LIMITATIONS OF TRADITIONAL PRE-CLINICAL TUMOR MODELS

Beverly A. Teicher, PhD
DCTD/NCI

The content reflects my professional opinions, not an NCI policy statement.

Outline

1. Transplantable Syngeneic Tumors
2. Human Tumor Xenografts
3. Disseminated Disease Models
4. ‘Labeled’ Tumor Models
5. PDX: Personal Cancer Avatars
6. PDX: New Xenograft Models
7. GEMM Tumor Models
8. The Mouse is a Hardy Host
9. Tumor Microenvironments

Transplantable Syngeneic Tumor Models

Advantages

Low cost
Reproducible
Immuno-competent host
Some variety
Non-immunogenic
Long history/strong baseline data
Hosts readily available
Statistically valid numbers

Disadvantages

Rodent tumor cells
Tumor lines are old
Often implanted sc
Rodent targets
Rodent hosts
Rodent immune system
Grow very fast

Human Tumor Xenografts (Subcutaneous implant)

Advantages	Disadvantages
Human Tumor Cells	More costly
Reproducible	Rodent stroma
Wide variety	Immuno-deficient hosts
Long history	Non-natural site (sc)
Strong baseline data	Most tumor lines old
Hosts readily available	Genetic diversity limited
Tumor growth easily followed	
Statistically valid numbers	

Disseminated Disease Models (syngeneic or xenograft)

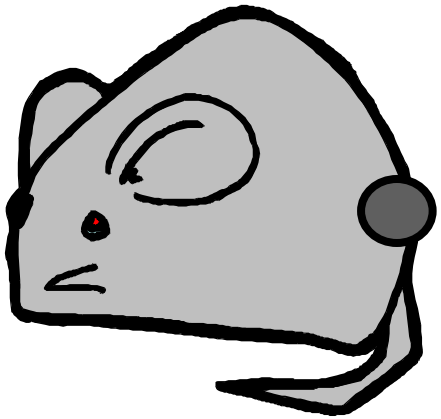
Advantages

More like clinical disease
Tumor cells home to tissues
Good Variety
Hosts readily available
Syngeneic immuno-competent

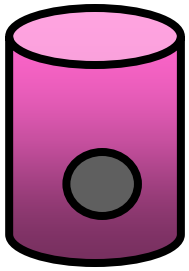
Disadvantages

Intracardiac/iv injection
Low animal numbers
Rodent stroma
Rodent immune system
Tumor difficult to follow
Most tumor lines old
Statistics difficult
Survival endpoint

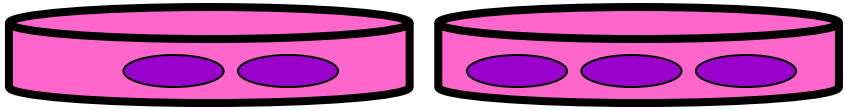
Disseminated Disease Models: Tumor Excision
Quantify tumor cell killing in vivo



