CURRICULUM VITAE

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EDUCATION

Dates	Institutions/Locations	Degree/Status	Subject/Area
1982—1986	Stanford University, Stanford, CA	B.S. highest honors	Biological Sciences
1982—1986	Stanford University, Stanford, CA	M.S.	Biological Sciences
1986—1995	UC San Francisco, San Francisco, CA	M.D.	
1989—1993	UC San Francisco, San Francisco, CA	Ph.D.	Genetics
1995—1999	Whitehead Institute, Cambridge, MA	Postdoctoral Fellow	

PRINCIPAL POSITIONS HELD

1984	*Teaching Assistant, Qualitative Organic Analysis* Department of Chemistry, Stanford University
1985	*Teaching Assistant, Undergraduate Core Laboratories* Department of Biological Sciences, Stanford University
1990	*Teaching Assistant, Introductory Biochemistry* Department of Biochemistry and Biophysics, UC San Francisco
1999—2005	*Assistant Professor* Department of Biochemistry and Biophysics, UC San Francisco
2005—2008	*Associate Professor* Department of Biochemistry and Biophysics, UC San Francisco
2008—present	*Professor* Department of Biochemistry and Biophysics, UC San Francisco

OTHER POSITIONS HELD CONCURRENTLY

1999—present	Tetrad Graduate Program	Member
2006—present	Comprehensive Cancer Center	Member
2008—present	Microbial Pathogenesis and Host Defense Training Program	Member
2009—present	California Institute of Quantitative Biology (QB3)	Member
2010—present	Integrated Program in Quantitative Biology	Member
2010—present	Systems Biology Graduate Program	Member
2012—present	Biophysics Graduate Program	Member
2012—present	Bioinformatics Graduate Program	Member
2014—present	Biomedical Sciences Graduate Program	Member

HONORS AND AWARDS

1986 Fox Award for Outstanding Undergraduate in Department of Biological Sciences, Stanford University
1986 Firestone Medal for Excellence in Research, Stanford University
1987 Dean's Prize for Student Research, UC San Francisco
1991 Chancellor's Fellowship, UC San Francisco
1995 Helen Hay Whitney Foundation Postdoctoral Research Fellowship
1996 Finalist, Pharmacia-Science Prize
1998 Burroughs-Wellcome Fund Career Award
2000 David and Lucille Packard Foundation Fellowship for Scientists and Engineers, UC San Francisco
2005 Leukemia and Lymphoma Society Scholar
2014 Elected Fellow, American Academy of Microbiology
2014 Haile T. Debas Academy of Medical Educators Excellence in Teaching Award, UC San Francisco
2015 Outstanding Faculty Mentor Award, UC San Francisco

KEYWORDS/AREAS OF INTEREST

Genome defense, host-pathogen interactions, gene expression, chromatin, RNA, pathogenic fungi, phagocytosis

PROFESSIONAL ACTIVITIES

PROFESSIONAL ORGANIZATIONS

Memberships

2013—present RNA Society
2014—present American Association for the Advancement of Science

SERVICE TO PROFESSIONAL PUBLICATIONS

1999—present Ad hoc reviewer: Many journals, most recently *Cell, Proceedings of the National Academy of Sciences, PLoS Pathogens, PLoS Genetics, Nucleic Acids Research, Cell Reports*
2008—present Editorial Board: *PLoS Genetics*
2008—present Editorial Board: *PLoS Pathogens*

INVITED PRESENTATIONS

International

2002 Transcription and Chromatin Workshop, Marie Curie Institute, Oxted, UK
2003 Seminar, Institute of Biochemistry, ETH Hönggerberg, Zürich, Switzerland
2003 Seminar, Department of Physiological Chemistry, UMC Utrecht, the Netherlands
2003 3rd *Cryptococcus neoformans* Genome Conference, Vancouver, BC, Canada
2003 FEBS Workshop: Wageningen, The Netherlands
2003 Seminar, Banting and Best Department of Medical Research, University of Toronto, Toronto, ON, Canada
2004 Seminar, graduate student-invited, Netherlands Cancer Institute
2007 Plenary Presentation: Banff Workshop in Stochastics in Biology

2009 Seminar, Department of Molecular Genetics, University of Toronto, Toronto, ON, Canada
2013 Plenary Presentation, FEBS Course, Human Fungal Pathogens, La Colle sur Loup, France
2014 Seminar, Department of Physiological Chemistry, Ludwig Maximillans-Universitat, Munich, Germany
2014 Plenary Presentation, 9th International Conference on Cryptococcus and Cryptococcosis, Royal Tropical Institute, Amsterdam, The netherlands
2015 Plenary Presentation, FEBS Course, Human Fungal Pathogens, La Colle sur Loup, France

