National Cancer Institute

The NCI Comparative Oncology Trials Consortium (COTC): Structure, Mission and Goals

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Institute of Medicine
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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Discussion points:

- **How does the COTC operate?**
- **Does the current COTC structure meet the needs of the drug development community?**
- **What are the challenges faced by the COTC?**
- **What new/innovative strategies could the COTC employ to improve relevance and accessibility, while fulfilling the NIH/NCI mission?**

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The COTC as a component of the NCI Comparative Oncology Program

CENTER FOR CANCER RESEARCH

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Comparative Oncology Program

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FEATURE

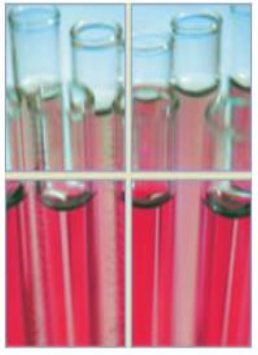
Man's Best Friend in More Ways Than One

Cancer drug development typically begins with in vitro research before proceeding through varying degrees of investigation in cell lines and laboratory animals, eventually culminating in human clinical trials. However, this often arduous development path may now find an ally in a relatively new branch of oncology research, referred to as comparative oncology. Initiated and directed by Chand Khanna, D.V.M., Ph.D., the CCR Comparative Oncology Program complements translational research through the characterization of relevant and naturally occurring cancer models that develop in pet animals as a window to evaluate novel therapies.

What's New

INDUSTRY

SCIENTISTS

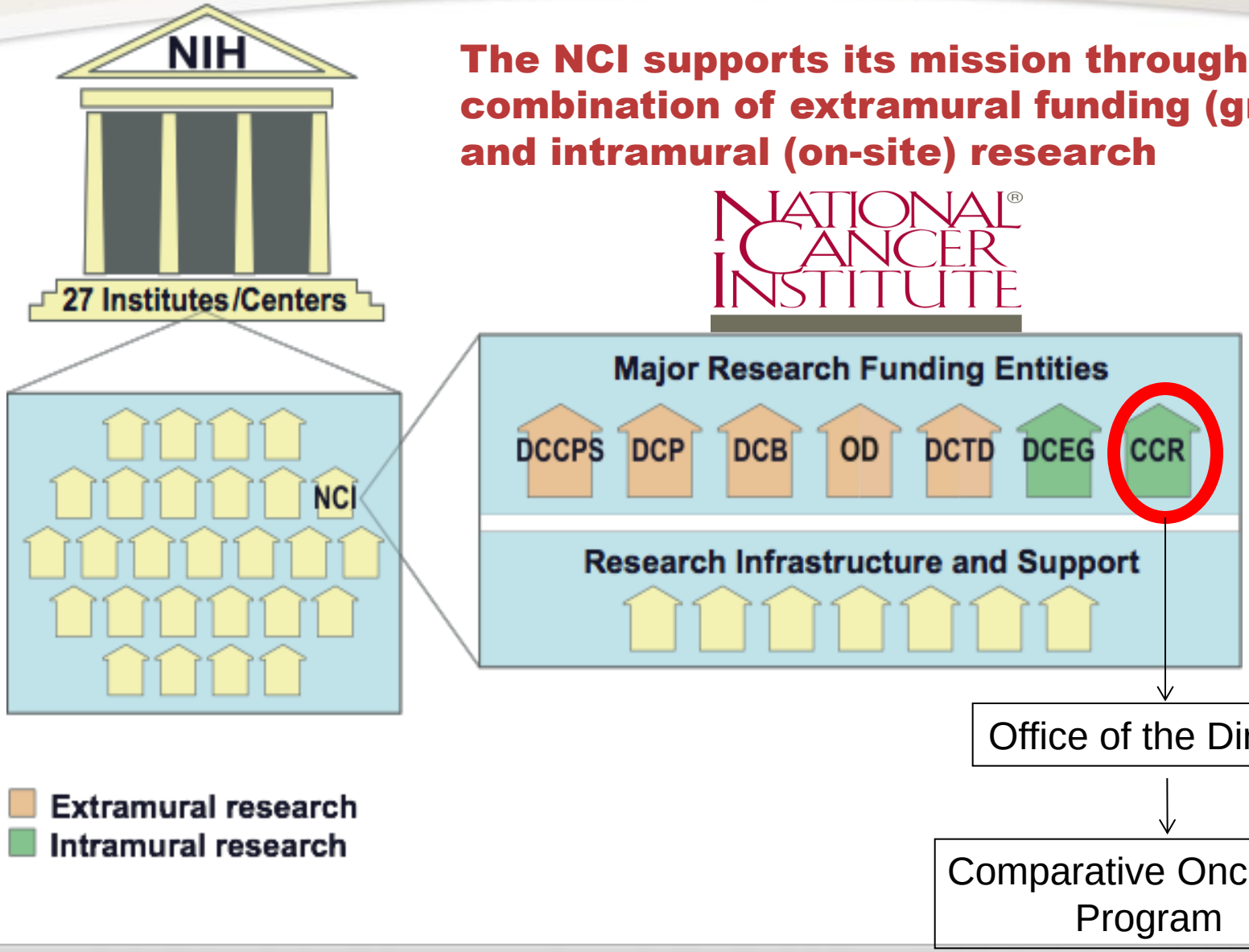


PUBLIC

CONSORTIUM MEMBERS

ANY QUESTIONS??

CCR is part of the Intramural Research Program (IRP) of NIH



The NCI supports its mission through a combination of extramural funding (grants) and intramural (on-site) research

Office of the Director

Comparative Oncology Program

Why is the COTC an attractive option for comparative oncology trial execution?

- Investigators and sites within veterinary academic centers
  - Expertise in clinical trial design
  - Criteria for membership
  - Access to patients
- Dedicated clinical trial support
  - Not a for-profit CRO mechanism
  - Politically neutral
- Ability to leverage existing NCI resources
  - C3D data management
  - Visibility in the community

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Members of the Comparative Oncology Trials Consortium