-Grow tumor
-Treat the host
-Excise the tumor

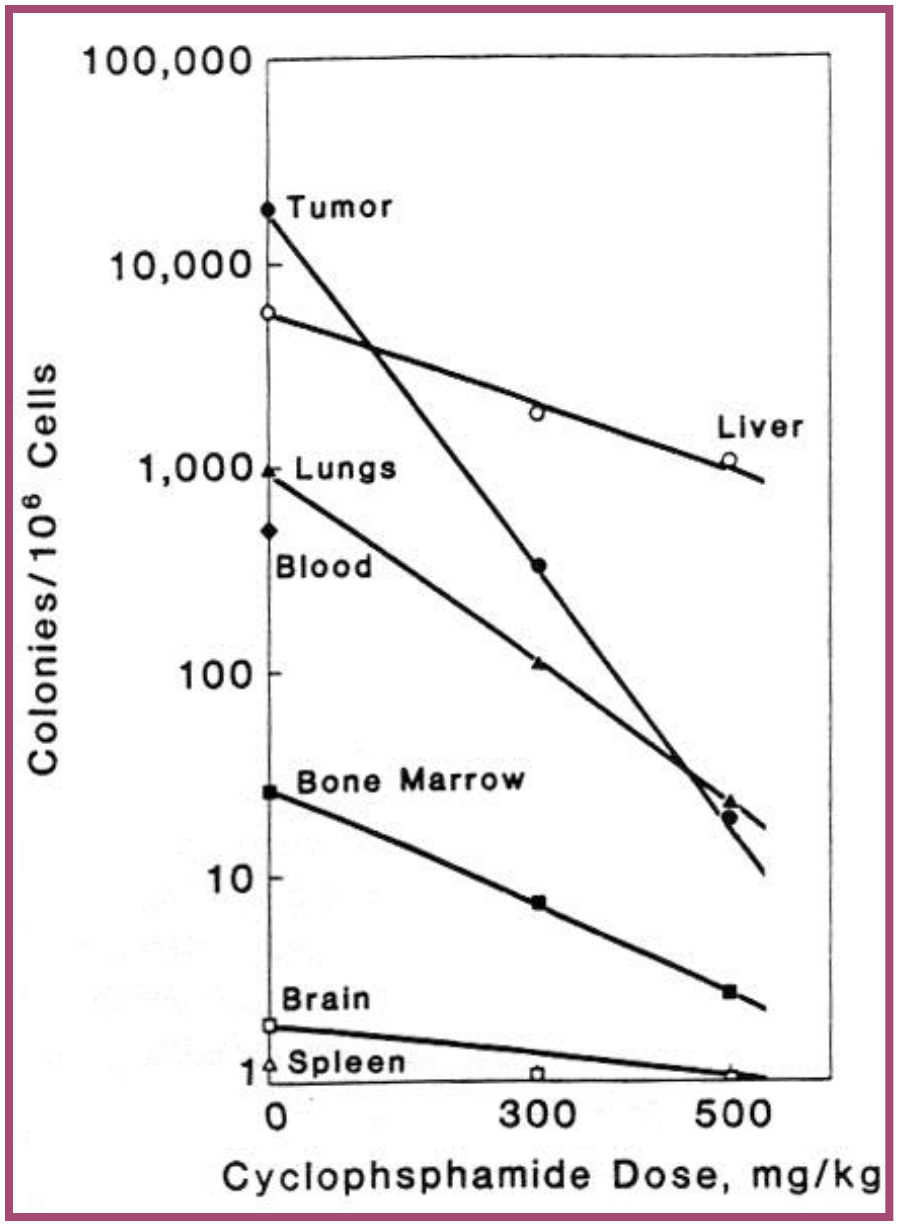


-Prepare single cell suspension
-Count cells
-Plate known number of cells



