SSSC Brown Bag Talk

Principle of Cancer Modeling in Mice:
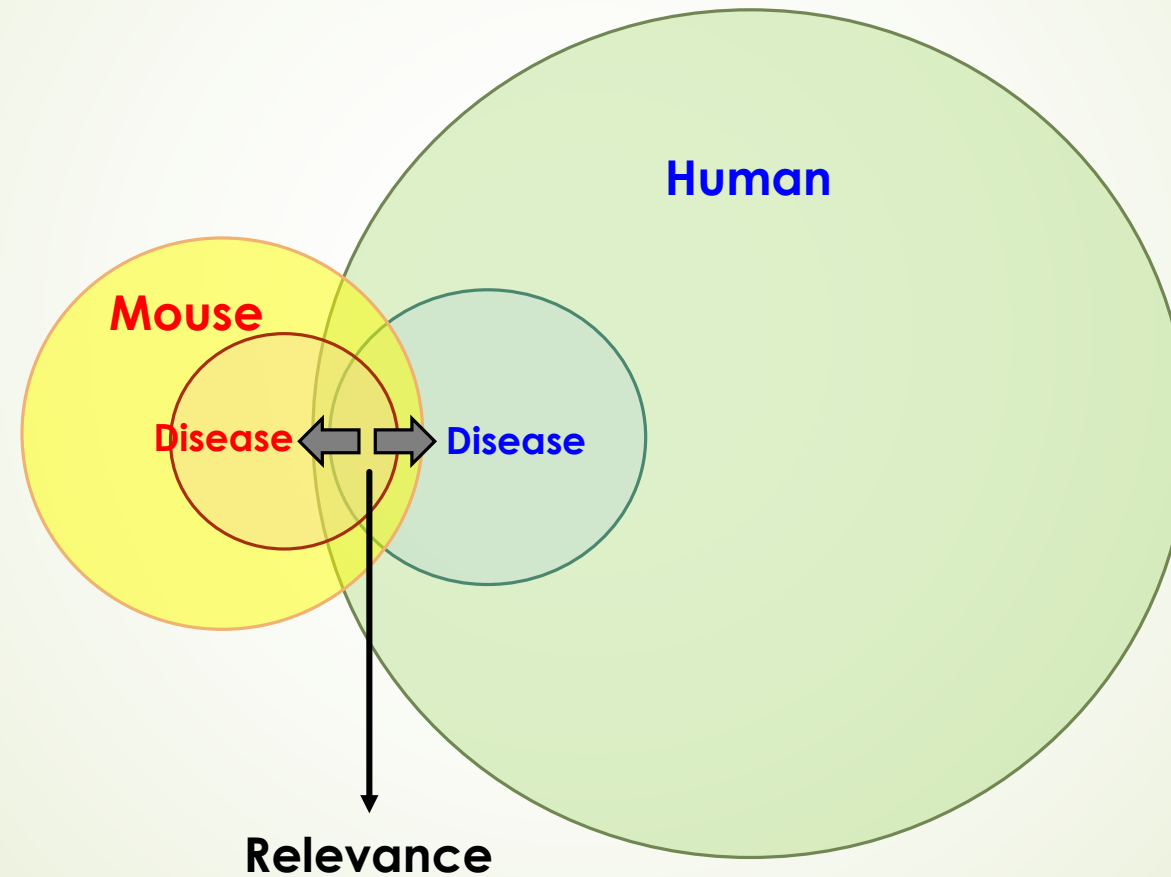## *How to Translate Preclinical Studies*
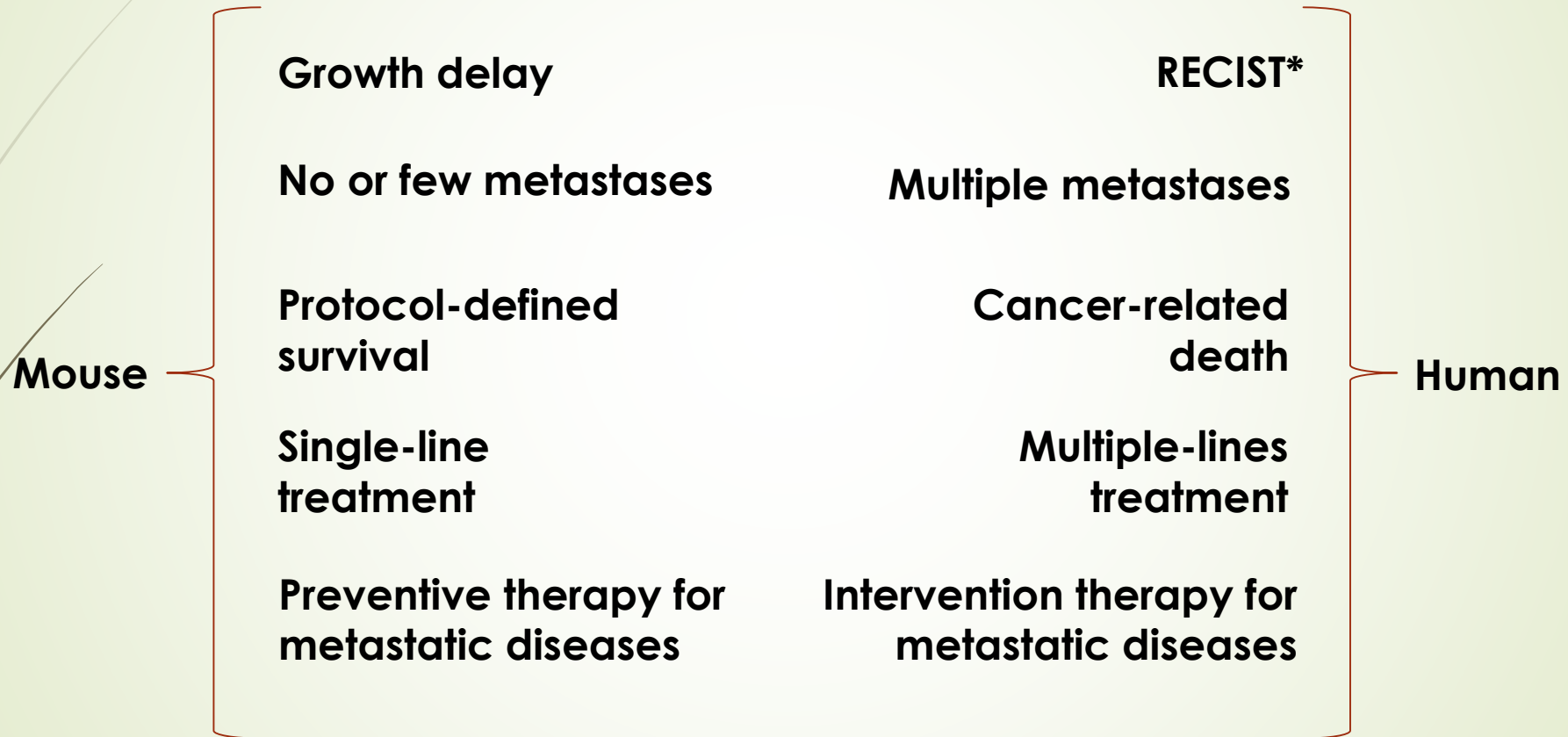
Chi-Ping Day, Ph.D.
Staff Scientist
Cancer Modeling Section,
Laboratory of Cancer Biology and Genetics,
National Cancer Institute, NIH

January 25th, 2019

Relevance of mouse models to human diseases depends on the "driving factors" in common

Irrelevance resulted from mismatch between model setting and human disease

Mouse

Growth delay

No or few metastases

Protocol-defined survival

Single-line treatment

Preventive therapy for metastatic diseases

RECIST*

Multiple metastases

Cancer-related death

Multiple-lines treatment

Intervention therapy for metastatic diseases

Human

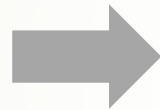*response evaluation criteria in solid tumors

Disease tracking and treatment in the preclinical models need to match those in clinical situations

Therapeutic setting
- **Intervention**
- **Adjuvant**
- **Neoadjuvant**
- **Maintenance**

→

Therapeutic response in the individual setting

→

Endpoint

Disease tracking and treatment in the preclinical models need to match those in clinical situations

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→ Therapeutic response in the individual setting → Endpoint

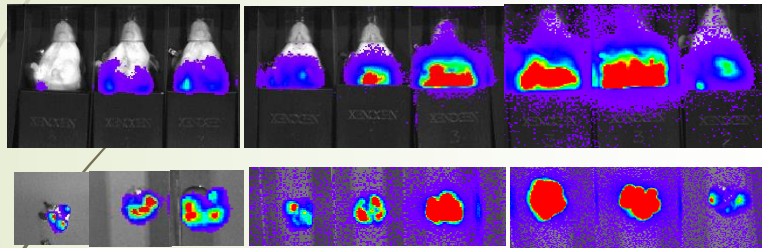# Different therapeutic settings target different disease states

Therapeutic setting	Targets of the treatment	Goals	Example
Intervention	Detected disease	Eliminating the detected disease	Surgical resection of tumors
Adjuvant	Residual disease	Preventing metastatic diseases	Chemotherapy following tumor resection
Neoadjuvant	Disseminating disease	Preventing the dissemination of the disease	Chemotherapy followed by tumor resection
Maintenance	Progressing disease	Slowing the progression for symptom relief	Palliative chemotherapy

