3rd Annual GCC Single Cell Omics Symposium

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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: Single Cell Omics, Antimicrobial Resistance, Cellular and Molecular Biophysics, Innovative Drug Discovery and Development, Immunology, Mental Health Research, Regenerative Medicine, Theoretical and Computational Neuroscience, and Translational Pain Research. GCC training programs currently focus on Biomedical Informatics, Cancer Therapeutics, 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**, PhD, MBA Gulf Coast Consortia **Rui Chen,** PhD Baylor College of Medicine
9:10-9:50	**Keynote Presentation** *Spatial Multi-Omics Driving the Next Wave of Biomedical Research Revolution* **Rong Fan**, PhD Yale University
9:50-10:20	Vendor Session
Session 1:	**Single Cell Application** Moderator: Weiyi Peng, PhD Univ. of Houston
10:20-10:40	*Implementing Single-Cell Transcriptional Profiling Approaches to Investigate Circuit Integration of Adult-Born Neurons* **Benjamin Arenkiel,** PhD Baylor College of Medicine
10:40-11:00	*Modulating Microglia in Alzheimer's Disease* **Shu-Hsia Chen**, PhD Houston Methodist Research Institute
11:00-11:15	*Single Cell Atlas of Human Glioma Identifies Immune Suppressive Macrophage Molecular Signatures and S100A4 as an Immunotherapy Target for GBM* **Nourhan Abdelfattah**, PhD Houston Methodist Research Institute
11:15-11:50	Lighting poster talks **Jinzhuang Dou**, MD Anderson Cancer Center **Thomas Gallup**, EMPIRI Inc. **Andrew Koval**, Rice Univ. **Jose Maldonado**, Houston Methodist Research Institute **Anna Naglis**, UT Health Science Center Houston **Noriaki Ono**, UT Health Science Center Houston **Eyad Shihabeddin**, UT Health Science Center Houston **Pavel Sumazin**, Baylor College of Medicine **Nicholas Tran**, Baylor College of Medicine **Kaile Wang**, MD Anderson Cancer Center **John Weinstein**, MD Anderson Cancer Center
11:50-1:45	Lunch and Poster Session 11:50-12:30 Lunch 12:30-1:45 Posters
1:50-2:30	**Keynote Presentation** *Super-Resolution Imaging of Chromatin Structure and Dynamics in Health and Disease* **Melike Lakadamyali**, PhD Univ. of Pennsylvania *Introduced by* Weiyi Peng, PhD Univ. of Houston

Agenda

Session 2:	**Single Cell Data Analysis** Moderator: Peter McCaffrey, MD UT Medical Branch at Galveston
2:30-2:50	*Quantitative Single-Cell Interactomes in Normal and Virus-Infected Mouse Lungs* **Margo Cain,** PhD MD Anderson Cancer Center
3:00-3:20	*Fast and Interpretable Consensus Clustering of Single Cell Data via Minipatch Learning* **Genevera Allen**, PhD Rice Univ.
3:20-3:35	*Robust Pathway Analysis for scRNA-seq and Spatial Transcriptomics Data* **Qingnan Liang**, PhD MD Anderson Cancer Center
3:35-4:05	Networking Break
Session 3:	**New Technologies and Application** Moderator: Rui Chen, PhD Baylor College of Medicine
4:05-4:25	*Decoding Premalignant Breast Cancer Progression with Single Cell Genomics* **Nicolas Navin**, PhD MD Anderson Cancer Center
4:25-4:45	*Studies of Genome Organization at the Single-cell Level* **Nir Guy**, PhD UT Medical Branch at Galveston
4:45-5:00	*Single-cell Multiomics Analysis of Human Retinal Development* **Zhen Zuo***,* MS Baylor College of Medicine
5:00 pm	Closing Remarks and reception

Symposium organizers:

Rui Chen, PhD
Baylor College of Medicine

Peter McCaffrey, MD
UT Medical Branch at Galveston

Weiyi Peng, PhD
Univ. of Houston

Presenters in alphabetical order

Nourhan Abdelfattah, PhD
Postdoc
Houston Methodist Research Institute

Single Cell Atlas of Human Glioma Identifies Immune Suppressive Macrophage Molecular Signatures and S100A4 as an Immunotherapy Target for GBM

Dr. Nourhan Abdelfattah received her PhD from UT Health San Antonio in Cancer Biology in 2018. Her dissertation was focused on identifying microRNAs that enhance the efficacy of chemo- and radiotherapy against pediatric medulloblastoma. She joined Yun's laboratory as a postdoctoral fellow in May 2018 to continue her training in pediatric and adult brain tumor research. In the Yun lab, she is studying the immune microenvironment of medulloblastoma and glioma using genetically engineered mouse models.

Nourhan received multiple prestigious honors, fellowships and awards including: (i) The Horizon Award from the DOD, (ii) The Faculty of the Future Fellowship Award from the Schlumberger Foundation (iii) Greehey Foundation Graduate Fellowship Award in Children's Health, (iV) Barbara Bowman Student of the Year Award, (V) David Carrillo Memorial Fellowship Award for Excellence in Graduate Studies.

She has two first author paper in Nature Communications one co-first author paper in cancer research communications and several co-author paper in Science Advances, Nature communications, Cancer research and other reputable journals.

Genevera Allen, PhD
Associate Professor
Electrical and Computer Engineering,
Statistics, and Computer Science
Rice University

Fast and Interpretable Consensus Clustering of Single Cell Data via Minipatch Learning

Genevera Allen is an Associate Professor of Electrical and Computer Engineering, Statistics, and Computer Science at Rice University and an investigator at the Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital and Baylor College of Medicine. She is also the Founding Director of the Rice Center for Transforming Data to Knowledge, informally called the Rice D2K Lab.

Dr. Allen's research develops new statistical machine learning tools to help people make reproducible data-driven discoveries. She is known for her work in the areas of interpretable machine learning, data integration, modern multivariate analysis, and graphical models with applications in neuroscience and bioinformatics. Dr. Allen is also a leader in data science education. In 2018, she founded the Rice D2K Lab, a campus hub for experiential learning and data science education. Through her leadership of the D2K Lab, Dr. Allen developed new interdisciplinary data science degree programs, established a novel capstone program in data science and machine learning, and led Rice's engagement with corporate and community partners in data science.

Dr. Allen is the recipient of several honors for both her research and educational efforts including a National Science Foundation Career Award, Rice University's Duncan Achievement Award for Outstanding Faculty, the Curriculum Innovation Award, and the School of Engineering's Research and Teaching Excellence Award. In 2014, she was named to the "Forbes '30 under 30′: Science and Healthcare" list. She is also an elected fellow of the International Statistics Institute and the American Statistical Association. Dr. Allen currently serves as an Action Editor for the Journal of Machine Learning Research and a Series Editor for Springer Texts in Statistics. Dr. Allen received her Ph.D. in statistics from Stanford University, under the mentorship of Prof. Robert Tibshirani, and her bachelors, also in statistics, from Rice University.

Benjamin Arenkiel, MD, PhD
Professor, Molecular and Human Genetics & Neuroscience
Baylor College of Medicine

Implementing Single-Cell Transcriptional Profiling Approaches to Investigate Circuit Integration of Adult-Born Neurons

Dr. Benjamin Arenkiel received his bachelor's degree in Microbiology and Chemistry from St. Cloud State University in Minnesota. In 2004 he received his doctoral degree in Genetics from the University of Utah, where he trained under Nobel Laureate Dr. Mario Capecchi. From 2005-2010, he was an HHMI post-doctoral fellow with Drs Lawrence Katz and Michael Ehlers in the Department of Neuroscience at Duke University. In December of 2010 Dr. Arenkiel joined the faculty of Baylor College of Medicine as an Assistant Professor in the Department of Molecular and Human Genetics. He is currently a Full Professor and holds adjunct positions in the Department of Neuroscience and Texas Children's Hospital. Dr. Arenkiel is currently investigating how genes and activity interface to build, maintain, and remodel neuronal connections in the brain, as well as how basal forebrain circuits influence eating disorders and neuropsychiatric disease.

Margo P. Cain, PhD
Technology Commercialization Analyst
MD Anderson Cancer Center

Quantitative Single-Cell Interactomes in Normal and Virus-Infected Mouse Lungs

Dr. Margo P. Cain graduated with her Ph.D. from the University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences in 2020. As a graduate student in the laboratory of Dr. Jichao Chen, she developed a single-cell interactome method to uncover novel interactions between various cell types in the lung, which she applied to models of disease including a lung virus infection model. After graduating, she continued her research in the Chen lab exploring the complex relationships of the cell types that make up the lung and how they coordinate the mammalian lung's response to injury and tissue repair. She is now a technology commercialization analyst at the MD Anderson Office of Technology Commercialization where she provides early patent assessment and commercialization guidance for new and existing technologies.

Shu-Hsia Chen, PhD
Emily Herrmann Chair in Immunology Research, Dr. Mary and Ron Neal Cancer Center
Director, Center for Immunotherapy Research
Professor of Oncology, Academic Institute
Full Member, Research Institute
Houston Methodist
Weill Cornell Medical College
Modulating Microglia in Alzheimer's Disease

Dr. Chen has focused her career on gene therapy and immune therapy to develop and identify the novel therapeutic modalities that can reconstruct or modulate the immune response. During the last decade at Icahn school of Medicine at Mount Sinai, she studied the mechanisms underlying the establishment of immune suppressive tumor microenvironment, which remains the major hurdle to the success of immune-based cancer therapies.

She is one of the pioneers in identification of the myeloid derived suppressor cell (MDSC) subset populations and their roles in the immune suppression in the tumor microenvironment. She is also the inventor for modulating myeloid suppressor cell function for treating autoimmune diseases and cancer. Currently she has an investigator-initiated Phase IIb clinical trial at Methodist Hospital that are derived from the research results generated in her laboratory.

Currently, she is an endowed Emily Herrmann Chair in Immunology Research, Director of Center for Immunotherapy Research at Neal Cancer Center of Excellence and Professor, Institute of Academic Medicine, and Methodist Research Institute (HMRI), Houston, Texas and Professor at Dep. Physiology, Biophysics and Systems Biology (PBSB), Weill Cornell School of Medicine, NY.

