

Evaluation of PCSK9 Mutant Mice

- Energy Expenditure Was Unchanged
 - *Respiration and Locomotor Activities*
- Exercise Capacity Unchanged
 - *Treadmill with Indirect Calorimetry*
- Body Weight and Composition
 - *No Differences in Baseline Body Weights, Het Mice Had Small Resistance to Weight Gain and Adiposity on the Western Diet*
- Oral Glucose Tolerance Test (OGTT)
 - *No Differences in Glucose Excursion, Small Decrease in Baseline Glucose Following Western Diet*

Evaluation of PCSK9 Mutant Mice cont.

- Insulin Tolerance Test
 - *Small Increase in Insulin Resistance Among Het and KO Mice Compared to WT Mice*
- Diuretic-Induced Stress Test
 - *Micturition Behavior Altered in Het and KO Mice*
- Novel Object Recognition
 - *Trends Towards Improved Cognition*
- Improved Survival of Cultured Neurons
 - *Potential Increase in Survival With Lactacystin Treatment*

Conclusions: PCSK9 Y119X Phenotype

- Comprehensive phenotyping revealed few differences beyond expected, robust LDL/cholesterol phenotype;
 - Despite extensive analysis, few other differences, relatively low magnitude
 - No significant effect on insulin or glucose homeostasis was observed
- Battery of CNS/behavioral assays revealed only a modest neurological phenotype;
 - The subtle CNS phenotypes are intriguing given the initial suggestion of a role for PCSK9 function in neurodevelopment
 - The neuroprotective and behavioral effects do not suggest that PCSK9 is a strong target for pharmacological intervention for CNS related indications
- The highly specific phenotype of the PCSK9 Y119X mouse reinforces the validation of PCSK9 as a safe and effective drug discovery target for reducing LDL-C and CV disease.

