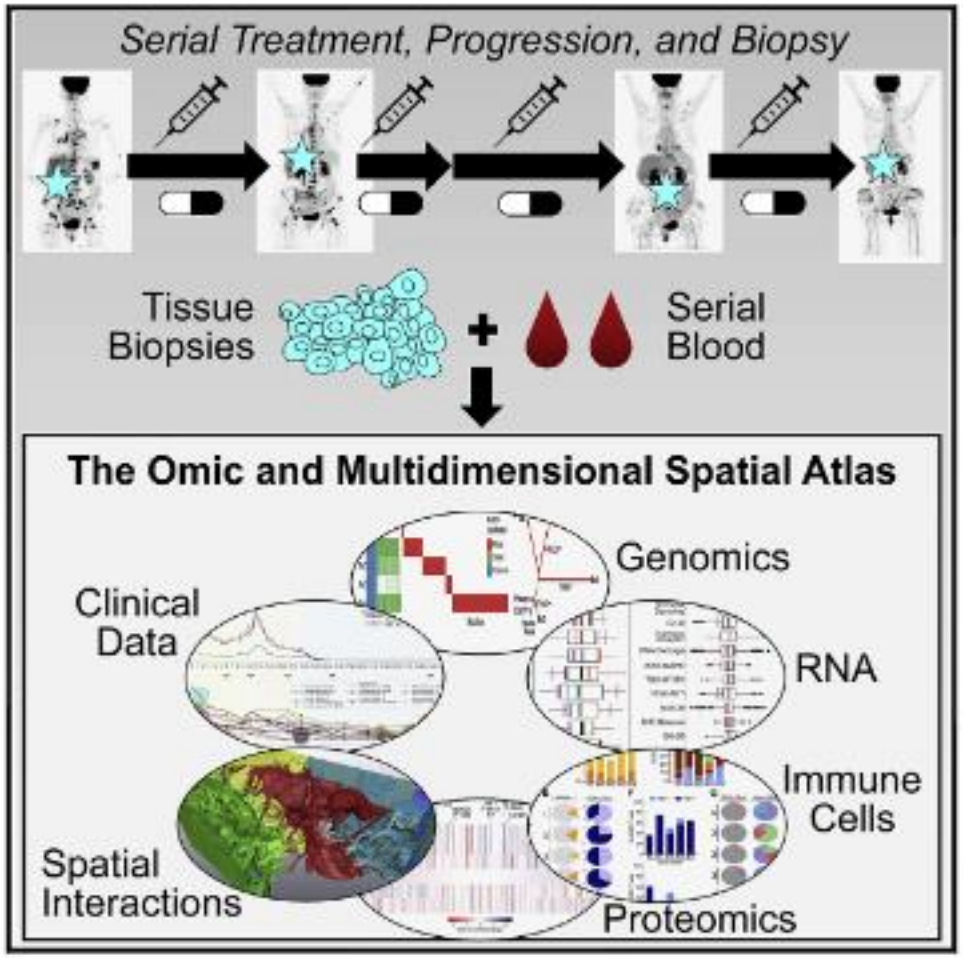
OHSU Advanced Cancer Atlas HTAN Center: Dynamics of Tumor Evolution and Clinical Implications

Joe W. Gray, Ph.D. for the OMS Atlas Team



Cell Rep Med. 2022 Feb 15;3(2):100525.

Overarching goals

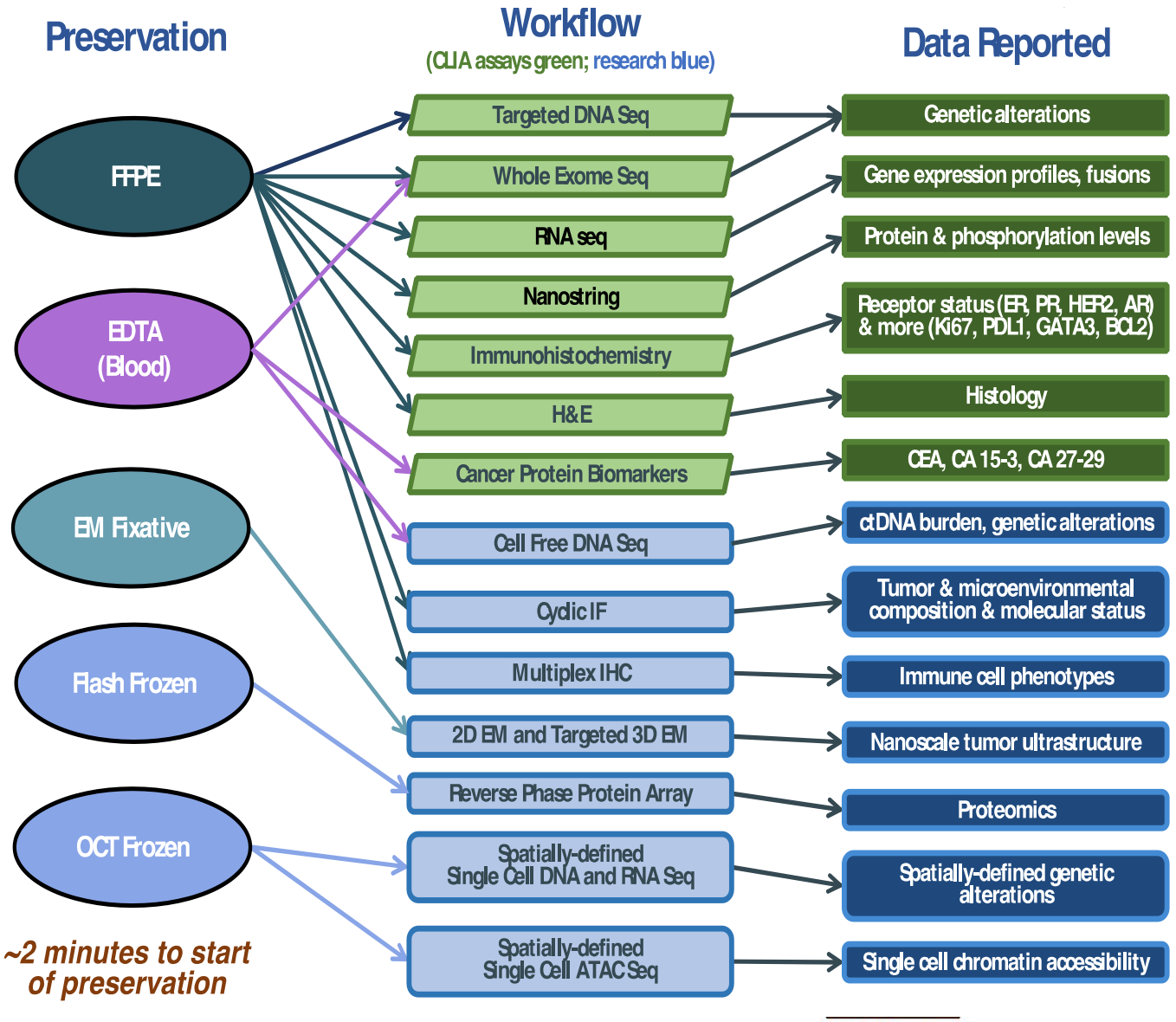
- Identify tumor intrinsic and extrinsic mechanisms of response and resistance to therapy
- Develop actionable guidance to address therapeutic resistance

