Translational impact of multimodal data analysis and integration in oncology
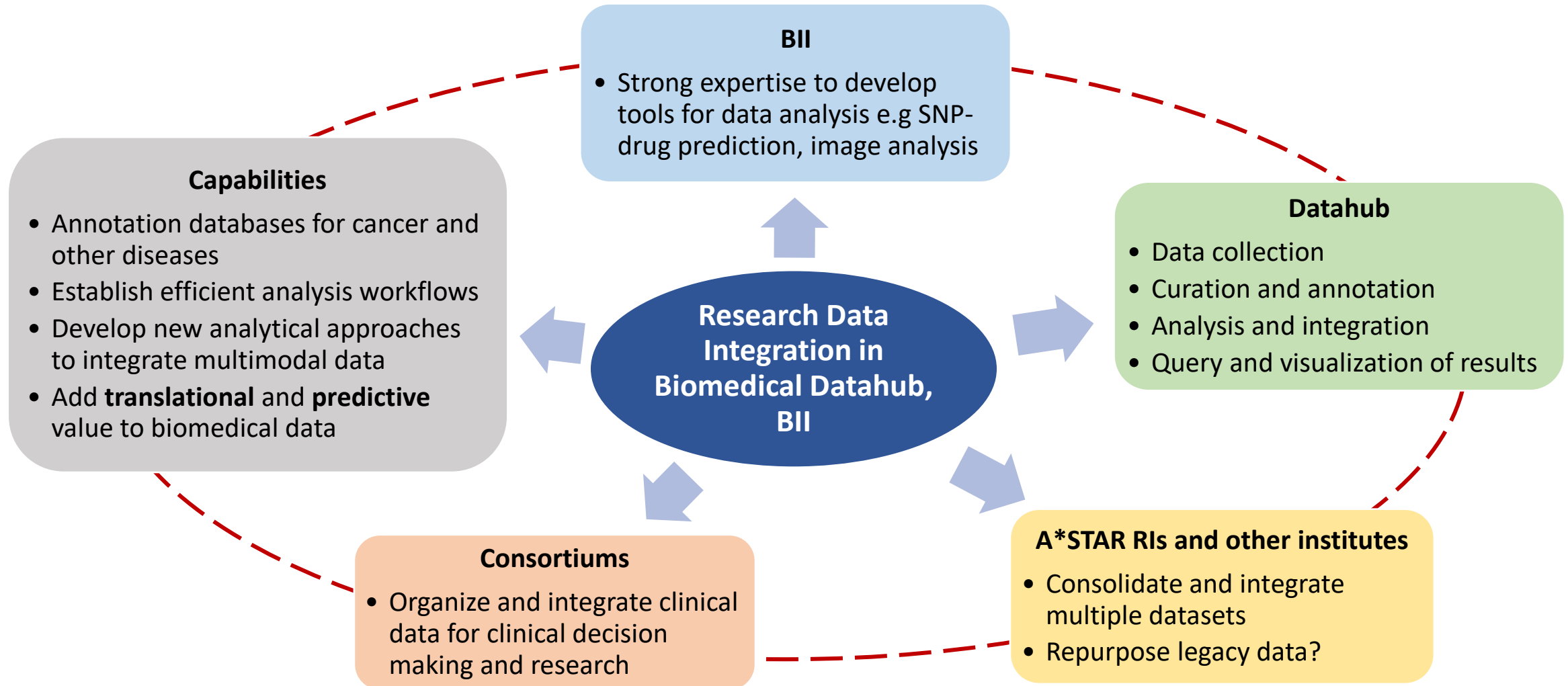
Xing Yi Woo

Senior Principal Investigator and Head of Research Data Integration (Biomedical Datahub)

Bioinformatics Institute A*STAR

woo_xing_yi@bii.a-star.edu.sg

Our mission: To build an ecosystem that bridges the complexity of computational biology and data science with the needs of researchers and clinicians to drive biological discoveries and predict translational outcomes.
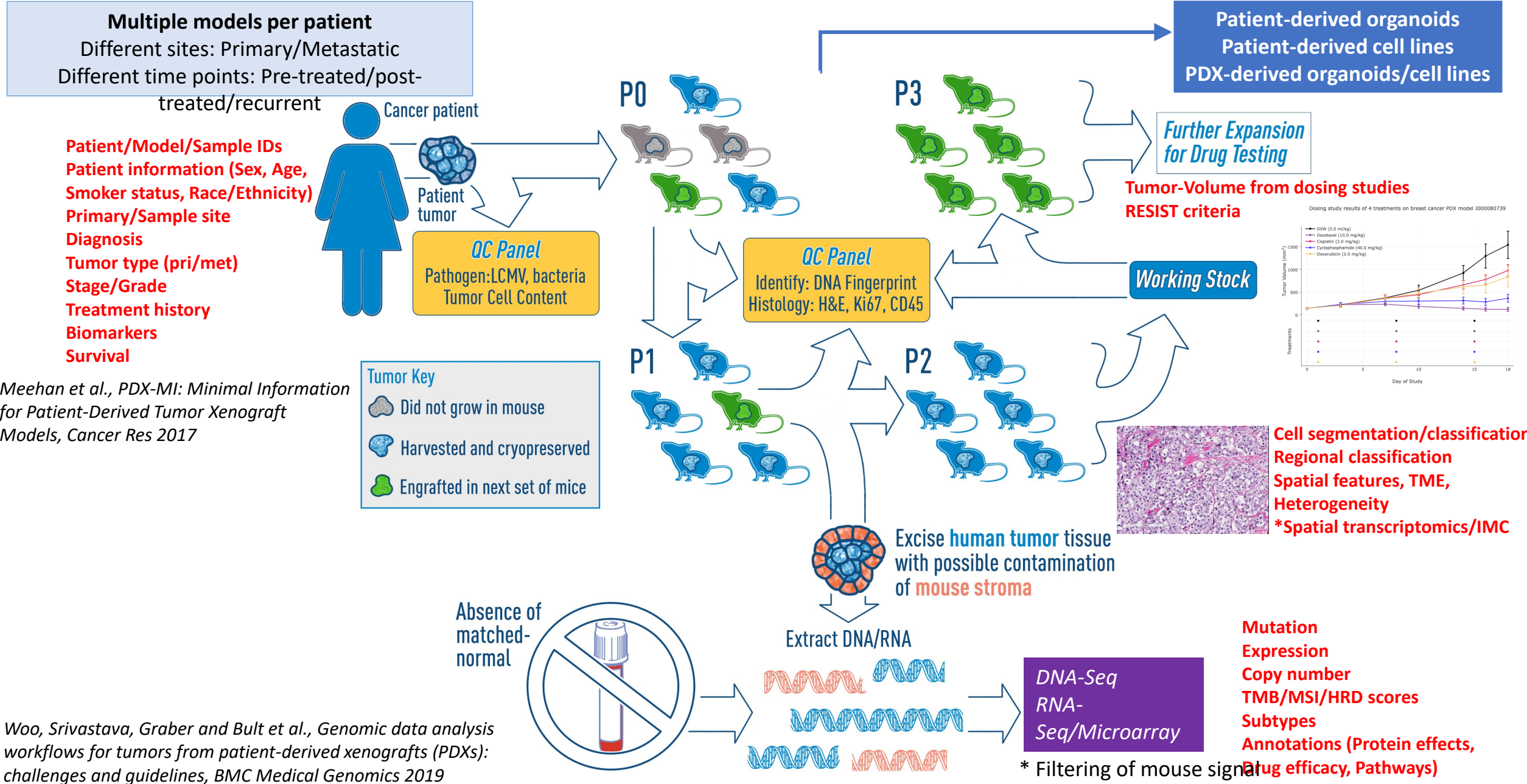

