Baylor College of Medicine

ADVANCED TECHNOLOGY CORES

2024 CATALOG


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ADVANCED TECHNOLOGY CORES

I am pleased to present the BCM Advanced Technology Cores catalog for 2024. This publication is designed to help you access the high-end instrumentation and specialized technologies you need for your research. The Advanced Technology Cores (ATC) at BCM expand the research capabilities of all researchers and essentially create unlimited research opportunities.

Each of the cores is staffed by faculty level directors and dedicated research technicians with highly specialized expertise in the technologies provided. A range of research support services are provided such as access to shared instrumentation, analysis of research samples provided by investigators and experiments with Core personnel performing specialized portions of the project. In addition to technical procedures, Cores provide consultation on experimental design, data analysis and training.

This catalog provides an introduction to each of the Cores including services and major instrumentation, technology platforms, core leadership, contact information and examples of scientific research supported by core. For more information about any of the Cores, visit bcm.edu/research/atc-core-labs.

On behalf of all the faculty and staff in the Cores, we look forward to working with you to advance science across all areas at BCM.

— Mary E. Dickinson, Ph.D.
Senior Vice President and Dean of Research

CORE LEADERSHIP

Dean P. Edwards, Ph.D.
Executive Director

Dr. Edwards provides scientific oversight and guidance and establishes policies for governance and funding.

Elyse K. Davis
Director, Business Operations

Ms. Davis administers financial and accounting policies, and provides strategic planning and guidance for business operations.

ACKNOWLEDGMENTS

Financial support to subsidize Core operations is provided by the following Institutional sources and extra-mural grants.

INSTITUTIONAL SUPPORT

Dan L Duncan Comprehensive Cancer Center

Baylor College of Medicine Seed and Capital Funds

Office of Research: Advanced Technology Cores unit

GRANT SUPPORT

NCI P30 Cancer Center Support Grant (CCSG)

NIH P30 Digestive Disease Center (DDC)

NIH U54 Intellectual & Development Disabilities Research Center (IDDRC)

Cancer Prevention and Research Institute of Texas (CPRIT) Core Facility Support Awards

NEI P30 Instrumentation Module Center

NIH UM1 Consortium for large-scale production and phenotyping of knockout mice

NIH S10 Shared Instrument Grants

NIEHS P42 Superfund Project

NIEHS P30 Gulf Coast Center for Precision Environmental Health (GC-CPEH)

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ADVANCED CELL ENGINEERING & 3D MODELS CORE (REORGANIZED IN 2023)

The Advanced Cell Engineering and 3D Models (ACE-3M) Core is a newly reorganized facility that represents a merger of the prior Advanced *In Vivo* Models (AIM) and Cell Based Assay Screening Services (C-BASS) Cores. The ACE-3M Core continues to provide services offered previously by AIM and C-BASS cores plus new expanded capabilities of tumor organoids grown in 3D matrices including from patient derived primary tumors (PDO) and from mouse PDX tumor collections from different organ/disease types. Prior AIM services include growth of human primary tumors or cancer cell lines on the chorioallantoic membrane (CAM-PDX) of the chicken embryo for pre-clinical functional studies (in ovo). Prior C-BASS services include generating knock-out and knock-in cell lines using various gene editing technologies and consultation and expert advice on sub-genome targeted screens. The merger leverages 3D tumor models with cell engineering technologies to provide expanded, cutting-edge functional genomics and genome editing services.

MAJOR EQUIPMENT

- IVIS Lumina III luminescence/fluorescence imager
- gentleMACS Octo Dissociator with heaters
- Biomek NX automated liquid handling workstation

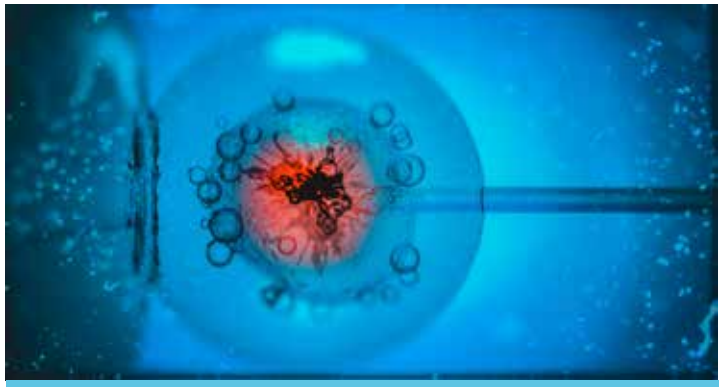
SERVICES

Cell Engineering and functional genomics

- Gene editing of cell lines and tumor organoids through CRISPR (KO, KI cell line generation and consultation)
- Vector design, construction, and testing
- Lentiviral production and stable cell line generation
- Individual vector distribution from whole-genome shRNA/cDNA collections (human and mouse)
- Pre-assembled Lenti-CRISPR-gRNA sub-libraries (e.g., kinase, transcription factors, etc.)
- Custom sub-libraries assembly (gene collection designed by investigator)

3D Tumor Models

- Conversion of 2D primary or cell lines into 3D vascularized tumors on CAM
- Patient Derived Xenograft (PDX) growth on the chicken egg CAM
- Custom bioassays including angiogenesis, invasion, and metastasis
- Drug sensitivity screening on 3D vascularized cell xenografts and PDX on CAM
- Assistance with preparation for end-point assays on CAM or tumor organoids (Flow cytometry, DNA/RNA purification, IHC, bioluminescence, omics sample prep)
- Investigator access to IVIS Lumina III fluorescence and bioluminescence instrument for in vitro and ex vivo experiment imaging
- Provision of cryopreserved, validated PDX-derived breast tumor organoid models (triple negative breast cancer, ER+, and HER2+ subtypes) with accompanying parent tumor clinical information for BCM investigators
- Development and expansion of PDO and PDX-derived tumor organoids for investigator-led compound or genetic screens
- User training provided for IVIS Lumina III imaging and gentleMACS octo dissociator equipment
- Assistance with characterization of PDO and PDX-derived tumor organoids



CORE LEADERSHIP

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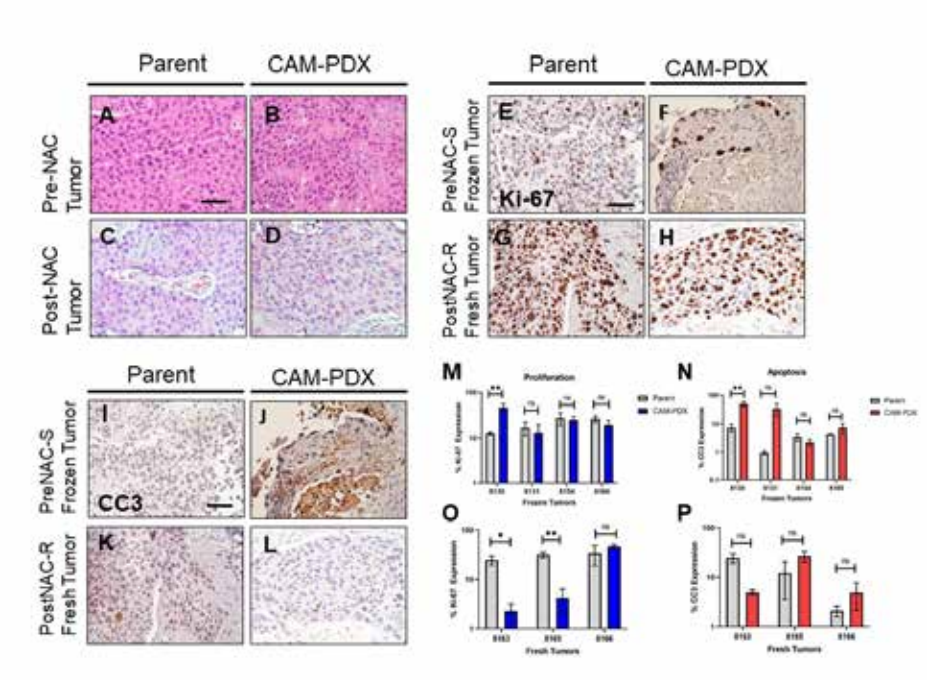
Characterizing treatment resistance in muscle invasive bladder cancer using the chicken egg chorioallantoic membrane patient-derived xenograft model.



Histopathological concordance between parent and CAM-PDX tumors. Histology of urothelial cancer from patients prior to receiving neoadjuvant chemotherapy in (**A**) Hematoxylin and eosin (H & E) parent tumors and (**B**) matching CAM-PDX and tumor specimens after receiving neoadjuvant chemotherapy in (**C**) hematoxylin and eosin parent tumor and (**D**) matching CAM-PDX. Immunohistochemistry of pre-NAC cryopreserved for Ki-67 in (**E**) parent tumors and (**F**) CAM-PDX and cleaved caspase 3 in (**I**) parent and (**J**) CAM-PDX. Post-NAC freshly obtained tumor stained for Ki-67 in (**G**) parent tumors and (**H**) CAM-PDX and cleaved caspase 3 in (**K**) parent tumors and (**L**) CAM-PDX. Scale bar = 50 μm. Quantification of Ki-67 and CC3 in (**M-N**) frozen and (**O–P**) fresh tumors. **P* <0.05, ***P* <0.01, ns: not significant. Data are represented as the mean ± S.E.M.

Villanueva H, Wells GA, Miller MT, Villanueva M, Pathak R, Castro P, Ittmann MM, Sikora AG, Lerner SP. Characterizing treatment resistance in muscle invasive bladder cancer using the chicken egg chorioallantoic membrane patient-derived xenograft model. Heliyon. 2022 Dec 24;8(12):e12570. doi: 10.1016/j.heliyon.2022.e12570. PMID: 36643309; PMCID: PMC9834740.

ANTIBODY-BASED PROTEOMICS

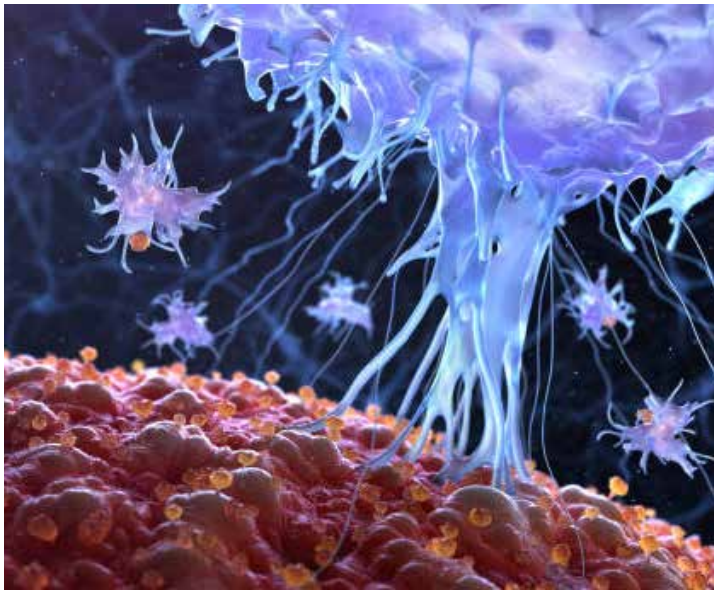
This Core provides customized services for high-throughput protein profiling by antibody-based proteomics platforms. These platforms provide targeted quantitative assays both for validation and protein biomarker discovery research, particularly for low abundance regulatory proteins, activation states of proteins with antibodies to specific phosphorylation sites and epigenetic core histone post-translation modifications. Services provided include reverse phase protein arrays (RPPA), Luminex bead technology for multiplex quantitative analyses of intracellular and extracellular signaling proteins and an Ella Automated Immunoassay System that performs assays similar to ELISA, but with the advantage of requiring smaller sample materials and incorporating automation.

MAJOR EQUIPMENT

- Bio-Plex 200 Luminex bead reader (Bio-Rad)
- Luminex bead washer (Bio-Tek ELx405)
- Ella Automated Immunoassay System (BioTechnique)
- Quanterix 2470 Microarrayer (Quanterix)
- Dako Autostainer Link 48 (Agilent)
- Axon Array Scanner 4200AL and GenePix software (Molecular Devices)
- TissueLyzer II (Qiagen)
- Molecular Devices Spectramax 340PC Plate Reader

SERVICES

- Consultation and experimental design.
- Protein sample preparation.
- Reverse Phase Protein Array assays. High density microarrays spotted with researchers' protein lysates and probed with validated specific antibodies (>260) to proteins and phosphorylation sites of major protein signaling pathways.
- RPPA epigenetic panel. Profiling of a wide range of histone post-translational modifications (PTMs) and histone and chromatin modifier proteins.
- Luminex bead assays (Luminex xMAP technology) for highly sensitive quantitative measurement with very small protein lysate or serum samples.
- Ella Automated Immunoassay System performs assays similar to ELISA with the advantages of full automation, higher sensitivity and smaller sample materials requirement. The system is suitable for clinical studies and research projects with limited materials or large numbers of samples.
- Image analyses of protein/antibody microarrays.
- Data management and analysis (Q/C, normalization, statistics and differential analysis).



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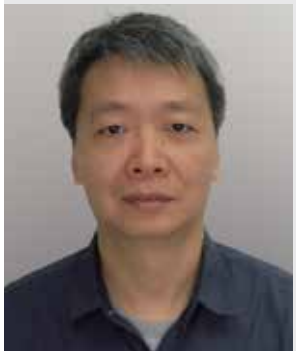

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Efficient cancer modeling through CRISPR-Cas9/HDR based somatic precision gene editing in mice

CRISPR-Cas9 has been used successfully to introduce indels in somatic cells of rodents; however, precise editing of single nucleotides has been hampered by limitations of flexibility and efficiency. The Li and Zhang labs developed technological modifications to the CRISPR-Cas9 vector system that enables homology-directed repair–mediated precise editing of any proto-oncogene in murine somatic tissues to generate tumor models with high flexibility and efficiency. Somatic editing of either Kras or Pik3ca in both normal and hyperplastic mammary glands generated tumors that shared some histological, transcriptome, and proteome features with those induced by lentivirus-mediated expression of the respective oncogenes, but showed less inter-tumor variation, thus potentially offering more consistent models for cancer studies and therapeutic development. This technological advancement fills a critical gap between the power of CRISPR technology and high-fidelity mouse models for studying human tumor evolution and preclinical drug testing. The Core employed Reverse Phase Protein Array (RPPA) analyses to identify distinct proteome features in tumors induced by overexpression of specific oncogenes. RPPA revealed that: 1) Genome-edited proto-oncogenes activated more consistent cellular signaling changes compared to lentiviral vector-delivered exogenous oncogenes; 2) induced more significant changes in signaling pathways than Lenti-oncogene overexpression models, particularly with a Wnt1 transgene (B&C); and 3) validated the more consistent and less inter-tumor variation of CRISPR models. These results highlight the effectiveness of genome editing models in providing valuable insights for cancer research and therapeutic advancements.

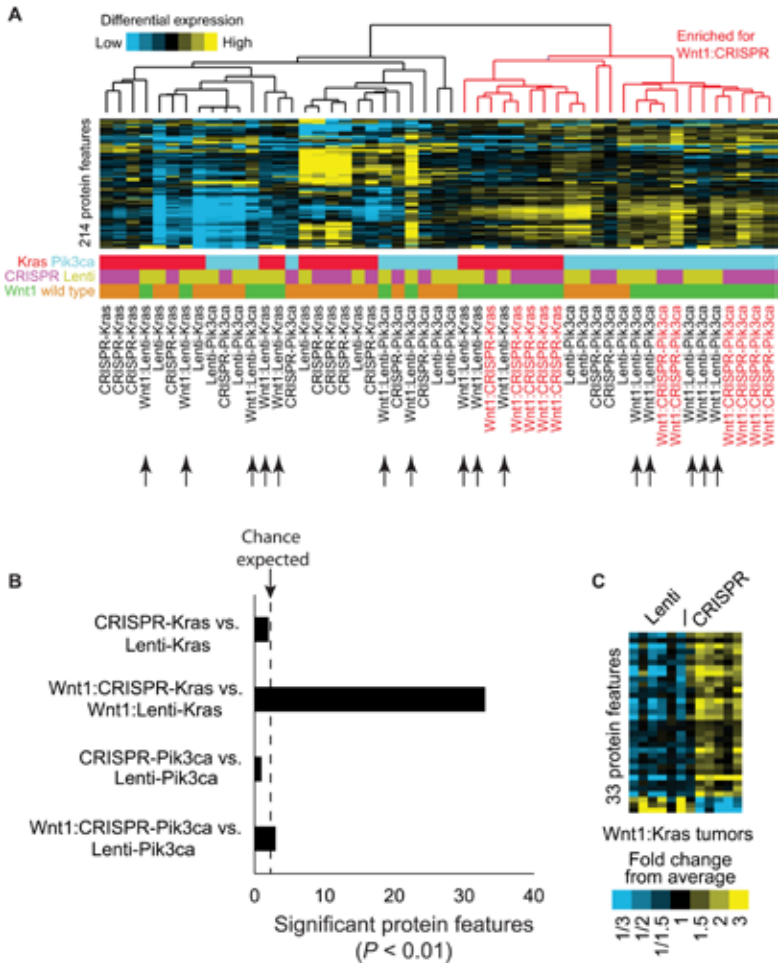

Figure: RPPA comparison of tumors generated by proto-oncogene editing and lentivirus-mediated oncogene delivery. (**A**) The unsupervised protein feature clustering of eight groups of mammary tumors. The somatically edited KrasG12D- or Pik3caH1047R-induced tumors on the MMTV-Wnt1 background cluster closely (red font labeled), but tumors induced by Lenti-KrasG12D or PIK3CAH1047R on the MMTV-Wnt1 background scatter wildly (arrow pointed). (**B**) Bar graph showing differential protein features detected by RPPA (P <0.01 cutoff by t test). The dashed line is the expected level of differences caused by random chance due to multiple testing. (**C**) Heatmap showing differential protein features between mammary tumors generated by somatically edited KrasG12D and lentivirus-delivered KrasG12D on the MMTV-Wnt1 background.

Bu W, Creighton CJ, Heavener KS, Gutierrez C, Dou Y, Ku AT, Zhang Y, Jiang W, Urrutia J, Jiang W, Yue F, Jia L, Ibrahim AA, Zhang B, Huang S, Li Y. Efficient cancer modeling through CRISPR-Cas9/HDR-based somatic precision gene editing in mice. Sci Adv. 2023 May 12;9(19):eade0059. doi: 10.1126/sciadv.ade0059. Epub 2023 May 12. PMID: 37172086; PMCID: PMC10181191

BIOENGINEERING

The Bioengineering Core provides investigators custom scientific instrumentation needed to conduct elegant experiments and ask truly cutting-edge research questions. The Bioengineering Core also provides clinicians custom, one-of-a-kind, medical devices to create innovative solutions for health care. The core is staffed with an experienced bioengineer and a machinist who can work with investigators and clinicians to design complex devices, identify suitable off-the-shelf devices, manufacture custom parts, and integrate the apparatuses/instruments into the research workflow or clinical practices.

MAJOR EQUIPMENT

- Hermle 5-axis CNC (Computer Numerical Control) Milling machine center capable of cutting solid materials such as metal, plastics, and wood into parts with complex geometries up to a size of 24″ x 18″ x 18″.
- Haas CNC Lathe – capable of machining custom cylindrical parts up to 14″ diameter and 14″ long.
- Hardinge manual precision lathe.
- Bridgeport manual milling machine.
- Vertical band saw and horizontal cutoff saw.
- Epilog Laser cutter – capable of cutting plastic, wood, or paper sheets up to 32″ x 20″ with 3/4″ thickness and engraving plastic, leather, metal, and glass.
- Stratasys 3D printer – capable of printing ABS plastics and supporting material up to a size of 8″ x 8″ x 6″.
- Thorlabs optical workstation equipped with vibration isolation optical table, laser diode mount, laser controller, and power meter allowing design and tests of optical devices.

SERVICES

- Customized instrumentation design and manufacture.
- Customized electronics/optics design and manufacture.
- High precision mechanical manufacture.
- 3D design and printing.
- Laser cutting and engraving.
- Stockroom of fasteners and raw materials such as aluminum, stainless steel, and plastics.
- Consultation for biomedical engineering projects.

CORE LEADERSHIP

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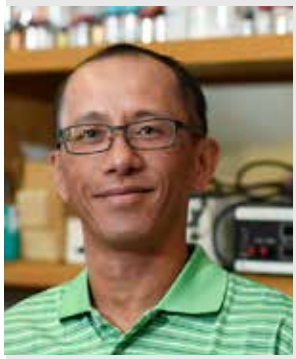

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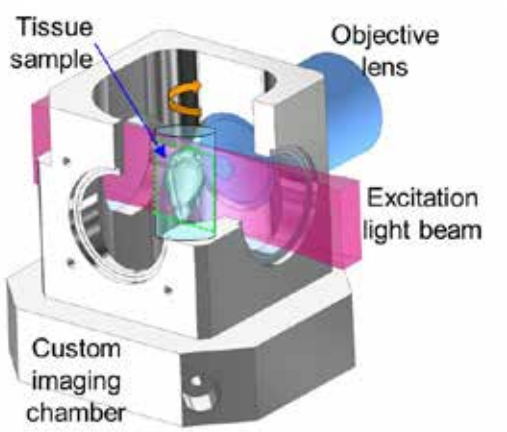
The Core produced a custom odor delivery and head fixing system for studying neural responses to various olfactory stimuli in mice.

Swanson JL, Ortiz-Guzman J, Srivastava S, Chin PS, Dooling SW, Hanson Moss E, Kochukov MY, Hunt PJ, Patel JM, Pekarek BT, Tong Q, Arenkiel BR. Activation of basal forebrain-to-lateral habenula circuitry drives reflexive aversion and suppresses feeding behavior. Sci Rep. 2022 Dec 21;12(1):22044

The Core designed and fabricated a custom apparatus for light-sheet microscopy.
Hsu CW, Cerda J 3rd, Kirk JM, Turner WD, Rasmussen TL, Flores Suarez CP, Dickinson ME, Wythe JD. EZ Clear for simple, rapid, and robust mouse whole organ clearing. Elife. 2022 Oct 11;11:e77419.



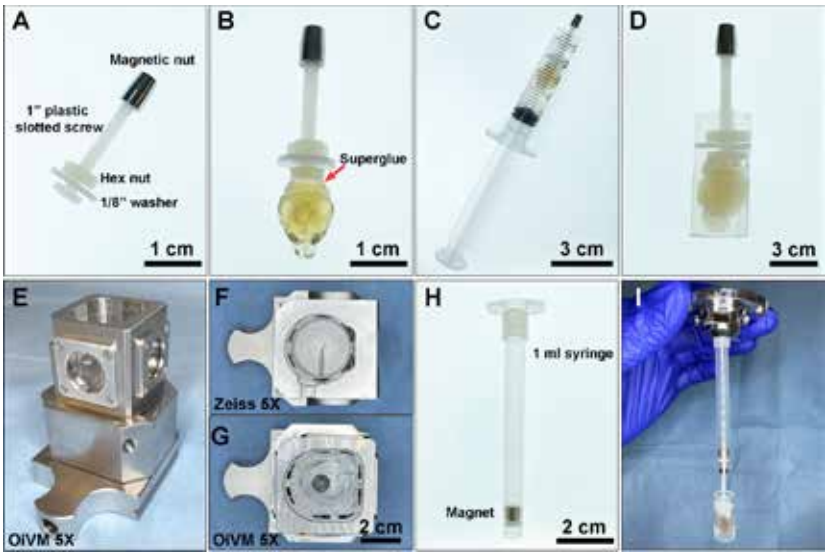


Figure: Sample holder (**A–D**), imaging chamber (**E, G**), and mounting probe (**H, I**) custom designed and fabricated by Bioengineering Core for light-sheet microscopy in Optical Imaging and Vital Microscopy (OiVM) Core.

BIOSTATISTICS & INFORMATICS SHARED RESOURCE

The goal of the Biostatistics and Informatics Shared Resource (BISR) is to provide state of the art biostatistical, bioinformatics, and computational support for clinical, translational and basic science research.