Center Concepts

- Diverse ‘omic and multiscale, multiplex image analyses for robust mechanistic exploration in clinical “real time”
- Detailed clinical data for reasoning about therapeutic response
  - Blood biomarkers and anatomic images provide quantitative response metrics
  - Dose-time treatment information enables treatments to be used as informative perturbations
  - CLIA analytics (IHC, DNA, RNA, spatial proteomics)
- Comparative analysis of pre and on-treatment biopsies reveals mechanisms of resistance
- Infrastructure to collect and manage serial biospecimens and associated clinical and research information
- Data sharing and collaboration within center and across consortium
  - Assay validation
  - Data interpretation and integration

Approach

- Acquire serial biosamples and clinical information from individual patients enrolled in the SMMART clinical program
- Consent patients for controlled release of clinical and research data
- Deploy validated ‘omic and image analysis tools to identify potential tumor intrinsic and extrinsic mechanisms
- Organize integrated results for discovery research and clinical action



SMMART: Serial Measurements or Molecular and Architectural Responses to Treatment

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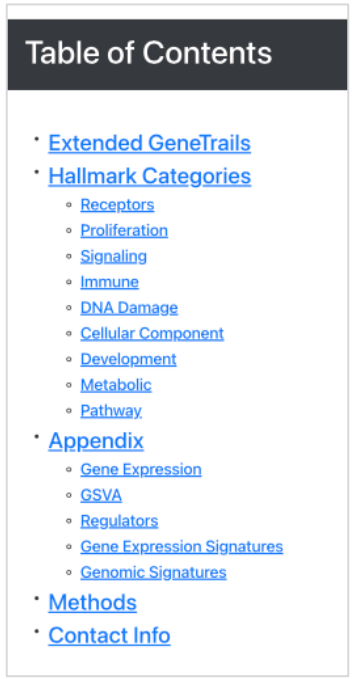
Data From EHR Automatically or with Minimal Curation

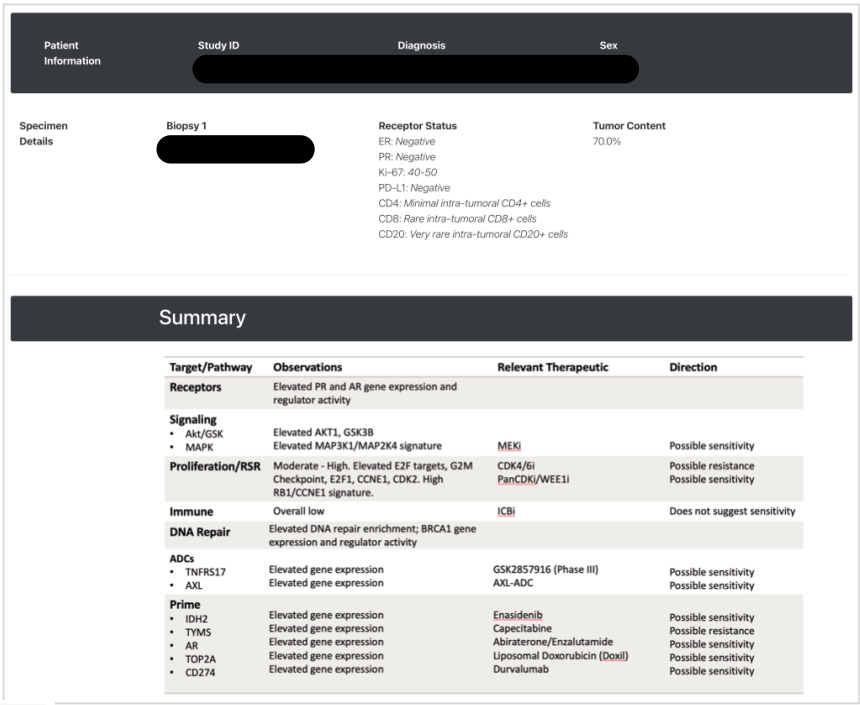
- Combination of clinical data elements and CLIA assay results
- Data is pulled into a clinical informatics system and combined with research use only (RUO) results
- Combination of CLIA and RUO results is presented at research tumor board for mechanistic exploration

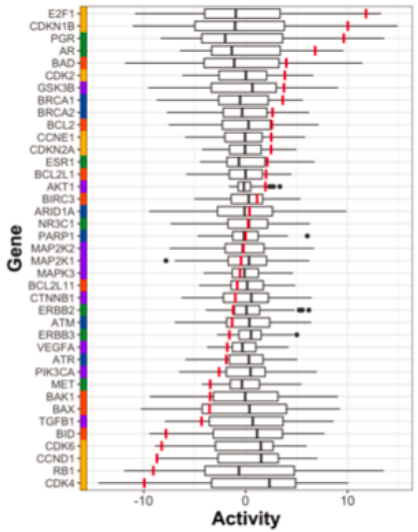
Ethnicity	Gene Symbol
Gender	Molecular Analysis Method
Race	Test Result
Current Vital Status	AA Change
Age at Diagnosis	Clinical Biospecimen Type
Year of Diagnosis	Chromosome
Primary Diagnosis	Molecular Consequence
Site of Resection or Biopsy	Pathogenicity
Tissue or Organ of Origin	Test Units
Morphology	Test Value
Tumor Grade	Variant Origin
Progression or Recurrence (Y/N)	Variant Type
Last Known Disease Status	Timepoint Label
Days to Last Follow up	Start Days from Index
Days to Last Known Disease Status	Known Genetic Predisposition Mutation
Days to Recurrence/Progression	Mismatch Repair System Status
Days to Follow up	Lab Tests for MMR Status
Progression or Recurrence (Y/N)	Timepoint Label
Days to Recurrence	Start Days from Index
Treatment Type	Breast Carcinoma Estrogen Receptor Status
Days to Treatment Start	Breast Carcinoma Progesterone Receptor Status
Days to Treatment End	Breast Carcinoma ER Status Percentage Value
Regimen or Line of Therapy	Breast Carcinoma PR Status Percentage Value
Therapeutic Agents	Breast Carcinoma HER2 Status
Timepoint Label	Breast Carcinoma ER Staining Intensity
Start Days from Index	