Auburn University
Auburn, AL

Colorado State University
Ft. Collins, CO

Kansas State University
Manhatten, KS

Michigan State University
East Lansing, MI

North Carolina State University
Raleigh, NC

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 Florida
Gainesville, FL

University of Georgia
Athens, GA

University of Guelph
Guelph, ON Canada

University of Illinois
Urbana, IL

University of Minnesota
St. Paul, MN

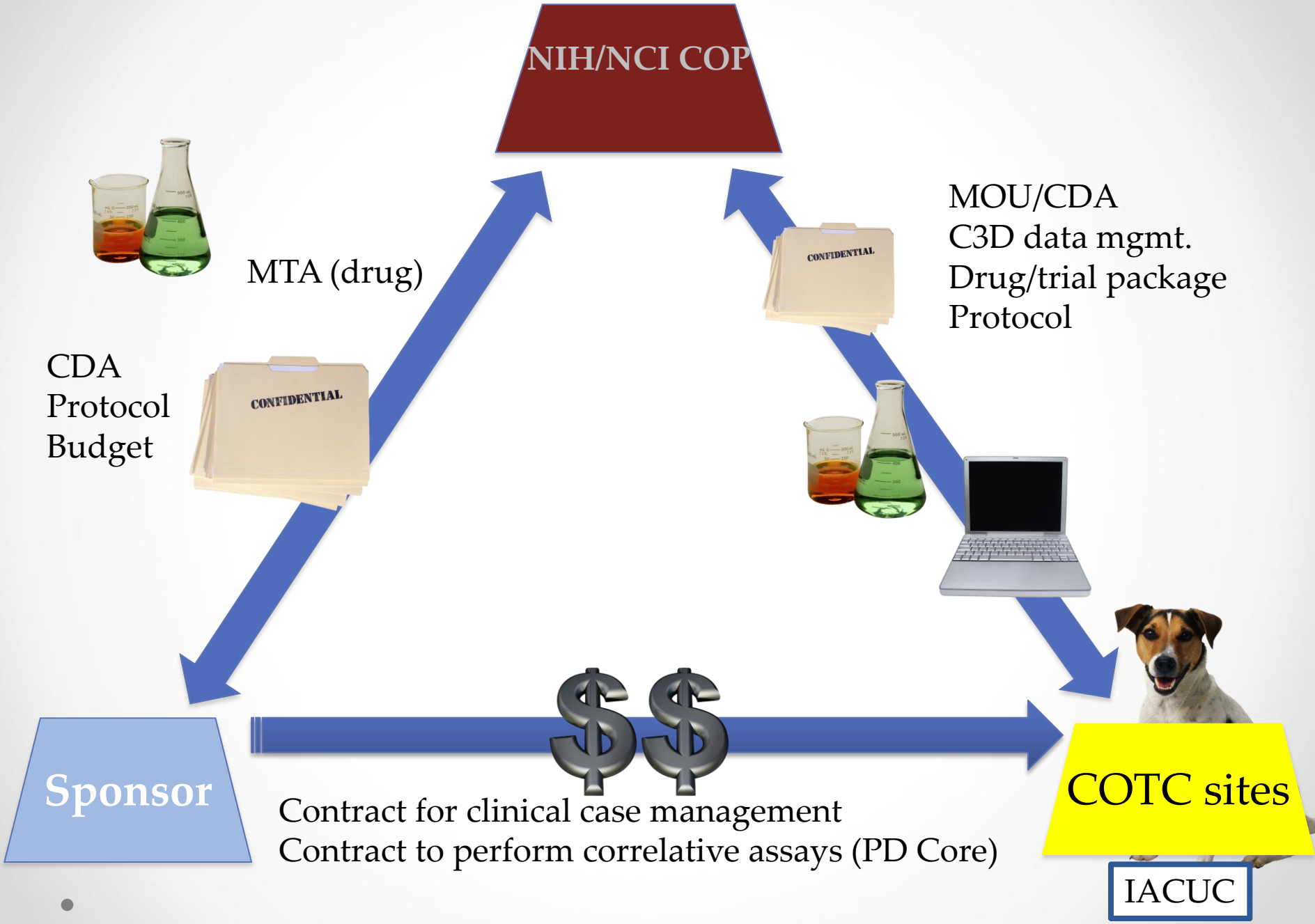
University of Missouri
Columbia, MO

University of Pennsylvania
Philadelphia, PA

University of Tennessee
Knoxville, TN

University of Wisconsin
Madison, WI

Washington State University
Pullman, WA


NIH/NCI COP
MTA (drug)
CDA
Protocol
Budget
CONFIDENTIAL
CONFIDENTIAL
MOU/CDA
C3D data mgmt.
Drug/trial package
Protocol
Sponsor
Contract for clinical case management
Contract to perform correlative assays (PD Core)
COTC sites
IACUC

Study budgeting

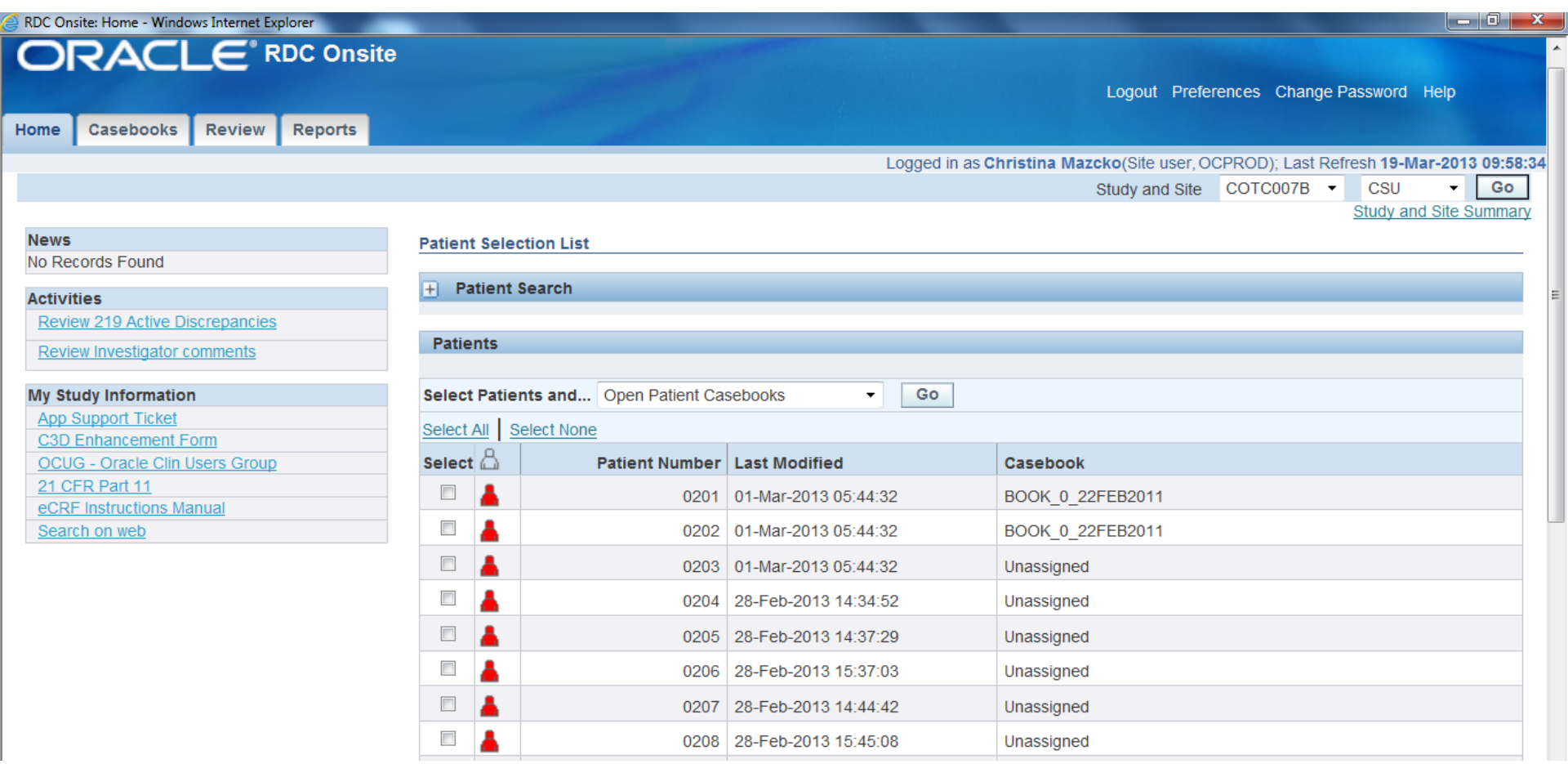
- Standardized structure/fee schedule
  - Study procedures and clinical management
  - Investigator/technical support
- Separate budgeting for correlative assays
  - PD core, Antech GLP, etc
- Study sponsor responsible for provision of the agent and any assays performed within their walls
  - PK, metabolite analysis
  - Biomarker discovery

Protocol and consent

- Generated by study sponsor and NCI/COP/COTC leadership
  - Input from PD core and COTC membership
- Informed consent tailored to study agent and procedures
  - Must include AE language
  - Must include summary of risks/benefits to patient
- Study sites do not go “off-protocol”
  - Violation of Memorandum of Understanding (MOU)
- Sites maintain IACUC approval documentation

