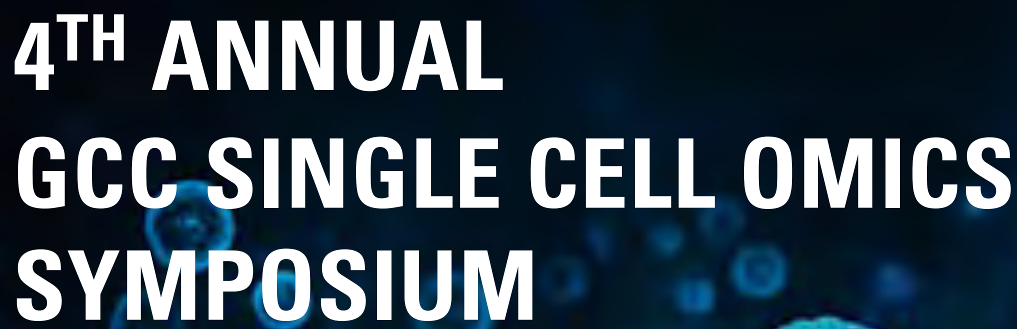

OCT. 18, 2023

HOUSTON, TEXAS

Gulf Coast Consortia

QUANTITATIVE BIOMEDICAL SCIENCES

The Gulf Coast Consortia (GCC), located in Houston, Texas, is a dynamic, multi-institution collaboration of basic and translational scientists, researchers, clinicians, and students in the quantitative biomedical sciences, who benefit from joint training programs, topic-focused research consortia, shared facilities and equipment, and exchange of scientific knowledge. Working together, GCC member institutions provide a cutting-edge collaborative training environment and research infrastructure beyond the capability of any single institution. GCC research consortia gather interested faculty around research foci within the quantitative biomedical sciences, and currently include Antimicrobial Resistance, Cellular and Molecular Biophysics, Innovative Drug Discovery and Development, Immunology, Mental Health Research, Single Cell Omics, and Translational Pain Research. GCC training programs currently focus on Biomedical Informatics, Computational Cancer Biology, Molecular Biophysics, Pharmacological Sciences, Precision Environmental Health Sciences and Antimicrobial Resistance. Current members include Baylor College of Medicine, Rice University, University of Houston, The University of Texas Health Science Center at Houston, The University of Texas Medical Branch at Galveston, The University of Texas M. D. Anderson Cancer Center, The Institute of Biosciences and Technology of Texas A&M Health Science Center and Houston Methodist Research Institute.

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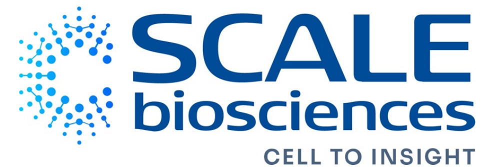


Agenda

9:00am	Welcome **Suzanne Tomlinson**, Gulf Coast Consortia **Rui Chen,** Baylor College of Medicine
Moderators:	Nicholas Navin, MD Anderson Cancer Center Naiju Thomas, University of Texas Medical Branch Galveston
9:10-9:50	**Keynote Presentation** *Dissecting Human Gliomas by Single-cell Genomics* **Mario Suvà**, Harvard University
9:50-10:20	Vendor Session-Pre Function and Event Hall
Session 1:	Single Cell Genomics in Cancer
10:20-10:40	*Dissecting Cancer Genetic and Microenvironment Factors Via Single-Cell Data Science* **Ken Chen**, MD Anderson Cancer Center
10:40-11:00	*Single Cell Insights into the Tumor Microenvironment* **Linghua Wang**, MD Anderson Cancer Center
11:00-11:15	*Tunable Tissue Engineered Model for 3D Culture and Single-Cell Proteomics Investigations of Ewing Sarcoma* **Jocelyn Baker,** Rice University
11:15-11:50	Lighting poster talks
11:50-2:00	Lunch and Poster Session-Event Hall 11:50-12:30 Lunch 12:30-2:00 Posters
Moderators:	Kurt Zhang, Texas A&M Institute of BioSciences and Technology Yiyun Lin, MD Anderson Cancer Center
2:00-2:40	**Keynote Presentation** *scONE-seq: A Versatile Single-cell Multi-omics Method for Simultaneous Dissection of Phenotype and Genotype Heterogeneity from Frozen Tumors* **Angela Wu**, Hong Kong University of Science and Technology
Session 2:	Single-Cell Analysis
2:40-3:00	*Quantitively Inferring Cellular Dynamics by Deep Learning* **Guangyu Wang**, Houston Methodist Research Institute
3:00-3:20	*Cellular Metabolism Modeling Using Fluorescence Lifetime Imaging Microscopy* **Jing Li,** Texas A&M Institute of BioSciences and Technology
3:20-3:35	*Using Single Cell Technologies to Uncover Key Characteristics in Natural Killer Antibody-Dependent Cellular Cytotoxicity* **Melisa Montalvo**, Univeristy of Houston
3:35-4:05	Networking Break

Agenda

Session 3:	Emerging Technologies
Moderators:	Guy Nir, University of Texas Medical Branch, Galveston Lei Yang, MD Anderson Cancer Center
4:05-4:25	*Characterization of Cancer Evolution Landscape Based on Accurate Detection of Somatic Mutations in Single Tumor Cells* **Chenghang Zong**, Baylor College of Medicine
4:25-4:45	*Deep and Scalable Single-Cell Analysis with Compression Sequencing* **Mingjie Dai**, Rice University
4:45-5:00	*Cytosnubar--A Simple Oligonucleotide-Based Method for Multiplexing Single-Cell Transcriptomics* **Rui Ye**, MD Anderson Cancer Center
5:00 pm	Closing Remarks, Fan Favorite Poster winners announced, Sponsor Card Drawing, and Reception **Guy Nir**, University of Texas Medical Branch, Galveston

Jocelyn (Jocie) Baker
PhD Student and Researcher
Rice University

Tunable Tissue Engineered Model for 3D Culture and Single-Cell Proteomics Investigations of Ewing Sarcoma

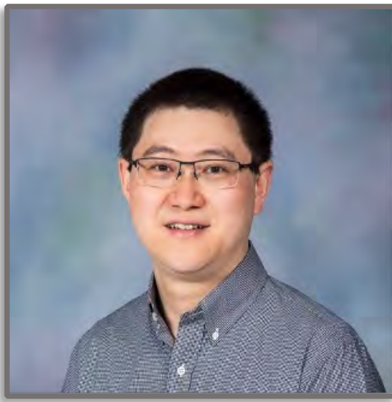
Jocelyn (Jocie) Baker is a current Ph.D. student and researcher in the department of Bioengineering at Rice University. She earned her bachelor's of science in bioengineering from the University of Pittsburgh in 2020 where she was a research fellow in the University of Pittsburgh Medical Center's Plastic Surgery Department. As an undergraduate researcher, Jocie was advised by Drs. Kacey G. Marra and Mario G. Solari and utilized tissue engineering approaches to investigate improved treatments for peripheral nerve injuries. Jocie continues to utilize tissue engineering as well as single-cell proteomics approaches in her graduate research projects at Rice where she is advised by Dr. Julea Vlassakis in the Microtechnologies Laboratory for Pediatric Oncology. Her current projects aim to develop in-vivo-representative, single-cell cancer research tools and methods for use in gaining a better understanding of metastatic pathways in Ewing Sarcoma which can be targeted for improved clinical outcomes and quality of life for Ewing sarcoma and other cancer patients.

Selected Abstract

Ken Chen, PhD
Professor
Bioinformatics and Computational Biology
MD Anderson Cancer Center

Dissecting Cancer Genetic and Microenvironment Factors Via Single-Cell Data Science

Dr. Chen obtained B. Eng. from Tsinghua University (Beijing) and Ph.D. in Electrical and Computer Engineering from University of Illinois at Urbana-Champaign. He is currently a full professor in the department of Bioinformatics and Computational Biology at the University of Texas MD Anderson cancer center. His primary interest is to develop computational methods to analyze and interpret high-throughput human genetic and clinical data towards understanding the evolution of cancer as a consequence of genetics and environment and identifying molecular targets useful for cancer diagnosis and therapeutics. Among the computational tools he developed, BreakDancer, VarScan and Monovar have been widely used for characterizing genomes and transcriptomes of tumor tissues and single cells.



Mingjie Dai, PhD
Assistant Professor
Bioengineering
Rice University
Deep and Scalable Single-Cell Analysis with Compression Sequencing

Mingjie Dai is an Assistant Professor of Bioengineering, and a technology developer in DNA nanotechnology, super-resolution microscopy, and high-throughput sequencing. Prior to joining Rice, he was a Systems Biology Department Fellow at Harvard Medical School and a Technology Development Fellow at the Wyss Institute for Biologically Inspired Engineering at Harvard. He has developed DNA-PAINT based super-resolution fluorescence microscopy methods capable of observing and tagging single molecules with high sensitivity and spatial resolution, next-generation sequencing based methods for scalable and high-sensitivity viral diagnostics, and functional DNA nanostructures for high-throughput single molecule biophysical studies. The molecular tools and microscopy methods developed in his work have broad applications in basic biomedical research and clinical use, from understanding the underlying cause and progression of disease, to sensitive and scalable viral diagnostics.

Dai earned his B.A. and M.Sci. in Physics from the University of Cambridge, U.K. in 2010, and his Ph.D. in Biophysics from Harvard University in 2016. He has published more than 15 peer-reviewed publications in journals including Nature, Science, Nature Methods, Nature Chemistry, and Nature Nanotechnology. His technology development efforts also resulted in more than 5 patents or provisional applications.

His research is supported by a CPRIT First-Time, Tenure-Track Faculty grant (2022), and an NIH Pathway to Independence (K99/R00) award (2021). He was a Systems Biology Department Fellow at Harvard Medical School (2017), an HHMI International Student Research Fellow (2012), and a Gold Medalist and Einstein Centennial Prize winner at the International Physics Olympiad (2005).

Jing Li, PhD
Postdoctoral Research Associate
Institute of Biosciences and Technology (IBT), Texas A&M University Health Science Center
Cellular Metabolism Modeling Using Fluorescence Lifetime Imaging Microscopy

Jing Li is a postdoctoral researcher at IBT, Texas A&M University Health Science Center. He received a Ph.D. in Biomedical Engineering from Purdue University before starting the position at IBT. His previous work resulted in several publications including topics in single cell discrete, mechano-dynamic models that focused on intracellular cytoskeletal dynamics during cell morphogenesis. The modeling components include cytoskeletal proteins such as actin filaments and microtubules. He has been proactively pursing research with the goal of developing multiscale model for single and collective cell dynamics, which also requires integrative data analysis across various spatiotemporal scales. He is currently committed to single cell spatial transcriptomics study which involves the development of an innovative mapping technique to understand patterning of cardiac progenitor cells during early embryonic stages in mice. He has started serving as a steering committee member at the Gulf Coast Consortia (GCC), for the GCC Single Cell Omics Scholars Program.

