BIOGRAPHICAL SKETCH

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NAME: Michelle Hays

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

POSITION TITLE: Postdoctoral Fellow

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	Start Date	Completion Date	FIELD OF STUDY
Colorado State University, Fort Collins CO, USA	B.Sc.	09/2001	12/2005	Microbiology and German Language and Literature
University of Washington, Seattle, WA, USA	Ph.D.	09/2013	12/2019	Molecular and Cellular Biology
Stanford University, CA, USA	Postdoctoral	02/2020	ongoing	Genetics and Evolution

A. **Personal Statement**

I am interested in how cells evolve to defend themselves against genetic parasites, and how an organism's genetic background and environment alter the available mechanisms and paths to adaptation. In my postdoc I am building on my prior training in systems genetics and genetic conflict, to learn new tools in experimental evolution and genomics. This combination of training makes me uniquely poised to study the genetic and evolutionary ramifications of host-parasite interactions using genetic screens, and both retrospective (using natural variation) and prospective (using experimental evolution) evolution studies. It is important to understand the complex ways in which antagonistic evolution drives biological innovation. For example, molecular processes that allow microbes to outcompete their neighbors can drive cancer, and infectious disease evolution is shaped by both environmental factors (such as therapeutics) and biotic selection (such as host cell compatibility and immune responses). These disease processes are complex, and studying them directly is further complicated by the fact that many of these processes are the result of many combinatorial and often competing selective pressures. I am developing budding yeast and their natural parasites as a model system to dissect these pressures to study host-parasite interactions from first principles.

In my early career I gained experience in systems genetics with Drs. Tim Galitski and Greg Carter at the Institute for Systems Biology (ISB) and first became excited for understanding the complex interactions between environment, epistasis and pleiotropy in shaping phenotypic output. When Dr. Carter moved on to be faculty, I joined Dr. Aimee Dudley's lab, also at ISB at that time, where I worked on a wide range of projects, including the study of the natural genomic and phenotypic diversity of *Saccharomyces cerevisiae*. This work piqued my interest further in how natural isolates reflect the results of natural "experiments" in fitness, evolution and selection. I had the opportunity to direct a project as co-first author for the first time where we demonstrated that the transition from euploidy to aneuploidy provides a mechanism for yeast strains that develop complex colony morphology to undergo a striking multicellular phenotypic switch. This work was featured on the cover of PNAS at publication and our poster was awarded at the 2012 GSA Yeast meeting. This mechanism of aneuploidy underlying an often-reversible, but inelegant, phenotypic switch piqued my further interest in understanding the mechanisms by which genomes evolve and the processes that give rise to adaptation and plasticity.

This interest in the mechanisms that underlie adaptive evolution led me to the University of Washington for graduate school. While obtaining my PhD in Dr. Harmit Malik's lab at the Fred Hutchinson Cancer Research Center I trained in genetic conflict and evolution. I used my prior experience in yeast genetics to develop a new model system within the Malik lab (experts on genetic conflict and evolution, but typically working in Drosophila chromatin and primate virus systems). I leveraged natural population diversity to dissect the genetic conflict between budding yeasts and the parasitic 2-micron plasmids that reside within them. In this project I developed new tools for single-cell phenotyping of intracellular parasites, and identified a novel gene variant responsible for parasite restriction. My Ph.D. work was supported by a competitive spot on UW's NIH NHGRI training grant (T32 HG000035) and through an NSF Graduate Research Fellowship (DGE-1256082).

Dr. Gavin Sherlock's lab at Stanford University (February 2020 - present) is the ideal place for me to achieve my postdoctoral training goals. The Sherlock lab has expertise in experimental evolution and have developed cutting-edge lineage tracking methods and genomics approaches for exploring beneficial mutations in evolving populations. I am building critical skills in experimental evolution, experience using cutting-edge lineage tracking methods, and furthering my genomic data analysis and bioinformatics training in the Sherlock lab. Just as I brought a new model system into my PhD thesis lab, I am currently bringing a new research direction into the Sherlock lab, and have initiated a new collaboration with Dr. Arjan de Visser's lab at Wageningen University in the Netherlands. I am applying the Sherlock lab's expertise in experimental evolution to a host-parasite system to study and contrast biotic and abiotic drivers of genome evolution.