Data management

- NCI's C3D system captures response data from each COTC site in real time
- Electronic Case Reporting Forms (eCRFs) are study and patient-specific
- Entire patient record is included for analysis
  - Eligibility/enrollment
  - On-study events and procedures
  - Drug administration
  - Owner questionnaires
  - Concurrent medications
  - Labwork
  - Response data
  - Follow-up/survival data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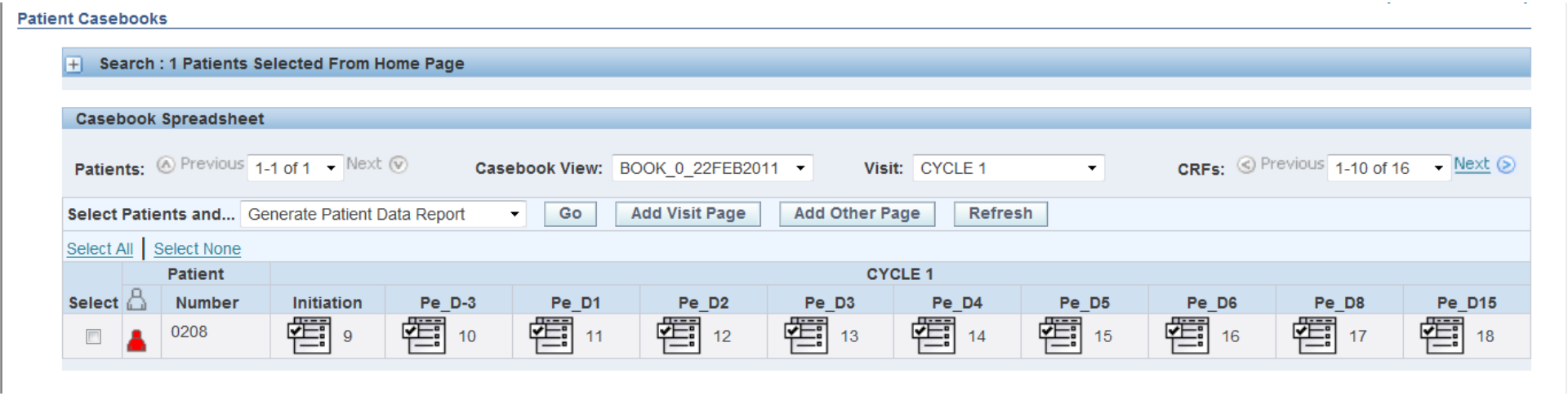
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0208 9 10 11 12 13 14 15 16 17 18

Data/Safety Monitoring Board

- DSMB convened for each COTC trial
- Chair + 4 members
  - All from non-participating institutions, if possible
- Quarterly discussion of all trial adverse events with site investigators and study sponsor
- Ad hoc discussion of unexpected and/or severe events

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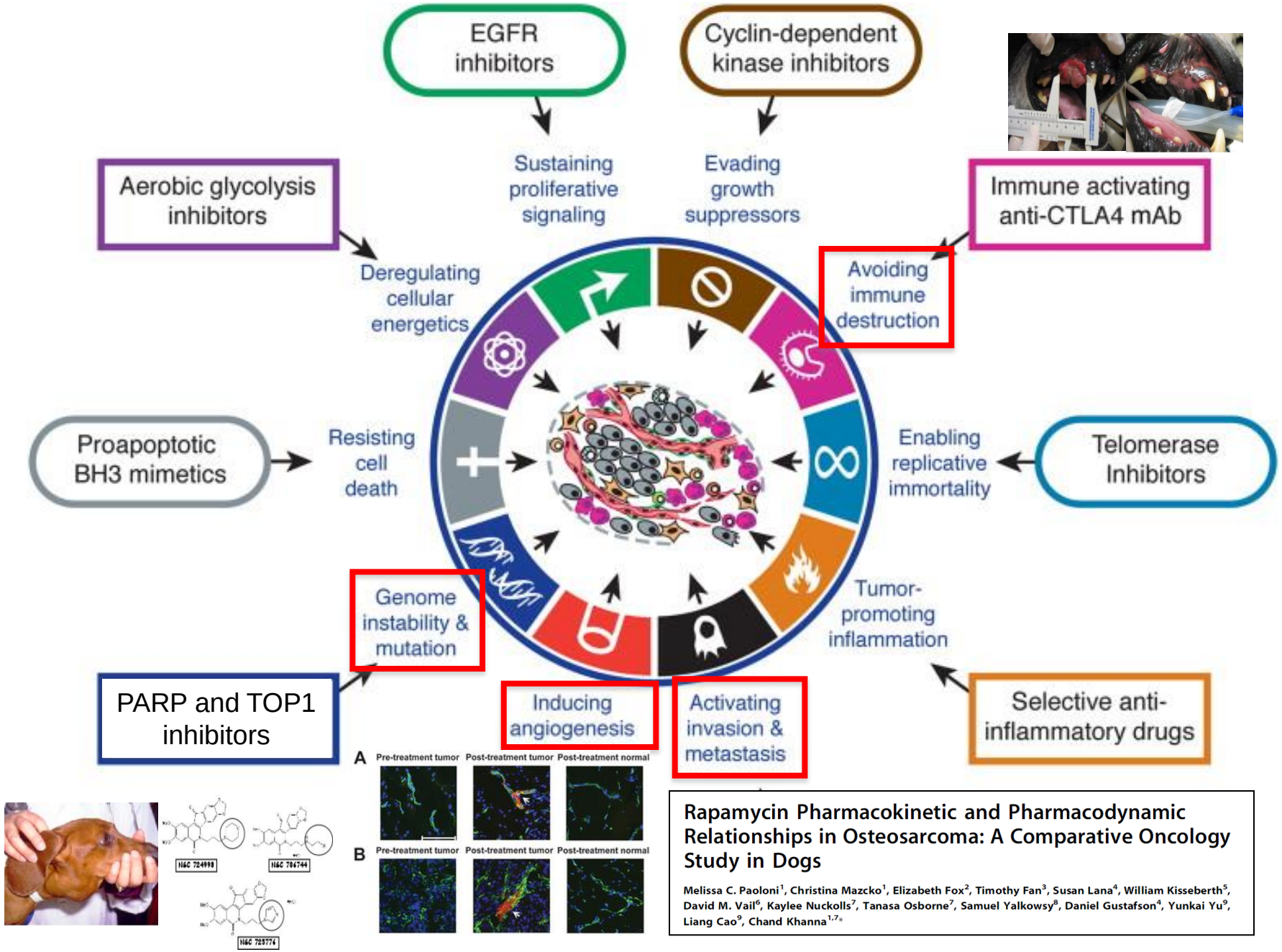


Rapamycin Pharmacokinetic and Pharmacodynamic Relationships in Osteosarcoma: A Comparative Oncology Study in Dogs

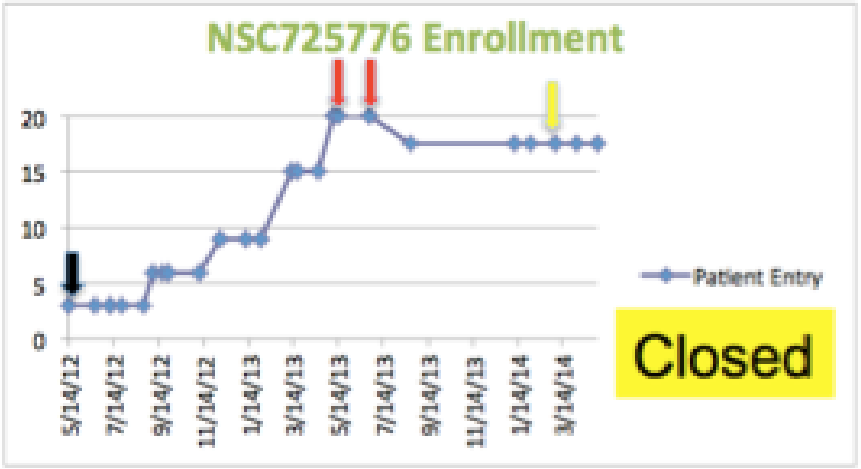
Melissa C. Paoloni[1], Christina Mazcko[1], Elizabeth Fox[2], Timothy Fan[3], Susan Lana[4], William Kisseberth[5], David M. Vail[6], Kaylee Nuckolls[7], Tanasa Osborne[7], Samuel Yalkowsy[8], Daniel Gustafson[4], Yunkai Yu[9], Liang Cao[9], Chand Khanna[1,7]*