Tumor models for studying adjuvant setting

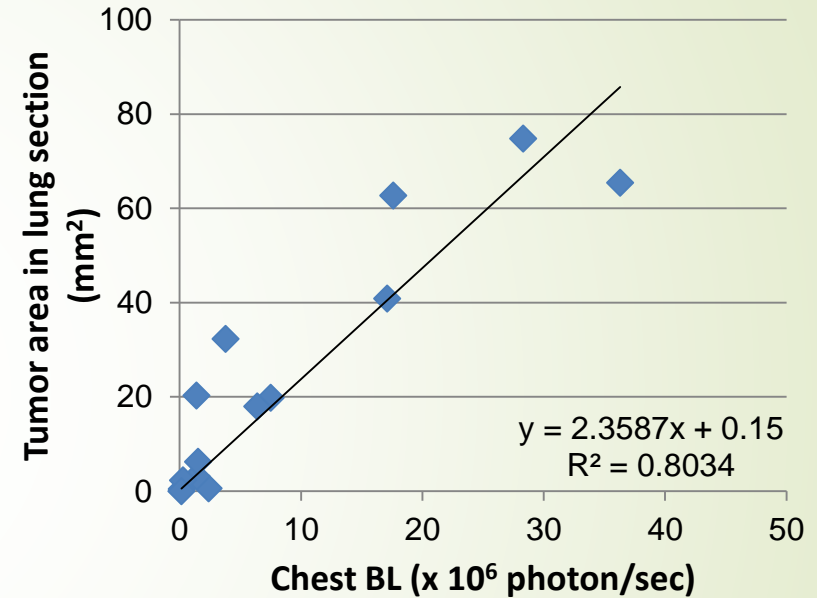Melinda Hollingshead, John Carter, Carrie Bonomi
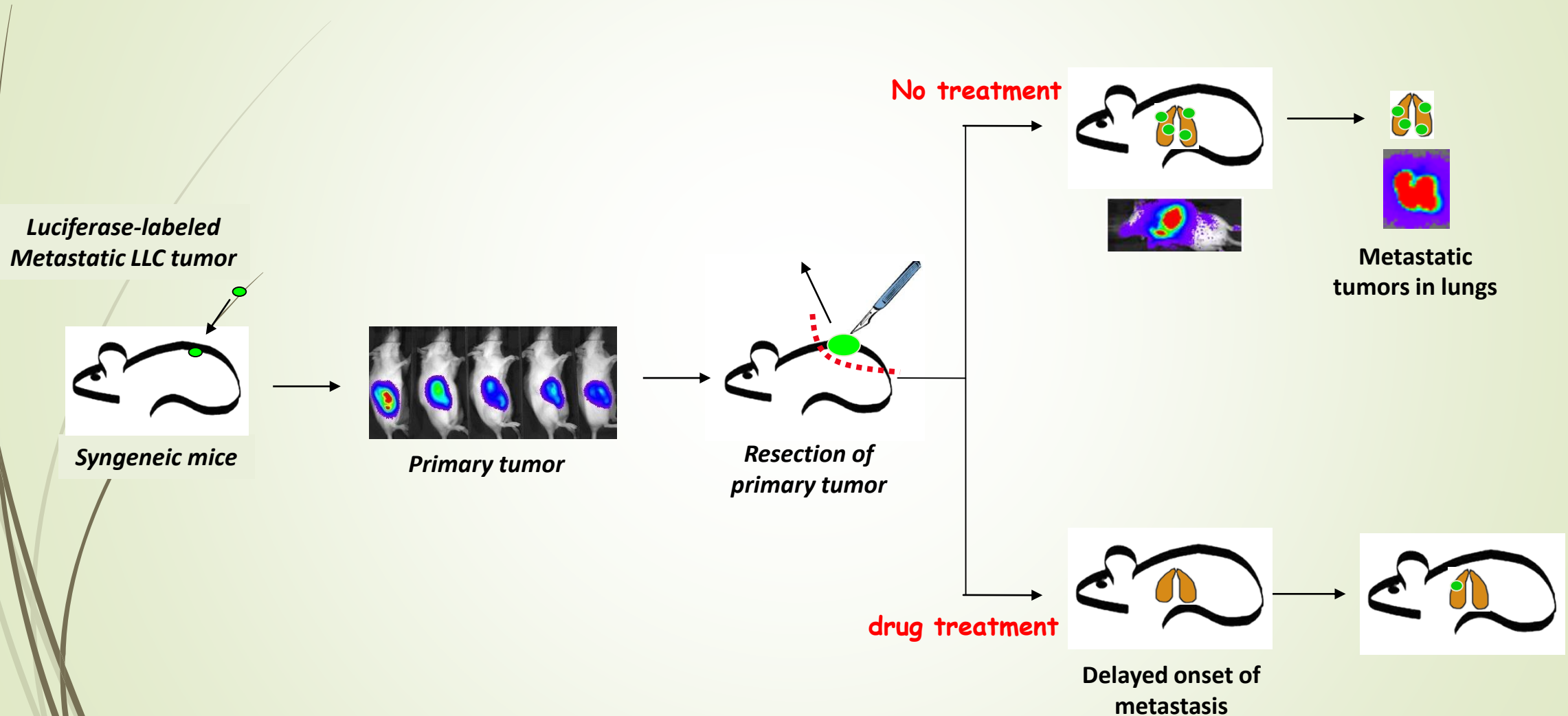
Adjuvant setting model should allow quantitative tracking of metastatic disease

Quantitation

$$y = 2.3587x + 0.15$$
$$R^2 = 0.8034$$

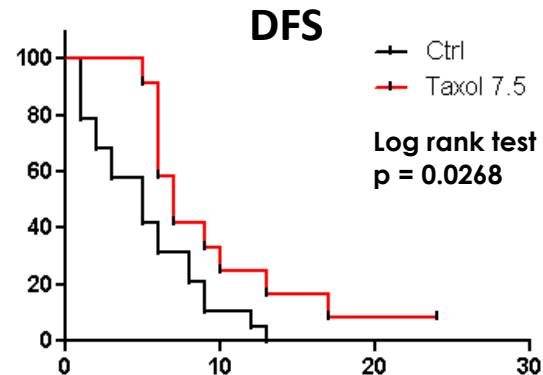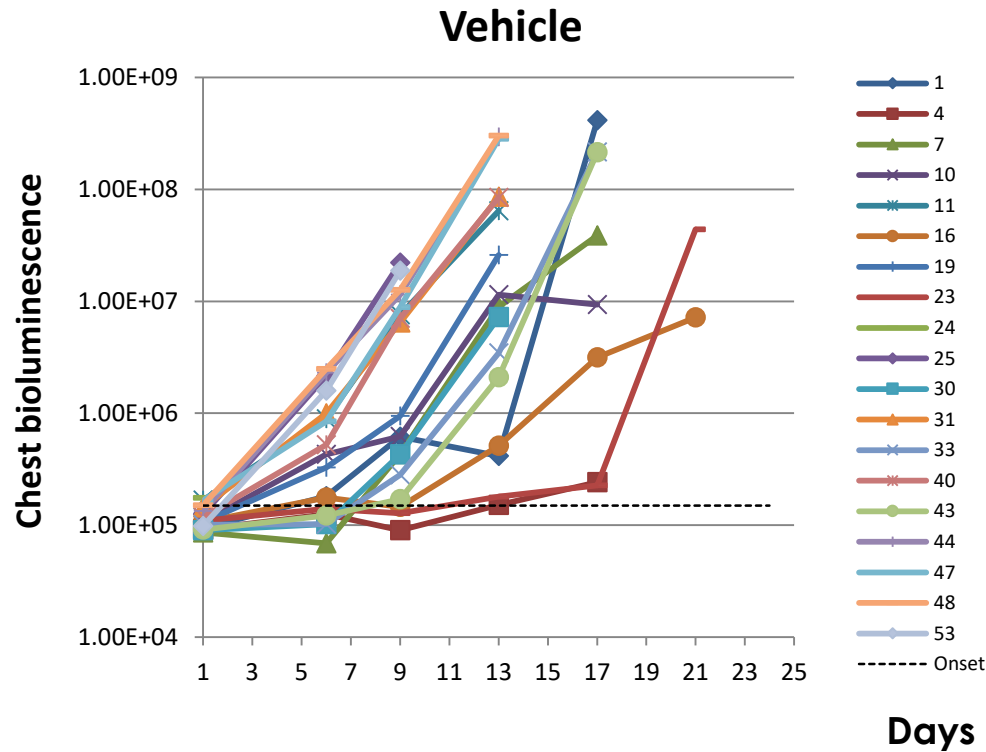**Pathological scoring**

