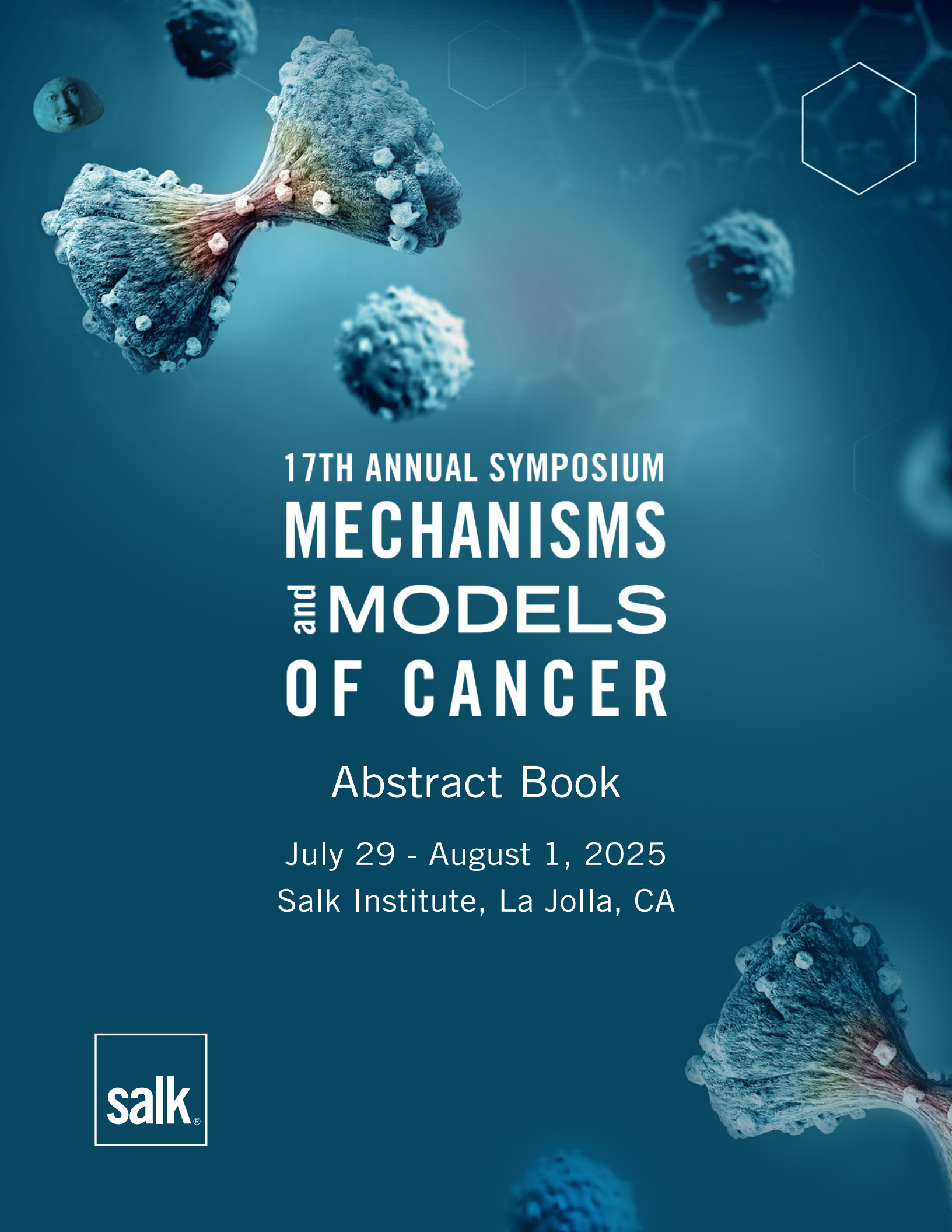

17TH ANNUAL SYMPOSIUM

MECHANISMS and MODELS OF CANCER

Abstract Book

July 29 - August 1, 2025

Salk Institute, La Jolla, CA

salk®

Abstracts of papers presented at

Mechanisms and Models of Cancer

July 29 – August 1, 2025

Organized by:

Dannielle Engle
Salk Institute for Biological Studies

Diana Hargreaves
Salk Institute for Biological Studies

Nikhil Joshi
Yale University

Reuben Shaw
Salk Institute for Biological Studies

Mara Sherman
Memorial Sloan Kettering Cancer Center

We are grateful to all those who contributed to
the organization of the meeting and especially thank
Sophia Pinto, Event Planner
Tess Mengel, Manager Salk Events

We thank our sponsors for their generous support

CORNING

Qkine

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SCHEDULE OF EVENTS

Date	Time	Session	Chairs	Pages
Tuesday July 29	4:00 p.m.	Session 1: **Metabolic signaling**	Liron Bar-Peled, Anna Trimble, Shruti Naik, Rushika Perera, Kamini Singh	v
		Dinner		
	7:10 p.m.	Session 1: **Metabolic signaling**	Krushna Patra, Reuben Shaw	v
		Welcome party		
Wednesday July 30	9:00 a.m.	Session 2: **Genetics and epigenetics**	Donita Brady, Shandon Amos, Caterina Bartolacci, Yael David, Hannah Rasby, Liling Wan, Brandon Murphy, Mallika Singh	vi - vii
	12:30 p.m.	Lunch and Poster Session 1		xiv - xvii
	2:00 p.m.	Session 3: **Tumor evolution**	Kornelia Polyak, Jennifer Loza, Pablo Tamayo, Sandra McAllister, Aria Vaishnavi, Ludmil Alexandrov	viii
		Reception/Dinner		
Thursday July 31	9:00 a.m.	Session 4: **Tumor macroenvironment**	Julio Aguirre-Ghiso, Shi Li, Bharti Garg, Cyrus Ghajar, Sheila Stewart, Nesli Dolcen, Florian Karreth	ix
	12:10 p.m.	Lunch and Poster Session 2		xviii - xxi
	2:00 p.m.	Session 5: **Plasticity of cancer cells and their niche**	Tuomas Tammela, Henry Arnold, Debadrita Bhattacharya, Cosimo Commisso, Peter Westcott, Shiri Gur-Cohen	x
		Reception/Dinner		
Friday August 1	9:00 a.m.	Session 6: **Immunity, inflammation, and cancer**	Christine Moussion, Melissa Reeves, Alex Jaeger, Michel DuPage, Yvonne Chen, Zeda Zhang, Helen McRae, Mikala Egeblad	xi - xii
	12:40 p.m.	Lunch		
	1:40 p.m.	Session 7: **Last Hurrah!**	Kailash Chandra Mangalhara, Yuwenbin Li, Suzanne Dufresne, Jasper Hsu, Silvio Gutkind	xiii
		Reception		

TUESDAY, JULY 29 - 4:00 P.M.

SESSION 1: METABOLIC SIGNALING

1 Liron Bar-Peled
Massachusetts General Hospital/Harvard Medical School
Identification of druggable and redox vulnerabilities in cancer

2 *Anna Trimble, Casie Kubota, Elaine Zhao, Maureen Ruchhoeft, Jonathan Weitz, Andrew Lowy, Dannielle Engle, and Christian Metallo
Salk Institute for Biological Studies
Using *ex vivo* tissue slice culture to elucidate the role of the tumor microenvironment in PDAC tumor lipid metabolism

Shruti Naik
Mount Sinai
TBD

3 Rushika M. Perera
University of California, San Francisco
Uncovering lysosome dependent mechanisms of cellular adaptation in cancer

4 *Jacky Chuen, Ankita Shrivastava, Eric Nels Pederson, Trang Uyen Nguyen, Shivangi Pande, Ana Ruiz Toribio, Nicolas Lecomte, Jerry Melchor, John C. McAuliffe, Paul M Grandgenett, Vinagolu K. Rajasekhar, Christine A. Iacobuzio-Donahue, Zhengqing Ouyang, and Kamini Singh
Albert Einstein College of Medicine
Decoding immune recognition in pancreatic cancer: Through the lens of the ribosome

5 *Krushna C. Patra, Grant A. Hagedorn, Jackson C. Spieser, Sierra Kanemoto, Jake Valentine, Noriko Hirai, and Yuki Sato
University of Cincinnati
Metabolic remodeling of mitochondrial forms supports GNAS ($G\alpha_s$) mutant pancreas cancer growth

Reuben Shaw
Salk Institute for Biological Studies
TBD

*Short Talk

WEDNESDAY, JULY 30 - 9:00 A.M.

SESSION 2: GENETICS AND EPIGENETICS

6 Donita Brady

University of Pennsylvania

Unlocking the chemical space of cancer: A chemoproteomic strategy to map protein function and therapeutic response

7 *Shandon Amos, Chichao Chen, Yichen Xiang, Varun Narenda, Keisuke Motoyama, Grace Johnson, Natalie O'Hearn, Arianna Arroyo-Ortega, Oindrila Sarkar, Ziyang Ye, Yu-Jui Ho, Francisco J. Sánchez-Rivera, Angela Koehler, Scott Lowe, and Yadira Soto-Feliciano

Massachusetts Institute of Technology

Epigenetic reactivation of neutrophil differentiation to target acute leukemia

8 *Cristina Andreani, Caterina Bartolacci, Nicola Sargentoni, Margherita Melegari, Lorenzo Luciani, Agnese Marucci, Roberta Galeazzi, Gina DeNicola, Jessica Kilgore, Noelle Williams, Stefano Berto, Massimiliano Gaetani, Prasad Pattabhi, Sagid Osman, Stefania Pucciarelli, Rossana Galassi, and Pier Paolo Scaglioni

University of Cincinnati

Thioredoxin reductase 1 inhibition triggers ferroptosis in KRAS-independent lung cancers

9 Yael David

Memorial Sloan Kettering Cancer Center

Targeting a new metabolism-epigenetic axis towards improved CAR T therapy in multiple myeloma

*Short Talk

WEDNESDAY, JULY 30 - 9:00 A.M.
SESSION 2: GENETICS AND EPIGENETICS

*Hannah Rasby
Corning Life Sciences
TBD

10 Liling Wan
University of Pennsylvania
Chromatin-associated condensates in gene regulation and cancer

11 *Brandon Murphy, Haley Hunt, Sage Lichfield, and Martin McMahon
University of Utah
Elucidating the mechanisms sustaining DTPCs following MAPKi in LUAD

12 Mallika Singh
Revolution Medicines
Targeting the oncogenic state of RAS with tri-complex inhibitors

*Short Talk

WEDNESDAY, JULY 30 - 2:00 P.M.

SESSION 3: TUMOR EVOLUTION

13 Kornelia Polyak
Dana-Farber Cancer Institute
Breast tumor evolution

14 *Jennifer Loza, Ishan Bansal, Brian Hunt, Kelli Connolly, Srividhya Venkatesan, and Nikhil Joshi
Yale University
Exploring the impact of neoantigen expression on lung tumor development

15 *Pablo Tamayo and William Kim
University of California, San Diego
Computational modeling of cancer as an adaptive emergent complex system

16 Sandra S McAllister, PhD
Harvard University
Overcoming age-related immune dysfunction and chemoresistance in triple-negative breast cancer

17 * Melanie A. Dacheux, Lea Montegut, Cheng Pei Wu, James McEvoy May, Dylan De Bellis, Emilia Scalco Wachter, Miriam Merad, Dani Dixon, Tony Hunter, and Aria Vaishnavi
University of Texas MD Anderson Cancer Center
Unraveling the molecular mechanisms of radon and air pollution-induced lung cancers with novel mouse models

18 Ludmil B Alexandrov
University of California, San Diego
Geographic and age-related variations in mutational processes in colorectal cancer

*Short Talk

THURSDAY, JULY 31 - 9:00 A.M.
SESSION 4: TUMOR MACROENVIRONMENT

19 Julio A. Aguirre-Ghiso, Luis Valencia-Salazar, Anna Adam-Artigues, Lucia Petriz Otaño, Rama Kadamb, Lornella Seeneevassen, Deisy Segura Villalobos, Deepak Singh, Nyima Sherpa, and Lionel Colon
Albert Einstein College of Medicine
Disseminated cancer cell dormancy: Molecular triggers of entry and exit

20 *Shi Li
Fred Hutchinson Cancer Center
Discovery of astrocytic checkpoints regulating disseminated tumor cell survival

21 *Bharti Garg, Evangeline Sari Mose, Edgar Esparza, Jay Patel1, Kevin Gulay, Rithika Medari, Sarah Sass, Alexei Martsinkovskiy, Asmina Courelli, Carrie Bishop, Gisselle Gonzalez, Adam Engler, Parag Katira, Vivien Ileana Maltez, Herve Tiriac, and Andrew M. Lowy
University of California, San Diego
Actin cytoskeleton dynamics in tumor cells mediate Immune-suppressive microenvironment and sensitize pancreas tumors to PD-1 blockade therapy

22 Cyrus Ghajar
Fred Hutch Cancer Center
Understanding and overcoming the numbers game that underlies disseminated tumor cell immune evasion

23 Sheila Stewart
Washington University School of Medicine in St. Louis
Senescent stromal changes drive breast tumorigenesis and contribute to therapy-induced bone loss

24 *D. Nesli Dolcen, Haiqing Xu, Laura Andrejka, Daniel Lee, Dmitri A. Petrov, and Monte M. Winslow
Stanford University
Genetic dissection of metabolic tumor suppression *in vivo*

25 *Kaizhen Wang and Florian A. Karreth
H. Lee Moffitt Cancer Center
Non-canonical RNA binding of the MYBL2 transcription factor nucleates transcriptional condensates and promotes melanoma

*Short Talk

THURSDAY, JULY 31 - 2:00 P.M.

SESSION 5: PLASTICITY OF CANCER CELLS AND THEIR NICHE

26 Tuomas Tammela and colleagues
Memorial Sloan Kettering Cancer Center
Functional and molecular interrogation of a malignant high-plasticity cell state in carcinomas

27 *Henry U. Arnold, Gabriela Fort, Soledad Camolotto, Kayla O'Toole, Rushmeen Tariq, Anna Waters, Katherine Gillis, and Eric L. Snyder
University of Utah
Opposing lineage specifiers induce a protumor hybrid identity state in lung adenocarcinoma

28 *Debadrita Bhattacharya, Sarah Groves, Cameron Walker, Yamina Chtourou, Marcus Hsieh, Michael Angelo, Vito Quaranta, and Julien Sage
Stanford University
Investigating transcriptional regulators of intratumoral heterogeneity in small cell lung cancer

29 Cosimo Commisso
Sanford Burnham Prebys Medical Discovery Institute
Reprogramming the stroma: Metabolic plasticity and aging in pancreatic tumor evolution

30 *Yihan Qin, Alex Cicala, Daniel Zhang, Nischal Bhandari, Nikita Persaud, Emma Arboleda, Zakeria Aminzada, Colin McLaughlin, Song Han, Rodrigo Romero, Claire Regan, William Rideout III, Santiago Naranjo, Karen Yee, Jonathan Preall, Semir Beyaz, Sepideh Gholami, Zhen Zhao, Tyler Jacks, and Peter Westcott
Cold Spring Harbor Laboratory
Tumor cell state and niche remodeling during benign-to-malignant transition in the colon

31 Shiri Gur-Cohen
University of California, San Diego
Lymphovascular niches as hubs of cancer plasticity and evolution

*Short Talk

FRIDAY, AUGUST 1 - 9:00 A.M.

SESSION 6: IMMUNITY, INFLAMMATION, AND CANCER

Christine Moussion
Genentech
TBD

32 *Robert Letchworth, Savannah Hughes, Abigail Keku, Emilio Cortes-Sanchez, Piyush Chaudhary, Joshua Tay, Matthew Lieberman, and Melissa Reeves
University of Utah
Tumor cells drive the spatial organization of intratumoral immune cells and chemokine landscapes in heterogeneous tumors

33 *Emily Brennan, Christopher Polera, Emma Adhikari, Andrew Weeden, Emily Paul, Anika Ali, Andrew Deonarine, Bin Fang, Victoria Izumi, John Koomen, Paul Stewart, and Alex Jaeger
Moffitt Cancer Center
KP/RiboMHC: A novel mouse model for proteogenomic analysis of tumor-specific antigen presentation *in vivo*

Michel DuPage
University of California, Berkley
TBD

34 Yvonne Y. Chen
University of California, Los Angeles
Engineering multi-pronged CAR-T cells for cancer therapy

35 *Zeda Zhang, Yu-Jui Ho, Xin Fang, Clemens Hinterleitner, Sascha Haubner, Friederike Kogel, Edwin Pratt, Marguerite Li, Wei Luan, Minseo Kim, Elif Ozcelik, Jose Reyes, Qingwen Jiang, Stella V. Paffenholz, Sha Tian, Eric Chan, Eric Rosiek, Elisa de Stanchina, Paul B. Romesser, Britta Weigelt, Judith Feucht, Dmitriy Zamarin, Sohrab Shah, Jason Lewis, Corina Amor, Jorge Mansilla-Soto, MSK Clinical Teams, Aveline Fillio, Michel Sadelain, and Scott Lowe
Memorial Sloan Kettering Cancer Center
Targeting dysregulated wound healing programs in cancer and fibrosis with immune engineering

*Short Talk

FRIDAY, AUGUST 1 - 9:00 A.M.

SESSION 6: IMMUNITY, INFLAMMATION, AND CANCER

36 *Helen McRae and Diana Hargreaves
Salk Institute for Biological Studies
Epigenetic control of tumor associated macrophages – targeting the BAF nucleosome remodeling complex

37 Mikala Egeblad
Johns Hopkins University
Neutrophils drive vascular occlusion, pleomorphic tumor necrosis, and metastasi

*Short Talk

FRIDAY, AUGUST 1 - 1:40 P.M.
SESSION 7: LAST HURRAH!

38 *Kailash Chandra Mangalhara, Gladys Rojas, Pau Bernat Esparza Moltó, Sagnika Ghosh, and Gerald Shadel
Salk Institute for Biological Studies
Mitochondrial complex II inhibition promotes tumor inflammation

39 *Yuwenbin Li, Morgan Truitt, Daniel Cao, Jonathan Zhu, Yang Dai, Mariel Burquez-Escobedo, Gaoyang Liang, Michael Downes, Annette Atkins, Ruth Yu, and Ronald Evans
Salk Institute for Biological Studies
Stromal education of pancreatic cancer cells drives an NFκB-mediated immune evasion program

40 *Suzanne Dufresne, Ramya S Kuna, Kristiana Wong, Anvita Komarla, Angelica Rock, Joel Rosada-Encarnación, Celina Shen, Payel Mondal, Louis R Parham, Fabiana Izidro Layng, Kristina L. Peck, Alexandra Fowler, Andrew M. Lowy, Dannielle Engle, Herve Tiriac6, Reuben Shaw, Nicholas Cosford, Christian Metallo, and Christina Towers
Salk Institute for Biological Studies
Leveraging autophagy and pyrimidine metabolism to target pancreatic cancer

41 *Jasper Hsu, Hyemin Song, Satoshi Ogawa, Kristina Peck, Tae Gyu Oh, Jonathan Weitz, Chelsea Bottomley, Kassidy Curtis, McKenna Stamp, Shira Okhovat, Angelica Rock, Michael Downes, Ronald Evans, Andrew Lowy, Herve Tiriac, and Danielle Engle
Salk Institute for Biological Studies
CA19-9 induces microenvironment remodeling and promotes immunosuppression in pancreatic ductal adenocarcinoma

42 J. Silvio Gutkind, PhD
University of California, San Diego
Understanding precancer to cancer transition at single-cell resolution: The Hippo in the room

WEDNESDAY, JULY 30 - 12:30 P.M.
POSTER SESSION 1

44 Valentin Barthet, Clemens Hinterleitner, Hailey Goldberg, Almudena Chaves-Perez, Kristen Vogt, Stephen Ruiz, Ana Perea, Xiang Li, Yu-Jui Ho, Daniel Heller, and Scott Lowe

Memorial Sloan-Kettering Cancer Center

Targeting senescent cells with precision: A nanoparticle approach to combat fibrosis and enhance cancer immunotherapy

45 Jason E. Chan, Chun-Hao Pan, Jonathan Rub, Klavdija Krause, Emma Brown, Carleigh Sussman1, Zeda Zhang, Hannah Styers, Gary Guzman, Griffin Hartmann, Zhuxuan Li, Xueqian Zhuang, Scott W. Lowe, Doron Betel, Yan Yan, and Tuomas Tammela

Memorial Sloan Kettering Cancer Center

Functional genomics uncovers a critical role for canonical NF-kB to mediate a high-plasticity cell state in lung adenocarcinoma

46 Brayden Chin, Nancy Leon-Rivera, and Dr. Teresa Monkkonen

San Diego State University

Impacts of inhibition of endothelial cell autophagy on tumorigenesis in breast cancer

47 Rebecca Chinn, Bryan Rinde, Jaroslav Slamecka, Heidi Cook-Andersen, Mana Parast, and Christian Metallo

Salk Institute for Biological Studies

Atypical flux through polyunsaturated lipid pathways influence pluripotency and metabolism of stem cells

48 Peter Dib, Andrew Van Praagh, Paul Ballieu, Ali Bahadur, Kristin Granlund, Saaussan Madi, Mark Mattingly, Todd Sasser, Dianne Begemann, and Fallon Noto

Bruker Preclinical Imaging

A novel multimodal animal cradle system facilitates optical, PET, µCT, and MRI co-registrations of a metastatic, colorectal cancer syngeneic mouse model

49 Joel Encarnacion-Rosado, Suzanne Dufresne, Alec C. Kimmelman, and Christina Towers

Salk Institute for Biological Studies

Dissecting the cell-autonomous and non-autonomous mechanisms of adaptation to autophagy inhibition in pancreatic cancer

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50 Headtlove Essel Dadzie, Yangsook Song Green, and Eric Snyder MD, PhD
University of Utah
HNF4α controls gastric identity and KRAS^{G12D} inhibitor response in Invasive Mucinous Adenocarcinoma (IMA)

51 Emily Fennell, Mack Reynolds, Shrikaar Kambhampati, and Christian Metallo
Salk Institute for Biological Studies
Metabolic tracing to identify critical reactions in nucleic acid homeostasis

52 Makenzie N. Fourman, Sajad A. Wani, Nina Lazic, Patrick M. Krause, and Amanda R. Wasylishen
University of Cincinnati
Delineating tumor suppressive function of Men1 in the exocrine pancreas

53 Linnea Hases, Sihao Liu, Satoshi Ogawa, Gia H. Quach, Mingxiao He, Jonathan Zhu, Nidhi Jyotsana, Morgan Truitt, Weiwei Fan, Yang Dai, Annette R. Atkins, Ruth T. Yu, Michael Downes, and Ronald M. Evans
Salk Institute for Biological Studies
Targeting protein fatty acylation to inhibit colorectal cancer growth

54 Araceli Herrera Morales, Kassidy Curtis, Vasiliki Pantazopoulou, and Dannielle Engle
Salk Institute for Biological Studies
Establishing gemcitabine resistant organoid models of pancreatic cancer

55 Brian G Hunt, Julie F Cheung, Shudipto Wahed, Elaine Cheng, Kelli A. Connolly, Srividhya Venkatesan, Jennifer Loza, Ishan Bansal, Eric Fagerberg, Emily Kessler, Clémence Riffard, Jessica Buck, John Attanasio, Emily Borr, Wei Wei, Ivana William, Brittany Fitzgerald, and Nikhil S. Joshi
Yale School of Medicine
Distinct T cell functions enable efficient immunoediting and prevent tumor emergence in developing sarcomas

56 Julia A. Ju, Keyata N. Thompson, Michele I. Vitolo, and Stuart S. Martin
University of Maryland School of Medicine
Microtentacle-mediated heterotypic clustering of tumor cells and neutrophils in breast cancer metastasis

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57 Nidhi Jyotsana, Nandhana Nair, Gabriela Estepa, Daniel Cao, Morgan L Truitt, Weiwei Fan, and Ronald M Evans
Salk Institute for Biological Studies
Targeting undruggable drivers using lipid nanoparticle-RNA delivery to prevent pancreatic cancer

58 Elham Khosrowabadi and Cosimo Commisso
Sanford Burnham Prebys Medical Discovery Institute
Rewiring of intracellular pH and glycosylation by oncogenic Kras

59 Jung Yun Kim, Anupriya Singhal, John Guthrie, Hannah Styers, Qianzi Li, Leslie Christina, and Tuomas Tammela
Memorial Sloan Kettering Cancer Center
SOX11 regulates basal cell identity and plasticity in pancreatic ductal adenocarcinoma

60 Siva K. Kolluri, Prasad R. Kopparapu, Martin C. Pearce, Christiane V. Löhr, Cathy Duong, Hyo Sang Jang, Shanthakumar Tyavanagimatt, Edmond F. O'Donnell, Arnold C Satterthwait, Xiao-kun Zhang, and Harikrishna Nakshatri
Oregon State University
Small molecule Bcl-2 functional converters

61 Anvita Komarla and Christina Towers
Salk Institute for Biological Studies
Identifying novel mechanisms of mitochondrial quality control in cancer cells

62 Evodie Koutouan, Ayano Niibe, Rory L. Smoot, and Elena B. Pasquale
Sanford Burnham Prebys Medical Discovery Institute
EPHA2 canonical and non-canonical signaling in cholangiocarcinoma development and progression

63 Klavdija Krause, Jason E. Chan, Chun-Hao Pan, Jonathan Rub, Gary Guzman, Emma Brown, Xueqian Zhuang, Zhuxuan Li, Carleigh Sussman1, Hannah Styers, and Tuomas Tammela
Memorial Sloan Kettering Cancer Center
Plasminogen activation drives plasticity in lung cancer

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64 Casie S Kubota, Maureen L. Ruchhoeft, Kristina L. Peck, Dannielle D. Engle, and Christian M. Metallo

Salk Institute for Biological Studies

Investigating adaptive metabolic responses to RAS inhibition in pancreatic cancer

65 Brayden Chin, Nancy León-Rivera, and Teresa Monkkonen

San Diego State University

Impact of endothelial cell autophagy inhibition on tumorigenesis

THURSDAY, JULY 31 - 12:10 P.M.
POSTER SESSION 2

66 Alejandro Lillo, John Chen, Tanaya Roya, Kalina Hristova, and Elena B. Pasquale
Sanford Burnham Prebys Medical Discovery Institute
Eph receptor heterointeractions in cancer cell signaling

67 Yingluo Liu, Xinyi Wang, Nishta Krishnan, Timothy Hsiao, Yichun Ji, Marcos G. Teneche, Peter D. Adams, Elina Zuniga, Susan M Kaech, Liangfang Zhang, and Gen-Sheng Feng
University of California, San Diego
Efficacious suppression of primary and metastasized liver tumors by polyIC-loaded lipid nanoparticles

68 Sofia Lombardi, Meenakshi Sudhakaran, Tristan Courau, Matthew F. Krummel, and Kelly Kersten
Sanford Burnham Prebys Medical Discovery Institute
Dissecting the role of T_{EX}-derived CCL3 in antitumor immunity

69 Telma R. Lourenço, Justin Wang, Lei Jiang, Ze Liu, and Xiang-Lei Yang
Scripps Research Institute
Non-canonical function of serine tRNA synthetase (SerRS) in inhibiting metastasis in breast cancer

70 Mona Foth, Wontak Kim, Kayla O'Toole, Brandon Murphy, Montserrat Justo Garrido, Sanjana Boggaram, Phaedra Ghazi, Euan Brennan, Tate Shepherd, Yingyun Wang, Jennifer Roth, Matthew Rees, Melissa Ronan, Jingjing Jiang, Emilio Cortes-Sanchez, Siwen Hu-Lieskovan, Conan Kinsey, Jeffery Russell, Ignacio Garrido-Laguna, Matthew Holderfield, Mallika Singh, and Martin McMahon
University of Utah
Genetic determinants of sensitivity or resistance to pan-RAS(ON) inhibitors in NRAS-driven melanoma

71 Benjamin Minden-Birkenmaier, Ruishan Wang , Spencer Douglas, Srishti Tiwari, and Myriam Labelle
St. Jude Children's Research Hospital
ZBTB18 restricts tumor cell pliancy, reducing metastasis via macrophage attack

THURSDAY, JULY 31 - 12:10 P.M.
POSTER SESSION 2

72 Christopher W. Murray, Hector M. Galvez, Ruoxi Wang, Karl A. Wessendorf Rodriguez, Sandy Lee, Fernando Lopes, Aubrey N. Michi, Jose A. Sandoval, Antonio F.M. Pinto, Maureen L. Ruchhoeft, Yuning J. Tang, Nianfei Xian, Monte M. Winslow, Michael La Frano, David Shackelford, Christian M. Metallo, Alan Saghatelian, and Reuben J. Shaw
Salk Institute for Biological Studies
A lipid metabolic checkpoint in the progression to lung adenocarcinoma