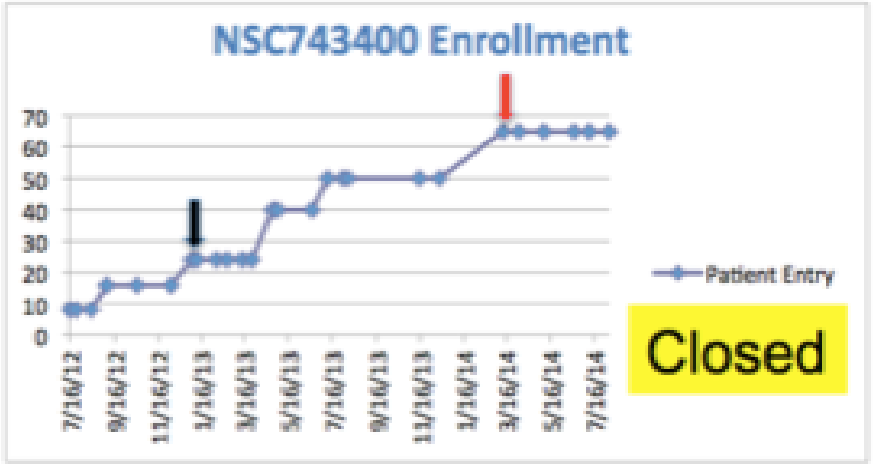
Hanahan and Weinberg; Hallmarks of Cancer: The Next Generation; Cell 144 (5), 2011: 646 - 674

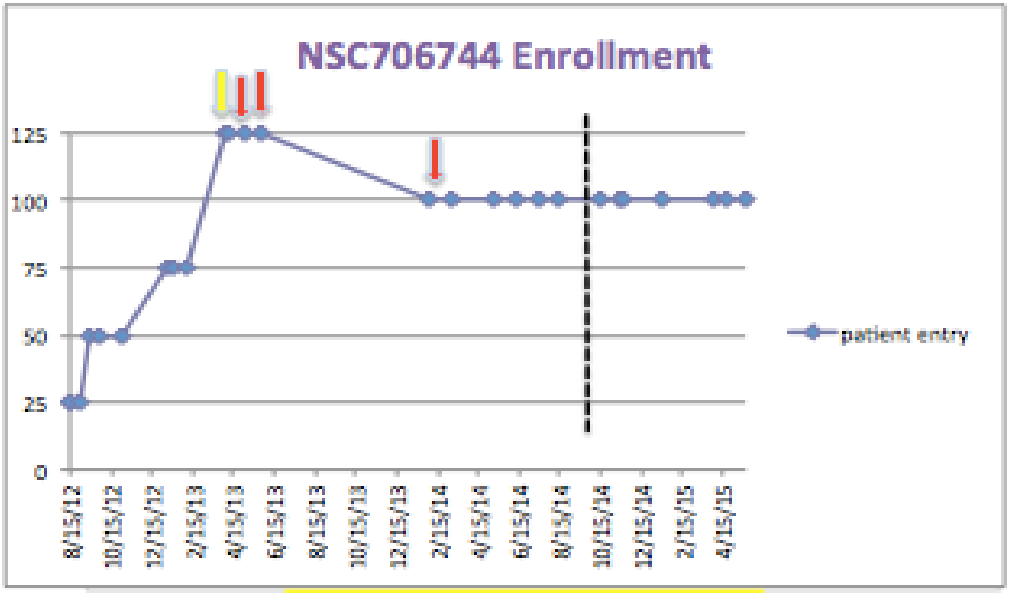
COTC trials: Intent and Scope

- Data generated in response to specific need in (human) drug development

- Trial design reflects specific questions being asked of the disease model in dogs
  - Tumor biology or drug target > histology
  - Dose/schedule, selection of lead compound, PK/PD relationships, biomarker validation
  - Evaluation of combination therapies
  - Efficacy often not primary endpoint







