BIOGRAPHICAL SKETCH

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NAME: MA, SAI

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

POSITION TITLE: Assistant Professor of Genetics and Genomic Sciences

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
Zhejiang University, China	B.S.	05/2011	Chemistry
Virginia Tech, Blacksburg, VA	Ph.D.	05/2017	Biomedical Engineering
Wake Forest University, Winston-Salem, NC	Ph.D.	05/2017	Biomedical Engineering
Broad Institute of MIT and Harvard, Cambridge, MA	Postdoctoral Fellow	06/2022	Genomics; epigenomics; single-cell technology
Harvard University, Cambridge, MA	Postdoctoral Fellow	06/2022	Stem cell biology; development
MIT, Cambridge, MA	Postdoctoral Fellow	06/2022	Stem cell; tumor progression; gene regulation

A. Personal Statement

I am an Assistant Professor of Genetics and Genomic Sciences at the Icahn School of Medicine at Mount Sinai and am eligible as an Early Stage Investigator (ESI). I completed my postdoctoral training between Aviv Regev and Jason Buenrostro Labs at the Broad Institute and Harvard University. Research in my lab is directed toward innovating new genomic and microfluidic technologies to understand how cells regulate their genes and how these mechanisms influence cell fate in stem cells and cancer. Our research combines advances in genomics, engineering, chromatin biology, stem cell biology, and large-scale bioinformatics to create cross-disciplinary platforms for profiling and manipulating cells and their interactions. My primary goal is to help transform the way the community thinks about gene regulation, cell-cell interactions, diseased tissues and processes, and therapeutics, ultimately leading to a new paradigm for understanding and designing multicellular behaviors at the systems level.

My track record demonstrated my strong inclination to take intellectual risks and develop novel approaches when new challenges arise. First, I pioneered developing new technologies for mapping chromatin states and non-coding regulatory elements at single-cell resolution. These technologies include SHARE-seq (*Cell* 2020; *Cell* 2023), which allows simultaneous mapping of epigenome and transcriptome at the single-cell level, SurfaceChIP-seq (*Science Advances* 2018) and MID-RRBS (*Nature Biomedical Engineering* 2018), microdevices that enable highly sensitive profiling of histone modifications and DNA methylation in rare cell populations. These advanced sequencing approaches have proven valuable for understanding gene regulation. Second, in addition to these technologies, I develop complementary computational tools, including Chromatin Potential and FigR (*Nature Communications* 2020; *Cell* 2020; *Nature Methods* 2020; *Cell Genomics* 2022), to identify molecular drivers that specify lineage and predict cell behavior during cell fate commitment. Third, I have constantly explored topics outside my comfort zone by applying our tools to various biological contexts. Our research has revealed epigenetic mechanisms that play a role in cell fate determination and altered cell states, including hair follicle regeneration (*Nature* 2021; *Nature* 2020), neuronal cell fate determination (*Nature*

Neuroscience 2022), drug response (*Nature Biomedical Engineering* 2018), and tumor progression (*Cancer Discovery* 2021; *Cancer Cell* 2020).

In addition to my role in the Department of Genetics and Genomic Sciences at Mount Sinai, I am a member of Icahn Genomics Institute, a member of the Skin Biology and Diseases Resource-based Center (SBDRC), and an affiliate member of the New York Genome Center (NYGC). My past experiences have resulted in **2** patents, **35** publications (10 first-author), and an additional **10** manuscripts (1 corresponding author) currently being reviewed or prepared.

1. **Ma, S.**, Zhang, B., LaFave L., Chiang, Z., Hu Y., Ding, J., Brack, A., Kartha, V., Law, T., Lareau C., Hsu, C.H., Regev, A. & Buenrostro, J. Chromatin potential identified by shared single-cell profiling of RNA and chromatin. ***Cell***, 183, 1-14 (2020). PMC7669735

2. **Ma, S.**, Revenga, M., Sun, Z., Sun, C., Murphy, T. W., Xie, H., González-Maeso, J. & Lu. C. Cell-type-specific brain methylomes profiled via ultralow-input microfluidics. ***Nature Biomedical Engineering*** 2, 183-194 (2018). PMC6023403