MAJOR EQUIPMENT

Two high performance computing clusters totaling more than 2800 CPUs and 25 PB RAM. In addition, there are 4 GPU nodes featuring 26 discrete GPUs totaling 100,000 cores and 500 GB VRAM. Cluster storage is either on the ATC's direct-attached enterprise class high performance storage with nearly 1.5 PB of raw capacity with the capability to expand 10-fold OR on network-attached enterprise class storage owned and managed by Baylor College of Medicine Office of Information Technology (BCM OIT). The clusters are maintained by an expert HPC system administrator in the BCM corporate data center under standard governance structures.

SERVICES

- **Biostatistics and Analytics:** Experimental design and analysis of laboratory and translational studies; Assistance with design, conduct, analysis and reporting of clinical trials
- **Bioinformatics:** Analysis of 'omics' data and publically datasets including downstream multi-omic integrative bioinformatic analyses
- **High Performance Computing (HPC):** cluster management and storage allocation; user training, central software library maintenance; troubleshooting
- **REDCap Projects:** Assistance with specialty add-on modules; project set-up, instrument creation and troubleshooting
- **Other:** Assistance with grant applications; education; statistical review for the Protocol Review and Monitoring and Data Review Committees

Investigators needing assistance with the following, please use the indicated contacts

- HPC Cluster (cluster-help@breastcenter.tmc.edu)
- Redcap support (redcap-support@bcm.edu)

Additional tools managed by the Biomedical Informatics Group:

- OnCore® and Clinical Trials Data Management (oncore-support@bcm.edu)
- eREG® and electronic regulatory affairs (ereg-support@bcm.edu)
- Biobanking Data Management (biobank-support@bcm.edu)
- Clinical Omics Data Lake (ClinOmics_Admin@bcm.edu)
- PDX Portal (pdxportal-help@bcm.edu) biobank-support@breastcenter.tmc.edu)
- Software licensing for Oncomine™, Ingenuity®, SAS®, and SPSS® (licensing@breastcenter.tmc.edu)

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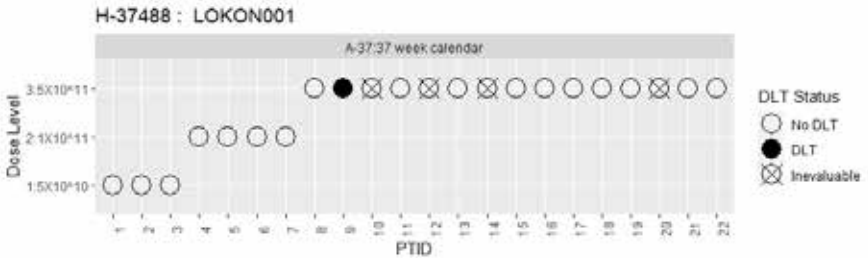
A Phase I/II Study of LOAd703 for Unresectable or Metastatic Pancreatic Cancer

Pancreatic ductal adenocarcinoma (PDAC) is characterized by low immunogenicity, an immunosuppressive tumor microenvironment, and negligible responsiveness to immunotherapy. LOAd703, an oncolytic adenovirus with transgenes encoding TMZ-CD40L and 4-1BBL, lyses cancer cells selectively, activates cytotoxic T-cells, and induces tumor regression in preclinical models. This Phase I/II study in unresectable or metastatic PDAC used a Bayesian Optimal INterval design to evaluate the safety of standard of care nab-paclitaxel/gemcitabine (nPG) plus intratumoral injections of escalating doses LOAd703 coupled with a single stage test of efficacy in a small expansion cohort. At the highest dose level, LOAd703 was safe while inducing immune responses and demonstrating sufficient anticancer activity for further development. **BISR helped design the trial, assisted in building the trial in OnCore, handled reporting and data exported to the Sponsor and developed the graphical visualization to use in reports for this and other Phase 1 trials to determine the dose level for the next cohort of patients.**

BOIN Decision Rules Regulating of Dose Escalation in LOKON001

Number of Patients treated in a Defined Dose Cohort	3	6	9	12	15	18
Escalate dose if number of DLT≤	0	1	2	2	3	4
Treat additional 3 pts on current dose if number of DLT=	1	2	4	3,4	4,5	5,6
De-escalate dose if number of DLT≥*	2	3	4	5	6	7
Eliminate dose level and all higher doses from further use if number of DLT≥	3	4	5	7	8	9

** At the lowest dose level, if the recommendation is to de-escalate AND the dose level has not been eliminated from consideration, 3 additional pts will be accrued at the same dose level; otherwise the trial will stop.*



Musher BL, Rowinsky EK, Smaglo B, Abidi W, Othman M, Patel K, Jawaid S, Jing J, Brisco A, Leen AM, Wu MF, Wenthe J, Eriksson E, Ullenhag G, Sandin LC, Grilley B, Leja-Jarblad J, Hilsenbeck SG, Brenner MK, Loskog ASI. A Phase I/II Study of LOAd703, an Oncolytic Virus-Based Immunostimulatory Gene Therapy, Combined with Chemotherapy for Unresectable or Metastatic Pancreatic Cancer. Lancet Oncology. In Press.

CORE FOR ADVANCED MAGNETIC RESONANCE IMAGING (CAMRI)

The Core for Advanced Magnetic Resonance Imaging (CAMRI) is a state-of-the-art resource for Baylor College of Medicine (BCM) and the Houston research community that makes possible advanced imaging studies of the function, physiology and anatomy of humans and animals, with special expertise in human blood-oxygen level dependent functional MRI (BOLD fMRI). Conveniently located in the heart of the BCM main campus, the Core maintains and operates two cutting edge MR imaging systems.

MAJOR EQUIPMENT

- Two Siemens 3 Tesla Prisma Fit MRI Scanners with 80/200 gradients.
- A wide variety of equipment for functional brain imaging studies, including sensory stimulation devices, response buttons, eye trackers, and MR-compatible transcranial magnetic stimulation (TMS).
- Multiple MRI coils with the ability to scan all body parts.
- Additional space available for animal preparation, TMS, behavioral testing, and stimulus recording.

SEQUENCES

- Functional MRI (fMRI), including multiband acceleration.
- Diffusion tensor imaging (DTI)
- Single and multi-voxel magnetic resonance spectroscopy (MRS)
- Arterial spin labeling (ASL), both pulsed and continuous.
- High-resolution structural imaging: FLASH, TSE, FLAIR, etc.
- All Siemens standard sequences for whole body.

SERVICES

- Imaging technologist available to assist in data collection.
- Operator training available to enable safe use of MRI equipment by new users.
- Access to the instruments for fully trained users is available 24/7, facilitating subject recruitment and retention.
- Monthly journal club and seminar series, details on our wiki at http://openwetware.org/wiki/CAMRI

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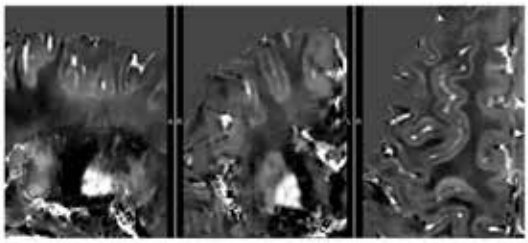
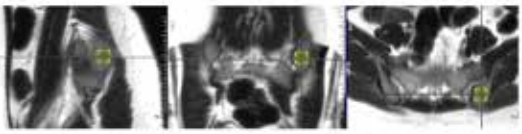
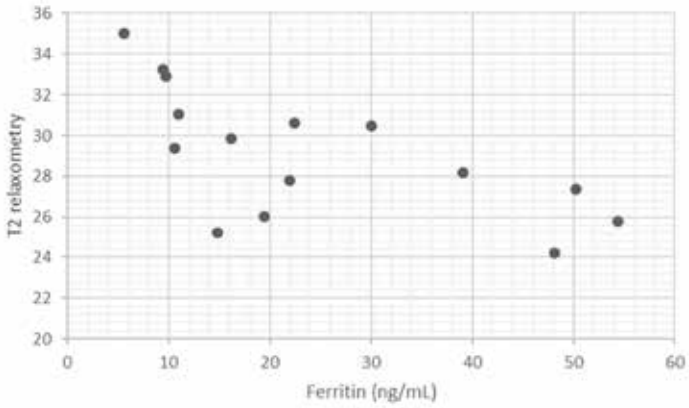
In a current study at CAMRI, Drs. Calarge and Xu and their colleagues are investigating how to best estimate body and brain iron stores in adolescents. They are collecting brain and bone marrow MR scans at CAMRI from adolescents with and without iron deficiency. The group is using Quantitative Susceptibility Mapping to estimate brain iron content and Magnetic Resonance Spectroscopy to estimate bone marrow iron content in the iliac and lumbar spine. In addition, they are collecting neuropsychiatric data and biological samples. This data will help examine how body iron stores may affect brain iron level and how this, in turn, relates to brain development and function. It will also allow them to optimize MR-based approaches to better quantify bone marrow iron content in a safe and noninvasive way.



Quantitative susceptibility (X) mapping: whole brain



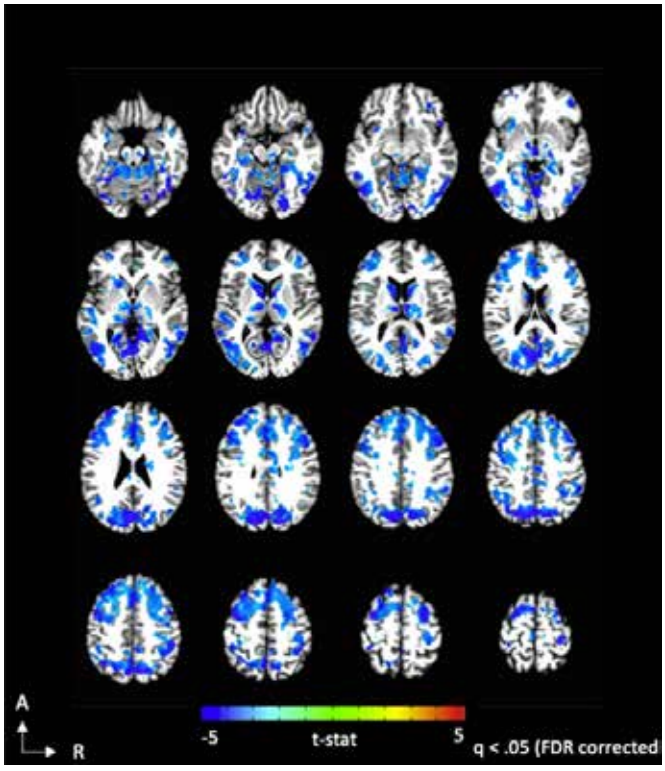
T2 relaxometry (MR spectroscopy): iliac bone marrow



T2 relaxometry values in the lumbar spine bone marrow as a function of ferritin. Higher values of T2 correspond to lower bone marrow iron content while higher values of ferritin correspond to higher iron content in the blood.

Drs. Ramiro Salas, Michelle Patriquin, and their colleagues collected MRI images at CAMRI from more than 500 psychiatric patients at The Menninger Clinic, a BCM affiliated psychiatric inpatient clinic. Julia Myerson, Dr. Hyuntaek Oh, and their team used this data to explore dysfunctions in reward processing related to chronic substance use by examining brain responses to reward stimuli. The team found that individuals with high-risk substance use showed low responses to reward stimuli in the dorsal striatum, insula, and middle cingulate cortex (see figure at right), and those responses were correlated with a high risk of suicidal behaviors, particularly in the left dorsal striatum.

Figure adapted from Myerson J, Montelongo M, Rufino K, Patriquin M, Salas R, Oh H. Examination of reward processing dysfunctions in the left dorsal striatum and other brain regions among psychiatric inpatients with substance use. Drug and Alcohol Dependence. 2024. 111097.



CRYO ELECTRON MICROSCOPY (CRYOEM)

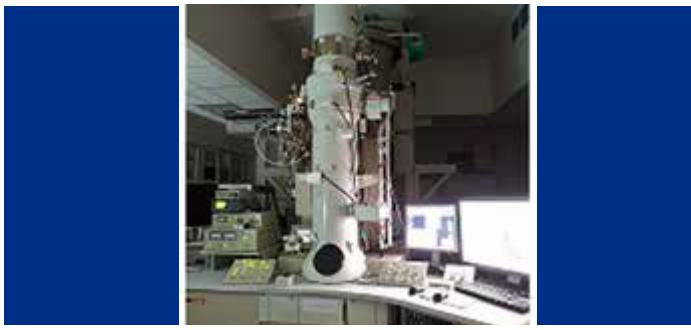
The Cryo Electron Microscopy (CryoEM) Core is a state-of-the-art resource for near-atomic resolution 3-D analysis of the structure and dynamics of macromolecules and assemblies, either purified or within cells. This includes the established technique of single particle analysis, wherein images of tens of thousands to millions of isolated macromolecules are reconstructed to produce one or more 3-D structures at resolutions as high as 0.2 nm (near atomic resolution), as well as in-situ electron cryotomography which permits the 3-D study of cells or regions of cells at nanometer resolutions,100x better than optical microscopy. Single particle analysis is a direct alternative to X-ray crystallography, and can provide additional information about dynamics and compositional variability, which crystallography cannot access. We can also work with users to optimize specimens and provide preliminary data to gain free access to the new 'beamline' style CryoEM facilities sponsored by the NIH.

MAJOR EQUIPMENT

- **ThermoFisher Glacios** – 200 keV instrument with a field-emission gun, Falcon 4 and Apollo detectors and Krios-compatible autoloader. Equipped with MAPS software compatible with Krios at UTHSC.
- **ThermoFisher Aquilos 2 with EasyLift and iFlm** – Cryo-dual beam FIB for cellular lamella preparation and SEM imaging. Capable of milling thin lamella from vitrified whole cells and tissue for imaging with one of the TEMs. Equipped with an integrated 4 channel Fluorescence Light Microscope (iFLM) to mill targeted areas, it also features an Easylift needle for cryo lift-out.
- **Leica EM ICE High Pressure Freezer** – High pressure freezer with the optional light and electrical stimulation. Can vitrify (rapidly freeze) specimens thicker than 10 microns including cells and small tissue sections. Used prior to FIB-milling or freeze-substitution.
- **JEOL-3200FSC** - 300 keV instrument with a field-emission gun, energy filter and a K2 summit detector. Capable of single particle reconstructions beyond 3 Å resolution, and nanometer resolution cellular tomography of thin specimens. Automated with SerialEM.
- **JEOL-2200FS** - 200 keV instrument with a field-emission gun, phase plate, energy filter, Gatan CCD camera and a DE-20 direct detector. Workhorse instrument for single particle reconstruction at subnanometer resolution, able to look at particles smaller than the 300 keV instrument.
- **JEOL-2100** - 200 keV instrument with DE-12 direct detector. This is our primary cryo screening instrument.
- **JEOL-1230** – 120 keV instrument with 4k Gatan CCD for negative stain and fixed section imaging. No cryo specimens.
- **FEI Vitrobot Mark IV** with 2-sided blotting for specimen preparation.
- **Leica EMGP** automatic plunge freezer with 1-sided blotting for specimen preparation.
- **Fischione Model 1070 Nanoclean** plasma cleaner for grid preparation.
- **PELCO easiGlow™** Glow Discharge Cleaning System.
- **ÄKTA Pure HPLC** for on-site size exclusion chromatography.

SERVICES

- CryoEM/CryoET project consultation
- Near-atomic resolution CryoEM Single particle analysis. We can support all stages of the pipeline from specimen preparation through computer reconstruction.
- Cellular CryoET to provide 3-D structure of intact cellular material ~5 nm resolution in bulk leading to ~1 nm after averaging.
- Cryo-FIB milling of thick cells/tissue, as specimen preparation for CryoET
- Screening and optimizing new specimens for CryoEM and/or CryoET
- Training students and staff in all aspects of the CryoEM/CryoET pipeline.



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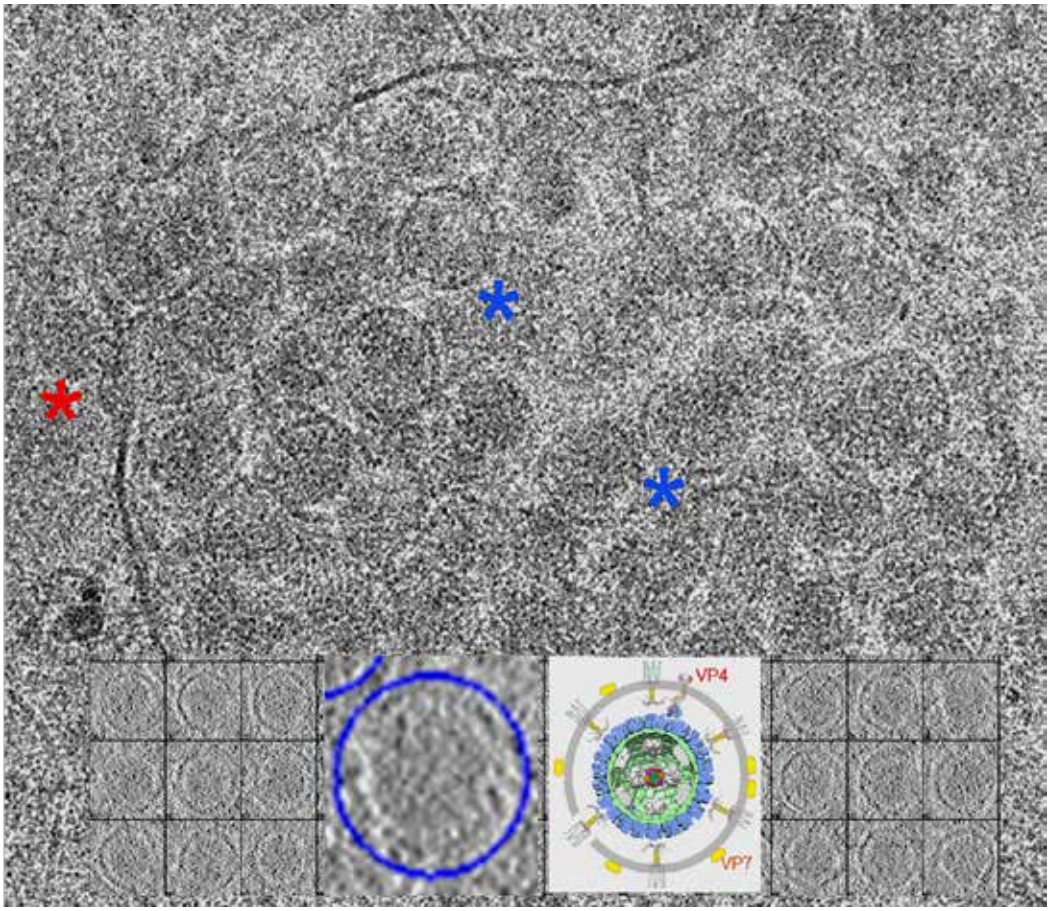
Enable *In situ* imaging of rotavirus transiently enveloped particles use cryoFIB and cryoET

Rotaviruses are the leading cause of infantile gastroenteritis. These are non-enveloped icosahedral viruses of ~1000 A in diameter with a complex architecture consisting of three concentric capsid layers that enclose 11 strands of genomic dsRNA segments. Researchers at Baylor College of Medicine have been at the forefront of major advances in understanding the structural and mechanistic aspects of rotavirus replication from entry to exit. A unique feature of RV morphogenesis is the budding of the intermediate double-layered particles into vesicular compartments, forming transiently enveloped particles. The enigmatic structure of these particles is not known, and how these particles subsequently mature into non-enveloped rotavirus particles is a mystery. Dr. Prasad's lab uses the BCM cryo-EM facility to determine the first structural details of these TEPs using cryo-electron tomography of rotavirus-infected cells grown on EM grids and milled to appropriate thickness using focused ion beam technology. The structure of the TEPs is determined by collecting many tilt series of the frozen-hydrated thin lamellae of the infected cells obtained by FIB milling using 300 kV cryo-electron microscope.

Cryo-ET of rotavirus-infected cells that are treated with tunicamycin to arrest the transiently enveloped particles (TEPs). The budding DLP and the TEPs are indicated by red and blue asterisks, respectively. Boxed TEPs for tomographic reconstructions, along with the expected structural model, are shown below.

Unpublished data courtesy BCM Cryo-EM core, Drs. Anish, R. and Crawford, S.E, and Prasad, B.V.V.



CYTOMETRY & CELL SORTING

Cytometry is an integral part of BCM faculty research across all disciplines. Flow, mass and image cytometry, continues to develop at a rapid pace driven by advances in instrumentation, labeling reagents, and computational capabilities. The Core provides state-of-the-art instrumentation, technologies, and specialized expertise and training in cytometry. Services include analysis by mass, imaging and flow cytometry as well as fluorescence-activated cell sorting (FACS) supported by an in-house bank of validated antibodies. Additional services include large particle sorting, magnetic cell separation, automated cell counting and viability, consultation, data analysis and training. Access to instruments in the facility for fully trained users is 24 hours and 7 days a week.

MAJOR EQUIPMENT

- Fluidigm Helios Mass Cytometry with Hyperion mass imaging platform
- Cytek Aurora Full Spectrum 4 laser Cytometer
- BD Symphony A5 30+ Parameter Flow Cytometer
- Amnis ImageStreamX MKII, 4 laser imaging cytometer providing a multispectral image for every cell
- Seven Flow Cytometric Cell Analyzers; two 5 laser BD LSRs, one 4 laser LSRII, and a 3 laser LSRII, two 3 laser BD Canto IIs (one violet and one yellow-green), and 4 laser Invitrogen Attune NxT
- High Through-put autosampler systems available on flow cytometric analyzers
- Four Flow Cytometric Cell Sorters; two 5 laser BD SORP Aria IIs, a 4 Laser BD Aria IIu and a 4 laser Sony MA900
- Union Biometric BioSort Large Particle Cell sorter; 30 – 300um objects using Blue and YG lasers
- Viability Analyzer; Beckman Coulter Vi-CELL
- Magnetic Cell Separator; Miltenyi AutoMACS Pro
- Cell Tissue Dissociator; Miltenyi gentleMACS Octo Tissue Dissociator
- Three Computer Work Stations including an Mass, Imaging Mass Cytometry and Imaging Cytometry Work Station

SERVICES

- Cellular Analysis: Assisted and unassisted flow cytometric and viability analysis using up to 5 separate lasers and 30 parameters for multiple assays including small particles.
- Cell Sorting: Assisted and unassisted flow cytometric and magnetic cell sorting services that include parity with analyzers so any project capable of analysis can be moved to cell sorting.
- Mass and Fluorescent Antibody Bank for high-parameter cytometry
- Data Analysis: Assisted and unassisted data analysis including a dedicated server for data storage, workstations for data analysis as well as Astrolabe, VisioPharm and FlowJo software site licenses available to investigators.
- Panel Design: Easypanel Panel Design software available for all users of the core for designing experimental antibody panels.
- Training: Didactic Flow Analyzer course as well as individual training on cell sorting and other instrumentation, software or equipment updates.