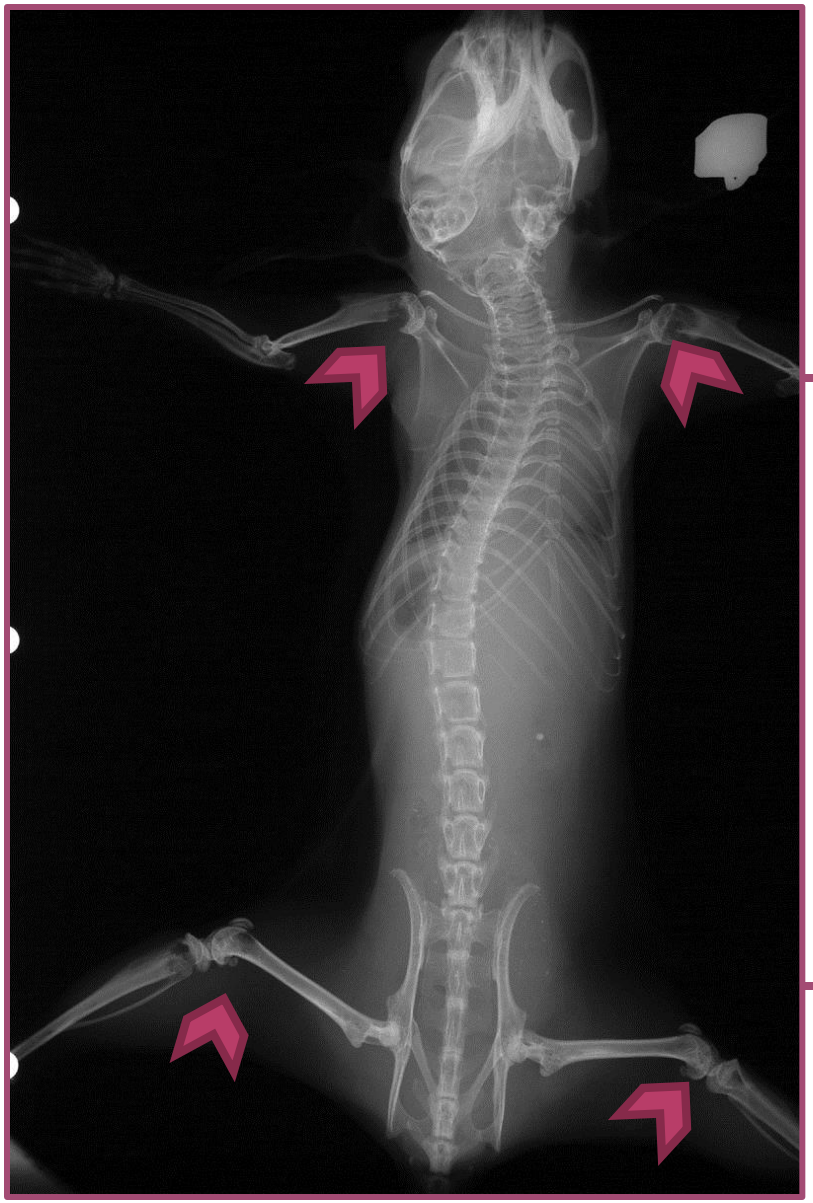
-Count colonies
-Calculate survival

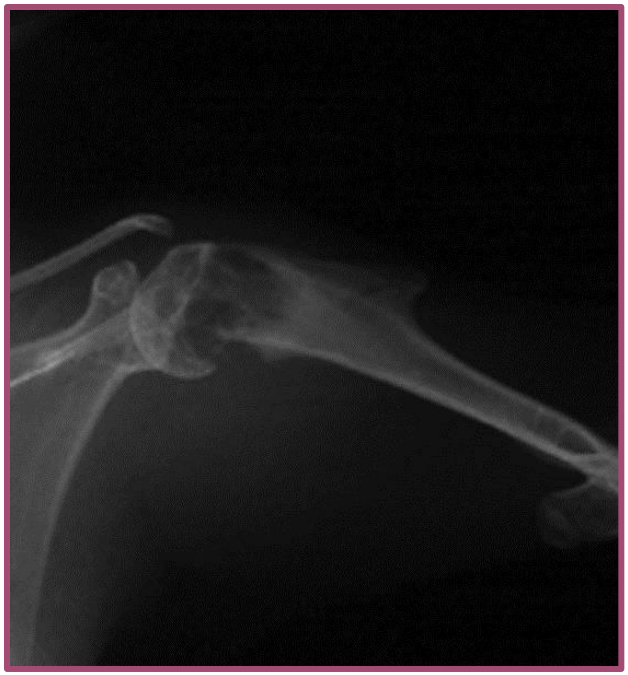
Disseminated disease Models:
Metastatic Spread & Kinetics of Tumor Growth

