BIOGRAPHICAL SKETCH

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NAME: Morris IV, John P

eRA COMMONS USER NAME (credential, e.g., agency login): MORRISIJ

POSITION TITLE: Assistant Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Harvard University	A.B.	06/1998	Biochemical Sciences
University of California, San Francisco	Ph.D.	11/2011	Biomedical Sciences
Memorial Sloan Kettering Cancer Center	Postdoctoral	08/2020	Cancer Biology and Genetics
University of North Carolina School of Medicine, Department of Pharmacology/Lineberger Cancer Center		Present	Determinants of Cancer Cell Fate

A. Personal Statement

A hallmark of cancer cells is aberrant cell fate. Specifically, tumorigenesis reflects the emergence of lineages that no longer conform to the differentiation programs essential for organ development, maintenance, and regeneration. Identifying how the mutations that drive cancer initiation and progression establish lineages that no longer "play by the rules" of stereotypical fate specification is essential for identifying lethal cells and ultimately eliminating them. My long-term research goal is to understand how malignant cells resist normal programs of differentiation and regeneration to establish new, aberrant malignant identities.

My academic and research training has provided me with extensive skills and experience in genetics, developmental, and cancer biology, constituting a strong theoretical foundation from which to pursue my research objectives. As an undergraduate I was introduced to forward and reverse genetic techniques useful for developing animal models of human disease as a thesis student and research technician with Thomas Look, MD. As a part of the Look Lab I helped develop methods to generate zebrafish with mutations in conserved human cancer drivers. I optimized approaches to freeze zebrafish sperm in order to archive genetic material from animals subjected to mutagenesis. During my graduate training I became interested in the relationship between intrinsic cellular plasticity and tumorigenesis. Under the mentorship of Matthias Hebrok, PhD I used mouse models of pancreatic ductal adenocarcinoma (PDAC) to investigate how oncogenic Kras, the most common mutation in PDAC, alters pancreatic cell fate. I found that mutant Kras establishes de-differentiated, pre-malignant cells by preventing pancreatic exocrine cells from regenerating. As a postdoctoral fellow with Scott Lowe, PhD I focused on pre-malignant to malignant progression through the lens of tumor suppressor function, with a focus on the most commonly mutated gene in human cancer—the tumor suppressor gene p53. I helped develop a suite of PDAC and liver cancer mouse models that permit temporal control of gene expression, permitting stage dependent analysis of tumor suppressor gene function. Using models that allows restoration of p53 in malignant cells, I discovered a metabolic connection between p53 and cell fate that not only antagonizes malignant progression but can also be reestablished in cancer cells to promote pre-malignant differentiation. Tumor suppressive p53 triggers metabolic reprogramming that results in accumulation of αKG, an obligate

substrate for a number of chromatin modifying enzymes necessary for proper differentiation during development. Thus, my work places p53 upstream of metabolically sensitive drivers of differentiation and highlights a novel route by which p53 dictates cell fate by tuning the epigenetic landscape. Furthermore, I have integrated genotype specific lineage tracing into germline and transplantable analogues of these models that allow pre-clinical evaluation of candidate approaches to prevent and target malignant "de-differentiation" that also serve as powerful platforms to directly visualize distinct evolutionary paths that connect different cancer drivers to heterogeneous cancer populations.

As an assistant professor I am using these approaches as a basis to explore connections between cancer drivers, aberrant cell fate, and the pre-malignant to malignant transition in order to identify therapeutic strategies to most effectively target lethal cancers. My lab was established in October, 2020 and despite the challenges of the COVID-19 pandemic I have since recruited 3 graduate students and secured 2 career development grants to support our work in understanding how inactivation of p53 enables malignant heterogeneity in pancreatic cancer (see below).

