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: McKim, Kim

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

POSITION TITLE: Professor

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)	END DATE MM/YYYY	FIELD OF STUDY
Simon Fraser University, Burnaby, BC	BS	05/1986	Biology
University of British Columbia, Vancouver, BC	PHD	12/1990	Medical Genetics
Simon Fraser University, Burnaby, BC	OTH	12/1991	Genetics
University of California, Davis CA, Davis, CA	OTH	10/1996	Genetics

A. Personal Statement

The goal of the research in my lab is to understand the mechanisms and regulation of meiotic chromosome behavior, including homolog pairing, genetic recombination, spindle assembly and chromosome segregation. All of these processes work in progression to promote the production of euploid gametes. We specialize in using genetic and cytological methods with the power of the Drosophila model system to identify and characterize proteins required for meiosis. While much of our work focuses on meiosis specific events like synaptonemal complex formation and acentrosomal spindle assembly in oocytes, many of the genes and processes we are studying have important roles in mitotic cells. In the course of these studies, I have supervised 11 graduate students who have completed their PhD and 3 postdocs.

I have a broad background in genetics and molecular biology of Drosophila, which is enhanced by applying sophisticated imaging techniques. My interest in meiosis began with Graduate work in C. elegans. Starting with my post-doctoral research with Scott Hawley, I have been working on fly meiosis for 24 years. Past work has focused on analyzing the product of genetic screens. This has been successful and we have identified and cloned many genes by a forward genetics approach. More recently, we have been using reverse genetics and sophisticated tools in Drosophila such as site-specific mutagenesis and tissue specific RNAi to analyze the meiotic functions of genes. We use a variety of methods to characterize the most important meiotic phenotypes. We have adopted or developed several genetic and cytological methods to measure these key parameters of meiosis such as homolog pairing, synapsis, DSB formation, DSB repair, crossing over, spindle assembly and chromosome segregation. The Drosophila ovary is particularly amenable to cytological analysis, which is facilitated by the availability of Leica SP8 confocal microscopes with super resolution capability in our imaging core. Thus, we combine our genetics expertise with immunoflourescence and high resolution confocal microscopy. Indeed, few labs perform the types of analysis of fixed and living oocytes that we do and we often get requests for help or collaboration. I have the expertise, leadership and motivation necessary to successfully carry out the proposed work.

1. McKim KS. Highway to hell-thy meiotic divisions: Chromosome passenger complex functions driven by microtubules: Bioessays. 2022 Jan;44(1):e2100202. PubMed Central PMCID: PMC8688318.
2. Radford SJ, Nguyen AL, Schindler K, McKim KS. The chromosomal basis of meiotic acentrosomal spindle assembly and function in oocytes. Chromosoma. 2017 Jun;126(3):351-364. PubMed Central PMCID: PMC5426991.
3. Radford SJ, McKim KS. Techniques for Imaging Prometaphase and Metaphase of Meiosis I in Fixed Drosophila Oocytes. J Vis Exp. 2016 Oct 31; PubMed Central PMCID: PMC5226183.
4. McKim KS, Joyce EF, Jang JK. Cytological analysis of meiosis in fixed Drosophila ovaries. Methods Mol Biol. 2009;558:197-216. PubMed PMID: 19685326.

B. Positions, Scientific Appointments

2009 -	Professor, Waksman Institute/ Rutgers, Piscataway, NJ
2003 - 2009	Associate Professor, Waksman Institute/ Rutgers, Piscataway, NJ
1996 - 2003	Assistant Professor, Waksman Institute/ Rutgers, Piscataway, NJ

C. Contribution to Science

1. It was originally demonstrated in budding yeast that meiotic recombination is initiated by a double strand break (DSB). If this paradigm applied to other organisms was not known. In my own lab, we showed that meiotic recombination is induced by a double strand break in Drosophila based on several lines of evidence. We isolated two genes required for all meiotic recombination (mei-W68 and mei-P22), one of which, mei-W68, encodes a Spo11/ TopVIA homolog, the enzyme that generates the DSBs in budding yeast. Recent studies in mouse have suggested mei-P22 encodes the essential TopVIB subunit of this enzyme. We also generated a phospho-specific H2AV antibody that recognizes DSBs and showed these are present during Drosophila meiosis and depend on mei-W68 and mei-P22. More recently, we discovered that the DSB-dependent kinase ATM is part of a negative feed-back loop to regulate DSB formation, a function that is conserved in mouse.

