BIOGRAPHICAL SKETCH

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NAME: Chan, Michelle Mei Wah

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

POSITION TITLE: Assistant Professor, Lewis-Sigler Institute of Integrative Genomics and Department of Molecular Biology, Princeton University

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
University of British Columbia	B.Sc	05/2007	Computer Science and Microbiology and Immunology
Massachusetts Institute of Technology	Ph.D.	06/2013	Computational and Systems Biology
University of California, San Francisco	Postdoctoral	08/2020	Computational Biology, Molecular Biology

A. Personal Statement

I am a formally trained computational biologist with an extensive background in genomics. My undergraduate degree is in Computer Science and Microbiology and Immunology. I worked on a number of research projects during my undergraduate training spanning studies on the transcriptional response in mucosal immune cells to metagenomics of ecological niches. I did my Ph.D. in computational biology under the supervision of Aviv Regev at MIT and the Broad Institute. The specialty of the Regev lab is gene regulation and cellular network remodeling, and my first project in the group focused on modeling transcriptional module evolution over many yeast strains. The core of my graduate work is on epigenetic regulation during mammalian embryogenesis and utilized data sets from DNA methylation profiling, RNA-seq, and ChIP-seq. In the last year of my Ph.D., the Regev lab began pioneering work on single cell RNA-seq. In my postdoc, I expanded my molecular biology skills by transitioning to the bench in Jonathan Weissman's lab at UCSF. There, I lead the development of a new genomics technology, the CRISPR-Cas9 molecular recorder and the analysis of a new data type, the evolving lineage barcode, which I analyzed in tandem with complementary single cell RNA-seq data. My work produced the first whole organism, single cell fate map for mammalian embryogenesis. Jonathan Weissman's lab is a leader in the development and analysis of genetic screening platforms. In collaboration with the Regev lab, the Weissman lab created the first screening platform with single cell RNA-seq as a read-out termed Perturb-seq. My knowledgebase of this field will be very useful in the design and implementation of studies to perform screens of bioelectric stimulation. Having trained at a leading genomics center, the Broad Institute, I am exceptionally qualified to perform genomics research and have successfully worked with many types of sequencing data resulting in multiple publications. While my lab at Princeton predominantly focuses on studies of mammalian embryogenesis, ultimately, we are interested in understanding the gene regulation that alters cell state. The goal of this project, assembling a transcriptional manifold, is in line with my work but in this case, the signals that modify cell state are well defined and controllable compared to the signals that occur during the process of development.

Ongoing projects that I would like to highlight include:

DP2HD111537
Chan (PI)
09/01/2022-08/31/2025
Building a Systematic, Comprehensive Mammalian Cell Fate Map

Citations:

1. **MM Chan***, ZD Smith*, S Grosswendt, H Kretzmer, T Norman, B Adamson, M Jost, JJ Quinn, D Yang, MG Jones, A Khodaverdian, N Yosef, A Meissner, JS Weissman. Molecular recording of mammalian embryogenesis. *Nature*, June 2019. PMCID: PMC7229772
2. **MM Chan***, ZD Smith*, D Egli*, A Regev, A Meissner. Mouse ooplasm confers context-specific reprogramming capacity. *Nature Genetics*, **44**(9):978-80, Sep 2012. PMCID: PMC3432711
3. ZD Smith*, **MM Chan*,** TS Mikkelsen, H Gu, A Regev, A Meissner. A unique regulatory phase of DNA methylation in the early mammalian embryo. *Nature*, 484(7394):339-44, Mar 2012. PMCID: PMC3331945

* denotes equal contribution

B. Positions and Honors

Positions and Employment

2020 Assistant Professor, Lewis-Sigler Institute of Integrative Genomics, Molecular Biology, Princeton University

Honors

2022 NIH Director's New Innovator Award
2015-2018 Life Science Research Foundation Fellow sponsored by the Gordon and Betty Moore Foundation