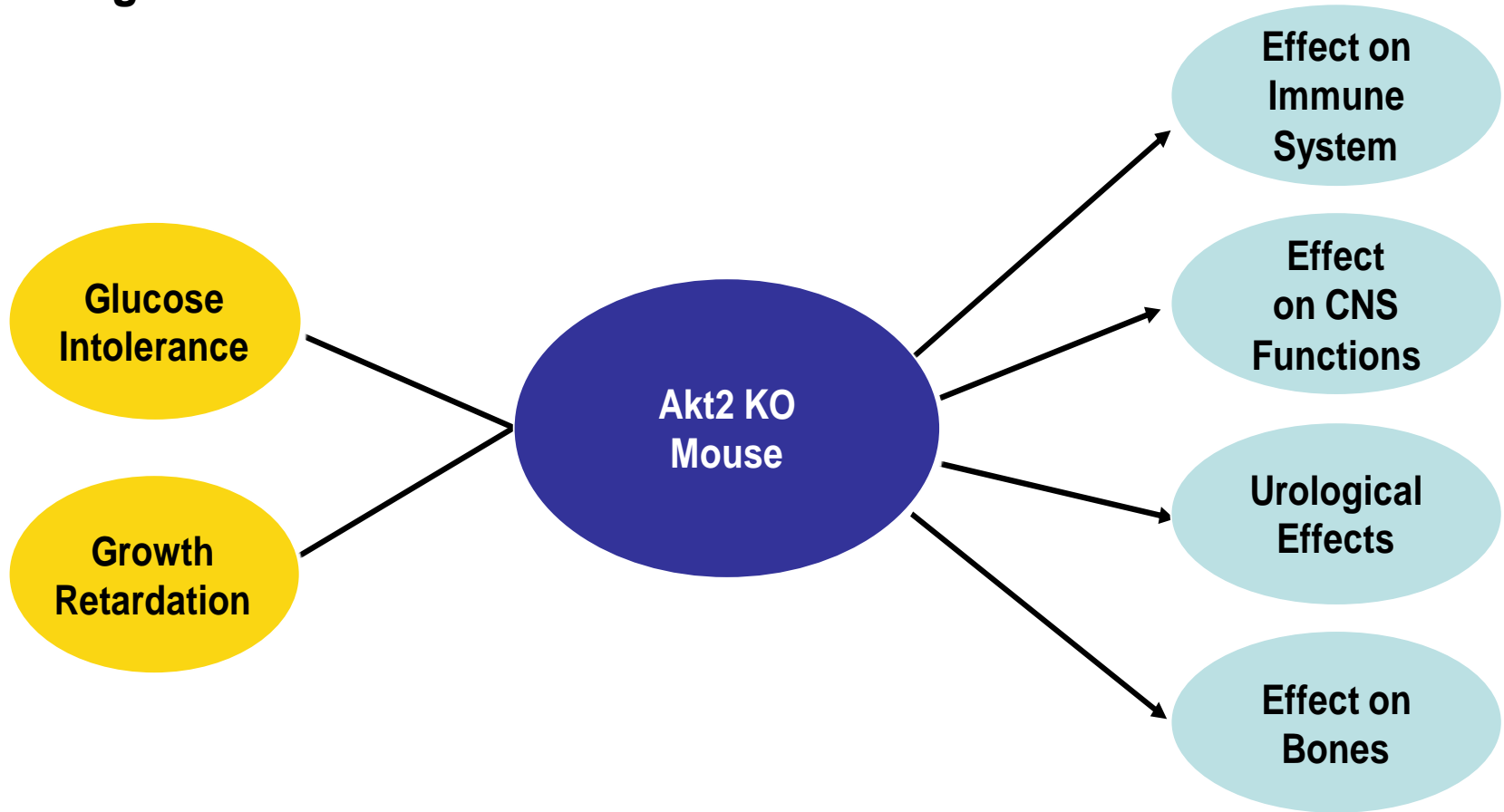
The Akt/PKB Gene Family

Gene Family Member	Expression Pattern	Reported KO Phenotype
Akt1 (PKB α)	High ubiquitous expression	Mild growth retardation and increased apoptosis
<i>Akt2 (PKBβ)</i>	High expression in insulin-responsive tissues	Insulin resistance and mild growth retardation
Akt3 (PKB γ)	Low levels except in brain and testes	No overt phenotype