National

1992 RNA Processing Meeting, Cold Spring Harbor, NY
1993 RNA Processing Meeting, Cold Spring Harbor, NY
1996 Yeast Genetics and Molecular Biology Meeting, Madison, WI
1997 Yeast Cell Biology Meeting, Cold Spring Harbor, NY
1998 RNA Tumor Viruses Meeting, Cold Spring Harbor, NY
Massachusetts General Hospital Cancer Center, Charlestown, MA
1999 Yeast Cell Biology meeting, Cold Spring Harbor, NY
2002 Seminar, Department of Molecular Oncology, Genentech, Inc
2003 Keystone Symposium: Chromatin: Organizing the Genome for Patterns of Gene Expression in Health and Disease, Big Sky Resort, MO
Biochemistry and Biophysics Department Seminar, Texas A&M University, College Station, TX
Institute Seminar, Fred Hutchinson Cancer Research Center, Seattle, WA
Gordon Research Conference: Molecular and Cellular Biology, Tilton, NH
2004 Gordon Research Conference: Cellular and Molecular Fungal Biology, Holderness School, Plymouth, NH
FASEB Meeting: Yeast Chromosome Structure, Replication & Segregation, Pine Mountain, GA
Genetics Society Meeting: Yeast Genetics & Molecular Biology, Seattle, WA
Colloquium, Biology Department, M.I.T., Cambridge, MA
Seminar, Department of Cell Biology, Harvard Medical School, Boston, MA
Seminar, UMDNJ Medical School, Department of Microbiology and Molecular Genetics, Newark, NJ
Seminar, Section of Molecular and Cellular Biology, UC Davis, Davis, CA
Seminar, Department of MCD Biology, University of Michigan, Ann Arbor, MI
2005 Seminar, Molecular Biology Program, Memorial Sloan-Kettering Cancer Center, New York, NY
Keystone Symposium: Epigenetics and Chromatin, Snowbird, UT
University of Utah Genetics Program, Snowbird, UT
FASEB Meeting: Chromatin and Transcription, Snowmass, CO
David and Lucile Packard Foundation Fellows Meeting, Monterey, CA
Frontiers Lecture, Stanford University School of Medicine, Stanford, CA
2006 Seminar, graduate student-invited, UC Irvine
Seminar, graduate student-invited, University of Georgia
2007 Seminar, Department of Biochemistry and Biophysics, SUNY Stony Brook
Keystone Symposium: Epigenetics: Regulation of Chromatin Structure in Development and Disease: Co-organizer
Gordon Epigenetics Conference
2008 Seminar, postdoctoral fellow-invited, University of Wyoming
2009 Seminar, Department of Microbiology, University of Minnesota
Seminar, Department of Biochemistry and Biophysics, University of Toronto

2010 Seminar, Department of Pharmacology and Cell Biology, Duke University
Seminar, Department of Biochemistry and Molecular Genetics, University of Colorado
Gordon Chromatin Conference
2011 Seminar, Department of Biological Chemistry, UC Irvine
Seminar, Department of Molecular Oncology, Genentech, Inc
Seminar, Whitehead Institute/MIT
Penn State Summer Symposium in Molecular Biology: Chromatin and Epigenetics
Seminar, Department of Cell Biology, Johns Hopkins School of Medicine
Seminar, UCI-INSERM Symposium on Epigenetics and Cellular Plasticity
2012 Plenary Presentation, Keystone Symposium on Fungal Pathogens
Seminar, The Scripps Research Institute
Seminar, Department of Microbiology, Columbia University
Seminar, Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical Center
Seminar, Molecular Biology Program, memorial Sloan-Kettering Cancer Center
Seminar, Department of Pathology, University of Utah School of medicine
Seminar, Department of Biology, Stanford University
Seminar, National Institute of Environmental Health Sciences, Chapel Hill, NC
Seminar, Fred Hutchinson Cancer Center
2013 Biology Colloquium, Massachusetts Institute of Technology
2014 Seminar, Department of Molecular Biochemistry and Biophysics, Yale University
Seminar, Molecular Biology Program, Skirball Institute, New York University
Plenary Presentation, Gordon Conference on Post-Transcriptional Regulation of Gene Expression
Seminar, Department of Cell Biology, Harvard Medical School
Seminar, Molecular Biology Institute, UCLA
2015 Plenary Presentation, 28th Fungal Genetics Conference
Seminar, Department of Biochemistry, Columbia University (scheduled)
Seminar, Department of Biology, UC San Diego (scheduled)
Seminar, Department of Molecular Genetics, John Hopkins (scheduled)
2016 Seminar, Department of Molecular, University of Chicago (scheduled)
Plenary Presentation, Gordon Conference on Epigenetics (scheduled)
Plenary Presentation, Gordon Conference on Post-Transcriptional Gene Regulation (scheduled)

Regional and Other Invited Presentations

1999 Seminar, Department of Biochemistry and Biophysics, UC San Francisco
2000 Seminar, UC San Francisco Comprehensive Cancer Center
2002 Seminar, UC San Francisco Tetrad Pro gram Annual Retreat, Tahoe City, CA
2003 Seminar, Cancer Genetics Group, UC San Francisco Comprehensive Cancer Center
2005 Seminar, UC San Francisco Tetrad Program Annual Retreat, Tahoe City, CA
2008 Seminar, UC San Francisco Tetrad Program Annual Retreat, Tahoe City, CA
2010 Seminar, UC San Francisco Tetrad Program Annual Retreat, Tahoe City, CA
2012 Seminar, Biophysics, Biomedical Informatics, Chemistry and Chemical Biology (BBC)
2012 Seminar, UC San Francisco Tetrad Program Annual Retreat, Tahoe City, CA
2015 Seminar, UC San Francisco Tetrad Program Annual Retreat, Tahoe City, CA (scheduled)

Government and Other Professional Service

2000	NIH Review Panel, P41 site visit, University of Washington Yeast Resource Center
2005	University of Utah NIH Genetics Program External Reviewer
2006	NIH Review Panel, P41 site visit, University of Washington Yeast Resource Center
2007	NIH Review Panel, MGB, ad hoc member
2007—present	Scientific Advisory Board Member, Saccharomyces Genome Database (NIH-funded genome resource at Stanford)
2007-2011	NIH Review Panel, CSRS, permanent member; Chairman from 2009—20111
2012	NIH Review Panel, Special Emphasis Panel for Director's Early Path to Independence Award (DP5)
2013—present	NIH Review Panel, PTHE, permanent member

UNIVERSITY AND PUBLIC SERVICE

UNVERSITY SERVICE

UCSF Campus-Wide

2002—2004	Basic Science Research Oversight Committee
2004—present	Medical Scientist Training Program Council

