Frederick National Laboratory
for Cancer Research

Center for Advanced Preclinical Research

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CAPR Center for Advanced Preclinical Research

The Frederick National Laboratory is a federally funded research and development center operated by SAIC-Frederick, Inc., for the National Cancer Institute
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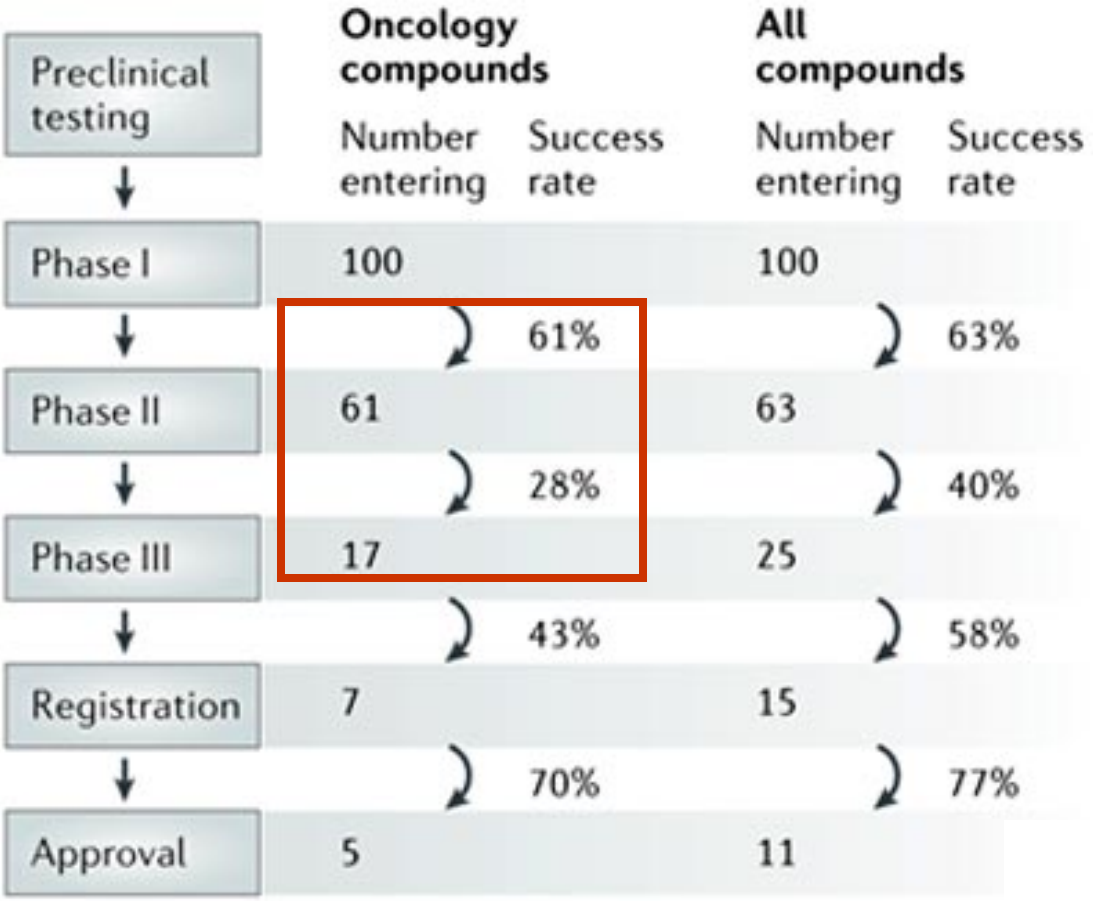
Current Cancer Drug Development



	Oncology compounds		All compounds	
Preclinical testing	Number entering	Success rate	Number entering	Success rate
↓				
Phase I	100		100	
		61%		63%
Phase II	61		63	
		28%		40%
Phase III	17		25	
		43%		58%
Registration	7		15	
		70%		77%
Approval	5		11	

adapted from: Sharpless and DePinho; Nature Reviews Drug Discovery '06

Emerging Strategies in Cancer Modeling

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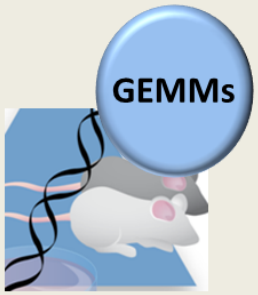
+	PATIENTS are *THE* target for care
-	disease complexity access to tissue limited experimental variables cost limited patient resource

