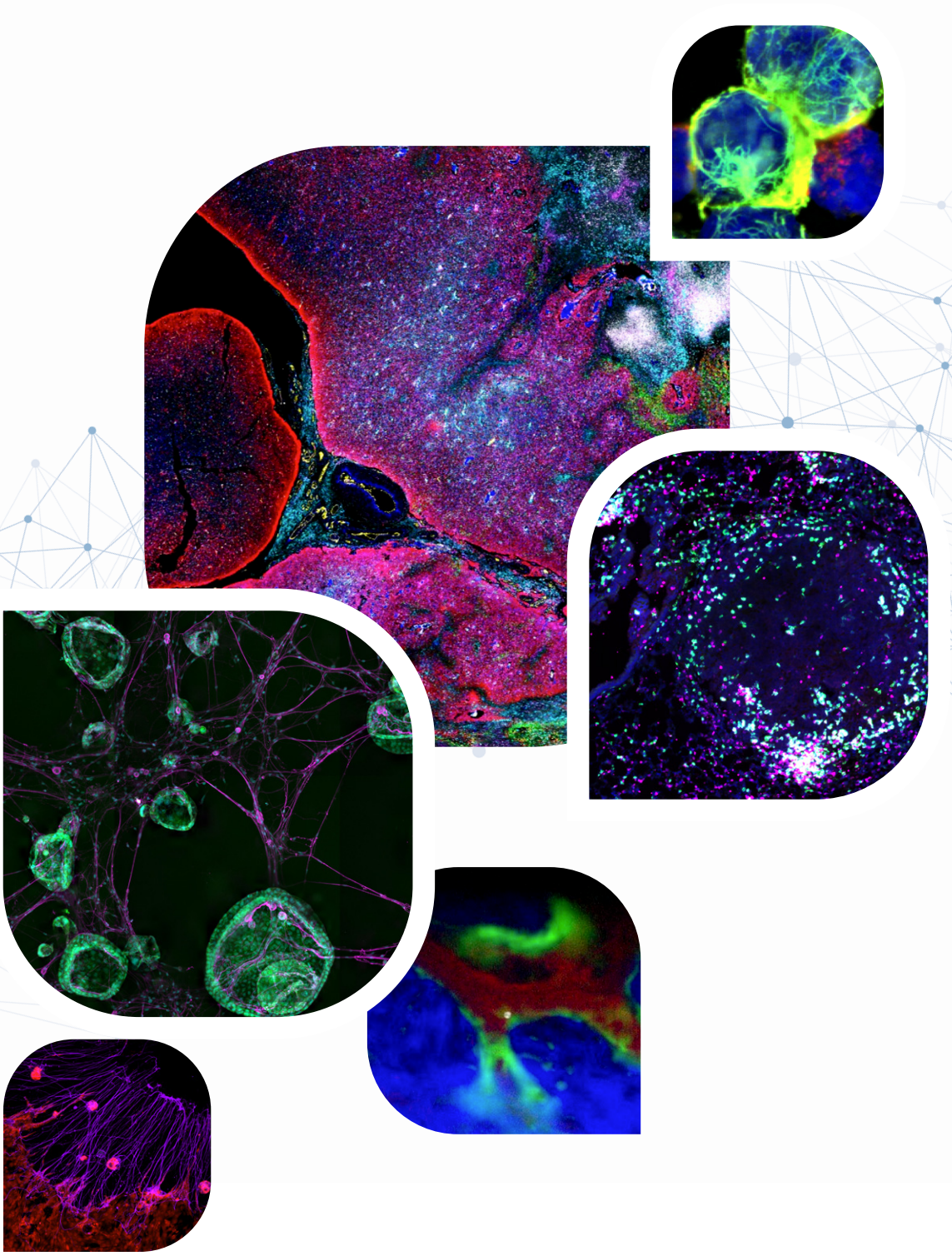
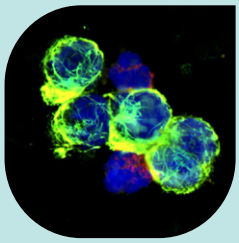
KRANTZ FAMILY
Center for Cancer Research

Annual Report 2025-2026



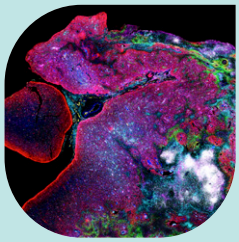
Mass General Brigham
Cancer Institute

Featured images from front cover



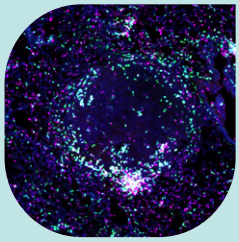
TROP2 expression on a Circulating Tumor Cell (CTC) cluster isolated from the blood of a patient being treated with TROP2 ADC. CTCs can act as a biomarker to guide targeted therapies.

Image courtesy of the Avanish Mishra Laboratory



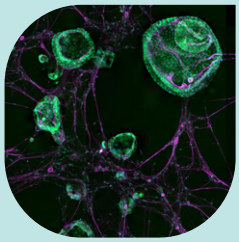
Highly multiplexed spatial proteomic profiling (CODEX) of a CAR-T cell treated patient tumor specimen.

Image courtesy of the Christopher Mount Laboratory



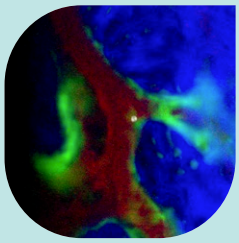
Immunofluorescence image of a tumor-bearing murine lung showing a tertiary lymphoid structure (TLS). $CD4^+$ T cells (green) and $CD8^+$ T cells (purple) are organized into a compact cluster, highlighting an emergent immune architecture associated with anti-tumor activity.

Image courtesy of Yongjune Choi, PhD of the Shawn Demehri laboratory



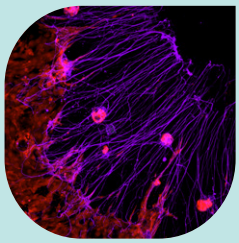
3d mouse pancreatic cancer organoid-nerve co-culture

Image courtesy of the William Hwang laboratory



We are interested in physiology resolved to single cell and single molecule events. How a tissue responds to stress is ultimately conducted at cell and molecular levels that offer opportunities for manipulation to improve resilience. Above is a high resolution in vivo image obtained in collaboration with Dr. Charles Lin that captures a single hematopoietic stem cell after transplantation as the engraftment process begins.

Image courtesy of the David Scadden laboratory



Pancreatic cancer cell aggregates(red) moving along neurites (purple) extending from a dorsal root ganglion (removed).

Image courtesy of the William Hwang laboratory

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Director's Message

I am pleased to share with you the **2025 Krantz Family Center for Cancer Research Annual Report,** which highlights a remarkable year and reflects our unwavering commitment to cancer research as a cornerstone of our identity and our mission. Fueled by the dedication of our researchers, the generosity of our donors, and a shared urgency to improve outcomes for all cancer patients, the Krantz Center is proud to reflect on a year marked by significant progress and discovery. Individual faculty research programs and publications are listed in the following pages.

Since receiving a transformative gift from the Krantz Family in 2023, we have launched bold, collaborative, and highly impactful initiatives. Our 2023 Quantum Award initiated a major effort in covalent cysteine-binding chemistry to target cancer-driving transcription factors (Drs. Bar-Peled, Lawrence, Ott); and our Breakthrough Awards supported projects aimed at optimizing CAR-T cell biology (Drs. Jan, Manguso, Maus and Sen), defining the clinical parameters for the harvesting and analysis of TIL-cell immunotherapy (Drs. Boland, Jenkins, Sade-Feldman), and creating an initiative in cancer metabolomics (Drs. Bardeesy and Mostoslavsky). Our 2024 Quantum Award began a major collaboration in the application of spatial transcriptomics to better understand autoimmune complications of immune checkpoint cancer therapy (Drs. Hwang, Ting, Villani); and our Breakthrough Awards advancing research into immune niches in brain tumors (Drs. Brastianos and Suva), defining the role of disordered protein domains within cancer-associated transcription factors (Drs. Rheinbay and Rivera), and defining mechanisms of acquired HIF inhibitor drug resistance in kidney cancer (Drs. Haas, Iliopoulos, Motamedi). Our upcoming 2025 Krantz Awards are listed on the opposite page. Together, these major research collaborations are enabling our investigators and collaborators to chart new territory in cancer research, seeking to accelerate discovery and impact.

Every year, we have the honor of presenting a major award to a cancer researcher who has had an exceptional impact on the field and who exemplifies commitment to academic scholarship and mentoring. The 2025 Jonathan Kraft Prize for Excellence in Cancer Research was awarded to Dr. Jennifer Wargo from MD Anderson Cancer Center, for her groundbreaking work in microbiome and cancer immunology. In addition, we were pleased to present the annual Jonathan Kraft Team Science Award, honoring an exceptional clinical-laboratory partnership, to Drs. Andrew Brunner, Jooho Chung, Nir Hacohen, Robert Manguso, and Elliot Wood, for their collaborative project to enhance T cell anti-tumor immunity in hematologic cancers.

This year, in collaboration with the Departments of Medicine, Pathology and Radiation Oncology, we are excited to welcome seven new faculty members to the Krantz Center: Drs. Steve Blum, Zhixun Dou, Christopher Mount, David Scadden, Diana Shi, Ignacio Vazquez-Garcia, and Bo Xia, with research interests in cancer immunology, cellular senescence, neuro-immunology, hematopoietic stem cell biology, neuro-oncology, molecular cancer evolution, and computational genomics, respectively. Their diverse expertise will strengthen our collaborative research environment and accelerate progress across multiple areas of cancer research.

The success of the Krantz Family Center for Cancer Research has been built by generations of investigators, trainees, and staff dedicated to scientific discovery and clinical impact. As we transition from the Mass General Cancer Center to the newly created Mass General Brigham Cancer Institute, we are committed to building on that legacy to create additional research expertise, multidisciplinary collaborations, and ultimately improving the outcome for patients with cancer across the globe.

With your dedication and support, we are shaping the future of cancer research. Thank you!

Daniel A. Haber, MD, PhD

Director, Krantz Family Center for Cancer Research
Mass General Brigham Cancer Institute
Harvard Medical School

Daniel Haber photo by Scott Eisen

Inspired by the vision, creativity, care and leadership that define the spirit of the Mass General Cancer Center,

JASON R. AND KEELY F. KRANTZ

are honored to name the

KRANTZ FAMILY CENTER FOR CANCER RESEARCH

With the enduring intent that this philanthropic endeavor will pioneer impactful advances in cancer detection, treatment and prevention, and enable scientists to launch bold and innovative research to vanquish this disease.

The Krantz Family Center for Cancer Research Awards Fund was established to accelerate groundbreaking cancer research and drive discoveries that will produce fundamental changes in our understanding of cancer biology and how we treat cancer patients. The 2025 Krantz Awards include:

2025 Quantum Award

Marcela Maus, MD, PhD, Matthew Frigault, MD, and Robert Manguso, PhD
Mario-CART cells to discover the best next-generation engineered T cell therapies for cancer patients

2025 Breakthrough Awards

Andrea McClatchey, PhD and Nabeel Bardeesy, PhD
Targeting epithelial heterogeneity in liver cancer

Debattama R. Sen, PhD, Andrew E. Elia, MD, PhD and Daphne A. Haas-Kogan, MD
Studying DNA repair to enhance cancer immunotherapy

Konrad Hochedlinger, PhD, Hanno Hock, MD, PhD, and Peter van Galen, PhD
Dissecting the role of H3K27 methylation in B cell oncogenesis using novel histone tools

2025 Spark Awards

A. John Iafrate, MD, PhD and Liron Bar-Peled, PhD – Targeting ALK Fusion Proteins with COUPLrs: Mechanistic Insights and Therapeutic Development

Avanish Mishra, PhD and David Walt, PhD – Combining high-sensitivity automated protein quantification with CTC enrichment for selecting immune-based cancer therapies

Raul Mostoslavsky, MD, PhD – Using spatial transcriptomics to define roles for aging in cancer progression

Moshe Sade-Feldman, PhD and Meghan Mooradian, MD – Overcoming resistance to checkpoint blockade immunotherapy with cryoablation in metastatic melanoma

Mikołaj Słabicki, PhD – Proof of Concept for a Peptide-PROTAC Strategy

The 2025 Technology Awards will fund hardware (GPU) and resources for computational biology to enable high-throughput and AI-based analytics

Jason and Keely Krantz photo by Austin Wilder/Catalumet Creative

About the Krantz Family Center for Cancer Research

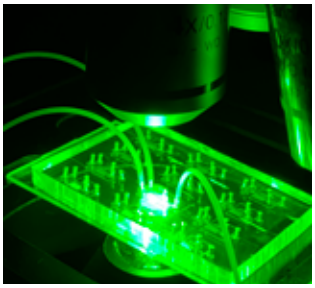
The *KF-CCR* includes 59 Principal Investigators with Harvard Medical School (HMS) appointments in the Departments of Medicine, Pathology, Radiation Oncology, Surgery, Dermatology and Pediatrics, as well as the Broad Institute of MIT and Harvard. Together with over 500 laboratory investigators, they conduct research in 80,000 square feet of laboratory space in three MGH research facilities: Charlestown Navy Yard (CNY), Simches Research Building, and Jackson Building. Ongoing research projects range from exploring cancer genetics, genomics, epigenetics and proteomics, to developmental biology, cell signaling, cancer diagnostics, molecular therapeutics and drug resistance, immunology and immunotherapy, cellular metabolism, cell cycle regulation, and computational biology.

Since the creation of the Mass General Cancer Center in 1988, early landmark publications from our faculty have included the first discovery of germline mutations (*TP53* gene) conferring familial susceptibility to cancer (*Malkin et al., Science* 1990) and the major contribution of "founder BRCA1 mutations" to early-onset breast cancer in Ashkenazi populations (*FitzGerald et al., NEJM* 1996). Our investigators first cloned the E2F gene, the primary cell cycle regulator that is unleashed by cancer-associated mutations in the RB Retinoblastoma tumor suppressor (*Helin et al., Cell* 1992). Using functional screens in fruit-fly genetic models, scientists first discovered the Fbxw7/Ago (*Moberg et al., Nature* 2001) and Hippo/YAP (*Harvey et al., Cell* 2003) pathways, major drivers of cancer proliferation. In 2004, researchers identified activating mutations in the EGFR gene, which drive 10% of all lung cancers and underlie their extreme sensitivity to targeted kinase inhibitors (*Lynch et al., NEJM* 2004). This discovery helped launch the field of "precision oncology" in solid tumors; it set in motion major initiatives in molecular genotyping of cancers to guide therapy and the application of accelerated early phase clinical trials of targeted therapies for genotyped cancers. Mass General Hospital was the first hospital in the US to establish genotyping as part of standard clinical care for cancer in 2008, and in 2011 the Cancer Center launched the Termeer Center for Targeted Therapies, which has emerged as an internationally renowned center of excellence for First-in-Human clinical trials.

Bringing together high-throughput cellular screens, proteome-wide targeting of reactive cysteines, metabolomics-directed drug targets, and unique patient-derived tumor models, investigators in our Center for Molecular Therapeutics are pioneering new chemistry strategies, including the publication of a proteome-wide Drug-Map of

reactive cysteines (*Takahashi et al., Cell* 2024). Our Cancer Immunology Program and our CAR-T & Cellular Immunotherapy Program have made major contributions to our understanding of immune checkpoint responses and the tumor microenvironment (*Baumgartner et al., Nature* 2023; *Sun et al, Nature* 2023; *Wu et al., Science* 2024), and created and tested the first promising CAR-T therapy targeting glioblastoma (*Choi et al., NEJM* 2024). In collaboration with our clinical colleagues, our investigators are contributing technological innovations in liquid biopsies for early cancer detection, including both mass spectrometry-based proteomics and microfluidics-based isolation of circulating tumor cells; and in partnership with our Pathology colleagues, we are contributing major discoveries in the field of spatial transcriptomics and single cell analytics (*Cui et al., Nature* 2024; *Greenwald et al., Cell* 2024; *You et al, Cell* 2024). It is through this integration of transformative research and exceptional clinical care that the Mass General Cancer Center has emerged internationally as a recognized leader in cancer research and innovation (ranked #5 in 2025 by US News and World Reports). In 2025, with the integration of Mass General Hospital and Brigham & Women's Hospital, the Mass General Cancer Center transitioned into the Mass General Brigham Cancer Institute.

The Krantz Family Center for Cancer Research was named in 2023, following a transformative gift by Jason and Keely Krantz, supporting major research initiatives through collaborative awards, with the goal of accelerating fundamental discovery and their clinical translational applications. As an engine for cancer research and discovery, *KF-CCR* greatly values creativity and innovation across multiple disciplines of cancer research, and we are proud of our strong culture of collaboration and collegiality, demonstrated by multiple co-authored manuscripts, joint laboratory meetings, and cross-laboratory team science. We are committed to training and mentoring the next generation of young scientists who will continue to harness the power of science and uncover new and more effective ways to fight cancer.



Scientific Advisory Board

2025–2026 Members

Paul Joseph Anderson, MD, PhD
Mass General Brigham

Dafna Bar-Sagi, PhD
NYU Langone Health

Nick Dyson, PhD
Scientific Director Emeritus, Mass General KF-CCR

Robert E. Kingston, PhD
Massachusetts General Hospital

Arlene Sharpe, MD, PhD
Harvard Medical School

M. Celeste Simon, PhD
University of Pennsylvania

Past Members

Julian Adams
Gamida Cell, Ltd

Spyros Artavanis-Tsakonas, PhD
Harvard Medical School

Joseph Avruch, MD
Massachusetts General Hospital

David Baltimore, PhD
Broad Institute

Cori Bargmann, PhD
Rockefeller University

Edward J. Benz Jr., MD
Dana-Farber Cancer Institute

Joan S. Brugge, PhD
Harvard Ludwig Cancer Center

David E. Fisher, MD, PhD
Massachusetts General Hospital

Donald Ganem, MD
University of California, San Francisco

Walter J. Gehring, PhD[♇]
Biozentrum, University of Basel

Richard O. Hynes, PhD
Massachusetts Institute of Technology

David Hogness, PhD[♇]
Stanford University School of Medicine

David Housman, PhD
Massachusetts Institute of Technology

Peter Howley, MD
Harvard Medical School

Tyler Jacks, PhD
Massachusetts Institute of Technology

Alfred G. Knudson Jr., MD, PhD[♇]
Fox Chase Cancer Center

David Livingston, MD[♇]
Dana-Farber Cancer Institute

David N. Louis, MD
Massachusetts General Hospital

Scott Lowe, PhD
Memorial Sloan Kettering Cancer Center

Frank McCormick, PhD
University of California, San Francisco

Stuart Orkin, MD
Children's Hospital and
Dana-Farber Cancer Institute

Terry Orr-Weaver, PhD
Whitehead Institute

Anthony Pawson, FRS, PhD
Samuel Lunenfeld Research Institute

Carol Prives, PhD
Columbia University

Gerald M. Rubin, PhD
University of California, Berkeley

Gary Ruvkun, PhD
Massachusetts General Hospital

Jeffrey Settleman, PhD
Pfizer, Inc.

Phillip A. Sharp, PhD
Massachusetts Institute of Technology

Eileen White, PhD
Rutgers University Cancer Institute of New Jersey

[♇]*In Memoriam*

The Jonathan Kraft Prize for Excellence in Cancer Research

Presented by the Mass General Cancer Center

2026
Scott W. Lowe, PhD

Chair, Cancer Biology and Genetic Program
Chair, Geoffrey Beene Cancer Research Center
Memorial Sloan Kettering Cancer Center

2025
Jennifer A. Wargo, MD, MMSc

R. Lee Clark Endowed Professor
Professor, Dept. of Surgical Oncology
Professor, Dept. of Genomic Medicine
The University of Texas MD Anderson Cancer Center

2024
Howard Y. Chang, MD, PhD

Virginia and D.K. Ludwig Professor of Cancer Genomics
Professor of Dermatology and of Genetics
Stanford University School of Medicine

2023
Michelle Monje, MD, PhD

Professor of Neurology
Stanford University School of Medicine

2021
Aviv Regev, PhD

Head, Genentech Research and Early Development
Core Member (on leave), Broad Institute of Harvard and MIT
Professor of Biology, MIT

2019
Carl H. June, MD

Professor in Immunotherapy
Director, Center for Cellular Immunotherapies
University of Pennsylvania Perelman School of Medicine

2018
Charles Swanton, MD, PhD

Professor and Chair, Personalized Cancer Medicine
University College London Cancer Institute, London, UK

2017
Kevan M. Shokat, PhD

Professor and Chair, Department of Cellular and Molecular Pharmacology, UCSF
Professor, Department of Chemistry, UC Berkeley

2016
Joan A. Steitz, PhD

Sterling Professor of Molecular Biophysics and Biochemistry Yale School of Medicine

2015
C. David Allis, MD, PhD[ϰ]

Joy and Jack Fishman Professor, Laboratory of Chromatin Biology and Epigenetics, Rockefeller University

[ϰ] *In Memoriam*

The Annual MGH Award in Cancer Research

In memory of Nathan and Grace Shiff

2014
Hans Clevers, MD, PhD

President of the Royal Netherlands Academy of Arts and Sciences
Professor of Molecular Genetics
University Utrecht, Netherlands

2013
James Allison, PhD

Chair, Department of Immunology
MD Anderson Cancer Center, Houston, Texas

2012
Craig Thompson, MD

President and Chief Executive Officer
Memorial Sloan-Kettering Cancer Center, New York

2011
Michael Stratton, MD, FRS

Director, Wellcome Trust Sanger Institute, Cambridge, UK

2010
Charles Sawyers, MD

Chairman of the Human Oncology and Pathogenesis Program
Memorial Sloan-Kettering Cancer Center, New York

2009
Bert Vogelstein, MD

Director of the Ludwig Center for Cancer Genetics & Therapeutics
Sidney Kimmel Comprehensive Cancer Center
Johns Hopkins University, Maryland

2008
Titia de Lange, PhD

Associate Director of the Anderson Cancer Center
Rockefeller University, New York

2007
Joan Massague, PhD

Chairman of the Cancer Biology and Genetics Program
Memorial Sloan-Kettering Cancer Center, New York

2006
Anton Berns, PhD

Director of Research and Chairman of the Board of Directors,
Netherlands Cancer Institute and Antoni van Leewenhoek Hospital, Netherlands

Faculty

Krantz Family Center for Cancer Research Faculty

Leadership

Daniel A. Haber, MD, PhD
Director, Krantz Family Center for Cancer Research
Director Emeritus, Mass General Cancer Center
Kurt J. Isselbacher Professor of Oncology (Medicine)
Investigator, Howard Hughes Medical Institute

Raul Mostoslavsky, MD, PhD
Scientific Director, Krantz Family Center for Cancer Research
Laurel Schwartz Professor in Medicine in the Field of Oncology
Professor of Medicine

Andrea I. McClatchey, PhD
Director for Academic Affairs, Krantz Family Center for Cancer Research
Poitras Family Endowed Chair in Oncology
Professor of Pathology

Nir Hacohen, PhD
Director, Center for Cancer Immunology, Krantz Family Center for Cancer Research
Director, Center for Cell Circuits, Broad Institute of Harvard and MIT
David P. Ryan Endowed Chair in Cancer Research
Professor of Medicine

Charlestown Laboratories

Liron Bar-Peled, PhD
Rullo Family Endowed Chair in Cancer Research
Associate Professor of Medicine

Lloyd Bod, PhD
Assistant Professor of Medicine

Ryan B. Corcoran, MD, PhD
Director, Cancer Center-Tucker Gosnell Center for Gastrointestinal Cancers
Mark J. Kusek Endowed Chair in Colorectal Cancer
Associate Professor of Medicine

Shawn Demehri, MD, PhD
Arthur and Sandra Irving Endowed Chair in Cancer Immunology
MGH Research Scholar 2023-2028
Associate Professor in Dermatology (Cutaneous Biology Research Center)

Andrew Elia MD, PhD
Assistant Professor of Radiation Oncology

David E. Fisher, MD, PhD
Director, Cancer Center Melanoma Program
Director, Cutaneous Biology Research Center
Lancer Professor of Dermatology
Edward Wigglesworth Professor and Chair of Dermatology

Gaddy Getz, PhD
Director of Bioinformatics, Cancer Center and Pathology
Director of Cancer Bioinformatics, Broad Institute of Harvard and MIT
Paul Zamecnik, MD Endowed Chair in Oncology Basic Research
Professor of Pathology

Francesca Gazzaniga, PhD
Assistant Professor of Pathology (Molecular Pathology Unit)

Doğa C. Gülhan, PhD
Assistant Professor of Medicine and Assistant Professor of Biomedical Informatics

Wilhelm Haas, PhD
Assistant Professor of Medicine

Daniel A. Haber, MD, PhD

Nir Hacohen, PhD

Aaron Hata, MD, PhD
Associate Professor of Medicine
Kristine and Bob Higgins MGH Research Scholar 2025-2030

Anthony John Iafrate, MD, PhD
Austin L. Vickery, Jr. Professor of Pathology

Othon Iliopoulos, MD
Associate Professor of Medicine

Max Jan, MD, PhD
Assistant Professor of Pathology

David M. Langenau, PhD
Atul K. Bhan, MBBS, MD, Endowed Chair in Experimental Pathology
Professor of Pathology (Molecular Pathology Unit)

Michael S. Lawrence, PhD
Associate Professor of Pathology

Mark B. Leick, MD
Assistant Professor of Medicine

Abner Louissaint, Jr., MD, PhD
Aziz and Nur Hamzaogullari Endowed Scholar in Hematologic Malignancies
Associate Professor of Pathology (Molecular Pathology Unit)

Shyamala Maheswaran, PhD
Mary B. Saltonstall Endowed Chair in Oncology
Professor of Surgery

Robert Manguso, PhD
Co-Director Tumor Immunotherapy Discovery Engine, Broad Institute
Associate Professor of Medicine

Marcela V. Maus, MD, PhD
Director, Cancer Center Program in Cellular Immunotherapy
Paula J. O'Keeffe Endowed Chair in Thoracic Oncology
Professor of Medicine

Andrea I. McClatchey, PhD

Avanish Mishra, PhD
Assistant Professor of Surgery

David T. Miyamoto, MD, PhD
Associate Professor of Radiation Oncology

Mo Motamedi, PhD
James and Patricia Poitras Endowed Chair in Cancer Research
Assistant Professor of Medicine

Christopher W. Mount, MD, PhD
Faculty Member (Molecular Pathology Unit)*

Eugene Oh, PhD
Assistant Professor of Medicine

Christopher J. Ott, PhD
Assistant Professor of Medicine

Luca Pinello, PhD
MGH Research Scholar 2024-2029
Associate Professor in Pathology (Molecular Pathology Unit)

Esther Rheinbay, PhD
Assistant Professor of Medicine

Miguel N. Rivera, MD
Associate Professor of Pathology (Molecular Pathology Unit)

Krantz Family Center for Cancer Research Faculty

Debattama Sen, PhD
Assistant Professor of Medicine

Dennis C. Sgroi, MD
Executive Vice-Chair of Pathology
Professor of Pathology

Diana D. Shi, MD
Faculty Member (Radiation Oncology)*

Toshihiro Shioda, MD, PhD
Associate Professor of Medicine

Mikołaj Słabicki, PhD
Assistant Professor of Medicine

Shannon Stott, PhD
d'Arbeloff MGH Research Scholar 2022-2027
Associate Professor of Medicine

Mario L. Suvà, MD, PhD
Vice-Chair of Pathology for Research
Director, Molecular Pathology Unit
Janet and William Ellery James MGH Research Scholar 2020-2025
Associate Professor of Pathology

David A. Sweetser, MD, PhD
Chief of Medical Genetics and Metabolism, Department of Pediatrics
Leslie Meyer and Lewis Ball Holmes Chair in Genetics and Teratology
Associate Professor of Pediatrics (Pediatrics, Genetics)

David T. Ting, MD
Associate Clinical Director for Innovation, Cancer Center
Amin and Zebunisha Juma Endowed Chair in Oncology
Associate Professor of Medicine

Ignacio Vázquez-García, PhD
Assistant Professor of Pathology (Molecular Pathology Unit)

Alexandra-Chloé Villani, PhD
Assistant Professor of Medicine (Center Immunology & Inflammatory Diseases)

Bo Xia, PhD
Assistant Professor of Pathology (Molecular Pathology Unit)

Jackson Laboratories

Steven M. Blum, MD
*Faculty Member**

Genevieve M. Boland, MD, PhD
Vice Chair for Research, Department of Surgery
MGH Research Scholar 2023-2028
Associate Professor of Surgery

Nir Hacohen, PhD

Moshe Sade-Feldman, PhD
Assistant Professor of Medicine

Simches Laboratories

Nabeel Bardeesy, PhD
John R. Gallagher III and Katherine A. Gallagher Endowed Chair in Gastrointestinal Cancer Research
Professor of Medicine

Priscilla Brastianos, MD
Terry and Jean de Gunzburg MGH Research Scholar 2021-2026
Associate Professor of Medicine (Neuro-Oncology)

Zhixun Dou, PhD
Assistant Professor of Medicine

Leif W. Ellisen, MD, PhD
Director, Cancer Center Program in Breast Medical Oncology
Nelson Family and Jerry Younger, MD Endowed Chair in Breast Cancer Research
Professor of Medicine

Konrad Hochedlinger, PhD
Gerald and Darlene Jordan Endowed Chair
Professor of Medicine (Genetics)

Hanno Hock, MD, PhD
Brant Carleton Endowed Chair in Acute Myeloid Leukemia Research
Assistant Professor of Medicine

William L. Hwang, MD, PhD
Assistant Professor of Radiation Oncology (Center for Systems Biology)

Peter Miller, MD, PhD
Assistant Professor of Medicine

Raul Mostoslavsky, MD, PhD

Ioannis Sanidas, PhD
Assistant Professor of Medicine

David T. Scadden MD
Gerald and Darlene Jordan Professor of Medicine

**Assistant Professor appointment process initiated*

Faculty Listing by Theme

Cancer Cell Biology
Liron Bar-Peled, PhD
Nabeel Bardeesy, PhD
Genevieve Boland, MD, PhD
Priscilla Brastianos, MD
Shawn Demehri, MD, PhD
Zhixun Dou, PhD
Andrew Elia, MD, PhD
Aaron Hata, MD, PhD
Konrad Hochedlinger, PhD
William L. Hwang, MD, PhD
David M. Langenau, PhD
Shyamala Maheswaran, PhD
Andrea I. McClatchey, PhD
Christopher W. Mount, MD, PhD
Eugene Oh, PhD
Miguel Rivera, MD
Ioannis Sanidas, PhD
David T. Scadden, MD
Diana D. Shi, MD
Toshihiro Shioda, MD, PhD
Mikołaj Słabicki, PhD
David T. Ting, MD
Bo Xia, PhD

Cancer Genomics, Epigenetics and Proteomics
Liron Bar-Peled, PhD
Nabeel Bardeesy, PhD
Lloyd Bod, PhD
Genevieve Boland, MD, PhD
Priscilla Brastianos, MD
Zhixun Dou, PhD
Andrew Elia, MD, PhD
Leif Ellisen, MD, PhD
Gaddy Getz, PhD
Wilhelm Haas, PhD
Aaron Hata, MD, PhD
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Breast Cancer

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Genitourinary Cancers

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Head and Neck Squamous Cell Cancer

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Hematologic Malignancies

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Liver, Pancreatic and Gastrointestinal Cancers

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Lung Cancer

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Melanoma and Skin Cancers

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Pediatric Cancers

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Sarcoma

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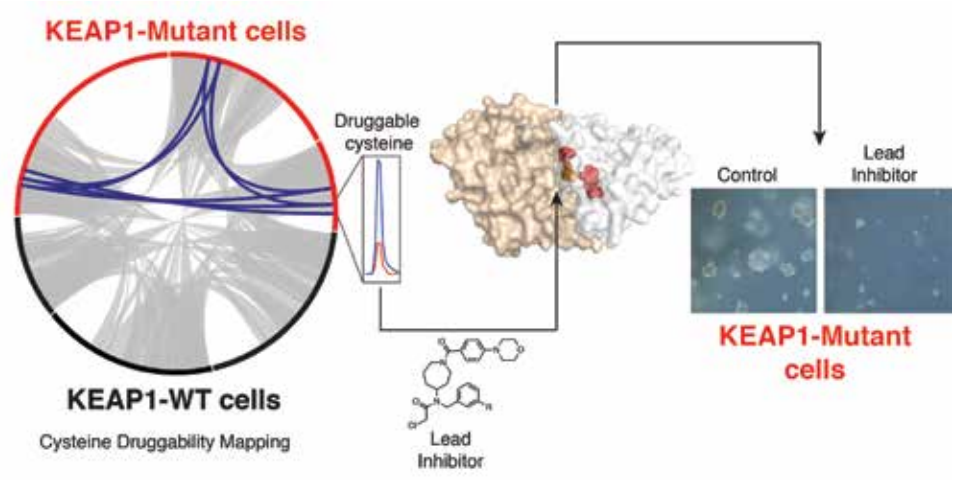
Research in **the Bar-Peled laboratory** sits at the interface of cellular metabolism and signal transduction and focuses on understanding how cancer cells respond to altered metabolic states. Rapidly proliferating cancer cells are characterized by increased production of toxic metabolic byproducts known as reactive oxygen species (ROS) that at high levels potently block cancer cell growth. To neutralize high ROS levels, cancer cells activate the NRF2 pathway, which governs the cellular antioxidant response. While the NRF2 pathway is critical for cancer growth, the molecular mechanisms by which this pathway functions and provides cancer cells with a proliferative advantage remain poorly understood. By combining frontier molecular, chemical and proteomic approaches, research in our lab has revealed that NRF2 establishes a unique cellular environment that protects critical proteins required for cancer cell growth from inactivation by ROS. Our studies indicate that these ROS-regulated proteins are highly targetable by small molecule inhibitors and may be exploited to develop chemical tools to inactivate these dependencies in cancers.

Cancer cells display remarkable plasticity allowing them to adapt to ever changing environments. A key feature of this plasticity is their ability to rewire core metabolic networks to provide a steady source of energy and building blocks needed for rapid growth. This demand for energy produces byproducts, including ROS that alters the function of proteins, DNA and lipids, and if left unchecked, results in oxidative stress and impairs cancer cell viability. To counter a rise in oxidative stress, cells activate the NRF2 transcription factor leading to the expression of a vast network of antioxidant and detoxification genes that restore redox homeostasis. Multiple cancer cells, including ~30% of non-small cell lung cancers (NSCLCs) activate NRF2 through the genetic disruption of its negative regulator KEAP1. Despite its clear importance in cancer cell proliferation, we know remarkably little about how the NRF2/KEAP1 pathway functions within cancer cells or how ROS modification of proteins alters their function. Our long-term goal is to understand how cancer cells sense and respond to ROS and to pharmacologically modulate these pathways in cancers where they are deregulated.

Redox control pathways in lung cancer

Our recent studies focus on how the intracellular environment generated by NRF2 in NSCLCs is required for cancer cell proliferation. By employing a chemical proteomics platform (isotopes-ABPP) that identifies changes in cysteine reactivity mediated by ROS, we demonstrated that NRF2 is required for the protection of dozens of proteins from ROS modification. We found that silencing NRF2 in NSCLCs reduced the reactivity of the catalytic cysteine of the glycolytic enzyme GAPDH without changing GAPDH protein abundance. Concomitant knockdown of NRF2 significantly reduced GAPDH enzyme activity and glycolytic flux, a metabolic pathway required to fuel cancer cell proliferation. These results illustrate how NRF2 can regulate enzyme and pathway activity, not through direct transcriptional control, but rather by fostering a favorable redox environment required for proper enzyme function. Current studies in our



(Left) A cysteine druggability map identifies proteins exclusively druggable in KEAP1-mutant NSCLC cells enabling the development of small molecule inhibitors that disrupt NR0B1 protein interactions (middle) and block KEAP1-mutant cell growth (right).

Images from Bar-Peled et al., 2017.

lab seek to elucidate how other proteins are post-translationally regulated by NRF2 and feedback into this pathway. To address these questions, we are studying the function of ROS-regulated sites on proteins as well as the identifying reactive metabolites that modify them.

Druggable co-dependencies

Our investigations suggest that the cellular state created by NRF2 may be exploited to develop inhibitors targeting proteins whose expression and function are stimulated by this environment. Because of their importance to protein function, cysteines are targeted by multiple clinically approved inhibitors. To identify pharmacological targets of the NRF2 pathway, we use powerful chemical proteomic platforms (cysteine druggability mapping) to identify the landscape of protein druggability (e.g. ligand-protein interactions) in genetically defined lung cancers. Our studies reveal that multiple proteins, including the orphan nuclear receptor NR0B1, are exclusively druggable in KEAP1-mutant, NRF2-activated cells. By developing a small molecule inhibitor that disrupts NR0B1 protein interactions we show that NR0B1 functions as a critical signaling node within the NRF2 pathway to support its proproliferative transcriptional output required for anchorage-independent growth. Recently we uncovered that cysteine residues that are sensitive to ROS modification are highly targetable by covalent inhibitors. Our current studies suggest that these sites may be exploited to develop inhibitors that target proteins required for the proliferation of NRF2-activated cancers.

Ongoing projects:

1. Determine how cancer proteomes respond to changes in the intracellular redox environment
2. Elucidate the role of NRF2-regulated reactive metabolites on protein function
3. Decipher how cells adapt to anchorage-independent growth
4. Identify druggable transcriptional dependencies in genetically-defined cancers

Selected Publications:

Takahashi M†, Chong HB, Zhang S, Yang TY, Lazarov MJ, Harry S, Maynard M, Hilbert B, White RD, Murrey HE, Tsou CC, Vordermark K, Assaad J, Gohar M, Dürr BR,... Oh E, Fisher DE, Maheswaran S, Haber DA, Boland GM, Sade-Feldman M, Jenkins RW, Hata AN, Bardeesy NM, Suvà ML, Martin BR, Liau BB, Ott CJ, Rivera MN, Lawrence MS†, **Bar-Peled L**†. DrugMap: A quantitative pan-cancer analysis of cysteine ligandability. *Cell.* 2024 Apr 17:S0092-8674(24)00318-0.

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Bar-Peled L*, Chantranupong L*, Cherniack AD, Chen WW, Ottina KA, Grabiner BC, Spear ED, Carter SL, Meyerson ML, and Sabatini DM. (2013). A tumor suppressor complex with GAP activity for the Rag GTPases that signal amino acid sufficiency to mTORC1. *Science* 340: 1100-1106.

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Nabeel Bardeesy, PhD

Pancreatic cancer and biliary cancer are among the most aggressive types of human cancers. **The Bardeesy laboratory** has developed a series of genetically engineered mouse models and patient-derived models to define the role of key gene mutations that drive these cancer types. Current projects focus on understanding the functions of key cancer genes in controlling cancer growth, nutrient utilization, and evasion of the immune system. Additional studies are exploring how therapies targeting these cancer genes are initially effective and why resistance eventually develops. Each of these studies is being used to inform improved therapeutic approaches.

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The Bardeesy lab studies the pathways driving the pathogenesis of pancreatic and biliary cancers. The lab has developed a series of genetically engineered mouse models and patient-derived models of these diseases. Using these systems, the team has focused on oncogenic programs downstream of driver mutations, as well as mechanisms of response and resistance to targeted therapies.

Interplay between metabolism and chromatin regulation

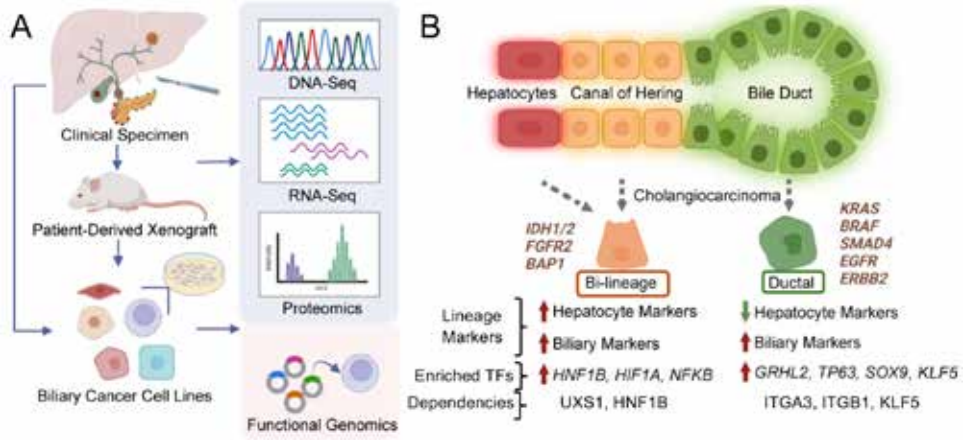
A key area of current focus is to elucidate metabolic regulators of pancreatic and biliary cancers, with particular attention to factors that reprogram cancer cell metabolism. We have linked mutations in the IDH1 gene to changes in metabolism that alter epigenetic states. Identifying these pathways has provided insight into mechanisms of transformation driven by IDH1 mutations and has revealed novel therapeutic vulnerabilities. Mutant IDH proteins acquire a neomorphic enzymatic activity that converts alpha-ketoglutarate (αKG) to 2-hydroxyglutarate (2HG), which inhibits multiple αKG-dependent dioxygenases, including the TET family of DNA demethylases. We are investigating how IDH-mediated epigenetic defects, particularly via TET inhibition, alter tumor–immune interactions to support cancer growth.

Oncogenic functions of protein kinase A signaling in pancreatic and liver cancers

The protein kinase A (PKA) signaling pathway is activated by mutations in several tumor types, including a subset of pancreatic and biliary tumors with GNAS mutations (an upstream regulator of PKA), and fibrolamellar carcinoma, a liver cancer characterized by activating PKA gene fusions. While PKA is a known driver of tumor growth in these settings, its specific oncogenic mechanisms remain less well defined. Our work has focused on elucidating these mechanisms and has identified the salt-inducible kinases (SIK1–3) as critical effectors of oncogenic PKA signaling. In addition, we have uncovered downstream epigenetic mechanisms that control proliferation and reprogram mitochondrial function and tumor cell metabolism.

Understanding and targeting FGFR2-driven biliary cancer

Genetic alterations that activate Fibroblast Growth Factor Receptor 2 (FGFR2) signaling are common in biliary cancer and predict response to pharmacological FGFR inhibition. However, tumor responses are often modest and resistance invariably emerges. We are investigating mechanisms



Biliary tract cancers (BTCs) are aggressive and molecularly heterogeneous malignancies. In collaboration with the Getz lab and the Broad Institute's DepMap program, the Bardeesy lab generated a comprehensive atlas of 63 BTC cell lines using multi-omic profiling and genome-scale CRISPR screening (Panel A). This study defines biologically distinct subtypes based on differentiation programs and genotype, each with unique dependencies and therapeutic vulnerabilities. Panel B highlights that intrahepatic cholangiocarcinomas, a major subtype of BTCs arising within the liver, comprise two transcriptionally defined subtypes: Bi-lineage, with gene expression features of both hepatocytes and biliary epithelial cells, and Ductal, with biliary-restricted programs. These subtypes are driven by distinct master transcription factors and exhibit subtype-specific vulnerabilities. This atlas provides a foundational resource for dissecting BTC heterogeneity and informing subtype-targeted therapeutic strategies.

of acquired resistance to FGFR inhibitors and are developing therapeutic strategies targeting additional signaling and immunomodulatory pathways to potentiate FGFR inhibitor efficacy and overcome resistance.

Models of biliary cancer

Recent genetic studies have identified multiple recurrent mutations in biliary cancers and revealed considerable intertumoral heterogeneity. A major limitation in the field has been the lack of experimental systems to define the contributions of individual genetic lesions to tumor progression. We have established a series of genetically engineered mouse models incorporating combinations of key mutations found in human disease. In parallel, we are developing a human biliary cancer cell line bank, which we are using in large-scale genetic and small-molecule screens to systematically define targetable vulnerabilities across molecularly defined subtypes.

Selected Publications:

Vijay V, Karisani N, Shi L, Hung YH, Vu P, Kattel P, Kenney L, Merritt J, Adil R, Wu Q, Zhen Y, Morris R, Kreuzer J, Kathiresan M, Herrera Lopez XI, Ellis H, Gritti I, Lecorgne L, Farag I, Popa A, Shen W, Kato H, Xu Q, Balasooriya ER, Wu MJ, Wan J, Kondo H, Chaturantabut S, Raghavan S, Hall MD, Patnaik S, Shen M, Kelley RK, Cleary JM, Lawrence MS, Root DE, Patra KC, Silveira VS, Benes CH, Deshpande V, Juric D, Sellers WR, Ferrone CR, Haas W, Vazquez F, Getz G, **Bardeesy N**. Generation of a biliary tract cancer cell line atlas identifies molecular subtypes and therapeutic targets. *Cancer Discov*. 2025 May 12.

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Steven M. Blum, MD

Blum Laboratory

(Opens Fall of 2025)
Steven M. Blum, MD

Recent advances in cancer immunotherapy have delivered life-saving benefits to patients with many types of cancer. However, most tumors do not respond to current treatments, especially when the cancer has spread to certain parts of the body. These therapies can also cause serious side effects called immune-related adverse events (irAEs), which happen when the immune system attacks healthy organs. **The Blum Laboratory** works to make cancer immunotherapy both safer and more effective. We study patient samples and use advanced techniques to find new treatment strategies. Our early work has focused on two main challenges: (1) understanding irAEs and how they relate to the cancer-fighting effects of immunotherapy and (2) developing better treatments for cancers that spread to the abdomen and cause a condition called malignant ascites. Our long-term goal is to improve the lives of cancer patients by boosting anti-tumor immunity while reducing the harm caused by treatments.

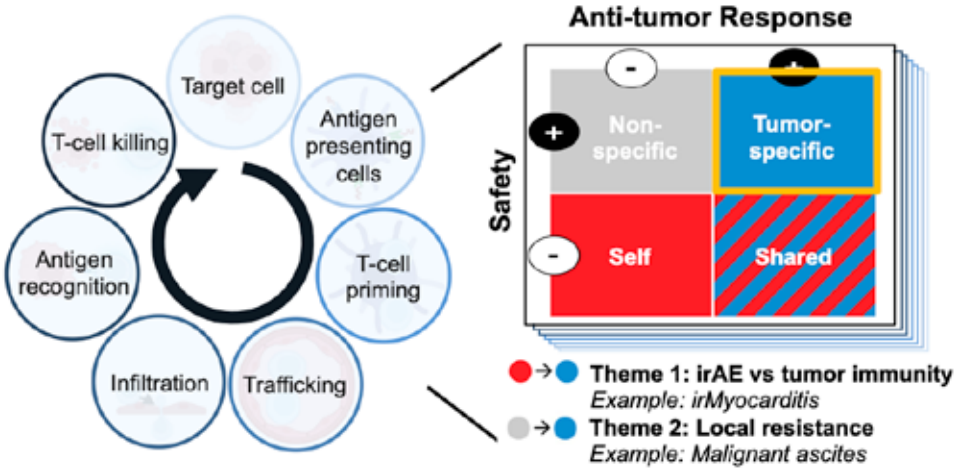
Immune checkpoint inhibitors (ICIs) have transformed cancer therapy and can produce durable responses in some patients with solid tumors. Unfortunately, most patients do not benefit from these treatments. Many tumors are resistant to ICIs, particularly when cancer cells have spread to certain anatomical sites. Additionally, ICI use can be complicated by immune-related adverse events (irAEs), which occur when the immune system attacks healthy organs. IrAEs can lead to the discontinuation of effective therapies, hospitalizations, permanent disability, or even death.

The Blum Laboratory aims to develop safer and more effective immunotherapy strategies for patients with solid tumors. Using patient samples, systems immunology, and disease-relevant model systems, we investigate the cellular and molecular drivers of toxicity and treatment resistance across the tumor immunity cycle (*see Figure*). Our long-term goal is to uncover broadly applicable principles that can improve clinical outcomes by (Theme 1) mitigating irAEs while preserving anti-tumor immunity and (Theme 2) overcoming local immunotherapy resistance. The examples below illustrate current projects within these broader themes.

Theme 1: Investigating irAEs and Anti-Tumor Immunity through irMyocarditis

IrAEs can affect any organ system and have clinical manifestations that range in severity from mild to life-threatening. Current treatments for severe irAEs rely on broadly immunosuppressive medications, which can compromise tumor control and may not optimally treat the mechanisms driving the organ-specific irAE.

Our first efforts to explore the relationship between irAEs and anti-tumor immunity have focused on ICI-related myocarditis (irMyocarditis), a particularly dangerous irAE that occurs in ~1% of ICI recipients but is frequently fatal. We used single-cell RNA sequencing, T-cell receptor (TCR) sequencing, multiplexed imaging, and TCR functional assays to map the immune responses associated with irMyocarditis onset and severity. These studies have revealed potentially pathogenic pathways in both immune and non-immune cells that could be targeted by existing drugs not yet used for this condition. We also found that T-cell responses in the heart differ from those in the tumor, raising the possibility that anti-tumor immunity and irAEs could be therapeutically separated.



Model for improving outcomes for cancer patients receiving immunotherapy.
Each step of the tumor immunity cycle (adapted from Mellman I, et al. Immunity 2023.) presents an opportunity to identify safe, tumor-specific mechanisms that can help to improve both the safety and efficacy of cancer immunotherapy. The lab's main research themes of (Theme 1) improving safety without compromising efficacy and (Theme 2) safely overcoming local immunotherapy resistance are shown with example projects.

Building on these findings, we are developing cutting-edge models to identify mechanistic drivers of irMyocarditis and test targeted interventions. While irMyocarditis serves as an important example for understanding irAEs and anti-tumor responses, our larger program is applying this framework to understand and manage irAEs affecting all organ systems.

Theme 2: Improving Immune Responses in Patients with Malignant Ascites

The spread of cancer to the peritoneal cavity can lead to the development of malignant ascites, a condition where fluid accumulates in the abdomen due to cancer. Malignant ascites occurs in ~8% of all cancer patients and up to 40% of those with gastroesophageal adenocarcinoma (GEA). Ascites is associated with severe symptoms and poor response to systemic therapies, including ICIs. The immunologic barriers in this unique microenvironment remain incompletely understood.

Our initial studies have focused on GEA-associated ascites. Using paired single-cell transcriptomic and surface proteomic profiling of more than 500,000 immune and tumor cells from ascites and matched blood, combined with proteomic analysis of ascites fluid and plasma, we have identified:

- A dendritic cell subset enriched in malignant ascites across multiple tumor types that is anticipated to have an immunosuppressive function in the tumor microenvironment.
- Targetable soluble proteins and novel immune checkpoints concentrated in the peritoneal microenvironment.

We are now using patient-derived *ex vivo* models to dissect the biology of these targets and test therapeutic strategies. Ultimately, these insights aim to guide the development of approaches that would overcome local immunosuppression while minimizing systemic toxicity. Such strategies could benefit a wide range of cancers that metastasize to body cavities through either systemic or intraperitoneal delivery.

Selected Publications:

Blum SM*, Ouyang B*, Zubiri L, Leonard D, Slowikowski K, Wang M, Grealish KA, Hathaway NK, Molina G, Shah N, Lawrence DP, Dougan M, Villani AC, Mino Kendusen M, Reynolds KL**, Sullivan RJ**. Tumor location as a risk factor for severe immune-related adverse events. *J Immunother Cancer*. 2025 May 15;13(5):e011312.

Blum SM*, Zlotoff DA*, Smith NP*, Kernin IJ*, Ramesh S*, Zubiri L, Caplin J, Samanta N, Martin S, Wang M, Tirard A, Song Y, Xu KH, Barth J, Sen P, Slowikowski K, Tantivit J, Manakongtreecheep K, Arnold BY, Nasrallah M, Pinto CJ, McLoughlin D, Jackson M, Chan P, Lawless A, Michaud WA, Sharova T, Nieman LT, Gainor JF, Wu CJ, Juric D, Mino-Kenudson M, Oliveira G, Sullivan RJ, Boland GM, Stone JR, Thomas MF**, Neilan TG**, Reynolds KL**, Villani AC**. Immune responses in checkpoint myocarditis across heart, blood and tumour. *Nature*. 2024 Dec;636(8041):215-223.

Zhao JJ*, Ong CJ*, Srivastava S, Chia DKA, Ma H, Huang K, Sheng T, Ramnarayanan K, Ong X, Tay ST, Hagihara T, Tan ALK, Teo MCC, Tan QX, Ng G, Tan JW, Ng MCH, Gwee YX, Walsh R, Law JH, Shabbir A, Kim G, Tay Y, Her Z, Leoncini G, Teh BT, Hong JH, Tay RYK, Teo CB, Dings MPG, Bijlsma M, Lum JHY, Mathur S, Pietrantonio F, **Blum SM**, van Laarhoven H, Klempner SJ, Yong WP, So JBY, Chen Q**, Tan P**, Sundar R**. Spatially Resolved Niche and Tumor Microenvironmental Alterations in Gastric Cancer Peritoneal Metastases. *Gastroenterology*. 2024 Dec;167(7):1384-1398.e4.