Rong Fan, PhD
Professor
Biomedical Engineering
Yale University

Spatial Multi-Omics Driving the Next Wave of Biomedical Research Revolution

Dr. Rong Fan is Harold Hodgkinson Distinguished Professor of Biomedical Engineering at Yale University and Professor of Pathology at Yale School of Medicine. He received a Ph.D. in Chemistry from the University of California at Berkeley and completed the postdoctoral training at California Institute of Technology before joining the faculty at Yale University in 2010. His current interest is focused on developing microtechnologies for single-cell and spatial omics profiling to interrogate functional cellular heterogeneity and inter-cellular signaling network in human health and disease (e.g., cancer and autoimmunity). He co-founded IsoPlexis (NASDAQ: ISO), Singleron Biotechnologies, and AtlasXomics. He served on the Scientific Advisory Board of Bio-Techne. He is the recipient of a number of awards including the National Cancer Institute's Howard Temin Career Transition Award, the NSF CAREER Award, and the Packard Fellowship for Science and Engineering. He has been elected to the American Institute for Medical and Biological Engineering (AIMBE), the Connecticut Academy of Science and Engineering (CASE), and the National Academy of Inventors (NAI).

Abstract: Despite latest breakthroughs in single-cell sequencing that revealed cellular heterogeneity, differentiation, and interactions at an unprecedented level, the study of multicellular systems needs to be conducted in the native tissue context defined by spatially resolved molecular profiles to better understand the role of spatial heterogeneity in biological, physiological and pathological processes. In this talk, I will begin with discussing the emergence of a whole new field – spatial multi-omics, and then focus mainly on a new technology platform called "Deterministic Barcoding in Tissue (DBiT)" for spatial omics sequencing developed in our laboratory over the past years. We conceived the concept of "spatial multi-omics" and demonstrated for the first time by co-mapping whole transcriptome and proteome (~300 proteins) pixel-by-pixel directly on a fixed tissue slide in a way compatible with clinical tissue specimen processing including FFPE. It has been applied to the study of developing mouse brain, human brain, and human lymphoid tissues associated with normal physiology, disease, or aging. Recently, our research enabled another new field – "spatial epigenomics" – by developing multiple DBiT-based spatial sequencing technologies for

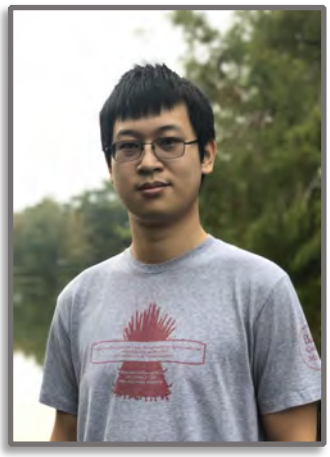
mapping chromatin accessibility (spatial-ATAC-seq), histone modification (spatial-CUT&Tag), or further combined with transcriptome or proteins. These new technologies allow us to visualize gene expression regulation mechanisms pixel by pixel directly in mammalian tissues with a near single cell resolution. The rise of NGS-based spatial omics is poised to fuel the next wave of biomedical research revolution. Emerging opportunities and future perspectives will be discussed with regard to the impact on clinical biomarker discovery and therapeutic development.

Melike Lakadamyali, PhD
Associate Professor
Physiology
University of Pennsylvania

Super-Resolution Imaging of Chromatin Structure and Dynamics in Health and Disease

Dr. Lakadamyali obtained her BS in Physics in 2001 from the University of Texas, Austin and her PhD in Physics in 2006 from Harvard University. Dr. Lakadamyali started her independent group at ICFO-Institute of Photonic Sciences in Barcelona in 2010 and was awarded tenure in 2015. In 2017 she moved to the University of Pennsylvania´s Department of Physiology at the Perelman School of Medicine as an Assistant Professor and was promoted to Associate Professor in 2020.

She received several honors including the European Molecular Biology Organization (EMBO) Young Investigator award, Technical University of Munich-Institute for Advanced Study Hans Fischer Fellowship and the Linda Pechenik Montague Investigator award. Her research focuses on the development of advanced light microscopy methods that provide high spatial and temporal resolution. Her lab is applying these advanced microscopy methods to study how the cytoskeleton and motor proteins regulate trafficking and spatial organization of organelles in the cytoplasm. In addition, her lab is studying how chromatin structure regulates gene activity and cell identity.



Qingnan Liang, PhD
Postdoc
MD Anderson Cancer Center

Robust Pathway Analysis for scRNA-seq and Spatial Transcriptomics Data

Qingnan Liang obtained his bachelor's and master's degree in 2013 and 2016, majored in biology and biophysics, both from Fudan University in China. Qingnan worked in Dr. Rui Chen's lab in Baylor College of Medicine for his PhD working on single-cell multi-omics profiling of the human retina. After graduation in 2022, Qingnan joined Dr. Ken Chen's lab in MDACC focusing on development of bioinformatics tools and analysis of high-throughput data.

Nicholas E. Navin, PhD
Professor & Chair
Department of Systems Biology
Grady Saunders Distinguished Professor
Director, CPRIT Single Cell Genomics Center
MD Anderson Cancer Center

Decoding Premalignant Breast Cancer Progression with Single Cell Genomics

Dr. Nicholas Navin is the Professor & Chair of the Department of Systems Biology at the MD Anderson Cancer Center. He is the director of the CPRIT Single Cell Genomics Center and co-director of the Advanced Genomic Technology Center (AGTC). He is the co-leader of the Human Breast Cell Atlas Project that aims to define cell types and states in normal mammary tissues. Dr. Navin completed his Ph.D. and postdoctoral studies at the Cold Spring Harbor Laboratory and Stony Brook University. He is internationally recognized for his seminal work on developing single cell DNA sequencing techniques to study cancer. Dr. Navin developed one of the first single cell DNA sequencing methods called SNS (Navin et al. 2011 Nature) which played a pivotal role in establishing the field of single cell genomics. His current research work focuses on understanding clonal evolution in cancer, in the context of invasion, metastasis and therapy resistance. His research group has identified a punctuated model of copy number evolution in breast cancer, multi-clonal invasion in DCIS breast cancer and transcriptional reprogramming during chemotherapy resistance in triple-negative disease. Dr. Navin has been the recipient of many awards, including the AAAS Wachtel Award, the ACS Research Scholar Award, the Living Legend Basic Science Award, the Damon-Runyon Innovator Award, the AAAS Fellow Award, the AACR Outstanding Achievement in Basic Research Award and was a Finalist for the 2019 Blavatnik Award.

Guy Nir, PhD
Assistant Professor
Biochemistry and Molecular Biology
Univ. of Texas Medical Branch Galveston

Studies of Genome Organization at the Single-cell Level

Dr. Nir's lab studies how genome organization and gene expression impact cell fate. This is challenging because each cell may adopt a high number of structural and functional states, which results in a significant degree of cell-to-cell heterogeneity. Therefore, we combine single-cell spatial omics technologies with molecular genetics and computational tools to simultaneously visualize transcriptional activity and chromosome structure. Primarily, they utilize Oligopaint Fluorescence in situ Hybridization (FISH) probes to detect RNA expression levels and their relationship to the folding of chromosomes. Additionally, through a technology they call 'sequential OligoSTORM', they image the expression and folding of many loci within the same single cells while distinguishing their parental origin and achieving high genomic and spatial resolution.

Using this technology, they discovered that active and inactive chromosomal segments fold differently and are spatially segregated from one another. Thus, they established a connection between structure and function at the single-cell level. However, they noticed a high structural variability as several chromosomal segments showed contrasting structural signatures between cells. That is, they observed a high degree of variability in the identity of the chromosomal segments that interacted with each other between cells of the same type. Therefore, they now study why chromosomes packaged by specific folding mechanisms exhibit a high degree of heterogeneity and whether this structural variability impacts genome function. They strive to make accurate models of how genome organization, gene expression, and cell fate are connected to one another and how their relationship is influenced by heterogeneity. His quantitative approach originating from my background in physics, experience in multiplexed and super-resolution imaging technologies, and extensive knowledge of genome organization make me an excellent candidate to lead this proposal.

Zhen Zuo, MS
Graduate Student
Quantitative & Computational Biosciences
Baylor College of Medicine

Single-cell Multiomics Analysis of Human Retinal Development

Zhen is a Ph.D. candidate in the Quantitative & Computational Biosciences Graduate Program at Baylor College of Medicine. Before joining Chen Lab, he received his bachelor's and master's degrees from the University of Illinois Urbana-Champaign in Statistics. He is interested in single-cell analysis.

Rapid Fire Presenters

Jinzhuang Dou, MD Anderson Cancer Center
Monopogene: Variant Calling and Genetic Ancestry Inference from Single Cell Sequencing
Poster 4

Thomas Gallup, EMPIRI Inc.
Single Cell RNA-sequencing Data from Needle Biopsy Cores from Clinical Trials
Poster 6

Andrew Koval, Rice Univ.
Estimating The Timing Of Past Events In Cancer, Based On Single-Cell DNA Sequencing Data
Poster 10

Jose Maldonado, Houston Methodist Research Institute
Elucidating Cell: Cell Communication and Immunotherapy Responses in Deeply Characterized Mouse Glioma Models Representing Human Glioma Subtypes
Poster 12

Anna Naglis, UT Health Science Center Houston
The Role Of Microglia And Macrophages In Rod Photoreceptor Regeneration
Poster 16

Noriaki Ono, UT Health Science Center Houston
Integrative Single-Cell Genomic Analysis Identifies a New Type of Skeletal Stem Cells in Bone Marrow Endosteum
Poster 17

Eyad Shihabeddin, UT Health Science Center Houston
Rod Photoreceptor Regeneration In A Zebrafish Model of Retinitis Pigmentosa.
Poster 18

Pavel Sumazin, Baylor College of Medicine
Effective Methods for Bulk RNA-Seq Deconvolution using scRNA-Seq and snRNA-Seq Derived Transcriptomes
Poster 20

Nicholas Tran, Baylor College of Medicine
Identifying Gene Targets for Neuroprotection and Axon Regeneration Using scRNA-seq
Poster 21

