

Molecule-Targeted Immune Modulation: Current Summary

Antibody-based modulation of tumor immunity

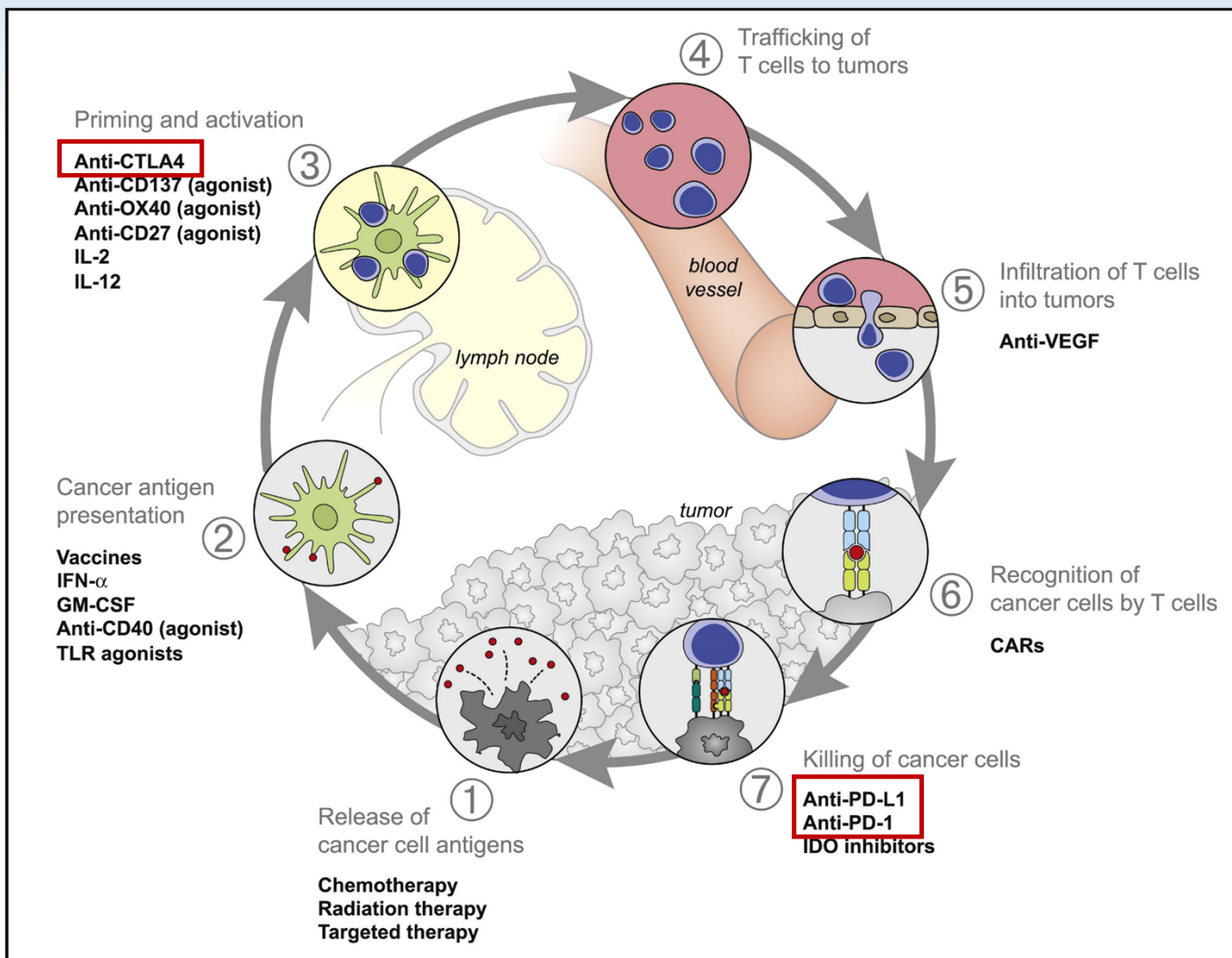
Ab antagonists of suppression elicit durable responses in patient subsets

- α CTLA4 (ipilimumab)
 - response rates 11-13 %
 - FDA approved for late-stage melanoma
 - active clinical trials for several cancers
 - success similar at multiple independent clinical sites
 - significant autoimmune toxicity
- α PD-1 (nivolumab, lambrolizumab, pidilizumab, AMP-224), and
- α PD-L1 (MPDL3280A, MEDI-4736)
 - response rates 13-38 %
 - activity demonstrated in non-traditional immune-responsive cancers (lung, colon H&N, gastric)
 - toxicity can be significantly lower than α CTLA4

Ab agonists of stimulators show early promise after initial setback

- α CD40
- α OX40
- α GITR

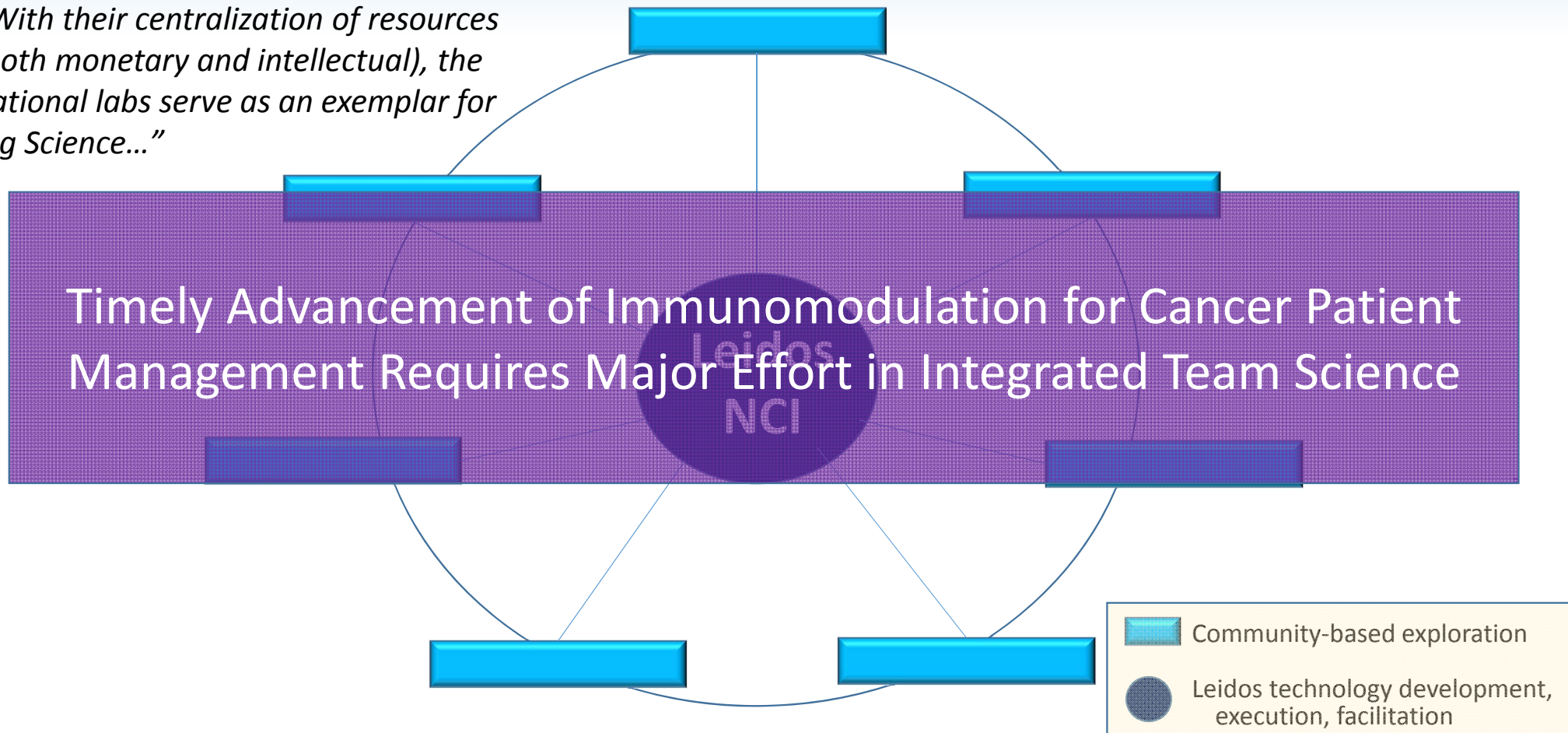
Therapies Targeting the Cancer-Immunity Cycle



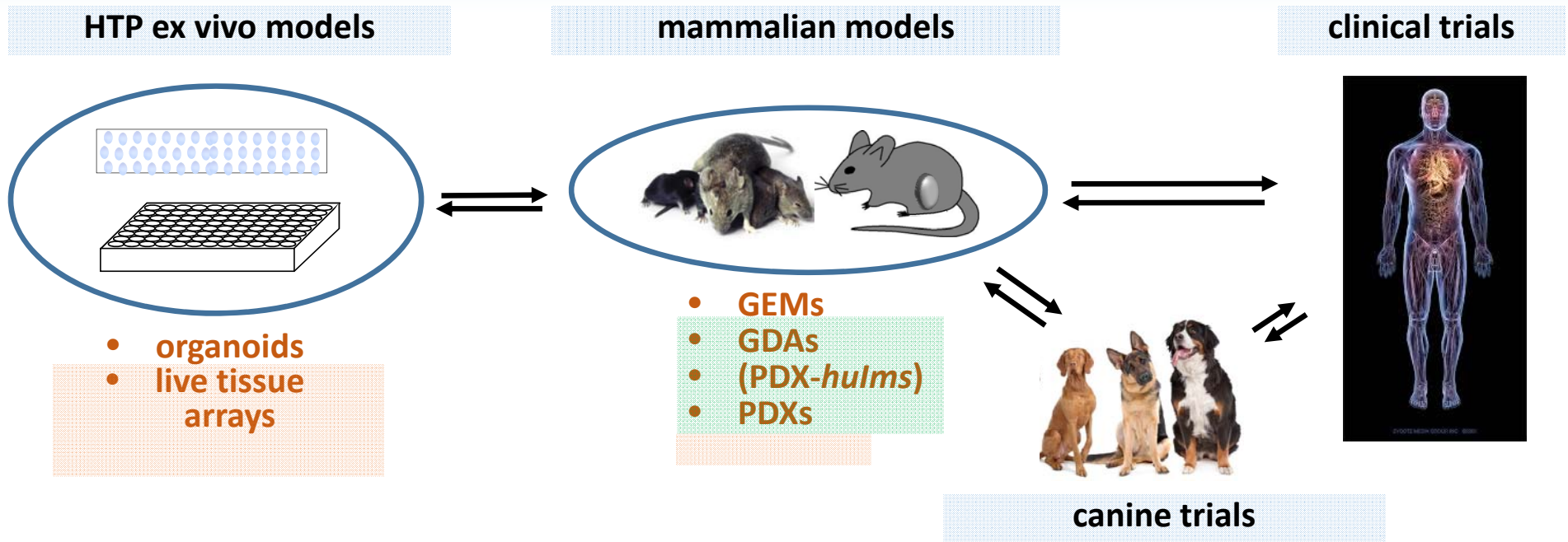
Chen and Mellman,
Immunity 2013

National Laboratory “Hub and Spoke” Execution to Solve Major Biomedical Challenges

“With their centralization of resources (both monetary and intellectual), the national labs serve as an exemplar for Big Science...”