73 Kha The Nguyen, Tianyu Zhao, and Laura D. Attardi
Stanford University School of Medicine
Inhibition of the epitranscriptomic writer METTL3 is a therapeutic vulnerability specific for *p53*-deficient Pancreatic Ductal Adenocarcinomas

74 Walter A. Orellana, Sydney N. Larsen, Katherine Gillis, and Eric L. Snyder
University of Utah
MEK/ERK signaling and lineage specifying transcription factors coordinately regulate cell identity in lung adenocarcinoma and pancreatic ductal adenocarcinoma

75 Chun-Hao Pan, Jason E Chan, Klavdija Krause, Emma Brown, Hannah C Styers, Gary Guzman, Zhuxuan Li, Xueqian Zhuang, Yan Yan, and Tuomas Tammela
Memorial Sloan Kettering Cancer Center
Functional interrogation of a high-plasticity cell state in lung adenocarcinoma

76 Ponmathi Panneerpandian, Kevin Gulay, Herve Tiriac, and Andrew M. Lowy
University of California, San Diego
Therapeutic targeting of MICAL2 enhances the anti-tumor activity of gemcitabine in pancreatic cancer

77 Vasiliki Pantazopoulou, Casie Kubota, Satoshi Ogawa, Kassidy Curtis, Araceli Herrera, and Dannielle Engle
Salk Institute for Biological Studies
Investigating combination therapies to overcome RAS inhibitor resistance in pancreatic cancer

THURSDAY, JULY 31 - 12:10 P.M.
POSTER SESSION 2

78 Yihan Qin, Alex Cicala, Daniel Zhang, Nischal Bhandari, Nikita Persaud, Emma Arboleda, Zakeria Aminzada, Colin McLaughlin, Song Han, Rodrigo Romero, Claire Regan, William Rideout III, Jonathan Preall, Semir Beyaz, Sepideh Gholami, Zhen Zhao, Tyler Jacks, and Peter M Westcott
Cold Spring Harbor Laboratory
Capturing the early benign-to-malignant transition of colon cancer in the mouse

79 Thomas Arturo Rodriguez, Borja Ruiz-Fernández de Córdoba, Cathy Samayoa, and Alejandro Sweet-Cordero
University of California, San Francisco
Harnessing replication stress: Targeting ENPP1-induced vulnerabilities in Osteosarcoma

80 Kate Ryan, Anupriya Singhal, Sam Rose, Hannah C. Styers, Nikhita Pasnuri, Jonathan Rub, Jung Yun Kim, Ashlyn Moore, Stefan R. Torborg, Wenfei Kang, Eric Rosiek, Olivera Grbovic-Huezo, Zeynep Cagla Tarcan, Olca Basturk, Doron Betel, Yan Yan, Mark Burgess, Elisa de Stanchina, Dana Pe'er, and Tuomas Tammela
Memorial Sloan Kettering Cancer Center
Decoding pancreatic cancer cellular circuitry controlled by basal cancer cells

81 Harshada Sapre, Gregory Jordan, Mikella Robinson, and Carrie House
San Diego State Univesity
Characterization of TWEAK in an immunocompetent murine ovarian cancer model

82 Anirban Sarkar, Spencer Douglas, and Myriam Labelle
St. Jude Children's Research Hospital
Influence of primary tumors on metastatic seeding efficiency

83 Hyemin Song, Satoshi Ogawa, Kristina Peck, Jasper Hsu, Kassidy Curtis, Xiaoxue Lin, Chelsea Bottomley, and Dannielle Engle
Salk Institute for Biological Studies
Fibulin-3 drives tumor progression and microenvironment remodeling in CA19-9-induced pancreatic ductal adenocarcinoma

THURSDAY, JULY 31 - 12:10 P.M.
POSTER SESSION 2

84 Jonathan Weitz, Kevin Gulay, Rithika Medari, Deepa Sheik Pran Babu, Isabella Ng, Kersi Pestonjamasp, Shira Yomtoubian, Nidhi Jyotsana, Elias Warren, Brian Wishart, Jordan Rull, Rebekah White, Jingjing Zou, Karen Messer, Tatiana Hurtado de Mendoza, Herve Tiriac, and Andrew M. Lowy
University of California, San Diego
Benchmarking human tumor slices from GI malignancies for precision reveals synergistic effects of RASi with CDK4/6i and in tumors with concomitant with KRAS and GNAS mutations

85 Yang Yang, Wenping Wang, Gilles Rademaker, Mirunalini Ravichandran, Jingjie Hu, Joseph D. Mancias, Jessie Yanxiang Guo, and Rushika M. Perera
University of California, San Francisco
Mechanism of MAT2A regulation in response to hypoxia in pancreatic cancer

86 Hiroyuki Yoda, Nathaniel Mabe, Kimberly Stegmaier, and William Weiss
University of California, San Francisco
Epigenetic and microenvironmental regulation of GD2 in Mycn-driven neuroblastoma mouse models

87 Shira Yomtoubian, Jan Pencik, Stephen Sakamura, Brent Chick, Jingting Yu, Jingwen Liao, Victor Y. Du, Hector M. Galvez, Christopher W. Murray, Dan Chen, Filipe A. Hoffmann, Sam Van de Velde, Marc Montminy, April E. Williams, Diana Hargreaves, Susan M. Kaech, and Reuben J. Shaw
Salk Institute for Biological Studies
NR4A1 directly represses Interferon Response genes and mediates checkpoint immunotherapy resistance in STK11/LKB1 mutant NSCLC

88 Xueqian Zhuang, Jeyaram Ravichandran Damodaran, Brooklyn Christensen, Qing Wang, Simon Joost, Klavdija Krause, Emily S. Wong, and Tuomas Tammela
Memorial Sloan Kettering Cancer Center
Aging-associated iron insufficiency suppresses lung cancer initiation and progression

SPEAKER ABSTRACTS

Identification of druggable and redox vulnerabilities in cancer

Liron Bar-Peled
Massachusetts General Hospital/Harvard Medical School

Reactive oxygen species (ROS) underlie human pathologies including cancer and neurodegeneration. However, the proteins which sense ROS levels and regulate their production through their cysteines remain ill defined. Systematic base-editor and computational screens revealed cysteines in VPS35–a Retromer trafficking complex member, when mutated phenocopy inhibition of mitochondrial translation. We find that VPS35 underlies a reactive metabolite-sensing pathway that lowers mitochondrial translation to decrease ROS levels. Intracellular H2O2 oxidizes cysteines within VPS35, resulting in Retromer dissociation from endosomal membranes and subsequent plasma membrane remodeling. We demonstrate that plasma membrane localization of Retromer substrate SLC7A1 is required to sustain mitochondrial translation. Furthermore, lowering VPS35 levels or oxidation of its ROS-sensing cysteines confers resistance to ROS-generating chemotherapies including cisplatin in ovarian cancer models. Thus, we identify that intracellular ROS levels are communicated to the plasma membrane through VPS35 to regulate mitochondrial translation, connecting cytosolic ROS sensing to mitochondrial ROS production.

Using *ex vivo* tissue slice culture to elucidate the role of the tumor microenvironment in PDAC tumor lipid metabolism

Anna Trimble[1], Casie Kubota[2, 3], Elaine Zhao[4], Maureen Ruchhoeft[3], Jonathan Weitz[5], Andrew Lowy[5], Dannielle Engle[2], and Christian Metallo[3]
[1]Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093
[2]Regulatory Biology Laboratory, Salk Institute, La Jolla, CA, 92037
[3]Molecular and Cell Biology Laboratory, Salk Institute, La Jolla, CA, 92037
[4]Department of Biological Sciences, University of California, San Diego, La Jolla, CA 92093
[5]Department of Surgery, Moores Cancer Center, University of California, San Diego, La Jolla, 92037

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal malignancy for which effective therapeutics are limited. The development of therapeutics is plagued by poor translation of preclinical success into clinical settings as well as a high rate of acquired resistance. Metabolic dysregulation within PDAC tumors can confer both survival and therapeutic resistance. This metabolic dysregulation extends beyond tumor cells themselves and involves contributions from the notably diverse PDAC tumor microenvironment (TME). However, methods for investigating these stromal contributions to tumor metabolism are limited. *In vitro* tissue culture models fail to account for the native cellular diversity and distribution within the tumor, while *in vivo* methods conflate local and systemic contributions. We developed a methodology for performing metabolic flux assays in *ex vivo* cultures of organotypic PDAC tumor slices using stable isotope tracers. By quantifying metabolites across multiple pathways using GC-MS and LC-MS/MS methods, we identified key biosynthetic and salvage fluxes in KPC and human PDAC tumors. While *in vivo* flux studies show a contribution of newly synthesized fatty acids, *ex vivo* tissue slice studies revealed that there is low de novo synthesis of palmitate through FASN (DNL) within the local TME. Despite this low DNL, there is high synthetic flux for complex lipids, including storage lipids and membrane lipids, using salvaged fatty acids. Strikingly, even orthotopic tumors generated from 2D cell lines with high *in vitro* DNL demonstrate this reliance on palmitate salvage in the in situ TME. By comparing responses in tissue slices to those in 2D cultures of PDAC cells, we establish the importance of both neutral and lysosomal lipolysis as a source of fatty acids for specific lipid classes within the PDAC TME. Furthermore, we demonstrate the role of the TME in adapting to perturbations from clinically relevant therapeutics targeting lipid metabolism.

Uncovering lysosome dependent mechanisms of cellular adaptation in cancer

Rushika M. Perera
Department of Anatomy and Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco CA, USA

Pancreatic ductal adenocarcinoma (PDAC) is the most common and aggressive cancer of the pancreas. PDAC tumors are highly reliant on nutrient scavenging pathways such as autophagy, and the lysosome to sustain metabolic homeostasis and cellular quality control. To fully understand the functions of the lysosome in PDAC progression, our lab uses biochemical approaches to isolate intact lysosomes from PDAC cells, followed by mass spectrometry-based proteomics. Using this strategy, we have uncovered unique features and functions of PDAC lysosomes that promote cellular adaptation to stress and tumor growth. We have now developed techniques to profile lysosome content and composition during different stages of tumor evolution including metastasis to the liver and lungs – the two major sites of secondary tumor growth in PDAC patients. Our proteomics analysis uncovered pathways and proteins that are unique to lysosomes of tumors growing in these three tissues. For instance, lysosomes isolated from the primary tumor show enrichment for cargo proteins involved in MHC-I mediated antigen processing and presentation, while lysosomes isolated from liver and lung metastases show enrichment for proteins involved in lipoprotein transport and mitophagy, respectively. In addition, we identified hydrolases and transporters that are unique to lysosomes of tumor cells growing in the pancreas, liver or lungs, and their functional inactivation leads to organ specific defects in tumor growth. These studies highlight how dynamic changes in lysosome composition *in vivo*, enables PDAC cells to rapidly adapt to growth at different organ sites.

Decoding immune recognition in pancreatic cancer: Through the lens of the ribosome

Jacky Chuen[1], Ankita Shrivastava[1], Eric Nels Pederson[2], Trang Uyen Nguyen[1], Shivangi Pande[1], Ana Ruiz Toribio[1], Nicolas Lecomte[3], Jerry Melchor[3], John C. McAuliffe[4], Paul M Grandgenett[5], Vinagolu K. Rajasekhar[6], Christine A. Iacobuzio-Donahue[3], Zhengqing Ouyang[2], and Kamini Singh[1*]

[1]Department of Molecular Pharmacology, Stem Cell and Cancer Biology Program, Cancer Dormancy Institute, Immunotherapy for Cancer and Inflammatory Disease, Albert Einstein College of Medicine, Montefiore Einstein Comprehensive Cancer Center, Bronx, NY 10461

[2]Department of Biostatistics and Epidemiology, School of Public Health and Health Sciences, University of Massachusetts Amherst, Amherst, MA 01003

[3]David M. Rubenstein Center for Pancreatic Cancer Research, Memorial Sloan-Kettering Cancer Center, New York, NY 10065

[4]Department of Surgery and Pathology, Albert Einstein College of Medicine, Montefiore Medical Center, Bronx, NY 10461

[5]Eppley Institute for Research in Cancer and Allied Diseases, Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE 68198

[6]Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY 10065, USA

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal and treatment-refractory malignancies, with a dismal 5-year survival rate of only ~13%. A major barrier to effective immunotherapy in PDAC is the scarcity of identifiable neo-antigens. This underscores the urgent need for alternative strategies to uncover novel immune epitopes and enhance the efficacy of immunotherapy. Dysregulated mRNA translation is recognized as a critical driver of tumor progression and immunity. Building on our previous work implicating RNA helicase EIF4A in the translational control of oncogenes such as MYC and KRAS, we investigated whether targeted disruption of EIF4A could reprogram the translational landscape to favor immune activation. We demonstrate that pharmacologic blockade of EIF4A up-regulates non-canonical mRNA translation resulting in generation of neo-antigens. mRNA translation of proteins involved in antigen processing and presentation (APP) machinery including B2M, HLA-A/B/C, and PDIA3 is up-regulated through an EIF4A-independent and EIF4G2-dependent mechanisms.

Our work revealed that EIF4A inhibition leads to the emergence of novel immune epitopes and promotes their presentation via HLA-A/B/C, effectively converting immunologically "cold" tumors into "hot" ones. This reprogramming enhances cytotoxic CD8 T-cell infiltration and sensitize murine KPC PDAC tumors to anti-PDL1 immunotherapy. Our findings establish therapy induced mRNA translation as a previously under-appreciated source of neo-antigens and a key regulator of immune response in PDAC. By exploiting the cancer-intrinsic translational machinery, we reveal a novel immunotherapeutic mechanism that not only identifies neo-antigens but also offers a powerful strategy to synergize with checkpoint blockade. Our work presents a "paradigm shift in PDAC immunotherapy", transforming mRNA translational control into a targetable axis for the design of next-generation T-cell based cancer therapeutics.

Metabolic remodeling of mitochondrial forms supports GNAS ($G\alpha_s$) mutant pancreas cancer growth

Krushna C. Patra[1,2,3], Grant A. Hagedorn[1,2], Jackson C. Spieser[1], Sierra Kanemoto[1], Jake Valentine[1], Noriko Hirai[1,3], and Yuki Sato[1,2]
[1]Department of Cancer Biology, University of Cincinnati, Cincinnati, OH, USA
[2]Cancer and Cell Biology Graduate Program, University of Cincinnati, Cincinnati, OH, USA
[3]University of Cincinnati Cancer Center, Cincinnati, OH, USA

Oncogenic signaling controls many tumorigenic pathways via remodeling organellar forms and homeostasis. Mutant KRAS is an important regulator of mitochondrial dynamics (fission vs fusion) in pancreas cancer. Specifically, KRAS activates the pro-fission protein dynamin-related protein1(DRP1) and induces mitochondrial fission. Maintenance of a fissed mitochondrial state is essential for the growth of KRAS mutant cancer. During analysis of a genetically distinct subset of pancreatic cancer lesions driven by mutant GNAS and KRAS, we discovered that hyperactive GNAS overrides the KRAS-induced fission and maintains mitochondria predominantly in a fused state. Multiplex proteomics and molecular analysis pointed out that GNAS-controlled metabolic processes promote mitochondrial fusion, in addition to the suppression of DRP1 activity. Loss- and gain-of-function studies coupled with metabolite rescue experiments revealed that the branched-chain amino acid(BCAA) pathway is a novel regulator of mitochondrial dynamics. Mechanistically this pathway couples to the TCA cycle, and the generation and oxidation of reducing equivalents that support mitochondrial fusion. Finally, we showed that the enforced mitochondrial fission via inhibition of the BCAA pathway or core fusion machinery suppresses the growth of GNAS-KRAS mutant cancer. While previous studies have shown the contribution of mitochondrial dynamics in controlling metabolic processes, our data support a model that metabolic signals are recruited by oncogenic machinery, to control mitochondrial dynamics. Thus, our overall findings demonstrate the combination of oncogenic signaling and metabolism maintains heterogeneity in mitochondrial forms in distinct genetic subsets of KRAS-mutant pancreatic cancer. We envision that such regulation of mitochondrial dynamics can be controlled by metabolic states induced by intracellular and tumor microenvironment— which may provide maximum flexibility to adapt unique mitochondrial functions.

Unlocking the chemical space of cancer: A chemoproteomic strategy to map protein function and therapeutic response

Donita Brady
University of Pennsylvania

While genetic mutations are essential for cancer initiation, they are often not sufficient on their own to drive malignant transformation. Our lab studies how changes in the local vascular environment, particularly lymphatic remodeling, shape the early cellular decisions that enable oncogenic adaptation. Using *in vivo* models and 3D imaging strategies, we investigate how evolving microenvironmental cues influence stem cell behavior, plasticity, and vulnerability during tumor progression. By examining these overlooked vascular circuits, our work aims to uncover non-genetic mechanisms that prime epithelial tissues for malignant progression and therapeutic resistance.

Epigenetic reactivation of neutrophil differentiation to target acute leukemia

Shandon Amos[1,2], Chichao Chen[3], Yichen Xiang[1], Varun Narenda[3], Keisuke Motoyama[1], Grace Johnson[1,2], Natalie O'Hearn[1], Arianna Arroyo-Ortega[1], Oindrila Sarkar[1], Ziyang Ye[1,2], Yu-Jui Ho[3], Francisco J. Sánchez-Rivera[1,2], Angela Koehler[1], Scott Lowe[3], and Yadira Soto-Feliciano[1,2]
[1]Koch Institute for Integrative Cancer Research at MIT,Cambridge, MA 02139
[2]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139
[3]Cancer Biology and Genetics, MSKCC, New York, NY 10065

Chromatin is tightly regulated by a complex network of factors that integrate intra- and extracellular cues into changes in gene expression and genome organization. Chromatin adaptors play a central role within this regulatory landscape, which direct recruitment of protein complexes to specific genomic loci in a context-dependent manner. Here, we identify TRIM28 as a previously uncharacterized vulnerability in acute myeloid leukemia (AML). TRIM28 (also known as KAP-1), a multi-domain chromatin adaptor, is known for its roles in heterochromatin formation and cellular differentiation. Our group identified TRIM28 as an essential epigenetic regulator in AML, where its depletion markedly impairs leukemia cell proliferation both *in vitro* and *in vivo*. This anti-leukemic effect is accompanied by widespread transcriptional changes, including the induction of gene programs associated with neutrophil differentiation. Using integrative transcriptomics and chromatin profiling, we defined TRIM28's genomic targets, and employed cellular and *in vivo* models to characterize the consequences of TRIM28 loss. Our findings revealed that TRIM28 acts as a dual transcriptional regulator, leveraging its scaffold-like structure to engage in both co-repressor and co-activator functions through context-specific protein-protein and protein-chromatin interactions. These insights position TRIM28 as a compelling therapeutic target in AML, with the potential to inform novel strategies for targeted intervention.

Thioredoxin reductase 1 inhibition triggers ferroptosis in KRAS-independent lung cancers

Cristina Andreani[1], Caterina Bartolacci[1*], Nicola Sargentoni[2], Margherita Melegari[1], Lorenzo Luciani[2], Agnese Marucci[3], Roberta Galeazzi[4], Gina DeNicola[5], Jessica Kilgore[6], Noelle Williams[6], Stefano Berto[7], Massimiliano Gaetani[8], Prasad Pattabhi[1], Sagid Osman[1], Stefania Pucciarelli[3], Rossana Galassi[2], and Pier Paolo Scaglioni[1]

[1]Department of Internal Medicine, University of Cincinnati College of Medicine, Cincinnati, OH 45219, USA.
[2]School of Science and Technology, Chemistry Division, University of Camerino, Camerino, MC 62032, Italy
[3]School of Biosciences and Veterinary Medicine, University of Camerino, Camerino, MC 62032, Italy
[4]Department of Life and Environmental Sciences, Università Politecnica delle Marche, Ancona, AN, Italy
[5]Department of Metabolism and Physiology, H. Lee. Moffitt Cancer Center, Tampa, Florida
[6]Department of Biochemistry, University of Texas Southwestern Medical Center, Dallas, TX 75390
[7]Department of Neuroscience, Medical University of South Carolina, Charleston, SC, USA

Ferroptosis, a form of iron-dependent cell death driven by lipid peroxide accumulation, represents a promising therapeutic avenue in cancer. While mutant KRAS (KM) lung cancers evade ferroptosis through altered lipid metabolism, the KRAS wild-type (KRAS-WT) subset is more molecularly diverse. In this study, we identify thioredoxin reductase 1 (TrxR1, encoded by TXNRD1) as a synthetic lethal target in KRAS-WT and KRAS-independent lung cancer (LC) cells. Through DepMap CRISPR screening and experimental validation, we show that KRAS-WT and EGFR-mutant LC cells are selectively vulnerable to TrxR1 inhibition, in contrast to KM cells. We introduce novel non-covalent gold(I)-based TrxR1 inhibitors (CS47, DM20), which trigger ferroptosis by promoting lipid peroxidation, iron accumulation, and oxidative stress. Among them, CS47 exhibits favorable selectivity, *in vivo* efficacy, and reduced toxicity compared to auranofin. Mechanistically, TrxR1 inhibition induces ferroptosis via upregulation of heme oxygenase 1 (HO-1/HMOX1), which is both necessary and sufficient for this process in KRAS-WT LC. Importantly, KRAS inhibitor-resistant LC cells regain sensitivity to TrxR1 inhibition, revealing a redox-based therapeutic vulnerability. These findings pose TrxR1 as a context-specific ferroptosis driver and support the combined targeting of KRAS and TrxR1 pathways to overcome resistance in lung cancer.

Targeting a new metabolism-epigenetic axis towards improved CAR T therapy in multiple myeloma

Yael David
Chemical Biology Program, Memorial Sloan Kettering Cancer Center, New York, NY

Metabolic diseases such as diabetes and obesity impair immune surveillance and elevate cancer risk, yet the molecular links between metabolic dysfunction, immune exhaustion, and cancer progression remain elusive. Mechanistically, abrogated cellular metabolism can alter chromatin through the non-enzymatic addition of reactive metabolic byproducts to proteins and nucleotides, leading to changes in the cellular transcriptional program. One such byproduct, methylglyoxal (MGO), accumulates in glycolytic cells and is elevated in metabolic disease. In chromatin, MGO modifies histones, disrupting its structure and function. Here, we show that both endogenous and exogenous MGO induce histone glycation and reprogram T cells, driving transcriptional changes and a dysfunctional state marked by reduced cytokine production and terminal exhaustion-phenotypes also observed in T cells from patients with diabetes. Overexpression of the MGO-detoxifying enzyme DJ-1 reduced histone glycation and T cell dysfunction. DJ-1-overexpressing CAR T cells exhibited enhanced stemness, reduced exhaustion, and improved tumor control in myeloma models *in vivo*. These findings reveal a targetable metabolic-epigenetic axis linking systemic disease to immune failure in cancer.

Chromatin-associated condensates in gene regulation and cancer

Liling Wan
Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

Our lab investigates chromatin-based gene regulation and how its disruption contributes to cancer. A major focus is on how chromatin regulators form or influence biomolecular condensates to control transcriptional programs that govern cell fate and oncogenic transformation. We identified ENL as a critical histone acetylation reader in leukemia and demonstrated that recurrent ENL mutations found in Wilms tumor and leukemia drive the formation of aberrant transcriptional condensates at selective oncogenic loci. Building on these and other findings, we are actively investigating how condensate dysregulation reshapes chromatin architecture and transcriptional control during development and tumorigenesis. I will present our recent work on the formation, regulation, and functional significance of aberrant chromatin-associated condensates in cancer and how we may target these protein assemblies.

Elucidating the mechanisms sustaining DTPCs following MAPKi in LUAD

Brandon Murphy, Haley Hunt, Sage Lichfield, and Martin McMahon
Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112

Targeted therapies are a cornerstone in the treatment of lung adenocarcinoma (LUAD) driven by oncogenic activation of the RAS>RAF>MEK>ERK (MAPK) signaling pathway. These agents frequently induce substantial tumor regression, with many patients achieving prolonged disease control beyond one year. Nevertheless, indefinite treatment is required due to the persistence of minimal residual disease maintained by drug-tolerant persister cells (DTPCs), which can drive relapse upon therapy discontinuation. DTPCs are sustained through non-genetic adaptive mechanisms and serve as a reservoir for the emergence of genetic alterations that enable proliferation in the face of treatment. However, the underlying non-genetic mechanisms sustaining DTPCs remain elusive. Using a panel of KRAS and BRAF-mutant human and mouse lung cancer cell lines, we first sought to identify the cell death mechanisms induced by MAPK pathway inhibition (MAPKi) to decipher how DTPCs may adapt to remain viable amidst treatment. Here, we discover that both cellular detachment and MAPKi are required to induce apoptosis in lung cancer cells, which corresponds with an overall decrease in the apoptotic threshold within these cells. Pointing toward a role of cellular adhesion in fostering resistance to therapy, we discovered that disrupting a key adhesion-associated signaling pathway cooperates with MAPKi to impede cellular proliferation. Moreover, pharmacological inhibition of this pathway dampens the activation of a critical pro-survival signaling cascade that is hyperactivated following prolonged MAPKi treatment. As pharmacological inhibition of this pro-survival pathway similarly cooperates with MAPKi to impede cell growth, these findings suggest that compensatory signaling through this adhesion-linked pro-survival axis is an important non-genetic mechanism of resistance toward MAPKi treatment in lung cancer.

Targeting the oncogenic state of RAS with tri-complex inhibitors

Mallika Singh
Revolution Medicines, Redwood City, California, USA

KRAS oncogenic driver mutations are among the most frequent genomic aberrations in human cancers, prevalent in pancreas, colon, and lung tumors. Small molecule inhibitors that selectively target the inactive, GDP-bound state of KRAS G12C mutant proteins have demonstrated clinical efficacy as monotherapy in NSCLC and in combinations in CRC. However, there are no currently approved RAS-targeted therapy options for patients with non-G12C RAS mutant cancer.

We have designed a series of tri-complex inhibitors that selectively target the GTP-bound, active state of RAS (RAS(ON)), thereby mitigating some of the resistance mechanisms observed with inhibitors that preferentially bind to the OFF state. This includes daraxonrasib (RMC-6236), a RAS(ON) multi-selective inhibitor that noncovalently inhibits the GTP-bound state of mutant and wild-type variants of the canonical RAS isoforms (KRAS, NRAS, and HRAS) and the mutant-selective inhibitors elironrasib (RMC-6291) and zoldonrasib (RMC-9805) that covalently engage RAS(ON) G12C and RAS(ON) G12D, respectively. These investigational agents demonstrate profound antitumor activity in preclinical models of RAS mutant NSCLC and PDAC, which has translated into promising monotherapy clinical activity. We will describe the mechanism of action of these investigational agents and their activity in a variety of RAS-driven preclinical models that supports their clinical evaluation in RAS-addicted cancers. Moreover, our emerging understanding of acquired resistance to RAS(ON) inhibitor monotherapy is informing potential combination regimens, including with RAS(ON) inhibitor doublets.

Breast tumor evolution

Kornelia Polyak
Dana-Farber Cancer Institute

Immune escape during the transition from ductal carcinoma in situ (DCIS) to invasive breast cancer (IBC) plays a critical role in tumor evolution. To dissect the underlying mechanisms, we have conducted a comprehensive analysis of the immune landscapes of normal breast, DCIS, and IBC tissues through large-scale single-cell RNA sequencing (scRNA-seq) in a substantial cohort of healthy women and breast cancer patients. Our findings revealed that T cells and myeloid cells are the two primary features that differentiate DCIS from IBC. Notably, we identified a subpopulation of regulatory T cells as key orchestrators of immune suppression during the DCIS-to-IBC transition. The frequency of these cells was found to be predictive of cytotoxic CD8+ T cell frequency, T cell receptor (TCR) diversity, and disease-specific survival in IBC, as well as the risk of invasive recurrence in DCIS. Experiments in an outbred rat model of breast cancer demonstrated a key role for these Treg subpopulation in establishing an immunosuppressive environment in IBC. These insights pave the way for the design of novel therapeutic strategies aimed at enhancing anti-tumor immunity and improving patient outcomes.

Exploring the impact of neoantigen expression on lung tumor development

Jennifer Loza, Ishan Bansal, Brian Hunt, Kelli Connolly, Srividhya Venkatesan, and Nikhil Joshi
Department of Immunobiology, Yale University School of Medicine, New Haven, CT 06520

Lung adenocarcinoma (LUAD) remains a clinical challenge despite advances in immunotherapy. Immune responses, particularly those driven by T cells recognizing tumor-specific neoantigens, play a critical role in shaping tumor progression. While T cell infiltration has been linked to reduced tumor grade, the influence of neoantigen expression on LUAD progression remains unclear.