BII
- Strong expertise to develop tools for data analysis e.g SNP-drug prediction, image analysis

Capabilities
- Annotation databases for cancer and other diseases
- Establish efficient analysis workflows
- Develop new analytical approaches to integrate multimodal data
- Add **translational** and **predictive** value to biomedical data

Datahub
- Data collection
- Curation and annotation
- Analysis and integration
- Query and visualization of results

Research Data Integration in Biomedical Datahub, BII

Consortiums
- Organize and integrate clinical data for clinical decision making and research

A*STAR RIs and other institutes
- Consolidate and integrate multiple datasets
- Repurpose legacy data?

Large-scale collection of cancer genomic and molecular data

Cancer data sources

- COSMIC (Catalogue Of Somatic Mutations In Cancer)
- CCLE (Cancer Cell Line Encyclopedia)
- Depmap: Cancer Dependency Map for genetic and pharmacologic dependencies in cell lines
- TCGA (The Cancer Genome Atlas)
- ICGC (International Cancer Genome Consortium)
- PCAWG (Pan-Cancer Analysis of Whole Genomes)
- AACR Project GENIE
- CPTAC (Clinical Proteomic Tumor Analysis Consortium)
- HTAN (Human Tumor Atlas Network)
- TCIA (The Cancer Imaging Archive)
- PDXNet (PDX Development and Trial Centers Research Network)
- …

Multimodal data of preclinical cancer models – Patient derived xenografts (PDX)

Multiple models per patient
Different sites: Primary/Metastatic
Different time points: Pre-treated/post-treated/recurrent

Patient-derived organoids
Patient-derived cell lines
PDX-derived organoids/cell lines

Patient/Model/Sample IDs
Patient information (Sex, Age, Smoker status, Race/Ethnicity)
Primary/Sample site
Diagnosis
Tumor type (pri/met)
Stage/Grade
Treatment history
Biomarkers
Survival

Meehan et al., PDX-MI: Minimal Information for Patient-Derived Tumor Xenograft Models, Cancer Res 2017

Cancer patient

Patient tumor

QC Panel
Pathogen:LCMV, bacteria
Tumor Cell Content

P0

P1

P2

P3

QC Panel
Identify: DNA Fingerprint
Histology: H&E, Ki67, CD45

Further Expansion for Drug Testing

Tumor-Volume from dosing studies
RESIST criteria

Working Stock

Tumor Key
Did not grow in mouse
Harvested and cryopreserved
Engrafted in next set of mice

Cell segmentation/classification
Regional classification
Spatial features, TME, Heterogeneity
*Spatial transcriptomics/IMC

Excise **human tumor** tissue with possible contamination of **mouse stroma**

Absence of matched-normal

Extract DNA/RNA

DNA-Seq RNA-Seq/Microarray

Mutation
Expression
Copy number
TMB/MSI/HRD scores
Subtypes
Annotations (Protein effects, Drug efficacy, Pathways)

* Filtering of mouse signal

Woo, Srivastava, Graber and Bult et al., Genomic data analysis workflows for tumors from patient-derived xenografts (PDXs): challenges and guidelines, BMC Medical Genomics 2019

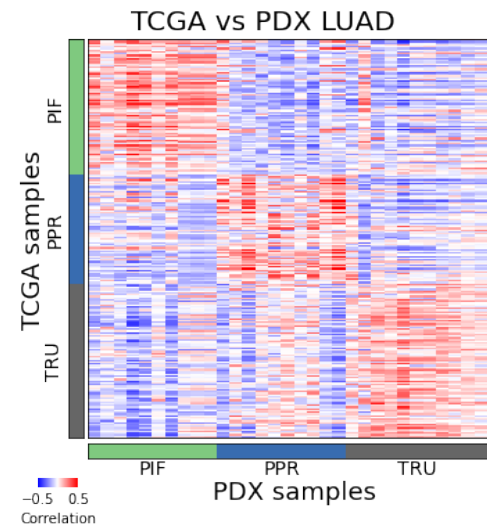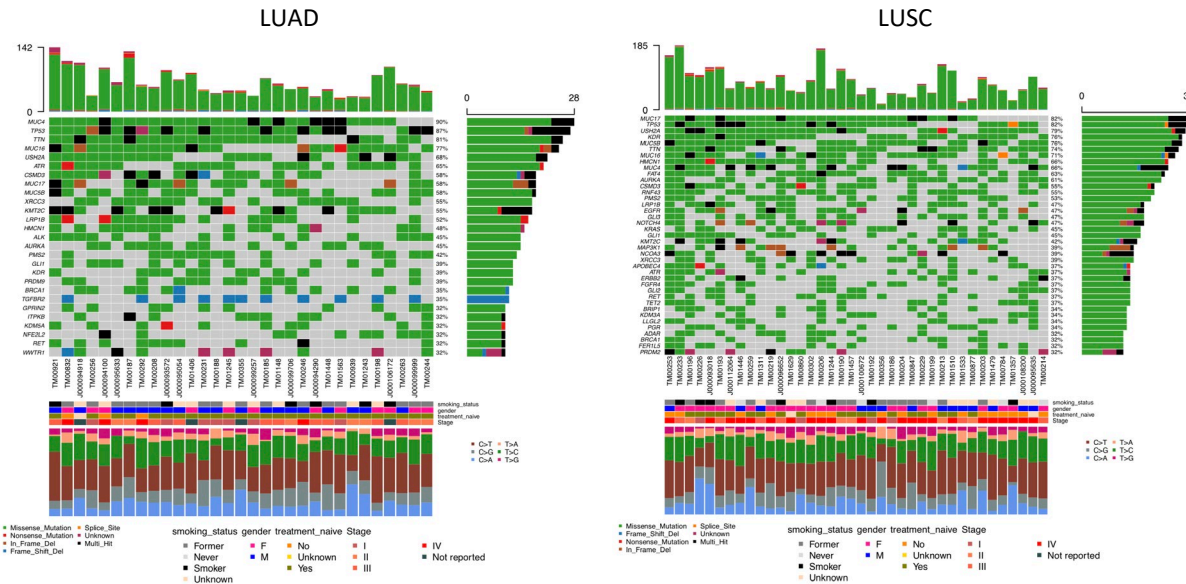# Development of multimodal data platforms