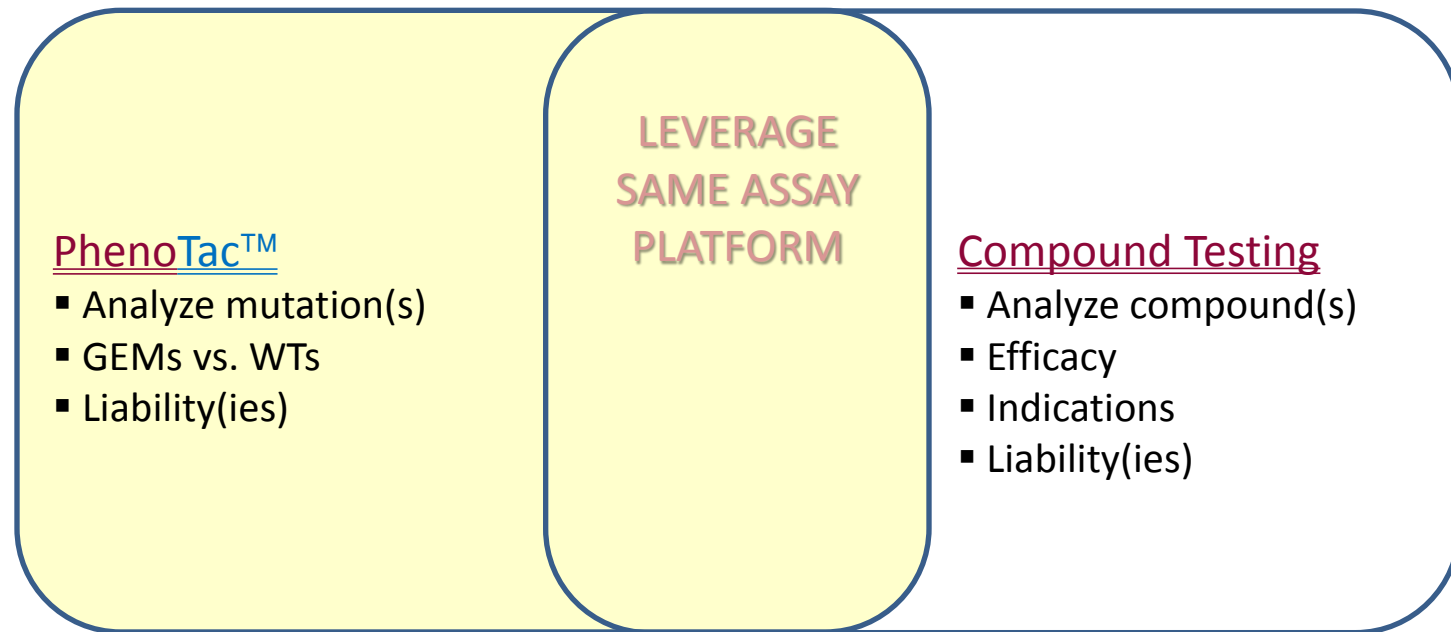
PROOF-OF-CONCEPT: *Akt2* KO Data

Previously reported
findings confirmed

New effects uncovered



PhenoTac™ Assays = Compound Testing Assays



Pain

Neuropathic Pain

Inflammatory Pain

Bone Cancer Related Pain

Autoimmune Disease

Multiple sclerosis

Rheumatoid Arthritis

Inflammatory Bowl Disease

Alzheimer Disease



Metabolism

Diabetes

Metabolic Syndrome

Obesity

Metastatic Cancer