3. **Ma, S.**, Hsieh, Y., Ma, J. & Lu, C. Low-input and multiplexed microfluidic assay reveals epigenomic variation across cerebellum and prefrontal cortex (SurfaceChIP-seq). ***Science Advances*** 4, eaar8187 (2018). PMC5906078

4. Zhang, B., **Ma, S.** et al. Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells. ***Nature***, 577, 676-681 (2020). PMC7184936

5. Joung, J., **Ma, S.***, Tay, T.* Geiger-Schuller, K. R.*, Kirchgatterer, P. C., Verdine, V. K., Guo, B. Arias-Garcia, A.A., E. Allen, W.E., Singh, A., Kuksenko, O., Abudayyeh, O.O., Gootenberg, J. S. Fu, Z., Macrae, R.K., Buenrostro, J.D., Regev, A. & Zhang, Z. A transcription factor atlas of directed differentiation. ***Cell***, 186, 209-229 (2023). PMID: 36608654

I have not published or created research products under a different name.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2022 - Present	Assistant Professor, Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, NYC, NY
2022 - Present	Member, Icahn Genomics Institute, Icahn School of Medicine at Mount Sinai, NYC, NY
2022 - Present	Member, Skin Biology and Diseases Resource-based Center, Icahn School of Medicine at Mount Sinai, NYC, NY
2022 - Present	Affiliate Member, New York Genome Center, NYC, NY
2022 - Present	Program committee for the Genomic Health Initiative, NYC, NY
2018 – 2019	Lecturer, Harvard University, Cambridge, MA
2018	Guest editor, BioMed Research International
2015 - 2017	Consultant, Scribe, San Francisco, CA
2014 - Present	Member, Biomedical Engineering Society
2013 - Present	Member, American Institute of Chemical Engineers (AIChE)
2013 - Present	Member, AES Electrophoresis Society

Honors

2022	Scholar Award: HKU-100 Scholar
2010	National College Students' Science and Technology Innovation Award
2009, 2010, 2011	Student Research Training Award
2007-2011	Fellowship: The Second/Third Prize Scholarship
2006	Second Prize, National Olympiad in Chemistry
2006	Third Prize, National Olympiad in Biology

C. Contributions to Science

1. **Single-cell genomic technology development.** The development of new experimental technologies can drive the discovery of new biology. We have developed tools to measure chromatin accessibility, transcriptome, and DNA methylation at the single-cell level. These methods improve the data sparsity in single-cell approaches and motivate the further development of new technologies. Examples include high-sensitivity chromatin profiling in primary tissues (***Cancer Cell*** 2020; ***Nat. Neurosci.*** 2022), DNA methylation profiling at single-cell resolution (***Nat. Biomed. Eng.*** 2018), and massive-scale (>10^5 cells) single-cell co-mapping chromatin accessibility and gene expression using SHARE-seq (***Cell*** 2020). We are also keen on expanding these technologies further to gain an understanding of the gene regulatory principles. For example, we combined single-cell tools with pooled genetic perturbation for large-scale functional screens of transcription factors in stem cell differentiation (***Cell*** 2023).

   1. **Ma, S.**, Zhang, B., LaFave L., Chiang, Z., Hu Y., Ding, J., Brack, A., Kartha, V., Law, T., Lareau C., Hsu, C.H., Regev, A. & Buenrostro, J. Chromatin potential identified by shared single-cell profiling of RNA and chromatin. ***Cell***, 183, 1-14 (2020). PMC7669735

   2. LaFave, L., Kartha, V.*, **Ma, S.*** et al. Epigenomic state transitions characterize tumor progression in lung adenocarcinoma, ***Cancer Cell***, 38, 212-228, (2020). (* equal contribution) PMC7641015

   3. **Ma, S.**, Revenga, M., Sun, Z., Sun, C., Murphy, T. W., Xie, H., González-Maeso, J. & Lu. C. Cell-type-specific brain methylomes profiled via ultralow-input microfluidics. ***Nature Biomedical Engineering*** 2, 183-194 (2018). PMC6023403