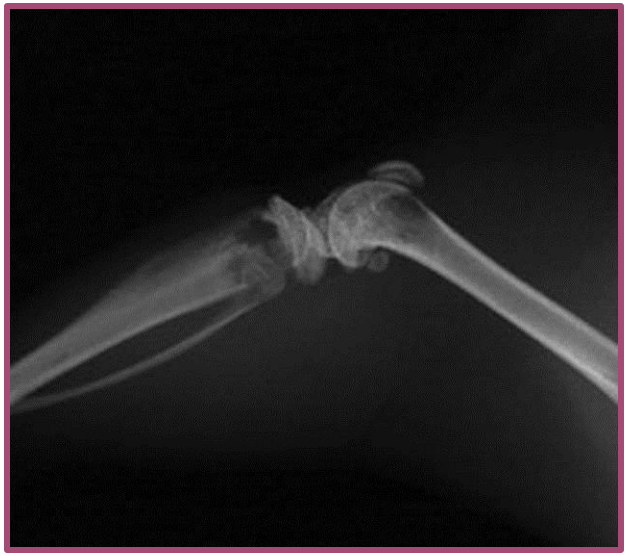


Mouse EMT6 Mammary Ca
sc implant
Day 9

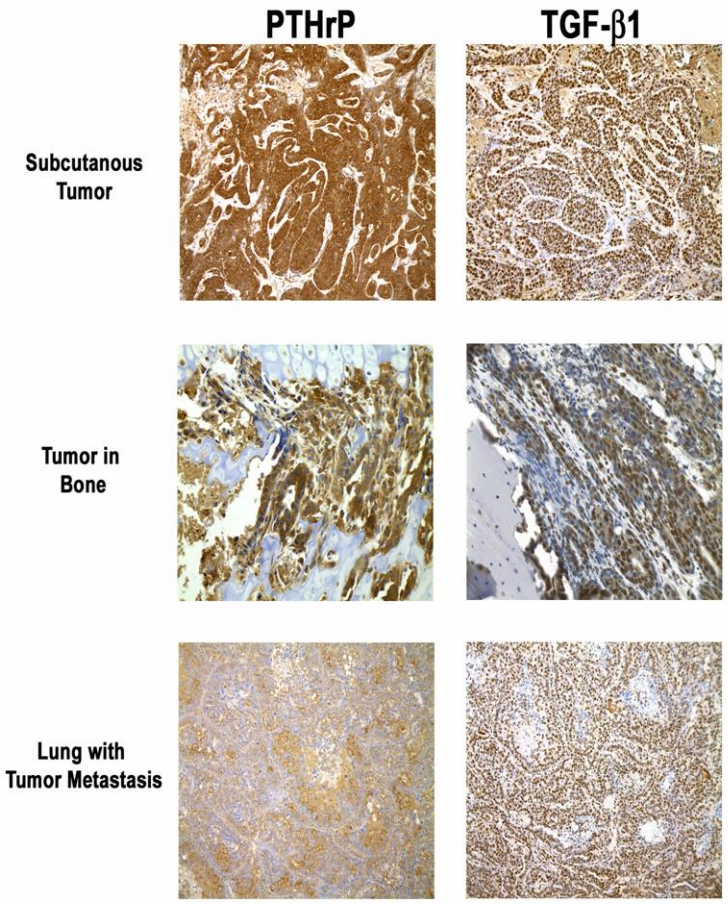
Disseminated Disease Models: 4T1 Intra-cardiac injection model