Prostate

Ovarian

Breast

Pancreatic

Other

Lung Inflammation

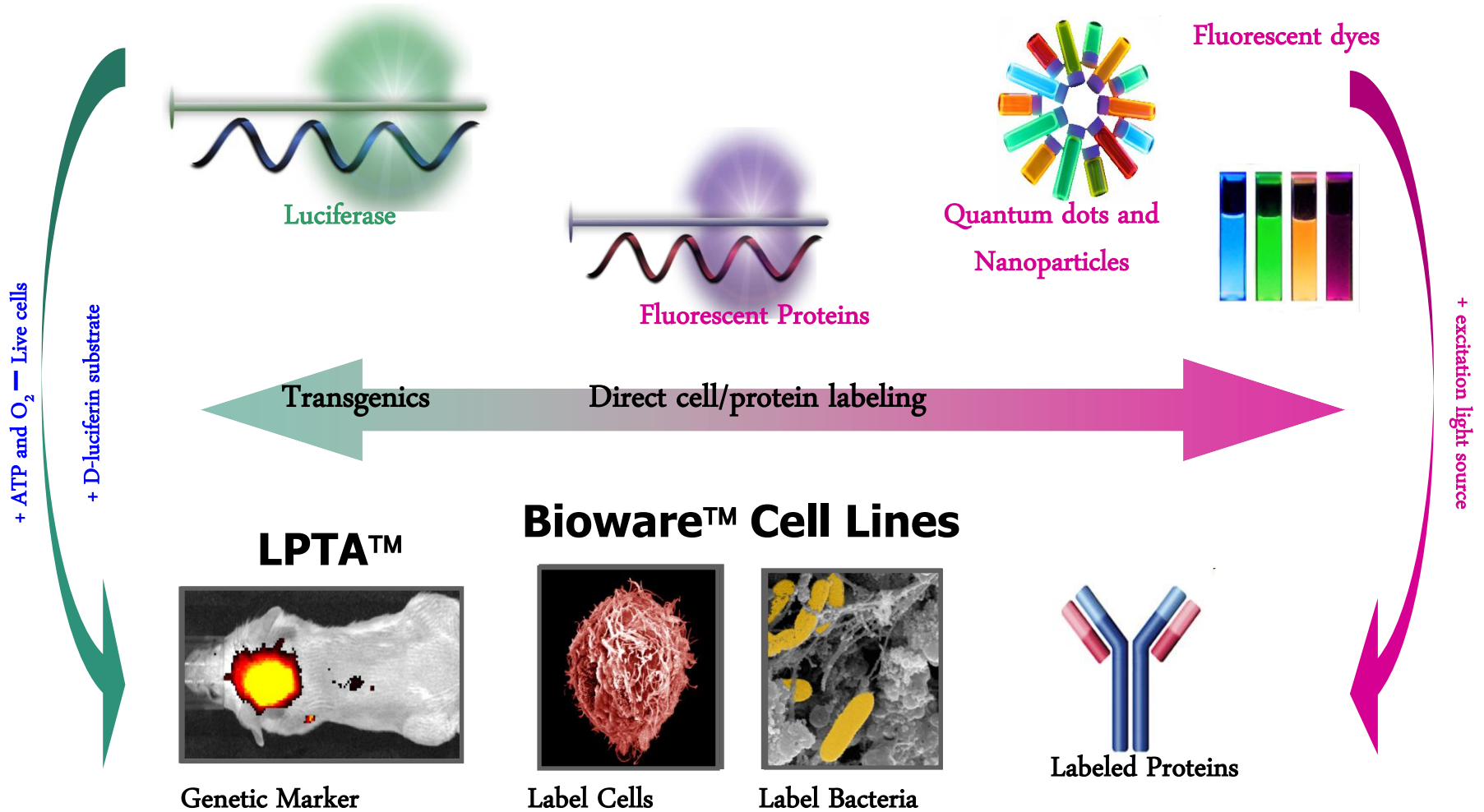
Asthma

Acute Lung Injury

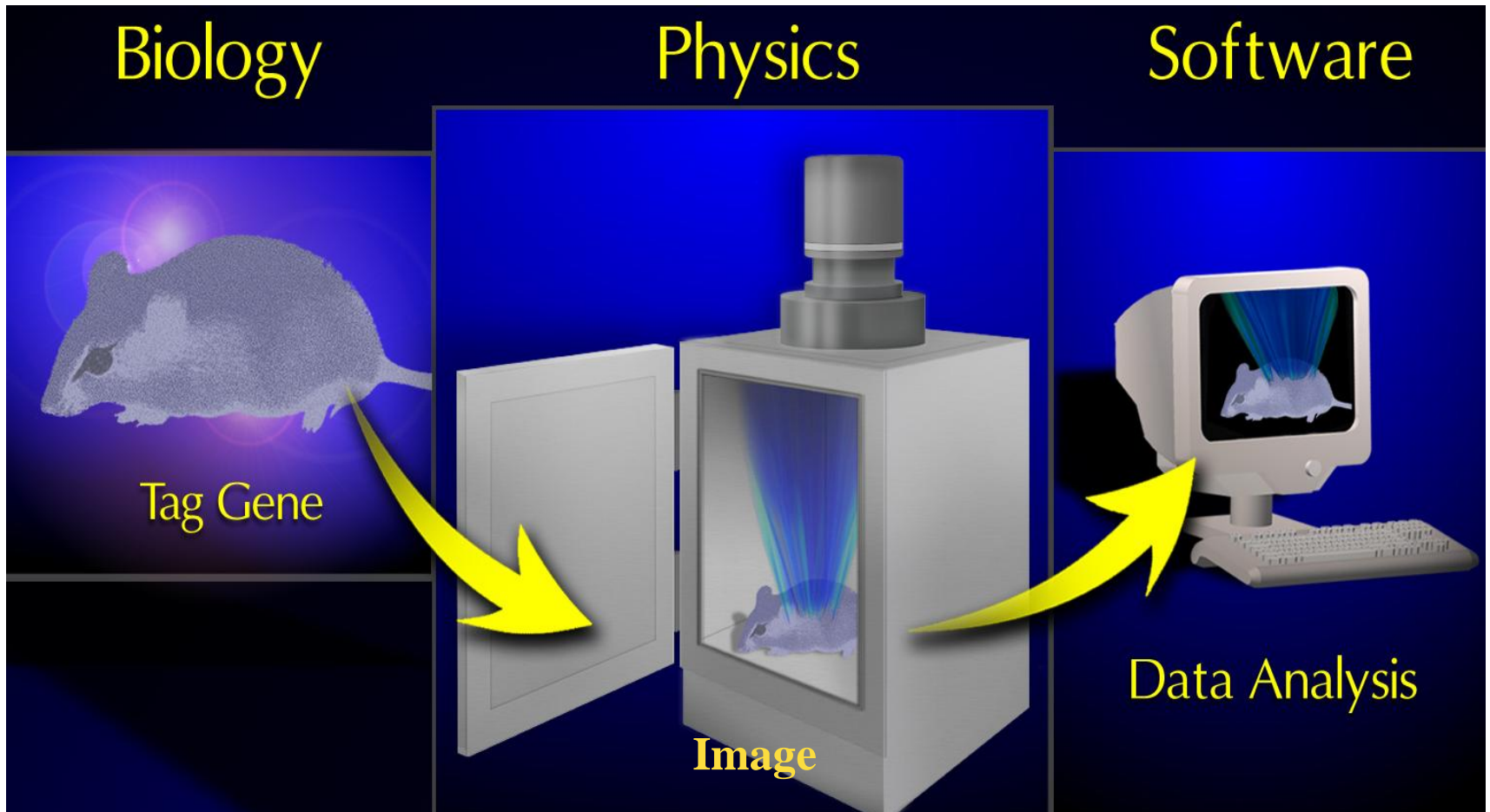
LPTA

Light Producing Transgenic Animal
Models

Imaging Basics: Reporter Molecules

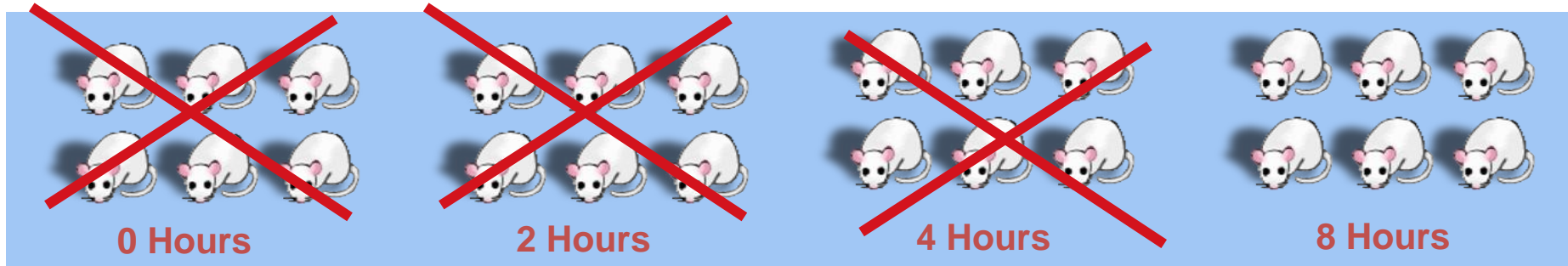


Integration with Biophotonic Imaging Assays

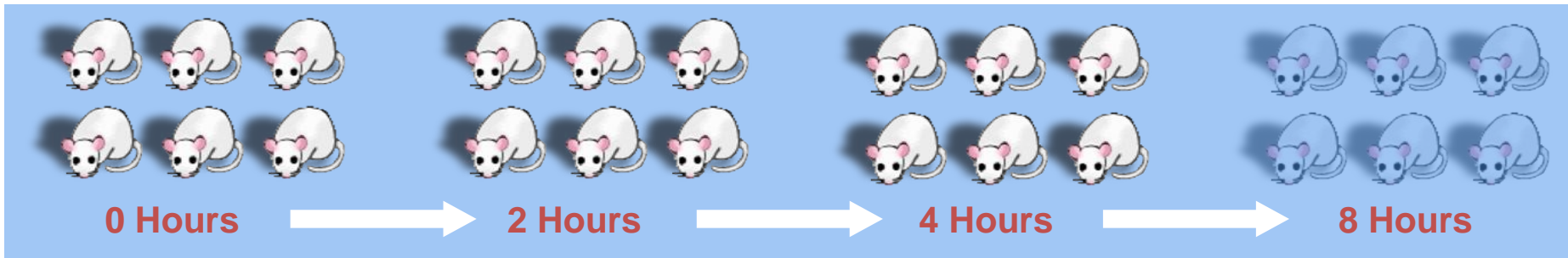


Biophotonic Imaging Methodology