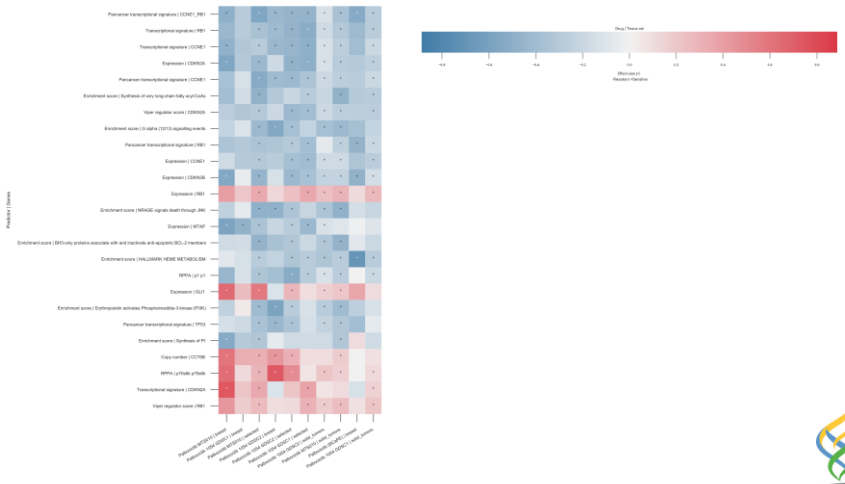
'Omics Analysis

- Identify mechanisms through comparative analyses of RNA-seq, DNA-seq, and RPPA
  - Pre vs on treatment
  - Patient vs SMMART cohort and TCGA
  - Identify features associated with response in preclinical datasets
  - Emphasis on actionable mechanisms
- Multiple measures quantified:
  - Single-gene expression and protein abundance
  - Gene set enrichment
  - Master regulator activity
  - Transcriptional signatures
- Both tumor intrinsic and extrinsic mechanisms considered
- Reflex testing using CLIA-approved assay









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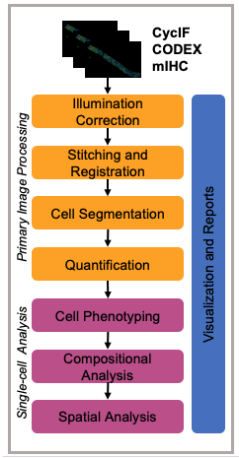
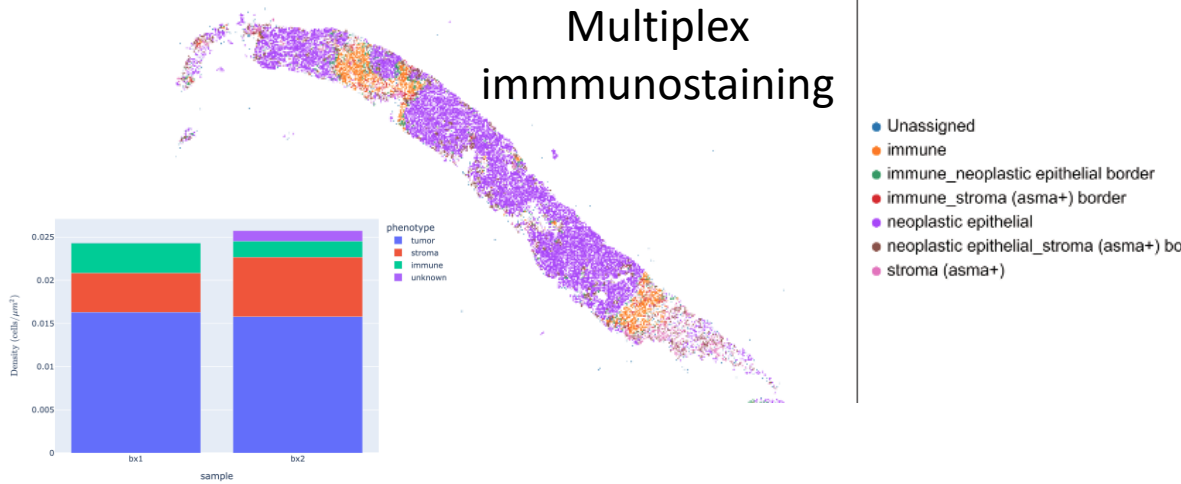
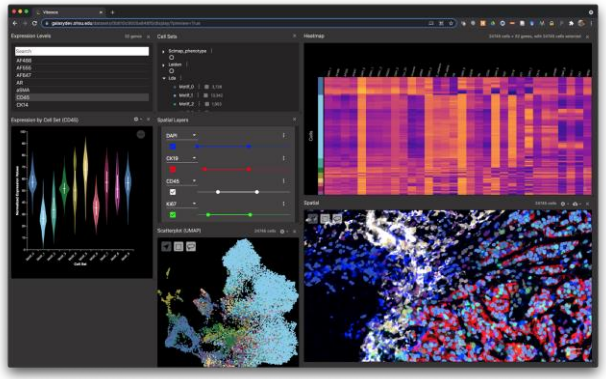
Multiscale, Multiplex Tissue Imaging

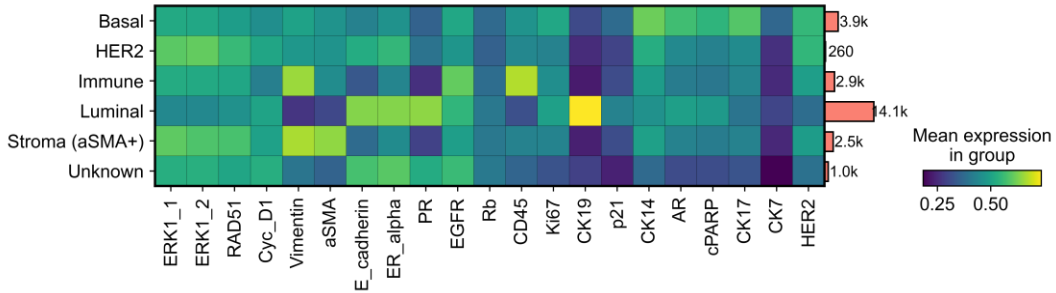
- HTAN collaborations for multiplex immunoanalysis
  - Assay Development
  - Metadata standards
  - Unified analysis approach across assays, e.g. mIHC, cycIF, and CODEX
  - Cell segmentation and proximity analysis
  - Image management
  - Cell dictionaries
- 2D and 3D EM analysis for ultrastructure elucidation
- Actionability
  - Mechanisms from the literature
  - Drug associated pathways



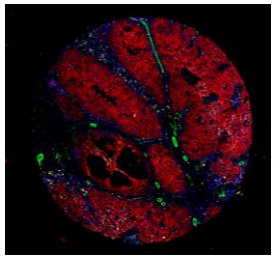
Multiplex immmunostaining





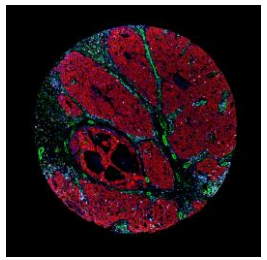


t-CyCIF (HMS, Slide 5)



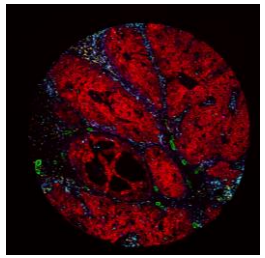
Total: 9575 cells

mIHC (OHSU, Slide 6)

