Experimental Tissue Resource

UCI Chao Family Comprehensive Cancer Center

Leadership

Robert Edwards, MD, PhD
Director

Wendy Cozen, DO, MPH
Co-Director

Delia Tifrea, PhD, MBA
Manager

Mission

To support the research mission across UC Irvine and the campus research community

To fulfill this mission **ETR** assists investigators with tissue procurement, processing, and histopathology interpretation.

Services

- Fresh and FFPE Tissue Procurement and Interpretive Histopathology Consultation
- Tissue Histology and IHC services
- Mouse Pathology services/consultation on mouse models of human disease
- Biorepository/tissue banking services, including a user-searchable de-identified database of archival tissue

Inventory (Available Samples)

TISSUE	SURGICAL RESECTIONS FFPE (# 5 years)	BIOPSIES FFPE (# 5 years)	FROZEN tissue
brain	589 (326)	3,006 (1297)	644
colon	2,204 (956)	23,352 (13,546)	259
pancreas	875 (266)	398 (211)	98
breast	5,808 (2,505)	1,211 (354)	118
uterus	899 (547)	237 (99)	219
ovary, adnexa	1,671 (713)	206 (77)	280
prostate	1,858 (602)	377 (239)	735
kidney	1,180 (422)	169 (78)	295
bladder	535 (288)	1,308 (513)	29
lung	285 (130)	177 (133)	36
TOTAL	328,987		5,682

Support Provided (Annual) 65% cancer related

- Clinical trials..... **97**
- Individual patients..... **1,348**
- Investigator-initiated trials..... **8**
- Basic research projects..... **43**
- ETR consultation for database, IRB, sample collection, protocol review..... **84**
- TMA..... **10**

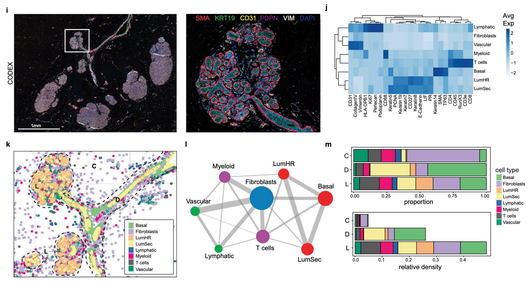
Research Highlights

1 | A spatially resolved single cell genomic atlas of the adult human breast

Kessenbrock K (SPT), Lawson DA (SPT), Edwards R (SPT), Lin E (SPT), Parajuli R (SPT)

Nature 2023; 620 (7972): 181-191. 5966421

A comprehensive Human Breast Cell Atlas (HBCA) at single-cell and spatial resolution, with focus on non-epithelial cell types was detailed. This single-cell transcriptomics study profiled 714,331 cells from 126 women, and 117,346 nuclei from 20 women, identifying 12 major cell types and 58 biological cell states. These data reveal abundant perivascular, endothelial and immune cell populations, and highly diverse luminal epithelial cell states. Spatial mapping using four different technologies revealed an unexpectedly rich ecosystem of tissue-resident immune cells, as well as distinct molecular differences between ductal and lobular regions.



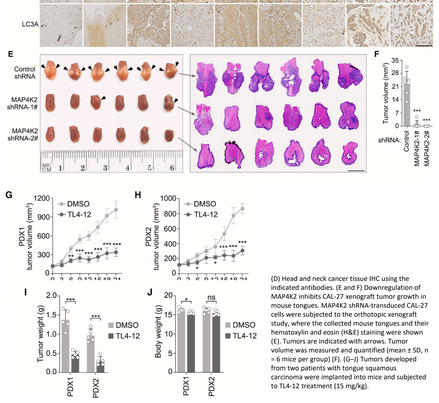
j, Heatmap showing protein levels for markers that were used to identify different cell types. **k**, Cell segmentation using combinations of markers to identify cell types in the CODEX data from one tissue sample, with topographic areas annotated. **l**, Spatial colocalization graph of segmented cell types in the CODEX data from 4 tissues. **m**, Cell type and cell density frequencies from the CODEX data summarized across 4 tissue samples.

2 | The Hippo pathway noncanonically drives autophagy and cell survival in response to energy stress

Wang W (SPT), Edwards R (SPT), Huang L (BIDD)

Molecular Cell 2023; 83 (17):3155-3170.e8

The Hippo pathway is known for its crucial involvement in development, regeneration, organ size control, and cancer. While energy stress is known to activate the Hippo pathway and inhibit its effector YAP, the precise role of the Hippo pathway in energy stress response remains unclear. Here, we report a YAP-independent function of the Hippo pathway in facilitating autophagy and cell survival in response to energy stress, a process mediated by its upstream components MAP4K2 and STRIPAK. Mechanistically, energy stress disrupts the MAP4K2-STRIPAK association, leading to the activation of MAP4K2. Subsequently, MAP4K2 phosphorylates ATG8-family member LC3, thereby facilitating autophagic flux. MAP4K2 is highly expressed in head and neck cancer, and its mediated autophagy is required for head and neck tumor growth in mice. Altogether, our study unveils a noncanonical role of the Hippo pathway in energy stress response, shedding light on this key growth-related pathway in tissue homeostasis and cancer.



