BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Sarah Elizabeth Zanders

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

POSITION TITLE: Assistant Investigator

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 Iowa, Iowa City IA	B.S.	05/2005	Biology
Cornell University, Ithaca NY	Ph.D.	08/2010	Genetics
Fred Hutch Cancer Research Center, Seattle WA	Postdoc	07/2016	Molecular Evolution

A. Personal Statement

I have a long-standing passion for understanding the causes of meiotic chromosome missegregation and infertility. I have spent my career, starting as an undergraduate, acquiring expertise on the factors that affect the transmission of DNA between generations. I trained with leaders in their fields to gain an exceptionally broad skill set in genetics, genomics, biochemistry, and molecular evolution approaches. I have demonstrated my ability to leverage my knowledge and skills to gain novel insights on gametogenesis. Even as a graduate student, my main research projects were largely self-designed and executed. I also designed projects and trained undergraduates both as a graduate student and post-doc. I therefore had an easy transition to becoming a principle investigator. Five years into my appointment, I have already recruited a talented team and led them to make impactful discoveries. We have published six research papers describing some of these findings. Currently, my lab is working to identify genes important for executing gametogenesis and to identify genes that mitigate the cost of meiotic drivers. I have considerable expertise in both these areas. My graduate thesis research focused on mechanisms of meiotic genes and I discovered meiotic drivers in fission yeast as a postdoc.

1. **Zanders, S**. & Alani, E. (2009) The *pch2Delta* mutation in baker's yeast alters meiotic crossover levels and confers a defect in crossover interference. *PLoS Genetics* 5:e1000571.
2. Nuckolls, N.L.*, Bravo Núñez, M.A.*, Eickbush, M.T., Young, J.M., Lange, J.J., Yu, J.S., Smith, G.R., Jaspersen, S.L., Malik, H.S. & **Zanders, S.E.** (2017) *wtf* genes are prolific dual poison-antidote meiotic drivers. *eLife* 6:e26033.
3. Bravo Núñez, M.A., Sabbarini, I.M., Eide, L.E., Unkless, R.L., & **Zanders, S.E.** (2020) Atypical meiosis can be adaptive in outcrossed *S. pombe* due to *wtf* meiotic drivers. *eLife* 9:e57936.
4. Nuckolls, N.L., Mok, A.C., Lange, J.J., Yi, K., Kandola, T.S., Hunn, A.M., McCroskey, S., Snyder, J.L., Bravo Núñez, M.A., McClain, M.L., McKinney, S.A., Wood, C., Halfmann, R., & **Zanders, S.E** (2020) The *wtf4* meiotic driver utilizes controlled protein aggregation to generate selective cell death. *eLife* 9:e55694.

B. Positions and Honors

Positions and Employment

Assistant Investigator, Stowers Institute for Medical Research, Kansas City MO   2016-
Vice Dean Graduate School of the Stowers Institute for Medical Research , Kansas City MO   2019-

Other Experience and Professional Memberships
Chair, Gordon Research Seminar on Meiosis   2014
Editorial Board, PLOS Biology   2019-

Honors
Presidential Life Sciences Fellowship, Cornell University   2005-06
NIH Training Grant support, Cornell University   2009-10 and 2007-08
Outstanding Teaching Assistant Award, Cornell University   2006
NIH Training Grant support, University of Washington   2012-13
NIH Ruth L. Kirschstein National Research Service Award (declined)   2012
American Cancer Society Postdoctoral Fellowship   2013-16
NIH K99/R00 Research Transition Award   2015-2019
March of Dimes Basil O'Connor Starter Scholar Research Award   2018-20
Searle Scholar Award   2018-21
NIH Director's New Innovator Award   2018-23
High Recognition PLOS Genetics Research Prize   2019
Honorable mention Rosalind Franklin Young Investigator Award   2019
Science News SN10 young scientist to watch   2020

C. Contributions to Science

1) The origins of infertility in natural populations of fission yeasts: This project was based on the idea that identifying the origins of infertility in model natural populations should illuminate potential causes of infertility within humans. In this project, I investigated the cause of reproductive isolation between two closely related isolates of *Schizosaccharomyces pombe*: the lab strain (*Sp*) and a wild strain *S. kambucha* (*Sk*). I found that despite the two isolates sharing 99.5% DNA sequence identity, *Sp/Sk* hybrids could produce few viable progeny. Moreover, the progeny they could produce were generally aneuploid. To investigate the cause of this infertility, our team generated an assembly of the *Sk* genome and developed the first genetic tools in *Sk*. I then used these tools to demonstrate that multiple selfish loci known as meiotic drive alleles and linked chromosome rearrangements cause the infertility of *Sp*/*Sk* hybrids (Zanders et al. 2014). I also proposed a hypothesis in which the meiotic drivers could also underlie the aneuploidy of the *Sp/Sk* hybrid progeny. This work was the first to demonstrate that gamete-killing meiotic drive alleles exist in fission yeast and are erecting strong reproductive barriers in natural populations. It also highlighted how traditional genetic approaches using single inbred isolates are blind to detect meiotic drivers: fission yeast was intensely studied genetically for over 50 years without appreciating that the genome is plagued by these parasites. Finally, the work provided experimental evidence supporting the relatively unpopular chromosomal speciation model in which meiotic drivers cause speciation by facilitating the evolution of chromosome rearrangements. I conceived this project, designed the experiments, executed most of the experiments, and wrote the paper with guidance from my mentors Dr. Smith and Dr. Malik. In addition, I trained three of my co-authors (a high school student, an undergraduate and a technician) and supervised their work on the project.