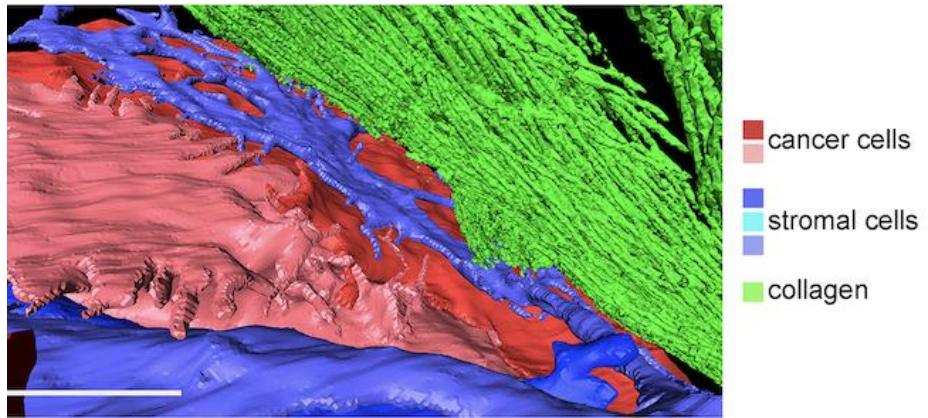


Total: 12392 cells

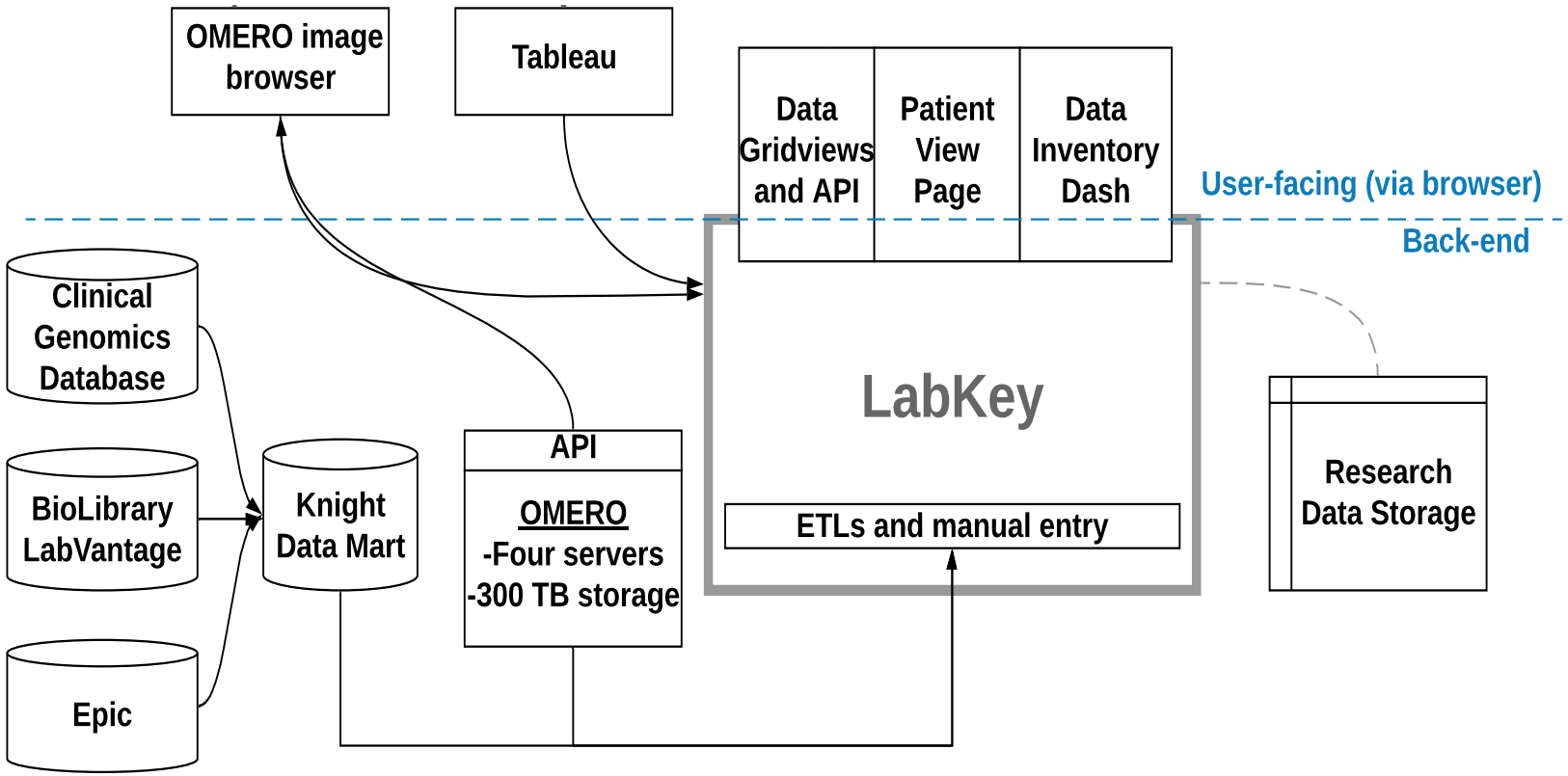
cmIF (OHSU, Slide 7)



Total: 11942 cells



Managing Data from Multiple Sources



- LabKey is the integration and access point
- Multiple data sources, including ‘chart’, imaging, and omics data systems
- Web browser used to explore data - plots, image viewers, Excel-like gridviews, Tableau reports
- Data exportable via API –> DCC and beyond