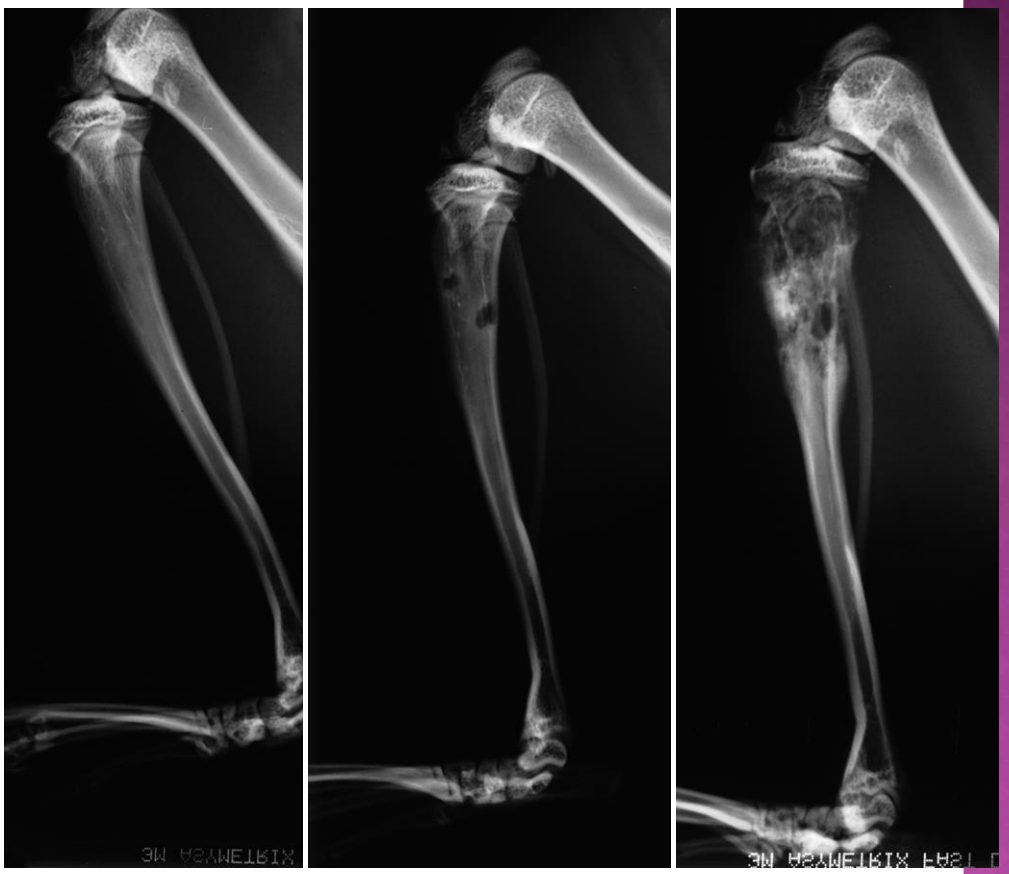






Rat 13672 Mammary Carcinoma Bone Metastasis &TGF-β Antagonists





‘Labeled’ Tumor Models (synegenic or xenograft): Orthotropic or subcutaneous

Advantages

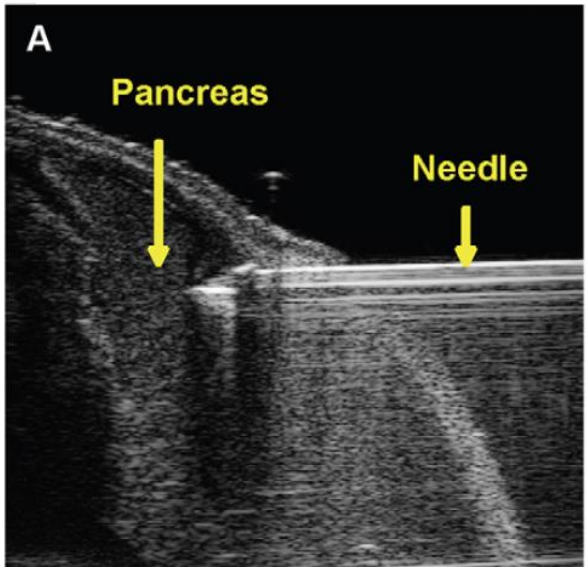
Tumor can be followed by
fluorescence or
luminesence
Metastasis visualized
Tumor measurement
Variety limited
Hosts readily available

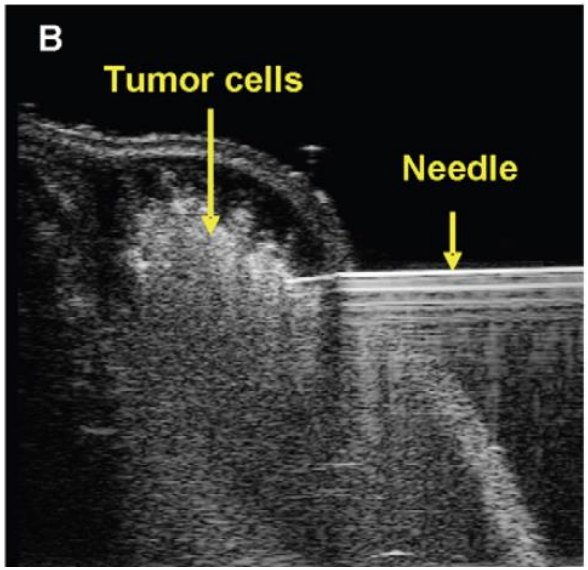
Disadvantages

Genetically altered sub-lines
Many clonal lines
Poor representation of disease
Low animal numbers
Rodent stroma
Immuno-deficient host
Costly equipment
Statistics difficult

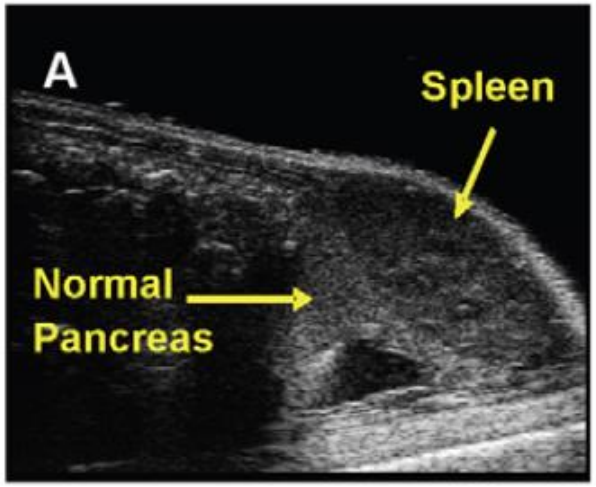
Development of an Orthotopic Human Pancreatic Cancer Xenograft Model Using Ultrasound Guided Injection of Cells