C. Contributions to Science

1. My graduate work has contributed to the understanding of epigenetic regulation during mammalian early development. In collaboration with the Meissner lab at Harvard University, we were the first to produce high resolution, single basepair, genome-scale maps of an epigenetic mark, DNA methylation, during mouse early development. We addressed fundamental questions, such as the existence of passive demethylation during fertilization (it likely does not exist since we observed changes that were not tied to replication) and made novel discoveries, including characterizing the dynamic regulation of retrotransposon families and the presence of many transiently stabilized, differentially methylated regions between the gametes, which still have unknown function. We then extended many of these observations to human early development and highlighted human-specific retrotransposon dynamics that are tied to evolution. My specific role in these projects was to process and analyze the data, and I worked closely with the experimentalist to interpret results and write the manuscripts. In addition to our biological findings, I believe many groups have been inspired by our conceptual framework for analysis and interpretation of DNA methylation data, including a focus on retrotransposons and allele specific methylation patterns.

   a. ZD Smith*, **MM Chan***, TS Mikkelsen, H Gu, A Regev, A Meissner. A unique regulatory phase of DNA methylation in the early mammalian embryo. *Nature*, **484**(7394):339-44, Mar 2012. PMCID: PMC3331945

   b. ZD Smith*, **MM Chan*,** KC Humm*, Rahul Karnik, S Mekhoubad, A Regev, K Eggan, A Meissner. DNA methylation dynamics of the human pre-implantation embryo. *Nature*, **511**(7511):611-5, July 2014. PMCID:PMC4178976

2. Complementary to our work on *in vivo* development, we produced the first, single basepair, genome-scale maps of embryos after reprogramming by somatic cell nuclear transfer (SCNT). The change in the

methylation profile of the genome after SCNT is similar to that of the sperm genome after fertilization. This outcome is not especially surprising since the ooplasm can be viewed as a reprogramming factor. The major differences in global dynamics are in repetitive elements, which appear to be more resistant to demethylation in SCNT than fertilization, and may be due to the difference in genome packaging between the somatic and paternal genomes. SCNT is often considered the gold standard of reprogramming but we show that barriers exist in SCNT that are not present during natural development.

a. **MM Chan*,** ZD Smith*, D Egli*, A Regev, A Meissner. Mouse ooplasm confers context-specific reprogramming capacity. *Nature Genetics*, **44**(9):978-80, Sep 2012. PMCID: PMC3432711

3. A comprehensive mammalian cell fate map has been difficult to characterize due to the complexity and scale of mouse embryogenesis and the inaccessibility of *in utero* development. I developed a CRISPR-Cas9 molecular recording technology and applied it as a lineage tracer to chart the mammalian cell fate map from fertilization to gastrulation in mouse. In addition to the cell lineage read out, the technology can simultaneously report on molecular phenotype through single cell RNA-seq. The reconstructed fate map recapitulated the expected differentiation patterns of embryogenesis and also identified an alternative route to achieve embryonic endoderm. Moreover, the proportion of cells that arise from different differentiation routes is quantified, which provides an exciting opportunity for further exploration. I engineered the molecular recorder such that it would be useful for studies outside of development. We applied it in two different studies of cancer to understand how a tumor originates, evolves, and metastasizes. One of the studies included a dissection of the primary tumor as well as collection of several metastatic tumors. The lineage tracing data revealed spatial restriction of cellular proliferation as well as independent origins of metastatic tumors.

a. **MM Chan***, ZD Smith*, S Grosswendt, H Kretzmer, T Norman, B Adamson, M Jost, JJ Quinn, D Yang, MG Jones, A Khodaverdian, N Yosef, A Meissner, JS Weissman. Molecular recording of mammalian embryogenesis. *Nature*, June 2019. PMCID: PMC7229772

b. JJ Quinn, MG Jones, R Okimoto, S Nanjo, **MM Chan**, N Yosef, TG Bivona, JS Weissman. Single-cell lineages reveal the rates, routes, and drivers of metastasis in cancer xenografts. *Science*, Jan 2021 PMCID: PMC7983364

c. D Yang, MG Jones, S Naranjo, WM Rideout, K Hoi, J Min, R Ho, W Wu, JM Repogle, JL Page, JJ Quinn, F Horns, X Qiu, MZ Chen, WA Freed-Pastor, CS McGinnis, DM Patterson, ZJ Gartner, ED Chow, TG Bivona, **MM Chan**, N Yosef, T Jacks, JS Weissman. Lineage tracing reveals phylodynamics, plasticity, and paths of tumor evolution. *Cell*, 185(11):1905-1923.e25, May 2022 PMCID: PMC9452598

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http://www.ncbi.nlm.nih.gov/sites/myncbi/1fC6hGh96eoQ9/bibliography/44618571/public/?sort=date&direction=ascending