I am using experimental evolution and lineage tracking to profile beneficial mutations in evolved yeast populations under genetic conflict: specifically using the killer system. Killer yeast harbor two viruses that allow them to produce a toxin they secrete into the environment, as well as an intracellular antidote to that toxin. This allows killer yeast to kill environmental competitors that are sensitive to the toxin. At the same time, the viral infection associated with killer imposes its own metabolic cost to the host cell. Killer yeast provide a complex system: with multiple genomic players and frequency-dependent costs and benefits established by environment and ecological context. Consequently, this is an ideal system for studying complex evolutionary dynamics from first-principles.

My postdoctoral training (in genomics and prospective experimental evolution) complements my Ph.D. studies, where I used quantitative genetics and standing natural variation to study host resistance to a parasitic plasmid. My projects in both the Malik and Sherlock labs are of my own design, and are mine to take with me into my own future laboratory. Additionally, during my time in the Galitski, Dudley and Malik labs I contributed to new methods development: including high throughput phenotyping assays for mating efficiency, barcode enabled high throughput tetrad dissection and a single-cell assay measuring plasmid retention. Taken together this combination of training, diversity of approaches and range of host-parasite interactions will leave me uniquely poised to study the consequences and mechanisms of host-parasite coevolution in my own future laboratory.

Long-term, my goal is to have a career as academic faculty: pursuing independent research, teaching and mentoring the next generation of scientists. As a first-generation college student, the mentorship I received in my technician positions changed my career trajectory. As such, I am also pursuing formal career development training in pedagogy and building inclusive classrooms and laboratories, to prepare me to be a mentor and teacher as well as independent scientist. In spring of 2020 I took Stanford's Preparing for Faculty Careers course, and I am actively working towards Stanford's Postdoc Teaching Certificate currently. During my time in the Malik lab I mentored two undergraduate students (one of whom is in medical school and the other who is applying for MD/PhD programs currently) as well as 2 rotation students. I am continuing my commitment to mentoring junior researchers in the laboratory in my postdoc: I mentored two Stanford HB-REX summer interns in 2020 and have started mentoring a new bioinformatics undergraduate researcher. Mentorship allowed me to see myself as a scientist for the first time, and helped me build the self-confidence to pursue my passion; I hope to be that same mentor for the next generation of scientists.

B. Positions and Honors

Positions and employment

2002-2006	Peer tutor - Academic Advancement Center, Colorado State University
2005	Summer Research Intern - Deutscher Akademischer Austausch Dienst (DAAD) Research Internship in Science and Engineering (RISE) - Dr. Rita Bernhardt lab, Universität des Saarlandes
2006	Quality Control Laboratory Technician - Insmed Therapeutic Proteins, Boulder, CO
2006-2007	Research Associate I - Dr. Richard Slayden lab, Colorado State University
2008	Diagnostics Laboratory Technician - GeneCheck, Greeley, CO
2008-2009	Quality Control Analyst II – Contract - Bayer HealthCare, Seattle, WA
2009	Quality Control Analyst II – Contract - Zymogenetics, Seattle, WA
2009-2011	Research Associate II - Dr. Tim Galitski lab, Institute for Systems Biology
2011-2013	Research Associate II - Dr. Aimée Dudley, Institute for Systems Biology
2013-2019	Ph.D. student - Dr. Harmit Malik's lab, Fred Hutchinson Cancer Research Institute
2020-present	Postdoctoral scholar - Dr. Gavin Sherlock's lab, Stanford University

Honors

2020- 2021 - Stanford Center for Computational, Evolutionary and Human Genomics (CEHG) Postdoctoral Fellow

2020 - 2021 NIH NHGRI Stanford Genomics Training Program (SGTP) Training Grant (5 T32 HG 000044-24)