+	patient-derived tumors experimental replicates
-	lacks immunobiology mouse stroma bypasses initiation/progression change possible



+	initiation to progression pathway-specific engineering intact immune system experimental replicates
-	not human complex experimental systems biology often not relevant to disease

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CAPR Mission

Frederick National Laboratory for Cancer Research

Develop strategies for effective preclinical evaluation in *genetically and biologically engineered murine cancer models*

AND to facilitate routine application in clinical research for *optimal* outcomes in cancer patient management.

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Integration with FNLCR Core Facilities

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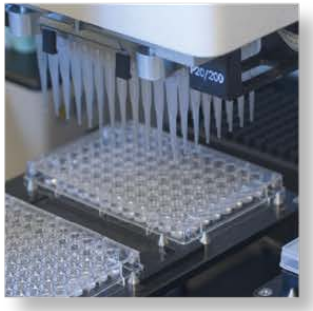
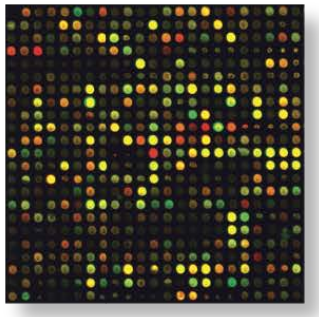
Laboratory of Molecular Technology
Genotyping

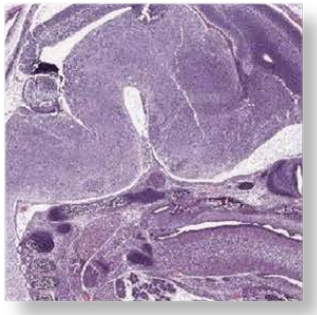


Laboratory of Molecular Technology
Microarray Analysis

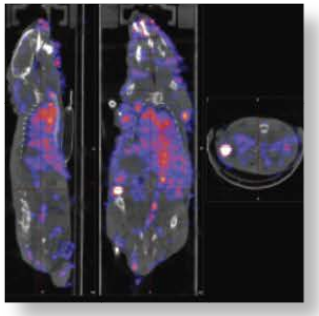


Laboratory Animal Sciences Program
Animal Resources

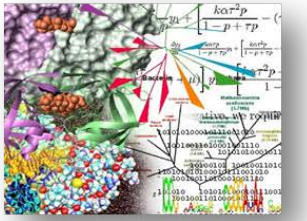
Laboratory Animal Sciences Program
Pathology/Histotechnology



Laboratory Animal Sciences Program
Small Animal Imaging



Advanced Biocomputing Center
Bioinformatics Analysis



CPR Center for Advanced Preclinical Research

CAPR Processes

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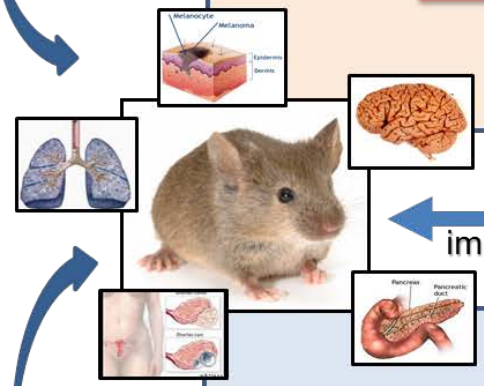
Model Retooling

Tumor-derived primary cells

- Potency Assays
- Molecular Profiling
- Combinatorial Therapies
- Derivation of Reprogrammed Cell Models
- In Vitro PD Assays
- Pathway Analysis
- Mechanisms of Resistance (in vitro)



Model improvement

Integrated Analysis:

- Efficacy assessment data
- Disease endpoints/biomarkers
- Collections of reagents
- Preclinical arena development

Clinical Data

- PK/PD Studies
- Drug Efficacy Evaluation: Imaging
- Mechanisms of Resistance (in vivo)
- Molecular Profiling of Blood/Tissue
- Drug Efficacy Evaluation: Histology/Pathology
- Drug Efficacy Evaluation: Biomarkers
- Biobanking of Tissues and Fluids