New Paradigms for Potential Therapeutic Development Workflows



Molecular architecture, genomics, systems of disease and therapeutic response

signaling targeted therapies

immunomodulatory , signaling-targeted therapies

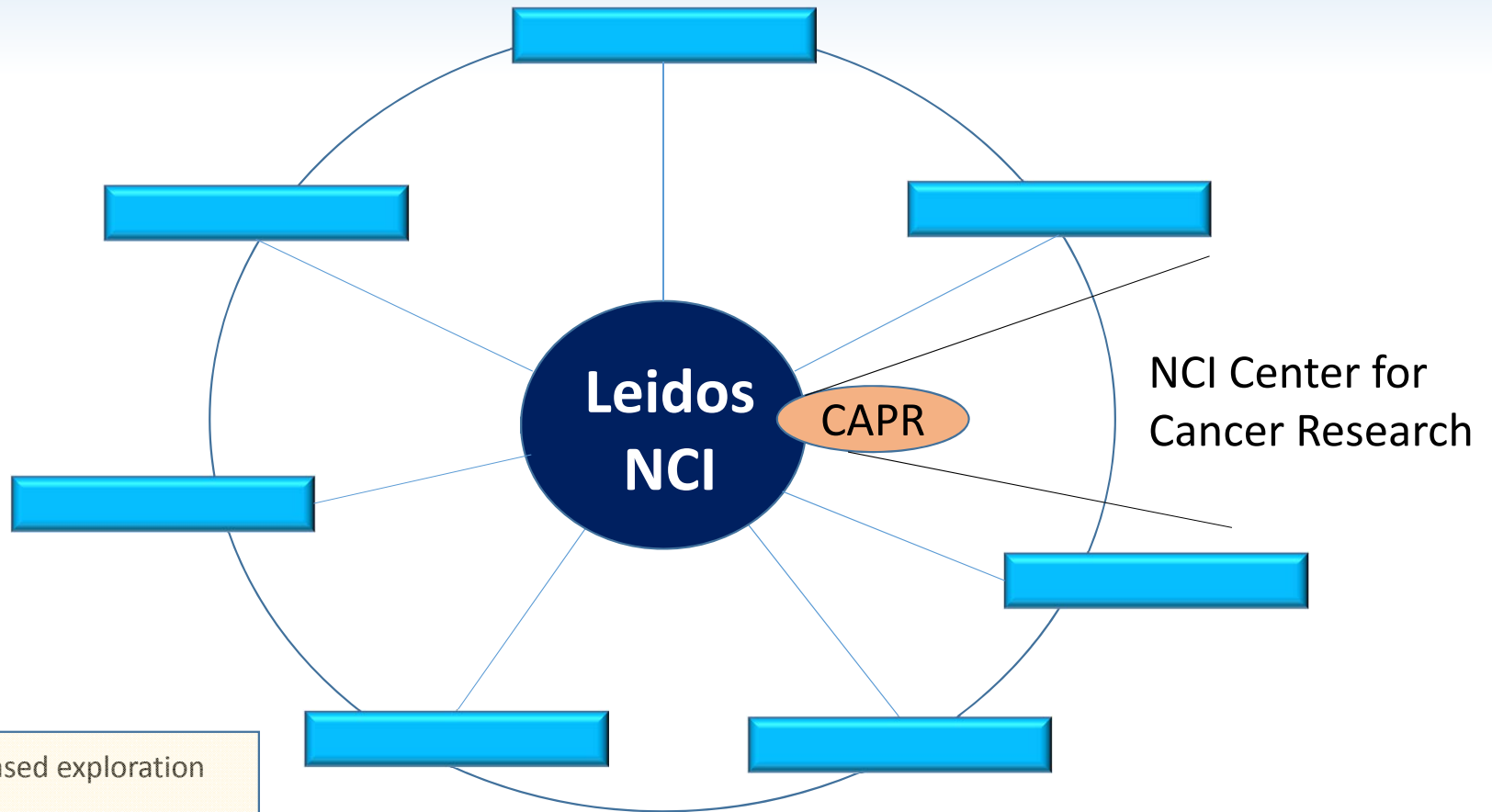


Operating Structure and Goals

**Mission ...to facilitate development of guiding
preclinical workflows for clinical research
and effective cancer management**

- Novel hybrid culture: integrated research rigor and project/goal management
- Business development (Leidos Biomedical)
- Dedicated staff drawn from public/private sectors along with NCI/NIH/LB technologies & research
- Integrated expertise in cancer mechanisms, pathways, murine models, genetics, drug development
- Dedicated pathology, histopathology, molecular pathology, quantitative morphometrics
- Cost effective through economy of scale and GEM model management

CAPR Interface with the National Laboratory



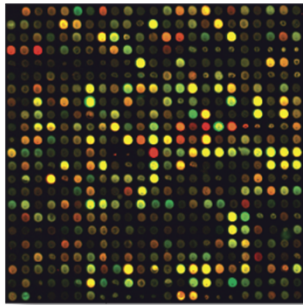


Objectives for Preclinical Development

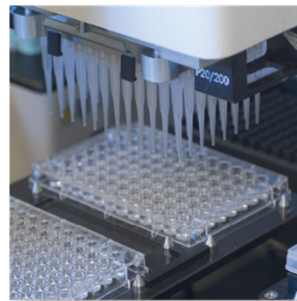
- Generation/adaptation of biologically and genetically engineered mouse models
 - PDXs, GEMs, syngeneic GEM-derived allograft transplants (GDAs)*
 - best possible representation of human cancer*
 - tractable for preclinical scale and timetables*
- Assessment of relative predictive power among engineered models
 - treatment /organ-specific PK/PD evaluation compared to clinical outcomes*
- Hypothesis generation for clinical and basic research
- Biomarker discovery via dynamic systems assessment
- Development of imaging technologies to monitor disease and treatment
- Development of preclinical/clinical interactive data management systems

Leidos Biomedical Scientific Technologies Integration

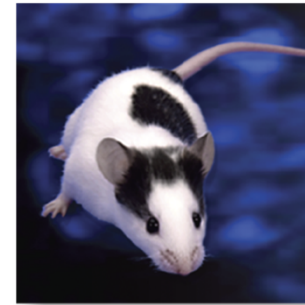
Laboratory of Molecular Technology
Microarray Analysis



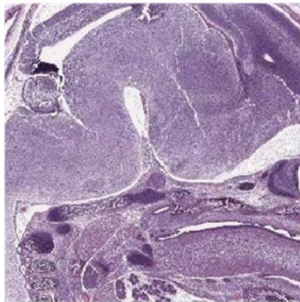
Laboratory of Molecular Technology
Genotyping



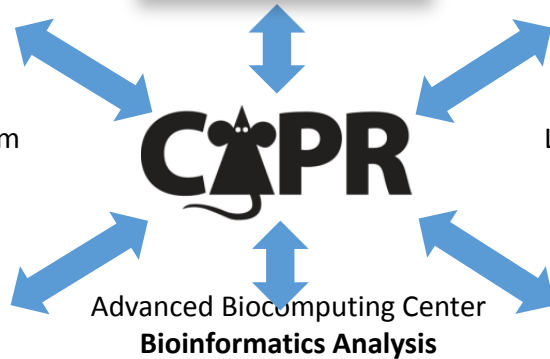
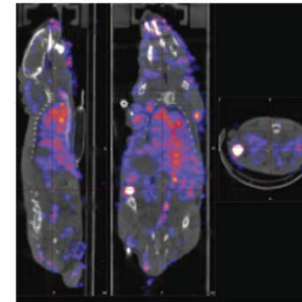
Laboratory Animal Sciences Program
Animal Resources



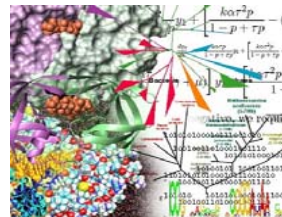
Laboratory Animal Sciences Program
Pathology/Histotechnology




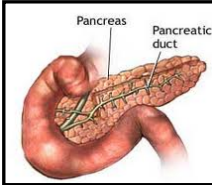


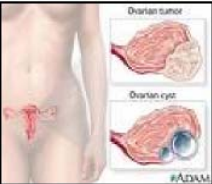

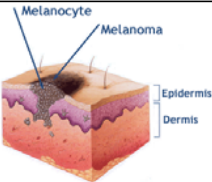
Laboratory Animal Sciences Program
Small Animal Imaging



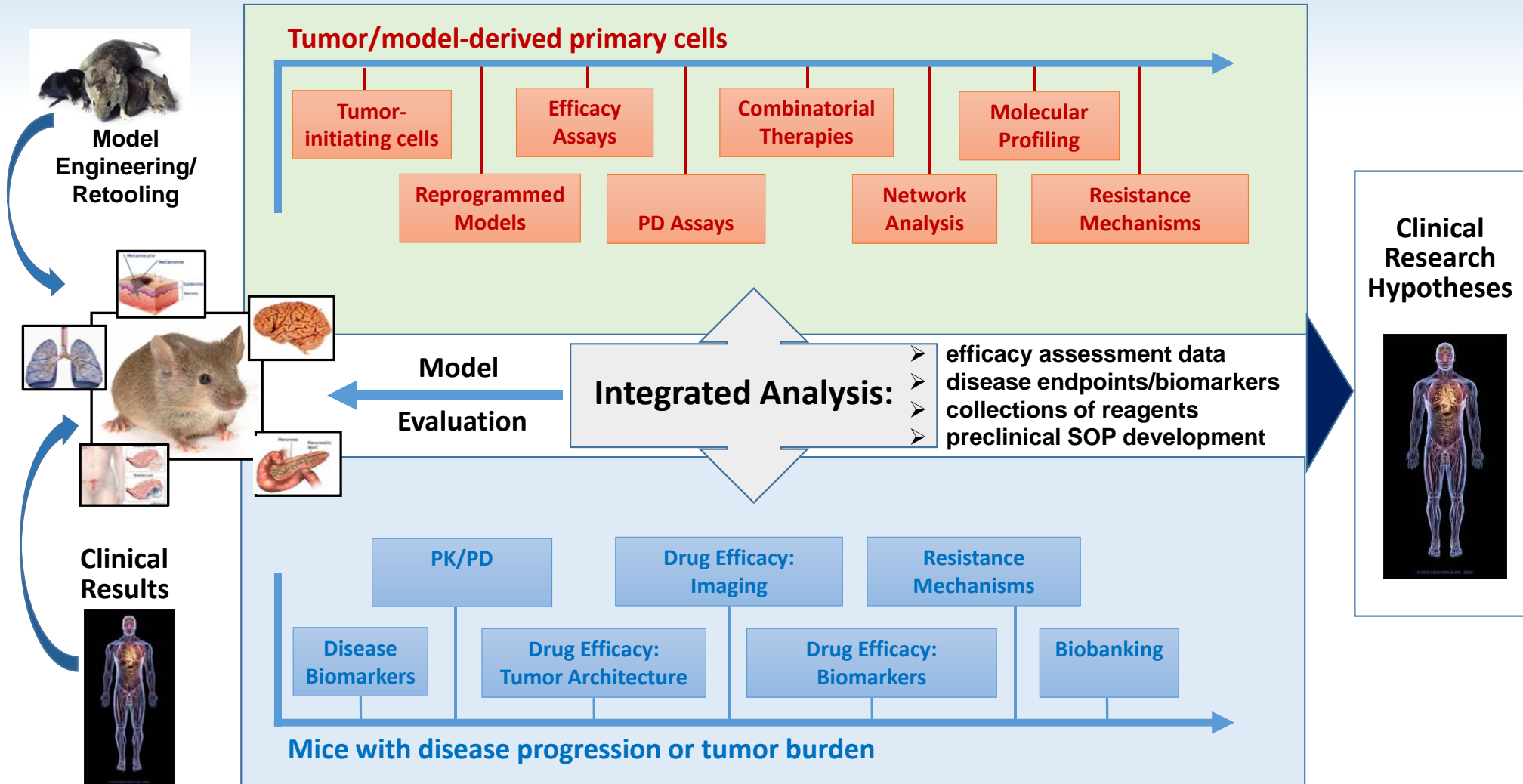
Advanced Biocomputing Center
Bioinformatics Analysis