Rapid Fire Presenters

Kaile Wang, MD Anderson Cancer Center
Archival Single Cell Sequencing Reveals Persistent Subclones Over Years to decades of DCIS Progression
Poster 23

John Weinstein, MD Anderson Cancer Center
Development of OmicPioneer-sc, A Tool that Integrates UMAPs with Clustered Heat Maps and Pathway Diagrams
Poster 24

Poster presenters
In alphabetical order

Presenter First Name	Presenter Last Name	Presenter Institution	Title of Submission	Poster #
James	Cai	Texas A&M University	A Quantum Circuit Model for inferring Gene Regulatory Networks with Application to Single-cell Transcriptomic Data	1
Xuesen	Cheng	Baylor College of Medicine	A Single Cell Multi-omics Atlas of the Human Retina	2
Jongsu	Choi	Baylor College of Medicine	Spatial Organization of the Mouse Retina at Single Cell Resolution	3
Jinzhuang	Dou	University of Texas MD Anderson Cancer Center	Monopogene: Variant Calling and Genetic Ancestry Inference from Single Cell Sequencing	4
Andre	Fonseca	University of Houston	Distinguishing Private and Public T-cell Repertoires from Pan-cancer Single-cell Datasets: Thoughts about T-cell Shareability and Antigen-specificity	5
Thomas	Gallup	EMPIRI Inc	Single Cell RNA-sequencing Data from Needle Biopsy Cores from Clinical Trials	6
Pablo	Guillen-Rondon	University of Houston Downtown	Machine Learning Applications on Intratumoral Heterogeneity in Glioblastoma Using Single-cell RNA-Seq Data	7
Jiakai	Hou	University of Houston	Single-Cell CRISPR Immune Screens Reveal Immunological Roles of Tumor Intrinsic Factors	8
Yuefan	Huang	University of Texas MD Anderson Cancer Center & University of Texas Health Science Center at Houston	Characterizing Cancer Metabolism from Bulk and Single-cell RNA-seq Data using METAFlux	9
Andrew	Koval	Rice University	Estimating The Timing Of Past Events In Cancer, Based On Single-Cell DNA Sequencing Data	10

Poster presenters
In alphabetical order

Presenter First Name	Presenter Last Name	Presenter Institution	Title of Submission	Poster #
Jin	Li	Baylor College of Medicine	Single Cell Atlas of the Human Retina	11
Jose	Maldonado	Houston Methodist Research Institute	Elucidating Cell:Cell Communication and Immunotherapy Responses in Deeply Characterized Mouse Glioma Models Representing Human Glioma Subtypes	12
Lianjie	Miao	University of Houston	Cells In Pro-epicardial Region Are Heterogenous With Pacemaker Progenitor Cells And SMC-like Cells	13
Rodrigo	Moreno-Campos	Rice University	Lifetime Single Cell Atlas of the Enteric Nervous System in Zebrafish Identifies p53 Transcriptional Landscapes May Be Involved in Developmental Neuron Death	14
Mizuki	Nagata	University of Texas Health Science Center at Houston	Single-cell Transcriptomic Analysis Reveals Developmental Relationships and Specific Markers of Mouse Periodontium Cellular Subsets	15
Anna	Naglis	The University of Texas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences (GSBS)	The Role Of Microglia And Macrophages In Rod Photoreceptor Regeneration	16
Noriaki and Jialin Liu, Univ. of Michigan	Ono	University of Texas Health Science Center at Houston	Integrative Single-Cell Genomic Analysis Identifies a New Type of Skeletal Stem Cells in Bone Marrow Endosteum	17

Poster presenters
In alphabetical order

Presenter First Name	Presenter Last Name	Presenter Institution	Title of Submission	Poster #
Eyad	Shihabeddin	University of Teas MD Anderson Cancer Center UTHealth Graduate School of Biomedical Sciences	Rod Photoreceptor Regeneration In A Zebrafish Model of Retinitis Pigmentosa.	18
Brenda Bin	Su	Baylor College of Medicine	Alteration of the Transcriptome in Response to Shrimp Allergens in Shrimp Allergic Peripheral Blood Mononuclear Cells	19
Pavel	Sumazin	Baylor College of Medicine	Effective Methods for Bulk RNA-Seq Deconvolution using scRNA-Seq and snRNA-Seq Derived Transcriptomes	20
Nicholas	Tran	Baylor College of Medicine	Identifying Gene Targets for Neuroprotection and Axon Regeneration Using scRNA-seq	21
Jun	Wang	Baylor College of Medicine	The Genetic Effect On Gene Expression And Chromatin State At Single-cell Resolution	22
Kaile	Wang	MD Anderson Cancer Center	Archival Single Cell Sequencing Reveals Persistent Subclones Over Years to decades of DCIS Progression	23
John	Weinstein	University of Texas MD Anderson Cancer Center	Development of OmicPioneer-sc, A Tool that Integrates UMAPs with Clustered Heat Maps and Pathway Diagrams	24
Yongjian	Yang	Texas A&M University	GenKI: A Variational Graph Autoencoder-Based Virtual Knockout Tool for Gene Function Prediction Via Single-Cell Gene Regulatory Network Perturbation	25

Poster 1

A Quantum Circuit Model for Inferring Gene Regulatory Networks with Application to Single-cell Transcriptomic Data

Cristhian Roman-Vicharra[1,2], James J. Cai[1,2,3,*]

1. Department of Electrical and Computer Engineering, Texas A&M University
2. Department of Veterinary Integrative Biosciences, Texas A&M University
3. Interdisciplinary Program of Genetics, Texas A&M University

Corresponding author: James Cai, VIBS, Texas A&M University, College Station, TX, E-mail: jcai@tamu.edu

Background: Quantum computing holds the promise to achieve certain types of computation that would otherwise be unachievable by classical computers. Recent advent in the development of quantum algorithms has enabled various applications in chemistry, finance, and cryptography. **Hypothesis/Goals**: In this work, we present a quantum circuit model for constructing gene regulatory networks (GRNs) from single-cell transcriptomic data. **Methods**: The model is based on the idea of using the entanglement of qubits to simulate the interactions between genes. Each qubit in the circuit represents a gene, and qubits are entangled to simulate the interaction between genes. The strength of gene interactions is estimated using the rotation angle of controlled unitary gates between qubits. **Results**: We provide preliminary results that suggest our quantum single-cell GRN (qscGRN) modeling method is competitive and warrants further investigation. Specifically, we present the preliminary results derived from the single-cell RNA sequencing (scRNA-seq) data of human lymphoblastoid cell lines, focusing on genes in the nuclear factor-kappa B (NF-κB) signaling pathway. We demonstrate that our qscGRN model can recover known and detect novel regulatory relationships, setting the stage for further investigations on GRNs, given that relationships between fully interconnected genes are approached more effectively by quantum modeling than by statistical correlations. **Conclusions**: Our quantum circuit model enables the modeling of vast feature space occupied by cells in different transcriptionally activating states, simultaneously tracking activities of thousands of interacting genes and constructing more realistic single-cell GRNs without relying on statistical correlation or regression. We anticipate that quantum computing algorithms based on our circuit model will find more applications in data-driven life sciences, paving the way for the future of predictive biology and precision medicine.

Poster 2

A Single Cell Multi-omics Atlas of the Human Retina

Cheng X[1], Liang Q[1, 2], Wang J[1] , Owen L[3, 4], Li Y[1], DeAngelis M[5], Chen R[1, 2]

1. HGSC, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, 77030, United States.
2. Verna and Marrs McLean Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX, 77030, United States.
3. Department of Ophthalmology and Visual Sciences, University of Utah, Salt Lake City, UT, 84132, United States.
4. Department of Population Health Sciences, University of Utah, Salt Lake City, UT, 84132, United States.
5. Department of Ophthalmology, Jacobs School of Medicine and Biomedical Engineering, University at Buffalo SUNY, and the VA Western New York Healthcare System, Buffalo, NY 14215, USA, Buffalo, NY 14215, United States.

Corresponding author: Rui Chen, Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, 77030, United States. E-mail: ruichen@bcm.edu

Background: The human retina, as part of the central nerve system and the key light sensing tissue in the eye, has high cell heterogeneity, with an estimate of over 60 distinct cell types distinguished by morphology and physiology.

Goals: To better understand the gene expression and regulation in each cell type, our study generates the multi-omics atlas at the single-cell level for adult human retina.

Methods: Single-nuclei RNA-seq and single-nuclei ATAC-seq were performed for retinae from human donors using the 10x Genomics technologies. For each donor retina, both the fovea and peripheral regions are profiled. Rare cell types, including the amacrine and retinal ganglion cell, are enriched based on the NeuN gradient. Integrative analysis of transcriptomic and epigenomic data is performed to identify gene regulator networks (GRNs), transcriptional factor binding motif enrichment, and putative gene cis-regulatory elements.

Results: A large single nuclei multi-omics dataset containing over 250K cells with single-nuclei RNA-seq and over 150K cells with single-nuclei ATAC-seq from human adult retina was generated. The atlas contains over 60 distinct cell types with an estimated sensitivity of 0.01%. Cross-species comparison among human, monkey, and mouse retina reveals that cell subtypes are overall conserved with RGCs are most divergent. In contrast, significant difference is observed at the transcriptomic level in corresponding cell types. With a large-scale single-nuclei ATAC-seq, we uncovered 10 times more open chromatin regions than the bulk study. Many of these regions are specific for rare cell types and were not observed in bulk ATAC-seq data. By combining snRNA/ATAC-seq data, 18% of these open chromatin regions (~47K) can be linked to their target genes as putative regulatory elements. Strikingly, a significant portion of these cis regulatory elements are novel and show cell-type-specific activity. Finally, the single nuclei multi-omics data allows fine mapping and functional annotation of genomic variants through integration of eQTL and GWAS results.

Conclusions: Our study represents the most comprehensive transcriptome and epigenome atlas of the human retina to date. This atlas enables in-depth integrative analysis at individual cell type resolution, making it a highly valuable resource for the research community.

Acknowledgements: This work is supported by Chan-Zuckerburg Foundation Grant CZF2019-002425.