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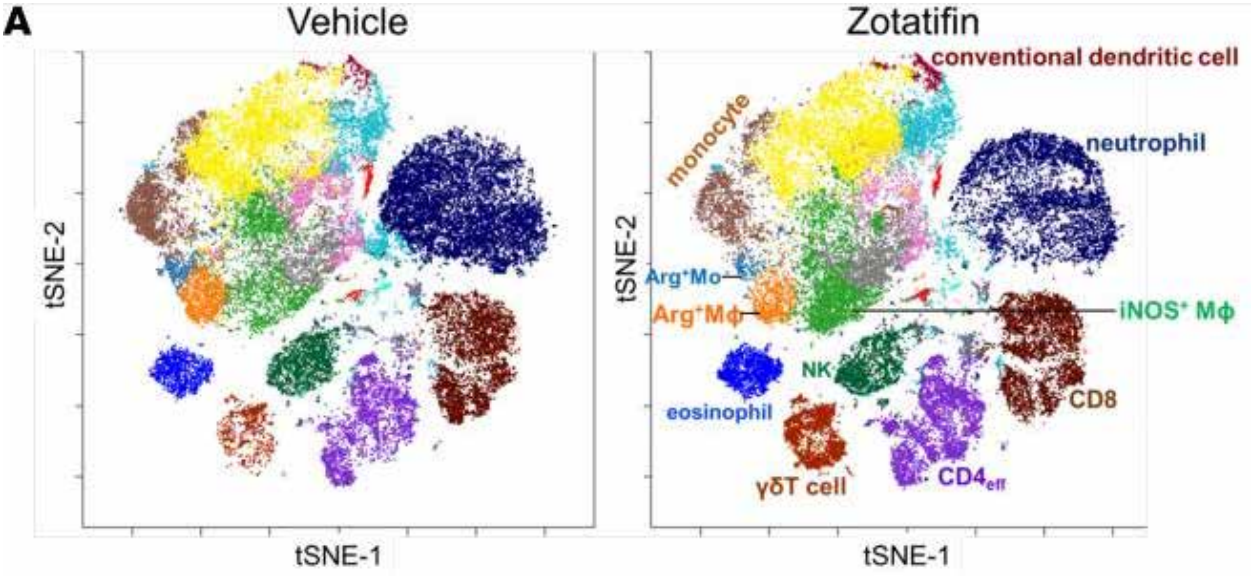
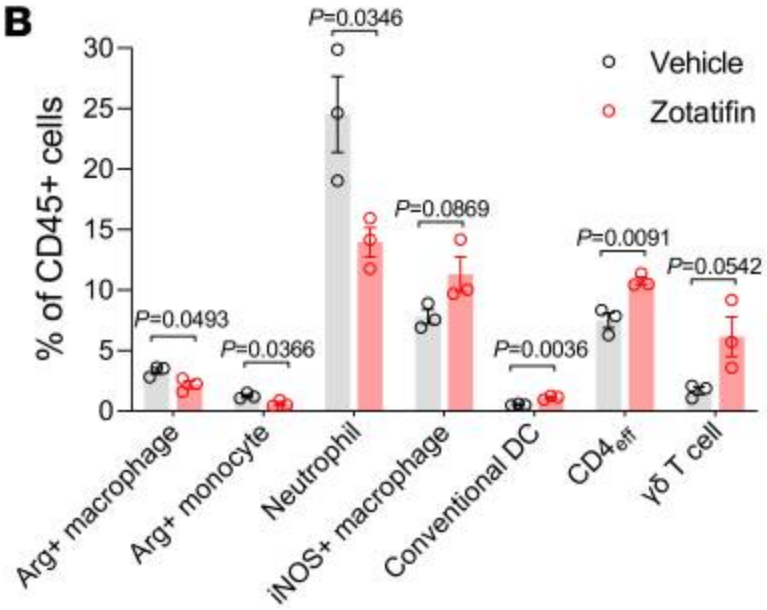
Zotatifin monotherapy alters the tumor immune microenvironment and sensitizes tumors to immune checkpoint blockade.

Figure. (**A**) t-Distributed stochastic neighbor embedding (t-SNE) projection of tumor-infiltrating immune cells in 2153L tumors that were treated for 7 days and analyzed using mass cytometry. Data from 3 biological replicates of each group were concatenated before t-SNE and FlowSOM analysis. Equal cell numbers are shown for each group. (**B**) Quantification of major immune cell populations in mass cytometry analysis. n = 3 per group.

Zhao N, Kabotyanski EB, Saltzman AB, Malovannaya A, Yuan X, Reineke LC, Lieu N, Gao Y, Pedroza DA, Calderon SJ, Smith AJ, Hamor CW, Safari K, Savage SR, Zhang B, Zhou J, Solis LM, Hilsenbeck SG, Fan C, Perou CM, Rosen JM, Targeting EIF4A triggers an interferon response to synergize with chemotherapy and suppress triple-negative breast cancer. The Journal of clinical investigation. 2023 Oct 24.





GENE VECTOR

The Gene Vector Core (GVC) assists investigators with the production of gene transfer vectors, which can be used for studying gene function by over-expression, ectopic expression, gene silencing, or gene editing. Recombinant viral vectors retain the native features of viruses that have been tested in nature for millions of years but can also take on unique desired features. The Vector Development Laboratory in the Center for Cell and Gene Therapy has merged with the GVC providing expanded services such as first-generation adenovirus (FGAd) production and several quality assurance assays available to all BCM investigators. The GVC has undertaken a variety of initiatives aimed at increasing productivity, cutting costs, developing quality control assays, improving existing services, and expanding the repertoire of viral vector-based research tools. The core offers several popular viral vector platforms and has extensive experience in the production of viral vectors including adeno-associated virus (AAV), FGAd, helper-dependent adenovirus (HDAd), lentivirus (LV), and retrovirus (RV). Our core is vigilant in keeping pace with recent advances in viral vector technology, provides expert consultation and advice, and works together with investigators to provide services most suited to each individual project.

SERVICES

- Packaging and purification of AAV (serotype 1, 2, 5, 6, 7, 7M8, 8, 9, 10, DJ, DJ8, 2-Retro, and PHP.eB) at various scales.
- Rescue, and/or amplification/purification of FGAd (serotype 5 and 5/35) and HDAd (serotype 2, 5, 5/11, and 5/35).
- Packaging and concentration/purification of VSVG-, MokolaG-, LCMV-Arm53b-Pseudotyped integrating or non-integrating LV with 2nd, or 3rd, or 4th generation packaging systems.
- Packaging of ecotropic, amphotropic, and pantropic VSVG-Pseudotyped RV
- Subcloning into viral transfer vectors and preparation of plasmids for viral vector production.
- Other supporting services: infectious titer, HPLC analysis, tests for RCA, sterility, endotoxin, and mycoplasma.
- The customer provides transfer vectors for transfection. Packaging plasmids or helper viruses are provided by the Core.
- Off-the-shelf packaged vectors are available in the catalog.
- Common viral transfer plasmid vectors developed by the Core have been deposited to Addgene https://addgene.org/Kazuhiro_Oka/. These plasmid DNAs are available from the Core.

MAJOR EQUIPMENT

- Ultraspeed Centrifuge (Beckman Optima XPN 90 and Sorvall WX80), CLARIOstar plus microplate reader, iBright FL1500 Imaging System, Zeiss Inverted Fluorescence Microscope.

CORE LEADERSHIP

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Characterization and quantification of adeno-associated virus capsid-loading states by multi-wavelength analytical ultracentrifugation with UltraScan

Adeno-associated virus (AAV) stands out as a prominent viral vector for human gene therapy and fundamental research. Empty AAV capsids, devoid of therapeutic ingredients, pose a challenge as they are indistinguishable from fully loaded capsids by the immune system. This challenge has gained significance following adverse events in clinical trials where patients experienced complications and fatalities after high-dose AAV intravenous injections. Analytical ultracentrifugation offers a comprehensive solution, allowing the characterization and quantitation of AAV samples in a single experiment with minimum preparation. Despite its potential, widespread adoption has been hindered by low sensitivity. In this study, Henrickson et al., have enhanced the UltraScan software, elevating sensitivity specifically in analytical buoyant density equilibrium (ABDE) by 20-40 fold. The method was applied to various AAV samples including GeneVector Core prepared AAV8, revealing the presence of high-density AAV species, potentially indicative of leaky capsids during AAV production, prompting further investigation.

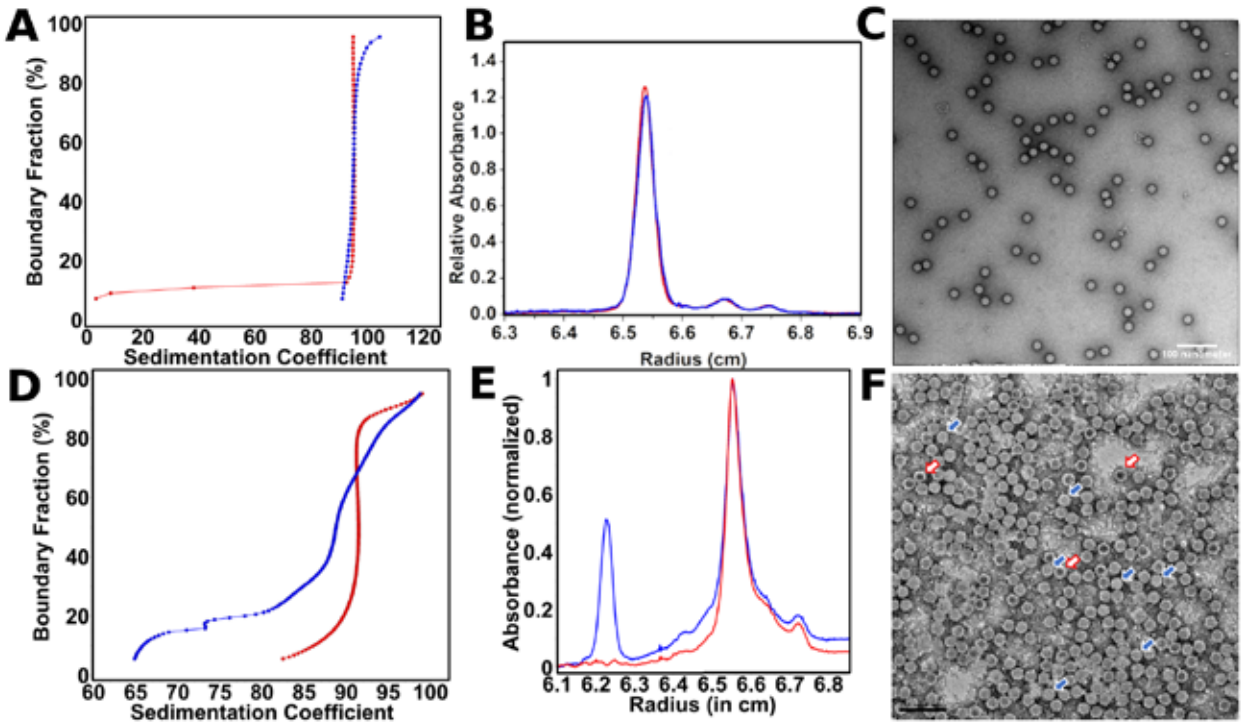

Figure: The top panel illustrates the analysis of AAV8 prepared by Gene Vector Core using CsCl ultracentrifugation. (**A**) Sedimentation velocity (SV) MW-AUC, (**B**) ABDE MW-AUS with protein and DNA deconvolutions normalized to 1.3 optical density, and (**C**) transmission electron microscopy (TEM) reveal no visible empty capsids. However, two minor peaks at high density are detected, prompting further investigation. The bottom panel displays the analysis of AAV9 purified by iodixanol density gradient. (**D**) SV MW-AUC, (**E**) ABDE MW-AUC, and (**F**) TEM. The blue arrows show full AAVs, and the red arrows show empty AAVs. A significant empty peak and minor high-density peaks, in addition to a major full capsid peak, are observed. MW-AUC: multi-wavelength analytical ultracentrifugation; OD: optical density.

Henrickson A, Ding X, Seal AG, Qu Z, Tomlinson L, Forsey J, Gradinaru V, Oka K, Demeler B. Characterization and quantification of adeno-associated virus capsid-loading states by multi-wavelength analytical ultracentrifugation (MV-AUC) with UltraScan. Nanomedicine 22:1519, 2023

GENETICALLY ENGINEERED RODENT MODELS (GERM) CORE

The Genetically Engineered Rodent Models (GERM) Core possesses specialized expertise and state-of-the-art equipment for providing essential mouse services to investigators at Baylor College of Medicine and collaborative investigators of other institutes. Our core assists investigators with projects involving the production of transgenic, targeted knockout, and targeted knock-in mouse lines. Knockout and knock-in mouse lines can be generated using gene targeting in embryonic stem (ES) cells with chimera production or CRISPR genome editing in mouse zygotes. For projects involving CRISPR genome editing, the GERM Core offers a genome editing design service (guide selection, donor DNA design, and genotyping design) in addition to an on- and off-target mutagenesis genotyping service. The GERM Core also performs cryopreservation of mouse embryos and sperm for long-term storage of mouse lines, mouse line rederivation, in vitro fertilization, and mouse colony expansion.

SERVICES

Transgenics
- Generation of Transgenic Mice by DNA Microinjection (Traditional)
- Generation of Transgenic Mice by DNA Microinjection (BAC clone)

Traditional Gene Targeting
- Gene targeting in mouse ES cells and chimera production
- Rosa26 targeting in mouse ES cells and chimera production
- Chimera production from investigator provided ES cells

CRISPR/Cas9 Genome Editing
- Guide RNA testing in mouse zygotes
- Generation of knockout mice using electroporation
- Generation of knock-in mice using single-stranded oligodeoxynucleotides (ssODNs)
- Generation of knock-in mice using long single-stranded DNA (lssDNA) or double-stranded DNA (dsDNA)
- CRISPR-assisted ROSA26 targeting using double-stranded DNA (dsDNA)

CRISPR/Cas9 Genotyping
- Founder and N1 animal PCR genotyping
- Founder and N1 animal Sanger sequencing
- Targeted analysis of off-target mutagenesis

Cryopreservation and Embryology
- Mouse sperm cryopreservation
- Mouse embryo cryopreservation
- Mouse in vitro fertilization
- Mouse colony expansion
- Mouse strain rederivation

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MAJOR EQUIPMENT

- Nikon Eclipse Te300 Microscopes with Hoffman objectives
- Nikon Diaphot inverted microscopes
- SMZ 800 and 1000 dissecting microscopes
- Embryoscope Plus
- CEROS II Animal Sperm Analysis System
- Narishige micromanipulators
- FemtoJet microinjectors
- Gene Pulser Xcell BioRad electroporation systems
- Nuaire laminar flow hoods
- Qiaxcel Advanced System
- Qiagility
- QuantStudio 7 Flex Real-Time PCR System
- QX100 ddPCR system

CORE SUPPORTED RESEARCH

Generation of a novel Stra8-driven Cre recombinase strain for use in pre-meiotic germ cells in mice (PI: Stephanie Pangas, Department Pathology & Immunology)

The development of oocytes occurs over a broad time frame, starting at the earliest stages of embryogenesis and continuing into adulthood. Conditional knockout technologies such as the Cre/loxP recombination system are useful for analyzing oocyte development at specific stages, but not every time frame has appropriate Cre drivers, for instance, during oocyte meiotic initiation through early prophase I in the embryo. To address this resource gap, a novel knockin mouse line that produces a bicistronic transcript from the endogenous Stra8 locus that includes a "self-cleaving" 2A peptide upstream of Cre recombinase was created (Stra8P2ACre) by the GERM Core.

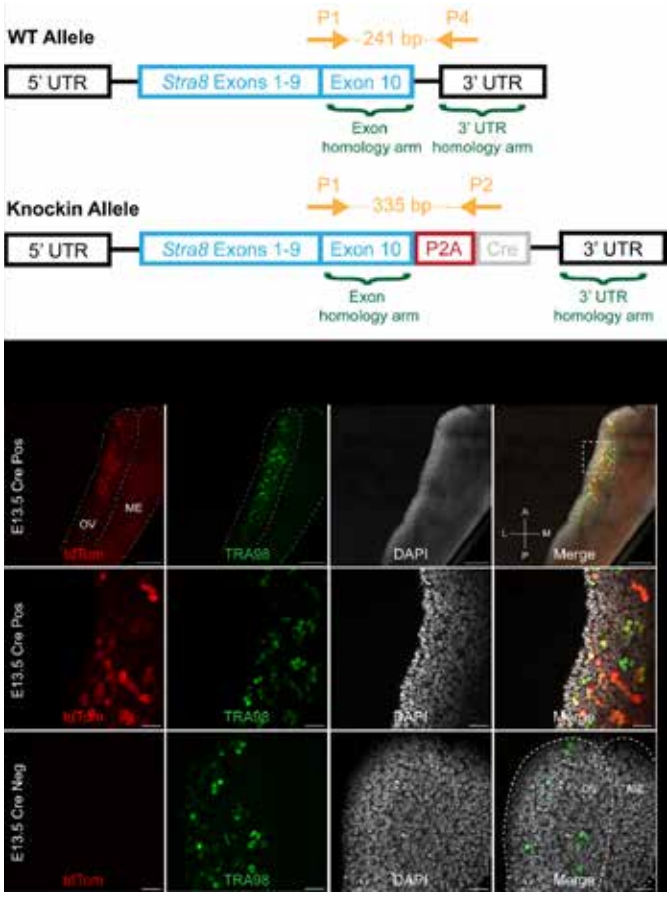

Figure: (**A**) The GERM Core designed and implemented the CRISPR genome editing approach, procured CRISPR reagents and a plasmid DNA donor, performed genome editing in mouse zygotes, and verified production of the desired allele by PCR genotyping and Sanger sequencing of founder animals and their offspring. The location of primers (P1, P2, and P4) and expected PCR products sizes used to confirm production of the desired allele are shown. Location of homology arms are indicated.

(**B**) Using a reporter allele of Cre activity, which expresses tdTomato (tdTom) after Cre/loxP recombination, Stra8P2Acre was shown to facilitate efficient recombination at embryonic day (E)13.5, the onset of meiosis, in female germ cells (TRA98-positive). DNA was stained with DAPI. **TOP**: whole mount immunofluorescence; **MIDDLE**: immunofluorescence of cryosectioned tissue; **BOTTOM**: control embryos that do not express Cre. OV = ovary; ME = mesonephros.

Ahmed AA, Salas E, Lanza DG, Heaney JD, Pangas SA. Generation of a novel Stra8-driven Cre recombinase strain for use in pre-meiotic germ cells in mice. 2023, 109(2):1184-191. PMC10427807

GENOMIC & RNA PROFILING (GARP)

The mission of the Genomic & RNA Profiling (GARP) Core Facility is to provide the most cutting-edge genomic technologies to research investigators with an emphasis on personal service and quality. In order to provide whole genome profiling we offer multiple Next-Generation Sequencing platforms (Illumina and Oxford Nanopore) and targeted NanoString nCounter assays.

MAJOR EQUIPMENT

- Illumina NovaSeq 6000 Sequencer
- Illumina iSeq 100 Sequencer
- Oxford Nanopore Promethion 24 Sequencer
- Hamilton NGS STAR (Library Prep Automation System)
- Nanostring nCounter Digital Quantification System
- ABI ViiA7 Real Time PCR/qPCR instrument
- Agilent Bioanalyzer
- Covaris Ultrasonicator
- 10X Genomics CytAssist

SERVICES

- Next-Generation Sequencing
  - Sequencing only
  - Library preparation
  - RNA-seq (polyA-selected, whole transcriptome, small RNA)
  - Spatial Transcriptomics (whole transcriptome)
  - ChIP-seq
  - Cut'N Run
  - Whole Genome Bisulfite Sequencing
  - Whole Exome Seq (WES)
  - Nanopore Sequencing
- Targeted NanoString nCounter assays (up to 800 multiplexed assays/sample)
- Nucleic acid shearing (self-use)

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Decoding the PITX2-controlled genetic network in atrial fibrillation

Single nuclei RNA-seq and single nuclei ATAC-seq libraries were generated using the 10X Genomics Chromium platform. The Genomic and RNA Profiling Core sequenced the libraries on an Illumina NovaSeq 6000 and on an Illumina NextSeq 500. Single nuclei profiling of the pulmonary vein and left atrium were performed and gene expression between Pitx2 controls and Pitx2 mutants was compared.

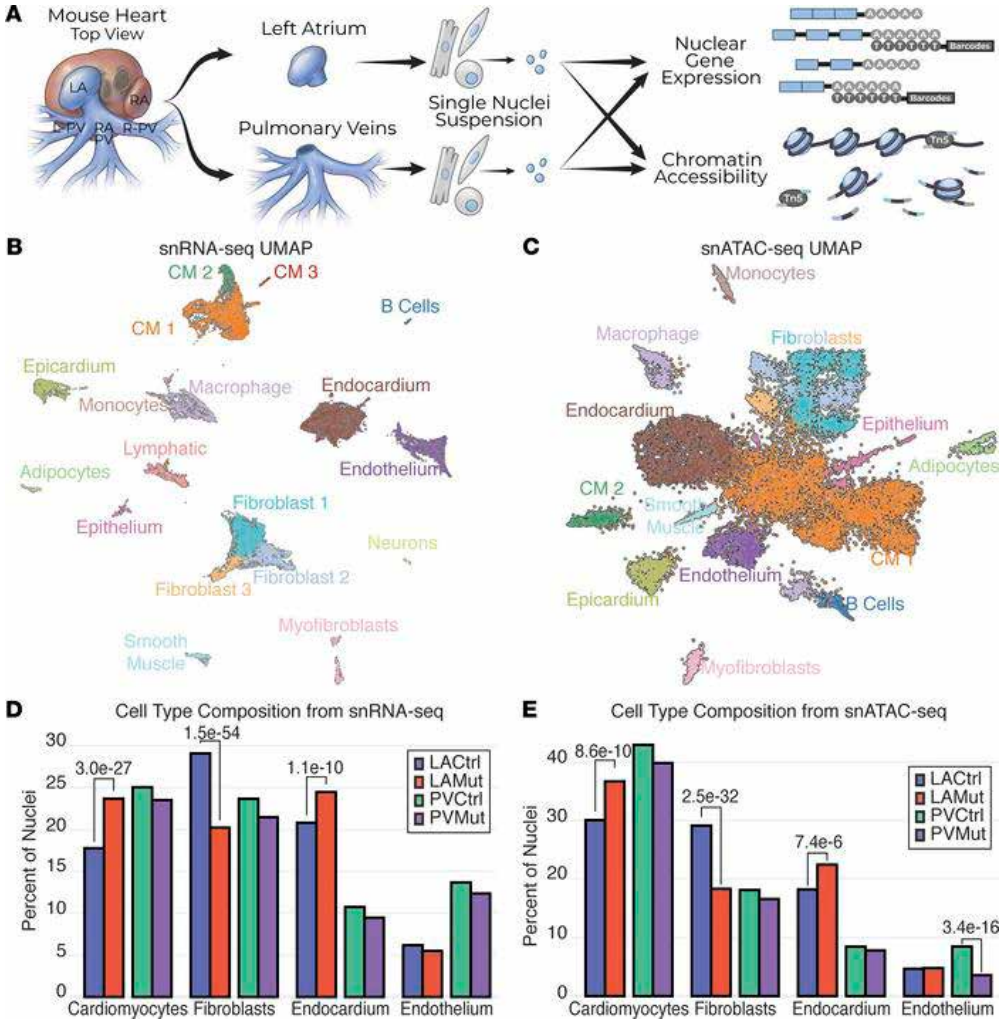

Figure:

(**A**) Experimental outline used to profile the transcriptome and chromatin accessibility of single nuclei of the left atrium (LA) and pulmonary vein (PV) from pools of 6- to 8-month-old Pitx2 control (Ctrl: Pitx2fl/+) and mutant (Mut: MCK-cre Pitx2fl/–) mice.

(**B**) Uniform manifold approximation and projection (UMAP) representation of all filtered nuclei identified by single nuclei RNA-sequencing (snRNA-Seq) and color-coded and labeled in clusters.

(**C**) UMAP representation of single nuclei assay for transposase-accessible chromatin using sequencing (snATAC-Seq) with colors and labels lifted from the snRNA-Seq

(**D**) Percentage of total nuclei per sample from the 4 major clusters identified in the snRNA-Seq data set.

(**E**) Percentage of total nuclei per sample identified in the snATAC-Seq data set. Adjusted P value (FDR) of significant comparisons (FDR <1 × 10–5) between LA or PV control and mutant samples are presented.

Steimle JD, Grisanti Canozo FJ, Park M, Kadow ZA, Samee MAH, Martin JF. Decoding the PITX2-controlled genetic network in atrial fibrillation. JCI Insight. 2022 Jun 8;7(11):e158895. doi: 10.1172/jci.insight.158895. PMID: 35471998; PMCID: PMC9221021.