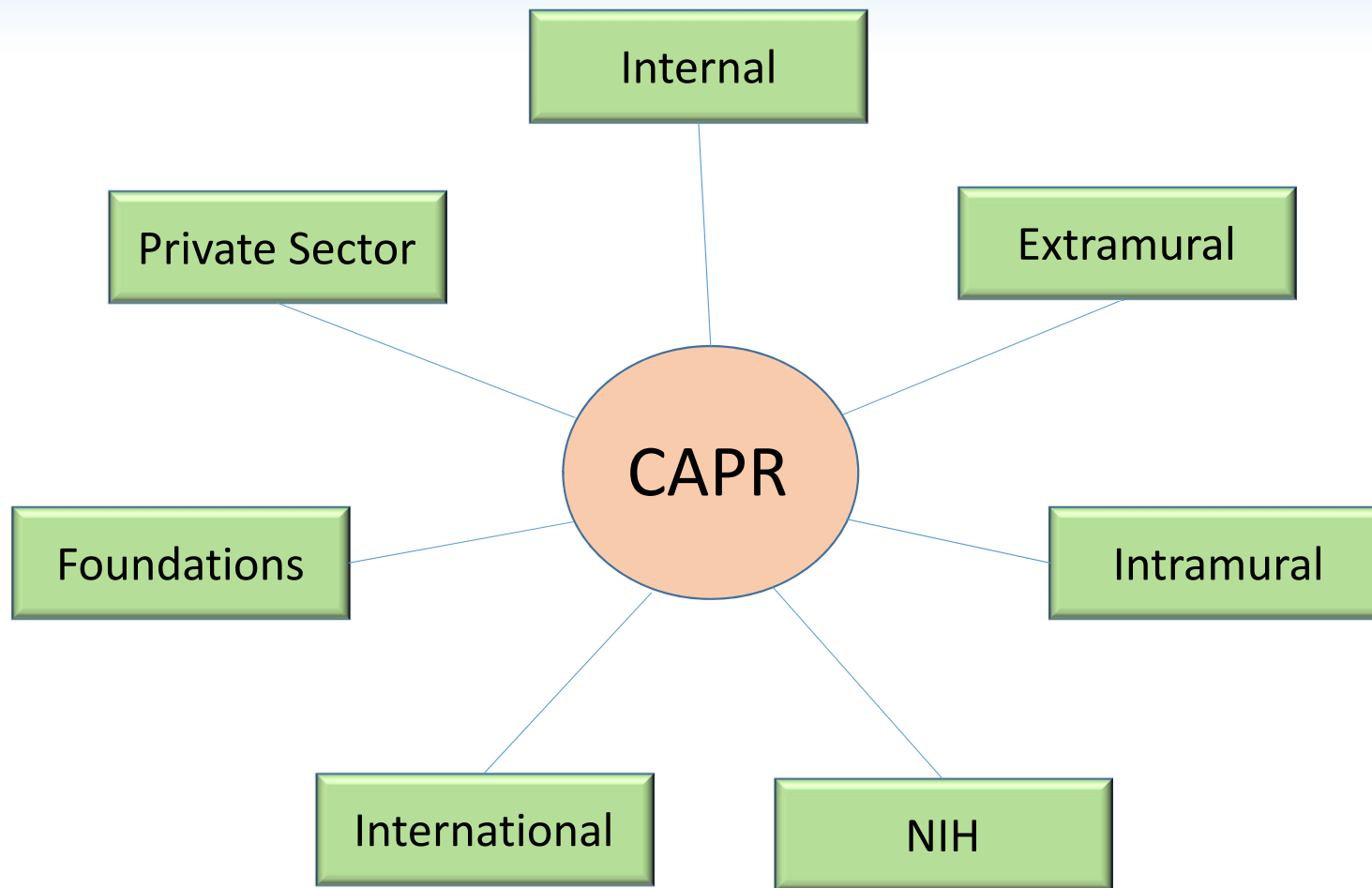
Major Models

Model Type	Genetic Events Induction Mode	Model Type	Genetic Events Induction Mode
 <p>Non-Small Cell Lung Cancer:</p> <ul style="list-style-type: none"> ➤ Lung Adenocarcinoma ➤ Squamous Cell Carcinoma 	<ul style="list-style-type: none"> ➤ EGFR-L858R ➤ EGFR-L858R/T790M ➤ Lkb1/Kras ➤ Doxycycline ➤ Adeno-Cre/Lenti-Cre 	 <p>Pancreatic Adenocarcinoma</p>	<ul style="list-style-type: none"> ➤ p53/Kras ➤ Ink4a/Kras ➤ PDX-Cre ➤ de novo, orthotopic
 <p>Anaplastic Astrocytoma III</p> <p>Glioblastoma</p>	<ul style="list-style-type: none"> ➤ pRb/Kras/PTEN ➤ Tamoxifen/Adeno-Cre ➤ de novo, orthotopic 	 <p>Prostate Carcinoma</p>	<ul style="list-style-type: none"> ➤ pRb/PTEN ➤ Tamoxifen
 <p>Serous Ovarian Carcinoma</p>	<ul style="list-style-type: none"> ➤ pRb/p53 ➤ pRb/p53/Brca1 ➤ pRb/p53/Brca2 ➤ Tamoxifen/Adeno-Cre ➤ de novo, orthotopic 	 <p>Small Cell Lung Cancer</p>	<ul style="list-style-type: none"> ➤ pRb/p53 ➤ Lenti-Cre
 <p>Melanoma</p>	<ul style="list-style-type: none"> ➤ BRAF-V600E ➤ HGF/MET ➤ N-Ras ➤ UV, Tamoxifen ➤ de novo, orthotopic 	<div style="border: 1px solid black; padding: 5px;"> <ul style="list-style-type: none"> <i>in therapeutic/biomarker evaluation</i> <i>in characterization or available</i> </div>	

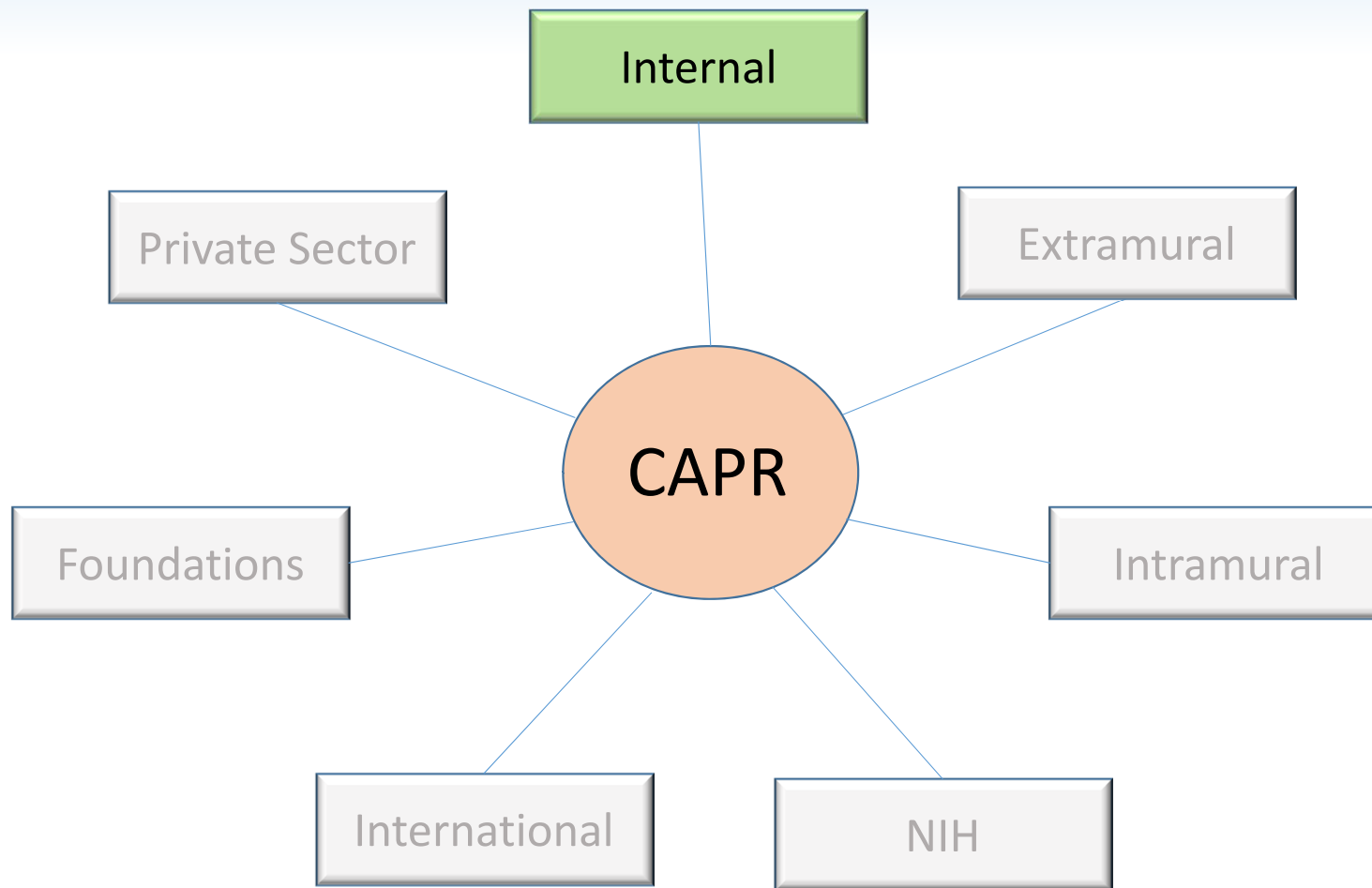
CAPR Preclinical Evaluation Workflow



CAPR Projects and Partnerships



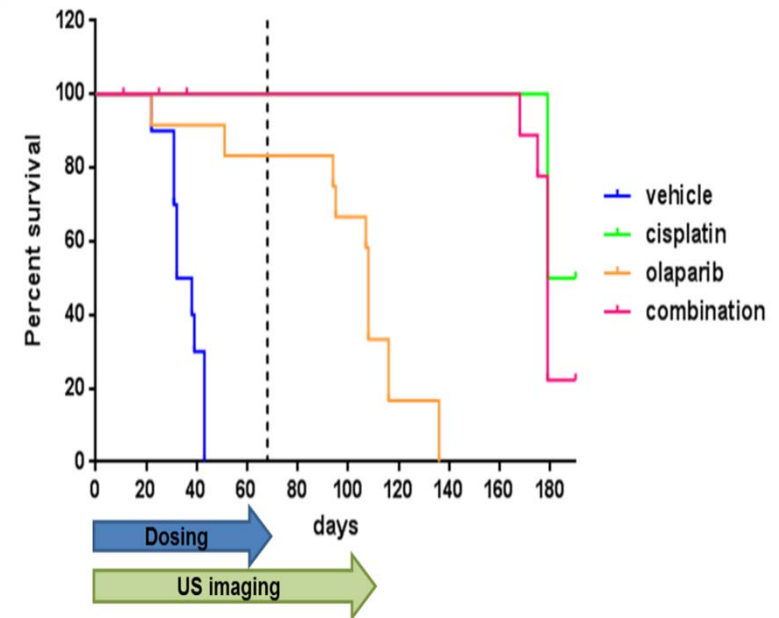
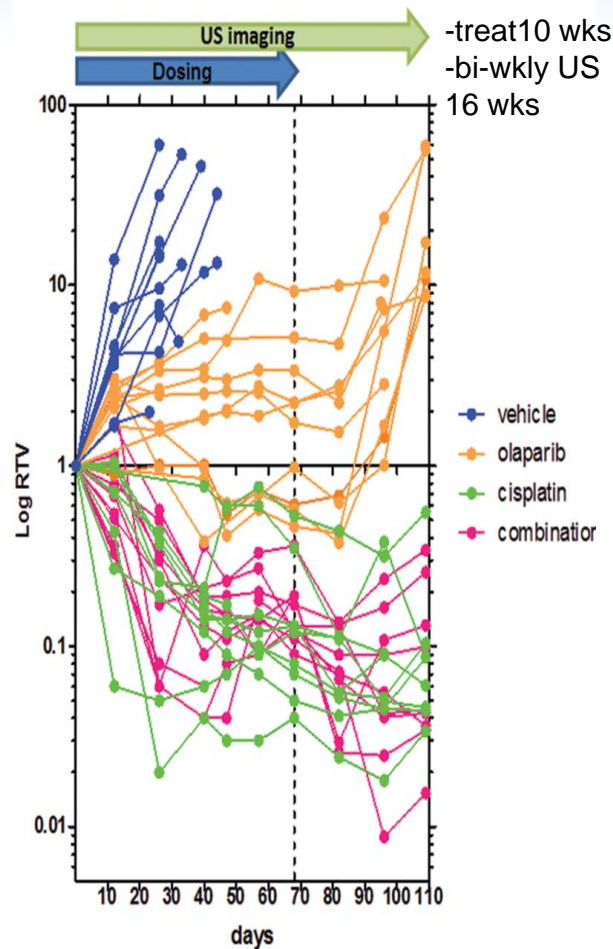
CAPR Projects and Partnerships