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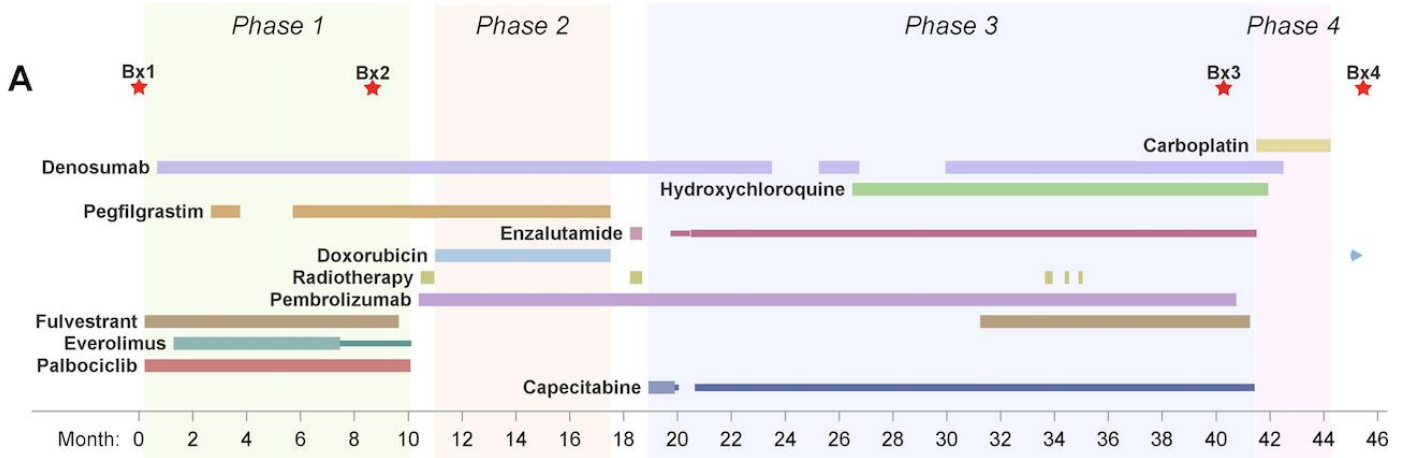
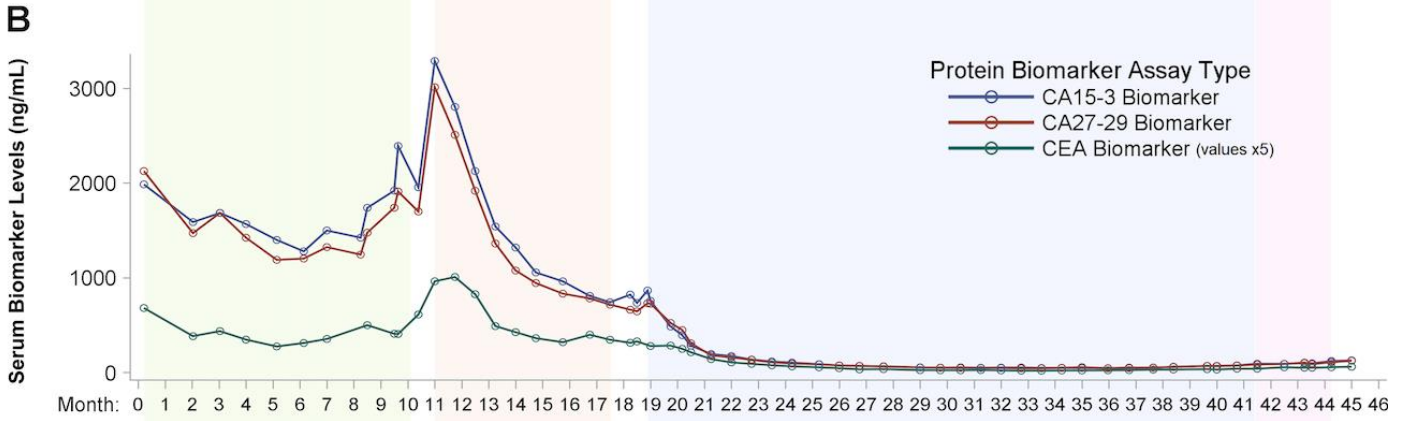
A Few Illustrative Results from Cell Rep Med. 2022 Feb 15;3(2):100525

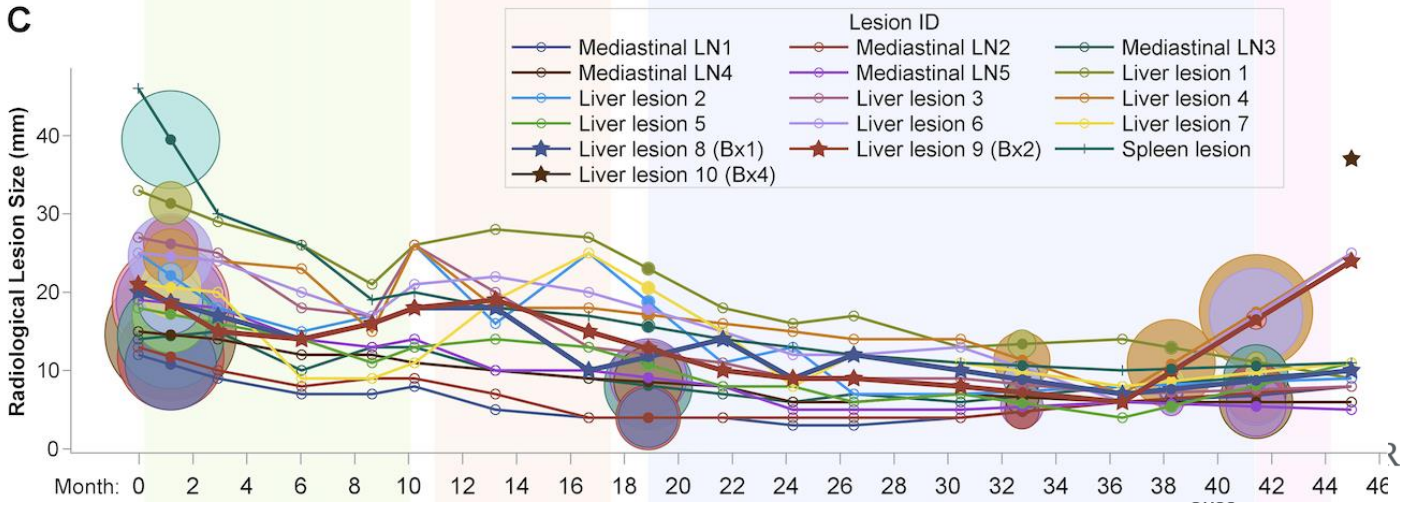
Clinical Perspective

Highlights

- Three phases of treatment with accurate recording of drug treatment time and dose
- Serum biomarker levels to inform on response
- CT/PET image analyses report on individual lesion responses
- Strong but transient responses to each treatment phase
- Heterogeneous responses temporally and between lesions