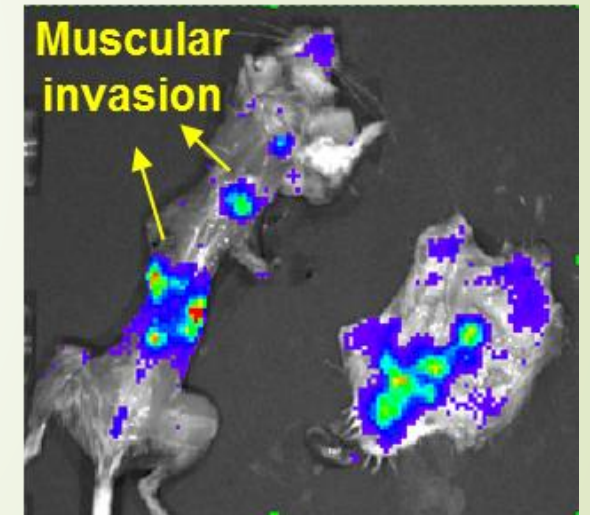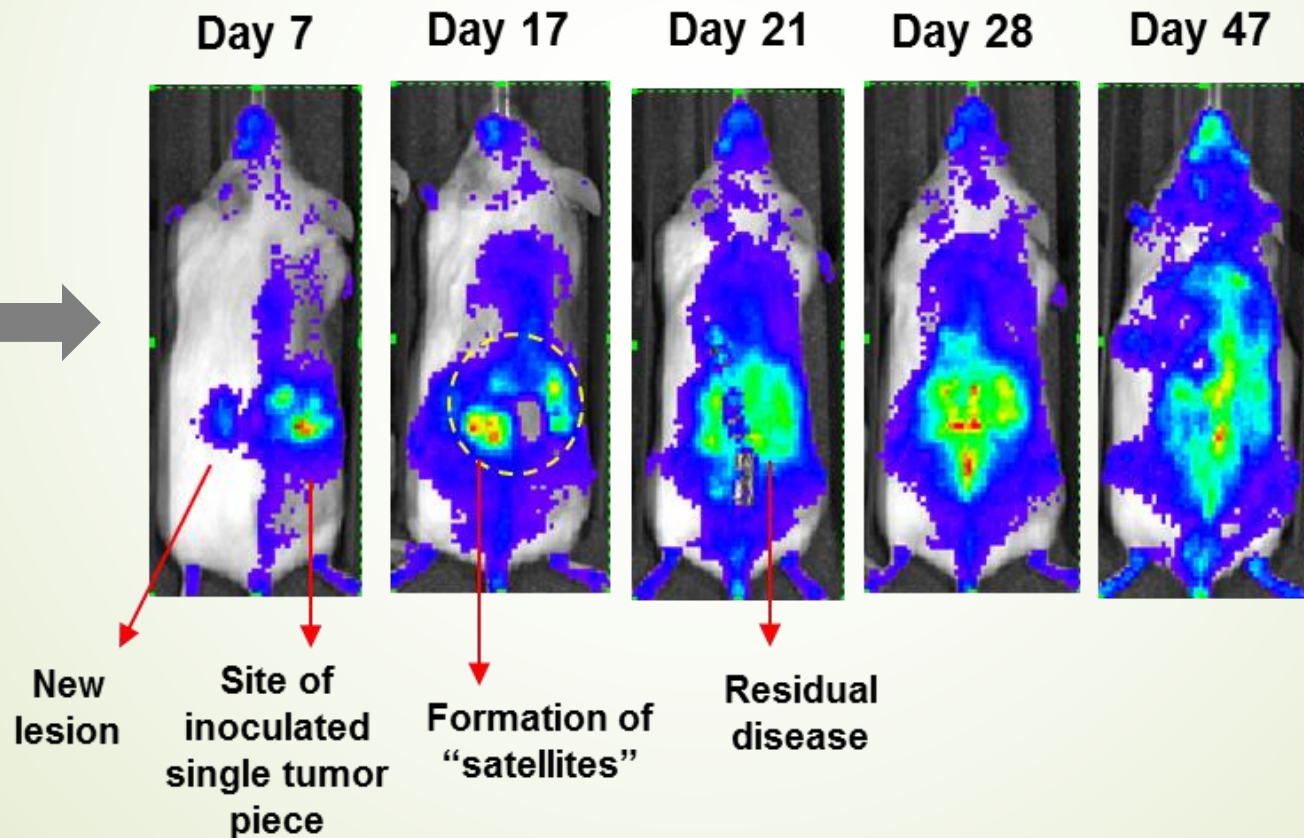| Chest BL	Corresponding Lung Pathology	Score
$1.5 \times 10^5 - 2 \times 10^5$	1-2 nodules	1
$2 \times 10^5 - 1 \times 10^6$	A few nodules	1-2
$1 \times 10^6 - 5 \times 10^7$	Mostly multifocal	3-4
$> 5 \times 10^7$	Diffuse	4

Clinically relevant readout can be generated from quantitative disease tracking in adjuvant setting model

Day et al (2012) Int. J. Cancer: 130, 190–199
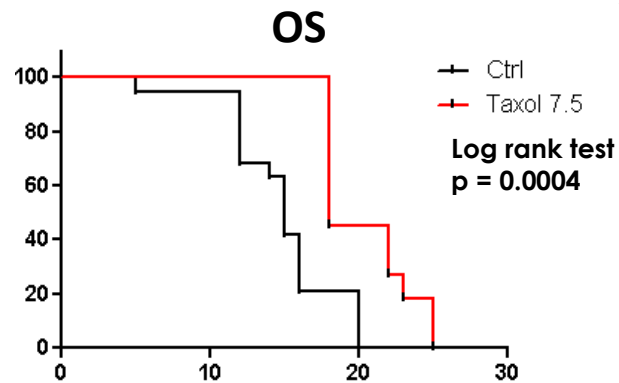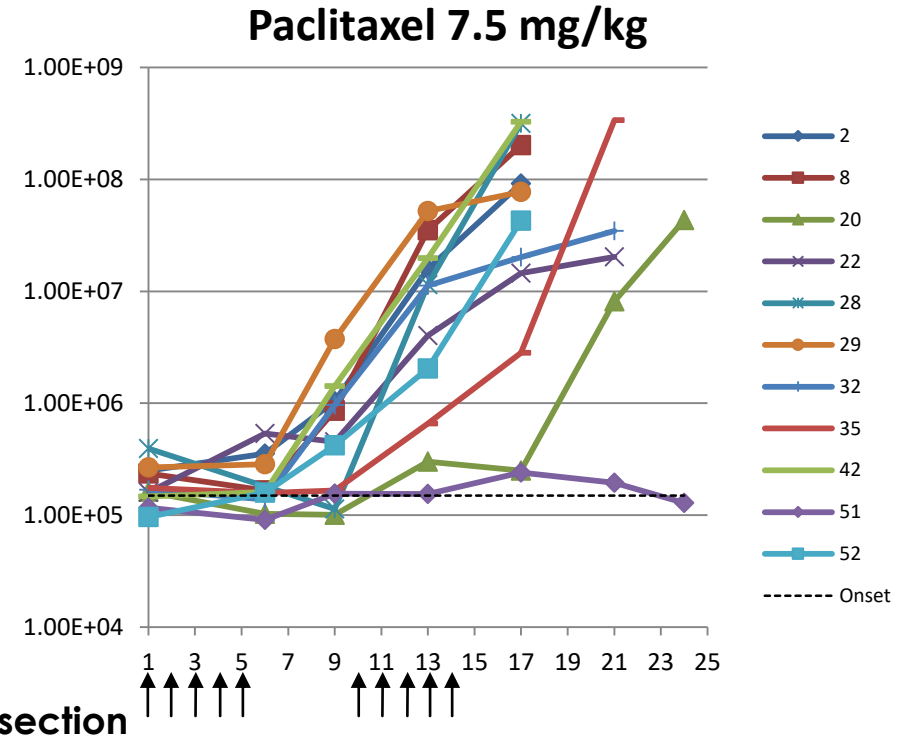
Models for neoadjuvant therapy should allow tracking of disseminated disease

DMBA-induced HGF-tg;CDK4^{R24} melanoma labeled with luciferase and GFP

Tumor reached 500 mm^3 and resected (Day 1)

Day 7 | Day 17 | Day 21 | Day 28 | Day 47

Muscular invasion

New lesion

Site of inoculated single tumor piece

Formation of "satellites"

Residual disease

Disease tracking and treatment in the preclinical models need to match those in clinical situations

Therapeutic setting
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→ **Therapeutic response in the individual setting** → **Endpoint**

Effects of disease stage on therapeutic response

Nonmetastatic disease, experimental therapy
Nonmetastatic disease, standard therapy
Metastatic disease, experimental therapy
Metastatic disease, standard therapy
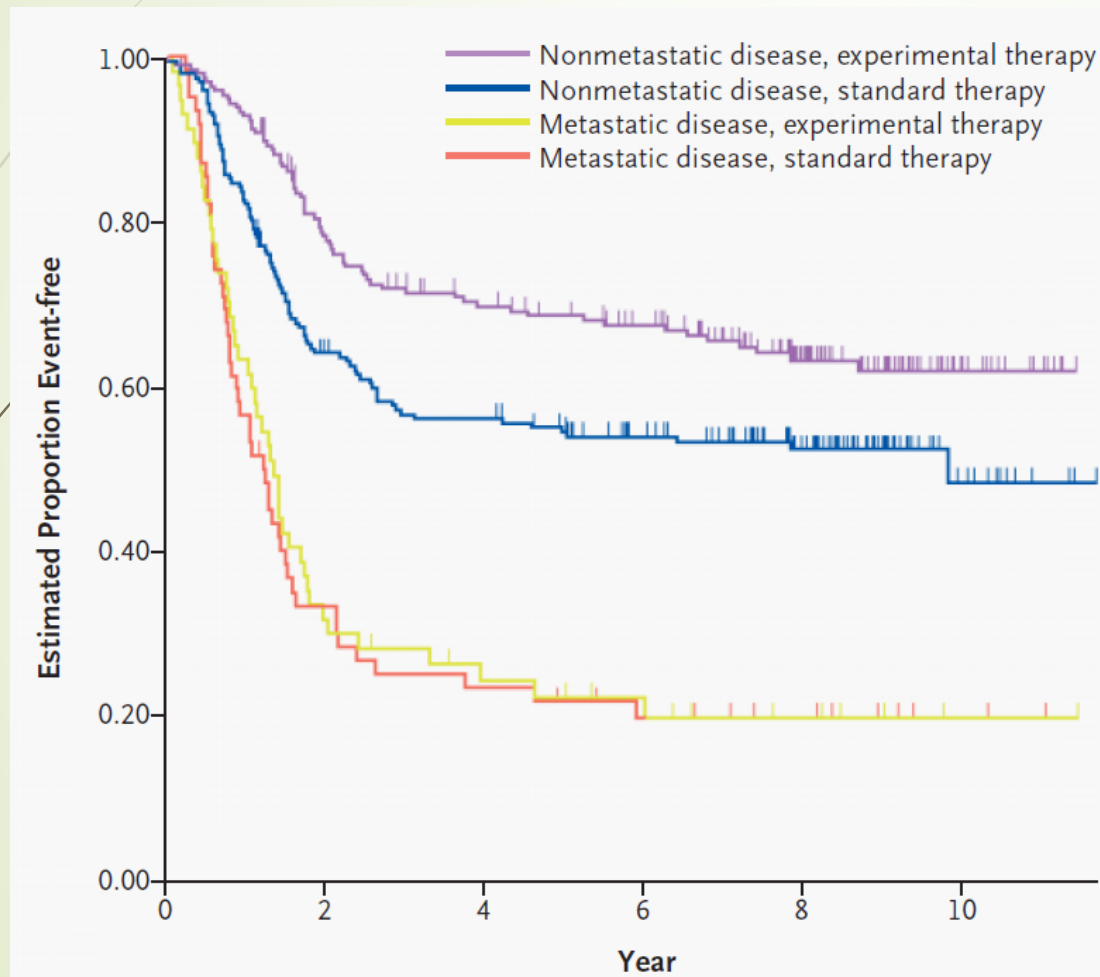
Ewing's Sarcoma