Poster 3

Spatial Organization of the Mouse Retina at Single Cell Resolution

Choi J[1], Li J[2], Ferdous S[2], Liang Q[1], Moffitt JR[3], Chen R[1,]

1. Department of Biochemistry and Molecular Biology, Baylor College of Medicine, Houston, TX, USA
2. Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA
3. Program in Cellular and Molecular Medicine, Boston Children's Hospital; Department of Microbiology, Harvard Medical School, Boston, MA, USA

Corresponding author: Rui Chen, Department of Molecular and Human Genetics, Baylor College of Medicine, One Baylor Plaza, Houston, Texas (ruichen@bcm.edu)

Background: The visual signal processing in the retina requires the precise organization of diverse neuronal types working in concert. Single-cell omics studies have identified more than 120 different neuronal subtypes in the mouse retina, each with a unique functional role within the circuitry.
Hypothesis/Goal: While the neuronal cell body position is critical for proper retinal circuitry, little is known about the spatial organization of retinal cells on the subtype level. We sought to investigate the intricate spatial organization of cell subtypes in the retina.

Methods: Using an imaging based transcriptomics method, multiplexed error-robust fluorescence in situ hybridization (MERFISH), we generated the first single-cell spatial atlas of the mouse retina using.

Results: We profiled over 100,000 retinal cells and identified all major cell types with over 100 cell subtypes through the integration with reference single-cell RNA sequencing data. Our high-resolution spatial atlas revealed a compelling laminar organization of retinal cells at the major cell type and subgroup level, both of which have strong correlation with the birth order with earlier born cell types and subtypes taking a basal position and later born cell types taking an apical position. We further identified 8 previously unknown displaced amacrine cell subtypes with unique lamination patterns. Within laminar sublayers, we observed overall random dispersion of cells at the subtype level, contradicting the common assumption that the soma of retinal neurons are assembled as regular arrays.

Conclusion: Our result indicate that laminar organization of cells extends beyond the major cell types to cell subtypes in the retina. Furthermore, our data shows that retinal mosaics are driven by dendritic field patterning rather than neuron soma placement.

Poster 4

Monopogene: Variant Calling and Genetic Ancestry Inference from Single Cell Sequencing

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Background

Distinguishing how genetics and environment impact gene expression among people from different ancestries can improve understanding of variable risk for diseases. Current single-cell omics measures cell types/states variation on ancestrally diverse tissue samples (such as Ancestry Networks for Human Cell Atlas). However, it is still challenging to identify population ancestry effects on cell-type-specific epigenomes and transcriptomes, due to a lack of genetic components in current single cell studies.

Goals

Here, we devise *Monopogene*, a computational tool enabling researchers to detect single nucleotide variants (SNVs) and infer genetic ancestry from a variety of single cell transcriptomic and epigenomic sequencing data.

Methods

Monopogene includes two major components:

Germline SNP scan: For variant sites in the 1000 Genome Phase 3 panel (1KG3), genotype likelihoods from Samtools are used to calculate genotypes by leveraging linkage disequilibrium (LD) from external reference panel. Genotypes showing discordance before and after LD based refinement are used to estimate a sequencing error model.

De novo SNV scan: Variant sites not in the 1KG3 are further analyzed if having high coverage and not flagged as sequencing errors. Monovar is used to identify potential somatic mutations or RNA editing events at cluster (or cell) level.

Results/Conclusions

Monopogene can identify 100K~2.5M germline SNPs from various single cell sequencing platforms (scRNA-seq, snRNA-seq, snATAC-seq etc). Genotyping accuracy is higher than 95% by comparison using matched whole genome sequencing (WGS) data. Down-sampling analysis demonstrates that number of germline SNPs can largely be predicted by the cell number in each sample. We applied *Monopogene* on Human Breast Atlas (HBCA) and Asian Immune Diversity Atlas (AIDA), showing that that genotypes from our tool enables to estimate both global and local ancestry components accurately for admixed samples.

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Poster 5

Distinguishing Private and Public T-cell Repertoires from Pan-cancer Single-cell Datasets: Thoughts about T-cell Shareability and Antigen-specificity

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Background: Characterizing the T-cell receptor (TCR) repertoire is critical for immune-based therapeutic development. However, identifying TCR clonotypes with therapeutic potential is a complex process due to distinct components related to T-cell biology, such as antigen-specificity, cellular phenotypes, and dysfunctional states i.e., T-cell exhaustion. **Goals:** To fill this gap, we leveraged paired single-cell TCR and RNA profiling to characterize T-cell specificity and functional states across 21 cancer types. We reason that integrating antigen-specificity and cellular phenotypes can uncover potential candidates for immunotherapy based on T cell functional state. Additionally, we classified clonotypes repertoire into private (cancer-specific) and public (e.g., potential memory T-cells). For the cancer-specific clonotypes, we analyze the shareability across patients per cancer type. **Methods:** We analyzed the TCR repertoire using GLIPH2 and immunarch packages. The GLIPH2 antigen-specificity analysis was used to distinguish between private and public status. To improve the GLIPH2 clustering process, we compiled data from distinct databases, including VDJDatabase and McPAS-TCR. The compiled CDR3β sequences were used as GLIPH2 background. Clonotypes clustered together with background sequences were considered as public repertoire. Next, we evaluated gold-standard metrics related to each TCR repertoire status, including T cell diversity, clonality, and gene usage. **Results:** In total, our background database encompassed 80649 TCR CDR3β sequences related to viral infection. The GLIPH2 analysis successfully categorized TCR repertoire into public and private CDR3β clonotypes. Furthermore, we found differences in clonality and gene usage between public and private sequences. In particular, private CDR3β sequences are enriched with hyperexpanded clonotypes across cancer types. The private clonotype shareability seems to be cancer-dependent. Hematopoietic tumors showed low shareability levels in comparison with other tumors. This finding might highlight the molecular heterogeneity in hematopoietic tumors. Finally, we correlate antigen-specificity groups derived from private repertoires with cellular phenotypes (e.g., activation and exhaustion). **Conclusions:** In conclusion, we demonstrate a promising approach to prioritize cancer-specific clonotypes for clinical applications. In this preliminary report, we presented a tumor-centered analysis that can easily be expanded for adjacent tissues and blood samples. Comparisons with adjacent and blood repertoire can further increment the TCR repertoire analysis and clonotype selection. Furthermore, it has not escaped our attention that public CDR3β sequences could also play an important role in immune response due to T-cell cross-reactivity to cancer antigens. Thus, public repertoire could be another valuable resource for identifying therapeutic T-cell candidates.

Poster 6

Single Cell RNA-sequencing Data from Needle Biopsy Cores from Clinical Trials

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Background: Single cell RNA-sequencing (scRNA-seq) yields valuable insights into the molecular heterogeneity of multiple cell types in normal and cancer tissues. scRNA-seq approach has the potential to not only answer basic research questions but also enhance clinical studies and clinical trials and accelerate drug development and testing. However, a consistent and reproducible method for isolating viable single cells and generating high quality single cell data from needle biopsy cores has been challenging to develop and apply to clinical samples.

Hypothesis/Goals: Based on our experience isolating single cells for scRNA-seq from a large number of surgical tumor tissues, we set out to optimize the dissociation and sample handling protocol to generate viable single cell suspensions in adequate quantity for scRNA-seq from needle biopsy cores.

Methods: A total of 17 de-identified 18-gauge needle biopsy core samples were collected in collaboration with MD Anderson Cancer Center investigators. Samples were from liver, lymph node, pelvis, abdominal, neck, and lung tissues and included matched pre- and post-treatment samples. Patient biopsies were kept in RPMI medium on ice and transferred to EMPIRI (time to capture ranged from 3 to 6.5 hours after biopsy collection). Samples were dissociated using mechanical and enzymatic methods to achieve a single cell suspension. Cells were washed and viability and cell counts were verified before capture via 10x Chromium Connect. Captured cells were processed through the 10x Genomics Chromium Next GEM Single Cell workflow before sequenced on Illumina NovaSeq 6000 sequencer. Raw sequencing data were processed through EMPIRI's computational pipeline that includes QC steps, doublet removal, and Seurat and other downstream analyses.

Results: Recovery of viable cells from individual 18-gauge biopsy cores ranged from 2,000-300,000 cell per core, depending on the tissue type and cellularity. Cell viability was strictly monitored and was maintained above 80% for 16 of 17 samples (most samples >90%). Cell counts after sequencing and pipeline analysis averaged 6,466 cells per sample. The median number of UMI counts per cell was 5,580, and an average of 1,699 genes were identified per cell. Average sequencing saturation was 73%.

Conclusions: Here, we demonstrate the feasibility of integrating scRNA-seq analysis into clinical trials or clinical studies to obtain rapid insights into on-target drug effects and anticipated cellular responses to therapies, including immunotherapies, within 3 weeks of biopsy collection. We have established a method for isolating high quality single cells for scRNA-seq from tissue biopsy core, as small as a single 18-gauge needle core. We tested our protocol on 17 human samples and showed successful isolation of highly viable cells from lung, lymph node, pelvis, abdominal, neck, and lung tissues. We were able to generate scRNA-seq data sets from all samples for downstream analysis.

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Poster 7

Machine Learning Applications on Intratumoral Heterogeneity in Glioblastoma Using Single-cell RNA-Seq Data

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Background
Artificial Intelligence (AI) is revolutionizing all fields that affect people's lives and health. One of the most critical applications is in the study of tumors. It is the case of glioblastoma (GBM) that has behaviors that need to be understood to develop effective therapies.

Hypothesis/Goals
Due to advances in single-cell RNA sequencing, it is possible to understand the cellular and molecular heterogeneity in the GBM. Given that there are different cell groups in these tumors, there is a need to apply Machine Learning (ML) algorithms. It will allow extracting information to understand how cancer changes and broaden the search for effective treatments.

Methods
We proposed multiple comparisons of ML algorithms to classify cell groups based on GBM RNA-Seq data. This broad comparison spectrum can show the scientific-medical community which models can achieve the best performance in this task. In this work are classified the following cell groups: Tumor Core (TC), Tumor Periphery (TP), and Normal Periphery (NP), in binary and multi-class scenarios.

Results
This work presents the biomarkers found for the models with the best results. The analyses presented here allow us to verify the biomarkers to understand the genetic characteristics of GBM, which may be affected by a suitable identification of GBM heterogeneity.

