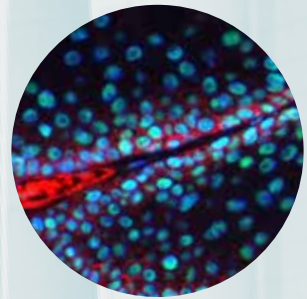
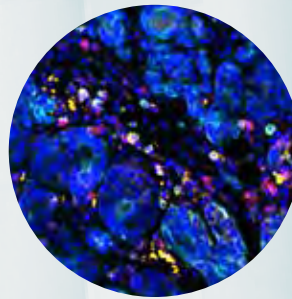
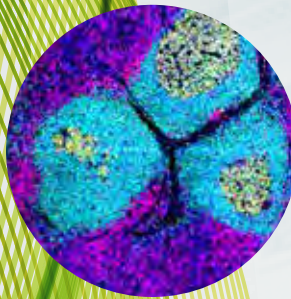
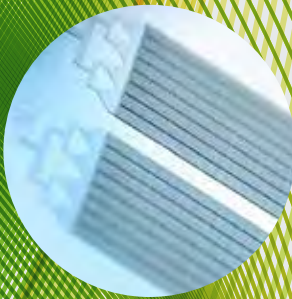
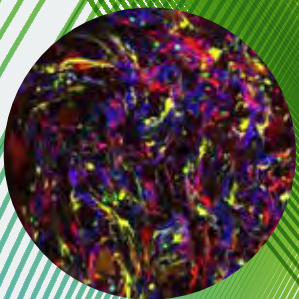


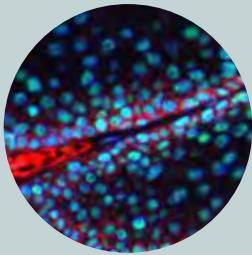
# Center for Cancer Research

Annual Report 2022



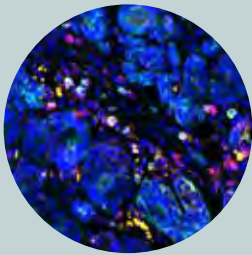


## Featured images from front cover



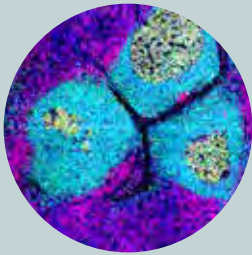
Immunofluorescence of a squamous cell carcinoma sample, stained for CD34 (red) and histone H3K56 acetylation (green), indicating that tumor propagating cells (CD34+) exhibit an increase in this chromatin mark, which leads to unique metabolic adaptations (for details, see Choi et al., Nat. Metab. 2021).

*Image courtesy of Jee-Eun Choi, PhD, Mostoslavsky laboratory*



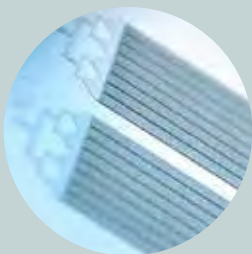
New research explores how the mutation-independent effect of environmental carcinogens leads to the recruitment of CD8+T cells, the dominant antitumor cell type. Here, T cells (red and green) attack carcinogen-exposed breast cancer cells (light blue).

*Image courtesy of Mei Huang, PhD, Demehri Laboratory*



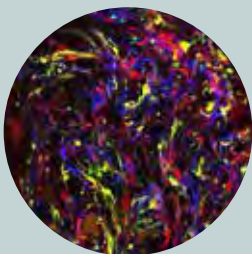
Early loss of germinal centers and Bcl-6 expressing B cells in COVID-19 thoracic lymph nodes. Overlay of low-power images of CD3 (red), CD19 (green), Bcl-6 (orange) and DAPI (blue) staining in a lymph node from a late COVID-19 patient and control.

*Image courtesy of Naoki Kaneko, DDS, PhD, Pillai Laboratory*



Photolithography wafer with features to mold a microfluidic device.

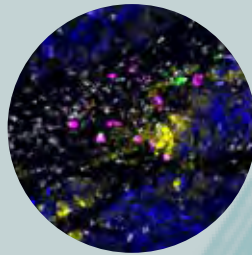
*Image courtesy of the Stott Laboratory*



Glioblastoma is an incurable brain cancer. The diversity of glioblastoma cells, described as rainbow-colored cells (in blue, green, yellow and red), is a major impediment for successful therapy.

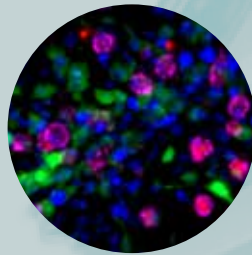
*Image courtesy of Toshiro Hara, PhD, Suvà Laboratory.*

## Featured images from back cover



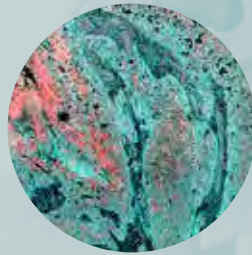
In the subset of mismatch repair-deficient human colorectal tumors, activated and likely tumor-reactive T cells (white, green, and magenta) are organized into "hubs" around malignant cells (blue) expressing chemokines (yellow) that attract T cells and other cells into spatially organized immune cell hubs.

*Image courtesy of Joshua Pirl, Vjola Jorgji, Linda Nieman, Jonathan Chen, Hacohen Laboratory*



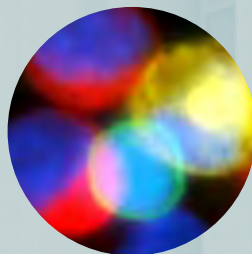
Murine-derived organotypic tumor spheroids (MDOTS) consisting of CT26 colon cancer cells labeled with green fluorescent protein (GFP = green). These MDOTS are grown in 3-dimensional microfluidic culture in collagen hydrogels. Cell nuclei are Blue. CD45+ immune cells are PINK. CD68+ macrophages are labeled in RED. Image acquired on the Leica Thunder 3D Imaging station.

*Image courtesy of Or-Yam Revach, PhD, Jenkins Laboratory*



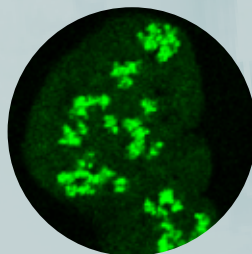
Damage-associated molecular patterns (red) expression in skin cancer.

*Image courtesy of Marjan Azin, MD, Demehri Laboratory*



Circulating prostate tumor cell cluster stained for PSA (green) along with Ki67 (orange) and CD45 (red). Image courtesy of the Haber/Maheswaran laboratory.

*Image courtesy of the Haber laboratory*



A new type of protein-RNA condensate induced by transcription inhibition. The RNA-binding protein TAF15 (in green) undergoes phase separation and forms condensates in nucleoli upon inhibition of RNA polymerase II.

*Image courtesy of Takaaki Yasuhara, PhD, Zou laboratory*

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## The MGH Center for Cancer Research: 35 years of discovery




The Center for Cancer Research (CCR) serves as the hub for basic and translational research within the Massachusetts General Hospital (MGH) Cancer Center. MGH hosts the largest hospital-based research program in the U.S.; founded in 1988, our comprehensive

cancer center is a state-of-the-art and dynamic enterprise, embedded within one of the nation's pre-eminent hospitals. The CCR is the “engine for discovery” for the entire MGH Cancer Center, stemming from the extraordinary scientists who make up our 51 faculty and 500 students, technicians and postdoctoral scientists, their deep commitment both to fundamental discovery and to its application in cancer, and an ingrained culture of collaboration between different laboratories, and between basic scientists and clinical researchers. Our trainees include Harvard Medical School (HMS) graduate and medical students, PhD postdoctoral fellows and subspecialty clinical fellows - all within an integrated community that stresses creative discovery together with clinical impact. CCR scientists pursue every facet of cancer research, 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, RNA biology, and computational biology. CCR faculty have academic appointments in multiple Departments at HMS, including Medicine, Pathology, Radiation Oncology, Surgery, Dermatology and Pediatrics, as well as the Broad Institute of MIT and Harvard. They conduct research in 80,000 square feet of laboratory space in three MGH research facilities: Charlestown Navy Yard, Simches Research Building, and Jackson Building.

Since its inception landmark discoveries by CCR investigators include the first discovery of germline

mutations conferring familial susceptibility to cancer (TP53 gene mutations in Li Fraumeni Syndrome; *Malkin et al., Science 1990*) and the major contribution of “founder mutations” in the BRCA1 gene to early-onset breast cancer in Ashkenazi populations (*FitzGerald et al., NEJM 1996*). In 1992, CCR investigators cloned the E2F gene, the primary regulator of cell cycle progression which 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, CCR 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, a CCR team 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. MGH 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.

Landmark publications from CCR investigators also include the first engineered microfluidic “Chip” to isolate Circulating Tumor Cells (CTCs) from the blood of patients with cancer (*Nagrath et al., Nature 2007*) and the role of CTC-Clusters in metastasis (*Aceto et al., Cell, 2014*); high throughput screening of a thousand cancer cell lines to uncover drug susceptibility patterns (*Garnett et al., Nature 2012*), with the first description of “persister cancer cells” that precede the emergence of drug resistance (*Sharma et al., Cell 2012*) and high throughput patient-derived cultures to predict drug resistance mechanisms (*Crystal et al., Science 2014*); dissection of chromatin deregulation underlying pediatric Ewings Sarcoma (*Boulay et al., Cell 2017*) and colorectal cancer



(Johnstone et al., *Cell* 2020); genome-wide analyses of non-coding cancer drivers (Rheinbay et al., *Nature* 2020); and single cell resolution molecular analyses to dissect the diverse origins of brain cancers (Nefitel et al., *Cell* 2019) and the discovery of immune cell “hubs” within cancers, linked to immunotherapy response (Pelka et al., *Cell* 2021). All together, these and many other publications point to the exceptional quality, the diverse breadth and the major impact of research discoveries from CCR investigators.

Today, our investigators continue to actively pursue fundamental questions in cancer biology, together with translational applications with potential clinical impact. Among current highlights are the cellular immunotherapy team led by *Marcela Maus*, which has created novel CAR-T cells, taken from original laboratory design to successful clinical proof-of-concept in patients with refractory cancers. Research on cancer immunotherapy also includes genetic engineering within CAR-T cells (*Max Jan*), *in vivo* CRISPR screens of immunoregulatory agents (*Robert Manguso*), epigenetic regulation of T cell exhaustion (*Deb Sen*), *ex vivo* modeling of immunotherapy (*Russ Jenkins*), definition of resistance to antibody-drug conjugates (*Leif Ellisen*), and neo-epitope cancer vaccination strategies (*Nir Hacohen*).

Molecular therapeutic efforts include disease-specific efforts linked to our Termeer Center, as well as innovative discovery strategies. These include the creation of a Cysteine Druggability Map for human cancers to target “undruggable” cancer drivers through covalent tagging of their cysteine residues (*Liron Bar-Peled*); targeting transcriptional factors in hematologic malignancies (*Chris Ott*) and hypoxia pathway regulators in kidney cancer (*Othon Iliopoulos*), and dissecting metabolomic targets linked to cancer metastasis (*Raul Mostoslavsky* and *Nabeel Bardeesy*). A fundamental discovery relating to APOBEC enzymes, key drivers of both tumor formation and acquired drug resistance, emerged from a combination of computational analysis of 3-dimensional DNA target structures, combined with expertise in both DNA damage repair pathways and patient-derived models of drug resistance (*Michael Lawrence*, *Lee Zou* and *Aaron Hata*).

Finally, the development of key molecular and bioengineering technologies aimed at early cancer detection is a major focus for multi-investigator collaborative efforts, including mass spectrometric analysis of serum proteins (*Wilhelm Haas*), ctDNA analyses (*Ryan Corcoran*, *Gaddy Getz*, *John Iafrate*), isolation of exosomes from blood (*Shannon Stott*), and novel technologies for high throughput enrichment of circulating tumor cells (CTCs) (*Daniel Haber* and *Shyamala Maheswaran*, with *Mehmet Toner*). These are just some of the many ways in which CCR labs are advancing the field of cancer research. Beyond these recent highlights, all CCR faculty pursue their scientific vision for their laboratories, as detailed in the individual reports of Principal Investigators.

The CCR greatly values creativity and innovation across the broad field of cancer biology, including fundamental insight into cellular and molecular mechanisms, as well as clinically-relevant discoveries that impact the care of patients with cancer. 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 increasing diversity among our faculty and trainees, and to directing scientific discovery toward areas of unmet need in our society. Finally, it is through training and mentoring the next generation of young scientists that we will continue to harness the power of science and uncover new and more effective ways to fight cancer.

We are pleased to share with you our Annual Scientific Report for 2022. Thank you for your interest in our mission of discovery and innovation.



Daniel A. Haber, MD, PhD  
Director, Cancer Center  
Massachusetts General Hospital  
Harvard Medical School





## Current Members

Julian Adams, PhD  
*Gamida Cell, Ltd.*

David E. Fisher, MD, PhD  
*Massachusetts General Hospital*

Robert E. Kingston, PhD  
*Massachusetts General Hospital*

David N. Louis, MD  
*Massachusetts General Hospital*

Phillip A. Sharp, PhD  
*Massachusetts Institute of Technology*

Arlene Sharpe, MD, PhD  
*Harvard Medical School*

M. Celeste Simon, PhD  
*The Abramson Family Cancer Research Institute  
University of Pennsylvania Perelman School of  
Medicine*

## Past Members

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  
*President Emeritus, Dana-Farber Cancer Institute  
Candel Therapeutics*

Joan S. Brugge, PhD  
*Harvard Ludwig Cancer Center*

Donald Ganem, MD  
*University of California, San Francisco*

Walter J. Gehring, PhD<sup>†</sup>  
*Biozentrum  
University of Basel*

Richard O. Hynes, PhD  
*Massachusetts Institute of Technology*

David Hogness, PhD<sup>†</sup>  
*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  
Founding Director, Koch Institute for Integrative  
Cancer Research at MIT*

Alfred G. Knudson Jr., MD, PhD<sup>†</sup>  
*Fox Chase Cancer Center*

David Livingston, MD<sup>†</sup>  
*Dana-Farber Cancer Institute*

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  
*Professor Emerita, Whitehead Institute*

Anthony Pawson, FRS, PhD  
*Samuel Lunenfeld Research Institute,  
Mount Sinai Hospital*

Carol Prives, PhD  
*Columbia University*

Gerald M. Rubin, PhD  
*University of California, Berkeley*

Gary Ruvkun, PhD  
*Massachusetts General Hospital*

Jeffrey Settleman, PhD  
*Pfizer, Inc.*

Eileen White, PhD  
*Rutgers University Cancer Institute of New Jersey*

<sup>†</sup>*In Memoriam*

# The Jonathan Kraft Prize for Excellence in Cancer Research

*Presented by the Massachusetts General Hospital Cancer Center*

**2021**

**Aviv Regev, PhD**

*Chair of the Faculty and Core Member, Broad Institute  
Director, Klarman Cell Observatory, Broad Institute  
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**

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

# The Annual MGH Award in Cancer Research

*2006–2014*

**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 Leeuwenhoek  
Hospital, Netherlands*



## Daniel A. Haber, MD, PhD

Director, Massachusetts General Hospital Cancer Center  
Kurt J. Isselbacher Professor of Oncology

## Raul Mostoslavsky, MD, PhD

Scientific Co-Director  
Laurel Schwartz Professor of Oncology

## Lee Zou, PhD

Scientific Co-Director  
James and Patricia Poitras Chair in Cancer Research  
Professor of Pathology

## Andrea I. McClatchey, PhD

Director of Academic Affairs and Education  
Poitras Family Chair in Cancer Research  
Professor of Pathology

## Nir Hacohen, PhD

Director, Center for Cancer Immunology  
David P. Ryan Chair in Cancer Research  
Professor of Medicine

## Charlestown Laboratories

Liron Bar-Peled, PhD  
Assistant Professor of Medicine

Lloyd Bod, PhD  
Faculty Member<sup>†</sup>

Priscilla K. Brastianos, MD  
Associate Professor of Medicine

Ryan B. Corcoran, MD, PhD  
Associate Professor of Medicine

Shawn Demehri, MD, PhD  
Associate Professor in Dermatology<sup>^</sup>

Nicholas Dyson, PhD  
Professor of Medicine

Andrew Elia MD, PhD  
Assistant Professor of Radiation Oncology<sup>#</sup>

David E. Fisher, MD, PhD  
Professor and Chief of Dermatology

Gaddy Getz, PhD  
Professor of Pathology<sup>\*</sup>

Timothy A. Graubert, MD  
Professor of Medicine

Wilhelm Haas, PhD  
Assistant Professor of Medicine

Daniel A. Haber, MD, PhD  
Professor of Medicine

Nir Hacohen, PhD  
Professor of Medicine

Aaron Hata, MD, PhD  
Assistant Professor of Medicine

Othon Iliopoulos, MD  
Associate Professor of Medicine

Max Jan, MD, PhD  
Assistant Professor of Pathology<sup>\*</sup>

Keith Joung, MD, PhD  
Professor of Pathology<sup>\*</sup>

Li Lan, MD, PhD  
Associate Professor of Radiation Oncology<sup>#</sup>

David M. Langenau, PhD  
Professor of Pathology<sup>\*</sup>

Michael S. Lawrence, PhD  
Assistant Professor of Pathology<sup>\*</sup>

Shyamala Maheswaran, PhD  
Professor of Surgery

Robert Manguso, PhD  
Assistant Professor of Medicine<sup>+</sup>

Marcela V. Maus, MD, PhD  
Associate Professor of Medicine

Andrea I. McClatchey, PhD  
Professor of Pathology

David T. Miyamoto, MD, PhD  
Assistant Professor of Radiation Oncology<sup>#</sup>

Mo Motamedi, PhD  
Assistant Professor of Medicine

Eugene Oh, PhD  
Assistant Professor of Medicine<sup>+</sup>

Christopher J. Ott, PhD  
Assistant Professor of Medicine

Shiv Pillai, MD, PhD  
Professor of Medicine<sup>◇◇</sup>

Luca Pinello, PhD  
Associate Professor of Pathology<sup>\*</sup>

Esther Rheinbay, PhD  
Assistant Professor of Medicine

Miguel N. Rivera, MD  
Associate Professor of Pathology<sup>\*</sup>

Debattama Sen, PhD  
Assistant Professor of Medicine<sup>+</sup>

Dennis C. Sgroi, MD  
Professor of Pathology<sup>\*</sup>

Toshihiro Shioda, MD, PhD  
Associate Professor of Medicine

Shannon Stott, PhD  
Assistant Professor of Medicine

Mario L. Suvà, MD, PhD  
Associate Professor of Medicine<sup>\*</sup>

David T. Ting, MD  
Associate Professor of Medicine

Alexandra-Chloé Villani, PhD  
Assistant Professor of Medicine<sup>◇</sup>

## Jackson Laboratories

Nir Hacohen, PhD  
Professor of Medicine

Anthony John Iafrate, MD, PhD  
Professor of Pathology<sup>\*</sup>

Russell W. Jenkins, MD, PhD  
Assistant Professor of Medicine

David R. Spriggs, MD  
Professor of Medicine  
(Thier Laboratories)

## Simches Laboratories

Nabeel Bardeesy, PhD  
Associate Professor of Medicine

Leif W. Ellisen, MD, PhD  
Professor of Medicine

Konrad Hochedlinger, PhD  
Professor of Medicine<sup>\*\*</sup>

Hanno Hock, MD, PhD  
Assistant Professor of Medicine

Peter Miller, MD, PhD  
Faculty Member<sup>†</sup>

Raul Mostoslavsky, MD, PhD  
Professor of Medicine

David A. Sweetser, MD, PhD  
Assistant Professor of Pediatrics<sup>□</sup>

Shobha Vasudevan, PhD  
Associate Professor of Medicine

\* Joint appointment with Molecular Pathology Unit

\*\* Joint appointment with Dept. of Molecular Biology and Center for Regenerative Medicine and Technology

<sup>^</sup> Joint appointment with MGH Cutaneous Biology Research Center

<sup>#</sup> Joint appointment with MGH Molecular Radiation Oncology Unit

<sup>◇</sup> Joint appointment with Center for Immunology and Inflammatory Diseases

<sup>◇◇</sup> Joint appointment with Ragon Institute of Harvard and MIT

<sup>□</sup> Joint appointment with MGH Pediatric Hematology Oncology Unit

<sup>†</sup> Appointment process initiated



# Faculty Listing by Theme

## Cancer Cell Biology

Liron Bar-Peled, PhD  
Konrad Hochedlinger, PhD  
David M. Langenau, PhD  
Andrea I. McClatchey, PhD  
Shyamala Maheswaran, PhD  
Eugene Oh, PhD  
Miguel Rivera, MD  
Shobha Vasudevan, PhD

## Cancer Diagnostics, Molecular Pathology and Technology Development

Daniel A. Haber, MD, PhD  
A. John Iafrate, MD, PhD  
Keith Joung, MD, PhD  
Shyamala Maheswaran, PhD  
David Miyamoto, MD, PhD  
Dennis Sgroi, MD  
Shannon Stott, PhD  
David T. Ting, MD

## Cancer Epigenetics, Genetics, Genomics and Proteomics

Liron Bar-Peled, PhD  
Priscilla Brastianos, MD  
Leif Ellisen, MD, PhD  
Timothy Graubert, MD  
Wilhelm Haas, PhD  
Konrad Hochedlinger, PhD  
Hanno Hock, MD, PhD  
David Miyamoto, MD, PhD  
Peter Miller, MD, PhD  
Mo Motamedi, PhD  
Raul Mostoslavsky, MD, PhD  
Eugene Oh, PhD  
Christopher J. Ott, PhD  
Shiv Pillai, MD, PhD  
Luca Pinello, PhD  
Esther Rheinbay, PhD  
Miguel N. Rivera, MD  
Debattama Sen, PhD  
Mario L. Suvà, MD, PhD  
David Sweetser, MD  
David T. Ting, MD

## Cancer Immunology

Lloyd Bod, PhD  
Shawn Demehri, MD, PhD  
David Fisher, MD, PhD  
Nir Hacohen, PhD  
Max Jan, MD, PhD  
Russell Jenkins, MD, PhD  
Robert Manguso, PhD  
Marcela V. Maus, MD, PhD  
Shiv Pillai, MD, PhD  
Debattama Sen, PhD  
Alexandra-Chloé Villani, PhD

## Cancer Metabolism

Liron Bar-Peled, PhD  
Nabeel Bardeesy, PhD  
Leif Ellisen, MD, PhD  
Othon Iliopoulos, MD, PhD  
Raul Mostoslavsky, MD, PhD

## Genomic Instability/Cell Cycle and DNA Damage

Nick Dyson, PhD  
Andrew Elia, MD, PhD  
Li Lan, MD, PhD  
Michael S. Lawrence, PhD  
Peter Miller, MD, PhD  
Raul Mostoslavsky, MD, PhD  
Eugene Oh, PhD  
Lee Zou, PhD

## Molecular Therapeutics

Liron Bar-Peled, PhD  
Ryan Corcoran, MD, PhD  
Daniel A. Haber, MD, PhD  
Aaron Hata, MD, PhD  
A. John Iafrate, MD, PhD  
Keith Joung, MD, PhD  
Christopher J. Ott, PhD  
David Spriggs, MD

## RNA Biology and Diagnostics

Daniel A. Haber, MD, PhD  
Keith Joung, MD, PhD  
Li Lan, MD, PhD  
Shyamala Maheswaran, PhD  
David Miyamoto, MD, PhD  
Miguel Rivera, MD  
Shannon Stott, PhD  
Mario L. Suvà, MD, PhD  
David T. Ting, MD  
Shobha Vasudevan, PhD  
Lee Zou, PhD

## Systems and Computational Biology

Gaddy Getz, PhD  
Nir Hacohen, PhD  
Keith Joung, MD, PhD  
Michael S. Lawrence, PhD  
Mo Motamedi, PhD  
Luca Pinello, PhD  
Esther Rheinbay, PhD  
Toshihiro Shioda, MD, PhD

# Faculty Listing by Disease

## Brain Cancer

Priscilla Brastianos, MD  
A. John Iafrate, MD, PhD  
Andrea I. McClatchey, PhD  
Miguel N. Rivera, MD  
Shannon Stott, PhD  
Mario L. Suvà, MD, PhD

## Breast Cancer

Andrew Elia, MD, PhD  
Leif Ellisen, MD, PhD  
Gaddy Getz, PhD  
Daniel A. Haber, MD, PhD  
A. John Iafrate, MD, PhD  
Li Lan, MD, PhD  
Shyamala Maheswaran, PhD  
Mo Motamedi, PhD  
Esther Rheinbay, PhD  
Dennis Sgroi, MD  
Toshihiro Shioda, MD, PhD  
Lee Zou, PhD

## Hematologic Malignancies

Hanno Hock, MD, PhD  
Timothy Graubert, MD  
David M. Langenau, PhD  
Max Jan, MD, PhD  
Marcela V. Maus, MD, PhD  
Peter Miller, MD, PhD  
Christopher Ott, PhD  
Shiv Pillai, MD, PhD  
Shobha Vasudevan, PhD  
Alexandra-Chloé Villani, PhD

## Liver, Pancreatic and Gastrointestinal Cancers

Nabeel Bardeesy, PhD  
Ryan Corcoran, MD, PhD  
Konrad Hochedlinger, PhD  
Andrea I. McClatchey, PhD  
Raul Mostoslavsky, MD, PhD  
Mo Motamedi, PhD  
David T. Ting, MD

## Lung Cancer

Liron Bar-Peled, PhD  
Nick Dyson, PhD  
Wilhelm Haas, PhD  
Daniel A. Haber, MD, PhD  
Aaron Hata, MD, PhD  
A. John Iafrate, MD, PhD

## Melanoma and Skin Cancers

Liron Bar-Peled, PhD  
Shawn Demehri, MD, PhD  
David Fisher, MD, PhD  
Daniel A. Haber, MD, PhD  
Nir Hacohen, PhD  
Russell Jenkins, MD, PhD  
Shyamala Maheswaran, PhD  
Robert Manguso, PhD  
Raul Mostoslavsky, MD, PhD  
Debattama Sen, PhD  
Mario L. Suvà, MD, PhD  
David A Sweetser, MD, PhD

## Ovarian Cancer

Liron Bar-Peled, PhD  
David Spriggs, MD  
Lee Zou, PhD

## Pediatric Cancers

David M. Langenau, PhD  
Miguel Rivera, MD  
David Sweetser, MD

## Prostate and Kidney Cancers

Daniel A. Haber, MD, PhD  
Othon Iliopoulos, MD, PhD  
Shyamala Maheswaran, PhD  
David Miyamoto, MD, PhD

## Sarcoma

David M. Langenau, PhD  
Miguel Rivera, MD

The image features a split background. On the left side, there are vibrant, overlapping, wavy lines in shades of red, orange, yellow, green, and blue, creating a sense of motion and energy. On the right side, there is a faded, light blue-tinted image of a classical building with a portico supported by several columns and a pediment. The overall composition is clean and professional.

**Reports *from the***  
**Principal Investigators**



# Liron Bar-Peled, PhD



## Bar-Peled Laboratory

Liron Bar-Peled, PhD  
Jacqueline Berner\*  
Alex Carlin  
Nicholas Chen\*  
Harrison B. Chong  
Maolin Ge, PhD  
Magdy Gohar  
Mariko Hara, PhD  
Stefan Harry, PhD  
Neha Khandelwal, PhD  
Matthew Lazarov  
Farah Makram  
Emily Nguyen  
Sanne Van Den Ouweland  
Himani Patel  
George Popoola  
Ricardo A. Pinto Rengifo, PhD  
Marianne Richter  
Tommy Weiss-Sadan, PhD  
Janice Wong  
James Woods  
Tzu-Yi Yang, PhD  
Junbing Zhang, PhD  
Siwen Zhang, PhD

\*Graduate student

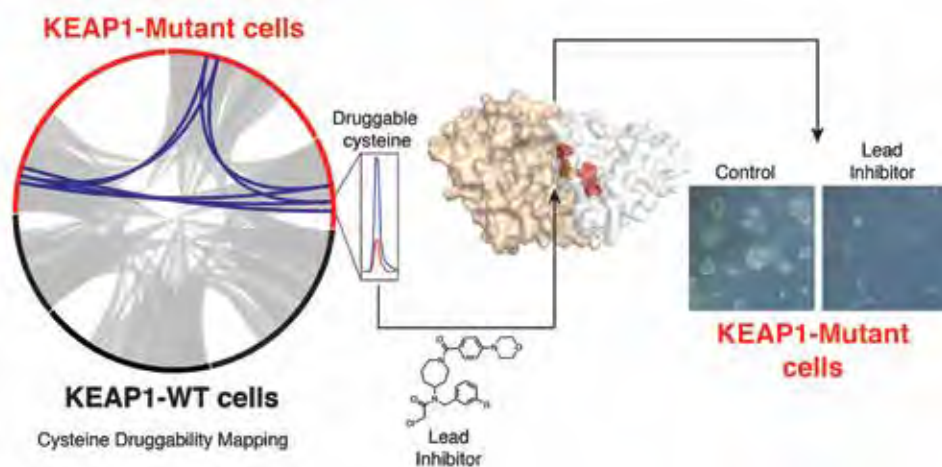
Research in **the Bar-Peled laboratory** sits at the interface of cellular metabolism and signal transduction and focuses on understanding how cancer cells respond to altered metabolic states. Rapidly proliferating cancer cells are characterized by increased production of toxic metabolic byproducts known 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 (isoTOP-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



(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.

redox environment required for proper enzyme function. Current studies in our 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 pro-proliferative 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:

Chen AL, Lum KM, Lara-Gonzalez P, Ogasawara D, Cognetta AB 3rd, To A, Parsons WH, Simon GM, Desai A, Petrascheck M<sup>†</sup>, Bar-Peled L<sup>†</sup>, Cravatt BF<sup>†</sup>. (2019) Pharmacological convergence reveals a lipid pathway that regulates *C. elegans* lifespan. *Nature Chemical Biology*, 15(5), 453–462.

Bar-Peled L<sup>\*†</sup>, Kemper EK<sup>\*</sup>, Suciu RM, Vinogradova EV, Backus KM, Horning BD, Paul TA, Ichu TA, Svensson RU, Olucha J, Chang MW, Kok BP, Zhu Z, Ihle N, Dix MM, Hayward M, Jiang P, Saez E, Shaw RJ, and Cravatt BF<sup>†</sup>. (2019) Chemical Proteomics Identifies Druggable Vulnerabilities in a Genetically Defined Cancer. *Cell*, 171(3), 696–709.e23.

Wang S, Tsun ZY, Wolfson RW, Shen K, Wyant GA, Plovovich ME, Yuan ED, Jones T D, Chantranupong L, Comb W, Wang T, Bar-Peled L, Zoncu R, Straub C, Kim C, Park J, Sabatini BL, and Sabatini DM. (2015) The amino acid transporter SLC38A9 is a key component of a lysosomal membrane complex that signals arginine sufficiency to mTORC1. *Science*. 347: 188-194.

Tsun ZY, Bar-Peled L<sup>\*</sup>, Chantranupong L<sup>\*</sup>, Zoncu R, Wang T, Kim C, Spooner E., Sabatini DM. (2013). The Folliculin Tumor Suppressor is a GAP for the RagC/D GTPases That Signal Amino Acid Levels to mTORC1. *Molecular Cell* 52: 495-505.

Bar-Peled L<sup>\*</sup>, Chantranupong L<sup>\*</sup>, 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.

Bar-Peled L, Schweitzer LD, Zoncu R., and Sabatini DM. Ragulator is a GEF for the Rag GTPases that signal amino acid levels to mTORC1 (2012). *Cell* 150: 1196-1208.

<sup>\*</sup>These authors contributed equally to this work

<sup>†</sup>Co-corresponding authors

# Nabeel Bardeesy, PhD



Pancreatic cancer and biliary cancer are among the most lethal 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 function of cancer genes in controlling the way cells modulate their growth and utilize energy in response to available nutrients. Additional studies are exploring how some therapies targeting key mutations initially cause tumor to stop growth and why resistance eventually develops. Each of these studies is being used to inform improved therapeutic approaches.

## Bardeesy Laboratory

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Hiroshi Kondo, PhD  
Joshua Merritt, BSc\*  
Vanessa Da Silva Silveira, PhD  
Vindhya Vijay, PhD  
Vajira Weerasekara, PhD  
Ting-Yu Wei, Staff Scientist  
Meng-Ju Wu, PhD  
Qibiao Wu, PhD  
Yuanli Zhen, PhD

\* Research technician

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 that has elucidated the functional interactions of major gene mutations associated with these diseases in humans. Studies have focused on the roles of key cancer genes in regulation of cell metabolism, the discovery of mechanisms of resistance to targeted therapies.

### Interplay between metabolism and chromatin regulation

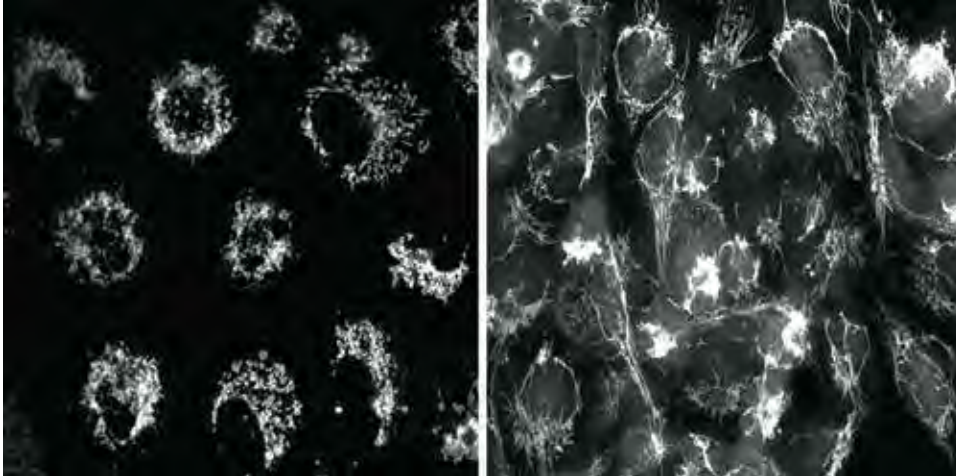
An important area of current focus in our lab is to elucidate the metabolic regulators of pancreatic cancer and biliary cancers, with particular attention paid to factors that reprogram cancer cell metabolism. We have linked mutations in the LKB1/STK11 and IDH1 genes to changes in metabolism that ultimately alter epigenetic states. Identifying these pathways has provided insights in mechanisms of cell transformation arising from these mutations and predict novel therapeutic vulnerabilities. Mutant IDH proteins acquire a novel enzymatic activity allowing them to convert alpha-ketoglutarate ( $\alpha$ KG) to 2-hydroxyglutarate (2HG), which inhibits the activity of multiple  $\alpha$ KG-dependent

dioxygenases, including the TET family DNA demethylases. We are focusing on how epigenetic defects caused by IDH-mediated inhibition of TET affects cross-talk between tumor and immune cells to support cancer growth.

