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. To date I have contributed >100 publications, with ~50 published in Cell, Science, and Nature journals, garnering >41,000 citations (h-index 82; i10-index 119). Collaboration is a cornerstone of my research philosophy, and I relish and thrive in collaborative settings.

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 enjoyed appointments or am a member of the Innovative Genomics Institute, the Helen Diller Comprehensive Cancer Center, the Diabetes Center, the Eli & Edythe Broad Center for Regeneration Medicine and Stem Cell Research, and the Chan Zuckerberg Biohub. Although my independent research career started in RNA biology, our publications and projects illustrate an increasingly trend to merge computational and synthetic biology to address systems biology questions related to human disease. My team currently has nine manuscripts in preparation, submitted, or revision, with three of them that directly related to this submission.

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 gene function and genomic dark matter related to molecular and cellular mechanisms. Currently funded NIH projects include:

U01CA272546 MPI McManus, et. al. 09/13/22-08/31/27
The cancer target discovery and development network at UCSF. This team-driven cooperative project aims to further the development of novel human cancer therapeutics the one-gene-at-a-time approach to studying functional genomics in mouse models.

R01DK133645 MPI Tang (Contact) 07/01/22-04/30/27
Genome editing of human pancreatic islets to withstand ischemic injuries and promote immune evasion. The major goals of this project are to develop strategy for highly efficient tissue transplantation without the need of immunosuppression, using McManus lab high throughput technologies.

iStar Tregs. This collaborative research program will advance immunotherapies by developing cell engineering strategies to target regulatory T cells and creating a platform for monitoring their activation in the target tissue– using barcoded exosome technologies developed in the McManus Lab.

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, 1524.: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, 517679.:247-250. PMCID: PMC5933935.

a. Integrative analysis of 111 reference human epigenomes 2015, Roadmap Epigenetics Consortium, Nature 5187539.:317-30. PMCID: PMC4530010

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. 362.:170-178. PMCID: PMC6072461.

B. Positions and Scientific Appointments

2022-present	CZB	Investigator, Chan Zuckerberg Biohub.
2017-present	UCSF	Member, Helen Diller Comprehensive Cancer Center
2017-2022	UCB	Member, Innovative Genomics Institute IGI, Berkeley
2003-present	NIH	Study section panels GCAT, ENCODE, MGB and >15 Review Committee
2003-present		*ad hoc* reviewer for many journals including Cell, Science, Nature, Molecular Cell, Genes and Development, Nature Biotechnology, Nature Review Genetics, Nature Genetics, Oncogene, Expert Opinion on Biological Therapy, Journal of Biological Chemistry, Lancet, PNAS, Chemistry & Biology, Developmental Dynamics, Journal of National Cancer Institute, BBA Cancer, Biotechniques, RNA, PLoS Computational Biology, Genome Biology, Nucleic Acids Research, Nature Protocols, Nature Medicine, Nature Methods, and PLoS Genetics, etc.
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

Honors

Nan Fung Award (2022), Chan Zuckerberg Biohub Award (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, 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,16910.:5754-5760.

b. 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

c. 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

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

Early phase as an independent investigator. Early in my independent career, I shifted from studying small RNAs in cell-based systems to exploring their roles directly in mouse models. One of my first studies introduced microRNA tools that allowed gene regulation to be tracked in vivo, including the first mammalian microRNA sensor that reports microRNA activity within tissues. That work also showed that endogenous microRNAs in the Hox locus can act as functional siRNAs in vertebrates, shaping developmental expression patterns. It became a widely used reference point for the developmental biology community.

We continued to investigate the developmental roles of noncoding RNAs, contributing one of the earliest mouse Dicer knockouts and generating the first microRNA knockout, miR-1-2, which produced a cardiac developmental defect. This effort eventually expanded into a larger project in which a small team in my lab created more than 100 conditional microRNA knockout lines using optimized recombination-based approaches in embryonic stem cells. All of these ES cell lines and mouse strains were shared broadly and continue to be used by groups studying noncoding RNA function in vivo. These studies, and the complexity they revealed in microRNA and target interactions, pushed my lab toward larger questions about gene:gene interactions and the genetic networks that shape disease.

a. 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, 14, 385-391. PMCID: PMC3345170

b. 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, 1292.:303-17. PMID: 17397913

c. 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, 10231.:10898-90. *equal corresponding authors PMCID: PMC1182454

d. 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

Recent work as an established investigator. My early research in RNAi and microRNA gene regulation helped establish core principles of small RNA biology and provided key tools that enabled many labs to interrogate gene function with high precision. Building on this foundation, my lab has spent the last decade expanding into high-throughput functional genomics and genome-scale regulatory biology, with a central aim of understanding how the noncoding genome encodes cell identity, disease susceptibility, and therapeutic response. This trajectory has produced multiple highly cited resources and technologies that have shaped several fields, including epigenomics, genetic interaction mapping, CRISPR screening, and more recently, synthetic systems for immune sensing and cell–cell communication.

