

Future Directions in Clinical Research

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Outline

1. Status of Cancer Treatment

2. Overview of Clinical Research at UCDCC

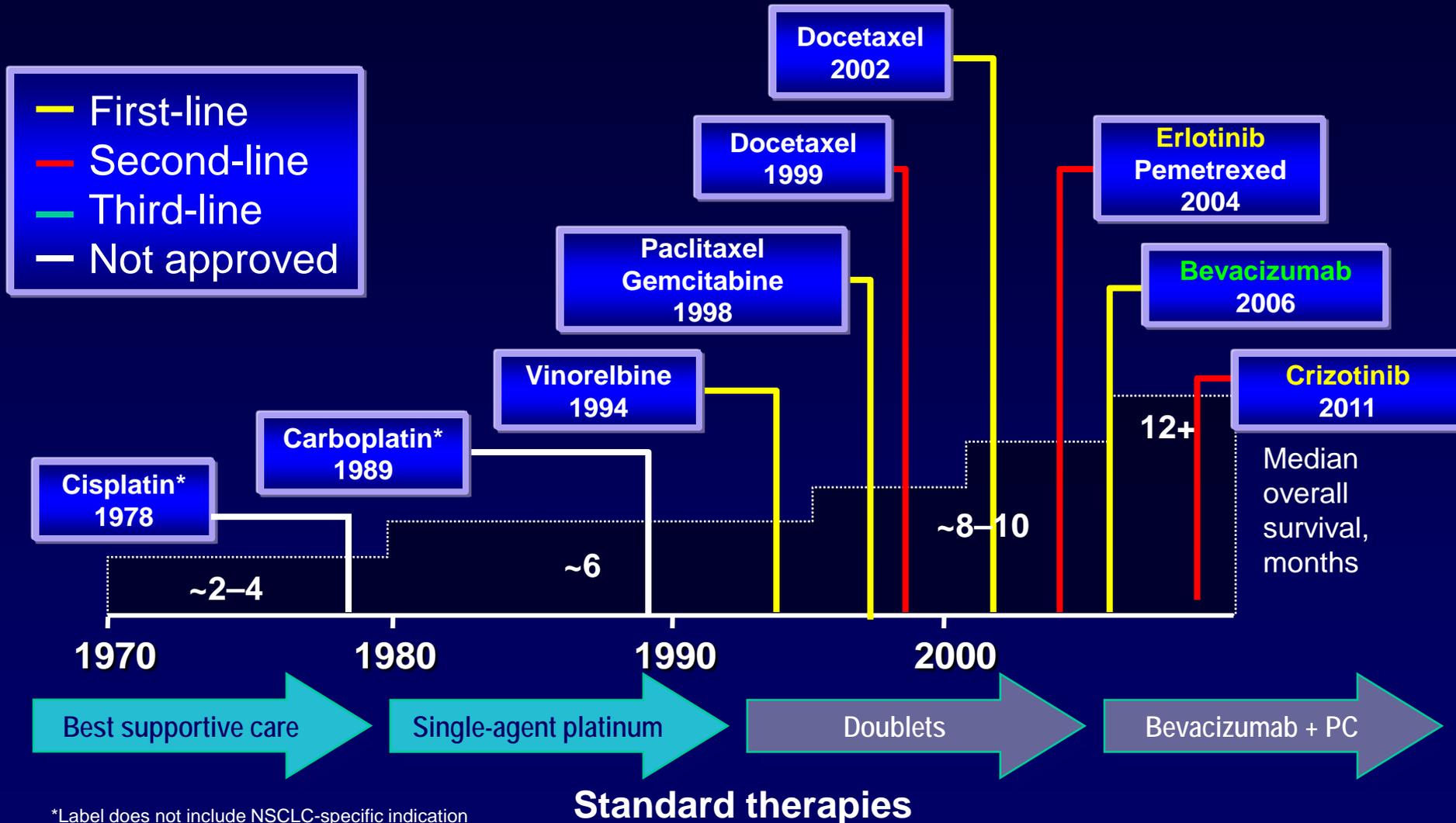
3. Examples of Clinical Research at UCDCC

Carboplatin microdosing study

iGXT platform

BGI

History of Therapy in Advanced NSCLC: FDA Approval Dates

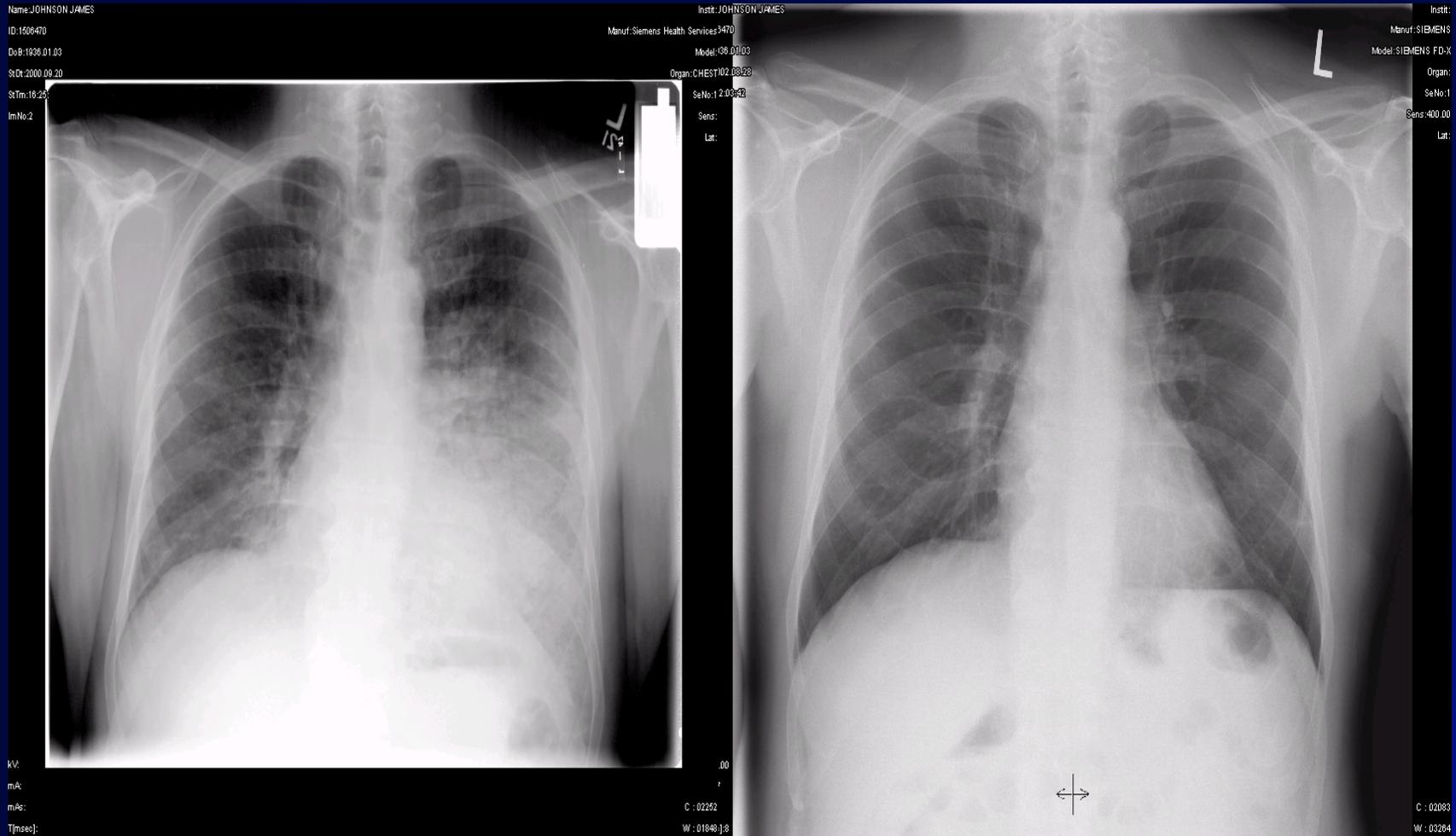


*Label does not include NSCLC-specific indication

Food and Drug Administration. At <http://www.fda.gov/cder/cancer/druglistframe.htm>. Accessed August 28, 2006.; National Comprehensive Cancer Network (NCCN). Practice Guidelines in Oncology. Non-small cell lung cancer v2.2006. Accessed August 28, 2006. Schump et al. Non-small cell lung cancer. In: *Cancer: Principles and Practice of Oncology*. 7th ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2005.