 (Analysis team)

 (Data coordination center)

 (Data coordination center)

- Coordination of PDX generation, genomic technologies, pathology, bioinformatics and customer service teams

- Data curation, organization and QC

- Analysis workflows and benchmarking/validation

- Database of metadata and genomic/spatial data

- Annotation of mutations

- Public portal

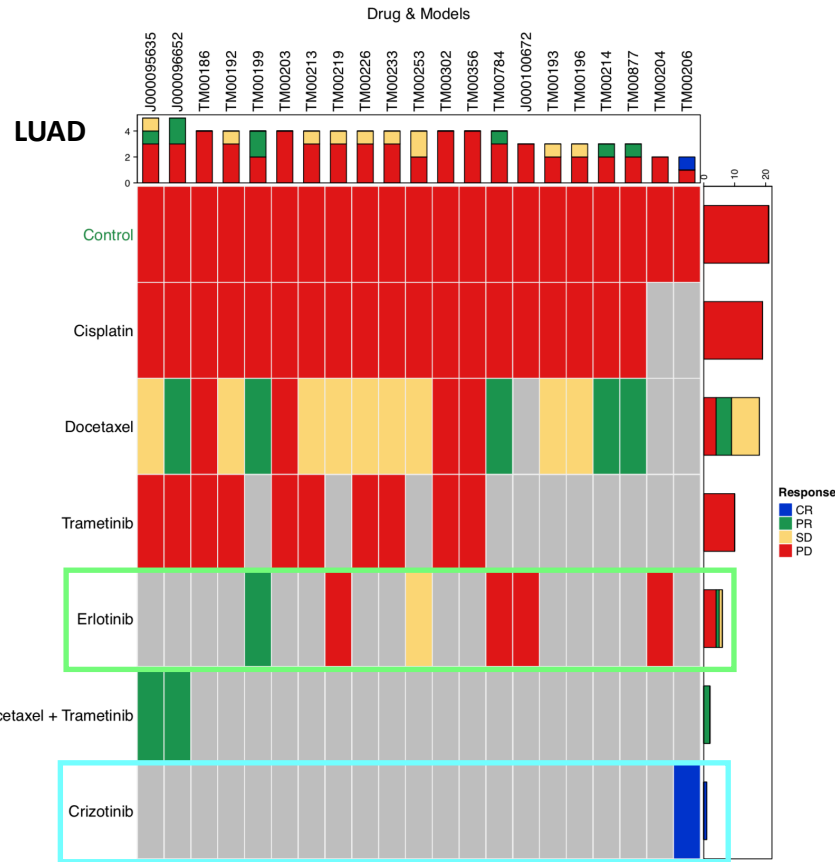- Further research – integration of data of different modalities

Genomic characterization JAX PDX resource – Non-small cell lung cancer
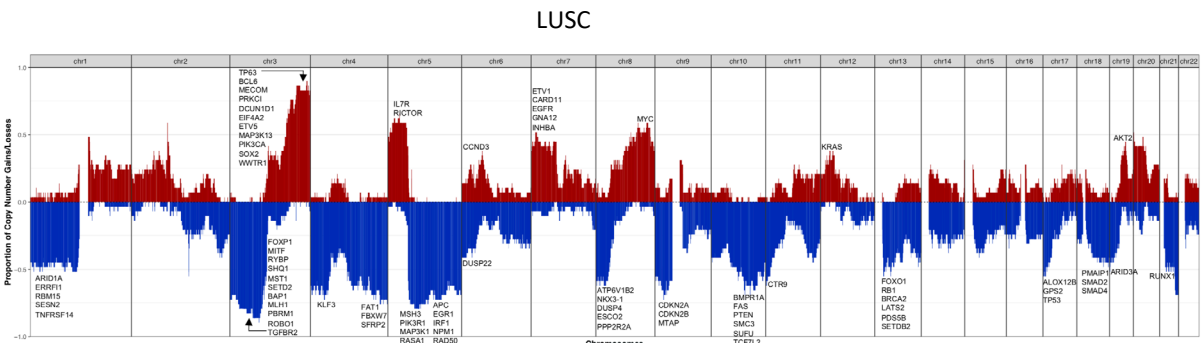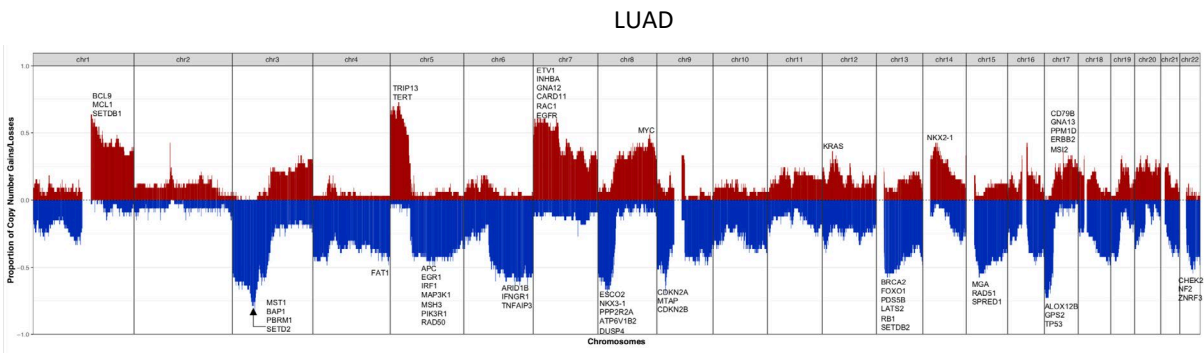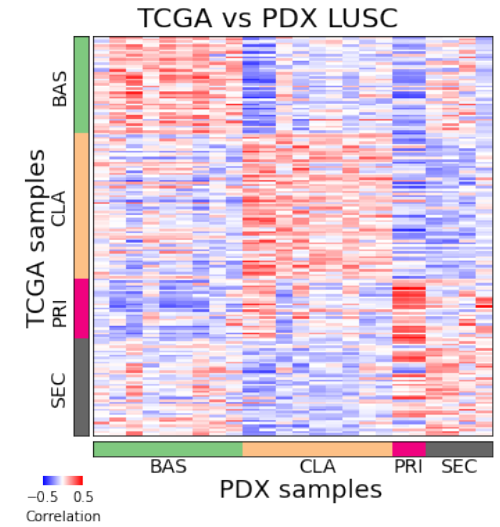
Majority of patient markers are found in PDXs

Woo, Srivastava, Mack, Graber and Bult et al., A Genomically and Clinically Annotated Patient Derived Xenograft (PDX) Resource for Preclinical Research in Non-Small Cell Lung Cancer, bioRxiv 2022, In review

