Opportunities for Preclinical Evaluation of Novel Therapies

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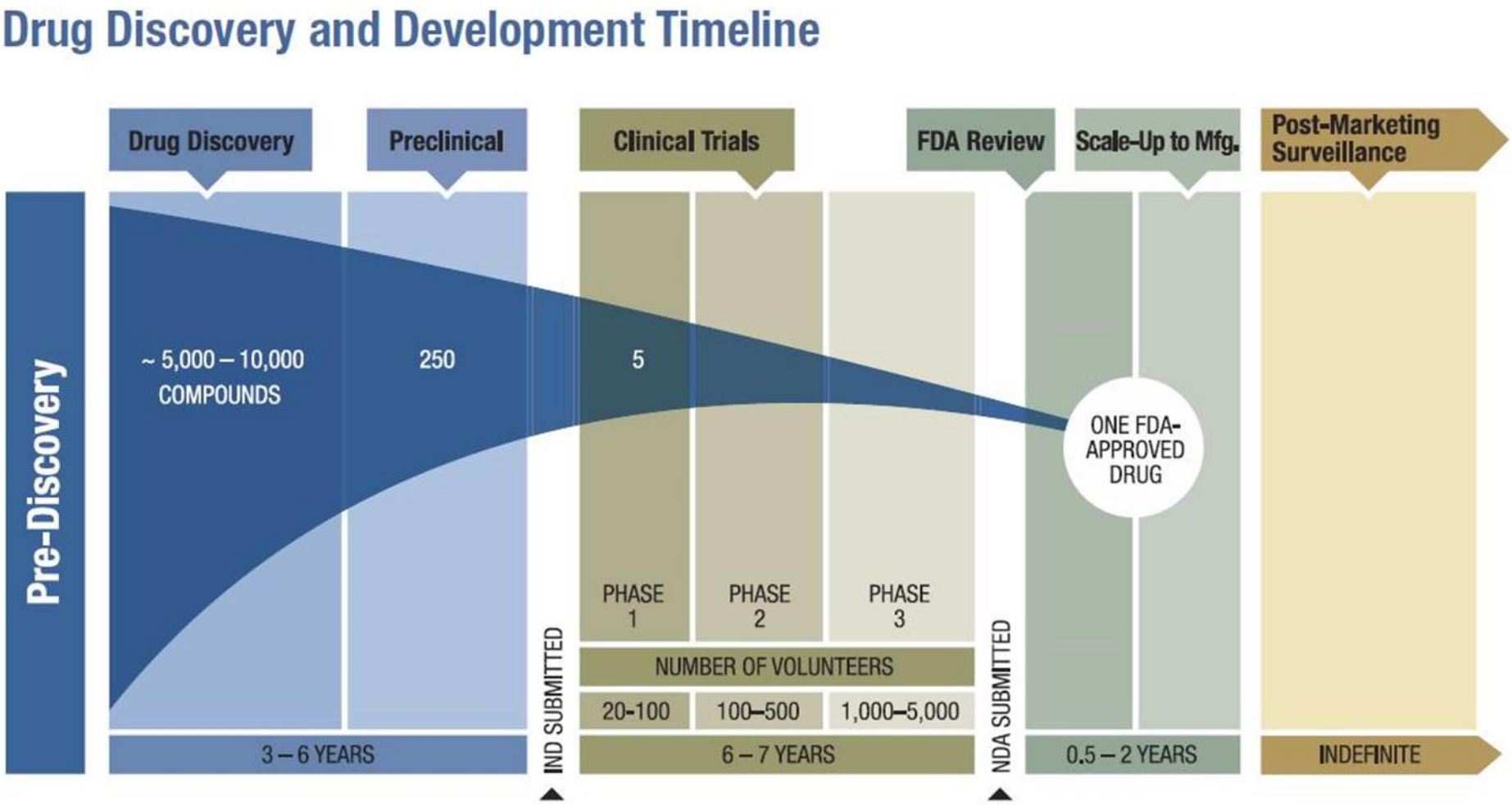
Conflict of Interest Disclosure

- Paid Consultant
- Sponsored Research
- Shareholder

Can more sophisticated preclinical models improve success?



Companion Dogs- A unique resource

- 70 million dogs in US
  - 25% will be diagnosed with cancer
- Advantages for some cancer histologies
  - Spontaneous and competent immunity
  - Similar genetic and biologic behaviors
  - Represents genetic heterogeneity (host and tumor)
  - Rapidly translational (metabolism and physiology)
  - Similar allometric scaling and PK
  - Repeat or serial endpoint documentation
- Areas of potential limitation
  - Multiple variables to be considered, too heterogeneous?
  - Uniform and broad scientific awareness & acceptance

NCI Infrastructure and Scientific Awareness

National Cancer Institute

CENTER FOR CANCER RESEARCH

Comparative Oncology Program

Cancer researchers usher in dog days of medicine

The dog as a cancer model

To the editor:

The dog has long been used as a model in drug discovery and development research because of its similarities to human anatomy and physiology, particularly with respect to the cardiovascular, urogenital, cancer research, scientific and clinical leaders from both human and veterinary oncology have come together to form a multidisciplinary consortium, the Canine Comparative Oncology and Genomics Consortium (CCOGC).

SCIENCE AND SOCIETY

Translation of new cancer treatments from pet dogs to humans

Melissa Paoloni and Chand Khanna

Abstract | Naturally occurring cancers in pet dogs and humans share many features, including histological appearance, tumour genetics, molecular targets, biological behaviour and response to conventional therapies. Studying dogs with cancer is likely to provide a valuable perspective that is distinct from that generated by the study of human or rodent cancers alone. The value of this opportunity has been increasingly recognized in the field of cancer research for the identification of cancer-associated genes, the study of environmental risk factors, understanding tumour biology and progression, and, perhaps most importantly, the evaluation and development of novel cancer therapeutics.

The University of Illinois Experience
Hallmarks of cancer

1 Produce growth factors

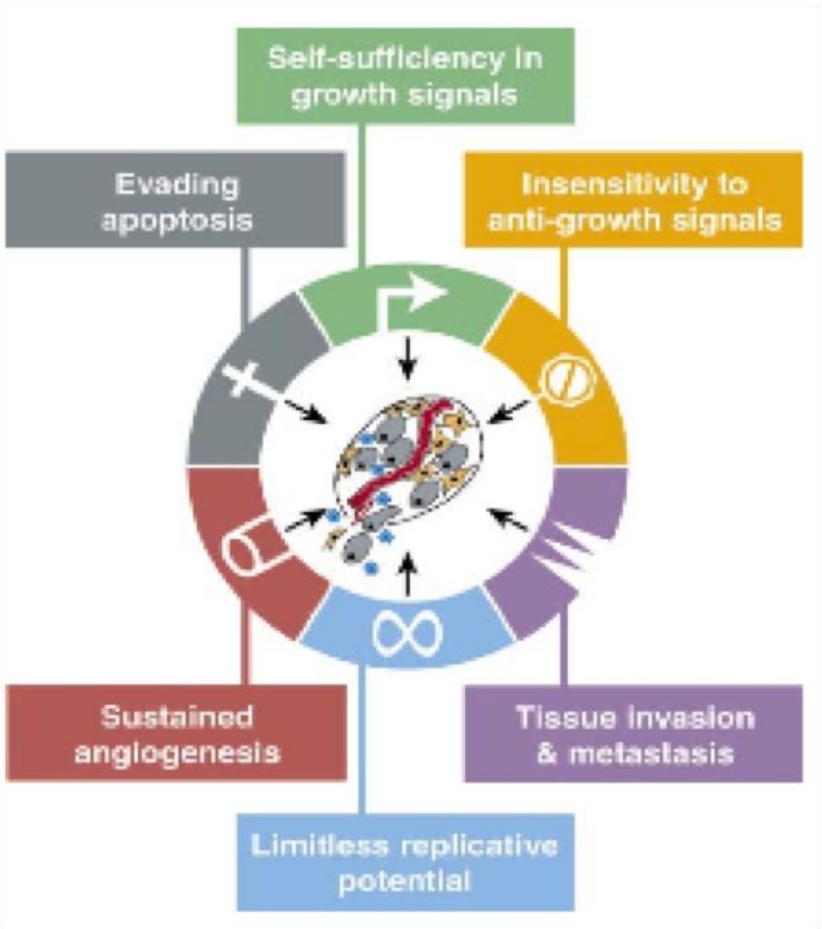
2 Evade inhibitory signals

3 Invade neighboring tissues and metastasize to other parts or organs

4 Uncontrolled replication

5 Form new blood vessels

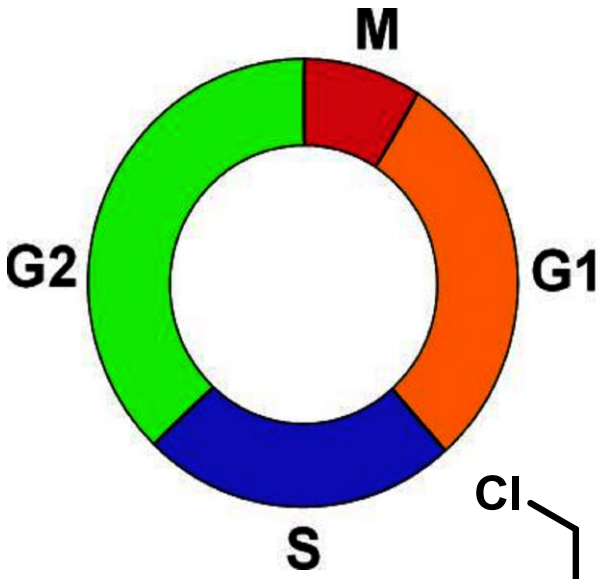
6 Evade apoptosis



Each categorical Hallmark can serve as a drugable target

Hanahan & Weinberg *Cell* 2000

Conventional Agents and Apoptosis

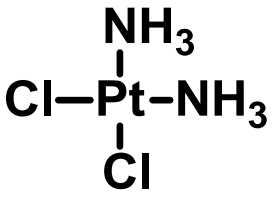


Vast majority of anticancer drugs perturb

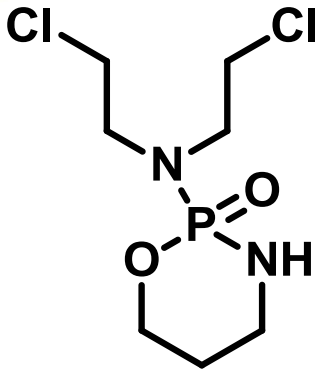
DNA synthesis/replication (S)

Cell division (M)