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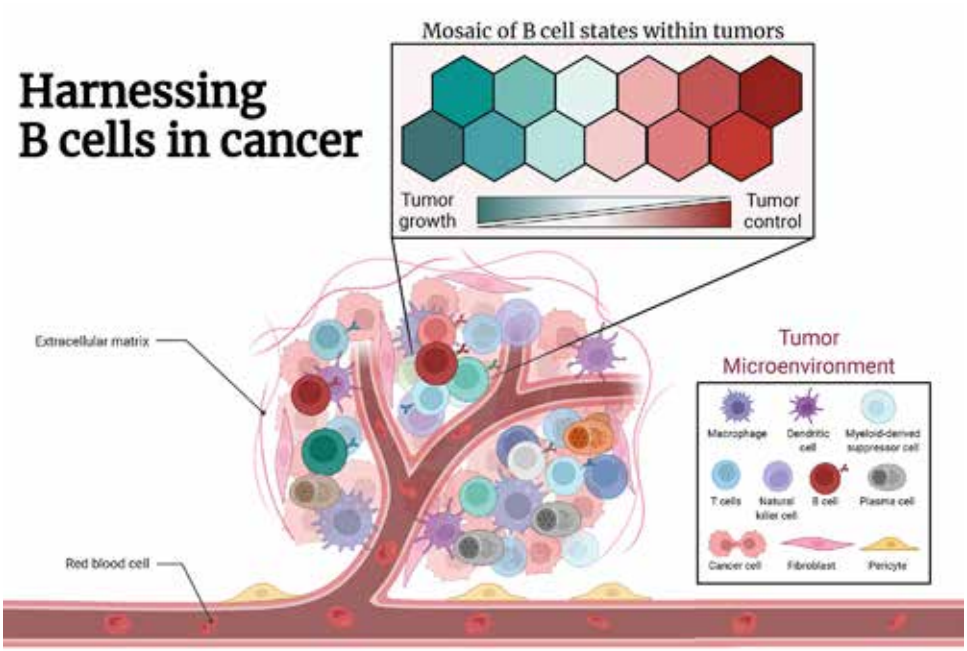
Immunotherapies have demonstrated remarkable clinical success in the treatment of various cancers mainly by boosting the function of endogenous T cells to attack neoplastic cells. Unfortunately, the frequency of patients responding to these therapies is modest and a significant fraction of patients develop severe immune-related adverse events. These observations have catalyzed a more thorough investigation of other cell types in the tumor microenvironment that could be targeted to increase treatment efficacy while mitigating toxicity. B cells are an important arm of the adaptive immune system frequently infiltrating solid tumors, however, their function on cancer progression has not been sufficiently explored. **The Bod laboratory** focuses on deciphering the landscape of phenotypic and functional B cell states within tumors. In particular, we are interested in exploring which B cell subset is favorable or detrimental for cancer progression, and by which mechanisms these B cells control tumor growth. Our thorough examination of the B cell response towards cancer aims to provide a new angle to harness the anti-tumor immune response more effectively.

Historically, B cells have been at the forefront of research in allergies, infectious diseases, and vaccines. Beyond mediating the humoral response, B cells are potent antigen presenting cells (APCs). They can provide co-stimulatory or co-inhibitory signals and secrete cytokines and chemokines that regulate functions of other cell types including effector T cells.

However, the role of B cells in the cancer scenario is unclear. While some studies have shown that B cells are critical for promoting anti-tumor immunity, others report that they may play a detrimental role, favoring relapse and metastasis. Indeed, on one hand, B cells form tertiary lymphoid structures (TLS) in the context of successful immune checkpoint blockade (ICB) therapy in human cancer patients, suggesting that B cells and TLS provide critical help to promote anti-tumor immunity and inhibit tumor growth.

On the other hand, B cells may also play an inhibitory role through the expression of soluble and/or inhibitory molecules on their surface which contribute to dismantle the anti-tumor T cell immunity. Whether the paradoxical effects of B cells in these settings is due to their functional diversity or distinct roles within different tumor types remains to be elucidated.

A more comprehensive understanding of B cell heterogeneity in tumors will allow us to identify B cell subsets and their respective functionality arising during different stages of tumor growth and regulating anti-tumor immunity. Growing evidence suggests that lymphocytes occupy a vast and continuous landscape of possible cellular states, as opposed to the idea of disconnected discrete subtypes. Recent advances in genomic analysis and sophisticated computational methods are enabling us to explore such diversity and are transforming our comprehension of immunology. Using such approaches, the lab aims to generate new insights into the role of B cells in inducing and regulating anti-tumor immunity. The main axes of research in our laboratory are:



While existing anti-cancer immunotherapies mainly engage effector T cells, harnessing both arms of the adaptive immune system might be more favorable. Illustrated by the mosaic of diverse B cell states, B cells are a highly dynamic cell population in the tumor microenvironment (TME) favoring or impeding tumor growth. In our lab, we want to thoroughly dissect the diverse and complex functions of TME-associated B cells to pave the way for new therapeutic avenues and improve the anti-cancer immune response. Adapted from "Tumor Microenvironment", by BioRender.com (2022).

1. Deciphering the landscape of B cell states within the tumor microenvironment using multi-omics technologies. Our goal is to establish an atlas of B cell states in cancer, and to thoroughly interpret the spatial, transcriptomic, and epigenetic status of B cells in different contexts (e.g., different tumor types, healthy tissues, post-treatment with immune checkpoint blockade therapy, chemotherapy, or radiotherapy).
2. Identifying B cell-specific biomarkers and/or -targets in cancer. Using genetic and genomics approaches, we aim to explore potential B cell biomarkers and novel targets that are expressed on B cells, which may synergize with T cell-based checkpoint blockade therapy to enhance anti-tumor immunity.
3. Dissecting the underlying cellular and molecular mechanisms that govern the B cell response to cancer. The tumor microenvironment is layered with multiple tissular, cellular and molecular components which are associated with distinct tumor-promoting or -inhibiting mechanisms, and ultimately, open distinct therapeutic windows. We are interested in elucidating how B cells integrate these components and how the anti-tumor B cell response evolves in response to these signals.

Selected Publications:

Revach OY, Cicerchia AM, Shorer O, Petrova B, Anderson S, Park J, Chen L, Mehta A, Wright SJ, McNamee N, Tal-Mason A, Cattaneo G, Tiwari P, Xie H, Sweere JM, Cheng LC, Sigal N, Enrico E, Miljkovic M, Evans SA, Nguyen N, Whidden ME, Srinivasan R, Spitzer MH, Sun Y, Sharova T, Lawless AR, Michaud WA, Rasmussen MQ, Fang J, Palin CA, Chen F, Wang X, Ferrone CR, Lawrence DP, Sullivan RJ, Liu D, Sachdeva UM, Sen DR, Flaherty KT, Manguso RT, **Bod L**, Kellis M, Boland GM, Yizhak K, Yang J, Kanarek N, Sade-Feldman M, Hacohen N, Jenkins RW. Disrupting CD38-driven T cell dysfunction restores sensitivity to cancer immunotherapy. *Cell Report Medicine* 2025, Volume 6, Issue 7, 15 July 2025, 102210.

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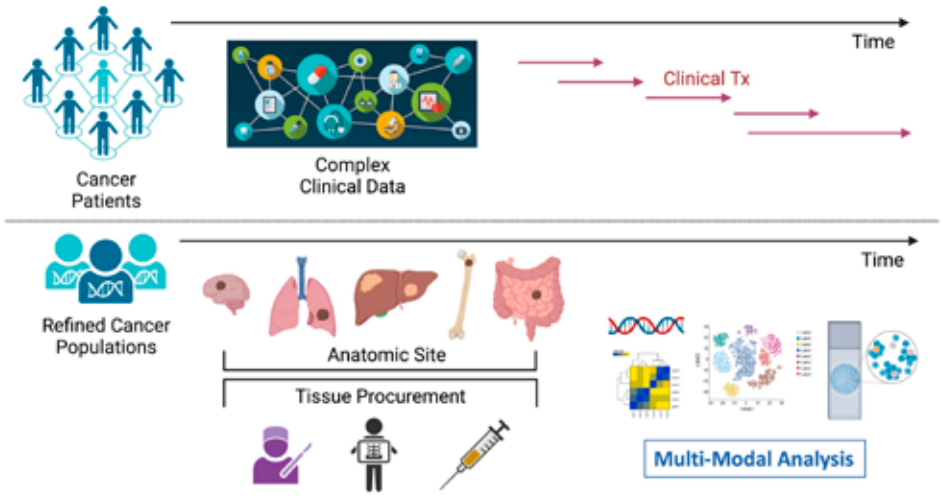
As a translational immuno-oncology laboratory, **the Boland laboratory** is focused on questions relating to tumor and immune interactions. The group uses a variety of complex approaches to characterize tumor biology and understand the interactions between tumor and immune cells and how these modify the surrounding tumor and tissue. Additionally, the Boland Lab is focused on identification of blood-based biomarkers to inform clinical decision-making. The areas of interest to the laboratory span from early cancer biology (why tumors form and/or metastasize) to how tumors respond to a variety of modern therapies with a focus on immune-based therapies. Our lab bridges the complementary but disparate environments of clinical and basic research, with a primary goal of translating interesting research findings into meaningful clinical interventions based on the newest available technology.

The Boland Lab leads the Mass General correlative immuno-oncology efforts in melanoma and GI malignancies. The goal is to utilize patient-derived specimens (tumors/blood) to understand cancer biology, identify mechanisms of response and resistance to current therapies, identify biomarkers of therapeutic responses and immune-related toxicities, and nominate new targets for combinatorial trials. The group uses emerging technology to deconvolve tumor and immune interactions, integrating multiple complex datasets to understand the dynamic interplay occurring in the tumor microenvironment. Our translational research pipeline spans from clinical tissue and blood-based analyses to ex vivo tumor/ immune modeling to small animal models of cancer. Our focus is not limited to cutaneous melanoma but also includes rare melanoma subtypes and a variety of solid tumor histologies in which tumor-immune interactions are critical for tumor formation and propagation including T cell based therapies. Through these efforts, the Boland Lab has identified novel relationships between these resistant cell types and immune cells in the tumor microenvironment, allowing refinement of combinatorial therapeutic approaches.

In parallel, we are using the tumor-level analysis to identify and validate blood-based biomarkers allowing more cost-effective and clinically viable platforms to inform clinical decision making in real time.

Finally, the group is focused on T cell-based therapies being actively used in the clinic. In this way, the Boland Lab is uniquely positioned between the clinical and translational realms, seamlessly creating a bidirectional pipeline informed by the clinical care of patients and feeding into the next generation of clinical trials.



The Boland Lab creates a translational pipeline arising directly from patient care and feeding back to next-generation clinical trials.

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Domingues ACM, de Oliveira SB, Tessarollo NG, Lepique AP, Rodrigues O, Sharova T, Lawless A, Li D, Basnet M, **Boland GM**, Cohen S, Jenkins RW, Strauss BE. Use of patient-derived organotypic tumor spheroids for testing of viral vector gene therapy in combination with checkpoint blockade. *Mol Ther Oncol*. 2025 Jan 28;33(1):200942.

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Sun Y, Maggs L, Panda A, Wright SJ, Cicerchia AM, Jenney A, ..., Flaherty KT, **Boland GM**, Mehta A, Sade-Feldman M, Ferrone CR, Jenkins RW. TBK1 Targeting Is Identified as a Therapeutic Strategy to Enhance CAR T-Cell Efficacy Using Patient-Derived Organotypic Tumor Spheroids. *Cancer Immunol Res*. 2025 Feb 3;13(2):210-228.

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Holder AM, Dedeilia A, Sierra-Davidson K, Cohen S, Liu D, Parikh A, **Boland GM**. Defining clinically useful biomarkers of immune checkpoint inhibitors in solid tumours. *Nat Rev Cancer*. 2024 Jul;24(7):498-512.

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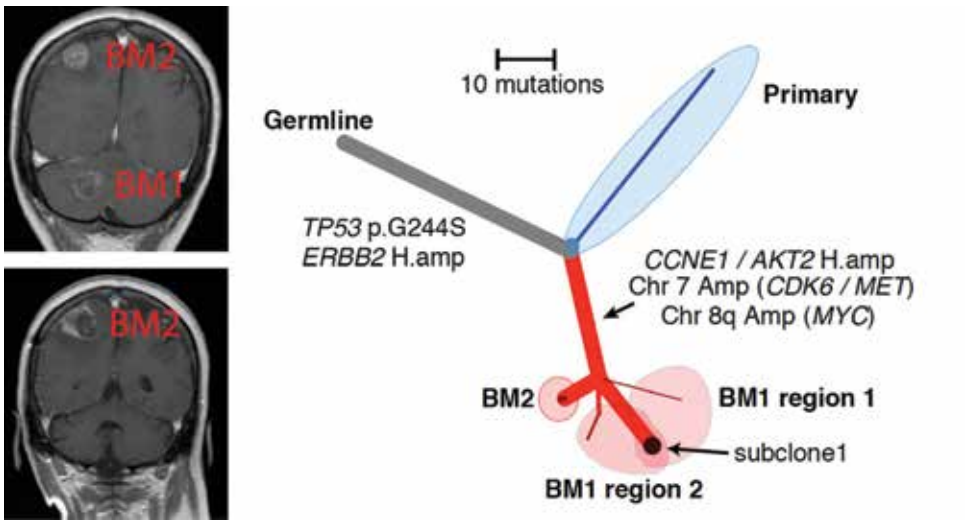
The Brastianos laboratory studies molecular drivers of human brain tumors. A lack of understanding of the molecular drivers of many brain tumors has hampered the development of novel therapies for many brain cancers. Our overarching objective is to characterize the tumor and immune microenvironment in primary brain tumors and brain metastases, and to accelerate the development of novel therapeutic approaches for these diseases. Through large-scale genomic efforts, we have discovered clinically significant genetic drivers in meningiomas, craniopharyngiomas, hemangioblastomas, glioneuronal tumors and brain metastases. We are currently investigating the role of these genomic drivers as potential therapeutic targets in several national NCI-sponsored multi-center clinical trials. Samples from our prospective trials are characterized to identify mechanisms of resistance to therapy in the brain. Additionally, we are expanding our in vitro and in vivo investigations to further elucidate the molecular evolution of the metastatic process to the central nervous system.

Characterizing genomic drivers of craniopharyngiomas

Craniopharyngiomas are a rare brain tumor that can cause profound clinical sequelae both through mass effect at presentation and through morbidity of treatment. Historically, incomplete knowledge of the molecular mechanisms that drive craniopharyngiomas has limited the development of targeted therapies for this tumor. We discovered activating mutations in CTNNB1 in nearly all adamantinomatous craniopharyngiomas and recurrent mutations in BRAF (resulting in p.Val600Glu) in nearly all papillary craniopharyngiomas (Brastianos et al. *Nature Genetics* 2014). These findings have important implications for the diagnosis and treatment of these neoplasms. Based on these data, we conducted a national multicenter trial evaluating the role of BRAF/MEK inhibition in patients with papillary craniopharyngioma (Alliance A071601); all patients with newly diagnosed papillary craniopharyngioma who received one or more cycles of vemurafenib/cobimetinib had dramatic responses to therapy (Brastianos et al. *NEJM* 2023).

Identifying molecular drivers of meningiomas

Meningiomas are the most common primary nervous system tumor with no known effective systemic therapy after failure of radiation and surgery. We demonstrated that meningiomas harbor recurrent oncogenic clinically actionable mutations, including in AKT1 and SMO (Brastianos et al. *Nature Genetics* 2013). Notably, these mutations were present in therapeutically challenging tumors of the skull base. We also recently identified potential genetics drivers of progression in meningiomas (BAP1, TERT promoter mutations, DMD). Our lab is working on developing better preclinical models of meningioma with the goal of testing new therapeutic targets in this disease. We are now conducting a prospective national multicenter Phase 2 study (A071401) of targeted therapy in patients with recurrent or progressive meningiomas harboring clinically actionable mutations, respectively, with promising results in patients (Brastianos et al. *JCO* 2023).



Representative phylogenetic tree of a primary tumor and 2 anatomically distinct brain metastases. Different regions of the brain metastases shared the same amplifications in CCNE1, AKT2, CDK6, MET and MYC, which were not present in the primary tumor biopsy.

Central nervous system metastasis center

Brain metastases are a common complication of cancer, with a dismal prognosis. There is a limited understanding of the oncogenic alterations harbored by brain metastases and whether these are shared with their primary tumors or other metastatic sites. The objectives of the Central Nervous System Metastasis Center are to (1) identify novel therapeutic targets through comprehensive molecular characterization, (2) functionally characterize candidate drivers through in vitro and in vivo models of metastasis, and (3) accelerate the application of our scientific findings to the clinical setting. With large-scale multi-omic approaches, we are comprehensively characterizing the tumor and immune microenvironment of brain metastases to understand how they evolve in the CNS. We demonstrated that brain metastases harbor clinically actionable drivers not detected in the primary tumors (Brastianos, Carter et al. *Cancer Discovery* 2015). We are evaluating the roles of these genetic alterations using various assays of metastasis (Shih, Nayyar et al. *Nature Genetics* 2020) and inhibiting pathways commonly altered in brain metastases with novel therapies (Ippen et al. *CCR* 2018; Nayyar et al. *CCR* 2023; de Sauvage et al. *Neuro-Oncol* 2024). In addition, using single-cell RNA sequencing, we are characterizing the dynamic changes in the immune microenvironment of the central nervous system during treatment (Prakadan et al. *Nature Communications* 2021; Alvarez-Breckenridge C et al. *CIR* 2022). Based on the work in the lab, we have now initiated several clinical trials (Brastianos et al. *Nature Cancer* 2021) including an NCI-sponsored genomically guided brain metastasis trial (A071701). Our hope is that the findings from our genomic and functional investigations will allow us to develop more rational therapeutic approaches for this disease.

Selected Publications:

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Alvarez-Breckenridge C, .. **Brastianos PK****, Carter SL.** Microenvironmental landscape of human melanoma brain metastases in response to immune checkpoint inhibition. *Cancer Immunol Res*. 2022 Jun 15:canimm.CIR-21-0870-E.2021.

Prakadan SM, Alvarez-Breckenridge C.A., Markson SC, … Carter SL**, **Brastianos PK****, Shalek AK**. Genomic and transcriptomic correlates of immunotherapy response within the tumor microenvironment of leptomeningeal metastases. *Nat Commun*. 2021 Oct 12;12(1):5955.

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Shih DJH, Nayyar N,…Carter SL*, **Brastianos PK***. Genomic characterization of human brain metastases identifies drivers of metastatic lung adenocarcinoma. *Nat Genet*. 2020; Apr;52(4):371-377.

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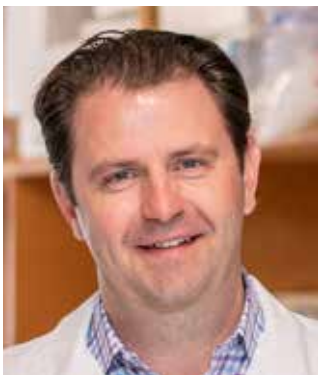

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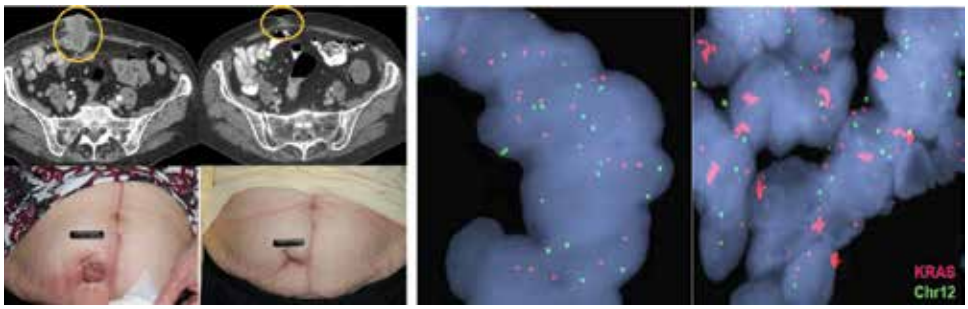
The Corcoran laboratory focuses on developing new and effective therapies for gastrointestinal cancers, including colorectal, pancreatic, stomach, and esophageal cancers, by targeting the specific survival signals that are active in a given patient's cancer. Our research utilizes targeted therapies, which are drugs that inhibit signaling pathways activated by the specific mutations that drive individual tumors. Since cancer cells often become resistant to these targeted therapies by activating alternative signaling pathways, we focus on identifying these key resistance signals in cancer cells. We utilize this information to devise effective combinations of targeted therapies that anticipate and ultimately overcome these mechanisms of drug resistance. Overall, our goal is to develop promising therapeutic strategies that can be evaluated in clinical trials for patients whose cancers are driven by specific mutations.

Targeted therapy strategies for gastrointestinal cancers

Historically, the standard clinical approach for patients with advanced cancers has been used to treat all patients with the same tumor type with the same generalized chemotherapy strategy. However, even among patients with the same type of tumor, the genetic mutations driving tumor growth in each individual patient can be vastly different. As an alternative approach, by identifying the key gene mutations present in an individual patient's tumor, we can "personalize" therapy by matching each patient with specific therapies that target those mutations essential for tumor growth. Our laboratory focuses on developing targeted therapy strategies directed against specific mutations commonly found in gastrointestinal cancers, including cancers with BRAF and KRAS mutations. However, while targeted therapy strategies can lead to dramatic tumor responses, clinical benefit is often limited by the ability of tumor cells to evolve and develop resistance to therapy. By identifying and understanding the key signals driving resistance, our laboratory aims to devise combinations of targeted agents that can overcome or even prevent resistance.

BRAF-mutant colorectal cancer

BRAF mutations occur in 10-15% of colorectal cancers and confer poor prognosis. While BRAF inhibitors have shown dramatic anti-tumor activity in melanomas harboring BRAF mutations, these agents are ineffective in BRAF-mutant colorectal cancers. Therefore, our laboratory has focused on determinants of resistance to BRAF inhibitors in BRAF-mutant colorectal cancers. We have found that reactivation of the MAPK signaling pathway (often mediated through EGFR), contributes to the relative insensitivity of BRAF mutant colorectal cancers to BRAF inhibition. However, we found that combining BRAF inhibitors with EGFR and/or MEK inhibitors can overcome resistance, leading to improved efficacy (*Cancer Discovery*, 2012). We have also identified multiple mechanisms of resistance that can arise to these newer BRAF inhibitor combinations, and are utilizing this information to develop therapeutic strategies to surmount resistance (*Cancer Discovery*, 2015; *Cancer Discovery*, 2018).



Pre-treatment Week 16 Pre-treatment Post-progression

Response and resistance in BRAF-mutant colorectal cancer. (Left) Example of a dramatic tumor response in a patient treated with the combination of a BRAF and a MEK inhibitor. (Right) KRAS amplification (red probes) can lead to BRAF inhibitor resistance in BRAF mutant colorectal cancer patients.

KRAS-mutant cancers

KRAS is the most commonly mutated oncogene in human cancer, mutated in ~20% of all cancers, including pancreatic (~90%) and colorectal cancers (~40%). Currently no effective therapies exist for KRAS-mutant cancers because KRAS itself has proven difficult to target directly with small molecules. Currently, our work focuses on identifying novel target pathways in KRAS-mutant cancers through hypothesis-based and large-scale pooled RNA interference screening approaches, with the goal of developing new targeted therapy combination approaches for KRAS-mutant cancers. We have identified adaptive feedback signals that impede the ability of MEK inhibitors to suppress MAPK signaling and have explored the role of novel agents (ERK inhibitors) or convergent signaling nodes to overcome feedback. We have expanded these approaches to identify other potentially effective targets in KRAS-mutant cancers, including direct KRAS inhibitors. Despite promising clinical responses in KRAS-G12C mutant NSCLC, there has been limited efficacy of G12C inhibitors as single agents in colon cancer. To address this limitation, we have defined key mechanisms of adaptive feedback resistance in response to KRAS inhibition and have employed vertical pathway inhibition strategies targeting the RAS-MAPK pathway as described in a recent publication (*Clinical Cancer Research*, 2020).

Translational Oncology

The overall goal of our research is to develop improved treatments for patients with gastrointestinal cancers and to identify molecular markers that may help us identify those patients most likely to respond to a given therapy. As such, our laboratory takes a highly translational approach to bringing new therapeutic strategies into the clinic for evaluation in novel clinical trials. Based on our observations, we have launched several clinical trials of BRAF inhibitor combinations in BRAF-mutant colorectal cancers that are showing increased efficacy (*J Clinical Oncology*, 2015). We have also developed a clinical trial combining the BCL-XL/BCL-2 inhibitor navitoclax with the MEK inhibitor trametinib in KRAS-mutant cancers.

To guide our laboratory investigations, we are utilizing key clinical specimens, including tumor biopsies and patient-derived tumor models to understand how tumors become resistant to therapy. We also utilize serial blood collections for circulating tumor DNA analysis to monitor the tumor heterogeneity and clonal dynamics associated with the emergence of therapeutic resistance (*Cancer Discovery* 2015, *Nature Medicine* 2015, *Cancer Discovery* 2016, *Cancer Discovery* 2017, *Cancer Discovery* 2018.)

Selected Publications:

Riedl JM, Fece de la Cruz F, Lin JJ, Parseghian C, Kim JE, Matsubara H, Barnes H, Caughey B, Norden BL, Morales-Giron AA, Kushner EW, Ehnstrom S, Nakamura H, Patel PS, Ellis H, Pappas L, Vakaris A, Gainor JF, Kopetz S, Klempner SJ, Parikh AR, Hata AN, Heist RS, **Corcoran RB**. Genomic landscape of clinically acquired resistance alterations in patients treated with KRASG12C inhibitors. *Ann Oncol.* 2025 Jun;36(6):682-692.

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Tanaka N, Lin JJ, Li C, Ryan MB, Zhang J, Kiedrowski LA, Michel AG, Syed MU, Fella KA, Sakhi M, Baiev I, Juric D, Gainor JF, Klempner SJ, Lennerz JK, Siravegna G, Bar-Peled L, Hata AN, Heist RS, **Corcoran RB**. Clinical acquired resistance to KRASG12C inhibition through a novel KRAS switch-II pocket mutation and polyclonal alterations converging on RAS-MAPK reactivation. *Cancer Discov.* 2021 Aug;11 (8):1913-1922.

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*Denotes equal contribution

Shawn Demehri, MD, PhD

The focus of **the Demehri laboratory** is to determine the role of the immune system in regulating the early stages of cancer development in order to harness its anti-tumor potential for cancer prevention and treatment. To date, several cancer immunotherapies have been developed with proven efficacy against late-stage cancers; however, the role of the immune system in preventing the early development of cancer remains uncertain. The research in the Demehri laboratory is focused on identifying the immune mechanisms that drive an immune activation sufficient to prevent cancer formation from pre-cancerous lesions. This approach raises a great opportunity to discover novel immune pathways that can be leveraged in cancer prevention and therapy.

Demehri Laboratory

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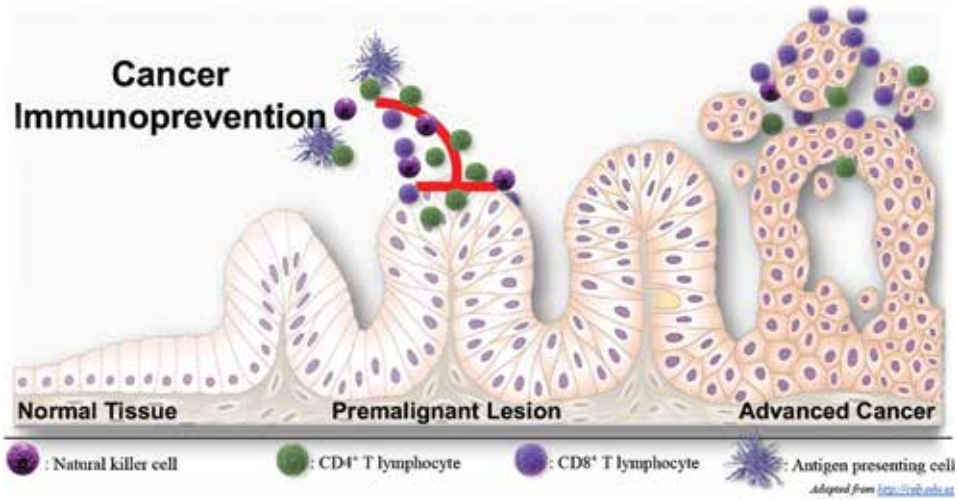
The field of cancer immunology has made substantial advances in recent years by deciphering the role of the tumor infiltrating CD8+ cytotoxic T lymphocytes (CTLs) in attacking cancer cells, which have led to promising new cancer immunotherapeutics. The current immunotherapeutic approaches, however, are largely designed to boost the anti-tumor immune response that has already formed against late-stage metastatic cancers. Therefore, the current cancer immunotherapies like immune checkpoint blockade, which rely on a pre-existing CTL infiltrate in the tumor for their effects, are proven ineffective to treat cancers that frequently lack a significant anti-tumor immune infiltrate, especially during the early in-situ phases of their development. In order to expand the potential of cancer immunotherapy, our laboratory studies the pathways that lead to immune system activation against early phases of cancer development. Devising a mechanism to activate the immune system against early-stage cancers has clear immunopreventive implications by directly blocking the cancer promotion and immunotherapeutic benefits by potentiating the immunity against late disease.

To pursue this goal, our laboratory studies the role of alarmins, damage-associated molecular patterns (DAMPs)/stress signals, commensal viruses, carcinogens, and aging associated factors in regulating early cancer development. The major areas of research in our laboratory are:

1) Mechanisms of CD4+ T cell activation against cancer. Our laboratory has studied the mechanism of thymic stromal lymphopoietin (TSLP) in evoking tumor suppression. TSLP is an epithelial-derived cytokine that plays a central role in stimulating CD4+ T helper 2 (Th2)-mediated allergic diseases like atopic dermatitis and asthma. We have shown that high TSLP levels establish a dominant anti-tumorigenic immune environment preventing cancer promotion. Currently, our team investigates the detailed mechanism of TSLP anti-tumor function against solid cancers and examines its application for the treatment of pre-cancerous skin and breast lesions in patients.

2) Mechanisms of natural killer (NK) cell recruitment and activation against cancer. NK cells are known for their potent anti-tumor properties. However, their role in controlling cancer development in vivo remains unclear. Our laboratory utilizes an NK cell-specific activating ligand to determine the combination of signals necessary to activate NK cells against early stages of carcinogenesis and to identify the mechanism of anti-tumor immunity mounted



Immune Regulation of Early Cancer Development.

by the activated NK cells to block cancer promotion and progression.

3) The impact of commensal viruses-immune system interplays on the homeostasis of the organs exposed to environmental carcinogens. We aim to determine how the immune system's control of commensal virome regulates the homeostasis of the virus-colonized tissues. Through this effort, we aim to realize the beneficial functions of commensal virome for the prevention and treatment of cancer and other chronic diseases that affect humans.

4) Mechanisms of cancer promotion by the immune system. Although immune cells can mount anti-tumor immunity against cancer, they are also implicated in promoting cancer development in chronic inflammation. Our laboratory studies the initiating mechanisms of cancer-prone chronic inflammation development in the skin, pancreas, colon and liver, which are the major organs affected by chronic inflammation and its cancer sequela.

Selected Publications:

Huang M, Wang D, Huang J, Bae AN, Xia Y, Zhao X, Mortaja M, Azin M, Collier MR, Semenov YR, Park JH, **Demehri S**. Hepatitis B virus promotes liver cancer by modulating the immune response to environmental carcinogens. *Nature Communications* 2025: 16; 5360.

Oka T, Smith SS, Oliver-Garcia VS, Lee T, Son HG, Mortaja M, Azin M, Garza-Mayers AC, Huang JT, Nazarian RM, Horn TD, **Demehri S**. Epigenomic regulation of stemness contributes to the low immunogenicity of the most mutated human cancer. *Cell Reports* 2025: 44; 115561.

Oka T, Smith SS, Son HG, Lee T, Oliver-Garcia VS, Mortaja M, Trerice KE, Isakoff LS, Conrad DN, Azin M, Raval NS, Tabacchi M, Emdad L, Das SK, Fisher PB, Cornelius LA, **Demehri S**. T helper 2 cell-directed immunotherapy eliminates precancerous skin lesions. *The Journal of Clinical Investigation* 2025: 135.

Son HG, Ha DT, Xia Y, Li T, Blandin J, Oka T, Azin M, Conrad DN, Zhou C, Zeng Y, Hasegawa T, Strickley JD, Messerschmidt JL, Guennoun R, Erlich TH, Shoemaker GL, Johnson LH, Palmer KE, Fisher DE, Horn TD, Neel VA, Nazarian RM, Joh JJ, **Demehri S**. Commensal papillomavirus immunity preserves the homeostasis of highly mutated normal skin. *Cancer Cell* 2025: 43; 36-48 e10.

Hasegawa T, Oka T, Son HG, Oliver-Garcia VS, Azin M, Eisenhaure TM, Lieb DJ, Hacohen N, **Demehri S.** Cytotoxic CD4(+) T cells eliminate senescent cells by targeting cytomegalovirus antigen. *Cell* 2023: 186; 1417-1431 e1420.

Strickley JD, Messerschmidt JL, Awad ME, Li T, Hasegawa T, Ha DT, Nabeta HW, Bevins PA, Ngo KH, Asgari MM, Nazarian RM, Neel VA, Jenson AB, Joh J, **Demehri S**. Immunity to commensal papillomaviruses protects against skin cancer. *Nature* 2019: 575; 519-522.

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Dou Laboratory

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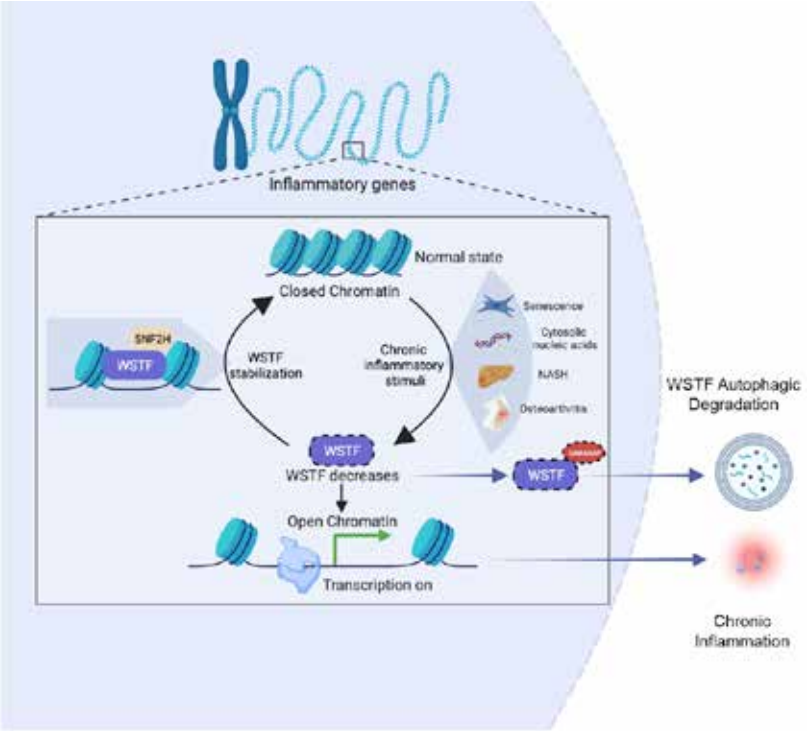
Aging is the greatest risk factor for cancer. **The Dou laboratory** aims to uncover the mechanisms of mammalian aging, with the ultimate goal of developing novel strategies to suppress aging and age-related diseases, including cancer. A major focus of the lab is chronic inflammation, a hallmark of aging and many chronic conditions. Inflammation in the absence of infection drives pain and tissue deterioration, promoting the progression of age-associated diseases. Our research investigates cellular senescence, autophagy, chromatin, and epigenetics in the context of aging and cancer. Through these studies, we aim to understand and target chronic inflammation to promote "healthy aging without diseases."

1. Nuclear Degeneration in Aging and Cancer

The nucleus is a central cellular entity. Studies within the Dou Laboratory suggest that the nucleus undergoes profound degeneration during aging and tumorigenesis. Nuclear components, including nuclear lamina and chromatin, can be degraded by autophagy in response to oncogene activation (Dou et al, *Nature*, 2015). While autophagy is generally viewed as a cytoplasmic recycling mechanism, the degradation of nuclear materials is beginning to unravel. Recently we reported the degradation of other nuclear substrates of autophagy, including SIRT1 (Xu et al, *Nat Cell Biol*, 2020) and WSTF of the ISWI chromatin remodeling complex (Wang et al, *Nature*, 2025). Interestingly, WSTF degradation by autophagy specifically occurs under chronic and not acute inflammation. Restoring WSTF does not affect acute inflammation but suppresses chronic inflammation in cellular senescence as well as NASH and osteoarthritis in mouse models and patient samples. The ability to specifically target chronic inflammation without blunting acute inflammation offers a new approach for treating common chronic inflammatory diseases. Overall, we are interested in exploring novel nuclear substrates of autophagy and studying their significance in aging and cancer.

2. The Biology of Cellular Senescence

Cellular senescence, also referred to as the Hayflick limit, is a stable form of cell cycle arrest associated with pro-inflammatory responses. Senescence restricts proliferation of damaged cells and hence is a tumor suppressive mechanism. However, senescent cells accumulate in aged and diseased tissues, contributing to aging and many chronic diseases. Research in the Dou Laboratory shows that senescent cells generate chromatin fragments in the cytoplasm. This is interpreted by the cell as a "danger signal," triggering the cytosolic DNA sensing cGAS-STING pathway and inflammation (Dou et al, *Nature*, 2017). The pro-inflammatory feature of senescence induces immuno-surveillance of oncogenic cells but contributes to age-associated diseases. Recently, we reported the upregulation of PD-L1 in senescence and aging (Onorati et al, *Mol Cell Biol*, 2020), as a consequence of chronic inflammation. This finding helps to explain why senescent cells are not effectively removed by the immune system during aging and chronic diseases. Furthermore, we discovered that chromatin fragments in the nucleus undergo nuclear egress, a membrane trafficking process at the nuclear envelope, to enter the cytoplasm, which is required to activate the cGAS-STING pathway and inflammation. Interestingly, nuclear egress is suppressed by AMPK and



Roles of WSTF, a chromatin remodeling complex, in regulating chronic inflammation. Under chronic inflammatory stimuli, including senescence, chronic cytosolic nucleic acid exposure, NASH, and osteoarthritis, WSTF is downregulated by nuclear autophagy via a direct interaction with GABARAP. Consequently, loss of WSTF results in increased chromatin accessibility and transcription of inflammatory genes. By stabilizing WSTF protein levels through overexpression or utilizing a peptide that disrupts the WSTF-GABARAP interaction, chromatin accessibility over inflammatory genes is inhibited, suppressing chronic inflammation. Notably, WSTF degradation is not observed under acute inflammation, offering a mechanistic separation of chronic and acute inflammation.

metformin (Kumazawa, et al, *bioRxiv*, 2024). Overall, we aim to unravel the genetic identity of cytoplasmic chromatin and to explore the mechanisms of its formation, with the goal to target it to block chronic inflammation associated with senescence and aging. We are also broadly interested in the biology of senescence beyond aging and cancer.

We are a founding member of the NIH SenNet Program aiming to comprehensively identify and characterize the differences in senescent cells across the body, across various states of human health, and across the lifespan. We are also part of the Technology Development and Application (TDA) Projects, employing single-cell proteomic technology to investigate senescent cells, using the lung as a model system. Our team contributed to several review papers from the consortium, improved the single-cell proteomic platform, deposited several single-cell datasets of mouse lungs, and made new discoveries in the lung using single-cell technologies.

Selected Publications:

Wang Y, Eapen VV, Liang Y, Kournoutis A, Sherman M, Xu Y, Onorati A, Li X, Zhou X, Corey K, Du K, Burkard AC, Ho CK, Xie J, Zhang H, Díaz R, Ma X, Rieprecht U, O'Brien T, Cetinbas M, Wang L, Liu J, Bretz C, Havas A, Zhou Z, Sui SH, Saladi SV, Sadreyev R, Adams PD, Kingston RE, Diehl AM, Alman B, Goessling W, Yue Z, Wang XF*, Johansen T*, **Dou Z***. WSTF nuclear autophagy regulates chronic but not acute inflammation. *Nature*. 2025 Aug; 644(8077): 780-789.

Kumazawa T, Xu Y, O'Brien TC, Lee JW, Wang Y, Cetinbas M, Sadreyev RI, El-Bardeesy N, Cheng CW, He B, **Dou Z**. Metformin inhibits nuclear egress of chromatin fragments in senescence and aging. *bioRxiv*. 2024.

Onorati A, Havas AP, Lin B, Rajagopal J, Sen P, Peter D. Adams PD, **Dou Z**. Upregulation of PD-L1 in senescence and aging. *Mol Cell Biol*. 2022 Oct 20;42(10):e0017122.

Xu C, Wang L, Fozouni P, Evjen G, Chandra V, Jiang J, Lu C, Nicastri M, Bretz C, Winkler JD, Amaravadi R, Garcia BA, Adams PD, Ott M, Tong W, Johansen T, **Dou Z***, Berger SL.* SIRT1 is downregulated by autophagy in senescence and ageing. *Nat Cell Biol*. 2020 Oct; 22(10):1170-1179.

Dou Z, Ghosh K, Vizioli MG, Zhu J, Sen P, Wangensteen KJ, Simithy J, Lan Y, Lin Y, Zhou Z, Capell BC, Xu C, Xu M, Kieckhaefer JE, Jiang T, Shoshkes-Carmel M, Tanim KMAA, Barber GN, Seykora JT, Millar SE, Kaestner KH, Garcia BA, Adams PD, Berger SL. Cytoplasmic chromatin triggers inflammation in senescence and cancer. *Nature*. 2017. Oct 19;550(7676):402-406.

Dou Z, Xu C, Donahue G, Shimi T, Pan J-A, Zhu J, Ivanov A, Capell BC, Drake AM, Shah PP, Catanzaro JM, Ricketts MD, Lamark T, Adam SA, Marmorstein R, Zong W-X, Johansen T, Goldman RD, Adams PD, Berger SL. Autophagy mediates degradation of nuclear lamina. *Nature*. 2015 Nov 5;527(7576):105-9.

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In response to DNA damage from environmental or endogenous sources, cells evoke an elaborate signaling network known as the DNA damage response (DDR). This response functions to preserve genomic integrity, which is necessary for normal development and the prevention of cancer. **The Elia laboratory** studies the DNA damage response, focusing on pathways regulated by ubiquitin-dependent signaling and pathways that promote the stabilization and repair of stalled replication forks. We utilize innovative proteomic and genetic approaches to investigate these processes. Our ultimate goal is to understand how DDR disruption influences cancer progression and can be exploited to target tumors with specific DNA repair defects.

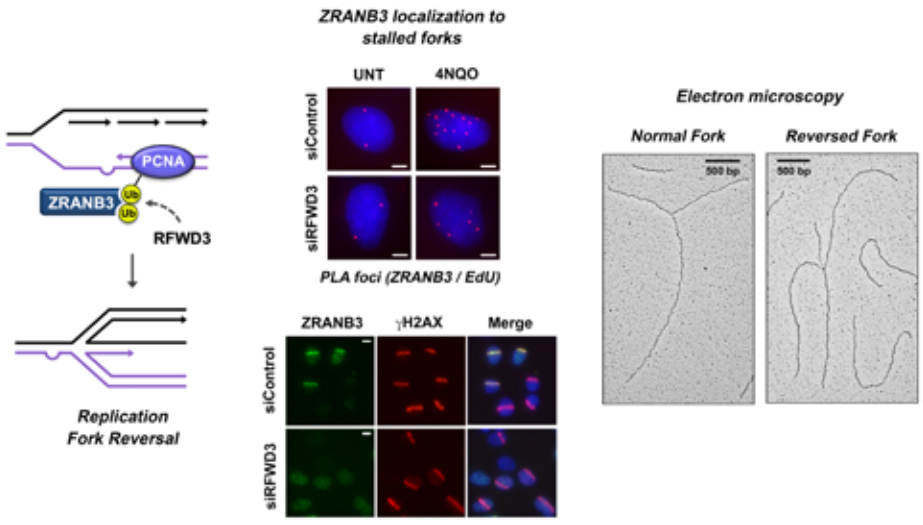
Ubiquitin signaling in the DNA damage response

DNA within cells is under continual assault from metabolic and environmental sources. In response to the ensuing damage, cells activate a signaling network called the DNA damage response (DDR). Defects in this response can lead to hereditary cancer syndromes and can underlie the genomic instability which is a hallmark of sporadic cancers. The DDR promotes genomic integrity by targeting hundreds of factors in diverse pathways ranging from DNA replication and repair to cell-cycle arrest, senescence, and immune regulation. Execution of the DDR relies upon a dynamic array of protein modifications, with ubiquitination playing a central role. Our lab elucidates ubiquitin-dependent signaling pathways that regulate and integrate diverse DDR factors.

Replication-coupled repair and cancer

Replication fork collapse can induce chromosome instability and mutagenic events that cause cancer. Organisms have therefore evolved pathways to stabilize stalled replication forks and to repair collapsed forks through processes such as homologous recombination (HR). Multiple factors involved in HR and replication fork stabilization, such as BRCA1 and BRCA2, are mutated in hereditary cancer syndromes, highlighting the importance of these pathways. We have demonstrated that the ubiquitin ligase RFWD3, which is mutated in the cancer predisposition syndrome Fanconi anemia, ubiquitinates the single-stranded DNA binding factor RPA to promote homologous recombination at stalled replication forks and replication fork restart (*Mol Cell* 2015b).

Replication fork reversal is an important mechanism to protect the stability of stalled forks. While multiple enzymes have been identified that can remodel forks, their regulation remains poorly understood. We have recently discovered a new function for RFWD3 in the regulation of fork remodeling (*J Cell Biol* 2023). We have found that RFWD3 promotes PCNA polyubiquitination to recruit the DNA translocase ZRANB3 to stalled replication forks. Through the analysis of replication intermediates by electron microscopy, we found that RFWD3 promotes replication fork reversal in a ZRANB3-epistatic manner. We are continuing to elucidate novel mechanisms of replication-coupled repair and fork stabilization regulated by ubiquitin signaling.



RFWD3 promotes PCNA polyubiquitination to recruit the DNA translocase ZRANB3 to remodel stalled replication forks (J Cell Biol 2023).

Quantitative proteomics

Numerous ubiquitin ligases have been implicated in the DNA damage response, yet finding their substrates by simple binding techniques can be difficult due to weak substrate interactions. To circumvent this problem, we have pioneered a quantitative proteomic approach to globally profile ubiquitination. Initially, we used this approach to identify substrates of Cullin-RING ubiquitin ligases (*Cell* 2011), which are involved in numerous DNA repair processes. Subsequently, we used it to uncover novel ubiquitination events directly stimulated by DNA damage (*Mol Cell* 2015a), demonstrating the vast breadth of ubiquitin signaling in the DDR. We are continuing to use innovative proteomic approaches to characterize novel and poorly understood ubiquitin ligases in DNA damage signaling pathways.

Targeted cancer treatment and immunotherapy

Defects in the DNA damage response can render tumors dependent upon specific DNA repair pathways for survival. Moreover, targeted modulation of the DDR can affect tumor sensitivity to genotoxic treatments and immunotherapy. Increased understanding of DNA repair pathways in cancer and immune cells will enhance opportunities for developing therapies that target cancers with DNA repair defects and for improving the combination of genotoxic agents with immunotherapy. We are employing methods to translate our work to the development of such therapies.

Selected Publications:

Elia AE, Chowdhury S, DeNight WR. Lost in translation: SLFN11 induces p53-independent apoptosis. (*corresponding) *Molecular Cell*. 2025; 85(6):1043-45.

Moore CE, Yalcindag SE, Czeladko H, Ravindranathan R, Wijesekara Hanthi Y, Levy JC, Sannino V, Schindler D, Ciccia A, Costanzo V, **Elia AE**. RFWD3 Promotes ZRANB3 Recruitment to Regulate the Remodeling of Stalled Replication Forks. *J Cell Biol*, 2023; 222(5): e202106022.

Elia AE, Wang DC, Willis NA, Boardman AP, Hajdu I, Adeyemi RO, Lowry E, Gygi SP, Scully R, Elledge SJ. RFWD3-Dependent Ubiquitination of RPA Regulates Repair at Stalled Replication Forks. *Molecular Cell*. 2015; 60(2):280-93.

Elia AE, Boardman AP, Wang DC, Huttlin EL, Everley RA, Dephoure N, Zhou C, Koren I, Gygi SP, Elledge SJ. Quantitative Proteomic Atlas of Ubiquitination and Acetylation in the DNA Damage Response. *Molecular Cell.* 2015; 59(5):867-81.

Emanuele MJ, **Elia AE**, Xu Q, Thoma CR, Izhar L, Leng Y, Guo A, Chen YN, Rush J, Hsu PW, Yen HC, Elledge SJ. Global identification of modular cullin-RING ligase substrates. *Cell.* 2011; 147(2):459-74.

Elia AE, Cantley LC, Yaffe MB. Proteomic screen finds pSer/pThr-binding domain localizing Plk1 to mitotic substrates. *Science*. 2003; 299:1228-31.

Elia AE, Rellos P, Haire LF, Chao JW, Ivins FJ, Hoepker K, Mohammad D, Cantley LC, Smerdon SJ, Yaffe MB. The molecular basis for phosphodependent substrate targeting and regulation of Plks by the Polo-box domain. *Cell*. 2003; 115:83-95.

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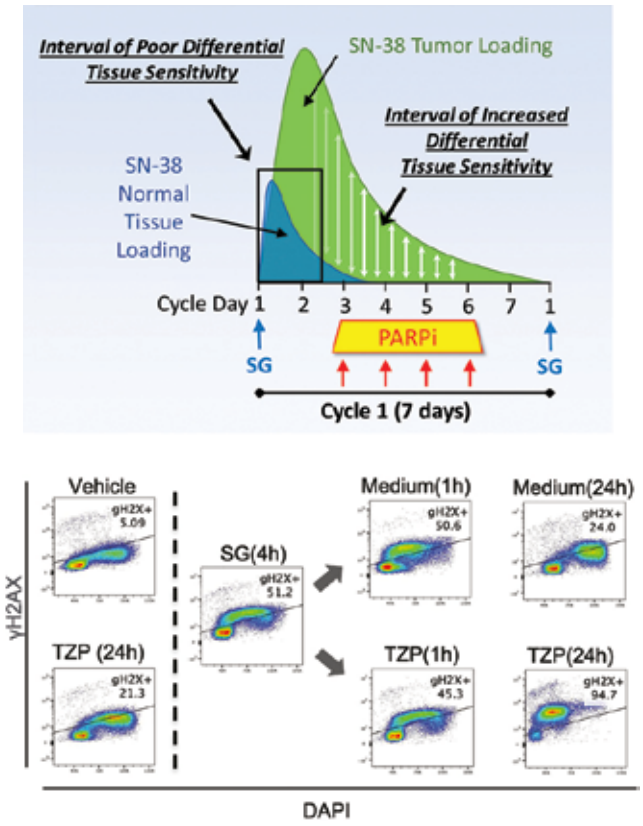
The Ellisen laboratory has a broad interest in how genetic abnormalities in breast cancer and related malignancies influence tumor biology and how that biology can, in turn, be exploited to therapeutic advantage. We address these questions through basic research studies of key cancer hallmarks, including DNA repair defects through BRCA1/2 and related pathways and transcriptional reprogramming through the p53 gene family. Supporting and complementing these studies are sophisticated analyses of patient-derived precancerous and cancerous tissues. Recent innovative tissue-based studies have led to our discovery of novel cancer drivers and have provided a unique window into early cancer pathogenesis, intratumoral heterogeneity, and therapeutic resistance. Our discoveries in the basic laboratory and through human tumor analysis are being applied in ongoing clinical trials that seek to identify predictive markers of response to innovative therapeutics for breast and other cancers. Our ability to work at the interface of basic tumor biology and therapeutic application is strongly supported by our network of collaborators and by the research and clinical infrastructure of the Mass General Cancer Center. For more details, please see our website, Ellisenlab.com.

Novel drivers of aggressive breast cancer subtypes

Our work employing advanced tumor molecular diagnostics has revealed gene fusions as novel drivers of an aggressive breast cancer subset. In triple-negative breast cancer (TNBC), extensive intratumoral heterogeneity is itself a driver that we have characterized through single-cell genomic and transcriptomic analysis, leading to our discovery of unanticipated drug resistance mechanisms with immediate therapeutic implications. Of particular interest is resistance to novel Antibody Drug Conjugates (ADCs) that are transforming cancer therapy. Unraveling the complex nature of ADC resistance is a long-term goal of ours that touches every aspect of tumor biology and will have major clinical impact. Our longstanding work on the biology of TNBC is supported by the institution-wide Triple-Negative Breast Cancer Program, which integrates basic research, translational and clinical studies together with human tumor propagation and high-throughput drug screening, all focused on overcoming drug resistance and improving outcomes for patients with TNBC.