   a. **Zanders, S.E.**, Eickbush, M.T., Yu, J.S., Kang, J.W., Fowler, K.R., Smith, G.R. & Malik, H.S. (2014) Genome rearrangements and pervasive meiotic drive cause hybrid infertility in fission yeast. *eLife* 3:e02630.

2) Characterization of the *wtf* genes as meiotic drive loci: Meiotic drive alleles are selfish DNA loci that act to bias their own transmission into gametes. These selfish genes can also directly and indirectly cause infertility, so understanding what genes can cause drive and how they work is important. The actions of many meiotic drivers have been described in a myriad of organisms, but few genes underlying drive phenotypes have actually been cloned. Even amongst cloned drivers, there is little molecular understanding of drive mechanisms. Largely through our work, the *wtf* genes of *S. pombe* are now amongst the best characterized drive systems. Our lab demonstrated that one *wtf* drive gene can cause meiotic drive by killing the gametes that do not inherit it from a heterozygote. We showed *wtf* drivers act via a poison and antidote mechanism in which all the developing gametes are poisoned, but only those that inherit the driving *wtf* locus, are rescued by the antidote. We found that the driving *wtf* genes make distinct poison and antidote proteins using alternate

transcriptional start sites, a previously undescribed strategy for selfish genes. We also discovered that some *wtf* genes encode only antidotes and act as suppressors of *wtf* drivers. Our investigations of the *wtf* drive mechanism revealed that the Wtf^{poison} proteins form toxic aggregates that indiscriminately kill cells. We found that the Wtf^{antidote} proteins can neutralize Wtf^{poison} proteins by co-assembling with the Wtf^{poison} aggregates and promoting their recruitment to the vacuole. I conceived these projects, mapped the first *wtf* driver, supervised the experiments characterizing the *wtf* genes, and helped my trainees write the papers.

    a. Nuckolls, N.L.*, Bravo Núñez, M.A.*, Eickbush, M.T., Young, J.M., Lange, J.J., Yu, J.S., Smith, G.R., Jaspersen, S.L., Malik, H.S. & **Zanders, S.E.** (2017) *wtf* genes are prolific dual poison-antidote meiotic drivers. *eLife* 6:e26033.
    b. Bravo Núñez, M.A., Lange, J.J. & **Zanders, S.E.** (2018) A suppressor of a *wtf* poison-antidote meiotic driver acts via mimicry of the driver's antidote. PLOS Genet. 14:e1007836.
    c. Bravo Núñez, M.A., Sabbarini, I.M., Eickbush, M.T., Liang, Y., Lange, J.J. Kent, A.M., & **Zanders, S.E.** (2020) Dramatically diverse *S. pombe wtf* meiotic drivers all display high gamete-killing efficiency. PLOS Genet. 16(2):e1008350.
    d. Nuckolls, N.L., Mok, A.C., Lange, J.J., Yi, K., Kandola, T.S., Hunn, A.M., McCroskey, S., Snyder, J.L., Bravo Núñez, M.A., McClain, M.L., McKinney, S.A., Wood, C., Halfmann, R., & **Zanders, S.E** (2020) The *wtf4* meiotic driver utilizes controlled protein aggregation to generate selective cell death. *eLife* 9:e55694.

3) Demonstrating the potential for meiotic drivers to shape the evolution of meiosis: Meiotic drivers are genetic parasites that manipulate gametogenesis to gain a transmission advantage into progeny. Theoretical studies have identified meiotic drivers as a major evolutionary force and have suggested that they may shape key aspects of genome organization and transmission between generations. Although the evolutionary support for this idea is compelling, there are few empirical experiments that address this idea directly. We explored the potential impact of *wtf* meiotic drivers on the evolution of meiosis in *S. pombe*. We found that non-haploid gametes (aneuploids and diploids) are more fit than the typical haploid gametes produced by heterozygotes due to the actions of *wtf* meiotic drivers. This suggested that *wtf* drivers could promote the evolution of variants that cause meiotic chromosome missegregation. We tested this hypothesis using computational models and *in vivo* genetic analyses. We found that mutations that decrease the fidelity of meiosis could be favored by natural selection in outcrossed *S. pombe*. In addition, we found that variants that produce non-haploid gametes are common in natural populations. This work was the first to demonstrate that meiotic drivers can promote the evolution of error-prone meiosis.

    a. Bravo Núñez, M.A., Sabbarini, I.M., Eide, L.E., Unkless, R.L., & **Zanders, S.E.** (2020) Atypical meiosis can be adaptive in outcrossed *S. pombe* due to *wtf* meiotic drivers. *eLife* 9:e57936.