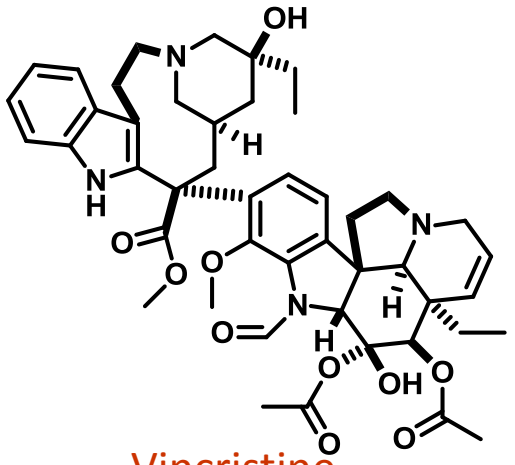
Directly damage DNA



cisplatin



cyclophosphamide



Vincristine

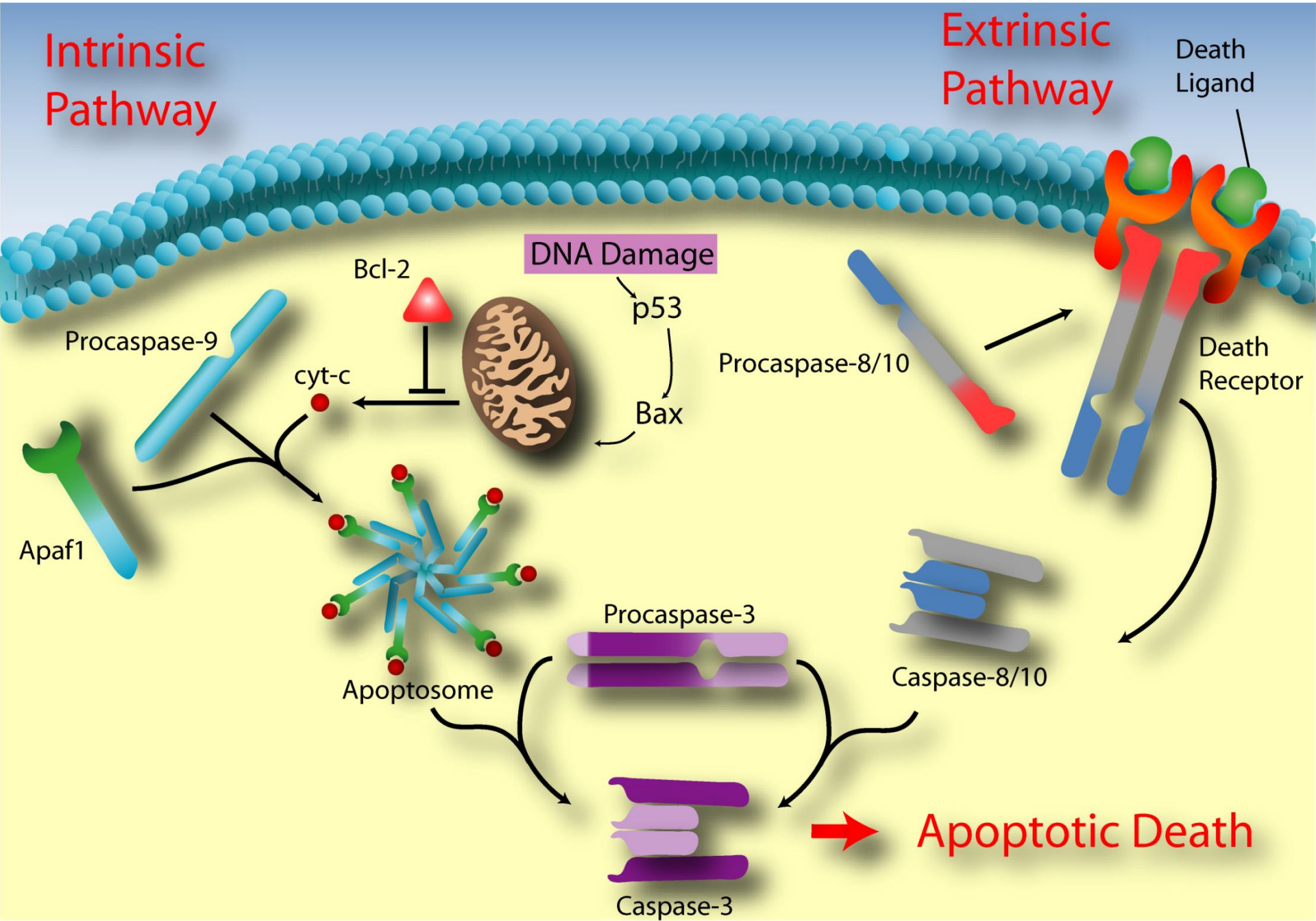
1) *General* cytotoxins that induce death in all rapidly dividing cells

2) Requires *competent* apoptotic pathway

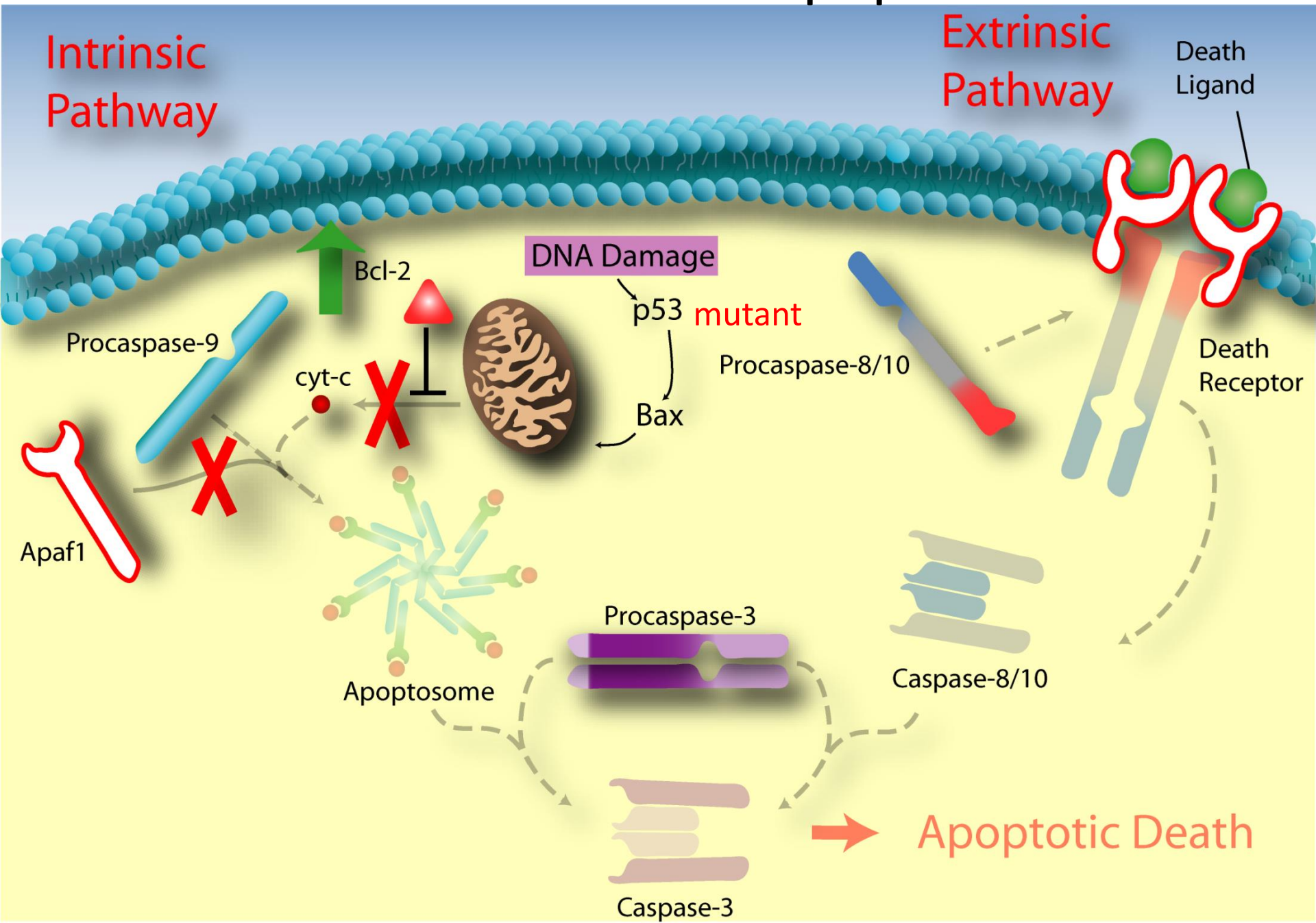
3) Further intensification unlikely to improve therapeutic outcomes