BRCA1/2, hereditary cancer predisposition and prevention

Germline mutations in the DNA repair genes BRCA1 and BRCA2 confer dramatically elevated risk of cancers of the breast, ovary, and pancreas, yet the precise pathogenesis of BRCA1/2-associated cancer remains to be elucidated. Together with an international team of collaborators we are carrying out systematic studies of early events that give rise to these cancers, in part through detailed molecular analysis of normal and precancerous tissues from BRCA1/2 mutation carriers. Defining the altered signaling and early cooperating events in this context is likely to reveal new markers of breast cancer predisposition and new targets for prevention. For example, our published single-cell genome analysis has revealed extensive chromosomal damage in BRCA mutant breast tissues that precedes



The schematic at the top demonstrates that tumor-selective delivery of cytotoxic SN-38 via the Antibody-Drug Conjugate Sacituzumab govitecan (SG) allows normal cells to rapidly clear the drug, while sequential PARP inhibitor (PARPi) treatment is toxic to tumor cells with residual SN-38. Above, flow cytometry plots showing SG induces DNA damage (γ-H2AX) that is rapidly repaired following washout (Medium) but progresses to lethal damage in the presence of PARP inhibitor Talazoparib (TZP). The concept of sequential SG/TZP dosing was successfully applied in our clinical trial for advanced breast cancer (Bardia, Ellisen et al, Clin. Cancer. Res. 2024).

any histological abnormalities. This seminal finding implies the existence of early cellular defects and associated vulnerabilities that could be exploited for cancer prevention in this setting.

The p53 family network in cancer biology and therapy

As a transcription factor and key nodal point for integrating cellular stress responses, the p53 tumor suppressor controls diverse cellular processes, including cell cycle progression, survival, and metabolism. Through analysis of two p53-related genes, p63 and p73, we and others have defined a functional network including a tissue-specific role for p63 as the enforcer of an epigenetically controlled stem/progenitor state. Tumor-selective deregulation of p63 and associated chromatin remodeling factors reprogram the transcriptome to inhibit differentiation and promote immune evasion. These findings likely explain why p63 is over-expressed in a large variety of epithelial tumors, particularly squamous cell and breast carcinomas. Collectively, this work serves as a paradigm for the analysis of transcriptional reprogramming in cancer.

Selected Publications:

Liu T, **Ellisen LW**. Exploring the "chemo" in chemoimmunotherapy for triple-negative breast cancer. *Cancer Cell*. 2025 Mar 10;43(3):332-334.

Wu B, Thant W, Bitman E, Liu T, Liu J, Paschalis EI, Xu KH, Nieman LT, Ting DT, Thimmiah N, Sun S, Abelman RO, Isakoff SJ, Spring LM, Bardia A, **Ellisen LW**. A TROP2/Claudin Program Mediates Immune Exclusion to Impede Checkpoint Blockade in Breast Cancer. *bioRxiv* [Preprint]. 2024 Dec 5:2024.12.02.626446.

Coates JT, Sun S, Leshchiner I, Thimmiah N, Martin EE, McLoughlin D, Danysh BP, Slowik K, Jacobs RA, Rhrissorrakrai K, Utro F, Levovitz C, Denault E, Walmsley CS, Kambadakone A, Stone JR, Isakoff SJ, Parida L, Juric D, Getz G, Bardia A, and **Ellisen LW**. Parallel genomic alterations of antigen and payload targets mediate polyclonal acquired clinical resistance to sacituzumab govitecan in triple-negative breast cancer. *Cancer Discovery*. 2021 11:1-10.

Karaayvaz M, Silberman RE, Langenbucher A, Saladi SV, Ross KN, Zarcaro E, Desmond A, Yildirim M, Vivekanandan V, Ravichandran H, Mylavagnanam R, Specht MC, Ramaswamy S, Lawrence M, Amon A, **Ellisen LW**. Aneuploidy and a deregulated DNA damage response suggest haploinsufficiency in breast tissues of BRCA2 mutation carriers. *Science Advances*. 2020;6:5.

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The Fisher laboratory focuses on mechanistic studies which underlie the biology and pathophysiology of melanocytes and melanoma. Research studies range from molecular analyses of pigment cell biology to risk factors responsible for the formation of melanoma and other skin cancers. The laboratory utilizes deep molecular tools to understand how genes are regulated, how they contribute to cancer formation, and how they may be successfully targeted by drugs in order to improve disease treatments or to prevent disease formation altogether. Several areas of particular focus include 1) the study of redhair, fair skinned pigmentation and the manner in which such individuals are at increased risk for skin cancer; 2) identification and analysis of oncogenes which control melanoma cell survival; 3) discovery of new drugs that affect pigmentation, melanoma survival, and other skin-related effects; and 4) examination of the ways in which a gene called MITF plays a master-regulatory role in specifying the development of pigment-producing cells in the body.

We study cell death, proliferation, and lineage differentiation signals in relation to development and disease, particularly in cancer of pigment cells (melanoma). We attempt to understand critical modes of cell homeostasis with a goal of enhancing therapeutic as well as prevention opportunities for melanoma and other cancers. Areas of particular focus are explained below.

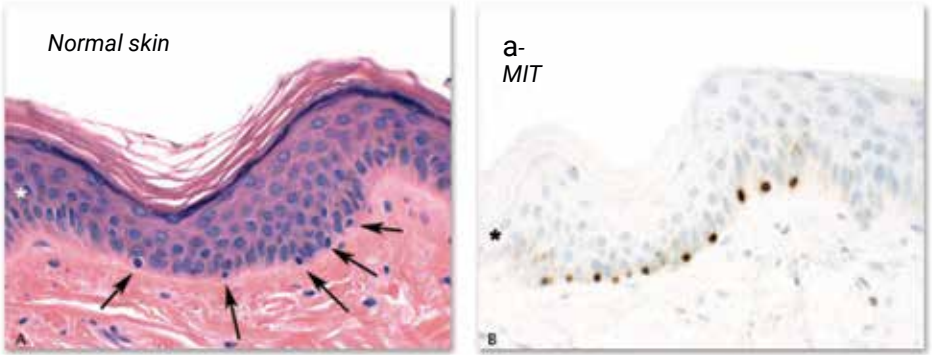
Lessons for malignancy from normal development

We focus heavily on the study of melanocytes, the cells responsible for production of constitutive as well as environmentally responsive pigmentation. This area of research includes examination of the mechanisms transmitting the signals from ultraviolet radiation to the pigmentation machinery in skin. We also study the growth/survival of benign melanocytic nevi, most of which contain mutations in either BRAF or N-Ras oncogenes. One extreme example, Giant Congenital Nevi, is a common cause of childhood melanoma, and we have modeled this in mice, as well as developed potential topical drug approaches to regressing them. We also study melanocyte death in hair follicles, a process associated with hair graying. Our work led to the identification of pathways linking graying to melanocyte and melanoma survival, offering potential leads for novel therapies.

Technology development is an important component of our work. We now routinely develop melanocytes and keratinocytes from iPS cells, and are actively studying production of Dermal Papilla cells (also from iPS) and utilize novel grafting approaches to produce human genetically controlled models of in vivo skin and hair.

Control of life and death in melanoma

Malignant transformation of melanocytes produces one of the most treatment-resistant malignancies in human cancers. We have identified a transcriptional network that regulates melanoma cell survival and proliferation and melanocyte differentiation during development. Using



Histologic images of human skin. Left image shows hematoxylin and eosin (H&E) stain. The top layer is Stratum Corneum (consisting of dead cell derivatives) followed by the deeper purple keratinocyte cell layers constituting the epidermis. Beneath the epidermis is the pink, collagen containing dermis. Melanocytes reside at the base of the epidermis and are highlighted by arrows. The image to the right shows antibody staining for the melanocytic transcription factor MITF, which highlights the melanocytes at the dermal-epidermal junction.

Histologic images were generated by Dr. Scott Granter.

diverse methods— including mouse models, human tumor omics, and cellular assays— we examine mechanisms through which melanoma cells evade death with the goal of improving therapy. Studies include preclinical and clinical analyses of immunotherapy mechanisms and other novel melanoma treatments. Finally we discovered that UV triggers production of endorphin in skin, leading to sun-seeking behavior. We have also identified vitamin D as evolutionary driver of this response, leading to potentially important implications for opiate addiction.

MITF transcription factor family in development and cancer

MITF is a helix-loop-helix factor homologous to the Myc gene which, when mutated in humans, produces absence of melanocytes. MITF acts as a master regulator of melanocyte development and is targeted by several critical signaling pathways. Recently, members of the MITF family have been identified as oncogenes in a variety of human malignancies, particularly sarcomas of childhood. We are currently investigating their roles in cancer as well as strategies to target them therapeutically. Detailed mechanistic studies focus on transcription factor interactions with chromatin, and epigenetic control of gene expression.

Selected Publications:

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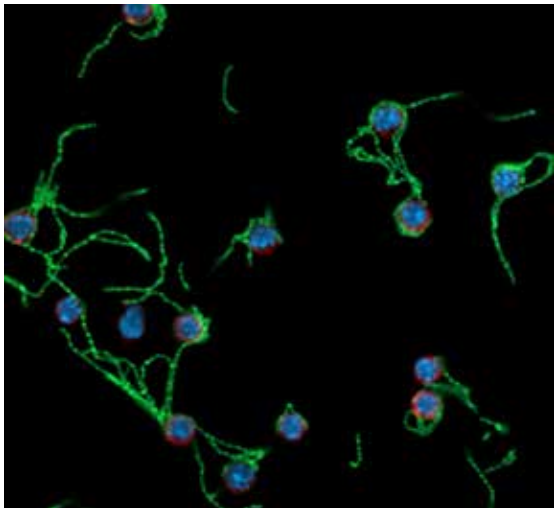
Gut microbiota — the trillions of bacteria, fungi, viruses, and archaea that reside in our gut — contain a dynamic arsenal of products that can protect from or contribute to disease. Diet, medication, exercise, and disease impact the composition of the microbiota and influence the products the microbes produce. In turn, specific microbes influence immune cell function in both normal and disease states. **The Gazzaniga laboratory** focuses on unraveling this complex ecosystem that holds huge therapeutic potential, and that reveals the dynamic interplay of environmental factors, microbes, microbial products, and immune cells. Specifically, we focus on three main questions: (1) Which bacteria are associated with response in cancer patients? (2) Which gut bacterial produced molecules impact anti-tumor immunity? (3) How do microbe-mediated immune responses impact the anti-tumor response to immunotherapy? Our ultimate goal is to uncover mechanistic information to develop microbe-based therapies that fine-tune the immune system to fight cancer.

The trillions of bacteria that inhabit our intestinal tract as part of our gut microbiota have a dynamic relationship with our immune system. For example, the bacteria in the gut impact the anti-tumor response of immune checkpoint inhibitors on tumors outside of the gut. Treatment with checkpoint inhibitors, such as antibodies targeting programmed cell death protein 1 (PD-1) or programmed cell death ligand 1 (PD-L1), disrupts interactions between PD-1 on T cells and PD-L1 on tumors, reinvigorating T cells to kill cancer cells. Although checkpoint inhibitors are used to treat a wide variety of cancers, the response rates are variable. Understanding what impacts the efficacy of checkpoint inhibitors is critical to increase the number of patients who respond to treatment.

Fecal transplants from melanoma patients who responded to PD-1 blockade can overcome resistance in non-responders. However, the efficacy of the fecal transplants varies with different donors, highlighting the need to understand how bacteria impact anti-tumor immunity. The purpose of the Gazzaniga lab is to translate the notion that the microbiome plays a role in anti-tumor immunity into reliable, microbiome-inspired treatments that increase the number of patients who respond to checkpoint blockade.

Patient stool samples: What is associated with response?

Many studies examining the role of the gut microbiome in response to checkpoint blockade therapy focused on melanoma. However, PD-1 blockade is approved for over 25 different cancers. Depending on the cancer type, PD-1 blockade efficacy ranges from 2%-87%. Therefore, understanding how the microbiome impacts the anti-tumor responses of checkpoint blockade in other cancers is critical to increase the number of patients who respond. We collaborate with clinicians at MGB to analyze stool samples from patients with different cancers at the beginning and end of treatment with checkpoint inhibitors. We investigate which treatments impact the gut microbiome and which bacteria are associated with anti-tumor responses in different cancers.



Bacteria isolated from a melanoma patient who had a complete response to immunotherapy can directly interact with and stimulate CD8 T cells in vitro. Bacteria (green), CD8 (red), DAPI (blue).

Searching for patient-derived therapeutics: What bacterial molecules promote anti-tumor immunity?

Many have sought to identify individual bacteria that could be used as probiotics in the clinic to promote anti-tumor immunity. However, several obstacles make probiotics an unreliable therapy. There are difficulties in delivering live anaerobic bacteria, difficulties in engraftment of probiotics in humans already colonized with bacteria, and differences between lab culture conditions and the human intestine that could contribute to the anti-tumor activity of the bacteria. Bacterial molecules, on the other hand, can be delivered and tested more reproducibly and thus bypass the variability of probiotics and fecal transplants. Using germ-free mice, which lack all microbes, we can investigate how different bacteria impact tumor outcomes. We have isolated two bacterial strains from a healthy human microbiome that promote anti-tumor immunity to PD-1 blockade and are currently identifying the anti-tumor molecules they produce. Next, we will isolate bacterial molecules from patient responder stool to develop reproducibly delivered patient-derived bacterial therapeutics to increase the efficacy of checkpoint inhibitor therapy.

Learning from bacteria: Which microbe-mediated immune mechanisms can we harness to promote anti-tumor immunity?

By comparing mice colonized with healthy human microbiota to mice treated with broad spectrum antibiotics, we have identified several immune pathways in the tumor-draining lymph nodes that are impacted by gut bacteria and associated with anti-tumor immunity. By targeting these immune pathways, we can convert non-responders to responders in multiple tumor models. To make our mouse models more clinically relevant, we compare mice colonized with patient non-responder or responder microbiota to identify immune pathways impacted only by responder microbes. Our overall goal is to learn from bacteria and develop therapeutics that target the immune pathways impacted by responder microbiota to increase the number of patients who respond to treatment.

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The Getz laboratory is focused on cancer genome analysis, which includes two major steps: (i) Characterization – cataloging of all genomic events and the mechanisms that created them during the clonal evolution of cancer (starting from normal cells and progressing to premalignancy, primary cancer, and emergence of resistance), comparing events at the DNA, RNA, and protein levels between one or more tumor and normal samples from an individual patient; and (ii) Interpretation – analysis of the characterization data across a cohort of patients with the aim of identifying the alterations in genes and pathways that drive cancer progression, drive resistance, or increase its risk as well as identifying molecular subtypes of the disease, their markers, and relationship to clinical variables. Recently the Getz lab is also studying the tumor and its immune microenvironment using bulk, single-cell RNA-sequencing (RNA-seq) and spatial data. In addition to developing tools for high throughput analysis of cancer data and experimentally testing the findings, the Getz lab develops computer platforms that enable large-scale analytics and visualization.

Characterizing the cancer genome

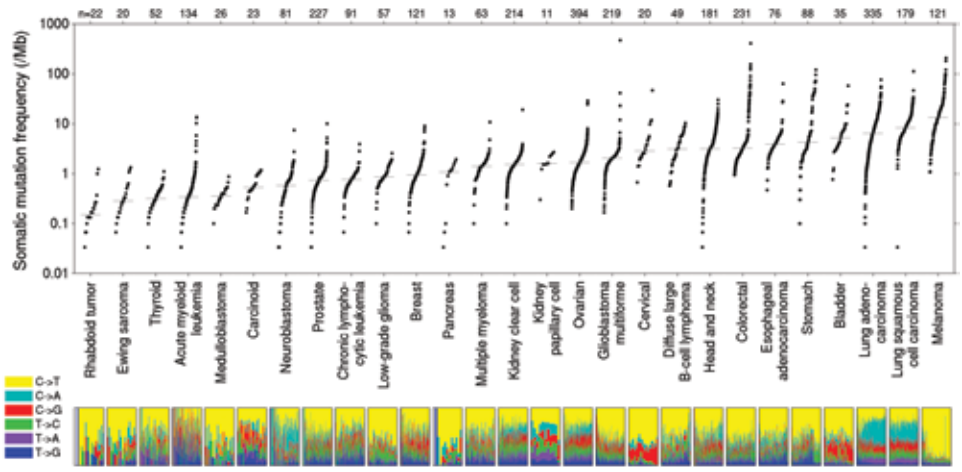
Cancer is a disease of the genome driven by a combination of possible germline risk-alleles, together with a few 'driver' somatic mutations that increase fitness and promote clonal expansion. Mutations occur at all levels and scales, including (i) DNA point mutations; (ii) small insertions and deletions; (iii) larger genomic rearrangements and copy-number alterations; and (iv) epigenetic, transcriptional, and proteomic changes. To generate a comprehensive list of all germline and somatic events that occurred during (and prior to) cancer development, we are developing and applying highly sensitive and specific tools to detect these events in sequencing data. The complexity of the underlying cancer genomes requires state-of-the-art statistical and machine learning approaches to most efficiently extract the signal from the noise.

Detecting cancer-associated genes

After detecting genomic events, we search for genes (and pathways) that show significant signals of positive selection (e.g., the number of mutations exceeds what is expected by chance) across a cohort of samples by constructing a detailed statistical model of the background mutational processes and detecting genes that deviate from it. We developed tools to discover genes significantly gained or lost (GISTIC), and genes with increased density or irregular mutational patterns (MutSig, CLUMPS). In these analyses, correctly modeling the heterogeneity of mutational processes across patients, sequence contexts, and the genome is critical. We are constantly improving methods and working towards a unified method for all types of alterations. We also discovered drivers in non-coding regions of the genome in breast cancer (e.g., hotspot mutations in FOXA1 promoter that likely alter its expression) and, more recently, across cancer, as part of a large international effort.

Heterogeneity and clonal evolution of cancer

Cancer samples are heterogeneous: noncancer cells intermingle with a cancer cell population that typically contains multiple subclones. Since cancer is a dynamic



Somatic mutation frequencies across cancer.
Each dot represents the total frequency of somatic mutations (in the exome) in each tumor–normal pair. Tumor types are ordered by their median somatic mutation frequency, from haematological and paediatric tumors (left), to tumours induced by carcinogens such as tobacco smoke and ultraviolet light (right). Mutation frequencies vary more than 1,000-fold between lowest and highest across different cancers and also within several tumour types. The bottom panel shows the relative proportions of the six different possible base-pair substitutions. Taken from Lawrence et al. (2013).

system, these subclones may represent (i) remaining cells of less-fit clones not yet overtaken by the expanding the most-fit clone, (ii) interacting subclones that coevolved and have reached an equilibrium, or (iii) a combination of both. We have developed tools (ABSOLUTE, PhylogicNDT) to characterize the heterogeneity and dynamics of cancer using copy-number, mutational, and other data measured on bulk samples and single cells. These tools can analyze multiple samples per patient to infer clonality of mutations, number of subclones, and subclonal evolution over time or space. We previously demonstrated that subclonal driver mutations are associated with outcome, emphasizing the importance of including clonal information in clinical trials. We are integrating this clonal evolution knowledge with other information about the tumors to build computational models that can predict tumor outcome, subtypes, molecular mechanisms, and response to therapy.

Mutational processes

Processes that damage, repair, replicate, and deliberately alter DNA create mutations. Mutation data can thus be used to study these processes, understand their mutational "signatures," infer their molecular mechanisms, and identify alterations associated with their activity. By studying asymmetries in mutational processes, we detected a mechanism that acts on the lagging DNA strand during replication and a new mutational process that generates mutations on the non-transcribed strand. We also used the association between a mutational signature and homologous recombination (HR) defects to show that epigenetic silencing of RAD51C within the HR pathway is an important mechanism for HR deficiency in breast cancer. With international collaborators, we are mapping all common mutational signatures affecting single- and di-nucleotide substitutions as well as small insertions and deletions (indels). We also study indels that occur at microsatellites and, in particular, tumors that have microsatellite instability (MSI) that may benefit from immune checkpoint inhibitor treatment (e.g., anti-PD1). We are developing a method to computationally detect the presence of MSI tumors from cell-free DNA (cfDNA) containing DNA shed from tumor cells, easily obtained from non-invasive blood biopsies.

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Alberge JB, Dutta AK, Poletti A, ..., **Getz G**, Ghobrial IM. Genomic landscape of multiple myeloma and its precursor conditions. *Nat Genet.* 2025 Jun;57(6):1493-1503.

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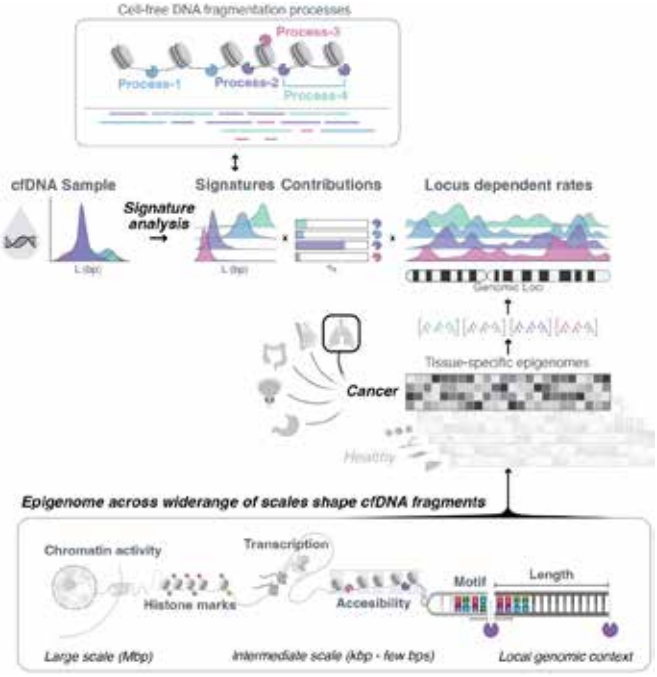
The Gülhan laboratory advances cancer diagnosis and treatment by studying tumors' genetic makeup. We develop methods to classify patients for personalized treatments, ensuring effective therapies. Genomic instability, a hallmark of cancer, enhances tumor growth. We create algorithms to break down mutation patterns into characteristic footprints of biological processes causing genomic instability, distinguishing mechanisms such as repair deficiencies that signal vulnerabilities to targeted- and immune-therapies. Cancer cells evolve and develop treatment resistance; therefore, effective profiling strategies must capture the disease's dynamic nature. We use blood-based liquid biopsy tests for non-invasive monitoring. We design machine learning algorithms to detect trace amounts of circulating tumor DNA with high sensitivity, distinguishing signals through fragment and mutational patterns amid high noise levels and inferring gene expression using epigenetic imprints on fragmentation patterns. Additionally, we study long-term tumor evolution from bulk sequencing data and short-term cellular heterogeneity and dynamics using single-cell sequencing of cancer tissues. Collaborating closely with clinical researchers, we apply these methods to detect and study cancer at early stages and resistance in metastatic disease.

Characterizing Genomic Instability

Cancer cells have elevated mutation rates arising from a blend of factors, such as exogenous mutagens and intrinsic genomic instability. The latter, resulting from events like DNA repair deficiencies, cell cycle dysregulation, polymerase errors, and editing by APOBEC cytidine deaminases, provides cancer cells with growth advantages and evolutionary flexibility. This trait is a defining hallmark of cancer. However, genomic instability can also be a vulnerability for cancer cells. For instance, tumors with homologous recombination deficiency (HRD) are sensitive to PARP inhibitors that exacerbate DNA damage to an unsustainable level. Genomic instability also interacts intricately with the immune system. Mismatch repair deficiency (MMRD), which causes hypermutations, makes tumors susceptible to anti-PD-1 therapy. The clinical relevance of genomic instability, as exemplified by MMRD and HRD, underscores the need to assess tumors for such mechanisms. Currently, personalized treatments cater to only a fraction of patients. Expanding the clinical interpretation of cancer genomes is essential to bridge this gap, and mutational signature analysis, which identifies patterns corresponding to distinct mechanisms of genomic instability, could aid in this pursuit.

We aim to further enhance the capabilities of signature analysis methodologies by developing methods that can deconvolute not only process-specific patterns but also the temporal and genomic locus-dependent changes in their activity. We are also interested in separating the contributions of damage and repair activities and studying their roles in mutagenesis to improve the interpretation of complex cancer genomes. Utilizing rapidly growing datasets of whole-genome sequenced cancers and our algorithms, we aim to achieve a more detailed map of genomic instability. In addition to gaining



Cell-free DNA (cfDNA) fragmentation patterns arise from distinct biological processes driven by the underlying epigenomic context. Using signature analysis methodologies we developed, we identify unique fragmentation signatures and map the genome-wide distribution of individual fragmentation activities. Our generative algorithm models the relationship between epigenomic features and fragmentation rate profiles across multiple genomic scales, enabling sensitive cancer detection and accurate identification of tissue-of-origin.

mechanistic insights, these advancements can improve the interpretability of signature results, which is crucial for their integration into clinical applications.

A Dynamic View of Cancer

Although comprehensive characterization of cancer genomes can improve personalized treatment strategies, it is not sufficient due to genomic and transcriptomic selections and adaptations that cancer cells undergo, especially under the pressure caused by cancer treatments. We utilize multiple strategies to improve our dynamic understanding of cancer genomes.

Circulating tumor DNA offers a noninvasive means of capturing tumors' temporal evolution and comprises DNA from multiple sites, providing a better representation of heterogeneity. We develop algorithms to sensitively detect tumor DNA, which constitutes a trace proportion of all cell-free DNA in plasma and monitor its changes more robustly. We utilize mutations and fragment characteristics and apply signature-based noise reduction and mixture modeling to improve tumor detection, genotyping, and patient classification. Additionally, we build effective fragmentomics algorithms that infer transcription from the location and length distributions of cfDNA fragments. We are implementing these methods for early cancer detection, particularly in patients with genetic predisposition, and resistance monitoring in serial samples collected from metastatic cancer patients.

Additionally, we are interested in the multimodal characterization of intratumor heterogeneity and building methods to model temporal dynamics. Through mutation timing and lineage tracing strategies applied to bulk genome and transcriptome profiling or single-cell genome-plus-transcriptome sequencing datasets, we aim to infer the long- and short-term dynamics of cancer cells, respectively. We apply these methodologies to study two clinically relevant stages: (i) early cancer development to improve early detection strategies and (ii) late evolution under treatment pressure in metastatic cancer patients to combat resistance.

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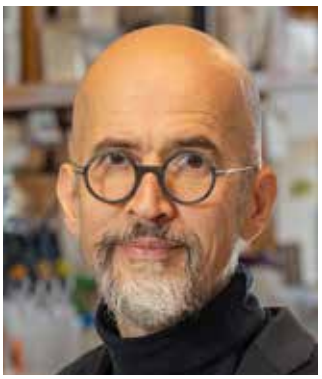

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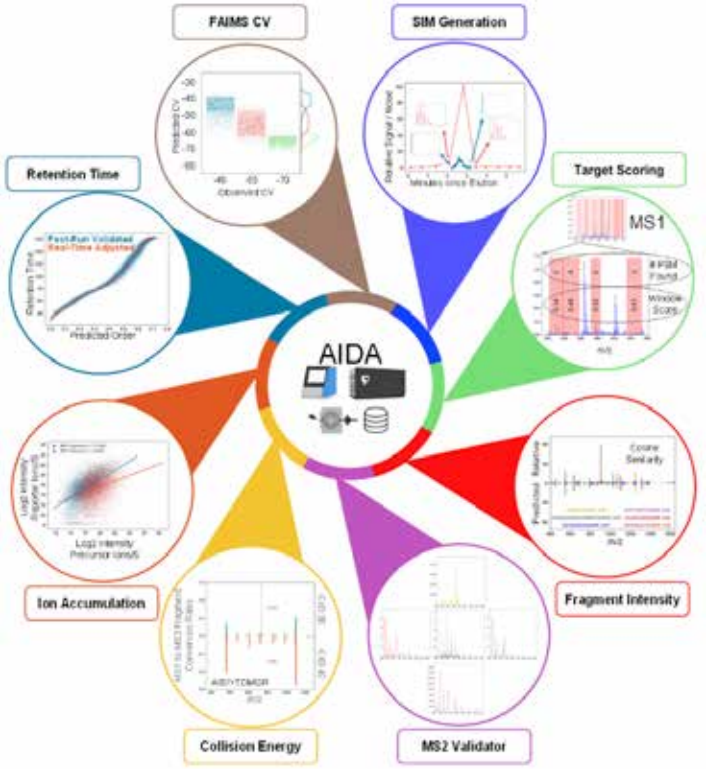
Proteins are the central molecular players in virtually all biological processes and cellular functions. The proteome is the entirety of all proteins in a biological system. The proteome's vast complexity is not only defined by the number of expressed genes but also driven through post-translational protein modifications - such as phosphorylation – and the interaction of proteins to form functional units in the form of multiprotein complexes. **The Haas laboratory** utilizes mass spectrometry-based proteomics to decipher this complexity. The lab aims to understand the extensive changes the proteome undergoes in cancer and to leverage these changes for early cancer detection, cancer diagnosis, cancer treatment guidance, and the development of new treatment strategies.

Cancer is based on dynamic changes of the genome that ultimately translate into an altered proteome, optimized for uncontrolled cell growth and division. In addition, many pathways, initially causing cancer, further promote the propagation of altered genetic information, accelerating the adaption of cancer cells to new environments. This dynamic process becomes even more complex if taking into account the dynamic state of the cellular proteome that is regulated by protein synthesis and degradation, post-translational modifications, protein localization, and the interaction of proteins with other proteins, as well as with different classes of biomolecules. While the cancer genome is now established as a source for cancer diagnosis and for directing treatment strategies, we are only beginning to tap into the information contained in the cancer proteome. Yet, the proteome holds enormous potential to improve our understanding of the basic principles underlying cancer, to revolutionize the early diagnosis of the disease, and to improve patient care. To date, virtually all targeted therapeutics in cancer treatment are targeting proteins. Understanding how these drugs alter the proteome and the interactome – the global map of protein-protein interactions – has the potential to help us refine our approaches to drug design. The core technology used in our research group is high-throughput quantitative proteomics enabled through multiplexed mass spectrometry. Sample throughput is a key requirement in cancer proteomics as it allows handling the analysis of the large number of samples that have to be examined to generate the basis for understanding a disease that displays such heterogeneity. Foremost, throughput is essential in the early detection of cancer through mapping blood plasma proteomes to detect cancer biomarkers. If such assays are successful, they will eventually be used to map millions of blood plasma samples. To enable such applications of mass spectrometry, we have developed a novel high-throughput proteomics platform centered around an autonomous artificial intelligence (AI)-powered data acquisition method (AIDA, AI-directed data acquisition). Unbiased screening of >2000 proteins from blood plasma samples (in less than 6 minutes per sample) rather than mapping a small number of biomarkers will allow us to enable a multi-biomarker assay for multiple cancer types that is constantly improved through adaptation to the detection accuracy. We have used this technology to analyze the proteome of >1,400 human blood plasma samples to map the plasma proteome landscape of lung cancer.



Our novel method, AIDA (AI-directed data acquisition), autonomously controls mass spectrometry-based proteomics experiments using eight interplaying AI modules that direct data acquisition in real time. This approach enables the quantification of >2,000 proteins from blood plasma in under 6 minutes per sample, forming the basis for our development of novel biomarker assays for early cancer detection

This technology also allows mapping >8000 proteins of cancer cell line or tumor tissue samples at the same high throughput. Analyzing the proteome maps across a panel of cancer cell lines, we observed that the concentration of proteins in known complexes is accurately correlated across all analyzed cell lines. We showed that protein co-regulation analysis allows the genome-wide mapping of protein-protein interactions with an accuracy tenfold higher than that when using co-expression analysis based on RNA-seq data. We identified the E3 ligase UBR4 as a key regulator in adjusting the concentration level of interacting proteins – the molecular mechanism enabling our interactome mapping – and we have shown that this role presents UBR4 as a target for treating aneuploid cancer. We further found that deviations from co-regulation of two interacting proteins in specific cancer cell lines reflect perturbed cellular circuitry, and they remarkably predict sensitization to therapeutics targeting regulatory modules in the associated pathway. This novel method enables an interactome-wide mapping of protein-protein interaction dysregulation (DysReg mapping) and the inference of cancer vulnerabilities of any cancer sample based on a proteome map acquired at ultra-high throughput. Our goals are to apply these technologies to (i) identify novel cancer vulnerabilities that direct new treatment strategies, to (ii) map cancer vulnerability dynamics, such as those occurring in the development of therapy resistance, to identify novel targets that enable to overcome the treatment resistance, and to (iii) use our technology in a clinical setting to inform treatment strategies in a patient-specific manner.

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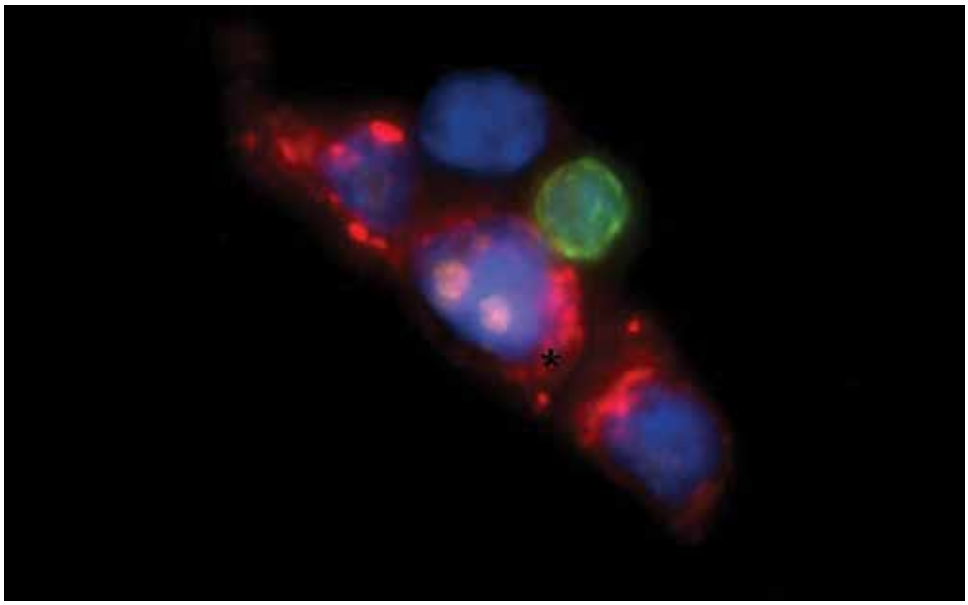
The Haber laboratory focuses on understanding mutations that are acquired by tumors and render them susceptible to specific targeted drug therapies. In 2004, we identified mutations in the EGFR gene in lung cancers which confer dramatic sensitivity to drugs that specifically inhibit that pathway. This finding triggered the application of targeted therapies in lung cancer, and more generally pointed to the critical importance of mutational analysis for treatment selection in common epithelial cancers. Since then, we have collaborated with the bioengineering team led by Dr. Mehmet Toner, the molecular biology group led by Dr. Shyamala Maheswaran, and the MGB Cancer Institute clinical disease centers to develop, characterize, and apply microfluidic devices to isolate rare circulating tumor cells (CTCs) in the blood of patients with cancer. Using these technologies, our lab seeks to explore: 1) blood-based early detection of cancer, 2) noninvasive monitoring of cancer for the emergence of drug resistance, and 3) understanding mechanisms of tumor cell dissemination and metastasis, with the ultimate goal of suppressing blood-borne spread of cancer.

Our laboratory is interested in the genetics of human cancer. Current projects include the use of a microfluidic device to capture circulating tumor cells (CTCs) and its application in early detection of invasive cancer, molecular-directed therapy, and in the study of human cancer metastasis.

Circulating tumor cells and molecular genetics underlying targeted cancer therapeutics

Activating mutations in the epidermal growth factor receptor (EGFR) were identified in our laboratory in the subset of non-small cell lung cancer (NSCLC) with dramatic responses to the tyrosine kinase inhibitor gefitinib. We have studied mechanisms underlying such oncogene addiction, as well as the pathways that lead to the acquisition of resistance to targeted therapies, including the application of irreversible kinase inhibitors to circumvent mutations that alter drug binding affinity. Following these efforts to monitor the emergence of drug resistance mutations, we established collaborations with the Toner and Maheswaran laboratories to characterize novel microfluidic devices capable of isolating CTCs from the blood of cancer patients. Our most advanced version of these CTC-Chips relies upon blood flow through a specialized chamber, which allows the high efficiency depletion of antibody-tagged leukocytes, thereby enriching for intact CTCs without selection bias. We have shown that the number of captured CTCs correlates with clinical evidence of tumor response, and that the cells can be used to define molecular markers characteristic of the underlying malignancy, including EGFR mutations in lung cancer and measurements of androgen receptor (AR) activity in prostate cancer. We have applied next generation single-molecule RNA sequencing and RNA-in-situ hybridization to characterize the heterogeneous expression profiles of individual CTCs in breast, prostate and pancreatic cancers, as well as melanoma and glioblastoma. To facilitate



Circulating prostate tumor cell cluster stained for PSA (green) along with Ki67 (orange) and CD45 (red).

CTC quantitation and provide the sensitivity and specificity required for early cancer detection, we have applied high throughput CTC isolation from blood with molecular genetic and epigenetic markers.

Understanding metastasis through CTC biology

In addition to noninvasive detecting and monitoring of cancer, CTCs provide a window to study the process of blood-borne metastasis. We demonstrated treatment-associated epithelial-to-mesenchymal transitions (EMT) within CTCs from women with breast cancer. Using a combination of mouse models and patient-derived studies, we observed that tumor-derived fragments generate CTC-Clusters, which have greatly enhanced metastatic propensity compared with single CTCs. CTC-Clusters are held together by plakoglobin, whose knockdown dramatically suppresses CTC- Cluster formation and metastatic spread of breast cancer cells. We successfully established long-term in vitro cultures of CTCs from patients with estrogen-receptor (ER)-positive breast cancer, identifying treatment-associated mutations in the estrogen receptor (ESR1), as well as acquired mutations in druggable therapeutic targets, such as PIK3CA and FGFR. In a recent study of prostate tumorigenesis, from the earliest Gleason stages through to metastatic CTCs, we tracked, at single cell level, core DNA hypomethylation domains that arise early in tumorigenesis, thereby silencing genes that are colocalized within a chromosomal locus. Early hypomethylation-induced silencing targets immune-related genes, notably the lipid antigen presentation pathway involved in native immunity, while sparing proliferation-associated genes. Ongoing studies are directed at using patient-derived CTCs and mouse models to understand key steps in cancer metastasis, including the shift from cell quiescence to proliferation, viability during blood-borne transit, and resistance to targeted and immune therapies.

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The Hacohen laboratory consists of immunologists, geneticists, biochemists, technologists, physicians and computational biologists working together to develop new and unbiased technologies and strategies to understand basic immune processes and immune-mediated diseases, with an emphasis on the innate immunity, tool development and personalized medicine. We address three key questions in immunology (1) how are immune responses against cancer initiated, maintained and evaded? (2) what are the immune circuits that sense and control pathogens, such as viruses and bacteria? (3) how does immunity against the body develop, in particular, in patients with autoimmune lupus? In addition to discovering and studying specific molecular and cellular mechanisms, we also address how and why the immune response (to tumors, pathogens or self) varies so dramatically across individuals, such as in sepsis. Finally, we are adapting our unbiased analytical strategies into real-world therapeutics including via protein engineering, having performed clinical trials (with our collaborator Dr. Catherine Wu), in which patients are vaccinated against their own tumors with a fully personal vaccine that is designed based on a computational analysis of their tumor genome.

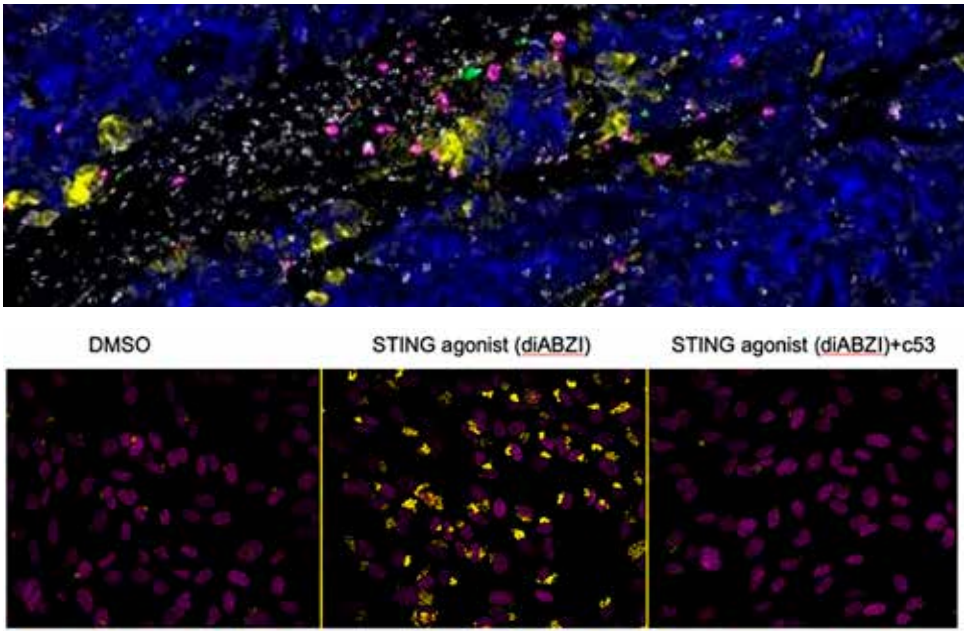
Initiators, resistors and targets of tumor immunity

While cancer immunology has been deeply studied in animal models, human tumor immunology has been more challenging to study. We develop genetic and genomics approaches to explain the large variance in anti-tumor immunity across people, and to discover how tumors evolve to resist immunity. We've identified somatic mutations in tumors associated with anti-tumor immunity in patients, found T cell subtypes associated with a response to anti-PD-1 immunotherapy in melanoma (Sade-Feldman et al., *Cell* 2018), and discovered spatially-organized immune cell hubs in colon cancer (Pelka, Hofree, Chen et al, *Cell* 2021; Chen et al, *Nat Imm* 2024). We have also developed new methods to predict which tumor antigens are presented (Abelin et al., *Immunity* 2017; Sarkizova et al., *Nat Biotech* 2020), which are now being used for novel therapeutic approaches and targets for immunotherapy, such as personal tumor vaccines targeting multiple HLA-associated neoantigens in human tumors (together with Dr. Catherine Wu at DFCI, Ott et al., *Nature* 2017; Keskin, *Nature* 2018).

Genes and networks underlying innate immunity

We've used genome-wide CRISPR libraries to discover mammalian genes mediating the sensing of pathogens (Parnas et al., *Cell* 2015), HIV infection (Park et al., *Nat Gen* 2017) and influenza infection (Li et al., *Nat Comm* 2020). We have characterized innate myeloid cells (DCs and monocytes) in human blood as part of the human Immune Cell Atlas (Villani et al., *Science* 2017). We defined regulators of viral RNA-sensing (Carlson et al., *PNAS* 2023) and DNA-sensing pathways using FACS- and imaging-based screens (Gentili et al, *Cell Systems* 2024). Recently, we discovered that the STING protein, a protein required for sensing cyclic di-nucleotides, is a proton channel that can trigger LC3B lipidation, inflammasome activation and cell death (Liu, Carlson et al., *Science* 2023).

Genetic basis for inter-individual



STING, a critical immune sensor, is shown to be a proton channel, which can explain how STING induces the inflammasome, non-canonical autophagy and cell death. Here, cells stimulated with a STING agonist (diABZi) exhibit a pH change (green) that is blocked by C53, a small molecule that binds the putative pore of the STING protein. Credit: Becca Carlson and Bingxu Liu.

Source: Liu, Carlson, Pires et al. Science. 2023

variations in immune responses

We have also developed genomic strategies to analyze human immune responses and explain immune phenotypes with germline genotypes. We characterized the genetic basis for inter-individual variation in the innate immune response to viruses and bacteria (Lee et al., *Science* 2014; Raj et al., Science 2014; Ye et al., *Science* 2014). For example, we found that common alleles of IRF7 tune the strength of an individual's anti-viral response, and that genetic control of splicing is prevalent and important for the immune response (Ye et al., *Genome Res* 2018). Building on these studies, we developed systematic methods to analyze variants (Ray et al., *Nat Comm* 2021; Mouri, *Nat Genetics*, 2022). We also study non-genetic variations in human immunity, and found a myeloid cell type and state ('MS1' that corresponds to MDSCs) strongly associated with severe infections (bacterial and viral, including COVID-19) and sepsis (Reyes et al., *Nat Med* 2020; *Sci Transl Med* 2021), leading us to new hypotheses underlying these dangerous clinical trajectories.

Drivers of autoimmunity

Deficiencies in nucleases that degrade DNA lead to accumulation of self DNA, activation of innate immune responses and development of autoimmune disorders, including systemic lupus erythematosus and Aicardi-Goutières syndrome in humans. How does autoimmunity develop upon triggering of innate immunity by self DNA? We made the surprising observation that immunostimulatory DNA can arise from host damaged DNA that is exported from the nucleus to the lysosome (Lan et al., *Cell Rep* 2014), a likely source of inflammation in autoimmunity, cancer, chemotherapy and aging. To further find drivers of autoimmunity, we've been analyzing kidney biopsies and blood from lupus patients in a small (Arazi et al., *Nat Imm* 2019) and large patient cohort (ongoing) and in comparison to animal lupus models (Hoover et al., *JEM* 2025).

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Aaron Hata, MD, PhD

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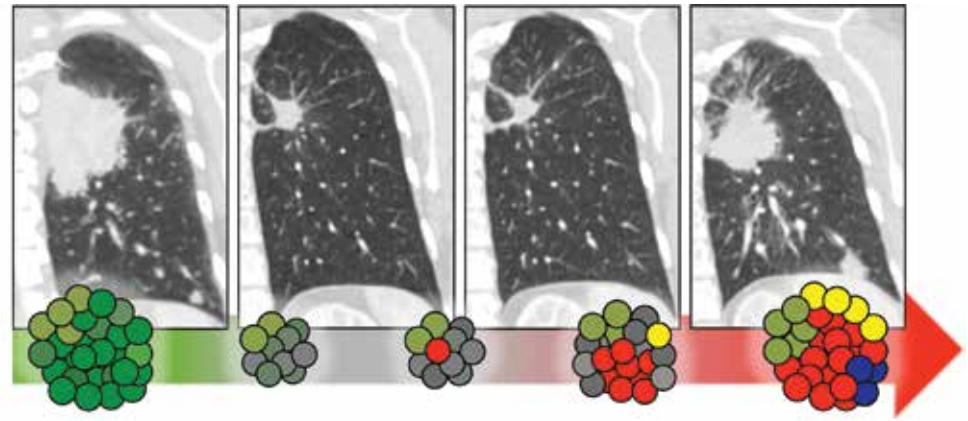
The research goal of **the Hata laboratory** is to advance the development of novel targeted and immunotherapy approaches for lung cancer. We seek to understand the biological mechanisms that dictate drug sensitivity and resistance in oncogene-addicted lung cancers (those with activating genetic alterations EGFR, ALK, KRAS, etc.). Our approach is highly translational, integrating assessment of clinical specimens with generation and analysis of patient-derived cell culture and mouse tumor xenograft (PDX) models, performed in close collaboration with the MGH Thoracic Oncology group. We have discovered clinical mechanisms of acquired drug resistance and developed therapeutic strategies to overcome them. Our work has also shed light on how cancer cells adapt and evolve during the course of therapy, and we are currently working to identify vulnerabilities of residual drug tolerant cancer cells and the surrounding tumor microenvironment that can be exploited to prevent the emergence of drug resistance. Our ultimate goal is to translate our laboratory discoveries into adaptive clinical trials testing novel therapeutic approaches.

Mechanisms of acquired drug resistance to targeted therapies

Lung cancers that harbor activating EGFR mutations and ALK fusions are exquisitely sensitive to small molecule EGFR and ALK tyrosine kinase inhibitors, respectively. However, even though most patients experience dramatic responses, drug resistance invariably develops leading to disease relapse. Similar patterns of sensitivity and acquired resistance are also observed in other subsets of oncogene-addicted lung cancers treated with molecularly targeted therapies (e.g. ROS1 fusions, RET fusions, BRAF mutations, MET exon 14 skipping mutations). In collaboration with oncologists in the Mass General Center for Thoracic Cancers, we have identified acquired secondary mutations and other genomic alterations that cause drug resistance and disease progression after initial response to targeted therapies. To functionally interrogate mechanisms of drug resistance, we have developed a robust infrastructure for generating patient-derived cell lines and mouse patient-derived xenograft (PDX) models from lung cancer patients treated with targeted therapies at the MGH Cancer Center. These models enable functional screens to identify novel mechanisms of acquired resistance and testing of novel next-generation therapies to overcome them.

Targeting KRAS mutant lung cancers

Mutant-selective KRAS inhibitors have recently entered the clinic, however responses are seen in only a minority of patients. Work by our group revealed that many KRAS mutant lung cancers exhibit decreased oncogenic dependency and a dampened apoptotic response that contributes to intrinsic resistance to KRAS targeted therapy. To overcome this limitation, we are exploring next-generation KRAS inhibitors and novel therapeutic combinations that can modify these mechanisms and increase sensitivity to KRAS inhibitors. In addition, we are focused on understanding how intratumoral epigenetic heterogeneity may influence initial drug response and clonal evolution of drug resistance.



Oncogene-addicted lung cancers can develop acquired drug resistance by selection of pre-existing resistant cells, or via evolution of residual drug tolerant persister cells that subsequently acquire resistance mechanisms during the course of treatment. Therapeutic strategies that eliminate persisters or block their ability to evolve may preempt the development of acquired drug resistance.

Tumor adaptation and evolution during treatment

Our discovery that drug tolerant clones that survive initial therapy can acquire a "second genomic hit" enabling outgrowth of fully resistant clones suggests that these "persister" cells may comprise a cellular reservoir from which heterogeneous mechanisms of resistance may arise. We have observed that these cells enter unique cell states with enhanced potential for lineage plasticity, activation of innate immune response pathways, and induction of mutagenic enzymes such as the cytidine deaminase APOBEC3A that increases genomic instability and accelerates the development of drug resistance. Ongoing efforts are focused on characterizing persistent tumor cells in patients and experimental models to identify additional mechanisms that drive adaptation to drug, with the goal to develop therapeutic strategies to preempt acquired drug resistance.

Impact of tumor microenvironment on drug response and resistance

Non-cancer cells within the tumor microenvironment (TME), such as fibroblasts and macrophages, can potentiate or attenuate drug response. We have uncovered a striking degree of complexity in functional interactions between cells in the TME that may impact the sensitivity of tumor cells to targeted therapies. By unraveling these mechanisms, we hope to develop orthogonal TME-targeting therapies that augment the effectiveness of current targeted therapies.

Developing novel immunotherapy approaches for lung cancers with low mutation burden

EGFR mutant and ALK fusion lung cancers typically occur in never-smokers and consequently have low tumor mutation burden and poor response to currently approved immune checkpoint inhibitors. We are developing TCR cellular therapies and novel methods for reprogramming tumor cell antigenicity to direct the immune system to recognize and fight EGFR and ALK lung cancers.

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Yoda S, Lin JJ,...**Hata AN***, Shaw AT*. Sequential ALK Inhibitors Can Select for Lorlatinib-Resistant Compound ALK Mutations in ALK-Positive Lung Cancer. *Cancer Discovery*. 2018 Jun;8(6):714-729.

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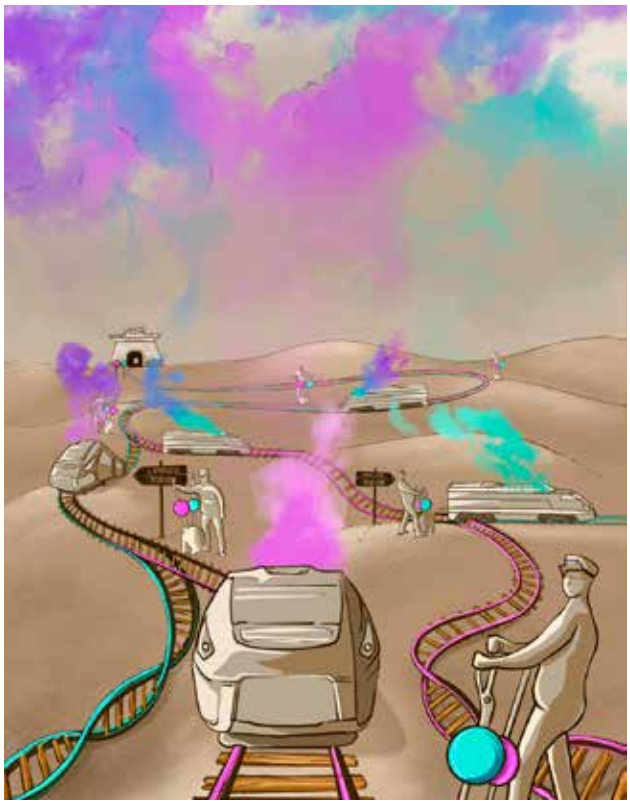
The Hochedlinger laboratory explores the fundamental question of how cells maintain their identity. We hypothesize that factors that reinforce specific cell states, such as pluripotency and differentiation, continue to play functional roles in other cellular contexts including development, tissue homeostasis and cancer. Using stem cell models and reprogramming systems as discovery tools ex vivo, our laboratory has elucidated novel mechanisms that maintain cell identity and function upstream of cell type specific transcription and chromatin factors. Specifically, work from our lab over the past five years revealed that common cellular processes such as protein sumoylation, chromatin assembly, alternative mRNA polyadenylation and P-body homeostasis play key roles in the maintenance of cell identity across distinct lineages. We now aim to probe the functional conservation of these mechanisms across physiological cell fate transitions in vivo using animal models and cell transplantation. As our strategy is not confined to one particular cell type or tissue, we are in a position to uncover shared regulatory principles crucial for the maintenance of cell identity across different developmental contexts.