Conclusions
This work obtained for the four scenarios covered cross-validation results of 93.03% ± 5.37%, 97.42% ± 3.94%, 98.27% ± 1.81% and 93.04% ± 6.88% for the classification of TP versus TC, TP versus NP, NP versus TP and TC (TPC), and NP versus TP versus TC, respectively.

Poster 8

Single-Cell CRISPR Immune Screens Reveal Immunological Roles of Tumor Intrinsic Factors

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Background: Genetic screens are widely exploited to develop novel therapeutic approaches for cancer treatment, but it is still time- and resource- intensive to individually validate identified factors and elucidate their working mechanisms. Here, we aim to establish single-cell CRISPR screen (scCRISPR) platforms which are suitable for immune-related screens involving multiple cell types.

Method: We integrated two scCRISPR platforms, namely Perturb-seq and CROP-seq, with both *in vitro* and *in vivo* immune screens. We knocked out three tumor intrinsic factors with the potential to modulate antitumor immune responses, namely *Prmt1, Ripk1,* and *Axl*, which were selected and well validated from our previous genetic screening, in a murine MC38 tumor cell line by gRNA-expressing vectors compatible with either Perturb-seq or CROP-seq. Then, we evaluated the effects of each perturbation on gene expression profile and responses to *in vitro* T cell killing and *in vivo* anti-PD-1 treatment at the single-cell level. Meanwhile, we optimized experimental conditions including the optimization of capture sequence selection, sample preparation and data analysis pipelines to achieve better consistency between results from high-throughput and individual validations. Furthermore, we applied results from scCRISPR immune screens to better understand mechanisms of tumor immune resistance.

Results: Our results showed that scCRISPR platforms can simultaneously characterize gene expression profiles and perturbation effects present in individual cells in different immune screen conditions. Results from scCRISPR immune screens also predict transcriptional phenotype associated with clinical responses to cancer immunotherapy. Furthermore, scCRISPR screen platforms reveal the interactive relationship between targeting tumor intrinsic immune factors and T cell-mediated antitumor immune response which cannot be easily assessed by bulk RNA-seq. Analyses from interactive relationship highlight several novel mechanisms by which targeting these factors modulate response to cancer immunotherapy, such as regulating FAT10 signaling, protein ubiquitination and oxidative phosphorylation.

Conclusion: In this study, experimental protocols and bioinformatics pipelines have been established and optimized for both in vitro and in vivo immune screens using two different scCRISPR platforms. Our optimized experimental design and data analysis method can better capture the phenotype changes of genetic perturbation and immune treatment and generate reliable transcriptional profiles. More importantly, our results demonstrate that scCRISPR immune screens can predict transcriptional phenotype associated with clinical responses to cancer immunotherapy.

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Poster 9

Characterizing Cancer Metabolism from Bulk and Single-cell RNA-seq Data Using METAFlux

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Abstract
Cells often alter metabolic strategies under nutrient-deprived conditions to support their survival and growth. Characterizing metabolic reprogramming in the tumor microenvironment (TME) is of emerging importance in cancer research and patient care. However, recent technologies only measure a subset of metabolites and cannot provide *in situ* measurements. Computational methods such as flux balance analysis (FBA) have been developed to estimate metabolic flux from bulk RNA-seq data and can potentially apply to single-cell RNA-seq (scRNA-seq) data. However, it is unclear how reliable current methods are, particularly in tissue TME characterization. Here, we present a computational framework METAFlux (METAbolic Flux balance analysis) to infer metabolic fluxes from bulk or single-cell transcriptomic data. Large-scale experiments using cell-lines, the cancer genome atlas (TCGA), and scRNA-seq data obtained from diverse cancer and immunotherapeutic context validated METAFlux's capability to characterize metabolic heterogeneity and metabolic interaction amongst cell types.

Poster 10

Estimating The Timing of Past Events In Cancer, Based On Single-Cell DNA Sequencing Data

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Background: A malignant tumor is often composed of clusters (i.e., clones) of cells that compete for scarce resources in the tumor micro-environment. Estimating the growth rates, mutation rates, and birth times (i.e., the evolutionary parameters) of these clones can be used to detect whether newer, more malignant tumor clusters arrive early or late in the lifetimes of tumors for a given cancer type. However, estimating these parameters from typically noisy single-cell sequencing data of single-nucleotide variants (SNVs) remains challenging, even as the high-resolution data provides opportunities for more precise estimation.

Hypotheses/Goals: We use theory from population genetics, a set of neutral mutation equations, and the site frequency spectrum (SFS) of single-cell DNA sequencing data to estimate the evolutionary parameters of each clone.

Methods: We simulate tumors from a branching process that explicitly incorporates our evolutionary parameters of interest: the growth rates, mutation rates, and birth times of each clone. We devise criteria to partition the frequencies of mutations found in each clone, allowing for model identifiability in estimating the evolutionary parameters.

Results: Our model generates unbiased estimates of the evolutionary parameters of each clone. Furthermore, we demonstrate that our model is robust to varying the true underlying evolutionary parameters, to increases in sequencing errors, and to moderate misclassification of cells to clones.

Conclusions: We propose a novel method to estimate the evolutionary histories of tumors. Our method remains robust to sequencing errors because our criteria to partition the mutation frequencies is insensitive to moderate levels of noise in the data. Future work is needed to better quantify and reduce the uncertainty of our estimates. However, our model can be used to provide guidance when making decisions about screening times for a given cancer type by potentially detecting patterns of the birth times of faster growing clones.

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Poster 11

Single Cell Atlas of The Human Retina

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Background

Single-cell technologies have become powerful tools for studying cellular components, transcriptome relationships, and regulatory mechanisms underlying various retinal diseases and biological processes. Single-cell RNA sequencing (scRNA-seq) has advanced the assessment of cellular heterogeneity by detecting transcriptional similarities and differences at single cell resolution. However, the number, size, and complexity of scRNA-seq datasets are restricted by the limited availability of human samples, resulting in the lack of a complete single-cell reference of the human retina.

Goals

To fill the gap, we have generated the most comprehensive single-cell/nucleus RNA-seq dataset for the adult human retina to date. By incorporating community annotation from experts in the retina field, this single-cell atlas serves as an easy-to-use data resource for the retinal genomics community.

Methods

First, we generated the largest single-cell/nucleus RNA-seq dataset to date from in-house donor samples. We then incorporated publicly available datasets to assemble the most comprehensive collection of single cells for the human retina. The collected data underwent our standardized preprocessing pipeline to filter out empty droplets, estimated doublets, and ambient RNA. The major human retina cell types were annotated for each sample using pre-trained SVM classifiers by scPred. To annotate subtypes of amacrine cells, bipolar cells, and retinal ganglion cells (RGCs), cells of each major cell type were first harmonized across samples. The integration methods were evaluated by a benchmark analysis of major cell types using scIB, and scVI had the top performance and was selected for subtype integration of three cell types. The low-dimensional representations of integrated cells were used to measure cell similarities and calculate cell clustering by the Leiden algorithm. To facilitate public use of the reference, we deposited the reference at CELLxGENE for visualization and gene signature inspection. Pretrained classifiers for annotating new human retinal cells using scPred were also made available.

Results and conclusions

We have collected over 2 million single cells from in-house single-cell/nucleus RNA-seq experiments of retinas from 26 donors and 6 public datasets. The cell atlas contains 11 major cell types and over 70 subtypes. Specifically, the RGC atlas is the most comprehensive to date, facilitated by our optimized protocol for RGC enrichment. The resulting cell labeling forms a single-cell reference of the human retina. The reference has been shared at CELLxGENE, and pretrained classifiers are available by public URL. Furthermore, downstream analysis generates updated gene patterns of identified major and subtypes. The complexity of the dataset also enables discovery of single-cell transcriptomic landscapes associated with age, gender, and ethnicity. Therefore, this single cell atlas yields a valuable data resource of the human retina for the field.

Poster 12

Elucidating Cell:Cell Communication and Immunotherapy Responses in Deeply Characterized Mouse Glioma Models Representing Human Glioma Subtypes

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Background: Immunotherapy is a promising treatment modality for glioma; however, clinical trials thus far have failed to provide significant clinical benefit to most GBM patients. GBM is one of the "immune cold" tumors characterized by poor infiltration of T cells even though, in some patients, more than 40% glioma cells are composed of immune cells. Most of these immune cells in GBM, however, are immune suppressive myeloid cells that block T cell infiltration and/or activation. To elucidate the mechanisms of immune evasion and to understand how the immune system interacts with glioma and stromal cells that shape the immune suppressive landscape in GBM, there is an urgent need for immune-competent preclinical models that recapitulate the human disease.

Hypothesis/Goals: The goal of this project is to generate and characterize immune-competent mouse models of glioma that faithfully recapitulate the genetic and molecular heterogeneity of human gliomas, and use them to assess molecular subtype-specific immune phenotypes and differential susceptibility to immunotherapies.

Methods: We report multi-dimensional analyses of six different mouse glioma models in the C57BL6/J background that represent all three human GBM molecular subtypes. To compare the immune phenotype of each model, we performed flow cytometry and single cell RNA sequencing from the six models to determine the cellular heterogeneity of glioma and immune cells in each model. We also analyzed cell:cell communications using CellChat to identify novel immunotherapy targets.

Results: Glioma cell analysis at the single cell level revealed that cell-of-origin rather than the oncogenic driver plays a dominant role in determining the molecular phenotypes of glioma cells and their molecular subtypes. Importantly, consistent with human GBM, each mouse model contained glioma cells of multiple molecular subtypes. Furthermore, we identified six molecular subtypes of glioma associated myeloid cells (GAMs) and nine different subtypes of T cells. Cross-species comparisons of glioma and immune cell subtypes between human and mouse at the single cell level revealed a strong correlation between the human immune cell molecular phenotypes and those in mouse gliomas. Furthermore, we report qualitative and quantitative differences in cell:cell communication among different stromal cells and glioma cells in each model, and propose that these interactions shape the local niche and functional neighborhoods. Finally, we leverage these preclinical models to elucidate underlying molecular mechanisms that drive differential sensitivities of each model to immune checkpoint inhibitors.