### Genetic regulation of metabolic reprogramming in pancreatic cancer

In order to couple rapid growth with available nutrients, cancers employ profoundly altered networks of biosynthetic and catabolic pathways. This requirement for metabolic reprogramming is particularly acute in pancreatic cancer, which is characterized by hypoxia and limited nutrient availability, and activates anti-oxidant gene expression and autophagy (cellular self-catabolism) as necessary adaptive metabolic changes. Our recent studies demonstrate that distinct metabolic programs are activated in pancreatic cancer depending on which gene mutations are present. While these pathways offer attractive new therapeutic targets, the underlying mechanisms driving altered PDAC metabolism are unclear. We have focused on identifying master transcriptional regulators that broadly orchestrate metabolic reprogramming in PDAC.





*Genetic control of expression of the Mitochondrial Fission Factor (MFF) dictates mitochondrial architecture and metabolic phenotypes of cancer cells. The image shows mitochondrial staining (Mitotracker) of cancer cells which express high levels of MFF (left panel) or low levels of MFF (right panel). The MFF-high cancer cells show hyper-fragmented mitochondria compared to the fused mitochondrial network of MFF-low cancers. This differential control of mitochondrial dynamics results in distinct metabolic programs and vulnerabilities.*

### Understanding and targeting FGFR2-driven biliary cancer

Genetic alterations that activate Fibroblast Growth Factor 2 (FGFR2) signaling are common in biliary cancer and predict response to pharmacological inhibition of the FGFR in patients. However, tumor shrinkage is often modest and acquired resistance invariably arises. We are investigating oncogenic mechanisms controlled by FGFR2 in biliary cancer, including direct targets of FGFR2 signaling as well as downstream impact on cellular metabolism and differentiation. Additionally, we are investigating resistance mechanisms and approaches to prevent and overcome resistance.

### Models of biliary cancer

Recent genetic studies have identified multiple recurrent mutations in biliary cancers and have indicated considerable genetic heterogeneity between individual tumors. A key limitation in the field includes a paucity of experimental systems with

which to define the contributions of the lesions to biliary cancer progression. We have established a series of genetically engineered mouse models that incorporate combinations of the major mutations found in the human disease. In addition, our ongoing efforts include the development of a human biliary cancer cell line bank and the use of this system in large-scale genetic and small-molecule screens to systematically define targetable vulnerabilities in molecularly defined subtypes of this cancer.

### Selected Publications:

Wu MJ, Shi L, Dubrot J, Merritt J, Vijay V, Wei TY,... Manguso RT, **Bardeesy N**. Mutant IDH Inhibits IFN $\gamma$ -TET2 Signaling to Promote Immuno-evasion and Tumor Maintenance in Cholangiocarcinoma. *Cancer Discov.* 2022 Mar 1; 12(3):812-835.

Wu, Q, Zhen, Y, Shi, L. and **Bardeesy N**. EGFR inhibition potentiates FGFR inhibitor therapy and overcomes resistance in FGFR2 fusion-positive cholangiocarcinoma *Cancer Discov.* 2022 *in press*.

Cleary JM, Raghavan S, Wu Q, Li YY,... (**Bardeesy N\***, Wolpin BM\*). FGFR2 Extracellular Domain In-Frame Deletions are Therapeutically Targetable Genomic Alterations that Function as Oncogenic Drivers in Cholangiocarcinoma. *Cancer Discov.* 2021 Apr 29.

Goyal L, Shi L, Liu LY, Fecce de la Cruz F,... Corcoran RB, **Bardeesy N**. TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion-Positive Intrahepatic Cholangiocarcinoma. *Cancer Discov.* 2019 Aug 9; (8):1064-1079.

Patra KC, Kato Y, Mizukami Y,... **Bardeesy N**. Mutant GNAS drives pancreatic tumorigenesis by inducing PKA-mediated SIK suppression and reprogramming lipid metabolism. *Nat Cell Biol.* 2018 Jul 20; (7):811-822.

Kottakis F, Nicolay BN, Roumane A, Karnik R,... **Bardeesy N**. LKB1 loss links the serine metabolism to DNA methylation and tumorigenesis. *Nature.* 2016 Nov 17; 539(7629): 390-395.

Saha SK, Gordan JD, Kleinstiver BP, Vu P,... Benes CH, **Bardeesy N**. Isocitrate Dehydrogenase Mutations Confer Dasatinib Hypersensitivity and SRC Dependence in Intrahepatic Cholangiocarcinoma. *Cancer Discov.* 2016 Jul 6; (7):727-39.

Perera RM, Stoykova S, Nicolay BN,... **Bardeesy N**. Transcriptional control of the autophagy-lysosome system drives amino acid metabolism in pancreatic cancer. *Nature* 2015 July 13.

\*Co-corresponding authors

# Lloyd Bod, PhD



## Bod Laboratory

[Opens fall of 2022]

Lloyd Bod, PhD

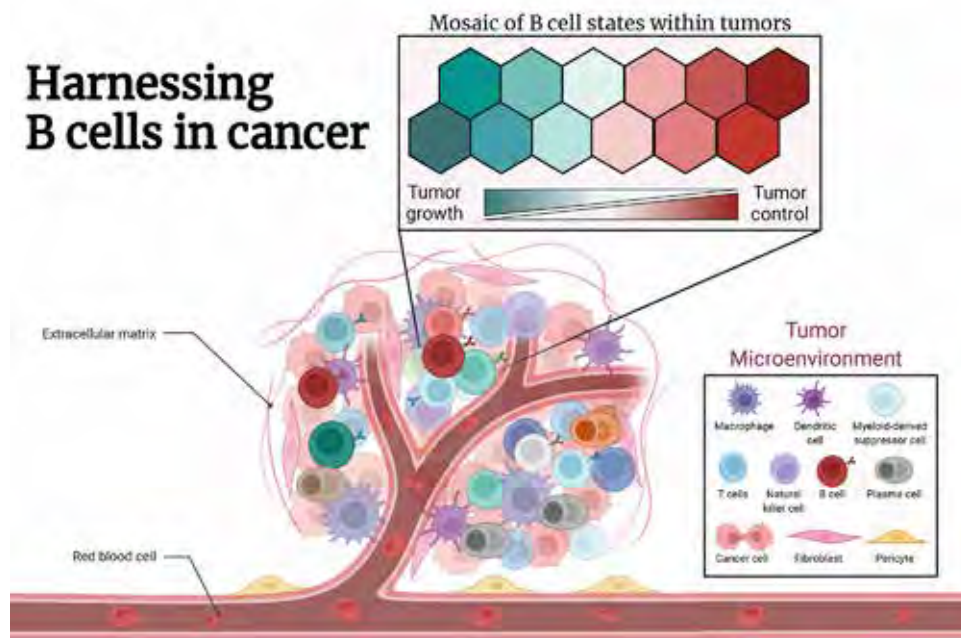
Immunotherapies have demonstrated remarkable clinical success in the treatment of various cancers mainly by boosting the function of endogenous T cells to attack neoplastic cells. Unfortunately, the frequency of patients responding to these therapies is modest and a significant fraction of patients develop 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

## Harnessing B cells in cancer



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).

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:

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:

Bod L, Shi J, Kye YC, Torlai Triglia E, Schnell A, Ashenberg O, Fessler J, Kuchroo JR, Barilla RM, Zaghouani S, Christian E, Delorey TM, Mohib K, Xiao S, Slingerland N, Rothstein DM, Rozenblatt-Rosen O, Sharpe AH, Apetoh L, Regev A, Kuchroo V.K: Temporal single cell profiling identifies B-cell specific checkpoint molecules that regulate anti-tumor immunity. *In revision.*

Schnell A, Bod L, Madi A, Kuchroo VK. (2020). The yin and yang of co-inhibitory receptors: toward anti-tumor immunity without autoimmunity. *Cell Res*, 30(4), 285-299. <https://doi.org/10.1038/s41422-020-0277-x>

Xiao S, Bod L, Pochet N, Kota SB, Hu, D, Madi A, Kilpatrick J, Shi J, Ho A, Zhang H, Sobel R, Weiner HL, Strom TB, Quintana FJ, Joller N, Kuchroo VK. (2020). Checkpoint Receptor TIGIT Expressed on Tim-1(+) B Cells Regulates Tissue Inflammation. *Cell Rep*, 32(2), 107892. <https://doi.org/10.1016/j.celrep.2020.107892>

Bod L, Douguet L, Auffray C, Lengagne R, Bekkat F, Rondeau E, Molinier-Frenkel V, Castellano F, Richard Y, Prevost-Blondel A. (2018). IL-4-Induced Gene 1: A Negative Immune Checkpoint Controlling B Cell Differentiation and Activation. *J Immunol*, 200(3), 1027-1038. <https://doi.org/10.4049/jimmunol.1601609>

Bod L, Lengagne R, Wrobel L, Ramspott JP, Kato M, Avril MF, Castellano F, Molinier-Frenkel V, Prevost-Blondel A. (2017). IL4-induced gene 1 promotes tumor growth by shaping the immune microenvironment in melanoma. *Oncoimmunology*, 6(3), e1278331. <https://doi.org/10.1080/2162402X.2016.1278331>



# Priscilla K. Brastianos, MD



## Brastianos Laboratory

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Magali de Sauvage  
Albert Kim, MD  
Juliana Larson  
Olivia Michaels  
Joana Mora  
Naema Nayyar, BSc  
Matthew Strickland, MD

**The Brastianos laboratory** studies genomic 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 molecular drivers of both progression in primary brain tumors and brain metastases, and accelerate the development of novel therapeutic approaches for these diseases. We recently 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. 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.

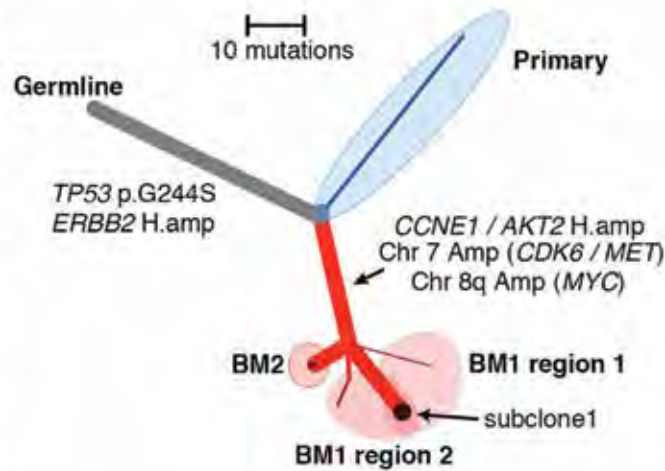
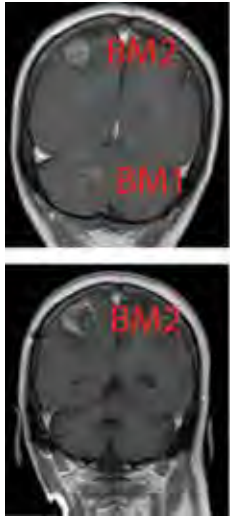
## Characterizing Genomic Drivers of Craniopharyngiomas

Craniopharyngiomas are epithelial tumors that arise in the pituitary stalk along the path of the craniopharyngeal duct. There are two main subtypes of craniopharyngiomas, the adamantinomatous form that is more common in children, and the papillary form that predominantly occurs in adults. Craniopharyngiomas can cause profound clinical sequelae both through mass effect at presentation and through morbidity of treatment. No effective treatment besides surgery and radiation is known for craniopharyngiomas, and incomplete knowledge of the molecular mechanisms that drive craniopharyngiomas has limited the development of targeted therapies for this tumor. We recently comprehensively characterized the molecular drivers of craniopharyngiomas. We identified 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. We recently treated a patient with multiple recurrent papillary craniopharyngioma with a BRAF and MEK inhibitor and achieved an exceptional therapeutic response. We have initiated a national multicenter trial in craniopharyngiomas (Alliance A071601) to investigate the role of targeted therapies in these tumors. Circulating biomarkers and genomic analysis of craniopharyngiomas will be employed to investigate mechanisms of resistance.

## Identifying Molecular Drivers of Meningiomas

Meningiomas are the most common primary nervous system tumor with no known effective systemic therapy. Recently, we comprehensively characterized meningiomas. Through whole-genome, whole-exome and targeted sequencing, we have demonstrated that meningiomas harbor recurrent oncogenic clinically actionable mutations in AKT1 (E17K) and SMO (W535L) (Brastianos et al. *Nature Genetics* 2013). Notably, these mutations were present



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.

in therapeutically challenging tumors of the skull base. We also recently identified potential genetics drivers of progression in meningiomas (*BAP1*, *TERT* promoter mutations, *DMD*). Because therapeutic targets for *SMO* and *AKT1* mutations are currently in clinical use in other cancers, 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. The trial is activated at more than 400 sites throughout the US. We will be genomically characterizing prospectively collected samples to identify biomarkers of response and mechanisms of resistance.

### Central Nervous System Metastasis Program

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

Program are to (1) identify novel therapeutic targets through comprehensive genomic 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. In collaboration with many national and international institutions, currently we are comprehensively characterizing the genomics of brain metastases to understand the molecular pathways that drive these tumors. We have demonstrated that brain metastases harbor clinically actionable drivers not detected in the primary tumors. We are evaluating the roles of these genetic alterations using various assays of metastasis. Based on this work, we have now initiated a national 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:

Brastianos PK\*, Kim AE\*, et al. Palbociclib demonstrates intracranial activity in progressive brain metastases harboring cyclin-dependent kinase pathway alterations. *Nature Cancer*. 2021; May;2 (5):498-502.

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.

Brastianos PK, et al. Single-arm, open-label phase 2 trial of pembrolizumab in patients with leptomeningeal carcinomatosis. *Nat Med*. 2020; Aug;26(8):1280-1284.

Ippen FM, Alvarez-Breckenridge CA,... Brastianos PK. The dual PI3K/mTOR-pathway inhibitor GDC-0084 achieves antitumor activity in PIK3CA-mutant breast cancer brain metastases. *Clinical Cancer Research*. 2019; 25(11):3374-3383.

Juratli TA, McCabe D,...Brastianos PK. DMD genomic deletions characterize a subset of progressive/higher-grade meningiomas with poor outcome. *Acta Neuropathologica*. 2018; 136(5):779-792.

Alvarez-Breckenridge C,...Brastianos PK. Clinical and radiographic response following targeting of novel *BCAN-NTRK1* fusion in glioneuronal tumors. *Nature Precision Oncology*. 2017; 1(1):5.

Shankar GM,... Brastianos PK\*\*, Santa-gata S\*\*. Germline and somatic *BAP1* mutations in high-grade rhabdoid meningiomas. *Neuro-Oncology*. 2017; 19(4):535-545.

Brastianos PK\*, Carter SL\* et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discovery*. 2015; 5(11): 1-13.

\* Co-first authors

\*\*Co-senior authors

# Ryan Corcoran, MD, PhD



## Corcoran Laboratory

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Bryanna Leigh Norden  
Princy Sindurakar  
Noritaka Tanaka, PhD  
Jun Tian, PhD  
Edmond Wong

**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

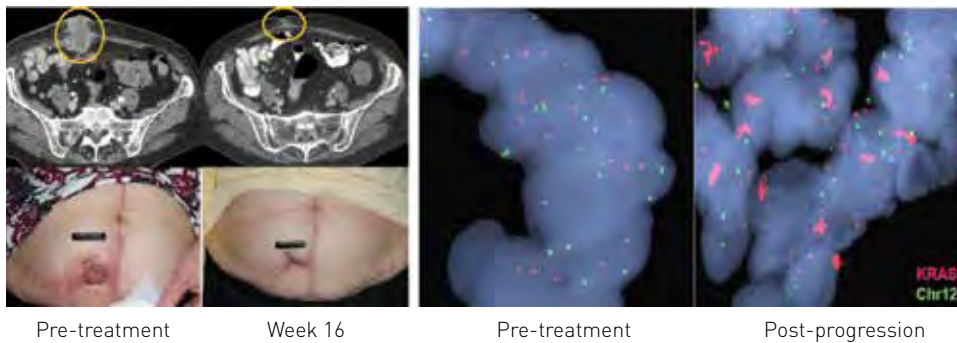
Historically, the standard clinical approach for patients with advanced cancers has been to treat all patients with the same tumor type with the same generalized chemotherapy strategy. However, even among patients with the same type of tumor, the genetic mutations driving tumor growth in each individual 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).





*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:

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, Klemptner 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.

Ryan MB, Fece de la Cruz F, Phat S, Myers DT, Wong E, Shahzade HA, Hong CB, Corcoran RB. Vertical pathway inhibition overcomes adaptive feedback resistance to KRASG12C inhibition. *Clin Cancer Res.* 2020. 26:1633-1643.

Goyal L, Shi L, Liu LY, Fece de la Cruz F, Lennerz JK, Raghavan S, Leschiner I, Elagina L, Siravegna G, Ng RWS, Vu P, Patra KC, Saha SK, Uppot RN, Arellano R, Reyes S, Sagara T, Otsuki S, Nadres B, Shahzade HA, Dey-Guha I, Fetter IJ, Baiev I, Van Seventer EE, Murphy JE, Ferrone CR, Tanabe KK, Deshpande V, Harding JJ, Yaeger R, Kelley RK, Bardelli A, Iafrate AJ, Hahn WC, Benes CH, Ting DT, Hirai H, Getz G, Juric D, Zhu AX\*, Corcoran RB\*, Bardeesy N\*. TAS-120 Overcomes Resistance to ATP-Competitive FGFR Inhibitors in Patients with FGFR2 Fusion-Positive Intrahepatic Cholangiocarcinoma. *Cancer Discov.* 2019 Aug; (9):1064-1079.

Parikh AR\*, Leshchiner I\*, Elagina L\*, Goyal L, Levovitz C, Siravegna G, ... Iafrate AJ, Adalsteinsson VA, Bardelli A, Parida L, Getz G, Juric D, Getz G, Corcoran RB. Liquid versus tissue biopsy for detecting acquired resistance and tumor heterogeneity in gastrointestinal cancers. *Nature Medicine* /2019 Sep;25(9):1415-1421).

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Hazar-Rethinam M, Kleymann M, ... Iafrate AJ, Van Allen EM, Corcoran RB. Convergent Therapeutic Strategies to Overcome the Heterogeneity of Acquired Resistance in BRAFV600E Colorectal Cancer. *Cancer Discovery.* 2018; 8: 417-427.

\*Denotes equal contribution

## Shawn Demehri, MD, PhD



### Demehri Laboratory

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Sabrina Smith  
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Elizabeth Trerice  
Maulik Vyas, PhD  
Yun Xia, PhD  
Eray Zhou  
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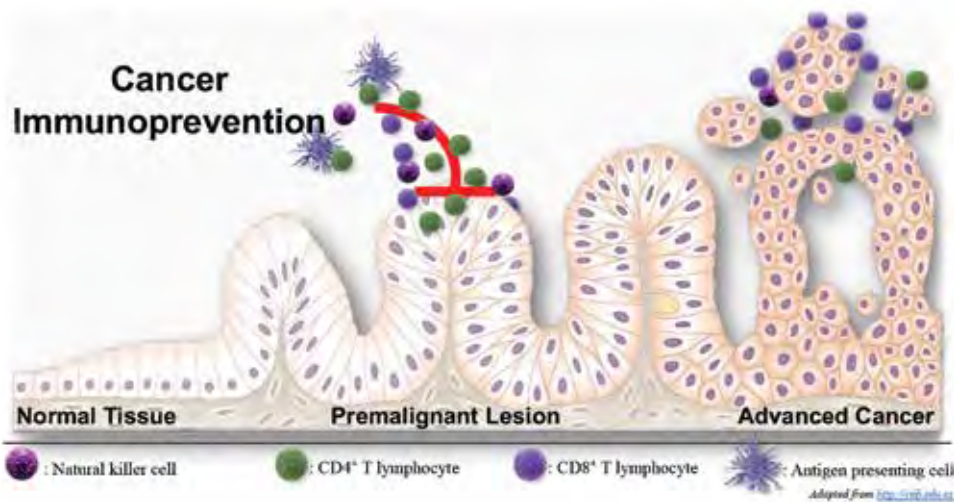
The focus of **the Demehri laboratory** is to determine the role of the immune system in regulating the early stages of cancer development in order to harness its anti-tumor potential for cancer prevention and treatment. To date, several cancer immunotherapies have been developed with proven efficacy 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 therapy and prevention.

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, the Demehri laboratory is currently focused on three areas of research:

**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 the cancer development in vivo remains unclear. Our laboratory is utilizing a virally encoded ligand for NK cells to determine the combination of signals necessary to activate NK cells against early



### *Immune Regulation of Early Cancer Development.*

stages of carcinogenesis and to identify the mechanism of anti-tumor immunity mounted by the activated NK cells in order to block cancer promotion and progression.

**3) Mechanisms of tumor promotion by the immune system.** Although immune cells can mount anti-tumor immunity against cancer, they are also implicated in promoting cancer development under certain conditions. Chronic inflammation is one of the conditions that can predispose patients to cancer; however, the mechanism of such immune-mediated tumor promotion is unclear. To determine this mechanism, our laboratory studies skin and colorectal cancer development as ideal cancer models in which the spatial and temporal relationship between inflammation and cancer development can be determined with exceptional precision. We are currently investigating the immune mechanisms that promote skin cancer development in the context of chronic allergic contact dermatitis and cutaneous lupus and colorectal cancer development in the context inflammatory bowel disease.

### **Selected Publications:**

Schiferle EB, Cheon SY, Ham S, Son HG, Messerschmidt JL, Lawrence DP, Cohen JV, Flaherty KT, Moon JJ, Lian CG, Sullivan RJ, Demehri S. Rejection of benign melanocytic nevi by nevus-resident CD4(+) T cells. *Science Advances*. 2021 Jun 23; 7(26): eabg4498.

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. *Science Advances*. 2021 June 18; 7(25): eabdB936.

Park JH, Ameri AH, Dempsey KE, Conrad DN, Kem M, Mino-Kenudson M, Demehri S. Nuclear IL-33/SMAD signaling axis promotes cancer development in chronic inflammation. *EMBO J* 40, (2021).

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, and Demehri S. Immunity to commensal papillomaviruses protects against skin cancer. *Nature*. 2019 Nov;575(7783):519-522.

Ameri AH, Moradi Tuchayi S, Zaalberg A, Park JH, Ngo KH, Li T, Lopez E, Colonna M, Lee RT, Mino-Kenudson M, Demehri S. IL-33/regulatory T cell axis triggers the development of a tumor-promoting immune environment in chronic inflammation. *Proceedings of the National Academy of Sciences of the United States of America*. 2019. Epub 2019/01/31.

Cunningham TJ, Tabacchi M, Eliane JP, Tuchayi SM, Manivasagam S, Mirzaalian H, Turkoz A, Kopan R, Schaffer A, Saavedra AP, Wallendorf M, Cornelius LA, and Demehri S. Randomized trial of calcipotriol combined with 5-fluorouracil for skin cancer precursor immunotherapy. *J Clin Invest* 2017; 127(1): 106-116.



# Nicholas Dyson, PhD



## Dyson Laboratory

Brian Brannigan  
Nicholas Dyson, PhD  
Marcello Stanzione, PhD  
Jun Zhong, BS

**The Dyson laboratory** studies the role of the retinoblastoma tumor suppressor (RB). RB is expressed in most cell types and its functions enable cells to stop dividing. RB is inactivated in many types of cancer. We have three main goals: we want to understand the molecular details of how RB acts, we want to know how the inactivation of RB changes the cell, and we are using these insights to target tumor cells.

My laboratory investigates mechanisms that limit cell proliferation in normal cells and the ways that these controls are eroded in cancer cells. Our research focuses on RB, the protein product of the retinoblastoma susceptibility gene (*RB1*), and on E2F, a transcription factor regulated by RB. RB/E2F control the expression of a large number of genes that are needed for cell proliferation. This transcription program is activated when normal cells are instructed to divide but it is deregulated in tumor cells, providing a cellular environment that is permissive for uncontrolled proliferation. RB has multiple activities but one of its key roles is to limit the transcription of E2F targets. As a result, most tumor cells select for changes that compromise RB function. Our research program spans three areas of RB biology.

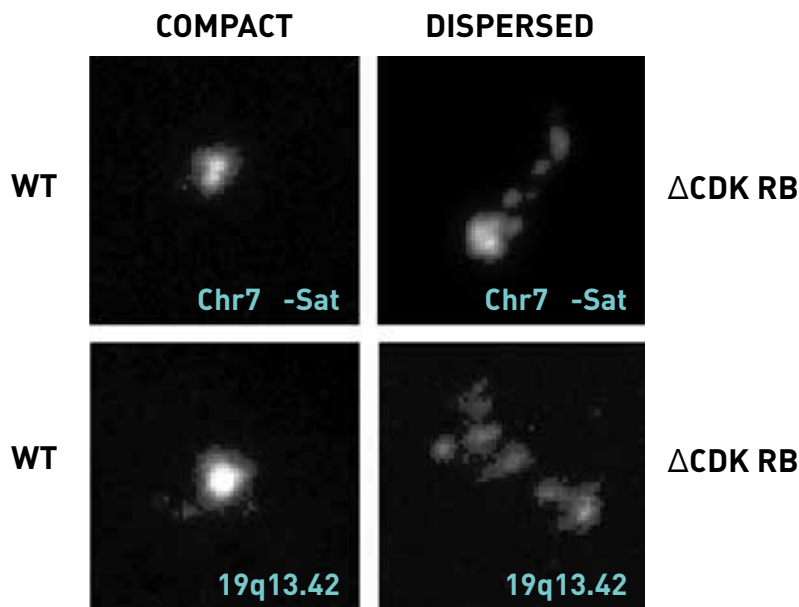
### Dissecting the molecular functions of RB

RB's precise mechanism of action remains an enigma. RB has been linked to hundreds of proteins and has been implicated in many cellular processes. However, purification of endogenous RB complexes has been a major challenge and, consequently, it is uncertain which proteins physically interact with RB in any specific context. We solved this problem and, in collaboration with the Haas lab, have used Mass Spectrometry to take detailed snapshots of RB in action. We used this approach to test the hypothesis that RB's activity is tailored by mono-phosphorylation. Our data shows that the various mono-

phosphorylated forms of RB interact with different cellular proteins, regulate different sets of genes and have distinct functional properties [Sanidas et al 2019].

### Active RB alters the organization of chromosomal domains

ChIP-seq experiments revealed that RB does not simply act at a few cell cycle-regulated promoters but targets thousands of sites that are distributed in euchromatin and heterochromatin. We have taken advantage of Oligopaint/FISH technology to visualize the impact of active RB on the nuclear organization of relatively large chromosomal regions (1-2 MB) that contain RB binding sites but lack canonical E2F-regulated, cell cycle genes. Induced expression of  $\Delta$ CDK-RB (an active mutant protein that is impervious to CDK regulation) caused major changes in the organization of four different regions. Changes were quantified in both euchromatin and heterochromatin, but were most obvious with heterochromatic probes that typically gave a tight focal signal in cycling or quiescent cells. Following  $\Delta$ CDK-RB expression these focal signals became diffuse, dispersed and scattered into multiple punctas (see Figure). Similar changes occurred following long-term palbocyclib treatment and in IMR-90 cells induced to enter senescence. These changes were time-dependent, and wash-out experiments suggest that they correlate with irreversible cell cycle exit. Interestingly, analysis of a



Consistent with the idea that RB is a master regulator of cell proliferation and that its activity leads to major changes in transcription, the expression of active RB ( $\Delta$ CDK-RB) leads to changes in the organization of large chromosomal domains.  $\Delta$ CDK-RB was induced in RPE1 cells, a non-transformed cell line, and the organization of a 4MB heterochromatic region ( $\alpha$ -satellite) of chromosome 7 and 2.3MB euchromatic region of chromosome 19 was detected by FISH.

panel of mono-phosphorylation RB mutants revealed that some RB forms strongly induce these changes in G1-arrested cells while others do not, even though all repress E2F-dependent transcription. We infer that unphosphorylated RB does not simply suppress E2F-dependent transcription but drives changes in the nuclear organization of large chromosomal regions.

### Targeting tumor cells with RB1 mutations

Our long-term goal is to use information gleaned from molecular studies to improve cancer treatment. RB is functionally compromised in most types of cancer, but the specific mutation of the RB1 gene is a hallmark of just three tumor types (retinoblastoma, osteosarcoma and small cell lung cancer (SCLC)). This implies that the complete elimination of RB function is especially important in these tumors. Together with Dr. Anna Farago, our clinical

collaborator, and with help from members of the Haber/ Maheswaran laboratories we have generated an extensive panel of patient derived xenograft (PDX) models of SCLC. These PDX models accurately reflect the genomic features and the drug sensitivities of the tumors from which they were derived (Drapkin et al 2018). We are using this panel of models to compare the effectiveness of different therapies, and to understand which SCLC tumors will respond best to each type of treatment (Farago et al 2019).

### Selected Publications:

Farago AF, Yeap BY, Stanzione M, Hung YP, Heist RS, Marcoux JP, Zhong J, Rangachari D, Barbie DA, Phat S, Myers DT, Morris R, Kem M, Dubash TD, Kennedy EA, Digumarthy SR, Sequist LV, Hata AN, Mahreswaran S, Haber DA, Lawrence MS, Shaw AT, Mino-Kenudson M, Dyson NJ, Drapkin BJ. Combination Olaparib and Temozolomide in relapsed small cell lung cancer. *Cancer Discovery*. 2019; Aug15.

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## Andrew Elia, MD, PhD



### Elia Laboratory

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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, with current projects focusing on DDR pathways regulated by ubiquitin-dependent signaling and DDR 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.

### 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 numerous hereditary cancer syndromes and can underlie the genomic instability which is a hallmark of many 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. While much is known about these core pathways, the complex regulatory events coordinating them are less well understood. Our lab aims to elucidate biochemical and genetic relationships between DDR factors to understand how they are integrated and collectively regulated.

### Quantitative proteomics in ubiquitin signaling

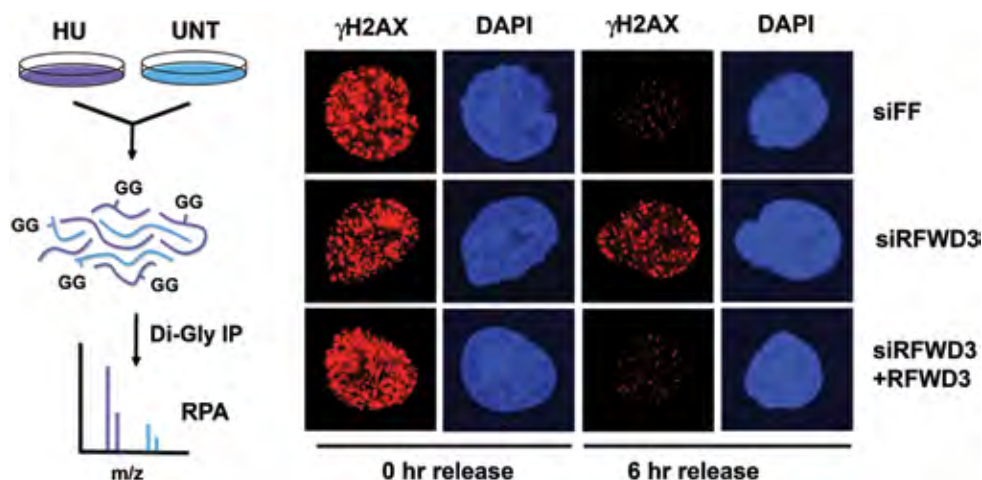
Execution of the DDR relies upon a dynamic array of protein modifications, with phosphorylation playing a historically central role. It is now evident that the DDR also

depends on ubiquitin signaling. Numerous ubiquitin ligases have been implicated in the 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.

### Replication stress 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





(Left) Quantitative proteomics identifies RPA ubiquitination mediated by the ubiquitin ligase RFWD3, which is mutated in the cancer predisposition syndrome Fanconi anemia. (Right) Depletion of RFWD3 inhibits the repair of collapsed replication forks, as demonstrated by delayed resolution of  $\gamma$ H2AX foci six hours after release from hydroxyurea-induced replication fork stalling and collapse.

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 protein RPA to promote homologous recombination at stalled replication forks and replication fork restart (*Mol Cell* 2015b). We are currently studying RFWD3 function in the replication stress response and elucidating novel mechanisms of replication fork stabilization and repair.

### Targeted cancer therapy

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 chemotherapy and radiation. Increased understanding of DNA repair pathways will lead to enhanced opportunities for developing therapies that target cancers with DNA repair defects, and for improving the efficacy of genotoxic

treatments. We are employing methods to translate our work to the development of such therapies.

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Duan H, Mansour S, Reed R, Gillis MK, Parent B, Liu B, Sztupinszki Z, Birkbak N, Szallasi Z, Elia AE, Garber JE, Pathania S. E3 ligase RFWD3 is a novel modulator of stalled fork stability in BRCA2-deficient cells. *J Cell Biol.* 2020; 219(6):e201908192.

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# Leif William Ellisen, MD, PhD



## Ellisen Laboratory

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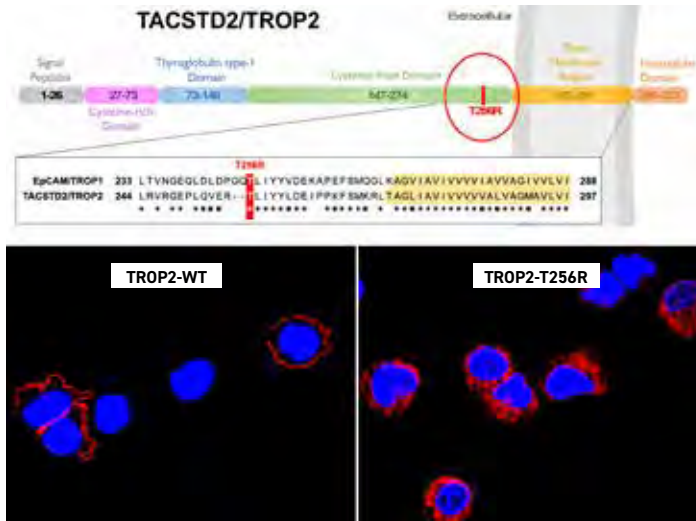
Our laboratory specializes in work at the interface between basic tumor biology and therapeutic application. Understanding how key genes and pathways trigger the early, stepwise progression of cancer will be essential to moving beyond incremental steps and toward revolutionary advances in cancer treatment and prevention. **The Ellisen laboratory** is broadly interested in identifying such genetic abnormalities, understanding how they influence the biology of cancer cells, and discovering how that biology can inform the selection of the most effective therapy for each patient. We address these questions through basic research studies of key tumor-cell signaling pathways, and through molecular analysis of patient tumor samples conducted in partnership with collaborators in the fields of molecular diagnostics and computational biology. Our discoveries in the basic laboratory and through tumor analysis have already been translated to clinical trials that seek to identify new predictive markers, and new prevention and therapeutic strategies for breast and other cancers.

Our group 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 drivers 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 on 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 specific 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](http://Ellisenlab.com).

## Novel drivers of aggressive breast cancer subtypes

Our recent 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. 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.



*TROP2* is a cell-surface protein selectively expressed on tumor cells and targeted by emerging therapeutics including the antibody-drug conjugate sacituzumab govitecan (SG). Immunofluorescence (bottom) for *TROP2* (red) in TNBC cells shows that the novel resistance mutation T256R results in *TROP2* cytoplasmic mislocalization, which prevents SG binding.