4) Identification of Pch2 as a major regulator of meiotic break repair: My graduate work focused primarily on elucidating the mechanisms underlying the regulation of meiotic DNA double-strand break (DSB) repair, which is essential for fertility in most eukaryotes. Obligate crossover formation, crossover interference, and crossover homeostasis are all manifestations of DSB repair collectively known as crossover control. Little was known about the mechanisms or relatedness of these control systems before my work demonstrated that one conserved protein, Pch2, is required for full efficacy of each aspect of crossover control in budding yeast. These results were surprising given that previous studies of Pch2 reported the protein was a checkpoint factor and had no role in recombination outside the rDNA. The work was significant because it suggested a unified and conserved mechanism underlies all known aspects of crossover control. In subsequent work, I showed that Pch2 has an even broader role in meiotic DSB repair in that it contributes to the temporal barrier to using the sister-chromatid (as opposed to the homologous chromosome) as a repair template. I designed the studies with guidance from my advisor, Dr. Eric Alani. I executed almost all the experiments and I wrote the papers with help from Dr. Alani.

    a. **Zanders, S**. & Alani, E. (2009) The *pch2Delta* mutation in baker's yeast alters meiotic crossover levels and confers a defect in crossover interference. *PLoS Genetics* 5, e1000571.
    b. **Zanders, S**., Sonntag Brown, M., Chen, C. & Alani E (2011) Pch2 modulates chromatid partner choice during meiotic double-strand break repair in *S. cerevisiae*. *Genetics* 188:511-21.

5) The role of rapid chromosome motions in meiosis: During budding yeast meiotic prophase, telomeres attach to the nuclear periphery and are vigorously shaken. These movements are widely conserved in eukaryotes but are surprising given that the genome is fragmented into hundreds of pieces at this stage by induced DNA double strand breaks (DSBs). As part of a collaborative project, I explored the role of these chromosome movements. This work revealed that the motions promote timely repair of DSBs, efficient completion of meiosis, faithful chromosome segregation, and thereby fertility. We also provided the first direct evidence supporting the experimentally elusive hypothesis that rapid chromosome movements act to break apart chromosomal interlocks, which are predicted to result from meiotic recombination and chromosome synapsis. This research gave valuable insights into the intriguing mechanism by which meiotic cells promote the integrity of the shattered genome by shaking it. I contributed to the design of the study and executed some of the experiments.

a. Sonntag Brown, M., **Zanders, S.** & Alani, E. (2011) Sustained and Rapid Chromosome Movements are Critical for Chromosome Pairing and Meiotic Progression in Budding Yeast. *Genetics* 188:21-32.
b. Wanat, J*., Kim, K.P.*, Koszul, R.*, **Zanders, S.**, Weiner, B., Kleckner, N. & Alani, E. (2008) Csm4, in collaboration with Ndj1, mediates telomere-led chromosome dynamics and recombination during yeast meiosis. *PLoS Genetics* 4:e1000188.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1-spkgWxvH5AW/bibliography/public/

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

Ongoing Research Support
NIH DP2 GM132936   09/18-05/23
Models of Selfishness: Molecular and Evolutionary Analyses of the Wtf Meiotic Drivers
The major goals of this project are to characterize how the poison protein generated by the *S. kambucha wtf4* meiotic drive gene enters developing gametes and destroys them. We will also identify if the antidote protein generated by *wtf4* interacts with the poison and more generally determine what determines specificity between the antidote and poison proteins generated by *wtf* meiotic drive genes. Finally, we will use experimental evolution analyses to determine how meiotic drive genes can spread both within a genome and within a population.
Role: PI

Searle Scholars Award   07/18-06/21
Selfish Genes in Gametogenesis
The major goal of this project is to determine how *wtf* meiotic drivers execute gametes
Role: PI

Institutional support, Stowers Institute for Medical Research   07/16–12/22
Role: PI

Completed Research Support
Basil O'Connor Starter Scholar Research Award   03/18-02/20
The effect of selfish genes on the frequency of gamete aneuploidy
The major goals of this project are to explore the direct and indirect effects of meiotic drive alleles on the production of aneuploid gametes.
Role: PI

NIH K99/R00 GM114436-03   05/15–06/19
Mechanisms of meiotic drive and the functional consequences of rapid genome evolution
The goals of this study are to 1) identify selfish DNA loci 2) to characterize the functional consequences of genome evolution on the fidelity of meiotic divisions 3) to assay how the suite of genes essential for life and gametogenesis changes over time.
Role: PI