Standard combination chemotherapy:
Doxorubicin
Vincristine
Cyclophosphamide
Dactinomycin

Experimental therapy:
Combination chemotherapy alternating with courses of ifosfamide and etoposide

Grier et al. (2003) N Engl J Med; 348:694-701.

Comparing therapeutic responses of diseases at distinct progression stages

Luciferase-labeled Metastatic LLC tumor
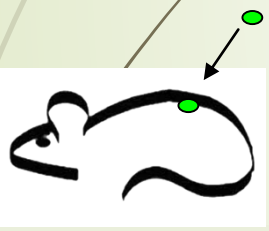
Syngeneic mice
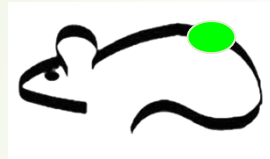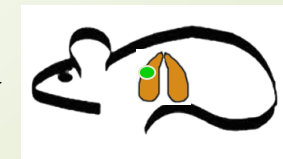
Vehicle

drug

Treatment of primary tumor
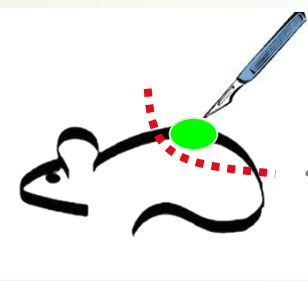
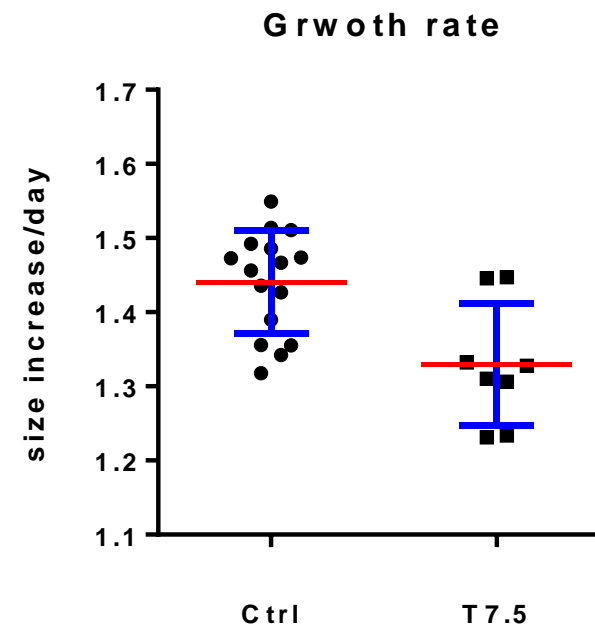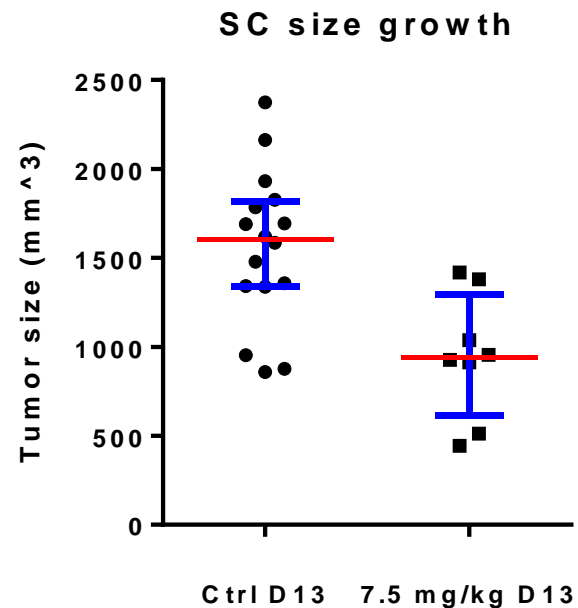**Resection of primary tumor**

Vehicle
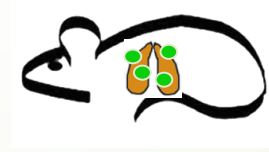
drug

Treatment of metastasis

Responses of primary and metastatic tumors to the same chemotherapeutic agent are driven by different factors
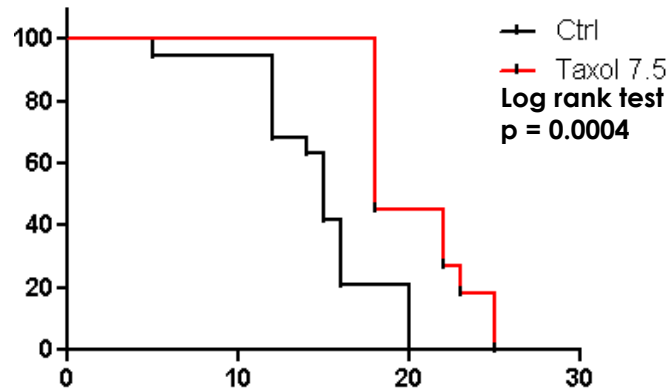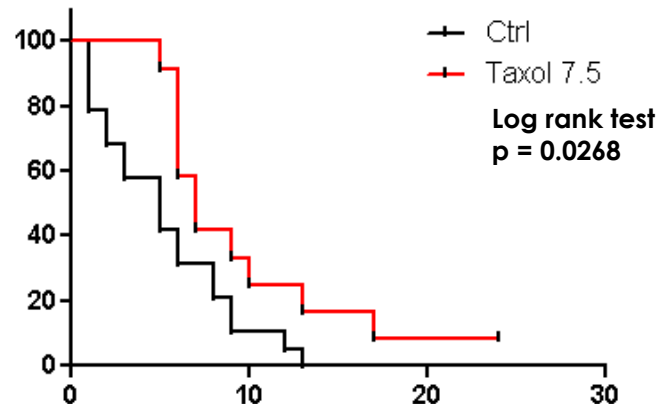
Subcutaneous tumor

Responses of primary and metastatic tumors to the same chemotherapeutic agent are driven by different factors
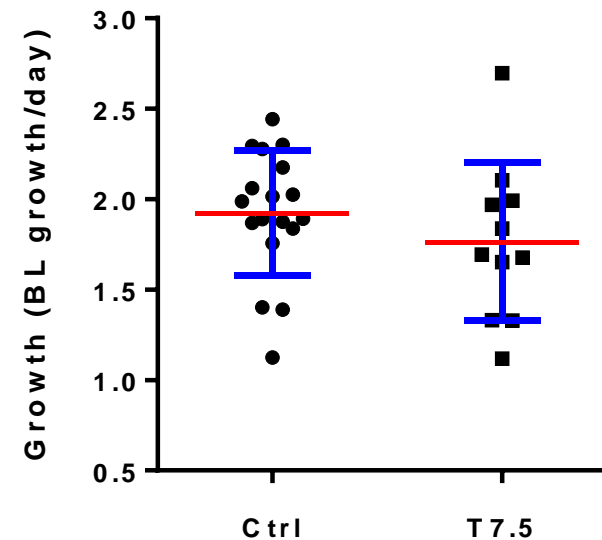
Metastatic disease