2015 - 2020 National Science Foundation Graduate Research Fellow (NSF GRFP Grant No. DGE-1256082)

2019 - MCB Departmental Nominee for UW Graduate Medal

2018 - Finalist, UW Excellence in Teaching Award

2018, 2019 - Finalist FHCRC Nancy Hutchison Mentoring award

2014 - 2015 - NIH NHGRI Genome Training Grant, UW 2014- 2015 (5 T32 HG000035-20)

2014 – 2019 - Portal to the Public Science Communication Fellow, Pacific Science Center

2017 - 2018 - Summer Institute for Scientific Teaching; National Academy of Sciences Scientific Teaching Fellow

2017 - Hutch United Travel Award for Gordon Research Conference on Molecular Mechanisms in Evolution

2018 - SMBE Registration Award, Annual Conference in Tokyo

2018 - FHCRC Student-Postdoc Advisory Committee Travel Award for EMBO Yeast Eco-Evo meeting

2016, 2018 - Work featured in GSA meeting reports for both 2016 and 2018 EMBO Experimental Approaches to Ecology and Evolution Using Yeast and Other Model Systems conferences

Presentation awards

2018 - EMBO Experimental Approaches to Ecology and Evolution using Yeast and Other Model Systems best poster,

2017 - American Indian Science and Engineering Society (AISES) awarded excellence in biology,

2016 - AISES best graduate oral presentation biology track

2015 - AISES honorable mention, graduate student oral presentation

2015, 2018 - Best poster, Fred Hutchinson Basic Sciences Division retreat

Leadership activities

2017, 2019 - Elected joint Chair for Gordon Research Seminar in Molecular Mechanisms in Evolution, 2019 meeting

2018 - FHCRC Invited speaker student committee member - selected and invited speakers for the ongoing Fred Hutch Current Biology Seminar series

2017-2018 - Creation of STEP-UP: an MCB Mentored Teaching Experience program – worked with MCB directors to create and participate in first ever curriculum development and mentored teaching experience for UW MCB program. This program continues on as an NSF funded program through UW.

2016 – 2019 - MCB program Student Area Director for Genetics, Genomics and Evolution: helped incoming graduate students select courses and rotation labs in area of interest, shaped MCB core curriculum offerings for subfield

2017 - Weintraub Award Selection Committee

2015 - Co-organizer for Seattle Genetic Instability and Cancer Symposium

C. Contributions to Science

Complete list of my published works available in my bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/michelle.hays.1/bibliography/public/

1. **Genetic conflict between the selfish 2-micron plasmid and budding yeast**: I did my Ph.D. work with Dr. Harmit Malik at the Fred Hutchinson Cancer Research Center (2013-2019). In the Malik lab I had the opportunity to completely design and implement a new research program from start to finish, in a model system that was new to the lab but that I was comfortable with. *Saccharomyces cerevisiae* has abundant molecular and genetic tools and substantial natural diversity, but even after decades as a model organism, little is known about how its near-ubiquitous selfish 2-micron plasmids shape its evolution. Although yeast biologists have known of 2-micron (2u) plasmids for nearly 50 years, many questions about their biology remain unanswered. I found evidence that host genomes can adapt to curb the fitness of 2u plasmids and identified a novel pathway by which they do so. These findings provide strong evidence in favor of the model that 2u plasmids are coevolving parasites of budding yeasts and provided the first direct evidence that natural variation in *S. cerevisiae* can combat 2u plasmids, and that there is a natural ongoing arms-race between yeast and 2u plasmids. Additionally, this work found the first direct link between the essential Smc5/6 chromosomal machinery and these selfish plasmids that need to hijack host machinery to mediate their own propagation: a complex known to be important in antiviral processes in mammalian cells.
   Leveraging standing population variation, I identified yeast isolates that naturally restrict the 2-micron plasmid – this trait is both heritable and dominant, suggestive of an evolved host restriction factor, rather than the loss of an essential plasmid-supporting permissivity factor. I developed new tools, including a single-cell assay to measure plasmid loss dynamics (SCAMPR). I found that most plasmid loss events are