HUMAN STEM CELL & NEURONAL DIFFERENTIATION CORE

The Human Stem Cell and Neuronal Differentiation Core (HSCNDC) is located in the Jan and Dan Duncan Neurological Research Institute (NRI). The core provides a wide range of products and services related to human pluripotent stem cell (hPSC) research, as well as hands-on training classes for basic and advanced stem cell culture techniques. We offer cost-effective solutions to generate and characterize new induced pluripotent stem (iPS) cells for in vitro disease modeling, employing non-integrating vector technologies such as Sendai virus-based and episomal vector-based reprogramming. We also offer customized research support for experimental design and validation assays, as well as genome editing of hPSCs using CRISPR/Cas9. The core is also deriving neural progeny from iPSCs, including protocols for directed differentiation and direct conversion of iPSCs to neurons.

MAJOR EQUIPMENT

- EVOS XL and FL inverted microscope systems
- Lonza 4D-Nucleofector transfection system
- NuAire In-VitroCell CO_2 Incubators with O_2 control
- Beckman Coulter Allegra X-14R centrifuge
- ABI StepOnePlus Real-Time PCR system
- MVE TEC 3000 LN2 cryostorage system
- NanoCellect WOLF Cell Sorter and N1 Single-Cell Dispenser
- Keyence BZ-X810 epifluorescence microscope
- Proteins Simple WES for automated western blot
- Axion Maestro Pro multielectrode array system
- CellInk Bio X 3D bioprinter
- Calcium imaging and patch clamp systems

SERVICES

- Hands-on training classes and workshops
- Human pluripotent stem cell (hPSC) culture services
- Generation of induced pluripotent stem (iPS) cell lines
- Stem cell line characterization (PluriTest & KaryoStat assays)
- Mycoplasma testing
- Consultation on experimental design
- Customized genome editing of hPSCs using CRISPR/Cas9
- Generation of iPSC derived neural models

CORE LEADERSHIP

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Transdifferentiation of patient fibroblasts followed with RNA-Seq significantly boosts clinical diagnosis.

This study led by the Pengfei Liu group aimed to facilitate diagnoses of Mendelian disorders by utilizing RNA sequencing (RNA-Seq) in a translational research set. The team developed a workflow to overcome the low or absent expression of a significant number of disease genes/transcripts in clinically accessible samples which was a significant obstacle for clinical laboratories in adopting RNA-Seq. As this is especially problematic in neurological diseases, Dr. Li and colleagues requested HSCNDC to implement and optimize the protocol for neuronal differentiation of human fibroblast and provide this protocol as a new service with fee. Based on successful service provided from the core, Dr. Liu's group developed a clinical diagnostic approach that enhanced the detection and evaluation of tissue-specific genes/transcripts through fibroblast-to-neuron cell transdifferentiation. The approach is designed specifically to suit clinical implementation, emphasizing simplicity, cost effectiveness, turnaround time, and reproducibility. The overall diagnostic yield was 25.4%. Over a quarter of the diagnostic findings benefited from transdifferentiation and could not be achieved by fibroblast RNA-Seq alone. This iNeuron transcriptomic approach can be effectively integrated into diagnostic whole-transcriptome evaluation of individuals with genetic disorders.

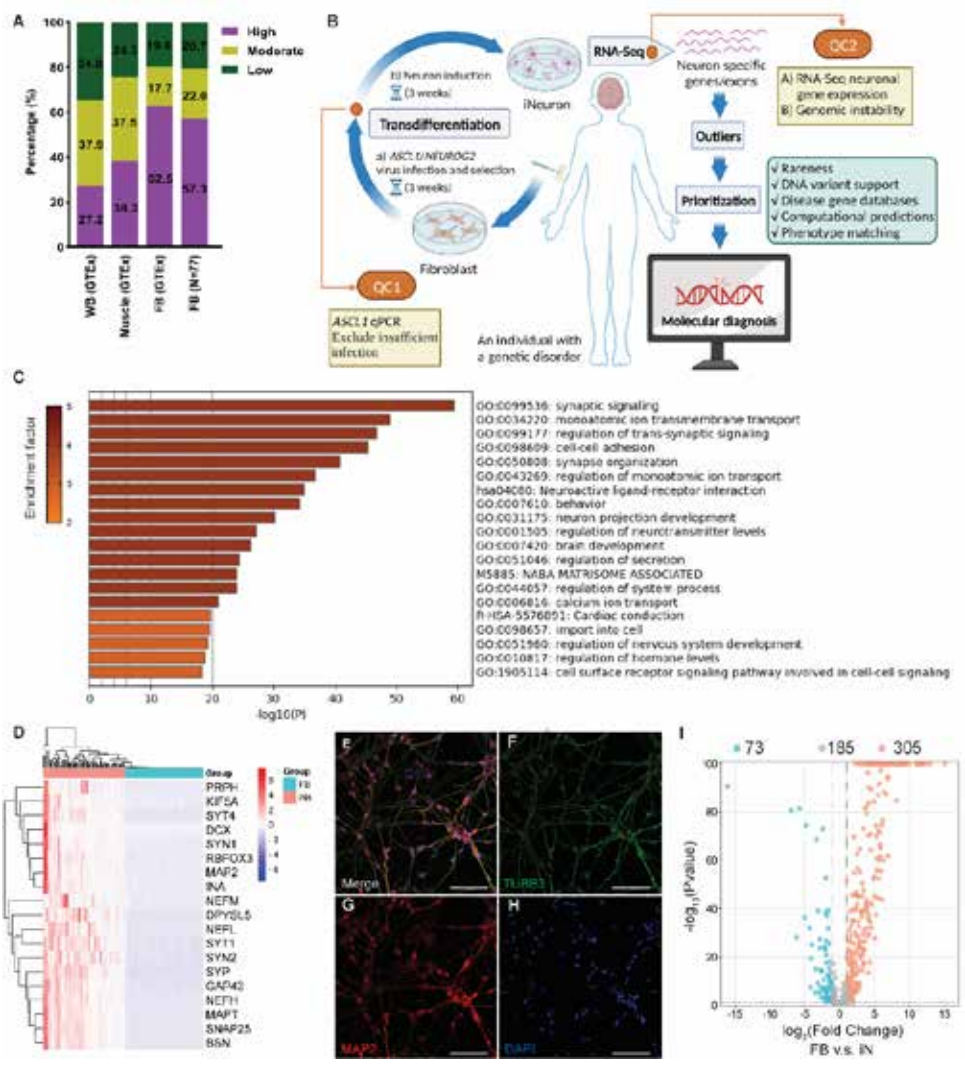

Figure: Activation of low-expression OMIM-N genes in participants' fibroblasts. (**A**) Expression levels of OMIM-N genes in clinically assessable tissues. Gene expression levels were classified as follows: low (TPM <1), moderate (TPM ≥1 and <10), and high (TPM ≥10). Fibroblasts (FB) RNA-Seq data from GTEx and UDN participants (n=77) were used for the assessment. (**B**) Schematic of the workflow of iNeuron transdifferentiation and RNA-Seq. (**C**) Functional enrichment analysis of DEGs up-regulated in iNeurons. (**D**) Robust expression of neuron-specific genes in iNeurons. (**E-H**) Immunofluorescence staining of neuronal markers beta3-tubulin (**F**) and MAP2 (**G**) in iNeurons. Nuclei were stained using DAPI (**H**). The merged image is shown in (**E**). Scale bar represents 100μm. (**I**) Volcano plot showing activation of low expression OMIM-N genes. Figure 1B was created with BioRender.com.

Shenglan Li, Sen Zhao, Jefferson Sinson, et. al. The clinical utility and diagnostic implementation of human subject cell transdifferentiation followed by RNA sequencing. AJHG. Unpublished.

HUMAN TISSUE ACQUISITION & PATHOLOGY (HTAP)

The Human Tissue Acquisition and Pathology (HTAP) Core provides services for collecting and processing of tissues for research. HTAP serves as the primary centralized tissue bank at BCM and provides human specimens to BCM researchers and others with IRB approved research. Requests for human materials can be made by completing this form: https://redcap.link/orj3l97d.

Pathology Services are performed on both human and animal tissues by expert technical staff with the assistance of pathologists who provide consultation and review of slides and images. Histology, tissue microarray development, immunohistochemistry (IHC), multi-immunofluorescence (mIF), RNAScope, and imaging are available on a fee-for-service basis.

MAJOR EQUIPMENT

- Vectra3 imaging system
- inForm or Visiopharm image analysis
- Nikon whole slide scanning for brightfield and fluorescence
- Shandon Excelsior ES Tissue Processor
- Shandon HistoCentre Embedding System
- Sakura TissueTek SCA Coverslipper
- Shandon Varistain Gemini Slide Stainer
- Microm HM 315 Microtome
- Epredia Cryostar NX50
- Visium CytAssist 10X Genomics

SERVICES

- **Human Tissue Procurement:** Collection and quality review of human tissues [live, frozen, FFPE] from BCM affiliated hospitals. For projects requiring prospective collection of tissue, investigators must have an IRB approved research protocol and cost sharing is expected. Fees for sectioning, data collection, and sample preparation will be charged for distribution of human tissues and TMA slides.
- **Histology:** Tissue processing, embedding, cutting, and staining of human and animal tissues.
- **Special Stains:** Periodic acid–Schiff (PAS) to detect polysaccharides, Oil Red O for fatty acids (frozen tissue only), Trichrome or Picro Sirius Red for collagen and fibrosis.
- **Spatial Transcriptomics:** Specialized sectioning, staining and imaging of 10X Genomics Visium slides for spatial transcriptomics (coordinated with GARP Core). Specialized sectioning for other spatial platforms: e.g. NanoString CosMx, Akoya CODEX/ PhenoCycler, Curio Seeker, MERFISH, and others.
- **Immunohistochemistry (IHC) and TUNEL Assays:** IHC for proliferation and apoptosis are performed using methods and antibodies provided by HTAP. Investigator supplied antibodies are used for other IHC assays which are optimized for performance.
- **Multiplex immunofluorescence:** Customized mIF antibody development using TSA technology for up to 5 markers in human or mouse tissues. A standardized 5-color tumor/lymphocyte marker panel for human studies is also available.
- **RNAScope:** Advanced Cell Diagnostics Technology for detection of RNA in paraffin embedded tissue.
- **Brightfield or Fluorescence Digital imaging:** State-of-the-art whole tissue section scans or representative images of tissue sections or TMAs using Nikon slide scanner or Vectra imaging system.
- **Image Analysis:** Image analysis using inForm software or Visiopharm for pattern recognition analysis and quantitative scoring.
- **Tissue microarray (TMA):** TMAs are developed using the Core's archival FFPE or tissues provided by individual researchers.
- **Consultation with pathologists.** Experienced pathologists will assist with review of stained slides.

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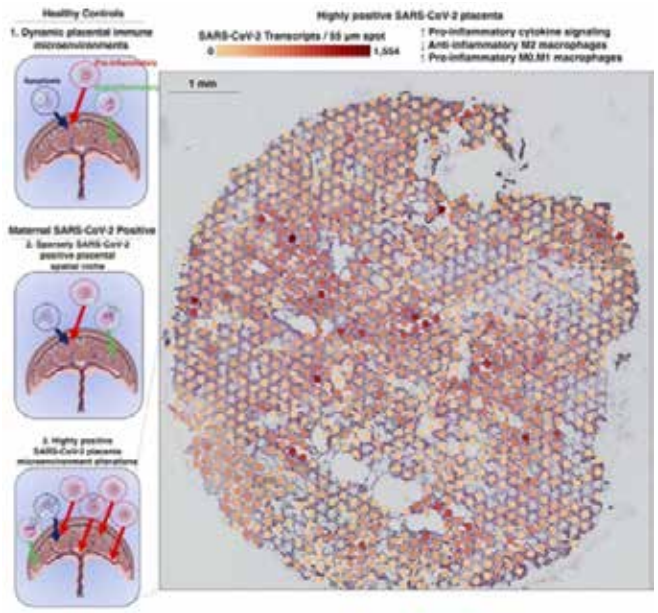
Mapping SARS-CoV-2 Microenvironments in Placenta

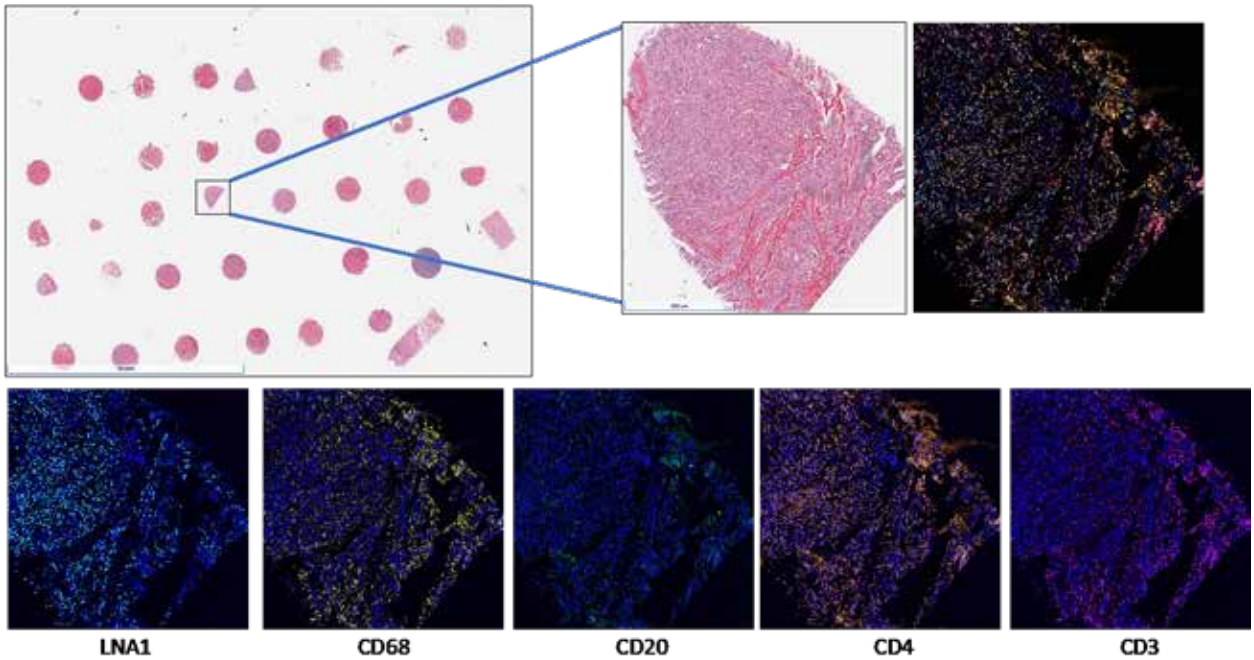
Mapping of gene expression in term placental microenvironments with orthogonal bulk and spatial approaches to parse how functional placental niches restrict vertical transmission of pathogens. Applying this atlas to cases of maternal SARS-CoV-2 infections revealed divergent placental immune microenvironments associated with asymptomatic infection and clinically evident disease.

Barrozo ER, Seferovic MD, Castro ECC, Major AM, Moorshead DN, Jochum MD, Rojas RF, Shope CD, Aagaard KM. SARS-CoV-2 niches in human placenta revealed by spatial transcriptomics. Med. 2023 Sep 8;4(9):612-634.e4.



Spatial proteomics of Kaposi Sarcoma using Tissue Microarrays

A tissue microarray of Kaposi Sarcomas from patients with extensive clinical data and follow up was developed by the AIDS and Cancer Specimen Resource (ACSR.org). HTAP developed a custom panel of antibodies for multi-immunofluorescence to profile lymphocyte composition within the tumor microenvironment. These images will become part of the ACSR specimen resource and will be made publicly available for image analysis and spatial proteomic evaluation.



Zelazowski, Castro, et. al., unpublished

INTEGRATED MICROSCOPY

The Integrated Microscopy Core (IMC) is a state-of-the-art imaging facility. The IMC provides extensive training for users on all instruments, consultation for new and ongoing project development and troubleshooting for a wide range of light microscopy imaging needs for samples from 2D cell culture models, 3D organoids and tissue sections. A key longstanding strength of the IMC is support for assay development, high content analysis leading to high throughput microscopy, including a new BigPharma scale high throughput spinning disk confocal supporting 4 color simultaneous imaging with robotic capabilities for screening and bioprinting. IMC instrumentation supports multiplexing several channels for live or fixed cell confocal and epifluorescence deconvolution microscopy, or automated high throughput microscopy. A full suite of image analysis, statistics and reporting software is available for data mining and management.

MAJOR EQUIPMENT

- Yokogawa CV8000 high throughput spinning disk confocal microscope integrated with Biomek i5 and ASI BAB400 robotic systems.
- Nikon A1-Rs laser scanning spectral confocal microscope.
- Olympus IX83 automated epifluorescence microscope with image deconvolution with near IR capabilities.
- Biotek Cytation 5 microscope-in-a-box (fluorescence, color, slide scanning, live imaging), plus plate reader (fluorescence, absorbance, luminescence).
- Sartorius IncuCyte S3 long term live imager.
- Nikon Ci-L upright brightfield microscope with color camera.
- *NEW (coming Spring 2024):* Nanolive CX96 automated optical holotomography for label-free live imaging

SERVICES

- One-on-one training for all instruments and assisted use, as needed.
- Assay development and project consultations.
- Fully automated and assisted high throughput microscopy for 96/384 well plates for small- to large-scale image-based screens.
- Image Analysis (limited): custom or pre-set (i.e., cell count, subcellular localization, spot counting, translocation, cell cycle, toxicity, live/dead).
- Training in immunofluorescence and RNA FISH protocols.
- *Coming in 2024:* Cell Painting service which includes sample processing, imaging and image analysis.

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Cell Painting imaging and analysis using the Yokogawa CV8000 high throughput spinning disk confocal integrated with robotic processing & plate handling, plus open-source automated single cell image analysis platform.

The CV8000 is capable of both live and fixed cell high throughput imaging of 2D and 3D models. It can image up to 5 five fluorescence channels, plus brightfield/phase, with objectives ranging from 4x to 60x/water. The Cell Pathfinder high content analysis software is available with the instrument for basic and advanced image analysis.

Cell Painting is a cost effective and rapid method to characterize a cell phenotypic state by illuminating specific cellular compartments. It can currently be applied and analyzed in HT on 2D models. The IMC developed an open-source analysis software (SPACE) that performs single cell distribution analysis of >400 features/cell.

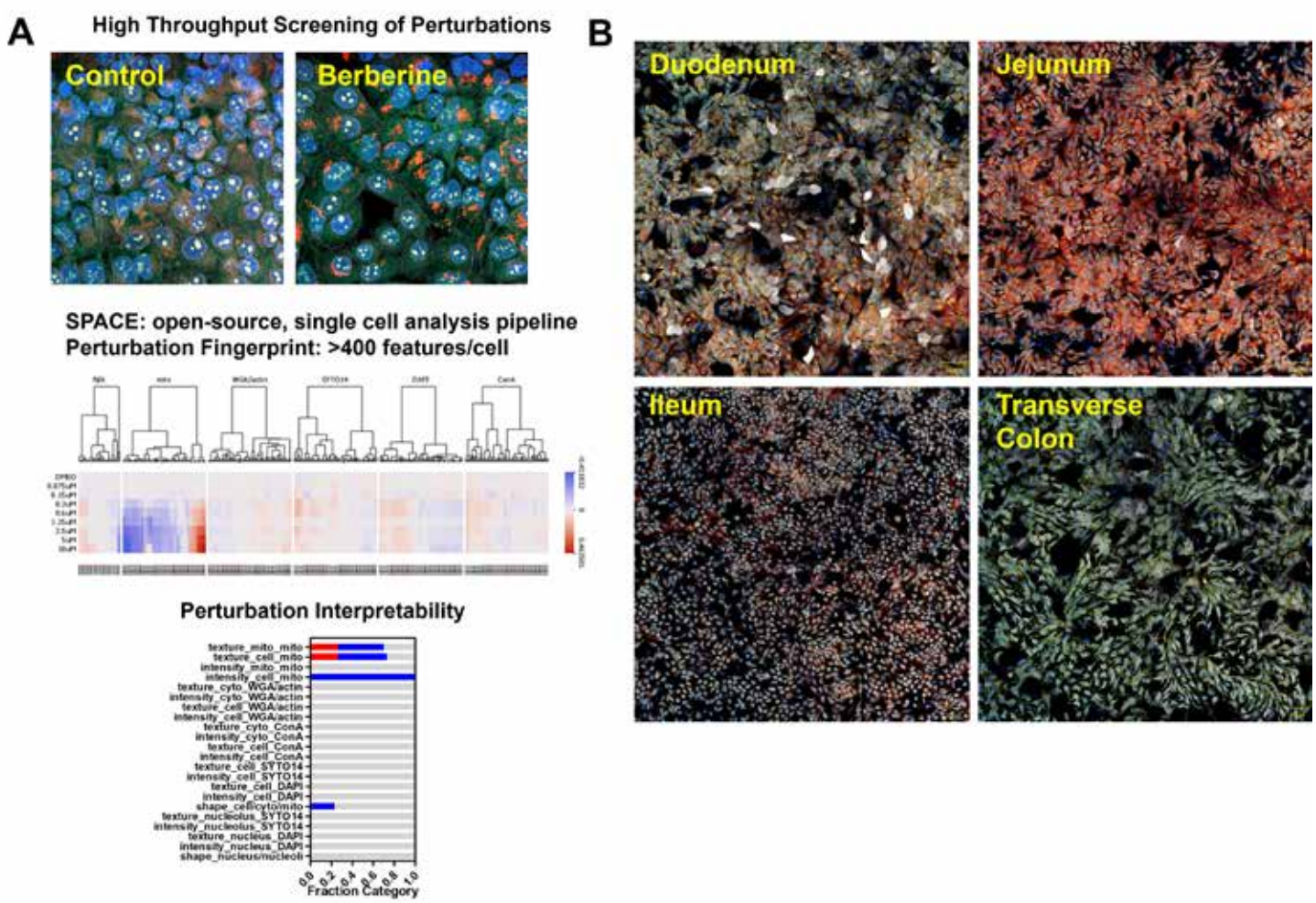


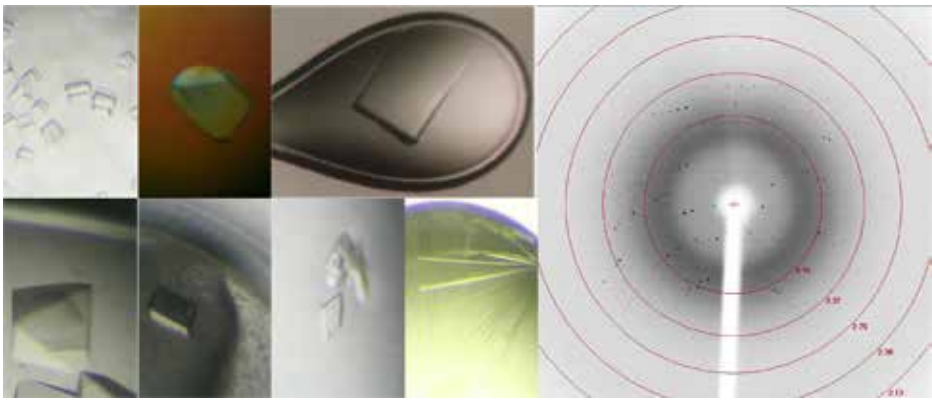
Figure. (**A**) example of workflow for the cell painting service: from any perturbation (in 2D models, an example of the compound berberine chloride is shown in the **top** panel) we can extract phenotypic fingerprints (middle panel shows a berberine chloride dose-response) that can then be used to interpret the observed phenotype (**bottom** panel). (**B**) example of Cell Painting images from 2D enteroids provided by the Digestive Disease Center 3D Organoid core (unpublished Sarah Blutt).

MACROMOLECULAR X-RAY CRYSTALLOGRAPHY

Single-crystal X-ray diffraction is the most powerful technique to determine the atomic structure of biologically important macromolecules and their functional complexes with small molecules or natural ligands. The Macromolecular X-ray Crystallography Core provides a cost-efficient solution for researchers and trainees at Baylor College of Medicine and its neighboring institutions to pursue high-resolution structural studies. Furthermore, X-ray crystallography allows the 3D structure determination of macromolecules bound to an agonist or antagonist, often with little additional effort. The atomic structures of these complexes are highly valuable and can be exploited for rational structure-based drug design. To expand our capability to access protein structure information and analysis, we recently added AlphaFold 2 protein structure prediction and virtual drug screening to our list of core services. Access to core equipment for fully trained users is available 24/7.