While development and cellular differentiation were long thought to be irreversible processes, our ability to reprogram differentiated cells to an embryonic-like state revealed that mechanisms that safeguard cell identity and thus restrict developmental plasticity can be overcome through experimental manipulation. Indeed, seminal somatic cell nuclear transfer (SCNT) experiments proved that the nuclei of terminally differentiated cells and even certain cancer cells retain full developmental potential. While SCNT is a powerful assay to test the developmental potential of a given genome, it does not allow one to study *how* differentiated cell states are established and maintained. By contrast, transcription factor-induced reprogramming of somatic cells into induced pluripotent stem cells (iPSCs) is a molecularly defined and tractable system to dissect fundamental questions of cell state. Our lab initially used this approach to provide crucial insight into the basic mechanisms by which transcription factors and chromatin signaling establish and maintain identity in either pluripotent or differentiated cells, and we began to probe the conservation of these principles in other cellular contexts. For example, we discovered that the transcription factor Sox2, which is essential for the establishment and maintenance of pluripotent stem cells, is re-expressed in adult gastric stem cells where it maintains tissue identity by suppressing an alternative intestinal cell program and tumorigenesis. Similarly, we demonstrated that the manipulation of safeguard mechanisms previously identified during iPSC reprogramming in other cellular contexts facilitate the derivation of self-renewing muscle stem-like cells, which have been notoriously difficult to capture using conventional strategies. More recently, our lab uncovered two post-transcriptional processes, alternative polyadenylation (APA) and Processing body (P-body) turnover, as novel safeguard mechanisms using unbiased screens. While APA and P-bodies are thought to control different aspects of gene regulation in the nucleus (APA) and cytoplasm



The image illustrates the resolution of bivalent chromatin associated with uncommitted hematopoietic stem cells into monovalent chromatin associated with mature myeloid and lymphoid cells. Chromatin is shown as train tracks that originate at a stem cell station and continuously bifurcate during hematopoiesis to give rise to the various blood cell types. Stem cells carry bivalent chromatin that is still plastic but poised for differentiation (red and purple signals are on), while differentiating cells switch to either the purple or green signals, as illustrated by colored levers that are in a neutral position (bivalent) or pushed to purple or green (monovalent) by signalmen.

Image: Sayo-Art

(P-bodies), a key commonality that emerged from our work is that both processes regulate the protein homeostasis of hundreds of fate-instructive genes. Together, these examples underscore the power of our approach to gain insights into tissue identity through the study of pluripotency and cellular reprogramming.

Considering that several of the safeguard mechanisms we previously identified in reprogramming converge on chromatin regulators, we have recently developed versatile histone-mutant transgenic tools to directly probe the physiological role of chromatin modifications in cell fate change. These lysine-to-methionine (K-to-M) mutants, which dominantly block methylation at specific sites, have allowed us to uncover previously unappreciated functions of H3K4, H3K9, H3K27 and H3K36 methylation in the regulationof pluripotency, reprogramming, tissue homeostasis and aging, which is the basis for ongoing work in the lab. We are also using these tools to identify epigenetic vulnerabilities in cancer.

Thus, by pursuing our hypothesis that different physiological as well as experimentally induced cell fate transitions utilize common mechanisms, our lab has uncovered novel epigenetic, transcriptional and post-transcriptional regulators of cell identity. As we pursue a deeper understanding of how these underexplored regulators and processes guide cell fate transitions in vivo, we are poised to discover shared principles by which they safeguard cell identity during development and tissue homeostasis and how this knowledge may be exploited in a therapeutic setting to alter cell fate.

Selected Publications:

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Hanno Hock, MD, PhD

Hock Laboratory

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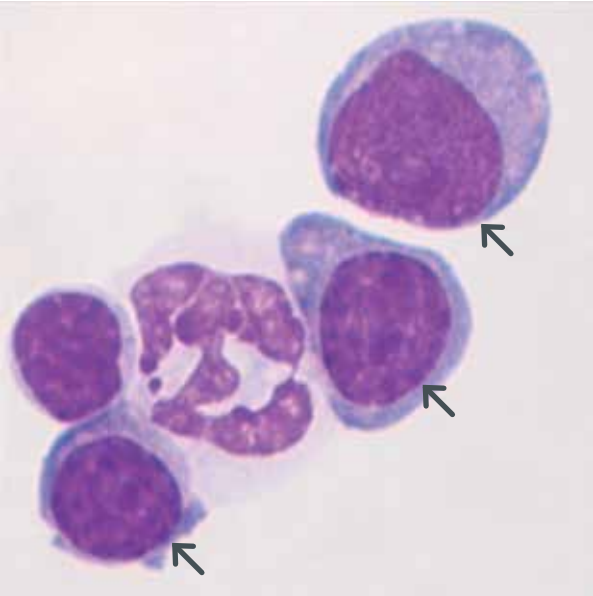
The Hock laboratory explores the molecular basis of blood cell formation and the pathogenesis of leukemia and lymphoma. Specifically, we study the transcription factors that regulate gene activity during normal blood cell development and how the transcriptional apparatus goes awry in cancer. For example, we have developed important insights into a network of transcription factors that help maintain blood stem cells in the bone marrow; this work could lead to new strategies for increasing the yield of stem cells for bone marrow transplantation. Another project in our laboratory focuses on deciphering the multistep process that leads to lymphoblastic leukemia of childhood, with the goal of identifying new drug targets for this devastating disease. Finally, we are interested in how DNA packaging affects the interaction between genes and transcription factors, especially with regard to oncogenes and tumor suppressor genes important in human cancer.

Our laboratory is interested in the molecular control of normal and malignant stem cells with an emphasis on the hematopoietic system. Blood cells need to be continuously replenished by a small population of hematopoietic stem cells (HSCs) that have the capacity to both self-renew and mature stepwise into all known blood lineages. HSCs are also the ancestors of leukemia and lymphoma cells. As HSCs mature, they undergo successive changes in gene expression. The transcriptional apparatus must ensure that genes specific to immature cells are repressed as differentiation proceeds, while genes that are necessary for mature cells become activated. This activating and inactivating of genes is achieved by cooperative action of a variety of lineage-specific and general transcription factors and the complex molecular machinery that regulates the accessibility of different regions of the genome in chromatin. We investigate how transcription factors establish differentiation-specific transcriptional programs and how such programs can become derailed in cancer, leukemia and lymphoma.

Transcriptional control of normal and malignant hematopoietic stem cells in the adult bone marrow

Hematopoiesis in the bone marrow emanates HSCs. We are studying the basic biology of HSCs. Specifically we explore how a network of transcription factors that includes Tel- Etv6, Gfi1, Gfi1b and Gata2 maintains HSCs in the bone marrow (Hock et al. 2004, *Genes & Development*; Hock et al. 2004, *Nature*). The goal is to exploit the biology of transcriptional regulation of HSCs to maintain, expand, and possibly even generate HSCs ex vivo so that more patients will have the option of bone marrow transplantation. In a closely related effort, we are exploring the molecular programs of stem cells in leukemia and lymphoma to identify differences in their molecular regulation compared with normal HSCs. Such differences may allow us to specifically target tumor stem cells while sparing normal blood formation.



Dr. Hock's laboratory works on molecular mechanisms of normal differentiation and malignant transformation. The image shows normal blood cells and leukemic cells (arrows) from a novel experimental model generated in the lab.

Deciphering the molecular events leading to acute lymphoblastic leukemia of childhood

About one in 2000 children develops this catastrophic illness, most often with a t(12;21) translocation. Despite very aggressive treatments, not all children can be cured, and some suffer from long-term side effects of their therapy. Rational development of more specific, less toxic treatments requires a precise understanding of the molecular mechanisms that cause the disease. We have discovered that TELAML1, the first hit in childhood leukemia, generates a preleukemic, latent lesion in HSCs. We are now exploring how additional genetic hits cooperate to derail normal blood development and generate leukemia. Deciphering the multistep pathogenesis of this entity is likely to serve as a paradigm for the development of other malignant diseases.

Exploration of novel epigenetic regulators in stem cells

Our understanding of how specialized cells of the body establish their identity by regulating access to genes continues to increase. For example, a large fraction of the genes active in brain cells are inactive in blood cells and, therefore, are stored in a very dense, inaccessible state. As most molecules involved in the regulation of gene accessibility have only recently been identified, studying their biology is likely to provide unique opportunities for the development of entirely novel therapies. We are investigating the utility of a group of proteins termed MBT-proteins, which is very important for condensing DNA and modifying histones. Evidence suggests that this protein family may play important roles in normal and malignant blood formation, but its precise functions remain poorly understood. Our laboratory has recently discovered an entirely novel, essential function of the family member L3mbtl2 in pluripotent stem cells.

Selected Publications:

Yagi M, Bonilla G, Hoetker MS, Tsopoulidis N, Horng JE, Haggerty C, Meissner A, Sadreyev RI, **Hock H***, Hochedlinger K*. Bivalent chromatin instructs lineage specification during hematopoiesis. *Cell*. 2025 Aug 7;188(16):4314-4331.e29.

Nardi V, Ku N, Frigault MJ, Dubuc AM, Tsai HK, Amrein PC, Hobbs GS, Brunner AM, Narayan R, Burke ME, Foster J, Dal Cin P, Maus MV, Fathi AT, **Hock H**.Clinical response to larotrectinib in adult Philadelphia chromosome-like ALL with cryptic ETV6-NTRK3 rearrangement. *Blood Adv*. 2020;4(1):106-11.

Brumbaugh J, Kim IS, Ji F, Huebner AJ, Di Stefano B, Schwarz BA, Charlton J, Coffey A, Choi J, Walsh RM, Schindler JW, Anselmo A, Meissner A, Sadreyev RI, Bernstein BE, **Hock H***, Hochedlinger K*. Inducible histone K-to-M mutations are dynamic tools to probe the physiological role of site-specific histone methylation in vitro and in vivo. *Nat Cell Biol*. 2019;21(11):1449-61.

Hock H, and A. Shimamura. 2017. ETV6 in hematopoiesis and leukemia predisposition. Seminars in hematology 54:98-104. PMC5584538 Foudi A, Kramer DJ, Qin J, Ye D, Behlich AS, Mordecai S, Preffer FI, Amzallag A, Ramaswamy S, Hochedlinger K, Orkin SH and Hock H. Distinct, strict requirements for Gfi-1b in adult bone marrow red cell and platelet generation. *J Exp Med*. 2014; 211, 909–927.

Qin J, Whyte WA, Anderssen E, Apostolou E, Chen H, Akbarian S, Bronson RT, Hochedlinger K, Ramaswamy S, Young RA, and **Hock H**. The Polycomb Group Protein L3mbtl2 Assembles an Atypical PRC1-family Complex with Essential Roles in Pluripotent Stem Cells and Early Development. *Cell Stem Cell*. 2012; 11, 319-332, 2012.

Schindler JW, Van Buren D, Foudi A, Krejci O, Qin J, Orkin SH, **Hock H**. TELAML1 corrupts hematopoietic stem cells to persist in the bone marrow and initiate leukemia. *Cell Stem Cell*. 2009; Jul 2, 5(1):43-53.

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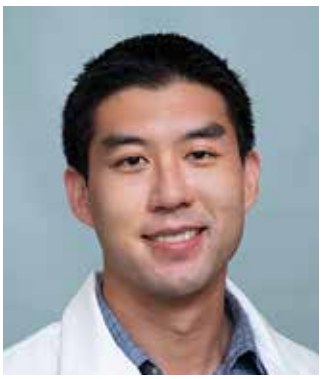

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The Hwang laboratory focuses on the immense phenotypic, temporal and spatial heterogeneity of tumor ecosystems and the many insights that can only be gleaned by studying these systems at the level of their individual components. We study tumor-stroma interactions at unprecedented resolution through the development and application of techniques in spatial and systems oncology, advanced microscopy, genetic engineering and computational biology to patient-derived specimens, stromal tumoroids and mouse models. Our goals are to elucidate mechanisms of (1) therapeutic resistance mediated by genetic, epigenetic, and phenotypic factors including cell state plasticity; (2) treatment-mediated remodeling of the spatial microarchitecture of tumors and underlying cancer cell-stromal interactions; and (3) tumor-nerve crosstalk, which plays a critical role in the pathophysiology and morbidity of many malignancies but remains understudied.

Single-cell dynamics

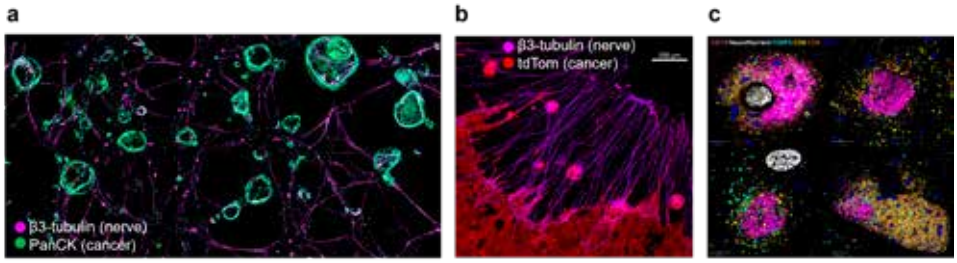
Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal and treatment refractory disease. Molecular subtyping of PDAC is rudimentary and does not currently inform clinical management or therapeutic development. We optimized single-nucleus RNA-seq to discover treatment-associated changes in cellular composition and state, including enrichment of a novel neural-like malignant program in residual tumors after chemoradiation. Our high-resolution molecular framework elucidates the inter- and intra-tumoral diversity of PDAC, treatment-associated remodeling and clinically relevant prognostication to enable precision oncology in PDAC.

Ongoing projects:

1. Identifying key regulators, context dependence and therapeutic vulnerabilities of resistant cell states
2. Elucidating (epi)genetic contributions to cell state plasticity in therapeutic resistance
3. Investigating mechanisms of tumorigenesis using single-cell multiomics to enable chemoprevention and early detection
4. Studying developmental lineages and mechanisms of metastasis in pancreatic neuroendocrine tumors

Spatial oncology

Dissociative single-cell approaches enable detailed characterization of the different cell types and states that compose a heterogeneous tumor but sacrifice in situ spatial relationships among cells. Leveraging recent advances in spatial proteo-transcriptomics enabling single-cell resolution and high molecular plex, we performed spatial molecular profiling (SMI) on a cohort of patient-derived PDAC tumors and developed a novel method for inferring multicellular interactions. Spatially Constrained Optimal Transport Interaction Analysis (SCOTIA) that considers both spatial distance and ligand-receptor (LR) expression (collaborator: Martin Hemberg). We used SCOTIA to dissect the remodeled pancreatic tumor microenvironment in response to neoadjuvant chemoradiation and uncovered marked changes in LR interactions between cancer-associated fibroblasts and malignant cells, which was supported by orthogonal experiments using a murine tumoroid co-culture system (https://tinyurl.com/2xtdytxt).



(a) 3D mouse pancreatic cancer organoid-nerve co-culture. (b) Pancreatic cancer cell aggregates (red) moving along neurites (purple) extending from a dorsal root ganglion (removed). (c) Representative immune aggregates in the pancreatic cancer tumor microenvironment identified by 100+ plex spatial proteomics. NF = neurofilament; MC TRY = mast cell tryptase.

Overall, we demonstrated the immense potential of a translational spatial biology paradigm for deriving novel biological insights and identifying actionable therapeutic targets — one that can be broadly applied to other malignancies and treatment contexts.

Ongoing projects:

1. Discovering gene regulatory networks that modulate tumor-stroma interactions through perturbative spatial screens
2. Developing computational models to infer cell state from integrating intrinsic and extrinsic influences
3. Creating a platform for correlating morphological changes to transcriptional changes through combining live-cell imaging with spatial transcriptomics
4. Integrating matched liquid and spatial biomarkers to assess response to therapy

Cancer neuroscience

Active recruitment of nerve fibers into tumors plays an important role in cancer development, treatment resistance, metastasis and mortality for many malignancies, but the diverse molecular mechanisms underlying tumor-nerve crosstalk remain largely unknown. To address this gap in knowledge, we performed a comprehensive, cell-type specific, spatially resolved whole transcriptome analysis of human PDAC using custom tissue microarrays derived from intratumorally matched malignant areas with (N+) and without (N-) nerve involvement. Whole-transcriptome digital spatial profiling revealed that classical malignant cells were depleted near nerves while basal/mesenchymal and neural-like cancer cells were enriched near nerves. Differential gene expression analysis comparing malignant cells in N+ versus N- regions enabled selection of subtype-specific candidate genes for functional investigation. This research will provide a detailed understanding of the mechanisms by which pancreatic cancer cells and the peripheral nervous system collaborate to confer numerous pro-tumorigenic effects, and guide prioritization for therapeutic intervention in the burgeoning cancer neuroscience field.

Ongoing projects:

1. Identifying cell-type specific mediators of nerve outgrowth, invasion and colonization using patient-derived tumors, tumoroids and GEMMs
2. Determining influence of neuronal subtype and activity on the immune response to cancer in primary tumors and draining lymph nodes
3. Dissecting molecular mechanisms of dynamic physical interactions between cancer cells and nerves
4. Discovering the mechanistic basis for differential central nervous system versus peripheral nervous system tropism across the spectrum of cancer

Selected Publications:

Guo JA*, Gong D*, Evans K*, Takahashi K, Jambhale AD, Shiau C, Yu P, Wang S, Wu WW, Chugh S, Kapner KS, Dilly J, Zhao D, Chen P, Smith EL, Mancias JD, Vazquez F, Singh H, **Hwang WL**†, Aguirre AJ†.Integrative genomic identification of therapeutic targets for pancreatic cancer. *Cell Reports.* 2025;44(9):116191.

Gong D*, Arbesfeld-Qiu JM*, Perrault E*, Bae JW, **Hwang WL**†. Spatial oncology: translating contextual biology to the clinic. *Cancer Cell.* 2024;42(10):1653-1675.

Hwang WL*†, Perrault EN*, Birbrair A, Mattson BJ, Gutmann DH, Mabbott DJ, Cukierman E, Repasky EA, Sloan EK, Zong H, Demir IE, Saloman JL, Borniger JC, Hu J, Dietrich J, Breunig JJ, Çifcibaşı K, Ahmad Kasm KA, Valiente M, Wintermark M, Acharya MM, Scheff NN, D'Silva NJ, Vermeer PD, Wong RJ, Talbot S, Hervey-Jumper SL, Wang TC, Ye Y, Pan Y, Bunimovich YL, Amit M†. Integrating priorities at the intersection of cancer and neuroscience. *Cancer Cell.* 2025;43(1):1-5.

Shiau C*, Cai J*, Gregory MT, Gong D, Yin X, Cho J-W, … Fernandez-del Castillo C, Mino-Kenudson M, Ting DT, Hemberg M†, **Hwang WL**†. Spatially resolved analysis of pancreatic cancer identifies therapy-associated remodeling of the tumor microenvironment. *Nature Genetics.* 2024 Nov;56(11):2466-2478.

Hwang WL*, Jagadeesh KA*, Guo JA*, Hoffman HI*, Yadollahpour P, Reeves J, … Fernandez-del Castillo C, Liss AS, Ting DT, Jacks T†, Regev A†. Single-nucleus and spatial transcriptome profiling of pancreatic cancer identifies multicellular dynamics associated with neoadjuvant treatment. *Nature Genetics* 2022 Aug;54(8):1178-1191.

Hwang WL*, Deindl S*, Harada BT, Zhuang X†. Histone H4 tail mediates allosteric regulation of nucleosome remodeling by linker DNA. *Nature.* 2014;512(7513):213-7.

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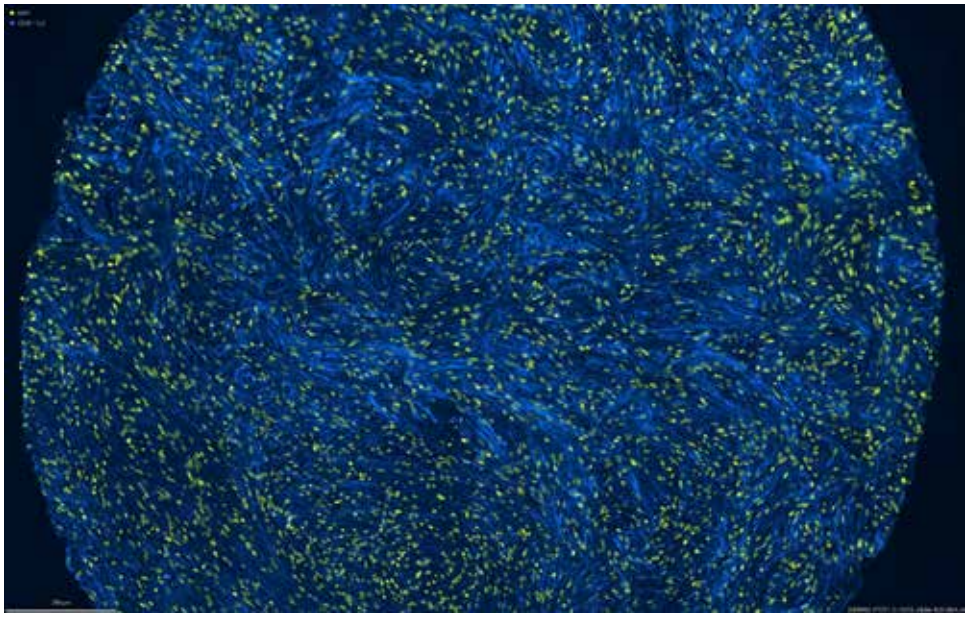
The Iafrate laboratory has focused efforts on developing highly complex molecular analyses of tumor genetics using novel technologies. We have a strong interest in the clinical implementation of genetic screening technologies that can help direct targeted therapies, focusing on lung, breast, head and neck, and brain tumors. Our contributions in the treatment of a subset of non-small cell lung carcinoma (NSCLC) with rearrangements of the ALK tyrosine kinase, rearrangements of the ROS1 tyrosine kinase and MET exon 14 skipping with a small molecule kinase inhibitor (crizotinib), underscore the promise of personalized cancer care. We currently are focusing on using spatial protein and RNA technologies to understand how tumors grow and avoid the immune system. In addition, we have built a strong chemical biology team that is developing a novel and exciting new class of covalent drugs termed COUPLrs.

The Iafrate laboratory has been focused on translational and clinical cancer research, with successful development of diagnostic technology development and more recently on the development of novel therapeutics. In response to the rapidly growing number of actionable gene fusions and consequent need for comprehensive genotyping, two fellows in the lab developed a next generation assay termed 'Anchored Multiple PCR', or AMP, in 2014 (Zheng et al. 2014). This sequencing assay allowed the identification of a large number of gene fusions, including unknown partners and novel breakpoints, starting with archived FFPE RNA. We have developed and deployed next generation sequencing to detect chromosomal rearrangements in tumor tissue, with on-going studies that assess the relative sensitivity in much larger clinical cohorts (Kaluziak et al., 2024). Our lab is now focused on modeling novel fusions in vitro and developing therapeutic approaches to screening these fusions building on work we did in the development of practice-changing ALK and ROS1 fusion in lung cancer (Kwak et al, 2010; Shaw et al., 2014).

We have also initiated studies of tumor heterogeneity; these efforts focus on gene amplification of receptor tyrosine kinases in glioblastoma. This work has revealed a new subclass of brain tumors with mosaic gene amplification of up to three kinases in distinct but intermingled cell populations within the same tumor, forming a mosaic pattern. We found that each subpopulation was actively proliferating and contributing to tumor growth. Our lab has developed novel highly-multiplexed FISH and protein immunofluorescence technology to address how protein and DNA copy number heterogeneity, and to study the spatial distribution of such populations. We are exploring the therapeutic implications of such cellular heterogeneity in cell line model systems of gliomas and meningiomas (*see image*).

More recently we have adapted the AMP sequencing technology in other areas, including developing tissue-specific cell-free DNA (cfDNA) panels to examine the most important cancer genes in common tumors, including lung, melanoma, breast and colon cancer. Such panels are allowing us to track, with a simple blood draw, the tumor



Meningioma "Starry Sky": multiplex Immunofluorescence to detect changes in the immune landscape of brain tumors. In this case a meningioma showing DAPI pseudocolored in yellow and CD56 in blue.

burden in patients. We are able to use cfDNA analysis in patients with metastatic cancer to see if they are responding to therapy, and also can track the development of resistance mutations. Most recently we have developed a methylation-based sequencing assay to allow efficient analysis of tumor-specific methylation patterns in cfDNA samples, as well as bespoke patient-specific fusion tracking assays, and assays to detect HPV in cfDNA of head and neck tumors. We hope that these approaches can be a lot more sensitive in the detection of small amounts of circulating tumor DNA, allowing potential early detection of tumors before they are clinically symptomatic.

Our lab has more recently turned its focus to other areas of immune-oncology, as well, including developing spatial technology – at present, multiple immunofluorescence and spatial transcriptomics – to study immunotherapy resistance in cancer: we are now actively researching ways to turn cold tumors into hot tumors. We recently published a detailed analysis of one such cold tumor, the salivary gland tumor Adenoid Cystic Carcinoma, after analyzing its immune microenvironment, and have initiated clinical approaches to provide novel therapies for this devastating disease (Li et al., 2025). Finally, we have an active therapeutics/drug screening team, and have recently described a novel class of very exciting covalent drugs with two warheads termed 'COUPLRs' (Yang et al., 2024). COUPLrs will have a major impact on anti-cancer therapy, we predict, and will form a major expanding research focus.

Selected Publications:

Li A, Gonda B, von Paternos A, Codd E, Mitchell D, Herrmann M, Dzu T, Kalyan P, Gao C, Zhang E, Mendel J, Thierauf JC, Sadow PM, Denize T, Yang D, Park JC, Fintelmann FJ, Gao X, Merkin RD, Bhan AK, Faquin WC, Wirth LJ, Faden DL, Kaluziak ST, **Iafrate AJ**. Reversible Downregulation of HLA Class I in Adenoid Cystic Carcinoma. *J Immunother Cancer.* 2025 13(4):e011380.

Yang D, Harry SA, Chong HB, Zhang E, Nordenfelt NS, Chen N, Lee C, Kaluziak S, Codd E, Trivedi S, Gohar M, McKnight G, Mitchell DR, Ge M, Gao C, Holmes Z, Yang W, Smith AE, Carlin AD, Lazarov MJ, Khandelwal N, Hara M, Zhang S, Leong HXY, Martinez Luna H, Chearavanont Z, Emonds K, Popoola G, Barakat I, Onozato M, Mahamdeh M, Fujino T, Seo H-S, Dhe-Paganon S, Sun Z-YJ, Heffron GJ, Hata A, Soberman RJ, Liau BB, **Iafrate AJ***, Bar-Peled L*. Systematic Targeting of Protein Complexes with Molecular COUPLrs. *bioRxiv*. 2024:2024.07.16.603666.

Kaluziak ST, Codd AM, Purohit R, Melli B, Kalyan P, Fordham J, Kirkpatrick G, McShane LM, Chang TC, Yang G, Wang J, Williams PM, Karlovich CA, Sklar J, **Iafrate AJ**. Discovery of Gene Fusions in Driver-Negative Cancer Samples from the NCI-MATCH Screening Cohort. *JCO Precis Oncol*. 2024 Dec;8:e2400493.

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Shaw AT, Ou SH, Bang YJ, Camidge DR, Solomon B, Salgia R, Riely GJ, Varella-Garcia M, Shapiro GI, Costa DB, Doebele RC, Le LP, Zheng Z, Tan W, Stephenson P, Shreeve SM, Tye LM, Christensen JG, Wilner K, Clark JW, **Iafrate AJ**. Crizotinib in ROS1-Rearranged Non-Small Cell Lung Cancer. *N Engl J Med*. 2014; Sept. 27.

Kwak EL, ... , **Iafrate AJ**. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. *N Engl J Med.* 2010;363(18):1693-703.

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Iliopoulos Laboratory

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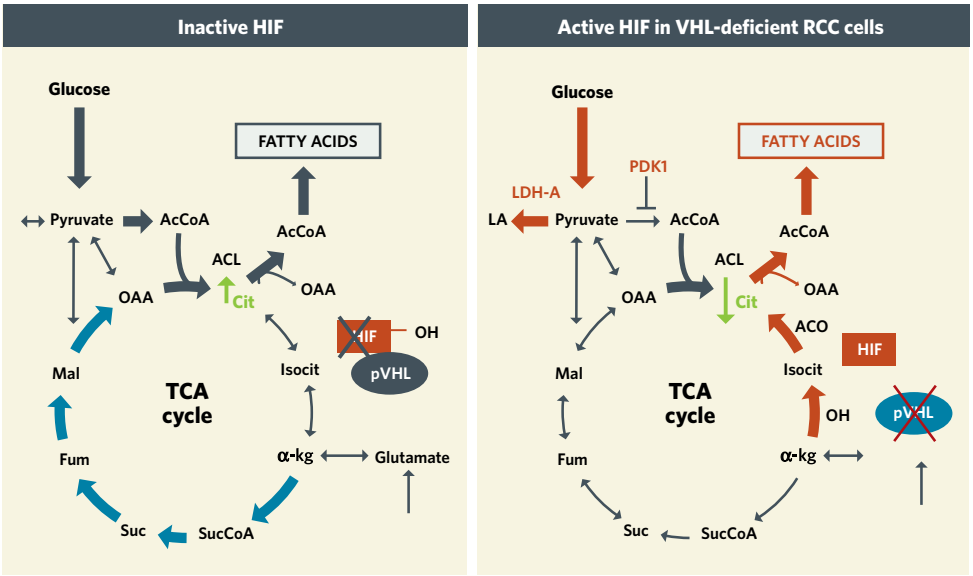
The Iliopoulos laboratory works on the main mechanisms underlying the reprogramming of cancer cell metabolism and cancer angiogenesis with the goal to develop mechanism-based strategies for selectively killing cancer cells. We use Renal Cell Carcinoma (RCC) as a model disease of altered cancer metabolism and angiogenesis mechanisms. Cancer cells transform their metabolism to adapt to the needs of fast growth and to compete with the surrounding normal cells for nutrients and oxygen. In addition to a reprogrammed metabolism, cancer cells stimulate the growth of new blood vessels that bring blood to them, a phenomenon known for many years as "cancer angiogenesis". The laboratory identifies and validates therapeutic targets that disrupt these processes.

Discovery and development of hypoxia inducible factor 2a (HIF2a) inhibitors for treatment of renal cell carcinoma and other HIF2a-dependent cancers

We screened libraries of chemical compounds and discovered chemical molecules that significantly and specifically decrease the expression of HIF2a (Zimmer M. et al. *Molecular Cell* 2008; 32(6): 838-48). We used these HIF2a inhibitors as chemical biology probes and discovered that they suppress the expression of HIF2a by activating IRP1. We thus proved a crosstalk between the iron and oxygen sensing mechanisms within the cell. We demonstrated that the HIF2a inhibitors discovered are "active" and that they reverse the consequences of VHL protein loss (Metelo AM. *Journal Clinical Investigation* 2015; 125(5): 1987-97). Our chemical HIF2a inhibitors are very promising agents for treating RCC

Targeting the metabolic reprogramming of RCC and HIF2a expressing tumors; from the lab to the bedside

We used metabolic flux analysis to show that hypoxic cells use glutamine as a carbon source for anabolism. We showed that low oxygen levels or HIF2a expression reprogrammed cells to use glutamine in a "reverse" TCA cycle to produce the metabolites required for anabolic reactions, a process called Reductive Carboxylation. These observations provided insights into a mechanism by which hypoxic and HIF2a expressing cancer cells compensate for the Warburg phenomenon (Metallo et al. *Nature* 2012; 481(7381): 380- 4). We delineated the mechanism driving Reductive Carboxylation and proved that reductive carboxylation does not only happen in cultured cells, but can also be detected in human RCC tumors growing as xenografts in mice. We therefore provided for the first time, in vivo evidence for the utilization of glutamine in tumors through reductive carboxylation (Gameiro et al. *Cell Metabolism* 2013; 17(3): 372-385). Recently, we showed that inhibition of Glutaminase 1 (GLS1) decreases significantly the intracellular pyrimidines and results in DNA replication stress in HIF-hypoxia driven cancer cells. Treatment of cancer cells with GLS1 and PARP inhibitors resulted in dramatic suppression of RCC in xenograft models (*J Clin Invest*.2017; 127(5): 1631-1645). We brought these fundamental observations of our laboratory on glutamine metabolism to the clinic, testing the combination of GLS1 inhibitors with PARP



Expression of Hypoxia Inducible Factor HIF2a rewires the central carbon metabolism in renal cell cancer.

inhibitors in renal cancer, clear cell ovarian and prostate cancer

Clinical and translational studies to identify resistance to the HIF2a inhibitor Belzutifan

Belzutifan has been approved by FDA for treatment of VHL disease related RCC, hemagioblastoma and pancreatic neuroendocrine tumors. Our laboratory and the MGH VHL and Hemangioblastoma Centers are leading clinical trials for the optimal use of this first in class oral medication. In addition, we use patient derived tissue, as well as in vitro and in vivo models to discover mechanisms of resistance to this medication.

Selected Publications:

Iliopoulos O, Iversen A, Narayan V, Maughan BL, Beckermann KE, Oudard S, et al. Belzutifan for patients with von Hippel-Lindau disease-associated CNS haemangioblastomas: a multicentre, single-arm, phase 2 study. *Lancet Oncology* 2024; 25(11): 1325-1336

Okazaki A, Gameiro PA, Christodoulou D, Laviollette L, Schneider M, Chaves F, Stemmer-Rachamimov A, Yazinski SA, Lee R, Stephanopoulos G, Zou L, **Iliopoulos O**. Glutaminase and poly(ADP-ribose) polymerase inhibitors suppress pyrimidine synthesis and VHL-deficient renal cancers. *J Clin Invest*. 2017; 127(5): 1631-1645

Laviolette LA, Mermoud J, Calvo IA, Olson N, Boukhali M, Steinlein OK, Roider E, Sattler EC, Huang D, Teh BT, Motamedi M, Haas W, **Iliopoulos O**. Negative regulation of EGFR signalling by the human folliculin tumour suppressor protein. *Nat Commun*. 2017; 28;8: 15866.

Gameiro PA, Yang J, Metelo AM, Pérez-Carro R, Baker R, Wang Z, Arreola A, Rathmell WK, Olumi A, López-Larrubia P, Stephanopoulos G and **Iliopoulos O**. HIF mediated reductive carboxylation occurs in vivo through regulation of citrate levels and sensitizes VHL-deficient cells to glutamine deprivation. *Cell Metabolism*. 2013; 17 (3): 372-385.

Metallo CM, Gameiro PA, Bell EL, Mattaini KR, Yang J, Hiller K, Jewell CM, Zachary R. Johnson JR, Irvine DJ, Guarente G, Kelleher JK, Vander Heiden MG, **Iliopoulos O***, Stephanopoulos G*. Reductive glutamine metabolism by IDH1 mediates lipogenesis under hypoxia. *Nature*. 2011; 481 (7381): 380-4, Nov 20.

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The Jan laboratory primarily focuses on developing clinically suitable synthetic biology platforms in order to advance next-generation cellular immunotherapies. Harnessing elegant protein degradation cellular machinery that has evolved to control fast biologic transitions related to information flow and signal processing, we have developed molecular switch technologies regulated by the FDA-approved drug lenalidomide as generalizable chemical biology tools and cell therapy controllers. We use genomics, synthetic biology, and biochemistry to build new technologies, explore design principles for adaptive, user-controllable immune cells, and investigate clinical settings to deploy smart cell therapies.

Programming cellular immunotherapies using targeted protein degradation

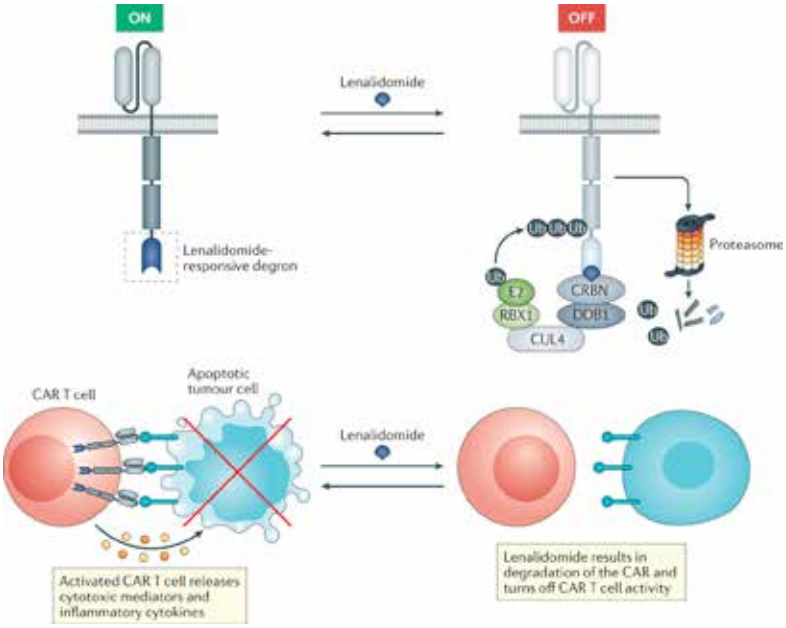
Genetically modified (CAR) T cells have emerged as transformative agents in the care of people with cancer. To reach their full potential, cellular immunotherapies must become safer, more effective, and more accessible. We recently developed chemical genetic control systems around the FDA-approved drug lenalidomide and its analogs, which act as molecular glue targeted protein degraders, recruiting neosubstrate proteins to E3 ubiquitin ligases for polyubiquitination and proteasomal degradation. We engineered clinically suitable lenalidomide-inducible dimerization and degradation systems, and with them drug ON- and OFF-switch CAR T cells (see Figure), prototypes for remote controlled CAR T cell therapies which are now entering clinical testing.

To supercharge the anti-tumor potency of CAR T cells, we have developed chemogenetic systems for precision spatiotemporally controlled delivery of cytokines and transcription factors. For highly potent and/or novel investigational cell therapies with unproven safety profiles, together with the Manguso lab, we are developing cell therapy suicide switches induced by lenalidomide that may act as safeguards in early-stage clinical testing.

We have also developed a new technology to genetically reprogram E3 ubiquitin ligases to bind and degrade customizable sets of endogenous proteins. Leveraging transformative progress in computational structural biology and de novo protein design, we are leveraging this protein interaction-based molecular logic for post-translational endogenous protein regulation, exploring diverse applications for engineering CAR T cell tumor sensing and dysfunction resistance.

Design and evaluation of cellular immunotherapies targeting novel antigens

CAR T cells can be highly effective and well-tolerated therapeutics when they are targeting antigens that are homogenously expressed on tumor cells and are also absent from essential normal tissues. In collaboration with the Villani lab, we are leveraging single cell genomics and large-scale tumor and normal tissue gene expression datasets to nominate novel target antigens in select solid tumors including anaplastic, poorly differentiated, and oncocytic thyroid cancers with protein-based validation using archival tissues from the MGH Department of Pathology. We have



Molecular switch control of genetically engineered cell therapies. *Incorporation of a lenalidomide-responsive degron tag enables drug-dependent degradation mediated by the ubiquitin-proteasome system. Pharmacologic control can be used to mitigate CAR T cell hyperactivation toxicities or to tune CAR signaling.*

Image credit: Nature Reviews Clinical Oncology.

identified novel CAR target antigens and with them are developing logical multi-antigen targeting CAR T cells to treat these rare and aggressive endocrine cancers.

Understanding anti-tumor T cell fate and plasticity using dynamic perturbations

Having developed a suite of tools, including small molecule-controllable genome editing proteins, that can be used in primary human T cells for fast and reversible perturbations of target genes and proteins, we seek to understand how dynamic perturbations can reprogram T cell fate and function. Transient and traceable perturbations may enable the study of stage-specific molecular mechanisms governing T cell lineage and differentiation trajectories, as well as therapeutic opportunities leveraging in vivo delivery modalities.

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*Equal contribution

David M. Langenau, PhD

Most pediatric patients whose sarcoma or leukemia recurs will succumb to their disease. The focus of **the Langenau laboratory** is to uncover the mechanisms that drive progression and relapse in pediatric tumors with the long-term goal of identifying new drug targets and therapies to treat relapse and refractory disease.

Langenau Laboratory

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Identifying molecular pathways that drive progression and relapse in pediatric cancer

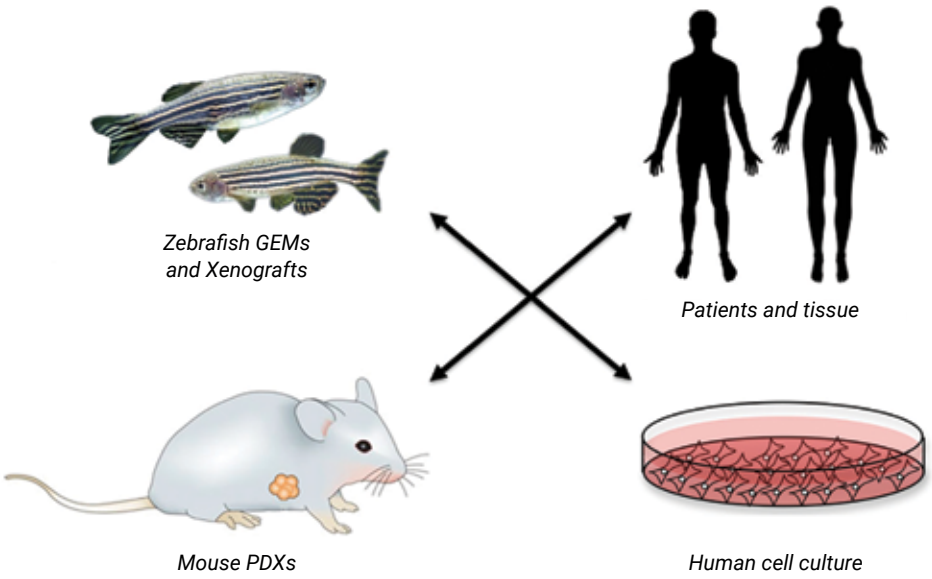
The Langenau laboratory uses zebrafish genetic models, human cell lines, patient derived xenografts, and patient samples to uncover progression and relapse mechanisms in pediatric T-cell acute lymphoblastic leukemia (T-ALL) and rhabdomyosarcoma (RMS) muscle cancer. Our work has detailed the remarkable conservation of molecular mechanisms in zebrafish and human cancer and discovered novel biology and new therapies for these diseases. For example, we identified combination Olaparib and temozolomide therapy for the treatment of RMS that is in clinical trial evaluation for RMS patients at Mass General and Dana-Farber Cancer Institute in Boston (NCT01858168).

Uncovering progression-associated driver mutations in T-cell acute lymphoblastic leukemia

T-ALL is an aggressive malignancy of thymocytes that affects thousands of children and adults in the United States each year. Recent advancements in conventional chemotherapies have improved the five year survival rate of patients with T-ALL. However, patients with relapse disease are largely unresponsive to additional therapy and have a very poor prognosis. Ultimately, 70% of children and 92% of adults will die of relapse T-ALL, underscoring the clinical imperative for identifying the molecular mechanisms that cause leukemia cells to re-emerge at relapse. Utilizing a novel zebrafish model of relapse T-ALL, large-scale transgenesis platforms, high-throughput cell transplantation, and unbiased bioinformatic approaches, we have uncovered new oncogenic drivers associated with aggression, therapy resistance and relapse. A large subset of these genes exerts important roles in regulating human T-ALL proliferation, apoptosis and response to therapy. Discovering new relapse-driving oncogenic pathways will likely identify drug targets for the treatment of T-ALL.

Cancer stem cell pathways in pediatric muscle cancer

Rhabdomyosarcoma is a common soft-tissue sarcoma of childhood and phenotypically recapitulates fetal muscle development arrested at early stages of differentiation. Our laboratory has developed transgenic zebrafish models of RMS that mimic the molecular underpinnings of human disease to discover functionally-distinct cell subpopulations, including cancer stems that drive continued tumor growth at relapse. Remarkably these same cell states are found in human disease and drive therapy resistance (Wei et al, *Nature Cancer* 2022; Wei et al., *Nature Comm* 2024). Our group has also uncovered important roles for WNT, MYOD transcription factors, the VANGL2/non-canonical WNT pathway, NOTCH, and P53 loss in driving continued RMS growth.



The Langenau lab uses a wide array of cancer models to discovery new mechansims of progression and relapse. Genetically-engineered models (GEMs) and patient-derived xenografts (PDXs).

Selected Publications:

Danielli SG, Wei Y, Dyer MA, Stewart E, Sheppard H, Wachtel M, Schäfer BW, Patel AG, **Langenau DM**. Single cell transcriptomic profiling identifies tumor-acquired and therapy-resistant cell states in pediatric rhabdomyosarcoma. *Nat Commun.* 2024;15(1):6307.

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Michael S. Lawrence, PhD

Lawrence Laboratory

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Hui Wang, PhD

The Lawrence laboratory uses computation as a powerful microscope to study how cancer develops from normal cells, and how it evolves resistance to anti-cancer drugs. When treated with targeted therapy, cancer cells often hijack the APOBEC family of DNA-mutating enzymes to generate many random DNA mutations, including resistance mutations. By studying recurrent APOBEC mutations in tumors, we discovered that a specific DNA shape called a "hairpin", where one of the strands folds back on itself, is APOBEC's favorite kind of substrate, an insight that can guide the development of APOBEC inhibitors. By blocking APOBEC, we hope to put the brakes on the evolution of resistant tumors. However, cancer cells have many other tactics for escaping therapy: for instance, they can copy oncogenes onto small highly amplified extrachromosomal DNA circles. We study these mechanisms using DNA sequencing. In other collaborations, we use ChIP-Seq to study chromatin architecture, and chemical proteomics to discover potential new "druggable" sites on proteins.

Cancer cells use APOBEC mutagenesis to evolve drug resistance

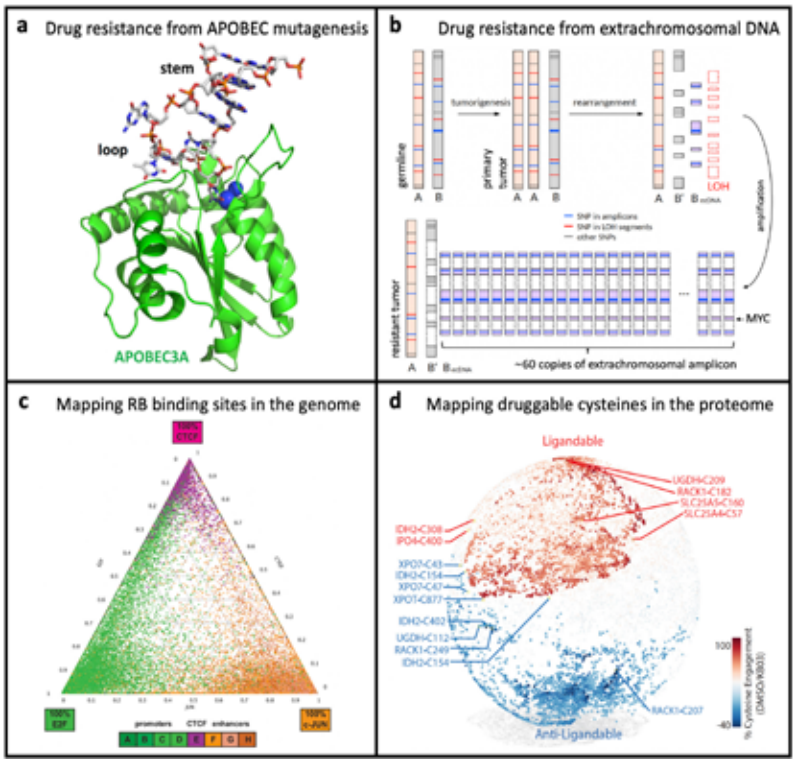
APOBEC proteins are cytidine deaminase enzymes that cause mutations throughout the genome. Over half of all human tumors show the APOBEC mutation signature. It plays a special role in the emergence of drug resistance. For instance, a lung cancer patient whose initial biopsy and clinical sequencing revealed an ALK fusion and no sign of APOBEC mutations was treated with the ALK inhibitor crizotinib and achieved a year-long remission. However, the patient relapsed, and the resistant tumor showed widespread APOBEC mutagenesis, including the known resistance mutation ALK E1210K. Treatment with brigatinib and then lorlatinib continued a cycle of remission and relapse, with new resistant clones emerging full of APOBEC mutations, and double and triple compound resistance mutations in ALK. To definitively prove the causal role of APOBEC mutagenesis (in collaboration with the Hata lab) we showed that in a cell line model, knocking out APOBEC3A slows the evolution of drug resistance, and overexpressing APOBEC3A speeds it up. We are now exploring DNA hairpins as a strategy for inhibiting APOBEC enzymes and delaying resistance.

Cancer cells make extrachromosomal DNA to evolve drug resistance

Activation of APOBEC enzymes is not the only tactic cancer cells use to evolve resistance. We recently showed (in collaboration with the Drapkin lab at UTSW) that small cell lung cancer (SCLC) can acquire cross-resistance to cisplatin, etoposide, olaparib, temozolomide, and topotecan, through amplification of the MYC oncogene on extrachromosomal DNA (ecDNA). By careful analysis of whole-genome sequencing from serial biopsies from SCLC patients before and after emergence of resistance, as well as serially derived PDX models, we mapped the precise structures of these ecDNAs and revealed how cancer cells can modulate the number of ecDNA copies they carry, to dial up and down their level of MYC expression as needed in response to treatment conditions.

Finding new roles for familiar proteins

The retinoblastoma protein (RB) was one of the first tumor suppressors to be



(a) APOBEC3A protein bound to a DNA hairpin stem-loop structure, with a cytosine base flipped out into the enzyme active site, where it will be deaminated, leading to a mutation. (b) Extra-chromosomal DNA formation mechanism, with rearrangement and amplification leading to a small circle of DNA carrying the oncogene MYC. (c) Distribution of mapped RB (retinoblastoma protein) binding sites in the genome, including where it co-binds with E2F at promoters (green), with JUN at enhancers (orange), and with CTCF at insulators (purple). (d) Proteome-wide map of cysteine reactivity, showing specific cysteines that can be liganded by small-molecule scouts (red) or show anti-ligandability (blue), possibly indicating allosteric effects.

understood. Its classic function in cells is to bind E2F-driven promoters and block the expression of genes needed for cell cycle progression and cellular proliferation. However, this textbook synopsis of RB's function has been called into question by recent studies from many groups showing complex effects of RB loss. To shed light on this situation, we mapped the landscape of RB binding sites in the genome. To our surprise, we found RB not only at promoters, but also at enhancers and insulators, suggesting it has functions beyond its classic role in suppressing proliferation genes. We are now using HiChIP and Micro-C (in collaboration with the Sanidas lab) to study how RB loss affects the 3D structure of the genome.

Finding druggable sites on proteins

Targeted anti-cancer therapies have greatly improved patient outcomes. However, only a small fraction of known cancer driver genes have been successfully targeted. Many drivers, especially tumor suppressors, have traditionally been considered "undruggable", because their highly flexible protein structures lack obvious drug-binding sites. To overcome this limitation, in project "DrugMap" with the Bar-Peled Lab, we are mapping the full landscape of druggable sites in proteins, using high-throughput mass spectrometry to identify all cysteine residues that react with small-molecule scouts. Our findings are freely available on www.drugmap.net to empower the drug-development community.

Selected Publications:

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Redirecting the adaptive immune system, particularly through T cells engineered as chimeric antigen receptor (CAR) T cells, has emerged as a groundbreaking clinical strategy for treating relapsed and refractory malignancies. This approach has shown dramatic responses and even cures in a significant subset of patients. However, most patients undergoing CAR-T cell therapy do not achieve long-lasting anti-tumor responses. **The Leick laboratory** is dedicated to understanding and overcoming the challenges associated with CAR-T cell therapy. We focus on integrating investigative knowledge of the mechanisms of response, resistance, and toxicity in CAR-T cell patients to design novel methods for enhancing the next generation of CAR-T cell therapies. Through a virtuous cycle of correlation, design, and testing in patients in the context of thoughtful clinical trials, the Leick Lab continually refines CAR-T cell therapies. By applying these findings, we aim to design CAR-T cells that not only extend and enhance patient responses but also minimize adverse effects.

Since the early days of stem cell transplants, when the graft-versus-leukemia effect was first discovered, the remarkable ability of T cells to eradicate malignant cells has been firmly established. In recent years, immune checkpoint antibodies, which block inhibitory signals to endogenous anti-cancer T cells, have emerged as a cornerstone therapy for many solid tumors by non-specifically activating the immune system. However, this approach can lead to significant collateral damage and is constrained by the natural limits of endogenous T-cell targeting machinery. Enter chimeric antigen receptor (CAR) T cell therapy — a revolutionary treatment that combines genetic engineering with novel T cell signaling modulation to target the tumor surfaceome and enhance anti-tumor responses.