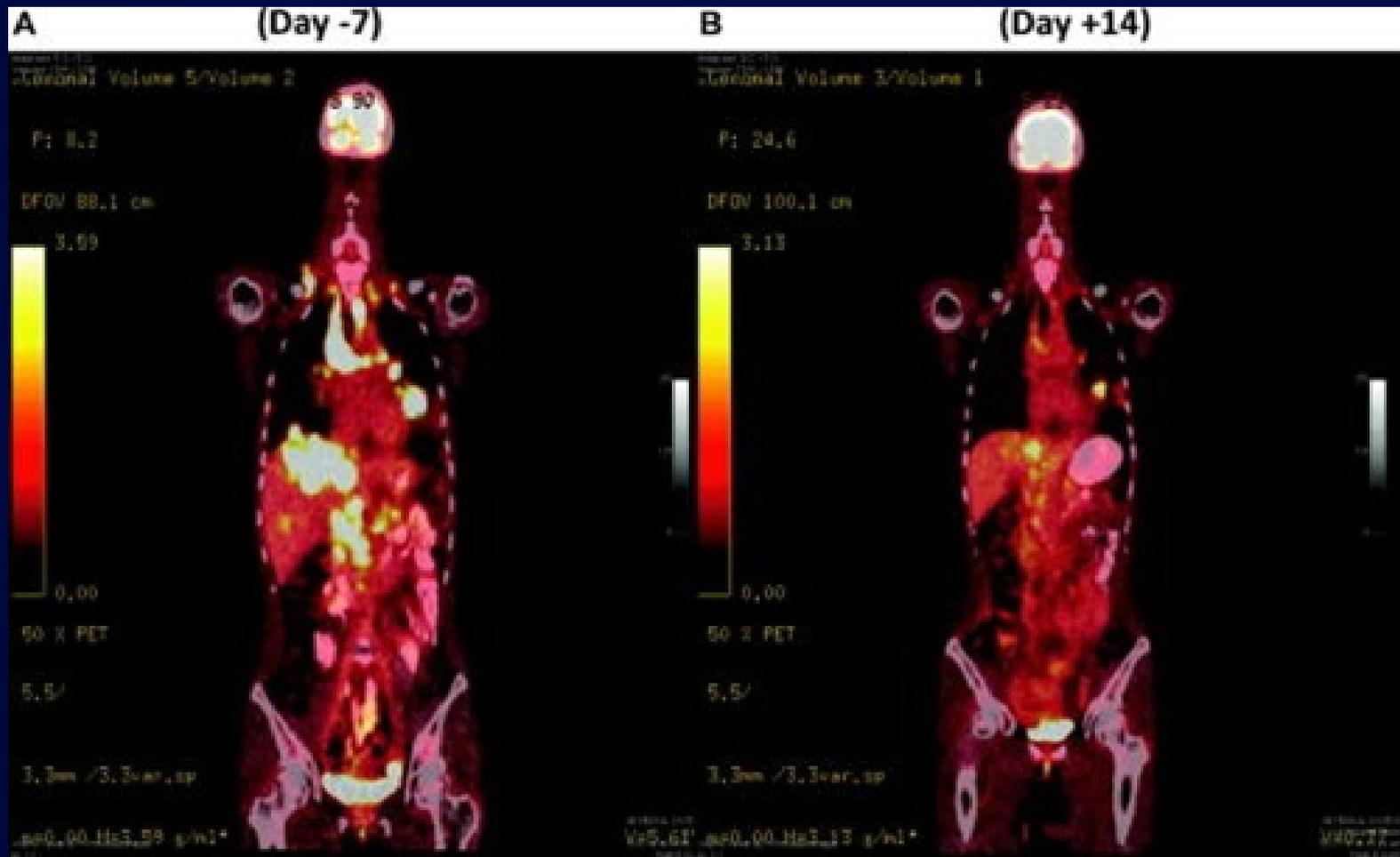
The Power of Personalized Medicine

EGFR mutation treated with Erlotinib



The Power of Personalized Medicine

ALK Positive Treated with Crizotinib



Personalized Medicine

Traditional therapy



**Patients with
same diagnosis
receive the same
treatment**

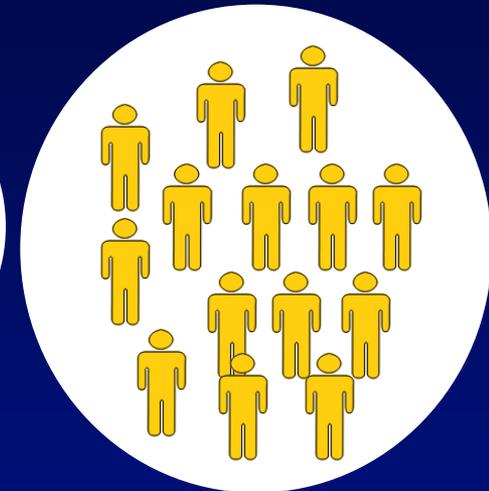
Personalized therapy



Genetic profile :
EGFR mutation
Targeted therapy:
Erlotinib



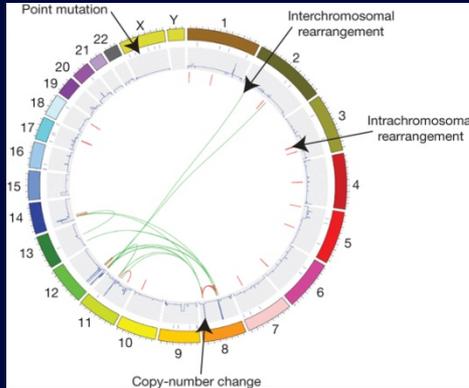
Genetic profile
ALK fusion gene
Targeted therapy
Crizotinib