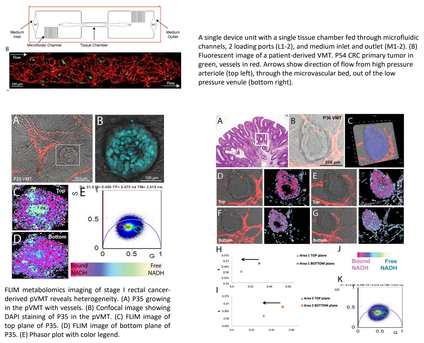
(D) Head and neck cancer tissue IHC using the indicated antibodies. (E and F) Downregulation of MAP4K2 inhibits CAL-27 xenograft tumor growth in mouse tongues. MAP4K2 shRNA-transduced CAL-27 cells were subjected to the orthotopic xenograft study, where the collected mouse tongues and their hematoxylin and eosin (H&E) staining were shown (E). Tumors are indicated with arrows. Tumor volume was measured and quantified (mean ± SD, n = 6 mice per group) (F). (G–J) Tumors developed from two patients with tongue squamous carcinoma were implanted into mice and subjected to TL4-12 treatment (15 mg/kg).

3 | A human vascularized microtumor model of patient-derived colorectal cancer recapitulates clinical disease

Hughes CCW (BIDD), Edwards RA (SPT), Lowengrub JS (SPT), Waterman ML (SPT), Zell JA (CC)

Translational research: the journal of laboratory and clinical medicine 2023; 255:97-108.

Accurately modeling tumor biology and testing novel therapies on patient-derived cells is critically important to developing therapeutic regimens personalized to a patient's specific disease. The vascularized microtumor (VMT), or "tumor-on-a-chip," is a physiologic preclinical cancer model that incorporates key features of the native human tumor microenvironment within a transparent microfluidic platform, allowing rapid drug screening in vitro. This study is optimizing the methods for generating patient-derived VMT (pVMT) using fresh colorectal cancer (CRC) biopsies and surgical resections to test drug sensitivities at the individual patient level. In response to standard chemotherapy and TGF-βR1 inhibition, the study reports heterogeneous responses between pVMT derived from 6 patient biopsies, with the pVMT recapitulating tumor growth, histological features, metabolic heterogeneity, and drug responses of actual CRC tumors. This results suggest that a translational infrastructure providing rapid information from patient-derived tumor cells in the pVMT can be used support efforts to improve patient outcomes.



A single device unit with a single tissue chamber fed through microfluidic channels, 2 loading ports (L1-2), and medium inlet and outlet (M1-2). (B) Fluorescent image of a patient-derived VMT. P54 CRC primary tumor in green, vessels in red. Arrows show direction of flow from high pressure arteriole (top left), through the microvascular bed, out of the low pressure venule (bottom right).

FLIM metabolomics imaging of stage I rectal cancer-derived pVMT reveals heterogeneity. (A) P35 growing in the pVMT with vessels. (B) Confocal image showing DAPI staining of P35 in the pVMT. (C) FLIM image of top plane of P35. (D) FLIM image of bottom plane of P35. (E) Phasor plot with color legend.

Key Equipment & Technologies

We acquired additional space and added the second histotechnologist with complementary skills

- Whole Slide Ventana Scanners

- Automated tissue microarray (TMA Grand Master)

# core/block	core diameter
558	0.6 mm
286	1 mm
135	1.5 mm
84	2 mm

Feasible for proteomics ***nanoString***- GeoMx DSP

Future Plans

- To continue to expand procurement of fresh specimens for clinical trialists and integration into clinical trials workflow.
- To increase utilization of basic histology services and expand the utilization of current Discovery Automated Ventana stainer to immunofluorescence and custom IHC
- To advertise and increase utilization of the new services: **automated tissue microarrays (TMA) and specialized histology services for special transcriptomics**
- To complete the build-out of new, dedicated **ETR** facility space for processing, annotation, and storage of high quality solid organ and hematopoietic malignancy specimens, **with the goal of meeting CAP accreditation requirements for Biorepositories**
- To enhance the EMR-LIS integration platforms utilization to link surgical pathology specimen data with patient data to facilitate outcomes research
- To establish regular Open house- Training sessions for FFPE and frozen tissue sectioning

Publications

CFCCC Investigator	Program	Published Journal	Year
Robert Edwards, MD, PhD Erin Lin, DO Ritesh Parajuli, MD Qing Nie, PhD Kai Kessenbrock, PhD	SPT SPT SPT SPT SPT	*Nature genetics*	2023
Mei Kong, PhD	SPT	*Nature communications*	2023
Matthew Inlay, PhD	SPT	*EMBO molecular medicine*	2023
Edward Uchio, MD Xiaolin Zi, PhD	CC CC	*Biomolecules*	2023
Jogeshwar Mukherjee, PhD	BIDD	*International journal of molecular sciences*	2023