Therapeutic response in PDX models

CR: Complete response
PR: Partial response
SD: Stable disease
PD: Progressive disease

Model	Treatment naïve?	EGFR act mut	Response	Resistance mut
TM00199	Erlotinib	EGFR L858R	PR	
TM00204	Erlotinib	EGFR exon 19 del	PD	EGFR T790M
TM00219	Erlotinib	EGFR exon 19 del	PD	EGFR T790M
TM00253	Erlotinib	EGFR L858R	SD	EGFR V834L
TM00784	Erlotinib	EGFR L858R	PD	MET amp
J000100672	Yes		PD	EGFR exon 20 ins
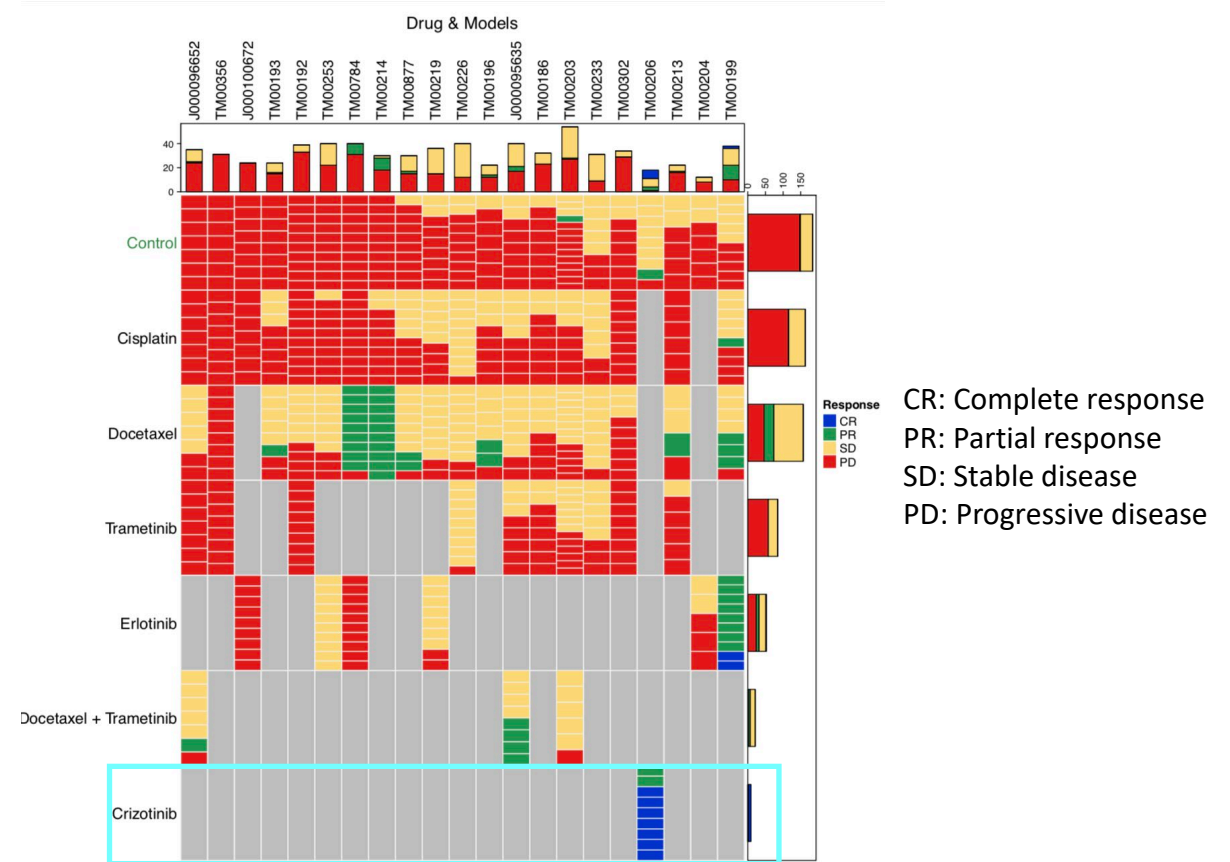
Model	Treatment naïve?	ALK act mut	Response	Resistance mut
TM00206	Crizotinib	EML4-ALK fusion	CR (2PR, 7 CR)	ALK L1196M (Alt AF 22%) KIT amp (low) [P0 – mouse A]
				ALK, EML4 amp (low) [P0 – mouse B]

Dosing studies in PDXs recapitulate treatment response in patients and explain cause of resistance with markers found in PDX   7

PDXNet

NATIONAL CANCER INSTITUTE (NIH)

The Jackson Laboratory

SevenBridges

PDMR — NCI Patient-Derived Models Repository
An NCI Precision Oncology Initiative℠ Resource

UNIVERSITY OF UTAH — HUNTSMAN CANCER INSTITUTE

Baylor College of Medicine®

THE UNIVERSITY OF TEXAS — MD Anderson Cancer Center
Making Cancer History®

THE WISTAR INSTITUTE

WASHINGTON UNIVERSITY IN ST. LOUIS · 1853 · Per Veritatem Vis

UC DAVIS COMPREHENSIVE CANCER CENTER

EurOPDX — Translating Knowledge in Oncology

Conservation of copy number profiles during engraftment and passaging of patient-derived cancer xenografts

Xing Yi Woo [1,64,65], Jessica Giordano [2,3,64], Anuj Srivastava[1], Zi-Ming Zhao[1], Michael W. Lloyd[4], Roebi de Bruijn[5], Yun-Suhk Suh[6], Rajesh Patidar[7], Li Chen[7], Sandra Scherer[8], Matthew H. Bailey[8,9], Chieh-Hsiang Yang[8], Emilio Cortes-Sanchez[8], Yuanxin Xi[10], Jing Wang [10], Jayamanna Wickramasinghe[11], Andrew V. Kossenkov[11], Vito W. Rebecca[11], Hua Sun[12], R. Jay Mashl[12], Sherri R. Davies [12], Ryan Jeon[13], Christian Frech[13], Jelena Randjelovic[13], Jacqueline Rosains[13], Francesco Galimi[2,3], Andrea Bertotti[2,3], Adam Lafferty[14], Alice C. O'Farrell[14], Elodie Modave[15,16], Diether Lambrechts [15,16], Petra ter Brugge[5], Violeta Serra [17], Elisabetta Marangoni [18], Rania El Botty[18], Hyunsoo Kim[1], Jong-Il Kim[6], Han-Kwang Yang[6], Charles Lee[1,19,20], Dennis A. Dean II[13], Brandi Davis-Dusenbery[13], Yvonne A. Evrard[7], James H. Doroshow[21], Alana L. Welm[8], Bryan E. Welm[8,22], Michael T. Lewis[23], Bingliang Fang[24], Jack A. Roth[24], Funda Meric-Bernstam[25], Meenhard Herlyn[11], Michael A. Davies [26], Li Ding[12], Shunqiang Li[12], Ramaswamy Govindan[12], Claudio Isella[2,3,65], Jeffrey A. Moscow[27,65], Livio Trusolino [2,3,65], Annette T. Byrne[14,65], Jos Jonkers [5,65], Carol J. Bult[4,65], Enzo Medico [2,3,65], Jeffrey H. Chuang[1,65], PDXNET Consortium* and EurOPDX Consortium*