Therapeutic responses in different settings may not be associated with each other
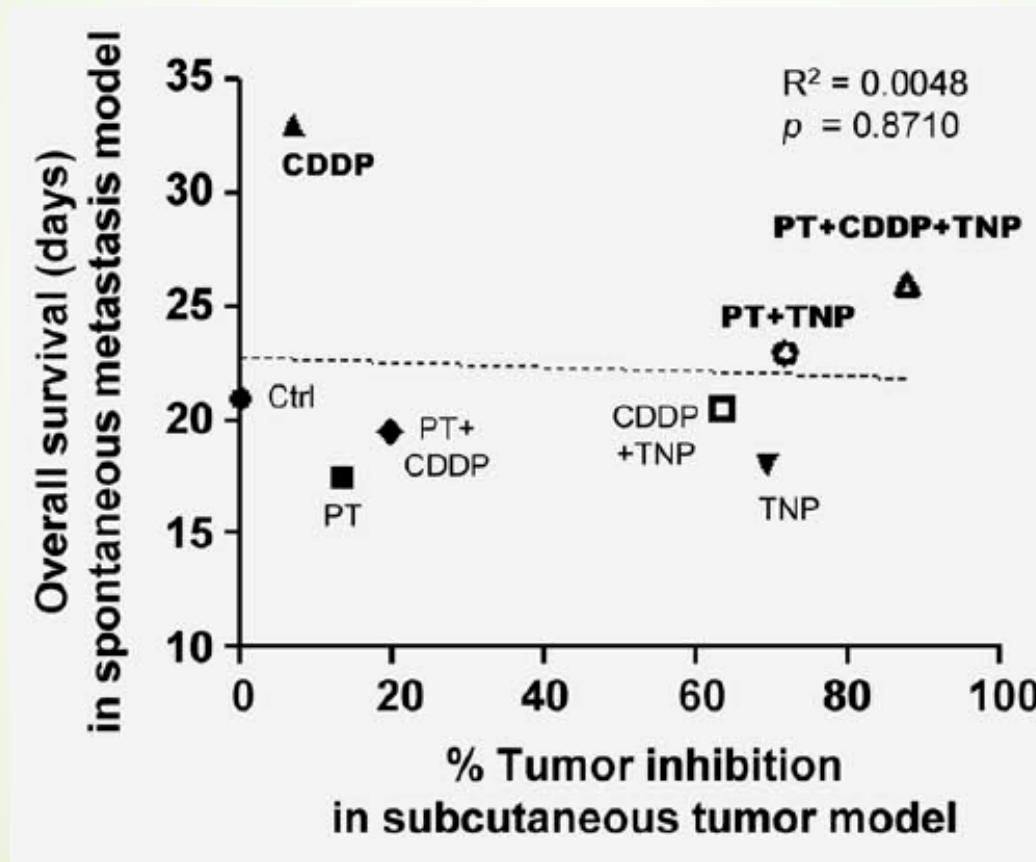
Day et al (2012) Int. J. Cancer: 130, 190–199

Disease tracking and treatment in the preclinical models need to match those in clinical situations

Therapeutic setting
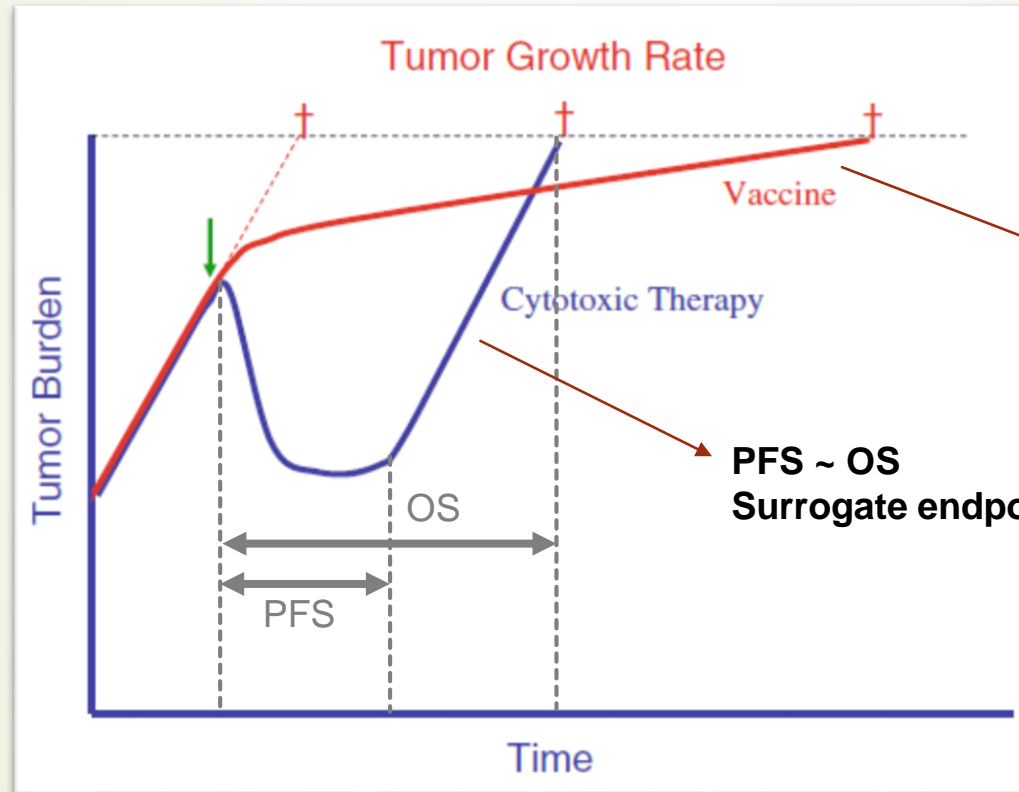- Intervention
- Adjuvant
- Neoadjuvant
- Maintenance

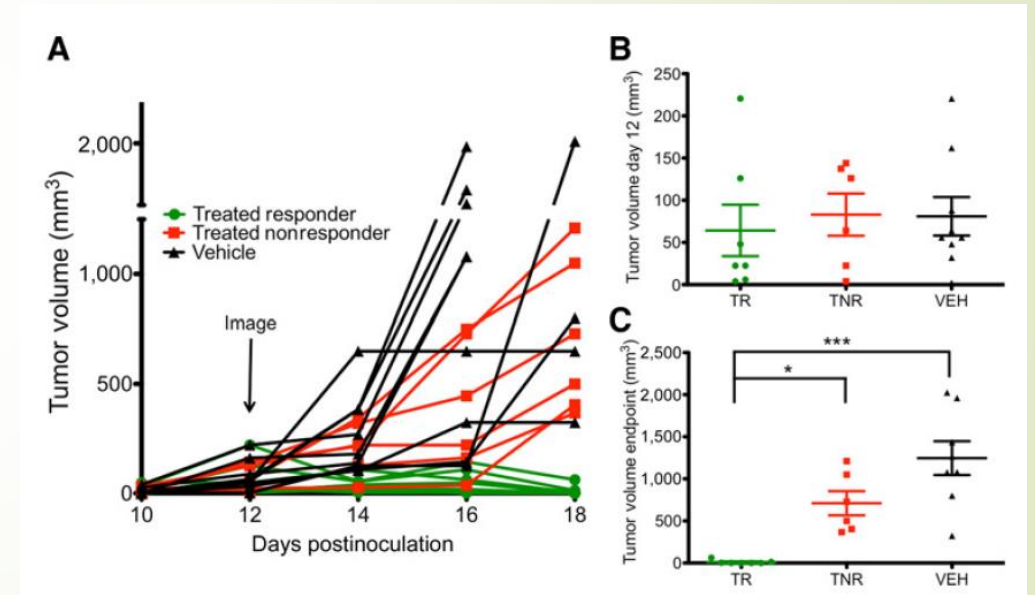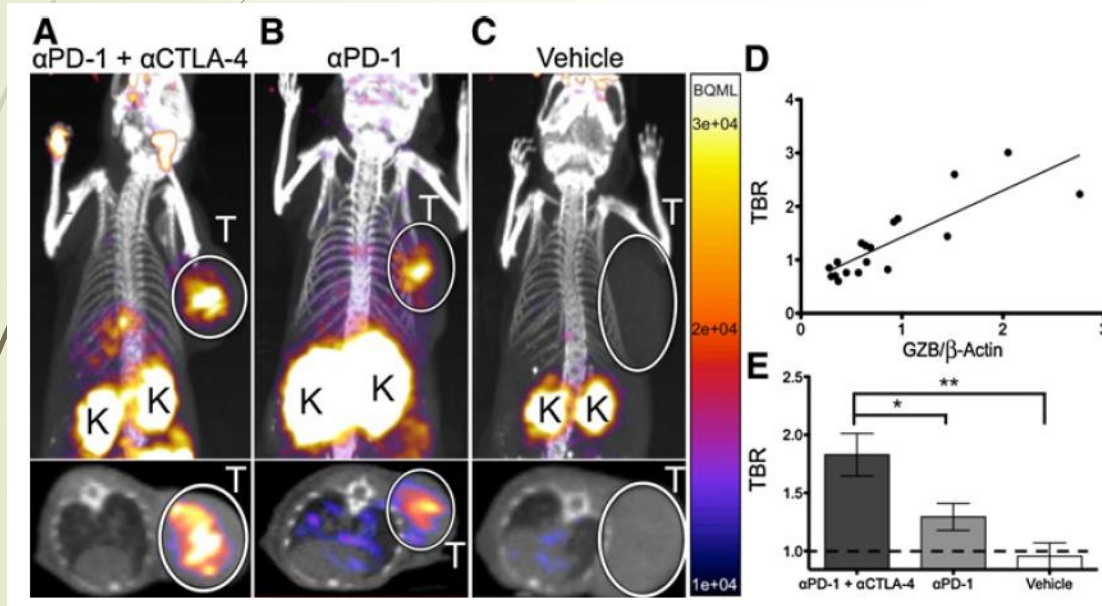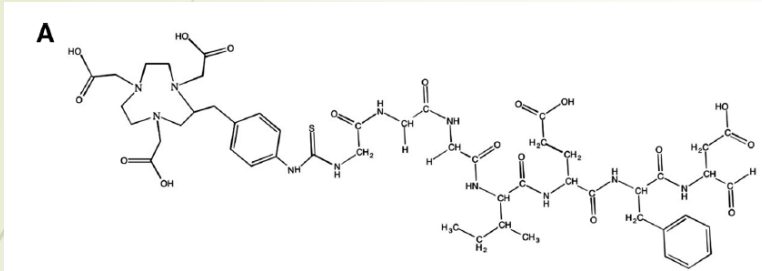→ Therapeutic response in the individual setting → **Endpoint**

Different types of therapies require different modeling endpoints

Bilusic & Gulley (2012). Cancer Immunol Immunother. 61:109–117

Tumor response to immune checkpoint inhibitors is associated with effector T cell levels and growth delay

Larimer et al. (2017) Cancer Res; 77(9):2318

Implications

1. PFS and DFS are the surrogate endpoints for cytotoxic therapy study. Metastatic models could be more relevant setting.