Departmental Service

1999—2005	Biochemistry Department Seminar Committee
2000—present	Tetrad Program Graduate Admissions Committee
2004	QB3 Search Committee Diversity Committee
2005	Graduate Curriculum Reform Committee Cell and Molecular Biology Faculty Search Committee
2006—present	Tetrad Program Graduate Curriculum Committee
2011—2012	Chair, Faculty Search Committee, Department of Biochemistry and Biophysics
2011—2014	Co-chair, Friday Faculty Lunch Committee, Department of Biochemistry and Biophysics
2013—2014	Chair, Faculty Search Committee, Department of Biochemistry and Biophysics (2 searches)
2013—2014	Co-chair, Seminar Committee, Department of Biochemistry and Biophysics

Summary of Service Activities

My major form of scientific community service has been as an NIH study section panel member (Cellular Signaling and Regulatory Systems; CSRS which I chaired) and now as a permanent member of the Pathogenic Eukaryotes (PTHE) review panel. I am also on the editorial boards of *PLoS Pathogens* and *PLoS Genetics* and handle numerous papers for each journal. I also established of a new type of online teaching resource called "PLoS Pearls" (http://www.plos.org/cms/node/476) and was its founding editor.

My major form of University Service has been as a member of the Medical Scientist Training Program (MSTP) Council, which involves admissions work and student advising. I have served on the MSTP Council since 2004.

Department Service includes membership on the Tetrad Graduate Admissions Committee (includes graduate recruitment activity) and membership on the Graduate Curriculum Committee (GCC). I have served on the Tetrad Admission Committee since 2000. I have been a member of the GCC since 2006. I have also joined the iPQB program (specifically the Biophysics, Biomedical Informatics programs) and taught in the Systems course in 2011—2014. I have also recently joined the Biomedical Sciences graduate program.

TEACHING AND MENTORING

TEACHING

Formal Scheduled Classes for UCSF Students

Quarters	Course Number and Title	Teaching Contribution	Units	Class Size
Fall 2000	Genetics 200A	Lecturer	4.5	~40
Fall 2001	Genetics 200A	Lecturer	9	~40
Fall 2002	Genetics 200A	Lecturer	9	~40
Winter 2002	Cancer Block, Medical School	Lecturer	3	~160
Spring 2002	Cell Biology 245	Discussion Section	8	8
Fall 2003	Genetics 200A	Lecturer	9	~40
Winter 2003	Cancer Block, Medical School	Lecturer	5	~160
Spring 2003	Cell Biology 245	Discussion Section	8	8
Fall 2004	Genetics 200A	Course Director	8	8
		Discussion Section	-	~40
Winter 2004	Cancer Block, Medical School	Lecturer	5	~160
Spring 2004	Cell Biology 245	Discussion Section	8	8
Fall 2005	Genetics 200A	Course Director	-	35
		Discussion Section	8	8
Winter 2005	Cancer Block, Medical School	Lecturer	5	~160
Spring 2005	Cell Biology 245	Discussion Section	8	~8
Fall 2006	Genetics 200A	Course Director	-	40
		Minicourse Leader	8	6
	Cancer Block, Medical	Lecturer	5	~160
Fall 2007	Genetics 200A	Lecturer	6	21
Fall 2008	Genetics 200A	Lecturer	6	26
	Cancer Block, Medical School	Small Group Leader	5	12
Fall 2009	Cancer Block, Medical School	Small Group Leader	5	12
	Genetics 200A	Course Director	-	22
		Lecturer	6	22
		Discussion Section	8	8
Fall 2010	Genetics 200A	Course Director	-	16
		Lecturer	8	16
		Discussion Section	6	8
	Cancer Block, Medical School	Small Group Leader	5	12
Fall 2011	Cancer Block, Medical School	Lecturer	2	~160
	Genetics 200A	Course Director	-	~20

Quarters	Course Number and Title	Teaching Contribution	Units	Class Size
Spring 2012	Tetrad Program Minicourse, small RNAs and Genome Defense	Course co-director with Pat O'Farrell	2	~10-12
Fall 2013	Cancer Block, Medical School	Small Group Leader	5	12
Winter 2013	Genetics 200A	Discussion Section	6	8
Spring 2013	Tetrad Program Minicourse, small RNAs and Genome Defense	Course co-directory with Pat O'Farrell	2	~10-12
Winter 2014	Genetics 200A	Course Director	-	~20
Spring 2014	Tetrad Program Minicourse, small RNAs and Genome Defense	Course co-director with Pat O'Farrell	2	~10-12
Spring 2015	Tetrad Program Minicourse small RNAs and Genome Defense	Course co-director with Pat O'Farrell	2	~10-12

Informal Teaching

Rotation Students Supervised:

Winter 2000	Monic Schwartz, Ellie Heckscher
Summer 2000	Gregg Whitworth
Fall 2000	Jason MacGurn
Winter 2001	Jacob Bertrand, Shiv Venkatasubrahmanyam
Winter 2002	Bill Hwang, Bryant McLaughlin
Spring 2002	Ryan Raisner, Erika Woodbury
Summer 2002	Alexandra Ianculescu (MSTP)
Fall 2002	Rachel Tompa
Winter 2003	Teresa Shock, Marie Bao
Spring 2003	Chris Campbell, Nathan Gosse
Fall 2003	Emma McCullagh
Winter 2004	Tetsuya Matsuguchi
Spring 2004	Paul Hartley
Winter 2005	Cheryl Chun
Summer 2005	Amethyst Gillis
Fall 2005	Irma Rangel
Fall 2006	Bill Dowdle, Jennifer Garcia
Winter 2007	Ken Finn, Ian Foe
Spring 2007	Nick Lyons
Fall 2007	Stancey Hanlon, Kai Chew
Spring 2008	Diana Marina
Summer 2008	Phillip Dumesic
Fall 2008	Mark Slabodnick, Prashanthi Natarajan
Spring 2009	Teresa Berens
Fall 2009	Kelly Nissen
Spring 2010	Scott Coyle
Fall 2010	Elizabeth Boydson
Summer 2011	Eric Dang
Fall 2011	Liron Noiman
Winter 2011	Kay Aull
Fall 2011	Liron Noiman
Spring 2012	Nicole Michael
Summer 2012	Desiree Stanley
Spring 2013	Charles Seller