The Leick lab is focused on CAR-T cell engineering and clinical translation. Although multiple CAR-T cell therapies have received FDA approval for treating lymphoid malignancies and others have shown promise in solid tumors, most patients currently treated with CAR-T cell therapy will unfortunately not be cured. Nonetheless, we believe these early successes underscore the tremendous potential of CAR-T cell therapy when developed and applied with precision and care.

Our goal is to develop safer, more effective cellular therapies that transform the lives of cancer patients.

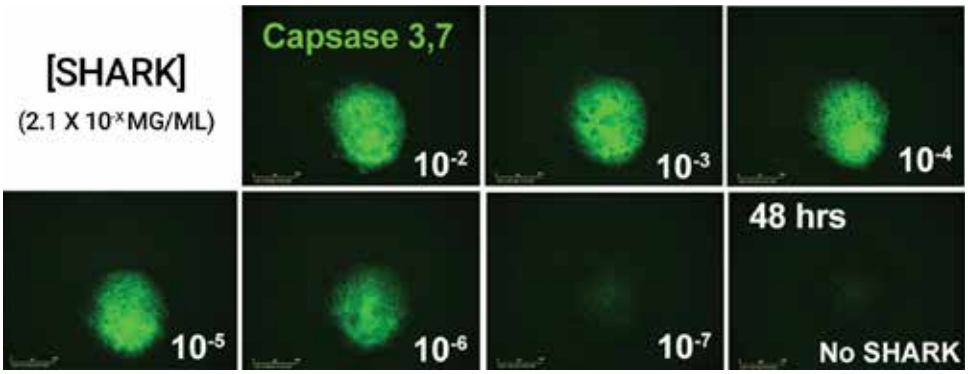
Research Focus Areas:

1. **Innovative CAR-T Cell Design**

   Our team leverages cutting-edge insights in immunology, tumor biology, and clinical strategies to develop innovative approaches for enhancing CAR-T cell efficacy and regulating toxicity. By rationally designing these therapies, we aim to improve their therapeutic potential and patient outcomes.

2. **Tumor Microenvironment Modulation**

   Suppressive factors within the tumor microenvironment can impede CAR-T cell performance. We use T cells as powerful micro-pharmacies to deliver secreted biologics that target and remodel the immunologic niche. This



Off-the-shelf SHARK CAR-T cell kill-switch inducing dose-dependent CAR-T cell apoptosis.

Photo credit Filippo Birocchi

approach engages other immune cells and augments CAR-T cell potency while avoiding systemic administration of potentially toxic agents, thus expanding the therapeutic window.

3. **Clinical Translation and Trials**

   While in vitro and in vivo models are invaluable for identifying promising CAR-T cell candidates, they cannot fully replicate the complexity of human physiology. To achieve meaningful progress, we conduct well-designed clinical trials to test innovative strategies directly in patients. Collaborating with Dr. Marcela Maus, Director of the Cellular Immunotherapy Program at MGH, and Dr. Kathleen Gallagher's immune monitoring lab, we develop assays and clinical trials that ensure safe clinical deployment and provide insights into CAR-T cell behavior, fostering a virtuous cycle of continuous improvement.

4. **Deciphering CAR-T Cell Heterogeneity**

   CAR-T cell therapy is a complex and dynamic field. Unlike traditional pharmacological compounds, CAR-T cells exhibit significant inter- and intra-patient heterogeneity, complicating the understanding of variable patient responses. By utilizing multi-omics approaches with expert collaborators, we explore the genomic, transcriptomic, and proteomic landscapes of CAR-T cells, uncovering novel insights into their mechanisms of action and failure.

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The Louissaint laboratory is interested in understanding how intrinsic genetic alterations and interactions of the lymphoma microenvironment drive lymphoma biology and determine the distinctive clinical behaviors of different lymphoma types. As part of our efforts, we aim to identify biomarkers of prognosis and responsiveness to therapy and to discover potential novel therapeutic targets that may be translated into improved outcomes for lymphoma patients. Traditionally, such investigation has been limited by the paucity of in-vitro and in-vivo models that faithfully capture the genetic and functional heterogeneity of human lymphomas. To overcome this challenge, our laboratory creates novel in-vivo patient-derived xenograft models and in-vitro primary cell models of lymphoma to investigate the role of genetic alterations, intratumoral heterogeneity, and microenvironment in lymphoma pathogenesis and to test the efficacy of specific therapeutic agents.

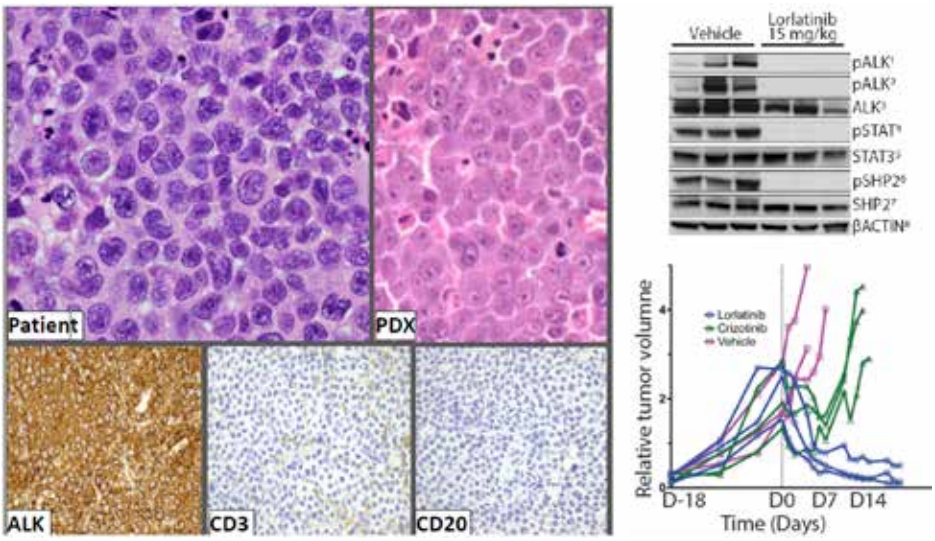
Defining novel therapeutic vulnerabilities in aggressive subtypes of large B-cell lymphoma

There are several aggressive lymphoma subtypes of B-cell lineage for which effective therapies do not exist and for which clinical trials sometimes cannot be performed due to the rarity of the diseases and the rapidity with which patients succumb to disease. Some of these lymphomas characterized by plasmablast phenotype do not respond well to standard B-cell chemotherapies and have particularly poor prognosis. These include 1) anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma (ALK-LBCL), characterized by the abnormal expression of ALK fusion protein derived from ALK rearrangement; 2) plasmablastic lymphoma (PBL); and 3) primary effusion lymphoma (PEL), which presents as pleural and/or peritoneal serous effusion in the absence of lymph node involvement. Patients who acquire these lymphoma have a dismal prognosis — often dying within two years of diagnosis after failed attempts with standard chemotherapy regimens. We recently created multiple patient-derived xenograft (PDX) models of each of these lymphomas that recapitulate the phenotypes and molecular features of the patient lymphomas. Using ALK-LBCL xenograft models, we showed for the first time that next-generation ALK inhibitors (ALKi) (alectinib and lorlatinib) are active in ALK-LBCL, while the first generation crizotinib inhibitors are not. In collaboration with clinical colleagues, we translated these findings to patients in a multi-institutional study in which advanced stage, chemotherapy refractory ALKLBCL patients were treated with alectinib followed by allogeneic transplantation, resulting in the first long-term remissions reported in this disease.

We have recently developed similar patient xenograft and xenograft-derived organoid models of ALK+ LBCL and PBL. Most recently, we have created a PDX model of PEL that retains the characteristic body fluid tropism of this lymphoma. We are currently using these models in functional studies to further understand the pathobiological mechanisms and to identify novel targetable vulnerabilities.

Unraveling the role of the tumor microenvironment in follicular lymphoma

Follicular lymphoma (FL) is the second most common non-Hodgkin lymphoma,



Efficacy of ALK inhibitors (ALKi) in patient derived xenograph (PDX) models of ALK+ Large B-cell lymphoma. The image on the left shows the histology and immunophenotype of the PDX. The Western (upper right) show activity of ALKi (Lorlatinib) on ALK phosphorylation and signaling in the PDX tumor. The figure (lower right) shows efficacy of third-generation ALKi Lorlatinib on PDX ALK+ LBCL tumor (in contrast to transient partial response to first-generation ALKi Crizotinib).

accounting for approximately one quarter of new cases worldwide. As the quintessential indolent B-cell lymphoma, FL is an incurable disease characterized by multiple relapses and frequent transformation (t-FL) to more aggressive lymphomas. Approximately 20% of patients requiring chemotherapy at diagnosis show early progression, usually associated with poor outcomes.

FL, like other indolent B-cell lymphomas, is comprised of heterogeneous population of malignant B cells within a prominent tumor microenvironment including various T cell populations, follicular dendritic cell and other stromal cell populations and some myeloid populations. Interactions between these malignant B cells and elements of tumor microenvironment are critical for FL to thrive. We aim to understand the role of these interactions in lymphoma pathogenesis, and in driving early progression of disease, with the goal of possibly targeting these mechanisms therapeutically.

A major impediment to answering these questions has been the lack of models of human disease that can recapitulate the complexity of genetic alterations and cellular interactions between FL clones and microenvironment that define these lymphomas. We are creating patient-derived ex vivo primary co-culture models of follicular lymphoma for the purpose of studying these critical cellular interactions within the tumor microenvironment. To unravel and dissect these critical interactions, we are applying single cell sequencing technologies, together with powerful new single cell resolution multi-modal spatial genomics technologies in collaboration with colleagues Vignesh Shanmugam, Fei Chen and Todd Golub. These efforts will accelerate our understanding of the interplay of genetic alterations and microenvironment in driving the biology of indolent lymphomas and drive the discovery of novel targets of these diseases.

Selected Publications:

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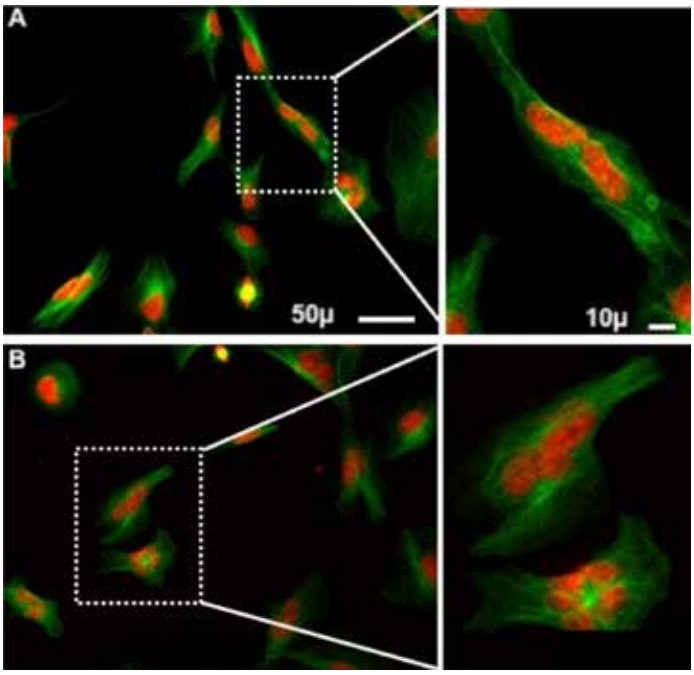
Studies to understand the molecular events governing cancer metastasis and response to drugs are heavily reliant on the contribution of alterations in the genomic DNA. Alternatively, factors independent of aberrations in the underlying DNA sequence are known to influence several developmental processes that are reinstated in cancer and have been shown to promote cancer progression, and alter drug sensitivity and resistance. These developmental processes involve changes in cell states, including a switch from an epithelial to mesenchymal state that occurs during embryogenesis as well as senescence, a process akin to aging. Changes in cell states are not binary, instead they are continuous and reversible, as such, defining their precise contribution to cancer is challenging. **The Maheswaran laboratory** is focused on developing models to define the factors that promote these cell states, their functional interactions, and how they restructure the cellular environment of the tumor and its impact on therapeutic responses and disease progression.

In a highly collaborative translational effort, we exploit a rare population of tumor cells that circulate in the blood: circulating tumor cells (CTCs). These cells harbor the entire complement of molecular information within cancers and can be used as non-invasive read outs of DNA and protein, and RNA expression in cancers in real time. We have developed assays to characterize CTCs enriched from blood to monitor therapeutic responses and disease progression in patients with metastatic cancers and also in early detection of disease in individuals at high-risk to develop cancers.

Advances in deciphering mechanisms that regulate cancer metastasis, and therapeutic responses and resistance are extensively reliant on the contribution of genomic alterations to these processes. In contrast, our understanding of the influence of cancer cell states - driven by nongenetic mechanisms that define their phenotypic plasticity - to cancer progression is less understood. Some of the challenges in this field include their context-dependent, sometimes paradoxical functions, as well as the continuum and plasticity of the transition states. Our lab is specifically focused on how epithelial-to-mesenchymal plasticity and senescence programs govern tumor progression and therapeutic responses. This includes understanding the tumor-microenvironmental factors including TGFß and hypoxia, that promote these cell states, developing models to study the intermediate transition states/plasticity and their function, as well as defining the interplay between these tumor cell states themselves and how they remodel the cellular microenvironment of the tumor and responses to various classes of drugs. We address these questions using in vitro and in vivo mouse models, patient-derived tumor tissues, and ex-vivo cultures, including those derived from circulating tumor cells (CTC) collected from patients with metastatic breast and other cancers. Our goal is to exploit the molecular vulnerability and druggability of these states to curtail cancer progression and improve therapeutic responses.



Photomicrographs of early (A) and late (B) senescent cells induced by TGFß under normoxia and hypoxia, respectively. Right panels show high-magnification images of binucleated early senescent and multinucleated late senescent cells within the highlighted area.

The collaborative translational work in the lab involves the enrichment and characterization of circulating tumor cells (CTCs) to monitor therapeutic responses of the metastatic disease and for early detection of cancer. CTCs represent population of cells shed into the blood by primary and metastatic cancers. They are extremely rare and estimated to be present at a frequency of one in a billion cells. They are unique blood-based biomarkers as they can provide protein, transcriptomic and genomic readouts non-invasively in real time. The current projects involve interrogating CTCs for expression of proteins targeted by antibody-drug conjugates, a new class of immuno-therapeutics enabling targeted delivery of drugs to the tissue of interest, and monitoring tumor responses and evolution over time. Our study of CTCs also extends to early detection of cancer by evaluating the presence of CTCs in larger volumes of blood with an initial focus on patients at high risk to develop cancer.

Our integrated approach combining mechanistic studies of cellular plasticity with translational CTC research positions us to make meaningful contributions to cancer biology and clinical care. Through collaborative efforts spanning basic research and clinical applications, we aim to transform our understanding of cancer progression and ultimately improve patient outcomes through more precise, targeted therapeutic interventions.

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Mishra A, Abelman R, Cunneely Q, Putaturo V, Deshpande AA, Bell R, Seider EM, Xu KH, Shan M, Kelly J, Huang SB, Gopinathan KA, Kikkeri K, Edd JF, Walsh J, Dai CS, Ellisen L, Ting DT, Nieman L, Toner M, Bardia A, Haber DA, **Maheswaran S**. Epitope expression persists in circulating tumor cells as breast cancers acquire resistance to antibody drug conjugates. *bioRxiv*. 2025 Apr 3:2025.04.02.646822.

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Dubash TD, Bardia A, Chirn B, Reeves BA, LiCausi JA, Burr R, Wittner BS, Rai S, Patel H, Bihani T, Arlt H, Bidard FC, Kaklamani VG, Aftimos P, Cortés J, Scartoni S, Fiascarelli A, Binaschi M, Habboubi N, Iafrate AJ, Toner M, Haber DA, **Maheswaran S**. Modeling the novel SERD elacestrant in cultured fulvestrant-refractory HR-positive breast circulating tumor cells. *Breast Cancer Res Treat*. 2023 Aug;201(1):43-56.

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The Manguso laboratory is working to improve the efficacy of cancer immunotherapy. We use a range of approaches including mouse models, functional genomics, cellular immunology, and single-cell profiling to understand how cancers evade the immune system. Our lab has pioneered the use of *in vivo* genetic screens with CRISPR to identify new immunotherapy targets and resistance mechanisms. Using these approaches, we identified the tyrosine phosphatase PTPN2, a critical regulator of immunotherapy sensitivity in tumor cells. We also identified the dsRNA-editing enzyme ADAR1 as a checkpoint that regulates the sensing of self-dsRNA by tumor cells. Our results indicate that there are dozens of ways that cancers can be targeted by the immune system, and we are working to understand the new mechanisms revealed by our studies. In the long term, these approaches will enable a new understanding of how the immune system interacts with cancerous tissue and how the interaction can be manipulated to destroy tumors.

Over the last decade, critical discoveries in immunology and cancer biology have revealed how tumors are shaped by the immune system and how they evolve to evade it. We now know that disrupting immune checkpoints such as CTLA-4 and PD-1/PD-L1 can lead to T cell-mediated elimination of tumors. However, there is still a critical unmet need, as the vast majority of patients with cancer do not benefit from current immunotherapies. Our most pressing challenge is to discover the next generation of immunotherapies that can bring clinical benefit to the majority of patients.

To discover immunotherapy targets and resistance mechanisms in high throughput, we have developed an *in vivo*, CRISPR-based genetic screening system to identify genes that regulate tumor cell sensitivity to immunotherapy (Manguso et al, *Nature* 2017). We genetically modify mouse cancer cell lines that can be transplanted into animals and used as immunotherapy models. After delivery of Cas9 and libraries of single guide RNAs (sgRNAs), we implant pools of modified tumor cells into animals that are treated with immunotherapy. In a single experiment we can determine genes that, when deleted, increase or decrease sensitivity to immunotherapy (Figure 1). This strategy has enabled the rapid and simultaneous identification of new targets and resistance mechanisms that are potent regulators of anti-tumor immunity.

This powerful, unbiased discovery system allows us to identify targets and resistance mechanisms with no previously identified roles in immunotherapy. Three examples illustrate the power of this system for discovery: 1) we found that deletion of the phosphatase PTPN2 increased tumor cell sensitivity to immunotherapy; 2) we discovered that the non-classical MHC-I gene HT-T23/Qa-1 (HLA-E) is a major immune checkpoint that limits anti-tumor immunity by T cells and NK cells; 3) our screens identified that deletion of ADAR1, an adenosine deaminase, enhances recognition of endogenous dsRNA by cytosolic pattern recognition receptors and can overcome resistance to immunotherapy caused by loss of antigen presentation (Ishizuka & Manguso et al, *Nature* 2018).

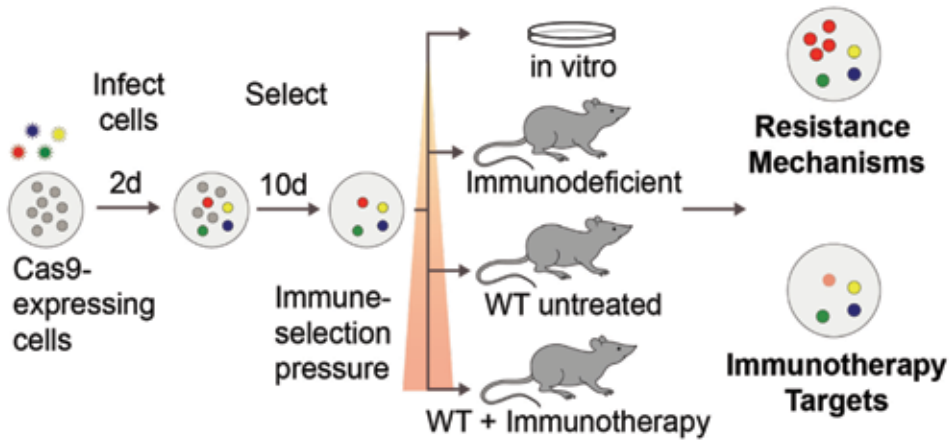

Diagram of in vivo CRISPR screening system. Pools of Cas9-expressing, sgRNA library transduced tumor cells are implanted into either wild-type or immunocompromised mice. After 2 weeks, tumors are harvested and genomic DNA is extracted from tumor tissue. Next generation sequencing of the sgRNA library is used to identify resistance mechanisms or immunotherapy targets.

More recently, in collaboration with Calico Life Sciences and Abbvie, we discovered and characterized ABBV-CLS-484 (AC484), a first-in-class, orally bioavailable, potent PTPN2 and PTPN1 active-site inhibitor, now in early stage clinical trials. Our work in preclinical models showed that the inhibitor works both as a monotherapy and in combination with checkpoint blockade, acting to simultaneously enhance immune cell functions while also increasing cancer cell sensitivity to immune cell killing (Baumgartner & Ebrahimi-Nik et al, *Nature* 2023).

We have demonstrated that in vivo CRISPR screens are a powerful way to discover new targets and probe the interaction of tumor cells with the host immune system. We can now broadly apply these genetic tools to advance our understanding of how immunotherapy works, why it may fail, and how we can improve it. Ongoing projects in the lab include:

1. Discover novel immunotherapy targets and mechanisms of resistance across several well-characterized mouse cancer models
2. Use functional genomics approaches to improve the efficacy of cell-based immunotherapies such as CAR T cell therapy.
3. Investigate the mechanisms by which PTPN2 inhibition improves anti-tumor immune responses in both animal models and cancer patients.

These projects will define new ways to generate anti-tumor immune responses, reveal pathways that can be targeted to enhance these responses across cancer types, and anticipate and overcome the mechanisms by which tumors will become resistant. More broadly, these studies will improve our understanding of how tumors evolve under the selective pressure of immune surveillance and enable the development of more effective therapeutics.

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* Denotes equal contribution

Marcela V. Maus, MD, PhD

The immune system has become a powerful tool in the fight against cancer. In particular, T cells of the immune system are potent pathogen killers and maintain memory to provide long-term protection for many years. Therefore, using T cells as a cancer treatment has the potential to induce long-term, durable remissions, and perhaps even cure some patients. **The Maus laboratory** uses genetic engineering techniques to re-direct T cells to find and kill tumor cells, while sparing healthy tissues. We aim to develop new ways to design and re-direct T cells to target tumors, use T cells as delivery vehicles for other drugs, use drugs to help T cells work against tumors, and understand how T cells can work as "living drugs" to treat patients with cancer. We achieve these goals through translational research, initiating clinical trials with our T cell designs, and learning from how these T cells function in patients.

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Our laboratory focuses on T cell biology and T cell engineering. We design chimeric antigen receptors (CARs) to re-direct T cells to specific antigens. This re-direction has shown great promise in the clinical setting for B cell malignancies, such as in leukemia and lymphoma. However, application of this therapy to other cancers has not been as successful. We are working to make CAR-T cells safe and effective across tumor types.

The goal of the Maus lab is to design and evaluate next-generation genetically-modified T cells as immunotherapy for patients with cancer.

The Mass General Cellular Immunotherapy Program, directed by Dr. Maus, aims to generate a pipeline of genetically engineered CAR-T cells to use as "living drugs" in patients with cancer. The program is composed of a "research and discovery" arm that designs and examines the novel CAR-T cells, "a regulatory/translational" arm to test the CAR-T cells in human subjects, and a "reverse translation" arm to learn how the CAR-T cells engraft, persist, and function following infusion into patients. From this knowledge, we then design and evaluate the next generation of CAR-T cells that are even more likely to eliminate their target tumor.

Specifically, the collective goals of the Maus lab are to:

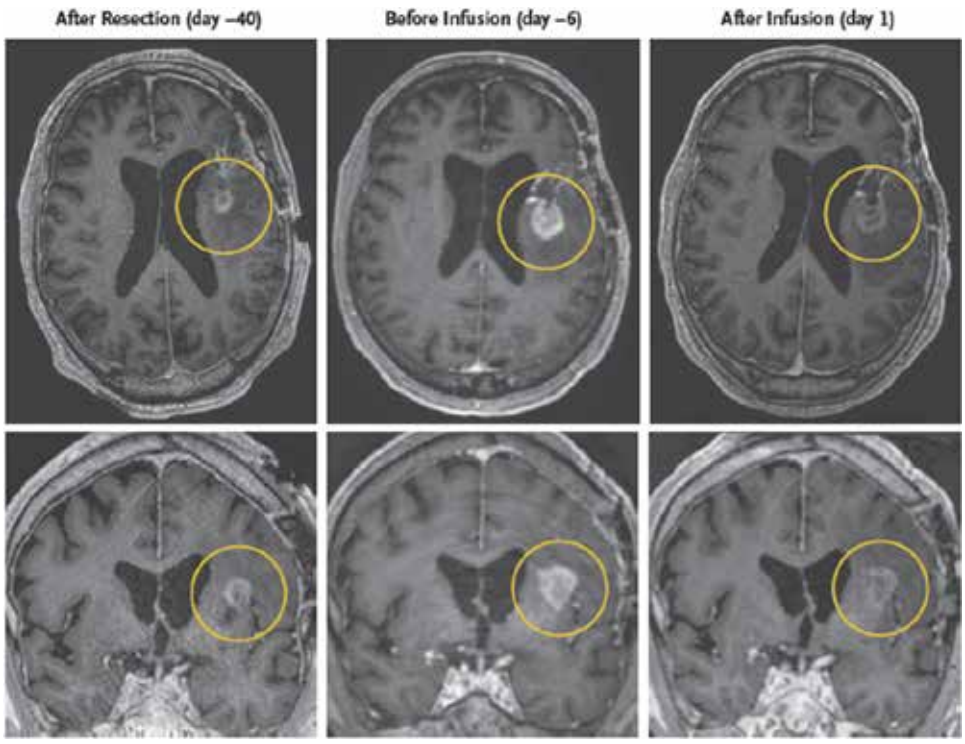
1. *Identify novel target antigens and engineering strategies to improve CAR-T cell recognition of target cells.*

   We are developing antigen receptors and secreted molecules to target new tumor antigens and/or multiple antigens at a time on tumor cells with the aim of improving the elimination of heterogenous tumor cells and preventing antigen-negative relapse while decreasing the risk of targeting healthy cells. In addition to targeting cancer, we are also developing CAR-T cells to treat autoimmune diseases.

2. *Combine CAR-T cells with other drugs to sensitize tumors to T cell-mediated killing, potentiate T cell function, or improve safety.*

   Many of the small molecule drugs and antibodies used in the clinic exert their effects on signaling pathways in tumor cells, T cells, and other immune cells. We aim to discover synergistic drug/T cell combinations to increase safety and efficacy, and use genetic engineering tools to confer specific drug sensitivity, resistance, or enhanced molecular switches.

3. *Use in vivo screens to rapidly identify CAR-T cell designs that improve efficacy*



CARv3-TEAM-E T Cells induce rapid and dramatic regression of a patient's glioblastoma on radiographic imaging. Choi et al ***New England Journal of Medicine*** *2024*

We have predicted several modifications to CAR-T cells that could improve their efficacy, but testing them one at a time is time consuming. To speed up this process, we have developed an in vivo screening technique where a pool of CAR T cells with different modifications is injected into mice with tumors and the one(s) that best infiltrate the tumor and expand are identified over time. Doing this in vivo increases our chances of identifying designs that will work in patients.

4. *Understand how CAR-T cells are functioning in patients.*

   After translating our novel CAR-T cells from the lab to the clinic, we carefully follow how CAR-T cells expand, persist, and/or change phenotype over time in patients. We then correlate this data with patient outcomes and changes in the tumor. Based on these findings, we go back to the lab and redesign CAR-T cells to be more effective in patients. This area of research is led by Dr. Kathleen Gallagher, Director of our Immune Monitoring Laboratory.

5. *Improve the CAR-T cell manufacturing processes.*

   Variations in CAR-T cell manufacturing regulate their activity in patients, and novel CAR-T cell designs require different manufacturing processes compared to CAR-T cells currently approved for patients. Our process development lab is working to streamline the manufacturing of novel CAR-T cells while also striving to make CAR-T cells more readily available to patients. This area of research is led by Dr. Magdi Elsallab, Director of the Process Development Lab.

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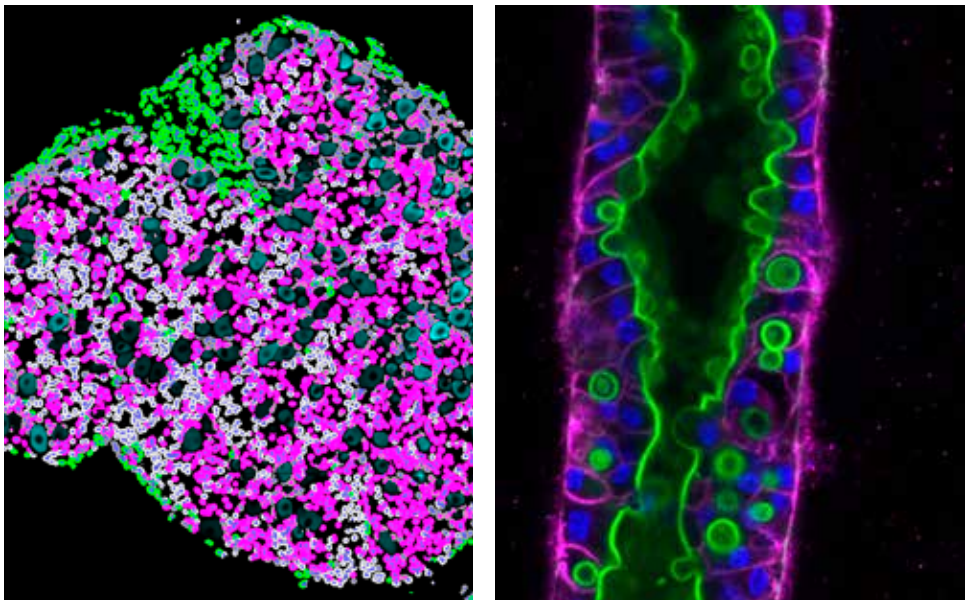
The McClatchey laboratory focuses on understanding how cells spatially organize their outer surface to build and regenerate functioning tissues and how defects in that organization can drive tumor formation. Using in vivo and physiologic 3D models and quantitative imaging, we have uncovered important ways cells spatially coordinate receptor tyrosine kinase trafficking and signaling with cell-cell adhesion and actomyosin organization during tissue morphogenesis. Our studies have focused on the process of de novo lumen formation that drives morphogenesis of tubular bile ducts and other organs, and on the polarization and plasticity of Schwann cells in the peripheral nervous system. In each case, we uncovered unexpected ways that tumor-causing mutations hijack the mechanisms that normally spatially pattern the cell surface to drive tumor initiation and heterogeneity. Our research establishes new models and therapeutic avenues for both biliary (cholangiocarcinoma) and Schwann cell (schwannoma) tumors and highlights the value of convergent studies of morphogenesis and tumorigenesis.

Convergent studies of morphogenesis and tumorigenesis

The vast array of forms and functions exhibited by different cell types is enabled by the intrinsic organization of specialized domains within the cell cortex such as the leading edge of migratory cells, immunological synapse, and microvillus-studded apical surfaces of epithelial cells. The spatial organization of individual cells, in turn, governs their organization into three-dimensional structures that carry out organ-specific functions, such as the tubular networks of the liver, kidney, breast and lung and the heterotypic axoglial junction of peripheral nerves. The spatial organization of cortical domains in individual cells and tissues provides an essential layer of regulation to both biochemical and adhesive receptors on the cell surface. Alterations in cellular architecture are the earliest evidence of a developing tumor and signatures of tumor invasion and metastasis.

The overarching goal of my laboratory is to understand how the dynamic organization of the outer cell surface contributes to morphogenesis and tumorigenesis. We have focused particular attention on the liver and peripheral nervous system. For example, we discovered that biliary epithelial cells self-organize into a tubular network during development via the de novo formation, extension and interconnection of apical lumens. Using a physiologic and quantitative 3D model we found that FGFR signaling is important for biliary morphogenesis, and that FGFR2 mutants that are common drivers of cholangiocarcinoma disrupt this process. Unexpectedly, we found that the trafficking and signaling of normal FGFR2 and phenotypic consequences of FGFR2 mutants are governed by the epithelial state of the cell and nature of the mutation, highlighting the value of using mutants as tools to study morphogenesis and of physiological models to study tumor-causing mutants.



Left: Digital image analysis highlights intra-tumoral heterogeneity of autocrine ligand production in a dorsal root ganglia from a six-month old Postn-Cre/Nf2flox/flox mouse. The Highplex FL algorithm in HALO imaging software was used to achieve single cell segmentation and detect neuregulin-1 positive (magenta), phospho-S6 positive (green), or neuregulin-1/phospho-S6 positive (gray) cells (in collaboration with the laboratory of Dr. Shannon Stott). Image credit: Christine-Chiasson MacKenzie, PhD

Right: Confocal image of a three dimensional cell culture model of biliary tube formation labelled for E-cadherin (green) and actin (magenta). Image credit: Evan O'Loughlin, PhD

Related studies center on a longstanding focus on the role of the membrane:cytoskeleton linking neurofibromatosis type 2 (NF2) tumor suppressor, Merlin, and closely related ERM proteins (Ezrin, Radixin and Moesin) in organizing the Schwann cell surface, We found that in the absence of Merlin, Schwann cells exhibit unstable polarity, which, in turn, yields intrinsic heterogeneity in an otherwise genetically 'cold' (homogeneous) tumor. Through quantitative imaging in mouse models we created an initial atlas of how schwannoma heterogeneity develops, evolves and responds to drug treatment. These studies have provided desperately needed insight into the histological, clinical and therapeutic heterogeneity exhibited by schwannomas and a framework for overcoming it – something desperately needed for NF2 patients who often develop multiple debilitating spinal and cranial schwannomas.

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O'Loughlin E, Zhang Y, Chiasson-MacKenzie C, Dave P, Rheinbay E, Stott S, **McClatchey AI**. Distinct phenotypic consequences of cholangiocarcinoma-associated FGFR2 alterations depend on epithelial maturity. *bioRxiv*, 10.1101/2024.08.30.610360, 2024.

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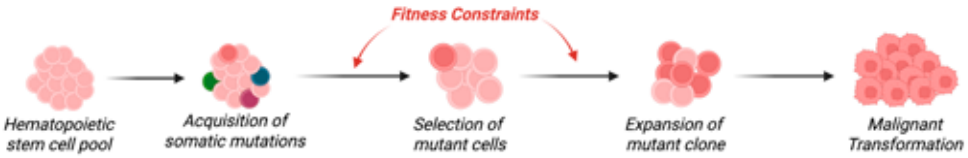
Ruxin Yang, MS

The Miller laboratory seeks to understand how somatic mutations in blood cells arise and drive abnormal cellular states including the development of blood cancers such as leukemia. We incorporate orthogonal tools including human genetics, mouse models, cellular assays, genetic screens, and molecular techniques to identify genes that are recurrently altered in blood disorders and determine how these alterations alter cellular programs such as self-renewal, response to DNA damage, and inflammation. We are particularly interested in using these tools to understand (1) the role of *PPM1D*, a gene that regulates the DNA Damage Response, in blood cell development (2) how mutations in *PPM1D* allow cells to be more resistant to chemotherapy and (3) how mutations in blood cells more generally influence inflammatory programs and pathophysiologic processes across multiple tissue-types. We seek to use our understanding of this biology to develop new therapies for the prevention and treatment of blood cancers.

Over the lifespan of an organism, somatic mutations arise in stem cells in many organs, some of which confer a competitive survival or growth advantage to the mutant cells. In such cases, a clonally selected population emerges in which additional mutational events can lead to malignant transformation and the development of cancer. This is particularly true in the blood system where mutations can drive selection of a non-malignant population, so called clonal hematopoiesis (CH), with subsequent mutational events leading to the development of blood cancers including myeloid neoplasms such as myeloproliferative neoplasms, myelodysplastic syndrome (MDS), and acute myeloid leukemia (AML). We believe that understanding the molecular mechanisms by which mutations arise in hematopoietic cells and drive neoplastic transformation can highlight novel therapeutic opportunities for the treatment of blood cancers, particularly MDS and AML.

DNA sequencing studies have informed our understanding of the genetic landscape of many hematologic malignancies, including MDS and AML. Further efforts have catalogued the genes that are mutated in CH by identifying somatic alterations present in the peripheral blood of individuals without blood cancers. Taken together, these human genetic studies can inform the timing and context in which various mutations arise, and in so doing identify critical mediators of both normal hematopoiesis and malignancy. We utilize these studies to define testable hypotheses in the lab, the results of which can further inform clinical decision-making.

Our work has largely focused on mutations in the gene *PPM1D*. Using selected patient cohorts, we have found that individuals who have received cytotoxic therapy (chemotherapy or radiation) are significantly more likely to harbor activating mutations in *PPM1D*, in the form of CH or frank malignancy (MDS or AML). We now know that these mutations, which arise in hematopoietic stem cells, lead to increased levels of *PPM1D* protein via impaired proteasomal degradation. This in turn allows *PPM1D* to suppress the DNA damage response and P53 activation more effectively, thereby allowing *PPM1D*-mutant



A model for clonal evolution in the hematopoietic system. As we age, somatic mutations accumulate in our hematopoietic stem cells, the vast majority of which confer no biological activity. However, in the presence of various stresses on the bone marrow, a fitness constraint arises that drives selection of mutant cells that have a competitive advantage relative to wildtype cells. Further selection may result in the outgrowth of the mutant clonal population which we commonly refer to as clonal hematopoiesis, and subsequent genetic alterations can result in malignant transformation.

cells to have a survival advantage relative to unmutated cells in the presence of cytotoxic stress. We now seek to more deeply characterize the biological processes driving these observations using novel genetically engineered mouse models, functional genetic techniques, and biochemical assays. We hypothesize that defining the role of *PPM1D* in normal and malignant hematopoiesis will both drive our efforts to therapeutically target *PPM1D* in numerous oncologic contexts, and more broadly inform our understanding of the DNA damage response in normal and cancerous cells. This is particularly important in individuals who have therapy-related cancers that tend to be highly resistant to our standard therapies and have very poor outcomes.

We also are interested in understanding how CH mutations drive aberrant inflammatory states. Numerous groups have shown that individuals with CH have a greater risk of adverse cardiovascular outcomes, via enhanced inflammatory programs within mature, mutant immune cells. Using analogous approaches, we found that individuals with CH are more likely to have chronic obstructive pulmonary disease (COPD), particularly severe forms, and that mice with hematopoietic loss of Tet2, a gene commonly mutated in CH, have enhanced pulmonary emphysema in numerous models, akin to what is seen in human COPD. We now seek to understand which mutant blood cell types and the specific molecular pathways that drive this enhanced lung inflammation. We believe that a deep understanding of the link between CH and COPD will define new therapeutic opportunities to treat inflammatory disease of the lung and beyond.

Taken together, our lab seeks to leverage observations from human genetic studies to make clinically meaningful biological insights with the goal of developing new therapies to improve the outcome of our patients with hematologic malignancies.

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Gibson CJ, Fell G, Sella T, Sperling AS, Snow C, Rosenberg SM, Kirkner G, Patel A, Dillon D, Bick AG, Neuberg D, Partridge AH, **Miller PG**. Clonal Hematopoiesis in Young Women Treated for Breast Cancer. *Clin Cancer Res.* 2023 Jul 5;29(13):2551-2558.

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*Denotes equal contribution

Avanish Mishra, PhD

Mishra Laboratory

Avanish Mishra, PhD

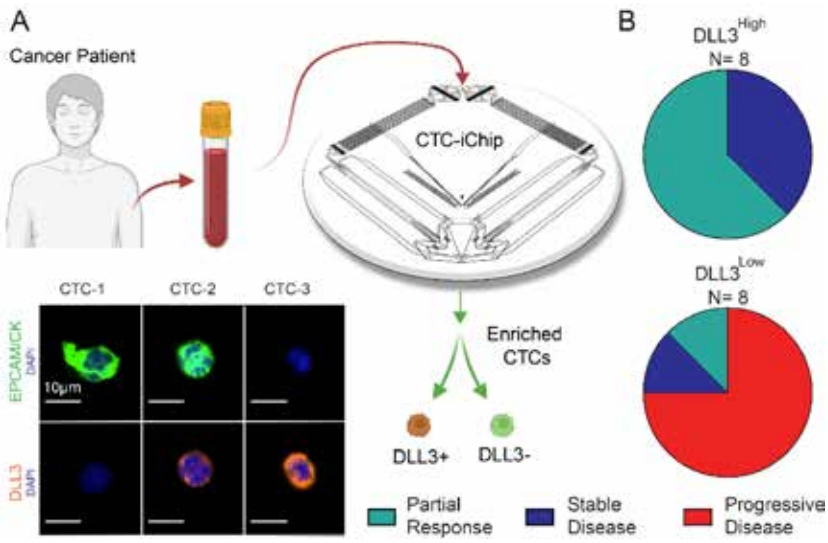
In **the Mishra laboratory**, we develop bioengineering approaches for cancer diagnostics, monitoring, and cell therapy manufacturing. Specifically, we focus on two research directions: 1) the application of large-volume microfluidics for liquid biopsy of cancer cells from blood, pleural, and peritoneal fluids, and 2) to develop cell-therapy-on-a-chip platforms that can perform all steps of cell therapy manufacturing in a single functionally closed microfluidic device. Driven by fundamental flow physics, we are focused on developing advanced microfluidic tools for cell sorting and manipulation. We operate at an intersection of engineering, microfluidics, biology, and translational medicine. Our work is clinically driven and grounded in the belief that microfluidic technologies can be harnessed to process large volumes of complex clinical fluids, advancing therapeutics and diagnostics.

Tumor-cell based liquid biopsies have emerged as a promising tool for cancer diagnostics, treatment selection, and response monitoring. Intact tumor cells provide the full complement of analytes, including DNA, RNA, proteins, and metabolic markers. However, these cells are often extremely rare and exist in large sample volumes. For instance, clinical biofluids, like blood products, require large sampling volumes of tens to hundreds of milliliters, where tumor cells can be as rare as 1 in 50 million nucleated cells. We leverage the precision and controllability of microfluidics, enabled by semiconductor manufacturing techniques, to uncover viable and untouched rare cells at high cellular throughputs (100 million cells/min).

Single-cell analysis of CTCs for guiding targeted therapies

Over the last decade, a host of targeted cancer therapies (such as Bispecific T Cell Engagers (BiTEs) and Antibody Drug Conjugates (ADCs)) have transformed cancer treatment. These therapies rely on a cytotoxic payload coupled to a tumor cell-specific target antibody (ADCs) or a bispecific antibody that recruits cytotoxic T cells to destroy the tumor (BiTE). Despite the remarkable effectiveness of these therapies, a great number of patients don't respond, exhibiting de novo resistance or acquiring drug resistance after only a few weeks of therapy. Thus, two critical challenges arise: 1) how to identify patients who are likely to respond to a targeted therapy? 2) Given a multitude of ADCs and BiTEs, how to select an ideal therapy or combinations thereof?

By combining microfluidic isolation of circulating tumor cells (CTCs) with quantitative single-cell imaging analysis, we are developing techniques for quantifying the expression of tumor epitopes targeted by BiTEs or ADCs. The relative ease of non-invasive blood-based sampling, together with technical improvements in processing and imaging CTCs, is allowing us to use CTCs as a real-time biomarker for guiding and selecting these therapies. In a prospective cohort of 16 small-cell lung cancer (SCLC) patients, we showed that pretreatment DLL3 expression in CTCs predicts response to DLL3 BiTE therapy (tarlatamab) with 80% sensitivity and 100% specificity. Our finding that CTC expression of DLL3 is predictive of clinical response in advanced SCLC offers a path toward patient stratification for this potentially effective treatment. In the future, longitudinal monitoring using CTCs will help us elucidate the possible mechanisms of resistance, guiding the development of more potent ADCs and BiTEs.



CTC enrichment and phenotypic classification in patient samples. (A) Schematic illustrating the processing of whole blood samples from small cell lung cancer (SCLC) patients receiving tarlatamab using the CTC-iChip microfluidic platform. (B) Representative fluorescence microscopy images of CTCs stained with Epithelial markers and DLL3 (BiTE Target). (C) A Venn diagram shows the fraction of patients exhibiting partial response (PR), progressive disease (PD), or stable disease (SD) upon tarlatamab treatment across DLL3^{Low} CTCs (<25%) or DLL3^{High} CTCs (>25%) at baseline. All the patients with DLL3^{High} CTCs respond to therapy.

Comprehensive tumor-cell-based liquid biopsy

CTCs are extremely rare and current technologies cannot process the blood volumes required to isolate a sufficient number of tumor cells for in-depth multiomic assays. We developed a high-throughput microfluidic platform utilizing high-flow channels and amplification of cell sorting forces through magnetic lenses for processing concentrated large-volume blood products. In collaboration with the Haber, Maheswaran, and Toner labs, this technology has been applied to analyze patient-derived blood products, screening leukapheresis products from patients with metastatic cancer, with a median yield of 2,799 CTCs purified per patient. Isolation of 100-fold more CTCs from individual patients enables the characterization of their morphological and molecular heterogeneity, including cell size and RNA expression. It also allows robust detection of gene copy number variation, a definitive cancer marker with potential diagnostic applications. High-volume microfluidic enrichment of CTCs constitutes a new dimension in liquid biopsies.

Microfluidic devices for cell and gene therapy manufacturing

Cellular therapies based on the ex vivo editing of hematopoietic stem cells or immune T cells have emerged as a transformative disease-modifying option for treating various diseases such as Sickle Cell Disease and hematologic cancers. In its current form, the cell therapy manufacturing process involves obtaining mononuclear cells via leukapheresis, shipping the product to a central manufacturing facility, isolation of target cells, activation, transduction, expansion, cryopreservation, and infusion of cells into the patient. The rapid increase in demand for cellular therapies has strained manufacturers, putting patients at risk of progressing while waiting for manufacturing slots. The current autologous cell therapy manufacturing paradigm is built around conventional lab technology, distributed in numerous machines and components, making it manually intensive, highly expensive, and inefficient to scale. To address these challenges, we are building a platform technology termed cell-therapy-on-a-chip that can perform all steps of cell therapy manufacturing in a single microfluidic chip in an automated manner.

Selected Publications:

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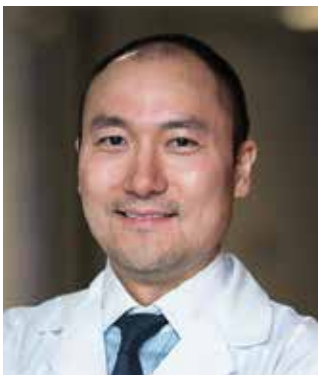
David T. Miyamoto, MD, PhD



Miyamoto Laboratory

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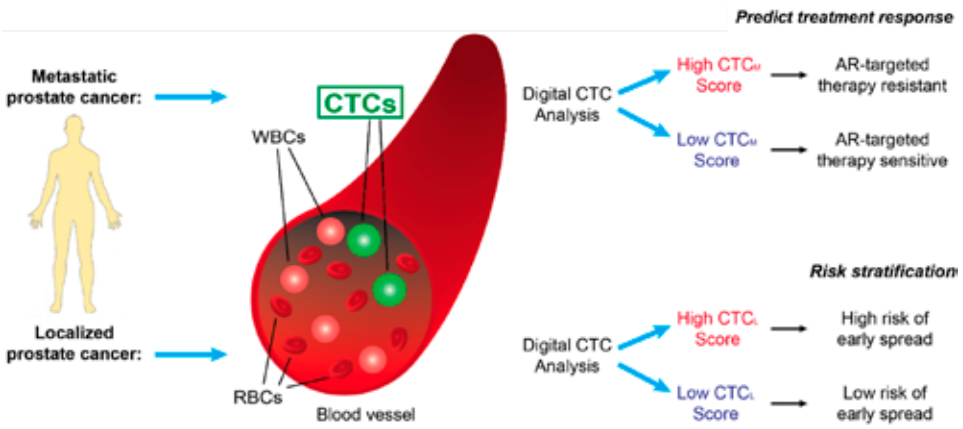
The Miyamoto laboratory focuses on the discovery and development of novel biomarkers to guide the personalized treatment of patients with prostate and bladder cancer. We analyze molecular profiles of tumor biopsies as well as circulating tumors cells (CTCs) in the blood that can be sampled non-invasively and repeatedly. By studying these patient-derived specimens, we have identified new molecular predictors of response to therapy and potential mechanisms of treatment resistance. Our overall aim is to develop tools for "real-time precision medicine" to probe the molecular signatures of cancers as they evolve over time, and to guide the rational selection of appropriate therapies for each individual patient with cancer.

The mission of our translational research laboratory is to discover and develop molecular biomarkers that inform clinical decisions in the management of patients with genitourinary malignancies. We aim to develop circulating and tissue-based biomarkers in a variety of clinical contexts to actualize the concept "real-time precision medicine," integrating genomic analyses of liquid and tissue biopsies to guide the personalized care of patients with genitourinary malignancies.

Prostate cancer is the most common cancer in men and the second leading cause of cancer-related death in men. There is a critical unmet need for predictive biomarkers to guide the rational selection of appropriate treatment options for each patient with prostate cancer in settings ranging from localized to metastatic disease. A major focus of our laboratory is the investigation of circulating tumors cells (CTCs), which are rare cancer cells shed by primary and metastatic tumors into the peripheral blood circulation. CTCs represent a type of "liquid biopsy" that may be performed repeatedly and non-invasively to monitor treatment efficacy and study tumor evolution during therapy. As part of a collaborative, multidisciplinary team at the MGB Cancer Institute, we have developed novel molecular assays using microfluidic technologies to isolate and analyze CTCs from cancer patients. Our recent studies include the use of CTC expression profiling to interrogate signaling pathways and derive CTC RNA signatures that predict resistance to androgen receptor (AR)-targeted therapy in metastatic cancer and early dissemination in localized cancer. Ongoing projects include the development of CTC molecular signatures to predict clinical outcomes after radioligand therapy as well as novel prostate cancer therapies currently in Phase 1/2 clinical trials. Another focus is the development of novel tissue-based biomarkers. We utilize technologies including next-generation sequencing and RNA in situ hybridization (RNA-ISH) to evaluate prognostic and predictive molecular signatures in limited quantities of archival prostate tumor tissues from clinical trials or carefully selected clinical cohorts. Our ongoing efforts are directed at correlating molecular findings with clinical outcomes to identify novel biomarkers predictive of treatment response that can be useful in the clinic.

Bladder cancer cancer is the fifth most common cancer in the US, causing 18,000 deaths per year. Muscle-invasive bladder cancer has a high propensity for metastasis



Potential clinical applications of digital CTC analysis in metastatic and localized prostate cancer. AR, androgen receptor; CTC, circulating tumor cell; LN, lymph node; RBC, red blood cell; SVI, seminal vesicle invasion; WBC, white blood cell (adapted from Miyamoto et al. Cancer Discovery 2018).

and requires aggressive treatment with either radical cystectomy or bladder-sparing trimodality therapy (transurethral tumor resection followed by a combination of chemotherapy and radiotherapy). However, the decision regarding which treatment to pursue is often made based on arbitrary factors including patient or physician preference. There is an urgent unmet need for molecular biomarkers to guide patients towards the most appropriate therapy based on the biology of their tumor. We have performed whole transcriptome gene expression profiling of bladder tumors from patients treated with trimodality therapy and identified immune and stromal molecular signatures predictive of outcomes after chemoradiation. More recently, we used whole exome sequencing to reveal that mutations in DNA damage response genes are associated with sensitivity to chemoradiation therapy, including *ERCC2*, a DNA helicase in the nucleotide excision repair pathway. Ongoing projects include the development of CTC and circulating tumor DNA (ctDNA) biomarkers to predict outcomes and monitor for minimal residual disease after bladder cancer therapy. We are currently evaluating these and other candidate biomarkers as predictors of treatment response in prospective clinical trials and carefully defined retrospective clinical cohorts.

Selected Publications:

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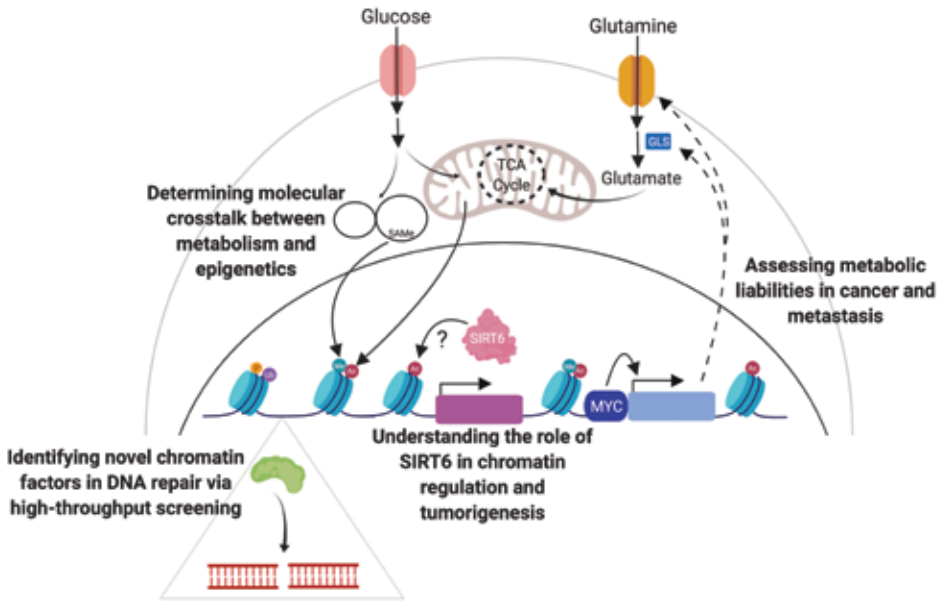
Research in **the Mostoslavsky laboratory** focuses on the crosstalk between chromatin dynamics and cellular metabolism. Most of our previous work involves the Sir2 mammalian homolog known as SIRT6, an enzyme that plays a role in compacting the DNA scaffolding structure known as chromatin. Using a combination of in vitro and in vivo transgenic mice, our research indicates that SIRT6 modulates glucose metabolism and DNA repair and functions as a strong tumor suppressor gene. More recently, we have expanded our work to understand roles for metabolic heterogeneity in modulating chromatin dynamics and how cancer cells adapt to specific nutrient stressors. In particular, we have started to explore the unique adaptations of metastatic cells, and how they manage to set and grow in a new niche environment. We have found that they do so mainly through non-genetic adaptations, and we have identified novel genes uniquely upregulated as drivers of metastatic disease, and strikingly, inhibition of these genes completely halted metastatic growth in our animal models. We are currently exploring the molecular mechanisms by which these genes drive metastatic outgrowth.