2. Growth delay is associated with levels of infiltrated effector T cells. Subcutaneous models therefore can be used in immunotherapy study.

3. Selection of models with similar therapeutic response in growth kinetics and endpoints is critical for the clinical relevance of the model.
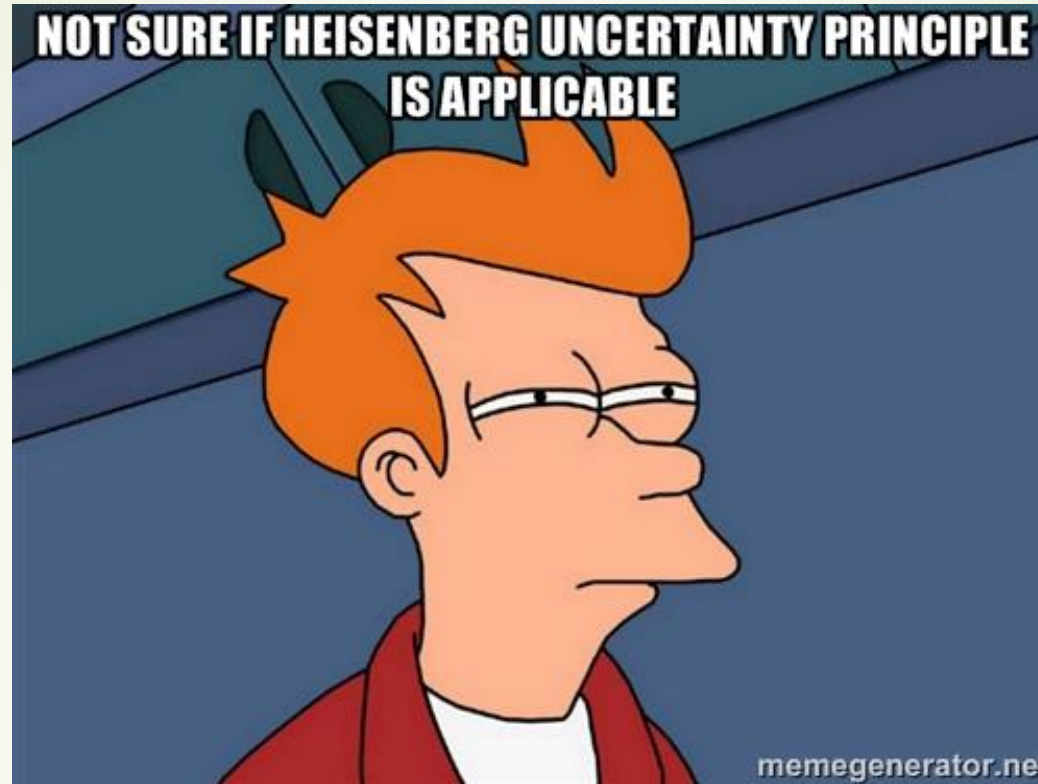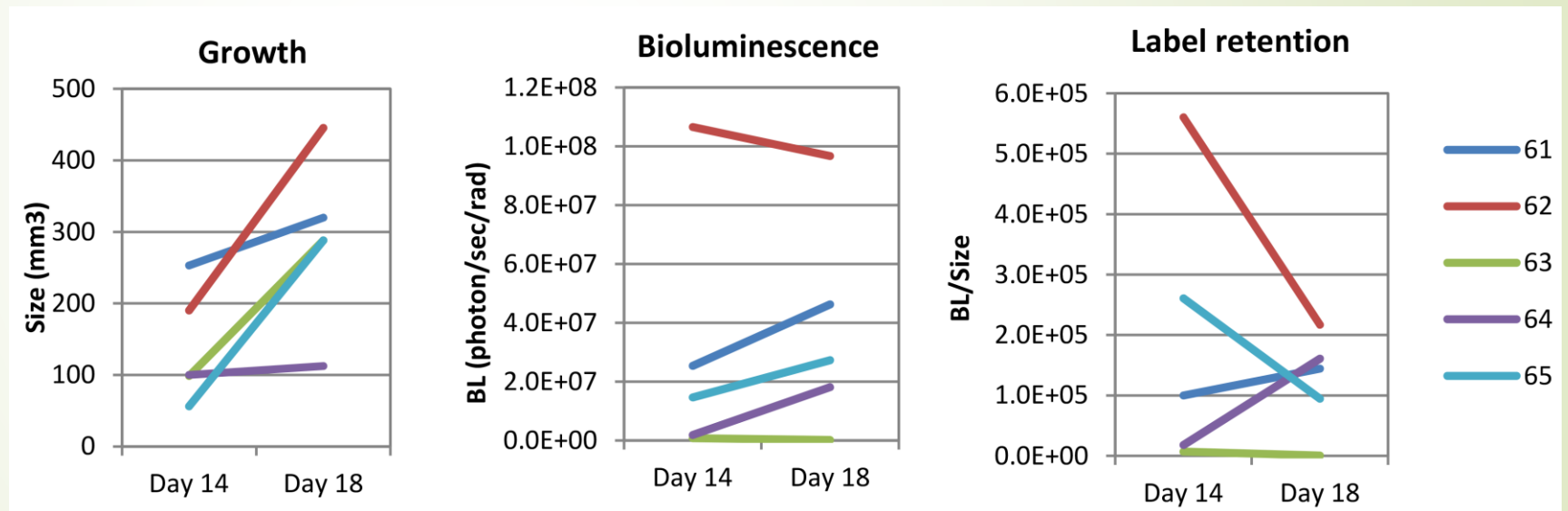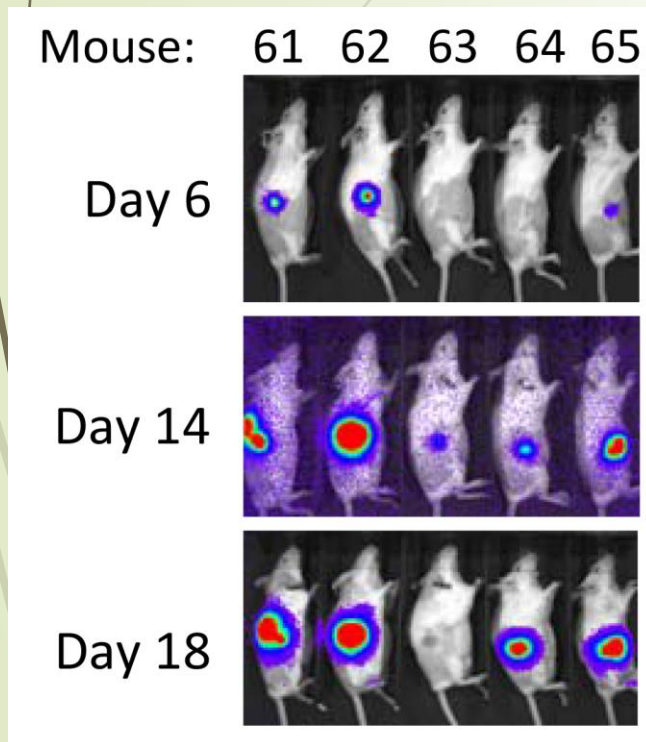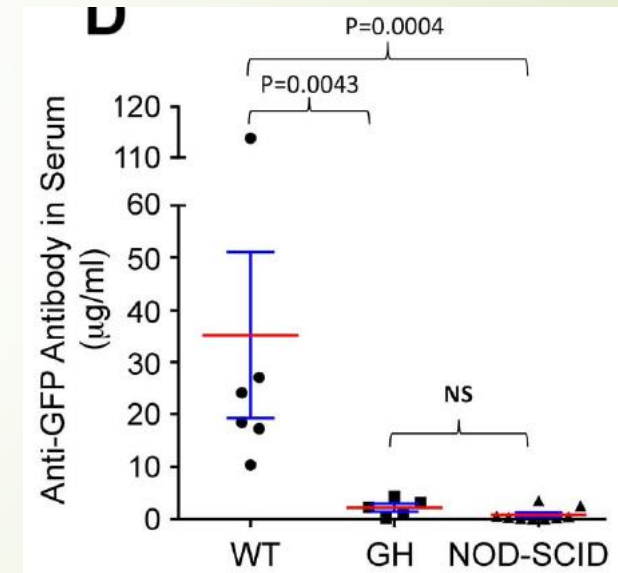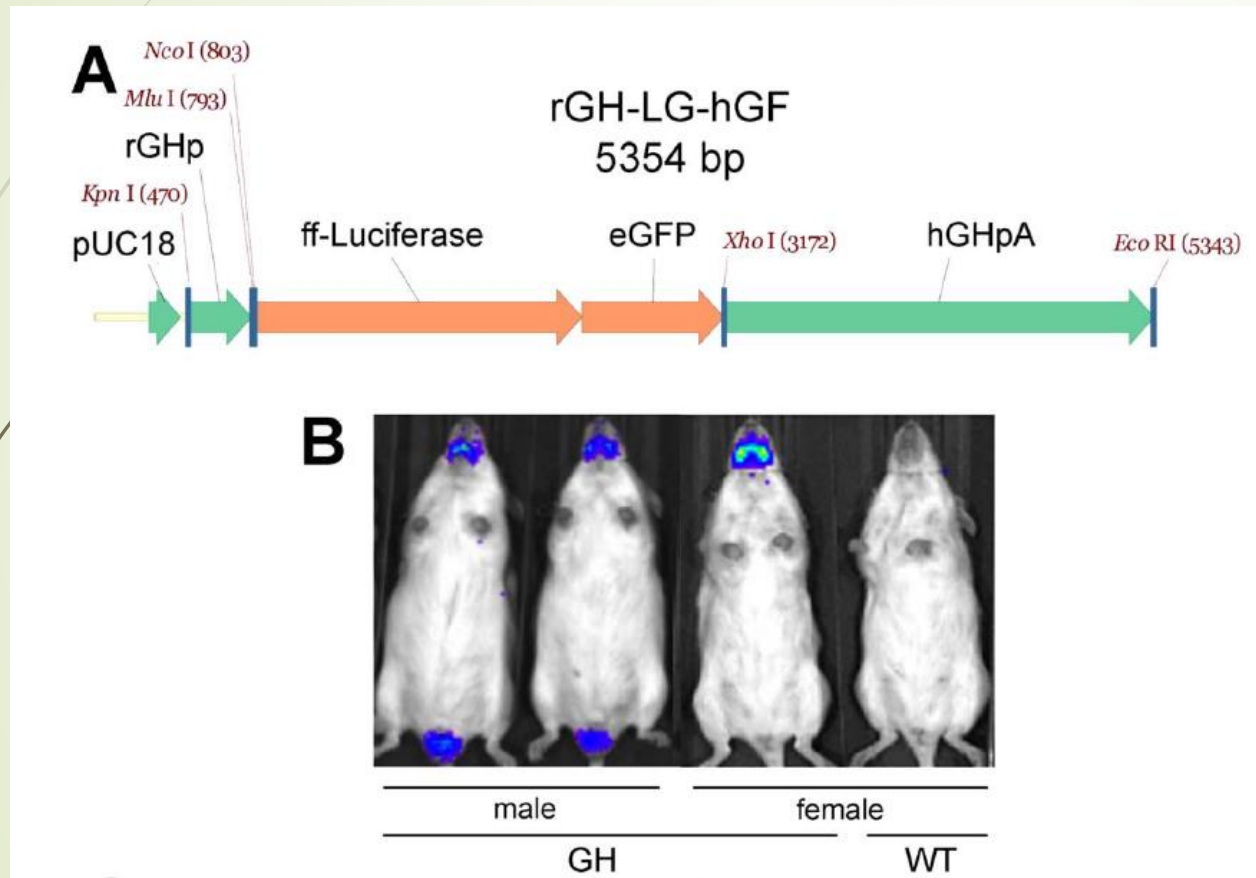
"Observer Effect"