due to plasmid missegregation, rather than copy number attrition. Using Quantitative Trait Locus mapping, I determined the genetic loci underlying this trait. I found that a natural polymorphism of an essential host gene, *MMS21*, contributes to this plasmid resistance phenotype. Mms21 is a mitotic SUMO E3 ligase and member of the Smc5/6 complex, a cohesin- and condensin-like protein complex important in DNA damage repair. Interestingly, we find that across budding yeast strains this *MMS21* polymorphism correlates with decreased presence of a specific 2-micron genotype: the genotype used in our study. We speculate that ongoing antagonistic coevolution drives both host and plasmid natural variation.

   a. **Hays M,** Young JM, Levan P, Malik HS. A natural variant of the essential host gene *MMS21* restricts the parasitic 2-micron plasmid in *Saccharomyces cerevisiae*. eLife 2020;9:e62337 DOI:10.7554/eLife.62337

2. **Aneuploidy can facilitate phenotypic toggling in a multicellular yeast trait**: While in Dr. Aimée Dudley's lab at the Institute for Systems Biology (2011-2013) I worked across many research projects, but my primary contribution was demonstrating that the transition from euploidy to aneuploidy provides a mechanism for yeast strains that develop complex colony morphology to undergo a striking multicellular phenotypic switch. Euploid strains create "fluffy" colonies, while aneuploid cells develop "smooth" colonies in this strain background. I was co-first author on this project which arose from my observation that two yeast strains thought to be genetically identical, but phenotypically distinct, actually differed by an unexpected whole chromosome aneuploidy. In this work we identified one of the genes on the aneuploid chromosome that was partially responsible for the trait. Additionally, it was my intellectual contribution to drive and select for the gain and loss of *specific* chromosomes to test cause and effect of whole chromosomal aneuploidies on this phenotype. We leveraged a conditional centromere construct created by Dr. Kerry Bloom in a method described by Dr. Kirk Anders. This was an important project direction for establishing causality rather than just correlation between aneuploidy and colony morphology. We followed up this initial paper with subsequent transcriptional analyses to better understand the molecular mechanism that drives colony morphology changes. Although many genes and pathways that are essential for complex colony formation are known, it remains unclear how fluffy yeast strains create reproducible complex colony shapes from a single cell, or how these specific shapes (often unique to a strain) are determined. Fluffy colonies are a multicellular phenotype encoded by a unicellular organism and can be used as a model for understanding the transition from unicellular to multicellular lie styles.
   a. Tan Z*, **Hays M***, Cromie GA, Jeffery EW, Scott AC, Ahyong V, Sirr A, Skupin A, Dudley AM. Aneuploidy underlies a multicellular phenotypic switch. *Proc Natl Acad Sci U S A*. 2013 Jul 23;110(30):12367-72. PMCID: PMC3725063 https://doi.org/10.1073/pnas.1301047110
   b. Cromie GA, Tan Z, **Hays M**, Jeffery EW, Dudley AM. Dissecting Gene Expression Changes Accompanying a Ploidy-Based Phenotypic Switch. *G3 (Bethesda)*. 2017 Jan 5;7(1):233-246.