Mice with tumor burden

Resource-Effective Preclinical Development

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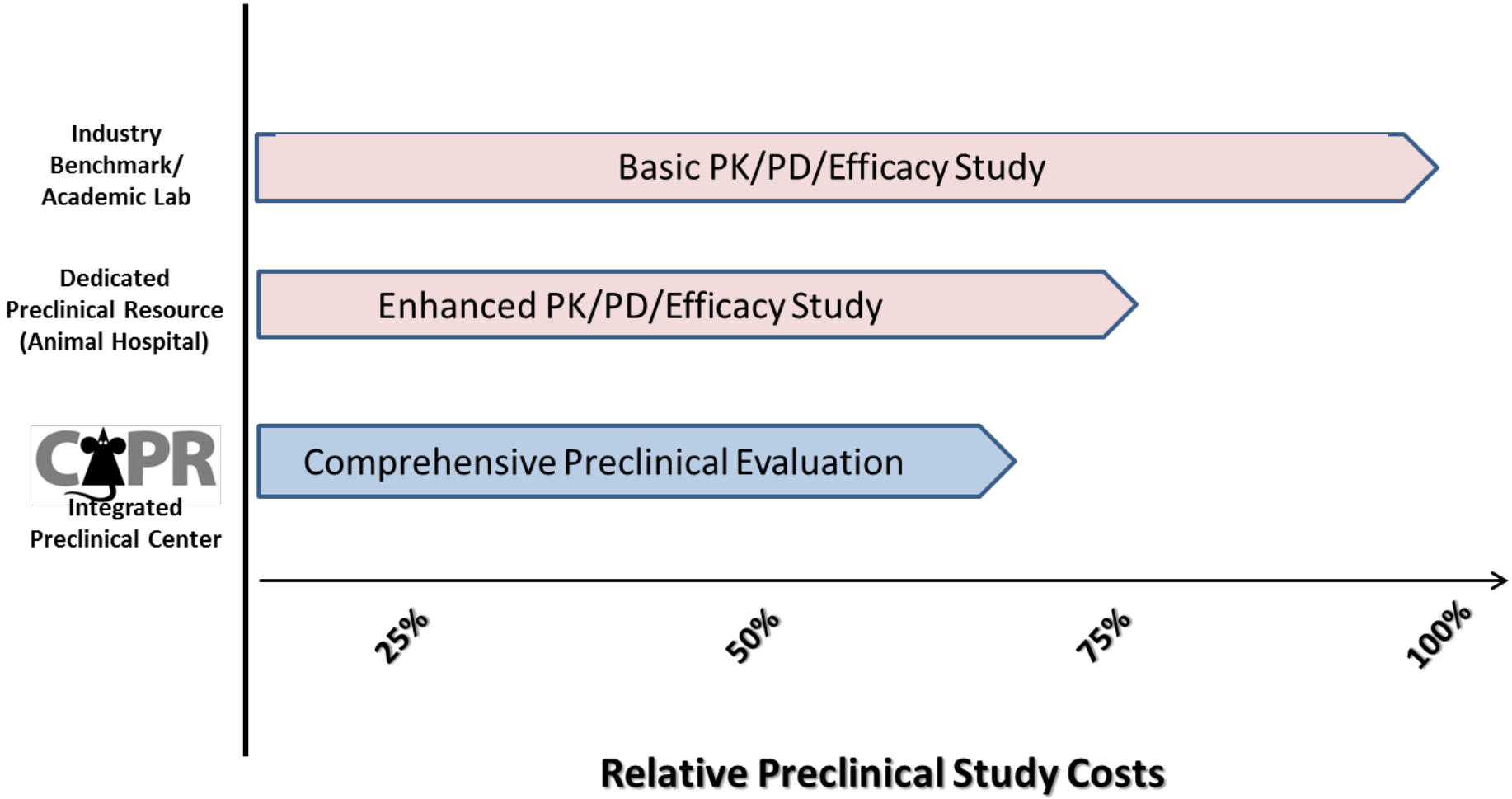

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CAPR Portfolio of Preclinical Models