Open-100mg/m2

Grade 5 event

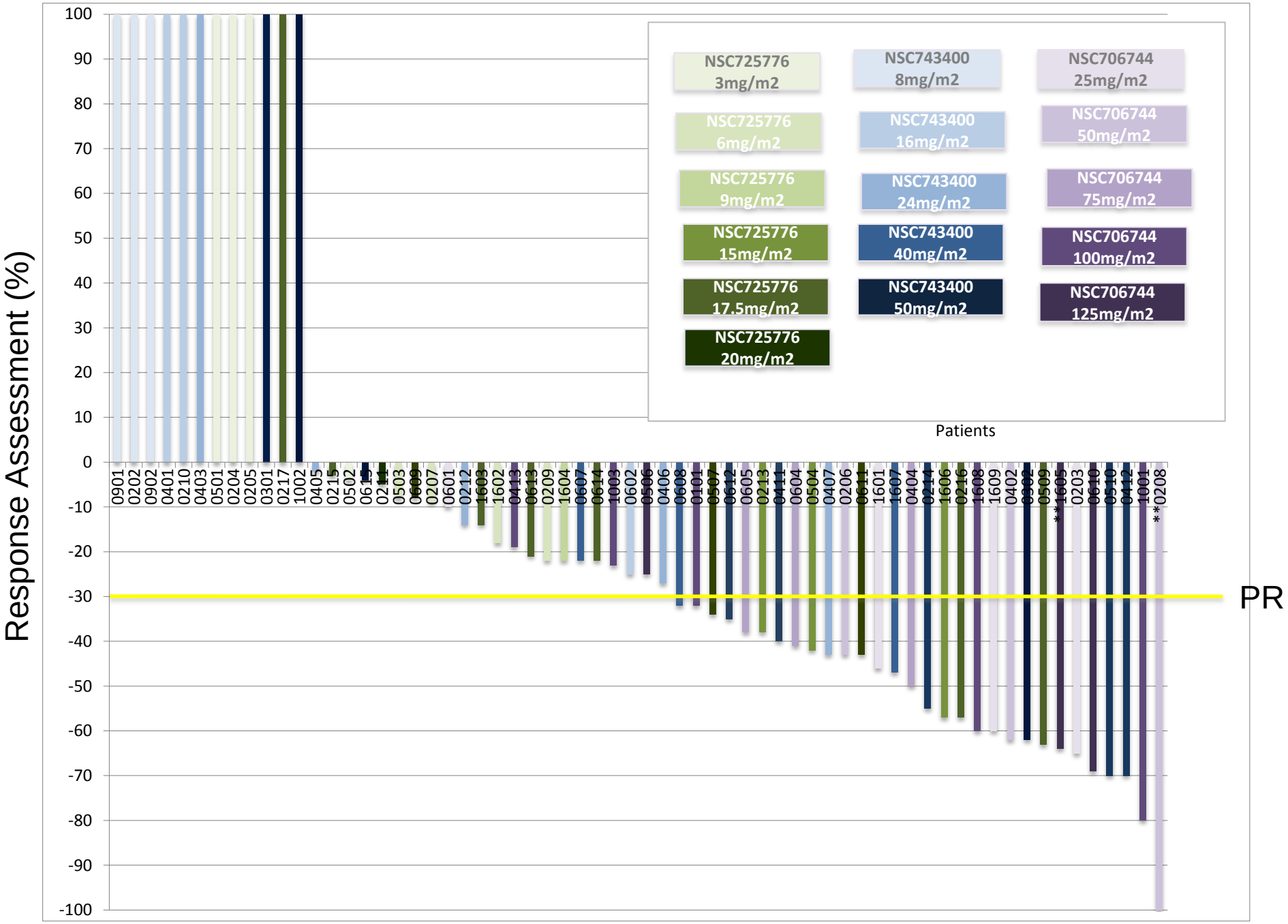
Grade 4 event

Grade 3 event

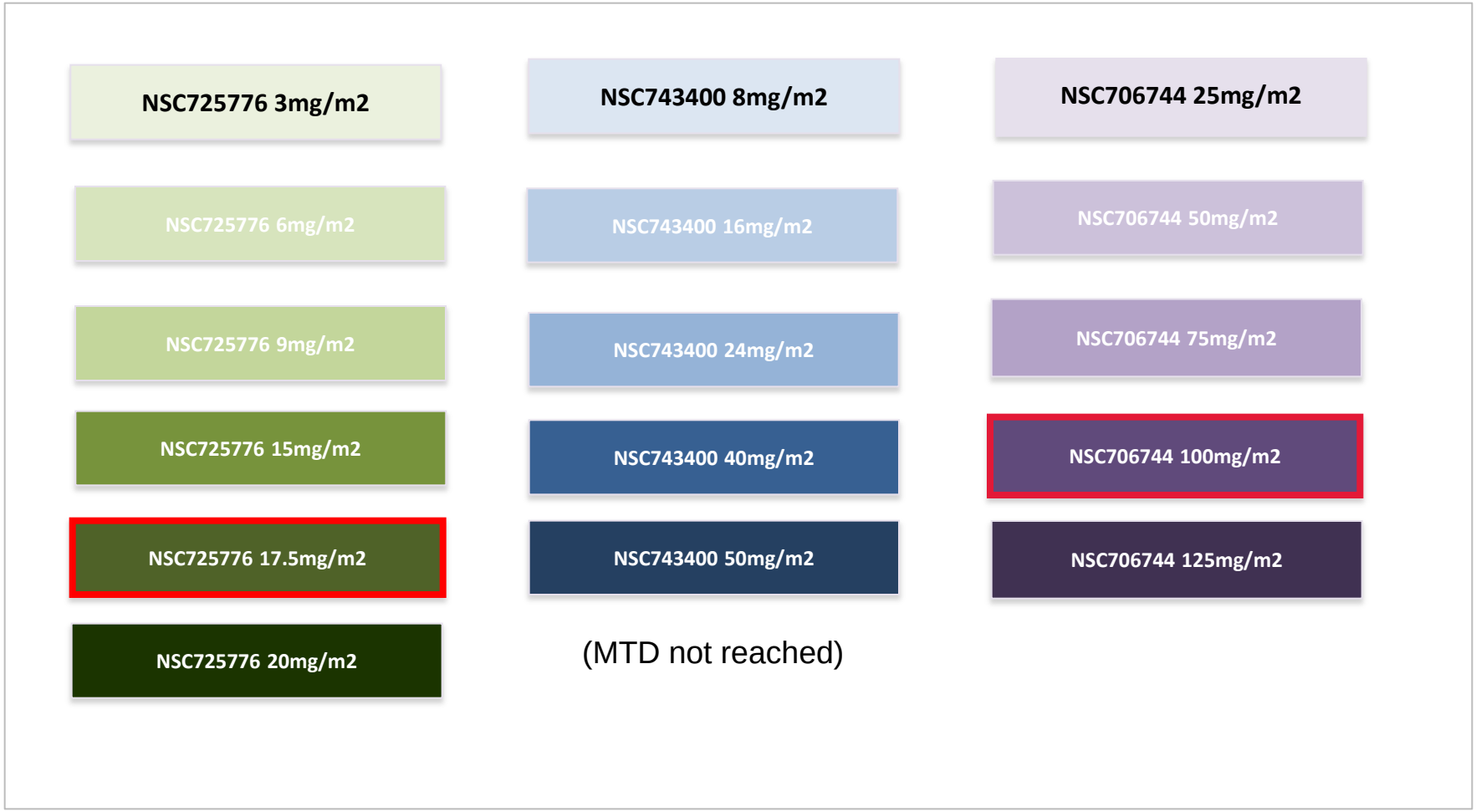
Dose escalation complete:
68 dogs treated

Cohort expansion open:
7 dogs treated

Best Overall Response




www.StrangeZoo.com
SESAME STREET .org



Overall response rate (PR or better)

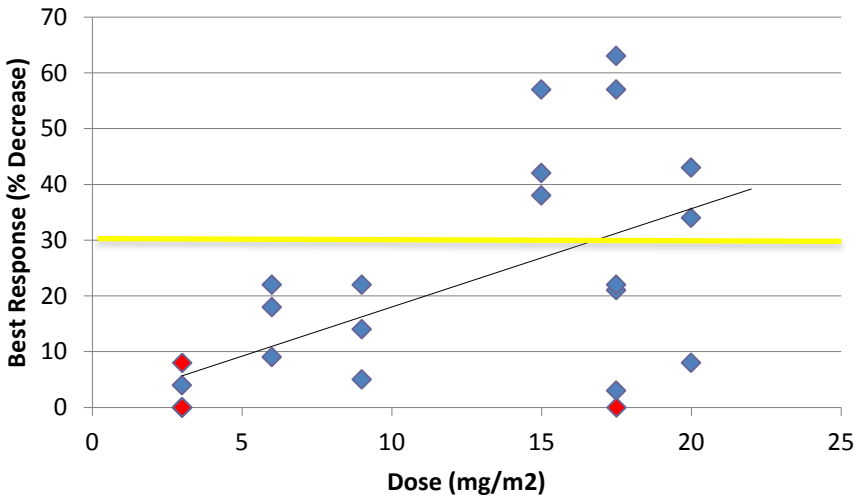
7/23 (30%) 9/23 (39%) 18/23 (78%)

Response at the MTD

2/6 (33%) N/A 8/11 (73%)

Evidence for a dose-response relationship

NSC725776



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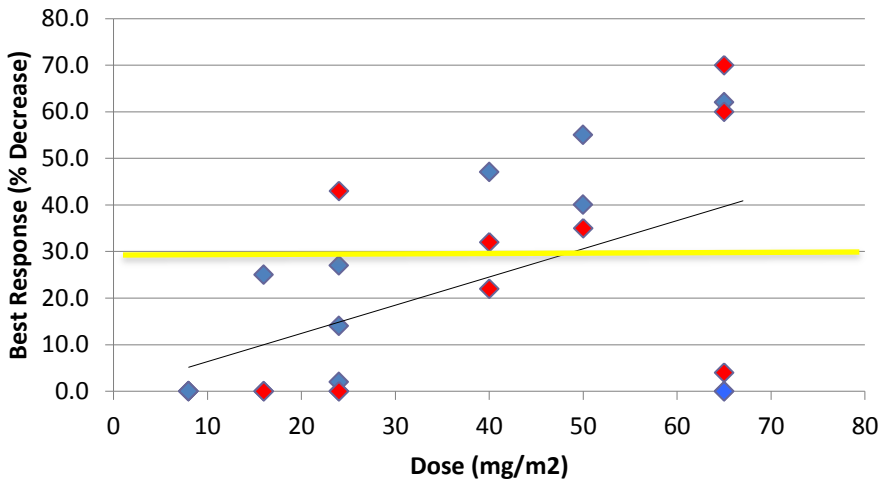

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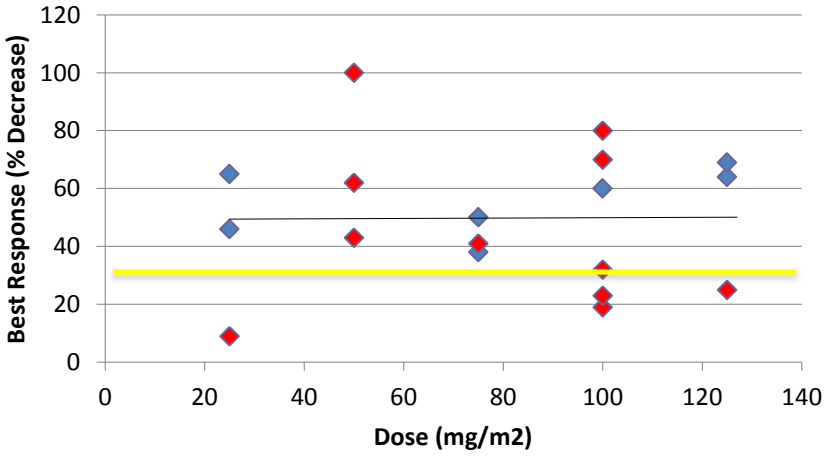
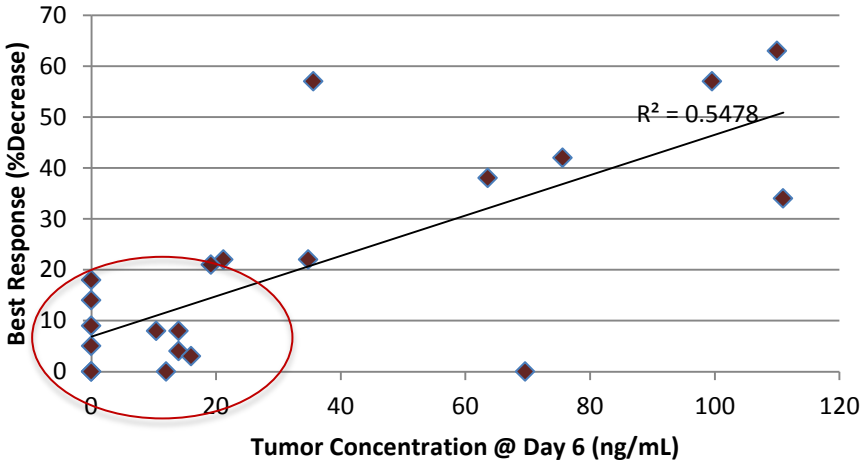