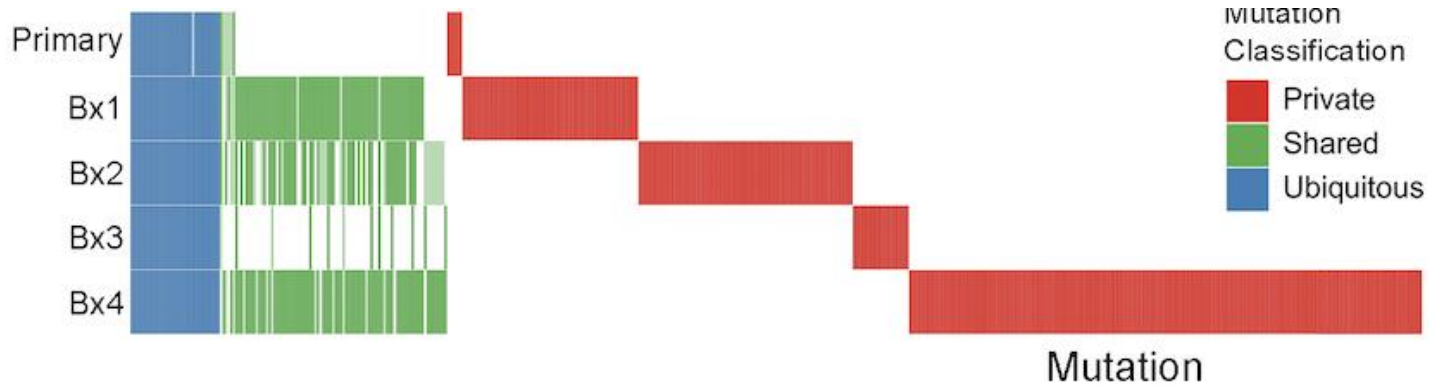


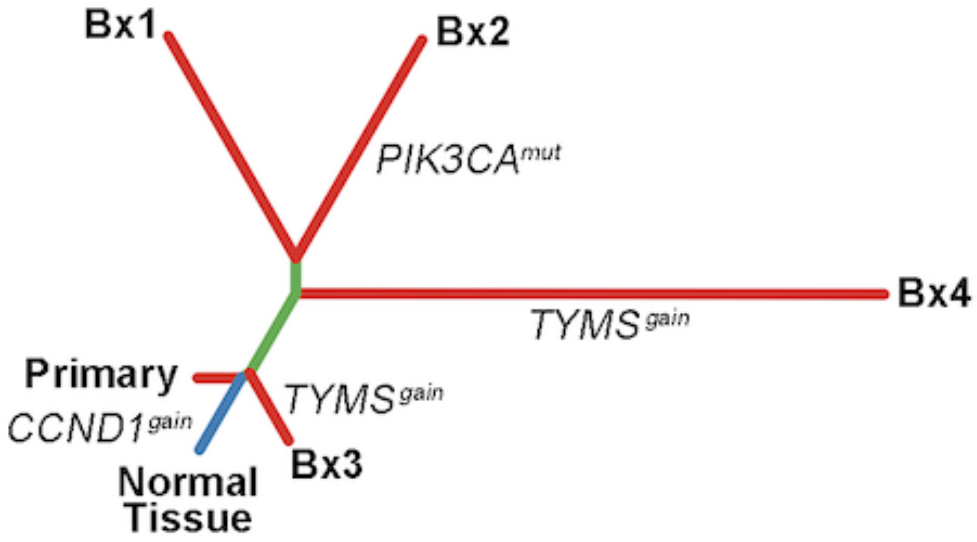
Z. Mitri, S. Mitri, Corless, Thomas, Kong, Guimaraes, Bergan, Mills

Genomic Evolution Under Treatment

Highlights

- A few ubiquitous and many private mutations
- Clinically relevant mutations
  - $CDKN2A^{del}$, $CCND1^{amp}$, $ESR1^{wt}$
  - $PIK3CA^{mut}$ in after PI3K Rx (everolimus)
  - $TYMS/YES1^{amp}$ after capecitabine
- Bx3 is an evolutionally “earlier” tumor



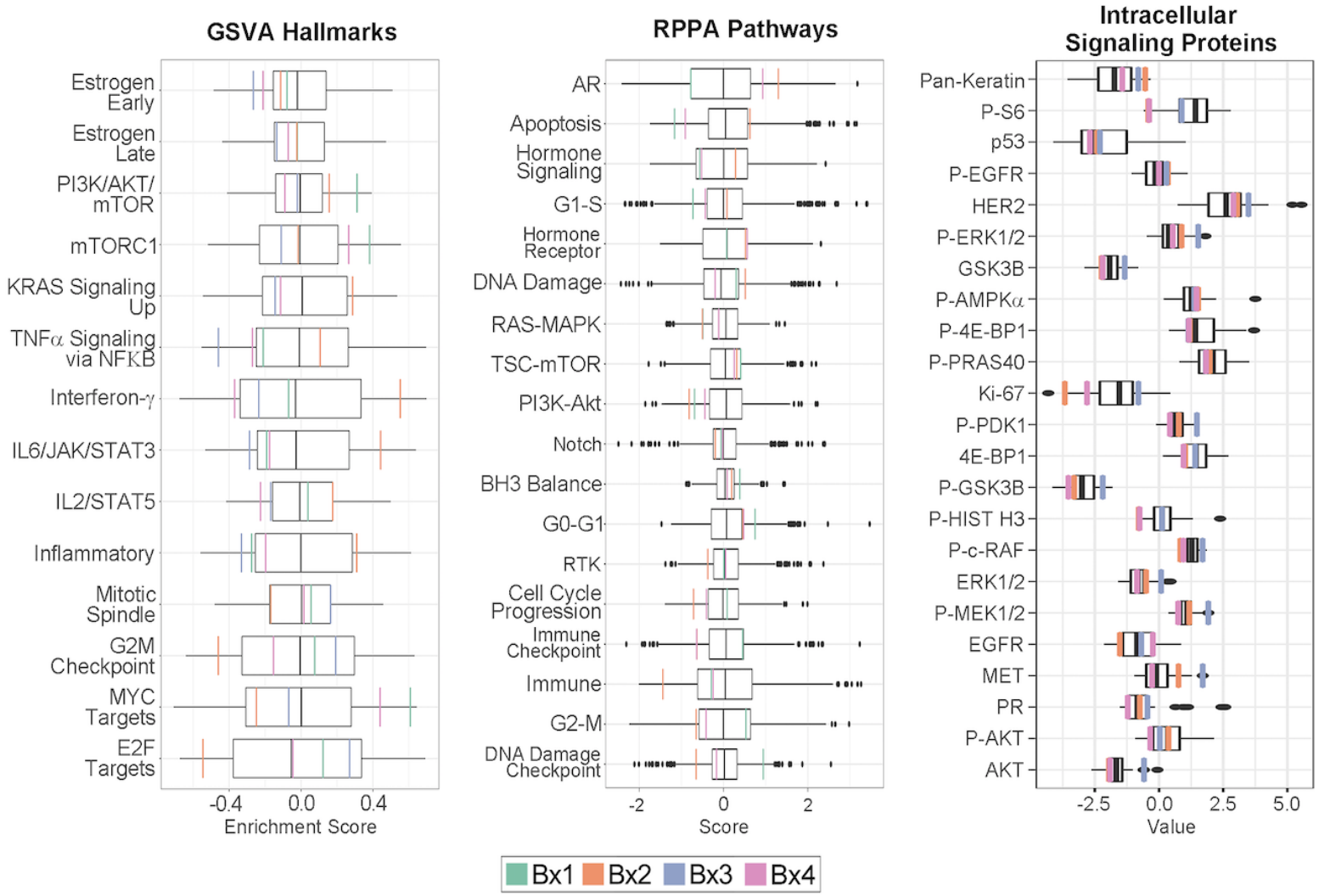


Johnson, Creason, Patterson, Labrie, Heiser, Demir, Boniface, Spellman, Goecks

Comparative Transcriptomic and Proteomic Analyses

highlights
Bx2 (Palbociclib) vs Bx1/3,4 vs cohort

- Increased IFN/STAT, numerous interleukins
- Increased KRAS signaling
- Increased AR signaling
- Non canonical CDK2 and mTORC2 activation