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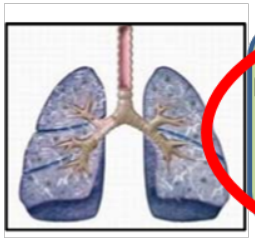
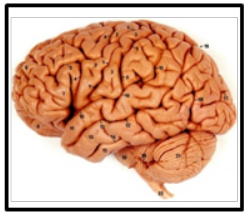
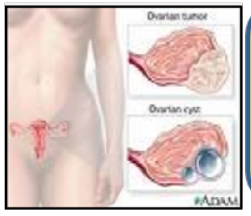
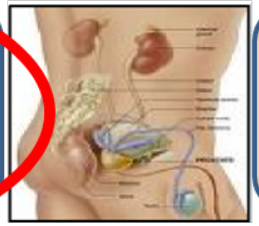
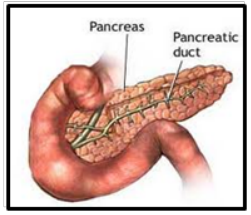
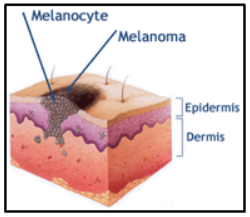
Models in Therapeutic/Biomarker Evaluation

Model Type	Genetic Events Induction Mode
 Non-Small Cell Lung Cancer: ➢ Lung Adernocarcinoma ➢ Squamous Cell Carcinoma	➢ EGFR-L858R ➢ EGFR-L858R/T790M ➢ Lkb1/Kras ➢ Doxycycline ➢ Adeno-Cre/Lenti-Cre
 ➢ Anaplastic Astrocytoma III ➢ Glioblastoma	➢ pRb/Kras/PTEN ➢ Tamoxifen/Adeno-Cre ➢ Orthotopic
 ➢ Serous Ovarian Carcinoma	➢ pRb/p53/Brca1/Brca2 ➢ Tamoxifen/Adeno-Cre ➢ Orthotopic

Models in Characterization

Model Type	Genetic Events Induction Mode
 ➢ Prostate Carcinoma	➢ pRb/PTEN ➢ Tamoxifen
 ➢ Small Cell Lung Cancer	➢ pRb/p53 ➢ Lenti-Cre
 ➢ Pancreatic Adenocarcinoma	➢ p53/Kras ➢ *de novo*
 ➢ Melanoma	➢ BRAF-V600E ➢ HGF/SF ➢ UV ➢ Tamoxifen

Erlotinib-Resistant huEGFR T790M-L858R Driven NSCLC

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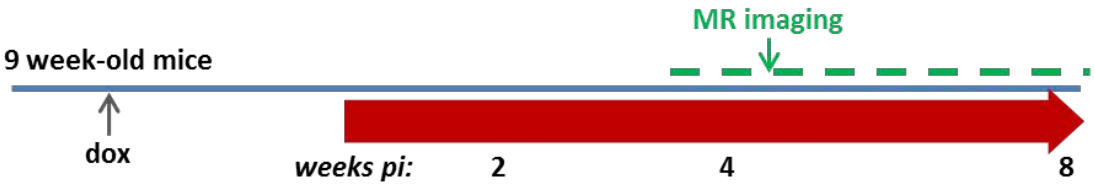
Inducible event:

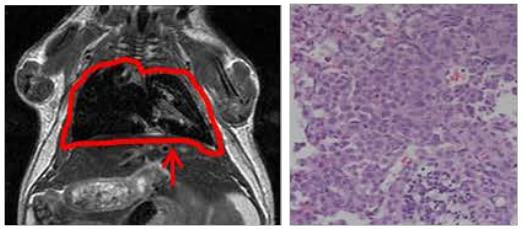
*EGFR T790M-L858R

*via Tg*CCSP-rtTA and Tet-op (EGFR TL)