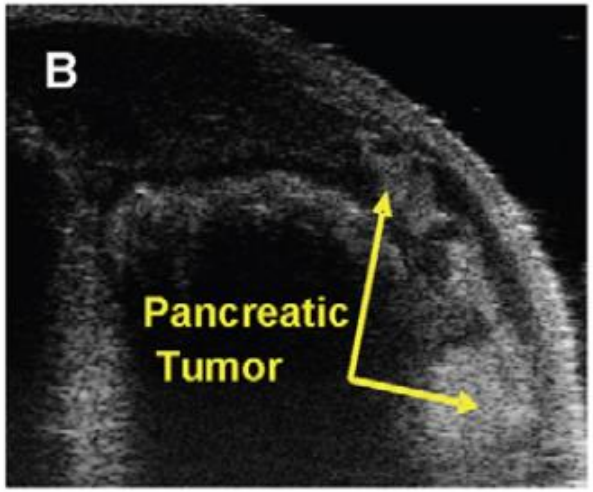
Amanda Shanks Huynh[1], Dominique F. Abrahams[2], Monica S. Torres[2], Margaret K. Baldwin[2], Robert J. Gillies[1], David L. Morse[1]*

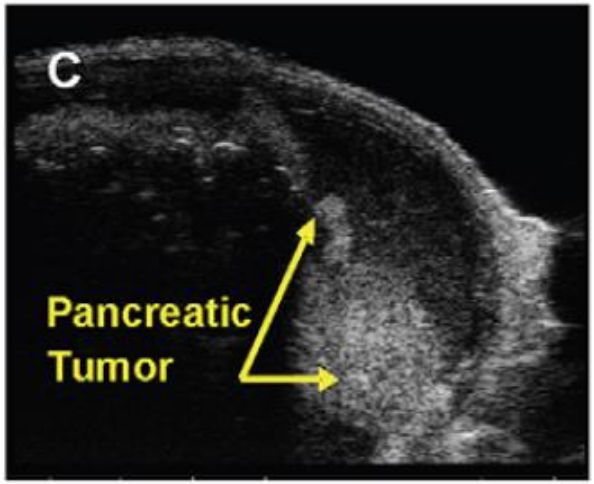




Ultrasound guided tumor implant & images.







(Plos One 2011; 6: e20330)

PDX (Patient-Derived Xenograft) Models
1) Personal Cancer Avatars

Advantages

Tumor cells recently from patient (P1)
Genetically similar to patient
Tumor measurement (sc)
Hosts readily available

Disadvantages

Require large tumor specimen to start
Slow growing
Immuno-deficient host
Mouse stroma
Low animal numbers
Very costly
Statistics difficult
Not validated predictors

PDX (Patient-Derived Xenograft) Models
2) New Xenograft Models

As understanding of human malignant disease complexities emerge & preclinical investigators attempt to match clinical disease to available human tumor xenograft models, it is strikingly apparent that there are not enough xenograft models & that those used as drug discovery drivers fall short of representing the diversity of the clinical disease.

Advantages

Recently from patient (P4-?)
Many genetically characterized
Tumor measurement (sc)
Hosts readily available

Disadvantages

Immuno-deficient host
Rodent stroma
No baseline data
Very costly
Low animal numbers
Often slow growing
Statistics difficult
Not validated

GEMM Tumor Models

GEMM models have come a long way; however, genetically they are too 'clean' compared with human malignant disease. GEMM models can be useful for understanding the biology & kinetics of changes caused by specific mutations.

Advantages

Tumor arises in desired tissue
Well-defined lesion; defined mutations
Can follow time course to cancer
Immunocompetent host

Disadvantages

Limited mutations not reflective of human disease
Rodent tumors
Slow tumor development
Very costly breeding
Variable tumor stage
Tumor difficult to follow
Statistics difficult
Survival endpoint