Mentoring and training plays an important part of my research philosophy. I not only develop individual mentoring plans with each graduate trainee joining my group, but I also actively take part in programs such as the UNC BBSP first year group program that welcomes and orients students joining our graduate programs. I support my graduate trainees in applying for training grants, fellowships, and meetings that focus on career development and scientific enrichment (such as the UNC department of Genetics and Molecular Biology T32 training grant, the UNC miBio program, and the UNC Cancer Cell Biology Training Program). As reflected by my publication record, I am a multi-disciplinary and collaborative researcher. Given that this approach is central to my scientific approach, I am dedicated to supporting the development of graduate trainees who collaborate actively and are equipped to analyze and robustly interpret a wide variety of data. While I hope all of my graduate trainees are inspired to pursue academia, our research approach reflects the evolution of modern molecular genetics, preparing students from my lab to engage across a spectrum of scientific careers. Training opportunities that emphasize the development of communication and analytical skills as well as exposure to diverse research topics and approaches play an important role in this effort.

Current and recently completed research support I would like to highlight:

Pancreatic Cancer Action Network Career Development Award
"Dissecting malignant evolution unleashed by p53 inactivation in PDAC "
828280 Morris (PI) 07/01/2021-07/01/2023

National Pancreas Foundation Research Grant
"Leveraging evolutionary lineage tracing to dissect heterogeneity in pancreatic ductal adenocarcinoma initiation and therapeutic response"
Morris (PI) 06/01/2022-06/01/2023

American Cancer Society Postdoctoral Fellowship
Role of IDH mutations in cholangiocarcinoma development and maintenance
26337-PF-14-066-01-TBE Morris (PI) 07/01/2014-06/30/2017
The goal of this project was to study mutant isocitrate dehydrogenase in cholangiocarcinoma development
Role: Postdoctoral Fellow

B. Positions, Appointments, and Honors

Positions and Employment

1999-2001 Undergraduate Research Assistant. Brigham and Women's Hospital, Boston MA. Laboratory of George Topulos, Richard Brown, and Jim Butler
2001-2002 Undergraduate Thesis Student**,** Dana Farber Cancer Institute, Boston, MA. Laboratory of Thomas A. Look, MD
2002-2004 Research Technician, Dana Farber Cancer Institute, Boston, MA Laboratory of Thomas A. Look, MD
2004-2011 Graduate Student, Biomedical Sciences Program, University of California San Francisco, San Francisco, CA, Laboratory of Matthias Hebrok, PhD

2011-2012 Post-doctoral Researcher**,** Diabetes Center**,** University of California San Francisco, San Francisco, CA**,** Laboratory of Matthias Hebrok, PhD
2012-2020 Postdoctoral Fellow, Department of Cancer Biology and Genetics**,** Memorial Sloan Kettering Cancer Center, New York, NY, Laboratory of Scott W. Lowe, PhD
2020-present Assistant Professor, University of North Carolina School of Medicine, Department of Pharmacology/Lineberger Cancer Center

Honors

2021-2023 Pancreatic Cancer Action Network Career Development Award
2018 CSHL Young Scholars Symposium
2014-2017 American Cancer Society Postdoctoral Fellowship
2007 UC Cancer Research Coordinating Committee Fellowship
2006 UCSF Genentech Fellowship
2005 UCSF Graduate Dean's Health Science Award
2004 UCSF Graduate Dean's Health Science Award

C. Contribution to Science

Key publications:

a. **Morris JP 4th**, Yashinskie JJ, Koche R, Chandwani R, Tian S, Chen CC, Baslan T, Marinkovic ZS, Sánchez-Rivera FJ, Leach SD, Carmona-Fontaine C, Thompson CB, Finley LWS, and Lowe SW. *Alpha-ketoglutarate links p53 to cell fate during tumor suppression. Nature*. 2019;573(7775):595-599

b. Ruscetti M*, **Morris JP 4th***, Mezzadra R*, Russell J, Leibold J, Romesser PB, Simon J, Kulick A, Ho Y, Fennell M, Li J, Norgard RJ, Wilkinson JE, Alonso-Curbelo D, Sridharan R, Heller DA, de Stanchina E, Stanger BZ, Sherr CJ, and Lowe SW. *Senescence triggers vascular remodeling and new therapeutic vulnerabilities in pancreas cancer. Cell*. 2020;181(2):424-441.e21. *Equal Contribution