Melisa J. Montalvo
Doctoral Candidate
Biomolecular Engineering
University of Houston
Using Single Cell Technologies to Uncover Key Characteristics in Natural Killer Antibody-Dependent Cellular Cytotoxicity

Melisa J. Montalvo is a doctoral candidate in the William A. Brookshire Chemical & Biomolecular Engineering Department at the University of Houston, under the guidance of Dr. Navin Varadarajan. She received her bachelor's degree in chemical and Biological Engineering from the University of Alabama with honors. She was awarded the Graduate Fellowship Scholarship in Chemical Engineering by the UH Foundation three years in a row and has contributed substantially to numerous publications. Her research focuses on using single cell technologies to uncover the intricacies of T cell and NK cell cytotoxicity.

Selected Abstract

Mario L. Suvà, MD, PhD
Associate Professor, Pathology
Massachusetts General Hospital and
Harvard Medical School
Institute Member at the Broad Institute of
MIT and Harvard
Dissecting Human Gliomas by Single-cell Genomics

Mario Suvà is a physician-scientist in the Department of Pathology at Massachusetts General Hospital (MGH) and at the Broad Institute of MIT and Harvard. Suvà's expertise is in neuro-oncology, single-cell genomics and chromatin analysis.

Suvà's laboratory focuses on the biology of brain tumors, both in adults and children. A particular effort of the laboratory is on dissecting the heterogeneity of diffuse gliomas and relating transcriptional and genetic programs of individual cancer cells. Suvà directed landmark studies characterizing glioblastoma, oligodendroglioma, astrocytoma, pediatric gliomas and medulloblastoma with single-cell genomic technologies, shedding light on tumor heterogeneity, tumor classification, glioma cell lineages, cancer stem cell programs, tumor evolution and the composition of the tumor microenvironment.

Suvà obtained his Ph.D. in Lausanne, Switzerland, studying cancer stem cells in gliomas and sarcomas. He earned his M.D. from the University of Lausanne and his certification in Neuropathology from the Swiss Medical Association. He did his post-doctoral research at MGH and the Broad Institute, applying chromatin analysis and functional approaches to identify master regulators of glioma stem cell programs.

Keynote presenter

Guangyu Wang, PhD
Assistant Professor, Cardiovascular Sciences
Houston Methodist Research Institute
Quantitively Inferring Cellular Dynamics by Deep Learning

Guangyu Wang received his PhD in Bioinformatics in Beijing institute of genomics, Chinese academy of sciences. After graduated, he came to Houston Methodist and Harvard Medical School for postdoc training. In 2021, he started his lab at Houston Methodist. His lab is focusing on applying computational approaches to investigate the regulation mechanism for developmental lineages and cellular dynamics. His studies were published on Nature, Nature Biotechnology, Nature Commination, and Genome Biology etc. His lab is supported by NIH, NASA, CIPRIT, and Houston Methodist.

Linghua Wang, MD, PhD
Associate Professor
Computational Biology
MD Anderson Cancer Center
Single Cell Insights into the Tumor Microenvironment

Dr. Linghua Wang is a tenured Associate Professor in the Department of Genomic Medicine at MD Anderson Cancer Center. She earned her MD in Clinical Medicine and her PhD in Cancer Genomics. Dr. Wang has extensive expertise in computational biology, cancer genomics and immuno-oncology. Her group specializes in deep profiling of cellular and molecular heterogeneity, phenotypic plasticity, and the evolution of tumor cells and the tumor microenvironment, employing integrative single-cell and spatial omics approaches. Dr. Wang has a distinguished record of research productivity, having authored >100 publications. Her groundbreaking studies have revolutionized our understanding of tumor cell heterogeneity, evolution, and immune microenvironment interactions. She actively collaborates with experts both nationally and internationally, harnessing data science in the fight against cancer.

Angela Wu, PhD
Associate Professor
Division of Life Science
Department of Chemical and Biological Engineering
Hong Kong University of Science and Technology

scONE-seq: A Versatile Single-cell Multi-omics Method for Simultaneous Dissection of Phenotype and Genotype Heterogeneity from Frozen Tumors

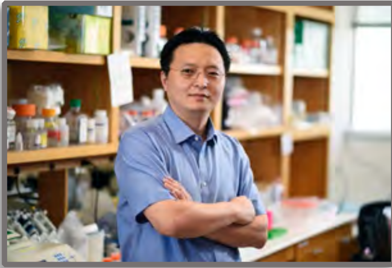
Angela Ruohao Wu is an associate professor in the Division of Life Science and the Department of Chemical and Biological Engineering at the Hong Kong University of Science and Technology. She completed her Ph.D. and post-doctoral training in Bioengineering at Stanford University, and soon after that co-founded Agenovir Corporation, a genome editing-based antiviral therapeutics company that was ultimately acquired by Vir Biotechnologies. Angela is one of the earliest scientists to work in single cell genomics, and she pioneered the field of microfluidic chromatin immunoprecipitation (ChIP). Her current research focuses on using genomics and microfluidics to address complex biological questions, as well as applying genomics in the clinic. Angela's interdisciplinary work has been recognized for bridging important gaps between microfluidics and biology; she was named one of MIT Technology Review Innovators under 35 Asia; a World Economic Forum Young Scientist, and an Outstanding Young Faculty by IEEE EMBS (Micro and Nanotechnology in Medicine).

Rui Ye, BS, MPH
Graduate Student
University of Texas MD Anderson Cancer Center
UTHealth Graduate School of Biomedical Sciences

Cytosnubar--A Simple Oligonucleotide-Based Method for Multiplexing Single-Cell Transcriptomics

Rui Ye received his B.S. degree in healthcare management from Capital Medical University in Beijing, China. Then he went to Yale university for his master's degree in public health. His is currently a graduate student co-mentored by Dr. Steven Lin and Dr. Nicholas Navin at the University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences (GSBS). His primary research interest is to develop novel single cell genomics technologies and apply them to better understand how inter- and intra-tumor heterogeneity contribute to tumorigenesis and therapeutic resistance. In particular, he is interested in identifying novel biomarkers and actionable targets to enhance the chemoradiation treatment efficacy.

Selected Abstract



Chenghang (Chuck) Zong, PhD
Assistant Professor
Molecular and Human Genetics
Baylor College of Medicine
Characterization of Cancer Evolution Landscape Based on Accurate Detection of Somatic Mutations in Single Tumor Cells

Dr. Zong's research focuses on the development of various single-cell analysis tools, in particular, single-cell whole genome sequencing methods for characterizing genome variations among individual cells. His lab developed the first single-cell WGA method to profile spontaneous DNA damage level and distribution in single cells. His lab also developed the first total-RNA based single-cell RNA-seq method (MATQ-seq). His lab further developed the MATQ-drop platform for high-throughput profiling of single cells and more importantly, transcriptome profiling of individual synaptosomes. Besides method development, his lab also focuses on tumorigenesis and tumor evolution processes and they are expanding the research into constructing brain connectome and understanding the roles of synapses in the context of neurological diseases.

SCO Fellows

The goal of this program is to identify and support up and coming scientists through scientific mentoring and networking opportunities with the greater Houston research community.

Rachel Sue Gilbert
Undergraduate Junior at Texas Southern University

As a senior chemistry major, my career goals are to complete my bachelor's and continue my education by getting my Ph.D. While I've completed research in biophysics, I've become extremely interested in reducing the carbon footprint. I also have an interest in the assessment of pollutants and organic chemicals in soil and wastewater, as well as the effects of the pollutants on the ecosystem.

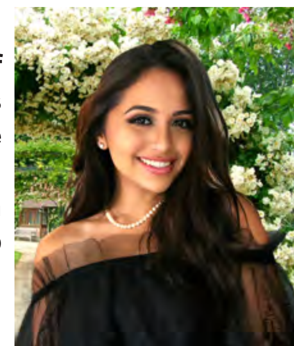
Naiyah McDaniel
Graduate Student at Prairie View A&M University

Naiyah McDaniel is a graduate student at Prairie View A&M University. She completed her bachelor's degree in chemistry in 2022 with the highest honors and is now pursuing a Master of Science in chemistry with a concentration in chemical biology. Her research interests include using nanoparticles synthesized using green methods and exploring their applications in improving human and environmental health. Her current research project involves using traditionally medicinal plants for nanoparticle synthesis and testing their efficienc in antioxidant, antibacterial, and cytotoxicity studies. After completing her master's degree, she hopes to begin her research career in industry and continue performing research to impact the population by discovering affordable and accessible methods to address human and environmental health concerns. She is excited to participate in the 2023-2024 Gulf Coast Consortia Single Cell Omics Fellowship class and looks forward to being exposed to new research areas and networking with Consortia members.

Kevin Nickl
Undergraduate Junior at University of St. Thomas

Kevin Nickl is currently an undergraduate student studying Cell and Molecular Biology at the University of St. Thomas in Houston, Texas. Upon completing his undergraduate degree, Kevin plans on pursuing his Ph.D. in Molecular Biology and pursuing a career in academic research and teaching. Kevin hopes to pursue research projects related to virology and disease during his career, as well as teach in those subjects.

Kevin Nickl finds the field of biology to be fascinating and is passionate about STEM education. Kevin hopes to leave a lasting impact on the scientific community through his research, as well as inspire the next generation of scientists and doctors through teaching.



Grace Orendorff
Undergraduate Junior at University of St. Thomas

Pushing the boundaries of what medicine can do for our society is a passion I share with every individual in the healthcare industry. I fell in love with chemistry as an undergrad and wish to pursue chemistry in graduate school. After obtaining my PhD in either organic or analytical chemistry, I wish to work for a hospital in clinical trials/lab research. Saving lives and helping people on a molecular level is my biggest drive in life.

Gracin Ray
Undergraduate Junior at Prairie View A&M University

My name is Gracin Ray, and I am a junior chemistry major from Prairie View A&M University. My research interests lie within chemical synthesis, pharmaceutical studies, biochemistry, and histology. After I graduate with my bachelor's in chemistry from Prairie View, I will be getting my Ph.D. in pharmacology or inorganic chemistry. I will use my degree to become a medical liaison and act as an advocate and educator for pharmaceutical companies and maintain relations with the public to present notable information on health advancements.

Poster presenters in alphabetical order

Rapid Fire presenters are noted in blue.