CANCER RESEARCH | TUMOR BIOLOGY AND IMMUNOLOGY

Systematic Establishment of Robustness and Standards in Patient-Derived Xenograft Experiments and Analysis 🅐🅒

Yvonne A. Evrard[1], Anuj Srivastava[2], Jelena Randjelovic[3], The NCI PDXNet Consortium, James H. Doroshow[4], Dennis A. Dean II[3], Jeffrey S. Morris[5], and Jeffrey H. Chuang[2,6]

CSH Cold Spring Harbor Laboratory · **bioRχiv**

PDXNet Portal: Patient-Derived Xenograft model, data, workflow, and tool discovery

(in revision)

Soner Koc, [ID] Michael W. Lloyd, Jeffrey Grover, Sara Seepo, Sai Lakshmi Subramanian, Manisha Ray, Christian Frech, John DiGiovanna, Phillip Webster, Steven Neuhauser, Anuj Srivastava, Xing Yi Woo, Brian J. Sanderson, Brian White, Paul Lott, PDXNet Consortium, Yvonne A. Evrard, Tiffany A. Wallace, Jeffrey A. Moscow, James H. Doroshow, Nicholas Mitsiades, Salma Kaochar, Chong-xian Pan, Moon S. Chen Jr., Luis Carvajal-Carmona, Alana L. Welm, Bryan E. Welm, Michael T. Lewis, Ramaswamy Govindan, Li Ding, Shunquang Li, Meenherd Herlyn, Mike Davies, Jack Roth, Funda Meric-Bernstam, Peter N. Robinson, Carol J. Bult, Brandi Davis-Dusenbery, Dennis A. Dean II, [ID] Jeffrey H. Chuang, for the PDXNet Consortium Members

---
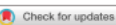
A human breast cancer-derived xenograft and organoid platform for drug discovery and precision oncology

Katrin P. Guillen[1,2,13], Maihi Fujita[1,2,13], Andrew J. Butterfield[1,2,13], Sandra D. Scherer [1,2], Matthew H. Bailey[2,3], Zhengtao Chu[1,2], Yoko S. DeRose[1,2], Ling Zhao[1,2], Emilio Cortes-Sanchez[1,2], Chieh-Hsiang Yang[1,2], Jennifer Toner[1,2], Guoying Wang[1,2], Yi Qiao[3], Xiaomeng Huang[3], Jeffery A. Greenland[1,2], Jeffery M. Vahrenkamp[1,2], David H. Lum [2], Rachel E. Factor[2,4], Edward W. Nelson[2,5], Cindy B. Matsen[2,5], Jane M. Poretta[2,5], Regina Rosenthal[2,5], Anna C. Beck[2,6], Saundra S. Buys[2,6], Christos Vaklavas[2,6], John H. Ward[2,6], Randy L. Jensen[1,2,7], Kevin B. Jones[1,2,8], Zheqi Li[9], Steffi Oesterreich [9], Lacey E. Dobrolecki[10], Satya S. Pathi[1,2], Xing Yi Woo[11], Kristofer C. Berrett[1,2], Mark E. Wadsworth[1,2], Jeffrey H. Chuang [11,12], Michael T. Lewis[10], Gabor T. Marth[2,3], Jason Gertz[1,2], Katherine E. Varley[1,2], Bryan E. Welm [2,5 ✉] and Alana L. Welm [1,2 ✉]

---

nature COMMUNICATIONS

Comprehensive characterization of 536 patient-derived xenograft models prioritizes candidates for targeted treatment

---

AACR ANNUAL MEETING 2022 New Orleans — American Association for Cancer Research® — JOIN US APRIL 8–13!

← Search Results   🔗 Share Page   🖨 Print Page

Session PO.BCS01.03 - Database Resources and Web Applications
1202 / 14 - A repository of PDX histology images for exploring spatial heterogeneity and cancer dynamics

📅 April 11, 2022, 9:00 AM - 12:30 PM   📍 Section 28   *(manuscript in preparation)*

☆ Add to My Itinerary

Presenter/Authors

Brian S. White*, Xingyi Woo*, Soner Koc*, Todd Sheridan, Steven B. Neuhauser, Akshat M. Savaliya, Lacey E. Dobrolecki, John D. Landua, Matthew H. Bailey, Kurt W. Evans, Bingliang Fang, Junya Fujimoto, Maria Gabriela Raso, Shidan Wang, Guanghua Xiao, Yang Xie, Sherri R. Davies, Ryan C. Fields, R Jay Mashl, Jacqueline L. Mudd, Yeqing Chen, Min Xiao, Xiaowei Xu, Melinda G. Hollingshead, Shahanawaz Jiwani, PDXNet Consortium, Yvonne A. Evrard, Tiffany A. Wallace, Jeffrey A. Moscow, James H. Doroshow, Nicholas Mitsiades, Salma Kaochar, Chong-xian Pan, Moon S. Chen Jr., Luis G. Carvajal-Carmona, Alana L. Welm, Bryan E. Welm, Michael T. Lewis, Ramaswamy Govindan, Li Ding, Shunqiang Li, Meenherd Herlyn, Michael A. Davies, Jack A. Roth, Funda Meric-Bernstam, Carol J. Bult, Brandi Davis-Dusenbery, Dennis A. Dean II, Jeffrey H. Chuang. The Jackson Laboratory for Genomic Medicine,

PDXNET Portal and workflows

NCI Cancer Genomics Cloud

> 800 PDX models with multiple samples and data of different modalities

Koc and Llyod et al., PDXNet Portal: Patient-Derived Xenograft model, data, workflow, and tool discovery, bioRxiv 2021, In revision