Underscores the need for personalized approaches to cancer therapy

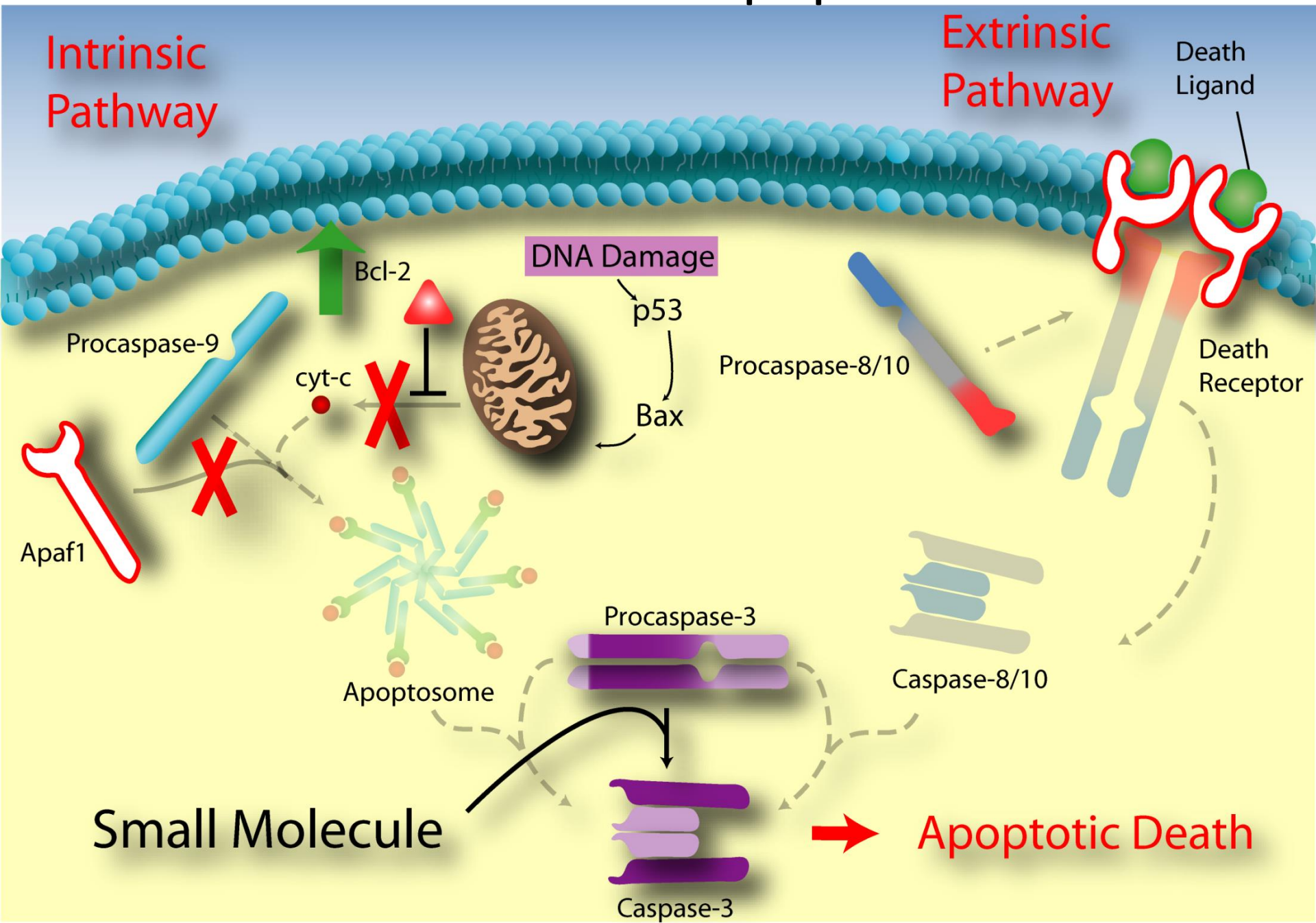
The apoptotic cascade



Cancer cells evade apoptosis



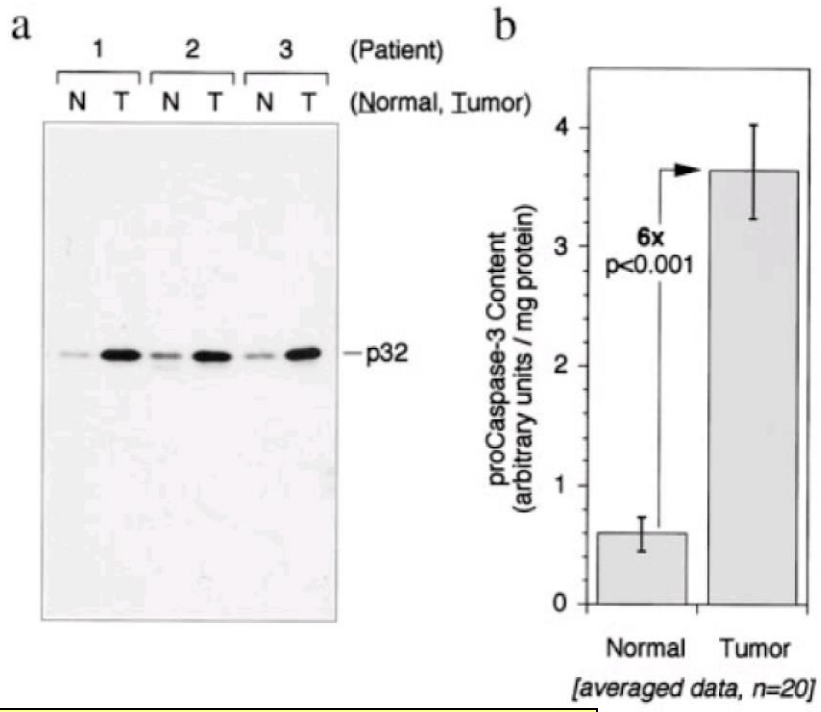
Direct reactivation of apoptosis in cancer



Benefits of direct procaspase-3 activation

- **Apoptotic pathways funnel to procaspase-3**
- **Mutations in cancer are typically upstream of procaspase-3**

Procaspase-3 levels are <u>elevated</u> certain cancers providing a preferential target



Procaspase-3 elevated
6-fold in colon cancer

Roy, S. *et al. Proc. Natl. Acad. Sci.* 2001, *98*, 6132

PC-3 elevated in lung cancer
- *Biol. Chem.* 2004, *385*, 153

PC-3 elevated in breast cancer
- *Clin. Cancer Res.* 2003, *9*, 738

PC-3 elevated in hepatocellular carcinomas
- *Mod. Path* 2004, *17*, 861

PC-3 elevated in certain neuroblastomas
- *Cancer Res.* 1997, *57*, 4578

PC-3 elevated in certain lymphomas
- *Am. J. Path.* 1999, *154*, 1439

PC-3 elevated in melanoma
- *Melanoma Res.* 2001, *11*, 385

Biochemistry of procaspase-3

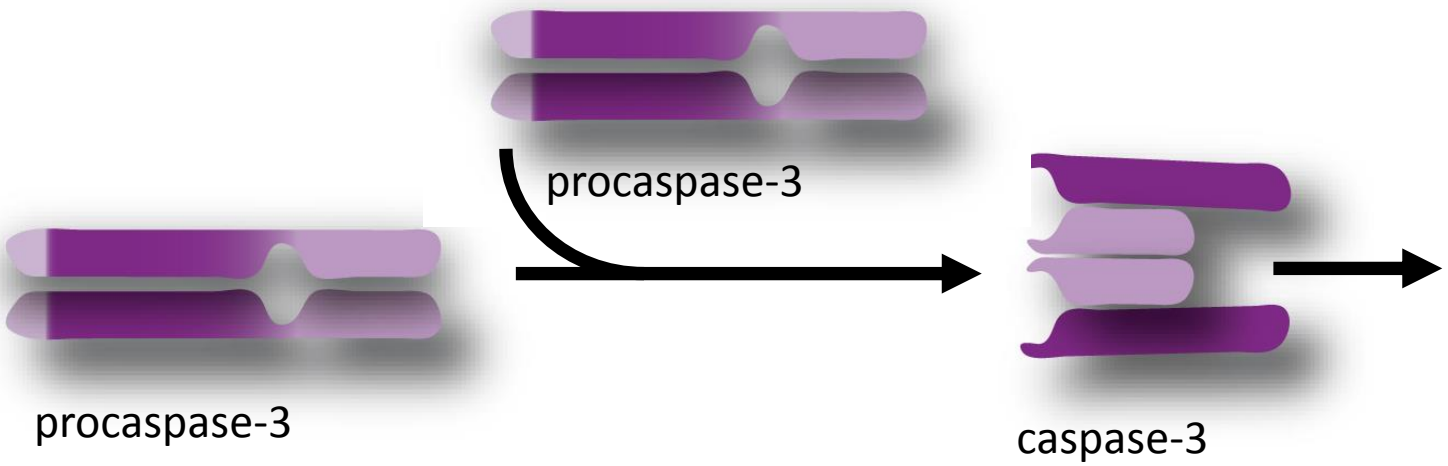
Procaspase-3 itself is active, ~200-fold less than caspase-3

Clark, C. and co-workers *Biochemistry* 2003, *42*, 12298

Procaspase-3 can cleave procaspase-3 to active caspase-3

Roy, S. *et al. Proc. Natl. Acad. Sci.* 2001, *98*, 6132

Thus, if we can enhance procaspase-3 activity and commit cells to die…could serve as a novel anticancer strategy platform



Rationale to screen a library of molecules with pro-apoptotic activity

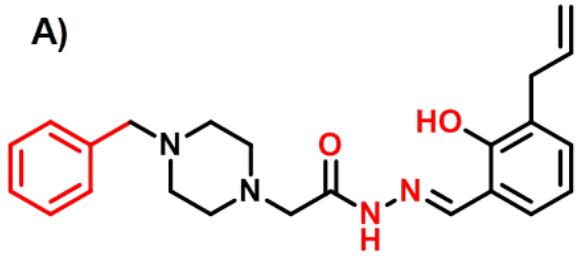
PAC-1- 1st Procaspase-3 Activating Compound

Paul Hergenrother Laboratory

PAC-1 is chelating labile zinc inside cells

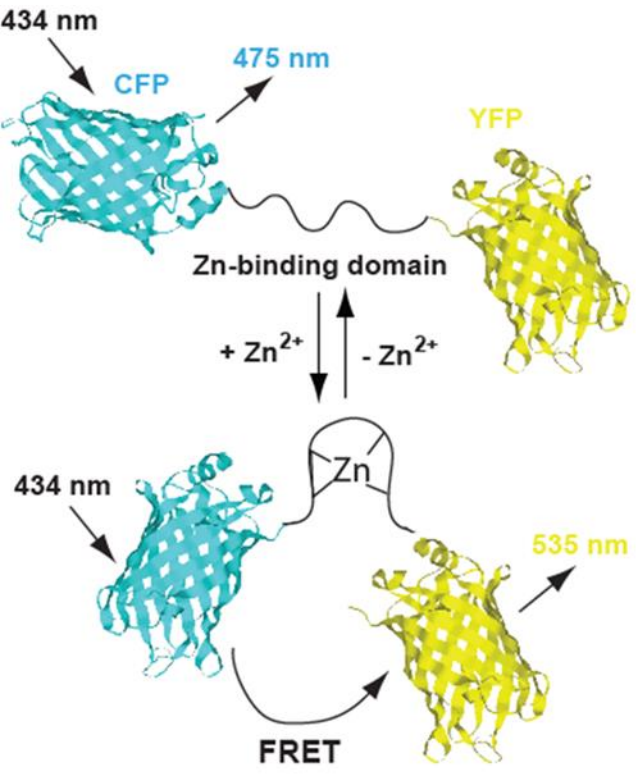
PAC-1 **PAC-1:** Zn^{2+}

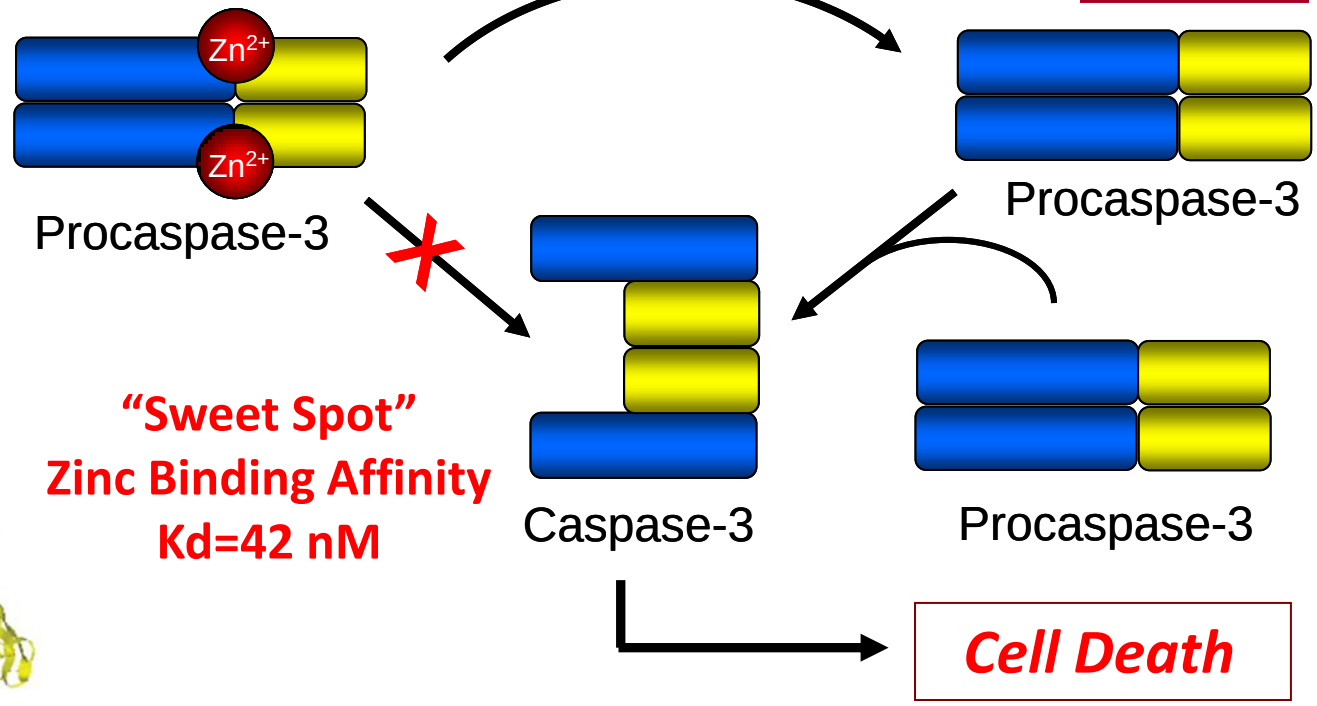
A)



