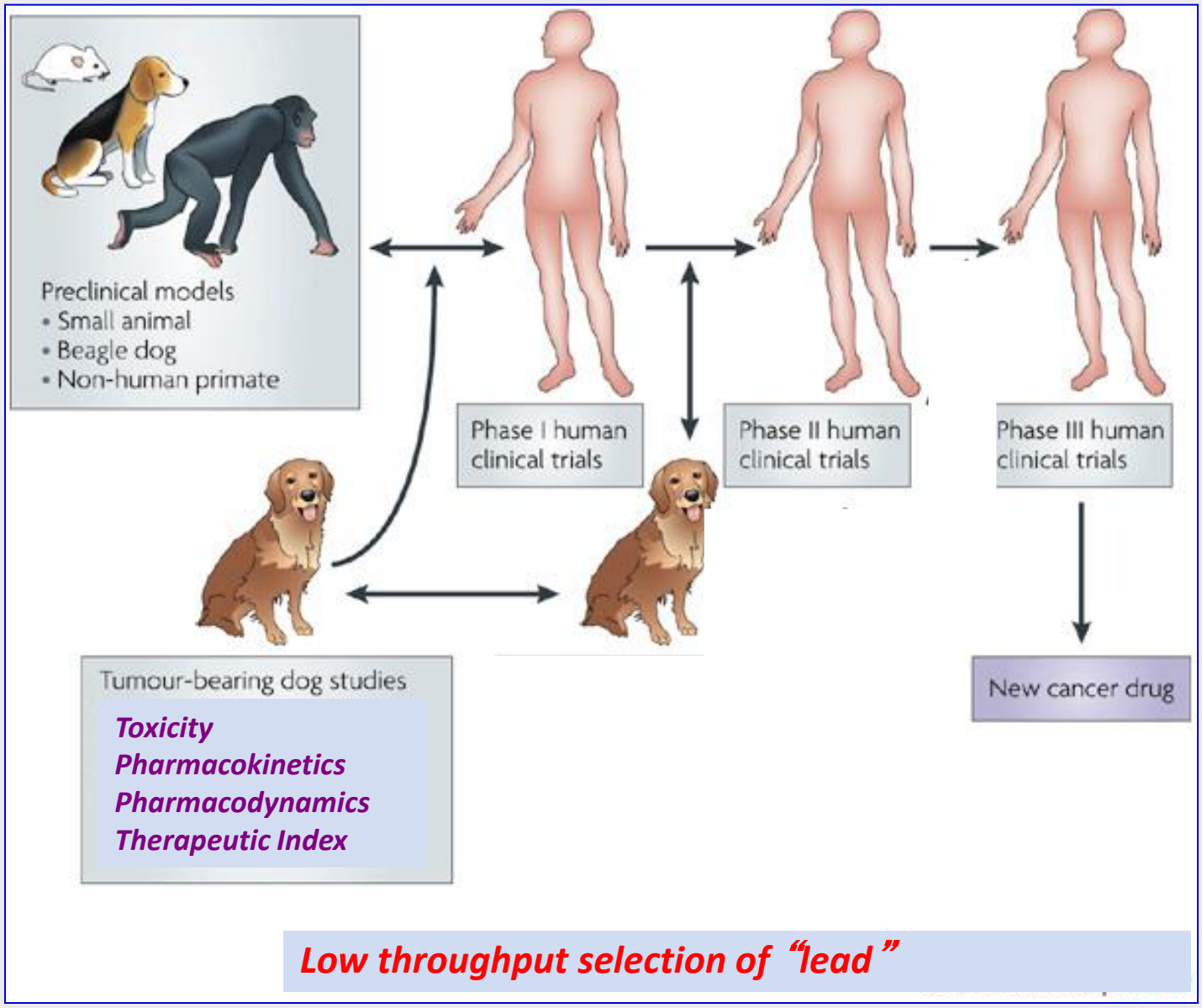