Fall 2013	Bettie Osuna, Dan Santos, Diana Summers
Winter 2013	Jade Sales-Lee
Winter 2014	Athena Lin

Orals Committees:

Eric Guisbert (Carol Gross, Advisor)
Karen Kim (Christine Guthrie, Advisor)
Matt Miller (Sandy Johnson, Advisor)
Jonathan Zalevsky (Dyche Mullins, Advisor)
Ann Wehman (Hervig Baier, Advisor)
Susanna Mlynarcyk (Barbara Panning, Advisor)
Tamara Brenner (Christine Guthrie, Advisor)—chaired committee
Mark Dayel (Dyche Mullins, Advisor)
Jason MacGurn (Jeff Cox, Advisor)
Roby Bhattacharya (Wendell Lim, Advisor)
Sridharan Raghavan (Jeff Cox, Advisor)
Eileen Woo (Erin O'Shea, Advisor)
Erika Woodbury (David Morgan, Advisor)—chaired committee
Morgan Royce-Tolland (Barbara Panning, Advisor)
Ashwini Jambhekar (Joe DeRisi, Advisor)
Sebastian Bernales (Peter Walter, Advisor)
Mona Sridharan (Jonathan Weissman, Advisor)
Sean Pintchowski (Steve Finkbeiner, Advisor)
Carla Bonilla (David Toczyski, Advisor)
Rebecca Zordan (Sandy Johnson, Advisor)
Rachel Hanby (Anita Sil, Advisor)
Stacy Chen (Jennifer Fung, Advisor)
Tet Matsuguchi (Elizabeth Blackburn, Advisor)—chaired committee
Claire Rowe (Geeta Narlikar, Advisor)
Holly Ramage (Jeff Cox, Advisor)
Brandon Toyama (Jonathan Weissman, Advisor)—chaired committee
Georgette Charles (Geeta Narlikar, Advisor)—chaired committee
Alex Plocek (Christine Guthrie, Advisor)
Martin Jonikas (Jonathan Weissman, Advisor)
David Breslow (Jonathan Weissman, Advisor)
Lisa Racki (Geeta Narlikar, Advisor)—chaired committee
Eleanor Clowney (BMS program—Stavros Lomvardas, Advisor)
Jacob Stuart-Ornstein (Jonathan Weissman and Hana El-Samad, co-advisors)—chaired committee
Kiyoshi Egami (Yifan Cheng, Advisor)
Michael Sachs (BMS program—Miguel Ramos, Advisor)
Lauren Booth (Sandy Johnson, Advisor)
John Leonard (Geeta Narlikar, Advisor)
Dustin Dovala (Jeff Cox, Advisor)
Isabel Nocedal (Sandy Johnson, Advisor)
Lindsey Peck (Danica Fujimore, Advisor)
Siang-Yun Ang (BMS program, Benoit Bruneau, Advisor)
John Leonard (Geeta Narlikar, Advisor)
Trevor Parry (Jeff Cox, Advisor)
Stefan Isaac (Geeta Narikar, Advisor)

Trevor Parry (Jeff Cox, Advisor)
Liron Noiman (Sandy Johnson, Advisor)
Joel Hrit (Barbara Panning, Advisor)
Lauren Rodriguez (Anita Sil, Advisor)
Dana Neel (BMS program, Trever Bivonia, Advisor)
Jessica Witchley (Suzanne Noble, Advisor)
Brittany Gianetti (BMS Program, Suzanne Noble, Advisor)

Teaching Narrative

In the Spring of 2013, I taught a mini course on genome defense by small RNAs for the third year. The course received exceptionally positive reviews, and we plan on teaching again in the Spring of 2015.

In Winter of 2014, I also ran a discussion section and served as Course Director (as I have since the Fall of 2007).

In Fall 2013, I taught small groups for the medical school Cancer Block as I have for many years. In September of 2014, I was awarded the Haile T. Debas Academy of Medical Educators Excellence in Teaching Award.

In Fall 2013, 2014 and 2015 I taught in the iPQB systems course.

In addition to these formal opportunities, my laboratory has a weekly group meeting and a weekly journal club. I also meet individually with each member of the lab weekly, alternating between individual meetings and subgroup meetings. Furthermore, I informally advise many students and postdoctoral fellows from other laboratories.

MENTORING

Predoctoral Students Supervised or Mentored

Dates	Name	Program or School	Role	Current Position
2000—2006	Monica Schwartz	Tetrad PhD student	PhD Advisor	Scientist, Achaogen, Inc.
2001—2007	Shiv Venkatasubrahmanyam	Tetrad PhD student/HHMI fellowship	PhD Advisor	Scientist, Amgen, Inc.
2002—2009	Bill Hwang	Tetrad PhD student	PhD Advisor	Scientist, Radiant Genomics
2002—2008	Ryan Raisner	Tetrad PhD student	PhD Advisor	Scientist, Genentech
2002—2008	Oliver Liu	Tetrad PhD student/HHMI fellowship	PhD Advisor	Founder, Radiant Genomics
2003—2008	Marie Baro	Tetrad PhD student/NSF fellowship	PhD Advisor	Editor, Developmental Cell
2003—2007	Rachel Tompa	Tetrad PhD student/NSF fellowship	PhD Advisor	Science Writer, Fred Hutchinson Caner Institute