Presenter First Name	Presenter Last Name	Presenter Institution	Title of Submission	Poster #
Tuba	Aksoy	MD Anderson Cancer Center	Radiation Insult Mimics Early-Onset Alzheimer’s Disease by Dysregulating DNA Methylation and Gene Expression in Pyramidal Cells	1
Jessica	Alsing	University of Texas Medical Branch	Do Genomic Rearrangements Contribute to Glioblastoma Multiforme (GBM) Tumor Heterogeneity?	2
Sohini	Banerjee	Baylor College of Medicine	Delineating Cellular Differences Between Human Intestinal Enteroids from Infants and Adults Using Single Cell Rna-Seq Analysis	3
Kumaraswamy Naidu	Chitrala	University of Houston	Analysis of transcriptome level differences in Triple-negative breast cancer among the African American and White participants	4
Gabrielle	Dewson	University of Texas Medical Branch	Uncovering the Structural Rearrangements of the Philadelphia Chromosome	5
Rachel	Dittmar	MD Anderson Cancer Center	Using Single Cell DNA and RNA Sequencing in Post-mortem Tissues to Delineate Tumor Evolution in Metastatic Breast Cancer	6
Victoria	Flores	University of Texas Medical Branch	Elucidating The Role of Genome Organization in Salmonella Lifestyle Adaptation	7
Anat	Galis Vivante	University of Texas Medical Branch	Determining the Role of Rigidity Sensing on Genome Organization and Gene Expression	8
Shreyan	Gupta	Texas A&M University	Stochastic Transient Gene Silencing Reveals Key Insights on Cell-State Specific Gene Function	9
Haijing	Jin	MD Anderson Cancer Center	Development and Applications of a High-Fidelity Cancer Genome Simulator	10
Jean	Li	Baylor College of Medicine	Single-nuclei Multiomics Meta-analysis of Human Organoids and Fetal Retina Reveals Developmental Transcriptional and Epigenetic Differences	11
Jin	Li	Baylor College of Medicine	Integrative Multi-Omics Single Cell Atlas of the Human Retina V1.0	12
Qingnan	Liang	MD Anderson Cancer Center	Interpretable Spatial Gradient Analysis for Tumor Spatial Transcriptomics Data	13
Andi	Liu	University of Texas Health Science Center	Unraveling the Intercellular Communication Disruption and Key Pathways in Alzheimer's Disease: An Integrative Study of Single-nucleus Transcriptomes and Genetic Association	14
Atulya	Mandyam	Baylor College of Medicine	Comprehensive Single-cell Multiomics Study of the Developmental Stages of the Human Fetal Cornea	15

Poster presenters in alphabetical order | Rapid Fire presenters are noted in blue.

Presenter First Name	Presenter Last Name	Presenter Institution	Title of Submission	Poster #
Mariam	Mosaad	MD Anderson Cancer Center	Structural and Conformational Chromosomal Variations in Breast Cancer Identified with a Single Cell Hi-C and WGS Co-assay	16
Anna	Naglis	University of Texas Health Science Center	Long Non-Coding RNA (lncRNA) Expression is Upregulated in Microglia/Macrophages During Regeneration of Rods in Zebrafish Retina	17
Shion	Orikasa	University of Texas Health Science Center	Dissecting Intercellular Interactions in Developing Bones by Curio Seeker	18
Edgar	Ruiz Bello	Rice University	Microfluidic 2D Electrophoretic Separation to Identify Aberrant Protein Networks and Subunit Constituents	19
Udhaya Kumar	Siva Kumar	Baylor College of Medicine	Single-nuclei Multi-Omics Dissection of Exercise Effects in Human Skeletal Muscle	20
Gerda Cristal	Villalba Silva	Baylor College of Medicine	Molecular and Spatial Signatures of Mouse Trigeminal and Dorsal Root Ganglia Cells at Single-Cell Resolution	21
Kaile	Wang	MD Anderson Cancer Center	Archival Single Cell Genomics Reveals Persistent Subclones During DCIS Progression	22
Meng	Wang	Baylor College of Medicine	Comprehensive Characterization of Single-Cell Isoform in Mouse Retina with Long-Read RNA Sequencing	23
Qian	Xu	Texas A&M University	Role of Rspo3 in Estrogen-Mediated Sex-Difference: A Single Cell-Based Study.	24
Fangfang	Yan	MD Anderson Cancer Center	Single-Cell Multiomics Decodes Regulatory Programs for Mouse Secondary Palate Development	25
Yun	Yan	MD Anderson Cancer Center	Decoding the Archetypes and Eco-traits of Triple-Negative Breast Cancer in Response to Chemotherapy	26
Hanghui	Ye	MD Anderson Cancer Center	A Pan-Cancer Single-Cell Analysis of Intratumoral Copy Number Diversity and Evolution	27
Yun	Zhang	Baylor College of Medicine	Expansion of Trem2+CD11b+ Macrophages and Loss of SiglecF+ Pulmonary Tissue Macrophages in Vaping Associated Acute Lung Injury	28
Zhen	Zuo	Baylor College of Medicine	Single-nuclei Multiome Analysis of Human Fetal Retina	29

Poster 1

Radiation Insult Mimics Early-Onset Alzheimer's Disease by Dysregulating DNA Methylation and Gene Expression in Pyramidal Cells

Tuba Aksoy[1,2], Pavel Sumazin[4,7], Yue Lu[3], Mohammad Javad Najaf Panah[4,8], Miriam Zamorano[2,7], Thanh Lam[1,2], Wei Zhou[2], Ines Veselinovic[2], Joseph Duman[5], Waleed Gaber[4,8], Cobi Heijnen[2], David R Grosshans[2]

1. The University of Texas MD Anderson Cancer Center and UT Health Graduate School of Biomedical Sciences
2. The University of Texas MD Anderson Cancer Center / Department of Experimental Radiation Oncology
3. The University of Texas MD Anderson Cancer Center/ Department of Epigenetics and Molecular Carcinogenesis
4. Baylor College of Medicine/ Department of Pediatrics
5. Baylor College of Medicine/ Department of Neuroscience
6. Baylor College of Medicine/ Department of Pediatrics and Oncology
7. The University of Texas Health Science Center at Houston (8) Texas Children's Hospital / Department of Cancer and Hematology Center

ABSTRACT

Cranial radiation therapy plays an integral role in the treatment of brain tumors but can lead to progressive cognitive deficits in survivors. Despite this, the mechanism by which cranial radiation therapy leads to cognitive decline is poorly understood and few models are available. We sought to investigate epigenetic changes as a potential driver of persistent cellular dysfunction following radiation. Thirteen-week-old mice underwent whole-brain radiation at clinically relevant doses. We observed a deterioration of cognitive skills accompanied by dysregulation of DNA methylation and gene expression. While the observed molecular changes were most pronounced in pyramidal and endothelial cells in hippocampal CA1-3 regions, no specific brain cell types were lost following radiation. Instead, our analyses revealed that cranial radiation resulted in consistent dysregulation of key genes and pathways across cell types, as well as specific pyramidal-cell gene dysregulation that closely resembled early neurochemical alterations seen in Alzheimer's' Disease, including deficits in synaptic function. Moreover, radiation altered the DNA methylation states of regulatory regions in profiled cells, and these were significantly associated with the observed dysregulation of gene expression in each region. Overall, our results suggested that cranial radiation alters gene expression in the hippocampus and prefrontal cortex at least in part by dysregulating chromatin accessibility and induces cell-type specific pathologies that mimic early-onset Alzheimer's Disease.

Poster 2

Do Genomic Rearrangements Contribute to Glioblastoma Multiforme (GBM) Tumor Heterogeneity?

Alsing J[1], Nir G[2]

1. Department of Pharmacology and Toxicology, University of Texas Medical Branch
2. Department of Biochemistry and Molecular Biology, University of Texas Medical Branch

Corresponding author: Jessica Alsing, Department of Pharmacology and Toxicology, UTMB, 301 University Blvd., Galveston, Texas, E-mail: jealsing@UTMB.edu

Glioblastoma Multiforme (GBM) is the most common type of malignant primary brain tumor as well as one of the most aggressive, with an average patient survival time of around 15 months. With recent studies beginning to highlight the important role genome organization plays in cancers, it is unknown how this organization plays a role in the large degree of heterogeneity seen in GBM. Here, we aim to use super-resolution microscopy to elucidate rearrangements in the 3D organization of oncogenic loci in the genome of patient-derived glioma stem cells (GSCs) and how this may be contributing to tumor heterogeneity, as well as the increased expression of these oncogenes, at the single cell level. A DNA-FISH library of Oligopaint oligos for use in SMLM imaging was designed specific to the epidermal growth factor receptor (EGFR) locus, a gene which is known to be mutated and/or amplified in many GBM cases. Additionally, an RNA FISH Oligopaints library for EGFR mRNA transcripts was designed to visualize EGFR expression in the same single cells as DNA FISH. This will be done in normal microglia (HMC3) and astrocyte (HA) cells to serve as a controls, as well as in GSCs derived from patient GBM samples to identify structural changes that may be contributing to higher expression levels of EGFR. Preliminary images have been acquired for the entirety of the DNA FISH library in the control HMC3 cell line and cluster analysis has begun. We have been able to image both RNA and DNA FISH successfully on the same cells in widefield, and have been able to image a single step of the DNA FISH library in super-resolution. Experiments that combine RNA FISH widefield imaging with our protocol for tracing of the entire 2 Mb DNA FISH region in super-resolution are currently in progress. Our protocols for library design/amplification and SMLM imaging are shown to be working well in our control cell line (HMC3). This process will then be repeated on the patient-derived GSC lines and these results will be compared to the controls to identify any significant changes seen in the cancer cells. We hypothesize that the changes seen in individual glioma stem cells will not only correlate to the expression patterns of oncogenes, but will also allow us to identify tumor cell subpopulations that are known to occur in GBM.

Acknowledgements: This research is supported by the Cancer Prevention and Research Institute of Texas (CPRIT, grant ID: RR210018).

Poster 3

Delineating Cellular Differences Between Human Intestinal Enteroids from Infants and Adults Using Single Cell Rna-Seq Analysis

Sohini Banerjee, Tajhal D Patel, Victoria Bethanie Poplaski, Grace O. Adeniyi-Ipadeola, Cristian Coarfa, Sarah E Blutt, Mary K Estes, Sasirekha Ramani

Abstract

The cellular landscape and the physiological characteristics of the human gastrointestinal (GI) tract is dynamic during early infancy, changing in response to development, functional requirements and environmental exposures. Human intestinal enteroids (HIE) are physiologically relevant models of the human intestine. In previous work, we performed transcriptional analysis of jejunal HIEs using total RNA sequencing from infants and adults and identified transcriptional differences in pathways associated with RNA processing, ribonucleoprotein complex biogenesis, cell-cell adhesion, and immune responses. Functional validation studies also showed significant differences in cell differentiation and proliferation, barrier function and innate immune response to a poliovirus vaccine. Total RNA sequencing analysis does not allow elucidation of which intestinal cell types contribute to observed differences between infant and adult HIEs. The goal of the present study is to use single-cell RNA sequencing to explore the diversity of individual cell types in HIEs derived from children and adults, to quantitatively analyze and infer intercellular communication networks, and to obtain deeper insights into the differential responses of each cell type in differentiated HIEs.