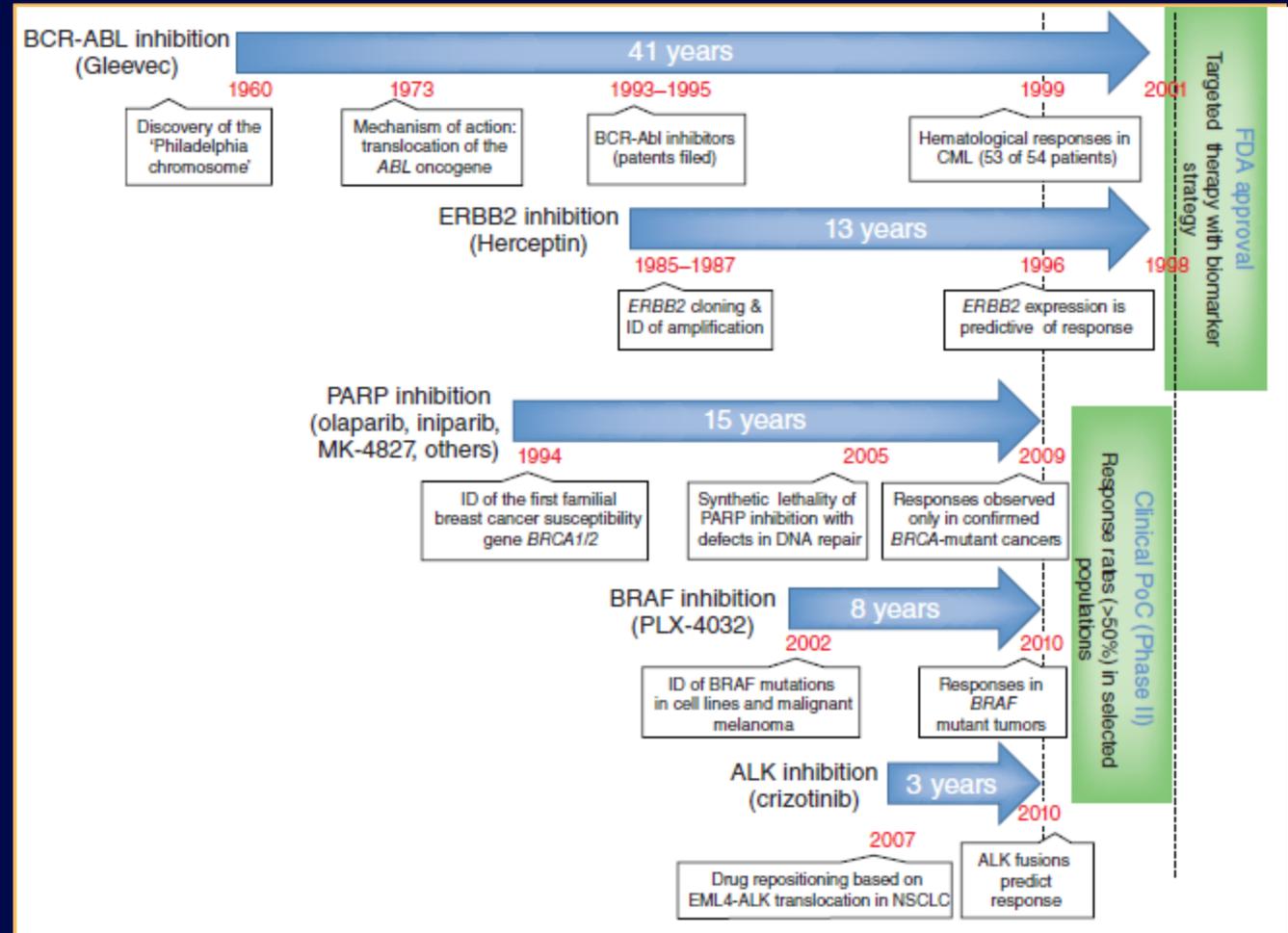
Genetic profile
Wild type
Chemotherapy

**Treatment based on a patients
unique genetic profile**

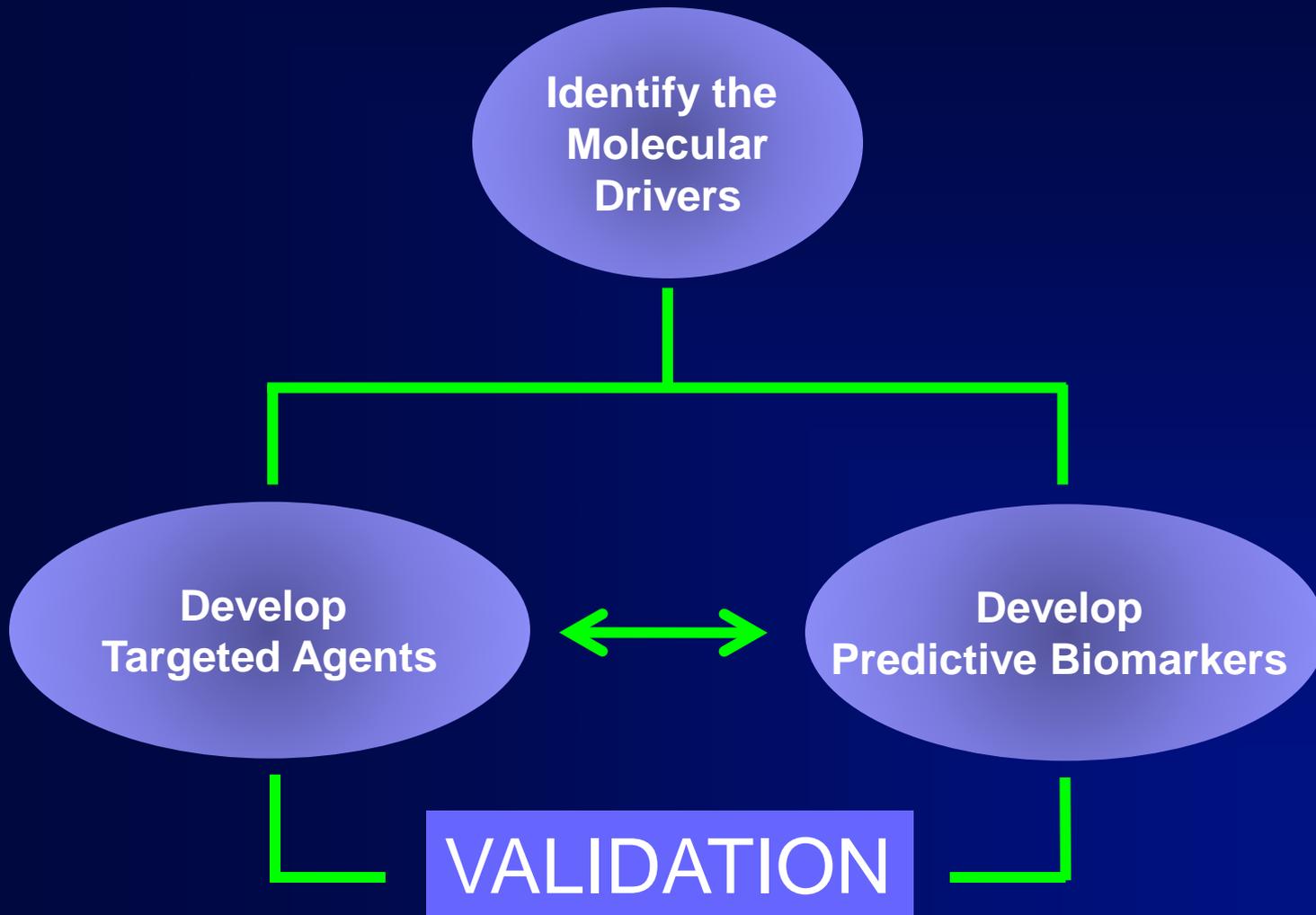
Acceleration of genomic discoveries to personalized medicine



Cancer is a Disease of the Genome



Pathway to Personalized Therapy



UCDCC Clinical Research

GOAL: Design, conduct, and publish impactful translational and clinical cancer trials that will contribute to reducing the cancer burden.

1. Promote, cultivate and support multidisciplinary collaborations to assist in the expeditious translation of scientific discoveries to clinical application through innovative investigator initiated trials and team science awards.
2. Support the clinical trials infrastructure
3. Accrue patients to clinical trials

The Importance of Clinical Trials

- The ability to translate biomedical discoveries into advances in cancer care is **DEPENDENT** on clinical trials.
- Knowledge gained guides further scientific research.
- Establishes evidence based “standards of care”.