### 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 pre-cancerous 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 BRCA1/2-mutant breast tissues that precedes 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

The p53 tumor suppressor is inactivated in

more than 50% of sporadic human cancers, and heterozygous germline p53 mutation confers striking tumor predisposition. As a transcription factor and key nodal point for integrating cellular responses to DNA damage, p53 controls diverse cellular processes including cell cycle progression, apoptosis and angiogenesis. Through analysis of two p53-related genes, p63 and p73, we and others have defined a functional network through which these factors interact in human tumorigenesis. We have further defined a tissue-specific role for p63 as the enforcer of an epigenetically-controlled stem/progenitor state. Tumor-selective deregulation of p63 and its associated chromatin remodeling factors reprograms the transcriptome and thereby promotes proliferation, inhibits differentiation, and contributes to immune evasion. These findings likely explain the observation that 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 analysis of transcriptional reprogramming in cancer, while potentially providing new therapeutic possibilities for multiple treatment-refractory malignancies.

### Selected Publications:

Coates JT, Sun S, Leshchiner I, Thimmiah N, Martin EE, McLoughlin D, Danysh BP, Slowik K, Jacobs RA, Rhrissorakkrai 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.

Qiao S, Koh SB, Vivekanandan V, Salunke D, Patra KC, Zaganjor E, Ross K, Mizukami Y, Jeanfavre S, Chen A, Mino-Kenudson M, Ramaswamy S, Clish C, Haigis M, Bardeesy N, and **Ellisen LW**. REDD1 loss reprograms lipid metabolism to drive progression of RAS-mutant tumors. *Genes & Development*. 2020 Jun 1;34(11-12):751-766.

Karaayvaz M, Silberman RE, Langenbucher A, Saladi SV, Ross KN, Zarcaro E, Desmond A, Yildirim M, Vivekanandan V, Ravichandran H, Mylavaganam 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.

Karaayvaz M, Cristea S, Gillespie SM, Patel AP, Mylavaganam R, Luo CC, Specht MC, Bernstein BE, Michor F, and **Ellisen LW**. Unravelling subclonal heterogeneity and aggressive disease states in TNBC through single-cell RNA-seq. *Nature Communications*. 2018 9:3588-97.

Matissek KJ, Onozato ML, Sun S, Zheng Z, Schultz A, Lee J, Patel K, Jerevall PL, Saladi SV, Finkelstein DM, Le LP, Bardia A, Goss PE, Sgroi DC, Iafrate AJ, **Ellisen LW**. Expressed Gene Fusions as Frequent Drivers of Poor Outcomes in Hormone Receptor-Positive Breast Cancer. *Cancer Discovery*. 2018; 8:336-353.

Saladi SV, Ross K, Karaayvaz M, Tata PR, Mou H, Rajagopal J, Ramaswamy S, and **Ellisen LW**. ACTL6A is co-Amplified with p63 in Squamous Cell Carcinoma to Drive YAP Activation, Regenerative Proliferation and Poor Prognosis. *Cancer Cell*. 2017 31:35-49.

# David E. Fisher, MD, PhD



## Fisher Laboratory

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**The Fisher laboratory** focuses on mechanistic studies which underlie the biology and pathophysiology of skin 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.

Our group studies cell death/proliferation signals in relation to development and disease, particularly in cancer of pigment cells (melanoma) and tumors of childhood. We attempt to understand critical modes of cell homeostasis with a goal of molecular targeted therapy as well as prevention of melanoma and other human cancers. Areas of particular focus are explained below.

### Lessons for malignancy from normal development

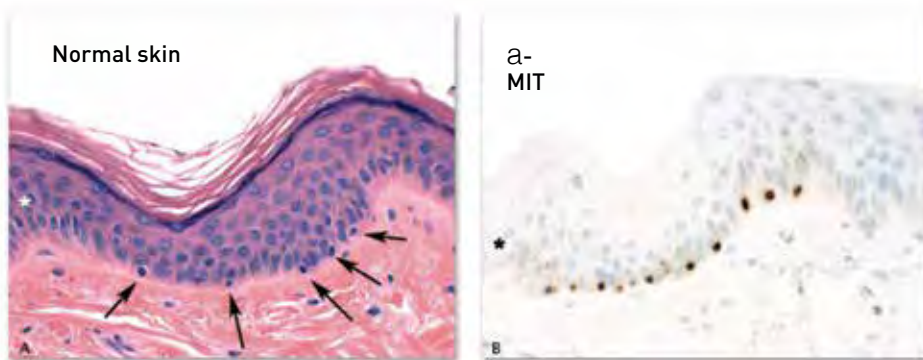
We study the biology of melanocytes as a means of identifying pathways which drive human melanoma. This area of research includes examination of the mechanisms underlying the growth/survival of benign moles, most of which contain mutations in either BRAF or N-Ras oncogenes. We also study melanocyte death 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. Other studies focus on pathways modulating melanocytic responses to environmental cues and employ oncogene-transformed melanocytic lines which exhibit growth factor independence, mimicking human melanoma in a genetically controlled manner, and clinical analyses of novel melanoma treatments. We also study the role of UV in pigmentation responses and carcinogenesis.

### 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 diverse methods— including mouse models, human tumor expression arrays, and cellular assays— we examine mechanisms through which melanoma cells evade death with the goal of improving therapy. Studies include





*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.*

preclinical and clinical analyses of novel melanoma treatments. We also study the role of UV in pigmentation responses and carcinogenesis.

### **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:**

Allouche J, Rachmin I, Adhikari K,... Ruiz-Linares A, **Fisher DE\***, Roider E\*. NNT mediates redox-dependent pigmentation via a UVB- and MITF-independent mechanism. *Cell*. 2021 Aug 5;184(16):4268-4283.e20.

Lo JA, Kawakubo M, Junega VR, Su MY,... Sharpe AH, Manstein D, **Fisher DE**. Epitope spreading toward wild-type melanocyte-lineage antigens rescues suboptimal immune checkpoint blockade responses. *Sci Transl Med*. 2021 Feb 17;13(581)

Kato S, Weng QY, Insko ML,... Jin J, Newton-Bishop J, Zon LI, Bernstein BE, **Fisher DE**. Gain-of-function genetic alterations of G9a drive oncogenesis. *Cancer Discov*. 2020 Jul;10(7):980-997.

Kemeny L, **Fisher DE**. Targeting the (Un)differentiated State of Cancer. *Cancer Cell*. 2018 May 14;33(5):793-795.

Lo JA, **Fisher DE**. The melanoma revolution: from UV carcinogenesis to a new era in therapeutics. *Science*. 2014 Nov 21;346(6212):945-9. PMID: PMC4701046

Fell GL, Robinson KC, Mao J, Woolf CJ, **Fisher DE**. Skin  $\beta$ -endorphin mediates addiction to UV light. *Cell*. 2014 Jun 19;157(7):1527-34.

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# Gad Getz, PhD



## Getz Laboratory

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(Continued on next page)

**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 both bulk and single-cell RNA-sequencing (RNA-seq) 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.

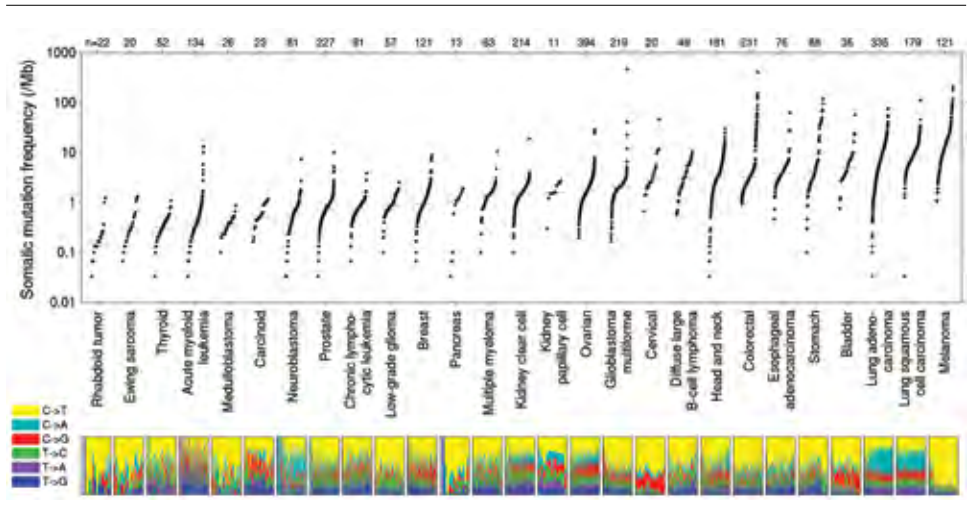
## Detecting Cancer-Associated Genes

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: non-cancer cells intermingle with a cancer cell



**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).

population that typically contains multiple subclones. Since cancer is a dynamic 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 co-evolved 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. By analyzing RNA-seq, we recently showed that most healthy adult tissues contain genetic clones with somatic mutations, some in known cancer-associated genes.

**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.

**Selected Publications:**

Freeman SS, Sade-Feldman 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).

Morton L, Karyadi D, Stewart C, [...], **Getz G**, Chanock S. Radiation-related genomic profile of papillary thyroid cancer after the Chernobyl accident. *Science.* 2021 May 14;372(6543):eabg2538.

Rheinbay E, Nielsen MM, Abascal F, Wala JA, Shapira O, [...], Weischenfeldt J, Martincorena I, Pedersen JS, **Getz G**. Analyses of non-coding somatic drivers in 2,658 cancer whole genomes. *Nature.* 2020 Feb;578(7793):102-111.

(Continued from previous page)

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- Xavi Loinaz
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- Petar Stojanov, PhD
- Chip Stewart, PhD
- Kai Stewart
- Kaitlyn Toy
- Junko Tsuji, PhD
- Michael Vinyard
- Sam Wiseman
- Timothy Wood
- Ting Wu
- Estelle Yao
- Thomas Zhang
- Binyamin Zhitomirsky, PhD

# Timothy A. Graubert, MD



## Graubert Laboratory

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Samuli Eldfors, PhD  
Angelique Gilbert  
Timothy A. Graubert, MD  
Ashwini Patil, PhD  
Sumit Raj, PhD  
Vineet Sharma, PhD

**The Graubert laboratory** focuses on the molecular basis of human blood cancers, including acute myeloid leukemia and myelodysplastic syndromes. The laboratory utilizes a variety of genomic platforms to interrogate primary samples from patients with myeloid malignancies to identify inherited and somatic mutations that drive these diseases. The goal of these studies is to gain insight into the biological basis of myeloid leukemias, and to improve strategies for diagnosis, risk stratification, and targeted therapy.

### Clonal heterogeneity of myelodysplastic syndromes

Myelodysplastic syndromes are the most common form of acquired bone marrow failure in adults. Despite the ineffective hematopoiesis that is characteristic of this disease in its early stages, we found through whole genome sequencing that nearly all cells in the bone marrow of these patients are clonally derived (see Figure). When patients evolve to acute myeloid leukemia (which occurs in approximately one third of cases), new subclonal populations emerge that are derived from the original (“founding”) clone. These findings raise the possibility that the prognostic value of recurrent mutations in myelodysplastic syndrome and the efficacy of therapies that target these mutations may depend not only on the presence or absence of these mutations, but also on their position within the clonal hierarchy of this disease.

### RNA splicing defects at the root of myelodysplastic syndromes

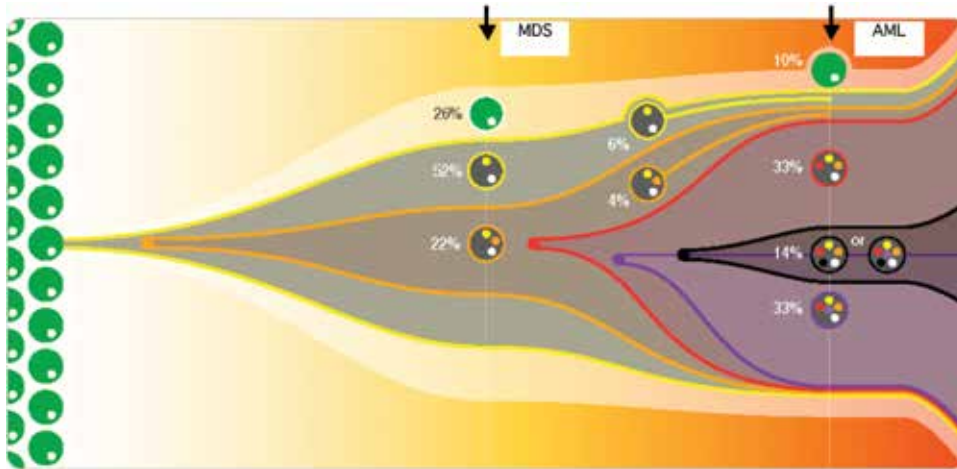
We and several other groups discovered recurrent somatic mutations in genes encoding core components of the RNA splicing complex (the “spliceosome”) in patients with myelodysplastic syndrome. Mutations in this pathway tend to be mutually exclusive, suggesting that more than one splicing gene mutation in a cell provides

no additional selective advantage, or is deleterious to the clone. We have focused on *U2AF1* which encodes a component of the U2 snRNP that binds to the AG dinucleotide at the 3’ intronic splice acceptor site. Mutations in *U2AF1* arise early in the pathogenesis of myelodysplastic syndromes (in the founding clone) and affect almost exclusively two codons in predicted zinc finger domains. We have shown that the most common mutation (S34F) has gain-of-function activity in splicing assays. Current work in the Graubert laboratory is focused on comprehensive analysis of the impact of *U2AF1* mutations on splicing, the functional consequences of these mutations for blood cell development, and vulnerabilities created by splicing gene mutations that provide opportunities for novel therapies.

### Inherited predisposition to myelodysplastic syndrome/acute myeloid leukemia

Acute myeloid leukemia and myelodysplastic syndromes are usually sporadic, late-onset cancers, but in rare instances (<1%) these diseases aggregate in families. In these families, predisposition to acute myeloid leukemia/myelodysplastic syndrome may be a consequence of an inherited bone marrow failure syndrome, but in other cases these are highly penetrant, autosomal dominant, Mendelian disorders. Three





Clonal evolution from myelodysplastic syndrome (MDS) to acute myeloid leukemia (AML). Whole genome sequencing at the time of MDS diagnosis (left arrow) in a representative patient identified a founding clone comprising ~26% of the bone marrow cellularity and a subclone derived from the founding clone in ~22% of cells. When this patient progressed to AML (right arrow), the original clones were still present and had spawned three new subclones that were dominant in the bone marrow at this time point.

genes (*RUNX1*, *GATA2*, *CEBPA*) explain fewer than half of these Mendelian cases. The genetic basis in the majority of families is not yet known. Furthermore, the latency and incomplete penetrance of acute myeloid leukemia/ myelodysplastic syndrome in mutation carriers suggest that acquisition of cooperating somatic mutations is required for malignant transformation. We have accumulated a large panel of samples from affected and unaffected members of these families. Ongoing studies in the Graubert laboratory are focused on identification of novel germline variants in families that lack known predisposing factors, and characterization of the landscape of cooperating somatic mutations that arise in these cases. This information is important for genetic counseling in these families, for selection of optimal bone marrow transplant donors, and to increase our understanding of the biological basis of acute myeloid leukemia and myelodysplastic syndromes.

## Selected Publications:

Nguyen HD, Zou L, and Graubert TA. Targeting R-loop Associated ATR Response in Myelodysplastic Syndrome. *Oncotarget*. 2019 Apr 5; 10(27):2581-2582.

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Brunner AM, Graubert TA. Genomics in childhood acute myeloid leukemia comes of age. *Nature Medicine*. 2018 Jan 9;24(1):7-9.

Saez B, Walter MJ, Graubert TA. Splicing factor gene mutations in hematologic malignancies. *Blood*. 2017 Mar 9;129(10):1260-1269.

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## Wilhelm Haas, PhD



### Haas Laboratory

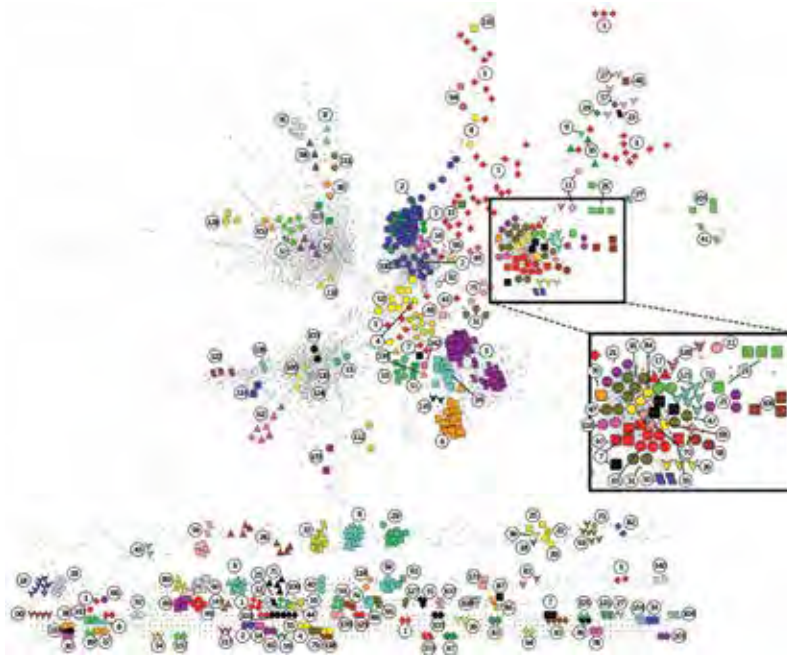
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**The Haas laboratory** uses quantitative mass spectrometry-based proteomics to characterize cancer cells and their vulnerabilities in a comprehensive proteome-wide manner. This is fueled by recent discoveries that have enhanced the depth and throughput of proteomics in quantifying proteins and their post-translational modification. These improvements have put us at a pivotal point in the field of mass spectrometry, where, for the first time, we are able to handle the analysis of the large number of samples that have to be examined to generate the basis for understanding a disease that displays the heterogeneity found in cancer. We are specifically interested in mapping changes in the global landscape of protein-protein interactions - the interactome - that occur in cancer cells, and we have shown that dysregulations in the interactome are enabling the prediction of cancer vulnerabilities. Another focus in the lab is to develop high-throughput plasma proteome mapping technologies to enable early detection of cancer across multiple cancer types in an unbiased manner. We believe that our proteomics technologies have the potential to become a powerful tool in basic and clinical cancer research and may be used to diagnose cancer, predict its susceptibility, and monitor its progression.

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, posttranslational modifications, protein localization, and the interaction of proteins with other proteins as well as with different classes of biomolecules. While the "cancer genome" can now be easily accessed due to advances in DNA sequencing technology, the information contained in the "cancer proteome" has remained largely untapped due to technical challenges in quantifying the large number

of proteins expressed in mammalian cells. 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. Up 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. This technology allows us to map the proteome of a cancer cell line or tumor tissue at high throughput. Analyzing the proteome maps across a panel of cancer cell lines, we recently made the observation that the concentration of proteins in known complexes are accurately



*A Map of Protein-Protein Interactions Identified Using the IMAHP Technology Based on Protein Concentration Co-Regulation across Cancer Cell Lines.*

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 ten-times larger than when using co-expression analysis based on RNAseq data. We further found that deviations from co-regulation of two interacting proteins in specific cancer cell lines reflect perturbed cellular circuitry, and it remarkably predicts sensitization to therapeutics targeting regulatory modules in the associated pathway. We have termed this approach to fast, in-depth characterization of protein-protein interaction landscapes interactome dysregulation (DysReg) mapping. This novel method has been developed in collaboration with the laboratory of Cyril Benes. It enables an interactome-wide mapping of protein-protein interaction dysregulation and inferred cancer vulnerabilities of any cancer sample based on a proteome map that is acquired at high throughput.

We are further interested in the development and application of high-throughput

proteomics methods to globally map protein phosphorylation dynamics in cancer samples and to use the data to specifically identify new kinase targets as cancer vulnerabilities.

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 for mapping tumor vulnerabilities to inform treatment strategies in a patient-specific manner.

Another goal of our group is to develop a novel high-throughput proteomics platform to enable unbiased deep proteome mapping of plasma proteomes to enable early detection of cancer. Unbiased screening of more than 1000 plasma proteins rather than mapping a small number of biomarkers will allow to enable a multi-biomarker assay for multiple cancer types that is constantly improved through adaptation to the detection accuracy.

## Selected Publications:

Kreuzer J, Edwards A, Haas W. Multiplexed quantitative phosphoproteomics of cell line and tissue samples. *Methods Enzymol.* 2019; 626, 41-65.

Lapek JD Jr, Greninger P, Morris R, Amzallag A, Pruteanu-Malinici I, Benes CH\*, Haas W\*. Detection of dysregulated protein-association networks by high-throughput proteomics predicts cancer vulnerabilities. *Nat. Biotechnol.* 2017; 35, 983-989.

Edwards A, Haas W. Multiplexed Quantitative Proteomics for High-Throughput Comprehensive Proteome Comparisons of Human Cell Lines. *Methods Mol. Biol.* 2016; 1394,1-13.

Braun CR\*, Bird GH, Wühr M, Erickson BK, Rad R, Walensky LD, Gygi SP\*, Haas W.\* Generation of Multiple Reporter Ions from a Single Isobaric Reagent Increases Multiplexing Capacity for Quantitative Proteomics. *Anal. Chem.* 2015; 87, 9855-9863.

McAlister GC, Nusinow DP, Jedrychowski MP, Wühr M, Huttlin EL, Erickson BK, Rad R, Haas W, Gygi SP. MultiNotch MS3 enables accurate, sensitive, and multiplexed detection of differential expression across cancer cell line proteomes. *Anal Chem.* 2014; 86, 7150-7158.

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# Daniel A. Haber, MD, PhD



## Haber Laboratory\*

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Ajinkya Revandkar, PhD  
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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 of Dr. Shyamala Maheswaran, and the MGH Cancer Center 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.

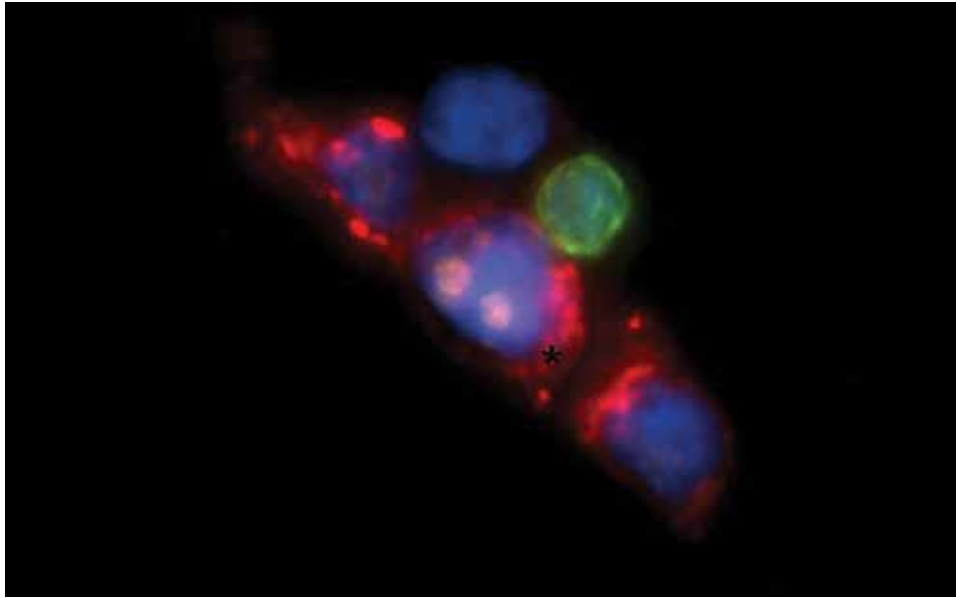
Our laboratory is interested in the genetics of human cancer. Current projects include the use of a microfluidic device to capture circulating tumor cells (CTCs) and its application in early detection of invasive cancer, molecular-directed therapy, and in the study of human cancer metastasis.

## 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 CTC





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

quantitation and provide the sensitivity and specificity required for early cancer detection, we have established a droplet digital PCR readout for CTC-derived RNA, with promising applications in the early detection of liver cancer.

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*. The development of such CTC-derived cultures may enable functional predictive drug testing, combined with detailed genetic analysis of tumor cells sampled noninvasively during the course of cancer treatment. In a recent study of metastasis initiation, we identified a critical role for the nuclear orphan receptor *NR4A1*, as a regulator of transcriptional elongation for replication stress-induced Immediate Early Genes (IEG). Both genetic and drug treatment studies point to *NR4A1* as a “non-oncogene dependent” target in tumorigenesis. 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.

## Selected Publications:

Guo H, Golczer G, Wittner BS, Langenbacher A,...Vasudevan S, Zou L, Mostoslavsky R, Maheswaran S\*, Lawrence MS\*, Haber DA\*. NR4A1 regulates expression of immediate early genes, suppressing replication stress in cancer. *Mol Cell*. 81(19): 4041-4058, 2021 PMID: 34624217.

Hong X, Roh W, Sullivan RJ, Wong KHK, Wittner BS,...Toner M, Stott SL, Getz G, Maheswaran S\*, Haber DA\*. The lipogenic regulator SREBP2 induces transferrin in circulating melanoma cells and suppresses ferroptosis. *Cancer Discovery*. 11:678-95, 2021 PMID 33203734.

Ebright RY, Lee S, Wittner BS, Niederhoffer KL,...Ting DT, Toner M, Vasudevan S, Haber DA\*, Maheswaran S, Micalizzi DS. Deregulation of ribosomal protein expression and translation promotes breast cancer metastasis. *Science*. 367(6485):1468-1473, 2020. PMID 32029688.

Zheng Y, Comaills V, Burr R, Boulay G, Miyamoto DT, Wittner BS,...Rivera MN, Maheswaran S, Haber DA. COX-2 mediates tumor-stromal prolactin signaling to initiate tumorigenesis. *Proc Natl Acad Sci USA*. 116:5223-5232, 2019. PMID: 30819896.

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Jordan NV, Bardia A, Wittner BS, Benes C, Ligorio M, Zheng Y, Yu M, Sundaresan TK, LiCausi JA, Desai R, O’Keefe RM, Ebright RY, Boukhali M, Sil S, Onozato ML, Iafrate AJ, Kapur R, Sgroi D, Ting DT, Toner M, Ramaswamy S, Haas W, Maheswaran S, Haber DA. HER2 expression identifies dynamic functional states within circulating breast cancer cells. *Nature*. 537(7618):102-106, 2016.

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# Nir Hacohen, PhD



## Hacohen Laboratory

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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. Finally, we are adapting our unbiased analytical strategies into real-world therapeutics, having initiated 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 personal tumor genome.

## Initiators, resistors and targets of tumor immunity

While cancer immunology has been deeply studied in animal models, there remain many open questions in human tumor immunology due to lack of tools to investigate human samples. We have developed genetic and genomics approaches to explain the large variance in anti-tumor immunity across people, and to discover how tumors evolve to resist productive immunity. We've identified somatic mutations in tumors that are associated with anti-tumor immunity in patients, and found T cell subtypes that are associated with a response to anti-PD-1 immunotherapy in melanoma and are studying their properties now (Sade-Feldman et al., *Cell* 2018). 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 to develop novel therapeutic approaches and targets for immunotherapy,

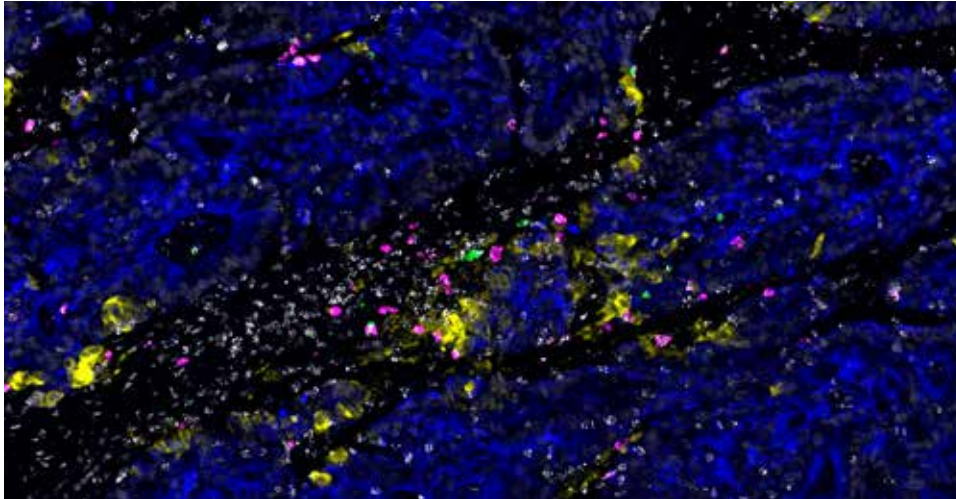
such as personal tumor vaccines targeting multiple HLA-associated neoantigens in human tumors (together with Dr. Catherine Wu at DFCI, Ott et al., *Nature* 2017, Keskin *Nature* 2018).

## 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), impacting HIV infection (Park et al, *Nat Gen* 2017) and affecting influenza infection (Li et al., *Nat Comm* 2020) and other sensing pathways (ongoing). We have also characterized innate myeloid cells (DCs and monocytes) in human blood as part of the human Immune Cell Atlas (Villani et al, *Science* 2017).

## Genetic basis for inter-individual variations in immune responses

We have also developed genomic strategies to analyze human immune responses and



In the subset of mismatch repair-deficient human colorectal tumors, activated and likely tumor-reactive T cells (white, green, and magenta) are organized into "hubs" around malignant cells (blue) expressing chemokines (yellow) that attract T cells and other cells into spatially organized immune cell hubs. Credit : Joshua Pirl, Vjola Jorgji, Linda Nieman, Jonathan Chen.

Source: Pelka, Hofree, Chen et al. *Cell*. 2021

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 have recently developed and are now using systematic methods to analyze the role of genetic (Ray et al., *Nat Comm* 2021). 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 (including COVID-19) and sepsis (Reyes et al, *Nat Med* 2020, *Science Tr 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, and autoimmune arthritis, nephritis and myocarditis in mice. We have been interested in understanding how autoimmunity develops upon triggering of innate immunity by self DNA (rather than pathogen-derived DNA). In studying this question, 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). We hypothesize that this cellular process is a source of inflammation in autoimmunity, cancer, chemotherapy and aging (Lan et al., *Aging Cell* 2019). To deepen our understanding of pathways that drive autoimmunity, we have been analyzing immune responses in lupus nephritis patients, with an emphasis on cellular and molecular analysis of kidney biopsies and blood samples from lupus patients in a small (Arazi et al., *Nat Imm* 2019) and large patient cohort (ongoing) and more recently in comparison to animal lupus models.

### Selected Publications:

Pelka K, Hofree M, Chen JH, Sarkizova S, Pirl JD, Jorgji V... Ng K, Giannakis M, Nieman LT, Boland GM, Aguirre AJ, Anderson AC, Rozenblatt-Rosen O, Regev A, **Hacohen N**. Spatially organized multicellular immune hubs in human colorectal cancer. *Cell*. 2021 Aug 24:S0092-8674(21)00945-4.

Reyes M, Filbin MR, Bhattacharyya RP, Sonny A, Mehta A, Billman K... Baron RM, Goldberg MB, Blainey PC, **Hacohen N**. Plasma from patients with bacterial sepsis or severe COVID-19 induces suppressive myeloid cell production from hematopoietic progenitors in vitro. *Sci Transl Med*. 2021 Jun 16;13(598):eabe9599.

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# Aaron Hata, MD, PhD



## Hata Laboratory

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The research goal of **the Hata laboratory** is to advance the development of novel targeted and immunotherapy approaches to benefit patients with lung cancer. Our focus is on understanding 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 clinicians in the MGH Thoracic Oncology group. We have discovered clinical mechanisms of acquired drug resistance and identified 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 targetable vulnerabilities in cancer cells that can be exploited to prevent resistance from developing in the first place. Our ultimate goal is to translate our laboratory discoveries into clinical trials.

## Mechanisms of acquired drug resistance to targeted therapies

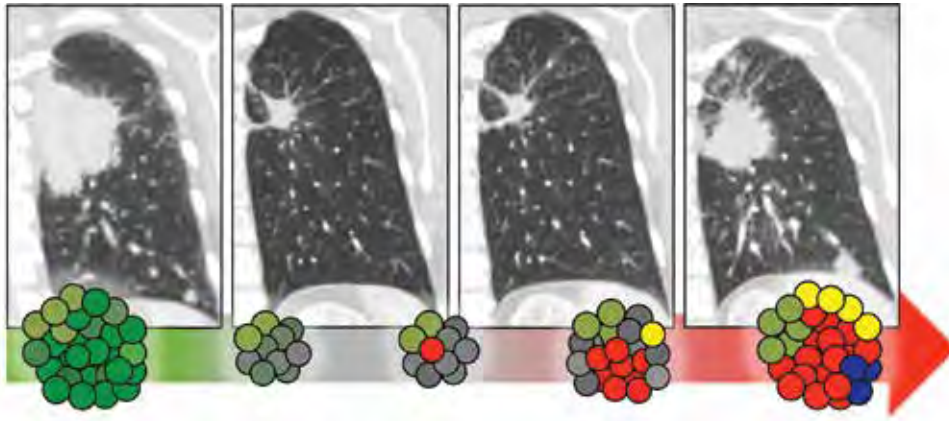
Lung cancers that harbor activating EGFR mutations and ALK fusions are exquisitely sensitive to small molecule EGFR and ALK tyrosine kinase inhibitors, respectively. However, even though most patients experience dramatic responses, drug resistance invariably develops leading to disease relapse. Similar 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). We work closely with oncologists in the MGH Center for Thoracic Cancers to identify and characterize mechanisms of acquired resistance in lung cancer patients treated with targeted therapies. By analyzing tumor biopsies or tumor DNA isolated from blood, we have identified acquired secondary mutations and other genomic alterations

that cause drug resistance. 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 have allowed us to identify novel mechanisms of acquired resistance and test potential new 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 novel therapeutic combinations that can overcome these





EGFR mutant lung cancers can develop acquired resistance to EGFR inhibitors (e.g. acquisition of the gatekeeper EGFR<sup>T790M</sup> mutation) by selection of pre-existing EGFR<sup>T790M</sup> cells, or via evolution of initially EGFR<sup>T790M</sup>-negative drug tolerant cells that then develop the mutation during the course of treatment. EGFRi denotes EGFR inhibitor treatment, such as gefitinib or erlotinib. Reproduced from Hata and Niederst, et al. *Nature Medicine* 2016.

mechanisms and increase sensitivity to KRAS inhibitors. In addition, we are focused on understanding how both inter-patient and intratumoral heterogeneity may influence initial drug response and the development of acquired drug resistance.

### Tumor adaptation and evolution during treatment

Despite the development of successive generations of targeted therapies with improved selectivity and potency, acquired resistance inevitably develops. To halt this perpetual cycle of drug resistance, we are investigating novel therapeutic strategies to alter the tumor evolution prior to the development of drug resistance. 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 cells may comprise a cellular reservoir from which heterogeneous mechanisms of resistance may arise. Ongoing efforts are focused on characterizing persistent tumor cells that survive during drug treatment in both experimental models and patients and defining mechanisms that drive drug adaptation. By identifying targetable

vulnerabilities of these cells, we hope to develop novel therapeutic strategies that will prevent acquired drug resistance.