Our lab developed a genetically engineered mouse model capable of inducing a fluorescent neoantigen in KRAS-mutant, P53-null, tdTomato-labeled lung adenocarcinoma cells. This model enables temporal tracking of tumor initiation and progression over 20 weeks. Tumors arising in this system become heterogeneous for neoantigen expression, allowing investigation of T cell-driven selection. Using multiplexed immunofluorescence, we found that neoantigen+ tumors show increased T cell infiltration, reduced volume, and prolonged survival. Unexpectedly, advanced tumors in the lung retain neoantigen+ cells, suggesting that endogenous lung T cells fail to fully eliminate antigen-expressing tumor cells. To examine how tissue context shapes immune pressure, we transplanted a 1:1 mix of neoantigen+ and – tumor cells subcutaneously. In contrast to the lung, neoantigen+ cells were selectively eliminated, indicating that the lung presents a unique barrier to effective immunoediting. Despite this, infiltrated tumors were correlated with reduced p-ERK expression. Consistently, *in vitro* co-cultures demonstrated that neoantigen-specific T cells and their conditioned media directly suppress p-ERK expression in tumor cells, suggesting that T cells may limit tumor progression not only through direct killing but also by altering oncogenic signaling pathways.

Altogether, these findings highlight complex, tissue-specific mechanisms of immune surveillance in LUAD. By dissecting how neoantigen expression shapes tumor-immune dynamics, this study provides new insight into T cell–mediated control of lung cancer progression.

Computational modeling of cancer as an adaptive emergent complex system

Pablo Tamayo[1,3] and William Kim[2,3]
[1]Department of Medicine, Division of Genomics and Precision Medicine, UC San Diego, La Jolla, CA 92037
[2]Department of Urology, Yale University Medical School, New Haven, CT 06520
[3]Broad Institute of Harvard and MIT, Cambridge MA, 02142

Over the past ten years, the field of oncology has seen significant advancements in targeted and immune-based therapies, as well as the incorporation of molecular diagnostics to personalize initial cancer treatments. However, cancer's propensity for evolution and resistance to therapies remains a formidable challenge due to its dynamic nature. Cancer's complex and adaptive behavior surpasses the capabilities of simple models, complicating our comprehension at every level. This knowledge gap exists across various domains, from basic science and fundamental biology to clinical practice, underscoring the urgent need for innovative approaches to model, understand, predict, and ultimately prevent poor clinical outcomes resulting from cancer's dynamic behavior. Cancer exhibits emergent complex system characteristics, with properties arising at higher levels through the intricate interactions and dynamics of lower-level components. These include dysregulated signaling pathways and interactions between cancer cells and the tumor microenvironment. Cancer's complexity spans from the molecular and genetic underpinnings within cancer cells to cellular population interactions and the emergence of a stable configuration driven by tumor dynamics. Overcoming these challenges requires better ways to model cancer's complexity and dynamic behavior. We will present an overview of the development of dimensionality-reduced state-based computational models for cellular (pathways) and tumor (populations) states, based on our Cancer States and Archetypes (CSA) framework. The approach is data-driven and integrates multiomics and response data using dimensionality reduction, clustering, visualization, and other computational analysis techniques.

Overcoming age-related immune dysfunction and chemoresistance in triple-negative breast cancer

Sandra S McAllister, PhD
Brigham & Women's Hospital, Harvard Medical School

Unraveling the molecular mechanisms of radon and air pollution-induced lung cancers with novel mouse models

Melanie A. Dacheux[1], Lea Montegut[2], Cheng Pei Wu[1], James McEvoy May[3, 4], Dylan De Bellis[3, 4], Emilia Scalco Wachter[1], Miriam Merad[2], Dani Dixon[4], Tony Hunter[4], and Aria Vaishnavi[1]
[1]University of Texas MD Anderson Cancer Center, Houston, Texas, 77054, USA
[2]Icahn School of Medicine at Mount Sinai Hospital, New York, New York, 10029, USA
[3]University of Adelaide, Adelaide, South Australia, 5005. Australia
[4]Flinders University, Adelaide, South Australia, 5005. Australia

As tobacco use trends down, the incidence of lung cancer in never smokers (LCINS) has evolved into a global health crisis, and accounts for 25% of all lung cancer cases. The two largest risk factors for developing LCINS are exposure to radon gas, and air pollution or $PM_{2.5}$. We set out to investigate how different components of the lung epithelium cooperate in LCINS following environmental exposures to create a preneoplastic state. To elucidate the mechanisms underpinning LCINS, we developed mouse models for both radon gas and $PM_{2.5}$-induced exposures.

We deployed a sensitized GEMM where treatment with tamoxifen unlocks conditional expression of CRE Recombinase in the Surfactant Protein C (SPC)-driven alveolar type II pneumocytes (AT2) cells of the lung. The expression of Trp53R172H and tdTomato are targeted to AT2 cells using Spc-Cre:ERT2 (*PTC*). *PTC* mice were exposed to chronic Radon-222 daily for 24 weeks and aged out an additional 12 weeks. *PTC* mice develop radon-induced lung injury, as diffuse alveolar hemorrhaging, followed by fully malignant lung cancer by 16-20 weeks of chronic exposures. Separately, *PTC* mice inhaled PM2.5 daily for 6 or 12 weeks and were aged out for 6-12 additional weeks.

PTC mice develop pulmonary fibrosis, or lung tumors by 12 weeks of chronic exposure to $PM_{2.5}$, and high-grade lung adenocarcinoma by 18 weeks post-exposure. We noted clear lymphocyte infiltration and activated endothelial cells following exposures, and tertiary lymphoid structures within these tumors. We observed high levels of pERK in the lung tissue, suggesting hyper activation of the MAPK pathway. Single-cell RNA-sequencing analyses of early $PM_{2.5}$ treated *PTC* lungs revealed a loss of AT2 identity and the emergence of an intermediate transitioning state. Collectively, our models of exposure-induced lung tumors promise to provide an unprecedented window into their evolution and illuminate novel angles of attack to short-circuit LCINS growth.

Geographic and age-related variations in mutational processes in colorectal cancer

Ludmil B Alexandrov[1-4]
[1]Department of Cellular and Molecular Medicine, University of California San Diego, La Jolla, CA, USA
[2]Department of Bioengineering, University of California San Diego, La Jolla, CA, USA
[3]Moores Cancer Center, University of California San Diego, La Jolla, CA, USA
[4]Sanford Stem Cell Institute, University of California San Diego, La Jolla, CA, USA

Colorectal cancer incidence rates vary geographically and have changed over time. Notably, in the past two decades, the incidence of early-onset colorectal cancer, affecting individuals under the age of 50 years, has doubled in many countries. The reasons for this increase are unknown. Here, we investigate whether mutational processes contribute to geographic and age-related differences by examining 981 colorectal cancer genomes from 11 countries. No major differences were found in microsatellite unstable cancers, but variations in mutation burden and signatures were observed in the 802 microsatellite-stable cases. Multiple signatures, most with unknown etiologies, exhibited varying prevalence in Argentina, Brazil, Colombia, Russia, and Thailand, indicating geographically diverse levels of mutagenic exposure. Signatures SBS88 and ID18, caused by the bacteria-produced mutagen colibactin, had higher mutation loads in countries with higher colorectal cancer incidence rates. SBS88 and ID18 were also enriched in early-onset colorectal cancers, being 3.3 times more common in individuals diagnosed before age 40 than in those over 70, and were imprinted early during colorectal cancer development. Colibactin exposure was further linked to *APC* driver mutations, with ID18 responsible for about 25% of *APC* driver indels in colibactin-positive cases. This study reveals geographic and age-related variations in colorectal cancer mutational processes, and suggests that early-life mutagenic exposure to colibactin-producing bacteria may contribute to the rising incidence of early-onset colorectal cancer.

Disseminated cancer cell dormancy: Molecular triggers of entry and exit

Julio A. Aguirre-Ghiso, Luis Valencia-Salazar, Anna Adam-Artigues, Lucia Petriz Otaño, Rama Kadamb, Lornella Seeneevassen, Deisy Segura Villalobos, Deepak Singh, Nyima Sherpa, and Lionel Colon
Department of Cell Biology, Cancer Dormancy Institute, Montefiore Einstein Comprehensive Cancer Center, Albert Einstein College of Medicine, Bronx, NY, US

Preventing and treating metastasis remains one of the greatest challenges in cancer management. Early-evolved disseminated breast cancer cells (DCCs) can seed distant organs and persist in a dormant state for extended periods. However, the mechanisms by which target organ niches restrict the expansion of both early and late-evolved DCCs are not fully understood. Moreover, the signals that trigger the awakening and outgrowth of dormant DCCs remain an area of active investigation. In this presentation, I will discuss several mechanisms uncovered through our research. I will highlight our discovery that embryo-derived tissue-resident alveolar macrophages (AMs) possess a novel innate immune function, enabling them to suppress metastatic outgrowth by inducing dormancy in DCCs. Additionally, I will present evidence illustrating how host mosaicism and viral infections can reactivate dormant DCCs. I will also share new findings on how damage to peripheral sympathetic nerves (PSN) may influence the development of brain metastases.

Discovery of astrocytic checkpoints regulating disseminated tumor cell survival

Shi Li
Public Health Sciences Division/Translational Research Program, Fred Hutchinson Cancer Center, Seattle, WA 98109, USA

Brain metastases are among the most lethal manifestations of advanced cancer. Once they develop, there are limited treatment options. Our work demonstrated that escape from the single cell state is a major, underappreciated rate limiter to brain metastasis. Therefore, identifying how these disseminated tumor cells (DTCs) evade surveillance by the brain's immune cells could provide novel avenues to prevent metastasis and improve patient survival. In the brain, immune surveillance is carried out primarily by microglia, specialized immune cells responsible for detecting and eliminating damaged neurons and cellular debris. Whereas direct evidence of microglial phagocytosis of DTCs is limited, their innate capacity for engulfing aberrant cells suggests they may play a role in restricting metastatic colonization. Our data reveals that - in the setting of NOD-SCID mice and Rag2-deficient hosts, microglial immunosurveillance has a minimal impact on DTC survival and on metastatic progression. This raised question as to why microglia do not recognize DTCs. Our work suggests that astrocytes - glial cells that support neuronal function, regulate synaptic homeostasis, and influence neuroimmune interactions - play a key role in suppressing microglial function. Using advanced imaging techniques, we observed that when astrocytes neighboring DTCs are eliminated, microglia effectively clear DTCs. Using chemical depletion approaches, we demonstrate that astrocyte-ablation mediated DTC clearance is microglia-dependent. Live imaging studies have provided some clues into underlying mechanisms, which I aim to probe further using spatial approaches. Overall, our results suggest a novel mechanism by which astrocytes shield DTCs from microglia-mediated immune surveillance, allowing them to survive and retain metastasis-initiating potential. We believe identifying and targeting this axis may instruct new therapeutic approaches to restore microglial function and prevent brain metastasis.

Actin cytoskeleton dynamics in tumor cells mediate Immune-suppressive microenvironment and sensitize pancreas tumors to PD-1 blockade therapy

Bharti Garg[1], Evangeline Sari Mose[1], Edgar Esparza[1], Jay Patel[1], Kevin Gulay[1], Rithika Medari[1], Sarah Sass[2], Alexei Martsinkovskiy[1], Asmina Courelli[1], Carrie Bishop[3], Gisselle Gonzalez[3], Adam Engler[3], Parag Katira[3], Vivien Ileana Maltez[4], Herve Tiriac[1], and Andrew M. Lowy[1]

[1]University of California - San Diego, Division of Surgical Oncology, Department of Surgery, Moore's Cancer Center, San Diego, CA, USA

[2]Alabama College of Osteopathic Medicine, Dothan, Alabama, USA

[3]Sanford Consortium for Regenerative Medicine, University of California, San Diego, USA

[4]Department of Allergy, Immunology and Rheumatology

PDAC is defined by a dense, immunosuppressive TME composed of ECM proteins, CAFs, and diverse immune cells. ChIP-seq on resected human PDAC samples identified MICAL2 as a super-enhancer-associated gene. MICAL2, a flavin monooxygenase, promotes actin depolymerization and SRF transcription. This study investigates how tumor-intrinsic MICAL2 alters the PDAC TME. Orthotopic implantation of KPC-MICAL2 knockdown (M2KD) dox-inducible cells had reduced tumor growth. Immunofluorescence, flow cytometry and atomic force microscopy showed M2KD tumors were more cellular with marked reduction in PDPN+/α-SMA+ CAFs, collagen and fibronectin resulting in reduced stiffness. MICAL2 loss also reprogrammed CAF gene expression and increased infiltration of activated CD8+ T cells, skewing from an M2 to M1 macrophage phenotype. scRNA-seq revealed major shifts in immune populations, including increased cycling T and plasma cells. CD8+ T cell depletion reversed tumor suppression in both immune-hot and -cold syngeneic models, and adoptive transfer of MICAL2-KD tumor-infiltrating T cells suppressed the growth of Shcontrol tumors. RNAScope showed reduced IL-1α, IL-6, TGF-β expression and decreased p38 and STAT3 phosphorylation in M2KD tumors. To test if MICAL2 regulates the PDAC TME transcriptionally, we generated KPCM tumors and lines (by crossing PDX1-Cre; LSL-KRASG12D/+; P53R172H/WT (KPC) with Mf/f mice) and reintroduced WT MICAL2 or MICAL2 lacking nuclear localization signal (ΔNLS) or FAD enzymatic domain in the KPCM line. ΔNLS and FAD mutant MICAL2 cells were deficient in tumor growth, had reduced stromal deposition and SRF activity, and increased CD8+ T cells. Anti-PD-1 significantly reduced M2KD tumor size and 50% of M2KD-bearing mice had complete regression with anti-PD-1 and IL-1α antibodies. MICAL2-ASO treatment in human PDAC slice cultures increased T cell activation and M1 polarization. MICAL2 drives immunosuppression in PDAC and could be a potential therapeutic target.

Understanding and overcoming the numbers game that underlies disseminated tumor cell immune evasion

Cyrus Ghajar
Fred Hutch Cancer Center

The period between "successful" treatment of localized breast cancer and the onset of distant metastasis can last many years, representing an unexploited window to eradicate disseminated disease and prevent metastases. We find that the source of recurrence – disseminated tumor cells (DTCs) – evade endogenous immunity directed against tumor neoantigens. Although DTCs downregulate major histocompatibility complex I, this does not preclude recognition by conventional T cells. Instead, the scarcity of interactions between two relatively rare populations, DTCs and antigen-specific T cells, underlies persistence of cancer cells at distant sites. This 'relative scarcity' is overcome by therapies that increase the ratio of T cells to DTCs above a given threshold, resulting in robust DTC elimination. Our preliminary investigations of breast tumors and associated bone marrows suggest that the concept of relative scarcity applies also to humans, motivating discovery of DTC antigens that can be targeted with T cell-based immunotherapies to eliminate the reservoir of metastasis-initiating cells in patients.

Senescent stromal changes drive breast tumorigenesis and contribute to therapy-induced bone loss

Sheila Stewart
Washington University
Department of Cell Biology and Physiology, Washington University School of Medicine, St. Louis, MO 63110, USA
College of Arts and Sciences, Washington University in St. Louis, MO 63110, USA
Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110, USA
Siteman Cancer Center, Washington University School of Medicine, St. Louis, MO 63110, USA
ICCE Institute, Washington University School of Medicine, St. Louis, MO 63110, USA

Age is the single largest risk factor for the development of cancer, but how age impacts the molecular mechanisms that drive cancer remain poorly understood. While it is clear that age-related accumulation of cell autonomous mutations contributes to tumorigenesis, the central role age-related changes in the tumor microenvironment play in the transformation process is becoming more fully appreciated. Underscoring the importance of an aged microenvironment in cancer development are findings that senescent fibroblasts, which accumulate with age, directly stimulate preneoplastic and neoplastic cell growth and tumor progression. Investigations into how senescent fibroblasts promote tumorigenesis revealed that they express a plethora of growth factors, extracellular matrix remodeling enzymes, chemokines, and cytokines collectively referred to as the senescence associated secretory phenotype (SASP). We find that a subset of senescent cancer associated fibroblasts (senCAFs) limit NK cell killing, increasing tumorigenesis. Chemotherapy induces similar changes that can negatively impact a patients quality of life. We will discuss how these changes impact tumor progression and therapy-induced bone loss.

Genetic dissection of metabolic tumor suppression *in vivo*

D. Nesli Dolcen[1], Haiqing Xu[1,2], Laura Andrejka[1], Daniel Lee[1], Dmitri A. Petrov[2], and Monte M. Winslow[1]

[1]Department of Genetics, Stanford University School of Medicine, Stanford, California, 94305

[2]Department of Biology, Stanford University, Stanford, California, 94305

How metabolic pathways dictate cancer phenotypes across genetic and physiological contexts remain poorly understood. *In vitro* tumor metabolism screens are complicated by non-physiological conditions while transplantation studies likely are impacted by their super-physiologic growth. Genetically engineered mouse models allow tumor growth within the appropriate *in vivo* context but have only been used to investigate a few metabolic genes. To quantify the impact of inactivating >500 genes across all major metabolic pathways on autochthonous KRAS-driven lung tumorigenesis, we used tumor barcoding and multiplexed CRISPR/Cas9-mediated somatic genome editing. While metabolic pathways are generally considered essential for cell growth (a belief that we confirm for many anabolic pathways), we uncovered many metabolic tumor suppressor genes. Top metabolic tumor suppressors in KRAS-driven tumors belong to the glucose and fatty acid oxidation pathways exemplified by the increased size of Cpt2-, Etfb-, and Sdha-deficient tumors. Dual gene inactivation of glucose and fatty acid oxidation enzymes showed that inactivation of enzymes in the carnitine shuttle and mitochondrial fatty acid beta-oxidation lead to dependence on glucose oxidation and suggests that long-chain fatty acylcarnitine accumulation increases tumor growth. Parallel *in vivo* screens in autochthonous KRAS-driven/p53-deficient and BRAF-driven lung cancer models show that these pathways are even more important in suppressing p53-deficient tumors but are essential in BRAF-driven tumors. Ongoing work focuses on establishing the molecular mechanisms by which inhibiting the carnitine shuttle and fatty acid oxidation increases growth of KRAS-driven lung tumors, as well as uncovering how oncogenic context defines metabolic tumor suppression. This work establishes a foundation of metabolic gene function during lung cancer growth *in vivo* and uncovers an unexpected network that links energy metabolism to tumor suppression.

Non-canonical RNA binding of the MYBL2 transcription factor nucleates transcriptional condensates and promotes melanoma

Kaizhen Wang and Florian A. Karreth
Department of Molecular Oncology, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612

Transcription factor dysregulation is a critical driver of melanoma progression, yet the molecular mechanisms are poorly understood. We uncovered a non-canonical function of the cell cycle-associated transcription factor MYBL2 in melanomagenesis. MYBL2 overexpression through copy number gains and MAPK pathway activation correlates with poor melanoma patient survival. Unexpectedly, while MYBL2 promotes melanoma growth *in vitro* and *in vivo*, its transcriptional activity is dispensable for its oncogenic effects. Instead, we found that MYBL2 promotes melanoma growth through a non-canonical RNA-binding function. CLIP-seq revealed that MYBL2 binds predominantly to intronic regions of protein-coding mRNAs without directly affecting their expression or splicing. Rather, RNA binding enhances the association of MYBL2 with chromatin, indirectly activating a non-canonical transcriptional program associated with poor prognosis. Moreover, MYBL2 forms nuclear condensates and promotes chromatin association of transcription factors with oncogenic potential in melanoma such as MAFG and FRA1. The RNA binding-dependent MYBL2 transcriptional program is enriched for MAFG and FRA1 binding sites, suggesting that MYBL2 coordinates transcriptional condensates to promote melanoma growth. Interestingly, the MYBL2 RNA-binding capability is specifically acquired in melanoma cells and not evident in melanocytes. Cross-binding RNA-IP experiments demonstrated that the melanoma RNA transcriptome, not MYBL2 protein modifications, enables this interaction. MYBL2-interacting transcripts are upregulated in melanoma through copy number gains that significantly co-occur with MYBL2 amplification, suggesting a coordinated genomic program. Our findings reveal how cancer cells can repurpose transcription factors through context-dependent RNA interactions, providing new insights into melanoma progression mechanisms and identifying the MYBL2-RNA interface as a potential therapeutic target.

Functional and molecular interrogation of a malignant high-plasticity cell state in carcinomas

Tuomas Tammela and colleagues
Memorial Sloan Kettering Cancer Center, New York, NY, USA

Plasticity—the ability of cells to undergo phenotypic transitions—drives cancer progression and treatment resistance. Thus, plasticity is one of the most fundamental problems in cancer biology and one of the foremost challenges in clinical cancer management today. To date, targeting cancer plasticity has not succeeded in the clinic due to the lack of a fundamental understanding of the underlying mechanisms. Our recent published and ongoing work indicates that plasticity in lung cancer, pancreas cancer, and other carcinomas is concentrated in a minority subset of cancer cells. However, functional studies interrogating such high plasticity cell states (HPCSs) *in situ* have been lacking. Over the past several years, we have generated mouse models that allow for detection, longitudinal lineage-tracing, and ablation of the HPCS and other defined cancer cell states in lung and pancreas tumors *in vivo*. Using lineage-tracing, we uncover the HPCS cells are dedifferentiated but possess high capacity for cell state transitions, giving rise to both differentiated and advanced-stage cancer cells *in situ* in tumors. Longitudinal lineage tracing using secreted luciferases reveals HPCS-derived cells harbor more robust capacity for growth when compared to bulk cancer cells or another defined cancer cell state predicted to possess low plasticity. Suicide gene-mediated ablation of the HPCS in early-stage lesions abrogates tumor progression, whereas ablating HPCS cells in established tumors robustly reduces tumor burden. Leveraging these models, we demonstrate that the HPCS gives rise to treatment-resistant cell states, whereas ablation of the HPCS abrogated resistance to chemotherapy and oncoprotein-targeted therapy. Interestingly, we find an HPCS-like state is ubiquitous in regenerating epithelia and carcinomas of multiple other tissues, revealing a convergence of plasticity programs in healthy and malignant epithelial tissues. In parallel studies, we have uncovered unexpected molecular drivers of this cell state, which operate system-wide in epithelial regenerative processes. These molecular mechanisms offer multiple therapeutic entry points, which may enable targeting of malignant plasticity in cancer patients. This work establishes the HPCS as a critical hub enabling reciprocal transitions between cancer cell states, including acquisition of states adapted to cancer therapies. Targeting the HPCS may suppress cancer progression and eradicate treatment resistance.

Opposing lineage specifiers induce a protumor hybrid identity state in lung adenocarcinoma

Henry U. Arnold[1,2], Gabriela Fort[1,2], Soledad Camolotto[1,4], Kayla O'Toole[1,2], Rushmeen Tariq[1,2], Anna Waters[1,2], Katherine Gillis[1,2], and Eric L. Snyder[1,2,3]
[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah 84112
[2]Department of Oncological Sciences, University of Utah, Salt Lake City, Utah 84112
[3]Department of Pathology, University of Utah, Salt Lake City, Utah 84112
[4]Present Address: Recursion Pharmaceuticals, Salt Lake City, UT 84101

Cellular plasticity in cancer presents a significant obstacle to effective therapy. It is increasingly apparent that cellular plasticity affects tumor progression and therapeutic response. This phenomenon is pronounced in lung adenocarcinoma (LUAD), the most prevalent form of lung cancer and leading cause of cancer-related mortality. Acquisition of alternative, non-pulmonary cellular identities in LUAD can intersect on a hybrid-identity state, which is postulated to be a transition state between low and high-grade tumors. This state is characterized by co-expression of ordinarily incompatible identity programs. We have elucidated that gastrointestinal (GI) lineage specifier HNF4α has a protumor effect and drives GI programs in the hybrid-identity state. In hybrid-identity LUAD cells that express the pulmonary lineage regulator NKX2-1, HNF4α can regulate GI lineage programs by binding its canonical targets. HNF4α also dampens expression of pulmonary programs by disrupting NKX2-1 genomic localization. RAS/MEK signaling is required for HNF4α expression, activation of GI identity programs, and suppression of pulmonary programs. This is potentially regulated through the genomic localization of NKX2-1 and known cofactors FOXA1/2, as MEK inhibition dramatically increases binding of these lineage specifiers near pulmonary-specific genes. Finally, HNF4α ablation sensitizes hybrid identity LUAD cells to $KRAS^{G12D}$ inhibition, highlighting a potential therapeutic vulnerability of the hybrid identity state.

Investigating transcriptional regulators of intratumoral heterogeneity in small cell lung cancer

Debadrita Bhattacharya[1], Sarah Groves[2], Cameron Walker[3], Yamina Chtourou[1], Marcus Hsieh[1], Michael Angelo, Vito Quaranta[2], and Julien Sage[1]
[1]Department of Pediatrics and Genetics, Stanford University, Stanford, CA 94305, USA
[2]Department of Biochemistry, Vanderbilt University, Nashville, TN 37235, USA
[3]Department of Pathology, Stanford University School of Medicine, Stanford, CA, USA

Lineage plasticity in cancer cells drives intratumoral heterogeneity (ITH), a feature of advanced-stage human cancers often linked to poor prognosis. This is particularly relevant in small cell lung cancer (SCLC), the deadliest form of neuroendocrine (NE) cancer, where plasticity and ITH are hallmarks of multi-therapy resistance. However, currently, we have limited insights into the cancer cell states that drive tumor heterogeneity and the molecular factors that promote SCLC cell fate diversification.

To uncover the molecular drivers of ITH, I performed single-cell multi-omic analyses on cancer cells isolated from a preclinical SCLC mouse model. This approach revealed diverse cancer cell states, each defined by unique epigenetic and transcriptional programs. Notably, I identified a subset of dedifferentiated SCLC cells characterized by low expression of NE genes and heightened levels of inflammation and antigen presentation pathways—features typically suppressed in NE cancer cells. Using in silico transcription factor network modeling, I pinpointed the nuclear receptor RORβ as a key repressor of this "low NE" cell state and a gatekeeper of immunosuppressive classical NE lineages. Supporting this prediction, genetic and pharmacological inhibition of RORβ in SCLC tumor-organoid models promoted a shift from classical NE cancer cells to a "neuroendocrine-low" immunogenic state. RORβ-deficient SCLC tumors demonstrated slower growth in immunocompetent mice and showed increased infiltration by anti-tumor macrophages.

These findings indicate that targeting RORβ can alter cancer cell states, decrease lineage plasticity, and potentially boost the efficacy of immunotherapy in SCLC. This work offers a foundation for developing new treatments that can overcome immune evasion and improve outcomes for this highly lethal cancer type.

Reprogramming the stroma: Metabolic plasticity and aging in pancreatic tumor evolution

Cosimo Commisso
Sanford Burnham Prebys Medical Discovery Institute

Pancreatic ductal adenocarcinoma (PDAC) is characterized by a complex tumor microenvironment where stromal dynamics dictate tumor progression and therapeutic response. In the first part of this talk, I will present recent work demonstrating how metabolic stress shapes CAF plasticity. We show that under glutamine deprivation, cancer-associated fibroblasts (CAFs) activate macropinocytosis to maintain a myofibroblastic phenotype. Inhibiting this pathway drives a myCAF-to-iCAF transition via MEK-ERK signaling, remodeling the stroma into a more permissive, less fibrotic environment that enhances both immunotherapy and chemotherapy responses. In the second part, I will discuss how organismal aging independently reprograms the tumor microenvironment. Using orthotopic and heterochronic PDAC models, we find that stromal aging promotes immune exclusion and metastasis through a conserved CAF-derived fibrotic gene signature. Rejuvenation of the aged stroma with young CAFs restores immune infiltration and reduces metastatic burden. Together, these studies uncover distinct but complementary mechanisms—nutrient stress and aging—that govern stromal identity, immune dynamics, and therapeutic vulnerability in PDAC.

Tumor cell state and niche remodeling during benign-to-malignant transition in the colon

Yihan Qin[1], Alex Cicala[1], Daniel Zhang[2], Nischal Bhandari[1], Nikita Persaud[1], Emma Arboleda[1], Zakeria Aminzada[1], Colin McLaughlin[1], Song Han[1], Rodrigo Romero[3], Claire Regan[1], William Rideout III[4], Santiago Naranjo[4], Karen Yee[4], Jonathan Preall[1], Semir Beyaz[1], Sepideh Gholami[1,5], Zhen Zhao[1,5], Tyler Jacks[4], and Peter Westcott[1]
[1]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY
[2]University of California San Francisco, San Francisco, CA
[3]Memorial Sloan Kettering Cancer Center, New York, NY
[4]Massachusetts Institute of Technology, Cambridge, MA
[5]Northwell Health, New Hyde Park, NY

Early-onset colorectal cancer (CRC) is rising and now ranks as the leading cause of cancer deaths in men and the 2nd in women under 50 in the US. We hypothesize that environmental and lifestyle factors may accelerate the progression of benign polyps to malignancy. However, the non-genetic mechanisms driving this transition are poorly understood.