A major early contribution from my group was our role in generating reference epigenomic maps across primary human tissues as part of the Roadmap Epigenomics Consortium (Nature 2015). Our work helped define a coherent structure to the human epigenome, showing that ~5% of the genome carries enhancer or promoter signatures enriched for conserved non-exonic elements. These features enabled inference of lineage relationships and developmental trajectories directly from chromatin state, providing a functional complement to the human genome sequence. We also contributed to one of the first comprehensive long intergenic noncoding RNA (lincRNA) surveys (PLoS Genetics, 2013), demonstrating that pervasive transcription reflects regulated, chromatin-linked promoter logic rather than noise. Together, these studies established noncoding sequence and epigenetic marks as a major regulatory architecture underlying human cell-type diversity.

Our interest in noncoding regulation naturally motivated our work on gene regulatory networks in cancer. We explored how chromatin state and gene expression plasticity contribute to therapeutic resistance. Our work with Hangauer and colleagues (*Nature*, 2017) revealed a mechanism of drug-tolerant persister cancer cells and demonstrated that these cells are selectively vulnerable to ferroptosis. This study connected noncoding regulation, metabolic stress responses, and treatment resistance, influencing how the field conceptualizes minimal residual disease.

As my lab matured, I increasingly oriented our efforts toward developing high-throughput genetic tools capable of probing complex biological systems. A central problem in human genetics is polygenicity: most diseases arise not from single genes but from interactions among many loci. Traditional one-gene-at-a-time approaches cannot capture this complexity. We co-developed one of the first systematic mammalian genetic interaction maps, enabled by innovations in pooled screening and RNAi library construction (Bassik et al., *Cell*, 2013). This project established a broadly adopted paradigm for conducting pooled screens and remains a key reference for genetic interaction studies in mammalian cells. We then expanded these concepts into CRISPR-based methods and published a high-throughput dual-perturbation system that tested >2 million gene–gene interaction constructs in single cells (*Nat. Biotechnol.*, 2018). This work helped initiate a new research direction in combinatorial CRISPR screening and continues to influence approaches to studying emergent genetic relationships underlying cancer vulnerabilities.

To translate these genomic tools into in vivo contexts, we developed a CRISPR interference (CRISPRi) mouse model based on dCas9-KRAB. This model enables stable and tissue-specific silencing of genes using programmable guide RNAs. In a series of collaborative studies, we applied this system to neurons (*Neuron*, 2019; *Cell Reports*, 2019) and metabolic tissues (*Nature*, 2019; *Nature*, 2020), demonstrating its broad utility for functional genomics in vivo. These collaborations highlight one of the defining features of my lab: a strong commitment to team science, resource sharing, and the development of community-impactful technologies.

In the period surrounding the COVID-19 pandemic, I took a deliberate step back to reassess my labs long-term scientific direction and identify areas where we could make the greatest impact. This strategic reset led us to concentrate on building a new generation of high-throughput technologies for single-cell, combinatorial, and intercellular phenotyping. Some of these efforts have now matured, resulting in nine manuscripts currently in preparation, submission, or revision. Our recent work can be grouped into three major technology pillars:

(1) High-content and combinatorial pooled screening platforms. To understand how cells integrate multiple perturbations and environmental cues, a requirement for engineering precisely controlled mRNA delivery, we developed RainBar and CellPool, microscopy-based pooled CRISPR platforms that capture single-cell phenotypes, reporter activation, morphological states at scale, and geared for studying immune:cancer cell interactions (these are in consideration at *Nature Methods* and *Nature Biotechnology*). These systems reveal how thousands of perturbations influence cell behavior simultaneously, an essential capability for dissecting the regulatory logic that governs mRNA production, export, stability, and immune visibility. We complemented these platforms with a high-multiplicity-of-infection (high-MOI) pooled screening strategy for combinatorial gene perturbations (in revision at *Nature Methods*) and a streamlined small-RNA library protocol that improves

transcript quantification (*in preparation*). Together, these tools provide a technical roadmap needed to study cell:cell interaction via imaging and engineer multi-component RNA-handling systems inside immune cells.