### 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.

### Selected Publications:

Noritaka T<sup>†</sup>, Lin JJ<sup>†</sup>, Li C<sup>†</sup>,... 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.

Dagogo-Jack I<sup>†</sup>, Yoda S<sup>†</sup>,... Shaw AT\*, Hata AN\*. MET Alterations Are a Recurring and Actionable Resistance Mechanism in ALK-Positive Lung Cancer. *Clin Cancer Res.* 2020 Jun 1;26(11):2535-2545.

Piotrowska Z<sup>†</sup>, Isozaki H<sup>†</sup>,... Hata AN\*, Sequist LV\*. Landscape of acquired resistance to osimertinib in EGFR-mutant NSCLC and clinical validation of combined EGFR and RET inhibition with osimertinib and BLU-667 for acquired RET fusion. *Cancer Discovery.* 2018 Dec;8(12):1529.

Nangia V<sup>†</sup>, Siddiqui FM<sup>†</sup>,... Benes CH, Hughes PE, Hata AN. Exploiting MCL-1 dependency with combination MEK + MCL-1 inhibitors leads to induction of apoptosis and tumor regression in KRAS mutant non-small cell lung cancer. *Cancer Discovery.* 2018 Dec;8(12):1598-1613.

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.

Hata AN<sup>†</sup>, Niederst MJ<sup>†</sup>,... Engelman, JA. Tumor cells can follow distinct evolutionary paths to become resistant to epidermal growth factor receptor inhibition. *Nature Medicine.* 2016; 22:262-9

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# Konrad Hochedlinger, PhD



## Hochedlinger Laboratory

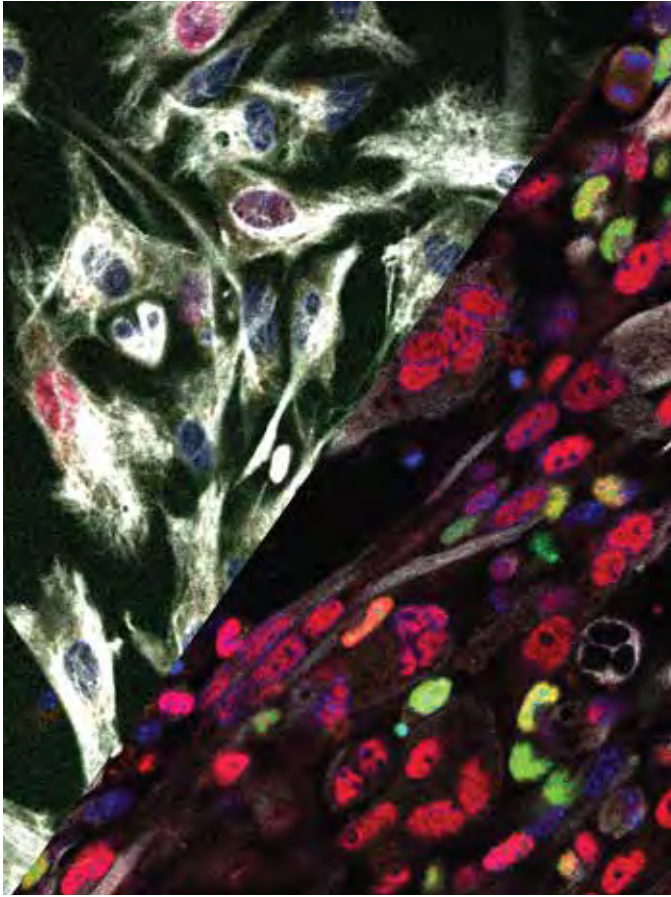
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**The Hochedlinger laboratory** explores the fundamental question of how cells safeguard their identity. We hypothesize that factors that reinforce specific cell states, such as pluripotency and differentiation, continue to play functional roles in 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 safeguard mechanisms that 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 barriers safeguarding cell identity and thus restricting 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. Most recently, our lab uncovered two post-transcriptional processes, alternative polyadenylation (APA)



Immunofluorescence images showing myogenic cells derived from fibroblasts via “transdifferentiation” (i.e. transient MyoD expression; left image) or “dedifferentiation” (i.e. transient MyoD expression together with small molecules; right image). Note that only dedifferentiated myogenic cells activate the stem cell marker Pax7 (green signal) and maintain endogenous MyoD expression (red signal). White signal highlights Desmin+ myotubes (see Yagi et al., *Genes & Development* 2021 Sep 1;35(17-18):1209-1228).

Image: Masaki Yagi, PhD

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 (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.

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:

Yagi M, Ji F, Charlton J, Cristea S, Messemer K,...Goldhamer DJ, Wagers AJ, Michor F, Meissner A, Sadreyev RI, **Hochedlinger K**. Dissecting dual roles of MyoD during lineage conversion to mature myocytes and myogenic stem cells. *Genes Dev.* 2021 Sep 1;35(17-18):1209-1228.

Brumbaugh J, Kim IS, Ji F, Huebner AJ, Di Stefano B,...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 Nov;21(11):1449-1461.

Di Stefano B, Luo EC, Haggerty C,...Gygi SP, Sadreyev RI, Meissner A, Yeo GW, **Hochedlinger K**. The RNA Helicase DDX6 Controls Cellular Plasticity by Modulating P-Body Homeostasis. *Cell Stem Cell.* 2019 Nov 7;25(5):622-638.e13.

Di Stefano B, Ueda M, Sabri S, Brumbaugh J,...Shioda K, Gygi SP, Gu H, Shioda T, Meissner A, Takashima Y, Plath K, **Hochedlinger K**. Reduced MEK inhibition preserves genomic stability in naive human embryonic stem cells. *Nat Methods.* 2018 Aug 20.

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Choi J, Huebner AJ, Clement C, Walsh RM,...Charron J, Shioda T, Gnirke A, Gygi SP, Koseki H, Sadreyev R, Xiao A, Meissner A & **Hochedlinger K**. Prolonged Mek1/2 suppression impairs the developmental potential of embryonic stem cells. *Nature.* 2017 Aug 10;548(7666):219-223.

# Hanno Hock, MD, PhD



## Hock Laboratory

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Ryan LeGraw

**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.

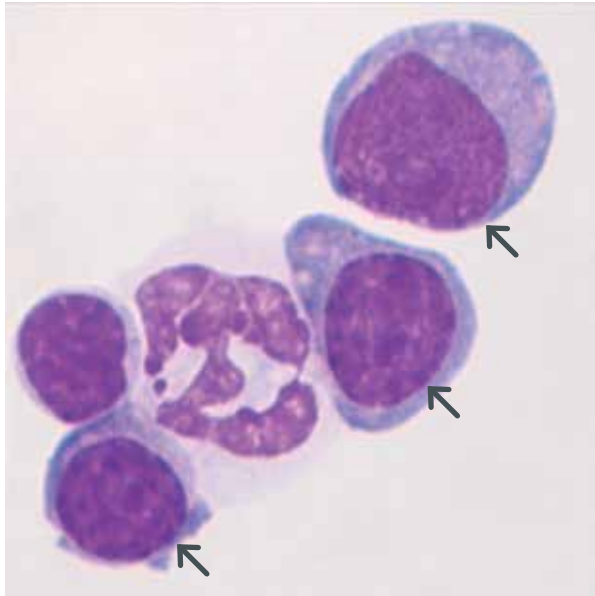
Our laboratory is interested in the molecular control of normal and malignant stem cells with an emphasis on the hematopoietic system. Blood cells need to be continuously replenished by a small population of hematopoietic stem cells (HSCs) that have the capacity to both self-renew and mature stepwise 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 from 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 TEL-AML1, 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 L3mbt2 in pluripotent stem cells.

### Selected Publications:

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.

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## A. John Iafrate, MD, PhD



### Iafrate Laboratory

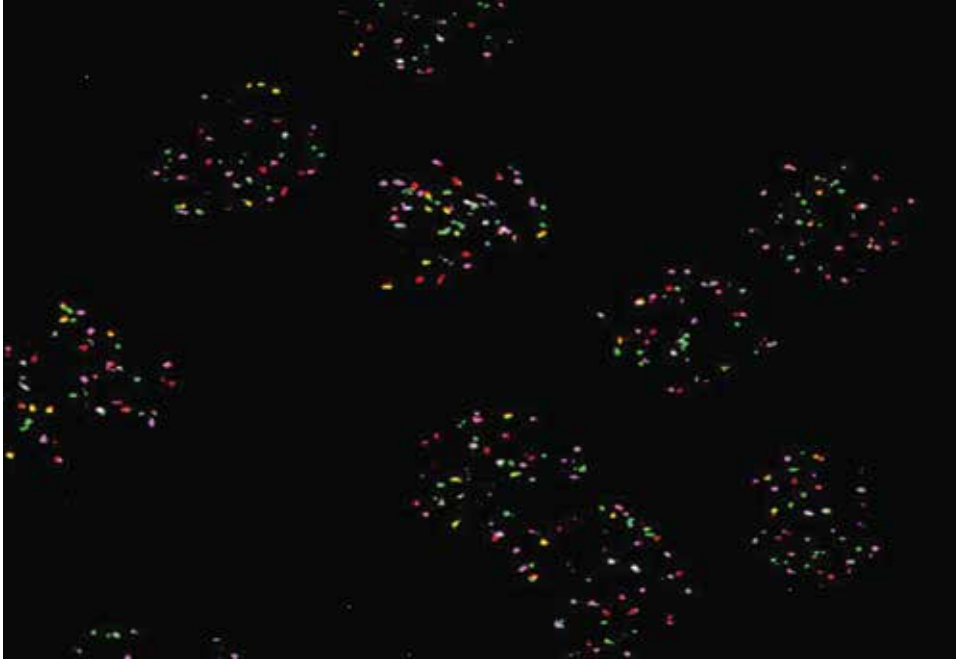
Cristhian Jose Berrios  
Elizabeth Codd  
Cosima Hoch  
A. John Iafrate, MD, PhD  
Stefan Kaluziak, PhD  
Grace Kirkpatrick  
Vivek Naranbhai, PhD  
Maristela Onozato, MD  
Zavontae Oppong-Homes  
Rashi Purohit  
Julia Cara Thierauf, MD  
Diane Yang, PhD

**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 and brain tumors. Our recent 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 (1, 2). We currently are focusing on detecting tumor DNA in blood samples (“liquid biopsies”) to allow for efficient and convenient tracking of cancer progression. In addition we are developing new techniques to allow for early detection of cancers by detecting tumor-specific DNA in circulation.

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. The method we have developed, termed “anchored multiplex PCR” or AMP, is an efficient target enrichment technology, allowing for 100s of targets to be simultaneously analyzed from small tissue samples (3). We have used AMP to screen thousands of tumor samples, and have uncovered numerous novel driver fusion genes. Our lab is now focused on modeling novel fusions in vitro and developing therapeutic approaches to screening these fusions. We have also initiated studies of tumor heterogeneity; these efforts focus on gene amplification of receptor tyrosine kinases in glioblastoma (4). 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. Detailed genetic analysis found that different subpopulations within a particular tumor shared other gene mutations, indicating that they had originated from the same precursor cells. Mapping the location of different subpopulations in the brain of a glioblastoma patient suggested that each subpopulation may serve a different function in the growth and spread of the tumor. Our lab has developed novel highly-multiplexed FISH technology to address how many genes show copy number heterogeneity, and to study the spatial distribution of such populations (5), see image. We are exploring the therapeutic implications of such driver gene heterogeneity in cell line model systems of glioblastoma using genome-wide CRISPR knock out screens.

More recently we have adapted the AMP sequencing technology in other areas, including (1) mapping off-target rates for CRISPR-CAS genome editing; (2) sequencing and mapping the distribution of IgH and TCR rearrangements in tumor samples; and (3) ultra-high sensitive mutation calling in



*Multiplex FISH to detect copy number changes in circulating tumor cells.*

circulating tumor cells and cell free plasma samples. Using AMP we have developed 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 burden in patients. We are able to use cfDNA analysis in metastatic patients to see if they are responding to therapy, and also can track the development of resistance mutations. This allows a real-time dynamic optimization of therapy. Most recently we have developed a methylation-based sequencing assay to allow efficient analysis of tumor-specific methylation patterns in cfDNA samples. We hope that such an approach 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. In addition, the methylation patterns are actually specific

to the type of tumor the DNA is derived from, potentially allowing us to determine the actual anatomic site of origin.

## Selected Publications:

Garcia-Beltran WF, Iab EC, Astudillo MG, Yang D, Miller TE, Feldman J, Hauser BM, Caradonna TM, Clayton KL, Nitido AD, Murali MR, Alter G, Charles RC, Dighe A, Branda Ja, Lennerz JK, Lingwood D, Schmidt AG, **Iafrate AJ**, Balazs AB. Covid-19-neutralizing antibodies predict disease severity and survival. *Cell*. 2021; 21;184(2):476-488.

Cheng J, Cao Y, MacLeay A, Lennerz JK, Baig A, Frazier RP, Lee J, Hu K, Pacula M, Meneses E, Robinson H, Batten JM, Brastianos PK, Heist RS, Bardia A, Le LP, **Iafrate AJ**. Clinical Validation of a Cell-Free DNA Gene Panel. *J Mol Diagn*. 2019; 21(4): 632-645.

Onozato ML, Yapp C, Richardson D, Sundaresan T, Chahal V, Lee J, Sullivan JP, Madden MW, Shim HS, Liebers M, Ho Q, Maheswaran S, Haber DA, Zheng Z, Clancy B, Elliott HL, Lennerz JK, **Iafrate AJ**. Highly Multiplexed Fluorescence in Situ Hybridization for in Situ Genomics. *J Mol Diagn*. 2019; 21(3):390-407.

Heist RS, Shim HS, Gingipally S, Mino-Kenudson M, Le L, Gainor JF, Zheng Z, Aryee M, Xia J, Jia P, Jin H, Zhao Z, Pao W, Engelman JA, and **Iafrate AJ**. MET Exon 14 Skipping in Non-Small Cell Lung Cancer. *Oncologist*. 2016; 21(4):481-486.

Zheng Z, Liebers M, Zhelyazkova B, Cao Y, Panditi D, Chen J, Robinson HE, Chmielecki J, Pao W, Engelman JA, **Iafrate AJ\***, Le LP\*. Anchored multiplex PCR for targeted next-generation sequencing. *Nat Medicine*. 2014; Nov. 10.

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.

\*Co-corresponding authors

# Othon Iliopoulos, MD



## 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**

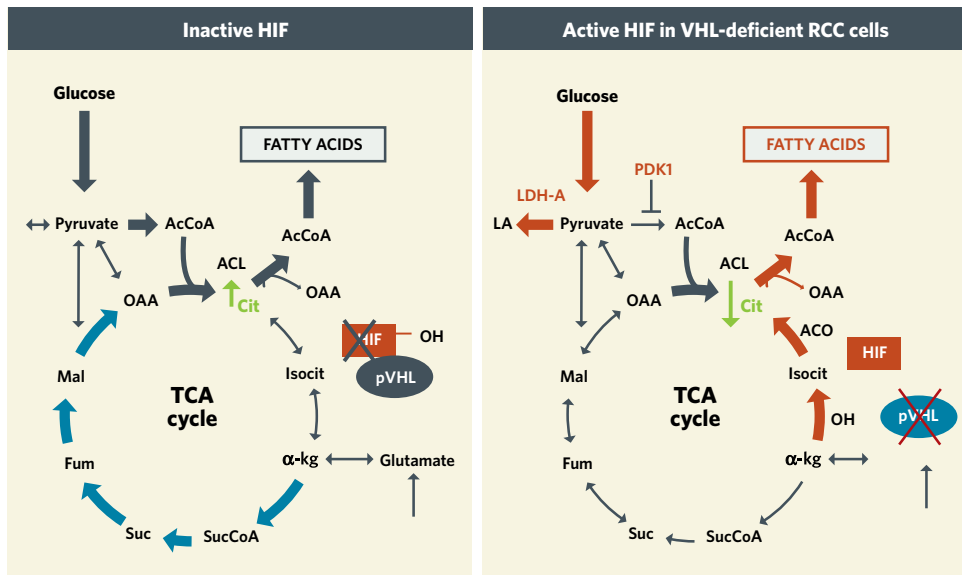
We screened libraries of chemical compounds and discovered chemical molecules that significantly and specifically decrease the expression of HIF2a [Zimmer M. et al. *Molecular Cell* 2008; 32(6): 838-48]. We used these HIF2a inhibitors as chemical biology probes and discovered that they suppress the expression 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].





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

We brought these fundamental observations of my laboratory on glutamine metabolism to the clinic. We initiated a Phase 1 trial with Glutaminase 1 (GLS1) inhibitors for patients with RCC and triple negative breast cancers nationwide. We are now opening a new clinical trial of GLS1 inhibitor CB-839 and PARP inhibitor combination treatment for patients with RCC, prostate, triple negative and ovarian cancer.

### Modeling Renal Cell Carcinoma in the zebrafish

Zebrafish with homozygous inactivating mutations in VHL gene recapitulate aspects of the human VHL disease, including abnormal proliferation of their kidney epithelium. We are using the zebrafish as a model system to model the diverse pathways that lead to renal cell carcinoma development.

### Selected Publications:

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. Targeting metabolism in RCC. *Nature Reviews Nephrology*. 2017; 13, 320.

Laviollette LA, Mermoud J, Calvo IA, Olson N, Boukhali M, Steinlein OK, Roeder 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.

Metelo AM, Noonan HR, Li X, Jin YN, Baker R, Kamentsky L, Zhang Y, van Rooijen E, Shin J, Carpenter AE, Yeh JR, Peterson RT, Iliopoulos O. Treatment of VHL disease phenotypes with small molecule HIF2a inhibitors. *Journal Clinical Investigation*. 2015; 125 (5):1987-97.

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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# Max Jan, MD, PhD



## Jan Laboratory

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Jo Kim  
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\* co-affiliated with Marcela Maus Lab

The current moment in cancer immunotherapy has been likened to the early days of the space race, and in this all-too-accurate analogy the patients are the astronauts sent on ballistic therapeutic arcs at the leading edge of human possibility. **The Jan laboratory** seeks to refine cell therapies as safe, effective, accessible, and ultimately routine modalities that ask less of people with cancer. We contribute to these goals by harnessing elegant protein degradation cellular machinery that has evolved to control fast biologic transitions related to information flow and signal processing. Our multidisciplinary translational research group investigates the following questions: How does protein degradation shape immune cell function? How can our protein degradation machinery be retargeted to tune and customize therapeutic cell programs? What are the design principles for adaptive, user-controllable cell therapies? What are the clinical settings to deploy smart next-generation cellular immunotherapies?

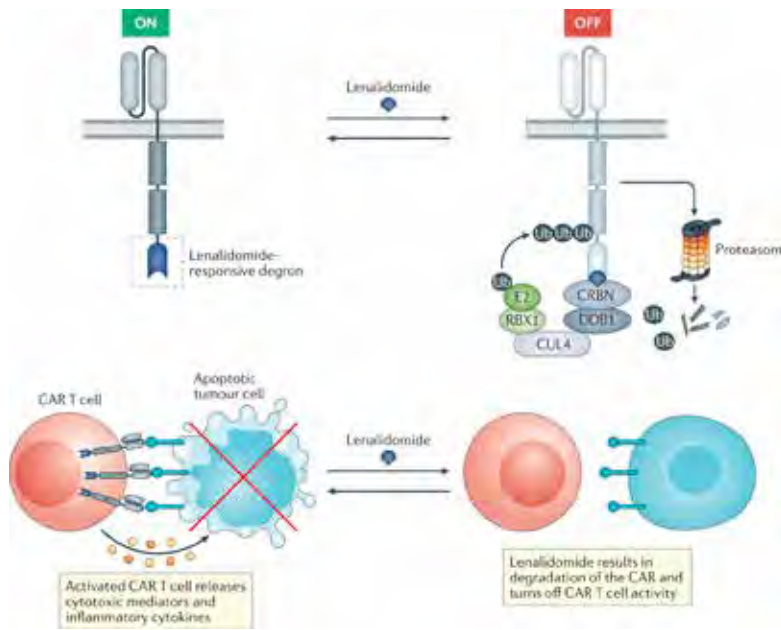
### Targeted protein degradation for cell therapy

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. Mentored by Marcela Maus and Ben Ebert, we recently developed chemical genetic controls 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 lenalidomide ON- and OFF-switch CAR T cells (see: Figure). In collaboration with Amit Choudhary and David Liu, we have further demonstrated the generalizability of these tools by engineering a suite of lenalidomide switchable, sequence programmable Cas9-derivative genome editing proteins. Looking forward, we have

established a multidisciplinary research program using functional genomics, biochemistry, and synthetic biology to explore the design principles of immune cell programming and advance next-generation cellular immunotherapies to treat cancers with limited treatment options.

### Ubiquitin-dependent control of immune cell function

Our >600 E3 ubiquitin ligases encode diverse post-translational regulatory programs that are particularly well-suited to govern fast, activity-dependent transitions in signal transduction and gene expression. While important examples of E3 ligases that govern individual functional modules and lineage decisions are known, a systems-level understanding of ubiquitin-dependent control in the immune system remains elusive. As an entry point to engineering with the ubiquitin code, we leverage functional genomics and biochemistry to systematically identify mechanisms of control over immune cell state, fate, and function.



**Molecular switch control of genetically engineered cell therapies.** Incorporation of a lenalidomide-responsive degron tag into a chimeric antigen receptor (CAR) 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.

### Reprogramming protein degradation

Molecular glue degraders are frontline anti-cancer agents and herald extraordinary promise for degrader drug development. The target-drug-E3 ligase ternary complexes enforced by small molecule degraders are our starting point for synthetic biology development. We are learning to chemically and genetically retarget protein degradation machinery in order to control immune cell programming in new and therapeutically impactful ways. By advancing clinically suitable tools composed of human proteins and FDA-approved small molecules, we envision a platform for direct clinical translation.

### Expanding the design space of cellular immunotherapy

Cellular states of dysfunction undermine CAR T effectiveness and are a prominent mechanism of treatment failure that could in theory be overcome by tuning therapeutic cell self-renewal and differentiation. Yet there are

few static, irreversible genetic modifications that can safely manipulate these core cell fate dynamics. We are leveraging user-controlled, chemical biology approaches to hack the central cellular processes that determine therapeutic potential.

### Design and evaluation of cellular immunotherapies targeting novel antigens

In the current CAR T cell paradigm, target antigens must be present on tumor cells and absent from essential normal tissues (e.g. CD19, BCMA). We and collaborators have identified novel antigens consistent with this pattern in select solid tumors. Integrating novel targeting and molecular switch systems, we seek to pre-clinically validate candidate next-generation cellular immunotherapies targeting malignancies with limited treatment options. The MGH Cellular Immunotherapy Program can advance promising designs via investigator-initiated clinical trials.

### Selected Publications:

Jan M\*, Sperling AS\*, & Ebert BL (2021). Cancer therapies based on targeted protein degradation—lessons learned with lenalidomide. *Nature Reviews Clinical Oncology*, 1-17.

Jan M, Scarfò I, Larson RC, Walker A, Schmidts A, Guirguis AA,... Maus MV & Ebert BL (2021). Reversible ON-and OFF-switch chimeric antigen receptors controlled by lenalidomide. *Science Translational Medicine*, 13(575).

Miller PG, Sperling AS, Brea EJ, Leick MB, Fell GG, Jan M,... & Ebert BL (2021). Clonal hematopoiesis in patients receiving chimeric antigen receptor T-cell therapy. *Blood Advances*, 5(15), 2982-2986.

Sperling AS, Burgess M, Keshishian H, Gasser JA, Bhatt S, Jan M,... & Ebert BL (2019). Patterns of substrate affinity, competition, and degradation kinetics underlie biological activity of thalidomide analogs. *Blood, The Journal of the American Society of Hematology*, 134(2), 160-170.

Jan M, Leventhal MJ, Morgan EA, Wengrod JC, Nag A, Drinan SD,... & Ebert BL (2019). Recurrent genetic HLA loss in AML relapsed after matched unrelated allogeneic hematopoietic cell transplantation. *Blood Advances*, 3(14), 2199-2204.

Jan M\*, Snyder TM\*, Corces-Zimmerman MR\*, Vyas P, Weissman IL, Quake SR, & Majeti R (2012). Clonal evolution of preleukemic hematopoietic stem cells precedes human acute myeloid leukemia. *Science Translational Medicine*, 4(149), 149ra118-149ra118.

\*Equal contribution

# Russell W. Jenkins, MD, PhD



## Jenkins Laboratory

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Izabela Panova  
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\*\*PhD Candidate

Immunotherapy has transformed the treatment of metastatic melanoma and other cancers, allowing a new avenue of therapeutic options and prolonging lives of many patients. Unfortunately, while immunotherapy is highly effective in some patients, it does not work for every patient and there are no available tests to determine whether or not a patient will respond to immunotherapy before treatment begins. To understand why immunotherapy works for some patients and not others, **the Jenkins laboratory** uses sophisticated tools and techniques to study and investigate the complex and dynamic interactions between cancer cells and the immune system. Our solution to this problem involves a specialized 3-dimensional culture of a patient's own tumor enabling researchers to examine interactions between tumor cells and immune cells. The integration of this novel approach with other emerging technologies is helping us navigate the complex landscape of the tumor immune microenvironment and learn which patients will respond to immunotherapy as well as how to effectively treat cancer patients that do not respond immunotherapy alone.

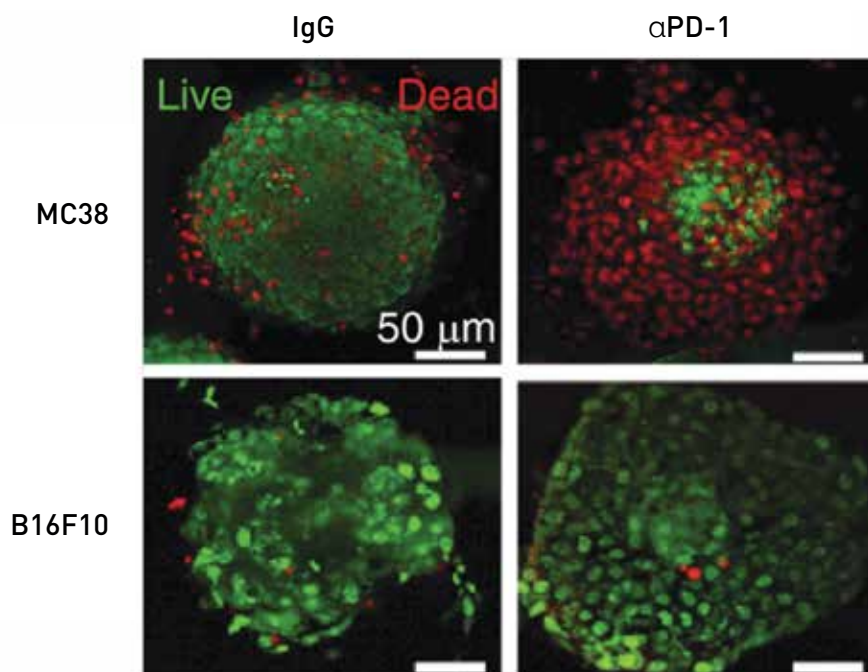
Precision cancer medicine currently focuses on knowledge of the cancer mutation repertoire and the tailored application of drugs that target altered genes or pathways in individual patients, such as use of BRAF inhibitors in patients with BRAF mutant melanoma. Immune checkpoint inhibitors targeting the PD-1/PD-L1 pathway have shown dramatic and durable clinical responses in melanoma and others cancers, but robust predictive biomarkers are lacking and innate resistance is common. Thus, a critical need exists for more sophisticated ex vivo functional testing modalities that recapitulate human tumor biology to predict response to targeted and immune-based therapies and to develop personalized treatment plans in real-time.

Major focus areas of the Jenkins lab include (1) identifying and characterizing mechanisms of response and resistance to PD-1 blockade, (2) discovering novel therapeutic strategies to overcome

resistance to PD-1 blockade, and (3) using the MDOTS/PDOTS as a functional precision medicine platform for the development of novel combinations, and ultimately, personalized immunotherapy to tailor immunotherapy treatment to individual patients. Improved understanding of the response to immune checkpoint inhibitors within the tumor microenvironment will facilitate efforts to identify predictive biomarkers/models for immune checkpoint blockade in real-time, as well as future efforts to screen for therapeutic combinations that enhance the response to immune checkpoint blockade, and may ultimately provide a platform for the 'personalization' of immunotherapy.

Our novel approach for evaluating ex vivo response to PD-1 blockade utilizes murine- and patient-derived organotypic tumor spheroids (MDOTS/PDOTS) cultured in a 3-dimensional microfluidic system. Our study which was recently published





*Live/Dead analysis (Acridine Orange – Green-Live; Propidium Iodide – Red-Dead) of murine-derived organotypic tumor spheroids (MDOTS) from PD-1 sensitive (MC38) and resistant (B16F10) syngeneic mouse models treated ex vivo with IgG or anti-PD-1 (10 μg/mL) for 6 days in 3D microfluidic culture [ref: Jenkins et al. Cancer Discovery 2018].*

in *Cancer Discovery* [Jenkins et al., *Cancer Discovery* 2018; PMID: 29101162], has shown that organotypic tumor spheroids isolated from fresh mouse and human tumor samples retain autologous lymphoid and myeloid cell populations, including antigen-experienced tumor infiltrating CD4 and CD8 T lymphocytes, and respond to PD-1 blockade in short-term *ex vivo* culture. Furthermore, we have demonstrated that tumor killing was recapitulated *ex vivo* using MDOTS derived from the anti-PD-1 sensitive MC38 syngeneic mouse cancer model, whereas relative resistance to anti-PD-1 therapy was preserved in the CT26 and B16F10 syngeneic models. Our focused evaluation of rational therapeutic combinations to enhance response to PD-1 blockade using *ex vivo* profiling of MDOTS revealed TBK1 inhibition as a novel strategy to enhance sensitivity to PD-1 blockade, which effectively predicted tumor response *in vivo*. Our findings demonstrated the feasibility of

*ex vivo* profiling of PD-1 blockade and offer a novel functional approach for the selection of immunotherapeutic combinations. The ultimate goals of these efforts are to identify and characterize novel features of response/resistance to PD-1 blockade and to identify novel therapeutic strategies to overcome resistance to anti-PD-1 therapy, ultimately to bring forward into human clinical trials.

## Selected Publications:

Revach OY, Liu S, Jenkins RW. Targeting TANK-binding kinase 1 (TBK1) in cancer. *Expert Opin Ther Targets*. 2020 Nov;24(11):1065-1078.

Sade-Feldman M, Yizhak K, Bjorgaard SL, Ray JP, de Boer CG, Jenkins RW, Lieb DJ, Chen JH, Frederick DT, Barzily-Rokni M, Freeman SS, Reuben A, Hoover PJ, Villani AC, Ivanova E, Portell A, Lizotte PH, Aref AR, Eliane JP, Hammond MR, Vitzthum H, Blackmon SM, Li B, Gopalakrishnan V, Reddy SM, Cooper ZA, Paweletz CP, Barbie DA, Stemmer-Rachamimov A, Flaherty KT, Wargo JA, Boland GM, Sullivan RJ, Getz G, Hacohen N. Defining T Cell States Associated with Response to Checkpoint Immunotherapy in Melanoma. *Cell*. 2018 Nov 1;175(4):998-1013.

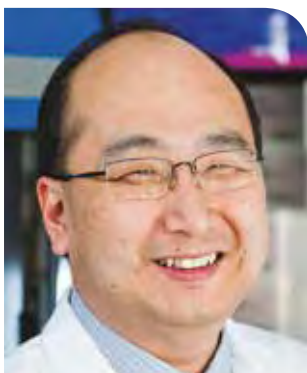
Aref AR, Campisi M, Ivanova E, Portell A, Larios D, Piel BP, Mathur N, Zhou C, Coakley RV, Bartels A, Bowden M, Herbert Z, Hill S, Gilhooley S, Carter J, Cañadas I, Thai TC, Kitajima S, Chiono V, Paweletz CP, Barbie DA, Kamm RD, Jenkins RW. 3D microfluidic ex vivo culture of organotypic tumor spheroids to model immune checkpoint blockade. *Lab Chip*. 2018 Oct 9;18(20):3129-3143.

Cañadas I, Thummalapalli R, Kim JW, Kitajima S, Jenkins RW, et al. Tumor innate immunity primed by specific interferon-stimulated endogenous retroviruses. *Nat Med*. 2018 Aug;24(8):1143-1150.

Jenkins RW, Aref AR, Lizotte PH, et al. Ex Vivo Profiling of PD-1 Blockade Using Organotypic Tumor Spheroids. *Cancer Discov*. 2018;8(2):196-215.

Deng J, Wang ES, Jenkins RW, et al. CDK4/6 Inhibition Augments Antitumor Immunity by Enhancing T-cell Activation. *Cancer Discov*. 2018;8(2):216-33.

## J. Keith Joung, MD, PhD



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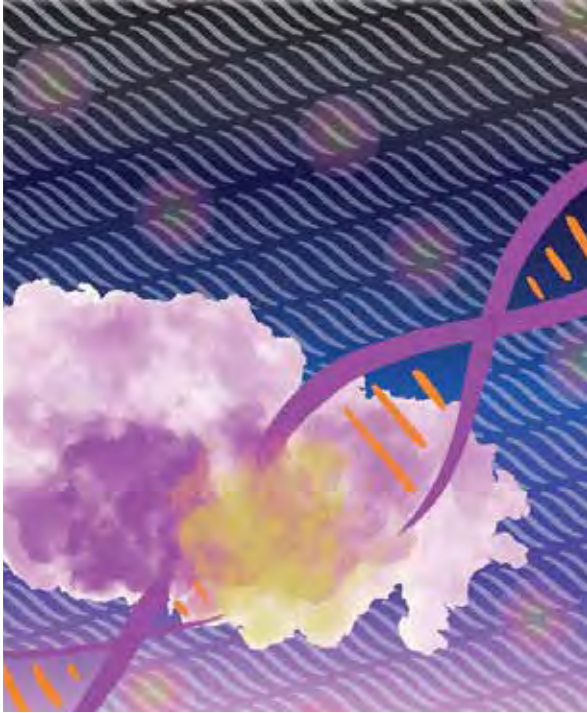
**The Joung laboratory** is developing strategies to reprogram the genomes and epigenomes of living cells to better understand biology and treat disease. We have developed and continue to optimize molecular tools for customized genome editing including engineered zinc finger, transcription activator-like effector (TALE), and RNA-guided CRISPR-Cas-based systems. These platforms enable scientists to alter the DNA sequence of a living cell—from fruit flies to humans—with great precision. These technologies are based on designer DNA-binding and RNA-guided proteins engineered to recognize and cleave specific genomic sequences. We also use these targeting methodologies to direct various other regulatory elements to enable activation, repression, or alteration of histone modifications of specific genes. These tools have many potential uses in cancer research and may lead to more efficient gene therapy capable of correcting disease-related mutations in human cells.

The Joung Laboratory develops technologies for genome and epigenome editing of living cells and organisms using engineered zinc finger, transcription activator-like effector (TALE), and RNA-guided CRISPR-Cas9-based systems and explores their applications for biological research and gene therapy.