MAJOR EQUIPMENT

- Mosquito Crystallization robot
- Formulatrix Rock Imager 2 with UV/ multi-fluorescence option (New NIH S10 Shared Instrument Grant).
- Rigaku Ultimate Home Lab X-ray diffraction system



SERVICES

- **Consultation:** Custom service to develop a structure solution strategy, provide answers to protein expression, purification, and crystallization needs, discuss data collection requirements.
- **Training:** Provide training for unassisted use of the crystallization robot, imager, and X-ray home source.
- **Crystallization setup:** Assisted and unassisted crystal growth screening in 96-well plate format using the hanging- or sitting-drop vapor diffusion technique.
- **Crystal imaging:** Assisted and unassisted service to capture and record crystallization experiments.
- **Crystal optimization:** Assisted service to optimize crystal growth.
- **Cryo optimization:** Assisted service to identify cryo-protectants for X-ray diffraction experiment.
- **X-ray data collection (home source):** Assisted and unassisted use of the in-house X-ray source for data collection.
- **X-ray data collection (National Synchrotron facility):** Assisted data collection using the high-intensity synchrotron radiation beamline at the Argonne National Laboratory.
- **Data processing:** Assisted data processing of X-ray diffraction data and microcrystal electron diffraction data.
- **Structure determination:** Custom service to determine the crystal structure of a macromolecule of interest.
- **Protein structure prediction using AlphaFold 2:** Custom service to predict protein structures using artificial intelligence, including oligomers and molecular complexes
- **Virtual drug screening:** Custom service for in silico drug screening including custom library generation

Researchers are responsible for making their own macromolecule in purified form (1 to 10 mg scale). Expression and purification of recombinant proteins of interest are available as services through the Recombinant Protein Production and Characterization Core.

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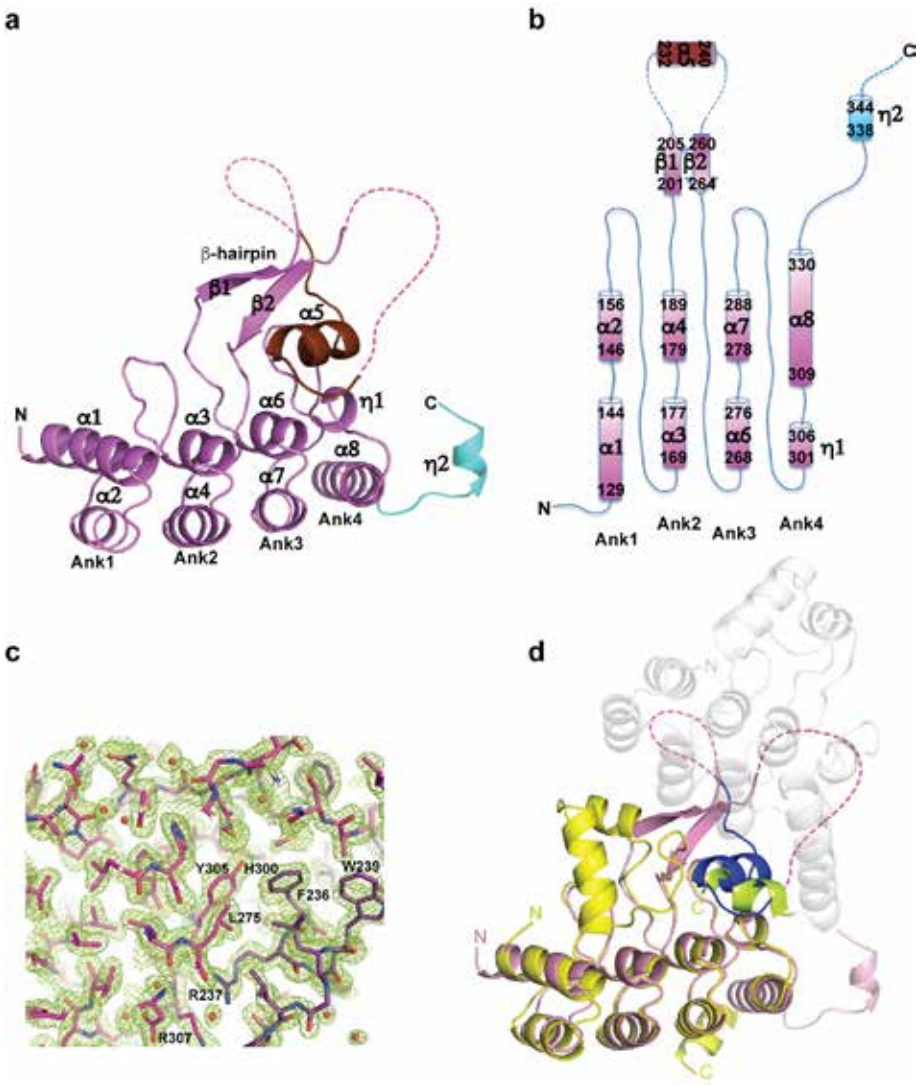
Structural Basis of Impaired Disaggregase Function in the Oxidation-sensitive SKD3 Mutant Causing 3-Methylglutaconic Aciduria

L3-methylglutaconic aciduria type 7 (MGCA7) is an inborn error of metabolism associated with variable neurologic deficits and an abnormally low number of neutrophils in the blood. The latter condition, known as congenital neutropenia, can lead to increased susceptibility to life-threatening bacterial and fungal infections, and a predisposition to myelodysplastic syndrome and acute myeloid leukemia, which are aggressive cancers of the blood and bone marrow.

SKD3, also known as human CLPB, is a ring-forming, ATP-dependent protein disaggregase that is found in the intermembrane space compartment of vertebrate mitochondria. SKD3 is essential for maintaining mitochondrial integrity and structure. It was reported that SKD3 deficiency or loss-of-function causes MGCA7. For instance, mutations in the ATPase domain impair protein disaggregation, with the observed loss of function correlating with disease severity. How mutations in the non-catalytic N-domain cause disease is unknown.



To uncover the structural basis of the MGCA7 pathomechanism, the core helped to solve the crystal structures of the N-domain of SKD3.

Figure: Crystal structure of the N-domain of human SKD3 isoform-1 and isoform-2. (**a**) Ribbon diagram of the N-domain of isoform-1 (magenta) with the first 310 helix of the ATP-binding domain (cyan). The long β-hairpin of Ank2 is labeled with the disordered regions flanking helix α5 (brown) indicated by dashed lines. (**b**) Topology diagram of the N-domain of isoform-1. (**c**) Section of the simulated-annealing 2Fo-Fc composite omit map (green mesh) contoured at the 1.0 σ level. (**d**) Superposition of the crystal structures of the N-domain of SKD3 isoform-1 (magenta) and isoform-2 (yellow). The superposition shows the location of the long β-hairpin-helix motif, including helix α5 (blue), which is only found in ANKiso1. It is entirely fortuitous that the C-terminal His6-tag (light green) of a crystal symmetry-related neighboring Ank domain (grey) is bound in trans to ANKiso2 (yellow). The figure shows that the His6-tag binds to the same concave surface that is occupied by helix α5 (blue) in the ANKiso1 structure.

Lee S, Lee SB, Sung N, Xu WW, Chang C, Kim H-E, Catic A, Tsai FTF. Structural basis of impaired disaggregase function in the oxidation-sensitive SKD3 mutant causing 3-methylglutaconic aciduria. Nat Commun 14:2028 (2023).

MASS SPECTROMETRY PROTEOMICS

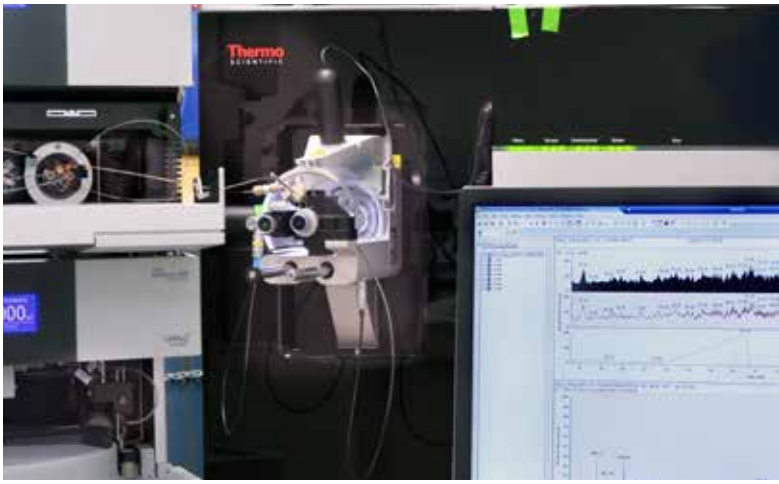
The Mass Spectrometry Proteomics Core offers services for quantitative proteome-wide profiling of cells and tissues, isolation and characterization of protein complexes and other affinity-based pulldowns, post-translational modification (PTM) analysis, and routine or targeted identification of purified proteins. We specialize in providing comprehensive project-based support that includes experimental design, optimization of biochemical procedures for sample preparation, state-of-the-art mass spectrometry technology, and custom data analysis to address specific challenges of different proteomics approaches. The core offers specialized support for preclinical PDX cancer models with mixed-species proteomes and clinical sample processing for multiomics.

MAJOR EQUIPMENT

- Thermo Scientific Mass Spectrometers:
  - Orbitrap Fusion Tribrid
  - Orbitrap Lumos ETD Tribrid
  - Orbitrap Exploris 480
  - Orbitrap Eclipse
- EASY-nLC1200 and EASY-nLC1000 UHPLC Systems
- Agilent 1260 Infinity II HPLC System
- Agilent AssayMAP Bravo Protein Sample Prep Platform

SERVICES

- Proteome Profiling (label-free or TMT-based) services that combines efficient non-detergent sample preparation procedure with dual reverse phase fractionation procedure and optimized mass spectrometry acquisition methods to allow identification and quantification of up to 10,000 proteins from as little as 100,000 cells or 20 micrograms of tissue lysate. The core provides specialized support for mixed species samples, such as patient-derived xenografts, with species-specific protein quantification software.
- PTM Profiling (TMT-based) service is offered as matched proteome and PTM profiling. This includes global profiling of phosphoproteome, ubiquitome, and/or acetylome.
- Affinity Purification/Mass Spectrometry service is a suite of assays for characterization of immunoprecipitated protein complexes, enrichment and identification of proteins that assemble on immobilized DNA baits, and characterization of protein targets of small molecules. The core's unique emphasis is in purification of endogenous complexes. Custom data analysis against BCM's own complexome database and filtering of non-specific precipitants is included in this package service.
- Post-translational modification (PTM) analysis includes identification and quantification of phosphorylation, ubiquitination or acetylation sites on purified proteins.
- Routine MS sequencing of purified protein samples for single-protein identification or targeted verification via parallel reaction monitoring.
- Consultation, experimental design and data analysis.



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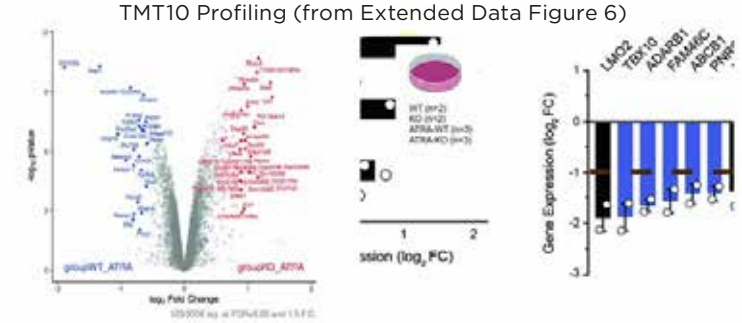
DNMT3A-Coordinated Splicing Governs the Stem State Switch Towards Differentiation in Embryonic and Haematopoietic Stem Cells.

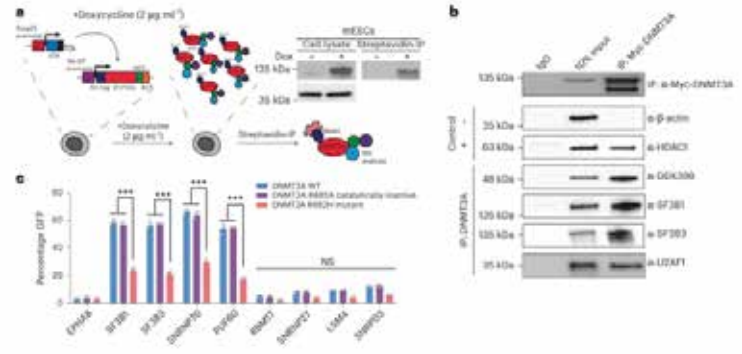
This study unveiled a critical role of DNMT3A in coordinating splicing efficiency during the transition from stem cell self-renewal to differentiation and suggests the spliceosome as a potential target in DNMT3A-mutated leukemias.

Our core performed proteome profiling and protein interaction characterization to analyze changes in splicing-associated factors in WT- versus KO-activated stem cells. There were no significant changes in spliceosome-related proteins at a timepoint where changes in splicing are observed suggesting that DNMT3A facilitates the stem state switch by interacting directly with splicing machinery.

TMT10 Profiling (from Extended Data Figure 6)



DNM T3 Interactome (from Figure 5)



The laboratory then performed co-immunoprecipitation to determine DNMT3A interacting partners (from Figure 5A). Spliceosome-associated proteins were enriched in the pulldown, exemplified by SF3B1, a core U2 small nuclear ribonucleoprotein frequently mutated in individuals with clonal disorders. The laboratory further corroborated this finding through co-IP with Myc-tagged DNMT3A (from Figure 5B) and *in vivo* bimolecular fluorescence complementation (BiFC) screen.

Ramabadran R, Wang JH, Reyes JM, Guzman AG, Gupta S, Rosas C, Brunetti L, Gundry MC, Tovy A, Long H, Gu T, Cullen SM, Tyagi S, Rux D, Kim JJ, Kornblau SM, Kyba M, Stossi F, Rau RE, Takahashi K, Westbrook TF, Goodell MA. DNMT3A-coordinated splicing governs the stem state switch towards differentiation in embryonic and haematopoietic stem cells. Nat Cell Biol. 2023 Apr;25(4):528-539. PMCID: PMC10337578

METABOLOMICS

The Metabolomics Core provides targeted metabolic profiling for discovery and validation of biomarkers of various diseases with state-of-the-art high throughput mass spectrometry as the main platform. Metabolites can be measured in tissues, cell lines, fecal samples, and biofluids. The entire process starting from sample preparation to mass spectrometry is monitored using spiked isotopic standards that have been characterized for their chromatographic behavior as well as fragmentation profile. Bioinformaticians are available for further analysis of the resulting output data.

MAJOR EQUIPMENT

- Agilent 6495 Triple Quadruple (QQQ) Mass Spectrometry
- Agilent 6495B Triple Quadruple (QQQ) Mass Spectrometry
- AB SCIEX 5600 Triple TOF Mass Spectrometry
- Thermo Orbitrap IQX Mass Spectrometry (New NIH S10 Shared Instrument Grant)
- HPLC Systems

SERVICES

Targeted metabolite steady-state profiling: The Core has the capability of identification, quantification and, characterization of over 600 metabolites using the targeted multiple reaction monitoring approaches (MRM) developed for different chemical classes of compounds.

Data can be reported either in absolute concentrations or as intensity ratios to internal standards.

Metabolic Flux: Isotope flux and metabolite profiling help formulate and test hypotheses about the metabolic consequences of various changes to guide further integrative systems biology analyses of the underlying mechanisms in disease. The Core has the capability of characterizing [13C] Glutamine and [13C] Glucose flux using LC-QQQ Mass Spectrometry.

Lipidomics: Using an ABSCIEX 5600 Triple TOF MS, identification of lipids is accomplished by data-dependent production (MS/MS) information of human plasma, tissues, and urine and in both positive and negative ionization modes. MS/MS acquisition or MS/MS ALL acquisition provides information on the nature of the lipid head group and/or neutral loss of the head group from the molecular ion adducts. Information on the fatty acid composition of the lipids is obtained in the negative mode.

Unbiased Metabolomics: Metabolomics Core has acquired the IQX Orbitrap Mass Spectrometry from Thermo Scientific through an NIH S10 grant, aiming to establish an unbiased metabolomics platform. This advanced technology enables the identification of approximately 1600 metabolites from samples. The resulting data will be presented in terms of the relative levels of metabolites, accompanied by preliminary statistical analysis. The Core is currently engaged in the development and implementation of this service through pilot projects, indicating a thorough and careful approach to ensure the platform's effectiveness. The unbiased metabolomics platform is expected to be fully operational in 2024.

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DATA ANALYSIS

- Pathway mapping using OCM, GSA or NETGSA
- Developing classification models
- Integration with other OMICS datasets

CLASSES OF STEADY-STATE METABOLITES MEASURED BY MRM ANALYSIS

Assay 1	Amino sugars
Assay 2	Amino acids
Assay 3	Prostaglandins
Assay 4	Carnitines
Assay 5	Polyamines
Assay 6	Glycolysis Intermediates
Assay 7	TCA
Assay 8	Nucleotides
Assay 9	Vitamins
Assay 10	Steroids
Assay 11	Bile acids
Assay 12	Short-Chain Fatty Acids
Assay 13	Methylated Metabolites
Assay 14	Fatty acids
Assay 15	Neurotransmitters and related metabolites

CORE SUPPORTED RESEARCH

Metabolomic rewiring promotes endocrine therapy resistance in breast cancer

Dr. Kaipparettu's lab previously demonstrated that mitochondrial fatty acid β-oxidation (FAO) is a major metabolic pathway in triple-negative breast cancer (TNBC), and FAO activates Src signaling in metastatic TNBC. In this study, the Metabolomics core performed unbiased lipidomics and targeted metabolomics and identified alterations of lipids and metabolites upon knockdown of CPT1B. Further analysis identified metabolic reprogramming-driven FAO-mediated Src activation as a critical mechanism of resistance to endocrine therapy in estrogen receptor-positive breast cancer (ER+ BC). Briefly, a metabolically relevant, integrated gene signature was derived from the transcriptomic, metabolomic, and lipidomic analyses of the FAO rate-limiting enzyme carnitine palmitoyl transferase 1 (CPT1) inhibited TNBC cells. This TNBC-derived signature predicted the endocrine resistance in tumors from ER+ BC patients. Further molecular, genetic, and metabolomic experiments confirmed the activation of AMPK-FAO-oxidative phosphorylation (OXPHOS) signaling in endocrine-resistant ER+ BC. CPT1 knockdown or treatment with FAO inhibitors, both in vitro and *in vivo*, significantly enhanced the response of ER+ BC cells to endocrine therapy. Finally, the preclinical studies revealed a novel therapeutic strategy targeting the FAO, OXPHOS, or Src pathways to overcome endocrine resistance in ER+ BC patients.

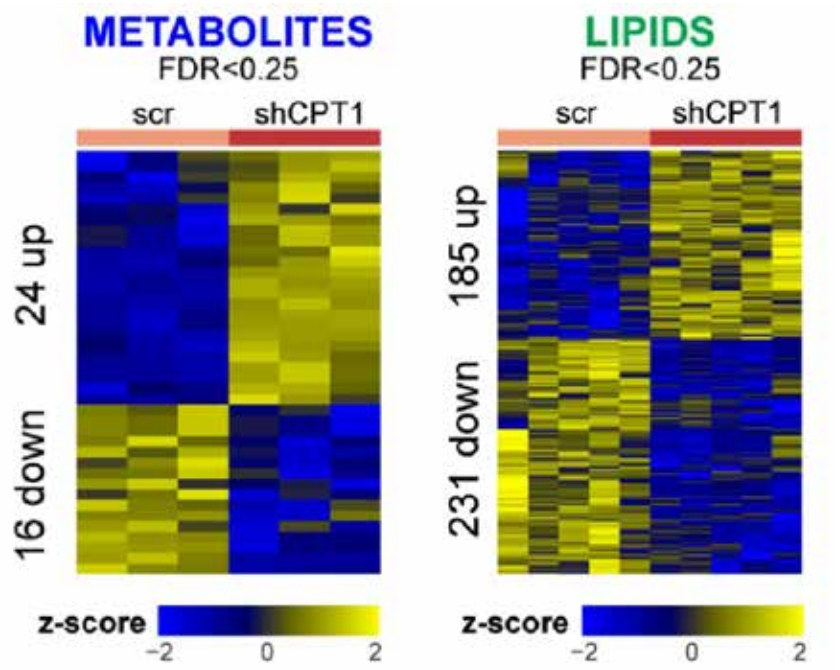

Figure: Integration of metabolomics and lipidomics genes led to a 3-model CPT1 suppression union signature, with 28 increased genes and 16 decreased genes

Ahn S, Park JH, Grimm SL, Piyarathna DWB, Samanta T, Putluri V, Mezquita D, Fuqua SAW, Putluri N, Coarfa C, Kaipparettu BA. Metabolomic rewiring promotes endocrine therapy resistance in breast cancer. Cancer Res. 2023 Oct 31. doi: 10.1158/0008-5472.CAN-23-0184. Epub ahead of print. PMID: 37906431.

MHC TETRAMER

MHC Tetramer technique has become a “gold standard” for the quantification of T cell immune responses. The T cell antigen-receptor (TCR) recognizes antigens through peptides bound to major histocompatibility complex molecules (MHC), also called HLA (human leukocyte antigens) in humans. Joining multiple copies of the MHC/antigen complex into a single probe resolves the difficulties presented by the low affinity of the MHC molecule for the CD8 receptor. This unique technique can offer exquisite antigen specificity and sensitivity to monitor T cell responses, which makes it suitable for basic and clinical studies including cancer prevention, cancer therapy, cell and gene therapy, immunotherapy, and non-cancer related immunology research. The mission of the core is to provide customized MHC/peptide tetramers for identification of antigen specific T lymphocytes by flow cytometry.

STANDARD SERVICES

- Standard or customized MHC/peptide class I tetramers
- We offer more than sixty human, mouse, macaque, and chimpanzee alleles for customized production of class I MHC reagents with desired epitopic peptides. Researches will also have two fluorescent labels choices: R-phycoerythrin (PE) or allophycocyanin (APC).
- Biotinylated or Non-biotinylated MHC/peptide class I monomers
- For customers who intend to label tetramers with fluorophores of their own choice or to use monomers in several special applications.

SPECIAL SERVICES

- CD8 binding-deficient MHC Class I tetramers: Containing mutations in the MHC α3 domain that ablate CD8 binding; can be used to quantitate and to sort CD8-independent T cells.
- Chimeric Tetramer: Containing MHC Human/Mouse chimeric heavy-chain
- MHC Monomers for generating TCR-like antibodies
- Developing high-affinity soluble antibody molecules endowed with a TCR-like specificity toward tumor epitopes, termed TCR-like antibodies, recently became a hot topic for cancer immunotherapy studies.
- MHC Class I monomers designed for ligand exchange
- When trying to analyze multi epitopes of an antigen, generating individual tetramers can be very time consuming and less practical. The MHC monomers specially designed for ligand exchange can address this issue well. We now have ligand exchange monomers designed for six commonly used HLA alleles.

CORE LEADERSHIP

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ATR-mediated CD47 and PD-L1 upregulation restricts radiotherapy-induced immune priming and abscopal responses in colorectal cancer

Radiotherapy (RT) of colorectal cancer (CRC) can prime adaptive immunity against tumor-associated antigen (TAA)-expressing CRC cells systemically. However, abscopal tumor remissions are extremely rare, and the post-irradiation immune escape mechanisms in CRC remain elusive. Dr. Curran's group at MD Anderson Cancer Center found that irradiated CRC cells utilized an ATR-mediated DNA repair signaling pathway to upregulate both CD47 and PD-L1, which through engagement of SIRPα and PD-1 respectively, prevented phagocytosis by antigen-presenting cells and thereby limited TAA cross-presentation and innate immune activation. This post-irradiation CD47 and PD-L1 upregulation was observed across various human solid tumor cells. Therefore, they proposed RT combined with SIRPα and PD-1 blockade to promote robust anti-tumor immune priming leading to systemic tumor regressions. Their data showed significantly higher complete response rates to RT/anti-SIRPα/anti-PD-1 in both irradiated and abscopal tumors and prolonged survival. The H-2Kb-SIINFEKL tetramers produced by our core were used to validate antigen-specific T cells in their murine CRC models.