To investigate these mechanisms, we developed a mouse model that recapitulates the stepwise progression of human CRC, including carcinoma in situ, by temporally uncoupling *Apc* loss from subsequent activation of oncogenic *Kras* and deletion of *Trp53*. In parallel, we analyzed stage 0 human intramucosal carcinomas of the colon, applying spatial transcriptomics to both mouse and human specimens.

Our findings reveal that benign-to-malignant transition is marked by a shift from a homeostatic stem cell-like to a regenerative stem cell–like state. While oncogenic *Kras* drives this transcriptional reprogramming, it is not sufficient to induce histologic carcinoma. In fact, in the absence of *Trp53* loss, *Kras* activation leads to slower proliferation and reduced fitness. However, oncogenic *Kras* combined with *Trp53* loss in rare cells of benign polyps enables malignant transformation— albeit inefficiently— highlighting the importance of additional factors.

We identified adaptive immune infiltration as a hallmark of early carcinoma in both species. In the mouse, T cell depletion impairs both the emergence of regenerative stem cell states and carcinoma formation. Moreover, co-culture experiments demonstrate that CD8+ T cells and IFN-γ selectively promote the outgrowth of *Kras*-mutant precancerous organoids.

These findings support a model in which adaptive immune inflammation fosters tumor progression by promoting stem cell plasticity. Our work introduces powerful new *in vivo* systems to dissect non-mutational mechanisms of benign-to-malignant transition and offers insights into early CRC biology with implications for early detection and prevention.

Lymphovascular niches as hubs of cancer plasticity and evolution

Shiri Gur-Cohens
University of California, San Diego

While genetic mutations are essential for cancer initiation, they are often not sufficient on their own to drive malignant transformation. Our lab studies how changes in the local vascular environment, particularly lymphatic remodeling, shape the early cellular decisions that enable oncogenic adaptation. Using *in vivo* models and 3D imaging strategies, we investigate how evolving microenvironmental cues influence stem cell behavior, plasticity, and vulnerability during tumor progression. By examining these overlooked vascular circuits, our work aims to uncover non-genetic mechanisms that prime epithelial tissues for malignant progression and therapeutic resistance.

Tumor cells drive the spatial organization of intratumoral immune cells and chemokine landscapes in heterogeneous tumors

Robert Letchworth[1,2], Savannah Hughes[1,2], Abigail Keku[1,2], Emilio Cortes-Sanchez[1], Piyush Chaudhary[1,2], Joshua Tay[1,2], Matthew Lieberman[1,2], and Melissa Reeves[1,2]
[1]1Huntsman Cancer Institute, University of Utah, Salt Lake City, UT 84112
[2]2Department of Pathology, University of Utah, Salt Lake City, UT 84112

Tumor heterogeneity is associated with impaired immune responses and inferior efficacy of immunotherapy. To understand how tumor heterogeneity limits anti-tumor immunity, our lab has developed a unique model system in which tumors are comprised of multiple fluorescently labeled tumor cell populations, enabling precise spatial tracking of how tumor cells shape their local microenvironment. We find across multiple models that T cells preferentially localize near specific tumor cell populations over others. Further, the number of CD4+ T cells in a tumor region significantly correlates with the abundance of functionally active IFNγ+ CD8+ T cells. This implies that a coordinated, effective anti-tumor response forms in some spatial regions of a tumor while failing to form in others, and that tumor cells themselves are major determinants of where these regions of effective coordinated immunity form and where they are diminished. Strikingly, interrogation of the intratumoral chemokines within heterogeneous tumors reveals that the local tumor cells also dictate the local chemokine profile. In heterogeneous tumors comprised of two of cutaneous squamous cell carcinoma cell lines, CIT6 and CIT18, the chemokine profile of tumors regions around CIT18 tumor cells are enriched in inflammatory chemokines CCL5, CXCL10, CXCL11, CCL17, and CCL22, mirroring CIT18 homogeneous tumors. By contrast, both CIT6-occupied regions of mixed tumors and CIT6 homogeneous tumors lack this signature, and this corresponds with a microenvironment diminished in T cell infiltration and function. Together, these data demonstrate that the identity of the local tumor cells creates a blueprint for the spatial architecture of both the intratumoral chemokine landscape and intratumoral T cell infiltration, and that immune-evasive tumor populations use multiple mechanisms to limit anti-tumor immune activity in their local vicinity.

KP/RiboMHC: A novel mouse model for proteogenomic analysis of tumor-specific antigen presentation *in vivo*

Emily Brennan[1], Christopher Polera[1], Emma Adhikari[1], Andrew Weeden[1], Emily Paul[1], Anika Ali[1], Andrew Deonarine[1], Bin Fang[2], Victoria Izumi[2], John Koomen[2], Paul Stewart[3], and Alex Jaeger[1]
[1]Department of Molecular Oncology, Moffitt Cancer Center, Tampa, FL 33612
[2]Proteomics and Metabolomics Core Facility, Moffitt Cancer Center, Tampa, FL 33612
[3]Department of Bioinformatics and Biostatistics, Moffitt Cancer Center, Tampa, FL 33612

Antigen presentation is critical for successful anti-tumor immunity. Development of antigen-specific immunotherapies using computational prediction of antigenic targets remains challenging, likely due to our incomplete understanding of the physiological and molecular inputs that shape the antigen landscape *in vivo*. Recent advances in mass spectrometry have enabled direct interrogation of peptides presented by MHC-I, collectively known as the "immunopeptidome". Immunopeptidomics has also revealed that cryptic translation events from novel unannotated open reading frames (nuORFs) comprise a significant source of tumor-specific antigens. These observations highlight the critical need to understand the interplay between translation and antigen presentation, but the field still lacks tools to study these molecular events *in vivo*.

To address this, we have developed a novel mouse model termed "KP/RiboMHC". KP/RiboMHC mice leverage Cre inducible affinity tags on ribosomes (Rpl22) and MHC-I (H2-Kb) allowing for simultaneous ribosome footprint sequencing (RiboSeq) and immunopeptidomics from specific cells *in vivo*. Using KP/RiboMHC models we mapped the translational landscape of LUAD and PDAC with codon level resolution *in vivo* and correlated these patterns to the antigen landscape, revealing post-translational influences on antigen presentation. Comparison of data obtained from autochthonous LUAD tumors to tumor derived organoids revealed translational events, nuORFs, and MHC-I antigens that are specific to the *in vivo* context. Finally, treatment of KP/RiboMHC LUAD and PDAC with KRAS inhibitors revealed acute shifts in translation that results in a unique antigenic fingerprint that could be leveraged for combination immunotherapies. Collectively, these data demonstrate the broad value of the KP/RiboMHC model and provide a blueprint for interrogating how physiological contexts and cellular states influence tumor immune interactions.

Engineering multi-pronged CAR-T cells for cancer therapy

Yvonne Y. Chen
University of California, Los Angeles

The adoptive transfer of T cells expressing chimeric antigen receptors (CARs) has demonstrated robust efficacy in the treatment of advanced hematological malignancies. However, challenges such as antigen escape and immunosuppression limit the long-term efficacy of adoptive T-cell therapy, particularly for solid tumors. Here, I will discuss the development of next-generation T cells that can target multiple cancer antigens, modify the tumor microenvironment, and/or engage endogenous immunity to overcome tumor-defense mechanisms. This presentation will highlight the potential of synthetic biology in generating novel mammalian cell systems with multifunctional outputs for therapeutic applications.

Targeting dysregulated wound healing programs in cancer and fibrosis with immune engineering

Zeda Zhang[1], Yu-Jui Ho[1], Xin Fang[1], Clemens Hinterleitner[1], Sascha Haubner[2], Friederike Kogel[3], Edwin Pratt[4], Marguerite Li[1], Wei Luan[1], Minseo Kim[1], Elif Ozcelik[1], Jose Reyes[1], Qingwen Jiang[4], Stella V. Paffenholz[1], Sha Tian[1], Eric Chan[5], Eric Rosiek[5], Elisa de Stanchina[6], Paul B. Romesser[7], Britta Weigelt[8], Judith Feucht[9], Dmitriy Zamarin[10], Sohrab Shah[11], Jason Lewis[4], Corina Amor[12], Jorge Mansilla-Soto[13], MSK Clinical Teams, Aveline Fillio[11†], Michel Sadelain[2†], and Scott Lowe[1,14†]

[1]Cancer Biology and Genetics Program, Memorial Sloan Kettering Cancer Center, New York, NY
[2]Columbia Initiative in Cell Engineering and Therapy, Department of Medicine, Columbia University, New York, NY
[3]Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, NY
[4]Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, NY
[5]Molecular Cytology Core Facility, Memorial Sloan Kettering Cancer Center, New York, NY
[6]Antitumor Assessment Core Facility, Memorial Sloan Kettering Cancer Center, New York, NY
[7]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY
[8]Department of Pathology, Memorial Sloan Kettering Cancer Center, New York, NY
[9]Cluster of Excellence iFIT, University Children's Hospital Tübingen, Germany
[10]Precision Immunology Institute, Icahn School of Medicine at Mount Sinai, New York, NY
[11]Department of Computational Oncology, Memorial Sloan Kettering Cancer Center, New York, NY
[12]Cold Spring Harbor Laboratory, New York, NY
[13]Departments of Immunology, Bioengineering, BMT and Cellular Immunotherapies. H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL
[14]Howard Hughes Medical Institute, Memorial Sloan Kettering Cancer Center, New York, NY
[†]Corresponding Authors

Chronic inflammation disorders contribute to over 30% of global mortality and underline major diseases such as cancer and autoimmunity. Fibrosis—a key outcome of chronic inflammation following tissue injury, plays a pivotal role in organ function decline and cancer progression. Current anti-fibrotic therapies remain limited by suboptimal efficacy and systemic toxicity. We hypothesize that precise elimination of fibrogenic and inflammatory effector cells can disrupt the propagation of injury and inflammation signaling, offering a targeted therapeutic strategy. Through proximity-based surface proteomics, we identified the urokinase plasminogen activator receptor (uPAR) broadly upregulated in senescent and chronically injured tissues. uPAR is a GPI-anchored membrane protein central to the wound healing response and is consistently elevated during tissue injury and chronic inflammation. uPAR-targeted CAR T cells selectively eliminated these cells, reducing fibrosis in murine models of liver and lung injury. uPAR is also upregulated in aggressive cancers, marking epithelial to mesenchymal transition (EMT)-like tumor cells and senescent stromal cells within immunosuppressive niches. In preclinical models, human uPAR CAR T cells demonstrated potent and durable activity across multiple tumor types. In an ovarian cancer model, adjuvant uPAR CAR T cell therapy following tumor debulking effectively prevented metastasis. Therapeutic responses were noninvasively tracked using circulating soluble uPAR and uPAR-targeted PET imaging. Despite uPAR's expression in some myeloid cells, treatment did not result in sustained myelodepletion. These findings position uPAR-targeted CAR T cells as a promising strategy to treat cancer, fibrosis, and degenerative diseases by eradicating shared pathological cell states.

Epigenetic control of tumor associated macrophages – targeting the BAF nucleosome remodeling complex

Helen McRae and Diana Hargreaves
Salk Institute for Biological Studies, La Jolla, CA, USA

The BAF complex is a multi-subunit nucleosome-remodeling complex. Inhibitors/degraders of the BAF complex have entered phase 1 and 2 clinical trials due to the dependency of several cancer types on the BAF complex. We hypothesized that BAF complex inhibitors would impact not only tumor cells, but also immune cells in the microenvironment.

Immunotherapy response of MC38 adenocarcinoma was boosted in mice treated with BAF inhibitors (FHD-286/BRM014). Multiome scRNA and scATAC sequencing revealed changes in the gene expression and chromatin accessibility across the microenvironment, including upregulation of interferon signature genes (ISGs) in tumor cells, CD8+ T cells and macrophages. Tumor associated macrophages (TAMs) displayed increased expression of antigen presentation (MHC-I) and co-stimulation (CD86) proteins, identifying a previously unrecognized role of the BAF complex in TAM function.

To directly study the role of BAF in TAMs, we used a mouse model with myeloid-specific deletion of ARID1A (the largest subunit of the canonical BAF complex). Growth of tumors, including orthotopic PyMT breast cancer, showed slower tumor growth and increased anti-PD-L1 response in mice lacking myeloid-ARID1A. ARID1A-deleted TAMs displayed widespread chromatin accessibility and gene expression changes, including an enrichment of ISGs. Upregulated ISGs with increased accessibility included Cd86. *In vitro* experiments established that upregulation of CD86 in ARID1A-deficient macrophages was not dependent on soluble factors, although could be hyperinduced by interferon or co-culture with T cells. *In vivo*, CD8+ T cells in tumors with myeloid-specific ARID1A displayed increased activation. Using depleting and blocking antibodies respectively, we established that increased immunotherapy response was dependent on CD8+ T cells, and partly dependent on CD86, indicating myeloid-specific BAF complex disruption promotes an anti-tumor immune response via TAM:CD8+ T cell cross talk.

Neutrophils drive vascular occlusion, pleomorphic tumor necrosis, and metastasis

Mikala Egeblad
Johns Hopkins University

Tumor necrosis is associated with poor prognosis in cancer and is thought to occur passively when tumor growth outpaces nutrient supply. However, in multiple cancer mouse models, we found a tumor-elicited $Ly6G^{High}Ly6C^{Low}$ neutrophil population that was unable to extravasate in response to inflammatory challenges but formed neutrophil extracellular traps (NETs) more efficiently than classical $Ly6G^{High}Ly6C^{High}$ neutrophils. The presence of these 'vascular-restricted' neutrophils correlated with the appearance of a 'pleomorphic' necrotic architecture in mice. In tumors with pleomorphic necrosis, we found intravascular aggregates of neutrophils and NETs that caused occlusion of the tumor vasculature, driving hypoxia and necrosis of downstream vascular beds. Furthermore, we found that cancer cells adjacent to these necrotic regions, in perinecrotic areas, underwent epithelial-to-mesenchymal transition, explaining the paradoxical metastasis-enhancing effect of tumor necrosis. Blocking NET formation genetically or pharmacologically reduced the extent of tumor necrosis and lung metastasis. Thus, by showing that NETs drive vascular occlusion, pleomorphic necrosis and metastasis, we demonstrate that tumor necrosis is not necessarily a passive byproduct of tumor growth and that it can be blocked to reduce metastatic spread.

Mitochondrial complex II inhibition promotes tumor inflammation

Kailash Chandra Mangalhara, Gladys Rojas, Pau Bernat Esparza Moltó, Sagnika Ghosh, and Gerald Shadel
Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037

Metabolic reprogramming in cancer cells facilitates proliferation, tumor growth, and metastasis by supplying energy, macromolecules, and antioxidants. However, the extent to which tumor metabolic reprogramming influences tumor infiltration by immune cells and elimination of cancer cells remains inadequately understood. Mitochondria are central hubs of cellular metabolism and key regulators of tumor-intrinsic inflammation. We recently demonstrated that mitochondrial electron transport chain (ETC) complex II, succinate dehydrogenase (SDH), regulates mouse melanoma growth by enhancing antigen processing and major histocompatibility complex class I (MHC-I) presentation on tumor cells. This increase in antigen presentation enhances tumor surveillance by T cells. Unexpectedly, although inhibition of complex II activates interferon signaling, the induction of MHC-I expression is independent of interferon receptor engagement. Here, we reveal that inhibition of complex II leads to the accumulation of cytosolic double-stranded RNA (dsRNA), which is sensed by the pattern recognition receptor MDA5, triggering MAVS-mediated expression of interferon stimulated genes (ISGs). Mechanistically, complex II inhibition stabilizes p53, which represses key mitochondrial and cytosolic dsRNA-metabolizing proteins, resulting in the buildup of cytosolic dsRNA. Our findings highlight mitochondrial complex II as a critical metabolic-immune checkpoint and provide a mechanistic basis for exploiting mitochondrial metabolism to boost tumor immunogenicity and improve responses to immunotherapy.

Stromal education of pancreatic cancer cells drives an NFκB-mediated immune evasion program

Yuwenbin Li[1], Morgan Truitt[1], Daniel Cao[1], Jonathan Zhu[1], Yang Dai[1], Mariel Burquez-Escobedo[2], Gaoyang Liang[1], Michael Downes[1], Annette Atkins[1], Ruth Yu[1], and Ronald Evans[1]
[1]Salk Institute for Biological Studies, La Jolla, CA, 92037
[2]Baylor College of Medicine, Houston, TX, 77030

Pancreatic ductal adenocarcinoma (PDAC) is among the most treatment-resistant cancers, particularly to immunotherapy, due to its immunosuppressive tumor microenvironment (TME), which impairs T cell infiltration and function. This TME is partly shaped by tumor to stroma crosstalk downstream of hyperactive KRAS signaling, yet how the TME reciprocally programs tumor cells for immune evasion remains less understood.

To address this, we used tumor interstitial fluid (TIF), a complex mixture of soluble factors from the PDAC TME, to model stroma to tumor crosstalk. We find that TIF treatment rendered PDAC cells resistant to antigen-specific T cell killing *in vitro*, with resistance persisting even after TIF removal, suggesting induction of a durable, likely epigenetic, immune evasion program. In line with this, treatment with the bromodomain inhibitor OTX-010 is able to intercept this immune evasion program.

RNA-seq analysis of TIF-induced and OTX-010 sensitive gene expression programs revealed a number of pathways with known immunomodulatory roles, including the NFκB pathway and the KRAS-MAPK pathway itself. Functionally, pharmacologic inhibition of NFκB effectively restored T cell killing in the presence of TIF. Targeting NFκB downstream effectors, such as COX2 and LIF, also enhanced tumor cell susceptibility to T cell-mediated cytotoxicity. We also found that MRTX-1133, a selective $KRAS^{G12D}$ inhibitor, could sensitize TIF-treated tumor cells to T cell killing. Notably, transcriptomic analysis showed that MRTX-1133 suppresses TIF-induced NFκB signaling, and preliminary studies suggest this occurs independently of canonical NFκB regulation. Importantly, inhibition of either NFκB effectors or KRAS signaling enhanced the efficacy of adoptive T cell therapy in mouse models of PDAC.

Together, these findings uncover a TME-driven NFκB signaling axis that promotes an immune evasion program in tumor cells. Targeting this tumor-intrinsic axis may improve immunotherapy response in PDAC.

Leveraging autophagy and pyrimidine metabolism to target pancreatic cancer

Suzanne Dufresne[1], Ramya S Kuna[1], Kristiana Wong[1,2], Anvita Komarla[1,3], Angelica Rock[1,2], Joel Rosada-Encarnación[1], Celina Shen[1,2], Payel Mondal[1], Louis R Parham[1], Fabiana Izidro Layng[4], Kristina L. Peck[5], Alexandra Fowler[5], Andrew M. Lowy[6], Dannielle Engle[5], Herve Tiriac[6], Reuben Shaw[1], Nicholas Cosford[4], Christian Metallo[1], and Christina Towers[1]

[1]Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037

[2]Division of Biological Sciences, University of California San Diego, La Jolla, CA 92037, USA

[3]Department of Bioengineering, University of California San Diego, La Jolla, CA 92037, USA

[4]Cancer Molecular Therapeutics Program, NCI-Designated Cancer Center, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA 92037,USA

[5]Regulatory Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA

[6]Department of Surgery, Division of Surgical Oncology, Moores Cancer Center, University of California San Diego, La Jolla, CA 92037, USA

Autophagy inhibitors are promising compounds to treat pancreatic ductal adenocarcinoma (PDA) but their efficacy in patients is unclear, highlighting a need to understand mechanisms of resistance. We used a novel approach to uncover metabolic adaptations that bypass autophagy inhibition. Utilizing PDA cells with acquired resistance to the autophagy inhibitors hydroxychloroquine and MRT68921, we found that severe autophagy depletion induces metabolic rewiring to sustain TCA intermediates and nucleotides for biosynthesis. Long-term autophagy inhibition results in altered pyruvate metabolism likely regulated by lower pyrimidine pools. Cells adapting to loss of autophagy preferentially salvage pyrimidines to replenish these pools instead of synthesizing them de novo. Exploiting this metabolic vulnerability, we found that acquired resistance to autophagy inhibition promotes increased salvage and therefore sensitivity to pyrimidine analogues, including gemcitabine and trifluridine/tipiracil leading to combinatory effects with autophagy inhibitors and pyrimidine analogs. These studies provide mechanistic insight defining how autophagy inhibition can be leveraged to treat pancreatic cancer.

CA19-9 induces microenvironment remodeling and promotes immunosuppression in pancreatic ductal adenocarcinoma

Jasper Hsu[1], Hyemin Song[1], Satoshi Ogawa[1], Kristina Peck[1], Tae Gyu Oh[2], Jonathan Weitz[3], Chelsea Bottomley[1], Kassidy Curtis[1], McKenna Stamp[1], Shira Okhovat[1], Angelica Rock[1], Michael Downes[1], Ronald Evans[1], Andrew Lowy[3], Herve Tiriac[3], and Danielle Engle[1]
[1]Salk Institute for Biological Studies, La Jolla, CA, USA
[2]University of Oklahoma School of Medicine, Oklahoma City, OK, USA
[3]University of California, San Diego, School of Medicine, La Jolla, CA, USA

Glycosylation is a common and complex type of post-translational modification, and plays critical roles in development, maintenance, and survival. Altered glycosylation is universal in cancer, yet our understanding of the role of glycans in tumorigenesis is incomplete, hampering translation of glycan vulnerabilities into treatment strategies. Pancreatic ductal adenocarcinoma (PDA) has a 13% five-year survival rate. For decades, serum levels of CA19-9, a terminal tetra-saccharide glycan conjugated to many proteins, has been the single-most effective biomarker to track PDA progression. However, mice are unable to naturally generate CA19-9, hampering investigation of its role in PDA. Within the PDA TME, several immune cells and subtypes of cancer associated fibroblasts (CAFs) contribute to desmoplasia, treatment resistance, and immunosuppression. For instance, antigen-presenting CAFs (apCAFs) express MHC class II and interact with CD4+ T cells, inducing regulatory T cell (Treg) differentiation. Prior studies relied on mice or monolayer cultures lacking CA19-9, our understanding of the TME has been studied in the absence of CA19-9 despite its prevalence in human PDA. We generated a novel KRASG12D mutant mouse with Doxycycline-induced CA19-9 expression. Substantial increases in multiple cell populations such as immune cells and all CAF subtypes occurred in 3 days of CA19-9 elevation. Furthermore, we find increases in apCAF and Treg numbers. Increased protein levels of IL1a and TGFb were observed following CA19-9 induction in mouse pancreata and KRAS-mutant pancreatic organoids. After treatment with anti-CA19-9 as well as combination anti-IL1a and -TGFb neutralizing antibodies, we observed abrogated TME remodeling, including decreased apCAF and Treg numbers. This project highlights both CA19-9 direct and indirect mechanisms of apCAF and Treg expansion to unveil essential molecular underpinnings of PDA biology that will inform effective therapies in the future.

Understanding precancer to cancer transition at single-cell resolution: The Hippo in the room

J. Silvio Gutkind, PhD
Department of Pharmacology, School of Medicine, and Moores Cancer Center, University of California, San Diego, La Jolla, California 92093

Tumor initiation represents the first step in tumorigenesis during which normal progenitor cells undergo a cell fate transition to cancer. Understanding the precancer-to-cancer transition as it occurs in vivo, however, remains elusive. We have recently employed spatiotemporally controlled oncogene activation and tumor suppressor inhibition, together with multiomics, to unveil the processes underlying the reprogramming of normal oral epithelial progenitor cells into head and neck squamous cell carcinoma (HNSCC) cancer-initiating cells (CICs) at single-cell resolution. HNSCC exhibits numerous genetic alterations that converge to impact a finite set of oncogenic molecular pathways. These include the near-universal loss of function of TP53 and CDKN2A tumor suppressors due to genomic alterations or human papillomavirus (HPV) E6 and E7 oncoprotein-mediated inhibition, as well as multiple molecular mechanisms leading to aberrant PI3K-mTOR activation. We have also reported that alterations in *FAT1*, a frequent event in HNSCC, disrupt Hippo pathway signaling and result in unrestrained activation of YAP. Using conditional genetically engineered mouse model systems, we have recently shown that the concomitant activation of YAP and HPVE6-E7-mediated inhibition of tumor suppressive pathways is sufficient to rapidly reprogram normal oral epithelial progenitor cells into HNSCC CICs. Single-cell analyses revealed that CICs display a distinct stem-like state, characterized by aberrant proliferative, hypoxic, and squamous differentiation, as well as partial epithelial-to-mesenchymal invasive gene programs. In addition, we found that YAP promotes the activation of oncogenic transcriptional networks and the PI3K-mTOR signaling pathway. Remarkably, CICs do not express collagenases, which are essential drivers of extracellular matrix remodeling. Instead, YAP orchestrates the paracrine recruitment collagenase-expressing myeloid cells to the invasive epithelial front, which ultimately initiates tumor invasion. These CIC transcriptional programs are highly conserved in human HNSCC. These findings illuminate the process underlying cancer initiation at single-cell resolution and identify candidate targets for early cancer detection and prevention.

POSTER ABSTRACTS

Targeting senescent cells with precision: A nanoparticle approach to combat fibrosis and enhance cancer immunotherapy

Valentin Barthet[1], Clemens Hinterleitner[1], Hailey Goldberg[1], Almudena Chaves-Perez[1], Kristen Vogt[2], Stephen Ruiz[2], Ana Perea[2], Xiang Li[1], Yu-Jui Ho[1], Daniel Heller[2], and Scott Lowe[1]
[1]Department of Cancer Biology and Genetics, Memorial Sloan-Kettering Cancer Center, NY, NY, 10021
[2]Molecular Pharmacology Program, Memorial Sloan-Kettering Cancer Center, NY, NY, 10021

Cellular senescence is characterized by stable cell-cycle arrest and a senescence-associated secretory program (SASP) that remodels the tissue microenvironment. Senescent cells accumulate with age and in chronic disease, driving fibrosis, immune dysfunction, and tumor progression. In cancer, senescent cells create a physical and immunosuppressive barrier that impairs T cell infiltration and limits immunotherapy efficacy. Genetic clearance of senescent cells reduces fibrosis, inflammation, and metastasis. Several compounds have been developed to preferentially kill senescent cells (senolytics) or inhibit the SASP (senomorphics). However, due to their limited selectivity and specificity, these agents often cause significant toxicities.

Here, we identified that p-selectin, a cell adhesion protein, is upregulated upon senescence induction across multiple mouse and human models. P-selectin expression colocalizes with canonical senescence markers p21 and β-galactosidase activity in models of lung and liver fibrosis. Fucoidan-based nanoparticles targeting p-selectin selectively accumulate in β-galactosidase^{+}/p-selectin^{+} senescent cells in fibrotic tissues. Delivery of either a senolytic or senomorphic drug through p-selectin-targeting nanoparticles significantly improved liver and lung fibrosis and reduced systemic toxicity compared to the corresponding free drugs.

Importantly, we found that the elimination of senescent cells in the fibrotic tumor microenvironment restored anti-tumor immunity. Senolytic nanoparticle treatment increased CD8^{+} T cell infiltration and sensitized fibrotic hepatocellular carcinoma and fibrotic lung adenocarcinoma models to immunotherapy. These findings establish senescence as a driver of fibrosis-associated immune exclusion and therapy resistance and present p-selectin-targeted nanoparticles as a novel, translational platform to safely eliminate pathogenic senescent cells in cancer and chronic disease.