Conclusions: We report deeply characterized mouse models of human GBM subtypes and highlight their utility as preclinical models for immunotherapy evaluation and foundational brain tumor immunology studies.

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Poster 13

Cells In Pro-epicardial Region Are Heterogenous With Pacemaker Progenitor Cells And SMC-like Cells

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Background: Epicardial cells (EpiCs), derived from pro-epicardium (PE), undergo epithelial-mesenchymal transition (EMT) and subsequently differentiate into multiple cell types during development. In the adult, following myocardial infarction, EpiCs will be activated, recapitulate the embryonic development program, and participate in cardiac remodeling and regeneration, making them a promising target for cardiac regeneration. However, it is unclear if pro-epicardial cells (pro-EpiCs) are heterogenous with different cell populations or homogenous representing a population of multipotent cells.

Hypothesis: Pro-EpiCs are heterogenous, containing several populations of fate-restricted unipotent cells.

Methods: We applied single-cell RNA-Deep-sequencing (scRNA-DSeq) paired with RNAScope, genetic network analysis, single and dual-reporter lineage tracing to identify the heterogeneity of the *Tbx18*$^{Cre/+}$ labeled cells in PE. We generated a *Myrf*$^{DreERT2/+}$ knockin line under the control of *Myrf*, a newly discovered gene specifically expressed in the PE region, to determine the specific region that the pacemaker progenitor cells (PMPC) derived from.

Results: The pro-epicardial cells are heterogeneous, with three clusters displaying distinct spatial locations and transcriptional profiles. Cluster 1 are mesothelial cells, and Cluster 2 express markers specific to smooth muscle cells (SMC). Surprisingly, Cluster 3 express genes specific to PMPCs. With the *Dre* line (*Myrf*$^{DreERT2/+}$), a PMPC-specific *Cre* line (*Shox2*$^{Cre/+}$), and Ai66D dual reporter, we found that PMPCs are derived from the region of PE that is close to the atrial wall.

Conclusions: *Tbx18*$^{Cre/+}$ labeled pro-EpiCs are heterogeneous with SMC-like cells and PMPC.

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Poster 14

Lifetime Single Cell Atlas of the Enteric Nervous System in Zebrafish Identifies p53 Transcriptional Landscapes May Be Involved in Developmental Neuron Death

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Background. Neural crest cells (NCC) are embryonic stem cells that are transient, highly migratory and multipotent that give rise to different cell types within many critical tissues; being one of them the Enteric Nervous System (ENS). Sox10 is expressed in NCCs during their cell fate specification and migration, and *sox10*-expressing NCC give rise to subpopulations of enteric neural progenitors that mature into enteric neurons (ENs). Recently, several separate scRNA-seq projects in zebrafish have profiled *sox10*-derived cells during different embryonic, larval and adult stages, capturing the development of enteric progenitors transitioning to ENs. While cell death in the developing ENS requires molecular mechanisms of triggered cell death *en route* to the gut and genetic and apoptotic targets have been identified, p53 contribution in apoptotic enteric neural crest-derived cells (ENCDC) or migratory ENs has not been clearly determined in network transcriptional landscapes.
Hypothesis. We anticipate the presence of differentially expressed p53 apoptotic pathway-encoding genes and inferred networks during ENs development in an integrated single cell atlas of the ENS.
Methods. Using the previously mentioned published datasets, we generated a combined *sox10* lifetime transcriptional atlas spanning several zebrafish stages to identify novel gene signatures of ENs that allow us to annotate cellular identities of the ENs. We subsetted ENs clusters to recognize enrichment pathways and network interactions.
Results. We identified p53 as a differentially expressed gene in two major EN populations, which are putative ENCDC. One cluster in particular exhibited higher expression of p53 and had several overrepresented biological process pathways where the intrinsic apoptotic signaling pathway was the major one. Additionally, STRING protein-protein interactions identified p53 as a hub regulator of different cellular processes as replication, translation, and response to stress.
Conclusions. In a lifetime zebrafish scRNA seq atlas, p53 has been identified in populations of enteric neural precursors mainly as part of apoptotic pathways, suggesting functional roles therein.

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Poster 15

Single-Cell Transcriptomic Analysis Reveals Developmental Relationships and Specific Markers of Mouse Periodontium Cellular Subsets

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Background:
The periodontium is essential for supporting the tooth, composed of diversity of mineralized and non-mineralized tissues such as the cementum, the periodontal ligament (PDL) and the alveolar bone. The periodontium is developmentally derived from the dental follicle (DF), a fibrous tissue surrounding the developing tooth bud. We previously showed through *in vivo* lineage-tracing experiments that DF contains mesenchymal progenitor cells expressing parathyroid hormone-related protein (PTHrP), which give rise to cells forming the periodontal attachment apparatus in a manner regulated by autocrine signaling through the PTH/PTHrP receptor. However, the developmental relationships between PTHrP$^+$ DF cells and diverse cell populations constituting the periodontium remain undefined.
Goals:
To identify the mesenchymal cell lineage and intercellular interaction in periodontium at a single-cell level
Methods:
We utilized a tamoxifen-inducible *PTHrP-CreER* transgenic line that specifically marks PTHrP$^+$ DF cells and tdTomato reporter alleles to visualize their descendants. We isolated fluorescently marked periodontal cells including PTHrP$^+$ descendants from mouse molars of *Col1(2.3kb)-GFP; PTHrP-CreER; R26R-tdTomato* at P25 after a tamoxifen pulse at P3. For scRNA-seq analysis, FACS-sorted cells were loaded onto the Chromium Single-Cell Gene Expression solution platform (10X Genomics). The dataset was integrated with the previously published dataset of PTHrP-mCherry$^+$ DF cells at P6 using LIGER.
Results:
This integrative scRNA-seq analysis revealed heterogeneity of cells of the periodontium and their cell type-specific markers, as well as their relationships with DF cells. Most importantly, our analysis identified a cementoblast-specific metagene that discriminate cementoblasts from alveolar bone osteoblasts, including Pthlh (encoding PTHrP). RNA velocity analysis indicated that cementoblasts were directly derived from PTHrP$^+$ DF cells in the early developmental stage and did not interconvert with other cell types. Further, CellPhoneDB cell-cell communication analysis indicated that PTHrP derived from cementoblasts acts on diversity of cells in the periodontium in an autocrine and paracrine manner.
Conclusions:
Our findings provide insights into the lineage hierarchy and intercellular interactions of cells in the periodontium, and PTHrP secreted by cementoblasts is important for cementogenesis via PTH/PTHrP receptor signaling.
Acknowledgements:
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Poster 16

The Role of Microglia and Macrophages in Rod Photoreceptor Regeneration

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Background *Retinitis Pigmentosa* (RP) is a suite of retinal degenerative diseases, characterized by rod photoreceptors loss, that can lead to critical vision impairment and vision loss. There is no effective therapy to treat patients with RP and there is a need to develop new therapeutic strategies. Unlike humans and mammals, zebrafish can regenerate rod photoreceptors and other retinal cell types and restore their impaired vision. We investigate the role of microglia/macrophages in rods regeneration using a P23H rhodopsin transgenic zebrafish. This zebrafish undergoes chronic rod photoreceptors degeneration and continuous rods regeneration.

Hypothesis/Goals We hypothesize that microglia respond to rods degeneration by transcriptomic and phenotypic changes that promote rods regeneration.

Methods Analysis of whole retina single-cell transcriptomes from P23H and WT zebrafish was performed using Seurat package for R. The two datasets were first integrated, cells were filtered, and the data were normalized and scaled. To identify retinal and microglia clusters unsupervised clustering was performed. Furthermore, to visualize microglia and macrophages, P23H and WT retinal sections from adult fish were stained with antibodies against L-plastin (Lcp1). Immunostaining against Proliferating cell nuclear antigen (PCNA) was performed to visualize rod progenitor cells.

Results Microglia and macrophages in P23H retinas migrated towards degenerating rods; immunostaining of retinal cryosections identified higher number of ameboid and ramified microglia/macrophages in the photoreceptor layer compared to WT. Some of the microglia were found to co-localize with rod progenitor cells. Analysis of scRNA seq data identified three distinct microglia clusters that differ in gene expression between P23H and WT microglia. Genes associated with cytokine and chemokine signaling were upregulated in microglia cluster 27. Whereas pathways related to phagocytosis were upregulated in microglia cluster 31. We also identified that expression of several long non-coding RNAs (lncRNAs) is upregulated in P23H microglia and that the expression of these lncRNAs was microglia cluster-specific.

Conclusions Our results show that microglia/macrophages in regenerating retinas of P23H fish undergo transcriptional change and migrate towards rod photoreceptor layer (ONL). Some of these microglia acquire ameboid shape suggesting that they phagocytose dying rods. Other microglia/macrophages have more ramified shape and might have regulatory roles during regeneration. We also have identified upregulation of lncRNA expression in P23H microglia. LncRNA regulate many cellular processes and we suggest that they might drive microglia/macrophage's transcriptional change to promote regeneration of rods.

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Poster 17

Integrative Single-Cell Genomic Analysis Identifies a New Type Of Skeletal Stem Cells in Bone Marrow Endosteum

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Skeletal stem cells (SSCs) provide an important source of bone-forming osteoblasts and support overall bone health. In bone marrow of endochondral bones, chondrocyte-to-osteoblast transformation plays a significant role in bone formation in fetal life, while leptin receptor (LepR)-expressing perivascular bone marrow stromal cells (BMSCs) participate in bone formation mainly in adulthood and aging. However, the identity of SSCs during the transition, and how they coordinate active osteogenesis particularly in young ages remain unclear. To identify putative SSCs in young bone marrow, we performed integrative single-cell genomic analyses of Prrx1-cre-marked bone marrow stromal cells (BMSCs) at young (P21) and old (18M) stages, with data integration by LIGER. Single-cell RNA-seq analyses revealed that a small group of cells with osteoblast-chondrocyte transitional (OCT) identities were abundant in young bone marrow, which were predicted as a cell-of-origin of osteoblasts and reticular stromal cells by RNA velocity and CellRank. Analyses of the isogenic single-nucleus ATAC-seq dataset summarized in a 3-dimensional simplex plot revealed that cells in the OCT cluster demonstrated "trilineage" potential toward all three fates, predominantly toward osteoblast and reticular fates. Transcription factors (TFs) binding motif enrichment analysis revealed that chromatin accessibility peaks in OCT cells are enriched for chondrocyte-related TF binding motifs but have lower levels of accessible osteoblast-related motifs, suggesting that the OCT stromal cells are still being regulated primarily by chondrocyte-related TFs, supporting their transitional identities. Subsequent validation by mouse transgenic lines revealed that these OCT stromal cells expressed *fibroblast growth factor receptor 3 (Fgfr3)*, resided in the endosteal space and robustly generated osteoblasts and in homeostasis and regeneration. Additionally, when isolated ex vivo, these $Fgfr3^{+}$ stromal cells were highly enriched for skeletal stem cell activities, and single-cell derived clones of these cells possessed serial transplantability. Therefore, our integrative single-cell genomic analysis identifies a new type of bone marrow stromal. cells with osteoblast-chondrocyte transitional identities, identifying these cells as endosteal SSCs particularly abundant in young bones and coordinating active osteogenesis.