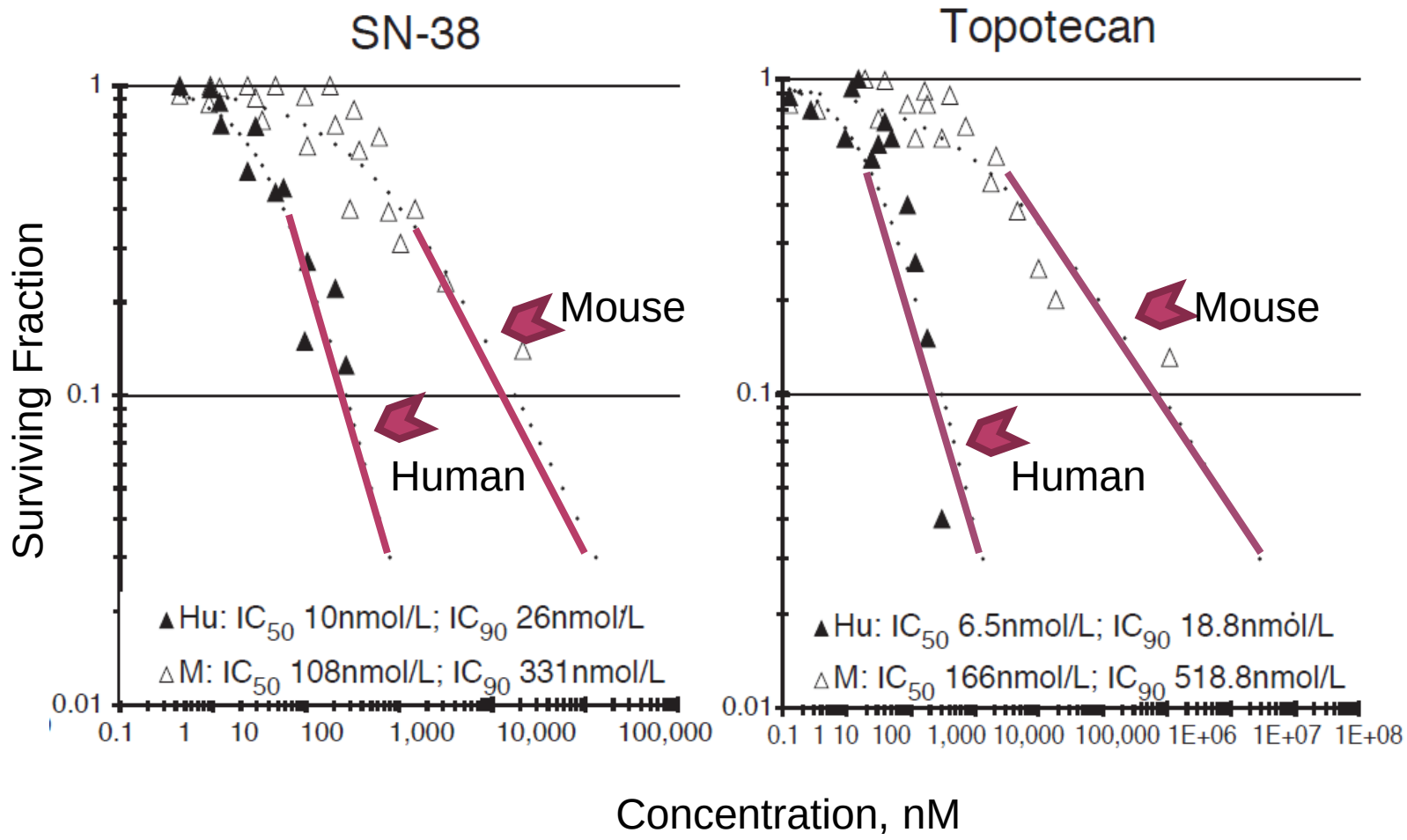
The Mouse is a Hardy Host

The mouse remains the most useful & most maligned host for cancer models. In-bred strains of conventional & immuno-deficient mice are, generally, hardy upon exposure to anticancer agents compared with humans.

The most commonly used measure of mouse normal tissue toxicity is body weight change. Treatments resulting in 20% net body weight loss associated with a moribund condition &/or >20% lethality are designated
'toxic'.

Bone marrow is often a dose-limiting toxicity in patients.

Response of Human & Mouse Bone Marrow: Toposiomerase 1 Inhibitors in Culture



Tumor Microenvironment

The tumor microenvironment plays a very important role in tumor progression. In fact, the microenvironment is involved during carcinogenesis initiation, progression to malignancy, & treatment response & resistance.