Functional genomics uncovers a critical role for canonical NF-kB to mediate a high-plasticity cell state in lung adenocarcinoma

Jason E. Chan[1,2*], Chun-Hao Pan[1*], Jonathan Rub[1,3], Klavdija Krause[1], Emma Brown[1], Carleigh Sussman[1], Zeda Zhang[1], Hannah Styers[1], Gary Guzman[1], Griffin Hartmann[1], Zhuxuan Li[4], Xueqian Zhuang[1], Scott W. Lowe[1], Doron Betel[5], Yan Yan[1,6], and Tuomas Tammela[1]

[1]Cancer Biology and Genetics Program, Memorial Sloan Kettering Cancer Center, New York, NY, 10065

[2]Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY 10065

[3]Tri-I Program in Computational Biology & Medicine, Weill Cornell Medicine, New York, New York 10065

[4]BCMB Allied Program, Weill Cornell Graduate School of Medical Science, Weill Cornell Medicine, New York, NY 10065

[5]Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY 10065

[6]College of Biomedicine and Health and College of Life Science and Technology, Huazhong Agricultural University, Wuhan, Hubei 430070, China

Plasticity—the ability of cells to undergo phenotypic transitions—drives cancer progression and treatment resistance. Targeting cancer plasticity has been unsuccessful due to a lack of fundamental understanding of its supporting mechanisms. Recent works have suggested that plasticity in solid tumors is concentrated in a minority subset of cancer cells, yet functional studies interrogating this high plasticity cell state (HPCS) in situ are lacking. Here, using novel mouse models enabling detection, longitudinal lineage-tracing, and ablation of the HPCS in autochthonous lung tumors *in vivo*, we uncovered that HPCS cells are dedifferentiated and possess high capacity for cell state transitions, giving rise to both early-stage (differentiated) and advanced-stage cancer cell states in situ in lung tumors. We demonstrate suicide gene-mediated ablation of the HPCS in early-stage lesions abrogates tumor progression, whereas ablating HPCS cells in established tumors by suicide gene or HPCS-directed CAR T cells robustly reduces tumor burden. Leveraging these models, we demonstrate that the HPCS gives rise to treatment-resistant cell states, whereas ablation of the HPCS abrogates resistance to chemotherapy and oncoprotein-targeted therapy. We combine shRNA-based functional perturbation of putative HPCS drivers with *in vivo* multiplexed molecular lineage tracing to uncover the critical role of canonical NF-kB in maintaining the HPCS in lung adenocarcinoma. Interestingly, we discover a similar HPCS-like state in other epithelial carcinomas and in regenerating normal epithelium, suggesting cancers co-opt pre-existing regenerative programs to enable plasticity. Our work establishes the HPCS as a critical hub enabling reciprocal transitions between cancer cell states, including acquisition of states adapted to cancer therapies. Targeting the HPCS in lung cancer and in other carcinomas may suppress cancer progression and eradicate treatment resistance.

Impacts of inhibition of endothelial cell autophagy on tumorigenesis in breast cancer

Brayden Chin, Nancy Leon-Rivera, and Dr. Teresa Monkkonen
San Diego State University

In 2025, the American Cancer Society estimates approximately 316,950 new cases of invasive breast cancer will be diagnosed in women. Breast cancers lacking hormone receptor expression have limited treatment options, leading to poor patient outcomes. Autophagy inhibition is being tested as a targeted therapy, but its effects on tumor vasculature remain largely unknown. To assess endothelial-specific autophagy inhibition in a physiological model of breast cancer, we generated Atg12 and Atg5 endothelial cell knockout (ECKO) mice using the Cdh5CreER vascular endothelial cadherin promoter driver. Efficient recombination was validated by FACS following tamoxifen induction in both Atg12 and Atg5 ECKO mice with limited Cre leakiness in controls. Orthotopic transplantation of MMTV-PyMT derived tumor organoids into Atg12 or Atg5 ECKO mice resulted in significantly delayed tumor growth and increased survival compared to controls. In an autochthonous PyMT model, Atg12 ECKO mice similarly exhibited delayed time to endpoint tumor volume. Following surgical resection of primary tumors, Atg12 ECKO mice demonstrated higher rates of tumor recurrence (46%) and lung metastasis (60%) compared to controls. Tail vein injection of PyMT cells into tumor naive mice showed an increase in lung metastasis size with Atg ECKO; similarly, end-stage PyMT lungs displayed larger metastases as well.To test whether these effects were tumor type specific, we used the Rat insulin promoter-SV40 Large T antigen (RIP-Tag) model of pancreatic neuroendocrine tumors, which are highly vascular and sensitive to anti-angiogenic therapy. Neither early nor late endothelial deletion of Atg12 altered primary tumor burden or survival, in contrast to the PyMT findings. However, Atg12 ECKO mice displayed a significant increase in liver micrometastases, suggesting that EC autophagy may limit dissemination. These results highlight the context-dependent roles of endothelial autophagy in tumor progression.

Atypical flux through polyunsaturated lipid pathways influence pluripotency and metabolism of stem cells

Rebecca Chinn[1,2], Bryan Rinde[1], Jaroslav Slamecka[3], Heidi Cook-Andersen[3], Mana Parast[3], and Christian Metallo[1]
[1]Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA
[2]Department of Bioengineering, University of California San Diego, La Jolla, CA
[3]Department of Reproductive Medicine, University of California San Diego, La Jolla, CA

Lipid metabolism plays a critical role in regulating the self-renewal, growth, and differentiation of human pluripotent stem cells (hPSCs), and these stem cell models offer a unique means of studying metabolism during the earliest stages of human development. While recent studies have demonstrated the importance of enzymes in phospholipid biosynthesis during embryogenesis and cellular reprogramming, sourcing of essential fatty acids and other polyunsaturated fatty acids in regulating pluripotency is underexplored. Polyunsaturated fatty acids (PUFAs) have multiple double bonds and play crucial roles in cell membrane structure and fluidity, formation of bioactive signaling molecules, and energy metabolism. While hPSCs potently upregulate lipid synthesis in chemically defined media, the impact on PUFA metabolism is not known. To this end, using isotopically labeled glucose and high-resolution orbitrap MS, we demonstrate a high level of flux through non-canonical PUFA synthesis pathways and incorporation of PUFAs into phospholipids and other membrane lipids. Inhibition of the critical desaturase enzymes in these pathways rapidly remodels the lipidome and leads to alterations in pluripotency. Notably, this phenomenon is specific to hPSCs, which can grow and proliferate in a lipid deficient state, in contrast to differentiated cells and cancer cell lines that require serum for proliferation. Surprisingly, the addition of a select PUFA to hPSCs also increases pluripotency while others alter central carbon metabolism and may confer sensitivity to redox stress. Altogether these findings indicate that alternate polyunsaturated fatty acid synthesis pathways may promote pluripotency and may be critical to embryonic development.

A novel multimodal animal cradle system facilitates optical, PET, µCT, and MRI co-registrations of a metastatic, colorectal cancer syngeneic mouse model

Peter Dib[1], Andrew Van Praagh[1], Paul Ballieu[1], Ali Bahadur[1], Kristin Granlund[1], Saaussan Madi[1], Mark Mattingly[1], Todd Sasser[1], Dianne Begemann[2], and Fallon Noto[2]
[1]Bruker Preclinical Imaging, 15 Fortune Dr, Billerica, MA 01821, USA
[2]Hera BioLabs, 2277 Thunderstick Dr. #500, Lexington, KY 40505

Multimodal imaging can dramatically enhance the diagnostic capabilities of pre-clinical animal research models. Investigators in the fields of oncology and immuno-oncology have sought to add optical imaging to their PET/µCT/MRI data sets because optical adds a sensitive, low-cost, high-throughput imaging capability that can predict the biodistributions of high-cost, low throughput PET/µCT/MRI data sets. In this poster, we demonstrate that a newly-developed multimodal animal cradle system from Bruker BioSpin readily enables optical/PET/µCT/MRI co-registrations.

Dissecting the cell-autonomous and non-autonomous mechanisms of adaptation to autophagy inhibition in pancreatic cancer

Joel Encarnacion-Rosado[1], Suzanne Dufresne[1], Alec C. Kimmelman[2], and Christina Towers[1]
[1]Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA
[2]Perlmutter Cancer Center, NYU Grossman School of Medicine, New York, NY, 10016, USA

Pancreatic ductal adenocarcinoma (PDAC) is a highly aggressive disease with a 5-year survival rate of less than 13% largely due to a lack of early detection methods, limited therapy alternatives, and inherent resistance. PDAC tumors display higher basal levels of autophagy, representing a potential therapeutic liability. Autophagy is a highly conserved process that sequesters organelles and macromolecules and targets them for lysosomal degradation to maintain cellular homeostasis during periods of starvation or stress. Autophagy is associated with various tumor promoting biological processes (e.g., immune evasion, tumor-stroma crosstalk, metabolism). As a result, multiple clinical trials have begun to evaluate the use of lysosomal inhibitors such as hydroxychloroquine for cancer treatment. However, the clinical progress has been modest, probably due to the acquisition of drug resistance, which is still a significant hurdle for cancer therapy. We hypothesize that cancer cells can rapidly reprogram their metabolome and transcriptome state in response to autophagy inhibition, resulting in adaptation. Yet, the cellular and molecular mechanisms of adaptation to autophagy inhibition are not fully identified. I propose dissecting the complex mechanisms cancer cells use to adapt to autophagy inhibition. Our central hypothesis is that cancer cells utilize cell-autonomous and non-autonomous programs to bypass autophagy inhibition. We will pursue this hypothesis in two parallel aims focusing on the cellintrinsic mechanisms of adaptation and the cell-extrinsic factors within the tumor microenvironment that help facilitate these adaptations. This work could advance our understanding of how tumors acquire resistance to autophagy inhibitors. These new insights will impact ongoing and new clinical trials using different autophagy inhibitors to improve PDAC patient outcomes.efficacy in PDAC. These results underscore the potential of multi-targeted therapeutic strategies to overcome resistance and improve durability of the treatment. We are also aiming at evaluating this combination using inducible system in patient-derived organoids.

HNF4*α* controls gastric identity and KRAS^{G12D} inhibitor response in Invasive Mucinous Adenocarcinoma (IMA)

Headtlove Essel Dadzie[1,2], Yangsook Song Green[1], and Eric Snyder MD, PhD[1,2,3]
[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, USA
[2]Department of Oncological Sciences, University of Utah, Salt Lake City, UT, USA
[3]Department of Pathology, University of Utah, Salt Lake City, UT, USA

Cellular plasticity is a hallmark of cancer, enabling tumor cells to alter identity and evade therapeutic pressure. In invasive mucinous adenocarcinoma of the lung (IMA), NKX2-1 loss triggers a pulmonary to gastric switch marked by aberrant activation of HNF4α, a master regulator of gastrointestinal/hepatic differentiation. Although FoxA1/2 are required for HNF4α expression in IMA, the role of HNF4α itself in IMA has remained unclear. Here, we find that HNF4α promotes IMA growth and activates a gastric pit cell-like program. Genetic deletion of *Hnf4a* induces IMA dedifferentiation, enabling FoxA1/2 to access de novo sites and activate alternative identities. HNF4α also induces a mucinous program associated with tolerance to KRAS blockade, and HNF4α loss enhances response to KRAS^{G12D} inhibition. Mechanistically, HNF4α blocks cell cycle exit in drug-tolerant persister cells and promotes activity of the antioxidant transcription factor NRF2. Analysis of TCGA LUAD data reveals a strong positive correlation between *HNF4A* and *NRF2* expression. NRF2 activation partially rescues effects of *Hnf4a* deletion on KRAS^{G12D} inhibition, whereas NRF2 inhibition enhances sensitivity to KRAS^{G12D} blockade. Our findings establish HNF4α as a central regulator of gastric identity and primary response to KRAS^{G12D} inhibition in IMA and suggest that co-targeting HNF4α and NRF2 may enhance the primary response to KRAS inhibition in IMA.

Metabolic tracing to identify critical reactions in nucleic acid homeostasis

Emily Fennell[1], Mack Reynolds[1], Shrikaar Kambhampati[2], and Christian Metallo[1]
[1]Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037
[2]Jack H. Skirball Center for Chemical Biology and Proteomics, Salk Institute for Biological Studies, La Jolla, CA 92037

Nucleotide metabolism plays a pivotal role across a variety of cellular functions, including DNA/RNA synthesis, bioenergetics, lipid metabolism, inflammation, and stress response signaling. Alterations of nucleotide metabolism are reported across diseases and cell states, including cancer, neurodegeneration, and immune regulation. Though canonical pathways of nucleotide *de novo* synthesis and salvage have been well characterized, adaptations of nucleotide metabolism to support cancer progression remain poorly understood. To determine metabolic flux of nucleic acid synthesis, $^{13}C_6$-glucose was utilized as a precursor for *de novo* nucleotide synthesis to generate ^{13}C-labeled nucleic acids from both mammalian (HEK293T) cells and *E. coli*. Liquid chromatography mass spectrometry (LC-MS) methods were used to monitor ^{13}C-labeling kinetics of both DNA and RNA over multiple passages (HEK293Ts) or hours (*E. coli*) to determine metabolic flux through nucleotide synthetic pathways. Additionally, isolated nucleic acids can be utilized as isotopic tracers to monitor nucleic acid metabolism in cells. Preliminary data in MDA-MB-231 cells, a model of triple-negative breast cancer (TNBC), demonstrate increased exogenous DNA uptake and ^{13}C-adenine labeling following 24-hour incubation, indicating basal levels of nucleotide salvage from environmental nucleic acids. To further our understanding of nucleic acid homeostasis in cancer cells, we will utilize these nucleic acid tracers to monitor nucleic acid uptake and utilization in TNBC cells with various metabolic perturbations (i.e., autophagic deficiency). Kinetic tracing data will also be used for metabolic flux analysis utilizing Stable Isotope-assisted Metabolomics for Pathway Elucidation (SIMPEL), a novel tool for high throughput metabolic kinetic studies, to elucidate metabolic pathway maps of nucleic acid/nucleotide metabolic fates.

Delineating tumor suppressive function of Men1 in the exocrine pancreas

Makenzie N. Fourman[1], Sajad A. Wani[2], Nina Lazic[2], Patrick M. Krause[2], and Amanda R. Wasylishen[1,2]
[1]Department of Cancer and Cell Biology, University of Cincinnati, United States
[2]Department of Cancer Biology, University of Cincinnati, United States

Pancreatic ductal adenocarcinoma (PDAC) is a devastating malignancy with a five-year survival rate of 13%. The pancreas maintains homeostasis in response to stress by undergoing cell state changes through a process called acinar to ductal metaplasia (ADM). ADM is one-way PDAC can develop. Our lab is interested in a known tumor suppressor, multiple endocrine neoplasia type 1 (MEN1), and discovered Men1 is critical for exocrine pancreatic homeostasis in response to either inflammatory or oncogenic stress. In the context of oncogenic Kras, Men1- deficient mice have robust oncogenic transformation of the exocrine pancreas compared to controls. Understanding the molecular mechanisms that restrain precancerous lesions and prevent tumor development will provide important insights for targeting early tumorigenesis in the pancreas. We hypothesize Men1 regulates homeostasis in the exocrine pancreas in response to stress and suppresses the development of PDAC. To identify the transcriptional changes and candidate molecular mechanisms downstream of Men1 loss, we have conducted single nucleus RNA-sequencing (snRNA-seq) on pancreas tissue from three $Kras^{LSL-G12D/+}Men1^{fl/fl}Pdx1\text{-}Cre^{Tg}$ (KMC) and three $Kras^{LSL-G12D/+}Men1^{fl/+}Pdx1\text{-}Cre^{Tg}$ ($KM^{+}C$) mice at 3-weeks of age, prior to robust oncogenic transformation. Differential gene expression analysis of acinar clusters identified 666 significantly upregulated genes in KMC pancreas compared with $KM^{+}C$ controls. Pathway analysis revealed significant enrichment in cell adhesion and invasion pathways. Similar results were also obtained from an analysis of TCGA data comparing MEN1 low to high expressing PDAC samples. We have conducted preliminary validation through Men1 overexpression *in vitro*. Current work is focused on delineating the molecular mechanism(s) that mediate altered gene expression and extending these findings to human PDAC models allowing for better our understanding of early tumorigenesis.

Targeting protein fatty acylation to inhibit colorectal cancer growth

Linnea Hases, Sihao Liu, Satoshi Ogawa, Gia H. Quach, Mingxiao He, Jonathan Zhu, Nidhi Jyotsana, Morgan Truitt, Weiwei Fan, Yang Dai, Annette R. Atkins, Ruth T. Yu, Michael Downes, and Ronald M. Evans
Gene Expression Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA

Excess intake of dietary fat is a risk factor for colorectal cancer (CRC), however the mechanistic underpinnings remain poorly understood. Aberrant fatty acid metabolism has long been recognized in CRC cells. While conventionally viewed as building blocks for membranes and energy substrates, fatty acids also covalently modify hundreds of proteins via fatty acylation. This modification regulates oncogenic signaling by affecting protein localization, stability, interactions, trafficking, and activity—linking metabolism to cellular function. Among regulators of this process, HDAC11, a lysine fatty acid deacylase, is significantly upregulated in CRC and exhibits over 10,000-fold greater catalytic efficiency for fatty acid deacylation than deacetylation. Using genetic knockouts and the HDAC11 inhibitor SIS17, we found thatHDAC11 is dispensable for normal function but crucial for CRC growth. To explore how HDAC11 drives tumor growth, we employed an unbiased click chemistry-based mass spectrometry screen for HDAC11 inhibition-sensitive protein palmitoylations. This analysis revealed numerous oncogenic receptor tyrosine kinases, including HER3. HER3, a member of the EGFR (ErbB) family, plays a critical role in cell growth and survival. Despite low kinase activity, HER3 forms heterodimers with HER2 or EGFR to activate downstream signaling. We found that HDAC11 inhibition increases HER3 palmitoylation, reducing its membrane localization and dimerization with EGFR/HER2, thereby suppressing HER3/EGFR signaling and downstream MAPK activation (p-ERK1/2). HER3 has also been implicated in CRC resistance to EGFR and KRAS-targeted therapies. Consistent with this, HDAC11 and HER3 are both induced by KRAS inhibition, cooperatively supporting HER3-driven resistance. Combining SIS17 with KRAS inhibition improves CRC suppression. These findings position HDAC11 as a promising therapeutic target in CRC with potential to overcome treatment resistance.

Establishing gemcitabine resistant organoid models of pancreatic cancer

Araceli Herrera Morales[1,2,3], Kassidy Curtis[1], Vasiliki Pantazopoulou[1], and Dannielle Engle[1]
[1]Regulatory Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037
[2]California State University San Marcos, San Marcos, CA 92096
[3]California Institute for Regenerative Medicine, San Francisco, CA 94080

Pancreatic ductal adenocarcinoma (PDA) has a dismal 5-year survival rate of only 13%. Most patients are diagnosed at an advanced stage, often with metastatic disease, and respond poorly to chemotherapy agents such as gemcitabine. Moreover, resistance to chemotherapy nearly always develops rapidly. Despite this, many preclinical models remain treatment-naïve, limiting their clinical relevance. To better model patient responses, it is critical to develop *in vitro* systems that are pre-treated and resistant to standard-of-care therapies like gemcitabine. Our lab routinely employs organoid models to study PDA. Organoids are 3D cell cultures derived from human or mouse tumors and grown in basement membrane extract, closely mimicking *in vivo* drug responses. In this study, we aimed to generate a gemcitabine-resistant PDA organoid line for use in future therapeutic screens. We used mT69A organoids, a mouse-derived PDA line, and first established a dose response curve to determine gemcitabine sensitivity in the parental line. Based on this, we initiated treatment at the EC20 concentration (7 nM) and gradually increased the dose over successive passages. Parental organoids cultured with DMSO served as controls throughout. After reaching a concentration 30-fold higher than the parental EC50 (221 nM), we reassessed gemcitabine sensitivity. The resistant line exhibited a 12-fold increase in EC50 compared to the control, confirming successful development of resistance. Future work will assess the response of these gemcitabine-resistant organoids to other targeted agents, including novel RAS inhibitors currently in clinical development. In summary, we have established a clinically relevant gemcitabine-resistant organoid model of PDA, which will serve as a valuable tool for evaluating alternative treatment strategies in the context of acquired chemoresistance.

Distinct T cell functions enable efficient immunoediting and prevent tumor emergence in developing sarcomas

Brian G Hunt[1], Julie F Cheung[1], Shudipto Wahed[1], Elaine Cheng[1], Kelli A. Connolly[1], Srividhya Venkatesan[1], Jennifer Loza[1], Ishan Bansal[1], Eric Fagerberg[1], Emily Kessler[1], Clémence Riffard[1], Jessica Buck[1], John Attanasio[1], Emily Borr[1], Wei Wei[2], Ivana William[1], Brittany Fitzgerald[1], and Nikhil S. Joshi[1]
[1]Department of Immunobiology, Yale School of Medicine, New Haven, CT 06519
[2]Department of Biostatistics, Yale University, New Haven, CT 06519

T cells shape developing tumors through immunoediting, eliminating immunogenic tumor cells based on their expression of neoantigens. Here, we studied how T cells suppress early growth using an autochthonous mouse model of soft-tissue sarcoma where tumors express fluorescent neoantigens, which allowed assessment of neoantigen-expressing tumor cells on a per-cell basis. Tumors emerged later in T cell-sufficient mice and with reduced penetrance (tumors formed in ~100% of T cell-deficient and ~53% of the T cell-sufficient mice). Analysis of the emergent tumors showed silencing of neoantigens in all tumor cells from T cell-sufficient mice, but surprisingly, tumors from T cell-deficient mice also contained significant fractions of neoantigen-negative tumor cells, suggesting neoantigen silencing was necessary but not sufficient for tumor emergence. Genetic removal of neoantigens rescued tumor development, but only when uniform removal occurred at day 5 post initiation, and not day 10 or later. In line with this, CD8 and CD4 T cells infiltrated muscles containing tumor-initiating cells and eliminated most pre-emergent sarcoma cells within 8 days of tumor initiation. Single-cell transcriptomic analysis at day 7 showed that oncogenic alterations led to enhanced proliferation and lineage program loss, but also T cell-dependent upregulation of the IFNγ-response gene Cd274 (PD-L1). Blockade of IFNγ rescued early tumor cells, but only those that were neoantigen-negative, demonstrating that T cells control early tumors via IFNγ-dependent (bystander killing) and IFNγ-independent (cytolytic) mechanisms. Together, these data mechanistically explain why neoantigen+ sarcomas in mice are efficiently edited and why a large fraction of T cell-sufficient mice never develop tumors.

Microtentacle-mediated heterotypic clustering of tumor cells and neutrophils in breast cancer metastasis

Julia A. Ju[1,2], Keyata N. Thompson[1,2], Michele I. Vitolo[1,2], and Stuart S. Martin[1,2,3]
[1]Department of Pharmacology and Physiology, University of Maryland School of Medicine, Baltimore, MD 21201
[2]Marlene and Stewart Greenebaum NCI Comprehensive Cancer Center, University of Maryland School of Medicine, Baltimore, MD 21201
[3]United States Department of Veterans Affairs, VA Maryland Health Care System, Baltimore, MD 21201

Current cancer therapies are mainly used clinically to target growth of the primary tumor, even though metastasis is what leads to patient mortality. Circulating tumor cells (CTCs) and CTC clusters serve as direct precursors of metastatic outgrowth in breast cancer. Before tumor cells colonize at distant sites, they engage with immune cells in the bloodstream to ultimately regulate tumor progression. Heterotypic clusters form between CTCs and neutrophils and contribute to a higher metastatic potential and are associated with decreased survival in patients compared to single CTCs. Our lab discovered that CTCs produce tubulin-based microtentacles (McTNs), which promote reattachment, retention in distant sites during metastasis and formation of tumor cell clusters. Neutrophil-CTC clusters help CTCs survive the harsh vascular environment to promote successful metastasis; however, the specific mechanism of this interaction is not fully understood. Utilizing TetherChip to recapitulate the nonadherent environments of metastasis, we found that neutrophils form McTNs that facilitate homotypic clustering, reattachment and migration and could be targeted using Vinorelbine, a microtubule depolymerizer. Co-culturing neutrophils and tumor cells form heterotypic clusters mediated by McTNs that enhanced migration toward multiple stimuli. Targeting McTNs on heterotypic clusters with Vinorelbine reduced heterotypic clustering as well as migration. Finally, we reveal a unique cytokine signature present in the co-culture that is associated with worse prognosis in patients with breast cancer. CTC-neutrophil clusters have higher metastatic efficiency, and by demonstrating that neutrophils form McTNs, we reveal a new possible mechanism for how neutrophils interact with tumor cells. These findings support the idea that developing cluster-disrupting therapies could provide a new targeted strategy to reduce the metastatic potential of cancer cells and yield more successful clinical outcomes.

Targeting undruggable drivers using lipid nanoparticle-RNA delivery to prevent pancreatic cancer

Nidhi Jyotsana, Nandhana Nair, Gabriela Estepa, Daniel Cao, Morgan L Truitt, Weiwei Fan, and Ronald M Evans
[1]Gene Expression Laboratory, Salk Institute for Biological Studies, La Jolla, San Diego, CA 92037

Intraductal papillary mucinous neoplasms (IPMNs) are cystic tumors of the pancreas that give rise to approximately 15% of all pancreatic ductal adenocarcinomas (PDAC). Overall, 96% of IPMNs harbor KRAS (~80%) or GNAS (~66%) driver mutations. Despite their early clinical recognition, no targeted therapies have been approved for IPMNs. KRAS inhibitors recently gaining traction in PDAC have not been tested in IPMN-specific settings. Notably, there are no clinically available inhibitors that specifically target mutant GNAS and the precise role of activating mutations in *GNAS* in neoplastic progression remains unclear.

We hypothesized that mutant GNAS acts as a critical driver of IPMN progression by modulating key oncogenic signaling pathways, and that selective knockdown of mutant *GNAS* could reveal actionable dependencies. Our objective was to investigate the molecular consequences of silencing mutant *GNAS* in IPMN-derived PDAC models using RNA interference.

Utilizing lipid nanoparticles (LNPs) to deliver mutant-KRAS-specific siRNA and/or mutant GNAS-specific siRNA, in IPMN cells, we identified novel targets and pathways associated with mutant KRAS and GNAS and uncovered a negative regulation of GNAS by KRAS in IPMN-derived PDAC cells. Our *in vitro* and *in vivo* results promise the potential of dual targeting mutant-KRAS and mutant-GNAS to prevent progression of IPMNs to PDAC. These findings support the rationale for incorporating *GNAS* modulation into therapeutic strategies for IPMNs and highlight the need for developing mutant-specific GNAS inhibitors.

Rewiring of intracellular pH and glycosylation by oncogenic Kras

Elham Khosrowabadi and Cosimo Commisso
NCI-Designated Cancer Center, Sanford Burnham Prebys Medical Discovery Institute 10901 N. Torrey Pines Road, La Jolla, CA 92037

Pancreatic ductal adenocarcinoma (PDAC) is driven by recurrent oncogenic mutations in KRAS and TP53, yet their impact on intracellular homeostasis and glycan processing remains incompletely defined. Using an isogenic human pancreatic epithelial (HPNE) cell model, we investigated how KRAS G12D reprograms Golgi function, pH regulation, and glycosylation.

We show that KRAS G12D elevates both intracellular and trans-Golgi pH, as measured by BCECF-AM and organelle-targeted pH biosensors. This alkalinization is accompanied by aberrant glycosylation, including increased α2,3-linked sialylation (MAL-II binding) and Tn-antigen exposure (HPA binding)—features commonly associated with tumor immune evasion and metastasis. These glycomic changes are recapitulated in KRAS-mutant PDAC cell lines (PANC-1, 1334) and are partially reversed upon treatment with the selective KRAS G12D inhibitor MRTX1133.

Western blotting confirmed KRAS expression and downstream MAPK pathway activation. Lectin staining and pH measurement further demonstrated that KRAS G12D expression in HPNE isogenic cells contributes to intracellular pH elevation and glycosylation changes but is insufficient to fully recapitulate the PDAC-associated glycan profile. To investigate sequential oncogenic cooperation, we are generating isogenic models harboring TP53 R273H in the KRASG12D background to assess additive effects on Golgi dysfunction and glycan remodeling.

These findings define a novel KRAS–Golgi–glycome axis in PDAC and highlight glycosylation and organelle pH as actionable vulnerabilities in KRAS-driven pancreatic cancer.

SOX11 regulates basal cell identity and plasticity in pancreatic ductal adenocarcinoma

Jung Yun Kim[1], Anupriya Singhal[1,2], John Guthrie[1], Hannah Styers[1], Qianzi Li[3,4], Leslie Christina[4], and Tuomas Tammela[1†]
[1]Cancer Biology and Genetics Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, New York, 10065, USA
[2]Gastrointestinal Oncology Service, Memorial Sloan Kettering Cancer Center, New York, NY, 10065, USA
[3]Weill Cornell Graduate School of Medical Sciences, Weill Cornell Medical College, New York, NY 10065, USA
[4]Computational and Systems Biology Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA
[†]Correspondence

Basal cell states in pancreatic ductal adenocarcinoma (PDAC) are associated with poor prognosis and therapy resistance, yet the transcriptional mechanisms that govern their identity remain unclear. Here, we identify SOX11 as a candidate pioneer transcription factor that is highly and specifically expressed in basal PDAC cells in both mouse and human tumors. Functional studies revealed that knockout (KO) of *Sox11* resulted in increased tumor growth and metastasis, accompanied by a significant reduction in basal cells and a concomitant increase in mesenchymal cell populations. Single-cell RNA sequencing demonstrated that while classical cell states remained unchanged, basal and mesenchymal states were notably altered, with KO-derived mesenchymal cells exhibiting expansion and spatial convergence toward the basal cluster. A triple knockout of SoxC family members led to smaller tumors, suggesting potential partial redundancy, though compensation was not definitive. Moreover, basal cell–specific KO of *Sox11* significantly reduced the *Slc4a11*$^{+}$ basal population, supporting its role in maintaining basal identity. Using ChromaFold predictions from scATAC-seq data, we found that SOX11 forms basal cell–specific chromatin loops with enhancers, implicating chromatin remodeling as a mechanism for its selective activity. Together, these results suggest that SOX11 is a critical regulator of the basal cell state in PDAC, influencing both cell fate and chromatin architecture.