- Early-cohort responders with 744 suggest dose-response may be plateaued
- Non-responders (SD + PD) across dose range with LMP 776 & 400

♦=Previously treated, ♦=naïve disease

10x increase in tumor drug accumulation at Day 6 for 744 compared to 776 and 400

NSC725776



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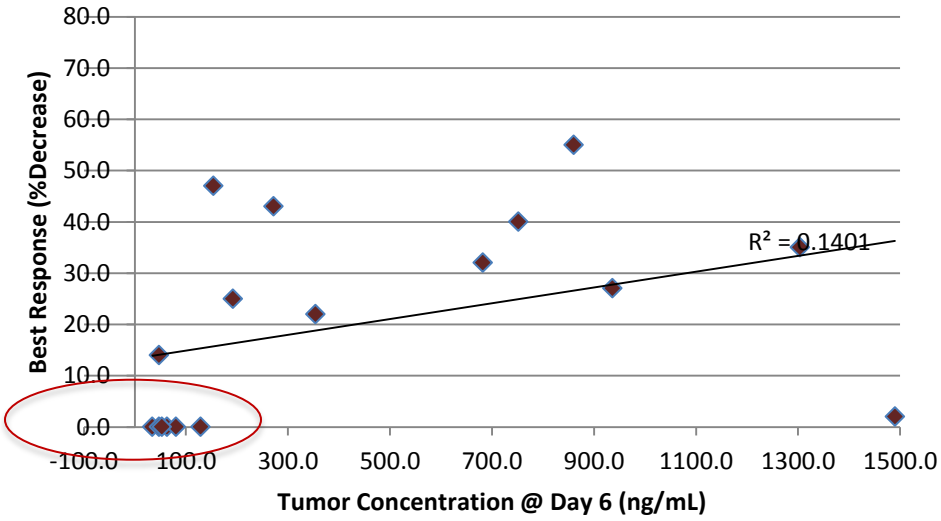

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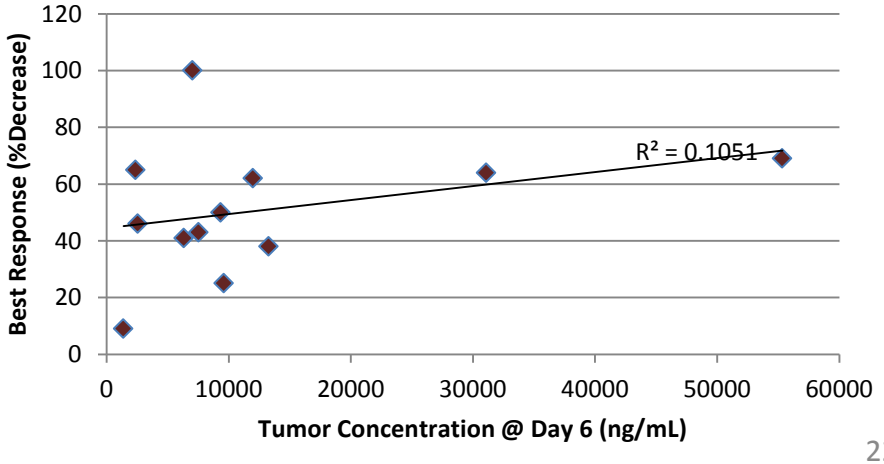
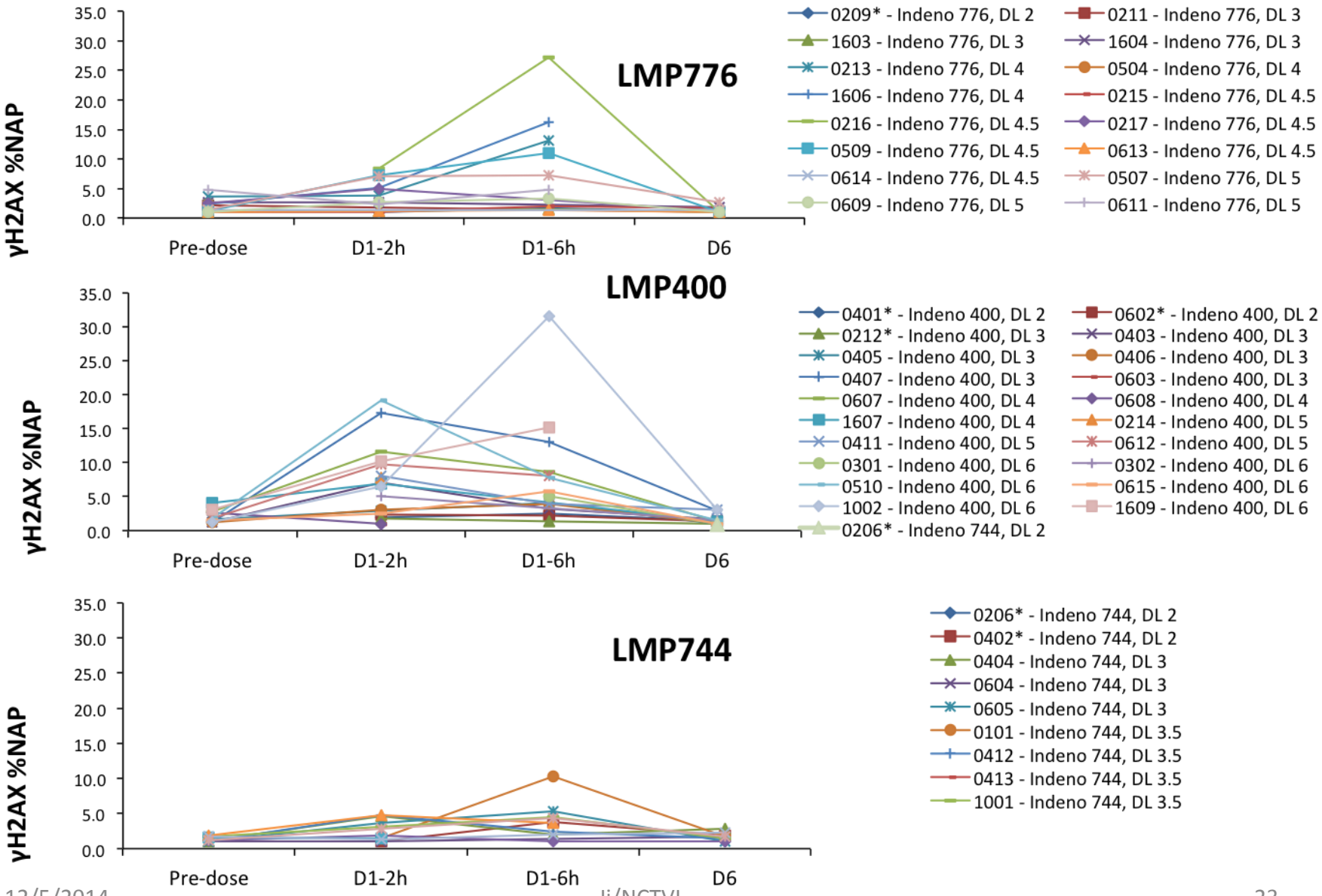


- Absolute tumor levels 776 < 400 <<744
- Day 6 exposure shows modest correlation with response for LMP 776
- Most non-responders clustered at low tumor levels

gH2AX at pre-dose, 2 hr, 6 hr, Day 6



How do we serve the community?