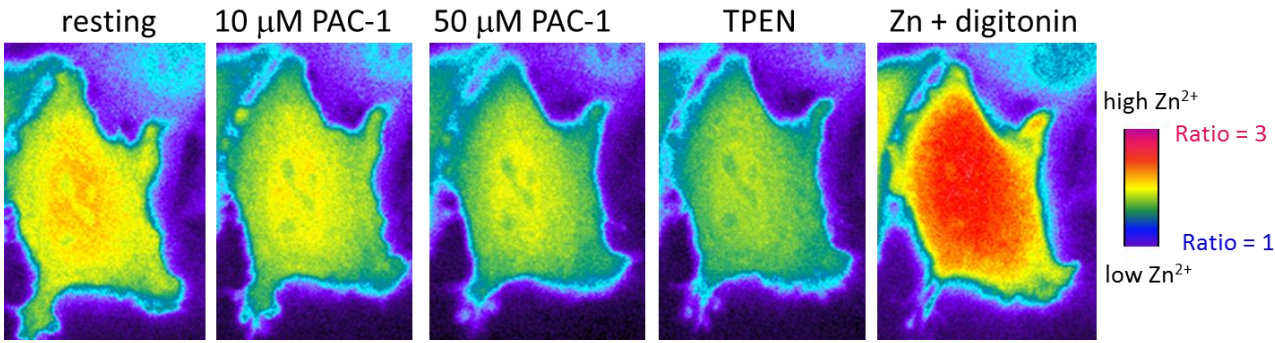
PAC-1

Essential for activity





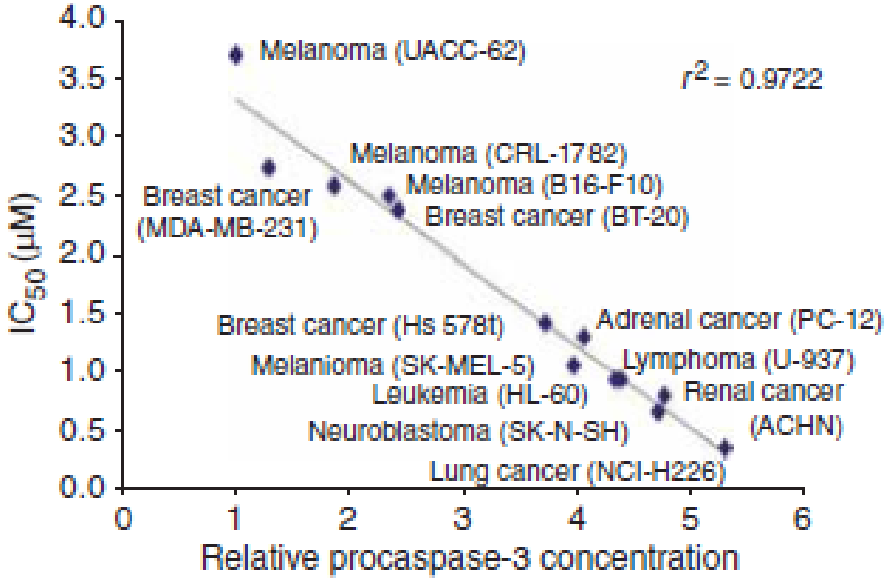
Data generated by Diana West and collaborator Amy Palmer

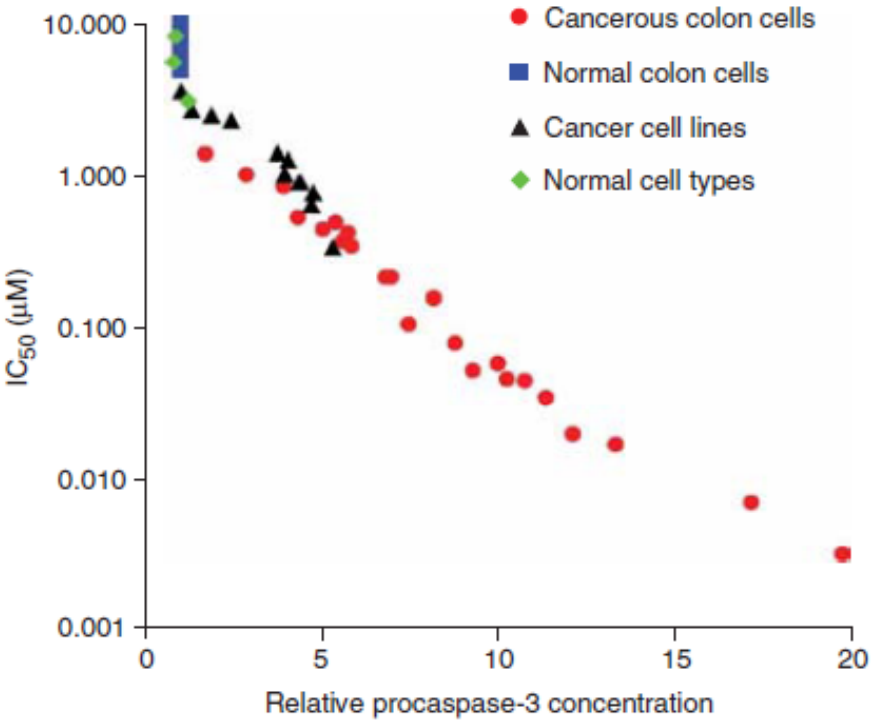


2 Pivotal and Key Findings for PAC-1

Inverse relationship between procaspase-3 concentrations and sensitivity to PAC-1

Preferential overexpression of procaspase-3 by malignant relative to normal cells

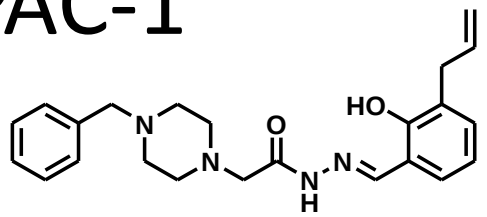




Potential opportunity to target the most malignant cancer cells with PAC-1

Identification of PAC-1

22,000 compounds



PAC-1

Hergenrother Laboratory | ***Fan Laboratory***

In vitro

Enzymatic activity

SDS-PAGE/ Western blot

Cell culture

Cancer cell lines

- Efficacy
- Apoptosis

Primary tumor samples

- Efficacy
- Procaspase-3 levels

In vivo

PK data/toxicology

Mouse studies

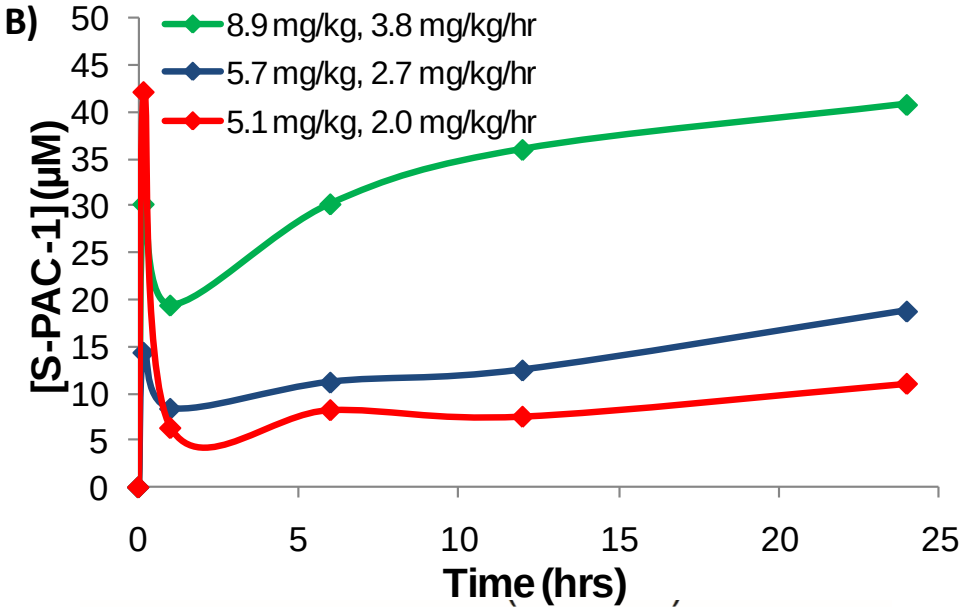
Dog studies- research and pet dogs

Combination studies- pet dogs

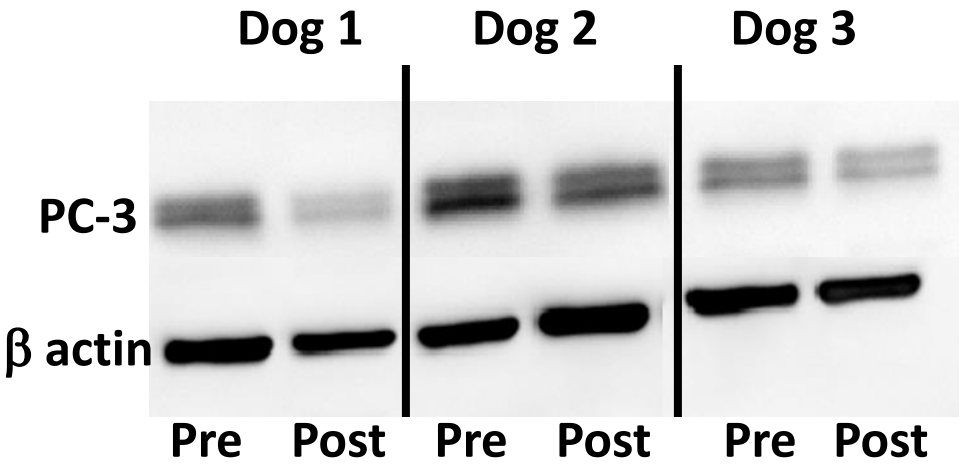
PAC-1 Derivatives

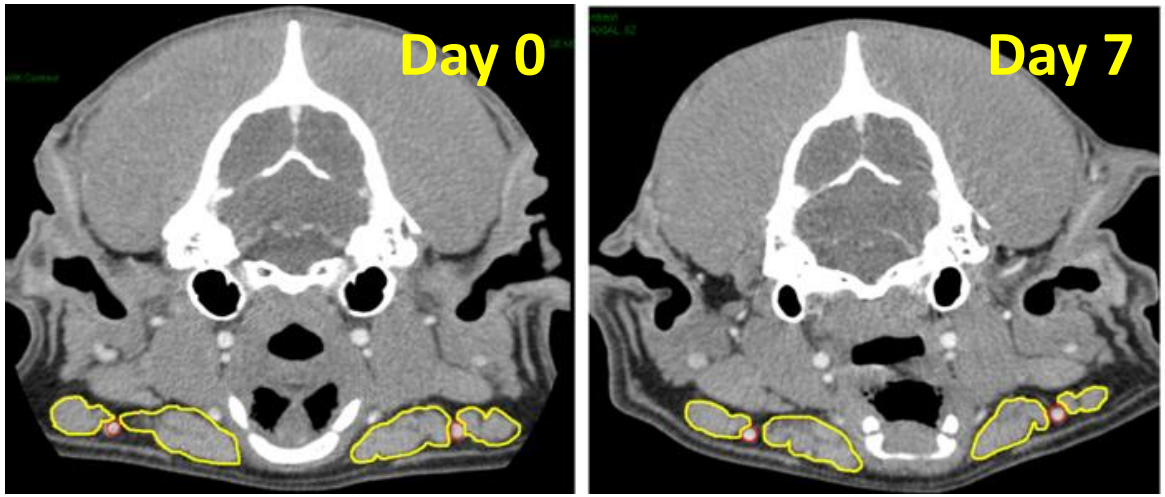
SAR PK/Biodistribution (BBB vs. Non-BBB)

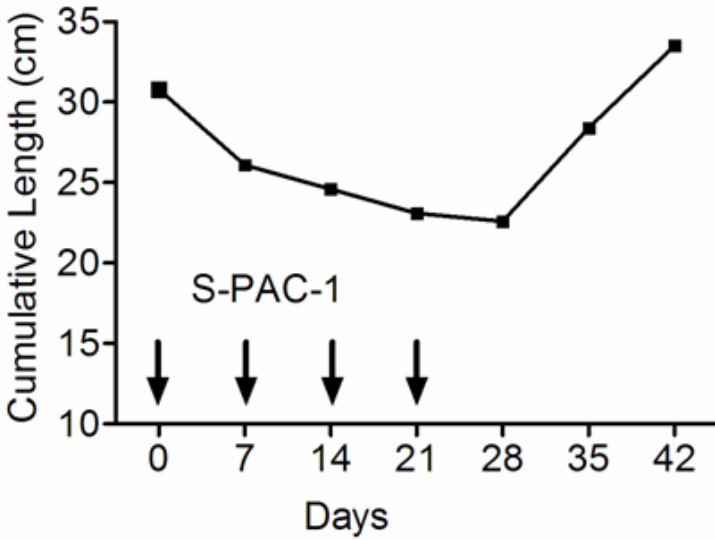
Non-BBB: Single agent S-PAC-1 in Dogs w/ Lymphoma