Small molecule Bcl-2 functional converters

Siva K. Kolluri[1,6], Prasad R. Kopparapu[1], Martin C. Pearce[1], Christiane V. Löhr[2], Cathy Duong[1], Hyo Sang Jang[1], Shanthakumar Tyavanagimatt[1], Edmond F. O'Donnell[1], Arnold C Satterthwait[3], Xiao-kun Zhang[4], and Harikrishna Nakshatri[5]
[1]Cancer Research Laboratory, Department of Environmental & Molecular Toxicology, Oregon State University, Corvallis, OR, 97331, USA
[2]Department of Biomedical Sciences, Carlson College of Veterinary Medicine, Oregon State University, Corvallis, Oregon, USA
[3]Sanford Burnham Prebys Medical Discovery Institute, 10901 North Torrey Pines Road, La Jolla, CA, 92037, USA
[4]School of Pharmaceutical Sciences, Xiamen University, Xiamen, 361005, China
[5]Department of Surgery, Indiana University School of Medicine, Indianapolis, Indiana, USA
[6]Linus Pauling Institute, Oregon State University, Corvallis, Oregon, USA

Bcl-2, an anti-cell death protein, is overexpressed in many human cancers and contributes to tumor development, progression, and resistance to chemotherapy. High Bcl-2 expression is associated with poor prognosis and treatment outcomes. We have discovered a pathway to convert Bcl-2 from a cytoprotective to cytodestructive protein through binding by the orphan nuclear receptor Nur77, which exposes a hidden "killer BH3 domain" of Bcl-2 (Science 289: 1159-64, 2000, PMID: 10947977; and Cell 116, 527-540, 2004, PMID: 14980220). Building on this mechanism, we developed Nur77-derived Bcl-2 Converting Peptides (NuBCPs) that bind Bcl-2 and convert Bcl-2 from a protector to a killer protein (Cancer Cell 14, 285-98, 2008, PMID: 18835031; Oncotarget 9, 26072-26085, 2018, PMID: 29899843; Apoptosis 10.1007, 2019, PMID: 30612317). More recently, we have identified small molecules, termed as 'Bcl-2 functional converters', that mimic NuBCP activity and selectively induce apoptosis in Bcl-2-overexpressing cancer cells (Cancer Research Communications 4(3):634-644, 2024, PMID: 38329389; ACS Pharmacol Transl Sci.;7(5):1302-1309, 2024, PMID: 38751629). This targeted conversion of Bcl-2 opens new avenues for treating cancers that rely on Bcl-2 for survival.

Identifying novel mechanisms of mitochondrial quality control in cancer cells

Anvita Komarla[1,2] and Christina Towers[2]
[1]Department of Bioengineering, University of California San Diego, La Jolla, CA 92093
[2]Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037

Mitophagy is a specialized form of autophagy where damaged mitochondria are engulfed by autophagosomes and shuttled to lysosomes for degradation. Surprisingly, cancer cells can circumvent autophagy inhibition and still exhibit normal mitochondrial function indicating that cells have alternative mitochondrial quality control mechanisms. To identify regulators of autophagy-independent mitochondrial degradation, we performed a genome-wide CRISPR screen using mitochondrial-localized pH-sensitive probes that can quantify lysosome-mediated degradation. Two top hits from the screen were SETDB1 and ATF7IP which complex together to regulate heterochromatin. My data shows that ATF7IP loss reduces mitochondrial delivery to the lysosome and impairs mitochondrial function. I am currently elucidating the mechanisms by which the SETDB1-ATF7IP complex regulates autophagy-independent mitochondrial quality control by identifying upstream and downstream interactors. Inhibiting this pathway could increase the anti-tumor efficacy of autophagy inhibitors or target autophagy-independent tumors.

EPHA2 canonical and non-canonical signaling in cholangiocarcinoma development and progression

Evodie Koutouan[1], Ayano Niibe[2], Rory L. Smoot[2], and Elena B. Pasquale[1]
[1]Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA 92037, USA
[2]Mayo Clinic, Rochester, MN 55905, USA

EPHA2, a member of the Eph receptor tyrosine kinase family, has been demonstrated to show elevated expression and dual role in many cancers. Studies of EPHA2 mutations from publicly available database revealed a substantial number of EPHA2 mutations in patient samples of cholangiocarcinoma (CCA), a cancer type originating from the biliary epithelia. Even though CCA is considered rare, there is a growing occurrence as well as a lack of effective methods grouping the current surgical interventions, chemotherapies, and immunotherapies. As an effort for uncovering the molecular pathways leading to the development and progression of CCA, I conducted a functional characterization of the EPHA2 mutations found in cases of CCA by monitoring tyrosine phosphorylation of the receptor as an indication of its ligand and kinase dependent signaling activity. I demonstrated that the missense mutations found in the ligand binding and the kinase domains compromise ligand and kinase dependent activity of the receptor. My analysis also highlights that the majority of the EPHA2 mutations leads to truncated forms of the receptor missing partially or completely the kinase domain, thus impairing the receptor's kinase activity. In addition, my data reveal the dominant negative effect of two truncated forms of EPHA2 as well as a kinase inactive EPHA2 mutant. These findings taken together with a collaborative work revealing that an EPHA2 kinase inactive mutant can induce proliferative lesions in a validated *in vivo* CCA model, support the tumor suppressive role of EPHA2 ligand and kinase dependent signaling in CCA development.

Plasminogen activation drives plasticity in lung cancer

Klavdija Krause, Jason E. Chan, Chun-Hao Pan, Jonathan Rub, Gary Guzman, Emma Brown, Xueqian Zhuang, Zhuxuan Li, Carleigh Sussman1, Hannah Styers, and Tuomas Tammela
Cancer Biology and Genetics Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065, USA

Cellular plasticity—the ability of cancer cells to transition between phenotypic states—drives tumor progression and therapy resistance. Our prior work suggests that in solid tumors, plasticity is concentrated in a minority subset of cells, termed the high-plasticity cell state (HPCS). As such, targeting the HPCS may suppress tumor progression and overcome treatment resistance. However, limited understanding of the underlying mechanisms has hindered efforts to therapeutically target plasticity. We utilized *in vivo* genetic screens, reporters, and pharmacologic inhibitors to identify druggable drivers of plasticity in lung cancer.

Using barcode-based lineage tracing and an *in vivo* multiplexed shRNA screen, we uncover canonical NF-κB signaling as a central regulator of the HPCS. Investigating upstream drivers, we found no enrichment of classic cytokine receptors involved in canonical NF-κB activation—such as Il1r1, Tnfrsf1a, and Tnfrsf1b—in the HPCS. Surprisingly, we uncovered that proteolytic activation of the anticoagulant plasminogen is a key upstream driver of plasticity in lung adenocarcinoma (LUAD). Expression of the urokinase-type plasminogen activator receptor (uPAR) and its activator (uPA) is restricted to the HPCS, enabling plasminogen activation within this niche. Plasmin, in turn, activates PAR1-mediated NF-κB signaling, which sustains HPCS maintenance and drives tumor progression.

We reveal key cellular and molecular mechanisms driving plasticity in lung cancer through a co-opted wound healing niche. Unlike normal wound healing, which restores tissue homeostasis upon resolution, plastic cancer cells hijack this process to maintain an unresolved, proinflammatory state. This insight opens new avenues for therapeutic strategies aimed at disrupting treatment resistance by targeting aberrant wound-healing mechanisms that fuel cancer plasticity.

Investigating adaptive metabolic responses to RAS inhibition in pancreatic cancer

Casie S Kubota[1,2], Maureen L. Ruchhoeft[2], Kristina L. Peck[1], Dannielle D. Engle[1], and Christian M. Metallo[2]
[1]Regulatory Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA
[2]Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA 92037, USA

Introduction: Pancreatic ductal adenocarcinoma (PDA) is the fourth-leading cause of cancer-related deaths among adults in the United States. The *KRAS* oncogene is mutated in nearly all PDA cases and has remained an elusive therapeutic target until recently. The $KRAS^{G12D}$ inhibitor MRTX1133 and the RAS(ON) inhibitor RMC-6236 have been shown to potently perturb tumor growth, however, resistance occurs rapidly, presenting a significant obstacle to improving patient outcomes. We hypothesize that lipid metabolic pathways are altered in response to RAS inhibitor treatment. **Methods**: To better understand these resistance mechanisms, we applied ^{13}C metabolic flux analysis (MFA) to RAS inhibitor-resistant 2D cell lines and mouse PDA tumor slice cultures derived from the *LSL-Kras*$^{G12D/+}$;*LSL-Trp53*$^{R172H/+}$;*Pdx-1-Cre* (KPC) PDA mouse model. Using [U-13C]glucose and [U-^{13}C]glutamine tracers, we measured ^{13}C incorporation into polar and lipid metabolites to determine how RAS inhibition affects flux through central carbon metabolism and lipid metabolic pathways. **Results**: In 2D cell culture, we observed that while matched parental and MRTX1133-resistant cells exhibit similar growth rates, resistant cells show differences in rates of lipogenesis. To test the effect of RAS inhibitor treatment on the intact tumor microenvironment (TME), we excised tumors from KPC mice and treated vibratome-cut tumor slices *ex vivo* with MRTX1133 and RMC-6236. Interestingly, we observed distinct effects on flux through central carbon metabolism and lipid synthetic pathways in slices treated with MRTX1133 and RMC-6236. **Conclusions**: Together, these results indicate that RAS inhibition alters fatty acid metabolism in 2D culture and tumor slice models. Further studies using MFA in 2D and 3D *in vitro* culture systems and in *ex vivo* slice cultures will elucidate the roles of specific cellular compartments within the TME that contribute to RAS inhibitor resistance. These studies will also inform new therapeutic strategies to mitigate drug resistance and improve treatment efficacies.

Impact of endothelial cell autophagy inhibition on tumorigenesis

Brayden Chin, Nancy León-Rivera, and Teresa Monkkonen
Department of Biology, San Diego State University, San Diego, CA

In 2025, the American Cancer Society estimates approximately 316,950 new cases of invasive breast cancer will be diagnosed in women. Breast cancers lacking hormone receptor expression have limited treatment options, leading to poor patient outcomes. Autophagy inhibition is being tested as a targeted therapy, but its effects on tumor vasculature remain largely unknown. To assess endothelial-specific autophagy inhibition in a physiological model of breast cancer, we generated Atg12 and Atg5 endothelial cell knockout (ECKO) mice using the Cdh5CreER vascular endothelial cadherin promoter driver. Efficient recombination was validated by FACS following tamoxifen induction in both Atg12 and Atg5 ECKO mice with limited Cre leakiness in controls. Orthotopic transplantation of MMTV-PyMT derived tumor organoids into Atg12 or Atg5 ECKO mice resulted in significantly delayed tumor growth and increased survival compared to controls. In an autochthonous PyMT model, Atg12 ECKO mice similarly exhibited delayed time to endpoint tumor volume. Following surgical resection of primary tumors, Atg12 ECKO mice demonstrated higher rates of tumor recurrence (46%) and lung metastasis (60%) compared to controls. Tail vein injection of PyMT cells into tumor naive mice showed an increase in lung metastasis size with Atg ECKO; similarly, end-stage PyMT lungs displayed larger metastases as well. To test whether these effects were tumor type specific, we used the Rat insulin promoter-SV40 Large T antigen (RIP-Tag) model of pancreatic neuroendocrine tumors, which are highly vascular and sensitive to anti-angiogenic therapy. Neither early nor late endothelial deletion of Atg12 altered primary tumor burden or survival, in contrast to the PyMT findings. However, Atg12 ECKO mice displayed a significant increase in liver micrometastases, suggesting that EC autophagy may limit dissemination. These results highlight the context-dependent roles of endothelial autophagy in tumor progression.

Eph receptor heterointeractions in cancer cell signaling

Alejandro Lillo[1], John Chen[1], Tanaya Roya[2], Kalina Hristova[2], and Elena B. Pasquale[1]

[1]Cancer Center, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA 92037, USA

[2]Department of Materials Science and Engineering, Johns Hopkins University, Baltimore, MD 21218, USA

The Eph receptor tyrosine kinase family is involved in numerous diseases, including cancer. Among these receptors, EphA2 is the one most profoundly linked to disease. The most unique feature of EphA2 is its capacity to signal through two different mechanisms: the canonical pathway, which is activated by binding to ephrin-A ligands, and the non-canonical pathway, which operates independently of ligand binding and instead relies on phosphorylation at serine 897 (S897). While EphA2 canonical signaling is generally associated with anti-oncogenic effects, non-canonical signaling promotes pro-oncogenic responses.

Increasing evidence suggests that EphA2 heterooligomerization with other Eph receptors can modulate both its canonical and non-canonical signaling. Using co-immunoprecipitation assays in transfected HEK293 cells, we identified specific interactions between EphA2 and multiple other Eph receptors. We then focused on the heterointeraction between EphA2 and EphB4, as both receptors are widely expressed in cancer and can mediate either tumor-suppressive or tumor-promoting responses, depending on their functional coupling to different downstream effectors.

Our aim is to determine whether the heterooligomeric context enhances the pro- or anti-oncogenic signaling activities of EphA2 and EphB4. By comparing control PC3 prostate cancer cells with PC3 cells in which EphA2 or EphB4 were individually silenced, we found that each receptor potentiates ephrin-induced tyrosine phosphorylation (activation) of the other receptor. We also observed that EphA2 and EphB4 cooperate in modulating key oncogenic signaling pathways, including Akt, Erk, and Crk.

Overall, our findings reveal that EphA2 and EphB4 can form heterooligomeric complexes and that their signaling properties differ significantly when co-expressed compared to when expressed individually. The discovery of new Eph receptor heterooligomeric functional units could expand the range of therapeutic options for combating cancer.

Efficacious suppression of primary and metastasized liver tumors by polyIC-loaded lipid nanoparticles

Yingluo Liu[1], Xinyi Wang[1], Nishta Krishnan[2], Timothy Hsiao[1], Yichun Ji[1], Marcos G. Teneche[3], Peter D. Adams[3], Elina Zuniga[4], Susan M Kaech[5], Liangfang Zhang[2], and Gen-Sheng Feng[1,4]

[1]Department of Pathology, Department of Molecular Biology, Moores Cancer Center, University of California San Diego, La Jolla, CA 92037, USA

[2]Aiiso Yufeng Li Family Department of Chemical and Nano Engineering, University of California San Diego, La Jolla, CA 92037, USA

[3]Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA

[4]Department of Molecular Biology, School of Biological Sciences, University of California San Diego, La Jolla, CA 92037, USA

[5]NOMIS Center for Immunobiology and Microbial Pathogenesis, Salk Institute for Biological Studies, La Jolla, CA 92037, USA

So far, there is no effective mechanism-based therapeutic agent tailored for liver tumors. Immune checkpoint inhibitors (ICIs) have demonstrated limited efficacy in liver cancer, often associated with severe adverse effects. Although poly-inosinic:cytidylic acid (polyIC) has shown an adjuvant effect when combined with anti-PD-L1 antibody (αPD-L1) in treating liver tumors in animal models, its systemic toxicity limits its clinical utility. To address this challenge, we constructed lipid nanoparticles (LNPs) encapsulating polyIC for selective delivery to the liver and evaluated the tumor-suppressive effects of polyIC-LNPs, free polyIC, and/or αPD-L1 in multiple murine liver tumor models. We also analyzed changes in the hepatic immune microenvironment using single-cell RNA sequencing and flow cytometry. Surprisingly, polyIC-LNPs alone robustly suppressed both primary and metastatic liver tumors, independent of αPD-L1. Even a single dose of polyIC-LNPs was sufficient to control liver tumor progression. Primarily taken up by hepatocytes, polyIC-LNPs induced sustained type I interferon signaling, reshaped the hepatic immune landscape, and promoted $CD8^+$ T cell infiltration and activation by enhancing the maturation of conventional dendritic cells (cDC1), ultimately resulting in a potent anti-tumor response. In conclusion, we found that polyIC-LNPs function as an efficacious monotherapy tailored for liver cancer, capable of coordinately modulating antitumor immunity. This novel approach eliminates the need for ICIs, thereby addressing key limitations of current immunotherapies.

Dissecting the role of T_{EX}-derived CCL3 in antitumor immunity

Sofia Lombardi[1], Meenakshi Sudhakaran[1], Tristan Courau[2], Matthew F. Krummel[2], and Kelly Kersten[1]

[1]Cancer Metabolism and Microenvironment Program, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA 92037

[2]Department of Pathology, University of California, San Francisco, San Francisco, CA 94143

Immune checkpoint blockade (ICB) has revolutionized clinical care and improved patient outcomes for many different cancers. Although ICB has shown promising results for some, only a small fraction of patients achieves a complete response. CD8 T cells play an essential part in ICB response, but in tumors, these cells are often characterized by a progressive loss of effector function, a process known as T cell exhaustion. Previously, we have shown that exhausted CD8 T cells (T_{EX}) in several mouse and human cancers express high levels of the myeloid-related chemokine CCL3. However, the molecular mechanisms by which CCL3 regulates antitumor immunity are not yet understood. The aim of this study is to dissect the role of T_{EX}-derived CCL3 in CD8 T cell response and efficacy of immunotherapy. To study the role of CCL3 in T cell exhaustion, we first developed a reductionist *in vitro* model to benchmark distinct stages of T cell exhaustion. We find that T_{EX} producing CCL3 belong to a $PD1^{+}TIM\text{-}3^{+}CX3CR1^{+}$ effector-like subpopulation that co-expresses high levels of cytokines TNFα and IFNγ. Additionally, these cells retain proliferative capacity and intermediate expression of transcription factor TCF1. Treatment with αPD1 *in vitro* increases the proportion of this subpopulation and upregulates expression of CCL3. Interestingly, we found that adoptive transfer of CCL3-deficient CD8 T cells significantly suppresses tumor growth in orthotopic breast cancer and melanoma models. Thus, CCL3 produced by effector-like T_{EX} cells promotes tumor growth and may potentiate acquired resistance to ICB therapy through the recruitment of immunosuppressive myeloid cells. Together, these findings reveal a functional role of T_{EX}-derived CCL3 in tumor progression, suggesting a novel target for immunotherapies.

Non-canonical function of serine tRNA synthetase (SerRS) in inhibiting metastasis in breast cancer

Telma R. Lourenço, Justin Wang, Lei Jiang, Ze Liu, and Xiang-Lei Yang
Department of Molecular Medicine, Scripps Research Institute, San Diego, California, 92037, United States

Breast cancer is the most common cancer in women and a leading cause of cancer-related death worldwide. Triple-negative breast cancer (TNBC), accounting for 10–15% of cases, is the most aggressive subtype and often relapses early with poor prognosis. Treatment options for TNBC remain limited, and once metastasis occurs, breast cancer becomes incurable, with a significantly reduced five-year survival rate. Identifying molecular regulators of metastasis is therefore essential to improve therapeutic strategies.Low expression of the SARS gene, encoding serine tRNA synthetase (SerRS), correlates with poor survival in breast cancer patients. While SerRS is classically known for its role in aminoacylating tRNA, recent studies have revealed non-canonical tumor-suppressive functions. In vivo overexpression of SerRS leads to a significant reduction in metastases in both spontaneous and experimental metastasis mouse models.To investigate the underlying mechanisms, RNA-seq analysis revealed that SerRS alters the expression of genes involved in the Wnt signaling pathway. In cell-based models, we confirmed that SerRS inhibits Wnt signaling and limits the expression of EMT-related genes, thereby impairing metastatic progression.We hypothesize that SerRS downregulates Wnt signaling through E-cadherin–mediated sequestration of β-catenin at the plasma membrane. These findings support further exploration of SerRS as a potential therapeutic target to reduce metastasis in TNBC.

Genetic determinants of sensitivity or resistance to pan-RAS(ON) inhibitors in NRAS-driven melanoma

Mona Foth[1], Wontak Kim[1], Kayla O'Toole[1], Brandon Murphy[1], Montserrat Justo-Garrido[1], Sanjana Boggaram[1], Phaedra Ghazi[1], Euan Brennan[1], Tate Shepherd[1], Yingyun Wang[3], Jennifer Roth[2], Matthew Rees[2], Melissa Ronan[2], Jingjing Jiang[3], Emilio Cortes-Sanchez[1], Siwen Hu-Lieskovan[1], Conan Kinsey[1], Jeffery Russell[1], Ignacio Garrido-Laguna[1], Matthew Holderfield[3], Mallika Singh[3], and Martin McMahon[1]

[1]Huntsman Cancer Institute, 2000 Circle of Hope Drive, University of Utah, Salt Lake City, UT 84112

[2]Broad Institute of MIT and Harvard Merkin Building 415 Main St Cambridge MA 02142

[3]Revolution Medicines Inc., 700 Saginaw Dr., Redwood City, CA 94063, USA

Mutationally-activated oncogenes such as NRAS or BRAF are drivers of ~75% of melanomas. However, regardless of driver mutations in NRAS or BRAF, melanoma patients receive front-line immunotherapy. Patients with BRAF-driven melanoma who are either ineligible for, or for whom immunotherapy fails, have effective second-line therapies that inhibit BRAF oncoprotein kinase signaling. By contrast, NRAS-driven melanoma patients have no such options. Recently, pan-RAS(ON) inhibitors (RMC-7977 & RMC-6236/daraxonrasib) have been developed that, in partnership with cyclophilin A (CYPA), inhibit RAS.GTP signaling. RMC-7977 demonstrates potent and selective anti-proliferative activity against NRAS-driven melanoma cell lines in tissue culture, and highly robust anti-tumor effects against NRAS-driven preclinical melanoma models in mice. However prolonged treatment leads to drug resistance due to: 1. Silencing of CYPA expression or; 2. Mutational activation of MEK1. In addition, an NRAS-mutated melanoma patient was enrolled into the RMC-6236 Phase I clinical trial but, after 6 weeks, was judged to be a non-responder. Retrospective analysis of the patient's baseline clinical genomics profile revealed the expected NRAS alteration but also revealed a MAP2K1 mutation that encodes MEK1(P124L) - a hot-spot, gain of function variant that is detected in both cancer and Cardio-Facio Cutaneous (CFC) Syndrome. Importantly, ectopic expression of MEK1(P124L) in RMC-7977 sensitive NRAS-driven melanoma cells renders them highly drug resistant thereby explaining the primary chemoresistance in this melanoma patient. These data clearly indicate: 1. The exquisite sensitivity of NRAS-driven melanoma to pan-RAS.GTP inhibition; 2. The essentiality of CYPA for the mechanism of action of RMC-7977; 3. The primacy of RAF>MEK>ERK signaling in the maintenance of NRAS-driven melanoma and; 4. The longer-term importance of combination therapy to sustain deep and durable responses to pan-RAS.GTP inhibition.

ZBTB18 restricts tumor cell pliancy, reducing metastasis via macrophage attack

Benjamin Minden-Birkenmaier, Ruishan Wang , Spencer Douglas, Srishti Tiwari, and Myriam Labelle
Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN 38105

Tumor cell pliancy, or the ability to adapt to unfamiliar stresses, is a key determinant of metastasis. By comparing a metastatic variant of the E0771 murine breast cancer cell line with its parental line, we found that target genes of the ZBTB18 transcriptional repressor were significantly associated with metastasis. We further observed that tumor cells could exclude ZBTB18 from their nucleus, removing its transcriptional repression, and this nuclear exclusion correlated with metastatic potential. Conversely, when we overexpressed ZBTB18 (ZBTB18OE) in a variety of mouse cancer lines, metastasis was repressed.

Although ZBTB18OE was found not to affect tumor cell seeding, extravasation, or proliferation, it did significantly decrease metastasis by day 7 post-injection. The anti-metastatic effect was lost in NOD scid and NSG mice, suggesting immune mediation. While depletions of most immune populations had no effect, monocyte and macrophage depletion allowed a partial recovery of metastasis by ZBTB18OE cells. RNA-seq and ATAC-seq showed that ZBTB18OE induces a global decrease in chromatin accessibility, suggesting a restriction of pliancy. RNA-seq and cytokine assays indicated that the *in vivo* environment causes tumor cells to increase production of inflammatory cytokines, as well as the corresponding receptors and response pathways, suggesting a pro-inflammatory autocrine loop. This inflammatory cycle increased the expression of phagocytosis-inhibitory markers, indicative of a protective response by the tumor cells against immune attack. However, ZBTB18OE repressed this pro-inflammatory autocrine loop, decreasing the expression phagocytosis-inhibiting markers. These findings indicate that ZBTB18 restricts tumor cell pliancy, repressing inflammatory signaling and anti-phagocytic protection to render metastasizing cells vulnerable to macrophages. By excluding ZBTB18 from their nuclei, tumor cells avoid this vulnerability and increase their metastatic potential.

A lipid metabolic checkpoint in the progression to lung adenocarcinoma

Christopher W. Murray[1], Hector M. Galvez[1], Ruoxi Wang[1], Karl A. Wessendorf-Rodriguez[1,2], Sandy Lee[3,4], Fernando Lopes[1], Aubrey N. Michi[1], Jose A. Sandoval[1], Antonio F.M. Pinto[5], Maureen L. Ruchhoeft[1], Yuning J. Tang[6], Nianfei Xian[1], Monte M. Winslow[6,7], Michael La Frano[2], David Shackelford[3,4], Christian M. Metallo[1,2], Alan Saghatelian[8], and Reuben J. Shaw[1]

[1]Molecular and Cell Biology Laboratory, Salk Institute for Biological Studies, La Jolla, CA, United States 92037

[2]Mass Spectrometry Core, Salk Institute for Biological Studies, La Jolla, CA 92037

[3]Department of Bioengineering, University of California, San Diego, La Jolla, CA 92093

[4]Department of Genetics, Stanford University School of Medicine, Stanford, CA 94305

[5]Department of Pathology, Stanford University School of Medicine, Stanford, CA 94305

[6]Division of Pulmonary and Critical Care Medicine, Department of Medicine, David Geffen School of Medicine, University of California, Los Angeles, CA 90095

[7]Jonsson Comprehensive Cancer Center, David Geffen School of Medicine, University of California, Los Angeles, CA 90095

[8]Clayton Foundation Laboratories for Peptide Biology, Salk Institute for Biological Studies, La Jolla, CA 92037

Lung cancer is the leading cause of cancer-related deaths worldwide. Lipid metabolism plays a key role in tumorigenesis, fuelling membrane biogenesis and shaping membrane dynamics, supporting energy storage, and generating signalling molecules. We and others have previously demonstrated a critical supportive role for *de novo* fatty acid synthesis in lung cancer. However, many lipid metabolic processes remain to be functionally defined in this disease context. Thus, we conducted a lipid metabolism-targeted CRISPR/Cas9 screens in a genetically engineered mouse model of oncogenic KRAS-driven lung adenocarcinoma. Surprisingly, among the most potent tumor suppressor genes, we noted Cpt2 (carnitine palmitoyltransferase 2), which operates as part of the carnitine shuttle to mediate the import of long-chain fatty acids into the mitochondrial matrix for beta oxidation. Consistent with its canonical function, the inactivation of Cpt2 in lung tumors resulted in the accumulation of long-chain acylcarnitines and fatty acids. We also noted a global decrease in phospholipids and an accumulation of glycerolipids, suggesting a shift from maintenance of membrane composition to lipid storage. At the transcriptional level, Cpt2 deficiency resulted in elevated expression of a series of targets of the central orchestrator of lipid catabolism, PPARα. Notably, multiple transcription factors involved in lipid homeostasis in hepatocytes, including HNF4α, HNF1α, and CREB-H, in addition to multiple markers of gastrointestinal identity were more highly expressed in the Cpt2-deficient setting. Interestingly, these transcriptional changes mirror features of transition states in the progression towards lung adenocarcinoma, suggesting that lipid metabolic alterations may underlie disease progression. Current efforts are centered on investigating putative links between fatty acid oxidation in lung tumors and proliferative control in addition to maintenance of lineage fidelity.