measurements of certain systems cannot be made without affecting the system

Inconsistent growth and/or labeling maintenance in a syngeneic tumor model
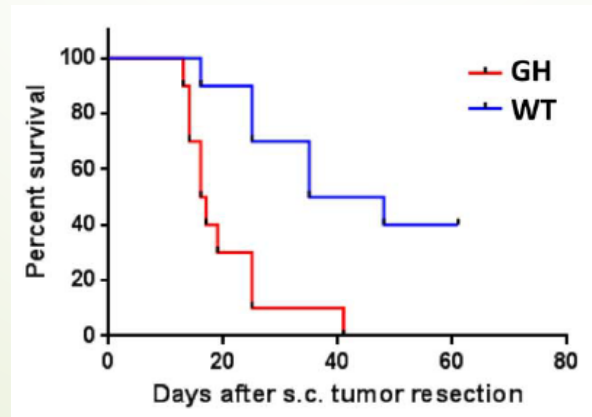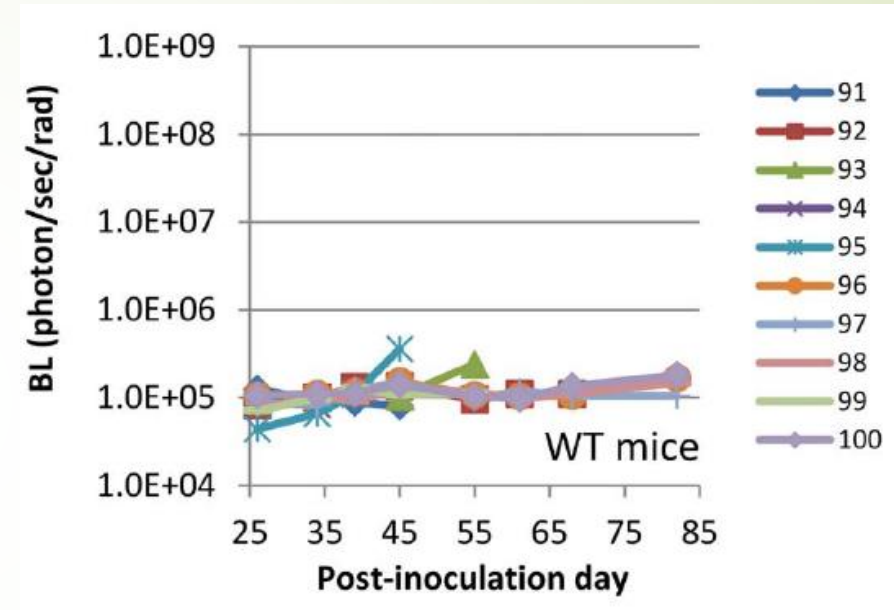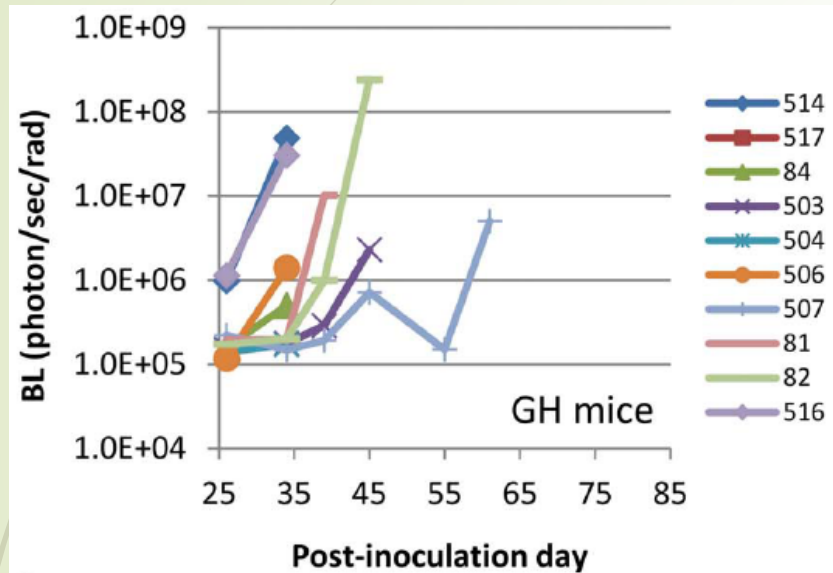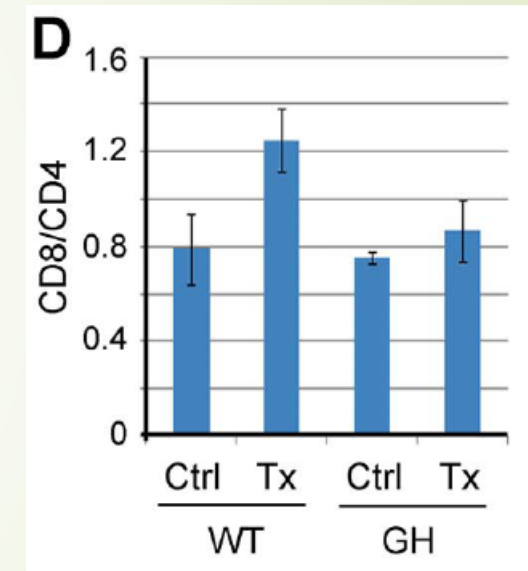

Day et al. (2014) PLoS ONE 9(11): e109956

Glowing head mice: GEM pre-tolerized with GFP and luciferase

Day et al. (2014) PLoS ONE 9(11): e109956
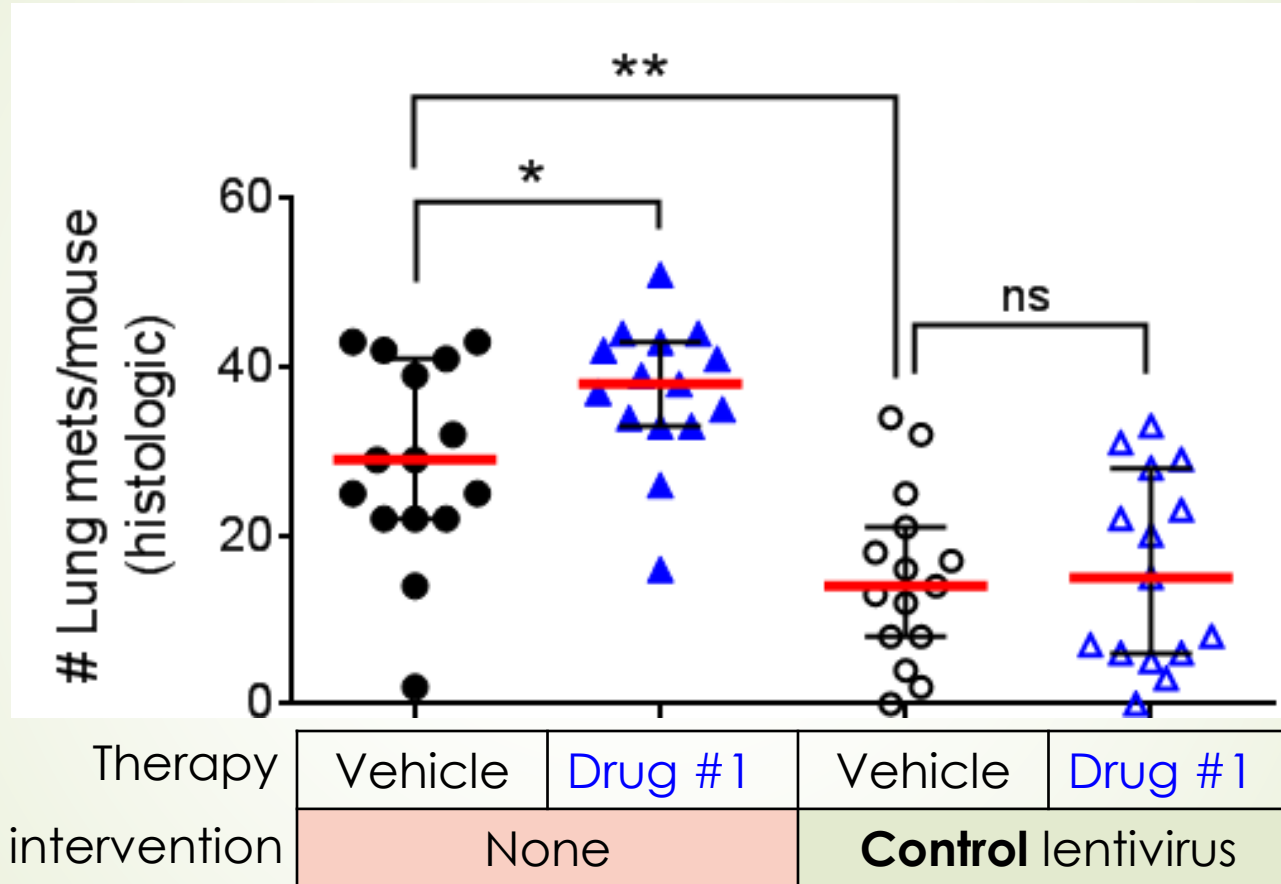
Antigenicity of labeling markers can alter disease progression