Cancer Clinical Trials

Therapeutic Trials

Phase I - Determine dose and schedule

Phase II - Determine efficacy

Phase III – Determine if better than current treatment

Non-Therapeutic Trials

Prognostic Biomarkers

Screening and Early Detection

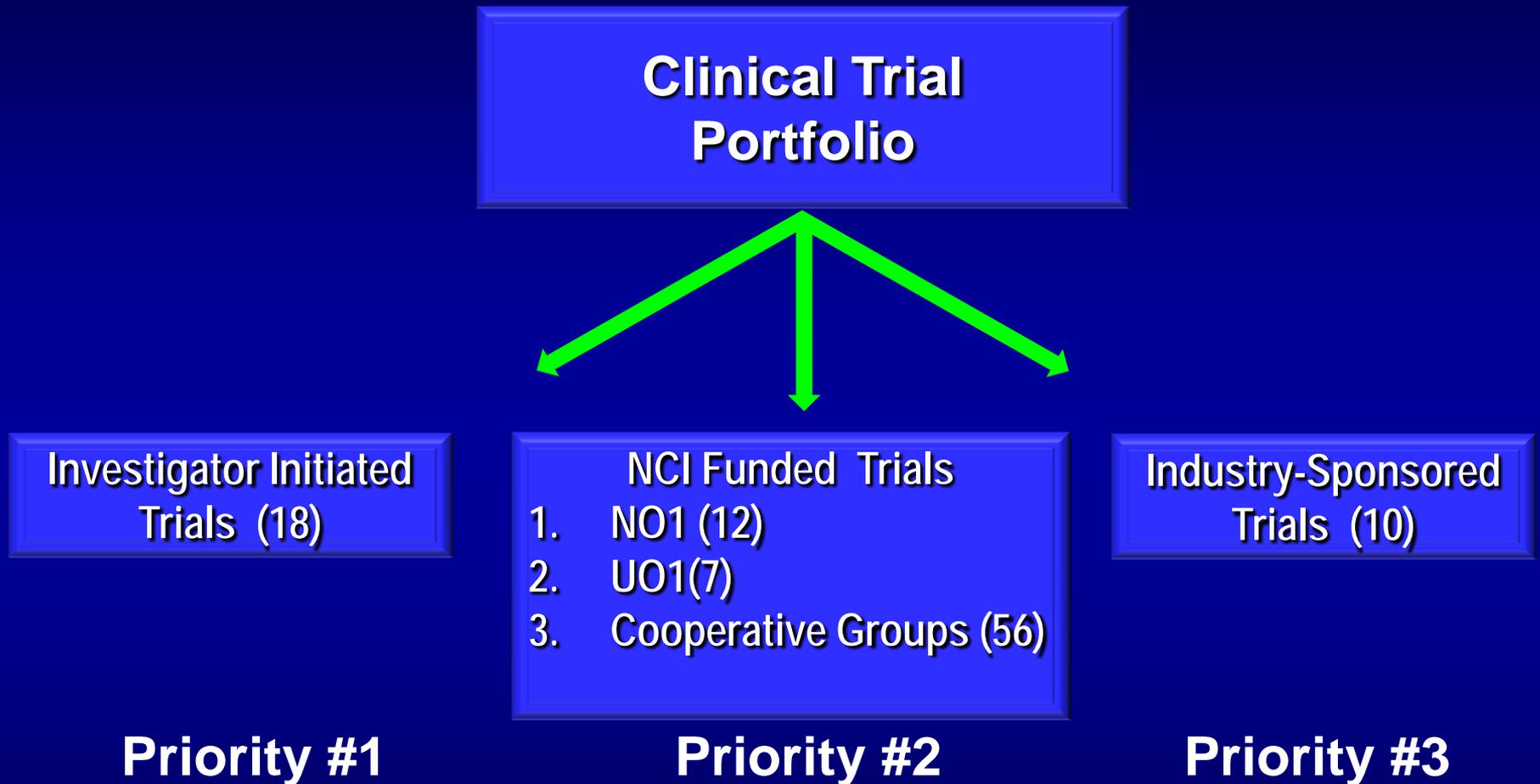
Cancer Prevention

Palliative Care/Quality of Life

Supportive Care

Comparative Effectiveness Research

Therapeutic Cancer Clinical Trials



**OVER 100 ACTIVE TRIALS
(Phase I Expansion Planned)**

The Clinical Trial Process



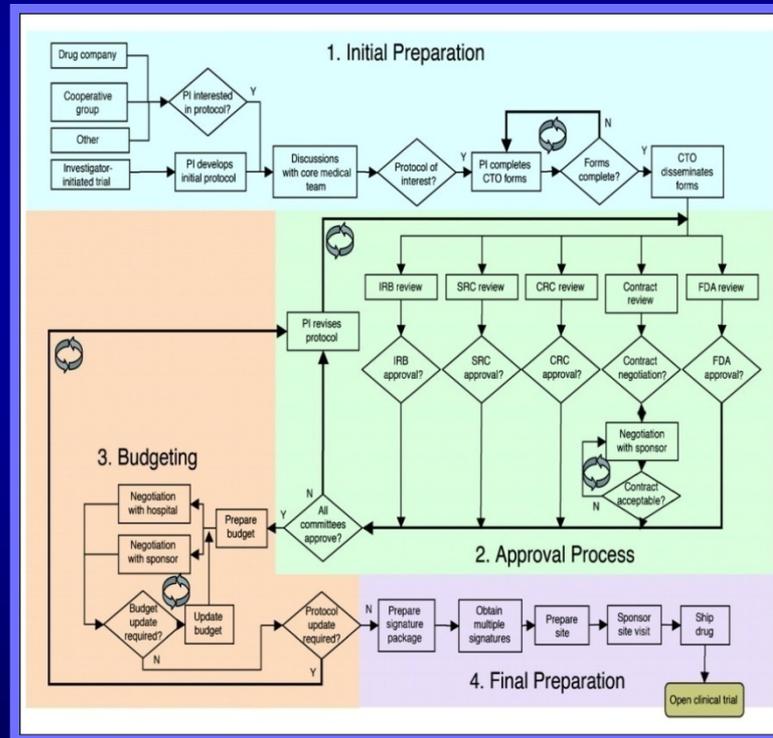
Idea



Draft Concept



Concept Approved



Timely Accrual



Data Quality



Data Analysis



Presentations & Publications



The Clinical Trials Infrastructure

Sample Listing of Participants Involved in the Opening of an Oncology Clinical Trial

Participant	Type
Primary	Principal investigators Sponsor Clinical trials office/ Regulatory staff Institutional review board Scientific review committee Contracts and grants office Division chair Department head Core medical team
Secondary	Clinical research center Director, medical affairs/oncology administration US Food and Drug Administration Finance department General hospital review board Human subjects radiation committee Pathology review Institutional biosafety committee Legal department Medical ethics board Office of sponsored research Pharmacy Radioactive drug research committee Site coordinator

Clinical Trials Infrastructure

Clinical Trials Shared Resource



2.5 Administrative staff
1.0 Patient navigator
.5 Protocol developer

Clinical Molecular Pharmacology Shared Resource



**UC Davis
Investigator Initiated
Clinical Trials**

Fully integrated with clinical trials team
Pre-clinical modeling/rationale
Develop hypotheses & studies
Collect/process/bank UCD specimens
Perform or coordinate analyses

**California Cancer
Consortium**

Develop hypotheses & studies
Collect, process & ship PK specimens
Collect & bank correlative specimens
Perform analysis on select trials

**Southwest Oncology
Group (SWOG)**

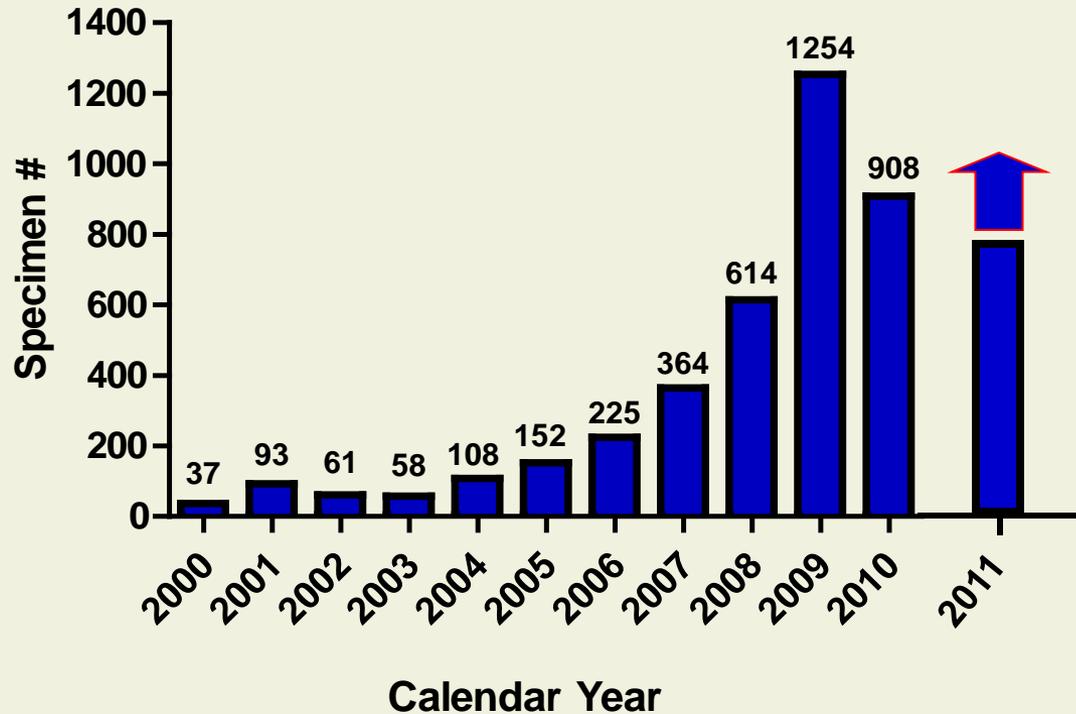
Develop hypotheses & studies on
select lung and GU trials
Collect & ship UC Davis specimens
Perform analysis on select trials

**Outside Institutions
or Industry**

Collect, process & ship specimens
Perform analysis
Advise on translational studies

UC Davis Clinical Trial Specimen Collection

Specimens from UCD Patients
Processed by CMPSR



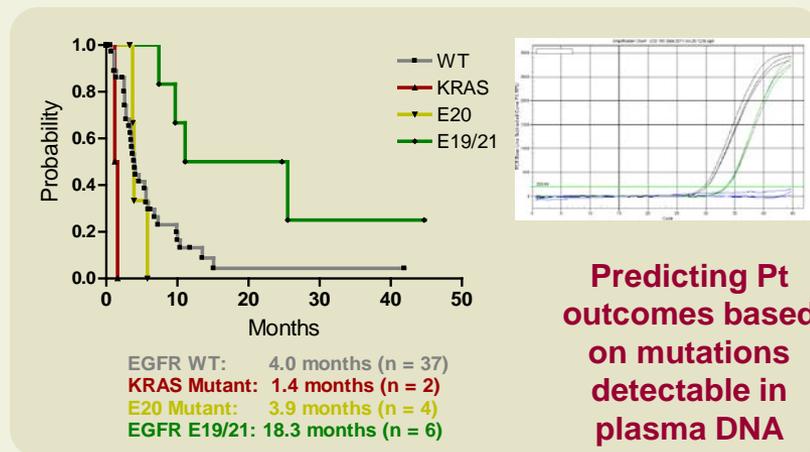
Graphs shows unique patient visits. One specimen = all draws at a given timepoint

68 active clinical trials supported with specimen accrual

20,564 individual aliquots currently stored (as of 10-04-11)

Translational Research Interests Associated with Clinical Trials

- Pre-clinical modeling
 - Signal transduction inhibitors
 - Aurora kinase inhibitors
 - HSP inhibitors
- Biomarker Development
 - Blood markers
 - Circulating tumor DNA mutations
 - Proteomics
 - Multispectral IHC
 - Predictive mutation profiles
- Clinical Trial Concept Development
 - Pharmacodynamic Separation
 - Enhancing EGFR-targeted agents
 - Overcoming resistance

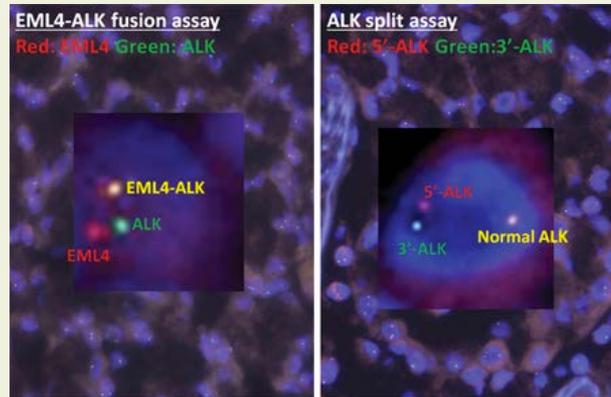


Genomics Resources

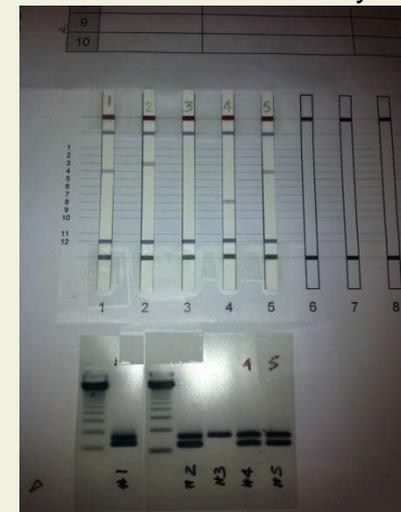
■ Molecular Diagnostic Laboratory

- CLIA/CAP certified
- Perform about 50,000 tests per year
- > 30% increase in testing each year
- Includes **ONCOLOGY**, genetic, hematology, infectious disease, and screening