Inhibition of the epitranscriptomic writer METTL3 is a therapeutic vulnerability specific for *p53*-deficient Pancreatic Ductal Adenocarcinomas

Kha The Nguyen[1], Tianyu Zhao[1], and Laura D. Attardi[1,2]
[1]Department of Radiation Oncology, Stanford University School of Medicine, Stanford, CA, 94305
[2]Department of Genetics, Stanford University School of Medicine, Stanford, CA, 94305

Pancreatic Ductal Adenocarcinoma (PDAC) is a very lethal cancer, with a 5-year survival rate of approximately 13%. In PDAC, *TP53* is one of the most frequently mutated genes, with mutations occurring in ~75% of cases, reflecting the critical role of p53 in suppressing PDAC. Therefore, there is an urgent need to develop effective precision therapies for this deadly disease, especially those targeting *TP53*-mutated PDAC cells without affecting surrounding normal cells. In previous studies from our laboratory, we identified the METTL3 methyltransferase 3, N6-adenosinemethyltransferase complex subunit, as a new p53-interacting protein. The p53-METTL3 interaction is important for co-transcriptionally installing m6A modifications on p53 target gene transcripts, and METTL3 thus amplifies p53 tumor suppressor activity. In contrast, when p53 is inactivated, we discovered a surprising synthetic lethal effect of inhibiting METTL3 in oncogeneexpressing fibroblasts. Here, we propose to test the therapeutic potential of METTL3 inhibition in *p53* null PDAC. We found that knocking down METTL3 using shRNAs inhibits growth of *p53* null but not *p53* wild-type mouse PDACs grown as xenografts in mice. Notably, attenuating METTL3 expression suppressed *p53* null PDAC tumors in immunocompetent mice but not in immunodeficient mice, suggesting a role for the immune system in tumor growth inhibition. RNAseq analysis revealed that METTL3 knockdown induces signatures reflecting an innate immune response in *p53* null PDAC cells. We are currently exploring the underlying connection between METTL3 knockdown and a tumor suppressive innate response, and these findings will be presented. Collectively, our findings suggest a new approach for treating *p53* null PDAC tumors, by targeting METTL3 to augment the innate immune response to eliminate cancer cells.

MEK/ERK signaling and lineage specifying transcription factors coordinately regulate cell identity in lung adenocarcinoma and pancreatic ductal adenocarcinoma

Walter A. Orellana[1,2], Sydney N. Larsen[1,2], Katherine Gillis[1,2], and Eric L. Snyder[1,2,3]

[1]Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, 84112

[2]Department of Oncological Sciences, University of Utah, Salt Lake City, UT, 84112

[3]Department of Pathology, University of Utah, Salt Lake City, UT, 84112

Transcription factors (TFs) establish the molecular networks that control cell identity through complex cooperative mechanisms. However, in cancer, these networks become highly dysregulated, creating a transcriptional environment permissive to changes in cellular identity. In lung adenocarcinoma (LUAD), loss of NKX2-1 leads to a pulmonary-to-gastric lineage switch, which is facilitated by the TFs FOXA1/2 through relocalization from pulmonary to gastric loci. Additionally, we have shown that the MEK/ERK signaling cascade regulates the expression of gastric cell type-specific differentiation programs in NKX2-1-negative LUAD wherein MEK/ERK promotes a pit cell identity at the expense of a chief cell identity. We have now found that MEK/ERK activity also controls the balance of pit vs. chief cell identity in pancreatic ductal adenocarcinoma (PDAC) organoids. In both LUAD and PDAC, FOXA1/2 and their downstream target, HNF4α, are required for the pit-to-chief cell lineage switch caused by MEK/ERK inhibition. We hypothesize that MEK/ERK signaling regulates the transcriptional activity and genomic binding of FOXA1/2 and HNF4α in PDAC and NKX2-1-negative LUAD by using human and murine *in vitro* models and genetically engineered mouse models (GEMMs). We find that binding of FOXA1/2 and HNF4α to pit marker genes is attenuated following MEK/ERK inhibition in NKX2-1-negative LUAD. Additionally, mutation of a putative ERK phosphorylation site on FOXA2 led to significant changes in its transcriptional activity, including inability to activate zymogenic chief cell markers. This suggests that FOXA2's phosphorylation state contributes to its ability to activate the zymogenic chief cell program. Overall, our results demonstrate the necessity of FOXA1/2 for controlling cell-type-specific identity programs in response to modulation of MEK/ERK signaling, providing crucial insights into changes in cellular identity that can occur in response to KRAS-targeted therapies for LUAD and PDAC.

Functional interrogation of a high-plasticity cell state in lung adenocarcinoma

Chun-Hao Pan, Jason E Chan, Klavdija Krause, Emma Brown, Hannah C Styers, Gary Guzman, Zhuxuan Li, Xueqian Zhuang, Yan Yan, and Tuomas Tammela
Department of Cancer Biology and Genetics, Memorial Sloan Kettering Cancer Center, New York, NY, 10065

Tumors consist of distinct cancer cell states, each with unique functions and molecular profiles. This heterogeneity has significant clinical implications, as different cancer cell states contribute to proliferation, differentiation, treatment resistance, and metastasis. Our team has been investigating tumor heterogeneity using genetically engineered mouse models (GEMMs) and single-cell genomics. Through computational analysis, we identified a high-plasticity cell state (HPCS) with a strong capacity for cell state transitions, which correlates with poor patient prognosis. However, a lack of model systems has limited our ability to study the role of HPCS *in vivo*. To functionally interrogate HPCS, we developed mouse models that enable detection, lineage-tracing, and ablation of HPCS in lung tumors. Using lineage-tracing and single-cell RNA sequencing (scRNA-seq), we found that HPCS cells are highly plastic, contributing to both early and advanced cancer states. We also demonstrated that HPCS-derived cells have greater growth potential than bulk tumor cells or differentiated cancer cells. Ablating HPCS in early lesions halts tumor progression, and its removal in established tumors significantly reduces tumor burden. Notably, HPCS cells generate treatment-resistant states, and their elimination sensitizes tumors to chemo- and KRAS-targeted therapies. Eradicating the HPCS is therefore a promising therapeutic concept. We are now focusing on identifying druggable targets on HPCS using proteomics and evaluating their therapeutic potential. In summary, we demonstrate that HPCS is essential for LUAD growth, cell state transitions, and treatment resistance. These findings lay the foundation for new treatments aimed at eradicating HPCS to prevent LUAD progression and resistance. If successful, it will lead to new therapeutic strategies enabling eradication of HPCS in LUAD and potentially other cancers.

Therapeutic targeting of MICAL2 enhances the anti-tumor activity of gemcitabine in pancreatic Cancer

Ponmathi Panneerpandian, Kevin Gulay, Herve Tiriac, and Andrew M. Lowy
Moores Cancer Center, Department of Surgery, University of California San Diego

Background: Pancreatic ductal adenocarcinoma (PDAC) ranks as the third leading cause of cancer-related deaths in the United States. MICAL (Molecule Interacting with CasL) family proteins, including MICAL2, are involved in cytoskeletal dynamics and have been implicated in tumorigenesis. MICAL2 is notably overexpressed in pancreatic cancer and correlates with poor prognosis. Initial investigations indicate that targeting MICAL2 in PDAC slows disease progression. However, how targeting MICAL2 impacts the therapeutic vulnerability of pancreatic cancer remains unclear.

Methods: To investigate the therapeutic potential of MICAL2 inhibition, we established an inducible MICAL2 knockdown (KD) model in PDAC cell lines. As MICAL2 drives SRF transcription, the knockdown was validated by assessing the downregulation of serum response factor (SRF) target genes in the KPC46 inducible stable line. Cell confluence monitoring was performed to evaluate drug sensitivity upon MICAL2 inhibition using cellcyte. We designed a combination therapy approach, integrating MICAL2 inhibition with a chemotherapeutic agent to assess for additive and synergistic effects.

Results: We successfully established an inducible model for MICAL2 silencing, achieving a 85 - 90% reduction in transcript. Despite successful MICAL2 knockdown, targeting MICAL2 alone showed minimal impact on PDAC cell viability, suggesting the presence of compensatory pathways that mitigate therapeutic effects. Transcriptomic analysis revealed a negative correlation between MICAL2 and MICAL1/MICAL3 expression, indicating that loss of MICAL2 may trigger upregulation of functionally related paralogs. To overcome this resistance, a combination therapy approach was explored. Combined treatment with gemcitabine and MICAL2 inhibition led to a significant reduction in pancreatic cell proliferation as quantified by CellCyte X assay (2.5-fold reduction, $p<0.001$). This combination also markedly impaired long-term survival, reducing colony forming capacity by 65% compared to gemcitabine alone ($p<0.0001$). Apoptosis was significantly enhanced in the combination group with a 2.1-fold increase in caspase 3/7 activity measured by Caspase Glo assay relative to single-agent treatments. These findings suggest synergistic anti-tumor effects when MICAL2 inhibition is combined with standard chemotherapy.

Conclusions: Our findings suggest that MICAL2 inhibition alone is insufficient to achieve substantial therapeutic benefits in vitro may be due to compensatory mechanisms involving MICAL1 and MICAL3, and the lack of a tumor microenvironment. However, strategic drug combinations incorporating MICAL2 inhibition with chemotherapy can enhance therapeutic efficacy in PDAC. These results underscore the potential of multi-targeted therapeutic strategies to overcome resistance and improve durability of the treatment. We are also aiming at evaluating this combination using inducible system in patient-derived organoids.

Investigating combination therapies to overcome RAS inhibitor resistance in pancreatic cancer

Vasiliki Pantazopoulou[1,2], Casie Kubota[1], Satoshi Ogawa[1], Kassidy Curtis[1], Araceli Herrera[1], and Dannielle Engle[1]

[1]Department of Regulatory Biology, Salk Institute for Biological Studies, La Jolla, CA 9207

[2]Department of Clinical Science, Intervention and Technology, Karolinska Institute, Stockholm, SE 17177

Pancreatic ductal adenocarcinoma (PDA) remains one of the most lethal malignancies, with a five-year survival rate of 13%. This poor prognosis is largely due to late diagnosis, limited curative treatment options, and the rapid development of resistance to therapies. Over 90% of PDA tumors harbor oncogenic KRAS mutations, making RAS a critical therapeutic target. The recent development of mutant-specific and pan-RAS inhibitors has renewed optimism for targeting this pathway in PDA. However, both clinical and preclinical studies demonstrate that resistance to RAS inhibitors (RASi) frequently arises, significantly limiting the durability of response. This study aims to investigate the molecular mechanisms that drive resistance to RASi and to identify rational combination strategies that improve therapeutic efficacy. We employ advanced 3D organoid cultures and genetically engineered *in vivo* models that recapitulate key features of PDA, including tumor heterogeneity and immune composition. We are evaluating how PDA responds to RAS pathway blockade, by identifying pathways altered in response to RASi treatment or resistance acquisition. Additionally, we are assessing combination strategies of RASi together with targeted therapies that may restore sensitivity to RASi or delay resistance onset. Treatment timing, sequence, and tumor microenvironmental factors, including immune components, are also being examined for their influence on therapeutic outcome. Ultimately, this work seeks to inform strategies that extend the efficacy of RAS targeting therapies. By uncovering mechanisms of resistance and identifying therapeutic vulnerabilities, this research will support the development of clinically actionable combination strategies with durable efficacy in PDA.

Capturing the early benign-to-malignant transition of colon cancer in the mouse

Yihan Qin[1], Alex Cicala[1], Daniel Zhang[2], Nischal Bhandari[1], Nikita Persaud[1], Emma Arboleda[1], Zakeria Aminzada[1], Colin McLaughlin[1], Song Han[1], Rodrigo Romero[3], Claire Regan[1], William Rideout III[2], Jonathan Preall[1], Semir Beyaz[1], Sepideh Gholami[1,4], Zhen Zhao[1,4], Tyler Jacks[2], and Peter M Westcott[1]
[1]Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA 11724
[2]David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA 02139
[3]Memorial Sloan Kettering Cancer Center, New York, NY, USA 10065
[4]Northwell Health Cancer Institute, New Hyde Park, NY, USA 11042

Colorectal cancer (CRC) is the second leading cause of cancer-related deaths worldwide. A critical knowledge gap exists in understanding why some benign polyps progress to malignancy while others do not. Studying this transition in patients is challenging, and new mouse models are needed that reliably capture the benign-to-malignant transition.

To address this, we developed a genetically engineered mouse model that recapitulates the stepwise progression of CRC by combining *in vivo* CRISPR-Cas9 editing in the distal colon and an inducible "split-Cre" system. Benign adenomas are induced via colonoscopy-guided injection of lentivirus expressing single guide RNA against the *Apc* gene (mutated in ~80% of human CRC) and the C-terminal half of Cre recombinase (CreC). Mice harbor N-terminal Cre (CreN) fused to a destabilization domain (dd) and an estrogen receptor (ERT2), which is expressed from the endogenous *Epcam* locus. Following adenoma formation, recombination of $Kras^{LSL\text{-}G12D}$ and $Trp53^{flox/flox}$ alleles (two major drivers of advanced CRC) can be specifically induced within rare cells of the tumor. This model decouples the genetic driver events of tumor initiation from malignant progression and captures the full histological continuum of CRC, including benign adenoma, intramucosal carcinoma, adenocarcinoma-in-adenoma, and early invasion, along with histological and transcriptional heterogeneity.

We have performed 10x Visium HD spatial transcriptomics analysis on these samples to elucidate the earliest transcriptional changes associated with benign-to-malignant transition, including a stem cell-state switch and immune remodeling. This approach holds significant potential to elucidate genetic and nongenetic mechanisms underlying malignant progression and may inform strategies for CRC early detection and prevention.

Harnessing replication stress: Targeting ENPP1-induced vulnerabilities in Osteosarcoma

Thomas Arturo Rodriguez[1,2], Borja Ruiz-Fernández de Córdoba[1], Cathy Samayoa[2], and Alejandro Sweet-Cordero[1]

[1]University of California San Francisco-Department of Pediatrics, San Francisco, CA 94158

[2]HER Lab, San Francisco State University Department of Biology, San Francisco, CA 94132

Background. The Osteosarcoma (OS) genome is characterized by having high chromosomal instability (CIN). CIN is a hallmark in human cancers, present in ~70% of patients and is associated with metastasis, immune evasion, and therapeutic resistance. ENPP1 is overexpressed in CIN-high tumors to co-opt this ongoing instability. ENPP1 expression has been linked to poor prognosis in patients and is associated with late stage tumor development as well as distant metastasis. The cell autonomous effects of ENPP1 have yet to be understood.

Results. Pan-RNAseq revealed ENPP1 expression was high in OS. ENPP1 over expression (OE) increased tumor growth kinetics after orthotopic inoculation in the paratibial periosteum as well as spontaneous lung metastasis post amputation of the leg. Mechanistically, RNA-seq revealed downregulation in KRAS signaling after inhibition of ENPP1 (ENPP1i, AVA-NP-695). Connectivity map unveiled MEKi recapitulate the signature of ENPP1i. Western Blot revealed an increase in replication stress markers in a dose-response manner after treatment with ENPP1i or MEKi. In addition, we also observed a downregulation in key DNA repair proteins (BRCA1/2 and RAD51) involved in homologous recombination repair (HR) which could be therapeutically exploited. These stress markers were leveraged with PARPi, which synergized with ENPP1i in a targeted-pharmacological screen. This novel vulnerability was validated in NSG mice by observing tumor regression upon ENPP1i-PARPi and MEKi-PARPi combination therapies in OS-PDX tumors.

Decoding pancreatic cancer cellular circuitry controlled by basal cancer cells

Kate Ryan, Anupriya Singhal, Sam Rose, Hannah C. Styers, Nikhita Pasnuri, Jonathan Rub, Jung Yun Kim, Ashlyn Moore, Stefan R. Torborg, Wenfei Kang, Eric Rosiek, Olivera Grbovic-Huezo, Zeynep Cagla Tarcan, Olca Basturk, Doron Betel, Yan Yan, Mark Burgess, Elisa de Stanchina, Dana Pe'er, and Tuomas Tammela
Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065

Pancreatic ductal adenocarcinoma (PDAC) is a deadly cancer characterized by transcriptional heterogeneity and immune evasion. Immunotherapy has been largely unsuccessful in PDAC, in contrast to resounding successes observed in many other cancers. Identifying and targeting immunosuppression drivers is critical to improving clinical outcomes. Malignant cells in PDAC reside in classical epithelial, basal, or mesenchymal differentiation states. These cell states are defined by distinct transcriptional programs, morphology, and spatial localization, with tumors exhibiting high frequencies of basal cells associating with resistance to chemotherapy and worse overall survival. Despite its critical role, the impact of the basal state on shaping the tumor microenvironment (TME) is poorly understood. To functionally interrogate the basal state in PDAC progression, we developed a novel *in vivo* ablation system. Strikingly, targeted suicide gene-mediated ablation of the basal state, but not the classical cell state, over short time periods resulted in a dramatic tumor collapse, underscoring a critical role for the basal state in tumor tissue maintenance. Ablation of the basal cell state led to rapid loss of cancer-associated fibroblasts, polarization of PDAC-resident macrophages towards a pro-inflammatory phenotype, and increased T and NK cell infiltration. Histological analysis revealed that basal cells, but not the classical cells, reside in close proximity to macrophages known to inhibit T cell activity. This spatial relationship suggests that the basal cell state may engage in distinct interactions with this macrophage population. Cytokine profiling of basal-ablated tumor tissues revealed a dramatic reduction in a battery of established and putative PDAC immunosuppressive cytokines. Together, our data suggest that the basal cell state is a main driver of immunosuppression in PDAC tumors and eradication of this cell state may increase efficacy of traditional immunotherapies.

Characterization of TWEAK in an immunocompetent murine ovarian cancer model

Harshada Sapre, Gregory Jordan, Mikella Robinson, and Carrie House
San Diego State Univesity, Department of Biology

High-Grade Serous Ovarian Cancer (HGSOC) is the most lethal gynecologic malignancy in the US, with 90% of patients experiencing resistance to standard-of-care chemotherapies, Carboplatin and Paclitaxel. Research implicates cancer stem-like cells (CSCs), a subpopulation of quiescent, multipotent cells. Our previous findings identified TWEAK, a pro-inflammatory cytokine, as a critical mediator of CSCs including spheroid formation, chemoresistance, and stem gene expression. TWEAK seems to induce chemosensitivity or chemoresistance in cancer cells, but this mechanism is ill-defined. Furthermore, the role of the immune system in modulating TWEAK activity is understudied. We hypothesize that in an immunocompetent model, TWEAK contributes to induction of CSC characteristics in the post-chemotherapy tumor microenvironment. Previous studies indicate murine ovarian surface epithelial cell lines ID8 and p53-mutant ID8 recapitulate human tumor microenvironment. To study the combination of Carboplatin and Paclitaxel, we calculated IC50 values in ID8 cell lines and found that p53-mutant cells are significantly more chemosensitive than wild-type cells. Next, we assessed a panel of surface markers by flow cytometry, including TWEAK receptor, Fn14, and CSC markers LGR5, GRP78, CD117, and αVβ3. Baseline expression of these markers was less than 5% for LGR5 and αVβ3 in both cell lines. Following chemotherapy treatment, LGR5, Fn14, and αVβ3 increased expression in both cell lines, while GRP78 only increased in p53-mutant cells. Further research will utilize FACS to sort for CSCs using the identified markers and comparing a panel of stem genes for both ID8 cell lines. Future work will investigate ID8 cell lines in CSC functional assays including spheroid formation, chemoresistance assays, and *in vivo* murine relapse models. Utilizing an immunocompetent mouse model to study the interaction of TWEAK with CSCs provides promising insights into the mechanisms driving chemoresistance.

Influence of primary tumors on metastatic seeding efficiency

Anirban Sarkar, Spencer Douglas, and Myriam Labelle
Division of Molecular Oncology, Department of Oncology, St. Jude Children's Research Hospital, Memphis, TN 38105, USA

Metastasis accounts for around 90% of cancer related death worldwide. Typically, only a small fraction of cancer cells break away from the primary tumor and spread to other parts of the body through the vascular system and form secondary colonies in distant organs. Data from clinical studies indicate surgical removal of primary tumor can sometimes lead to the rapid growth of distant metastases. This observation suggests, primary tumors might induce inhibitory mechanisms, which prevent metastatic growth. Further, data from experiments with mouse models suggest that the presence of a primary tumor can confer resistance to secondary tumor implants, a phenomenon described as concomitant tumor resistance (CTR). Breast cancer is highly metastatic to lung and is the second leading cause of death in women. Here, we explored the influence of primary breast tumors on early metastatic seeding to the lungs. We used a E0771 murine breast cancer cell line variant that is highly metastatic to the lungs. We observed mice with early primary tumors, but not with late tumors, are resistant to lung metastatic seeding. Metastatic seeding was inhibited as early as 24 hours post tumor cell injection into the blood stream in tumor-bearing mice compared to naïve mice with no primary tumor. Furthermore, our preliminary data suggest involvement of immune components in clearing the metastatic seeds from mice with early primary tumors. Mechanistic studies are currently underway to decipher how the early primary tumor influences the immune system to inhibit metastatic seeding but fails at later stages.

Fibulin-3 drives tumor progression and microenvironment remodeling in CA19-9-induced pancreatic ductal adenocarcinoma

Hyemin Song, Satoshi Ogawa, Kristina Peck, Jasper Hsu, Kassidy Curtis, Xiaoxue Lin, Chelsea Bottomley, and Dannielle Engle
Salk Institute for Biological Studies

Pancreatic ductal adenocarcinoma (PDA) is one of the deadliest malignancies, with a five-year survival rate under 13%. Notably, 95% of PDA patients exhibit Kras mutations, contributing to highly dysregulated cell signaling networks. Despite extensive research into the interplay of various oncogenic pathways in pancreatic tumorigenesis, targeted therapies against these signaling networks have displayed modest efficacy, with most patients rapidly developing therapeutic resistance. Recent studies highlight the significance of the carbohydrate antigen 19-9 (CA19-9) as a prognostic biomarker for PDA, predicting prognosis, monitoring disease progression, and assessing treatment response. However, the functional roles of CA19-9-modified proteins in PDA remain poorly understood, due to the lack of adequate models that can synthesize CA19-9. To address this challenge, we developed unique mouse and 3D organoid models capable of producing CA19-9. In mice with Kras mutation, CA19-9 elevation results in an aggressive PDA phenotype through increased tumor proliferation and microenvironment (TME) remodeling. Additionally, we identified Fibulin 3 (Fbln3), an extracellular matrix glycoprotein, as a secreted, CA19-9-modified protein in PDA. We found that Fbln3 promotes tumor growth *in vivo*. In CA19-9pos Kras-mutant PDA organoids, Fbln3 enhanced activation of the EGFR and STAT3 signaling pathways. Furthermore, Fbln3 upregulated the expression of IL1A and TGFB, cytokines known to drive cancer-associated fibroblast (CAF) subtype differentiation. In CA19-9-induced PDA mice, Fbln3 induced the expansion of antigen-presenting CAF (apCAFs), contributing to an immunosuppressive TME. Our findings highlight both the direct and indirect roles of Fbln3 in promoting tumor progression and TME remodeling in CA19-9-induced PDA, suggesting Fbln3 as a potential therapeutic target for PDA to improve patient outcomes.

Benchmarking human tumor slices from GI malignancies for precision reveals synergistic effects of RASi with CDK4/6i and in tumors with concomitant with KRAS and GNAS mutations

Jonathan Weitz[1], Kevin Gulay[1], Rithika Medari[1], Deepa Sheik Pran Babu[1], Isabella Ng[1], Kersi Pestonjamasp[2], Shira Yomtoubian[3], Nidhi Jyotsana[3], Elias Warren[4], Brian Wishart[4], Jordan Rull[4], Rebekah White[1], Jingjing Zou[5,6], Karen Messer[5,6], Tatiana Hurtado de Mendoza[1], Herve Tiriac[1], and Andrew M. Lowy[1]
[1]Department of Surgery, University of California, San Diego, La Jolla, CA 92037
[2]Cancer Center Microscopy Core, University of California, San Diego, La Jolla, CA, USA 92037
[3]Salk Institute for Biological Studies, La Jolla, CA 92037
[4]Department of Pathology, University of California San Diego, La Jolla, CA 92037
[5]Herbert Wertheim School of Public Health and Human Longevity Science, University of California, San Diego, La Jolla, CA 92037
[6]Moores Cancer Center, UCSD, La Jolla, CA 92037

The effectiveness of precision medicine depends on the precision and accuracy of diagnostic and predictive modeling systems. Organotypic tumor slices are an established model for multiple human tumor types, allowing study of tumor cells in a semi-intact microenvironment with stromal and immune compartments. However, standardized parameters for testing tumor slices in precision medicine remain undefined. We benchmarked the precision of living *ex-vivo* tumor slices from RAS-driven GI tumors in 35 patients with pancreatic, appendiceal, and colorectal cancers. Tumors from surgical resections were cut into 200 micron slices using a vibratome and cultured for 5 days, achieving 80–90% processing success. EdU was added to media to track tumor and stromal cell proliferation. In drug-free conditions, we quantified intra- and inter-tumoral standard deviations in proliferation to establish baseline biological variation: 10.4% in pancreatic, 5% in appendiceal, and 17% in colorectal tumors. These data support power analysis essential for predicting outcomes in future ex-vivo therapeutic studies. Using these metrics, we analyzed anti-tumor responses to the pan-RAS(On) inhibitor RMC-6236 (50 nM), in late stage clinical trials. We defined confidence intervals to stratify tumor samples as sensitive or resistant, revealing inherent resistance in roughly 20% of cases. Tumor cell-specific proliferation changes during RAS inhibition in slices matched responses in patient-derived 3D organoids. Lastly, given our previously reported findings that tumors harboring con-commitant KRAS and GNAS mutations had enhanced sensitivity to CDK4/6i, we investigated the effects of combining RASi and CDK4/6i in this subset of GI neoplasms. Here we observed that combination treatment improved *ex-vivo* anti-tumor proliferative responses compared to single agent controls. Using matching PDX models we validated anti-tumor proliferative responses of therapy in slices, predicted improved overall survival *in-vivo* compared to single agent. This study provides a foundational benchmark for slice culture parameters in multiple GI tumors and supports future use of these metrics in designing combinatorial strategies to enhance the durability of RAS-targeted therapies.

Mechanism of MAT2A regulation in response to hypoxia in pancreatic cancer

Yang Yang[1], Wenping Wang[2], Gilles Rademaker[1], Mirunalini Ravichandran[1], Jingjie Hu[1], Joseph D. Mancias[5], Jessie Yanxiang Guo[2,3,4], and Rushika M. Perera[1,6,7]

[1]Department of Anatomy, University of California, San Francisco, San Francisco, CA 94143, USA
[2]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ 08901, USA
[3]Department of Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ 08901, USA
[4]Department of Chemical Biology, Rutgers Ernest Mario School of Pharmacy, Piscataway, NJ 08854, USA
[5]Division of Radiation and Genome Stability, Department of Radiation Oncology, Dana-Farber Cancer Institute, Boston, MA 02215
[6]Department of Pathology, University of California San Francisco, San Francisco, CA 94143, USA
[7]Helen Diller Family Comprehensive Cancer center, San Francisco, CA 94143, USA

Hypoxia is a key feature of pancreatic ductal adenocarcinoma (PDAC) and triggers several programs that enable adaptive growth in low oxygen levels. These include transcriptional programs associated with increased histone methylation marks. S-adenosylmethionine (SAM) serves as the universal methyl-group donor for histone methyltransferase reactions and whether hypoxia impacts the rate of synthesis of SAM remains unknown. We show that the increased autophagy and lysosome activity intrinsic to PDAC cells serves to regulate the levels of Methionine adenosyltransferase 2A (MAT2A) – the enzyme responsible for biosynthesis of SAM – under normoxia versus hypoxia. We show that a subset of MAT2A is targeted via the autophagy pathway for degradation by the lysosome under normoxia in PDAC cells but is subsequently protected against degradation under hypoxia. Mechanistically, we show that the autophagy cargo receptor SQSTM1 (p62) binds to MAT2A under normoxia to regulate its autophagic capture. Under hypoxia, MAT2A evades autophagy-lysosome degradation via translocation into the nucleus, which is potentially due to decreased proline hydroxylation in proximity to the nuclear localization signal (NLS). A predominant nuclear localization of MAT2A was also detected in regions of hypoxia in patient PDAC specimens and may facilitate local production of SAM to promote H3K4me3 modification associated with activation of a certain set of genes in response to low oxygen. These findings suggest that nuclear translocation of MAT2A under hypoxia protects against its lysosomal degradation and promotes alterations in SAM synthesis to drive epigenetic and metabolic adaptations to nutrient scarcity.