### Genome Editing Using Targeted Nucleases and Base Editors

Genome editing technology using CRISPR-Cas nucleases was named “Breakthrough of the Year” for 2015 by *Science* magazine. We and our collaborators were the first to demonstrate that these nucleases can function *in vivo* (Hwang & Fu et al., *Nat Biotechnol.* 2013) to modify endogenous genes in zebrafish embryos and the first to show that they can induce significant off-target mutations in human cells (Fu et al., *Nat Biotechnol.* 2013). We have led the field in development of unbiased, genome-wide strategies for profiling the specificities of CRISPR-Cas nucleases including the widely used cell-based GUIDE-seq method (Tsai et al., *Nat Biotechnol.* 2015) and the *in*

*vitro* CIRCLE-seq method (Tsai et al., *Nat Biotechnol.* 2017). We have recently shown that CIRCLE-seq can be used to identify Cas9-induced off-targets *in vivo* (Akcakaya & Bobbin et al., *Nature*, 2018). In addition, we have engineered “high-fidelity” Cas9 variants (Kleinstiver & Pattanayak et al., *Nature* 2016) and Cas9 variants with novel DNA binding specificities (Kleinstiver et al., *Nature* 2015; Kleinstiver et al., *Nat Biotechnol.* 2015; Kleinstiver et al., *Nat Biotechnol.* 2019). More recently, we have developed novel CRISPR base editor architectures that include useful properties such as: improved precision and reduced off-target effects (Gehrke et al., *Nat Biotechnol.* 2018), dual concurrent cytosine and adenine editing activities (Grünewald & Zhou et al., *Nat Biotechnol.* 2020), and C-to-G transversion editing capabilities (Kurt & Zhou et al., *Nat Biotechnol.* 2020). We were also the first group to discover and minimize base editor-induced transcriptome-wide RNA off-target mutations (Grünewald et al., *Nature* 2019; Grünewald et al., *Nat Biotechnol.* 2019), developed dual deaminase and C-to-G



Schematic illustration of RNA off-target edits induced by CRISPR DNA base editors.

base editors (Grünwald & Zhou et al., *Nat Biotechnol.* 2020; Kurt & Zhou et al., *Nat Biotechnol.* 2021), and demonstrated the application of CRISPR prime editors (together with Joanna Yeh's lab at MGH) in zebrafish (Petri, Zhang, & Ma et al., *Nat Biotechnol.* 2021).

### Epigenome Editing Using Targeted Transcription Factors

We have also performed work showing that the Transcription Activator-Like Effector (TALE) and CRISPR-Cas platforms can also be utilized to create artificial transcription factors that can robustly alter expression of endogenous *human genes* (Maeder et al., *Nat Methods* 2013a; Maeder et al., *Nat Methods* 2013b). In addition, we have also developed fusions of engineered TALE domains with the catalytic domain of the TET1 enzyme, enabling the targeted demethylation of CpGs in human cells (Maeder et al., *Nat Biotechnol.* 2013). More recently, we have shown that the CRISPR-Cpf1 (Cas12a) platform can be modified to engineer robust transcriptional activators that can efficiently increase

endogenous gene expression in human cells (Tak et al., *Nat Methods* 2017). More recently, we have described a robust and general strategy to induce CRISPR-mediated long-range activation of endogenous genes in human cells (Tak et al., *Nat Methods* 2021).

### Selected Publications:

Tak YE, Horng JE, Perry NT, Schultz HT, Iyer S, Yao Q, Zou LS, Aryee MJ, Pinello L, Joung JK. Augmenting and directing long-range CRISPR-mediated activation in human cells. *Nat Methods.* 2021 Sep;18(9):1075-1081.

Petri K, Zhang W, Ma J, Schmidts A, Lee H, Horng JE, Kim DY, Kurt IC, Clement K, Hsu JY, Pinello L, Maus MV, **Joung JK\***, Yeh JJ\*. CRISPR prime editing with ribonucleoprotein complexes in zebrafish and primary human cells. *Nat Biotechnol.* 2021 Apr 29: 10.1038/s41587-021-00901-y.

Kurt IC, Zhou R, Iyer S, Garcia SP, Miller BR, Langner LM, Grünwald J, **Joung JK.** CRISPR C-to-G base editors for inducing targeted DNA transversions in human cells. *Nat Biotechnol.* 2021 Jan;39(1):41-46.

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## Li Lan, MD, PhD



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Elevated oxidative stress and DNA replication stress are common in cancers. On one hand, these intrinsic stresses in cancer cells promote tumor initiation and progression. On the other hand, these stresses render cancer cells sensitive to radiation and chemotherapies. **The Lan laboratory** is especially interested in understanding how cancer cells respond to oxidative and replication stresses through DNA repair pathways and developing new strategies to target these pathways in cancer therapy. The Lan lab developed the first molecular assay to study the oxidative damage response at specific chromosomal loci. Recently, we discovered and delineated a novel DNA repair pathway—mRNA-mediated repair—that protects the transcribed regions of the genome. We also study mechanisms of telomere protection, a cancer survival mechanism, in cancer therapy and investigate cross-talk between DNA damage response and immune response. We aim to open new avenues to understanding the oxidative DNA damage response in different chromosomal environments.

### Targeting RNA modifying enzymes and R-loops in homologous recombination proficient breast and ovarian cancer

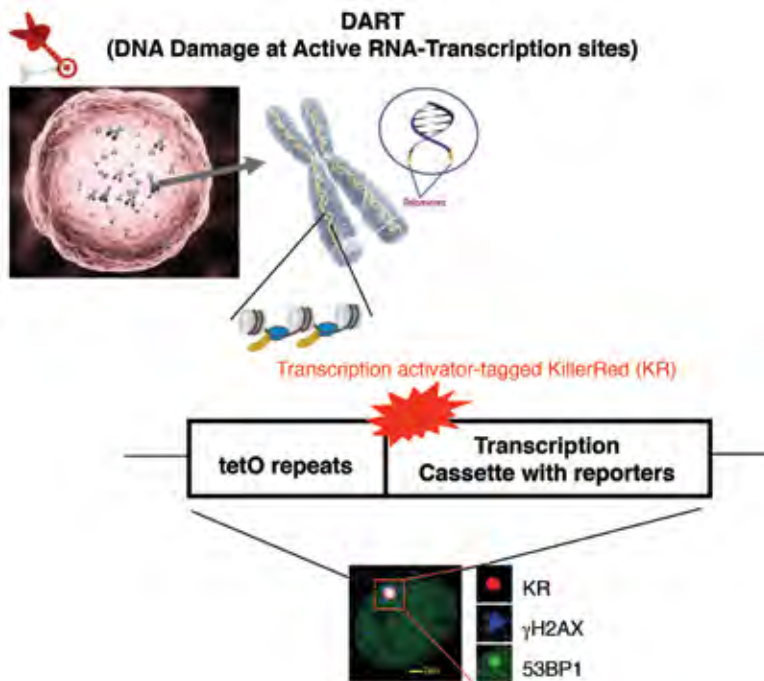
PARP inhibitors (PARPi) are DNA repair targeted drugs that have improved outcomes for tumors which are resistant to hormone therapy and exhibit homologous recombination (HR) deficiency (HRD). However, PARPi are effective only in ~10% of breast or ovarian cancer patients, and patients treated with PARPi inevitably develop drug resistance. Therefore, it is critical to identify HRD-independent vulnerabilities of cancer cells and find new therapeutic targets to complement PARPi therapy. My group has provided fundamental insights into HR in breast cancer and is one of the first to discover an RNA-loop and mRNA-dependent DNA Repair (RDDR) pathway, which is upregulated in cancer and maintains cancer cell survival. We set up platforms to validate RDDR activity, keep identifying novel factors of RDDR, develop and validate RDDR inhibitors for cancer therapy. We are

also developing RDDR biomarkers to identify tumors harboring increased RDDR activity and predict drug sensitivity. We currently focus on understanding the function and targeting mRNA modifying enzymes of RDDR. RDDR inhibitors should be effective in treating a significant fraction of breast cancer patients, including those who do or do not have HRD and significant fraction of PARPi and hormone therapy-resistant breast cancer patients.

### Targeting R-loop-dependent telomere protections upon damage in cancer

Oxidative DNA damage at telomeres is a source of genomic instability, which fuels both aging and tumorigenesis. To bypass senescence, cancer cells have to extend and maintain telomeres during cell division. While the majority of human cancers activate telomerase, a small but significant fraction (~10-15%) of cancers use the alternative lengthening of telomere (ALT) pathway to extend telomeres. We discovered a novel DNA repair pathway contributing to telomere





The Lan laboratory developed the DNA Damage at RNA Transcribed sites [DART] method to precisely introduce oxidative DNA damage at specific transcribed loci in a dose-dependent manner. This is achieved by site-specific positioning of the photo-excitable and ROS-releasing protein KillerRed (KR). This unique method provides a tool to understand how oxidative DNA damage response is differentially regulated in transcribed and un-transcribed regions, and in dividing and non-dividing cells.

maintenance. This pathway involves TERRA, a non-coding RNA generated at telomeres and R-loops. Our goal is to understand and develop new strategies to exploit the cellular dependency on telomerase, ALT, and R-loop-mediated repair pathways to kill cancer cells harboring high telomeric oxidative damage.

### Crosstalk between DDR and immune response upon damage in cancer

DNA sensor cGAS triggers STING-dependent innate immune response and subsequently alters the tumor microenvironment to enhance anti-tumor immunity. The Lan laboratory focuses on 1) understanding how DDR inhibition and/or damage trigger cGAS-STING activation; and 2) how the function of cGAS in the nucleus regulates replication, transcription, and chromatin accessibilities in cancer cells. Our goal is to elucidate the

function of cGAS and efficiently target it with the combination with DDR-based therapy in cancer.

### Selected Publications:

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Ouyang J, Yadav T, Zhang JM, Yang H, Rheinbay E, Guo H, Haber DA, Lan L, Zou L. RNA transcripts stimulate homologous recombination by forming DR-loops. *Nature*. 2021 Jun;594(7862):283-288.

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# David M. Langenau, PhD



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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.

### 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 have recently identified combination Olaparib and temozolomide therapy for the treatment of RMS that is in clinical trial evaluation for RMS patients at MGH and Dana-Farber Cancer Institute in Boston (NCT01858168, Yan et al., Cell 2019).

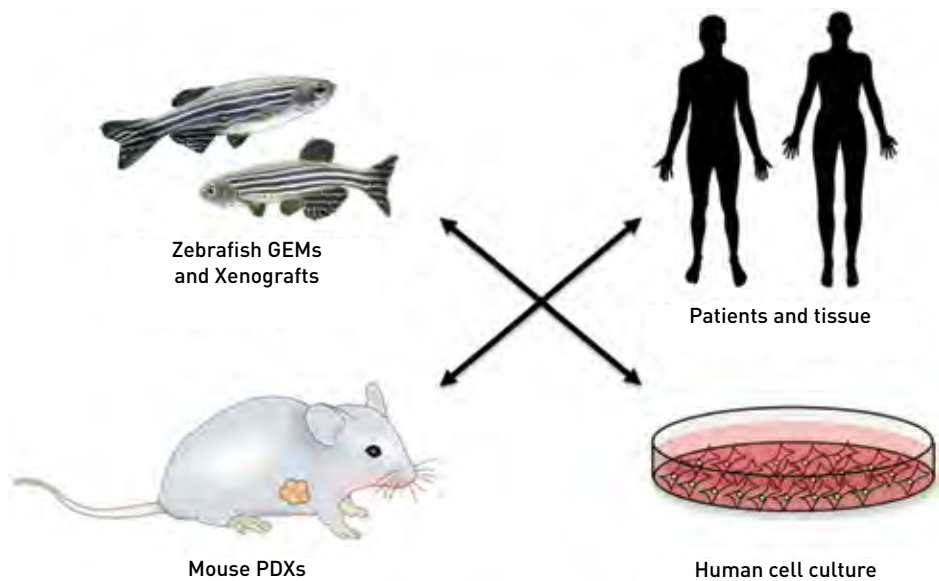
### Uncovering progression-associated driver mutations in T-cell acute lymphoblastic leukemia

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. Using these models and extending findings to human disease, we have also identified 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 mechanisms of progression and relapse. Genetically-engineered models (GEMs) and patient-derived xenografts (PDXs).

### Zebrafish Avatars of Human Cancer

The Langenau Lab has generated a number of immunocompromised zebrafish strains that efficiently engraft human tumors. These models are amenable to real-time imaging of cancer hallmarks at single cell resolution and have been used in preclinical modeling experiments to identify drug combinations and new immunotherapy approaches for the treatment of human rhabdomyosarcoma. This work has led to the first clinical trial for pediatric cancer originating from findings made in the zebrafish.

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# Michael S. Lawrence, PhD



## Lawrence Laboratory

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Cancer results from alterations to DNA that lead to the activation of oncogenes or the inactivation of tumor suppressors. **The Lawrence laboratory** focuses on understanding the many ways this can happen, using computation as a powerful microscope to study the processes of DNA damage and repair, gene expression and genome replication, and cancer driver genes. Over our lifetimes, DNA slowly accumulates mutations due to environmental toxins and radiation, as well as from naturally occurring copying errors. The vast majority of mutations have little or no effect on a cell, but out of all possible mutations, a few may hit exactly the right place in the genome, where they can act as a “driver mutation,” pushing the cell toward aggressive growth and tumor formation. Sequencing the DNA in a tumor reveals not only its driver mutations, but also all the other “passenger mutations” that were present in the tumor-initiating cell. We seek insights about cancer from both driver and passenger mutations.

## Analyzing Mutational Signatures

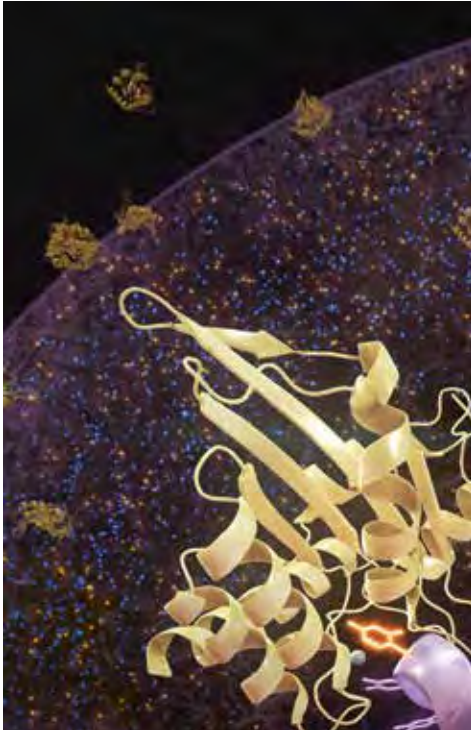
Cancers vary over many orders of magnitude in their total background mutation burden, ranging from very quiet tumor types such as leukemias and childhood tumors, which may have fewer than 10 somatic mutations in their exome, to carcinogen-associated tumor types such as lung cancer and melanoma, which may have over 1000. Mutations have many causes, and each mutagen can leave a telltale signature. For instance, spontaneous deamination of methylated CpG’s causes the transition mutations that dominate many tumor types. Mutagens in tobacco smoke cause G-to-T transversions. Ultraviolet radiation causes C-to-T at dipyrimidines. Agitated APOBEC enzymes cause mutations at C’s preceded by T. Loss of mismatch repair causes microsatellite instability (MSI), marked by expansion and contraction of simple-sequence repeats, as well as characteristic types of single-base changes. Tumors carrying mutations in the proofreading exonuclease domain of polymerase epsilon (POLE) tend to accrue C-to-A mutations at the trinucleotide TCT. Very rare “MSI+POLE”

cancers show the highest yet known somatic mutation burdens, with upwards of 10,000 coding mutations per patient. Patients affected by MSI and/or POLE mutagenesis are known to experience better clinical outcomes, probably thanks to their high neoantigen loads which attract a powerful immune response. Our most recent research has focused on a less well-studied signal in somatic mutation datasets, mutational asymmetries between the two DNA strands. These illuminate transcriptional or “T-class” mutational patterns, associated with exposure to tobacco smoke, UV radiation, and a yet-unknown agent in liver cancer, as well as replicative or “R-class” patterns, associated with MSI, APOBEC, POLE, and a yet-unknown agent in esophageal cancer.

## APOBEC Mutations and Mesoscale Genomic Features

Statistical approaches for distinguishing driver mutations from passenger mutations have relied on the gold standard of recurrence across patients. Seeing exactly the same DNA base-pair mutated recurrently across patients has been taken as proof that the mutation





*The mutational landscape of a cancer cell across size regimes. At the smallest scale, local DNA trinucleotide sequences (lower-left foreground) correlate with the “mutational signatures” induced by various mutagens. At the largest scale (background of image), chromatin is organized into multi-megabase domains comprising Compartment B (tightly packed, gene-poor DNA lining the nuclear periphery) and Compartment A (gene-rich open DNA in the nuclear interior). Mutations induced by APOBEC enzymes (yellow points) are distributed equally across the two compartments, but most other types of mutations (blue points) are concentrated in Compartment B. Between the large and small extremes lies the “mesoscale” regime, where genomic features like hairpin-forming ability are determined. DNA exposed in a hairpin loop is vulnerable to attack by the enzyme APOBEC3A (center), giving rise to highly recurrent passenger mutations in cancer.*

must be under functional selection for contributing to tumor fitness. The assumption is that mutational processes, being essentially random, are unlikely to hit the exact same base-pair over and over again. Our recent discoveries about APOBEC mutagenesis have cast doubt on this assumption. We have shown that APOBEC3A has a very strong preference for mutating cytosines presented in a short loop at the end of a strongly paired DNA hairpins. Our results indicate that there are multiple routes to cancer mutational hotspots. Driver mutation hotspots in oncogenes can rise to prominence through positive selection, and are not restricted to the “favorite” sites of any particular mutagen. In contrast, special DNA sites (like hairpins) that happen to be optimal substrates for a mutagen (like APOBEC) can give rise to “passenger hotspot mutations” that owe their prevalence to substrate optimality, not to any effects on tumor fitness. These findings apply not just to APOBEC but to all mutation signatures, and remind us of the need to be careful about assuming that all recurrent mutations are causative drivers of disease.

## Selected Publications:

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# Shyamala Maheswaran, PhD



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Metastasis, the leading cause of cancer-related deaths, is governed by multiple steps, which are not well understood. Using cell culture and mouse models, as well as patient-derived tumor tissues and tumor cells circulating in the blood (Circulating Tumor Cells/CTCs), **the Maheswaran laboratory** has uncovered novel tumor cell characteristics that promote metastasis in breast cancer patients. Our findings show that cancer cells exist in multiple cellular states, each state exhibiting different characteristics. As such, each breast cancer patient harbors a mixture of tumor cells with different functional properties. We intend to define the functional and molecular properties of different subclasses of tumor cells and their contribution to metastasis, tumor evolution and drug sensitivity using appropriate experimental models and patient-derived samples. These findings will provide insight into the contribution of heterogeneous cancer cell populations to metastasis and their significance as biomarkers and therapeutic targets.

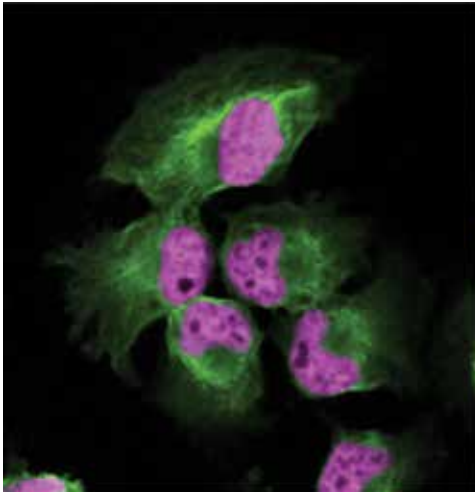
## Mechanisms of Breast Cancer Metastasis

The research in my laboratory is focused on defining the molecular mechanisms that drive breast cancer progression and metastasis. Cancer, initially confined to the primary site, eventually spreads to distal sites, including lung, liver, bone and brain, by invading into the bloodstream. Upon reaching these distal sites, the tumor cells continue to grow and evolve well after removal of the primary tumor resulting in overt metastasis and disease recurrence, the leading causes of cancer-related deaths. Using cell culture and mouse models, patient derived tissues, and circulating tumor cells (CTCs) enriched from the blood of women with breast cancer, we characterize the contribution of oncogenic-and tumor-microenvironment-derived signals to cellular states including: epithelial to mesenchymal plasticity, senescence, and how these aspects of tumor heterogeneity influence cancer progression and therapeutic responses.

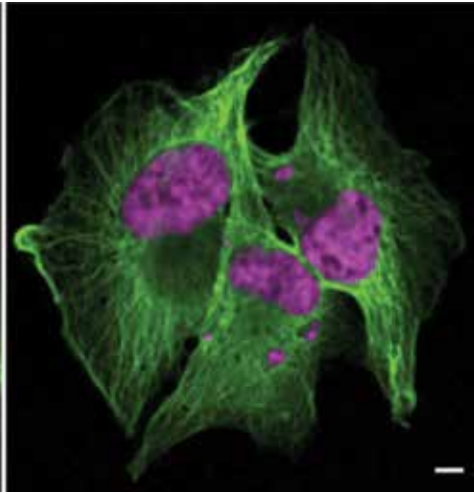
## Oncogenic and Epigenetic Cues in Senescence

Senescence, a state of prolonged growth arrest induced by stress, contributes to aging and age-related degenerative diseases. It is an important tumor suppressor mechanism in premalignant tumors, which override this safeguard machinery through the loss of the tumor suppressors RB and p53 and progress to become malignant tumors. Senescence is also an alternative cellular response to chemo- and radiation therapies, from which a few rare cells escape and exhibit highly drug resistant phenotypes. Taken together, there is a critical need to identify mechanisms that induce and maintain senescence independent of the RB and p53 signaling axes, which are often inactivated in cancers. Identification of druggable targets that can induce and maintain senescence as future therapies complementing current therapeutic interventions is an unmet need that is gaining significant attention from a clinical perspective. Based on our published

shGFP escape



shSETD1A escape



Confocal images of cells stained with tubulin (green) and DAPI (magenta) show that SETD1A-KD cells escaping senescence harbor chromosome segregation defects visualized as micronuclei (circled). The scale bar represents 50 $\mu$ m.

work on SETD1A, we are investigating (a) the functional and mechanistic roles of SETD1A in cells, the deregulation of which induces senescence. (b) the role of SETD1A in maintaining the cellular equilibrium between proliferation, senescence and escape from senescence and (c) how SETD1A-KD-induced senescent cells remodel the microenvironment and its impact on tumor progression and drug responses. The long-term goal of this work is to ultimately exploit SETD1A, a druggable enzyme, to unleash the tumor suppressor effects of senescence and curtail cancer progression, drug resistance and possibly age-related diseases.

### Selected Publications:

Tajima K, Matsuda S, Yae T, Drapkin B, Morris R, Boukhali M, Niederhoffer K, Comaills V, Dubash T, Nieman L, Guo H, Magnus NKC, Dyson N, Shioda T, Haas W, Haber DA, **Maheswaran S**. SETD1A protects from senescence through regulation of the mitotic gene expression program. *Nature Comm*. 2019 Jun 28;10(1):2854.

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Aceto N, Bardia A, Miyamoto DT, Donaldson MC, Wittner BS, Spencer JA, Yu M, Pely A, Engstrom A, Zhu H, Brannigan BW, Kapur R, Stott SL, Shioda T, Ramaswamy S, Ting DT, Lin CP, Toner M, Haber DA\*, **Maheswaran S\***. Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. *Cell*. 2014; 158(5):1110-22.

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**The Manguso lab** 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 enhanced tumor cell sensitivity to immunotherapy. While PTPN2 was known to negatively regulate T cell receptor activation, our screens determined that it is also the most potent suppressor of interferon-gamma sensing in tumor cells; 2) we discovered that the non-classical MHC-I gene HT-T23/Qa-1 (HLA-E) is a



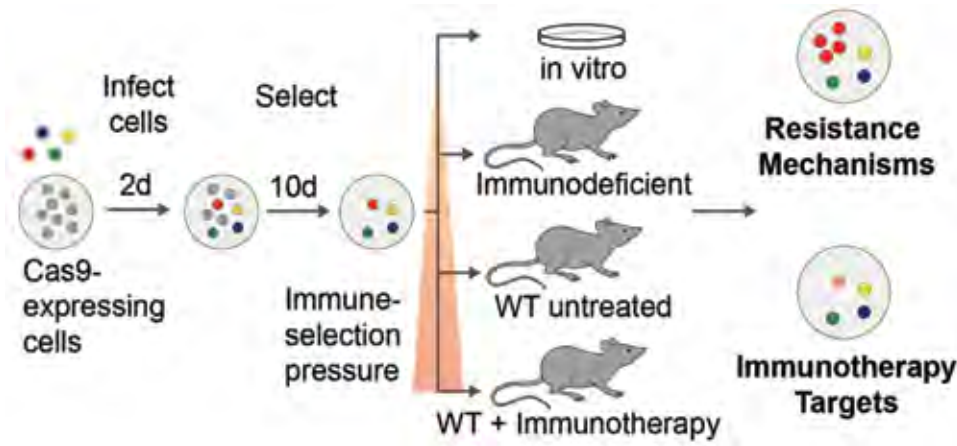


Diagram of *in vivo* CRISPR screening system. Pools of Cas9-expressing, sgRNA library-transduced tumor cells are implanted into either wild-type or immunocompromised mice. After 2 weeks, tumors are harvested and genomic DNA is extracted from tumor tissue. Next generation sequencing of the sgRNA library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

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 acting on RNA unmasks endogenous dsRNA that can be recognized by the cytosolic pattern recognition receptors PKR and MDA5, and can overcome resistance to immunotherapy caused by loss of antigen presentation [Ishizuka & Manguso et al, *Nature* 2019].

Previously, these genes were not known or prioritized targets in immuno-oncology, but our unbiased approach enables discoveries that would have otherwise been unlikely.

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. Identify pathways that can overcome acquired resistance to immunotherapy
3. Understand how we can manipulate antigen presentation to enhance immunotherapy

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.

## Selected Publications:

Miller BC, Sen DR, Al Abosy R, Bi K, Virkud YV, LaFleur MW, Yates KB, Lako A, Felt K, Naik GS, Manos M, Gjini E, Kuchroo JR, Ishizuka JJ, Collier JL, Griffin GK, Maleri S, Comstock DE, Weiss SA, Brown FD, Panda A, Zimmer MD, Manguso RT, Hodi FS, Rodig SJ, Sharpe AH, Haining WN. Subsets of exhausted CD8+ T cells differentially mediate tumor control and respond to checkpoint blockade. *Nat Immunol.* 2019 Mar;20(3): 326-336.

Ishizuka JJ\*, Manguso RT\*, Cheruiyot C, Bi K, Panda A, Iracheta-Vellve A, Miller BC, Yates KB, Dubrot J, Du P, Buchumenski I, Ayer A, Comstock DE, Griffin GK, Brown FD, Ahmad S, Collins NB, Long AH, Pope HW, Zimmer MD, Kohnle I, Sen DR, Doench JG, Kozono D, Hur S, Levanon EY, Haining WN. Loss of the RNA editing enzyme ADAR1 in tumors improves response to immunotherapy and overcomes therapeutic resistance. *Nature.* 2019 Jan;565(7737):43-48.

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\* Denotes equal contribution

# Marcela V. Maus, MD, PhD



## Maus Laboratory

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Charlotte Graham, PhD  
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Kathleen Ho  
Lu Huang, PhD  
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Katelin Katsis  
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Felix Korell, MD  
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Rebecca Larson, PhD  
Mark Leick, MD  
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Using the immune system as a cancer treatment has the potential to induce long-term, durable remissions, and perhaps even cure some patients. The T cells of the immune system are able to specifically kill the target cells they recognize. T cells are also able to persist in the body for many years, and form immune ‘memory,’ which enables the possibility of long-term protection.

**The Maus laboratory** is interested in using 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 molecular receptors to target T cells to liquid and solid tumors; use T cells as delivery vehicles for other drugs, and use drugs to help T cells work against tumors; and understand how T cells can work as “living drugs” to treat patients with cancer.

Immune therapies that engage T cells have the potential to induce long-term durable remissions of cancer. In hematologic malignancies, allogeneic hematopoietic stem cell transplant can be curative, in part due to T-cell mediated anti-tumor immunity. In solid tumors, checkpoint blockades with anti-CTLA-4 or anti-PD-1 monoclonal antibodies can mediate long-term responses by releasing T cells from tightly controlled peripheral tolerance. 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. Re-directing T cells with CARs is an alternative method of overcoming tolerance and has shown great promise in the clinical setting for B cell malignancies such as leukemia and lymphoma. However, successful application of this form of therapy to other cancers is likely to require refinements in the molecular and clinical technologies.

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

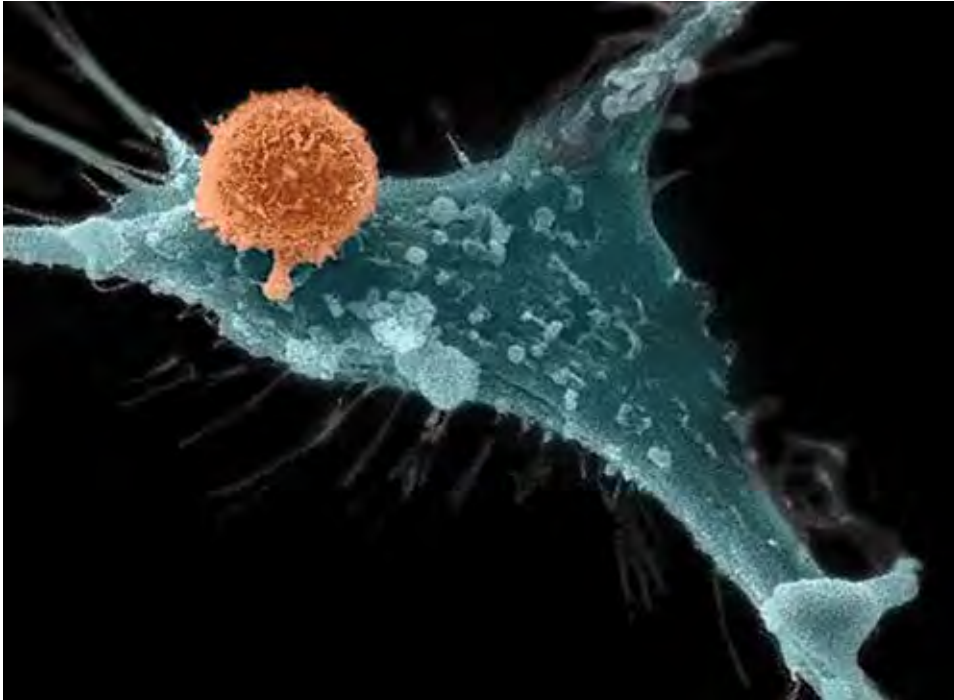
The MGH Cellular Immunotherapy Program, directed by Dr. Maus, aims to generate a

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, “a regulatory/translational” arm to test genetically-modified T cells in human subjects, and a “reverse translation” arm to examine the engraftment, persistence, and bioactivity of T cell products infused into patients. The immune profiling of patients is performed by the Immune Monitoring Laboratory, directed by Dr. Kathleen Gallagher.

Specifically, the engineered T cells that the Maus lab generates are intended to overcome specific obstacles observed in the clinic. The next generation T cells will:

### **1. Contain molecular designs to enhance specificity, potency, and safety.**

Novel types of antigen receptors are in development to target multiple antigens on tumor cells, which improves elimination of heterogeneous tumor cells and prevents antigen-negative relapse while also decreasing the risk of targeting healthy cells. We are also using novel techniques to improve CAR T cell safety by regulating their activation and the molecules they release when



CAR-T Cell Targeting a Glioblastoma Cell Expressing EGFRvIII, Scanning Electron Micrograph; Credit: Bryan D. Choi, Mark B. Leick, and Marcela V. Maus.

activated. In liquid tumors, the focus is on improving the safety of CAR T cells, while in solid tumors, the focus is increasing their potency.

**2. Be administered in combination with other drugs to sensitize tumors to T cell mediated killing and/or potentiate T cell function.**

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. Have additional modifications that make CAR T cells (a) resistant to inhibitory mechanisms, (b) imageable, or (c) more feasible to manufacture and administer.**

Control of T cell function is a complex

process orchestrated by a variety of molecules, some of which deliver inhibitory signals. Tumors often express ligands or cytokines to inhibit T cell function. Using a single vector, genetically modified T cells can be re-directed not only to recognize a new antigen on tumor cells, but also to be resistant to the inhibitory tumor microenvironment.

**4. Further build on the basic biology and mechanisms that drive natural and engineered T cell functions.**

We aim to understand the signaling mechanisms and effector functions used by CAR T cells versus native T cells, to further improve CAR T cell efficacy and safety. By understanding how CAR T cells kill tumor cells, we can also decipher how tumors cells become or are intrinsically resistant to killing by CAR T cells. We can then better engineer CAR T cells to prevent resistance from occurring.

**Selected Publications:**

Jan M, Scarfò I, Larson RC, Walker A, Schmidts A, Guirguis AA, Gasser JA, Słabicki M, Bouffard AA, Castano AP, Kann MC, Cabral ML, Tepper A, Grinshpun DE, Sperling AS, Kyung T, Sievers QL, Birnbaum ME, Maus MV, Ebert BL. Reversible ON- and OFF-switch chimeric antigen receptors controlled by lenalidomide. *Sci Transl Med.* 2021 Jan 6;13(575):eabb6295.

Boroughs AC, Larson RC, Marjanovic ND, Gosik K, Castano AP, Porter CBM, Lorrey SJ, Ashenberg O, Jerby L, Hofree M, Smith-Rosario G, Morris R, Gould J, Riley LS, Berger TR, Riesenfeld SJ, Rozenblatt-Rosen O, Choi BD, Regev A, Maus MV. A Distinct Transcriptional Program in Human CAR T Cells Bearing the 4-1BB Signaling Domain Revealed by scRNA-Seq. *Mol Ther.* 2020 Jul 25:S1525-0016(20)30374-9.

Ormhøj M, Scarfò I, Cabral ML, Bailey SR, Lorrey SJ, Bouffard AA, Castano AP, Larson RC, Riley LS, Schmidts A, Choi BD, Andersen RS, Cédile O, Nyvold CG, Christensen JH, Gjerstorff MF, Ditzel HJ, Weinstock DM, Barington T, Frigault MJ, Maus MV. Chimeric Antigen Receptor T Cells Targeting CD79b Show Efficacy in Lymphoma with or without Cotargeting CD19. *Clin Cancer Res.* 2019 Dec 1;25(23):7046-7057.

Schmidts A, Ormhøj M, Choi BD, Taylor AO, Bouffard AA, Scarfò I, Larson RC, Frigault MJ, Gallagher K, Castano AP, Riley LS, Cabral ML, Boroughs AC, Velasco Cárdenas RM, Schamel W, Zhou J, Mackay S, Tai YT, Anderson KC, Maus MV. Rational design of a trimeric APRIL-based CAR-binding domain enables efficient targeting of multiple myeloma. *Blood Adv.* 2019 Nov 12;3(21):3248-3260.

Choi BD, Yu X, Castano AP, Bouffard AA, Schmidts A, Larson RC, Bailey SR, Boroughs AC, Frigault MJ, Leick MB, Scarfò I, Cetrulo CL, Demehri S, Nahed BV, Cahill DP, Wakimoto H, Curry WT, Carter BS, Maus MV. CAR-T cells secreting BiTEs circumvent antigen escape without detectable toxicity. *Nat Biotechnol.* 2019 Sep;37(9):1049-1058.