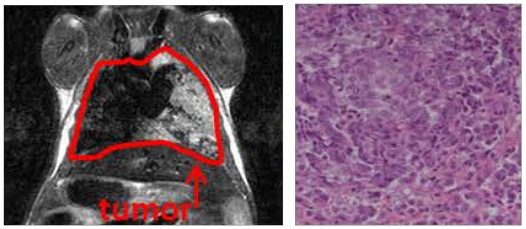
De novo model: induction by dox feed

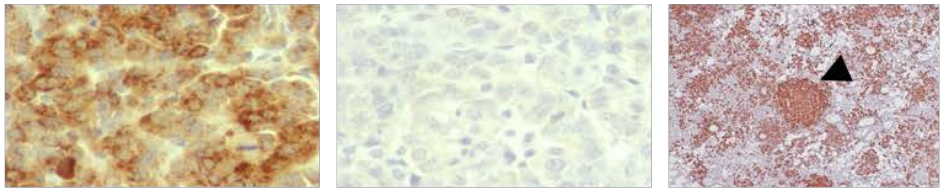


2 wks post-induction: adenoma



6 to 8 wks post-induction: adenocarcinoma





SPC **C10** **EGFR**

**Collaborator: Kwok-Kin Wong, DFCI*

CAPR Veterinary Pathology Scoring System: Lung

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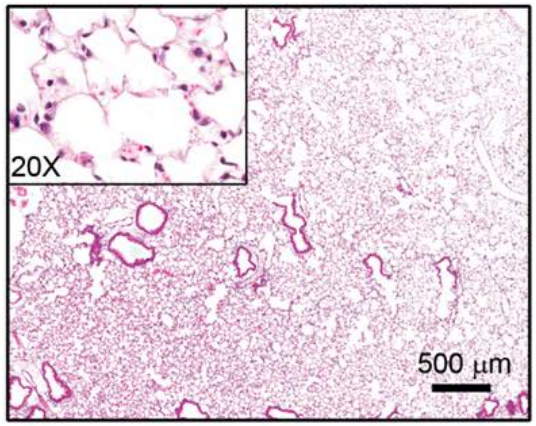
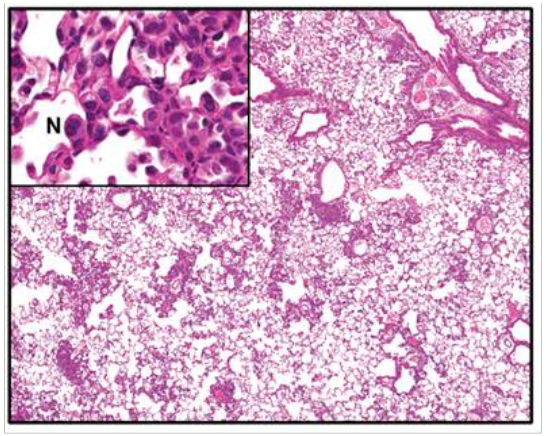
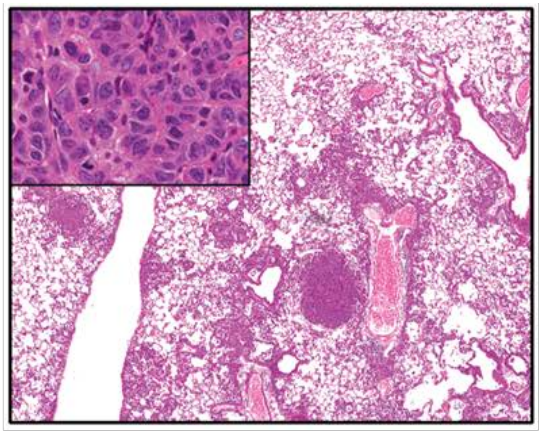