Poster 18

Rod Photoreceptor Regeneration in a Zebrafish Model of Retinitis Pigmentosa

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Background

A cellular hallmark of inherited retinal degenerative diseases, such as Retinitis Pigmentosa (RP), is progressive loss of photoreceptors until the individual is completely blind. Unlike mammalian models, Zebrafish (Zf) have a remarkable capacity to regenerate neurons following retinal injury or disease, making them a suitable model organism for regenerative studies. Current studies in Zf have indicated that upon detection of retinal insult, Müller glial cells (MGCs) are reprogrammed to re-enter the cell cycle and produce progenitor cells that replace lost retinal cells. The mechanisms by which genes work together to regenerate rod photoreceptors in a model with chronic retinal degeneration remain unknown.

Hypothesis/Goals

The goal of this study is to understand the regeneration mechanisms of rod photoreceptors in Zf and to identify the master regulatory genes crucial for their lineage trajectory. We hypothesize that single cell analysis of a Zf model replicating the rod degeneration pathology of a P23H rhodopsin mutation will allow us to assess the trajectory of genes driving rod photoreceptor regeneration

Methods

Single cell 3' RNA sequencing analysis was performed separately on dissociated WT AB and P23H rhodopsin transgenic Zf retinas. Cells were normalized, filtered, and scaled to generate UMAP clusters through Seurat and Monocle3. Single cell trajectory analysis was then performed in Monocle3. DrivAER analysis was performed on each trajectory to identify master regulators involved at each stage of regeneration. Immunohistochemistry was performed on retinal slices and whole mounts.

Results

UMAP clustering reveals all cell types in both WT and P23H data, including a group of cells identified as retinal progenitor cells (RPCs). In the P23H dataset, these RPCs are part of the trajectory predicted in rod photoreceptor regeneration. DrivAER analysis of this trajectory reveals master regulator genes at each stage of regeneration: proliferation, differentiation, and maturation of RPCs into rod photoreceptors. In the WT dataset, this trajectory was not present. Immunostaining reveals a group of proliferating cells continuously found in the photoreceptor nuclear layer of P23H retina. BrdU pulse chase experiments show they differentiate into rod photoreceptors and have a turnover rate within 1 week.

Conclusions

Our results show that RPCs are present in both WT and P23H Zf retinas, however, a trajectory for rod photoreceptor regeneration is only predicted in the P23H model. This indicates that the RPCs may be present normally in WT retinas, but in a quiescent state. In the P23H model, where constant degeneration and regeneration are occurring, these RPCs may be continuously activated to help replenish lost rod photoreceptors. Immunostaining images show that there is little activity from MGCs in the P23H model. Future experiments plan to test the suite of master regulators predicted to be involved as well as trace the origins of the RPCs.

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Poster 19

Alteration of the Transcriptome in Response to Shrimp Allergens in Shrimp Allergic Peripheral Blood Mononuclear Cells

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Rationale: Molecular cellular pathogenesis in shrimp allergy remains incompletely understood. In this study, we reveal the transcriptome from a single cell analysis in response to major shrimp allergen tropomyosin in total peripheral blood mononuclear cells (PBMCs) from shrimp allergic (SA) and control patients.
Methods: Total PBMCs from four healthy controls and four SA patients were recovered and stimulated with shrimp tropomyosin (TM) 1 ug/ml for 24 hours. The single-cell gene expression library was prepared according to the Chromium Single Cell Gene Expression 3v2 kit (10× Genomics) before and after TM stimulation. The result was analyzed using Scanpy and Seurat programs. The levels of the cytokine secretion were measured using Bio-Rad Cytokine 9 and 12 -Plex Kit and Luminex.
Results: The association plot of single-cell RNA seq analysis showed a lower frequency of B cells and higher frequency of natural killer cells and dendritic cells in PBMCs, lower frequency of naive and memory B cells, and heat shock rich clusters from the shrimp allergic patients vs healthy controls. TM simulation resulted in upregulation of secretion of interleukin (IL)-13 and granulocyte-macrophage colony-stimulating factor (GM-CSF) in shrimp allergic patient PBMCs and secretion of IL-4, IL-5, and IL-10 shrimp allergic and healthy control PBMCs. Several genes in T regulatory cells (Treg) cells and gamma delta T (gdT) cells were differentially expressed in stimulated PBMCs compared to unstimulated, including pro-inflammatory transcripts nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alfa and signal transducer and activator of transcription 1 ($p=0.000002$, $p=0.002619$, respectively).
Conclusion: We established the transcriptomic immune profiles and identified mechanistic pathways in shrimp allergic cellular responses. Pro-inflammatory cell signaling proteins are involved in the activity of Treg and gdT cells in response to shrimp TM. This study gives insight into potential targets for the development of tolerance to shrimp.

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Poster 20

Effective Methods for Bulk RNA-Seq Deconvolution using scRNA-Seq and snRNA-Seq Derived Transcriptomes

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Background: The use of single-cell and single-nuclei RNA sequencing (scnRNA-Seq) is challenging because of their relatively high cost and exacting sample collection requirements. Computational deconvolution methods that infer the composition of RNA-Seq-profiled samples using scnRNA-Seq derived cell types can stretch the benefit of scnRNA-Seq but their effectiveness remains controversial.

Goal: Evaluate methods to deconvolve bulk RNA-Seq profiles based on scnRNA-Seq profiles.

Results: We produced the first systematic evaluation of deconvolution methods on datasets with either known composition or with concurrent RNA-Seq and scnRNA-Seq profiles. Our analyses revealed biases that are common to scnRNA-Seq assays and illustrated the importance of accurate and properly controlled data preprocessing and deconvolution method selection. Our results suggested that current scRNA-seq assays using the 10x Genomics platform can produce excellent sample-composition estimates, but even in ideal conditions, these assays produce relatively poor transcriptome characterizations for each identified cell type. This highlights the importance of using controlled datasets like our mixtures where the truth is known for evaluating and improving prediction functions. Using such datasets, methods can be fairly evaluated, and their strengths and weaknesses can be investigated. Moreover, our results suggested that the transformation of bulk RNA-Seq to scnRNA-Seq vector spaces using concurrent RNA-Seq and scnRNA-Seq profiles—when followed deconvolution using high-performing methods—dramatically improved deconvolution accuracy and outperformed other methods on each dataset tested. Our proposed method, Janus, combines bulk RNA-Seq transformation and deconvolution with a dampened weighted least squares approach to consistently outperform other deconvolution methods in predicting the composition of cell mixtures and patient samples from bulk RNA-Seq profiles. Finally, our analysis suggested that only Janus could identify outcomes-predictive cancer subtypes in our pediatric acute myeloid leukemia and neuroblastoma datasets.

Conclusions: Concurrent bulk RNA-Seq and snRNA-Seq profiles can be used to improve tertiary snRNA-Seq analysis and following efforts, including deconvolution.

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Poster 21

Identifying Gene Targets for Neuroprotection and Axon Regeneration using scRNA-seq

Tran N

Purpose: Neurons in the central nervous system have a limited ability to survive and regenerate their axons following injury. While >70 interventions have been identified that alter the regenerative capacity of retinal ganglion cell (RGC) axons, none achieve recovery and typically only a small subset of RGCs respond. We are investigating the molecular pathways associated with RGC populations that have differential responses to regenerative treatments: 1) continued degeneration, 2) survival but not regeneration, 3) and survival plus regeneration. Our goal is to determine the programs regulating each of these processes in order to identify new ways to promote neuroprotection and stimulate axon regeneration.

Methods: To dissect the molecular pathways associated with differential RGC responses, we applied single-cell RNA-sequencing (scRNA-seq) in two different ways following optic nerve crush (ONC) with or without regenerative interventions. Axon regeneration was stimulated using three established interventions: Pten conditional deletion from RGCs, Pcko + Cntf overexpression, and Pten, Socs3 double conditional deletion from RGCs + Cntf overexpression. First, we applied droplet-based scRNA-seq to profile >130,000 RGCs across these conditions at 0-21 days post-ONC. Second, we specifically profiled regenerative vs. non-regenerative RGCs by retrogradely labelling regenerating RGCs.

Results: Key results from scRNA-seq expression screens included the following. First, all interventions preserved the expression of cell type markers and suppressed injury-related changes following ONC; much of the effects were observed with *Pten* deletion alone. Second, each intervention resulted in neuroprotection and axon regeneration with distinct type-specificity. Third, we identified multiple population-specific transcriptional modules and gene regulatory networks correlating with degeneration, survival, and axon regeneration. We overexpressed three genes (Crh, Gal, and Wt1) associated with the regenerative program and all promoted neuroprotection and axon regeneration.

Conclusions: Our results identify gene expression programs correlating with distinct responses by RGC populations to regenerative interventions revealing three novel mediators of axon regeneration. These studies describe core molecular programs associated with regeneration, which could have broad translational implications for the treatment of acute nerve injuries. These studies are detailed in a recent publication (Jacobi*, Tran* et al. Neuron https://doi.org/10.1016/j.neuron.2022.06.002).