DNA and histones are arranged in the nucleus in a highly condensed structure known as chromatin. Cellular processes that unwind the double helix—such as transcription, replication, and DNA repair—have to overcome this natural barrier to DNA accessibility.

Multicellular organisms also need to control their use of cellular energy stores. Nutrient metabolism plays a crucial role in organismal homeostasis, influencing energy consumption, cell proliferation, stress resistance, and lifespan. Defective glucose utilization causes numerous diseases ranging from diabetes to an increased tendency to develop tumors. In order to respond appropriately to changes in energy status, cells need a finely tuned system to modulate chromatin dynamics and to respond to metabolic cues. Reciprocally, chromatin changes necessary for cellular functions need to be coupled to metabolic adaptations.

Our lab is interested in understanding the influence of chromatin on nuclear processes (gene transcription, DNA recombination, and DNA repair) and the relationship between chromatin dynamics and the metabolic adaptation of cells. One of our interests is studying a group of proteins called SIRTs, the mammalian homologues of the yeast Sir2. In particular, our work has focused on the mammalian Sir2 homologue, SIRT6. In past years, we identified SIRT6 as a key modulator of metabolism, functioning as a histone H3K9 deacetylase to silence glycolytic genes; thus directing pyruvate to the TCA cycle to promote ATP synthesis. This function appears critical for glucose homeostasis, as SIRT6 deficient animals die early in life from hypoglycemia. Remarkably, we found SIRT6 to act as a tumor suppressor in multiple cancers by inhibiting aerobic glycolysis, a process described by biochemist and Nobel laureate Otto Warburg decades ago (i.e., the Warburg effect), yet



Understanding the crosstalk between metabolism and Epigenetics

Image Credit: Lara Roach

the molecular mechanisms behind this metabolic switch remained a mystery. We found that SIRT6 is a critical epigenetic modulator of the Warburg effect, providing a long-sought molecular explanation to this phenomenon. Importantly, new work from the lab suggests that tumors exhibit metabolic heterogeneity, and current work from the lab aims to understand whether such heterogeneity is dynamic, and whether it influences chromatin changes in cancer cells, as a mechanism to acquire "epigenetic plasticity". In recent years, we have broadened our research to explore roles of one carbon metabolism (1C) in chromatin dynamics, particularly how the universal donor SAM is modulated in cells, exploring novel metabolic liabilities in cancer, new chromatin modifications, and new chromatin modulators of DNA repair. Importantly, past work on metabolism and chromatin in cancer has focused on primary tumors. We are now exploring the unique metabolic and epigenetic adaptation of metastatic cells, something that remains mostly unknown. In recent studies we have uncovered novel genes that are upregulated in metastatic cells, driving the survival of disseminated tumor cells in the new niche. These genes include metabolic enzymes and transporters, suggesting that metabolic adaptations will be key for metastatic cells to outgrowth, and we are currently exploring whether metabolic heterogeneity is a feature of metastasis as well. We use a number of experimental systems, including biochemical and biological approaches, unique reporters of metabolic pathways as well as genetically engineered mouse models and analysis of human patient samples.

Specific projects:

1. Determining the role of SIRT6 in tumorigenesis and aging
2. Identifying novel histone modifications, and their roles in DNA repair
3. Determining molecular crosstalk between epigenetics and metabolism
4. Discovering non-genetic (epigenetic and metabolic) drivers of metastases

Selected Publications:

Ferrer CM., Cho HM, Boon R, Bernasocchi T, Wong LP, Cetinbas M, Haggerty ER, Mitsiades I, Wojtkiewicz GR, McLoughlin DE, Aboushousha R, Abdelhamid H, Kugel S, Rheinbay E, Sadreyev R, Juric D, Janssen-Heininger YMW, and **Mostoslavsky R**. The glutathione S-transferase Gstt1 drives survival and dissemination in metastases. *Nature Cell Biol.* 2024, 26, 975-990.

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Mo Motamedi, PhD

Motamedi Laboratory

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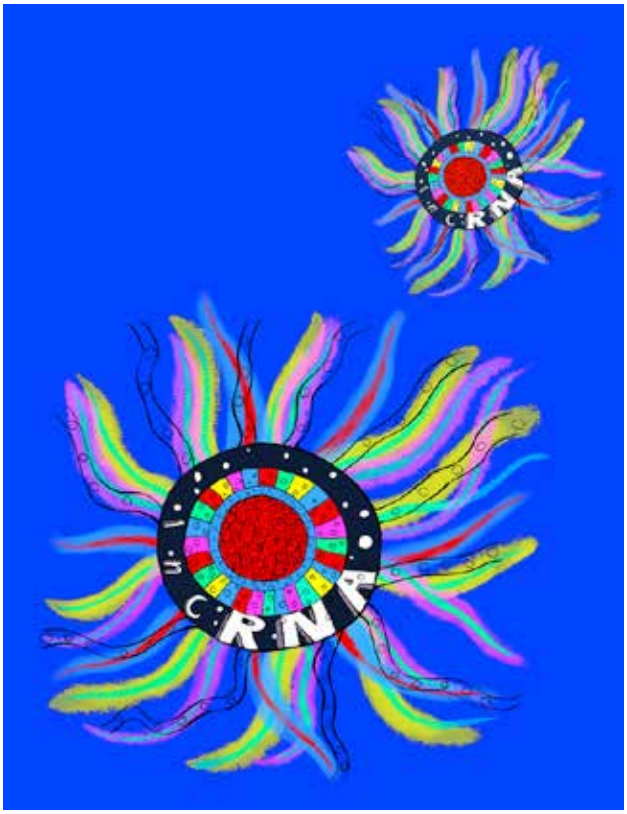
Research in **the Motamedi laboratory** focuses on a molecular memory system, called epigenetics. If our DNA is akin to the hard-drive of a computer, epigenetics is the operating system which instructs the hard-drive (DNA) to perform specific functions. In cells, different epigenetic programs instruct distinct groups of genes to be turned on or off, by which cells acquire new identities during development or develop new properties (such as resistance to stress) in response to environmental stimuli. Recently, it has been shown that cancer cells coopt epigenetic programs to become resistant to different types of treatments, including chemotherapy. By identifying and studying the molecular machinery that establish epigenetic states in model organisms, the Motamedi lab has identified a critical pathway that cancer cells use to establish resistance. The inhibition of this pathway reverses chemotherapy resistance stably in several cancers, providing a novel strategy for overcoming treatment resistance in several cancers.

Epigenetic changes are heritable, phenotypic alterations which occur without mutations to the underlying genes. Once triggered, these phenotypic changes persist through numerous cell divisions independently of the original inducing signal. Epigenetic changes are critical for the stable formation of distinct cell identities, upon which all developmental processes depend. Disruption to this process has serious pathological consequences including malignancies. Most of our molecular understanding about how epigenetic states are established comes from work in model organisms. Broadly, these studies have revealed that epigenetic states, such as those formed at constitutive heterochromatin, are established via several discernable steps: *nucleation*, which involves the recruitment of silencing complexes at specific sites in the genome (e.g. silencers), *cis spreading* of repressive histone marks and complexes, which requires iterative cycles of histone modification and histone binding, and heterochromatin *establishment*, which requires the recruitment of transcriptional (TGS) and posttranscriptional gene silencing (PTGS) complexes to these domains via their interactions with heterochromatic histone marks. The Motamedi lab uses the fission yeast and human cancer as models to understand how changes to eukaryotic chromatin are made, maintained and propagated, and how these changes establish alternative transcriptional programs particularly in response to persistent stress.

Noncoding RNAs and chromatin – partners in epigenetic regulation

One of the first models for how long and small noncoding RNAs regulate chromatin states was proposed in the fission yeast. It posits that noncoding RNAs, tethered to chromatin, provide a platform for the assembly of RNA-processing and chromatin-modifying proteins (Motamedi et al 2004), leading to transcriptional regulation of the underlying genes. The lab recently identified the first long noncoding RNA (lncRNA) capable of amassing all factors required to trigger heterochromatin formation in the fission yeast (Khanduja et al 2024). We plan to dissect how these molecules interact and how these interactions can lead to the



The heterochromatic long noncoding RNA (SPNCRNA.230) (black circle) coordinates deacetylation and methylation of newly incorporated nucleosomes (white balls) at pericentromeres. Sir2 (yellow/green) and Clr3 (pink) are recruited to SPNCRNA.230 by parallel mechanisms and work upstream of Clr4 (blue ribbon) to deacetylate histone H3 lysine 9 (H3K9) prior to its methylation. Clr4-mediated H3K9 methylation leads to recruitment of HP1 (red) and formation of phase-separated HP1 droplets (red ball) that mediate silencing by transcriptional and post-transcriptional mechanisms.

stepwise assembly of heterochromatin. Considering the conservation of heterochromatin machinery from yeast to human, we plan to test the conservation of this mechanism and associated proteins in human cells.

Another focus of the lab is epigenetic plasticity which permits cells to adopt distinct phenotypic states favoring survival by rewiring their transcriptional networks without underlying mutations. This allows cells to transiently adapt to stress while maintaining the fidelity of their genomes. Previously, using the fission yeast, which is an excellent organism to model this process, we found that in response to persistent stress, the constitutive heterochromatin protein Clr4/SUV39 - the sole histone H3 lysine 9 (H3K9) methyltransferase and a member of the conserved suppressor of variegated 3-9 homolog (SUV39) family of histone methyltransferases - is co-opted and deployed to euchromatic parts of the genome to regulate the expression of hundreds of linearly organized protein-coding genes. We showed that this function is required to for stress-resistance and promotes phenotypic plasticity favoring survival under persistent stress. This work revealed a new function of heterochromatin proteins and noncoding RNAs, which orchestrate the genome-wide deployment of heterochromatin factors in response to long-term stress. It also led to the proposal of several testable hypotheses. In collaboration with several groups, we are testing whether this pathway also plays an important role in treatment resistance in several cancers.

Selected Publications:

Khanduja JS, Joh RI, Perez MM, Paulo JA, Palmieri CM, Zhang J, Gulka AOD, Haas W, Gygi SP, **Motamedi M**. RNA quality control factors nucleate Clr4/SUV39H and trigger constitutive heterochromatin assembly. *Cell* 2024. 187: 3262-3283.

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Joh RI, Lawrence M, Aryee M, **Motamedi M**. Gene clustering coordinates transcriptional output of disparate biological processes in eukaryotes. *bioRxiv* 2023. doi: 10.1101/2021.04.17.440292*.

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Joh RI, Khanduja JS, Calvo IA, Mistry M, Palmieri CM, Savol AJ, Hoi Sui SJ, Sadreyev RI, Aryee MJ, and **Motamedi M**.Survival in quiescence requires the euchromatic deployment of Clr4/SUV39H by argonaute-associated small RNAs. †*Mol Cell*. 2016; 64: 1088-1101.

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*Equal Contribution

†This paper was the cover story in ***Molecular Cell*** and featured in ***Boston Magazine*** (***http://www.bostonmagazine.com/sponsor-content/mgh-study-potentially-finds-the-achilles-heel-for-dormant-cancer-cells/***)

††This article was the cover story in *Cell*

Christopher W. Mount, MD, PhD

Mount Laboratory

(Opens Winter of 2026)

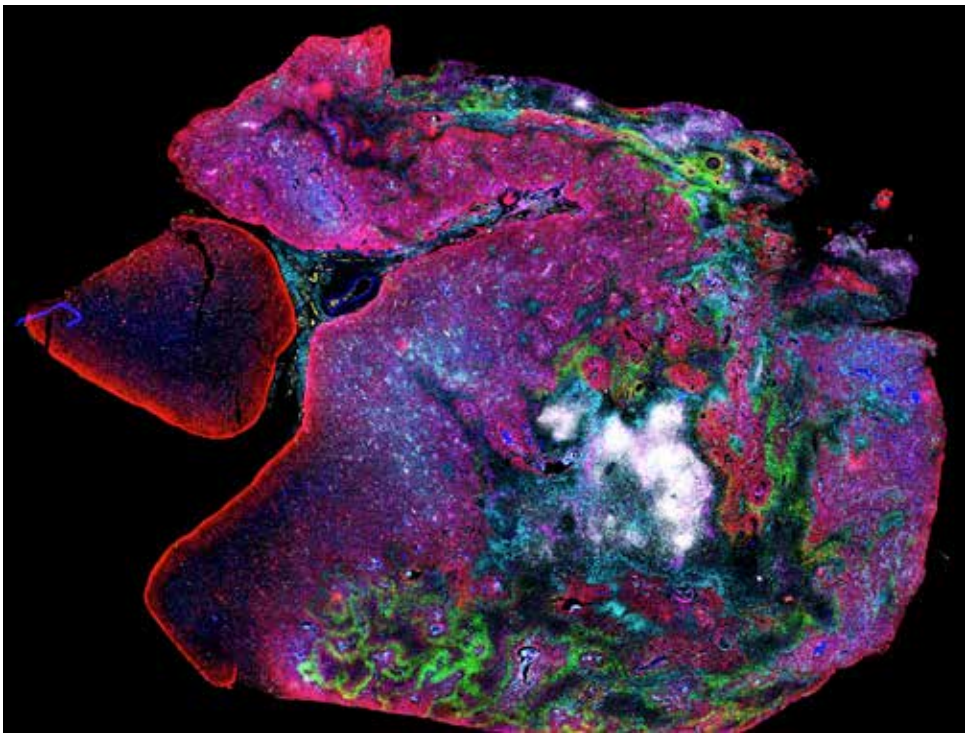
Christopher W. Mount, MD, PhD

The Mount laboratory uses single cell technologies to unravel the interactions between cell therapies and the glioma microenvironment. We leverage these fundamental insights to develop enhanced cell therapies for adult and pediatric glioma patients. Gliomas are the most common primary brain tumors and frequently have a devastatingly poor prognosis and few treatment options. Developing novel therapies for these tumors poses unique challenges, including extensive tumor heterogeneity, limited penetration of many targeted therapies into the brain, and difficulties in developing model systems of these diseases. Engineered cellular immunotherapies, in which a patient's immune cells are altered to fight tumor cells, may be capable of overcoming many of these limitations. In collaboration with colleagues across neuro-oncology, neurosurgery, and neuropathology, we champion a 'bedside to bench to bedside' philosophy that leverages primary human samples to inform development of faithful model systems to assess these therapeutics in the laboratory and evaluate their activity in clinical trials.

Gliomas are the most common and deadly brain tumors occurring in adults. Despite decades of concerted efforts, outcomes in this disease remain dismal, and there is a desperate need for improved therapies. While advances in immunotherapy have revolutionized patient care and achieved transformative benefits in other realms of oncology, these impacts have yet to be realized in glioma patients. Chimeric antigen receptor (CAR)-T cell therapies, in which engineered molecules encoding extracellular tumor-targeting domains are paired with intracellular T cell activation domains, have recently shown promising but heterogeneous results in early phase clinical trials for glioma patients. The transcriptional heterogeneity of gliomas across patient populations and within individual tumors is thought to be a major obstacle to these therapies, and emerging large single cell sequencing datasets of molecularly-defined glioma cohorts offer the potential to refine target selection strategies for adoptive cell therapies in these diseases. Evolving spatial multiomic platforms additionally provide the opportunity to understand this heterogeneity in the context of the complex glioma microenvironment, and the potential to uncover cellular mediators of resistance *in situ*. Integrating these approaches in faithful model systems of glioma-cell therapy interactions will allow us to probe the dynamics of these interactions and uncover mechanisms underlying immune effector cell infiltration, cytotoxic activity, exhaustion, and persistence in concert with the dynamic responses of tumor and microenvironmental phenotypes.

Identifying novel immune effector cell targets in gliomas using single cell sequencing

Our laboratory leverages single cell transcriptomics to understand the gene regulatory programs that drive the expression of cell surface targets in molecularly-defined gliomas. In contrast to traditional approaches, this strategy enables transcriptome-wide evaluation of target profiles across heterogeneous tumor cell populations and the background



Highly multiplexed spatial proteomic profiling (CODEX) of a CAR-T cell treated patient tumor specimen.

brain environment. From these data, we are building comprehensive atlases of the targeting landscape in these diseases to inform the design of next-generation combinatorial immune effector cell targeting strategies that will enhance our ability to overcome tumor heterogeneity. Using diverse model systems, including patient-derived glioma organoids, cell lines, and mice, we then probe the dynamics of these transcriptional programs under therapeutic pressure with panels of novel immune effector cell constructs. Using these systems, we have uncovered convergent transcriptional metaprograms of glioma cell responses to immune effector cell therapies, and we are now exploring targeting strategies to translate these opportunities into novel therapies.

Deciphering microenvironmental mediators of immune effector cell function and therapeutic resistance with spatial multiomics

In patients with brain tumors, how does an infused cellular therapy reach its target tumor cell population in the central nervous system? Despite the fundamental importance of this question, we have a limited understanding of the physical pathways and molecular mechanisms by which engineered T cell therapies infiltrate brain tumors. Evolving spatial multiomics platforms now offer the ability to interrogate these questions with unprecedented resolution and depth. In collaboration with colleagues in neurosurgery, neuro-oncology, and neuropathology, our laboratory conducts spatial multiomic profiling of patient tumor samples treated in immune effector cell clinical trials to unravel the molecular architecture of these interactions *in situ*. In model systems, we expand on these observations in collaboration with longstanding bioinformatics collaborators to understand the influence of spatial architecture and cellular neighborhoods on transcriptional dynamics and immune effector cell function in situ.

Selected Publications:

Greenwald AC, Darnell NG, Hoefflin R, Simkin D, **Mount CW**, Gonzalez Castro LN, Harnik Y, Dumont S, Hirsch D, Nomura M, Talpir T, Kedmi M, Goliand I, Medici G, Laffy J, Li B, Mangena V, Keren-Shaul H, Weller M, Addadi Y, Neidert MC, Suvà ML, Tirosh I. Integrative spatial analysis reveals a multi-layered organization of glioblastoma. *Cell.* 2024 May 9;187(10):2485-2501.e26.

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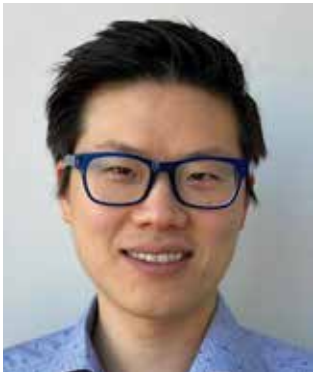
Theruvath J, Sotillo E, **Mount CW**, Graef CM, Delaidelli A, Heitzeneder S, Labanieh L, Dhingra S, Leruste A, Majzner RG, Xu P, Mueller S, Yecies DW, Finetti MA, Williamson D, Johann PD, Kool M, Pfister S, Hasselblatt M, Frühwald MC, Delattre O, Surdez D, Bourdeaut F, Puget S, Zaidi S, Mitra SS, Cheshier S, Sorensen PH, Monje M, Mackall CL. Locoregionally administered B7-H3-targeted CAR T cells for treatment of atypical teratoid/rhabdoid tumors. *Nat Med.* 2020 May;26(5):712-719.

Mount CW, Majzner RG, Sundaresh S, Arnold EP, Kadapakkam M, Haile S, Labanieh L, Hulleman E, Woo PJ, Rietberg SP, Vogel H, Monje M, Mackall CL. Potent antitumor efficacy of anti-GD2 CAR T cells in H3-K27M(+) diffuse midline gliomas. *Nat Med.* 2018 May;24(5):572-579.

Eugene Oh, PhD



Oh Laboratory

Meenakshi Basu, PhD
Brian Brannigan
Eugene Oh, PhD
Sneha Saxena, PhD
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Ubiquitylation is one of the most common protein modifications and arguably the most versatile. How this post-translational modification shapes the intracellular signaling networks that dictate specific cellular states and behaviors is a central focus of **the Oh laboratory**. We recently identified a novel ubiquitin-dependent mechanism that integrates gene expression with cellular division to preserve the identity of proliferating cell types. Our current focus is to elucidate how various cancer cell types hijack this system to confer specific proliferative and survival advantages. The goals of this exploration are to target the ubiquitin system for drug discovery and to find new strategies to rewire the gene expression landscape of cancer cells.

How cells process information and make decisions is essential for their survival. The intracellular signaling events that ultimately evoke specific cellular responses make frequent use of ubiquitylation. Failure to properly do so can cause abnormal cell growth and uncontrolled proliferation, both hallmarks of tumorigenesis. Our lab is broadly interested in understanding the ways in which ubiquitylation gates key decision-making processes and how misregulation of this modification contributes to various malignancies.

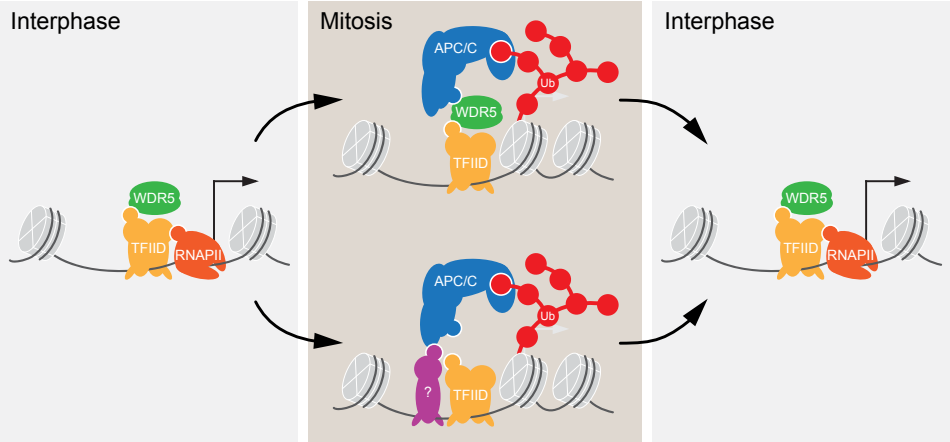
Ubiquitin-dependent control of gene expression

The identity of every cell is governed by the coordinated expression of specific gene networks. Yet dividing cells temporarily halt their transcriptional output during mitosis, thus how these cells preserve a transcriptional memory that defines their cellular state is not completely understood. Using modern genetic discovery platforms, we found that the ubiquitin ligase APC/C (anaphase-promoting complex) is required for controlling the pluripotent identity of human embryonic stem cells. Our studies revealed that the APC/C is recruited to a subset of gene promoters by the chromatin recruitment factor WDR5, which enables the APC/C to decorate nearby histone proteins with ubiquitin chains assembled through specific linkages. These ubiquitin polymers serve as potent extraction signals for the ATP-dependent segregase p97/VCP. The displacement of histone proteins removes a critical barrier to transcription, ensuring the rapid re-expression of pluripotency genes upon entry into the next cell cycle. Altogether, our work highlights an unexpected role for ubiquitylation in gene expression control.

A key implication of this mechanism is that the APC/C can direct the identity of any dividing cell type, including abnormally proliferating cancer cells. Our ongoing research focuses on identifying which cancer types are dependent on the APC/C for their identity and characterizing the molecular basis for this control. Interestingly, the APC/C binds to a number of cancer-linked transcription factors, with many of these interactions only observed in specific cancer lines, suggesting that a single enzyme can elicit a multi-faceted response by tailoring a custom gene expression program for each cancer type.

Decoding the chromatin-bound ubiquitin code

Ubiquitin can also form polymeric chains that adopt unique structures. This



A model for how APC/C controls gene activity in dividing cell types. The expression of self-renewal genes is dependent on WDR5, while the expression of cancer-specific genes requires factors that are yet to be identified.

topological diversity translates into a diversity of functional outcomes, making this modification exceptionally versatile as a regulatory system. Our lab found that the APC/C deposits defined ubiquitin polymers – linked via residues Lys11 and Lys48 – on chromatin-bound substrates. Yet whether and how other ubiquitin chain types control gene expression is unknown. Ongoing efforts in our lab include developing new strategies to probe for the various linkage types that regulate gene activity and understanding the molecular basis for these linkages. Our ultimate goal is to untangle the complexity of the chromatin-bound ubiquitin code and to decipher how this code is controlled. Major questions include understanding how specificity of this modification is achieved and whether ubiquitylation might crosstalk with other post-translational modifications.

Selected Publications:

Vuille J A, Tanriover C, Antmen E, Micalizzi DS, Ebright RY, Animesh S, Morris R, Hajizadeh S, Nicholson ZJ, Russell HC, Zaniewski EF, Wittner BS, Wesley BK, Kwak JE, Grünewald J, Szalay RN, Fox DB, Yang M, Joung JK, Gulhan DC, Elia AEH, Haas W, **Oh E**, Maheswaran S, Haber DA. The E3 ligase HECTD4 regulates COX-2-dependent tumor progression and metastasis. Proc. *Natl. Acad. Sci.* United States Am. 122, e2425621122 (2025).

Saxena S, Nabel CS, Seay TW, Patel PS, Kawale AS, Crosby CR, Tigro H, **Oh E**, Heiden MGV, Hata AN, Suo Z, Zou L. Unprocessed genomic uracil as a source of DNA replication stress in cancer cells. *Mol. Cell* 84, 2036-2052.e7 (2024).

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Christopher J. Ott, PhD

Ott Laboratory

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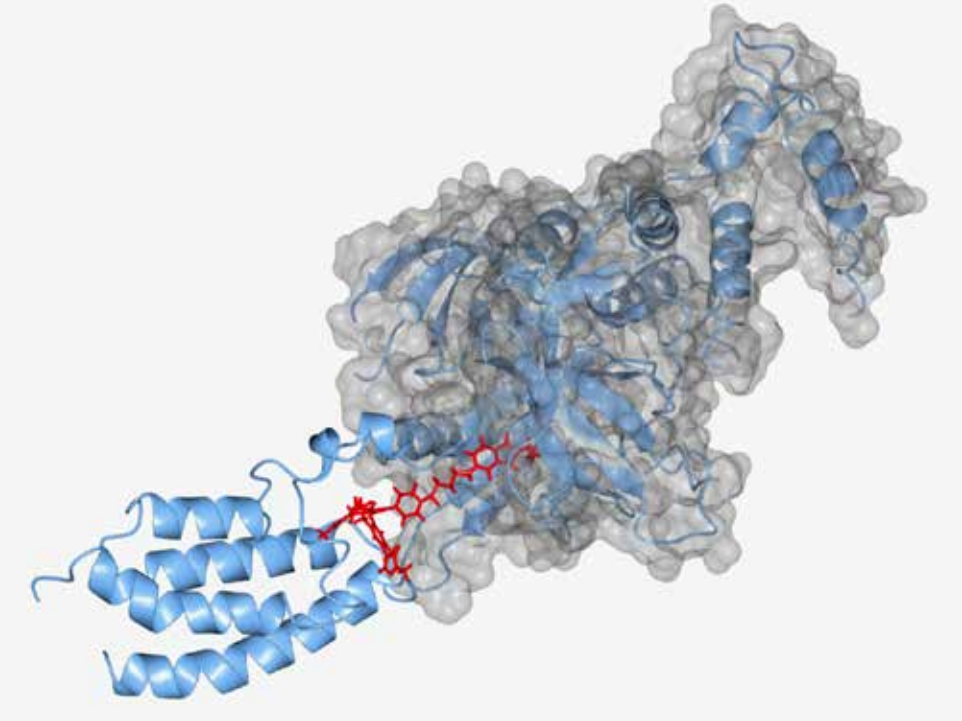
The Ott laboratory works at the intersection of chemistry and cancer biology. We are motivated to discover new therapeutics that target the intrinsic vulnerabilities of cancer cells in unique ways. To achieve this, we employ chemical synthesis, high-throughput drug screens, and multi-omic technologies to advance cancer drug discovery. One particular interest of our group is developing synthetic molecules that directly target transcription factors and chromatin regulators that control aberrant gene expression in cancer - signaling components of cells that make up the epigenome. In addition to this, we also rigorously pursue unbiased 'chemical epigenomic' screens using one of the world's largest repositories of tumor cell line models. By measuring the effects of a diverse array of bespoke chemical compounds on a diverse array of cancer cell types, we let the molecules teach us how they might be good starting points for cancer drug development by assessing statistical associations of cancer cell killing with other genetic and epigenetic features.

Targeting oncogenic enhancers

In normal cells, gene expression control is tightly regulated to ensure transcription occurs with appropriate timing and magnitude. This control is principally mediated by regulatory non-coding DNA elements in our genome called enhancers that coordinate the activity of sequence-specific transcription factors together with chromatin regulators to enforce gene transcription. Cancer cells often hijack this circuitry to enforce the dysregulated expression programs required for proliferation, survival, immune evasion, and other cancer hallmarks. The signaling interface of enhancers has historically been difficult to target with drugs, however new insights into their architecture are beginning to reveal ways in which this may be possible. Our lab takes structural insights together with new chemical methodologies to devise strategies to affect enhancer 'druggability'. Our efforts to target enhancers are organized around two distinct protein classes that effectively 'read' the distinct biochemical features of enhancers: bromodomain proteins and transcription factors (TFs). A primary focus is developing strategies to target a pair of proteins that are integral to enhancer function: CBP and p300. These factors uniquely contain both an acetyltransferase domain that writes acetyl groups to the amino acid lysine, and a protein domain called a bromodomain that binds to ('reads') acetylated lysine. Mutations in both CBP and p300 have been found in both hematologic (leukemia, lymphoma) and solid tumors (breast, lung, bladder, and others). Using bifunctional chemical technologies that induce targeted protein degradation, our group was the first to develop compounds that induce highly potent CBP/p300 degradation (Vannam et al, 2021; Tiwari et al, 2024). These compounds have significant anti-cancer properties, and a major current focus of the lab is advancing this technology towards clinical translation. We are also intently pursuing strategies to target TFs. Decades of molecular oncology studies unambiguously establish TFs as among the most compelling targets for cancer therapy. As TFs directly bind to enhancer DNA in a sequence-specific manner, they are the primary readers of enhancer regulatory codes. New insights gleaned from systematic enhancer mapping,



Structural model of the ternary complex formed by a novel chemical degrader of the acetyltransferases CBP/p300 (dCBP-1) developed by the Ott laboratory. dCBP-1 (in red) induces degradation of CBP/p300 by acting as a 'molecular glue' between an E3 ubiquitin ligase and the bromodomain of CBP/p300.

Model generated by Jan F. Sayilgan, PhD. Courtesy of the Mike Lawrence and Christopher Ott laboratories.

functional genetics, and structural biology have revealed ways that TFs are regulated in cancer cells, opening opportunities to therapeutically target them. Our group has established initiatives using several approaches to uncover TF regulation and advance TF-directed drugs.

Chemical epigenomic approaches to drug discovery

Advances in human genetics profiling, fueled by new DNA sequencing technologies, have led to a comprehensive map of cancer-causing mutations and a limited target list of oncogenes for drug development. Functional genomic screens have also revealed a comprehensive list of non-oncogene dependencies that promote the uncontrolled growth of cancer cells. These cancer drug targets are a boon for cancer drug hunters to interrogate with focused therapeutics discovery programs. However, we currently lack the chemical technologies to efficiently and reliably develop drugs for most of these genes. To discover new molecules with anti-cancer properties, our group is deploying phenotypic screening using highly annotated cancer models. Our lab possesses one of the world's largest collections of cancer cell lines that grow in high-throughput drug screening plates without the need for specialized culture systems. We are actively profiling these models with an ever-increasing array of multi-omic assays to finely map and annotate their genomic and epigenomic states. By screening these cell lines with large compound libraries, we can correlate activity with multi-omic features: *high-throughput chemical epigenomics*. These efforts reveal compounds with new mechanisms of action, provide insights into the actions of drugs with known targets, and generate novel starting points for drug discovery. Our chemical epigenomic screening approaches rely on synthesis of focused chemical libraries with defined features amenable to cellular bioactivity designed by chemists in our group.

Selected Publications:

Tiwari PK*, Doda SR*, Vannam R*, Hudlikar M*, Harrison DA, Ojeda S, Rai S, Koglin A-S, Gilbert AN, **Ott CJ**^. Exploration of bromodomain ligand-linker conjugation sites for efficient CBP/p300 heterobifunctional degrader activity. *Bioorganic & Medicinal Chemistry Letters*. 2024; 102:129676.

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Shortt J*, **Ott CJ***, Johnstone R, Bradner JE. A chemical probe toolbox for dissecting the cancer epigenome. *Nature Reviews Cancer*. 2017; 17: 160-183.

Koblan LW*, Buckley DL*, **Ott CJ***, Fitzgerald ME*, Ember S, Zhu J-Y, Lui S, Roberts JM, Remillard D, Vittori S, Zhang W, Schonbrunn E, Bradner JE. Assessment of bromodomain target engagement by a series of BI2536 analogues with miniaturized BET-BRET. *Chem Med Chem*. 2016; 11: 2575-2581.

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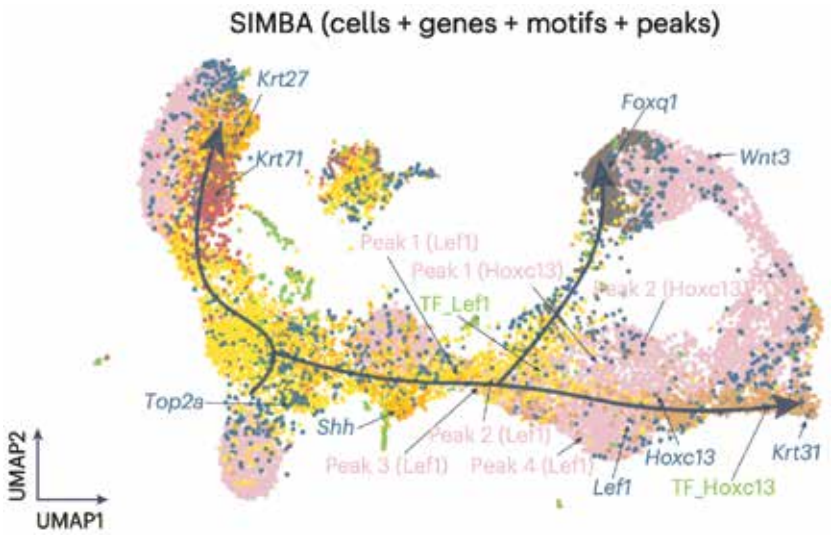
The focus of **the Pinello laboratory** is to use innovative computational approaches and cutting-edge experimental assays, such as CRISPR genome editing and single-cell sequencing, to systematically analyze sources of genetic and epigenetic variation and gene expression variability that underlie human traits and diseases. The lab uses generative AI, machine learning, and high-performance computing technologies to solve computationally challenging and Big Data problems associated with gene regulation, functional genomics, and sequencing data analysis. Our mission is to use computational strategies to further our understanding of disease etiology and to provide a foundation for the development of new drugs and novel targeted treatments.

The Pinello laboratory is at the forefront of computational biology, focusing on deciphering the role of chromatin structure, dynamics, and non-coding regions in gene regulation. Our mission is to integrate multiomics data to explore and better understand the functional mechanisms of the genome and to provide accessible tools for the scientific community to accelerate discovery in this field.

We have made significant contributions to the genome editing field, developing computational tools like CRISPResso, which has become the standard for quantifying and visualizing CRISPR editing outcomes. Our work on the BCL11A enhancer led to the development of clinical trials for sickle cell disease and β-thalassemia, and ultimately contributed to the first FDA-approved CRISPR-based drug, Casgevy. Recently, we developed CRISPRme, a tool that considers genetic variants to provide a more comprehensive assessment of off-target risks in CRISPR-based therapies. This work uncovered unappreciated off-targets for therapeutic guides based on genetic diversity, with immediate implications for ongoing clinical trials in diseases ranging from blood disorders to cancer.

In the field of single-cell genomics, we have developed methods like STREAM for trajectory inference from transcriptomic and epigenomic data, SIMBA for clustering-free marker discovery and omics data integration, and Dictys for recovering dynamic regulatory networks from single-cell multiomics data. These tools are enabling deeper insights into cellular heterogeneity, developmental processes, and gene regulatory dynamics across various biological contexts.

Our lab is also leading one of the characterization centers of the NHGRI Impact of Genomic Variation on Function (IGVF) Consortium. Here, we are combining CRISPR genome editing, single-cell assays, and novel computational tools to characterize the impact of genetic variants on different phenotypes at scale. This work has already led to significant advancements in variant classification and effect size quantification, particularly in the context of cardiovascular diseases. Our recent publication in *Nature Genetics* (Ryu et al., 2024) introduces BEAN, a Bayesian network that integrates genotypic and phenotypic data from base editing screens. This innovative approach significantly improves the accuracy of variant effect



SIMBA (Single-cell embedding along with features) co-embedding of cells and multi-omic features reveals regulatory circuits and master regulators in mouse hair follicle differentiation. The visualization shows cells, top-ranked genes, TF motifs, and associated chromatin accessibility peaks in a shared embedding space. Key regulators like Lef1 and Hoxc13 are positioned along the differentiation trajectory, with their associated genes and regulatory elements clustered nearby. This co-embedding approach enables the identification of cell type-specific features, master regulators, and potential target genes, providing insights into the gene regulatory dynamics during cellular differentiation.

Image Credit: Adapted from Chen et al., Nature Methods, 2023

predictions, outperforming existing methods in classifying pathogenic variants and quantifying their effect sizes.

Our lab has recently pioneered DNA-Diffusion, a groundbreaking generative AI approach that designs synthetic DNA regulatory elements capable of controlling chromatin accessibility and gene expression. This technology has demonstrated remarkable therapeutic potential, particularly in cancer treatment. In a proof-of-concept study, we successfully used DNA-Diffusion to reactivate AXIN2, a tumor suppressor gene silenced in B-cell leukemia. Remarkably, our AI-designed sequences outperformed a naturally occurring protective variant, achieving activation levels comparable to strong positive controls while maintaining cell-type specificity. This work, establishes generative AI's ability to create therapeutic regulatory sequences that surpass natural evolution, opening new avenues for precision gene therapy.

Looking ahead, we are excited to explore cutting-edge spatial profiling technologies and expand our generative AI approaches for therapeutic applications. Our ultimate goal is to further our understanding of disease etiology involving poorly characterized genomic regions and to provide a foundation for the development of new drugs and more targeted treatments. By leveraging state-of-the-art computational approaches and experimental assays, we aim to systematically analyze sources of genetic and epigenetic variation that affect gene regulation in different human traits and diseases.

Selected Publications:

DaSilva LF, et al. DNA-Diffusion: Leveraging Generative Models for Controlling Chromatin Accessibility and Gene Expression via Synthetic Regulatory Elements. *bioRxiv*. 2024 Feb 1:2024.02.01.578352.

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Cancellieri S, et al. Human genetic diversity alters off-target outcomes of therapeutic gene editing. *Nat Genet.* 2023 Jan;55(1):34-43.

Wei Y, et al. Single-cell analysis and functional characterization uncover the stem cell hierarchies and developmental origins of rhabdomyosarcoma. *Nat Cancer*. 2022 Aug;3(8):961-975.

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** Co-mentored with Brastianos Lab

The Rheinbay laboratory studies different types of genetic mutations that drive cancer. One research direction is focused on how loss of the male Y chromosome contributes to higher incidence of cancer and different outcomes in men. The lab develops analysis strategies tailored to the Y chromosome, and uses analytic and functional approaches to understanding the consequences of Y chromosome loss. Understanding the driver genes on the sex chromosomes will help us explain differences in male and female tumors, and forge a path to a novel class of therapies targeting these alterations.

The lab also works on finding and describing specific alterations that disturb the regulation of cellular processes in cancer which are mediated by master transcription factors. We study how mutations in these factors, and their binding targets in the genome, affect cancer cell state and drive cancer.

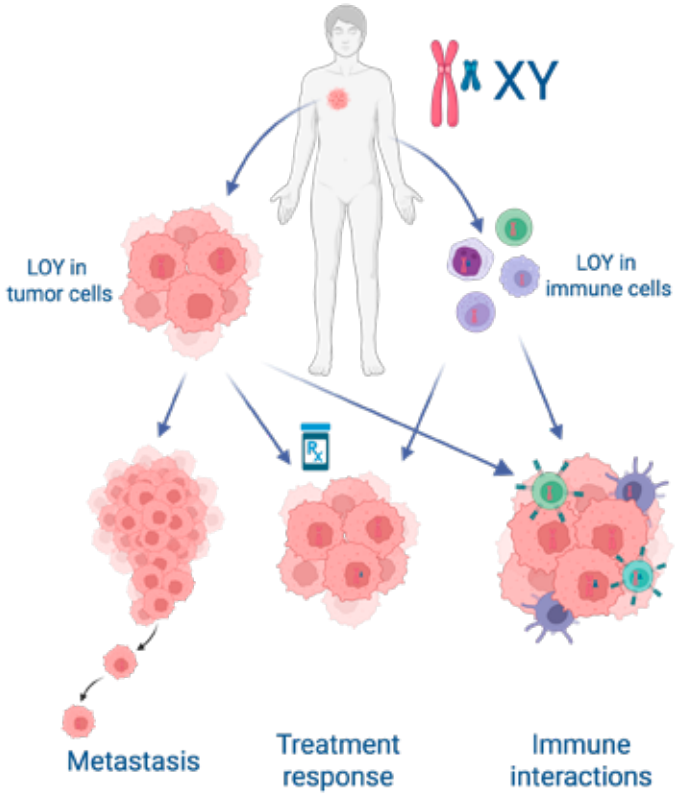
Role of the Y chromosome in cancer

Cancer affects men and women disparately, with strong differences in incidence and outcome in some tumor types. Human sex is determined by the sex chromosomes X and Y. Because men only have one X chromosome, they are particularly vulnerable to congenital and acquired somatic variants in X-linked genes. It is known that both sex chromosomes can be lost in normal blood cells with age, as well as certain tumor cells. Yet the meaning of Y chromosome loss (LOY), and possible cancer genes on this chromosome, are poorly understood. This is because Y is technically challenging to study with commonly used 'omics' profiling approaches. Our group develops analysis strategies and methods to tackle these technical challenges and use them to find new X and Y-linked drivers in published tumor genome sequences.

We have recently published a landmark study on the frequency and implications of Y chromosome loss across 29 cancer types. This study highlighted the importance of this alteration by identifying associations with genome instability, and cellular dependencies that could be therapeutically exploited. In uveal melanoma, a rare tumor of the eye, LOY in primary tumors is strongly associated with metastatic spread and outcome. Combining both analytic and functional approaches, the lab is focused on unraveling the exact mechanisms behind LOY that lead to these observed phenotypes. Ongoing work concerns the characterization of sex chromosome alterations in multiple pediatric and adult tumor types, interactions with the tumor immune microenvironment and continued development of analysis methods. Our goal is to fully understand the mechanisms by which LOY drives cancer initiation and progression, and how we can therapeutically target them.

Regulatory driver mutations in cancer genomes

Genomic cancer driver discovery has traditionally focused on protein-coding genes (the human exome), and large-scale sequencing of these genes in thousands of tumors has led to the discovery of novel frequently altered genes. However, exome sequencing focused only on coding genes does not allow analysis of non-coding regions in the human genome. Protein-coding genes are regulated by several types of genomic elements that control their expression (promoters, distal enhancers



The Rheinbay lab studies how Y chromosome loss in tumors, and aging-related loss in immune cells, impact tumor biology, immune and therapeutic response.

and boundary elements), translation and mRNA stability. Alterations in the DNA sequence of these elements thus directly affect the expression and regulation of the target gene. Several such non-coding elements have been identified as recurrently altered in human cancer, and functionally characterized, although these non-coding drivers appear infrequent compared to protein-coding oncogenes and tumor suppressors. One reason might be that gene regulation is highly tissue-specific, and therefore driver alterations in non-coding regions might create a fitness advantage in only a single tumor type. Finding such a specific driver requires a sufficient number of whole genomes from this tumor type. With recent advances in DNA sequencing technology and an increasing number of whole cancer genomes available for analysis, we are just starting to map out and characterize regulatory driver alterations. The Rheinbay laboratory works on the development of novel methods to identify non-coding driver candidates using genomic and epigenomic sources of information, and to understand their impact on tumor initiation, progression and treatment resistance through collaborations with experimental colleagues.

Breast Cancer Genomics

Breast cancer affects many women in the U.S. and worldwide. The lab studies the somatic genetic alterations that lead to breast cancer, and its progression. Utilizing the power of whole-genome and targeted sequencing, we have discovered novel driver alterations in the master transcriptional regulators FOXA1 and HOXB13. We currently have several collaborations with clinical and experimental investigators in the Krantz Family Center for Cancer Research focused on the full understanding of genetic and transcriptional changes in breast cancer.

Selected Publications:

Mitsiades IR, Onozato M, Iafrate AJ, Hicks D, Gülhan DC, Sgroi DC, **Rheinbay E**. ERBB2/HOXB13 co-amplification with interstitial loss of BRCA1 defines a unique subset of breast cancers. *Breast Cancer Res*. 2024; Dec 18;26(1):185.

Qi M, Pang J, Mitsiades I, Lane AA, **Rheinbay E**. Loss of chromosome Y in primary tumors. *Cell*, 2023; 186(14): 3125-3136.

Qi M, Nayar U, Ludwig, LS, Wagle N, **Rheinbay E**. cDNA-detector: detection and removal of cDNA contamination in DNA sequencing libraries. *BMC Bioinformatics*. 2021; 22:611

Rheinbay E*, Nielsen MM*, Abascal F*, Wala J*, Shapira O* et al. Analyses of non-coding drivers in 2,658 cancer whole genomes. *Nature*. 2020; 578:102-111.

Rheinbay E, Parasuraman P, Grimsby J,et al. Recurrent and functional regulatory mutations in breast cancer. *Nature*. 2017;547:55-60.

*Equal contribution

Miguel N. Rivera, MD

Research in **the Rivera laboratory** focuses on using genomic tools to identify and characterize gene regulation pathways that are altered in cancer. An important feature shared by most tumors is the dysregulation of complex gene expression programs that control cell proliferation and differentiation. Our work combines the use of genomic technologies for the direct identification of gene regulation abnormalities in tumors with functional analysis of critical mechanisms and pathways. Given that the mechanisms that drive changes in gene expression programs in cancer are poorly understood, we anticipate that our studies will point to new therapeutic approaches.

Rivera Laboratory

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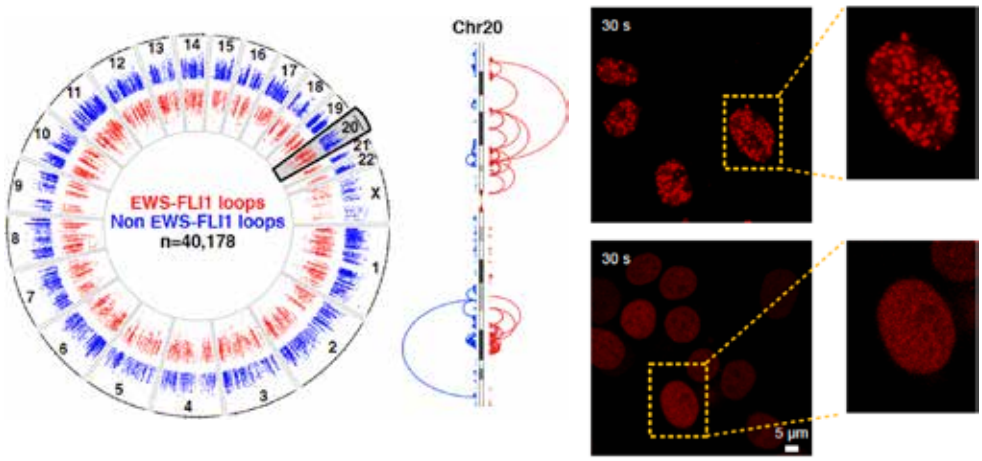
Epigenomic approaches for the identification of novel pathways in cancer

The complex mechanisms that regulate gene expression play a central role in driving growth and survival pathways in tumor cells. In fact, many mutations observed in cancer cells directly alter proteins involved in gene regulation, including transcription factors, chromatin regulators and histones. Our laboratory studies the mechanisms that lead to gene regulation abnormalities by combining genomic technologies with biochemical assays and CRISPR based epigenome editing. We expect that our work will reveal pathogenic mechanisms and also identify opportunities to develop new therapies for cancer.

One of these genomic technologies is chromatin profiling, which combines chromatin immunoprecipitation and high-throughput sequencing. This approach has been used to study how genes are activated or repressed by regulatory elements in the genome such as promoters and enhancers. As a complement to gene expression studies, chromatin profiling provides a unique view of gene regulation programs by allowing the identification of both active and repressed genomic domains based on patterns of histone modification. Several studies have shown that prominent active histone marks are associated with genes that play key roles in cell identity and proliferation, including oncogenes that promote the growth of tumor cells. In contrast, repressive marks are found at loci that are maintained in an inactive state to prevent cellular differentiation. Recently, our work has also incorporated new 3D chromatin configuration technologies (e.g. HiC and HiChiP) that can measure the critical contributions of spatial organization to gene regulation in a genome-wide scale.

We have performed extensive chromatin profiling of several tumor types, including pediatric tumors such as Ewing sarcoma and medulloblastoma that have been linked to abnormalities in transcriptional regulation. Our work has uncovered novel genes and pathways involved in these diseases by comparing chromatin patterns in primary tumor samples and normal tissue specific stem cells. In addition, we have identified gene regulation mechanisms that play critical roles in tumor formation through functional studies of transcription factors and chromatin regulators. We are now characterizing these pathways in detail and extending our epigenomic analysis to other tumor types where oncogenic pathways are



Looping patterns and IDR condensation in Ewing sarcoma cells. Left panels: The oncogenic transcription factor EWS-FLI1 is a dominant force in establishing the 3D configuration of DNA in Ewing sarcoma. EWS-FLI1 accounts for almost half of all loops in tumor cells (shown as red dots in the circle plot and as loops for a magnified view of Chromosome 20. Right panels: Optogenetic experiment showing induction of condensates by a transcription factor with an intrinsically disordered domain (IDR, top). This effect is lost if the IDR is removed (bottom).

poorly defined. These analyses have led us to identify new therapeutic targets for tumors where no targeted therapies are currently available.

Role of intrinsically disordered regions (IDRs) in cancer

Our studies of gene regulation in cancer have led us to identify unexpected oncogenic mechanisms that have broad implications. In particular, our work has shown that the intrinsically disordered region (IDR) of the EWS-FLI1 oncogenic fusion protein is essential for its function and enables the activation of tumor specific regulatory elements. Given that EWS-FLI1 is part of a large group of fusion oncogenes that share the same disordered domains, we have used this insight to study similar mechanisms in other tumor types (e.g. Clear Cell Sarcoma). Moreover, IDRs are present in many other oncogenes involved in gene regulation and we are developing new methods to study these domains. For example. we recently developed DisP-seq, a method that allows us to identify genomic locations with high concentrations of IDRs. Similarly, given that IDRs often form condensates that can promote gene activation, we are using optogenic tools to study IDRs from different transcription factors involved in cancer.

Selected Publications:

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Moshe Sade-Feldman, PhD

Sade-Feldman Laboratory

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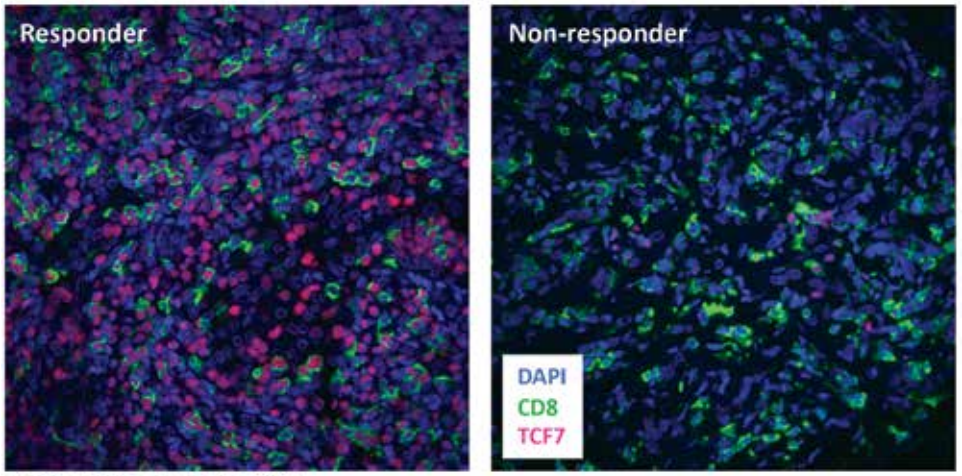
The Sade-Feldman laboratory focuses on identifying response and resistance mechanisms in cancer patients treated with immunotherapies. In the last decade, the treatment of solid tumors has been revolutionized by the development and FDA approval of checkpoint blockade (CPB) immunotherapies. While long-lasting responses are induced, only a small subset of patients benefits from these treatments. Thus, identifying the key components that drive or prevent effective immunity against tumors remains an unmet clinical need. Treatment response to immunotherapy and other therapies (e.g., targeted and chemotherapies) is influenced by complex interactions between multiple cell types in the tumor microenvironment (TME) and the heterogeneous population of tumor cells. The Sade-Feldman laboratory integrates single-cell multi-omics methods, computational biology, patient data-driven functional genomic screens, and detailed mechanistic studies to delve deeper into this intricate ecosystem and the mechanisms behind therapy response and resistance. Combining these approaches enables us to understand resistance mechanisms to immunotherapy, predict patient response, prioritize targets for validation, and identify new drug targets and combinations for cancer treatment.