Single cell transcriptional profiles were obtained from HIE lines established using surgical samples from one infant (J1005) and one adult (J11). 13445 cells passed standard quality control metrics for downstream analysis. UMAP clustering identified distinct clusters of cells for the infant and adult HIEs. Differential transcriptional profiles were observed for the infant and adult HIEs. Further analysis of the gene expression is being performed which will help predict signaling interactions between cellular populations in these lines. The present study will advance our fundamental knowledge of developmental differences between adult and infant HIEs and provide deeper understanding of intestinal maturation, disease susceptibility, and potential for development of therapeutics.

Poster 4

Analysis of Transcriptome Level Differences in Triple-Negative Breast Cancer Among the African American and White Participants

Kumaraswamy Naidu Chitrala[1], Inara Momin[1]

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Health disparities (HD) among the populations have long been an unresolved public health issue. Among the diseases where HD plays a key role, it is more seen in triple-negative breast cancer (TNBC) where survival and incidence of TNBC tumors in black women compared to white women. The reasons for this disparity are unknown. In this study, we assessed the differences in the transcriptome among African American (AA) (n=3) and White (n=3) participants by isolating the RNA from the samples. We also explored the transcriptome profile of AA (n=23) and white (n=19) using the datasets downloaded from the Gene Expression Omnibus (GEO) database (GSE142731). Quality control was performed using the tools CASAVA, and Qphred, alignment with the reference genome was performed using HISAT2, and TOPHAT2 followed by Visualization of mapped results using the Integrative Genomics Viewer. Differential gene expression (DEG) analysis was performed using DeSeq2. Single-cell level transcriptome profile analysis was performed using the single-cell atlas. Our results demonstrated that 228 genes were upregulated, and 100 genes were downregulated in AAs compared to whites at a significant p-value< 0.01 and p-value adjusted (padj) <0.01. Pathway enrichment analyses showed that both up-and downregulated genes were enriched in DNA damage repair and downstream signaling pathways. In conclusion, the identified gene expression profiles, pathways, and functional annotations may be useful in further studies on elucidating the disparities in BC that underlie among AAs and whites.

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Poster 5

Uncovering the Structural Rearrangements of the Philadelphia Chromosome

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Philadelphia-positive leukemia accounts for over 90% of Chronic Myeloid Leukemia (CML) patients and around 25% of Acute Lymphoblastic Leukemia (ALL). Philadelphia-positive leukemia is characterized by the translocation t(9;22)(q34;q11), which results in the oncogene BCR-ABL1 and a chromosome called the Philadelphia (Ph) chromosome (chr). In adults, Philadelphia-positive leukemia is a poor prognosis marker. While imatinib, a tyrosine kinase inhibitor (TKI), is the current front-line treatment for Philadelphia-positive leukemia, 20-30% of patients are initially non-responsive or will eventually gain resistance to the drug. A recent study by Fabian-Morales et al., 2022, linked inherent imatinib resistance to specific genome organization, mainly disordered chromatin domains. Genome organization is a highly complex process by which chromatin is segregated within the nucleus into specific domains, which are usually segregated by megabases of space and segregated by epigenetic marks, making stable translocations highly unfavorable. How translocations like the Philadelphia chromosome are stabilized has been historically understudied. Here we aim to examine how the Ph chromosome is stabilized through the similarity or differences of compartment states. This study aims to be the first to visualize an entire abnormal chromosome with high spatial and genomic resolution at the single-cell level. Using OligoSTORM, a super-resolution microscopy technique, we aim to image the entirety of the Ph chromosome at a nanoscale resolution. We designed an oligo library that traces the entire Ph chromosome at 100kb resolution. In addition to the DNA super-resolution trace, we have designed an RNA library to image a series of RNAs from the Ph chromosome on the same sample as the DNA trace, allowing us to connect the transcriptional data to the chromatin structure. We also submitted RNA-sequencing samples to identify any changes at the transcription level. We have successfully traced portions of the Ph chromosome, with plans to trace it in its entirety in the near future. We have preliminary data suggesting that chr9 and chr22 segregate close to each other in non-leukemia healthy cells. We have also proven that our library design and methodology work to achieve the primary 500kb resolution, with preliminary data showing the 100kb resolution is also achievable. Preliminary data suggests that chr9 and chr22 in cells, that don’t typically have a Ph chromosome, segregate within proximity to translocate successfully. The data also shows that our library design is capable of reaching nanoscale resolution by using 100kb steps to trace the Ph chromosome.

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Poster 6

Using Single Cell DNA and RNA Sequencing in Post-mortem Tissues to Delineate Tumor Evolution in Metastatic Breast Cancer.

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Metastasis is responsible for over 90% of cancer related deaths. This is especially true for metastatic breast cancer (MBC), which commonly spreads to the bones, liver, lungs, and brain. Despite this major clinical problem, the genomic alterations and transcriptional reprogramming required for dissemination and seeding of MBC cells remain understudied. Previously, difficulty obtaining tissue from matched primary tumor and metastatic sites for research purposes and a lack of adequate genomic resolution from bulk sequencing methods have made studying tumor dissemination challenging. Here, we propose to overcome these challenges using post-mortem tissue samples and by leveraging single cell DNA copy number variation and RNA-sequencing. Using these innovative tools and unique tissue samples, we are investigating genotypic and phenotypic alterations of metastatic cancer cells as they disseminate across multiple metastatic sites.

Our central hypothesis is that a metastatic phenotype is conferred by the combination of tumor-intrinsic genetic events and reprogramming of the tumor microenvironment to promote tumor cell dissemination to distant organ sites. To test this hypothesis, we are studying primary tumors and multiple matched metastatic sites from 20 patients with MBC. To obtain these tissues, we established the first-ever post-mortem tissue collection protocol at MD Anderson Cancer Center. This unique resource provides ample amounts of fresh tissue for single cell DNA and RNA sequencing.

Our preliminary data demonstrate that tissue collected post-mortem is of high quality and can be successfully used for both single cell DNA and RNA sequencing applications. We have found that cell viability, which is needed for high quality single cell RNA sequencing data from fresh tissues, varies across patients and organ sites. Cells from certain sites, such as the breast and pleural effusion, have higher viability compared to other sites, like the liver and brain. Viability also correlates with how quickly tissue is processed after the patient has expired. These findings have prompted us to optimize our tissue collection protocol to harvest tissue less than six hours after death.

We are currently using single-cell DNA copy number profiles to reconstruct clonal lineages of tumor dissemination. We are also using single-cell RNA sequencing to identify genes undergoing transcriptional reprogramming in tumor cells and cells within the surrounding tumor microenvironment, such as cancer associated fibroblasts, tumor associated endothelial cells, and immune cells. Using these strategies, we expect to uncover novel interactions between tumor cells and their microenvironment that can be exploited for therapeutic intervention. We also anticipate identifying genomic alterations that promote tumor cell dissemination and metastasis. Completing this work has high potential to improve our understanding of metastasis and may lead to new drug targets that could prevent metastasis to vital organs in patients with MBC.

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Poster 7

Elucidating The Role of Genome Organization in *Salmonella* Lifestyle Adaptation

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Salmonella Typhimurium is a bacterial pathogen that can infect a wide range of hosts including humans and livestock. Earlier work has shown that environmental factors such as pH or osmolarity affect which infective lifestyle *Salmonella* expresses. There are two types of infection lifestyles, active or dormant. An active Salmonella infection is consisted of planktonic cells found in the intestinal epithelium and characterized by symptoms within the host. An example of a dormant infection is a biofilm within the host. Bacteria form biofilms, which are multicellular communities made up of cellulose, proteins, and extracellular DNA. Changes in environmental pH and osmolality have also been shown to cause widespread transcriptional changes. Among these differentially expressed genes is *ssrA* and its cognate *ssrB,* which has been found to act as the lifestyle switch for Typhimurium. When *ssrB* is phosphorylated, it will depress H-NS, a nucleoid associated protein, at the site of virulence genes needed to survive intercellularly. When *ssrB* is unphosphorylated, the bacteria will adopt a biofilm lifestyle. The unphosphorylated *ssrB* upregulates *csgD*, which is the biofilm master regulator. Such differences in transcription between the two lifestyles lead us to investigate how the genome is altered due to environmental stimuli. To visualize the entire genome, we used sequential OligoSTORM (STochastic Optical Reconstruction Microscopy) techniques. This super resolution approach allows for the determination of genome folding at both high genomic and spatial resolution. The entire chromosome was labelled with oligonucleotide probes that correspond to specific genomic regions. With subsequent rounds of imaging, the entire chromosome is traced and then reconstructed into high-resolution images of the entire *Salmonella* genome. Preliminary data show that both virulence and biofilm genes are near each other, but do not interact in the neutral state. This project is the first to trace a whole chromosome (and in fact, genome) with super-resolution microscopy and demonstrate whether various genes interact with each other.

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Determining the Role of Rigidity Sensing on Genome Organization and Gene Expression

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The genome organization in the nucleus is crucial for cellular functions such as transcription and gene regulation. Abnormal folding of chromosomes can cause developmental defects and diseases, such as cancer. A change in the cellular state often requires reprogramming of genomic functions, such as transcription. Thus, chromosomes may be required to refold for transcription to proceed. Changing the cellular state is often triggered by external cues. However, whether the 3D structure of the genome is critical for properly responding to external cues to facilitate a change in the cellular state is unknown.

The external cues arise from the extracellular matrix (ECM) surrounding the cells 8. It provides various mechanical/physical cues to the cells that are important for cellular function. In particular, the ECM/surface rigidity is critical for many cellular processes, such as cell migration, differentiation, proliferation, apoptosis, and plays a vital role in cell development. The rigidity sensing enables cells to determine how stiff is the surface they adhere to and regulates the cells' growth. Accordingly, rigidity sensing is one of the most critical aspects of cancer - loss of rigidity sensing results in the transformation of normal cells to cancer cells, while restoring rigidity sensing inhibits tumor formation and can transform cancer cells into normal cells.

The overall objective of this proposal is to understand how the 3D genome responds to mechanical cues and influences cell state transitions, such as apoptotic cell death (Fig. 1). More specifically, by using genome-wide and single-cell methods, we aim to determine whether genome organization, which regulates transcriptional activity, as shown by numerous studies, is altered in response to variations in matrix rigidity sensing, and if such alteration may result in gene expression changes .

We suggest that regulation of gene expression through rigidity sensing is facilitated by repositioning of Lamina-Associated Domains (LADs). Since LADs are coupled to actin filaments, a change in the contraction, may induce structural variations in genome organization, which would result in an altered transcriptional program.