(2) Modular systems for building TCR- and pMHC-guided mRNA delivery. Engineering a T-cell based mRNA courier requires modular systems that can load and package RNA with high efficiency. To overcome the recombination and template-switching that limit standard lentiviral and retroviral approaches we developed PRECISE, a recombination-free packaging platform capable of generating exceptionally high-titer and architecturally stable libraries. This recombination problem has been a pervasive, field-wide constraint that quietly corrupts complex libraries, so solving it with PRECISE suddenly makes a whole class of highly modular, information-dense constructs and screens realistically achievable. PRECISE is the basis of three manuscripts *in preparation*: (i) the PRECISE platform itself, (ii) a massively parallel peptide-MHC (pMHC) epitope-mapping technology, and (iii) a high-throughput TCR specificity-mapping system built on that same architecture. These TCR and pMHC projects will help us engineer specificity in T cell programming and open the door to delivering mRNA directly to diseased cells or even reprogram other immune cells to fight disease and restore healthy function.

(3) Intercellular platforms for cell:cell mediated mRNA delivery. T cell behavior is all about cell:cell interaction; we developed platforms that record and analyze how cells exchange information in vivo, and importantly-- how to harness T cells to deliver functional mRNA to target cells. In the first project, we engineered exoRelay, where immune cells secrete RNA barcodes in their exosomes. These barcodes can be captured and sequenced from a single drop of blood, revealing how cells broadcast molecular messages throughout tissues. In a second project, Relay maps direct cell:cell contact by tracking RNA transfer through trogocytosis. This approach provides high-resolution deep-sequencing based readouts of interactions between immune cells and antigen-presenting cancer cells (in preparation). These technologies show that RNA can serve as a transferable, trackable medium for communication between living cells: precisely the conceptual foundation that underlies the RELAY program. Together, they demonstrate that immune cells can be engineered not only to sense disease but also to transmit tailored genetic messages to neighboring cells, forming the mechanistic basis for our T-cell mediated mRNA delivery platform proposed in this application. Collectively, these platforms define a research program built around functional genomics and engineered cell:cell communication, and position us to next link antigen-resolved pMHC/TCR mapping with therapeutic RNA cargos so that immune cells can be programmed to rewrite local tissue states in autoimmunity, infection, and cancer.

a. Choudhary K, McManus MT 2025. Scalable imaging-based profiling of CRISPR perturbations with protein barcodes, bioRxiv, 2025.11.11.687767. doi: 10.1101/2025.11.11.687767.

b. Oberlin S, Tay N, Xue A, Pimentel H, McManus MT 2025. Multiplexed perturbation enables scalable pooled screens, bioRxiv, 2025.08.14.669942. doi: 10.1101/2025.08.14.669942.

c. Mosadeghi R, Foyt D, Sharp L, Taylor C, Tay N, Oberlin S, Fan J, Bourke S, Kattah M, Huang B, McManus MT 2025. RainBar: optical barcoding for pooled live-cell imaging with single-cell resolution, bioRxiv, 2025.11.04.686676. doi: 10.1101/2025.11.04.686676.

d. Tay NQ, Juan T, Muldoon JJ, Tepper A, Brown BD, Eyquem J, McManus MT 2025. Tracking cell-cell interactions using intercellular barcode transfer, in preparation.

e. Tay NQ, Asaki J, Xing G, Feng X, Ferrara E, DeRisi J, Marson A, Bruno P, McManus MT 2025. High-throughput MHC I immunopeptidomics via nanoparticle relays, in preparation.

f. Xing G, Asaki J, Tay NQ, Feng X, Stickels RR, DeRisi J, McManus MT, Marson A 2025. T cell receptor discovery using pooled nanoparticles, in preparation.

g. Tay NQ, Goodman DB, Chua C, Oberlin S, Roybal KT, McManus MT 2025. Recombination-free clonal lentivirus production using PRECISE landing pad cells, in preparation.

Complete List of Published Work in My Bibliography:
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