Representative Internal Developments for Export

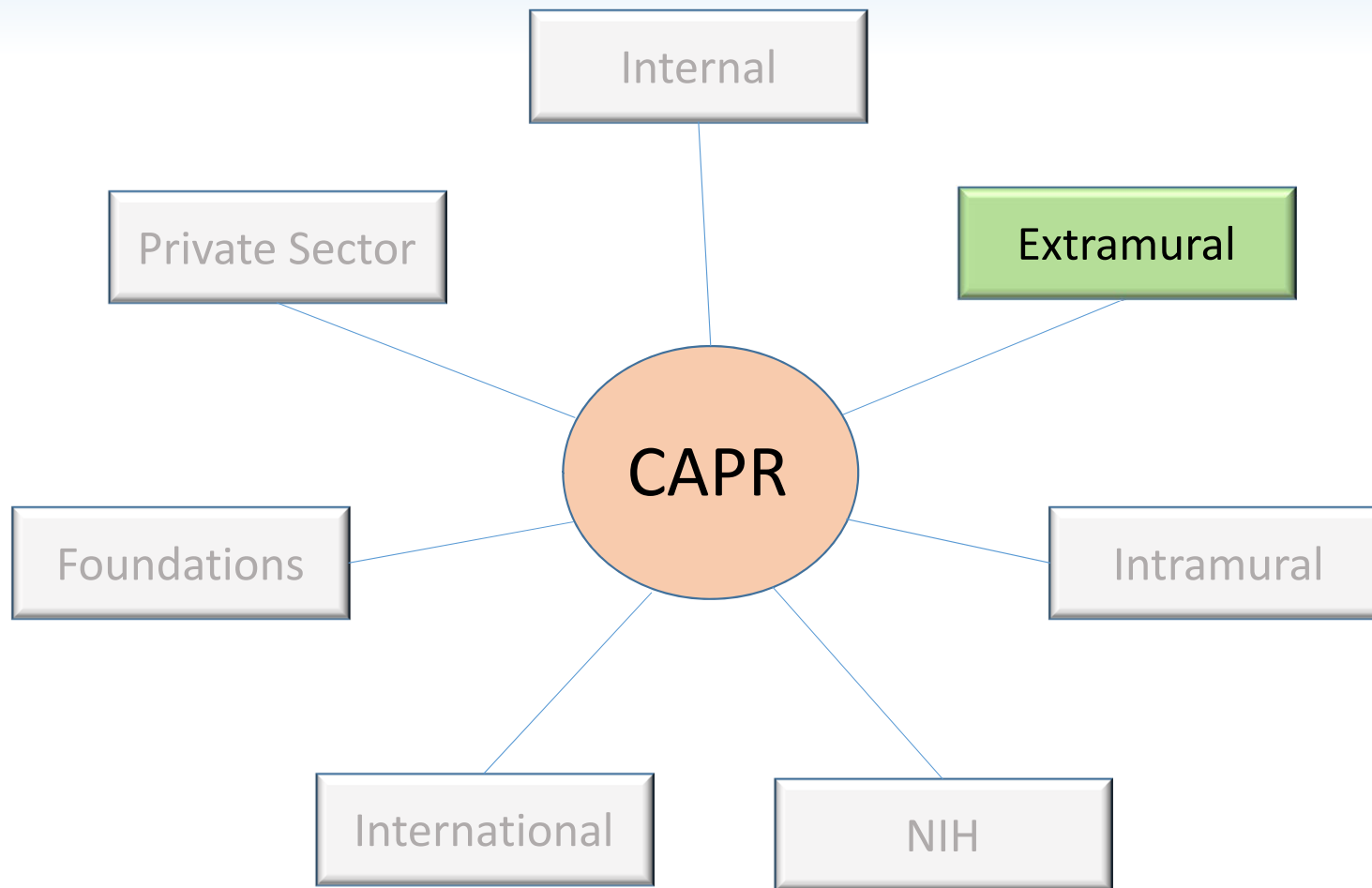
- Matched GEM/GDA/primary culture sets established for GBM and serous ovarian cancers
- Inducible human EML4-ALK lung cancer models (3 primary, 2 resistant)
- Inducible human EGFR erlotinib-resistant focal lung cancer model established
- p53 missense-mutant alleles retooled
- Therapeutic and biomarker evaluation SOPs developed for all models
- ESC-derived non-germline cohorts developed for complex genetic models
- Colony management database developed
- Preclinical workflow database developed

Long-Term Treatments in GDA-SEOCs Mirror Lesion-Specific Human Responses

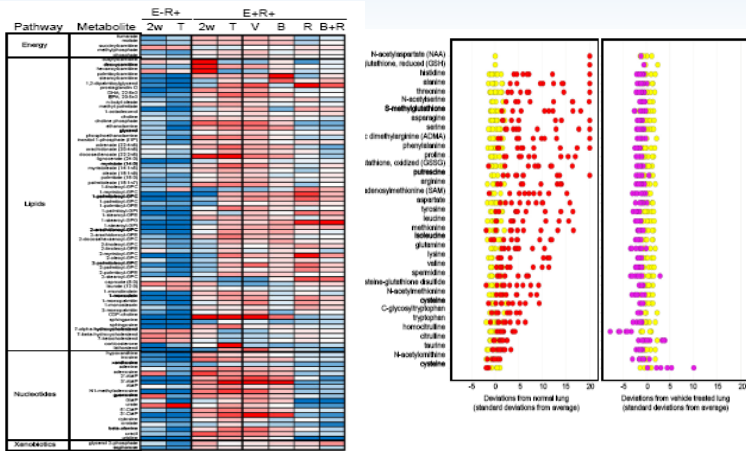


- Olaparib treatment in mice- suppressed tumor growth but did not translate into sustained increase in survival
- Olaparib treatment in humans: progression-free survival benefit but no overall survival benefit

CAPR Projects and Partnerships



Extramural Collaboration Examples



Molecular Responses to Treatment of Erlotinib-Resistant Lung Cancer

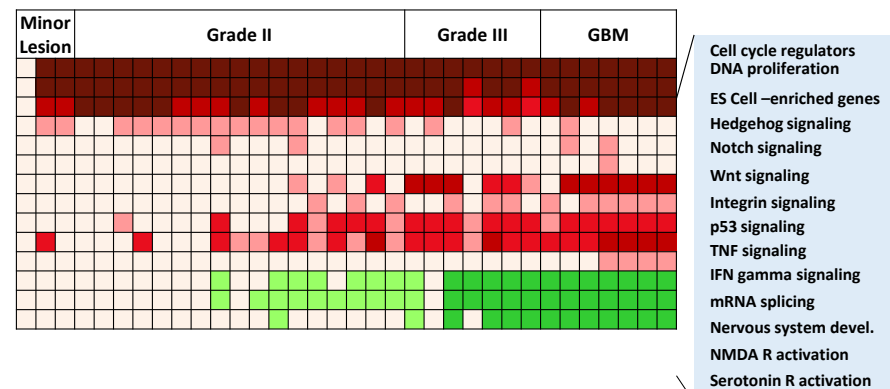
Kwok-Kin Wong Dana Farber
 Julien Carretero Spanish Nat'l Cancer Centre
 Fatima Al-Shahrour Broad Institute

Weaver Z, Difilippantonio S, Carretero J et al. *Cancer Res.* 2012 Nov 15;72(22):5921-33.

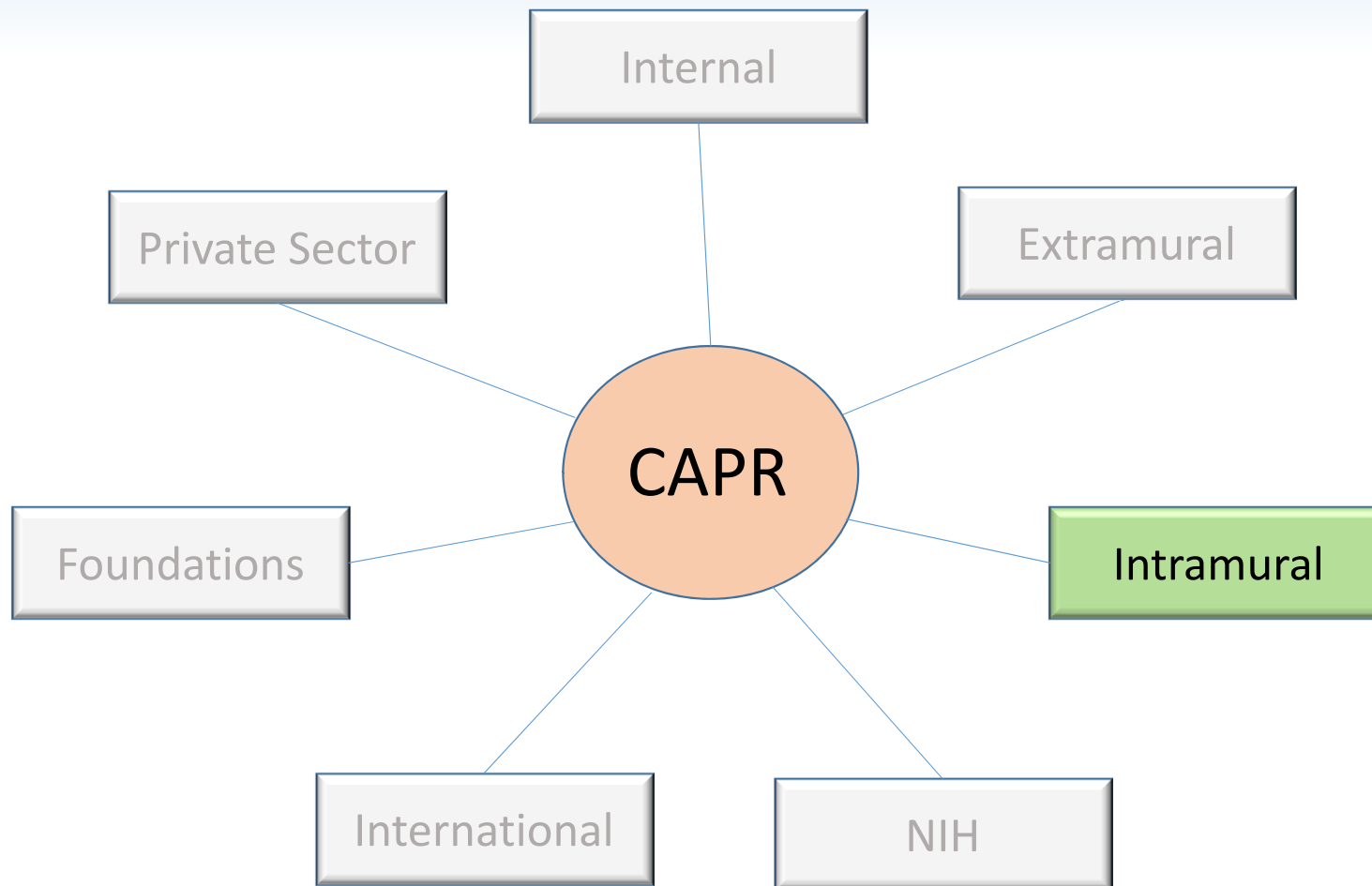
Biological Systems in the Progression to GBM

Lee Hood Institute for Systems Biology
 Terry Van Dyke Center for Cancer Research, NCI

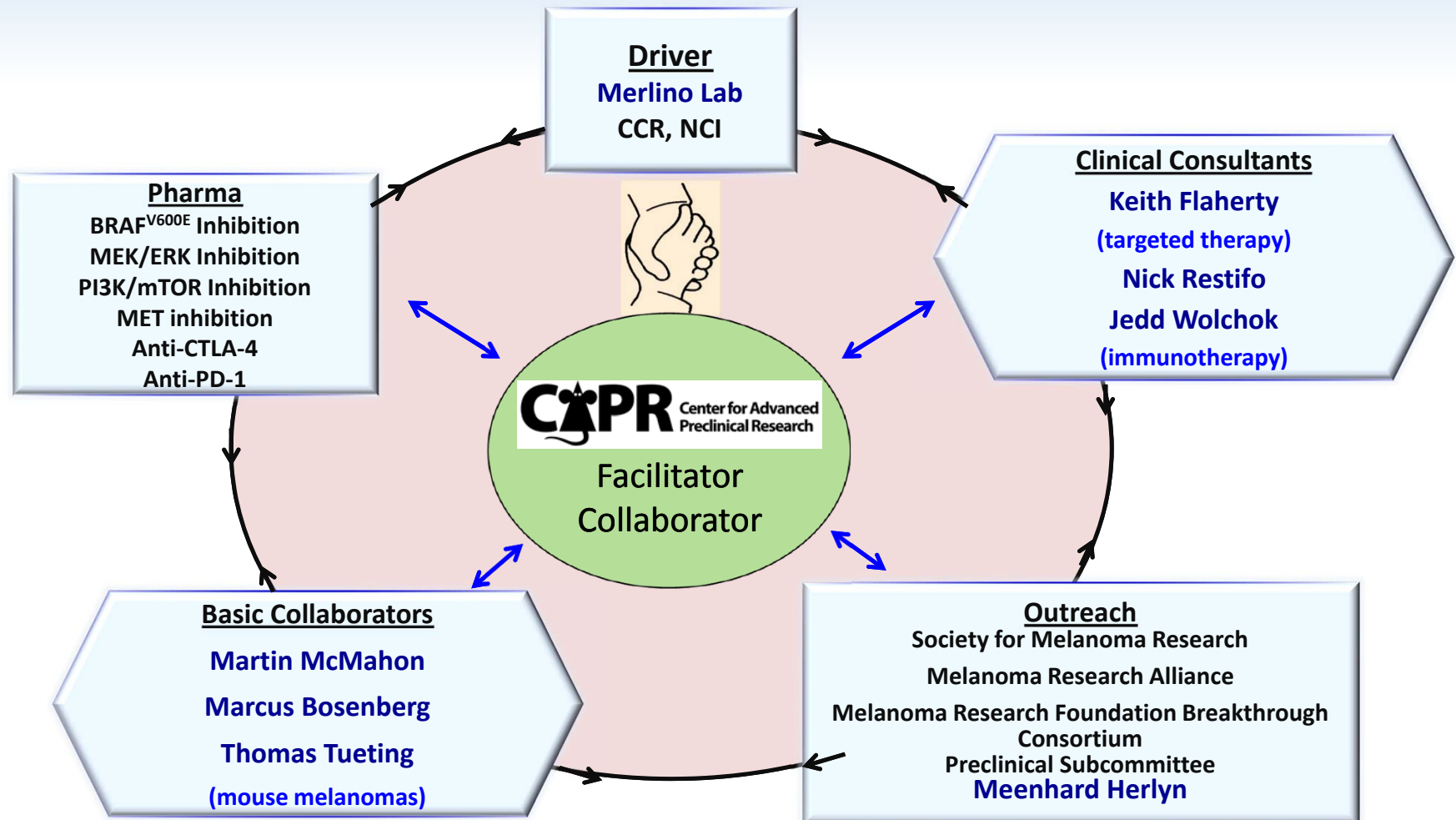
Kutlu, B, Ruzankina, Y et al. (2014) in preparation.