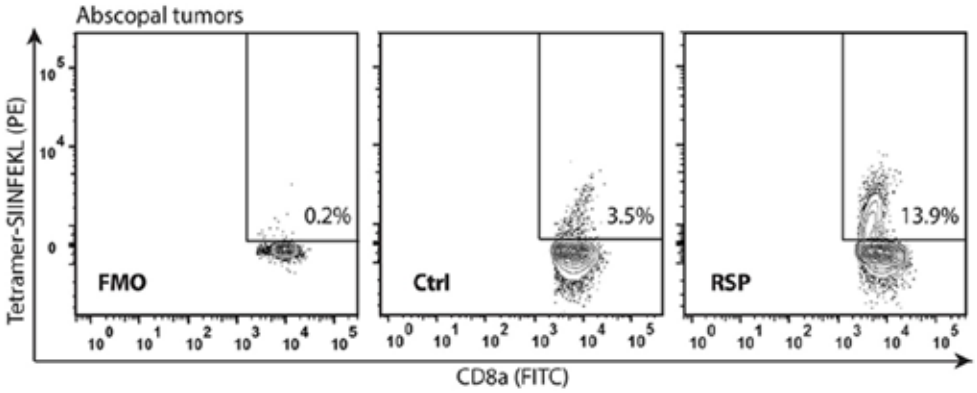

Figure: RT/anti-SIRPa/anti–PD-1 (RSP) promoted antitumor T cell activation. T cells in irradiated tumors, abscopal tumors, and peripheral blood were harvested from mice bearing bilateral MC38-OVA tumors treated ± unilateral 8-Gy RT (R; day 12), anti-SIRPa (S; days 12, 14, 16, and 18), and/or anti–PD-1 (P; days 12, 15, and 18) for flow cytometry analyses. Frequencies of H-2Kb-SIINFEKL-tetramer+ CD8 T cells in irradiated and abscopal tumors as well as the peripheral blood were analyzed. Contour plots depict the percentages of H-2Kb-SIINFEKL-tetramer+ cells in CD8 T lymphocytes of abscopal tumors in FMO, control and RSP sample groups.

Hsieh R CE, Curran M. ATR-mediated CD47 and PD-L1 upregulation restricts radiotherapy-induced immune priming and abscopal responses in colorectal cancer. Sci. Immunol. 2022; 7(72). PMID: 35687697, PMCID: PMC9373855, DOI: 10.1126/sciimmunol.abl9330

MOUSE METABOLISM & PHENOTYPING CORE

The Mouse Metabolism and Phenotyping Core (MMPC) is a comprehensive phenotyping core that provides investigators with a wide variety of state-of-the-art equipment and techniques for testing rodent models from embryo to adult. The mission of the MMPC is to provide equipment, services, and resources for the expert characterization of whole animal and organ systems phenotypes within rodent models. The MMPC has standardized key methodologies and can expedite comprehensive research analyses on diseases related to cancer, cardiovascular dysfunction, metabolic disorders, rodent models of human disease and drug studies. The MMPC also provides advanced analysis of metabolic pathways and related physiological and biochemical parameters in mice and rats, as well as in isolated/cultured cells in vitro. Workstations for image reconstruction and data analysis are also available within the core. MMPC personnel provide consultation on selecting the appropriate tests and procedures, and the interpretation of data.

MAJOR EQUIPMENT

- Vevo F2 Ultrasound (VisualSonics)
- 7.0T Pharmascan MRI (Bruker)
- eXplore CT 120 (TriFoil Imaging)
- IVIS Lumina X5 (Revvity)
- Unrestrained Whole Body Plethysmography (Buxco and DSI)
- Oxymax FAST Indirect Calorimetry System (Columbus Instruments)
- Comprehensive Lab Animal Monitoring System [CLAMS-HC] (Columbus Instruments)
- UltraFocus [X-ray and Body Composition Analyzer] (Faxitron)
- EchoMRI-100™ [Body Composition Analyzer] (EchoMRI)
- Non-Invasive Blood Pressure (IITC Life Sciences)
- Blood Pressure and ECG Telemetry (DSI)
- 6-lane treadmill (Columbus Instruments)
- Running wheels (Minimitter)
- Metabolic cages (Techniplast)
- ECG-Mouse Monitor (Indus Instruments)
- Pulse oximetry (Indus Instruments)
- Grip strength meter (Columbus Instruments)
- XFe96 Seahorse Analyzer (Agilent)
- Versamax System (Accuscan)
- Vessel Doppler (Indus Instruments)
- Rectal probe for body temp measurement
- Isoflurane anesthesia stations

SERVICES

- Hyperinsulinemic-euglycemic clamp in conscious mice: direct quantification of the role of specific organs and tissues in glucose-insulin homeostasis
- Cellular oxygen consumption & glycolysis monitoring of cultured cells by use of the Seahorse instrument
- Metabolic monitoring of food intake, energy expenditure and real-time body temperature for small animals (mouse) after 72 hours of acclimation using the Comprehensive Laboratory Animal Monitoring System (HC-CLAMS)
- Echocardiography
- Home cage activity monitoring
- Hypoxia chamber animal housing
- Plasma/Blood parameter Analysis
- Lipid Metabolism
- Glucose metabolism
- Glucose tolerance test
- Insulin tolerance test
- Pyruvate tolerance test (gluconeogenesis)
- Telemetry Device Implantation
- Osmotic Pump Implantation
- Additional Surgical Services (by request)
- Intact Animal Phenotyping Services: consultation for behavior, physiology, and metabolic assay testing battery design, technical services for data collection and analysis.

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The RA drug auranofin and miR-30a exhibit similar activities.

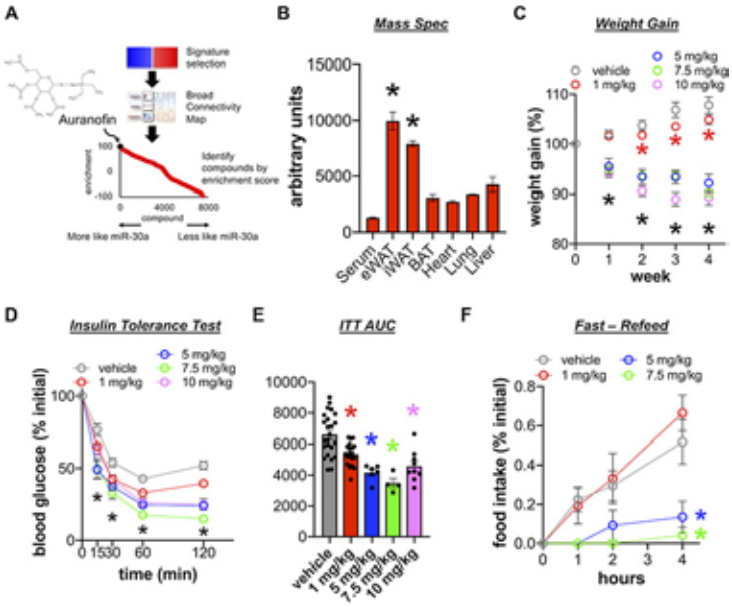

Figure. (**A**) The Broad Connectivity Map identified that auranofin regulates gene expression in a similar way as miR-30a expression in iWAT. (**B**) Diet-induced obese mice injected with auranofin i.p. (10 mg/kg) and sacrificed 24 h later for mass spectrometry analysis of tissue distribution. Wild-type mice fed high-fat diet (HFD) for 12 weeks i.p. injected with auranofin (1, 5, 7.5, 10 mg/kg) or vehicle for 4 weeks. (**C**) Weight gain for vehicle n=24, 1 mg/kg n=29, 5 mg/kg n=6, 7.5 mg/kg n=4, 10 mg/kg n=10. (**D**) ITT with corresponding (**E**) area under the curve measurements. (**F**) Food intake measured in mice fasted 16 h and re-fed after auranofin injection (n=4-5/group). All data are mean ± SEM. *p<0.05, #p<0.10 by one-way ANOVA with Tukey's multiple comparison test (**B**; **E**), mixed-effects analysis with Tukey's multiple comparisons test (**C**, black asterisks are week 1 vehicle vs 5, 7.5, 10 mg/kg and red asterisks are weeks 2-4 vehicle vs 1 mg/kg; **D**, ITT% vs vehicle; **F**, hours 2-4 vehicle or 1 mg/kg vs 5 and 10 mg/kg).

Cox AR, et. al. The rheumatoid arthritis drug auranofin lowers leptin levels and exerts antidiabetic effects in obese mice. Cell Metab. 2022 Dec 6;34(12):1932-1946.e7. doi: 10.1016/j.cmet.2022.09.019. Epub 2022 Oct 14. PMID: 36243005.

Hypoxia-inducible factor 1-alpha (HIF-1α) inhibition prevents AF inducibility in FKBP5 (FK506 binding protein 5)–cardiomyocyte-specific knockdown (cKD) mice.

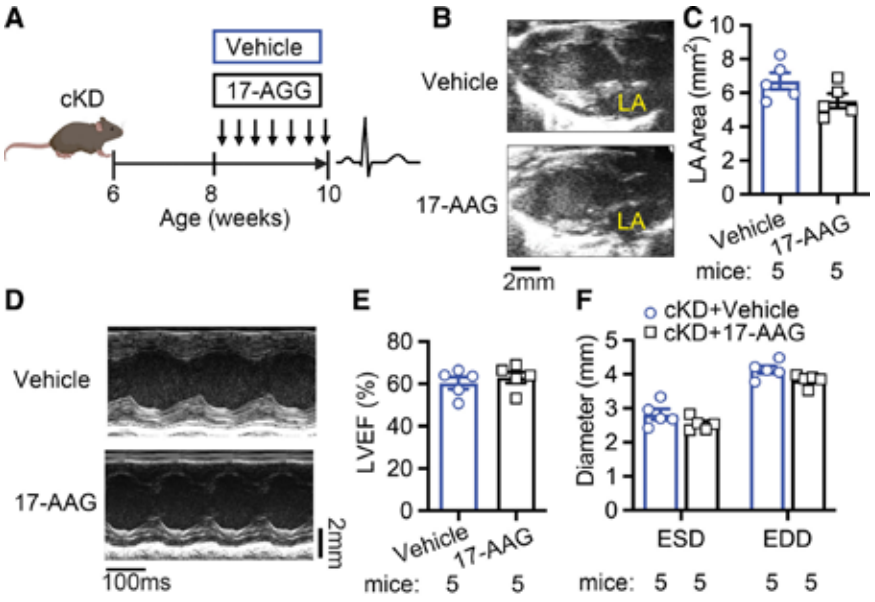

Figure. (**A**) Timeline of HIF-1α inhibition studies in cKD mice. Representative long-axis echocardiography images (**B**) and quantification (**C**) of left atrial (LA) area in cKD mice treated with vehicle (control) or 17-AAG. D–F, Representative M-mode echocardiography images (**D**) and quantification of left ventricular ejection fraction (LVEF%) (**E**) and diameters (**F**) of left ventricles in cKD mice treated with vehicle (control) or 17-AAG.

Wang X, et. al. Downregulation of FKBP5 Promotes Atrial Arrhythmogenesis. Circ Res. 2023 May 8; PMID: 37154033.

MULTI-OMICS DATA ANALYSIS CORE (RE-ORGANIZED 2024).

The goal of the Multi-Omics Data Analysis Core (MODAC) is to provide state of the art bioinformatic analysis of multi-omics data and computational support for translational and basic science research. As a previous unit of the Biostatistics and Informatics Shared Resource (BISR), MODAC was re-organized in 2024 as a separate core.

SERVICES

- **Support of ATC "Omics" Cores:** Data processing and QC is provided for data generated by other ATC cores including Metabolomics, Genomics and RNA Profiling (GARP) and Antibody-Based Proteomics.
- **Single-omics analysis:** Data analysis including basic processing and differential expression is provided for omics including bulk RNA-Seq, microRNA-Seq, ChIP-Seq, proteomics, and metabolomics
- **Single cell and spatial transcriptomics analysis:** Support is provided for analysis of single-cell and single-nuclei RNA-Seq, and of spatial transcriptomics generated using the Visium and the NanostringGeoMX platforms.
- **Multi-Omics Bioinformatics:** Multi-omics integrative analyses are provided, including metabolomics/transcriptomics, ChIP-Seq/transcriptomics, and bulk RNA-Seq/microRNA-Seq. Integration with publicly available omics datasets is also provided.
- **Training:** Training courses are provided for bulk and single-cell RNA-Seq, and for metabolomics, lipidomics, and proteomics assays.
- **Other:** Assistance with grant applications; education; deposition of 'omics-scale' datasets

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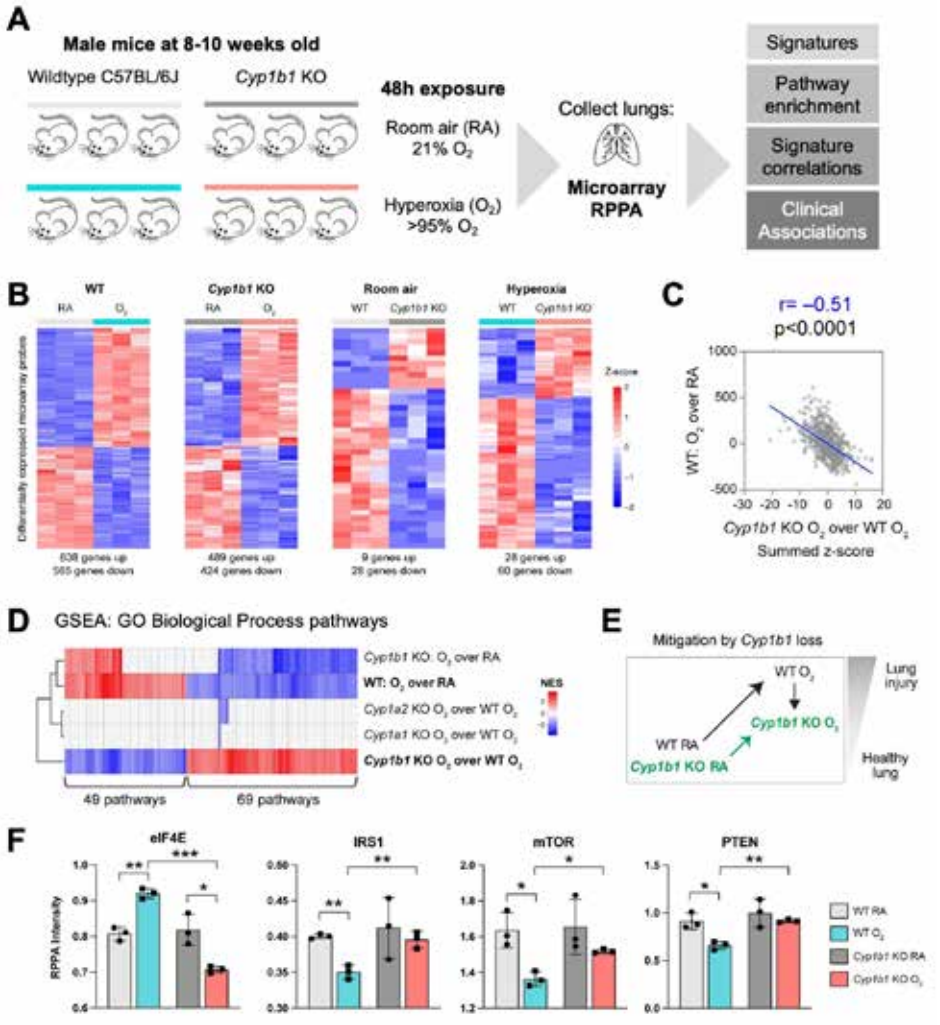
Loss of cytochrome P450 (CYP)1B1 mitigates hyperoxia response in adult mouse lung by reprogramming metabolism and translation.

Oxygen supplementation is life saving for premature infants but can induce long-term pulmonary injury, with xenobiotic-metabolizing CYP enzymes playing a critical role. Murine studies showed that CYP1B1 enhances, while CYP1A1 and CYP1A2 protect from hyperoxic injury. In this study, wild-type (WT) and *Cyp1b1*-null mice were exposed to room air or hyperoxia (>95% O_2), with transcriptomic and RPPA proteomics performed in mice lungs (panel **A**). Robust gene signatures were determined for both exposure and genotype (panel **B**). Mining human lung transcriptomes showed mitigation of the hyperoxia response in *Cyp1b1*-null mice (panel **C**). Pathway enrichment determined 49 pathways induced and 69 suppressed by hyperoxia that were ameliorated only in *Cyp1b1*-null mice (panel **D**). Our overall model is that WT and *Cyp1b1*-null mice are affected by hyperoxia, but *Cyp1b1*-null mice show reduced lung injury, partially explained by amelioration of genes and pathways (panel **E**). Further amelioration was observed for several key proteins (panel **F**). This study was performed in collaboration with the the NIEHS-funded P42 BCM-Rice Superfund Center.



Grimm SL, Stading RE, Robertson MJ, Gandhi T, Fu C, Jiang W, Xia G, Lingappan K, Coarfa C, Moorthy B. Loss of cytochrome P450 (CYP)1B1 mitigates hyperoxia response in adult mouse lung by reprogramming metabolism and translation. Redox Biol. 2023 Aug;64:102790. PMID: 37348155.

NMR & DRUG METABOLISM

The Nuclear Magnetic Resonance (NMR) and Drug Metabolism Core offers tools to support the discovery, synthesis, screening, identification, metabolism, pharmacokinetics and imaging within tissues of small molecules. Expert NMR services are available to determine small molecule identity or conformation, to identify and quantify metabolites that may serve as biomarkers, to determine macromolecular structure or to detect structural perturbations upon ligand binding. The Core also investigates the metabolism and pharmacokinetics of small molecules using liquid chromatography-mass spectrometry (LC-MS and MS/MS) and metabolic stability in liver microsomes or by reaction phenotyping assays with CYP450s. Core personnel provide advice on the use of our instrumentation for a wide variety of applications, which now include imaging the spatial distribution of small molecules in tissue sections with our newly installed imaging mass spectrometer. Assistance is available in project experimental design and data analysis. NMR spectrometers are available for unassisted use by trained and qualified users, as is user training in simple 1D and 2D NMR data acquisition and analysis.

MAJOR EQUIPMENT

- 800 MHz Bruker Avance HD III spectrometer
- 800 MHz Bruker QCI Cryoprobe
- SampleJet automated sample changer
- 600 MHz Bruker Avance HD III spectrometer
- SampleXpress automated sample changer
- Thermo Q Exactive Hybrid Quadropole-Orbitrap LC-MS system
- Thermo Quantis Triple Quadrupole LC-MS/MS system
- Bruker timsTOF fleX MALDI imaging mass spectrometer system (new NIH S10 Shared Instrument Grant)

SERVICES

- Compound identification and quality control
- Small molecule conformational analysis
- Ligand/target screening
- Chemical shift perturbation mapping of protein/ligand interactions
- Feasibility studies for NMR structure determination
- NMR user training
- Drug quantification in fluids or tissues
- Drug metabolite identification
- Drug stability assays in microsomes
- Reaction phenotyping
- Pharmacokinetic profiles
- Tissue imaging for small molecules or lipids

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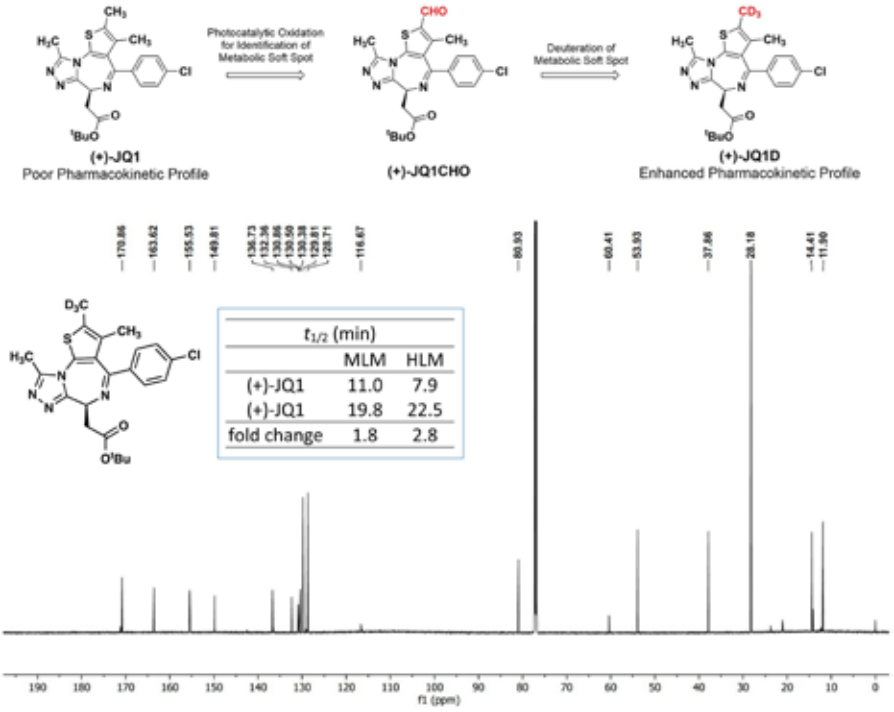

Figure 1. Characterization of a deuterated analog and the fold change in metabolic stability. Previous work that identified the primary metabolic site on the compound JQ1 led the Young group to design a deuterated analog (scheme at **top**). Synthesis of the analog was confirmed by NMR spectroscopy in the Core, including the 1H-decoupled 1D 13C spectrum (**bottom**). Stability of the parent and analog measured in mouse liver microsomes (MLM) and human liver microsomes (HLM) by the Core show that the analog is metabolized more slowly (inset table).

Holmes S, Jain P, Rodriguez KG, Williams J, Yu Z, Cerda-Smith C, Samuel ELG, Campbell J, Hakenjos JM, Monsivais D, Li F, Chamakuri S, Matzuk MM, Santini C, MacKenzie, KR, Young DW. Chemical Catalysis Guides Structural Identification for the Major In Vivo Metabolite of the BET Inhibitor JQ1. ACS Medicinal Chemistry Letters 15, 107-115 (2024).

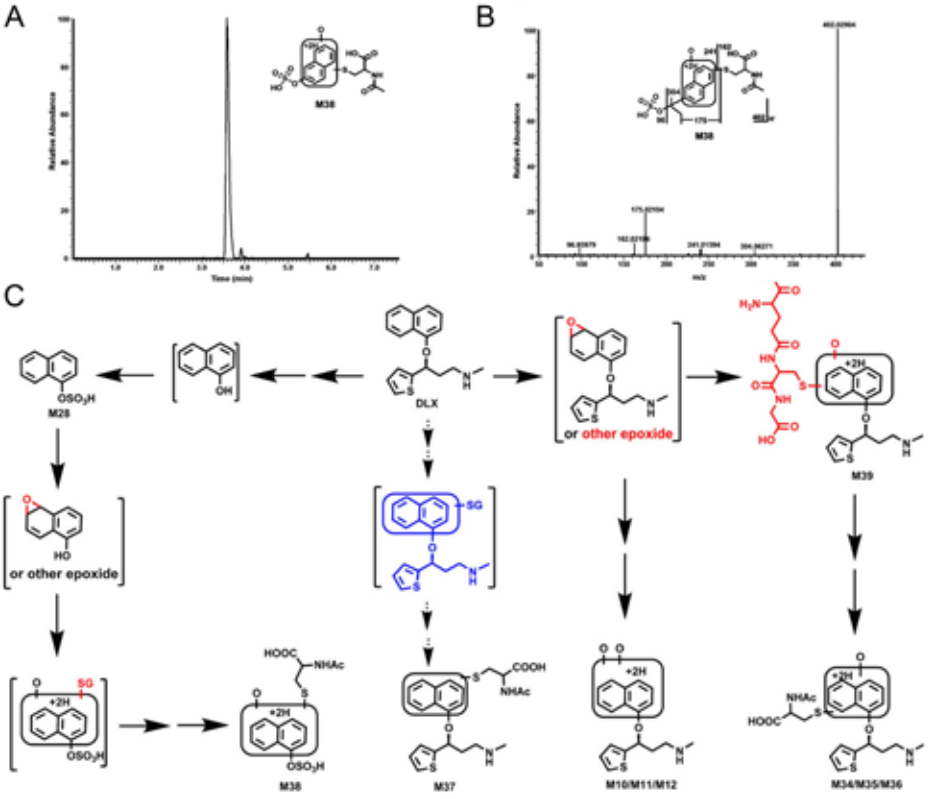

Figure 2. Identification of novel adducts in metabolism of the anti-depressant drug duloxetine. (**A**) LC-MS resolves N-acetyl cysteine adduct M38. (**B**) Structure of adduct M38 is confirmed by MS-MS fragmentation analysis. (**C**) inferred pathways for generating glutathione-adduct mediated metabolites of duloxetine in mice.