Epigenetic and microenvironmental regulation of GD2 in Mycn-driven neuroblastoma mouse models

Hiroyuki Yoda[1], Nathaniel Mabe[2], Kimberly Stegmaier[2], and William Weiss[1]
[1]Department of Neurology, University of California San Francisco, San Francisco, CA 94158
[2]Department of Pediatric Oncology, Dana-Farber Cancer Institute, Boston, MA 02215

GD2-targeted therapies have significantly improved outcomes in neuroblastoma, yet the mechanisms underlying GD2 loss remain incompletely understood. Prior studies demonstrated that EZH2 inhibition can enhance GD2 surface expression in human neuroblastoma cells exhibiting mesenchymal (MES) gene signatures.

We recently developed a Mycn-driven non-germline genetically engineered mouse model (Mycn-nGEMM) of neuroblastoma using neural crest cells derived from C57BL/6J embryos. RNA sequencing revealed that Mycn-nGEMM cells resemble high-risk human neuroblastoma with MES characteristics and exhibit low expression of St8sia1, the key enzyme in GD2 biosynthesis, resulting in suppressed GD2 production.

To investigate mechanisms of GD2 silencing, we overexpressed St8sia1 in Mycn-nGEMM cells, which led to increased GD2 surface expression. We further tested the effects of epigenetic modulation by treating cells with inhibitors targeting Ezh2, Men1 and Dot1l. All three compounds elevated St8sia1 mRNA levels in both Mycn-nGEMM-high and -low lines (defined by Mycn RNA and protein expression levels). However, increased GD2 expression was observed only in Mycn-nGEMM-high cells, suggesting that GD2 regulation in Mycn-nGEMM-low cells may involve epigenetic-independent mechanisms.

To assess GD2 expression *in vivo*, Mycn-nGEMM cells were orthotopically implanted into C57BL/6J mice, and tumors were harvested after three weeks. Surprisingly, Mycn-nGEMM-high tumors lacked GD2 surface expression, while Mycn-nGEMM-low tumors exhibited approximately 40% GD2-positive cell populations. These findings suggest that Mycn-nGEMM-low tumors demonstrate phenotypic plasticity in response to the tumor microenvironment.

Our results highlight Mycn-nGEMM-low cells as a valuable model for investigating non-epigenetic mechanisms of GD2 regulation and for developing novel strategies to enhance GD2-targeted therapy in neuroblastoma.

NR4A1 directly represses Interferon Response genes and mediates checkpoint immunotherapy resistance in STK11/LKB1 mutant NSCLC

Shira Yomtoubian[1], Jan Pencik[1], Stephen Sakamura[2], Brent Chick[1,2], Jingting Yu[3], Jingwen Liao[1,2], Victor Y. Du[2], Hector M. Galvez[1], Christopher W. Murray[1], Dan Chen[2], Filipe A. Hoffmann[2], Sam Van de Velde[4], Marc Montminy[4], April E. Williams[3], Diana Hargreaves[1,2], Susan M. Kaech[2], and Reuben J. Shaw[1*]
[1]Molecular and Cell Biology Laboratory
[2]NOMIS Center for Immunobiology and Microbial Pathogenesis
[3]Razavi Newman Integrative Genomics and Bioinformatics Core,
[4]Peptide Biology Laboratory
Salk Institute for Biological Studies, La Jolla, CA 92037, USA

In non-small cell lung cancer (NSCLC), loss of function mutations in the LKB1 (STK11) tumor suppressor gene are highly associated with resistance to immune checkpoint blockade (ICB). How LKB1 loss promotes resistance to ICB remains poorly understood. Here, unbiased transcriptional profiling revealed that LKB1 dominantly controls a cell-autonomous block in exogenous interferon-induced transcription. This effect was due to loss of SIK kinase signaling inhibition of CRTC-CREB1. We show here that the nuclear receptor NR4A1 is a single gene induced by CREB 30-fold in the LKB1-deficient state, that acts as a direct transcriptional repressor, binding directly to the promoters of Interferon Response genes, including IRF1, IRF7, IRF9, and PD-L1. The attenuated expression of interferon genes in the LKB1-deficient state was fully reversed by concomitant deletion of NR4A1. Paralleling this, the resistance to anti-PD-1 immunotherapy in the LKB1-deficient state was reverted by NR4A1 deletion, and this restored sensitivity to ICB was T-cell dependent. NR4A1 emerges as a tumor cell-autonomous dominant repressor of interferon signaling, providing a new therapeutic strategy to overcome ICB resistance in cancer.

Aging-associated iron insufficiency suppresses lung cancer initiation and progression

Xueqian Zhuang[1], Jeyaram Ravichandran Damodaran[1], Brooklyn Christensen[1], Qing Wang[2], Simon Joost[1], Klavdija Krause[1], Emily S. Wong[2], and Tuomas Tammela[1]

[1]Cancer Biology and Genetics Program, Sloan Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY 10065

[2]Victor Chang Cardiac Research Institute, Sydney, New South Wales, Australia

Aging is one of the most important risk factors for cancer development. However, our understanding of how aging impacts cancer initiation and evolution remains at an early stage. Using autochthonous genetically engineered mouse models (GEMMs), we demonstrated that aging suppressed lung cancer initiation and progression by degrading stemness of the cell of origin, the adult stem cell in the lung. Single-cell transcriptomics uncovered a distinct compositional landscape of cancer cell subsets in aged lung tumors, revealing a delay in the molecular progression of the cancers and an age-specific gene expression signature. Functional interrogation of key component of this gene signature indicated that aging-specific iron insufficiency was the key mechanism underlying the tumor suppressive role of aging. Supplementation of iron to the aged cells of origin, but not the young counterparts, restored their transformative capacity and unleashed the progression of lung tumors arised from these aged cells of origin. Consistently, aged lung cancer cells were prone to iron deprivation. Interestingly, iron treatment also enhanced the proliferation and differentiation of aged cells of origin in the normal regeneration during lung injury repair. Our results indicate that aging-associated iron insufficiency in the cell of origin are imprinted on evolving tumors, which determines tumor initiation potential, alters trajectory of tumor evolution, and leads to age-dependent vulnerabilities. These findings suggest that the biology of tumors is fundamentally altered by aging, raising new possibilities for cancer treatment and prevention in patients of different ages.

INDEX
OF
ATTENDEE
EMAIL ADDRESSES

Full Name	Institution	Email Address
Adams, Christina	Genesis Therapeutics	christina@genesistherapeutics.ai
Aguirre-Ghiso, Julio	Albert Einstein College of Medicine	julio.aguirre-ghiso@einsteinmed.edu
Alagesan, Brinda	Memorial Sloan Kettering Cancer Center	brindaa@gmail.com
Alexandrov, Ludmil	University of California, San Diego	L2alexandrov@health.ucsd.edu
Amos, Shandon	Massachusetts Institute of Technology	samos@mit.edu
Amuzie, Dozie	Johnson and Johnson Innovative Medicine	Camuzie@its.jnj.com
Andritsogianni, Ioanna	Salk Institute for Biological Studies	ioannaandritsogianni@gmail.com
Arnold, Frank	Memorial Sloan Kettering Cancer Center	arnoldf1@mskcc.org
Arnold, Henry	University of Utah	henry.arnold@hci.utah.edu
Auger, Julie	Salk Institute for Biological Studies	jauger@salk.edu
Bar-peled, Liron	Massachusetts General Hospital	lbar-peled@mgh.harvard.edu
Barthet, Valentin	Memorial Sloan Kettering Cancer Center	barthetv@mskcc.org
Bartolacci, Caterina	University of cincinnati	bartolcn@ucmail.uc.edu
Batty, Skylar	University of California, San Diego	sbatty@health.ucsd.edu
Bhattacharya, Debadrita	Stanford University	dbh@stanford.edu
Black, Morgan	Salk Institute for Biological Studies	mblack@salk.edu
Brady, Donita	University of Pennsylvania	bradyd@pennmedicine.upenn.edu
Bruning, Jessica	Salk Institute for Biological Studies	jebruning@salk.edu
Cao, Daniel	Salk Institute for Biological Studies	ycao@salk.edu
Chan, Jason	Memorial Sloan Kettering Cancer Center	chanj2@mskcc.org
Chang, Blair (Yating)	Salk Institute for Biological Studies	bchang@salk.edu
Chen, Yvonne	University of California, Los Angeles	yvchen@ucla.edu
Chen, Joyce	Memorial Sloan Kettering Cancer Center	chenj17@mskcc.org
Chick, Brent	Salk Institute for Biological Studies	bchick@salk.edu
Chin, Brayden	San Diego State University	bchin9542@sdsu.edu
Chinn, Becky	Salk Institute for Biological Studies	rchinn@salk.edu
Cisneros, Metztli	Salk Institute for Biological Studies	mcisneros@salk.edu
Commisso, Cosimo	Sanford Burnham Prebys Medical Discovery Institute	ccommisso@sbpdiscovery.org
Coz, Susan	LICORbio	susan.coz@licorbio.com
Dausch, Alex	Salk Institute for Biological Studies	adausch@salk.edu
David, Yael	Memorial Sloan Kettering Cancer Center	davidshy@mskcc.org
Dayn, Yelena	Salk Institute for Biological Studies	dayn@salk.edu
Deota, Shaunak	Salk Institute for Biological Studies	sdeota@salk.edu
Dib, Peter	A Bruker Company	jennifer.havist@bruker.com
Doglioni, Ginevra	Salk Institute for Biological Studies	gdoglioni@salk.edu
Dolcen, Deniz Nesli	Stanford University	dnesli@stanford.edu
Donnelly, Matthew	Salk Institute for Biological Studies	mdonnelly@salk.edu
Dufresne, Suzanne	Salk Institute for Biological Studies	sdufresne@salk.edu
DuPage, Michel	University of California, Berkeley	dupage@berkeley.edu
Ebadi, Humayra	Salk Institute for Biological Studies	hebadi@salk.edu
Egeblad, Mikala	Johns Hopkins University	mikala.egeblad@jhmi.edu
Egel, Sam	LICORbio	Susan.Coz@licorbio.com
Eichner, Lillian	Northwestern University	eichner@northwestern.edu
Elewaut, Anais	Salk Institute for Biological Studies	aelewaut@salk.edu
Encarnacion Rosado, Joel	Salk Institute for Biological Studies	jencarnacionrosado@salk.edu
Engle, Dannielle	Salk Institute for Biological Studies	engle@salk.edu

Full Name	Institution	Email Address
Esparza Moltó, Pau Bernat	Salk Institute for Biological Studies	pesparzamolto@salk.edu
Essel Dadzie, Headtlove	University of Utah	U1317053@utah.edu
Evans, Ron	Salk Institute for Biological Studies	evans@salk.edu
Evensen, Garrett	Salk Institute for Biological Studies	gevensen@salk.edu
Evodie, Koutouan	Sanford Burnham Prebys Medical Discovery Institute	ekoutouan@sbpdiscovery.org
Feng, Anqi	Salk Institute for Biological Studies	afeng@salk.edu
Fennell, Emily	Salk Institute for Biological Studies	efennell@salk.edu
Feuer, Mia	San Diego State University	Mfeuer1626@sdsu.edu
Finlay, Darren (Ben)	Sanford Burnham Prebys Medical Discovery Institute	dfinlay@sbpdiscovery.org
Fourman, Makenzie	University of Cincinnati, College of Medicine	fourmame@mail.uc.edu
Fuks, Francois	University of Brussels	francois.fuks@ulb.be
Gagne, Lynne	Corning Life Sciences	gagnel@corning.com
Galvez, Hector	Amgen	hgalvez@amgen.com
Gamas, Susanne	Sanford Burnham Prebys Medical Discovery Institute	sgamasvis@sbpdiscovery.org
Garg, Bharti	Moores Cancer Centre	bhgarg@health.ucsd.edu
Garman, Emma	Salk Institute for Biological Studies	egarman@salk.edu
Ghajar, Cyrus	Fred Hutchinson Cancer Center	cghajar@fredhutch.org
Ghosh, Sagnika	Salk Institute for Biological Studies	sghosh@salk.edu
Ghosh-Janjigian, Sharmistha	NIH/NCI	sharmistha.ghosh-janjigian@nih.gov
Gulay, Kevin	Salk Institute for Biological Studies	kgulay@salk.edu
Gupta, Romi	The University of Alabama at Birmingham	romigup@uab.edu
Gur-Cohen, Shiri	University of California, San Diego	sgurcohen@health.ucsd.edu
Gutkind, J. Silvio	University of California, San Diego	sgutkind@health.ucsd.edu
Haigis, Marcia	Harvard Medical School	Marcia_haigis@hms.harvard.edu
Hargreaves, Diana	Salk Institute for Biological Studies	dhargreaves@salk.edu
Hases, Linnea	Salk Institute for Biological Studies	lhases@salk.edu
Hatanaka, Tomoko	Salk Institute for Biological Studies	thatanaka@salk.edu
Havist, Jennifer	Spectral Instruments Imaging, A Bruker Company	daniel.dougherty@bruker.com
Havist, Jennifer	A Bruker Company	jennifer.havist@bruker.com
Herdy, Joseph	Salk Institute for Biological Studies	jherdy@salk.edu
Herrera Morales, Araceli	Salk Institute for Biological Studies	aherreramorales@salk.edu
Hsu, Jasper	Salk Institute for Biological Studies	jahsu@salk.edu
Hunt, Brian	Yale School of Medicine	brian.hunt@yale.edu
Hunter, Tony	Salk Institute for Biological Studies	hunter@salk.edu
Huynh, Vincent	Salk Institute for Biological Studies	vhuynh@salk.edu
Ianniciello, Angela	Salk Institute for Biological Studies	aianniciello@salk.edu
Im, Hannah	Salk Institute for Biological Studies	him@salk.edu
Inagaki, Akiko	Salk Institute for Biological Studies	ainagaki@salk.edu
Iyer, Mohini	Salk Institute for Biological Studies	miyer@salk.edu
Jaeger, Alex	Moffitt Cancer Center	alex.jaeger@moffitt.org
Johnson, Jálin B.	Salk Institute for Biological Studies	jjohnson@salk.edu
Johnson, Melissa	Salk Institute for Biological Studies	mjohnson@salk.edu
Joshi, Nikhil	Yale University	elizabeth.ferris@yale.edu
Ju, Julia	University of Maryland, School of Medicine	jju@som.umaryland.edu
Jyotsana, Nidhi	Salk Institute for Biological Studies	njyotsana@salk.edu
Kaech, Susan	Salk Institute for Biological Studies	Skaech@salk.edu

Full Name	Institution	Email Address
Kaiser, Melanie	Salk Institute for Biological Studies	mkaiser@salk.edu
Karlseder, Jan	Salk Institute for Biological Studies	karlseder@salk.edu
Karreth, Florian	H. Lee Moffitt Cancer Center	florian.karreth@moffitt.org
Kelly, Cory	Salk Institute for Biological Studies	ckelly@salk.edu
Kerk, Samuel	Salk Institute for Biological Studies	skerk@salk.edu
Khosrowabadi, Elham	Sanford Burnham Prebys Medical Discovery Institute	ekhosrowabadi@sbpdiscovery.org
Kim, Jung Yun	Memorial Sloan Kettering Cancer Center	kimj43@mskcc.org
Kirk, Brian	Salk Institute for Biological Studies	bkirk@salk.edu
Kolluri, Siva	Oregon State University	siva.kolluri@oregonstate.edu
Komarla, Anvita	Salk Institute for Biological Studies	akomarla@salk.edu
Krause, Klavdija	Memorial Sloan Kettering	bastlk@mskcc.org
Kubota, Casie	Salk Institute for Biological Studies	ckubota@salk.edu
Kuo, Elysia	Salk Institute for Biological Studies	ekuo@salk.edu
Kwan, Sharon	Salk Institute for Biological Studies	skwan@salk.edu
Kwo, Sophie	Salk Institute for Biological Studies	skwo@salk.edu
Laguerre, Aurélie	Salk Institute for Biological Studies	alaguerre@salk.edu
Lau, Calvin	Salk Institute for Biological Studies	clau@salk.edu
Learn, Julie	University of California, Davis	jlearn@ucdavis.edu
Leon Rivera, Nancy	San Diego State University	nleonrivera2206@sdsu.edu
Li, Shitian (Steven)	Salk Institute for Biological Studies	sli@salk.edu
Li, Min	Salk Institute for Biological Studies	mili@salk.edu
Li, Shi	Fred Hutchinson Cancer Center	sli7@fredhutch.org
Li, Yuwenbin	Salk Institute for Biological Studies	yuwli@salk.edu
Liang, Gaoyang	Salk Institute for Biological Studies	gliang@salk.edu
Lillo Marquez, Alejandro	Sanford Burnham Prebys Medical Discovery Institute	alillo@sbpdiscovery.org
Little, Margot	Corning Life Sciences	gagnel@corning.com
Liu, Yingluo	University of California, San Diego	yil243@ucsd.edu
Liu, Aaron	Salk Institute for Biological Studies	aaliu@salk.edu
Lombardi, Sofia	Sanford Burnham Prebys Medical Discovery Institute	slombardi@sbpdiscovery.org
Longtine, Abigail	Salk Institute for Biological Studies	alongtine@salk.edu
Lopes, Fernando	Salk Institute for Biological Studies	flopes@salk.edu
Loza, Jennifer	Yale University	jenniferlynneloza@gmail.com
Loza Sanchez, Liliana	University of California, Davis	lozasan@ucdavis.edu
Mahajan, Mukesh	University of California San Diego	mmahajan@ucsd.edu
Mainz, Laura	Salk Institute for Biological Studies	lmainz@salk.edu
Mangalhara, Kailash Chandra	Salk Institute for Biological Studies	kmangalhara@salk.edu
McAllister, Sandra	Harvard Medical School	smcallister1@bwh.harvard.edu
McCullough, Brandon	Salk Institute for Biological Studies	bmccullough@salk.edu
McMahon, Martin	University of Utah	martin.mcmahon@hci.utah.edu
McRae, Helen	Salk Institute for Biological Studies	hmcrae@salk.edu
Melegari, Margherita	University of Cincinnati College of Medicine	melegama@ucmail.uc.edu
Metallo, Christian	Salk Institute for Biological Studies	metallo@salk.edu
Michi, Aubrey	Salk Institute for Biological Studies	amichi@salk.edu
Miller, Matthew	Salk Institute for Biological Studies	mamiller@salk.edu
Minden-Birkenmaier, Benjamin	St. Jude Children's Research Hospital	benjamin.minden-birkenmaier@stjude.org
Mondal, Payel	Salk Institute for Biological Studies	pmondal@salk.edu

Full Name	Institution	Email Address
Montoya, Alejandro	Corning Life Sciences	gagnel@corning.com
Moussion, Christine	Genentech	moussion.christine@gene.com
Moyzis, Alexandra	Salk Institute for Biological Studies	amoyzis@salk.edu
Murphy, Brandon	University of Utah	brandon.murphy@hci.utah.edu
Murray, Christopher	Salk Institute for Biological Studies	cmurray@salk.edu
Naik, Shruti	Icahn School of Medicine at Mt Sinai	Shruti.Naik@mssm.edu
Nash, David	Salk Institute for Biological Studies	dnash@salk.edu
Nguyen, Kha	Stanford University School of Medicine	tknguyen@stanford.edu
Nguyen, Ha	Salk Institute for Biological Studies	hnguyen@salk.edu
Nikkhah, Mehdi	Arizona State University	mnikkhah@asu.edu
Ning, Jia	Salk Institute for Biological Studies	jning@salk.edu
Nixon, Rob	Qkine	rob.nixon@qkine.com
Ogawa, Satoshi	Salk Institute for Biological Studies	sogawa@salk.edu
Oluwasuyi, Elizabeth	Salk Institute for Biological Studies	eoluwasuyi@salk.edu
Oon, Chet	Memorial Sloan Kettering Cancer Center	oonc@mskcc.org
Orellana, Walter	University of Utah	walter.orellana@hci.utah.edu
Osorio Vasquez, Victoria	Salk Institute for Biological Sciences	vosoriovasquez@salk.edu
Palma, Emily	Corning Life Sciences	gagnel@corning.com
Pan, Xingxiu	Scintillon Institute	xpan@scintillon.org
Pan, Chun-Hao	Memorial Sloan Kettering Cancer Center	panc@mskcc.org
Panneerpandian, Ponmathi	University of California, San Diego	ppanneerpandian@health.ucsd.edu
Pant, Ami	Salk Institute for Biological Studies	apant@salk.edu
Pantazopoulou, Vasiliki	Salk Institute for Biological Studies	vpantazopoulou@salk.edu
Parham, Louis	Salk Institute for Biological Studies	lparham@salk.edu
Patra, Krushna	University of Cincinnati	patraka@ucmail.uc.edu
Peck, Kristina	Salk Institute for Biological Studies	kpeck@salk.edu
Perera, Rushika	University of California, San Francisco	rushika.perera@ucsf.edu
Perez, Samantha	Salk Institute for Biological Studies	sperez@salk.edu
Polyak, Kornelia	Dana-Farber Cancer Institute	kornelia_polyak@dfci.harvard.edu
Popay, Tessa	Salk Institute for Biological Studies	tpopay@salk.edu
Potter, Ellen	Salk Institute for Biological Studies	epotter2@me.com
Powale, Krushali	Salk Institute for Biological Studies	kpowale@salk.edu
Qin, Yihan	Cold Spring Harbor Laboratory	yqin@cshl.edu
Qiu, Abbie	Salk Institute for Biological Studies	aqiu@salk.edu
Ramanan, Deepshika	Salk Institute for Biological Studies	dramanan@salk.edu
Rasby, Hannah	Corning Life Sciences	gagnel@corning.com
Reeves, Melissa	University of Utah	Melissa.reeves@hci.utah.edu
Rivera, Samuel	Salk Institute for Biological Studies	srivera@salk.edu
Rodrigues Lourenço, Telma	Scripps Research Institute	tlourenco@scripps.edu
Rodriguez, Thomas Arturo	University of California, San Francisco	Thomas.rodriguez@ucsf.edu
Rodriguez, Matt	LICORbio	Susan.Coz@licorbio.com
Ruchhoeft, Mo	Salk Institute for Biological Studies	mruchhoeft@salk.edu
Ryan, Kate	Memorial Sloan Kettering Cancer Center	ryank4@mskcc.org
Sahid, Imaan	Salk Institute for Biological Studies	isahid@salk.edu
Sakuma, Stephen	Salk Institute for Biological Studies	ssakuma@salk.edu
Salinas, Steve	Salk Institute for Biological Studies	ssalinas@salk.edu

Full Name	Institution	Email Address
Sandoval, Jose	Salk Institute for Biological Studies	josandoval@salk.edu
Sapre, Harshada	San Diego State University	hsapre6524@sdsu.edu
Sarkar, Anirban	St Jude Children's Research Hospital	asarkar@stjude.org
Scaglioni, Pier Paolo	University of Cincinnati College of Medicine	Scaglipr@ucmail.uc.edu
Schneeberger, Richard	Salk Institute for Biological Studies	rschneeberger@salk.edu
Schuele, Roland	Medical Center University of Freiburg	roland.schuele@uniklinik-freiburg.de
Shadel, Gerald	Salk Institute for Biological Studies	gshadel@salk.edu
Shaw, Reuben	Salk Institute for Biological Studies	shaw@salk.edu
Sherman, Mara	Memorial Sloan Kettering Cancer Center	shermam1@mskcc.org
Singh, Mallika	Revolution Medicines	msingh@revmed.com
Singh, Kamini	Albert Einstein College of Medicine	kamini.singh@einsteinmed.edu
Song, Hyemin	University of California, San Diego	hyesong@salk.edu
Stewart, Sheila	Washington University	sheila.stewart@wustl.edu
Suman, Ethan	Salk Institute for Biological Studies	esuman@salk.edu
Sun, Xueqin Sherine	Sanford Burnham Prebys Medical Discovery Insitute	xsun@sbpdiscovery.org
Sung, Tsung-Chang	Salk Institute for Biological Studies	sung@salk.edu
Tamayo, Pablo	University of California, San Diego	ptamayo@ucsd.edu
Tammela, Tuomas	Memorial Sloan Kettering Cancer Center	tammelat@mskcc.org
Terry, Jake	Salk Institute for Biological Studies	jterry@salk.edu
Tiriac, Herve	Salk Institute for Biological Studies	htiriac@salk.edu
Towers, Christina	Salk Institute for Biological Studies	ctowers@salk.edu
Trimble, Anna	Salk Institute for Biological Studies	atrimble@salk.edu
Tripple, Victoria	Salk Institute for Biological Studies	vtripple@salk.edu
Truitt, Morgan	Salk Institute for Biological Studies	mtruitt@salk.edu
Tzompantzi De Ita, Juan Manuel	Salk Institute for Biological Studies	jtzompantzideita@salk.edu
Vaishnavi, Aria	University of Texas MD Anderson Cancer Center	avaishnavi1@mdanderson.org
Vallmajó Martín, Queralt	Salk Institute for Biological Studies	qvallmajo@salk.edu
Vuori, Kristiina	Sanford Burnham Prebys Medical Discovery Insitute	kvuori@sbpdiscovery.org
Wajapeyee, Narendra	University of Alabama at Birmingham	nwajapey@uab.edu
Wan, Liling	University of Pennsylvania	Liling.wan@pennmedicine.upenn.edu
Wang, Lily	Scripps Research	liwang@scripps.edu
Wang, Mark Xinyi	Salk Institute for Biological Studies	xiywang@salk.edu
Wang, RUOXI	Salk Institute for Biological Studies	ruowang@salk.edu
Wasserman, David	LICORbio	Susan.Coz@licorbio.com
Weitz, Jonathan	University of California, San Diego	jweitz@health.ucsd.edu
Wessendorf-Rodriguez, Karl	Salk Institue for Biological Studies	kwessendorf@salk.edu
West, Tommy	Pfizer	Thomas.west@pfizer.com
Westcott, Peter	Cold Spring Harbor Laboratory	westcott@cshl.edu
Wichmann, Romy	Salk Institute for Biological Studies	rwichmann@salk.edu
Wilcox, Nora	Salk Institute for Biological Studies	nwilcox@salk.edu
Williams, April	Salk Institute for Biological Studies	awilliams@salk.edu
Winslow, Monte	Stanford University	mwinslow@stanford.edu
Yang, Yang	University of California, San Francisco	yang.yang3@ucsf.edu
Yang, Jing	University of California, San Diego	jingyang@ucsd.edu
Yarden, Yosef	Weizmann Institute	Yosef.yarden@weizmann.ac.il
Yoda, Hiroyuki	University of California, San Francisco	hiroyuki.yoda@ucsf.edu

Full Name	Institution	Email Address
Yomtoubian, Shira	Salk Institute for Biological Studies	syomtoubian@salk.edu
Young, Robert	Memorial Sloan Kettering Cancer Center	youngrobert@gmail.com
Yu, Jingting	Salk Institute for Biological Studies	jyu@salk.edu
Zhang, Cheng	HKUST(GZ)	mr.chengzhang@gmail.com
Zhang, Zeda	Memorial Sloan Kettering Cancer Center	zhangz3@mskcc.org
Zhao, Ming	Sanford Burnham Prebys	mzhao@sbpdiscovery.org
Zhu, Jonathan	Salk Institute for Biological Studies	jzhu@salk.edu
Zhu, Xiaoyan	Salk Institute for Biological Studies	xzhu@salk.edu
Zhuang, Xueqian	Memorial Sloan Kettering Cancer Center	zhuangx@mskcc.org

Full Name	Institution	Email Address
Andrade, Leonardo	Salk Institute for Biological Studies	landrade@salk.edu
Diaz Zarco, Jonathan	Salk Institute for Biological Studies	jdiazzarco@salk.edu
Doan, Khoa	University of California, San Diego	kddoan@health.ucsd.edu
Hartsough, Michele	Cancer Discovery, AACR	michele.hartsough@aacr.org
Kisling, Sophia	American Association for Cancer Research	sophia.kisling@aacr.org
Li, Yixuan	University of California, San Diego	yil315@ucsd.edu
Morrell, Taneashia	Salk Institute for Biological Studies	Tmorrell@salk.edu
Pasquale, Elena	Sanford Burnham Prebys Medical Discovery Insitute	elenap@sbpdiscovery.org
Rodrigues Lorenzetti, Alan Pericles	Salk Institute for Biological Studies	alorenzetti@salk.edu
Sawai, Hisako	Freelance	hsawai22@gmail.com
Snyder, Eric	University of Utah	eric.snyder@hci.utah.edu
Wang, Hunter	Salk Institute for Biological Studies	HUWang@salk.edu
Wang, Xue	Salk Institute for Biological Studies	xuwang@salk.edu
Young, Carissa	Salk Institute for Biological Studies	cayoung@salk.edu
Zhao, Chuntao	Cincinnati Children's Hospital Medical Center	chuntao.zh@gmail.com
Zhou, Wenjing	University of California, San Diego	wez066@ucsd.edu

10010 N Torrey Pines Rd
La Jolla, CA 92037-1099
(858) 453-4100
www.salk.edu