BIOGRAPHICAL SKETCH

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NAME: McManus, Michael T

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POSITION TITLE: Professor, UCSF Vincent and Stella Coates Endowed Chair; Director, Keck Center for Noncoding RNAs; Core Director, ViraCore at UCSF

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	COMPLETION	FIELD OF STUDY
Auburn University, Auburn, Alabama	B.S.	05/1991	Horticultural Science
University of Alabama at Birmingham	Ph.D.	12/2000	Biochem & Mol Genetics
Massachusetts Institute of Technology	Postdoctoral	12/2004	Small RNA Biology

A. Personal Statement

My work has a strong technology component, and my lab uses systematic and synthetic approaches to conquer fundamental problems in understanding gene function in health and disease. I maintain a very diverse research program, encouraging students and postdocs and research technicians to follow their research interests, by developing new tools and approaches to solve long-standing problems in their field of interest. Having successfully trained in different areas (plant molecular biology, molecular parasitology, RNA biology, and human development/disease) my broad language for basic science has expanded my appreciation of systems biology. Consequently, my ability to integrate diverse sources of information has helped develop innovations and ideas that we have shared with other labs, yielding high impact discoveries in multiple fields throughout my career. This includes several examples where I have derived novel approaches in team settings and applied them to basic biology that intersects complex biological systems.

I have been a principal investigator at UCSF since 2005, overseeing a very productive and interactive lab at UCSF, studying diverse biological processes relating to gene regulation and function, using cultured cells and the mouse as a model. I was awarded tenure in 2010 in the Department of Microbiology and Immunology at UCSF, and a year later bestowed the Vincent and Stella Coates Endowed Chair. I have appointments or am a member of the Helen Diller Comprehensive Cancer Center, the Diabetes Center, the Eli & Edythe Broad Center for Regeneration Medicine and Stem Cell Research, and the Innovative Genomics Institute. Although my independent research career started in RNA biology, our publications and grants illustrate an increasingly trend to merge computational and synthetic biology to address systems biology questions related to human disease. My contribution to this project is part of this growing directionality and focus, and my commitment to share ideas, reagents, and technologies to solve fundamental problems in biology and my enduring commitment to training the next generation of scientists to help further illuminate genomic dark matter. Ongoing and completed projects that I would like to highlight include:

R01GM123556 PI McManus 05/19/17 – 02/28/21
NIH/NIGMS
Regulation of developmental potency by the transposon LINE1
This research aims to understand the molecular regulation of developmental progression in the early mammalian embryo.

U01CA217882 MPI McManus, et. al. 07/01/17-06/30/22
The cancer target discovery and development network at UCSF
This team-driven cooperative project aims to bridge the gap between the enormous volumes of data generated by the comprehensive molecular characterization of a number of cancer types– and the ability to use these data for the development of human cancer therapeutics.

1R01CA212767 McManus (PI) 08/01/17-07/31/22
Functional networks for persister cell sensitivities
This research project aims to uncover genetic dependeiceis for drug tolerant cancer persister cells.

1U24DK116214 McManus and Jan (MPI) 08/01/17-07/31/23
Illuminating druggable dark matter
This is a large team-driven cooperative research program program whose goal is to use a unique CRISPR technologies to uncover poorly annotated gene function in cells and mice.

U01 CA199241 PI Kuo – Stanford Subcontract 04/14/16-03/31/21
Modeling KRAS-dependent synthetic lethality in human colon organoids
This team-driven grant relates to uncovering critical information that will help target Ras driven cancers.

U42OD026647 MPI: McManus and Lloyd 09/15/18-08/31/20
Bay Area CRISPR Reporters
The goal of this project is to develop tangible resources and standard operating procedures that will advance this fundamental mission.

UC Berkeley IGI PI: McManus 01/01/18-12/31/20
Unlocking the Hidden Architecture of Complex Gene Interactions
To develop a technology to study epistatic gene interactions in mouse models using a high-throughput CRISPR technology suitable for interrogating specific genes implicated in a given pathway or disease.

1R01CA195770 PI: McManus 08/01/14-07/31/19
Tracing cell lineages
The aims of this NIH High Risk Transformative Research Award relate to a novel cell tracing technology.