   4. Joung, J., **Ma, S.***, Tay, T.* Geiger-Schuller, K. R.*, Kirchgatterer, P. C., Verdine, V. K., Guo, B. Arias-Garcia, A.A., E. Allen, W.E., Singh, A., Kuksenko, O., Abudayyeh, O.O., Gootenberg, J. S. Fu, Z., Macrae, R.K., Buenrostro, J.D., Regev, A. & Zhang, Z. A transcription factor atlas of directed differentiation. ***Cell***, 186, 209-229 (2023). PMID: 36608654

   5. Yuan, W., **Ma, S.**, Brown, J., Kim, K., Murek, V., Trastulla, L., Meissner, A., Lodato, S., Shetty, A., Levin, J., Buenrostro, J., Ziller, M. & Arlotta P. Temporally-Divergent regulatory mechanisms govern neuronal development and diversification in the neocortex. ***Nature Neuroscience***, 25, 1049–1058 (2022). PMC9343253

2. **Development of computational tools for multi-omic analysis.** In addition to developing experimental methods, we have significantly contributed to computational tools for analyzing single-cell (***Nat. Commun.*** 2020) and spatial-omics data (***Nat. Methods*** 2021). Leveraging the variations across cells, we developed tools to link distal regulatory elements to their target genes (***Cell Genomics*** 2022). In addition, we demonstrated that chromatin accessibility generally activates before the onset of corresponding gene expression during lineage commitment (***Cell*** 2020), providing strong evidence of lineage-priming mediated by chromatin accessibility. Based on this finding, we developed a computational approach, Chromatin Potential, to infer cell fate outcomes during stem cell differentiation, leveraging large-scale bioinformatics.

   1. **Ma, S.**, Zhang, B., LaFave L., Chiang, Z., Hu Y., Ding, J., Brack, A., Kartha, V., Law, T., Lareau C., Hsu, C.H., Regev, A. & Buenrostro, J. Chromatin potential identified by shared single-cell profiling of RNA and chromatin. ***Cell***, 183, 1-14 (2020). PMC7669735

   2. Lareau, C., **Ma, S.**, Duarte F., & Buenrostro J. Inference and effects of barcode multiplets in droplet-based single-cell assays. ***Nature Communications***, 11, 866 (2020). PMC7018801

   3. Biancala, T., Scalia, G., Buffoni, L., Avasthi, R., Lu, Z., Sanger A., Tokcan, N., Vanderburg, C., Segerstolpe, A., Zhang M., Avraham-Davidi, I., Vickovic, S., Nitzan, M., **Ma, S.** et al. Deep learning and alignment of spatially-resolved whole transcriptomes of single cells in the mouse brain with Tangram, ***Nature Methods***, 18, 1352–1362 (2021). PMC8566243

   4. Kartha, V.K., Duarte, F., Hu, Y., **Ma, S.** et al. J. Gene regulation inference using FigR identifies immunologically-primed chromatin accessibility states. ***Cell Genomics***, 2, 100166, (2022). PMC9534481

3. **Develop ultralow-input microfluidic assays.** One primary goal of my research is to investigate the cellular and molecular identity of rare cell populations in primary tissues. To achieve this goal, we have developed ultralow-input epigenomic assays, such as MID-RRBS and SurfaceChIP-seq (***Nat. Biomed. Eng.*** 2018, ***Sci. Adv.*** 2018), using microfluidic devices that are compatible with tiny quantities of cell samples from primary tissues. We improved the sensitivities of the assays over 1,000 times over conventional approaches. With these new tools, we systematically evaluated the differences in DNA methylation and histone modifications between neurons and glia and their cell-type-specific impact on the transcriptome. Such work advanced our

understanding of gene regulation in rare cell populations and laid the foundation for my interest in pursuing a research career focusing on cell fate decisions.