Qin X, Hakenjos JM, MacKenzie KR, Barzi M, Chavan H, Nyshadham P, Wang J, Jung SY, Guner JZ, Chen S, Guo L, Krishnamurthy P, Bissig KD, Palmer S, Matzuk MM, Li F. Metabolism of a Selective Serotonin and Norepinephrine Reuptake Inhibitor Duloxetine in Liver Microsomes and Mice. Drug Metab Dispos. 50, 128-139 (2022).

OPTICAL IMAGING & VITAL MICROSCOPY (OIVM)

The Optical Imaging & Vital Microscopy Core (OiVM) is a light microscopy core facility specializing in 3D optical sectioning tools for fluorescence microscopy. We operate as a 24/7 independent-use core, providing expert training and support that gives our investigators the tools and technical expertise they need to obtain reliable, reproducible imaging data using state-of-the-art Confocal, 2-Photon and Lightsheet imaging modalities.

We have over 20 years of experience educating, training, and assisting scientists with experiments using the latest cutting-edge microscopy techniques in a variety of applications such as understanding cell migration, optimizing angiogenic therapies, how blood flow influences development and cancer, immune cell recruitment, stem cell-niche interactions and cancer metastasis.

MAJOR EQUIPMENT

- Zeiss LSM 880 with AiryScan FAST – High Speed Super Resolution/Confocal point scanning microscope
- Zeiss LSM 780 Multi-Photon – Visible/Multi-Photon Spectral Confocal point scanning microscope
- Zeiss Lightsheet Z.1 – Light-sheet fluorescence microscope
- Bruker Skyscan 1272 - X-ray µCT
- Leica TCS SP8 MP – Confocal and Multi-Photon microscope
- Zeiss AxioObserver Widefield Fluorescence microscope
- Zeiss Axio Zoom.V16 Stereomicroscope
- Logos Biosystems X-Clarity Tissue Clearing System
- 2x - High End Image Processing Workstations equipped with Imaris, Arivis Vision 4D, Bruker CT, Zeiss ZEN and Fiji.

SERVICES

- Expert training/instruction on core instrumentation
- 24/7 Core Access for Trained Users
- Tissue Clearing with CLARITY protocol provided on a per sample basis
- Super Resolution Microscopy with AiryScan detection system
- Confocal microscopy with spectral array detection for imaging multiple fluorophores (up to 8) simultaneously
- Automated 3D tile scanning of image large fields with high resolution
- LightSheet fluorescence microscopy for 3D imaging of thick tissues cleared with Scale, CLARITY, etc.
- Two-photon and second harmonic generation (SHG) intravital imaging
- Live imaging of tissue/organ development in embryos and live animals with environmental control of the stage and anesthesia support of live animals
- High speed imaging of blood and fluid flow such as fluorescent beads, fluorescently labeled erythroblasts, etc.
- Imaging and 3D rendering of embryos, organs, bioengineered gels, etc. using the X-ray microCT scanner
- Imaging and 3D rendering of optically cleared (BABB) embryos, mammary glands, etc. using the OPT microscope
- Quantitative analysis of cellular dynamics and cell tracking
- 3D/4D Image Rendering using high end workstations equipped with latest image visualization/analysis software

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EZ Clear is a simple, rapid, and efficient tissue clearing method developed by the Optical Imaging and Vital Microscopy core for clearing whole mount adult mouse organs in three simple steps. Samples processed with EZ Clear can retain endogenous fluorescence and allow 3D whole organ lightsheet imaging. Samples can also be cryo-sectioned for histology and immunofluorescence staining following processing with EZ Clear.

Hsu CW, Cerda J 3rd, Kirk JM, Turner WD, Rasmussen TL, Flores Suarez CP, Dickinson ME, Wythe JD. EZ Clear for simple, rapid, and robust mouse whole organ clearing. Elife. 2022 Oct 11;11:e77419. doi: 10.7554/eLife.77419. PMID: 36218247; PMCID: PMC9555867.

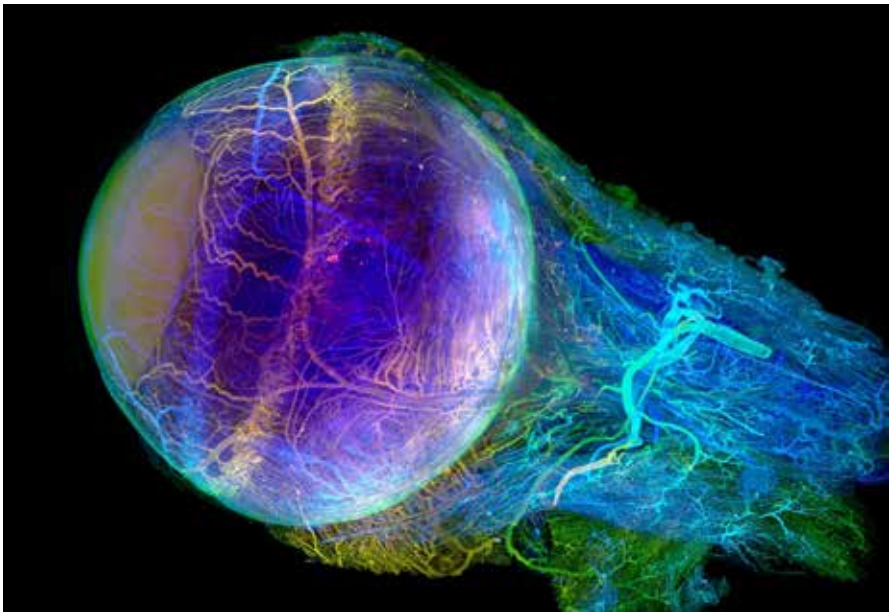

Figure: Depth-coded projection of intact mouse eye illustrating blood vessels perfused with lectin-649. Cleared with EZ Clear and imaged on Zeiss Lightsheet Z.1.

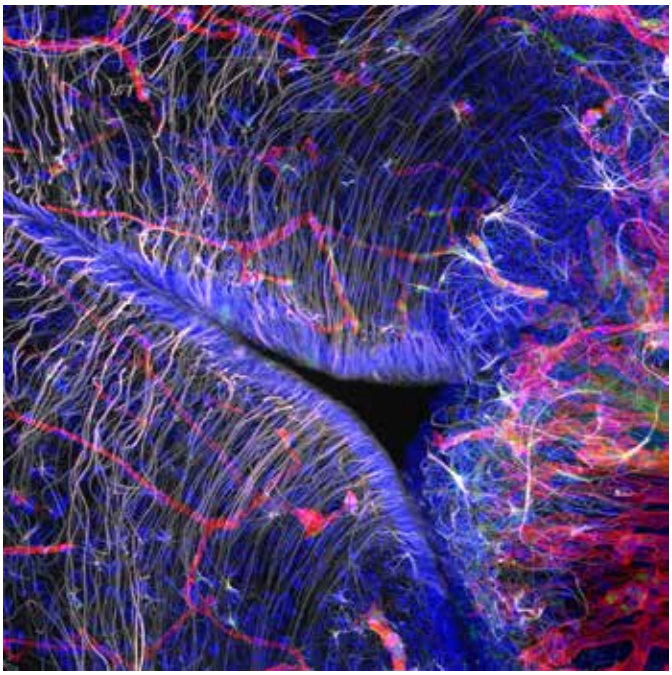

Figure: Coronal cryosection (100 um) of mouse brain with GFP^{+} tumor cells (green), blood vessels perfused with lectin-649 (red), stained with GFAP (white) and Hoechst (blue). The section was imaged on our Zeiss LSM 880 Airyscan FAST confocal microscope at 20×.

PATIENT-DERIVED XENOGRAFT

The Patient-Derived Xenograft (PDX) Core of Baylor College of Medicine was created to facilitate the establishment and use of PDX models for the BCM research community. The core's primary mission is to develop, and provide to the Baylor PDX community, computational and bioinformatics infrastructure to support large-scale generation, characterization and use of PDX models. PDX models from a variety of organ sites including brain, bladder, breast, head and neck, leukemia, pancreas, sarcoma and pediatric cancers are available. The core also provides expertise in transplantation and animal handling to those wishing to generate PDX from various cancer types. Finally, the core will coordinate and assist with the evaluation of experimental therapeutics using PDX platforms in conjunction with those investigators maintaining PDX collections for each organ/disease type.

All PDX work involving animals is conducted in dedicated housing and surgical suites in the Alkek Building for Biomedical Research of BCM, a fully AAALAC-accredited animal care and housing facility. Work is supported by the Center for Comparative Medicine (CCM), which administers the facility. CCM provides full veterinary care, administrative and regulatory oversight, and assistance with animal husbandry.

MAJOR EQUIPMENT

- IVIS Lumina X5 *In Vivo* Imaging Systems
- Vega Preclinical Ultrasound System
- gentleMACS Octo Dissociator with heaters
- Tissue Cassette Labeler
- Alabama Tissue Slicer and Coring Press
- Computation and Bioinformatics Infrastructure for managing clinical and PDX associated data elements

SERVICES

- Development of computational/bioinformatics infrastructure to support PDX-based research
- Assist with, or facilitate, the generation of PDX models
- Facilitate *in vivo* treatment experiments with investigational drugs with PDX models.
- Provide training for PDX related procedures
- Coordinate provision of snap frozen tissue, viably frozen tissue, serum/plasma, and FFPE blocks/slides from PDX models from PDX program leads
- Coordinate provision of molecular derivatives of PDX models from PDX program leads
- IVIS Lumina X5 instruments provide high-throughput bioluminescent, fluorescent, and X-ray imaging for immunodeficient or immunocompetent animals
- Vega Ultrasound provides hands-free, high-throughput ultrasound imaging of immunodeficient animals
- Provide excess immunocompromised mice from our breeding colony to BCM investigators

Organoids developed from PDX models (PDXOs) are now available from validated PDX models provided by the PDX core. See the "Advanced Cell Engineering and 3D Models Core" page for details and requests.

MOUSE PDX CANCER MODELS AVAILABLE

- 82 Breast
- 26 Pancreatic
- 23 Leukemia
- 21 Sarcoma
- 10 Pediatric Liver
- 10 Bladder
- 7 Head & Neck
- 5 Mesothelioma
- 4 Glioblastoma Multiforme
- 2 Ovarian
- 1 Lung
- 1 Esophageal

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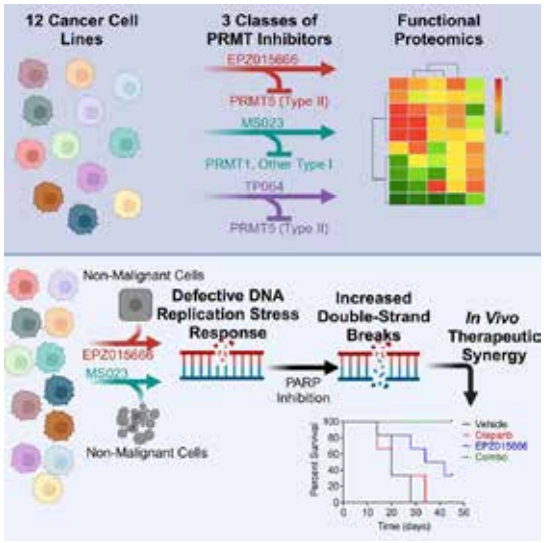
PRMT blockade induces defective DNA replication stress response and synergizes with PARP inhibition



The PDX Core performed all aspects of the breast and ovarian PDX studies including transplantation of the mice, body weight and tumor volume measurements, drug formulation, dosing of the animals, and the collection of tumor tissue and blood.

Figure 1. In brief: Li et al (PI: Nidhi Sahni MDACC) performed a comprehensive proteomic analysis of cells following inhibition of symmetric and asymmetric arginine methylation, discovering that PRMT inhibition suppresses ATR expression and induces DNA replication stress response defects. They further show inhibition of PRMT5 provides potent synergy with PARP inhibitors with no evidence of toxicity.

Combination PRMT5 and PARP Inhibition is well tolerated and inhibits patient-derived xenograft growth in vivo.

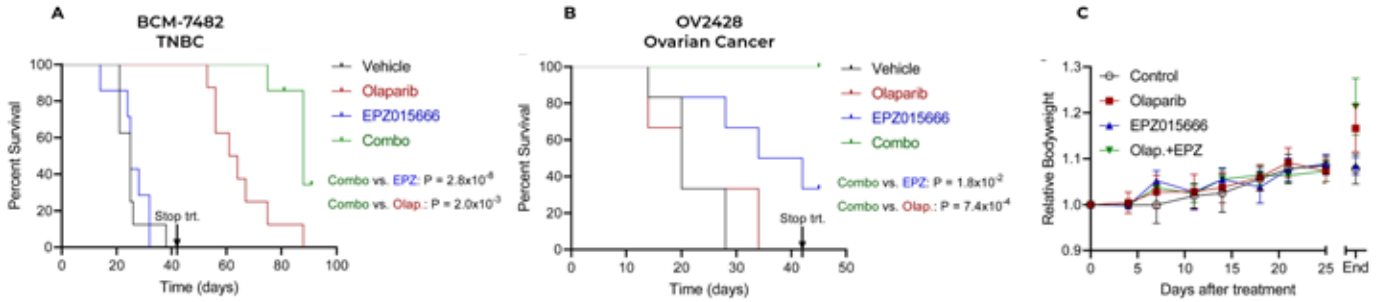


Figure 2. Combination of the PRMT5i EPZ015666 and the PARPi olaparib is effective and well tolerated "*in vivo.*" (**A**) The triple-negative breast cancer patient-derived xenograft BCM-7482 was allowed to reach ~175 mm^3 before treatment initiation with vehicle control (N = 8), 50 mg/kg olaparib 3× weekly (N = 8), 200 mg/kg EPZ015666 5× weekly (N = 7), or combination thereof (N = 7). Treatment was continued for 6 weeks or until mice reached maximum tumor volume. Log-rank test. (**B**) The ovarian patient-derived xenograft OV2428 was allowed to reach ~175 mm^3 before treatment initiation with vehicle control, 50 mg/kg olaparib 3× weekly, 200 mg/kg EPZ015666 5× weekly, or combination thereof. Treatment was continued for 6 weeks or until mice reached maximum tumor volume. Log-rank test. N = 5 per arm. (**C**) Bodyweights during treatment up until median survival time (25 days) of vehicle-control-treated mice, followed by bodyweights at endpoint for each treatment arm after axis break. Mean ± SD.

Li Y, Dobrolecki LE, Sallas C, Zhang X, Kerr TD, Bisht D, Wang Y, Awasthi S, Kaundal B, Wu S, Peng W, Mendillo ML, Lu Y, Jeter CR, Peng G, Liu J, Westin SN, Sood AK, Lewis MT, Das J, Yi SS, Bedford MT, McGrail DJ, Sahni N. PRMT blockade induces defective DNA replication stress response and synergizes with PARP inhibition. Cell Rep Med. 2023 Dec 19;4(12):101326. doi: 10.1016/j.xcrm.2023.101326. PMID: 38118413.

POPULATION SCIENCES BIOREPOSITORY (PSB)

The Population Sciences Biorepository (PSB) serves as a resource for centralized cost-effective biospecimen processing and storage for epidemiological, translational, and clinical studies. The PSB also provides risk factor and clinical data collection. Services are available for individually funded investigators as well as for clinical centers that require prospective banking of specimens from patients for future research projects. The PSB team will consult with you to plan for data collection and specimen processing and storage needs for your projects. In addition, the PSB has a banked collection of annotated samples from a variety of cancer types that are available for individual investigator use. Contact the PSB to learn how to gain access to these important samples. Learn more about the PSB by viewing our video on the ATC core website (bcm.edu/research/atc-core-labs/population-sciences-biorepository).

MAJOR EQUIPMENT

- Hamilton Verso Automated -20°C freezer system
- CryoBioSystem MAPI high-security straw system
- QIAcube robotic workstation
- Chemagic Prepito-D extraction system
- Chemagic 360 exatraction system
- Perkin Elmer Janus automated workstation
- Nano-drop 1000
- MVE 1536P LN2 vapor freezers
- VWR -80°C mechanical freezers
- Thermo Scientific VisionMate scanner
- Thermo Scientific 8-channel decapper
- Barcode printers and scanner system
- Centrifuges
- Freezer Monitoring System

SERVICES

- Patient consenting, phlebotomy, sample and data collection
- Questionnaire development and administration
- Full fractionation and aliquoting for blood, bone marrow and urine samples
- Mononuclear cell isolation and cryopreservation
- DNA extraction from whole blood, buffy coat, plasma, or saliva
- RNA extraction from whole blood or buffy coat
- DNA Quantitation (absorbance and pico-green fluorescence)
- Whole Genome Amplification
- Long-term specimen archival

CORE LEADERSHIP

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Genetic susceptibility to cognitive decline following craniospinal irradiation for pediatric central nervous system tumors

Survivors of pediatric central nervous system (CNS) tumors treated with craniospinal irradiation (CSI) exhibit long-term cognitive difficulties. Goals of this study were to evaluate longitudinal effects of candidate and novel genetic variants on cognitive decline following CSI. The PSB-supported study identified, in genome-wide analyses, novel loci associated with accelerated declines in Intelligence quotient (IQ) and that inherited genetic variants involved in baseline cognitive functioning and novel susceptibility loci jointly influence the degree of treatment-associated cognitive decline in pediatric CNS tumor survivors.

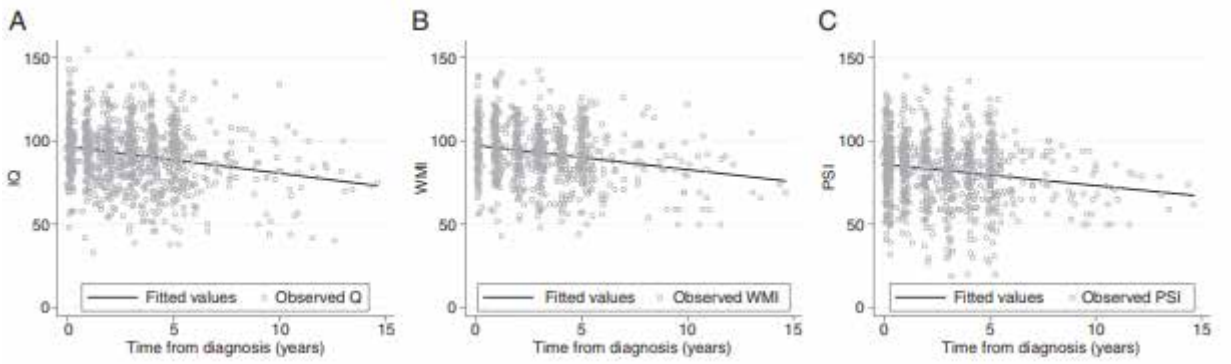

Figure. Mean trajectory and observed scores for intelligence (**A**), working memory (**B**), and processing speed (**C**) among pediatric CNS tumor patients following CSI.

Brown AL, Sok P, Raghubar KP, Lupo PJ, Richard MA, Morrison AC, Yang JJ, Stewart CF, Okcu MF, Chintagumpala MM, Gajjar A, Kahalley LS, Conklin H, Scheurer ME. Genetic susceptibility to cognitive decline following craniospinal irradiation for pediatric central nervous system tumors. Neuro Oncol. 2023 Sep 5;25(9):1698-1708.

RECOMBINANT PROTEIN PRODUCTION & CHARACTERIZATION CORE (RE-ORGANIZED 2024)

The Recombinant Protein Production and Characterization Core (RPPCC) provides investigators with high quality purified recombinant proteins and cutting-edge biomolecular characterization to facilitate their research programs. The Core has extensive experience in expression and purification of recombinant proteins with services ranging from consultation on design and construction of expression vectors, protein overexpression in the baculovirus insect cell system, *E. coli* or mammalian cells, and purification of the expressed protein. Instrumentation and expertise for biophysical and molecular characterization of proteins is a parallel service that includes quality control to assure suitability for biochemical and structure analysis studies, folding and stability analysis, binding interactions, and assembly and oligomerization.

MAJOR EQUIPMENT

- GE Healthcare ÄKTA FPLC systems
- Bioreactors for large scale insect cell cultures
- Microfluidizer LM20 High Shear Fluid Processor
- Thermo MaxQ HP incubator and refrigerated console shaker for multi-liter scale bacteria cultures
- Beckman Analytical Ultracentrifugation.
- Malvern Auto-Isothermal Titration Calorimetry (ITC).
- Forte Bío Octet Bio-Layer Interferometry.
- Optima L-90 Ultracentrifuge
- Avanti high-speed preparative centrifuge
- Customized and Integrated Multi-Angle Light Scattering (MALS)-based Multi-detection System for SEC-MALS (New NIH S10 Shared Instrument Grant).
- AKTA FPLC systems

SERVICES

- Production & purification of monoclonal antibodies from existing hybridomas (up to gram-scale).
- Generation of recombinant baculovirus for protein production in insect cells.
- Overexpression of recombinant proteins in any of three systems below.
  - Insect cells (using baculovirus vectors)
  - *E. coli*
  - Mammalian cells (Expi293F)
- Purification of recombinant proteins of interest from overexpression systems.
- Analytical Ultracentrifugation for determination of protein molecular size, shape and oligomerization states
- Auto-Isothermal Titration Calorimetry (ITC) for determination of protein binding affinities and high throughput binding measurements
- Forte Bío Octet Bio-Layer Interferometry (BLI) for determination of binding kinetics and affinities
- Differential Scanning Fluorimetry (DSF) by high throughput PCR for protein stability buffer screens.
- Analysis of proteins and protein complexes by size exclusion chromatography-multi-angle light scattering (SEC-MALS). New NIH S10 shared instrument grant.
- Consultation and project design for recombinant protein expression, purification and molecular/biophysical characterization of proteins of interest.
- Training for unassisted use of protein characterization instruments.

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Atomic structure of the predominant GII.4 human norovirus capsid reveals novel stability and plasticity (Venkataram Prasad)

Human noroviruses (HuNoVs) cause sporadic and epidemic viral gastroenteritis worldwide. The GII.4 variants are responsible for most HuNoV infections, and GII.4 virus-like particles (VLPs) are being used in vaccine development. The atomic structure of the GII.4 capsid in the native T=3 state has not been determined. Here we present the GII.4 VLP structure with T=3 symmetry determined using X-ray crystallography and cryo-EM at 3.0 Å and 3.8 Å resolution, respectively, which reveals unanticipated novel features. A novel aspect in the crystal structure determined without imposing icosahedral symmetry is the remarkable adaptability of the capsid protein VP1 driven by the flexible hinge between the shell and the protruding domains. In both crystal and cryo-EM structures, VP1 adopts a stable conformation with the protruding domain resting on the shell domain, in contrast to the 'rising' conformation observed in recent cryo-EM structures of other GII.4 VLPs. Our studies further revealed that the resting state of VP1 dimer is stabilized by a divalent ion, and chelation using EDTA increases capsid diameter, exposing new hydrophobic and antigenic sites and suggesting a transition to the rising conformation. These novel insights into GII.4 capsid structure, stability, and antigen presentation may be useful for ongoing vaccine development.