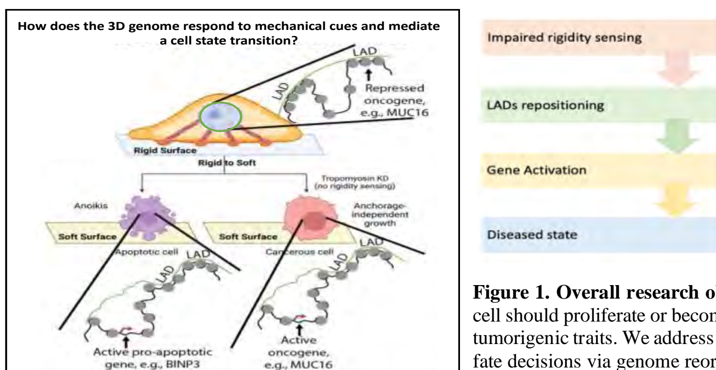

Figure 1. Overall research objective: Rigidity sensing signals whether the cell should proliferate or become apoptotic. When it is impaired, cells develop tumorigenic traits. We address the gap of whether rigidity sensing dictates cell fate decisions via genome reorganization.

Poster 8

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Poster 9

Stochastic Transient Gene Silencing Reveals Key Insights on Cell-State Specific Gene Function

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Gene perturbations on a genetic landscape are a key area of research in biology which can be studied by examining the transcriptomic profile of the cells. However, due to the intricate interconnectivity of gene regulations, gene perturbations lead to a plethora of changes in the tissue, and often perturbations are compensated for by the cell's genetic machinery. Hence, the genetic picture drawn by these perturbation experiments only considers the cells that survived the gene perturbation, implying these cells were efficiently able to adapt to carry out essential cellular functions. This raises a dilemma of whether the perturbation effects undergo a survivorship bias and hamper the research on genes essential for survival. On top of that, genetic perturbation experiments often fail to provide significant information on regulatory elements upstream of the perturbed gene. Mammalian cells exhibit transcriptional bursting of genes leading to dynamic expression patterns of gene modules in a cell. Large cell samples often show natural stochastic silencing for a given gene at a time point. We hypothesize that studying this variability with respect to our Gene of Interest in a healthy (wild-type) sample can provide significant information about that gene's role in cellular processes without the interference of compensatory mechanisms. Our method leverages stochastic transient silencing (STS) in a gene's expression captured by single-cell experiments to classify the cell sample into expressing and silenced subsets. This facilitates differential expression and enrichment analysis generally practiced in genetic perturbation analyses. Using publicly available datasets we show that studying STS not only demonstrates similar differential expression patterns as real-life knockout experiments but further provides information on immediate upstream and downstream regulatory elements. Differential genes captured by STS analysis also show variability based on cell type and cell state, enabling further scrutiny on cell type- and state-specific gene functions. In addition, input samples, being wild-type, are free from survivorship bias and potential batch effects. Thus, studying STS is a promising approach for comprehensively analyzing gene function in cell state-specific manner leveraging the natural single-cell gene expression variability without the need for multiple genetically perturbed systems.

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Poster 10

Development and Applications of a High-Fidelity Cancer Genome Simulator

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Cancer is a complex disease driven by accumulated mutations and selective pressures on somatic cells. This evolutionary progression across spatial and temporal dimensions gives rise to intratumor heterogeneity (ITH), a significant contributor to the cancer therapeutic resistance. The advancement of high-throughput sequencing technology and single-cell barcoding technology in recent years has empowered researchers to conduct in-depth and quantitative analyses of cancer genomes. However, the challenges associated with sampling and data generation have hindered the systematic development and evaluation of computational methods for reconstructing the clonal architecture of cancer. To address these challenges, we are developing a cancer genome simulator to recapitulate the essential technical and biological characteristics of human cancer genome sequencing data. The simulator will incorporate multiple types of somatic alterations, including single nucleotide polymorphisms (SNPs), single nucleotide variations (SNVs), copy number variations (CNVs), and whole-genome doublings (WGDs), into a virtual cancer genome. It will then synthesize both bulk and single-cell level sequencing data. Additionally, the simulator models the dynamics of cancer evolution by simulating the birth-death process of cancer cells, which allows for the generation of realistic tumor growth patterns and the emergence of intratumor heterogeneity. Our main objectives are to create a high-fidelity simulation of dynamic cancer genome data, develop a coordinate tracing system that can monitor WGDs, CNVs, and SNVs across dynamically changing genomic landscapes, and ensure the scalability of the simulation process. This system is anticipated to offer researchers a detailed roadmap of genomic alterations occurring during cancer progression, assisting in benchmarking, experimental design, algorithm development, and parameter space exploration of theoretical models.

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Poster 11

Single-nuclei Multiomics Meta-analysis of Human Organoids and Fetal Retina Reveals Developmental Transcriptional and Epigenetic Differences

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Retinal organoid represents a potentially excellent model system to study developmental processes in vivo. We aim to perform a systematic comparison of gene expression profiles, transcriptional trajectories, and chromatin accessibility between retinal organoids and the developing human retina. Retinal organoid samples from 5- and 45-weeks and human fetal retinal samples between 10- and 23-weeks gestational age were collected and subjected to single nuclei multiome profiling using the 10X Genomics platform to generate transcriptomic and open chromatin data from the same nuclei. Additionally, this data was integrated with single-nuclei transcriptomic data from previous publications. After co-embedding, RNA velocity and pseudotime trajectory were calculated with Monocle and MultiVelo. ArchR was used to identify changes in chromatin openness. In total, single nuclei multiome profiling of more than 450,000 nuclei has been generated from 10 retinal organoid samples and 24 fetal retinal samples (350,000 from our samples and 100,000 from previous publications). All major cell classes and more than 30 cell types have been identified in the organoid. Furthermore, based on pseudotime analysis, the organoid trajectory was well matched to the trajectory inferred from fetal samples. By analyzing cells within the same cell type between organoid and fetal samples, transcriptional and chromatin openness similarities/differences were identified. Our study has produced a multiomics atlas of both the human fetal retina and retinal organoid across different developmental stages. Through integrative and comparative analysis of these datasets, we identified both shared and unique regulatory mechanisms that control the developmental process. These mechanisms were revealed through the comparison between the transcriptome and open chromatin profile in the organoid and fetal samples and involve complex and dynamic interactions between the genome and epigenome. Overall, our study broadens our understanding of the extent to which retinal organoids mimic normal human retinal development.

Integrative Multi-Omics Single Cell Atlas of the Human Retina V1.0

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As the light sensing part of the visual system, the human retina is composed of five classes of neurons, including photoreceptors, horizontal cells, amacrine, bipolar, and retinal ganglion cells. Each class of neuron can be further classified into subgroups with the abundance varying three orders of magnitude. Therefore, to capture all cell types in the retina and generate a complete single cell reference atlas, it is essential to scale up from currently published single cell profiling studies to improve sensitivity. In addition, to gain a better understanding of gene regulation at the single cell level, it is important to include sufficient scATAC-seq data in the reference. To fill the gap, we performed snRNA-seq and snATAC-seq for the retina from healthy donors. To further increase the size of the dataset, we then collected and incorporated publicly available datasets. All data underwent a unified preprocessing pipeline and data integration. Multiple integration methods were benchmarked by scIB, and scVI was chosen. To harness the power of multiomics, snATAC-seq datasets were also preprocessed, and scGlue was used to generate co-embeddings between snRNA-seq and snATAC-seq cells. To facilitate the public use of references, we employed CELLxGENE for visualization and cell annotation. By combining previously published and newly generated datasets, a single cell atlas of the human retina that is composed of over 2 million single cells from 48 donors has been generated. As a result, over 90 distinct cell types are identified based on the transcriptomics profile with the rarest cell type accounting for about 0.01% of the cell population. In addition, open chromatin profiling has been generated for over 400K nuclei via single nuclei ATAC-seq, allowing systematic characterization of cis-regulatory elements for individual cell type. Integrative analysis reveals intriguing differences in the transcriptome, chromatin landscape, and gene regulatory network among cell classes, subgroups, and types. In addition, changes in cell proportion, gene expression and chromatin openness have been observed between different genders and over ages. Accessible through interactive browsers, this study represents the most comprehensive reference cell atlas of the human retina to date. As part of the human cell atlas project, this resource lays the foundation for further research in understanding retina biology and diseases.

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Poster 13

Interpretable Spatial Gradient Analysis for Tumor Spatial Transcriptomics Data

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Cellular anatomy and signaling vary across niches, which can induce gradated gene expressions in subpopulations of cells. Such spatial gradient in gene expression makes a significant source of intra-tumor heterogeneity and can influence tumor invasion, progression, and response to treatment. Spatial transcriptomics (ST) data contain sufficient information for identifying spatial gradients in tissue sections, while challenges remain in the identification and interpretation of these gradients. Here we report *Local Spatial Gradient Inference* (LSGI), a computational framework that identify spatial locations where cells display transcriptomic phenotypes with prominent spatial gradients. With a sliding window strategy, LSGI employs non-negative matrix factorization (NMF) combined with linear regression to obtain interpretation of the local gradient wherever exists. We applied LSGI to 135 tumor ST datasets reported from 10 studies and identified both pan-cancer and tumor-type specific pathways with gradated expression patterns, such as immunoregulatory interactions, autophagy, and hypoxia. The local gradients were further categorized according to their association to tumor-TME (tumor microenvironment) interface, highlighting the pathways preferentially activated at tumor-TME interfaces and inside tumor cores. Lastly, spatial relationships between gradients of different pathways were investigated. We conclude that LSGI enables highly interpretable spatial gradient analysis which can reveal novel insights in tumor biology from the increasingly reported tumor ST datasets.

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Poster 14

Unraveling the Intercellular Communication Disruption and Key Pathways in Alzheimer's Disease: An Integrative Study of Single-nucleus Transcriptomes and Genetic Association

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Recently, single-nucleus RNA-seq (snRNA-seq) analyses have revealed important cellular and functional features of Alzheimer's disease (AD), a prevalent neurodegenerative disease. However, our knowledge regarding intercellular communication mediated by dysregulated ligand-receptor (LR) interactions remains very limited in AD brains. We systematically assessed the intercellular communication networks by using a discovery snRNA-seq dataset comprising 69,499 nuclei from 48 human postmortem prefrontal cortex (PFC) samples. We replicated the findings using an independent snRNA-seq dataset of 56,440 nuclei from 18 PFC samples. By integrating genetic signals from AD genome-wide association studies (GWAS) summary statistics and whole genome sequencing (WGS) data, we prioritized AD-associated Gene Ontology (GO) terms containing dysregulated LR interactions. We further explored drug repurposing for the prioritized LR pairs using the Therapeutic Targets Database. We identified 316 dysregulated LR interactions across six major cell types in AD PFC, of which 210 pairs were replicated. Among the replicated LR signals, we found globally downregulated communications in astrocytes-to-neurons signaling axis, characterized, for instance, by the downregulation of APOE-related and Calmodulin (CALM)-related LR interactions and their potential regulatory connections to target genes. Pathway analyses revealed 60 GO terms significantly linked to AD, highlighting Biological Processes such as ‘amyloid precursor protein processing’ and ‘ion transmembrane transport’, among others. We prioritized several drug repurposing candidates, such as cromoglicate, targeting the identified dysregulated LR pairs. Our integrative analysis identified key dysregulated LR interactions in a cell type-specific manner and the associated GO terms in AD, offering novel insights into potential therapeutic targets involved in disrupted cell-cell communication in AD.