Dates	Name	Program or School	Role	Current Position
2004—2010	Paul Hartley	Tetrad PhD student/NIH supplement	PhD Advisor	Scientist, Startup
2003—2009	Teresa Shock	Tetrad PhD student/AHA fellowship	PhD Advisor	Scientist, Radiant Genomics
2004—2010	Emma McCullagh	Tetrad PhD student/NSF fellowship	PhD Advisor	Scientist, Medivation
2005—2010	Cheryl Chun	Tetrad PhD student/NSF fellowship	PhD Advisor	Science Director, KnowledgePoint360 Group
2007—2012	Jennifer Garcia	Tetrad PhD student/NIGMS fellowship	PhD Advisor	Postdoctoral Fellow, Roy Parker
2008—2013	Diana Marina	Tetrad PhD student	PhD Advisor	Scientist, NASA
2009—present	Prashanthi Natarajan	Tetrad PhD student	PhD Advisor	Current student
2009—2014	Phillip Dumesic	Tetrad PhD student/MSTP student	PhD Advisor	Medical School
2012—present	Christina Homer	Biophysics PhD student/MSTP student	PhD Advisor	Current student
2014—present	Jade Sales-Lee	Tetrad PhD student	PhD Advisor	Current student
2014—present	Diana Summers	Tetrad PhD student	PhD Advisor	Current student

Postdoctoral Fellows and Residents Directly Supervised or Mentored

Dates	Name	Fellowship	Faculty Role	Current Position
2001—2007	Marc Meneghini	Burroughs-Wellcome Career Award, 2004	Research Supervisor	Associate Professor, University Toronto
2005—2008	Anupuma Seshan	NIH	Research Supervisor	Assistant Professor, Emanuel College
2005—2010	Changbin Chen		Research Supervisor	Group Leader, Institute Pasteur of Shanghai
2005—2011	Sigurd Braun	DFG fellowship (Germany)	Research Supervisor	Professor, LMU-Munchen
2007—2011	Smita Shankar	Leukemia and Lymphoma Society	Research Supervisor	Scientist, Impossible Food Inc.
2008—2009	Mathieu Rougemaille	Human Frontiers	Research Supervisor	Researcher, CNRS, France
2008—2013	Suzanne Komili	Jane Coffin Childs	Research Supervisor	
2009—2014	Jessica Brown		Research Supervisor	Assistant Professor, University of Utah
2011—2013	Bassem Al-Sady		Research Supervisor	Assistant Professor, UC San Francisco
2012—present	Jahan Parsa		Research Supervisor	Current Postdoc
2012	Ratika Krishnamurty		Research Supervisor	Research Scientist, University of Washington

Dates	Name	Fellowship	Faculty Role	Current Position
2013—present	Selim Boudoukha	None	Research Supervisor	Current Postdoc
2013—present	Jordan Burke	ACS fellowship	Research Supervisor	Current Postdoc
2015—present	Sandra Catania	EMBO fellowship	Research Supervisor	Current Postdoc

Mentoring Narrative

I continue to mentor postdoctoral fellows and graduate students in my laboratory. This primarily involves weekly meetings to discuss research results and directions as well as a weekly group meeting and journal club.

OTHER

Published sole-author textbook "From **a** to α: yeast as a model for cellular differentiation" Cold Spring Harbor Press, 2007.

Other Teaching Activities

Weekly laboratory group meeting/journal club (3 hrs/week)
Individual and subgroup meetings (14 hrs/week)

SUMMARY OF TEACHING AND MENTORING HOURS

2013—2014	900 total hours of teaching (including preparation) Formal class or course teaching hours: 35 hours Informal class or course teaching hours: 315 hours Mentoring hours: 550 hours
2011—2012	900 total hours of teaching (including preparation) Formal class or course teaching hours: 35 hours Information class or course teaching hours: 315 hours Mentoring hours: 550 hours
2010—2011	900 total hours of teaching (including preparation) Formal class or course teaching hours: 35 hours Informal class or course teaching hours: 315 hours Mentoring hours: 550 hours
2014—2015	Total anticipated hours of teaching: 865 hours

PEER REVIEWED PUBLICATIONS

1. Madhani, H.D., Leadon, S.A., Smith, C.A., and Hanawalt, P.C. (1986). α-DNA in African Green Monkey Cells is Organized into Extremely Long Tandem Arrays. ***Journal of Biological Chemistry*** 261: 2314-2318.

2. Madhani, H.D., Bohr, V.A. and Hanawalt, P.C. (1986). Differential DNA Repair in Transcriptionally Active and Inactive Proto-oncogenes: c-*abl* and c-*mos*. ***Cell*** 45:417-423.

3. Jacks, T., Madhani, H.D., Masiarz, F.R., and Varmus, H.E. (1988). Signals for Ribosomal Frameshifting in the Rous Sarcoma Virus *gag-pol* Region. ***Cell*** 55:447-458.

4. Madhani, H.D., Jacks, T. and Varmus, H.E. (1988). Signals for the Expression of the HIV pol gene by Ribosomal Frameshifting in The Control of Human Retrovirus Gene Expression, B. Cullen and F. Wong-Staal, eds. (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York, 1988), pp. 119-125.

5. Madhani, H.D., Bordonné, R. & Guthrie, C. (1990). Multiple Roles for U6 snRNA in the Splicing Pathway. ***Genes and Development*** 4:2274-2287.

6. Guthrie C, Madhani HD. Greetings from the RNA world. RNA Processing sponsored by the Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA, May 16-20, 1990. ***New Biologist*** 2(8):684-7. PMID: 1704252

7. Madhani, H.D. & Guthrie, C. (1992). A Novel Base-Pairing Interaction Between U2 and U6 snRNAs Suggests a Mechanism for the Catalytic Activation of the Spliceosome. ***Cell*** 71: 803-817.