Current Methodology = 24 animals over four treatment points



Imaging Methodology = the same 6 animals over four treatment points



Same group of anesthetized test animals at each time point of an experiment results in the use of far fewer animals than other methodology(ies).

Mouse Models of Multiple Sclerosis

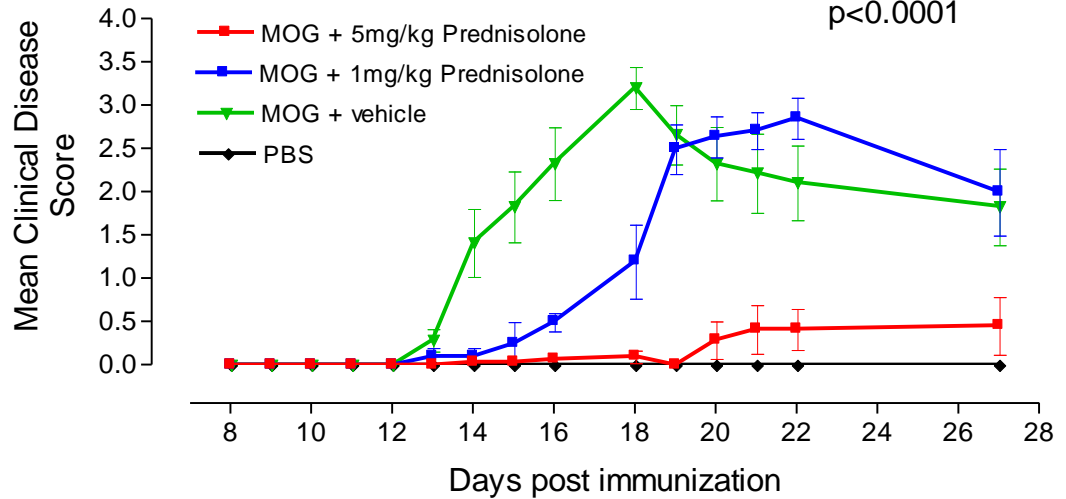
MOG₃₅₋₅₅ Induced-Experimental Autoimmune Encephalitis (EAE) in C57BL/6 Mice