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Poster 15

Comprehensive Single-cell Multiomics Study of the Developmental Stages of the Human Fetal Cornea

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The human anterior segment (HAS) is an essential component of the eye, responsible for both focusing incoming light onto the retina and regulating intraocular pressure. The anterior segment plays a pivotal role in preserving the eye's health and integrity by delivering essential visual signals to the optic nerve. The main structures in the HAS are the cornea, limbus, ciliary body, lens, and the anterior chamber. This study focuses on the cornea, which is a transparent, dome-like structure that refracts light entering the eye to enhance focus on the retina. There are currently many diseases related to the development of the HAS and the cornea in which underlying molecular mechanisms have not been completely understood. Additionally, resources available to the scientific community concerning the development of the HAS are limited. Therefore, the current study focuses on investigating the cellular composition as well as the genomic landscape of the HAS and its potential relationship to developmental disorders.

This study used samples from human fetal anterior segments aged from 12 weeks post conception to 21 weeks post conception. We collected and dissociated samples to obtain corneal and limbal tissues, from which individual cells were cultured. We performed single-cell multiomics analysis using the 10xGenomics platform. Pre-processing was performed with Cellranger 7.1.0. Quality control, which consists of utilizing dropkick for identification of droplet-based single cell data, SoupX for ambient RNA identification, and doublet finder for removing doublets (cells mistakenly adjoined together) in the dataset was performed with CellQC pipeline developed by the Chen Lab. Clustering was performed with Seurat 4.3.0. Lastly, annotation was performed using a combination of ScPred 1.9.2, known cell-type marker genes, and canonical genetic markers. These steps led to the production of comprehensive multi omics atlases generated for each stage of fetal development. For all samples, we identified 84,099 cells in total.

The datasets and visualizations generated in the current study provide a clear insight into the development of the fetal HAS. Being able to observe the changing cellular composition and transcriptomics and chromatin landscape of the HAS at different time points in development is crucial in understanding how different diseases/disorders progress. Overall, this study provides a strong platform for future research to utilize in investigating disorders/diseases as well as molecular pathways underlying the HAS.

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Structural and Conformational Chromosomal Variations in Breast Cancer Identified with a Single Cell Hi-C and WGS Co-assay

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The role of genomic structural variation and changes in DNA compartmentalization is understudied in early breast cancer progression. Capturing these events is technically difficult, as low tumor purity and intratumoral heterogeneity (ITH) obfuscates linking these phenomena to progression. Here we present a single-cell co-assay measuring copy number variants (CNVs), structural variants such as translocations and inversions, as well as chromatin folding at the same time. We have done this by adapting acoustic cell tagmentation (ACT-seq) with a single-cell Hi-C protocol. We call this method GCC-ACT (genome conformation capture with ACT-seq). The genome is organized into a hierarchy of three-dimensional structures, including topologically associated domains (TADs) and further subdivisions of chromatin loops. Transcription is regulated across genes as a unit within these TADs and loops. The inappropriate folding of chromatin, either by dysregulation or structural variants disrupting TADs across the genome, results in a crucial stage in early oncogene activation and tumor suppressor silencing. We present here a proof-of-concept study, wherein we apply GCC-ACT to profile 600 single cells in a triple negative breast cancer cell line (MDA-MB-231). We identified 8 CNV-defined subclones, which recapitulates what we have also identified in standard ACT-Seq. We profiled 128 SK-BR-3 cells and identified a single clone in both Hi-C and ACT, consistent with previous data. We observed different chromatin interactions between subclones in MDA-MB-231 and benchmarked our results by performing Oxford nanopore sequencing and comparing this data to existing cytogenetic data of the same cell line. Future applications will apply GCC-ACT to investigate the chromatin conformation in early breast cancer lesions (Ductal-carcinoma-in-situ) and invasive breast cancer, to understand breast cancer progression.

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Poster 17

Long Non-Coding RNA (lncRNA) Expression is Upregulated in Microglia/Macrophages During Regeneration of Rods in Zebrafish Retina.

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Microglia are resident immune cells of the retina that can change their function in a disease state. While their transition between states in disease has been documented, their state specific functional roles in regeneration and how this transition is regulated remain unclear. Our lab has established a transgenic P23H rhodopsin zebrafish model of *Retinitis Pigmentosa* with concomitant degeneration of rod photoreceptors and regeneration of new rods. We hypothesize that microglia undergo transcriptomic and phenotypic changes that might promote rod regeneration. The aim of this study was to Identify transcriptomic and phenotypic changes of microglia/macrophages in regenerating retina of P23H zebrafish that might promote regeneration of rod photoreceptors. We therefore analyzed whole retina single-cell transcriptomes from three P23H and WT zebrafish utilizing Seurat package. Unsupervised clustering was performed to identify microglia clusters. To visualize microglia/macrophages, retinal sections from adult P23H and WT fish were stained with 7.4.C4 and lcp1 antibodies. Immunostaining of retinal sections with 7.4.C.4 and lcp1 antibodies revealed that microglia/macrophages in P23H retinas acquired a more ameboid morphology compared to WT. We detected a higher number of microglia/macrophages in the ONL and subretinal space. Analysis of scRNA seq data identified three distinct microglia clusters in both WT and P23H. Gene expression changed in all clusters in P23H. Genes associated with cytokine/chemokine signaling (*tnfrsf9b*, *traf1*, *ccl38.6*) were upregulated in P23H microglia cluster 27, whereas expression of genes in pathways related to phagocytosis (*p2ry12*, *lamp2*) were increased in P23H microglia cluster 31. Furthermore, we detected downregulated expression of genes associated with mechanosensation (*klf2a-1*, *stoml3b*). We also found that expression of several lncRNAs, *si:ch211-214p16.2*, *LOC103909107*, *LOC103910136*, *LOC103909099* and *LOC110439915* was microglia cluster-specific. Furthermore, these were among the top differentially-expressed genes and were upregulated by 3.5 to 17.6 fold in P23H microglia compared to WT. Our results indicate that microglia/macrophages in regenerating retinas of P23H fish undergo transcriptional changes and migrate towards rod photoreceptors in the ONL and subretinal space. Some of these microglia acquire ameboid shape suggesting that they phagocytose dying rods. We also have identified upregulation of lncRNAs expression in P23H microglia. LncRNAs regulate many cellular processes and we suggest that they might drive microglia/macrophage's transcriptional change to promote regeneration of rods. Further knock-down studies will reveal specific roles of the lncRNAs in retinal regeneration.

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Poster 18

Dissecting Intercellular Interactions in Developing Bones by Curio Seeker

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Bone development is a prime example of organogenesis requiring sequential steps of cell proliferation and differentiation, executed through dynamic interactions among multiple cell types in distinct locations. Understanding the fundamental process of bone development – the transition from cartilage to bone and bone marrow – is essential not only for unraveling mechanisms of bone diseases but also for defining how the hematopoietic stem cell niche is established. The growth plate is composed of three layers of resting, proliferating, and hypertrophic chondrocytes. Parathyroid hormone-related protein (PTHrP) plays an essential role in regulating endochondral bone development by maintaining growth plate activities via the PTHrP-Indian hedgehog (Ihh) feedback loop. PTHrP knockout mice die soon after birth by respiratory failure due to incomplete rib cage development. However, it is still unclear how PTHrP orchestrates bone development through both Hedgehog-dependent and independent cell-cell communication. Previously, we and others have revealed cells constituting developing bones using droplet-based single-cell RNA-seq. However, the current methodology has significant limitations. First, spatial information is permanently lost in cell dissociation, and second, hypertrophic chondrocytes, the master regulator of bone development that releases several cytokines, cannot be encapsulated due to large size and fragility. The lack of a comprehensive cell atlas with precise spatial information hampers further in-depth understanding of mechanisms of bone development. In this study, we performed spatial transcriptomics using CurioSeeker (v1.0) to comprehensively define the spatial transcriptomic landscape of developing bones at a single-cell level. We utilized PTHrP-mCherry knock-in reporter mice in which the *Pthrp* allele is engineered so that a red fluorescent protein is expressed instead of a functional PTHrP protein. Fresh frozen sections of $Pthrp^{mCherry/+}$ (Control) and $Pthrp^{mCherry/mCherry}$ (PTHrP-KO) mice at embryonic day (E) 18.5 were used to generate cDNA libraries. Histologically, PTHrP-KO mice show a distinctly shorter femur at this stage. We preliminarily analyzed the CurioSeeker (v1.0) datasets and found that both the numbers of UMIs and detected genes were at the level expected from previous studies. For future plans, we plan to integrate these spatial transcriptomic data with droplet-based scRNA-seq datasets of the same time point in collaboration with computational biologists, Dr. Josh Welch's group at the University of Michigan. Our plan is to define spatial intercellular interactions using newly-developed algorithms and learn how perturbation of a critical paracrine factor alters spatial intercellular interactions and halts bone development due to impaired proliferation and accelerated hypertrophy. We expect that our innovative integrative approach will revolutionize our understanding of the fundamental process of organogenesis and demonstrate the utility of single-cell level spatial transcriptomics in developmental biology.

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Poster 19

Microfluidic 2D Electrophoretic Separation to Identify Aberrant Protein Networks and Subunit Constituents

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Differences in tumor cell phenotypes result from heterogenous protein expression and cannot be effectively evaluated with traditional bulk protein identification techniques, such as western blots or mass spectrometry data from whole cell lysates employing millions of cells. Recent efforts in cancer therapeutics development and the study of novel targeted approaches have pointed to stable multicomponent protein complexes formed selectively in certain cancer types. Precise understanding of protein interactions at the single-cell level is required, and methods to identify and quantify these species are lacking. To date, few assays provide sufficient specificity to identify protein expression at the single-cell level while offering high throughput. One method that achieves protein measurements at this scale is the single-cell western blot, where the conventional bulk electrophoretic separation is scaled down, allowing identification of proteins in-gel through immunoprobes. Currently, single-cell western blots are limited to measuring denatured proteins and fractionating monomers from complexes, thus, identifying the composition of multimeric protein complexes associated with diseases such as cancer is still needed. To this end, we have developed a microfluidic two-dimensional (2D) electrophoretic separation assay that distinguishes protein complexes and measures individual subunit constituents by incorporating native and SDS-PAGE into a single microscale platform (Figure 1). The first step of the assay (1st dimension) is designed to separate multimeric complexes from single-cell lysates under native conditions, followed by an *in situ* denaturation step. A subsequent orthogonal separation (2nd dimension) informs about the abundance and stoichiometries of subunit proteins. Approximately, 10^3 simultaneous separations are possible using a 40 μm thick polyacrylamide gel in a 37.5 x 25 mm microwell array. We validated each separation dimension using a fluorescently labeled purified protein complex consisting of 3 subunits with molecular weights resembling complexes found in malignancy. We found a separation resolution of 1.1 for two denatured subunits and migration distances ranging from 165.5 to 541.9 μm for the different native and denatured species. This assay will allow on-chip single-cell lysis for the identification of intact multicomponent complexes, enabling assessment of heterogeneous distributions across cell populations due to its short dimensions and separation times (~10 min per dimension) that prevent heat-based complex dissociation during native separations.