Evidence for target modulation in vivo by serial biopsy of lymph nodes







Marginal single-agent activity, cumbersome delivery, and toxicity- ***No Go Decision***

Synergistic potential of low dose, pulsatile PAC-1

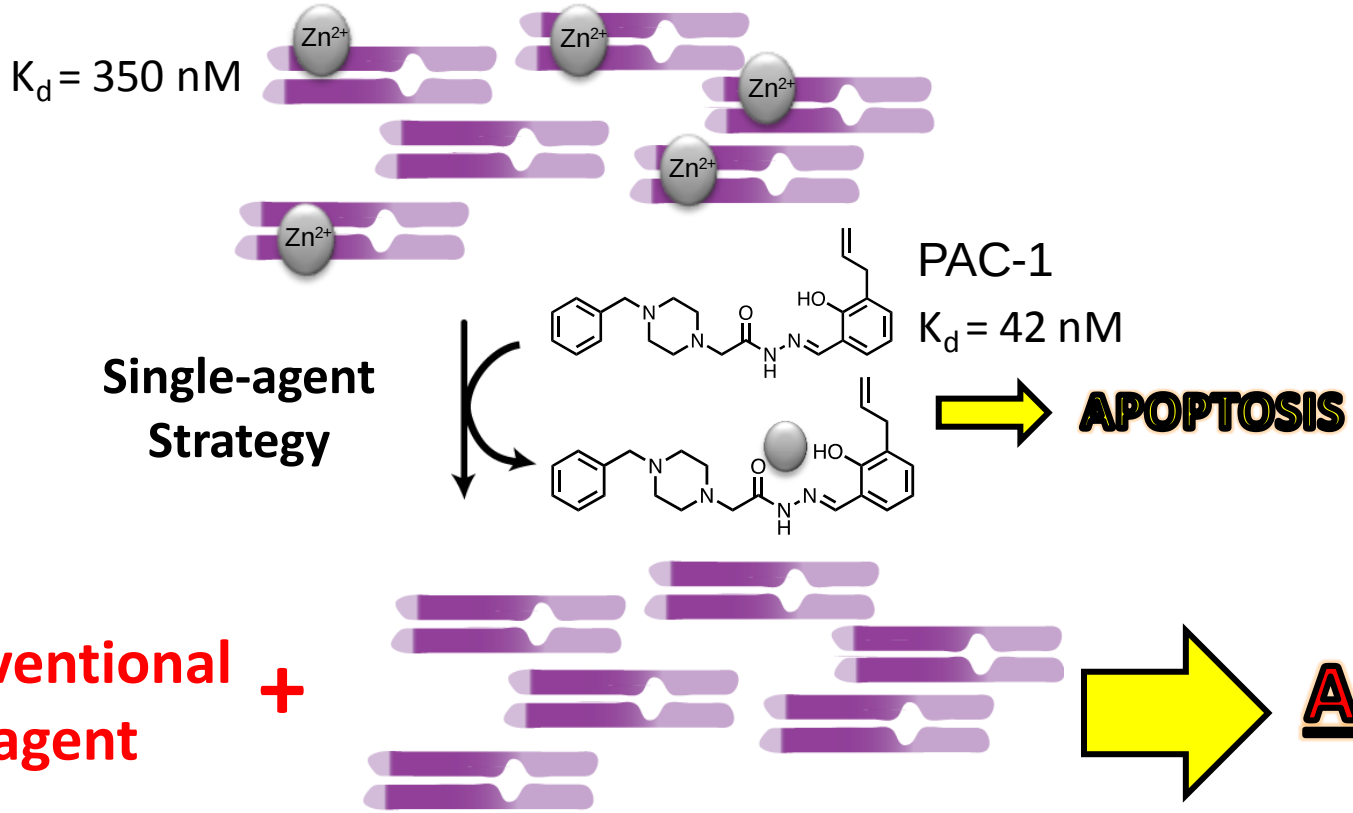
Virtually all cancer treatments are now “cocktails” of chemotherapeutics

Can the chelation of labile zinc from procaspase-3 synergize with:

1) Conventional anticancer drugs

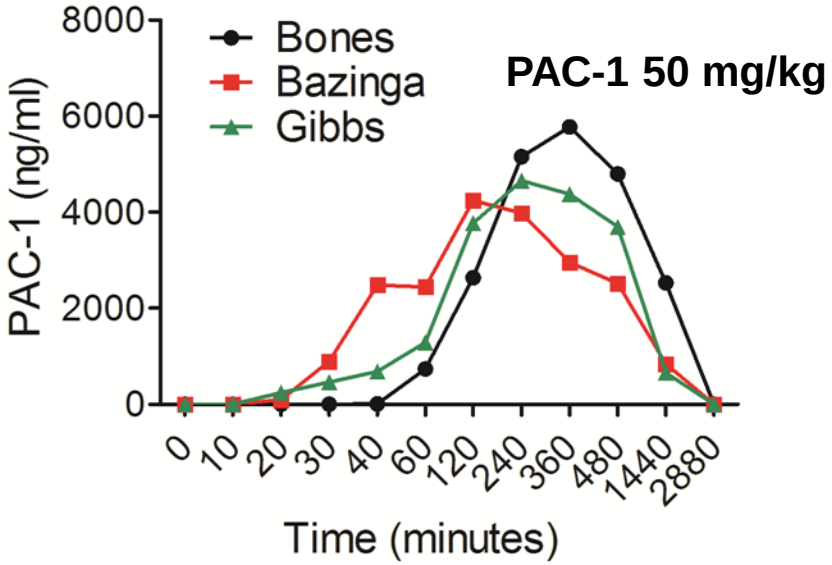
2) Ionizing radiation therapy

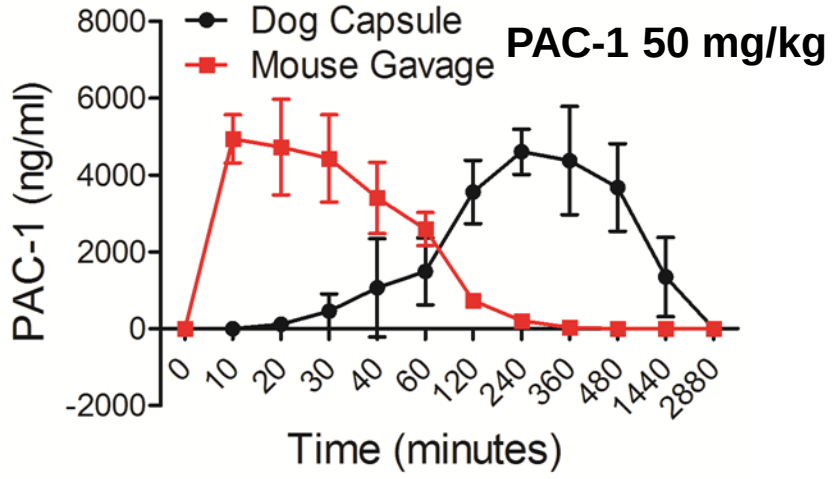
3) Small molecule strategies



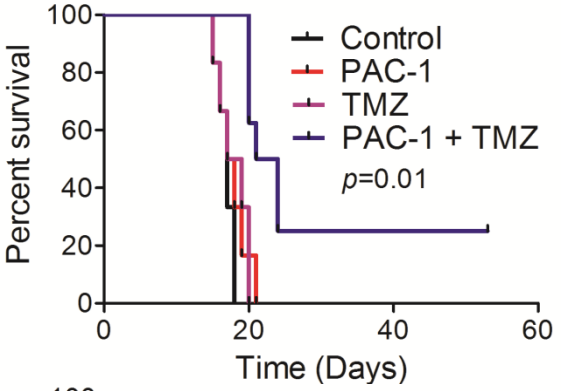
Oral PAC-1 and Chemotherapy

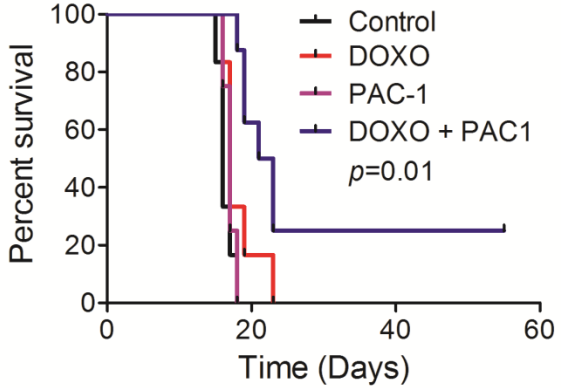
- PAC-1 PK: Mice & dogs





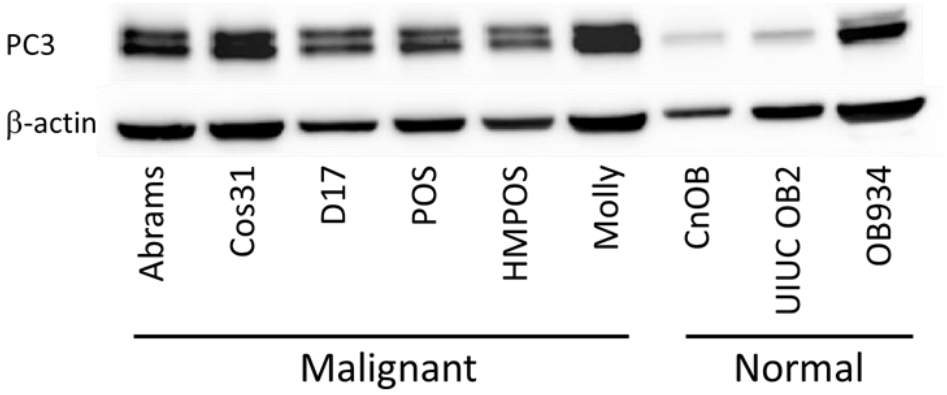
Anticancer Activity in OS

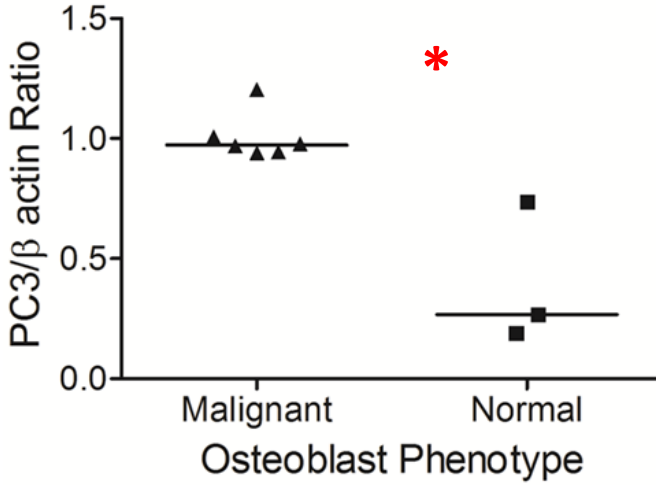


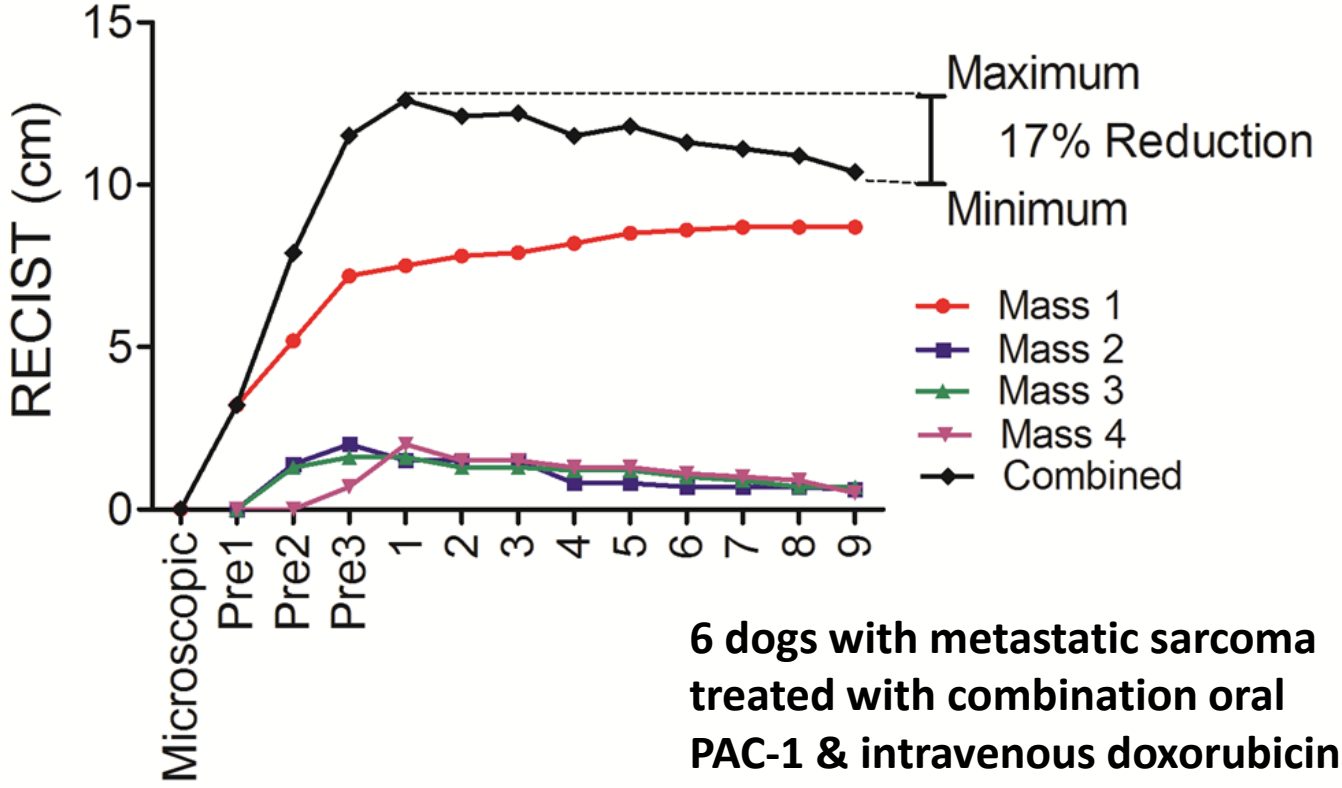


Day 53 PAC-1/TMZ Day 18 Control

PC3 Expression in K9 OS

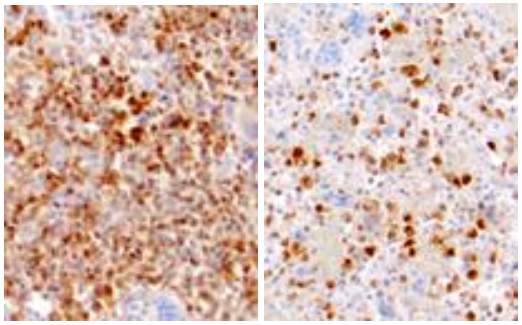






Paired Samples

Primary **Metastases**



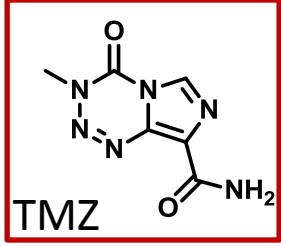
Primary 18/20 (90%)

Metastases 6/7 (86%)

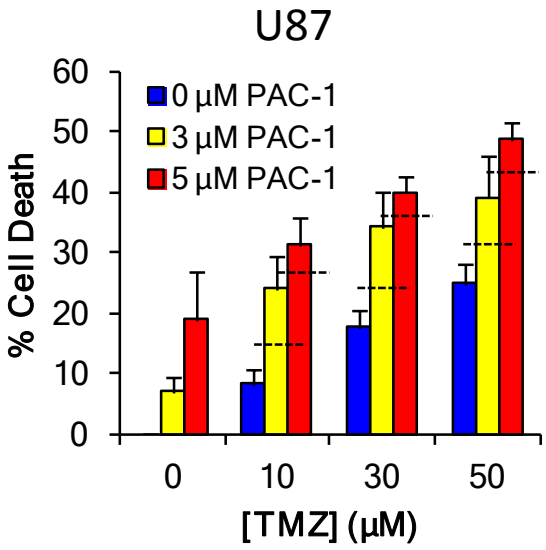
6 dogs with metastatic sarcoma treated with combination oral PAC-1 & intravenous doxorubicin.

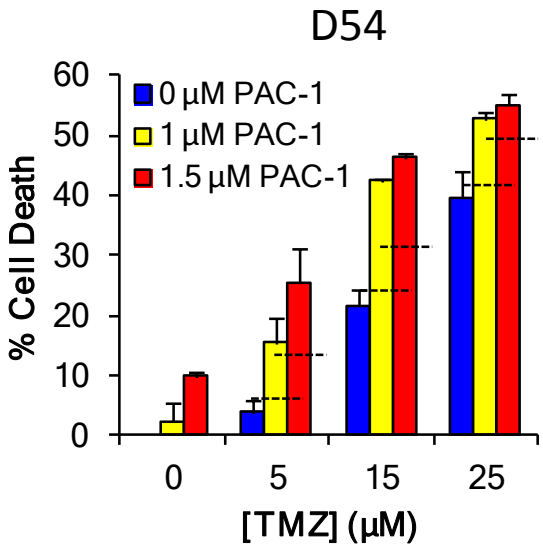
Pulsatile therapy well tolerated- ***Go Decision***

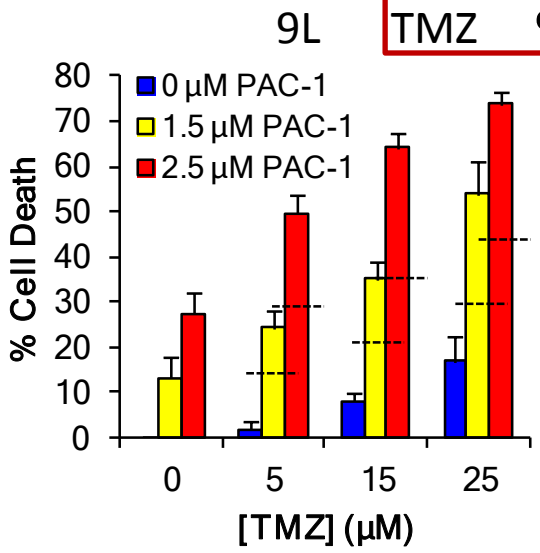
Exploiting BBB:PAC-1 synergizes w/ TMZ



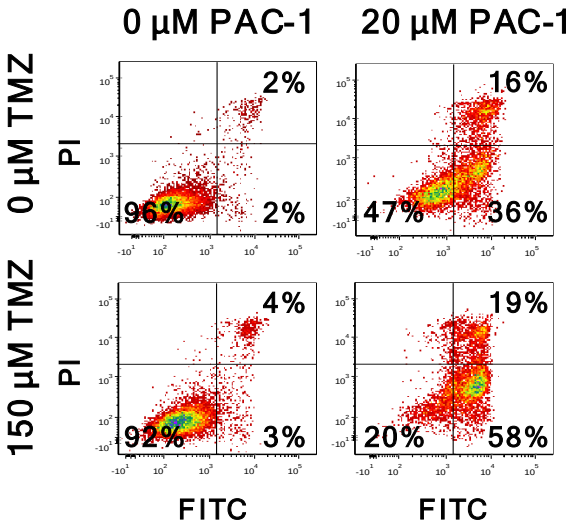
Cell death:

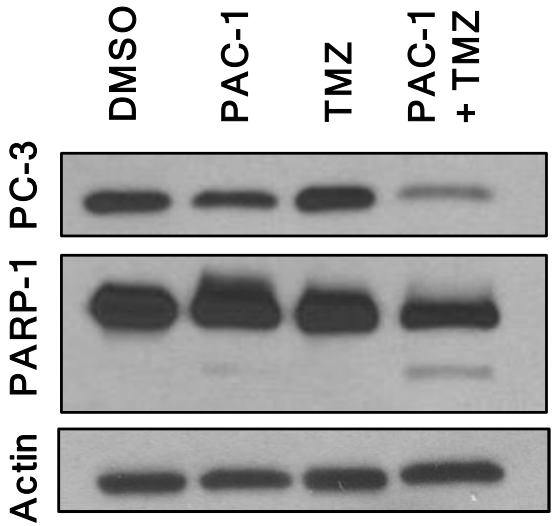






Apoptosis:

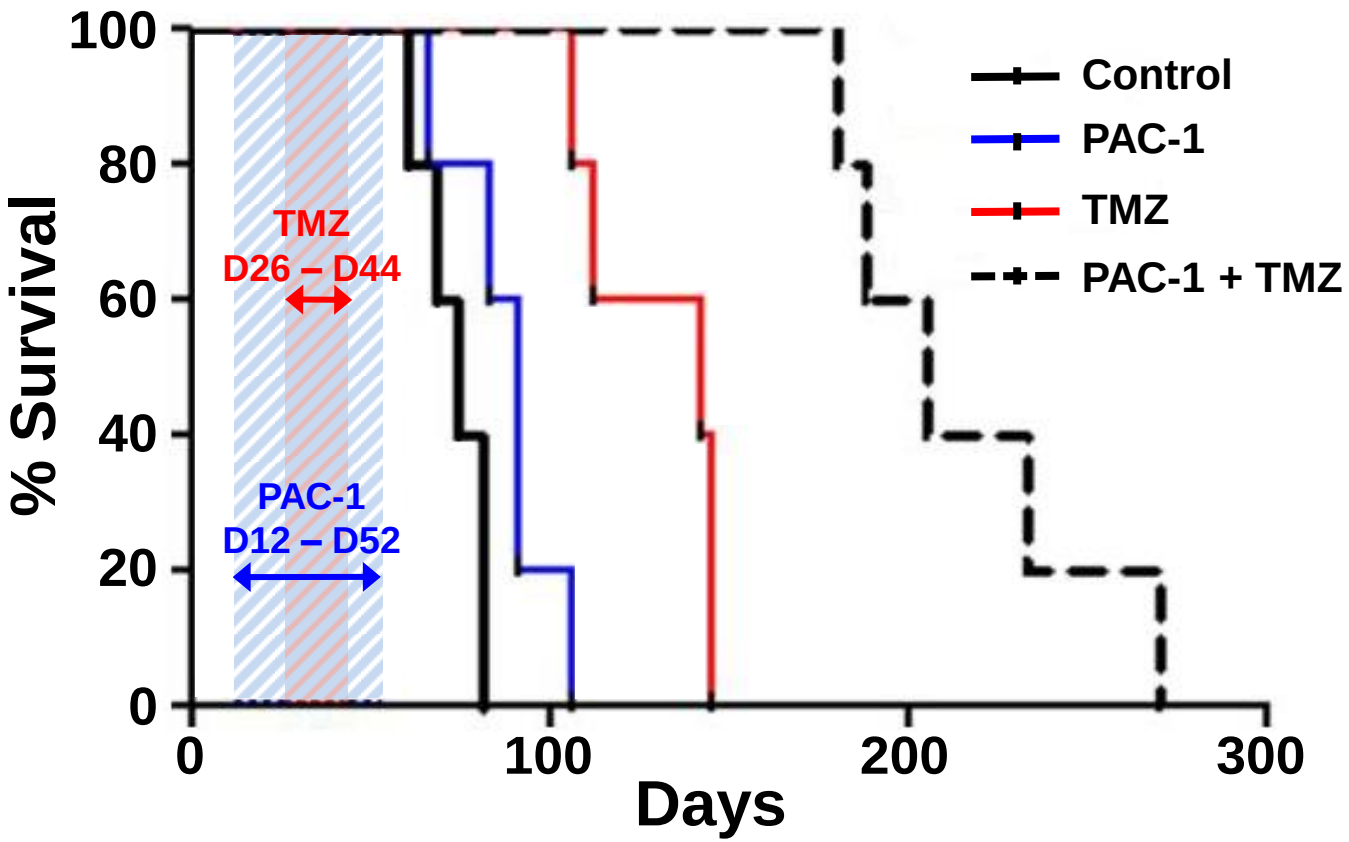




Data provided by Rachel Botham

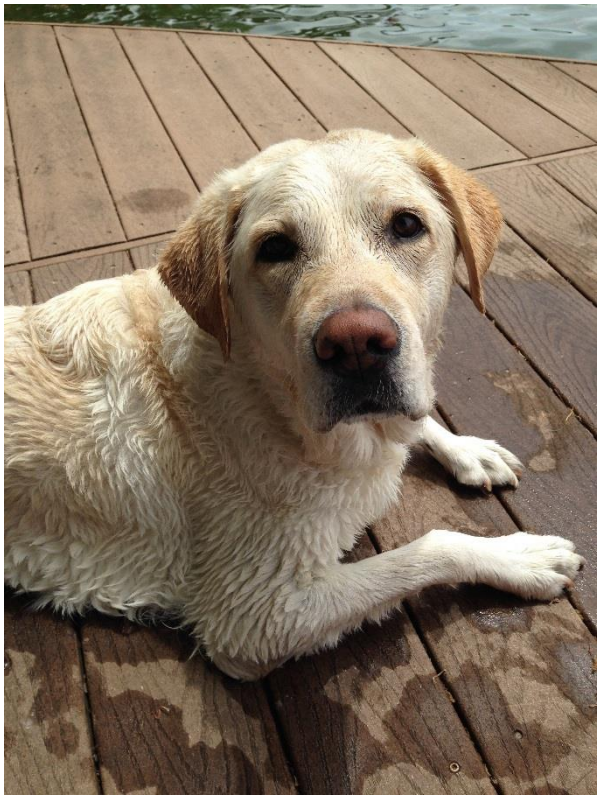
PAC-1 synergizes with TMZ to extend survival in a mouse model of glioblastoma

Human oncosphere cells intracranially implanted
PAC-1 and TMZ given orally at 50 mg/kg each:

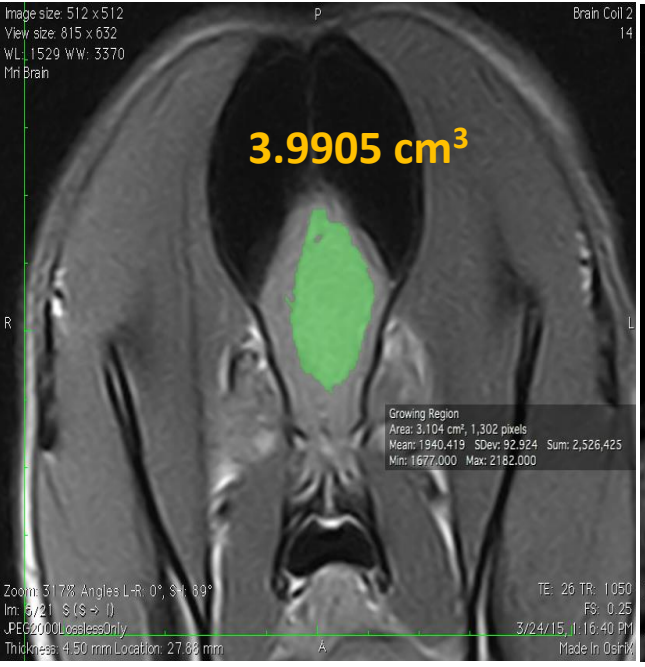


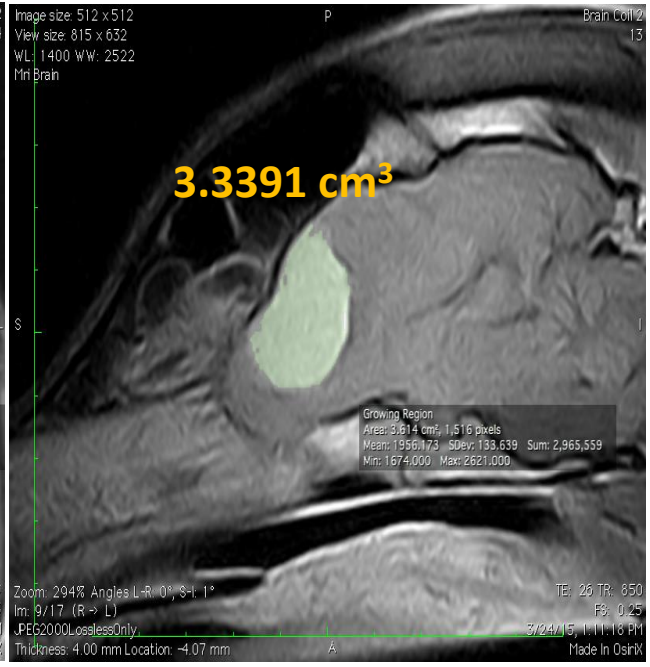
Prof. Greg Riggins, Johns Hopkins

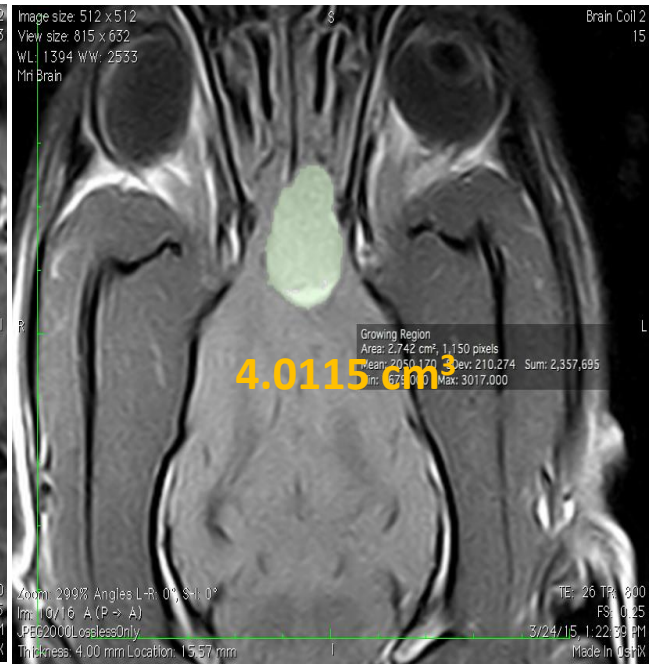
Early findings with combination oral PAC-1 and temozolomide

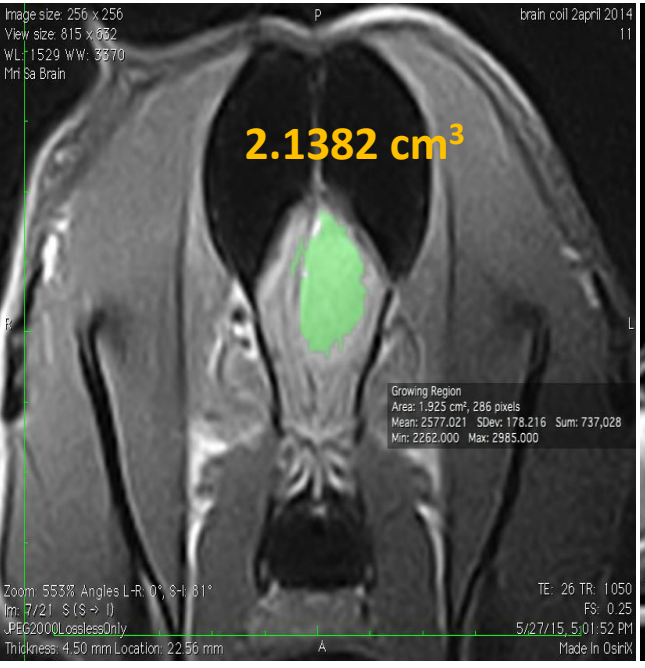


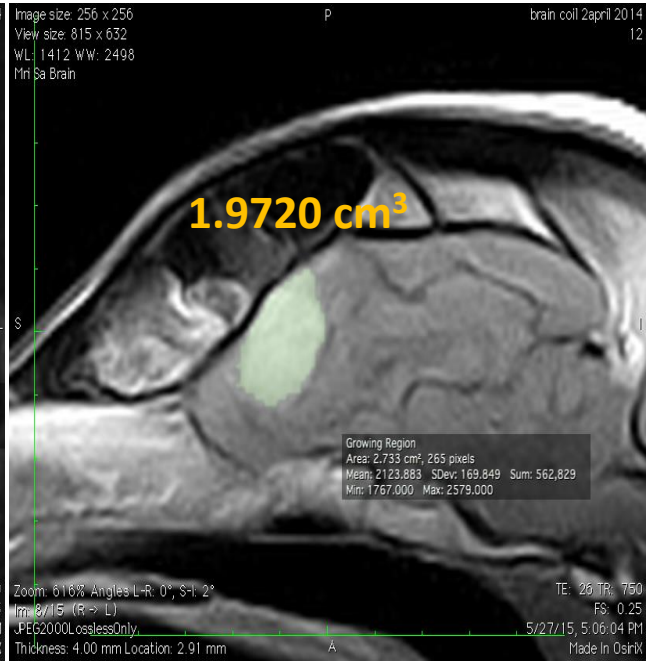
- 8 yr old, FS Labrador
- Acute onset cluster seizures
- Symptomatic management
  - Anticonvulsants
  - Oral prednisone
- MRI consistent w/meningioma
- Treatment with investigational combination
  - Oral PAC-1 (12.5 mg/kg), days 1-21
  - Oral Temozolomide (100 mg/m^2), days 8-12
  - Repeat cycle 28 days