Citations:

a. Bassik MC, Kampmann M, Lebbink RJ, Wang S, Hein MY, Poser I, Weibezahn J, Horlbeck MA, Mann M, Hyman AA, LeProust EM, McManus MT and Weissman JS (2013). A Systematic Mammalian Genetic Interaction Map Reveals Pathways Underlying Ricin Susceptibility, Cell, 152(4):909-22. PMCID: PMC3652613

b. Hangauer M, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, Galeas J, Dhruv HD, Berens ME, Schreiber S, McCormick F, McManus MT (2017). Drug-tolerant persister cancer cells are vulnerable to ferroptosis, Nature, 51(7679):247-250. PMCID: PMC5933935.

c. Boettcher M, Tian R, Blau J, Markegard E, Wu D, McCormick F, Kampmann M, McManus MT (2018). Dual gene activation and knockout screen reveals directional dependencies in genetic networks, Nature Biotechnology, Nat Biotechnol. 36(2):170-178. PMCID: PMC6072461.

Positions and Scientific Appointments

2022-present	CZB	Investigator, Chan Zuckerberg Biohub
2017-present	UCB	Member, Innovative Genomics Institute (IGI, Berkeley)
2017-present	UCSF	Member, Helen Diller Comprehensive Cancer Center
2016-present	UCSF	Full Professor- Dept of Microbiology and Immunology/Diabetes Center
2012-present	UCSF	Vincent and Stella Coates Endowed Chair
2010-present	UCSF	Associate Professor- Dept of Microbiology and Immunology/Diabetes Center
2009-present	UCSF	Member, Center of Regeneration Medicine and Stem Cell Research
2008-present	UCSF	Director, WM Keck Center for Noncoding RNA
2004-present	UCSF	Core Director, ViraCore
2004-2010	UCSF	Assistant Professor- Dept of Microbiology and Immunology/Diabetes Center
2001-2004	MIT	Cancer Research Institute Postdoctoral Fellow- Center for Cancer Research

B. Positions, Scientific Appointments, and Honors

Honors
Chan Zuckerberg Biohub (2022), Robert J. Kleberg, Jr. and Helen C. Kleberg Award (2020), Vincent and Stella Coates Award (2019), Kagle Technology Award (2019), NIH Directors Office Award (IDG2-2017), NIH Cancer Target Discovery and Development Award (2017), Coates Gift for Research Excellence (2016), NIH Transformative Research Award (2014), NIH Illuminating the Druggable Genome Award (2014), Tom and

Michelle Parker gift for stellar research (2012, 2013), Vincent and Stella Coates Endowed Chair (2012), NIH Cancer Target Discovery and Development Award (2012), UCSF IT Innovator Award (2012), Breakthrough Technologies Award (2011), New Technologies Award (2009), WM Keck Award (2007), Deans Recognition for Excellence in Teaching (2007-2010), New Technologies Award (2006), Integrative Science Award (2006), Sandler Award in the Basic Sciences (2005), MIT School of Science Spot Appreciation Award (2003), Cancer Research Institute (CRI) Fellowship (2002).

C. Contribution to Science

Early phase as a trainee. After an early stint studying plant molecular biology, my career interests began developing around the study of small RNAs in the biological systems, I was excited to study biological roles for small RNAs and develop new approaches that harness RNAi pathways to explore gene function. As a student, my first impactful manuscript was the discovery of an RNA editing ligase that plays a role in small RNA directed gene expression. This was the first identification of an insertional/deletional RNA editing enzyme and cemented a model for the enzymatic cascade mechanism, overturning a transesterification model proposed by Tom Cech. As a postdoc, I provided evidence and practical methodologies for small RNA activity in the mammalian system, and my contributions impacted the development of a new field focused on the biology of RNAi and the use of it as a tool in many contexts. One manuscript showed the first observance of RNAi in primary cells. Another significant manuscript constituted one of the first reports to describe the means to silence genes using shRNAs. The invention of shRNAs was conceived and developed by me during my postdoctoral studies. Within a ~3 month window of this publication, other labs reported similar technology and thousands of labs around the world have used shRNA technology to silence genes.

a. McManus MT, Adler BK, Pollard VW, and Hajduk SL (1998). *Trypanosoma brucei* guide RNA poly(U) tail formation is stabilized by cognate mRNA. Mol. Cell. Bio, 20:833-891. PMCID: PMC85205

b. McManus MT, Shimamura MS, Grams J, and Hajduk SL (2001). Identification of candidate mitochondrial RNA editing ligases from *Trypanosoma brucei*. RNA, 7:167-175. PMCID: PMC1370075

c. McManus, MT, Petersen, CP, Haines, BB, Chen, J, and Sharp, PA 2002. Gene silencing using microRNA designed hairpins. RNA 8:842-850.12088155. PMCID: PMC1370301

d. McManus MT, Haines, BB, Dillon C, Whitehurst, CE, van Parijs L, Chen, J and Sharp PA (2002). siRNA-mediated gene silencing in T-lymphocytes, J. of Immunology,169(10):5754-5760