Conservation of copy number profiles during engraftment and passaging of PDXs
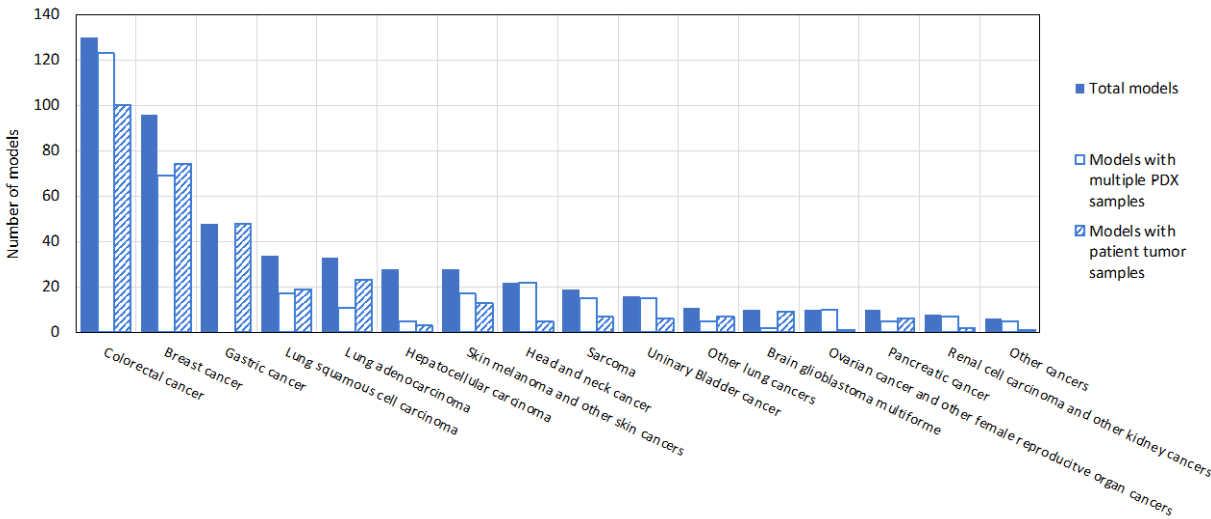
10 contributing centers
16 tumor types
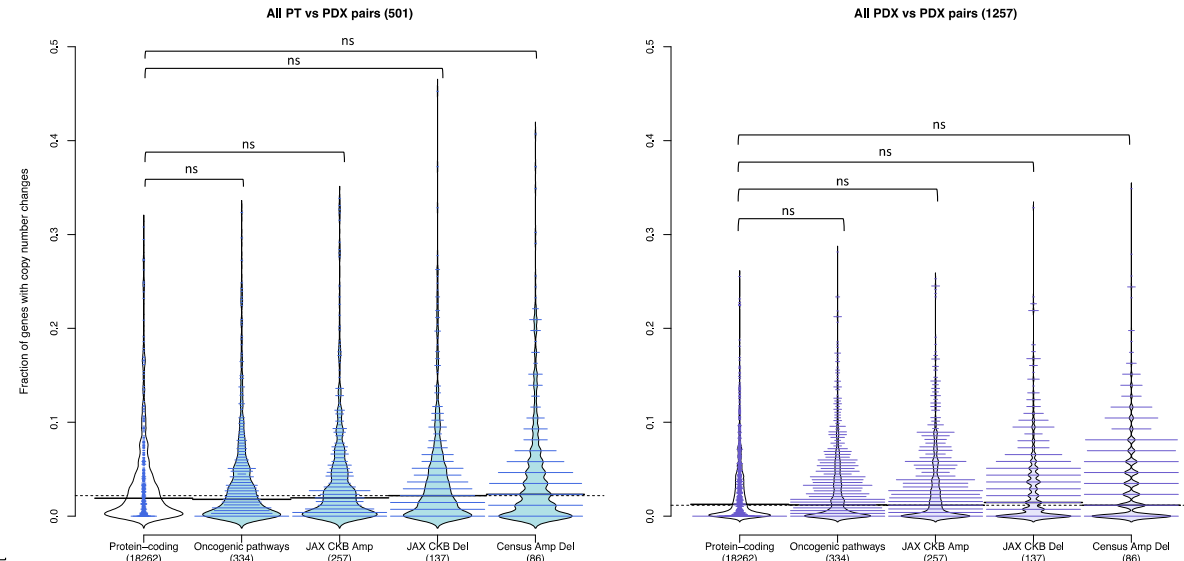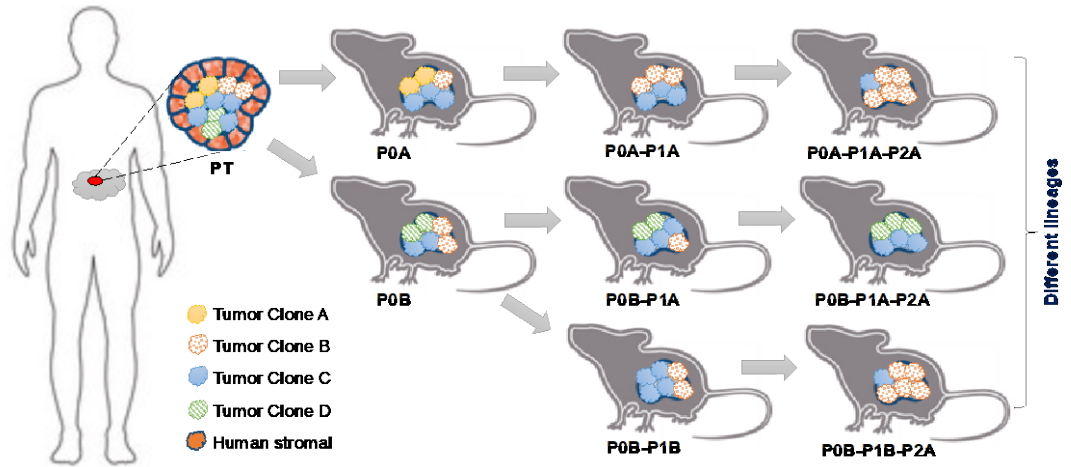509 PDX models
1,451 PT/PDX samples
1,548 tumor datasets
(WES, WGS, SNP array, RNA-Seq & microarray expression)

CNA profiles with gene annotations

Woo and Giordano et al., Conservation of copy number profiles during engraftment and passaging of patient-derived cancer xenografts, Nature Genetics 2021