8. Madhani, H.D. & Guthrie, C. (1994a). Randomization-selection analysis of snRNAs in vivo: Evidence for a tertiary interaction in the spliceosome. ***Genes and Development*** 8: 1071-1086.

9. Madhani HD, Guthrie C. (1994) Dynamic RNA-RNA interactions in the spliceosome. ***Annual Review of Genetics*** 28:1-26. PMID: 7534458

10. Madhani, H.D. & Guthrie, C. (1994b). Genetic interactions between the yeast helicase homolog Prp16 and spliceosomal snRNAs identify candidate ligands for the Prp16 RNA-dependent ATPase. ***Genetics*** 137(3):677-87. PMID: 8088513. PMCID: PMC1206027.

11. Madhani, H.D. & Fink, G.R. (1997). Combinatorial control required for the specificity of yeast MAPK signaling. ***Science*** 275(5304): 1314-7. PMID: 9036858.

12. Madhani, H.D., Styles, C.A. & Fink, G.R. (1997). MAP kinases with distinct inhibitory functions impart signaling specificity during yeast differentiation. ***Cell*** 91(5): 673-84. PMID: 9393860.

13. Madhani HD. (1997) Genetic abnormalities in Friedreich's ataxia. ***New England Journal of Medicine*** 336(14):1022; author reply 1022-3. PMID: 9091787

14. Madhani HD, Fink GR. (1998) The riddle of MAP kinase signaling specificity. ***Trends in Genetics*** 14(4):151-5. PMID: 9594663

15. Madhani HD, Fink GR. (1998) The control of filamentous differentiation and virulence in fungi. ***Trends in Cell Biology*** 8(9):348-53. PMID: 9728395

16. Rupp, S., Summers, E., Lo, H., Madhani, H.D. & Fink, G.R. (1999) MAP kinase and cAMP filamentation signaling pathways converge on the unusually large promoter of the yeast *FLO11* gene. ***EMBO J.*** 18(5): 1257-69. PMID: 10064592. PMCID: PMC1171216.

17. Madhani, H.D., Galitski, T., Lander, E.S.& Fink, G.R. (1999) Effectors of a developmental MAP kinase cascade revealed by expression signatures of signaling mutants. ***Proc. Natl. Acad. Sci. USA*** 96(22): 12530-5. PMID: 10535956. PMCID: PMC22972.

18. Madhani HD. (2000) Interplay of intrinsic and extrinsic signals in yeast differentiation ***Proceedings of the National Academy of Sciences USA*** 97(25):13461-3. PMID: 11095703. PMCID: PMC34079

19. Madhani HD. (2001) Accounting for specificity in receptor tyrosine kinase signaling. ***Cell*** 106(1):9-11. PMID: 11461696

20. Brugnera, E., Haney, L., Grimsley, C., Lu, M., Walk S.F., Tosello-Trampont, A.C., Macara I.G., Madhani, H., Fink G.R., Ravichandran K.S. (2002) Unconventional Rac-GEF activity is mediated through the Dock180-ELMO complex. ***Nature Cell Biology*** 4:574-82. PMID: 12134158.

21. Hwang, W., Venkatasubrahmanyam, S., Ianculescu, A.G., Tong, A., Boone, C., Madhani, H.D. (2003) A conserved RING finger protein required for histone H2B monoubiquitination and cell size control. ***Molecular Cell*** 11: 261-266. Published online Dec. 28, 2002. PMID: 12535538.

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Patents Issued or Pending (Allowed)

1. 10/16/2001 “Regulation of Fungal Gene Expression” 6,303,302

RESEARCH PROGRAM

We investigate the biology of *Cryptococcus neoformans*, the most common cause of fungal meningitis. As an opportunistic pathogen, this encapsulated yeast is the major fungal driver of mortality in HIV/AIDS, where it is estimated to cause up to 1/3 of deaths in this patient population, thereby exceeding the worldwide death toll from breast cancer. As a model organism, *C. neoformans* is highly tractable, offering haploid genetics and facile gene targetting. It is thus well-suited for addressing important biological questions using a range of powerful cutting-edge approaches. Our current work is divided into translational and basic science areas:

1. Genome Defense

The emergence of the earliest life forms was likely quickly followed by the appearance of the first selfish nucleic acid parasites. Whatever their form, these could have extinguished early life (via genome damage or the exhaustion of cellular resources) were it not for the evolution of cellular countermeasures. Transposable elements are a ubiquitous class of endogenous parasites that

hitchhike on the host genome. Because they violate Mendel's Laws, sexual reproduction allows transposons to spread through populations despite a negative impact on host fitness. Clustered repeats, sometimes referred to as satellites, are also a major driver of genome expansion and instability. The risk for species extinction has been linked to genome size increases, suggesting a profound impact of selfish nucleic acids on evolution.

The intrinsically deleterious nature of genomic parasites, together with their ability to out-replicate the rest of the genome, likely drove the evolution of a rich set of defense mechanisms. The primary mechanisms by which eukaryotic cells silence transposons and other repeated sequences are small silencing RNAs and chromatin modifications. Whereas the core biochemistry of both mechanisms is well-developed, the central question remains unanswered: how do cells distinguish "normal" from threatening nucleic acid sequences? Without the ability to distinguish "good" from "bad" nucleic acids, any genome defense scheme would fail. Our work focuses on this question. In mechanistic terms, it translates into "what determines the templates for small RNA synthesis and what defines where silent chromatin marks are placed"? The answers have been full of interesting surprises.