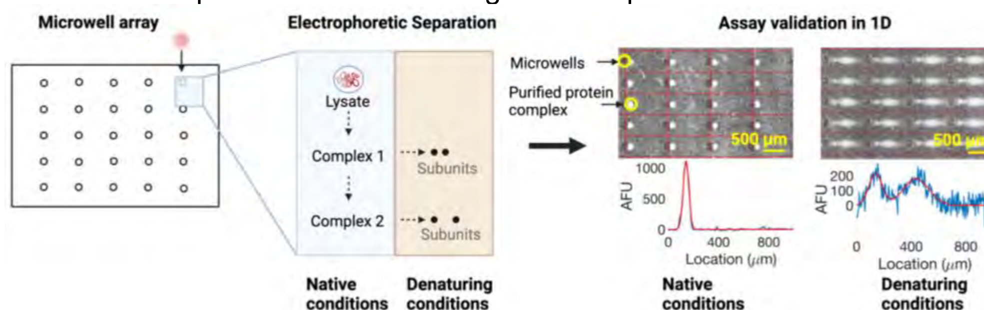

Figure 1. 2D microscale assay. 1st and 2nd separation workflow (left). False-colored micrographs and intensity profiles of native and denatured bands (right).

Poster 19

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Poster 20

Single-nuclei Multi-Omics Dissection of Exercise Effects in Human Skeletal Muscle

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Background: The skeletal muscle is essential for glucose homeostasis. In addition to serving as a calorie sink, physical exercise can ameliorate diabetes without affecting BMI, likely through remodeling muscle gene expression and the endocrine system, although the exact mechanism is unclear. **Aim:** We aimed to identify cell type-specific gene expression patterns (snRNA-seq) in human skeletal muscles and cis-regulatory elements (snATAC-seq) dynamics in response to an acute bolus of exercise. We also aimed to determine intercellular communications and interplays between myocytes, fibro–adipogenic progenitors, satellite cells, and other cell types in the muscle in response to exercise. **Methods:** We have collected paired human vastus lateralis muscles from young, healthy, sedentary subjects before and after an acute bolus of bicycling exercise. We have employed multi-omic profiling (combined snRNA-seq + snATAC-seq) on the 10x Genomics platform to profile gene expression and chromatin accessibility of exercise effects in 6 muscle samples from 3 human subjects (pre- and post-exercise for each subject for pairwise comparison). **Results:** We have computed quality control (QC) metrics for the combined snRNA-seq + snATAC-seq experiment. We obtained ~ 45,017 high-quality nuclei after QC in total from all subjects combined. As an additional QC parameter, we computed TSS enrichment score. Along with other cell types, we identified the Type I and Type II muscle fiber signatures that are typically missed by single-cell RNA-seq techniques. The DEGs and DARs revealed exercise-dependent genes and peaks. Our ongoing investigation includes functional enrichment analysis, transcription factor binding motifs, pseudo trajectory analysis, and myofiber type-specific response to exercise. **Conclusion:** Our study will generate testable hypotheses for how exercise benefits glucose metabolism, which has broad implications for preventing and treating type 2 diabetes.

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Poster 21

Molecular and Spatial Signatures of Mouse Trigeminal and Dorsal Root Ganglia Cells at Single-Cell Resolution

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The diversity and complex organization of cells in dorsal root ganglia (DRG) and trigeminal ganglia (TG) have hindered systematic characterization of changes in its cellular and molecular architecture, limiting our ability to understand the mechanisms underlying pain. Here, we generated a high-resolution cell atlas of DRG and TG using Multiplexed Error-Robust Fluorescence in situ Hybridization (MERFISH) and quantified changes in gene expression and spatial organization of major cell types in these regions. We collected the most comprehensive datasets and employed a meta-analysis. We collected four public datasets for DRG and TG tissues across different technologies. Raw sequencing reads were aligned to the mm10 reference genome using CellRanger . Standardized quality control analysis has been performed to exclude estimated empty cells, ambient RNAs, and doublets using dropkick, SoupX, and DoubletFinder. Processed datasets are integrated to reduce the sample effects by using scVI. We clustered the cells using the Leiden algorithm. UMAP was used to generate cell clusters. We annotated clusters using known cell type marker genes, and Cellkb database. Regarding the single cell changes, we observed substantially more pronounced changes gene expression of non-neuronal cells over neurons. We also identify several pathways regarding glial and immune cell activation. To facilitate the public use of the generated atlases, we generate a R shiny web-based tool, accessible at https://u247700.shinyapps.io/drg_atlas/ for DRG, and https://u247700.shinyapps.io/trigeminal_mice/ for trigeminal data. Our results can provide critical insights regarding the molecular mechanisms of pain. These cell atlases may serve as a valuable data resource for the mouse dorsal root ganglia and trigeminal community

Poster 22

Archival Single Cell Genomics Reveals Persistent Subclones During DCIS Progression

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Abstract

Ductal carcinoma in situ (DCIS) is a common precursor of invasive breast cancer. Our understanding of its genomic progression to recurrent disease remains poor, partly due to challenges associated with the genomic profiling of formalin-fixed paraffin-embedded (FFPE) materials. Here, we developed Arc-well, a high-throughput single cell DNA sequencing method that is compatible with FFPE materials. We validated our method by profiling 40,330 single cells from cell lines, a frozen tissue and 27 FFPE samples from breast, lung and prostate tumors stored for 3-31 years. Analysis of 10 patients with matched DCIS and cancers that recurred 2-16 years later show that many primary DCIS had already undergone whole-genome-doubling and clonal diversification, and that they shared genomic lineages with persistent subclones in the recurrences. Evolutionary analysis suggests that most DCIS cases in our cohort underwent an evolutionary bottleneck, and further identified chromosome aberrations in the persistent subclones that were associated with recurrence.

Comprehensive Characterization of Single-Cell Isoform in Mouse Retina with Long-Read RNA Sequencing

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As a complex neuronal tissue, the mouse retina is composed of a large number of cell types that can be distinguished based on morphology, function, location, and transcriptomic profile. In addition, distinct mRNA transcript isoforms have been observed among different cell types. However, the extent of mRNA alternative splicing in the mouse retina has not been systematically characterized in a cell type specific context. Single cell RNA sequencing was performed by combining short read and long read high throughput sequencing with droplet based single cell technology. Customized data analysis pipeline is developed to allow accurate cell barcode/unique molecular identifier assignment, high-confidence transcript isoforms identification and characterization in each cell type in the retina.The transcriptome from a total of 16,323 single cells from the mouse retina has been profiled with 726 million Illumina short reads and 275 million Oxford Nanopore long reads. Our dataset includes 8,497 bipolar cells (BCs), 5,789 rods, 1,022 cones, 869 Müller glial (MGs) and 146 amacrine cells (ACs). In addition to the cell class level, sufficient cells are captured for each BC type. Based on our preliminary analysis, in total, 235,861 transcript isoforms are identified, and 69.43% of those are novel. Furthermore, over 13% of isoforms are cell class specific, including 19,208 unique isoforms in BC, 9,136 in rod, among others. Finally, isoforms that are differentially expressed among the five major retinal cell classes are identified. Our study represents the first comprehensive characterization of the full-length transcription isoforms in single cell in mouse retina with over 160,000 novel isoforms in five retina cell class identified. These data correspond a substantial addition to the annotated/known mouse transcriptome from previous studies. We also identified 31,807 cell-class specific isoforms. Based on our analysis, long read scRNA-seq approach is highly conducive to novel isoform identification especially the cell-class specific isoforms and further improves cell sub clustering using splicing information. Further insights gained from deep analysis of this dataset will be reported.

Poster 23

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Role of Rspo3 in Estrogen-Mediated Sex-Difference: A Single Cell-Based Study.

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Obesity, a global health concern, affects over a third of the adult population worldwide. Epidemiological studies indicate that the location and distribution of excess fat, rather than general adiposity, are more informative for predicting risk of obesity sequelae, including cardiometabolic disease and cancer. R-spondin 3 (Rspo3) is an oncogenic gene that acts as an activator of Wnt/β-catenin pathway and is associated with body fat distribution, measured by waist-to-hip ratio (WHR) adjusted for body mass index (WHRadjBMI). Growing evidence suggests that there are sex differences in fat distribution in human and experimental animals, with sex hormones plays a crucial role. However, the role of estrogen in mediating sex differences in fat distribution via Rspo3 has rarely been studied. Hence, this study aims to provide an answer to the following question:

Does estrogen controls sex – dimorphism in fat distribution partially through Rspo3? If so, how?

In this study, we revealed that Rspo3 expression displays sexual dimorphism, being more elevated in males within human adipose tissue. Moreover, we found that degrading the estrogen receptor could induce the expression of Rspo3 in the mammary glands of mice. These findings imply that estrogen may suppress the expression of Rspo3, providing a potential explanation for the sex-specific differences observed in fat distribution. We further explored the functioning mechanism of Rspo3 in mouse liver and human colon cancer scenarios. Our findings suggest that Rspo3 primarily operates via a paracrine mechanism, being secreted by a distinct subset of cells and influencing neighboring cells. Particularly in mouse liver, Rspo3 is secreted by endothelial cells and hepatic stellate cells, promoting hepatocyte expansion, largely through the Wnt/β-catenin pathway. To the best of our knowledge, our study reveals that for the first time, estrogen controls the expression of Rspo3, and Rspo3 controls hepatocyte expansion and fat deposition in liver, which explains why fat distribution and its associated disease, such as fatty liver disease, shows a sex dimorphism. Our study provided a significant role of Rspo3 in estrogen-mediated, sex-dimorphic fat distribution.

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Poster 25

Single-Cell Multiomics Decodes Regulatory Programs for Mouse Secondary Palate Development

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The development of the secondary palate is programmed by the precise regulation of gene expression by transcription factors through binding to the accessible regulatory DNA elements. Perturbations in gene regulation during palatogenesis can lead to cleft palate, which is among the most common congenital birth defects. However, currently there is no comprehensive multiomics map of the developing secondary palate. In this study, we performed single-cell multiome sequencing and profiled chromatin accessibility and gene expression simultaneously within the same cells (n = 36,154) isolated from mouse secondary palate across embryonic days (E) 12.5, E13.5, E14.0, and E14.5. Distinct cranial neural crest-derived mesenchymal subpopulations reflect *in vivo* anatomical locations. We then employed Waddington-Optimal Transport (WOT) to resolve the differentiation dynamics of CNC-derived mesenchymal cells. We constructed five trajectories representing continuous differentiation of multipotent cells into distinct lineages. By linking open chromatin signals to gene expression changes, we characterized the underlying lineage-determining transcription factors. *In silico* perturbation analysis identified transcription factors SHOX2 and MEOX2 as drivers of the development of the anterior and posterior palate, respectively. In conclusion, our study charted epigenetic and transcriptional dynamics in palatogenesis, serving as a valuable resource for further cleft palate research.