c. Baslan T*, **Morris JP 4th*,** Zhao Z*, Reyes J, Ho Y, Tsanov KM, Bermeo J, Tian S, Zhang S, Askan G, Yavas A, Lecomte N, Erakky A, Varghese AM, Zhang A, Kendall J, Ghiban E, Chorbadjiev L, Wu J, Dimitrova N, Chadalavada K, Nanjangud GJ, Bandlamudi C, Gong Y, Donoghue MTA, Socci ND, Krasnitz A, Notta F, Leach SD, Iacobuzio-Donahue CA, and Lowe SW. *Ordered and deterministic cancer genome evolution after p53 loss. Nature. In press.* *Equal Contribution.

1. **Early Career:** As an undergraduate student I was introduced to important concepts in understanding genotype-phenotype relationships using animal model systems. As an undergraduate thesis student and research technician I served as part of a team developing techniques for generating zebrafish lines possessing mutations in conserved genes relevant to human cancer via chemical mutagenesis. I contributed techniques for cryopreserving zebrafish sperm in order to efficiently archive genetic material while mutant lines for follow up study were being screened. I also applied the PCR based mutation analysis used in zebrafish forward genetic approaches to targeted mutation analysis in human cancer samples.
    a. Morris JP 4th, Berghmans S, Zahrieh D, Neuberg DS, Kanki JP, Look AT. *Zebrafish sperm cryopreservation with N,N-dimethylacetamide.* Biotechniques. 2003. 35:956-8, 960, 962 passim.
    b. Berghmans S, Murphey RD, Wienholds E, Neuberg D, Kutok JL, Fletcher CD, Morris JP 4th, Liu TX, Schulte-Merker S, Kanki JP, Plasterk R, Zon LI, Look AT. *tp53 mutant zebrafish develop malignant peripheral nerve sheath tumors*. Proc Natl Acad Sci U S A. 2005. 102:407-12.
    c. Weng AP, Ferrando AA, Lee W, Morris JP 4th, Silverman LB, Sanchez-Irizarry C, Blacklow SC, Look AT, Aster JC. *Activating mutations of NOTCH1 in human T cell acute lymphoblastic leukemia*. Science. 2004. 306:269-71.
    d. Berghmans S, Morris JP 4th, Kanki JP, Look AT. *Zebrafish sperm cryopreservation.* Methods Cell Biol. 2004. 77:645-59.

2. **Graduate Career:** My graduate research focused on understanding how mechanisms of tissue homeostasis are altered during the earliest stages of cancer development. I focused on oncogenic Kras, the most common genetic event in PDAC, and specification of premalignant lineages. My work revealed that oncogenic Kras

prevents acinar cell regeneration, and instead drives specification of de-differentiated, duct like cells characterized by persistent expression of characteristics of embryonic pancreas progenitors. This process depends on inhibition of regeneration associated Wnt/Beta-Catenin signaling and intact miRNA biogenesis suggesting that aberrant, preneoplastic lineage specification depends on remodeling of developmental pathways critical for responding to organ damage. Collaborative work revealed insight into lineage defining transcription factors, epigenetic remodelers, and inflammatory mediators that interact with mutant Kras to drive premalignant development.