MOG₃₅₋₅₅ Induced-Experimental Autoimmune Encephalitis (EAE) in GFAP-Luc Light Producing Tg Mice

MOG₃₅₋₅₅ Induced-Experimental Autoimmune Encephalitis (EAE)

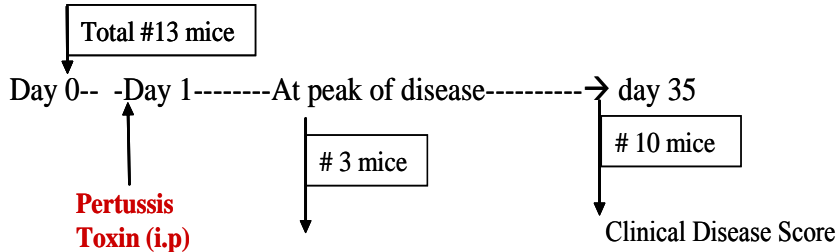
Modulation with Prednisolone

ANOVA
p<0.0001



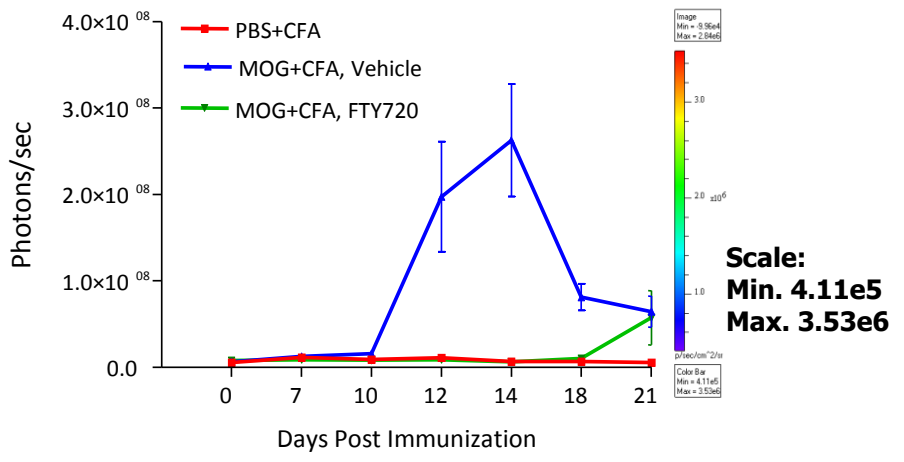
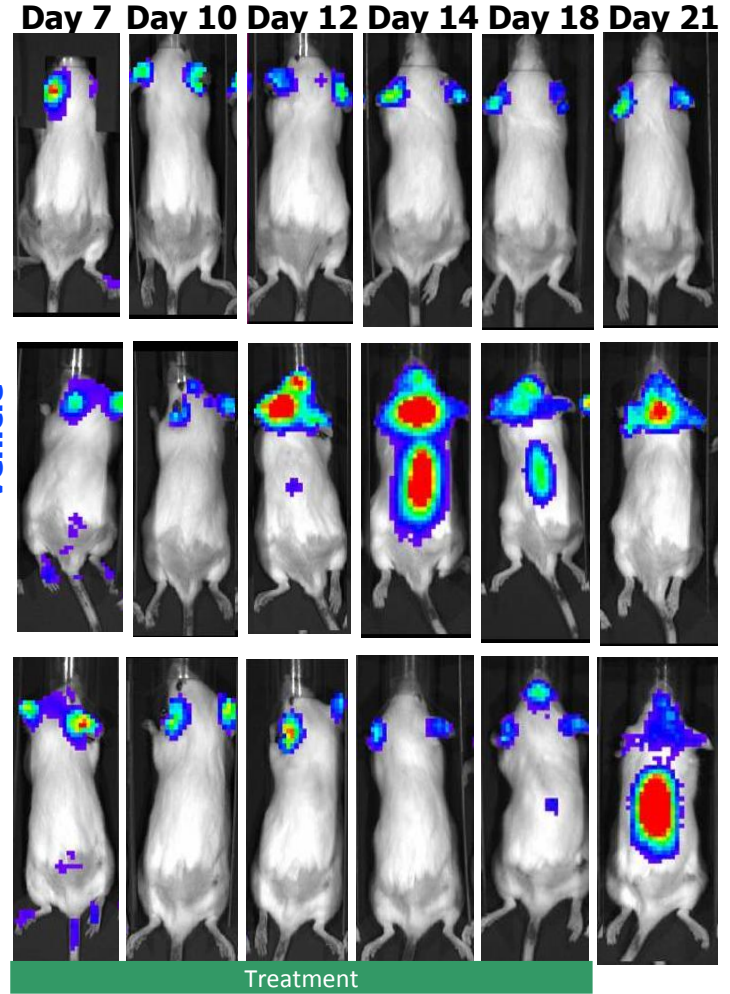
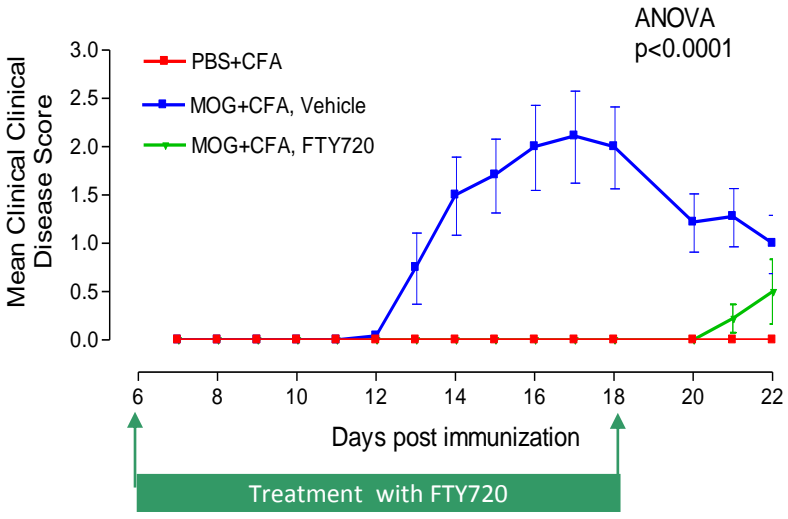
MOG₃₅₋₅₅ + CFA
s.c immunization