Crizotinib Therapy
Lung Cancer



Cetuximab Therapy
Colon Cancer
K ras mutation assay



Microdosing approach to identify chemoresistance in bladder cancer

Henderson et al. Intl J Cancer 2011

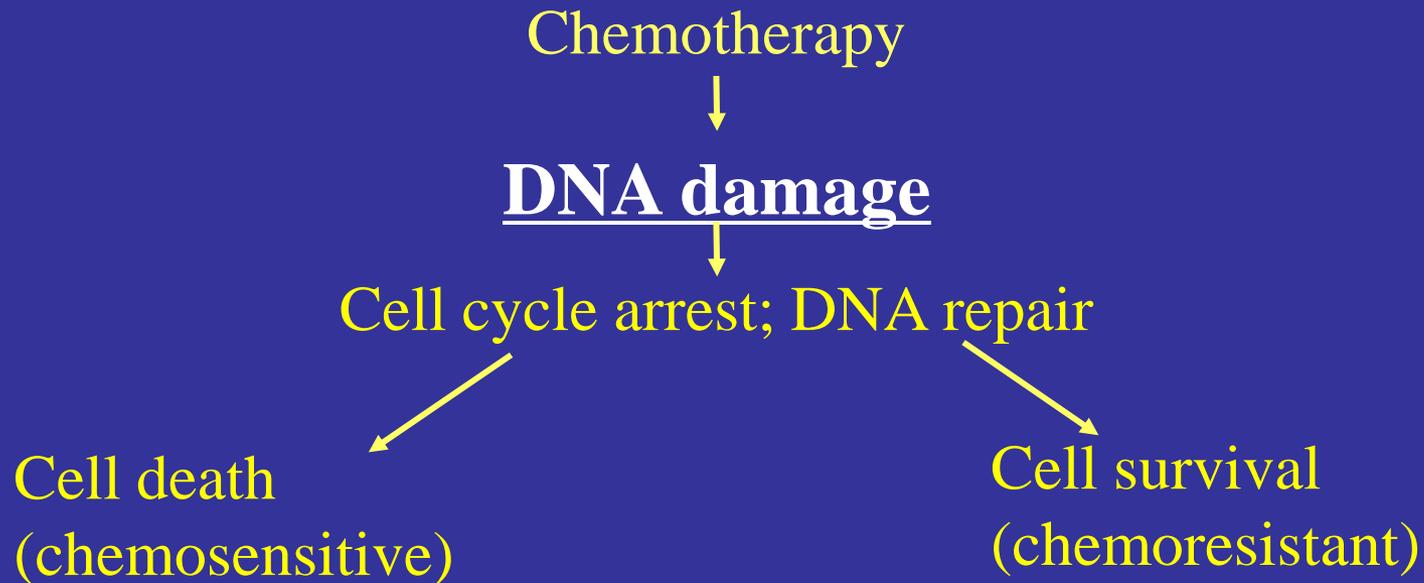
Wang et al. Chem Res Toxic 2010

Henderson and Pan. Bioanalysis. 2010

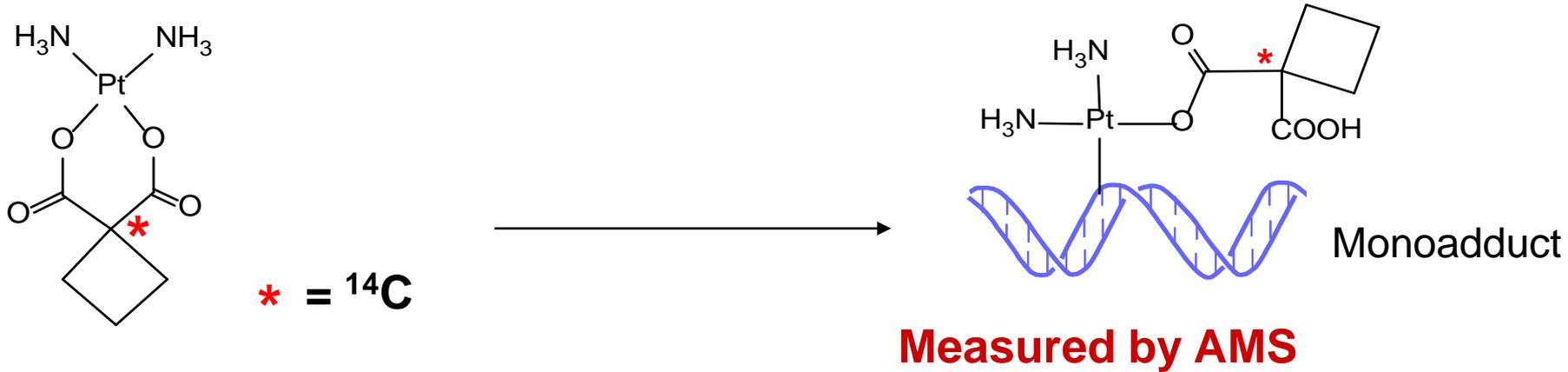
Objectives:

- 1. To identify resistance to platinum chemotherapy before administration of chemotherapy; If so, chemotherapy can be avoided or modified in those patients with chemoresistant cancer.**
- 2. To analyze the underlying mechanisms of chemoresistance for personalized therapy, drug development and design of clinical trials.**

Outline of response to platinum chemotherapy



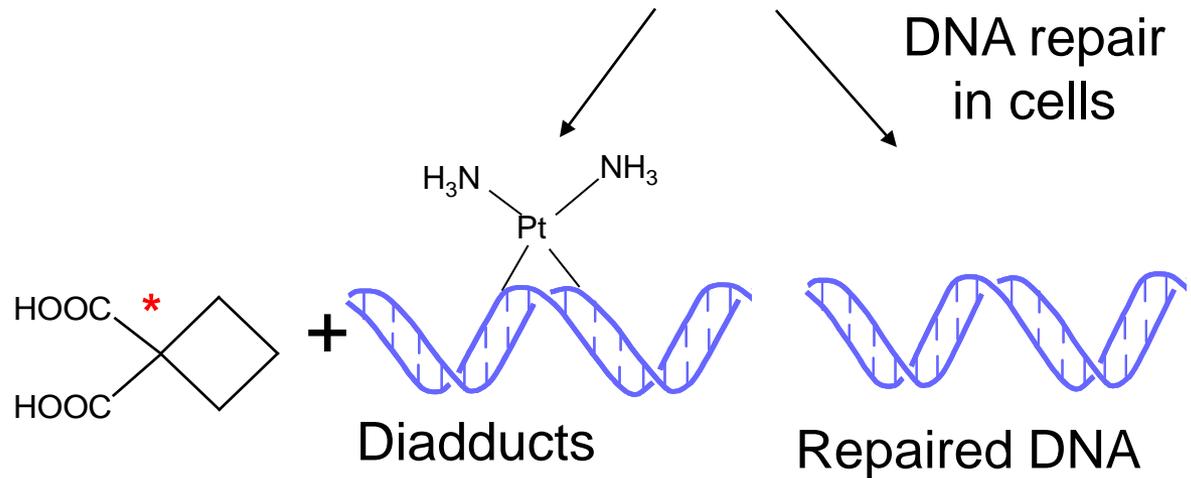
Carboplatin-DNA Adduct Formation



$[^{14}\text{C}]$ carboplatin

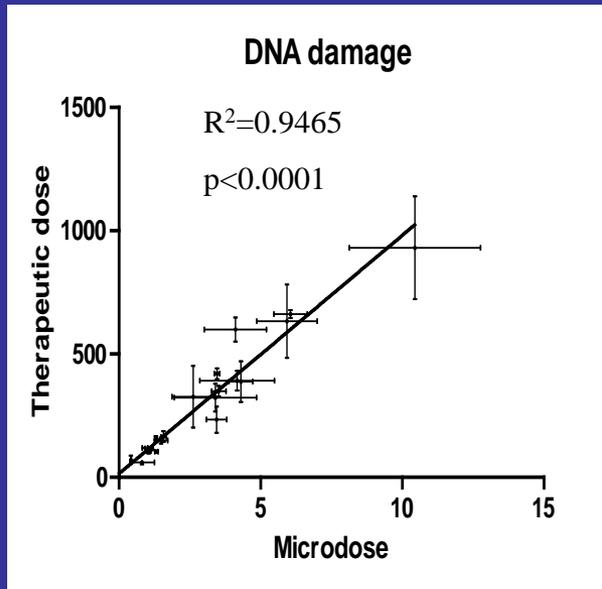
* ^{14}C , which can be detected by accelerator mass spectrometry (AMS)

(10^{-18-21} mole)