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## Andrea I. McClatchey, PhD



### McClatchey Laboratory

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MacKenzie, PhD  
Elizabeth Flynn\*  
Andrea I. McClatchey, PhD  
Evan O'Loughlin

\*Jointly with the laboratory of  
Dr. Shannon Stott

**The McClatchey laboratory** focuses on understanding how cells organize their outer surface – an important cellular compartment created by the interface between the cell membrane and underlying cortical cytoskeleton. This compartment governs the shape, identity and behavior of individual cells, as well as how they interact biochemically and mechanically with the extracellular environment. Normal cells modulate the features of the membrane:cytoskeleton interface to carry out key developmental processes and build functioning tissues. On the other hand, cancer cells exploit this compartment to interact inappropriately with other cells and with their environment during tumor initiation, invasion and metastasis. Our research stems from a longstanding quest to understand the molecular basis of a familial cancer syndrome caused by mutation of the *neurofibromatosis type 2 (NF2)* tumor suppressor gene. The *NF2*-encoded protein, Merlin, and closely related ERM proteins (Ezrin, Radixin and Moesin) are central architects of the cell cortex that have important roles in development and in many human cancers.

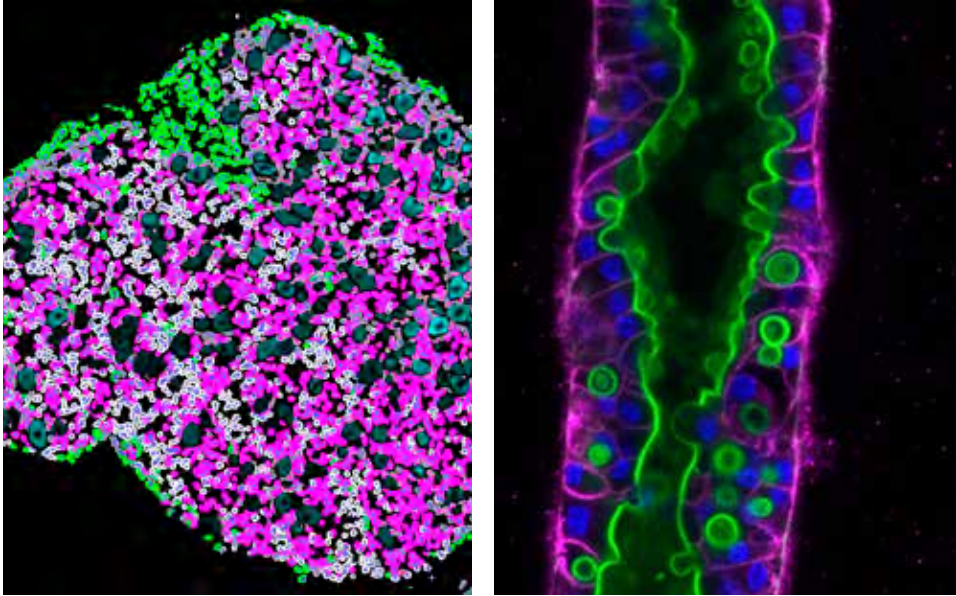
### Understanding morphogenesis and tumorigenesis

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 lung, kidney, breast and liver 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 assembly of cortical domains requires the coordination of processes occurring at the plasma membrane and underlying cytoskeleton. The overarching goal of my laboratory is to understand how the dynamic organization of this cellular compartment contributes to morphogenesis and tumorigenesis. We have focused particular attention on the neurofibromatosis type 2 (NF2) tumor suppressor, Merlin, and closely related ERM proteins (Ezrin, Radixin and Moesin) - membrane:cytoskeleton linking proteins that simultaneously influence membrane complexes and the cortical actomyosin cytoskeleton. The activities of Merlin/ERM proteins are critical for the morphogenesis of many tissues and have been implicated in many cancers.

Ongoing projects utilize mouse models, bioengineered 3D models and quantitative imaging to study the roles of Merlin/ERM proteins in the morphogenesis





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

of intrahepatic bile ducts in the liver and Schwann cell:axon relationships in peripheral nerves, and in the development of biliary and schwann cell tumors. Our studies have uncovered novel design principles that govern tissue morphogenesis and are hijacked by tumor-causing alterations, identified mechanisms by which aberrant cortical organization can drive intrinsic tumor heterogeneity, and yielded unexpected therapeutic targets and avenues of translation for cancer therapy.

It is increasingly clear that cancer fundamentally reflects the aberrant re-enactment of developmental processes. We believe that the continued partnering of discovery-based science and translational studies will lead to novel therapeutic avenues while continuing to advance our understanding of the basic cellular activities that contribute to many human cancers.

## Selected Publications:

Chiasson-MacKenzie C, Liu CH, Vitte J, Giovannini M and McClatchey AI. Cellular mechanisms of heterogeneity in NF2-mutant schwannoma. *bioRxiv* MS ID#: BIORXIV/2020/424999 [Preprint], 2020.

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Benhamouche-Trouillet S\*, O'Loughlin E\*, Liu CH, Polacheck W, Fitamant J, McKee M, El-Bardeesy N, Chen CS, McClatchey AI. Proliferation-independent role of NF2 (merlin) in limiting biliary morphogenesis. *Development* 145(9), 2018 April 30.

Chiasson-MacKenzie C, Morris ZS, Baca Q, Morris BA, Coker JK, Mirchev R, Jensen AE, Carey T, Stott S, Golan DE, McClatchey AI. NF2/Merlin mediates contact-dependent inhibition of EGFR mobility and internalization via cortical actomyosin. *J Cell Biol.* 211(2):391-405, 2015 Oct 26.

Hebert AM, Duboff B, Casaletto JB, Gladden AB, McClatchey AI. Merlin/ERM proteins establish cortical asymmetry and centrosome position. *Genes Dev.* 26(24): 2709-23, 2012 Dec 15.

Benhamouche S, Curto M, Saotome I, Gladden AB, Liu CH, Giovannini M, McClatchey AI. Nf2/Merlin controls progenitor homeostasis and tumorigenesis in the liver. *Genes Dev.* 24(16):1718-30, 2010 Aug 15.

\*Denotes equal contribution

## Peter Miller, MD, PhD



### Miller Laboratory

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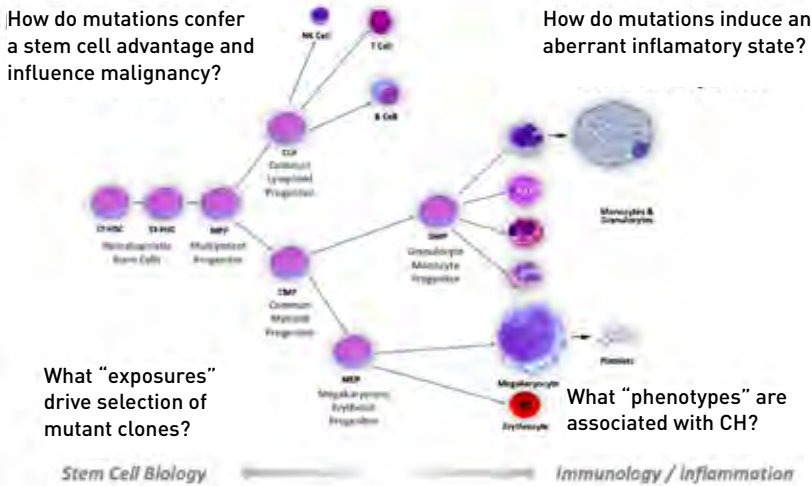
Peter Miller, MD, PhD

**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



Framework for thinking about how somatic mutations arise in hematopoietic stem cells and drive aberrant stem cells processes including malignancy (left) and how these mutations influence aberrant inflammatory programs when present in mature immune cells and contribute to various disease phenotypes (right).

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 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.

## Selected Publications:

Miller PG\*, Qiao D\*,...Cho MH, Ebert BL. Association of Clonal Hematopoiesis with Chronic Obstructive Pulmonary Disease. *Blood*. 139(3):357-368, 2022.

Miller PG, Sperling AS, Gibson CJ,... Ebert BL. Contribution of clonal hematopoiesis to adult-onset hemophagocytic lymphohistiocytosis. *Blood*. 136(26):3051-3055, 2020.

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Hartwell KA\*, Miller PG\*,...Ebert BL, Golub TR. Niche-based screening identifies small-molecule inhibitors of leukemia stem cells. *Nat Chem Biol*. 9(12):840-8, 2013.

\* Denotes equal contribution

## David T. Miyamoto, MD, PhD



**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 tumor 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.

### Miyamoto Laboratory

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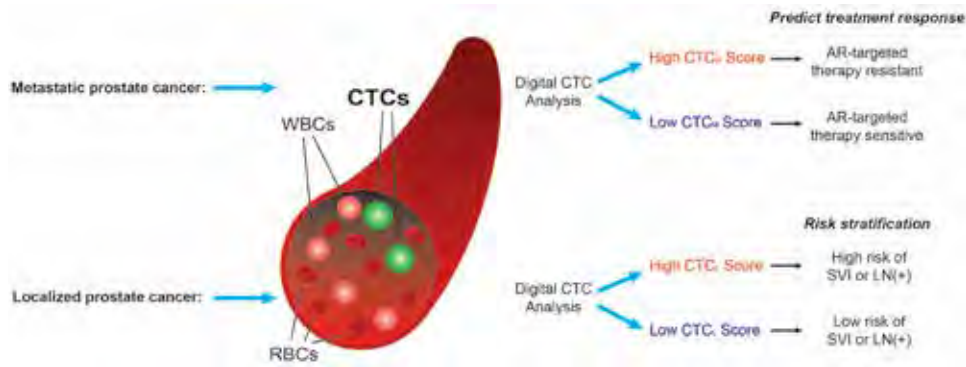
\* Graduate student

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 tumor 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 MGH, 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 radiation 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.





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 (Miyamoto et al. *Cancer Discovery* 2018).

**Bladder 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 and requires aggressive treatment with either radical cystectomy or bladder-sparing trimodality therapy (transurethral tumor resection followed by chemoradiation). 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 recently performed gene expression profiling of bladder tumors from patients treated with trimodality therapy and identified immune and stromal molecular signatures predictive of outcomes after chemoradiation. Ongoing projects include the development of CTC RNA signatures 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:

Efstathiou JA, Mouw K, Gibb E, Liu Y, Wu CL, Drumm M, da Costa JB, du Plessis M, Wang NQ, Davicioni E, Feng FY, Seiler R, Black PC, Shipley WU, Miyamoto DT. Impact of immune and stromal infiltration on outcomes following bladder-sparing trimodality therapy for muscle-invasive bladder cancer. *European Urology*. 2019; 76:59-68.

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# Raul Mostoslavsky, MD, PhD



## Mostoslavsky Laboratory

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\* Graduate student

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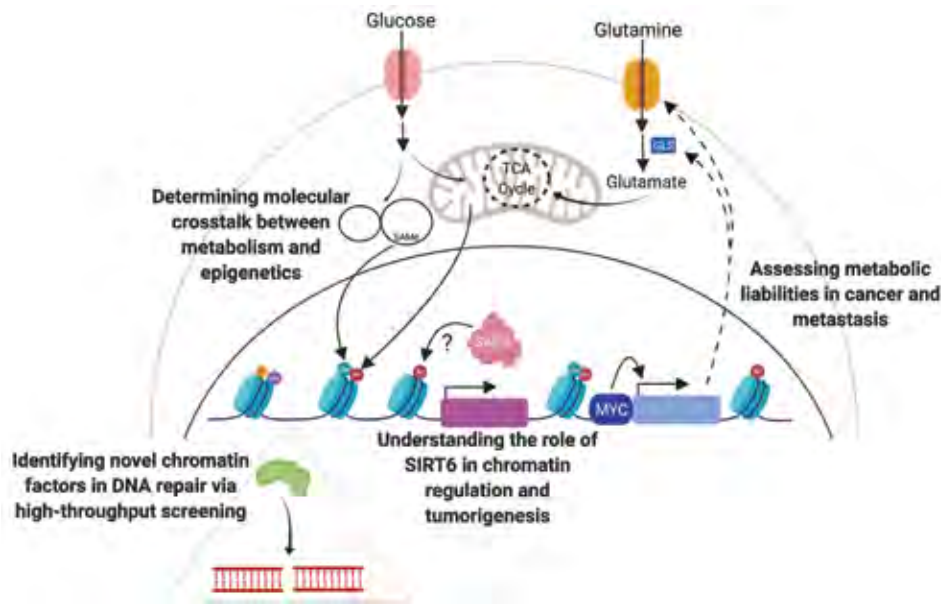
Research in **the Mostoslavsky laboratory** focuses on the crosstalk between chromatin dynamics and cellular metabolism. In particular, we have focused on sirtuins, a family of proteins first discovered in yeast that plays a critical role in many human diseases, including cancer. Most of our previous work involves the Sir2 mammalian homolog known as SIRT6, an enzyme with roles in compacting the DNA scaffolding structure known as chromatin. Our research indicates that SIRT6 modulates glucose metabolism and DNA repair and functions as a strong tumor suppressor gene. Using transgenic mouse models and other experimental systems, we are exploring the role of SIRT6 and metabolism in tumorigenesis and other disease processes, as well as trying to understand the crosstalk between metabolism and epigenetics. Our current projects involve understanding the molecular roles of chromatin in DNA repair, identifying chromatin and metabolic drivers of metastatic disease, and the crosstalk between metabolic pathways and chromatin structure.

The DNA and the 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. Glucose 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. For cells to respond appropriately to changes in energy status, they need a finely tuned system to modulate chromatin dynamics in order to respond to metabolic cues. Reciprocally, chromatin changes necessary for cellular functions need as well 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 on the study of a group of proteins called SIRT6s, the mammalian homologues of the yeast Sir2. Sir2 is a chromatin silencer that functions as an NAD-dependent histone deacetylase to inhibit DNA transcription and recombination. In the past few years, we have been exploring the crosstalk between epigenetics and metabolism. In particular, our work has focused on the mammalian Sir2 homologue, SIRT6. In recent years, we have identified SIRT6 as a key modulator of metabolism. Mice lacking SIRT6 exhibit severe metabolic defects, including severe hypoglycemia. SIRT6 functions as a histone H3K9 deacetylase to silence glycolytic genes acting as a co-repressor of Hif1alpha, in this way directing glucose away from the TCA cycle to reduce intracellular ROS levels. This function appears critical for glucose homeostasis, as SIRT6 deficient animals die early in life from hypoglycemia. Remarkably, SIRT6 acts as a tumor suppressor in



### Understanding the crosstalk between metabolism and Epigenetics

Image Credit: Lara Roach

colon and skin cancer, regulating cancer metabolism through mechanisms that bypass known oncogenic pathways. Cancer cells prefer fermentation (i.e., lactate production) to respiration. Despite being described by biochemist and Nobel laureate Otto Warburg decades ago (i.e., the Warburg effect), 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 such metabolic adaptation occurs in a rare population of cells, indicating that tumors exhibit metabolic heterogeneity. We have also uncovered key roles for SIRT6 in DNA repair (anchoring the chromatin remodeler SNF2H to DNA breaks) and early development (acting as a repressor of pluripotent genes), indicating broad biological functions for this chromatin deacetylase. Lastly, we have also identified SIRT6 as a robust tumor suppressor in pancreatic cancer, where it silences the oncofetal protein Lin28b, protecting against aggressive tumor phenotypes. As such,

SIRT6 represents an example of a chromatin factor modulated in cancer cells to acquire “epigenetic plasticity”.

In recent years, we have broadened our research to explore roles of one carbon metabolism (1C) in chromatin dynamics, exploring novel metabolic liabilities in cancer, new chromatin modulators of DNA repair, and the use of screening strategies to identify novel epigenetic/metabolic drivers of metastatic disease. We use a number of experimental systems, including biochemical and biological approaches, as well as genetically engineered mouse models.

### Specific Projects:

1. Determining the role of SIRT6 in tumorigenesis using mouse models
2. Elucidating the role of histone modifications and chromatin dynamics in DNA repair
3. Determining molecular crosstalk between epigenetics and metabolism
4. Discovering non-genetic (epigenetic and metabolic) drivers of metastases

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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, which allows cells to develop distinct identities during development or become resistant to different types of stress such as chemotherapy. Epigenetic states are formed when groups of genes are turned on and off at a given time in a given cell. Recent work has shown that cancer cells exploit epigenetic mechanisms to develop resistance to radiation, chemo- or immune-therapy. By studying the molecular machinery that establish epigenetic states in model organisms, the Motamedi lab has identified a critical pathway that helps cancer cells establish resistance to therapy. By inhibiting this pathway, they aim to reverse chemotherapy resistance stably in several cancers. This discovery will help in addressing this difficult unmet need in cancer therapy.

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 cellular identities, upon which all developmental processes depend. Disruption to epigenetic regulation underlies a variety of human maladies, including cancers. In fact, epigenetic pathways can contribute to all stages of cancer progression, including initiation, metastasis, resistance and recurrence. Indeed, understanding the molecular mechanisms that establish epigenetic states is fundamental to the development of therapies that target the epigenetic components of cancers.

Often, but not always, epigenetic changes are concomitant with alterations to the chromatin state of underlying genes. Most of what is known about how chromatin states are altered in response to epigenetic triggers comes from decades of research in model organisms. These studies have revealed highly conserved protein families, which are now

used for therapeutic or diagnostic purposes in cancers. The Motamedi lab uses the fission yeast as a model 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. These principles now have emerged as conserved mechanisms by which noncoding RNAs partake in chromatin regulation in eukaryotes including in humans.

A focus of the lab is cellular quiescence (or G0). G0 is a ubiquitous cellular state in which cells exit proliferation and enter a state of reversible dormancy. Developmental





The image depicts as cells enter quiescence (moon), they load Ago1 (ships) with euchromatic small RNAs to mediate Quiescent-induced Transcriptional Repression (Q) of a set of euchromatic genes. Exosome activity separates heterochromatin (dark blue) from euchromatic (yellow) regions. When entering quiescence, the exosome barrier opens, permitting euchromatic transcripts (differently colored dots) to become substrates for RNAi degradation. Ago1, acquiring new color (sRNAs) as it crosses the exosome barrier, targets Q to the corresponding color in euchromatin.

programs, such as wound healing, or exposure to a variety of stress, such as starvation, can trigger entry into or exit from G0. G0 cells have distinct transcriptional programs through which they acquire new properties compared to their proliferative selves, including long life, thrifty metabolism and resistance to stress. Loss of G0 regulation results in defects in developmental and adaptive programs. How cells enter, survive and exit G0 is a critical question in basic biology, which is largely unexplored. To address this knowledge gap, we modeled G0 in fission yeast and showed that when cells transition to G0, new ncRNAs emerge which coopt and deploy constitutive heterochromatin proteins (histone H3 lysine 9 methyltransferase, Clr4/SUV39H) to several euchromatic gene clusters to regulate

the expression of a set of developmental, metabolic and cell cycle genes. We show that this pathway is critical for survival and the establishment of the global G0 transcriptional program. 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 hypotheses that we are currently testing. Moreover, in collaboration with several groups, we have begun to test whether this pathway also plays an important role in cancer dormancy and treatment resistance.

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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 euchromatin deployment of Clr4/SUV39H by argonaute-associated small RNAs. *Mol Cell*. 2016; 64: 1088-1101.

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<sup>†</sup>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/>)

<sup>††</sup>This article was the cover story in *Cell*

## Eugene Oh, PhD



### Oh Laboratory

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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.

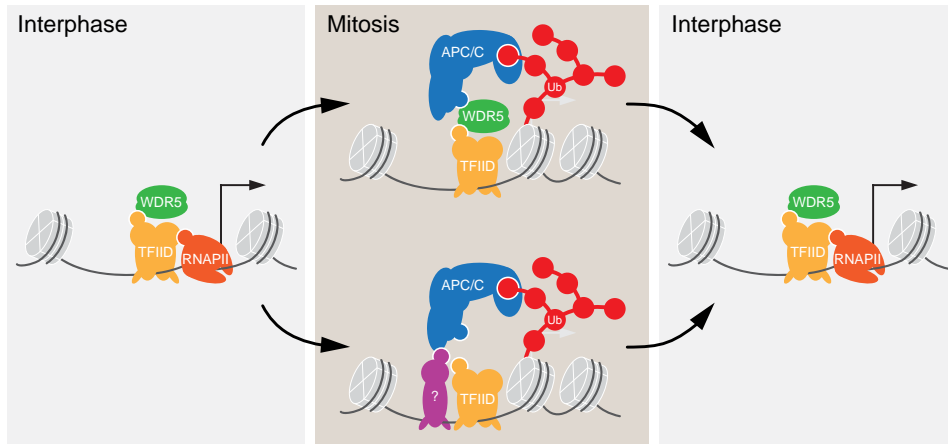
How cells process information and make decisions is essential for their survival. The intracellular signaling events that ultimately evoke specific cellular responses make frequent use of ubiquitylation. Failure to properly do so can cause abnormal cell growth and uncontrolled proliferation, both hallmarks 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.



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.

### Decoding the chromatin-bound ubiquitin code

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

Oh E<sup>†</sup>. Monitoring bacterial translation rates genome-wide. *Methods Mol Biol.* 2021 Mar 26; 2252:3–26.

Oh E\*, Mark K\*, Mocchiari A, Watson ER, Prabu JR, Kampmann M, Cha D, Gamarra N, Zhou CY, and Rape M. Gene expression and cell identity control by anaphase-promoting complex. *Nature.* 2020 Feb 19;579(7797):136–140.

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# Christopher J. Ott, PhD



## Ott Laboratory

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Mutations in cancer cells lead to malfunctioning control of gene expression. **The Ott laboratory** is dedicated to discovering the gene expression control factors that are essential for cancer cell survival. Discovery of these factors prompts further efforts in our group to design chemical strategies for the synthesis and deployment of prototype drugs targeting aberrant mechanisms of gene control. Biologically, gene control factors represent compelling therapeutic targets for cancer treatment as they are master regulators of cell identity. Yet despite this clear rationale, many are perceived as intractable drug targets owing to their large size, disordered shapes, and orchestration of complex cellular circuits. Recent advances in discovery chemistry, high-throughput assay technology, and gene editing have advanced our capability to rapidly identify targetable components of gene control machinery. We use these chemical and genetic tools to probe cancer cells for new vulnerabilities ripe for therapeutics development.

## Chemical modulation of bromodomains

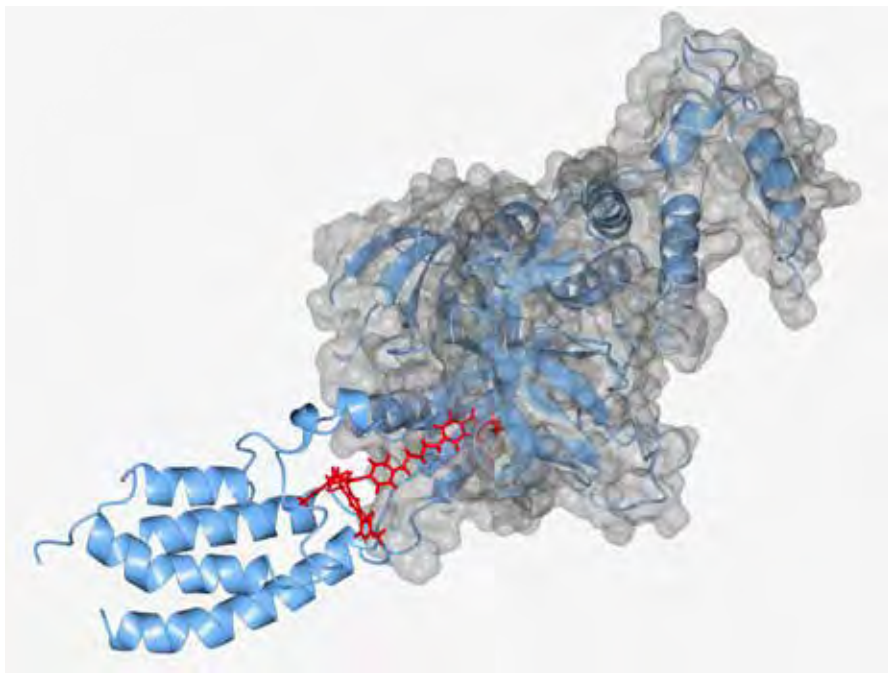
Gene control factors bind to regions of transcriptionally active chromatin called enhancers. Enhancers are critical for driving cell-type specific gene expression, and their chromatin structures are typically marked with specific histone modifications. Among the most distinctive is lysine side-chain acetylation, recognized (or 'read') by protein modules called bromodomains. Recently, novel chemical compounds have been advanced that selectively target bromodomains. These compounds efficiently displace these proteins from enhancers, and we and others have found them to be active agents in models of acute leukemia, lymphoma, and several solid tumor types [Ott et al, *Blood* 2012; Ott et al, *Cancer Cell* 2018]. Using a suite of genome-wide chromatin and transcriptomic assays, we aim to understand principles of bromodomain dependency in cancer. Efforts are ongoing to establish biomarkers for response and resistance, and

realize promising rationales for combination therapies with other targeted agents.

## Essential enhancers

Classic studies have described oncogenic enhancers in leukemia and lymphoma cells. This aberrant enhancer activity can occur by chromosomal translocation of proto-oncogenes such as *MYC* and *BCL2*. In addition to chromosomal translocations, cancer-specific enhancers have been described at proto-oncogene loci like *TAL1* and *MYC*, which are aberrantly bound by transcription factors through direct somatic mutation of enhancer DNA elements or focal amplification. We have generated high-resolution enhancer landscapes derived from primary patient samples, including a large cohort of chronic lymphocytic leukemia samples [Ott et al, *Cancer Cell* 2018]. Current projects include construction of core regulatory transcription factor circuitries, and the discovery of inherited and somatic variants leading to aberrant gene expression.





Structural model of the ternary complex formed by a novel chemical degrader of the 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 (structural model generated by J. Sayilgan).

Using genetic and epigenetic genome editing techniques, we are functionally dissecting malfunctioning enhancers and their cognate bound factors to derive mechanistic understanding of the essential enhancers principally responsible for maintaining leukemia and lymphoma cell states.

### Expanding the chromatin chemical probe toolbox

The successful discovery chemistry efforts that yielded bromodomain inhibitors have revealed chromatin reader domains broadly, and bromodomains specifically, as protein modules amenable for small molecule ligand development. Used experimentally, enhancer-targeting compounds enable precise and acute modulation of chromatin factors and can be used to identify and validate discrete biophysical and biochemical functions of target proteins. Paired with an understanding of integrated epigenomics, these probes elucidate fundamental aspects of epigenome structure and function. We use

high-throughput protein-protein interaction assays and cellular assays of chromatin reader activity to identify reader domain inhibitors. Lead compounds are iteratively optimized for potency and selectivity, followed by functional assessments in cancer cells. Our recent efforts have led us to describe the first chemical degrader of the enhancer lysine acetyltransferases CBP and p300 (Vannam et al, *Cell Chemical Biology* 2021). Ongoing projects seek to expand our current toolbox of enhancer-targeting small molecules, and to develop these compounds into prototype cancer therapies.

### Selected Publications:

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Ott CJ<sup>\*^</sup>, Federation AJ<sup>\*</sup>, Schwartz LS, Kasar S, Klitgaard JL, Lenci R, Li Q, Lawlor M, Fernandes SM, Souza A, Polaski D, Gadi D, Freedman ML, Brown JR<sup>^</sup>, Bradner JE<sup>^</sup>. Enhancer architecture and essential core regulatory circuitry of chronic lymphocytic leukemia. *Cancer Cell*. 2018; 34: 982-995.

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

Koblan LW<sup>\*</sup>, Buckley DL<sup>\*</sup>, Ott CJ<sup>\*</sup>, Fitzgerald ME<sup>\*</sup>, 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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# Shiv Pillai, MD, PhD



## Pillai Laboratory

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Grace Yuen, PhD

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**The Pillai laboratory** asks questions about the biology of the immune system and susceptibility to disease. Some of these questions are 1) can we manipulate the immune system to treat autoimmunity and cancer and to increase immunological memory? 2) can we understand how genetics and the environment affect lymphoid clones to drive common diseases? and 3) can this latter information be used to better understand and develop new therapies for inflammatory human diseases such as COVID-19, systemic sclerosis and IgG4-related disease? We have discovered an underlying basis for why natural infection will not lead to herd immunity in COVID-19, emphasizing the need for vaccination. Our earlier discovery of the role of an enzyme called Btk in the activation of B cells has contributed to the generation of Btk inhibitors that are effective in B cell malignancies and in trials of autoimmunity. One of the pathways we are currently studying suggests new approaches for the treatment of autoimmune disorders.

## Pathogenesis of Inflammatory diseases (NIAID Autoimmune Center of Excellence at MGH)

In studies on COVID-19 we have described the underlying reason for the defect in humoral immunity by interrogating immune activation processes in lymph nodes, spleen and the blood. We have shown that a block in the final stage of T follicular helper cell differentiation leads to the collapse of germinal centers and accounts for the lack of durable immunity. A detailed understanding of adaptive immune changes in the lung in COVID-19 has also been obtained. In systemic sclerosis and IgG4-related disease we have shown that apoptosis of specific cell types in each disease, induced by cytotoxic T cells, is a prelude to fibrosis.

## Studies on murine and human B and T cell biology

We are using a number of single cell transcriptomic, epigenetic and genetic approaches to examine the heterogeneity and

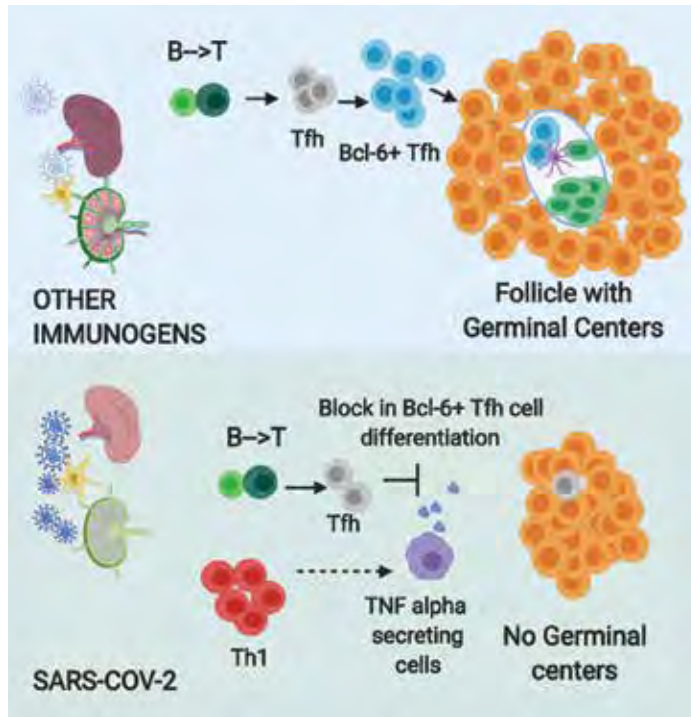
development of selected murine and human B and T cells, as well as the molecular bases of the processes of T-B collaboration and germinal center formation.

## DNA methylation, B cell self-renewal and chronic lymphocytic leukemia

We have long been interested in cell fate decisions in B cell development and in the development of self-renewing B cell subsets. The roles of DNMT3a in B-1a B cell self-renewal and of specific methylation events in chronic lymphocytic leukemia are being investigated. The contributions of DNA methylation and demethylation to the biology of CD4+ CTL and TFH cells are also being investigated.

## Studies on Human CTLA4 and NFκB1 mutations and early B cell development

The underlying mechanism for the human B cell developmental defect in individuals with CTLA4 and NFκB1 mutations has been



A model for the humoral immune defect in COVID-19.

studied helping us to better understand how regulatory T cells can influence early B cell development and humoral autoimmunity.

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\* Denotes equal contribution

# Luca Pinello, PhD



The focus of **the Pinello laboratory** is to use innovative computational approaches and cutting-edge experimental assays, such as 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 machine learning, data mining and high performance computing technologies, for instance parallel computing and cloud-oriented architectures, to solve computationally challenging and Big Data problems associated with next generation 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.

## Pinello Laboratory

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Jonathan Hsu\*  
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Nikolaos Trasanidis†

Michael Vinyard\*  
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\* Visiting PhD student

† Visiting research fellow

## Epigenetic variability in cellular identity and gene regulation

We are studying the relationship between epigenetic regulators, chromatin structure and DNA sequence and how these factors influence gene expression patterns.

We recently developed an integrative computational pipeline called HAYSTACK (6). HAYSTACK is a software tool (<https://github.com/lucapinello/Haystack>) to study epigenetic variability, cross-cell-type plasticity of chromatin states and transcription factor motifs and provides mechanistic insights into chromatin structure, cellular identity and gene regulation. By integrating sequence information, histone modification and gene expression data measured across multiple cell-lines, it is possible to identify the most epigenetically variable regions of the genome, to find cell-type specific regulators, and to predict cell-type specific chromatin patterns that are important in normal development and differentiation or potentially involved in diseases such as cancer.

## Computational methods for genome editing

We embraced the revolution in functional genomics made possible by the novel genome editing approaches such as CRISPR/

Cas9, base editing and prime editing by developing computational tools for the design (1), quantification of CRISPR edits (3) and for the analysis of coding and non-coding tiling screens for functional genomics (4).

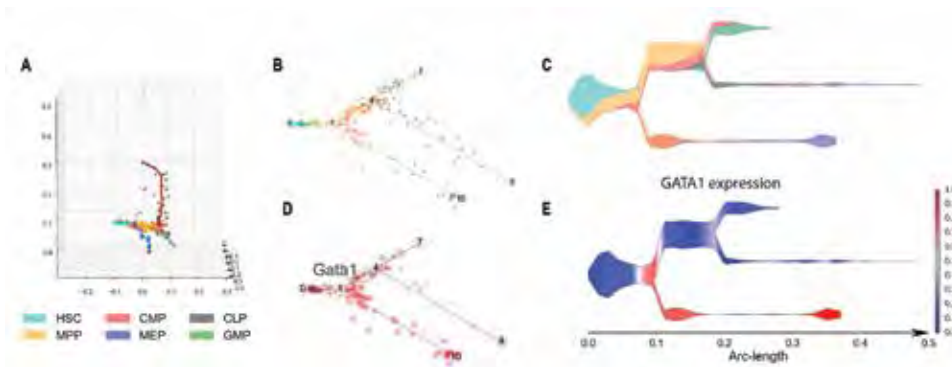
We have developed CRISPREsso2 (<http://crispresso2.pinellolab.org>), a software for the quantification of genome editing events that is now the standard de facto for the genome editing community. In collaboration with the groups of Daniel Bauer and Stuart Orkin, we applied our computational strategies to aid the development of several CRISPR screens for dissecting enhancer functionality in the blood system (4).

We have recently proposed a protocol that describes in detail both the computational and benchtop implementation of an arrayed and/or pooled CRISPR genome editing experiments that serves as a key resource for labs interested in adopting CRISPR genome editing (5).