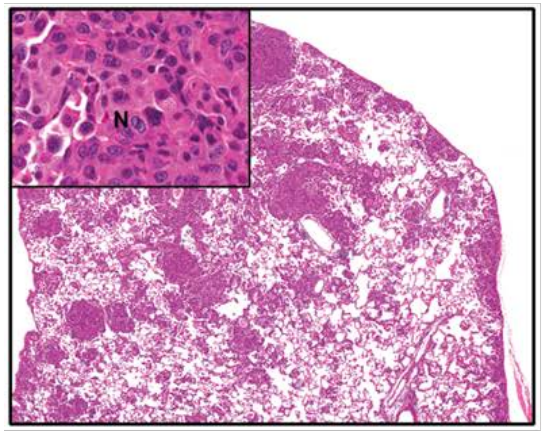
0=No Lesions



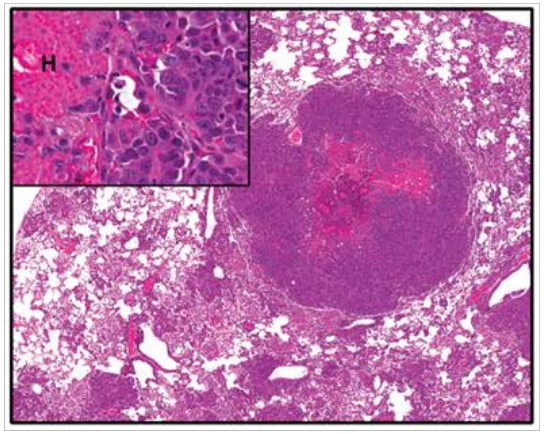
1=Minimal



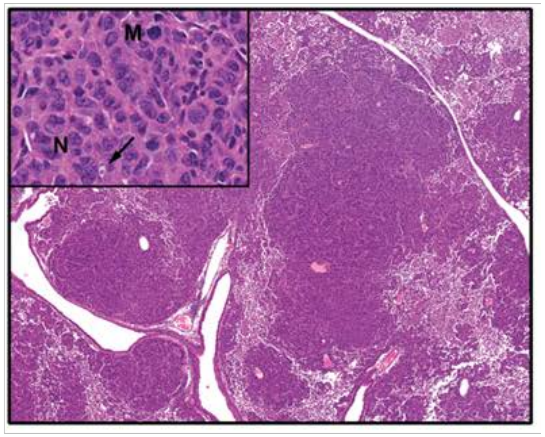
2=Mild



3=Moderate



4=Severe



5=Most Severe

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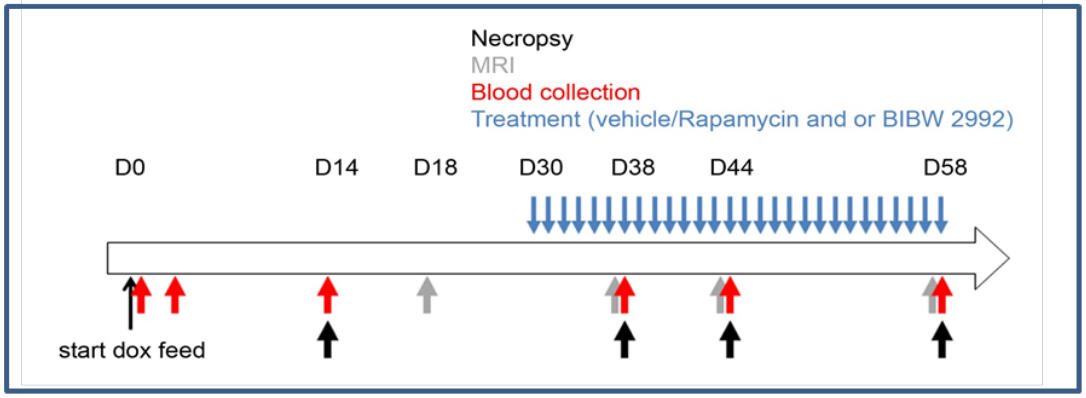
Integrated Treatment Response Study in NSCLC Model: Summary



- treatment for 1 week, 2 weeks or 4 weeks/concurrent blood and tissue biomarker study
- 160 mice in drug treatment study (including add'l PK/PD); 46 mice assessed for tumor induction

❖Unbiased histopathology scoring by a veterinary pathologist
❖Quantitative IHC with proliferation markers using an automated counting system
❖Quantitative imaging (MRI) analysis
❖Evaluation of drug levels and drug target response in blood and lung (PK/PD)
❖Temporal assessment of lung tumorigenesis (transcription)
❖Temporal assessment of lung tumorigenesis (metabolites)
❖Molecular (transcriptional/metabolic) response to drug treatment at 3 time points during efficacy evaluation
❖Integrated gene expression and metabolic pathway profiling; potential tumor progression and treatment response biomarkers, therapy-induced feedback loops