- Centralized trial management at no cost to sponsor
  - “PD-rich” studies in naturally-occurring cancer
  - Patients with both naïve and resistant disease
  - Direct access to expertise, reagents and assays to support veterinary trials
- Link to comparative cancer imaging with ability to recruit dogs for imaging studies on the NIH Bethesda campus
- Basic science laboratory component: unique resources, cell lines, animal model techniques geared toward metastasis biology

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Challenges for the COTC

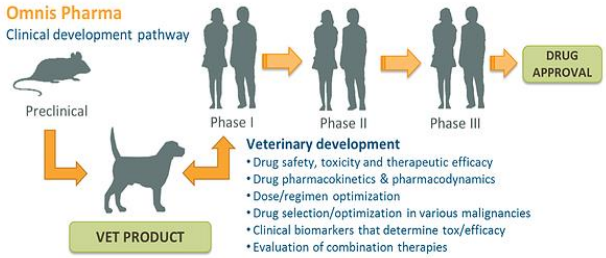
- # of agreements and time to execute them
- Agreement terms relating to IP
  - Minimized by the MOU terms: sites do not go “off protocol”, so no IP is generated by COTC members
  - Drug provider ultimately owns the data

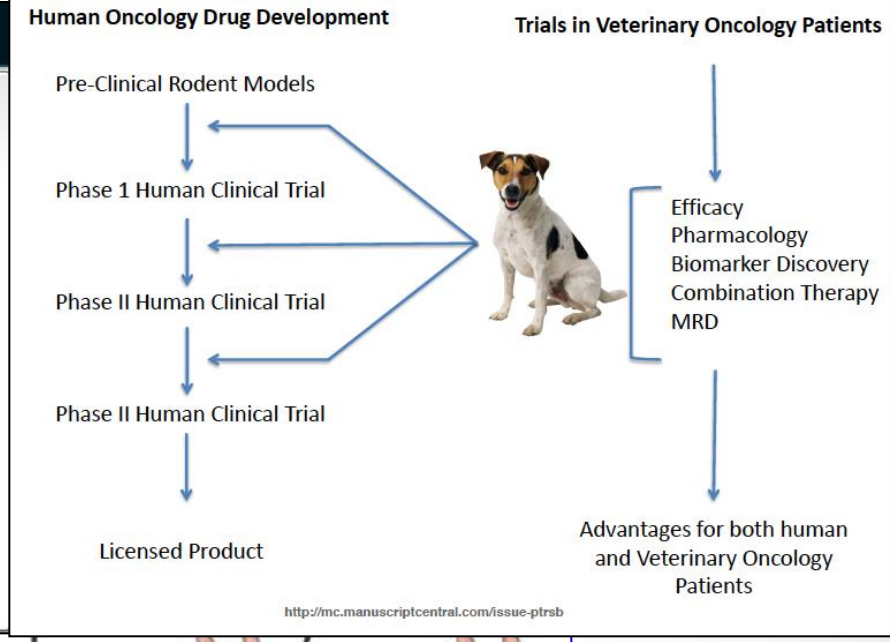
- Competition for cases
  - COTC trials typically more labor-intensive than other trials

Veterinary Oncology

Cancer is a leading cause of death in man and man's best friend. In addition to our ongoing clinical development, Omnis is developing cancer therapies to meet the needs of pets and pet owners.

Omnis utilizing a unique comparative oncology approach to improve and optimize the process of clinical drug development.





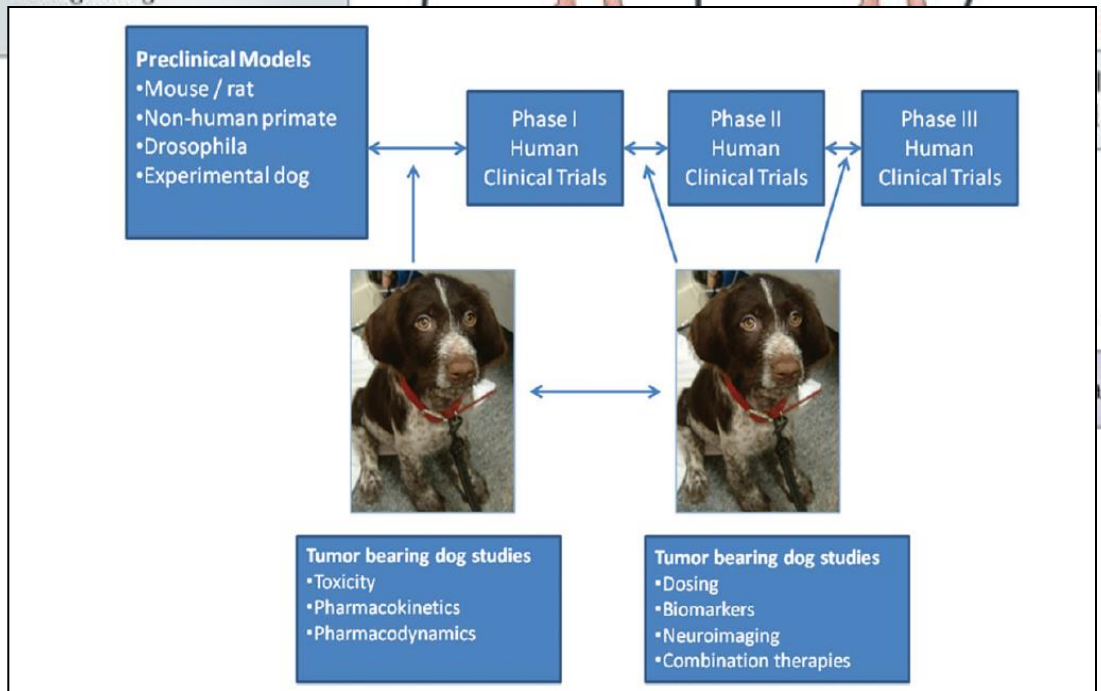
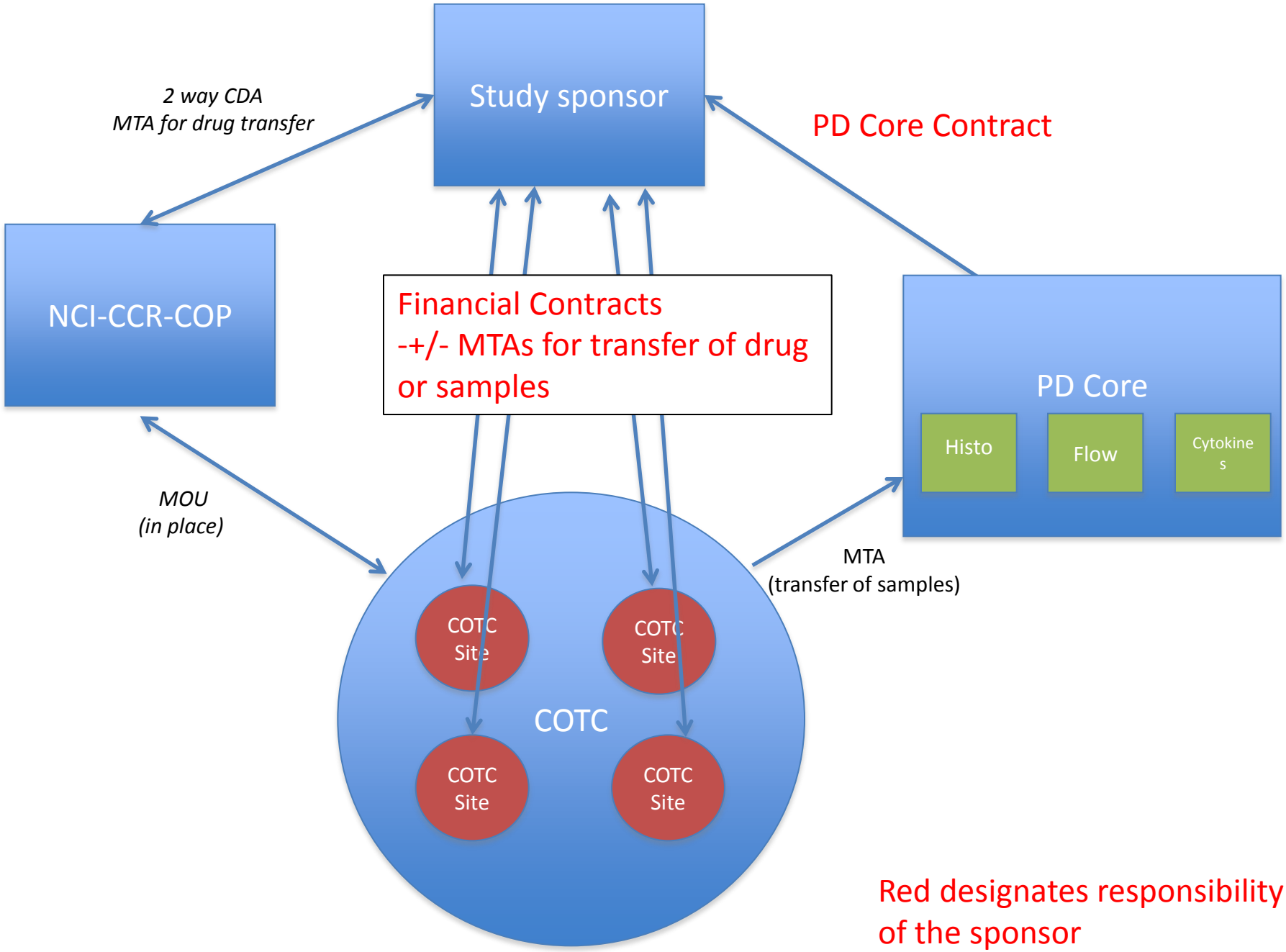
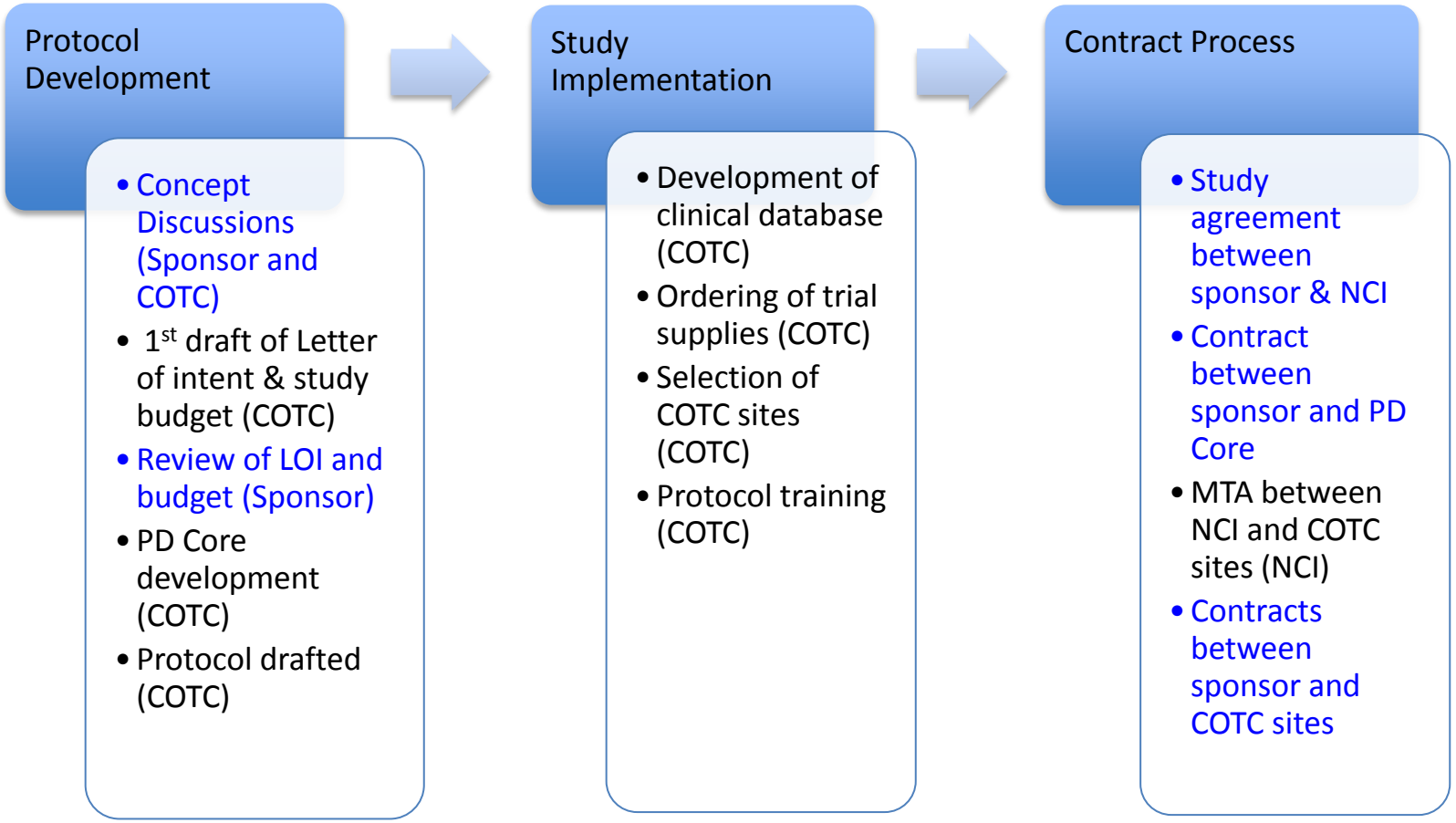