    a. Lake CM, Nielsen RJ, Bonner AM, Eche S, White-Brown S, McKim KS, Hawley RS. Narya, a RING finger domain-containing protein, is required for meiotic DNA double-strand break formation and crossover maturation in Drosophila melanogaster. PLoS Genet. 2019 Jan;15(1):e1007886. PubMed Central PMCID: PMC6336347.
    b. Joyce EF, Pedersen M, Tiong S, White-Brown SK, Paul A, Campbell SD, McKim KS. Drosophila ATM and ATR have distinct activities in the regulation of meiotic DNA damage and repair. J Cell Biol. 2011 Oct 31;195(3):359-67. PubMed Central PMCID: PMC3206348.
    c. Joyce EF, McKim KS. Drosophila PCH2 is required for a pachytene checkpoint that monitors double-strand-break-independent events leading to meiotic crossover formation. Genetics. 2009 Jan;181(1):39-51. PubMed Central PMCID: PMC2621188.
    d. Mehrotra S, McKim KS. Temporal analysis of meiotic DNA double-strand break formation and repair in Drosophila females. PLoS Genet. 2006 Nov 24;2(11):e200. PubMed Central PMCID: PMC1657055.

2. Early in meiotic prophase, the chromosomes are aligned and joined by the synaptonemal complex (SC). The nature of the sites where SC assembly initiates is poorly understood. We have discovered a reproducible pathway of SC initiation and an important role for cohesin proteins in this process. At least two cohesin-related pathways function in parallel for complete SC assembly, DSB formation, and the generation of crossovers. One of these pathways is required for cohesion and loaded during S-phase. The other is loaded throughout meiotic prophase and is required only for homolog interactions and SC assembly.

    a. Gyuricza MR, Manheimer KB, Apte V, Krishnan B, Joyce EF, McKee BD, McKim KS. Dynamic and Stable Cohesins Regulate Synaptonemal Complex Assembly and Chromosome Segregation. Curr Biol. 2016 Jul 11;26(13):1688-1698. PubMed Central PMCID: PMC4942336.
    b. Joyce EF, Paul A, Chen KE, Tanneti N, McKim KS. Multiple barriers to nonhomologous DNA end joining during meiosis in Drosophila. Genetics. 2012 Jul;191(3):739-46. PubMed Central PMCID: PMC3389970.
    c. Tanneti NS, Landy K, Joyce EF, McKim KS. A pathway for synapsis initiation during zygotene in Drosophila oocytes. Curr Biol. 2011 Nov 8;21(21):1852-7. PubMed PMID: 22036181.
    d. Joyce EF, McKim KS. Chromosome axis defects induce a checkpoint-mediated delay and interchromosomal effect on crossing over during Drosophila meiosis. PLoS Genet. 2010 Aug 12;6(8) PubMed Central PMCID: PMC2920846.

3. In oocytes of many animals, including Drosophila and humans, the meiotic spindle forms in the absence of centrosomes. We identified a protein, Subito (a Kinesin-6, MKLP2 in mammals) that is required for spindle organization and chromosomes segregation at meiosis I. Subito is required to bundle the antiparallel

microtubules of the central spindle. In mitosis, it is required for cytokinesis. In meiosis, our evidence supports a model where Subito organizes an enhanced central spindle during prometpahase I, which compensates for the absence of centrosomes and organizes the microtubules into a bipolar structure. The importance of the central spindle in acentrosomal meiosis appears to be conserved in other organisms.