MRI and Pathology Confirmation of Drug Treatment Response

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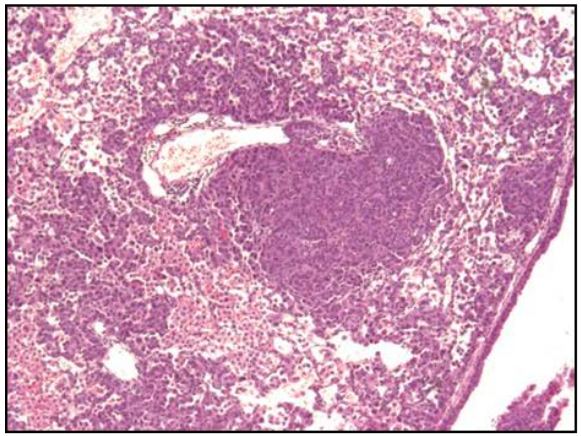
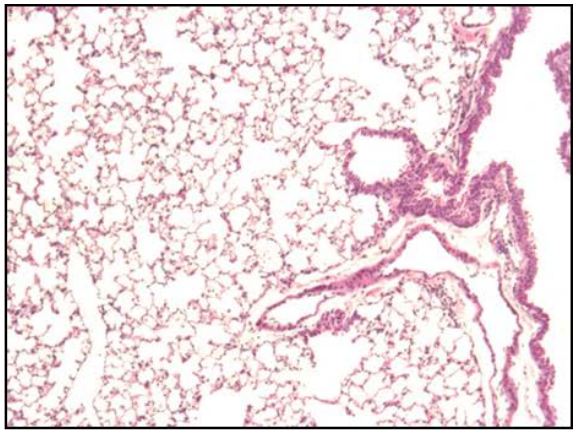
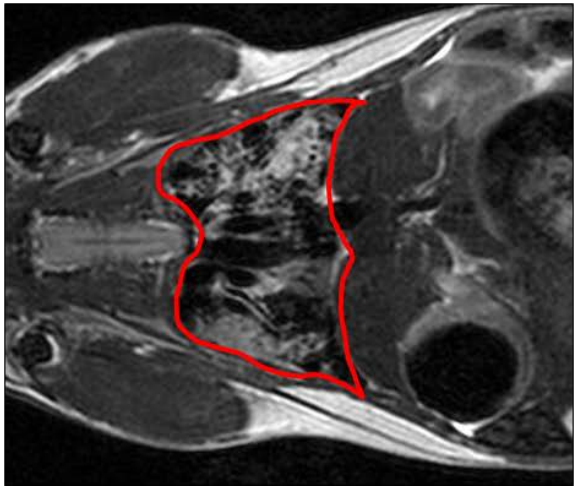


Post-treatment histology: minimal to no remaining lesions

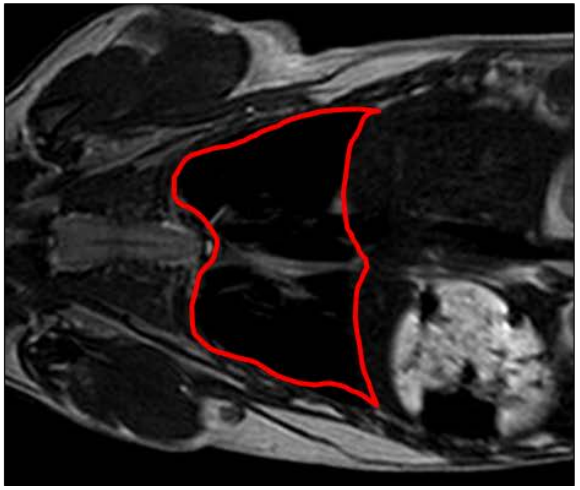


Pre-treatment



MRI scans: Regression of diffuse masses

BIBW2992+Rapamycin (4 weeks treatment)