1. **Ma, S.**, Revenga, M., Sun, Z., Sun, C., Murphy, T. W., Xie, H., González-Maeso, J. & Lu. C. Cell-type-specific brain methylomes profiled via ultralow-input microfluidics. ***Nature Biomedical Engineering***, 2, 183-194 (2018). PMC6023403

2. **Ma, S.**, Hsieh, Y., Ma, J. & Lu, C. Low-input and multiplexed microfluidic assay reveals epigenomic variation across cerebellum and prefrontal cortex. ***Science Advances***, 4, eaar8187 (2018). PMC5906078

3. **Ma, S.**, Bryson, B.D., Sun, C., Fortune, S. M. & Lu, C. RNA extraction from a mycobacterium under ultrahigh electric field intensity. ***Analytical Chemistry*** 88, 5053-5057 (2016). PMC4872636

4. **Ma, S**., Loufakis, D. N., Cao Z., Chang Y., Achenie, L. EK & Lu C. Diffusion-based microfluidic PCR for "one-pot" analysis of cells. ***Lab on a Chip*** 14, 2905-2909 (2014). PMC4113400

5. **Ma, S.**, Schroeder, B., Sun, C., Loufakis, D. N., Cao, Z. Sriranganathan, N. & Lu, C. Electroporation-based delivery of cell-penetrating peptide conjugates of peptide nucleic acids for antisense inhibition of intracellular bacteria. ***Integrative Biology*** 2014, 973-978 (2014). PMID: 25160797

4. **Investigate malignant cell states and tumor ecosystems by single-cell sequencing.** We seek to define cellular programs and epigenetic mechanisms pertinent to cancer biology. To anchor this work in relevant contexts and maximize impact, we have innovated and applied single-cell technologies to characterize lung tumors and breast tissue with the *BRCA1* mutation (***NAR Genom. Bioinform.*** 2021). We identified an epigenomic continuum representing the loss of cellular identity and progression toward a metastatic state (***Cancer Cell*** 2020). We defined co-accessible regulatory programs and inferred key activating and repressive chromatin regulators of these cell states. Most recently, we identified that the Smarca4 mutation sensitizes club cells within the lung, resulting in highly advanced dedifferentiated tumors and increased metastatic incidence (***Cancer Discov.*** 2022). This research grounds our experimental models and investigations in clinical contexts and should thus maximize impact.

1. Concepcion, C., **Ma, S.**, et al. *Smarca4* inactivation promotes lineage-specific transformation and early metastatic features in the lung. ***Cancer Discovery***, 12, 1–24 (2022). PMC8831463

2. LaFave, L., Kartha, V.*, **Ma, S.*** et al. Epigenomic state transitions characterize tumor progression in lung adenocarcinoma, ***Cancer Cell***, 38, 212-228, (2020). (* equal contribution) PMC7641015

3. Hsieh, Y.P., Naler, L., **Ma, S.** & Lu C. Cell-type-specific epigenomic variations associated with *BRCA1* mutation in pre-cancer human breast tissues. ***NAR Genomics and Bioinformatics***, 4(1), lqac006 (2022). PMC8808540

5. **Epigenetic control of skin development and stress response.** A primary goal of my research is to investigate the cellular and molecular identity of the skin stem cell niche. Somatic stem cells are often quiescent but occasionally divide to generate Transit-Amplifying Cells (TACs). With new tools that we established, we systematically identified the differentiation potential of TACs and their roles in making cell fate decisions (***Cell*** 2020). In addition to niche, stem cells must also respond to varying external perturbations, such as stress. We demonstrated how stress influences cell-cell interactions, stem cell behavior, and the fate of hair follicles and melanocyte stem cells (***Nature*** 2020; ***Nature*** 2021).

1. **Ma, S.**, Zhang, B., LaFave L., Chiang, Z., Hu Y., Ding, J., Brack, A., Kartha, V., Law, T., Lareau C., Hsu, C.H., Regev, A. & Buenrostro, J. Chromatin potential identified by shared single-cell profiling of RNA and chromatin. ***Cell***, 183, 1-14 (2020). PMC7669735

2. Choi, S., Zhang, B., **Ma, S.**, et al. Corticosterone inhibits *GAS6* to govern hair follicle stem-cell quiescence. ***Nature***, 592, 428-432 (2021). PMC8923613

3. Zhang, B., **Ma, S.** et al. Hyperactivation of sympathetic nerves drives depletion of melanocyte stem cells. ***Nature***, 577, 676-681 (2020). PMC7184936

Complete List of Published Work:
https://www.ncbi.nlm.nih.gov/sites/myncbi/sai.ma.2/collections/62222921/public/