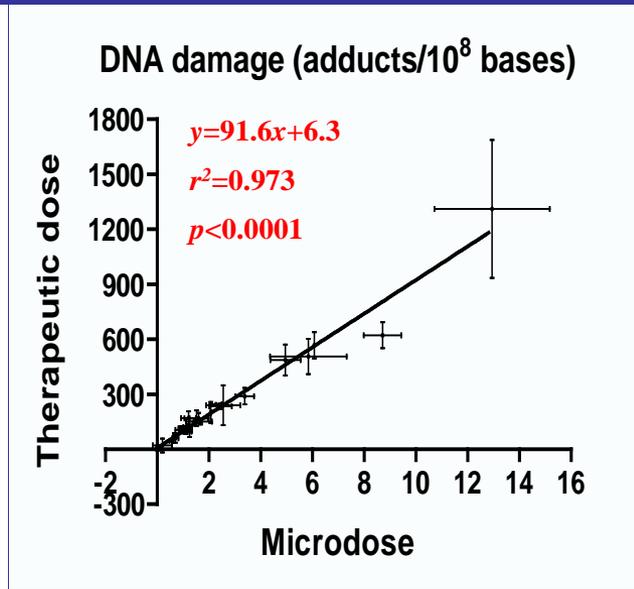


Goal: Use carboplatin-DNA monoadducts as a predictive biomarker of patient response to platinum-based chemotherapy

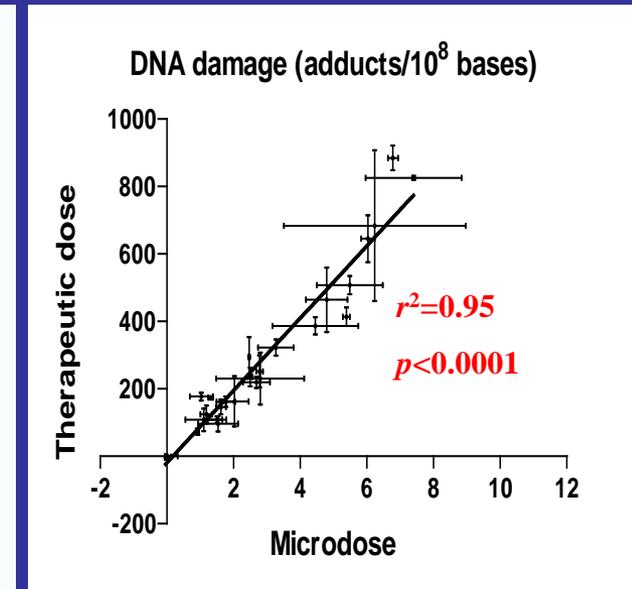
Linear relationship of DNA monoadducts induced by carboplatin



Bladder cancer

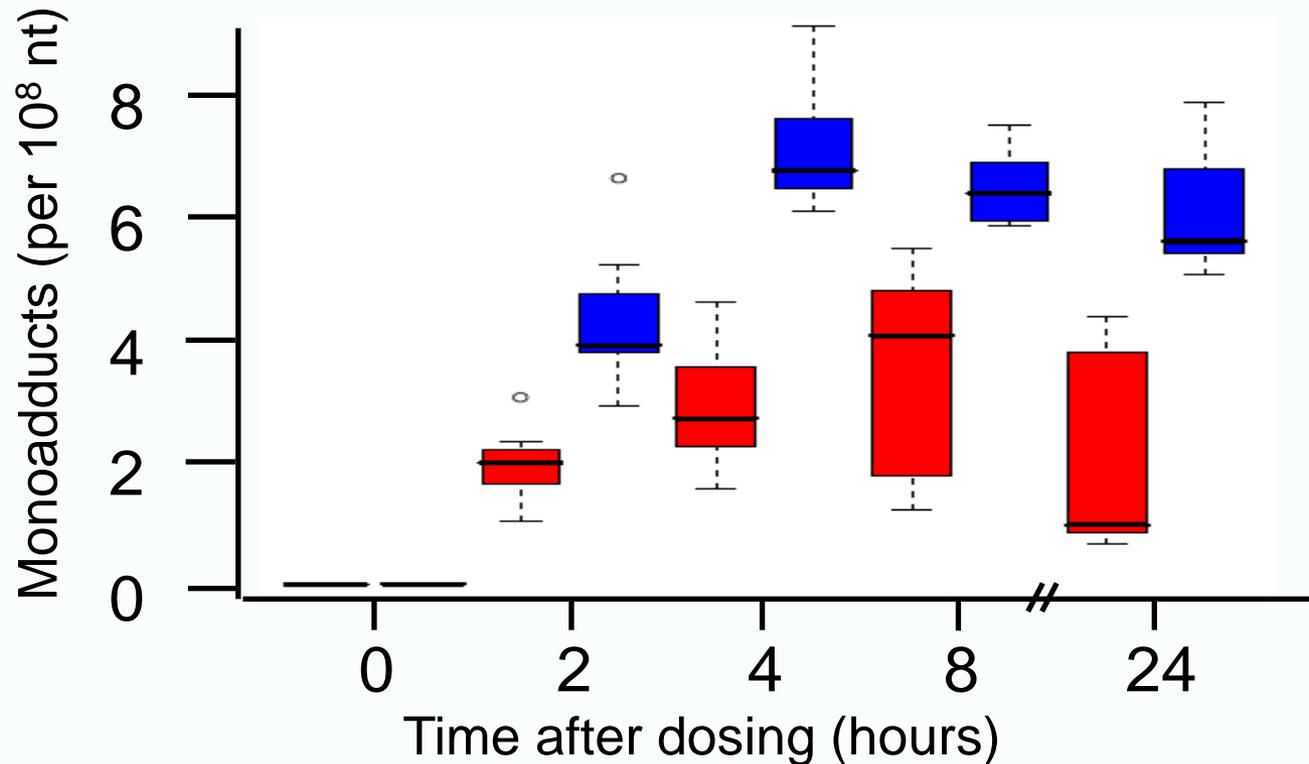


NSCLC



Breast cancer

Levels of DNA damage predict chemoresistance in NSCLC cell lines



Significant differences between in monoadducts between resistant cell lines (red) and sensitive cell lines (blue)

Phase 0 trial design

Bladder cancer and NSCLC

Phase 0 study: One microdose (1/100th) of ¹⁴C-carboplatin:

1. PK study (drug metabolism);
2. Cell uptake in PBMC;
3. DNA adducts of PBMC.
4. Repair of DNA adducts in cultured PBMC.
5. DNA adducts in bladder cancer specimens from TURBT

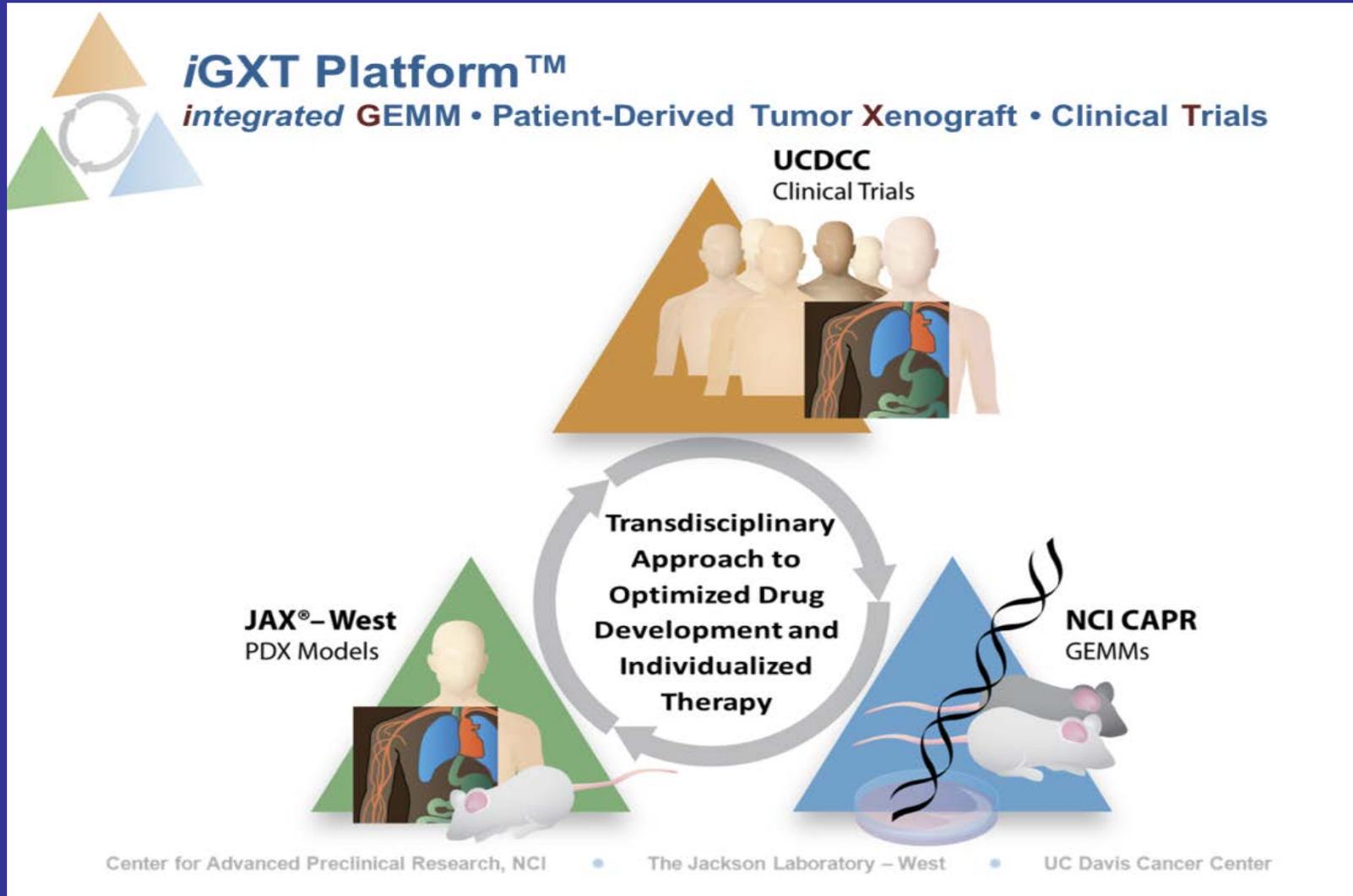
Off study therapeutic chemo with platinum chemotherapy