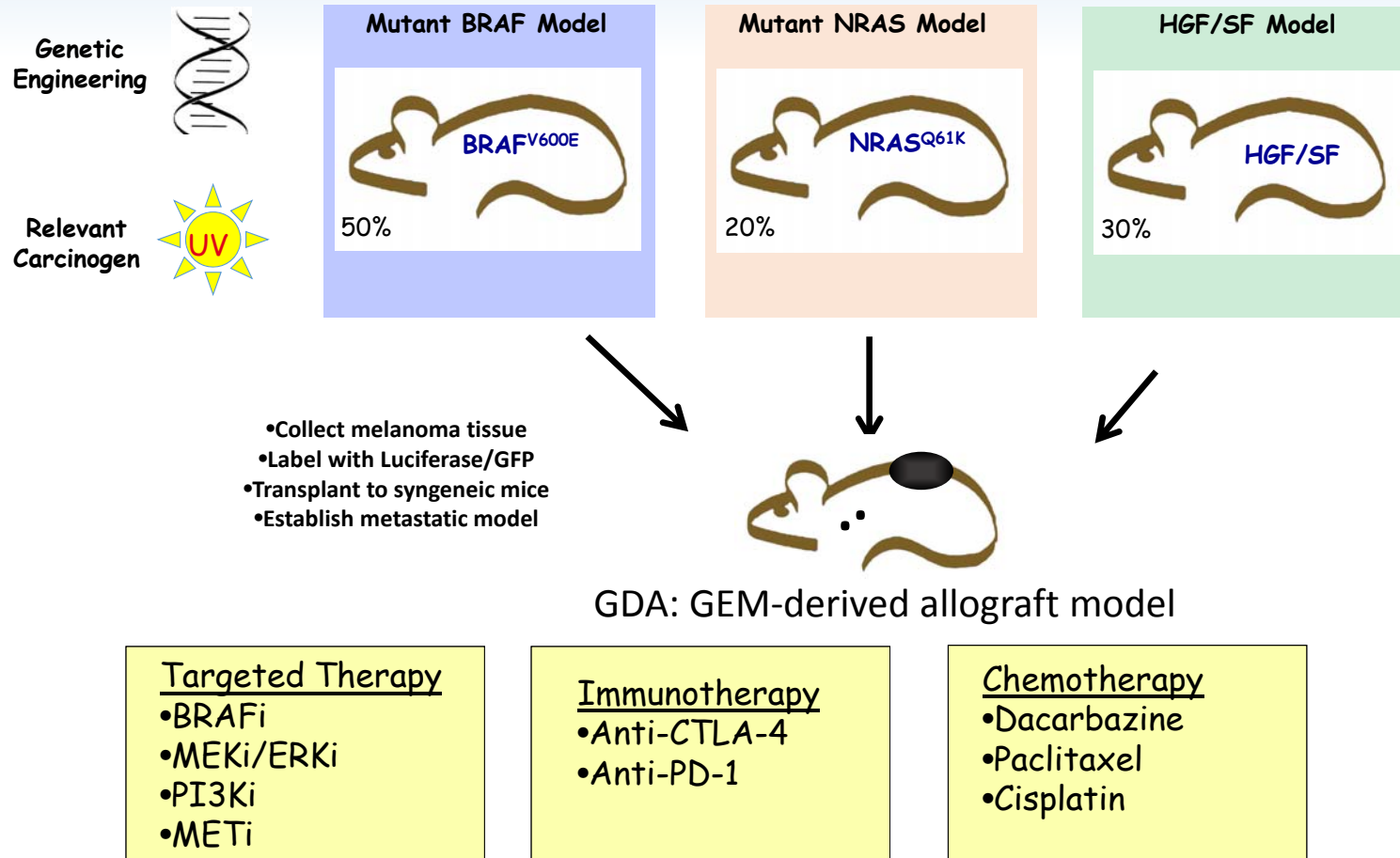
CAPR Projects and Partnerships



Integrated Basic/Translational/Clinical Team Exploration in Cutaneous Melanoma

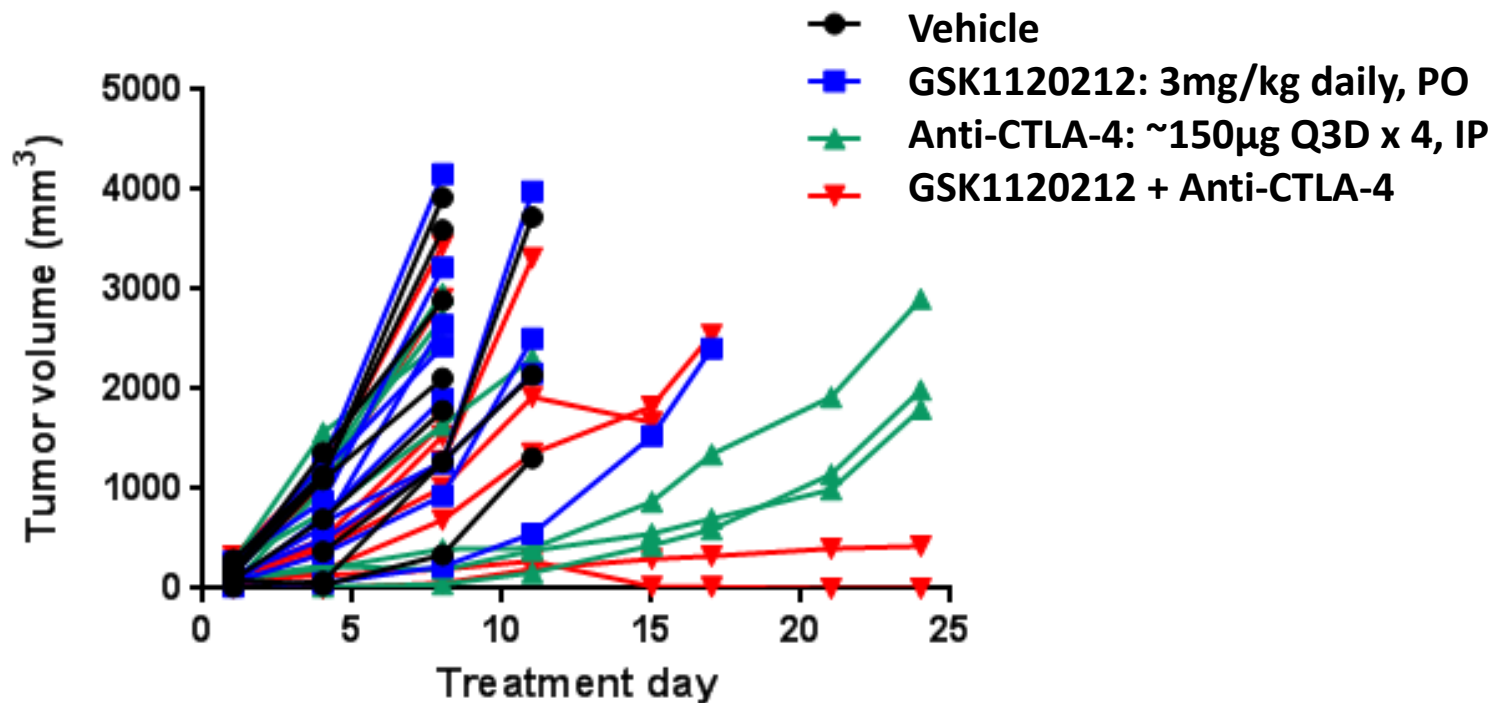


Driver-Specific Models of Primary and Metastatic Melanoma in Preclinical Evaluation



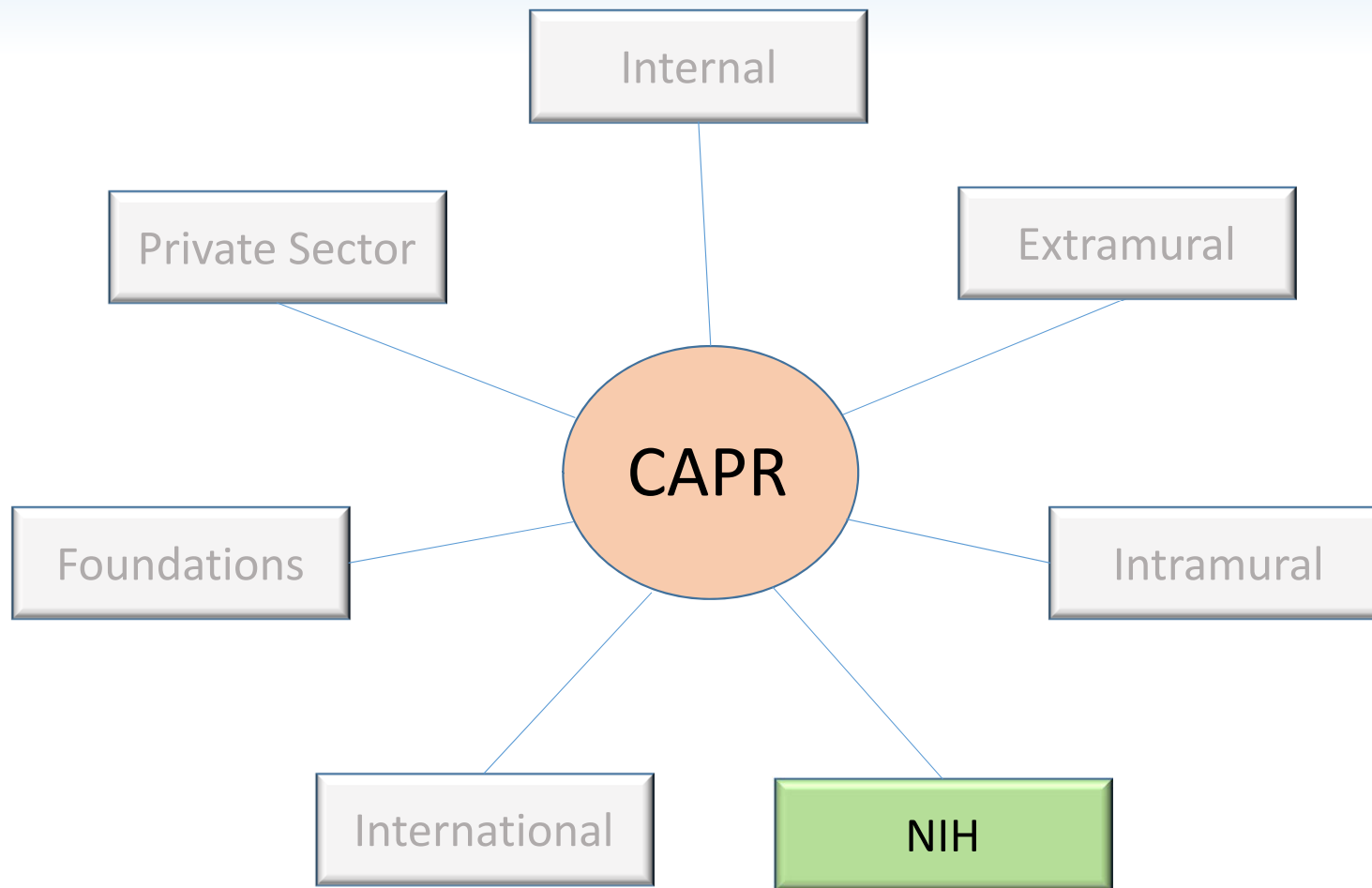
Glenn Merlino and CAPR, NCI

Responses to Anti-CTLA4 Mono and Combination MEK Inhibition Therapy in HGF/MET Melanoma GDAs



HGF;CDK4^{R24C} allograft model

CAPR Projects and Partnerships



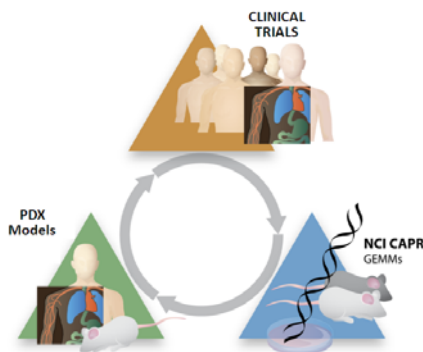
NIH Initiative Partnerships

DCTD

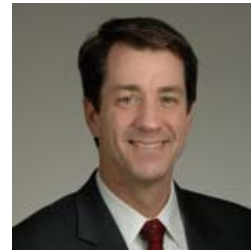
**Division of Cancer Treatment and
Diagnosis**