Creason, Patterson, Labrie, Heiser, Demir, Goecks

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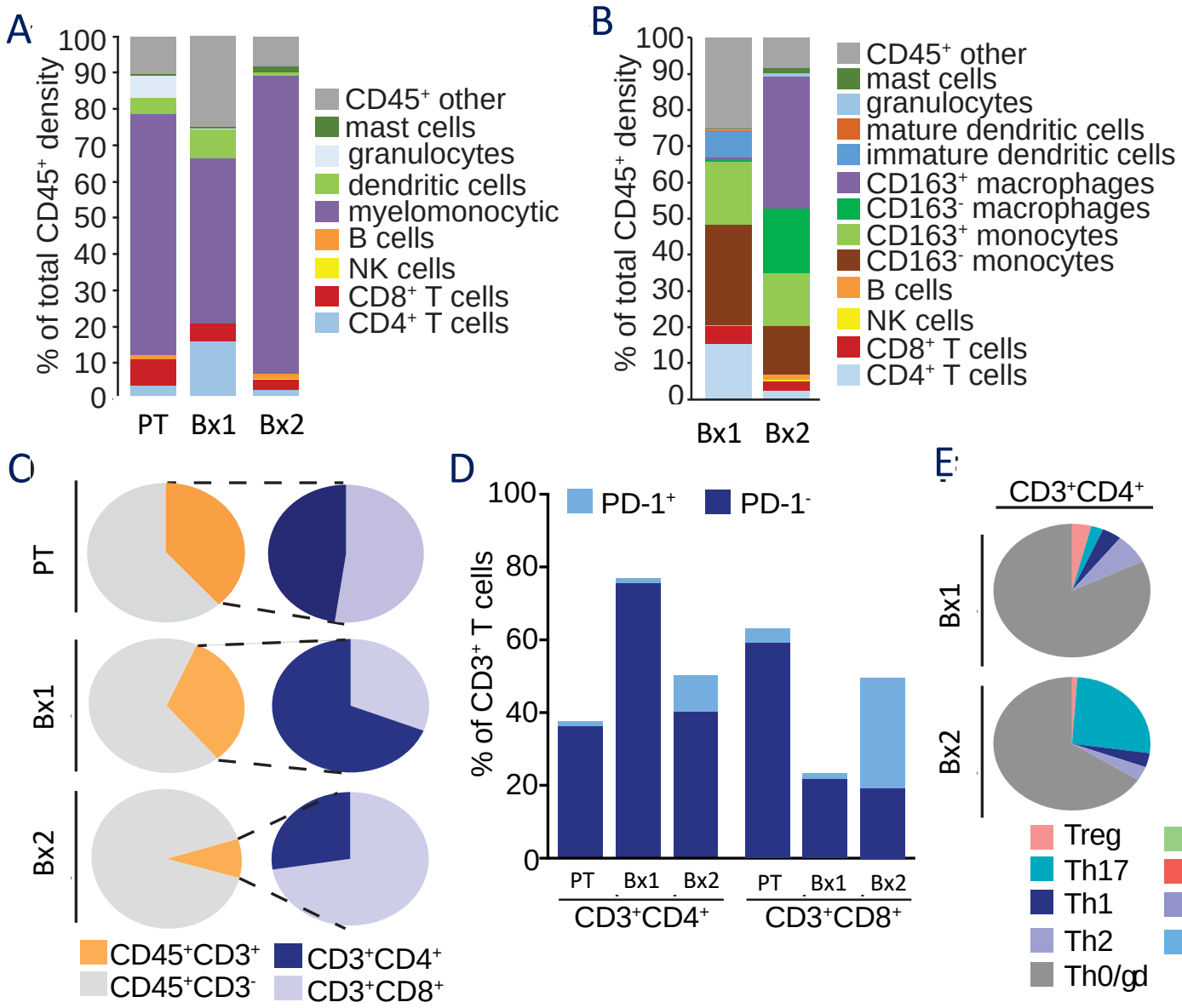
The Immune Perspective From mIHC

Highlights

- Palbociclib induced increase in macrophage/monocytes and increased pro-inflammatory T helper cells (Th17) and reduced T regulatory cells
- Decreased ”exhausted”/late effector EOMES+ T cells indicating potential anti-PD-1 response



Betts, Sivagnanam, Goecks, Coussens

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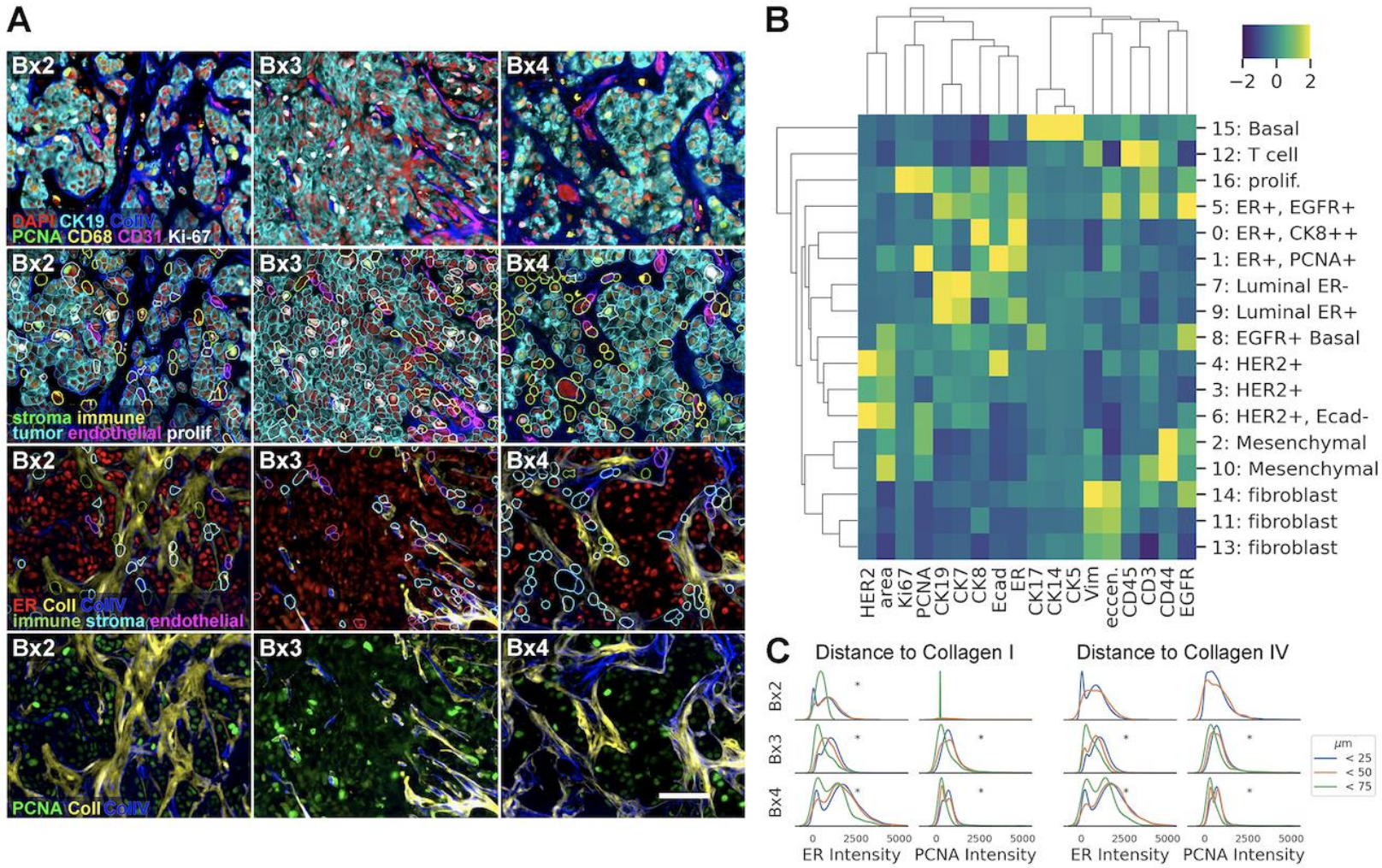
The Tumor Microenvironment from CyCIF