1. Evaluate response, and correlate with DNA damage and repair, PK, cell uptake and efflux,.
2. Molecular correlation (such as ERCCs and XRCCs)

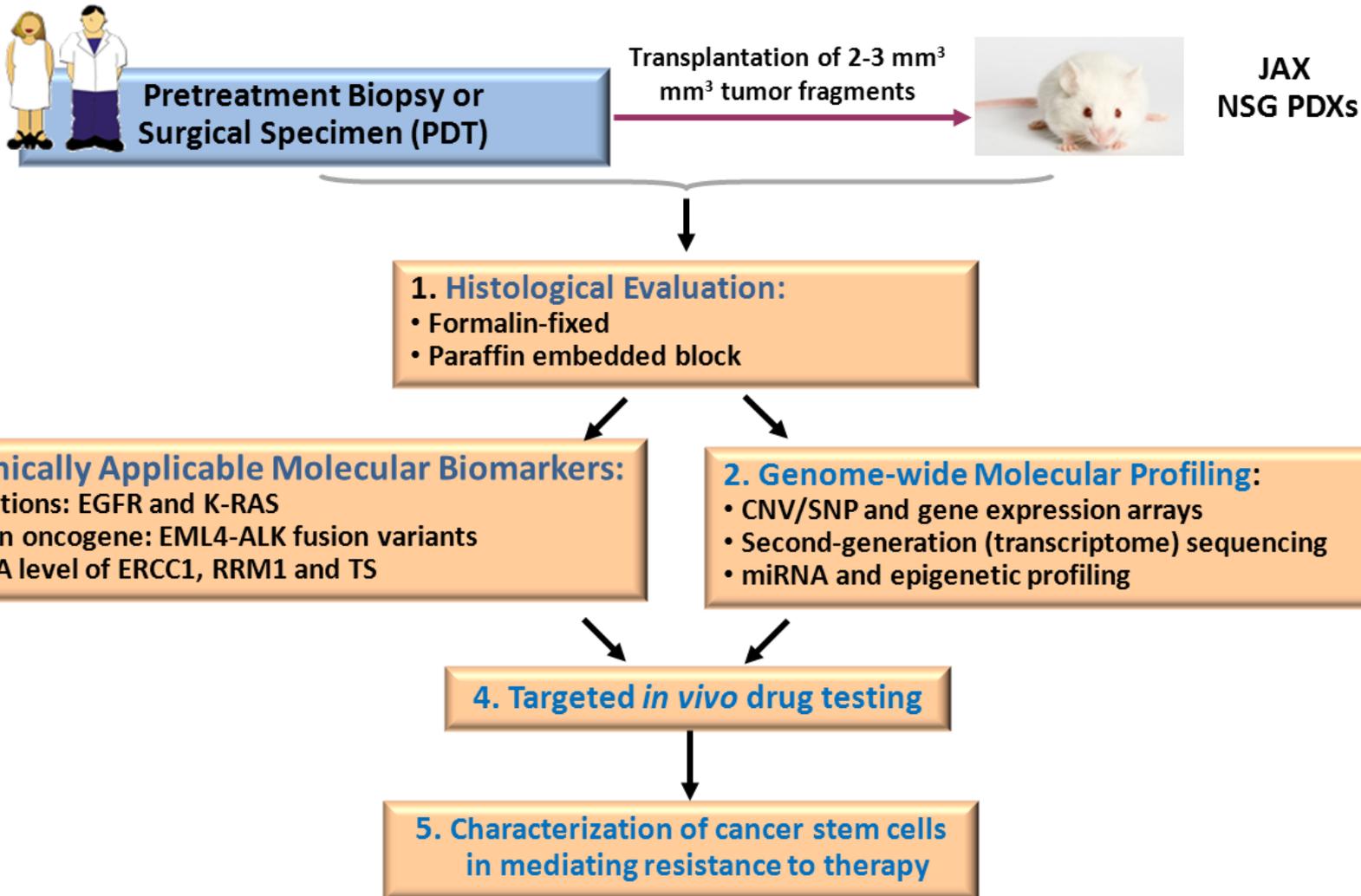
Current status of the Phase 0 trial:

- The recommended Phase II dose of ^{14}C -carboplatin will be 10^7 dpm/kg of body weight.
- The recommended Phase II dose of carboplatin will be 1% of therapeutic dose.
- The radiation exposure is less than 1% of an abdominal CT scan.
- This study is well tolerated without any detectable toxicity.
- The half-life of ^{14}C -carboplatin in blood is 1.5-2.0 hours.

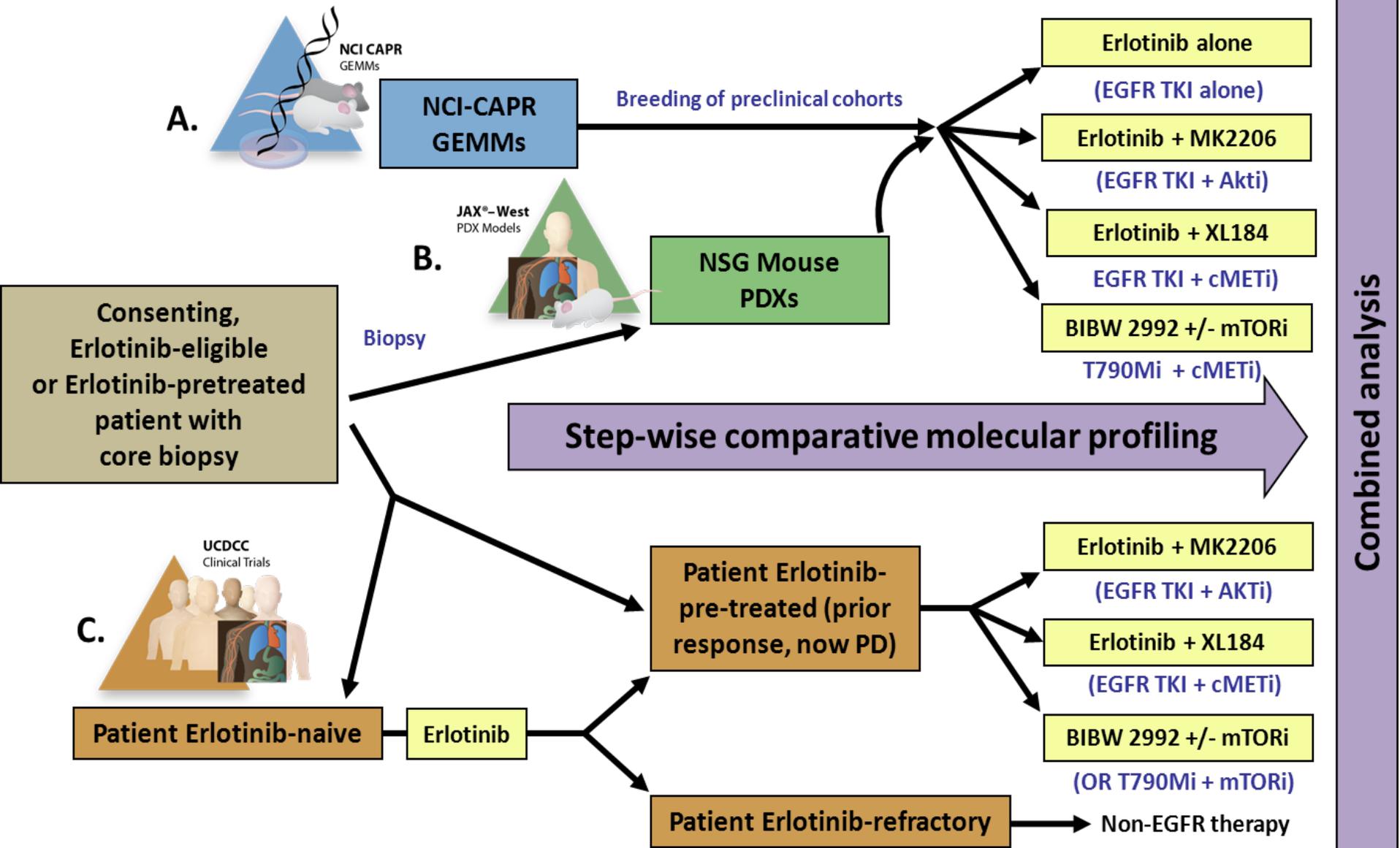
(integrated Genetically Engineered Mice/Patient Derived Xenografts/Clinical Trials) research platform