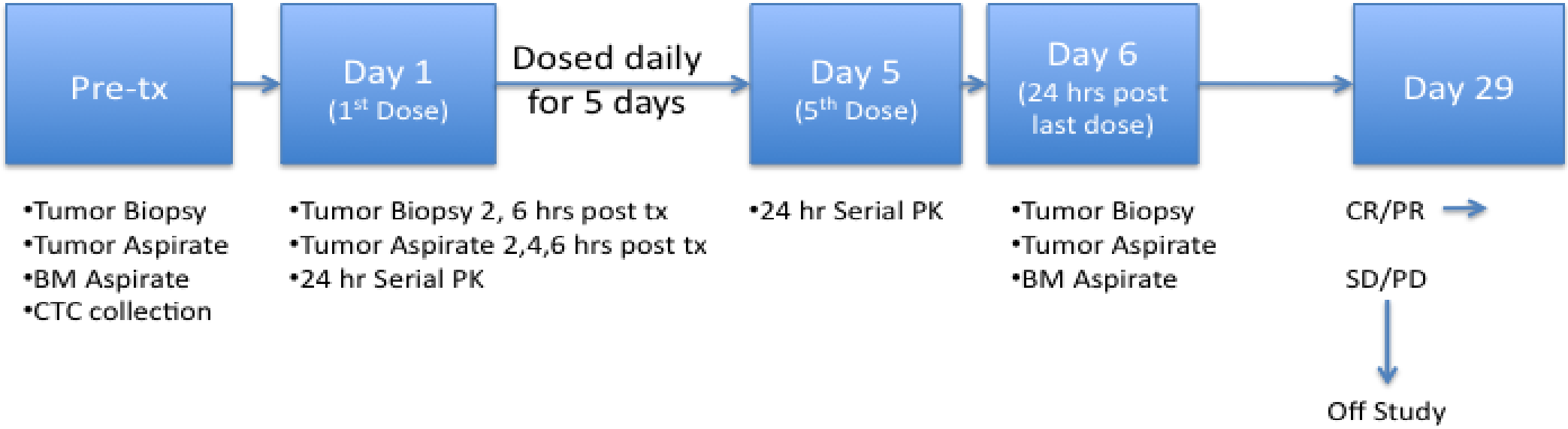