Early phase as an independent investigator. In addition to the early contributions described above, I began to develop my skillsets and expertise in mouse models that have developed during my time as an independent investigator. This work set a foundation for my work as an independent investigator. During my early training, I had focused on the biology of small RNAs and the use of it as a tool in biological contexts. However, I really wanted to move into mouse models, exploring in vivo biological developing aspects of noncoding RNAs. I also wanted to explore fundamental questions relating to human development and disease. I published one study that provided microRNA tools and reagents for the field, expediting the study of gene expression and noncoding RNA in in vivo contexts. It is first paper to describe microRNA activity in an organism, revealing reflecting expression patterns consistent with known developmental programs. This paper was the first description of in vivo mammalian microRNA 'sensor' which detects the activity of a microRNA in a tissue. Sensor technology is used by hundreds of mammalian labs working in the microRNA field and has become a standard for assessing microRNA activity in a live cell. It was also one of two competing papers that showed that an endogenous microRNA could act as a bona-fide siRNA in vertebrates. More specifically, this study showed that the vertebrate Hox locus contains microRNAs that sculpt Hox expression patterns and developmental programs. As such this paper was seminal in the noncoding RNA developmental biology field.

MicroRNAs have often been referred to as the Dark Matter of the genome, and their surprising discovery completely changed our concept of how complex organisms develop and function. We contributed a number of papers in this area, starting with one of the first descriptions of a mouse Dicer knockout, followed by the first description of the first mouse microRNA knockout (miR-1-2) which exhibited a developmental heart defect. Another study expanded our efforts to ambitiously ablate all evolutionarily conserved noncoding RNA genes in the mouse. This latter project represented a moderately high-throughput pipeline for three people in my lab to eventually produce more than 100 loxP conditional microRNA targeted lines in only a few years' time. We developed and optimized streamlined protocols and technologies that allowed us to accelerate recombination-based genetic modification of embryonic stem cells and adapt expression reporters typically used for coding

genes. Despite millions of years of evolutionary conservation for microRNAs, and their broad acting roles in regulating hundreds to thousands of genes, for the first time we showed that most microRNA knockouts fail to have obvious phenotypes when ablated singly in mice. We believe this to be due to genetic redundancy of microRNA families and pathways and their roles in micromanaging global gene expression. We shared all the generated microRNA transgenic ES cells and mouse reagents freely available to the academic scientific community, which met a compelling need in the field of genetics and noncoding RNA field. These reagents are currently distributed around the world. This project generated a significant resource that continues to make an impact in labs studying noncoding RNAs in mouse models. The fascinating complexity of microRNA:target interactions motivated my interested to explore gene:gene interactions in disease contexts.

a. Mansfield, JH, Harfe B, Nissen, R, Obenaur J, Srineel J, Chaudhuri A, Farzan-Kashani R, Zuker M, Pasquinelli AE, Ruvkyun G, Sharp PA, Tabin CJ, McManus MT (2004). microRNA-responsive transgenes reveal Hox-like and other developmentally regulated patterns of vertebrate microRNA expression. Nature Genetics, 36 (10):1079-1083. PMID: 15361871

b. Harfe BD*, McManus MT*, Jennifer Mansfield, and Tabin CJ (2005). The RNAse III enzyme Dicer is required for morphogenesis but not patterning of the vertebrate limb, PNAS, 102(31):10898-90. *equal corresponding authors PMCID: PMC1182454

c. Zhao Y, Ransom JF, Li A, Vedantham V, von Drehle M, Muth AN, Tsuchihashi T, McManus MT, Schwartz RJ, Srivastava D (2007). Dysregulation of Cardiogenesis, Cardiac Conduction, and Cell Cycle in Mice Lacking miRNA-1-2. Cell, 129(2):303-17. PMID: 17397913

d. Park CY, Jeker LT, Carver-Moore K, Oh A, Liu HJ, Cameron R, Richards H, Li Z, Adler D, Yoshinaga Y, Martinez M, Nefadov M, Abbas AK, Weiss A, Lanier LL, de Jong PJ, Bluestone JA, Srivastava D, McManus MT (2012). A resource for the conditional ablation of microRNAs in the mouse, Cell Reports, 1(4), 385-391. PMCID: PMC3345170