Comparisons of CNAs from PTs with early and late PDX passages
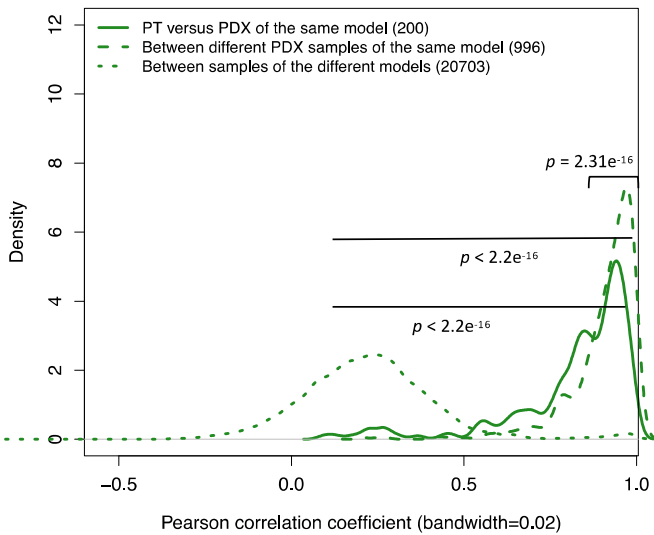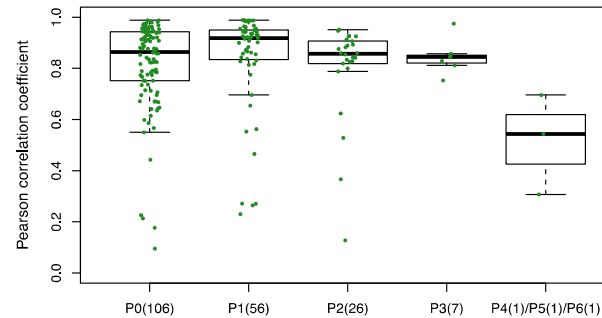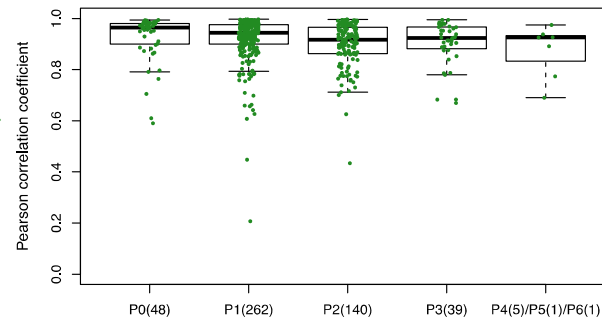

- **Pairwise comparison of CNA between PT-PDX and PDX-PDX**

- **No systematic CN changes during engraftment (PT-PDX) and passaging (PDX-PDX)**

- **Genes with CNAs acquired during engraftment and passaging show no preference for cancer or treatment-related functions**

- **No mouse-specific selection to alter the CNA profile different from the evolutionary process of the original patient tumor**

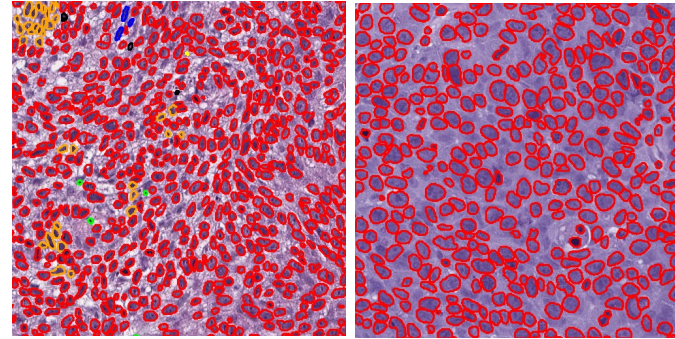# Evolution across PDX lineages and intra-patient samples
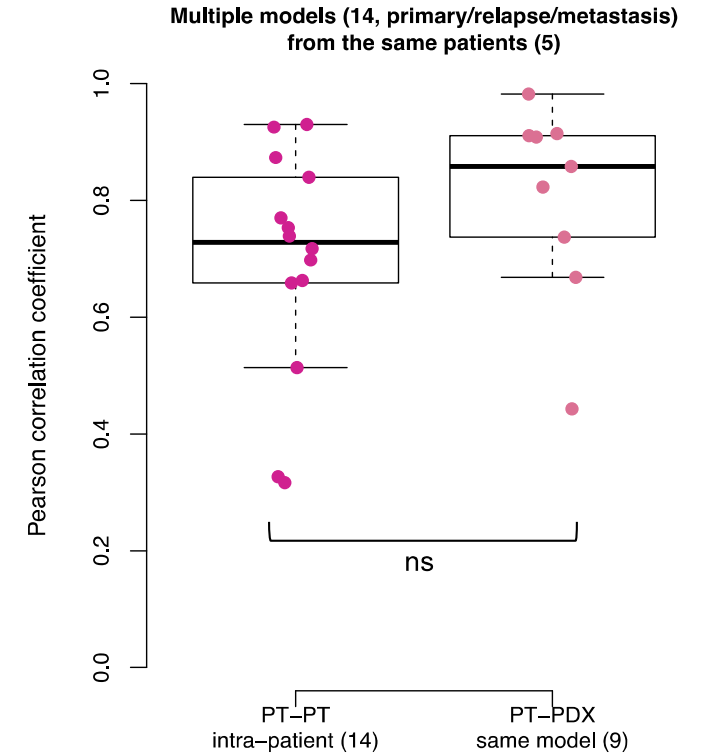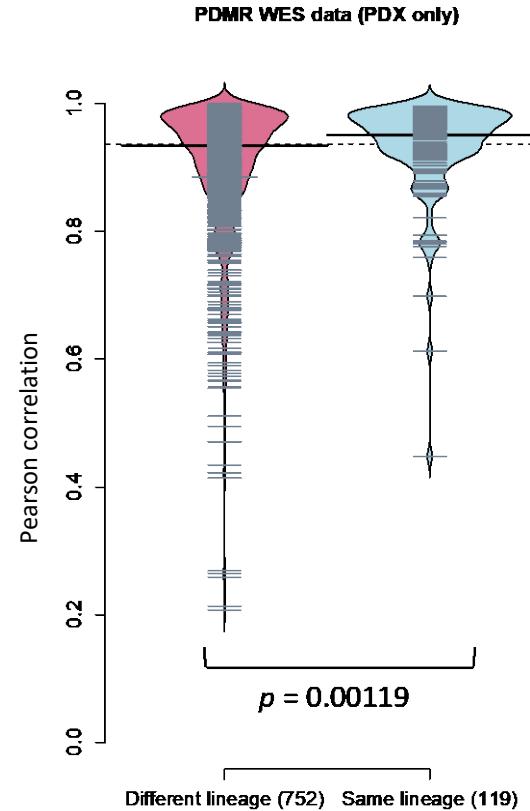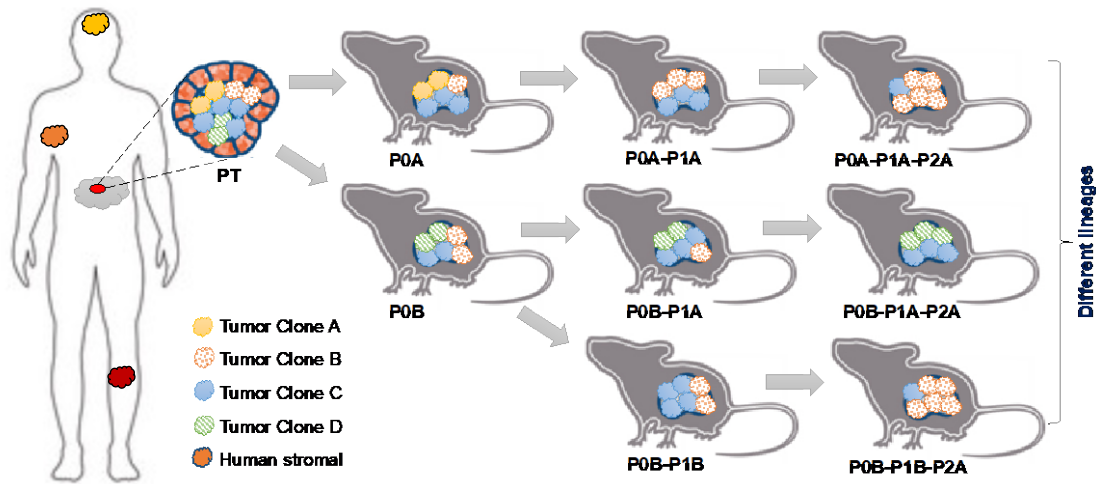
- **Random sampling of heterogenous tumor can result in divergence in copy number**
- **Genetic stability of the PDX system are likely to be less important than the evolution and heterogeneity of solid tumors themselves which can affect successful treatment**
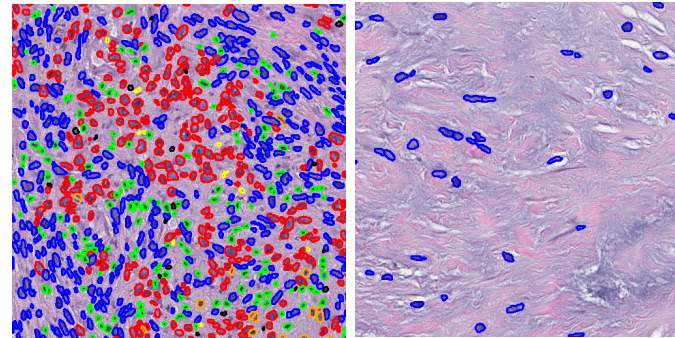
Spatial features of PDX tumors from image analysis