Comparative Characterization of NSCLC Patient Tumors (PDTs) & Patient-Derived Xenografts (PDXs) in NSG Mice (JAX-West & UC-Davis)



Pathway-Driven Approach to Deciphering EGFR TKI Resistance





Efficacy Study Results: MRI

Treatment	n	Diffuse masses/ 1-2 lobes	1-2 large nodules	Minimal tumors	No visible tumors
Vehicle	10	10			
Erlotinib	10	1	1	3	5
BIBW2992	10			6	4
Erlotinib + BIBW2992	10			5	5
MK-2206	10	5		3	2
Erlotinib + MK-2206	10			3	7

- MRI scans show diffuse, multifocal tumors in all mice of vehicle group
- Response seen in erlotinib, BIBW2992, erlotinib + BIBW2992, erlotinib + MK-2206, and ~50% of MK-2206-treated groups by pathology lesion score and MRI

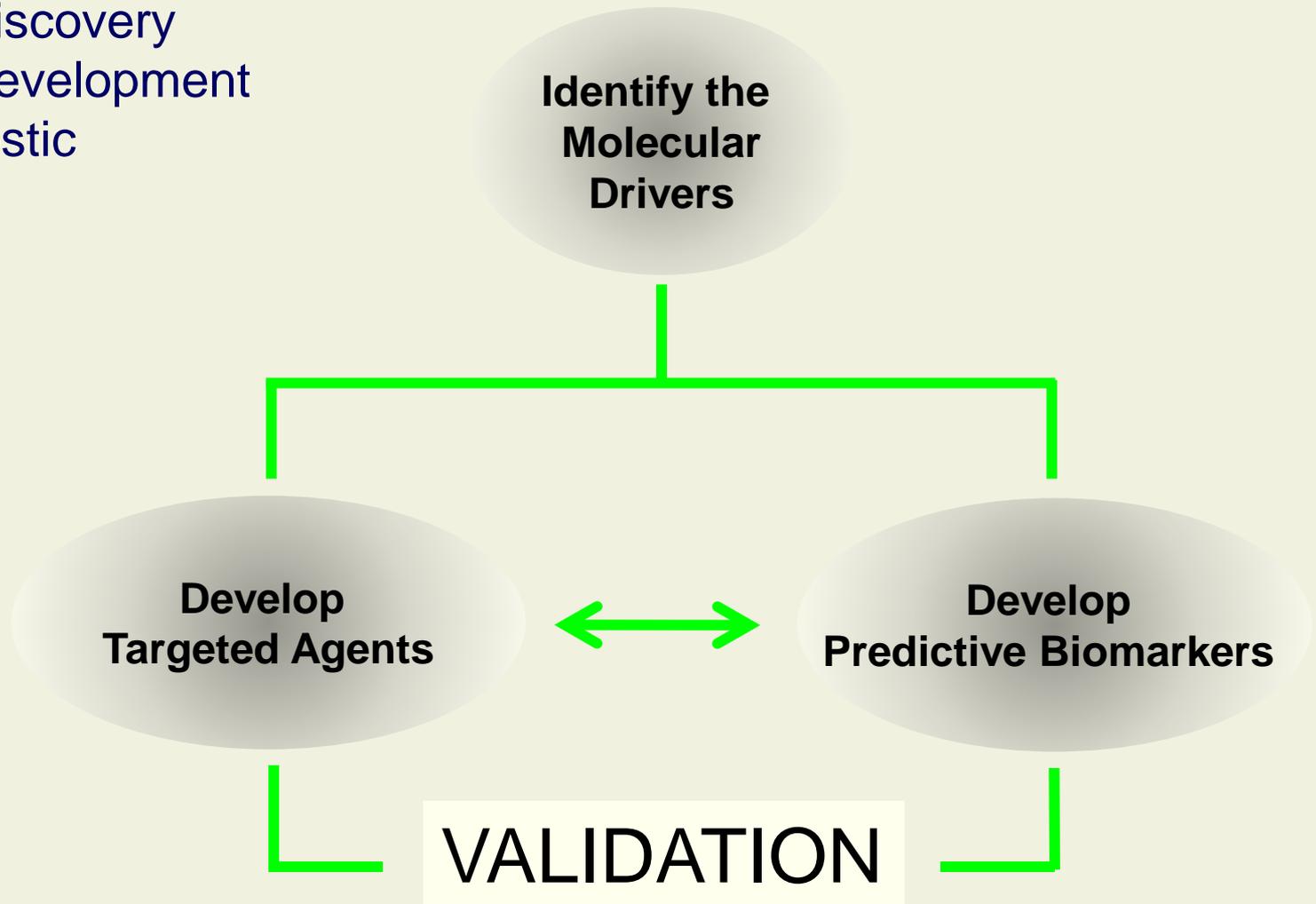
Genomics Resources- BGI@UCDAVIS

- BGI is one of the world's premier genome sequencing centers
- Its sequencing output is expected to soon surpass the equivalent of more than **15,000 human genomes** per year.
- Powered by over 150 next-generation sequencing platforms and 500 bioinformatics professionals
- Expanding to the Americas - UC Davis will be the primary site in the Americas (10-24-11 signing)

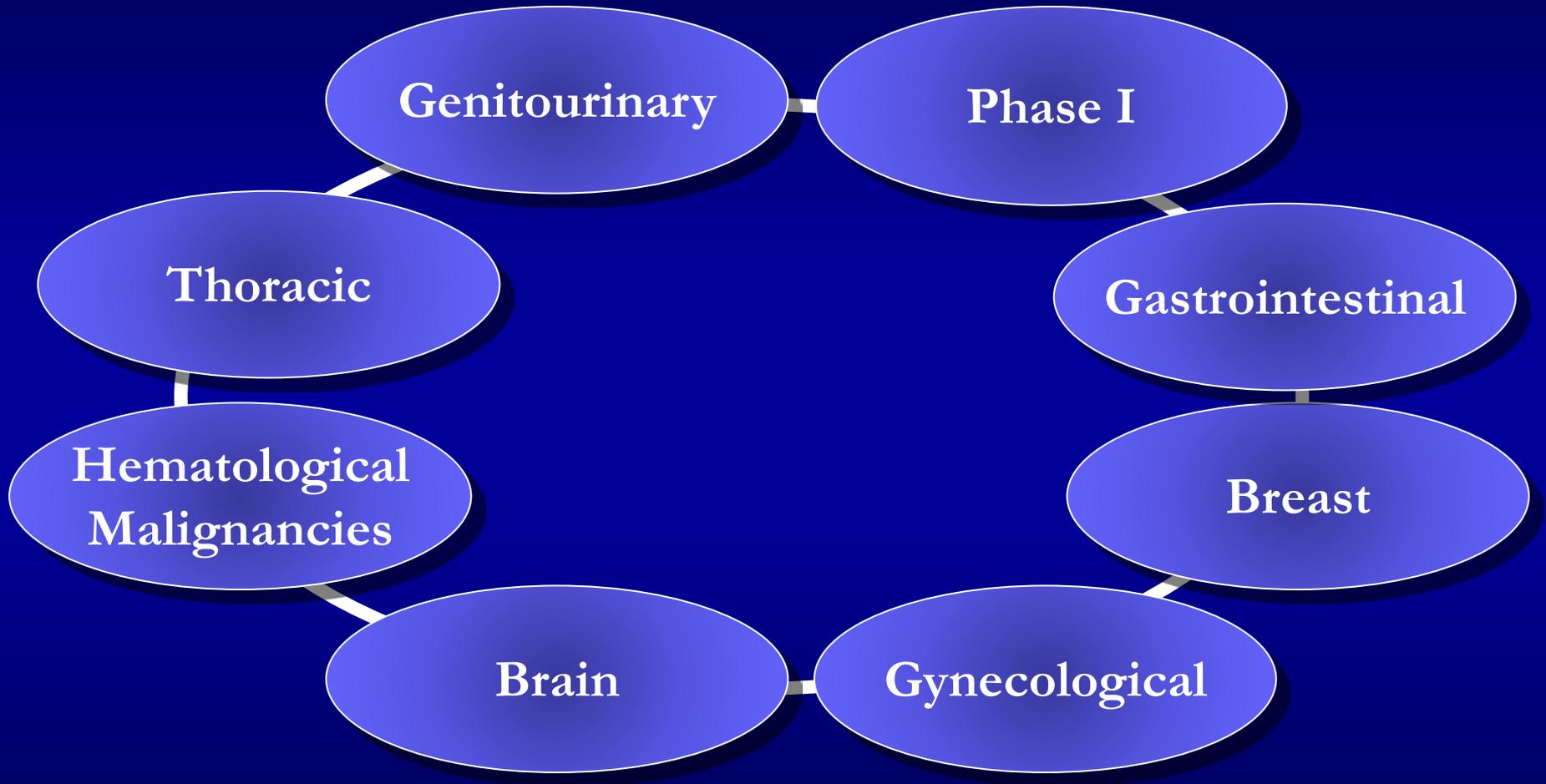
Oncology

Develop a pipeline for personalized therapy

- Drug discovery
- Drug development
- Diagnostic



Cancer Innovation Groups



Foster multidisciplinary collaborations that will lead to INNOVATIVE bench to bedside investigator initiated & national protocols