## Exploring single cell gene expression variation in development and cancer

Cancer often starts from mutations occurring in a single cell that results in a heterogeneous cell population. Although traditional gene expression assays have





*STREAM on transcriptomic data from the mouse hematopoietic system. A) Dimensionality reduction, reconstructed hierarchical structure composed of curves approximating the inferred trajectories. Single cells are represented as circles and colored according to the FACS sorting labels. B) Flat tree representation at single cell resolution; branches are represented as straight lines, (cells are represented as in A). The length of the branches and the distances between cells and assigned branches are proportional to the original representation in the 3D space. C) Rainbow plot: intuitive visualization to show cell type distribution and density along different branches. D) Single cell resolution expression pattern of GATA1, each circle is red filled proportionally to the relative expression of GATA1 in the whole population. E) Relative expression of GATA1 in each branch using the representation in C.*

provided important insights into the transcriptional programs of cancer cells, they often measure a combined signal from a mixed population of cells and hence do not provide adequate information regarding subpopulations of malignant cells. Emerging single cell assays now offer exciting opportunities to isolate and study individual cells in heterogeneous cancer tissues, allowing us to investigate how genes transform one subpopulation into another. Characterizing stochastic variation at the single cell level is crucial to understand how healthy cells use variation to modulate their gene expression programs, and how these patterns of variation are disrupted in cancer cells. We are developing tools to characterize cellular types and states at single cell resolution by using data from single cell transcriptomic or epigenomics data. For example, we recently released STREAM [2] (Single-cell Trajectories Reconstruction, Exploration And Mapping), an interactive computational pipeline for reconstructing

complex cellular developmental trajectories from sc-qPCR, scRNA-seq or scATAC-seq data available at <http://stream.pinellolab.org>. This method can be used for disentangling complex cellular types and states in development, cancer, differentiation or in perturbation studies.

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Hsu JY, Grünewald J, Szalay R, Shih J, Anzalone AV, Lam KC, Shen MW, Petri K, Liu DR, Joung JK\*, Pinello L\*. PrimeDesign software for rapid and simplified design of prime editing guide RNAs. *Nat Commun.* 2021 Feb 15;12(1):1034.

Cancellieri S, Canver MC, Bombieri N, Giugno R†, Pinello L†. CRISPRitz: rapid, high-throughput, and variant-aware in silico off-target site identification for CRISPR genome editing. *Bioinformatics.* 2019 Nov 25. pii: btz867.

Chen H, Albergante L, Hsu JY, Lareau CA, Lo Bosco G, Guan J, Zhou S, Gorban AN, Bauer DE, Aryee MJ, Langenan DM, Zinoviyev A, Buenostro JD, Yuan GC†, Pinello L†. Single-cell trajectories reconstruction, exploration and mapping of omics data with STREAM. *Nat Commun.* 2019 Apr 23;10(1):1903.

Clement K, Rees H, Canver MC, Gehrke JM, Farouni R, Hsu JY, Cole MA, Liu DR, Joung JK, Bauer DE†, Pinello L†. CRISPResso2 provides accurate and rapid genome editing sequence analysis. *Nat Biotechnol.* 2019 Mar;37(3):224-226.

Hsu JY, Fulco CP, Cole MA, Canver MC, Pellin D, Sher F, Farouni R, Clement K, Guo JA, Biasco L, Orkin SH, Engreitz JM, Lander ES, Joung JK, Bauer DE†, Pinello L†. CRISPR-SURF: discovering regulatory elements by deconvolution of CRISPR tiling screen data. *Nat Methods.* 2018 Dec;15(12):992-993.

Canver MC\*, Haeussler M\*, Bauer DE, Orkin SH, Sanjana NE, Shalem O, Yuan GC, Zhang F, Concordet JP & Pinello L. Integrated design, execution, and analysis of arrayed and pooled CRISPR genome-editing experiments. *Nat Protocols.* 2018 May;13(5):946-986.

Pinello L\*†, Farouni R\*, Yuan GC†. Haystack: systematic analysis of the variation of epigenetic states and cell-type specific regulatory elements. *Bioinformatics.* 2018; 34(11):1930-1933.

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# Esther Rheinbay, PhD



## Rheinbay Laboratory

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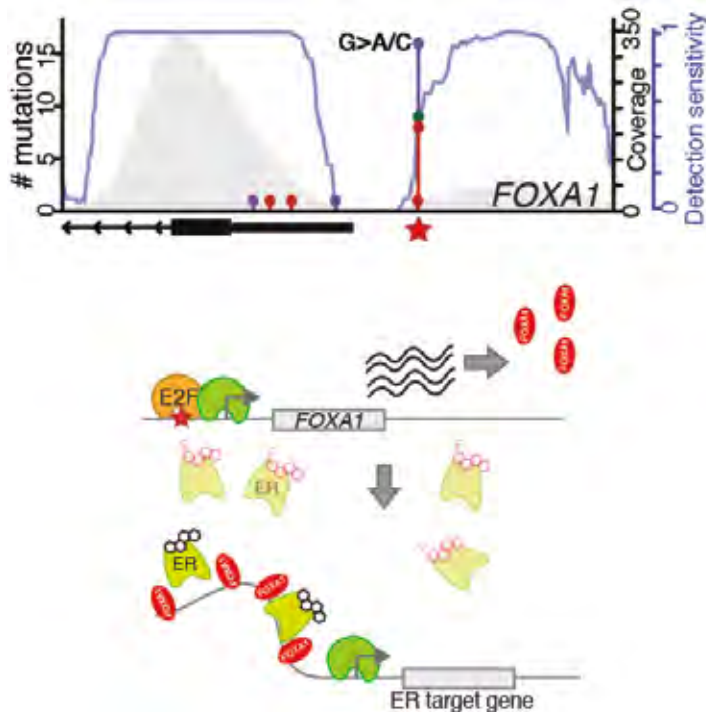
Most known genomic drivers of cancer are in coding genes, affecting the encoded protein's interaction with other proteins, DNA or biological compounds. Recent advances in DNA sequencing technology have made it possible to study non-coding regions that regulate these protein-coding genes. Several cancer drivers have been identified and characterized in these regulatory regions, however, this genomic territory remains relatively unexplored in human tumors. **The Rheinbay laboratory** concentrates on identifying and functionally characterizing these non-coding drivers in the sequences of tumor whole genomes through development of novel analysis strategies and collaborations with experimental investigators.

We are also interested in the contribution of the sex chromosomes, especially the Y chromosome, to cancer. Loss of Y is known to be associated with morbidity and mortality in aging men, yet its role in tumors is largely unclear. Much of this is due to technical challenges that our group aims to solve. Understanding the driver genes on the sex chromosomes will help us explain differences in male and female tumors, and forge a path to more effective, sex-informed treatment.

### 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 and boundary elements), translation (5'UTRs) and mRNA stability (3'UTRs). 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



Hotspot mutation in the FOXA1 promoter in breast cancer and proposed mechanism of action.

treatment resistance through collaborations with experimental colleagues. We have recently identified a recurrent mutation in the promoter of the breast cancer oncogene FOXA1. This mutation increases expression through augmenting a binding site for E2F, leading to E2F protein recruitment. In addition, FOXA1 overexpression leads to resistance to the breast cancer drug, fulvestrant. We are now investigating the implications and mechanism of action of this mutation in breast cancer progression and treatment resistance.

### Role of the sex chromosomes 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 has been shown that both sex chromosomes can be lost in both normal blood cells with age, as well as certain tumor cells. Yet the meaning of Y chromosome loss, 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. We develop analysis strategies and methods to tackle the technical challenges, with the goal of identifying sex-specific, and potentially targetable, vulnerabilities in human cancer.

### Selected Publications:

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.

Suva ML\*, Rheinbay E\*, Gillespie SM, et al. Reconstructing and reprogramming the tumor-propagating potential of glioblastoma stem-like cells. *Cell*. 2014;157:580-94.

Rheinbay E\*, Suva ML\*, Gillespie SM, et al. An aberrant transcription factor network essential for Wnt signaling and stem cell maintenance in glioblastoma. *Cell Reports*. 2013;3:1567-79.

\*Equal contribution

# Miguel N. Rivera, MD



## Rivera Laboratory

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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 pathways in several model systems. Given that the mechanisms that drive changes in gene expression programs are poorly understood, we anticipate that our studies will point to new therapeutic approaches.

### Epigenomic approaches for the identification of novel pathways in cancer

While genetic studies have led to the development of important cancer therapies, most genetic alterations in cancer do not point to specific therapeutic targets. In the case of pediatric cancers, which are often driven by low numbers of recurrent mutations, the identification of therapeutic targets through genetic studies has been particularly challenging. In order to discover new pathways involved in these tumors, we are using new genomic technologies to identify abnormalities in the mechanisms that regulate gene expression programs controlling cell proliferation and differentiation.

One of these technologies is genome-wide 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

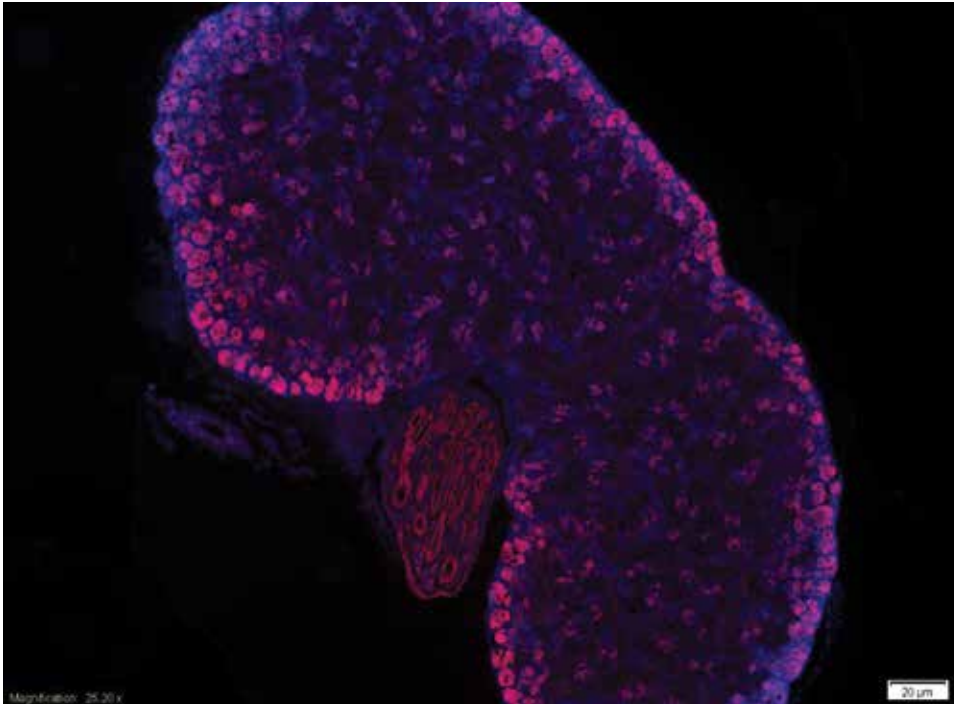
shown that prominent active histone marks are associated with genes that play key roles in cell identity and proliferation, including oncogenes that promote the growth of tumor cells. In contrast, repressive marks are found at loci that are maintained in an inactive state to prevent cellular differentiation.

We have performed extensive chromatin profiling of Wilms tumor, Ewing sarcoma and medulloblastoma, three pediatric tumors that are thought to arise from stem cell precursors and 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 poorly defined.

### Role of the WTX gene family in cancer and development

Wilms tumor, the most common pediatric kidney cancer, is a prime example of





Immunofluorescence image of a developing mouse kidney. The transcription factor Pax2 (red) is present in the stem cells that can give rise to Wilms tumor (adjacent to the surface of the organ) and in precursors to collecting ducts.

the connection between cancer and development, because it arises from kidney-specific stem cells and is composed of several cell types that resemble the earliest stages of kidney formation. We identified WTX, an X-linked tumor suppressor gene, which is inactivated in up to 30% of cases of Wilms tumor, by comparing the DNA of primary tumor samples with that of normal tissues using array comparative genomic hybridization (CGH). More recently, large tumor sequencing studies have shown that WTX is also inactivated in several other tumor types. WTX is the founding member of a new protein family (FAM123/AMER) and is expressed in the stem cells of the developing kidney, as well as in a variety of other tissues during embryogenesis. In collaboration with the Haber and Bardeesy laboratories, we have demonstrated that inactivation of WTX in mice leads to profound

alterations in the development of several organs including kidneys, bones and fat by causing changes in the differentiation programs of mesenchymal stem cells. In particular, we observed an expansion of mesenchymal kidney stem cells, suggesting that WTX regulates the balance between proliferation and differentiation in these cells. We are now using a combination of in vitro and in vivo approaches to elucidate the molecular mechanisms by which WTX and related proteins regulate stem cells. Given that the same mechanisms are likely to be operative in tumors where WTX is inactivated, we expect that our studies may reveal new therapeutic opportunities for a variety of tumor types.

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Boulay G, Sandoval GJ, Riggi N, Iyer S, Buisson R, Naigles B, Awad ME, Rengarajan S, Volorio A, McBride MJ, Broyle LC, Zou L, Stamenkovic I, Kadoch C, Rivera MN. Cancer-specific retargeting of BAF complexes by a prion-like domain. *Cell*. 171(1-16), 2017 Sept 21.

Boulay G, Awad ME, Riggi N, Archer TC, Iyer S, Boonseng WE, Rossetti NE, Naigles B, Rengarajan S, Volorio A, Kim JC, Mesirov JP, Tamayo P, Pomeroy SL, Aryee MJ, Rivera MN. OTX2 Activity at Distal Regulatory Elements Shapes the Chromatin Landscape of Group 3 Medulloblastoma. *Cancer Discovery*. 7(3):288-301, 2017.

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\*Co-authors

## Debattama Sen, PhD



### Sen Laboratory

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Richard Davidson, MMSc  
Rohan Hosuru  
Paola Lirofonis  
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Debattama Sen, PhD  
Cansu Yerinde, PhD

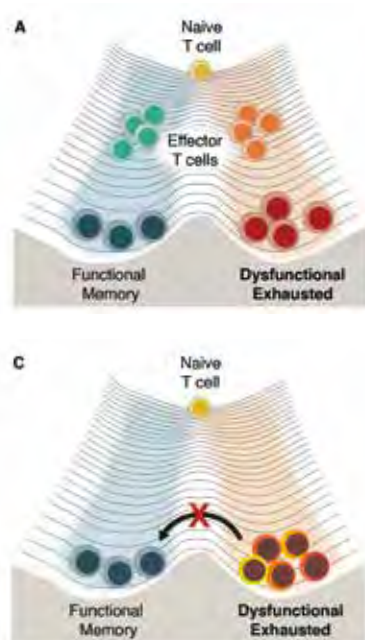
Dysfunction of the immune system is central to disease progression in cancer. **The Sen laboratory** investigates the regulation of T cell dysfunction in tumors and explores epigenetic approaches for T cell engineering. Our work lies at the interface of human immunology, systems biology, and functional epigenomics – merging clinical observations with mechanistic mouse studies to develop novel therapeutic strategies. We have found that the regulatory “circuitry” of dysfunctional T cells differs remarkably from functional T cells fighting off acute viruses. By comparing chronic viral infections and cancer, we demonstrate that this altered epigenetic wiring is a fundamental adaptation to chronic diseases and cannot be rescued by current treatments. Therefore, improved understanding of this altered regulation 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, thereby minimizing unwanted side-effects in patients.

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. To overcome technical limitations imposed by low cell numbers, we performed ATAC-seq in exhausted cells and profiled the landscape of accessible chromatin, which is enriched for active enhancers and other regulatory elements. 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



*Epigenetic regulation of T cell exhaustion and its implications: A) Exhausted CD8+ T cells acquire a state-specific epigenetic landscape that precedes onset of dysfunction; B) Exhausted epigenome arises in both cancer and chronic viral infection, and is shaped by specific micro-environments; C) Epigenetic "scars" in exhausted T cells cannot be reversed by current treatment strategies.*

## Selected Publications:

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.*

Collier JL\*, Weiss SA\*, Pauken KE, Sen DR, Sharpe AH. Not-so-opposite ends of the spectrum: CD8+ T cell dysfunction across chronic infection, cancer, and autoimmunity. *Nature Immunology*. 2021 Jul;22(7):809-819.

Brown FD, Sen DR, Godec J, LaFleur MW,... Sharpe AH, Haining WN, Turley SJ. Fibroblastic reticular cells enhance T cell metabolism and survival via epigenetic remodeling. *Nature Immunology*. 2019 Oct 21.

Mani V, Bromley SK, Carrizosa E, Warner RD, Hamze MM, Sen DR, Chasse AY, Åijö T, Jeffrey KL, Marangoni F, Lacy-Hulbert A, Mempel TR. Conditioning of naïve CD8+ T cells for tissue-resident memory formation. *Science*. 2019 Oct 11;366(6462).

Miller BC\*, Sen DR\*, Al-Aboosy 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. the Dec 2016 issue of Science.*

\*Equal contribution

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 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.

It is becoming evident that alleviating T cell exhaustion 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 early differentiation of CD8+ T cells *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.

## Dennis Sgroi, MD



### Sgroi Laboratory

Wayland Chiu  
Dennis Sgroi, MD  
Marinko Sremac, PhD

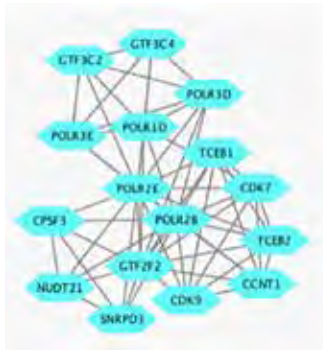
The overarching goals of research in **the Sgroi laboratory** are to develop better ways to identify patients who are at risk for the development of breast cancer and to identify those breast cancer patients who are likely to benefit from targeted drug therapies. We are taking several different approaches to achieving these goals. First, we are deciphering specific molecular events that occur during the earliest stages of tumor development and using this knowledge to develop biomarkers that will predict for increased risk of progression to cancer. Second, using various high-throughput genetic and proteomic technologies, we are searching for novel breast cancer biomarkers to identify patients with hormone-receptor-positive breast cancer who are most likely to benefit from extended hormonal therapy. Finally, we are taking a combined approach—based on analysis of tissue from breast cancer patients and various laboratory studies—to identifying biomarkers that will predict how individual breast cancer patients will respond to novel targeted therapeutics.

Presently, my laboratory is focused on applying high-throughput molecular technologies to identify biomarkers that will predict the clinical behavior of human estrogen receptor positive breast cancer in the setting of specific hormonal and chemotherapeutic regimens. We have developed the Breast Cancer Index (BCI) biomarker which is an algorithmic gene expression-based signature comprised of two functional biomarker panels, the Molecular Grade Index (MGI) and the two-gene ratio, HOXB13/IL17BR (H/I), that evaluate tumour proliferation and estrogen signalling, respectively. Integration of MGI and H/I generates a prognostic BCI score quantifying the risk of overall (0-10 years) and late (5-10 years) distant recurrence in ER+ HER2- breast cancer patients. The

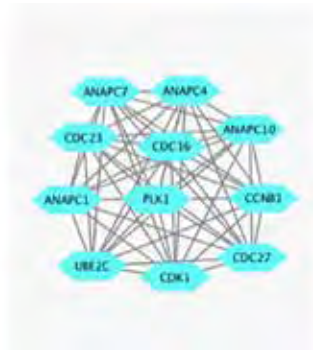
predictive component of BCI, the H/I ratio (henceforth BCI-H/I), has been shown to significantly predict endocrine response across several different treatment scenarios. In ER+ HER2- breast cancer patients in the extended endocrine setting, BCI predicted benefit from an additional 5 years of letrozole after ~5 years of initial tamoxifen in the MA.17 study, and most recently BCI predicted benefit from an additional 5 years of tamoxifen after 5 years of initial tamoxifen in the aTTom trial. These data provided further validation and established BCI as a unique biomarker that can help inform the decision to extend or not extend endocrine therapy beyond 5 years. BCI has been adopted in the most recent 2020 NCCN guidelines. We are currently collaborating with the NSABP to assess our biomarker in the NSABP-42



Network of Group 1

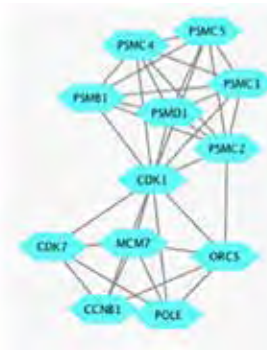


Network of Group 2



Protein Set 1

(REACTOME\_MITOTIC\_G1\_G1\_S\_PHASE)



*STRING* network of leading edge dysregulated groups of proteins for HOXB13/IL17BR-low ER+ breast cancers. Several intriguing clusters of dysregulated protein-protein interactions are associated with the regulation of CDK4/6, cyclin E1, cyclin B1 and CDK1.

clinical trial. Lastly, we are currently studying protein-protein dysregulations in H/I-low breast cancers to identify therapeutic vulnerabilities. In a comparative analysis of H/I-high versus H/I-low breast cancers, we have identified several dysregulated pathways that may be susceptible to therapeutic intervention.

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\*Denotes equal contribution

## Toshihiro Shioda, MD, PhD



### Shioda Laboratory Molecular Profiling Laboratory

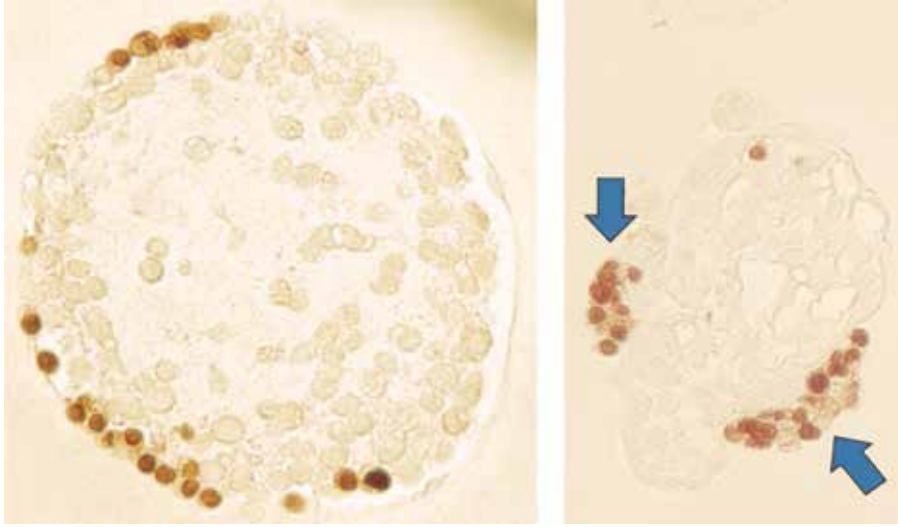
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Toshihiro Shioda, MD, PhD

**The Shioda laboratory** is interested in human primordial germ cells (PGCs), the most upstream precursors of gametes (eggs and sperm). Due to the technical and ethical barriers to obtain PGCs from human embryos, a cell culture model of human PGC-like cells (hPGC-LCs) has been generated from pluripotent stem cells in several laboratories, including ours. Overcoming the well-known difficulties in maintaining hPGC-LC cultures over three weeks, our lab has recently accomplished long-term culture of actively proliferating hPGC-LCs that can be maintained for at least three months without losing their PGC state. This novel resource provides unprecedented opportunities to study development, epigenetics, and diseases of human PGCs. For example, as transformed male PGCs cause testicular cancer (the most common malignancy in juvenile and young-adult men), we took advantage of our long-term hPGC-LC culture and genetic engineering techniques and have successfully generated hPGC-LCs harboring various genetic mutations linked to testicular cancers. Attempts are currently ongoing in our lab to establish the first synthetic tumor model of human testicular cancer with defined genetic mutations.

### Long-term maintenance of hPGC-LCs

Several laboratories, including ours, have developed various protocols of hPGC-LC production from human ESCs or iPSCs. Our previous study demonstrated strong transcriptomal similarities among hPGC-LCs generated using various protocols, supporting the notion that these hPGC-LCs are reflecting the same type of cells that exist *in vivo* – namely, embryonic PGCs. We also reported that our iPSC-derived hPGC-LCs reflect a very early stage of human embryonic PGCs during their passive midline movement before the CXCL12/CXCR4-guided, active lateral migration towards gonadal anlagen. The major technical barrier that prevents immediate application of hPGC-LCs to various biological studies such as chemical or CRISPR-knockout screening has been their limited lifespan in cell culture conditions and relatively low yields achievable by each experiment performed in the standard lab settings. The latest published study claimed

only three weeks of hPGC-LC maintenance in cell culture before cells were lost or nonspecifically differentiated. To overcome this hurdle, our laboratory has performed a systemic evaluation of cell culture conditions and successfully established a protocol that permits active proliferation of hPGC-LCs over at least three months without losing their PGC-like state. We have developed two variations of the long-term hPGC-LC culture protocols that reproducibly support stable maintenance of hPGC-LCs derived from various human iPSCs, males or females. The amplified hPGC-LCs are readily stored frozen in the conventional freezing media without losing viability or the PGC-like state. This novel resource will provide the relevant fields of research with unique and important opportunities to use practically unlimited amounts of hPGC-LCs without generating relatively small numbers of them from the precursor pluripotent stem cells each time through laborious protocols.



*Emergence of human PGC-LCs on the surface of embryoid bodies. Human PGC-LCs are visualized by anti-OCT4 immunohistochemistry of FFPE slides. Most PGC-LCs are localized in the outermost surface layer of embryoid bodies (left). PGC-LCs often form dense clusters (arrows; right), which may mimic the embryonic niche involved in germline commitment of precursor cells.*

### Genetic modeling of human testicular cancers

Testicular cancer is the most common malignancy that hits juvenile and young-adult males of 15-35 years old. The vast majority of various subtypes of testicular cancer is the Type II germ cell tumor, which derives from PGCs. Most pathologically diagnosed invasive testicular cancers are associated with adjacent Germ Cell Neoplasia In Situ (GCNIS), which consist of morphologically atypical PGC-like cells harboring chromosome 12p amplification in practically all cases and are believed to be precursor lesions of the invasive carcinoma. Testicular cancers uniquely lack genetic mutations commonly found in many other types of adult cancers, and instead they often harbor a specific set of mutations such as heterozygous gain-of-function, c-KIT, and genome-wide association studies have repeatedly suggested the involvement of the pro-apoptotic gene *BAK1* in testicular carcinogenesis. Genes locating in chromosome 12p, such as the pluripotency gene *NANOG*, are also candidates of the driver genes. However, due to the unexplained difficulties in modeling human testicular cancers in rodent models harboring genetic

mutations (except for embryonic carcinoma, a subtype of testicular cancer), experimental demonstrations of the importance of these driver gene candidates in human testicular carcinogenesis are still awaited. Taking advantage of our long-term hPGC-LC culture technique, our lab has generated a panel of hPGC-LCs harboring various driver mutation candidates – for example, gain-of-function c-KIT knock-in, *BAK1/BAX* single or double mutations that remarkably affected cellular sensitivities to apoptotic stimuli, and/or overexpression of *NANOG*. Attempts are being made to establish hPGC-LC cell cultures that show reproducible evidence of partial or full malignant transformation caused by defined genetic changes. On the other hand, in collaboration with Dr. Chin-Lee We of MGH Urological Pathology, we have established novel human testicular cancer cell lines with accompanying normal testicular somatic cell cultures. Attempts are being made in our lab to reprogram these cancerous and normal human testicular cells harboring the same genetic background into iPSCs and then hPGC-LCs. This compensating approach will determine whether genetic mutations alone can readily cause human testicular cancers.

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# David Spriggs, MD



## Spriggs Laboratory

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Raj Kumar, PhD  
Ian Laster, BS  
Kwangkook Lee, PhD  
David Spriggs, MD  
Irva Veillard, BS  
Mengyao Xu, MD  
*shared with Liron Bar-Peled lab*  
Oladapo Yeku, MD, PhD

**The Spriggs laboratory** has been focused on proteins present on the ovarian cancer cell surface and how those proteins regulate function in health and cancer. In particular, we are interested in MUC16 and Galectin 3. Our studies over the past several years have provided insights into the function of MUC16. It is now apparent that the MUC16 regulates functions like cancer growth and spreads through changes in the structure of sugars (glycosylation) on the surface of cancer cells. This regulation requires interaction with specialized sugar binding proteins called Galectins, which are key components of the tumor microenvironment. We are actively developing new antibodies against MUC16 and Galectin 3 for diagnosis, imaging and treatments. Our work has shown that antibodies which inhibit these cell – cell interactions can slow tumor growth and block the spread of cancer cells locally and inhibit the spread to new organs.

Our research group is actively examining the role of glycosylation, especially on mucins in tumor specific behaviors including uncontrolled growth, oncogene activation, invasion, immune system evasion angiogenesis, and metastatic spread. This work includes potential therapeutic antibodies against MUC16 and Galectin-3 in cancer.

### Anti-MUC16 biology

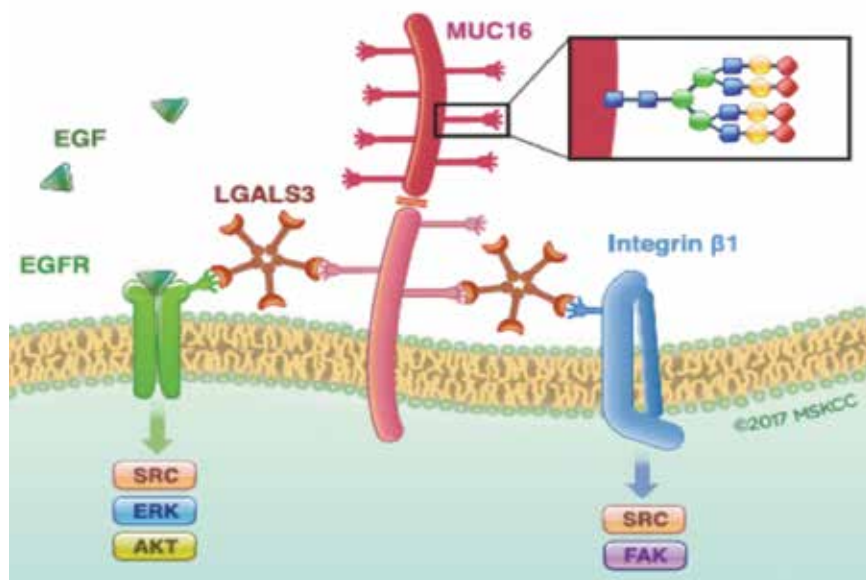
Our current MUC16 work concentrates on development of our human MUC16 antibodies for targeting ovarian cancer. Our antibodies uniquely target the most proximal, retained portion of the MUC16 following cleavage and release of the CA125 antigen into the circulation. This retained ectodomain is a 58 amino acid peptide, linked to the membrane via a short transmembrane domain and a 31 amino acid cytoplasmic tail which is linked to the cellular cytoskeleton for mobility. We have shown that most of the adverse consequences relate to MUC16 expression. As little as 114 amino acids from the carboxyl terminal of the intact MUC16 sequence is sufficient to promote increased soft agar colony formation, Matrigel invasion

with increased MMP2/MMP9 expression, activation of both AKT and ERK proto-oncogenes, and enhanced growth in nude mice. Deletion experiments demonstrate that the 58 amino acid MUC16 ectodomain is required for this effect. If one examines the ectodomain in greater detail, the portion of the sequence containing 2 N-glycosylation sites is the essential element. We (esp. Dr. Lee) are now actively examining the structure of the MUC16 – antibody interaction to improve the therapeutic efficacy of antibodies.

### MUC16-directed Chimeric Antigen Receptor (CAR) T Cells

Chimeric Antigen Receptor (CAR) T cells have not been successful in the management of solid tumor malignancies. Reasons for this include: poor trafficking, the presence of an immunosuppressive tumor microenvironment, CAR T-cell dysfunction and immune escape via antigen-loss. In conjunction with Dr. Oladapo Yeku, from our junior faculty, we are using our antibodies as MUC16 targeted CAR T cells. We are developing strategies to further modify CAR





*MUC16 is an example N-glycosylation - rich molecule which can regulate the cellular location and signal transduction mediated by TK receptors like EGFR or adhesion molecules (integrins) through Galectin 3 mediated interactions.*

T cells to optimize their efficacy for ovarian cancer and gynecologic malignancies. Our approaches to further engineering these CAR T cells with Human Artificial Chromosomes (Dr. Kononenko) are informed by the ovarian cancer tumor microenvironment. Using syngeneic immune competent mouse models and subsequent validation in genetically engineered and xenograft models, we are able to effectively evaluate these rationally optimized CAR T cells as monotherapy or in combination with other immunomodulatory agents prior to initiation of clinical trials.

### Glycosylation Dependence

Our work has been the first to show that the oncogenic effects of MUC16 require MGAT5 dependent tetra-antennary glycosylation of the MUC16 ectodomain and interaction with Galactin 3 (LGALS3). This complex then binds to glycosylation sites on growth factors including EGFR, Integrins, and immune receptors like CTLA4. This has provided us with new opportunities for MUC16+ cancer cell targeting.

### Galectin 3 Targeting

LGALS3 regulates the interaction of surface proteins with the extracellular membrane domain and mediates a signal cascade leading to invasion, oncogene activation and growth. While anti-MUC16 glycosylation site antibodies inhibit oncogenic properties, LGALS3 represents a more general strategy for targeting glycosylation dependent oncogenesis. We have developed high-affinity anti-galectin-3 antibodies directed at the carbohydrate recognition domain (CRD) of the galectin-3 carboxyl-terminus (to block sugar binding). These antibodies are able to block the oncogenic effects of MUC16 expression including invasion, oncogene activation (AKT, ERK, SRC) and reduced growth in nude mice. In addition, these antibodies appear able to decrease metastatic behaviors in lung metastasis models. Dr. Xu is focused on the functions of Galectin 3 in cancer while Dr. Lee has been producing a structural model of binding to the Galectin-3 surgery binding elements.

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Yeku OO, Purdon TJ, Koneru M, Spriggs D, Brentjens RJ. Armored CAR T cells enhance antitumor efficacy and overcome the tumor microenvironment. *Sci Rep*. 2017 Sep 5;7(1):10541.

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## Shannon Stott, PhD



### Stott Laboratory

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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 tumor cells (CTCs) and extracellular vesicles (EVs) 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 look at tumor specimens using multispectral imaging, hoping that the exploration of the spatial relationships between immune cells and tumor 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.

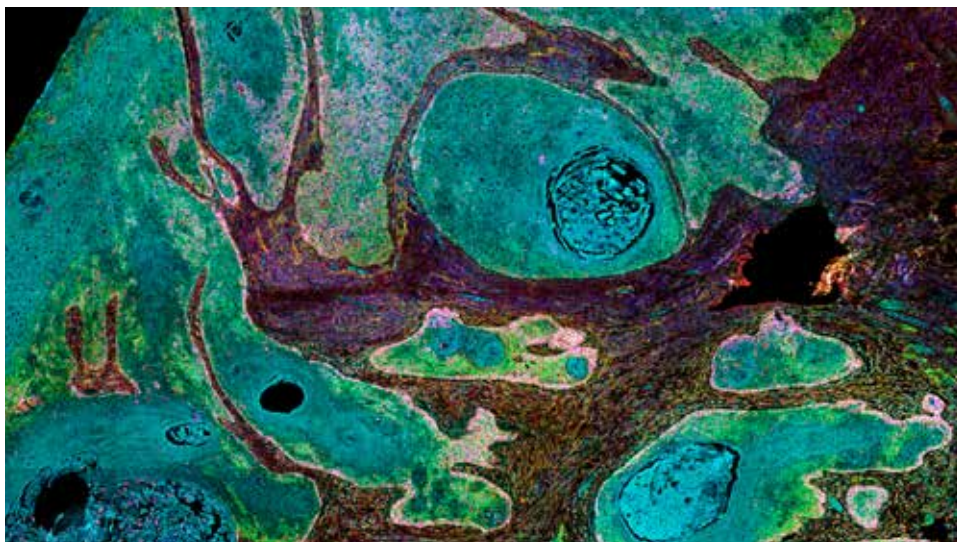
### Extracellular Vesicle Isolation and Characterization

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 João Paulo Oliveira-Costa, PhD

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 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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Tessier SN, Bookstaver LD, Angpraseuth C, Stannard CJ, Marques B, Ho UK, Muzikansky A, Aldikacti B, Reategui E, Rabe DC, Toner M, Stott SL. Isolation of intact extracellular vesicles from cryopreserved samples. *PLoS One*. 16(5):e0251290, 2021.