- **Cell/regional classification of histopathology images to understand spatial heterogeneity, tumor-microenvironment and tumor-stromal infiltration**

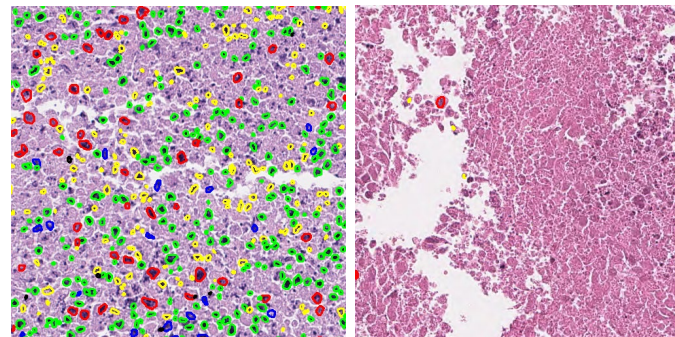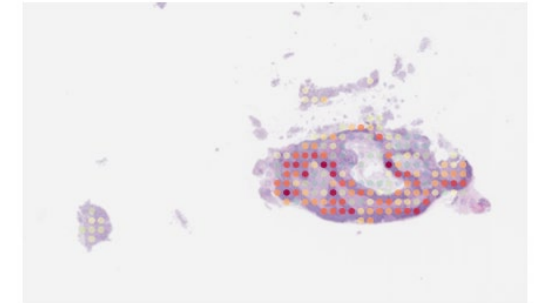- **To associate spatial features with genomics and clinical/treatment outcomes**

Neoplastic | Non-Neoplastic Epithelial | Inflammatory | Connective | Dead

Sargent and Warner et al., Genetically diverse mouse platform to xenograft cancer cells, 2022, in revision
White, Woo, Koc et al., A repository of PDX histology images for exploring spatial heterogeneity and cancer dynamics, AACR Annual Meeting 2022, manuscript in preparation

13
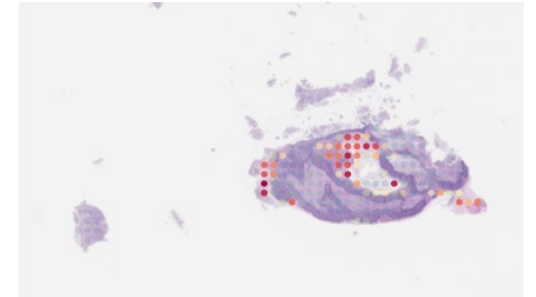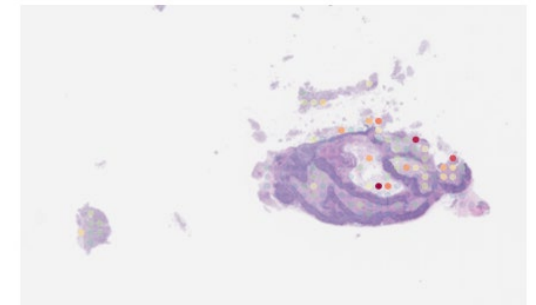
Data analysis and integration of multimodal cancer data and its translation outcomes

Multimodal ML models integrate features across modalities

- PDX models are robust and <u>genomically</u> stable for preclinical studies, where mouse-specific pressures to alter <u>cancer or treatment-related functions</u> is clearly absent

- Integrating <u>omics</u> data of PDX models with <u>curated clinical annotations</u> for efficient mining of PDX models for preclinical trials

- Integrating <u>annotated genomic/molecular profiles</u> with <u>dosing studies</u> of PDX resources to validate and discover biomarkers

- Explore effects of <u>tumor heterogeneity, subclonality and spatial features</u> on <u>clinical/treatment outcomes</u>

Boehm et al. Harnessing multimodal data integration to advance precision oncology. Nat Rev Cancer 2022

Genomics Multi-omics Spatial features	➕	Cancer functions Clinical annotations Treatment data	➡	Preclinical trials Biomarker discovery Clinical outcomes

- **Better prediction of treatment outcomes and patient stratification**

- **Multimodal features can uncover new understanding of cancer biology underlying patient outcomes**

Acknowledgements

Sebastian Maurer-Stroh
Neerja Karnani
Wong Wing Cheong

CS
Joshy George
Krishna Karuturi
Anuj Srivastava
Mike Lloyd
Brian Sanderson
Brian White
Sergii Domanskyi
Grace Stafford
Carolyn Paisie
Jim Peterson
Stephen Grubb
Al Simons
Mandy Chen

Chuang Lab
Jeffrey Chuang
Ali Foroughi pour
Todd Sheridan
Jill Rubinstein
Yun-Suhk Suh
Ziming Zhao

JAX PDX Resource
Carol Bult
Steven Neuhauser
Emily Jocoy
Margaret Bundy
Susie Airhart
Muneer Hasham

Liu Lab
Edison Liu
Francesca Menghi
Koichiro Inaki

JAX CKB
Susan Mockus
Sara Patterson

Questions and feedback…

Actively recruiting scientists, postdocs and research officers…

woo_xing_yi@bii.a-star.edu.sg