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*i*GXT Platform™

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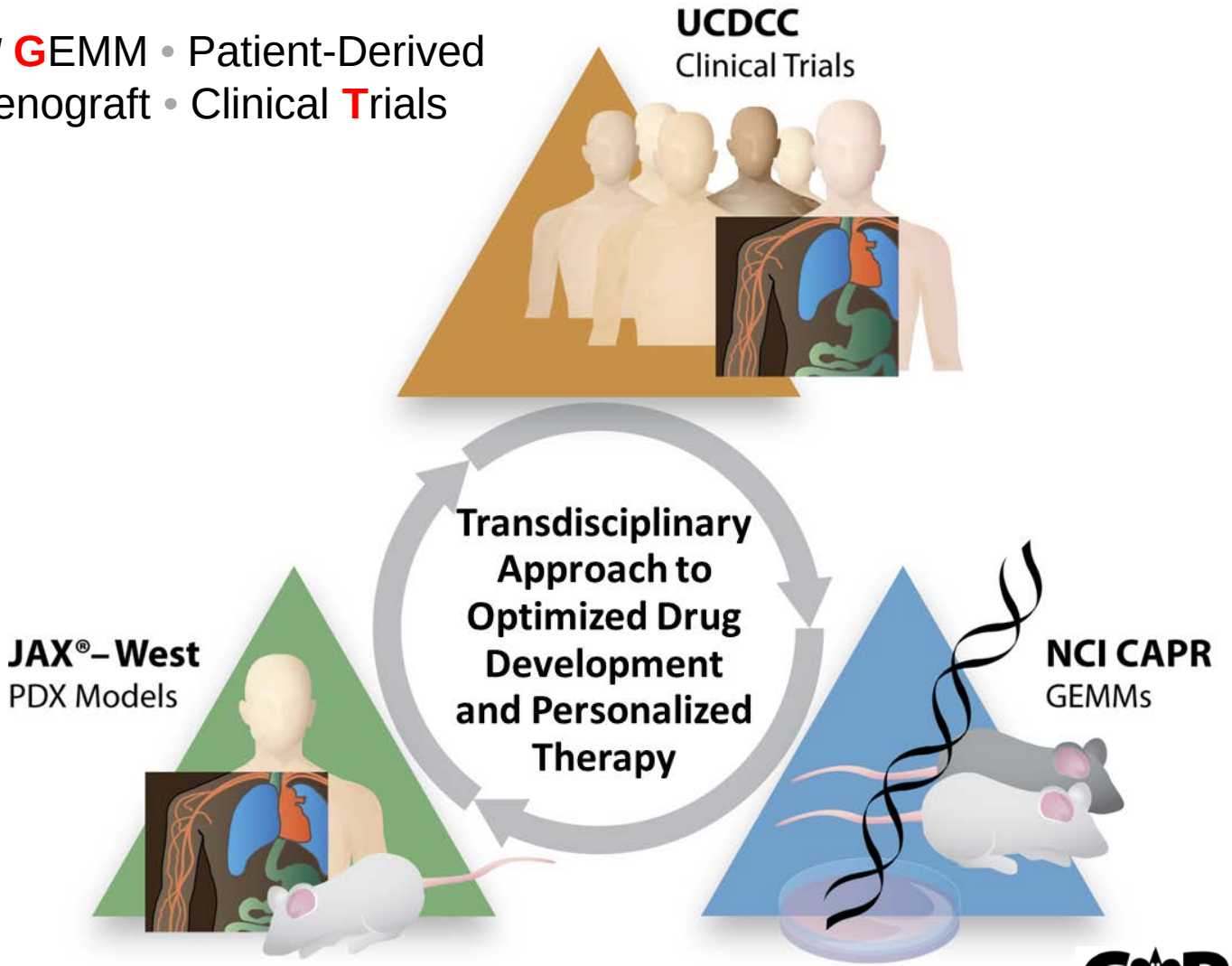
integrated **G**EMM • Patient-Derived Tumor **X**enograft • Clinical **T**rials



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Optimal Preclinical Guidance via Cross-Model/Cross-Species Unbiased Evaluation

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disease appropriate, pathway-specific GEMs/GDAs

Patient-derived xenografts (PDXs)

Consenting, therapy-eligible patient with core biopsy

Patient (therapy-naïve)

therapeutic

Patient –therapy resistant (prior response, now PD)

Patient therapy-refractory

Standard of care (SOC)

AND

SOC+ drug A

AND

SOC+ drug B

AND

Drug A + drug B

SOC

OR

SOC + drug A

OR

SOC + drug B

distinct target and therapy

Combined Systems Biology Analyses biomarkers/drug responses

Questions

Answers