**Cross-utilization and
Development of PDX and
GEM-related Preclinical
Models in Clinical Guidance**

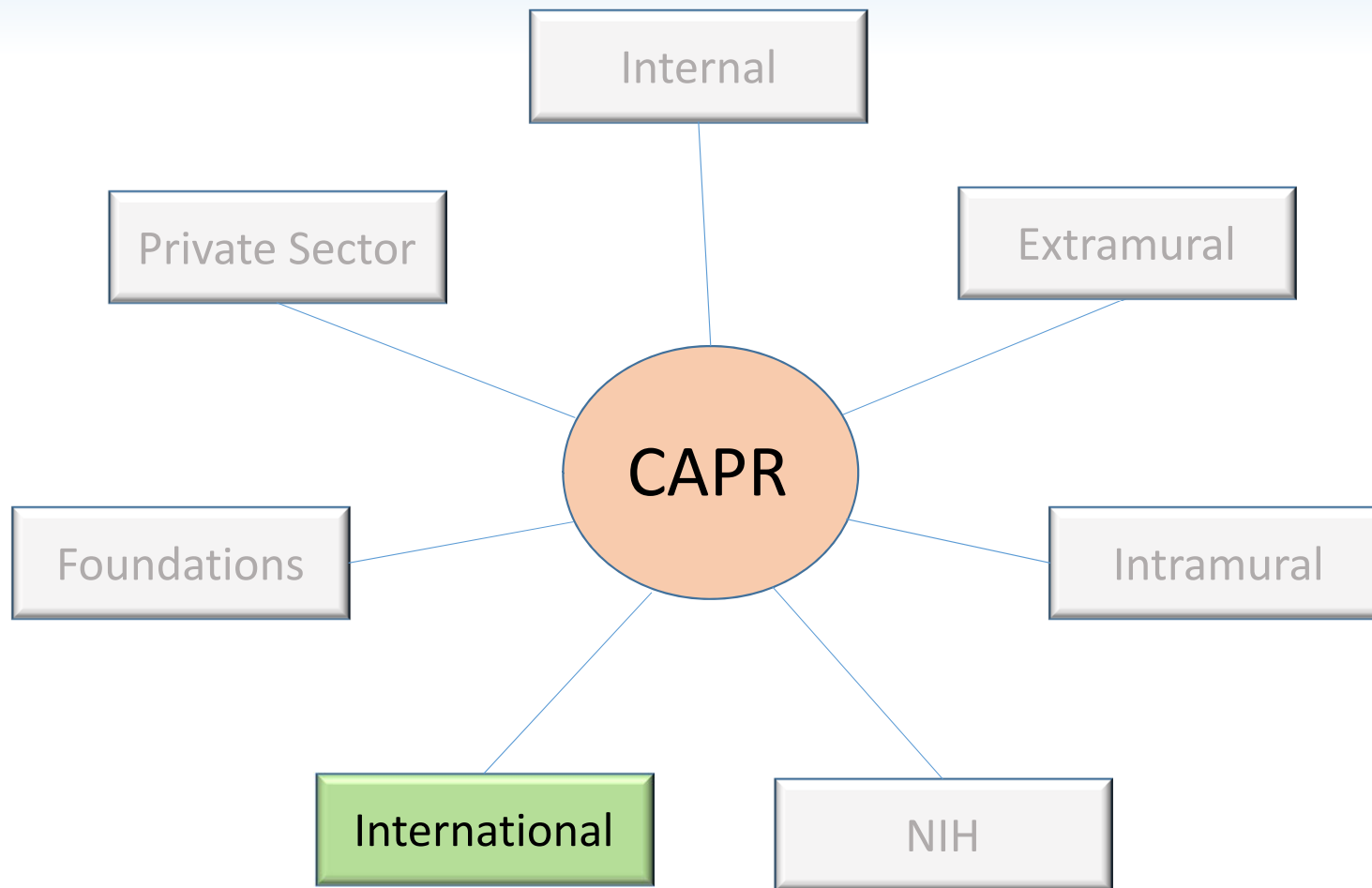


**National Center for
Advancing Translational Science**



**Integration of Preclinical Systems (Ex
Vivo and In Vivo) into Target
Identification and Treatment
Development**

CAPR Projects and Partnerships





- PREDECT/CAPR MOU in progress to collaborate in development of live tissue slice arrays for therapeutic screening
- Invited partnership possibility under investigation

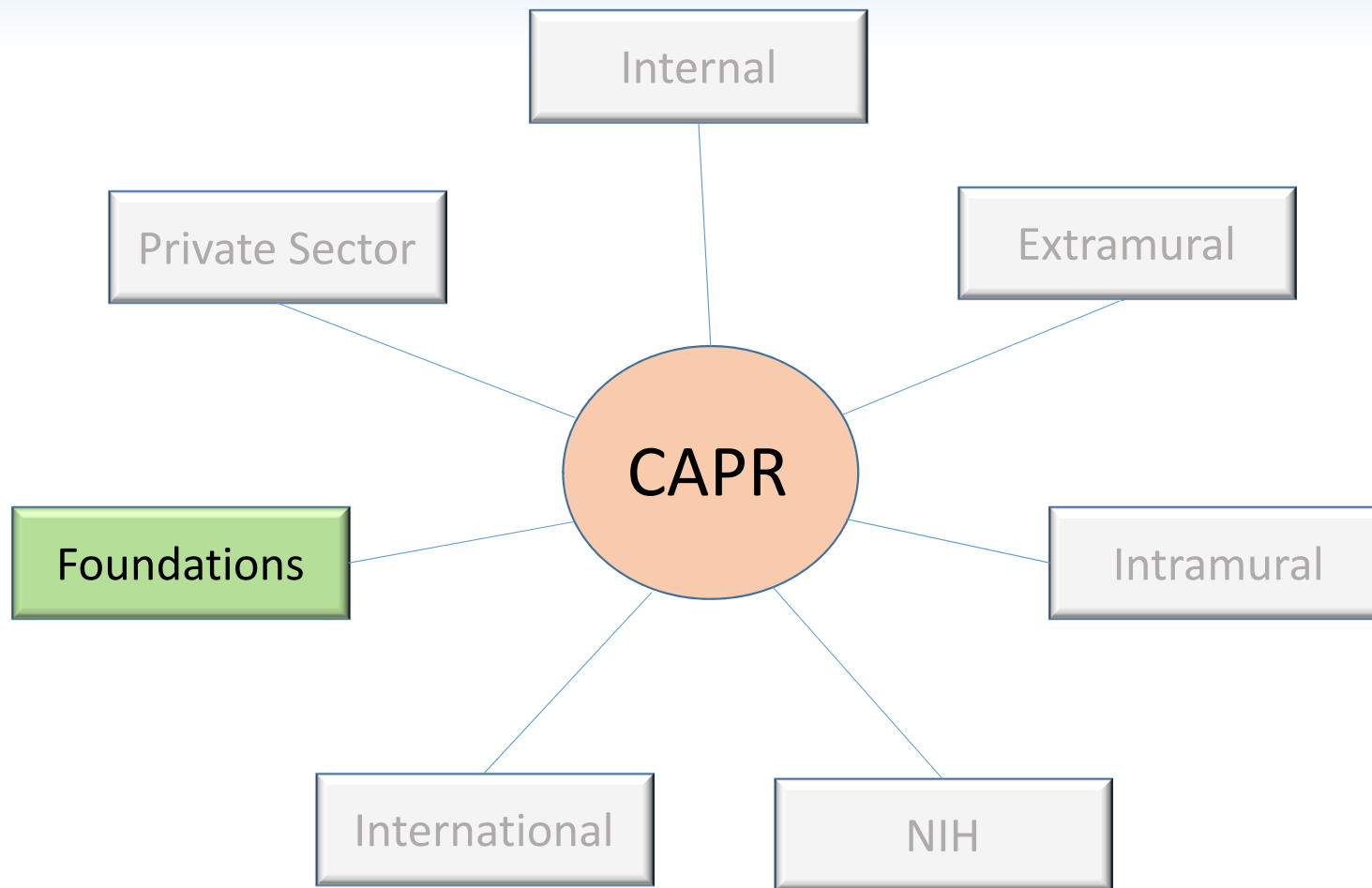


A consortium of 19 members (Pharma, Academic, CROs) aligned to develop
New models for preclinical evaluation of drug efficacy in common solid tumours
funded by the IMI, EFPIA and other entities

Specific areas:

- • in vitro 2D/3D organotypic (co-)cultures, stirred bioreactor aggregates and tissue slice systems
- novel (orthotopic) grafts of human and mouse tumour samples
- genetically-engineered and mosaic mouse models.

CAPR Projects and Partnerships





- RFAs for Partnership Opportunities

- **Eight thematic RFA's enlisting CAPR support (Released April 1st, 2013):**

- Early Detection and Risk Assessment in Pancreatic Cancer
 - Testing New Drug Delivery Approaches in Pancreatic Cancer
 - Novel Imaging Technologies in Pancreatic Cancer
 - Therapies for Pancreatic Cancer
 - Novel Agents for Pancreatic Cancer
 - Identification of Clinical and Molecular Markers for Metastatic Burden
 - Early Target Validation for Pancreatic Cancer
 - New Models for PDAC

- Active Partnership: Lustgarten/Evans (Salk)/CAPR (NCI)

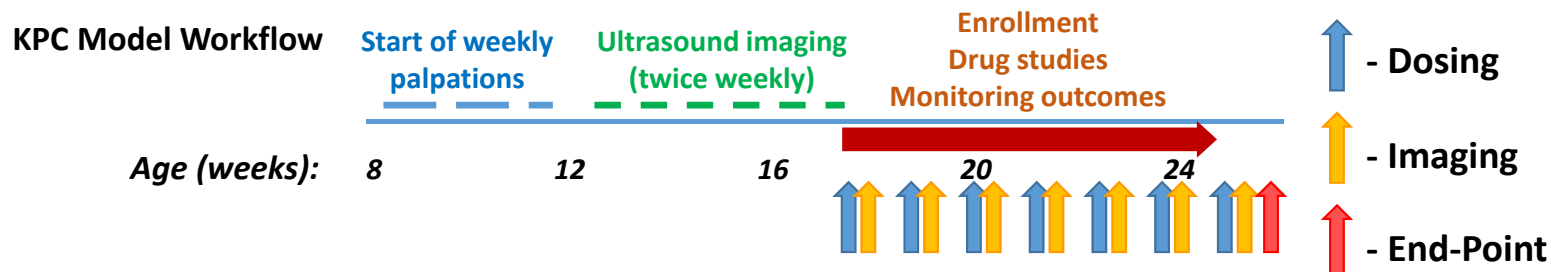
Kras-G12D/p53-R172H Driven Pancreatic Ductal Adenocarcinoma (KPC Model)



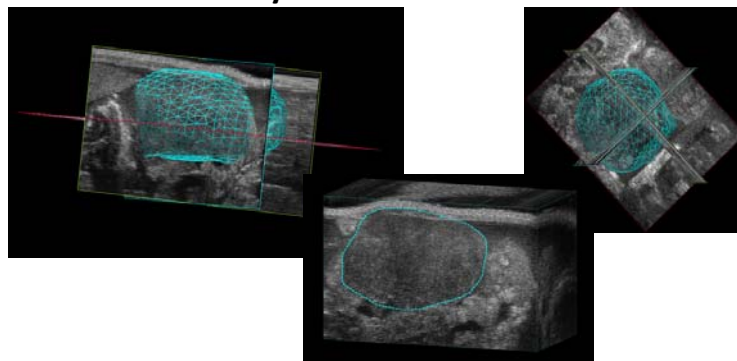
Cre-dependent de novo induction:

- Pdx-Cre
- Kras-G12D (Cre-dependent)
- P53-R172H (Cre-dependent)