C57/Black6J



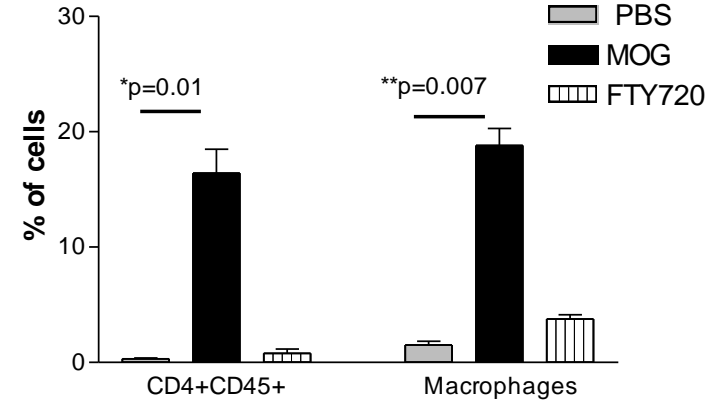
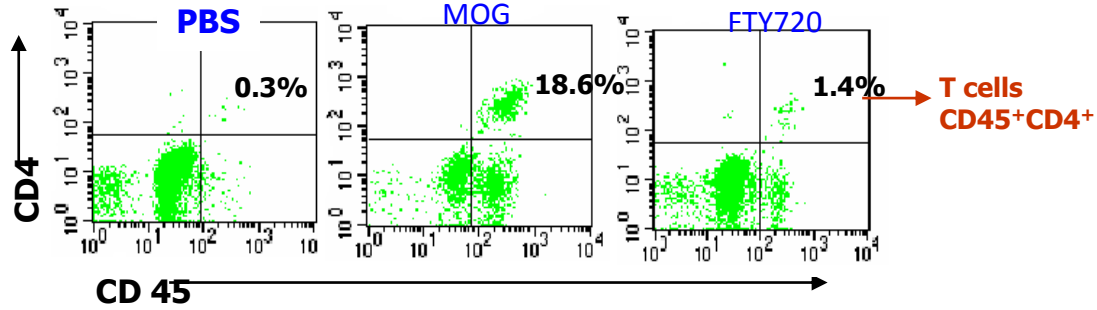
Bonferroni's post hoc test: Group1 significantly different from Group 3 (p<0.0001)
Group2 significantly different from Group 3 (p<0.0001)