a. Das A, Cesario J, Hinman AM, Jang JK, McKim KS. Kinesin 6 Regulation in *Drosophila* Female Meiosis by the Non-conserved N- and C- Terminal Domains. G3 (Bethesda). 2018 May 4;8(5):1555-1569. PubMed Central PMCID: PMC5940148.
b. Radford SJ, Go AM, McKim KS. Cooperation Between Kinesin Motors Promotes Spindle Symmetry and Chromosome Organization in Oocytes. Genetics. 2017 Feb;205(2):517-527. PubMed Central PMCID: PMC5289833.
c. Das A, Shah SJ, Fan B, Paik D, DiSanto DJ, Hinman AM, Cesario JM, Battaglia RA, Demos N, McKim KS. Spindle Assembly and Chromosome Segregation Requires Central Spindle Proteins in Drosophila Oocytes. Genetics. 2016 Jan;202(1):61-75. PubMed Central PMCID: PMC4701103.
d. Jang JK, Rahman T, Kober VS, Cesario J, McKim KS. Misregulation of the kinesin-like protein Subito induces meiotic spindle formation in the absence of chromosomes and centrosomes. Genetics. 2007 Sep;177(1):267-80. PubMed Central PMCID: PMC2013708.

4. We are interested in understanding the mechanisms of bi-orientation and the features of the oocyte spindle that make it susceptible to chromosome segregation errors. From previous research, we have shown that the kinetochore interacts with the microtubules in two ways. First, lateral attachments, where the kinetochores move along the sides of microtubules, establish bi-orientation. Second, end-on attachments, where the kinetochores make a stable attachment to the ends of microtubules, maintain connections to a pole and segregate the homologs. Stabilizing end-on attachments too rapidly leads to errors in chromosome segregation.

a. Jang JK, Gladstein AC, Das A, Shapiro JG, Sisco ZL, McKim KS. Multiple pools of PP2A regulate spindle assembly, kinetochore attachments and cohesion in Drosophila oocytes. J Cell Sci. 2021 Jul 15;134(14) PubMed Central PMCID: PMC8325958.
b. Fellmeth JE, McKim KS. Meiotic CENP-C is a shepherd: bridging the space between the centromere and the kinetochore in time and space. Essays Biochem. 2020 Sep 4;64(2):251-261. PubMed PMID: 32794572.
c. Wang LI, Das A, McKim KS. Sister centromere fusion during meiosis I depends on maintaining cohesins and destabilizing microtubule attachments. PLoS Genet. 2019 May;15(5):e1008072. PubMed Central PMCID: PMC6581285.
d. Radford SJ, Hoang TL, Głuszek AA, Ohkura H, McKim KS. Lateral and End-On Kinetochore Attachments Are Coordinated to Achieve Bi-orientation in Drosophila Oocytes. PLoS Genet. 2015 Oct;11(10):e1005605. PubMed Central PMCID: PMC4608789.

5. Because oocytes lack centrosomes, they also lack the canonical microtubule organizing centers at these locations. We have investigated several pathways that have been proposed to promote microtubule assembly in the absence of centrosomes. We found that in the absence of the chromosome passenger complex (CPC), which includes the kinase Aurora B, spindle assembly does not occur. Our evidence suggests that Aurora B is recruited to chromatin by HP1 and activates spindle assembly via the central spindle, kinetochores, and other chromatin-based sites. Our most recent work has been to investigate the kinetochores, and how the interact with the central spindle to ensure accurate bi-orientation. We have found that bi-orientation occurs through lateral-microtubule attachments to the kinetochores.

a. Wang LI, DeFosse T, Jang JK, Battaglia RA, Wagner VF, McKim KS. Borealin directs recruitment of the CPC to oocyte chromosomes and movement to the microtubules. J Cell Biol. 2021 Jun 7;220(6) PubMed Central PMCID: PMC8185691.
b. Radford SJ, Harrison AM, McKim KS. Microtubule-depolymerizing kinesin KLP10A restricts the length of the acentrosomal meiotic spindle in Drosophila females. Genetics. 2012 Oct;192(2):431-40. PubMed Central PMCID: PMC3454874.

c. Radford SJ, Jang JK, McKim KS. The chromosomal passenger complex is required for meiotic acentrosomal spindle assembly and chromosome biorientation. Genetics. 2012 Oct;192(2):417-29. PubMed Central PMCID: PMC3454873.

d. Cesario J, McKim KS. RanGTP is required for meiotic spindle organization and the initiation of embryonic development in Drosophila. J Cell Sci. 2011 Nov 15;124(Pt 22):3797-810. PubMed Central PMCID: PMC3225268.

Complete List of Published Work in My Bibliography:

https://www.ncbi.nlm.nih.gov/myncbi/kim.mckim.1/bibliography/public/