3. **Systems genetics: predictive models of phenotype based on genotype.**
My early career contributions are mainly in the area of systems genetics, with an eye towards predictive models of phenotypic output, when given limited genotypic input. Additionally, many laboratory studies focus on known phenotypes of knock out mutations; however, in natural populations alleles are unlikely to be precise deletions. As a research technician in Dr. Tim Galitski's group at the Institute for Systems Biology I worked with Dr. Greg Carter (2009-2011) developing computational methods that use individual allele phenotypes to dissect genetic network interactions and predict combinatorial phenotypic output. This modeling informs how genetic variation affects complex traits in populations with extensive genetic diversity, including polymorphisms and copy number variation. For these projects I was the sole experimentalist on largely computational projects. I generated all training and test set data, and cowrote the manuscripts with my mentor Dr. Carter. In addition to learning standard yeast genetics and molecular biology techniques, I collaborated with Dr. Amir Sherman to develop a new high throughput mating efficiency assay.
   a. Carter GW, **Hays M**, Sherman A, Galitski T. Use of pleiotropy to model genetic interactions in a population. *PLoS Genet*. 2012;8(10):e1003010. https://doi.org/10.1371/journal.pgen.1003010
   b. Carter GW, **Hays M**, Li S, Galitski T. Predicting the effects of copy-number variation in double and triple mutant combinations. *Pac Symp Biocomput*. 2012:19-30. https://doi.org/10.1142/9789814366496_0003
   c. Cromie GA, Tan Z, **Hays M**, Sirr A, Jeffery EW, Dudley AM. Transcriptional Profiling of Biofilm Regulators Identified by an Overexpression Screen in *Saccharomyces cerevisiae*. *G3 (Bethesda)*. 2017 Aug 7;7(8):2845-2854

4. **Developing tools to understand quantitative traits in natural populations**. A secondary focus of my time in the Dudley lab was in developing resources for leveraging budding yeast natural variation in quantitative genetics studies. To this end I collaborated on projects screening for novel *S. cerevisiae* isolates from single-origin fermentation niches. By focusing on unroasted coffee and cocoa beans from single origin farms across the globe we were able to isolate several yeast strains and compare the genetic diversity to explore how geography vs. niche correlated with genomic diversity. In this joint work between Dr. Justin Fay's lab and the Dudley lab, I collected samples, isolated yeasts, verified their species and prepared genomic DNA for analyzing genomic diversity within budding yeasts. The rapidly expanding number of natural isolates available (now more than ever due to several large strain collection projects in the greater yeast community) is a powerful tool for exploring evolutionary and quantitative genetics. I also helped develop new methods for exploring this natural genetic diversity, and its contribution to phenotype, in the laboratory. The Dudley lab developed a high throughput tetrad dissection method (BEST) that uses genetic barcodes to facilitate large scale genetic crosses in yeast. This method generates a large number of progeny from a cross, on the scale of using random spore methods, but preserves the sister-spore relationships that are so valuable for mapping, but are historically only available in smaller, low throughput hand-dissected crosses. The sister-spore relationships in BEST are established through the introduction of unique barcodes into diploid cells prior to sporulation.
    a. Ludlow CL, Cromie GA, Garmendia-Torres C, Sirr A, **Hays M**, Field C, Jeffery EW, Fay JC, Dudley AM. Independent Origins of Yeast Associated with Coffee and Cacao Fermentation. *Curr Biol*. 2016 Apr 4;26(7):965-71. https://doi.org/10.1016/j.cub.2016.02.012
    b. Ludlow CL*, Scott AC*, Cromie GA, Jeffery EW, Sirr A, May P, Lin J, Gilbert TL, **Hays M**, Dudley AM. High-throughput tetrad analysis. *Nat Methods*. 2013 Jul;10(7):671-5. https://dx.doi.org/10.1038%2Fnmeth.2479

D. Additional Information: Research Support and/or Scholastic Performance

YEAR	COURSE TITLE	GRADE
	University of Washington	Cum: 3.81
2013	Transcriptional regulation	3.9
2013	Survey of technology for molecular biology	3.5
2013	Advanced genetic analysis	3.3
2014	Gene regulation	3.7
2014	Statistical and computational genomics	4.0
2014	Microbial population biology	4.0
2014	Microbial evolution	3.7
2014	Laboratory based biostatistics	3.7
2014	Biomedical research integrity series	CR
2014	Dynamic chromosome	3.7
2015	Scientific ethics	CR
2015	Evolutionary genetics & genomics	4.0
2016	Scientific speaking	4.0

Except for the scientific ethics and biomedical research integrity (BRI) courses the University of Washington grades on a 0.0-4.0 scale. Ethics and BRI are graded credit (CR) or no credit (NC), with all sessions required to be attended and participation in small group discussions accompanying each seminar session to receive credit.