Poster 22

The Genetic Effect on Gene Expression and Chromatin State at Single-cell Resolution

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Background:
Gene regulation is cell type dependent and the modulation of this process by genetic variation among individuals is a major contributor to complex traits and diseases.

Goals:
In this study, we sought to systematically characterize how genetic variation modulates gene regulation in cell type specific context.

Methods:
To address this question, we performed whole genome sequencing (WGS), single nuclei RNA-sequencing (snRNA-seq) and single-nuclei assay for transposase-accessible chromatin sequencing (snATAC-seq) on the cells of healthy retinae from 20 human donors. We mapped single-cell eQTL (sc-eQTLs), single-cell caQTLs (sc-caQTLs), single-cell allelic specific expression (sc-ASE), and single-cell allelic specific chromatin accessibility (sc-ASCA) for major retinal cell types.

Results:
A significant proportion of the QTLs are cell type specific, indicating the genetic variants modulate gene expression and chromatin state in a cell type dependent manner. Contrary to the widely accepted assumption, only a moderate proportion of sc-caQTLs overlaps with sc-eQTLs, suggesting the decoupling modulation of chromatin state and gene expression for a large proportion of variants. Finally, by integrating the single cell multiomics data, genetic association results and GWAS, we identified the enriched cell types, candidate causal variants and regulatory mechanisms underlying GWAS loci.

Conclusions:
Our results indicate that the impact of most of genetic variants on gene regulation is highly context specific.

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Poster 23

Archival Single Cell Sequencing Reveals Persistent Subclones over Years to Decades of DCIS Progression

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Abstract

Ductal carcinoma in situ (DCIS) is a common precursor of invasive breast cancer (IBC), yet the genomic progression to recurrent disease remains poorly understood. This gap in knowledge is mainly due to technical challenges associated with genomic profiling of formalin-fixed paraffin-embedded (FFPE) materials. To address this challenge, we developed Arc-well, the first high-throughput method that can perform single cell DNA sequencing of thousands of cells from FFPE materials. We profiled genomic copy number in 35,941 single cells from archival FFPE tissues that were stored from 3-31 years, as well as fresh and frozen tissue samples. Analysis of genomic evolution of 10 patients with matched DCIS and recurrent DCIS or IBC FFPE samples that were separated by years to decades of time showed that many primary DCIS lesions had already undergone whole-genome-doubling and showed extensive clonal diversity that is comparable with recurrent cancers. In most patients (8/10) our data support an evolutionary bottleneck of a single persistent subclone during the progression to the recurrent disease, revealing copy number aberrations associated with invasion and recurrence.

Poster 24

Development of Omicpioneer-Sc, a Tool That Integrates Umaps with Clustered Heat Maps and Pathway Diagrams

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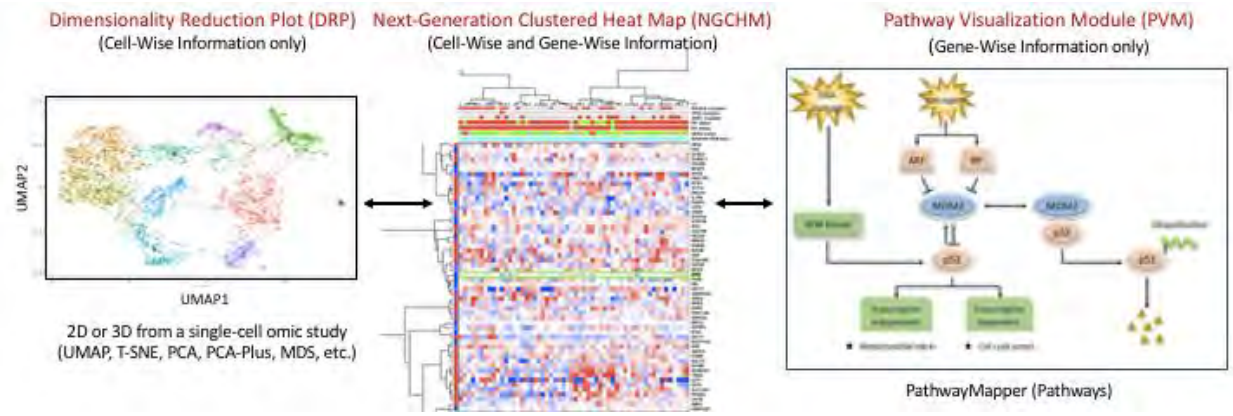
Background: UMAPs (and other dimensionality reduction plots), clustered heat maps, and pathway diagrams are three of the most popular visualization paradigms for single-cell studies.

Hypothesis/Goals: A software tool that integrates the three types of visualization in user-friendly, dynamically interactive form would be a useful complement to other types of data analyses and data visualization forms for single-cell sequencing and other single cell studies. Our primary goal has been to develop such a tool and make it available open-source, primarily as a plug-in for various single-cell data analysis environments.

Methods: We developed OmicPioneer using a high-performance client-server architecture that enables multi-resolution views of the entire genomic dataset and linkage to pathway visualization tools. OmicPioneer has been implemented in containerized form with an API that allows for incorporation into various bioinformatic environments, including Seurat, Galaxy, cBioPortal, and InferCNV.

Results: OmicPioneer-sc integrates interactive (i) UMAPs (or other 2- or 3-D dimensionality reduction plots), (ii) Next-Generation Clustered Heat Maps (NG-CHMs), and (iii) pathway diagrams (or potentially Gene Ontology categories) so that a group of points selected in one of those modules is automatically projected into the others. The NG-CHM module enables rapid, extreme, interactive zooming and panning without loss of resolution, link-outs to dozens of external information resources on selected genes or cells, re-coloring on the fly, high-resolution graphics, and preservation of metadata necessary to reproduce the map even months or years later. Omic Pioneer NG-CHMs can be multi-layered for multi-omic visualization. Both gui-driven and R input formats are available.



Conclusions: We have developed OmicPioneer-sc, a containerized, open-source dynamically interactive exploratory tool that can, e.g., be used in single-cell annotation. It has been added as a plug-in to a number of existing data analysis environments. At https://doi.org/10.1101/2020.10.31.363580,see a BioRxiv preprint that points to our collections of descriptive and instructional videos, github code repositories, and downloads for OmicPioneer. Try a working example at https://bioinformatics.mdanderson.org/TCGA/NGCHMPortal/NGCHM/chm.html?map=d897cc0d4d2cd5c94801a3187996d3023e3b1f28. We welcome collaborations on further development or application.

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Poster 25

GenKI: A Variational Graph Autoencoder-Based Virtual Knockout Tool For Gene Function Prediction Via Single-Cell Gene Regulatory Network Perturbation

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Abstract

The current method for single-cell RNA sequencing (scRNA-seq) enables the high-throughput research of cell populations and gene activity. scRNA-seq of gene knockout (KO) samples, for instance, is an unprecedentedly effective method for elucidating gene function. Due to a paucity of experimental and animal resources, thorough KO investigations targeting many genes of interest are currently not possible. For gene function analysis, we introduce GenKI (**Gen**e **K**nockout **I**nference), a computational method based on variational graph autoencoder (VGAE) to perform virtual gene KO using only scRNA-seq data as input. In the GenKI analysis, a single-cell gene regulatory network (scGRN) is initially constructed from scRNA-seq data of wild-type (WT) sample, and a mirrored knockout (KO) sample is obtained by virtually deleting a target gene from the WT samples, for which we attenuate the target gene expression to zero and remove all its edges linking to its regulated genes. The WT sample data are used to train the VGAE model, which comprises a two-layer graph convolutional network (GCN) encoder and an inner product decoder. After training, simulated KO sample data are fed to the learned model. In both instances, we gather the parameters of the latent bivariate Gaussian distribution for each gene to determine the extent of disturbance caused by the KO. Finally, a permutation test is utilized to find substantially altered genes, which are then used to deduce the roles of the KO gene and biological processes involving chosen cells. We employ GenKI to analyze the function of the triggering receptor expressed on myeloid cells 2 (Trem2) in microglia using real scRNA-seq data. We show that the GenKI analysis finds 20 genes highly disturbed by the Trem2-KO, and the enrichment analysis shows lipid metabolism as a strongly enriched function, indicating that Trem2 plays a crucial role in regulating lipid metabolism. This result is consistent with the findings of several Trem2-KO investigations. In addition, we demonstrate that Apoe and Lpl are among the most significantly regulated genes, suggesting that Trem2 controls Apoe and Lpl, which are involved in lipid transport and catabolism in microglia. In conclusion, we demonstrate that GenKI, the graph-based model that uses scGRNs, can adequately capture node characteristics and restore the functions of KO genes. We hope our methodology will improve the feasibility and efficacy of KO-based hypothesis generating and experimental design.

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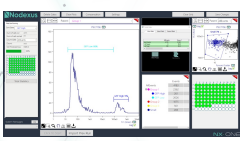
The NX One analyzes, sorts, and isolates live cells into tubes or microtiter plates in an integrated, easy-to-use manner. It offers on-chip detection and microfluidic isolation for walk-up usability by untrained users and provides unprecedented affordability for individual labs and Cores.

Faster Results With Walk-Up Usability
No tuning, no alignment, and no drop delay needed. All-in-one instrument is easy to operate by any untrained user.

Universal Affordability
Never-before-seen pricing allows for deployment beyond the centralized facility for any individual lab benchtop/hood.

Contamination-Free
Fluidic design and disposable cartridges eliminate contamination and aerosol concerns. The system comfortably fits in a tissue culture hood.

High Viability Microfluidic Sorting
Low-shear flow-switching maximizes cell survival. Non-target cells stay in the cartridge for secondary processing or easy disposal.



Versatile Output Formats
Universal cartridge nozzle delivers cells to tubes or microtiter plates (up to 384 wells) without any external attachments.

Sample Flexibility
Can process heterogeneous or homogeneous samples of volumes up to 2.5 mL.

Multi-Parameter Profiling
Integrates particle sizing and 3+ color fluorescence. Reach out regarding adding more and/or customizing colors!

Intuitive Software
Clean interface enables setup in < 1 minute. Users can monitor runs wirelessly or via system screen.

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- Gain greater differentiation in cell types without perturbing cell type calls

*Data from PBMC's, some variance expected with different cell types

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