Antigenicity of labeling markers confounded study results by altering therapeutic response of the tumor
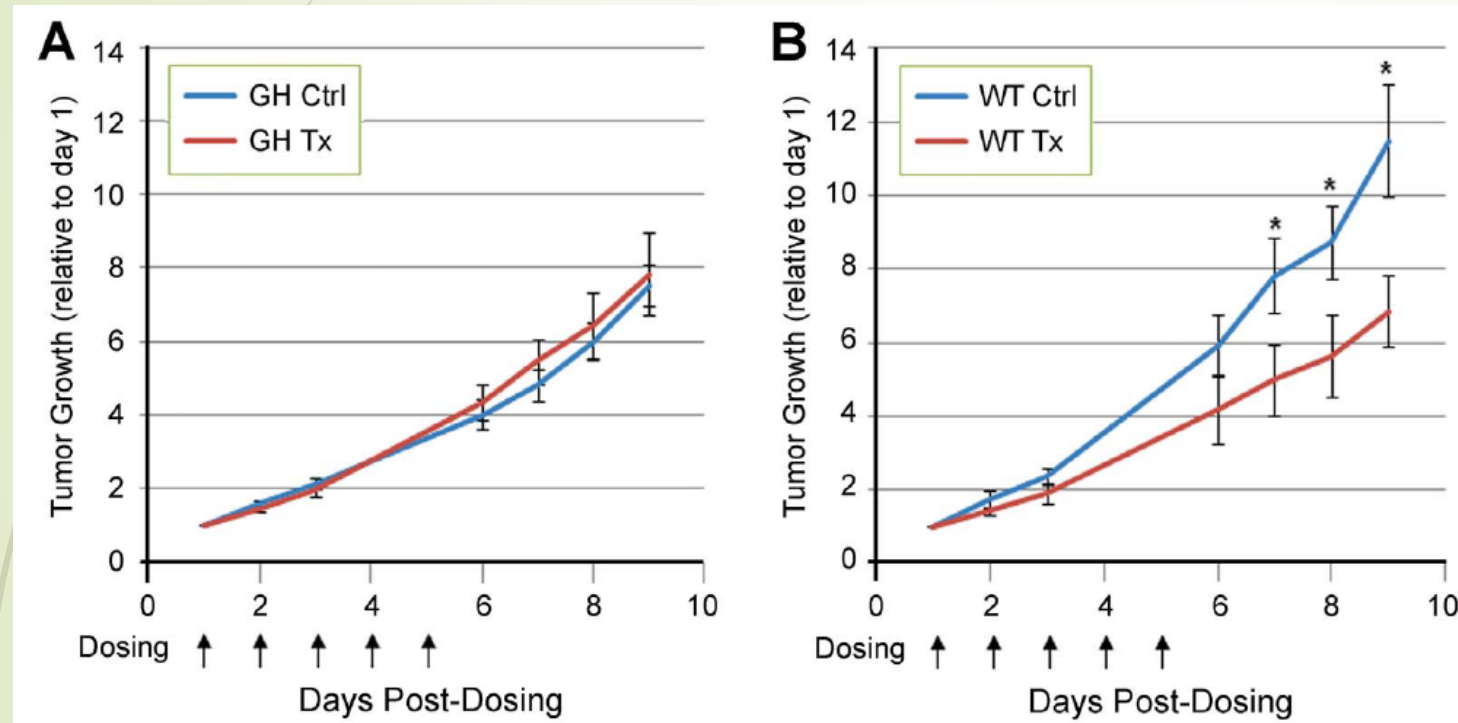
Gene integration of "control" vector can cause confounding effects

Transduction with **control** lentivirus suppresses metastasis and alters therapeutic response in the Mvt1 model

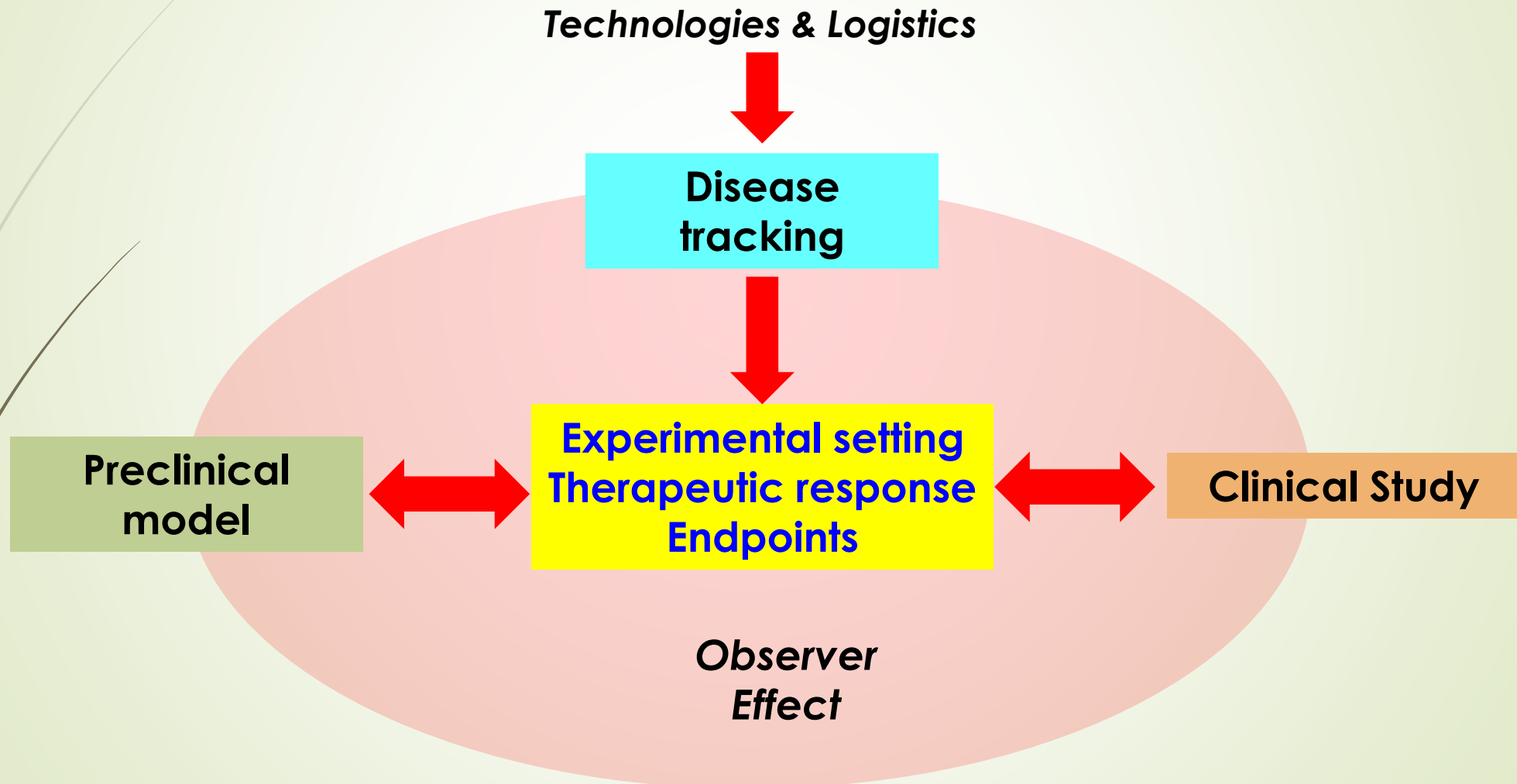Lalage Wakefield (LCBG, NCI)

Confounding effect from non-expressing gene integration: Independent of immune response

1. Effect seen with multiple independent control lentiviruses in multiple experiments.

2. Not an immune response to the lentivirus: Effect is also seen in **fully immunodeficient** (NSG) mouse hosts.

Lalage Wakefield (LCBG, NCI)

Relevance of Preclinical Models: Revisited

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