COTC007: Novel Topo Inhibitors:
Integrated Comparative Approach to Identify Lead Agent



Lead Candidate Discrimination/Selection Study: COTC007b



Biological Endpoints

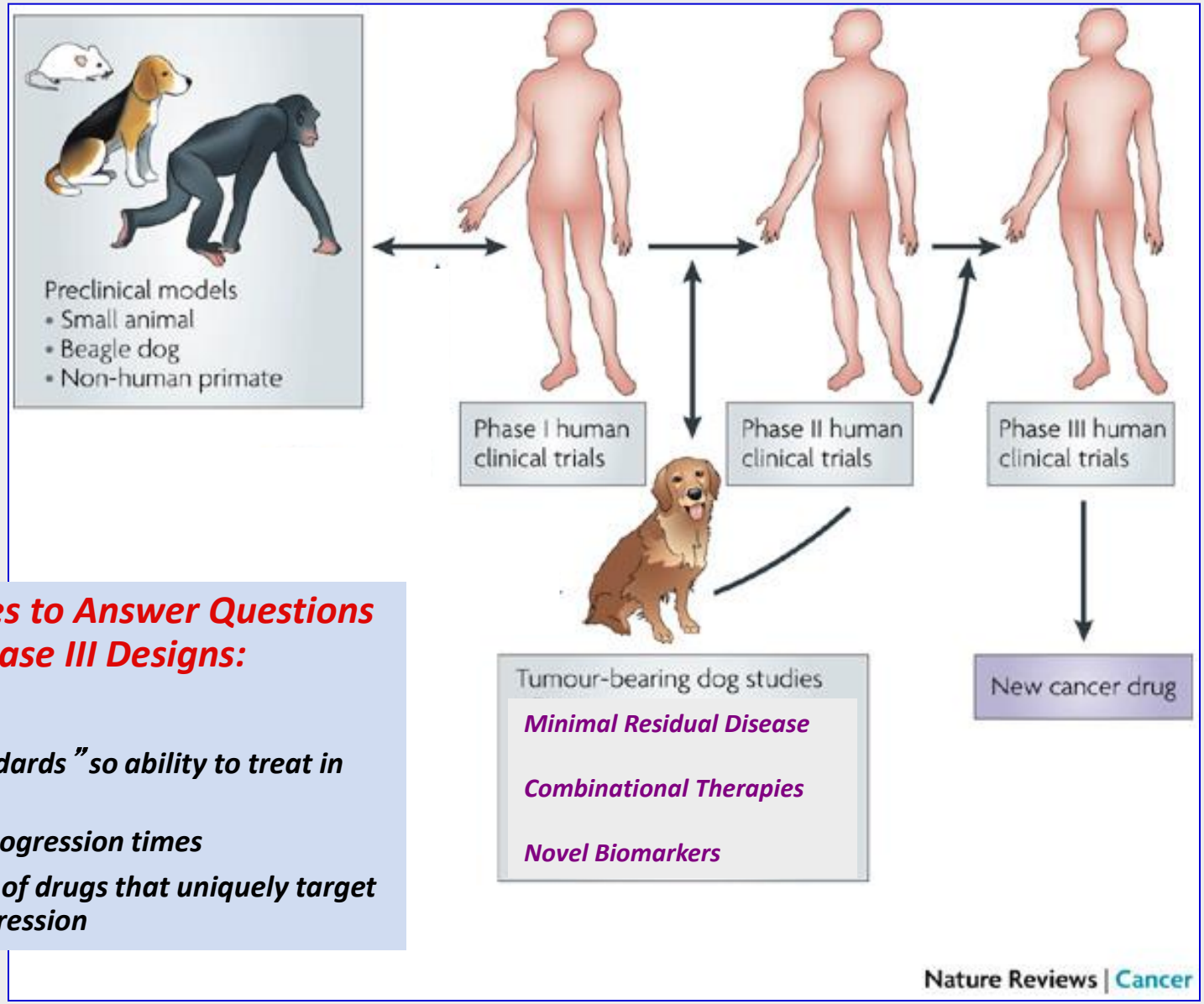
Serum Pharmacokinetics

Tumoral
Drug Levels
Drug Target/Modulation
Biological Activity

Circulating Tumor Cell Numbers
Target Modulation
Biological Activity

Normal tissue (Bone marrow)
Target Modulation
Biological Activity

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

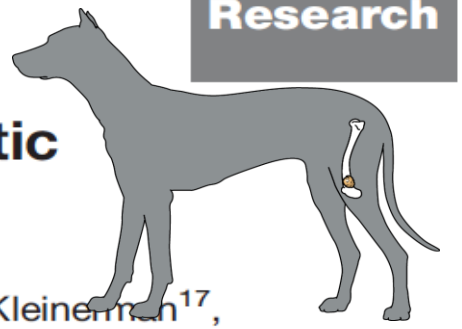


Opportunities to Answer Questions to Inform Phase III Designs:

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

Clinical Cancer Research

Perspectives



Toward a Drug Development Path That Targets Metastatic Progression in Osteosarcoma