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Poster 26

Decoding the Archetypes and Eco-traits of Triple-Negative Breast Cancer in Response to Chemotherapy

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Triple-negative breast cancer (TNBC) is an aggressive subtype of breast cancer that is often treated with chemotherapy. While about half of the patients completely respond, the remaining patients develop drug resistance and progress to metastatic disease, leading to poor survival rates. Currently, it remains unclear which tumor cell expression programs and cell states in the tumor microenvironment (TME) are associated with response to chemotherapy. To investigate this question, we conducted single-cell RNA sequencing (scRNA-seq) on fresh core biopsies collected from 101 treatment-naïve TNBC patients. These patients were subsequently treated with neoadjuvant chemotherapy, in which 45 patients achieved complete pathological response (pCR) and 37 had residual disease (RD). The scRNA-seq data included a total of 427,857 cells encompassing eight major cell types: cancer cells, myeloid cells, T/NK cells, B-cells, fibroblasts, endothelial cells and perivascular cells. The unsupervised pseudo-bulk analysis using the cancer cells alone revealed four gene expression **archetypes** at patient level: luminal secretory-associated (LSA), basal-associated (BA), immunoreactive (IR), and luminal androgen receptor (LAR). Notably, the BA and IR archetypes were more likely to exhibit RD and pCR, respectively. At the single-cell level of cancer cells, we discovered 13 meta-modules that were heterogeneously expressed in a tumor and shared across patients, including cell cycling, stress, hypoxia, interferon response, HLA, epithelial-mesenchymal transition, and others. Within the TME, we identified 15 myeloid cell states, 14 T/NK cell states, 6 B cell states, 4 fibroblast cell states, 7 endothelial cell states, and 4 pericyte cell states. Based on these single-cell resolved results, we created a generalized and quantitative blueprint of the TNBC ecosystem as a network of co-occurring tumor cell expression programs and TME cell states. This network was composed of eight **eco-traits**, reflecting the possible functional interplays of cancer and TME cells. Importantly, we found the association of archetypes and chemotherapy response was rooted in the combinations of eco-traits. For instance, both the IR and pCR patients predominantly showed presence of the eco-trait which was characterized by high co-occurrences of interferon-related immune cells, actively proliferating and interferon-responding cancer cells. Finally, we developed a gene expression-based logistic regression model to predict chemotherapy response. Overall, this study has delivered a comprehensive single-cell atlas of treatment-naïve TNBC, revealed the archetypes for stratifying patients, and pinpointed the cancer and TME cells that were strongly associated with chemotherapy response.

Poster 27

A Pan-Cancer Single-Cell Analysis of Intratumoral Copy Number Diversity and Evolution

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Aneuploidy is a hallmark of cancer and large-scale cancer genome studies have shown that cancer patients harbor many differences between their copy number profiles. However, the intratumoral heterogeneity (ITH) of copy number aberrations (CNAs) across human cancers remains understudied. Here, we conducted a pan-cancer analysis of 94 human tumor samples at single cell genomic resolution, representing seven major cancer types: bladder, breast, colon, glioblastoma, kidney, lung, and ovary. In total, 62,646 aneuploid cells were analyzed by single cell copy number profiling and bulk exome sequencing in a subset (84/94) of patients. In most cancers, increased clonal diversity was associated with higher CNA burden, whole genome doubling (WGD), and *TP53* mutations. In all tumors, our data show that cancer cells share a clonal set of CNAs or mutations, suggesting the tumors evolved from a single ancestral cell. In 18/94 cases we identified subclonal WGD events, which resulted in a higher number of copy number losses after tetraploidization. Macro-spatial sampling showed that increased clonal diversity also correlated with increased spatial geographical diversity. We estimated a Punctuated Evolution Index, which showed that punctuated copy number evolution is common across human cancers. Collectively, these data show that copy number ITH is correlated with specific features across human cancers.

Poster 28

Expansion of Trem2$^+$CD11b$^+$ Macrophages and Loss of SiglecF$^+$ Pulmonary Tissue Macrophages in Vaping Associated Acute Lung Injury

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E-cigarettes & vaping-associated lung injury (EVALI) is an epidemic in the US since 2019. EVALI is strongly associated with Vitamin E Acetate (VEA) inhalation. How VEA causes lung injury is unknown. Using VEA vaping as a prototype model for lung injury, we found that two-week exposure induced protein leakage and neutrophil inflammation in the lung. Using the surface expression of CD11b and SiglecF to distinguish two subsets of steady-state pulmonary macrophages, we found SiglecF$^+$ macrophages significantly reduced while CD11b$^+$ macrophages were increased in the lung. We also found that SiglecF$^+$ macrophages were the first target during VEA vaping and the loss of SiglecF$^+$ tissue-resident macrophages occurred before any detectable increase in CD11b$^+$ macrophages recruitment or changes in pulmonary parenchymal cells. We next used multiplex CITE-seq to comprehensively profile the pulmonary macrophage in VEA vaping and under steady-state. CITE-seq confirmed the flow cytometry findings and revealed the expansion of Trem2$^+$CD11b$^+$ macrophages in the VEA-injured lung. RNA-velocity analysis suggests that Trem2$^+$CD11b$^+$ macrophages represent the least differentiated state among all pulmonary macrophages. To determine the reversibility of VEA-induced macrophage disturbances, we performed VEA vaping cessation studies and found that the macrophage subset disturbances recovered after the termination of VEA vaping, suggesting that Trem2$^+$CD11b$^+$ macrophages might be a transient intermediate stage during monocyte differentiation into tissue-resident macrophages. Notably, alveolar type 2 epithelial cells remained markedly reduced despite immune recovery following cessation. Rag1KO and IFNAR1KO phenocopied wild-type mice in both acute and recovery phases of VEA-induced lung injury indicating the dispensability of adaptive immunity and type I interferon signaling in injury and recovery. Using an influenza lung injury model, we showed that influenza infection at lethal doses induces loss of SiglecF$^+$ macrophages and an increase of CD11b$^+$ macrophages in the lung at the height of viral replication like the observations in VEA-induced lung injury. Together, these results established a longitudinal history of how the lung responds to injury and recovers. We are currently investigating the function and ontogeny of Trem2$^+$CD11b$^+$ macrophages in the lung and the source of SiglecF$^+$ recovery following cessation of insults. Overall, we aim to determine how circulating monocytes contribute to tissue-resident macrophages in the lung after injury and how these nascent immigrant macrophages might differ from steady-state and embryonically derived tissue macrophages.

Poster 29

Single-nuclei Multiome Analysis of Human Fetal Retina

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Purpose: We aim to apply the single-cell multi-omics tools to gain insights into epigenetic mechanisms that regulate transcriptional networks in human retinal development at single-cell resolution.

Methods: Samples from the macula and peripheral human fetal retina between PWC (post conception week) 10 and 23 were collected and subjected to single nuclei multiome profiling using the 10X Genomics platform to generate transcriptomic and open chromatin data from the same nuclei. Batch-corrected data obtained from all samples were analyzed together to identify cell classes and types and developmental trajectories. Transcription factors (TFs) and gene regulatory networks (GRNs) that correlate with the developmental process were identified.

Results: In total, single nuclei multiome profiling of 290,000 nuclei has been generated from 25 samples of the different regions of the human retina. All major cell classes and over 50 cell types have been identified in our dataset. We identified three gene modules during naïve progenitor maturation and classified neurogenic precursors for all major classes and subclasses. Overall, we observed a hierarchical cell differentiation pattern consisting of multiple intermediate competence windows through sequential binary commitments. By analyzing the GRNs, we identified more than 300 TFs whose expression and activity correlate with the developmental process, including many TFs that are known to play an important role in cell fate specification. Our data suggest that cells have already formed distinct clusters in both gene expression and chromatin accessibility, implying biased subtype decisions during the neuron precursor stages. Both concordant and discordant regulations of transcripts and open chromatin were observed, providing insights into different modes of the regulatory switch during development. Finally, genes and pathways that show transcriptional differences between the macula and periphery retina at the early developmental stage were identified and linked to diseases.

Conclusions: Our study produces a multi-omics atlas of the developing human retina for investigating transcriptional regulatory mechanisms and fate determination. We identified transcriptional and epigenetic programs distinguishing each major cell type, developmental time, and retinal region. Integrative analysis of this multi-omics dataset reveals candidate TFs and GRNs controlling the developmental process.

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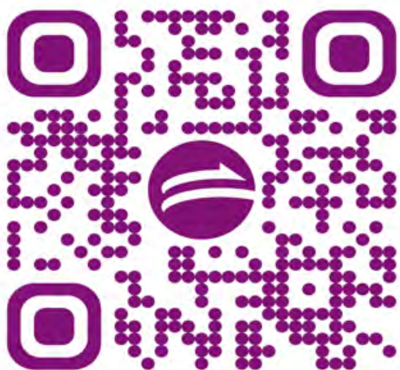

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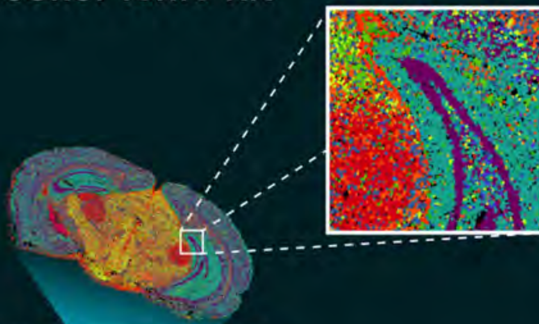

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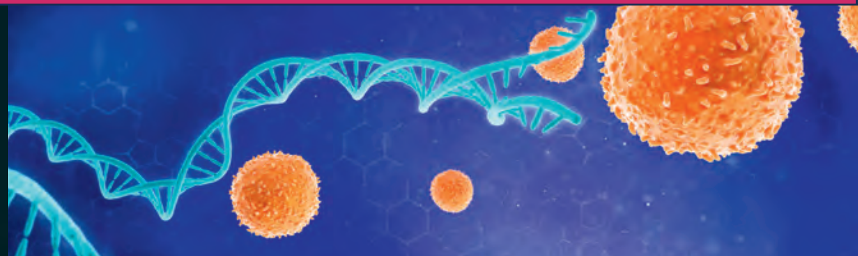

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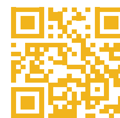

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