De novo model: Cre-dependent activation of Kras (G12D) and p53 (R172H) mutations

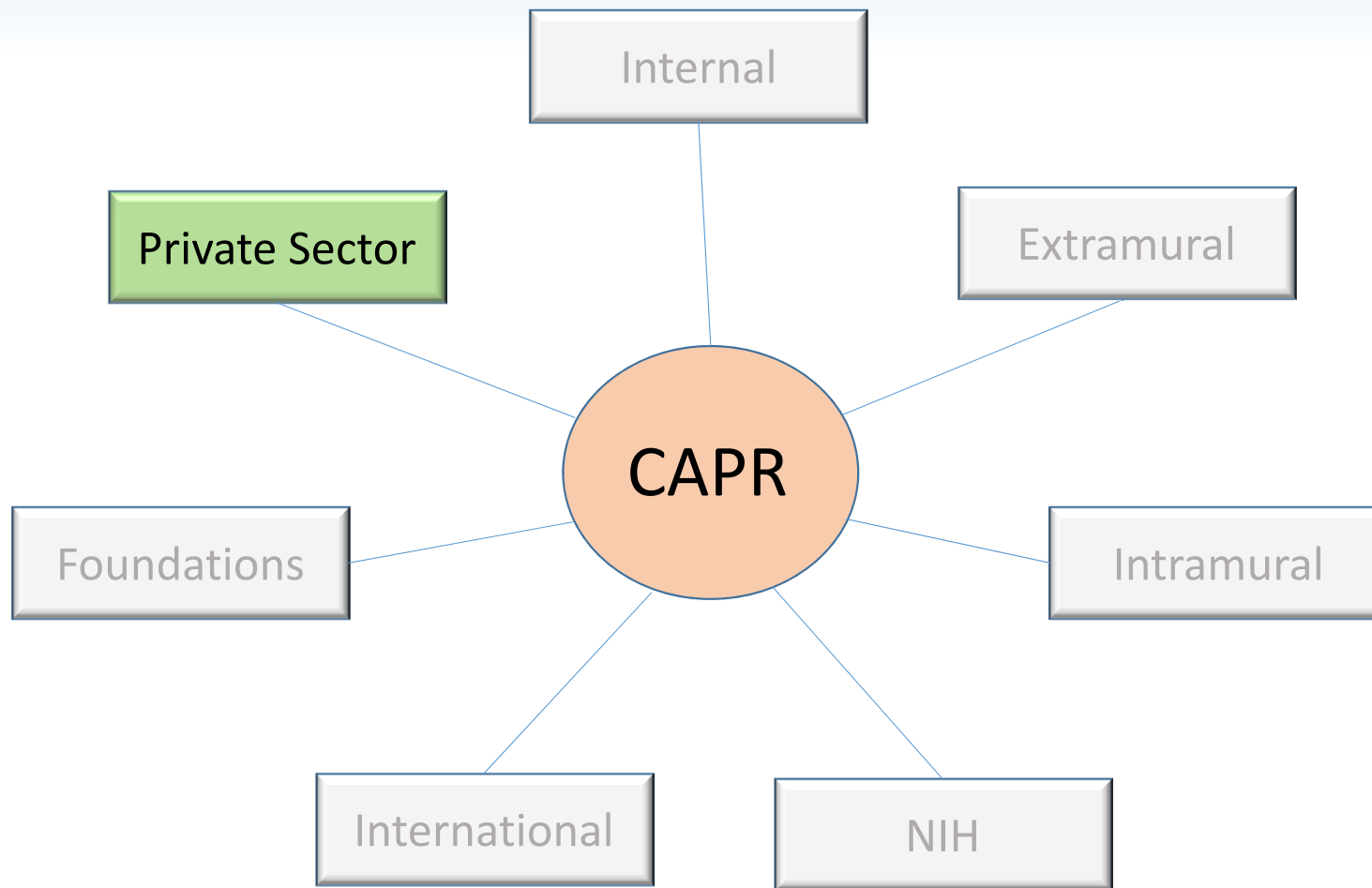


Ultrasound analysis: advanced PDAC tumor



Consultants: Dr. David Tuveson, CSHL
Dr. Kenneth Olive, Columbia U.

CAPR Projects and Partnerships



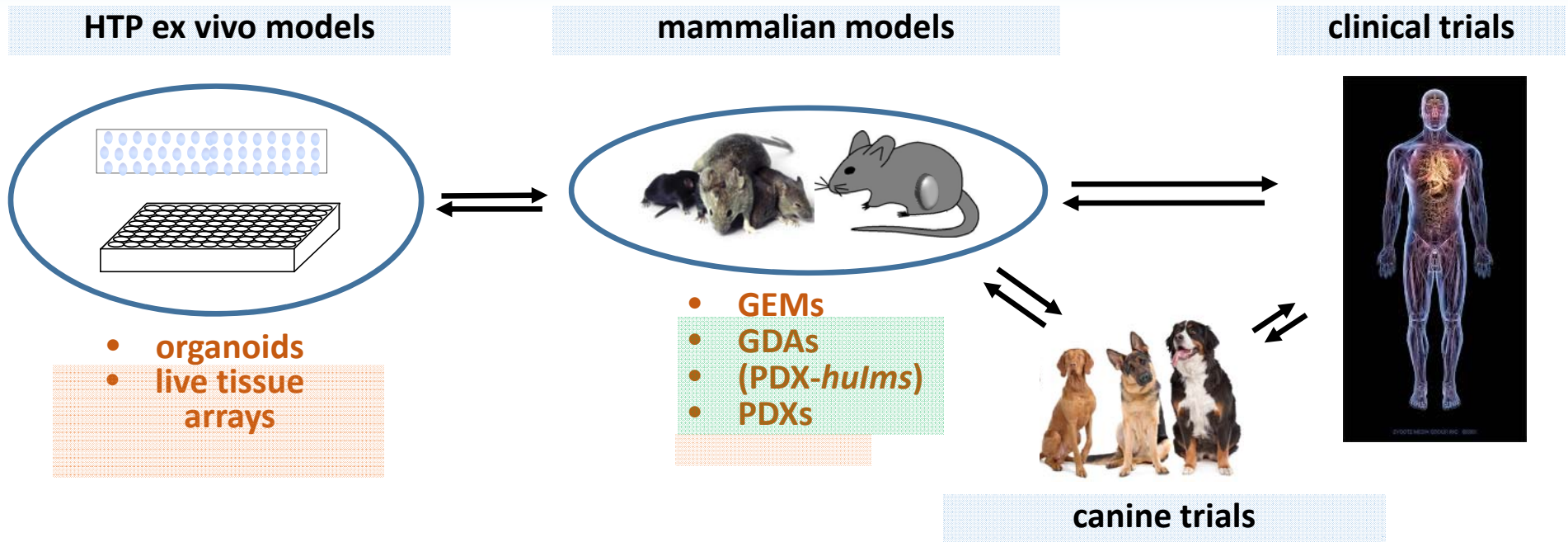
Discovery of a Mutant-Selective Covalent Inhibitor of EGFR that Overcomes T790M-Mediated Resistance in NSCLC

Annette O. Walter¹, Robert Tjin Tham Sjin², Henry J. Haringsma¹, Kadoaki Ohashi³,
Jing Sun³, Kwangho Lee², Aleksandr Dubrovskiy², Matthew Labenski², Zhendong Zhu²,
Zhigang Wang², Michael Sheets², Thia St Martin², Russell Karp², Dan van Kalken²,
Prasoon Chaturvedi², Deqiang Niu², Mariana Nacht², Russell C. Petter², William Westlin²,
Kevin Lin¹, Sarah Jaw-Tsai¹, Mitch Raponi¹, Terry Van Dyke^{4,5}, Jeff Etter¹, Zoe Weaver⁵,
William Pao³, Juswinder Singh², Andrew D. Simmons¹, Thomas C. Harding¹, and Andrew Allen¹

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New Paradigms for Potential Therapeutic Development Workflows



Molecular architecture, genomics, systems of disease and therapeutic response

signaling targeted therapies

immunomodulatory , signaling-targeted therapies

Project Focus

Mechanisms and optimization of therapeutic responses by targeted immunomodulation

- Selective patient response mechanisms
- Optimization of efficacy and breadth of individual responses

- Why are positive responses patient-specific?
- Can combination signaling-targeted and immune-targeted therapies improve efficacy?
- What dosing schedules are most effective?
- What are the potential resistance rates? Mechanisms?
- To what extent can immunocompetent mouse model studies predict human mechanisms?
(success in α CD40)
- Can biomarkers of responsiveness be developed to identify susceptible individuals? To monitor PD?
Successful outcomes?
- Can PDX models harboring humanized immune systems be incorporated into effective preclinical workflows?

Value Added

- Robust preclinical technologies to provide reproducible bridge to basic and clinical investigators
- Integration of ex vivo technologies already in development in the research community into the FNLCR and collaborators
- Community access to tractable vetted GEM and GDA models
- Development of PDX-hu-Imm models
- Development of robust preclinical SOPs and export to community
- Facilitation of collaborations/partnerships, including the private sector
- Resource optimization through economy of scale, team science, and shared technologies
- Training

Center for Advanced Preclinical Research

Scientific Director: Terry Van Dyke, PhD
Administrative Director: Lionel Feigenbaum, PhD

Zoë Weaver Ohler, PhD

Serguei Kozlov, PhD, MBA

Preclinical Evaluation

- Efficacy studies on therapeutic candidates
- Molecular and *in-vivo* imaging endpoints
- Biodistribution (PK/PD)
- Biomarkers/molecular signatures of treatment response.

Research and Development

- Derivation, modification & validation of hypothesis-predictive GEMMs
- Biomarkers/molecular signatures of tumorigenesis
- Breeding strategies for scale-up

Technology and Optimization

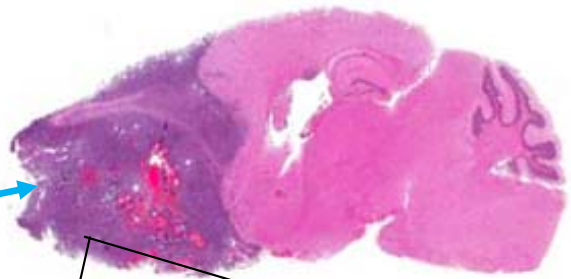
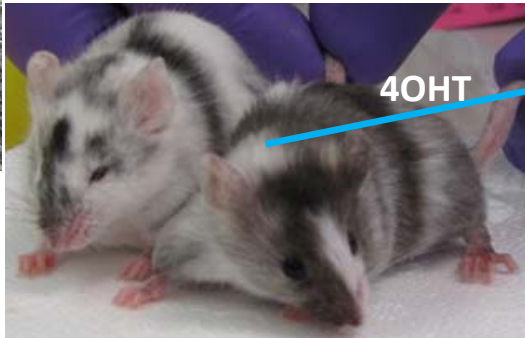
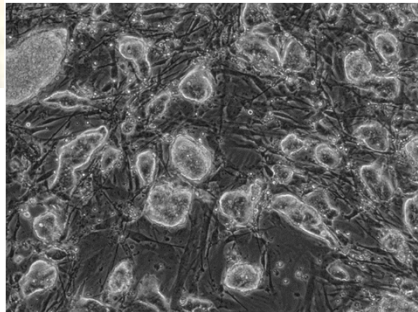
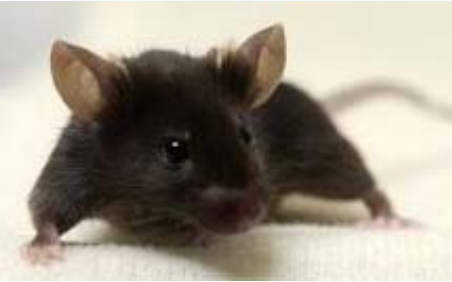
- Throughput/scale up facilitation
- ES and iPSC technologies for non-germline cohorts and preservation
- Optimization/retooling of GEMs
- Preclinical evaluation of/in PDAC models

Animal Research Support

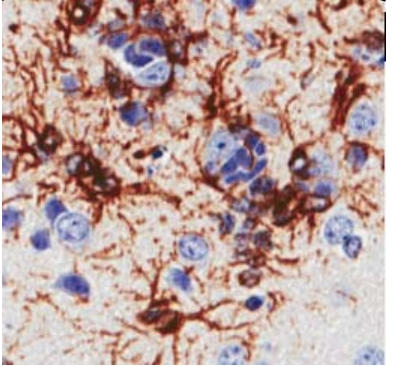
Philip Martin, DVM, DACVP

- Histopathology, Molecular Pathology, Quantitative Morphometrics,
- BioBank: TMAs, tissues, blocks, slides (glass/digital), fluids, nucleic acids

Conversion of Complex GEMs to Non-Germline Cancer-Bearing Cohorts



4OHT

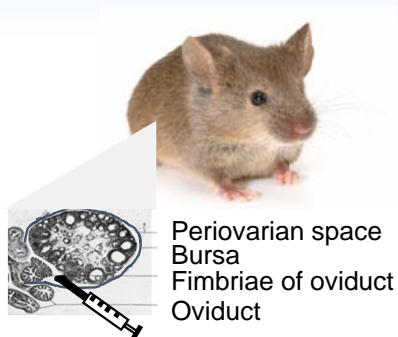


*Tg/KI-G(Z)T₁₂₁;KRas^{lsIG12D/+};
PTEN^{fl/+};GFAPCre^{ERT2}*

Develop GBM upon
4OHT induction

penultimate cross → blastocysts → ES cells

Mouse Models of Pathway-Specific Serous Epithelial Ovarian Cancer (SEOC)

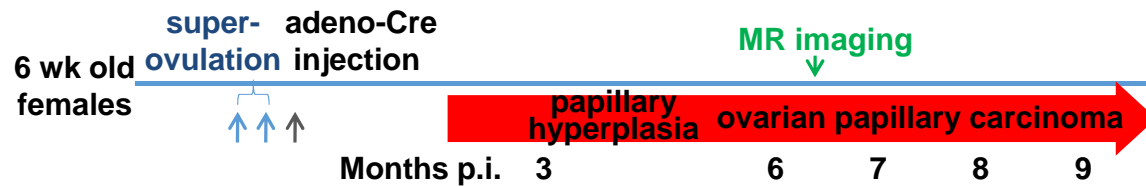


Induced events:

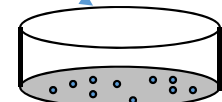
Rb_{tumor} suppression inactivation
 p53 mutation/loss
 Brca1 or Brca2 loss

Szabova, Yin et al, Cancer Research 2012

De novo model: Intra-bursal injection of adeno-Cre



Tumors

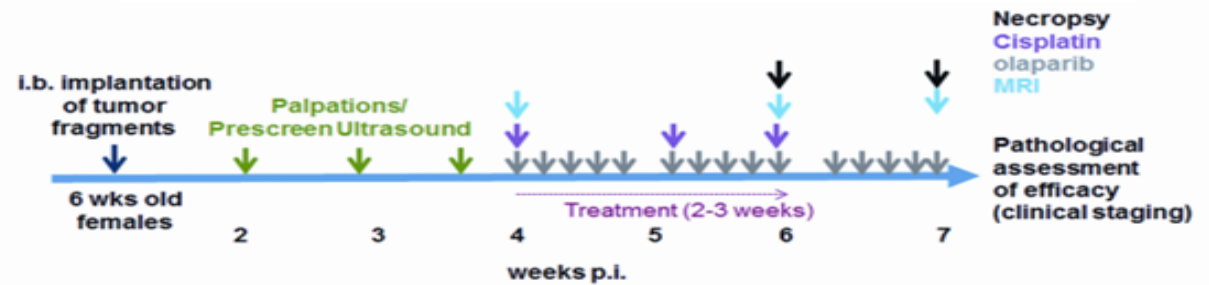
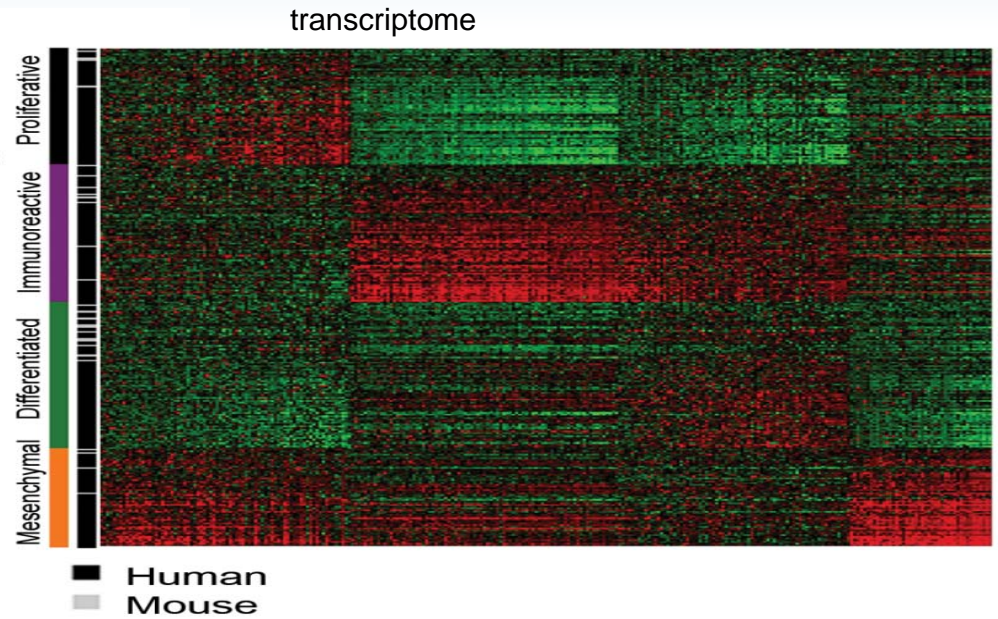
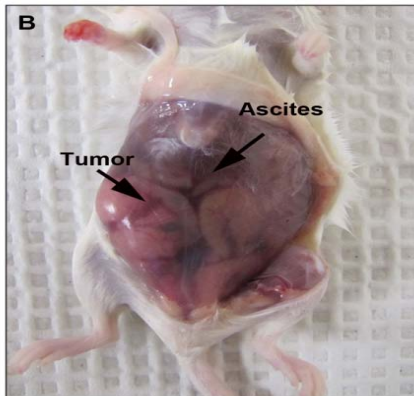
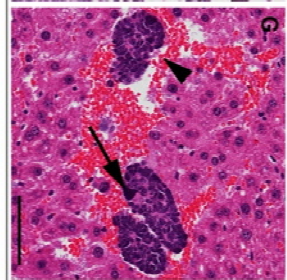
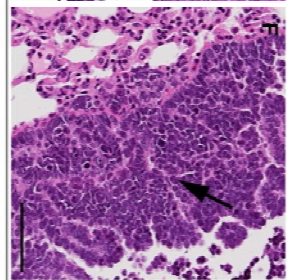
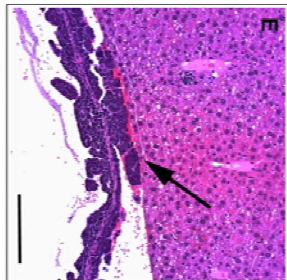
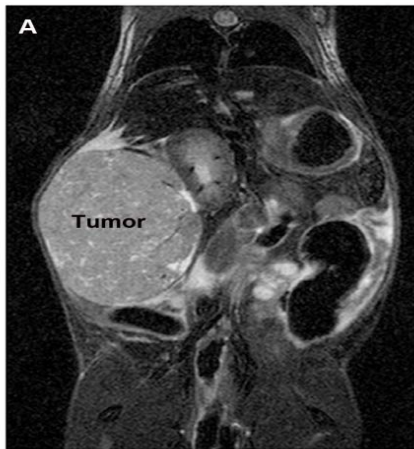


Cell lines

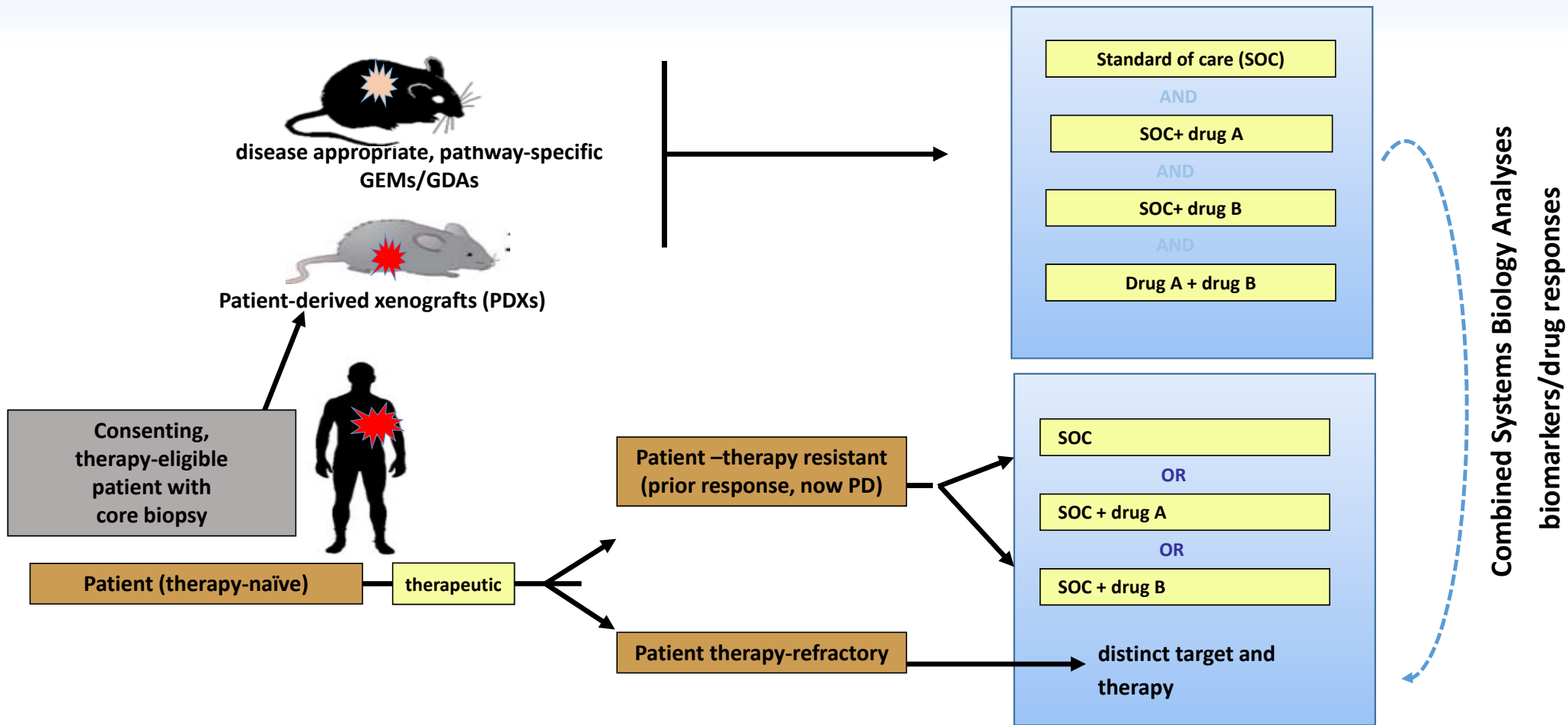
GDA model: Intra-bursal passage of tumor fragments

Recapitulates histopathology and molecular profiles of GEM models
 Tumors develop in 1-2 months

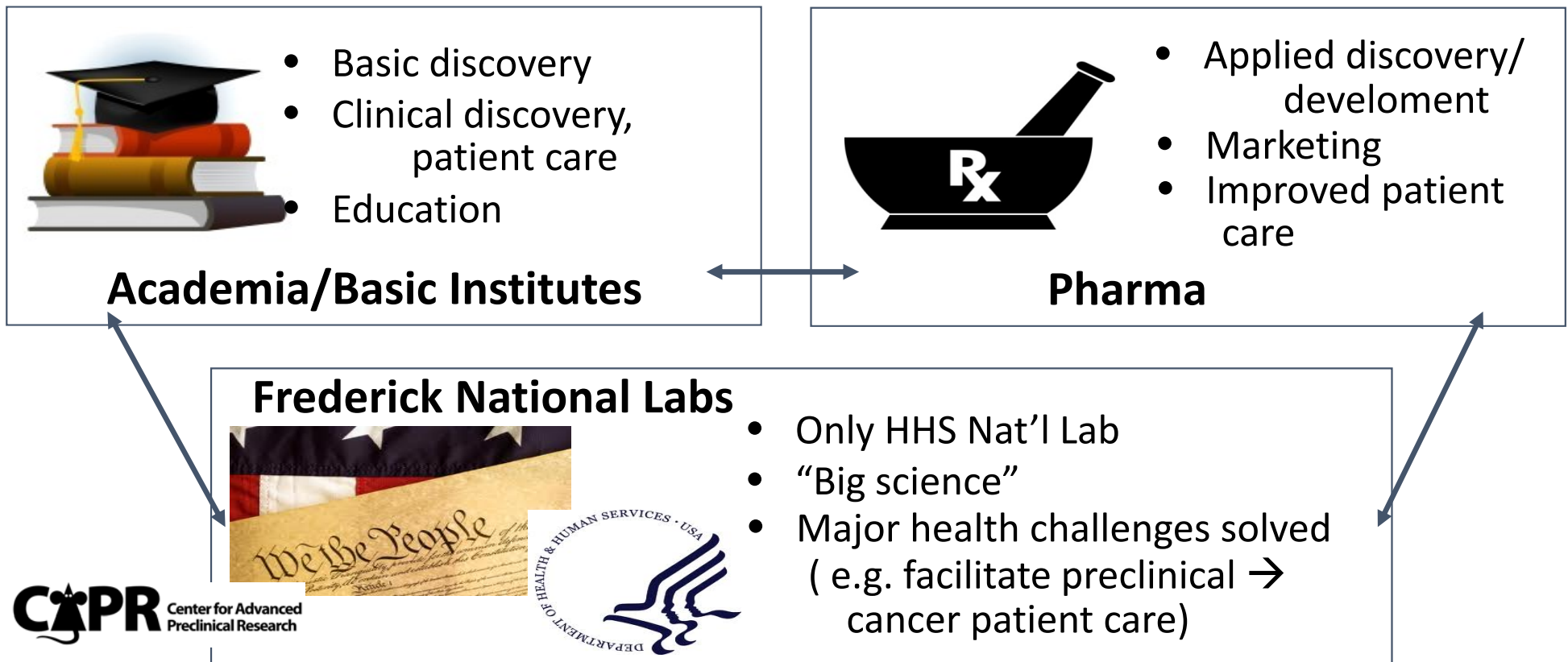
Preclinical Models of Serous Ovarian Cancer : Similarity to Human Disease



Optimal Preclinical Guidance via Cross-model Cross-species Unbiased Evaluation



A Path to Improved Cancer Patient Care: Development and Implementation of Preclinical Systems Predictive of Human Hypotheses



With their centralization of resources (both monetary and intellectual), the national labs serve as an exemplar for Big Science