While there have been numerous successful trials and FDA approvals of antibodies that block the immune regulatory checkpoints, CTLA4, PD-1, PD-L1, and LAG3, for the treatment of multiple cancer types, most patients will not respond and will succumb to the disease. The success of these immune-based therapies mainly relies on identifying tumor antigens presented on MHC-I molecules by cytotoxic immune cells. Working together with scientists, computational biologists, oncologists, surgeons, and pathologists at Mass General, our lab has discovered several mechanisms underlying the control of tumors by the immune system: I. Point mutations, deletions, or loss of heterozygosity (LOH) in beta-2-microglobulin (B2M) as a resistance mechanism to immunotherapy (Sade-Feldman et al. *Nature Comm* 2017); II. High expression of the transcription factor TBX3 in de-differentiated malignant cells as a resistance mechanism (Freeman et al. *Cell Reports Med* 2022); III. T cell states associated with clinical outcomes in melanoma patients treated with CPB inhibitors (Sade-Feldman et al. *Cell* 2018); IV. Inflammatory factors that control the differentiation and function of suppressive myeloid cells (MDSCs) (Sade-Feldman et al. *Immunity* 2014) and their clinical significance in melanoma patients treated with CPB inhibitors (Sade-Feldman et al. *Clinical Cancer Research* 2015); and V. Interferon-induced APOBEC3 as an acquired resistance mechanism to CPB in HNSCC (Lin et al. *NPJ Precis Oncol* 2022) and the prognostic impact of CXCL9/SPP1 polarity of tumor-associated macrophages in HNSCC patients with recurrent advanced disease (Bill R et al. *Science* 2023).

While these studies enabled us to understand some mechanisms of resistance to checkpoint blockade immunotherapy, still many questions remain open:

1. Despite the FDA approval of standard chemotherapy with immune checkpoint blockade (in NSCLC, SCLC, and HNSCC),



Representative overlaid images of melanoma tumors from responder and non-responder patients stained with DAPI (blue), CD8 (green), and TCF7 (red). A higher proportion of CD8+TCF7+ at baseline is observed in patients who responded to anti-PD1 immunotherapy.

we still don't fully understand how drug A affects the activity of drug B and the contribution of each drug to therapy resistance when combined.

2. Are there any shared primary or acquired resistance mechanisms between different diseases (e.g., melanoma, NSCLC, and HNSCC)?
3. While our translational efforts generate many hypotheses and predictors of outcomes, we still don't know the function of those genes/pathways and their impact on treatment response.
4. Can we identify ways to overcome resistance mediated by the loss of antigen presentation by perturbing tumor intrinsic pathways?
5. To date, most of our efforts have been focused on patients with metastatic disease receiving immunotherapy. However, there is an unmet clinical need to identify targets that can synergize with traditional therapies for local and recurrent advanced disease, particularly in cancers with a poor response to such treatments.

To address the above questions, we use a systems biology approach that involves three main steps: I. discover cellular and molecular factors associated with effective/failed therapy using integrative analysis of single-cell multi-omics datasets from human tumors; II. Perform systematic functional genetic screens to determine the role of human genes associated with outcomes; III. Characterize the key sensitivity/resistance mechanisms to understand the intra- and inter-cellular circuits underlying their action.

Main current projects in the lab:

1. Identify and validate factors conferring sensitivity and resistance to patients treated with mono or combinatorial (e.g., targeted and chemotherapy) immunotherapy by bridging together analyses of human tumors with systemic perturbations and mechanistic studies in animal and human models.
2. Identify tumor intrinsic pathways that can sensitize cells to immunotherapy in the absence of the MHC-I antigen-presentation machinery.
3. Discover targets to overcome radiation and chemotherapy resistance in local and recurrent advanced cancers.

By combining detailed human observations and rigorous functional tests, these studies are expected to reveal the basis for therapeutic resistance and response, creating a roadmap for identifying targets for therapeutic development.

Selected Publications:

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LaSalle TJ, Gonye ALK, Freeman SS, Kaplonek P, ..., Filbin MR, Villani AC, Hacohen N, **Sade-Feldman M**. Longitudinal characterization of circulating neutrophils uncovers phenotypes associated with severity in hospitalized COVID-19 patients. *Cell Rep Med*. 2022 Sep 26:100779.

Freeman SS*, **Sade-Feldman M***, Kim J, Stewart C, ..., Stemmer-Rachamimov AO, Wargo JA, Flaherty KT, Sullivan RJ, Boland GM, Meyerson M, Getz G, Hacohen N. Combined tumor and immune signals from genomes or transcriptomes predict outcomes of checkpoint inhibition in melanoma. *Cell Rep Med*. 2022 Feb 15;3(2):100500.

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Sade-Feldman M*, Kanterman J*, Klieger Y, Ish-Shalom E, Olga M, Saragovi A, Shtainberg H, Lotem M, Baniyash M. Clinical Significance of Circulating CD33+CD11b+HLA-DR- Myeloid Cells in Patients with Stage IV Melanoma Treated with Ipilimumab. *Clin Cancer Res*. 2016 Dec 1;22(23):5661-5672.

* Co-first authorship

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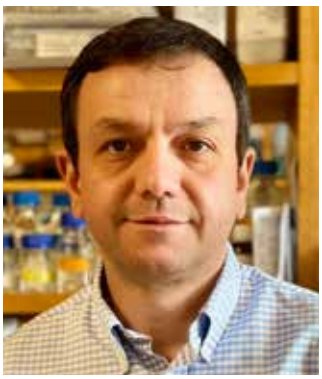


Sanidas Laboratory

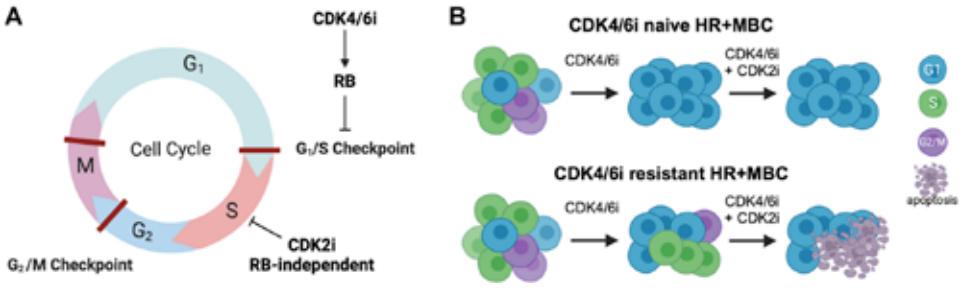
Kazi Islam, PhD
Connor G. McGrath
Ioannis Sanidas, PhD
Nicole J. Smith
Alice Zheng

Cell cycle deregulation is a hallmark of cancer. **The Sanidas laboratory** investigates how cancer cells bypass cell cycle control to uncover vulnerabilities that can be targeted for new therapeutic strategies. Our research focuses on the retinoblastoma (RB) tumor suppressor protein, a key regulator of cell division. In healthy cells, RB prevents unnecessary cell proliferation, but in many cancers, its function is turned off by proteins called cyclin-dependent kinases (CDKs). Although RB is a universal regulator of the cell cycle, RB loss is more common in certain tumors, and CDK inhibitors benefit only a subset of patients. The Sanidas laboratory aims to understand the molecular complexity of RB function and identify the context-specific implications of RB inactivation across human cancers. Our goal is to maximize the clinical potential of the recently developed selective CDK inhibitors and guide the development of next-generation targeted therapies that restore or mimic RB's tumor-suppressive activity.

Over the last decade, a substantial amount of research has been devoted to molecular therapeutics targeting RB's activation, leading to the development of highly selective CDK inhibitors. These efforts have resulted in advanced cancer therapy methods, significantly prolonging the survival rate in Breast Cancer patients. Despite the widespread deregulation of the RB pathway in cancer cells, the effectiveness of these drugs remains limited to specific tumor types. At the Sanidas laboratory, we aim to address this conundrum through two lines of investigation: 1) Understanding the molecular complexity of RB and deciphering the context-specific implications of RB inactivation in cancer cells. 2) Investigating how CDK inhibitors work in various tumor types, with the goal of enhancing drug efficacy and determining the group of patients that will primarily benefit from this treatment.

Investigation of RB's mechanism of action

RB has often been described as a highly conserved cell cycle regulator with a universal mechanism of action. According to this conventional model, RB targets the E2F-promoters to suppress the expression of cell cycle genes. This interaction is dependent on the cell cycle and inhibited by CDKs. However, this description explains only a part of RB's activity; RB is essential for the control of multiple transcriptional programs, the maintenance of chromosome stability, the commitment to cell lineage, and the emergence of drug resistance in cancer cells. These RB functions are context-specific and largely independent of RB/E2F regulation. It is acknowledged that additional investigations are required to decipher the mechanisms governing this "non-canonical" RB activity. A significant obstacle hindering progress in this area has been that the RB research community has never really figured out how to deal with the molecular complexity of RB. Many studies have focused on the consequences of RB loss without being able to capture the details of RB in action. In the Sanidas laboratory, we have successfully developed sophisticated molecular tools to unravel the complexity of RB's action. Precisely, we can now dissect RB into its distinct functional forms (Sanidas et al., 2019), separate the different pools of the chromatin-associated RB (Sanidas et al.,



Distinct mechanisms of CDK4/6 and CDK2 inhibition in hormone receptor (HR)-positive, human epidermal growth factor receptor-2 (HER2)-negative metastatic breast cancer (MBC). (A) CDK4/6 inhibitors (CDK4/6i) block cell cycle progression at the G1/S transition by activating RB. In contrast, CDK2 inhibitors (CDK2i) act independently of RB to suppress DNA replication and prevent mitotic entry. (B) Combination of CDK4/6i and CDK2i in HR+/HER2− MBC. In CDK4/6i-naive cells, CDK4/6i induces a robust G1 arrest, limiting the impact of CDK2 inhibition. In CDK4/6i-resistant models, CDK2i targets DNA replication in cells that bypass CDK4/6i-induced G1-arrest, resulting in enhanced synergistic activity between CDK4/6i and CDK2i.

2022), and identify, using Micro-C analysis, the RB-mediated regulation of chromatin organization. These groundbreaking tools can finally provide the information needed to study RB. We aim to i) define the cell type-specific functions of RB, ii) elucidate why RB's tumor suppressor activity varies among different tumor types, and iii) determine the factors contributing to the tumor type-specific efficacy of drugs targeting RB activation. With the aid of these innovative tools, we can look into RB's mechanism of action with a significantly improved resolution, shedding light on previously uncharted aspects of RB's activity in cancer biology.

Targeting the cell cycle machinery in cancer therapy

Reactivating the tumor suppressor function of RB represents a pivotal approach in molecular cancer therapeutics. In Estrogen Receptor-positive metastatic breast cancer, CDK4/6 inhibitors are now a standard treatment. Building on this approach, new selective CDK2 and CDK4 inhibitors are currently being tested in early-phase clinical trials, particularly for tumors that have developed resistance to CDK4/6 inhibition. The Sanidas laboratory collaborates with clinician scientists at the **Termeer Center for Investigational Cancer Therapeutics** at MGH to investigate the mechanisms of action of these next-generation cell cycle-targeting agents. Our goals are to: i) optimize the efficacy of cell cycle-targeting therapies by identifying synergistic combinations with other agents, and ii) discover predictive biomarkers of drug response to guide patient selection and improve clinical outcomes.

Selected Publications:

Knudsen ES*, Witkiewicz AK*, **Sanidas I***, Rubin SM* (2025). Targeting CDK2 for cancer therapy. *Cell Rep. 2025 Aug 26:44(8):116140.*

Sanidas I, Lawrence MS, & Dyson NJ. Patterns in the tapestry of chromatin-bound RB. *Trends Cell Biol*. 2023 Aug 28:S0962-8924(23)00156-3.

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Sanidas I, Lee H, Rumde PH, Boulay G, Morris R, Golczer G, Stanzione M, Hajizadeh S, Zhong J, Ryan MB, Corcoran RB, Drapkin BJ, Rivera MN, Dyson NJ, Lawrence MS. Chromatin-bound RB targets promoters, enhancers, and CTCF-bound loci and is redistributed by cell-cycle progression. *Mol Cell.* 2022 Aug 12:S1097-2765(22)00710-9.

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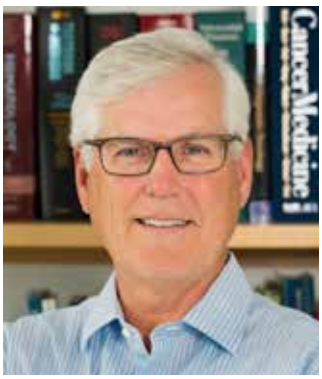
Sanidas I, Morris R, Fella KA, Boukhali M, Tai EC, Ting DT, Lawrence MS, Hass W and Dyson NJ. "A code of mono-phosphorylation modulates the function of RB." *Mol Cell* 2019, Mar 7;73(5):985-1000.

* Denotes equal contribution

David T. Scadden, MD



The Scadden Laboratory focuses on blood and bone marrow. Our goals are to define what governs blood cell production, how those processes are corrupted in disease, and how that information can be leveraged to develop novel therapies. We emphasize molecular, genetic, computational, and high-resolution imaging techniques to define how single molecules and single cells contribute to homeostasis, the success of stem cell transplantation, and the development of cancer. We emphasize those projects that can teach fundamental principles of biology while pointing the way to clinical advances.

Scadden Laboratory

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It is increasingly evident that both bone marrow stroma and the hematopoietic stem cells (HSCs) they support comprise a heterogeneous mix of clones, each with defined functional traits. Stromal stem cells that form niches and HSCs are distinct and have limited plasticity, constrained by epigenetic features set early in development. These features persist under physiological stress, leading to selective expansion of specific clones. As a result, hematopoietic tissue begins with a diverse mix of stem cells that becomes progressively constrained through the stresses of aging and environmental challenges. These stresses, including random mutations, affect different clones in distinct ways. Additionally, the interaction between stromal and hematopoietic clones in vivo further diversifies clonal outcomes. Thus, hematopoiesis serves as an excellent model for studying clonal dynamics and their impact on tissue behavior, resilience, and vulnerability.

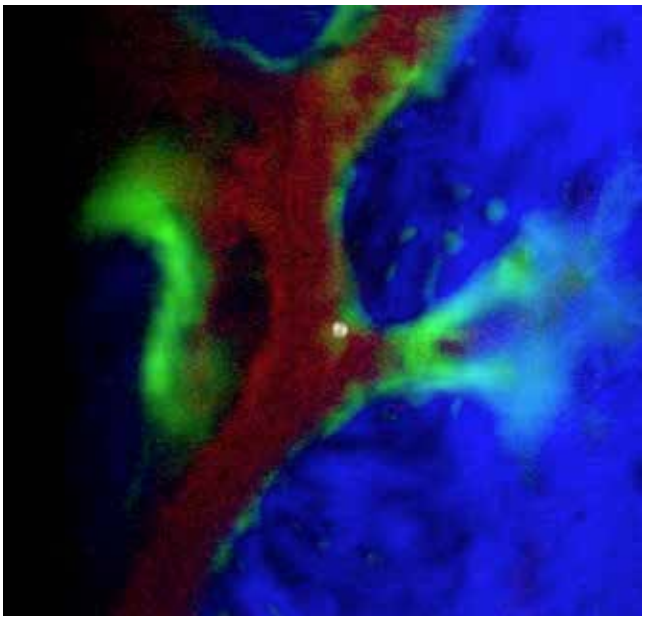
We apply this framework to study several disease states:

1. **Selective outgrowth of pathogenic inflammatory clones:**

   Clonal hematopoiesis, characterized by overgrowth of HSCs with specific mutations, is linked not only to malignancy but also to chronic conditions such as cardiac, lung, liver, kidney diseases, and osteoporosis. We suggest that mutations mark clonal selection, which more broadly reflects selection based on functional traits like cytokine sensitivity. Chronic conditions such as hypertension or obesity—and even temporary states like pregnancy—may select for particular HSC subpopulations. These positively selected populations establish a new homeostatic baseline that retains a "memory" of prior stress, shaping future responses. We term this concept *clonal hematopoiesis of epigenetic provenance* (CHEP), which is currently under investigation.

2. **Selective HSC-stroma interactions supporting malignancy:**

   Our prior work demonstrated that leukemic clones alter bone marrow stromal composition. Additionally, acquired genetic abnormalities in stroma alone can induce myelodysplastic syndromes (MDS) and the expansion of malignant clones. We hypothesize that a bidirectional selection between hematopoietic and stromal clones promotes malignancy. Ongoing studies aim to identify the molecular mediators of this intercellular cooperation. Pinpointing these modifiers may reveal new therapeutic targets to disrupt disease-promoting interactions.



We are interested in physiology resolved to single cell and single molecule events. How a tissue responds to stress is ultimately conducted at cell and molecular levels that offer opportunities for manipulation to improve resilience. Above is a high resolution in vivo image obtained in collaboration with Dr. Charles Lin that captures a single hematopoietic stem cell after transplantation as the engraftment process begins.

3. Transient vulnerability to eliminate chemotherapy persistence:

Exogenous exposures reshape clonal composition, and we propose the same holds true for leukemia under chemotherapy. We tested whether chemotherapy selects for leukemic cells with metabolic features that enable survival during the stress of treatment. Using untargeted metabolomics in vivo, we profiled acute myeloid leukemia (AML) cells before, immediately after, and during relapse. Post-chemotherapy cells showed distinct metabolic traits not seen during relapse or detected via genetics. Persistence-related pathways were identified using small molecule and CRISPRi screens. We validated several gene products critical to this persistent state and showed that inhibiting them post-chemotherapy improved survival and reduced relapse in humanized mouse models of chemoresistant AML. Drug development efforts targeting these vulnerabilities are now underway.

4. Thymus niche manipulation to enhance adaptive immunity:

Building on earlier identification of HSC niche components in bone marrow, we examined the thymus, essential for α/β T cell development and adaptive immunity. Though long thought to be vestigial in adults, we recently showed that the thymus remains vital to human health; thymectomy in middle age increases 10-year mortality, primarily due to cancer. Others have demonstrated thymus regeneration via lymphoid progenitor infusion. We have now identified a mesenchymal cell subset in the thymus that acts as a niche, recruiting circulating T-competent progenitors. Furthermore, we found that some HSC subclones exhibit enhanced T cell potential, a trait that persists through serial transplantation. We are currently developing strategies for thymic regeneration by simultaneously enhancing niche function and HSC T cell competence, aiming to restore immune function in aging.

Selected Publications:

Kooshesh K, Foy BH, Sykes DB, Gustafsson KU, **Scadden DT**. The adult thymus is critical for health. *N Engl J Med.* 2023;389:406-417.

Baryawno N, Przybylski D, Kowalczyk MS, Kfoury Y, Severe N, Gustafsson K, Kokkaliaris KD, Mercier F, Tabaka M, Hofree M, Dionne D, Papazian A, Lee D, Ashenberg O, Subramanian A, Vaishnav ED, Rozenblatt-Rosen O, Regev A, **Scadden DT**. A cellular taxonomy of the bone marrow stroma in hematopoiesis and leukemia. *Cell.* 2019 Jun 13;177:1915.

Yu V, Yusuf RZ, Oki T, Wu J, Saez B, Wang X, Cook C, Baryawno N, Ziller MJ, Lee E, Gu H, Meissner A, Lin CP, Kharchenko PV, **Scadden DT**. Epigenetic memory underlies cell-autonomous heterogeneous behavior of hematopoietic stem cells. *Cell.* 2016 Nov 17;167(5):1310-1322.

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Lo Celso C, Fleming HE, Wu JW, Zhao CX, Miake-Lye S, Fujisaki J, Cote D, Rowe DW, Lin CP, **Scadden DT**. Live-animal tracking of individual haematopoietic stem/progenitor cells in their niche. *Nature.* 2009;457(7225):92-96.

Calvi LM, Adams GB, Kronenberg H, **Scadden DT**. Osteoblastic cells regulate the hematopoietic stem cell niche. *Nature.* 2003;425(6960): 841-846.

Debattama Sen, PhD

Sen Laboratory

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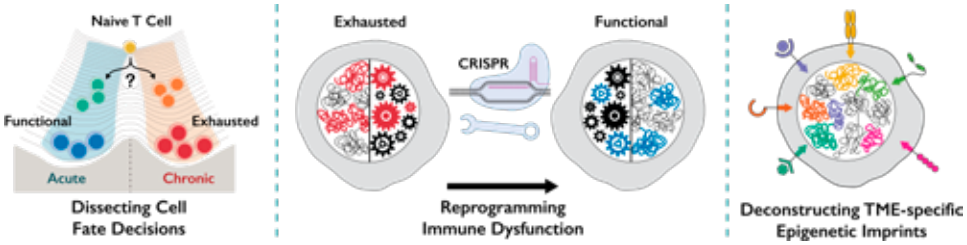
Dysfunction of the immune system is central to disease progression in cancer. **The Sen laboratory** investigates the drivers of T cell dysfunction in tumors and explores epigenetic approaches for T cell engineering. Epigenetic reprogramming tunes gene activity (and thus cell behavior) without permanently removing gene function. We have found that the regulatory "circuitry" of dysfunctional or exhausted T cells differs remarkably from functional T cells and cannot be rescued by current treatments. Therefore, improved understanding of this altered regulatory circuit will be critically important for reversing cancer-associated immune dysfunction. We also pinpoint a radical new approach where we can "tune" specific components of the circuitry in immune cells to remedy their pathological state in cancer while preserving their physiological role in other contexts, minimizing unwanted side-effects in patients. Thus, our work lies at the interface of human immunology, systems biology, and functional epigenomics – merging clinical observations with mechanistic studies to develop novel therapies.

Effective immunotherapy responses have been limited in 50-70% of patients, in part due to the development of T cell exhaustion wherein CD8+ T cells become dysfunctional and fail to control tumor growth. Despite ongoing clinical efforts to target exhaustion, the fundamental mechanisms specifying this state, and the potential for reinvigorating exhausted T cells, remain poorly understood.

Cell fate and behavior are governed at the level of the epigenome, through transcription factors (TFs) binding to regulatory enhancers. Therefore, we have used the gold-standard mouse model of chronic viral infection to ask whether distinct epigenetic regulation drives CD8+ T cell exhaustion. These studies revealed for the first time that exhausted cells acquire an extensive, state-specific epigenetic program that is distinct from memory T cells. We then integrated systems-level characterization of T cell state with CRISPR/Cas9-based enhancer editing in mouse T cell lines to show that these putative enhancers are organized into functional modules and can directly regulate exhaustion-associated genes such as PD-1.

We have sought to translate these findings to other disease contexts. First, by comparison of mouse T cells to those isolated from HCV and HIV chronic infection, we identified a conserved epigenetic program of exhaustion across species. Second, using a mouse melanoma model, we found that tumor-specific CD8+ T cells also share critical epigenetic and transcriptional features with chronic viral infection. Thus, we address a long-standing controversy about how T cell states in cancer relates to chronic viral infection by showing that T cell exhaustion is a fundamental immune adaptation to settings of chronic stimulation. Simultaneously, we have identified epigenetic signatures unique to either disease paradigm, highlighting our ability to define context-specific regulation in an unbiased way.

Nevertheless, major questions still remain about whether the exhausted epigenetic state is fixed or plastic in response to current treatment modalities. Recently, we examined two of the most prominent therapies to



Leveraging the epigenetic regulation of T cell exhaustion to address fundamental and translational questions: How do T cells commit to exhaustion? How can we rescue exhausted T cells? How do disease-specific tumor microenvironments (TME) shape T cell exhaustion?

treat chronic infection and cancer: curative anti-viral regimens and immune checkpoint blockade, respectively. In chronic infection, ATAC-seq analysis of HCV-specific CD8+ T cells after cure of viremia did not reverse canonical features of exhaustion, including active super-enhancers near key TFs. In cancer, anti-PD-1 treatment of melanoma tumors also could not rescue the exhausted epigenetic state. T cell exhaustion is therefore an evolutionarily conserved epigenetic state that becomes fixed and is not reversed by some of the most common therapies. Most recently, we have investigated the etiology and effect of age-related immune dysfunction in cancer. We dissected the independent contribution of *cell-intrinsic* vs. *cell-extrinsic* mechanisms towards age-related decline of anti-tumor immunity and identified a novel state of age-associated T cell dysfunction (T_{TAD}) that is conserved in mouse and human tumors.

It is becoming evident that alleviating T cell dysfunction will require new targeted approaches to reprogram exhausted cells. Our studies strongly suggest that large-scale epigenetic analysis, paired with precise CRISPR/Cas9 manipulation, will provide a roadmap for rational engineering to prevent T cell exhaustion and improve patient outcomes. To accomplish this, my lab focuses on the following:

1. Dissecting epigenetic mechanisms that govern differentiation of CD8 T *in vivo*
2. Defining context-dependent epigenetic map of T cell dysfunction to guide patient therapies
3. Engineering exhaustion-resistant CD8 T cells through epigenetic manipulation

These projects will generate new insights into the mechanisms and contexts in which T cell exhaustion develops in order to better design patient-specific immunotherapy regimens. In addition, they will enable unprecedented context-specific manipulation of T cell responses and create an integrative framework for characterizing and reprogramming epigenetic regulation of immune dysfunction.

Selected Publications:

Ji KY, Yerinde C, Davidson RA, Gerdemann U, Schwartz MA, **Sen DR**. Scalable hit-and-run platform for enhancer deletion reveals state-specific IFNG regulation in primary human T cells. *Nature Communications* (in review)

Weiss SA, Huang AY, Fung ME, Martinez D, Chen ACY, LaSalle TJ, Miller BC, Scharer CD, Hegde M, Nguyen TH, Rowe JH, Osborn JF, Patterson DG, Sifnugel N, Mei-An Nolan C, Davidson RA, Schwartz MA, Bally APR, Neeld DK, LaFleur MW, Boss JM, Doench JG, Nicholas Haining W, Sharpe AH*, **Sen DR***. Epigenetic tuning of PD-1 expression improves exhausted T cell function and viral control. *Nature Immunology.* 2024 Oct;25(10):1871-1883.

Chen ACY, Jaiswal S*, Martinez D*, Yerinde C,... Garris CS, Mempel TR, Hacohen N, **Sen DR**. The aged tumor microenvironment limits T cell control of cancer. *Nature Immunology.* 2024 Jun;25(6):1033-1045.

Yates KB, Tonnerre P, Martin GE, Gerdemann U,...Chung RT, Allen TM, Kim AY, Fidler S, Fox J, Frater J, Lauer GM, Haining WN*, **Sen DR***. Epigenetic scars of CD8+ T cell exhaustion persist after cure of chronic infection in humans. *Nature Immunology*. 2021 Aug;22(8): 1020-1029.

Paper was highlighted on the cover of the Aug 2021 issue of Nature Immunology.

Miller BC*, **Sen DR***, Al-Abosy R, Bi K,... Hodi FS, Rodig SJ, Sharpe AH, Haining WN. Subsets of exhausted CD8+ T cells differentially mediate tumor control and respond to checkpoint blockade. *Nature Immunology*. 2019 Mar;20(3):326-336.

Sen DR*, Kaminski J*, Barnitz RA, Kurachi M,...Chung RT, Allen TM, Frahm N, Lauer GM, Wherry EJ, Yosef N, Haining WN. The epigenetic landscape of T cell exhaustion. *Science*. 2016 Dec 2;354(6316): 1165-1169.

Paper was highlighted on the cover of the Dec 2016 issue of Science.

*Equal contribution

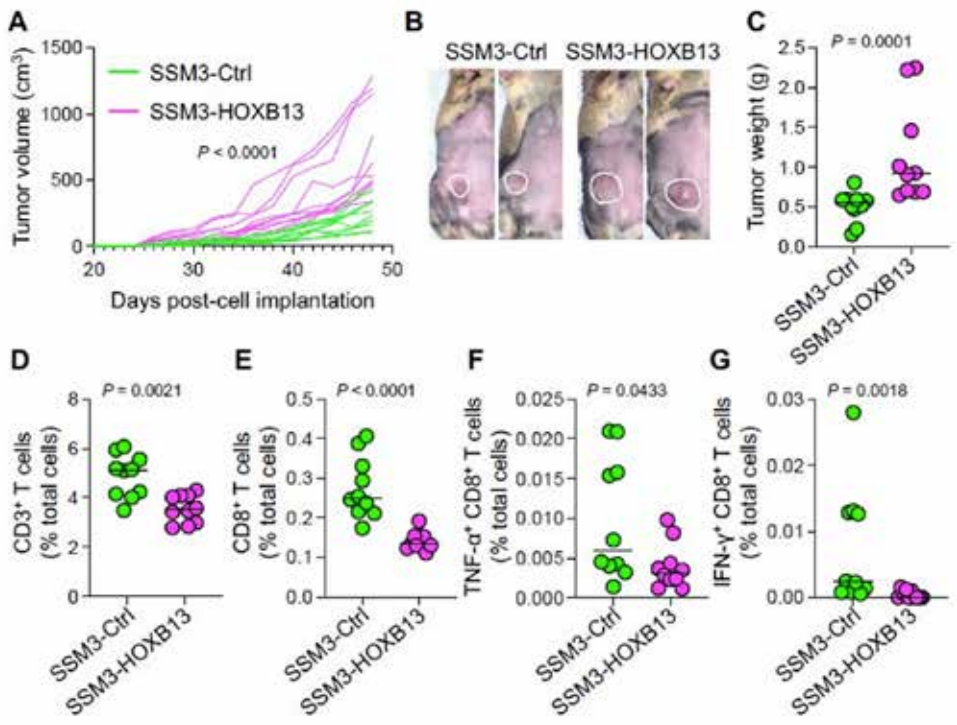
Dennis Sgroi, MD

Sgroi Laboratory

Dennis Sgroi, MD
Marinko Sremac, PhD

The overarching goals of research in **the Sgroi laboratory** are to detect molecular alterations in breast cancer that identify breast cancer patients who are at risk of developing a recurrence and those who will benefit from specific therapies to prevent disease recurrence. We have developed a clinical test in which the measurement of two genes, HOXB13 and IL17RB predicts whether a patient with estrogen receptor (ER) positive breast cancer will benefit from extending hormonal targeted therapy. Using mouse models of ER-positive and ER-negative breast cancer, we have recently demonstrated that the gene HOXB13 confers a tumoral growth advantage by suppressing the local tumor immune response. Our lab is currently using advanced spatial genomic technologies in human breast cancer samples to dissect the molecular mechanisms resulting in tumoral immune suppression. We anticipate that our findings will lead to the development of novel therapeutic strategies for women with breast cancer.

Our laboratory focuses on integrating multi-omic approaches to identify biomarkers that will predict clinical outcome and treatment response. Our lab has developed the Breast Cancer Index (BCI) gene expression biomarker, and we have validated its prognostic and treatment-predictive performance in multiple randomized clinical trials of extended adjuvant hormonal therapy in post-menopausal women with ER+ breast cancer. Our successful validation of the BCI biomarker has led to clinical adoption in the NCCN and ASCO treatment guidelines. As a natural extension of our biomarker studies, we are currently exploring the role of the gene *HOXB13*, the primary determinant of the prognostic and predictive performance of the BCI assay. Our group performed comparative gene expression analysis of *HOXB13*-expressing (*HOXB13*+) and *HOXB13* non-expressing (*HOXB13*-) TCGA tumors as well as comparative mass spectometry-based proteomic analysis of *HOXB13*+ and *HOXB13*- tumors and identified multiple interferon pathway gene sets common to both analyses, suggesting that *HOXB13* plays a role in the tumor immune microenvironment. To assess the role of *HOXB13* in the tumor immune microenvironment, we ectopically expressed *HOXB13* in the SSM3 mouse model of ER+ breast cancer. In this ER+ model, we have demonstrated that *HOXB13* confers a tumoral growth advantage by creating an immunosuppressive tumor microenvironment characterized by a significant decrease in tumoral activated CD8 T cells. In the triple negative (ER-, PR- and HER2-) PyMT mouse model of breast cancer, we have shown that *HOXB13* creates an identical alteration of the tumor immune microenvironment, and that *HOXB13*-mediated immunosuppression can be reversed through manipulation of reproductive hormones. Taking advantage of the large human breast cancer tissue repository in the Department of Pathology, our laboratory is performing comparative spatial immuno-oncology transcriptomic profiling in well-annotated cohorts of ER+ and TNBC *HOXB13*+ and *HOXB13*- human breast cancers.



HOXB13expression promotes ER+ breast tumor growth. A, SSM3-HOXB13 and SSM3-Control (Ctrl) breast tumor volume in wild-type (WT) mice over time. WT mice on the 129S6/SvEv background were challenged with 1 x 105 cancer cells implanted in the inguinal mammary fat pad. B, Representative macroscopic images of tumors developed from SSM3-HOXB13 and SSM3-Ctrl cells at endpoint. C, The tumor weights at endpoint, D-G, Quantification of tumor-infiltrating CD3+ T cells (D), CD8+ T cells (E), TNF-a+ CD8+ T cells (F), and IFN-g+ CD8+ T cells (G) in SSM3-HOXB13 and SSM3-Ctrl breast tumors as a percentage of total cells in the tumor by flow cytometry. n=10 tumors per group, two-way ANOVA (A), unpaired t-test (C-G)

Lastly, our laboratory is also studying the potential role of *HOXB13* in HER2 (*ERBB2*) positive breast cancer. In the TCGA breast cancer cohort, we discovered that *HOXB13* gene expression was significantly higher in HER2+ versus HER2- breast cancers, and its expression was also significantly higher in the ER- versus ER+ breast cancers. *HOXB13* is frequently co-gained or co-amplified with *ERBB2*. Joint copy gains of *HOXB13* and *ERBB2* occurred with low-level co-gains or high-level co-amplifications (co-amp), the latter of which is associated with an interstitial loss that includes the tumor suppressor BRCA1. *ERBB2*/*HOXB13* co-amp tumors with interstitial BRCA1 loss exhibit a mutational signature associated with APOBEC deaminase activity and copy number signatures associated with chromothripsis and genomic instability. Among *ERBB2*-amplified tumors of different tissue origins, *ERBB2*/*HOXB13* co-amp with a BRCA1 loss appeared to be enriched in breast cancer compared to other tumor types. Notably, in patients with *ERBB2*/*HOXB13* co-amplified and BRCA1 lost tumors displayed a significantly shorter progression-free survival than those with *ERBB2*-only amplifications and this difference in progression-free survival was restricted to the ER- subset patients. We are currently exploring therapeutic strategies to treat such tumors.

Selected Publications:

Mitsiades IR, Onozato M, Iafrate AJ, Hicks S, Gulhan DC, **Sgroi DC**** and Rheinbay E. ERBB2/HOXB13 co-amplification with interstitial loss of BRCA1 defines a unique subset of breast cancers. *Breast Cancer Res*. 2024; 24:185.

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Sgroi DC, Treuner K, Zhang, Y, Piper T, Salunga R, Ahmed I, Doos L, Thornber S, Taylor KJ, Brachtel E, Pirrie S, Schnabel CA, Rea D, Bartlett JMS. Correlative studies of the Breast Cancer Index (HOXB13/IL17BR) and ER, PR, AR, AR/ER ratio and Ki67 for prediction of extended endocrine therapy benefit: a Trans-aTTom study. *Breast Cancer Res.* 2022 Dec 16;24(1):90.

Bartlett JMS, **Sgroi DC***, Treuner K, Zhang Y, Piper T, Salunga RC, Ahmed I, Doos L, Thornber S, Taylor KJ, Brachtel EF, Pirrie SJ, Schnabel CA, Rea D. Breast Cancer Index is a predictive biomarker of treatment benefit and outcome from extended tamoxifen therapy: final analysis of the Trans-aTTom study. *Clin Cancer Res.* 2022; 28:1871-80.

Li K, Li T, Feng Z, Huang M, Wei L, Yan Z, Long M, Hu Q, Wang J, Liu S, **Sgroi DC**, Demehri S. CD8+ T cell immunity blocks the metastasis of carcinogen-exposed breast cancer. *Sci Adv.* 2021 Jun 18;7(25): eabd 8936.

Bartlett JMS, **Sgroi DC***, Treuner K, Zhang Y, Ahmed I, Piper T, Salunga R, Brachtel EF, Pirrie SJ, Schnabel CA, Rea DW. Breast Cancer Index and prediction of benefit from extended endocrine therapy in breast cancer patients treated in the Adjuvant Tamoxifen-To Offer More? (aTTom) trial. *Ann Oncol.* 2019 Nov 1;30(11):1776-1783.

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Diana D. Shi, MD

Shi Laboratory

[Opens Fall of 2025]

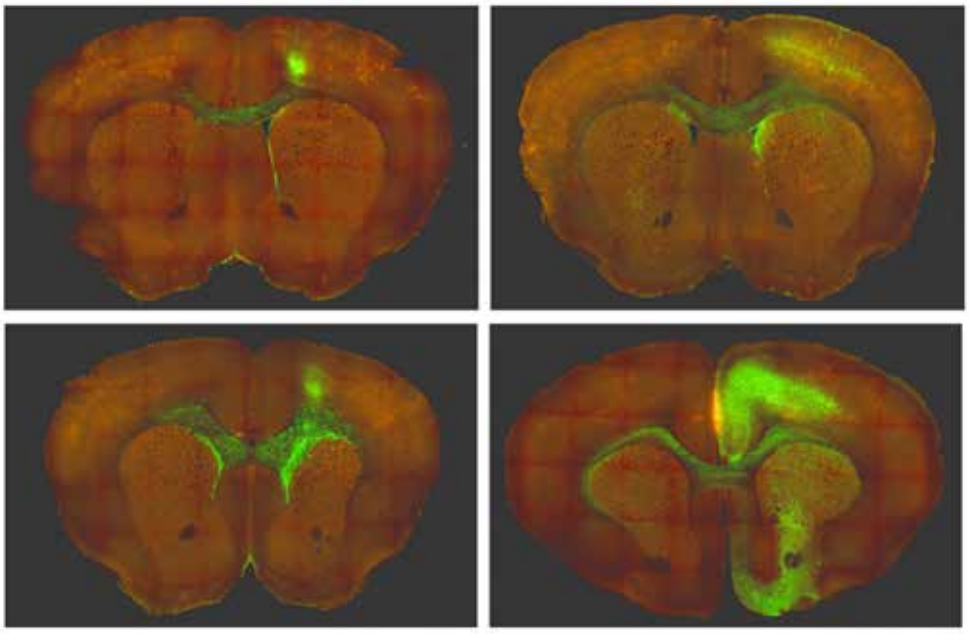
Dorothy Junginger, BA
Diana D. Shi, MD
Alexander Tsai, BA

Gliomas are the most common primary brain tumors, a subset of which have mutations in the gene isocitrate dehydrogenase 1 (*IDH1*). Though IDH-mutant gliomas are distinct in their clinical behavior, much remains unknown about how IDH mutations alter glioma biology. **The Shi laboratory** aims to understand how IDH mutations induce metabolic, epigenetic, and transcriptional changes in glioma in order to develop new treatments for this disease. To achieve this goal, we have developed and use genetically engineered mouse models that capture key biology of IDH mutations in glioma. In addition, we employ engineered patient-derived cell and animal models to test preclinical treatment strategies that are poised for clinical translation. We couple these studies with functional genomic screening, pharmacologic screening, and mechanistic experimental cell biology to identify new therapies for both IDH-mutant gliomas and other epigenetically and/or metabolically dysregulated cancers.

Gliomas are the most common primary brain tumors in adults, a subset of which have mutations in the metabolic gene isocitrate dehydrogenase 1 *(IDH1)*. Cancer-associated IDH1 mutants are gain-of-function mutations that produce the oncometabolite 2-hydroxyglutarate [(*R*)-2HG]. (R)-2HG is thought to transform cells by competitively inhibiting 2OG-dependent dioxygenases, many of which are epigenetic regulators, given the structural similarity of (R)-2HG and 2OG. However, much remains unknown about how these downstream effects of mIDH drive tumor growth and therapeutic efficacy. My research interests center on understanding the biology of IDH-mutant gliomas and their response to treatment, and using that information to uncover central functions of epigenetic and metabolic reprogramming in cancer. To address these questions, we made a genetically engineered mouse (GEM) model that can be used to study key IDH-mutant biology in glioma. We have leveraged this GEM and other models to show that IDH-mutant gliomas are sensitive to de novo pyrimidine synthesis inhibitors (e.g. dihydroorotate dehydrogenase (DHODH) inhibitors) due to an increased susceptibility of IDH-mutant cells to replication stress caused by these drugs. Ongoing work aims to build on these findings across three areas of investigation:

Identifying and functionally assessing mutant IDH inhibitor response and resistance in glioma

The mutant IDH (mIDH) inhibitor vorasidenib has been recently FDA approved for the treatment of select IDH-mutant glioma patients and has become standard-of-care. However, response to mIDH inhibitors is heterogeneous, and our understanding of how these drugs work in glioma has been severely limited by a lack of faithful animal models that respond to mIDH inhibition. To address this gap, we developed an IDH-mutant GEM model and found that it responds to mIDH inhibitor treatment. We are now using this model to perform single-cell multiomics sequencing, spatial transcriptomics, metabolomics, and methylation profiling to understand mechanisms underlying response to mIDH inhibitors in glioma. Our goal is to leverage



Green fluorescent protein (GFP) imaging of glioma tumor development over time in a genetically engineered mouse model of IDH-mutant glioma developed by the lab. Glioma tumor cells are GFP+.

the knowledge gained from these studies to perform functional testing to understand how IDH-mutant gliomas respond, or become resistant to, mIDH inhibitor therapy.

Understanding the interaction between mutant IDH inhibition and radiation

While many patients benefit from mIDH inhibitor therapy, patients inevitably progress and require second-line treatment with chemotherapy and/or radiation. While mIDH is known to cause altered response to DNA damage, it is unknown how mIDH inhibition affects efficacy of chemoradiation. We are using our IDH-mutant GEM to perform efficacy and molecular profiling studies to understand how mIDH inhibitors alter chemoradiation efficacy. We are profiling both tumor-intrinsic and immune microenvironmental effects of mIDH (and mIDH inhibition) that affect response to radiation and alkylating agents. Results from this work may inform rational concurrent and/or sequential treatment regimens combining mIDH inhibitors, radiation, and chemotherapy.

Identifying how epigenetic alterations affect response to therapeutic stress

IDH-mutant glioma patients who are resistant to mIDH inhibition require effective alternative treatment options. Our previous work identified that DHODH inhibitors are effective in IDH-mutant gliomas due to a sensitivity to replication stress conferred by mIDH. We have since identified that inhibition of specific dioxygenases mediates this sensitivity to replication stress, and we are interested in (1) whether inhibition of these dioxygenases sensitizes to drugs that induce replication stress across non-glioma cancer types, and (2) how epigenetic alterations functionally alter replication stress response.

Taken together, these areas of investigation aim to pursue mechanistic investigations with faithful preclinical models to inform rational therapeutic strategies for IDH-mutant glioma patients. More broadly, our goal is to use insights from IDH-mutant glioma to understand how metabolic and epigenetic alterations affect tumor biology and therapeutic stress across cancer types.

Selected Publications:

Xiao Y, **Shi DD**, et al. Mutant IDH silences GSX2 to reprogram neural progenitor cell fate and promote gliomagenesis. *BioRxiv*. 2025 Aug 13.

Sternisha AC, Li H, Traylor JI, Guo L, Jun JH, Zhao X, Gajendra K, Ouyang Q, Schmidt M, Fleishman M, **Shi DD**, Savani MR, Xiao Y, Lee JH, Zacharias LG, Mathews TP, Gordillo R, Kim YJ, Xu L, Doench JG, Koduri V, Abdullah KG, Banaszynski LA, Agathocleous M, DeBerardinis RJ, Morrow EM, McBrayer SK. A transcriptional biosensor reveals mechanisms of α-ketoglutarate signaling to chromatin. *BioRxiv*. 2025 April 21.

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Shi DD, Lee JH, Wang AC, Khanal J, Gao W, Kaelin WG Jr, McBrayer SK. Protocol to establish a genetically engineered mouse model of IDH1-mutant astrocytoma. *STAR Protoc*. 2023 May 6;4(2):102281.

Shi DD, Savani MR, … Kaelin WG Jr, McBrayer SK. De novo pyrimidine synthesis is a targetable vulnerability in IDH mutant glioma. *Cancer Cell*. 2022 Sep 12;40(9):939-956.e16.

Shi DD, Youssef GC, Nassar AH, Lim-Fat MJ, Ligon KL, Wen PY, Rahman R. Improved survival among females and association with lymphopenia in patients with newly diagnosed glioblastoma. *Neuro Oncol*. 2022 Nov 2;24(11):2005-2007.

Toshihiro Shioda, MD, PhD

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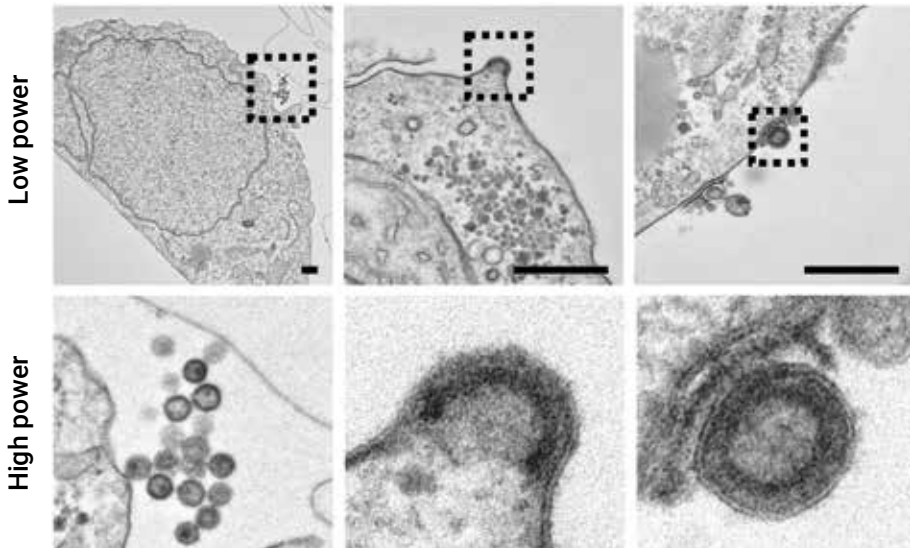
The Shioda laboratory studies Primordial Germ Cells (PGCs), which emerge in embryos as the common precursor of all germ cells. Transformation of male PGCs causes testicular cancer, the most common malignancy among young men. Injuries of male germ cells reduce normal sperm counts and quality, causing worldwide and rapid increase in the male infertility ratio. The use of chemotherapy agents to treat cancer in pregnant women or young children may impair the genome of germ cells to cause not only infertility but also heritable disorders. To overcome technical and ethical hurdles to study germ cells in embryos or children, our laboratory uses PGCLCs (PGC-Like Cells), a cell culture surrogate model of PGCs derived from human iPS cells. Our goals are (i) to recapitulate the process of testicular cancer formation using PGCLCs generated from patients-derived iPS cells; (ii) to identify environmental toxicants that harm PGCLCs transplanted into organ culture mouse embryonic testes; and (iii) to evaluate genomic toxicity of chemotherapy agents to human germ cells.

Long-term maintenance of human PGCLCs *in vitro*

The Primordial Germ Cell-Like cells (PGCLCs) is a cell culture model derived from iPS cells and faithfully resembling embryonic PGCs. However, human PGCLCs rapidly lose their PGC-like characteristics in 10-14 days of culture. This technical barrier has prevented the use of PGCLCs in various studies that require large numbers of homogeneous cells. Our laboratory has successfully overcome this hurdle and established a novel protocol that supports amplification of PGCLCs perpetually in a serum-free, feeder-free condition without losing their PGC-like characteristics, achieving one-billion-fold increase in cell number over 160-days of culture. Our Long-Term Culture (LTC) PGCLCs proliferate with no sign of senescence while strictly maintaining their PGC-like transcriptomal profile and marker protein expression. The LTC-PGCLC provided us with a unique opportunity to perform proteomics analysis (with Dr. Wilhelm Haas, KF-CCR), which detected strong expression of retrovirus-like proteins. We found that LTC- PGCLCs robustly produce retrovirus-like particles from their surface and that the HML-2 human endogenous retrovirus is responsible for the formation of these virus-like particles. Focused re-analysis of previously published single-cell RNA-seq data of human embryos also supported strong HML-2 activation in PGCs *in vivo*. Because evidence is rapidly accumulating that HML-2 activation is relevant to various cancers such as melanomas as well as autoimmune diseases or aging, our LTC-PGCLC model provides unprecedented opportunities to study the mechanisms behind the physiological activation of HML-2 in PGCs and the subsequent epigenetic suppression in early-stage germ cells, which may provide clues to understand the malignancy/aging-associating reactivation of HML-2.

In vitro modeling of human testicular cancers

Testicular cancer is the most common malignancy among 15-35 year-old men. The vast majority of testicular cancer is



HML-2 human-specific endogenous retroviruses form virus-like particles at the surface of human primordial germ cell-like cells (hPGCLCs). hPGCLC is a pluripotent stem cell-derived cell culture model of human primordial germ cells, which are the earliest precursor of all germline cells. The viral capsid is assembled beneath the cell surface (center) and eventually pinched out of the cells with plasma membrane surrounding it as viral envelope (right). The virus-like particles are often released from hPGCLCs as aggregates (left).

the Type II germ cell tumor, which consists of various pathological subtypes that significantly differ in their biological and clinical characteristics. All subtypes of testicular cancer arise from PGC, although the mechanism of subtype determination is unknown. In collaboration with members in MGH Urology (Keyan Salari, Philip Saylor, Richard Lee) and Urological Pathology (Chin-Lee Wu), we have established novel testicular cancer cell lines that reflect the representative testicular cancer subtypes – namely, seminoma, embryonal carcinoma, and yolk sac tumor. One of these novel cell lines are capable of differentiating from seminoma-like characteristics to yolk sac tumor via embryonal carcinoma in mice as transplanted tumor tissues, and similar differentiation is recapitulated in cell culture. We suspect that this multi-potency testicular cell line may reflect the Germ Cell Neoplasia In Situ (GCNIS), which are transformed cells amplifying within the seminiferous tubules and presumed as the precursor lesion of invasive testicular cancers. We are currently expanding and characterizing multiple novel testicular cancer cell lines, patients-derived iPS cells, and PGCLCs derived from these iPSCs. By systematically introducing genetic mutations found in the cancer cell lines to the counterpart human PGCLCs, we attempt to recapitulate testicular carcinogenesis in organ culture of mouse embryonic testes and reconstituted, cell suspension-derived organoid culture *in vitro*.

Selected Publications:

Pierson Smela MD et al. Rapid human oogonia-like cell specification via transcription factor-directed differentiation. *EMBO Rep*. 2025. 26:1114-1143.

Vargas BC and **Shioda T**. Association Between Activated Loci of HML-2 Primate-Specific Endogenous Retrovirus and Newly Formed Chromatin Contacts in Human Primordial Germ Cell-like Cells. *Int J Sci*. 2024. 25:13639.

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Pierson Smela MD et al. Directed differentiation of human iPSCs to functional ovarian granulosa-like cells via transcription factor overexpression. *eLife*. 2023. 12:E83921.

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Mikołaj Słabicki, PhD

The Słabicki laboratory is dedicated to expanding the druggable proteome by employing functional genomics and targeted protein degradation. We harness the body's own waste disposal machinery, especially the E3 ligases which can flag malfunctioning proteins for disposal, to develop new treatments. Leveraging our extensive expertise in functional genomics, cell biology, bioinformatics, molecular biology, chemical biology, and biochemistry, we reprogram the ubiquitin-proteasome system to identify and characterize novel therapeutic modalities. Our work enhances our fundamental understanding of biology and enables the creation of new treatments for diseases that currently lack therapeutic options.