GFAP-Luc Expression in the EAE Model

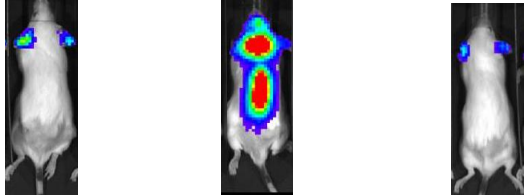
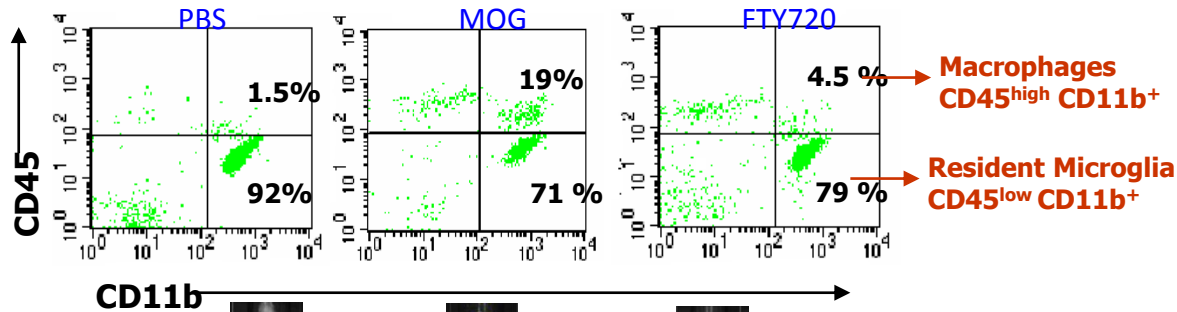


FACS Analysis of Spinal Cord Infiltrates in the EAE Model

A) Infiltrated CD4⁺ T cells



B) Infiltrated macrophages, CD45^{high} CD11b⁺

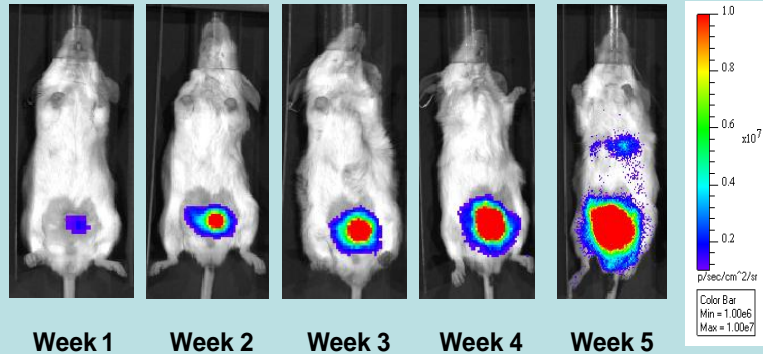


Oncology Program

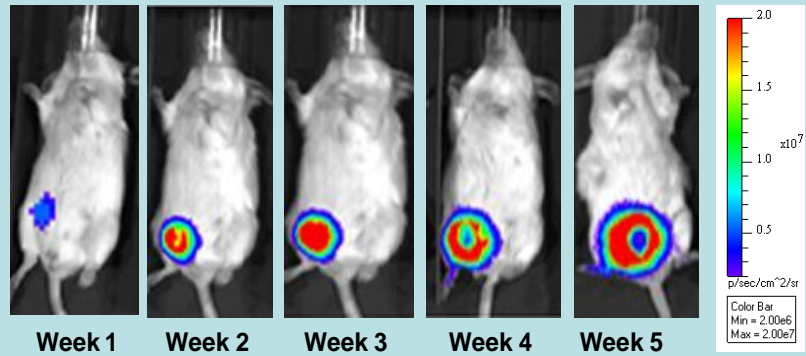
Taconic's Orthotopic and Metastatic Tumor Xenograft Models Utilizing Biophotonic Imaging

Tumor Growth by Biophotonic Imaging

Orthotopic PC-3M-luc Prostate Tumor Growth Kinetics



Orthotopic MDA-231-luc Breast Tumor Growth Kinetics



Orthotopic SKOV3-luc Ovarian Tumor Growth Kinetics