Recent work as an established investigator. My previous experience in the study of RNAi and microRNA gene regulation shaped my current research program aimed at understanding the complexity of the genome and how it relates to human disease. I have boldly steered my lab into new areas, especially expanding on our high-throughput approaches and genomic enterprises that help inform human disease. Although the DNA sequence of our genome is essentially identical in all cells of the body, each cell type and tissue are uniquely susceptible to various diseases. Epigenetic marks on DNA are the major means to differentiate the more than 200 cell types in the human body. One recent contribution from our group constituted a major team effort to create reference maps for all major tissues in the body. Although the number of genome-centric team driven papers has been on the rise over the last two decades, this particular study began with heated contention (see 'Epigenomics: A Roadmap, But to Where?', Science 2008). We contributed to a manuscript in a special issue in Nature covering the epigenome; it has been highly referenced (>4,200 citations). We also contributed a study centered on RNA expression, the molecular signature of transcription activity governed by epigenetic marks (see below "Pervasive Transcription of the Human Genome Produces Thousands of Previously Unidentified Long Intergenic Noncoding RNAs", 2013). In our genome-scale epigenome study discovered that approximately 5% of each reference epigenome shows enhancer and promoter signatures, which are twofold enriched for evolutionarily conserved non-exonic elements on average. Moreover, the dynamics of epigenomic marks allow for data-driven approach to learn biologically meaningful relationships between cell types, tissues and lineages. I like to think that this manuscript constitutes the 'sequencing of the human epigenome' and as such provided a complement to the first published human genome sequence (Nature, 2001). The incredible richness of noncoding sequence and epigenetic decorations paint an astonishing degree of complex hidden gene regulation. This includes molecular and cellular studies of drug resistance behaviors (Hangauer et al, Nature 2017) where we have identified novel mechanisms for epigenetic drug resistance in cancer biology. In collaboration with the He lab we have continued to be productive in microRNA biology, describing a role for miR-200 in restricting lung cancer metastasis via Notch signaling in cancer-associated fibroblasts.

As my lab has matured, I have steered parts of my lab towards developing and using high-throughput approaches to fundamental biological questions i.e. genetic interaction in cancer cells. A major challenge is that most human diseases are polygenic, and there have been no efficient means to address the functional relationships between human genetic variants. The complexity of gene interactions creates an incredible technical challenge. Partnering with the Weissman lab, we developed a powerful technology for quantitatively measuring genetic interaction in a high-throughput assay in mammalian cells. This work helped pave a new research direction for

me and cemented my desire to connect noncoding pathways in cells and in vivo. It was made possible by our earlier publication, where we presented a revolutionary new way to create and use RNAi libraries (Bassik, 2009). Screening labs around the world have adopted our ultra-high throughput quantitative methods and concepts described in our publications as a general paradigm for conducting pooled screens. A significant portion of my lab takes high-throughput approaches to dissecting major problems in human biology and disease. In fact, our RNAi approaches have largely moved to CRISPR based tools, and we are developing additional novel systems. We recently described an approach where we have developed CRISPR technologies to screen multiple orthogonal perturbations per cell, interrogating >2M gene interaction constructs (Boettcher et al, Nature Biotech 2018). We are working hard to transition our fundamental studies into cancer biology, applying our unique toolsets and technologies to address fundamental cancer biology questions.

Mouse models continues to be an important component of my lab's research program. We developed a CRISPRi mouse model and established it as a powerful means to silence genes using dCas9-KRAB. In a series of publications, we used our CRISPRi mice to silence genes in neurons (Neuron, 2019, PMC6639135 and Cell Rep, 2019, PMC6750766) and metabolic tissues (Nature, 2019, PMC6715529 and Nature, 2020, PMC7415677). It is precisely these types of technologies that are applicable to our Multimer GEMMs which truly enable high-throughput mouse genetics and cancer-centric functional genomics.

a. Hangauer MJ, Vaughn IW, McManus MT (2013). Pervasive Transcription of the Human Genome Produces Thousands of Previously Unidentified Long Intergenic Noncoding RNAs. PLoS Genet June; 9(6). PMCID: PMC3688513.
b. Integrative analysis of 111 reference human epigenomes (2015), Roadmap Epigenetics Consortium, Nature (518(7539):317-30). PMCID: PMC4530010
c. Hangauer M, Viswanathan VS, Ryan MJ, Bole D, Eaton JK, Matov A, Galeas J, Dhruv HD, Berens ME, Schreiber S, McCormick F, McManus MT (2017). Drug-tolerant persister cancer cells are vulnerable to ferroptosis, Nature, 51(7679):247-250. PMCID: PMC5933935.
d. Xue B, Chuang CH, Prosser HM, Fuziwara CS, Chan C, Sahasrabudhe N, Kühn M, Wu Y, Chen J, Biton A, Chen C, Wilkinson JE, McManus MT, Bradley A, Winslow MM, Su B, He L. (2021). miR-200 deficiency promotes lung cancer metastasis by activating Notch signaling in cancer-associated fibroblasts, Genes Dev, 35(15-16):1109-1122. PMCID: PMC8336896

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/41586096/?sort=date&direction=descending