- Tumor and stromal compositions, states and interactions
- Tumor ”nests” encompassed by stromal cellular and ECM boundaries
- Tumor ER expression and proliferation increase in close proximity to collagen boundaries



Chin, Eng, Bucher, Chang, Hu, Burlingame, Sorger, Gray

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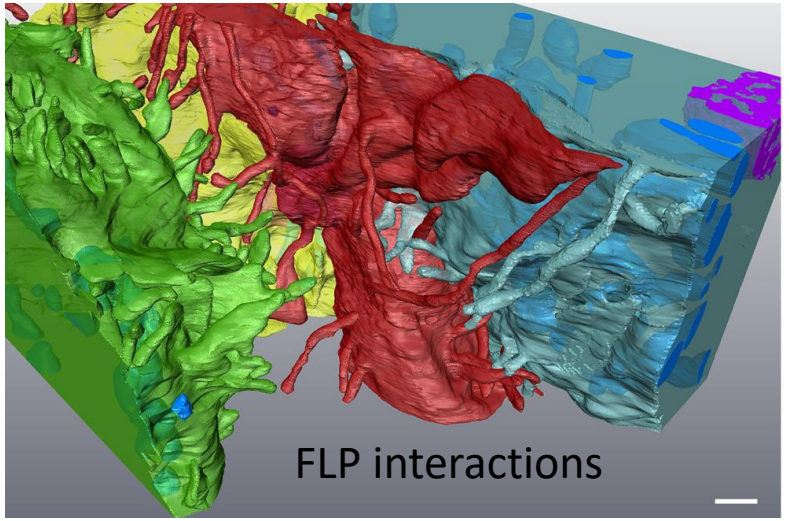
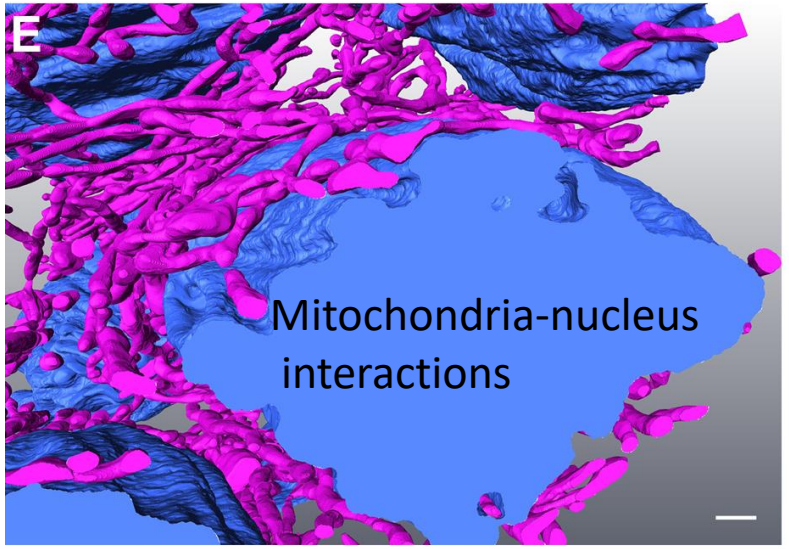
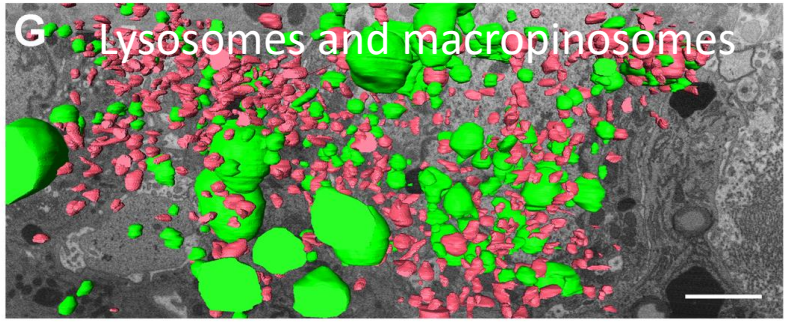
Actionable Subcellular Biology from 3D EM

highlights

- FLP mediated motility and inhibition of receptor recycling
- Forced mitochondrial-nuclear interactions deregulate metabolism and DNA damage repair
- Sequestration of basic drugs by acidic lysosomes
- Nutrient scavenging via macropinocytosis







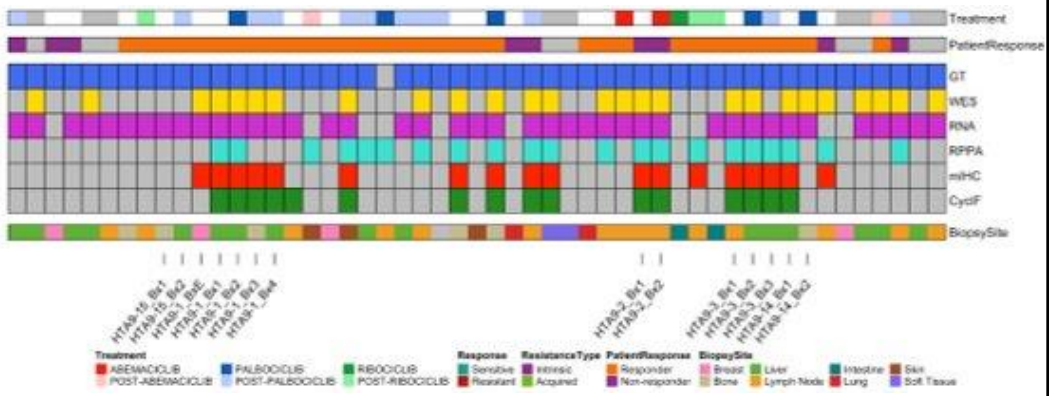
Riesterer, Smith, Bueno, Machireddy, Song, Thibault, Lopez, Gray

Opportunities for Current and Future HTAN Efforts

- Integrative analyses of serial data from large cohorts
- Predicting/imputing measures to define minimum assay requirements
- 3D reconstruction of tumors using clearing and lightsheet approaches
- Multimodal and spatial biomarkers of response/resistance
- Connecting with systems biology to elucidate functions and identify synergistic treatments that counter temporal evolution and spatial heterogeneity
- Alternatives or adjuncts to invasive biopsies
  - Liquid biopsies including after focal radiation
  - Molecularly targeted anatomic imaging

Initial cohort analyses now underway

5 metastatic ER+ breast cancers with paired pre- and on-progression biopsies



- Tumor intrinsic mechanisms of resistance are diverse, with many ways to increase proliferation
- Tumor extrinsic mechanisms of resistance are similar and center on immune modulation

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Summary

- Serial, multimodal analyses of evolving cancers can be executed in clinical “real time”
- Each analysis modality provides novel insights into resistance and response mechanisms
- Careful monitoring of treatments and timing allows them to be treated as informative perturbations
- Analyses of serial biopsies reveal actionable differences between lesions
- Blood biomarker monitoring allows early treatment switching to counter emerging resistance mechanisms
- Data and study description available in the HTAN DCC

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