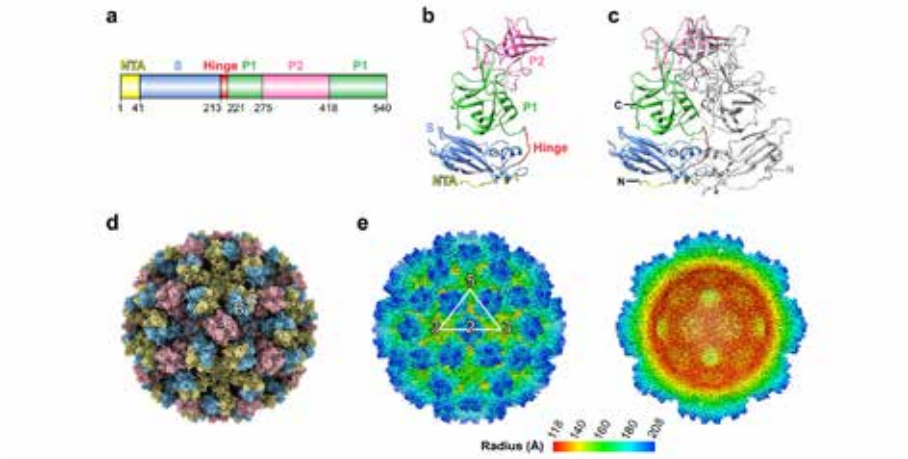

Figure 1. Crystal structure of GII.4 HOV VLP. (**a**) schematic VP1 primary structure colored by domain. (**b**) Ribbon representation of VP1 monomer. The NTA, S domain, hinge, P1 subdomain, and P2 subdomain are colored corresponding to the schematic **a**. (**c**) the VP1 dimeric formation. One subunit is colored as in **b**, and the other subunit is shown in gray. The N– and C– termini of the structure are labeled. (**d**) GII.4 HOV VLP structure viewed along the icosahedral twofold access. The subunit a, b, and c are colored yellow, blue, and pink. (**e**) the surface and cutaway views of a GII.4 crystal surface colored by radial distance showing an inner diameter of ~230 Å and an outer diameter of ~410 Å.

- The RPPCC expressed the VP1 and VP2 of GII.4 norovirus in the baculovirus system
- The RPPCC performed BLI (Bio-Layer Interferometry) using Octet (Fig 6d)

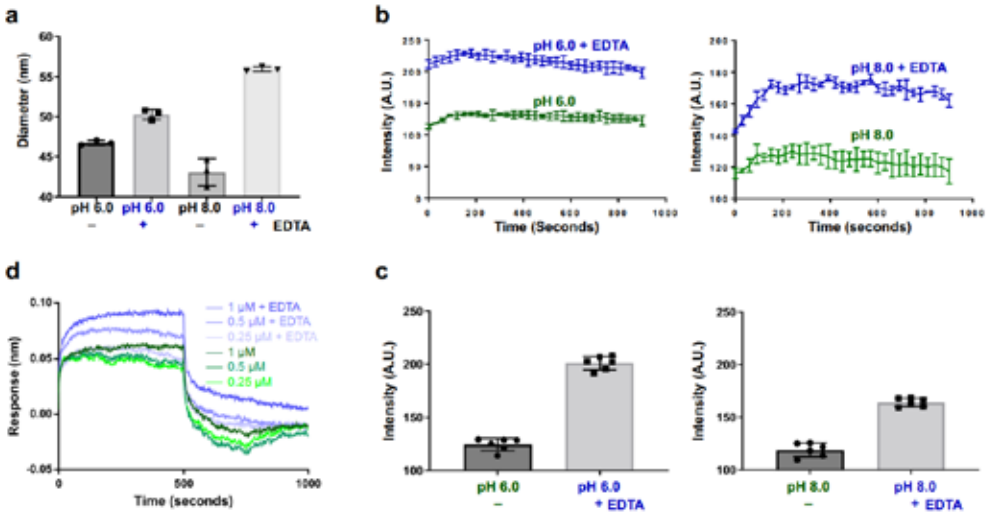

Fig. 6 Dynamic light scattering, Bis-ANS, and BLI binding assays. a DLS analysis shows the hydrodynamic radius increase upon removal of metal ions by chelation with EDTA at pH 6.0 and pH 8.0, indicating the rising of P domain above shell in the absence of ion at the dimeric interface. **b** Changes in bis-ANS binding in the absence or presence of EDTA show increased fluorescence intensity when VLPs are incubated with 20 mM EDTA, suggesting more hydrophobic surfaces of VLP bound with bis-ANS. **c** Stabilized fluorescence intensities measured during the last minute for each sample were averaged and presented as a bar graph. **d** BLI analysis of NORO-320 Fab and GII.4 HOV VLP shows that more VLPs bind to the immobilized Fab of GII.4 mAb NORO-320 in the presence of 20 mM EDTA, suggesting the exposure of mAb-binding epitope with EDTA-treatment. Data presented in each panel are means ± SE ($n = 3$ independent study repliates) are shown. Source data are provided.

Liya Hu, Wilhelm Salmen, Rong Chen, Yi Zhou, Frederick Neill, James E. Crowe Jr., Robert L. Atmar, Mary K. Estes & B. V. Venkataram Prasad. Atomic structure of the predominant GII.4 human norovirus capsid reveals novel stability and plasticity. Nature Communications. 2022. 13:1241

RNA *IN SITU* HYBRIDIZATION

The Core performs non-radioactive RNA *in situ* hybridization (ISH) on tissue sections. A unique high-throughput technology developed by the Core is used to determine gene expression patterns on sections, with an emphasis on tissues from rodent experimental models. The Core provides a full service that includes collection of rodent tissue specimens, preparation of frozen sections, preparation of RNA probes from customer templates, high-throughput ISH and documentation and quantification of expression patterns by microscopy.

MAJOR EQUIPMENT

- Tecan EVO Genepaint robot (for automated RNA *in situ* hybridization)
- Two cryostats (Leica)
- Autostainer (Leica)
- Automated coverslipper
- Zeiss Axio Scan.Z1 slide scanner (brightfield and fluorescence)

SERVICES

- RNA ISH on tissue sections–brightfield or fluorescence development
- Tissue processing and embedding (frozen tissue)
- Sectioning (frozen tissue)
- Preparation of non-radioactive RNA *in situ* probes (DIG- or FITC-labeled)
- Imaging (slide scanner–automated tiled images)
- Automated quantification of *in situ* hybridization signals, brightfield only (gene expression levels and cell counts)

CORE LEADERSHIP

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Pontine nuclei (PN) subtypes have different vulnerabilities to Atoh1 hypomorphic mutation.

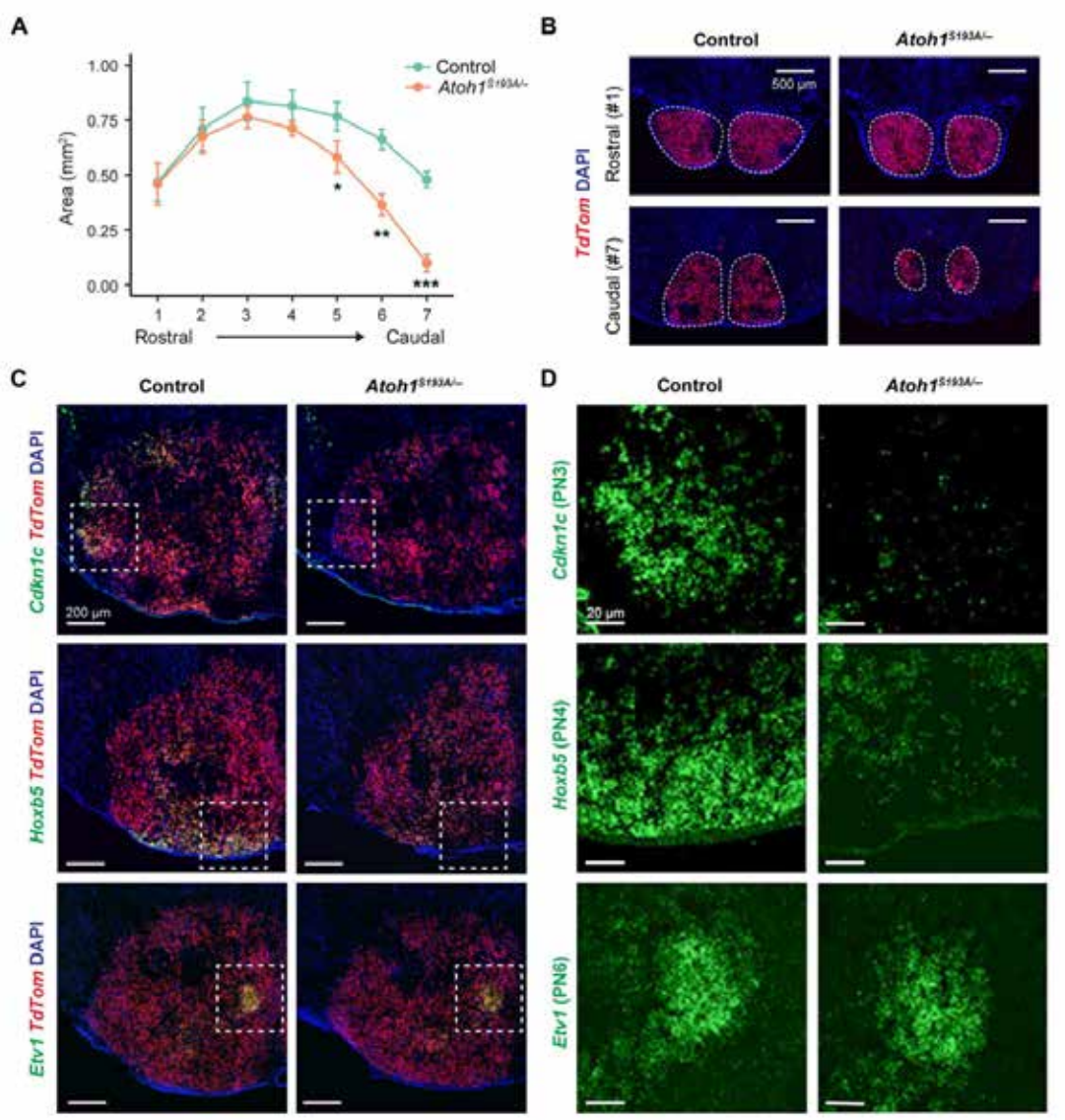


Figure. (**A**) The size of the PN was determined by the areas across seven coronal sections (*n* = 3 per genotype). Data are presented as means ± SD. **P* <0.05; ***P* <0.01; ****P* <0.001 by two-tailed unpaired *t* test. (**B**) Representative RNA ISH images for the most rostral (**top**) and the most caudal (**bottom**) sections from control (**left**) and *Atoh*$^{1S193A/-}$ (**right**) mice at P5. The PN neurons were labeled with *TdTomato* probes. The nuclei were stained with DAPI. The dashed line encloses the area of the PN. Scale bars, 500 μm. (**C**) RNA ISH on control (**left**) and *Atoh*$^{1S193A/}$ (**right**) mice at P5 using *Cdkn1c* (**top**), *Hoxb5* (**middle**), and *Etv1* (**bottom**) probes. PN neurons were labeled with *TdTom* probes. The nuclei were stained with DAPI. The box denotes the area shown in (**D**). Scale bars, 200 μm. (**D**) The zoom-in view of PN from the boxes in (**C**). The expression of *Cdkn1c* (**top**), *Hoxb5* (**middle**), and *Etv1* (**bottom**) were shown in green. Scale bars, 20 μm.

Wu SR, Butts JC, Caudill MS, Revelli JP, Dhindsa RS, Durham MA, Zoghbi HY. Atoh1 drives the heterogeneity of the pontine nuclei neurons and promotes their differentiation. Sci Adv. 2023 Jun 30;9(26):eadg1671. doi: 10.1126/sciadv.adg1671. Epub 2023 Jun 30. PMID: 37390208; PMCID: PMC10313176.

SINGLE CELL GENOMICS CORE

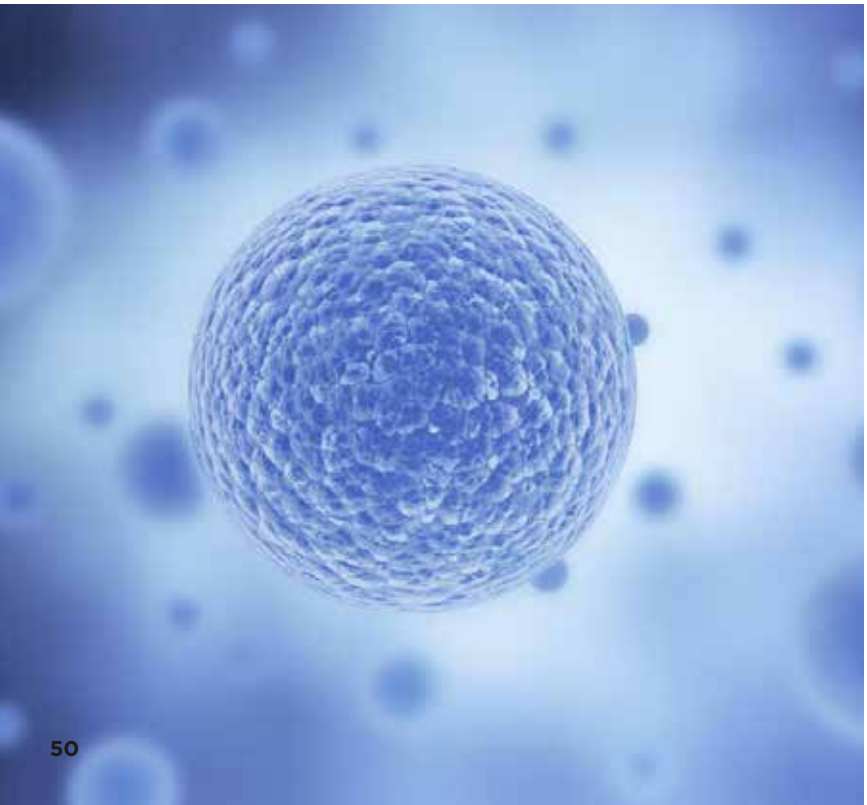
Single Cell Genomics Core (SCGC) provides services to conduct high throughput genome profiling, including DNA, RNA, and Epigenetics profiling, on a single cell. We provide cost-effective and time-efficient access to cutting-edge genomic technologies and expert assistance with experimental design and sample preparation for 10X genomics single cell library preparation. We coordinate with the Genomic and RNA Profiling (GARP) core for sequencing of single cell libraries on the latest generation Illumina instrument.

MAJOR EQUIPMENT

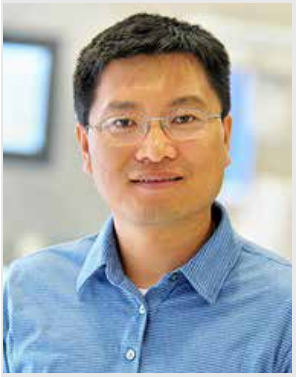
- **10x Genomics Chromium:** Droplet based system capable of profiling the transcriptome of up to 10,000 cells.
- **10x Genomics Chromium X:** Advanced hardware for all single cell assays featuring high-throughput capability
- **10x Genomics Connect:** High performance liquid handler facilitating single cell library from cell/nuclei.
- **Pala Cell sorter:** Benchtop sorter designed for single cell isolation.
- **10X Genomics Xenium:** Droplet-based spatial gene expression profiling platform in tissue at the single cell resolution.
- **Vizgen Merscope**: Advanced single cell genomics platform, designed for spatial transcriptomic profiling.

SERVICES

- **Single cell capture and 3' RNAseq**: Provide service for single cell capture and 3' RNAseq using chromium from 10x Genomics and ICEll8 from Takara.
- **Single cell capture and V(D)J/5' RNAseq**: Provide service for single cell capture, VDJ profiling and 5' RNAseq using 10x Genomics.
- **Single cell capture and ATAC-seq**: Provide service for single nuclei capture and ATACseq using 10x Genomics.
- **Single cell Multiome-seq:** Provide service for performing single cell RNA-seq and ATAC-seq on the same cell using 10x Genomics.
- **Single cell spatial transciptomic profiling**: Vizgen Merscope platform
- **Single cell spatial transciptomic profiling**: 10x Genomics Xenium platform



CORE LEADERSHIP



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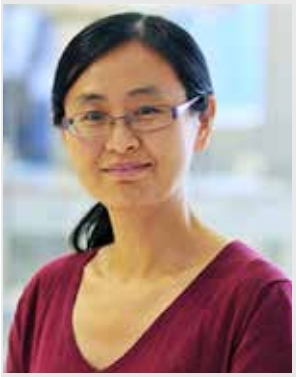

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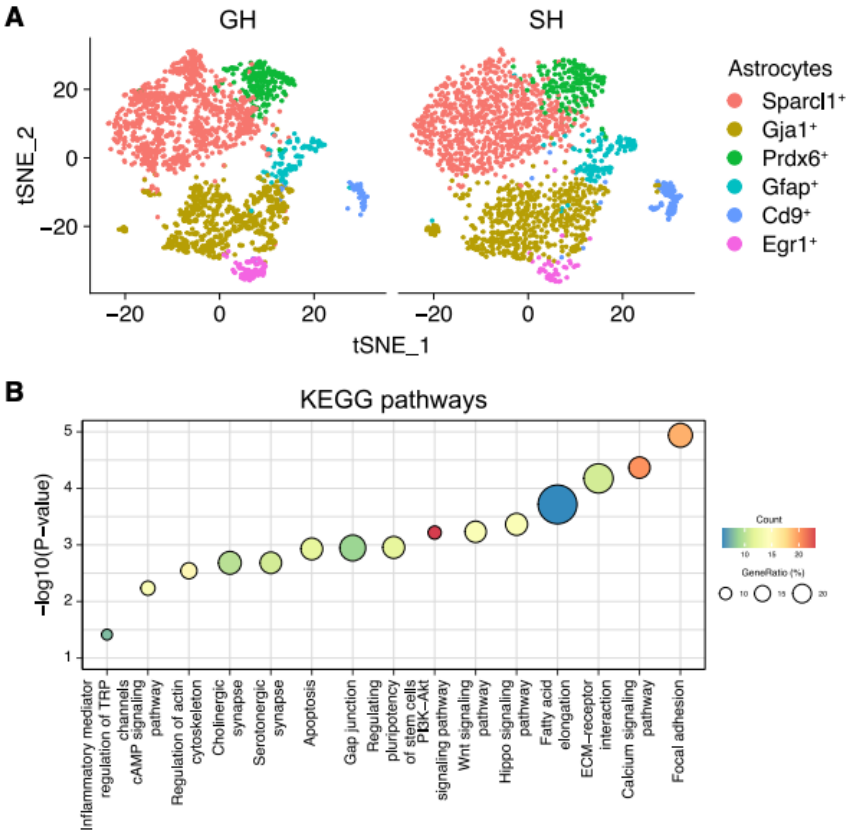

Figure. Single-Cell RNA-Seq analysis of astrocytes after social deprivation. TRPA1 expression is increased in astrocytes after social deprivation. (**A**) Serut analysis of single-cell RNA-seq (scRNA-seq) of hippocampal astrocytes from a pair of GH and SH cohorts. (**B**) KEGG pathway analysis of differentially expressed gene (DEG) between GH and SH cohorts (cutoff for DEGs, adjusted *P* <1015, average log2 fold change >2).

Yi-Ting Cheng, Junsung Woo, Estefania Luna-Figueroa, Ehson Maleki, Akdes Serin Harmanci, Benjamin Deneen. Neuron 2023 111, 1301–1315. Social deprivation induces astrocytic TRPA1-GABA suppression of hippocampal circuits.

ZEBRAFISH CORE

The Zebrafish Core provides expertise and equipment to support your zebrafish experiments. This includes projects to knockdown or knockout gene expression in zebrafish, generation of transgenic zebrafish to monitor expression of a gene of interest or to mark a cell population of interest and watch cell proliferation and differentiation in live embryos. We can also help to analyze phenotypes of mutant zebrafish. We can assist in preparing zebrafish for experiments requiring live imaging, histology, next generation sequencing or mass spectrometry. We can also help you design and execute a chemical screen to identify small molecules that cause or rescue a phenotype of interest in zebrafish embryos. For those who want a more hands-on experience, we provide basic training in zebrafish handling, breeding, embryo care, genotyping, anesthesia, euthanasia, and other techniques pertaining to zebrafish. If you are interested in using zebrafish as a model to answer your research question, but do not want to get your hands wet, then contact us.

MAJOR EQUIPMENT

- Harvard Instruments pressure injection system, Narishige micromanipulators, Flaming/Brown micropipette puller
- Leica brightfield and fluorescent dissecting microscopes
- DanioVision chamber for behavior analysis
- Loligo swim tunnel & respirometer for metabolic/cardiac phenotyping
- BioRad CFX Opus Touch real-time PCR instrument for genotyping
- Liquid nitrogen freezer for storing cryopreserved sperm

SERVICES

Transgenics

- Generation of transgenic zebrafish
- Screening transgenic zebrafish

CRISPR Genome Editing

- Guide RNA testing in zebrafish embryos
- Generation of mutant zebrafish
- Genotyping using high-resolution melting curve analysis, Sanger sequencing

Cryopreservation and Embryology

- Zebrafish sperm cryopreservation
- Zebrafish in vitro fertilization
- Strain rederivation
- Colony expansion
- Strain import and maintenance

PROJECTS OF NOTE & PUBLICATIONS

Transgenics and CRISPR Genome Editing

- Collaboration with 2 research labs on new genetic models
- Collaboration to generate and characterize phenotype of soga3a and soga3b mutants and overexpress human soga3 disease-causing variants in zebrafish. Resulted in figure for publication provided to Yamamoto lab (manuscript in progress).

Cryopreservation and Embryology

- Collaboration and cryopreservation of 30+ distinct genetic lines
- Collaboration with 2 research labs on embryological chemical exposure, fixation, and imaging
- High Throughput Screening Collaboration with the Integrated Microscopy Core (Mancini Lab) . Screening of Tg(5xERE:GFP) zebrafish embryos to identify chemicals that act as nuclear estrogen receptor agonists *in vivo* and visualize tissues in which they are active. PMID 38169792

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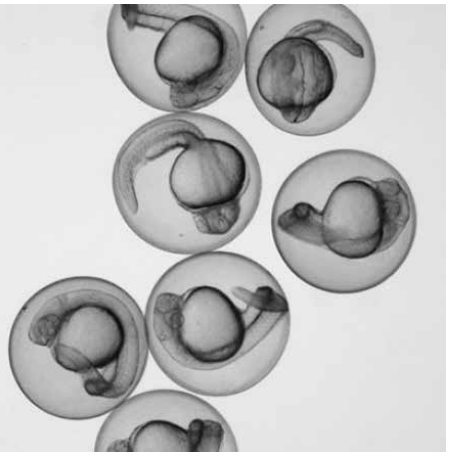
Using Zebrafish in Your Research

Zebrafish are a powerful model system to study human development and disease. Zebrafish have several advantages: ability to rapidly generate targeted mutations; external fertilization and development of embryos provide unparallel access to cells and tissues for live imaging; high fertility of adults provides a cost-effective method to generate and test large numbers of embryos in experiments; cost-effective to perform unbiased genetic and chemical screens for a wide range of phenotypes including abnormal behavior, gene expression and anatomic development. In addition, zebrafish can be housed in high densities, maximizing animal housing space.

Adult zebrafish



Zebrafish embryos

State-of-the-art zebrafish facility in Center for Comparative Medicine

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Baylor St. Luke's
Medical Center


Baylor St. Luke's Medical Center

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Baylor College of Medicine

To learn more about Core labs, scan the QR code using your SmartPhone camera.

GC109991