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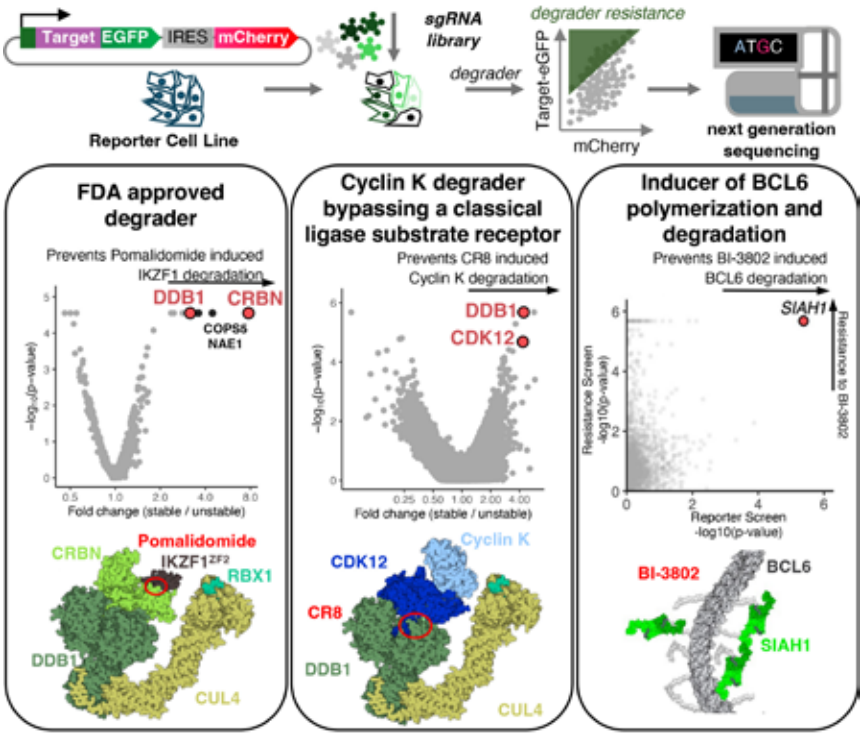
Mikołaj Słabicki, PhD
Alicia Stein, PhD

Targeted protein degradation (TPD) is an exciting and novel pharmacological modality in which the ubiquitin proteasome system (UPS) is reprogrammed to induce depletion of targets that are often otherwise undruggable. Unlike traditional occupancy-based inhibitors, TPD utilizes event-based pharmacology, degrading multiple target protein molecules with a single drug molecule, possibly enhancing clinical effectiveness. Two main classes of degraders exist. First, monovalent molecular glue degraders - such as the clinically-used thalidomide, lenalidomide, and pomalidomide - were discovered to work by binding to an E3 ligase and degrading neo-substrates. Second, PROteolysis TArgeting Chimeras (PROTACs) are rationally designed bi-functional molecules that contain two moieties: one that binds to a target protein and one that engages an E3 ubiquitin ligase.

The Słabicki laboratory will advance both foundational knowledge and therapeutic innovation in protein degradation by developing new approaches and establishing new workflows. For example, we have extensively optimized a generalizable fluorescent reporter and flow cytometry-based CRISPR screening method to identify genes that regulate the post-translational stability of any protein of interest. By elucidating the mechanisms governing target-ligase interactions, we aim to expedite the discovery and optimization of promising drug candidates.

Our recent research led to the identification of the kinase inhibitor CR8 as a molecular glue degrader. Unlike previous examples of degraders, CR8 induces an interaction between a target and a substrate adaptor in the absence of a traditional substrate receptor. CR8 induces a neo-interaction between the CDK12-cyclin K complex and DDB1, inducing the ubiquitination and subsequent degradation of cyclin K (Słabicki M, Kozicka Z, Petzold G, et al., *Nature*. 2020). We also identified the intricate mechanism through which the small molecule BI-3802 promotes the polymerization of the oncogenic transcription factor BCL6, leading to enhanced ubiquitination by the E3 ligase SIAH1 and subsequent proteasomal degradation (Słabicki M, Yoon H, Koeppel J, et al., *Nature*. 2020). Both findings revealed novel mechanisms by which proteins can be degraded, expanding the repertoire of therapeutic opportunities for otherwise difficult-to-target proteins.

Building on the small molecule-induced polymerization of BCL6, our team has developed a drug-induced, reversible polymerization switch. By fusing BCL6-BTB



The Słabicki laboratory is dedicated to expanding the druggable proteome by employing functional genomics and targeted protein degradation. To understand how small molecules lead to target degradation reporter cell lines are infected with the CRISPR library, and the degrader-resistant population is flow-sorted, with enriched sgRNAs deconvoluted by next-generation sequencing. Results for different molecular mechanisms of targeted protein degradation are presented alongside the drug-induced complexes.

domain to the epidermal growth factor receptor (EGFR), we were able to activate downstream signaling pathways and promote cellular proliferation, when the polymerization-inducing drug was present, even in the absence of epidermal growth factor (EGF), (Nitsch, L. et al. *Cell Rep Methods*, 2022). We also defined how the human E3 ligase RNF185 influences the stability of the SARS-CoV-2 Envelope protein (Zou, C., et al., *iScience*, 2023). Currently, our team is engaged in a project that aims to broaden the scope of human zinc finger degrons targeted by glutaramide analogs via CRBN.

The Słabicki laboratory's future research will use high throughput chemical genomic approaches to systematically dissect the protein homeostasis machinery for clinically relevant targets. We will further elucidate the mechanisms governing protein-ligase interactions, establish comprehensive E3-ligase target maps, and expand the array of targets amenable to small molecule-mediated degradation. Our ultimate objective is to advance the development of precision-based therapeutic interventions, particularly in the field of oncology, while simultaneously establishing a comprehensive framework for identifying E3 ligases for unique protein targets.

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The Stott laboratory is comprised of bioengineers, biologists and chemists focused on translating technological advances to relevant applications in clinical medicine. Specifically, we are interested in using microfluidics, imaging, and biopreservation technologies to create tools that increase our understanding of cancer biology and of the metastatic process. The Stott laboratory has co-developed innovative microfluidic devices that can isolate extraordinarily rare circulating biomarkers such as extracellular vesicles (EVs) and circulating tumor cells (CTCs) from the blood of cancer patients. New microfluidic tools are being developed to both manipulate and interrogate these cells and vesicles at a single particle level. We also explore tumor heterogeneity using multispectral imaging, hoping that the exploration of the spatial relationships between cells within the tissue will help us better predict treatment response. Ultimately, we hope that by working in close partnership with the clinicians and cell biologists at the Mass General Cancer Center, we can create new tools that directly impact patient care.

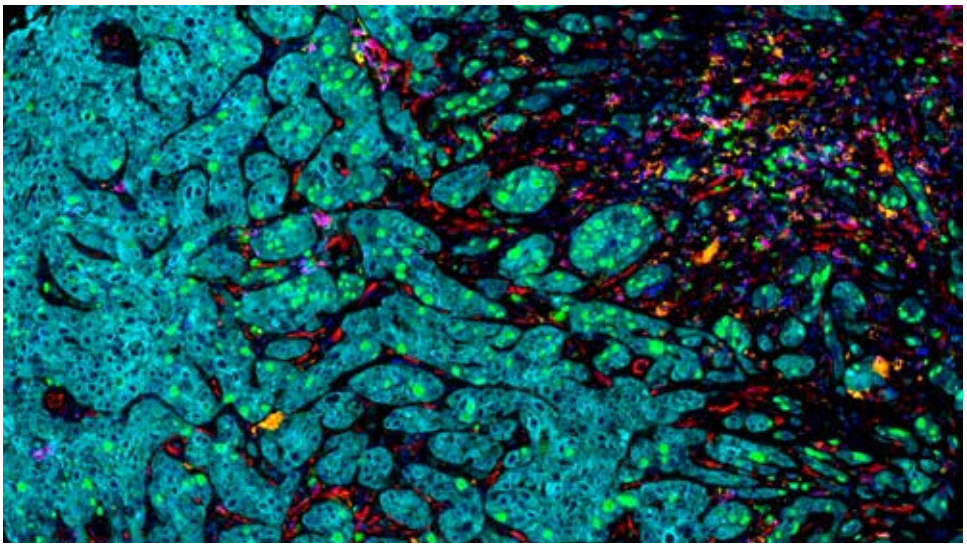
Rapid technological advances in microfluidics, imaging and digital gene-expression profiling are converging to present new capabilities for blood, tissue and single-cell analysis. Our laboratory is interested in taking these advances and creating new technologies to help build understanding of the metastatic process. Our research focus is on 1) the development and application of microfluidic devices and biomaterials for the isolation and characterization of extracellular vesicles, 2) the enrichment and analysis of CTCs at a single cell level, and 3) novel imaging strategies to characterize tumor tissue, cancer cells, and extracellular vesicles.

Extracellular vesicle isolation and characterization

Extracellular vesicles (EVs), such as exosomes, microvesicles, and oncosomes, are small particles that bud off of cancer cells, with some cancer cells releasing up to thousands of EVs per day. Researchers have hypothesized that these EVs shed from tumors transport RNA, DNA and proteins that promote tumor growth, and studies have shown that EVs are present in the blood of most cancer patients. Ongoing work in my lab incorporates microfluidics and novel biomaterials to enrich cell-specific EVs from cancer patients, using as little as 1mL of plasma. Once isolated, we are exploring their protein and nucleic acid content to probe their potential as a less invasive biomarker.

Microfluidics for circulating tumor cell analysis

One of the proposed mechanisms of cancer metastasis is the dissemination of tumor cells from the primary organ into the blood stream. A cellular link between the primary malignant tumor and the peripheral metastases has been established in the form of CTCs in peripheral blood. While extremely rare, these cells provide a potentially accessible source for early detection, characterization and monitoring of cancers that would otherwise require invasive serial biopsies. Working in collaboration with Drs. Mehmet Toner, Shyamala Maheswaran and Daniel Haber, we have designed a



Multispectral image of a section of tumor tissue from a patient with head and neck cancer. Various markers were selected for cell identification to explore the relationship between immune cells and cancer cells within the tumor.

Image courtesy of Daniel Ruiz Torres, MD.

high throughput microfluidic device, the CTC-Chip, which allows the isolation and characterization of CTCs from the peripheral blood of cancer patients. Using blood from patients with metastatic and localized cancer, we have demonstrated the ability to isolate, enumerate and molecularly characterize putative CTCs with high sensitivity and specificity. Ongoing projects include translating the technology for early cancer detection, exploring the biophysics of the CTC clusters, and the design of biomaterials for the gentle release of the rare cells from the device surface. We are also developing new strategies for the long term preservation of whole blood such that samples can be shipped around the world for CTC analysis.

High-content and high-throughput imaging of tumor specimens

Tumors can be highly heterogeneous, and their surrounding stroma even more so. Traditionally, the tumor and surrounding cells are dissociated from the tissue matrix for high throughput analysis of each cell. While this allows for important information to be gained, the spatial architecture of the tissue and corresponding interplay between tumor and immune cells can be lost. The Stott lab is developing quantitative, robust analysis for individual cells within the tumor and neighboring tissue using multispectral imaging. We are using this technology alongside downstream imaging processing algorithms to interrogate signaling activity in cancer cells, immune cell infiltration into to the tumor and pEMT in cancer cells. These data will be used to gain an increased understanding in the relationship between pharmacologic measurements and clinical outcomes, ultimately leading to the optimization of patient therapy.

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Rabe DC, Ho UK, Choudhury A, Wallace JC, Luciani EG, Lee D, Flynn EA and **Stott SL**, Aryl-Diazonium Salts Offer a Rapid and Cost-Efficient Method to Functionalize Plastic Microfluidic Devices for Increased Immunoaffinity Capture. *Adv. Mater. Technol.* 2300210, 2023.

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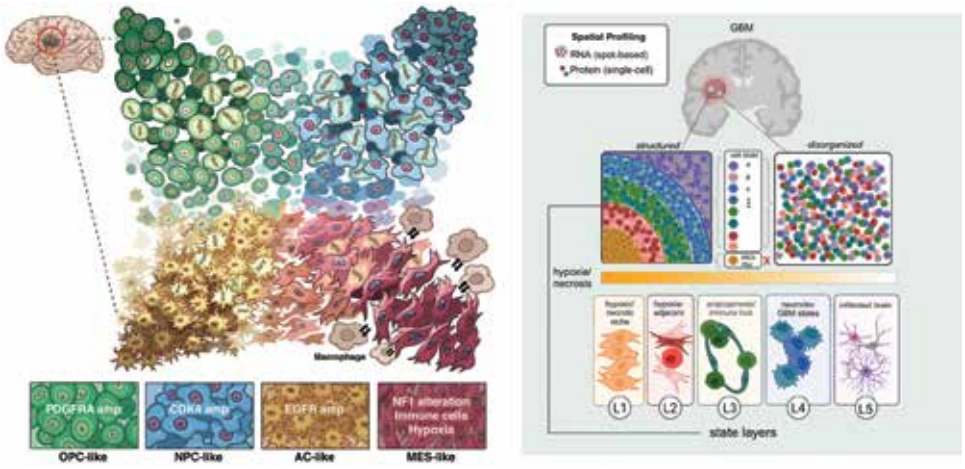
The Suvà laboratory develops and applies multi-dimensional spatial genomic, single-cell multi-omic and advanced computational analyses to dissect the biology of adult and pediatric gliomas. We study clinical samples at single-cell resolution and establish genetically and epigenetically faithful cellular models directly from patient tumors. We model how brain cancer cells exploit their plasticity to establish phenotypically distinct populations of cells, with a focus on malignant cell states that we defined. We seek to redefine tumor cell lineages, stem cell programs and immune cells subsets across all subtypes of gliomas, and to leverage the information for renewed therapeutics. The laboratory additionally leverages single-cell and spatial genomics to characterize the cellular and molecular response of brain tumors to experimental therapies.

Cell state heterogeneity is an important disease hallmark of both IDH-mutant glioma and IDH-wildtype glioblastoma, with genetic clonal diversity intermingled with neurodevelopmental trajectories. Stemness-to-differentiation diversity is central to the glioma stem cell (GSC) model, which posits that stem-like cells are uniquely capable of self-renewal, tumor propagation and preferential resistance to therapy. Recent single-cell RNA-sequencing efforts in glioma led by my laboratory provided high-resolution mapping of cell state diversity and offered additional granularity to the GSC model by revealing multiple transcriptionally-defined cell states related to neurodevelopmental cell types. Yet, while cellular states can be precisely delineated by scRNAseq, glioma cell state heritability and transition dynamics are not defined, and the epigenetic underpinning of glioma cellular states is still largely unknown. Equally unaddressed are cellular cross-talks within the glioma ecosystem (e.g. cancer-immune interactions). In order to dissect those influences and obtain a comprehensive view of gliomas biology, my laboratory is leveraging joint capture of transcriptional, genetic, and epigenetic information (DNAme, chromatin accessibility) at the single-cell resolution to primary diffuse gliomas. Additionally, we integrate single-cell genomics of human tumors with mouse models, computational deconvolution of profiles from The Cancer Genome Atlas (TCGA) and functional experiments. Our approach offers a compelling framework to comprehensively dissect the glioma ecosystem, both at diagnosis and under therapeutic pressure.

Assessing malignant cells heterogeneity at the single-cell level in gliomas

The Suvà Lab is performing large-scale single-cell RNA-seq analyses in IDHmutant gliomas, histone H3-mutant midline gliomas, IDH-wildtype glioblastoma, and medulloblastoma to assess tumor cell lineages, stem cell programs and genetic heterogeneity at an unprecedented scale and depth. Our work in IDH-mutant gliomas highlighted a rare subpopulation of actively dividing stem/progenitor cells, solely responsible for fueling tumor growth in patients. Single cell profiling of H3K27-mutant pediatric gliomas highlighted specific vulnerabilities and revealed a differentiation block, maybe explaining the more aggressive nature of this cancer type.



Model for the cellular states of glioblastoma, their genetic determinants and their spatial organization.

More recently, we provided a comprehensive model of glioblastoma biology that integrates single-cell expression programs, genetic composition and tumor subtypes (see figure). Our study of medulloblastoma single-cell programs provided clarifications on tumor histogenesis and classification. The lab is currently performing such single-cell analyses with constantly increased throughput, resolution and in broader clinical settings (e.g. rare entities, novel clinical trials). Overall, our goal is to identify both lineage-defined and somatically-altered therapeutic targets in brain cancer in both children and adults.

Dissecting the ecosystem of gliomas

The composition of the tumor microenvironment (TME) has an important impact on tumorigenesis and modulation of treatment responses. For example, gliomas contain substantial populations of microglia and macrophages, with putative immunosuppressive functions but whose precise programs remains uncharted at single-cell resolution. In addition, very little is known about the functional state of T cells in human gliomas. As is the case in diverse other conditions, the CNS may create a unique microenvironment that impacts T cell function by distinct mechanisms. The laboratory leverages single-cell analyses in clinical samples to dissect the functional programs of immune cells in gliomas that can be used to elucidate mechanisms relevant to immuno-oncology. We profile both dysfunctional T cells that express multiple inhibitory receptors and T cells that are functional based on expression of multiple genes required for T cell cytotoxicity. We find these modules to be distinct from observations in other types of tumors (such as melanoma), underscoring the necessity to perform these analyses directly in gliomas. By analyzing modules of co-expressed genes in subsets of T cells in patients with glioma we seek to shed light on mechanism of activation and exhaustion in patient tumors and to highlight candidate novel regulatory programs that can be exploited for therapeutics.

Selected Publications:

Spitzer AS†, Johnson KC†, Nomura M†, Garofano L†, Nehar-belaid D, Galili Darnell N, Greenwald AC, Bussema L, Oh YT, Varn FS, D'Angelo F, Gritsch S, Anderson KJ, Migliozzi S, Gonzalez Castro LN, ..., Yung WKA, Lasorella A, Iavarone A, Verhaak RGW, Tirosh I, **Suvà ML**. Deciphering the Longitudinal Trajectories of Glioblastoma Ecosystems by Integrative Single-Cell Genomics. *Nature Genetics*. 2025 May;57(5):1168-1178.

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David A. Sweetser, MD, PhD

Sweetser Laboratory

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The Sweetser laboratory investigates how leukemia and other cancers form with the goal of developing novel, safer, and more effective therapies. Our lab has identified a novel family of tumor suppressor genes, the Groucho/TLE family of co-repressors and defined how TLE1 and TLE4 function as potent tumor suppressors of acute myeloid leukemia and how they have critical roles in hematopoiesis, bone, lung, and brain development, and limiting inflammation. It is this latter function that appears to underlie their tumor suppressor role. Currently, we are defining a cooperative role of TLE1 in melanoma development. A second line of research seeks to define and target critical signaling pathways within the cancer niche that are required for the proliferation and survival of leukemia. As the Mass General Site Director for the Undiagnosed Diseases Network and Chief of Medical Genetics and Metabolism at Mass General, Dr. Sweetser is also leading a group of clinicians and researchers actively engaged in elucidating the underlying basis of a wide variety of human diseases.

Cooperativity of TLE1 loss and BRAF in melanoma

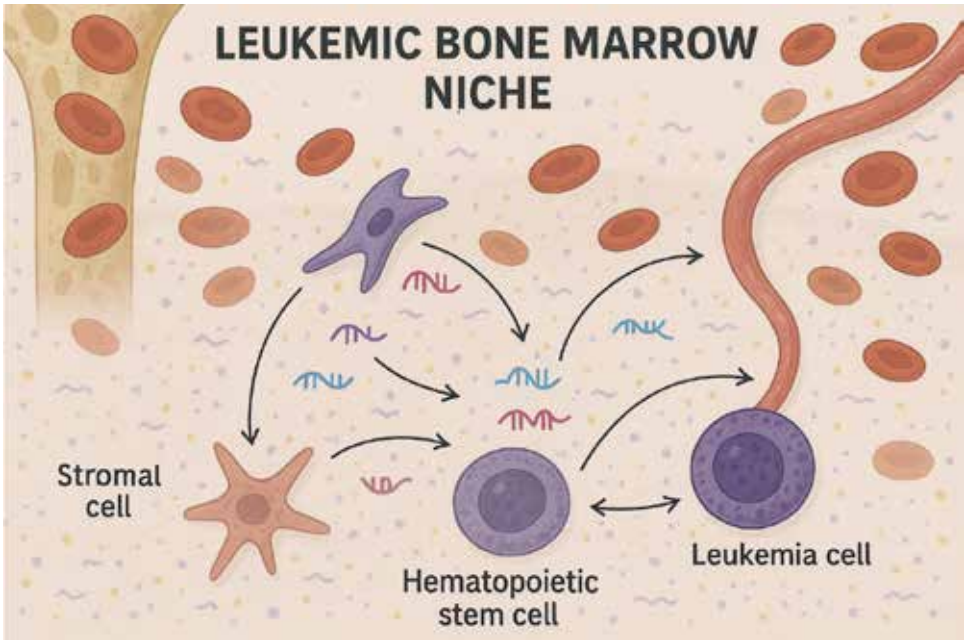
Our lab identified TLE1 and TLE4 as tumor suppressors within the Groucho/TLE corepressor family, which modulates key developmental and oncogenic pathways like Wnt/β-catenin, Notch, and NFκB. TLEs act as tumor suppressors in myeloid malignancies and lymphomas but can function as oncogenes in synovial sarcoma. TLE1 and TLE4 inhibit the RUNX1-RUNX1T1 oncogene in common AML subtypes, likely through effects on transcription, chromatin, Wnt, and inflammatory signaling. Mutations and deletions of TLE are seen in melanoma, though a role for this TLE1 loss has not yet been investigated. We are currently using a mouse model to study the role of TLE1 in melanomas using conditional knockout of Tle1 and conditional oncogenic V600E BRAF expression. This might reveal other targetable pathways to inhibit melanoma growth or increase response to immunotherapies.

The Bone Marrow Niche as a Supportive Environment for Leukemia

During leukemia development, the bone marrow niche undergoes significant remodeling to create a microenvironment that promotes leukemic cell proliferation, survival, and resistance to therapy. Although most current treatments focus on targeting leukemia cells directly, they often overlook the essential role of the leukemic niche in sustaining the disease. This transformed niche is enriched with cytokines, growth factors, and regulatory nucleic acids, particularly microRNAs (miRNAs).

miRNAs are small non-coding RNAs that post-transcriptionally regulate gene expression and play key roles in hematopoiesis and leukemia pathogenesis. In the leukemic niche, dysregulated miRNAs influence both stromal and leukemic cells by modulating pathways involved in cell survival, immune evasion, and drug resistance. Some miRNAs are secreted in extracellular vesicles such as exosomes, facilitating communication between leukemic cells and the surrounding stroma, further enhancing a supportive microenvironment.

Using diagnostic bone marrow aspirates from leukemia patients and healthy



Schematic diagram of the leukemic bone marrow niche. Remodeling of the bone marrow niche creates a necessary and supportive environment for the development and expansion of leukemia. This synergistic cross talk involves a complex milieu of compounds including cytokines, growth factors, miRNAs and other nucleic acids and proteins. Disruption of critical signals in this niche could represent a valuable therapeutic strategy.

controls, we have profiled many of these aberrant signals—focusing on miRNA expression patterns in stromal cells, plasma, and leukemic blasts. We are now systematically evaluating these components to identify novel therapeutic strategies aimed at disrupting key miRNA-mediated interactions and signaling pathways that are critical for leukemic cell maintenance and therapy resistance. Given their regulatory power and specificity, and the ability to modulate miRNA function with Agomirs and Antagomirs, miRNAs also represent promising therapeutic targets, with the potential to reverse leukemic niche reprogramming and sensitize leukemia cells to existing treatments.

The Undiagnosed Diseases Network

Dr. Sweetser is also engaged in rare and undiagnosed disease research. The Harvard Medical School Hospital consortium of Mass General, Brigham and Women's Hospital and Children's Hospital together with 14 other clinical sites around the US comprise the NIH sponsored Undiagnosed Diseases Network. As Chief of Medical Genetics at Mass General, and the Mass General site director for the UDN, Dr. Sweetser coordinates a team of expert clinicians and researchers, using comprehensive clinical phenotyping, whole exome/whole genome sequencing, paired with RNASeq and metabolomics profiling, in vitro functional modeling, and collaboration with zebrafish and Drosophila model organism cores to identify the underlying basis of a variety of challenging human diseases. Over three dozen new genetic disorders have been characterized with these efforts. His lab is also developing stem cell models of several inherited neurological disorders to understand alterations in brain development and potential novel therapies.

Selected Publications:

Galazo M, **Sweetser DA**, D. Macklis J. Tle4 controls both developmental acquisition and postnatal maintenance of corticothalamic projection neuron identity. *Cell Rep*. 2023 Aug 29;42(8):112957.

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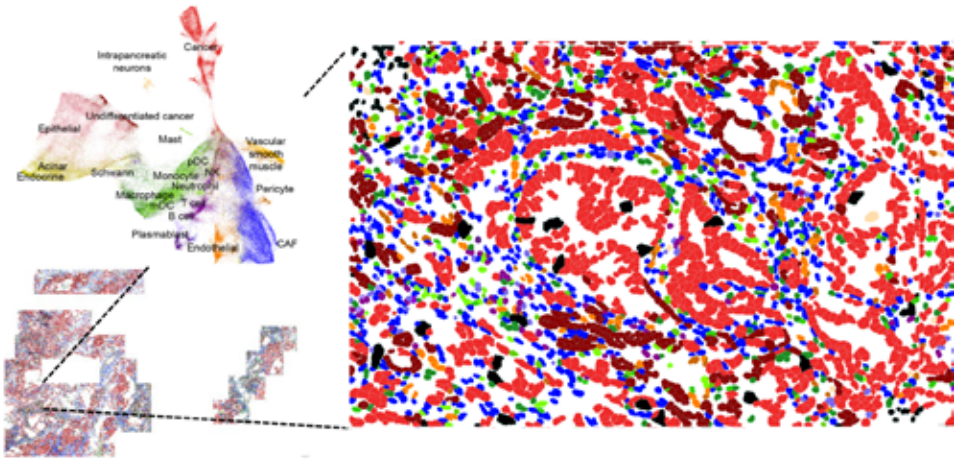
Gastrointestinal cancers are highly lethal cancers where the vast majority of patients are diagnosed too late and conventional therapies have largely been ineffective, making early detection and novel drug targets greatly needed. **The Ting laboratory** has been utilizing innovative technologies to characterize RNA expression patterns in cancer. Our lab has identified aberrant expression of repeat RNA in cancer, which have been found to mimic viruses. We have demonstrated that these viral-like repeat sequences can stimulate innate immune responses, replicate through reverse transcriptional intermediates, and infect cells through extracellular vesicles. We have demonstrated that these repeat RNAs can serve as biomarkers of immunological response, identified therapeutic targets that can disrupt repeat element biology, and visualized the spatial distribution of these viral-like species in tumors and the surrounding microenvironment using spatial transcriptomics. These studies are providing new mechanistic insight into the contribution of repeat elements in cancer progression, identifying novel biomarkers, and discovering new repeat targeting agents.

The Ting laboratory has utilized RNA-sequencing, RNA in situ hybridization, and spatial transcriptomic technologies to understand the complex transcriptional landscape of cancers. We have used these technologies to characterize non-coding repeat RNA expression across cancer and normal tissues. This has provided novel insight into the role of the repeatome in cancer development and offers a method to identify novel biomarkers and therapeutic targets. In addition, we have used single cell, spatial transcriptomic, and microfluidic technologies that have revealed the importance of repeatome biology in driving cellular plasticity and tumor cell heterogeneity. Genetic and molecular disruption of repeat element function can activate innate immune signaling that has been shown to affect tumor growth and block epithelial mesenchymal transition (EMT) plasticity, a cell fate change important for metastasis.

Repeat RNA Viral Response Alters Cellular Plasticity

RNA sequencing of a broad spectrum of carcinomas demonstrated a highly aberrant expression of repeat RNAs emanating from regions of the genome previously thought to be inactive due to epigenetic silencing. Our initial work identified the HSATII satellite as being exquisitely specific for epithelial cancers, including carcinomas of the pancreas, colon, liver, breast, and lung. This initial work identified a correlation of satellite expression with neuroendocrine differentiation, a type of cellular plasticity related to EMT and known to occur in the setting of therapy resistance. Furthermore, our work using a microfluidic device to isolate rare circulating tumor cells (CTCs) and single cell RNA-seq revealed high enrichment of repeat element expression in these precursors of metastasis. We have recently demonstrated that repeat RNA expression in cancer cells can induce EMT cellular plasticity through activation of an interferon response, which supports a functional effect of repeat elements on metastatic potential. Using customized probes for repeat RNAs, we have now visualized the spatial localization of repeat RNAs in human cancers using spatial transcriptomics (see figure), which has shown high levels in tumor



This image represents a spatial transcriptomic "map" of a pancreatic cancer with individual molecules of repeat and coding RNAs quantified with precise spatial coordinates in a human primary tumor sample. Individual cell types can be determined based on transcriptional profiles with mapping to understand cell-cell interactions within tissue.

cells that are undergoing EMT. Moreover, spatial transcriptomic analysis has revealed presence of repeat RNAs in multiple cells types in the diverse tumor microenvironment ecosystem including cancer associated fibroblasts (CAFs), neurons, and immune cells. We have demonstrated that repeat RNAs can be delivered to other cell types through extracellular vesicles (EVs) that mimic viral particles, which induce innate immune responses that alter the phenotype of different cell types. Altogether, this represents a model of a cancer driven inflammatory response in the tumor microenvironment through an "infection" of repeat RNA containing EVs.

Repeat Elements as Novel Cancer Therapeutic Targets

Different repeat elements have been shown to replicate through reverse transcriptional intermediates, including human endogenous retroviruses (HERVs), the LINE-1 retrotransposon, and satellite repeats. These insertions and expansions in the genome have been found to be a poor prognostic marker in cancer. In preclinical tumor models, we showed the ability to inhibit replication of repeat elements using nucleoside reverse transcriptase inhibitors (NRTIs), drugs commonly used for viral infection. This led to a Phase II clinical trial of the NRTI 3TC in metastatic colorectal cancer, which demonstrated promising single agent activity in 25% of patients. Preclinical models indicate that NRTIs affect migratory capability and clonal growth, which supports a role of retrotransposon activity. We are expanding our studies on the impact of NRTIs on cancer cells and the surrounding microenvironment. Recently, we have focused on the RNA binding protein component of the LINE-1 retrotransposon called ORF1p. Suppression of ORF1p with shRNA had significant effects on tumorsphere and xenograft growth, which was linked with alterations in interferon response and diminished EMT. Altogether, these findings have opened new therapeutic avenues to target repeatome biology.

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You E, Patel BK, Rojas AS, Sun S, Danaher P, Ho NI, Phillips IE, Raabe MJ, Song Y, Xu KH, Kocher JR, Richieri PM, Shin P, Taylor MS, Nieman LT, Greenbaum BD, and **Ting DT**†. LINE-1 ORF1p Mimics Viral Innate Immune Evasion Mechanisms in Pancreatic Ductal Adenocarcinoma. *Cancer Discovery*, (2025); 15 (5): 1063–1082.

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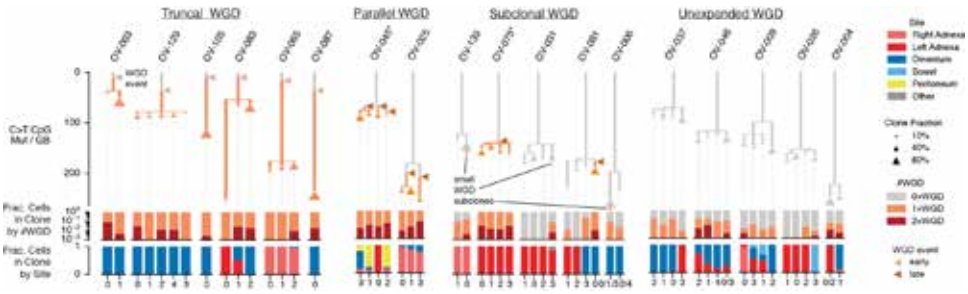
The Vázquez-García laboratory develops quantitative approaches to study somatic evolution in cancer, focusing on the rapidly evolving genomes of tumors and their interactions with the immune system. Throughout life, somatic cells acquire genetic and epigenetic alterations, forming a mosaic of mutant clones that typically remain benign. Genome instability disrupts this balance, driving malignant transformation and generating tumor clones with distinct evolutionary capacities that fuel immune evasion, metastasis, and therapy resistance. We integrate innovations in AI/ML and high-throughput genomics to dissect how genome instability shapes tumor evolution and immune dynamics. New single-cell and spatial technologies enable large-scale profiling of genomic, transcriptomic, and epigenetic states, revealing intra-tumoral heterogeneity, spatial organization, and temporal dynamics. Leveraging multimodal data with advanced computational models, we uncover how genomic adaptations confer selective advantages to tumor cells and how they activate, evade, or suppress immune responses. Our ultimate goal is to define the principles of somatic evolution and immune surveillance, and to translate these insights into predictive biomarkers and therapeutic strategies that anticipate and overcome tumor progression.

Single-cell cancer dynamics

Cancer evolves through the continual acquisition of somatic alterations, with genome instability acting as a catalyst for rapid diversification, clonal evolution and clinical progression. Large-scale genomic alterations such as whole-genome doubling, chromosomal copy number changes, and extrachromosomal DNA dominate the evolutionary landscape of many cancers. These mutational processes precipitate intra-tumor diversification and shape recurrent evolutionary trajectories across cancers. Our work leverages single-cell genomics and spatial technologies to resolve how these processes emerge, propagate, and influence tumor progression, therapeutic resistance, and metastatic potential. To advance these efforts, we have pioneered high-throughput single-cell genome sequencing technologies, applying them in high-grade serous ovarian cancer as an archetypal tumor driven by genome instability. These single-cell approaches can reveal genomic alterations arising from individual cell division errors and enable lineage tracing using native markers. Integrating these measurements with longitudinal monitoring and clinical data, we aim to define conserved evolutionary trajectories and mechanisms of genome rearrangement driving diversity, resistance, and metastasis.

Genetic alterations alone rarely explain why some mutant clones remain dormant while others progress, adapt, or metastasize. Genome instability drives widespread aneuploidy, altering gene dosage across hundreds of loci and disrupting cellular processes by rewiring transcriptional and epigenetic programs. These dosage-driven effects, combined with transcriptional and epigenetic plasticity, generate dynamic and reversible phenotypes that enable therapy resistance and metastatic dissemination. Using single-cell multi-omics, we are mapping genotype-phenotype relationships to identify the regulatory mechanisms that shape these adaptive states. We are also engineering defined genomic alterations and causally testing their impact on cellular fitness to



Single-cell genome sequencing enables evolutionary timing of whole-genome doubling (WGD) events in ovarian cancer. The clone phylogenies illustrate the evolutionary histories and timing of WGD, revealing a complex role for WGD expansions across the evolutionary continuum. Branch length shows the number of age-associated SNVs (C-to-T at CpG sites) assigned to each branch, adjusted for coverage depth. Expanded WGD events are shown as triangles at the predicted location along WGD branches, colored by relative timing. Branches are colored by the number of WGD events in the evolutionary history of each tumor cell. Bar plots show, for each leaf, the fraction of cells grouped by the number of WGD events and the fraction of cells from each anatomical site.

reveal how genomic changes and phenotypic adaptability jointly promote tumor evolvability.

Tumor-immune co-evolution

Genome instability not only enhances tumor adaptation but also reshapes tumor-immune interactions, often driving immune suppression and resistance to immunotherapy. Emerging evidence suggests that genome instability can also activate immune signaling early in tumorigenesis, potentially triggering immune editing before tumors adapt to suppress these responses. To dissect these dynamics, we leverage single-cell and spatial technologies to map the determinants of immune recognition, avoidance, and evasion in genomically unstable cancers. In recent work, we found that distinct mutational processes shape ovarian cancer evolution by altering intra-tumoral immune phenotypes and enabling immune escape.

Building on these insights, we are developing predictive models that integrate tumor evolutionary history with spatially resolved phenotypes to capture the interplay between genome instability, antigen clonality, and immune selection. Unstable tumor genomes generate diverse immunogenic and tolerogenic signals. For example, chromosome missegregation and micronucleus rupture can release DNA into the cytosol and engage the innate immune system. At the same time, the clonal distribution of tumor-derived neoantigens modulates adaptive immune responses, influencing whether tumor clones are eliminated or persist. By mapping how somatic mutations accrue and spatially evolve under immune pressure, we aim to identify signatures distinguishing lesions that evade immune surveillance from those that elicit productive anti-tumor immunity. These insights will directly inform the design of immunotherapies to target genomically unstable clones that evade immune clearance.

Multimodal AI in cancer biology

To address these challenges, we develop multimodal AI frameworks that integrate genomic, transcriptomic, imaging, and clinical data into unified models of tumor evolution. We use representation learning as a foundational approach to align diverse single-cell and tissue-scale measurements into a shared latent space that captures the multi-scale organization of tumor ecosystems. Building on this, we leverage generative models, from single-cell dynamics to population-level frameworks, to simulate tumor and immune trajectories under therapeutic pressures. By contextualizing genomic variants within cellular states, embedding them in tissue architectures, and connecting these patterns to clinical phenotypes, we aim to move beyond static biomarkers toward dynamic, anticipatory frameworks that guide precision prevention and targeted intervention.

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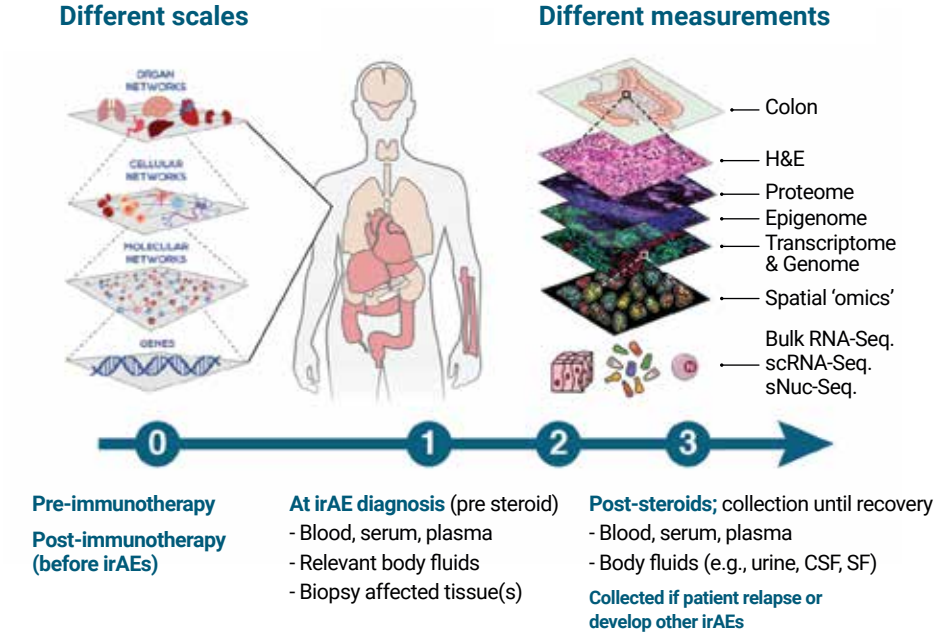
The Villani laboratory seeks to establish a comprehensive roadmap of the human immune system by achieving a higher resolution definition and functional characterization of cell subsets and rules governing immune response regulation, as a foundation to decipher how immunity is dysregulated in diseases. We use unbiased systems immunology approaches, cutting-edge immunogenomics, single-cell 'multi-omics' strategies, and integrative computational frameworks to empower the study and modeling of the immune system as a function of "healthy" and inflammatory states, disease progression, and response to treatment. Our multi-disciplinary team of immunologists, geneticist, computational biologists, and physicians work towards addressing several fundamental questions: Have we identified all existing human immune cell subsets across blood and tissue compartments? Can we systematically define the cellular and transcriptional programs that drive immune-related disease pathogenesis in humans? Can we discover therapeutic targets that enhance the efficacy of cancer immunotherapy while minimizing side effects though increasing specificity? Collectively, our groundwork is paving the way for developing a human immune lexicon that is key to promoting effective bench-to-beside translation of findings.

Leveraging systems immunology and single-cell 'multi-omics' to unravel new insights into the human immune system

Achieving detailed understanding of the composition and function of the immune system at the fundamental unit of life — the cell — is essential to determining the prerequisites of health and disease. Historically, leukocyte populations have been defined by a combination of morphology, localization, functions, developmental origins, and the expression of a restricted set of markers. These strategies are inherently biased and recognized today as inadequate. Single-cell RNA sequencing (scRNAseq) and 'multi-omics' analysis provides unbiased, data-driven means to define cellular states, capturing both discrete cell types to dynamic transitions that cannot be resolved by conventional surface markers or for which markers are not yet known. To address these limitations, we integrate scRNAseq, systems immunology, and spatial omics strategies with follow-up phenotypic and functional characterization of newly defined cell subsets. By applying this strategy, we redefined the taxonomy of human blood mononuclear phagocytes. We identified five new subsets, which revised the existing classification of these cells and demonstrated the power of our integrative strategies (Villani, *Science* 2017). This work also underscored the importance of pursuing a comprehensive Human Cell Atlas initiative and offered a framework for studying a wide range of tissues and conditions. We are now advancing this effort by charting at high-resolution the human blood cellular landscape through analyzing over 40 million cells across 40 immune-related diseases to map shared and disease-specific cellular and transcriptional programs. Concurrently, we study paired blood and human tissues specimens to better establish how circulating immune cells reflect and interact with local tissue microenvironment in health and disease.

In addition, we continue to develop and refine systems immunology, single-cell and spatial



Overview of our strategy for exploring scale, time and modalities to discover underpinnings of disease pathogenesis.

'multiomics' experimental and computational strategies (Fisher F, *Nat Commun* 2024; Ding, *Nat Biotechnol* 2020; Li, *Nat Methods* 2020; Tukiainen, Villani, *Nature* 2017; Ranu, Villani, *Nucleic Acid Res* 2019), and apply them to uncover the underpinnings of health and disease pathogenesis in tumors and inflamed tissues (Sade-Feldman, *Cell* 2019; Di Pilato, *Nature* 2019; Olah, *Nat Commun* 2018; Delorey, *Nature* 2021; Alladina, *Science Immunol* 2023; Oh, *Cell Rep* 2025; Rengarajan, *bioRxiv* 2025; Smith, *JCI Insight* 2025; Halvorsen, *Nat Commun* 2025).

Deciphering immune-related adverse events (irAEs) induced by immune-checkpoint inhibitor (ICI) therapy

While ICI therapy is revolutionizing the treatment of solid cancers, its success is currently limited by treatment-induced irAEs, which can resemble autoimmune diseases and affect nearly every organ system. With ICI now established as first- and second-line therapies, and increasingly used in adjuvant and neoadjuvant settings, the incidence of irAE is expected to rise, posing a major barrier to durable immunotherapy success. Our multidisciplinary team of scientists and clinicians aims to elucidate the biological drivers and molecular mechanisms of irAEs by directly analyzing patient blood and matched affected tissue using systems immunology, immunogenomics, single-cell and spatial'omics' strategies. Through integrative analysis, we seek to define the fundamental rules of immune tolerance by studying irAE, focusing on: (i) identifying the cellular subsets and networks sustaining pathology in situ and determining whether T cells alone or additional populations are responsible; (ii) mapping the molecular pathways underlying irAEs and their overlap with canonical autoimmune processes; (iii) investigating whether shared antigens link tumor and irAE affected tissues; and (iv) uncovering circulating factors perpetuating loss of immune tolerance and systemic inflammation (Zubiri, *J Immunother Cancer* 2021; Villani, *Immunol Rev* 2024; Thomas, *Nature Med* 2024; Blum, *Nature* 2024). Ultimately, our translational program will result in identifying cellular and molecular targets that could enable both the development of 'primary-prevention' approach to prevent irAE, and of targeted therapeutic intervention after onset of irAEs, without compromising the anti-tumor efficacy of ICI therapy.

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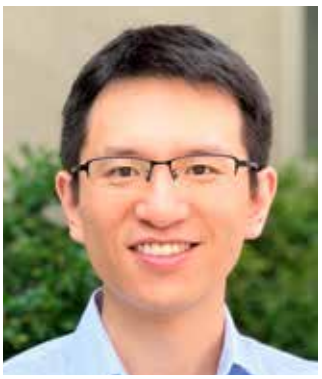
†Co-senior authorship

Bo Xia, PhD



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The Xia laboratory focuses on addressing one of biology's most fundamental questions: how does the human genome control the identity and function of thousands of different cell types, and what goes wrong in diseases like cancer? To address this grand challenge, we need advanced technologies that exponentially accelerate the investigation pace beyond the traditional experimental approaches. In our lab, we develop state-of-the-art multimodal artificial intelligence (AI) tools that can predict how genes are regulated upon perturbations, allowing us to run large-scale in silico experiments before validating them in the lab. Using these technologies, we have discovered key proteins and genetic elements that shape how human genome folds and functions, and uncovered novel factors that regulate T cell fate transitions. By combining AI with advanced single-cell methods, our goal is to understand the core regulatory program that determine cell fate — and engineer these programs open new possibilities for regenerative medicine, aging research, and cancer therapy.

Multimodal AI Technology Development

How does the human genome encode the regulatory programs that specify thousands of cell types in health and disease? Genome regulation and cell fate determination are intrinsically multimodal, integrating DNA sequence, chromatin state, protein complexes, and their intricate interactions. My laboratory develops interdisciplinary technologies to address these challenges.

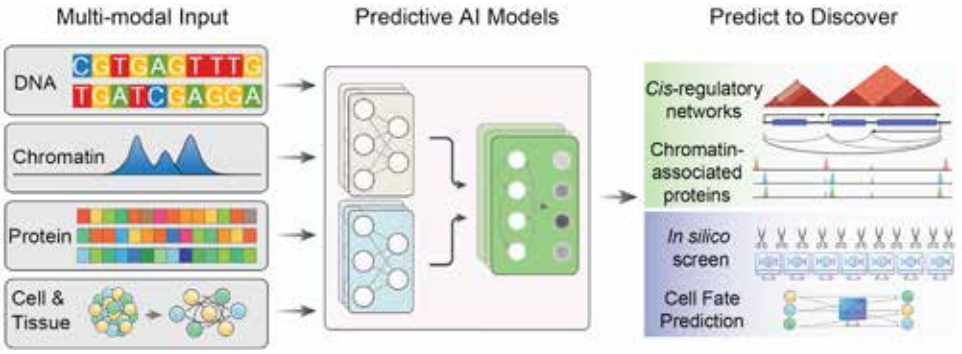
Traditional experimental biology has relied on iterative cycles of observation, perturbation, and measurement—a process powerful in principle but inefficient at scale. To accelerate the investigation of cell fate determination, we build predictive AI/ML models and high-throughput in silico screening frameworks that extend the reach of experiments into computational space. Our team has developed foundational multimodal genomics AI models—including C.Origami (*Nature Biotechnology*, 2023) and Chromnitron (*bioRxiv*, 2025)—that capture the key principles of genome regulation and enable high-throughput computational genetic screens.

By coupling predictive genomics with targeted experimental validation, we aim to transform how fundamental discoveries are made, opening new avenues for manipulating cell fate and function. These technologies are designed not only to accelerate scientific progress but also to provide a generalizable platform with applications across cancer, regeneration, and aging.

Genome Regulation

The human genome encodes ~2,500 chromatin-associated proteins—including ~1,600 transcription factors—that collectively define the regulatory landscape. Understanding how DNA sequence, chromatin state, and protein networks specify gene expression remains one of the central unsolved problems in biology. The mammalian genome is hierarchically organized, with interactions spanning from local sequence motifs to higher-order 3D architecture. Dissecting this complexity requires new technologies.

We apply our multimodal genomics AI tools—trained on DNA sequence,



Multimodal predictive AI technologies to decode gene regulation and predict cell fate transitions.

accessibility, and protein features—to predict regulatory interactions and discover key regulators. By coupling these models with single-cell, spatial, and molecular assays, we investigate how gene regulation is orchestrated from base-pair resolution to chromosome-scale architecture. Recently, we identified ZNF654 and JMJD6 as long-sought regulators that work together with CTCF to shape mammalian genome organization (manuscript in preparation); and discovered novel factors that regulates T cell fate transition during chronic stimulation. We further extend these approaches to disease, examining how dysregulation of genome organization contributes to cancer and other pathologies, and how regulatory circuits can be manipulated, restored, or synthetically designed for therapeutic benefit.

Cellular Dynamics

At the cellular level, gene regulation underlies the extraordinary diversity and plasticity of mammalian cell types. Our work seeks to uncover the fundamental mechanisms by which regulatory programs drive cell fate transitions, tissue homeostasis, and organismal responses to stress and aging. We introduced the "periodic table of cell types" framework (*Development*, 2019), which organizes cellular identities across development. Using single-cell technologies, we previously charted spermatogenesis at unprecedented resolution (*Cell*, 2020) and mapped dynamic cellular interactions in the first pig-to-human kidney xenotransplantation (*Med*, 2024). More recently, we discovered the first plausible genetic mechanism that a single Alu element insertion in the ancestral genome may drive tail-loss evolution in humans and apes (*Nature*, 2024). This discovery also uncovered a previously unappreciated cis-regulatory mechanism that intronic repeat pairing can induce exon skipping splicing. Meanwhile, this discovery inspired a new investigation to control gene regulation as a new approach to chordoma, a rare tumor in spine or the base of skull.

Building on our earlier exploration of cellular dynamics in health and diseases, we now integrate predictive AI with gene regulatory analysis to address core questions: what factors ultimately determine a cell's fate? How can we reprogram or de novo design cell types with novel functions? We focus particularly on chromatin-associated proteins, which form the regulatory circuits governing every cellular state. Through predictive modeling, single-cell epigenomics, and synthetic genetics, we aim to establish scalable approaches to engineer cell fate—providing insights for immunology, cancer biology, and aging biology.

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Publications September 1, 2024 – August 31, 2025

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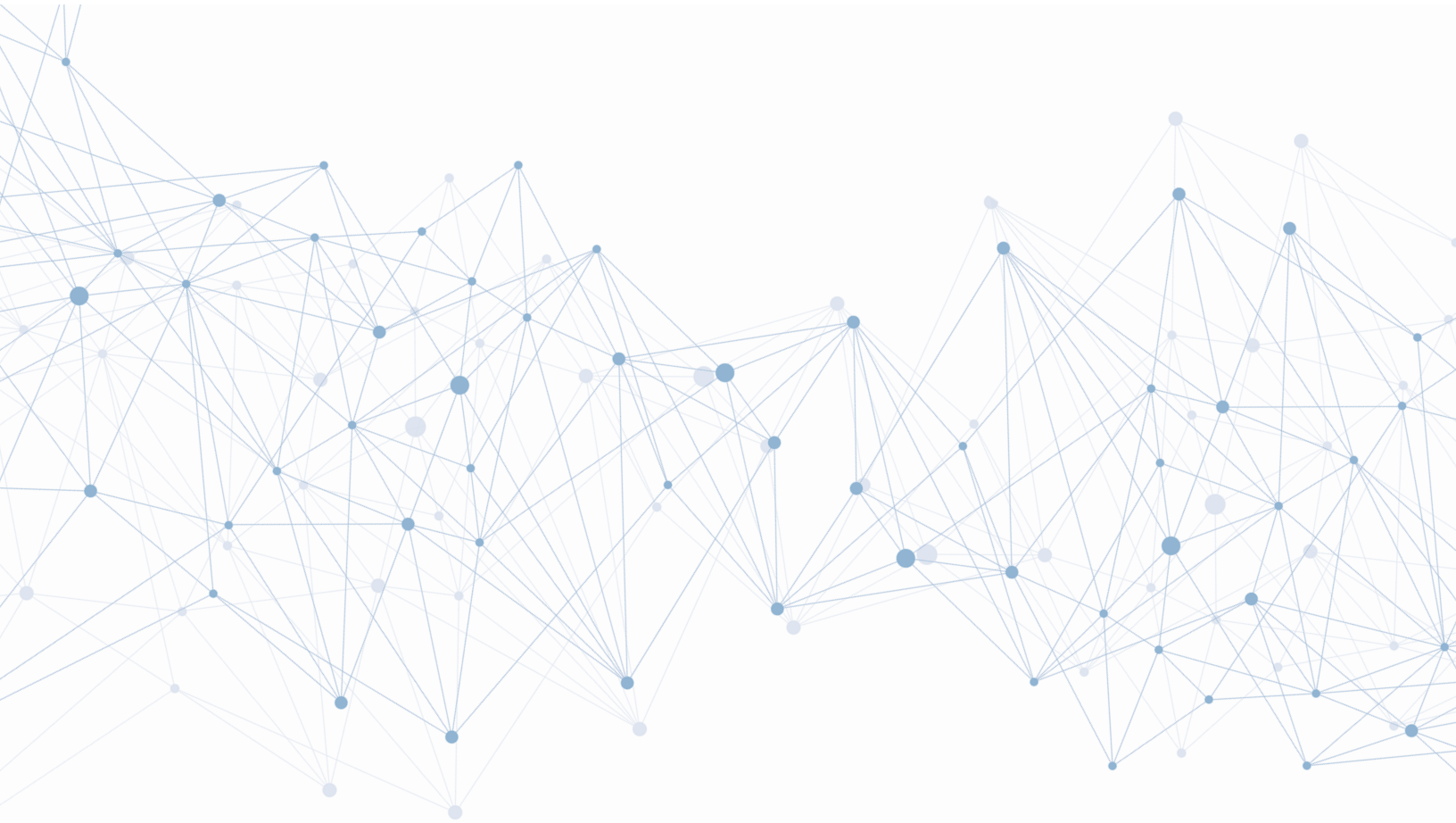

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