Stalled spliceosomes are a signal for RNAi-dependent genome defense

We have discovered a fundamentally new function for introns and the spliceosome in RNAi-dependent genome defense (Dumesic et al., 2013). Unlike *S. cerevisiae* and *S. pombe*, *C. neoformans* uses RNAi to suppress the movement of transposable elements. We sequenced the small RNA repertoire of *C. neoformans* and discovered that siRNAs are surprisingly generated from both intronic and exonic sequences. We characterized a nuclear RNA-dependent RNA polymerase complex, SCANR, required for siRNA biogenesis, and found that it associates with an SR-like protein that itself is a component of the spliceosome. We also noticed that pre-mRNAs that template siRNA synthesis display suboptimal splicing features, particularly in terms of length. This led us to hypothesize that the stalling of spliceosomes is a necessary signal for targeting pre-mRNAs to SCANR for double-stranded RNA synthesis. This model predicted that pre-mRNAs targeted for RNAi should be stalled on the spliceosome and that introns would be required for siRNA production. Furthermore, the model predicted that a normally poor RNAi candidate could be converted into a strong one if stalled splicing of the transcript could be engineered. Each of these predictions was experimentally verified. Moreover, we identified the lariat debranchase as an essential siRNA biogenesis factor, suggesting that the lariat-intermediate product of the first catalytic step of splicing is a precursor to dsRNA.

Our results address a profound mystery in eukaryotic biology: why genes-in-pieces? More generally, our studies promote a paradigm in which the efficiency of gene expression is used as a metric to distinguish which nucleic acids need to be silenced (Dumesic and Madhani, 2014). Indeed, many aspects of eukaryotic gene expression ranging from chromatin to mRNA modifications to mRNA quality control mechanisms may have been selected for because of the need to protect cells from parasitic nucleic acids (Madhani, 2013a).

Understanding how stalled spliceosomes lead to the production of siRNAs is a major current focus. We plan to employ a combination of genetic and biochemical approaches to understand how stalled spliceosomes engage siRNA synthesis. Our pursuit of a mechanism is inspired by strong hints that the principles will turn out to be conserved in animals and plants (Dumesic and Madhani, 2013). We also plan to investigate if and how transposons escape spliceosomal surveillance. Finally, we are

applying forward genetics to investigate how transposable elements are tightly repressed by small RNAs.

HP1-dependent chromatin silencing of repeats

Since the electrifying discovery of the first chromatin-modifying enzyme in the mid-1990s and its homology to a yeast protein required for transcription (Brownell et al., 1996), the field of chromatin biology has grown rapidly. Early investigations of chromatin modification in my laboratory demonstrated that the histone variant H2AZ functions in euchromatin to prevent the ectopic spread of heterochromatin in *S. cerevisiae* from repetitive regions (Meneghini et al., 2003). This finding changed our view of chromatin because it indicated that euchromatin is not a default state on which heterochromatin was assembled but rather that both types of chromatin contain mutually antagonistic modifications. In collaboration with Jasper Rine (UC Berkeley), we identified the Swr1 complex required for H2AZ deposition genomewide (Kobor et al., 2004). We also discovered the ubiquitin ligase, Bre1, responsible for euchromatin histone H2B monoubiquitylation (Hwang et al., 2003). We next discovered that H2AZ is deposited at nucleosomes that flank a nucleosome-free region (NFR) that characterizes eukaryotic promoters (Raisner et al., 2005). Subsequently, we defined widely acting DNA binding proteins and a chromatin-remodeling enzyme that act in a pathway to produce this promoter nucleosome pattern (Hartley and Madhani, 2009). We also found that, *in vivo*, nucleosome-free regions are upstream of H2AZ deposition, suggesting that the NFRs trigger H2AZ deposition. These early studies revealed mechanisms that instruct euchromatic chromatin organization.

Because of our interest in repeat sequence and transposon silencing, we shifted our studies from *S. cerevisiae* to *S. pombe* when it became clear that histone H3 lysine 9 methylation (H3K9Me) is a conserved mark of heterochromatin in *S. pombe* and many other species but that this mark was lost during the evolution of *S. cerevisiae*. In *S. pombe*, H3K9Me recruits HP1 proteins to pericentromeric and other repeat sequences. We used single nucleosome mapping to show that the silencing machinery triggers elimination of nucleosome free regions thereby limiting access of transcriptional regulator proteins to DNA (Garcia et al., 2010). In collaboration with Geeta Narlikar (UCSF), we have investigated how HP1 bridges nucleosomes (Canzio et al., 2011; Canzio et al., 2013) and functions with the Clr4 histone methyltransferase to accomplish silencing (Al-Sady et al., 2013). We have also studied how boundaries are formed between heterochromatin and euchromatin, in the process discovering a Cul4-type ubiquitin ligase that sculpts the heterochromatic landscape via regional degradation of an anti-silencing factor (Braun et al., 2011).

Despite great progress in understanding the fundamental biochemistry of heterochromatin assembly, the question of what determines why repeats and transposons are selected for heterochromatin assembly remains unsolved. The finding that RNAi plays a role in heterochromatin assembly in fission yeast over ten years ago was an important discovery. Curiously, while RNAi plays an important role in establishing H3K9Me in *S. pombe*, it is largely dispensable for its subsequent inheritance at endogenous sequences. Likewise, siRNAs are insufficient to trigger stable heterochromatin assembly. These observations suggested the existence of RNAi-independent mechanisms for propagating RNAi-triggered histone methylation. A key breakthrough was our identification of a sequence-specific ncRNA-binding protein, Seb1, that mediates this RNAi-independent pathway (Marina et al., 2013). We demonstrated that this protein acts via recruitment of a deacetylase/remodeling complex (Marina et al., 2013). We are investigating the concept that heterochromatin can be epigenetically inherited independently of an initial RNAi trigger, but only if licensed by specific ncRNA signals.