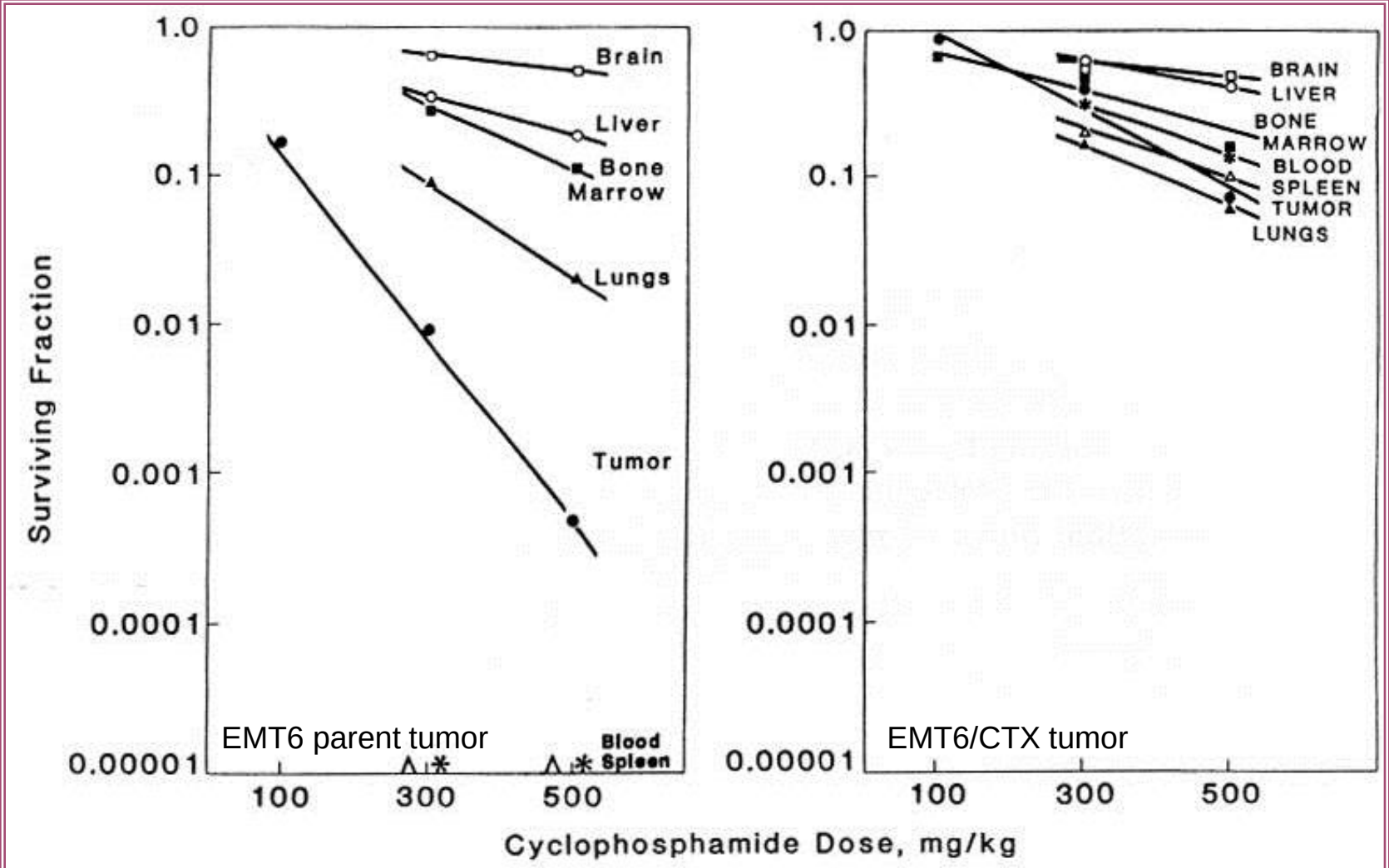
The mouse subcutaneous space is a poor microenvironment for syngeneic or xenograft tumors. Most orthotopic implantations are confounded with the cytokine & growth factor 'storm' produced by wound healing.

The 'communication' between human and mouse signaling pathways is imperfect & in some cases such as interferons, some interleukins & some growth factors (HGF), non-functional.

The mouse immune system is quite different from the human & has led to a great effort to produce humanized mice.

The mouse pharmacokinetic & metabolic handling of drugs can be very different from human.

Microenvironment effect on tumor response



Conclusions

- Transplantable tumors in mice are poor mimics of human cancer whether syngeneic or xenograft
- GEMM models have advantages and disadvantages.
  Are they ‘better’ models of human disease?
- The mouse is a hardy host & thus has led to inaccurate predictions of activity in human cancer
- The mouse microenvironment does not accurately reflect the microenvironment of human cancer