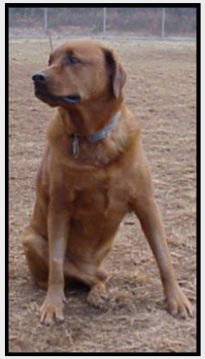
Chand Khanna[1,11,12], Timothy M. Fan[13], Richard Gorlick[14,15], Lee J. Helman[11,12], Eugenie S. Kleinerman[17], Peter C. Adamson[19], Peter J. Houghton[20], William D. Tap[16], Danny R. Welch[21], Patricia S. Steeg[7,11,12], Glenn Merlino[8,11,12], Poul H.B. Sorensen[34,35], Paul Meltzer[9,11,12], David G. Kirsch[22], Katherine A. Janeway[23,24], Brenda Weigel[25], Lor Randall[26], Stephen J Withrow[27], Melissa Paoloni[3,11,12], Rosandra Kaplan[2,11,12], Beverly A. Teicher[10,11,12], Nita L. Seibel[4,11,12], Malcolm Smith[12], Aykut Üren[28,29], Shreyaskumar R. Patel[18], Jeffrey Trent[30], Sharon A. Savage[5,11,12], Lisa Mirabello[6,11,12], Denise Reinke[31], Donald A. Barkaukas[32], Mark Krailo[33], and Mark Bernstein[36]

Published Online May 6, 2014

Integrated Approach to Osteosarcoma Drug Development

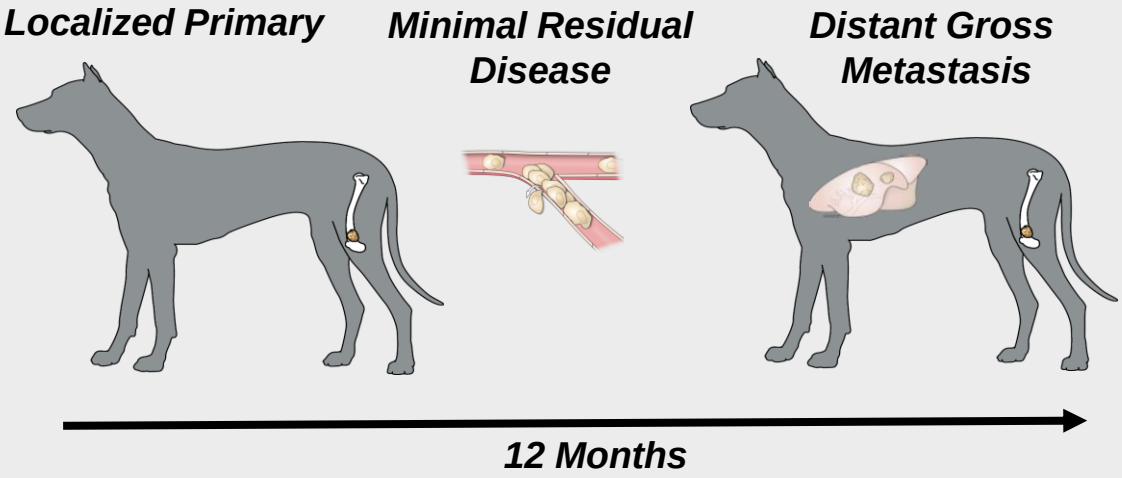
Translational studies of agents that target "vulnerable" metastatic cells.

Canine OS Trials

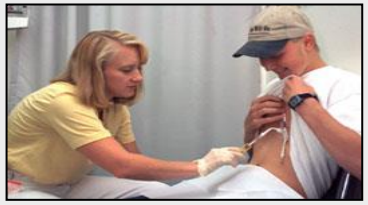


Minimal residual disease studies

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



Early Phase Trials

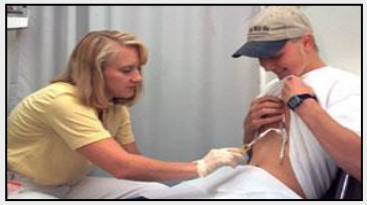


Measurable Disease

Therapeutic Approach:

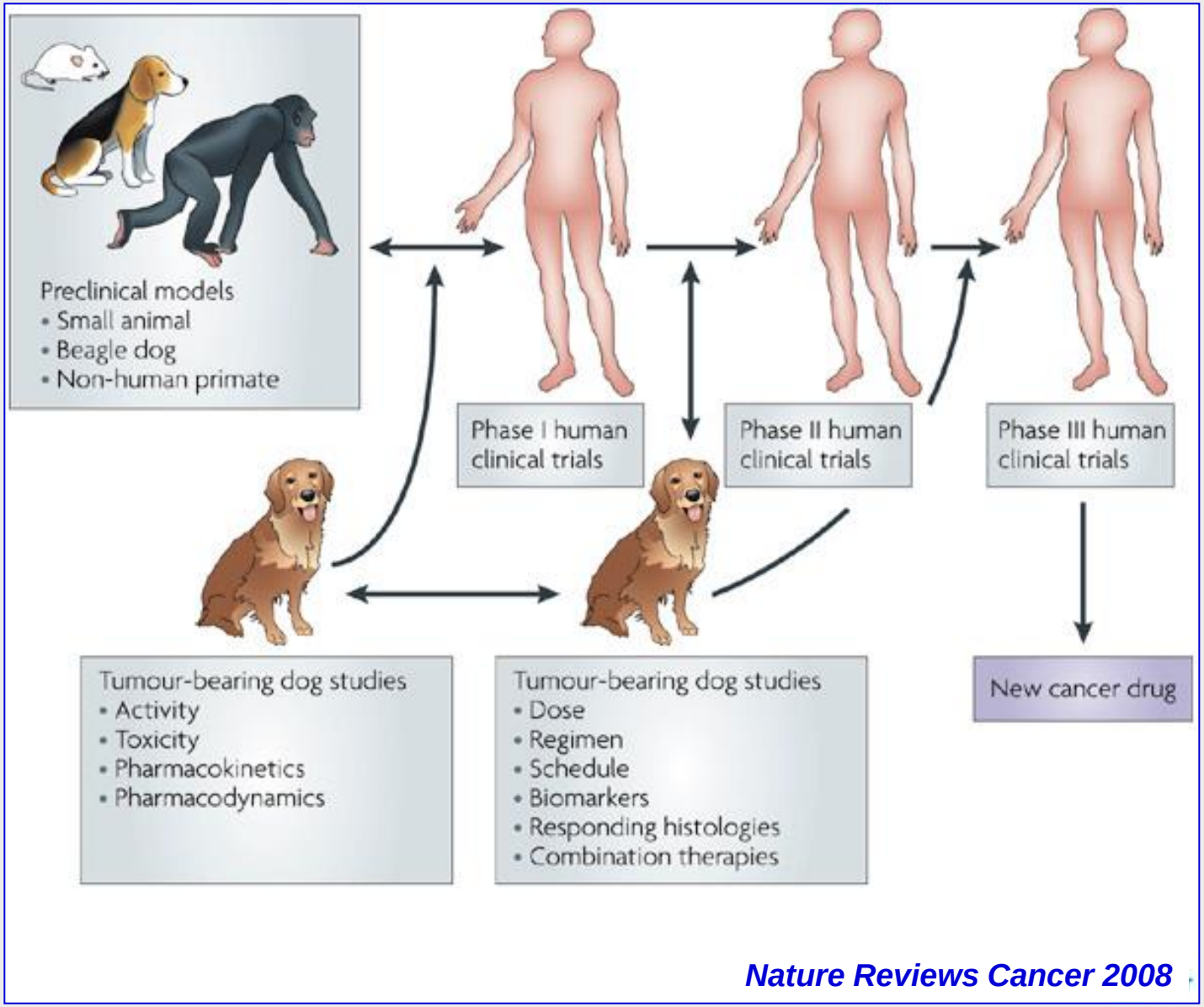
Aminobisphosphonates
Rapalog inhibition of mTOR
Ezrin small molecule inhibitors

Later Phase Trials



Minimal Residual Disease

A Comparative and Integrated Approach to Cancer Drug Development



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*

Perceived Risks and Concerns with Integration of a Comparative Approach

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

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