Polycomb in yeast

Polycomb repressors mediate the formation of facultative heterochromatin and play extraordinarily important roles in animal and plant development and in many human cancers. They also function to silence repeats. Dissecting how these repressors work would clearly benefit from a tractable unicellular system. However, Polycomb was lost in almost all fungal lineages including those that gave rise to *S. cerevisiae* and *S. pombe*.

We have discovered that orthologs of components of the Polycomb Repressive Complex 2 (PRC2) are retained in *Cryptococcus* and, furthermore, they form a five-protein complex that strongly resembles the human complex. This complex deposits the H3K27Me3 mark at repetitive subtelomeric regions thereby silencing genes in these regions, which are enriched for nutrient transport and catabolism genes as well transposable elements.

We have obtained remarkable results with one subunit of the *C. neoformans* PRC2 complex, a Polycomb-like chromodomain-containing protein. The chromodomain of this protein directly binds to the H3K27Me product, and our analysis revealed that mutational disruption of mark recognition results in a new genome-wide pattern of H3K27Me that, strikingly, coincides with the pattern of H3K9Me. Introduction of an additional mutation that removes all H3K9Me results in the concomitant loss of all H3K27Me. Thus, the PRC2 complex in *Cryptococcus* posseses an intrinsic "latent promiscuity" that attracts it to H3K9Me heterochromatin. This tendency is normally masked by the ability of the complex to recognize its enzymatic product.

We will continue to investigate this system to understand how the two types of repressive chromatin (constitutive vs. facultative) are separated, the normal biological role of PRC2 in this organism and the mechanisms that recruit PRC2 to repetitive subtelomeric regions.

2. Fungal pathogenesis

Infections represent quintessential conflicts between microbes and hosts and have had a major impact on human history. Fungal infections are an especially difficult class of infections to treat, resulting in high morbidity and mortality. It is estimated that 50% of AIDS-related deaths are due to fungal infections. Chief among these is fungal meningitis caused by *C. neoformans*, which is responsible for 500,000 annual deaths, greater than the annual worldwide toll from breast cancer. We seek to identify and understand the specializations that endow *C. neoformans* with the ability produce a lethal infection in mammals.

In our early studies, we sought to investigate virulence factors by targeted gene deletion. Unfortunately, the genome sequence was unannotated, transformation was cumbersome (requiring biolistics --"a gene gun"), and homologous recombination was inefficient even with kilobases of targeting homology. Nonetheless, by developing homology-based gene annotation and optimizing biolistic targeting, we succeeded in constructing 1200 targeted mutations in our initial effort. We screened these mutants in mice and *in vitro* to identify several dozen genes required for success in the host but not for growth *in vitro* under a variety of conditions or for the production of known virulence factors such the polysaccharide capsule (Liu et al., 2008). Our ability to find numerous novel virulence genes in a nonsaturating genetic screen implied that much remained to be discovered. Early on, we identified adaptation to hypoxia as a key pathogenicity determinant that is mediated by a pathway homologous to the human SREBP sterol homeostasis pathway (Chun et al., 2007). Subsequent work showed that the pathway is conserved in another lethal fungal pathogen, *Aspergillus fumigatis*, where it is also required for hypoxic adaptation and virulence. Taking

advantage of refined gene models, we are well on the way towards constructing a complete nonessential gene deletion collection in *C. neoformans*.

Host-pathogen conflict: phagocytosis and its evasion

C. neoformans effectively evades phagocytosis by macrophages, a central cell type of the innate immune system. Progress towards understanding why this is the case came from our identification of a *C. neoformans* transcription factor whose inactivation results in strongly increased susceptibility to phagocytosis by macrophages and a loss of virulence (Chun et al., 2011). Importantly, neither defects in the polysaccharide capsule nor exposure of known fungal molecular patterns is responsible for the phenotype, again implying novel mechanisms. We identified the direct targets of the transcription factor and found among these a family of highly expressed, signal sequence-bearing proteins harboring a double-*psi* beta barrel of unknown function. We have clear evidence that at least one member of this family is required for phagocytosis inhibition (Chun et al., 2011). We will continue to investigate this protein family to elucidate their precise molecular roles virulence and the inhibition of phagocytosis. Specifically, we will investigate the possibility is that the pathogen produces a ligand for receptors on phagocytes that recognize "don't eat me" signals on normal cells that prevent self-phagocytosis. These receptors are rapidly evolving, suggesting conflict with pathogens.

Cell-cell communication and virulence

Quorum sensing systems are instrumental regulators of population behavior in bacteria, which control community activities ranging from bioluminescence to virulence. However, whether eukaryotes possess analogous systems is unclear. We have identified a gene encoding a secreted peptide, Qsp1, as a direct target of three transcription factors that we had discovered in earlier studies to be required for virulence (Chun et al., 2011; Liu et al., 2008). We found that deletion of this gene produces cells that grow normally but are highly attenuated for virulence in the animal. The mutant also exhibits changes in surface properties evident as increased adhesiveness and altered colony morphology. Remarkably, wild-type cells or the purified peptide can complement these *in vitro* defects in *trans*, indicative of cell-cell signaling. Investigations of the role of cell-cell communication in pathogenesis are a major current focus.

SIGNIFICANT RECENT PUBLICATIONS

1. Dumesic, P.A., Homer, C.M., Moresco, J.J., Pack, L.R., Shanle, E.K., Strahl, B.D., Fujimori, D.G., Yates, J.R., Madhani, H.D. (2014) Product binding enforces the genomic specificity of a yeast Polycomb repressive complex. ***Cell*** 160(1-2):204-18. PMID: 25533783. PMCID: PMC4303595.

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