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Park MH\*, Reategui E\*, Li W, Jensen AE, Toner M, Stott SL<sup>†</sup>, Hammond PT<sup>†</sup>. Enhanced Isolation and Release of Circulating Tumor Cells Using Nanoparticle Binding in a Microfluidic Chip Via Place-Exchangeable Ligands. *JACS*. 139(7), 2017.

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\*Co-authors

<sup>†</sup>Joint corresponding

# Mario L. Suvà, MD, PhD



## Suvà Laboratory

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**The Suvà laboratory** develops and applies single-cell genomic technologies and advanced computational analyses to dissect the biology of brain tumors, in particular 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 programs governing glioma stem cells. We seek to redefine tumor cell lineages and stem cell programs across all subtypes of gliomas, and to leverage the information for renewed therapeutics. In close collaborations, the laboratory additionally leverages single-cell genomics to dissect the immune system of gliomas and to chart the cellular programs in sarcomas.

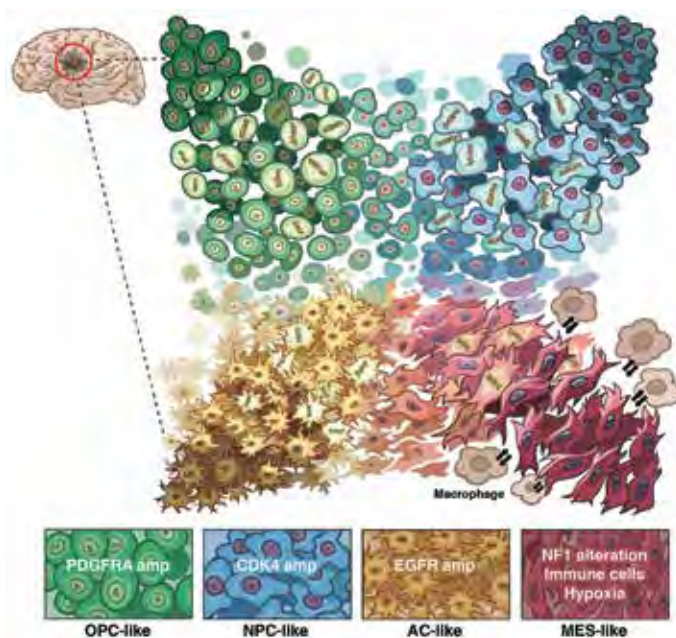
Cell state heterogeneity is an important disease hallmark of both IDH-mutant glioma and IDH-wildtype glioblastoma, with genetic clonal diversity intermingled with neurodevelopmental trajectories. Stemness-to-differentiation diversity is central to the glioma stem cell (GSC) model, which posits that stem-like 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 (DNAm, 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 IDH-mutant 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





*Model for the cellular states of glioblastoma and their genetic and micro-environmental determinants. Mitotic spindles indicate cycling cells. Lighter/darker tones indicate strength of each program. Intermediate states are shown in between the four states and indicate transitions.*

vulnerabilities and revealed a differentiation block, maybe explaining the more aggressive nature of this cancer type. 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 micro-environment (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:

Hara T<sup>†</sup>, Chanoch-Myers R<sup>†</sup>, Mathewson ND, Myskiw C, Fan J, Bussema L, Atta L, Eichhorn SW, Greenwald A, Kinker G,... Hunter T, Verma IM, Wucherpennig KW, Regev A, Suvà ML\*, Tirosh I\*. Interactions between cancer cells and immune cells drive transitions to mesenchymal-like states in glioblastoma. *Cancer Cell*. 2021 Jun 14;39(6):779-792.

Mathewson ND<sup>†</sup>, Ashenberg O<sup>†</sup>, Tirosh I<sup>†</sup>, Gritsch S<sup>†</sup>, Perez EM<sup>†</sup>, Marx S<sup>†</sup>, Jerby-Arnon L, Chanoch-Myers R, Hara T,... Louis DN, Ligon KL, Marson A, Chiocca EA, Reardon DA, Regev A\*, Suvà ML\*, Wucherpennig KW\*. Inhibitory CD161 Receptor Identified in Glioma-infiltrating T cells by Single Cell Analysis. *Cell*. 2021 Mar 4;184(5):1281-1298.

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Filbin MG<sup>†</sup>, Tirosh I<sup>†</sup>, Hovestadt V<sup>†</sup>, Shaw ML, Escalante LE,... Getz G, Rozenblatt-Rosen O, Wucherpennig KW, Louis DN, Monje M, Slavc I, Ligon KL, Golub TR, Regev A\*, Bernstein BE\*, Suvà ML\*. Developmental and oncogenic programs in H3K27M gliomas dissected by single-cell RNA-seq. *Science*. 2018 Apr 20;360(6386).

Venteicher AS<sup>†</sup>, Tirosh I<sup>†</sup>, Hebert C, Yizhak K, Neftel C, Filbin MG, Hovestadt V,... Cahill DP, Rozenblatt-Rosen O, Louis DN, Bernstein BE, Regev A\*, Suvà ML\*. Decoupling genetics, lineages and micro-environment in IDH-mutant gliomas by single-cell RNA-seq. *Science*. 2017 Mar 31;355(6332).

Tirosh I<sup>†</sup>, Venteicher AS<sup>†</sup>, Hebert C, Escalante LE, Patel AP, Yizhak K, Fisher JM,... Rivera MN, Getz G, Rozenblatt-Rosen O, Cahill DP, Monje M, Bernstein BE, Louis DN, Regev A\*, Suvà ML\*. Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma. *Nature*. 2016 Nov 10;539(7628).

<sup>†</sup>Co-senior authorship

<sup>†</sup>Co-first authorship

# David A. Sweetser, MD, PhD



## Sweetser Laboratory

David A. Sweetser, MD, PhD  
Evangelos Theodorou, PhD

**The Sweetser laboratory** investigates how leukemia and other cancers develop with the goal of developing novel, safer, and more effective therapies. We have two major lines of research - the first investigating the function of a novel family of tumor suppressor genes and the second investigating the supportive role of the bone marrow niche in leukemia. Our lab has identified how the Groucho/TLE family of co-repressors function as potent tumor suppressors of acute myeloid leukemia and has been defining their roles in normal development and cell function. Knock-out mice for Tle1 and Tle4 have identified critical roles for these proteins in hematopoiesis, bone, lung, and brain development, as well as a critical role in limiting inflammation. It is this ability to regulate inflammatory pathways that appears to underlie their tumor suppressor activity. We have defined critical inflammatory signaling pathways mediating cell proliferation and synergistic cross talk within the cancer niche that stimulated the proliferation and survival of leukemia. The laboratory is also involved in characterizing cancer predisposition genes and genes influencing therapy toxicity. As the MGH site director for the Undiagnosed Diseases Network and Chief of Medical Genetics and Metabolism at MGH, 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.

### Genetics of Acute Myeloid Leukemia

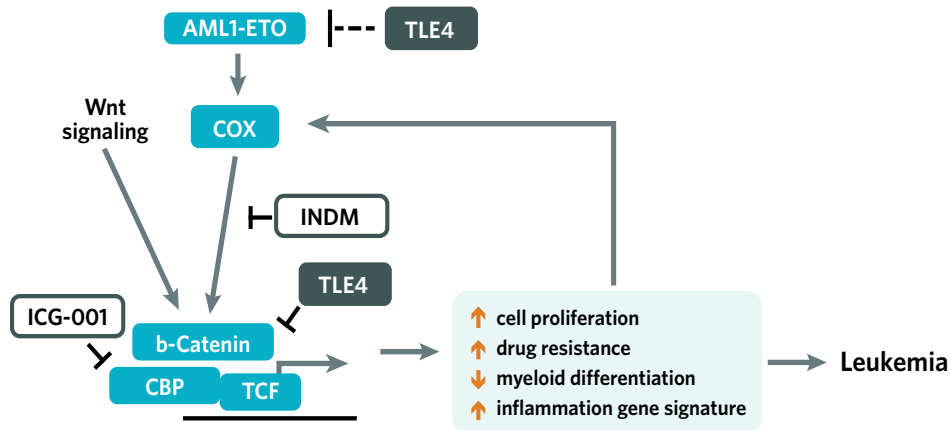
Our laboratory is working to elucidate cooperating networks underlying leukemogenesis and to develop novel targeted therapies for cancer. Current projects are detailed below.

### Evaluation of the Role of the Groucho/TLE Family of Corepressors in Cancer and Development

Our laboratory has defined TLE1 and TLE4 as members of a novel family of tumor suppressor genes, the TLE/Groucho proteins, the inactivation of which appears to be a key cooperating event with other oncogenes in the development of a subset of acute myeloid leukemias and other cancers including melanoma.

The Groucho/TLE family of corepressor proteins can modulate many of the major pathways involved in development and

oncogenesis, including Wnt/ $\beta$ -catenin, Notch, Myc, NF $\kappa$ B, and TGF $\beta$ . However, we are only beginning to understand their potential role in oncogenesis. These genes appear to behave as tumor suppressor genes in the pathogenesis of other myeloid malignancies and lymphomas, but as an oncogene in synovial cell sarcoma. TLE1 and TLE4 are potent inhibitors of the AML1-ETO oncogene in the most common subtype of AML. The mechanism of this inhibition appears to involve both regulation of gene transcription and chromatin structure. Our work indicates this cooperative effect appears to involve regulation of Wnt signaling and inflammatory gene pathways. This work has led to the demonstration that specific anti-inflammatory agents can have potent anti-leukemic effects. We have also been studying the role of TLE1 in melanomas using conditional knockout of Tle1 and conditional oncogenic BRAF expression



Schematic diagram summarizing proposed TLE4 regulation of AML1-ETO/COX/Wnt axis. The TLEs have potent anti-inflammatory effects and inhibitory effects on oncogene pathways involving AML1-ETO and B-catenin, which also underlie their tumor suppressor activity.

in a mouse model. In this context we have shown loss of Tle1 cooperates with oncogenic BRAF to cause melanoma development. The mechanism of this inhibition is being investigated.

Our laboratory is also working to understand the role these proteins play in normal development. To assist in this evaluation, we have generated conditional Tle1 and Tle4 knockout mice and are characterizing the role these proteins play in the development of a variety of tissues. Our studies to date indicate TLE1 is a potent repressor of inflammation via its ability to repress NF $\kappa$ B, while TLE4 is a critical modulator of neuronal and B-cell and T-cell differentiation, and is required for hematopoietic stem cell maintenance. We have demonstrated a critical previously unknown role for TLE4 in mediating the function of Runx2 in osteogenesis and this suggests a potential mechanism for the osteopenia often accompanying leukemia.

### The Role of the Bone Marrow Niche in Nurturing Leukemia

The bone marrow niche is remodeled in the process of leukemia development to provide

a supportive environment that contributes to leukemic cell proliferation, survival, and resistance to chemotherapy. Our lab is working to define the critical cells and components of this niche with an eye towards designing targeted adjunctive therapies.

### The Undiagnosed Diseases Network

The Harvard Medical School hospital consortium of MGH, Brigham and Women's Hospital and Children's Hospital together with 10 other clinical sites around the US comprise the NIH sponsored Undiagnosed Diseases Network. As Chief of Medical Genetics at MGH, and the MGH site director for the UDN, Dr. Sweetser is coordinating 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.

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# David T. Ting, MD



## Ting Laboratory

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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. Using single molecule sequencing, we have discovered a significant amount of “non-coding” repeat RNAs to be produced in high amounts at the earliest stages of cancer development, but not in normal tissues. These repeat RNAs can serve as a novel early detection cancer biomarker and they can be targeted as a new therapeutic avenue. In parallel, we have used single cell and microfluidic chip technologies to understand the factors involved in the development of metastatic behavior in individual tumor cells. We capture circulating tumor cells (CTCs) and using single cell RNA-seq we have gained unprecedented insight into the programs that drive metastatic spread. We are using these studies to develop blood based biomarkers and generate new therapies to stop the spread of cancer.

The Ting laboratory has utilized RNA-sequencing and RNA in situ hybridization technology 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 to understand cancer cell heterogeneity and plasticity.

## Repeat Non-coding RNAs

RNA sequencing of a broad spectrum of carcinomas demonstrated a highly aberrant expression of non-coding repeat RNAs emanating from regions of the genome previously thought to be inactive due to epigenetic silencing. Analysis of all human repeats identified the HSATII satellite as being exquisitely specific for epithelial cancers,

including carcinomas of the pancreas, colon, liver, breast, and lung. HSATII expression was confirmed by RNA in situ hybridization (RNA-ISH), and was present in preneoplastic lesions in mouse models and human specimens of the pancreas and colon suggesting satellite expression occurs early in tumorigenesis, which provides for a potential biomarker for early detection and a novel therapeutic avenue. Recently, we have discovered that HSATII is reverse transcribed in cancer cells and can integrate back into the genome and expand these pericentromeric regions. These expansions were found to be a poor prognostic marker in cancer. Moreover, our work has found that these satellite repeats can affect the local tumor microenvironment with implications for immunotherapies. This has led to a Phase II clinical trial of a nucleoside reverse transcriptase inhibitor (NRTI) 3TC in metastatic colorectal cancer, which demonstrating promising single agent activity in 25% of patients. We are now trying to identify the HSATII reverse transcriptase





This image represents a “blueprint” of a pancreatic cancer with distinct tumor gland phenotypes observed through single cell spatial analysis. These distinct tumor glands are represented here with different colors (yellow, orange, purple, and green), which reveals the spectrum of these glands in human primary pancreatic tumors.

and better understand the biological role of satellites in cancer progression and tumor immune response.

### Pancreatic Cancer Cellular Heterogeneity

The high lethality of pancreatic cancer results from an intrinsic ability to resist chemotherapy and the propensity to metastasize. The etiology of this behavior is multifactorial, but our group has identified cancer cell heterogeneity and plasticity as key elements of aggressive pancreatic cancer. Our initial work using a microfluidic device to isolate rare circulating tumor cells (CTCs) offered a window into understanding the metastatic cascade. These studies demonstrated the inherent heterogeneity of pancreatic CTCs and their ability to seed metastases through a partial epithelial mesenchymal transition (EMT) program. We have recently uncovered the importance of stromal cancer associated fibroblasts (CAFs) in inducing EMT single cell heterogeneity

consistent with phenotypes observed in CTCs and the plasticity of EMT phenotypes in the setting of chemoresistance and metastasis. Moreover, we defined pancreatic cancer intratumoral heterogeneity in discrete tumor glands using RNA-ISH and high content digital image analysis. We are now using spatial transcriptomic methods to fully characterize the relationship of tumor cell plasticity and CAF heterogeneity. In addition, this platform provides a strategy to understand the spatial relationship of these cell types important for pancreatic cancer pathogenesis. The understanding of the role of CAF phenotypes on pancreatic cancer EMT plasticity will provide new mechanistic insight in the drivers of cancer cell heterogeneity and CTC generation, identify biomarkers in predicting patient outcomes, and reveal novel therapeutic avenues targeting tumor cell microenvironment interactions.

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Porter RL, Magnus NKC, Thapar V, Morris R, Szabolcs A, Neyaz A, Kulkarni AS, Tai E, [...] Ferrone CR, Haber DA, and Ting DT. Epithelial to mesenchymal plasticity and differential response to therapies in pancreatic ductal adenocarcinoma. *PNAS* (2019); 116(52): 26835-26845.

Ligorio M\*, Sil S\*, Malagnon-Lopez J, Nieman LT, [...] Fernandez-Del Castillo C, Ferrone CR, Haas W, Aryee M†, Ting DT†. Stromal Microenvironment Shapes the Intratumoral Architecture of Pancreatic Cancer. *Cell* (2019); 178(1):160-175.e27. .

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## Shobha Vasudevan, PhD



### Vasudevan Laboratory

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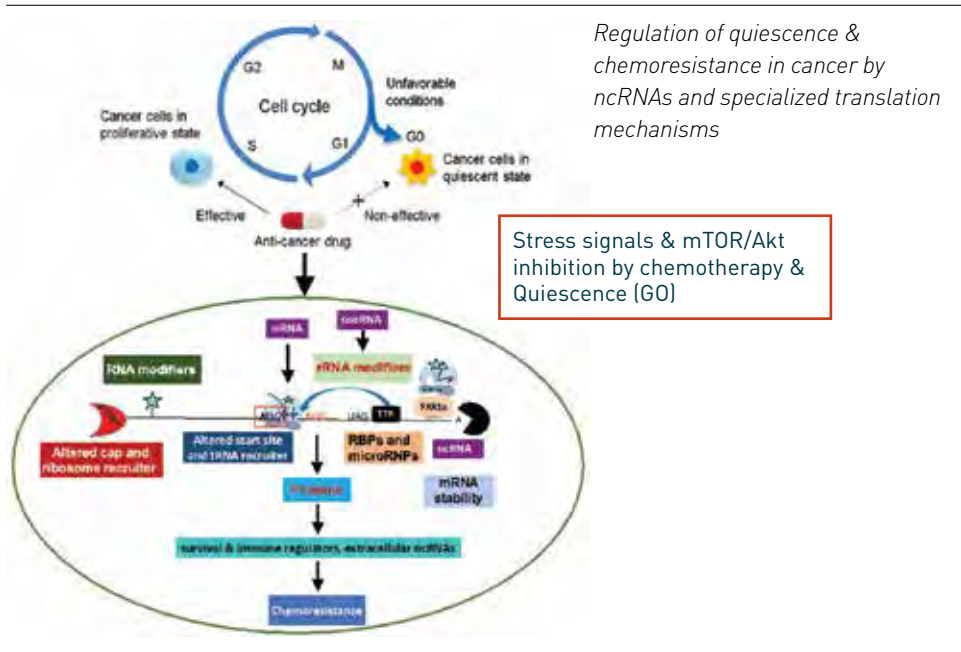
**The Vasudevan laboratory** focuses on the role of post-transcriptional mechanisms in clinically resistant quiescent cancer cells. Tumors demonstrate heterogeneity, harboring a small subpopulation that switch from rapid proliferation to a specialized, reversibly arrested state of quiescence that decreases their susceptibility to chemotherapy. Quiescent cancer cells resist conventional therapeutics and lead to tumor persistence, resuming cancerous growth upon chemotherapy removal. Our data revealed that post-transcriptional mechanisms are altered, with modification of noncoding RNAs, associated complexes and ribosomes. These control vital genes in cancer and are important for chemoresistance and persistence of quiescent cancer cells. The primary goal of our research is to characterize the specialized gene expression and their post-transcriptional regulators that underlie persistence of resistant cancer cells. A complementary focus is to investigate the modification of post-transcriptional regulators and their mechanisms in response to quiescent conditions and chemotherapy-induced signaling. Our goal is to develop a comprehensive understanding of the versatile roles of regulatory RNAs in cancer as a basis for early detection of refractory cancers and for designing new therapies.

Quiescent (G0) cells are observed as a clinically relevant population in leukemias and other tumors associated with poor survival. G0 is a unique, nonproliferative phase that provides an advantageous escape from harsh situations like chemotherapy, allowing cells to evade permanent outcomes of senescence, differentiation, and apoptosis in such tumor-negative environments. Instead, the cell is suspended reversibly in an assortment of transition phases that retain the ability to return to proliferation and contribute to tumor persistence. G0 demonstrates a switch to a distinct gene expression program, upregulating the expression of mRNAs and regulatory non-coding RNAs required for survival. Quiescence regulators that maintain the quiescent, chemoresistant state remain largely undiscovered.

Our studies revealed that specific post-transcriptional regulators, including AU-rich

elements (AREs), microRNAs, RNA-protein complexes (RNPs), ribosome factors and RNA modifiers, are directed by G0- and chemotherapy-induced signaling to alter expression of clinically important genes. AU-rich elements (AREs) are conserved mRNA 3'-untranslated region (UTR) elements. MicroRNAs are small noncoding RNAs that target distinct 3'UTR sites. These associate with RNPs, ribosome associated factors and their modifiers to control post-transcriptional expression of cytokines and growth modulators. Their deregulation leads to a wide range of diseases, including tumor growth, immune and developmental disorders.

We identified post-transcriptional effectors associated with mRNAs and noncoding RNAs by developing in vivo crosslinking-coupled RNA affinity purification methods to purify endogenous RNPs. Our recent studies revealed mechanistic changes in



Regulation of quiescence & chemoresistance in cancer by ncRNAs and specialized translation mechanisms

Stress signals & mTOR/Akt inhibition by chemotherapy & Quiescence (G0)

G0: uncovering inhibition of conventional translation and its replacement by non-canonical mechanisms that enable specific gene expression in G0 to elicit chemoresistance. These specialized mechanisms are driven by modifications of mRNAs, associated regulator RNAs and proteins, and ribosomes, which are induced in G0- and chemotherapy-induced signaling. These investigations reveal gene expression control by RNA regulators and non-canonical translation mechanisms that cause tumor persistence. Based on our data demonstrating altered RNPs, modifications, and specific translation in G0, we propose that transiently quiescent, chemoresistant subpopulations in cancers are maintained by specialized post-transcriptional mechanisms that permit selective gene expression, necessary for chemotherapy survival and tumor persistence. The primary goal of our research is to characterize the specialized gene expression program in quiescent, chemoresistant cancers, and its underlying post-transcriptional and translational regulators that contribute to G0 and tumor persistence. A concurrent focus is to investigate RNA modifications and mechanisms of noncoding RNAs, RNPs, and ribosomes in G0 that contribute to chemoresistance, using cancer

cell lines, in vivo models, patient samples, and stem cells. An important direction is to identify unique G0-specific RNA markers and develop novel therapeutic approaches to block selective translation in G0, of targets that encode for critical immune and tumor survival regulators—and thereby curtail chemoresistance.

The lab has four core directions:

1. To characterize microRNAs and noncoding RNAs, and their cofactors that control the expression of tumor survival regulators, using in vivo biochemical purification methods.
2. To investigate the mechanisms of post-transcriptional and translational regulation by noncoding RNAs, RNPs, and ribosome regulators.
3. To elucidate the modification and regulation of key mRNAs and ribosomes, by G0- and chemotherapy-induced signaling.
4. To develop therapeutic approaches that interfere with selective translation, and manipulate interactions of noncoding RNAs with targets that encode for critical tumor survival regulators. These studies should lead to a greater understanding of the versatile role of post-transcriptional mechanisms in cancer persistence and to novel approaches in RNA-based therapeutics.

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## Alexandra-Chloé Villani, PhD



### Villani Laboratory

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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 answering several key questions: Do we know all existing blood immune cell subsets? How do circulating immune cells mirror those in tissue microenvironment in the context of health and disease? Can we identify targets that would improve immunotherapy efficacy by 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.

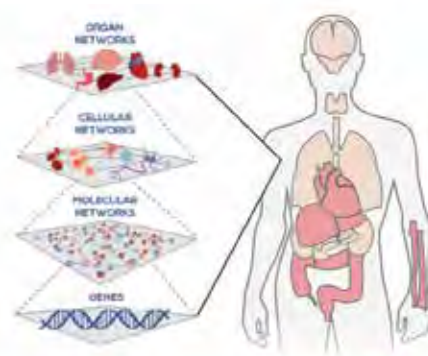
### Leveraging single-cell ‘omics’ to unravel new insights into the human immune system

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) analysis provides an unbiased, data-driven way of systematically detecting cellular states that can reveal diverse simultaneous facets of cellular identity, from discrete cell types to continuous dynamic transitions, which cannot be defined by a handful of pre-defined markers or for which markers are not yet known. We combine scRNAseq

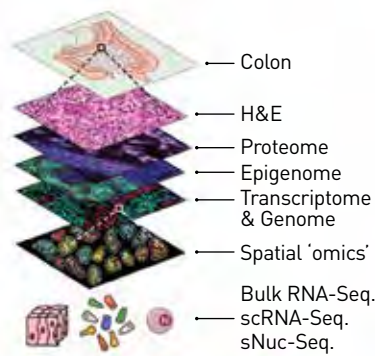
strategies together with in-depth follow-up profiling, phenotypic and functional characterization of prospectively isolated immune subsets defined by scRNAseq data to overcome such limitations. Our analyses of the human blood mononuclear phagocyte system resulted in the identification of six dendritic cell (DC), four monocyte, and one DC progenitor populations, thus revising the taxonomy of these cells (*Villani et al., Science 2017*). Noteworthy, five of these subsets had never been reported, illustrating the power of our integrative strategies to reopen the definition of these cell types. Our study highlighted the value of embarking on a comprehensive Human Cell Atlas initiative and offered a useful framework for conducting this kind of analysis on other cell types and tissues. We are currently contributing to the immune cell atlas effort by charting at high-resolution the human blood cellular landscape, and are studying paired human tissues with blood to better



## Different scales



## Different measurements



**Pre-immunotherapy**  
**Post-immunotherapy**  
**(before irAEs)**

**At irAE diagnosis** (pre steroid)

- Blood, serum, plasma
- Relevant body fluids
- Biopsy affected tissue(s)

**Post-steroids;** collection until recovery

- Blood, serum, plasma
- Body fluids (e.g., urine, CSF, SF)

**Collect if patient relapse or develop other irAEs**

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

establish how circulating immune cells mirror those in tissue microenvironment in the context of health and disease.

We also continuously support development of in-depth expertise in single-cell 'multi-omics' experimental and computational strategies (Ding, *Nat Biotechnol* 2020; Li, *Nat Methods* 2020; Tukiainen, Villani, *Nature* 2017; Ranu, Villani, *Nucleic Acid Res* 2019; Villani, *Methods Mol Biol* 2016), and its application to study immune cells infiltrates in healthy, tumor lesions and inflamed tissue (Izar, *Science* 2016; Sade-Feldman, *Cell* 2019; Di Pilato, *Nature* 2019; Olah, *Nat Commun* 2018; Balan, *Cell Rep* 2018; Popescu, *Nature* 2019; Smillie, *Cell* 2019; Abbas, *Nat Immunol* 2020; Delorey, *Nature* 2021).

## 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 being limited by treatment-induced

irAEs resembling autoimmune diseases that are affecting nearly every organ system. With ICI becoming first- and second-line of cancer treatments, it is expected that irAE incidence will continue rising and limit immunotherapy efficacy unless we find solutions. Our multi-disciplinary translational group of scientists and clinicians are working towards developing a better understanding of the biological players and underlying molecular and cellular mechanisms involved in driving irAEs by directly studying patient blood and matched affected tissue samples using a range of systems immunology, immunogenomics and single-cell 'omics' strategies (Zubiri, *J Immunother Cancer* 2021; Thomas, *BioRxiv* 2021). Our translational research program may result in identifying putative cellular components and mechanisms that could be (i) targeted in a 'primary-prevention' approach to prevent irAE development, and/or (ii) targeted after onset of irAEs, without reducing the efficacy of the immunotherapy.

## Selected Publications:

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†Co-senior authorship

## Lee Zou, PhD



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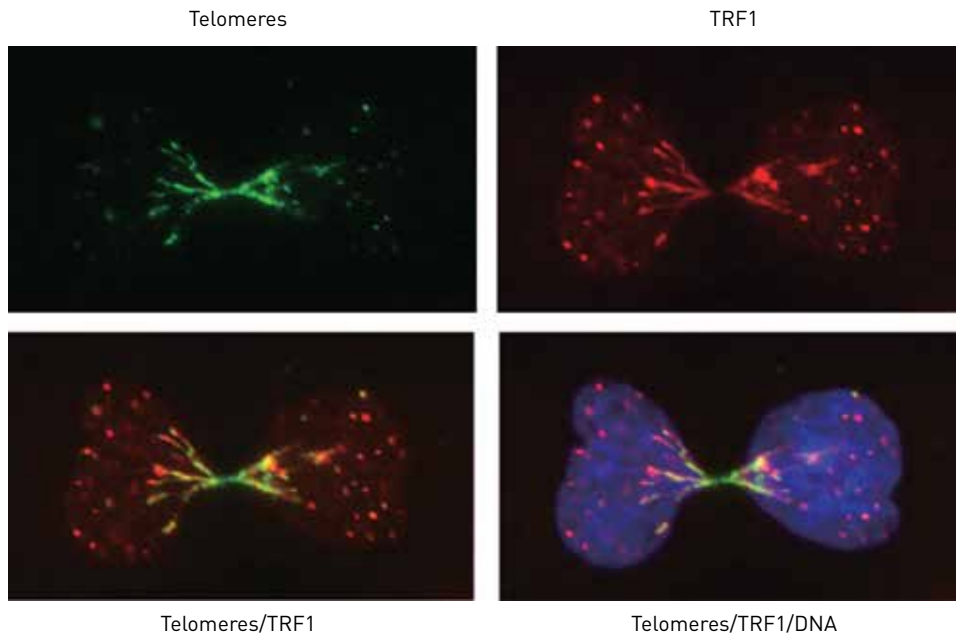
Cancer is a complex disease driven by genetic and epigenetic alterations in the genome. To prevent these detrimental alterations, cells have evolved an intricate signaling network, called the DNA damage checkpoint, to detect and signal problems in the genome. During cancer development, the activation of oncogenes and loss of tumor suppressors leads to genomic instability, rendering cancer cells increasingly dependent upon specific DNA repair and checkpoint signaling proteins to survive. **The Zou laboratory** is particularly interested in understanding how the checkpoint detects DNA damage and genomic instability, and how the checkpoint can be targeted in cancer therapy. Our current studies are focused on understanding the molecular mechanisms by which different types of oncogenic events give rise to replication stress and genomic instability. Furthermore, we are developing new strategies to exploit the genomic instability and checkpoint addiction of different cancer cells in targeted cancer therapy.

### Sensing of DNA Damage, Replication Stress, and Genomic Instability

ATM and ATR are two master checkpoint kinases in human cells. In particular, ATR is the key responder to a broad spectrum of DNA damage and DNA replication problems. We are especially interested in the mechanisms by which ATR is activated by replication stress and its functions in the replication stress response. Our recent studies have revealed that ATR plays an important role in the cellular responses to R loops, which arise from stable DNA:RNA hybrids during transcription. We found that ATR is activated by the collisions between replication forks and R loops, and it suppresses R loop-induced genomic instability through multiple mechanisms. We are extending our investigation to elucidate how ATR protects replication forks at R-loops and how ATR stabilizes the genome in response to aberrant R-loops.

### Functions of ATR in regulating DNA Repair, Telomeres, Centromeres and the Cell Cycle

The ATR checkpoint plays a key role in regulating and coordinating DNA replication, DNA repair, and cell cycle transitions. Recently, we have discovered a surprising function of ATR in mitosis. We have shown that ATR is localized to centromeres in mitosis, where it is activated by centromeric R loops. The activation of ATR at centromeres is critical for faithful chromosome segregation, thus revealing the unexpected importance of ATR in suppressing chromosomal instability (CIN). We have also developed new assays to understand how the alternative lengthening of telomere (ALT) pathway, which is regulated by ATR, is activated at telomeres. These new assays have helped us establish the framework of the ALT pathway for the first time, and uncovered the key mechanisms by which the ALT pathway is temporarily and spatially regulated during the cell cycle.



**Telomeric bridges in an ALT+ cancer cell lacking the BLM helicase.** *Alternative lengthening of telomere (ALT) is a recombination-based mechanism to extend telomeres in cancer cells. We find that the BLM helicase is critical for resolving telomere recombination intermediates in ALT+ cancer cells. In the absence of BLM, unresolved recombination intermediates at telomeres result in chromosomal bridges in mitosis. Green: telomeres; Red: the telomere-binding protein TRF1; Blue: DNA.*

*Images were generated by Dr. Jiamin Zhang in the Zou lab!*

### Functions of transcription and RNA in DNA repair

We are interested in the impacts of RNAs, including coding and non-coding RNAs, on genomic integrity. We recently discovered that RNA transcripts stimulate homologous recombination by forming a novel intermediate that contains both DNA:DNA and RNA:DNA hybrids. This intermediate, which we dubbed DR-loop, enhances the function of RAD51 in donor DNA. Our results demonstrate for the first time that RNA transcripts directly participate in DNA recombination, opening a new avenue to study the roles of RNA in DNA repair. These new findings will significantly change the current view of the functions of RNAs in DNA repair, providing new opportunities for cancer therapy.

### Cancer Genomics, Tumor evolution and Targeted Cancer Therapy

During the evolution of tumors, cancer cells acquire mutations through a variety

of mechanisms. We recently discovered that APOBEC3A/B proteins, two cytidine deaminases that are aberrantly expressed in multiple types of cancers, induce DNA replication stress and render cancer cells susceptible to ATR inhibition. Working with the team of Dr. Michael Lawrence, we find that APOBEC3A prefers substrate sites in DNA hairpins, leading to the discovery of passenger hotspot mutations in cancer. Furthermore, we find that the splicing factor mutations associated with myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML) induce R loops and trigger an ATR response. Cells that express these splicing factor mutants are sensitive to ATR inhibitors, providing a new strategy for the treatment of MDS and possibly other malignancies associated with RNA splicing defects.

### Selected Publications:

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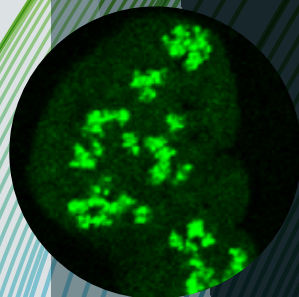
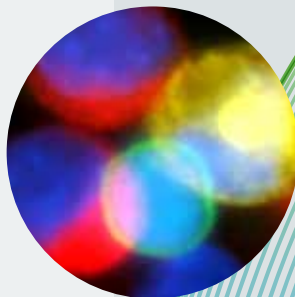
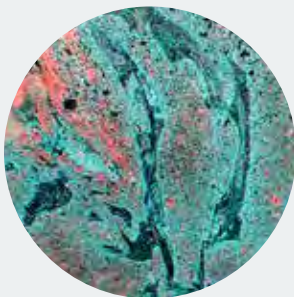
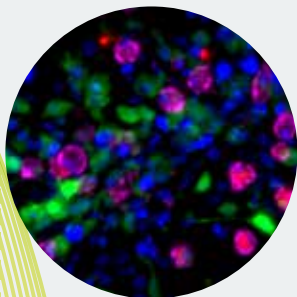
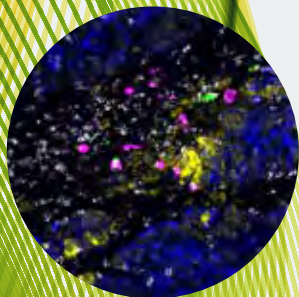
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