Figure 1. An integrated approach is necessary to improve pre-clinical and clinical trial design utilizing dogs as pre-clinical models, similar to mice and non-human primate work, and as 'bridges' between the different phases of clinical trials. Modified with permission from ref. [7].

Flow of agreements for COTC studies



COTC Trial Development Process



Estimated time: 6-8weeks.

Estimated time: 4-6 weeks. Can occur simultaneously with Contract Process

Estimated time: 6-8weeks. Can occur simultaneously with Study Implementation

Blue = responsibility of sponsor

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Comparative oncology studies should employ drug development questions that cannot be effectively asked or answered in other animal models or humans

Old Questions

Will dogs with measurable cancer respond to Drug X?

Will Drug X make dogs with cancer sick?

Do dogs get the same kinds of cancer as humans?

Does tumor histology and/or grade predict the response to Drug X?

New Questions

Can the dog tell us why Drug X succeeded or failed in humans?

Will Drug X retard or prevent the onset of metastatic disease in the adjuvant setting?

Can Drug X be safely combined with the standard of care?

Are actionable targets shared between human and canine cancer, agnostic of histologic diagnosis?

Strengths of a multi-site consortium to solve complex issues in drug development

- When large numbers of patients are needed with a specific disease that is directly translatable to humans
  - e.g. canine osteosarcoma
- To minimize geographical and/or investigator bias
- To support early-stage investigators whom can leverage the COP's administrative support to conduct a large trial
- To vertically integrate NCI and community preclinical drug discovery tools and methods (*in vitro* & *in vivo* mouse models) into the development path of a novel agent

New initiatives for consideration for the NCI-COP

- Emphasis on novel study designs
  - Combination therapies, biomarker validation
- Exploration of safety data generated in pet dogs
  - How to manage perception and risk?
- Contract core to facilitate agreements
- Directed programs in addition to clinical trials of drugs

  e.g. Exceptional responder program

  e.g Comparative brain tumor consortium

  e.g. NCI Comparative Cancer Imaging fellowship

Summary and Conclusions

- **The COTC is an integrated, high-quality, multicenter clinical trial network, conducting studies in response to a specific need in human cancer drug development**
- **Comparative oncology efforts have flourished worldwide after the NCI COP inception in 2004**
- **New initiatives that extend beyond clinical trials are needed:**
  - **Ongoing molecular validation of canine cancer as a model for human cancer**
  - **Deeper contribution to cancer drug and imaging agent development**

Acknowledgements

NIH-NCI Center for Cancer Research
-Office of the Director (Lee Helman)
-Molecular Imaging Program (Peter Choyke)
-Pediatric Oncology Branch (Kathy Warren, Paul Meltzer, Javed Khan)
-Neurooncology Branch (Mark Gilbert)

NIH-NCI Comparative Oncology Program
-Chand Khanna
-Christina Mazcko
-Ling Ren
-Arnulfo Mendoza

NCI Division for Cancer Treatment & Diagnosis (DCTD)

COTC member institutions, investigators, and support staff: past, present and future

Canine Comparative Oncology Genomics Consortium

Dogs and their owners