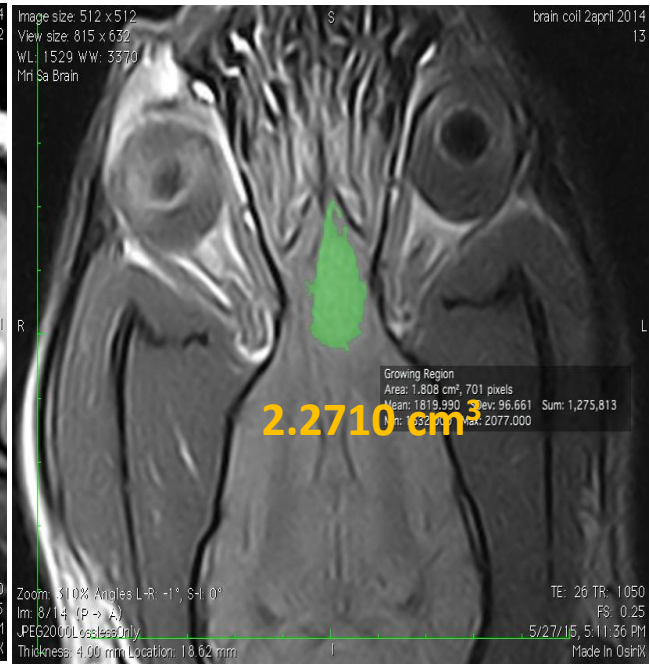






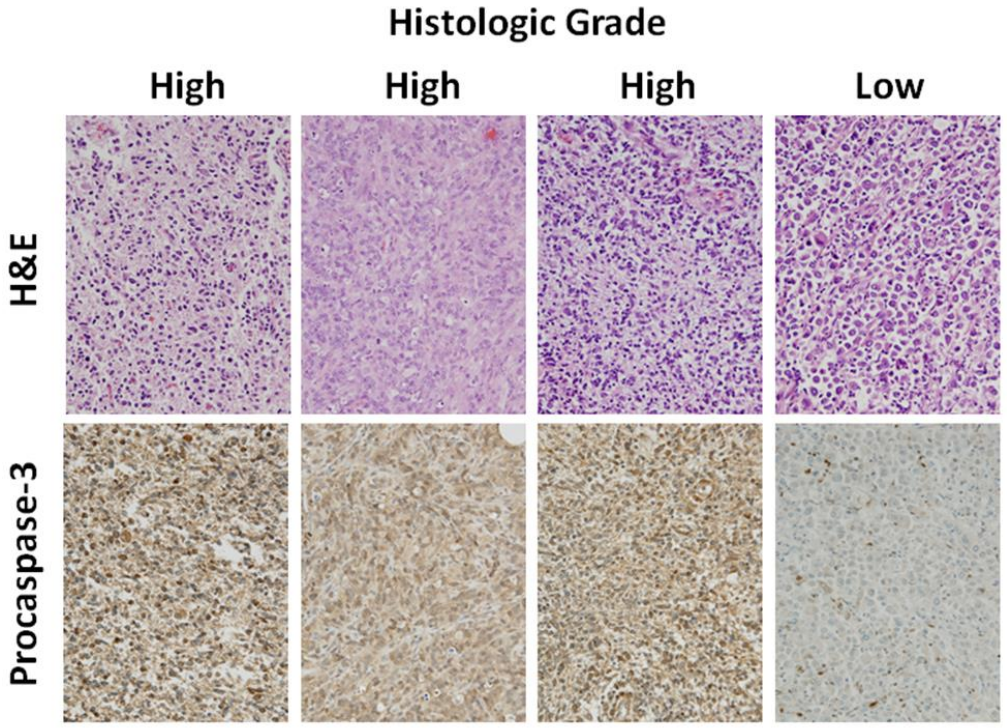


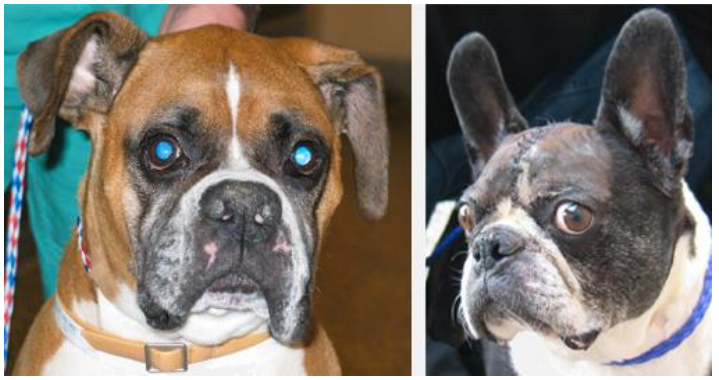


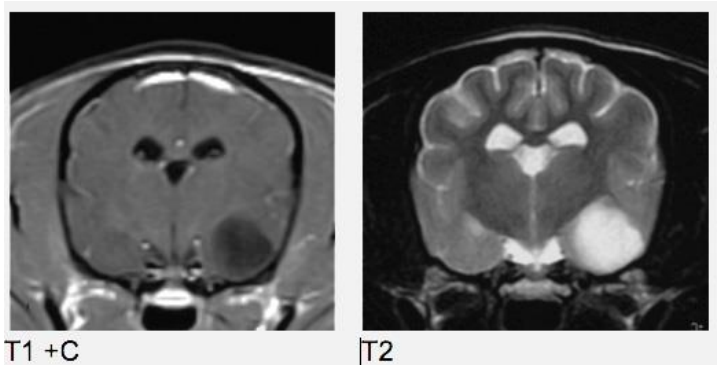


Combination pulsatile therapy well tolerated with activity- *Go decision*

Feasibility Studies in Dogs with Astrocytoma







Jayme Looper
Radiation Oncology

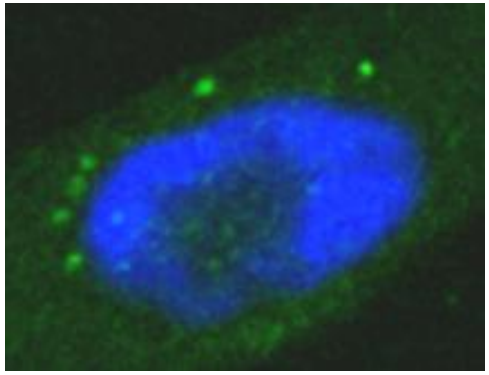
Michael Podell
Neurology

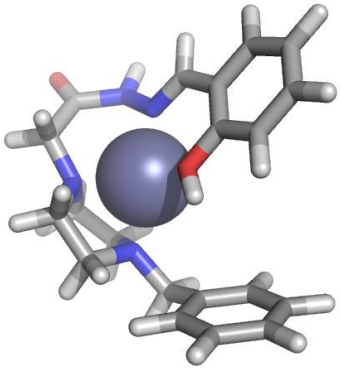
2 Pivotal Canine
Feasibility Studies to be conducted in Chicago, IL

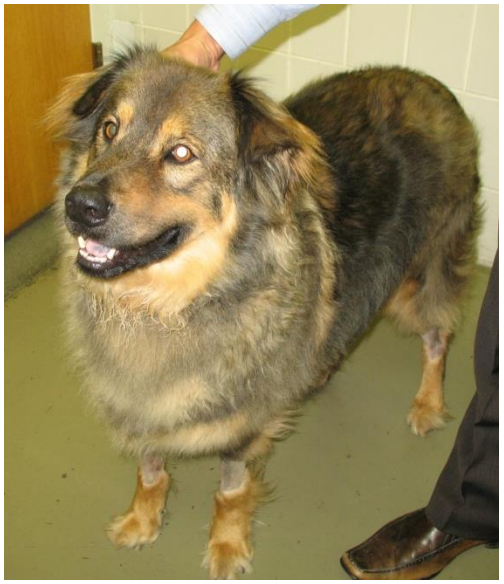
1) **Oral TMZ + oral PAC-1**
2) **Definitive RTH + oral PAC-1**

Conclusions

PAC-1 directly activates procaspase-3 *in vitro* through the sequestration of inhibitory zinc ions







PAC-1 readily penetrates the BBB and has potential in CNS cancers

PAC-1 is orally available and can be given with conventional cytotoxins

PAC-1 shows synergy with a wide variety of standard-of-care cancer drugs in various cancer models

Use of pet dogs with cancer in drug development and dose scheduling

1) ***Critical for the realization of toxicity and limited single agent activity***
2) ***Necessary for development of tolerable dosing regimens to inform human trials***
3) ***Provides preliminary evidence for combination studies to inform human trials***

Phase I human clinical trials of PAC-1

Component 1:

Late stage cancer patients

UI Cancer Center, Chicago

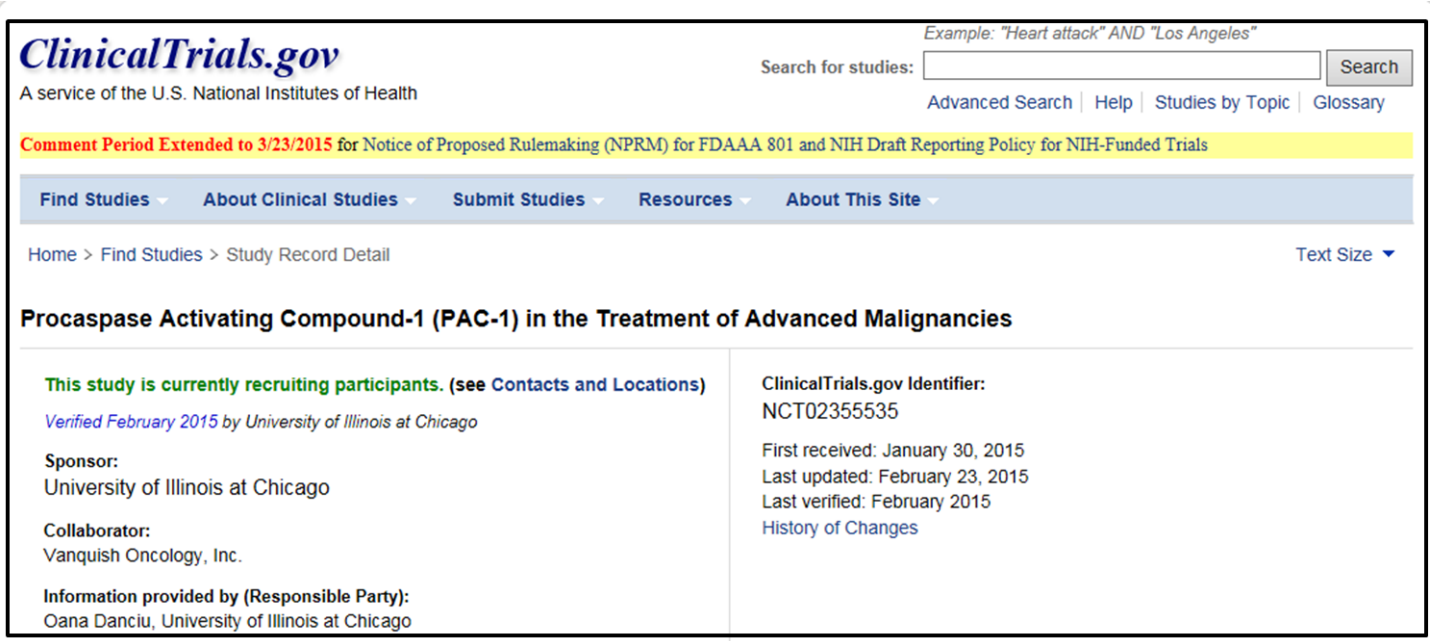
Once-a-day for 21 days, escalation to MTD

Component 2:

Glioblastoma patients

Johns Hopkins

Once-a-day for 21 days, + TMZ



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Text Size

Procaspase Activating Compound-1 (PAC-1) in the Treatment of Advanced Malignancies

This study is currently recruiting participants. (see Contacts and Locations)

Verified February 2015 by University of Illinois at Chicago

Sponsor:
University of Illinois at Chicago

Collaborator:
Vanquish Oncology, Inc.

Information provided by (Responsible Party):
Oana Danciu, University of Illinois at Chicago

ClinicalTrials.gov Identifier:
NCT02355535

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VANQUISH Oncology
Targeted therapies for the treatment of cancer

University of Illinois at Urbana-Champaign
College of Veterinary Medicine