a. Morris JP 4th, Greer R, Russ HA, von Figura G, Kim GE, Busch A, Lee J, Hertel KJ, Kim S, McManus M, Hebrok M. Dicer regulates differentiation and viability during mouse pancreatic cancer initiation. PLoS One. 2014. 9:e95486.
b. Kopp JL, von Figura G, Mayes E, Liu F, Dubois CL, Morris JP 4th, Cheng Pan F, Akiyama H, Wright CVE, Jensen K, Hebrok M, Sander M. *Identification of Sox9-dependent acinar-to-ductal reprogramming as the principal mechanism for initiation of pancreatic ductal adenocarcinoma.* Cancer Cell. 2012. 22:737-50.
c. Fukuda A, Wang SC, Morris JP 4th, Folias AF, Liou A, Kim GE, Akira S, Boucher KM, Firpo MA, Mulvihill SJ, Hebrok M. *Stat3 and MMP7 Contribute to Pancreatic Cancer Initiation and Progression.* Cancer Cell. 2011. 19:441-55.
d. Zhang Y, Morris JP 4th, Yan W, Schofield HK, Gurney A, Simeone DM, Millar SE, Hoey T, Hebrok M, Pasca di Magliano M. *Canonical Wnt Signaling Is Required for Pancreatic Carcinogenesis.* Cancer Research.2013.73:4909-4922.

3. **Postdoctoral Career:** As a postdoctoral fellow I focused on the relationship between cancer drivers and malignant cell fate. I developed a suite of embryonic stem cell based genetically engineered mouse models of PDAC and liver cancer that allow temporal control of gene expression. These models have provided novel tools for studying cancer maintenance and malignant evolution. Using these tools to restore tumor suppressive levels of wildtype p53 in malignant cells provided a platform to identify p53 outputs directly related to antagonizing malignancy. This approach identified p53 triggered metabolic reprogramming that leads to accumulation of the metabolite □KG, required for the function of developmentally conserved enzymes that, amongst other activities, direct differentiation by controlling histone and DNA methylation. As activity of these enzymes are selected against in tumorigenesis (e.g. via mutation of specific enzymes and mutations that produce competitive inhibitors of □KG (e.g. cancer associated isocitrate dehydrogenase 1/2 mutations), my work highlights a novel connection between p53 and a metabolically sensitive set of epigenetic and differentiation mediators. Current independent work is aimed at dissecting this tumor suppressive axis and better characterizing malignant evolution in order to identify markers and therapeutic targets. Furthermore, I have developed platforms that allow for the lineage tracing of cells following selective loss of critical tumor suppressors which constrain the pre-malignant to malignant switch in pancreatic cancer. Lineage tracing following loss of p53 function has revealed principles underlying evolutionary routes of malignancy that have important implications in managing cancer heterogeneity involved in therapy resistance and relapse. My independent work will leverage this new-found granularity to establish not only genotype specific susceptibilities, but therapeutic strategies that stratify and target specific aspects of evolutionary routes that led to malignant identity and fitness.

a. Alonso-Curbelo D, Ho YJ, Burdziak C, Maag JLV, Morris JP 4th, Chandwani R, Chen HA, Tsanov KM, Barriga FM, Luan W, Tasdemir N, Livshits G, Azizi E, Chun J, Wilkinson JE, Mazutis L, Leach SD, Koche R, Pe'er D, Lowe SW. A gene-environment-induced epigenetic program initiates tumorigenesis. Nature. 2021 Feb;590(7847):642-648. doi: 10.1038/s41586-020-03147-x. Epub 2021 Feb 3. PMID: 33536616.
b. Livshits G, Alonso-Curbelo D, Morris JP 4th, Koche R, Saborowski M, Wilkinson JE, Lowe SW. *Arid1a restrains Kras-dependent changes in acinar cell identity.* Elife. 2018 Jul 17;7. pii: e35216. doi: 10.7554/eLife.35216.
c. Saborowski M, Saborowski A, Morris JP 4th, Bosbach B, Dow LE, Pelletier J, Klimstra DS, Lowe SW. *A modular and flexible ESC-based mouse model of pancreatic cancer.* Genes and Development. 2014. 28:85-97.
d. Chen C, Liu Y, Lu C, Cross JR, Morris JP 4th, Shroff AS, Ward PS, Bradner JE, Thompson C, Lowe SW. *Cancer-associated IDH2 mutants drive an acute myeloid leukemia that is susceptible to Brd4 inhibition.* Genes and Development. 2013. 27:1974-85.

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/1-W9f2Yy9X6Uzb/bibliography/public/